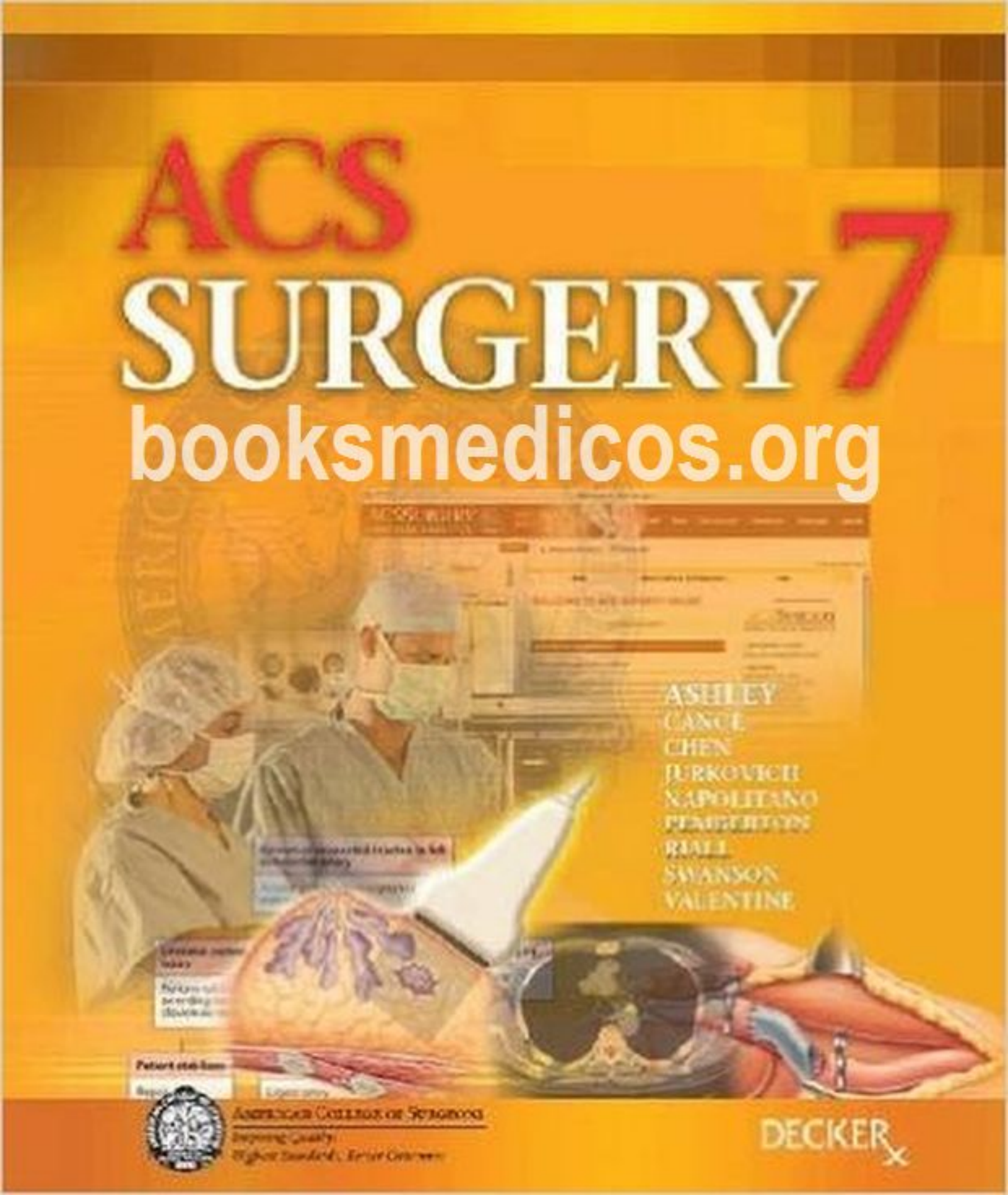


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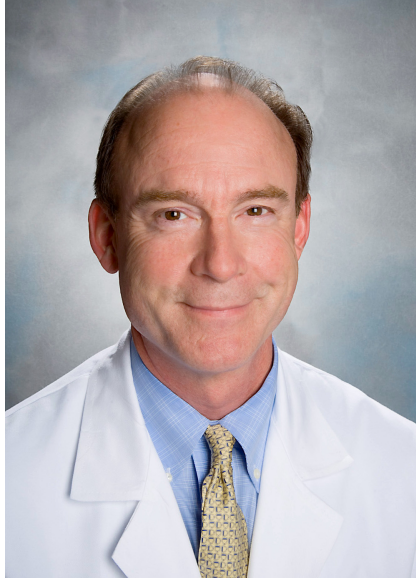


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New Editor, New Vision for *ACS Surgery*



BC Decker Inc, publisher of the acclaimed general surgical reference, *ACS Surgery*, is honored to announce the appointment of Stanley W. Ashley, MD, FACS as the new Editor-in-Chief.

Dr. Ashley is the Frank Sawyer Professor and Vice Chairman of the Department of Surgery, and Program Director of the General Surgery Residency Program at Brigham and Women's Hospital/Harvard Medical School, Boston. He is also Chief of General Surgery for Harvard Vanguard Medical Associates.

As the new Editor-in-Chief, Dr. Ashley brings his estimable experience in, and unique vision of, surgery to bear on *ACS Surgery*, an official publication of the American College of Surgeons. "The opportunity to adapt *ACS Surgery* to the evolving needs of surgical residents and practicing surgeons is extremely exciting to me," remarked Dr. Ashley.

"Stan Ashley will be a wonderful new editor of *ACS Surgery*, who will build on the outstanding work Dr. Souba did in transitioning the original loose-leaf work into the modern era. Dr. Ashley will continue that trend by taking this excellent educational product to the next level," said ACS Executive Director Thomas R. Russell, MD, FACS.

In addition to many exciting changes, Dr. Ashley envisions adding operative videos to the online home of *ACS Surgery*, www.acssurgery.com. He believes that these videos, teaching slide sets, and pod casts will enhance the educational experience for residents and practicing surgeons before entering the OR. He also would like the text to begin to integrate with the new general surgery residency curriculum being developed by the Surgical Committee on Resident Education (SCORE). He also hopes to expand the scope of the work by including chapters by a variety of experts with differing perspectives on general surgery and the subspecialties. Together with Decker, Dr Ashley will promulgate the effort to make *ACS Surgery* an internationally adopted surgical reference.

Optimism for the new Editor-in-Chief is described succinctly by Brian Decker, President and Publisher: "We are persuaded that Dr. Ashley's stewardship will enhance the already remarkable success of *ACS Surgery*. The work draws its strength from its rich history, but its vitality stems from the fresh vision that Dr. Ashley brings to the enterprise. Since its first incarnation as *Scientific American Surgery*, this work has been the benchmark for innovation in surgical education. We expect the track record to be extended during the Ashley regime."

About Stanley W. Ashley, MD, FACS

Stanley W. Ashley is a graduate of Oberlin College and Cornell University Medical College. He completed a residency in general surgery at Washington University in St. Louis and subsequently joined the faculty. He spent seven years at UCLA before assuming his current position at Brigham and Women's Hospital/ Harvard Medical School in 1997. Dr. Ashley is a gastrointestinal surgeon whose primary interests are diseases of the pancreas and inflammatory bowel disease. His research, which has been funded by the VA the NIH, has examined the pathophysiology of small bowel and pancreas. An author of more than 200 journal articles, he serves on numerous editorial boards, including the Journal of Gastrointestinal Surgery, the Journal of the American College of Surgeons, and Current Problems in Surgery. He is a director of the American Board of Surgery and member of the Board of Trustees of the Society for Surgery of the Alimentary Tract.

About BC Decker Inc

BC Decker Inc has published some of the most important works in medicine and surgery, including Cameron's *Current Surgical Therapy*, Cameron-Sandone's *Atlas of Gastrointestinal Surgery*, and Grillo's *Surgery of the Trachea*. Decker is respected for the quality of its titles and renowned for its authors. The company realizes half of its sales outside the United States through its relationships with the best international houses. Decker also publishes *ACP Medicine*, née *Scientific American Medicine*, and 20 specialty journals in medicine and dentistry. Every Decker publication is available in print and digital formats. The company's publishing partners include American College of Surgeons, American Board of Surgery, American Board of Otolaryngology, American Academy of Otolaryngology, and the American College of Physicians.

About the American College of Surgeons

The American College of Surgeons is a scientific and educational organization of surgeons that was founded in 1913 to raise the standards of surgical practice and to improve the care of the surgical patient. The College is dedicated to the ethical and competent practice of surgery. Its achievements have significantly influenced the course of scientific surgery in America and have established it as an important advocate for all surgical patients. The College has more than 76,000 members and is the largest organization of surgeons in the world.

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1 PROFESSIONALISM IN SURGERY

Jo Shapiro, MD, FACS, Steven M. Steinberg, MD, FACS, and Wiley W. Souba, MD, ScD, MBA, FACS

Over the past decade, the American health care system has had to cope with and manage an unprecedented amount of change. As a consequence, the medical profession has been challenged along the entire range of its cultural values and its traditional roles and responsibilities. It would be difficult, if not impossible, to find another social issue directly affecting all Americans that has undergone as rapid and remarkable a transformation—and oddly, a transformation in which the most important protagonists (i.e., the patients and the doctors) remain dissatisfied.¹

Nowhere is this metamorphosis more evident than in the field of surgery. Marked reductions in reimbursement, explosions in surgical device biotechnology, a national medical malpractice crisis, and the disturbing emphasis on commercialized medicine have forever changed the surgical landscape, or so it seems. The very foundation of patient care—the doctor-patient relationship—is in jeopardy. Surgeons find it increasingly difficult to meet their responsibilities to patients and to society as a whole. In these circumstances, it is critical for us to reaffirm our commitment to the fundamental and universal principles and values of medical professionalism.

The concept of medicine as a profession grounded in compassion and sympathy for the sick has come under serious challenge.² One eroding force has been the growth and sovereignty of biomedical research. Given the high position of science and technology in our societal hierarchy, we may be headed for a form of medicine that includes little caring but becomes exclusively focused on the mechanics of treatment, so that we deal with sick patients much as we would a flat tire or a leaky faucet. In such a form of medicine, healing becomes little more than a technical exercise, and any talk of morality that is unsubstantiated by hard facts is considered mere opinion and therefore carries little weight.

The rise of entrepreneurialism and the growing corporatization of medicine also challenge the traditions of virtue-based medical care. When these processes are allowed to dominate medicine, health care becomes a commodity. As Pellegrino and Thomasma remark, “When economics and entrepreneurship drive the professions, they admit only self-interest and the working of the marketplace as the motives for professional activity. In a free-market economy, effacement of self-interest, or any conduct shaped primarily by the idea of altruism or virtue, is simply inconsistent with survival.”²

Another profound change in the practice of medicine is the shift from a largely autonomous focus, with the surgeon both shouldering tremendous personal responsibility and wielding considerable control and independence, to a complex, team-based focus. Within this new paradigm, leadership of a surgical team requires vastly different competencies than

were previously required or even valued. Many surgeons have flourished in this new environment: leading a cohesive team dedicated to excellent outcomes is highly rewarding. Unfortunately, however, as a profession, we have not explicitly taught these teamwork and leadership skills, nor have we always helped our colleagues remediate deficiencies in such skills.

The Meaning of Professionalism

Professionalism is the basis of our contract with society. A profession is a collegial discipline that regulates itself by means of mandatory, systematic training. It has a base in a body of technical and specialized knowledge that it both teaches and advances; it sets and enforces its own standards; and it has a service orientation, rather than a profit orientation, enshrined in a code of ethics.³⁻⁵ To put it more succinctly, a profession has cognitive, collegial, and moral attributes. These qualities are well expressed in the familiar sentence from the Hippocratic oath: “I will practice my art with purity and holiness and for the benefit of the sick.”

Historically, the legitimacy of medical authority is based on three distinct claims^{2,6}: first, that the knowledge and competence of the professional have been validated by a community of peers; second, that this knowledge has a scientific basis; and third, that the professional’s judgment and advice are oriented toward a set of values. These aspects of legitimacy correspond to the collegial, cognitive, and moral attributes that define a profession.

The American College of Surgeons (ACS) Task Force on Professionalism has developed a Code of Professional Conduct,⁷ which emphasizes the following four aspects of professionalism:

1. A competent surgeon is more than a competent technician.
2. Whereas ethical practice and professionalism are closely related, professionalism also incorporates surgeons’ relationships with patients and society.
3. Unprofessional behavior must have consequences.
4. Professional organizations are responsible for fostering professionalism in their membership.

Specifically, the ACS Code of Professional Conduct includes tenets of professionalism that relate to both our care of individual patients and our role in society [see Table 1].

The Accreditation Council on Graduate Medical Education (ACGME) has identified six competencies that must be demonstrated by the surgeon: (1) patient care; (2) medical knowledge; (3) practice-based learning and improvement; (4) interpersonal and communication skills; (5) professionalism; and (6) systems-based practice. These competencies are now being integrated into the training programs of all accredited surgical residencies.

Being a professional demands unwavering personal integrity and a commitment to lifelong learning and improvement. It

Financial disclosure information is located at the end of this chapter before the references.

Table 1 American College of Surgeons' Code of Professional Conduct²⁷

During the continuum of pre-, intra-, and postoperative care, we accept responsibilities to

- Serve as effective advocates for our patients' needs;
- Disclose therapeutic options, including their risks and benefits;
- Disclose and resolve any conflict of interest that might influence the decisions of care;
- Be sensitive and respectful of patients, understanding their vulnerability during the perioperative period;
- Fully disclose adverse events and medical errors;
- Acknowledge patients' psychological, social, cultural, and spiritual needs;
- Encompass within our surgical care the special needs of terminally ill patients;
- Acknowledge and support the needs of patients' families; and
- Respect the knowledge, dignity, and perspective of other healthcare professionals.

Our profession is also accountable to our communities and to society. In return for their trust, as Fellows of the American College of Surgeons, we accept responsibilities to

- Provide the highest quality of surgical care;
- Abide by the values of honesty, confidentiality, and altruism;
- Participate in lifelong learning;
- Maintain competence throughout our surgical careers;
- Participate in self-regulation by setting, maintaining, and enforcing practice standards;
- Improve care by evaluating its processes and outcomes;
- Inform the public on subjects within our expertise;
- Advocate strategies to improve individual and public health by communicating with government, healthcare organizations, and industry;
- Work with society to establish a just, effective, and efficient distribution of healthcare resources;
- Provide necessary surgical care without regard to gender, race, disability, religion, social status, or ability to pay; and
- Participate in educational programs addressing professionalism.

places the responsibility to serve (care for) others above self-interest and reward [see *Sidebar* Elizabeth Blackwell: A Model of Professionalism⁸].

Regrettably, examples of unprofessional behavior exist. An excerpt from a note from a third-year medical student to the core clerkship director reads as follows: "I have seen attendings make sexist, racist jokes or remarks during surgery. I have met residents who joke about deaf patients and female patients with facial hair. [I have encountered] teams joking and counting down the days until patients die" (personal communication, 2004). This kind of exposure to unprofessional conduct and language can influence young people negatively, and it must change.

Most of us went to medical school because we wanted to help and care for people who are ill. This genuine desire to care is unambiguously apparent in the vast majority of personal statements that medical students prepare as part of their application process. To quote William Osler, "You are in this profession as a calling, not as a business; as a calling which extracts from you at every turn self-sacrifice, devotion, love and tenderness to your fellow man. We must work in the missionary spirit with a breath of charity that raises you far above the petty jealousies of life."⁹ To keep medicine a calling, we must explicitly incorporate into the meaning of professionalism those nontechnical practices, habits, and attributes that the compassionate, caring, and competent physician exemplifies. We must remind ourselves that a true professional places service to the patient above self-interest and above reward.

One of the core tenets of professionalism is being consistently respectful not only toward our patients and their families but also toward our colleagues and other health care team members. Although no one would argue with this in principle, there are many factors that challenge our ability to hold true to this precept, including poor interpersonal communication skills, lack of training in conflict resolution, resource constraints, and cultural tradition.

Given that professionalism is so multifaceted, it is not surprising that various important professional values may

conflict with one another, creating tension sometimes internally and at other times between various groups. For example, the patient may want a specific treatment that is not yet supported by evidence but may be of benefit. Meeting the patient's expectations and needs may directly conflict with the expectation that we are advocates for "efficient distribution of health care resources." Another direct challenge to several professionalism obligations is trying to balance the important adherence to the duty hours mandate with the equally important value of continuity of care.¹⁰

The underpinning of medicine as a compassionate, caring profession is the doctor-patient relationship, a relationship that has become jeopardized and sometimes fractured over the past decade. Our individual perceptions of what this relationship is and how it should work will inevitably have a great impact on how we approach the care of our patients.²

The view of the physician-patient relationship as a covenant does not demand devotion to medicine to the exclusion of other responsibilities and is not inconsistent with the fact that medicine is also a science, an art, and a business.² Nevertheless, in our struggle to remain viable in a health care environment that has become a commercial enterprise, efforts to preserve market share cannot take precedence over the provision of care that is grounded in charity and compassion. It is exactly for this reason that medicine always will be, and should be, a relationship between people. To fracture that relationship by exchanging a covenant based on charity and compassion for a contract based solely on the delivery of goods and services is something none of us would want for ourselves. The nature of the healing relationship is itself the foundation of the special obligations of physicians as physicians.²

Translation of Theory into Practice

It is encouraging to note that many instances of unprofessional conduct that once were routinely overlooked—such

Elizabeth Blackwell: A Model of Professionalism⁸

Elizabeth Blackwell was born in England in 1821, the daughter of a sugar refiner. When she was 10 years old, her family emigrated to New York City. Discovering in herself a strong desire to practice medicine and care for the underserved, she took up residence in a physician's household, using her time there to study using books in the family's medical library.

As a young woman, Blackwell applied to several prominent medical schools but was snubbed by all of them. After 29 rejections, she sent her second round of applications to smaller colleges, including Geneva College in New York. She was accepted at Geneva—according to an anecdote, because the faculty put the matter to a student vote, and the students thought her application a hoax. She braved the prejudice of some of the professors and students to complete her training, eventually ranking first in her class. On January 23, 1849, at the age of 27, Elizabeth Blackwell became the first woman to earn a medical degree in the United States. Her goal was to become a surgeon.

After several months in Pennsylvania, during which time she became a naturalized citizen of the United States, Blackwell traveled to Paris, where she hoped to study with one of the leading French surgeons. Denied access to Parisian hospitals because of her gender, she enrolled instead at La Maternité, a highly regarded midwifery school, in the summer of 1849. While attending to a child some 4 months after enrolling, Blackwell inadvertently spattered some pus from the child's eyes into her own left eye. The child was infected with gonorrhea, and Blackwell contracted a severe case of ophthalmia neonatorum, which later necessitated the removal of the infected eye. Although the loss of an eye made it impossible for her to become a surgeon, it did not dampen her passion for becoming a practicing physician.

By mid-1851, when Blackwell returned to the United States, she was well prepared for private practice. However, no male doctor would even consider the idea of a female associate, no matter how well trained. Barred from practice in most hospitals, Blackwell founded her own infirmary, the New York Infirmary for Indigent Women and Children, in 1857. When the American Civil War began, Blackwell trained nurses, and in 1868 she founded a women's medical college at the Infirmary so that women could be formally trained as physicians. In 1869, she returned to England and, with Florence Nightingale, opened the Women's Medical College. Blackwell taught at the newly created London School of Medicine for Women and became the first female physician in the United Kingdom Medical Register. She set up a private practice in her own home, where she saw women and children, many of whom were of lesser means and were unable to pay. In addition, Blackwell mentored other women who subsequently pursued careers in medicine. She retired at the age of 86.

In short, Elizabeth Blackwell embodied professionalism in her work. In 1889 she wrote, "There is no career nobler than that of the physician. The progress and welfare of society is more intimately bound up with the prevailing tone and influence of the medical profession than with the status of any other class."

as mistreating medical students, speaking disrespectfully to coworkers, and fraudulent behavior—are now being dealt with. Still, from time to time, an incident is made public that makes us all feel shame. In March 2003, the *Seattle Times* carried a story about the chief of neurosurgery at the University of Washington, who pleaded guilty to a felony charge of obstructing the government's investigation and admitted that he asked others to lie for him and created an atmosphere of fear in the neurosurgery department.¹¹ According to the US Attorney in Seattle, University of Washington employees destroyed reports revealing that university doctors submitted inflated billings to Medicare and Medicaid. The department chair lost his job, was barred from participation in Medicare, and, as part of his plea bargain, had to pay a \$500,000 fine, perform 1,000 hours of community service,

and write an article in a medical journal about billing errors. The university spent many millions in legal fees and eventually settled the billing issues with the federal government for one of the highest Physicians at Teaching Hospitals (PATH) settlements ever.

Fortunately, such extreme cases of unprofessionalism are quite uncommon. Nevertheless, there are numerous reports in the literature of other types of unprofessional behavior, such as disruptive behavior,⁷ that can lead to patient safety risks.^{12–14} To this end, The Joint Commission has mandated that all of our hospitals have zero tolerance for disruptive behavior. Regardless of the practice setting, it remains our responsibility as professionals to prevent such behaviors from developing and from being reinforced. A study published in 2004 demonstrated an association between displays of unprofessional behavior in medical school and subsequent disciplinary action by a state medical board.¹⁵ The authors concluded that professionalism is an essential competency that students must demonstrate to graduate from medical school. Who could disagree? Yet we know that throughout our careers, there will be challenges, both personal and external, to our consistently behaving professionally.

In addition to the reports recounting acts of unprofessional behavior, various publications describing methods of teaching and assessing professionalism have begun to appear in the past few years.^{16,17} As an example, Kumar and colleagues found that using ACS case-based multimedia materials enhanced the ability of residents to recognize and discuss matters related to professional behavior.¹⁸ Surgical residents who viewed these materials scored higher on an assessment tool than did residents with the same level of experience who did not use the materials. An additional encouraging finding was that residents of all years were able to define the components of professionalism. In another publication, Gauger and colleagues described an evaluation instrument used to evaluate residents with respect to the aspects of professionalism.¹⁹ They divided the concept of professionalism into 15 domains and modified a standard resident evaluation form to assess the faculty's perception of resident performance in each domain. This evaluation tool proved to be internally consistent, but in the absence of any other gold standard tools with which to compare it, its validity could not be determined.

Hickson developed a system to monitor patient complaint data and use this to improve the behavior of individual physicians.²⁰ Others have developed 360° assessment tools to give feedback to physicians regarding how their professionalism skills are perceived by their team members.²¹

Assessment tools and formal courses alone are not enough to support the significant adaptive challenge²² that is involved in maintaining a culture of professionalism.¹⁰ Several authors have argued for a nuanced approach to supporting professional behaviors—one that acknowledges that professionalism is not a fixed trait but rather a set of developmental skills that need to be continuously taught, role-modeled, and reflected on throughout one's career.²³ Understanding that professional behavior is contextual and situation dependent is crucial to developing programs to support professionalism.

The Future of Surgical Professionalism

It is often subtly implied—or even candidly stated—that no matter how well we adjust to the changing health care

environment, the practice of surgery will never again be quite as rewarding as it once was. This need not be the case. The ongoing advances in surgical technology, the increasing opportunities for community-based surgeons to enrol their patients into clinical trials, the growing emphasis on lifelong learning, and the increased focus on teamwork and shared responsibility are factors that not only help satisfy social and organizational demands for quality care but also are in the best interest of our patients.

In the near future, maintenance of certification for surgeons will involve much more than taking an examination every decade. The ACS is taking the lead in helping to develop new measures of competence. Whatever specific form such measures may take, displaying professionalism and living up to a set of uncompromisable core values²⁴ will always be central indicators of the performance of the individual surgeon and the integrity of the discipline of surgery as a whole.

Although surgeons vary enormously with respect to personality, practice preferences, areas of specialization, and style of relating to others, they all have one role in common: that of healer. Indeed, it is the highest of privileges to be able to care for the sick. As the playwright Howard Sackler once wrote, "To intervene, even briefly, between our fellow creatures and their suffering or death, is our most authentic answer to the question of our humanity."²⁵ Inseparable from this privilege is a set of responsibilities that are not to be taken lightly: a pledge to offer our patients the best care possible and a commitment to teach and advance the science and practice of medicine. Commitment to the practice of patient-centered, high-quality, cost-effective care is what gives our work meaning and provides us with a sense of purpose.²⁶ As surgeons, we must participate actively in the current evolution of integrated health care. By doing so, we help build our own future.

Jo Shapiro, MD, FACS, or their significant other, has disclosed a potential conflict of interest as follows: grants and/or salary by Health Dialog

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2 PERFORMANCE MEASUREMENT IN SURGERY

Justin B. Dimick MD, MPH, and John D. Birkmeyer MD

With growing recognition that the quality of surgical care varies widely, good measures of performance are in high demand. Patients and their families are looking to make informed decisions about where and from whom to get their surgical care.¹ Employers and payers need measures on which to base their contracting decisions and pay-for-performance initiatives.² Finally, clinical leaders need measures that can help them identify “best practices” and guide their quality improvement efforts. An ever-broadening array of performance measures is being developed to meet these different needs.

However, considerable uncertainty remains about which measures are most useful for measuring surgical quality. Current measures are remarkably heterogeneous, encompassing different elements of health care structure, process of care, and patient outcomes. Although each of these three types of performance measures has unique strengths, each is also associated with conceptual, methodological, and/or practical problems. The baseline risk and frequency of the procedure are obviously important considerations in weighing the strengths and weaknesses of different measures.³ So too is the underlying purpose of performance measurement. Measures that work well when the primary intent is to steer patients to the best hospitals or surgeons (selective referral) may not be optimal for quality improvement purposes and vice versa.

Expanding on other recent reviews of performance measurement,^{3–5} this chapter provides an overview of measures commonly used to assess surgical quality, considers their main strengths and limitations, and closes with recommendations for selecting the optimal quality measure [see Table 1].

Overview of Current Measures

The number of performance measures that have been developed for the assessment of surgical quality is already large and continues to grow. Many surgical quality indicators are already used in hospital accreditation, pay-for-performance, or public reporting efforts. Over the past few years, the National Quality Forum (NQF) has emerged as the leading organization endorsing quality measures. Many influential organizations, including the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and the Centers for Medicare and Medicaid Services (CMS), rely on the endorsement of the NQF before applying a measure to practice. The number of measures relevant to surgery that have been endorsed by the NQF has grown rapidly.

Although the NQF is the central organization for evaluating quality measures, many organizations develop candidate measures and submit them for endorsement. The Agency for Healthcare Research and Quality (AHRQ) has focused primarily on quality measures that take advantage of readily available administrative data, such as the hospital discharge data sets comprising the Healthcare Cost and Utilization Project (HCUP) [see Table 2]. Because little information on process of care is available in these data sets, these measures are mainly structural (e.g., hospital procedure volume) or outcome based (e.g., risk-adjusted mortality).

The Leapfrog Group (<http://www.leapfroggroup.org>), a coalition of large employers and purchasers, has developed perhaps the most visible set of surgical quality indicators for its value-based purchasing initiative. The organization's original standards focused exclusively on procedure volume but later expanded its standards to include selected process variables (e.g., the use of beta blockers in patients undergoing abdominal aortic aneurysm repair) and outcome measures, such as mortality. Most recently (2010), the Leapfrog Group began using a composite of operative mortality and hospital volume, the so-called “Survival Predictor,” as the primary measure for its evidence-based hospital referral initiative. Such composite measures are discussed further below.

Several surgical professional organizations have played a large part in developing many of the quality measures endorsed by the NQF. The Society of Thoracic Surgeons (STS) has been a leader in the development of quality measures for cardiac and thoracic procedures [see Table 3 and Table 4]. These measures include the structure, process, and outcomes of cardiac surgical care. In addition, the STS recently developed a composite measure that combines all of these domains of quality into a single hospital rating. The National Surgical Quality Improvement Program (NSQIP) has also developed measures for colectomy, lower extremity bypass, and elderly surgical patients [see Table 3 and Table 4]. Finally, the Society for Vascular Surgery (SVS) has acted as the steward for measures of process of care for carotid endarterectomy [see Table 4].

Structural Measures of Quality

Health care structure reflects the setting or system in which care is delivered. Many structural measures describe hospital-level attributes, such as the physical plant and resources or staff coordination and organization (e.g., nurse-to-bed ratios, designation as a Level I trauma center). Other structural measures reflect attributes associated with the relative expertise of individual physicians (e.g., board certification, subspecialty training, or procedure volume).

STRENGTHS

From a measurement perspective, structural measures of quality have several attractive features. First, many of these

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Table 1 Primary Strengths and Limitations of Structure, Process, and Outcome Measures

	<i>Structure</i>	<i>Process</i>	<i>Outcomes</i>
Examples	Procedure volume, intensivist-managed ICUs	Appropriate use of prophylactic antibiotics	Risk-adjusted mortality rates for CABG from state or national registries
Strengths	Expedient, inexpensive Efficient—one measure may relate to several outcomes For some procedures, better predictor of subsequent performance than other measures	Reflect care that patients actually receive—buy-in from providers Directly actionable for quality improvement activities Do not need risk adjustment for many measures	Face validity Measurement alone may improve outcomes (i.e., Hawthorne effect)
Limitations	Limited number of measures Generally not actionable Do not reflect individual performance, considered unfair by providers	Many measures hard to ascertain with existing databases Variable extent to which process measures link to important patient outcomes Lack of high leverage, procedure-specific processes	Sample size constraints Expense of clinical data collection Concerns about risk adjustment with administrative data

CABG = coronary artery bypass grafting; ICU = intensive care unit.

Table 2 Surgical Performance Measures that Apply to Multiple Surgical Procedures Endorsed by the National Quality Forum

<i>Diagnosis or Procedure</i>	<i>Performance Measure</i>	<i>Steward</i>
All surgical procedures	Appropriate antibiotic prophylaxis (selection, timing, and duration)	AMA
	Hair clipping prior to surgery	CMS
	Appropriate venous thromboembolism prophylaxis	AMA/CMS
	Perioperative temperature management	CMS
	Preoperative beta blockers continued after surgery	CMS
	Urinary catheter removed postoperative day 2	CMS
	Risk-adjusted surgical mortality or major complications in elderly patients	ACS/NSQIP
	Accidental puncture or laceration	AHRQ
	Iatrogenic pneumothorax	AHRQ
	Wound dehiscence	AHRQ
	Postoperative respiratory failure	AHRQ
	Failure to rescue	AHRQ
	Postoperative venous thromboembolism	AHRQ
	Foreign body left after procedure	AHRQ
	Superficial surgical site infection	CDC
Cardiac and thoracic surgery	Participation in a systematic quality improvement database	STS
Pediatric surgery	Risk-adjusted mortality in neonates undergoing noncardiac surgery	CHOP

ACS = American College of Surgeons; AHRQ = Agency for Healthcare Research and Quality; AMA = American Medical Association; CDC = Centers for Disease Control and Prevention; CHOP = Children's Hospital of Pennsylvania; CMS = Centers for Medicare and Medicaid Services; JCAHO = Joint Commission on Accreditation of Healthcare Organizations; NSQIP = National Surgical Quality Improvement Program; STS = Society of Thoracic Surgeons.

measures are strongly related to patient outcomes. For example, with esophagectomy and pancreatic resection, operative mortality rates at very high-volume hospitals are as much as 10% lower, in absolute terms, than at lower-volume centers.^{6,7} In some instances, structural measures such as procedure volume are more predictive of subsequent hospital performance than any known processes of care or direct mortality measures⁸ [see Figure 1].

A second advantage is efficiency. A single structural measure may be associated with numerous outcomes. For example, with some types of cancer surgery, hospital or

surgeon procedure volume is associated not only with lower operative mortality but also with lower perioperative morbidity and higher late survival rates.^{9–11} Intensivist model intensive care units are linked to shorter length of stay and reduced resource use, as well as lower mortality.^{12,13}

The third and perhaps most important advantage of structural variables is expediency. Many can be assessed easily with readily available administrative data. Although some structural measures require surveying hospitals or providers, such data are much less expensive to collect than measures requiring patient-level information.

Table 3 Surgical Performance Measures Endorsed by the National Quality Forum that Apply to Specific Cardiac and Vascular Procedures

<i>Diagnosis or Procedure</i>	<i>Performance Measure</i>	<i>Steward</i>
Coronary artery bypass grafting	Hospital volume	STS
	Risk-adjusted mortality rate	STS
	Postoperative renal failure	STS
	Internal mammary artery use	STS
	Preoperative beta blockade	STS
	Postoperative glucose controlled by 6 am the day after surgery	JCAHO
	STS composite measure	STS
	Reoperation for tamponade, bleeding, or other cardiac reason	STS
	Antiplatelet therapy at discharge	STS
	Beta-blocker therapy at discharge	STS
	Antilipid therapy at discharge	STS
	Deep sternal wound infection rate	STS
	Prolonged intubation	STS
	Stroke	STS
Aortic valve replacement	Risk-adjusted mortality rate	STS
	Hospital volume	STS
Mitral valve replacement/repair	Risk-adjusted mortality rate	STS
	Hospital volume	STS
Pediatric heart surgery	Hospital volume	AHRQ
	Risk-adjusted mortality rates	AHRQ
Abdominal aneurysm repair	Hospital volume	AHRQ
	Risk-adjusted mortality rates	AHRQ
Lower extremity bypass	Risk-adjusted mortality or major complications	CMS
Carotid endarterectomy	Perioperative antiplatelet therapy	SVS
	Patch closure of arteriotomy	SVS

AHRQ = Agency for Healthcare Research and Quality; CMS = Center for Medicare and Medicaid Services; JCAHO = Joint Commission on Accreditation of Healthcare Organizations; STS = Society of Thoracic Surgeons.

DISADVANTAGES OF STRUCTURAL VARIABLES

Among the downsides, there are relatively few structural measures that may be potentially useful as quality indicators. Second, in contrast to process measures, most structural measures are not readily actionable. For example, a small hospital can increase the number of surgical patients receiving antibiotic prophylaxis but cannot readily make itself a high-volume center. Thus, although selected structural measures may be useful for selective referral initiatives, they have limited value for quality improvement purposes.

Finally, structural measures generally describe groups of hospitals or providers with better performance but do not adequately discriminate performance among individuals. For example, in aggregate, high-volume hospitals have much lower mortality rates than lower-volume centers for pancreatic resection. However, some individual high-volume hospitals may have high mortality rates. Although difficult to confirm empirically (for sample size reasons), some low-volume centers may have excellent performance.¹⁴ For this reason, structural measures are viewed as “unfair” by many providers.

Process of Care Measures

Processes of care are the clinical interventions and services provided to patients. Process measures have long been the predominant quality indicators for both inpatient and outpatient medical care, and their popularity as quality measures for surgical care is growing rapidly. Perhaps the best example of the trend toward using process measures is the CMS Surgical Care Improvement Program (SCIP). The SCIP mandates all hospitals to collect and publicly report process measures related to prevention of surgical site infections (SSIs), postoperative cardiac events, venous thromboembolism (VTE), and respiratory complications.

STRENGTHS

Given that processes of care reflect the care that physicians deliver, they have face validity and enjoy greater buy-in from providers. They are usually directly actionable and thus good substrate for quality improvement activities.

Although risk adjustment may be important for outcomes, it is not required for many process measures. For example, when measuring appropriate prophylaxis

Table 4 Surgical Performance Measures Endorsed by the National Quality Forum that Apply to Specific General Surgical Procedures

<i>Diagnosis or Procedure</i>	<i>Performance Measure</i>	<i>Steward</i>
Esophageal resection	Hospital volume	AHRQ
	Risk-adjusted mortality	STS/AHRQ
	Preoperative assessment of performance status	STS
Pancreatic resection	Hospital volume	AHRQ
	Risk-adjusted mortality rates	AHRQ
Colon resection	Risk-adjusted mortality or major complications	ACS/NSQIP
	For cancer, adjuvant chemotherapy within 4 months for lymph node-positive disease	ACS
	For cancer, at least 12 lymph nodes are harvested	ACS
	For cancer, complete pathology reporting	ACS
Melanoma	Coordination of care	AMA
Breast cancer	Post-breast conservation radiation	ACS
	Appropriate axillary staging	Intermountain Healthcare
	Adjuvant hormonal therapy in receptor-positive patients	ACS
	Adjuvant chemotherapy in appropriate patients	ACS
	Needle biopsy to establish diagnosis of cancer precedes surgical excision/resection	ACS
Appendicitis	Proportion with perforation	AHRQ
	Incidental appendectomy in the elderly	AHRQ

ACS = American College of Surgeons; AHRQ = Agency for Healthcare Research and Quality; AMA = American Medical Association; NSQIP = National Surgical Quality Improvement Program; STS = Society of Thoracic Surgeons.

against postoperative VTE, one of the SCIP measures, it is not necessary to account for patient differences in risk. Given that virtually all patients undergoing open abdominal surgery should be offered some form of prophylaxis, there is little need to collect detailed clinical data about illness severity for the purpose of risk adjustment.

Finally, process measures are generally less constrained by sample size problems than direct outcome measures. Whereas important outcomes (e.g., perioperative death) are relatively rare, most targeted process measures are relevant to a larger proportion of patients. Moreover, because they generally target aspects of general perioperative care, process measures can often be assessed on patients undergoing numerous different procedures, increasing sample sizes and measurement precision.

LIMITATIONS

At the current time, a major limitation of process measures is the lack of a reliable data infrastructure for ascertaining them. Administrative data sets lack the requisite clinical detail and specificity for this purpose. Measurement systems based on clinical data, including that of the NSQIP,¹⁵ focus on patient characteristics and outcomes and do not collect information on process of care. Presently, pay-for-performance programs rely on self-reported information from hospitals, but the reliability of such data is uncertain (particularly when reimbursement is at stake).

Even if this limitation were overcome, a second limitation remains to be considered—namely, that process variables are limited in their ability to explain observed variations in

mortality. A growing body of empirical data supports this statement. Most of the data come from the literature on medical diagnoses (e.g., acute myocardial infarction), where the link between process and outcome is much stronger than it is in surgery.¹⁶⁻¹⁸ For example, the JCAHO/CMS process measures for acute myocardial infarction explained only 6% of the observed variation in risk-adjusted mortality for this condition.¹⁷

There is reason to believe that existing process measures explain very little of the variation in important outcomes in surgery. First, most process measures currently used in surgery relate to secondary rather than primary outcomes. For example, although the value of antibiotic prophylaxis in reducing the risk of superficial SSI should not be underestimated, this process is not among the most important adverse events of major surgery (including death). Second, process measures in surgery often relate to complications that are very rare. For example, there is a consensus that prophylaxis for VTE is necessary and important. Accordingly, the SCIP measures, endorsed by the NQF, include the use of appropriate prophylaxis. However, pulmonary embolism is very uncommon; therefore, improving adherence to these measures will not avert many deaths.

Several recent empirical studies on the relation between SCIP processes and patient outcomes support this assertion. For example, Nicholas and colleagues examined the relation between hospital SCIP process compliance and risk-adjusted rates of mortality, thromboembolism, and surgical infection.¹⁹ Despite wide variation in process compliance, there was no association between adherence to SCIP measures

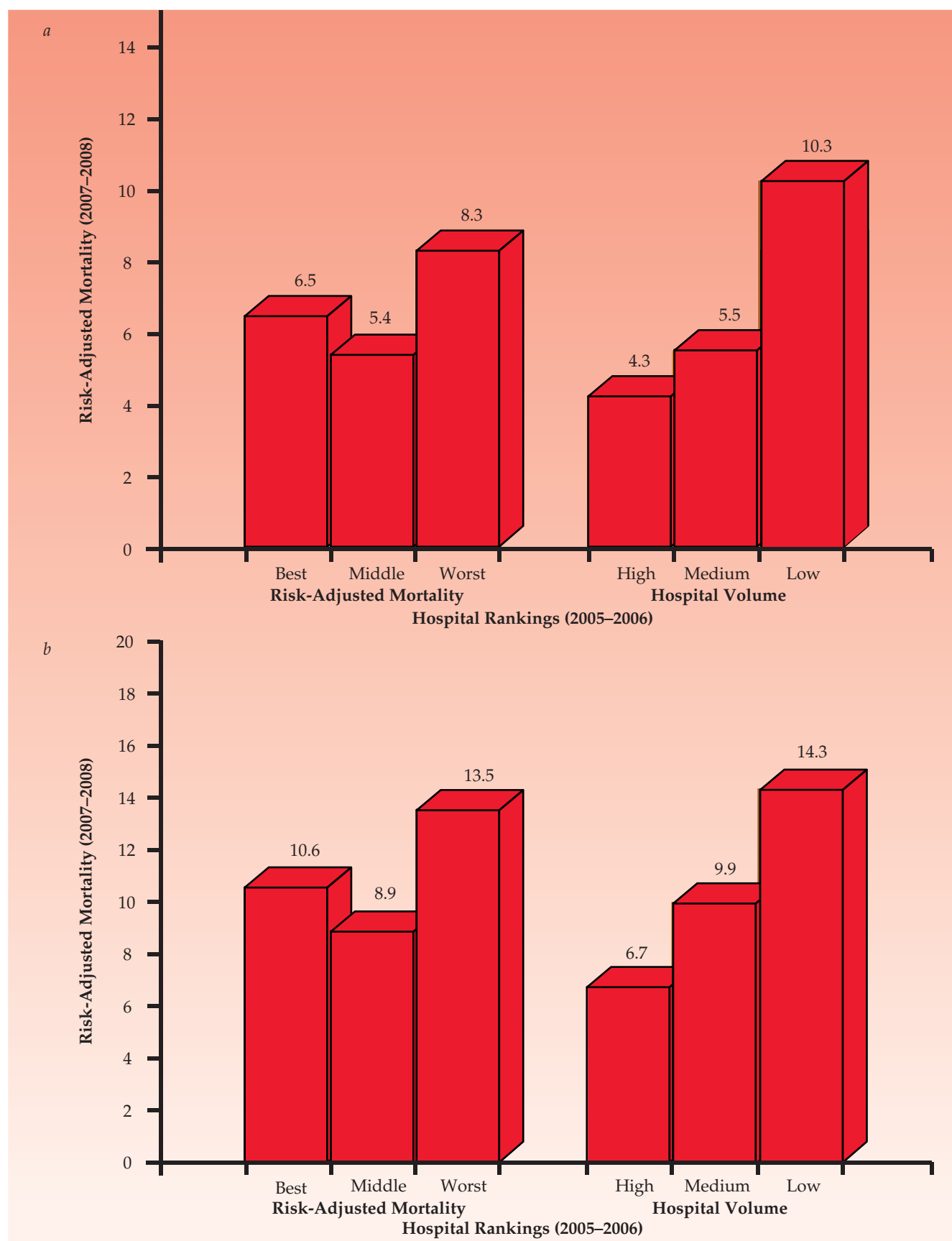


Figure 1 Relative ability of historical (2005–2006) measures of hospital volume and risk-adjusted mortality to predict subsequent (2007–2008) risk-adjusted mortality in US Medicare patients. (a) Pancreatic resection. (b) Esophageal resection.

and any of these risk-adjusted outcomes. Until a better understanding is achieved regarding which details account for variations in the most important complications, especially those adverse events leading to death, process measures will continue to be of limited usefulness in surgical quality improvement.

Direct Outcome Measures

Direct outcome measures reflect the end result of care, from a clinical perspective or as judged by the patient. Although mortality is by far the most commonly used measure in surgery, other outcomes that could be used as quality indicators include complications, hospital readmission, and a variety of patient-centered measures of satisfaction or health status.

There are several ongoing, large-scale initiatives involving direct outcomes assessment in surgery. Proprietary health care rating firms (e.g., Healthgrades) and state agencies are assessing risk-adjusted mortality rates using Medicare or state-level administrative data sets. However, most of the current interest in outcomes measurement involves large clinical registries. Cardiac surgery registries in New York, Pennsylvania, and a growing number of other states are perhaps the visible examples. At the national level, the STS and the American College of Cardiology (ACC) have implemented systems for tracking morbidity and mortality with cardiac surgery and percutaneous coronary interventions, respectively. Although most outcomes measurement efforts have been procedure specific (and largely limited to cardiac procedures), the NSQIP of the American College of Surgeons (ACS) assesses hospital-specific morbidity and mortality rates aggregated across surgical specialties and procedures.¹⁶

STRENGTHS

Direct outcome measures have at least two major advantages. First, direct outcome measures have obvious face validity and thus are likely to get the greatest “buy-in” from hospitals and surgeons. Second, outcomes measurement alone may improve performance—the so-called Hawthorne effect. For example, surgical morbidity and mortality rates in Veterans Affairs’ hospitals have fallen dramatically since implementation of NSQIP in 1991.¹⁵ No doubt many surgical leaders at individual hospitals made specific organizational or process improvements after they began receiving feedback on their hospitals’ performance. However, it is very unlikely that even a full inventory of these specific changes would explain such broad-based and substantial improvements in morbidity and mortality rates.

DISADVANTAGES OF DIRECT OUTCOME MEASURES

Hospital- or surgeon-specific outcome measures are severely constrained by small sample sizes. For the large majority of surgical procedures, very few hospitals (or surgeons) have sufficient adverse events (numerators) and cases (denominators) for meaningful, procedure-specific measures of morbidity or mortality. For example, Dimick and colleagues used data from the Nationwide Inpatient Sample to study seven procedures for which mortality rates have been advocated as quality indicators by the AHRQ.²⁰ For six of these procedures, a very small proportion of US

hospitals had adequate caseloads to rule out a mortality rate twice the national average. Although identifying poor quality outliers is an important function of outcomes measurement, focusing on this goal alone significantly underestimates problems with small sample sizes. Discriminating among individual hospitals with intermediate levels of performance is even more difficult.

Other limitations of direct outcomes assessment depend on whether outcomes are being assessed from administrative data or clinical information abstracted from medical records. For outcomes measurement based on clinical data, the major problem is expense. For example, it costs over \$100,000 annually for a private sector hospital to participate in the NSQIP.

With administrative data, the adequacy of risk adjustment remains a major concern. High-quality risk adjustment may be essential for outcome measures to have face validity with providers. It may also be useful for discouraging gaming, for example, hospitals or providers avoiding high-risk patients to optimize their performance measures. However, it is not clear how much the scientific validity of outcome measures is threatened by imperfect risk adjustment with administrative data. Although administrative data lack clinical detail on many variables related to baseline risk,^{21–24} it is not clear to what extent case mix varies systematically across hospitals or surgeons. Among patients undergoing the same surgical procedure, there is often surprisingly little variation. For example, we examined risk-adjusted mortality rates for hospitals performing coronary artery bypass grafting in New York State, as derived from their clinical registries.²⁵ Unadjusted and adjusted hospital mortality rates were nearly identical in most years (correlations exceeding 0.90). Moreover, hospital rankings based on unadjusted and adjusted mortality were equally useful in predicting subsequent hospital performance.

Matching the Measure to the Purpose

Performance measures will never be perfect. Over time, analytical methods will be refined. Access to higher-quality data may improve with the addition of clinical elements to administrative data sets or broader adoption of electronic medical records. However, some problems with performance measurement, including sample size limitations, are inherent and not fully correctable. Thus, clinical leaders, patient advocates, payers, and policy makers will not escape having to make decisions about when imperfect measures are good enough to act upon.

A measure should be implemented only with the expectation that acting will result in a net improvement in health quality. Thus, the direct benefits of implementing a particular measure cannot be outweighed by the indirect harms. Unfortunately, these benefits and harm are often difficult to measure and heavily influenced by the specific context and who—patients, payers, or providers—is doing the accounting. For this reason, there is no simple answer for where to “set the bar.”

It is important to ensure a good match between the performance measure and the primary goal of measurement. The right measure depends on whether the underlying goal is (1) quality improvement or (2) selective referral—directing patients to higher-quality hospitals and/or providers.

Although many pay-for-performance initiatives have both goals, one often predominates. For example, the ultimate objective of CMS's pay-for-performance initiative with prophylactic antibiotics is improving quality at all hospitals—not directing patients to those centers with high compliance rates. Conversely, although it may indirectly incentivize quality improvement, the Leapfrog Group's efforts in surgery are primarily aimed at getting patients to hospitals likely to have the best outcomes (selective referral).

For quality improvement purposes, a good performance measure—most often a process of care variable—must be actionable. Measurable improvements in the given process should translate to clinically meaningful improvements in patient outcomes. Although quality improvement activities are rarely “harmful,” their major downsides relate to their opportunity cost. Initiatives hinged on bad measures siphon away resources (e.g., time and focus of physicians and other staff) from more productive activities.

With selective referral, a good measure will steer patients to better hospitals or physicians (or away from worse ones). As one basic litmus test, a measure based on prior performance should reliably identify providers likely to have superior performance now and in the future. At the same time, an ideal measure would not incentivize perverse behaviors (e.g., surgeons doing unnecessary procedures to meet a specific volume standard) or negatively affect other domains of quality (e.g., patient autonomy, access, and satisfaction).

Measures that work well for quality improvement may not be particularly useful for selective referral, and vice versa. For example, appropriate use of perioperative antibiotics in surgical patients is a good measure for quality improvement. This process of care is clinically meaningful, linked to lower risks of SSIs, and directly actionable. Conversely, antibiotic use would not be particularly useful for selective referral purposes. It is unlikely that patients would use this information to decide where to have surgery. More importantly, surgeons with high rates of appropriate antibiotic use may not necessarily do better with more important outcomes (e.g., mortality). Physician performance with one quality indicator is often poorly correlated with other indicators for the same or other clinical conditions.²⁶

As a counter example, the two main quality indicators for pancreatic cancer—hospital volume and operative mortality—are very informative in the context of selective referral. Patients would markedly improve their odds of surviving surgery by selecting hospitals highly ranked by either measure [see Figure 1]. However, neither measure would be particularly useful for quality improvement purposes. Volume is not readily actionable; mortality rates are too unstable at the level of individual hospitals (because of small sample size problems) to identify top performers, identify best practices, or evaluate the effects of improvement activities.

Many believe that a good performance measure must discriminate performance at the individual level. From the provider perspective in particular, a “fair” measure must reliably reflect the performance of individual hospitals or physicians. Unfortunately, as described earlier, small case-loads (and sometimes case-mix variation) conspire against this objective for most procedures. Patients, however, should value information that improves their odds of good

outcomes on average. Many measures meet this latter interest while failing on the former.

For example, Krumholz and colleagues used clinical data from the Cooperative Cardiovascular Project to assess the usefulness of Healthgrades' hospital ratings for acute myocardial infarction (based primarily on risk-adjusted mortality rates from Medicare data).²⁷ Relative to one-star (worst) hospitals, five-star (best) hospitals had significantly lower mortality (16% versus 22%, $p < .001$) after risk adjustment with clinical data. They also discharged significantly more (appropriate) patients on aspirin, beta blockers, and angiotensin-converting enzyme (ACE) inhibitors, all recognized quality indicators. However, the Healthgrades' ratings poorly discriminated among any two individual hospitals. In only 3% of head-to-head comparisons did five-star hospitals have statistically lower mortality rates than one-star hospitals.

Thus, some performance measures that clearly identify groups of hospitals or providers with superior performance may be limited in their ability to discriminate individual hospitals from one another. There may be no simple solution to resolving the basic tension implied by performance measures that are unfair to providers yet informative for patients. However, it underscores the importance of being clear about both the primary purpose (quality improvement or selective referral) and whose interests are receiving top priority (provider or patient).

Future of Performance Measurement

Although great progress has been made, the science of surgical quality measurement is still in its infancy. Several barriers must be overcome before performance measures can be optimally used to improve patient care. Perhaps the biggest barrier is the lack of an accurate and affordable measurement infrastructure. One practical solution that may reduce the expense of detailed data collection with clinical registries is to create hybrid systems that join data elements from administrative and clinical data sets. Although administrative data are criticized for their lack of accuracy in identifying coexisting diseases, they can reliably identify the type of procedure performed, certain demographic variables (e.g., age, gender, and race), and some outcome variables (e.g., vital status, discharge to a skilled nursing facility, and length of stay). This set of variables could then be linked to a limited set of clinical risk factors that would allow robust risk adjustment. This solution will be even more attractive as administrative data come to contain more accurate information (e.g., present-on-admission codes to distinguish complications from coexisting problems).²⁸

In addition to improving the efficiency of data collection, it would be worthwhile to rethink how existing registries are designed so as to make them less expensive and more useful. For example, although the ACS-NSQIP is in a key position to become the leading measurement platform for surgical quality improvement, several changes could be made to ensure its success.²⁹ First, the burden of data collection could be reduced; this would substantially decrease the costs of participating. The number of data elements could be reduced by creating more parsimonious risk adjustment models.³⁰ Second, the sampling strategy could be changed to sample 100% of the most important operations; this change

would allow assessment of procedure-specific outcomes. Ultimately, participating hospitals would need procedure-specific outcome data to target specific operations for improvement. Third, clinical processes of care could be added to the data collection process; this would allow hospitals to respond to national pay-for-performance mandates and to provide more actionable quality measures. This last change would require the ACS-NSQIP to manifest a level of flexibility that it has not exhibited to date. With the flexibility to change data measurement periodically, the ACS-NSQIP would not only be able to add other measures that are used in national mandates (e.g., SCIP) but also to evaluate their importance.

One of the biggest limitations of surgical quality measurement is the statistical noise from the small sample sizes at most hospitals. An emerging technique, reliability adjustment, directly addresses the problem of statistical noise. This technique, based on hierarchical modeling, quantifies and subtracts statistical noise from the measurement process.³¹ Essentially, it “shrinks” a provider’s performance back toward average, unless they deviate to such an extreme that it is safe to assume that they are truly different. In this way, it gives providers the benefit of the doubt. For example, Figure 2 shows the risk-adjusted mortality and morbidity rates for colon resection in 20 ACS-NSQIP hospitals before and after reliability adjustment. Prior to reliability adjustment, rates of mortality and morbidity vary greatly across these hospitals. After reliability adjustment, however, the “noise” has been removed and rates of morbidity and mortality vary much less, yielding a range of performance that is clinically more realistic. These reliability-adjusted mortality rates are much more accurate at capturing true performance, as assessed by their ability to predict future performance.

Despite increasing use in other fields, such as ambulatory care, reliability adjustment is only beginning to find applications in surgery. Perhaps the most prominent example is the Massachusetts cardiac surgery report card, which publishes reliability-adjusted mortality rates for each hospital. This approach will also likely be applied to general and vascular

surgery, as described with other changes in a recent “blueprint” for a new NSQIP, discussed above. As the advantages of this technique become more widely known, there is no doubt that it will become the standard technique for reporting risk-adjusted outcomes.

Another barrier to improving surgical performance is the lack of good global measures of performance. With the proliferation of pay-for-performance pilot programs, various stakeholders have been confronted with the problem of how to make sense of multiple competing measures of quality. Most have responded by combining multiple domains to create a composite measure of performance. The Premier/CMS Hospital Quality Incentive Demonstration uses a composite of process and outcome as a quality measure for coronary artery bypass surgery. The STS’s Task Force on Quality Measurement advocates a composite score based on a set of outcome and process measures endorsed by the NQF.³² In these composite approaches, the different measures are essentially weighted equally, with no empirical determination of which ones are the most important. There are, however, emerging techniques that use empirically derived weighting to create a composite score that optimally predicts future mortality for high-risk surgery.³³ As such methods become more fully developed, composite measures will no doubt continue to gain popularity.

Given that most existing quality improvement efforts focus on optimizing measurement of technical quality, it is important not to lose sight of the fact that many quality concerns arise upstream from the operation itself—that is, with the decision to operate in the first place. Wide variations in the use of surgery have long been recognized. Some of these variations are attributable to differences in disease prevalence and physician practice style. Some, however, arise from overuse, underuse, or misuse of surgical management. For a full accounting of surgical quality, it will be necessary to develop reliable means of measuring the appropriateness of surgical treatment and the extent to which patient preferences are incorporated into clinical decisions, in addition to measures assessing how well patients do after surgery.

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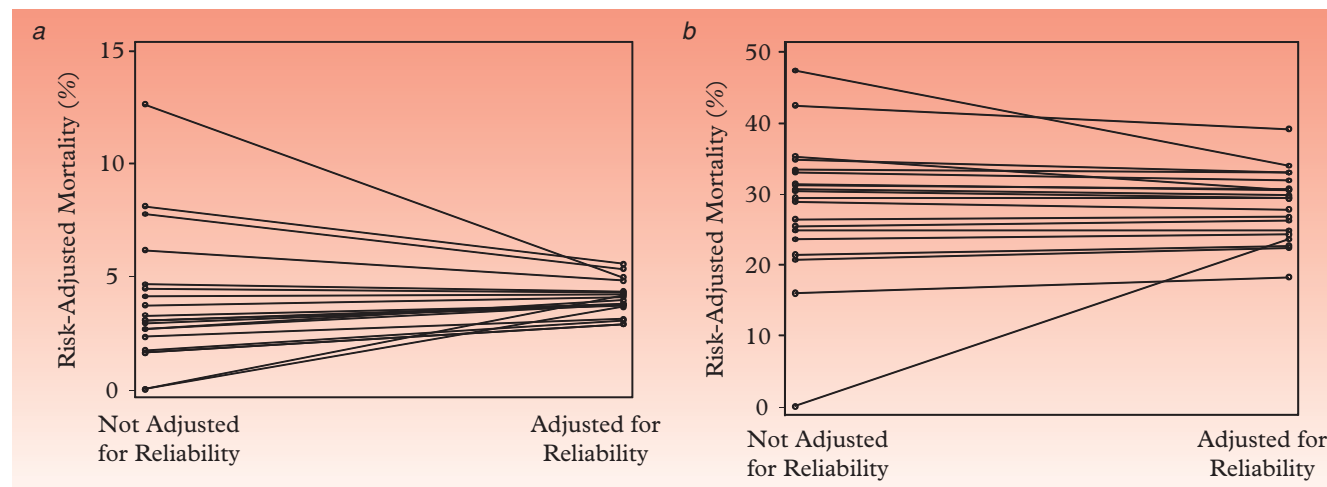


Figure 2 Risk-adjusted (a) mortality and (b) morbidity rates for colon resection at individual hospitals before and after adjustment for reliability. Data are from the 2007 American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP).

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3 STRATEGIES FOR IMPROVING SURGICAL QUALITY

Nancy J.O. Birkmeyer, PhD

Surgical morbidity and mortality are major public health concerns. At least 1 million surgical patients die, and many times more experience a serious complication each year worldwide.¹ The outcomes of surgery have been shown to differ among providers²⁻⁷ and according to provider attributes such as procedure volume⁸⁻¹⁰ and subspecialty training.¹¹⁻¹³ This variability in the outcomes of surgical procedures has long suggested opportunities to improve the quality of surgical care. For this reason, many large-scale quality improvement efforts target patients undergoing surgery.

Payers, health care policy makers, and surgeons' professional organizations have implemented a range of strategies to improve surgical quality. With selective referral, payers use various methods to try to steer patients to providers that they have deemed to be of higher quality. Pay-for-performance programs, such as the Surgical Care Improvement Project (SCIP), provide incentives for providers' compliance with specific evidence-based processes of perioperative care. Many professional organizations, including the American College of Surgeons National Surgical Quality Improvement Program (NSQIP), have instituted outcomes measurement and feedback programs to stimulate quality improvement at the local level. Regional collaborative quality improvement programs go beyond outcomes measurement and feedback to broad-scale implementation of quality improvement interventions.

These strategies, which we refer to as selective referral, process compliance, outcomes measurement and feedback, and regional collaborative quality improvement, are the current, dominant approaches to surgical quality improvement in the United States. This chapter reviews these strategies and some of the major ongoing initiatives in each [see Table 1]. In addition, the evidence to date for the effectiveness of each of these strategies in improving surgical quality is summarized.

Selective Referral

Selective referral includes strategies that aim to identify and steer patients toward providers with the best results for certain procedures. Payers' selective referral programs may involve the use of tiered health plans and benefits packages that give patients' financial incentives (e.g., lower copayments or monthly premiums) for selecting providers that they have deemed to be of higher quality. Some payers restrict their enrollees' choice of providers to selected Centers of Excellence (COE) for certain high-risk procedures, whereas others simply provide information about approved

COE to their enrollees without restricting choice. Examples of selective referral programs include the Leapfrog Group's Evidence-Based Hospital Referral program, Blue Cross and Blue Shield Association Blue Distinction Centers for Specialty Care, and bariatric surgery COE programs of the American College of Surgeons and the American Society for Metabolic and Bariatric Surgery.

The extent to which selective referral programs result in improvements in surgical quality has been assessed in a number of recent studies. One group of studies has examined whether COE programs successfully identify hospitals with better outcomes. For example, one study investigated whether Medicare patients undergoing major cancer resections (1994 to 1999) at National Cancer Institute (NCI) cancer centers have lower mortality rates than patients at control hospitals matched for procedure volume.¹⁴ NCI cancer centers had significantly lower adjusted surgical mortality rates than control hospitals for four of the six procedures assessed, including colectomy, pulmonary resection, gastrectomy, and esophagectomy. Trends toward lower adjusted operative mortality rates at NCI cancer centers were also observed for cystectomy and pancreatic resection. However, there were no important differences in subsequent 5-year mortality rates between NCI cancer centers and control hospitals for any of the procedures. A subsequent study including Survival, Epidemiology, and End Results (SEER)-Medicare patients from 1999 to 2003 did find improved survival rates for patients undergoing surgery for colorectal cancer at NCI cancer centers compared with other hospitals, reflecting perhaps the difference in time periods between the two studies and/or the ability to control for tumor stage with the data source used in the later study.¹⁵ In bariatric surgery, two studies found that bariatric COE hospitals do not have lower rates of surgical complications than other hospitals.^{16,17}

Two recent studies considered whether selective referral programs have altered referral patterns for high-risk surgery and whether these trends have resulted in improvements in operative mortality with those procedures. One study found that increased market concentration was strongly associated with declining mortality with some high-risk cancer operations [see Figure 1], including pancreatectomy, esophagectomy, and cystectomy.¹⁸ A smaller proportion of mortality improvements could be attributed to market concentration for lung resection, abdominal aortic aneurysm repair, and aortic valve replacement, but trends in market concentration had no role in declining mortality with coronary artery bypass grafting (CABG) and carotid endarterectomy. A study based on data from Washington State found that the proportion of patients undergoing surgery in hospitals meeting the Leapfrog Groups' volume standard had significantly increased for pancreatectomy and esophagectomy, but not aortic aneurysm repair, since

Financial disclosure information is located at the end of this chapter before the references.

Table 1 Characteristics of Different Strategies for Improving Surgical Quality

	<i>Selective Referral</i>	<i>Process Compliance</i>	<i>Outcomes Measurement and Feedback</i>	<i>Regional Collaborative Quality Improvement</i>
Mechanism	Steer patients to best hospitals or surgeons	Increase compliance with evidence-based processes of care	Spur internal quality improvement with feedback on benchmarked outcomes	Identify and broadly implement best practices
Examples	Leapfrog Group's Evidence-Based Hospital Referral Program Payers' Center of Excellence (COE) programs	Surgical Care Improvement Project (SKIP) Surgical Checklist projects	National Surgical Quality Improvement Program (NSQIP) Society of Thoracic Surgeons (STS) National Cardiac Surgery Database	Northern New England Cardiovascular Disease Study Group Blue Cross and Blue Shield of Michigan/Blue Care Network Value Partnership program
Evidence: pro	Effective for relatively rare procedures with strong evidence linking provider characteristics (e.g., procedure volume) and outcomes	Programs that involve active participation of surgeons and other clinicians (e.g., checklists) may be effective regardless of actual content of intervention	Effective for motivating internal quality improvement efforts among low-performing providers	Improved outcomes in the areas where it has been tried: cardiovascular procedures, other general and vascular surgery, and bariatric surgery
Evidence: con	COE programs based on self-reported, unreliable data not effective in identifying higher-quality providers	Disappointing results for other process compliance interventions	Do not provide guidance for how to improve either to low-performing providers or others	Strategy has not been widely adopted perhaps because expense and complexity and lack of a natural sponsor

implementation of the Leapfrog Groups' Evidence-Based Hospital Referral Program.¹⁹ Although mortality rates tended to be lower for hospitals meeting the volume thresholds, statewide mortality rates did not improve over the time period.¹⁹

Selective referral is arguably the most controversial of the quality improvement strategies discussed in this chapter. Although selective referral strategies are effective in improving outcomes in a number of procedures, they are less useful for many others. This strategy is also highly divisive, with many arguing that providers should be judged by their own clinical outcomes rather than having their outcomes judged by imperfect proxy measures, such as volume.²⁰ Selective

referral is probably best reserved for high-risk procedures where a strong relation between provider structural characteristics (such as procedure volume or subspecialty training) and outcomes has been demonstrated. Selective referral programs should not rely on self-reported and/or unverifiable information to determine which providers have the highest quality.^{16,17,21}

Process Compliance

Another strategy for improving surgical quality is for hospitals to increase their use of evidence-based processes of care. Public and private payers' ongoing pay-for-performance programs, which provide financial incentives for high rates of compliance, best exemplify this strategy. The largest pay-for-performance program targeting surgery is the SCIP, which links Medicare hospital reimbursement to satisfactory adherence to processes for reducing rates of surgical site infection, postoperative cardiac events, venous thromboembolism, and ventilator-associated pneumonia.

SURGICAL CARE IMPROVEMENT PROJECT (SCIP)

The relation between SCIP measure compliance and outcomes has been assessed in a number of studies [see Table 2]. Nicholas and colleagues used national Medicare data to examine whether rates of compliance with the SCIP measures were associated with rates of surgical site infection, venous thromboembolism, or surgical mortality for patients undergoing high-risk cancer or cardiovascular procedures.²² Although process compliance ranged from 53.7% for hospitals in the bottom tercile to 91.4% for hospitals in the top tercile, there was no relation between rates of process compliance and rates of surgical site infection, venous thromboembolism, or surgical mortality overall or for any of

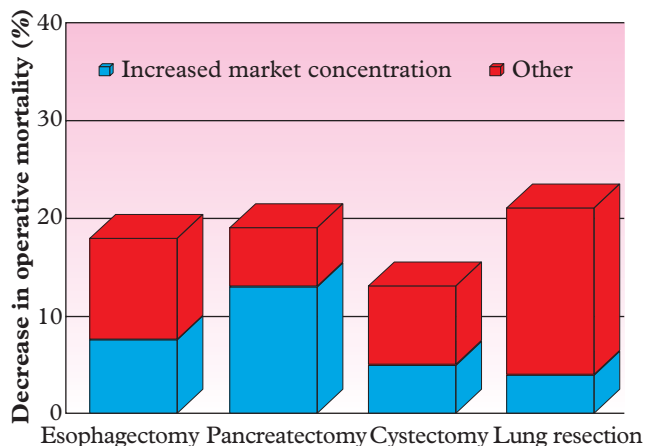


Figure 1 Percent of mortality decline for esophagectomy, pancreatectomy, cystectomy, and lung resection attributable to increases in market concentration, based on 2001 to 2008 national Medicare data.¹⁸

Table 2 Evidence Regarding the Relation between Compliance with Surgical Care Improvement Project (SCIP) Measures and Clinical Outcomes

Study, Year	Data Sources (Year)	Patient Population (n)	SCIP Measure*	Infection	VTE	Mortality
Nicholas et al, 2010 ²²	2000 US hospitals/ Medicare/Hospital Compare (2005–2006)	6 high-risk procedures (325,052)	SCIP INF/VTE- Composite	No	No	No
Ingraham et al, 2010 ²³	200 ACS-NSQIP hospitals/ Hospital Compare (2008)	General and vascular surgery (81,524)	SCIP INF-1 SCIP INF-2 SCIP INF-3 SCIP INF-6	No Yes No No		No No No No
Stulberg et al, 2010 ²⁵	398 Premier Inc. hospitals/ Hospital Compare (2006–2008)	Inpatient surgery (405,720)	SCIP INF-1 SCIP INF-2 SCIP INF-3 SCIP INF-4 SCIP INF-6 SCIP INF-7 SCIP INF-Composite	No No No No No No Yes		
Lehtinen, 2010 ⁴¹	1 ACS-NSQIP hospital (2006–2009)	Gastrointestinal surgery (469)	SCIP INF-10	No		
Pastor, 2010 ⁴²	1 US hospital (2006–2008)	Colorectal surgery (491)	SCIP INF-Composite	No		
Hawn et al, 2008 ²⁶	95 Veterans Affairs hospitals (2005–2006)	Elective orthopedic, colon, and vascular surgery (9,195)	SCIP INF-1	No		
Forbes et al, 2008 ²⁷	1 Canadian hospital (2004–2007)	Major hepatobiliary or colorectal surgery (208)	SCIP INF-Composite	Yes—NS		
Berenguer, 2010 ²⁹	1 ACS-NSQIP hospital (2006–2008)	Colorectal surgery (197)	SCIP INF-Composite			
Hedrick et al, 2007 ²⁸	1 hospital (2000–2005)	Colorectal surgery (307)	SCIP INF-Composite	Yes		

ACS-NSQIP = American College of Surgeons-National Surgical Quality Improvement Program; NS = not statistically significant; VTE = venous thromboembolism.

*SCIP measures: SCIP INF-1: prophylactic antibiotic received within 1 hour prior to surgical incision; SCIP INF-2: prophylactic antibiotic selection for surgical patients; SCIP INF-3: prophylactic antibiotics discontinued within 24 hours after surgery end; SCIP INF-4: cardiac surgery patients with controlled 6 am postoperative blood glucose; SCIP INF-6: surgery patients with appropriate hair removal; SCIP INF-7: colorectal surgery patients with immediate postoperative normothermia; SCIP INF-10: surgery patients with perioperative temperature management; SCIP VTE-1: surgery patients with recommended venous thromboembolism prophylaxis ordered; SCIP VTE-2: surgery patients who received appropriate venous thromboembolism prophylaxis within 24 hours prior to surgery to 24 hours after surgery.

the six procedures individually. Numerous studies have examined the relation between the subset of SCIP measures related to the prevention of surgical site infection (SCIP INF) and clinical outcomes. Of these, one found that just one of the measures (SCIP 2: appropriate antibiotic given) was associated with rates of surgical site infection.²³ Another study found that only SCIP 1 (antibiotic given within 1 hour of surgery) was associated with rates of surgical site infection among colorectal surgery patients.²⁴ Another study found that none of the individual SCIP INF measures were associated with rates of surgical site infection but that a global composite measure was.²⁵ The other studies found no relation between SCIP INF measures and clinical outcomes.²⁶

Taken as a whole, these studies provide scant evidence for the effectiveness of process compliance in improving outcomes in surgery. Given that the SCIP measures were chosen on the basis of randomized trials supporting their effectiveness, these findings are somewhat counterintuitive. One explanation may be that in the randomized trials, these interventions were assessed under tightly controlled conditions (e.g., patient populations, hospital environments) that

simply are not representative of their use in general practice. This is sometimes referred to as the difference between the effectiveness and the efficacy of an intervention. Another plausible explanation is that high rates of compliance or improvements in rates of compliance are really indicative of better documentation rather than actual compliance or clinical care processes. The three single-site studies^{27–29} showing the effectiveness of these process changes in the prevention of surgical site infections for colorectal surgery patients at their sites following changes in clinical care would support this explanation.

Checklists

Although not yet a target of pay-for-performance or other incentive programs, surgical checklists can be considered another process compliance strategy. Checklists, which have long been used in aviation, came to be used in health care following the publication of a study documenting their effectiveness for the prevention of catheter-related bloodstream infections in intensive care units.³⁰ Surgical checklists range from simple preoperative “timeouts” to prevent rare

but dreadful errors, such as operating on the wrong site or patient, to broad lists of practices known to reduce complications and/or improve teamwork.

Checklists have been the subject of two recent process compliance studies in surgery. A study supported by the World Health Organization (WHO) tested the effects of a 19-item intraoperative checklist among nearly 4,000 patients undergoing noncardiac surgery at eight large hospitals around the world using a pre/post study design.³¹ The second study evaluated the effects of a comprehensive checklist (11-part instrument with more than 100 items, encompassing all phases of care) in six regional and tertiary care centers and five control hospitals in the Netherlands.³² Despite differences in the extensiveness of checklists and in the scientific rigor of the study designs, both studies found that the use of a surgical checklist resulted in dramatic reductions in surgical morbidity and mortality. In the WHO study, mortality was reduced by almost 50% and complications dropped from 11% to 7%. In the de Vries and colleagues study, mortality was also cut in half and rates of complications were reduced from 15% to 11%.³²

In each of the two surgical checklist studies, all types of complications were reduced rather than just those that would be expected based on the content of the checklists. This suggests that checklists may have indirect effects that may be as, if not more important, than their specific content. For example, checklists could reduce the rates of surgical complications by improving hospitals' safety culture, lead to more effective communication and/or handoffs between different types of providers, or reduce distractions in the operating room. The durability of improvements in outcomes attained with checklists is yet to be determined as neither of the two studies had a very long duration of postintervention study time (3 to 6 months). It is also to be determined what specific items are essential for an effective surgical checklist. Nonetheless, checklists should be considered among the more promising interventions for improving rates of morbidity and mortality with surgery.

Outcomes Measurement and Feedback

Many of the professional organizations in surgery have focused their quality improvement efforts on the development and dissemination of clinical registries for tracking surgical outcomes. The goal of these efforts is to provide benchmarking data with which hospitals and surgeons can compare their outcomes with those of their peers. The rationale for benchmarking performance is to allow hospitals to identify opportunities for quality improvement and therefore to be motivated to engage in internal quality improvement activities. The Society of Thoracic Surgeons (STS) is considered a pioneer in this area, and virtually all US hospitals involved in cardiac surgery now participate in its registry. The NSQIP is the largest outcomes measurement platform in noncardiac surgery. The NSQIP was developed for use in Veterans Affairs (VA) hospitals, but since being adapted for use in the private sector by the American College of Surgeons, several hundred private sector hospitals now participate. Finally, a number of states have been measuring and publicly reporting risk-adjusted outcomes

for certain high-risk procedures, most frequently coronary bypass surgery.

There is strong evidence that outcomes measurement and feedback are an effective strategy for reducing rates of surgical morbidity and mortality. For example, surgical complication rates decreased by more than 40% in VA hospitals following the implementation of the NSQIP.³³ Surgical complication rates also dropped among private sector hospitals after the implementation of NSQIP, although much less dramatically than in the VA hospitals.³⁴ Mortality among Medicare patients undergoing coronary bypass surgery in the state of New York declined by 41% between 1989 and 1992 with the implementation of the New York State Department of Health Cardiac Reporting Systems.³⁵ During this same time period, mortality among Medicare patients undergoing coronary bypass nationally declined by only 13%.³⁶ Another study assessed rates of mortality with coronary artery bypass with (Ohio, New Jersey, New York, and Pennsylvania) and without public outcomes reporting systems between 1994 and 1999.³⁷ Coronary bypass mortality rates in states with public reporting systems decreased between 20 and 33% more than those in states without these systems.

Outcomes measurement and feedback can be an effective way to improve surgical care. However, certain conditions are necessary for the success of this approach, including mandatory reporting of all hospitals, audits of data quality, a neutral third party to analyze and report data, and some kind of pressure (e.g., public reporting) for poor performers to improve.³⁸ It also probably works best for procedures where the primary outcomes occur within the perioperative period and can be measured and verified at a relatively low cost. Finally, the way that this approach works is by stimulating improvements among low-performing providers. However, it does not provide those institutions in need of improvement with information they will need to accomplish that goal. Outcomes measurement and feedback programs also do not provide the motivation or the information required to improve care overall.

Regional Collaborative Quality Improvement

Regional collaborative quality improvement goes beyond the measurement and feedback of outcomes data with region-wide implementation of explicit quality improvement interventions. Similar to outcomes measurement and feedback programs, regional collaborative quality improvement programs are based on clinical registry data, which are used to provide regular feedback on performance. Where regional collaborative quality improvement programs differ from straight outcomes measurement and feedback programs is that they convene regularly to review and interpret registry data with a specific focus on areas of variation in practice or outcomes. Once the processes that are associated with the best outcomes (best practices) are identified, they are broadly implemented throughout the region. The Northern New England Cardiovascular Disease Study Group, which started in 1987, is the original regional collaborative quality improvement collaborative. In Michigan, Blue Cross and Blue Shield of Michigan/Blue Care Network (BCBSM/BCN) has funded similar programs in many clinical areas,

including surgery (cardiac, bariatric, and other types of general and vascular surgery).

For many years, the only evidence for the effectiveness of regional collaborative quality improvement has been from the Northern New England Cardiovascular Disease Study Group. During the first 5 years of the collaborative (1987 to 1992), the group received regular feedback on outcomes and training in continuous quality improvement techniques, and teams from each of the hospitals engaged in round robin site visits to observe perioperative care for CABG patients at other sites.³⁹ The CABG mortality rate decreased by 24% over the study time period. A subsequent study based on Medicare data showed that northern New England and New York State had a combination of the lowest CABG mortality rates in 1992 and the greatest improvement in mortality rates over this time period in the country.³⁶

With the funding of numerous regional collaborative quality improvement programs in the state of Michigan, there are now many more data on which to gauge the effects of this approach.⁴⁰ For example, risk-adjusted morbidity rates among patients undergoing general or vascular surgery in hospitals participating in ACS-NSQIP in Michigan fell from 13.1% in 2005 to 10.5% in 2009 ($p < .001$). In contrast, morbidity rates in non-Michigan hospitals participating in ACS-NSQIP remained essentially flat between 2005 and 2008 at approximately 12.5%, before dipping slightly to 11.5% in 2009. Risk-adjusted 30-day mortality with bariatric surgery in Michigan fell from 0.21% in 2007 to 0.02% in 2009 ($p = .004$) [see Figure 2]. During this time period, bariatric surgery mortality at non-Michigan hospitals participating in ACS-NSQIP did not improve significantly (0.18% to 0.11%). In cardiac surgery, during its initial reporting periods (2006 to 2007 and 2007 to 2008), composite quality scores for Michigan hospitals as a whole were statistically indistinguishable from national benchmarks. Michigan hospitals have now achieved a three-star rating from the STS (on an 11-item composite quality measure, which includes risk-adjusted mortality, complications, internal mammary graft use, and several other important processes of care, as

defined by the Adult Cardiac Surgery Registry of the STS), indicating that its aggregate performance exceeded national norms and falls within the top 10th of hospitals nationwide.

Despite growing evidence of the effectiveness of regional, collaborative quality improvement, this approach has not been widely adopted because it is expensive, is complicated to coordinate, and lacks a natural sponsor. The programs in Michigan exist because the state's largest private insurer has not only funded the costs of running them but has also offered additional financial incentives for hospitals to participate. Convincing others, including other private payers, public payers, purchasers, and provider systems, to invest in regional, collaborative quality improvement will require a convincing demonstration of return on investment. Although there are substantial obstacles to more widespread adoption, this is the only approach that works by reducing variation in practice and improving quality overall. In contrast, the other strategies aim to improve performance among poor performers or, in the case of selective referral, to steer patients away from them.

Summary

Each of the approaches to surgical quality improvement addressed in this chapter has advantages and disadvantages. Selective referral strategies are probably best reserved for relatively rare procedures for which outcomes have been shown to vary dramatically according to provider factors such as procedure volume. COE programs that rely on self-reported and unaudited information have not been effective in identifying high-quality providers. As they are currently configured, process compliance programs have mainly focused on improving adherence to a small number of evidence-based practices in perioperative care. That many of the results for process compliance programs have been disappointing may reflect that what these programs have improved is the documentation of clinical care practices rather than the actual clinical care processes. Process compliance efforts involving surgical checklists and the active participation of surgeons and other members of operative teams are having more promising results. Outcomes measurement and feedback programs, especially where they are publicly reported, can motivate local quality improvement efforts among hospitals with poor performance. Finally, regional collaborative quality improvement programs may accelerate improvement by having the ability to rapidly identify and broadly implement best practices. However, this strategy has not been widely adopted, perhaps because of the expense and complexity of these programs as well as their lack of a natural sponsor.

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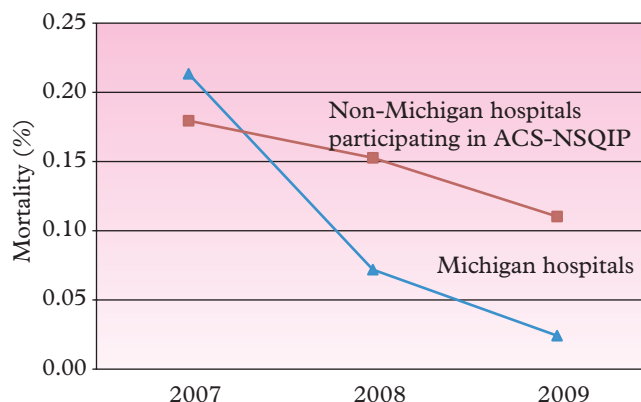


Figure 2 Mortality after (30-day) bariatric surgery: Michigan hospitals versus non-Michigan hospitals participating in the American College of Surgeons-National Surgical Quality Improvement Program (ACS-NSQIP), based on data from the 2007 to 2009 Michigan Bariatric Surgery Collaborative and national ACS-NSQIP registries.⁴⁰

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4 EVIDENCE-BASED SURGERY

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Evidence-based surgery describes the consistent and judicious use of the best available scientific evidence in making decisions about the care of surgical patients. Evidence-based surgery is part of a broader movement—evidence-based medicine—to apply the scientific method to medical practice. This movement has its historical roots in the pioneering work of the Scottish epidemiologist Archibald Cochrane (1909–1988), for whom the preeminent international organization for research in evidence-based medicine, the Cochrane Collaboration, is named. The term “evidence-based medicine” itself was popularized through a landmark article advocating a new approach to medical education that appeared in the *Journal of the American Medical Association* in 1992.¹ This article urged the de-emphasis of “intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making.” In essence, advocates of evidence-based medicine seek to demote “expert opinion” to the least valid basis for clinical decision making. The practice of surgery, once driven more by the eminence of tradition than the evidence of science, now increasingly requires its students to adopt evidence-based scientific standards of practice.

The imperative that surgical care be delivered in accordance with the best available scientific evidence is only one facet of evidence-based surgery. In addition, evidence-based surgery refers to systematic efforts to establish standards of care supported by science, as well as the movement to popularize evidence-based practice. Systematic reviews of the literature are often generated by independent researchers or collaborative study groups (e.g., Cochrane collaborations) and published as review articles in journals or disseminated as practice guidelines. The movement to propagate evidence-based surgical practice is a relatively recent phenomenon exemplified by the collaborative efforts to develop the Surgical Care Improvement Project Core Measure Set² and by the US federal government’s efforts to reward best practices with “pay for performance” policies.³ Although researchers are charged with generating and disseminating scientific evidence, the greatest responsibility for the success of evidence-based surgery is ultimately with individual surgeons, who must not only practice evidence-based surgery but also understand and appropriately interpret an immense surgical literature.

This chapter provides a framework for evaluating the strength of evidence for surgical practices, the validity of scientific studies in surgery, and the role of evidence-based surgery in assessing and improving the quality of surgical care. The intent is to provide the reader with conceptual and

analytic tools that a modern, evidence-based surgeon needs to navigate the surgical literature and implement practices that are based on sound science.

Guidelines and Secondary Sources of Scientific Evidence

To meet the growing demand for evidence-based practice information, a market has developed around the work of pooling and interpreting “best scientific evidence.” Scientific reviews serve as secondary sources for evidence-based practice and are increasingly found in journals, in books, and on the Internet. Prominent examples include *Clinical Evidence* (published semiannually by the *British Journal of Medicine* and continually updated online⁴), the *Cochrane Database of Systematic Reviews*,⁵ and the Institute for Healthcare Improvement.⁶ For surgical practices specifically, the Surgical Care Improvement Project serves as a clearinghouse for evidence-based guidelines.

Efforts to summarize and disseminate information about evidence-based surgery provide a convenient “user interface” for the surgical literature that can be very helpful to practicing surgeons. However, because such aids are far from complete and new evidence emerges continually, surgeons cannot rely on these sources entirely. The modern “evidence-based surgeon” must learn to assess the quality of individual scientific studies and interpret their implications for his or her practice.

Levels of Evidence

Evidence for surgical practice comes in many forms with variable reliability. At one end of the spectrum is an empirical impression that a practice makes physiologic sense and seems to work well. Much of what surgeons do in practice falls into this category and has not been formally tested. At the other end of the spectrum is evidence accumulated from multiple carefully conducted scientific experiments with consistent and reproducible results. The task of the evidence-based surgeon is to judge the reliability of scientific evidence and select practices that conform to the best evidence available.

To help clinicians judge the strength of scientific evidence, researchers have attempted to create hierarchies of evidence, which range from those sources that are most reliable to those that are least sure. With the understanding that not all practices have been subjected to the highest levels of scientific scrutiny, clinicians are advised to base practices on evidence gleaned from studies as high on the evidence hierarchy as possible.

A commonly cited example of such a hierarchy is the “levels of evidence” system popularized by the U.S. Preventive Medicine Task Force (USPMTF) [see Table 1].⁷ Since its inception, the hierarchy of scientific evidence created by the USPMTF has become common parlance among clinicians. Hence, frequently heard references to “level 1 evidence” refer to well-conducted randomized controlled trials. However, almost as soon as the USPMTF released its evidence grading system, debate about its adequacy began.⁸ The predominant criticism has been that the system is too simple and inflexible to accurately describe the strength of evidence for clinical practices. Although the system identifies the design of the study from which the evidence is drawn, it does not describe important factors that influence the quality of the study. For example, in the USPMTF system, the same grade is awarded to a randomized, double-blind, placebo-controlled trial with 50,000 subjects as to an unblinded randomized trial with 30 subjects. The latter trial would, in turn, be graded higher than a well-designed and conducted, multi-institution, prospective cohort study with 10,000 subjects.

In response to these deficiencies, numerous alternative grading systems have been developed that take into account factors other than study design, such as quality, consistency, and completeness. However, it is widely recognized that no single grading system is perfect,⁹ and surgeons are often required to judge the quality and applicability of scientific evidence for themselves.

Appraising Scientific Evidence

Specific study designs are associated with different levels of confidence about cause and effect. The clinical study design that is considered to have the greatest potential for determining causation is the randomized, controlled clinical trial.

Table 1 Levels of Evidence, as Stratified by the U.S. Preventive Services Task Force	
Level of Evidence	Source of Evidence
I	At least one properly randomized controlled trial
II – 1	Well-designed controlled trials without randomization
II – 2	Well-designed cohort or case-control analytic study, preferably from more than one center or research group
II – 3	Multiple time-series with or without intervention or possibly dramatic results from uncontrolled trials (e.g., penicillin treatment in the 1940s)
III	Opinions from respected authorities based on clinical experience, descriptive studies and case reports, or committees of experts
Category of Recommendation	Basis of Recommendation
Level A	Good and consistent scientific evidence
Level B	Limited or inconsistent scientific evidence
Level C	Consensus and/or expert opinion

This simple categorization scheme is generally considered inadequate but is still frequently referenced.

However, even studies with this design can lead to erroneous conclusions if they are not performed properly. Evaluating the quality of clinical evidence requires a close look at how the study that produced it was conceived, implemented, analyzed, and interpreted.

Scientific evidence from studies of clinical practice relies on two important inferences. The first inference is that the observed outcome is the result of the practice and cannot be attributed to some alternative explanation. When this inference is deemed true, the study is considered to have *internal validity*. The second inference is that what was observed in the clinical study is relevant to scenarios outside the study where the surgeon seeks to implement the practice. The extent to which this is true is called *external validity* or *generalizability*. Whereas internal validity relies on how well the study is conducted and the results analyzed, external validity relies on how well the study plan reflects the real-world clinical question that inspired it and how well the study’s conclusions apply to real-world scenarios outside the study [see Figure 1]. Poor external validity can also refer to the difference between an intervention’s efficacy (how well it works when applied perfectly) and its effectiveness (whether it has the same effect when applied generally in an uncontrolled environment).

Evaluating the Quality of a Study: Internal Validity

Assessment of the internal validity of a study requires an understanding of the potential influence of *chance*, *bias*, and *confounding* [see Table 2]. Chance refers to unpredictable randomness of events that might mislead researchers. Bias refers to systematic errors in how study subjects were selected or assessed. Confounding refers to differences in the comparison groups (other than the intended exposure) that lead to differences in outcomes.

CHANCE

In clinical studies that compare outcomes between two or more groups, the assumption that there is no difference in outcomes is called the *null hypothesis*. Erroneous conclusions with regard to the null hypothesis can sometimes occur by chance alone. There are two types of chance-related errors: type I and type II. Type I error (also called *error*) occurs when researchers erroneously reject the null hypothesis, that is, infer that there is a difference in outcomes when there is really no difference. Type II error (also called *error*) occurs when researchers erroneously confirm the null hypothesis, that is, infer that there is no difference in outcomes when, in reality, a difference exists.

Type I Errors

Statistical testing is used to quantify the likelihood of a type I error. A “*p* value” indicates the probability that observed differences between groups might be due to chance alone. The threshold for “statistical significance” is conventionally set at a *p* value of .05, signifying that the likelihood of the observed differences being due to chance alone is 5 out of 100. Although a likelihood of 5% falls short of absolute certainty, this level of confidence is generally accepted as scientific proof.

An alternative expression of statistical likelihood is confidence intervals. Confidence intervals show the range of

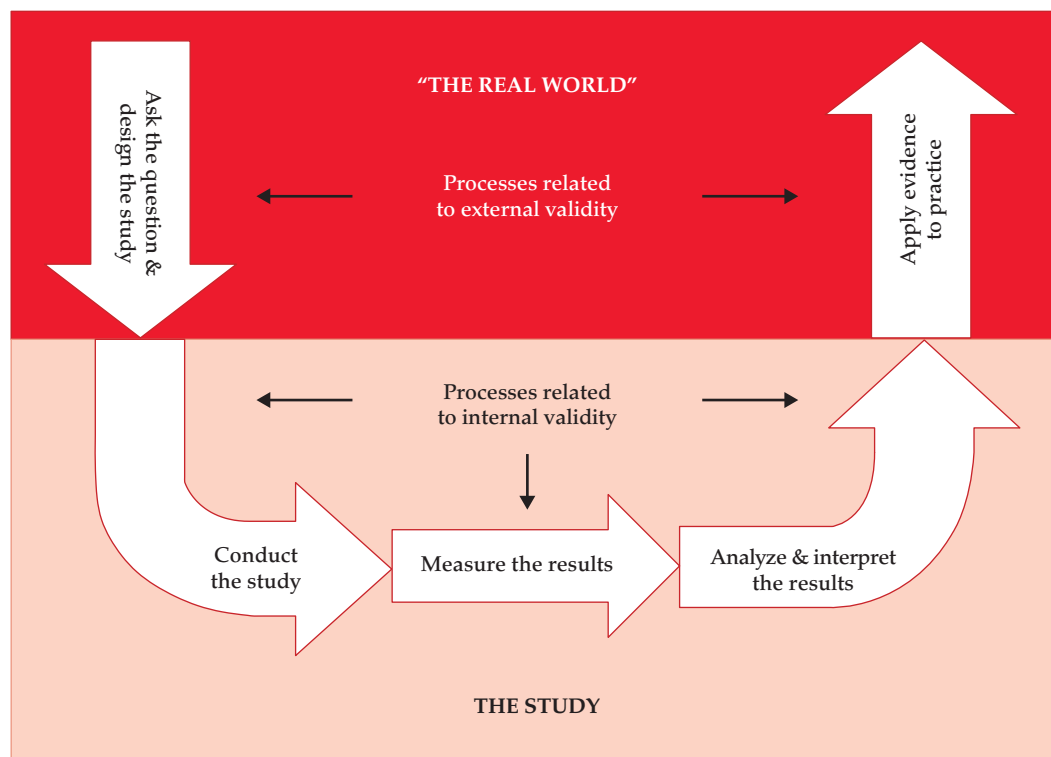


Figure 1 Processes that affect the internal and external validity of a clinical study.

Table 2 Methods Observed in Published Clinical Studies that Demonstrate Efforts to Minimize the Effects of Chance, Bias, and Confounding

Chance

Power calculations during design of the study
Appropriate statistical test to avoid type I error
Large enough sample size to avoid type II error

Bias

Prospective study designs
Careful subject selection
 Good sampling strategy
 Appropriate inclusion and exclusion criteria
Blinding
Clear and careful protocols for data collection

Confounding

Study design
 Randomization
 Restriction
 Matching
 Instrumental variables
Data analysis
 Risk adjustment
 Stratification
 Propensity scores

the observed difference that would be expected if the same study were repeated an infinite number of times. For example, a 95% confidence interval would include the observed difference 95% of the times that the study was repeated.

Many statistical tests can be used to calculate *p* values and confidence intervals. The appropriate statistical test must be selected according to several factors, including the number of observations in the comparison groups, the number of groups being compared, whether two or more groups are being compared with each other or one group is being compared with itself after some interval of time, what kind of numerical data are being analyzed (e.g. continuous, categorical), or whether risk adjustment is required. Although most surgeons are unlikely to fully comprehend all of the nuances of more complex statistical analyses, most clinical surgical studies are designed simply enough to employ statistical tests that are within reach of the nonstatistician. Fortunately, several useful and concise texts are available that can help surgeons become conversant in basic statistical methods.^{10–12}

Type II Errors

Type II errors (erroneously accepting the null hypothesis) often occur when sample size is simply insufficient to detect small but clinically important differences in outcomes. When a study's sample size is too small to detect differences in outcomes between comparison groups, it is said to lack sufficient statistical power. Once a study is complete, no amount of analysis can correct for insufficient statistical power. Before starting a study, researchers should perform a "power calculation," which involves determining the minimum size of a

meaningful difference in outcomes and then calculating the number of observations required to show that difference statistically. Surgeons should be particularly cautious when evaluating studies with null findings, particularly when no power calculation is explicitly reported. An evidence-based surgeon is wise to remember the adage, “No evidence for effect is not necessarily evidence of no effect.”

BIAS

Bias refers to a systematic problem with a clinical study that results in an inaccurate estimate of the differences in outcomes between comparison groups. There are two general types of bias: *selection bias* and *measurement bias*. The former results from errors in the choice of study subjects. The latter results from errors in the way information about exposures or outcomes (or other pertinent data) is obtained.

Selection bias refers to any imperfection in the selection process that results in either the wrong types of subjects (people who are not typical of the target population) or a sample of subjects that is for some reason (unrelated to the intervention) more likely to have the outcome of interest. For example, paid volunteer subjects may be more motivated to comply with treatment regimens and report favorable results, resulting in an overestimate of the effect of an intervention. This would affect both internal validity (inference about size of the effect) and external validity (generalizability to other populations). As another example, selecting subjects from among diners at a Szechuan Chinese restaurant for a trial of medical versus surgical treatment of gastroesophageal reflux might lead to results favoring medical treatment (people with reflux who consume Szechuan Chinese food are more likely to have symptoms that are already well-controlled medically). When assessing the validity of scientific evidence, surgeons must carefully consider the characteristics of the subjects selected for study.

Measurement bias refers to problems caused by the way information about outcomes or other pertinent data is obtained. For example, in a study of sexual function after surgery for rectal cancer, subjects may report symptoms differently in an in-person interview than they would in an anonymous mailed survey. As another example, using surgeons to assess hernia repair outcomes in their own patients might result in erroneous reported rates of chronic pain. Retrospective studies are particularly prone to a variety of types of measurement bias. For example “recall bias” may occur because of subjects’ selective memory of past events, and “ascertainment bias” may occur if the outcome is likely to influence how hard observers look for information about exposures. Sources of measurement bias may be more subtle than selection bias and require careful attention to reported study methods. Efforts to control measurement bias include blinding (not telling the subject or assessor what intervention was performed) and prospective study design.

Confounding

Confounding refers to differences in outcomes that occur because of differences in the baseline risks of the comparison groups. Confounding is often the result of selection bias. For example, a comparison of mortality after open versus laparoscopic colectomy might be skewed because of the greater likelihood of open colectomy being performed as an emergency in a critically ill patient. In this example, the severity of the

illness confounds the observed association between mortality and surgical approach.

In evaluating the strength of evidence in a published study, readers must assess how well the researchers accounted for the potential effect of confounding. Confounding can be minimized in several ways, both in the design of the study and in the analysis of the study’s results. In the design of a study, confounding is most effectively addressed with *randomization*. When subjects are randomized, potentially confounding variables (both recognized and unrecognized) are likely to be evenly distributed across comparison groups. Thus, whereas the baseline rate of outcomes in the entire cohort might be influenced by these factors, the differences across comparison groups are less likely to be affected.

Where randomization is not practical, *restriction* or *matching* can be used to prevent confounding. Restriction refers to the tight control of study entry criteria (e.g., enter only elective colectomy cases in the study described above). However, restrictive entry criteria can sometimes limit generalizability. Matching refers to using a comparison group of unexposed (control) subjects who are identical to the exposed (case) subjects across a set of characteristics (e.g., age, sex, residence) that have the potential to result in confounding.

A more complicated technique used to limit the effect of confounding is *instrumental variable analysis*. This approach involves studying the effect of a given exposure on outcomes by comparing groups with different levels of a third factor (the instrumental variable) that is highly correlated with the exposure but does not independently affect the outcome.¹³ For example, an observational study of the effect of catheterization and revascularization on mortality following acute myocardial infarction is prone to confounding related to differences in baseline health characteristics of the populations receiving or not receiving these treatments. To limit this potential source of confounding, a group of researchers studied the effect of these treatments (the exposure) on mortality after myocardial infarction (the outcome) by comparing groups of patients living at different distances from hospitals providing these services (the instrumental variable).¹⁴ The researchers assumed that potentially confounding health characteristics would be distributed randomly geographically and that geographic distance would affect mortality only indirectly through its correlation with access to treatment. In a way, they used distance to “randomize” their study population to different levels of treatment for acute myocardial infarction.

In addition to minimizing confounding through good study design, confounding can also be addressed during the analytic phase of a study. The most common approach is the use of *statistical risk adjustment* techniques, typically with multivariate regression analysis. This approach involves taking into account differences in the prevalence of recognized confounders across comparison groups. However, statistical risk adjustment has two important limitations. First, only recognized confounders can be addressed. Second, every potential confounding variable added to a statistical model decreases the model’s statistical power and thereby increases the chance of resulting in a type II error.

Other analytic techniques used to address confounding include *stratification* (subanalyses in which subjects with similar risk profiles are compared) and *propensity score risk*

adjustment.¹⁵ The latter technique addresses the problem created by unequal chances of receiving treatment caused by differences in health characteristics. In an observational study of the outcomes of a given treatment, a propensity score is a scalar summary of all observed confounders that predict the probability of receiving the treatment. Propensity scores are typically calculated using multivariate regression models and are used as the basis for stratified analysis or for matching cases and controls in observational studies.

Interpreting and Applying Evidence to Practice: External Validity

Once one is convinced that a clinical study is internally valid (i.e., that the observed outcome is the result of the exposure or intervention and cannot be attributed to some alternative explanation), then the challenge to the surgeon is judging the study's external validity (i.e., determining whether the findings are applicable to the clinical scenario he or she faces). An assessment of external validity requires attention to several components of a clinical study, including the patient population, the intervention, and the outcome measure. In the discussion that follows, a large prospective randomized clinical trial of laparoscopic versus open inguinal hernia repair performed in the Veterans Administration (VA) will be used as an illustrative example.¹⁶ This trial concluded that outcomes of open repair are superior to those of laparoscopic repair. The trial was well designed and well conducted but generated substantial discussion about the generalizability of the results.

As noted above, subject selection bias can adversely affect the external validity (or generalizability) of a study's results. If the population studied is in some important measure different from the population for which a surgeon is making clinical decisions, he or she may not achieve similar results. In the VA hernia trial, subjects were military veterans, who tend to be, on average, older than the nonveteran general population. If older subjects are more prone to the risks of laparoscopic hernia repair (e.g., general anesthesia), one might expect that the difference in morbidity outcomes would be exaggerated in the VA trial. In this respect, a surgeon might consider the evidence provided by the trial applicable to his or her older patients but reserve judgment on the use of laparoscopy to repair hernias in younger, healthier patients.

A striking example of the potential effect of selection bias on generalizability comes from the Asymptomatic Carotid Artery Stenosis (ACAS) trial.¹⁷ In this large prospective randomized study, volunteers for the trial were substantially younger and healthier than the average patient who undergoes carotid endarterectomy. As a result, the observed perioperative mortality rate in the trial was considerably lower than that observed in the general population or even in the very hospitals where the trial was conducted.¹⁸ Although the results of the ACAS trial significantly changed practice, one could argue that the evidence provided by the ACAS trial may have been generalizable only to younger populations.

The external validity of a clinical study can also be affected by who provides the intervention and by what type of intervention is provided. In the VA hernia trial, surgeons had variable experience with the laparoscopic approach, and the trial reported twofold differences in hernia recurrences between

surgeons who had done more than 250 cases and surgeons who had less experience. Surgeons deciding whether evidence supports the use of laparoscopic repair would need to examine their own experience before determining the generalizability of this study to their practices. Furthermore, some have argued that one of the laparoscopic techniques commonly used in the VA trial (transabdominal preperitoneal repair) is outmoded and more hazardous.¹⁹ Surgeons who avoid using this approach might reasonably question the generalizability of this study to their practices.

The type of outcome measured can also affect the generalizability of clinical studies. Outcomes chosen for clinical studies may be those that are most convenient or most easily quantified and may not be the outcomes of greatest interest to patients. In the VA hernia trial, several outcomes were studied, including operative complications, hernia recurrence, pain, and length of convalescence. Some of the outcome differences favored open repair, whereas some favored laparoscopic repair. The interpretation of the trial evidence for one type of repair versus the other involves implicit value judgments regarding which outcomes are most important to patients. Surgeons applying the VA hernia trial evidence to decisions about hernia repair must examine the specific outcomes measured before knowing whether a study is generalizable to an individual patient with specific values and interests.

Evidence-Based Surgery and Quality of Care

In clinical studies, the efficacy of a surgical practice is measured in terms of the resulting patient outcomes. Similarly, efforts to assess the quality of surgical care have until recently focused almost exclusively on clinical outcomes. In recent years, however, the movement to promote evidence-based surgery has offered an alternative measure of surgical quality: adherence to processes of care (e.g., routine use of perioperative antibiotics) supported by the best available scientific evidence.

The question of whether efforts to assess quality should focus on evidence-based processes of care or clinical outcomes is as much practical as philosophical. The practical argument against outcomes is largely driven by a growing recognition that individual hospitals and surgeons generally have too few adverse outcomes to provide enough statistical power to show meaningful differences between providers.²⁰ The practical argument against evidence-based processes of care is driven by the paucity of high-leverage, procedure-specific processes for which sound evidence is available, as well as the logistical challenge of measuring such processes. A more complete discussion of this topic is provided elsewhere [see *EC:2 Performance Measures in Surgical Practice*].

Given its current momentum, the evidence-based surgery movement will likely play a progressively larger role in efforts to assess and improve quality of surgical care. Furthermore, as payers increasingly turn to "pay for performance" strategies to improve quality and control costs, the demand for evidence-based practice guidelines will continue to grow. More importantly, efforts to identify and implement evidence-based surgical practices will ultimately provide patients with safer, better care.

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5 PATIENT SAFETY IN SURGICAL CARE: A SYSTEMS APPROACH

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High-profile catastrophes such as the explosion of the nuclear power plant at Chernobyl, the near meltdown of the nuclear power plant at Three Mile Island, the explosion of a chemical plant in Bhopal, numerous aviation disasters, and the loss of the space shuttles *Challenger* and *Columbia* share important characteristics. First, the casualties are notable for their number, their celebrity, or both. Second (and more germane to this chapter), each occurred as a result of multiple failures within complex systems. Human errors played a role in all of these failures, but the errors were not single acts of negligence as much as they were magnifications of multiple seemingly small interactions, the significance of which was initially unrecognized or underestimated.

Until about a decade ago, medical errors, unlike the above events, rarely received much publicity. This was in part because they affected only one patient at a time, and, as a result, their aggregate number was neither recognized nor well publicized. Another factor has been the tendency to regard error in medicine as a special case of medicine rather than as a special case of error.¹ The unfortunate result of this view has been the isolation of medical errors from much of the body of theory, analysis, and application that has been developed to deal with error in other high-risk work domains such as aviation and nuclear power.

Yet at least two factors now appear to be changing this view. One, the 1999 report of the Institute of Medicine (IOM), *To Err Is Human: Building a Safer Health System*, made national headlines with its estimates of the frequency and severity of adverse events in health care, including that as many as 98,000 medical error-related deaths occur each year in the United States.² This estimate far exceeds the number of casualties from more publicized nonmedical disasters, and if it is accurate, then medical errors would be one of the leading causes of death in the United States. Moreover, surgical adverse events represent over half of all adverse events experienced by hospitalized patients, and 75% of those have their origin in the operating room.³ This highlights the critical importance of patient safety in surgical care, particularly in the operating room.

A second factor affecting this view was advances in cognitive psychology that greatly increased the understanding of the influences that lead to error and affect human performance. The observation that the basic principles of human error are highly applicable to clinical practice has markedly advanced our understanding and willingness to address error in this setting. Medical errors are not a special case of medicine, and their underlying causes are not unique to medical practice.

These factors also challenged the notion that medical injury is primarily the result of “bad apples” and that safety can be improved largely by ridding the system of these persons. Undoubtedly, bad apples exist, but it is increasingly clear that health care-related injuries represent system failures and are rarely solely the result of negligence on the part of a single provider. Furthermore, there is a growing recognition that modern health care systems are as complex as—if not more complex than—the systems associated with nuclear power, aviation, and space flight.¹ The cognitive and technical complexity of the tasks performed in the operating room, the intensive care unit, and the emergency department certainly rivals that of these other endeavors. Furthermore, optimal patient care increasingly requires coordination among an expanding number of participants. For instance, in the early 20th century, it is estimated that health care involved the interaction of three persons, on average; a century later that number had risen to 16.

This chapter seeks to address the characteristics of systems in general and the system of surgical care in particular. It describes the growing knowledge of factors that affect human performance and how these factors contribute to adverse surgical outcomes. The chapter also outlines current obstacles to improving safety, identifies systems approaches to making improvements, and discusses ways in which surgeons can take the lead in overcoming these obstacles. An overall goal is that acceptance of error and a willingness to investigate its underlying causes will allow health care professionals to make use of the lessons learned from study of nonmedical systems. Although issues of patient safety are often intertwined with those of the overall cost-effectiveness and quality of surgical care,⁴ the latter are discussed in greater detail elsewhere.

Nature and Magnitude of Adverse Events in Surgical Care

For most of the important concepts bearing on patient safety in the surgical setting, generally accepted definitions exist [see *Sidebar Definitions of Terms Related to Patient Safety*]; the ensuing discussion is based on these definitions.⁵ A solid understanding of the key concepts—such as the distinctions between an adverse event (or adverse outcome), an error, and negligence—is critical for managing errors as system failures rather than as isolated incidents.⁶ In particular, such an understanding can help in navigating the often turbulent emotional milieu that can surround adverse patient events. Given their motivation to help patients, physicians tend to be highly sensitive to issues of causation, and this

Definitions of Terms Related to Patient Safety⁵

- An *adverse event* is an injury that was caused by medical management and that results in measurable disability.
- An *error* is the failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim. Errors can include problems in practice, products, procedures, and systems.
- A *preventable adverse event* is an adverse event that is attributable to error.
- An *unpreventable adverse event* is an adverse event resulting from a complication that cannot be prevented given the current state of knowledge.
- A *near miss* is an event or situation that could have resulted in accident, injury, or illness but did not, either by chance or through timely intervention.
- A *medical error* is an adverse event or near miss that is preventable with the current state of medical knowledge.
- A *latent error* is a condition of the system that is removed from the adverse event, such as poorly designed equipment, management decisions, or physical plan of the operating room. Latent errors set up the conditions in which an adverse event can occur, but their impact is not directly recognized.
- An *active error* is an action that directly leads to the adverse event.
- A *system* is a regularly interacting or interdependent group of items forming a unified whole.
- A *systems error* is an error that is not the result of an individual's actions but the predictable outcome of a series of actions and factors that make up a diagnostic or treatment process.

sensitivity can then interfere with the recognition and management of safety issues.

The two most widely cited estimates of adverse medical events derive from the Harvard Medical Practice Study (HMPS)⁷ and from a study in Colorado and Utah.³ The HMPS, a population-based study of patients hospitalized in New York State during 1984, found that nearly 4% of patients experienced an adverse event and that about half of such events occurred in surgical patients. The Colorado/Utah study, which randomly sampled 15,000 nonpsychiatric discharges during 1992, found that the annual incidence of adverse surgical events was 3.0% and that 54% of these events were preventable. Nearly half of all adverse surgical events were accounted for by technique-related complications, wound infections, and postoperative bleeding. This study also identified common operations that were associated with a significantly higher risk of an adverse event and a significantly higher risk of a preventable event.

Other studies yielded comparable or higher estimates,⁸ and still others evaluated the rates at which specific events occurred, as follows:

- Retained sponges or surgical instruments were estimated to occur at a rate between one in 8,801 and one in 18,760 inpatient procedures at nonspecialty acute care hospitals.⁹
- Wrong-site surgery is more than just an isolated event,¹⁰ and the apparent increased frequency at which such events are currently being reported probably reflects previous underreporting.
- Medication errors (e.g., wrong drug, wrong dose, wrong patient, wrong time, or wrong administration route) are alarmingly frequent.^{11,12} The US Pharmacopeia monitors these events through its reporting programs (www.usp.org/

patientsafety). In 2001, these programs received reports of 105,603 errors, 2,539 (2.4%) of which resulted in patient injury. Of these, 353 necessitated hospitalization or prolonged its duration, 70 necessitated interventions to sustain life, and 14 resulted in a patient's death. The main contributing factors were distractions (47%), workload increases (24%), and staffing issues (36%). Miscalculating patient weight conversions (e.g., from pounds to kilograms) and subsequent improper dosing are all too common among pediatric patients. Errors in the administration of radiopharmaceuticals are also frequent and may involve the wrong isotope (68.9%), the wrong patient (24%), the wrong dose (6.5%), or the wrong route (0.6%).¹² One study estimated that the US rates would have to be reduced by one third to match the benchmark rates in Germany and the United Kingdom with regard to medical mistakes, medication errors, or laboratory test errors.¹³

- Blood transfusions continue to be plagued by patient misidentification.
- Device-related deaths and serious injuries also occur at an alarming rate, even after premarket safety testing.¹⁴ The Food and Drug Administration (FDA) maintains a registry of the thousands of such injuries that occur each year.
- A survey noted that 35% of physicians and 42% of the public said that they had experienced a medical mistake in their own care or in the care of a family member.¹⁵

As might be expected, the IOM report prompted a great deal of debate. Some medical professionals questioned the accuracy of the estimates, whereas others disagreed with the definitions of medical error and adverse event, with the extent to which either or both were considered preventable. Still others argued that adverse events that are caused by conceptual errors (e.g., a contraindicated, unsound, or inappropriate approach) should be differentiated from the side effects of an intended action that is correct in the circumstances (e.g., an indicated diagnostic or therapeutic procedure).¹⁶ The aim of this argument was to sharpen the distinction between accidents (i.e., unplanned, unexpected, and undesired events) and true side effects (which result from correct management and which are often accepted as reasonable therapeutic tradeoffs).

The HMPS attempted to address these issues by characterizing adverse events as either preventable or unpreventable in the light of the prevailing state of knowledge. Preventable errors were further subclassified as either diagnostic errors or treatment errors; treatment errors included preventive errors such as failure of prophylaxis and failure to monitor and follow treatment.^{7,17} The HMPS found that preventability varied according to the type of event: 74% of early surgical adverse events were judged preventable, compared with 65% of nonsurgical adverse events, and more than 90% of late surgical failures, diagnostic mishaps, and nonprocedural therapeutic mishaps were judged preventable.

The above estimates of patient injury rates have also raised speculations about trends in the frequency of these events. To some, the observation that the rate of such events was lower in the Colorado/Utah study than in the HMPS suggests

that patient safety was improving even before the IOM report. Although there may be some improvements in care, wide gaps in quality persist (www.healthgrades.com/business/study/quality.aspx).

Regardless of any actual trend, there is agreement that progress since the IOM report has been slow, that the results have been modest at best, and that the gap between the best possible care and the care actually being delivered remains large.^{18–20} Although the lack of more evident improvement has been somewhat disappointing, clear progress has nevertheless been made with respect to (1) understanding the complexities of medical care systems, (2) identifying the challenges to improving these systems, and (3) developing new perspectives on the assessment of errors. Thus, an increase in estimates of the incidence of adverse events may simply reflect improved reporting rather than actual increases in their occurrence.

Nature and Characteristics of Systems

A system may be broadly defined as a regularly interacting or interdependent group of items that form a unified whole. System functions or tasks usually involve sequential steps that have human, technological, and logistical components. The overall probability of a system failure (i.e., an adverse outcome), then, is a function of the probability of error within each step, the total number of steps, and the degree to which the steps are coupled. The degree of coupling is the extent to which an error at one step can propagate through subsequent steps and adversely affect the final outcome. Loosely coupled systems tend to have built-in redundancy that acts as a safety barrier to prevent errors from propagating to subsequent steps. As a result, satisfactory outcomes in such systems are far less dependent on successful completion of each step. Errors in loosely coupled systems are more readily “trapped” by these safety barriers.

In contrast to loosely coupled systems, tightly coupled systems have relatively little redundancy and relatively few fail-safe mechanisms. Consequently, successful outcomes in tightly coupled systems are highly dependent on the success of each step in essentially a factorial fashion. Thus, the probability of success in a tightly coupled linear 20-step process with a 1% likelihood of error at each step is equivalent to 0.99 factored 20 times, or 0.818. Thus, even though the probability of error for each step is .01, the overall likelihood of an unintended outcome is 0.182.

Given that safety barriers are generally more numerous in loosely coupled than in tightly coupled systems, it is relatively unusual for an isolated error to produce an injury or system failure in the former. Thus, failures in loosely coupled systems typically involve malfunctions at multiple steps. A tradeoff with the level of redundancy in loosely coupled systems is that it makes the system more complex, and the added complexity can introduce its own errors.

James Reason was the first to distinguish between active and latent system errors and their individual importance in understanding the overall role in system failures.²¹ Active errors are what might be traditionally associated with the term “error”: a discrete action that produces an immediate effect. Latent errors, on the other hand, are structural characteristics of the system, features of the environment, or

decisions or plans that are removed from the point of care. They do not produce an immediate result but rather set up the conditions in which a given result can arise. The importance of a system’s latent failures as contributing factors in adverse outcomes may be illustrated by considering a general schema of an injury [see *Figure 1*].²¹ Whereas overt system problems are relatively easy to identify and correct, latent failures are insidious and often do not become evident until a seemingly improbable series of events produces errors in otherwise routine processes. Latent failures tend to be introduced by persons who work at the “blunt end” of the system (e.g., management or housekeeping) but do not actively participate in the main processes of care. A typical injury pathway is one in which organizational processes introduce latent failures, which in turn produce system defects, which in turn interact with external events so that persons who work at the “sharp end” of the system (e.g., anesthesiologists, nurses, or surgeons) commit unsafe acts. These unsafe acts precipitate an active failure that then penetrates the final safety barrier or barriers.²² Indeed, the greatest risk of an adverse event in a complex system may come not from a breakdown of one or more major subsystems or from isolated operator errors but from the presence or accumulation of latent failures.^{21,23,24}

Surgical Care as a System

The characteristics of systems already discussed (see above) have many attributes directly applicable to medicine in general and to surgery and anesthesiology in particular. In addition to the parallels between the habitats associated with surgery (e.g., the operating room, the intensive care unit, and the emergency department) and those associated with many high-tech, high-risk nonmedical endeavors, strong parallels exist between observed behavior in the operating room and behavioral issues in an airplane cockpit.^{25,26}

The nature of the operating room as a system and the complexity of the interactions that occur there have been studied extensively. The performance of the operating room system depends on the individual performance of practitioners, the interactions of those individuals or teamwork, and the environment in which the practitioners work. It is important to note the interdependence of each of these components of the system. To understand the role that each plays, we examine each and their impact on surgical safety in turn: individual performance, teamwork, and environmental or structural factors.

Factors that Affect Performance

COGNITIVE PSYCHOLOGY OF INDIVIDUAL PERFORMANCE

Because human factors play a major role in system failure, any attempt to improve patient safety must be based on an understanding of the factors that affect human performance and their relation to human error.²⁷ Major advances in the field of cognitive psychology over the past several decades have greatly enhanced the understanding of human performance. A widely accepted schema classifies such performance into the following three types,²⁸ in descending order of familiarity with the specific task:

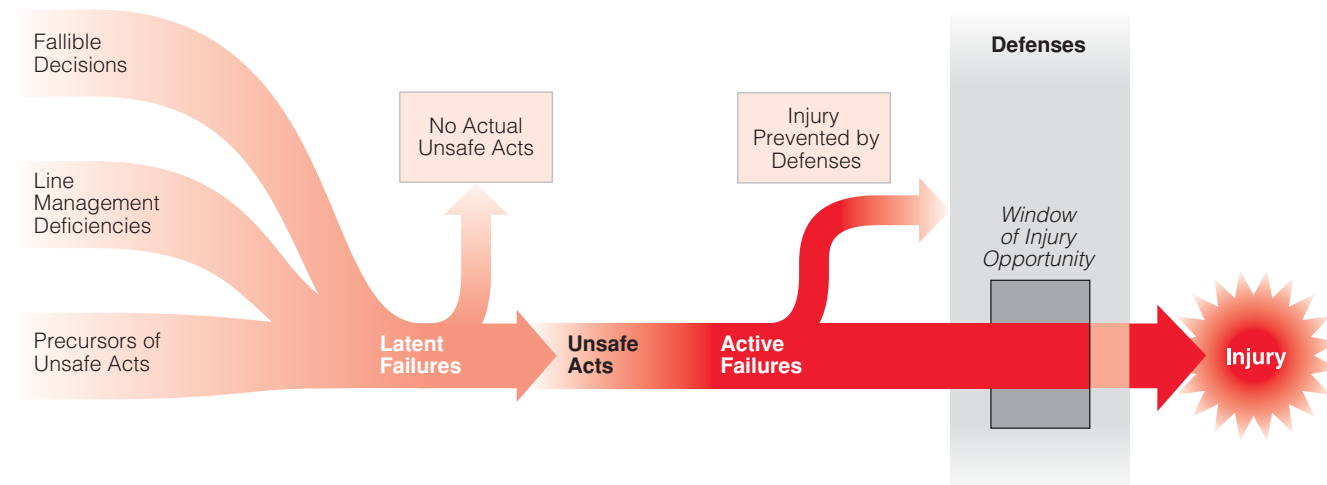


Figure 1 Schematic depiction of the process by which system failures (latent and active) may lead to injury. Defenses may be inadequate if they allow the formation of a window of injury opportunity.

1. *Skill-based performance.* This type of performance is governed by stored patterns of preprogrammed instructions. It occurs without conscious control and uses long-term memory.
2. *Rule-based performance.* This type involves solving problems by means of stored rules of the if-then variety. Like skill-based performance, it uses long-term memory; however, unlike skill-based performance, it is associated with a consciousness that a problem exists.²³ The rules are usually based on experience garnered from previous similar situations and are structured hierarchically, with the main rules on top; their strength appears to be a function of how recently and how frequently they are used.²⁷ Rule-based performance varies according to expertise: novices tend to rely on a few main rules, whereas experts have many side rules and exceptions.
3. *Knowledge-based performance.* This type involves conscious analytic processes and stored knowledge. It relies on working memory, which is comparatively slow and of relatively limited capacity. Typically, people resort to knowledge-based performance when their existing skills are not applicable or their repertoire of rules has been exhausted.

Successful performance or problem solving has three main phases: planning, storage, and execution. Errors resulting from failures in performance may be classified as slips, lapses, or mistakes,²¹ depending on which phase of the problem-solving sequence is involved. Slips are failures of the execution phase, the storage phase, or both, and they may occur regardless of whether the plan from which they arose was adequate. Lapses are failures of the storage phase. Generally, slips are overt, whereas lapses are covert. Mistakes are failures of planning, reflecting basic deficiencies or failures in selecting an objective or specifying the means to achieve it, regardless of how well the plan was executed.

A key concept is that specific types of error tend to be associated with specific modes of failure [see Table 1].²¹ Slips and lapses are failures of skill-based performance and generally precede recognition of a problem. Mistakes may be either

Table 1 Common Modes of Failure Associated with Specific Types of Performance²¹

Failures of Skill-Based Performance

Inattention

- Double-capture slips
- Omissions following interruptions
- Reduced intentionality
- Perceptual confusions
- Interference errors

Overattention

- Omissions
- Repetitions
- Reversals

Failures of Rule-Based Performance

Misapplication of good rules

- First exceptions
- Countersigns and nonsigns
- Informational overload
- Rule strength
- General rules
- Redundancy
- Rigidity

Application of bad rules

- Encoding deficiencies
- Action deficiencies
- Wrong rules
- Inelegant rules
- Inadvisable rules

Failures of Knowledge-Based Performance

Selectivity

- Workspace limitations
- Out of sight, out of mind
- Confirmation bias
- Overconfidence
- Biased reviewing
- Illusory correlation
- Halo effects
- Problems with causality
- Problems with complexity

failures of knowledge-based performance (i.e., attributable to lack of expertise) or failures of rule-based performance (i.e., attributable to failure of expertise). They typically arise during attempts to solve a problem. Mistakes tend to be more subtle,

more complex, and less well understood than slips or lapses and thus more dangerous. It has been suggested that experienced surgeons are more prone to slips and lapses and that junior surgeons and trainees are more prone to mistakes.²⁹

Underspecification of the problem is common in clinical practice and clearly affects performance. A problem may seem underspecified when limited attention is paid, when the wrong cues are picked up, when the problem is truly ill-defined, or when the problem falls outside the known rules. Underspecification is more likely to occur in situations where cues change dynamically or are ambiguous and is associated with two types of error forms: similarity matching and frequency bias (or frequency gambling). In similarity matching, a present situation is thought to resemble a previous one and consequently is addressed in the same way (which is not necessarily appropriate). In frequency gambling, a course of action is chosen that has worked before, and the more often that course of action has been successfully used, the more likely it is to be chosen. These behavior patterns have been confirmed among anesthesiologists, who, like many dynamic decision makers, use approximation strategies (or heuristics) to handle ambiguous situations.¹

Confirmation bias is another characteristic problem of performance. It may be defined as the propensity to stick with a chosen diagnosis or course of action and either to interpret new information so as to favor the original choice or to disregard such information entirely. It is also referred to as cognitive fixation, cognitive lockup, or fixation error and is often associated with knowledge-based performance.³⁰ Confirmation bias is particularly likely when the situation is unusual or evolving and when there is concomitant pressure to maintain coherence³¹—again, situations frequently encountered in surgical practice. A well-known adage is relevant here: good surgeons believe what they see; bad ones see what they believe.³² The issue of how cognitive psychology affects diagnostic and clinical reasoning has been addressed in detail elsewhere.^{33–35}

Confirmation bias may be considered an error of perception; other errors may be classified as errors of cognition or execution. Thus, classification schemes may be modified to meet specific needs.³⁶ For instance, some experts categorize errors according to whether they can be addressed by engineering, design, societal, or procedural changes; others prefer to emphasize psychological intervention and modification; and still others classify errors by their mode of appearance—for example, as errors of omission, errors of insertion, errors of repetition, or errors of substitution (e.g., misadministration of lidocaine, heparin, or potassium chloride as a result of poor package labeling).

RELATION OF INDIVIDUAL PERFORMANCE TO SURGICAL ERROR

To many, the concepts of performance and error, as they relate to patient care, seem straightforward—obvious, even. To others, however, it is crucial to make a distinction between human error and human performance, both because the assignment of error is often retrospective and thus subject to hindsight bias and because the term “error” is inherently prejudicial.

Important advances in our understanding of the role of surgeon performance in error come from an analysis of

surgeon-reported errors³⁷ and a review of closed malpractice claims.³⁸ In the former, cognitive factors (primarily involving errors in judgment or vigilance) were involved in 86% of the incidents, whereas inexperience or lack of competence contributed to 53% of errors. The latter study reported similar findings: errors in judgment, failure of vigilance or memory, and lack of technical competence or knowledge were factors in 66%, 63%, and 41% of the cases, respectively.

Further analysis revealed that 65% of the technical errors were linked to manual error, 9% to errors in judgment or knowledge, and 26% to both manual and judgment or knowledge error.³⁹ Seventy-three percent of technical errors occurred with experienced surgeons operating within their field of expertise, and over 80% were performing routine operations but often under extenuating circumstances, such as complicated patient factors (61%) or systems failures (21%). Current approaches to decreasing technical performance include such interventions as volume-based referral or regionalization, increased specialization, and more stringent credentialing for high-risk procedures. The results of this study, however, suggest that these approaches are unlikely to lead to significant improvement. Rather, attention should be paid to improving technical performance (including both manual and judgment) in general but particularly when operating under complicated conditions.

In one sense, a surgeon's performance is a system factor, but in another sense, their cognitive and technical abilities make up a large part of the system's safety barriers. There is much that can be learned about human performance by studying how providers compensate when things start to go wrong and return the system to a safe state. Legal concerns aside, it is vital that surgeons not overemphasize the first sense and interpret it as an excuse for avoiding responsibility for complications.⁴⁰ Nevertheless, placing too much emphasis on surgeons' individual role retards rather than advances understanding of system failure and tends to evoke defensiveness rather than constructive action.^{22,23,41} Regardless of whether these adverse events are performance failures or errors, eliminating them entirely is an impossible goal; a more realistic goal is to gain a better understanding of the contributing and compensatory factors and then to minimize—or possibly even eliminate—their consequences. The overall implication here is that to achieve meaningful improvements in safety, it is necessary to shift the focus from fallible individuals to the situational and organizational circumstances through which human performance leads to medical errors.²⁶

Another important consideration in performance is an individual's physical and psychological well-being. The effects of sleep deprivation and fatigue on performance and learning have been particularly studied.^{42–46} Fatigue, by impairing vigilance, can accentuate confirmation bias. In addition, errors increase as time on task increases; no other hazardous industry permits—let alone requires—employees to work the regular long hours common in hospitals.³⁰ Stress may increase the likelihood of error, but it is clearly neither necessary nor sufficient for cognitive failure.²¹ Unfortunately, physicians tend to have unrealistic beliefs about their ability to deal with stress and fatigue and so may not seek help even when they clearly need it.⁴⁷ Recent studies have highlighted the striking prevalence of burnout among surgeons and the high degree

of correlation between burnout and medical errors.⁴⁸ Surgeons also appear to have only a limited ability to assess their own learning needs, with those who are least skilled and those who are most confident being the worst at this task.⁴⁹ As a corollary, surgical skill is positively related to the ability to detect errors.²⁹

The mental overload that can occur in situations involving a plethora of tasks may compromise the ability to respond to secondary tasks. Errors related to loss of vigilance include not observing a data stream at all, not observing a data stream sufficiently frequently, and not observing the particular data stream that is optimal for the existing situation. In watching for rare occurrences (a not uncommon situation in medicine), it is difficult to remain fully alert for longer than 10 to 20 minutes. Knowing when and how to verify data is an important metacognitive skill. An analysis of intraoperative safety identified high workloads, poor workload leveling, and multiple competing tasks as a major threat to performance and safety.⁵⁰

In addressing these types of errors, a great deal of emphasis has been placed on reducing work hours, but there seems to have been relatively little consideration of the impact of workload and workflow on medical errors.³⁷ Yet data on resident work activities indicate that residents experience extremely fragmented workflows that result in frequent interruptions and changes in focus.⁵¹ Moreover, the current limit on resident work hours does not appear to have improved patient safety⁵² or reduced the incidence of technical complications.⁵³ Thus, demands for greater productivity within a health care system that is increasingly constrained by cost considerations may also contribute to an increase in medical errors.

Psychological framing effects also play a role in judgment. Examples of such effects are the irrational preference for established treatments when outcomes are framed in terms of gain (e.g., survival) and the similarly irrational preference for risky treatments when outcomes are framed in terms of loss (e.g., mortality). The impetus to “do the right thing” can adversely affect medical judgment.⁵⁴

RELATION OF SYSTEM FACTORS TO SURGICAL ERROR

Teamwork and Communication

Teamwork and communication among team members also play essential roles in determining performance, particularly when there is a lack of cohesion and mutual support among team members.^{1,30} On the one hand, a team structure that is too informal tends to undermine patterns of authority and responsibility and to hinder effective decision making. On the other hand, a hierarchy that is too strong may make it excessively difficult for juniors to question decisions made by those at higher levels of authority. Rigid behavior may impair the ability to cope with unforeseen events and discourage initiative.

Teamwork can be an especially complex matter in the operating room. The crews from nursing, surgery, and anesthesia often have fundamentally different perceptions of their respective roles, and these perceptual differences can adversely affect situational awareness. For example, anesthesiologists and nurse anesthetists are much more likely to feel that a preoperative briefing is important for team effectiveness than are surgeons and surgical nurses. In aviation, concern that

junior team members would not question the decisions of more senior staff led to significant policy changes and safety enhancements.⁵⁵ Given the traditional surgical hierarchy, similar attitudes may exist in the operating room. Such varying perceptions can not only compromise patient safety but also hinder teaching and learning. Unfortunately, there is no broad consensus on how to achieve optimal team coordination in this setting.

The critical role of communication in surgical errors has been described in a number of studies. Two or more clinicians substantially contributed to error in 70% of surgeon-reported errors, and three or more were involved in 18% of the incidents.³⁷ Communication breakdowns contributed to approximately one quarter of surgical errors that led to patient injury as detected on malpractice claims analysis.⁵⁶ These tended to be verbal communications between two or more people and were equally as likely to be cross-disciplinary as intradisciplinary. They occurred with equal frequency in the pre-, intra-, and postoperative period, and the surgical attending physician was most often involved either as the transmitter or the receiver. Intraoperative field observations suggest that communication breakdowns and failures are pervasive in the operating room, occurring in up to one third of communication events.^{50,57}

Environmental and Organizational Factors

The importance of the structural characteristics of the system in which care is provided is underscored by the relation between variations in the frequency of risk-adjusted outcomes among institutions and differences in the systems of care in place within those institutions.⁵⁸ The substantial similarities between medical and nonmedical systems notwithstanding, the complex content and organizational structure of health care make it distinctive. Many system concepts that derive primarily from analyses of human-engineered, highly technical, nonbiologic systems may not be fully applicable to the more complex issues of patient safety.⁵⁹ Linearly engineered systems are likely to be far more predictable than biologic systems, in which appropriate processes do not always result in good outcomes. Patients frequently differ greatly from each other in terms of their ability to communicate relevant issues, their severity of illness, their comorbidities, and their responses to diagnosis and treatment. When a system is not expected to work perfectly at all times—as health care is not—it becomes more difficult to distinguish problems related to individual error from problems related to flaws in the system. This distinction between nonmedical mechanical systems and medical systems may be akin to the distinction between complicated and complex endeavors.⁶⁰

Differences in organizational structure between medical and nonmedical systems may be particularly relevant. A non-medical system is typically a single structure that is managed vertically through hierarchical control. Patient care, in contrast, tends to consist of numerous diverse subsystems that may be only loosely aggregated.⁶¹ These subsystems tend to function in isolation, and intrasystem changes tend to be managed laterally across individual subsystems. The resulting loose structure often leads to the creation of ineffective or even contradictory policies, all of which increase the chances of error.

The potential role of a systems approach in improving safety is further suggested by data that correlate improved outcomes with higher hospital or surgeon volume.^{62,63} Whether these findings are explained by “practice makes perfect” or by “perfect makes practice” is yet to be resolved, but in either case, it seems likely that the improved outcomes reflect better care systems. That some high-volume hospitals and surgeons have below-average outcomes and many low-volume hospitals and surgeons have excellent ones is consistent with the role of systems.⁶⁴

The physical characteristics of the system in which care is provided can influence the safety of the system. Issues such as ergonomics, lighting, equipment malfunctions, noise levels, and interruptions can increase the vulnerability to error and adverse outcomes.

A system’s results may be summed up as follows: “Whether your output is good or bad, it is, nonetheless, the only output of which your systems, processes, and methods are currently capable.”⁵⁹ Otherwise stated, every system is perfectly designed for the results it gets.

Lessons from Other High-Risk Domains

A systems approach to safety improvement has led to major advances in a number of other high-risk work environments, such as aviation and other transportation domains. As we start to understand health care as a system and the role of human factors in system performance, we can learn from the advances made in these other fields. Patterson and colleagues identified handoff strategies that were identified in other settings with high consequences for failure (space shuttle mission control, nuclear power, railroad and ambulance dispatchings) that could be applied to improve the safety of handoffs in health care [see Table 2].⁶⁵

Significant advances have been made in adopting the technique of crew resource management (CRM) from aviation to health care and surgery. CRM was first used by the aviation industry to improve airline crew coordination, and the IOM report *To Err Is Human: Building a Safer Health System* identified it as a strategy to reduce medical errors and improve patient safety.² Since this call for its implementation, the use of CRM has been evaluated in various health care fields, including operating room teams. In one study, teams underwent an 8-hour training course that covered six key areas of CRM: managing fatigue; creating and managing a team; recognizing adverse situations; cross-checking and communication techniques; developing and applying shared mental models for decision making; and giving and receiving performance feedback.⁶⁶ Although 95% of respondents agreed that the training would reduce errors in their workplace, cultural barriers still exist within surgery. Whereas only 26% of pilots denied that fatigue has a detrimental effect on performance, 70% of surgeons and 47% of anesthesiologists felt that they can perform effectively even when fatigued.⁶⁷ In the same study, only about half of attending surgeons favored a flat hierarchy in which junior members of a team could question decisions made by senior team members, whereas 94% of pilots advocated for this approach. Perhaps more broad adoption of CRM will help bridge this cultural divide.

Table 2 Handoff Coordination and Communication Objectives and Relevant Strategies⁶⁵

Improve handoff update effectiveness 1. Face-to-face verbal update with interactive questioning 2. Additional update from practitioners other than one being replaced 3. Limit interruptions during update 4. Topics initiated by incoming and outgoing team members 5. Limit initiation of operator actions during update 6. Include outgoing team’s stance toward changes to plans and contingency plans 7. Readback to ensure that information was correctly received
Improve handoff update efficiency and effectiveness 8. Outgoing writes summary before handoff 9. Incoming assesses current status 10. Update information in the same order every time 11. Incoming scans historical data before update 12. Incoming reviews automatically captured changes to sensor-derived data before update 13. Intermittent monitoring of system status while “on call” 14. Outgoing has knowledge of previous shift activities
Increase access to data 15. Incoming receives primary access to the most up-to-date information 16. Incoming receives paperwork that includes handwritten annotations
Improve coordination with others 17. Unambiguous transfer of responsibility 18. Make it clear to others at a glance which personnel are responsible for which duties at a particular time
Enable error detection and recovery 19. Overhear others’ updates 20. Outgoing oversees incoming’s work following update
Delay transfer of responsibility during critical activities 21. Delay the transfer of responsibility when concerned about status/stability

Approaches to Improving Patient Safety

Given the similarities between medical and nonmedical systems, it should not be surprising that many safety improvement techniques derived from nonmedical settings have been successfully applied in medical contexts [see Table 3].^{68,69} Other useful strategies include prioritization of tasks, distribution of the workload over time or resources, changing the nature of the task, monitoring and checking all available data, effective leadership, open communication, mobilization and use of all available resources, and team building.¹ The

Table 3 Nonmedical System Techniques Also Applicable to Medical Systems

Simplify or reduce handoffs Reduce reliance on memory Standardize procedures Improve information access Use constraining or forcing functions Design for errors Adjust work schedules Adjust the environment Improve communication and teamwork Decrease reliance on vigilance Provide adequate safety training Choose the right staff for the job
--

general idea behind many of these approaches is to redesign the problem space to reduce the cognitive workload.^{28,70}

A vital early step in improving patient safety is to establish a safety culture throughout the workplace. An important development in this area is the ability to make valid measurements of an organization's safety climate.⁷¹ An appropriate organizational culture views errors as signals for needed changes and focuses on learning rather than on accountability. If the team or organization is designed to learn from and benefit from experience, its collective wisdom should be greater than the sum of the wisdom of its individual members. Needed changes often involve difficult choices among strategic factors and sometimes introduce new latent flaws.^{37,72} Accordingly, once a change in procedure or policy has been implemented, its impact must be monitored closely.⁷³ New latent failures may result from either oversimplification³¹ or redundancy. As noted (see above), the latter enhances reliability, but its benefits are often offset by greater complexity and a consequent increase in the risk of human failure.³⁰ In addition, the more complex the system, the greater the chance that a change will have more than local effects. How to control some errors without relaxing control over others is a general problem in error management.^{30,74}

Good teamwork requires that team members share a clear understanding of what is happening and what should happen (i.e., situational awareness).³⁰ Unfortunately, there is a common tendency to believe that the prevailing level of situational awareness is greater than it actually is. For example, the aviation industry further improved its safety record when it identified and removed barriers that impeded junior officers from communicating with the captain. This achievement is noteworthy because these improvements took place after good communication was already thought to exist.⁷⁵

Even though physicians have increasing access to information technology in practice (www.hschange.org/CONTENT/891), physician acceptance of computerization has been neither easy nor universal, and medicine is far behind other industries in terms of the extent to which it has adopted such technology. Studies from the past few years suggest that only about one third of physicians receive any data (process data, outcome data, or patient surveys) about the quality of care they provide.⁷⁶ This finding may be partly explained by the cost of introducing information technology (which can become outmoded relatively quickly).

Another possible factor here is concern that caregivers might become too dependent on computerized advice-giving systems and thus might start making a habit of perfunctorily acceding to the computer's advice rather than trusting their own judgment. Issues of legal liability then arise: how much computer advice is too much, and is relying on such advice tantamount to abandoning responsibility for critical independent thought? A related concern is that many patient care tasks may be too complex for computerization and thus may be better suited to human performance. The tradeoff for retaining the human ability to deal with such complexity is the human susceptibility to error: systems that rely on error-free human performance are destined to experience failures. Because the kinds of transitory mental states that cause errors are both unintended and largely unpredictable, they are the last and least manageable links in the error chain.

A further approach to improving patient safety has been the development of specific tools and indicators for identifying common safety problems. Examples of these are the Patient Safety Indicators from the Agency for Healthcare Research and Quality (AHRQ) (www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=techrev5) [see Table 4] and the serious reportable event list from the National Quality Forum (NQF) (www.qualityforum.org/Projects/s-z/SRE_Maintenance_2006/Fact_Sheet_-_Serious_Reportable_Events_in_Healthcare_2005-2006_Update.aspx) [see Table 5]. The lists are similar in some respects but not identical: the NQF further subcategorizes events into surgical events, product or device events, patient protection events, care management events, environmental events, and criminal events. Both lists specify clearly identifiable and readily measurable events, both include a variety of causes in addition to medical errors that lead to such adverse events, and both were developed by panels of experts. Yet a recent study indicated that, relative to risk managers, physicians were less aware of error-reporting systems in their hospitals or the adequacy of such mechanisms.⁷⁷

Techniques for Identifying System Flaws

Intensive examination of system flaws is most often triggered by a catastrophic failure or, less often, by a near miss. The appropriate investigation of such events is known as root cause analysis (RCA). The Joint Commission (formerly the JCAHO) (www.jointcommissioninternational.org/Books-and-E-books/Root-Cause-Analysis-in-Health-Care-Tools-and-Techniques-Fourth-Edition/1502) has a matrix for RCA, and experience with RCA in health care institutions has been reported.^{78,79}

In the case of an actual failure, the next steps are to identify all the relevant subsystems and to assemble a team whose members represent all of the components. Determining all of the components within a complex system can be challenging, and it may prove necessary to add members to the team as more subsystems are identified. In this regard, it is better to err on the side of inclusiveness rather than exclusivity to minimize the chances of missing latent flaws and maximize the number of possible solutions. Studies that relate nurse staffing to quality of care illustrate the important roles that

Table 4 Agency for Healthcare Quality and Research Patient Safety Indicators

Complications of anesthesia
Death in low-mortality diagnosis-related group
Decubitus ulcer
Failure to rescue
Foreign body left during procedure
Iatrogenic pneumothorax
Selected infections
Postoperative hip fracture
Postoperative hemorrhage or hematoma
Postoperative pulmonary embolism or deep vein thrombosis
Postoperative sepsis
Postoperative wound dehiscence
Accidental puncture or laceration
Transfusion reaction
Obstetric trauma

Table 5 National Quality Forum List of Health Care Facility–Related Serious Reportable Events

Category	Event
Surgical	A. Surgery performed on the wrong body part B. Surgery performed on the wrong patient C. Wrong surgical procedure on a patient D. Unintended retention of a foreign object in a patient after surgery or other procedure E. Intraoperative or postoperative death in an ASA class I patient
Product or device	A. Patient death or serious disability associated with use of contaminated drugs, devices, or biologics B. Patient death or serious disability associated with use or function of a device in patient care, in which the device is used or functions otherwise than intended C. Patient death or serious disability associated with intravascular air embolism
Patient protection	A. Infant discharged to the wrong person B. Patient death or serious disability associated with patient elopement (disappearance) C. Patient suicide or attempted suicide resulting in serious disability
Care management	A. Patient death or serious disability associated with a medication error B. Patient death or serious disability associated with a transfusion reaction C. Maternal death or serious disability associated with labor and delivery in a low-risk pregnancy D. Patient death or serious disability associated with hypoglycemia E. Death or serious disability associated with failure to identify or treat neonatal hyperbilirubinemia F. Stage 3 or 4 pressure ulcer acquired after admission G. Patient death or serious disability associated with spinal manipulative therapy H. Artificial insemination with wrong donor sperm or wrong egg
Environmental	A. Patient death or serious disability associated with electrical shock B. Any incident in which a line designated for oxygen or other gas to be delivered to a patient contains the wrong gas or is contaminated by toxic substances C. Patient death or serious disability associated with a burn incurred from any source D. Patient death or serious disability associated with a fall E. Patient death or serious disability associated with the use of restraints or bedrails
Criminal	A. Any care ordered by someone impersonating a physician or other licensed health care provider B. Abduction of a patient of any age C. Sexual assault of a patient D. Death or significant injury of a patient or staff member from a physical assault

ASA = American Society of Anesthesiologists.

other members of the health care team play in ensuring patient safety.^{80–82} In some situations, it may be difficult to generate interest in RCA because the circumstances are so unusual that they are unlikely ever to combine in the same way again.

Systems analyses in the presence of a near miss, or in the absence of any specific event, require a more global approach to help avoid future errors. Areas where such analyses might be fruitful include those identified by AHRQ [see Table 4], the NQF [see Table 5], and the Joint Commission. Another source for specific topics is AHRQ WebM&M (www.webmm.ahrq.gov), an AHRQ-developed Web site that provides expert analysis of medical errors in five specialty areas (including surgery), as well as interactive learning modules. AHRQ has also created extensive lists of other quality measures (www.qualitymeasures.ahrq.gov) and tools for improving patient safety. The next steps in this situation are to decide on measures for analysis and to identify appropriate data sources. Medical record audits yield far greater detail than claims data but are expensive, labor intensive, and time-consuming. Moreover, information on the environment or behavior in medical records may be irrelevant or even contradictory. This problem can sometimes be mitigated by employing appropriate screening criteria.⁸³ Some of the shortcomings of medical record audits can be avoided by using administrative data, but such data often lack sufficient accuracy or depth. Electronic health records can potentially simplify this process

and possess a number of other advantages.^{84,85} RCA can be automated,⁸⁶ but the potential advantages of doing so may be offset by a dependence on the developer's interpretation of the risk reduction process or by the factors identified as the principal event.

Regardless of the data source, the process is likely to be evolutionary: rarely is a perfect set of measures available from the start. Although the findings from such an analysis might seem to offer little benefit to the institution in which they occurred, such incidents may occur frequently enough at a regional or national level to make the analysis worthwhile.

Other analyses associated with successful quality improvement efforts include patient notification systems,⁸⁷ patient safety systems,⁸⁸ analyses of system failures in laparoscopic surgery,⁸⁹ and analyses of medical microsystems.⁷² Critical analyses of evidence-based practices also identified 11 surgically relevant quality improvement practices for which the data were strong enough to support more widespread implementation [see Table 6].^{90,91} A note of caution that should be sounded here is that exclusive emphasis on evidence-based data could skew safety priorities and might actually prevent relatively few adverse events.⁹² Another potential area for review involves changes in policy or equipment that might introduce unanticipated problems or unexplained variations in a relevant outcome measure. Every change in a system necessitates a new learning cycle, and the new environment may be conducive to failures from new latent errors.⁹³

Table 6 Surgically Relevant Quality Improvement Practices Appropriate for Widespread Implementation⁹⁰

Appropriate use of prophylaxis to prevent venous thromboembolism in patients at risk
Use of perioperative beta blockers in appropriate patients to prevent perioperative morbidity and mortality
Use of maximum sterile barriers while placing central venous catheters to prevent infection
Appropriate use of antibiotic prophylaxis to prevent postoperative infections
Requesting that patients recall and state what they have been told during the informed consent process
Continuous aspiration of subglottic secretions to prevent ventilator-associated pneumonia
Use of pressure-relieving bedding materials to prevent pressure ulcers
Use of real-time ultrasound guidance during central line placement to prevent complications
Patient self-management for warfarin to achieve appropriate outpatient anticoagulation and prevent complications
Appropriate provision of nutrition, with particular emphasis on early enteral nutrition in critically ill and surgical patients
Use of antibiotic-impregnated central venous catheters to prevent catheter-related infections

Successes and Obstacles to Success

In view of the complexities of health care, taking a systems approach to safety improvement may seem a daunting endeavor. Nevertheless, there are a number of cases in which this task has been successfully accomplished. For the purposes of illustration, it is worthwhile to review these examples briefly.

Anesthesiologists were among the first physicians to take a systems approach to patient safety, and their success is irrefutable: anesthesia-related mortality fell from approximately two in 10,000 to the current one in 200,000 to one in 300,000⁹⁴⁻⁹⁶—a degree of safety approaching that advocated for nonmedical industries (i.e., < 3.4 defects or errors/10⁶ products or events).⁹⁷ This improvement primarily resulted from a broad effort involving teamwork, practice guidelines, automation, simplification of procedures, and standardization of equipment and many functions. For instance, before the anesthesiologists' safety initiatives, design standards for anesthesia machines did not exist. As a result, it was not unusual to have one machine in which turning a valve in a given direction would increase gas flow and other machines in which turning it in the same direction would decrease flow; in fact, both types might be present in the same hospital. Equipment manufacturers subsequently worked together to standardize anesthesia equipment, and these kinds of arbitrary design variations are no longer seen.

The experience with safety efforts in anesthesiology underscores the importance of understanding the human-technology interface and the ergonomics of equipment design.⁹⁸ To improve patient safety, it is necessary to understand the devices and techniques employed, the ways in which individual persons use the technology, and the means by which these users interact with other aspects of the system.^{98,99} Similar considerations should be applied to innovative practices.¹⁰⁰

Another example is the recent high-profile application of procedural checklists. These checklists serve as the cornerstone of system-based interventions aimed at improving safety. A Michigan-wide collaborative targeting best practices around central line placement markedly reduced the morbidity and mortality associated with central lines in an intensive care setting.¹⁰¹ A surgical safety checklist implemented in eight international hospitals similarly was associated with a decrease in death and complications from nonpediatric surgical procedures.¹⁰² A number of different mechanisms may underlie the association between the checklists and improved outcomes, including better communication, less reliance on individual knowledge and memory, and increases

in situational awareness and a shared mental model; however, whatever the mechanism, the use of checklists, adopted from aviation, changes the system in which care is delivered and the behavior and interactions of the team and individual practitioners.

Another emerging success is the use of technological adjuncts in the tracking of surgical sponges. The traditional approach to preventing retained objects following surgery depends on several members of the surgical team manually counting every item that is introduced onto the sterile field and again at the end of the operation. These protocols have been shown to be labor intensive as well as unreliable.¹⁰³ Seventy to 88% of cases of retained surgical equipment are associated with a correct count.⁹ The recognition that manual counts will not be sufficient to completely ameliorate retained objects after surgery, making it a true “never event,” has led to the development of several technological solutions. Radio-frequency identification tags and bar codes are two examples of such solutions. A randomized, controlled trial suggests that bar-coding sponges can improve the ability to track sponges during an operation.¹⁰⁴

These examples of success are encouraging, but considerable obstacles to improving patient safety still exist. Specific obstacles include (1) a residual lack of awareness that a problem exists; (2) a traditional medical culture based on individual responsibility and blame (and shame); (3) a perceived vulnerability to legal discovery and liability; (4) primitive medical information systems; (5) the time and expense involved in defining and implementing evidence-based practice; (6) inadequate resources for quality improvement and error prevention; (7) the local nature of health care; and (8) the perception of a poor return on investment (i.e., the lack of a business case).¹⁰⁵ Although the need to redefine health care on the basis of value seems obvious, the current environment still appears to focus primarily on cost; value (i.e., quality per unit cost) is not part of the equation.¹⁰⁶

One hindrance to improving patient safety is the idea that traditional improvement methods are adequate to address the problem. The persistence of patient safety problems in the face of the ongoing use of these methods should be a sufficient argument for the inadequacy of existing approaches. For instance, morbidity and mortality (M & M) conferences are perhaps the most traditional venue for discussion of adverse events, but they often do not consider all complications, are not consistently well attended, do not categorize complications systematically, and often do not involve extensive debriefing.^{37,107-109} One study that compared NSQIP with traditional M & M conferences noted that the latter failed to consider about 50% of the deaths and about 75% of the

complications.¹¹⁰ Furthermore, M & M conferences tend to be intradepartmental and thus provide little opportunity for discussion of system problems that involve other departments (e.g., anesthesiology or nursing). M & M conferences also typically do not consider near misses (i.e., close calls), even though such events can identify important actual and potential system flaws. Finally, M & M conferences have a tradition of focusing on the actions of individuals rather than on the circumstances within which the individuals acted. This tradition serves to perpetuate a defensive attitude among trainees that is counterproductive. It is possible, however, that a more systematized review process could improve the value of the M & M conference.^{111,112}

Joint Commission accreditation of hospitals is based on analyses of safety and quality information (www.jointcommissionreport.org). However, it has been observed that the Joint Commission's accreditation program lacks the ability to identify many patient safety problems.¹¹³

Peer review organizations were originally intended as a mechanism for professional self-evaluation but subsequently became subject to anticompetitive abuse and other undesired consequences.¹¹⁴ The potential for inequity was a particular concern in that physicians who relinquished privileges on their own initiative might be treated more leniently than those against whom action was initiated by a peer review committee. Moreover, the data reviewed by peer review organizations were often legally discoverable, and this lack of anonymity and confidentiality tended to deter voluntary participation. Even when peer review organizations identified problems, they were often unable to implement solutions. Peer review organizations have now been largely supplanted by quality improvement organizations, although it is not yet clear whether the latter are substantially more effective.^{115,116}

Hospital incident reports have much the same shortcomings as the peer review process. They place limited emphasis on close calls and tend to lack systematic follow-up. Individuals also may be reluctant to file reports out of fear that their employment might be jeopardized or that the reported party might seek retribution.

The present professional liability system is particularly controversial with respect to whether it facilitates or hinders improvements in patient safety. This system has its basis in the traditional paradigm of surgical care (see below), which holds the individual surgeon accountable as the "captain of the ship." This paradigm has enabled many great achievements in surgical care, but it has also probably fostered a dangerous sense of infallibility. As a consequence, errors tend to be equated with negligence, and questions of professional liability tend to involve blaming individuals. Indeed, the very willingness of professionals to accept responsibility for their actions makes it convenient to focus more on individual errors than on collective ones²²; an individual surgeon is a more satisfactory target for the anger and grief of a patient or family than a faceless organization would be. This is certainly not to say that surgeons should avoid responsibility; rather, the point is that focusing on the errors of individual surgeons without addressing flaws in the underlying system does little to improve health care.

Another notable flaw in the liability process is that judgments of causality or fault are vulnerable to hindsight bias, which can skew experts' assessments of quality of care.

This tendency was illustrated by a study of anesthetic care in which differences in outcome significantly influenced the perception of negligence, even when the care provided was equivalent.¹¹⁷ Hindsight bias focuses too narrowly on adverse outcomes and pays insufficient attention to the processes of care. Yet another defect of the liability process is that it can be emotionally devastating for physicians (and their families),^{118–120} often adversely affecting their problem-solving abilities. To the extent that experience with or fear of a liability action deters efforts at quality improvement, it is counterproductive. Defensive medicine, with its attendant costs, adds very little value to health care.¹²¹

Many believe that major reform of the professional liability system is a prerequisite for achieving any significant improvements in quality. Undoubtedly, tort reform is highly desirable; however, the real prerequisite for improving identification and correction of system failures is the provision of increased protection for privileged discussion of such failures. The federal Patient Safety and Quality Improvement Act of 2005 (Public Law 109-41) was enacted for the purpose of improving patient safety by encouraging voluntary and confidential reporting of events that adversely affect patients. This act creates patient safety organizations whose goal is to collect, aggregate, and analyze confidential information reported by health care providers. It also calls for establishing a network of patient safety databases as an interactive, evidence-based management resource. The act limits the use of this information in criminal, civil, and administrative proceedings and includes provisions imposing monetary penalties for violations of confidentiality or privilege protections. The notion that a reduction in liability concerns may facilitate disclosure and discussion of mistakes is suggested by international comparisons of health care systems. In one study, patients in New Zealand, which has no-fault medical malpractice, were the most likely to report error discussions with their physicians.¹³

It is to be hoped that the tort reform movement and the patient safety movement can seek and find common ground.¹²² The improvements in patient safety achieved by anesthesiologists speak for the benefits of such an approach. Instead of pushing for laws to protect them against patients' lawsuits, anesthesiologists focused on improving patient safety. As a result, they pay less for malpractice insurance today, in constant dollars, than they did more than 20 years ago.¹²³

Even before the enactment of the Patient Safety Act, the view that open discussion of medical errors was appropriate appeared to be gaining adherents.²¹ Today, there is even more evidence that such open communication may reduce the likelihood of legal action and enhance public confidence in health care providers.^{124,125} Unfortunately, some hospitals persist in separating risk management from quality assurance issues, to the detriment of both.¹²⁶

The obvious need for liability reform notwithstanding, there are issues involved in enhancing safety and quality that are too complex to be addressed solely by changes in the liability system. Major safety and quality problems exist in nations where professional liability is not an issue; however, the higher rates of adverse events in these countries should not be taken as evidence of the benefits of the current US liability system. Physicians tend to act defensively even in a no-fault liability system. To minimize such defensiveness,

greater emphasis must be placed on measurement for improvement than on measurement for judgment.¹²⁷

Changing the Traditional Surgical Paradigm

Contemporary surgical practice requires that surgeons rethink the traditional paradigm of surgical practice (see above). The burgeoning growth of knowledge, the accompanying increase in specialization, the expanding role of technology, and the rising complexity of practice are making surgeons more and more dependent on persons or factors beyond their immediate control. As a result, surgeons are finding it more and more difficult even to appreciate, let alone manage, the larger context within which they provide care. The traditional surgical paradigm, despite its past successes, is no longer entirely adequate to the task now at hand [see Table 7].¹²⁸ Paradoxically, surgeons seeking to improve patient safety must acquire a deeper understanding of patient care systems at the very time when those systems are becoming increasingly difficult to understand.

To achieve the requisite understanding, it is necessary to have a reporting system that collects, tabulates, and analyzes data on the frequency and nature of both adverse events and near misses.¹²⁹ The primary function of a patient safety reporting system should be to identify both real and potential adverse consequences of latent flaws and make them visible to others. Once these real and potential adverse events are identified and made visible, the system can be redesigned so as to eliminate or minimize them.

A successful reporting system such as the highly successful Aviation Safety Reporting System (ASRS) is typically nonpunitive, confidential (and preferably anonymous), independent, timely, systems oriented, and responsive.^{22,88,130} In addition, it includes expert analysis, meaning that reports are evaluated by persons who understand the relevant circumstances and are trained to recognize underlying system-based causes. A successful reporting system usually also tabulates seemingly rare incidents (including near misses) even if there seems to be little direct or immediate benefit to doing so; in addition to their potential value in larger contexts, such analyses may help institutions predict and thereby avoid errors and system failures. The absence of a punitive focus reduces health care workers' concerns that reports might be used against them and thus minimizes underreporting.^{36,131,132} The concerns about the possible adverse consequences of a reporting system are quite strong—so much so that many

believe that a health care reporting system can succeed only if legal immunity is available.¹³³ The fear of being sued is widespread among physicians; however, the perceived risk of being sued is three times greater than the actual risk, and there is no good correlation between hospitals' claims ratings and their injury rates.⁷²

A mandatory, anonymous, confidential, and nondiscoverable reporting system has been instituted in the state of Pennsylvania. Founded in 2003, the Pennsylvania Patient Safety Reporting System, a statewide database maintained by the Pennsylvania Patient Safety Authority, collects over 200,000 annual reports of near miss and adverse events. (<http://patientsafetyauthority.org>). The events are evaluated, summarized, and analyzed to identify patterns that can be used to develop patient safety solutions and interventions.

Whether such reporting should be voluntary or mandatory is still a matter of debate. On the one hand, voluntary reporting has a high inaccuracy rate even when mandated by state or federal regulations. On the other hand, many surgeons believe that mandatory reporting may increase the pressure to conceal errors rather than analyze them; that it is unworkable in the current legal system; and that it may result not in constructive error-reducing solutions but merely in more punishment or censure.¹³⁴

Some argue that patient safety efforts should focus (at least initially) on medical injury rather than on medical errors.^{135,136} A focus on medical injury recognizes the difficulties of identifying medical errors and is based on a public health improvement model that has been useful in addressing other types of injuries; it also recognizes that most medical injuries are not caused by negligence. Such an approach may be more compatible with the current liability system and may help restore physicians' stature as patient advocates. Moreover, placing the initial focus on medical errors rather than injuries might divert attention from other system flaws, with the result that such flaws go uncorrected. Although, ultimately, a successful reporting system must focus both on errors and on injuries, an initial focus on injury may achieve greater initial buy-in from surgeons and may therefore be a more pragmatic first step. The issues associated with reporting errors or injuries must also be distinguished from those associated with reporting outcomes to the public. The latter type of report is currently being seen with increasing frequency, but it may have unintended consequences.¹³⁷

The complexities involved in understanding and improving health care systems make it likely that patients' expectations of improved safety may grow faster than they can be met.^{138,139} This potential disparity between expectations and performance may be further exacerbated by the likelihood that errors have been substantially underreported.¹⁴⁰ A reporting system that is punitive or not anonymous may discourage appropriate reporting of medical errors. Underreporting of adverse events is also more likely if side effects are delayed or unpredictable, if there is a longer survival or latency interval, or if a patient has been transferred from one facility to another. In addition, inadequate doses of drugs or anesthetics may not be reported if they cause no immediately evident injury.

Another challenge facing surgeons is how to incorporate current concepts of performance and error into undergraduate and residency education.¹⁴¹ The optimal basis for such education might be an objective-based curriculum that

Table 7 Contrasting Characteristics of Medical Practice in the 20th and 21st Centuries¹²⁹

20th century characteristics
Autonomy
Solo practice
Continuous learning
Infallibility
Knowledge
21st century characteristics
Teamwork/systems
Group practice
Continuous improvement
Multidisciplinary problem solving
Change

provides defined skills, rules, and knowledge.^{142,143} The blame-and-shame approach must be eliminated from both the educational setting and the practice atmosphere. If, instead, educators focus on making residents aware of their tendencies in the presence of uncertainty, residents (like pilots) may be able to develop better responses to underspecified situations. In addition, it is vital to monitor the residents to ensure that they learn to assess and address knowledge deficits, as well as acquire healthy and effective techniques for dealing with errors. Such monitoring will make the learning curve less painful for all concerned.¹⁴⁴

There is some question as to whether safety improvements are more likely to result from compliance with standards (i.e., individual performance) or from improvements in the system. Better training of individual physicians will certainly improve performance, but only so far. For substantial improvements in safety, it is probably necessary to make use of both approaches.¹⁴⁵ If every system is perfectly designed to achieve the results it gets, the obvious conclusion is that to obtain the desired results, it is necessary to change the system. Determining what form the new system should take is a critical step.^{106,146}

Conclusions

Reducing adverse events during the course of medical care is a dauntingly complex topic, and the progress made in reducing such errors has, in many cases, been disappointingly slow. Roughly a century ago, surgeons were called on to report their results, but over the intervening years, this call largely went unheeded.¹⁴⁷ It must be said, however, that at the beginning of the 20th century, the basic principles of human performance and error were not as well understood as they currently are, and the tools necessary for systems analysis did not exist. A further difference between then and now is the increase in public awareness of safety issues, as well as the potential consequences of this awareness.^{13,148} For instance, the growing concern about safety is changing the way in which patients select providers: there has been a

substantial increase in the percentage of patients who would choose a highly rated surgeon whom they had not seen before over a less highly rated surgeon whom they had seen before (www.ahrq.gov/qual/kffhigh00.htm). Improving patient safety thus becomes a matter of self-interest for the provider. It also may have a direct bearing on the maintenance of physicians' social contract with their patients.

The systems approach to improving patient safety is based on three principles: (1) human error, as an inherent aspect of human work, is unavoidable; (2) faulty systems allow human error to injure patients; and (3) systems can be designed that prevent or detect human error before such injuries occur.^{149,150} Support for a systems approach to patient safety will come from patients, purchasers from both the public and the private sector, professional societies, and specialty boards.¹⁵¹ It is crucial for all of these parties to acknowledge that most medical errors are attributable to system flaws rather than incompetence or neglect. It is also essential to recognize that the current systems of surgical care are shaped by the larger system within which all of these parties interact. This means that any worthwhile effort to improve such systems is likely to require substantial collaboration among the parties involved,¹⁵² as well as significant change in the larger system.

Medical errors have a substantial impact on 90-day costs and outcomes of surgical patients.¹⁵³ Moreover, there appears to be a business case for investing in patient safety.¹⁵⁴ Physicians, with their history of patient advocacy and scientific innovation, are in the best position to provide the leadership necessary for such changes.^{87,155} To restore the public's trust in the health care system, safety and quality must be made high priorities,¹⁵⁶ and transparency must be ensured.¹⁵⁷ If physicians do not take the opportunity to lead the movement to improve the safety and quality of care, they may anticipate further erosion of public trust and further loss of professional autonomy.

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Figure 1 Seward Hung

6 PREOPERATIVE TESTING, PLANNING, AND RISK STRATIFICATION

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In most circumstances in medicine, diagnosis precedes treatment. Consensus statements and regulatory guidelines endorse the long-hallowed practice of identifying patients at increased risk for complications. This is called “prognostic testing.” The implication is that the benefit of special risk reduction strategies should be confined to these patients. Most of the cardiovascular (and pulmonary) “screening” tests considered below are of the prognostic type only.

Much more useful than prognostic testing is predictive or directive testing, which means identifying patients who will benefit from a specified, available intervention. By definition, this discriminates a subset of “bad prognosis” patients who can be helped and thus requires the existence of a therapeutic intervention of demonstrated benefit. This often includes identifying those patients who are not too ill but not too well to benefit from the associated therapy.

Proof that a testing strategy is predictive, not merely prognostic, is best demonstrated by randomized trials comparing outcomes in groups receiving best conventional care with or without the proposed test. This is a high standard but has been met in situations such as screening mammography for breast cancer in women ages 50 to 70 and computed tomographic (CT) scans in closed-head injury.

In medicine and surgery, we like to think of ourselves as scientists who make decisions and perform procedures based on the results of studies and clinical trials that support our management strategies. Traditionally, we always obtain a clinical history and perform a physical examination. This interaction with our patients helps us focus and refine our therapies but, equally importantly, promotes the health literacy of our patients.¹ There is good evidence that patients who understand their disease and who participate actively in their therapy will fare better.¹

However, once we have finished talking with our patients, the data-driven support for the traditional model of preoperative testing begins to break down. We define a “routine test” as a test that we obtain on an asymptomatic, apparently healthy patient in the absence of any specific clinical indication.² Then we examine the frequency of abnormal routine test results, but it gets cloudier when we try to determine how often an abnormal test result changes our management. There is almost no information relating a test-driven alteration in management to any benefit in outcome. Intuitively, we do know that the more fragile the patient and the bigger the surgical procedure, the more likely it is that we should anticipate trouble.

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In addition to functional capacity and comorbid conditions, age is a robust determinant of operative risk, as is the type of operation. Vascular procedures and prolonged, complicated thoracic, abdominal, or head and neck procedures carry higher levels of risk. None of this is surprising.

The purposes of this chapter are as follows:

1. To explore the tools available to the surgeon for assessing patient vulnerability to operative stress
2. To examine the practical specifics of preoperative functional status testing
3. To analyze methods of quantifying surgical stress
4. To develop patient status and operative insult-specific indications for some “routine” preoperative tests
5. To suggest some strategies to reduce risk in specified groups of patients

Preoperative Laboratory Testing

There are at least 33 reasons why surgeons order preoperative laboratory tests; some are unique to teaching environments, and most are not clinically useful or relevant in the “otherwise healthy patient in the absence of a specific indicator.”³ There is poor correlation between the number of tests ordered and quality of care or physician competence, and the wide variation in test ordering suggests that some, or perhaps many, tests are ordered unnecessarily.⁴

As a corollary, surgeons order preoperative laboratory tests for fear of malpractice, for detection of an unsuspected disease, or because they “have always done it that way.” Note that detecting an unsuspected disease in the preoperative period is no different from screening for disease in a population, albeit a selected (preoperative) population.

Comprehensive literature reviews and government publications guiding reimbursement for preoperative testing (or lack thereof)^{2,5,6} lament the lack of Level I evidence to guide policy making, but most admit that the preponderance of nonrandomized clinical trial data demonstrates that preoperative testing is not clinically useful. Amazingly, this question has been studied formally for at least 50 years (yes, half a century), with the following strikingly similar conclusions. Preoperative laboratory testing

1. Has no clinical value for asymptomatic healthy individuals, in the absence of a specific clinical indication, such as a diuretic
2. Has only marginal value for those with known disease
3. Will yield abnormal results for 1 to 2% of all test results
4. Yields results that would have been predicted from the underlying patient diseases
5. Does not change treatment when abnormal results are obtained
6. Yields abnormal results that are often ignored by the ordering physician
7. Allows considerable unrealized cost savings derived from not performing these preoperative tests

So let us chronologically recapitulate selected studies chosen to demonstrate the evolution of this issue through the lenses of multiple medical specialties. In 1965, pathologists Bold and Corrin published their study titled "Use and Abuse of Clinical Chemistry in Surgery."⁷ This study was performed in the early days of clinical pathology, before automated analyzers were commercially available. One hundred fifty of 344 (44%) tests were preoperative tests of "urea and electrolytes and metabolic abnormalities in patients with renal calculi." Almost all of the preoperative test results were within accepted reference ranges and were euphemistically termed "useful negative" results. This study pioneered the acquisition of nonuseful preoperative laboratory data.

Automated clinical laboratory testing became widely available in the late 1960s, exponentially increasing the opportunity for unnecessary laboratory testing. In the early 1980s, several groups assessed preoperative laboratory testing (they termed it "screening") for 2,000 patients. Many tests were ordered "by protocol," including complete blood count (CBC), white blood cell (WBC) differential, prothrombin time (PT), partial thromboplastin time (PTT), platelet count, "six-factor automated multiple analysis" (sodium, potassium, chloride, total carbon dioxide content, serum urea nitrogen, creatinine), and glucose. Of 2,785 routine preoperative admission tests, the authors concluded that approximately 60% were "unindicated" (i.e., the patient lacked a recognizable clinical indication for testing). Four results (0.22%) were substantially significant so as to affect anesthetic or surgical management, yet there was no documentation that care management was altered based on these abnormal laboratory results. Furthermore, there was no documentation by physicians of further exploration of these abnormal results, presumably raising (rather than limiting) issues of legal liability for the ordering physician. The authors concluded that preoperative testing should be performed only for patients with an identified disease or for whom the surgical procedure would be altered based on the result. They extrapolated that approximately 9,000 tests annually could have been avoided, resulting in approximately \$147,000 decreased charges and a cost savings of \$95,800 (1985 dollar value).

Physicians and surgeons are perhaps guilty of a certain amount of intellectual inertia as similar studies paradoxically concluded that preoperative testing was "useful" even when the authors acknowledged that test abnormalities provoked no clinical consequences. A consistent finding was a 1 to 2% incidence of abnormal results, a lack of clinical consequences, and an absence of physician response to the abnormal laboratory tests.

Anesthesiologists have been the first discipline to substantively engage in the debate. When managed care capitation was introduced and cost containment became critical to the survival and success of health care organizations, anesthesiologists were the first group to responsibly respond. Allison and Bromley assessed the clinical usefulness of preoperative testing in 60 randomly selected veterans prior to ambulatory surgery.⁸ They concluded that two thirds of testing was inappropriate and estimated the unnecessary costs at \$47 for a veteran and \$80 for a community hospital patient (1996 dollar value), with potential savings of \$11,757

for their Veterans Affairs Medical Center alone. They concluded that preoperative testing limited exclusively to those patients with clinical indications would have no effect on the quality or safety of care.

In a similar study of 520 patients undergoing elective general, vascular, thoracic, and head and neck surgery, preoperative tests included electrolytes, blood urea nitrogen (BUN), creatinine, glucose, hemoglobin/hematocrit, total protein, albumin, total lymphocyte count, PT, PTT, platelet count, urinalysis, electrocardiography (ECG), and chest radiography.⁹ Age, gender, and specific concomitant illnesses were associated with predictably abnormal laboratory tests. Routine preoperative laboratory testing was identified as "neither useful nor cost-effective." Perhaps in response to this wave of data, preoperative testing practice at four institutions over 8 years and for only four surgical procedures was examined. Although wide variations from "operation to operation, test to test and institution to institution," were unexpectedly identified, an approximately 20% decrease in both unnecessary and medically indicated testing was achieved. For the unnecessary tests alone, the authors extrapolated to the entire United States and estimated an approximately \$320 million annual savings.

The obvious question is what happens to patients who do not enjoy the safety of preoperative laboratory testing? Narr and colleagues reviewed the outcomes of 1,044 randomly selected patients from 5,120 patients who had no laboratory tests performed within 90 days before a surgical procedure.⁹ Ninety-seven percent of the patients were "relatively healthy." Zero deaths or major perioperative complications resulted. Furthermore, this group observed that no laboratory test performed intra- or postoperatively changed surgical or medical management "substantially." They concluded that patients who, following a history and physical examination, are "determined to have no preoperative indication for laboratory tests can safely undergo anesthesia and operation with tests obtained only as indicated intra- and postoperatively."

In 1995, laboratory medicine, surgery, and anesthesia practitioners collaborated to develop laboratory testing guidelines before admission for elective surgery.¹⁰ Testing guidelines were developed and categorized into four major groups, as well as by age and gender. The surgeons then agreed to delegate test ordering to nurses and anesthesiologists who evaluated the patients before surgery. Volume and appropriateness of ordered tests were compared before and after guideline adoption. They observed a 67% reduction in the overall number of tests ordered per patient for the first 2 years after guideline implementation, with an improvement in the appropriateness of test ordering (65% were considered "appropriate" prior to guideline implementation and 81 to 86% postimplementation). They noted marked fiscal savings related to this performance improvement initiative, quantified as \$66,981 in year 1 and \$75,995 in year 2.

In the late 1990s, anesthesiologists Vogt and Henson conducted a prospective, cross-sectional study in a university hospital, studying 312 consecutive patients scheduled for elective surgery and evaluated by an anesthesiologist in a preoperative clinic.¹¹ **The goal of the study was to determine if there was a difference in the ordering of "unindicated**

preoperative laboratory tests" for healthy (American Society of Anesthesiologists [ASA] physical status I and II) versus sicker (ASA physical status III) patients. The anesthesiologists evaluated the test ordering by surgeons relative to ASA status and concluded that 72.5% of tests ordered by surgeons were considered not indicated by the anesthesiologists. Although there were fewer "unindicated" tests with worsening ASA status, the overall conclusion was that a large proportion of surgeon-ordered preoperative tests were unnecessary. By eliminating unnecessary testing, they estimated an annual cost savings of \$80,000 (1997 dollars).

In 2002, the ASA Task Force on Preanesthesia published its review and practice advisory.⁵ Regarding laboratory tests, a clear distinction was made between "routine" and "selective" preoperative tests. Routine tests were defined as those intended to discover a disease or disorder in an asymptomatic individual. The task force bluntly stated that routine tests "do not make an important contribution to the process of perioperative assessment and management of the patient by the anesthesiologist." In contrast, the task force recommended performing selective tests, that is, those tests medically indicated because of the history and physical findings, medical record review, and type of invasiveness of the planned procedure and anesthetic, because their results "may assist the anesthesiologist in making decisions about the process of perioperative assessment and management."⁵ Clinical studies are very hard to do, and it is easy to criticize them. Perhaps these studies were performed in settings where timely treatment of chronic diseases was available, allowing maximal optimization of patients prior to elective surgery. The recommendations of a conscientious task force are difficult to ignore, however. So what happens to surgical patients in developing countries where no chronic disease management is available?

Pal and colleagues retrospectively studied the benefit of preoperative testing in 216 asymptomatic healthy surgical patients in Pakistan.¹² Their findings were strikingly similar to those of previous studies; the most common preoperative laboratory abnormality was a low hemoglobin in 42 of 216 (19%) patients, almost all females. Chest x-ray abnormalities were the next most common abnormality, present in 11 of 103 (10.6%) patients, followed by mild hypokalemia in 6 of 123 (4.8%) patients and an elevated glucose in 1 of 113 (0.88%) patients. Aside from a single preoperative intervention for a patient with a preoperative hemoglobin of 4.8 g/dL, treatment plans or outcomes were not affected. The authors concluded that the history and physical examination were the most reliable and cost-effective preoperative screening tools available. They endorsed the existing ASA guidelines for class I (asymptomatic healthy) patients, that is, no preoperative testing is recommended.

In 2003, the general medicine and primary care practitioners entered the debate. Smetana and Macpherson reviewed the published literature on preoperative testing and concluded that "almost all 'routine' laboratory tests before surgery have limited clinical value."¹³ Based on their review, they recommended the following:

- "Clinicians should order tests only if the outcome of an abnormal test will influence management."
- "When an abnormal test results from such testing, it is critical that physicians document their thinking about the result."

- "Physicians should not be criticized for selective test ordering before surgery."
- "Physicians and institutions recommending routine preoperative testing for all patients provide no clinical value to their patients at considerable cost."

A subset of studies have noted specific abnormal laboratory results related to age, gender, and concomitant underlying illnesses. The latter, selective testing for concomitant underlying illnesses, is accepted practice for routine medical care regardless of anticipated surgery. The common theme appears to be that if the physician would request a test in the absence of anticipated surgery, the test is also warranted prior to surgery. Extremes of age and gender do keep reappearing as potential independent predictors of trouble.

AGE

Dzankic and colleagues assessed the importance of preoperative laboratory testing in 544 patients 70 years and older undergoing noncardiac surgery.¹⁴ They observed that 0.5 to 5% had electrolyte and platelet count abnormalities, 12% had elevated serum creatinine (> 1.5 mg/dL), 10% had hemoglobin less than 10 g/dL, and 7% had serum glucose greater than 200 mg/dL. None of these abnormalities were predictive of postoperative adverse outcomes. The ASA classification and surgical risk were stronger univariate predictors for adverse outcome than abnormal serum electrolyte or creatinine values, and only the ASA classification and surgical risk by multivariate logistic regression were predictive of postoperative adverse outcomes. The authors concluded that age alone was not sufficient justification for routine preoperative laboratory testing and recommended using the history and physical examination to guide preoperative testing.

Ophthalmologists Schein and colleagues conducted a landmark study of 9,408 patients aged 80 years and older who underwent 9,626 cataract surgeries without preoperative testing, compared with 9,411 patients undergoing 9,624 operations who had routine preoperative laboratory testing.¹⁵ They found no difference between groups relative to intraoperative or postoperative events. Routine preoperative testing offered no benefit over that attained from ASA classification and medical history. They concluded that routine preoperative testing before cataract surgery did not measurably increase the safety of surgery.

Schein and colleagues noted that cataract surgery was the most commonly performed operation in elderly people in developed countries, with 1.5 million cataract operations in 1996.¹⁵ From their study, it was estimated that the cost of routine preoperative testing prior to cataract surgery exceeded \$150 million annually and, given the lack of benefit from testing, suggested that these costs could be saved without a negative effect on patient outcome.

The screening value of preoperative laboratory findings in children is the same as that for adults: not clinically useful for healthy children presenting for minor elective surgery. Burk and colleagues encouraged preoperative coagulation testing to identify rare, undiagnosed congenital or hereditary bleeding disorders in children prior to tonsillectomy.¹⁶ This value, however, was clearly offset by the rarity of the disorders coupled with the high frequency of false positive bleeding histories and laboratory tests.

GENDER

A relatively common finding in many preoperative testing studies was anemia in women of childbearing age. This is the only gender-specific “abnormality” reported and would support preoperative inquiry if the clinical presentation would prompt the clinician to respond to an abnormal result.

Several decades ago, a group at the Mayo Clinic began to realize that subjecting patients to large numbers of preoperative tests did not change surgical results.^{17,18} They further observed that when preoperative testing returned an abnormal result, they rarely did anything differently anyway¹⁷ [see Table 1 and Table 2].

In summary, the overwhelming majority of studies have concluded that there is little to no value of screening preoperative laboratory tests in asymptomatic patients in the absence of a specific clinical indication [see Table 3]. Laboratory tests within 6 months of surgery to gauge surgical and anesthesia risk are acceptable if the patient’s condition has not changed clinically in the intervening period. Conversely, if the patient’s condition has changed, laboratory

Table 1 Effect of Abnormal Screening Results on Physician Behavior ¹⁸		
Screening Test	% Abnormal Test Results	% Resulting in Management Change
Bleeding time	3.8	Abnormal result rarely led to change
Chest x-ray	2.5–3.7	2.1
Coagulation time	4.8	Abnormal result rarely led to change
Electrocardiogram	4.6–31.7	0–2.2
Hemoglobin	5 (for < 10 g/dL; < 9 g/dL was rare)	Abnormal result rarely led to change
Partial thrombo-plastin time	15.6	Abnormal result rarely led to change
Total leukocyte count	< 1	Abnormal result rarely led to change
Urinalysis	1–34.1	0.1–2.8

Table 2 Minimum Preoperative Test Requirements at the Mayo Clinic (in 1993) ¹⁷	
Age (yr)	Tests Required
< 40	None
40–59	Electrocardiography, measurement of creatinine, measurement of glucose
≥ 60	Chest x-ray, complete blood cell count, electrocardiography, measurement of creatinine, measurement of glucose

In addition, the following guidelines apply: (1) a complete blood cell count is indicated in all patients who undergo blood typing and are crossmatched; (2) measurement of potassium is indicated in patients taking diuretics or undergoing bowel preparation; (3) a chest x-ray is indicated in patients with a history of cardiac or pulmonary disease or with recent respiratory symptoms; and (4) spirometry (forced vital capacity) is indicated in patients 40 years of age or older who have a history of cigarette smoking and are scheduled for an upper abdominal or thoracic procedure.

Table 3 American Society of Anesthesiologists' Physical Status Classification ⁵		
Classification	Description	Examples
Class I	Healthy patient with no systemic disorder	
Class II	Mild to moderate systemic disorder that need not be associated with the surgical problem	Chronic obstructive pulmonary disease Diet-controlled diabetes Extremes of age Medication-controlled hypertension Moderate obesity
Class III	Severe systemic disease that limits activity but is not incapacitating	Insulin-dependent diabetes Lifestyle-limiting pulmonary insufficiency Morbid obesity Stress-induced angina
Class IV	Incapacitating, life-threatening systemic disease	Active cardiac ischemia Advanced hepatic, pulmonary, or renal disease Refractory arrhythmia Signs of congestive heart failure Unstable angina
Class V	Moribund patient, not expected to survive 24 hours without an operation	Major cerebral trauma with increasing intracranial pressure Major trauma with shock Massive pulmonary embolus Ruptured aortic aneurysm with profound shock

testing is medically indicated as specifically dictated by the change in clinical condition.^{2,5,6,13}

A color-coded “at a glance” guide modeled on traffic signals (green = consensus to do a test; red = consensus not to do a test; amber = absence of consensus, “consider testing”) has been prepared to guide busy practitioners regarding when to order what preoperative test [see Figure 1]⁶; other similar guides abound [see Figure 2¹⁹ and Table 4]. Audits²⁰ of current preoperative laboratory testing practices will remain scrutinized by conscientious investigators, but professional guidelines consistently reveal persistent unnecessary preoperative testing.²¹

Changing Paradigms of Surgical Success

It is now clear that postoperative survival by itself is no longer an adequate assay of surgical success. Risk must be stratified before operation, and the degree of risk must be evaluated in light of both the quantity and the quality of postoperative life. Cost must then be judiciously assessed relative to a risk-stratified, quality-adjusted postoperative year of life. In 2008, Cohen and colleagues published an assessment of health economics.²² These authors calculated the cost-effectiveness ratio by dividing the incremental costs

ASA/Surgery	CXR	ECG	CBC	Lytes	BUN/Cr	Glucose	LFTs	PT/PTT	UA
ASA = 1	< 1 y/o	Red	Red	Red	Red	Red	Red	Red	Red
	1–60 y/o	Red	Red	Red	Red	Red	Red	Red	Red
	60–80 y/o	Red	Yellow	Green	Yellow	Red	Red	Red	Red
	> 80 y/o	Red	Green	Green	Green	Green	Red	Red	Red
ASA = 2	< 1 y/o	Red	Red	Red	Red	Red	Red	Red	Red
	1–60 y/o	Red	Red	Red	Red	Red	Red	Red	Red
	60–80 y/o	Red	Yellow	Green	Yellow	Red	Red	Red	Red
	> 80 y/o	Red	Green	Green	Green	Green	Red	Red	Red
ASA = 3	< 1 y/o	Red	Red	Yellow	Red	Red	Red	Red	Red
	1–60 y/o	Red	Red	Yellow	Yellow	Red	Red	Red	Red
	60–80 y/o	Yellow	Yellow	Green	Green	Red	Red	Red	Red
	> 80 y/o	Yellow	Green	Green	Green	Green	Yellow	Red	Red
ASA = 4	< 1 y/o	Red	Red	Green	Yellow	Red	Red	Red	Red
	1–60 y/o	Red	Red	Green	Yellow	Red	Yellow	Red	Red
	60–80 y/o	Yellow	Green	Green	Green	Yellow	Yellow	Red	Red
	> 80 y/o	Yellow	Green	Green	Green	Green	Yellow	Red	Red
Neurosurgery	< 1 y/o	Red	Red	Red	Red	Red	Red	Green	Yellow
	1–60 y/o	Red	Yellow	Yellow	Green	Red	Red	Green	Yellow
	60–80 y/o	Yellow	Yellow	Green	Green	Red	Red	Green	Green
	> 80 y/o	Yellow	Green	Green	Green	Red	Red	Green	Green
Cardiovascular	< 1 y/o	Green	Green	Green	Green	Green	Red	Green	Yellow
	1–60 y/o	Green	Green	Green	Green	Green	Red	Green	Green
	60–80 y/o	Green	Green	Green	Green	Green	Yellow	Green	Green
	> 80 y/o	Green	Green	Green	Green	Green	Yellow	Green	Green

Figure 1 Appropriate preoperative tests related to the patient's American Society of Anesthesiology (ASA) classification and age. *Red* indicates that the preponderance of evidence suggests that the test will not be useful (or positively influence patient care); *yellow* indicates that the test is controversial; *green* indicates that the test is useful. BUN = blood urea nitrogen; CBC = complete blood count; Cr = creatinine; CXR = chest x-ray; ECG = electrocardiogram; LFT = liver function test; PT = prothrombin time; PTT = partial thromboplastin time; UA = urinalysis; y/o = years old.

of surgical therapy by incremental benefits as quality-adjusted year of life (QALY), compared with standard medical care. They reported that cochlear implants for profoundly deaf children reduced lifetime aggregate costs and improved health; liver transplantation for primary sclerosing cholangitis cost \$41,000/QALY; implantation of cardioverter-defibrillators in patients with left ventricular dysfunction cost \$52,000/QALY, and surgery in 70-year-old men with a new diagnosis of prostate cancer increased costs and compromised health compared with watchful waiting.²² Thus, the purposes of this section are to add "dollar cost" and postoperative quality of life to the preoperative risk assessment equations. We also propose to describe the potential preoperative cardiac, pulmonary, and laboratory tests; analyze the significance of abnormal results; and ultimately develop a strategy for relating patient characteristics and the magnitude of the procedure to the menu of preoperative studies.

Although no one ever truly wants to undergo a surgical procedure, the results of surgery can be formidably gratifying to both patient and surgeon when the right operation is performed accurately, expeditiously, and for the right reasons, on the right patient at the right time. In attempting to bring about this state of affairs, surgeons must consciously and honestly balance the physiologic, psychological, social, and financial burdens of surgery against the anticipated benefits.²³ Although surgeons are not the only medical

professionals who must perform this kind of balancing act, we are the ones who do it most conspicuously.

Continuing refinement of the methods employed to stratify preoperative risks permits surgeons to "handicap" both patients and surgical procedures with greater precision. Outcome assessment must clearly incorporate the "sickness quotient," which is typically expressed in terms of the ratio of observed to expected outcome (O/E), into the assessment of therapeutic value. If a surgeon were to operate only on Olympic athletes with single-organ diseases (or no disease at all), his or her patients would likely do very well. Those of us who must operate on a more diverse patient population will have less gratifying results.

The most widely used risk classification system was developed by the ASA and is based on the patient's functional status and comorbid conditions (e.g., diabetes mellitus, peripheral vascular disease, renal dysfunction, and/or chronic pulmonary disease) [see Table 3].²⁴ The ASA index generally associates poorer overall health with increased postoperative complications, longer hospital stays, and higher mortality.

In addition to functional capacity and comorbid conditions, age is a robust determinant of operative risk, as is the type of operation. Vascular procedures and prolonged, complicated thoracic, abdominal, or head and neck procedures carry higher levels of risk. None of this is surprising.

ASA/Surgery		TESTS							Rx	
		Frailty "Eyeball" Test	Medical Consult	Cardiology Consult	Resting ECG	2–3 Flights Stairs	ETT	MUGA	PFTs	Beta Blockers
ASA = 1	< 1 y/o									
	1–60 y/o									
	60–80 y/o									
	> 80 y/o									
ASA = 2	< 1 y/o									
	1–60 y/o									
	60–80 y/o									
	> 80 y/o									
ASA = 3	< 1 y/o									
	1–60 y/o									
	60–80 y/o									
	> 80 y/o									
ASA = 4	< 1 y/o									
	1–60 y/o									
	60–80 y/o									
	> 80 y/o									
Neurosurgery	< 1 y/o									
	1–60 y/o									
	60–80 y/o									
	> 80 y/o									
Cardiovascular	< 1 y/o									
	1–60 y/o									
	60–80 y/o									
	> 80 y/o									

Figure 2 Preoperative assessment strategies and recommended risk-reducing therapy relative to American Society of Anesthesiologists (ASA) classification performed by the surgeon and age. *Red* indicates that the preponderance of evidence suggests that the strategy or therapy will not be useful (or positively influence patient care); *yellow* indicates that it will be controversial; *green* indicates that it will be useful. Each discipline has its own quasibjective test for perceived patient fortitude. The anesthesiologists term it the ASA classification; surgeons use the frailty index or the “eyeball” test. Nutritionists refer to the subjective global assessment, whereas oncologists rely on Karnofsky scoring. In each instance, the subjective “eyeball” impression of a seasoned clinician has traditionally proven to be gratifyingly valuable. ECG = electrocardiogram; ETT = exercise tolerance testing; MUGA = multigated acquisition; PFT = pulmonary function test; y/o = years old.

WHAT TO LOOK FOR IN THE PATIENT’S HISTORY

We all deteriorate as we age. In fact, the Mayo Clinic uses age alone as the initial filter in its selection of preoperative tests for “healthy” patients. The anesthesiologists refine this ASA policy by defining the “health” of the patient [see Table 3], which requires a search for comorbid disease. The diseases and other indicators that seem to count most are those that reflect cardiovascular compromise: angina, a past myocardial infarction, and surrogates for coronary artery disease, such as diabetes, hypertension, obesity, and advanced age. Nothing else seems to have much effect. Goldman and colleagues first reported this observation in 1977.²⁵ They followed 1,001 patients through a major surgical procedure and related their preoperative history, physical findings, and routine laboratory work to major complications: perioperative myocardial infarction, cardiogenic pulmonary edema, ventricular tachycardia/fibrillation, and death. They then applied univariate analysis to ascribe varying numbers of points to each preoperative factor that predicted postoperative problems. *All of the ominous preoperative signals were those that reflected cardiovascular disease: recent myocardial infarction (10 points),*

congestive heart failure (11 points), any nonsinus cardiac rhythm (7 points), and advanced age (5 points). These cardiac risk factors were assigned high numbers of points, although, perhaps surprisingly, no other warning signs received more than three—not even carbon dioxide tension (Pco₂) greater than 50 mm Hg, BUN greater than 50 mg/dL, bicarbonate less than 20 mM/L, or potassium less than 3.0 mM/L. Liver function tests were so insensitive that they were deemed insignificant. In 1995, Mangano and Goldman repeated this study and reported the same conclusions.²⁶

Many risk stratification systems refer to “otherwise healthy patients.” The term “healthy patient” should be translated as “asymptomatic patient.” When you are taking the patient’s history, you should focus on probing for the indicators of cardiac disease.

INDICATORS OF CARDIAC RISK

In a successful attempt to simplify Goldman and colleagues’ equation, Boersma and colleagues refined the Lee and colleagues Revised Cardiac Risk Index (RCRI), which is currently the most widely applied cardiac risk stratification system.^{27,28} The RCRI identifies six predictors of major

Table 4 Preoperative Assessment Strategies Related to Purposes and Potential Information Derived

<i>Assessment Strategy</i>	<i>Information Derived</i>	<i>Purpose(s)</i>	<i>Indication/Comments</i>
Medical consultation	Assessment of chronic disease	To stabilize chronic disease	ASA classes III and IV (not typically useful in ASA I, II, or V)
Cardiac clearance	Assessment of chronic cardiac disease	To stabilize chronic cardiopulmonary disease	ASA classes III and IV (not typically useful in ASA I, II, or V)
Frailty (“eyeball”) test	Global assessment of surgical risk/benefit	Practical guide to surgical risk/benefit	Useful in assessing necessity/benefits of surgical intervention
Resting ECG	(1) Cardiac rhythm; (2) may reflect prior muscle damage (Q waves)	To determine resting cardiac rhythm	Disappointing indicator of cardiac status
Climbing 2–3 flights of stairs	Practical indicator of strength and cardiopulmonary status	Subjective indicator of cardiopulmonary status	Useful indicator of cardiopulmonary status in sorting out ASA class III patients
Exercise tolerance test	Quantitative indicator of cardiopulmonary status	Objective indicator of cardiopulmonary status	Useful if results might lead to cardiac intervention in the absence of proposed elective general surgery
Multigated acquisition (MUGA) scan	Ejection fraction	To assess ventricular function	Low yield in ASA class I, II, and III patients
Pulmonary function tests (PFTs)	Pulmonary status	To assess medical reversibility of lung dysfunction	Valuable in discriminating patients with equivocal 2–3 flights of stairs climbing test

ASA = American Society of Anesthesiologists; ECG = electrocardiogram.

cardiac complications (high risk surgical procedures, ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, insulin use and a creatinine greater than 2.0 mg/dL). Scores range from 0 to 5, and the likelihood of major perioperative complications increases with rising scores [see Table 5].^{25,26} This index has weaknesses. It was derived from calculations that excluded emergency surgical patients and neurosurgical patients, whereas thoracic, vascular, and orthopedic patients were overrepresented. In addition, it classified surgical procedures simplistically into two categories: high risk and non-high risk. Despite these weaknesses, the predictive accuracy of the RCRI has been validated in large cohorts.²⁷

Whereas the RCRI documents cardiac risk factors, the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force guidelines (see below) were developed to serve as a national quality initiative for use of the RCRI and optimization of perioperative risk by medical or, rarely, surgical means. The goal of a preoperative cardiac consultation is to determine the most appropriate testing and treatment strategies for optimizing patient care while avoiding unnecessary testing. This represents a definite paradigm shift from the stratification and revascularization strategies commonly employed only a decade ago.

Interestingly, these guidelines are not always followed in clinical practice. One survey found that despite the availability of the guidelines, 40% of cardiology consultations resulted in the simple recommendation to proceed with surgery, without modification of perioperative plans or optimization of risk factors.²⁹ Patients selected for noninvasive testing do appear to receive more medical therapy (e.g., beta blockers, statins, and platelet inhibitors) than patients who are not referred for further cardiac evaluation.

ACC/AHA TASK FORCE GUIDELINES

Routine preoperative cardiac evaluation and testing suffer significant inherent limitations. The ACC and the AHA have

combined task forces to clarify current recommendations for national quality initiatives in perioperative stratification and risk modification.³⁰ Their strategy bases diagnostic and therapeutic approaches on clinical screening for disease state and functional capacity. Specialized testing is conservatively employed only when additional information provided by the proposed test is likely to impact the outcome. The ACC/AHA consensus guidelines recommend aggressive medical management to provide myocardial protection in the perioperative period to mitigate cardiac risk. This strategy has proven to be both efficient and cost-effective in vascular surgery patients. The most recent update of these guidelines was published in late 2007.³⁰

The ACC/AHA guidelines employ a five-step algorithm designed to guide patient risk stratification and subsequently determine appropriate cardiac evaluation. This algorithm is available on the ACC website (<http://www.acc.org/clinical/guidelines/perio/update/fig1.htm>).

Step 1 involves assessing the urgency of the operation. Step 2 is the process of looking for active cardiac conditions, including unstable coronary syndromes, decompensated heart failure, significant dysrhythmias, and severe valvular disease. If any of these conditions are present and the operation is elective, the patient should be evaluated further and treated according to ACC/AHA guidelines. Step 3 is activated when no active cardiac condition is present and the proposed operation is low risk. In this instance, the surgeon may proceed without further intervention. Step 4 includes operations that are deemed to be of intermediate to high risk. The patient's functional status must be determined [see Table 6]. If the patient is asymptomatic and functional status is good, the planned operation may proceed without further intervention. If the patient is symptomatic or functional status is undetermined or poor (defined as the inability to perform activities involving energy expenditure greater than 4 metabolic equivalents [METs]), further investigation is

Table 5 Revised Cardiac Risk Index²⁶

No. of Risk Factors	Risk of Major Cardiac Complications (%)
0	0.4
1	0.9
2	7.0
3+	11.0

There are six clinical risk factors: (1) high-risk surgery; (2) ischemic heart disease (myocardial infarction, positive treadmill test, use of nitroglycerin, current chest pain, pathologic Q waves on electrocardiogram); (3) congestive heart failure (documented history, pulmonary edema, paroxysmal nocturnal dyspnea, S₃ or chest x-ray with pulmonary vascular redistribution); (4) cerebrovascular disease (transient ischemic attack or cerebrovascular accident); (5) insulin-dependent diabetes mellitus; and (6) renal failure (progressive serum creatinine > 2.0 mg/dL).

necessary. In step 5, the final step, the surgeon searches for major clinical predictors of specific cardiac risk. As defined by the ACC/AHA Task Force, clinical cardiac risk factors include a history of ischemic heart disease, compensated or previous heart failure, cerebrovascular disease, diabetes mellitus, and/or renal insufficiency.³⁰ Patients with no history of clinical risk factors may proceed to surgery. Patients with one or two clinical risk factors who are undergoing a vascular procedure or patients with one or more clinical risk factors who are undergoing an intermediate-risk operation have the option of either proceeding with surgery after appropriate beta blockade or receiving additional evaluation,

but only if the results might change management. Patients with three or more clinical risk factors who are undergoing a vascular procedure should receive further evaluation, but, again, only if the results might change management.

Identification of Factors Affecting Cardiac Risk

Heart failure is the most common discharge diagnosis in hospitals across the United States. The prevalence of heart failure increases with age, and as our surgical population ages, we treat more and more elderly patients with relevant degrees of heart failure.

Numerous cardiac risk indices have been created over the past three decades. During that period, risk stratification has evolved from the early Goldman and colleagues criteria, the first substantial effort at risk assessment, to the RCRI developed by Lee and colleagues²⁷ [see Table 5]. A review of the initial and updated multivariate analysis of risk predictors prior to noncardiac surgery attributes the lion's share of risk to the cardiovascular system.^{25,26} If your patient suffers a major perioperative complication (myocardial infarction, cardiogenic pulmonary edema, sustained ventricular tachycardia/fibrillation, or death), the only organ system that appears to matter much is the heart.

To reiterate, Mangano and Goldman ascribe 11 points to any preoperative evidence of congestive heart failure, 10 points to a myocardial infarction within the last 6 months, 7 points to any ECG rhythm other than sinus rhythm, and

Table 6 Approximate Metabolic Equivalents and Peak Oxygen Intake Related to Common Daily Activities and Stages of the Bruce Protocol (Modified Duke Activity Status Index)

Activities: "Are you able to..."	Metabolic Equivalents (METs)	Peak Oxygen Intake* (mL/kg/min)	Bruce Protocol Correlates		
			Stage	% Grade	mph
Lie in bed with minimal movement (bedridden)?	≈ 1.00	< 10	NA [†]	NA [†]	NA [†]
Sit up in bed independently?	1.25				
Walk around the house?	1.75	10–15	1	10	1.7
Take care of yourself (toilet, feed, bathe, and clothe yourself?)	2.75				
Do light housework, such as washing dishes?	2.75				
Walk two blocks at ground level?	3.00	15–20			
Do moderate housework, such as vacuuming/sweeping floors?	3.50				
Do yard work, such as raking leaves?	4.50	20–25	2	12	2.5
Have sexual relations?	5.25				
Walk up a hill or climb two or three flights of stairs?	6.00				
Participate in moderate recreational activities such as swimming, golf, or slow dancing?	6.00	> 25	3	14	3.4
Do heavy housework such as lifting or moving heavy furniture?	8.00				
Run a short distance?	10.00		4	16	4.2
Participate in strenuous sports such as volleyball or basketball, run on a treadmill, or use an elliptical machine?	12.00				
Run a long distance?	12.00+				

NA = not applicable.

*Estimates of peak oxygen uptake are based on comparison data obtained from various levels of an exercise cardiac stress test (i.e., the Bruce protocol). These numbers vary by age and gender and hence represent estimates for women and men of differing ages.

[†]Bedridden patients are unable to participate in exercise stress testing. Hence, no data are available for this group in regard to Bruce protocol staging.

A physician may assess functional status as part of a preoperative checklist, but the patient usually provides only a snapshot of his or her most recent activities. Activity levels are not static but, rather, dynamic. Indeed, exercise tolerance can be gained over time with work ("training"). If patients are able to climb the ladder of activity status and tolerate more vigorous exercise, this is the ultimate cardiac stress test. Hence, increasing exercise in patients ("training") is a constructive preoperative formula.

5 points to age greater than 70 years of age (a surrogate for coronary disease).^{25,26} No other indices (including a PCO_2 greater than 50 mm Hg or a creatinine level greater than 3.0 mg/dL) warrant more than 3 points. So a seemingly innocuous sigmoid resection (abdominal surgery = 3 points) in a 70-year-old gentleman (5 points) in atrial fibrillation (7 points, and 20% of septuagenarians exhibit atrial fibrillation) who suffered just a “little” heart attack 3 months ago (10 points) climbs into the highest risk category with 26 total points. In the Goldman and colleagues and Mangano and Goldman studies, class IV risk (patients scoring more than 25 points) suffered a 26% chance of major complications such as ventricular tachycardia or ventricular fibrillation or death.^{25,26}

Now—15 to 30 years later—we may be doing a little better, but the cardiovascular system remains the culprit. The purposes of this section are to review the various tests of cardiovascular function and to develop a practical and safe algorithm for preoperative cardiac evaluation. There are no surprises here. The bigger the operation, the higher the cardiac risk; the older the patient, the riskier the outcome is likely to be. Conversely, even two decades ago, Warner and colleagues reviewed the 30-day mortality of over 45,000 patients undergoing outpatient anesthesia and surgery³¹ [see Figure 3]. Adjusting for age and gender, these authors concluded that the low-risk surgical procedure provoked no more deaths than would have occurred during a month without surgery. On the other hand, when a surgeon is confronted with a high-risk patient needing a high-risk procedure, a strategic alternative is not a retreat; it is responsible medicine. All too often, however, an elderly patient presents with a clear mesenteric vascular accident, and surgical intervention is the only option. This situation obligates a compassionate explanation to the patient, a sensitive discussion with the family, and a bold acceptance of reality by the surgeon. Most often, however, both the patient and the procedure are solidly positioned in an intermediate gray zone.

Conceptually, cardiac dysfunction may be comfortably discriminated into four broad categories. Each may be defined using standard cardiac function tests. These cardiac dysfunction categories are ventricular systolic compromise,

ventricular diastolic compromise, valvular heart disease, and myocardial ischemic disease resulting in electrophysiologic instability.

FUNCTIONAL CAPACITY

Patients who are able to exercise regularly without limitation generally have sufficient cardiovascular reserve to withstand stressful operations. Those with limited exercise capacity are prone to exhibit this poor cardiovascular reserve either during or after noncardiac surgery. Even outside the surgical arena, patients with poor functional status enjoy a shorter life span.³²

Functional capacity is readily expressed in terms of METs. One MET is equivalent to the energy expended (or the oxygen used) in sitting and reading this chapter (3.5 mL O_2 /kg/min). For a 70 kg person, one MET amounts to 70 kg $\times$ 3.5 mL O_2 /kg/min, or 245 mL O_2 /kg/min. Multiples of the baseline MET value can then be used to quantify the aerobic demands posed by specific activities. A modification of the Duke Activity Status Index³³ developed 20 years ago is still a practical guide [see Table 6].

Functional status correlates with exercise treadmill testing. Multiple studies have indicated that perioperative cardiac and long-term risks are increased in patients who are unable to meet the 4-MET demand associated with most normal daily activities. This higher-risk status can be signaled by poor performance on a treadmill test protocol [see Table 7]. However, just by talking with your patient, you can assess the patient's exercise capacity. This assessment is a practical, inexpensive, and accurate predictor of your patient's ability to tolerate a surgical stress.

RESTING ELECTROCARDIOGRAM

To determine whether a patient or an organ can tolerate a stress, we must stress that organ or patient. Intuitively, it does not make much sense to obtain a resting ECG in an asymptomatic young or middle-aged patient. With older patients, the resting ECG can exhibit abnormal rhythms and an old scar (big Q waves). In a retrospective analysis of 23,036 patients undergoing cardiac surgery, the preoperative ECG improved the predictive value of perioperative cardiac events in comparison with clinical risk stratification alone.³⁴ This predictive benefit was not apparent in low-risk patients undergoing low-risk procedures.³⁴ We conclude that a routine resting ECG prior to even major surgery in a young or middle-aged asymptomatic patient (ASA I/II) with no historical red flags is very low yield. Vascular disease, however, is systemic disease. Prior to vascular surgery, patients deserve a resting ECG.

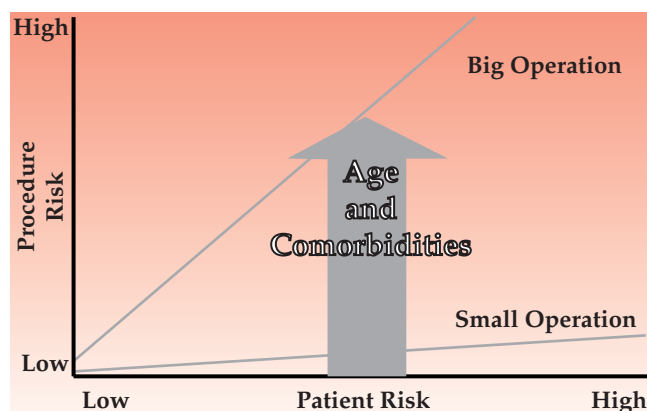


Figure 3 A low-risk operation (such as a cataract) renders negligible additional morbidity and mortality to a patient (irrespective of American Society of Anesthesiologists [ASA] status) with or without the surgical procedure.

Table 7 Bruce Protocol Stress Test

Stage	% Grade	mph	METs
1	10	1.7	4.7
2	12	2.5	7.0
3	14	3.4	10.1
4	16	4.2	12.9
5	18	5.0	15.0

MET = metabolic equivalent.

Current guidelines discourage routine preoperative non-invasive cardiac testing for most intermediate-risk preoperative patients. In a 2006 study, 1,476 patients were stratified according to their RCRI scores.³⁵ Of these, 770 patients on beta-blocker therapy with tight heart rate control met the criteria for intermediate risk. This intermediate-risk group was split and randomly assigned to receive either cardiac stress testing or continued beta-blocker therapy. Some degree of ischemia was noted in 25.8% of the patients in the testing group, but analysis of the 30-day outcomes after operation found no difference between the two groups with respect to the incidence of major cardiac adverse events. The major difference was that patients in the untested group underwent their procedures 3 weeks sooner than patients in the tested group. Noninvasive cardiac testing even in intermediate-risk patients just takes additional time without discernible benefit.

In general, indications for specialized testing are the same prior to surgery as in the nonoperative setting. If your patient exhibits the kind of cardiac indicators that might warrant coronary revascularization in the absence of an impending surgical procedure, proceed with noninvasive testing; otherwise, do not proceed.

The timing of cardiac testing depends on the urgency of the noncardiac procedure, the risk factors present, and specific considerations associated with the procedure. Coronary revascularization before noncardiac surgery has sometimes been advocated as a way of enabling a patient to tolerate a noncardiac procedure, but it is appropriate only for a very small subset of very high-risk patients.

The ACC/AHA guidelines provide the following summary recommendations. In each instance, evidence is persuasive, or only Level B:

1. Pre- and postoperative resting 12-lead ECG is not indicated in asymptomatic patients undergoing low-risk surgical procedures.
2. Vascular disease is a systemic disease, so resting 12-lead ECG is indicated in patients undergoing vascular surgery.
3. Preoperative resting 12-lead ECG is recommended in patients with the following clinical risk factors: cerebrovascular disease, diabetes mellitus, renal insufficiency, a history of ischemic heart disease, or a history of congestive heart failure.

This leaves a relatively wide gray zone, in which there is only Level C, or “pretty good,” evidence:

1. Preoperative resting 12-lead ECG is not helpful in asymptomatic patients undergoing intermediate-risk surgical procedures.
2. Resting 12-lead ECG is recommended in patients with known coronary artery disease prior to intermediate-risk operations.

CARDIAC EXERCISE STRESS TESTING

A monitored exercise stress test would logically appear to be a safe way of reproducing the hemodynamic components of surgical stress. Exercise testing on a treadmill has the advantage that the results can be quantified in METs achieved, and the test (unlike an operation) can be rapidly aborted. The patient walks on a treadmill as the speed and

slope are increased [see Table 7]. Four outcome variables are continuously monitored: angina, ST-T wave changes, ectopy as a reflection of ischemia, and, most importantly, blood pressure. When a healthy person exercises, the blood pressure should rise. No change, or a decrease in blood pressure, is ominous both for perioperative cardiovascular complications and as a prognostic indicator of nonoperative life expectancy.³²

In 2009, the ACC collaborated with the AHA Task Force on Practice Guidelines and produced a comprehensive analysis of exercise stress testing for myocardial ischemia and functional capacity.³⁶ These authors provided a table cataloging 10 published studies in which high-risk patients prior to peripheral vascular or abdominal aortic aneurysm (high-risk) surgery were subjected to exercise stress testing preoperatively.

When exercise tolerance testing (ETT) is used to identify obstructive coronary disease, the results are disappointing. As many as half of the patients with a single 70% coronary artery stenosis will sail through ETT with a “normal” result. For patients with involvement of all three major coronary arteries or even left main disease, the sensitivity is better at 86%, the specificity remains only 53%.³⁷

The mechanics of an ETT are relatively straightforward. A 12-lead ECG is continuously monitored as the patient walks on a treadmill. The Bruce protocol is most commonly used [see Table 7]. The patient is required to walk at 1.7 mph (not very fast) on a 10% incline. Every 3 minutes, the incline is increased by 2%, and the treadmill speed is increased, as indicated below.

The patient is questioned continuously concerning chest pain and fatigue, while the blood pressure is determined at the end of each stage. Although the early stages of the Bruce protocol do not seem like a lot of exercise, this may need to be modified to a lower workload for sedentary and elderly patients. Thus, the first two stages of a “modified Bruce protocol” are conducted at 1.7 mph at a zero grade (stage I) and then a 5% grade (stage II).

The inconvenience and expense of formal exercise testing have prompted many investigations to develop more accessible and practical historical questioning and functional testing strategies. Therefore, the ACC and the AHA equate the ability to walk around the block on level ground as stage I (Bruce protocol) or less than 4 METs; walking up two flight of stairs is around 6 METs or stage II (Bruce protocol).³⁷

Nikolić and colleagues refined stair climbing by monitoring pulse oximetry in 101 patients prior to thoracic surgery as they climbed stairs.³⁸ Eighty-seven of the 101 patients suffered at least one postoperative complication. Disappointingly, age, gender, and oximetry-monitored stair climbing were not predictive. This is an example of high-risk patients undergoing high-risk surgery, so the experienced surgeon should have been prepared for trouble irrespective of any preoperative tests.

Conversely, multiple groups have linked the graded results of an ETT to a patient’s annual mortality.³² These investigators identified 12% of a medically treated group of patients with coronary artery disease who could manage only stage I of a Bruce protocol. These patients suffered over 5% annual mortality. In this study, 34% of patients carrying the diagnosis of coronary artery disease who could accomplish stage III of a Bruce protocol suffered less than 1%

annual mortality. It would appear to be a minor conceptual leap to assume that the risk characteristics predicting a short life are similar to the patient limitations that cause perioperative morbidity and mortality. For example, Myers and colleagues retrospectively studied the ETT results of 6,000 veterans (with and without a diagnosis of coronary artery disease) and compared the maximum METs achieved with annual medically treated mortality data.³² Again, patients who could achieve 8 METs or more suffered less than half of the mortality of patients who could not complete Bruce protocol stage I. The predictive value of METs in this study also overwhelmed smoking, hypertension, body mass index of 30 or greater, chronic obstructive pulmonary disease (COPD), and diabetes.³²

So functional capacity, measured in METs, is a comprehensive assessment of cardiopulmonary status and muscle strength and would appear to be superior to tests specific for myocardial ischemia in calibrating a patient's risk for perioperative morbidity and mortality.

VENTRICULAR FUNCTION TESTING

Radionuclide angiography, cardiac ventriculography, gated blood pool imaging, and multigated acquisition (MUGA) scans are different names for the same procedure. An intravenous injection of technetium-99m (pertechnetate) labels the patient's red blood cells (RBCs) in vivo. The patient's heart is then scanned with a gamma camera. Low-level gamma radiation is emitted by RBCs tagged with technetium, and the radiation detected at end-systole is then related to the radiation at end-diastole and thus permits calculation of an ejection fraction. The radiation emitted during a single cardiac cycle is not sufficient signal to reliably calculate the ventricular volumes, so multiple cycles are acquired "gated" to the ECG (thus, "multigated acquisition"). A healthy ventricle ejects about 60% of its end-diastolic volume with each heartbeat.

Exercise MUGA scanning can also be performed, typically with the patient on a stationary bicycle. With exercise, both the patient's blood pressure and ejection fraction should rise.

With advancing age and congestive failure, the increasing stiffness of the ventricles can be measured in terms of the time to peak filling rate. The shorter this interval, the more compliant the ventricle. Diastolic dysfunction is now increasingly recognized as an etiology of heart failure; the ventricle becomes too stiff to fill during diastole. A healthy heart should be capable of filling completely within 130 to 200 milliseconds.

In patients with a normal, healthy exercise capacity, preoperative measurement of ventricular function will be very low yield, and the possibility of modifying any perioperative strategy by virtue of this test is unlikely.

In addition to the obvious patients who present with congestive failure and/or limited functional capacity, the surgeon should be mindful of patients on chemotherapeutic drugs. Two common culprits are doxorubicin (Adriamycin) and immunotherapy (trastuzumab [Herceptin]), which are both frequently cardiotoxic.

STAIR CLIMBING: PUTTING IT ALL TOGETHER

Arguably, climbing stairs incorporates cardiopulmonary status, muscle strength, and "vitality" into a single practical

and inexpensive test of performance capacity. Brunelli and colleagues studied 640 patients scheduled for pulmonary resective surgery with a preoperative, symptom-limited stair climbing test.³⁹ Patients who climbed less than 12 m (less than two flights of stairs) experienced a twofold increase in complications ($p < .0001$) and a 13-fold increase in mortality ($p < .0001$) and incurred costs 2.5 times higher than patients who could manage a climb of 22 m (more than two flights). These investigators then refined the stair climbing test by concurrently measuring finger oximetry. While studying 536 patients breathing room air during stair climbing, they sought to determine whether oxygen saturation less than 90% or desaturation greater than 4% drop from resting level better discriminated the likelihood of postoperative complications. The stair climbing was uniquely suited to elicit oxygen desaturation, and patients exhibiting oxygen desaturation greater than 4% were twice as likely to suffer postoperative problems. Exercise-induced desaturation ($> 4\%$) appeared superior to resting finger oximetry as a predictor of postoperative problems.

Pulmonary Function Tests

Conceptually, pulmonary dysfunction may comfortably be divided into four broad categories: obstructive airway disease, hyperinflation, restriction, and diffusion (compromise). Each of these categories may be defined through the use of standard pulmonary function tests (PFTs).

OBSTRUCTIVE AIRWAY DISEASE

When surgeons receive multiple-page PFT results, we almost always focus first on a single parameter: forced expiratory volume in 1 second (FEV_1). This measurement requires patients to inhale to maximum lung volume (total lung capacity) and then exhale as forcefully and quickly as they are able to [see Figure 4]. These tests may require a "race correction" for ethnicity of as much as 6 to 12%. Healthy young adults can exhale almost all of their total lung capacity within a second or two, so a healthy FEV_1 approaches 4 to 5 L! After 2 seconds, healthy lungs have emptied down to residual volume. A patient with asthma or COPD cannot move air through airways that have been constricted by bronchospasm [see Figure 4]. So if your patient, following bronchodilators, can only exhale in 1 second (FEV_1) less than 70% of all they can inhale (forced vital capacity [FVC]), they have met the Global Initiative for Obstructive Lung Disease (GOLD) criterion for COPD ($FEV_1/FVC < 70\%$).

In a patient with significantly compromised airway resistance, pulmonary function should also be assessed following inhaled aerosolized bronchodilators. These drugs come in three varieties: short-acting β_2 agonists, such as albuterol; long-acting β_2 agonists, such as salmeterol; and methylxanthines, such as caffeine and theophylline.

Many receptor agonist/antagonist drugs are somewhat, but not absolutely, receptor specific. So in this chapter, when we recommend a β_2 agonist for perioperative bronchodilation and simultaneously encourage a cardio-specific β_1 inhibitor (such as metoprolol or atenolol) for cardio-protection, you may appropriately envision a patient entering the operating room with one foot capably placed on the accelerator while the other foot is simultaneously placed on the brakes.

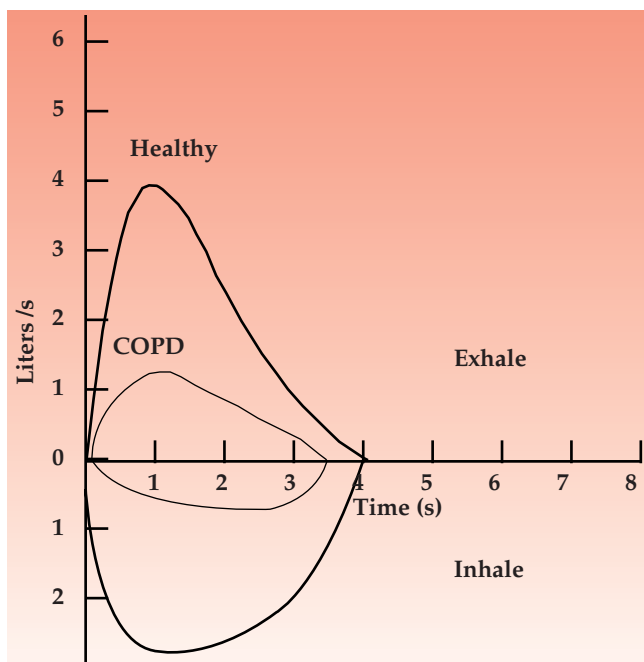


Figure 4 A flow-volume loop relates volume of exhaled/inhaled gas to time (seconds). Note that the volume of air that a young, healthy person can forcibly exhale in 1 second (FEV_1) can be as high as 4 to 8 L. Chronic obstructive pulmonary disease (COPD) dramatically reduces air flow.

HYPERINFLATION

Lung volumes are measured using a relatively simple dilutional principle. For example, 1 L of 100% nondiffusible helium is added to a spirometer and mixed. When the helium concentration gauge reads 10% helium, the volume of the spirometer can be calculated to be 10 L. The respiratory technician then places a tube into the patient's mouth and connects the tube to the spirometer with a handheld valve. The patient is instructed either to achieve total lung capacity (TLC) and exhale down to residual volume (RV) or just to breathe comfortably, initiating each breath from functional residual capacity (FRC) [see Figure 5]. When the technician observes the patient to be at the desired lung volume, the technician flips the valve connecting the patient to the spirometer. The increased volume of dilution equals the patient's lung volume at the time the valve was opened. So if the valve is opened at the end of a comfortable tidal breath (FRC) and the helium gauge concentration falls to 8%, then the total volume of dilution must be 12.5 L (spirometer plus FRC volume), or 12.5 L minus 10 L (for the spirometer) equals a 2.5-liter FRC.

If the patient continues to breathe while connected to the spirometer, the helium concentration should stabilize at 8%.

We all sigh frequently. Try not to sigh for several minutes, and you will become surprisingly uncomfortable. When a young patient sighs, the helium concentration will remain at 8% (no increased volume of distribution). But when an elderly patient sighs, the helium concentration, which had previously leveled off at 7.5%, revealing a higher "hyperinflated" FRC of 3.33 L, typically falls a little further, perhaps

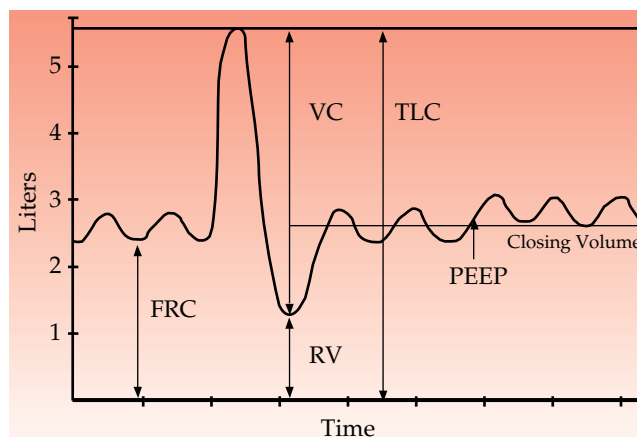


Figure 5 Spirometric lung volumes. The therapeutic purpose of positive end-expiratory pressure (PEEP) is to raise the functional residual capacity (FRC), or the lung volume following tidal exhalation, above closing volume so that terminal airways never close during tidal exhalation. RV = residual volume; TLC = total lung capacity; VC = vital capacity or the volume of the air exhaled from the TLC to RV.

to 7.35%. The sigh must have uncovered an additional volume of distribution or volume of previously trapped gas. The new total volume of helium distribution is now 13.61 L minus 10 L (spirometer) minus 3.33 L (FRC), and the volume of trapped gas is 280 mL. This volume of trapped gas cannot be due to atelectasis, because collapsed alveoli could not further dilute the helium concentration in the system. Therefore, this additional decrease in helium concentration must be due to previously trapped alveolar gas, producing perfused but not ventilated lung (shunt). Histologically, terminal airways have no cartilaginous rings to hold them open. With age, increasing interstitial lung water (which is characteristic of congestive heart failure), and obesity, these terminal airways collapse at lower lung volumes. The lung volume at which terminal airways collapse is termed "closing volume." Thus, a big barrel chest with a flat diaphragm, an increased anteroposterior diameter, and radiolucent lungs on a chest x-ray is a natural attempt by the patient to set the FRC above the closing volume. When the closing volume is above the FRC, terminal airways close during each tidal breath, creating a transient shunt.

Therapeutically, when we ventilate a patient, we can elevate FRC above closing volume by adding positive end-expiratory pressure (PEEP) [see Figure 5]. A decade ago, the Acute Respiratory Distress Syndrome Network (ARDSnet) reported that lower tidal volume ventilation (6 mL/kg) in patients with acute respiratory distress syndrome reduced mortality and increased ventilator-free days compared with traditional tidal volume ventilation (10 to 15 mL/kg).⁴⁰ Controversy lingers as to whether these lower tidal volumes promote further airway collapse.

RESTRICTIVE LUNG DISEASE

The ability to expand the lung can be constrained by chest wall scarring (secondary to a large burn), pleural fibrosis (secondary to tuberculosis), or a decrease in lung parenchymal compliance secondary to pulmonary interstitial fibrosis (multiple inflammatory etiologies).

Pulmonary function studies exhibit reduced lung volumes. The patient's vital capacity is reduced, but there is no obstruction to the airway flow, so the exhaled gas (the limited volume that there is) can be exhaled quickly. Therefore, the FEV₁/FVC ratio is normal or may actually be increased.

DIFFUSION COMPROMISE

Once oxygen arrives in an alveolus, it is uncommon for transfer across the alveolar-capillary membrane to be limited. One can imagine, however, circumstances in which this could occur. At extremely high pulmonary blood flow, blood might not linger in the pulmonary capillaries long enough to saturate hemoglobin. Conversely, with anemia, all available hemoglobin might be saturated very early as RBCs traverse the pulmonary capillaries. With hemorrhage into the lung parenchyma, oxygen can be diverted away from pulmonary capillaries. In late-stage emphysema, the alveolar septae are destroyed and the effective alveolar-capillary surface area is reduced, but this is not a diffusion problem. The classic pulmonary diffusion disease is an idiopathic interstitial pneumonitis (Hamman-Rich syndrome). Patients present with nonspecific shortness of breath. A lung biopsy reveals noncellular debris thickening the diffusion distance from alveolus to pulmonary capillary. The measured diffusion of carbon monoxide test (DLCO) should reveal compromised gas diffusion. Fortunately, true limitation of oxygen diffusion across the alveolar-capillary membrane is not common.

For a DLCO test, the patient inhales a tiny concentration of a maximally diffusible gas (carbon monoxide 0.3%) and a small volume of a maximally nondiffusible gas, such as helium, along with a large amount of room air. The patient holds his or her breath for 10 seconds and exhales. Concentrations of carbon monoxide and helium are then measured in the exhaled gas. Both gases will have been diluted by the inhaled breath, so the concentrations of both gases will decrease. Most of the diffusible carbon monoxide should have been transferred to the pulmonary capillary blood. The lower the exhaled carbon monoxide, the better the diffusion capability of the lung. Unfortunately, there are many ways to introduce error into this test. If the patient inhales rapidly, he or she can translocate additional blood into the pulmonary capillaries and falsely enhance the apparent diffusing capacity. Conversely, severe anemia permits rapid saturation of the limited hemoglobin with carbon monoxide, resulting in a false depression in the DLCO. A heavy smoker may live with carboxyhemoglobin as high as 10% and actually excrete carbon monoxide, thus confounding the test. Even most pulmonologists acknowledge that the DLCO is not a very good test.

Testing for Nutritional Abnormalities

For nutritional support, consensus statements and regulatory guidelines endorse the long-hallowed practice of identifying patients at increased risk for complications due to protein or calorie deficits. Again, this is called prognostic testing. The implication is that the benefit of special support will be confined to these patients. Poor functional status ("bedridden, requires assistance to ambulate") is a

bad prognostic sign [see Table 6]. In cancer patients, functional status is typically more important than nodal status, cytologic differentiation, or surgical margins in predicting morbidity and mortality. But assessing functional status provides no direct information on selection of therapy.

Much more therapeutically useful than prognostic testing is predictive (or directive) testing, which means identifying patients who will benefit from a specified, available intervention. By definition, predictive testing identifies that subset of "bad prognosis" patients who can be helped. This requires the existence of a therapeutic intervention of demonstrated benefit. It also requires the identification of those patients not too ill but not too well to benefit from the associated therapy.

Proof that a testing strategy is predictive or directive, not merely prognostic, is best demonstrated by randomized trials comparing outcome in groups receiving best conventional care with or without the proposed test. This is a high standard but has been met in some situations.

The therapy-prediction conundrum exists in nutritional support where possibly effective therapies have been applied in patients not able to benefit due to absence of an accurate predictive test to select the best target population. For example, identification of the role of vitamin B₁₂ in treating anemia awaited the ability to identify macrocytosis and, later, vitamin B₁₂ serum levels. Previously, most populations of anemic patients were dominated by those with iron deficiency, and no predictive test was available to find the subset benefiting from vitamin B₁₂ supplementation, so the benefit of vitamin B₁₂ remained unknown.

A vivid illustration of the difference between prognostic versus predictive/directive testing has recently arisen in breast cancer. The presence in breast tumor cells of human epidermal growth factor receptor type 2 (HER-2) has long been recognized as an indicator of poor prognosis, independent of stage, differentiation, or estrogen receptor status. Initially, nothing could be done in response to this information until the development of a blocker for HER-2, trastuzumab (Herceptin). Suddenly, HER-2 receptor testing permitted identification of a target patient capable of response. Patients with positive receptors given the blocker improved, whereas those with negative receptors did not. Not only was the HER-2 receptor test predictive, its prognostic implication also reversed itself. The receptor-positive patients now do better than average.

In nutrition for surgical patients, a variety of composite scores and indices have been proposed to predict prognosis. One clearly labeled prognostic measure, the Prognostic Nutritional Index (PNI), was proposed in 1980 to quantify surgical risk. This measure was used (in modified form) in the design of a large prospective, randomized trial of preoperative total parenteral nutrition (TPN) in veterans undergoing major general, vascular, or thoracic surgery.⁴¹ Patients judged too well nourished or too malnourished by this screen were omitted from the study, and the remainder, judged "moderately malnourished," were randomized into TPN or no TPN preoperatively. The modified PNI score was composed of albumin and weight loss scores only, which had previously been shown to be prognostic and easy to apply.

Unfortunately, after randomizing and treating 395 patients, the investigators found no outcome difference between the treatment groups, and in this sense, the trial's main result was negative.⁴² Retrospective subsetting by degree of severity within "moderate malnutrition" using a Subjective Global Assessment (SGA) tool⁴³ was then performed. This was interpreted to show that patients not severely enough malnourished to benefit from the extra protein and calories suffered increased septic complications and overall did worse with TPN. In contrast, the more malnourished patients did exhibit a net benefit.

For the studies reviewed in the following section, we use a scoring system that grades the conclusions as follows: Level A, supported by prospective, randomized, controlled trials (PRCTs) or meta-analyses of PRCTs; Level B, supported by nonrandomized, prospective, retrospective, or case-controlled studies; and Level C, supported by uncontrolled published experiences, case reports, or "expert opinion."

PREOPERATIVE TOTAL PARENTERAL NUTRITION

We have defined preoperative TPN to be intravenous provision of calories and nitrogen sufficient to meet metabolic needs for 5 or more days before elective surgery. Fourteen randomized, controlled trials of this approach, involving over 1,100 patients, have been examined,^{42,44-49} chiefly involving gastrointestinal cancer patients with at least moderate malnutrition and typically providing at least 7 to 10 days of preoperative TPN. Ten of these 14 studies found a benefit from TPN, which in five reached conventional statistical significance for reduced postoperative morbidity. The pooled results indicate an overall reduction in the risk of postoperative morbidity of about 10% in the TPN groups, that is, a reduction in the rate of complications of approximately 30%. Only one center found a statistically significant reduction in mortality [see Figure 6].

Based on these studies, we conclude that for malnourished gastrointestinal cancer patients, 7 to 10 days of preoperative TPN reduces postoperative morbidity (Level A).

POSTOPERATIVE TOTAL PARENTERAL NUTRITION

Routine administration of TPN to general surgical patients in the immediate postoperative period has been studied in nine randomized, controlled trials involving over 700 patients.^{46,50-54} No consistent benefit has been demonstrated, and the possibility of harm has been raised. These data are summarized in Figure 7.

Based on these studies, we conclude that, outside of a study situation in defined patient groups, routine use of postoperative TPN is not recommended (Level A).

It is also clear that nutritional support of patients unable to eat for long periods after surgery is needed to prevent starvation. The duration of starvation that can be tolerated without increased morbidity is unknown and depends in part on the previous nutritional status and current metabolic stresses the patient faces. Most feel that, after 5 to 10 days without adequate intake, special support is appropriate (Level C). For stressed or already malnourished patients, this interval will be shorter. Although the enteral route of administration is preferable, if the gut is not working adequately, TPN is needed (Level B).

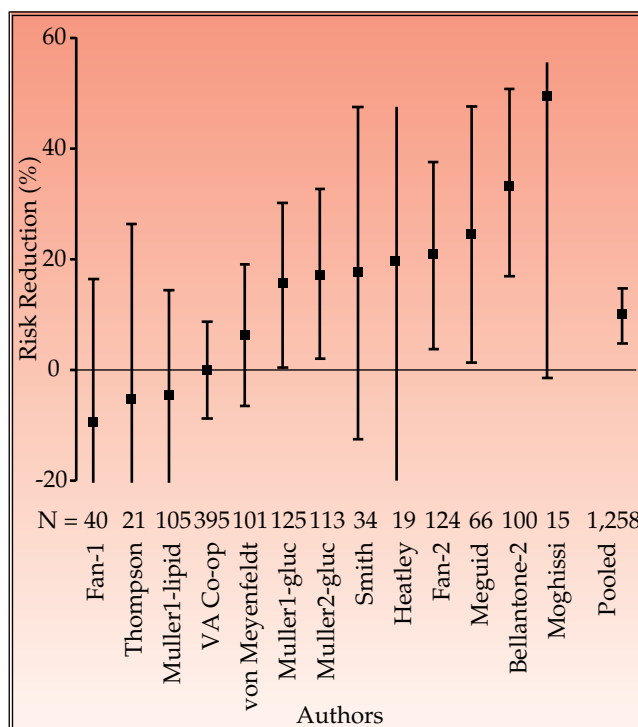


Figure 6 Effect of preoperative total parenteral nutrition on postoperative complications.¹⁰¹

In the majority of trials summarized here, the quantity and type of substrates given were not what is now thought to be optimal. For example, calories were often given in amounts substantially greater than metabolic needs. It is

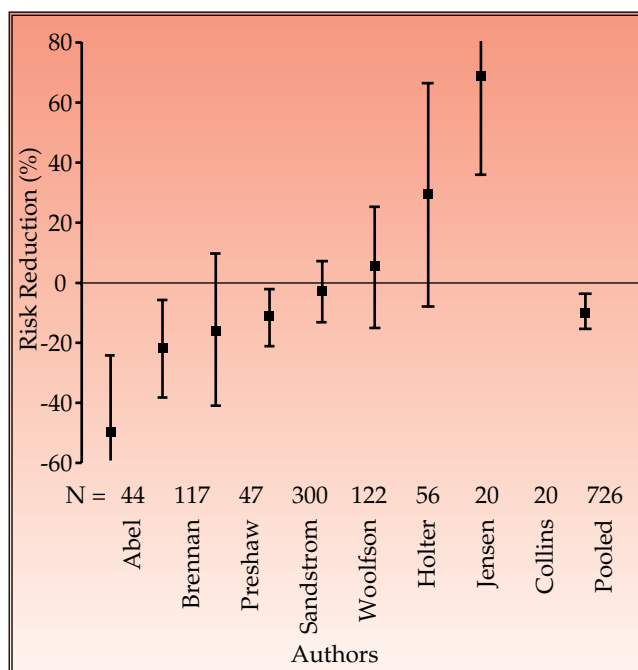


Figure 7 Effect of early postoperative total parenteral nutrition (TPN) on postoperative complications. These results are disappointing, but the quantity and type of substrates infused in these trials were not what is now thought to be optimal.¹⁰¹

probable that outcomes in many of these trials would improve if the trials were repeated using present-day understanding of caloric needs and other metabolic requirements in specific patient groups (Level C).

SPECIAL ENTERAL FEEDING

Provision of special enteral nutrition via tubes placed in the gastrointestinal tract perioperatively has been studied in 10 randomized trials.^{55–57} Five of these compared the enterally supported to patients receiving TPN, and the other five used a comparison group of routine oral feeding. In the enteral nutrition versus TPN trials for postoperative trauma patients, septic morbidity and mortality were minimized with enteral feeding, which is deemed superior to TPN.

One study reported a decrease in mortality in burned children provided with high-protein enteral supplementation compared with standard feeding.⁵⁶ A trial of nocturnal tube feeding in malnourished female hip fracture patients demonstrated speedier rehabilitation and shorter hospital stays.⁵⁷

On the basis of the available information, we conclude that special enteral nutrition is helpful in burn and malnourished hip fracture patients (Level A). In trauma patients requiring special support, the enteral route is associated with decreased septic morbidity compared with the parenteral route (Level A).

TIGHT GLUCOSE CONTROL

Extending work from the world of chronic diabetes management, in which ever-tighter glucose regulation is associated with improved outcomes, **Van den Berghe and colleagues presented two large randomized trials on intensive care (ICU) patients receiving supplemental calories early in their courses.^{58,59} The first of these, on surgical patients (chiefly postoperative cardiac patients), revealed a clear benefit in morbidity—and a raw reduction in mortality of 11%—when glucose levels were maintained below 110 mg/dL. Hypoglycemia in this ICU setting was not a serious problem.⁵⁸ A follow-up study from the same authors showed little or no benefit using the same approach in medical ICU patients.⁵⁹ Finally, a large (over 6,000 patients) multinational study coordinated from Australia and New Zealand found a worsening of mortality with tight glucose control in similar patients.⁶⁰**

The issue of tight control is of obvious importance in TPN patients, and it may be that disappointing results in the perioperative trials summarized above might be improved with better glucose regulation. Tighter glucose control carries risks of hypoglycemia and hypokalemia.³⁶

Target glucose levels in recent randomized trials appear to be converging toward about 140 to 150 mg/dL. Until more definitive data are available, this target seems safe for patients treated outside an ICU (Level C).

IMMUNONUTRITION AND “DESIGNER FEEDS”

The provision of special nutrients with the intent of stimulating the immune system, or providing targeted support for a failing liver or kidneys, and thereby reducing septic complications has been studied in a large number of trials that were reviewed by Dhaliwal and Heyland,⁶¹ with variable results. A fundamental problem is the use of ad hoc

mixtures of arginine, fish oil, RNA fragments, and sometimes glutamine, in various proportions, for which no rationale is given. The more recent of these trials have been much less encouraging than the earlier reports, with actual harm being reported in several trials of products containing high arginine levels. The recent publication from Holland of a randomized blinded trial of nearly 600 patients testing this strategy is unequivocally negative and may serve to foster a more cautious scientific approach toward evaluating such strategies.⁶²

Immunonutrition and “designer” feeds are not supported by a satisfactory evidence base (Level C).

PREOPERATIVE ORAL CARBOHYDRATE LOADING

The traditional dictum of nihil per os (NPO) after midnight for procedures to be performed under general anesthesia has been challenged in some centers in Scandinavia and eastern Europe since the 1990s. In these facilities, anesthesiologists provide several hundred milliliters of carbohydrate-enriched electrolyte solutions swallowed 2 hours prior to surgery. The rationale is that stress-induced insulin resistance is normalized and patient well-being improved by ingestion of these “potions.”⁶³ Interestingly, similar biochemical changes are also produced by glucose-containing intravenous lines in fasting preoperative patients.⁶⁴

Ingestion of 200 mL clear liquids does not increase the risk of aspiration pneumonia as long as there is a delay of 1.5 to 2 hours before anesthesia. A Cochrane Review first published in 2003 concludes that no strong evidence of harm from this practice can be adduced.⁶⁵ The generally small sample size in these reports contributes to this conservatism; most reports include fewer than 50 patients per group and are thus not powered to detect rare but catastrophic events. Gastric fluid secretion is traditionally quantified at approximately 100 mL/hr, so the gastric volumes are not likely to be influenced measurably by this preoperative cocktail.

Those concerned about insulin resistance might more easily and conventionally start the usual intravenous line an hour or two earlier and administer glucose by that route. But wetting the patient’s thirsty tongue with 200 mL of clear fluid 2 hours prior to surgery is very likely to enhance patient comfort at negligible risk of aspiration (Level B).

How Can We Make Surgery Safer?

The problem with searching the available, conscientiously conducted clinical trials for answers is that the patients recruited for those trials never really fit the patient you are currently considering for surgical therapy. As indicated above [see Figure 3], patients undergoing “low-risk” operations will do pretty well even if they present with significant comorbidities—or as well as they would do without surgery.³¹ The risk stratification strategies^{25,26} [see Table 3 and Table 5²⁷] each target the patient’s cardiovascular system as the overwhelmingly dominant culprit promoting perioperative trouble.

Over the past decades, the scope of perioperative efforts to reduce cardiac risk with cardioprotective therapy has changed. At present, the emphasis is on plaque stabilization, reduction of myocardial oxygen demand (reduction of oxygen delivery to oxygen consumption mismatch), and

myocardial protection, with revascularization reserved for a discrete subset of patients who would be candidates for cardiac revascularization regardless of any elective preoperative evaluation. It is hypothesized that the likelihood of coronary artery plaque rupture may be increased by perioperative stressors such as amplified sympathetic activation, vasospasm, disruption of coagulation homeostasis, and oxygen supply-demand mismatch.⁶⁶

Physicians, and perhaps more clearly surgeons, are sufficiently intellectually arrogant that we are more comfortable accepting a conclusion if we can understand the “mechanism” of the recommendation. Thus, if the heart is the organ that most endangers our patients, and we can reduce cardiac work/stress with a beta blocker, why not give this perioperative, antiadrenergic protection to all of our patients—or at least to all surgical patients with cardiovascular disease? Interestingly, and perhaps predictably, perioperative beta blockade produced a significant reduction in mortality in patients undergoing abdominal aortic aneurysmectomy (most likely patients with concurrent coronary artery disease).⁶⁷ No such benefit was appreciated in patients who were less likely to suffer comorbid coronary artery disease undergoing esophagectomy, hepatectomy, pancreatectomy, colectomy, gastrectomy, or pulmonary lobectomy.⁶⁷ These investigators concluded that evidence-based process measures are “procedure specific” and do not necessarily reflect overall hospital quality.

If some patients do not appear to benefit from perioperative beta blockade, is overuse of this particular therapy likely to hurt them? Some controversy remains regarding appropriate management of patients identified preoperatively as having significant but stable coronary artery disease. Current data support the use of presumptive medical therapy, and this has led to reductions in the extent of preoperative cardiac assessment, thereby decreasing the time from surgical diagnosis to surgical therapy. Perhaps surprisingly, documented coronary stenoses account for only 50% of perioperative myocardial infarctions; the remaining 50% occur in vascular distributions unrelated to documented coronary disease.^{68,69} The presence of severe stenosis is more a “marker” of disease, and thus the subset of patients at risk, rather than a finite predictor of endangered myocardial territory. In part, preoperative cardiac testing identifies this “at-risk” subset, even though the stenotic lesion may not be the cause of the postoperative ischemic event. The inability to assess the propensity for coronary plaque rupture proves to be the main challenge in both risk stratification and risk factor modification.

THE BETA-BLOCKER CONTROVERSY

The purported advantages of beta-blocker therapy include prolongation of diastole (and, thus, augmentation of diastolic filling with concurrent accompanying improvement in coronary artery perfusion), reduction of ischemic ventricular dysrhythmias, and reduction of sympathetic tone.^{70,71} Despite the plethora of available data, the argument for preoperative use of beta blockers to modify cardiac risk remains controversial. Except in high-risk vascular procedures, perioperative cardiac events are so rare among patients enrolled in randomized, controlled trials of perioperative beta blockade that any absolute reduction in cardiac risk is difficult

to detect. However, in high-risk vascular procedures, the data are overwhelmingly persuasive. Poldermans and colleagues screened 1,351 vascular patients (high risk) and identified 846 patients with one or more cardiac risk factors (very high risk).⁷² Of this group, 173 patients exhibited positive dobutamine stress echocardiography (very, very high risk). Fifty-nine patients were randomly assigned to perioperative beta blockade and were compared with 53 patients who received “standard” perioperative care. The primary end point of death or nonfatal myocardial infarction occurred in two (3.4%) of the beta-blocker group and in 18 (34%) of the standard care group (3.4% versus 34%; $p < .001$). It is clearly not permissible to extrapolate from this “very, very high risk” procedure-specific group to a “routine” general surgical patient.

Unfortunately, the studies on the opposite end of the risk spectrum are more confusing. Lindenauer and colleagues divided 782,969 patients (a huge number) into high, intermediate, and low risk for major, noncardiac surgery.⁷³ Again, perioperative beta blockade was associated with reduced risk for in-hospital death in high-risk patients. Perhaps surprisingly, beta blockade appeared to provoke increased trouble in the low-risk group. Subsequent review of this study design suggested that the low-risk patients did not receive beta blockers preoperatively and did not enter the beta-blocker arm of the study until after their operation, at a time when they were treated for a postoperative cardiac event.

The POISE Study Group attempted to resolve any recommendation to liberalize the use of beta blockers in noncardiac surgery by prospectively randomizing 8,351 patients at 190 hospitals in 23 countries.⁷⁴ The frighteningly formidable logistics of this study obligated a simplified investigative strategy. A large dose (two to eight times the standard dose) of extended-release metoprolol was given 2 to 4 hours before surgery to 4,174 patients unless their heart rate was below 60 beats/min. Fewer patients in the metoprolol group (5.8%) than in the placebo group (6.9%) reached the primary end point ($p < .0399$), but more patients in the beta-blocker group suffered a stroke (1.0% versus 0.5%) and/or died (3.1% versus 2.3%). In commentary on the POISE study, the 2009 ACC/AHA consensus document endorsed the use of beta blockers in high-risk patients but cautioned that: “routine administration of higher dose long-acting metoprolol in beta-blocker naïve patients on the day of surgery and in the absence of dose titration is associated with an increase in mortality.”⁷⁵ Clinical investigation is hard to do. To enhance patient recruitment and standardize the POISE experimental protocol, patients with a heart rate over 60 beats/min were given a large dose of an extended-release beta blocker. In high-risk patients, even this regimen provided protection. However, neither we, nor they, should be surprised that a large dose of beta blocker to a patient with a heart rate of 60 beats/min might provoke bradycardia and hypotension with a resultant increase in cerebrovascular accident and even death.

Multiple smaller studies examining noncardiac surgical patients with surrogates for coronary artery disease such as diabetes,⁷⁶ mild hypertension,⁷⁷ and advanced age⁷⁸ have typically reported fewer instances of perioperative myocardial ischemia in the beta-blocker group but were not sufficiently powered to detect more ominous outcomes.

To date, the issues of how, when, how long, titration limits and by whom beta blockers should be used in noncardiac surgical patients remain controversial. A conservative series of recommendations might include the following:

1. When preoperative beta-blocker therapy is used, it is optimally initiated 1 to 2 weeks prior to surgery, targeting a resting heart rate of 60 to 80 beats/min and monitored to avoid hypotension (Level A).
2. Although it is not permissible to extrapolate from patients following a myocardial infarction to patients during noncardiac surgery, Cucherat assembled 17 trials of beta blockers in post-myocardial infarction patients and estimated that each reduction in heart rate of 10 beats/min (in the absence of hypotension) accrued a relative reduction in cardiac death of 30% (Level A).⁷⁹
3. When a patient presents already on beta blockers, do not stop them (Level A).
4. The higher the perceived risk of the (especially vascular surgical) patient, the more likely it is that beta blockers will help (Level A).
5. Untitrated large doses of extended-release beta blockers in drug-naïve, low-risk patients are contraindicated (Level A).
6. This leaves a large middle “gray zone” group of patients in whom surgeons are on their own to use their best judgment.

STATINS

The statin (HMG-CoA [3-hydroxy-3-methylglutaryl coenzyme A] reductase inhibitor) story is complex but becoming clearer. HMG-CoA reductase is the rate-limiting step in cholesterol synthesis. Statins both inhibit cholesterol synthesis and increase expression of low-density lipoprotein (LDL) receptors, which results in an increased clearance of circulating LDL cholesterol. Cholesterol is, however, critically important to cell membrane stabilization. Cholesterol is the glue that holds the functionally important cell membrane phospholipids together. Only 20% of our cholesterol is ingested, whereas over 75% is synthesized by the liver. So, intuitively, it should be dangerous to manipulate this structurally pivotal molecule. Over 40 years ago, the Framingham study first associated hypercholesterolemia with atherosclerotic cardiovascular disease. So it made sense to try judiciously to lower cholesterol a little. A storm of inquiry followed. Law and colleagues recently reviewed several hundred trials and concluded that a reduction of LDL cholesterol by only 1.8 mmol/L conveyed a 60% decrease in ischemic heart disease and a 17% decrease in stroke.⁸⁰ Statins not only prevent heart disease; Poynter and colleagues reported a 47% reduction in the relative risk of colorectal cancer after adjusting for other recognized risk factors.⁸¹ If both atherosclerosis and malignant neoplastic degeneration are exacerbated by systemic inflammation, then statins might be effective in pacifying inflamed patients (as evidenced by an elevated C-reactive protein) even independent of absolute LDL levels. And, Albert and colleagues report that they are.⁸²

Surgery provokes inflammation. Logically, statins should help. Pan and colleagues and Ouattara and colleagues both reported a significant dose-dependent reduction in adverse cardiovascular outcomes with statins in coronary artery

bypass surgery.^{83,84} Biccard examined the implications of comorbid disease associated with perioperative cardiovascular risk for patients on statin therapy, the indications for perioperative statin protection, and the efficacy of acute perioperative beta blockade in addition to statin therapy and the effect of perioperative statin withdrawal.⁸⁵ Although many of the recent recommendations regarding retrospective reporting of statin trials may minimize some inherent investigator bias, the benefit of perioperative statins appears secure. Statins seem to benefit surgical patients with both cardiovascular and neoplastic disease; age overwhelms both of these indications. **Patients who benefit from perioperative beta blockers are the same group that will likely derive advantage from statins.** The data here are fuzzier, but in high-risk patients, both beta blockers and statins are useful. The dose and duration of preoperative prophylaxis are not clear, but 2 weeks is better than 2 hours. When a patient is already taking a statin, do not stop it.⁸⁵

Smoking Cessation Programs

It is hard to stop smoking; it is an addiction. Although there is a paucity of data indicating that smoking cessation just prior to surgery changes outcome, there are a lot of data linking smoking to perioperative trouble. So, intuitively, it makes sense to ask your patients to stop. A planned surgical procedure, especially if the purpose is to resect cancer, can provide persuasive incentive. Cooley and colleagues recommended smoking cessation to patients undergoing surgery for lung cancer.⁸⁶ Eighty-four patients (89%) were “ever-smokers,” and 35 (37%) reported smoking at diagnosis. Forty-six percent of the ever-smokers remained abstinent, 16% continued smoking, and 38% relapsed. In a separate analysis of lung cancer patients, these investigators catalogued the factors associated with failure to stop as young age, depression, and a household member who smokes.⁸⁷ A similar study identified the red flags of smoking cessation failure as mentholated cigarettes and a habit of enjoying the first cigarette within 30 minutes of awakening in the morning.⁸⁸

Several groups have tested smoking cessation programs in a prospective, randomized fashion.^{89,90} Prior to elective surgery, 210 smokers were randomly allocated to a nicotine replacement group or a “usual care” group. A whopping 73% of dependent smokers (> 10 cigarettes/day) reported (no confirmatory tests) abstinence prior to surgery compared with 56% abstinence in the “usual care” group. The bad news, however, is that 3 months following surgery, 82% and 95% of patients, respectively, were smoking again.⁸⁹

A single puff on a cigarette produces profound vasoconstriction. Some surgical groups believe that it is justified to refuse breast reconstructive surgery to smokers.⁹¹ Although it is clear that smokers suffer more postoperative complications, it is not evident that these problems will vanish if they stop.

The news is not all bad, however. Varenicline is a partial agonist/antagonist selective for $\alpha_4\beta_2$ nicotinic acetylcholine receptors that is touted as a first-line treatment smoking cessation option. Garrison and Dugan reviewed eight clinical trials and reported continuous abstinence rates ranging from 21.9 to 34.6% at a year.⁹² In a very slow race, even the lame can win.

Frailty Index: The “Eyeball” Test

Age is not the distance from the beginning but, more accurately, the proximity to the end. Although “frailty” has not yet achieved a standardized definition, we all recognize the status when we see it. Age and frailty are frequent, but not obligatory, partners. Frailty confers an increased risk of disability, falls, cognitive decline, hospitalization, and perioperative morbidity/mortality. Interestingly, the phenotype of frailty is not concordant with either disability or comorbidity, but the pathogenesis of frailty includes comorbidities, and disability is more the outcome than the cause.

Frailty can now be diagnosed as a medical syndrome.⁹³ Fried and colleagues identified this entity with three or more of the following: (1) unintentional weight loss of more than 10 pounds over a year; (2) self-reported exhaustion; (3) weak grip strength; and (4) slow walking speed or low physical activity [see Figure 4].⁹⁴ In this study, frailty was independently (stratifying for comorbidities) predictive (over 3 years) of falls, declining mobility, hospitalization (and intuitively perioperative morbidity/mortality), and death, with hazard ratios ranging from 1.82 to 4.46. Socioeconomic status resurfaces again, with frailty associated with lower education and income. As more statistics are successfully dissociating frailty from age,^{95,96} frailty has now been proposed as the missing element in predicting operative mortality.⁹⁷

Makary and colleagues prospectively measured frailty in 594 patients older than 65 years.⁹⁸ They used a 5-point scale, including weight loss, weakness, exhaustion, low physical activity, and walking speed. Frailty independently predicted postoperative complications, length of hospital stay, and nursing home discharge. Frailty even enhanced the predictive power of the ASA risk index ($p < .01$).

Although both the ASA and frailty indices aspire to quantitative status, the predictive (albeit subjective) value of the “eyeball” test performed by an experienced surgeon remains invaluable (although not formally tested). We continue to endorse this test.

An exercise prescription as an antidote to frailty^{99,100} would make intuitive sense in the preoperative period. Castillo-Garzón and colleagues provided compelling evidence that patient-specific exercise programs can attenuate the negative consequences of frailty.¹⁰⁰

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7 ELEMENTS OF COST-EFFECTIVE NONEMERGENT SURGICAL CARE

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Citizens of industrialized nations generally enjoy a high level of health, and the positive correlation between life expectancy and per capita income is among the best known relationships in international development.¹ Yet there are differences among the health care systems of these nations with regard to quality, cost, and access to care.^{2,3} There also appears to be a dynamic tension among these three characteristics, and the goal of providing broad access to high-quality health care at a reasonable cost is an increasing challenge. One particular challenge is that health care costs tend to rise at a faster pace than the costs of other goods and services. In the United States, for example, health care costs have consistently risen faster than overall inflation for the past 65 years. Interestingly, despite differences in the percentage of gross domestic product (GDP) that nations spend on health care, the slopes of these curves often appear to increase in parallel [see Figure 1].

The hyperinflation in health care costs, particularly in the context of the recent economic downturn, often forces choices among social goals (e.g., health care versus education). Such choices may be more readily rationalized when the costs of the chosen goal produce demonstrable value (i.e., if greater health care spending generates measurably better health, it is regarded as worthwhile; if it does not, it is regarded as wasteful). Unfortunately, the latter appears to be the case in the United States. Although the United States spends more on

health care as a percentage of its GDP [see Figure 1] and per capita [see Figure 2] than other industrialized nations, its citizens seem less healthy than those of many nations with respect to indices of population health, such as life expectancy and infant mortality [see Figure 3 and Figure 4]. Thus, per capita health care expenditures have only a modest correlation with life expectancy. Although some of this disparity in the apparent value of health care might be explained by specific characteristics of the US population, much of it cannot. Although the United States has slight advantages over some countries in 5-year survival rates for both breast and colorectal cancer, the cost of such benefits seems disproportionately large. Overall, the United States lags behind other nations in measures of illness and some chronic conditions amenable to health care.⁴ All of this suggests that the US health care system exhibits a relative lack of cost-effectiveness, the causes of which include higher prices for health care goods and services⁵ and waste related to overuse or misuse of resources.

As health care increasingly competes with other social goals for the same funds, individuals, employers, and governments all feel the strain. The impact on US citizens is reflected in the fact that in 2007, over 62% of personal bankruptcies were related to health care issues, up from 46% 6 years earlier.⁶ Also, the percentage of nonelderly Americans who lived in

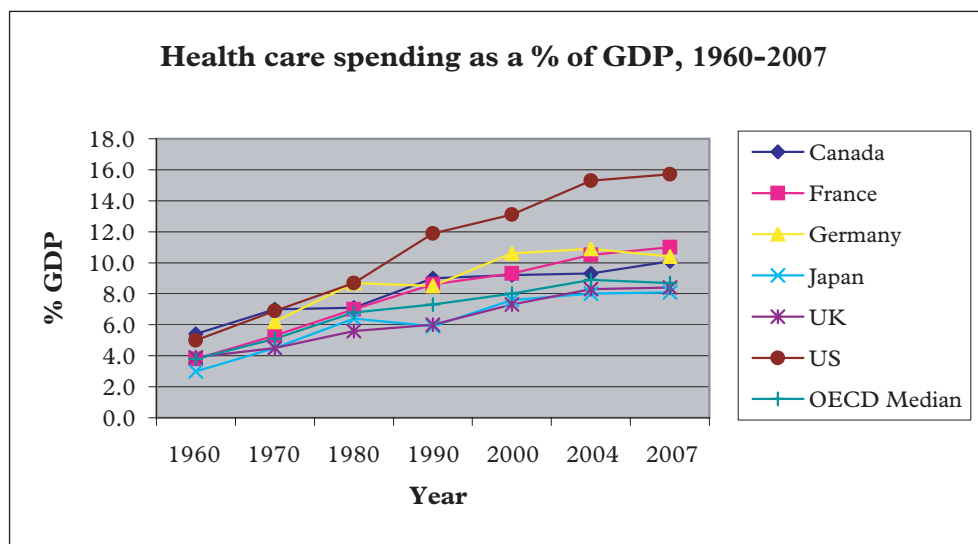


Figure 1 Health care spending as a percentage of gross domestic product (GDP) among selected countries within the Organisation for Economic Co-operation and Development (OECD). US health care spending has been increasing at a disproportionately faster rate. Note that the x-axis scale does not have constant intervals. (www.oecd.org/health/hcqi, accessed July 5, 2010).

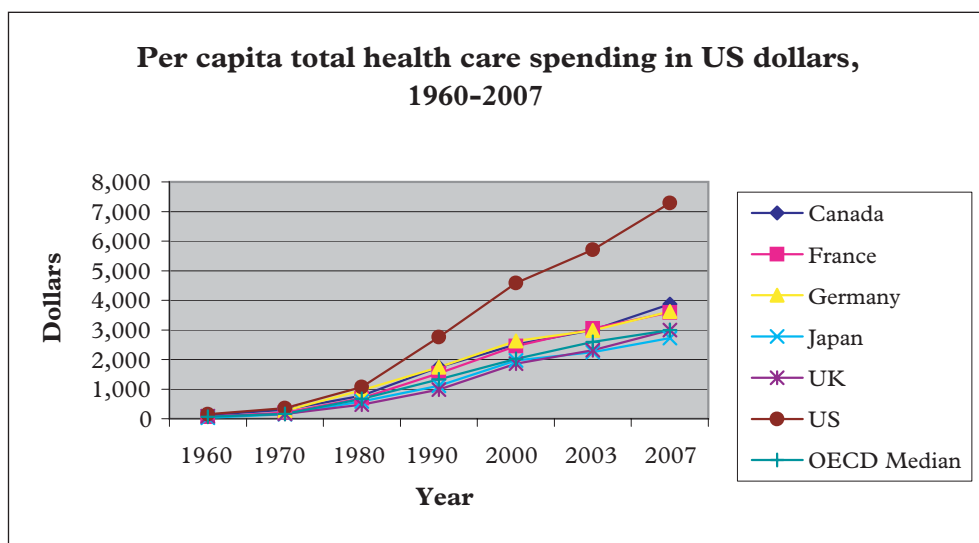


Figure 2 Health care spending per capita among selected countries within the Organisation for Economic Co-operation and Development (OECD) in US dollars. Again, US health care spending is increasing at a disproportionately faster rate. Note that the x-axis scale does not have constant intervals. (www.oecd.org/health/hcqi. accessed July 5, 2010).

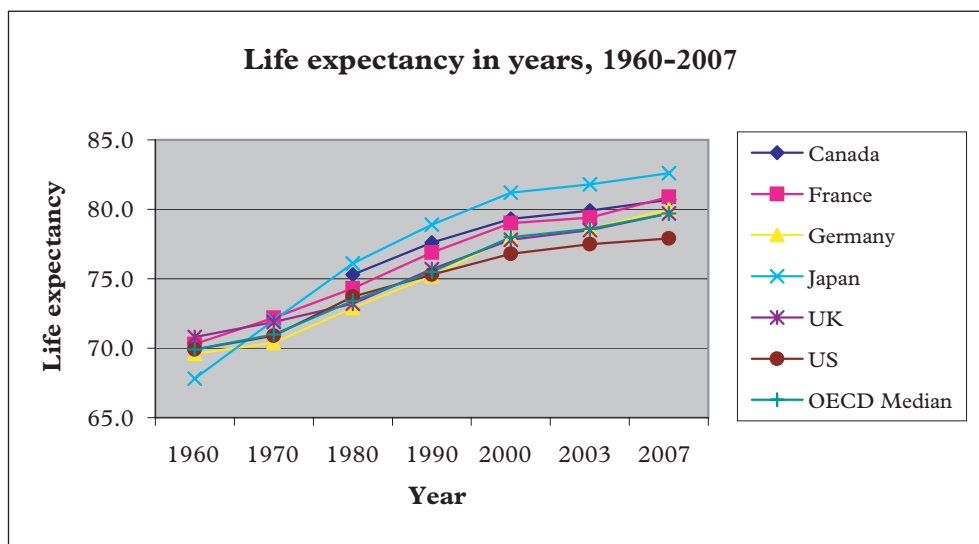


Figure 3 Life expectancy among selected countries within the Organisation for Economic Co-operation and Development (OECD). The increase in US life expectancy is falling behind the increases seen in other countries. Note that the x-axis scale does not have constant intervals. (www.oecd.org/health/hcqi. accessed July 5, 2010).

families spending more than 10% of their income on health care rose from 14.4% in 2001 to 19.1% in 2006.⁷

The phrase “bending the cost curve” refers to efforts to minimize or eliminate differences in inflation in general and inflation in the cost of health care. Accordingly, there is a long history of attempts to control health care costs that includes price controls (the Nixon era), prospective payment (the Reagan era), and managed care (the Clinton era). Unfortunately, these initiatives had little long-term impact.⁸ More recently, concerns about increases in health care costs were sufficient to engender federal legislation aimed at controlling costs; whether this effort will be more successful has yet to be determined.

Many factors contribute to the costs of health care, but physicians’ decisions are the largest single factor; they are estimated to account for 75% of these costs. This pronounced impact of physicians on health care costs explains, in turn, why those who pay the bills increasingly seek to identify the most cost-effective physicians. Surgeons in particular are likely to be a target of efforts to contain costs because surgical illnesses often are of relatively short duration, surgical outcomes are readily quantified, and surgeon reimbursement often involves global fees.

Given the impetus to improve the cost-effectiveness of surgical care, the goals of this chapter are to (1) explore the fundamental principles of cost-effectiveness, particularly as

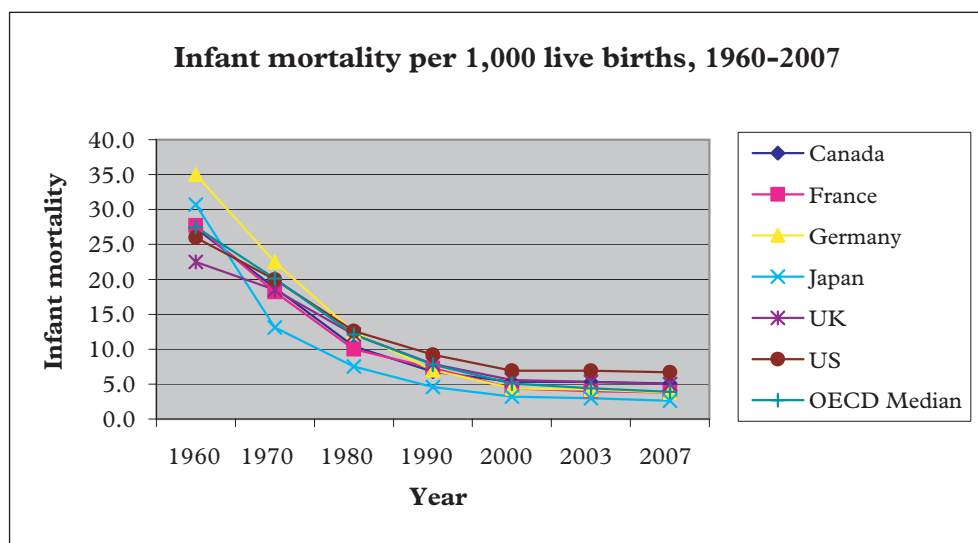


Figure 4 Infant mortality per 1,000 live births among selected countries in the Organisation for Economic Co-operation and Development (OECD). The decline in US infant mortality is not keeping pace with the declines seen in other countries. Note that the x-axis scale does not have constant intervals. (www.oecd.org/health/hcqi, accessed July 5, 2010).

applied to surgical care; (2) review the attributes and complexities of both cost and quality; (3) review current data on the relationship of cost and quality; and (4) identify specific skills and attributes to help surgeons deliver more cost-effective care.

Fundamental Principles of Cost-effectiveness

Cost-effectiveness expresses the cost of a given strategy (in dollars) relative to a given measure of quality. Developed in the military and in the evaluation of how to spend government monies on different public works projects (e.g., roads, dams, bridges), cost-effectiveness analysis (CEA) was first applied to health care in the mid-1960s. It was introduced with enthusiasm to clinicians in 1977 by Weinstein and Stason⁹ but was received with skepticism or reluctance. Cost-effectiveness can be an absolute term, but a more frequent application in health care is to compare the value of two or more clinical strategies. Expressed mathematically, it is the difference in the cost of a new strategy and the cost of current practice divided by the difference in the effectiveness of the new strategy and the effectiveness of current practice. Specific strategies might include assessing one intervention against another, assessing an intervention against no intervention, or assessing early treatment against delayed treatment. An example of the last is a study of appendicitis that concluded that each 10% increase in diagnostic accuracy was associated with a 14% increase in the perforation rate; the greater costs associated with higher morbidity from perforation might offset the cost savings associated with reducing negative appendectomies through greater diagnostic accuracy.¹⁰

Cost-effectiveness differs from cost-benefit, which measures return on investment (where the numerator and denominator are expressed in dollars), and from efficiency, which is an expression of productivity (with outputs divided by inputs).

Comparative effectiveness is another frequently used term that compares the effectiveness of two or more treatments.

Given that cost-effectiveness considers both cost and quality, changes in cost-effectiveness also represent changes in the value of care. The interaction of cost and quality also means that improvements in cost-effectiveness can result from changes in the numerator, the denominator, or both. Moreover, beneficial effects in one component of a strategy can be outweighed by adverse changes in the other, and vice versa. These interactions are represented in Figure 5. Here, strategies that increase quality and lower cost are highly desirable, and maximal cost-effectiveness is the optimal outcome that can be achieved with the least use of resources. Conversely, changes that lower quality and increase cost are clearly undesirable. In contrast, judgments of strategies where costs and quality move in the same direction tend to be controversial.

The controversial nature of such changes was evident during the debate on health care reform. Greater support for cost-effectiveness research was included in the American Reinvestment and Recovery Act (ARRA) of 2009, raising concerns that health care decisions going forward might be made by outside agencies. This fueled at least some of the opposition to health care reform.¹¹ Moreover, a recent survey indicated that a majority of consumers believed that more care meant higher-quality, better care.¹² Many of these consumer beliefs, values, and knowledge are at odds with what policy makers described as evidence-based health care. These beliefs likely account for the recent pushback on the changes in recommendations proposed by the U.S. Preventive Services Task Force regarding the appropriateness of routine mammography screening for women ages 40 to 49.¹³

Attributes of Health Care Costs

Assessing cost-effectiveness may seem simple, but measures of costs have multiple dimensions that are reflected in the phrase “cost is a noun that never stands alone.” Thus,

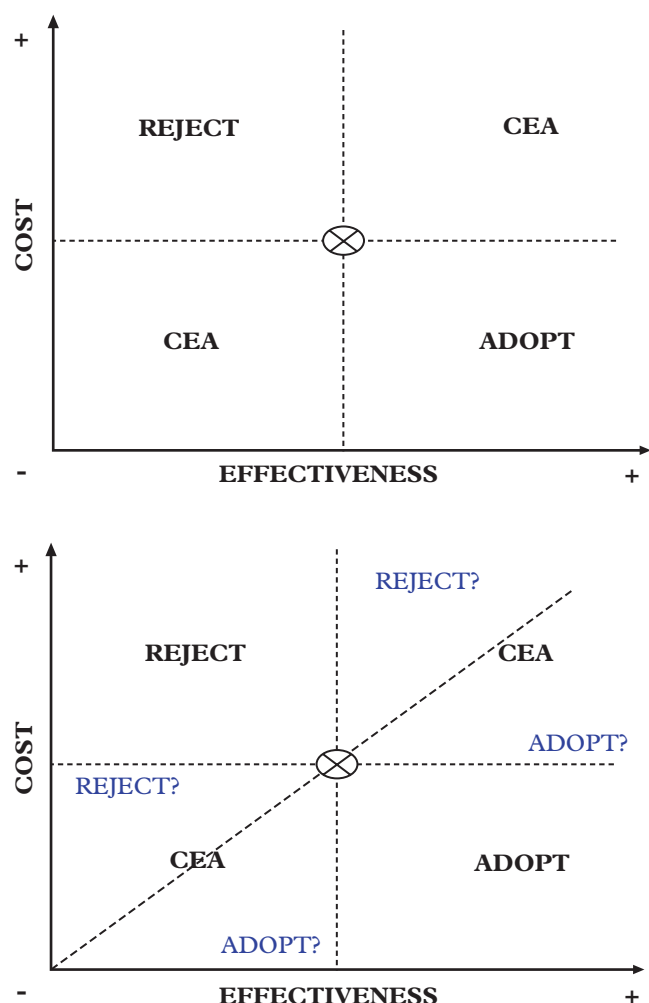


Figure 5 Cost analysis methods. Adapted from the National Information Center on Health Services Research and Health Care technology of the US National Library of Medicine, National Institutes of Health. Available at: <http://www.nlm.nih.gov/nichsr/hta101/ta10106.html>. accessed January 10, 2011. CEA = cost-effectiveness analysis.

assessing the relative cost-effectiveness of a specific strategy requires a precise definition of the costs being considered.¹⁴

An important first step is to appreciate the distinction between costs and charges. Charges are the price at which a “seller” provides a given product or service, but this price may not reflect the actual cost of that product or service (e.g., a loss leader). Although aggregate hospital costs can be a relatively constant fraction of hospital charges, there are often substantial variations among institutions in the cost-to-charge ratio for specific goods and services. These differences can be attributed to differences in cost attribution among different accounting systems but are also evident within the relatively standardized accounting standards required by the Centers for Medicare and Medicaid Services (CMS). Whether such variations result from differences in efficiency or differences in accounting practices is often not clear.

Third-party reimbursements to hospitals and surgeons reflect contractual agreements and, like charges, also do not reflect costs.

Table 1 lists ways to categorize health care costs. Cost traceability and its behavior in relation to output or activity are particularly important concepts for surgeons and hospitals.¹⁵ Examples of direct costs are salaries, supplies, rents, and utilities, whereas indirect costs might be depreciation and/or administrative costs associated with regulatory compliance. Yet these definitions are not cast in stone, and some indirect costs might be considered direct costs depending on the cost objective.

Cost behavior relative to an output or activity costs can be variable, fixed, semivariable, or semifixed. Variable costs (e.g., supplies) change in a constant, proportional manner with changes in output, whereas fixed costs (e.g., equipment) do not change in response to changes in volume. Semivariable costs (e.g., utilities) include elements of both fixed and variable costs: there is a fixed basic cost per unit of time and a direct, proportional relation between volume and cost. Semifixed costs (also known as step costs) also change with changes in output, but the changes occur in discrete steps rather than linearly. An example of a semifixed cost is the number of full-time equivalents (FTEs) needed to run one operating room; labor costs will be constant whether that room is used all the time or part-time. Conversely, when operating room use is reduced, there may not be any cost savings until a room is completely taken out of service. Unless the step threshold is attained, costs do not change.

Physicians affect hospital costs primarily via their impact on fully variable and semifixed costs. Such costs typically constitute 15 to 35% of total hospital costs, and this range often reflects substantial variations in the use of resources among surgeons for similar types of patients or procedures.

Table 1 Categories and Types of Hospital Costs

Category	Type	Example or Definition
Traceability to the object being costed	Direct	Salaries, supplies, rents, and utilities
	Indirect	Depreciation and employee benefits
Behavior of cost in relation to output or activity	Variable	Supply
	Fixed	Depreciation
	Semivariable	Utilities
	Semifixed	Number of full-time equivalents per step in output
Management responsibility for control	—	Often limited to direct, variable costs
Future versus historical	Avoidable costs	Costs affected by a decision under consideration
	Sunk costs	Costs not affected by a decision under consideration
	Incremental costs	Changes in total costs resulting from alternative courses of action
	Opportunity costs	Value forgone by using a resource in a particular way instead of in its next best alternative way

This variability, in turn, can affect the “profitability” of a given disease-related group (DRG). Hospital administrators often are aware of this variability but seem reluctant to bring it to a surgeon’s attention. Physicians also affect fixed costs as they influence investments in technology. This is discussed in greater detail in a later section.

Perspectives on costs also vary among payers (e.g., insurers), providers, and patients.¹⁶ Payers’ perspectives primarily focus on the impact of price and use, a perspective exemplified by the introduction of laparoscopic cholecystectomy.¹⁷ Lower per procedure hospital costs were offset by an increase in procedure volume and an increase in aggregate costs to payers. This effect often accounts for differing opinions among patients, providers, and insurers regarding the value of new technology. In this context, regional variation in per capita Medicare spending appears to be more related to differences in use than in price.¹⁸

The interval between an intervention and the point of measurement may also affect estimates of value.^{19,20} Patients are likely to view outcomes over the long term, whereas providers and purchasers tend to have a shorter horizon (e.g., the term of a health care contract). To improve the comparability of cost-effectiveness, the Panel on Cost-Effectiveness in Health and Medicine (a nonfederal panel with expertise in CEA, clinical medicine, ethics, and health outcomes measurement convened by the US Public Health Service) recommended that calculations of cost-effectiveness be based on a broad societal perspective rather than on that of patients, providers, or insurers. Such a perspective would more likely include costs incurred by patients or others (e.g., outpatient medication or home care after hospital discharge).

Defining Quality in Health Care

Assessing cost-effectiveness also requires suitable measures of quality. Unfortunately, defining quality can be even more complex than assessing cost.^{21,22} Measures such as operative mortality are straightforward but have become increasingly rare; therefore, mortality alone is not useful in the vast majority of cases.

A long-held standard of health care quality was the appropriateness of care, and an individual physician’s knowledge was the authority with regard to judging quality. In recent decades, several factors have seriously undermined appropriateness (and perhaps even physician authority) as a primary indicator of quality. These factors included findings that some procedures had a high incidence of inappropriate indications; judgments as to appropriate care relative to groups differed from such judgments relative to individuals²³; retrospective assessments often judged appropriateness on the basis of outcome without considering processes of care²⁴; and a realization that variations in procedure frequency often related to provider capacity (e.g., the number of hospital beds per 1,000 persons). Unexplained variations in the use of health care services across small geographic areas, in particular, have undermined physician authority on quality and are discussed in more detail in a later section.

The overall consequence is that appropriateness is not sufficiently granular to be a useful measure of quality. These shortcomings were addressed by Donabedian, who characterized quality in terms of structure (faculties, equipment, and

services), process (content of care), and outcomes.²⁵ These three components can be measured more objectively than appropriateness and allow application of the quality control techniques pioneered in industry by W. Edwards Deming. These techniques minimize variation in quality by examining production systems. The analogy to health care is that the production systems are the systems of care; the health care systems’ structure and processes are independent variables, and patient outcome is a dependent variable.

Although outcomes are unquestionably a more definitive measure of quality than process, the nature of health care is such that measuring processes of care (i.e., what is done to a patient) may be more immediately relevant to improving the quality of care than measuring outcome per se (i.e., what happens to a patient). One reason for placing greater emphasis on process in health care is that all the factors that affect outcomes in biologic systems may not be known or controllable. This differs from mechanical systems such as aircraft, where a given perturbation has a fairly predictable result. Conversely, the adaptability inherent in biologic systems means that a poor outcome may not occur every time there is an incorrect decision or an error in process.²⁶ Another reason to identify critical processes of care is that it avoids the methodological problems of risk-adjusting outcomes and/or the statistical limitations of comparing outcomes for low-frequency procedures and/or events.

Ultimately, efforts to improve quality will need to account for outcomes, but attempts to improve outcomes without consideration for the relevant processes are likely to prove frustrating. Therefore, it is critically important to identify processes that have the greatest impact on outcomes²⁷; the time and effort spent measuring processes not directly linked to outcomes are likely to be wasteful. The ARRA seeks to promote the burgeoning field of cost-effectiveness research, which informs health care decisions by providing evidence on the effectiveness, benefits, and harm of different treatment options, whether they are drugs, medical devices, surgical procedures, or ways to deliver health care. Evidence can come from existing data or by generating new evidence.

Connecting the Dots: Linking Quality to Systems of Care

Given the importance of processes of care, a surgeon’s (or hospital’s) systems of care reflect the consistency with which the same processes of care are applied to a given situation. Indirect evidence for this link comes from data on the relationship between volume and outcomes for complex procedures; surgeons and/or hospitals that do a given operation more frequently (i.e., high volumes) often have better outcomes.^{28–33} Moreover, the relative impact of hospital volume and surgeon volume on outcomes can vary by procedure. Thus, complex, team-dependent procedures such as cardiac surgery, pancreatectomy, and esophagectomy have a stronger relation with hospital volume even if performed by low-volume surgeons; by comparison, carotid endarterectomy and thyroidectomy have a strong relation with surgeon volume. A positive relation with outcomes also has been noted for surgical subspecialty training.^{28,32,34}

These volume-outcome relations data are intriguing, although they only represent associations and probabilities, not cause-and-effect relationships.³⁵ This raises the question

of whether practice makes perfect or perfect makes practice. The answer is not known but has produced two schools of thought. The practice makes perfect school of thought advocates that quality improvements on a widespread basis will derive from the adoption of better systems or processes of care. These proponents note that low volume is not always associated with worse outcomes, and high volume is not always associated with improved outcomes. Thus, the findings apply to surgeons in general but not to specific surgeons. This means that good outcomes can be achieved even with low volumes if carried out using good systems. Conversely, high volumes may result in worse outcomes in the presence of poor systems. As a further caveat, the relative applicability of the role of systems to complex care is suggested by findings from the Department of Veterans Affairs' (VA) National Surgical Quality Improvement Project (NSQIP). One study of eight common surgical procedures noted no correlation between hospital operative volume and postoperative mortality.³⁶

In comparison, the perfect makes practice school advocates regionalizing care to those centers with better outcomes. Perhaps the best known of these advocates is the Leapfrog Group (www.leapfroggroup.org), a large consortium of major employers. They used empirical observations of cost and outcomes to identify the minimum volumes for procedures such as coronary artery bypass grafting, esophagectomy, carotid endarterectomy, and aortic aneurysm repair that were associated with optimal outcomes. The empirical basis of these determinations is subject to methodological problems.³⁷ Moreover, changes in technology, such as the advent of endovascular aortic aneurysm repair, have substantially undermined the experience levels that were the basis of the original recommendations.

Other proponents of regionalization are the Institute of Medicine's National Cancer Policy Board and the National Research Council. They concluded that complicated cancer operations had better initial outcomes with high-volume providers.³⁸ Higher volumes also were associated with improved long-term survival.

Although regionalization has proven effective in trauma care, the basis of the improved quality in this setting may be better systems of care, not higher volume per se.³⁹ Moreover, the perception of preventability of trauma deaths increased in parallel with the appreciation of the importance of the system. Thus, regionalization of care without a solid understanding of the basis of the volume-outcome relation has the potential to create unintended or adverse consequences for overall care. Consequently, many believe that it is too soon to use volume-outcome data as a surrogate for quality or as criteria for establishing policy.⁴⁰ The higher quality of care at level I trauma centers comes with a price; these centers' better outcomes are also more expensive.⁴¹ This reflects both the relative and absolute aspects of cost-effectiveness. Regionalization of trauma care appears to be cost-effective relative to lack of regionalization, with an associated incremental cost of less than \$50,000/life-year saved (LYS); LYS is a measure of the number of life-years saved as a result of a health intervention. The \$50,000 figure is a threshold conventionally used to ascertain cost-effectiveness. A corollary is that cost-effectiveness does not always equate to cost saving.

Linking Processes to Performance

The desire to link processes to performance has become manifest in pay-for-performance (P4P) programs that provide incentives to adopt evidence-based process measures.^{42,43} The most conspicuous of these is Medicare's Physician Quality Reporting Initiative (PQRI) (www.cms.hhs.gov/pqri). The list of applicable measures has expanded considerably in the last several years, and some specific measures related to surgical care are listed in Table 2. A recent notable finding is that the infection control measures of the Surgical Care Improvement Project (SCIP), which are closely aligned with similar PQRI measures, appear to be most effective when used in the aggregate rather than as individual measures.⁴⁴

Although the rationale for these programs seems straightforward, there are concerns about their long-term potential effectiveness. One such concern is that only a small number of surgical process measures have been identified so far. In addition, these measures tend to be related to general aspects of care, with many processes of care more specific to the outcome of a given procedure or disease process yet to be identified.

There are also concerns that the magnitude of the cost reductions relative to the incentives is presently not known. This is particularly relevant if health care finance is a zero-sum game. If incentive payments exceed the savings, there will be increased pressure to reduce other payments to maintain budget neutrality. If the savings exceed the incentives, there may be increased pressure to increase the incentives.

A further concern relates to assigning the benefits from P4P. Surgeon-related quality improvements that appear to confer disproportionate financial benefits on the insurer rather than on the surgeon may reduce the incentive for surgeons to implement improvements. This concern also relates to P4P measures where implementation requires coordination of systems among providers rather than an isolated action on the part of an individual or an institution. For example, compliance with the measures for prophylactic antibiotics may reward or penalize a surgeon even though she or he may have little control over whether antibiotics are given in a timely fashion; the hospital systems needed for compliance may be a more important determinant of compliance with this measure. Indeed, one study found that a major barrier to compliance was that no single participant in the perioperative routine had acknowledged responsibility to administer prophylactic antibiotics.⁴⁵ The need for coordination among individuals in such situations has been recognized among commercial health maintenance organizations' (HMOs) P4P programs: only 13.3% of the physician-oriented programs focus solely on the individual physician as the unit of payment.^{42,43} The need for such coordination has raised concern that the dispersion of patient care among multiple physicians could limit the effectiveness of initiatives that rely on a single retrospective method for assigning responsibility.⁴⁶

Another concern is that P4P may not be so much pay for performance as it is pay for compliance. It is argued that the real goal should be to encourage innovation to optimize cost-effectiveness. Moreover, not all P4P programs focus on evidence-based measures. For example, one study found that 24% of physicians faced incentives derived from patient satisfaction surveys and 14% faced incentives derived from

Table 2 Current Physician Quality Reporting Initiative Measures by Surgical Specialty

General and Perioperative Measures, All Specialties

- 20. Perioperative Care: Timing of Antibiotic Prophylaxis — Ordering Physician**
Percentage of surgical patients aged 18 years and older undergoing procedures with the indications for prophylactic parenteral antibiotics, who have an order for prophylactic parenteral antibiotic to be given within 1 hour (if fluoroquinolone or vancomycin, 2 hours) prior to the surgical incision (or start of procedure when no incision is required)
- 21. Perioperative Care: Selection of Prophylactic Antibiotic — First- OR Second-Generation Cephalosporin**
Percentage of surgical patients aged 18 years and older undergoing procedures with the indications for a first- OR second-generation cephalosporin prophylactic antibiotic, who had an order for cefazolin OR cefuroxime for antimicrobial prophylaxis
- 22. Perioperative Care: Discontinuation of Prophylactic Antibiotics (Noncardiac Procedures)**
Percentage of noncardiac surgical patients aged 18 years and older undergoing procedures with the indications for prophylactic parenteral antibiotics who received a prophylactic parenteral antibiotic and have an order for discontinuation of prophylactic parenteral antibiotics within 24 hours of surgical end time
- 23. Perioperative Care: Venous Thromboembolism (VTE) Prophylaxis (When Indicated in ALL Patients)**
Percentage of patients aged 18 years and older undergoing procedures for which VTE prophylaxis is indicated in all patients, who had an order for low-molecular-weight heparin, low-dose unfractionated heparin, adjusted-dose warfarin, fondaparinux, or mechanical prophylaxis to be given within 24 hours prior to incision time or within 24 hours after surgery end time
- 30. Perioperative Care: Timely Administration of Prophylactic Parenteral Antibiotics**
Percentage of surgical patients aged 18 years and older who receive an anesthetic when undergoing procedures with the indications for prophylactic parenteral antibiotics for whom administration of the prophylactic parenteral antibiotic ordered has been initiated within 1 hour (if fluoroquinolone or vancomycin, 2 hours) prior to the surgical incision (or start of procedure when no incision is required)
- 46. Medication Reconciliation: Reconciliation after Discharge from an Inpatient Facility**
Percentage of patients aged 65 years and older discharged from any inpatient facility (e.g., hospital, skilled nursing facility, or rehabilitation facility) and seen within 60 days following discharge in the office by the physician providing ongoing care who had a reconciliation of the discharge medications with the current medication list in the medical record documented
- 76. Prevention of Catheter-Related Bloodstream Infections: Central Venous Catheter (CVC) Insertion Protocol**
Percentage of patients, regardless of age, who undergo CVC insertion for whom CVC was inserted with all elements of maximal sterile barrier technique (cap AND mask AND sterile gown AND sterile gloves AND a large sterile sheet AND hand hygiene AND 2% chlorhexidine for cutaneous antisepsis [or acceptable alternative antiseptics per current guideline]) followed
- 114. Preventive Care and Screening: Inquiry Regarding Tobacco Use**
Percentage of patients aged 18 years or older who were queried about tobacco use one or more times within 24 months
- 115. Preventive Care and Screening: Advising Smokers and Tobacco Users to Quit**
Percentage of patients aged 18 years and older who are smokers or tobacco users and who received advice to quit smoking
- 124. Health Information Technology: Adoption/Use of Electronic Health Records (EHRs)**
Documents whether provider has adopted and is using health information technology. To qualify, the provider must have adopted and be using a certified/qualified EHR.
- 193. Perioperative Temperature Management**
Percentage of patients, regardless of age, undergoing surgical or therapeutic procedures under general or neuraxial anesthesia of 60 minutes' duration or longer, except patients undergoing cardiopulmonary bypass, for whom either active warming was used intraoperatively for the purpose of maintaining normothermia or at least one body temperature $\geq 36^{\circ}\text{C}$ (or 96.8°F) was recorded within the 30 minutes immediately before or the 15 minutes immediately after anesthesia end time

Cardiac Surgery

- 43. Coronary Artery Bypass Graft (CABG): Use of Internal Mammary Artery (IMA) in Patients with Isolated CABG Surgery**
Percentage of patients aged 18 years and older undergoing isolated CABG surgery using an IMA graft
- 44. Coronary Artery Bypass Graft (CABG): Preoperative Beta Blocker in Patients with Isolated CABG Surgery**
Percentage of patients aged 18 years and older undergoing isolated CABG surgery who received a beta blocker within 24 hours prior to surgical incision
- 45. Perioperative Care: Discontinuation of Prophylactic Antibiotics (Cardiac Procedures)**
Percentage of cardiac surgical patients aged 18 years and older undergoing procedures with the indications for prophylactic antibiotics who received a prophylactic antibiotic and who have an order for discontinuation of prophylactic antibiotics within 48 hours of surgical end time
- 164. Coronary Artery Bypass Graft (CABG): Prolonged Intubation (Ventilation)**
Percentage of patients aged 18 years and older undergoing isolated CABG surgery who require intubation > 24 hours
- 165. Coronary Artery Bypass Graft (CABG): Deep Sternal Wound Infection Rate**
Percentage of patients aged 18 years and older undergoing isolated CABG surgery who developed deep sternal wound infection (involving muscle, bone, and/or mediastinum requiring operative intervention) within 30 days postoperatively
- 166. Coronary Artery Bypass Graft (CABG): Stroke/Cerebrovascular Accident (CVA)**
Percentage of patients aged 18 years and older undergoing isolated CABG surgery who had a stroke/CVA within 24 hours postoperatively
- 167. Coronary Artery Bypass Graft (CABG): Postoperative Renal Insufficiency**
Percentage of patients aged 18 years and older undergoing isolated CABG surgery who develop postoperative renal insufficiency or require dialysis
- 168. Coronary Artery Bypass Graft (CABG): Surgical Reexploration**
Percentage of patients aged 18 years and older undergoing isolated CABG surgery who require a return to the operating room for mediastinal bleeding/tamponade, graft occlusion (attributable to acute closure, thrombosis, or technical or embolic origin), or other cardiac reason
- 169. Coronary Artery Bypass Graft (CABG): Antiplatelet Medications at Discharge**
Percentage of patients aged 18 years and older undergoing isolated CABG surgery who have antiplatelet medication at discharge
- 170. Coronary Artery Bypass Graft (CABG): Beta Blockers Administered at Discharge**
Percentage of patients aged 18 years and older undergoing isolated CABG surgery who were discharged on beta blockers
- 171. Coronary Artery Bypass Graft (CABG): Lipid Management and Counseling**
Percentage of patients aged 18 years and older undergoing isolated CABG surgery who have antilipid treatment at discharge

Table 2 Continued

197. Coronary Artery Disease (CAD): Drug Therapy for Lowering Low-Density Lipoprotein Cholesterol Percentage of patients aged 18 years and older with a diagnosis of CAD who were prescribed a lipid-lowering therapy (based on current American College of Cardiology/American Heart Association guidelines)
<i>General Surgery/Colorectal Surgery</i> 185. Endoscopy and Polyp Surveillance: Colonoscopy Interval for Patients with a History of Adenomatous Polyps — Avoidance of Inappropriate Use Percentage of patients aged 18 years and older receiving a surveillance colonoscopy and with a history of colonic polyp(s) in a previous colonoscopy who had a follow-up interval of 3 or more years since their last colonoscopy documented in the colonoscopy report
<i>Ophthalmology</i> 12. Primary Open-Angle Glaucoma (POAG): Optic Nerve Evaluation Percentage of patients aged 18 years and older with a diagnosis of POAG who have an optic nerve head evaluation during one or more office visits within 12 months 14. Age-Related Macular Degeneration (AMD): Dilated Macular Examination Percentage of patients aged 50 years and older with a diagnosis of AMD who had a dilated macular examination performed that included documentation of the presence or absence of macular thickening or hemorrhage AND the level of macular degeneration severity during one or more office visits within 12 months 139. Cataracts: Comprehensive Preoperative Assessment for Cataract Surgery with Intraocular Lens (IOL) Placement Percentage of patients aged 18 years and older with a procedure of cataract surgery with IOL placement who received a comprehensive preoperative assessment of (1) dilated fundus examination; (2) axial length, corneal keratometry measurement, and method of IOL power calculation reviewed; and (3) functional or medical indication(s) for surgery prior to the cataract surgery with IOL placement within 12 months prior to cataract surgery 141. Primary Open-Angle Glaucoma (POAG): Reduction of Intraocular Pressure (IOP) by 15% OR Documentation of a Plan of Care Percentage of patients aged 18 years and older with a diagnosis of POAG whose glaucoma treatment has not failed (the most recent IOP was reduced by at least 15% from the preintervention level), OR if the most recent IOP was not reduced by at least 15% from the preintervention level, a plan of care was documented within 12 months 191. Cataracts: 20/40 or Better Visual Acuity within 90 Days following Cataract Surgery Percentage of patients aged 18 years and older with a diagnosis of uncomplicated cataract who had cataract surgery and no significant ocular conditions impacting the visual outcome of surgery and had best-corrected visual acuity of 20/40 or better (distance or near) achieved within 90 days following the cataract surgery 192. Cataracts: Complications within 30 Days following Cataract Surgery Requiring Additional Surgical Procedures Percentage of patients aged 18 years and older with a diagnosis of uncomplicated cataract who had cataract surgery and any of a specified list of surgical procedures in the 30 days following cataract surgery that would indicate the occurrence of any of the following major complications: retained nuclear fragments, endophthalmitis, dislocated or wrong power IOL, retinal detachment, or wound dehiscence
<i>Orthopedics</i> 24. Osteoporosis: Communication with the Physician Managing Ongoing Care Postfracture of Hip, Spine, or Distal Radius for Men and Women Aged 50 Years and Older Percentage of patients aged 50 years and older treated for a hip, spine, or distal radial fracture with documentation of communication with the physician managing the patient's ongoing care that a fracture occurred and that the patient was or should be tested or treated for osteoporosis 40. Osteoporosis: Management following Fracture of Hip, Spine, or Distal Radius for Men and Women Aged 50 Years and Older Percentage of patients aged 50 years and older with fracture of the hip, spine, or distal radius who had a central dual-energy x-ray absorptiometry measurement ordered or performed or pharmacologic therapy prescribed
<i>Otolaryngology</i> 91. Acute Otitis Externa (AOE): Topical Therapy Percentage of patients aged 2 years and older with a diagnosis of AOE who were prescribed topical preparations 92. Acute Otitis Externa (AOE): Pain Assessment Percentage of patient visits for those patients aged 2 years and older with a diagnosis of AOE with assessment for auricular or periauricular pain 93. Acute Otitis Externa (AOE): Systemic Antimicrobial Therapy — Avoidance of Inappropriate Use Percentage of patients aged 2 years and older with a diagnosis of AOE who were not prescribed systemic antimicrobial therapy 94. Otitis Media with Effusion (OME): Diagnostic Evaluation — Assessment of Tympanic Membrane Mobility Percentage of patient visits for those patients aged 2 months through 12 years with a diagnosis of OME with assessment of tympanic membrane mobility with pneumatic otoscopy or tympanometry
<i>Surgical Oncology</i> 71. Breast Cancer: Hormonal Therapy for Stage IC–IIIC Estrogen Receptor/Progesterone Receptor (ER/PR)-Positive Breast Cancer Percentage of female patients aged 18 years and older with stage IC through IIIC, ER- or PR-positive breast cancer who were prescribed tamoxifen or aromatase inhibitor during the 12-month reporting period 72. Colon Cancer: Chemotherapy for Stage III Colon Cancer Patients Percentage of patients aged 18 years and older with stage IIIA through IIIC colon cancer who are referred for adjuvant chemotherapy, are prescribed adjuvant chemotherapy, or have previously received adjuvant chemotherapy within the 12-month reporting period 99. Breast Cancer Resection Pathology Reporting: pT Category (Primary Tumor) and pN Category (Regional Lymph Nodes) with Histologic Grade Percentage of breast cancer resection pathology reports that include the pT category (primary tumor), the pN category (regional lymph nodes), and the histologic grade 100. Colorectal Cancer Resection Pathology Reporting: pT Category (Primary Tumor) and pN Category (Regional Lymph Nodes) with Histologic Grade Percentage of colon and rectum cancer resection pathology reports that include the pT category (primary tumor), the pN category (regional lymph nodes), and the histologic grade

Table 2 Continued

- 112. Preventive Care and Screening: Screening Mammography**
Percentage of women aged 40 through 69 years who had a mammogram to screen for breast cancer within 24 months
- 113. Preventive Care and Screening: Colorectal Cancer Screening**
Percentage of patients aged 50 through 75 years who received the appropriate colorectal cancer screening
- 136. Melanoma: Follow-up Aspects of Care**
Percentage of patients, regardless of age, with a new diagnosis of melanoma or a history of melanoma who received all of the following aspects of care within 12 months: (1) patient was asked specifically if he/she had any new or changing moles; AND (2) a complete physical skin examination was performed and the morphology, size, and location of new or changing pigmented lesions were noted; AND (3) patient was counseled to perform a monthly self skin examination
- 137. Melanoma: Continuity of Care — Recall System**
Percentage of patients, regardless of age, with a current diagnosis of melanoma or a history of melanoma whose information was entered, at least once within a 12-month period, into a recall system that includes a target date for the next complete physical skin examination AND a process to follow-up with patients who either did not make an appointment within the specified time frame or who missed a scheduled appointment
- 138. Melanoma: Coordination of Care**
Percentage of patients, regardless of age, with a new occurrence of melanoma who have a treatment plan documented in the chart that was communicated to the physician(s) providing continuing care within 1 month of diagnosis
- 157. Thoracic Surgery: Recording of Clinical Stage for Lung Cancer and Esophageal Cancer Resection**
Percentage of surgical patients aged 18 years and older undergoing resection for lung or esophageal cancer who had clinical TNM staging provided prior to surgery
- 194. Oncology: Cancer Stage Documented**
Percentage of patients, regardless of age, with a diagnosis of breast, colon, or rectal cancer who are seen in the ambulatory setting who have a baseline AJCC cancer stage or documentation that the cancer is metastatic in the medical record at least once within 12 months

Urology

- 102. Prostate Cancer: Avoidance of Overuse of Bone Scan for Staging Low-Risk Prostate Cancer Patients**
Percentage of patients, regardless of age, with a diagnosis of prostate cancer at low risk of recurrence receiving interstitial prostate brachytherapy, OR external-beam radiotherapy to the prostate, OR radical prostatectomy, OR cryotherapy who did not have a bone scan performed at any time since diagnosis of prostate cancer
- 104. Prostate Cancer: Adjuvant Hormonal Therapy for High-Risk Prostate Cancer Patients**
Percentage of patients, regardless of age, with a diagnosis of prostate cancer at high risk for recurrence receiving external-beam radiotherapy to the prostate who were prescribed adjuvant hormonal therapy (GnRH agonist or antagonist)
- 105. Prostate Cancer: Three-Dimensional Radiotherapy**
Percentage of patients, regardless of age, with a diagnosis of clinically localized prostate cancer receiving external-beam radiotherapy as a primary therapy to the prostate with or without nodal irradiation (no metastases; no salvage therapy) who receive three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiation therapy

Vascular Surgery

- 126. Diabetes Mellitus: Diabetic Foot and Ankle Care, Peripheral Neuropathy — Neurologic Evaluation**
Percentage of patients aged 18 years and older with a diagnosis of diabetes mellitus who had a neurologic examination of their lower extremities within 12 months
- 127. Diabetes Mellitus: Diabetic Foot and Ankle Care, Ulcer Prevention — Evaluation of Footwear**
Percentage of patients aged 18 years and older with a diagnosis of diabetes mellitus who were evaluated for proper footwear and sizing
- 158. Carotid Endarterectomy: Use of Patch During Conventional Carotid Endarterectomy**
Percentage of patients aged 18 years and older undergoing conventional (noneversion) carotid endarterectomy who undergo patch closure of the arteriotomy
- 163. Diabetes Mellitus: Foot Examination**
Percentage of patients aged 18 through 75 years with diabetes who had a foot examination
- 172. Hemodialysis Vascular Access Decision Making by Surgeon to Maximize Placement of Autogenous Arteriovenous (AV) Fistula**
Percentage of patients aged 18 years and older with a diagnosis of advanced chronic kidney disease (stage 4 or 5) or end-stage renal disease requiring hemodialysis vascular access documented by surgeon to have received autogenous AV fistula
- 186. Wound Care: Use of Compression System in Patients with Venous Ulcers**
Percentage of patients aged 18 years and older with a diagnosis of venous ulcer who were prescribed compression therapy within the 12-month reporting period
- 195. Stenosis Measurement in Carotid Imaging Studies**
Percentage of final reports for all patients, regardless of age, for carotid imaging studies (neck magnetic resonance angiography, neck computed tomographic angiography, neck duplex ultrasonography, carotid angiography) performed that include direct or indirect reference to measurements of distal internal carotid diameter as the denominator for stenosis measurement
- 201. Ischemic Vascular Disease (IVD): Blood Pressure Management Control**
Percentage of patients aged 18 years and older with IVD who had most recent blood pressure in control (less than 140/90 mm Hg)
- 202. Ischemic Vascular Disease (IVD): Complete Lipid Profile**
Percentage of patients aged 18 years and older with IVD who received at least one lipid profile within 12 months
- 203. Ischemic Vascular Disease (IVD): Low-Density Lipoprotein (LDL) Cholesterol Control**
Percentage of patients aged 18 years and older with IVD who had most recent LDL cholesterol level in control (less than 100 mg/dL)
- 204. Ischemic Vascular Disease (IVD): Use of Aspirin or Another Antithrombotic**
Percentage of patients aged 18 years and older with IVD with documented use of aspirin or other antithrombotic

The number of each measure is that assigned by the Centers for Medicare and Medicaid Services. Available at: https://www.cms.gov/PQRI/Downloads/2010_PQRI_MeasuresList_111309.pdf. accessed January 10, 2011.
AJCC = American Joint Committee on Cancer; GnRH = gonadotropin-releasing hormone.

profiling based on use of medical resources, whereas 19% faced incentives derived from quality of care measures. Patient satisfaction is undoubtedly important, but it is not clear that improved patient satisfaction alone suffices to address problems of cost-effectiveness.

Lastly, there is the issue of how providers might react when there are differences in P4P programs among the various health plans in which they participate. Many providers would prefer health plans to use a single standardized set of measures, but local market environments can make such standardization unlikely.⁴⁷ As a result, providers may ignore measures that seem to be contradictory, are perceived as too complex, or derive from health plans from which they get relatively few patients. A related concern is that some P4P programs could have unintended negative consequences if physicians are convinced that the program does not incorporate adequate risk adjustment mechanisms. Providers then might simply opt out of seeing challenging patients.^{48,49} To avoid some of these problems, the Agency for Healthcare Research and Quality (AHRQ) has a specific section of their website (www.ahrq.gov/qual/p4pguide.htm) devoted to P4P programs, including a decision guide for purchasers.

P4P and “value-based purchasing” are incentive payment or shared savings programs that are related to “gainsharing.” The Office of the Inspector General (OIG) has defined gainsharing as an “arrangement in which a hospital will share with each physician group a percentage of the hospital’s cost savings arising from the physician groups’ implementation of cost reduction methods.”⁵⁰ Although intended to encourage physicians to deliver quality care, such gainsharing arrangements can technically look like a model of a kickback; moreover, they are barred by the civil monetary penalty law, which prohibits hospitals from rewarding physicians for reducing services to patients. The Deficit Reduction Act of 2005 directed the CMS to conduct demonstration projects, and these are now under way.

These programs notwithstanding, substantial direct evidence of the link between systems and quality comes from the quality improvement efforts of organizations that analyze and standardize systems of care. Perhaps the most notable of these efforts is the multi-institutional Northern New England Cardiovascular Disease Study Group (NNECVDSG).⁵¹ This group began in 1990 and consisted of cardiac surgical teams (e.g., surgeons, nurses, anesthesiologists, pump technicians) that received feedback on outcomes, were trained in Deming’s quality improvement techniques, and site-visited other participating centers. They also periodically met to share data and discuss processes of care. The result has been to substantially reduce morbidity and mortality from cardiac surgery and to minimize the year-to-year mortality variations among the institutions. They also had a low incidence of procedures that did not adhere to recommended indications for surgery.⁵²

The group’s success can be attributed to several characteristics: there is no ambiguity of purpose, the data are not owned by any member or subgroup of members, members have an established safe place to work, a forum is set up for discussion, and there is regular feedback. This was achieved without personal criticism or an attempt to identify any proverbial “bad apples.” Despite concerns that the findings would lead to unfavorable publicity, this did not occur. Three

important conclusions to be drawn from these efforts are as follows: physician-initiated interventions can be as effective as external review (and possibly more effective) in improving quality; a systems approach to quality improvement is better than a bad apple approach; and it is possible to conduct quality improvement programs involving practice groups that might otherwise be viewed as competitors.

The VA’s NSQIP is another example of a successful quality initiative, achieving a 27% reduction in 30-day mortality after major procedures and a 45% decrease in morbidity.⁵³ NSQIP found the two most important risk factors for prolonged hospital stay after major elective surgery to be the intraoperative processes of care and postoperative adverse events.⁵⁴ Notably, the savings from improved surgical care far exceeded investment in the project.⁵⁵ NSQIP has now expanded into the broader community under the auspices of the American College of Surgeons (ACS). NSQIP data also have been used to validate the AHRQ Patient Safety Indicators (www.academyhealth.org/2005/ppt/tsilimingras.ppt).

Other successful surgically related quality improvement efforts include Intermountain Health Systems in Utah; the Maine Medical Assessment Foundation⁵⁶; the Washington State Surgical Clinical Outcomes Assessment Program (SCOAP)⁵⁷; Quality Surgical Solutions in Kentucky⁵⁸; the Michigan Surgical Quality collaborative⁵⁹; the Society for Thoracic Surgery national database, which is now widely accepted as a benchmark for quality in cardiac surgery⁶⁰; the New England Colorectal Cancer Quality Project⁶¹; the Vascular Study Group of Northern New England⁶²; and the National Surgical Infection Collaborative.⁴⁵

The Maine and Michigan efforts are notable in that they have been carried out in conjunction with insurers.^{63–65} Moreover, none of these efforts increased liability exposure; indeed, they often reduced it. Because the practice profiles were physician initiated, there was little risk that the findings would be used to make decisions about credentialing, reimbursement, or contracting.⁵⁶ It is also noteworthy that the parties that funded these efforts (including insurers) usually agreed to confidentiality in return for the benefit associated with voluntary physician involvement.

Measuring Health Outcomes

As noted above, the primary goal of investigating the structure and process components of care is, ultimately, to improve outcomes. Using outcomes to assess quality can be confounded by a number of factors, however. One such factor is the reduced usefulness of traditional metrics. For instance, mortality is infrequent with most surgical procedures, and morbidity such as wound infection rates can be difficult to assess in an era of early discharges. Other short-term outcome metrics, such as length of stay, readmission, or return to work, are often influenced by deeply rooted social and economic factors. A further issue is that many measures of quality lack standard definitions.⁶⁶

Another factor confounding the measurement of health care outcomes has been the growth of knowledge and technology that has increased surgical care related to chronic and/or degenerative diseases. Recent data show that 133 million people, or almost half of all Americans, live with a chronic condition.⁶⁷ That number is projected to increase by more

than 1% per year by 2030, resulting in an estimated chronically ill population of 171 million. Moreover, almost half of all people with chronic illnesses have multiple conditions. Integrated health care delivery via the chronic care model is intended to address the many deficiencies in the current management of diseases such as diabetes, heart disease, depression, and asthma. Traditional measures of quality (e.g., 30-day mortality) that are applied to acute conditions such as perforated ulcer are not as applicable here. Given that the number and complexity of treatment options for many surgical conditions have increased, it has become necessary to identify quality metrics for each treatment strategy. There also is increasing emphasis on patient-centered care; given the multicultural nature of US society, the result is substantial heterogeneity in patient perspectives on quality. Overall, there has been little research (i.e., clinical trials) on the quality perspectives of vulnerable populations.

Health care quality in this context is typically assessed in terms of quality-adjusted life years (QALYs),^{68,69} a measure that reflects the length of time during which a patient experiences a given health status. The lexicon of research in this area is extensive. Cost-utility analysis is the form of CEA of alternative interventions where costs are measured in monetary units and outcomes in terms of patient utility, usually to the patient, in QALYs. A patient utility is the relative desirability or preference from the patient's perspective for a given health outcome. QALYs are units of health outcomes that adjust gains or losses of years of life subsequent to a health care intervention by the quality of life during those years. Other (although less frequently employed) measures for patient utilities include disability-adjusted life-years (DALYs) and health-year equivalents (HYEs). DALYs are units of health status adjusting age-specific life expectancy by loss of health and years of life attributable to disability from disease or injury, whereas HYE are the number of years of perfect health considered to be equal to the remaining years of life in their respective health states.

QALYs are applicable to assessing surgical outcomes. They can be calculated by several different methods; some include objective measures (e.g., functional status), whereas others only consider subjective estimates of well-being. Even the objective measures consider patient-desired outcomes to capture the meaningfulness of a given functional status. For instance, a patient may not be able to walk as far as another, but whether the former has a worse quality of life depends on each patient's lifestyle.⁷⁰ The result is that QALYs data tend not to follow a normal distribution, and comparative analyses often require use of nonparametric techniques.⁷¹

Estimates of QALYs can be affected by other factors.^{26,72} For instance, estimates of the future value of an outcome measure may vary with the prevailing circumstances at the time of assessment (e.g., acute pain) or with the patient's age (e.g., elderly patients often place great value on the ability to live independently). Calculation of QALYs may also be affected by gender, ethnicity, socioeconomic status, religious beliefs, time away from work, and other factors that affect attitudes about health care. One study noted that surgeons tended to underestimate the importance of patients' social and spiritual themes.⁷³ Adjusting outcome measures to account for health status and severity of illness before treatment also can be difficult.⁷⁴

As with other aspects of cost-effectiveness, estimates of QALYs are confounded by different perspectives among patients, providers, and payers with regard to the experiential, physiologic, and resource-related dimensions that should apply. Thus, the weight given to clinical probabilities, patient utilities and preferences, and cost will affect the calculations. Assessment of quality is further complicated when there is no consensus across perspectives with regard to the preferred strategy or outcome. Finally, quality of life studies can be compromised by other methodological flaws, such as a relative paucity of validated instruments for measuring health-related quality of life, especially in certain specialty areas.⁷⁵ In this context, a 2008 review could not identify a fully validated instrument for assessing postoperative recovery.⁷⁶

INTERPRETING AND/OR INITIATING COST-EFFECTIVENESS ANALYSES

A primer to initiate and/or interpret CEA is available at www.acponline.org/shell/cgi/printhappy.pl/journals/ecp/sepect00/primer.htm.

Several important principles that must be considered when performing and/or interpreting a CEA are the comparison, perspective, direct and indirect costs, time horizon, discounting, and sensitivity analyses.^{77–79} The specific comparison between one health care intervention and another should be precisely defined at the outset of the analysis. Alternative perspectives are of society overall (favored by many), a third-party payer, a physician, a hospital, or a patient. CEA should incorporate two types of cost; direct costs represent the value of all goods, services, and other resources consumed in providing health care or dealing with the side effects of the care, whereas indirect costs (or productivity losses) include the costs of lost work attributable to absenteeism or early retirement, impaired productivity at work, or premature mortality. Intangible costs (i.e., pain, suffering, and grief) are often omitted, which is an important limitation of most CEA. The time horizon of a CEA is the time frame of the study and should be long enough to capture streams of health and economic outcomes; depending on the research question, the time horizon might encompass a disease episode, patient life, or even multiple generations. Discounting allows the model to account for the effect of the passage of time on the values of costs and outcomes, such that costs and outcomes are discounted relative to their present value (e.g., at a rate of 3 to 5% per year). Inflation should be a separate consideration. Finally, sensitivity analyses should be performed to determine if plausible variations in the estimates of certain variables thought to be subject to significant uncertainty affect the results of the cost analysis.

Lower values of cost-effectiveness are understood to be “more cost-effective” or have “increased cost-effectiveness.” In contrast “less cost-effective” and “decreased cost-effectiveness” refer to higher costs per LYS. Cost-effectiveness that has a negative value implies that money would be saved.

Particular points that warrant consideration are as follows:

- CEA is highly sensitive to the choice of compared strategies: it often involves marginal benefits, and excluding a simple strategy in which the only comparison is between

treatment and no treatment can make a particular strategy appear far more cost-effective than it otherwise might seem. CEA does not answer the question of which strategy is economically preferred; rather, it identifies which strategy is more effective in terms of LYS for a given expenditure.⁸⁰

- The quality of supporting evidence is another important consideration. Data garnered in real practice or from a registry are more likely to be generalizable than data that are modeled or collected from a clinical trial.
- Determinations made under optimal circumstances (efficacy) tend to overestimate cost-effectiveness compared with determinations made under real-world conditions (true effectiveness). This distinction between efficacy and effectiveness is reflected in how differences in postoperative stroke rates influence the cost-effectiveness of carotid endarterectomy. Randomized, controlled trials (RCTs) show this procedure to be efficacious when performed by surgeons, with low rates of perioperative stroke and death. As the incidence of stroke and other complications increases with more general use, the procedure becomes less effective or even ineffective.^{81–83} If effectiveness can vary over a relatively narrow range of outcomes, there is a strong ethical motivation for surgeons to be familiar with their own clinical outcomes and seek their patients' informed consent based on their personal results.⁸⁴ In this context, differences in quality or cost measures may be more a function of patient mix than the abilities of the wider surgeon population.
- There needs to be awareness of recent concerns that there may be a bias related to the funding of the study.

These and other considerations require surgeons to possess fundamental skills related to critical analysis of the medical literature, technology assessment, use of diagnostic testing, and clinical decision analysis. Specifics on these skills are further detailed below.

CRITICAL ANALYSIS OF THE MEDICAL LITERATURE

The medical literature is so expansive that one can keep current only with a small fraction of it. Moreover, the potential value of a given study is assigned a level of evidence based on the study's methodology. Yet even here there are a number of accepted techniques for grading level of evidence that include that from the Centre for Evidence Based Medicine (CEBM; www.cebm.net/index.aspx?o=1025), the U.S. Preventive Health Task Force, or the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system.⁸⁵ The GRADE Working Group is an international collaboration of guideline developers, methodologists, and clinicians whose recommendations on clinical practice guidelines have been increasingly validated in a number of practice settings. Many guideline organizations and medical societies have endorsed the system and adopted it for their guideline processes. Further discussion of guidelines is in the section on Clinical Guidelines below.

RCTs are at the high end of all these scales, and meta-analyses of RCTs have even higher validity. Still, even RCTs have shortcomings: the reporting methods are not fully standardized; their stringent inclusion criteria tend to limit their

applicability to highly specific groups of patients (e.g., elderly and/or pregnant patients are often excluded); they can be expensive; and the numbers of patients needed for statistical purposes can be impractical. In addition, study findings that might seem to apply to a particular patient may be difficult to reproduce in settings that differ from the controlled conditions of the original trial. Also, the pressure to enroll patients in such trials has, on occasion, led to questionable ethical behavior by the investigators.

Three particularly valuable sources for identifying studies relevant to cost-effectiveness and judging the quality of those studies are MEDLINE (www.ncbi.nlm.nih.gov/PubMed/medline.html), the Cochrane Collaboration (www.cochrane.org), and the CEBM (www.cebm.net). Each site has relative advantages and disadvantages. The Cochrane Collaboration is an international network of epidemiologists and clinicians who systematically review the best available medical evidence; it includes sources not always accessible through MEDLINE but, in contrast to MEDLINE, requires a subscription. Recent Cochrane Collaboration reviews are abstracted monthly in the *Journal of the American College of Surgeons* (JACS).

The ACS also makes several literature resources available. These include *Selected Readings in General Surgery* (SRGS), a trusted point of reference that is also available in a Web-based version; and *Evidence Based Reviews in Surgery* (EBRS), a Web-based program developed jointly with the Canadian Association of General Surgeons. Each month during the academic year, EBRS presents a clinical and methodological article that teaches critical appraisal skills. More information about these programs is available at www.facs.org. A series of publications by the Evidence-Based Medicine Working Group also provides further insight into critical literature analysis (<http://jamaevidence.com/resource/520>).

The complexities of literature analysis are reflected in a prospective study of the value of computed tomography (CT) in diagnosing appendicitis. This study compared the clinical likelihood of appendicitis (as estimated by the referring surgeon) to the estimated probability of appendicitis (as determined by CT) and the pathologic condition (or absence thereof), which was then confirmed by operation or recovery.⁸⁶ The clinical likelihood of appendicitis was assigned to one of four categories: (1) definitely appendicitis (80 to 100% likelihood), (2) probably appendicitis (60 to 79%), (3) equivocally appendicitis (40 to 59%), and (4) possibly appendicitis (20 to 39%). The real-life observed incidence of appendicitis in these four categories was 78%, 56%, 33%, and 44%, respectively. Thus, CT interpretations had a sensitivity of 98%, a specificity of 98%, a positive predictive value of 98%, a negative predictive value of 98%, and an accuracy of 98% for either diagnosing or ruling out appendicitis.

Although these results may seem relatively clear-cut, it is possible that the study could have yielded different results and reached other conclusions if it had been performed at another institution. For example, the clinical diagnosis of appendicitis is more accurate among men than among women, and, as a result, the relative value of CT scanning will vary according to the gender distribution of the study group. Also, variability in the estimates of the clinical likelihood of appendicitis among surgeons in that institution, the availability of less expensive alternatives to in-hospital observation, and

use of the emergency department for triage all might lead to substantially different results. The impact of variability in clinical estimates of appendicitis is reflected by the fact that in this report, 53% of the patients had appendicitis; in contrast, other studies have shown that only 30% of patients with an admitting diagnosis of appendicitis eventually underwent appendectomy.⁸⁷ The impact of the accuracy of CT or ultrasonography on negative appendectomies also has been reported.⁸⁸

Literature analysis also requires a distinction between relative and absolute risk reduction. The degree of relative improvement is a function of the baseline results such that a treatment that reduces the incidence of an undesired outcome from 5% to 4% and a treatment that reduces it from 50% to 40% both achieve a 20% relative reduction in risk. However, the second treatment achieves a 10-fold greater absolute risk reduction. In addition, the cost-effectiveness of these two treatments is likely to be very different. This distinction between absolute and relative improvement is an important aspect of patient-centeredness in decision making. It is particularly relevant to patients' willingness to participate in trials of adjuvant cancer therapy. Their decisions for or against such therapy may be affected more by the potential for absolute benefit than by relative benefit.

Interpretation of the literature also needs to consider disease staging. Earlier diagnosis may appear to improve long-term survival but actually only identifies the condition for a longer time. This is known as lead-time bias, and it can lead to overestimation of disease prevalence.⁸⁹

Literature assessment skills are also needed to keep pace with patients' growing access to medical information. There are tens of thousands of health-related Web sites, and tens of millions of adults find health information online. Patients also get information from poorly monitored sources, such as disease-specific bulletin boards. At least some of this information will be inaccurate, misleading, out-of-date, incomplete, or unconventional.⁹⁰ For example a recent study of thyroid cancer information on the Internet determined that the data pertaining to surgical treatment, in particular, were wanting, and only 38% of Web sites were updated in the previous 2 years. No predictors of quality were identified.⁹¹ Indeed, a study of the methodological quality of economic analyses of surgical procedures concluded that studies of cost-effectiveness in surgery in the medical literature often do not meet established criteria.⁹²

TECHNOLOGY ASSESSMENT

The "technological imperative" reflects a prevailing societal attitude that equates the latest with the best and creates considerable pressure to acquire the newest equipment and techniques, even before its value is evident. The explosive growth of technology in recent years has been a particularly important contributor to the rapid growth of health care costs.^{93,94} Although many technological advances have undeniably improved surgical care, some new technologies do not prove to be useful. Accordingly, surgeons need to know how to make decisions about technology acquisition⁹⁵ and how they may contribute to excess capacity and increase health care costs. The problem begins with providers who succumb to the technological imperative before a technology's value is

fully known. Other providers, fearful of being left behind, then follow suit. If the new technology is beneficial, capacity may grow to the point that it exceeds community's needs; if not beneficial, injudicious adoption severely reduces cost-effectiveness. Although some advocate competition among providers as a way of restraining health care costs, competition driven by the technological imperative can contribute to inflationary increases in these same costs. A further consideration is the opportunity costs related to differences in efficiency among competing surgical devices.⁹⁶

Innovations that involve new applications of existing technology are a particular challenge.⁹⁷ Laparoscopic cholecystectomy is a striking example of an existing technology that was rapidly and widely adopted into a new surgical procedure before its nuances were fully appreciated or mastered. Although now a relatively safe procedure, the learning curve of laparoscopic cholecystectomy was associated with a number of bile duct injuries; it is conceivable that at least some of these adverse events could have been avoided had the procedure been introduced in a more systematic fashion. Important lessons here come from a study that analyzed the time needed to learn minimally invasive cardiac surgery.⁹⁸ Fast-learning teams were characterized by members who worked well together in the past, had gone through the early learning phase together before adding new members, scheduled several of the new procedures close together, discussed each case in detail beforehand and afterward, and carefully tracked results. Notably, surgeons on the fast-learning teams were less experienced than those on the slow-learning teams but were more willing to accept input from others on the team.

Given this background, there are a number of questions that should be asked whenever a new technology or an innovation in surgical care is being considered:

- Has the new technology or innovation been adequately tested for safety and efficacy?
- Is the new technology or innovation at least as safe and effective as existing, proven techniques?
- Is the individual proposing to perform the new procedure fully qualified to do so? This raises issues pertaining to surgeon education, skill acquisition, team identification, credentialing, and systems preparation failure.
- Is the new technology effective for the intended purpose? Does the new technology or innovation improve cost-effectiveness?
- Has allowance been made for appropriate patient selection and informed consent?
- What is the appropriate role of industry in new technology education efforts?
- What role do media and public expectations and desires play in driving the application of new technology?

USE OF DIAGNOSTIC TESTING

Laboratory and imaging studies account for a large share of health care costs, and there are substantial variations in the use of such studies. Improving cost-effectiveness goes beyond just being aware of a test's sensitivity (i.e., the ability to identify patients with a disease) and specificity (i.e., the ability to identify patients without a disease). It also depends on the prevalence of the disease in the population in question.⁹⁹ As an example, if a given test has a 98% sensitivity and a 98%

specificity and is applied to a group of patients with a disease prevalence of 10% (i.e., 10% of them has the disease), the results of 49 of 500 patients will be true positives ($500 \times 0.98 \times 0.1$) and 9 ($500 \times 0.02 \times 0.9$) will be false positives. If this same test is applied to a population with a disease prevalence of 1% (a more likely prevalence in the real world), the results of fewer than five of every 500 patients tested ($500 \times 0.98 \times 0.01$) will be true positives and just under 10 ($500 \times 0.02 \times 0.99$) will be false positives. Thus, for any given sensitivity, the ratio of false true positives to true positives increases inversely with disease prevalence.

If this example was applied to a screening test, which if positive might then indicate the need for a riskier downstream test, the likelihood is that an increasing number of false positives would be exposed to the cost and safety risks of the follow-up test without potential benefit. This illustrates the shortcomings of appropriateness as a measure of quality where the relation between health care cost and quality was seen exclusively as positive. Given that complications of downstream tests are just as likely to occur among patients with false positives as among patients with true positives, the net effect of such testing is to decrease the slope of the cost-benefit curve and increase the slope of the cost-harm curve. The differential effects of such testing on these curves alter the relation of quality to cost and produce a negative slope [see Figure 6].¹⁰⁰ This is more than just a theoretical relation as there are now data to show that hospitals' performance on quality of care is not associated with the intensity of their spending.¹⁰¹ Another key point is that the slope between two points represents the incremental changes in cost-effectiveness.⁸⁰ Thus, changes in cost-effectiveness may vary, depending on which portion of the curve is considered.

This effect of disease prevalence on the incidence of false positives establishes a test's value or utility and explains why a test may have relatively little value as a screening test in

general practice (where the disease prevalence is low) but may have high value as a diagnostic tool in a specialty practice (where referrals increase the relative prevalence of the disease). The above calculations illustrate how CEAs can be performed on diagnostic tests and screening techniques as well as more traditional comparisons of treatment.

A specific example of how test utility might affect clinical decision making is that of the functional assessment of incidental adrenal masses.¹⁰² Biochemical testing of patients with these masses in the absence of concrete signs and symptoms may be of relatively little value. Analyses of many other "routine" preoperative tests also suggest that they may add little value.^{103,104} Whether a recent increase in testing noted among cancer patients has added value is unknown.¹⁰⁵

CLINICAL DECISION ANALYSIS

Clinical decision analysis involves identifying and quantifying the effect or impact of each option involved in a diagnostic or therapeutic decision. On the basis of the best estimates available, the outcome of each decision acquires a probability, and each component of the decision tree carries an explicit assumption that allows an appreciation of how specific factors affect the outcome. Management of penetrating colon trauma¹⁰⁶ and treatment of asymptomatic carotid artery stenosis¹⁰⁷ are two examples subject to such analyses. It is important to emphasize that physicians should not feel unduly constrained by these clinical decision analyses; depending on individual patient circumstances, it may be reasonable to give greater consideration to some options and discount others. Thus, decision trees are not intended as absolute mandates but rather as tools for reducing uncertainty and thereby increasing cost-effectiveness.^{108–110}

Some find the mathematics and lexicon of clinical decision analyses intimidating; others may perceive such analyses as exemplifying a "cookbook" approach to health care. Markov modeling involves a set of mutually exclusive states for which there are transition probabilities of moving from one state to another. States have a uniform time period, and transition probabilities remain constant over time, which is often not a realistic circumstance. Nonetheless, it is clear that formal clinical decision analysis yields estimates of the importance of specific facets of health care that might be difficult to obtain otherwise.¹¹¹

PRACTICE GUIDELINES/CRITICAL PATHWAYS

Practice guidelines, also known as critical pathways, intend to indicate the best known processes of care for improving safety and quality. They seek to standardize medical processes, especially in high-volume, high-risk, or complex procedures.¹¹² Such standardization is intended to minimize the variations in practice that imply consequent variations in the cost and quality of care. These pathways are increasingly developed by specialty societies and consensus conferences; they are also available commercially and through focused publications. Online guidelines are available through the National Guideline Clearinghouse (NGC) of the AHRQ at www.guideline.gov or through evidence-based practice centers. Critical pathways seek to improve cost-effectiveness by displaying optimal goals for both patients and providers. The potential benefit of these pathways can be quantified using deviation-based cost modeling.¹¹³

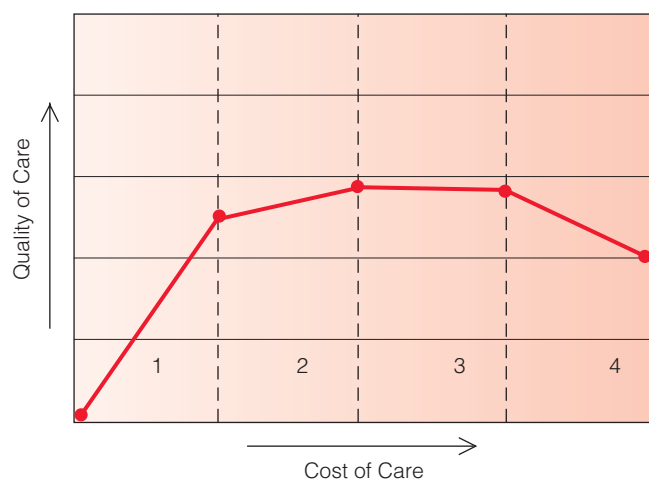


Figure 6 The new concept of quality and cost.⁹⁹ A positive association between quality and cost still exists in zones 1 and 2, but the slope of the curve flattens in zone 3 and actually becomes negative in zone 4. Here, further cost increases are associated with decreasing quality because increased use of sophisticated (albeit riskier) technology in earlier (or even just suspected) stages of disease may result in a flat slope (zone 3) or even a negative one (zone 4).

These guidelines have been criticized on several accounts: the evidence and knowledge needed for such guidelines are often lacking¹¹⁴; there may be a lack of consensus regarding what constitutes “best practice”; guidelines from different sources may be at odds with each other; they may not adhere to established methodological standards^{115,116}; they may become quickly outdated¹¹⁷; they have been criticized as embodying an overly simplistic approach to health care; the focus on quality and efficiency of care is often adopted after a decision has been made to admit a patient or perform a procedure; and they often do not apply to particular patients and can be difficult to use in patients with other, more urgent medical problems. Finally, there are emerging data calling into question whether published practice guidelines are incorporated adequately into all aspects of day-to-day practice, particularly with regard to vulnerable populations, such as the elderly.^{118,119}

In summary, use of these guidelines may not automatically improve quality. Thus, they should best be understood not as rigid rules but rather as ways to codify experiences so that others can avoid mistakes. Accordingly, critical pathways should be considered flexible and should be modified on the basis of experience.

COORDINATION OF CARE

The growing complexity of health care makes teamwork and communication increasingly essential. Lack of coordination can increase costs through the duplication of tests and unnecessary delays; it can also decrease patient satisfaction. One study categorized delays as being attributable to test scheduling (31%), availability of other facilities postdischarge (18%), physician decision making (13%), discharge planning (12%), and surgical scheduling (12%).¹²⁰ Moreover, poor coordination of care is a notable factor in professional liability claims against surgeons.¹²¹

ELECTRONIC MEDICAL RECORDS

Electronic medical records have been advocated as a means of expediting the transfer of important information and improving the coordination of care. Indeed, a key portion of the ARRA was the Health Information Technology for Economic and Clinical Health Act (HITECH), which includes substantial funding for implementation of “meaningful use” of information technology. The goal is to bring US health care fully into the Information Age. To date, the effect of introducing information technology (IT) into hospitals and practices has been a mixed bag. The VA has estimated substantial benefits from its investment,¹²² but the benefit of electronic medical records at private sector hospitals and in private practices appears to be marginal. Electronic medical records are not a panacea, and their benefit in reducing failure to inform patients of clinically significant outpatient tests was greatest in practices that already had good processes for recording progress notes and test results.¹²³

IT is invaluable in improving safety^{124,125} as it facilitates use of strategies to reduce medical errors. Such strategies include tools to improve communication, make information more readily accessible, acquire key pieces of information for subsequent process steps, assist with calculations, perform checks in real time, assist with monitoring information, and provide

decision support.¹²⁶ Studies of computerized clinical decision support systems indicate that practitioners perform better with systems that provide automatic prompts than systems that first require system activation. Such studies also find that there is a greater likelihood of better performance in systems developed by the authors than in those who were not.¹²⁷ Computerized physician order entry has been shown to reduce medication errors¹²⁸ and facilitate ventilator weaning¹²⁹ but is not foolproof and can introduce other types of errors.¹³⁰

Strategies for Improving Cost-effectiveness

It is human nature that every surgeon believes that she or he is among the best. Yet data often show considerable variations in resource use, cost, and outcomes among surgeons. Moreover, these variations cannot readily be accounted for by differences in disease prevalence or severity. Furthermore, areas with higher frequencies of procedures do not have demonstrably better procedure-related health.^{131,132} As a result, these variations are thought to be related more to community signatures or physician uncertainty. Curiously, data on individual surgeon performance are often available to hospital administrators and insurance companies but not the surgeons themselves. The result has been that strategies for cost containment and/or quality improvements often originate at the “blunt” end of a system rather than focusing on direct surgeon involvement. Examples of some of these strategies are outlined in the following sections.

BENCHMARKING CLAIMS DATA

Insurers use claims data to create hospital and physician performance profiles of costs and outcomes. The most favorable data are then used to establish benchmarks. Unfortunately, such benchmarks have limitations. For example, they tend to reflect an ideal or exceptional patient population and may not fully account for severity factors that affect outcome.¹³³ Adjustments for disease severity are particularly difficult to make on the basis of claims data because in many cases, the requisite data either are not collected or are mis-coded.¹³⁴ Medical record review is effective at accounting for severity but is more time-consuming and costly. Even with medical record review, the effects of comorbid conditions on cost and outcome can be difficult to sort out. As a result, it is still difficult to account for much of the cost variation.¹³⁵ Another limitation of benchmarks is that some differences in cost and length of stay are related to factors that are not under surgeons’ direct control, such as patient age, gender, and various cultural, ethnic, or socioeconomic factors extrinsic to the medical care system.^{136–138} Selection bias can affect outcome reporting.¹³⁹ High rates of functional health illiteracy also can adversely affect compliance and thereby outcomes.¹⁴⁰ In the end, some efforts to meet benchmark performance levels actually have the unintended effect of increasing the risk of adverse outcomes in patients with complicated health problems who need more complex care.

PUBLIC REPORT CARDS

Another approach to improving cost-effectiveness has been to distribute provider outcomes directly to the public in the

form of report cards.¹⁴¹ The rationale is that patients armed with this information will choose providers with better outcomes. Such an effort by the CMS (then the Health Care Financing Administration, or HCFA) in the 1980s calculated mortality data for individual hospitals using a risk adjustment model based on DRGs. Subsequently, however, the CMS acknowledged the flaws in the associated mortality model and stopped releasing these data. Subsequently, the CMS (using Medicare data) and some states publicly disclosed provider-specific data on the outcomes of cardiac surgery. Although these efforts used more criteria than were available through DRGs alone,^{142,143} the profiles remained controversial because they still did not adequately account for all the differences in case mix and disease severity. Good surgeons operating on high-risk patients could be adversely affected and less qualified surgeons operating on low-risk patients (or perhaps even without indications for surgery) inappropriately rewarded.

Although release of these data did lower patient mortality, it also might have had the unintended consequence of creating incentives to reduce mortality by avoiding high-risk patients.^{144,145} These report cards also appeared to have limited credibility among cardiovascular specialists.¹⁴⁵ Moreover, the data seemed to be of limited value to the target audience (i.e., patients undergoing cardiac surgery) in that there were few changes in market share among the involved institutions.

The success of provider report cards in prompting quality improvement depends on several factors.^{146,147} These include the strength of the research design and the ease with which the public can understand the text and/or the data display. Despite their shortcomings, use of report cards has now expanded to other specialties. One Web site (www.healthgrades.com) contains hospital outcomes for cardiac, orthopedic, neurologic, pulmonary, and vascular surgery. Transplantation outcomes are also available from the United Network for Organ Sharing (UNOS) at www.unos.org.

To date, evidence supporting a positive effect from these various strategies remains mixed. A 2002 literature review concluded that, based on limited evidence, explicit incentives placing physicians at financial risk appeared to be effective in reducing resource use.¹⁴⁸ However, the empirical evidence regarding the effectiveness of bonus payments on physician resource use was mixed. A more recent review of the value of publicly reported performance data on effectiveness, safety, and patient-centeredness failed to identify conclusive evidence that such reporting was effective.¹⁴⁹ Moreover, only a minority of providers appear to be participating in the PQRI program. This makes it difficult to assess the effect of the program on overall quality. It is still not clear whether the refusal to pay for some “never events” (i.e., shocking medical errors that should never occur) by Medicare¹⁵⁰ and by some private insurers will beneficially impact quality and safety.

Given the limitations of these externally initiated efforts and the remarkable success of physician-initiated efforts noted above, the most difficult step in enhancing cost-effectiveness may be developing a local willingness to initiate the process. Studies of factors associated with practice change in relation to continuing medical education (CME)

consistently emphasize that effective change strategies include reminders, patient-mediated interventions, outreach visits, input from opinion leaders, and multifaceted activities. Specific factors associated with an increased probability of practice change are peer interaction, commitment to change, and assessment of the results of change.^{151–153} Successful activities place substantial emphasis on performance change rather than simply on learning.^{154,155} Additional evidence suggests that improvement in care is more likely to occur with CME activity that is directly linked to processes of care.¹⁵⁶

An underlying tenet from the outset should be that improving cost-effectiveness is an ongoing process akin to peeling an onion: initial steps inevitably lead to deeper analyses. A starting place may be as simple as choosing a particularly bad outcome and taking steps to avoid its occurrence or recurrence. Simple data charts may reveal changes or patterns in outcomes or resource consumption that might not otherwise be obvious. On occasion, merely standardizing a process is sufficient to substantially improve outcomes. With time, strategies for optimal practice are likely to emerge. However, the majority of these efforts are unlikely to eliminate all variations in provider outcomes. For instance, when advances in the care of cystic fibrosis were adopted nationwide, outcomes improved for most centers, but some centers still had better risk-adjusted outcomes than others.¹⁵⁷ Identifying the factors responsible for these remaining differences is a difficult but critical undertaking to achieve the next level of improvement.

Improving Cost-effectiveness in the Operating Room

The operating room is a frequent target for efforts to improve efficiency. Delays in room turnover are a common complaint, the responsibility for which is variously ascribed to nurses, anesthesiologists, and surgeons themselves. Maintaining large inventories to satisfy individual surgeon preferences also contributes to higher costs, and the growth of minimally invasive surgery has added new dimensions to this challenge.¹⁵⁸ Key issues in this setting include reusable versus disposable equipment, variations in the costs of different types of equipment used to accomplish the same task, and just-in-time inventory. Major pieces of equipment often are duplicated to allow similar cases to be performed simultaneously in different rooms, but this duplication often means that the equipment may then be idle for relatively long periods. More efficient use of such equipment reduces costs, but this requires levels of cooperation and coordination among surgical staff members that heretofore have been hard to achieve.

To improve efficiency, surgeons, who have heretofore often been steeped in the view that they are the “captain of the ship,” must embrace the view that all members of the surgical team have interdependent goals for quality, safety, and efficient use of the operating room. Indeed, the team concept requires abandoning the idea that the operating room is staffed by separate surgical, nursing, and anesthesia crews. Models for achieving greater efficiency have been proposed, largely based on the airline industry and aerospace travel coordination.¹⁵⁹ Successful team efforts have led to cost reductions in trauma care^{160,161} and to the development of

protocols to guide ventilator weaning.^{162,163} More human factors research is needed to identify and overcome insidious barriers to human communication.^{164–168}

Ambulatory surgical units often are heralded as cost-effective. However, potential savings are likely to depend on existing operating room capacity and on specific payer issues.¹⁶⁹ By taking less complex cases away from the hospital, there may be fewer cases on which the hospital can amortize fixed costs. Another reason ambulatory surgical units may cost less is that they do not have to maintain standby capability to deal with emergencies. As more surgical procedures are performed on an outpatient basis, there is a growing tension between hospitals and surgeons over the facilities used for such procedures. Independent facilities may be able to eliminate some costs, but they also contribute to excess capacity and probably will not reduce health costs in the long run. This means that sooner or later, surgeons and hospitals will have to address their common interests.¹⁷⁰ Eliminating some of the barriers to gainsharing is likely to facilitate such efforts.

Ethical and Legal Concerns

Efforts to improve cost-effectiveness are often seen as forcing health professionals to face conflicts among the needs of individual patients, the interests of society as a whole, and third parties. Physicians are no strangers to such potential conflicts. Indeed, the vast majority of physicians successfully avoid the temptations inherent in fee-for-service care. The managed care era raised some concerns about conflicts between corporate and patient interests, but these concerns proved to have relatively little foundation and have since abated. Some have suggested that evidence-based data derived from large populations may not readily apply to individual patients, but the rationale for this view is not clear.²³ Thus, physicians should be able to represent both an individual patient's viewpoint and a societal perspective.

The high costs of the terminally ill frequently generate controversy, particularly among patients who require intensive care. To mitigate the dilemmas that may face physicians in making life-ending decisions, increasing emphasis is being placed on patient self-determination. Even the best efforts of physicians and institutions to comply with patient or family choices in the setting of terminal illness may not substantially reduce costs or improve outcomes.¹⁷¹ Actual savings may be small.¹⁷²

Quality in the Aggregate: Small Geographic Area Variation

Earlier in this chapter, it was noted that physician decisions powerfully impact a large proportion of health care costs. The traditional approach has been to honor physicians' deference in such decisions. An increasing challenge to physicians' authority as an arbiter of quality is the long recognized, poorly explained variation in the frequency of surgical procedures among small geographic areas.^{173–175} These variations have been intensively studied and found to remain relatively constant over time. The result is that some communities acquire distinct "surgical signatures"—a finding that supports the

idea that many operative decisions are based on opinion rather than on evidence.¹⁷⁶ This idea is further supported by data indicating that variations in procedure frequency are often procedure specific and inversely related to the degree of consensus regarding indications.¹⁷⁷ Procedures with highly specific indications (e.g., repair of a fractured hip or appendectomy) often show minimal frequency variation, whereas procedures with seemingly less definitive indications (e.g., carotid endarterectomy, hysterectomy, and coronary angiography) often show a great deal of variation.¹⁷⁸ Variations in frequency also can have downstream effects¹⁷⁹; one example of this is the relatively close relation between the intensity of local diagnostic testing and the subsequent performance of invasive cardiac procedures.¹⁸⁰

One issue of debate in interpreting these geographic frequency variations is whether high rates of use are too high or low rates are too low. The association between variation and the ratio of hospital beds to population has raised concerns that low frequency of use may reflect restricted access to care.¹⁸¹ In one study where patients in the aggregate received about half the recommended level of care,¹⁸² a lack of access to health services did not appear to be the underlying problem. To date, efforts to find evidence supporting other possible explanations for these variations (e.g., differences in disease incidence and in the appropriateness of use) have not been successful.¹⁸³

Although some might attribute variations in frequency to the potential conflict of interest inherent in a fee-for-service system, similar variations in procedure frequency are known to occur among VA medical care facilities,¹⁸⁴ as well as in countries that do not have fee-for-service reimbursement.

The current belief is that the high use rates are too high and is supported by findings that patients from areas with widely disparate use rates have comparable health status. These findings have led to the conclusion that "marked variability in surgical practices and presumably in surgical judgment and philosophy must be considered to reflect absent or inadequate data by which to evaluate surgical treatment."¹⁸⁵ This was supported by a study in the 1970s that estimated that only about 15% of common medical practices had documented foundations in medical research.¹⁸⁶ Although this does not necessarily mean that only 15% of care is effective, it does raise concerns about the lack of hard evidence for most care. A more recent estimate is that one third of current health care spending may be wasteful.¹⁸⁷

A related issue is whether these variations should be used to formulate public policy.^{188,189} Some discount these variations by arguing that they are not risk adjusted for differences among patients and cannot predict which will be better at saving lives. Others acknowledge that the Dartmouth analyses are not perfect but are better than other existing methods. Both views agree that these variations should not be used as the sole method to set hospital payment rates and that end-of-life data used for these analyses provide only limited insight into the overall quality of care.

The point is that in addition to misuse, overuse and underuse also can reflect quality. Although there has been some improvement in the adoption of processes of proven value (e.g., the optimal timing and duration of perioperative

antibiotics), overall progress has been disappointingly slow.¹⁹⁰

Reassessing the Relationship between Cost and Quality in Health Care

This chapter sought to emphasize that health care costs do not necessarily have to have a direct relation to quality (i.e., better care does not need to be more expensive). Indeed, higher-quality health care can cost less. Unfortunately, US physicians are more likely than physicians in other countries to report that interventions in patient care geared to cost control were threatening the quality of care they could provide their patients.¹⁹¹ Thus, recognizing that quality does not have to be sacrificed with reductions in cost is essential to overcoming fears that health care reform will adversely affect quality. In this context, it is likely to take time for evidence supporting higher-quality/lower-cost care to evolve. Hopes that such evidence might come quickly have been dashed by reports showing that hospital P4P measures were not strongly associated with better outcomes^{192,193} or produced only modest reductions in mortality.¹⁹⁴ On the positive side, there are studies that show an inverse relation between volume and cost.^{195,196} Thus, high volume might improve cost-effectiveness by affecting both the numerator and the denominator of the equation.

Although it is clear that more data are needed with regard to the relation between cost and quality in health care, an activity likely to bear fruit is reducing costs by reducing the complications of surgical care. A useful approach here may be to consider the added costs of a complication in a given patient with respect to the frequency of that complication in the entire population undergoing a given treatment.¹⁹⁷ The goal is to establish priorities for quality improvement efforts to prevent complications based on both the incidence of the complication and its contribution to resource use.¹⁹⁸

Reassessing the relation between cost and quality may also suffer if there is a relative lack of emphasis on the latter by hospital boards.¹⁹⁹ Similarly, a national survey found that 39% of managed care organizations were moderately or largely influenced in their initial physician selection by previous patterns of costs or use, and nearly 70% profiled their member physicians.²⁰⁰ On the other hand, at least one HMO recognized that practices with high scores on service and quality indicators attracted significantly more new enrollees than practices with lower scores. A challenge in considering both cost and quality is that potential benefits may not occur concurrently. Thus, cost savings may appear before quality improvement, or quality might improve before long-term cost savings are evident.

The Future

All indications are that the efforts to reduce the cost and/or improve the quality of the US health care system will remain strong for the foreseeable future. As an example, large employers increasingly provide incentives to use “high-performance” health provider networks.²⁰¹ Physicians may dispute the validity of cost profiling²⁰² and other challenges to their authority as arbiters of quality; regardless, they will have to bear an

increasing burden of proof as to the quality of care. Moreover, health care payers are likely to address substantial variations in frequency and cost of care by using apparent similarities in quality to contract for less expensive care. How this tension will be resolved remains to be determined. One view is that the pressure on physicians will be based on an assumption by payers that physicians will not knowingly or willingly sacrifice quality. Indeed, some believe that value-based competition may spark physicians to provide care that exceeds patients’ expectations.^{203,204}

In response, physicians need to remain cognizant of a predominant theme of this chapter: physician-led organizations appear to be more successful in improving the cost-effectiveness of care than external policies. Practicing surgeons, who are at the “sharp” end of the system, will need to access data on their performance and participate in the development of better outcome measures. These metrics then can be used to improve performance by redesigning processes of care.²⁰⁵ Physicians need to acknowledge variations in intervention rates and outcomes and to increasingly make medical decisions that are evidence based. They are the best equipped participants in the health care system to identify cost-effective care because they have the necessary knowledge and skill set. If physicians can respond constructively to these challenges, rather than simply ignore or dismiss them, they stand a good chance of recapturing much of their lost stature and autonomy.

In this context, the fee-for-service payment system may be increasingly criticized because it lacks incentives that reimburse physicians based on quality. It seems likely, therefore, that new payment systems will emerge that are more closely linked to quality than the current P4P programs. In one such approach, the Geisinger Health System established incentives through a warranty program for elective cardiac surgery in which there is no added reimbursement for managing complications occurring within the first 90 days after surgery. Geisinger was able to adopt this approach because many of its patients were also insured through the Geisinger system. This eliminated many of the conflicts that might otherwise be present with third-party payers. In creating this program, Geisinger embedded best practices within their processes of care, and the program’s initial success is largely attributed to high compliance rates.²⁰⁶ Interestingly, Geisinger patients insured by other payers also benefit from this system.²⁰⁷

Although such changes may seem daunting, surgeons should recognize that the growing interest in assessing performance is not new. In the early 1900s, Ernest Codman, a Boston surgeon, crusaded for hospitals and surgeons to publicize their results, yet his efforts often met with disinterest, defensiveness, or outright opposition.²⁰⁸ The current call to assess surgeon performance is clearly here to stay. If physicians respond dismissively or defensively (e.g., explaining variations in outcomes by invoking care for sicker patients), they may miss an important opportunity to reestablish their authority on quality. Surgeons who preemptively familiarize themselves with their own outcomes will be better positioned to participate in efforts to improve the cost-effectiveness of surgical care.

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8 HEALTH CARE ECONOMICS: THE BROADER CONTEXT

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In a companion chapter [search ACS Surgery for information on cost-effective nonemergency surgical care], we review the principles of cost-effective surgical care and discuss the implications of such principles for health care spending. Our primary focus there is on the interaction between an individual surgeon and an individual patient. In this chapter, we explore some of the issues surrounding health care spending on a larger (i.e., national) scale. It is important for surgeons to have a broad understanding of these issues, in particular because such concerns are increasingly becoming the subject of political debate.

US Health Care Expenditures and Health Outcomes

In 2009, US national health expenditures amounted to \$2.5 trillion (approximately 17.6% of the gross domestic product [GDP]).¹ According to data from the World Health Organization, if the current level of US health care spending were viewed as a separate economy, it would be the seventh largest economy in the world, nearly equal to the GDPs of France and the United Kingdom.² This level of spending translates into a per capita expenditure of \$8,086, which is more than double the average of other Organisation for Economic Co-operation and Development (OECD) countries and which surpasses the per capita expenditure of the next highest-spending country, Switzerland, by more than 30%. Between 1950 and 2001, US per capita spending on health care in constant dollars increased more than 11-fold.

Since the end of World War II, the growth rate of health care spending has exceeded the overall growth of the economy. Although the rate of growth of per capita health care spending has slowed over the past 4 years, there is reason to believe that this slowing trend will be short-lived.³ Over the past 30 years, total national spending on health care has more than doubled as a share of GDP. According to Congressional Budget Office (CBO) projections, total health care spending will reach \$4 trillion by 2015, and in the absence of a significant change in the long-term trends, the share of GDP will double again by 2035, to 31% of GDP. Only a small percentage of this spending growth can be attributed to general inflation, growth in the size of the population, and changes in the age distribution of the population.⁴ The majority is projected to be attributable to rising costs of care and increasing amounts of care.

Economists differ on the extent to which such spending represents a risk to the overall economic well-being of the United States. Those who are concerned about both the amount that is spent on health care and the rate at which this amount is growing cite a number of concerns:

1. In spending more on health care, society spends less on other goods and services—a process referred to as displacement. Thus, health care consumes resources that might otherwise have been allocated to services such as education or public safety.
2. The health care sector of the economy is so large—not only in terms of the amounts of money involved but also in terms of the number of people employed—that short-term changes in its growth rate (in either direction) necessarily exert substantial and painful economic effects. Moreover, the potential magnitude of these effects thwarts political consideration of potential changes to the system.
3. As costs increase, voluntary participation by employers in the provision of health insurance to employees and retirees comes under increasing pressure, with the result that employers either shift more and more of the costs of insurance to employees or decide to stop providing health insurance altogether. Between 2001 and 2006, the contribution of households to health care expenditures increased by more than 35%.³
4. A specific concern also relates to the extent to which spending on Medicare threatens the long-term solvency of the US government. In 2009, Medicare spending grew 7.9% to \$502.3 billion. Absent policy change, the CBO estimates that Medicare spending will grow at an average of 7% each year from 2010 to 2018, rising to \$879 billion annually and 4% of GDP. The rate of growth of Medicare spending over the long term is predicted to exceed the rate of growth of federal revenues and the overall economy,⁵ which most believe is unsustainable. As a result, discussions of health care reform have focused not only on reducing the number of uninsured but also on “bending the health care cost curve” to reduce the rate of growth of health care spending (see below).

Others dismiss these concerns and argue that the health care share of GDP has no natural limit as long as health care is more highly valued than the goods and services that it displaces.⁶ Proponents of this viewpoint distinguish between spending that is affordable (i.e., sustainable) and spending that the country is unwilling to sustain.

The proponents of these two perspectives agree that increases in spending should reflect the increased value placed on health care services relative to non-health care goods and services that are forgone. There is substantial

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evidence, however, that increased health care expenditures are not invariably associated with demonstrable improvements in health outcomes. Although the United States spends more on health care than any other OECD country, its health status rankings do not compare well with those of other industrialized countries. OECD data indicate that of the 30 OECD countries, the United States has the highest rate of obesity and ranks 15th in infant mortality, 13th in cancer mortality, 21st in mortality from ischemic heart disease, and 15th in life expectancy at 65 years.⁷ An analysis of mortality from causes that were potentially avoidable with timely and effective health care in 19 industrialized countries found that the United States ranked last in the level of decline in these deaths between 1997 and 2002.⁸

Within the United States, several major studies have shown that patients treated in higher-spending regions do not have either better health outcomes or greater satisfaction with their care than patients treated in lower-spending regions.⁹ One such study reported that the differences in spending were largely attributable to the higher frequency of physician visits, the tendency to consult specialists more readily, the ordering of more tests, the performance of more minor procedures, and the more extensive use of hospital and intensive care services in the higher-spending regions. The authors could find no evidence that these types of increased use resulted in improved survival, better functional status, or enhanced satisfaction with care. These findings have profound implications for efforts aimed at containing the further growth of health care spending.

Discrepancy between Costs and Outcomes

Many factors influence the cost of health care and the health outcomes of a population. The increase in the size of the uninsured population is often cited as contributing to poorer health outcomes of US residents and the slow decline in the US amenable mortality.⁸ Wider availability of advanced technology, an increasingly older population, newer and more expensive prescription drugs, inefficiencies in health care delivery, and the rising costs of medical malpractice insurance are all contributors to rising health care costs. However, the single factor that distinguishes health care in the United States from that in other developed countries is the market-based delivery system that characterizes US health care. With the exception of the aging of the population, the health care market influences all of the factors that contribute to the cost of health care and health care outcomes in the United States. A simple review of how the health care market functions reveals why a market-based health care delivery system contributes to rising costs and poor health outcomes.

MODEL OF SUPPLY AND DEMAND

The model of supply and demand is a useful tool for understanding the behavior of buyers and sellers in a market [see Figure 1]. With price on the vertical axis and quantity of a particular good or service on the horizontal axis, the demand curve represents the total demand by all consumers for that good or service. The downward slope of this curve reveals that as price decreases, consumers are willing to purchase more. The demand curve also shows the

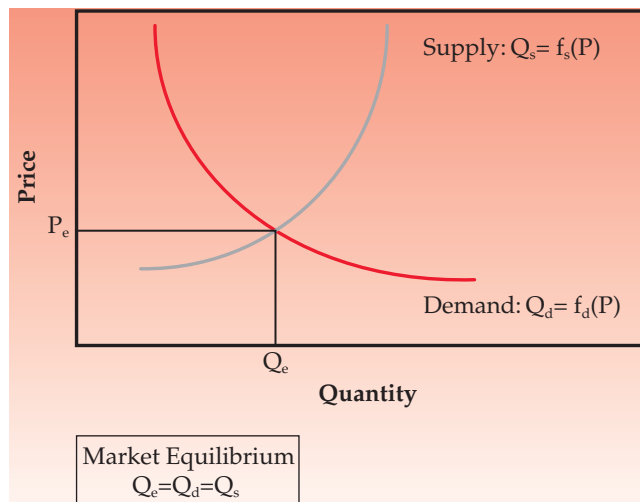


Figure 1 The model of supply and demand determines the quantity produced at a given price. Illustrated here is the application of this model to health care. Persons who fall below the equilibrium point on the demand curve cannot afford health care at the market price and must either do without care or seek it in the safety-net health care system. P = price; Q = quantity; Q_d (quantity demanded) = $f_d(P)$ (the demand equation, which includes price); Q_s (quantity supplied) = $f_s(P)$ (the supply equation, which includes price).

amount of a good or service that the market is willing and able to purchase at a given price. Similarly, the supply curve represents the total quantity of a good or service that suppliers are willing to produce at a given price. The point where the two curves intersect represents the equilibrium price and quantity of the good or service.

This equilibrium between supply and demand gives markets their most valued attributes. A competitive market price forces producers to satisfy consumers' demands for a quality product with the least-cost methods of production. Markets also ensure the most efficient and least wasteful allocation of resources in that only the quantity demanded at a specific price is produced. Markets assume, however, that consumers who cannot afford to pay the market price either will find a less expensive substitute product or will do without. They also assume that consumers can be knowledgeable enough about a product to assess its quality and appropriateness for their needs. Finally, markets exist to maximize both the utility of consumers through the purchase of goods and services and the profits of suppliers. Research and the development of innovative products are driven by the opportunity to be the first to enter a market with a new or improved product and thus reap maximum profits.

A key question is whether the features that are normally associated with well-functioning markets in other areas are also applicable to health care. Further analysis of the supply-and-demand model as it relates to the health care market may shed some light on this question.

AFFORDABILITY OF HEALTH CARE

Despite the massive growth of employer-sponsored health insurance, the universal coverage of the Medicare

population over the age of 65, the addition of more than 1 million disabled persons under Medicare, and widespread coverage of the poor under Medicaid, more than 45 million US citizens (almost one of every six) have no health insurance coverage.

Health insurance, in and of itself, leads to distortions in the market because consumers of health care do not see the actual price being paid for health care goods and services. This creates a situation referred to as moral hazard. This term originated with the purchase of fire insurance in the 19th century, when it was recognized that the owner of a property that was insured might have an incentive to incur a loss either by deliberately setting a fire (a moral hazard) or by not taking steps to reduce the likelihood of a fire. The implication of the moral hazard effect for health care spending is that those who are insured (or more generously insured) will tend to use more health services without regard to cost. Insurers seek to reduce the extent of the moral hazard problem by increasing the coinsurance and making the consumer pay a larger share of the full cost.

A more significant economic and ethical concern centers on those persons with no health insurance coverage, who fall below the equilibrium point on the demand curve [see Figure 1]. In a well-functioning market, it is expected that those who cannot afford to pay the market price for a good or service will do without, but our society seems unwilling to allow this when it comes to health care. The result is a patchwork of substitute care that serves the uninsured and underinsured. The so-called safety-net health care system comprises hospitals, community health centers, “free” clinics, and emergency departments. The Institute of Medicine estimated that in 2001, the safety-net health care system cost \$99 billion in direct services and \$65 to \$130 billion in lost productivity.¹⁰ Under current arrangements, the costs of this care are built into the prices charged to those who do have the ability to pay. A 1992 analysis of the distribution of the health care financing burden associated with the US health care system showed that the greatest financial burden fell on those in the middle class: the fourth to seventh income deciles devoted approximately 12% of their cash income to finance health care, whereas the highest income decile devoted about 8%.¹¹

Despite this degree of public spending, the safety-net health care system does not ensure continuity of care or access to all needed care, and as a consequence, the uninsured have poorer health outcomes than those with continuous health insurance coverage.¹² Not only does this safety-net system cost a great deal and result in suboptimal health outcomes for the population it serves, but there is also increasing evidence that in the United States, all patients seeking emergency care for critical conditions wait longer for needed attention as a consequence of overcrowding and the use of emergency departments by uninsured patients who lack a regular source of health care.¹³ The structure of any market assumes that there are those who cannot or will not pay for the good or service at the market price. As long as a market structure for health care delivery is maintained, there will be those who will not have access to appropriate health care.

ASYMMETRICAL KNOWLEDGE

Consumers rely heavily on the advice of their physicians for guidance regarding diagnosis and treatment. In this

setting, not only do physicians function as suppliers of health care services, but they also play a major role in determining the level of demand for these services. For example, physicians advise patients about the frequency of office visits, the types of diagnostic tests to undergo, and the treatment or treatments that may be needed. Asymmetry of knowledge between patients and their physicians forces patients to rely on this advice for health care decisions.

Substantial evidence exists to support the notion that physicians do increase the demand for health care. Supply-and-demand theory dictates that the entry of more sellers into a market should result in increased competition, lower prices, and lower total costs for goods and services. Yet in health care, it has been demonstrated repeatedly that an increased supply of health care services results in an increased demand for services and an increase in costs. Initial concerns about this unusual market behavior stemmed from the observation that in geographic areas that were similar with respect to demographics, socioeconomic characteristics, and burden of disease, hospital use rates were higher in areas with a greater supply of hospital beds.¹⁴ In a study of the supply of surgeons and the demand for surgery, it was estimated that a 10% increase in the supply of surgeons, as measured by the surgeon-to-population ratio, led to a 3% increase in the per capita surgery rate.¹⁵ A number of other studies have addressed the effect of physician ownership on health care use rates. In a study examining the issue of physician ownership of ancillary services, 50% more visits were ordered at physician-owned physical therapy clinics in Florida than were ordered at clinics that received no referrals from owners.¹⁶ The authors of the study could find no discernible difference in the quality of care across ownership structures. An analysis of more than 65,000 insurance claims found that doctors who owned imaging machines ordered more than four times more imaging studies than those who referred to independent radiologists.¹⁷ Finally, in a study addressing the impact of the 1990 Medicare physician reimbursement changes on thoracic surgeons who were predicted to lose substantial income if surgical volumes remained unchanged, the Medicare fee cuts led to volume increases in both Medicare and private-pay patients, to the point where 70% of the fee loss from Medicare was recaptured through higher patient volume.¹⁸

These findings make supplier-induced demand (SID) one of the most controversial issues in health economics. If SID exists to a substantial extent, economic analysis would then suggest that competitive markets are useless as a means of managing health care delivery and reducing costs [see Figure 2]. Although numerous other hypotheses have been offered to explain the empirical findings of the increases in demand associated with increased supply, none disprove SID.

Physicians find the SID hypothesis disturbing because it suggests that they manipulate the demand for health care to advance their own economic interests. Most physicians are aware of the relation between service volume and income, but various other factors (e.g., rapidly evolving technologies, medical uncertainties at all levels of care, and defensive practices to avoid the risk of litigation) make it impossible to determine the exact impact of SID. The concept of target

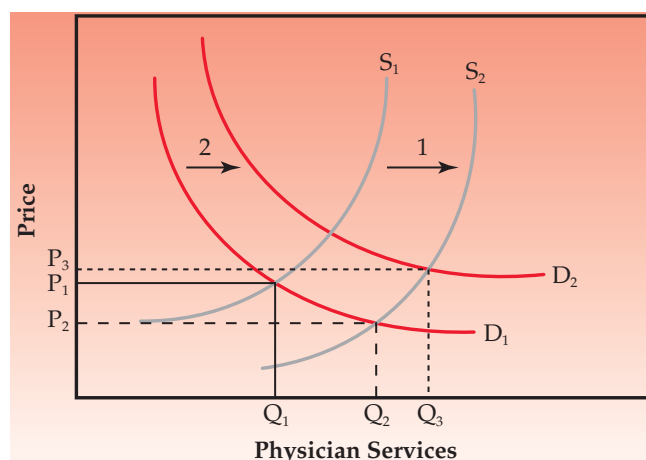


Figure 2 Given an initial supply and demand for physician services at S_1 and D_1 , assume that the number of physicians increases (arrow 1), thereby shifting the supply curve to the right. In normal economic conditions, the quantity of physician services would increase (to Q_2), and the price would fall (to P_2). Empirical evidence, however, suggests that the demand for services also increases, shifting the demand curve to D_2 (arrow 2) and resulting in an increase in both price (P_3) and quantity (Q_3). D = demand; P = price; Q = quantity; S = supply; subscripts 1, 2, and 3 reflect the order in which quantity and price change in response to a change in supply (arrow 1) followed by a change in demand (arrow 2).

incomes is certainly known to be a factor in other arenas of the economy. Regardless of the true extent of SID's impact on the cost of health care, it is the market-based structure of health care that creates incentives for physicians to influence the demand for health care.

MARKETS, MONOPOLIES, NEW DRUGS, AND TECHNOLOGY

The market is uniquely effective in fostering innovation and technological advances. Firms compete to introduce new products, and in doing so, they gain monopoly power and enhance profits through increased market share and monopoly pricing. Unlike competitive markets, where supply and demand determine the price of a good or service, monopolies set their own price. The profit-maximizing price is achieved by equating the marginal cost of producing one additional unit to the marginal revenue from selling one additional unit [see Figure 3]. This results in a higher price and a lower level of production than would be achieved in a competitive market. Monopoly profits are typically short-lived because as more suppliers enter the market, the marginal revenue curve shifts so that it eventually equals the demand curve, thereby reducing the price and increasing the quantity supplied.

In virtually every other sector of the economy, the introduction of new technology tends to reduce the cost of a particular good or service. Health care is one of the few exceptions to this general rule. A 2003 analysis of the relation between the availability of advanced technologies and health care spending found that for certain technologies (e.g., diagnostic imaging, cardiac catheterization facilities, and intensive care facilities), increased availability was often accompanied by increased use (and hence increased

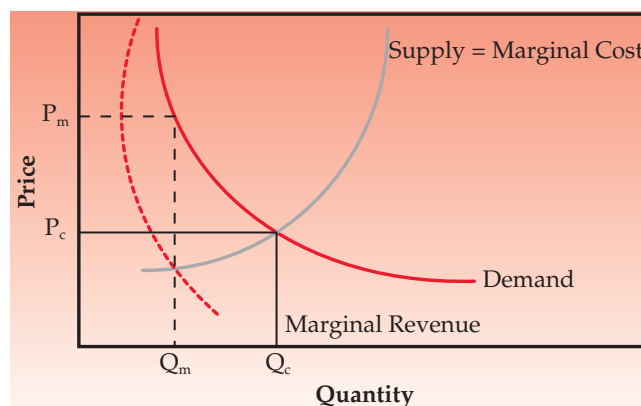


Figure 3 Monopolies set prices to maximize profits by equating the marginal cost of production and the marginal revenue. This process results in higher prices and lower levels of production than would be found in a competitive market. P_c = competitive price; P_m = monopoly price; Q_c = competitive quantity; Q_m = monopoly quantity.

spending).¹⁹ Similarly, expenditures on prescription drugs doubled between 1990 and 2000 and are expected to account for one seventh of total health care costs by 2012 [see Table 1].²⁰ Moreover, whereas consumers pay less than 3% of hospital service costs out of their own pockets, they pay about 32% of pharmaceutical costs.

One of the factors contributing to these increased costs is the presence of legal restrictions, in the form of patents afforded to pharmaceuticals and medical devices that prevent other firms from entering the market with a similar product. Patents give pharmaceutical companies and device manufacturers legal monopolies for a period of 20 years. The purpose of this law, as expressed in Article 1, Section 8 of the US Constitution, is "to promote the progress of science and the useful arts by securing for limited times to inventors the exclusive right to their respective discoveries." In addition, at the end of the patent period, pharmaceutical companies can switch their products from prescription to over-the-counter status and gain 3 additional years of market exclusivity if they can demonstrate that any misuse of a drug will not endanger a consumer's health. During these protected periods, companies work to establish brand loyalty among physicians and consumers.

Pharmaceutical companies and device manufacturers argue that the costs of research, development, and testing would be impossible to recoup without these legal

Table 1 Major Components of Health Spending, 1999–2009

	1990	1993	1997	2000	2003	2006	2009
Hospital care	9.6	8.0	3.6	5.6	7.5	7.0	5.1
Physician and clinical services	12.8	8.5	4.6	7.0	8.5	5.9	4.0
Prescription drugs	12.8	8.2	11.1	15.3	10.5	8.5	5.3

Adapted from Martin A et al.³⁸

protections. Others, however, are concerned that companies are using their monopoly power to raise prices, restrict output, and earn excessive profits. Since 1980, the rate of growth in drug prices has exceeded consumer price inflation rates. In addition, the profitability of drug firms has been consistently higher than that of the manufacturing industry average.²¹

Again, pharmaceutical companies argue that the high rate of profit observed in the industry is justified by the significant risk and cost of innovations. However, not all innovations are costly to the company, risky to investors, or beneficial to society. One of the most notable examples of profiteering by a pharmaceutical company was the introduction of the “new little purple pill.” The original purple pill, Prilosec (a trade name for omeprazole), was introduced in 1989 by AstraZeneca. In 2000, it was the best-selling drug in the world, with over \$6 billion in sales per year. When the patent was due to expire in 2001, the company applied for a patent for the “new little purple pill,” Nexium (esomeprazole magnesium), which was simply a chemical isomer of Prilosec. Despite the Food and Drug Administration’s determination that Nexium offered no significant clinical advance over Prilosec, a patent was awarded. The company launched a very successful marketing campaign, and in 2006, sales of Nexium exceeded \$5 billion. The price of Prilosec for consumers is \$30 per month, whereas that of Nexium is \$200 per month. The current market-based model of new product development accompanied by long periods of monopoly protection can be predicted to increase the costs of health care substantially.

PRICE TRANSPARENCY

For most goods and services, price transparency leads to lower and more uniform prices, a view consistent with standard economic theory. Currently, there is considerable variation in prices for similar procedures. For example, a comprehensive metabolic panel costs \$97 at San Francisco General Hospital and \$1,733 at Doctors Hospital in Modesto, California. A single Percocet tablet costs \$6.68 at San Francisco General, \$15.00 at UC Davis in Sacramento, and \$35.50 at Doctors Hospital in Modesto.²² If evidence from other markets could be applied to health care, then reforms that increase transparency should result in lower and more uniform prices.^{23,24} However, there are reasons to be concerned that greater price transparency would not have the desired effect. Health care differs from other consumer goods in ways that make it difficult to apply empirical evidence from other markets. For one, patients with insurance pay little of the cost of their medical care and are therefore less price sensitive. In addition, there is evidence to suggest that price acts as a proxy for quality in health care, with many believing that higher-cost care is better care.²⁵ Second, physicians typically make choices for patients, such as what tests to order, whether and where to hospitalize, and which specialists to recommend. Patients are unlikely to challenge this advice to save a few dollars. Finally, transparency could create an incentive to raise prices. Hospitals that charge different payer types different prices would be inclined to publish the higher price. For these reasons, pricing may have a more muted effect on the health care market than

it has on other markets, and improvements in price transparency may be less effective. So far, preliminary data from New Hampshire²⁶ and California²² suggest that this is the case. Neither state demonstrated any effect of hospital price transparency 2 years after initiation.

ADMINISTRATIVE COSTS

In general economic terms, markets function best and society benefits most when multiple suppliers compete to produce the highest-quality product at the lowest cost. With health care, however, this process has resulted in a bewildering array of insurers and contracts. Virtually every physician in the United States has had to expend considerable time and effort dealing with complicated, arcane, and apparently deliberately confusing rules and requirements.

The repeal in 1986 of laws that sought to regulate the growth of the health care industry resulted in an abandonment of all efforts to constrain market-based entrepreneurship in health care. Not-for-profit hospitals and health maintenance organizations converted to for-profit status. Consolidation of the insurance industry reduced the number of plans available in a market area, thus affording insurers monopoly power and leading to higher prices. The cost of administering private health insurance in the United States reached \$143 billion in 2005.²⁷ For-profit insurance companies have reaped impressive profits and gains in stock value, as well as significant political power.

As a reaction to this state of affairs, some critics of the US system have asserted that the adoption of a simplified, Canadian-style, single-payer health insurance system would yield large savings in administrative costs, which could then be used to expand coverage to those who are currently uninsured. A 2003 study compared administrative health care costs in the United States with those in Canada.²⁸ In 1999, per capita health administration costs amounted to \$1,059 in the United States (for a total cost of \$294 billion), in contrast to \$307 in Canada [see Table 2]. The authors arrived at these figures by analyzing data from governments, hospitals, insurance companies, and physicians. They argued that much of the difference between the two countries was accounted for by the multiple sources of health coverage in the United States, as opposed to the single source in the Canadian system. This analysis has not been replicated by others, and an accompanying editorial questioned the methodology used.²⁹ Nevertheless, the author of the editorial did agree that the current system is “an administrative monstrosity, a truly bizarre mélange of thousands of payers with payment systems that differ for no socially beneficial reason.”

THE PATIENT PROTECTION AND AFFORDABLE CARE ACT AND OTHER LEGISLATIVE INITIATIVES

The most significant impact of the Patient Protection and Affordable Care Act (ACA) is that an estimated 32 million Americans will gain insurance coverage by 2019. The health reform law mandates that currently uninsured Americans obtain health insurance. Medicaid eligibility is expanded and substantial subsidies are provided to make insurance more affordable for those ineligible for public insurance programs. Currently, the uninsured rely heavily on the safety-net health care system, which is associated with

Table 2 Administrative Costs of Health Care: United States versus Canada

Administrative Cost Category	United States		Canada	
	Total Cost (\$ billion)	Per Capita Cost (\$)	Total Cost (\$ billion)	Per Capita Cost (\$)
Insurance overhead	72	259	1.43	47
Employer costs	15.9	57	0.257	8
Hospital administration	87.6	315	3.1	103
Practitioners	89.9	324	3.3	107
Total	294.3	1,059	9	307

higher costs and poorer health outcomes. If previous trends hold, the newly insured will enjoy better health outcomes, but the cost implications of health care reform are less clear.

Both the Centers for Medicaid & Medicare Services (CMS) and the CBO have projected that health care reform will result in an expansion of national health care expenditures.^{30,31} The ACA includes a number of mechanisms to offset the new spending, including a reduction in the update factor for Medicare hospital reimbursement, a reduction in the overpayment to Medicare Advantage insurers, an assessment on employers whose employees use subsidies rather than employer-sponsored insurance, and an increase in the Medicare tax for high-income families. The CBO estimates that the revenue increases will exceed the increased costs and ultimately reduce the federal deficit by more than \$100 billion in the first decade and more than \$1 trillion in the second decade.²² However, critics argue that although these measures may pay for health care reform, they do nothing to rein in the growth of health care costs. Health care spending in the United States already accounts for 17% of GDP. At the current rate of growth, it will reach 38% of GDP by 2075. The ACA includes a variety of provisions intended to lower the rate of cost growth (bend the health care cost curve), including physician payment reform, incentives to coordinate care for patients with chronic conditions, increased access to electronic health records, and funding for comparative effectiveness research, but there is currently little evidence that any of these measures actually work.

A second implication of increased access to health insurance is the need for a larger primary care workforce. Numerous studies have demonstrated that access to primary care is associated with improved outcomes at reduced cost. Although primary care physicians provide 57% of all patient visits, they represent only 35% of the US physician workforce.³² Even without the new demands created by health care reform, the aging of the population and the increasing proportion of the population with a chronic medical condition have strained the capacity of the primary care workforce. The 2008 Medicare Payment Advisory Commission (MedPAC) beneficiary survey found that 28% of beneficiaries without a primary care physician reported a problem finding one.³³ This represented a 17% increase from 2006. The number of beneficiaries reporting a problem finding a new specialist declined. The Massachusetts experience with expanded health insurance coverage illustrates the disconnection between access to health insurance and access to care. The average wait time for a new patient to obtain an

appointment to see an internist in Massachusetts was 31 days in 2008, up from 17 days in 2005.³⁴ Patients without access to primary care will be forced to continue to seek care at high-cost, poor-continuity sites, such as emergency departments. General surgery also faces shortages that are likely to be exacerbated by health care reform. The overall number of general surgeons has declined by 26% over the past 25 years.³⁵ Rural areas are most acutely affected. The income gap between generalist and subspecialist careers and rising medical student debt account for most of the decline in medical student interest in both of these generalist careers.

The ACA and the American Recovery and Reinvestment Act of 2009 include several provisions aimed at highlighting the importance of primary care and general surgery. The economic stimulus package provided about \$500 million for training programs in health professions, including \$300 million for expanding the National Health Service Corps, a program that offers scholarships and loan repayment for health professionals who agree to serve in shortage areas for 2 to 5 years. The ACA includes additional funding to support training of primary care providers, redistributes approximately 900 unfilled residency positions into primary care and general surgery, provides a 10% bonus under the Medicare fee schedule for primary care providers, and requires that states increase Medicaid payment to Medicare rates for primary care services. Notably missing in the provisions is a lifting of the cap on the total number of residency positions, which were frozen by the Balanced Budget Amendment of 1997. In the absence of an expansion of total residency training positions, it is not clear that the provisions will make a significant dent in the projected primary care and general surgery shortages.

Implications for Surgeons

Market-based health care has not only increased the costs of care but has also changed the professional behavior of physicians. Organized medicine's priorities place the financial interests of physicians above access to and quality of care. Hospitals invest in programs that promise a high return on investment with less regard for evidence of benefit or greater societal need. The fragmentation of the profession into over 130 specialties and subspecialties has resulted in competition among disciplines, further promoting self-interest over best practices. In this environment and despite advances in evidence-based medicine, individual physicians are equally tempted to place their own interests above those

of patients by recommending interventions of limited value. A 2007 study highlighted these disturbing trends by revealing that median wait times for both routine and urgent dermatology appointments were nearly four times longer than wait times for an appointment to receive cosmetic botulinum toxin injections.³⁶ Patients with a potentially cancerous skin lesion wait a median of 26 days to be seen by a dermatologist.

Adam Smith's 1776 book *An Inquiry into the Nature and Causes of the Wealth of Nations* is considered the first full-scale treatise in classical economics. In it, Smith espoused the virtues of the market as a means toward national wealth. He made the case that self-interest leads naturally to greater public good: "It is not from the benevolence of the butcher, the brewer, or the baker, that we expect our dinner, but from their regard for their own interest. We address ourselves, not to their humanity, but to their self-love and never talk to them of our own necessities but to their advantages."³⁷ However, Smith was also quick to draw a distinction between self-interest and greed. He criticized those who desired excessive wealth, for whom "the chief enjoyment of riches consists in the parade of riches, which in their eyes is never so complete as when they appear to possess those decisive marks of opulence which nobody can possess but themselves." In his view, the market's ability to foster the growth of a nation depended on social cooperation, discipline, and respect for others. Greed denied others and thereby weakened the whole.

Finally, Smith understood the intrinsic failure of the market to ensure equity and the vital role of government in this regard:

Is this improvement in the circumstances of the lower ranks of the people to be regarded as an advantage or as an inconvenience to the society? The answer seems at first sight abundantly plain. Servants, labourers, and workmen of different kinds, make up the far greater part of every great political society. But what improves the circumstances of the greater part can never be regarded as an inconvenience to the whole. No society can surely be flourishing and happy, of which the far greater part of the members are poor and miserable. It is but equity, besides, that they who feed, clothe, and lodge the whole body of the people, should have such a share of the produce of their own labour as to be themselves tolerably well fed, clothed, and lodged.³⁷

Arguably, health care is as necessary to the prosperity of a society as food and lodging are.

Although individual physicians can do little to fix the society-wide problems created by market-based health care, surgeons can help restore confidence in the profession by helping to develop and then adhering to evidence-based approaches to surgical intervention. Communication skills and attention to the needs of patients should be stressed as vital to the best patient care. Equally important is remembering that the profession of medicine is not merely another way of making a living. The importance of education in evidence-based and compassionate care, preferably one on one, for the training of surgical residents and students must also be emphasized. Mastery of these skills, which place patient interests ahead of surgeon interests, truly defines professionalism.

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9 MINIMIZING VULNERABILITY TO MALPRACTICE CLAIMS

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No surgeon wants to be sued. The threat of a medical malpractice suit is, however, a reality for everyone who practices surgery. Lawsuits can extract a tremendous price from those who are sued. The surgeon who has been sued bears the burden of the lawsuit for a period of years while it slowly works its way through a system that is not designed for speed or efficiency. Life decisions are often postponed. Sometimes careers are forever changed. Confidence is shaken, and sleep is lost. For some, there is no relief until it is over; for others, it repeatedly intrudes on life. It is better to never be sued. The situation, however, is not totally out of the surgeon's control—nor is it hopeless. Armed with knowledge of the legal system and an understanding of why patients seek the courts, the surgeon can decrease the likelihood of ever being named. This chapter provides strategies for avoiding lawsuits and advice for dealing with a suit if one is ever filed against you.

What Is Medical Malpractice?

Medical malpractice law is a subset of the law of torts or law that concerns itself with civil injuries as a result of negligent behavior or a failure to practice due diligence. For a medical malpractice suit to be successful, a number of elements must be satisfied. A plaintiff (the patient or the patient's estate) must prove, by a preponderance of the evidence, that the defendant (the surgeon) was negligent or failed to exercise due care in the circumstances. A plaintiff must also show that the defendant's negligence caused his injuries and that he has suffered injuries or quantifiable damages as a result.

Four conditions must be met:

1. There must be a "relationship" of some kind between the patient and the surgeon. The relationship can be a direct one, in which the surgeon operated on the patient, or a more indirect one, in which the surgeon only consulted.
2. The surgeon must be "negligent," which means that he or she did not perform to the "standard of care." The definition of the standard of care varies from state to state but usually means that the surgeon failed to perform in a manner consistent with the care that would be given by the average physician practicing in the same specialty. To help the judge and the jury understand the evidence in relation

to the standard of care, both sides use "expert" witnesses to provide opinions about the care.

3. The surgeon's negligence must have been the cause of the injuries that the patient sustained.
4. The injuries that the patient has suffered must have caused measurable damage. This reflects the civil nature of malpractice, whereby injuries are compensated with a payment.

The judge and/or the jury are responsible for determining whether each of these conditions has been met and uses a standard of "more likely than not." Unlike criminal law, the evidence does not have to reach the level of "beyond a reasonable doubt"—only that there is a greater than 50% chance that the conditions were met. In our judicial system, the judge and the jury interpret and decide whether the "standard of care" was met.

Malpractice lawsuits often begin with the filing of suit papers that are delivered or "served" to those being sued. A written demand for compensation for an injury from the patient or an attorney is usually called a claim and can precede the filing of a suit. Suits and claims can end in different ways, and not all involve a jury trial. They can be dropped by the patient at any time; denied by the insurance carrier and not pursued by the patient; settled with a payment before, during, or after a trial; dismissed by the court; or ended with a jury verdict.

Personal Issues for the Defendant Physician

How physicians cope personally with being a defendant in a medical malpractice suit varies, but a number of factors come to bear on the amount of stress that litigation inflicts. These factors include the physician's previous exposure to litigation claims, degree of familiarity with the legal system and the litigation process, and previous experience testifying in the courtroom or in depositions; the size of the claim as measured by the seriousness of the alleged injury; and the presence or absence of a claim for punitive damages—which, of course, are not insured by professional liability policies. Some physicians experience a sense of profound isolation when they are first named in a suit, particularly when service of suit papers is accompanied by the standard instruction from their risk management office or legal counsel not to discuss the case with anyone.

Allegations of negligence or substandard care, in and of themselves, are bitter pills to swallow, but they are all the more painful when they are accompanied with a claim for punitive damages. Such claims, announced in the formal complaint, are then typically followed promptly with a grim

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letter to the defendant physician from the insurers involved, reminding the physician that there is no coverage for punitive damages awarded. The allegations in the plaintiff's complaint necessary to support a claim for punitive damages are hurtful and sometimes outrageous; the physician is accused of willful, reckless, and wanton behavior bordering on intent to injure the plaintiff. The awards sought in such cases reach far beyond fair compensation for the injured plaintiff. Rather, punitive damages are calculated to punish the defendant physician—the perceived wrongdoer—and to serve as public sanctions. The physician against whom punitive damages are sought then undergoes pretrial discovery, sometimes shortly after suit is filed. This process involves requests (interrogatories) for detailed accounting of personal assets that might be available to be attached in the event of a judgment in the plaintiff's favor.

Whether or not punitive damages are sought, it is difficult for most physicians to regard being harpooned by a medical malpractice claim as merely a cost of doing business, and for many, the arduous and seemingly never-ending nature of the claim is distracting and potentially debilitating.

Who Brings Medical Malpractice Claims?

Brennan and colleagues have shown that there is no relation between the occurrence of adverse events and the assertion of claims, nor is there any association between adverse events and negligent or substandard care.¹ These authors did, however, find a relation between the degree of disability and the payment of claims. They found that patients who were injured through negligent care usually did not file suit and that the patients who did file suit often did not suffer from negligent care. Further, they also found that patients do turn to the courts when they are disabled in the course of medical care. The need to pay for long term care for themselves or a dependent often contributes to the filing of the suit.

Only a small fraction of patients who are injured through substandard care or treatment actually bring claims or suits.² Localio and colleagues concluded that although 1% of hospitalized patients sustain a significant injury as a result of negligent care, fewer than 2% of these patients initiate a malpractice claim.³ Other authors have found that only 2 to 4% of patients injured through negligence file claims, yet five to six times as many patients who sustained injuries that do not meet the threshold for malpractice also file malpractice claims.⁴

Strategies for Preventing Malpractice Suits

Clearly, not every malpractice suit can be prevented. When catastrophic injuries follow surgery or treatment, the emotional impact of the tragedy, coupled with overwhelming economic pressures, can create an environment in which a claim is likely. On the other hand, not all adverse outcomes from treatment result in claims. Why is it that some patients and families sue for adverse outcomes and some do not? Why do some patients sue for adverse outcomes that are expected and that occur in the context of high-quality care? The answers to those questions typically have to do with physician-patient relationships rather than professional skill.

It has become increasingly clear that surgeons can reduce the likelihood of litigation by adopting a few key habits and practices with their patients and their patients' families. These include building trust through open communication, making effective use of the informed consent process, keeping accurate and complete medical records, and educating office staff.

COMMUNICATION AND INTERPERSONAL SKILLS IN THE PHYSICIAN-PATIENT RELATIONSHIP

Although advancing medical technology has elevated patients' level of expectation regarding treatment outcome, easy public access to medical information on the Internet has encouraged patients to become partners with their physicians in their own care. Experience with juries over the past few decades continues to support the belief that, in general, laypersons have a high regard for physicians and a deep respect for their superior level of knowledge and training. At the same time, patients expect and deserve to receive thorough understandable explanations from their physicians regarding their diagnosis, their treatment plan, and the risks and benefits of their treatment. Even when the disease process is beyond the physician's control, the physician can create an environment for effective communication with the patient. Years of listening to patients and their family members relate their experiences at depositions and trials have confirmed that the quality of communication and the presence of trust between physician and patient are the most important factors in the patient's decision to file a medical malpractice suit.

Several researchers have analyzed physician-patient communication and its relation to claims for damages for alleged professional negligence. Beckman and colleagues studied 45 deposition transcripts of plaintiffs in settled malpractice suits, focusing on the question of why these plaintiffs decided to bring malpractice actions.⁵ They concluded that the process of care, rather than the adverse outcome, determined the decision to bring the claim. They found that 71% of the depositions revealed problems with physician-patient communication in four major categories: (1) perceived unavailability ("You never knew where the doctor was," "You asked for a doctor and no one came," "No one returned our calls"); (2) devaluing of the patient's or the family's views (e.g., perceived insensitivity to cultural or socioeconomic differences); (3) poor delivery of medical information (e.g., lack of informed consent, failure to keep patients informed during care, or failure to explain why a complication occurred); and (4) failure to understand the patient's perspective.

Vincent and colleagues examined the reasons patients and their relatives take legal action in a survey of 227 patients and relatives.⁶ Over 70% of respondents were seriously affected by incidents that gave rise to litigation. However, the decision to take legal action was determined not only by the original injury but also by insensitive handling and poor communication after the original incident. Patients taking legal action wanted greater honesty, an appreciation of the severity of the trauma they had suffered, and assurances that lessons had been learned from their experiences.

Levinson and colleagues studied specific communication behaviors associated with malpractice history.⁷ Although they did not discover a relation between those two factors in the

surgeons they studied, they found that primary care physicians who had no claims filed against them used more statements of orientation (i.e., they educated patients about what to expect), used humor more with their patients, and employed communication techniques designed to solicit their patients' level of understanding and opinions (i.e., they encouraged patients to provide verbal feedback).

Hickson and colleagues studied specific factors that led patients to file malpractice claims after perinatal injuries by surveying patients whose claims had been closed after litigation.⁸ Dissatisfaction with physician-patient communication was a significant factor: 13% of the sample believed that their physicians would not listen, 32% felt that their physicians did not talk openly, 48% believed that their physicians had deliberately misled them, and 70% indicated that their physicians had not warned them about long-term developmental problems.

The American College of Surgeons' Patient Safety and Professional Liability Committee performed a closed claims study of 460 liability claims between April 2004 and February 2006.⁹ Ninety of the claims (19.8%) were filed because of failures in communication that predominantly involved patients or their families. Among some of the claims, the standard of care was clearly met. However, defendants suffered litigation solely because they failed to spend the time required to provide the insight and satisfaction necessary to defuse anger and mistrust.

Many defense attorneys recount stories of surgeons who had developed a positive rapport with their patients and were not named in a suit, whereas other physicians involved in the patient's care were named. Patients apparently made these decisions without regard to the extent of each defendant's factual involvement in the case but instead sued physicians with whom they had poor or weak relationships. A component of the motivation to sue may be simply an unsatisfactory or incomplete explanation of how and why an adverse outcome occurred. Patients who remain uninformed often assume the worst: that their physician is uncomfortable talking about the complication because he or she made a mistake, was careless, or is hiding something. Malpractice plaintiffs have sometimes claimed that when they sat through the process of jury education during the trial, it was the first time they received any explanation of the complication for which they had brought suit. Physicians should make a point of explaining to patients and their families how and why adverse conditions arose, independent of any possible deficiencies in the quality of care received at home or in patient compliance. Patients and their families are keenly sensitive to unintended inferences that blame for the bad outcome rests with them.

The principles of good communication are the same, whether or not an adverse event has occurred. They include the following:

1. *Educating and informing the patient.* Convey medical information in descriptive terms that patients can understand, using illustrations, sketches, and diagrams. Ask about the response to the therapeutic regimen. Provide counseling and instruction if no improvement is observed. Inform the patient about specific steps in the examination or treatment plan.

2. *Ensuring patient understanding.* Ask patients whether they understand what they have been told; check the understanding by listening to the patient after providing an explanation. Demonstrate respect for any cultural or socioeconomic differences that may be impeding the patient's understanding.
3. *Emotionally engaging the patient.* Demonstrate concern and understanding of the patient's complaints. Express empathy; use humor where appropriate. Demonstrate awareness of the patient's occupation, social circumstances, hobbies, or interests.
4. *Following up with the patient.* Return telephone calls. Explain the protocol for substitute or resident coverage and introduce patients to other personnel who may be following their care. During longer hospitalizations, keep the patient and the family informed of the patient's progress or treatment plan. Keep the referring physician promptly informed by providing treatment or discharge summaries. In the event of a patient's death, meet with the family several weeks later to review and explain autopsy findings and answer questions that they might have about what happened to their loved one.

Further guidelines apply when an adverse outcome occurs. In the hospital setting, prompt disclosure of an untoward or unexpected event that causes injury or harm is mandated by the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO). JCAHO standards require disclosure of unanticipated outcomes "whenever those outcomes differ significantly from the anticipated outcome."¹⁰ The responsibility to communicate lies with both the attending physician and, in the case of a complication incident to surgery, the person accountable for securing consent for the procedure.

When possible, it may be advisable to invite other responsible caregivers to take part in the discussion of the adverse event with the patient and the family. Consideration should also be given to inviting other persons who may be sources of support for the patient and could benefit from the disclosure. During the discussion, express regret for the occurrence, without ascribing blame, fault, or neglect to oneself or any other caregiver. Describe the decisions that led to the adverse event, including those in which the patient participated. Explain and outline the course of events, using factual, nontechnical language, without admitting fault or liability or ascribing blame to anyone else. Do not speculate or hypothesize. State the nature of the mistake or error, if one was made, and highlight the expected consequences and prognosis, if known. Outline the plan of corrective action with respect to the patient. In the event that certain information is unknown at the time of the discussion (e.g., the etiology of the condition, suspected equipment malfunction in the absence of controlled testing, or pending laboratory test results), tell the patient and family that such information is currently unknown and offer to share the information with them when it becomes available.

A special case exists when children suffer injuries. Parents may seek subconsciously to avoid blaming themselves and so may attempt to transfer the responsibility to the health care providers. After a complication or adverse event arises in a pediatric case, the physician should speak openly with the

parents. The discussion should cover possible or known causes or mechanisms of the injury or death that are independent of any care rendered by the parents, including prenatal care or home care of a chronically ill child.

THE INFORMED CONSENT PROCESS

Effective informed consent can reduce the risk of litigation. The informed consent process is an extension of good communication practices, albeit one that is mandated by law. The tort of informed consent is derived from the concept of battery—for example, unauthorized touching. Patients are deemed not to have consented to a procedure unless they have been advised of all the risks involved in it and all the alternatives to it. Although differing somewhat from state to state, in most jurisdictions, the standard is objective rather than subjective. In other words, the risks and alternatives that must be disclosed are those that a “reasonable patient, in similar circumstances”—not necessarily the plaintiff—would regard as material to the decision whether to undergo the surgery in question. With procedures for which the statistical incidence of risks has been published or is known, the physician has a duty to quantify for the patient the likelihood of the risk being realized. If the patient’s particular condition or situation is such that the likelihood of the risk occurring is higher than average, the physician has the duty to so inform the patient.

Many physicians ignore another critical element in the required informed consent discussions: describing the range of reasonable alternative procedures or modalities other than the procedure in question that are available to the patient. The hazard that such omissions entail is illustrated by a case in which the physician performed a transesophageal balloon dilatation of the esophagus to address achalasia that had not responded to conservative medical therapy. The risk of esophageal perforation was disclosed as part of informed consent, and the procedure was performed totally within the standard of care, but the patient suffered perforation of the esophagus with serious permanent and long-term disability. Although an alternative approach, via thoracotomy, was a known option, it was not used at the defendant hospital, and the informed consent discussion therefore did not include the surgical alternative. The defendants were forced to settle the case for a significant amount of money, even though there had been no negligence and the patient acknowledged that the risk of esophageal perforation had been thoroughly disclosed. A breach of informed consent was easily established because one of the reasonable alternatives was not disclosed to the patient. The argument that a reasonable person would probably have rejected the surgical alternative had it been disclosed was not a valid defense; nondisclosure of a reasonable alternative, in and of itself, created strict liability.

Some surgeons regard the informed consent discussion as an inconvenient imposition on their time. However, the few minutes needed for this discussion pale in comparison with the time needed to defend a lawsuit involving a breach of informed consent, either as the central claim or as an ancillary one. In addition, given that the surgeon’s personal interaction with a patient may be significantly limited in comparison with that of the primary care physician, obstetrician, gynecologist, or medical specialist, the informed consent

discussion presents an important opportunity for the surgeon to develop a rapport and a positive relationship with the patient. Such a rapport can be invaluable in the event of a later complication or adverse outcome. An effective informed consent discussion may reduce the likelihood of a claim for a particular adverse outcome if the patient remembers that the risk of its occurrence was disclosed and discussed.

Informed consent is not the consent form; it is the process of informing the patient. The form is merely a piece of evidence documenting that informed consent occurred; the critical factor is the content of the discussion. For the form to be effective, it must cogently summarize the discussion in a manner that makes it difficult for the patient later to refute, in a “he said, she said” controversy, the version of the discussion that the physician may be rendering in the courtroom under oath.

An effective discussion of informed consent based on custom and habit is essential because of the slow pace of the legal system. In most jurisdictions, the statute of limitations for bringing claims involving adult patients is 2 years. By the time the defendant physician’s pretrial deposition is taken, another 1 to 3 years may have elapsed, and after that, even more time passes before the conversation will have to be relayed under oath if the claim goes to trial. It is exceedingly rare that physicians can actually recall the informed consent discussion in question at the time of the suit. However, the content of the communication can be proved more reliably through custom and habit than through direct recollection, particularly when the elements of the discussion are corroborated with a comprehensive and clear form signed by the patient.

In some cases, physicians encourage the showing of a patient education video that explains the intended procedure; such a video should also communicate the risks of the procedure. The use of educational videos can provide additional evidence to support the defense that the patient gave informed consent. Each version of the video should be labeled with the dates when it was routinely used and should not be discarded when it is replaced with updated versions. The patient’s chart should reflect that the patient watched the video and had no questions after a review of its contents.

The physician who will perform the procedure, not the nurse or resident who will assist at it, has the duty to secure the patient’s consent. However, information provided by other health care providers can be used by the defense as evidence.

DOCUMENTATION

Along with effective communication techniques and informed consent protocols, good documentation practices can minimize a surgeon’s risk of becoming a defendant in a medical malpractice suit, or at least provide a more effective defense if litigation is commenced. Although the purpose of keeping medical records is to provide subsequent caregivers with important information relevant to the patient’s condition and treatment, in the context of litigation, medical records are used to demonstrate what care was or was not rendered. A standard question that plaintiffs’ attorneys ask defendants at pretrial depositions is whether the defendant agrees with the adage, “If it is not documented, it wasn’t done.” Time and time again, otherwise defensible cases are compromised

because of inadequate documentation, such as failure to document an order, the time an order was given, a critical telephone call from the patient or patient's family, a critical informal consultation, or critical symptoms reported by a patient during the course of an examination or clinic visit.

Various tort provisions have been enacted with the intention of upgrading the quality of expert witnesses in some states. Better qualified witnesses will generally be more objective, authoritative, and credible than less well-qualified witnesses. Such witnesses may nonetheless be influenced, sometimes to the defendant physician's detriment, by the quality of the documentation provided. On the one hand, if the chart is well documented and the case is defensible, many reputable experts will be loath to give an opinion stating that substandard care was provided. On the other hand, absence of adequate documentation sometimes prejudices expert case reviewers in favor of the plaintiff, even though subsequent deposition testimony may provide a cogent and defensible explanation for how and why the adverse event or complication occurred.

It is crucial to ensure that telephone conversations are documented. Cases have been saved in the courtroom simply because a resident who received a call jotted a short note of the patient's complaint and the advice given and pasted it in the patient's chart. All appointments, cancellations of appointments, and reasons for cancellations should be logged. If printed images of bedside ultrasound scans are relevant, the printed copy should be stapled and placed into the progress notes of the patient's chart. If the surgeon provided the patient with a sketch to help explain an operative procedure, the sketch should be placed in the patient's chart, with the date written on it. In one case involving an informed consent issue, the defense was able to produce a sketch of the operation that the surgeon had made on the reverse side of a laboratory report in the patient's chart, thereby refuting the patient's contention that no explanation of the procedure had ever been given. If equipment malfunction was involved in an adverse outcome, such as a death in which a postmortem examination was conducted, the surgeon should insist that the risk management office provide a secure place to store the specimen or equipment in question for later testing or use as a trial exhibit. If an anomalous condition contributed to an adverse outcome in a fatal case, efforts should be made to ensure that the pathologist at least photographs the abnormality at the time of the autopsy if the specimen is not to be preserved for later use.

Whenever an untoward outcome or event occurs, the event should be documented in the chart in a purely factual manner, without resort to expressions of opinion or suggestions that other health care providers are to blame. If additional relevant information subsequently becomes available, it can be helpful to make a late entry in the chart, with the time of the entry appropriately documented. Be cautious of using self-serving language in notes that are dictated or recorded after complications have occurred, that is, the "late" operative report that explains how "carefully" the surgeon operated to avoid complications.

If one realizes that an error in documentation has been made in the patient's chart (e.g., inaccurate information is recorded), it is vital not to remove the page and start over and not to scratch out, write over, or "white out" the mistake.

The appropriate way of handling such an error is to draw a single line through the inaccurate information, record the correct information, and initial and date the amendment. Clearly, a medical record should never be altered in an attempt to cover up something. In the event of a suit, this act could lead to the loss of an otherwise defensible case.

The following are guidelines for documentation:

1. Time and date your notes.
2. Write legibly.
3. Record the information that is important to subsequent caregivers. When an unusual treatment course is planned, include a clear explanation.
4. Record pertinent negative findings.
5. Do not criticize colleagues in your notes. The record is not a place to settle disputes.

EDUCATING AND INFORMING OFFICE STAFF

More than ever before, every practicing surgeon must recognize that his or her office staff must also be well informed and well educated about malpractice issues. In-service training of office staff is pivotal to reducing the risk of being sued. All office personnel should be well informed and educated on issues of confidentiality, including how to answer the telephone, what kinds of conversations are inappropriate, and the dissemination of medical information. It is also critical to maintain good relationships with patients; many avoidable lawsuits have arisen simply because a member of the physician's office staff was rude to a patient on the telephone or because the patient waited too long to see the doctor without an explanation. Whenever patients or family members call or write to express displeasure with service they received—whether that service was provided by the surgeon, the resident, the clinic staff, or the nursing team—courtesy and common sense decree that the dissatisfied customers should be contacted and allowed to vocalize their complaints, either over the telephone or in person. Willingness to listen to these persons indicates a genuine interest in improving the delivery of patient care and may well prevent some claims.

ADDITIONAL STRATEGIES

In the current malpractice climate, it is important to be vigilant for patients who tend to be inordinately dissatisfied, to complain unreasonably, or to exhibit rudeness. Such patients should receive the same high-quality medical care as any other patient, but extra attention should be paid to documentation of missed appointments, telephone instructions given, and the informed consent process. Paranoia is neither necessary nor helpful in dealing with these patients, but care should be taken to inform the staff of any concerns. Litigious patients may feel short-changed by the medical system because of past adverse experience with the medical delivery system or economic pressures exacerbated by the expense of testing and treatment, and when they are not given satisfactory explanations for a poor outcome or a therapeutic failure, they may seek to elicit derogatory statements about another physician's advice or treatment. Accordingly, whereas dialogue and open discussion of adverse outcomes with patients are essential, it is important to steer clear of criticizing another physician or health care provider. The proper forum for constructive criticism of other health care professionals with a view toward improvement is the peer

review system, not a discussion with the patient or the patient's family. If the critique is made in the context of peer review, the proceedings are shielded from discovery in litigation.

If you receive a complaint from a patient about his or her care, it should be responded to promptly and respectfully. If the patient was hospitalized, turning to the hospital's patient representatives for guidance can be helpful. You should investigate the complaint and communicate in a clear and sympathetic manner your findings. Make certain that you follow through. Although not every patient can be satisfied in this way, even minor complaints can escalate into lawsuits if they are ignored.

With the enormous attention currently focused on minimizing health care expenditures, virtually all surgeons feel pressured to shorten the duration of hospitalization and decrease the use of diagnostic tests and medications. Such feelings, although completely understandable, should never be allowed to influence patient care decisions. Juries persuaded that treatment was withheld or delayed because of a lack of medical insurance have been known to award substantial punitive damages. In cases where denial of coverage by the health care plan is a particular problem, it can often be helpful to talk directly with the medical director of the health plan.

What Should Surgeons Do If Sued or If Threatened with a Suit?

If you receive notice that a patient intends to file a suit or has actually filed a suit, you should immediately notify your insurance carrier and follow its advice. Every state has unique standards and procedures that must be followed in response to suits and claims that the insurance carrier can help you with. Most carriers have representatives who will handle the claim or suit and most often will arrange for you to have defense counsel appointed for you. Do not respond to a lawyer representing a previous patient in a potential claim or suit without first contacting your insurance carrier or defense counsel. If the patient is currently under your care and wishes to continue to have you care for him or her and you feel comfortable continuing to care for the patient, you can usually continue to provide care. However, it is also appropriate to arrange for referral to another surgeon if necessary. However, you should never speak directly to the patient about the claim or suit if you continue to provide care. If you receive proper written authorization from the patient or his or her attorney, you should honor the request and provide a complete copy of the record to them. If you suspect that the records are being requested because of a potential malpractice claim, you should notify your insurance carrier.

MEASURES FOR ASSISTING IN THE DEFENSE

First, all relevant records, telephone logs and messages, and e-mail correspondence or other notes should be assembled, and every effort should be made to cooperate fully with the claims representative of the insurer and the representative of the hospital risk management team if the hospital is involved in the case. Under no circumstances should any records be altered, amended, or discarded when a suit is initiated. The facts of the case should not be discussed with

any colleagues until legal counsel has become involved because anyone who takes part in such discussions may be asked to repeat the substance of the conversation at the time of pretrial depositions. The available records should be reviewed and a confidential summary of the case prepared; this summary should be addressed only to legal counsel, with no copies to anyone. If the media are involved at the outset of the suit, under no circumstances should defendants attempt to be spokespersons on their own behalf; this task should be left to others who are better equipped to determine how much information to provide to the media about the controversy.

It is advisable to find out the name of the defense lawyer assigned to the case and arrange an initial meeting to familiarize him or her with the relevant medical issues. Any medical research done to assist the defendant and legal counsel with the issues should be carried out with the understanding that the research is performed in the context of communication with counsel: all independent research that is conducted for the defendant's own edification, rather than for communication with counsel, is discoverable by the plaintiff. It is vital to take whatever time is necessary to educate the defense attorney on the medical issues involved so that the attorney can then gather more information effectively. The defendant can recommend and discuss with counsel certain fact-gathering tasks to be done by counsel on the defendant's behalf. Both defendant and counsel can begin thinking about whom to engage as an outside expert to assist in identifying weak points or issues in the case before the defendant submits to a deposition by the plaintiff's lawyer. Once defendant and counsel have agreed on an expert, however, only counsel should approach or contact the expert.

SETTLING THE CLAIM VERSUS TRYING THE CASE

Although many professional liability policies require the consent of the insured before a settlement offer can be made, it still is usually possible for the insurer to settle the claim over the objection of the insured physician after review and consideration of the objecting physician's argument against settlement. Nevertheless, the preferences of the defendant physician typically exert a heavy influence on the insurer's decision to try or settle the case. Defense attorneys' recommendations to the insurer are often affected by the degree of rapport they enjoy with their physician client, the client's conviction (or lack of conviction) regarding whether he or she met the standard of care, and the level of the client's commitment to defending the case in a jury trial.

From the insurer's standpoint, the decision to settle a case is guided by a number of factors, such as (1) the strength and quality of the defense expert who has evaluated whether the standard of care has been met, (2) the reputation and ability of the plaintiff's trial counsel, (3) the likely verdict potential and the risk of an adverse verdict, (4) the general competence and demeanor of the defendant physician, and, of course, (5) the costs of mounting a defense, which include defense attorney fees, expert witness fees, expenses for daily transcripts during trial, technology costs associated with the preparation and trial of the case, and the likelihood of an extended and expensive appeal by the losing party after the verdict. Insurers also consider the potentially beneficial longer-range impact of earning a reputation for defending their clients against all

meritless claims, regardless of cost, on the assumption that strong and successful defenses against such claims will discourage future meritless claims against the physicians they insure.

From the standpoint of an insured physician who is a named defendant, the risk of an adverse verdict is, or should be, an important consideration, as should the emotional wear and tear incurred in preparing for and enduring the stresses of a trial; the time spent away from work and family; the degree to which a settlement, as opposed to a successful verdict, may affect future insurance premiums; and the extent to which a favorable jury verdict will result in clearing of the physician's good name and restoration of his or her professional reputation. How these considerations affect the decision between settlement and trial is strongly influenced by the psychological makeup of the defendant physician: a physician with a strong emotional support structure who also has a personality capable of standing up to the emotional stress and rigors of the courtroom is more suited to participation in a trial than a physician with a more fragile personality who is intolerant of criticism and distrustful of the jury and the legal system. A physician who favors going to trial over settling the claim should be willing to become fully invested in preparing the case for trial, should have a high degree of confidence in the preparation and skills of the defense attorney trying the case, and should be willing to spend the time required to read the voluminous pretrial discovery depositions, medical literature, and medical records associated with the case.

Many physicians would rather have professional negligence claims judged by other physicians than by laypersons from all walks of life and of different education levels. These attitudes have their roots in the 19th century, when the judicial system was struggling to resolve the claims of injured patients against a backdrop of inconsistent medical standards, relatively unsophisticated scientific knowledge and information technology, and antiquated means of communicating medical concepts to laypersons, many of whom were illiterate and lacked what would currently be considered a minimal education. Today, the situation is different: jurors with college degrees are the norm, rather than the exception, in many venues, and the expanded use of technology in the courtroom enables illustrations, concepts, and documentation to be displayed clearly and effectively while witnesses discuss and interpret them for the jury. Accordingly, it is likely that at least some of the traditional suspicion of lay juries may be misplaced. As Struve has noted, "Juries' liability determinations in malpractice cases are not random; rather, studies find some degree of correlation between jury outcomes and medical reviewers' findings of negligence and causation."¹¹ The statistics released for the year 2005 demonstrate that in Pennsylvania, more than 80% of the verdicts in malpractice trials courts continue to be rendered in favor of the defendant.¹²

It is noteworthy that medical malpractice cases seem to account for a far higher share of tort trials than other types of tort actions do. For example, in Philadelphia County in 1996, malpractice accounted for only 3% of tort case filings but 18.7% of tort trials. To make the comparison in another way, about one of every eight malpractice filings went to trial, compared with about one of every 100 automobile accident filings.¹³

Preparing for a Deposition

Depositions are part of the process of gathering evidence and information in preparation for a malpractice trial. They are often held in an attorney's office. State law controls depositions, so there is some variation, but, in general, they follow similar guidelines. During a deposition, you will usually be questioned by the plaintiff's attorney first, with follow-up questions asked by your own counsel during cross-examination. Additional questions by both attorneys are possible to further clarify points. The entire proceeding will be transcribed by a court reporter, and objections are allowed in most states. It is important to prepare for your deposition by reviewing the available records so that you are familiar with them. It is also important to take the time to understand the questions that you are being asked and to answer them carefully. Depositions may be used at trial to demonstrate inconsistencies in your answers to questions, so it is important to carefully consider answers before you give them. Your attorney can help you in your preparation for the deposition and is usually present while it is being taken.

How Should Surgeons Act When They Are Defendants or Witnesses in a Courtroom Trial?

Although the experience of a medical malpractice trial is not inevitable for all practicing physicians, it is a significant possibility for many. If the suit is held to have merit, no settlement has been arrived at and the case goes to trial, an understanding of what to expect at trial is helpful. In addition, strategies for more effectively, credibly, and persuasively presenting the defense of a medical case to a jury of laypersons charged with the duty to arrive at a verdict can be useful.

Many witnesses who have to testify in court feel frightened or intimidated as they approach the witness stand to be sworn in. Sometimes the truth that the witness is attempting to tell is distorted because of this fear and because of the tactics of the opposing lawyer. The perception and judgment of the jurors who listen to the witness are affected not only by what the witness says but also by the manner in which the testimony is given, the degree to which the witness is acclimated to the facts of the case, and the demeanor of the witness on and off the witness stand. Rightly or wrongly, how the witness testifies is often more critical than what he or she actually says. The jury members' responsibility is to weigh the facts that they are presented with and to come to a judgment. The trust that they have in the witnesses is a crucial element of this process.

Preparation for an appearance in the courtroom is critical for any physician testifying in a trial to best use the opportunity to present the facts in a fair and convincing light. Not surprisingly, under the stress of the moment, intelligent, experienced, and articulate witnesses often abandon their habits of good judgment and solid common sense the moment they walk into a courtroom. The guidelines presented are applicable to both physicians who are actual defendants in a medical malpractice trial and those who are merely witnesses.

GENERAL PREPARATION

Most persons who have rarely or never been a witness in a trial are nervous and anxious at the thought of testifying in

front of a jury. A major reason for this reaction is the fear that one's words will be twisted by the opposing lawyer or that the intended testimony will be unfairly distorted or misrepresented as a result of deceptively phrased trick questions. You can overcome, or at least alleviate, this nervousness and anxiety by preparing painstakingly and familiarizing yourself with the case well before the trial, as well as by concentrating on and paying close attention to the content of any questions posed by opposing counsel during your testimony.

Defense counsel should discuss the key case issues with you in detail before your appearance, but, obviously, not all questions and answers can be (or should be) rehearsed. For your part, you should make sure that you are thoroughly familiar with the portions of the medical records for which you are responsible (either directly or in a supervisory capacity). You should also read and study your pretrial deposition transcript to prevent inconsistencies in your trial testimony. If possible, you should review the pretrial depositions of other witnesses in the case. Stenographers are now able to generate word index transcripts that allow you to search the index of another witness's deposition, quickly find all locations in that deposition where the witness or the examiner mentions your name, and then focus on any portion of the testimony that has a bearing on you or your involvement in the case. Currently available trial presentation software also allows such searches to be linked to corresponding segments of the video portion of a videotaped deposition, with the written transcript appearing below the video as the witness testifies. This approach can be an extremely effective tool for a trial lawyer during cross-examination, in that it facilitates demonstration of inconsistencies in a witness's statements through verbal and visual comparison of trial testimony with a pretrial deposition.

Unless a sequestering order has been issued, you should try, if possible, to come to court to watch other witnesses testify before you. This will not only familiarize you with the process of cross-examination but will also help you feel more comfortable with the courtroom environment as a whole by the time you testify. Of course, if you are a named defendant in the case, you will have been there almost all the time during all phases of the trial anyway.

BEHAVIOR AT TRIAL

During Jury Selection

If you are a named defendant, it is very important that you be present during jury selection, a process known as *voir dire*, which is used in most states. At this time, you will first be introduced to the jurors who will be hearing the case. Some information is elicited from the potential jurors before the selection process actually takes place. You will have an opportunity to communicate with your counsel if you have any preferences or concerns about any individual potential juror. Each party to the case generally has a limited number of so-called peremptory challenges. This means that your counsel can eliminate a preset number of potential jurors for virtually any reason. In addition, each party has an unlimited number of so-called challenges for cause, which involve making the argument that a particular potential juror cannot sit on the case fairly and impartially. If the reasons underlying

this argument are demonstrated to the satisfaction of the judge during the questioning of the juror, the challenge is upheld; if not, it is denied.

Ideally, before the selection process begins, you and your counsel should spend some time discussing the qualities your team would like your jurors to have and developing a consensus on what responses to questions should be considered favorable and what responses should not. You should feel free to offer suggestions to your counsel regarding questions to ask the jurors, even if the questions you think of may seem obvious. In some instances, your counsel may retain jury consultants to assist in developing *voir dire* questions aimed at identifying positive or adverse jurors. In the last analysis, jurors are generally selected on the basis of nothing more than a hunch. Most of the time, decisions made during the selection process are based mainly on a "gut feeling" derived from observing the jurors as they react to the lawyer's questions during *voir dire*.

During Lawyers' Opening Statements

After the jury is empaneled, each side has the opportunity to make an opening statement to the jury before the evidence is actually presented. An effective opening statement can go a long way toward persuading the jury to accept one side's view of the case, even though the jury is cautioned by the judge to withhold judgment until all the evidence is heard. If you are not a named party to the case but merely a witness, you should still try to be present during the opening statements; doing so will help you quickly develop a feel for the case and will alert you to the issues you may face when you testify on the witness stand a few days later. In some instances, however, you may not have this option. Certain trial judges may allow opposing counsel to obtain a sequestering order preventing witnesses (but not parties) from being present during the opening statements or during the testimony of other witnesses.

During Presentation of Evidence

Because the burden of proof is on the plaintiff, the plaintiff's case commences first, after the opening statements. Sometimes the first witness called is not the plaintiff but the defendant (or one of the defendants if the suit was brought against multiple physicians). Plaintiffs' lawyers like to use this tactic early in the case, when the witnesses are likely to be more nervous and have not yet had time to observe and warm up to the pace and facts of the case. By applying this tactic, they hope to take advantage of the initial unfamiliarity with the testifying process, sometimes attempting to strong-arm a nervous or inexperienced witness or manipulate his or her testimony. Sometimes all the plaintiff's attorney is trying to accomplish is simply to make the witness appear unsettled, evasive, or defensive so as to prejudice the jury against that witness.

The upside of being called in the plaintiff's case as one of the first witnesses is that it gives you an excellent opportunity to present the defense's side before the plaintiff's points are firmly established in the jurors' minds. Although the questions asked in this situation are, of course, under the control of the plaintiff's lawyer, they may—depending on how narrowly they are phrased—yield you an opening through which you can make the central points of the defense at the outset of the case.

When being questioned by opposing counsel, you must pay close attention to how the questions posed to you are phrased and whether improper assumptions and inaccurate statements of fact are loaded into these questions before you answer. If the question contains an improper predicate or attempts to make you assume facts that are contested, you must point this out before you attempt to answer the question. At the same time, you must never be evasive or fail to give a truthful and direct answer if the questions are straightforward, fair, and simple.

After you have been questioned by the plaintiff's attorney to establish the basic facts the plaintiff needs to prove, your defense counsel may cross-examine you in an effort to make, through your testimony, as many key points for the defense as the judge will then allow, even to the extent of assisting the defense in introducing documents or exhibits that the jury has not seen before. The defense thereby has a chance to place its case before the jury before the plaintiffs rest their case. If all the key points for the defense can be established, it may not be necessary to call you back to the witness stand later, during the defense's formal presentation of its case after the plaintiff rests. The decision as to whether you will be recalled during the presentation of the defense is usually made later in the trial, well after the defense has formally opened its case. Defense counsel should prepare you for this possibility in advance of the trial so that you are aware of the critical defense points that should be made in your subsequent testimony.

Many defense attorneys elect to defer this type of pro-defense cross-examination to the formal presentation of the defense, the rationale being that it may be best to hold the strong points of the defense in reserve until after the plaintiff has taken his or her "best shots." You should discuss this issue with your attorney in advance of the trial and decide on the strategy that works best for you.

DEMEANOR AS A WITNESS

General Recommendations

Numerous trial lawyers, acting for plaintiffs and defendants alike, have observed that it is better to have a poor case with a client whom the jury likes than a good case with a client whom the jury dislikes. The particular challenge for the physician acting as a witness is to avoid the appearance of being disengaged, aloof, or, worse, arrogant. Therefore, when testifying on the witness stand, you should always convey an attitude of caring, concern, and respect for the patient who is the subject of the suit. As difficult as it may be, you should always be polite and respectful toward the opposing counsel who will be cross-examining you. If, as sometimes occurs, the opposing attorney treats you with disrespect or ridicule, you should not respond by becoming defensive or overly aggressive. If you act respectfully, the jury will invariably come to feel displeased with and offended by the attorney and will resent the attorney for continuing in this manner in the face of your professionalism and politeness. This is true even if the attorney otherwise appears to be making some powerful points during the questioning.

Above all, it is imperative to avoid the ever-present temptation to condescend to or ridicule the plaintiff's attorney during questioning on technical matters. Although it may

well appear to you that the opposing attorney is "out of his (or her) league" in trying to play doctor, your interests are not served by making this attitude apparent: the jury will quickly identify with and side with a lawyer who is patronized or belittled because of a lack of technical knowledge or mispronunciation of medical terms. If you are perceived as defensive, sarcastic, or hostile toward opposing counsel, the jury may well dismiss the logical point you are making on the witness stand out of a feeling of empathy for the examining attorney, especially if that attorney has been polite to you during the questioning. Physician witnesses, particularly those who are professors and researchers, must be on their guard not to be seen as arrogant, ivory tower types who are out of touch with the human, caring side of medicine (the side that jurors typically prefer to see). The jury generally wants to like you and understands that you are human. Building their trust is crucial.

You should refrain from humorous quips or anecdotes, especially if you are a defendant or a fact witness in the case. You should project your answers in a strong voice and look the examining attorney in the eye when questioned, but without appearing hostile in any way. If you do not know the answer to a question, the best response is simply to say so. You will get into difficulty if you continually try to outsmart the cross-examiner by trying to anticipate where the questioning is headed or giving equivocal or facetious answers.

When being examined by the plaintiff's attorney, you should try not to look at your own counsel at the defense table while the question is being asked, while you are answering it, or right after you have given your answer. Looking back at the defense lawyers with whom you have associated is a natural impulse, especially when the courtroom scene is strange to you and you feel a need for reassurance or approval. However, this impulse should be restrained because it suggests to the jury that you are unsure about your testimony or, even worse, that the testimony might never have been yours to begin with. You should look at the defense attorneys only when they are questioning you.

When medical concepts must be explained to a jury, it is important to avoid medical jargon. "Cause" is universally understood; "etiology" is not. Generally speaking, most medical concepts can be clearly explained with nonmedical words, basic illustrations, or even crude diagrams. However, the complexity level of your testimony and the extent to which you use technical medical language may vary depending on the point in the trial at which your testimony is given. For example, if you are the last witness testifying and the jury has already heard three physicians explain a particular medical issue, you risk insulting the jurors if you talk to them as if they are in a seventh grade health class; you are better served by using language that matches their current acquired understanding of the issue in question. You must use your own judgment as to what level of medical explanation is appropriate at any given point in the trial, but it is important that you are clearly understood.

Most jurors are keenly interested in medical science and human physiology. If you can respond to this interest by testifying in a clear and accurate manner, without condescension, you have a better chance of ensuring that the

technical aspects of your testimony are remembered and understood long after you leave the witness stand.

Strategy on Cross-examination at Trial

The strategy that should govern your testimony at the trial is quite different from the one that governed your testimony at the pretrial deposition. At the deposition, there was no jury, and your counsel instructed you to answer all questions concisely, without volunteering any information that would lead to more questions. At the trial, it may be to your advantage on occasion to play a more active role. For example, you may forcefully but politely correct a misimpression that is being conveyed by the cross-examiner's questions, or you may add another point that disputes a particular point the questioner is attempting to make. In doing so, however, you must maintain and convey a sense of balance and fairness because it is certainly not to your advantage to dispute or equivocate on obvious points.

Correction of Misleading Questions

If the cross-examining lawyer asks you a leading question that contains an unfair or improper assumption in the question itself, you should politely correct him or her and make it clear that you do not accept the assumption in the question.

Vulnerability to this sort of tactic is heightened when the examining attorney uses deposition testimony or characterizes a particular document during the formation of a question. It is astounding how often witnesses feel compelled to agree with the examiner's characterization of the testimony in a deposition or of the contents of a particular document, without even asking to see the portion of the deposition or document to which the examining attorney is referring in the question. Unless you know for certain that the portion of the deposition or document used in the question is characterized accurately, we suggest that you do the following:

1. *Always ask to see the deposition transcript or document referred to in the question before beginning to answer.* Quite often, the questioning attorney is taking the passage out of context, is ignoring relevant passages immediately before or after the passage quoted, or, even worse, is directly misrepresenting the content of the document or deposition passage in question. Most judges will accord a witness the courtesy of being provided with the document if the witness requests it. If, as sometimes happens, your request is not granted, this refusal may actually be to your advantage: jurors are almost certain to be sympathetic to any witness who requests to see a document and is denied the opportunity to see it.
2. *Do not answer the question until you have received the document you requested.* When you are given the document, ask for a moment to see the passage that was the subject of the question but take a few extra seconds to examine the paragraphs before and after the passage, both to confirm your understanding of the context and to determine whether the preceding and following passages help clarify the passage in question.
3. *If you then remember the question, answer it.* If you do not remember, ask the court reporter to read back the question after you have read the document. When you answer the question, correct any misrepresentation made in the question or add anything you have found that would

clearly establish that the passage was taken out of context or misquoted. If, however, the examiner's question was fair and accurate, simply concede that the passage says what was represented in the question and wait for the next question. Finally, if the judge denied your request to see the document before you answer, you are then permitted to testify that because you cannot recall the exact wording of the document referred to in the question, you are unable to answer the question.

Not surprisingly, witnesses who fail to follow these instructions often find their testimony to be unfairly mischaracterized and manipulated and sometimes discover that they have been tricked into conceding points that were untrue or unsubstantiated. A witness who does follow these instructions, however, will find, more often than not, that the examining attorney will abandon further attempts to misrepresent the document with him or her and will adopt a more measured and cautious approach to questioning.

It is important not to quibble about well-established facts or undisputed data that appear in medical records. A successful strategy is always to be on the side of facts that the jury will most likely regard as true—even if some of those facts, considered individually, do not appear to be favorable to the defense.

Handling of Cross-examination Questions Based on Deposition Transcript

Questions referring to your own pretrial deposition transcript should be dealt with in precisely the same manner as questions based on any other documents (see above). You should ask to see the transcript, you should review its context before beginning your answer, and when you answer, you should take the chance to correct any misleading assumptions or add crucial context. It is to your advantage that your cross-examination testimony be consistent with your deposition insofar as this is possible. Unprepared trial attorneys sometimes make the mistake of trying to impeach a witness with a document that, instead of contradicting the witness's testimony, turns out to be consistent with it, thereby strengthening the very point under attack. This tactic can cause the lawyer to lose all credibility in front of a jury, especially when the witness can politely explain why the previous testimony is consistent with the current testimony.

Another unfortunate tactic some lawyers use with deposition transcripts is to suggest that the witness just testified inconsistently because the in-court testimony did not appear in the deposition at all. For example, the examining lawyer might say to the witness, "You just testified here in court that 'fact A' occurred. Show me where in your deposition you ever testified that 'fact A' occurred." The witness should then say something like the following: "At the deposition, I was instructed to answer only the questions asked. I looked at my deposition before testifying today, and I do not believe that you ever asked me about 'fact A' in my deposition. If I am mistaken, could you show me the point in my deposition where you asked about that subject?"

Handling of Exhibits

When you are handed any exhibit, whether it is a demonstrative exhibit or some other record in the case, you should make a point of holding it and moving it with care and

respect. This nonverbal communication with the jury is important because it is representative of your caring and respectful attitude toward the entire case. If you are asked to identify an exhibit, you should take the time to examine it carefully before verbally identifying it.

When you are asked to show the exhibit to the jury or to explain something while using the exhibit, you should first ask for permission to step down from the witness box and then place the exhibit on an easel or otherwise position it and yourself in such a way that you do not obstruct any juror's view of the exhibit as you are testifying. During your testimony, you have an excellent opportunity to make eye contact with each juror and build a rapport. Sometimes, in dealing with an exhibit, you will have to face away from the court reporter. Therefore, you should make sure that you always speak loudly enough to be heard easily by the court reporter so that the key portions of your testimony will not be interrupted by the court reporter's requests for you to repeat a statement or to speak louder.

Conduct While Not Testifying

When your testimony is concluded, or when the judge orders a pause, you should not attempt to communicate non-verbally with any of the attorneys, parties, or other witnesses. You should walk away from the witness chair with an erect and confident posture and resume the seat you occupied before you testified (unless you have been dismissed from the courtroom by the judge).

While other witnesses are testifying in the courtroom, you must avoid any emotional facial expressions signaling either approval or disapproval of the witnesses or the attorneys. Facial expressions showing exasperation, disbelief, approval,

or other emotions will be seen by the jury as contrived and self-serving and may cause you to be perceived as less objective, factual, and trustworthy. You should also endeavor to distance yourself physically from other defense witnesses who are in the room to avoid the appearance of collusion. If you are a defendant or the physician whose care is being called into question, you should not wave to or acknowledge any other witnesses (including the defense expert) who may come into the courtroom during the proceedings when the jury is in the room.

You should not stare or smile at the jurors: they will resent any attempt, subtle or overt, to influence or curry favor with them. Especially if you are sitting at the counsel table, it is a good idea to take notes occasionally during the proceedings or to have something in front of you at the table to read. If you have a suggestion to make to your attorney during another witness's testimony, you should write it down and hand the note to the attorney or else discuss the matter during the next recess.

During recesses, at lunch, in the elevator, or en route to or from the courtroom, you must be extremely careful not to discuss the case with anyone if there is a risk that you may be overheard by a juror or a friend of the plaintiff. During recess, when the jury is not in the courtroom, you may want to converse with courtroom personnel, witnesses, attorneys, or other persons in the courtroom. Once the bailiff has called for the jurors, however, you should return to your seat promptly, before the jurors return to the courtroom. Again, you should be careful not to stare at the jurors as they leave and enter.

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10 SURGICAL PALLIATIVE CARE: CLINICAL AND ETHICAL CONSIDERATIONS

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The last 15 years have seen a renewed interest in and concern about the end of life and the care of the dying, both in American society and in the practice of medicine and surgery. This can be traced to the growth of the hospice movement, patient-centered care, and the change in demographics permitting many more adults to live longer with chronic, life-limiting illness. Simultaneously, it can also be seen as a reaction to the increasing emphasis of American medicine on technology, cure and prolongation of life at the expense of the relief of suffering, humanism, and the “art” of medicine. The last decades of the 20th century saw an unprecedented growth in life-prolonging technology but also an increasing awareness of the erosion of the doctor-patient relationship, the dehumanizing effect of much of medical care, and the shift from physician as healer to physician as technician and gatekeeper. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) in the 1990s observed that most Americans died in institutions, usually on life support, with untreated pain and suffering,^{1,2} yet most Americans wish to die at home and fear untreated pain and artificial extension of life.³ At the same time, ethical and judicial decisions that emphasize patient autonomy provided the legal foundation for the care of the dying today, ensuring that physicians can both relieve suffering and avoid burdensome or futile treatments for their patients at the end of life. The convergence of these developments has perhaps fostered the renewal of the twin goals of medicine and surgery: the relief of suffering alongside life-prolonging, curative therapy.

Surgical palliative care has evolved in this context over the last 10 years, drawing not only from the fields of hospice and palliative medicine but also surgery itself. The emergence of this field of surgery has in one sense reclaimed the long surgical traditions of palliation and compassion from a time when to bear witness and relieve suffering were all the surgeon could offer, attributable in part to the limitations of medical knowledge or surgical technique. Historically, much of surgery and surgical care has focused not on cure but on palliation of symptoms and restoration of quality of life, with burn care, vascular surgery, and surgical oncology being prime examples. The contemporary practice of surgery now includes the integration of technical competence with knowledge and skill in relief of suffering, restoration of quality-of-life, communication, and, when the end of life is near, appropriate decision making and withholding or withdrawing of life support. The following chapter describes the evolution of surgical palliative care, its ethical basis, and its approach and clinical applications in surgical practice.

Evolution of Surgical Palliative Care

The roots of surgical palliative care can be traced first to the hospice movement founded by Dr. Cicely Saunders in the 1960s. She focused on the needs of the terminally ill, particularly their intense suffering from untreated pain at the end of life. She defined the model of “Total Pain” and distinguished “pain” from “suffering.” She described the four dimensions of pain as physical, psychological, social/economic, and spiritual, which lead to suffering. Hospice care developed to treat all four aspects of pain, for both patient and family, at the end of life. This model focused initially on those dying of cancer, where the trajectory of illness encouraged the aggressive treatment of suffering only when death was imminent or life-prolonging care had been exhausted.

During the 1980s and 1990s, palliative care extended this model of care to patients dying of other illnesses, such as dementia, cardiovascular disease, and organ failure, where the trajectory of decline is long and unpredictable and the dichotomy of cure versus comfort is blurred. Concomitantly, other concepts of suffering, such as that proposed by Eric Cassell, brought the realization that medical care itself might be the cause of suffering rather than the relief. He described suffering as arising from a threat to the integrity or wholeness of a person. Cassell noted that “the relief of suffering and the cure of disease must be seen as twin obligations of a medical profession that is truly dedicated to the care of the sick. Physicians’ failure to understand the nature of suffering can result in medical intervention that (though technically adequate) not only fails to relieve suffering but becomes a source of suffering itself.”⁴ Now palliative care has evolved to a model of interdisciplinary care that aims to relieve suffering and improve quality of life for patients with advanced illness and their families. It is offered simultaneously with all other appropriate medical treatment.

In 2010, surgical palliative care has evolved from these trends in palliative care and long traditions in surgical care. Although the goal of cure is paramount in much of surgical care, the relief of suffering and palliation of symptoms are equally important. The core values of surgical culture include ethical decision making, preservation of hope, nonabandonment, relief of suffering, and improvement in quality of life. Certainly, surgeons have always prided themselves as being the doctors of last resort, taking on the most difficult cases and thereby maintaining hope and presence when others have “given up.” Coronary artery bypass graft for the treatment of angina, organ transplantation, and vascular surgery were developed as palliative procedures, with their primary goal to

improve quality of life as well as prolong it. Fields such as burn care, trauma, and critical care are examples of surgical specialties that emphasize not only aggressive, technology-based, lifesaving care but also aggressive attention to pain relief, rehabilitation, and quality of life. Both are considered equally important, neither is mutually exclusive, and usually both are delivered simultaneously to patients.^{5,6} It is no surprise, therefore, that surgical palliative care would be embraced as a specialty inasmuch as it is a renewal of core surgical values and the adoption of other disciplines.

Contemporary practice of end-of-life care was officially recognized in the surgical profession when the American College of Surgeons endorsed its *Statement of Principles Guiding Care at the End of Life* in 1998 [see Table 1].⁷ Over the next decade, the principles of end-of-life care were integrated into the surgical canon, and the palliative approach to care was moved upstream to include those patients with chronic, serious illness and the critically ill, not just those who are imminently dying. In 2005, the American College of Surgeons endorsed the *Statement of Principles of Palliative Care* [see Table 2],⁸ thereby codifying a new discipline of surgery. Over the last 10 years, the field of surgical palliative care has grown, culminating in recognition by the American Board of Surgery and the American Board of Medical Specialties as a distinct discipline with board certification.

Ethical and Legal Foundations of Palliative Care

The current practice of palliative and end-of-life care is guided by bioethical principles and established judicial decisions. The vast majority of deaths in America now occur in hospitals and institutions, where active decisions must be made to withhold or withdraw interventions to allow a “natural” death. Over 70% of patients dying in an intensive care unit have at least one intervention withheld or withdrawn prior to death.⁹ Surgeons must be familiar with the ethical principles and judicial decisions that form the basis of this practice.

Clinical decisions in palliative care are grounded in the four ethical principles that guide all of modern medicine: autonomy, beneficence, nonmaleficence, and justice [see

Table 1 American College of Surgeons Statement of Principles Guiding Care at the End of Life

Respect the dignity of both patient and caregivers.
Be sensitive to and respectful of the patient's and family's wishes.
Use the most appropriate measures that are consistent with the choices of the patient or the patient's legal surrogate.
Ensure alleviation of pain and management of other physical symptoms.
Recognize, assess, and address psychological, social, and spiritual problems.
Ensure appropriate continuity of care by the patient's primary and/or specialist physician.
Provide access to therapies that may realistically be expected to improve the patient's quality of life.
Provide access to appropriate palliative care and hospice care.
Respect the patient's right to refuse treatment.
Recognize the physician's responsibility to forego treatments that are futile.

Adapted from the American College of Surgeons.⁷

Table 2 Statement of Principles of Palliative Care

1. Respect the dignity and autonomy of patients, patients' surrogates, and caregivers.
2. Honor the right of the competent patient or surrogate to choose among treatments, including those that may or may not prolong life.
3. Communicate effectively and empathically with patients, their families, and caregivers.
4. Identify the primary goals of care from the patient's perspective and address how the surgeon's care can achieve the patient's objectives.
5. Strive to alleviate pain and other burdensome physical and nonphysical symptoms.
6. Recognize, assess, discuss, and offer access to services for psychological, social, and spiritual issues.
7. Provide access to therapeutic support, encompassing the spectrum from life-prolonging treatments through hospice care, when they can realistically be expected to improve the quality of life as perceived by the patient.
8. Recognize the physician's responsibility to discourage treatments that are unlikely to achieve the patient's goals and encourage patients and families to consider hospice care when the prognosis for survival is likely to be less than a half-year.
9. Arrange for continuity of care by the patient's primary and/or specialist physician, alleviating the sense of abandonment patients may feel when “curative” therapies are no longer useful.
10. Maintain a collegial and supportive attitude toward others entrusted with care of the patient.

Adapted from American College of Surgeons.⁸

Table 3].¹⁰ Each clinical situation requires consideration of all four principles for each patient; however, frequently, fulfillment of one principle conflicts with fulfillment of others. For example, a surgeon may perform a surgical procedure that can successfully remove a cancer (beneficence) but may cause pain or even death from complications (nonmaleficence). Treatment of pain may be beneficial but can theoretically hasten death in some cases. Patients may refuse lifesaving surgery (autonomy) even if it means imminent death or disability. The ethical principle of double effect allows the surgeon to perform surgery and aggressively treat pain and suffering at the end of life if the *intent* is to do good, even though the side effect of the treatment may harm the patient. The bad effect may be a foreseen, but not intended, consequence or purpose of the treatment.

In Western culture in general, and the United States in particular, the principle of autonomy has been codified and supported by the judicial and legal system as the prevailing ethical principle to guide medical decision making. Patient autonomy is considered a fundamental right of Americans; this includes the right to be informed about medical illness, prognosis, and treatment options and the right to choose or refuse these options even if they are lifesaving. The Patient Self-Determination Act of 1990, passed by the US Congress, legally ensures that patients have the right to facilitate their own health care decisions, accept or refuse medical treatment, and create an advance directive. This allows patients to determine their future health care decisions by completing a living will. Surgeons are ethically and legally bound to observe the wishes set forth in a living will in the event the patient becomes incapable of making such decisions. In practice, however, this is complicated by the reality that specific clinical scenarios are rarely laid out in a living will, situations

Table 3 Common Ethical Issues in the Practice of Surgical Palliative Care

Issue	Commentary
Disclosure of bad news	Broad legal and ethical consensus supports disclosure of bad news when permitted by patient or surrogate. Disclosure of bad news does not “take away hope” if conveyed with empathy in the spirit of nonabandonment. Empathic truth telling fosters trust, which is the basis of hope.
Perioperative do-not-resuscitate (DNR) orders	The American College of Surgeons, the Association of Operating Room Nurses, and the American Society of Anesthesiologists support a policy of “required reconsideration” of DNR orders in the perioperative period. This is a preoperative discussion between patient/surrogate and anesthesiologist and surgeon to clarify goals and limits of care, with either revision or continuation of the DNR order in the operating and recovery room. Automatic rescinding of DNR orders during surgery is not recommended.
Withholding/withdrawal of life support	The withholding of medical treatments is considered legally and ethically equivalent to withdrawal. This is based on the principle of autonomy. In practice, for both physicians and surrogates, it is more difficult to withdraw a life-supporting treatment once it has been started than to withhold it. A surrogate’s persistent reluctance to consider termination of life support is usually related to the fear that he or she will be “killing the patient” or the fear that withdrawing life support will cause suffering. Legally and ethically, termination of undesired medical treatment of the properly informed patient/surrogate is not considered homicide, suicide, or euthanasia.
Aggressive symptom management	Aggressive management of unbearable symptoms at the end of life is a moral imperative, even at the risk of hastening or causing death, as long as causing death is not the intention of treatment. The risk of hastening death is present with any surgical treatment for serious illness, including attempts to cure. The rule of double effect, broadly accepted by ethicists, is invoked: • The act must be good or morally neutral. • Bad effects are foreseen but not intended. • A good end cannot justify a bad means. • The risk/benefit ratio must be reasonable.
Donation after cardiac death (DCD)	Ethical and legal principles support DCD, invoking principles of autonomy and double effect. DCD should be considered for patients where withdrawal of life support is contemplated. The Organ Procurement Organization personnel should be consulted prior to decision making to evaluate feasibility and medical suitability before approaching this option.

arise that are unforeseen, and written documents cannot substitute for informed discussions between physician and patient. This reality has led to reliance on surrogate decision makers and health care proxies to interpret a patient’s living will or advance directive in consultation with the physician. Although the Patient Self-Determination Act did not specifically address the issue of surrogate decision maker or the ethical basis of substituted judgment in medical decision making, the legal and ethical basis has been clearly established by the Supreme Court decisions of the Karen Anne Quinlan and Nancy Cruzan cases.^{11–13} These two cases established that it is consistent with autonomy, beneficence, non-maleficence, and justice if a surrogate decision maker acts based on the patient’s best interest and/or in accordance with the patient’s previously expressed wishes. This provides the legal basis for decisions to withhold or withdraw life support in patients who are incapacitated, as long as these principles are maintained.

The Practice of Surgical Palliative Care

Surgical palliative care is the treatment of suffering and the restoration of quality of life for seriously ill or terminally ill patients with surgical disease, regardless of the prognosis. The surgeon brings all the tools in his or her armamentarium to treat distress, not just disease. The measure of surgical palliative skill in this context is not disease specific, such as complications, morbidity, or mortality, but rather patient

centered. Quality of life, relief of symptoms, and the opportunity for spiritual comfort or closure at the end of life are more important measures of success in this discipline. This constitutes a cultural shift in surgery, where the morbidity and mortality conference reinforces the notion that death is a “failure” of the surgeon and brings “shame” on him or her.¹⁴ It is not a large leap to see how this stigma would cause some surgeons to view end-of-life care as the sine qua non of “giving up” and therefore distinct from their aggressive, life-prolonging care. Surgical palliative care is currently moving away from this false dichotomy to an affirmative concept upstream in the patient’s care, when symptom control and restoration of quality of life can be delivered alongside life-prolonging surgery.

PALLIATIVE CARE ASSESSMENT

The first goal of the assessment for palliative care is to gauge the level of overall distress. The assessment is, in a sense, a “staging procedure” to determine the scope and severity of palliative care needs. Palliative care assessment includes the identification of the current illness, treatments, and likely prognosis; sources of pain in all dimensions; personal, social, and spiritual resources; and individual values and hopes. The patient’s decision-making capacity, advance directives, and health care proxy should be identified as well. Table 4, adapted from the American Medical Association Education for Physicians on End-of-Life Care Curriculum (EPEC), describes the domains of palliative care assessment

Table 4 Ethical Principles in Palliative Care

Principle	Ethical Imperative
Autonomy	Respect the capacity of individuals to make their own choices and act accordingly
Beneficence	Relieve pain and suffering, foster the interests and well-being of other persons and society
Nonmaleficence	Do no harm; do not inflict pain or suffering
Justice	Act fairly; distribute benefits and harms equitably

Adapted from Beauchamp TL and Childress JF.¹⁰

with sample questions for each. Immediate relief of pressing symptoms should be a priority and initiated concurrently with the assessment if necessary. Further discussions around goals of care cannot ensue if untreated symptoms are allowed to persist. Who should be included in the discussions should also be established at this time as the patient may or may not want family present.

The assessment of physical symptoms is usually the first priority in palliative care. This is focused on pain and non-pain symptoms, that is, the patient's subjective report, not on disease processes or disease-based review of systems (Table 5). The patient's self-report is the gold standard. Validated pain assessment tools using numeric scoring from 0 to 10 are the most common. Assessment tools are also available for nonpain symptoms but are generally validated for specific disease or patient populations. The Edmonton Symptom Assessment Scale (ESAS) is a validated tool for palliative care patients and includes assessment for nonpain symptoms such as fatigue, thirst, dyspnea, and nausea.^{15,16} Assessment should include not only the severity of the symptom but also questions as to the level of distress the symptom causes.

GOALS OF CARE

The patient's goals of care that emerge from this initial assessment and discussion should guide the scope of all further surgery and treatments. The goals of care are generated by the patient's preferences and wishes in the context of the medical realities and the prognosis. Goals may be fluid and evolve over time. Singer and colleagues identified five domains of quality of life that patients with life-limiting illness hope for: adequate pain and symptom management, avoidance of inappropriate prolongation of dying, sense of control, relief of burdens, and strengthening of relationships with loved ones.³ More recent studies suggested that seriously ill patients weigh treatment options based on the treatment burden, treatment outcome, and likelihood of the outcome, with cognitive or severe functional impairment often considered more unacceptable outcomes than death.¹⁷ Although the surgeon must elicit preferences from the patient, he or she must provide the medical information and prognosis to the patient, especially likely and unlikely outcomes from contemplated therapy. Physicians are notoriously poor at prognostication, but ranges of life expectancy can be provided, keeping in mind that in some disease trajectories, death may be years away, but chronic, debilitating decline may be the life-limiting feature. Some trajectories are more predictable, such as cancer, and assessment of function, or progression of symptoms, is an indication of life expectancy. The Karnofsky Performance

Scale score is a widely used scale for the assessment of function and prognosis in cancer patients.¹⁸ Patients with congestive heart failure or chronic respiratory failure who may be contemplating surgery have a more unpredictable trajectory to death but will need prognostic information about the likely decline in quality of life over time, with or without surgery.

All therapy should be evaluated by both patient and surgeon based on the goals of care established. Surgery or procedures are weighed, not by their defined complications or indications but by their benefits or burdens for the patient, in the context of his or her goals. Palliative surgery to relieve malignant bowel obstruction should be considered based on the likelihood of eating again and the relief of nausea, vomiting, and pain (benefit) versus the likelihood of pain, open wounds, infection, or death in the operating room or the hospital (burdens). The patient's decision will depend on his or her goals ("I want to die at home," "I want to see my daughter's wedding"), as well as the information the surgeon provides about the surgery and alternatives. Each treatment or therapy should be considered independent of other therapies and based solely on its benefits or burdens. Patients who want do-not-resuscitate (DNR) orders in the event of cardiopulmonary arrest will still need symptom relief or simple, life-extending treatments. Surgery to relieve malignant obstruction or antibiotics to treat pneumonia would still meet their goals, even if they do not want cardiopulmonary resuscitation (CPR).

Establishing goals of care can be a difficult transition for both patient and surgeon. The surgeon is often consulted as the last hope and held up as the "rescuer," bringing lifesaving surgery or other "miracles." It is not difficult to see that changing the goals of care is, in a sense, breaking this "covenant for cure"; the surgeon may feel that he or she is "taking away hope" or abandoning the patient by not performing futile surgery that would only add burden, not benefit.^{14,19} Conversely, the surgeon may have a long relationship with a patient, always focusing on aggressive, life-prolonging care, but now the prognosis has shifted, and a transition to comfort and relief of suffering changes this role. This is further complicated if the patient's condition has changed after surgery because of complications or iatrogenic events; this is frequently the case in the intensive care unit when unforeseen postoperative events have changed the course or patients linger with multiple organ failure and uncertain prognosis. The ability of the surgeon to reflect on his or her own sense of failure or loss is the first step in making a transition in goals of care. The surgeon has the unique role of helping the patient and family find new hope, whether it is hope for symptom relief or time with family. If likely outcomes are uncertain, the surgeon can convey this range of possibilities, and goals of care can include a focus on relief of suffering alongside other life-prolonging therapies, not in an either/or fashion.

INTERDISCIPLINARY TEAM

The relief of "total pain" or suffering requires an interdisciplinary approach, particularly if suffering is extreme. The collaboration of pain medicine specialists, clinical pharmacists, palliative medicine and nursing colleagues, and spiritual and psychosocial care providers is essential. Surgeons may not be familiar with nonsurgical alternatives for treatment of nonpain symptoms. Similarly, the best approach to breaking

Table 5 Palliative Care Assessment

Domain	Sample Questions to Ask the Patient
Illness/treatment summary	Tell me what you know about your illness. Could you give me an account about your illness and treatment you have had until now? Tell me what stands out in your memory (about your illness, about treatment to date). I will review (have reviewed) your medical history in your chart, but I am really interested in hearing about it from your point of view.
Physical symptoms	How long have you had (symptom)? Are you having this (symptom) all the time or on and off? How would you describe what you are feeling? Is the (symptom) staying the same, getting better, or getting worse? Using a scale (provide a scale), what is the lowest you have been in the past day? The highest? Where are you now? Does anything make the (symptom) better? Worse? To what extent does the (symptom) interfere with what you want to do? Is the (symptom) causing problems in your relations to others? Have any treatments helped your (symptom)? How much? What do you think is causing it (symptom)? Does it (symptom) frighten you? Why?
Psychological symptoms	Does everything happening make any sense to you? What do you think will happen next? How has your illness affected your life? What do you see as the biggest problem facing you now? What frightens you most about your illness? How would you describe your mood? How well do you think you are coping now? Do you feel depressed? Have you ever thought of taking your life? Do you have a plan? Have you been sad? Frightened? Anxious? Are you afraid of being a burden to others? How have you handled tough times in your life previously? Whom do you turn to for support in tough times? Have you ever had problems with depression, alcohol, or other psychological difficulties before your illness? Did you ever have treatment for these? Are you afraid we won't be there when you need us?
Spiritual issues	Do you consider yourself a religious or spiritual person? How important is your faith or belief in your life? Do you belong to a community of faith? What sustains your hope? Do you have religious or spiritual beliefs that help you through difficulty? What gives your life meaning? Does your faith influence your feelings about your illness? Your surgery? Do you see any possible conflicts between your health care and your beliefs? Do you have any specific observances or rituals we should be mindful of during your care?
Social/cultural context	Can you tell me about other people in your everyday life, at work, at home, etc.? What language is spoken in your home or community? Do you have a community or spiritual leader whom you would like to involve in your medical decisions?
Communication preferences	Is it your preference to be alone or have someone close to you present when we discuss important matters? Is there anyone with whom you would like me to discuss your care? If I am approached by family members with questions about your situation, do I have your permission to discuss it? To what extent?
Decision making	Who will make decisions about your medical care if (when) you are not able to? What would you like them to know?
Practical concerns	Where do you hope to go after this hospitalization? When you are ready for home, will your home be ready for you? Are you concerned about being a financial burden on your family?
Anticipatory planning	Have you given any thought of what comes after your hospitalization? What plans have you made for your future? Are there things you need to know right now for planning for the future? Would it be helpful for us to schedule a meeting with us and your family to plan your future treatment and care?

Adapted from palliative care assessment in EPEC, American Medical Association's Education for Physicians on End-of-life Care. 1999.

bad news, communication under conflict, or relief of existential pain may be beyond the scope of the usual surgical practice. In palliative care, the patient and family are considered part of the unit of care. Attention to bereavement, grief, and the needs of family at the end of life is especially important. Studies show that the nature of communication, access to the dying patient, and the patient's relief of distressing symptoms all affect the bereavement outcome of family members.^{20,21} Furthermore, the majority of hospitalized patients, particularly in the intensive care unit, are incapacitated and cannot make any medical or end-of-life decisions for themselves. Decision making generally falls on their surrogates, who are likely in crisis themselves because of the illness of a loved one. Emotional and educational support for their decision-making role is critical in avoiding conflict or prolonging the dying process, whether in the form of bereavement counselors, pastoral care, or other members of the palliative care team. Studies clearly show that interdisciplinary communication, whether in the form of family meetings, ethics, or palliative care consultation, has a salutary effect on both patient and family psychosocial outcomes.²²⁻²⁴ Surgeons may also benefit from this team approach as they seek balance in the dual imperatives to rescue and to relieve suffering. The death of a patient is also a loss for the surgeon; reflection and the ability to seek support are important steps for adapting to the multiple roles of the surgeon in palliative care.

COMMUNICATION

Shared decision making between the physician and the patient/family is the foundation of end-of-life care. Communication of bad news, along with treatment of distressing symptoms, is perhaps the fundamental "procedure" of palliative care. The emphasis on patient autonomy, the patient-doctor relationship, and professionalism and the realization that clinical and litigation outcomes are improved now require competency in communication skills in all aspects of surgical practice. Although as late as the 1960s, most physicians did not reveal a distressing diagnosis to their patients, it is now the expectation and legal obligation that all medical information be disclosed, no matter how upsetting. Communication around death and dying can be one of the most stressful aspects of practice. Surgical myths and fears abound: surgeons are poor communicators or lack empathy, truth telling will take away hope, talking is too time consuming—all further compound these stressful encounters. In fact, good communication is a skill. Increasing studies demonstrate that patients and families' satisfaction and understanding of the illness are improved when physicians do less talking and more listening, impart information clearly and simply, allow time and space for emotion, connect the emotional distress with its source (the medical information), and provide support.²⁵⁻²⁷ Several communication protocols for delivering bad news or conducting a family meeting have been proposed and studied.^{28,29} The SPIKES protocol developed by Baile and colleagues is one example, as shown in Table 6.²⁹ All of these emphasize preparation for the meeting, the appropriate setting, providing a "warning shot" for bad news, clear delivery of information, empathic reflection of emotion, and concluding with recommendations for treatment. Following these steps will provide support to the patient and family and allow for further communication. This is particularly

Table 6 SPIKES: A Six-Step Protocol for Delivering Bad News

Step 1: S – Setting Up the Interview - Arrange for some privacy - Involve significant others - Sit down - Make connection with the patient - Manage time constraints and interruptions
Step 2: P – Assessing the Patient's Perception
Step 3: I – Obtaining the Patient's Invitation
Step 4: K – Giving Knowledge and Information to the Patient - Avoid medical jargon - Give information in small amounts at a time
Step 5: E – Addressing the Patient's Emotions with Empathetic Responses - Allow time for expression of emotion - Identify patient's emotion - Identify cause of emotion - Connect emotion with cause of emotion
Step 6: S – Strategy and Summary - Discuss goals of care - Treatment plans - Future meetings

Adapted from Baile WF et al.²⁹

important when end-of-life decisions will be discussed; if initial communications are not clear and compassionate, conflicts around withdrawal and withholding of life support can ensue. The timing of communication is important, particularly with families of critically ill or injured patients. Family meetings to discuss prognosis and end-of-life decisions in the intensive care unit are more effective if held within 72 hours of admission.^{22,30}

WITHDRAWING AND WITHHOLDING OF LIFE SUPPORT

The vast majority of deaths in the United States, whether in the hospital or at home, now occur in the setting of withdrawing or withholding of life support. Although use of hospice during the last months of life has increased in the last decade, multiple studies suggest that the largest percentage of Centers for Medicare and Medicaid Services expenditures result from high-technology care in hospitals and intensive care units in the last 6 months of life.³¹ Death after end-of-life decision making and withholding or withdrawing of life support have become the norm, and expertise in this area is now part of standard surgical practice.

The process of withholding or withdrawing life support is based on shared decision making around end-of-life issues between patient, family, physician, and other health care providers. The decision should be based on patient preferences and goals, knowledge of the likely outcome of continuing life support versus withdrawing it, and the benefits and burdens of each option. Conducting these discussions requires skill in communication and knowledge of the ethical issues, symptoms, and therapies available to treat them. There continues to be misunderstanding around the difference between withdrawal of life support, euthanasia, and physician-assisted suicide. Families may worry that if they decide to withdraw the ventilator they "are killing the patient"; similarly, they

fear that their loved one may “suffocate.” Part of the discussion should include assurances that dyspnea, pain, and other symptoms can be treated successfully and that physicians will not abandon the patient once a decision is made. The “DNR discussion” can be particularly difficult; following available guidelines is helpful.³² These include the basic steps of good communication: preparation, appropriate setting, and reflecting troubling emotions around difficult issues. It is helpful to describe CPR as a procedure with certain indications, benefits, and burdens and to make a recommendation about whether or not to withhold it based on the medical prognosis and condition.

Confusion on the part of physicians still exists about their role in withholding and withdrawing life support. Many are more comfortable withholding therapy rather than withdrawing it because of unfounded fears that they may be causing death, abandoning the patient, or vulnerable to litigation. Historically, several studies have noted high variability in physician practice around DNR orders, withdrawal, and withholding, with some preferring to withhold rather than withdraw, whereas others withdraw therapy in a particular sequence or avoid withdrawal of the ventilator altogether.^{33–36} Ethical and legal precedents are clear that withdrawing is equivalent to withholding and the decision for each therapy should be based on patient’s preference (autonomy) and burdens and benefits.³⁷

Withdrawal of the ventilator deserves special consideration as it is a procedure that continues to cause anxiety among physicians. Several protocols have been developed for this procedure, which include family and patient preparation, use of terminal wean versus direct extubation, and guidelines for the use of opioids and benzodiazepines for the treatment of refractory dyspnea.³⁸ It is ethically and legally sound to

aggressively treat dyspnea with opioids based on the principle of double effect. The fears of hastening death by administration of opioids or benzodiazepines have not been borne out in several studies, where the time to death was equivalent for patients who did and did not receive these medications after withdrawal of the ventilator.^{39,40}

The practice of withdrawing life support can be perceived as a conflict between the patient-centered goals of palliative care and societal goals of organ donation. In fact, the two are not mutually exclusive. If the patient is likely to proceed to brain death and organ donation is possible, efforts to stabilize and support a patient can coincide with attention to patient’s pain relief and comfort and family support until brain death protocols are completed. In other clinical situations near the end of life, once the surgeon contemplates withdrawing or withholding life support for a patient, the issue of organ donation must also be considered. With the advent of donation after cardiac death (DCD), it is theoretically possible for patients to donate organs if cardiac death ensues after withdrawal of the ventilator or pressors. For some families, the prospect of organ donation is comforting in the face of otherwise bad news. Organ Procurement Organization personnel should be contacted prior to any communication with the family about this option to evaluate if medically appropriate. Any request for organ donation should be made by the organ procurement organization, not the physician caring for the patient. The decision to withdraw life support should be made before and separately from any consideration of organ donation. With DCD, organ donation may increasingly become part of the end-of-life decisions around withdrawal of life support.

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11 BEDSIDE PROCEDURES FOR GENERAL SURGEONS

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Innovative equipment and advances in pain management have helped to expand the number and types of procedures that can now be performed safely and comfortably at the bedside of the surgical patient. However, success is unlikely unless the surgeon has detailed knowledge of the procedure, has assembled in advance all of the necessary equipment, and has a thorough appreciation for potential complications. Equally important is preparation of the patient for what he or she will experience and involvement of the responsible nurse prior to initiating any procedure. This chapter focuses on these essential aspects for each technique described. Additionally, we offer suggestions about training for and attaining competencies in these areas for surgeons in various stages of their professional careers.

Ultrasound-Guided Procedures

GENERAL PRINCIPLES: INSTRUMENTATION AND SCANNING TECHNIQUES

Over the past several years, ultrasonography has emerged as an increasingly useful bedside imaging technique, offering sharp two-dimensional and even three-dimensional imaging capabilities housed in smaller and more portable units. Thus, a working knowledge of ultrasonography is essential for a general surgeon and is now a requirement for all certified surgical training programs. Although a wide variety of excellent ultrasound machines are available from several manufacturers, the basic instrumentation and scanning techniques that are common to all are reviewed here.

In general, obtaining an ultrasound image begins with providing a path for transmission of the sound wave between the transducer and the object being scanned. This process, which is termed coupling, is accomplished at the bedside by replacing the air between the transducer and the skin with a gel surface (contact coupling). Standard ultrasound gels can be heated to enhance imaging and improve patient comfort, but, most importantly, these gels should be applied liberally to the skin for optimal imaging. In fact, if the object of interest appears dark on the screen, it is likely that the amount of contact gel is inadequate. The second major focus for the surgeon sonographer is choosing the correct transducer. The frequency of the transducer (measured in megahertz) determines the depth of penetration in the tissues; a low-frequency transducer travels deep in the tissue but loses resolution. For sharper images on the surface, one would choose a high-frequency transducer, which penetrates only a few centimeters deep. Table 1 describes the uses for transducers of various frequencies.

The image seen on the screen while scanning in real time is produced by a series of echoes returning from the organ of interest. Enhancement of this image requires adjustment of the controls on the ultrasound console. Enhancement might require brightening or darkening the entire picture on the screen (turning up or down the overall gain) or increasing or decreasing the gain in the area of interest only (near or far gain). It is helpful to adjust the gain such that a structure known to be anechoic (without echoes), such as blood within the heart or within a blood vessel, looks black to the observer's eye. Adjusting the focus to concentrate on the target area can also be easily accomplished. Because the ultrasound wave becomes attenuated as it passes deep into the tissue, the returning signal from the deepest region may require enhancement by adjusting the time-gain compensation slide pots on the console. Magnification of the image is also possible. Once the desired image is obtained, it can be "frozen" to print or store the image or to perform measurements. Annotation (e.g., labeling) is also performed on the frozen image. The series of images obtained just prior to freezing the image can be reviewed using the cine-loop function in case the frozen image missed the target. The initial images are usually displayed in grayscale (B-mode or brightness modulation), but most machines have both color-flow and Doppler imaging features as well, which can be added during real-time scanning and are essential for vascular procedures.

Traditionally, ultrasound examinations are performed with the patient in a supine position. When the transducer is held in a sagittal orientation (the transducer directional marker

Table 1 Transducers and Their Applications

Transducer Frequency (MHz)	Application
2–3.5	Abdominal Cardiac Obstetrics
5.0	Neonates/pediatrics Peripheral vascular Cerebrovascular Breast Thyroid
10	Vein mapping Soft tissues

toward the patient's head), the left side of the screen is oriented toward the head, with the right side toward the feet. When the marker is turned toward the patient's right for transverse imaging, the patient's right side is on the left side of the screen, and the head would now be toward the top of the screen. Holding transducers incorrectly results in serious errors in interpretation of the images. Other tricks for obtaining the best possible images (in addition to those listed above) include darkening the room as much as possible; sliding, tilting, and rocking the transducer on the skin rather than picking it up and moving it abruptly; using gentle but firm pressure; applying graded compression when air is present; or repositioning the patient if needed. Most importantly, the surgeon sonographer should take his or her time to obtain the best possible images under the circumstances. Rushing through an examination is the most common source of error.

Although ultrasound technology has an excellent safety profile, with the added benefit of high image quality and portability without radiation, there is still the possibility to inflict harm on a patient. Each unit must be well maintained and checked routinely to be sure that the ALARA principle (As Low As Reasonably Achievable) is adhered to, in reference to power and exposure time while obtaining the necessary clinical information. Tissues will heat up during lengthy examinations, and cavitation is also possible if the power is too high. Each transducer should be inspected regularly for breaks in the housing or cable that could potentially produce an electrical shock. After each examination, the transducers should be thoroughly cleaned using a solution recommended by the manufacturer so that blood or fluids are not transmitted from one patient to the next. Surgeons must also be involved in performance improvement programs where diagnostic decisions and procedures performed using ultrasound are reviewed for accuracy and patient safety.

USE OF ULTRASONOGRAPHY IN TRAUMA

The FAST Scan

The use of ultrasonography to query the pericardium and peritoneal cavity for blood has become standard in trauma centers. Referred to as the FAST examination (Focused Assessment for the Sonographic examination of the Trauma patient), it has rapidly replaced diagnostic peritoneal lavage as the preferred method for detecting hemoperitoneum in the unstable patient following blunt trauma.¹ It is also appropriate for pregnant and pediatric patients, for whom radiation exposure is more dangerous. In penetrating trauma, the abdominal portion of the FAST examination is not always helpful, because the amount of intra-abdominal fluid associated with hollow viscous injuries (most likely to be injured in penetrating trauma) is often too small to detect with ultrasonography. On the other hand, a limited echocardiographic examination is extremely sensitive in detecting penetrating injuries to the heart associated with pericardial fluid and has replaced all other noninvasive (e.g., central venous pressure [CVP], serial electrocardiograms) and invasive (i.e., pericardial window) methods of initial evaluation.²

Technique Sonographic detection of pericardial effusion is straightforward, requiring no specialized knowledge of echocardiographic cardiac anatomy. This echocardiographic portion of the FAST examination is performed using a curved

array transducer (2.0–5.0 MHz) with a small footprint held in the subxiphoid position at 30° to the skin and aimed toward the left shoulder [see Figure 1]. Note that for all views, the marker groove points toward the left side of the screen. From this same position, the transducer is rotated transversely, and a four-chamber view can be seen in most patients depending on body habitus. The third view is obtained from the left parasternal area (long axis of the heart) with the transducer oriented along a line between the right shoulder and the left hip. Pleural effusions may be confused with pericardial effusions, but this is minimized in the subcostal view because there is no pleural reflection between the liver and the heart. Additionally, intrapericardial fluid will conform to the contour of the heart. Viewing the heart in more than one plane will also help reduce interpretation errors. Echocardiography can also be used to detect the presence of cardiac motion when no blood pressure is obtainable after trauma (pulseless electrical activity [PEA]). Following penetrating trauma, the detection of PEA may be an indication for emergency department thoracotomy, particularly in the presence of pericardial tamponade.

The abdominal portion of the FAST examination begins in the right upper quadrant with the transducer placed in sagittal orientation along the right anterior midaxillary line between the 11th and 12th ribs. The liver, diaphragm, and right kidney are imaged and, in particular, the Morison pouch (between the kidney and liver) is examined for fluid. In the supine position, this is the most likely spot for fluid or blood to accumulate [see Figure 2]. On the left side, the spleen and left kidney are found in the posterior midaxillary line slightly higher (between the ninth and 10th ribs). Once again, the transducer is oriented in a sagittal plane. It is extremely important to examine not only the space between the spleen and the kidney but also the space between the left hemidiaphragm and the spleen, where many splenic injuries will manifest. Because rib shadows may prevent full visualization of the spleen, having a cooperative patient take a deep breath can be helpful. The final abdominal image is of the pelvis. Here the bladder serves as an acoustic window and must contain fluid to be seen. The transducer is oriented for transverse sections over the pubis, aimed at the feet. If a Foley catheter is in place, fluid should be instilled into the bladder to facilitate detection of pelvic fluid [see Figure 2].

Detection of Hemothorax

Other uses for ultrasonography following injury include scanning for the presence of hemothorax, or pneumothorax, and in serial follow-up of intra-abdominal solid organ injuries being managed conservatively. Surgeons from Emory University were among the first to describe the evaluation of the pleural space using a standard 3.5 MHz transducer in the trauma room as part of the FAST examination.³ Briefly, the transducer is held in the sagittal position and advanced in the midaxillary line from the 10th and 11th intercostal spaces (where the liver, diaphragm, and kidney are seen) cephalad until the supradiaphragmatic space is visualized. Fluid in the pleural space will appear as a black triangle above the hyperechoic (white) diaphragm [see Figure 3]. On the left side, the spleen and kidney are first viewed at approximately the ninth or 10th intercostal space in the posterior axillary line, and the transducer is simply advanced cephalad until the left hemidiaphragm and the supradiaphragmatic space are identified. The 97.5%

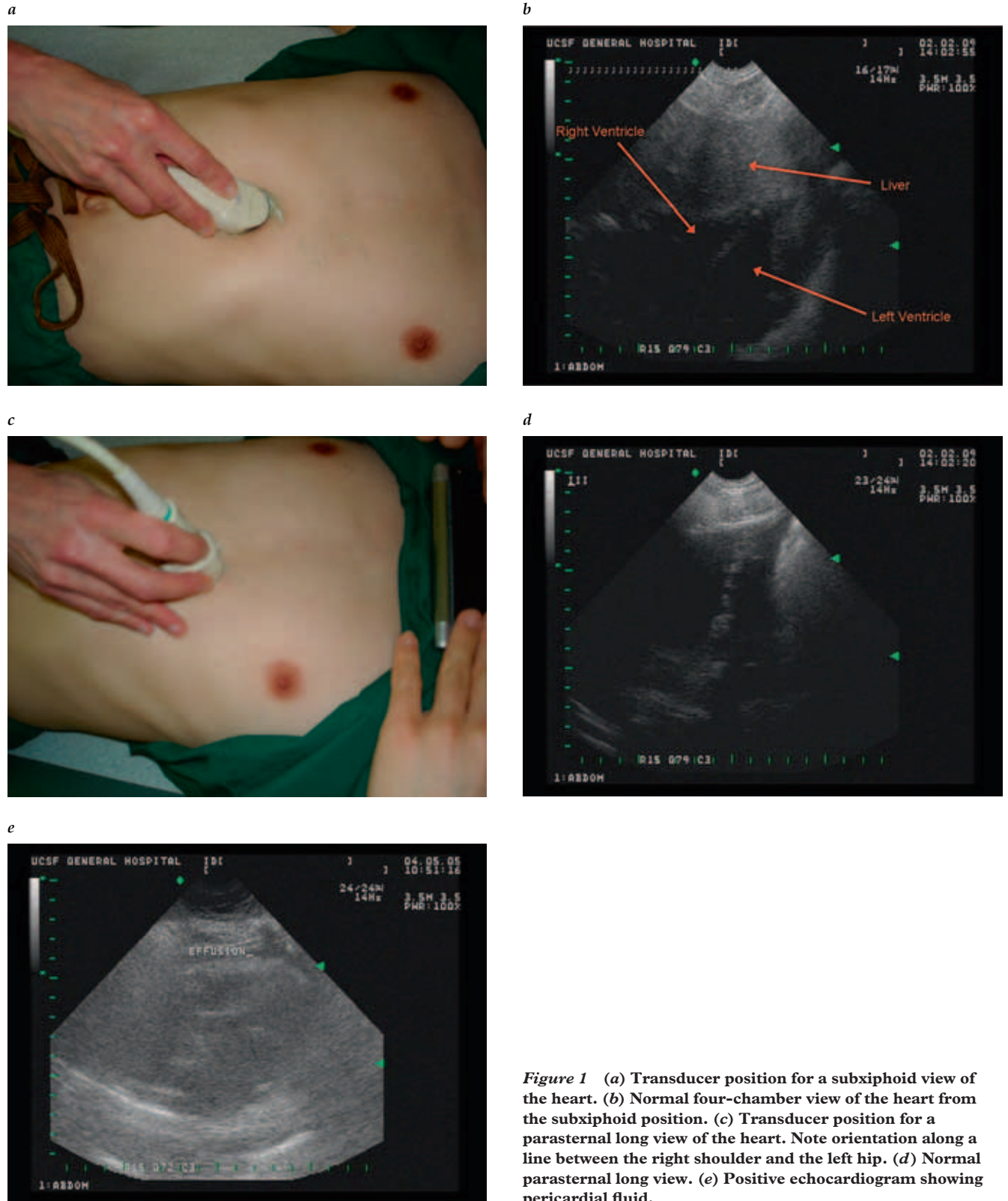


Figure 1 (a) Transducer position for a subxiphoid view of the heart. (b) Normal four-chamber view of the heart from the subxiphoid position. (c) Transducer position for a parasternal long view of the heart. Note orientation along a line between the right shoulder and the left hip. (d) Normal parasternal long view. (e) Positive echocardiogram showing pericardial fluid.

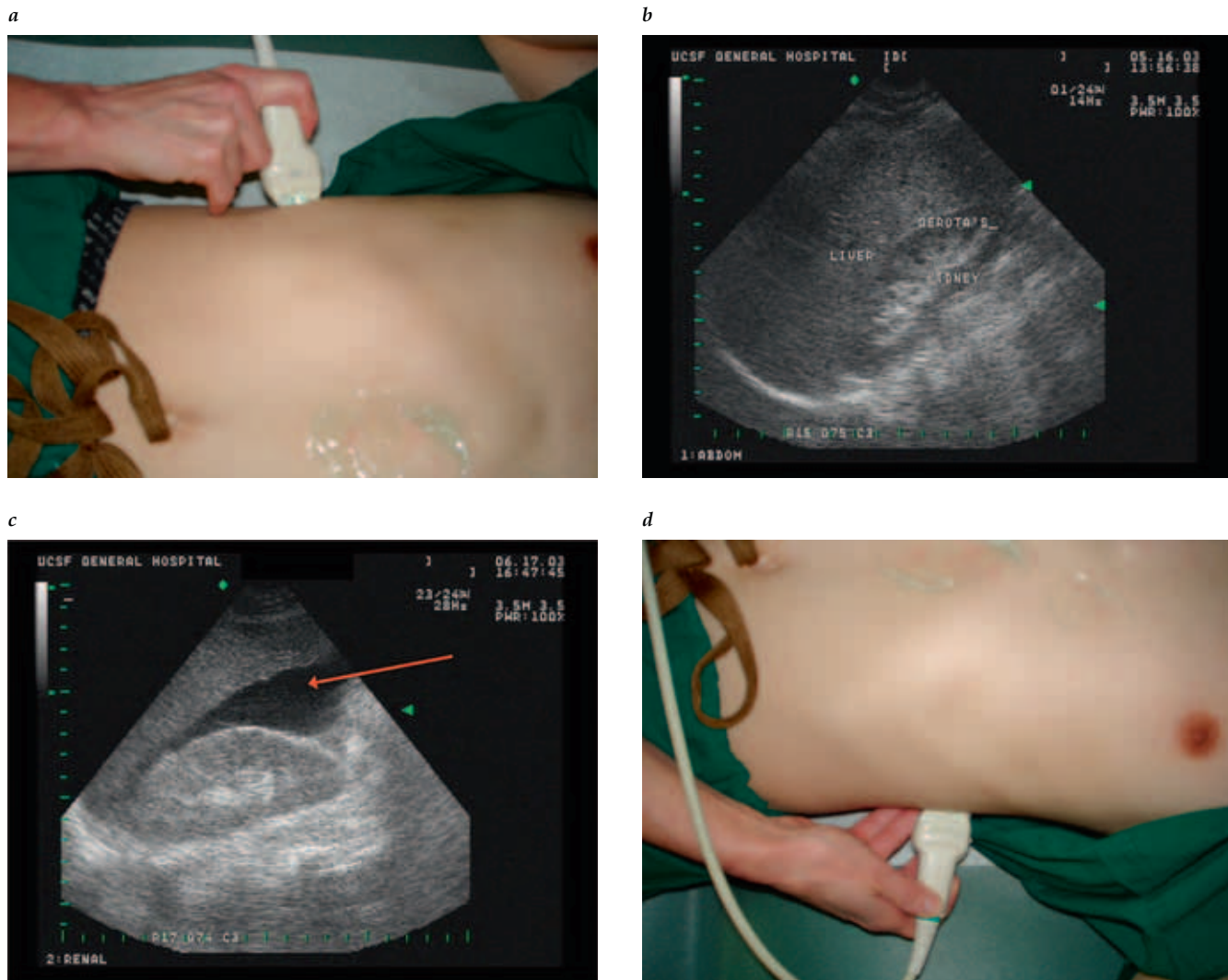


Figure 2 (a) Transducer position for the right upper quadrant (RUQ) portion of the FAST examination for trauma. (b) Normal RUQ scan showing the liver and kidney. (c) Fluid seen in the Morison pouch in an RUQ scan (arrow). (d) Transducer position for the left upper quadrant (LUQ) portion of the FAST examination for trauma. Note the slightly higher position and more posterior than that for the RUQ.

sensitivity and 99.7% specificity observed for thoracic ultrasonography were similar to those for portable chest x-rays in the trauma bay. The accuracy of this technique was only slightly less when used in the critical care setting to detect pleural effusion (94% accuracy).⁴

Detection of Pneumothorax

Using ultrasonography to detect pneumothorax is slightly more challenging as it requires recognition of the “absence” of the normal findings seen with an expanded lung. To perform this examination, a 3.5 MHz phased array transducer is held in a sagittal orientation in the second intercostal space in the midclavicular line. The examination is performed over several respiratory cycles. A normal lung will demonstrate a “lung-sliding” sign, seen as a to-and-fro motion at the interface between the visceral and parietal pleura with respirations [see Figure 4].

A comet tail artifact, manifested by hyperechoic streaks extending down from the visceral and the parietal pleural interface, is also commonly seen when imaging a normal lung. In the absence of these two findings, a pneumothorax will be present 99% of the time.^{5,6} Visualizing of the lung slide can be enhanced by using a linear array transducer (7.5 MHz) oriented for sagittal sections and applying power color Doppler mode (“power slide”).⁷ Although neither of these methods eliminates completely the need for a chest x-ray, they may be very useful in situations such as the operating room, the intensive care unit (ICU), or an austere environment when an x-ray is delayed or unavailable.

Evaluation of Patients with Solid Organ Injuries

The treatment of a stable patient with a solid organ injury (liver, spleen, kidney) identified on a computed tomographic

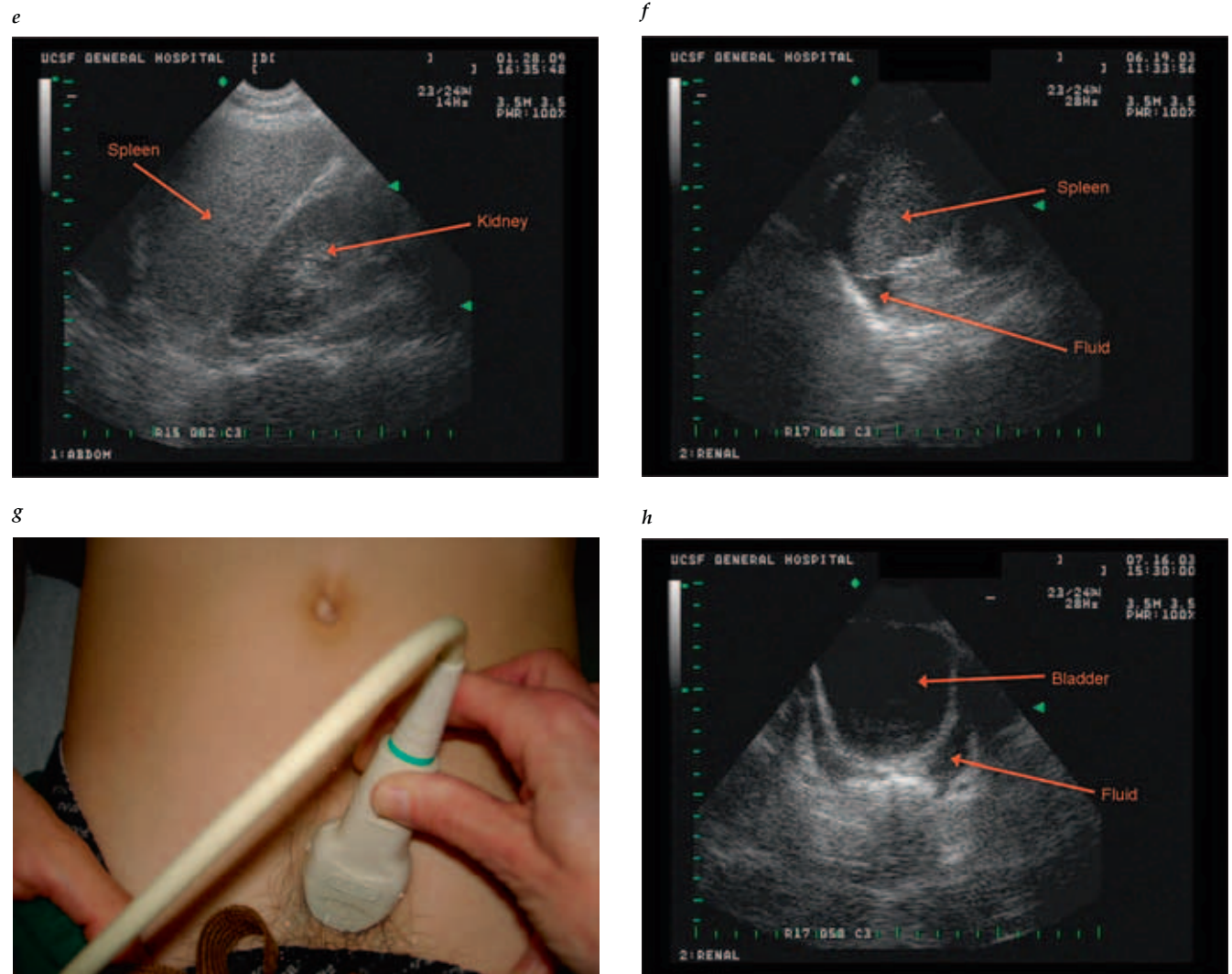


Figure 2 (e) Normal LUQ view showing the spleen and kidney. (f) Positive LUQ scan showing fluid around the spleen (arrow). (g) Transducer position for a pelvic image of the FAST examination (sitting on the pubic bone and aimed toward the feet). (h) Fluid in the pelvis using a full bladder as the acoustic window.

(CT) scan is most often observational. However, the need for follow-up imaging to identify patients whose injuries have progressed and/or those who have developed complications is controversial. Abdominal CT scanning, although extremely accurate, is expensive and delivers additional radiation (of particular concern in the management of pediatric trauma). We hypothesized that surgeon sonographers could successfully follow these injuries using ultrasonography. The surgeons involved in our study had considerable training and experience in performing ultrasound examinations, but we were only able to visualize the actual organ injury approximately one third of the time.⁸ However, we successfully detected 13 of the 15 complications, including intra-abdominal abscesses, arterial pseudoaneurysms, and bilomas. More importantly, we were able to assess the amount of hemoperitoneum present during serial examinations and thus determine more accurately than by following hematocrits that patients were still bleeding.

USE OF ULTRASONOGRAPHY IN THE SURGICAL ICU

Central Line Placement Using Ultrasound Guidance

In the United States, an estimated 5 million central venous catheters are inserted annually for the purposes of monitoring hemodynamic variables, administering fluids and medications, or providing parenteral nutrition.⁹ Unfortunately, the use of central venous catheters is associated with a number of complications, which are both hazardous for the patient and expensive to treat. Mechanical complications occur in 5 to 19% of patients, infectious complications in 5 to 26%, and thrombotic events in 2 to 26%. Using ultrasound guidance during insertion of an internal jugular (IJ) catheter has been demonstrated to reduce the time required for insertion, the rates of unsuccessful attempts, and the number of carotid artery punctures. A recent meta-analysis of 18 trials concluded that the use of ultrasonography to place central lines resulted in a significant reduction

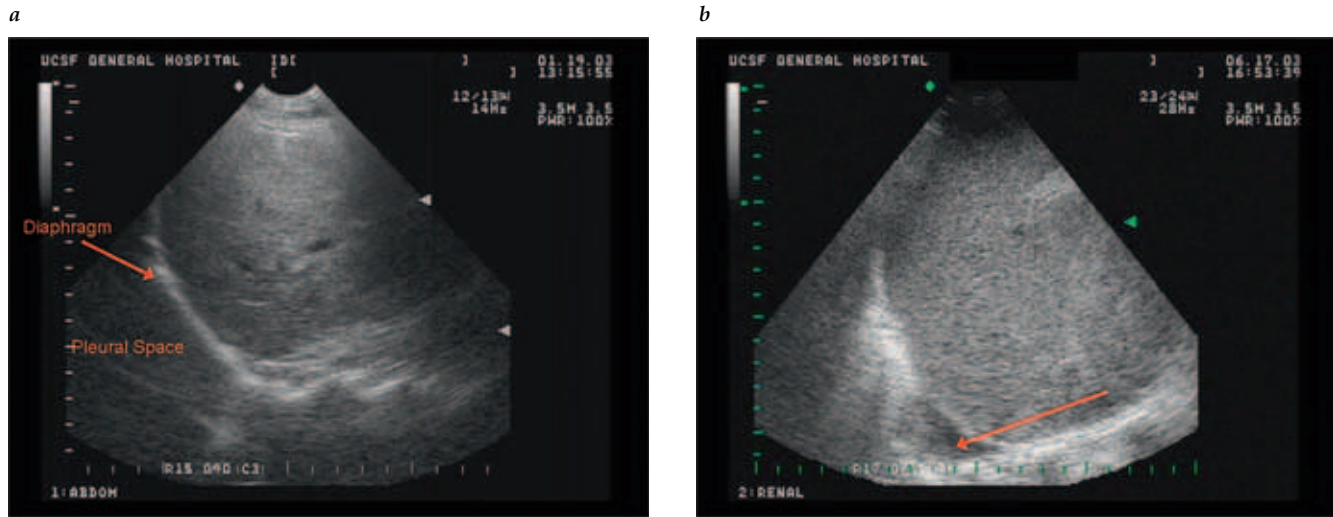


Figure 3 (a) Normal ultrasound view of the pleural space (arrow at diaphragm). (b) Ultrasound view of a hemothorax (arrow).



Figure 4 (a) A 7.5 MHz transducer in the second intercostal space for evaluation of a potential pneumothorax. (b) Normal lung markings. Note the “comet tail” effect from a normal air artifact. The interface between the parietal and visceral pleura is marked with the upper arrow (point of observation for the “lung slide”).

in failure rates (risk difference -12 , 95% confidence interval [CI] -0.18 to -0.06), the number of attempts (risk reduction 1.41 , 95% CI 1.15 to 1.67), and arterial puncture rates (risk difference -0.07 , 95% CI -0.10 to -0.03).¹⁰ Ultrasonography improved outcomes most convincingly for IJ vein cannulation (as opposed to the subclavian vein) and when used by clinicians less experienced at line placement. Karakitsos and colleagues performed a prospective comparison of the landmark technique versus real-time ultrasound-guided catheterization of the IJ veins in critically ill patients.¹¹ This randomized study included 450 patients in each of the two study arms. There were no significant differences between the two groups in gender, body mass index, previous catheterization, skeletal deformities, or other factors that could make line placement difficult. The clinicians involved in the study had considerable experience in inserting central lines (10 years on average). Cannulation of the IJ vein was accomplished in all 450 patients

using ultrasound guidance versus 425 patients using surface landmark techniques ($p < .001$). The time for line placement and the number of attempts were also significantly reduced in the ultrasound group. In the landmark group, hematoma formation occurred in 8.4%, hemothorax in 1.7%, pneumothorax in 2.4%, and central venous catheter-associated bloodstream infection in 18%, which were all significantly more common than in the ultrasound group ($p < .001$).

Technique of Placing an IJ Catheter Under Ultrasound Guidance

- Step 1:** Assemble the equipment listed in Table 2.
- Step 2:** Don personal protective gear and a sterile gown and gloves.
- Step 3:** Place the patient in the head-down position if possible.

Table 2 Equipment Needed for Central Line Placement

Standard commercial central catheter insertion kit
Large barrier drape
Sterile gown/gloves
Mask, eyewear, hat (personal protective gear)
7.5 linear array transducer connected to standard ultrasound unit
Sterile conduction gel
Sterile plastic sheath/probe cover

- Step 4:** Standing at the head of the bed, identify the relevant surface anatomy: the mastoid process, clavicle, and clavicular and sternal heads of the sternocleidomastoid muscle.
- Step 5:** Prepare the area widely with chlorhexidine and drape widely.
- Step 6:** Insert the ultrasound transducer into the sterile sheath after placing conduction gel into the bottom of the probe cover.
- Step 7:** Place a small amount of sterile conduction gel on the skin surface at the junction of the two heads of the sternocleidomastoid muscle.
- Step 8:** Holding the transducer parallel to and just above the clavicle, locate the IJ vein. It will be larger and flatter than the adjacent carotid artery, which is located medial to the vein [see Figure 5a]. A patent IJ vein should be compressible if it does not contain thrombus. Rarely, color flow or Doppler applications may be needed. Once the vein is located, orient the probe so that the vein appears on the right side of the screen (for right IJ vein cannulation) or on the left side of the screen if the left IJ vein is used. This will minimize confusion during the procedure.
- Step 9:** Continue to visualize the vein holding the transducer with one hand while introducing the needle with the other hand. The direction of the needle must be at right angles to the middle of the transducer and at an angle of 45° to the skin [see Figure 5b].
- Step 10:** Once the needle is seen to enter the vein, aspirate back with a syringe to confirm free venous flow [see Figures 5c to 5e].
- Step 11:** Pass the guide wire through the needle, monitoring for any cardiac arrhythmias (should they occur, pull the guide wire back). The needle can now be withdrawn from the vein, leaving the wire intact.
- Step 12:** Using a blade, make a small skin incision at the entrance of the wire and pass the catheter-dilator assembly over the wire into the vein. The catheter can also be visualized by ultrasonography.
- Step 13:** Remove the dilator and wire together, then use a syringe to aspirate air from the catheter, confirm venous return, and demonstrate that fluid can be infused without excessive pressure.
- Step 14:** Suture the catheter securely in place.
- Step 15:** Confirm the position with x-ray.

Complications associated with placement of an IJ catheter The most common immediate complications of

central venous catheter placement are arterial puncture, hematoma formation, and pneumothorax. A chest radiograph should be obtained immediately after any central venous catheterization attempt to evaluate for pneumothorax and to confirm proper catheter position prior to its use. Arterial puncture, which occurs in 6 to 9% of attempts, is more common with IJ line placement than with subclavian catheterization. If arterial puncture is recognized at the time of needle placement, it is managed by withdrawing the needle and maintaining gentle pressure over the artery for several minutes while observing for hematoma formation. If the injury is recognized after the dilator is in place, it should be left in place and a vascular surgeon consulted; removal of the catheter may require endovascular stenting or suture closure of the carotid artery. Pneumothorax (incidence of 0.2 to 1% with IJ catheters) is slightly less likely than with subclavian lines and is generally caused by advancing the needle too far in search of the vein instead of withdrawing to reassess the position and course of the needle. Small pneumothoraces (< 10%) may be observed and reevaluated with chest imaging 6 hours later; larger or symptomatic pneumothoraces require tube thoracostomy.

Assessment of Volume Status in the ICU with Ultrasound Techniques

Surgeons are beginning to use bedside ultrasonography to assess cardiac function and to estimate volume status in the ICU. One simple measure is to note the relative collapse of the right ventricle in a patient who is volume depleted. Another method is to measure the diameter of the inferior vena cava (IVC) during resuscitation. Using a standard abdominal transducer held for sagittal scanning, the anteroposterior diameter of the IVC can be measured just below the diaphragm in the hepatic segment.¹² Given that the diameter will change with respiration, it should be measured in both phases. A second measurement is taken in a transverse orientation [see Figure 6]. Yanagawa noted that the IVC diameter was significantly smaller (average 6.5 mm) in patients who became hypotensive again after an initial response to fluid resuscitation (so-called transient responders) as opposed to stabilized patients, in whom the IVC diameter averaged 10.7 mm.¹² In a more advanced study, Gunst and colleagues measured both stroke volume and IVC diameter using ultrasonography and compared their estimates of cardiac index based on ultrasound data compared with the results found with more directly measured indices using pulmonary artery catheterization.¹³ These surgeons were very accurate in estimating cardiac index and CVP; however, each of these investigators had completed 2 days of focused cardiac ultrasound training and had 5 to 15 years of ultrasound training prior to participating in this study. Nonetheless, it is clear that the utility of bedside ultrasonography in estimating volume status will continue to expand in the near future.

Ultrasound-guided Thoracentesis

Pleural effusions can be easily diagnosed and aspirated under ultrasound guidance in the ICU.¹⁴ In one recent study of ultrasound-guided thoracentesis in patients receiving mechanical ventilation, pneumothorax occurred in only 1.3% of the 232 patients who underwent this procedure.¹⁵ Pigtail catheters can

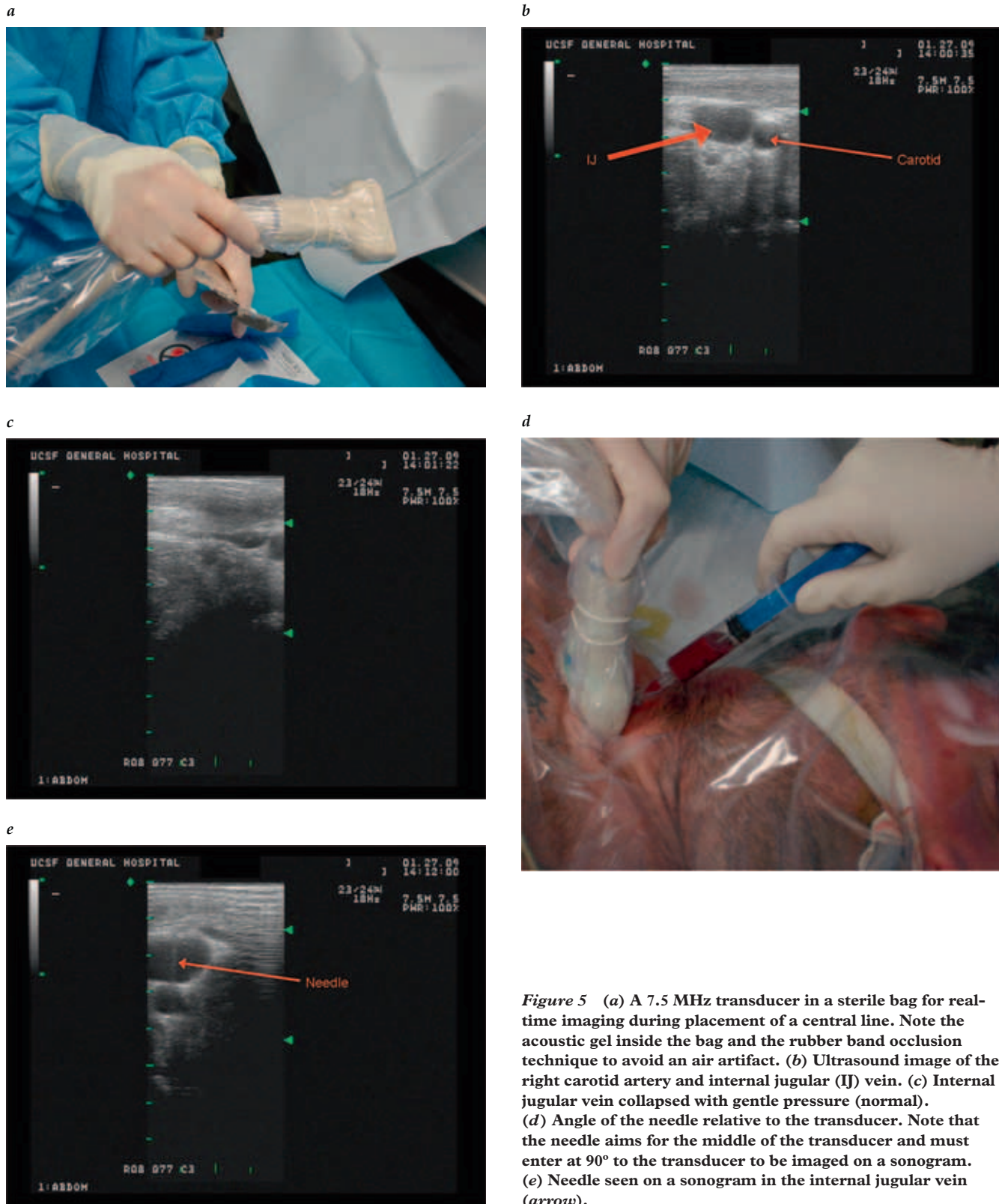


Figure 5 (a) A 7.5 MHz transducer in a sterile bag for real-time imaging during placement of a central line. Note the acoustic gel inside the bag and the rubber band occlusion technique to avoid an air artifact. (b) Ultrasound image of the right carotid artery and internal jugular (IJ) vein. (c) Internal jugular vein collapsed with gentle pressure (normal). (d) Angle of the needle relative to the transducer. Note that the needle aims for the middle of the transducer and must enter at 90° to the transducer to be imaged on a sonogram. (e) Needle seen on a sonogram in the internal jugular vein (arrow).

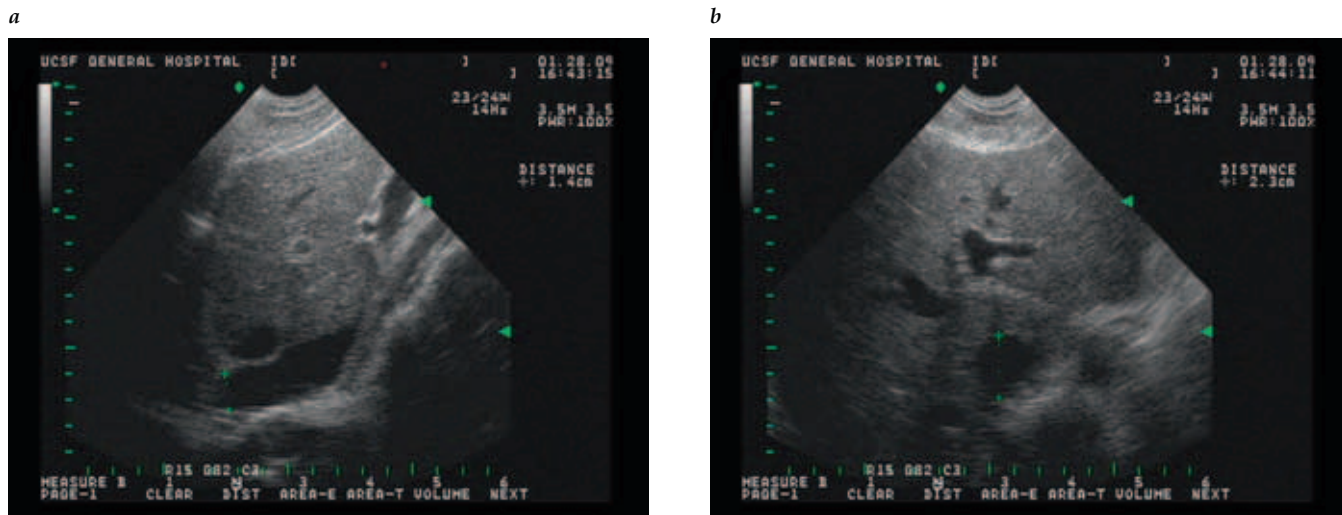


Figure 6 (a) Measurement of the inferior vena cava diameter (sagittal) at the level of the diaphragm (+ markings are calipers). (b) Transverse measurement of the inferior vena cava at the same level.

Table 3 Equipment Needed for Thoracentesis/Paracentesis

Standard central line insertion kit
Large barrier drape
Sterile gown/gloves
Mask, eyewear, hat (personal protective gear)
Caldwell needle (15 gauge)
Sterile extension tubing
Syringe
Scalpel
Local anesthetic

also be inserted using ultrasonography.¹⁶ The equipment needed for these procedures is outlined in Table 3.

Technique for Performing Ultrasound-Guided Thoracentesis

- Step 1:** Position the patient either in the lateral decubitus (the affected side up) or the supine position. Elevation of the head of the bed may also be useful.
- Step 2:** Perform the ultrasound examination (using a 3.5 MHz convex transducer) to locate the diaphragm, liver (or spleen), and targeted pleural fluid.
- Step 3:** If possible, switch to a 7.5 MHz linear probe to visualize the ribs and vascular structures within the chest.
- Step 4:** Choose a puncture site allowing at least one rib space of fluid above and below.
- Step 5:** Mark the site, prepare the chest, and then inject the area generously with local anesthesia, including the pleural surface.
- Step 6:** Insert a 18- to 20-gauge sheath needle into the targeted area, confirming the location of the needle with ultrasonography, and perform the aspiration.
- Step 7:** Once the fluid has been completely removed, withdraw the needle while applying constant negative pressure to minimize the chance of pneumothorax.

- Step 8:** If prolonged drainage is necessary, a larger catheter can be advanced into this area using the Seldinger technique, attaching the catheter to a water-sealed drainage system.¹⁷

Ultrasound and Paracentesis

Paracentesis is another useful technique that is also made safer under ultrasound guidance. In the ICU, paracentesis can be used to sample abdominal fluid for diagnosis (blood, intestinal contents, infection) or as a method of relieving pressure (ascites or secondary intra-abdominal hypertension following burns or overzealous resuscitation). The right and left lower quadrants are the most dependent locations and the easiest to access (generally above and medial to the superior iliac spine). Safe entry points for paracentesis that avoid the inferior epigastric vessels were mapped out recently by Saber and colleagues.¹⁸

Technique for Performing Ultrasound-Guided Paracentesis

- Step 1:** Assemble the equipment listed in Table 3.
- Step 2:** The abdomen is scanned using a 3.5 MHz curved array transducer to locate the fluid collection(s).
- Step 3:** Place the patient in a supine position of comfort.
- Step 4:** Don personal protective gear, including a gown and gloves.
- Step 5:** Scrub the anterior abdominal wall with chlorhexidine solution and drape the region.
- Step 6:** Infiltrate the skin of the intended puncture site with local anesthetic.
- Step 7:** Use the scalpel to make a nick in the skin to allow passage of the needle.
- Step 8:** Advance the Caldwell needle through the abdominal wall while aspirating with a syringe (note: ultrasonography can be used to guide the needle into the fluid collection).
- Step 9:** Once fluid is seen to enter the syringe, stop advancing the needle. The drainage catheter should be advanced over the needle into the fluid and the needle removed.

Step 10: If prolonged drainage is required (as with tense ascites), the catheter can be attached to a collection canister.

Step 11: Observe the wound for ascetic leak and/or the development of a hematoma, and then dress it with a transparent dressing.

Complications of thoracentesis and paracentesis

The principal complications of thoracentesis are pneumothorax and hemothorax. Drainage of very large effusions may also lead to reexpansion pulmonary edema, although this is a rare entity. In one recent study of ultrasound-guided thoracentesis in patients receiving mechanical ventilation, pneumothorax occurred in only 1.3% of the 232 patients who underwent this procedure.¹⁵ As noted above with IJ cannulation, small pneumothoraces may be observed, but larger (> 10%) or symptomatic cases require tube thoracostomy. Hemothorax complicating thoracentesis is particularly troubling because it suggests injury to an intercostal vessel, which may bleed significantly and potentially require operative ligation. A routine chest radiograph should be obtained following the procedure, and attention should be paid to significant hematoma or oozing from the puncture site.

Paracentesis may be complicated by abdominal wall hemorrhage and by hemodynamic instability resulting from fluid shifts. Large-volume paracentesis leads to fluid and protein losses with accompanying hypovolemia, hypotension, and even acute renal insufficiency. Empiric replacement of proteinaceous solute by infusion of salt-poor albumin is generally practiced (50 mL of 25% albumin for each liter of ascites drained). If the puncture site is not carefully selected, inferior epigastric vessel injury may occur, leading to expanding abdominal wall hematoma and/or hemoperitoneum. If this occurs and the hematoma does not tamponade the bleeding, exposure and ligation of the vessels will be necessary.

Detection of Venous Thrombosis with Duplex Ultrasonography

Critically ill and injured patients are at high risk for potentially lethal venous thromboembolism. Unfortunately, the current methods of venous thromboembolism prophylaxis are often contraindicated in the patients who are at greatest risk, and surveillance for deep vein thrombosis (DVT) is frequently used even in the absence of symptoms. Additionally, an immediate DVT scan can be helpful when pulmonary embolism is suspected in ICU patients. The sensitivity and specificity for duplex ultrasonography in symptomatic patients are very high, and this study has now replaced venography as the primary imaging procedure for the detection of DVT. Compressibility under probe pressure is the most accurate test, reaching 97 to 100% sensitivity and 99% specificity for the diagnosis of femoral and popliteal DVT.¹⁹ In contrast, the visibility of the thrombus as a fixed, echogenic image within the lumen has a sensitivity of only 50%. DVT should also be suspected when there is a lack of augmentation of flow above the area being compressed. As with any ultrasound examination, the accuracy is highly dependent on the expertise of the examiner, and we do not mean to imply that surgeons will have the same excellent results as registered vascular technicians. However, focused venous ultrasound examinations should be within the skill set of a general surgeon.

Technique for Performing a Venous Ultrasound Examination

Step 1: Position the patient in a supine and reversed Trendelenburg position (if possible), with the leg abducted and externally rotated and the knee flexed.

Step 2: Using a 7.5 MHz linear transducer held in a transverse position, identify the common femoral vein and artery at the level of the inguinal ligament.

Step 3: The initial imaging should be done using the B-mode (grayscale).

Step 4: Focusing on the vein, apply pressure until the vein collapses. Follow the vein down in a transverse plane, using serial compression applied at 1 to 2 cm intervals.

Step 5: The vein will dive deep above the knee but can be visualized again posterior to the knee.

Step 6: Although the hallmark of DVT is a lack of compressibility, occasionally, a thrombus will be visible within the lumen [see Figure 7].

Step 7: Flow can be visualized within the vein by applying color and Doppler imaging. With the transducer still in a transverse orientation, find the common femoral vein or artery and apply color flow. Keeping the vein in view, orient the transducer for longitudinal imaging. Once flow is visualized in the thigh, squeezing the calf muscles should increase the flow signal. Clinically significant DVT below the level of the thigh is unlikely if augmentation is present.

Step 8: Repeat these same steps on the opposite side and compare images and results.

Other Bedside Procedures

PERCUTANEOUS TRACHEOSTOMY

Operative tracheostomy has been performed for several centuries, and the typical modern technique was standardized by Jackson in 1909. A percutaneous Seldinger technique was developed in the 1980s by Ciaglia and colleagues and has gained popularity in recent years because of its suitability for performance at the bedside.²⁰ Use of videobronchoscopic guidance has reduced immediate complications, but it should be recognized that operative (“open”) tracheostomy remains the gold standard as it allows for more control and has lower rates of long-term complications, such as subglottic stenosis.^{21,22}

Indications for tracheostomy include orofacial trauma, resection of head or neck malignancy, and the need for prolonged mechanical ventilation. The timing of tracheostomy in critically ill patients has long been debated, and ongoing clinical trials strive to determine the optimal timing. The basic principle is to perform the procedure early enough to facilitate subacute care and reduce oropharyngeal, sinus, and pulmonary complications; however, performing tracheostomy too early in a course of mechanical ventilation will lead to unnecessary procedures on those patients who were nearing extubation at the time of operation. The TracMan clinical trial conducted at Oxford University randomized over 900 critically ill patients to early (days 1 to 4) versus late (day 10 or later) tracheostomy. This represents the largest coordinated effort yet to determine the optimal timing of tracheostomy; recruitment completed in December 2008, and the results are expected to be reported in 2009.²³

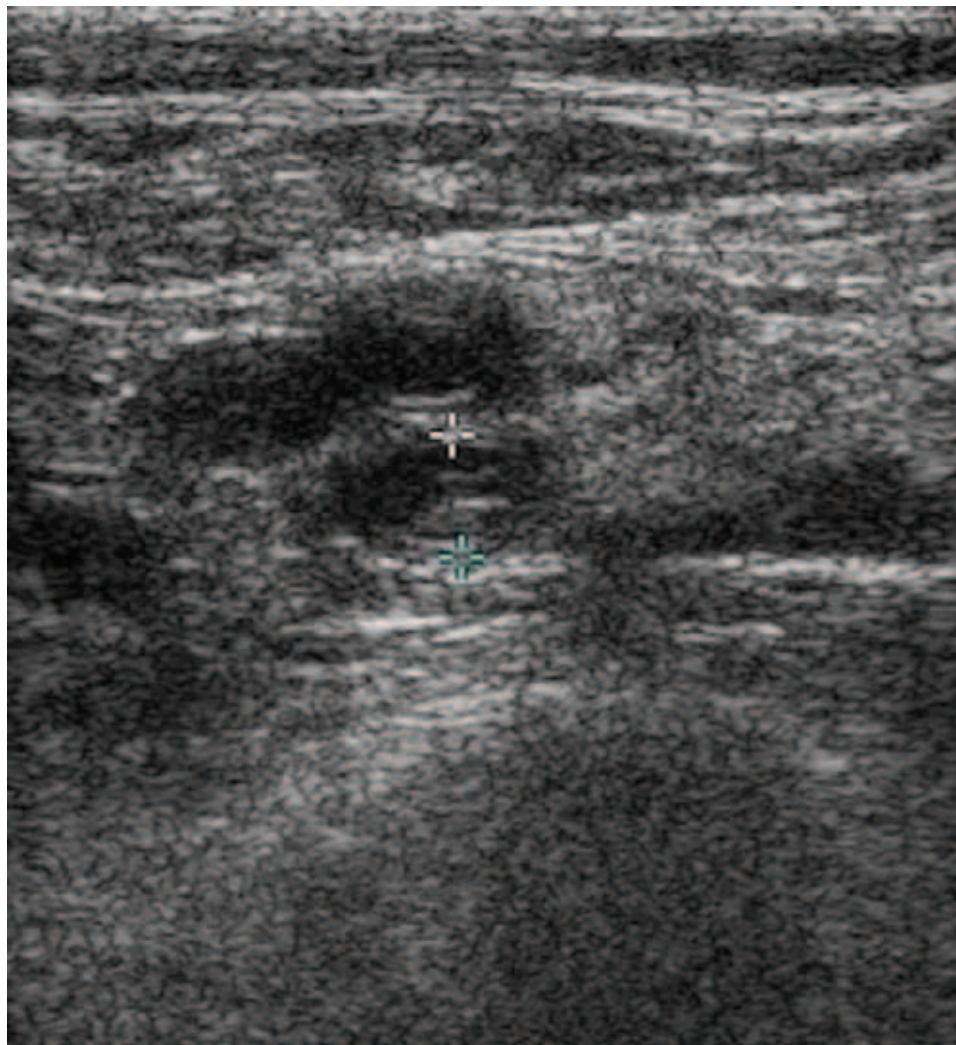


Figure 7 Ultrasound image of a femoral vein deep vein thrombosis (*markers*).

Tracheostomy is a clean-contaminated operation because the respiratory tract is entered. These wounds are far from sterile as there is considerable contamination by respiratory secretions and saliva. However, infections are infrequent, and there is no role for prolonged courses of antibiotic therapy beyond a single preincision dose, as is the general recommendation for clean-contaminated operations.

Technique for Percutaneous Tracheostomy

- Step 1:* Assemble the equipment listed in Table 4.
- Step 2:* Position the patient so as to slightly raise the shoulder off the bed and extend the neck.
- Step 3:* Don personal protective gear, including a sterile gown and gloves.
- Step 4:* Scrub the anterior neck from the chin to the sternal notch with chlorhexidine solution and place sterile drapes.
- Step 5:* Ask the bronchoscopist to advance the scope down the endotracheal tube and visualize the carina and then withdraw the scope to a position

a centimeter below the vocal folds. Maintain this endoluminal view of the trachea.

Table 4 Equipment Needed for Percutaneous Tracheostomy

Large barrier drape
Sterile gown/gloves
Mask, eyewear, hat (personal protective gear)
Bronchoscope
Laryngoscope and endotracheal tube
Tracheostomy tube (at least two sizes)
Seldinger tracheostomy kit with dilator
Skin suture and needle holder
Ventilator tubing adapter for bronchoscope and accordion extension for tracheostomy
Scalpel
Syringe

- Step 6:* Withdraw the endotracheal tube so that the tip is repositioned just distal to the bronchoscope tip.
- Step 7:* Identify a point in the midline of the anterior neck, midway between the cricothyroid membrane and sternal notch. Apply local anesthetic to this site and then use an 18-gauge needle attached to a 10 mL syringe to puncture the trachea. It is critical that the puncture be visualized by the bronchoscope and be in the midline of the anterior trachea and not too close to the cricothyroid cartilage [see Figure 8].
- Step 8:* Pass the guide wire through the needle into the trachea and remove the needle.
- Step 9:* Make a 2 cm transverse skin incision centered on the wire. Do not cut deep to the skin as bleeding from the thyroid or thyroid vessels can be problematic and require operative repair.
- Step 10:* Apply generous sterile lubricant to the assembled tracheostomy tube–dilator device, then pass it over the wire and twist it while pushing posteriorly to dilate the tracheal puncture site and pass the tracheostomy tube. Once in the trachea (visualized by the bronchoscope), immediately remove the dilator while holding the tracheostomy tube in place.
- Step 11:* Confirm proper ventilation through the tracheostomy tube and then remove the endotracheal tube.
- Step 12:* Suture the faceplate of the tracheostomy tube to the adjacent skin and further secure it with a necklace-type tie around the neck.

- Step 13:* Remove instruments for reprocessing and dispose of sharp waste.

Complications of percutaneous tracheostomy

Following tracheostomy, patients should initially be cared for in an ICU owing to the potential severity of complications. The site should be observed for bleeding, cellulitis, or development of subcutaneous emphysema. Dislodgment or misplacement of the tracheostomy tube must be immediately corrected as this will lead to death in short order. If possible, the tube should be reinserted, but often the safest approach is to resecure the airway by orotracheal intubation and then convert to a formal (“open”) tracheostomy in the operating room. Significant bleeding around the tracheostomy tube usually signifies injury to the thyroid parenchyma or one of its vessels; if this does not abate with hematoma tamponade in a matter of minutes, this, too, requires operative intervention.

A first tracheostomy tube change should be avoided at all costs during the first 10 days as there is the potential for fatal airway loss. Even after 10 days, any tracheostomy tube change should be performed with airway rescue equipment and supplemental oxygen available, an informed nurse at the bedside to assist as needed, knowledge of the patient’s native anatomy by the surgeon (i.e., is the larynx patent, thus permitting orotracheal intubation), and a spare tracheostomy tube one size smaller than the one in the patient’s airway. The presence of a respiratory therapist is encouraged, especially for the first change.



Figure 8 Anatomic land markings of the neck. V = thyroid notch; box at the cricothyroid membrane; broken line at the thyroid isthmus; solid line at the first tracheal ring; curved line at the sternal notch.

TUBE THORACOSTOMY

Thoracostomy tubes (“chest drains” or “chest tubes”) are placed to evacuate air or fluid in the pleural space and have become a primary treatment modality for pleural disease since first described by Hewett in 1876. Pneumothorax may occur spontaneously, following injury, or as the result of instrumentation, such as with percutaneous biopsy or thoracentesis. Pneumothoraces can be treated with standard chest tubes (of any size) or with pigtail catheters inserted using a Seldinger technique. Fluid can accumulate in the pleural space as a result of many different processes, including trauma, pneumonia, malignancy, and congestive cardiac disease. Drains placed for simple fluid may be of smaller caliber, but those placed for hemothorax should be larger to prevent blockage by coagula (typically 36 French for adults).

All hemothoraces should be promptly drained to prevent fibrothorax and possible trapped lung. Failure to promptly drain blood in the pleural space will render this technique ineffective, and formal decortications (i.e., via video-assisted thoracic surgery) will be required. Other fluid collections should be drained and the underlying pathology addressed to prevent recurrent accumulation. Special caution should be taken when addressing malignant effusions because these have a tendency to reaccumulate after drain removal. If the underlying disease is not going to be treated, the patient should generally either be treated with pleurodesis (to obliterate the pleural space and prevent recurrence) or placement of a chronic, tunneled pleural drain.²⁴

These chest procedures must always be performed in as sterile a fashion as possible, although the immediacy of tension physiology may sometimes require the surgeon to forgo

fastidious draping. It remains unclear whether presumptive or prophylactic antibiotics prevent empyema related to chest drain placement. Although the answer remains unclear, a recent multicenter trial in trauma patients failed to demonstrate a benefit of antibiotic administration.²⁵ If antibiotics are administered, they should be given prior to beginning the procedure and be limited to one dose of a first-generation cephalosporin.

Technique for Tube Thoracostomy

- Step 1:** Assemble the equipment listed in Table 5. If the patient is stable, consider administering an intravenous narcotic.
- Step 2:** Position the patient with the affected side tilted up and the ipsilateral arm raised above the head [see Figure 9].

Table 5 Equipment Needed for Tube Thoracostomy

Large barrier drape
Sterile gown/gloves
Mask, eyewear, hat (personal protective gear)
Standard commercial central catheter insertion kit
Suitably sized chest tube
Scalpel, large hemostat, needle driver
Heavy silk or nylon suture
Local anesthetic
Drain trap/suction regulator
Occlusive dressing

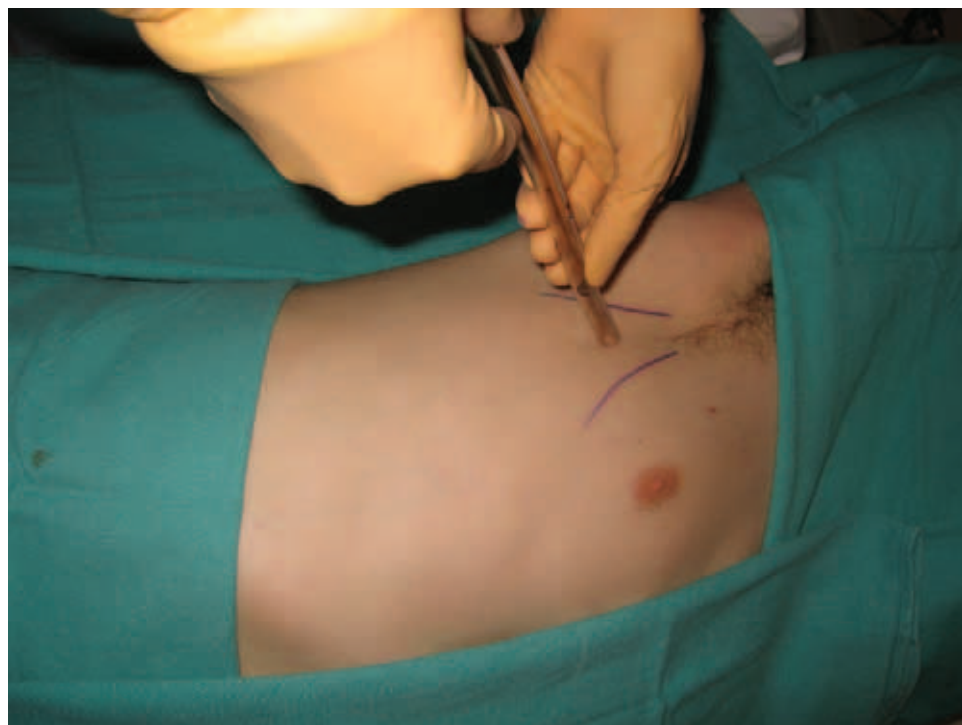


Figure 9 Correct position for placement of a chest tube. Note that the tube is directed posterior and cephalad and the right arm is raised above the head.

- Step 3:* Don personal protective gear, including a sterile gown and gloves.
- Step 4:* Scrub the anterolateral chest wall with chlorhexidine solution and drape the region.
- Step 5:* Palpate the chest wall to identify an intercostal space around the fifth rib. In men, the nipple is a useful surface landmark to indicate the height of the dome of the diaphragm, below which one should generally not stray.
- Step 6:* Infiltrate the skin with local anesthetic and make a skin incision at the interspace below the intended thoracostomy site. Bluntly separate the subcutaneous tissue and overlying muscle to arrive at the rib and intercostal musculature. Infiltration of local anesthetic in the periosteum and pleura is a useful but often ignored step.
- Step 7:* Blunt spreading over the top of a rib allows puncture through the pleura into the intercostal space, after which the tube can be slid in while pointing it superiorly and posteriorly. Creation of a proper subcutaneous tract and direction of the tube toward the thoracic apex decrease the likelihood of the tube entering a pulmonary fissure.
- Step 8:* Secure the tube to the adjacent skin with a heavy suture of silk or nylon.
- Step 9:* Connect the tube to the drain trap–suction device and apply an occlusive dressing.
- Step 10:* Remove instruments for reprocessing and dispose of sharp waste.

For a visual reference, readers are referred to the video featured in the *New England Journal of Medicine*.²⁶

Traditionally, all chest drains were initially placed to suction (20 cm water) and subsequently transitioned to water seal (a one-way safety valve with no applied suction) as the volume of output decreased. For many chest tube indications, a growing body of evidence supports placement of chest drains to water seal from the outset. This has been demonstrated to accelerate the resolution of air leaks and duration of chest tubes.²⁷

Complications of tube thoracostomy The most common immediate complication of this procedure is a malpositioned tube, whether in an interlobar fissure, occluded by a kink, or even placed completely within the chest wall rather than the pleural space. A chest radiograph should be obtained after the placement of any chest drain to verify tube position and to determine if the pleural air or fluid is beginning to drain properly. Inadequate tube position may sometimes be addressed by sterile withdrawal and resuturing, but once a tube has been placed, it should never be advanced. Much more rarely, tube placement may cause injury to the pulmonary parenchyma or bleeding from an intercostal or pulmonary vessel. The latter should be suspected with persistent voluminous bloody output and/or any hemodynamic instability after tube placement. Such vascular injuries require operative intervention for definitive control.

Removal of chest tubes should be done with care not to allow air to entrain into the pleural space. This is primarily accomplished by maintaining an occlusive dressing over the tube site and asking the patient to cooperate with tube

removal. Some prefer tube removal during forced expiration to increase intrapleural pressure and thus decrease the risk of recurrent pneumothorax. With this approach, however, some patients suddenly gasp with surprise or pain, suddenly dropping the intrapleural pressure and potentially drawing air in through the tube tract. Another school of thought is to remove the tube while the patient maintains maximal inspiration.

Principles and Process of Documenting Competency in Surgical Skills

Although documenting knowledge in surgery has been standardized by the American Board of Surgery, demonstration of skills has not as yet become part of the certification process. How one acquires, practices, and perfects a surgical skill is an area of great interest to educators and the public alike. Although, certainly, the time spent learning and practicing will vary with the task, with each new skill, the essentials include the following:

1. A period of didactic, hands-on instruction by an expert
2. A period of practice, often while being mentored
3. Demonstration of acquisition of the skill
4. Continued practice-based learning including participation in performance improvement programs and continued education

The Surgical Institutes, currently being developed through the Education Division of the American College of Surgeons (ACS), will form the basis for development of a standard curriculum (including skills training) for each level of residency. Another group that has been very proactive in this arena is the Society of Gastrointestinal Surgeons (SAGES), which has developed and propagated the “Fundamentals of Laparoscopic Surgery” course. In ultrasonography, the ACS Ultrasound Education Committee has developed a series of courses including Level I certification (attendance at the course), Level II certification (passing a skill set), and Level III certification (acquisition of skills under proctorship until reaching the expert or instructor level). In particular, the skills-oriented postgraduate course “Ultrasound in the Surgical ICU” is an excellent model for introducing bedside ultrasound techniques. Once learned, how many examinations are necessary before proficiency is attained is unclear but certainly varies with the nature of the examination. In trauma, 25 FAST examinations performed under supervision is generally considered adequate, although it is important that some of those examinations include patients with positive findings. The American Society of Breast Surgeons requires at least 100 breast ultrasound examinations prior to applying for credentialing. There has been limited success in using simulators to introduce ultrasound skills.²⁸ Recently, Hutton and Wong documented improvement in placement of chest tubes by junior house staff after practicing on a patient simulator.²⁹ A recent systematic review concluded that simulation-based training seems to be transferable to the operating room.³⁰ In this era of decreased time spent in training, surgical educators are challenged to develop more efficient methods of ensuring that general surgeons have acquired competency in both operative and bedside skills, with patient safety and satisfaction as the ultimate measures of success.

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1 PREVENTION OF POSTOPERATIVE INFECTION

Jonathan L. Meakins, MD, DSc, FACS

Epidemiology of Surgical Site Infection

Historically, the control of wound infection depended on antiseptic and aseptic techniques directed at coping with the infecting organism. In the 19th century and the early part of the 20th century, wound infections had devastating consequences and a measurable mortality. Even in the 1960s, before the correct use of antibiotics and the advent of modern preoperative and postoperative care, as much as one quarter of a surgical ward might have been occupied by patients with wound complications. As a result, wound management, in itself, became an important component of ward care and of medical education. It is fortunate that many factors have intervened so that the so-called wound rounds have become a practice of the past. The epidemiology of wound infection has changed as surgeons have learned to control bacteria and the inoculum and to focus increasingly on the patient (the host) for measures that will continue to provide improved results.

The following three factors are the determinants of any infectious process¹:

1. The infecting organism (in surgical patients, usually bacteria)
2. The environment in which the infection takes place (the local response)
3. The host defense mechanisms, which deal systemically with the infectious process

Wounds are particularly appropriate for analysis of infection with respect to these three determinants. Because many components of the bacterial contribution to wound infection now are clearly understood and measures to control bacteria have been implemented, the host factors become more apparent. In addition, interactions between the three determinants play a critical role, and with limited exceptions (e.g., massive contamination), few infections will be the result of only one factor [see Figure 1].

Definition of Surgical Site Infection

Wound infections have traditionally been thought of as infections in a surgical wound occurring between the skin and the deep soft tissues—a view that fails to consider the operative site as a whole. As prevention of these wound infections has become more effective, it has become apparent that definitions of operation-related infection must take the entire operative field into account; obvious examples include sternal and mediastinal infections, vascular graft infections, and infections associated with implants (if occurring within 1 year of the procedure and apparently related to it). Accordingly, the Centers for Disease Control and Prevention currently prefers to use the term *surgical site infection* (SSI). SSIs can be

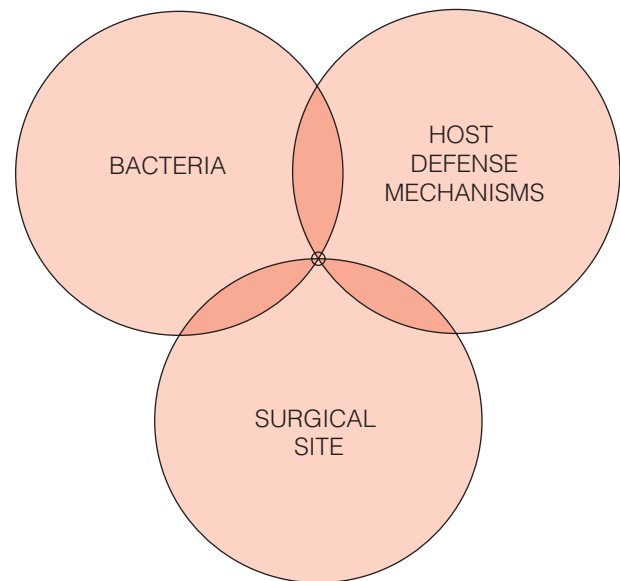


Figure 1 In a homeostatic, normal state, the determinants of any infectious process—bacteria, the surgical site, and host defense mechanisms (represented by three circles)—intersect at a point indicating zero probability of sepsis.

classified into three categories: superficial incisional SSIs (involving only skin and subcutaneous tissue), deep incisional SSIs (involving deep soft tissue), and organ or space SSIs (involving anatomic areas other than the incision itself that are opened or manipulated in the course of the procedure) [see Figure 2].^{2,3}

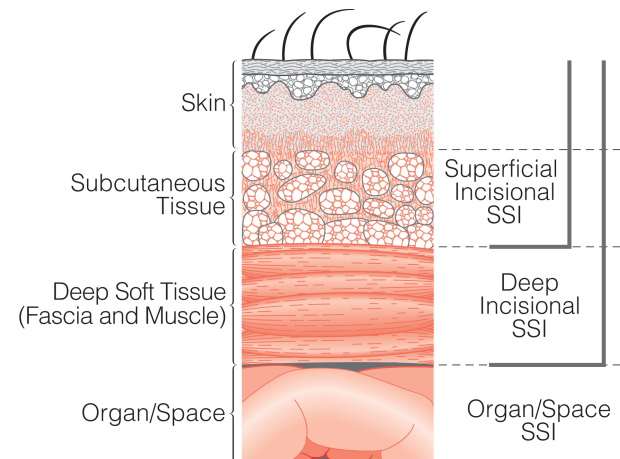
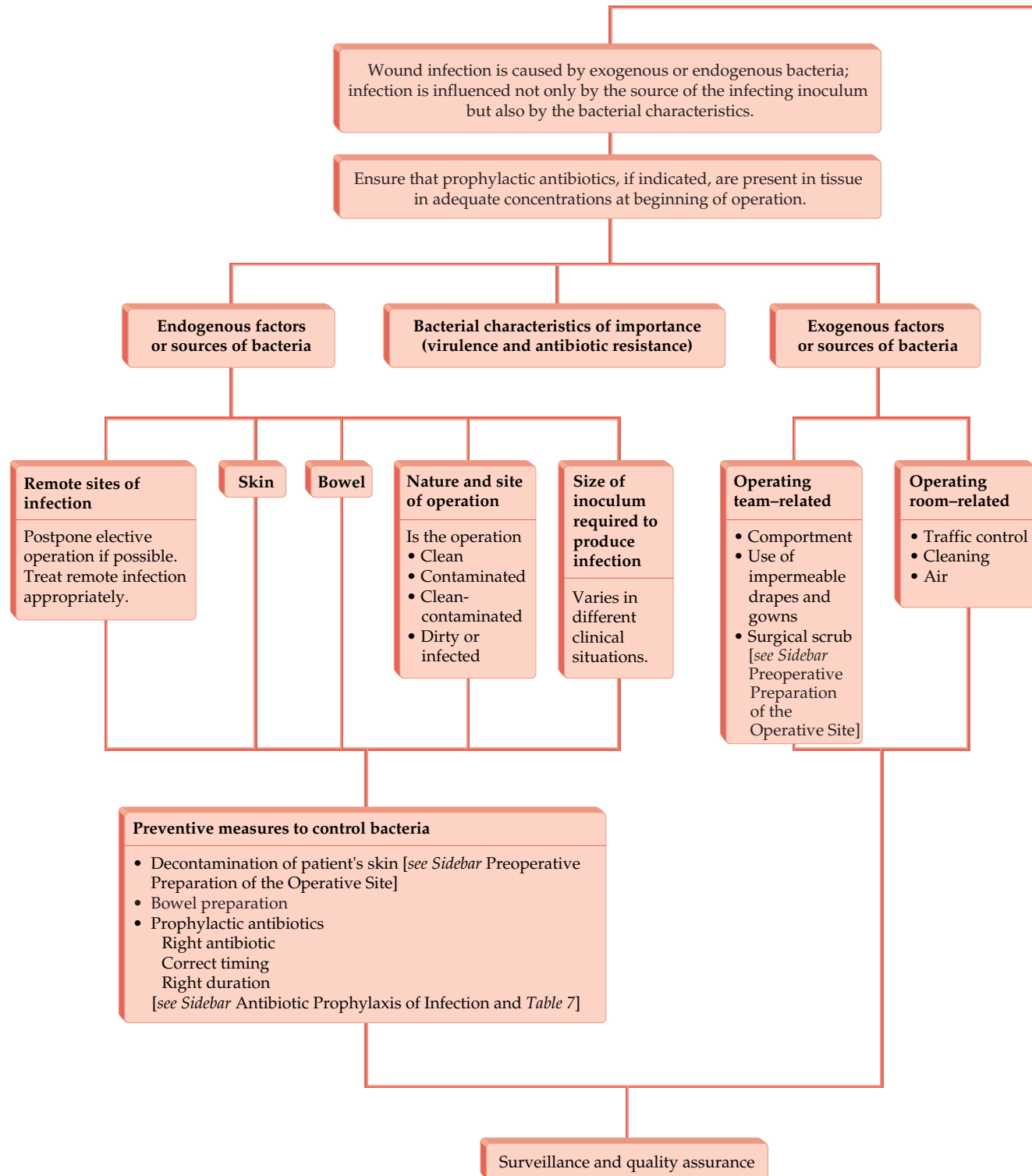
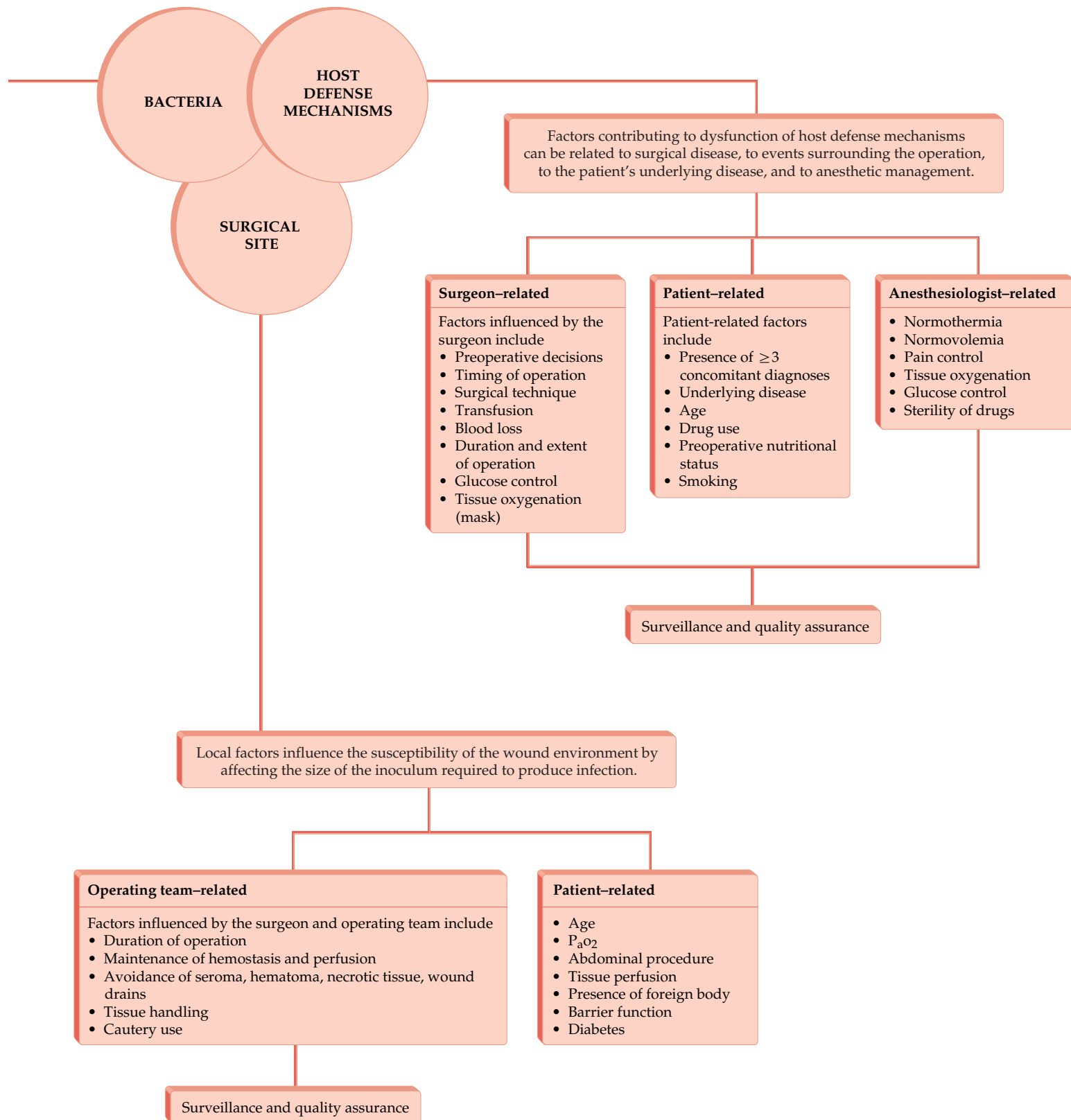


Figure 2 Surgical site infections (SSI) are classified into three categories, depending on which anatomic areas are affected.³

Epidemiology of Surgical Site Infection





Standardization in reporting will permit more effective surveillance and improve results, as well as offer a painless way of achieving quality assurance. The natural tendency to deny that a surgical site has become infected contributes to the difficulty of defining SSI in a way that is both accurate and acceptable to surgeons. The surgical view of SSI recalls one judge's (probably apocryphal) remark about pornography: "It is hard to define, but I know it when I see it." SSIs are usually easy to identify. Nevertheless, there is a critical need for definitions of SSI that can be applied in different institutions for use as performance indicators.⁴ The criteria on which such definitions must be based are more detailed than the simple apocryphal remark just cited; they are outlined more fully elsewhere [see 1:8 *Preparation of the Operating Room*].

STRATIFICATION OF RISK FOR SSI

The National Academy of Sciences–National Research Council classification of wounds [see *Table 1*], published in 1964, was a landmark in the field.⁵ This report provided incontrovertible data to show that wounds could be classified as a function of probability of bacterial contamination (usually endogenous) in a consistent manner. Thus, wound infection rates could be validly compared from month to month, between services, and between hospitals. As surgery became more complex in the following decades, however, antibiotic use became more standardized and other risk variables began to assume greater prominence. In the early 1980s, the Study on the Efficacy of Nosocomial Infection Control (SENIC) identified three risk factors in addition to wound class: location of the operation (abdomen or chest),

duration of the operation, and patient clinical status (three or more diagnoses on discharge).⁶ The National Nosocomial Infection Surveillance (NNIS) study reduced these four risk factors to three: wound classification, duration of the operation, and American Society of Anesthesiologists (ASA) class III, IV, or V.^{7,8} Both risk assessments integrate the three determinants of infection: bacteria (wound class), local environment (duration), and systemic host defenses (one definition of patient health status), and they have been shown to be applicable outside the United States.⁹ However, the SENIC and NNIS assessments do not integrate other known risk variables, such as smoking, tissue oxygen tension, glucose control, shock, and maintenance of normothermia, all of which are relevant for clinicians (although they are often hard to monitor and to fit into a manageable risk assessment). In addition, they do not incorporate a variety of other host variables or operation characteristics derived from the Patient Safety in Surgery Study/National Surgical Quality Improvement Program (NSQIP). These give high, medium, and low probabilities of SSI, which appear to be more accurate but more complex to ascertain than NNIS prediction [see *Integration of Determinants below*].¹⁰

Bacteria

Clearly, without an infecting agent, no infection will result. Accordingly, most of what is known about bacteria is put to use in major efforts directed at reducing their numbers by means of asepsis and antisepsis. The principal concept is based on the size of the bacterial inoculum.

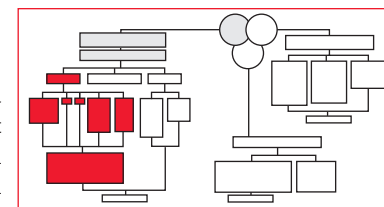
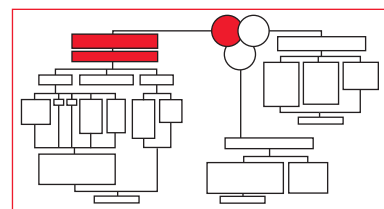
Wounds are traditionally classified according to whether the wound inoculum of bacteria is likely to be large enough to overwhelm local and systemic host defense mechanisms and produce an infection [see *Table 1*]. One study showed that the most important factor in the development of a wound infection was the number of bacteria present in the wound at the end of an operative procedure.¹¹ Another quantitated this relation and provided insight into how local environmental factors might be integrated into an understanding of the problem [see *Figure 3*].¹² In the years before prophylactic antibiotics, as well as during the early phases of their use, there was a very clear relation between the classification of the operation (which is related to the probability of a significant inoculum) and the rate of wound infection.^{5,13} This relation is now less dominant than it once was; therefore, other factors have come to play a significant role.^{6,14}

CONTROL OF SOURCES OF BACTERIA

Endogenous bacteria are a more important cause of SSI than exogenous bacteria. In clean-contaminated, contaminated, and dirty-infected operations, the source and

Table 1 National Research Council Classification of Operative Wounds⁵

Clean (class I)	Nontraumatic No inflammation encountered No break in technique Respiratory, alimentary, or genitourinary tract not entered
Clean-contaminated (class II)	Gastrointestinal or respiratory tract entered without significant spillage Appendectomy Oropharynx entered Vagina entered Genitourinary tract entered in absence of infected urine Biliary tract entered in absence of infected bile Minor break in technique
Contaminated (class III)	Major break in technique Gross spillage from gastrointestinal tract Traumatic wound, fresh Entrance of genitourinary or biliary tracts in presence of infected urine or bile
Dirty and infected (class IV)	Acute bacterial inflammation encountered, without pus Transection of "clean" tissue for the purpose of surgical access to a collection of pus Traumatic wound with retained devitalized tissue, foreign bodies, fecal contamination, delayed treatment, or all of these or from dirty source



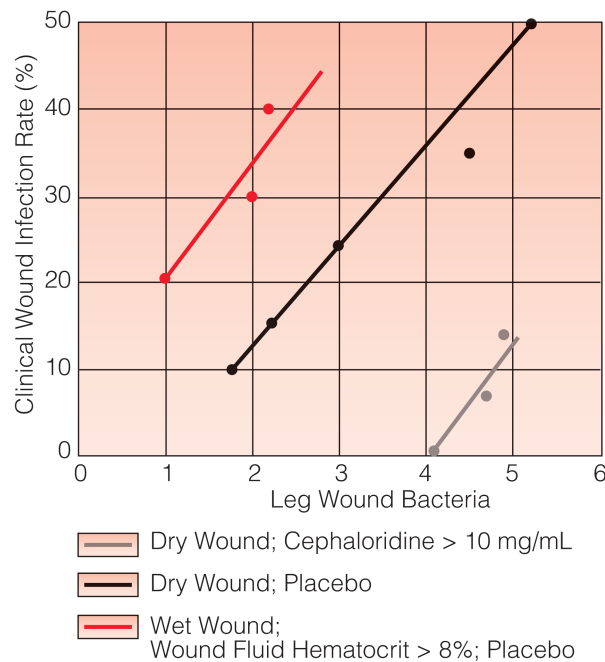


Figure 3 The wound infection rate is shown here as a function of bacterial inoculum in three different situations: a dry wound with an adequate concentration of antibiotic (cephalexin > 10 µg/mL), a dry wound with no antibiotic (placebo), and a wet wound with no antibiotic (placebo, wound fluid hematocrit > 8%).¹²

the amount of bacteria are functions of the patient's disease and the specific organs being operated on.

Operations classified as infected are those in which infected tissue and pus are removed or drained, providing a guaranteed inoculum to the surgical site. The inoculum may be as high as 10^{10} bacteria/mL, some of which may already be producing an infection. In addition, some bacteria could be in the growth phase rather than the dormant or lag phase and thus could be more pathogenic. The heavily contaminated wound is best managed by delayed primary closure. This type of management ensures that the wound is not closed over a bacterial inoculum that is almost certain to cause a wound infection, with attendant early and late consequences.

Patients should not have elective surgery in the presence of remote infection, which is associated with an increased incidence of wound infection.⁵ In patients with urinary tract infections, wounds frequently become infected with the same organism. Remote infections should be treated appropriately, and the operation should proceed only under the best conditions possible. If the operation cannot be appropriately delayed, the use of prophylactic and therapeutic antibiotics should be considered [see *Sidebar Antibiotic Prophylaxis of Infection and Tables 2 through 4*].

Preoperative techniques of reducing patient flora, especially endogenous bacteria, are of great concern. Bowel preparation, antimicrobial showers or baths, and preoperative skin decontamination have been proposed frequently. These techniques, particularly preoperative skin decontamination

[see *Sidebar Preoperative Preparation of the Operative Site*], may have specific roles in selected patients during epidemics or in units with high infection rates. As a routine for all patients, however, these techniques are unnecessary, time-consuming, and costly in institutions or units where infection rates are low.

The preoperative shave is a technique in need of reassessment. It is now clear that shaving the evening before an operation is associated with an increased wound infection rate. This increase is secondary to the trauma of the shave and the inevitable small areas of inflammation and infection. If hair removal is required,¹⁵ clipping is preferable and should be done in the OR or the preparation room just before the operative procedure. Shaving, if ever performed, should not be done the night before the operation.

In the past few years, the role of the classic bowel preparation [see *Table 5*] has been questioned [see *Discussion, Infection Prevention in Bowel Surgery, below*].^{16–21} The suggestion has been made that selective gut decontamination (SGD) may be useful in major elective procedures involving the upper gastrointestinal (GI) tract and perhaps in other settings. At present, SGD for prevention of infection cannot be recommended in either the preoperative or the postoperative period.

When infection develops after clean operations, particularly those in which foreign bodies were implanted, endogenous infecting organisms are involved, but the skin is the primary source of the infecting bacteria. The air in the operating room (OR) and other OR sources occasionally become significant in clean cases; the degree of endogenous contamination can be surpassed by that of exogenous contamination. Thus, both the operating team—surgeon, assistants, nurses, and anesthetists—and OR air have been reported as significant sources of bacteria [see *1:8 Preparation of the Operating Room*]. In fact, personnel are the most important source of exogenous bacteria.^{22–24} In the classic 1964 study by the National Academy of Sciences–National Research Council, ultraviolet light (UVL) was efficacious only in the limited situations of clean and ultraclean cases.⁵ There were minimal numbers of endogenous bacteria, and UVL controlled one of the exogenous sources.

Clean air systems have very strong advocates, but they also have equally vociferous critics. It is possible to obtain excellent results in clean cases with implants without using these systems. However, clean air systems are here to stay. Nevertheless, the presence of a clean air system does not mean that basic principles of asepsis and antisepsis should be abandoned, because endogenous bacteria must still be controlled.

The use of impermeable drapes and gowns has received considerable attention. If bacteria can penetrate gown and drapes, they can gain access to the wound. The use of impermeable drapes may therefore be of clinical importance.^{25,26} When wet, drapes of 140-thread-count cotton are permeable to bacteria. It is clear that some operations are wetter than others, but, generally, much can be done to make drapes and gowns impermeable to bacteria. For example, drapes of 270-thread-count cotton that have been waterproofed are impermeable, but they can be washed only 75 times.

Antibiotic Prophylaxis of Infection

Selection

Spectrum. The antibiotic chosen should be active against the most likely pathogens. Single-agent therapy is almost always effective except in colorectal operations, small bowel procedures with stasis, emergency abdominal operations in the presence of polymicrobial flora, and penetrating trauma; in such cases, a combination of antibiotics is usually used because anaerobic coverage is required.

Pharmacokinetics. The half-life of the antibiotic selected must be long enough to maintain adequate tissue levels throughout the operation.

Administration

Dosage, route, and timing. A single preoperative dose that is of the same strength as a full therapeutic dose is adequate in most instances. The single dose should be given IV immediately before skin incision. Administration by the anesthetist is most effective and efficient.

Duration. A second dose is warranted if the duration of the operation exceeds either 3 hours or twice the half-life of the antibiotic. No additional benefit has been demonstrated in continuing prophylaxis beyond the day of the operation, and mounting data suggest that the preoperative dose is sufficient. When massive hemorrhage has occurred (i.e., blood loss equal to or greater than blood volume), a second dose is warranted. Even in emergency or trauma cases, prolonged courses of antibiotics are not justified unless they are therapeutic.^{79,114}

Indications

CLEAN CASES

Prophylactic antibiotics are not indicated in clean operations if the patient has no host risk factors or if the operation does not involve placement of prosthetic materials. Open heart operation and operations involving the aorta of the vessels in the groin require prophylaxis.

Patients in whom host factors suggest the need for prophylaxis include those who have more than three concomitant diagnoses, those whose operations are expected to last longer than 2 hours, and those whose operations are abdominal.⁶ A patient who meets any two of these criteria is highly likely to benefit from prophylaxis. When host factors suggest that the probability of a surgical site infection is significant, administration of cefazolin at induction of anesthesia is appropriate prophylaxis. Vancomycin should be substituted in patients who are allergic to cephalosporins or who are susceptible to major immediate hypersensitivity reactions to penicillin.

When certain prostheses (e.g., heart valves, vascular grafts, and orthopedic hardware) are used, prophylaxis is justified when viewed in the light of the cost of a surgical site infection to the patient's health. Prophylaxis with either cefazolin or vancomycin is appropriate for cardiac, vascular, or orthopedic patients who receive prostheses.

Catheters for dialysis or nutrition, pacemakers, and shunts of various sorts are prone to infection mostly for technical reasons, and prophylaxis is not usually required. Meta-analysis indicates, however, that antimicrobial prophylaxis reduces the infection rate in CSF shunts by 50%.¹¹⁵ Beneficial results may also be achievable for other permanently implanted shunts (e.g., peritoneo-venous) and devices (e.g., long-term venous access catheters and pacemakers); however, the studies needed to confirm this possibility will never be done, because the infection rates are low and the sample sizes would have to be prohibitively large. The placement of such foreign bodies is a clean operation, and the use of antibiotics should be based on local experience. A recent meta-analysis indicates that antibiotic prophylaxis (cefazolin) prevents SSI in breast surgery.¹¹⁶

CLEAN-CONTAMINATED CASES

Abdominal procedures. In biliary tract procedures (open or laparoscopic), prophylaxis is required only for patients at high risk: those whose common bile duct is likely to be explored (because of jaundice, bile duct obstruction, stones in the common bile duct, or a reoperative biliary procedure); those with acute cholecystitis; and those older than 70 years. A single dose of cefazolin is adequate. In hepatobiliary and pancreatic procedures, antibiotic prophylaxis is always warranted because these operations are clean-contaminated, because they are long, and because they are abdominal. Prophylaxis is also warranted for therapeutic endoscopic retrograde cholangiopancreatography. In gastroduodenal procedures, patients whose gastric acidity is normal or high and in whom bleeding, cancer, gastric ulcer, and obstruction are absent are at low risk for infection and require no prophylaxis; all other patients are at high risk and require prophylaxis. Patients undergoing operation for morbid obesity should receive double the usual prophylactic dose¹¹⁷; cefazolin is an effective agent.

Operations on the head and neck (including the esophagus). Patients whose operation is of significance (i.e., involves entry into the oral cavity, the pharynx, or the esophagus) require prophylaxis.

Gynecologic procedures. Patients whose operation is either high-risk cesarean section, abortion, or vaginal or abdominal hysterectomy will benefit from cefazolin. Aqueous penicillin G or doxycycline may be preferable for first-trimester abortions in patients with a history of pelvic inflammatory disease. In patients with cephalosporin allergy, doxycycline is effective for those having hysterectomies and metronidazole for those having cesarean sections. Women delivering by cesarean section should be given the antibiotic immediately after cord clamping.

Urologic procedures. In principle, antibiotics are not required in patients with sterile urine. Patients with positive cultures should be treated. If an operative procedure is performed, a single dose of the appropriate antibiotic will suffice.

(continued)

Economics plays a role in the choice of drape fabric because entirely disposable drapes are expensive. Local institutional factors may be significant in the role of a specific type of drape in the prevention of SSI.

PROBABILITY OF CONTAMINATION

The probability of contamination is largely defined by the nature of the operation [see Table 1]. However, other factors contribute to the probability of contamination; the most obvious is the expected duration of the operative procedure, which, whenever examined, has been significantly correlated with the wound infection rate.^{6,11,13} The longer the procedure lasts, the more bacteria accumulate in a wound; the sources

of bacteria include the patient, the operating team (gowns, gloves with holes, wet drapes), the OR, and the equipment. In addition, the patient undergoing a longer operation is likely to be older, to have other diseases, and to have cancer of—or to be undergoing an operation on—a structure with possible contamination. A longer duration, even of a clean operation, represents increased time at risk for contamination. These points, in addition to pharmacologic considerations, suggest that the surgeon should be alert to the need for a second dose of prophylactic antibiotics [see Sidebar Antibiotic Prophylaxis of Infection].

Abdominal operation is another risk factor not found in the NNIS risk assessment.^{6,8} Significant disease and age are

Antibiotic Prophylaxis of Infection (*continued*)

CONTAMINATED CASES

Abdominal procedures. In colorectal procedures, antibiotics active against both aerobes and anaerobes are recommended. In appendectomy, SSI prophylaxis requires an agent or combination of agents against both aerobes and anaerobes; a single dose of cefoxitin, 2 g IV, or, in patients who are allergic to β -lactam antibiotics, metronidazole, 500 mg IV, is effective. A combination of an aminoglycoside and clindamycin is effective if the appendix is perforated; a therapeutic course of 3 to 5 days is appropriate but does not seem warranted unless the patient is particularly ill. A laparotomy without a precise diagnosis is usually an emergency procedure and demands preoperative prophylaxis. If the preoperative diagnosis is a ruptured viscus (e.g., the colon or the small bowel), both an agent active against aerobes and an agent active against anaerobes are required.

Trauma. The proper duration of antibiotic prophylaxis for trauma patients is a confusing issue—24 hours or less of prophylaxis is probably adequate, and more than 48 hours is certainly unwarranted. When laparotomy is performed for nonpenetrating injuries, prophylaxis should be administered. Coverage of both aerobes and anaerobes is mandatory. The duration of prophylaxis should be less than 24 hours. In cases of penetrating abdominal injury, prophylaxis with either cefoxitin or a combination of agents active against anaerobic and aerobic organisms is required. The duration of prophylaxis should be less than 24 hours, and in many cases, perioperative doses will be adequate. For open fractures, management should proceed as if a therapeutic course were required. For grade I or II injuries, a first-generation cephalosporin will suffice, whereas for grade III injuries, combination therapy is warranted; the duration may vary. For operative repair of fractures, a single dose of cefazolin may be given preoperatively, with a second dose added if the procedure is long. Patients with major soft tissue injury with a danger of spreading infection will benefit from cefazolin, 1 g IV every 8 hours for 1 to 3 days.

DIRTY OR INFECTED CASES

Infected cases require therapeutic courses of antibiotics; prophylaxis is not appropriate in this context. In dirty cases,

particularly those resulting from trauma, contamination and tissue destruction are usually so extensive that the wounds must be left open for delayed primary or secondary closure. Appropriate timing of wound closure is judged at the time of débridement. Antibiotics should be administered as part of resuscitation. Administration of antibiotics for 24 hours is probably adequate if infection is absent at the outset. However, a therapeutic course of antibiotics is warranted if infection is present from the outset or if more than 6 hours elapsed before treatment of the wounds was initiated.

Prophylaxis of Endocarditis

Studies of the incidence of endocarditis associated with dental procedures, endoscopy, or operations that may result in transient bacteremia are lacking. Nevertheless, the consensus is that patients with specific cardiac and vascular conditions are at risk for endocarditis or vascular prosthetic infection when undergoing certain procedures; these patients should receive prophylactic antibiotics.^{118,119} A variety of organisms are dangerous, but viridans streptococci are most common after dental or oral procedures, and enterococci are most common if the portal of entry is the GU or GI tract. Oral amoxicillin now replaces penicillin V or ampicillin because of superior absorption and better serum levels. In penicillin-allergic patients, clindamycin is recommended; alternatives include cephalexin, ceftriaxone, azithromycin, and clarithromycin. When there is a risk of exposure to bowel flora or enterococci, oral amoxicillin may be given. If an IV regimen is indicated, ampicillin may be given, with gentamicin added if the patient is at high risk for endocarditis. In patients allergic to penicillin, vancomycin is appropriate, with gentamicin added in high-risk patients. These parenteral regimens should be reserved for high-risk patients undergoing procedures with a significant probability of bacteremia. [see Tables 3 and 4]

The new recommendations of the American Heart Association have reduced the cardiac conditions needing prophylaxis and the procedures that warrant antibiotics.^{118,119} There should be a reduction in antibiotic use as a result.

additional factors that play a role in outcome; however, because the major concentrations of endogenous bacteria are located in the abdomen, abdominal operations are more likely to involve bacterial contamination.

For some years, postoperative contamination of the wound has been considered unlikely. However, one report of SSI in sternal incisions cleaned and redressed 4 hours postoperatively clearly shows that wounds can be contami-

Table 2 Parenteral Antibiotics Recommended for Prophylaxis of Surgical Site Infection

	Antibiotic	Dose	Route of Administration
For coverage against aerobic gram-positive and gram-negative organisms	Cefazolin	1 g	IV or IM (IV preferred)
If patient is allergic to cephalosporins or if methicillin-resistant organisms are present	Vancomycin	1 g	IV
Combination regimens for coverage against gram-negative aerobes and anaerobes	Cefoxitin	1–2 g	IV
	or Cefazolin	1–2 g	IV
	plus Metronidazole	0.5 g	IV
	or Ampicillin/sulbactam	3 g	IV
Allergic to penicillin or cephalosporins	Clindamycin plus Gentamicin, ciprofloxacin, aztreonam	600 mg	IV
For single-agent coverage against gram-negative aerobes and anaerobes	Cefoxitin	1–2 g	IV

Table 3 Conditions and Procedures that Require Antibiotic Prophylaxis against Endocarditis^{118,119}

Conditions that Warrant Prophylaxis

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis
Congenital heart disease (CHD)
Unrepaired cyanotic CHD, including palliative shunts and conduits
Complete repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

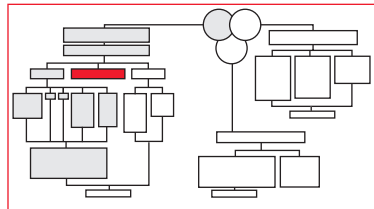
Procedures that Warrant Prophylaxis

Dental or oropharyngeal procedures that
1. manipulate gingival tissue or the periapical region of the teeth
2. perforate the oral mucosa
Incision and drainage, manipulation, or débridement of infected sites regardless of location
Gastrointestinal (GI) or genitourinary (GU) procedures for which antibiotics to prevent surgical site infection would be administered
Endoscopy of GI tract or uninfected GU tract prophylaxis is NO longer recommended

nated and become infected in the postoperative period.²⁷ Accordingly, use of a dry dressing for 24 hours seems prudent.

BACTERIAL PROPERTIES

Not only is the size of the bacterial inoculum important; the bacterial properties of virulence and pathogenicity are also significant. The



most obvious pathogenic bacteria in surgical patients are gram-positive cocci (e.g., *Staphylococcus aureus* and streptococci). With modern hygienic practice, it would be expected that *S. aureus* would be found mostly in clean cases, with a wound infection incidence of 1 to 2%; however, it is, in fact, an increasingly common pathogen in SSIs. Surveillance can be very useful in identifying either wards or surgeons with increased rates. Operative procedures in infected areas have an increased infection rate because of the high inoculum with actively pathogenic bacteria.

Table 4 Antibiotics for Prevention of Endocarditis^{118,119}

Manipulative Procedure	Prophylactic Regimen*	
	Usual	In Patients with Penicillin Allergy
Dental procedures likely to cause gingival bleeding; operations or instrumentation of the upper respiratory tract	Oral Amoxicillin 2 g 1 hr before procedure	Oral Clindamycin, [†] 600 mg 1 hr before procedure or Cephalexin, [†] 1 g 1 hr before procedure or Azithromycin or clarithromycin, 500 mg 1 hr before procedure
	Parenteral Ampicillin, 2 g IM or IV 30 min before procedure or Cefazolin or ceftriaxone 1 g IM or IV	Parenteral Clindamycin, 600 mg IV within 30 min before procedure or Cefazolin or ceftriaxone, 1 g IM or IV within 30 min before procedure
Infected gastrointestinal or genitourinary operation; abscess drainage	Oral Amoxicillin, 2 g 1 hr before procedure Parenteral Ampicillin, 2 g IM or IV within 30 min before procedure; if risk of endocarditis is considered high, add gentamicin, 1.5 mg/kg (to maximum of 120 mg) IM or IV 30 min before procedure	Parenteral Vancomycin, 1 g IV infused slowly over 1 hr, beginning 1 hr before procedure; if risk of endocarditis is considered high, add gentamicin, 1.5 mg/kg (to maximum of 120 mg) IM or IV 30 min before procedure [‡]

*Pediatric dosages are as follows: oral amoxicillin, 50 mg/kg; oral or parenteral clindamycin, 20 mg/kg; oral cephalexin or cefadroxil, 50 mg/kg; oral azithromycin or clarithromycin, 15 mg/kg; parenteral ampicillin, 50 mg/kg; parenteral cefazolin, 25 mg/kg; parenteral gentamicin, 2 mg/kg. The total pediatric dose should not exceed the total adult dose.

[†]Patients with a history of immediate-type sensitivity to penicillin should not receive these agents.

[‡]High-risk patients should also receive ampicillin, 1 g IM or IV, or amoxicillin, 1 g PO, 6 hours after the procedure.

Preoperative Preparation of the Operative Site

The sole reason for preparing the patient's skin before an operation is to reduce the risk of wound infection. A preoperative antiseptic bath is not necessary for most surgical patients, but their personal hygiene must be assessed and preoperative cleanliness established. Multiple preoperative baths may prevent postoperative infection in selected patient groups, such as those who carry *Staphylococcus aureus* on their skin or who have infectious lesions. Chlorhexidine gluconate is the recommended agent for such baths.¹²⁰

Hair should not be removed from the operative site unless it physically interferes with accurate anatomic approximation of the wound edges.¹⁵ If hair must be removed, it should be clipped in the OR.¹⁵ Shaving hair from the operative site, particularly on the evening before operation or immediately before wound incision in the OR, increases the risk of wound infection. Depilatories are not recommended, because they cause serious irritation and rashes in a significant number of patients, especially when used near the eyes and the genitalia.¹²¹

In emergency procedures, obvious dirt, grime, and dried blood should be mechanically cleansed from the operative site by using sufficient friction. In one study, cleansing of contaminated wounds by means of ultrasound débridement was compared with high-pressure irrigation and soaking. Both ultrasound débridement and high-pressure irrigation were also effective in reducing the wound infection rate in experimental wounds contaminated with a subinfective dose of *S. aureus* and colloidal clay.¹²²

For nonemergency procedures, the necessary reduction in microorganisms can be achieved by using povidoneiodine (10% available povidoneiodine and 1% available iodine) or chlorhexidine gluconate both for mechanical cleansing of the intertriginous folds and the umbilicus and for painting the operative site. Which skin antiseptic is optimal is unclear. The best option appears to be chlorhexidine gluconate or an iodophor.¹²³ The patient should be assessed for evidence of sensitivity to the antiseptic (particularly if the agent contains iodine) to minimize the risk of an allergic reaction. What some patients report as iodine allergies are actually burns. Iodine in alcohol or in water is associated with an increased risk of skin irritation,⁹⁶ particularly at the edges of the operative field, where the iodine concentrates as the alcohol evaporates. Iodine should therefore be removed after sufficient contact time with the skin, especially at the edges. Iodophors do not irritate the skin and thus need not be removed.

The preoperative hospital stay has frequently been found to make an important contribution to wound infection rates.¹³ The usual explanation is that during this stay, either more endogenous bacteria are present or commensal flora is replaced by hospital flora. More likely, the patient's clinical picture is a complex one, often entailing exhaustive workup of more than one organ system, various complications, and a degree of illness that radically changes the host's ability to

deal with an inoculum, however small. Therefore, multiple factors combine to transform the hospitalized preoperative patient into a susceptible host. Same-day admission should eliminate any bacterial impact associated with the preoperative hospital stay.

Bacteria with multiple antibiotic resistance (e.g., methicillin-resistant *S. aureus* [MRSA], *Staphylococcus epidermidis*, and vancomycin-resistant enterococci [VRE]) can be associated with significant SSI problems. In particular, staphylococci, with their natural virulence, present an important hazard if inappropriate prophylaxis is used.

Many surgeons consider it inappropriate or unnecessary to obtain good culture and sensitivity data on SSIs; instead of conducting sensitivity testing, they simply drain infected wounds, believing that the wounds will heal. However, there have been a number of reports of SSIs caused by unusual organisms^{24,27,28}; these findings underscore the usefulness of culturing pus or fluid when an infection is being drained. SSIs caused by antibiotic-resistant organisms or unusual pathogens call for specific prophylaxis, perhaps other infection control efforts, and, if the problem persists, a search for a possible carrier or a common source.^{22-24,27,28}

SURGEONS AND BACTERIA

The surgeon's perioperative rituals are designed to reduce or eliminate bacteria from the operative field. Many old habits are obsolete [see 1:8 *Preparation of the Operating Room and Discussion, Hand Washing, below*].

Nonetheless, it is clear that surgeons can influence SSI rates.¹⁴ The refusal to use delayed primary closure or secondary closure is an example. Careful attention to the concepts of asepsis and antisepsis in the preparation and conduct of the operation is important. Although no single step in the ritual of preparing a patient for the operative procedure is indispensable, it is likely that certain critical standards of behavior must be maintained to achieve good results.

The measurement and publication of data about individuals or hospitals with high SSI rates have been associated with a diminution of those rates [see Table 6].^{13,14,29} It is uncertain by what process the diffusion of these data relates to the observed improvements. Although surveillance has unpleasant connotations, it provides objective data that individual surgeons are often too busy to acquire but that can contribute to improved patient care. For example, such data can be useful in identifying problems (e.g., the presence of MRSA, a high SSI incidence, or clusters), maintaining quality assurance, and allowing comparison with accepted standards.

Environment: Local Factors

Local factors influence SSI development because they affect the size of the bacterial inoculum that is required

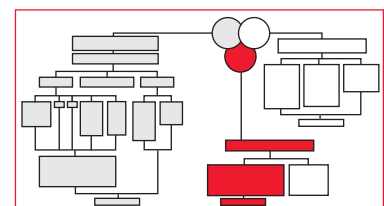
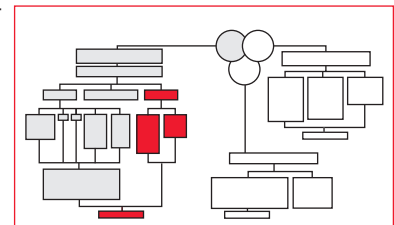


Table 5 Effect of Surveillance and Feedback on Wound Infection Rates in Two Hospitals²⁹

		Period 1	Period 2*
Hospital A	Number of wounds	1,500	1,447
	Wound infection rate	8.4%	3.7%
Hospital B	Number of wounds	1,746	1,939
	Wound infection rate	5.7%	3.7%

*Periods 1 and 2 were separated by an interval during which feedback on wound infection rates was analyzed.

Table 6 Determinants of Infection and Factors that Influence Wound Infection Rates²⁹

Variable	Determinant of Infection		
	Bacteria	Wound Environment (Local Factors)	Host Defense Mechanisms (Systemic Factors)
Bacterial numbers in wound	a		
Potential contamination	a		
Preoperative shave	a		
Presence of three or more diagnoses			c
Age		b	c
Duration of operation	a	b	c
Abdominal operation Relative value unit > 10 Emergency surgery	a	b	c
ASA class III, IV, or V			c
O ₂ tension		b	
Glucose control			c
Normothermia		b	c
Shock		b	c
Smoking		b	c
Diabetes ¹⁰		b	c
Dyspnea ¹⁰			c
Steroid use ¹⁰		b	c
Serum albumin ≤ 3.5 g/L ¹⁰			c
Age ≥ 40 ¹⁰			c
Radiotherapy ¹⁰			c
> 2 alcoholic drinks ¹⁰			c

ASA = American Society of Anesthesiologists.

to produce an infection: in a susceptible wound, a smaller inoculum produces infection [see Figure 2].

THE SURGEON'S INFLUENCE

Most of the local factors that make a surgical site favorable to bacteria are under the control of the surgeon. Although Halsted usually receives, deservedly so, the credit for having established the importance of technical excellence in the OR in preventing infection, individual surgeons in the distant past achieved remarkable results by careful attention to cleanliness and technique.³⁰ The halstedian principles dealt with hemostasis, sharp dissection, fine sutures, anatomic dissection, and the gentle handling of tissues. Mass ligatures, large or braided nonabsorbable sutures, necrotic tissue, and the creation of hematomas or seromas must be avoided, and foreign materials must be judiciously used because these techniques and materials change the size of the inoculum required to initiate an infectious process. Logarithmically fewer bacteria are required to produce infection in the presence of a foreign body (e.g., suture, graft, metal, or pacemaker) or necrotic tissue (e.g., that caused by gross hemostasis or injudicious use of electrocautery devices).

The differences in inoculum required to produce wound infections can be seen in a model in which the two variables

are the wound hematocrit and the presence of an antibiotic [see Figure 3]. In the absence of an antibiotic and in the presence of wound fluid with a hematocrit of more than 8%, 10 bacteria yield a wound infection rate of 20%. In a technically good wound with no antibiotic, however, 1,000 bacteria produce a wound infection rate of 20%.¹² In the presence of an antibiotic, 10⁵ to 10⁶ bacteria are required.

Drains

The use of drains varies widely and is very subjective. All surgeons are certain that they understand when to use a drain. However, certain points are worth noting. It is now recognized that a simple Penrose drain may function as a drainage route but is also an access route by which pathogens can reach the patient.³¹ It is important that the operative site not be drained through the wound. The use of a closed suction drain reduces the potential for contamination and infection.

Many operations on the gastrointestinal (GI) tract can be performed safely without employing prophylactic drainage.³² A review and meta-analysis from 2004 concluded that (1) after hepatic, colonic, or rectal resection with primary anastomosis and after appendectomy for any stage of appendicitis, drains should be omitted (recommendation grade A),

and (2) after esophageal resection and total gastrectomy, drains should be used (recommendation grade D). Additional randomized, controlled trials will be required to determine the value of prophylactic drainage for other GI procedures, especially those involving the upper GI tract.

Duration of Operation

In most studies, contamination certainly increases with time (see above).^{6,11,13} Wound edges can dry out, become macerated, or in other ways be made more susceptible to infection (i.e., requiring fewer bacteria for development of infection). Speed and poor technique are not suitable approaches; expeditious operation is appropriate.

Electrocautery

The use of electrocautery devices (but not the harmonic scalpel) has been clearly associated with an increase in the incidence of superficial SSIs. However, when such devices are properly used to provide pinpoint coagulation (for which the bleeding vessels are best held by fine forceps) or to divide tissues under tension, there is minimal tissue destruction, no charring, and no change in the wound infection rate.³¹

PATIENT FACTORS

Local Blood Flow

Local perfusion can greatly influence the development of infection, as is seen most easily in the tendency of the patient with peripheral vascular disease to acquire infection of an extremity. As a local problem, inadequate perfusion reduces the number of bacteria required for infection, in part because inadequate perfusion leads to decreased tissue levels of oxygen. Shock, by reducing local perfusion, also greatly enhances susceptibility to infection. Fewer organisms are required to produce infection during or immediately after shock [see Figure 4].

To counter these effects, the arterial oxygen tension (P_{aO_2}) must be translated into an adequate subcutaneous oxygen level (determined by measuring transcutaneous oxygen tension)³³; this, together with adequate perfusion, will provide local protection by increasing the number of bacteria required to produce infection. Provision of supplemental oxygen in the perioperative period may lead to a reduced SSI rate, probably as a consequence of increased tissue oxygen tension,³⁴ although the value of this practice has been questioned.³⁵ If the patient is not intubated, a mask, not nasal prongs, is required.³⁶

Barrier Function

Inadequate perfusion may also affect the function of other organs, and the resulting dysfunction will, in turn, influence the patient's susceptibility to infection. For example, ischemia-reperfusion injury to the intestinal tract is a frequent consequence of hypovolemic shock and bloodstream infection. Inadequate perfusion of the GI tract may also occur during states of fluid and electrolyte imbalance or when cardiac output is marginal. In experimental studies, altered blood flow has been found to be associated with the breakdown of bowel barrier function—that is, the inability of the

intestinal tract to prevent bacteria, their toxins, or both from moving from the gut lumen into tissue at a rate too fast to permit clearance by the usual protective mechanisms. A variety of experimental approaches aimed at enhancing bowel barrier function have been studied; at present, however, the most clinically applicable method of bowel protection is initiation of enteral feeding (even if the quantity of nutrients provided does not satisfy all the nutrient requirements) and administration of the amino acid glutamine [see 8:22 *Nutritional Support*]. Glutamine is a specific fuel for enterocytes and colonocytes and has been found to aid recovery of damaged intestinal mucosa and enhance barrier function when administered either enterally or parenterally.

Advanced Age

Aging is associated with structural and functional changes that render the skin and subcutaneous tissues more susceptible to infection. These changes are immutable; however, they must be evaluated in advance and addressed by excellent surgical technique and, on occasion, prophylactic antibiotics [see *Sidebar Antibiotic Prophylaxis of Infection*]. SSI rates increase with aging until the age of 65 years, after which point, the incidence appears to decline.³⁷

Host Defense Mechanisms

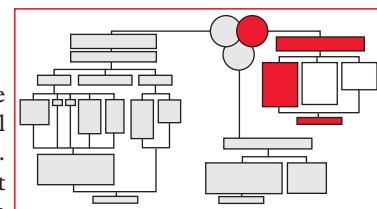
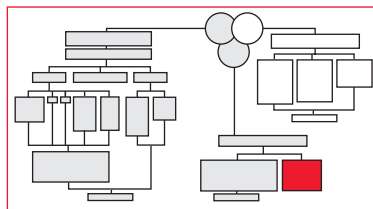
The systemic response is designed to control and eradicate infection. Many factors can inhibit systemic host defense mechanisms; some are related to the surgical disease and others to the patient's underlying disease or diseases and the events surrounding the operation.

SURGEON-RELATED FACTORS

There are a limited number of ways in which the surgeon can improve a patient's systemic responses to surgery. Nevertheless, when appropriate, attempts should be made to modify the host. The surgeon and the operation are both capable of reducing immunologic efficacy; hence, the operative procedure should be carried out in as judicious a manner as possible. Minimal blood loss, avoidance of shock, and maintenance of blood volume, tissue perfusion, and tissue oxygenation will minimize trauma and will reduce the secondary, unintended immunologic effects of major procedures.

Diabetes has long been recognized as a risk factor for infection and for SSI in particular. Three studies from the past decade demonstrated the importance of glucose control for reducing SSI rates in both diabetic and nondiabetic patients who underwent operation,^{38,39} as well as in critically ill intensive care unit patients.⁴⁰ Glucose control is required throughout the entire perioperative period. The beneficial effect appears to lie in the enhancement of host defenses. The surgical team must also ensure maintenance of adequate tissue oxygen tension^{33,34} and maintenance of normothermia.⁴¹

When abnormalities in host defenses are secondary to surgical disease, the timing of the operation is crucial to outcome. With acute and subacute inflammatory processes, early



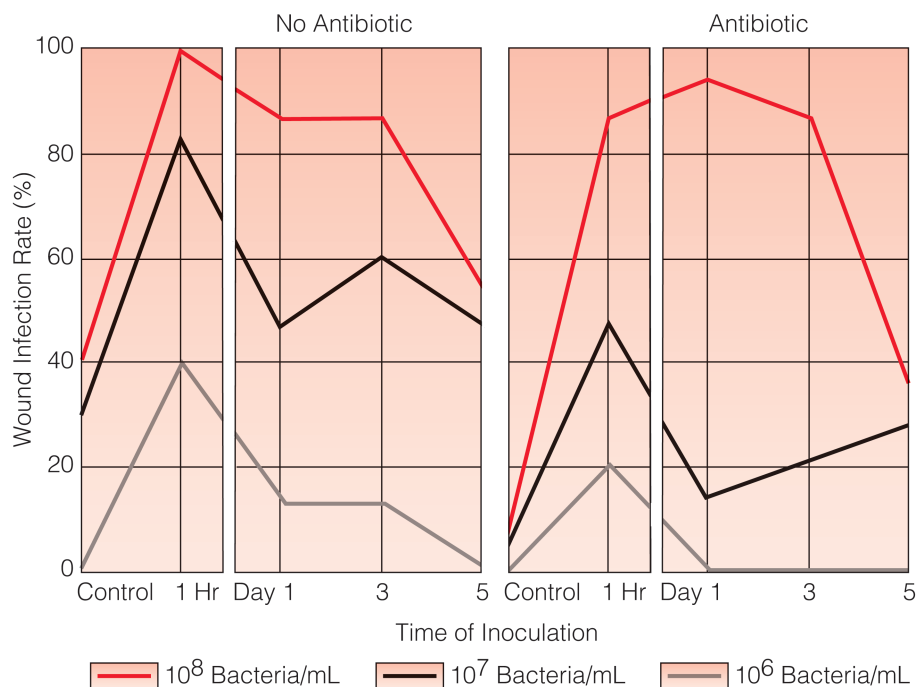
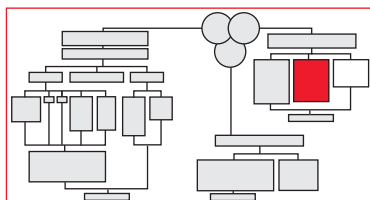


Figure 4 Animals exposed to hemorrhagic shock followed by resuscitation show an early decreased resistance to wound infection. There is also a persistent influence of shock on the development of wound infection at different times of inoculation after shock. The importance of inoculum size (10^6 /mL to 10^8 /mL) and the effect of antibiotic on infection rates are evident at all times of inoculation.¹⁰⁹

operation helps restore normal immune function. Deferral of definitive therapy frequently compounds problems.

PATIENT FACTORS

Surgeons have always known that the patient is a significant variable in the outcome of operation. Various clinical states are associated with altered resistance to infection. In all patients, but particularly those at high risk, SSI creates not only wound complications but also significant morbidity (e.g., reoperation, incisional hernia, secondary infection, impaired mobility, increased hospitalization, delayed rehabilitation, or permanent disability) and occasional mortality.²³ SENIC has proposed that the risk of wound infection be assessed not only in terms of probability of contamination but also in relation to host factors.^{6,7,9} According to this study, patients most clearly at risk for wound infection are those with three or more concomitant diagnoses; other patients who are clearly at risk are those undergoing a clean-contaminated or contaminated abdominal procedure and those undergoing any procedure expected to last longer than 2 hours. These last two risk groups are affected by a bacterial component, but all those patients who are undergoing major abdominal procedures or lengthy operations generally have a significant primary pathologic condition and are usually older, with an increased frequency of concomitant conditions. The NNIS system uses most of the same concepts but expresses them differently. In the NNIS study, host factors in the large study are evaluated in terms of the ASA score. The duration of the operation is measured differently as well, with a lengthy



operation being defined by the NNIS as one that is at or above the 75th percentile for operating time. Bacterial contamination remains a risk factor, but the operative site is eliminated.⁸

Shock has an influence on the incidence of wound infection [see Figure 4]. This influence is most obvious in cases of trauma, but there are significant implications for all patients in regard to maintenance of blood volume, hemostasis, and oxygen-carrying capacity. The effect of shock on the risk of infection appears to be not only immediate (i.e., its effect on local perfusion) but also late because systemic responses are blunted as local factors return to normal.

Advanced age, transfusion, and the use of steroids and other immunosuppressive drugs, including chemotherapeutic agents, are associated with an increased risk of SSI.^{42,43} Often, these factors cannot be altered; however, the proper choice of operation, the appropriate use of prophylaxis, and meticulous surgical technique can reduce the risk of such infection by maintaining patient homeostasis, reducing the size of any infecting microbial inoculum, and creating a wound that is likely to heal primarily.

Smoking is associated with a striking increase in SSI incidence. As little as 1 week of abstinence from smoking will make a positive difference.⁴⁴

Pharmacologic therapy can affect host response as well. Nonsteroidal anti-inflammatory drugs that attenuate the production of certain eicosanoids can greatly alter the adverse effects of infection by modifying fever and cardiovascular effects. Operative procedures involving inhalational anesthetics result in an immediate rise in plasma cortisol concentrations. The steroid response and the associated immunomodulation can be modified by using high epidural anesthesia as the method of choice; pituitary adrenal

activation will be greatly attenuated. Some drugs that inhibit steroid elaboration (e.g., etomidate) have also been shown to be capable of modifying perioperative immune responses. Using this vast database of NSQIP, Neumayer and colleagues integrated most of these variables into an expanded risk assessment [see Table 6].¹⁰

ANESTHESIOLOGIST-RELATED FACTORS

A 2000 commentary in *The Lancet* by Donal Buggy considered the question of whether anesthetic management could influence surgical wound healing.⁴⁵ In addition to the surgeon- and patient-related factors already discussed (see above), Buggy cogently identified a number of anesthesiologist-related factors that could contribute to better wound healing and reduced wound infection. Some of these factors (e.g., pain control, epidural anesthesia, and autologous transfusion) are unproven but nonetheless make sense and should certainly be tested. Others (e.g., tissue perfusion, intravascular volume, and—significantly—maintenance of normal perioperative body temperature) have undergone formal evaluation. Very good studies have shown that dramatic reductions in SSI rates can be achieved through careful avoidance of hypothermia.^{41,46} Patient-controlled analgesia pumps are known to be associated with increased SSI rates, through a mechanism that is currently unknown.⁴⁷ Infection control practices are required of all practitioners; contamination of anesthetic drugs by bacteria has resulted in numerous small outbreaks of SSI.^{48,49}

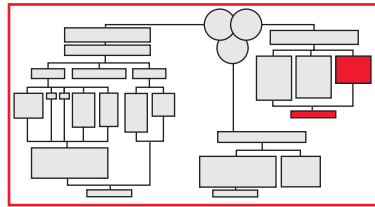
As modern surgical practice has evolved and the variable of bacterial contamination has come to be generally well managed, the importance of all members of the surgical team in the prevention of SSI has become increasingly apparent. The crux of Buggy's commentary may be expressed as follows: details make a difference, and all of the participants in a patient's surgical journey can contribute to a continuing decrease in SSI. It is a systems issue.

INTEGRATION OF DETERMINANTS

As operative infection rates slowly fall, despite the performance of increasingly complex operations in patients at greater risk, surgeons are approaching the control of infection with a broader view than simply that of asepsis and antisepsis. This new, broader view must take into account many variables, of which some have no relation to bacteria, but all play a role in SSI [see Table 6 and Figure 1].

To estimate risk, one must integrate the various determinants of infection in such a way that they can be applied to patient care. Much of this exercise is vague. In reality, the day-to-day practice of surgery includes a risk assessment that is essentially a form of logistic regression, although not recognized as such. Each surgeon's assessment of the probability of whether an SSI will occur takes into account the determining variables:

$$\begin{aligned} \text{Probability of SSI} = & \\ & x + a \text{ (bacteria)} + b \text{ (environment: local factors)} \\ & + c \text{ (host defense mechanisms: systemic factors)} \end{aligned}$$



Discussion

ANTIBIOTIC PROPHYLAXIS OF SSI

It is difficult to understand why antibiotics have not always prevented SSI successfully. Certainly, surgeons were quick to appreciate the possibilities of antibiotics; nevertheless, the efficacy of antibiotic prophylaxis was not proved until the late 1960s.¹² Studies before then had major design flaws—principally, the administration of the antibiotic some time after the start of the operation, often in the recovery room. The failure of studies to demonstrate efficacy and the occasional finding that prophylactic antibiotics worsened rather than improved outcome led in the late 1950s to profound skepticism about prophylactic antibiotic use in any operation.

The principal reason for the apparent inefficacy was inadequate understanding of the biology of SSIs. Fruitful study of antibiotics and how they should be used began after physiologic groundwork established the importance of local blood flow, maintenance of local immune defenses, adjuvants, and local and systemic perfusion.⁵⁰

The key antibiotic study, which was conducted in guinea pigs, unequivocally proved the following about antibiotics⁵¹:

1. They are most effective when given before inoculation of bacteria.
2. They are ineffective if given 3 hours after inoculation.
3. They are of intermediate effectiveness when given between these times [see Figure 5].

Although efficacy with a complicated regimen was demonstrated in 1964,⁵² the correct approach was not defined until 1969.¹² Established by these studies are the philosophical and practical bases of the principles of antibiotic prophylaxis of

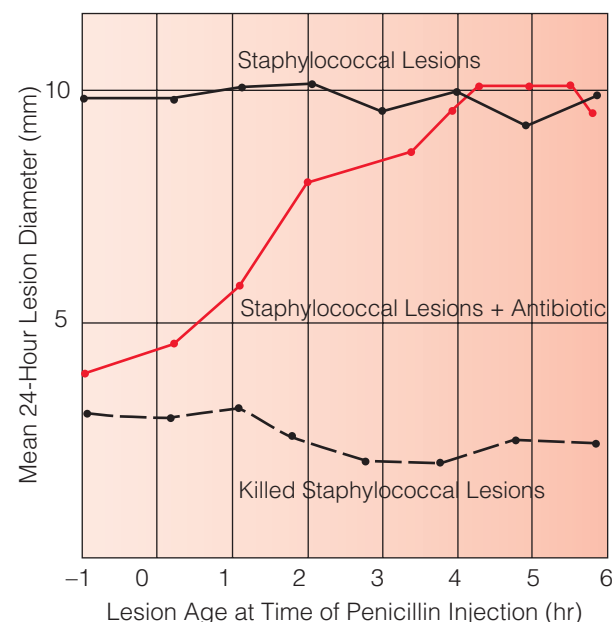


Figure 5 In a pioneer study of antibiotic prophylaxis,⁵¹ the diameter of lesions induced by staphylococcal inoculation 24 hours earlier was observed to be critically affected by the timing of penicillin administration with respect to bacterial inoculation.

SSI in all surgical arenas^{12,51}: that prophylactic antibiotics must be given preoperatively within 2 hours of the incision, in full dosage, parenterally, and for a very limited period. These principles remain essentially unchanged despite minor modifications from innumerable subsequent studies.^{53–57} Prophylaxis for colorectal operations is discussed elsewhere [see Infection Prevention in Bowel Surgery, *below*].

Principles of Patient Selection

Patients must be selected for prophylaxis on the basis of either their risk for SSI or the cost to their health if an SSI develops (e.g., after implantation of a cardiac valve or another prosthesis). The most important criterion is the degree of bacterial contamination expected to occur during the operation. The traditional classification of such contamination was defined in 1964 by the historic National Academy of Sciences–National Research Council study.⁵ The important features of the classification are its simplicity, ease of understanding, ease of coding, and reliability. Classification is dependent on only one variable—the bacterial inoculum—and the effects of this variable are now controllable by antimicrobial prophylaxis. Advances in operative technique, general care, antibiotic use, anesthesia, and surveillance have reduced SSI rates in all categories that were established by this classification.^{6,13,14,51}

In 1960, after years of negative studies, it was said, “Nearly all surgeons now agree that the routine use of prophylaxis in clean operations is unnecessary and undesirable.”⁵⁸ Since then, much has changed: there are now many clean operations for which no competent surgeon would omit the use of prophylactic antibiotics, particularly as procedures become increasingly complex and prosthetic materials are used in patients who are older, sicker, or immunocompromised.

A separate risk assessment that integrates host and bacterial variables (i.e., whether the operation is dirty or contaminated, is longer than 2 hours, or is an abdominal procedure and whether the patient has three or more concomitant diagnoses) segregates more effectively those patients who are prone to an increased incidence of SSI [see Integration of Determinants of Infection, *below*]. This approach enables the surgeon to identify those patients who are likely to require preventive measures, particularly in clean cases, in which antibiotics would normally not be used.⁶

The prototypical clean operation is an inguinal hernia repair. Technical approaches have changed dramatically over the past 10 years, and most primary and recurrent hernias are now treated with a tension-free mesh-based repair. The use of antibiotics has become controversial. In the era of repairs under tension, there was some evidence to suggest that a perioperative antibiotic (in a single preoperative dose) was beneficial.⁵⁹ Current studies, however, do not support antibiotic use in tension-free mesh-based inguinal hernia repairs.^{60,61} On the other hand, if surveillance indicates that there is a local or regional problem⁶² with SSI after hernia surgery, antibiotic prophylaxis (again in the form of a single preoperative dose) is appropriate. Without significantly more supportive data, prophylaxis for clean cases cannot be recommended unless specific risk factors are present.

Data suggest that prophylactic use of antibiotics may contribute to secondary *Clostridium difficile* disease; accordingly, caution should be exercised when widening the indications

for prophylaxis is under consideration.⁶³ If local results are poor, surgical practice should be reassessed before antibiotics are prescribed.

Antibiotic Selection and Administration

When antibiotics are given more than 2 hours before operation, the risk of infection is increased.^{53,55} IV administration in the OR or the preanesthetic room guarantees appropriate levels at the time of incision. The organisms likely to be present dictate the choice of antibiotic for prophylaxis. The cephalosporins are ideally suited to prophylaxis: their features include a broad spectrum of activity, an excellent ratio of therapeutic to toxic dosages, a low rate of allergic responses, ease of administration, and attractive cost advantages. Mild allergic reactions to penicillin are not contraindications for the use of a cephalosporin.

Physicians like new drugs and often tend to prescribe newer, more expensive antibiotics for simple tasks. First-generation cephalosporins (e.g., cefazolin) are ideal agents for prophylaxis. Third-generation cephalosporins are not: they cost more, are not more effective, and promote emergence of resistant strains.^{64,65}

The most important first-generation cephalosporin for surgical patients continues to be cefazolin. Administered IV in the OR at the time of skin incision, it provides adequate tissue levels throughout most of the operation. A second dose administered in the OR after 3 hours will be beneficial if the procedure lasts longer than that. Data on all operative site infections are imprecise, but SSIs can clearly be reduced by this regimen. No data suggest that further doses are required for prophylaxis.

Fortunately, cefazolin is effective against both gram-positive and gram-negative bacteria of importance, unless significant anaerobic organisms are encountered. The significance of anaerobic flora has been disputed, but for elective colorectal surgery,⁶⁶ abdominal trauma,^{67,68} appendicitis,⁶⁹ or other circumstances in which penicillin-resistant anaerobic bacteria are likely to be encountered, coverage against both aerobic and anaerobic gram-negative organisms is strongly recommended and supported by the data.

Despite several decades of studies, prophylaxis is not always properly implemented.^{53,55,69,70} Unfortunately, didactic education is not always the best way to change behavior. Preprinted order forms⁷¹ and a reminder sticker from the pharmacy⁷² have proved to be effective methods of ensuring correct use.

The commonly heard decision “This case was tough; let’s give an antibiotic for 3 to 5 days” has no data to support it and should be abandoned. The extended duration is associated with an increase in MRSA SSIs.⁷³ Differentiation between prophylaxis and therapy is important. A therapeutic course for perforated diverticulitis or other types of peritoneal infection is appropriate. Data on casual contamination associated with trauma or with operative procedures suggest that 24 hours of prophylaxis or less is quite adequate.^{74–76} Mounting evidence suggests that a single preoperative dose is good care and that additional doses are not required.

Trauma Patients

The efficacy of antibiotic administration on arrival in the emergency department as an integral part of resuscitation has

been clearly demonstrated.⁷⁷ The most common regimens have been (1) a combination of an aminoglycoside and clindamycin and (2) cefoxitin alone. These two regimens or variations thereof have been compared in a number of studies.^{41,68,76,77} They appear to be equally effective, and either regimen can be recommended with confidence. For prophylaxis, there appears to be a trend toward using a single drug: cefoxitin or cefotetan.⁵⁶ If therapy is required because of either a delay in surgery, terrible injury, or prolonged shock, the combination of an agent that is effective against anaerobes with an aminoglycoside seems to be favored. Because aminoglycosides are nephrotoxic, they must be used with care in the presence of shock.

In many of the trauma studies just cited, antibiotic prophylaxis lasted for 48 hours or longer. Subsequent studies, however, indicated that prophylaxis lasting less than 24 hours is appropriate.^{75,76,78} Single-dose prophylaxis is appropriate for patients with closed fractures.⁷⁹

Complications

Complications of antibiotic prophylaxis are few. Although data linking prophylaxis to the development of resistant organisms are meager, resistant microbes have developed in every other situation in which antibiotics have been used, and it is reasonable to expect that prophylaxis in any ecosystem will have the same result, particularly if selection of patients is poor, if prophylaxis lasts too long, or if too many late-generation agents are used.

A rare but important complication of antibiotic use is pseudomembranous enterocolitis, which is induced most commonly by clindamycin, the cephalosporins, and ampicillin [see 8:16 *Nosocomial Infection*].⁶³ The common denominator among different cases of pseudomembranous enterocolitis is hard to identify. Diarrhea and fever can develop after administration of single doses of prophylactic antibiotics. The condition is rare, but difficulties occur because of failure to make a rapid diagnosis.

Current Issues

The most significant questions concerning prophylaxis of SSIs already have been answered.

The problem has been the implementation of the strategies known to work. Table 7 outlines seven measures known with hard data to be important in the reduction of SSI. These management approaches are integrated into the Surgical Care Improvement Project⁸⁰ and the Surgical Infection Prevention Project.⁸¹ Single hospitals have used these criteria in ongoing quality improvement programs.⁸² More impressive is the collaborative reported by Dellinger and colleagues in which 56 hospitals tracked, monitored, and internally fed back the seven variables in Table 7 and demonstrated that as compliance increased, SSI rates came down.⁸³ An important remaining issue is the proper duration of prophylaxis in complicated cases, in the setting of trauma, and in the presence of foreign bodies. No change in the criteria for antibiotic prophylaxis is required in laparoscopic procedures; the risk of infection is lower in such cases.^{84,85} Cost factors are important and may justify the endless succession of studies that compare new drugs in competition for appropriate clinical niches.

Further advances in patient selection may take place but will require analysis of data from large numbers of patients

Table 7 Quality Improvement Objectives to Reduce Surgical Site Infections^{80,83}

Timeliness of antibiotics
Appropriate selection of antibiotics
Correct duration of antibiotics
Preventing hyperglycemia
Maintaining normothermia
Optimizing oxygen tension
Avoidance of shaving surgical site

and a distinction between approaches to infection of the wound, which is only part of the operative field, and approaches to infections directly related to the operative site. These developments will define more clearly the prophylaxis requirements of patients whose operations are clean but whose risk of wound or operative site infection is increased.

A current issue of some concern is loss of infection surveillance capability. Infection control units have been shown to offer a number of benefits in the institutional setting, such as the following:

1. Identifying epidemics caused by common or uncommon organisms^{24,27,57}
2. Establishing correct use of prophylaxis (timing, dose, duration, and choice)^{53,56,74}
3. Documenting costs, risk factors, and readmission rates^{86,87}
4. Monitoring postdischarge infections and secondary consequences of infections⁸⁸⁻⁹⁰
5. Ensuring patient safety⁹¹
6. Managing MRSA and VRE⁹²

S. aureus—in particular, MRSA—is a major cause of SSI.⁹² Cross-infection problems are a concern, in a manner reminiscent of the preantibiotic era. Hand washing (see below) is coming back into fashion, consistent with the professional behavior toward cross-infection characteristic of the preantibiotic era. At present, hard evidence is lacking, but clinical observation suggests that *S. aureus* SSIs are especially troublesome and destructive of local tissue and require a longer time to heal than other SSIs do. When *S. aureus* SSIs occur after cardiac surgery, thoracotomy, or joint replacement, their consequences are significant. Prevention in these settings is important. When nasal carriage of *S. aureus* has been identified, mupirocin may be administered intranasally to reduce the incidence of *S. aureus* SSIs.⁹³

The benefits of infection surveillance notwithstanding, as the business of hospital care has become more expensive and financial control more rigid, the infection control unit is a hospital component that many administrators have come to consider a luxury and therefore expendable. Consequently, surveillance as a quality control and patient safety mechanism has been diminished.

It is apparent that SSIs have huge clinical and financial implications [see *Sidebar Patient Safety and Antibiotic Use*]. Patients with infections tend to be sicker and to undergo more complex operations. Therefore, higher infection rates translate into higher morbidity and mortality as well as higher cost to the hospital, the patient, and society as a whole. With increasingly early discharge becoming the norm, delayed diagnosis of postdischarge SSI and the complications thereof

Patient Safety and Antibiotic Use

Prophylactic antibiotics have been considered to be a harmless manner in which to prevent surgical site infections. The evidence is that a single dose of prophylactic antibiotics can precipitate *Clostridium difficile* pseudomembranous enterocolitis.⁶³ These can be as malignant as the same entity caused by therapeutic antibiotic regimens.

Although the principles of delivery of added prophylactic antibiotics and their duration have been established for a long time, the evidence is clear that adherence to these principles is frequently poor. Two areas that are primarily at fault are the timing of administration of the first dose and whether it gets given and the duration of use of prophylactic antibiotics.^{43,70-72} The principles are (1) that the drug must be at the site of the wound at the time of incision and (2) a duration longer than 24 hours has no positive impact on SSI and may have a negative one. The inability of hospitals around the world to ensure the short postoperative duration of prophylaxis is a puzzle but is clear in all studies thus far performed.

Although prophylactic antibiotics are not the only stimulus to produce resistant microflora, their control and correct management will contribute to decreasing the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE). MRSA, in particular, is now found in community practice clearly as a result of excessive antibiotic use. The key to effective prophylactic antibiotics use and decreased pressure for antibiotic resistance can be simplified to the right drug, the right timing, and the right duration. The increased use of third- and fourth-generation antibiotics is to be strongly discouraged.

The new recommendations for the use of antibiotics in the prevention of infective endocarditis in association with either dental or other operative procedures are clear. The number of conditions has been reduced and clarified, and the recommendations regarding procedures have been greatly simplified.^{118,119}

All recommendations for prophylactic antibiotics, whatever the indication, suggest the use of first- or second-generation cephalosporins, ampicillin or its derivatives, metronidazole, and first-generation erythromycins and aminoglycosides.^{56,118}

is a growing problem.⁸⁸⁻⁹⁰ Effective use of institutional databases may contribute greatly to identification of this problem.⁸⁹

Clearly, the development of effective mechanisms for identifying and controlling SSIs is in the interests of all associated with the delivery of health care.⁹¹ The identification of problems by means of surveillance and feedback can make a substantial contribution to reducing SSI rates [see Table 6].^{13,91}

HAND WASHING

The purpose of cleansing the surgeon's hands is to reduce the numbers of resident flora and transient contaminants, thereby decreasing the risk of transmitting infection. Although the proper duration of the hand scrub is still subject to debate, evidence suggests that a 120-second scrub is sufficient, provided that a brush is used to remove the bacteria residing in the skin folds around the nails.⁹⁴ The nail folds, the nails, and the fingertips should receive the most attention because most bacteria are located around the nail folds and most glove punctures occur at the fingertips. Friction is required to remove resident microorganisms that are attached by adhesion or adsorption, whereas transient bacteria are easily removed by simple hand washing.

Solutions containing either chlorhexidine gluconate or one of the iodophors are the most effective surgical scrub preparations and have the fewest problems with stability, contamination, and toxicity.⁹⁵ Alcohols applied to the skin are among the safest known antiseptics, and they produce the greatest and most rapid reduction in bacterial counts on clean skin.⁹⁶ All variables considered, chlorhexidine gluconate followed by an iodophor appears to be the best option [see Table 8].

The purpose of washing the hands after surgery is to remove microorganisms that are resident, that flourished in the warm, wet environment created by wearing gloves, or that reached the hands by entering through puncture holes in the gloves. On the ward, even minimal contact with colonized patients has been demonstrated to transfer microorganisms.⁹⁷ As many as 1,000 organisms were transferred by simply touching the patient's hand, taking a pulse, or lifting the patient. The organisms survived for 20 to 150 minutes, making their transfer to the next patient clearly possible.

A return to the ancient practice of washing hands between each patient contact is warranted. Nosocomial spread of numerous organisms—including *C. difficile*; MRSA, VRE, and other antibiotic-resistant bacteria; and viruses—is a constant threat.

Hand washing on the ward is complicated by the fact that overwashing may actually increase bacterial counts. Dry, damaged skin harbors many more bacteria than healthy skin and is almost impossible to render even close to bacteria free. Although little is known about the physiologic changes in skin that result from frequent washings, the bacterial flora is certainly modified by alterations in the lipid or water content of the skin. The so-called dry hand syndrome was the impetus behind the development of the alcohol-based gels now available. These preparations make it easy for surgeons to

Table 8 Characteristics of Three Topical Antimicrobial Agents Effective against Both Gram-Positive and Gram-Negative Bacteria⁹⁶

Agent	Mode of Action	Antifungal Activity	Comments
Chlorhexidine	Cell wall disruption	Fair	Poor activity against tuberculosis-causing organisms; can cause ototoxicity and eye irritation
Iodine/iodophors	Oxidation and substitution by free iodine	Good	Broad antibacterial spectrum; minimal skin residual activity; possible absorption toxicity and skin irritation
Alcohols	Denaturation of protein	Good	Rapid action but little residual activity; flammable

clean their hands after every patient encounter with minimal damage to their skin.

INFECTION PREVENTION IN BOWEL SURGERY

At present, the best method of preventing SSIs after bowel surgery is, once again, a subject of debate. There have been three principal approaches to this issue, involving mechanical bowel preparation in conjunction with one of the following three antibiotic regimens^{56,98–103}:

1. Oral antibiotics (usually neomycin and erythromycin),^{16–21,102}
2. Intravenous antibiotics covering aerobic and anaerobic bowel flora,^{16–21,56,100,101} or
3. A combination of regimens 1 and 2 (meta-analysis suggests that the combination of oral and parenteral antibiotics is best).¹⁰³

With respect to mechanical bowel preparation, there are now many trials that in modern times have failed to be supportive.^{16–19} Meta-analysis suggests no value in the prevention of infection and the possibility of increasing complications.^{16,21} The increased SSI and leak rates noted have been attributed to the complications associated with vigorous bowel preparation, leading to dehydration, overhydration, or electrolyte abnormalities.

An observational study reported a 26% SSI rate in colorectal surgery patients.¹⁰⁴ Intraoperative hypotension and body mass index were the only independent predictive variables. All patients underwent mechanical bowel preparation the day before operation and received oral antibiotics and perioperative IV antibiotics. Half of the SSIs were discovered after discharge. Most would agree that the protocol was standard. These and other results suggest that a fresh look at the infectious complications of surgery—and of bowel surgery in particular—is required.

INTEGRATION OF DETERMINANTS OF INFECTION

The significant advances in the control of wound infection during the past several decades are linked to a better understanding of the biology of wound infection, and this link has permitted the advance to the concept of SSI.² In all tissues at any time, there will be a critical inoculum of bacteria that would cause an infectious process [see Figure 3]. The standard definition of infection in urine and sputum has been 10^5 organisms/mL. In a clean dry wound, 10^5 bacteria produce a wound infection rate of 50% [see Figure 3].¹² Effective use of antibiotics reduces the infection rate to 10% with the same number of bacteria and thereby permits the wound to tolerate a much larger number of bacteria.

All of the clinical activities described are intended either to reduce the inoculum or to permit the host to manage the number of bacteria that would otherwise be pathologic. One study in guinea pigs showed how manipulation of local blood flow, shock, the local immune response, and foreign material can enhance the development of infection.¹⁰⁵ This study and two others defined an early decisive period of host antimicrobial activity that lasts for 3 to 6 hours after contamination.^{51,105,106} Bacteria that remain after this period are the infecting inoculum. Processes that interfere with this early response (e.g., shock, altered perfusion, adjuvants, or foreign material) or support it (e.g., antibiotics or total care) have a major influence on outcome.

One investigation demonstrated that silk sutures decrease the number of bacteria required for infection.¹⁰⁷ Other investigators used a suture as the key adjuvant in studies of host manipulation,¹⁰⁸ whereas a separate study demonstrated persistent susceptibility to wound infection days after shock.¹⁰⁹ The common variable is the number of bacteria. This relation may be termed the inoculum effect, and it has great relevance in all aspects of infection control. Applying knowledge of this effect in practical terms involves the following three steps:

1. Keeping the bacterial contamination as low as possible via asepsis and antisepsis, preoperative preparation of patient and surgeon, and antibiotic prophylaxis
2. Maintaining local factors in such a way that they can prevent the lodgment of bacteria and thereby provide a locally unreceptive environment
3. Maintaining systemic responses at such a level that they can control the bacteria that become established

These three steps are related to the determinants of infection and their applicability to daily practice. Year-by-year reductions in wound infection rates, when closely followed, indicate that it is possible for surgeons to continue improving results by attention to quality of clinical care and surgical technique, despite increasingly complex operations.^{5,14,29–31} In particular, the measures involved in the first step (control of bacteria) have been progressively refined and are now well established.

The integration of determinants has significant effects [see Figures 3 and 4]. When wound closure was effected with a wound hematocrit of 8% or more, the inoculum required to produce a wound infection rate of 40% was 100 bacteria [see Figure 3]. Ten bacteria produced a wound infection rate of 20%. The shift in the number of organisms required to produce clinical infection is significant. It is obvious that this inoculum effect can be changed dramatically by good surgical technique and further altered by use of prophylactic antibiotics. If the inoculum is always slightly smaller than the number of organisms required to produce infection in any given setting, the results are excellent. There is clearly a relation between the number of bacteria and the local environment. The local effect can also be seen secondary to systemic physiologic change, specifically shock. One study showed the low local perfusion in shock to be important in the development of an infection.^{105,106}

One investigation has shown that shock can alter infection rates immediately after its occurrence [see Figure 4].¹⁰⁹ Furthermore, if the inoculum is large enough, antibiotics will not control bacteria. In addition, there is a late augmentation of infection lasting up to 3 days after restoration of blood volume. These early and late effects indicate that systemic determinants come into play after local effects are resolved. These observations call for further study, but, obviously, the combined abnormalities alter the outcome.

Systemic host responses are important for the control of infection. The patient has been clearly implicated as one of the four critical variables in the development of wound infection.⁶ In addition, the bacterial inoculum, the location of the procedure and its duration, and the coexistence of three or more diagnoses were found to give a more accurate prediction of the risk of wound infection. The spread of risk is defined better with the SENIC index (1 to 27%) than it

is with the traditional classification (2.9 to 12.6%). The importance of the number of bacteria is lessened if the other factors are considered in addition to inoculum. The inoculum effect has to be considered with respect to both the number of organisms and the local and systemic host factors that are in play. Certain variables were found to be significantly related to the risk of wound infection in three important prospective studies.^{6,11,13} It is apparent that the problem of SSI cannot be examined only with respect to the management of bacteria. Host factors have become much more significant now that the bacterial inoculum can be maintained at low levels by means of asepsis, antisepsis, technique, and prophylactic antibiotics.¹¹⁰

Important host variables include the maintenance of normal homeostasis (physiology) and immune response. Maintenance of normal homeostasis in patients at risk is one of the great advances of surgical critical care.¹¹⁰ The clearest improvements in this regard have come in maintenance of blood volume, oxygenation, and oxygen delivery.

One group demonstrated the importance of oxygen delivery, tissue perfusion, and P_{aO_2} in the development of wound infection.¹¹¹ Oxygen can have as powerful a negative influence on the development of SSI as antibiotics can.¹¹² The

influence is very similar to that seen in other investigations. Whereas a P_{aO_2} equivalent to a true fractional concentration of oxygen in inspired gas (F_{IO_2}) of 45% is not feasible, maintenance, when appropriate, of an increased F_{IO_2} in the postoperative period may prove an elementary and effective tool in managing the inoculum effect.

Modern surgical practice has reduced the rate of wound infection significantly. Consequently, it is more useful to think in terms of SSI, which is not limited to the incision but may occur anywhere in the operative field; this concept provides a global objective for control of infections associated with a surgical procedure. Surveillance is of great importance for quality assurance. Reports of recognized pathogens (e.g., *S. epidermidis* and group A streptococci) and unusual organisms (e.g., *Rhodococcus* [Gordona] *bronchialis*, *Mycoplasma hominis*, and *Legionella dumoffii*) in SSIs highlight the importance of infection control and epidemiology for quality assurance in surgical departments.^{22-24,27,28} (Although these reports use the term *wound infection*, they are addressing what we now call SSI.) The importance of surgeon-specific and service-specific SSI reports should be clear [see Table 6]^{13,14,113} and their value in quality assurance evident.

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2 INFECTION CONTROL IN SURGICAL PRACTICE

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Surgical procedures, by their very nature, interfere with the normal protective skin barrier and expose the patient to microorganisms from both endogenous and exogenous sources. Infections resulting from this exposure may not be limited to the surgical site but may produce widespread systemic effects. Prevention of surgical site infections (SSIs) is therefore of primary concern to surgeons and must be addressed in the planning of any operation. Standards of prevention have been developed for every step of a surgical procedure to help reduce the impact of exposure to microorganisms.¹⁻³ Traditional control measures include sterilization of surgical equipment, disinfection of the skin, use of prophylactic antibiotics, and expeditious operation.

The Study on the Efficacy of Nosocomial Infection Control (SENIC), conducted in US hospitals between 1976 and 1986, showed that surgical patients were at increased risk for all types of infections. The nosocomial, or hospital-acquired, infection rate at that time was estimated to be 5.7 cases out of every 100 hospital admissions.⁴ These infections included surgical site infections (SSIs), as well as bloodstream, urinary, and respiratory infections. Today, the increased use of minimally invasive surgical procedures and early discharge from the hospital necessitates postdischarge surveillance⁵ in addition to in-hospital surveillance for the tracking of nosocomial infections. With the reorganization of health care delivery programs, nosocomial infections will appear more frequently in the community and should therefore be considered a part of any patient care assessment plan.

The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) strongly recommends that the reduction of healthcare associated infections be prioritized as a national patient safety goal (<http://www.jointcommission.org/PatientSafety/InfectionControl>). Effective infection control and prevention require an organized, hospital-wide program aimed at achieving specific objectives. The program's purpose should be to obtain relevant information on the occurrence of nosocomial infections among both patients and employees. The data should be documented, analyzed, and communicated along with a plan for corrective measures. Such surveillance activities, combined with education, form the basis of an infection control program.

Data relating to host factors are an integral part of infection data analysis. Documentation of host factors has made for a better appreciation of the associated risks and has allowed comparative evaluation of infection rates. Development of new surgical equipment and technological advances have influenced the impact of certain risk factors, such as the length of an operation and the duration of a hospital stay. Clinical investigations have helped improve the

understanding of host factors and have influenced other aspects of surgical practice.⁶⁻¹¹ Excessive use of and reliance on antibiotics have led to the emergence of multidrug-resistant microorganisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), glycopeptide-intermediate *S. aureus* (GISA), multidrug-resistant *Mycobacterium tuberculosis*, and multidrug-resistant *Enterococcus* strains.¹²⁻¹⁵ Such complications reemphasize the need to focus on infection control as an essential component of preventive medicine.

Besides the impact of morbidity and mortality on patients, there is the cost of treating nosocomial infections, which is a matter of concern for surgeons, hospital administrators, insurance companies, and government planners alike. Efforts to reduce the occurrence of nosocomial infections are now a part of hospital cost-control management programs.^{16,17} The challenge to clinicians is how to reduce cost while maintaining control over, and preventing spread of, infection. A review of 30 studies published between 1990 and 2003 reported that approximately 20% of nosocomial infections were preventable.¹⁸

The Surgical Wound and Infection Control

NOSOCOMIAL INFECTIONS AND SURGICAL SITE INFECTIONS

Nosocomial infections are defined as infections acquired in the hospital. There must be no evidence that the infection was present or incubating at the time of hospital admission. Usually, an infection that manifests 48 to 72 hours after admission is considered to be nosocomially acquired. An infection that is apparent on the day of admission is usually considered to be community acquired, unless it is epidemiologically linked to a previous admission or to an operative procedure at the time of admission.

SSIs account for 14 to 16% of all nosocomial infections. They occur in 2 to 5% of patients undergoing clean procedures and in as many as 20% of patients undergoing intra-abdominal operations.¹⁹ To encourage a uniform approach among data collectors, the Centers for Disease Control and Prevention (CDC) has suggested three categories of SSIs, supplying definitions for each category [see Table 1].²⁰ The CDC defines an incisional SSI as an infection that occurs at the incision site within 30 days after surgery or within 1 year if a prosthetic implant is in place. Infection is characterized by redness, swelling, or heat with tenderness, pain, or dehiscence at the incision site and by purulent drainage. Other indicators of infection include fever, deliberate opening of the wound, culture-positive drainage, and a physician's diagnosis of infection with prescription of antibiotics. The category of

Table 1 Surgical Site Infections (SSIs)²⁰

Superficial SSIs
Skin
Deep incisional SSIs
Fascia
Muscle layers
Organ or space SSIs
Body organs
Body spaces

organ or space SSI was included to cover any part of the anatomy other than the incision (ie, organs or spaces) that might have been opened or manipulated during the operative procedure. This category would include, for example, arterial and venous infections, endometritis, disk space infections, and mediastinitis.²⁰

There should be collaboration between the physician or nurse and the infection control practitioner to establish the presence of an SSI. The practitioner should complete the surveillance with a chart review and document the incident in a computer database program for analysis. The data must be systematically recorded; many commercial computer programs are available for this purpose. One group reported that their experience with the Health Evaluation through Logical Processing system was useful for identifying patients at high risk for nosocomial infections.²¹

IDENTIFICATION OF RISK FACTORS

The risk of development of an SSI depends on host factors, perioperative wound hygiene, and the duration of the surgical procedure. Identification of host and operative risk factors can help determine the potential for infection and point toward measures that might be necessary for prevention and control.

Host Risk Factors

Host susceptibility to infection can be estimated according to the following variables: older age, severity of disease, physical-status classification (see below), prolonged preoperative hospitalization, morbid obesity, malnutrition, immunosuppressive therapy, smoking, preoperative colonization with *S. aureus*, and coexistent infection at a remote body site.²²

A scale dividing patients into five classes according to their physical status was introduced by the American Society of Anesthesiologists (ASA) in 1974 and tested for precision in 1978.²³ The test results showed that the ASA scale is a workable system, though it lacks scientific definition [see Table 2].

Significant differences in infection rates have been shown in patients with different illnesses. In one prospective study, the severity of underlying disease (rated as fatal, ultimately fatal, or nonfatal) was shown to have predictive value for endemic nosocomial infections; the nosocomial infection rate in patients with fatal diseases was 23.6%, compared with 2.1% in patients with nonfatal diseases.²⁴

Operative Risk Factors

Several factors related to the operative procedure may be associated with the risk of development of an SSI [see 1:1 *Prevention of Postoperative Infection*]. These include method of

Table 2 American Society of Anesthesiologists Physical Status Scale

Class	Patient Description
1	A normally healthy individual
2	A patient with mild systemic disease
3	A patient with severe systemic disease that is not incapacitating
4	A patient with incapacitating systemic disease that is a constant threat to life
5	A moribund patient who is not expected to survive 24 hr with or without operation
E	Added for emergency procedures

hair removal (and likelihood of consequent skin injury), inappropriate use of antimicrobial prophylaxis, duration of the operation, and wound classification. The influence of hair removal methods on SSI has been examined by many investigators. Infection rates were reported to be lower with depilatory agents and electric clippers than with razors.^{6,7} Antimicrobial prophylaxis is used for all operations that involve entry into a hollow viscus. Antimicrobial prophylaxis is also indicated for clean operations in which an intra-articular or intravascular prosthetic device will be inserted and for any operation in which an SSI would have a high morbidity.²² A comprehensive study determined that there is considerable variation in the timing of administration of prophylactic antibiotics, but that administration within 2 hours before surgery reduces the risk of SSI.⁸

Operative wounds are susceptible to varying levels of bacterial contamination, by which they are classified as clean, clean-contaminated, contaminated, or dirty.²⁵ In most institutions, the responsibility for classifying the incision site is assigned to the operating room circulating nurse; one assessment suggests that the accuracy of decisions made by this group is as high as 88%.²⁶

Composite Risk Indices

The CDC established the National Nosocomial Infections Surveillance (NNIS) system in 1970 to create a national database of nosocomial infections.²⁷ The NNIS system has been used to develop definitions of infections and indices for predicting the risk of nosocomial infection in a given patient. The NNIS system has been integrated into the National Healthcare Safety Network (NHSN).²⁸

NNIS Basic Risk Index NNIS developed a composite risk index composed of the following criteria: ASA score, wound class, and duration of surgery. Reporting on data collected from 44 US hospitals between 1987 and 1990, NNIS demonstrated that this risk index is a significantly better predictor for development of SSI than the traditional wound classification system alone.^{29,30} The NNIS risk index is a useful method of risk adjustment for a wide variety of procedures.

The NNIS risk index assigns patients scores of 0, 1, 2, or 3. A patient's score is determined by counting the number of risk factors present from among the following: an ASA score of 3, 4, or 5; a surgical wound that is classified as

contaminated or dirty/infected; and an operation lasting longer than T hours (where T represents the 75th percentile of distribution of the duration of the operative procedure being performed, rounded to the nearest whole number of hours).

Modified NNIS Basic Risk Index for Procedures Using Laparoscopes For cholecystectomy and colon surgery procedures, the use of a laparoscope lowered the risk of SSI within each NNIS risk index category.³¹ Hence, for these procedures, when the procedure is performed laparoscopically, the risk index should be modified by subtracting 1 from the basic NNIS risk index score. With this modification, the risk index has values of M (or -1), 0, 1, 2, or 3. For appendectomy and gastric surgery, use of a laparoscope affected SSI rates only when the NNIS basic risk index was 0, thereby yielding five risk categories: 0—Yes, 0—No, 1, 2, and 3, where Yes or No refers to whether the procedure was performed with a laparoscope.³¹

Operation-Specific Risk Factors It is likely that operation-specific logistic regression models will increasingly be used to calculate risk. For example, in spinal fusion surgery, Richards and colleagues identified diabetes mellitus, ASA score greater than 3, operation duration longer than 4 hours, and posterior surgical approach as significant independent predictors of SSI.³² Other logistic regression models have been developed for craniotomy and cesarean section.^{33,34} These models should permit more precise risk adjustment.

PREVENTIVE MEASURES

In any surgical practice, policies and procedures should be in place pertaining to the making of a surgical incision and the prevention of infection. These policies and procedures should govern the following: (1) skin disinfection and hand-washing practices of the operating team, (2) preoperative preparation of the patient's skin (e.g., hair removal and use of antiseptics), (3) the use of prophylactic antibiotics, (4) techniques for preparation of the operative site, (5) management of the postoperative site if drains, dressings, or both are in place, (6) standards of behavior and practice for the operating team (e.g., the use of gown, mask, and gloves), (7) special training of the operating team, and (8) sterilization and disinfection of instruments.

Surgical Infection Prevention and Surgical Care Improvement Projects

In 2002, the Centers for Medicare and Medicaid Services, in collaboration with the CDC, implemented the National Surgical Infection Prevention (SIP) Project.³⁵ The goal of the SIP Project is to decrease the morbidity and mortality associated with postoperative SSI by advocating appropriate selection and timing of prophylactic antibiotics. Three performance measures were developed: (1) the percentage of patients who receive parenteral antimicrobial prophylaxis within 1 hour before incision (within 2 hours for vancomycin or fluoroquinolone), (2) the percentage of patients who are given a prophylactic antimicrobial regimen consistent with published guidelines, and (3) the percentage of patients whose prophylactic antimicrobial is discontinued within 24 hours after surgery. These three performance measures were

the focus of improvement in a 1-year collaborative project that included 56 hospitals and 43 Medicare quality improvement organizations.³⁶ Other performance measures included maintenance of patient normothermia, use of supplemental oxygenation, maintenance of euglycemia and appropriate hair removal. In this collaborative project, hospitals reported a 27% mean reduction in their SSI rates.³⁶

The Surgical Care Improvement Project (SCIP) was developed in 2003 and evolved from the SIP project.³⁵ This initiative is a national partnership of organizations (including the American College of Surgeons [ACS]) that is committed to the reduction of postoperative complications in four areas: (1) prevention of SSIs, (2) prevention of venous thromboembolism, (3) prevention of adverse cardiac events, and (4) prevention of respiratory complications.³⁵

Hand Hygiene

Although hand hygiene is considered the single most important measure for preventing nosocomial infections, poor compliance is frequent.³⁷ Role modeling is important in positively influencing this behavior. One study showed that a hand-washing educational program contributed to a reduction in the rate of nosocomial infections.³⁸ Good hand-washing habits can be encouraged by making facilities (with sink, soap, and paper towels) visible and easily accessible in patient care areas [see 1:1 *Prevention of Postoperative Infection*].

Agents used for hand hygiene include plain nonantimicrobial soaps, antimicrobial soaps, and waterless alcohol-based hand antiseptics. Plain soaps have very little antimicrobial activity; they mainly remove dirt and transient flora.³⁹ Compared with plain soaps, antimicrobial soaps achieve a greater log reduction in eliminating transient flora and have the additional advantage of sustained activity against resident hand flora.³⁹ Alcohol-based hand antiseptics have an excellent spectrum of antimicrobial activity and rapid onset of action, dry rapidly, and do not require the use of water or towels.⁴⁰ Therefore, they are recommended for routine decontamination of hands during patient care, except when hands are visibly soiled. Emollients are often added to alcohol-based waterless hand antiseptics because of these antiseptics' tendency to cause drying of the skin.⁴⁰

Sterilization and Disinfection

Spaulding proposed in 1972 that the level of disinfection and sterilization for surgical and other instruments be determined by classifying the instruments into three categories according to the degree of infection risk involved in their use: critical, semicritical, and noncritical.⁴¹

Critical items include objects or instruments that directly enter the vascular system or sterile areas of the body. These items should be sterilized by steam under pressure, dry heat, ethylene oxide, or other approved methods. Flash sterilization is the process by which surgical instruments are sterilized for immediate use should an emergency situation arise (e.g., an instrument that was accidentally dropped). This is usually achieved by leaving instruments unwrapped in a container and using a rapid steam cycle.⁴² Instruments must still be manually cleaned, decontaminated, inspected, and properly arranged in the container before sterilization. Implantables should not be flash sterilized. Flash sterilization is not intended

to replace conventional steam sterilization of surgical instruments or to reduce the need for adequate instrument inventory.⁴²

Semicritical items are those that come into contact with mucous membranes or skin that is not intact (eg, bronchoscopes and gastroscopes). Scopes have the potential to cause infection if they are improperly cleaned and disinfected. Transmission of infection has been documented after endoscopic investigations, including infection with *Salmonella typhi* and *Helicobacter pylori*.^{43,44} Semicritical items generally require high-level disinfection that kills all microorganisms except bacterial spores.⁴⁵ Glutaraldehyde 2% is a high-level disinfectant that has been used extensively in flexible endoscopy. Before disinfection, scopes should receive a thorough manual cleaning to eliminate gross debris. To achieve high-level disinfection, the internal and external surfaces and channels should come into contact with the disinfecting agent for a minimum of 20 minutes.⁴⁵ Glutaraldehyde has certain disadvantages. In particular, it requires activation before use; moreover, it is irritating to the skin, eyes, and nasal mucosa, and thus, its use requires special ventilation or a ducted fume hood.⁴⁵ An alternative to glutaraldehyde is orthophthalaldehyde (OPA), a newer agent that is approved by the Food and Drug Administration (FDA) for high-level disinfection. OPA is odorless and nonirritating and does not require activation before use.⁴⁶

Noncritical items are those that come in contact with intact skin (e.g., blood pressure cuffs). They require only cleaning with a detergent and warm water or disinfection with an intermediate-level or low-level germicide for 10 minutes.

The reuse of single-use medical devices has become a topic of interest because of the implied cost savings. The central concerns are the effectiveness of sterilization or disinfection according to category of use, as well as maintenance of the essential mechanical features and the functional integrity of the item to be reused. The FDA has issued regulations governing third-party and hospital reproducers engaged in reprocessing single-use devices for reuse. These regulations are available on the FDA's Web site (<http://www.fda.gov/cdrh/reprocessing/index.html>).

Hair Removal

An infection control program should have a hair-removal policy for preoperative skin preparation [see 1:1 *Prevention of Postoperative Infection*].

Operating Room Environment

Environmental controls in the OR have been used to reduce the risk of SSI [see 1:8 *Preparation of the Operating Room*]. The OR should be maintained under a positive pressure of at least 2.5 Pa in relation to corridors and adjacent areas. In addition, there should be 20 to 25 air changes per hour for ceiling heights between 9 and 12 feet.⁴⁷

HEALTH STATUS OF THE HEALTH CARE TEAM

The health care team has a primary role in the prevention of infection. Continued education and reinforcement of policies are essential: the team must be kept well informed and up to date on concepts of infection control. Inadvertently, team members may also be the source of, or the vector in, transmission of infection. Nosocomial infection outbreaks

with MRSA have been traced to MRSA carriers among health care workers.⁴⁸ Screening of personnel to identify carriers is undertaken only when an outbreak of nosocomial infection occurs that cannot be contained despite implementation of effective control measures and when a health care worker is epidemiologically linked to cases.

Protecting the health care team from infection is a constant concern. Preventive measures, such as immunizations and preemployment medical examinations, should be undertaken at an employee health care center staffed by knowledgeable personnel.⁴⁹ Preventable infectious diseases, such as chickenpox and rubella, should be tightly controlled in hospitals that serve immunocompromised and obstetric patients. It is highly recommended that a record be maintained of an employee's immunizations. Knowledge of the employee's health status on entry to the hospital helps ensure appropriate placement and good preventive care.

When exposure to contagious infections is unavoidable, susceptible personnel should be located, screened, and given prophylactic treatment if necessary. In collaboration with the occupational health department, infection control personnel should define the problem, establish a definition of contact, and take measures to help reduce panic.

Isolation Precautions

CDC guidelines have been developed to prevent the transmission of infections.⁵⁰ These isolation guidelines promote two levels of isolation precautions: standard precautions and transmission-based precautions.

Standard Precautions The standard precautions, which incorporate the main features of the older universal precautions and body substance isolation guidelines, were developed to reduce the risk of transmission of microorganisms for all patients, regardless of their diagnosis.^{50,51} Standard precautions apply to blood, all body fluids, secretions and excretions, and mucous membranes.

Transmission-Based Precautions Transmission-based precautions were developed for certain epidemiologically important pathogens or clinical presentations. These precautions comprise three categories, based on the mode of transmission: airborne precautions, droplet precautions, and contact precautions.⁵⁰ Precautions may be combined for certain microorganisms or clinical presentations (e.g., both contact and airborne precautions are indicated for a patient with varicella).

Airborne precautions are designed to reduce transmission of microorganisms spread via droplets that have nuclei 5 μ m in size or smaller, remain suspended in air for prolonged periods of time, and have the capability of being dispersed widely.⁵⁰ Airborne precautions include wearing an N95 respirator, placing the patient in a single room that is under a negative pressure of 2.5 Pa in relation to adjacent areas, keeping the door closed, providing a minimum of 6 to 12 air changes per hour, and exhausting room air outside the building and away from intake ducts or, if recirculated, through a high-efficiency particulate air (HEPA) filter.⁵⁰ Airborne precautions are indicated for patients with suspected or confirmed infectious pulmonary or laryngeal tuberculosis; measles; varicella; disseminated herpes zoster; and Lassa,

Ebola, Marburg, and other hemorrhagic fevers with pneumonia. Varicella, disseminated herpes zoster, and hemorrhagic fevers with pneumonia also call for contact precautions (see below).

Droplet precautions are designed to reduce the risk of transmission of microorganisms spread via large-particle droplets that are greater than 5 μm in size, do not remain suspended in the air for prolonged periods, and usually travel 1 m or less.⁵⁰ No special ventilation requirements are required to prevent droplet transmission. A single room is preferable, and the door may remain open. Examples of patients for whom droplet precautions are indicated are those with influenza, rubella, mumps, and meningitis caused by *Haemophilus influenzae* and *Neisseria meningitidis*.

Contact precautions are designed to reduce the risk of transmission of microorganisms by direct or indirect contact. Direct contact involves skin-to-skin contact resulting in physical transfer of microorganisms.⁵⁰ Indirect contact involves contact with a contaminated inanimate object that acts as an intermediary. Contact precautions are indicated for patients colonized or infected with *Clostridium difficile* and multidrug-resistant bacteria that the infection control program judges to be of special clinical and epidemiologic significance.⁵⁰

Exposure to Bloodborne Pathogens

The risk of transmission of HIV and hepatitis B virus (HBV) from patient to surgeon or from surgeon to patient has resulted in a series of recommendations governing contact with blood and body fluids.⁵²⁻⁵⁴ The risk of acquiring a bloodborne infection (e.g., HBV, hepatitis C virus [HCV], or HIV) depends on three factors: type of exposure to the bloodborne pathogen, prevalence of infection in the population, and the rate of infection after exposure to the bloodborne pathogen.⁵²⁻⁵⁴ Postexposure management has been discussed in CDC guidelines (<http://www.cdc.gov/mmwr/pdf/rr/rr5011.pdf>).⁵² Management of occupational exposures to HIV was updated in 2005 (<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5409a1.htm>).⁵⁴

Protection of the face and hands during the operative procedure is important. A study of 8,502 operations found that the rate of direct blood exposure was 12.4%, whereas the rate of parenteral exposure via puncture wounds and cuts was 2.2%. Parenteral blood contacts were twice as likely to occur among surgeons as among other OR personnel.⁵⁵ These findings support the need for OR practice policies and the choice of appropriate personal protective equipment for the OR staff. OR practice policy should give particular attention to methods of using sharp instruments and to ways of reducing the frequency of percutaneous injuries: sharp instruments should be passed in a metal dish, cautery should be used, and great care should be taken in wound closures. It is important that face shields and masks protect the operating team from splashes and aerosolized fluids. For optimal protection, a mask should be fluid-capture efficient and air resistant.⁵⁶

For invasive surgical procedures, double gloving has become routine. However, there are recognized differences among the gloves available. Latex allergy is an important issue; nonlatex alternatives are available for those who are allergic.

Hepatitis B Virus For active surgeons and other members of the health care team, HBV infection continues to

pose a major risk. It is estimated that in the United States, about 1.25 million people have chronic HBV infection, and more than 4 million have chronic HCV infection. Transmission of these infections to health care workers continues to occur, and each year, approximately 250 health care workers die of chronic HBV infection alone.⁵⁷ Hepatitis B vaccination has proved safe and protective and is highly recommended for all high-risk employees; it should be made available through the employee health care center.

Despite the efficacy of the vaccine, many surgeons and other personnel remain unimmunized and are at high risk for HBV infection.⁵⁷ Whereas younger surgeons have been routinely immunized, an estimated 25 to 30% of surgeons who have been in practice for longer than 10 to 15 years remain at substantial risk.⁵⁷ HBV is far more easily transmitted than HIV and continues to have a greater impact on the morbidity and mortality of health care personnel.⁵³ The risk of seroconversion is at least 30% after percutaneous exposure to blood from a hepatitis B e antigen-seropositive source.⁵³ Given that a patient's serostatus may be unknown, it is important that health care workers follow standard precautions for all patients.

Hepatitis C Virus The average incidence of seroconversion after percutaneous exposure from an HCV-positive source is 1.8% (range, 0 to 7%).^{53,58,59} Mucous membrane exposure to blood rarely results in transmission, and no transmission has been documented from exposure of intact or nonintact skin to blood.⁵³ There is no recommended postexposure prophylaxis regimen for HCV. The use of immunoglobulin has not been demonstrated to be protective.⁵³ There are no antiviral medications recommended for postexposure prophylaxis.⁵³

Human Immunodeficiency Virus Exposure to blood and body substances of patients who have AIDS or who are seropositive for HIV constitutes a health hazard to hospital employees. The magnitude of the risk depends on the degree and method of exposure [see 8:21 *Acquired Immunodeficiency Syndrome*].⁵⁴ Because screening for HIV infection is not mandatory among patients, the CDC recommends following the same guidelines for all patients undergoing invasive procedures that one would use in cases of known HIV-infected patients [see Table 3].⁵²

There have been isolated reports of transmission of HIV, HBV, and HCV from healthcare workers to patients. It is imperative to prevent transmission of these bloodborne pathogens from surgeons to patients. Accordingly, the CDC has developed specific guidelines for health care workers and exposure-prone activities [see Table 3].⁵² Similarly, the ACS has issued additional recommendations regarding the surgeon's role in the prevention of hepatitis transmission and HIV [see Table 4].^{52,57,60}

Exposure to Tuberculosis

In studies of health care workers, the incidence of positive results on tuberculin skin testing have ranged from 0.11 to 10%.^{61,62} Health care workers who are immunocompromised are at high risk for the development of disease after exposure.⁶¹

Table 3 CDC Recommendations for Prevention of HIV and HBV Transmission during Invasive Procedures⁵²

Health care workers with exudative lesions or weeping dermatitis should cover any unprotected skin, or they should not provide patient care until the damaged skin has healed.
Hands should be washed after every patient contact.
Health care workers should wear gloves when contact with blood or body substances is anticipated; double gloves should be used during operative procedures; hands should be washed after gloves are removed.
Gowns, plastic aprons, or both should be worn when soiling of clothing is anticipated.
Mask and protective eyewear or face shield should be worn if aerosolization or splattering of blood or body substances is expected.
Resuscitation devices should be used to minimize the need for mouth-to-mouth resuscitation.
Disposable containers should be used to dispose of needles and sharp instruments.
Avoid accidents and self-wounding with sharp instruments by following these measures:

- Do not recap needles.
- Use needleless systems when possible.
- Use cautery and stapling devices when possible.
- Pass sharp instruments in metal tray during operative procedures.

In the case of an accidental spill of blood or body substance on skin or mucous membranes, do the following:

- Rinse the site immediately and thoroughly under water.
- Wash the site with soap and water.
- Document the incident (i.e., report to Occupational Safety and Health Administration or to the Infection Control Service).

Blood specimens from all patients should be considered hazardous at all times.
Prompt attention should be given to spills of blood or body substances, which should be cleaned with an appropriate disinfectant.

CDC = Centers for Disease Control and Prevention; HBV = hepatitis B virus.

The CDC recommendations for tuberculosis prevention place emphasis on a hierarchy of control measures, including administrative engineering controls and personal respiratory protection (<http://www.cdc.gov/mmwr/PDF/rr/rr5417.pdf>).⁶³ The following measures should be considered:

1. The use of risk assessments and development of a written tuberculosis control protocol.
2. Early identification, treatment, and use of airborne precautions for persons who have tuberculosis.
3. Tuberculosis screening and respiratory protection programs for health care workers.
4. Training and education.
5. Evaluation of tuberculosis infection control programs.⁶³

Activities of an Infection Control Program

SURVEILLANCE

The cornerstone of an infection control program is surveillance. This process depends on the verification, classification, analysis, reporting, and investigation of infection occurrences, with the intent of generating or correcting policies and procedures. Five surveillance methods can be applied^{64,65}:

1. Total, or hospital-wide, surveillance: collection of comprehensive data on all infections in the facility, with the aim of correcting problems as they arise. This is labor intensive.

Table 4 ACS Recommendations for Preventing Transmission of Hepatitis⁵⁷

Surgeons should continue to utilize the highest standards of infection control, involving the most effective known sterile barriers, universal precautions, and scientifically accepted measures to prevent blood exposure during every operation. This practice should extend to all sites where surgical care is rendered and should include safe handling practices for needles and sharp instruments.
Surgeons have the same ethical obligations to render care to patients with hepatitis as they have to render care to other patients.
Surgeons with natural or acquired antibodies to HBV are protected from acquiring HBV from patients and cannot transmit the disease to patients. All surgeons and other members of the health care team should know their HBV immune status and become immunized as early as possible in their medical career.
Surgeons without evidence of immunity to HBV who perform procedures should know their HBsAg status and, if this is positive, should also know their HBeAg status. In both instances, expert medical advice should be obtained and all appropriate measures taken to prevent disease transmission to patients. Medical advice should be rendered by an expert panel composed and convened to fully protect practitioner confidentiality. The HBeAg-positive surgeon and the panel should discuss and agree on a strategy for protecting patients at risk for disease transmission.
On the basis of current information, surgeons infected with HCV have no reason to alter their practice but should seek expert medical advice and appropriate treatment to prevent chronic liver disease.

HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus

2. Surveillance by objective, or targeted surveillance, in which a specific goal is set for reducing certain types of infection. This concept is priority directed and can be further subdivided into two distinct activities:
 - a. The setting of outcome objectives, in which the objectives for the month or year are established and all efforts are applied to achieving a desired rate of infection. As with the hospital-wide approach, a short-term plan would be made to monitor, record, and measure infections and to provide feedback on the results.
 - b. The setting of process objectives, which incorporates the patient care practices of doctors and nurses as they relate to outcome (e.g., wound infections and their control).
3. Periodic surveillance: intensive surveillance of infections and patient-care practices by unit or by service at different times of the year.
4. Prevalence survey: the counting and analysis of all active infections during a specified time period. This permits identification of nosocomial infection trends and problem areas.
5. Outbreak surveillance: the identification and control of outbreaks of infection. Identification can be made on the basis of outbreak thresholds if baseline bacterial isolate rates are available and outbreak thresholds can be developed. Problems are evaluated only when the number of isolates of a particular bacterial species exceeds outbreak thresholds.

Surveillance techniques include the practice of direct patient observation and indirect observation by review of microbiology reports, nursing Kardex, or the medical record

to obtain data on nosocomial infections.^{6,64} The sensitivity of case finding was found to be 33 to 65% with microbiology reports, 85% with Kardex, and 90% with total chart review.⁶⁴ These methods may be used either separately or in combination to obtain data on clinical outcomes.

The increasing practice of same-day or short-stay surgical procedures has led to the need for postdischarge surveillance. This may be done by direct observation in a follow-up clinic, by surveying patients through the mail or over the telephone, by reviewing medical records, or by mailing questionnaires directly to surgeons. The original CDC recommendation of 30 days for follow-up was used by one hospital to randomly screen post-joint arthroplasty patients by telephone. This screening identified an infection rate of 7.5%, compared with 2% for hospitalized orthopedic patients.⁶⁶ Results from another medical center suggested that 90% of cases would be captured in a 21-day postoperative follow-up program.⁵ The use of prosthetic materials for implants requires extending the follow-up period to 1 year.

Verification and Definition of Infection

The CDC provides definitions for specific nosocomial infections (<http://www.cdc.gov/ncidod/dhqp/pdf/nnis/NosInfDefinitions.pdf>).⁶⁷ The use of standardized definitions is critical for consistency, particularly if interhospital comparisons are made. A complete assessment should include clinical evaluation of commonly recognized sites (e.g., wound, respiratory system, urinary tract, and intravenous access sites) for evidence of infection, especially when no obvious infection is seen at the surgical site. Laboratory and radiologic data should complement the clinical information. Microbiologic evaluation should aim at identification of the microorganism (which depends on an adequate specimen for Gram's staining and culture).

Use of Denominators

The choice of denominators depends on the patients at risk of acquiring nosocomial infections and on the ease or difficulty of collecting the data for denominators. Commonly used denominators include the number of admissions, the number of patient-days, and the number of procedures. For device-related infections, the appropriate denominator is the number of days of device exposure; this variable takes into account the differences in the risks experienced by the monitored patient.

Data Analysis

The original practice of presenting overall hospital-wide crude rates provided little means for adjustment of variables (e.g., risk related to the patient or to the operation). The following three formulas, however, are said to offer more precision than traditional methods⁶⁸:

$$\begin{aligned} & \text{(Number of nosocomial infections/Service operations)} \\ & \quad \times 100 \\ & \text{[Number of site-specific nosocomial infections/Specific} \\ & \quad \text{operations (e.g., number of inguinal hernias)]} \times 100 \\ & \text{[Number of nosocomial infections/Hospital} \\ & \quad \text{admissions (patient-days)]} \times 1,000 \end{aligned}$$

Data on infections of the urinary tract, respiratory system, and circulatory system resulting from exposure to devices

such as Foley catheters, ventilators, and intravascular lines can be illustrated as device-associated risks according to site, as follows:

$$\begin{aligned} & \text{(Number of device-associated infections of a site/} \\ & \quad \text{Number of device days)} \times 1,000 \end{aligned}$$

Reporting

One use of surveillance data is to generate information for individual surgeons, service chiefs, and nursing personnel as an indicator of their progress in keeping infections and diseases under control. Infection notification to surgeons has been shown to have a positive influence on clean-wound infection rates.^{6,7} This technique was used by Cruse and Foord in 1980 to show a progressive decrease in the infection rates of clean surgical wounds to less than 1% over 10 years.⁷ In other settings, endemic rates of bloodstream, respiratory, and urinary tract infection were corrected and reduced by routine monitoring and reporting to medical and nursing staff.²⁴

In a medical setting, Britt and colleagues also reported a reduction in endemic nosocomial infection rates for urinary tract infections, from 3.7% to 1.3%, and for respiratory tract infections, from 4.0% to 1.6%, simply by keeping medical personnel aware of the rates.²⁴

Outbreak Investigation

There are 10 essential components to an outbreak investigation:

1. Verify the diagnosis and confirm that an outbreak exists. This is an important step, because other factors may account for an apparent increase in infections. These factors may include a reporting artifact resulting from a change in surveillance methodology, a laboratory error or change in laboratory methodology, or an increase in the denominator of the formula used for data analysis (if this increase is proportionate to the rise in the numerator, the infection rate has not changed).
2. Formulate a case definition to guide the search for potential patients with disease.
3. Draw an epidemic curve that plots cases of the disease against time of onset of illness. This curve compares the number of cases during the epidemic period with the baseline. In addition, the epidemic curve helps to determine the probable incubation period and how the disease is being transmitted (i.e., a common source versus person to person).
4. Review the charts of case patients to determine demographics and exposures to staff, medications, therapeutic modalities, and other variables of importance.
5. Perform a line listing of case patients to determine whether there is any common exposure.
6. Calculate the infection rate. The numerator is the number of infected patients, and the denominator is the number of patients at risk.
7. Formulate a tentative hypothesis to explain the reservoir and the mode of transmission. A review of the literature on similar outbreaks may be necessary.
8. Test the hypothesis, using a case-control study, cohort study, prospective intervention study, or microbiologic study. A case-control study is usually used, because it is less labor intensive. For a case-control study, control

subjects should be selected from an uninfected surgical population of patients who were hospitalized at the same time as those identified during the epidemic period and matched for age, gender, service operation, operation date, and health status (ASA score). Two or three control patients are usually selected for every case patient. The cases and controls are then compared with respect to possible exposures that may increase the risk of disease. Patient, personnel, and environmental microbiologic isolates (if any) should be kept for fingerprinting (e.g., with pulsed-field gel electrophoresis or random amplified polymorphic DNA polymerase chain reaction).

9. Institute infection control measures. This may be done at any time during the investigation. The control measures should be reviewed after institution to determine their efficacy and the possible need for changing them.
10. Report the incident to the infection control committee, and submit a report at the completion of the investigation. The administrators, physicians, and nurses involved should be informed and updated as events change.⁶⁹

ANTIMICROBIAL-RESISTANT MICROORGANISMS

Staphylococci

Hospitals and communities worldwide are facing the challenge posed by the spread of antimicrobial-resistant microorganisms. Strains of MRSA are increasing in hospitals and are an important cause of nosocomial infections; in a sample of intensive care units in the United States in 2003, approximately 59.5% of *S. aureus* isolates were resistant to methicillin or oxacillin.²⁸ MRSA strains not only replace methicillin-susceptible strains as a cause of hospital-acquired infections but also actually increase the total burden of nosocomial infections.⁷⁰ Moreover, there are reports that MRSA is becoming a community-acquired pathogen.^{71,72} A population-based surveillance of invasive MRSA infections in the United States performed from July 2004 to December 2005 determined that 85% were healthcare associated and 14% were community associated; 1% could not be classified.⁷² A proactive approach to controlling MRSA at all levels of health care can result in decreased MRSA infection rates.^{73,74}

Strains of GISA, an emerging pathogen first isolated in 1996 in Japan,⁷⁵ exhibit reduced susceptibility to vancomycin and teicoplanin. DNA fingerprinting suggests that these GISA strains evolved from preexisting MRSA strains that infected patients in the months before the GISA infection. Contact precautions are indicated for patients infected or colonized with GISA; infection control guidelines to prevent the spread of GISA are available.⁷⁶

Enterococci

Vancomycin-resistant *Enterococcus* (VRE) accounts for 38.2% of all enterococci in the ICUs participating in the NNIS program.²⁸ Transmission usually occurs through contact with the contaminated hands of a health care worker. The environment is an important reservoir for VRE, but it is not clear whether the environment plays a significant role in transmission.⁷⁷ Risk factors for VRE acquisition include a prolonged hospital stay, liver transplantation, the presence of feeding tubes, dialysis, and exposure to cephalosporins.⁷⁸ Contact precautions are indicated for patients infected or colonized with VRE.^{76,79}

Strategies for preventing and controlling the emergence and spread of antimicrobial-resistant microorganisms have been developed (<http://www.cdc.gov/ncidod/dhqp/pdf/ar/mdroGuideline2006.pdf>). These guidelines include optimizing antimicrobial prophylaxis for surgical procedures; optimizing the choice and duration of empirical therapy; improving antimicrobial prescribing patterns by physicians; monitoring and providing feedback regarding antibiotic resistance; formulating and using practice guidelines for antibiotic usage; developing a system to detect and report trends in antimicrobial resistance; ensuring that caregivers respond rapidly to the detection of antimicrobial resistance in individual patients; incorporating the importance of controlling antimicrobial resistance into the institutional mission and climate; increasing compliance with basic infection control policies and procedures; and developing a plan for identifying, transferring, discharging, and readmitting patients colonized or infected with specific antimicrobial-resistant microorganisms.⁷⁶

Clostridium difficile

C. difficile is recognized as the leading cause of nosocomial infectious diarrhea.⁸⁰ The best-described *C. difficile* virulence factors are toxins A and B.⁸¹ The most important risk factor for *C. difficile*-associated infection (CDI) is previous antibiotic use.⁸⁰ After exposure to *C. difficile*, some patients remain asymptomatic, whereas others experience illnesses ranging from mild diarrhea to fulminant colitis.⁸⁰ The incidence of severe disease leading to death, colectomy, or the need for intensive care is usually no more than 1 to 5%.

In the past few years, CDI outbreaks characterized by increased morbidity and mortality have been reported in the United States, Canada, and Europe. These outbreaks have been attributed to the emergence of a hypervirulent strain of *C. difficile*, which is now referred to as the North American pulsed-field type 1 (NAP1) or PCR ribotype 027.^{82–84} Compared with control strains, the NAP1 strain produces 16-fold greater quantities of toxin A and 23-fold greater quantities of toxin B.⁸⁵

For control of CDI outbreaks, a multifaceted approach is required, including close attention to hand hygiene, use of contact precautions when providing care to CDI patients, environmental disinfection, antibiotic restriction, and rapid laboratory diagnosis.⁸⁶

ENVIRONMENTAL CONTROL

Control of the microbial reservoir of the patient's immediate environment in the hospital is the goal of an infection control program. Environmental control begins with design of the hospital's physical plant. The design must meet the functional standards for patient care and must be integrated into the architecture to provide traffic accessibility and control. Since the 1960s, the practice of centralizing seriously ill patients in intensive care, dialysis, and transplant units has accentuated the need for more careful analysis and planning of space. The primary standards for these special care units and ORs require planning of floor space, physical surfaces, lighting, ventilation, water, and sanitation to facilitate easy cleaning and disinfecting of surfaces, sterilization of instruments, proper food handling, and garbage disposal. These activities should then be governed by practical policies that

are understandable to the staff. Preventive maintenance should be a basic and integral activity of the physical plant department.

Surveillance of the environment by routine culturing of OR floors and walls was discontinued in the late 1970s. Autoclaves and sterilization systems should, however, be continuously monitored with quality control indicators. The results should be documented and records maintained.

Investigations of the physical plant should be reserved for specific outbreaks, depending on the organism and its potential for causing infection. This was demonstrated by an outbreak of sternal wound *Legionella* infections among post-cardiovascular surgery patients after they were exposed to tap water during bathing.⁸⁷ The CDC provides guidelines for infection control issues related to the environment.^{88,89}

Hospital-acquired aspergillosis is caused by another ubiquitous microorganism that is often a contaminant of ambient air during construction. The patients most at risk are usually immunosuppressed (i.e., neutropenic). It is recommended that preventive measures be instituted for these patients when construction is being planned.⁹⁰ The provision of clean (i.e., HEPA-filtered) air in positive pressure-ventilated rooms, with a minimum of 12 air exchanges per hour, is the basic requirement for these patients.⁴⁷

A comprehensive review of environmental infection control in health care facilities is available at the CDC Web site (http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/Enviro_guide_03.pdf). This review contains recommendations for preventing nosocomial infections associated with construction, demolition, and renovation.⁸⁹

EDUCATION

A strategy for routine training of the health care team is necessary at every professional level. The process may vary from institution to institution, but some form of communication should be established for the dissemination of information about the following:

1. Endemic infection rates.
2. Endemic bacterial trends.
3. Updates on infection prevention measures (especially during and after an outbreak).
4. Updates on preventive policies pertaining to hand hygiene, isolation precautions, and other areas of concern.

Although members of the infection control team are the responsible resource persons in the hospital system, each member of the health care team also has a responsibility to help prevent infection in hospitalized patients.

PUBLIC HEALTH AND COMMUNITY HEALTH SERVICE

According to existing public health acts, certain infectious diseases must be reported by law. Differences exist between the reporting systems of one country and those of another, but on the whole, diseases such as tuberculosis, sexually transmitted diseases, and meningococcal meningitis are reported for community follow-up.

Open communication with community hospitals and other health care facilities provides for better management of patients with infections, allowing for notification and planning for additional hospitalization or convalescence as the patient moves to and from the community and hospital.

Benefits of an Infection Control Program

The establishment of an infection control program can greatly benefit a hospital. An infection control program supports patient safety and is a means for continuous quality improvement in the care that is given, in addition to being an accreditation requirement. In Canada and the United States, the need for infection control programs is supported by all governing agents, including the Canadian Council on Hospital Accreditation, JCAHO, the American Hospital Association (AHA), the Canadian Hospital Association, the Association for Practitioners in Infection Control (APIC), the Society of Hospital Epidemiologists of America (SHEA) Joint Commission Task Force, and the Community and Hospital Infection Control Association-Canada (CHICA-Canada).

The effectiveness of infection surveillance and control programs in preventing nosocomial infections in US hospitals was assessed through the SENIC Project.⁹¹ In a representative sample of US general hospitals, infection control programs with a trained infection control physician or microbiologist and at least one infection control nurse per 250 beds were associated with a 32% lower rate of four infections studied (central venous catheter-associated bloodstream infections, ventilator-associated pneumonias, catheter-related urinary tract infections, and SSIs).

Reductions in nosocomial infections have a substantial impact on morbidity, mortality, length of stay, and cost.⁹² In one study, for example, the extra costs associated with treating bloodstream infections in an intensive care setting were estimated to be \$40,000 per survivor.⁹³ Accomplishing a high-quality infection control program requires organization and the dedicated service of all health care employees.

Organization of an Infection Control Program

INFECTION CONTROL COMMITTEE

The chair of the infection control committee should have an ongoing interest in the prevention and control of infections. Members should represent administration, infectious diseases, microbiology, nursing, the OR, central supply, medicine, surgery, pharmacy, and housekeeping. This multidisciplinary group becomes the advocate for the entire hospital. The members work with the infection control service to make decisions in the following areas: (1) assessing the effectiveness and pertinence of infection control policies and protocols in their areas and (2) raising infection control-related concerns.

INFECTION CONTROL SERVICE

Collecting surveillance data on nosocomial infections and taking actions to decrease nosocomial infections are the principal functions of the infection control service. This service usually consists of a trained hospital epidemiologist, infection control practitioners (ICPs), and secretarial and informatics support. The scope of the ICPs' responsibilities has expanded in keeping with the increasing complexity of health care. It is currently recommended that there be 0.8 to 1.0 ICP for every 100 occupied acute care beds.⁹⁴ Training programs to assist with the professional and organizational development of ICPs are available through SHEA (<http://www.shea-online.org>),

APIC (<http://www.apic.org>), and CHICA-Canada (<http://www.chica.org>), and the APIC certification program supports continuous professional improvement. A viable and useful program for surveillance requires a computer database program networked to microbiology, the OR, and

nursing units. Methods for collecting, editing, storing, and sharing data should be based on the CDC's NSHN system, which promotes the use of high-quality indicators for future monitoring and comparison among health care institutions.²⁸

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3 PERIOPERATIVE CONSIDERATIONS FOR ANESTHESIA

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Advancements in modern surgical care are complemented by alterations in anesthetic management to provide maximum patient benefit. During the last two decades, anesthesia practice has changed enormously—with the proliferation of airway devices; the routine employment of patient-controlled analgesia; the wider popularity of regional anesthesia, including thoracic epidural anesthesia and peripheral nerve blocks; the development of computer-controlled devices for infusing short-acting drugs; the discovery and use of quickly reversible inhalational drugs, opiates, and muscle relaxants; the availability of online monitoring of central nervous system (CNS) function; and the increased application of transesophageal echocardiography, to name but a few examples. Our aim in this chapter is to offer surgeons a current perspective on perioperative considerations for anesthesia to facilitate dialogue between the surgeon and the anesthesiologist and thereby ensure optimum care for our patients. The primary focus is on the adult patient: the special issues concerning pediatric anesthesia are beyond the scope of our review. In addition, the ensuing discussion is necessarily selective; more comprehensive discussions may be found elsewhere.^{1,2}

Perioperative Patient Management

Preoperative medical evaluation is an essential component of preoperative assessment for anesthesia. Of particular importance to the anesthesiologist is any history of personal or family problems with anesthesia. Information should be sought concerning difficulty with airway management or intubation, drug allergy, delayed awakening, significant postoperative nausea and vomiting (PONV), unexpected hospital or intensive care unit (ICU) admission, and post-dural puncture headache (PDPH). Previous anesthetic records may be requested.

The airway must be carefully examined to identify patients at risk for difficult ventilation or intubation [*see Special Scenarios, Difficult Airway, below*], with particular attention paid to teeth, caps, crowns, dentures, and bridges. Patients must be informed about the risk of trauma associated with intubation and airway management. Anesthetic options [*see Choice of Anesthesia, below*] should be discussed, including the likelihood of postoperative ventilation and admission to the hospital or ICU. When relevant, the possibility of blood product administration should be raised [*see 1:4 Bleeding and Transfusion*], and the patient's acceptance or refusal of transfusion should be carefully documented. Postoperative pain management [*see 1:6 Postoperative Pain*] should be addressed, particularly when a major procedure is planned. The risks

associated with general or regional anesthesia (see below) should be discussed in an informative and reassuring manner; a well-conducted preoperative anesthesia interview plays an important role in alleviating anxiety.

The medications the patient is taking can have a substantial impact on anesthetic management. Generally, patients should continue to take their regular medication up to the time of the operation. It is especially important not to abruptly discontinue medications that may result in withdrawal or rebound phenomena (e.g., beta blockers, alpha antagonists, barbiturates, and opioids). With some medications (e.g., oral hypoglycemics, insulin, and corticosteroids), perioperative dosage adjustments may be necessary [*see 8:10 Endocrine Problems*]. Angiotensin-converting enzyme inhibitors have been associated with intraoperative hypotension and may be withheld at the discretion of the anesthesiologist.³ Drugs that should be discontinued preoperatively include monoamine oxidase inhibitors (MAOIs) and oral anticoagulants [*see Table 1*].

Many surgical patients are taking antiplatelet drugs. Careful consideration should be given to the withdrawal of these agents in the perioperative period [*see Table 1*] because of the possibility that discontinuance may lead to an acute coronary syndrome. Patients with recently placed coronary artery drug-eluting stents (< 1 year) may be at particular risk, so elective surgery should be postponed.⁴ If surgery is necessary, and patients are deemed to be at increased risk for medication-related bleeding during surgery, the longer-acting agents (e.g., aspirin, clopidogrel, and ticlopidine) can be replaced with nonsteroidal antiinflammatory drugs (NSAIDs) that have shorter half-lives. Typically, these shorter-acting drugs are given for 10 days, stopped on the day of surgery, and then restarted 6 hours after operation. Platelet transfusion can be considered if there is a very high potential for significant bleeding.⁵

The increasing use of herbal and alternative medicines has led to significant morbidity and mortality as a consequence of unexpected interactions with traditional drugs. Because many patients fail to mention such agents as part of their medication regimen during the preoperative assessment, it is advisable to question all patients directly about their use. Particular attention should be given to Chinese herbal teas, which include organic compounds and toxic contaminants that may produce renal fibrosis or failure, cholestasis, hepatitis, and thrombocytopenia. Specific recommendations exist for the discontinuance of many of these agents [*see Table 1*].

Prophylactic administration of perioperative beta blockers in patients with or at risk for atherosclerotic disease undergoing noncardiac surgery is controversial and merits specific

Table 1 Recommendations for Preoperative Discontinuance of Drugs and Medicine^{68–81}

Type of Drug	Agent	Pharmacologic Effects	Adverse Effects	Discontinuance Recommendations
MAOIs	Isocarboxazid Phenelzine Pargyline Tranylcypromine Selegiline	Irreversible inhibition of monoamine oxidase with the resultant increase in serotonin, norepinephrine, epinephrine, dopamine, and octamine neurotransmitters	Potential of sympathomimetic amines, possible hypertensive crisis May prolong and intensify effects of other CNS depressants Severe idiopathic hyperpyrexia reaction with meperidine and possibly other narcotics Potential catastrophic interaction with tricyclic antidepressants, characterized by high fever and excessive cerebral excitation and hypertension	Elective surgery: discontinue at least 2 wk in advance; consider potential for suicidal tendency—mental health specialist should be involved Emergency surgery: avoid meperidine; consider regional anesthesia
Oral anticoagulants	Warfarin	Inhibition of vitamin K–dependent clotting factors II, VII, IX, X	Bleeding	Elective surgery: discontinue 5–7 days in advance; replace with heparin if necessary
	Aspirin and NSAIDs Aspirin Fenoprofen Ibuprofen Sodium meclofenamate Tolmetin Indomethacin Ketoprofen Diflunisal Naproxen Sulindac Piroxicam	Inhibition of thromboxane A ₂ 80% of platelets must be inhibited for therapeutic effect Susceptibility to aspirin varies between patients	May increase intraoperative and postoperative bleeding but not transfusion requirement Perioperative hemorrhagic complications increase with increasing half-life of drug	Primary hemostasis normalizes in 48 hr in healthy persons; platelet activity fully recovered in 8–10 days Patients on long-term aspirin therapy for coronary or cerebrovascular pathology should not discontinue drug in perioperative period unless hemorrhagic complications of procedure outweigh risk of acute thrombotic event
Antiplatelet agents	Thienopyridines Ticlopidine Clopidogrel	Inhibition of platelet aggregation Inhibition of platelet ADP-induced amplification	Synergistic antithrombotic effect with aspirin	Discontinue ticlopidine 2 wk in advance; discontinue clopidogrel 7–10 days in advance Patients with coronary artery stents may receive aspirin plus ticlopidine for prolonged period after angioplasty; stopping therapy considerably increases risk of coronary thrombosis; elective surgery should be delayed for 1–3 mo
	Antiglycoprotein agents Eptifibatide Tirofiban Abciximab	Competitive inhibition of GPIIb/IIIa receptors to prevent platelet aggregation Rapid onset of action Short half-lives Often combined with aspirin and/or heparin	Literature (mainly from cardiac surgery) shows increased hemorrhagic risk if surgery undertaken < 12 hr after discontinuance of abciximab Individual variability in recovery time of platelet function	Discontinue at least 12 hr in advance Transfuse platelets only if needed to correct clinically significant bleeding
Herbal medicines	Chaparral	Used as an alternative anticancer agent This herbal agent should be considered as dangerous	Hepatotoxicity	As soon as possible
	Coltsfoot	Used as an antitussive and demulcent agent Considered dangerous	Carcinogenic	As soon as possible
	Comfrey	Used as a general healing agent Considered dangerous	Hepatotoxicity, liver failure	As soon as possible
	Ephedra/ma huang (<i>Ephedra sinica</i>)	Noncatecholamine sympathomimetic agent with α_1 , β_1 , and β_2 activity; both direct and indirect release of endogenous catecholamines	Dose-dependent increase in HR and BP, with potential for serious cardiac and CNS complications Possible adverse drug reactions: MAOIs (life-threatening hypertension, hyperpyrexia, coma), oxytocin (hypertension), digoxin and volatile anesthetics (dysrhythmias), guanethedine (hypertension, tachycardia)	Discontinue at least 24 hr in advance

Table 1 Continued

Type of Drug	Agent	Pharmacologic Effects	Adverse Effects	Discontinuance Recommendations
Herbal medicines	Echinacea (<i>Echinacea purpurea</i>)	Immunostimulatory effect	Hepatotoxicity Allergic potential	Discontinue as far in advance as possible in any patient with hepatic dysfunction or surgery with possible hepatic blood flow compromise
	Feverfew		May increase bleeding especially in patients already on anticlotting medications	At least 7 days
	Garlic (<i>Allium sativum</i>)	Irreversible dose-dependent inhibition of platelet aggregation	Increased bleeding may potentiate other platelet inhibitors	Discontinue at least 7 days in advance
	Germander	Choleretic, antiseptic properties Used in weight control Considered dangerous	Hepatotoxicity	As soon as possible
	Ginkgo (<i>Ginkgo biloba</i>)	Inhibition of platelet-activating factor Modulation of neurotransmitter receptor activity	Increased bleeding May potentiate other platelet inhibitors	Discontinue at least 36 hr in advance
	Ginger (<i>Zingiber officinale</i>)	Potent inhibitor of thromboxane synthase	Increased bleeding May potentiate effects of other anticoagulants	Discontinue at least 36 hr in advance
	Ginseng (<i>Panax ginseng</i>)	Inhibition of platelet aggregation, possibly irreversibly Antioxidant action Antihyperglycemic action “Steroid hormone”-like activity	Prolonged PT and PTT Hypoglycemia Reduced anticoagulation effect of warfarin Possible additive effect with other stimulants, with resultant hypertension and tachycardia	Discontinue at least 7 days in advance
	Goldenseal		May worsen swelling and/or high BP	At least 7 days
	Kava (<i>Piper methysticum</i>)	Dose-dependent potentiation of GABA-inhibitory neurotransmitter with sedative, anxiolytic, and antiepileptic effects	Potential of sedative anesthetics, including barbiturates and benzodiazepines Possible potentiation of ethanol effects	
	Licorice (<i>Glycyrrhiza glabra</i>)		Hypertension Hypokalemia Edema Contraindicated in chronic liver and renal insufficiency	
	Lobelia	Used as an antinausea and mild expectorant Considered dangerous	Respiratory depression, tachycardia, hypotension, hallucinations, coma, death	As soon as possible
	Sassafras	Stimulant, antispasmodic Considered dangerous	Carcinogenic	As soon as possible
	Saw palmetto		May interfere with other hormone therapies	At least 7 days
	St. John's wort (<i>Hypericum perforatum</i>)	Inhibits reuptake of serotonin, norepinephrine, and dopamine by neurons Increases metabolism of some P-450 isoforms	Possible interaction with MAOIs Evidence for reduced activity of cyclosporine, warfarin, calcium channel blockers, lidocaine, midazolam, alfentanil, and NSAIDs	Discontinue on day of surgery; abrupt withdrawal in physically dependent patients may produce benzodiazepine-like withdrawal syndrome
	Valerian (<i>Valeriana officinalis</i>)	Dose-dependent modulation of GABA neurotransmitter and receptor function	Possible potentiation of sedative anesthetics, including barbiturates and benzodiazepines	Discontinue at least 24 hr in advance
	Vitamin E		May increase bleeding, especially in patients taking anticlotting agents May affect thyroid function in otherwise healthy patients In doses greater than 400 IU per day, further increase in BP may be seen in already hypertensive patients	
	Yohimbe	Aphrodisiac, sexual stimulant Considered dangerous	Hypertension, tachycardia, paralysis, death	As soon as possible

ADP = adenosine diphosphate; BP = blood pressure; CNS = central nervous system; GABA = β -aminobutyric acid; GP = glycoprotein; HR = heart rate; MAOIs = monoamine oxidase inhibitors; NSAIDs = nonsteroidal antiinflammatory drugs; PT = prothrombin time; PTT = partial thromboplastin time.

consideration. Although a subgroup of patients may benefit from such treatment with respect to decreased cardiac morbidity, overall, an increased risk of death, stroke, and clinically significant hypotension and bradycardia has been reported.⁶ As such, it is anticipated that guidelines regarding the role for beta blockers in the perioperative setting will continue to evolve.⁷

Inpatient versus Outpatient Surgery

An ever-increasing number of operations are performed on an ambulatory basis [see *ECP:5 Patient Safety in Surgical Care: A Systems Approach*]. Operations considered appropriate for an ambulatory setting are associated with minimal physiologic trespass, low anesthetic complexity, and uncomplicated recovery.^{8,9} The design of the ambulatory facility may impose limitations on the types of operations or patients that can be considered for ambulatory surgery. Such limitations may be secondary to availability of equipment, recovery room nursing expertise and access to consultants, and availability of ICU or hospital beds. Patients who are in class I or class II of the American Society of Anesthesiologists (ASA) physical status scale are ideally suited for ambulatory surgery; however, a subset of ASA class III patients may be at increased risk for prolonged recovery and hospital admission [see *Table 2*].

Premedication to produce anxiolysis, sedation, analgesia, amnesia, and reduction in PONV and aspiration may be considered for patients undergoing outpatient procedures, as it may for those undergoing inpatient procedures. Such premedication should not delay discharge. Fasting guidelines [see *Table 3*] and intraoperative monitoring standards for ambulatory surgery are identical to those for inpatient procedures [see *Patient Monitoring, below*].

A number of currently used anesthetics (e.g., propofol, sevoflurane, desflurane), narcotics (e.g., alfentanil, fentanyl, sufentanil, and remifentanyl), and muscle relaxants (e.g., succinylcholine, atracurium, mivacurium, and rocuronium) demonstrate rapid recovery profiles. Nitrous oxide also has desirable pharmacokinetic properties, but it may be associated with increased PONV. Titration of anesthetics to indices of CNS activity (e.g., the bispectral index) may result in decreased drug dosages, faster recovery from anesthesia, and fewer complications.^{10,11} Multimodal analgesia (involving the use of local anesthetics, ketamine, α_2 -adrenergic agonists, beta blockers, acetaminophen, or NSAIDs) may reduce

Table 3 Fasting Recommendations* to Reduce Risk of Pulmonary Aspiration⁸³

Ingested Material	Minimum Fasting Period [†] (hr)
Clear liquids [‡]	2
Breast milk	4
Infant formula	6
Nonhuman milk [§]	6
Light meal	8

*These recommendations apply to healthy patients undergoing elective procedures; they are not intended for women in labor. Following the guidelines does not guarantee complete gastric emptying.

[†]These fasting periods apply to all ages.

[‡]Examples of clear liquids include water, fruit juices without pulp, carbonated beverages, clear tea, and black coffee.

[§]Because nonhuman milk is similar to solids in gastric emptying time, the amount ingested must be considered in determining the appropriate fasting period.

^{||}A light meal typically consists of toast and clear liquids. Meals that include fried or fatty foods or meat may prolong gastric emptying time. Both the amount and type of foods ingested must be considered in determining the appropriate fasting period.

intraoperative and postoperative opioid requirements and accelerate patient discharge. Use of a laryngeal mask airway rather than an endotracheal tube is ideal in the outpatient setting because lower doses of induction agent are required to blunt the hypertension and tachycardia associated with its insertion; in addition, it is associated with a decreased incidence of sore throat and does not require muscle paralysis for insertion. On the other hand, a laryngeal mask airway may not protect against aspiration.^{12,13}

The benefits of regional anesthesia [see *Regional Anesthesia Techniques, below*] may include decreases in the incidence of aspiration, nausea, dizziness, and disorientation. Spinal and epidural anesthesia may be associated with headache (dural puncture) and backache. Compared with spinal anesthesia, epidural anesthesia takes more time to perform, has a slower onset of action, and may not produce as profound a block; however, the duration of an epidural block can readily be extended intraoperatively or postoperatively if necessary. Care should be exercised in choosing a local anesthetic for neuraxial blockade: spinal lidocaine may be associated with a transient radicular irritation, and bupivacaine may be associated with prolonged motor block; narcotics may produce pruritus, urinary retention, nausea and vomiting, and respiratory depression. Various dosing regimens, including minidose spinal techniques, have been proposed as means of minimizing these side effects.¹⁴⁻¹⁷

Monitored anesthesia care [see *Choice of Anesthesia, below*] achieves minimal CNS depression, so the airway and spontaneous ventilation are maintained and the patient is able to respond to verbal commands. Meticulous attention to monitoring is required to guard against airway obstruction, arterial desaturation, and pulmonary aspiration.

In the recovery room, the anesthetic plan is continued until discharge. Shorter-acting narcotics and NSAIDs are administered for pain relief, and any of several agents may be given for control of nausea and vomiting. Criteria for discharge from the recovery room have been established [see *Table 4*]. Recovery of normal muscle strength and sensation (including proprioception of the lower extremity, autonomic function, and ability to void) should be demonstrated after spinal or epidural anesthesia. Delays in discharge are usually the result

Table 2 Association between Preexisting Medical Conditions and Adverse Outcomes⁸²

Medical Condition	Associated Adverse Outcome
Congestive heart failure	12% prolongation of postoperative stay
Hypertension	Twofold increase in risk of intraoperative cardiovascular events
Asthma	Fivefold increase in risk of postoperative respiratory events
Smoking	Fourfold increase in risk of postoperative respiratory events
Obesity	Fourfold increase in risk of intraoperative and postoperative respiratory events
Reflux	Eightfold increase in risk of intubation-related adverse events

Table 4 Postanesthetic Discharge Scoring System (PADSS)⁸⁴

Category	Score*	Explanation
Vital signs	2	Within 20% of preoperative value
	1	Within 20 to 40% of preoperative value
	0	Within 40% of preoperative value
Activity, mental status	2	Oriented and steady gait
	1	Oriented or steady gait
	0	Neither
Pain, nausea, vomiting	2	Minimal
	1	Moderate
	0	Severe
Surgical bleeding	2	Minimal
	1	Moderate
	0	Severe
Intake/output	2	Oral fluid intake and voiding
	1	Oral fluid intake or voiding
	0	Neither

*Total possible score is 10; patients scoring ≥ 9 are considered fit for discharge home.

of pain, PONV, hypotension, dizziness, unsteady gait, or lack of an escort.¹⁸

Elective versus Emergency Surgery

Surgical procedures performed on an emergency basis may range from relatively low priority (e.g., a previously cancelled case that was originally elective) to highly urgent (e.g., a case of impending airway obstruction). For trauma, specific evaluation and resuscitation sequences have been established to facilitate patient management [see 7:1 *Initial Management of Life-Threatening Trauma*]. The urgency of the situation dictates how much time can be allotted to preoperative patient assessment and optimization. When it is not possible to communicate with the patient, information obtained from family members and paramedics may be crucial. Information should be sought concerning allergies, current medications, significant past medical illnesses, nihil per os (NPO) status, personal or family problems with anesthesia, and recent ingestion of alcohol or drugs. Any factor that may complicate airway management should be noted (e.g., trauma to the face or the neck, a beard, a short and thick neck, obesity, or a full stomach). When appropriate, blood samples should be obtained as soon as possible for typing and cross-matching, as well as routine blood chemistry, complete blood count, and toxin screen. Arrangements for postoperative ICU monitoring, if appropriate, should be instituted early.

Clear communication must be established between the surgical team and anesthesia personnel so that an appropriate anesthetic management plan can be formulated and any specialized equipment required can be mobilized in the operating room (OR). The induction of anesthesia may coincide with resuscitation. Accordingly, the surgical team must be immediately available to help with difficult intravenous (IV) access, emergency tracheostomy, and cardiopulmonary resuscitation. Patients in shock may not tolerate standard anesthetics, which characteristically blunt sympathetic outflow. The anesthetic dose must be judiciously titrated, and

definitive surgical treatment must not be unduly delayed by attempts to “get a line.”

Choice of Anesthesia

Anesthesia may be classified into three broad categories: (1) general anesthesia, (2) regional anesthesia, and (3) monitored anesthesia care. General anesthesia can be defined as a state of insensibility characterized by loss of consciousness, amnesia, analgesia, and muscle relaxation. This state may be achieved either with a single anesthetic or, in a more balanced fashion, with a combination of several drugs that specifically induce hypnosis, analgesia, amnesia, and paralysis.

There is, at present, no consensus as to which general anesthetic regimen best preserves organ function. General anesthesia is employed when contraindications to regional anesthesia are present or when regional anesthesia or monitored anesthesia care fails to provide adequate intraoperative analgesia. In addition, a few situations specifically mandate general anesthesia and controlled ventilation: the need for abdominal muscle paralysis, lung isolation, and hyperventilation; the presence of serious cardiorespiratory instability; and the lack of sufficient time to perform regional anesthesia. Alternatives to general anesthesia should be considered for patients who are susceptible to malignant hyperthermia (MH), for those in whom intubation is likely to prove difficult or the risk of aspiration is high, and for those with pulmonary compromise that may worsen after intubation and positive pressure ventilation.

Regional anesthesia is achieved by interfering with afferent or efferent neural signaling at the level either of the spinal cord (neuraxial blockade) or of the peripheral nerves. Neuraxial anesthesia (i.e., epidural or spinal administration of local anesthetics) is commonly employed as the sole anesthetic technique for procedures involving the lower abdomen and the lower extremities; it also provides effective pain relief after intraperitoneal and intrathoracic procedures. Combining regional and general anesthesia has become increasingly popular.¹⁹ Currently, some physicians are using neuraxial blockade as the sole anesthetic technique for procedures such as thoracotomy and coronary artery bypass grafting, which are traditionally thought to require general anesthesia and endotracheal intubation.²⁰

Neuraxial blockade has several advantages over general anesthesia, including better dynamic pain control, shorter duration of paralytic ileus, reduced risk of pulmonary complications, and decreased transfusion requirements; it is also associated with a decreased incidence of renal failure and myocardial infarction [see 1:6 *Postoperative Pain*].^{21–24} Contrary to conventional thinking, however, the type of anesthesia used (general or neuraxial) is not an independent risk factor for long-term cognitive dysfunction.²⁵ Neuraxial blockade is an essential component of multimodal rehabilitation programs aimed at optimization of perioperative care and acceleration of recovery [see ECP:3 *Perioperative Considerations for Anesthesia*].^{26,27}

For short, superficial procedures, a variety of peripheral nerve blocks may be considered.²⁸ With procedures on the upper or lower extremity, an IV regional (Bier) block with diluted lidocaine may be useful. Anesthesia of the upper extremity and shoulder may be achieved with the brachial plexus block. Anesthesia of the lower extremity may be

achieved by blocking the femoral, obturator, and lateral femoral cutaneous nerves (knee surgery) or the ankle and popliteal sciatic nerves (foot surgery). Anesthesia of the thorax may be achieved with intercostal or intrapleural nerve blocks. Anesthesia of the abdomen may be achieved with celiac plexus and paravertebral blocks. Anesthesia of the head and neck may be achieved by blocking the trigeminal, supraorbital, supratrochlear, infraorbital, and mental nerves and the cervical plexus. Local infiltration of the operative site may provide intraoperative and postoperative analgesia.

Unlike the data on neuraxial blockade, the data on peripheral nerve blockade neither support nor discourage its use as a substitute for general anesthesia. Generally, however, we favor regional techniques when appropriate: such approaches maintain consciousness and spontaneous breathing while causing only minimal depression of the CNS and the cardiorespiratory systems, and they yield improved pain control in the immediate postoperative period.

Monitored anesthesia care involves the use of IV drugs to reduce anxiety, provide analgesia, and alleviate the discomfort of immobilization. This approach may be combined with local infiltration analgesia provided by the surgeon.²⁹ Monitored anesthesia care requires monitoring of vital signs and the presence of an anesthesiologist who is prepared to convert to general anesthesia if necessary. Its benefits are substantially similar to those of regional anesthesia. These benefits are lost when attempts are made to overcome surgical pain with excessive doses of sedatives and analgesics.

Patient Monitoring

Patient monitoring is central to the practice of anesthesia. A trained, experienced physician is the only truly indispensable monitor; mechanical and electronic monitors, although useful, are, at most, aids to vigilance. Wherever anesthesia is administered, the proper equipment for pulse oximetry, blood pressure measurement, electrocardiography, and capnography should be available. At each anesthesia workstation, equipment for measuring temperature, a peripheral nerve stimulator, a stethoscope, and appropriate lighting must be immediately available. A spirometer must be available without undue delay.

Additional monitoring may be indicated, depending on the patient's health, the type of procedure to be performed, and the characteristics of the practice setting. Cardiovascular monitoring, including measurement of systemic arterial, central venous, pulmonary arterial, and wedge pressures; cardiac output; and continuous arterial and mixed venous oximetry, is covered in detail elsewhere [see 8:3 *Shock*]. Additional information about the cardiovascular system may be obtained by transesophageal echocardiography.³⁰ Practice guidelines for this technique have been developed.³¹ It may be particularly useful in patients who are undergoing valve repair or who have persistent severe hypotension of unknown etiology.

The effects of anesthesia on the CNS may be assessed by monitoring electroencephalographic (EEG) activity that is either spontaneous (raw or processed) or evoked (e.g., somatosensory, auditory, or visual). Commercially available devices that employ spectral analysis of spontaneous EEG activity (e.g., bispectral index) are relatively easy to use and

are advocated by some as measures of hypnosis to guide the administration of anesthetics.^{32,33} However, their effectiveness in preventing intraoperative awareness remains controversial, particularly when anesthesia is maintained by inhalational drugs.³⁴ CNS function may also be assessed by measurement of cerebral blood flow, using transcranial Doppler, jugular bulb venous oxygen saturation, and cerebral oximetry monitoring techniques. Although there is growing clinical experience with these noninvasive intraoperative neurologic monitors, randomized, prospective, and adequately powered studies to support and guide their use are currently lacking.

General Anesthesia Techniques

An ever-expanding armamentarium of drugs is available for premedication and for induction and maintenance of anesthesia. Selection of one agent over another is influenced by the patient's baseline condition, procedure, local standard of practice, and predicted duration of hospitalization.

PREMEDICATION

Preoperative medications are given primarily to decrease anxiety, to reduce the incidence of nausea and vomiting, and to prevent aspiration. Other benefits include sedation, amnesia, analgesia, drying of oral secretions, and blunting of undesirable autonomic reflexes.

Sedatives and Analgesics

Benzodiazepines produce anxiolysis, sedation, hypnosis, amnesia, and muscle relaxation; they do not produce analgesia. They may be classified as short acting (midazolam), intermediate acting (lorazepam), or long acting (diazepam). Adverse effects [see Table 5] may be marked in debilitated patients. Their central effects may be antagonized with flumazenil.

Muscarinic antagonists (e.g., scopolamine and atropine) were commonly administered at one time; this practice is not as popular today. They produce, to varying degrees, sedation, amnesia, lowered anesthetic requirements, diminished nausea and vomiting, reduced oral secretions, and decreased gastric hydrogen ion secretion. They blunt the cardiac parasympathetic reflex responses that may occur during certain procedures (e.g., ocular surgery, traction on the mesentery, and manipulation of the carotid body). Adverse effects include

Table 5 Benzodiazepines: Doses and Duration of Action⁸⁵

Benzodiazepine	Dose (for Sedation)	Elimination Half-Life	Comments
Midazolam	0.5–1.0 mg, repeated	1.7–2.6 hr	Respiratory depression, excessive sedation, hypotension, bradycardia, anticonvulsant activity (withdrawal)
Lorazepam	0.25 mg, repeated	11–22 hr	See midazolam Venous thrombosis
Diazepam	2.0 mg, repeated	20–50 hr	See midazolam and lorazepam

tachycardia, heat intolerance, inhibition of gastrointestinal (GI) motility and micturition, and mydriasis.

Opioids are used when analgesia, in addition to sedation and anxiolysis, is required. With morphine and meperidine, the time of onset of action and the peak effect are unpredictable. Synthetic opioids (e.g., fentanyl) have a more rapid onset and a predictable time course, which make them more suitable for premedication immediately before surgery. Adverse effects [see Table 6] can be reversed with full (naloxone) or partial (nalbuphine) antagonists.

The α_2 -adrenergic agonists clonidine and dexmedetomidine are sympatholytic drugs that also exert sedative, anxiolytic, and analgesic effects. They reduce intraoperative anesthetic requirements, thus allowing faster recovery, and attenuate sympathetic activation secondary to intubation and surgery, thus improving intraoperative hemodynamic stability. Major drawbacks are hypotension and bradycardia; rebound hypertensive crises may be precipitated by their discontinuance.^{35,36}

Prevention of Aspiration

Aspiration of gastric contents is an extremely serious complication that is associated with significant morbidity and mortality. Fasting helps reduce the risk of this complication [see Table 3]. When the likelihood of aspiration is high,

pharmacologic treatment may be helpful [see Table 7]. H_2 receptor antagonists (e.g., cimetidine, ranitidine, and famotidine) and proton pump inhibitors (e.g., omeprazole) reduce gastric acid secretion, thereby raising gastric pH without affecting gastric volume or emptying time. Nonparticulate antacids (e.g., sodium citrate) neutralize the acidity of gastric contents. Metoclopramide promotes gastric emptying (by stimulating propulsive GI motility) and decreases reflux (by increasing the tone of the esophagogastric sphincter); it may also possess antiemetic properties.

In all patients at risk for aspiration who require general anesthesia, a rapid sequence induction is traditionally considered a standard of practice, although this has been recently questioned.³⁷ A rapid sequence induction is achieved through adequate preoxygenation, administration of drugs to produce rapid loss of consciousness and paralysis, and exertion of pressure on the cricoid cartilage (the Sellick maneuver) as loss of consciousness occurs to occlude the esophagus and so limit reflux of gastric contents into the pharynx. An alternative is the so-called modified rapid sequence induction, which permits gentle mask ventilation during the application of cricoid pressure (thereby potentially reducing or abolishing insufflation of gas into the stomach). The advantages of the modified approach are that there is less risk of hypoxia and more time to treat cardiovascular responses to induction

Table 6 Opioids: Doses and Duration of Action⁸⁶

Agent Induction	Relative Analgesic Potency Maintenance	Dose		Time to Peak Effect	Duration of Action	Comments
		Induction or Loading	Maintenance			
Morphine	1	1 mg/kg For perioperative analgesia: 0.1 mg/kg IV, IM	0.05–0.2 mg/kg/hr	5–20 min	2–7 hr	Respiratory depression, nausea, vomiting, pruritus, constipation, urinary retention, biliary spasm, neuroexcitation ± seizure, tolerance Cough suppression, relief of dyspnea-induced anxiety (common to all opioids) Histamine release, orthostatic hypotension, prolonged emergence
Meperidine	0.1	For perioperative analgesia: 0.5–1.5 mg/kg IV, IM, SC	NA	2 hr (oral); 1 hr (SC, IM)	2–4 hr	See morphine Orthostatic hypotension, myocardial depression, dry mouth, mild tachycardia, mydriasis, histamine release Attenuates shivering; to be avoided with MAOIs Local anesthetic-like effect
Remifentanyl	250–300	1 µg/kg	0.25–0.4 µg/kg/min	3–5 min	5–10 min	See morphine Awareness, bradycardia, muscle rigidity Ideal for infusion; fast recovery, no postoperative analgesia
Alfentanil	7.5–25	50–300 µg/kg	1.25–8.0 µg/kg/min	1–2 min	10–15 min	See morphine Awareness, bradycardia, muscle rigidity
Fentanyl	75–125	5–30 µg/kg	0.25–0.5 µg/kg/min	5–15 min	30–60 min	See morphine and alfentanil
Sufentanil	525–625	2–20 µg/kg	0.05–0.1 µg/kg/min	3–5 min	20–45 min	See morphine and alfentanil Ideal for prolonged infusion

IM = intramuscular; IV = intravenous; MAOI = monoamine oxidase inhibitor; NA = not applicable; SC = subcutaneous.

Table 7 Pharmacologic Prevention of Aspiration^{87,88}

Agent	Dose	Timing of Administration before Operation	Comments
H ₂ receptor antagonists Cimetidine Ranitidine Famotidine	300 mg, PO 50 mg IV 20 mg IV	1–3 hr	Hypotension, bradycardia, heart block, increased airway resistance, CNS dysfunction, reduced hepatic metabolism of certain drugs Bradycardia Rare CNS dysfunction
Sodium citrate	30 mL PO	20–30 min	Increased gastric fluid volume
Omeprazole	40 mg IV	40 min	Possible alteration of GI drug absorption, hepatic metabolism
Metoclopramide	10 mg IV	15–30 min	Extrapyramidal reactions, agitation, restlessness (large doses); to be avoided with MAOIs, pheochromocytoma, bowel obstruction

CNS = central nervous system; GI = gastrointestinal; IV = intravenous; MAOI = monoamine oxidase inhibitor; PO = oral.

agents before intubation. Regardless of which technique is used, consideration should be given to emptying the stomach via an orogastric or nasogastric tube before induction.

INDUCTION

Induction of general anesthesia is achieved by administering drugs to produce unconsciousness. It is one of the most crucial and potentially dangerous moments for the patient during general anesthesia because of the precipitous depression of the cardiorespiratory systems and airway protective mechanisms. Various agents can be used for this purpose; the choice depends on the patient's baseline medical condition and fasting status, the state of the airway, the surgical procedure, and the expected length of the hospital stay. The agents most commonly employed for induction are propofol, sodium thiopental, ketamine, and etomidate [see Table 8]. The opioids alfentanil, fentanyl, sufentanil, and remifentanyl may also be used for this purpose; they are associated with a very stable hemodynamic profile during induction and surgery but only invariably produce unconsciousness [see Table 6].

Volatile agents [see Table 9] may be employed for induction of general anesthesia when maintenance of spontaneous ventilation is of paramount importance (e.g., with a difficult airway) or when bronchodilation is required (e.g., with severe

hyperreactive airway disease). Inhalation induction is also popular for ambulatory surgery when paralysis is not required. Sevoflurane is well suited for this application because it is not irritating on inhalation, as are most other volatile agents, and it produces rapid loss of consciousness. Sevoflurane has mostly replaced halothane as the agent of choice for inhalation induction because it is less likely to cause dysrhythmias and is not hepatotoxic.

MAINTENANCE

Balanced general anesthesia is produced with a variety of drugs to maintain unconsciousness, prevent recall, and provide analgesia. Various combinations of volatile and IV agents may be employed to achieve these goals. The volatile agents isoflurane, desflurane, and sevoflurane are commonly used for maintenance [see Table 9]. Nitrous oxide is a strong analgesic and a weak anesthetic agent that possesses favorable pharmacokinetic properties (fast onset, fast offset). Because of its relatively high blood:gas partition coefficient compared with nitrogen, nitrous oxide rapidly diffuses into and expands air-filled cavities. Thus, it should be avoided in situations in which expansion of such cavities is undesirable (e.g., pneumothorax, air embolism, bowel obstruction, and middle ear surgery). It cannot be used as the sole anesthetic agent unless

Table 8 Induction Agents: Doses and Duration of Action⁸⁸

Agent	Induction Dose (mg/kg)	Time to Peak Effect (s)	Duration of Action (min)	Comments
Propofol	1.0–2.5	90–100	5–10	Hypotension, apnea, antiemetic (low dose), sexual fantasies and hallucinations, convulsions ± seizures (rare), pain on injection, thrombophlebitis
Thiopental	2.5–4.5	60	5–8	Hypotension, apnea, emergence delirium, prolonged somnolence, anaphylactoid reaction, injection pain, hyperalgesia Anticonvulsant effect Contraindicated with porphyria
Ketamine	0.5–2	30	10–15	Analgesia; increased BP, HR, CO; lacrimation and salivation; bronchial dilatation; elevated ICP Dreaming, illusions, excitement Preservation of respiration (apnea possible with high doses)
Etomidate	0.2–0.6	60	4–10	Minor effects on BP, HR, CO Adrenocortical suppression, injection pain and thrombophlebitis, myoclonus, nausea and vomiting

BP = blood pressure; CO = cardiac output; HR = heart rate; ICP = intracranial pressure.

Table 9 Volatile Drugs^{89,90}

Agent	Oil/Gas Coefficient*	MAC† (atm)	Blood/Gas Coefficient‡	Rank Order (FA/FI)§
Halothane	224	0.0074	2.5	6
Enflurane	96.5	0.0168	1.8	5
Isoflurane	90.8	0.0115	1.4	4
Desflurane	18.7	0.060	0.45	2
Sevoflurane	47.2	0.0236	0.65	3
Nitrous oxide	1.4	1.04	0.47	1

FA/FI = alveolar concentration of gas/inspired concentration; MAC = minimum alveolar concentration to abolish purposeful movement in response to noxious stimulation in 50% of patients.

*Lipid solubility correlates closely with anesthetic potency (Meyer-Overton rule).

†Correlates closely with lipid solubility.

‡Relative affinity of an anesthetic for blood compared to gas at equilibrium. The larger the coefficient, the greater the affinity of the drug for blood and hence the greater the quantity of drug contained in the blood.

§Rise in alveolar anesthetic concentration toward the inspired concentration is most rapid with the least soluble drugs and slowest with the most soluble.

it is administered in a hyperbaric chamber; it is usually administered with at least 30% oxygen to prevent hypoxia. Nitrous oxide is commonly used in combination with other volatile agents. Potent volatile agents can trigger malignant hyperthermia in susceptible patients.

The IV drugs currently used to maintain general anesthesia, whether partially or entirely, feature a short, context-sensitive elimination half-life; thus, pharmacologically significant drug accumulation during prolonged infusion is avoided. Such agents (including propofol, midazolam, sufentanil, and remifentanyl) are typically administered via computer-controlled infusion pumps that use population-based pharmacokinetic data to establish stable plasma (and CNS effector site) concentrations. Because of the extremely rapid

hydrolysis of remifentanyl, its administration may be labor intensive, necessitating frequent administration of boluses and constant vigilance. Its short half-life also limits its usefulness as an analgesic in the postoperative period and may even contribute to acute opioid intolerance. To help circumvent these problems, various dosing regimens have been proposed in which the patient is switched from remifentanyl to a longer-acting narcotic.

NEUROMUSCULAR BLOCKADE

The reversible paralysis produced by neuromuscular blockade improves conditions for endotracheal intubation and facilitates surgery. Neuromuscular blocking agents are classified as either depolarizing (succinylcholine) or nondepolarizing (pancuronium, rocuronium, vecuronium, atracurium, cisatracurium, and mivacurium) and may be further differentiated on the basis of chemical structure and duration of action [see Table 10]. The blocking effect of nondepolarizing muscle relaxants is enhanced by volatile drugs, hypothermia, acidosis, certain antibiotics, magnesium sulfate, and local anesthetics and is reduced by phenytoin and carbamazepine. Patients with weakness secondary to neuromuscular disorders (e.g., myasthenia gravis and Eaton-Lambert syndrome) may be particularly sensitive to nondepolarizing muscle relaxants.

EMERGENCE

General anesthesia is terminated by cessation of drug administration, reversal of muscle paralysis, and extubation (or removal of an upper airway device). During this potentially dangerous period, close scrutiny of the patient is essential, and all OR personnel must coordinate their efforts to help ensure a smooth and safe emergence from general anesthesia. In this phase, patients may demonstrate hemodynamic instability, retching and vomiting, respiratory compromise (including laryngospasm), and, occasionally, uncooperative or aggressive behavior.³⁸

Table 10 Neuromuscular Blocking Agents: Doses and Duration of Action⁹¹

Agent	Dose (mg/kg)	Duration of Action (min)	Metabolism	Elimination	Comments
Succinylcholine chloride	0.7–2.5	5–10	Plasma cholinesterase	Renal < 2%, hepatic 0%	Fasciculations, elevation of serum potassium, increased ICP, bradycardia, MH trigger; prolonged effect in presence of atypical pseudocholinesterase
Pancuronium	0.04–0.1	60–120	Hepatic 10–20%	Renal 85%, hepatic 15%	Muscarinic antagonist (vagolytic), prolonged paralysis (long-term use)
Rocuronium	0.6–1.2	35–75	None	Renal < 10%, hepatic > 70%	Minimal histamine release
Vecuronium	0.08–0.1	45–90	Hepatic 30–40%	Renal 40%, hepatic 60%	Prolonged paralysis (long-term use)
Atracurium	0.3–0.5	30–45	Hoffman elimination, nonspecific ester hydrolysis	Renal 10–40%, hepatic 0%	Histamine release; laudanosine metabolite (a CNS stimulant)
Cisatracurium	0.15–0.2	40–75	Hoffman elimination	Renal 16%, hepatic 0%	Negligible histamine release; laudanosine metabolite
Mivacurium	0.15–0.2	15–20	Plasma cholinesterase	Renal < 5%, hepatic 0%	Histamine release; prolonged effect in presence of atypical pseudocholinesterase

CNS = central nervous system; ICP = intracranial pressure; MH = malignant hyperthermia.

Reversal of neuromuscular blockade is achieved by administering anticholinesterases such as neostigmine or edrophonium. These drugs should be given in conjunction with a muscarinic antagonist (atropine or glycopyrrolate) to block their unwanted parasympathomimetic side effects. Neostigmine is more potent than edrophonium in reversing profound neuromuscular blockade. It is imperative that paralysis be sufficiently reversed before extubation to ensure that spontaneous respiration is adequate and that the airway can be protected. Reversal can be clinically verified by confirming the patient's ability to lift the head for 5 seconds. Reversal can also be assessed by muscle contraction response to electrical nerve stimulation.

Causes of failure to emerge from anesthesia include residual neuromuscular blockade, a benzodiazepine or opioid overdose, the central anticholinergic syndrome, an intraoperative cerebrovascular accident, preexisting pathophysiologic conditions (e.g., CNS disorders, hepatic insufficiency, and drug or alcohol ingestion), electrolyte abnormalities, acidosis, hypercarbia, hypoxia, hypothermia, and hypothyroidism. As noted, the effects of narcotics and benzodiazepines can be reversed with naloxone and flumazenil, respectively. Physostigmine may be given to reverse the reduction in consciousness level produced by general anesthetics. Electrolyte, glucose, blood urea nitrogen, and creatinine levels should be measured; liver and thyroid function tests should be performed; and arterial blood gas values should be obtained. Patients should be normothermic. Unexplained failure to emerge from general anesthesia warrants immediate consultation with a neurologist.

Risk and General Anesthesia

Determining the risk(s) attributed solely to anesthesia is difficult because of the confounding variables of patient characteristics, concurrent medications, and the surgical procedure itself, including context (e.g., elective versus emergency). Prospective, unbiased studies sufficiently powered to reveal the frequency of rare events are lacking, and reliance on self-reporting of negative outcomes likely results in an underestimation of risk. Given these limitations, attempts have been made to define the risks associated with anesthesia, based on extensive and critical literature reviews [see Table 11].³⁹ Perioperative mortality associated with anesthesia increases with age, ASA status, and emergency procedures. Factors contributing to anesthesia-related mortality include inadequate assessment, preparation and resuscitation, inappropriate anesthetic technique, inadequate perioperative monitoring, lack of supervision, and poor postoperative care. Morbidity ranges from major permanent disability to relatively minor events without long-term consequence. Peripheral nerve injury, although rare, may have serious disability. The etiology includes direct injury from needles, instruments, suturing, injection of toxic substances, and thermal insults. Less obvious but more frequent events involve mechanical factors such as nerve compression or stretch. Ischemia associated with a low cardiac output state is often implicated.⁴⁰ Great caution must be used during patient positioning, with careful attention to proper padding. Loss of vision is a rare but catastrophic event that may be associated with compression of the eye by a facemask or by padding of

the headrest used in the prone position.⁴¹ The relationship between postoperative cognitive dysfunction (POCD) and anesthesia per se remains unclear and may occur in patients who receive general (intravenous or inhalational) or regional anesthesia. POCD does not seem to be associated with intraoperative hypoxemia, hypotension, or acid-base disturbances. Certain procedures, such as cardiac and orthopedic surgery, have been associated with this disorder, and a common etiology (air, particulate, or fat microemboli) is implicated. There is a growing appreciation that even with other types of surgery, POCD can occur, with elderly patients (more than 60 years) being at particular risk during the first week after the procedure. Presently, there is little evidence that POCD persists longer than 6 months.⁴²

Regional Anesthesia Techniques

Neuraxial (central) anesthesia techniques involve continuous or intermittent injection of drugs into the epidural or intrathecal space to produce sensory analgesia, motor blockade, and inhibition of sympathetic outflow. Peripheral nerve blockade involves inhibition of conduction in fibers of a single peripheral nerve or plexus (cervical, brachial, or lumbar) in the periphery. Intravenous regional anesthesia involves IV administration of a local anesthetic into a tourniquet-occluded extremity. Perioperative pain control may be facilitated by administering local anesthetics, either infiltrated into the wound or sprayed into the wound cavity. Procedures performed solely under infiltration may be associated with patient dissatisfaction caused by intraoperative anxiety and pain.^{43,44}

CONTRAINDICATIONS

Strong contraindications to regional (particularly neuraxial) anesthesia include patient refusal or inability to cooperate during the procedure, elevated intracranial pressure, anticoagulation, vascular malformation or infection at the needle insertion site, severe hemodynamic instability, and sepsis. Preexisting neurologic disease is a relative contraindication.

ANTICOAGULATION AND BLEEDING RISK

Although hemorrhagic complications can occur after any regional technique, bleeding associated with neuraxial blockade is the most serious possibility because of its devastating consequences. Spinal hematoma may occur as a result of vascular trauma from placement of a needle or catheter into the subarachnoid or epidural space. Spinal hematoma may also occur spontaneously, even in the absence of antiplatelet or anticoagulant therapy. The actual incidence of spinal cord injury resulting from hemorrhagic complications is unknown; the reported incidence is estimated to be less than 1 in 150,000 for epidural anesthesia and 1 in 200,000 for spinal anesthesia [see Table 12].⁴⁵ With such low incidences, it is difficult to determine whether any increased risk can be attributed to anticoagulant use [see Table 13] without data from millions of patients, which are not currently available. Much of our clinical practice is based on small surveys and expert opinion.

Antiplatelet Agents

There is no universally accepted test that can guide antiplatelet therapy. Antiplatelet agents can be divided into

Table 11 Predicted Incidence of Complications of Anesthesia³⁹

Mortality and Morbidity	Approximate Incidence	Rate per 10,000 Population	Remarks
Total perioperative deaths (within 30 days)	1:200 (elective surgery) 1:40 (emergency surgery) × 2 (60–79 yr) × 5 (80–89 yr) × 7 (> 90 yr)	50 250	
Death related to anesthesia	1:50,000 (anesthesia related) 1:100,000 (ASA physical status I and II)	0.2 0.1	
Cardiac arrest	1:10,000–1:20,000 (general anesthesia) 1:3,000 (local anesthesia) 1:1,500 (spinal: 25% fatal)	0.5–1.0 3 7	Mortality ≈ 1:15,000–1:150,000
Myocardial reinfarction	1:20 (0–3 mo after myocardial infarction) 1:40 (4–6 mo after myocardial infarction)	500 250	
Respiratory complications			
Aspiration during general anesthesia	1:3,000 1:60,000 (death)	3 0.16	× 4 in emergencies × 3 in obstetrics
Difficult intubation	1:50	200	
Failure to intubate	1:500	20	Obstetrics ≈ 1:250
Failure to intubate and ventilate	1:5,000	2	
Postoperative cognitive dysfunction (> 60 yr)	1:4 at 1 wk 1:10 at 3 mo 1:100 permanent	2,500 1,000 100	Regional anesthesia General anesthesia
Postoperative delirium	1:7 (general surgery) Up to 1:2 for elderly fractures of neck or femur	1,400 5,000	× 3 >75 yr × 3 if requiring intensive care
Drowsiness	1:2	5,000	Day surgery
Dizziness	1:5	2,000	Day surgery
Headache	1:5	2,000	
Cerebrovascular accident (CVA)	1:50 if previous stroke 1:100 general surgery	200 100	46% mortality 60% mortality if previous CVA (≈ 1:700 in the nonsurgical population)
Carotid endarterectomy (CVA + death)	1:15 if symptomatic 1:25 if asymptomatic	700 400	
Disabling CVA + death Awareness			
With pain	1:3,000	3	2/3 with neuromuscular blockade
Without pain	1:300	30	1/3 without neuromuscular blockade
Total intravenous anesthesia	1:500 1:10,000	20 1	
Anaphylaxis	1:10,000	1	
Deafness			
“Idiopathic” (general anesthesia)	1:10,000	1	≈ 1:1,000 cardiac surgery
Transient after spinal anesthesia	1:7	1,500	
Loss of vision	1:125,000 1:100 (cardiac surgery)	0.08 100	
Pain	~1:3 (moderate)	3,000	
After major surgery	1:10 (severe)	1,000	
Day surgery	1:2	5,000	
Postoperative nausea and vomiting	1:4	2,500	2/3 nausea and 1/3 vomiting Female:male 3:1

Table 11 Continued

Mortality and Morbidity	Approximate Incidence	Rate per 10,000 Population	Remarks
Sore throat	1:2 (if tracheal tube) 1:5 (if laryngeal mask) 1:10 (if facemask only)	5,000 2,000 1,000	
Dental damage			
Requiring intervention	1:5,000	2	
All dental damage	1:100	100	
All oral trauma after tracheal intubation	1:20	500	
Peripheral nerve injury	1:300 ulnar neuropathy	30	
General anesthesia	1:1,000 (other nerves)	10	
Thrombophlebitis	1–2:20 (water-soluble drugs) 1:4 (propylene glycol based)	500–1,000 2,500	
Arterial cannulation complication	<1:100 (permanent)	< 100	
Pulmonary artery perforation	1:2,000	5	
Arterial puncture (during central venous cannulation)			
Internal jugular vein cannulation	1:35	350	
Subclavian vein cannulation	1:200	50	

ASA = American Society of Anesthesiologists.

four major classes: (1) aspirin and related cyclooxygenase inhibitors (NSAIDs); (2) ticlopidine and selective adenosine diphosphate antagonists; (3) direct thrombin inhibitors (e.g., hirudin); and (4) glycoprotein IIb/IIIa inhibitors. Only with aspirin is there sufficient experience to suggest that it does not increase the risk of spinal hematoma when given at clinical dosages.⁴⁶ Caution should, however, be exercised when aspirin is used in conjunction with other anticoagulants.⁴⁷

Oral Anticoagulants

Therapeutic anticoagulation with warfarin is a contraindication to regional anesthesia.⁴⁸ If regional anesthesia is planned, oral warfarin can be replaced with IV heparin (see below).

Heparin

There does not seem to be an increased risk of spinal bleeding in patients receiving subcutaneous low-dose (5,000 U) unfractionated heparin [see 6:6 *Venous Thromboembolism*] if the interval between administration of the drug and initiation of the procedure is greater than 4 hours.⁴⁹ Higher doses, however, are associated with increased risk. If neuraxial anesthesia or epidural catheter removal is planned, heparin infusion must be discontinued for at least 6 hours, and the partial thromboplastin time should be measured. Recommendations for standard heparin cannot be extrapolated to low-molecular-weight heparin (LMWH), because the biologic actions of LMWH are different and the effects cannot be monitored by conventional coagulation measurements. After the release of LMWH for general use in the United States in 1993, more than 40 spinal hematomas were reported

during a 5-year period. LMWH should be stopped at least 24 hours before regional blockade, and the first postoperative dose should be given no sooner than 24 hours afterward.⁴⁷

COMPLICATIONS

Drug Toxicity

Systemic toxic reactions to local anesthetics primarily involve the CNS and the cardiovascular system [see Table 14]. The initial symptoms are light-headedness and dizziness, followed by visual and auditory disturbances. Convulsions and respiratory arrest may ensue and necessitate treatment and resuscitation.

The use of neuraxial analgesic adjuncts (e.g., opioids, clonidine, epinephrine, and neostigmine) decreases the dose of local anesthetic required, speeds recovery, and improves the quality of analgesia. The side effects of such adjuncts include respiratory depression (opioids), urinary retention (opioids), tachycardia (epinephrine), hypotension (clonidine), and nausea and vomiting (neostigmine, opioids).

Neurologic Complications

The incidence of neurologic complications ranges from 2 in 10,000 to 12 in 10,000 with epidural anesthesia and from 0.3 in 10,000 to 70 in 10,000 with spinal anesthesia.^{49,50} The most common serious complication is neuropathy, followed by cranial nerve palsy, epidural abscess, epidural hematoma, anterior spinal artery syndrome, and cranial subdural hematoma [see Table 12]. Vigilance and routine neurologic testing of sensory and motor function are of paramount importance for early detection and treatment of these potentially disastrous complications.

Table 12 Predicted Incidence of Complications of Regional Anesthesia³⁹

Complication	Incidence	Rate per 10,000 Population	Remarks
Paraplegia	≈ 1:100,000	0.1	
Permanent nerve injury			
Spinal	1–3:10,000	1–3	
Epidural	0.3–10:10,000	0.03–10	
Peripheral nerve block	≈ 1:5,000	2	2% brachial plexus neuropraxia lasting > 3 mo
Epidural hematoma	≈ 1:150,000 (epidural)	0.07	≈ 1:1,000,000 (spontaneous)
	≈ 1:200,000 (spinal)	0.05	≈ 1:14,000 (USA)
			≈ 1:2,250,000 (Europe)
			≈ 1:10,000 (spontaneous)
Epidural abscess	1:2,000–1:7,500	0.7–5.0	
Transient neural complications	1:1,000–1:10,000 (epidural)	1–10 (epidural)	
	1:125–1:2,500 (spinal)	4–80 (spinal)	
Transient radicular irritation (spinal)	Up to 1:3 (heavy lidocaine and mepivacaine)	3,000	
Cardiac arrest	≈ 1:1,500 (spinal)	5 (spinal)	
	≈ 1:3,000 (local anesthesia)	3 (local anesthesia)	
	≈ 1:10,000 (epidural)	1 (epidural)	
	≈ 1:10,000 (regional blocks)	1 (regional)	
Post–dural puncture headache	≈ 1:100	100	80% following inadvertent dural tap
	≈ 1:10 (day surgery)	1,000	Blood patch 70–100%
			Immediate success, but headaches recur in 30–50%
Backache	< 1 hr surgery ≈ 20%	2,000	GA = LA
	> 4 hr surgery ≈ 50%	5,000	
Urinary dysfunction	≈ 1:50	200	
Pneumothorax	≈ 1:20 (supraclavicular blocks)	500	
Systemic LA toxicity	≈ 1:10,000 (epidural)	1	
	≈ 1:1,500 (regional blocks)	7	
Cerebral seizures	≈ 1:4,000 (intravenous regional anesthesia)	2.5	Axillary ≈ 1:1,000
	≈ 1:500 (brachial plexus)	20	Supraclavicular ≈ 1:125
Eye blocks			
Retrobulbar hemorrhage	1:250–1:20,000	0.5–40	
Brainstem anesthesia	≈ 1:700	15	
Globe perforation	≈ 1:10,000	1	
Ptosis—transient after eye block	≈ 1:2 at 24 hr	5,000	
	≈ 1:5 at 1 mo	2,000	
Diplopia—transient after eye block	8–70%	800–7,000	

GA = general anesthesia; LA = local anesthesia.

Transient Neurologic Symptoms

The term *transient neurologic symptoms* (TNSs) refers to backache with pain radiating into the buttocks or the lower extremities after spinal anesthesia. It occurs in 4 to 33% of patients, typically 12 to 36 hours after the resolution of spinal anesthesia, and lasts for 2 to 3 days.⁵¹ TNSs have been

described after intrathecal use of all local anesthetics but are most commonly noted after administration of lidocaine, in the ambulatory surgical setting, and with the patient in the lithotomy position during operation. Discomfort from TNSs is self-limited and can be effectively treated with NSAIDs.

Table 13 Pharmacology of Anticoagulant Agents

Drug	Coagulation Tests		Time to Peak Effect	Time to Normal Hemostasis after Discontinuation
	INR	PTT		
Heparin				
IV	↔	↑↑	min	4–6 hr
SC	↔	↑	1 hr	4–6 hr
LMWH	↔	↔	2–4 hr	12 hr
Warfarin	↑↑	↔	2–6 days	4–6 days
Aspirin	↔	↔	hr	5–8 days
Thrombolytic agents (t-PA, streptokinase)	↔	↑↑	min	1–2 days

↑↑ = clinically significant increase; ↑ = possibly clinically significant increase; ↔ = clinically insignificant increase or no effect; INR = international normalized ratio; LMWH = low-molecular-weight heparin; PTT = partial thromboplastin time; t-PA = tissue plasminogen activator.

Post-Dural Puncture Headache

Use of small-gauge pencil-point needles for spinal anesthesia is associated with a 1% incidence of PDPH. The incidence of PDPH after epidural analgesia varies substantially because the risk of inadvertent dural puncture with a Tuohy needle is directly dependent on the anesthesiologist's training. PDPH is characteristically aggravated by upright posture and may be associated with photophobia, neck stiffness, nausea, diplopia, and tinnitus. Meningitis should be considered in the differential diagnosis. Although PDPH is not life-threatening, it carries substantial morbidity in the form of restricted activity. Medical treatment with bed rest, IV fluids, NSAIDs, and caffeine is only moderately effective. An epidural blood patch is the treatment of choice: the success rate is approximately 70%.

Recovery

Admission to the postanesthetic care unit (PACU) is appropriate for patients whose vital signs are stable and whose pain is adequately controlled after emergence from

anesthesia. Patients requiring hemodynamic or respiratory support may be admitted to the PACU if rapid improvement is expected and appropriate monitoring and personnel are available. Hemodynamic instability, the need for prolonged respiratory support, and poor baseline condition mandate admission to the ICU. Common complications encountered in the PACU include postoperative pulmonary insufficiency, cardiovascular instability, acute pain, and nausea and vomiting [see Table 15]. These complications are discussed in greater detail elsewhere [see 8:5 *Pulmonary Insufficiency*, 8:2 *Acute Cardiac Dysrhythmia*, 1:6 *Postoperative Pain*, and ECP:5 *Patient Safety in Surgical Care: A Systems Approach*].

Special Scenarios

DIFFICULT AIRWAY

Airway management is a pivotal component of patient care because failure to maintain airway patency and ventilation can lead to permanent disability, brain injury, or death. The difficult airway should be managed in accordance with contemporary airway guidelines, such as the protocols established by the ASA, to reduce the risk of adverse outcomes during attempts at ventilation and intubation. (The ASA protocols may be accessed on the organization's Web site: <http://www.asahq.org/Newsletters/2005/11-05/2003TraumaAlgorithm.html>). The emphasis on preserving spontaneous ventilation and the focus on awake intubation options are central themes whose importance cannot be overemphasized.

It is crucial that all patients who are undergoing difficult or prolonged airway instrumentation be appropriately treated with topical anesthesia, sedation, and monitoring so as to ensure adequate ventilation and to attenuate, detect, and treat harmful neuroendocrine responses that can cause

Table 15 Pharmacologic Treatment of Postoperative Nausea and Vomiting⁸

Agent	Dose	Comments
Propofol	10 mg IV, repeated dose	[See Table 8]
Ondansetron	4.0–8.0 mg IV	Highly effective, costly; headache, constipation, transiently increased LFTs
Dexamethasone	4.0–8.0 mg IV	Adrenocortical suppression, delayed wound healing, fluid retention, electrolyte disturbances, psychosis, osteoporosis
Droperidol	0.5–1.0 mg IV	Sedation, restlessness, dysphoria, dysrhythmia (?)
Metoclopramide	10–20 mg IV	Avoid in bowel obstruction, extrapyramidal reactions
Scopolamine	0.1–0.6 mg SC, IM, IV	Muscarinic side effects, somnolence
Dimenhydrinate	25–50 mg IV	Drowsiness, dizziness

IM = intramuscular; IV = intravenous; LFT = liver function test; SC = subcutaneous.

Table 14 Local Anesthetics for Infiltration Anesthesia: Maximum Doses* and Duration of Action

Drug	Without Epinephrine		With Epinephrine (1:200,000)	
	Maximum Dose (mg)	Duration of Action (min)	Maximum Dose (mg)	Duration of Action (min)
Chloroprocaine	800	15–30	1,000	3–90
Lidocaine	300	30–60	500	120–360
Mepivacaine	300	45–90	500	120–360
Prilocaine	500	30–90	600	120–360
Bupivacaine	175	120–240	225	180–420
Etidocaine	300	120–180	400	180–420

*Recommended maximum dose can be given to healthy, middle-aged, normal-sized adults without toxicity. Subsequent doses should not be given for at least 4 hours. Doses should be reduced during pregnancy.

myocardial ischemia, bronchospasm, and intracranial hypertension. Extubation is stressful as well and may be associated with intense mucosal stimulation and exaggerated glottic closure reflexes, resulting in laryngospasm and, possibly, pulmonary edema secondary to vigorous inspiratory efforts against an obstructed airway. Laryngeal incompetence and aspiration can also occur after extubation. Removal of an endotracheal tube from a known or suspected difficult airway should ideally be performed over a tube exchanger so as to facilitate emergency reintubation.

Alternatives to standard oral airways, masks, introducers, exchangers, laryngoscopes, and endotracheal tubes now exist that offer more options, greater safety, and better outcomes. It would be naive to believe that any single practitioner could master every new airway protocol and device. To keep up with technical and procedural advances, university hospital program directors should consider incorporating technical skill laboratories and simulator training sessions into their curricula.

MORBID OBESITY

Morbid obesity represents the extreme end of the overweight spectrum and is usually defined as a body mass index higher than 40 kg/m² [see 5:7 *Surgical Treatment of Morbid Obesity*].⁵² It poses a formidable challenge to health care providers in the OR, the postoperative recovery unit, and the ICU. The major concerns in the surgical setting are the possibility of a difficult airway, the increased risk of known or occult cardiorespiratory compromise, and various serious technical problems related to positioning, monitoring, vascular access, and transport. Additional concerns are the potential for underlying hepatic and endocrine disease and the effects of altered drug pharmacokinetics and pharmacodynamics. For the morbidly obese patient, there is no such thing as minor surgery.

Initial management should be based on the assumptions that (1) a difficult airway is likely; (2) the patient will be predisposed to hiatal hernia, reflux, and aspiration; and (3) rapid arterial desaturation will occur with induction of anesthesia as a consequence of decreased functional residual capacity and high basal oxygen consumption. Often the safest option is an awake fiberoptic intubation with appropriate topical anesthesia and light sedation. In expert hands, this technique is extremely well tolerated and can usually be performed in less than 10 minutes.⁵³ Morbidly obese patients often are hypoxemic at rest and have an abnormal alveolar-arterial oxygen gradient caused by ventilation-perfusion mismatching. The combination of general anesthesia and the supine position exacerbates alveolar collapse and airway closure. Mechanical ventilation, weaning, and extubation may be difficult and dangerous, especially in the presence of significant obstructive sleep apnea. Postoperative pulmonary complications (e.g., pneumonia, aspiration, atelectasis, and emboli) are common.⁵⁴

Morbid obesity imposes unusual loading conditions on both sides of the heart and the circulation, leading to the progressive development of insulin resistance, atherogenic dyslipidemias, systemic and pulmonary hypertension, ventricular hypertrophy, and a high risk of premature coronary artery disease and biventricular heart failure. Perioperative cardiac morbidity and mortality are therefore significant problems. Untoward events can happen suddenly,

and resuscitation is extremely difficult. Cardiorespiratory compromise may be attenuated by effective postoperative pain control that permits early ambulation and effective ventilation. Surgical site infection and dehiscence may result in difficult reoperation and prolonged hospitalization.

MALIGNANT HYPERTHERMIA

MH is a rare but potentially fatal genetic condition characterized by life-threatening hypermetabolic reactions in susceptible individuals after the administration of volatile anesthetics or depolarizing muscle relaxants.⁵⁵ Abnormal function of the sarcoplasmic reticulum calcium release channel in skeletal muscle has been identified as a possible underlying cause.

In making the diagnosis of MH, it is important to consider other possible causes of postoperative temperature elevation. Such causes include inadequate anesthesia, equipment problems (e.g., misuse or malfunction of heating devices, ventilators, or breathing circuits), local or systemic inflammatory responses (either related or unrelated to infection), transfusion reaction, hypermetabolic endocrinopathy (e.g., thyroid storm or pheochromocytoma), neurologic catastrophe (e.g., intracranial hemorrhage), and reaction to or abuse of a drug.

Immediate recognition and treatment of a fulminant MH episode are essential for preventing morbidity and mortality. Therapy consists of discontinuing all triggers, instituting aggressive cooling measures, giving dantrolene in an initial dose of 2.5 mg/kg, and administering 100% oxygen to compensate for the tremendous increase in oxygen use and carbon dioxide production. An indwelling arterial line, central venous access, and bladder catheterization are indispensable for monitoring and resuscitation. Acidosis, hyperkalemia, and malignant dysrhythmias must be rapidly treated, with the caveat that calcium channel blockers are contraindicated in this setting. Maintenance of adequate urine output is of paramount importance and may be facilitated by the clinically significant amounts of mannitol contained in commercial dantrolene preparations. When the patient is stable and the surgical procedure is complete, monitoring and support are continued in the ICU, where repeat doses of dantrolene may be needed to prevent or treat recrudescence of the disease.⁵⁵

MASSIVE TRANSFUSION

Massive blood transfusion, defined as the replacement of a patient's entire circulating blood volume in less than 24 hours, is associated with significant morbidity and mortality. Management of massive transfusion requires an organized multidisciplinary team approach and a thorough understanding of associated hematologic and biochemical abnormalities and subsequent treatment options.

Patients suffering from shock as a result of massive blood loss often require transfusions of packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate to optimize oxygen-carrying capacity and address dilutional and consumptive loss of platelets and clotting factors [see 8:3 *Shock and 1:4 Bleeding and Transfusion*]. Transfusion of large amounts of blood products into a critically ill patient can lead to coagulopathies, hyperkalemia, acidosis, citrate intoxication, fluid overload, and hypothermia.⁵⁶ Therapy should be guided by vital signs, urine output, pulse oximetry, electrocardiography, capnography, invasive hemodynamic

monitoring, serial arterial blood gases, biochemical profiles, and bedside coagulation screens. Fluids should be administered through large-bore cannulas connected to modern countercurrent warming devices. Shed blood should be salvaged and returned to the patient whenever possible. In refractory cases, transcatheter angiographic embolization techniques should be considered for control of bleeding.

Hemostatic agents, such as procoagulants (desmopressin, recombinant factor VIIa) and antifibrinolytics (aprotinin, tranexamic acid, ϵ -aminocaproic acid), have been used extensively in surgical procedures associated with considerable blood loss (e.g., solid organ transplantation, cardiac and orthopedic surgery [see 1:4 *Bleeding and Transfusion*]).⁵⁷ Although they are effective at reducing blood loss, a serious concern is the increased risk for thrombosis. Aprotinin, a serine protease inhibitor with unique antifibrinolytic and hemostatic properties, very effectively decreases blood loss and transfusion requirements, as well as attenuates potentially harmful inflammatory responses and minimizes reperfusion injury. However, recent evidence indicates that it may be associated with increased morbidity⁵⁸ (renal failure) and mortality,⁵⁹ so its availability has been suspended.⁶⁰ Recombinant factor VIIa was originally approved for hemophiliacs who developed antibodies against either factor VIII or factor IX. It may prove useful for managing hemorrhage deriving from trauma or surgery when standard interventions have failed.⁶¹

HYPOTHERMIA

Significant decreases in core temperature are common during anesthesia and surgery as a consequence of exposure to a cold OR environment and of disturbances in normal protective thermoregulatory responses. Patients lose heat through conduction, convection, radiation, and evaporation, especially from large wounds and during major intracavitary procedures. Moreover, effective vasoconstrictive reflexes and both shivering and nonshivering thermogenesis are severely blunted by anesthetics.⁶² Neonates and the elderly are particularly vulnerable.

Hypothermia may confer some degree of organ preservation during ischemia and reperfusion. For example, in cardiac surgery, hypothermic cardiopulmonary bypass is a common strategy for protecting the myocardium and the CNS. Intentional hypothermia has also been shown to improve neurologic outcome and survival in comatose victims of cardiac arrest. Perioperative hypothermia can have significant deleterious effects as well, however, including myocardial ischemia, surgical site infection, increased blood loss and transfusion requirements, and prolonged anesthetic recovery and hospital stay.

The sensation of cold is highly uncomfortable for the patient, and shivering impedes monitoring, raises plasma catecholamine levels, and exacerbates imbalances between oxygen supply and demand by consuming valuable energy for involuntary muscular activity. It is therefore extremely important to measure the patient's temperature and maintain thermoneutrality. Increasing the ambient temperature of the OR and applying modern forced-air warming systems are the most effective techniques available. In addition, all IV and irrigation fluids should be heated. After the patient has been transferred from the OR, aggressive treatment of

hypothermia with these techniques should be continued as necessary. Shivering may also be reduced by means of drugs such as meperidine, nefopam, tramadol, physostigmine, ketamine, methylphenidate, and doxapram.⁶³

INTRAOPERATIVE AWARENESS

One of the goals of anesthesia is to produce a state of unconsciousness during which the patient neither perceives nor recalls noxious surgical stimuli. When this objective is not met, awareness occurs, and the patient will have explicit or implicit memory of intraoperative events. In some instances, intraoperative awareness develops because human error, machine malfunction, or technical problems result in an inappropriately light level of anesthesia. In others (e.g., when the patient is severely hemodynamically unstable or efforts are being made to avoid fetal depression during cesarean section), the light level of anesthesia may have been intentionally chosen. Regardless of the cause, intraoperative awareness is a terrifying experience for the patient and has been associated with serious long-term psychological sequelae.⁶⁴ Prevention of awareness depends on regular equipment maintenance, meticulous anesthetic technique, and close observation of the patient's movements and hemodynamic responses during operation. CNS monitoring may reduce the risk of intraoperative awareness, particularly when anesthesia is maintained exclusively by intravenous drugs (total intravenous anesthesia).³⁴

ANAPHYLAXIS

Allergic reactions range in severity from mild pruritus and urticaria to anaphylactic shock and death. Inciting agents include, but are not limited to, antibiotics, contrast agents, blood products, volume expanders, protamine, aprotinin, narcotics, induction agents, muscle relaxants, latex,⁶⁵ and, rarely, local anesthetic solutions. Many drug additives and preservatives have also been implicated.

True anaphylaxis presents shortly after exposure to an allergen and is mediated by chemicals released from degranulated mast cells and basophils. Manifestations usually include dramatic hypotension, tachycardia, bronchospasm, arterial oxygen desaturation, and cutaneous changes. Laryngeal edema can occur within minutes, in which case, the airway should be secured immediately. Anaphylaxis can mimic heart failure, asthma, pulmonary embolism, and tension pneumothorax. Treatment involves withdrawing the offending substance and administering oxygen, fluids, and epinephrine, followed by IV steroids, bronchodilators, and histamine antagonists. Prolonged intubation and ICU monitoring may be required until symptoms resolve. Appropriate skin and blood testing should be done to identify the causative agent.

PERIOPERATIVE DYSRHYTHMIAS

In 2005, current scientific developments in the acute treatment of cerebrovascular, cardiac, and pulmonary disease were merged with the evolving discipline of evidence-based medicine to produce the most comprehensive set of resuscitation standards ever created: a 14-part document from the American Heart Association entitled "2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care."⁶⁶ This document addresses a wide array of key issues in both in-hospital and out-of-hospital resuscitation, including a recommendation for

confirmation of tube position after endotracheal intubation and a warning about the danger associated with unintentional massive auto-positive end-expiratory pressure.

As regards the impact the new guidelines have on the management of cardiopulmonary resuscitation, an increase in ratios of compression to ventilation ratios (to 30:2) and an emphasis on effective chest compressions (“push hard, push fast”) are suggested. In addition, early chest compressions before defibrillation, a one-shock sequence for defibrillation as opposed to a three-shock sequence, and avoidance of prolonged interruption of chest compressions are recommended. For wide QRS dysrhythmias, amiodarone continues to be the drug of choice. It may also be administered for ventricular fibrillation or for pulseless ventricular tachycardia that does not respond to cardiopulmonary resuscitation, cardioversion, and a vasopressor.

Amiodarone is a complex, powerful, and broad-spectrum agent that inhibits almost all of the drug receptors and ion channels conceivably responsible for the initiation and propagation of cardiac ectopy, irrespective of underlying ejection fraction, accessory pathway conduction, or anatomic substrate. It does, however, have potential drawbacks, such as its relatively long half-life, its toxicity to multiple organs, and its complicated administration scheme. Furthermore, amiodarone is a potent noncompetitive alpha and beta blocker, which has important implications for anesthetized, mechanically ventilated patients who may be debilitated and experiencing volume depletion, abnormal vasodilation, myocardial depression, and fluid, electrolyte, and acid-base abnormalities. That said, no other drug in its class has ever demonstrated a significant benefit in randomized trials addressing cardiac arrest in humans.

Amiodarone is effective in both children and adults, and it can be used for prophylaxis and treatment. The recommended cardiac arrest dose is a 300 mg IV bolus. In less acute situations (e.g., wide-complex tachycardia), an initial 150 mg dose should be administered slowly over 10 minutes, and one or two additional boluses may be given similarly. A loading regimen is then initiated, first at 1 mg/min for 6 hours and then at 0.5 mg/min for 18 hours.

Vasopressin (antidiuretic hormone) continues to be listed as an alternative to epinephrine in the ventricular tachycardia/ventricular fibrillation protocol. Vasopressin is an integral component of the hypothalamic-pituitary-adrenal axis and the neuroendocrine stress response. The recommended dose for an adult in fibrillatory arrest is 40 units in a single bolus. For vasodilatory shock states associated with sepsis, hepatic failure, or vasomotor paralysis after cardiopulmonary bypass, infusion at a rate of 0.01 to 0.04 units/min may be particularly useful. Vasopressin is neither recommended nor forbidden in cases of pulseless electrical activity or asystolic arrest, and it may be substituted for epinephrine.

Table 16 Cardiac Conditions Associated with Risk of Adverse Outcome from Endocarditis for Which Prophylaxis Is Reasonable⁶⁷

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous infective endocarditis
Congenital heart disease (CHD)*
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Cardiac transplant recipients who develop cardiac valvulopathy

*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.

†Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

ANTIBIOTIC PROPHYLAXIS

Recently, the American Heart Association has revised the guidelines for administration of antibiotic drugs prophylactically to prevent infective endocarditis.⁶⁷ Infective endocarditis prophylaxis is no longer recommended for mitral valve prolapse or for the stenotic or regurgitant cardiac lesions associated with rheumatic heart disease [see Table 16]. A suggested antibiotic regimen is provided in Table 17.

Table 17 Antibiotic Protocol⁶⁷

Situation	Agent	Regimen: Single Dose 30–60 min before Procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin or cefazolin or ceftriaxone	2 g IM or IV	50 mg/kg IM or IV
		1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin oral	Cephalexin*† or clindamycin or azithromycin or clarithromycin	2 g	50 mg/kg
		600 mg	20 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone† or clindamycin	500 mg	15 mg/kg
		1 g IM or IV	50 mg/kg IM or IV
		600 mg IM or IV	20 mg/kg IM or IV

IM = intramuscular; IV = intravenous.

*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.

†Cephalosporins should not be used in a person with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

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A surgeon is frequently one of the first people to be called when a patient experiences massive hemorrhage. “Massive hemorrhage” is usually not hard to recognize in practice, but it can be defined as hemorrhage requiring at least 10 units of cellular blood products within 24 hours. To treat such a patient appropriately, the surgeon must rapidly and simultaneously accomplish three tasks: identify the source or cause of the bleeding, stop or limit the bleeding, and restore the patient’s circulation.

Causes fall into two main categories: (1) conditions involving loss of vascular integrity, such as a patient with bleeding from a peptic ulcer or a trauma patient with a severe liver laceration, and (2) conditions involving a derangement of the hemostatic process. Typically, massive hemorrhage begins with a loss of vascular integrity, but derangements of hemostasis frequently develop as a secondary problem and play a major role in the exacerbation of such hemorrhage. In this section, we focus on the immediate concerns to keep the patient alive with particular attention to how to address the associated coagulopathy. We consider derangements of hemostasis that are not associated with massive hemorrhage in the next section, "Approach to the Patient with a Derangement of Hemostasis."

If a coagulopathy develops as a result of uncontrolled hemorrhage from loss of vascular integrity, attempting to treat the coagulopathy without controlling the

source is an exercise in futility. Other sections of this text address the anatomic and technical considerations involved in controlling different sites of bleeding [see subcategories under “Bleeding” in the Index]. However, in contrast to the routine conduct of operations, control of the source of massive bleeding requires a fundamentally different mindset.

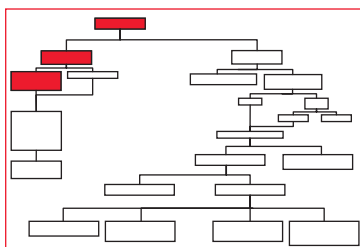
The goals of operative conduct change from definitive management of all issues to "damage control," in which the salient objective is to address immediately life-threatening problems: restoration of vascular integrity and, to the extent necessary and prudent, restoration of the circulation of the viscera and limbs. Other goals, such as reestablishment of intestinal continuity or closure of the wound, become secondary and can be addressed later if the patient survives. Even selected, more drastic maneuvers for exposure of the site of

bleeding should be considered when the patient is at appreciable risk of death; these apply even if the hemorrhage developed during an elective procedure. For example, right nephrectomy may be warranted to afford exposure of the infrahepatic inferior vena cava, or deliberate division of a common iliac artery may be necessary to expose bleeding from the corresponding common iliac vein. Temporary vascular shunts may be helpful to rapidly restore blood flow to ischemic limbs if it is still possible to salvage the limb. However, reperfusion of a large volume of ischemic tissue in the setting of shock can cause severe systemic problems, so expert judgment is necessary to decide whether to try to preserve or amputate the limb in such situations.

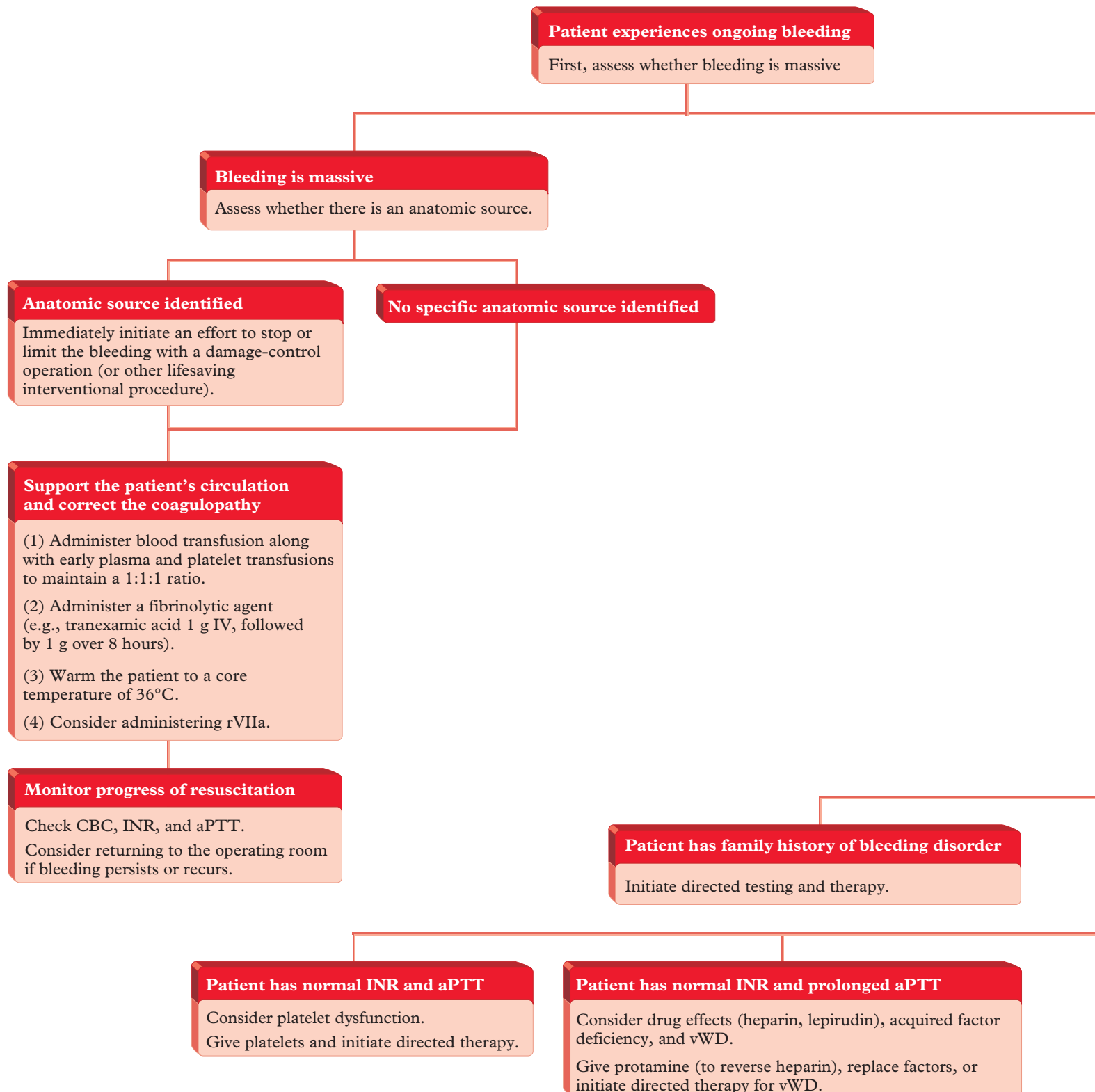
Sometimes, the best option to control massive hemorrhage is not necessarily an open operation. Increasingly, interventional radiologic and endovascular techniques are serving important roles: although long used for control of bleeding from sites not easily managed with open procedures, such as pelvic fractures, they have recently become an accepted approach for some problems traditionally managed with open procedures, such as ruptured abdominal aortic aneurysms,¹ because of the speed of access by an experienced interventionalist. However, the surgeon should be actively involved in decisions to use minimally invasive techniques and should never hesitate to operate if that is the best option in a given situation. Surgeons must individualize their approach to each patient based on their expertise, available resources, and the most current standards of care but be willing to use all tools in their armamentarium.

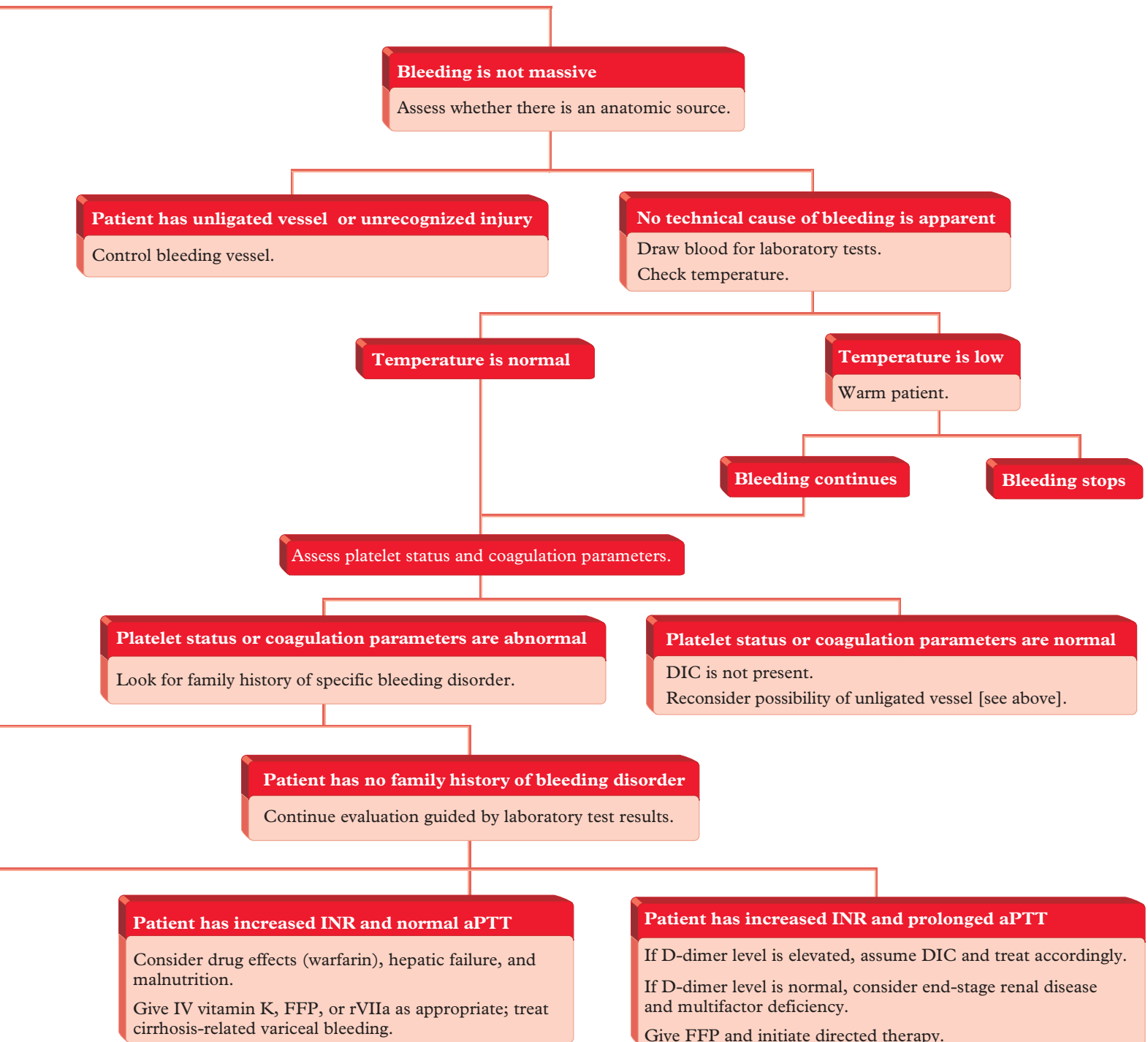
Just as massive hemorrhage should lead the surgeon to reprioritize the goals of an operation, it should also prompt a major shift in the fluid resuscitation strategy. Initially, when there is massive hemorrhage that can be addressed with an operation, resuscitation with blood products and other intravenous (IV) fluids should be implemented only as an adjunct while attempts are made to stop the loss of blood. Although surgeons continue to debate the merits of “permissive hypotension” (the concept that fluid resuscitation before control of hemorrhage should be minimized because it will lead to increased bleeding²), attempts at fluid resuscitation should not delay procedures to control massive hemorrhage, even temporarily.

When massive bleeding exists and direct control of the site of bleeding is under way, the decision to transfuse should be based primarily on hemodynamic status rather than on the hemoglobin or hematocrit level. These laboratory values do



Approach to the Patient with Hemorrhage



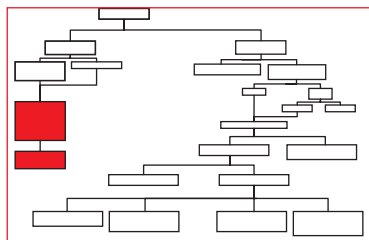


not reflect acute hemorrhage because there is a time lag before these levels equilibrate from fluid shift between the extravascular and vascular compartments and from administration of IV fluids. The goals of transfusion are therefore as much to increase the intravascular volume as to prevent the development of profound deficits in oxygen-carrying capacity. Stabilized patients who are at high risk for recurrent bleeding (e.g., those with a massive liver injury or gastrointestinal (GI) hemorrhage from an unknown source) should receive transfusions up to a level at which, should bleeding recur, enough reserve oxygen-carrying capacity would be available to allow diagnosis and correction of the hemorrhage without significant compromise of oxygen delivery (we advocate a target hematocrit of roughly 30% during this phase). The standard restrictive transfusion strategy used in stable intensive care unit (ICU) patients [see Approach to the Patient with Anemia, *below*] warrants modification in these circumstances because of the higher likelihood of occult active hemorrhage.

Management of the Coagulopathy

It is true that coagulopathy may promote massive hemorrhage and that massive hemorrhage causes a coagulopathy. As a rule, the massively hemorrhaging patient has a coagulopathy out of proportion to the abnormalities reflected with in vitro laboratory tests such as the prothrombin time (PT, commonly expressed as an international normalized ratio [INR]) or activated partial thromboplastin time (aPTT). Coagulopathy most typically occurs when there is massive hemorrhage in concert with injury to a large volume of tissue. Although the nature of this coagulopathy is not precisely defined, it probably involves a number of factors: (1) platelet dysfunction and diminished availability of platelets at the interface between the vascular endothelium and luminal flow; (2) dysfunctional formation of thrombi in the setting of acidosis and hypothermia; (3) accelerated thrombolysis (attributable to dysfunctional thrombosis); and, eventually, (4) consumption of clotting factors.

Increased recognition of this coagulopathy has prompted enthusiasm for administration of plasma and platelets early in the treatment of the patient with massive hemorrhage. This practice, frequently incorporated into a massive transfusion protocol, is described as “1:1:1 transfusion” because the goal is to transfuse one unit of plasma and one of platelets along with each unit of red blood cells (RBCs) such that the ratio stays balanced throughout the resuscitation phase. (Adjustment of these ratios is necessary for centers that use pooled quantities of plasma and/or platelets.) The rationale is that patients are already extensively coagulopathic by the time they manifest thrombocytopenia or prolongation of the INR or aPTT. Thus, during the first several hours during and after massive hemorrhage, plasma and platelets are necessary independent of the laboratory tests and help address a significant contributing factor for persistent hemorrhage.



The concept of liberal, early use of plasma and platelets developed in large part from the recent US-led military campaigns in Iraq and Afghanistan. Initially in those conflicts, the lack of a reliable supply of blood products near the scene of injury—and platelets especially—led to the use of fresh whole blood transfusion. Although fresh whole blood would be impractical in the civilian setting because of logistical issues and the risk of transmitting transfusion-related infections, the perception of improved outcomes associated with its use prompted military surgeons to advocate 1:1:1 transfusion.

Proponents of this approach argue that it restores hemostatic capacity and helps limit hemorrhage, leading to improved survival. Indeed, observational studies suggest that mortality is reduced.³ However, the ratios examined in these studies typically have been calculated retrospectively over relatively long (e.g., 12- or 24-hour) time periods after hemorrhage. Critics emphasize that patients who do not survive long enough to receive early plasma and platelets bias such observational comparisons (i.e., they are classified as receiving a large ratio of RBCs to plasma or platelets because they died early) and that plasma and platelets carry theoretical harms of transfusion-related acute lung injury and bacterial infection, respectively. Despite some uncertainty about the actual merits of the 1:1:1 approach, given that military conflicts have frequently spurred advances in transfusion medicine, it appears likely that the approach will be adopted more widely if the availability of blood products does not limit its application. In the absence of sufficient availability of blood products to allow a 1:1:1 approach, aggressive correction of abnormalities of the INR, aPTT, and platelet count are warranted for patients with massive hemorrhage.

More convincing information supports the use of antifibrinolytic agents in the setting of massive hemorrhage. Aprotinin, tranexamic acid, and ε-aminocaproic acid (Amicar) are known to reduce transfusion requirements in the setting of elective operations (primarily cardiac procedures). Furthermore, a recent large randomized trial, the CRASH-2 trial, showed that patients with or at risk for significant bleeding (i.e., hypotension or tachycardia) from traumatic injury had decreased all-cause and bleeding-related mortality when they received tranexamic acid within 8 hours of injury.⁴ In this study, tranexamic acid was administered intravenously as a 1 g loading dose, followed by an infusion of an additional 1 g over 8 hours. Tranexamic acid did not increase the likelihood of major vascular occlusion events (myocardial infarction, stroke, and pulmonary embolism).

Recombinant activated factor VII (rVIIa) is approved for the treatment of hemophilia in the United States. It has also been advocated for off-label use early in the course of uncontrolled hemorrhage⁵ and intracranial hemorrhage. Although rVIIa can be a rapid and highly specific form of treatment in certain instances of bleeding (e.g., traumatic brain injury in a patient on warfarin), the rationale for its use is not as highly targeted in the setting of massive hemorrhage, during which factor deficiencies are not typically an early abnormality. Two sponsor-initiated international randomized trials of rVIIa in severely injured trauma patients have been performed, and their results—although neither had overwhelming power to detect improved survival—suggest that rVIIa decreases blood transfusions but does not reduce mortality.^{6,7} One recent



report suggested that off-label use of rVIIa in certain populations significantly increased the risk of arterial thromboembolic complications.⁸ In the absence of better designed and conducted studies of patients with massive bleeding, surgeons will need to decide whether use of rVIIa is warranted despite its costs and incompletely understood efficacy and safety profile in this setting. Consensus recommendations have attempted to define appropriate use in light of insufficient evidence.⁹

There is relatively little controversy over the management of hypothermia. As a series of chemical reactions, the coagulation cascade slows with decreasing temperature.¹⁰ Thus, a patient with a temperature lower than 35°C (95°F) clots more slowly and less efficiently than one with a temperature

of 37°C (98.6°F). The resulting coagulopathy cannot be detected by laboratory tests because the laboratory warms the sample to 37°C to run the coagulation assays (INR and aPTT). Thus, bleeding hypothermic patients should be rewarmed, and active measures are warranted if the core temperature is 34.5°C (94.1°F) or lower.¹¹

Relatively new agents have been promulgated to facilitate hemostasis at sites of focal bleeding. QuikClot (Z-Medica, Newington, CT), a granular substance containing the mineral zeolite, and HemCon (HemCon, Inc., Portland, OR), a chitosan-based dressing, have been used in the setting of military trauma. Preliminary information suggests that whereas QuikClot appears to cause superficial burns, HemCon may carry few disadvantages.¹²

Approach to the Patient with a Derangement of Hemostasis

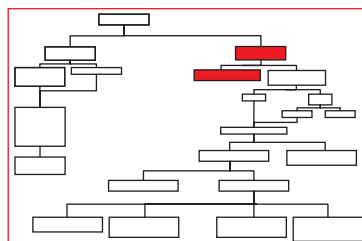
SCORE Not infrequently, surgeons encounter patients with actual or suspected derangements of hemostasis short of massive hemorrhage. These situations range from the preoperative assessment of asymptomatic patients potentially at risk for coagulopathic bleeding to the postoperative management of patients with an observed bleeding diathesis. Although it is still important to rule out the possibility of technical causes of bleeding, surgeons should also be able to recognize coagulopathic bleeding and know how to prevent it when possible or evaluate and manage its most common etiologies when it occurs.

Coagulopathies are varied in their causes, treatments, and prognoses. Although specialized hematologic tests exist to identify rare congenital or acquired clotting abnormalities, our goal in this section is to outline a practical, effective approach to the coagulopathies surgeons see most frequently. The vast majority of these coagulopathies can be diagnosed by means of a brief patient and family history, a review of medications, physical examination, and commonly used laboratory studies—in particular, PT (commonly expressed as an INR), aPTT, complete blood count (CBC), and D-dimer assay.

In the Discussion section later in this chapter, we present an overview of the physiology of hemostasis and consider some of the rarer conditions and theoretical considerations in greater detail.

Exclusion of Technical Causes of Bleeding

It is critical to emphasize that the most common causes of postoperative bleeding, even when it is not massive, are technical: an unligated vessel or an unrecognized injury is much more likely to be the cause of a falling hematocrit than either a drug effect or an endogenous hemostatic defect. Furthermore, if an unligated vessel is treated as though it were an endogenous hemostatic defect (i.e., with transfusions), the outcome is



frequently disastrous. For these reasons, in all cases of ongoing bleeding, the first consideration must always be to exclude a surgically correctable cause.

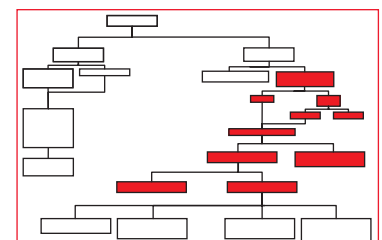
Ongoing bleeding may be surprisingly difficult to diagnose. Healthy young patients can usually maintain a normal blood pressure until their blood loss exceeds 40% of their blood volume (roughly 2 L). If the bleeding is from a laceration to an extremity, it will be obvious; however, if the bleeding is occurring internally, there may be few physiologic signs until the patient is at high risk for death.

Even when a technical cause of bleeding has seemingly been excluded, the possibility should be reconsidered periodically throughout assessment. Patients who are either unresuscitated or underresuscitated undergo vasospasm that results in decreased bleeding. As resuscitation proceeds, the catecholamine-induced vasospasm subsides and bleeding may recur. Only when the surgeon is confident that a missed injury or unligated vessel is not the cause of the bleeding should other potential causes be investigated.

Initial Assessment of Potential Coagulopathy

The first step in the assessment of a stable patient with a potential coagulopathy is to draw a blood sample. The blood should be drawn into a tube containing ethylenediaminetetraacetic acid (EDTA) for a CBC and into a citrated tube for coagulation analysis (these tubes commonly have purple and blue tops, respectively).

Concomitant with these laboratory tests, it is essential to obtain a personal and family history of bleeding tendencies. A patient who has had dental extractions without major problems or who had a normal adolescence without any history of bleeding dyscrasias is very unlikely to have a congenital or hereditary bleeding disorder.¹³ Alternatively, previous bleeding events and a familial history of bleeding are



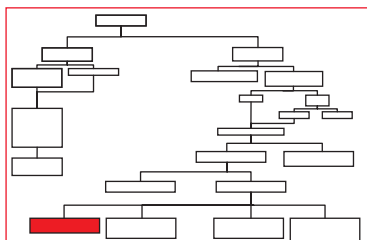
both suggestive of a congenital coagulopathy and warrant further testing to diagnose and treat the disorder [see Discussion, Bleeding Disorders, *below*]. Mucosal and superficial bleeding is suggestive of platelet abnormalities, and deep bleeding is suggestive of a factor deficiency. A thorough medication inventory is necessary to assess the possible impact of drugs on laboratory and clinical presentations. In the patient history query, it is advisable to ask explicitly about nonprescription drugs—using expressions such as “over-the-counter drugs,” “cold medicines,” and “Pepto-Bismol”—because unless specifically reminded, patients tend to equate the term “medications” with prescription drugs. If this is not done, many drugs that are capable of influencing hemostasis *in vivo* and *in vitro* (e.g., salicylates, cold and allergy medicines, and herbal supplements) may be missed.

Interpretation of Coagulation Parameters

NORMAL INR, NORMAL APTT

Patients with a normal INR and a normal aPTT who exhibit unexpected bleeding may have impaired platelet activity. Inadequate platelet activity is frequently manifested as persistent oozing from wound edges or as low-volume bleeding. Such bleeding is rarely the cause of exsanguinating hemorrhage, although it may be life-threatening when it occurs in certain locations (e.g., inside the cranium or the pericardium). Inadequate platelet activity may be attributable to an insufficient number of platelets, platelet dysfunction, or a platelet inhibitor. In the absence of a major surgical insult or concomitant coagulopathy, a platelet count of 20,000/ μ L or higher is usually adequate for normal coagulation.^{14,15} There is some disagreement regarding the threshold for platelet transfusion in the absence of active bleeding. Patients undergoing procedures in which even small-vessel oozing is potentially life-threatening (e.g., craniotomy) should be maintained at a higher platelet count (i.e., > 20,000/ μ L). Patients without ongoing bleeding who are not specifically at increased risk for major complications from low-volume bleeding may be safely watched with platelet counts as low as 10,000/ μ L.¹⁶

Oozing in a patient who has an adequate platelet count and normal coagulation parameters may be a signal of platelet dysfunction. The now-routine administration of acetylsalicylic acid (aspirin) and clopidogrel (Plavix) to reduce the risk of myocardial infarction and stroke has led to a rise in the incidence of drug-induced platelet dysfunction. Aspirin causes irreversible platelet dysfunction through the cyclooxygenase pathway. It takes approximately 10 days for sufficient numbers of new platelets to be formed such that the effect of aspirin lapses; however, because the half-life of aspirin is on the order of 2 to 5 hours, new platelet transfusions should be unaffected if at least a day has passed since the last use of aspirin. The platelet dysfunction caused by other nonsteroidal antiinflammatory drugs (e.g., ibuprofen) is reversible and consequently does not generally last as long as that caused by aspirin.



Newer platelet-blocking agents have been found to be effective in improving outcome after coronary angioplasty.¹⁷ These drugs function through different mechanisms. Some, such as abciximab (ReoPro), eptifibatide (Integrilin), and tirofiban (Aggrastat), block the platelet surface receptor glycoprotein (GP) IIb-IIIa, which binds platelets to fibrinogen. Others, such as clopidogrel, ticlopidine (Ticlid), and prasugrel (Effient), target the P2Y₁₂ receptor (also known as the adenosine diphosphate [ADP] receptor). Clopidogrel, the most commonly used among this group, permanently prevents the association of P2Y₁₂ receptors into functional oligomeric complexes. As a result, there is no way to inactivate this medication if the patient experiences bleeding during its therapeutic window, which typically lasts about 5 days from the last dose. In the face of life-threatening bleeding during this interval, it is reasonable to administer platelets based on the rationale that, in large-enough quantities, they may eventually bind all of the active metabolite. Some of the newest drugs in the P2Y₁₂ inhibitor class (which have not yet been evaluated for use in the United States), for example, ticagrelor, are reversible, which may help avoid such difficulties in the future.

von Willebrand disease (vWD), although sometimes associated with a slight prolongation of the aPTT (as a result of decreased factor VIII activity), most commonly shows no abnormalities with both the INR and the aPTT. The clinical expression is variable, but von Willebrand factor (vWF) levels of less than 30% are more likely associated with clinically important bleeding. Confirmation of the diagnosis can be obtained by specialized tests [see Discussion, Bleeding Disorders, *below*]. Correction is accomplished by administering desmopressin, directed therapy (vWF/factor VIII), or cryoprecipitate.

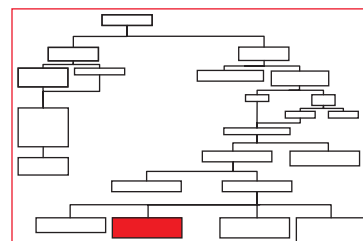
In patients with platelet dysfunction caused by an inhibitor of platelet function, such as an elevated blood urea nitrogen (BUN) level or aspirin, 1-desamino-8-D-arginine vasopressin (desmopressin) is capable of significantly improving the platelet dysfunction.¹⁸ The mechanism of this effect is not entirely understood but appears to involve more complex changes than simply increased release of factor VIII and vWF.

Supratherapeutic effects of the low-molecular-weight heparins (LMWHs) may also manifest with a normal INR and aPTT [see Normal INR, Prolonged aPTT, *below* for a discussion of both unfractionated heparin and the LMWHs].

Less common causes of bleeding in patients with a normal INR and a normal aPTT include factor XIII deficiency, hypofibrinogenemia or dysfibrinogenemia, and derangements in the fibrinolytic pathway [see Discussion, Mechanics of Hemostasis, *below*].

NORMAL INR, PROLONGED APTT

In the absence of a history of significant bleeding, patients with a normal INR and an abnormal aPTT are likely to have a drug-induced coagulation defect. The agent most commonly responsible is unfractionated heparin. Reversal of the heparin effect, if desired, can be



accomplished by administering protamine sulfate. Protamine should be given with caution, however, because it may induce both hyper- and hypocoagulable states.¹⁹ Protamine should also be used with caution because of the potential for allergic reactions, including anaphylaxis. Patients can become sensitized to impurities in protamine if they have previously received it. Also, diabetic patients have been described to become sensitized through their exposure to similar impurities in protamine-containing insulin formulations (e.g., neutral protamine Hagedorn, or “NPH,” insulin).²⁰

Importantly, the aPTT does not detect the anticoagulant activity of LMWHs. Because such heparins exert much of their anticoagulant effect by potentiating antithrombin to inactivate factor Xa rather than factor IIa, an assay that measures anti-Xa activity is needed to measure the anticoagulant effect. However, the anti-Xa effect of the LMWHs may not be as effectively reversed by protamine as the anti-IIa effect of unfractionated heparin. It is currently unclear which agent is best for reversal of LMWHs, but both protamine and rVIIa have been advocated. Whether or not bleeding has occurred, because the standard coagulation tests do not detect the effect of the LMWHs, suspicion for a supratherapeutic effect should be aroused if there is a concern that excessive doses have been administered or clearance has decreased (e.g., renal insufficiency).

One nuance of the anti-Xa laboratory assay is that it may not truly measure the degree of anticoagulation *in vivo*; rather, anti-Xa results for some of the available assays should be interpreted merely as the concentration of LMWH in plasma. Because heparins (including LMWHs) function to a large extent by catalyzing the activity of antithrombin, the therapeutic effect of heparin is critically dependent on adequate antithrombin levels. In fact, acquired antithrombin deficiency (as occurs with trauma and other critical illnesses) is the most common reason for LMWH to have an inadequate effect. The anti-Xa laboratory assay may not account for *in vivo* antithrombin levels, because some methods involve the addition of antithrombin to the test sample as a reagent. Consequently, the results of this assay may not be a reliable guide to the patient's coagulation status.

An additional crucial point is that the administration of plasma (e.g., fresh frozen plasma [FFP]) will not correct the anticoagulant effect of either unfractionated heparin or LMWHs. In fact, given that plasma contains antithrombin and that both unfractionated heparin and LMWHs act by potentiating antithrombin, administration of FFP could actually enhance the heparins' anticoagulant effect.

A variety of direct thrombin inhibitors (e.g., bivalirudin [Hirulog], lepirudin, argatroban, and dabigatran) are currently available in Europe, Asia, and North America.²¹ Many of them cause prolongation of the aPTT. Dabigatran is a new oral direct thrombin inhibitor that has been recently approved for use in the United States for atrial fibrillation. As an oral alternative to warfarin that does not require frequent laboratory tests to monitor its anticoagulant effect, dabigatran may become widely used. It has a variable impact on coagulation assays: the aPTT is typically elevated but may be only moderately prolonged with supratherapeutic levels of dabigatran.²² One disadvantage shared by most of the direct thrombin

inhibitors is that the effects are not reversible; if thrombin inhibition is no longer desired, FFP should be given to attempt to correct the aPTT. Because the inhibitor that is circulating but not bound at the time of FFP administration will bind the prothrombin in the FFP, the amount of FFP required to correct the aPTT may be greater than would be needed with a simple factor deficiency.

Hemophilia is also associated with prolongation of the aPTT. It can cause spontaneous bleeding or prolonged bleeding after a surgical or traumatic insult. As noted, hemophilia is rare in the absence of a personal or family history of the disorder. Although hemophilia can occur as an acquired autoimmune condition with production of antibodies against clotting factors, the most common forms of hemophilia are inherited and involve deficiencies of factors VIII, IX, and XI (hemophilia A, hemophilia B [Christmas disease], and hemophilia C, respectively). As X-linked recessive disorders, hemophilias A and B occur almost exclusively in males. The clinical presentations of hemophilia A and hemophilia B are similar: hemarthroses are the most common clinical manifestations, ultimately leading to degenerative joint deformities. Spontaneous bleeding may also occur, resulting in intracranial hemorrhage, large hematomas in the muscles of extremities, hematuria, and GI bleeding. Certain types of vWD can result in a deficiency of factor VIII and thus present like hemophilia A. Factor XI deficiency is relatively common in Jewish persons but rarely results in spontaneous bleeding. Such deficiency may result in bleeding after oral operations and trauma; however, a number of major procedures (e.g., cardiac bypass surgery) do not result in postoperative bleeding in this population.²³

In contrast to depletion of natural anticoagulants such as antithrombin and protein C, depletion of procoagulant factors rarely gives rise to significant manifestations until it is relatively severe. Typically, no laboratory abnormalities result from depletion of procoagulant factors until factor activity levels fall below 40% of normal, and clinical abnormalities are frequently absent even when factor activity levels fall to only 10% of normal. This tolerance for subcritical degrees of depletion is a reflection of the built-in redundancies in the procoagulant pathways.

If hemophilia is suspected, specific factor analysis is indicated. Appropriate therapy involves administering the deficient factor or factors. Hemophilic patients who have undergone extensive transfusion therapy may pose a particular challenge: massive transfusions frequently lead to the development of antibodies that make subsequent transfusion or even directed therapy impossible. Accordingly, several alternatives to transfusion or directed factor therapy (e.g., rVIIa) have been developed for use in this population.

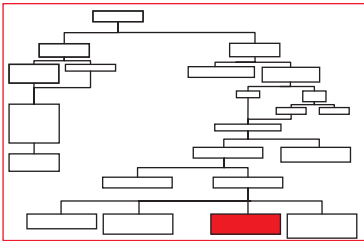
Other conditions may also have an isolated effect on the aPTT. Drotrecogin alfa (i.e., activated protein C), a medication approved for treatment of certain subgroups of patients with sepsis, may prolong the aPTT. Its use is contraindicated in the presence of active hemorrhage, but if bleeding should arise during its use, cessation of the infusion should suffice as a result of its short half-life. Lupus anticoagulant and contact factor deficiency can also cause prolongation of the aPTT; however, these phenomena do not clinically result in a hypocoagulable state.

INCREASED INR,
NORMAL APTT

An increased INR in association with a normal aPTT is potentially a more ominous finding in a patient with a coagulopathy. Any of a number of causes, all centering on factor deficiency, may be responsible.

An elevated INR occurs with the administration of vitamin K antagonists (e.g., warfarin), with variable effects on the aPTT. If the aPTT is normal, this usually demonstrates that warfarin was only recently started (usually < 3 days of treatment) or has been underdosed. Such a coagulopathy is the result of a pure factor deficiency, and its degree is proportional to the prolongation of the INR. Because warfarin acts by disrupting vitamin K metabolism, the coagulopathy may be corrected by giving vitamin K [see Table 1], but this process takes several hours for additional proteins to be synthesized.²⁴ If the patient is actively bleeding, vitamin K should still be given, but the primary corrective measures should be to administer FFP and/or rVIIa. FFP should be administered in an amount proportional to the patient's size and the relative increase in the INR, whereas rVIIa should be administered at a dose of 15 to 90 µg/kg. The INR should subsequently be rechecked to ensure that correction has been achieved. Because rVIIa has a relatively short half-life, in general, it should be used as an adjunct to FFP rather than a replacement for it. Aside from the time delay involved, the main potential disadvantage of vitamin K replacement therapy is that if the patient is to be reanticoagulated with warfarin in the near future, dosing will be difficult because the patient will exhibit resistance to warfarin for a variable period.

Cirrhosis is arguably the most serious of the causes of an elevated INR. It is a major problem not so much because of the coagulopathy itself but because of the associated deficits in wound healing and immune function that result from dysfunction of reticuloendothelial cells and hepatocytes.



Generally, factor replacement should be instituted with FFP, but use of rVIIa is reasonable in the setting of active hemorrhage or any intracranial hemorrhage. Although to date there is little information on its efficacy in this particular setting, the administration of rVIIa, 20 to 40 µg/kg, would be a reasonable approach. If the bleeding is a manifestation of portal hypertension (as in variceal bleeding), emergency portal decompression—typically via transjugular intrahepatic portosystemic shunting—should be considered. Modest elevations of the INR in patients with cirrhosis who are not actively bleeding, have not recently undergone operation, and are not specifically at increased risk for life-threatening hemorrhage may be observed without correction.

INCREASED INR,
PROLONGED APTT

Increases in both the INR and the aPTT may be the most problematic finding of all. When both assays show increases, the patient is likely to have multiple factor deficiencies; possible causes include disseminated intravascular coagulation (DIC), severe hemodilution, and renal failure with severe nephrotic syndrome. However, when dramatic elevations of the aPTT and the INR occur that are out of proportion to the patient's clinical status, the problem may simply be that the specimen tube was not adequately filled. If a life-threatening coagulopathy seems unlikely, the blood sample should be redrawn and the tests repeated.

Hemodilution and nephrotic syndrome result in a coagulopathy that is attributable to decreased concentration of coagulation proteins. Dilutional coagulopathy may occur when a patient who is given a large volume of packed RBC units is not also given coagulation factors.²⁵ Because of the tremendous redundancy of the hemostatic process, pure dilutional coagulopathy is rare. It is considered an unlikely diagnosis until after one full blood volume has been replaced (as when a patient requires 10 units of packed RBCs to

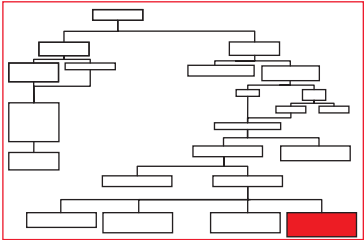


Table 1 Management of the Patient with an Increased International Normalized Ratio

Indication		Recommended Treatment
No significant bleeding	INR above therapeutic range but < 5.0	Lower or hold the next dose
	INR > 5.0 but < 9.0	
	Rapid reduction of INR is not required	In the absence of additional risk factors for bleeding, withhold next 1–2 doses; alternatively, withhold next dose and give vitamin K, 1.0–2.5 mg orally
	Rapid reduction of INR is required	Give vitamin K, 1.0–2.0 mg p.o.; expected reduction of INR should occur within 24 hr
	INR > 9.0	Give vitamin K, 3.0–5.0 mg p.o.; expected reduction of INR should occur within 24 hr
Serious bleeding	Any elevation of INR	Give vitamin K, 10 mg IV, supplemented with FFP, prothrombin complex concentrate, or rVIIa; further vitamin K supplementation may be required every 12 hr
Life-threatening bleeding	Any elevation of INR	Give FFP, prothrombin complex concentrate, or rVIIa supplemented with vitamin K 10 mg IV, repeated as necessary

FFP = fresh frozen plasma; INR = international normalized ratio; rVIIa = recombinant activated factor VII.

maintain a stable hematocrit). Nephrotic syndrome is associated with loss of plasma proteins (including coagulation factors) from the kidneys.



Both hemodilution and nephrotic syndrome should be distinguished from DIC (which is a consumptive rather than a dilutional process²⁶), although, on occasion, this distinction is a difficult one to make. A blood sample should be sent for D-dimer assay. If the D-dimer level is low (< 1,000 ng/mL), DIC is unlikely; if it is very high (> 2,000 ng/mL) and there is no other clear explanation (e.g., a complex pelvic fracture), DIC is more likely than dilutional coagulopathy. Treatment of dilutional coagulopathy should be directed at replacement of lost factors. FFP should be given first, followed by cryoprecipitate, calcium, and platelets. Transfusion should be continued until the coagulation parameters are corrected and the bleeding stops.

The term “DIC” refers to the phenomenon of diffuse, disorganized activation of the clotting cascade within the vascular space. It does not occur as an isolated process; rather, it is always secondary to an underlying problem. It typically results either from an overwhelming clotting stimulus (e.g., massive crush injury, overwhelming infection, or transfusion reaction) or from a more moderate clotting stimulus in the context of shock. The underlying problem that manifests as DIC has a range of severity, with mild and moderate cases represented by anything from a subclinical process to the development of organ dysfunction. One school of thought is that the systemic inflammatory response syndrome and DIC are simply different manifestations of the same process. However, severe cases are what surgeons traditionally think of as DIC: bleeding in the context of fibrinolysis and consumption of coagulation factors. Severe DIC arises when congestion of the microvasculature with thrombi occurs, resulting in large-scale activation of the fibrinolytic system. This fibrinolytic activity results in breakdown of clot at previously hemostatic sites of microscopic injury (e.g., endothelial damage) and macroscopic injury (e.g., IV catheter sites, fractures, or surgical wounds), as well as degradation of fibrinogen systemically. Bleeding and reexposure to tissue factor stimulate activation of factor VII with increased coagulation activity; thus, microthrombi are formed, and the vicious circle continues.

Beyond recognition and correction of the underlying problem causing DIC and the associated coagulopathy, the diagnosis of DIC represents something of an academic exercise because there is no specific treatment for the condition. Scoring systems that assess the severity of DIC are most useful for distinguishing DIC from other causes of coagulopathy (e.g., hypothermia, dilution, and drug effects) [see Table 2]. Heparin, antifibrinolytic agents, and antithrombotics

Table 2 Coagulopathy (DIC) Score

Score	INR (s)	aPTT (s)	Platelets (1,000/ μ L)	Fibrinogen (mg/dL)	D-Dimer (ng/mL)
0	< 1.2	< 34	> 150	> 200	< 1,000
1	> 1.2	> 34	< 150	< 200	< 2,000
2	> 1.4	> 39	< 100	< 150	< 4,000
3	> 1.6	> 54	< 60	< 100	> 4,000

aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulopathy; INR = international normalized ratio.

(e.g., antithrombin and protein C) have been used. Despite improvements in laboratory measures with some of these agents, they do not appear to improve survival. One interpretation of the PROWESS trial²⁷ that evaluated drotrecogin alfa (recombinant activated protein C) as treatment for sepsis is that the observed improvement in survival resulted from containment of intravascular coagulation. However, the mortality benefit in that study has not been replicated in other trials and may not apply to patients undergoing operations. Currently, the most appropriate treatment of severe DIC is removal of the clotting stimulus and aggressive transfusion to restore blood loss and clotting factor deficits. The high mortality associated with severe DIC probably relates more to the underlying pathology than to the hematologic derangement per se.

An increased INR with a prolonged aPTT may also be caused by various isolated factor deficiencies of the common pathway. Congenital deficiencies of factors X and V and prothrombin are very rare. Acquired factor V deficiencies have been observed in patients with autoimmune disorders. Acquired hypoprothrombinemia has been documented in a small percentage of patients with lupus anticoagulants who exhibit abnormal bleeding. Factor X deficiencies have been noted in patients with amyloidosis.

Several anticoagulant medications can affect both the INR and the aPTT. Patients receiving large doses of unfractionated heparin may have a prolonged INR, depending on the specific reagents used in the test, and the related oral anti-Xa inhibitors (e.g., rivaroxaban) may also prolong both the INR and the aPTT.²⁸ The oral direct thrombin inhibitors typically prolong the aPTT but can also affect the INR. Stabilized warfarin therapy will increase both the INR and the aPTT. Several rodenticides in the vitamin K antagonist class with warfarin (e.g., brodifacoum) exert the same effect; however, because they have a considerably longer half-life than warfarin, the reversal of the anticoagulation effect with vitamin K or FFP may be correspondingly longer.²⁹ Animal venoms may also increase the INR and the aPTT.

Approach to the Patient with Anemia

Anemia is common among hospitalized surgical patients. In large prospective cohort studies, the average hemoglobin level in surgical ICU patients was 11.0 g/dL,³⁰ and 55% of surgical ICU patients received transfusions.³¹ Anemia results from at least three factors: (1) blood loss related to the primary

condition or to the operation, (2) serial blood draws (totaling, on average, approximately 40 mL/day in the ICU),³⁰ and (3) diminished erythropoiesis related to the primary illness.

Treatment of anemia has evolved over the past few decades. Cellular transfusions have long been a common, available

means to treat anemia in the perioperative and critical care setting, but recognition in the 1980s that blood products were transmitting fatal viral infections changed the risk-benefit analysis. The blood-banking community in the United States and most developed countries adapted and systematically reduced the risk of transmission of the most likely infectious agents by restricting the eligible donor pool and routinely testing blood products for serologic and nucleic acid evidence of pathogens.³² Currently, the possibility that an unpredictable new pathogen might emerge, such as a novel or mutated virus, is thought to pose a greater risk to the safety of the blood supply than such recognized pathogens as HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV). These latter viruses are now so rarely transmitted in developed countries that the incidence of transfusion-related infection is difficult to quantify.

Transfusion of allogeneic blood products has also been associated with significant dysfunction of the immune system and inflammatory processes. These immunomodulatory effects are presumably much more frequent than rare cases of viral transmission, but it is not clear whether they are causally related to poorer outcomes [see Discussion, Mechanism and Significance of Transfusion-Related Immunomodulation, *below*]. Furthermore, transfusion also may not augment oxygen delivery as assumed as a result of a variety of changes that occur with red cell storage.

Moreover, randomized trials comparing a restrictive RBC transfusion protocol (hemoglobin concentration maintained at 7.0 to 9.0 g/dL) with a more liberal protocol (hemoglobin maintained at 10.0 to 12.0 g/dL) for critically ill patients have not demonstrated harm with the restrictive approach.³³ In fact, as suggested by the Transfusion Requirements in Critical Care (TRICC) study, the restrictive approach may even improve survival for younger or less severely ill patients.³⁴

Thus, for a variety of reasons, the conventional wisdom is to try to limit blood transfusions when possible. The decision whether to transfuse should be based on the patient's current and predicted need for additional oxygen-carrying capacity [see *Figure 1*]. First, it is important to determine whether significant hypovolemia or active bleeding is present. In such patients, liberal transfusion is indicated as a means of increasing intravascular volume and preventing the development of profound deficits in oxygen-carrying capacity [see Approach to the Patient with Massive Hemorrhage, *above*].

In a hemodynamically stable but critically ill patient without evidence of active hemorrhage, it is appropriate to take a more restrictive approach and administer transfusion only when the hemoglobin concentration is less than 7.0 g/dL (hematocrit 21%). Less acutely ill patients can even be followed for hemoglobin concentrations below 7.0 g/dL, especially if they are asymptomatic and at minimal risk for hemorrhage. In the absence of transfusion, iron supplementation should be considered, particularly for menstruating women. There is no specific hemoglobin concentration or hematocrit (i.e., transfusion trigger) at which all patients should receive transfusions.

The above approach should apply to most patients, but there are two groups for whom a more aggressive RBC transfusion policy should be considered. Although opinion is divided, patients who have acute coronary artery ischemic syndromes and those with acute neurologic conditions may

benefit from a more liberal transfusion strategy. To date, relatively few such patients have been included in the randomized trials on this topic.

Acute Coronary Artery Ischemic Syndromes

Currently, there is no consensus regarding the most appropriate transfusion strategy for patients with acute coronary artery ischemic syndromes, such as active myocardial infarction and unstable angina. The results of observational studies have been mixed,^{35,36} and no clinical trial has yet addressed this specific subgroup of patients. Some distinction should be drawn between patients who have acute coronary artery ischemic syndromes and those who merely have a history of coronary artery or other atherosclerotic disease. Although the TRICC trial did not enrol patients admitted after a routine cardiac surgical procedure,³⁴ it included enough patients with cardiovascular disease to allow a sizable subgroup analysis.³⁷ This post hoc analysis suggested that in patients with cardiovascular disease as a primary diagnosis or an important comorbid condition, survival was essentially the same regardless of whether a liberal transfusion protocol or a restrictive one was followed. In patients with confirmed ischemic heart disease, however, a nonsignificant decrease in survival was noted, generating some concern that adverse cardiovascular events (e.g., myocardial infarction and stroke) might increase in frequency at lower hemoglobin levels. Consequently, a target hemoglobin of 10 g/dL is generally considered acceptable for patients with acute coronary artery ischemic syndromes or significant coronary artery disease.

Neurologic Conditions

Some have argued that just as the heart may be sensitive to decreases in oxygen-carrying capacity, the injured central nervous system may be vulnerable to further damage from anemia because anemia may limit the delivery of oxygen to damaged tissue. According to this view, patients with traumatic brain injury, stroke, or spinal cord injury may be vulnerable to anemia-related damage; however, as yet, the clinical evidence—mostly from observational studies with significant methodological weaknesses—is insufficient either to support or to refute liberal transfusion of such patients.³⁸

Symptomatic Anemia

An additional consideration in the decision to transfuse blood is the oxygen-carrying capacity that is necessary to prevent patient fatigue or discomfort. Typical symptoms of anemia include lightheadedness, tachycardia, and tachypnea either during activity or at rest. Clearly, some degree of tachycardia is to be expected in any patient who has undergone a major operation or sustained a serious injury. The key judgment to make in deciding whether to treat symptomatic anemia with transfusion is whether the anemia is truly compromising the patient's health or recovery. It is not always easy, however, to determine whether symptoms or signs attributed to anemia will actually improve as a result of transfusion. For example, a liberal transfusion approach does not appear to lead to earlier discontinuation of mechanical ventilation.³⁹ A major randomized trial that is near completion, the Functional Outcomes in Cardiovascular Patients Undergoing

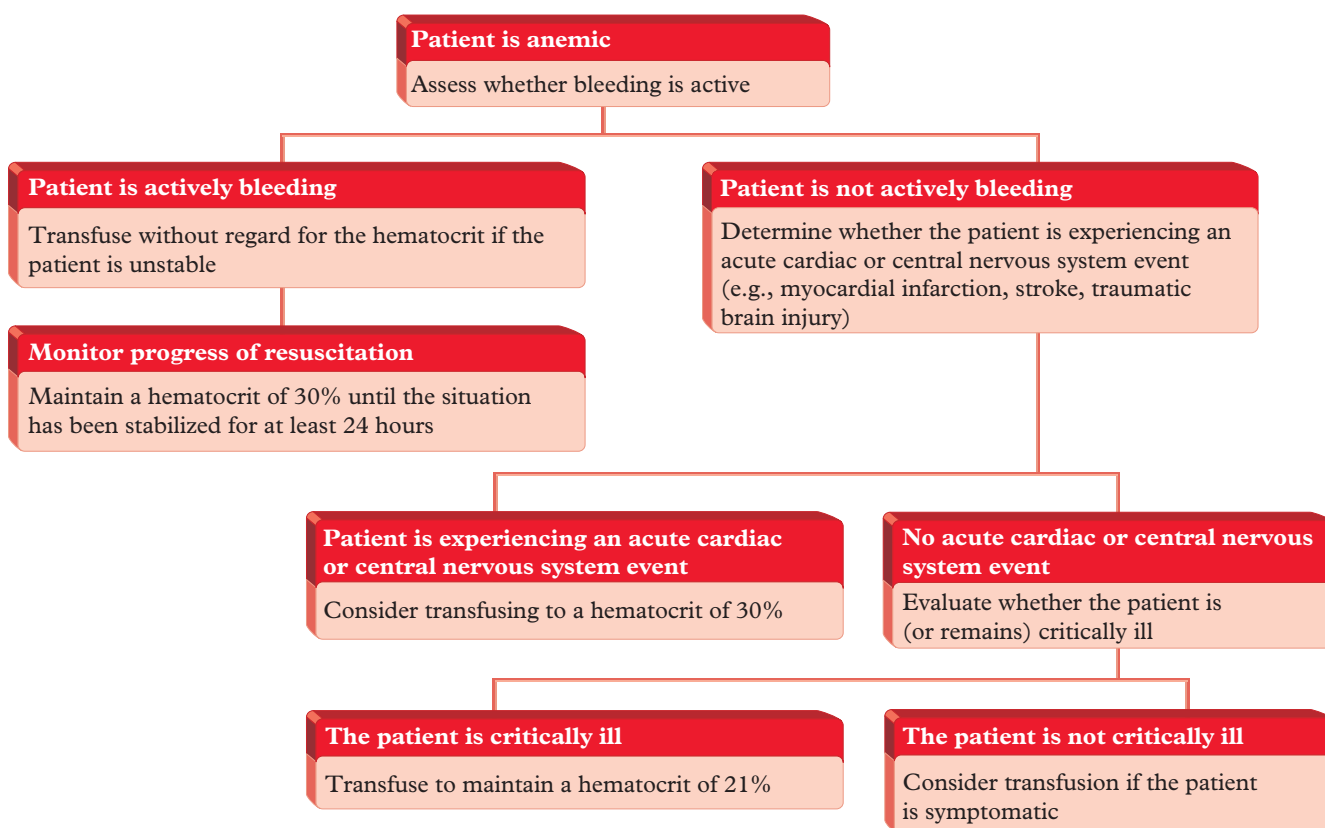


Figure 1 Algorithm depicting the decision-making process for transfusion in anemic patients.

Surgical hip fracture repair (FOCUS) study, is addressing the issue of functional recovery. Its primary aim is to determine whether liberal transfusion improves walking ability among anemic patients with a history of cardiovascular disease who undergo operative repair of a hip fracture.⁴⁰

Observation of Anemia

Although it is now standard practice to observe patients with hemoglobin concentrations of 6 to 7 g/dL, data suggest that the benefits of transfusion probably outweigh the risks below this level.

For all patients, if the hemoglobin level drops low enough, cellular metabolism cannot be sustained and death becomes a certainty. Followers of certain religious faiths who decline blood transfusion even when death is the probable or certain consequence have provided valuable observational data on the effects of severe anemia that would otherwise be unethical to obtain. Such cases have challenged surgeons and intensive care physicians to find techniques for supporting life at extremely low hemoglobin concentrations and have helped define the limits beyond which anemia may be fatal. Reviews of patients who have refused transfusion suggest that a hemoglobin below 5 g/dL results in substantial increases in mortality, especially in elderly persons and patients with cardiovascular disease.⁴¹

When RBC transfusion is not possible (whether because the patient declines transfusion or because compatible blood is unavailable), a number of temporizing measures can be

used. First, steps should be taken to minimize additional iatrogenic blood loss. Laboratory tests should be restricted to those that are most likely to benefit the patient and should be conducted with the smallest amount of blood possible (e.g., pediatric specimen tubes). Nonemergency operations that are likely to involve appreciable blood loss should be postponed if possible. Second, any impediments to native erythropoiesis should be removed: iron should be supplemented (orally if possible), and the administration of recombinant erythropoietin should be considered. Third, 100% oxygen should be administered because oxygen dissolved in plasma contributes a significant proportion of oxygen delivery at very low hemoglobin levels. Fourth, in extreme cases, consideration should be given to decreasing oxygen demand. Because the mechanical work of respiration itself becomes a significant contributor to oxygen demand in severely anemic patients, mechanical ventilation and even neuromuscular blocking agents should be considered to reduce oxygen demand from skeletal muscle. The metabolic rate can be further reduced by inducing hypothermia.

For decades, efforts have been in progress to augment oxygen-carrying capacity using RBC substitutes. Various different substitutes have been evaluated, some of which remain under investigation. None have been approved for routine use by the US Food and Drug Administration (FDA), largely because of significant adverse effects. The main categories of substitutes are those based on hemoglobin and those based on perfluorocarbons. Unmodified, acellular hemoglobin is nephrotoxic, so hemoglobin-based blood substitutes involve

either attempts to modify the hemoglobin molecule or encapsulate hemoglobin within synthetic membranes. Even with such modifications, however, these substitutes appear to increase the risk of death and myocardial infarction.^{42,43} Perfluorocarbon-based substitutes have attempted to take advantage of the high solubility of oxygen in these liquids, but their development has been impeded by practical hurdles in their

production and storage as well as adverse effects with their use.⁴⁴ Thus, although blood substitutes promise a number of advantages (increased shelf life, availability that is not limited by donor supply, and reduced or eliminated risk of incompatibility reactions and pathogen transmission), the extent to which they will ever be a suitable treatment for anemia in surgical patients is unclear.

Discussion

Mechanics of Hemostasis

Hemostasis is the term for the process by which cellular and plasma components interact in response to vessel injury to maintain vascular integrity and promote wound healing. The initial response to vascular injury (primary hemostasis) involves the recruitment and activation of platelets, which then adhere to the site of injury. Subsequently, plasma proteins, in concert with cellular components, begin to generate thrombin, which causes further activation of platelets and converts fibrinogen to fibrin monomers that polymerize into a fibrin clot (secondary hemostasis). The final step is the release of plasminogen activators that induce clot lysis and tissue repair.

The cellular components of hemostasis include endothelium, subendothelial cells and substrate, white blood cells (WBCs), RBCs, and platelets. The plasma components include a number of pro- and anticoagulant proteins that, once activated, can accelerate or downregulate thrombin formation or clot lysis to facilitate wound healing. In normal individuals, these hemostatic components are in a regulatory balance; thus, any abnormality involving one or more of these components can result in a pathologic state, whether of uncontrolled clot formation (thrombosis) or of excessive bleeding (hemorrhage). These pathologies can result from either hereditary or acquired causes.

CELLULAR COMPONENTS

Endothelium and Subendothelial Tissue

The endothelium has both procoagulant and anticoagulant properties. At baseline, in its normal, undamaged state, the endothelial surface is covered with endogenous antithrombins (antithrombin III, heparan sulfate, dermatan sulfate, and others) that protect against pathologic coagulation, thus providing a barrier between prothrombotic factors in the plasma and thrombogenic subendothelial factors. However, when vascular injury occurs, the endothelium and subendothelial tissues serve as a nidus for recruitment, adhesion, and aggregation of platelets. Disruption of the endothelium exposes collagen fibrils, to which platelets adhere, and tissue factor (TF), which serves as an integral, potent clotting stimulus [see Procoagulants, *below*]. TF is pervasive on the cell surfaces of subendothelial tissue and especially concentrated on such tissue as vascular adventitia, cerebral cortex, lung parenchyma, visceral organ capsules, and epidermis.⁴⁵ Damaged or activated endothelial cells express adhesion molecule receptors (E-selectin and P-selectin), and release of vWF from

the Weibel-Palade bodies of endothelial cells causes platelets to adhere to their surface. The presence of interleukin-1 β (IL-1 β), tissue necrosis factor (TNF), interferon gamma, and thrombin also promotes expression of TF on the endothelium.^{46,47} TF activates factors X and VII, and these activated factors generate additional thrombin, which increases both fibrin formation and platelet aggregation.

The endothelium also acts in numerous ways to downregulate coagulation.⁴⁸ Heparan sulfate and thrombomodulin are both downregulators of thrombin formation. In the presence of thrombin, the endothelium responds by expressing or releasing (1) membrane-bound thrombomodulin, which forms a complex with thrombin to activate protein C; (2) endothelium-derived relaxing factor (i.e., nitric oxide⁴⁹) and prostacyclin, which have vasodilating and platelet aggregation-inhibiting effects, respectively; and (3) tissue plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA), either of which converts the zymogen plasminogen to its active form, plasmin, that degrades fibrin and fibrinogen.^{47,50} Heparan sulfate, on the endothelium wall, forms a complex with plasma antithrombin to neutralize thrombin. The endothelium is also the source of tissue factor pathway inhibitor (TFPI), which downregulates TF-VIIa-Xa complexes.

Erythrocytes and Leukocytes

The nonplatelet cellular components of blood play indirect roles in hemostasis. RBCs contain thromboplastins that are potent stimulators of various procoagulant proteins. In addition, in the setting of laminar flow, a sufficient concentration of RBCs within the bloodstream (i.e., the hematocrit) assists in primary hemostasis by physically forcing the platelets toward the endothelial surfaces. When the RBC count is low enough, there is a reduction in this force, which results in inadequate endothelium-platelet interaction and subsequently a bleeding diathesis.

Leukocytes have several functions in the hemostatic process. The interaction between the adhesion molecules expressed on both leukocytes and endothelium results in cytokine production, initiation of inflammatory responses, and degradation of extracellular matrix to facilitate tissue healing. In the presence of thrombin and other stimuli, monocytes express TF, potentiating coagulation. Neutrophils and activated monocytes bind to stimulated platelets and endothelial cells that express P-selectin. Adhesion and rolling of neutrophils, mediated by fibrinogen and selectins on the endothelium, appear to help restore vessel integrity but may

also lead to inflammatory responses.^{51,52} Lymphocytes also adhere to endothelium via adhesion molecule receptors and appear to be responsible for cytokine production and inflammatory responses.

Platelets

Platelets facilitate hemostasis and subsequent fibrin formation both by generating the initial platelet plug and by providing a phospholipid surface on which the activation of coagulation factors is localized. Activation of platelets by agonists such as adenosine triphosphate (ATP), ADP, epinephrine, thromboxane A₂, collagen, and thrombin causes platelets to undergo morphologic changes and degranulation. Degranulation releases procoagulants (e.g., thrombospondin, vWF, fibrinogen, ADP, ATP, and serotonin) that promote further platelet adhesion and aggregation and surface expression of P-selectin, which induces cellular adhesion. Platelet degranulation also results in the release of β -thromboglobulin, platelet factor 4 (which has antiheparin properties), various growth factors, and calcium, as well as the formation of platelet microparticles. Plasminogen activator inhibitor-1 (PAI-1) released from degranulated platelets neutralizes the fibrinolytic pathway by forming a complex with t-PA.

On exposure to vascular injury, platelets adhere to the exposed endothelium via binding of vWF to the GPIb-IX-V complex.⁵³ Conformational changes in the GPIIb-IIIa complex on the activated platelet surface enhance fibrinogen binding, which results in platelet-to-platelet aggregation and complex morphologic changes. The end result of these changes is a platelet plug with such dense adherence of platelets and such dramatic changes in platelet shape that, on electron microscopy, each platelet resembles a piece within a three-dimensional jigsaw puzzle. The phospholipid surface of the membranes of activated platelets then anchors activated IXa-VIIIa and Xa-Va complexes, thereby localizing thrombin generation.⁵⁴

PLASMA COMPONENTS

Procoagulants

In primary hemostasis, circulating plasma vWF—in addition to the vWF secreted by endothelial cells in response to injury—facilitates adhesion of platelets to the endothelium. Plasma vWF also serves as the carrier protein for factor VIII, preventing its neutralization by the protein C regulatory pathway.

Secondary hemostasis involves numerous plasma components. Traditional diagrams of the coagulation cascade depict two distinct pathways, the intrinsic and extrinsic pathways, that join in a final common pathway. The historical reason for depicting the coagulation cascade this way is to emphasize differences between the aPTT test (which is prolonged in the absence of sufficient quantities of components in the intrinsic pathway: factor XII, prekallikrein, and high-molecular-weight kininogen) and the INR (which measures clotting time in response to the extrinsic stimulus, TF). In vivo, however, the primary stimulus for secondary hemostasis is the exposure of TF (i.e., the extrinsic pathway), and the thrombin generated from this process activates factor VIII, effectively bypassing the initial steps in the intrinsic pathway. Accordingly, our focus is not on the standard view of intrinsic and extrinsic

pathways but rather on the different roles contact factors (part of the intrinsic cascade) and TF play in coagulation.

The main role of the contact factors (factor XII, prekallikrein, and high-molecular-weight kininogen) appears to be in downregulation of coagulation rather than the generation of thrombin. Even in patients completely lacking these factors, who have a markedly prolonged aPTT, abnormal bleeding does not occur. However, the contact factors activate the bradykinin (BK) pathway, which exerts profibrinolytic effects by stimulating endothelial release of plasminogen activators. It also stimulates endothelial production of nitric oxide and prostacyclin, which play vital regulatory roles in vasodilation and regulation of platelet activation.⁵⁵

The key initiator of plasma procoagulant formation is the expression of TF on cell surfaces.^{46,56} TF activates factor VII and binds with it to form the TF-VIIa complex, which activates factors X and IX. Factor Xa enhances its own production by activating factor IX, which in turn converts more factor X to Xa. Factor Xa also produces minimal amounts of thrombin by cleaving the prothrombin molecule. The thrombin generated from this process cleaves the coagulation cofactors V and VIII to enhance production of the factor complexes IX-VIIIa (intrinsic tenase) and Xa-Va (prothrombinase), which dramatically catalyzes conversion of prothrombin to thrombin [see Figure 2].⁵⁷

Thrombin has numerous effects, including pro- and antithrombotic functions. Its procoagulant properties include cleaving fibrinogen, activating the coagulation cofactors V and VIII, inducing platelet aggregation, inducing expression of TF on cell surfaces, and activating factor XIII. In cleaving fibrinogen, thrombin causes the release of fibrinopeptides A and B (fibrin monomer). The fibrin monomer undergoes conformational changes that expose the α and β chains of the molecule, which then polymerize with other fibrin monomers to form a fibrin mesh. Activated factor XIII cross-links the polymerized fibrin (between the α chains and the γ chains) to stabilize the fibrin clot and delay fibrinolysis.

Fibrin(ogen)olysis

Plasminogen is the primary fibrinolytic zymogen that circulates in plasma. In the presence of t-PA or u-PA (released from the endothelium), plasminogen is converted to the active form, plasmin. Plasmin cleaves fibrin (or fibrinogen) between the molecule's D and E domains, causing the formation of X, Y, D, and E fragments from fibrinogen degradation, and D-dimers from polymerized fibrin degradation. The secondary function of the fibrinolytic pathway is the activation by u-PA of matrix metalloproteinases that degrade the extracellular matrix.⁵⁸

Endogenous Antithrombotic Factors

In persons with normal coagulation status, downregulation of hemostasis occurs simultaneously with the production of procoagulants (e.g., activated plasma factors, stimulated endothelium, and stimulated platelets). In addition to their procoagulant activity, both thrombin and contact factors stimulate downregulation of the coagulation process. Thrombin forms a complex with endothelium-bound thrombomodulin to activate protein C, which inhibits factors Va and VIIIa. The thrombin-thrombomodulin complex also regulates the fibrinolytic pathway by activating a circulating plasma protein

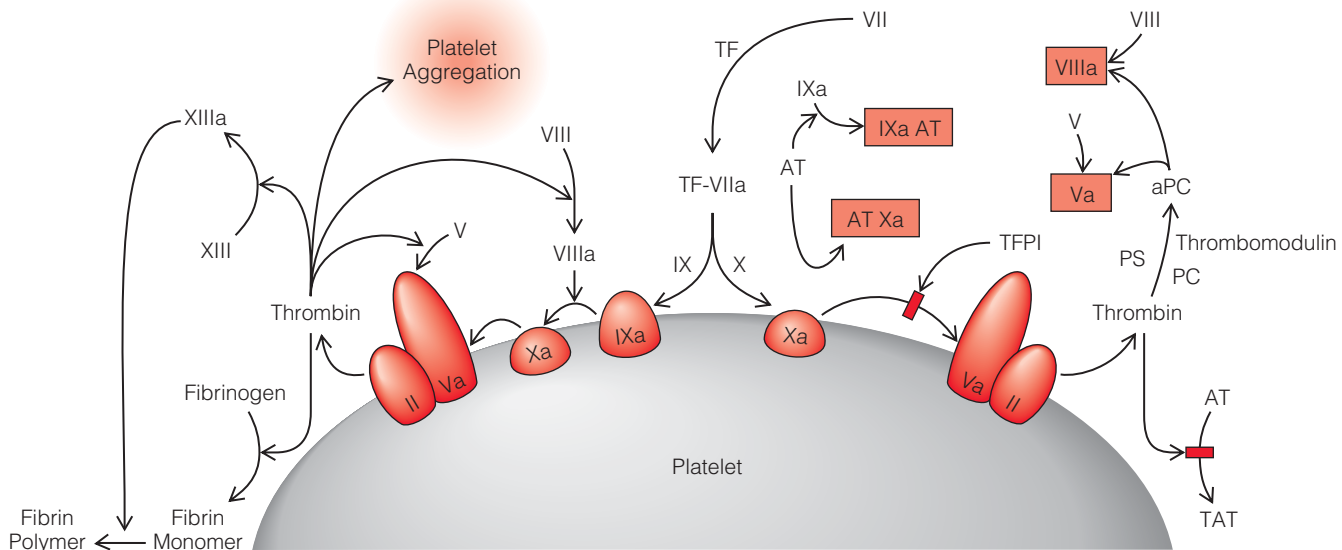


Figure 2 Schematic representation of the procoagulant pathways. aPC = activated protein C; AT = antithrombin; PC = protein C; PS = protein S; TAT = thrombin-antithrombin; TF = tissue factor; TFPI = tissue factor pathway inhibitor.

known as thrombin-activatable fibrinolysis inhibitor (TAFI), which appears to suppress conversion of plasminogen to plasmin.⁵⁹ Contact factors are known to be required for normal surface-dependent fibrinolysis, and there is some evidence that contact factor deficiencies can lead to thromboembolism. Another plasma protein responsible for regulation of fibrinolysis is α_2 -antiplasmin, which binds to circulating and bound plasmin to limit breakdown of fibrin.

Circulating downregulating proteins include antithrombin (a serine protease inhibitor of activated factors—especially factors IXa, Xa, and XIa—and thrombin⁴⁵), proteins C and S (regulators of factors VIIIa and Va⁶⁰), C1 inhibitor (a regulator of factor XIa), TFPI (a regulator of the TF-VIIa-Xa complex⁶¹), and α_2 -macroglobulin (a thrombin inhibitor—the primary thrombin inhibitor in neonates⁶²). Limitation of platelet activation occurs secondarily as a result of decreased levels of circulating agonists and endothelial release of prostacyclin [see Figure 2].

Bleeding Disorders

INHERITED COAGULOPATHIES

Numerous congenital abnormalities of the coagulation system have been identified. These include abnormalities of plasma proteins (e.g., hemophilia and vWD), platelet receptors (e.g., Glanzmann thrombasthenia and Bernard-Soulier syndrome), and endothelium (e.g., telangiectasia). Abnormalities can involve abnormal protein synthesis resulting in a dysfunctional coagulation protein (a “defect”) or decreased protein production (a “deficiency”).

Most of the coagulation defects associated with the endothelium are closely related to thrombosis or atherosclerosis. Defects or deficiencies of thrombomodulin, TFPI, and t-PA, albeit rare, are associated with thrombosis.^{63,64} Vascular defects (e.g., hemorrhagic telangiectasias) may carry an

increased risk of bleeding as a consequence of dysfunctional fibrinolysis, concomitant platelet dysfunction, or coagulation factor deficiencies.⁶⁵

Abnormalities of RBCs and WBCs may promote thrombosis (e.g., decreased blood flow from polycythemia vera, leukocytosis, and sickle cell anemia) but usually do not cause major bleeding unless there is an associated severe thrombocytopenia.

The most common heritable disease associated with bleeding is vWD, with some countries having a prevalence as high as 1 to 2%. This condition is characterized by a variety of qualitative and quantitative abnormalities of vWF. There are three main categories of vWD [see Table 3]: reduced concentration of normal vWF (type 1), dysfunctional vWF (type 2), and the absence of vWF altogether (type 3). Type 2 vWD is classified into four subtypes (A, B, M, and N) based on the nature of the dysfunction. Type 1 is most common, accounting for 70 to 80% of cases of vWD, and varies in severity, with most affected individuals manifesting only a mild bleeding tendency. Diagnosis of vWD is based on a combination of the patient history and laboratory parameters. Patients with vWD typically experience bleeding from the mucous membranes. Because the most prevalent forms of vWD are inherited in an autosomal dominant fashion, careful questioning typically reveals affected relatives. Laboratory tests to confirm the diagnosis and determine the subtype of vWD include vWF antigen tests, functional assays (e.g., the ristocetin cofactor assay), vWF multimer assays, ristocetin-induced platelet aggregation assays, platelet count, and factor VIII levels. The ratio of activity:antigen (ristocetin cofactor assay result relative to vWF antigen level) is typically approximately 1 for vWF type 1 vWD and less than 0.6 for type 2 vWD. Appropriate treatment depends on which type of vWD the patient has. Desmopressin is typically sufficient prophylaxis or treatment for patients with type I vWD but is not always effective, and tachyphylaxis can occur. vWF/factor VIII

Table 3 Classification and Management of von Willebrand Disease

Type of von Willebrand Disease	Pathology	Proportion among All Cases of vWD	Diagnostic Evaluation	Primary Treatment
1	Deficiency in the amount of vWF produced	70–80%	Decreased vWF Ag and vWF RCo	Desmopressin (vWF/factor VIII concentrate if unresponsive to desmopressin)
2A	Failure of mutant vWF to form appropriate multimers or increased proteolysis of mutant vWF	10%	Normal or decreased vWF Ag; vWF RCo substantially decreased; vWF MM with high- and high/medium-molecular-weight forms absent	vWF/factor VIII concentrate
2B	Increased binding of mutant vWF to platelet glycoprotein Ib receptor, resulting in decreased circulating vWF	5%	Similar to type 2A, but thrombocytopenia, increased RIPA (even with low dose of ristocetin), and increased vWF binding to normal platelets	vWF/factor VIII concentrate, platelet transfusion
2M	Abnormal vWF binding site for platelet glycoprotein Ib receptor, leading to decreased affinity between vWF and platelets	Rare	Normal or decreased vWF Ag; vWF RCo substantially decreased; vWF MM normal and decreased vWF binding to normal platelets	vWF/factor VIII concentrate
2N	Abnormal vWF binding site for factor VIII, leading to decreased circulating factor VIII levels	Rare	Normal vWF Ag, vWF RCo, and vWF MM; decreased factor VIII level and factor VIII binding to vWF	vWF/factor VIII concentrate
3	Complete absence of vWF	Very rare	Absent vWF Ag, vWF RCo, and vWF MM	vWF/factor VIII concentrate
Platelet type	Increased binding of vWF to mutant platelet glycoprotein Ib receptor, resulting in decreased circulating vWF	Rare	Similar to type 2B except that, as with normal individuals, vWF does not bind to normal platelets	Platelet transfusion

RIPA = ristocetin-induced platelet aggregation (not the same as vWF RCo); vWF = von Willebrand factor; vWF Ag = von Willebrand factor antigen test; vWF MM = von Willebrand factor multimer analysis; vWF RCo = von Willebrand factor ristocetin cofactor assay.

concentrate is necessary for patients with type 1 who are not responsive to desmopressin and for patients with types 2 and 3 who undergo operations or experience major bleeding. Desmopressin may be contraindicated for patients with type 2B vWD because it can exacerbate the thrombocytopenia that they typically experience.⁶⁶

There are rare inherited defects of the platelet surface, including Glanzmann thrombasthenia (a defect in the GPIIb-IIIa complex), Bernard-Soulier syndrome (a defect in the GPIb-IX complex), and Scott syndrome (a defect in the platelet's activated surface that promotes thrombin formation).⁶⁷ Intracellular platelet defects (storage pool diseases) are also rare but do occur; examples are gray platelet syndromes (e.g., alpha granule defects), Hermansky-Pudlak syndrome, dense granule defects, Wiskott-Aldrich syndrome, and various defects in intracellular production and signaling (involving defects of cyclooxygenase synthase and phospholipase C, respectively).

Numerous pathologic states are also associated with deficiencies or defects of plasma procoagulants. Hemophilias A, B, and C were previously discussed [*see Interpretation of Coagulation Parameters, Normal INR, Prolonged aPTT, above*]. Inherited deficiencies of the other coagulation factors are very rare. Factor XIII deficiencies result in delayed post-operative or posttraumatic bleeding. Congenital deficiencies

of factor V, factor VII, factor X, prothrombin, and fibrinogen may become apparent in the neonatal period (presenting, for example, as umbilical stump bleeding); later in life, they result in clinical presentations such as epistaxis, intracranial bleeding, GI bleeding, deep and superficial bruising, and menorrhagia.

Defects or deficiencies in the fibrinolytic pathway are also rare and are most commonly associated with thromboembolic events. α_2 -Antiplasmin deficiencies and primary fibrin(ogen)olysis are rare congenital coagulopathies with clinical presentations similar to those of factor deficiencies. In primary fibrin(ogen)olysis, failure of regulation of t-PA and u-PA leads to increases in circulating plasmin levels, which result in rapid degradation of clot and fibrinogen.^{68,69}

ACQUIRED COAGULOPATHIES

A wide range of clinical conditions may cause deficiencies of the primary, secondary, or fibrinolytic pathways. Acquired coagulopathies are very common, but most do not result in spontaneous bleeding.

As noted, coagulopathies related to the endothelium are primarily associated with thrombosis rather than bleeding. A number of disorders may cause vascular injury, including sickle cell anemia, hemolytic-uremic syndrome, and thrombotic thrombocytopenic purpura.

Acquired platelet abnormalities, both qualitative (i.e., dysfunction) and quantitative (i.e., decreases in absolute numbers), are common occurrences. Many acquired thrombocytopathies are attributable to medications (e.g., aspirin, ibuprofen, other nonsteroidal antiinflammatory drugs, various antibiotics, certain antihistamines, and phenytoin). Newer classes of antiplatelet drugs function by inhibiting platelet receptors [see Interpretation of Coagulation Parameters, Normal INR, Normal aPTT, *above*].⁷⁰ Thrombocytopenia can be primary or secondary to a number of clinical conditions. Primary bone disorders (e.g., myelodysplastic or myelophthitic syndromes) and spontaneous bleeding may arise when platelet counts fall below 10,000/ μ L.

Thrombocytopenia can be associated with immune causes (e.g., immune thrombocytopenic purpura and heparin-induced thrombocytopenia) or such conditions as a deficiency in the plasma metalloproteinase ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) (thrombotic thrombocytopenic purpura). Acquired platelet dysfunction (e.g., acquired vWD) that is not related to dietary or pharmacologic causes has been observed in patients with immune disorders or cancer.

Multifactorial coagulopathies are common as well. Patients with severe renal disease typically exhibit platelet dysfunction (from excessive amounts of uremic metabolites), factor deficiencies associated with impaired protein synthesis and protein loss (as with increased urinary excretion), or thrombocytopenia (from diminished thrombopoietin production).^{71,72} Patients with severe hepatic disease commonly have impairment of coagulation factor synthesis, increases in circulating levels of paraproteins, and splenic sequestration of platelets.

Massive cellular transfusion can dilute the levels of clotting factors if more than 10 packed RBC units are given within a short period without plasma supplementation. In addition, because RBC units contain citrate as an anticoagulant, massive transfusion can induce a coagulopathy from hypocalcemia. Immunologic reactions to ABO/Rh mismatches can induce immune-mediated hypercoagulation. Acquired multifactorial deficiencies associated with extracorporeal circuits (e.g., cardiopulmonary bypass, hemodialysis, and continuous venovenous dialysis) can arise as a consequence of hemodilution from circuit priming fluid or activation of procoagulants after exposure to thrombogenic surfaces. Thrombocytopenia can result from platelet destruction and activation caused by circuit membrane exposure or can be secondary to the presence of heparin antibody.

Animal venoms can be either pro- or antithrombotic. The majority of the poisonous snakes in the United States (rattlesnakes in particular) have venom that works by activating prothrombin, but cross-breeding has produced a number of new venoms with different hemostatic consequences. The clinical presentation of coagulopathies associated with snakebites generally mimics that of consumptive coagulopathies.⁷³

Drug-induced factor deficiencies are common, particularly as a result of anticoagulant therapy. The most commonly used anticoagulants are heparin and warfarin. Heparin does not cause a factor deficiency; rather, it accelerates production of antithrombin, which inhibits factor IXa, factor Xa, and thrombin, thereby prolonging clot formation. Warfarin reduces procoagulant potential by inhibiting vitamin K synthesis, thereby reducing carboxylation of factor VII, factor

IX, factor X, prothrombin, and proteins C and S. Newer drugs that may also cause factor deficiencies include direct thrombin inhibitors (e.g., lepirudin and bivalirudin⁷⁴) and fibrinogen-degrading drugs (e.g., anicrod⁷⁵).

Isolated acquired factor deficiencies are relatively rare. Clinically, they present in exactly the same way as inherited factor deficiencies, except that there is no history of earlier bleeding. In some cases, there is a secondary disease (e.g., lymphoma or an autoimmune disorder) that results in the development of antibody to a procoagulant (e.g., factor V, factor VIII, factor IX, vWF, prothrombin, or fibrinogen).

Disseminated Intravascular Coagulation

DIC is a complex coagulation process that involves massive activation of the coagulation system with deposition of fibrin in the microvasculature that causes the subsequent activation of the fibrinolytic pathway. The overwhelming microvascular fibrin deposition is the cause of both the activation of the fibrinolytic system (which promotes more bleeding) and eventually multiple organ dysfunction syndrome (MODS). The activation occurs at all levels, including platelets, endothelium, and pro- and anticoagulants. It is crucial to emphasize that DIC is an acquired disorder that occurs secondary to an underlying clinical event (e.g., child birth complicated by amniotic fluid embolism, severe gram-negative infection, shock, severe traumatic brain injury, polytrauma, severe burns, or cancer). As noted [see Interpretation of Coagulation Parameters, Increased INR, Prolonged aPTT, *above*], there is some controversy regarding the best approach to therapy, but there is no doubt that treating the underlying cause of DIC is paramount to patient recovery.

DIC is not always clinically evident: low-grade DIC may lack clinical symptoms altogether and manifest itself only through laboratory abnormalities, even when thrombin generation and fibrin deposition are occurring. In an attempt to facilitate recognition of DIC, the disorder has been divided into three phases, distinguished on the basis of clinical and laboratory evidence. In phase I DIC, there are no clinical symptoms, and the routine screening tests (i.e., INR, aPTT, fibrinogen level, and platelet count) are within normal limits.⁷⁶ Secondary testing (i.e., measurement of antithrombin, prothrombin fragment, thrombin-antithrombin complex, and soluble fibrin levels) may reveal subtle changes indicative of thrombin generation. In phase II DIC, there are usually clinical signs of bleeding around wounds, suture sites, IV sites, or venous puncture sites, and decreased function is noted in specific organs (e.g., lung, liver, and kidneys). The INR is increased, the aPTT is prolonged, and the fibrinogen level and platelet count are decreased. Other markers of thrombin generation and fibrinolysis (e.g., D-dimer level) show sizable elevations. In phase III DIC, MODS is observed, the INR and the aPTT are markedly increased, the fibrinogen level is markedly depressed, and the D-dimer level is dramatically increased. A peripheral blood smear shows large numbers of schistocytes, indicating RBC shearing from fibrin deposition.

The activation of the coagulation system seen in DIC appears to be primarily caused by TF. The brain, the placenta, and solid tumors are all rich sources of TF. Gram-negative endotoxins also induce TF expression. The exposure of TF on cellular surfaces causes activation of factors VII and

IX, which ultimately leads to thrombin generation. Circulating thrombin is rapidly cleared by antithrombin. Moreover, the coagulation pathway is downregulated by activated protein C and protein S. However, constant exposure of TF (as a result of underlying disorders) results in constant generation of thrombin, and these regulator proteins are rapidly consumed. TAFI and PAI also contribute to fibrin deposition by restricting fibrinolysis and subsequent fibrin degradation and clearance. Finally, it is likely that release of cytokines (e.g., IL-6, IL-10, and TNF) may play some role in causing the sequelae of DIC by modulating or activating the coagulation pathway.

Laboratory Assessment of Bleeding

Patients with massive or life-threatening hemorrhage should be treated presumptively and without a delay to obtain the results of laboratory tests [see Approach to the Patient with Massive Hemorrhage, *above*]. However, these tests serve an integral role in the diagnostic algorithm for patients with more modest bleeding. If the patient is not experiencing massive or life-threatening hemorrhage, blood samples for coagulation testing should be drawn before administering blood products or medication intended to promote coagulation. The CBC (including platelet count and differential count), the INR, and the aPTT tests should be the primary laboratory tests for differentiating coagulopathies [see Figure 3]. Technological advances have made it possible to perform these and other diagnostic laboratory tests outside the confines of the clinical laboratory (“near-care” or “point-of-care” testing). Whatever tests of coagulation are employed, it is important to recognize their limitations.

Several technical factors can influence the results of the INR and aPTT. These tests involve adding activators, phospholipids, and calcium to plasma in a test tube (or the equivalent) and determining the time to clot formation. Time to clot formation is a relative value in that it is compared with the time in a normal population, and each laboratory must periodically adjust the reference range accordingly. Poor sampling techniques (e.g., hemolysis, inadequately filled coagulation tubes, excessive tourniquet time, and clotted or activated samples) can influence the results. Hemolysis from poor phlebotomy technique can release thromboplastins from RBC membranes that initiate the coagulation process. An elevated hematocrit or inadequately filled specimen tube can prolong test results because the excess citrate chelates the calcium added in the assay. Hemolysis, jaundice, and lipemia can all interfere with the optical systems that modern instruments use to detect clot. In addition, factor VIII in particular is relatively labile, so failure to process and run coagulation samples expeditiously can prolong the aPTT.

Not all coagulation tests are functionally equivalent: different laboratory methods may yield differing results.⁷⁷ For most laboratories, coagulation reagents have been selected in such a way as to ensure that the tests are sensitive to factor VIII and IX deficiencies (i.e., diagnosis and monitoring of hemophilia) and the effects of warfarin and heparin. As a consequence, a normal aPTT in a patient with an abnormal INR may not exclude the possibility of common pathway deficiencies (e.g., deficiencies of factors X, V, and II), and most current methods of determining the INR and the aPTT

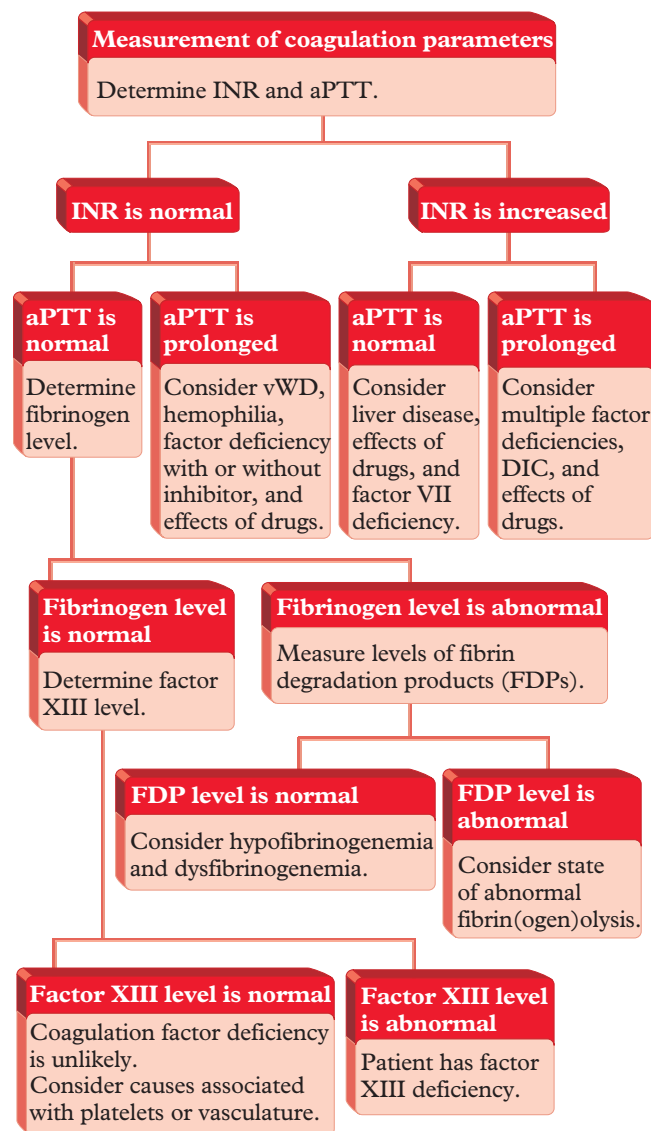


Figure 3 Algorithm depicting the use of coagulation parameters in assessment of coagulopathies. aPTT = activated partial thromboplastin time; DIC = disseminated intravascular coagulation; INR = international normalized ratio; vWD = von Willebrand disease.

do not detect low fibrinogen levels. In this chapter, we have assumed that the methods used with the INR and aPTT tests result in abnormalities when factor activity levels fall below 0.4 IU/mL.

Assessment of platelets also involves certain pitfalls. Platelet count and platelet function should be considered as completely independent metrics [see Figure 4]. Patients with congenital thrombocytopathies often have normal platelet counts; therefore, assessment of platelet function is required as well. Historically, the bleeding time has been used to assess platelet function. However, this test is grossly insensitive, yielding normal results in as many as 50% of patients with congenital thrombocytopathies.^{78,79} Numerous rapid tests of platelet function are currently available that can be used to screen for platelet defects; although the accuracy and clinical

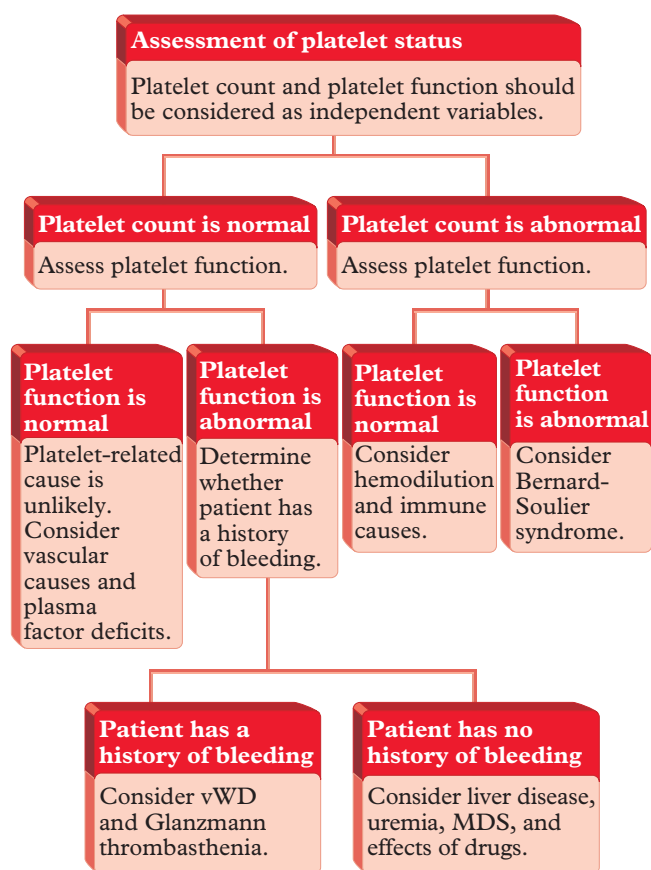


Figure 4 Algorithm depicting the use of platelet count and platelet functional status in assessment of coagulopathies. MDS = myelodysplastic syndrome; vWD = von Willebrand disease.

utility of these tests have not been thoroughly evaluated, they can be considered in the diagnostic approach to the bleeding patient [see Table 4].

The role of point-of-care testing appears to be expanding. The activated clotting time (ACT) has been used in the setting of cardiopulmonary bypass to monitor anticoagulation when such high levels of unfractionated heparin are used that no clotting would occur with the aPTT. A newer class of tests, commonly referred to as thromboelastography, measure viscoelastic changes in whole blood as it clots. In this technique, a pin is suspended from a torsion wire into a cup containing blood. The cup rotates periodically, and, as clot forms and later lyses over time, the device detects changes in torque transmitted to the immersed pin. The most commonly reported device is the thromboelastograph (TEG, Haemoscope Corporation, Niles, IL), but other devices using related methods include the rotational thromboelastogram (ROTEM, TEM International GmbH, Munich, DE) and the Sonoclot (Sienco Inc, Arvada, CO). The TEG and ROTEM report similar parameters [see Figure 5], but the values are not directly comparable. Modifications of the basic sample cup allow users to isolate specific abnormalities. Although certain patterns may reflect specific abnormalities, software applications have made graphs easier to interpret. Although these methods lack specificity and clinical outcome studies are not yet available, graphically depicted abnormalities may lead to

Product (Manufacturer)	Method
PFA-100 (Dade Behring)	Measures time required to occlude aperture after exposure to platelet agonists (collagen/epinephrine and collagen/ADP) at shear rates
hemoSTATUS (Medtronic)	Measures modified activated clotting time with platelet-activating factor as the platelet agonist
Whole Blood Aggregometers (Chronolog Corporation)	Measures changes in impedance after addition of platelet agonist(s)
Ultra Analyzer (Accumetrics)	Used primarily for measuring the effect of platelet glycoprotein blockers (e.g., abciximab and eptifibatide), aspirin, or P2Y12 inhibitors
Platelet Works (Helena Laboratories)	Compares platelet counts before and after addition of agonists (collagen and ADP)
Impact Cone and Plate(let) Analyzer (Diamd)	Measures platelet aggregates after exposure of whole blood to shear forces in a spinning cone
Multipate function analyzer (Verum Diagnostica GmbH)	Measures changes in impedance after addition of platelet agonist with four-channel impedance technology
Thromboelastometry	TEG analyzer with platelet mapping protocol, CSA and ROTEM with platelet function assessment [see Laboratory Assessment of Bleeding, above]

ADP = adenosine diphosphate.

better directed therapy. The trauma surgery community in particular has generated enthusiasm for thromboelastography to allow real-time monitoring of coagulopathic acutely injured patients. The main strength of the test may be to identify hyperfibrinolysis in a more timely fashion than traditional laboratory methods do, assisting clinicians in selecting patients for antifibrinolytic therapy (e.g., ϵ -aminocaproic acid).

At present, there are no laboratory or ex vivo methods capable of directly measuring the physiologic properties of the endothelium. Indirect assessments of endothelial damage can be obtained by measuring levels of several laboratory parameters (e.g., vWF, the soluble cytokines endothelin-1 and E-selectin, and thrombomodulin), but such measurements have no clinical utility in the assessment of a bleeding patient.

Mechanism and Significance of Transfusion-Related Immunomodulation

Although a unit of packed RBCs is an exceedingly complex biologic substance, blood is used frequently and somewhat casually, compared with many pharmaceutical agents that have undergone extensive regulatory review. A unit of allogeneic transfused blood contains antigenic RBCs, WBCs, and

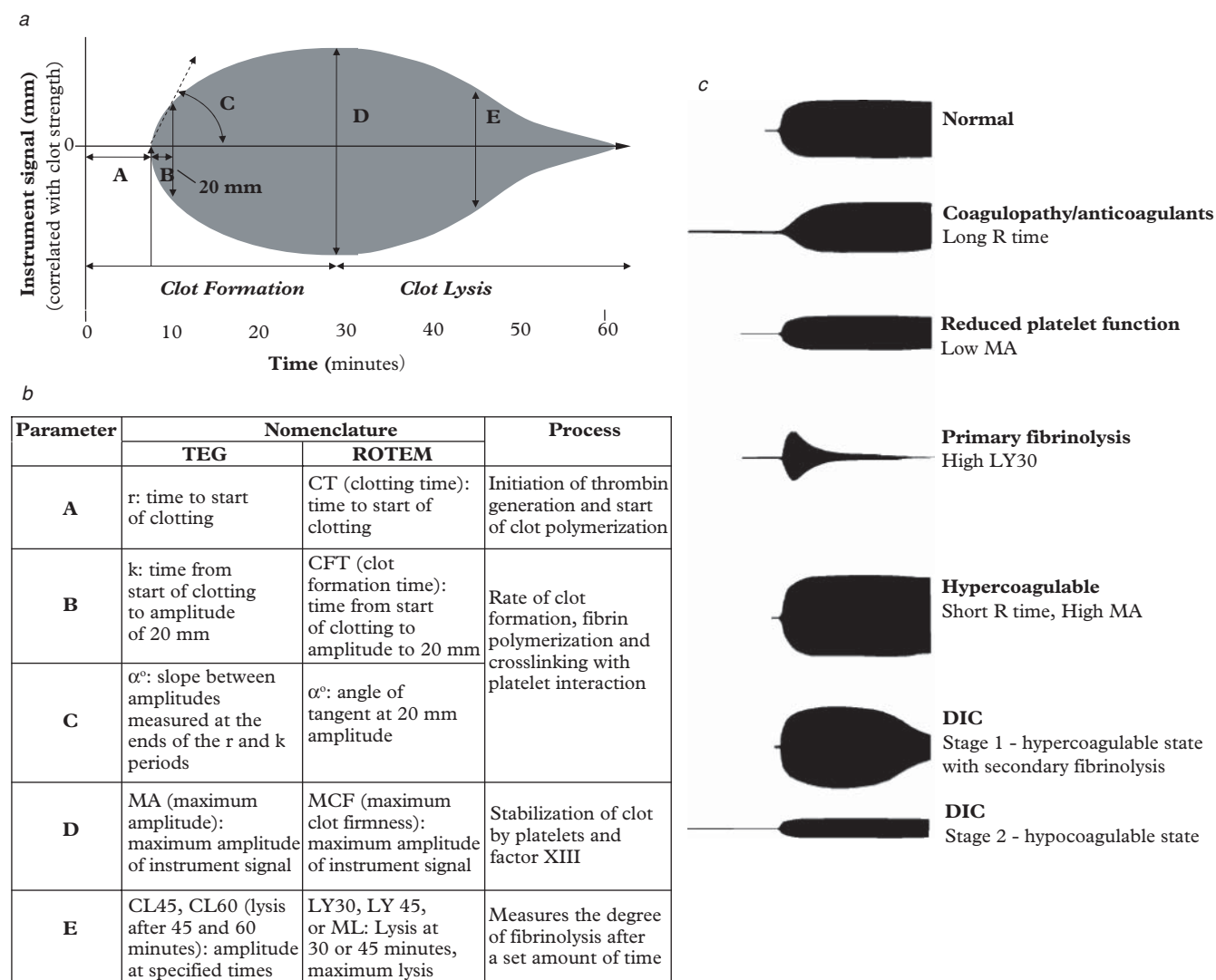


Figure 5 Schematic thromboelastogram (a), description of common thromboelastometry parameters (b), and illustration of selected abnormalities of coagulation (c). DIC = disseminated intravascular coagulation.

platelets; an array of antigenic or immunologically active substances in plasma (including both substances from donor plasma and substances that accumulate during storage); and, potentially, viral, bacterial, and parasitic pathogens. However, the specific transfusion-related factors that result in dysregulation of the innate or adaptive immune responses, as well as the clinical consequences of this immunomodulation, remain inadequately defined.

Interest in the immunosuppressive effect of blood transfusion stemmed in part from the observation by Opelz and colleagues in 1973 that recipients of cadaveric renal transplants experienced longer graft survival if they had undergone allogeneic blood transfusion before transplantation.⁸⁰ A number of different strategies for mitigating this immunosuppressive effect have been considered, including restrictive criteria for transfusion, administration of autologous blood products, and reduction of the quantity of donor leukocytes in units of blood. Buffy-coat reduction removes 70 to 80%

of donor leukocytes, but leukoreduction, typically through prestorage filtration techniques, removes more than 99.9% of donor leukocytes. Although leukoreduction has not been required by the FDA, it is required in Canada and several European countries and has been adopted by many blood banks in the United States, in part because it reduces the frequency of febrile transfusion reactions, cytomegalovirus transmission, and alloimmune platelet refractoriness.

Although donor leukocytes appear to be the most likely mediators of transfusion-related immunomodulation, donor erythrocytes or antibodies could also play a role. With increased storage time, donor erythrocytes develop a “storage lesion,” including morphologic changes that could impair their flow through the capillary microcirculation. A recent observational study of patients transfused in the setting of a cardiac operation found an association between older (i.e., greater than 14 days since donation) units of blood and increased postoperative complications and mortality.⁸¹

However, this study has been criticized for several methodologic issues, and many consider the issue unsettled. Transfusion-related acute lung injury (which some define very broadly to include underrecognized cases of immunomodulation) appears to be caused in some cases by donor antibodies to recipient leukocyte antigens. This has led some blood centers to exclude individuals likely to have such antibodies (e.g., previously pregnant women) from plasma donation.⁸²

A plethora of observational studies and some randomized trials have attempted to evaluate the role of blood transfusion in the recurrence of resected malignancies and postoperative infection. Most of the observational studies have compared the outcomes of transfused cohorts with those of nontransfused cohorts. The randomized trials, however, have mostly evaluated different kinds of blood transfusions against one

another (e.g., autologous versus allogeneic and leukoreduced versus nonleukoreduced). The literature is extensive, but many methodologic issues have been identified that limit the validity of the studies.⁸³ Accordingly, the evidence appears to be insufficient to establish a causal connection between allogeneic blood transfusion and either increased cancer recurrence or postoperative infection. Nonetheless, the heterogeneity of the study results and the finding of a major randomized trial, the TRICC trial, that a restrictive transfusion policy may improve survival in some patients continue to fuel debate over whether the avoidance or modification of allogeneic blood transfusion may improve patient outcomes.

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Acknowledgments

Figures 1, 3, and 4 Marcia Kammerer
Figure 2 Seward Hung

5 POSTOPERATIVE MANAGEMENT OF THE HOSPITALIZED PATIENT

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At the beginning of the modern era of surgery, operative procedures commonly took place in an operating theater, performed by plainclothes surgeons in aprons for audiences of students and other onlookers. Afterward, patients were typically cared for at home or in a hospital ward, with scarcely any monitoring and little to help them toward recovery besides their own strength and physiologic reserve. In the current era, surgery is a high-tech, rapid-paced field, with new knowledge and technological advances seemingly appearing around every corner. Many of these new discoveries have allowed surgeons to work more efficiently and safely, and as a result, a number of operations have now become same-day procedures. In addition, some very complex operations that were once thought to be impossible or to be associated with unacceptably high morbidity and mortality have now become feasible thanks to advances in surgical technique, anesthesia, postoperative management, and critical care. The focus of our discussion is on the postoperative considerations that have become essential for successful recovery from surgery.

Each patient is unique, and each patient's case deserves thoughtful attention; no two patients can be managed in exactly the same way. Nevertheless, certain basic categories of postoperative care apply to essentially all patients who undergo surgical procedures. Many of these categories are discussed in greater detail elsewhere in *ACS Surgery*. Our objective in this chapter is to provide a complete yet concise overview of each pertinent topic.

Disposition

The term disposition refers to the location and level of care and monitoring to which the patient is directed after the completion of the operative procedure. Although disposition is not often discussed as a topic in its own right, it is an essential consideration that takes into account many important factors. It may be classified into four general categories as follows:

1. Home or same-day surgery via the recovery room
2. The intensive care unit (ICU), with or without a stay in the recovery room
3. The surgical floor via the recovery room
4. The telemetry ward via the recovery room

The disposition category that is appropriate for a given patient is determined by considering the following four factors:

1. The patient's preoperative clinical status (including both the condition being treated and any comorbid conditions), as indicated by the history, the physical examination, and the input of other medical practitioners

2. The operative procedure to be performed
3. The course and duration of the operative procedure
4. The patient's clinical status at the completion of the procedure, as managed with the help of anesthesia colleagues

The initial phase of disposition planning begins preoperatively. After a full history has been obtained and a complete physical examination carried out, the procedure to be performed is decided on. This decision then initiates a discussion of the complexity and potential complications associated with the procedure, as well as of the concerns and special needs related to any comorbid conditions that may be present. If, as is often the case, the surgeon requires some assistance with planning the operation around the patient's other health problems, input from appropriate medical and surgical colleagues can be extremely helpful. Key factors to take into consideration include the potential complications related to the procedure and the urgency of their treatment; the level of monitoring the patient will require with respect to vital signs, neurologic examination, and telemetry; and the degree of care that will be necessary with respect to treatments, use of drains, and wound care. Relatively few published references describe specific criteria for the various disposition categories; however, most hospitals and surgery centers will have developed their own policies specifying a standard of care to be provided for each category.

SAME-DAY SURGERY

Same-day surgery is appropriate for patients who (1) have few or no comorbid medical conditions and (2) are undergoing a procedure that involves short-duration anesthesia or local anesthesia plus sedation and that carries a low likelihood of urgent complications. Operations commonly performed on a same-day basis include inguinal or umbilical hernia repair, simple laparoscopic cholecystectomy, breast biopsy, and small subcutaneous procedures.

The growth in the performance of minor and same-day procedures has led to the development of various types of short-stay units or wards. The level of care provided by a short-stay ward is generally equivalent to that provided by a regular nursing ward; however, the anticipated duration of care is substantially shorter, typically ranging from several hours to a maximum of 48 hours. Short-stay wards also undergo some modifications to facilitate the use of streamlined teaching protocols designed to prepare patients for home care. Many hospitals now have short-stay units, as do some independent surgery centers.

SURGICAL FLOOR

The vast majority of patients receive the postoperative care they require on the surgical floor (or regular nursing ward). Assessment of vital signs, control of pain, care of wounds, management of tubes and drains, and monitoring of intake and output are addressed every 2 to 8 hours (depending on the variable). Assignment of the patient to the regular nursing ward presupposes that he or she is hemodynamically stable and does not need continuous monitoring.

The telemetry ward is a variant of the regular nursing ward. The care provided in the telemetry ward is generally equivalent to that provided on other floor wards except that patients undergo continuous cardiac monitoring. Patients commonly assigned to the telemetry ward after operation include (1) those with a known medical history of arrhythmias that may necessitate intervention, (2) those with intraoperative arrhythmias or other electrocardiographic (ECG) changes who are not believed to require ICU monitoring but who do need this form of cardiac follow-up, and (3) those making the transition from the ICU to a regular ward who are hemodynamically stable but who require ongoing follow-up of a cardiac issue.

INTENSIVE CARE UNIT

When early postoperative complications may necessitate urgent intervention and close observation is therefore essential, patients should be admitted to the ICU for postoperative care. Postoperative ICU admission may also be appropriate for patients who are clinically unstable after the procedure; these patients often require ongoing resuscitation, intravenous (IV) administration of vasoactive agents, ventilatory support, or continuous telemetry monitoring for dysrhythmias. In addition, admission to the ICU should be considered for patients in whom the complexity of drain management, wound care, or even pain control may necessitate frequent postoperative monitoring that is not available on a regular nursing ward. At present, there is no single set of accepted guidelines directing ICU admission. There are, however, published sources that can provide some guidance. For example, a 2003 article supplied recommendations for the various services to be provided by differing levels of ICUs.¹ Published recommendations of this sort may be adopted or modified by individual hospitals and surgery centers as necessary.

Care Orders

Nurses and other ancillary personnel provide the bulk of the care received by patients after a surgical procedure; accordingly, it is essential that they receive clear and ample instructions to guide their work. Such instructions generally take the form of specific postoperative orders directed to each ancillary service. Services for which such orders may be appropriate include nursing, respiratory therapy, physical therapy (PT), occupational therapy (OT), and diet and nutrition. In what follows, we briefly outline some of the common tasks that require orders to be directed toward these services.

NASOGASTRIC TUBES

Nasogastric (NG) tubes are commonly placed after gastrointestinal (GI) operations, most frequently for drainage of

gastric secretions when an ileus is anticipated or offloading of the upper GI tract when a fresh anastomosis is located close by. Although NG tubes have often been placed routinely after abdominal surgery, the current literature cites a number of reasons why routine use is inadvisable and selective use is preferable. For example, significantly earlier return of bowel function, a trend toward fewer pulmonary complications, and enhanced patient comfort and decreased nausea are reported when NG tubes are not routinely placed or when they are removed within 24 hours after operation.²

When postoperative placement of an NG tube is considered appropriate, an order from a physician is required, along with direction regarding the method of drainage. Sometimes NG tubes are placed to low continuous suction; more often, however, they are placed to low intermittent suction to eliminate the chance of continuous suction against a visceral wall and to promote generalized drainage. If large volumes of secretions are not expected, continuous gravity may be used instead of suction. A key concern with NG tubes is maintenance of the patency of both the main port and the sump port. Should either port become blocked, the tube will be rendered ineffective. This concern should be discussed with the nursing staff. At times, it may be necessary to issue specific orders to ensure that this concern is appropriately addressed. As a rule, surgical nurses are well acquainted with tube maintenance; however, if thick secretions are expected, orders for routine flushing may be indicated. When the tube is no longer indicated, its removal may be ordered.

URINARY CATHETERS

Urinary catheters can serve a large variety of purposes. In the setting of bladder or genitourinary surgery, they are often employed to decompress the system so that it will heal more readily. After general surgical procedures—and many other surgical procedures as well—they are used to provide accurate measurements of volume output and thus, indirectly, to give some indication of the patient's overall volume and resuscitation status. Furthermore, after many procedures, patients initially find it extremely difficult or impossible to mobilize for urination, and a urinary catheter may be quite helpful during this time.

Their utility and importance notwithstanding, urinary catheters are associated with the development of nosocomial urinary tract infections (UTIs). As many as 40% of all hospital infections are UTIs, and 80 to 90% of these UTIs are associated with urinary catheters [see Postoperative Complications, *below*]. Accordingly, when catheterization is no longer deemed necessary, prompt removal is indicated. As a rule, orders specifically pertaining to urinary catheter care are few, typically including gravity drainage, flushing to maintain patency (if warranted), and removal when appropriate. At times, irrigation is employed after urologic procedures or for the management of certain infectious agents.

OXYGEN THERAPY

Supplemental administration of oxygen is often necessary after a surgical procedure. Common indicators of a need for postoperative oxygen supplementation include shallow breathing and pain, atelectasis, operative manipulation in the chest cavity, and postoperative impairment of breathing mechanics. Because supplemental oxygen is considered a

medication, a physician's order is required before it can be administered. In many cases, oxygen supplementation is ordered on an as-needed basis with the aim of enabling the patient to meet specific peripheral oxygen saturation criteria. In other cases, it is ordered routinely in the setting of known preoperative patient oxygen use.

An important factor to keep in mind is that oxygen supplementation protocols may vary from one nursing unit to another. Different units may place different limitations on the amount of supplemental oxygen permitted, depending on their specific monitoring and safety guidelines. Another important factor is that patients with known obstructive pulmonary disease and carbon dioxide retention are at increased risk for respiratory depression with hyperoxygenation; accordingly, particular care should be exercised in ordering supplemental oxygen for these patients.

DRAINS

Drains and tubes are placed in a wide variety of locations for a number of different purposes—in particular, drainage of purulent materials, serum, or blood from body cavities. Several types are commonly used, including soft gravity drains (e.g., Penrose), closed-suction drains (e.g., Hemovac, Jackson-Pratt, and Blake), and sump drains, which draw air into one lumen and extract fluid via a companion lumen. Traditionally, surgeons have often made the decision to place a drain on the basis of their surgical training and practice habits rather than of any firm evidence that drainage is warranted. Multiple randomized clinical trials have now demonstrated that routine use of drains after elective operations—including appendectomies and colorectal, hepatic, thyroid, and parathyroid procedures—does not prevent anastomotic and other complications (although it does reduce seroma formation). Consequently, it is recommended that drains, like NG tubes, be employed selectively.³⁻⁵ Once a drain is in place, specific orders must be issued for its maintenance. These include use of gravity or suction (and the means by which suction is to be provided if ordered), management and measurement of output, stripping, and care around the drain exit site.

Biliary tract drains include T tubes, cholecystostomy tubes, percutaneous drains of the biliary tree, and nasobiliary drains. Daily site maintenance, flushing, and output recording are performed by the nursing staff. Most biliary tract drains are removed by the practitioner or other trained midlevel staff members.

T tubes are generally placed after operative exploration or repair of the common bile duct (CBD). The long phalanges are left within the CBD, and the long portion of the tube is brought out to the skin for drainage. The tube is left in place until the CBD is properly healing and there is evidence of adequate distal drainage (signaled by a decrease in external drainage of bile). Before the T tube is removed, a cholangiogram is recommended to document distal patency and rule out retained gallstones or leakage.⁶

Cholecystostomy tubes are placed percutaneously—typically under ultrasonographic guidance and with local anesthesia—to decompress the gallbladder. Generally, they are used either (1) when cholecystectomy cannot be performed, because concomitant medical problems make anesthesia or the stress of operation intolerable, or (2) when

the presence of severe inflammation leads the surgeon to conclude that dissection poses too high an operative risk. Particularly in the latter setting, delayed elective cholecystectomy may be appropriate; if so, the cholecystostomy tube may be removed at the time of the operation.

Nasobiliary tubes are placed endoscopically in the course of biliary endoscopy. They are used to decompress the CBD in some settings. They are usually placed to gravity and otherwise are managed in much the same way as NG tubes.⁷

WOUND CARE

The topic of wound care is a broad one. Here we focus on initial postoperative dressing care, traditional wet-to-dry dressings, and use of a vacuum-assisted closure device (e.g., VAC Abdominal Dressing System, Kinetic Concepts, Inc., San Antonio, TX). These and other components of wound care are discussed in more detail elsewhere.

Initial wound management after an operative procedure generally entails placement of a sterile dressing to cover the incision. The traditional recommendation has been to keep this dressing in place and dry for the first 48 hours after operation; because epithelialization is known to take place within approximately this period, the assumption is that this measure will reduce the risk of wound infection. Although most surgeons still follow this practice, especially in general surgical cases, supporting data from randomized clinical studies are lacking. In addition, several small studies that evaluated early showering with closed surgical incisions found no increases in the rate of infection or dehiscence.^{8,9} It should be kept in mind, however, that these small studies looked primarily at soft tissue and other minor skin incisions that did not involve fascia. Thus, even though the traditional approach to initial dressing management is not strongly supported, the data currently available are insufficient to indicate that it should be changed.

Wet-to-dry dressings are used in a variety of settings. In a surgical context, they are most often applied to a wound that cannot be closed primarily as a consequence of contamination or inability to approximate the skin edges. Wet-to-dry dressings provide a moist environment that promotes granulation and wound closure by secondary intention. Moreover, their removal and replacement cause débridement of excess exudate or unhealthy superficial tissue. Postoperative orders should specify the frequency of dressing changes and the solution used to provide dampness. For most clean open incisions, twice-daily dressing changes using normal saline solution represent the most common approach. If there is excess wound exudate to be débrided, dressing changes may be performed more frequently. If there is particular concern about wound contamination or superficial colonization of organisms, substitution of dilute Dakin solution for normal saline may be considered.

A new era of wound management arrived in the late 1990s with the introduction of negative-pressure wound therapy (NPWT). In NPWT, a vacuum-assisted wound closure device places the wound under subatmospheric pressure conditions, thereby encouraging blood flow, decreasing local wound edema and excess fluid (and consequently lowering bacterial counts and encouraging wound granulation), and increasing wound contraction.^{10,11} Since the first published

animal studies, NPWT has been successfully employed for a multitude of wound types, including complex traumatic and surgical wounds, skin graft sites, and decubitus wounds. Before vacuum-assisted closure is used, however, it is necessary to consider whether and to what extent the wound is contaminated, the proximity of the wound to viscera or vascular structures, and the potential ability of the patient to tolerate dressing changes. Wounds that are grossly contaminated or contain significant amounts of nonviable tissue probably are not well suited to an occlusive dressing system of this type given that frequent evaluation and possibly débridement may be needed to prevent ongoing tissue infection and death. Furthermore, the suction effect of the standard vacuum sponge may cause serious erosion of internal viscera or exposed major blood vessels. Some silicone-impregnated nonadherent sponges are available that may be suitable in this setting, but caution should be exercised in using them. Finally, because of the adherence of the sponge and the occlusive adhesive dressing, some patients may be unable to tolerate dressing changes without sedation or anesthesia.

Nutrition

The patient's nutritional status has a significant effect on postoperative morbidity and even mortality. After most operative procedures that do not involve the alimentary tract or the abdomen and do not affect swallowing and airway protection, the usual practice is to initiate the return to full patient-controlled oral nutrition as soon as the patient is fully awake. In these surgical settings, therefore, it is rarely necessary to discuss postoperative nutrition approaches to any great extent.

After procedures that do involve the alimentary tract or the abdomen, however, the situation is different. The traditional practice has been to institute a *nil per os* (NPO) policy, with or without NG drainage, after all abdominal or alimentary tract procedures until the return of bowel function, as evidenced by flatus or bowel movement, is confirmed. The routine application of this practice has been challenged, however, especially over the past 15 years. Data from prospective studies of high statistical power are lacking, but many smaller studies evaluating early return to enteral nutrition after alimentary tract procedures have yielded evidence tending to favor more routine use of enteral intake within 48 hours after such procedures.

Issues related to postoperative nutritional support are discussed further and in greater detail elsewhere.

NPO STATUS

In the setting of elective colorectal surgery, it is well-accepted practice to initiate a return to patient-controlled enteral-oral feeding within 24 to 48 hours after operation; this practice yields no increase in the incidence of postoperative complications (e.g., anastomotic leakage, wound and intra-abdominal infection, and pneumonia) or the length of hospital stay and, according to some reports, may even decrease them.¹² In the setting of upper GI surgery (specifically, gastric resection, total gastrectomy, and esophagectomy), the situation is less clear-cut. Traditional concerns—in particular, the need to avoid distention stress on gastric or gastrojejunal

anastomoses after gastric resection, the more tenuous nature of a esophagojejunostomy after total gastrectomy, and the delayed gastric conduit emptying, aspiration risk, and anastomotic stress seen after esophagectomy or resection—have led to the current practice of instituting NG drainage and placing the patient on NPO status postoperatively until evidence of the return of bowel function is apparent, as well as, in some cases, investigating the anastomosis for possible leakage by means of contrast fluoroscopy. There are no clinical trial data to support this approach. In fact, many surgeons routinely remove the NG tube within 24 hours after gastric resection and early feeding without incurring increased complications. However, there are also no clinical trial data indicating that the current approach is potentially ineffective or harmful. Consequently, traditional management methods after upper GI procedures still are often endorsed in the literature.^{13,14}

ENTERAL NUTRITION

Enteral nutrition may be delivered via several routes. Most patients who have undergone an operation are able to take in an adequate amount of calories orally. When they are unable to do so, whether because of altered mental status, impaired pulmonary function, or some other condition, the use of enteral feeding tubes may be indicated. In the acute setting, NG and nasojejunal feeding tubes are the types most commonly employed to deliver enteral solutions into the GI tract. Either type is appropriate for this purpose; the two types are equivalent overall as regards their ability to provide adequate nutrition, and there are no significant differences in outcome or complications. In cases where prolonged inability to take in adequate calories orally is expected, the use of an indwelling feeding tube, such as a gastrostomy or jejunostomy tube, may be indicated. These tubes must be placed either at the time of operation or subsequently via surgical or percutaneous means, and there is some potential for complications. The specific indications for the use of such tubes are patient derived; they are not routinely associated with the performance of specific procedures.

TOTAL PARENTERAL NUTRITION

Total parenteral nutrition (TPN) is a surrogate form of nutrition in which dextrose, amino acids, and lipids are delivered via a central venous catheter. It is a reliable method in that it delivers nutrients and calories regardless of whether the patient's gut is functioning. Nevertheless, multiple studies over the past 20 years have shown that when the patient has a functioning intestinal tract, enteral feeding is clearly preferable to TPN. Although the specific mechanisms are not fully understood, enteral nutrition is known to foster gut mucosal integrity, to support overall immune function, and to be associated with lower complication rates and shorter hospital stays. In contrast, TPN is known to be associated with altered immune function, an increased rate of infectious complications, and, in some studies, a higher incidence of anastomotic complications after GI surgery. Moreover, there are as yet no data to indicate that acute use of TPN during short periods of starvation benefits patients who are adequately nourished preoperatively. TPN may, however, be lifesaving in patients who are malnourished and who do not have functioning GI tracts (e.g., those with short gut syndrome, severe gut

dysmotility or malabsorption, mesenteric vascular insufficiency, bowel obstruction, high-output enteric fistulas, or bowel ischemia).¹⁵

CALORIC GOALS

Once a route of nutritional support has been decided on, overall goals for caloric and protein intake may be established on the basis of the patient's ideal body weight (IBW) and expected postoperative metabolic state. One approach is to rely on a general estimate; a commonly used formula is 25 kcal/kg IBW. Another approach is to calculate a basal energy requirement by using the Harris-Benedict equation. This calculation is separate from the calculation of protein needs. A daily protein intake goal may be calculated on the basis of the patient's estimated level of physical stress. A well-nourished unstressed person requires a protein intake of approximately 1.0 g/kg IBW/day. A seriously ill patient under ongoing severe physical stress, however, may require 2.0 g/kg IBW/day; in some settings (e.g., extensive burns), a protein intake as high as 3.0 g/kg IBW/day may be recommended. Once the patient's specific needs have been calculated, the amount and type of nutrient solution to be provided enterally or via TPN are determined. If the patient is on a full oral diet, a calorie count or recording of the percentage of items eaten at each meal or snack may be made by the nursing staff and used to estimate the patient's intake, with nutritional supplementation provided as needed.¹⁶

Patients who require assistance with nutritional intake should be monitored to determine whether the interventions being carried out are having the desired effect. The most common method of monitoring patients' nutritional status with nutritional supplementation is to measure the serum albumin and prealbumin (transthyretin) concentrations. Albumin has a half-life of approximately 14 to 20 days and thus serves as a marker of longer-term nutritional status. A value lower than 2.2 g/dL is generally considered to represent severe malnutrition, but even somewhat higher values (< 3.0 g/dL) have been associated with poorer outcomes after elective surgery. Although the serum albumin concentration is a commonly used marker, it is not always a reliable one. Because of albumin's relatively long half-life, the serum concentration does not reflect the patient's more recent nutritional status. In addition, the measured concentration can change quickly in response to the infusion of exogenous albumin or to the development of dehydration, sepsis, and liver disease despite adequate nutrition. Prealbumin is a separate serum protein that has a half-life of approximately 24 to 48 hours and thus can serve as a marker of current and more recent nutritional status. Like the albumin concentration, the prealbumin concentration can be affected by liver and renal disease. Overall, however, it is more immediately reliable in following the effects of nutritional intervention.

Fluid Management

IV fluids may be classified into two main categories: resuscitation and maintenance. Supplemental fluids constitute a third category.

RESUSCITATION FLUIDS

Resuscitation fluids maintain tissue perfusion in the setting of hypovolemia by restoring lost volume to the intravascular

space. They may be further classified into two subcategories: crystalloids and colloids.

Crystalloids

Crystalloid solutions are water-based solutions to which electrolytes (and, sometimes, organic molecules such as dextrose) have been added. The crystalloid solutions used for resuscitation are generally isotonic to blood plasma and include such common examples as 0.9% sodium chloride, lactated Ringer solution, and Plasma-Lyte (Baxter Healthcare, Round Lake, IL). The choice to use one solution over another is usually inconsequential, but there are a few notable exceptions. For example, in the setting of renal dysfunction, there is a risk of hyperkalemia when potassium-containing solutions such as lactated Ringer solution and Plasma-Lyte are used. As another example, the administration of large volumes of 0.9% sodium chloride, which has a pH of 5.0 and a chloride content of 154 mmol/L, can lead to hyperchloremic metabolic acidosis. Regardless of which crystalloid solution is used, large volumes may have to be infused to achieve a significant increase in the circulating intravascular volume. Only one third to one quarter (250 to 330 mL/L) of the fluid administered stays in the intravascular space; the rest migrates by osmosis into the interstitial tissues, producing edema and potential impairment of tissue perfusion (the latter is a theoretical consequence whose existence has not yet been directly demonstrated).¹⁷

Colloids

Colloid solutions are composed of microscopic particles dispersed in a second substance in such a way that they are suspended and do not separate by normal filtration. Colloids are derived from three main forms of semisynthetic molecules: gelatins, dextrans, and hydroxyethyl starches. All of the commonly used synthetic colloids are dissolved in crystalloid solution. Nonsynthetic colloids also exist, including human albumin solutions, fresh frozen plasma, plasma-protein fraction, and immunoglobulin solutions. Compared with crystalloid solutions, colloid solutions increase the circulating intravascular volume to a much greater degree per unit of volume infused. In this respect, the various colloids may be thought of as a single group; however, in practice, they are most often given selectively on the basis of secondary characteristics other than their volume-increasing action, such as effect on hemostasis, risk of allergic reaction, and cost.

Crystalloids versus Colloids

The debate over whether crystalloids or colloids are superior for resuscitation has been going on for at least 30 years. Although multiple randomized, controlled trials have compared the two types of solutions in a variety of settings, including sepsis, trauma, burns, and surgery, the evidence accumulated to date has not established that one is clearly better than the other in terms of overall outcome. Supporters of crystalloid resuscitation cite the risk of altered hemostasis, the increased likelihood of drug interactions and allergic reactions, the potential for volume overload, and the relatively high cost as factors arguing against the use of colloids. Supporters of colloid resuscitation cite the large volume of crystalloid needed to produce significant volume effects, the subsequent tissue edema, and the potential for impaired

tissue perfusion and oxygenation as factors arguing against the use of crystalloids. Current recommendations favor crystalloid for resuscitation, with colloid an acceptable substitute when its secondary effects are desired in specific situations.^{17,18}

MAINTENANCE FLUIDS

Maintenance fluids provide required daily amounts of free water and electrolytes (e.g., sodium, potassium, and chloride) to balance expected daily losses and maintain homeostasis. A basic rule of thumb used by many practitioners to calculate the infusion rate for maintenance IV fluids is the so-called 4, 2, 1 rule:

- 4 mL/kg/hr for the first 10 kg of body weight
- 2 mL/kg/hr for the next 10 kg of body weight and
- 1 mL/kg/hr for every 1 kg of body weight above 20 kg

Generally accepted maintenance requirements include 30 to 35 mL/kg/day for free water, 1.5 mEq/kg/day for chloride, 1 mEq/kg/day for sodium, and 1 mEq/kg/day for potassium. In the setting of starvation or poor oral intake, dextrose 5% is often added to maintenance fluids to inhibit muscle breakdown. In regular practice, however, these specific values are not commonly used; more often, a rough estimate is made of expected daily fluid requirements, and solutions are ordered in accordance with this estimate. Although this practice is unlikely to cause noticeable harm in the majority of postoperative patients, there are situations where inaccurate calculations can lead to dehydration and volume overload. Three studies from the early 2000s evaluated patients undergoing elective colorectal surgery with the aim of determining whether providing higher volumes of fluid perioperatively had an impact on outcome.^{19–21} In all three, the data supported the use of smaller fluid volumes perioperatively, which was shown to result in earlier return of gut function after operation, shorter hospital stays, and overall decreases in cardiopulmonary and tissue-healing complications.

SUPPLEMENTAL FLUIDS

Supplemental fluids are given to replace any ongoing fluid loss beyond what is expected to occur via insensible loss and excretion in urine and stool. They are most commonly required by patients with prolonged NG tube output, enterocutaneous fistulas, diarrhea, high-output ileostomies, or large open wounds associated with excessive insensible fluid loss. In each case, the amount of fluid lost daily should be calculated, and replacement fluid should be given in a quantity determined by this measurement (either as a whole or in part) and by the patient's overall intravascular volume status. The particular solution to be used depends on the characteristics of the fluid loss. The components and volume of the fluids produced in the GI tract are different at different sites [see *Table 1*].

Pain Control

The topic of postoperative pain control covers a broad spectrum of possible interventions that serve a wide range of purposes. The most obvious purpose is simply to relieve the suffering and stress associated with postoperative pain. Another is to improve the patient's overall postoperative

status. Bringing the patient closer to the baseline sensory state by reducing pain allows him or her to engage in activities that promote healing and prevent complications, including mobilization to help prevent deep vein thrombosis (DVT) and deep breathing and coughing to help prevent pneumonia. Common methods of pain relief include IV infusion of narcotics, epidural analgesia using local anesthetics with or without narcotics, oral administration of narcotics, and the use of nonnarcotic oral medications such as nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen (see below). These and other issues related to postoperative pain control are discussed in greater detail elsewhere.

IV NARCOTIC ANALGESIA

IV narcotics may be administered either by the medical staff or, if patient-controlled analgesia (PCA) is feasible, by the patient. In most cases, with the exception of brief hospital stays (< 48 hours) and ICU settings where the patient may not be alert enough to manage a patient-controlled system, PCA is now generally considered preferable to as-needed nurse-administered IV narcotic analgesia. Numerous studies and reviews have shown that PCA is safe and is no more likely to cause side effects (e.g., oversedation, overdose, itching, and nausea) than nurse-administered IV narcotic analgesia is. In addition, the use of PCA improves patients' subjective perceptions of the efficacy of pain relief and the timeliness of drug administration.²²

EPIDURAL ANALGESIA

Epidural analgesia usually makes use of a local anesthetic (e.g., bupivacaine) with or without the addition of a narcotic (e.g., fentanyl). The anesthetic solution is instilled into the epidural space, bathing the nerve roots in a given region and thereby providing pain relief. Until the past decade or so, epidural analgesia was considered a more dangerous method of pain relief and was not routinely employed outside the ICU. With time and further observation has come the recognition that epidural analgesia is safe and effective for postoperative pain control in a routine floor setting if managed by the proper supporting team of physicians.

There has been some debate regarding whether epidural analgesia leads to earlier return of bowel function after GI surgery or reduces the incidence of pulmonary complications; at present, this debate remains unresolved. There is clear evidence, however, that patients subjectively experience less pain with epidural analgesia, both at rest and in the course of activities such as mobilization and coughing. Moreover, in patients who have sustained traumatic rib fractures, early use of epidural analgesia in place of IV narcotic analgesia has been shown to reduce the incidence of associated pneumonia and shorten the time for which mechanical ventilation is required.²³ Epidural analgesia does have certain drawbacks, including an increased incidence of orthostatic episodes and a need for more frequent adjustments of the medication dosage. Nevertheless, it can be highly effective and can be a reasonable option when judged appropriate by the anesthesiologist and agreed to by the patient.^{24,25}

ORAL ADMINISTRATION OF NARCOTICS

Oral administration of narcotics is one of the oldest methods of providing postoperative pain relief. Numerous

Table 1 Electrolyte Content and Rate of Production of Fluids Secreted in the Gastrointestinal Tract

Source of Secretion	Electrolyte Concentration (mEq/L)					Rate of Production (mL/day)
	Na ⁺	K ⁺	Cl ⁻	HCO ₃ ⁻	H ⁺	
Salivary glands	50	20	40	30		100–1,000
Stomach						
Basal	100	10	140		30	1,000
Stimulated	30	10	140		100	4,000
Bile	140	5	100	60		500–1,000
Pancreas	140	5	75	100		1,000
Duodenum	140	5	80			100–2,000
Ileum	140	5	70	50		100–2,000
Colon	60	70	15	30		

different narcotic agents are now available for use in this setting. When deciding which narcotic to prescribe, however, physicians typically do not select freely from the entire available range; rather, they tend to choose from a small subset of agents that they know well and are comfortable with. A key point to keep in mind is that in some formulations, narcotics are combined with other compounds (e.g., acetaminophen or aspirin), and these added medications can have side effects of their own if taken in excessively high doses. Such formulations may require more careful titration than narcotics alone would. Another key point is that many narcotics are available in both short-acting and long-acting versions. In patients who are experiencing substantial postoperative pain, a combination of long-acting agents and short-acting agents may yield more sustained and predictable pain relief than either type alone would.

Finally, for patients who have a history of chronic pain conditions and who regularly used pain medications preoperatively, the assistance of an acute pain service management team may be invaluable in treating pain postoperatively.

NSAIDS AND ACETAMINOPHEN

NSAIDs are available both by prescription and over the counter. They not only provide effective analgesia for pain from minor procedures but also may be a powerful adjunct to narcotics in more acute hospital settings. Their major disadvantages, which in some contexts are substantial enough to limit their use, include their propensity to cause gastric irritation and ulceration; their antiplatelet effects, which increase the tendency toward bleeding; and their potential nephrotoxic effects in some formulations. When employed in settings where these disadvantages are not considered to pose a high risk, NSAIDs can be a useful addition to narcotics, both by providing further pain relief and by reducing the required narcotic doses (and thus the incidence of narcotic-related side effects).

Like the NSAIDs, acetaminophen provides minor pain relief and is an antipyretic, but unlike the NSAIDs, it has no antiinflammatory effect. Acetaminophen also is often added to narcotic regimens or formulations to reduce the need for narcotics. Its greatest potential side effect is hepatic toxicity with excessive use. Accordingly, the dosage should be less

than 2 g/day in patients with normal hepatic function and even lower in those with impaired hepatic function. It is particularly important to keep these dose limits in mind when narcotic-acetaminophen combinations are prescribed on an as-needed basis; in this situation, safe dosage limits may well be exceeded if sufficient care is not taken.

Glycemic Control

Over the last decade, blood glucose control in the postoperative period has become a topic of great interest. Many studies, beginning with that of Van den Berghe and colleagues in 2001,²⁶ have found that strict glucose control reduces morbidity and mortality in critically ill surgical ICU patients. Although most of the data currently available are derived from ICU patients rather than from the surgical population as a whole, the principle of tight glycemic control has been generalized to apply to most postoperative patients.

The target glucose range has been the subject of debate, with most institutions using a range of 80 to 140 mg/dL. The ability to achieve this target range and the means of achieving it vary according to the level of nursing care that is provided. Options include continuous IV insulin infusion and combinations of subcutaneous injections that use various long- and short-acting insulin formulations. Episodes of hypoglycemia are an ever-present risk with tight glucose control; accordingly, the use of standard dosage regimens and careful monitoring are recommended to reduce the risk of such episodes.

The debate over the specifics of glycemic control notwithstanding, it is generally well accepted that this issue should be addressed in all patients who have undergone major operative procedures, regardless of whether they carry a preoperative diagnosis of diabetes mellitus.^{26,27}

Postoperative Complications

Numerous complications may arise in the postoperative period. Many of these are specific to particular operative procedures and hence are best discussed in connection with those procedures. Many others, however, may develop after virtually any operation and thus warrant a general discussion in this chapter (see below). Prompt discovery and treatment

of these latter complications rely heavily on a sufficiently high index of suspicion.

POSTOPERATIVE FEVER

Postoperative temperature elevations are quite common, occurring in nearly one third of patients after surgery. Only a relatively small number of these are actually caused by infection. Fevers that are caused by infections (e.g., pneumonias, wound infections, or UTIs) tend to reach higher temperatures ($> 38.5^{\circ}\text{C}$ [101.3°F]), usually are associated with moderate elevation of the white blood cell (WBC) count 3 or more days after operation, and typically extend over consecutive days. Noninfectious causes of postoperative fevers include components of the inflammatory response to surgical intervention, reabsorption of hematomas, and (possibly) atelectasis.²⁸

Beyond checking the WBC count, a shotgun approach to the workup of postoperative fever probably is not warranted. A focused approach based on well-directed questioning and a careful physical examination is more likely to obtain the highest diagnostic yield. Coughing, sputum production, and respiratory effort should be noted, and the lungs should be auscultated for rales. All incisions should be inspected for erythema and drainage, and current and recent IV sites should be checked for evidence of cellulitis. If a central line has been placed, particularly if it has been in place for several days, the possibility of a line infection should be considered. Patients who have undergone prolonged NG intubation may have sinusitis, which is most readily diagnosed through computed tomography (CT) of the sinuses. Further workup for fever may include, as indicated, chest x-ray, sputum cultures, urinalysis, blood cultures, or CT of the abdomen (after procedures involving laparotomy—especially bowel resections—where intra-abdominal abscess is a possible complication).

PNEUMONIA

Respiratory infections in the postoperative period are generally considered nosocomial pneumonias and, as such, are potentially serious complications. The estimated incidence of postoperative pneumonia varies significantly, with many estimates tending to run high. A 2001 study of more than 160,000 patients undergoing major noncardiac surgery provided what may be a reasonable overall figure, finding the incidence of postoperative pneumonia to be approximately 1.5%.²⁹ In the 2,466 patients with pneumonia, the 30-day mortality was 21%. Thoracic procedures, upper abdominal procedures, abdominal aortic aneurysm repair, peripheral vascular procedures, and neurosurgical procedures were all identified as placing patients at significantly increased risk for pneumonia. Patient-specific risk factors included age greater than 60 years, recent alcohol use, dependent functional status, long-term steroid use, and a 10% weight loss in the 6 months preceding the operation.²⁹

The diagnosis of postoperative pneumonia is based on the usual combination of index of suspicion, findings from the history and physical examination (e.g., fever, shortness of breath, hypoxia, productive cough, and rales on lung auscultation), imaging, and laboratory evaluation. Appropriate workup, directed by the clinical findings, typically starts with chest x-rays (preferably in both posteroanterior and lateral

views, if possible) and sputum cultures, sometimes accompanied by CT scanning of the chest and, possibly, bronchoscopy with bronchoalveolar lavage (which may be useful in directing antibiotic therapy when sputum cultures are non-diagnostic). Empirical broad-spectrum antibiotic therapy is typically initiated before the causative organism is identified; this practice has been shown to reduce mortality. Piperacillin-tazobactam, which is effective against *Pseudomonas aeruginosa*, is commonly used for this purpose; however, when Gram staining of the sputum identifies gram-positive cocci, vancomycin or linezolid may be used initially instead.³⁰ Once the causative organism is identified, specific antibiotic therapy directed at that organism is indicated, as in treatment of other infectious processes. Drainage of parapneumonic effusions may also be necessary, and this measure may be helpful in diagnosing or preventing the development of empyema.

SURGICAL SITE INFECTION

Surgical site infection (SSI) is one of the most common postoperative complications and may occur after virtually any type of procedure. Rates of infection vary widely (from less than 1% to approximately 20%) depending on the procedure performed, the classification of the operative wound (clean, clean-contaminated, contaminated, or dirty), and a host of patient-related and situation-specific factors. The majority of SSIs, regardless of site, are caused by skin-based flora, most commonly gram-positive cocci (e.g., staphylococci). Gram-negative infections are also commonly seen after GI procedures, and anaerobes may be present after pharyngo-esophageal procedures.³¹ With SSI, as with other postoperative infectious complications, prompt recognition of the signs and symptoms is the key to successful management. Hence, regular examination of the wound, particularly in the setting of postoperative fever, is critical. Erythema and induration (indicative of cellulitis) are obvious signs of SSI, as is active drainage of pus from the wound. A more subtle sign is pain that is greater than expected, especially when the pain seems to be increasing several days after operation.

In most cases, it is necessary to open and drain the wound (which is easily done at the bedside or in the clinic in most cases) and allow it to heal via secondary intention. Generally, wet-to-dry dressing changes with saline are employed; however, larger wounds may benefit from NPWT [see Care Orders, Wound Care, *above*]. Success with NPWT has been widely reported, and this technique has been used to treat difficult wounds such as exposed vascular grafts and sternotomy infections.^{32,33} The use of antibiotics depends on the presence and degree of cellulitis. The initial choice of an agent should be guided by the likelihood that particular organisms will be present, which is estimated on the basis of the site of the operation and the type of procedure being performed. Whenever possible, any purulent material in the SSI should be cultured; this step may permit more targeted antimicrobial therapy.

DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

In the absence of appropriate prophylaxis, the incidence of DVT may be as high as 30% in abdominal and thoracic surgery patients and that of fatal pulmonary embolism (PE) may be as high as 0.9%. Thus, prophylaxis against thromboembolism is clearly of high importance in the postoperative

care of many patients. Major risk factors for DVT and PE in this setting include the operation itself, physical immobility, advanced age, the presence of a malignancy, obesity, and a history of smoking.³⁴

DVT should be suspected postoperatively whenever a patient complains of lower-extremity pain or one leg is noticeably more swollen than the other. The gold standard for diagnosis remains a venous duplex examination, which has a sensitivity of 97% for detecting DVT of the femoral and popliteal veins.³⁵ In most cases, treatment involves starting a heparin infusion (typically without a loading bolus in the postoperative setting), targeting a partial thromboplastin time (PTT) that is double to triple the normal PTT (i.e., approximately 60 to 80 seconds), and then switching to warfarin therapy when the patient is stable and able to tolerate oral medications.

PE should be suspected whenever a postoperative patient experiences a decrease in oxygen saturation or shortness of breath; this decrease may be accompanied by chest pain, tachycardia, and diaphoresis, all of which may also be seen in the setting of myocardial infarction (MI). When PE is suspected, it may be appropriate to start heparin therapy even before the diagnosis has been confirmed, depending on the degree of suspicion and the relative risk anticoagulation may pose to the patient. Currently, the principal means of diagnosing acute PE is spiral CT. This modality has relatively wide availability, can be performed fairly rapidly, and has a sensitivity of 53 to 100% and a specificity of 81 to 100%. In addition, it is readily usable in most critically ill patients, including those undergoing mechanical ventilation (although the amount of IV contrast material it requires may limit its use in patients with renal insufficiency). Greater diagnostic yield may be obtained by combining spiral CT with a lower-extremity venous duplex examination.³⁶ For most patients with postoperative PE, anticoagulation is administered in the form of heparin. Low-molecular-weight heparins (LMWHs) are also generally safe and effective; however, because their effect cannot be turned off in the same way as that of IV unfractionated heparin, they may be less useful in the period after operation.³⁷ In patients with massive PE, surgical embolectomy or suction-catheter embolectomy may be considered as conditions warrant. Thrombolytic therapy is generally contraindicated in the postoperative setting.

CARDIAC COMPLICATIONS

Cardiac dysrhythmias may occur after a wide variety of surgical procedures; as one might imagine, they are most common after cardiac operations. Predisposing factors and possible causes are numerous and various, including underlying cardiac disease, perioperative systemic stress, electrolyte and acid-base imbalances, hypoxemia, and hypercarbia. Thus, controlling such conditions to the extent possible both preoperatively and postoperatively is an important part of preventing and managing postoperative cardiac dysrhythmias. Treatment generally involves first achieving hemodynamic stability and then converting the rhythm back to sinus if possible.

Supraventricular tachycardias (SVTs) are the dysrhythmias most commonly seen in the postoperative period, occurring after approximately 4% of noncardiac major operations.

Atrial fibrillation and atrial flutter account for the majority of SVTs.³⁸ Ventricular rate control may be achieved pharmacologically by infusing diltiazem. Digoxin has long been used for this purpose but is less effective in acute settings than diltiazem is. Amiodarone, which is used to treat ventricular dysrhythmias, may also be used to restore sinus rhythm postoperatively in some cases, especially after cardiac procedures.³⁹ When pharmacologic rate control is not possible, particularly in hypotensive patients, cardioversion is indicated.

Approximately one third of patients who undergo noncardiac surgery in the United States have some degree of coronary artery disease and thus are at increased risk for perioperative MI. The incidence of coronary artery disease is even higher in certain subpopulations, such as patients who undergo major vascular procedures.^{40,41} In the perioperative setting, however, the pathophysiology of coronary ischemia is different from that in nonsurgical settings, where plaque rupture is the most common cause of MI. Approximately 50% of all MIs occurring in surgical patients are caused by increased myocardial oxygen demand in the face of inadequate supply resulting from factors such as fluid shifts, physiologic stress, hypotension, and the effects of anesthesia. The majority of cardiac ischemic events occur in the first 4 days of the postoperative period.⁴¹

Perioperative beta blockade for patients at risk for MI is now routine. Multiple trials and meta-analyses have demonstrated that this practice yields significant risk reductions in terms of both cardiac morbidity and mortality^{42,43} and that these risk reductions are achieved regardless of the type of surgery being performed. Although there has been some variation in the protocols used by these trials and the results reported, there is general agreement that beta blockade should be initiated preoperatively, delivered at the time of surgery, and continued postoperatively for up to 1 week.⁴²

Diagnosis of postoperative MI is complicated by the fact that as many as 95% of patients who experience this complication may not present with classic symptoms (e.g., chest pain). Identification of MI may be further hindered by the ECG changes brought on by the stress of the perioperative period (including dysrhythmias). Ultimately, the most useful signal of an ischemic cardiac event in the postoperative period is a rise in the levels of cardiac enzymes, particularly troponin I. Accordingly, cardiac enzyme activity should be assessed whenever there is a high index of suspicion for MI or a patient is considered to be at significant perioperative risk for MI.⁴⁰

Treatment of postoperative MI focuses on correcting any factors contributing to or exacerbating the situation that led to the event (e.g., hypovolemia or hypotension). Typically, although antiplatelet agents (e.g., aspirin) are sometimes given, thrombolytic therapy is avoided because of concerns about postoperative bleeding. Acute percutaneous coronary intervention is also associated with an increased risk of bleeding but has nonetheless been used successfully in the perioperative setting and is recommended by some physicians.⁴⁴ Beta blockade is often advocated as a means of treating postoperative MI, although it is probably more effective when used both preoperatively and perioperatively as a means of preventing MI.⁴⁰

Discharge

Planning for discharge from the hospital is clearly an essential part of perioperative care. In the best of circumstances, discharge planning starts before admission for elective surgery and is discussed with the patient and family as part of preoperative patient education. Starting the process early enables the provider to estimate the patient's probable needs at the end of acute hospitalization and thus to make preliminary arrangements as needed. For example, if it appears likely that the patient will have to stay in a skilled nursing or extended care facility or will require prolonged physical therapy and rehabilitation, these matters can be addressed to the mutual satisfaction of both patient and physician in advance of hospital discharge. In this way, delays in discharge and unnecessary days of acute hospitalization can be avoided, at least in some instances.

Criteria for discharge or transfer from acute hospital care vary widely depending on the procedure, the provider, and the patient; rarely are they codified. For example, in a 2005 survey of 16 surgeons performing open colorectal resections within one hospital, only two factors—absence of complications and reported postoperative bowel movement—were considered criteria for early discharge by most (but not all) of the surgeons.⁴⁵ There was wide disagreement on all other criteria, including postoperative mobility and the ability to tolerate a general diet. Given such variation in discharge criteria for even one category of procedure, it is clear that a discussion of specific criteria for each type of surgery is well beyond the scope of this chapter. It is worth pointing out, however, that the various discharge criteria now in use, despite their differences, have a common basis—namely, the idea that at discharge, the patient should ideally be able to manage basic self-care activities (e.g., feeding, wound care, and mobility) without advanced assistance and that the likelihood of readmission should be minimized to the extent possible. Identification, investigation, and control of factors such as nausea, pain, fever, deconditioning, and fatigue are important in determining whether a patient is at risk for a return to the hospital in the postoperative period.⁴⁶

Over the past two decades, critical pathways, which are organized plans that outline the sequence of patient care and discharge, have been increasingly used in managing postoperative care after a variety of procedures from all disciplines. They have been shown to reduce hospital stays and maintain safety in patients undergoing common procedures (e.g., colectomy), patients undergoing complex procedures (e.g., esophagectomy),⁴⁷ and patients with high comorbidity.⁴⁸ Individual pathways are typically specific to a hospital or health care system; thus, the discharge criteria are those agreed on by the providers involved in the care of eligible patients at that particular institution. Critical pathways can be helpful not only by standardizing care and improving the relative appropriateness of postoperative discharge but also, in many cases, by decreasing the overall length of postoperative hospitalization.⁴⁶ In a 2003 study of 27 postoperative critical pathways used at the Johns Hopkins Hospital, the authors found that seven (27%) of the pathways were associated with significant (5 to 45%) decreases in length of stay.⁴⁹

Regardless of whether critical pathways are implemented, if discharge planning is not addressed preoperatively,

addressing it as early as possible in the postoperative period is extremely valuable not only for ensuring an appropriate length of stay but also for maintaining the satisfaction and comfort of both patient and family. Specific issues should be addressed at this point as needed, including the home resources and support available to the patient, wound care, ostomy care, management of feeding tubes and drains, IV antibiotic therapy, and physical rehabilitation. Thus, as soon as it appears that a patient is on track either for discharge home or for transfer to a rehabilitation or skilled nursing facility, a discussion with the appropriate social work or discharge planning personnel should be scheduled. PT/OT evaluations early in the postoperative course can also be of great assistance in determining a patient's needs on discharge, and such evaluations are essential for any patient who may need a stay in an inpatient rehabilitation facility. Typically, it requires at least 1 day to set up services such as home health care and outpatient PT, and it may take this long or longer to obtain a bed at an appropriate rehabilitation or skilled nursing facility. Consequently, the earlier these plans are made, the better. For many surgical patients, formal discharge planning and PT/OT evaluations are not actually necessary. Brief discussions with the patient, the family, or the nursing staff caring for the patient will assist in determining which surgical patients are most likely to benefit from this approach.

Current Controversies in Postoperative Management

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) has rapidly become the most prevalent sleep disorder over the last 20+ years. At present, estimates suggest that it affects 9% of women and 24% of men in the United States. Additionally, estimates also suggest that as many as 82% of men and 92% of women affected do not carry the formal diagnosis of OSA.^{50,51} Despite the large percentage of the population affected, no well-validated specific guidelines are present in the current literature. That being said, there is a wealth of discussion of the issue from which several more general guidelines may be drawn.

Preoperative screening for OSA is the first and most critical step in management. As a majority of affected patients have not been formally diagnosed, this allows the operative team the opportunity to detect the greatest number of patients at risk and to adjust their operative plan of care accordingly.⁵² Most commonly, screening is done by anesthesiology in the preanesthesia setting using one of a number of available screening tools. In addition to this, it is important for the surgeon to also consider the potential presence of OSA as this may significantly affect the choice of surgical setting and postoperative setting planned.⁵³ Although, again, there are no set guidelines provided in the literature dictating criteria for outpatient versus inpatient surgical settings, for patients with known or suspected OSA requiring significant sedation or general anesthesia, using a setting with access to difficult airway carts, advanced respiratory care, and the option of a prolonged postanesthesia recovery unit (PACU) observation is recommended.⁵⁴

The two greatest issues in postoperative management are the level of monitoring provided and the use of sedatives and narcotic analgesics. The choice of surgical/postoperative

setting is best made after consideration of known or potential OSA, any associated comorbidities, and the type of surgery to be performed. Patients with severe OSA generally require inpatient monitoring postoperatively. Outside of known severe OSA, the time observed in the PACU may also provide further information on which to base ongoing care or discharge.⁵¹ Any patient who currently uses a home continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) device should use this in the immediate postoperative period.⁵⁵ In the inpatient setting, the use of continuous pulse oximetry and telemetry should be considered, and supplemental oxygen should be used with caution.^{53,55}

Anesthetics and sedatives depress the central nervous system, inhibit respiration, depress skeletal muscle tone, and relax the upper airway.⁵⁵ Opiate drugs can depress respiratory drive and rate, decrease tidal volume, and lead to decreased sensitivity to arousal. Thus, the use of sedatives postoperatively should be avoided or used with great caution. Narcotic agents need to be titrated to adequate pain relief but should be used only when nonnarcotic agents are ineffective. Additionally, the need for opiates may be significantly decreased with the use of nonnarcotic agents such as acetaminophen, centrally acting agents such as tramadol hydrochloride, NSAIDs, or topical anesthetics when appropriate.⁵³

The prevalence of OSA is only likely to increase given current trends in associated comorbidities such as obesity. Further prospective data are needed for more definitive future recommendations, particularly regarding postoperative monitoring and admission status.

POSTOPERATIVE ILEUS

Ileus, or the cessation of bowel function and transit in the absence of mechanical obstruction, is a common postoperative phenomenon particularly after abdominal surgery and occurs in virtually all patients undergoing bowel resection. Its causes are multifactorial, including an overall increase in sympathetic tone, the inflammatory response to bowel as a result of direct manipulation, and the well-known effects of narcotic analgesics on GI motility.⁵⁶ Although the typical duration of postoperative ileus averages around 3 days, in up to 32% of patients, return of bowel function may be particularly delayed.⁵⁷

Multiple strategies have been employed in attempts to decrease the length of postoperative ileus, such as early feeding, the use of chewing gum, and pharmacologic agents particularly directed at blocking the GI effects of narcotics. Feeding patients early (i.e., before evidence of return of bowel function) after abdominal surgery has been demonstrated to be generally safe and forms an element of many postoperative pathways. However, various studies comparing early feeding with awaiting return of bowel function have yielded mixed results, and no clear recommendation for early feeding can be made across all procedures.^{56,58} Chewing gum is thought to represent a sham-feeding condition that may have benefit in stimulating GI motility after abdominal surgery. It is safe; has few, if any, significant risks; and is well tolerated by patients. A recent meta-analysis of seven randomized, controlled trials comparing chewing gum with no gum after abdominal surgery concluded that gum leads to a clinically significant improvement in return of bowel function as represented by a sooner return of flatus.⁵⁹ However, not all individual trials have demonstrated a benefit.⁵⁶ Of the pharmacologic agents that have been investigated in the treatment of postoperative ileus, alvimopan, which is a selective antagonist of the peripheral opioid mu receptor, appears to confer the most significant benefit and was recently approved by the Food and Drug Administration for this indication. The recommended dose is 12 mg orally given twice daily for up to 7 days.^{57,60,61} Alvimopan was shown to reduce the return to GI tract function after bowel resection by 12 hours compared with placebo in a meta-analysis of five randomized, controlled trials involving a total of 1,877 patients.⁶² Further, it does not appear to have serious side effects.

Postoperative ileus remains a major factor in determining the length of hospital stay after abdominal surgery, particularly after bowel resection. Both chewing gum and alvimopan appear to provide some benefit in reducing the time to bowel recovery after surgery, with the former being the most simple and cost-effective to implement. None of these measures eliminate the effects of surgical intervention on GI motility entirely, however, and this will continue to be an area of active investigation in improving the care of the postoperative patient.⁵⁶⁻⁶²

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6 POSTOPERATIVE PAIN

Spencer S. Liu, MD, and Henrik Kehlet, MD, PHD, FACS (Hon)

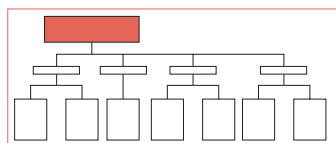
Clinical Approach to the Patient with Postoperative Pain

Postoperative pain consists of a constellation of unpleasant sensory, emotional, and mental experiences associated with autonomic, psychological, and behavioral responses precipitated by the surgical injury. Pain management has received increasing attention, and multiple government agencies and medical specialty organizations have now created guidelines for treatment of postoperative pain.¹ In 2001, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) introduced standards for pain management,² stating that patients have the right to appropriate evaluation and management and that pain must be assessed.

Postoperative pain relief has two practical aims. The first is provision of subjective comfort, which is desirable for humanitarian reasons. The second is inhibition of trauma-induced nociceptive impulses to blunt autonomic and somatic reflex responses to pain and to enhance subsequent restoration of function by allowing the patient to breathe, cough, and move more easily. Because these effects reduce pulmonary, cardiovascular, thromboembolic, and other complications, they may lead secondarily to improved postoperative outcome.

Inadequate Treatment of Pain

A common misconception is that pain, no matter how severe, can always be effectively relieved by opioid analgesics. It has repeatedly been demonstrated, however, that in a high proportion of postoperative patients, pain is inadequately treated.^{3,4} This discrepancy between what is possible and what is practiced can be attributed to a variety of causes [see Table 1], which to some extent can be ameliorated by increased teaching efforts. Recent evidence also indicates that overreliance on opioid therapy may be inherently limiting because of development of both acute tolerance and opioid-induced hyperalgesia.⁵ The ability of opioids in high doses or with chronic administration to potentially induce pain illustrates the importance of using multimodal analgesic regimens that target multiple analgesic pathways.



Guidelines for Postoperative Pain Treatment

In the past few years, efforts have been made to develop procedure-specific perioperative pain management guidelines. The impetus for these efforts has been the realization that the analgesic efficacy may be procedure dependent and that the choice of analgesia in a given case must also depend on the benefit-to-risk ratio, which varies among procedures. In addition, it is clear that some analgesic techniques will be considered only for certain specific operations (e.g., peripheral nerve blocks and intraperitoneal local anesthesia).⁶⁻⁸ At present, these procedure-specific guidelines are still largely in a developmental state and are available for laparoscopic cholecystectomy, open colon surgery, hysterectomy, inguinal hernia repair, thoracotomy, mastectomy, hemorrhoidectomy, and knee and hip replacement.^{9,10}

THORACIC PROCEDURES

Pain after thoracotomy is severe, and pain therapy should therefore include a combination regimen, preferably comprising epidural local anesthetics and opioids¹¹ combined with systemic nonsteroidal antiinflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors (depending on risk factors) [see algorithm]. If the epidural regimen is not available, then comparable analgesia may be achieved with continuous thoracic paravertebral block, with

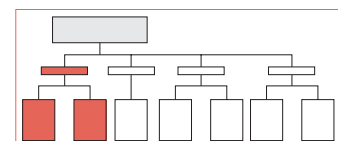
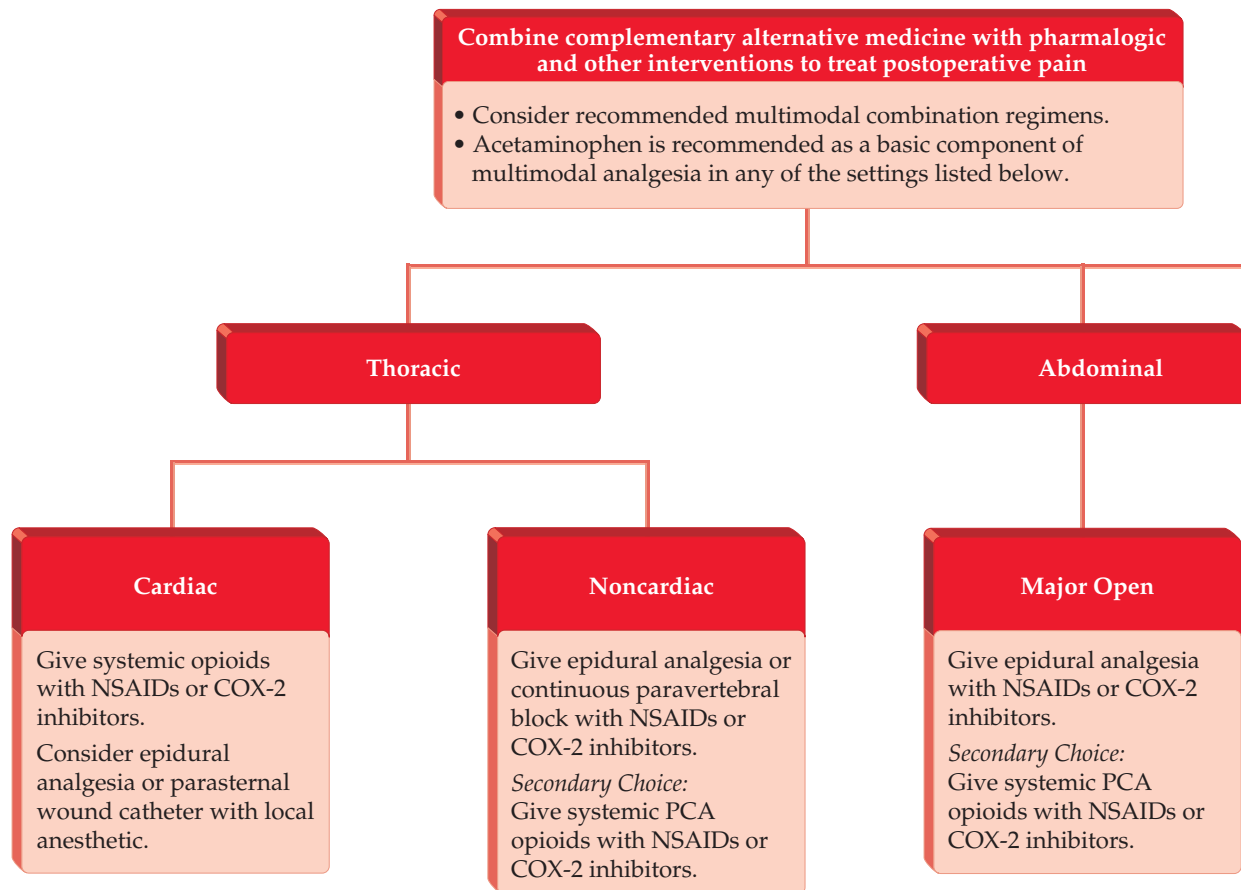


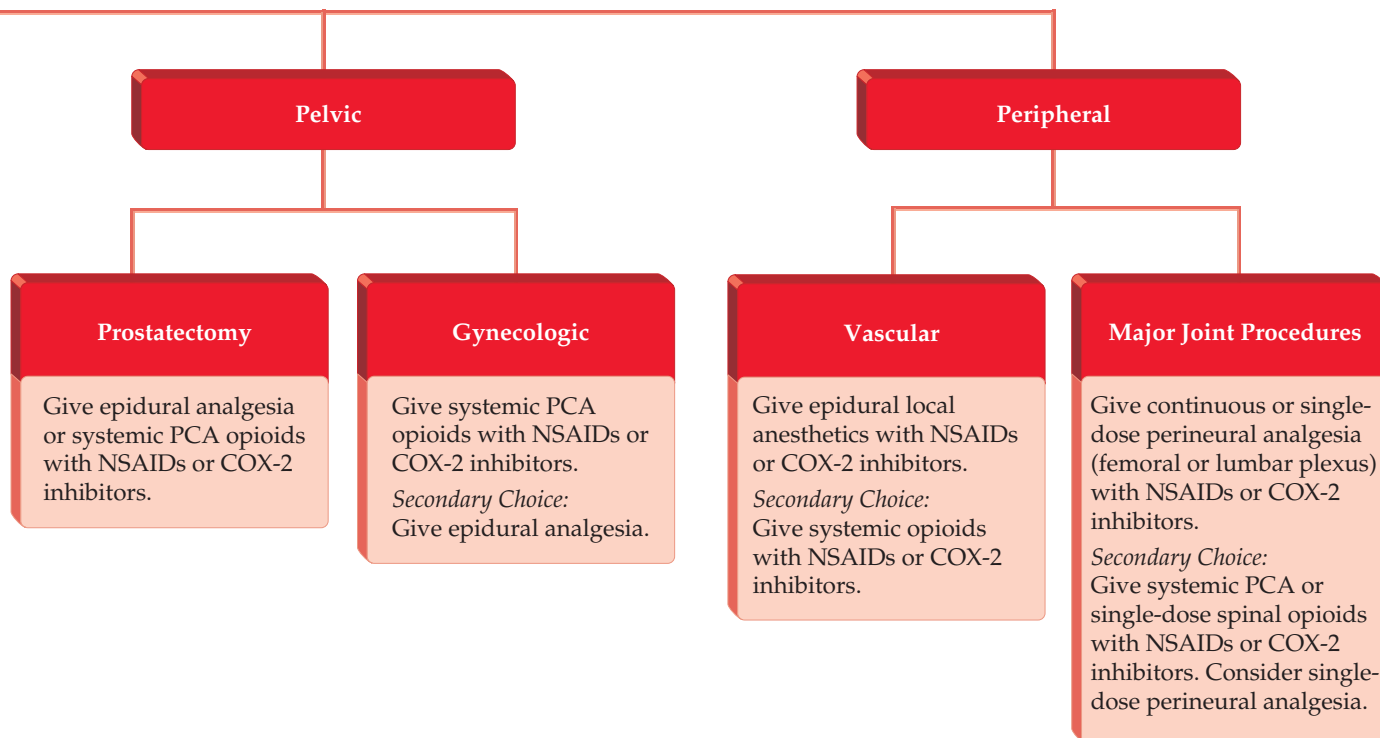
Table 1 Contributing Causes of Inadequate Pain Treatment

Insufficient knowledge of drug pharmacology among surgeons and nurses
Uniform (p.r.n.) prescriptions
Lack of concern for optimal pain relief
Failure to give prescribed analgesics
Fear of side effects
Fear of addiction



COX-2 = cyclooxygenase-2, NSAIDs = nonsteroidal antiinflammatory drugs; PCA = patient-controlled analgesia.

Clinical Approach to the Patient with Postoperative Pain



the potential for lesser incidence of urinary retention and postoperative nausea and vomiting.¹² Although comparable, the continuous paravertebral technique may be more technically difficult. If neither regional analgesic technique is available, then the inferior regimen of NSAIDs and systemic opioids may be used. Cryoanalgesia is not recommended as it is less effective.¹⁰ Acetaminophen is recommended as a basic analgesic for multimodal analgesia. Pain after cardiac operation with sternotomy is less severe, and systemic opioids plus NSAIDs are recommended. The combined regimen of epidural local anesthetics and opioids or parasternal wound catheters with continuous administration of local anesthetics¹³ is recommended when more effective pain relief is necessary, and it may reduce cardiopulmonary morbidity and perhaps length of stay.¹⁴

ABDOMINAL
PROCEDURES

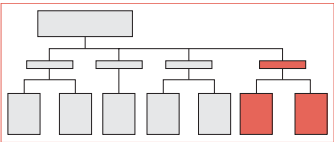
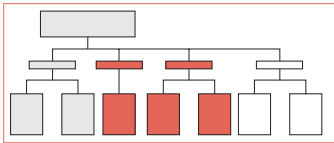
Pain after major and upper open abdominal operations is severe, and a combined regimen of epidural local anesthetics and opioids is recommended because it has proved to be superior to systemic opioids and to have few and acceptable side effects.^{10,11,15} Furthermore, the epidural regimen will reduce postoperative pulmonary complications and ileus compared with treatment with systemic opioids.¹⁶ Systemic NSAIDs or COX-2 inhibitors are added when needed. Acetaminophen is recommended as a basic analgesic for multimodal analgesia.

After gynecologic lower abdominal or pelvic operations,¹⁰ systemic opioids plus NSAIDs or COX-2 inhibitors are recommended except in patients in whom more effective pain relief is desirable. In such patients, the combined regimen of epidural local anesthetics and opioids is preferable. Acetaminophen is recommended as a basic analgesic for multimodal analgesia.

Pain following prostatectomy is usually not severe and may be treated with systemic opioids combined with NSAIDs or COX-2 inhibitors and acetaminophen. However, blood loss and thromboembolic complications are reduced when epidural local anesthetics are administered. This method is therefore recommended intraoperatively and continued in selected high-risk patients for pain relief after open prostatectomy and transurethral resection. In low-risk patients, systemic opioids with NSAIDs or COX-2 inhibitors and acetaminophen alleviate postoperative pain.

PERIPHERAL
PROCEDURES

After vascular procedures, postoperative pain control is probably best achieved with epidural local anesthetic–opioid mixtures, combined with systemic NSAIDs or COX-2 inhibitors.¹¹ Acetaminophen is recommended as a basic analgesic for multimodal analgesia. This regimen will be effective, and the increase in peripheral blood flow that is documented to occur with epidural local anesthetics may lower the risk of graft thrombosis.



Pain relief after major joint procedures (e.g., hip and knee operations)¹⁰ may involve an epidural regimen in certain high-risk patients because such regimens have been shown to reduce thromboembolic complications and intraoperative blood loss and to improve physical rehabilitation when compared with systemic opioid regimens.^{17,18} However, the severe pain noted after knee replacement is probably best treated with peripheral nerve blocks.^{10,19} Most of the benefit of continuous femoral nerve analgesia may also be achieved with a single-injection femoral nerve block.²⁰ Total hip replacement is a less painful procedure, but when pain is severe, a continuous lumbar plexus or femoral nerve block can be used.^{10,21} Alternatively and with less technical expertise, a single intrathecal dose of local anesthetic and low-dose morphine will provide effective analgesia for the first 8 to 16 hours,¹⁰ after which NSAIDs or COX-2 inhibitors may be added. Acetaminophen is provided as a basic analgesic for multimodal analgesia.

Treatment Modalities

COMPLEMENTARY AND ALTERNATIVE MEDICINE
INTERVENTIONS

Cognitive, behavioral, alternative, or social interventions should be used in combination with pharmacologic therapies to prevent or control acute pain, with the goal of such interventions being to guide the patient toward partial or complete self-control of pain.^{22,23} A recent survey by the American Hospital Association indicated that 27% of member hospitals offered complementary and alternative medications (CAMs).²⁴ Use of nonpharmacologic adjunctive analgesics has been endorsed by advisory bodies such as the Anesthesia Patient Safety Foundation and Institute of Healthcare Improvement.^{25,26}

Psychological preparation in patients with postoperative pain has been demonstrated to shorten hospital stay and reduce postoperative narcotic use [see Table 2].²⁷ Guided imagery, relaxation, and music techniques have been demonstrated to reduce postoperative opioid use and affective pain.²² Acupuncture and acupressure has been successfully used as an adjunct for postoperative analgesia and reduces pain scores, anxiety levels, and postoperative nausea.²⁸ Alternative techniques

Table 2 Psychological Preparation of Surgical Patients	
Procedural information	Give a careful and relevant description of what will take place.
Sensory information	Describe the sensations that will be experienced either during or after the operation.
Pain treatment information	Outline the plan for administering sedative and analgesic medication and encourage patients to communicate concerns and discomforts.
Instructional information	Teach patients postoperative exercises, such as leg exercises, and show them how to turn in bed or move so that pain is minimal.
Reassurance	Reassure those who are mentally, emotionally, or physically unable to cooperate that they are not expected to take an active role in coping with pain and will still receive sufficient analgesic treatment.

Table 3 Opioid Receptor Types and Physiologic Actions

Receptor Type	Prototypical Ligand		Physiologic Actions
	Endogenous	Exogenous	
Mu ¹	β-Endorphin	Morphine	Supraspinal analgesia
Mu ²	β-Endorphin	Morphine	Respiratory depression
Delta	Enkephalin	—	Spinal analgesia
Kappa	Dynorphin	Ketocyclazocine	Spinal analgesia, sedation, visceral analgesia

should be combined with pharmacologic or other interventions, but care must be taken to ensure that the pharmacologic treatment does not compromise the mental function necessary for the success of the planned psychological intervention.

SYSTEMIC OPIOIDS

Mechanisms of Action

Opioids produce analgesia and other physiologic effects by binding to specific receptors in the peripheral and central nervous system (CNS) [see Table 3]. These receptors normally bind a number of endogenous substances called opioid peptides. These receptor-binding interactions mediate a wide array of physiologic effects.²⁹ Three types of opioid receptors and their subtypes have been discovered: mu, delta, and kappa receptors. The most commonly used opioids bind to mu receptors. The mu₁ receptor is responsible for the production of opioid-induced analgesia, whereas the mu₂ receptor appears to be related to the respiratory depression, cardiovascular effects, and inhibition of GI motility commonly seen with opioids.

The discovery of peripheral opioid receptors has led to investigation into potential clinical applications. Phase III studies with alvimopan (a peripheral opioid antagonist that does not cross the blood-brain barrier) have demonstrated reduced ileus and hospitalization after abdominal surgery.³⁰

Other studies have also investigated the analgesic effects of applying opioids to wound sites in an attempt to provide peripheral analgesia without central side effects. Unfortunately, neither incisional³¹ nor intra-articular³² opioid administration has demonstrated significant beneficial effect.³⁰ This finding may be attributable to the need for chronic inflammatory mediators to facilitate expression of peripheral opioid receptors.³³

The relation between receptor binding and the intensity of the resultant physiologic effect is known as the intrinsic activity of an opioid. Most of the commonly used opioid analgesics are agonists. An agonist produces a maximal biologic response by binding to its receptor. Other opioids, such as naloxone, are termed antagonists because they compete with agonists for opioid receptor-binding sites. Still other opioids are partial agonists because they produce a submaximal response after binding to the receptor. (An excellent example of a submaximal response produced by partial agonists is buprenorphine's action at the mu receptor.)

Drugs such as nalbuphine, butorphanol, and pentazocine are known as agonist-antagonists or mixed agonist-antagonists.²⁹ These opioids simultaneously act at different receptor sites: their action is agonistic at one receptor and antagonistic at another [see Table 4]. The agonist-antagonists have certain pharmacologic properties that are distinct from those of the more common mu agonists: (1) they exhibit a ceiling effect and cause only submaximal analgesia compared with mu agonists and (2)

administration of an agonist-antagonist with a complete agonist may cause a reduction in the effect of the complete agonist.²⁹

Agents

Morphine Morphine is the opioid with which the most clinical experience has been gained. Sufficient pharmacokinetic and pharmacodynamic data are available. Use of this agent is recommended; it may be given orally, intravenously (IV), or intramuscularly (IM).

Meperidine Detailed and sufficient pharmacokinetic and pharmacodynamic data on meperidine are available. It is less suitable than morphine as an analgesic because its active

Table 4 Intrinsic Activity of Opioids

Opioid	Mu	Kappa	Delta
Agonists			
Morphine	Agonist	—	
Meperidine (Demerol)	Agonist	—	
Hydromorphone (Dilaudid)	Agonist		
Oxymorphone (Numorphan)	Agonist		
Levorphanol (Levo-Dromoran)	Agonist		
Fentanyl (Duragesic)	Agonist		
Sufentanil (Sufenta)	Agonist		
Alfentanil (Alfenta)	Agonist		
Methadone (Dolophine)	Agonist		
Agonist-Antagonists			
Buprenorphine (Buprenex)	Partial agonist		
Butorphanol (Stadol)	Antagonist	Agonist	Agonist
Nalbuphine (Nubain)	Antagonist	Partial agonist	Agonist
Pentazocine (Talwin)	Antagonist	Agonist	Agonist
Dezocine (Dalgan)	Partial agonist		
Antagonists			
Naloxone (Narcan)	Antagonist	Antagonist	Antagonist

metabolite, normeperidine, can accumulate, even in patients with normal renal clearance, and this accumulation can result in CNS excitation and seizures.²⁹ Other agents should be used before meperidine is considered. Like morphine, meperidine can be given orally, IV, or IM.

Side Effects

By depressing or stimulating the CNS, opioids cause a number of physiologic effects in addition to analgesia. The depressant effects of opioids include analgesia, sedation, and altered respiration and mood; the excitatory effects include nausea, vomiting, and miosis.

All mu agonists produce a dose-dependent decrease in the responsiveness of brainstem respiratory centers to increased carbon dioxide tension (P_{CO_2}). This change is clinically manifested as an increase in resting P_{CO_2} and a shift in the CO_2 response curve. Agonist-antagonist opioids have a limited effect on the brainstem and appear to elicit a ceiling effect on increases in P_{CO_2} .

Opioids also have effects on the gastrointestinal (GI) tract. Nausea and vomiting are caused by stimulation of the chemoreceptor trigger zone of the medulla. Opioids enhance sphincteric tone and reduce peristaltic contraction. Delayed gastric emptying is caused by decreased motility, increased antral tone, and increased tone in the first part of the duodenum. Delay in passage of intestinal contents because of decreased peristalsis and increased sphincteric tone leads to greater absorption of water, increased viscosity, and desiccation of bowel contents, which cause constipation and contribute to postoperative ileus. Opioids also increase biliary tract pressure. Finally, opioids may inhibit urinary bladder function, thereby increasing the risk of urinary retention.

Several long-acting, slow-release oral opioids are currently available, but their role (in particular, their safety) in the setting of moderate to severe postoperative pain remains to be established. In addition, modern principles of treatment increasingly emphasize the use of opioid-sparing analgesic approaches to enhance recovery (see below).

CLINICAL APPLICATION OF SYSTEMIC OPIOIDS

Traditional IM dosing of opioids is a suboptimal means of analgesia.³⁴ IM dosing does not result in consistent blood levels, because opioids are absorbed at a variable rate from the vascular bed of muscle. Moreover, administration of traditional IM regimens results in opioid concentrations that exceed the concentrations required to produce analgesia only

about 30% of the time during any 4-hour dosing interval. The optimal means to treat moderate to severe postoperative pain with systemic opioids is via IV patient-controlled analgesia (PCA). This delivery system compensates for the wide inter- and intraindividual variability in analgesic needs and blood levels after opioid administration. Self-delivery helps produce timely titration of analgesia and reduces administrative delay from conventional delivery (e.g., p.r.n.). Systematic reviews have noted that IV PCA delivery of opioids reduces pain scores and improves patient satisfaction over conventional delivery.³⁴ Typical regimens are provided in Table 5. Recent advances in iontophoretic technology have led to commercial release of a transdermal fentanyl iontophoretic PCA system. This system delivers 40 μ g fentanyl over 10 minutes after patient demand. Onset is rapid because of the active electrical current driving the fentanyl transdermally. The system deactivates after 24 hours or 80 administrations. Several clinical trials have reported equivalence between the fentanyl system and IV PCA opioid.³⁵ One pooled analysis suggested less analgesic gaps with the fentanyl system because of fewer technical failures and administrative delays than the IV PCA device³⁶; however, the role of this fentanyl system remains to be fully defined.

EPIDURAL AND SUBARACHNOID OPIOIDS

Opioids were first used in the epidural and subarachnoid spaces in 1979. Since that time, they have become the mainstay of postoperative management for severe pain. Epidural opioids may be administered in a single bolus or via continuous infusions. They are usually combined with local anesthetics in a continuous epidural infusion to enhance analgesia.³⁷

Mechanisms of Action

Opioids injected into the epidural or subarachnoid space cause segmental (i.e., selective, spinally mediated) analgesia by binding to opioid receptors in the dorsal horn of the spinal cord.³⁸ The lipid solubility of an opioid, described by its partition coefficient, predicts its behavior when introduced into the epidural or subarachnoid space. Opioids with low lipid solubility (i.e., hydrophilic opioids) have a slow onset of action and a long duration of action. Opioids with high lipid solubility (i.e., lipophilic opioids) have a quick onset of action but a short duration of action. This is attributable to more rapid diffusion across the dura into the spinal cord but also more rapid systemic uptake and clearance via uptake into

Table 5 Typical Intravenous Patient-Controlled Analgesia Regimens

Drug Concentration	Size of Bolus	Lockout Interval (min)
Agonists		
Morphine (1 mg/mL)		
Adult	0.5–2.5 mg	5–10
Pediatric	0.01–0.03 mg/kg (max. = 0.15 mg/kg/hr)	5–10
Fentanyl (0.01 mg/mL)		
Adult	10–20 μ g	4–10
Pediatric	0.5–1 μ g/kg (max. = 4 μ g/kg/hr)	5–10
Hydromorphone (0.2 mg/mL)		
Adult	0.05–0.25 mg	5–10
Pediatric	0.003–0.005 mg/kg (max. = 0.02 mg/kg/hr)	5–10

epidural and spinal cord blood vessels. In fact, current evidence suggests that a major site of action of spinal lipophilic opioids is not the spinal cord but the brain via systemic uptake.³⁹ Thus, lipophilic opioids as sole epidural analgesic agents are becoming less frequently recommended.

Subarachnoid opioids should be used when the required duration of analgesia after surgery is relatively short (< 24 hours) because of typical single-injection delivery. When protracted analgesia is required, epidural administration is preferred; repeated injections may be given through epidural catheters, or continuous infusions may be used. Smaller doses of subarachnoid opioids are generally required to produce analgesia. Ordinarily, no more than 0.1 to 0.25 mg of morphine should be used to provide 12 to 24 hours of analgesia. These doses, which are about 10 to 20% of the size of comparably effective epidural doses, provide reliable pain relief with few side effects.⁴⁰ Fentanyl has also been extensively used in the subarachnoid space in a dose range of 6.25 to 25 µg to provide 3 to 6 hours of analgesia. Recently, an extended duration formulation of epidural morphine has been commercially released.^{41–43}

This formulation consists of morphine encased in multivesicular lipid with predictable sustained release. Clinical studies have overall supported the efficacy and general safety of this formulation (10–15 mg doses) without demonstrating marked superiority over conventional central neuraxial opioid therapy. Thus, the role of this preparation remains to be determined.

Side Effects

The chief side effects associated with epidural and subarachnoid opioids are respiratory depression, nausea and vomiting, pruritus, and urinary retention.^{38,40,44} The poor lipid solubility of morphine is responsible for its protracted duration of action but also allows morphine to undergo cephalad migration in the cerebrospinal fluid (CSF). This migration can cause delayed respiratory depression, with a peak incidence 3 to 10 hours after an injection. The high lipid solubility of lipophilic opioids such as fentanyl allows them to be absorbed into lipids close to the site of administration. Consequently, the lipophilic opioids do not migrate rostrally in the CSF and cannot cause delayed respiratory depression. Of course, the high lipid solubility of lipophilic opioids allows them to be absorbed into blood vessels, which may cause early respiratory depression, as is commonly seen with systemic administration of opioids. Overall, the typical incidence of respiratory depression is similar to that seen with systemic opioids at approximately 0.2%.⁴⁴

Naloxone reverses the depressive respiratory effects of spinal opioids. In an apneic patient, 0.4 mg IV will usually restore ventilation. If a patient has a depressed respiratory rate but is still breathing, small aliquots of naloxone (0.2 to 0.4 mg) can be given until the respiratory rate returns to normal.

Nausea and vomiting are caused by transport of opioids to the vomiting center and the chemoreceptor trigger zone in the medulla via CSF flow or the systemic circulation. Nausea can usually be treated with antiemetics or, if severe, with naloxone (in 0.2 mg increments, repeated if necessary).

Pruritus is probably the most common side effect of the spinal opioids. Although not fully defined, the mechanism likely involves activation of “itch-specific” opioid receptors on spinal sensory neurons.⁴⁵ Although pruritus is commonly treated with antihistamines, there is minimal evidence for mechanism-specific effectiveness. An alternative and probably superior treatment is use of a mixed opioid agonist antagonist to directly block the opioid receptor–induced itching while maintaining opioid analgesias. Doses of 5 mg of nalbuphine IV or 2 to 4 mg of butorphanol intranasally or IV every 6 hours is commonly used.⁴⁵

The mechanism of spinal opioid–induced urinary retention involves inhibition of volume-induced bladder contractions and blockade of the vesical reflex. Naloxone administration is the treatment of choice, although bladder catheterization is sometimes required.

CLINICAL APPLICATION OF EPIDURAL AND SUBARACHNOID OPIOIDS

As stated earlier, subarachnoid opioids are limited in the duration of analgesia because of typical single-injection delivery. Epidural administration allows prolonged delivery of opioids, and typical regimens are listed in Table 6. However, side effects from opioids are common, and it is better to combine epidural opioids with local anesthetics to obtain multimodal and synergistic analgesia. This allows smaller doses of both agents to be used with better analgesia and fewer side effects. Typical regimens are listed in Table 7.

EPIDURAL LOCAL ANESTHETICS AND OTHER REGIONAL BLOCKS

Local anesthetic neural blockade is unique among available analgesic techniques in that it may offer sufficient afferent neural blockade, resulting in relief of pain; avoidance of sedation, respiratory depression, and nausea; and, finally, efferent sympathetic blockade, resulting in increased blood flow to the region of neural blockade.⁴⁶

Table 6 Typical Dosing of Neuraxial Opioids

Drug	Intrathecal or Subarachnoid Single Dose	Epidural Single Dose	Epidural Continuous Infusion
Fentanyl	5–25 µg	50–100 µg	25–100 µg/hr
Sufentanil	2–10 µg	10–50 µg	10–20 µg/hr
Morphine	0.1–0.3 mg	1–5 mg	0.1–1 mg/hr
Hydromorphone	—	0.5–1 mg	0.1–0.2 mg/hr
Meperidine	10–30 mg	20–60 mg	10–60 mg/hr

Lower doses may be effective when administered to the elderly or when injected in the cervical or thoracic region. Units vary across agents for single dose (mg versus µg) and continuous infusion (mg/hr versus µg/hr).

Table 7 Typical Patient-Controlled Epidural Analgesia Regimens

Analgesic Solution	Continuous Rate (mL/hr)	Demand Dose (mL)	Lockout Interval (min)
0.0625–0.125% bupivacaine + 2–5 µg/mL fentanyl	4–6	3–4	10–15
0.125–0.125% bupivacaine + 2–5 µg/mL sufentanil	3–5	2–3	12
0.1–0.2% ropivacaine + 2–4 µg/mL fentanyl	3–5	2–5	10–20

Mechanism of Action

Local anesthetic neural blockade is a nondepolarizing block that reduces the permeability of cell membranes to sodium ions.⁴⁷ Whether different local anesthetics have different effects on different nerve fibers is debatable.

Choice of Drug

For optimal management of postoperative pain, the anesthetic agent should provide excellent analgesia of rapid onset and long duration without inducing motor blockade. The various local anesthetic agents all meet one or more of these criteria; however, the ones that come closest to meeting all of the criteria are bupivacaine, ropivacaine, and levobupivacaine. This should not preclude the use of other agents, because their efficacy has also been demonstrated. Ropivacaine and levobupivacaine may have a better safety profile, but the improvement may be relevant only when high intraoperative doses are given.⁴⁷

Side Effects

The main side effects of epidural local anesthesia are hypotension caused by sympathetic blockade, vagal overactivity, and decreased cardiac function (during a high thoracic block). Under no circumstances should epidural local anesthetics be used before a preexisting hypovolemic condition is treated. Hypotension may be treated with ephedrine, 10 to 15 mg IV, and fluids, with the patient tilted in a head-down position. Atropine, 0.5 to 1.0 mg IV, may be effective during vagal overactivity.

Urinary retention occurs in 20 to 100% of patients, and urinary catheterization is typically used during epidural analgesia. Motor blockade may delay mobilization; however, its incidence can be reduced by using the weakest concentration of local anesthetic that is compatible with adequate sensory blockade.

The routine complications associated with the epidural catheter are minimal when proper nursing protocols are followed [see Table 8]. The decision to employ epidural local anesthetics in such patients should be made only after the risks^{44,48} are carefully compared with the documented advantages of such anesthetics.^{49,50}

Spinal hematoma attributable to the combination of epidural analgesia and anticoagulants is rare, but the risk may be increased by specific agents. Guidelines on the use of epidural analgesia and anticoagulation are currently listed on the American Society of Regional Anesthesia and Pain Medicine Web site.⁴⁸ Most anticoagulants can be safely managed with epidural analgesia; however, special care must be taken with thrombolytics, low-molecular-weight heparins, and newer antiplatelet, antithrombin, and anti-factor Xa agents.

CLINICAL APPLICATION OF CONTINUOUS EPIDURAL ANALGESIA

Typical regimens are listed in Table 7. As is similar with IV PCA, patient-controlled epidural analgesia (PCEA) has been demonstrated to provide superior analgesia, decreased analgesic consumption, and decreased side effects.⁵¹ The safety of PCEA regimens for hospital wards has been well documented.⁵² As all epidural analgesic agents are deliberately segmental (limited in anatomic spread) in nature, it is important for the vertebral site of epidural placement to match the site of surgery. For example, lumbar epidurals offer inferior analgesia to thoracic epidurals for thoracic surgery. Suggested epidural sites are also listed in Table 9.

OTHER REGIONAL ANALGESIA TECHNIQUES

Intraperitoneal administration of local anesthetics cannot be recommended for typical postoperative analgesia, because they are not efficacious,⁵³ except in laparoscopic cholecystectomy.^{8,10} Intra-incisional administration of bupivacaine or other long-acting local anesthetics, which has negligible side effects and demands little or no surveillance, is recommended for patients undergoing relatively minor procedures.

Continuous administration of local anesthetics into the wound via a catheter directly placed at the end of surgery is a simple and efficacious means to provide postoperative analgesia. A recent systematic review noted that wound catheters improved postoperative analgesia, reduced opioid

Table 8 Procedures for Maintenance of Epidural Anesthesia for Longer than 24 Hours

1. Administer appropriate drug in appropriate dosage at selected infusion rate as determined by physician
2. Nurse evaluates vital signs and intake and output as required for a postoperative patient
3. Nurse checks infusion pump hourly to ensure that it is functioning properly, that infusion rate is proper, and that alarm is on
4. Nurse also assesses
 - Bladder—for distention, if patient is not catheterized
 - Lower extremities—for status of motor function
 - Central nervous system—for signs of toxicity or respiratory depression
 - Skin integrity on back (breakdown may occur if motor function is not present)
 - Tubing and dressing (disconnection of tubing or dislodgment of catheter may occur)
5. Every 48 hr, the catheter dressing should be removed, the catheter entrance site cleaned, and topical antibiotic applied (much as in care of a central venous catheter)

Table 9 Recommended Location of Catheter Insertion for Surgical Procedures

Location of Incision	Examples of Surgical Procedures	Congruent Epidural Catheter Placement
Thoracic	Lung reduction, radical mastectomy, thoracotomy, thymectomy	T4–8
Upper abdominal	Cholecystectomy, esophagectomy, gastrectomy, hepatic section, Whipple procedure	T6–8
Middle abdominal	Cystoprostatectomy, nephrectomy	T7–10
Lower abdominal	Abdominal aortic aneurysm repair, colectomy, radical prostatectomy, total abdominal hysterectomy	T8–11
Lower extremity	Femoropopliteal bypass, total hip or total knee replacement	L1–4

L = lumbar; T = thoracic.

use, and decreased opioid-related side effects in a variety of procedures.¹³ However, there is still a need for more procedure-specific data before general recommendations can be made as a wide variety of surgical procedures, catheter locations, and analgesic regimens were included in the systematic review.

Continuous peripheral nerve blocks are growing in popularity, and the analgesic treatment may be continued after discharge.^{54,55} A systematic review has documented multiple benefits from the use of continuous perineural analgesia versus systemic opioids, such as reduced pain scores at rest and with activity, reduced opioid use, reduced opioid-related side effects, and increased patient satisfaction.⁵⁴ Use of outpatient perineural analgesia is also growing in popularity, and studies have observed that this form of analgesia reduces unplanned hospital admission after ambulatory procedures, improves patients quality of life at home, and may facilitate conversion of hospital procedures to short-stay procedures (e.g., total knee replacement).⁵⁶ A growing body of literature surveying the use of thousands of perineural catheters for postoperative analgesia documents a low incidence of complications and overall safety of this technique.⁵⁷ More recently, a high-volume infiltration technique with dilute concentrations of local anesthetics with or without adjuvants seems promising because of its apparent efficacy, simplicity, and safety.^{58,59}

NSAIDS, COX-2 INHIBITORS, AND ACETAMINOPHEN

NSAIDs and COX-2 inhibitors are modest analgesics that have both peripheral and central analgesic mechanisms and antiinflammatory effects [see Table 10]. Although these agents are typically less effective as sole analgesic agents than opioids,⁶⁰ they have an excellent efficacy to safety profile and are generally recommended after all kinds of operations for low-risk patients.^{61,62} Several reviews and systematic reviews report that NSAIDs and COX-2 inhibitors decrease systemic morphine use by approximately 13 to 18 mg over a 24-hour period.^{61,62} More importantly, these reviews indicate that NSAIDs decrease pain scores by approximately 1 cm on a 10 cm visual analogue scale pain score and reduce opioid-related side effects of sedation and nausea by approximately 30%. Conventional NSAIDs inhibit both COX-1 and COX-2. Selective COX-2 inhibitors, which do not inhibit COX-1, have the potential to achieve analgesic efficacy comparable to that of conventional NSAIDs but with fewer minor side effects.^{63–65}

Only a few of the NSAIDs may be given parenterally. The data now available on the use of NSAIDs for postoperative pain are insufficient to allow definitive recommendation of

any agent or agents over the others, and selection therefore may depend on the convenience of delivery, duration, and cost.⁶⁶ All of the NSAIDs have potentially serious side effects: GI and surgical site hemorrhage, renal failure, impaired bone healing, and asthma. The endoscopically verified superficial ulcer formation seen within 7 to 10 days after the initiation of NSAID therapy is not seen with selective COX-2 inhibitor treatment in volunteers. The clinical relevance of these findings for perioperative treatment remains to be established, however, given that acute severe GI side effects (bleeding, perforation) are extremely rare in elective cases.

Because prostaglandins are important for regulation of water and mineral homeostasis by the kidneys in the dehydrated patient, perioperative treatment with NSAIDs, which inhibit prostaglandin synthesis, may lead to postoperative renal failure. So far, specific COX-2 inhibitors have not been demonstrated to be less nephrotoxic than conventional NSAIDs.^{62,67} Although little systematic evaluation has been done, extensive clinical experience with NSAIDs suggests that the renal risk is not substantial.⁶⁸ Nonetheless, conventional NSAIDs and COX-2 inhibitors should be used with caution in patients who have preexisting renal dysfunction.⁶²

Although conventional NSAIDs prolong bleeding time and inhibit platelet aggregation, there generally does not seem to

Table 10 Typical Dosing for Common NSAIDs, COX-2 Inhibitors, and Acetaminophen

Drug	Typical Dose for Postoperative Analgesia	Maximum Recommended Dose (mg/day)
Acetaminophen	650–1,000 mg q 6 hr	4,000
Celecoxib	100–200 mg q 12 hr	400
Diclofenac	50 mg q 8 hr	150
Ibuprofen	400 mg q 6 hr	3,200
Indomethacin	25–50 mg q 8 hr	200
Ketorolac	10 mg q 4–6 hr	40
Ketorolac (intravenous)	15–30 mg q 6 hr	120
Meloxicam	7.5–15 mg q day	15
Naproxen	250 mg q 6–8 hr	1,375
Paracetamol (intravenous)	1,000 mg q 6 hr	4,000

COX-2 = cyclooxygenase; NSAIDs = nonsteroidal antiinflammatory drugs.

be a clinically significant risk of increased bleeding. However, in some procedures for which strict hemostasis is critical (e.g., tonsillectomy, cosmetic surgery, and eye surgery), these drugs have been shown to increase the risk of bleeding complications and should therefore be replaced with COX-2 inhibitors, which do not inhibit platelet aggregation.⁶⁹ The observation that prostaglandins are involved in bone and wound healing has given rise to concern about potential side effects in surgical patients. Although there is experimental evidence that both conventional NSAIDs and COX-2 inhibitors can impair bone healing,⁷⁰ the clinical data available at present are insufficient to document increased wound or bone healing failure with these drugs.⁷¹ This is a particularly important issue for future study in that many orthopedic surgeons remain reluctant to use NSAIDs.

Currently, there is widespread concern about the increased risk of cardiovascular complications associated with long-term treatment with selective COX-2 inhibitors. Generally, such side effects have appeared only after 1 to 2 years of treatment and led to the withdrawal of rofecoxib in 2004 and valdecoxib in 2005 from the US market.⁷² In the past few years, however, two studies of patients undergoing coronary artery bypass grafting (CABG) found that the risk of cardiovascular complications was increased significantly (two- to threefold) in this setting and led to the label change for COX-2 inhibitors and NSAIDs indicating that these agents are contraindicated in CABG patients.⁷² The larger question is whether these drugs should also be contraindicated for perioperative use, or at least used with caution, in high-risk cardiovascular patients who are undergoing procedures other than CABG. At present, the data are insufficient to allow final conclusions; nonetheless, reviews suggest that the benefits of short-term use of these agents in patients without cardiovascular risk factors probably outweigh the potential (low) risk of complications. Until further studies are performed, use in patients with cardiovascular risk factors should be cautious.⁷²

Acetaminophen also possesses analgesic capability, both peripherally and centrally. Its analgesic effect is somewhat (about 20 to 30%) weaker than those of conventional NSAIDs and COX-2 inhibitors. For example, use of acetaminophen typically reduces morphine consumption by approximately 9 mg over a 24-hour period,⁶¹ which may be insufficient to significantly reduce opioid-related side effects or dramatically improve analgesia. However, acetaminophen lacks the side effects typical of NSAIDs.⁶² Combining acetaminophen with NSAIDs may improve analgesia, especially in smaller and moderate-sized operations^{73,74}; accordingly, this agent is recommended as a basic component of multimodal analgesia in all operations.

OTHER ANALGESICS

Glucocorticoids are powerful antiinflammatory agents and have proven analgesic value in less extensive procedures,^{75,76} especially dental, laparoscopic, and arthroscopic operations. In addition, they have profound antiemetic effects.⁷⁷ Concerns about possible side effects in the setting of perioperative administration have not been borne out by the results of randomized studies.^{75,76}

Tramadol is a weak analgesic that has several relatively minor side effects (e.g., dizziness, nausea, and vomiting) and possesses weak opioid agonist activity and inhibits reuptake

of serotonin and norepinephrine.⁷⁸ It can be used as an intravenous analgesic but is less potent than opioids (morphine, meperidine)⁷⁹ and is a poor sole agent for control of postoperative pain.⁸⁰

Several systematic reviews have suggested that some analgesic and perioperative opioid-sparing effects can be achieved by adding an *N*-methyl-d-aspartate (NMDA) receptor antagonist (e.g., ketamine), gabapentin, or pregabalin [see Combination Regimens, below].^{34,81}

TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION

Transcutaneous electrical nerve stimulation (TENS) is the application of a mild electrical current through the skin surface to a specific area, such as a surgical wound, to achieve pain relief; the exact mechanism whereby it achieves this effect is yet to be explained but may involve spinal gating and activation of opioid receptors. Although several randomized controlled trials have reported efficacy after inguinal herniotomy,⁸² thoracotomy,⁸³ and other procedures,⁸⁴ the specific values and the proper uses of the various stimulation frequencies, waveforms, and current intensities have not been determined. In addition, blinding of subjects is difficult with TENS studies, and this effect of bias is difficult to assess. Overall, the effect of TENS on acute pain is too imprecise to warrant a recommendation for routine use.⁸⁵

COMBINATION REGIMENS

Because no single pain treatment modality is optimal, combination regimens (e.g., balanced analgesia or multimodal treatment) offer major advantages over single-modality regimens, whether by maintaining or improving analgesia, by reducing side effects, or by doing both.⁸⁶ Combinations of epidural local anesthetics and morphine,^{15,44} of NSAIDs and opioids,^{66,87,88} of NSAIDs and acetaminophen,^{73,74} of acetaminophen and opioids,⁸⁹ of acetaminophen and tramadol,⁹⁰ and of a selective COX-2 inhibitor and gabapentin⁹¹ or pregabalin⁸¹ have been reported to have additive effects. At present, information on other combinations (involving ketamine, clonidine, glucocorticoids, and other agents) is too sparse to allow firm recommendations; however, multimodal analgesia is undoubtedly promising, and multidrug combinations should certainly be explored further.

The potential of combination regimens is especially intriguing with respect to the concept of perioperative opioid-sparing analgesia. The use of one or several nonopioid analgesics in such regimens may enhance recovery in that the concomitant reduction in the opioid dosage will lead to decreased nausea, vomiting, and sedation.^{92–95} Both the adverse events associated with postoperative opioid analgesia and the relatively high costs of such analgesia argue for an opioid-sparing approach.^{96,97} The ability to reduce opioid-related and non-opioid-related side effects by use of multimodal analgesia may become especially attractive for several reasons. First, there is growing evidence that the use of opioids as sole analgesics can lead to opioid-induced hyperalgesia, whereby overstimulation of opioid receptors creates a nociceptive state (i.e., opioids increase sensitivity to painful stimuli).⁹⁸ Also, in light of the JCAHO pain initiative and overall increased focus on reducing pain,¹ a concern exists that these initiatives may precipitate increased use of opioids and thereby an increased risk of side effects.^{99,100}

Discussion

Physiologic Mechanisms of Acute Pain

The noxious stimuli from iatrogenic surgical injury or accidental trauma set a cascade of events in motion cumulating in the perception of “pain.” Many interrelated components contribute to the processing of nociceptive stimuli. Clinicians should recognize that the neurobiology of nociception is extremely complex, with multiple levels of redundancy, such that there is no “hardwired” or “final common” pathway for the process of nociception of acute pain. The basic mechanisms are (1) afferent transmission of nociceptive stimuli through the peripheral nervous system after tissue damage, (2) modulation of these injury signals by control systems in the dorsal horn, and (3) modulation of the ascending transmission of pain stimuli by a descending control system originating in the brain [see Figure 1].^{101–103}

PERIPHERAL PAIN RECEPTORS AND NEURAL TRANSMISSION TO THE SPINAL CORD

Peripheral pain receptors (nociceptors) can be identified by function but cannot be distinguished anatomically. The responsiveness of peripheral pain receptors may be enhanced by endogenous analgesic substances (e.g., prostaglandins, serotonin, bradykinin, nerve growth factor, and histamine), as well as by increased efferent sympathetic activity.¹⁰¹ Antidromic release of substance P may amplify the inflammatory response and thereby increase pain transmission. The peripheral mechanisms of visceral pain are different from somatic or neuropathic nociception and likely involve transient receptor potential vanilloid 1 receptors, acid-sensing ion channels, and tachykinins.¹⁰⁴ Peripheral opioid receptors have been demonstrated to appear in inflammation on the peripheral nerve terminals but probably have little clinical relevance.^{31–33} Somatic nociceptive input is transmitted to the CNS through A-delta and C fibers, which are small in diameter and either unmyelinated or thinly myelinated. Visceral pain is transmitted through afferent sympathetic pathways; the evidence that afferent parasympathetic pathways play a role in visceral nociception is inconclusive.^{104,105}

DORSAL HORN CONTROL SYSTEMS AND MODULATION OF INCOMING SIGNALS

All incoming nociceptive traffic synapses in the gray matter of the dorsal horn (Rexed laminae I to IV). Several substances may be involved in primary afferent transmission of nociceptive stimuli in the dorsal horn: substance P, enkephalins, somatostatin, neurotensin, γ -aminobutyric acid (GABA), glutamic acid, angiotensin II, vasoactive intestinal polypeptide (VIP), and cholecystokinin octapeptide (CCK-8).^{102,106} From the dorsal horn, nociceptive information is transmitted through the spinothalamic tracts to the hypothalamus, through spinoreticular systems to the brainstem and reticular formation, and finally to the cerebral cortex.

DESCENDING PAIN CONTROL SYSTEM

A descending control system for sensory input originates in the brainstem and reticular formation and in certain higher brain areas. The main neurotransmitters in this system are norepinephrine, serotonin, acetylcholine, and enkephalins. Stimulation

or augmentation of this descending system enhances analgesia. Epidural-intrathecal administration of alpha-adrenergic agonists (e.g., clonidine) or of anticholinesterases (e.g., neostigmine) works in this manner to provide pain relief.⁹⁴

SPINAL REFLEXES

Nociception may be enhanced by spinal reflexes that affect the environment of the nociceptive nerve endings. Thus, tissue damage may provoke an afferent reflex that causes muscle spasm in the vicinity of the injury, thereby increasing nociception. Similarly, sympathetic reflexes may cause decreased microcirculation in injury tissue, thereby generating smooth muscle spasm, which amplifies the sensation.

POSTINJURY CHANGES IN PERIPHERAL AND CENTRAL NERVOUS SYSTEMS

After an injury, the afferent nociceptive pathways undergo physiologic, anatomic, and chemical changes.^{102,103} These changes include increased sensitivity on the part of peripheral nociceptors, as well as the growth of sprouts from damaged nerve fibers that become sensitive to mechanical and alpha-adrenergic stimuli and eventually begin to fire spontaneously. Moreover, excitability may be increased in the spinal cord, which leads to expansion of receptive fields in dorsal horn cells. Such changes may lower pain thresholds, may increase afferent barrage in the late postinjury state, and, if normal regression does not occur during convalescence, may contribute to a chronic pain state.¹⁰²

Neural stimuli have generally been considered to be the main factor responsible for initiation of spinal neuroplasticity; however, it now appears that such neuroplasticity may also be mediated by cytokines released as a consequence of COX-2 induction.¹⁰³ Improved understanding of the mechanisms of pain may serve as a rational basis for future drug development and may help direct therapy away from symptom control and toward mechanism-specific treatment.¹⁰⁷

In experimental studies, acute pain behavior or hyperexcitability of dorsal horn neurons may be eliminated or reduced if the afferent barrage is prevented from reaching the CNS. Preinjury neural blockade with local anesthetics or opioids can suppress excitability of the CNS; this is called preemptive analgesia. Although this has been a consistent finding in laboratory studies, clinical studies have been less dramatic. A critical analysis of controlled clinical studies that compared the efficacy of analgesic regimens administered preoperatively with the efficacy of the same regimens administered postoperatively concluded that preemptive analgesia does not always provide a clinically significant increase in pain relief.^{108,109} Nonetheless, it is important that pain treatment be initiated early to ensure that patients do not wake up with high-intensity pain.

Effects of Pain Relief

SELECTED PHYSIOLOGIC RESPONSES TO OPERATION

Cardiovascular

It has traditionally been thought that an imbalance of myocardial oxygen supply and demand, such as an increase in

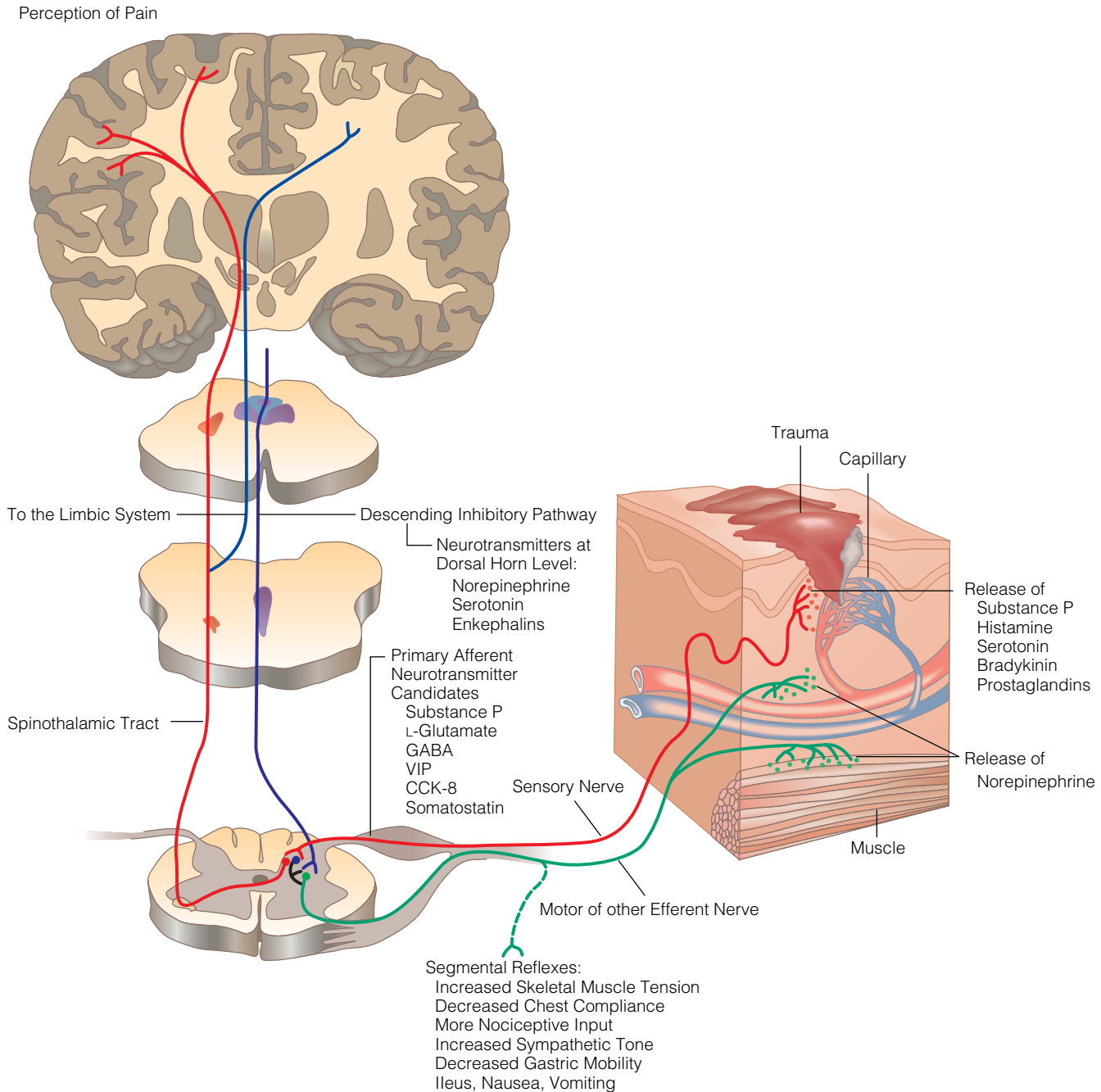


Figure 1 Shown are the major neural pathways involved in nociception. Nociceptive input is transmitted from the periphery to the dorsal horn via A-delta and C fibers (for somatic pain) or via afferent sympathetic pathways (for visceral pain). It is then modulated by control systems in the dorsal horn and sent via the spinothalamic tracts and spinoreticular systems to the hypothalamus, to the brainstem and reticular formation, and eventually to the cerebral cortex. Ascending transmission of nociceptive input is also modulated by descending inhibitory pathways originating in the brain and terminating in the dorsal horn. Nociception may be enhanced by reflex responses that affect the environment of the nociceptors, such as smooth muscle spasm. CCK = cholecystokinin-octapeptide; GABA = γ -aminobutyric acid; VIP = vasoactive intestinal peptide.

demand (e.g., increase in heart rate or blood pressure) or a decrease in supply (e.g., decreased coronary blood flow to the vulnerable subendocardial areas), may contribute to perioperative cardiac events, particularly in patients with decreased cardiac reserve.¹¹⁰ Although many factors may contribute to an imbalance of myocardial oxygen supply and demand,

uncontrolled postoperative pain may be especially detrimental and contribute to cardiac morbidity through activation of the sympathetic nervous system, other surgical stress responses, and the coagulation cascade. Increased sympathetic nervous system activity can increase myocardial oxygen demand by increasing heart rate, blood pressure, and

contractility or even decrease myocardial oxygen supply, which, in turn, may lead to angina, dysrhythmias, and areas of myocardial infarction.¹¹⁰ In addition, sympathetic activation may enhance perioperative hypercoagulability, which may contribute to perioperative coronary thrombosis or vasospasm, thus reducing myocardial oxygen supply.¹¹¹

Pulmonary

The pathophysiology of pulmonary dysfunction after surgery is multifactorial. Relevant factors include disruption of normal respiratory muscle activity, which may result from either surgery or anesthesia, reflex inhibition of phrenic nerve activity with subsequent decrease in diaphragmatic function, and uncontrolled postoperative pain, which may contribute to voluntary inhibition of respiratory activity, or splinting.¹¹² Although the pathophysiology of breathing and respiratory muscle function following surgery is complex, it is clear that anesthetic or analgesic agents administered in the perioperative period affect the central regulation of breathing and activities of respiratory muscles. This incoordination of respiratory muscle function (which may last well into the postoperative period) will impair lung mechanics, increasing the risk of hypoventilation, atelectasis, and pneumonia. Visceral stimulation may decrease phrenic motoneuron output, which results in a decrease in diaphragmatic descent and lung volumes.¹¹²

Gastrointestinal

Although decreased GI motility is expected after abdominal surgery, return of GI function usually occurs within several days postoperatively. Some patients will develop paralytic ileus, a protracted and more severe state of GI immotility. Although the pathophysiology of postoperative ileus and decreased GI motility is multifactorial, the primary mechanisms include neurogenic (spinal, supraspinal adrenergic pathways), inflammatory (i.e., local inflammatory responses initiate neurogenic inhibitory pathways), and iatrogenic pharmacologic (e.g., opioids) mechanisms.¹¹³ In the acute postoperative phase, neurogenic (spinal and supraspinal) mechanisms are primary mediators of decreased GI motility.¹¹³ Activation of splanchnic afferents and increased sympathetic outflow, along with the possible use of opioids, are the predominant mechanisms for decreased GI motility immediately following surgery. However, over the subsequent postoperative days, a prolonged phase of postoperative ileus occurs. The presumed etiology of the latter is distinct and involves an enteric molecular inflammatory response that impairs local neuromuscular function and activates neurogenic inhibitory pathways.¹¹³ Our understanding of the mechanisms of postoperative ileus is not complete, and it is likely that these three mechanisms are not discrete phenomena but interrelated.

Coagulation

It is recognized that hypercoagulability occurs in association with surgical procedures. Although the pathophysiology of coagulation-related events (e.g., formation of deep vein thrombosis has essentially been unchanged since Virchow's initial description of the triad of stasis, blood vessel injury, and hypercoagulability, our current understanding of the coagulation system is that it is a complex system with many

other functions, including tissue repair, autoimmune regulation, arteriosclerosis, and tumor growth and metastasis.¹¹⁴ Nevertheless, the primary components of the coagulation systems comprise cellular (e.g., platelets, endothelial cells, monocytes, and erythrocytes) and molecular (e.g., coagulation factors and inhibitors, fibrinolysis factors and inhibitors, adhesive and intercellular proteins, acute-phase proteins, immunoglobulins, phospholipids, prostaglandins, and cytokines) components.¹¹⁴ The normal process of coagulation involves several steps, including initiation (damaged vascular endothelium expresses tissue factor, which ultimately leads to generation of thrombin), amplification (augmentation of the effects of thrombin), propagation (formation of clot), and stabilization (formation of a stable fibrin meshwork that protects clot from fibrinolytic attack).¹¹⁴ However, following surgery, the normal process of coagulation may become unbalanced, which may result in a tendency toward thrombosis. Immediately after surgical incision, there are increases in the levels of tissue factor, tissue plasminogen activator, plasminogen activator inhibitor-1, and von Willibrand factor, which contribute to a hypercoagulable and hypofibrinolytic state postoperatively.¹¹⁴ Many of these detrimental responses may be reduced by excellent postoperative analgesia and in particular by the sympathetic and afferent block provided by thoracic epidural analgesia with local anesthetics.

POSTOPERATIVE MORBIDITY

Despite excellent theoretical reasons why high-quality analgesia should improve postoperative physiology and outcomes, the effects of nociceptive blockade and pain relief on postoperative morbidity remain controversial.¹⁶ There are several likely reasons why these effects are difficult to assess. Primarily, surgical techniques and perioperative care are constantly evolving and improving, with subsequent reduction in baseline morbidity and mortality. Thus, the positive effects of analgesia on outcomes may be apparent only on selected high-risk patients or procedures. Several systematic reviews have examined this question and have reached the following conclusions. For open major vascular and thoracic procedures, there is good evidence from systematic reviews and large randomized controlled trials that thoracic epidural analgesia may reduce cardiovascular and pulmonary morbidity when compared with systemic opioids.¹⁶ There is good evidence from meta-analyses that intraoperative spinal or epidural local anesthetics in lower-body procedures reduce estimated blood loss by about 30%.^{17,115} Finally, the duration of postoperative ileus is reduced by approximately 24 to 36 hours with the use of epidural analgesia with local anesthetic-containing solutions after major open abdominal procedures.¹⁶ This effect may be of major significance in that reduction of ileus allows earlier oral nutrition,⁵⁰ which has been demonstrated to improve outcome.

Another key feature in the difficulties assessing the impact of postoperative analgesia is that most studies to date have focused on the effects of a single factor (i.e., epidural analgesia) on overall postoperative morbidity. In current medical practice, this is probably too simplistic an approach as overall postoperative outcome is known to be determined by multiple factors.¹¹⁶⁻¹¹⁸ Besides postoperative pain relief, reinforced

psychological preparation of the patient, reduction of stress by performing neural blockade or opting for minimal invasive procedures, and enforcement of early oral postoperative feeding and mobilization may all play a significant role in determining outcome.¹¹⁸ Prevention of intraoperative hypothermia, avoidance of fluid overloading, and avoidance of hypoxemia may be important as well.^{118,119} Therefore, although adequate pain relief is obviously a prerequisite for good outcome, the best results are likely to be achieved by combining analgesia with all of the aforementioned factors in a multimodal rehabilitation effort.

DEVELOPMENT AND PREVENTION OF CHRONIC POSTOPERATIVE PAIN

Although not all nociceptive input results in a pathologic process, a substantial percentage of patients who undergo certain surgical procedures will exhibit prolonged central sensitization and chronic pain [see Table 11]. Pathologic nociceptive input may cause central sensitization, which is marked by hyperexcitable spinal neurons that exhibit a decreased threshold for activation, increased and prolonged response to noxious input, expansion of receptive fields, possible spontaneous activity, and activation by normally non-noxious stimuli.¹²⁰

Induction and maintenance of central sensitization emphasize different receptor-neurotransmitter combinations, including NMDA receptors, prostaglandins, and neuropeptides (substance P, calcitonin gene–related peptide, neurokinin A).¹²¹ Ultimately, transcriptional changes (including induction of genes), structural changes in synaptic connections (e.g., contact between low-threshold afferent and nociceptive neurons), and loss of inhibitory interneurons may result in a persistent state of central sensitization.¹²²

Multiple studies and reviews have noted that more severe acute postoperative pain is a risk factor for development of chronic postoperative pain.^{61,123} Although optimal strategies for prevention of chronic pain have not been identified, promising modalities include preemptive regional analgesia such as thoracic epidural local anesthetics, NMDA antago-

nists, and anticonvulsant analgesia adjuncts such as gabapentin.^{61,124,125} Future studies will need to define optimal strategies for high-risk procedures and patients.

BARRIERS TO EFFECTIVE POSTOPERATIVE ANALGESIA

In general, multiple advisory and supervisory organizations (e.g., JCAHO, World Health Organization) recognize the importance of adequate pain control.¹ Partially in response to these initiatives, there has been a marked increase in the creation and requirement of acute pain treatment services within hospitals across the world.¹²⁶ Work continues on attempting to create efficient and simple delivery techniques and technologies for postoperative analgesia. In addition to economic constraints, significant concerns regarding potential for opioid tolerance and addiction remain as a barrier.¹ Continued exposure of an opioid receptor to high concentrations of opioid will cause tolerance. Tolerance is the progressive decline in an opioid's potency with continuous use, so higher and higher concentrations of the drug are required to cause the same analgesic effect. Physical dependence refers to the production of an abstinence syndrome when an opioid is withdrawn. It is defined by the World Health Organization as follows:

A state, psychic or sometimes also physical, resulting from interactions between a living organism and a drug, characterized by behavioural and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects, and sometimes to avoid discomfort from its absence.¹²⁷

This definition is very close to the popular concept of addiction. It is important, however, to distinguish addiction (implying compulsive behavior and psychological dependence) from tolerance (a pharmacologic property) and from physical dependence (a characteristic physiologic effect of a group of drugs). Physical dependence does not imply addiction. Moreover, tolerance can occur without physical dependence; the converse does not appear to be true. The possibility that the medical administration of opioids could result in a patient becoming addicted has generated much debate about the use

Table 11 Approximate Incidences and Risk Factors for Development of Postoperative Chronic Pain

Surgical Procedure	Incidence of Chronic Pain (%)	Risk Factors
Thoracotomy	30–70	Increased acute pain
		Open vs thoracoscopic
		Not using thoracic epidural analgesia with local anesthetics
		Intercostal nerve injury
Mastectomy	11–60	Increased acute pain
		Increased acute opioid consumption
		Immediate adjuvant radiation therapy
		Axillary dissection vs sentinel node biopsy
Inguinal hernia repair	0–37	Increased acute pain
		Preoperative pain
		Female gender
		Surgery for recurrent hernia
		Open vs laparoscopic

of opioids. In a prospective study of 12,000 hospitalized patients receiving at least one strong opioid for a protracted period, there were only four reasonably well-documented cases of subsequent addiction, and in none of these was there a history of previous substance abuse.¹²⁸ Thus, the iatrogenic production of opioid addiction is very rare. It is hoped that continued physician and patient education will reduce this barrier to high-quality postoperative analgesia.

Conclusion

The choice of therapeutic intervention for acute postoperative pain is determined largely by the nature of the patient's problem, the resources available, the efficacy of the various

treatment techniques, the risks attendant on the procedures under consideration, and the cost to the patient. It is to be hoped that our growing understanding of basic pain mechanisms and appropriate therapy, combined with the promising data supporting the idea that adequate inhibition of surgically induced nociceptive stimuli may reduce postoperative morbidity, will stimulate more surgeons to turn their attention to this area. Effective control of postoperative pain, combined with a high degree of surgical expertise and the judicious use of other perioperative therapeutic interventions within the context of multimodal postoperative rehabilitation, is certain to improve acute and long-term patient outcomes.

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Acknowledgments

Figure 1 Carol Donner.

7 ACUTE WOUND CARE

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Approach to Acute Wound Management

Acute wounds are the result of local trauma and may be associated with severe life-threatening injuries. The approach to a patient with an acute wound begins with assessment of the ABCs (Airway, Breathing, and Circulation). Management of any life-threatening injuries present is addressed first; only after more urgent problems have been ruled out or corrected is management of the wound itself addressed. A complete history is obtained and a thorough physical examination performed, with special attention paid to both local and systemic wound environment factors that may affect healing. Information about the cause of injury is sought. In the case of a hand injury, the patient's hand dominance and occupation are determined. All patients with acute wounds should be assessed for malnutrition, diabetes, peripheral vascular disease, neuropathy, obesity, immune deficiency, autoimmune disorders, connective tissue diseases, coagulopathy, hepatic dysfunction, malignancy, smoking practices, medication use that could interfere with healing, and allergies. The local wound environment should be evaluated to determine the extent and complexity of injury, the tissues involved, the presence or absence of contamination by microorganisms or foreign bodies, and the degree of any damage related to previous irradiation or injury to surrounding tissues.

Gloves and a shielded mask are worn to protect the practitioner from exposure to body fluids. Gloves must be powder free, as well as latex free (to prevent allergic reactions to latex).¹ The wound is carefully examined, with particular attention paid to size, location, bleeding, arterial or venous insufficiency, tissue temperature, tissue viability, and foreign bodies. The possibility of damage to vessels, nerves, ducts, cartilage, muscles, or bones in proximity to the injury is assessed. X-rays and a careful motor and sensory examination may be required to rule out such coexisting injuries. While these tests are being performed, moist gauze should be applied to wounds. For thorough assessment of injuries, it may be necessary to probe ducts (e.g., the parotid duct or the lacrimal duct).

At this point, decisions must be made about acute wound care. The goal of acute wound management is a closed, healing wound that will result in the best functional and aesthetic outcome. In what follows, we address the key considerations in management of the acute wound, including anesthesia, choice of repair site (i.e., operating room or emergency department), debridement, irrigation, hemostasis, closure materials, timing and methods of closure, appropriate closure methods for specific wound types, dressings, adjunctive treatment (e.g., tetanus and rabies prophylaxis, antibiotics, and nutritional supplementation), postoperative wound care, and potential disturbances of wound healing. Finally, we briefly review the physiology of wound healing.

Wound Preparation

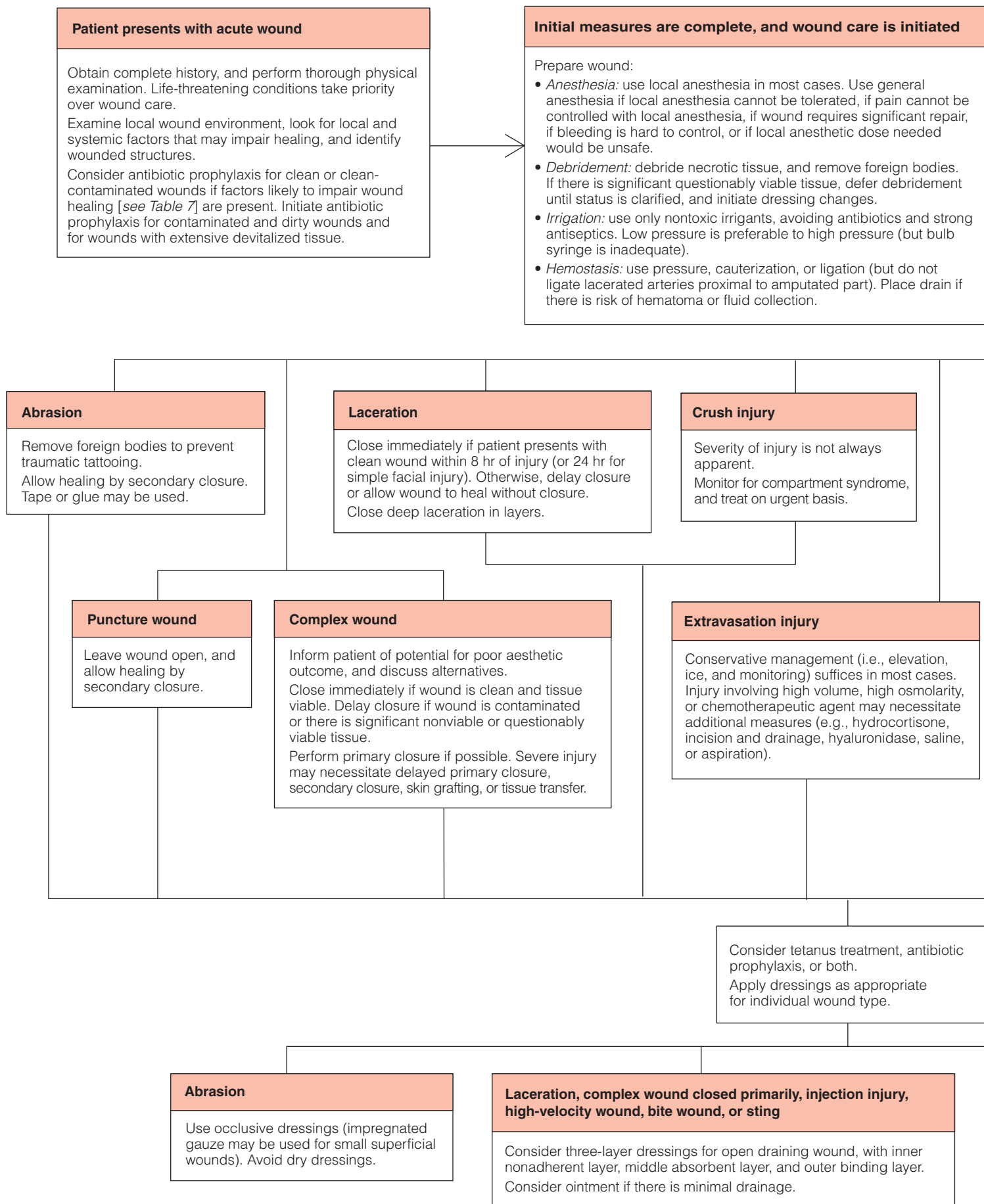
ANESTHESIA

Adequate general or local anesthesia, preceded by careful motor and sensory examination, must be instituted before examination and treatment of the wound can begin. General anesthesia in the OR is employed if the patient is unable to tolerate local anesthesia; adequate pain control cannot be achieved with a local block; the wound requires significant debridement, exploration, or repair; bleeding is difficult to control; or the local anesthetic dose required for adequate pain control exceeds the maximum dose that can be safely delivered. Local anesthesia is usually sufficient for debridement and closure of most small traumatic wounds. Often, the local anesthetic may be injected directly into wounded tissue. However, direct wound injection may be less reliable in inflamed or infected tissue or may distort important anatomic landmarks used to align wound edges. In these situations, regional nerve blocks directed at specific sensory nerves outside the injured field may be employed instead.

The main injectable anesthetics can be broadly divided into amides and esters [see Table 1]. (An easy way of remembering which category an agent belongs to is to recall that the amides all have two *Is* in their generic name, whereas the esters have only one.) Lidocaine, an amide, is the most commonly used local anesthetic. Its advantages include its rapid onset of action (< 2 minutes), its extended duration of action (60 to 120 minutes), its relative safety in comparison with more potent anesthetics (e.g., bupivacaine), and its availability in multiple forms (e.g., liquid, jelly, and ointment) and concentrations (e.g., 0.5%, 1.0%, and 2.0%). In addition, lidocaine rarely causes allergic reactions, whereas ester anesthetics (e.g., tetracaine) are metabolized to para-aminobenzoic acid, to which some persons are allergic. Cocaine, an ester, is an excellent local anesthetic for wounds in

Table 1 Common Injectable Anesthetics³

Amides	Esters
Lidocaine (Xylocaine)	Procaine (Novocain)
Bupivacaine (Marcaine)	Chloroprocaine (Nesacaine)
Mepivacaine (Carbocaine)	Tetracaine (Pontocaine)
Prilocaine (Citanest)	Benzocaine (multiple brands)
Etidocaine (Duranest)	Propoxycaine (Ravocaine)
Phenocaine	Cocaine
Dibucaine (Nupercainal)	
Ropivacaine (Naropin)	
Levobupivacaine (Chirocaine)	



Approach to Acute Wound Management

Wound is ready for closure

Select closure materials: sutures, tapes, staples, or adhesives.

Determine timing and methods of closure:

- *Immediate primary closure*: clean wound without contraindications to closure
- *Delayed primary closure*: contaminated wound, wound with questionably viable tissue, or patient who cannot tolerate immediate closure
- *Secondary closure (allowing wound to heal by itself)*: wound with contamination or contraindication to closure, patient who cannot tolerate closure, or wound for which closure is not needed for aesthetic result
- *Skin grafting*: large superficial wound
- *Tissue transfer*: large wound with exposed vital structure

Formulate specific closure approach suitable for individual wound type.

Injection injury

Wound appearance is often deceptively benign. Examine wound area carefully and obtain appropriate radiographs.

Treat aggressively with incision, wide exposure, debridement, and removal of foreign bodies.

Allow healing by secondary closure.

Bite wound

Take into account risks of rabies, bacterial and other viral infections, and envenomation.

Treat with exploration, irrigation, and debridement.

Close immediately if wound is clean and tissue viable. Delay closure if wound is contaminated or there is significant nonviable or questionably viable tissue.

Perform primary closure if possible. Severe injury may necessitate secondary closure, skin grafting, or tissue transfer.

Consider rabies treatment, rabies prophylaxis, or both.

High-velocity wound

Wound appearance is often deceptively benign; foreign bodies are frequently present. Examine wound area carefully and obtain appropriate radiographs.

Debride wound extensively and identify all injured tissue.

Avoid immediate primary closure. Perform delayed primary closure or allow healing by secondary closure.

Sting

Take into account risk of envenomation.

Symptoms may be local or systemic. Treatment is usually directed toward local symptoms. For systemic reactions, epinephrine, diphenhydramine, and supportive airway and BP care may be required.

Complex wound left open or closed after delay

Generally, use wet-to-dry dressings; use wet-to-wet dressings if wound bed contains tendons, arteries, nerves, or bone. Avoid compression dressings. Consider NPWT for large open wound.

Extravasation injury or crush injury

Avoid compression dressings.

mucous membrane (e.g., those in the nose or the throat). It is unique among local anesthetics in that it causes vasoconstriction, which helps reduce hemorrhage. Typically, cocaine is applied topically by soaking gauze or pledgets in a solution.

Vasoconstriction can also be produced by adding epinephrine to a local anesthetic, usually in a dilution of 1:100,000 or 1:200,000 (5 to 10 µg/ml). Through vasoconstriction, epinephrine prolongs the anesthetic agent's duration of action, allows a larger dose to be safely administered, and aids in hemostasis.² Traditionally, local anesthetics with epinephrine have not been used in finger and toe wounds, because of the theoretical risk of ischemia and tissue loss; however, these adverse effects have not yet been reported clinically or documented by any prospective studies.³

Local anesthetics can cause systemic toxicity when injected intravascularly or given in excessive doses. Manifestations of systemic toxicity begin with central nervous system effects (e.g., vertigo, tinnitus, sedation, and seizures) and may progress to cardiovascular effects (e.g., hypotension, cardiac conduction abnormalities, and cardiovascular collapse). Treatment for systemic toxicity is supportive, with oxygen, airway support, and cardiovascular bypass (if necessary) provided until the anesthetic has been metabolized by the liver. The maximum safe dose of lidocaine is 3 to 5 mg/kg without epinephrine and 7 mg/kg with epinephrine. Doses as high as 55 mg/kg have been used without toxicity for tumescent anesthesia in patients undergoing liposuction⁴; however, in this scenario, some of the anesthetic is aspirated by the liposuction, which means that the effective dose is lower. The lidocaine doses used for local wound injection should be substantially smaller than those used in liposuction. The maximum safe dose of cocaine is 2 to 3 mg/kg. To prevent local anesthesia from causing systemic toxicity, the recommended safe doses of the anesthetics should not be exceeded, and aspiration should be performed before injection into the wound to ensure that the agent will not be injected intravascularly.

The pain associated with injection of the local anesthetic can be minimized by using a small-caliber needle (27 to 30 gauge), warming the anesthetic, injecting the agent slowly, using a subcutaneous rather than an intradermal injection technique,⁵ providing counterirritation, buffering the anesthetic with sodium bicarbonate to reduce acidity (in a 1:10 ratio of sodium bicarbonate to local anesthetic),⁶ and applying a topical local anesthetic before injection. Topical local anesthetics (e.g., TAC [tetracaine, adrenaline (epinephrine), and cocaine] and EMLA [a eutectic mixture of lidocaine and prilocaine]) are as effective as injectable anesthetics when applied to an open wound.⁷ EMLA requires approximately 60 minutes to induce sufficient anesthesia for open wounds; TAC requires approximately 30 minutes.⁸ EMLA is more effective than TAC for open wounds of the extremity. Benzocaine 20% (in gel, liquid, or spray form) can also be used for topical anesthesia and is frequently employed before endoscopic procedures. It is poorly absorbed through intact skin but well absorbed through mucous membranes and open wounds. A 0.5- to 1-second spray is usually recommended, though even with a standardized spray duration, the delivered dose can vary considerably.⁹ A 2-second spray results in a statistically, though not clinically, significant increase in methemoglobin levels.¹⁰ Methemoglobinemia is a rare but life-threatening complication of benzocaine spray use. If symptoms of methemoglobinemia develop (e.g., cyanosis or elevated methemoglobin levels on cooximetry), prompt treatment with intravenous methylene blue, 1 to 2 mg/kg, is indicated.⁹

DEBRIDEMENT

Normal healing can proceed only if tissues are viable, if the wound contains no foreign bodies, and if tissues are free of exces-

sive bacterial contamination. To reduce the risk of infection in an acute wound, necrotic tissue and foreign bodies must be removed.¹¹ The wound and the surrounding local tissue must be exposed so that necrotic tissue can be identified and debrided. Hair may be trimmed with scissors or an electric clipper or retracted with an ointment or gel to facilitate exposure, debridement, and wound closure. Close shaving with a razor should be avoided, however, because it potentiates wound infections.¹² Clipping of eyebrows should also be avoided, both because the eyebrows may not grow back and because the hair is necessary for proper alignment.

Some wounds contain a significant amount of questionably viable tissue. If there is enough questionably viable tissue to preclude acute debridement, dressing changes may be initiated. When all tissue has been declared to be either viable or necrotic and when the necrotic tissue has been debrided surgically or by means of dressing changes, the wound can be closed.

Most foreign bodies are easily removed from wounds either by hand or via surgical debridement. Abrasion injuries or gunpowder explosions can cause small foreign body fragments to be embedded in and beneath the skin. These small foreign bodies are often difficult to extract but should be removed as soon after the injury as possible. Irrigation usually suffices for removal of loose foreign bodies, but surgical debridement with a small drill, a sharp instrument, or a brush may be required for removal of more firmly embedded foreign material. If the interval between injury and treatment exceeds 1 to 2 days, the wounds will begin to epithelialize and the embedded material will be trapped in the skin, resulting in traumatic tattooing.

IRRIGATION

After debridement of necrotic tissue and foreign bodies, the next step is irrigation of the wound. This may be accomplished by means of several different methods, including bulb syringe irrigation, gravity flow irrigation, and pulsatile lavage. These methods can be further divided into high-pressure (35 to 70 psi) and low-pressure (1 to 15 psi) delivery systems. High-pressure pulsatile lavage reduces bacterial concentrations in the wound more efficiently than low-pressure and bulb syringe irrigation do,¹³ but it also causes considerable disruption to soft tissue structure¹⁴ and results in deeper penetration and greater retention of bacteria in soft tissue than low-pressure lavage does.¹⁵ In general, low-pressure systems should be employed for acute wound irrigation, though merely running saline over a wound is of little value. To obtain continuous irrigation with pressures as low as 5 to 8 psi, one group recommended using a saline bag in a pressure cuff inflated to 400 mm Hg and connected to I.V. tubing with a 19-gauge angiocatheter.¹⁶

Only nontoxic solutions (e.g., 0.9% sterile saline, lactated Ringer solution, sterile water, and tap water) should be used for wound irrigation.¹⁷ Irrigation with an antibiotic solution appears to offer no advantages over irrigation with a nonsterile soap solution, and the antibiotic solution may increase the risk of wound-healing problems.¹⁸ Strong antiseptics (e.g., povidone-iodine, chlorhexidine, alcohol, sodium hypochlorite, and hydrogen peroxide) should not be placed directly into the wound, because they are toxic to the tissues and impede healing. The surrounding skin should be prepared with an antibacterial solution, and a sterile field created to limit contamination.

HEMOSTASIS

In most wounds, hemorrhage can be readily controlled with pressure, cauterization, or ligation of vessels. Lacerated arteries

proximal to amputated parts such as fingers or ears, however, should not be ligated, because an intact vessel is necessary for microsurgical replantation. Packing, wrapping, and elevating can help control hemorrhage temporarily. If necessary (though the need should be rare), a tourniquet may be applied to an injured extremity. Hemostasis prevents hematoma formation, which increases the risk of infection and wound inflammation. If there appears to be a potential risk of hematoma or fluid collection, drains should be placed. Although drains may help prevent accumulation of blood or serum in the wound, they are not a replacement for meticulous hemostasis. Drains facilitate approximation of tissues, particularly under flaps; however, they also tend to potentiate bacterial infections and should therefore be removed from the wound as soon as possible.¹⁹

As a rule, drains can be safely removed when drainage reaches levels of 25 to 50 ml/day. If a hematoma or seroma forms, the subsequent course of action depends on the size of the fluid collection. Small hematomas and seromas usually are reabsorbed and thus can be treated conservatively. Larger hematomas and seromas provide a significant barrier to healing, and treatment may require reopening the wound and placing drains. Intermittent sterile aspirations, followed by application of a compressive dressing, may be indicated for seromas. If this approach fails to eliminate the seroma, a drain may be reintroduced.

Wound Closure

MATERIALS

Once the appropriate preparatory measures have been taken (see above), the wound is ready to be closed. The first step is to choose the material to be used for wound closure. The materials currently available for this purpose include sutures, staples, tapes, and glues. Selection of the appropriate material is based on the type and location of the wound, the potential for infection, the patient's ability to tolerate closure, and the degree of mechanical stress imposed by closure. The selected material must provide wound edge approximation until the tensile strength of the wound has increased to the point where it can withstand the stress present.

The majority of wounds are closed with sutures. A suture is a foreign body by definition, and as such, it may generate an inflammatory response, interfere with wound healing, and increase the risk of infection. Accordingly, the number and diameter of sutures used to close a wound should be kept to the minimum necessary for coaptation of the edges.

Sutures are categorized on the basis of material used, tensile strength, configuration, absorbability, and time to degradation [see Table 2]. Suture material may be either natural or synthetic; natural fibers (e.g., catgut and silk) cause more intense inflammatory reactions than synthetic materials (e.g., polypropylene) do.²⁰ The tensile strength of suture material is defined as the amount of weight required to break a suture divided by the suture's cross-sectional area. It is typically expressed in an integer-hyphen-zero form, whereby larger integers correspond to smaller suture diameters (e.g., 3-0 sutures have a greater diameter and more tensile strength than 5-0 sutures do).²¹ Closure of acute wounds rarely requires sutures larger than 4-0. In terms of configuration, suture material may be composed either of a single filament or of multiple filaments. Multifilament suture material may be twisted or braided, and the interstices created by braiding may harbor organisms and

increase the risk of infection. Monofilament sutures hold knots less well than multifilament sutures, requiring five knots for security; multifilament sutures are easier to handle and require only three knots. With all sutures, the knots must be square to be secure and must be only tight enough to coapt the wound edges. To minimize foreign body bulk, buried suture knot ends should be cut right on the knot. In terms of absorbability, either absorbable or nonabsorbable sutures may be appropriate, depending on the situation. Absorbable sutures are generally used for buried sutures to approximate deep tissues (e.g., dermis, muscle, or fascia). Absorption of synthetic suture material occurs by hydrolysis and causes less tissue reaction than absorption of natural suture material, which occurs by proteolysis. Nonabsorbable sutures (e.g., those made of silk, nylon, polyester, or polybutester) are most commonly used for wounds in the skin, from where they will eventually be removed, or for wounds in deeper structures that require prolonged support (e.g., abdominal wall fascia, tendons, nerves, and blood vessels).

Staple closure is less expensive and significantly faster than suture closure, and it offers a slightly, though not significantly, better cosmetic outcome when used to close scalp wounds.^{22,23} Contaminated wounds closed with staples have a lower incidence of infection than those closed with sutures.²⁴ In addition, staple closure eliminates the risk that a health care provider will experience a needle stick, which is a particularly important consideration in caring for a trauma patient with an unknown medical history.

The tapes used for wound closure either are rubber-based or employ an acrylate adhesive. Rubber-based tapes (e.g., athletic tape) are a potential irritant to skin, degrade with exposure to heat, light, and air, and are occlusive, thereby preventing transepidermal water loss. Tapes that include acrylate adhesives (e.g., Micropore and Steri-Strip), however, are hypoallergenic, have a long shelf life, and are porous, thereby allowing water to evaporate.²⁵ Linear wounds in areas with little tension are easily approximated with tape alone, whereas wounds in areas where the skin is more taut (e.g., the extremities) generally require that tape skin closure be supplemented by dermal sutures. The use of tape alone is desirable when feasible, in that it spares the patient the discomfort associated with suture removal, prevents suture puncture scars, and avoids the emotional upset that may attend suture closure of small facial wounds on children.²⁵ Tape closure has some significant advantages: it immobilizes wound edges, permits early suture removal, is easy to perform and comfortable for the patient, leaves no marks on the skin, and yields a lower infection rate in contaminated wounds than suture closure does.²⁶ It also has a few disadvantages: patients may inadvertently remove the tapes, and wound edge approximation is less precise with tapes alone than with sutures. In addition, tape will not adhere to mobile areas under tension (e.g., the plantar aspects of the feet) or to moist areas (e.g., mucous membranes and groin creases), and wound edema can lead to blistering at the tape margins and to inversion of taped wound edges.

The use of tissue adhesives (e.g., octylcyanoacrylate) is a fast, strong, and flexible method of approximating wound edges. Compared with sutures, staples, and tapes, adhesives provide a faster closure and are essentially equivalent in terms of cosmetic outcome, infection rate, and dehiscence rate.²⁷ Adhesives can be used on most parts of the body and have been employed to close wounds ranging from 0.5 to 50 cm in length. Their advantages include reduced cost, ease of application, and the absence of any need for needles or suture removal; their major disadvantage is lack of strength.²⁸ They must not be applied to tissues within wounds but, rather, should be applied to intact skin at wound edges, where they serve to hold injured surfaces together. In addi-

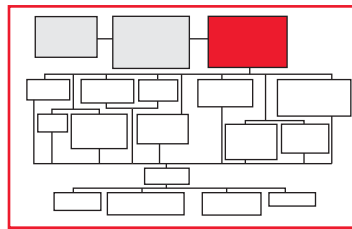


Table 2 Types and Characteristics of Suture Material Used for Wound Closure

Suture Type	Material	Comment	Configuration	Method of Absorption	Tensile Strength at 2 Wk	Time to Degradation
Absorbable	Plain catgut (bovine intestinal serosa)	Natural; high tissue reactivity	Monofilament	Proteolysis	0%	10–14 days
	Chromic catgut (bovine intestinal serosa treated with chromic acid)	Natural; stronger, less reactive, and longer-lasting than plain catgut	Monofilament	Proteolysis	0%	21 days
	Fast-absorbing catgut	Natural	Monofilament	Proteolysis	0%	7–10 days
	Polyglytone 6211 (Caprosyn)	Synthetic	Monofilament	Hydrolysis	10%	56 days
	Glycomer 631 (Biosyn)	Synthetic	Monofilament	Hydrolysis	75%	90–110 days
	Polyglycolic acid (Dexon)	Synthetic	Monofilament/multifilament	Hydrolysis	20%	90–120 days
	Polyglactic acid (Vicryl)	Synthetic	Multifilament	Hydrolysis	20%	60–90 days
	Polyglyconate (Maxon)	Synthetic	Monofilament	Hydrolysis	81%	180–210 days
	Polyglycolide (Polysorb)	Synthetic	Multifilament	Hydrolysis	80%	56–70 days
	Polydioxanone (PDS)	Synthetic	Monofilament	Hydrolysis	74%	180 days
	Polyglecaprone 25 (Monocryl)	Synthetic	Monofilament	Hydrolysis	25%	90–120 days
	Polyglactin 910 (Vicryl RAPIDE)	Synthetic	Multifilament	Hydrolysis	0%	7–14 days
Nonabsorbable	Polybutester (Novafil)	Synthetic; low tissue reactivity; elastic; good knot security	Monofilament	—	High	—
	Nylon (Monosof, Dermalon, Ethilon)	Synthetic; low tissue reactivity; memory effect necessitates more knots	Monofilament	—	High	—
	Nylon (Nurolon)	Synthetic; low tissue reactivity	Multifilament	—	High	—
	Nylon (Surgilon)	Synthetic; silicon coated; low tissue reactivity	Multifilament	—	High	—
	Polypropylene (Prolene, Surgilene, Surgipro)	Synthetic; low tissue reactivity; slippery	Monofilament	—	High	—
	Polyethylene (Dermalene)	Synthetic	Monofilament	—	High	—
	Stainless steel	Lowest tissue reactivity of all sutures; poor handling; creates artifact on CT scan; moves with MRI	Monofilament/multifilament	—	Highest	—
	Cotton	Natural	Multifilament	—	—	—
	Silk (Sofsilik)	Natural; high tissue reactivity; good knot security	Multifilament	—	Poor	—
	Polyester (Dacron, Mersilene, Surgidac)	Synthetic; uncoated; high friction; low tissue reactivity; poor knot security	Multifilament	—	High	—
	Polyester (Ticron)	Synthetic; silicon coated; low tissue reactivity; good knot security	Multifilament	—	High	—
	Polyester (Ethibond)	Synthetic; polybutylate coated; low tissue reactivity; good knot security	Multifilament	—	High	—
	Polyester (Ethiflex, Tevdek)	Synthetic; Teflon coated; low tissue reactivity; good knot security	Multifilament	—	High	—

tion, they should not be used for wounds in mucous membranes, contaminated wounds, deep wounds, or wounds under tension. Adhesives are particularly useful for superficial wounds or wounds in which the deep dermis has been closed with sutures.

TIMING AND METHODS

Appropriate materials having been selected, the next issue to address is the timing of wound closure. The choices are (1) to close the wound at the time of initial presentation, (2) to delay closure until after a period of healing or wound care, and (3) to allow the wound to heal on its own. The best choice in a given situation depends whether the patient is stable and able to undergo wound repair, whether hemorrhage is under control, whether necrotic material has been adequately debrided and foreign bodies removed, whether and to what degree bacterial contamination is present, and what the expected aesthetic outcome of immediate closure might be in comparison with that of delayed closure or secondary healing.

The timing of wound closure determines the method that will be employed. The closure methods available include (1) primary closure by direct approximation; (2) delayed primary closure, in which the wound is closed after a healing period; (3) secondary closure, in which the wound is allowed to heal on its own; (4) skin grafting; and (5) the use of local or distant flaps. The ideal wound closure method would support the wound until it has nearly reached full strength (i.e., about 6 weeks), would not induce inflammation, would not induce ischemia, would not penetrate the epidermis and predispose to additional scars, and would not interfere with the healing process. Unfortunately, no existing method accomplishes all of these goals in all cases; some sort of compromise is virtually always necessary. In the acute wound setting, the simplest method that will achieve a good closure is preferred.

Primary closure provides optimal wound healing when two perpendicular, well-vascularized wound edges are approximated without tension. Closure should proceed from deep to superficial. The initial step is to identify landmarks and line up tissues, using skin hooks or fine forceps to keep from causing wound edge trauma. Although wound closure is usually a straightforward process, situations occasionally arise in which special caution is necessary. For instance, when a wound crosses tissues with different characteristics (e.g., at the vermilion border of the lip, the eyebrow, or the hairline of the scalp), particular care must be taken to align the damaged structures accurately. In the repair of soft tissue, it is critical to handle tissue gently with atraumatic surgical technique, to place sutures precisely, and to minimize tension and contamination.

The next step is tissue-specific repair, which may require the consultation of an experienced surgeon. Bone fractures are reduced and repaired with plates, rods, or external fixation devices. Muscle lacerations should be repaired because muscle is capable of a significant degree of regeneration. A completely lacerated muscle that is properly repaired recovers approximately 50% of its ability to produce tension and 80% of its ability to shorten, whereas a partially lacerated muscle that is properly repaired recovers approximately 60% of its ability to produce tension and 100% of its ability to shorten.²⁹ Tendon lacerations should be meticulously approximated to allow gliding and restore tensile strength. Either 4-0 multifilament polyester or monofilament polypropylene is a reasonable choice for muscle and tendon repair.³⁰ Early active mobilization promotes the restoration of tensile strength in muscles and tendons. Penetrating nerve trauma is treated with tension-free coaptation at the time of wound closure by primary repair or repair with a nerve graft or nerve tube. Epineurial coaptation is typically achieved by placing 8-0 to 10-0 monofilament

nylon sutures under loupe or microscope magnification. For ischemic or amputated tissues (e.g., an ear, a digit, or a limb), vessel repair is performed with 8-0 to 10-0 monofilament nylon sutures under magnification.

In subcutaneous fat, suture placement should be avoided whenever possible; if sutures in this location are absolutely necessary, they should be placed at the fat-fascia junction or the fat-dermis junction, not in fat alone. Fat cannot hold sutures by itself, and because it has a poor blood supply, suturing may lead to fat necrosis. The deeper fascial layers that contribute to the structural integrity of areas such as the abdomen, the chest, and the galea should be closed as a separate layer to prevent hernias, structural deformities, and hematomas.

At the skin level, the deep dermis is responsible for the strength of the acute wound closure. Deep dermal repair is performed with 4-0 absorbable suture material (e.g., polyglactin 910) and a cutting needle. The sutures are buried and placed 5 to 8 mm apart, with care taken to evert the skin edges. Buried dermal sutures are often used in conjunction with tapes (e.g., Steri-Strips), fine epidermal sutures, or adhesives to facilitate precise alignment. Skin edges should be coapted and everted with 4-0 to 6-0 nylon or polypropylene sutures placed in the superficial dermis and the epidermis. The distance between the sutures and the distance between the wound edge and the suture insertion point should be equal to the thickness of the skin (epidermis and dermis combined).

Several different skin suturing methods may be used, depending on the nature of the wound. Simple interrupted sutures are useful for irregular wounds. Vertical mattress sutures are good for either thick (e.g., scalp) or thin (e.g., eyelid) skin. Horizontal mattress sutures can lead to ischemia and thus must be applied loosely; they may look untidy early after repair, but they generally achieve good wound-edge eversion and long-term healing. Half-buried horizontal and vertical mattress sutures are used for flap edges to minimize ischemia. A continuous intradermal or subcuticular suture is easy to remove and relatively inconspicuous visually. A simple continuous suture should be used only for linear wounds; it is quick to place but tends to invert the wound edges. Flap tips should be sutured with a three-point method to prevent strangulation [see Figure 1]. For children, suture removal can be both emotionally and physically traumatic; accordingly, when suturing is employed for skin closure in a pediatric patient, the use of fast-absorbing suture material (e.g., plain catgut) or a pullout continuous subcuticular suturing method should be considered.

Primary direct approximation of wounds is not always indicated. In cases where obvious bacterial contamination is present, there is a substantial amount of questionably necrotic tissue, or the patient is unstable and unfit to undergo primary repair at the time of presentation, delayed primary closure is performed. Delayed primary closure involves direct approximation of wound edges after a period (usually 4 to 5 days) of wound hygiene. This closure method markedly diminishes the incidence of wound infection in patients with contaminated wounds.

Secondary closure, in which the wound is left open and allowed to heal on its own, is also sometimes chosen. Secondary closure depends on contraction of the surrounding tissue and epithelialization from the wound margins. When this approach is followed, caution and close observation are essential because the process of tissue contraction can sometimes lead to contracture, a pathologic scar deformity. Secondary closure can, however, yield acceptable results with specific wound types and at specific anatomic sites. With puncture wounds, for example, secondary closure is preferred because it diminishes the likelihood of infection. For both abrasions and puncture wounds, the functional and aesthetic

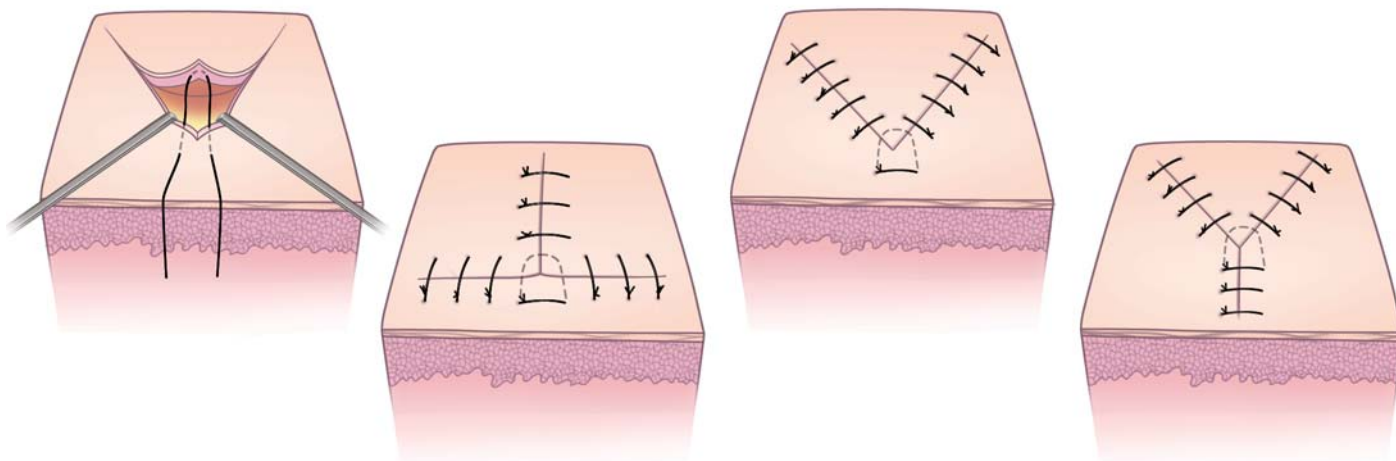


Figure 1 Shown is the method for inserting three-point sutures, along with three different applications of this method.

results of secondary closure are generally as good as or better than those obtained by primary or delayed primary closure. For wounds on anatomically concave surfaces (e.g., the medial canthal region, the nasolabial region, or the perineum), secondary wound healing generally yields excellent results.³¹ Secondary closure should also be considered for severely contaminated wounds, infected wounds, wounds with significant amounts of devitalized tissue, wounds with foreign bodies, lacerations older than 24 hours, wounds in patients who are in shock, and high-velocity wounds.³²

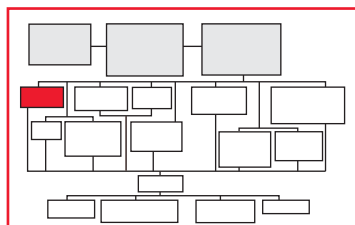
Occasionally, an acute wound is so large that neither primary nor secondary closure will suffice. Such wounds must be covered with skin grafts or transferred tissue (i.e., flaps) [see 3:3 *Open Wound Requiring Reconstruction* and 3:7 *Surface Reconstruction Procedures*]. Local or distant flaps must be considered for wounds that involve exposed bone denuded of periosteum, cartilage denuded of perichondrium, tendon denuded of paratenon, or nerve denuded of perineurium.

CLOSURE OF SPECIFIC TYPES OF WOUNDS

Wounds may be divided into 10 main types: abrasions, puncture wounds, lacerations, complex wounds, crush injuries, extravasation injuries, injection injuries, high-velocity wounds, bite wounds, and stings. In addition, the American College of Surgeons (ACS) has divided wounds into four major categories: clean, clean-contaminated, contaminated, and dirty [see Table 3]. The likelihood of infection after any surgical procedure is correlated with the ACS wound category: class I and II wounds have infection rates lower than 11%, whereas wounds in class IV have infection rates as high as 40%.³³

Abrasions

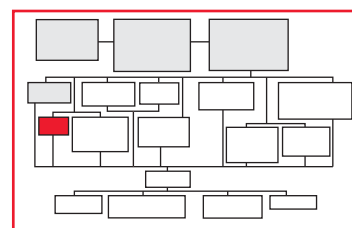
Abrasions are superficial wounds caused by scraping. They involve only the epidermis and a portion of the dermis and frequently heal secondarily within 1 to 2 weeks. If an abrasion is to be closed primarily, tape or glue may be used for epidermal approximation to prevent suture mark scars (which could be worse than the actual wound scar). In some patients who have experienced abrasion injuries (e.g., motorcycle accidents in which victims slide along asphalt) or blast injuries (e.g., firework explosions), small foreign body fragments become embedded in and beneath the skin, often



proving quite difficult to remove. Complete debridement of these embedded foreign bodies within 24 to 48 hours of injury is crucial in preventing so-called traumatic tattooing. In the early postinjury period, surgical debridement with a small drill, a sharp instrument, or a scrub brush may suffice for removal of the foreign material causing the traumatic tattoo; later, dermabrasion will be necessary.^{34,35} Once the wound is adequately debrided, semioclusive dressings should be applied to optimize epithelialization.

Puncture Wounds

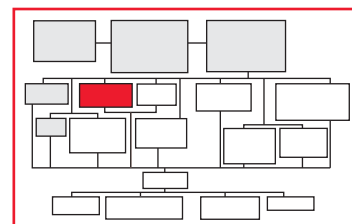
Puncture wounds should be examined for foreign bodies, which must be removed when found. They are typically left open, treated with wound care, and allowed to heal by secondary intention. With



puncture wounds, secondary closure reduces the risk of infection and generally yields excellent aesthetic results.

Lacerations

The type of wound most commonly encountered by surgeons is a superficial or deep acute traumatic or surgical wound that is suitable for primary closure by direct approximation of the wound



edges. In this setting, the goal is to provide the best possible chance for uncomplicated healing. If the wound is to be closed, primary closure at the time of evaluation is preferred if it is feasible. As a rule, closure should be completed within 6 to 8 hours of the injury, though simple noncontaminated wounds of the face can be safely closed as long as 24 hours after the injury. Primary closure is generally desirable in that it eliminates the need for extensive wound care, allows the wound to heal more quickly, and minimizes patient discomfort. However, lacerations containing foreign bodies or necrotic tissue that cannot be removed by irrigation or debridement and lacerations with excessive bacterial contamination should not be closed primarily, nor should wounds in which hemostasis is incomplete. Hematomas,³⁶ necrotic tissue,³⁷ and foreign bodies³⁸ all promote bacterial growth and place a mechanical barrier between healing tissues.

Complex Wounds

The term complex wounds includes stellate wounds and those caused by degloving, avulsion, and mutilation. The goals of treatment include achieving closure within 6 to 8 hours of the injury, providing treatment in a manner consistent with the patient's general health, keeping bacterial counts at a low level, protecting tissues from desiccation, applying only nonnoxious agents, and supplying adequate permanent coverage. In addition, it is important to discuss with the patient the particular treatment difficulties posed by these wounds. Often, a patient with a complex wound must be treated in the OR under general anesthesia because the injury is extensive or because there is a need for exploration of tissues, removal of foreign bodies, and debridement of nonviable tissue.

Stellate wounds can be approximated with careful placement of interrupted and three-point sutures. Severely injured tissue may have to be removed as an ellipse, with the resulting defect closed.

Degloving refers to circumferential elevation of skin and fat from muscle; the skin flap created by this process rarely survives. In the acute setting, questionably viable flaps of tissue may be evaluated by administering fluorescein, up to 15 mg/kg I.V., and observing the flap for fluorescence under an ultraviolet lamp after 10 to 15 minutes have elapsed.³⁹ Viable flap tissue fluoresces green. Tissue that is determined to be devascularized, on the basis of either physical examination or fluorescein testing, should be debrided. If the viability of a tissue segment is in doubt, the segment may be sewn back into its anatomic location and allowed to define itself as viable or nonviable over time.

Large open wounds resulting from avulsion can be either left to heal by secondary intention or treated with delayed skin grafting.³²

Mutilating wounds caused by machinery (e.g., farm equipment) are often contaminated by a mixture of gram-positive and gram-negative organisms, though not always excessively so.⁴⁰ When such a wound is grossly contaminated, antibiotic therapy (preferably with an agent or combination of agents that offers broad-spectrum coverage) is indicated. Contaminated wounds closed with either tape or staples have a lower incidence of infection than those closed with sutures.^{24,26}

Crush Injuries

A notable feature of crush injury is that the severity of the wound is not always readily apparent. In many cases, no external laceration can be seen, even though deep tissue damage may be extensive. Ultrasonography or magnetic resonance imaging may help identify a hematoma that is amenable to evacuation.³² Deep tissue injury can lead to compartment syndrome and subsequent extremity loss. Early diagnosis is the key to successful treatment. Generally, the diagnosis can be made on the basis of physical signs and symptoms, including increasing pain that is out of proportion to the stimulus, altered sensation, pain on passive stretching of the affected muscle compartment, muscle weakness, and palpable tenseness of the compartment.⁴¹

If compartment syndrome is suspected, the intracompartmental pressure should be measured.⁴² If the intracompartmental pressure exceeds 30 mm Hg or if the so-called delta pressure (i.e., the diastolic blood pressure minus the intracompartmental pres-

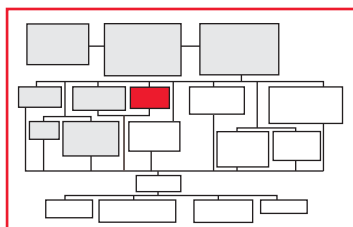
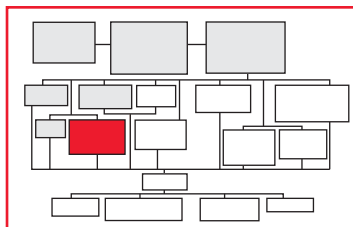


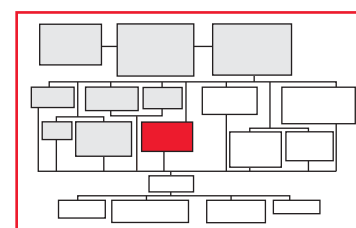
Table 3 Classification and Infection Rates of Operative Wounds

Classification	Infection Rate (%)	Wound Characteristics
Clean (class I)	1.5–5.1	Atraumatic, uninfected; no entry of GU, GI, or respiratory tract
Clean-contaminated (class II)	7.7–10.8	Minor breaks in sterile technique; entry of GU, GI, or respiratory tract without significant spillage
Contaminated (class III)	15.2–16.3	Traumatic wounds; gross spillage from GI tract; entry into infected tissue, bone, urine, or bile
Dirty (class IV)	28.0–40.0	Drainage of abscess; debridement of soft tissue infection

sure) is less than or equal to 30 mm Hg, compartment syndrome is considered to be present. If clinical symptoms develop or the delta pressure is below 30 mm Hg, appropriate therapeutic measures should be taken, including restoration of normal blood pressure in the hypotensive patient, removal of all constrictive dressings, and maintenance of the limb at heart level.¹ If the delta pressure remains below 30 mm Hg, clinical symptoms and signs persist despite conservative measures, or both, fasciotomies should be performed within 6 hours.⁴¹ Hyperbaric oxygen therapy may also be beneficial in cases of crush injury with compartment syndrome in an extremity.⁴³ Compartment syndrome with muscle damage can also lead to rhabdomyolysis and renal failure. If an elevated serum creatine kinase concentration is reported, intravascular volume is stabilized, and urine flow is confirmed, a forced mannitol-alkaline diuresis should be initiated as prophylaxis against hyperkalemia and acute renal failure.⁴⁴

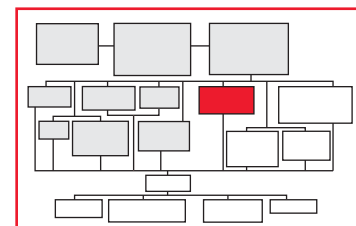
Extravasation Injuries

In some patients with arterial or venous catheters in place, a vessel may become occluded or a catheter dislodged from the intravascular space, leading to extravasation injury, whereby solutions or medicines are delivered into the interstitial space. The majority of acute extravasation injuries are quickly diagnosed and heal without complications, and in most cases, conservative management (i.e., elevation of the limb, application of ice packs, and careful monitoring) is adequate.⁴⁵ However, extravasation injuries involving high fluid volumes, high-osmolar contrast agents, or chemotherapeutic drugs can have more serious effects, resulting in skin ulceration and extensive soft tissue necrosis. Treatment of these injuries is not standardized; it may include conservative management, hydrocortisone cream, incision and drainage, hyaluronidase injection, saline injection, and aspiration by means of liposuction.^{45–47}



Injection Injuries

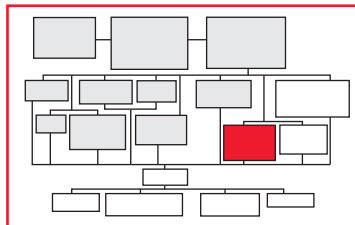
Wounds caused by injection of foreign materials (e.g., paint, oil, grease, or dirty water) can be severe. Injection injuries usually result from the use of high-pressure spray guns (600 to 12,000 psi) and



often occur on the nondominant hand.^{48,49} On initial examination, the injury may appear deceptively benign, with only a punctate entry wound visible; however, foreign material is often widely distributed in the deeper soft tissues. Radiographs are obtained to identify any fractures present and, in some cases, to determine the extent to which the injected material is distributed. Injection wounds must be treated aggressively with incision, wide exposure, debridement, and removal of foreign bodies to prevent extensive tissue loss and functional impairment. The functional outcome is determined by the time elapsed between injury and treatment and by the type of material injected. Oil-based paint is more damaging to tissues than water-based paint, oil, grease, water, or air.^{50,51}

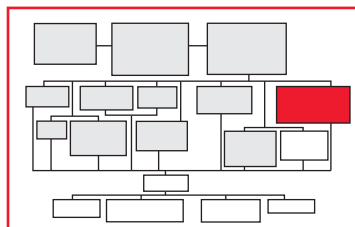
High-Velocity Wounds

High-velocity wounds from explosions or gunshots cause extensive tissue damage as a consequence of the release of kinetic energy. Small entry wounds are common, but the seemingly benign appearance of such a wound often belies the actual severity of injury: the exit wound and interspace may contain large areas of ischemic and damaged tissue that affect critical structures (e.g., bone and blood vessels). Clothing and dirt may also be transmitted into the deep spaces. Radiographs may identify radiopaque foreign bodies (e.g., metal objects or pieces of leaded glass).⁵² Treatment of wounds created by high-velocity missiles involves extensive debridement and identification of injured tissue. Wounds should be left open to heal by secondary or delayed primary closure.³²



Bite Wounds

Treatment of bite wounds involves thorough exploration, irrigation, and debridement. X-rays must be obtained and wounds explored to evaluate the patient for fractures or open joint injuries. If a joint capsule has been violated, the joint must be thoroughly cleaned. Because of the infection risk, wounds may be allowed to heal by secondary or delayed primary closure; primary closure is also possible if thorough debridement is performed.³² Rabies prophylaxis treatment should be considered for patients who have been bitten by wild animals [see Adjunctive Wound Treatment, Rabies Prophylaxis, below].



Humans and nonvenomous animals Most human bite wounds are clenched fist wounds sustained by young men.⁵³ Human bite wounds are considered infected from the moment of infliction and must be treated with antibiotics.^{54,55} The antibiotic regimen should be selected on the basis of the bacterial species believed to be present. Common isolates from bite wounds includes *Streptococcus anginosus*, *Staphylococcus aureus*, *Eikenella corrodens*, *Fusobacterium nucleatum*, *Prevotella melaninogenica*, and *Candida* species.⁵³ To cover these species, a broad-spectrum antibiotic or combination of antibiotics (e.g., amoxicillin-clavulanate or moxifloxacin) should be administered.⁵³

Nonhuman primates can cause viral infection, most commonly with cercopithecine herpesvirus type 1. If left untreated, such infection can lead to meningoencephalitis, which carries a 70% mortality. Accordingly, acyclovir prophylaxis is recommended.⁵⁶

Wounds caused by cat bites or scratches are at high (80%) risk for infection, usually attributable to *Pasteurella multocida*. The aer-

obic and anaerobic organisms commonly found in cat-bite wounds are similar to those found in dog-bite wounds, and antibiotic prophylaxis with amoxicillin-clavulanate is appropriate.⁵⁷ Acute regional lymphadenitis after a cat scratch is known as cat-scratch disease and is caused by *Bartonella henselae*⁵⁸; it is treated by administering azithromycin.⁵⁹

Dog-bite wounds are at lower (16%) risk for infection than human-bite or cat-bite wounds and tend to be less severely contaminated with bacteria. The aerobic species commonly isolated from such wounds include *Pasteurella* (*P. canis*), *Streptococcus*, *Staphylococcus*, *Moraxella*, and *Neisseria*; common anaerobic isolates include *Fusobacterium*, *Bacteroides*, *Porphyromonas*, and *Prevotella*.⁵⁷ Prophylactic treatment with a combination of a β -lactam antibiotic with a β -lactamase inhibitor (e.g., amoxicillin-clavulanate) is appropriate.^{57,60}

Venomous animals *Snake bites.* Four types of poisonous snakes are native to the United States: the coral snakes (*Micrurus* and *Micruroides* species), from the family Elapidae, and three species of pit vipers, from the family Viperidae (rattlesnakes [*Crotalus* species], copperheads [*Agkistrodon tortorix*], and cottonmouths or water moccasins [*Agkistrodon piscivorus*]).⁶¹⁻⁶³ Pit vipers can be identified by the pit between the eye and the nostril on each side of the head, the vertical elliptical pupils, the triangle-shaped head, the single row of subcaudal plates distal to the anal plate, and the two hollow fangs protruding from the maxillae that produce the characteristic fang marks.⁶⁴ Coral snakes have rounder heads and eyes and lack fangs; they are identified by their characteristic color pattern, consisting of red, yellow, and black vertical bands.

Patients bitten by any of the pit vipers must be examined for massive swelling and pain, which, in conjunction with fang marks, suggest envenomation. Local pain and swelling typically develops within 30 minutes of the bite, though in some cases, these manifestations may take up to 4 hours to appear. Erythema, petechiae, bullae, and vesicles are sometimes seen. Severe envenomation may induce systemic reactions, including disseminated intravascular coagulation (DIC), bleeding, hypotension, shock, acute respiratory distress syndrome (ARDS), and renal failure. Patients bitten by coral snakes, on the other hand, show no obvious local signs when envenomation has occurred. Consequently, the physician must look for systemic signs, such as paresthesias, increased salivation, fasciculations of the tongue, dysphagia, difficulty in speaking, visual disturbances, respiratory distress, convulsions, and shock. These symptoms may not develop until several hours after the bite.

If signs or symptoms suggestive of envenomation are found, appropriate laboratory tests (hematocrit, fibrinogen level, coagulation studies, platelet count, urinalysis, and serum chemistries) should be ordered. Laboratory tests should be repeated every 8 to 24 hours for the first 1 to 3 days to determine whether envenomation is progressing. Severe envenomation can cause decreased fibrinogen levels, coagulopathy, bleeding, and myoglobinuria.

Treatment of venomous snake bites includes immobilization and elevation. If envenomation is suspected or confirmed, antivenin should be administered intravenously and as early as possible. Antivenins commonly used in the United States include Antivenin (Crotalidae) Polyvalent (ACP) (Wyeth Pharmaceuticals, Collegeville, Pennsylvania) and Crotalidae Polyvalent Immune Fab (Ovine) (CroFab; Protherics Inc., Nashville, Tennessee).⁶⁵ Fab antivenom (FabAV) is less allergenic and more potent than ACP and thus has largely supplanted it in the United States.^{65,66} Patients are treated with a loading dose of four to six vials of FabAV, followed by three two-vial maintenance doses at 6, 12, and 18 hours to prevent recurrence of symptoms. If symptoms

progress despite antivenin treatment, an additional four to six vials of FabAV are given twice more; if symptoms continue to progress, consideration should be given to using ACP. ACP remains the most effective antivenin for patients with coral snake bites and those who do not respond to FabAV. Before ACP is administered, the patient must be tested for sensitivity. The major complication of antivenin therapy is serum sickness. This complication occurs in approximately 50% to 75% of patients treated with ACP but in only 16% of those treated with FabAV.^{65,67}

Compartment syndrome is a rare but severe complication of a snake bite. Fasciotomy is sometimes required to relieve extremity compartment syndrome, but it is not necessary for prophylactic purposes. Tourniquets, incision and suction, cryotherapy, and electric shock treatment are of little value for snake bites and may increase complication rates. There is no clear evidence to support antibiotic prophylaxis in this setting.⁶⁴

Spider bites. The bites of most spiders found in the United States cause little to no wound or local reaction; however, there are three types that are capable of injecting venom with skin-penetrating bites. Brown recluse spiders (*Loxosceles reclusa*) can be identified by a violin-shaped dorsal mark. They are nocturnal, live in dark and dry places, and are found in the central and southern United States. The venom is a phospholipase enzyme that acts as a dermal toxin and almost always causes a local reaction.⁶⁸ Local signs and symptoms may be limited to minor irritation, though they may also progress to extreme tenderness, erythema, and edema. The onset of local signs and symptoms may be delayed for as long as 8 hours after a bite, and tissue necrosis may then develop over the following days to weeks. Systemic reactions may include mild hemolysis, mild coagulopathy, and DIC, though severe intravascular hemolytic syndrome and death have also been reported.^{68,69} Oral administration of dapsone (50 to 100 mg/day) to minimize tissue necrosis has been advocated by some⁷⁰; however, this treatment is of uncertain efficacy, and no prospective data currently support its use. Moreover, dapsone can cause a serious unwanted side effect, hemolytic anemia.⁶⁹ If systemic symptoms develop, systemic corticosteroid therapy and supportive measures are indicated. Brown recluse antivenin is not available in the United States.

Black widow spiders (*Latrodectus mactans*) can be identified by a red-hourglass ventral mark.⁶³ They live in dark, dry, and protected areas and are distributed widely throughout the continental United States. The venom is a neurotoxin that produces immediate and severe local pain. Local signs and symptoms include two fang marks, erythema, swelling, and piloerection.⁶⁸ Systemic reactions with neurologic signs may develop within 10 minutes and may include muscle pain and cramps starting in the vicinity of the bite, abdominal pain, vomiting, tremors, increased salivation, paresthesias, hyperreflexia, and, with severe envenomation, shock. Systemic symptoms may last for days to weeks. High-risk persons (e.g., those who are younger than 16 years, the elderly, pregnant women, hypertensive patients, or persons who continue to show symptoms despite treatment) may experience paralysis, hemolysis, renal failure, or coma. Treatment includes 10% calcium gluconate I.V. for relief of muscle spasm, methocarbamol or diazepam for muscle relaxation, and a single dose of antivenin. Antivenin causes serum sickness in as many as 9% of patients; consequently, its use is controversial except in cases where the patient is at high risk.⁷¹

Hobo spiders (*Tegenaria agrestis*) can be identified by their long hairy legs and a cephalothorax that is marked by two stripes and butterfly markings dorsally and two stripes ventrally. Found

throughout the northwestern United States, they live in low places and build funnel-shaped webs in dark spaces. Hobo spiders have been reported to inflict painful bites that lead to wound ulceration, dermonecrosis, and a persistent headache, though the accuracy of such reports has been debated.^{69,72,73} A slow-healing ulcer that leaves a central crater has been described. Treatment consists of local wound care.

Stings

Scorpions Stings from most of scorpion species found in the United States cause only limited local reactions that can be managed conservatively; however, stings from *Centruroides sculpturatus*, which is found in California and many southern states, may be more severe. *Centruroides* has a sting that causes envenomation with a neurotoxin. Erythema, edema, and ecchymosis at the site of the sting are evidence that envenomation did not take place. Instead, envenomation is indicated by an immediate and intense burning pain at the wound site.⁷⁴ The initial local pain may then be followed by systemic symptoms such as muscle spasm, excess salivation, fever, tachycardia, slurred speech, blurry vision, convulsions, or death.⁶⁸ Treatment consists of icing and elevation of the wounded area, followed by administration of barbiturates for control of neuromuscular activity and institution of supportive therapy with antihistamines, corticosteroids, and analgesics.⁷⁴



Centipedes Centipedes are slender, multisegmented, and multilegged arthropods that range in size from 1 to 30 cm and in color from bright yellow to brownish black. The first pair of legs are modified into sharp stinging structures that are connected to venom glands. Centipedes prefer dark, damp environments and may be found throughout the southern United States. Local symptoms associated with centipede stings include pain, erythema, edema, lymphangitis, lymphadenitis, weakness, and paresthesia. Skin necrosis may occur at the envenomation site. Systemic symptoms may include anxiety, fever, dizziness, palpitations, and nausea.⁷⁵ Treatment consists of symptomatic pain control, infiltration of local anesthetics, administration of antihistamines, and local wound care.⁷⁵

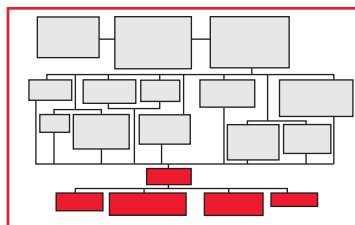
Hymenoptera The order Hymenoptera includes wasps, bees, and ants. Wasps, which are found across the United States, live in small colonies and may attack in groups when provoked. Honeybees (*Apis mellifera*) and bumblebees (*Bombus* species), also found across the United States, are generally docile and rarely sting unless provoked. Africanized honeybees (*Apis mellifera scutellata*, also referred to as killer bees), found primarily in the southwestern states, are far more aggressive than other bees. Fire ants (*Solenopsis invicta* and *Solenopsis richteri*) are wingless, ground-dwelling arthropods that are found in many southern states and that attack in an aggressive swarm.

Although Hymenoptera stingers are small, they can evoke severe local and systemic reactions. The local response to a Hymenoptera sting is a painful, erythematous, and edematous papule that develops within seconds and typically subsides in 4 to 6 hours. Some stingers are barbed and must be removed with a scraping, rather than pinching, motion to prevent the injection of more venom. Systemic reactions occur in about 5% of the population and may lead to anaphylaxis with syncope, bronchospasm, hypo-

tension, and arrhythmias. Wounds and local reactions are treated with ice, elevation, and analgesics. Systemic reactions are treated with subcutaneous epinephrine, diphenhydramine, and supportive airway and blood pressure care.⁶⁸ Persons with a history of systemic reactions to insect stings should carry epinephrine kits.

DRESSINGS FOR SPECIFIC TYPES OF WOUNDS

Generally, the functions of a wound dressing include protection, antiseptics, pressure, immobilization, debridement, provision of a physiologic environment, absorption, packing, support, information, comfort, and aesthetic appearance. More specifically, the functions of a dressing should be tailored to the wound type, and the purpose of the dressing must be carefully considered before application.



With sutured wounds, dressings are required only until drainage from the wound ceases. With nondraining wounds, dressings may be removed after 48 hours, by which time epithelial cells will have sealed the superficial layers of the wound. An alternative method of treating minimally draining incisional wounds is to apply an antibacterial ointment [see Adjunctive Wound Treatment, Topical Antimicrobials, *below*]. Such ointments are occlusive and maintain a sterile, moist environment for the 48 hours required for epithelialization. In anatomic areas that are difficult to dress (e.g., the scalp), it may be reasonable to forgo a dressing and simply apply ointments or allow a scab to form on the wound surface. Operative incisional wounds are also sometimes covered with an occlusive dressing to optimize epithelialization [see Abrasions, *above*]. Some of these dressings are transparent, allowing observation of the wound. The disadvantage of occlusive dressings is their limited absorptive capacity, which allows drainage from the wound to collect underneath.

Complex Wounds

Abrasions
Abrasions heal by epithelialization, which is accelerated by the warm, moist environment created by an occlusive dressing.^{76,77} Such an environment not only promotes epithelialization but also enhances healing, both because of the moisture itself and because of the low oxygen tension that promotes the inflammatory phase.⁷⁸ A variety of dressings are suitable for treatment of abrasions, including biologic dressings, hydrogels, hydrocolloids, and semipermeable films. These dressings need not be changed as long as they remain adherent. Small, superficial wounds also heal readily when dressed with impregnated gauze dressings (e.g., Xeroform and Scarlet Red [Kendall, Mansfield, Massachusetts]), which allow exudates to pass through while maintaining a moist wound bed.⁷⁸ These less adherent dressings must be changed more regularly.⁷⁹

Dry dressings (e.g., gauze) should be avoided with abrasions because they facilitate scab formation. Scabs slow epithelialization, in that advancing cells must enzymatically debride the scab-wound interface in order to migrate.⁸⁰ Wounds covered with a scab also tend to cause more discomfort than wounds covered with occlusive dressings.

For complex wounds containing questionably necrotic tissue, foreign bodies, or other debris that cannot be removed sharply, wet-to-dry dressings are effective, simple, and inexpensive. A single layer of coarse wet gauze is applied to a wound, allowed to dry over a period of 6 hours, and removed. Necrotic tissue, granulation tissue, debris, and wound exudate become incorporated within the gauze and are removed with the dressing. The disadvantages of wet-to-dry dressings are pain and damage to or removal of some viable tissue. If the wound bed contains tendons, arteries, nerves, or bone, wet-to-wet dressings should be used to prevent desiccation of these critical structures.

Wet-to-wet dressings, which are not allowed to dry, cause less tissue damage than wet-to-dry dressings but do not produce as much debridement. Most wet-to-wet dressings are kept moist with saline. Wounds with significant bacterial contamination may be treated with dressings that contain antibacterial agents (e.g., mafenide, silver sulfadiazine, silver nitrate, or iodine).

Biologic and semipermeable films also maintain a moist wound bed, but they are difficult to use on deep or irregular wounds and wounds with a great deal of drainage. Consequently, wet-to-wet dressings with agents such as silver sulfadiazine are often used for these types of wounds. Enzymatic agents can debride wounds effectively and are a reasonable alternative to wet-to-dry or wet-to-wet dressings for wounds that contain necrotic tissue.⁸²

Lacerations

For sutured deep wounds, the specific purposes of a dressing are to prevent bacterial contamination, to protect the wound, to manage drainage, and to facilitate epithelialization. Dressings used on such wounds usually consist of three basic layers. The inner (contact) layer is chosen to minimize adherence of the dressing to the wound and to facilitate drainage through itself to the overlying layers. Common choices for this layer include fine-mesh gauze, petrolatum gauze, Xeroform or Xeroflo (Kendall, Mansfield, Massachusetts) gauze, and Adaptic (Johnson & Johnson, New Brunswick, New Jersey). These substances should be applied only as a single layer; in multiple layers, they become occlusive. The middle layer is chosen for absorbency and ability to conform to shape of the wound area. It is usually composed of fluffs, Kerlix (Kendall, Mansfield, Massachusetts), or wide-mesh gauze, all of which facilitate capillary action and drainage.⁸¹ The middle layer must not be allowed to become soaked, because if it is, exudate will collect on the wound surface, and maceration and bacterial contamination may occur. The outer (binding) layer serves to secure the dressing. Common choices for this layer include Kling (Johnson & Johnson, New Brunswick, New Jersey), ACE bandages (BD Medical, Franklin Lakes, New Jersey), and Coban (3M, St. Paul, Minnesota).

Table 4 Recommendations for Tetanus Immunization^{89,90}

Tetanus Immunization History	Tt*	TIG
Unknown	Yes	Yes
> 10 yr since last booster	Yes	Yes
≥ 5 and ≤ 10 yr since last booster	Yes	No
< 5 yr since last booster	No	No

Note: Tetanus toxoid (Tt) and tetanus immune globulin (TIG) should be administered with separate syringes at different anatomic sites. Tetanus and diphtheria toxoids are contraindicated for the wounded patient if there is a history of a neurologic or severe hypersensitivity reaction after a previous dose. Local side effects alone do not preclude continued use. If a systemic reaction is suspected of representing allergic hypersensitivity, immunization should be postponed until appropriate skin testing is performed. If a contraindication to a Tt-containing preparation exists, TIG alone should be used.

*For patients younger than 7 years, diphtheria-tetanus-pertussis vaccine (DTP) (or tetanus and diphtheria toxoids, if pertussis vaccine is contraindicated) is preferable to Tt alone. For patients 7 years of age or older, Tt alone may be given.

Some wounds are difficult to dress and require special consideration. For wounds with flaps or questionably viable tissue, compression dressings should not be used, because they may cause ischemia. Wounds that cross joints are best dressed with plaster splints for temporary immobilization; semipermeable films are flexible and may also be used in this setting. Wounds with high levels of exudates may be dressed with hydrocolloids, hydrogels, or alginates.⁷⁸ For large or irregular wounds, negative-pressure wound therapy (NPWT) with the VAC system (Kinetic Concepts Inc., San Antonio, Texas) is recommended; VAC dressings conform well and remain adherent. Additionally, NPWT uses subatmospheric pressure to remove excess wound fluid, stimulates the formation of granulation tissue, improves peripheral blood flow and tissue oxygenation, and reduces the size of the wound.^{83,84} Use of the VAC system is contraindicated in wounds with exposed blood vessels or bowel.

Adjunctive Wound Treatment

PROPHYLACTIC SYSTEMIC ANTIBIOTICS

For most wounds, antibiotic prophylaxis is not indicated. When it is called for, the agent or agents to be used should be selected on the basis of the bacterial species believed to be present. The anatomic location of a wound may also suggest whether oral flora, fecal flora, or some less aggressive bacterial contaminant is likely to be present. Gram staining can provide an early clue to the nature of the contamination. Ultimately, the choice of a prophylactic antibiotic regimen is based on the clinician's best judgment regarding which agent or combination of agents will cover the pathogens likely to be present in the wound on the basis of the information available.

As a rule, clean and clean-contaminated wounds are adequately treated with irrigation and debridement. There are, however, some local factors (e.g., impaired circulation and radiation injury) and systemic factors (e.g., diabetes, AIDS, uremia, and cancer) that increase the risk of wound infection; in the presence of any of these factors, prophylactic antibiotics should be considered. In addition, prophylactic antibiotics should be given to patients with extensive injuries to the central area of the face (to prevent spread of infection through the venous system to the meninges), patients with valvular disease (to prevent endocarditis), and patients with prostheses (to reduce the risk of bacterial seeding of the prosthesis). Lymphedematous extremities are especially prone to cellulitis, and antibiotics are indicated whenever such extremities are wounded.

Contaminated and dirty wounds are associated with a higher risk of infection and are therefore more likely to necessitate antibiotic prophylaxis. Human bite wounds, mammalian bite wounds, and wounds contaminated with dirt, bodily fluids, or feces are all prone to infection and must be treated with antibiotics.^{54,55} Prophylactic administration of a combination of a β -lactam antibiotic with a β -lactamase inhibitor (e.g., amoxicillin-clavulanate) is appropriate.^{57,60} Antibiotic prophylaxis is also indicated for mutilating wounds with extensive amounts of devitalized tissue. Such wounds are often contaminated by a mixture of gram-positive organisms and gram-negative organisms.⁴⁰ When antibiotics are indicated for these injuries, broad-spectrum coverage is appropriate.

TOPICAL ANTIMICROBIALS

Topical antimicrobials (e.g., antibiotic ointments, iodine preparations, and silver agents) are commonly used to prevent wound infection. Application of mupirocin ointment to a clean surgical

wound before an occlusive dressing does not reduce the infection rate and may promote antibiotic resistance.⁸⁵ For uncomplicated traumatic wounds, however, application of bacitracin and neomycin ointment results in a significantly lower infection rate than application of petrolatum.⁸⁶ Neomycin-containing ointments reduce bacterial counts in partial-thickness wounds in animals, but many other over-the-counter antibiotic ointments are not effective at reducing bacterial counts in wounds.⁸⁷

Wounds contaminated by bacteria can be treated with dressings that contain antibacterial agents such as mafenide, silver nitrate, silver sulfadiazine, or iodine. Mafenide penetrates eschar well, but it can cause pain and has the potential to induce metabolic acidosis through inhibition of carbonic anhydrase. Silver has microbicidal effects on common wound contaminants and may also be effective against methicillin-resistant *S. aureus* (MRSA).⁸⁴ Silver nitrate does not cause pain, but it can cause hypochloremia, and it stains fingernails and toenails black. Silver sulfadiazine is frequently used because of its broad antibacterial spectrum, its relatively low side effect profile (transient leukopenia is occasionally seen), and its ability to maintain a moist wound environment (thereby speeding healing and epithelialization).⁸⁸

TETANUS PROPHYLAXIS

Tetanus is a nervous system disorder that is caused by *Clostridium tetani* and is characterized by muscle spasm. In the past, wounds were classified as either tetanus-prone or non-tetanus-prone on the basis of their severity. It is now clear, however, that wound severity is not directly correlated with tetanus susceptibility; tetanus has been associated with a wide variety of injury types over a broad spectrum of wound severity.⁸⁹ Accordingly, all wounds, regardless of cause or severity, must be considered tetanus prone, and the patient's tetanus immunization status must always be considered. Tetanus wound prophylaxis should be provided as appropriate [see Table 4].^{89,90}

RABIES PROPHYLAXIS

Rabies is an acute progressive encephalitis that is caused by viruses from the family Rhabdoviridae. The rabies virus can be transmitted by any mammal, but viral reservoirs are found only in carnivores and bats. In North America, raccoons, skunks, bats, and foxes are the animals most commonly responsible for transmission.⁹¹ Bite wounds in which the animal's saliva penetrates the dermis are the most common cause of exposure.

Postexposure treatment consists of wound care, infiltration of rabies immune globulin into the wound, and administration of vaccine.^{91,92} Wound care involves washing with soap and water, as well as the use of iodine- or alcohol-based virucidal agents.⁹³ Guidelines for postexposure prophylaxis have been established [see Table 5]. The vaccination regimen is determined by the patient's previous vaccination status [see Table 6].

Postoperative Wound Care

Closed wounds should be kept clean and dry for 24 to 48 hours after repair. Epithelialization begins within hours after wound approximation and forms a barrier to contamination. Gentle cleansing with running water will help remove bacteria and crusting. The patients should not place tension on the wound or engage in strenuous activity until the wound has regained sufficient tensile strength. In the first 6 weeks after repair, the wound's tensile strength increases rapidly; after this period, tensile strength increases more slowly, eventually reaching a maximum of 75% to 80% of normal skin strength [see Figure 2].

Table 5 Recommendations for Postexposure Rabies Prophylaxis⁹¹⁻⁹³

Animal Type	Animal Disposition and Evaluation	Prophylaxis
Dogs, cats, ferrets	If animal is healthy and available, it is confined for 10 days of observation	Start vaccination if animal exhibits rabies symptoms*
	If animal is rabid or suspected of being rabid, no observation is indicated	Provide immediate vaccination
	If animal's rabies status is unknown, consultation is indicated	Consult public health official
Bats, skunks, raccoons, foxes, bobcats, coyotes, mongooses, and most carnivores	Animal is regarded as rabid unless brain laboratory tests are negative	Provide immediate vaccination unless brain laboratory tests are negative
Livestock, small rodents (e.g., squirrels, chipmunks, rats, hamsters, gerbils, guinea pigs, and mice), large rodents (e.g., woodchucks and beavers), rabbits, hares, and other mammals	Each case is considered individually; rabies reported in large rodents in some areas	Consult public health officials; almost never require antirabies treatment

*If the isolated animal shows symptoms of rabies, postexposure prophylaxis is started immediately, and the animal is euthanized for laboratory testing. Vaccination prophylaxis is stopped if laboratory tests are negative for rabies.

Wounds at risk for infection should be assessed by a medical provider within 48 hours of care. In addition, the patient should be taught to look for signs of infection (e.g., erythema, edema, pain, purulent drainage, and fever).

The timing of suture or staple removal is determined by balancing the requirements for optimal cosmesis against the need for wound support. On one hand, it is clear that for optimal cosmesis, sutures should be removed early, before inflammation and epithelialization of suture tracts. An epithelialized tract will develop around a suture or staple that remains in the skin for longer than 7 to 10 days; once the suture or staple is removed, the tract will be replaced by scar.⁹⁴ On the other hand, it takes a number of weeks for the wound to gain significant tensile strength, and early removal of wound support can lead to dehiscence of wounds that are under substantial tension. Early suture removal is warranted for some wounds. For example, sutures in aesthetically sensitive areas (e.g., the face) may be removed on day 4 or 5, and sutures in areas under minimal tension (e.g., in wounds parallel to skin tension lines) may be removed on day 7. Sutures in wounds subject to greater stress (e.g., wounds in the lower extremities or the

trunk) should remain in place longer, as should sutures in wounds sustained by patients who have a condition that hinders healing (e.g., malnutrition). In such cases, suture-mark scars are considered acceptable. The appropriate method of removing a suture is first to cut it, then to pull on the knot parallel to or toward, rather than away from, the wound.

After suture removal, numerous methods are employed to minimize unsightly scar formation. The cosmetic outcome of a scar is largely determined by the nature and severity of the wound, which are outside the surgeon's control. The greatest impact a surgeon can have on cosmetic outcome is derived from providing meticulous care when the acute wound is initially encountered. Postoperative wound care measures employed to optimize cosmetic outcome include massage, the use of silicone bandages or pressure garments, and the application of lotions. These interventions appear to help, but prospective trials are needed to confirm their efficacy and establish treatment guidelines. The healing wound is fragile, and topical application of ointments to achieve an improved scar appearance may actually achieve the opposite result. For example, vitamin E, which is commonly applied to healing wounds, can induce contact dermatitis and cause scars to look worse.⁹⁵

Table 6 Recommendations for Postexposure Rabies Vaccination⁹¹⁻⁹³

Vaccine	Dosage	
	No Previous Vaccination	Previous Vaccination
Human rabies immune globulin (HRIG)	Full dose of 20 IU/kg infiltrated around wound(s) at initial presentation; use separate syringe and anatomic site from vaccine	Not administered
Human diploid cell vaccine (HDCV), rabies vaccine adsorbed (RVA), or purified chick embryo cell vaccine (PCECV)	1.0 ml IM on days 0, 3, 7, 14, and 28*	1.0 ml IM on days 0 and 3*

*Vaccine administration site for adults is the deltoid; for children, the anterolateral thigh may be used. To prevent sciatic nerve injury and reduce adipose depot delivery, the gluteus is never used.

Factors That May Hinder Wound Healing

Despite a surgeon's best efforts, healing does not always occur in an undisturbed fashion: sometimes, a closed wound dehisces. If the dehiscence is sudden, the wound is clean, and only skin and superficial tissues are involved, then the wound should be reclosed, and the cause of the dehiscence should be corrected if possible. If the dehiscence is slow and the wound is contaminated or infected, then the wound should be allowed to heal secondarily, with dressing changes and scar revision to be performed at a later date.

There are a number of local and systemic factors [see Table 7] that can interfere with wound healing (see below). Accordingly, it is essential for clinicians to be aware of and knowledgeable about these factors and, whenever possible, to take appropriate measures to improve the chances for optimal healing. The use of nutrients and growth factors to stimulate wound healing may be considered; this measure is currently the subject of extensive research.

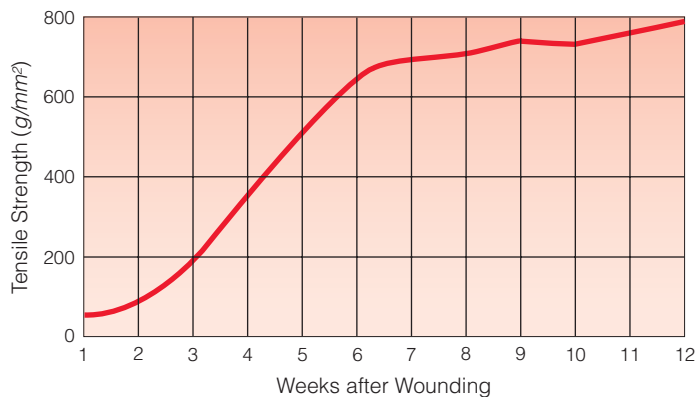


Figure 2 The tensile strength of skin wounds increases rapidly for approximately 6 weeks after wounding; it then continues to increase slowly for 6 to 12 months after wounding, though it never reaches the tensile strength of unwounded tissue. Collagen is remodeled and replaced with highly cross-linked collagen along tissue stress lines. The process of collagen replacement and scar remodeling continues for years.

LOCAL FACTORS

Tension

Tension—whether from inherent skin tension, poor surgical technique, movement of joints, or inadequate wound support—may lead to separation of wound edges. It should be minimized by undermining the wound edges during closure to allow easy coaptation. Tissue ellipses from complex wound edges should be kept as narrow as possible and should be created along relaxed skin tension lines. Adequate support of the wound after suture removal is critical; many surgeons keep tapes (e.g., Steri-Strips) over a wound for 3 weeks, until the strength of the wound equals that of the deep sutures and tapes. Wounds over joints should be splinted to reduce tension.

Foreign Body

All foreign bodies that contaminate a wound should be removed at the time of initial debridement and before wound closure. Retained foreign bodies may cause failed healing, infection, or traumatic tattooing. Iatrogenic foreign bodies may also interfere with wound healing and promote infection. Suture material is a foreign body; thus, the number and size of sutures placed in a wound should be kept to the minimum necessary for coaptation of the wound edges.

Infection

All traumatic wounds are contaminated and should therefore be irrigated to remove organisms. Infection occurs when bacteria are too numerous ($>10^5$ organisms/g tissue) or virulent for local tissue defenses to be able to control them.⁹⁶ As noted [see Adjunctive Wound Care, Prophylactic Antibiotics, *above*], local factors (e.g., impaired circulation and radiation injury) increase the risk of infection, as do various systemic diseases (e.g., diabetes, AIDS, uremia, and cancer). Wound cultures should be obtained, and broad-spectrum antibiotic therapy should be started when infection is diagnosed. The antibiotic regimen is adjusted on the basis of culture results and sensitivities.

Ischemia

Ischemic wound tissue readily becomes infected and therefore must be debrided. Tissue with dermal edges that do not bleed or

that show no perfusion on fluorescein testing is ischemic. Questionably viable tissue should be monitored closely and debrided when declared nonviable.

Hematoma and Seroma

Hematomas and seromas increase the risk of infection and the likelihood of wound dehiscence. To prevent their formation, hemostasis at the time of wound closure must be meticulous, and bleeding diatheses must be corrected. Because the rubbing of wound edges against one another is associated with the formation of hematomas and seromas, wound edge movement should be minimized and immobilization employed as necessary. Wounds at significant risk for hematoma or seroma formation should be closed over a drain.

Large hematomas or seromas that are recognized early, before infection develops, should be evacuated, and the wound should be reclosed. Small hematomas or seromas can usually be treated conservatively until they are reabsorbed, but close observation is required. If a hematoma or seroma is not recognized until late, when infection has already set in, the wound should be opened, drained, and allowed to heal secondarily; scar revision may be carried out at a later point.

Trauma

Tissue injury is obviously associated with external trauma, but it can also be iatrogenic. Rough handling of tissue edges with forceps produces minute crush injuries, which promote wound infection. It is preferable to handle wound edges with hooks, using gentle surgical technique.

Edema

Edema results from the accumulation of fluid in the interstitial space. It may occur as an acute process, in which tissue injury leads to histamine release, leaky capillaries, and inflammation, or as a chronic process, in which venous insufficiency, lymphatic insufficiency, and a low plasma oncotic pressure may cause fluid to collect in the interstitium. In both cases, edema raises tissue pressure and inhibits perfusion and healing. The proteinaceous and fibrin-rich fluid also forms clot and fibrous tissue, which hinder the supply of oxygen and inflammatory cells.⁹⁷ Clearance of wound edema is necessary for healing and may be successfully accomplished by means of compression therapy⁹⁸ or NPWT with a VAC device.⁸³

Table 7 Local and Systemic Factors That Impair Wound Healing

Local Factors	Systemic Factors
Tension	Inherited connective tissue disorders
Foreign body	Hypothermia
Infection	Oxygen
Ischemia	Tobacco smoking
Hematoma and seroma	Malnutrition
Edema	Jaundice
Irradiation	Age
	Diabetes mellitus
	Uremia
	Steroids
	Chemotherapeutic agents
	Other drugs

Irradiation

Irradiation damages the skin and can cause wounds to heal slowly. It also induces chronic skin changes: previously irradiated tissues demonstrate delayed healing when wounded.⁹⁹ Irradiated tissue is characterized by a thickened and fibrotic dermis, a thin epidermis, pigment changes, telangiectasia, decreased hair, and increased dryness (as a consequence of damage to sebaceous and sweat glands). The microvasculature of the skin is obliterated, leading to tissue ischemia and impaired healing. Keratinocytes, which are necessary for wound epithelialization, exhibit impaired mitotic ability and slow progressive desquamation (as a consequence of their superficial location and high replication rate).⁹⁷ Collagen bundles become edematous and fibrotic. Fibroblasts, which are necessary for collagen synthesis, also show diminished migration and proliferation.¹⁰⁰

Because irradiated skin is irreversibly damaged, tissue transfer may be required for repair of wounds in areas subjected to radiation. Vitamin A supplementation can lessen the adverse effects of irradiation on wound healing.¹⁰¹

SYSTEMIC FACTORS

Inherited Connective Tissue Disorders

Several inherited connective tissue disorders are known to interfere with normal wound healing. Ehlers-Danlos syndrome exists as multiple types that exhibit certain differences, but in general, the syndrome leads to deficient collagen cross-linking, which results in lax and fragile skin, lax joints, and impaired wound healing. For example, an Ehlers-Danlos patient who undergoes an elective hernia repair or facelift may have a poor outcome as a consequence of deficient collagen formation and poor wound healing.^{102,103} Osteogenesis imperfecta is a procollagen formation disorder that is clinically manifested by brittle bones, increased laxity of ligaments and skin, bone deformities, and impaired wound healing.¹⁰⁴ Marfan syndrome is an autosomal dominant disorder characterized by deficient synthesis of fibrillin, which is a key component in elastin formation. Patients with this syndrome have long extremities and hyperextendable joints; those who are seriously affected have lax ligaments, dissecting aneurysms, dislocated eye lenses, pectus excavatum, and scoliosis. Surgical repair of aneurysms and hernias is usually successful in this population, though healing difficulties may be encountered.¹⁰³ Cutis laxa is a disease in which an elastase inhibitor deficiency gives rise to defective elastic tissue. Patients with this disease have thick, coarse, and drooping skin, along with hernias, aneurysms, heart disease, and emphysema. Unlike patients with the other heritable diseases mentioned, cutis laxa patients often show no impairment of wound healing.¹⁰⁵

Hypothermia

Hypothermia may develop as a consequence of administration of anesthetic drugs, exposure to cold, or redistribution of body heat; it leads to peripheral vasoconstriction and impaired wound oxygen delivery.¹⁰⁶ Wound tensile strength increases more slowly when healing occurs in a cold environment. Prevention or correction of hypothermia reduces the wound infection rate and increases collagen deposition in patients undergoing abdominal surgery.¹⁰⁷ Preoperative systemic and local warming also reduces the wound infection rate in patients undergoing elective operations.¹⁰⁸ A warm body temperature must be maintained in all wounded patients to reduce subcutaneous vasoconstriction and maximize wound healing potential.

Oxygen

Tissue oxygenation is necessary for aerobic metabolism, fibroblast proliferation, collagen synthesis, and the antimicrobial oxidative burst of inflammatory cells. Transcutaneous oxygen tension is directly correlated with wound healing.¹⁰⁹ Wound tissue oxygenation is determined by blood perfusion, hemoglobin dissociation, local oxygen consumption, fraction of inspired oxygen ($F_{I}O_2$), oxygen-carrying capacity (as measured by hemoglobin content), arterial oxygen tension (P_aO_2), circulating blood volume, cardiac function, arterial inflow, and venous drainage.^{106,110} Each of these variables should be addressed in promoting wound healing.

Supplemental administration of oxygen (inspired or hyperbaric) has beneficial effects on wound healing. The incidence of infection in surgical wounds can be reduced by improving the $F_{I}O_2$ with supplemental oxygen.¹¹¹ In a study of patients undergoing colon surgery, for example, the wound infection rate was 50% lower when an $F_{I}O_2$ of 0.8 was maintained intraoperatively and for 2 hours postoperatively than when an $F_{I}O_2$ of 0.3 was maintained.¹¹² Hyperbaric oxygen therapy (i.e., the delivery of oxygen in an environment of increased ambient pressure) has been used for treatment of many types of wounds in which tissue hypoxia may impair healing.⁴³ It increases tissue oxygen concentrations tenfold while also causing vasoconstriction, which results in decreased posttraumatic edema and decreased compartment pressures.¹¹³ The elevated pressure and hyperoxia induced by hyperbaric oxygen therapy may promote wound healing; for patients with an acute wound, this modality may be a useful adjunct in treating limb-threatening injury, crush injury, and compartment syndrome.⁴³

Circulating volume can be improved by administering crystalloids or blood. However, anemia alone is not associated with impaired wound healing unless it is severe enough to limit circulating blood volume.¹¹⁴ The vasculature may be compromised either systemically (e.g., by diabetes mellitus or peripheral vascular disease) or locally (e.g., by trauma or scar). Vascular bypass may be necessary to improve tissue oxygenation in patients with poor arterial inflow.⁹⁷

Tobacco Smoking

Tobacco smoking reduces tissue oxygen concentrations, impairs wound healing, and contributes to wound infection and dehiscence.^{115,116} The effects of smoking are attributable to vasoconstriction (caused by nicotine), displacement of oxygen binding (resulting from the high affinity of carbon monoxide for hemoglobin), increased platelet aggregation,¹¹⁷ impairment of the inflammatory cell oxidative burst,¹¹⁸ endothelial damage, and the development of atherosclerosis.^{115,116,119} All acutely injured patients should stop smoking, and ideally, all noninjured patients scheduled to undergo surgery should stop smoking at least 3 weeks before an elective surgical wound is made.^{118,120} Like smoked tobacco, transcutaneous nicotine patches alter the inflammatory cell oxidative burst and cause vasoconstriction; accordingly, they too should not be used when a wound is present.¹¹⁸

Malnutrition

On average, hospitalized patients show a 20% increase in energy expenditure, and this increase calls for appropriate nutritional compensation.⁹⁷ Good nutritional balance and adequate caloric intake (including sufficient amounts of protein, carbohydrates, fatty acids, vitamins, and other nutrients) are necessary for normal wound healing.¹²¹

All patients who have sustained wounds should undergo nutritional assessment,¹²² which typically includes measuring serum

levels of albumin, protein, prealbumin, transferrin, and insulinlike growth factor-1 (IGF-1).⁹⁷ The serum albumin level is one of the best predictors of operative mortality and morbidity.¹²³ A value lower than 2.5 g/dl is considered severely depressed, and a value lower than 3.4 g/dl is associated with higher perioperative mortality.^{124,125} Protein provides an essential supply of the amino acids used in collagen synthesis, and hypoproteinemia results in impaired healing; consequently, it is not surprising that protein replacement and supplementation can improve wound healing.^{126,127} In particular, supplementation specifically with the amino acids arginine, glutamine, and taurine (which are essential for anabolic processes and collagen synthesis) is known to enhance wound healing.¹²⁸⁻¹³⁰ Glutamine is the most abundant free amino acid in the body, and under catabolic conditions, it is released from muscle unless provided as a supplement.

Vitamins C, A, K, and D are essential for normal healing. Vitamin C (ascorbic acid) hydroxylates the amino acids lysine and proline during collagen synthesis and cross-linking. A deficiency of this vitamin causes scurvy, marked by failed healing of new wounds and dehiscence of old wounds. Vitamin C supplementation (100 to 1,000 g/day) can improve wound healing.^{97,130} Vitamin A (retinoic acid) is essential for normal epithelialization, proteoglycan synthesis, and normal immune function.¹³¹⁻¹³³ Retinoids and topical tretinoin may help foster acute wound healing by accelerating epithelialization of full- and partial-thickness wounds, activating fibroblasts, increasing type III collagen synthesis, and decreasing metalloprotease activation.^{134,135} Oral retinoid treatment significantly increases the decreased hydroxyproline content, tumor growth factor- β (TGF- β) level, and IGF-1 concentration associated with corticosteroids.¹³⁴ In addition, all aspects of corticosteroid-impaired healing—other than wound contraction—can be reversed by providing supplemental oral vitamin A at a recommended dosage of 25,000 IU/day.¹³⁶ The retinoic acid derivative isotretinoin (13-*cis*-retinoic acid), however, impairs wound epithelialization and delays wound healing.¹³⁷ Vitamin K is a cofactor in the synthesis of coagulation factors II, VII, IX, and X, as well as thrombin. Consequently, vitamin K is necessary for clot formation and hemostasis, the first step in acute wound healing. Vitamin D is required for normal calcium metabolism and therefore plays a necessary role in bone healing.

Dietary minerals (e.g., zinc and iron) are also essential for normal healing. Zinc is a necessary cofactor for DNA and RNA synthesis. A deficiency of this mineral can lead to inhibition cell proliferation, deficient granulation tissue formation,¹³⁸ and delayed wound healing.¹³⁹ Zinc replacement and supplementation can improve wound healing.¹³⁰ However, daily intake should not exceed 40 mg of elemental zinc, because excess zinc can immobilize macrophages, bind copper, and depress wound healing.¹⁴⁰ Iron is also a cofactor for DNA synthesis, as well as for hydroxylation of proline and lysine in collagen synthesis.⁹⁷ However, iron deficiency anemia does not appear to affect wound strength.¹⁴¹

Jaundice

The effect of jaundice on wound healing is controversial. Jaundiced patients appear to have a higher rate of postoperative wound healing complications,¹⁴² as well as a lower level of collagen synthesis.¹⁴³ However, obstructive jaundice does not affect healing of blister wounds in humans.¹⁴³ Jaundiced animals show a significant delay in collagen accumulation within the wound, but no significant reduction in the mechanical strength of the wound.¹⁴⁴ Biliary drainage may be considered in jaundiced patients with

wounds; this measure will improve collagen synthesis, though it may not have any appreciable effect on the healing rate.¹⁴³

Age

Aging has a deleterious effect on the capacity for wound healing.¹⁴⁵ Increasing age is associated with an altered inflammatory response, impaired macrophage phagocytosis, and delayed healing.¹⁴⁶ Nevertheless, even though the wound healing phases begin later in elderly persons, proceed more slowly, and often do not reach the same level that they would in younger persons, elderly patients are still able to heal most wounds with ease.¹⁴⁷

Diabetes Mellitus

Diabetes mellitus is associated with poor wound healing and an increased risk of infection. Diabetic neuropathy leads to sensory loss (typically in the extremities) and diminished ability to detect or prevent injury and wounding. Once present, wounds in diabetic patients heal slowly. The etiology of this healing impairment is multifactorial. Diabetes is associated with impaired granulocyte function and chemotaxis, depressed phagocytic function, altered humoral and cellular immunity, peripheral neuropathy, peripheral vascular disease, and various immunologic disturbances, any of which may hinder wound healing.¹⁴⁸⁻¹⁵¹ In addition, it is associated with a microangiopathy that can limit perfusion and delivery of oxygen, nutrients, and inflammatory cells to the healing wound.¹⁵² Diabetes-induced impairment of healing, as well as the attendant morbidity and mortality, may be reduced by tightly controlling blood sugar levels with insulin.¹⁵³ Diabetic patients must also closely monitor themselves for wounds and provide meticulous care for any wounds present.

Uremia

Uremia and chronic renal failure are associated with weakened host defenses, an increased risk of infection, and impaired wound healing.¹⁵⁴ Studies using uremic animal models show delayed healing of intestinal anastomoses and abdominal wounds.¹⁵⁵ Uremic serum also interferes with the proliferation of fibroblasts in culture.^{103,155} Treatment of this wound healing impairment includes dialysis.

Uremic patients with wounds may experience bleeding complications. In this situation, appropriate evaluation includes determining the prothrombin time (PT), the activated partial thromboplastin time (aPTT), the platelet count, and the hematocrit. Treatment includes dialysis without heparin; administration of desmopressin (0.3 μ g/kg), cryoprecipitate, conjugated estrogens (0.6 mg/kg/day I.V. for 5 days),¹⁵⁶ and erythropoietin; and transfusion of red blood cells to raise the hematocrit above 30%.^{157,158}

Uremic patients with hyperparathyroidism may also exhibit the uremic gangrene syndrome (calciophylaxis), which involves the spontaneous and progressive development of skin and soft tissue wounds, usually on the lower extremities. Patients with this syndrome typically are dialysis dependent and have secondary or tertiary hyperparathyroidism. Wound biopsies demonstrate fat necrosis, tissue calcification, and microarterial calcification.¹⁵⁹ Treatment includes local wound care, correction of serum phosphate levels with oral phosphate binders,¹⁶⁰ correction of calcium levels with dialysis, and subtotal parathyroidectomy.¹⁵⁹

Drugs

Steroids Corticosteroids are anti-inflammatory agents that inhibit all aspects of healing, including inflammation, macrophage migration, fibroblast proliferation, protein and collagen synthesis,

development of breaking strength, wound contraction, and epithelialization.^{103,136,161} In the setting of an acute wound that fails to heal, corticosteroid doses may be reduced, vitamin A administered topically or systemically, and anabolic steroids given to restore steroid-retarded inflammation.^{103,136}

Unlike corticosteroids, anabolic steroids accelerate normal collagen deposition and wound healing. Oxandrolone is an oral anabolic steroid and testosterone analogue that is employed clinically to treat muscle wasting, foster wound healing, and mitigate the catabolism associated with severe burn injury. Supplementation with this agent leads to significant improvements in the wound healing rate.¹⁶² In burn patients treated with oral oxandrolone, hospital length of stay is significantly reduced, and the number of necessary operative procedures is decreased.¹⁶³ In ventilator-dependent surgical patients receiving oxandrolone, however, the course of mechanical ventilation is longer than in those not treated with oxandrolone. It has been suggested that the very ability of oxandrolone to enhance wound healing may increase collagen deposition and fibrosis in the later stages of ARDS and thereby prolong recovery.¹⁶⁴ Acute elevation of liver enzyme levels has been seen in some patients treated with oxandrolone; accordingly, hepatic transaminase concentrations should be intermittently monitored in all patients treated with this agent.¹⁶³

Chemotherapeutic agents Both wound healing and tumor growth depend on metabolically active and rapidly dividing cells. Consequently, chemotherapeutic anticancer drugs that hinder tumor growth can also impair wound healing. These agents (which include adrenocorticosteroids, alkylating agents, antiestrogens, antimetabolites, antitumor antibodies, estrogen, progestogens, nitroureas, plant alkaloids, and random synthetics) attenuate the inflammatory phase of wound healing, decrease fibrin deposition,

reduce the synthesis of collagen by fibroblasts, and delay wound contraction.⁹⁷ Some cytotoxic drugs (e.g., methotrexate and doxorubicin) substantially attenuate the early phases of wound repair and reduce wound tear strength.¹⁶⁵ The magnitude of these effects is influenced by the timing of the chemotherapeutic agent's delivery in relation to the time when the wound is sustained. Preoperative delivery has a greater adverse effect on healing; for example, doxorubicin impairs wound healing to a greater extent if given before operation than if treatment is delayed until 2 weeks after operation.¹⁶⁶ Chemotherapy also results in myelosuppression and neutropenia that can decrease resistance to infection, allowing small wounds to progress to myonecrosis and necrotizing soft tissue infections.¹⁶⁷ In all acutely wounded patients who have recently been treated with, are currently taking, or will soon begin to take chemotherapeutic agents, the wounds must be closely observed for poor healing and complications.

Other drugs Many other commonly used drugs affect wound healing and thus should be avoided in the setting of an acute wound. Nicotine, cocaine, ergotamine, and epinephrine all cause vasoconstriction and tissue hypoxia. Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen and ketorolac) inhibit cyclooxygenase production and reduce wound tensile strength. Colchicine decreases fibroblast proliferation and degrades newly formed extracellular matrix. Antiplatelet agents (e.g., aspirin) inhibit platelet aggregation and arachidonic acid-mediated inflammation. Heparin and warfarin impair hemostasis by virtue of their effects on fibrin formation.^{84,168,169} As noted [see *Malnutrition, above*], isotretinoin inhibits wound epithelialization and delays wound healing.¹³⁷ Vitamin E (α -tocopherol) impairs collagen formation, inflammation, and wound healing¹⁷⁰; topical application of this agent can cause contact dermatitis and worsen the cosmetic appearance of scars.⁹⁵

Discussion

Physiology of Wound Healing

Wound healing is not a single event but a continuum of processes that begin at the moment of injury and continue for months. These processes take place in much the same way throughout the various tissues of the body and, for the purposes of description, may be broadly divided into three phases: (1) inflammation, (2) migration and proliferation, and (3) maturation [see *Figure 3*]. Humans, unlike (for instance) salamanders, lack the ability to regenerate specialized structures; instead, they heal by forming a scar that lacks the complex and important skin structures seen in unwounded skin [see *Figure 4*].

INFLAMMATORY PHASE

The inflammatory phase of wound healing begins with hemostasis, followed by the arrival first of neutrophils and then of macrophages. This response is most prominent during the first 24 hours after a wound is sustained. Signs of inflammation (i.e., erythema, edema, heat, and pain) are apparent, generated primarily by changes in the venules on the distal side of the capillary bed. In clean wounds, signs of inflammation dissipate relatively quickly, and few if any inflammatory cells are seen after 5 to 7 days. In contaminated wounds, inflammation may persist for a prolonged period.

Because wounds bleed when blood vessels are injured, hemostasis is essential. In the first 5 to 10 minutes after wounding, vasoconstriction contributes to hemostasis, and the skin blanches as a result. Vasoconstriction is mediated by catecholamines (e.g., epi-

nephrine and norepinephrine) and prostaglandins (e.g., prostaglandin $F_{2\alpha}$ [$PGF_{2\alpha}$] and thromboxane A_2 [TXA_2]). As vessels contract, platelets aggregate and adhere to the blood vessel collagen exposed by the injury. Aggregating platelets release alpha-granule proteins, resulting in further platelet aggregation and triggering cytokine release. The cytokines involved in cutaneous wound healing include epidermal growth factors, fibroblast growth factors, transforming growth factor- β , platelet-derived growth factor, vascular endothelial growth factor (VEGF), tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), IGF-1, granulocyte colony-stimulating factor, and granulocyte-macrophage colony-stimulating factor.¹⁷¹ Some of these cytokines have direct effects early in the healing process; others are bound locally and play critical roles in later healing phases. The use of specific cytokines to reverse healing deficits or promote wound healing appears to be a promising clinical tool and is currently the subject of ongoing basic scientific and clinical research.¹⁷²

The coagulation cascade also contributes to hemostasis. The extrinsic pathway is essential to hemostasis and is stimulated by the release of tissue factor from injured tissue; the intrinsic cascade is not essential and is triggered by exposure to factor XII. Both coagulation pathways lead to the generation of fibrin, which acts with platelets to form a clot in the injured area [see *1:4 Bleeding and Transfusion*]. Fibrin both contributes to hemostasis and is the primary component of the provisional matrix [see *Migratory and Proliferative Phase, Provisional Matrix Formation, below*].

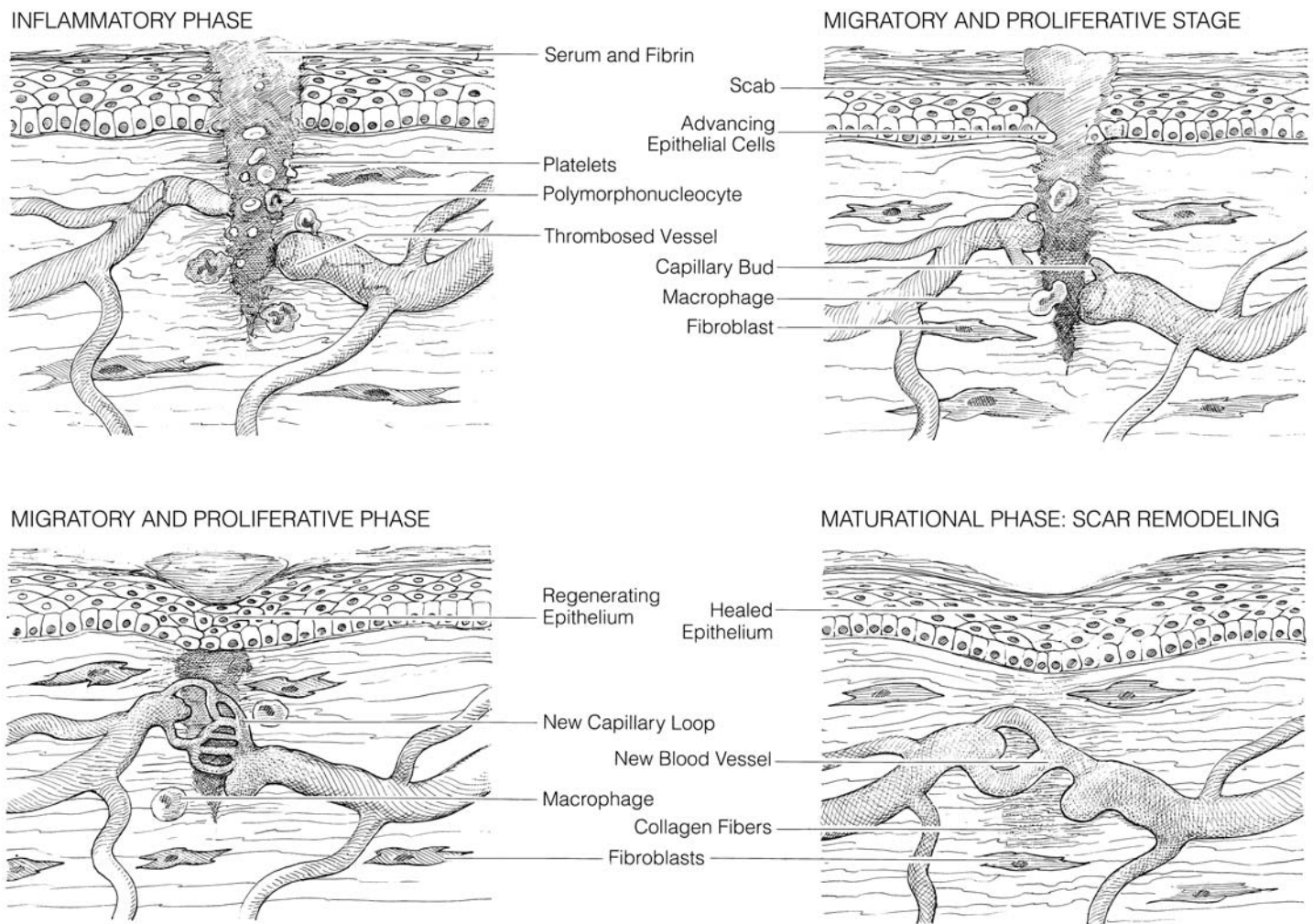


Figure 3 Depicted are the phases of wound healing. In the inflammatory phase (top, left), platelets adhere to collagen exposed by damage to blood vessels to form a plug. The intrinsic and extrinsic pathways of the coagulation cascade generate fibrin, which combines with platelets to form a clot in the injured area. Initial local vasoconstriction is followed by vasodilatation mediated by histamine, prostaglandins, serotonin, and kinins. Neutrophils are the predominant inflammatory cells (a polymorphonucleocyte is shown here). In the migratory and proliferative phase (top, right; bottom, left), fibrin and fibronectin are the primary components of the provisional extracellular matrix. Macrophages, fibroblasts, and other mesenchymal cells migrate into the wound area. Gradually, macrophages replace neutrophils as the predominant inflammatory cells. Angiogenic factors induce the development of new blood vessels as capillaries. Epithelial cells advance across the wound bed. Wound tensile strength increases as collagen produced by fibroblasts replaces fibrin. Myofibroblasts induce wound contraction. In the maturational phase (bottom, right), scar remodeling occurs. The overall level of collagen in the wound plateaus; old collagen is broken down as new collagen is produced. The number of cross-links between collagen molecules increases, and the new collagen fibers are aligned so as to yield an increase in wound tensile strength.

Vasoconstriction and hemostasis are followed by vasodilatation, which is associated with the characteristic signs of erythema, edema, heat, and pain. Vasodilatation is mediated by prostaglandins (e.g., PGE_2 and PGI_2 [prostacyclin]), histamine, serotonin, and kinins.^{173,174} As the blood vessels dilate, the endothelial cells separate from one another, thereby increasing vascular permeability. Inflammatory cells initially roll along the endothelial cell lining, subsequently undergo integrin-mediated adhesion, and finally trans-migrate into the extravascular space.¹⁷⁵

For the first 48 to 72 hours after wounding, neutrophils are the predominant inflammatory cells in the wound. About 48 to 96 hours after wounding, however, monocytes migrate from nearby tissue and blood and transform into macrophages, and eventually, macrophages become the predominant inflammatory cells in the wound. Both neutrophils and macrophages engulf damaged

tissue and bacteria and digest them. After neutrophils phagocytose damaged material, they cease to function and often release lysosomal contents, which can contribute to tissue damage and a prolonged inflammatory response. Macrophages, however, are essential to wound healing and do not cease to function after phagocytosing bacteria or damaged material.¹⁷⁶ In the wound environment, macrophages also secrete collagenase, elastase, and matrix metalloproteinases (MMPs) that break down damaged tissue. Macrophages also produce cytokines that mediate wound-healing processes, as well as IL-1 (which can lead to a systemic response, including fever) and $\text{TNF-}\alpha$.¹⁷¹

MIGRATORY AND PROLIFERATIVE PHASE

The migratory and proliferative phase is marked by the attraction of epidermal cells, fibroblasts, and endothelial cells to the

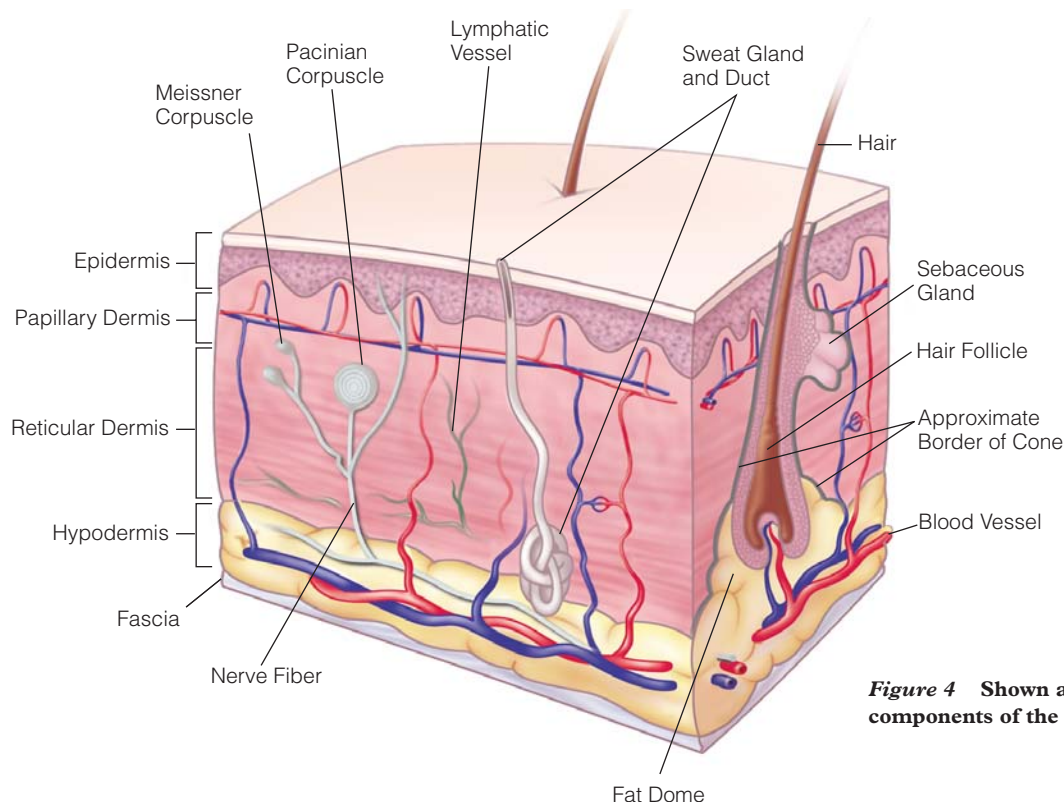


Figure 4 Shown are the key anatomic components of the skin.

wound. Cells migrate along the scaffolding of fibrin and fibronectin. This process involves the upregulation of integrin receptor sites on the cell membranes, which allows the cells to bind at different sites in the matrix and pull themselves through the scaffolding. Migration through the provisional matrix is facilitated by proteolytic enzymes. Cytokines and growth factors then stimulate the proliferation of these cells.^{171,176}

Epithelialization

Within approximately 24 hours of injury, epidermal cells from the wound margin and skin appendages begin to migrate into the wound bed. These migrating epidermal cells dissect the wound, separating desiccated eschar from viable tissue.⁸⁰ At 24 to 48 hours after wounding, epidermal cells at the wound margin begin to proliferate, producing more migrating cells.¹⁷¹ As epidermal migration is initiated, the desmosomes that link epidermal cells together and the hemidesmosomes that link the epidermal cells to the basement membrane disappear.¹⁷⁷ Migrating epidermal cells express integrin receptors that allow interaction with extracellular matrix proteins, laminin, collagen, and fibrin clot.¹⁷⁸ When epidermal cells migrating from two areas meet, contact inhibition prevents further migration. The cells making up the epidermal monolayer then differentiate, divide, and form a multilayer epidermis.

Provisional Matrix Formation

Formation of the provisional matrix and granulation tissue begins approximately 3 to 4 days after wounding. Fibroblasts synthesize an extracellular matrix of fibrin, fibronectin, and proteoglycans that supports epidermal and endothelial cell migration and proliferation.^{178,179} Proteoglycans (e.g., dermatan sulfate, heparin, heparan sulfate, keratan sulfate, and hyaluronic acid) consist of a protein core that is linked to one or more glycosaminoglycans; they anchor proteins and facilitate the alignment of collagen into fibrils.

Fibrin becomes coated with vitronectin and fibronectin, which are glycoproteins that facilitate the adhesion of migrating fibro-

blasts and other cells to the provisional extracellular matrix.¹⁸⁰ By influencing cellular attachment, fibronectin helps modulate cell migration into the wound.¹⁸¹ In addition, the fibrin-fibronectin lattice binds various cytokines that are released at the time of injury and serves as a reservoir for these factors in the later stages of healing.¹⁸²

Fibroblasts then replace the provisional extracellular matrix with a collagen matrix, and the wound gains strength. The rate of collagen synthesis increases greatly after the initial 3 to 5 days and continues at an increased rate for 21 days before gradually declining.¹⁸³ Of the many types of collagen, the ones that are of primary importance in the skin are types I and III. Approximately 80% to 90% of the collagen in the skin is type I collagen; the remaining 10% to 20% is type III. The percentage of type III collagen is higher in embryonic skin and in skin that is in the early stages of wound healing.

Collagen molecules are synthesized by fibroblasts. Lysine and proline residues within the collagen molecule become hydroxylated after being incorporated into polypeptide chains. This process requires specific enzymes, as well as various cofactors (i.e., oxygen, vitamin C, α -ketoglutarate, and ferrous iron). The result is procollagen, which is released into the extracellular space. Individual collagen molecules then align and associate with one another to form fibrils. Covalent cross-links form between various combinations of the hydroxylated residues (lysine and hydroxylysine) in aligned collagen fibrils, with the strongest links occurring between hydroxylysine and hydroxylysine. These cross-links are essential to the tensile strength of the wound. Cofactor deficiencies (e.g., vitamin C deficiency in scurvy) and the use of corticosteroids can lead to the synthesis of weak, underhydroxylated collagen that is incapable of generating strong cross-links.

Angiogenesis

The growth of new blood vessels, which is necessary to support the wound tissue, begins 2 to 3 days after wounding. This process of angiogenesis may be stimulated by the hypoxic and acidic

wound microenvironment, as well as by cytokines (e.g., VEGF) derived from epidermal cells and macrophages.^{171,184} Endothelial cells from surrounding vessels express fibronectin receptors and grow into the provisional matrix. These migrating endothelial cells create paths in the matrix for developing capillaries by releasing plasminogen activator, procollagenase, heparanase, and MMPs, which break down fibrin and basement membranes.^{171,185} The budding capillaries join and initiate blood flow. As the wounded area becomes better vascularized, the capillaries consolidate to form larger blood vessels or undergo apoptosis.¹⁸⁶

MATURATIONAL PHASE

Wound Contraction

Myofibroblasts are specialized fibroblasts containing alpha-smooth muscle actin microfilaments that contribute to wound contraction.^{187,188} The wound edges are pulled together by the contractile forces supplied by the myofibroblast. Wound contraction generally begins in the 4- to 5-day period after wounding and continues for 12 to 15 days or until the wound edges meet. The rate at which contraction occurs varies with the laxity of the tissue and is

highest at anatomic sites with redundant tissue. Excessive contraction can lead to contracture, a pathologic scarring that impairs the function and appearance of the scar.

Scar Remodeling

Collagen remodeling begins approximately 3 weeks after wounding. Collagen synthesis is downregulated, the rates at which collagen is synthesized and broken down reach equilibrium, and the wound becomes less cellular as apoptosis occurs. During this process, the extracellular matrix, including collagen, is continually remodeled and synthesized in a more organized fashion along stress lines.¹⁸³ Collagen breakdown is mediated by MMPs.¹⁸⁹ The number of cross-links between collagen fibers increases,¹⁸³ and the realigned, highly cross-linked collagen is much stronger than the collagen produced during the earlier phases of healing. The tensile strength of the wound increases rapidly for 6 weeks after injury; accordingly, during this period, heavy lifting and any other activity that applies stress across the wound should be avoided. After the initial 6 weeks, tensile strength increases more slowly for a further 6 to 12 months, though it never reaches the tensile strength of unwounded tissue [see Figure 2].

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Acknowledgments

Figures 1 and 4 Thom Graves.

Figure 2 Janet Betries.

Figure 3 Carol Donner.

8 PREPARATION OF THE OPERATING ROOM

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This chapter concentrates on the general principles of operating room (OR) design and operation. The OR is designed to permit sterile, safe, painless, and effective surgical intervention to improve the lives of patients. Advances in science and technology have significantly increased the complexity of the OR environment. With further advances, the OR will continue to evolve.

The basic aspects of OR design have not changed since the late 19th century, except for changes necessitated by the introduction of complex surgical imaging and monitoring equipment. Effective integration of this equipment into the confined OR space is essential. This chapter focuses on general principles of planning and operation rather than the specific requirements of individual surgical specialties.

Efficient operation of the OR depends on many individuals, some seldom seen, whose skills are essential. They are rarely acknowledged and easily overlooked. Continuous, respectful communication is essential for safe and successful outcomes.

General Principles of OR Design and Construction

PHYSICAL LAYOUT

The basic physical design of the OR is determined first by requirements for patient positioning, illumination, anesthesia, and instrumentation and second by considerations of storage, patient and staff movement, and communication. Basic OR design has not changed substantially over the past century. More recently, however, advances in minimally invasive surgery, intraoperative imaging, patient monitoring, surgical navigation, surgical robotics, and data connectivity have stimulated surgeons and architects to rethink the layout of the OR.

Positioning the Patient

The anesthesia machine is positioned at the head of the table so that the anesthesiologist has an unimpeded view of the machine, monitors, airway, and intravenous (IV) fluids. The suction tubing and electrocautery cords are usually brought off the field toward the feet. However, they may be brought off the side or head of the patient in selected cases depending on equipment location and room orientation.

Laparotomy

The patient is positioned supine on the operating table. The arms may be tucked in at the patient's sides or placed on well-padded arm boards at 90° angles to the table. Care must be taken to avoid hyperextending the arms to avoid injury to the brachial plexus. If the arms are tucked in at the side, the

area of the cubital tunnel must be well padded to avoid injury to the ulnar nerve. The surgeon generally stands on the patient's right and the assistant on the left. For pelvic procedures, the right-handed surgeon may elect to stand on the patient's left. The scrub nurse stands next to the instrument tray placed on a Mayo stand over the patient's legs. The back table containing additional instruments is placed at the foot of the bed (Figure 1A).

Two sets of ceiling lights are positioned over the field. In many cases, a head light worn by the surgeon provides additional focused illumination. For pelvic procedures, access to the perineum is either helpful or essential. The patient should be placed in the Lloyd-Davies position. The patient's legs are placed in well-padded leg holders attached to the side of the OR table. The distal portion of the table is lowered to form a right angle with the proximal table. The patient is moved distally so that the sacrum is positioned adjacent to the table brake. Care is taken to protect the airway, arms, and legs during repositioning. A foam pad is placed between the sacrum and the OR table. The leg holders are positioned to avoid abduction of the hips. Care is taken to ensure padding in the area of the peroneal nerves, feet, and calves. Peroneal nerve palsy and compartment syndrome attributable to prolonged pressure are risks. Morbid obesity is a relative contraindication to the Lloyd-Davies position because of the risk of a traction injury to the sciatic nerve.

Thoracotomy

The patient is placed in the full lateral position. A bean bag is a useful device to hold the patient in position. It holds its shape when a suction device is applied. An axillary roll, either a rolled sheet or an IV bag, is placed to protect the brachial plexus. Alternatively, a large pillow may be placed under the axilla and chest. Pillows are useful for supporting the legs. The bottom leg should be slightly flexed and the top leg extended. The position should be secured by the application of 2-inch tape to the area of the iliac crest. Care must be taken to protect the skin from the tape to avoid blister formation. The arms are extended in front of the patient. They may rest on an arm board protected by pillows or sheets. Alternatively, the top arm may be supported by a well-placed "airplane splint." As in laparotomy, the surgeon and assistant stand on either side of the patient and the scrub nurse stands toward the feet. Two lights are positioned over the patient. The use of a head light by the operating surgeon is routine in many situations (Figure 1B).

Thyroidectomy and Parathyroidectomy

Thyroidectomy and parathyroidectomy are the most common neck procedures performed by general surgeons.

a



b



c



Figure 1 Patient positioning: (a) laparotomy, (b) thoracotomy, and (c) thyroidectomy.

Preoperative evaluation should include assessment of cervical spine mobility. The patient is positioned supine on the OR table. After endotracheal intubation, a sheet roll is placed posterior to the scapula. The head is extended and placed on a foam "donut" pad, avoiding excess tension on the cervical spine. Extension of the head should be avoided in the presence of limited cervical spine mobility. The head of the table is elevated to reduce venous pressure. Two ceiling lights are positioned over the neck. Most surgeons use a head light to provide additional focused illumination. The scrub nurse stands next to the Mayo stand holding the instrument tray over the patient's feet (Figure 1C).

A similar position is employed for neck explorations. For unilateral neck exploration, the patient's head is turned away from the side of the planned incision.

DESIGN STANDARDS

Standards for new construction and major remodeling of ORs in the United States generally fall under the jurisdiction of state and local agencies. These agencies, in turn, often incorporate guidelines published by the Department of Health and Human Services,¹ as well as other groups and agencies,

such as the Occupational Safety and Health Administration (OSHA) and the Nuclear Regulatory Commission.²⁻⁵

Numerous articles and books discuss the various aspects of OR design.⁶⁻¹⁰ The American Institute of Architects has published a comprehensive set of guidelines for health care facility design that includes a detailed discussion of OR design.¹¹ Along with such guidelines and recommendations obtained from specialty surgical, anesthesiology, biomedical engineering and nursing associations, the design of new ORs must consider local needs and perspectives. The design of a new OR should be a collaborative effort reflecting the efforts of clinical services, support services, and administration.

DESIGN PROCESS AND CONSIDERATIONS

Designs must accommodate work flow and patient movement. Important considerations include the mix of inpatient and outpatient surgery, the design of the hospital or institution (including proximity to clinical services such as radiology and pathology), the surgical specialties to be served, accessibility to perioperative care units, accessibility of supplies, and removal of waste materials. The need for intraoperative fluoroscopy and sectional imaging, shielding, ceiling-mounted

microscopes, and surgical robotics and similar advanced technologies will be influential. It is important to allow for flexibility and to anticipate the introduction of new technologies over the life of the design. Time motion studies, simulations, and models may prove helpful and contribute to OR efficiency long term. Balancing flexibility and cost is a continuing challenge.¹²

The geography and physical relationship of clean and less clean areas in the operating suite determine many other aspects of the OR suite. There are two designs in common use. The first involves one or more clean hubs. The ORs are situated centrifugally in spokelike fashion. Clean and sterile equipment and supplies that must be on hand for immediate use are stored in the hub. A peripheral corridor typically affords access to perioperative care units, instrument and anesthesia workrooms, clean storage, staff lounges, and other facilities. Entry and egress from the suite and access to the OR front desk and reception area also involve the peripheral corridor. In the simplest embodiment, four ORs surround a hub. The number can be greater or smaller. Controlled movement through the hub or hubs drives this design.

The second model uses corridors rather than hubs and spokes. Supply rooms are typically situated between adjacent rooms. A less common variation builds a separate supply room next to each individual OR. Older ORs were designed with one door only. Current design favors two, one connecting to the more sterile area and the other to the less sterile area.

The OR must balance the restrictions on access needed for safety and efficiency with freedom of movement for personnel and patients. This balance is equally important in emergency situations and during complex and lengthy operations.

Should ORs be dedicated to specific surgical specialties? There are practical and logistical advantages to dedicated rooms, especially in cardiac surgery, neurosurgery, trauma, and ophthalmology. However, specialty-specific rooms can limit scheduling flexibility. Although it is hard to imagine justifying a room so narrowly designed that it absolutely cannot be used for more than one specialty, dedicated rooms might be emphasized in one institution and versatility in another. Each approach has its advocates. Design and equipment should ultimately reflect expected and projected case mix.

Finally, the design of the OR suite must facilitate cleaning, disinfection and efficient turnover, and the installation and maintenance of installed equipment.

STORAGE

The OR design must provide adequate storage space for urgently required supplies. Storage in hallways and inside the OR can create obstructions and hazards.

CRITICAL DEVICES AND EMERGENCY EQUIPMENT

Critical devices, as well as emergency supplies and instruments, must be prepared and positioned for immediate deployment. Accessories should be stored next to the instruments that need them.

Some hospitals have mass casualty response as part of their mission. These institutions will have special requirements for versatility, equipment, storage, and supplies. The specific design requirements for response to mass casualty events,

including nuclear, biological, chemical, and radiation incidents, are not addressed in this chapter.

PHYSICAL REQUIREMENTS

The fundamental model for OR design is a quadrangular room with minimum dimensions of 20 × 20 ft or 7 × 7 m. More often, the dimensions are closer to 30 × 30 ft or 10 × 10 m, so as to accommodate more specialized cardiac, neurosurgical, minimally invasive, orthopedic, and multiteam procedures. Smaller rooms are generally adequate for minor surgery and for procedures such as cystoscopy and eye surgery.

Ceiling height should be at least 10 ft or 3.5 m to allow ceiling mounting of operating lights, microscopes, robots, navigational systems, and other equipment. An additional 1 to 2 ft or 0.5 to 0.75 m of ceiling height may be advisable if x-ray or other boom equipment is to be permanently mounted. In ORs designed to accept intraoperative sectional imaging devices (computed tomography [CT] and magnetic resonance imaging [MRI]), the floors may be elevated to accommodate cabling and wiring for power and data connections. When floors are elevated, the overall height of the OR has to be increased.

Some institutions design or redesign the entire OR suite with the potential to accommodate oversized equipment as well as conduits and cables in both the ceiling and floor. Others prefer to customize individual rooms.

OR and perioperative facilities may be specially constructed to withstand environmental hazards such as earthquakes, tornadoes, and floods or hardened to contend with hostile military or terrorist attack. Standards and specifications for this type of construction fall outside the scope of this chapter.

COMPUTERIZATION, COMMUNICATION, AND DATA EXCHANGE: VOICE, VIDEO, AND DATA

Computers, telephones, imaging, and other systems for data capture, analysis, and exchange should be integrated into the OR design. The ubiquitous deployment of radiology Picture Archiving and Communication Systems (PACS) and the potential of digital pathology to improve surgical pathology services mandate the installation of high-speed broadband connections. Two-way audio with teleconferencing capabilities enables teleconsultation and teaching from and in the OR.

Effective communication systems capable of connecting the OR team, the OR front desk, and the rest of the hospital must be accessible. Emergency communication channels must be tested at regular intervals. Most importantly, systems for communication, data exchange, and data storage retrieval must be available, preferably off-site. Off-site data storage backup is essential for hospitals likely to respond to mass casualty events or subject to environmental hazards.

ASSIMILATING NEW TECHNOLOGIES

Advances in the medical device and information technology (IT) sectors stimulate a constant stream of innovation. Nevertheless, the undisciplined introduction of new technologies can be distracting, contraproductive, and expensive. ORs should be focused on measurable benefit and integration rather than novelty. The introduction of new technologies should reduce complexity and tangibly increase therapeutic

benefits and options for patients in ways that have been recognized for more than a decade.¹³

The OR of the future will be characterized by increasing dependence on technology. Although it is essential to track new technologies, they should be assessed and introduced in a disciplined manner. Technology acquisition should be strategic. A full discussion of technology assessment in surgery is outside the purview of this chapter, but the central principles are straightforward. First, the magnitude of unmet needs should be detailed and quantified. Second, the cost-effectiveness of a new technology should be assessed. Next, competitive solutions, including substitutes for the candidate technology acquisition, should be considered. Last, the marginal benefits and burdens of new technology introduction should be quantified.

Patient Safety, OR Efficiency, and Quality Improvement

The OR is a high-stress environment with inherent risk in which members of multiple disciplines temporarily congregate to treat surgical patients. The potential for error and inefficiency is great. Conversion of this group of individuals from disciplines with differing professional cultures and skill sets into a smoothly functioning surgical team is the key to increasing patient safety and efficiency.¹⁴ Surgical team training is an effective method to achieve a “team culture” resulting in improved communication and decreased risk of error.¹⁵ The use of perioperative care protocols reduces failures of communication.¹⁶

The Joint Commission Universal Protocol became effective on July 1, 2004. The key principles of the Universal Protocol are (1) the preoperative verification process, (2) marking the correct surgical site, (3) taking a “time-out” prior to surgery, and (4) adapting the requirements to non-OR settings. The elements of the time-out concept are evolving and may include introduction of team members; patient identification; review of the patient’s history, risk factors, medications, and allergies; availability of appropriate images and equipment; goals of surgery; and potential intra- and postoperative problems. The role of a discussion of planned postoperative care at the completion of the surgical procedure prior to the emergence from anesthesia is not clear at the present time.¹⁷

The use of a protocol during the hand-over of surgical patients to intensive care results in improved care.¹⁸ Extending the team concept to postanesthesia care has resulted in improved quality of care as measured by intubation times and hospital stay following cardiac surgery.¹⁹ The use of specialty teams during surgery to improve communication and efficiency is logical, but at present, there is a paucity of studies documenting its efficacy. Continuous monitoring is essential to maintain quality.²⁰

Patient safety²¹ begins with protection of patients from misidentification, physical and chemical hazards, medication error, operative error, and improper positioning.²² The surgeon is responsible for positioning the patient and preventing positioning injury.²³ The OR team is responsible for procuring and maintaining the equipment for proper positioning and monitoring the patient intraoperatively. The entire team is responsible for preventing falls.²⁴

The risks associated with malpositioning deserve further comment. Any bony prominence is subject to injury from excessive pressure. The fragile skin of infants and older patients may be injured by dragging rather than lifting into position. The American Society of Anesthesiologists (ASA) practice advisory on the prevention of perioperative peripheral neuropathies recommends that when practical, patients should be placed in the intended position before induction of anesthesia to test for comfort.²⁵ Uncomfortable positions should be modified. This is especially important with older patients or patients with degenerative spine and joint disease or skeletal instability.

Two major preventable consequences of malpositioning are neuropathy or plexopathy and skin burns or ulceration. Approximately 80% of surgical procedures are performed with patients in the supine position. Ulnar neuropathy and brachial plexopathy are the two most common complications in this position and constitute 28% and 20% of claims, respectively, in recent closed claims studies.^{26–31} Padding of the precondylar groove of the humerus and tucking of the arms or, at the least, restriction of abduction to less than 90° help prevent this problem.²⁵

The lithotomy position is used in approximately 9% of cases and is the next most commonly used position.^{27,29} Damage to the obturator, sciatic, lateral femoral cutaneous, and peroneal nerves has been observed. These injuries account for 5% of claims for nerve damage in the Closed Claims Data Base. They represent a small but not insignificant risk.²⁶ Other patient positions have also been associated with malpositioning injuries.

OCCUPATIONAL INJURY TO THE HEALTH CARE TEAM

Professionals engaged in perioperative and surgical care are exposed to biologic, ergonomic, chemical, physical, and psychosocial occupational risks.

Biologic Risks

These risks include (1) parenteral and mucocutaneous exposure to pathogens, (2) respiratory tract exposure to pathogens, (3) exposure to the biologic components of surgical smoke, and (4) exposure to allergens in latex gloves.³² Strategies to reduce mucocutaneous exposure to pathogens include double-gloving, blunt suture needles, a neutral zone for passage of sharps, and engineered sharps injury prevention devices.³³ The use of N-95 respirator masks reduces the risk of occupational exposure to aerosolized *Mycobacterium tuberculosis* and particulate matter greater than 1 micron in size.³⁴ Health care workers with allergies to latex should avoid contact with latex gloves and tubing.

Ergonomic Risks

Health problems related to ergonomics, especially back pain, are common. These problems are associated with awkward posture at the operating table, standing for long periods of time, and back injury incurred by lifting patients.

The OR table, monitors, imaging screens, and equipment should be positioned so that the OR team’s posture and position are as comfortable as possible within the limits of patient safety. Lifting injury can be minimized by using proper patient transfer techniques and obtaining additional assistance when moving patients in the OR. Repetitive motion injury is a less common but not insignificant risk.³²

Chemical Risks

Health care workers are exposed to numerous potentially hazardous chemicals in the OR, including anesthetic gases, disinfecting and sterilizing chemicals, specimen preservatives, and chemotherapeutic drugs.³² Scavenger systems are deployed broadly and have significantly reduced exposure to anesthetic gases.³⁵ Protective gowns and gloves prevent exposure to other chemicals in the OR.

Physical Risks

Physical risks to patients and the OR team include fire, electrocution, radiation exposure, and laser energy exposure.³²

Fire The first principle of fire prevention is control of the three elements of the fire triangle: oxygen, fuel, and an ignition source.³⁶ Air/oxygen mixtures should be adjusted to reduce the fraction of inspired oxygen (FiO_2) to the lowest level consistent with patient safety and satisfactory hemoglobin oxygen saturation.³⁶ Light, heat, and electrical sources of ignition should be carefully monitored and kept away from paper drapes. The use of alcohol-based skin preparation solutions should be minimized if possible.³⁷ The use of the electrocautery or laser energy in the airway or in the unprepared intestinal lumen in the presence of high concentrations of oxygen increases the risk of fire.

Radiation exposure Exposure to ionizing radiation is inherently dangerous. For this reason, the extent of exposure must be minimized through the use of all protective means available. Although the hazards of radiation were witnessed early in the 20th century, how exposure was to be calculated and what acute and cumulative doses were dangerous could not be determined until later. In 1928, the International Commission on Radiological Protection (ICRP) was formed to study and set standards for radiation protection. The National Council on Radiation Protection (NCRP) was established in the United States to help set US policy on radiation protection.³⁷ Until recently, guidelines for radiation exposure have been based on annual exposure limits (maximal permissible yearly dose). The historical means of dosimetry underestimated exposure because of technical limitations and sampling error. For this reason, guidelines now focus on lifetime accumulated exposure as a more useful surrogate for the real risks in those with chronic or prolonged exposure.

Concessions to higher annual dose limits were made for workers allowed higher radiation exposure because of occupational responsibilities. These were called “classified” workers, and they were subjected to strict monitoring and regular examination. Radiologists have been considered classified workers, but not surgeons. Classified workers were permitted more than three times the annual dose than nonclassified.³⁸

Empirical data suggest that the typical spinal surgeon performing fluoroscopically guided procedures may receive as much as 1.3-fold the annual whole-body radiation dose allowable for radiologists, although the level of thyroid exposure is less than 10% of the applicable limit specified by the NCRP.³⁹ A study of endovascular surgeons, in contrast, showed that their radiation exposure fell well within these limits, as well as the limits established by the ICRP.⁴⁰

Another study considered risks to the fetus of the pregnant surgeon. This risk is of particular importance early in gestation, before the pregnancy is recognized. In this study, the calculated accumulative dose received intraoperatively exceeded the threshold dose for the induction of radiation injury by at least two orders of magnitude. Approximately 2100 hours of fluoroscopy are required to reach this threshold.

Childhood cancer is another documented risk of low-dose fetal radiation exposure. The extent of this risk remains controversial. Nevertheless, the ICRP has recommended a maximum dose of 2 mSv and preferably less than 1 mSv during the declared pregnancy. With the protection afforded by a 0.5 mm lead-equivalent apron, however, the calculated expected cumulative fetal dose is less than 0.37 mSv, a figure that extrapolates to a significantly lower dose, and consequently a lower risk, than that derived from natural background radiation.

Surgeons exposed to intraoperative ionizing radiation may avail themselves of several protective strategies. A 1 mm lead-equivalent whole-body shield or apron provides 99% protection. A 0.5 mm lead-equivalent free-standing shield reduces exposure by 90%. A neck (thyroid) shield with 0.25 mm lead equivalence reduces exposure by 60%. Radiation-protective gloves reduce dosage to the hand by up to 40%.^{37,41}

Maintaining distance is also protective. Radiation attenuates with the square of the distance. For any given distance from the source of radiation, if the intensity of the radiation at a distance of $d = 1$, the intensity at any other distance is equal to $1/d^2$. Intensity diminishes as a function of the square of distance.

The effects of distance are manifested quickly. Staff exposure at 1 m distance from a C arm is 1/1000th that of the patient, even without shielding. In a model of femoral fracture, moving from the treated hip side of a patient to the contralateral side reduces exposure by a factor of 57 for the surgeon, 13 for the nurse, and 21 for the anesthetist. If the surgeon remains ipsilateral to the operative site but moves as little as 0.5 m away (cephalad) from the beam, the dose is reduced by a factor of 13, and at 1.5 m away, by a factor of 26. At 2 m from the source of radiation, the scattered radiation received by staff is very small.⁴² Nevertheless, because of the problem of accumulated lifetime exposure, no degree of exposure is ever deemed truly innocuous.

Image-guided surgery now plays a major role in many surgical disciplines, including orthopedics, vascular surgery, and urology. The cumulative radiation exposure associated with image guidance may be hazardous. The use of radionuclides for identification of sentinel nodes and intraoperative brachytherapy for the treatment of certain malignancies also creates the potential for radiation exposure.⁴³

Exposure to radiation comes from background radioactivity and from radiation sources in the workplace. The ICRP has established recommended yearly limits of radiation exposure for these two categories [see Table 1].⁴⁴ Recent studies of OR staff indicate that radiation exposure during surgical procedures employing radiation imaging techniques are well within the ICRP limits.^{45–47}

All OR personnel should wear radiation safety badges to allow monitoring of radiation exposure on a monthly basis.

Table 1 ICRP-Recommended Radiation Dose Limits⁴⁴

	Dose Limit	
	Occupational	Public
Effective dose	20 mSv/yr averaged over defined periods of 5 yr	1 mSv/yr
Annual equivalent dose in		
Lens of the eye	150 mSv	15 mSv
Skin	500 mSv	50 mSv
Hands and feet	500 mSv	—

ICRP = International Commission on Radiological Protection; mSv = millisievert.

OR personnel should wear protective lead aprons (0.25–0.5 mm in thickness) with thyroid shields during procedures in which fluoroscopy is used. Personnel frequently exposed to radiation should wear lead-containing lenses for eye protection. A mobile shield is useful for additional protection during cine runs.

OR personnel should stand as far away from the x-ray beam as possible to limit exposure. Even a distance of several feet can significantly reduce exposure. Equipment emitting ionizing radiation should be maintained and monitored to ensure proper function.⁴⁸ The use of pulsed fluoroscopy and effective collimation of images will help minimize the dose of radiation. Excessive and unnecessary imaging should be eliminated.

Laser exposure Surgical lasers are class 4 lasers that have the potential to irreparably damage the eye and burn the skin. A class 4 laser beam is 1 billion times brighter than a 100 W light bulb.⁴⁹ All OR personnel must wear protective glasses with lenses designed specifically for the wavelength of the specific laser being used. Glasses should be inspected prior to use to ensure that there are no scratches on the lens that could render the wearer vulnerable to an eye injury. The windows of the room should be shielded to protect individuals passing by. The number of personnel in a laser therapy room should be kept to a minimum.

Noise and light exposure General environmental hazards include high levels of noise and intense levels of light.^{50–52} These hazards are of equal significance to patients and to staff. One early study has indicated that elevated noise levels during orthopedic procedures (above the recommended limits of 110 dBA) were associated with significant hearing loss in orthopedic surgeons.⁵¹ Noise, excessive chatter, and even music can also pose a hazard to the patient by distracting the attention of OR personnel.

Psychosocial risks Perhaps the most underappreciated risks to the perioperative professional are psychosocial. Long hours and nighttime emergencies lead to fatigue. The high level of responsibility, the consequences of error, and the level of oversight have led to high levels of stress and burn-out.⁵³ Unfortunately, violence in the health care workplace, both verbal and physical, is common.⁵⁴ Stress reduction can be achieved by team training.¹⁵ Hospitals should have zero tolerance for workplace violence.⁵⁵

OR Design

Advances in videoendoscopic surgery and endoluminal vascular surgery since 1990 have led to the introduction of many complex electronic devices into an OR environment designed at the end of the 19th century. The promise of widespread robotics use in the future may further complicate equipment and use of space within the OR. At the same time, the importance of IT in both the performance of surgery and its documentation will only increase. These changes will inevitably require design adaptations in the OR to ensure adequate power and communication infrastructure support.⁵⁶

The ideal OR of the future will have videoendoscopic monitors, light sources, and CO₂ insufflators mounted on booms that can be introduced or withdrawn from patient care without moving heavy carts or reconnecting cables and power sources. ORs with ceiling- or floor-mounted fluoroscopy permit efficient use of catheter-based endoluminal and intravascular techniques during surgical care. Boom-mounted equipment can be easily moved, permitting more rapid room turnover between cases.

Designing rooms with the flexibility for multidisciplinary use may be more cost effective for many hospitals. In the long run, however, team training for subspecialty fields employing complex imaging equipment and catheter-based therapy may prove to be a more important factor for patient safety and efficiency than any particular OR design.⁵⁷ This is a key element in program development. Hospital administration must also commit the capital necessary to complete such a project before proceeding with program development. Balancing OR efficiency, new technology, and cost is a continuous challenge.

Environmental Issues in the OR

TEMPERATURE AND HUMIDITY

In Europe and North America, the OR is typically maintained at 18° to 26°C (64.4° to 78.8°F). A higher temperature is necessary during operations on infants and burn patients to conserve body heat. Fully gowned surgeons prefer the lower temperature of 18°C (64.4°F), but anesthesiologists prefer 21.5°C (70.7°F).⁵⁸ The optimum ambient temperature in the OR reflects a compromise between the comfort of gowned and ungowned staff. The ubiquitous deployment of patient warming devices has all but eliminated the problem of hypothermia in the adult during elective surgery.

Recent publications have indicated neurologic benefits from controlled hypothermia in the region of 34°C (93.2°F) in certain cases of asystole, cardiopulmonary arrest, and resuscitation.^{59–61} The equipment required for therapeutic hypothermia can be cumbersome.

Humidity in the OR is generally maintained between 50 and 60%. Humidity greater than 60% may cause condensation on cool surfaces. Humidity less than 50% may not suppress static electricity. Static electricity can adversely affect the function of modern computers and smart medical devices.

LIGHTING

ORs are no longer provided with skylights and northern exposure to maximize the benefit of natural illumination.

Nevertheless, effective lighting remains an important factor in reducing stress by providing clear views of the operative field, the anesthesia and monitoring systems, and the nursing area.

The standards for OR illumination were outlined by Dr. William Beck and the Illuminating Engineering Society.^{62,63} A general illumination brightness of up to 200 footcandles (ft-c) is desirable in new construction. The lighting sources should be free of glare and nonreflective.⁶⁴

The amount of light required during an operation varies with the surgeon and the operative site. Quantities of light can be measured as a function of the amount beamed on a subject (incident light) or the amount reflected (reflected light). In one study, general surgeons operating on the common bile duct found 300 ft-c sufficient because the reflectance of this tissue area is 15%. The corresponding incident light level would be 2,000 ft-c.²¹ Surgeons performing coronary bypass operations require an incident level of 3,500 ft-c.²¹ Whether changes in the color of light can improve discrimination of different tissues is unknown.

The powerful lights installed for surgery generate heat through the projection of infrared energy. This is an inefficient but inevitable byproduct of most forms of light appropriate for the OR. Much of the infrared energy can be eliminated by filtration or by heat-diverting dichroic reflectors.

There are several types of overhead lighting designs. For small ORs, a single large overhead light with one or two small satellites may suffice. Larger ORs may benefit more from several large lights with broader orbits. The larger the OR, the more important the installation of multiple light sources that can concentrate light in different areas of the operating field. This consideration is of particular importance where large body areas are exposed or where multiple sites are accessed simultaneously.

The illumination provided by overhead lighting can be usefully amplified and improved with headlights. Headlights have substituted for mobile lights in many OR suites, but both have their place. When headlights are used, spare bulbs must be kept on hand and cabling examined for damage and properly stored after each use.

During microsurgical and laparoscopic procedures, the surgical field is illuminated primarily by dint of the instruments used for visualization. The importance of ambient lighting for the remainder of the OR must not be forgotten.

All ORs should be equipped with battery-powered backup illumination and flashlights for emergency use.

OR EQUIPMENT

The modern OR is replete with medical devices designed to facilitate the work of the surgical team and to support, position, and protect the patient [see Table 2]. The equipment in the OR must be chosen and maintained with three concerns in mind: patient safety, surgical efficiency, and reduction of occupational hazards.

ELECTROSURGICAL DEVICES

The common electrosurgical device is a 500 W radiofrequency generator used to cut and coagulate tissue. A current passes from the cutting or coagulating surgical instrument to a dispersion electrode. Heat is generated at the tissue

interface as a function of resistance to the flow of current. The vaporization of intracellular water content leads to disintegration of the cell. Heat leads to the coagulation of proteins and hemostasis. Cellular debris is aerosolized. The smoke that is generated is comparable to that accompanying laser use. The smoke and its particulate content may be carcinogenic, allergenic, inflammatory, and infectious. There is little difference between laser plume and electrosurgical smoke.⁶⁵

The electrosurgical instrument requires close supervision.⁶⁶ It is very easy to become complacent in its use. The unit generates an electrical arc. In the past, these have been associated with explosions. This risk has been lessened because explosive anesthetic agents are no longer used. Nevertheless, explosion of hydrogen and methane gases in the large bowel remains a threat, especially when surgery must be performed on an unprepared bowel.⁶⁷ Because the unit and its arc generate a broad and unfiltered band of radiofrequencies, electrosurgical units may interfere with monitoring devices, most notably the electrocardiographic (ECG) monitor. Interference with cardiac pacemaker activity may occur.⁶⁸

Skin burns are the most frequently reported complication in use. Rarely are they fatal, but they are painful and may require skin grafts, raising the possibility of litigation. The burn site can be at the dispersive electrode, ECG monitoring leads, esophageal or rectal temperature probes, or areas of body contact with grounded objects. The dispersive electrode should be firmly attached to a broad area of dry, hairless skin, preferably over a large muscle mass.^{67,68}

Alcohol-based hair care products should be avoided during head and neck surgery because the risk of combustion during the use of electrocautery.

Preparation of the OR should include verification of the proper function and grounding of the unit and proper placement of the dispersive electrode. Smoke evacuators are highly recommended. The National Institute for Occupational Safety and Health (NIOSH) recommends a system that can pull 50 cubic feet per minute with a capture velocity of 100 to 150 feet per minute at the inlet nozzle and positioned within 2 inches of the surgical site.⁶⁹ Filters should be installed to capture the contents of the smoke. Used filters are deemed biohazardous. Routine, unfiltered suction is not adequate for this purpose.⁶⁹

LASERS AND LASER SAFETY

Lasers generate focused energy. They have been implicated in skin burns, retinal injuries, endotracheal tube fires, pneumothorax, and damage to viscera and the vasculature.⁷⁰ Both patients and staff have suffered injuries.

The laser-safe OR requires specific modifications. The OR should not have windows. Walls, ceilings, and equipment should be nonreflective. Equipment used in the operative field should be nonreflective and nonflammable. A sign warning personnel that a laser is in use should be posted.

Anesthetic technique should also take the use of lasers into consideration. When lasers are used in the vicinity of the face, airway, or chest cavity, the concentration of O₂ and N₂O in the inhaled gases should be reduced to decrease the possibility of fire. Personnel should wear appropriate eye protection. A smoke evacuator will improve visualization, reduce objectionable odor, and decrease the potential for papillomavirus infection or ingestion of toxic fumes from the laser smoke plume.^{65,71-74}

Table 2 Devices Used in the Operating Room

<i>Function</i>	<i>Device</i>
Support of patient	Anesthesia delivery devices Ventilator Physiologic monitoring devices Warming devices IV fluid warmers and infusers
Support of surgeon	Sources of mechanical, electrical, and internal power, including power tools and electrocautery, as well as laser and ultrasound instruments Mechanical retractors Lights mounted in various locations Suction devices and smoke evacuators Electromechanical and computerized assistive devices, such as robotic assistants Visualization equipment, including microscopes, endoscopic video cameras, and display devices such as video monitors, projection equipment, and head-mounted displays Data, sound, and video storage and transmission equipment Diagnostic imaging devices (e.g., for fluoroscopy, ultrasonography, MRI, and CT)
Support of OR team	Surgical instruments, usually packaged in case carts before each operation but occasionally stored in nearby fixed or mobile modules Tables for display of primary and secondary surgical instruments Containers for disposal of single-use equipment, gowns, drapes, etc. Workplace for charting and record keeping Communication equipment

CT = computed tomography; IV = intravenous; MRI = magnetic resonance imaging; OR = operating room.

POWERED DEVICES

The surgical table must be properly positioned and adjusted to ensure the safety of the patient and the efficient work of the surgical team. Manually adjustable tables are simple, but those with electrical controls are easier to manage. OR table attachments, such as the arm boards and leg stirrups used to position patients, must be properly maintained and secured to prevent injuries to patients or staff. During transfer to and from the OR table, care must be taken to ensure that the patient is not injured and that life support, monitoring, and intravenous (IV) systems remain connected. Proper transfer technique, adequate staff, and the use of assistive devices such as rollers will help prevent musculoskeletal injuries to the OR staff during this maneuver. Patients with fragile skin, including infants, small children, the ill, and the elderly, should be lifted and not dragged into position.

Other powered surgical instruments common in the OR include those used to obtain skin grafts, open the sternum and the cranium, and perform orthopedic procedures. Powered saws and drills can aerosolize body fluids, thereby creating a potential infection and contamination hazard for OR personnel.⁷⁵

OPERATING MICROSCOPE

Microsurgery is a routine part of many surgical specialties, including neurosurgery, plastic surgery, hand surgery, gynecologic surgery, and ophthalmology. Microscopes may be moved into the OR on wheeled stands or mounted on the ceiling, wall, or floor. Built-in microscopes are best employed in dedicated ORs.⁴⁶ All controls and displays must be properly positioned at or below the user's line of sight to allow comfortable and unobstructed viewing.

Modern operating microscopes are servo controlled and counterbalanced. The sequence for properly balancing a microscope should be carefully followed prior to every procedure and each time accessories are added or removed.

Improperly balanced instruments have been known to twist or fall, causing injury to patients and staff.

Many commercial microscope drapes are available. Where the laser is mounted to the microscope, it is essential to confirm that the drape is out of the line of fire to avoid contamination, melting, or kindling.

INTRAOPERATIVE IMAGING AND NAVIGATION

The advent of less invasive surgery requires accurate intraoperative confirmation of surgical anatomy through the use of x-ray, CT, MRI, and ultrasonography. These modalities are increasingly accompanied by and aligned with the use of surgical navigation systems. Intraoperative ultrasonography requires a high-quality portable ultrasound unit and specialized probes. Depending on the procedure and the training of the surgeon, the presence of a radiologist and an ultrasound technician may be requested.

The ultrasound unit should be positioned near the patient, and the surgical team must be able to view the image comfortably. In some cases, the image may be displayed on OR monitors by means of a video mixing device. Ultrasound units may also be used to modify the reference image in real time in surgical navigation systems.⁷⁶

Fluoroscopic and x-ray units may be portable or dedicated. Open radiologic units are usually installed either in the OR proper or immediately adjacent to the OR to permit intraoperative imaging of the selected body area. Intraoperative angiography and MRI devices are typically installed in dedicated ORs.⁷⁷ Intraoperative CT for neurosurgery, for example, may involve either portable or fixed devices.⁷⁸

The use of sequential compression stockings has become the standard of care for the prevention of venous thromboembolism in the majority of operations for which direct access to the lower extremities is not required [see 6:6 *Venous Thromboembolism*].⁷⁹ The air pump often must be placed near the patient on the floor or on a nearby cart. The pressure

tubing from the stockings to the pump must be carefully routed so as not to interfere with surgical access.

Suction devices are ubiquitous in the OR. A typical suction apparatus consists of a set of canisters on a wheeled base receiving suction from a wall- or ceiling-mounted source. The surgeon's aspirating cannula is connected sterilely to these canisters. Suction tubing is a common tripping hazard in the OR. In some procedures, the suction canisters may require repeated changing.

EQUIPMENT

Imaging Equipment

Imaging equipment for endovascular surgery can be fixed to the ceiling or portable. The fixed system is also employed in catheterization laboratories and dedicated interventional radiology suites. Portable systems use C-arms with dedicated vascular software packages designed for optimal endovascular imaging. Each of these systems has advantages and disadvantages.

Fixed ceiling-mounted systems have higher power output and smaller focal spot size and provide the highest-quality images. Larger image intensifiers (up to 16 in.) make possible larger visual fields for diagnostic arteriograms. Fewer runs are necessary, with the advantage of reducing the quantity of contrast injected and radiation exposure.

Fixed systems are accompanied by floating angiography tables, which allow the surgeon to move the patient easily beneath the fixed image intensifier. The variable distance between the x-ray tube and the image intensifier allows the intensifier to be placed close to the patient if desired, thereby improving image quality and decreasing radiation scatter. It is generally accepted that such systems afford the surgeon the most control and permit the most effective imaging of patients.

Fixed ceiling-mounted systems are quite expensive (typically \$1 to \$1.5 million), and major structural renovations are often required for installation in a typical OR. These systems are not particularly flexible. The floating angiography tables and the immobility of the image intensifiers render the rooms unsuitable for most conventional open surgical procedures. As a result, fixed imaging systems are generally restricted to high-volume centers where use rates justify the construction of dedicated endovascular ORs.

The imaging capability and versatility of portable digital C-arms have increased dramatically. State-of-the-art portable C-arms are considerably less expensive than fixed systems (\$175,000 to \$225,000) while retaining many of their advantages. The variable image intensifier size (from 6 to 12 in.) offers valuable flexibility, with excellent resolution at the smaller end and an adequate field of view at the larger end. With some portable C-arm systems, it is possible to vary the distance between the image intensifier and the x-ray tube, as with a fixed system (see above). Pulsed fluoroscopy, image collimation, and filtration are standard features for improving imaging and decreasing radiation exposure. Sophisticated software packages allow high-resolution digital subtraction angiography, variable magnification, road mapping (i.e., the superimposition of live fluoroscopy over a saved digital arteriogram), image fusion, and a number of other useful features. Improvements in C-arm design allow the surgeon to

use a foot pedal to select various imaging and recording modes and to play back selected images and sequences.

Unlike fixed systems, which require patients to be moved on a floating table to change the field of view, C-arm systems require the image intensifier to be moved from station to station over a fixed patient. Although more cumbersome than fixed systems, the newest C-arms have increased mobility and maneuverability. Patients must be placed on a special nonmetallic carbon fiber table. To provide a sufficient field of view and permit panning from head to toe, the tables must be supported at one end and completely clear beneath. Although these tables do not flex, they are sufficient for most operations. Furthermore, they are mobile and may be replaced with conventional operating tables when the endovascular suite is being used for standard open surgical procedures.

Interventional Equipment

The performance of endovascular procedures in the OR requires familiarity with a wide range of devices that may be unfamiliar to OR personnel. These include guidewires, sheaths, specialized catheters, angioplasty balloons, stents, and stent grafts [see Table 3]. In a busy endovascular OR, much of this equipment must be stocked for everyday use, with the remainder ordered on a case-by-case basis. The expense of establishing the necessary inventory of equipment can be substantial and can place a considerable burden on smaller hospitals that are already spending sizable amounts on stocking similar devices for their catheterization laboratories and interventional suites. Fortunately, many companies are willing to supply equipment on a consignment and case basis, allowing hospitals to pay for devices as they are used and reducing the volume of devices stocked.

ORs in Other Specialties

Specialty equipment is generally available for permanent installation in ophthalmologic, orthopedic, trauma, neurosurgical, and urologic ORs. The observations offered regarding microscopes, imaging devices and lasers, storage, and physical layout are broadly applicable. The cardiovascular OR and the neurosurgical OR often have complex needs that are more difficult to fill simply by equipping a general-purpose OR. Thus, a neurosurgical OR may need to be equipped for neuronavigation, laser and microsurgery, intraoperative angiography, neurointerventional surgery, and pediatric surgery. In addition, it may need shielding for neurophysiologic recordings necessary for cranial electrostimulation. The presence of fixed or mounted instrumentation per se rarely poses an insurmountable difficulty in adapting a general-purpose OR to specialty use, but the reverse is not the case.

Surgeon's Control of Equipment: Touch Panels, Voice Activation, and Robotics

Inherent shortcomings in the design of OR equipment have been exacerbated by the spread of minimally invasive procedures. Because most of the equipment needed for minimally invasive surgery resides outside the sterile field, the circulating nurse becomes the point person for critical control. Often the circulating nurse is out of the room at the precise moment important equipment adjustments must be made.

Surgeons grow frustrated at the inevitable delays that follow, and nurses often weary of these additional and sometimes distracting responsibilities. As a result, there is great

Table 3 Standard Equipment for Endovascular Operating Rooms

Diagnostic arteriography	Entry needle (16-gauge beveled) Entry wire (J wire or floppy-tip wire) Arterial sheath (5 Fr) Catheters Multipurpose nonselective (pigtail, tennis racquet, straight, etc.) Selective (cobra head, shepherd's crook, etc.) Guidewires (floppy, steerable, angled, hydrophilic, etc.) Contrast agent (nonionic preferred) Power injector
Balloon stent angioplasty	Sheaths (various lengths and diameters) Guide catheters Balloons (various lengths and diameters) Stents Balloon expandable (various lengths and diameters) Self-expanding (various lengths and diameters) Inflation device
Endovascular aneurysm repair	Large-caliber sheaths (12–24 Fr) Super-stiff guidewires Endovascular stent grafts Main body and contralateral iliac limb Aortic and iliac extension grafts Endovascular arterial coils

interest in improving the interface of surgical devices with the surgeon. Sterile touchscreens offered the first solution, but many two-handed surgical procedures still make it difficult for a surgeon to control ancillary equipment manually. Voice activation technology offers a potential solution.

Development of voice activation began in the late 1960s. The goal was a simple, safe, and universally acceptable voice recognition system that flawlessly carried out the verbal requests of the user. However, attempts to construct a system capable of accurately recognizing a wide array of speech patterns faced formidable technological hurdles that are only now beginning to be overcome.

In 1998, the first Food and Drug Administration (FDA)-approved voice activation system, Hermes (Computer Motion, Santa Barbara, CA), was introduced into the OR. Designed to provide surgeons with direct access and control of surgical devices, Hermes is operated via either a handheld pendant or voice commands from the surgeon. The challenges of advanced laparoscopic surgery provide a fertile ground for demonstrating the benefits of voice activation [see *Table 4*].

Voice activation offers surgeons immediate access to and direct control of surgical devices. At the same time, it

provides the OR team with critical information about the progress of the operation. To operate a device, the surgeon must take approximately 20 minutes to train the recognition system to his or her voice patterns and must wear an audio headset to relay commands. The learning curve for voice control is minimal (two or three cases, on average). Devices that can now be controlled by voice activation software include cameras, light sources, digital image capture and documentation devices, printers, insufflators, OR ambient and surgical lighting systems, operating tables, and electrocauteries.

Infection Control in the OR

Infection control is a major concern in health care in general, but it is a particularly important issue in the sterile environment of the OR, where patients undergo surgical procedures and are at significant risk for perioperative nosocomial infection. Even the best OR design will not compensate for improper surgical technique or failure to pay attention to infection prevention.

Surgical site infection (SSI) is a major cause of patient morbidity, mortality, and health care costs. In the United States, according to the Centers for Disease Control and Prevention (CDC), approximately 2.9% of nearly 30 million

Table 4 Benefits of Voice Activation Technology in the Laparoscopic Operating Room

Benefits to surgical team	Gives surgeons direct and immediate control of devices Frees nursing staff from dull, repetitive tasks Reduces miscommunication and frustration between surgeons and staff Increases OR efficiency Alerts staff when device is malfunctioning or setting off alarm
Benefits to hospital	Saves money, allowing shorter, more efficient operations Contributes to better OR use and, potentially, performance of more surgical procedures Lays foundation for expanded use of voice activation in ORs Allows seamless working environment
Benefit to patient	Reduces operating time, which—coupled with improved optics, ergonomics, and efficiency—leads to better surgical outcome

OR = operating room.

operations are complicated by SSIs each year. This percentage may, in fact, be an underestimate, given the known inherent problems with surgeons' voluntary self-reporting of infections occurring in the ambulatory surgical setting.⁸⁰ Each infection is estimated to increase total hospital stay by several days and add materially to costs and charges.

SSIs pose an increasingly difficult problem for institutions with a large Medicare population. Recently, the Centers for Medicare and Medicaid Services (CMS) published the Inpatient Prospective Payment System (IPPS) FY 2009 final rule expanding the list of hospital-acquired conditions (HACs) that will reduce Medicare payments. A number of SSIs figure prominently on this list.⁸¹ State Medicaid directors have also been authorized to deny payment for certain HACs.

The epidemiology and management of SSIs in older adults are receiving increasing attention.⁸² SSIs have been divided by the CDC into three broad categories: superficial incisional SSI, deep incisional SSI, and organ or space SSI [see Table 5 and 1:1 *Prevention of Postoperative Infection*].⁸³

Factors that contribute to the development of SSI include (1) the patient's health status, (2) the physical environment where surgical care is provided, and (3) clinical interventions that increase the patient's inherent risk. Careful patient selection and preparation, including judicious use of antibiotic prophylaxis, can decrease the overall risk of infection, especially after clean-contaminated and contaminated operations.

HAND HYGIENE

Hand antisepsis plays a significant role in preventing nosocomial infections. When outbreaks of infection occur in the perioperative period, careful assessment of the adequacy of hand hygiene among OR personnel is important. Agents used for surgical hand scrubs should substantially reduce microorganisms on intact skin, contain a nonirritating antimicrobial preparation, possess broad-spectrum activity, and be fast-acting and persistent.⁸⁴ The CDC offers the following guidelines⁸⁵:

- Surgical hand antisepsis using either an antimicrobial soap or an alcohol-based hand rub with persistent activity is recommended before donning sterile gloves when performing surgical procedures (evidence level IB).
- When performing surgical hand antisepsis using an antimicrobial soap, scrub hands and forearms for the length of time recommended by the manufacturer, usually 2 to 6 minutes. Long scrub times (e.g., 10 minutes) are not necessary (evidence level IB).
- When using an alcohol-based surgical hand-scrub product with persistent activity, follow the manufacturer's instructions. Before applying the alcohol solution, prewash hands and forearms with a nonantimicrobial soap and dry hands and forearms completely. After application of the alcohol-based product, allow hands and forearms to dry thoroughly before donning sterile gloves.

GLOVES AND PROTECTIVE BARRIERS

There is a high risk of pathogen transfer during surgery. This is a risk from which both the patient and the surgical team must be protected. The risk can be reduced by using protective barriers, such as surgical gloves. Wearing two pairs

of surgical gloves rather than a single pair provides an additional barrier and further reduces the risk of contamination. A 2002 Cochrane Review concluded that wearing two pairs of latex gloves significantly reduced the risk of hand exposure. The rate of single-glove perforations is approximately 15%. The rate of inner glove perforation when two pairs of gloves are worn is approximately 5%.⁸⁶

OSHA requires that personal protective equipment be available in the health care setting, and these requirements are specified in the OSHA standard on occupational exposure to bloodborne pathogens, which went into effect in 1992. Among the requirements is the implementation of the CDC's universal precautions, designed to prevent transmission of HIV, hepatitis B virus, and other bloodborne pathogens.⁸⁷ These precautions dictate the use of protective barriers (e.g., gloves, gowns, aprons, masks, and protective eyewear) to reduce the risk that the health care worker's skin or mucous membranes will be exposed to potentially infectious materials.

Performance standards for protective barriers are the responsibility of the FDA's Center for Devices and Radiological Health. FDA standards define the performance properties that these products must exhibit, including minimum strength, barrier protection, and fluid resistance. The current CDC recommendation is to use surgical gowns and drapes that resist liquid penetration and remain effective barriers when wet.

These standards are intuitively appealing, but few studies address the comparative benefits of specific types of drapes. A meta-analysis of over 5,000 surgical cases indicated that adhesive drapes increase the risk of SSI (relative risk = 1.23; $p = .03$) and iodine-impregnated drapes had no effect.⁸⁸

Compliance with universal precautions and barrier protection is a challenge. Educational efforts aimed at OR personnel improved compliance significantly, particularly with regard to the use of protective eyewear and double-gloving. These efforts were associated with a reduced incidence of blood and body fluid exposure.⁸⁹

ANTIMICROBIAL PROPHYLAXIS

SSIs are established several hours after contamination.⁹⁰ There is a well-recognized "golden period" during which prophylactic antibiotics can be effective. Administration of antibiotics before contamination reduces the risk of infection but is subsequently of little value.⁹¹ Selective use of short-duration, narrow-spectrum antibiotic agents should be considered for appropriate patients to cover the usual pathogens isolated from SSIs [see Table 6].⁹²

Recommendations for antibiotic prophylaxis are addressed in more detail elsewhere [see 1:1 *Prevention of Postoperative Infection*]. In brief, the principles of optimal surgical antimicrobial prophylaxis include (1) appropriate choice of an antimicrobial agent, (2) proper timing of antibiotic administration before incision, and (3) limited duration of antibiotic administration after operation.

When a preoperative antibiotic is indicated, a single dose of therapeutic strength, administered shortly before incision, usually suffices.⁹³ The dose may have to be increased if the patient is morbidly obese.⁹⁴ A second dose is indicated if the procedure is longer than two half-lives of the drug or if extensive blood loss occurs. Continuation of prophylaxis beyond 24 hours is not recommended.

Table 5 Criteria for Defining a Surgical Site Infection⁸³

Superficial incisional SSI

Infection occurs within 30 days after the operation, *and* infection involves only skin or subcutaneous tissue of the incisions, *and* at least *one* of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat; *and* superficial incision is deliberately opened by surgeon, *unless* incision is culture negative
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician

Do *not* report the following conditions as SSI:

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration)
2. Infection of an episiotomy or newborn circumcision site
3. Infected burn wound
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI)

Note: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds.

Deep incisional SSI

Infection occurs within 30 days after the operation if no implant* is left in place or within 1 yr if an implant is in place and the infection appears to be related to the operation, *and* infection involves deep soft tissues (e.g., fascial and muscle layers) on the incision, *and* at least *one* of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever ($> 38^{\circ}\text{C}$ [100.4°F]), localized pain, or tenderness, unless the site is culture negative
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician

Notes

1. Report infection that involves both superficial and deep incision sites as deep incisional SSI
2. Report an organ/space SSI that drains through the incision as a deep incisional SSI

Organ/space SSI

Infection occurs within 30 days after the operation if no implant* is left in place or within 1 yr if an implant is in place and the infection appears to be related to the operation, *and* infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation, *and* at least *one* of the following:

1. Purulent drainage from a drain that is placed through a stab wound[†] into the organ/space
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of an organ/space SSI by a surgeon or attending physician

SSI = surgical site infection.

*National Nosocomial Infection Surveillance definition; a non-human-derived implantable foreign body (e.g., prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during surgery.

[†]If the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth.

The provision of prophylactic antibiotics, where indicated, has been accepted as a measure of surgical quality aimed at a reduction in SSIs.^{95,96} A strong economic case has been made for infection control, including prophylactic antibiotics, benefiting the hospital as well as the patient.⁹⁷ The perioperative nursing team has a central role, together with the anesthesiologist, in monitoring the administration of preoperative prophylactic antibiotics.^{98–100}

NONPHARMACOLOGIC PREVENTIVE MEASURES

Several studies have confirmed that certain nonpharmacologic measures, including maintenance of perioperative normothermia and provision of supplemental perioperative oxygen, are efficacious in preventing SSIs.¹⁰¹

Perioperative Normothermia

A 1996 study showed that warming patients during colorectal surgery reduced infection rates.¹⁰² This finding was confirmed in a subsequent observational cohort study that reported a significantly increased incidence of SSI with hypothermia.¹⁰³ A randomized, controlled trial of 421 patients,

published in 2001, determined that warming patients before short-duration clean procedures (breast, varicose vein, or hernia) reduced infection ($p = .001$) and reduced wound scores ($p = .007$) in this setting as well.¹⁰⁴

The safest and most effective way of protecting patients from hypothermia is to use forced-air warmers with specialized blankets placed over the upper or lower body. Alternatives include placing a warming water mattress under the patient and draping the patient with an aluminized blanket. Second-line therapy involves warming all IV fluids. Any irrigation fluids used in a surgical procedure should be at or slightly above body temperature before use. Radiant heating devices placed above the operative field may be especially useful during operations on infants. Use of a warmer on the inhalation side of the anesthetic gas circuit can also help maintain the patient's body temperature during an operation.

Supplemental Perioperative Oxygen

Destruction by oxidation, or oxidative killing, is the body's most important defense against surgical pathogens. This

Table 6 Distribution of Pathogens Isolated from Surgical Site Infections: National Nosocomial Infections Surveillance System, 1986–1996⁸³

Pathogen	Percentage of Isolates*	
	1986–1989 (N = 16,727)	1990–1996 (N = 17,671)
<i>Staphylococcus aureus</i>	17	20
Coagulase-negative staphylococci	12	14
<i>Enterococcus</i> species	13	12
<i>Escherichia coli</i>	10	8
<i>Pseudomonas aeruginosa</i>	8	8
<i>Enterobacter</i> species	8	7
<i>Proteus mirabilis</i>	4	3
<i>Klebsiella pneumoniae</i>	3	3
Other <i>Streptococcus</i> species	3	3
<i>Candida albicans</i>	2	3
Group D streptococci (nonenterococci)	—	2
Other gram-positive aerobes	—	2
<i>Bacteroides fragilis</i>	—	2

*Pathogens representing less than 2% of isolates are excluded.

defensive response depends on oxygen tension in contaminated tissue. An easy method of improving oxygen tension in adequately perfused tissue is to increase the FiO_2 . Supplemental perioperative oxygen (i.e., an FiO_2 of 80% instead of 30%) significantly overcomes the decrease in phagocytosis and bacterial killing usually associated with anesthesia and surgery (and significantly reduces postoperative nausea and vomiting). Oxygen tension in wound tissue has been found to be a good predictor of SSI risk.¹⁰⁵

Avoidance of Blood Transfusion

The association between blood transfusion and increased perioperative infection rates is well documented. In a 1997 study, geriatric hip fracture patients undergoing surgical repair who received blood transfusion had significantly higher rates of perioperative infection than those who did not (27% versus 15%), and this effect was confirmed on multivariate analysis.¹⁰⁶ Another study yielded similar findings in colorectal cancer: the relative risk of infection was 1.6 for transfusion of one to three units of blood and 3.6 for transfusion of more than three units.¹⁰⁷

A large prospective cohort study published in 2003 evaluated the association between anemia, blood transfusion, and perioperative infection.¹⁰⁸ Regression analysis confirmed that intraoperative transfusion of packed red blood cells was an independent risk factor for perioperative infection (odds ratio 1.06; confidence interval 1.01 to 1.11; $p > .0001$). Furthermore, transfusion of more than four units of packed red blood cells was associated with a ninefold increased risk of infection (confidence interval 5.74 to 15.00; $p < .0001$).

Tight Glycemic Control

Hyperglycemia is common under conditions of physiologic stress, in the intensive care unit (ICU) and in the OR. Tight glycemic control using intensive insulin therapy and continuous glucose monitoring has been shown to reduce infection in the ICU and is emerging as a standard in surgical critical care and intraoperatively.^{109,110} It has been associated with a

decrease in mortality rate generally in critically ill patients.^{111,112} The effects are not restricted to diabetics. In fact, there is evidence to conclude that nondiabetics enjoy more protection than diabetics.¹¹³

Some questions remain about just how tight control must be to have an effect. There is a small but measurable risk of hypoglycemia with intensive IV insulin therapy, but this risk can be mitigated with continuous or near-continuous glucometry or dynamic scale nomograms.¹¹⁴

Housekeeping Procedures

FLOORS AND WALLS

Despite detailed recommendations for cleaning the OR [see Table 7], the procedures that are optimal to provide a clean environment while still being cost-effective have not been critically analyzed.¹¹⁵

Only a few studies have attempted to correlate surface contamination of the OR with SSI risk. In one randomized, controlled study, for example, the control rooms were cleaned with a germicidal agent and wet-vacuumed before the first case of the day and between cases, whereas in the experimental rooms, cleaning consisted only of wiping up grossly visible contamination after clean and clean-contaminated cases.¹¹⁶ Both rooms had complete floor cleanup after contaminated or dirty and infected cases. Bacterial colony counts obtained directly from the floors were lower in the control rooms, but counts obtained from other horizontal surfaces did not differ between the two OR groups. Wound infection rates were the same in the control rooms and the experimental rooms and were comparable with rates reported in other series.

Another study found that floor disinfectants decreased bacterial concentration on the floor for 2 hours only. Colony counts return to pretreatment levels as personnel walked about.¹¹⁷

Even when an OR floor is contaminated, the rate of redispersal of bacteria into the air is low, and the clearance rate is

Table 7 Operating Room Cleaning Schedules

Areas requiring daily cleaning	Surgical lights and tracks Fixed ceiling-mounted equipment Furniture and mobile equipment, including wheels OR and hall floors Cabinet and push-plate handles Ventilation grills All horizontal surfaces Substerile areas Scrub and utility areas Scrub sinks
Areas requiring routinely scheduled cleaning	Ventilation ducts and filters Recessed tracks Cabinets and shelves Walls and ceilings Sterilizers, warming cabinets, refrigerators, and ice machines

OR = operating room.

high. It seems unlikely, therefore, that bacteria from the floor contribute to SSI. Consequently, routine disinfection of the OR floor between clean or clean-contaminated cases appears to be unnecessary.

According to CDC guidelines for the prevention of SSI, when visible soiling of surfaces or equipment occurs during an operation, an Environmental Protection Agency (EPA)-approved hospital disinfectant should be used to decontaminate the affected areas before the next operation.⁸³ This statement is in keeping with the OSHA requirement that all equipment and environmental surfaces be cleaned and decontaminated after contact with blood or other potentially infectious materials.

Disinfection after a contaminated or dirty case and after the last case of the day is probably a reasonable practice, although it is not supported by directly pertinent data. Wet-vacuuming of the floor with an EPA-approved hospital disinfectant should be performed routinely after the last operation of the day or night.

DIRTY CASES

Operations are classified or stratified into four groups in relation to the epidemiology of SSIs [see 1:1 *Prevention of Postoperative Infection*]¹¹⁸:

- Clean operations are those elective cases in which the gastrointestinal (GI) tract or the respiratory tract is not entered and there are no major breaks in technique. The infection rate in this group should be less than 3%.
- Clean-contaminated operations are those elective cases in which the respiratory or the GI tract is entered or during which a break in aseptic technique has occurred. The infection rate in such cases should be less than 10%.
- Contaminated operations are those cases in which a fresh traumatic wound is present or gross spillage of GI contents occurs.
- Dirty or infected operations include those in which bacterial inflammation occurs or in which pus is present. The infection rate may be as high as 40% in a contaminated or dirty operation.

Fear that bacteria from dirty or heavily contaminated cases could be transmitted to subsequent cases has resulted in the

development of numerous and costly rituals of OR cleanup. However, there are no prospective studies and no large body of relevant data to support the usefulness of such rituals. In fact, one study found no significant difference in environmental bacterial counts after clean cases than after dirty ones.¹¹⁹ Numerous authorities have recommended that there be only one standard of cleaning the OR after either clean or dirty cases.^{115,119,120} This recommendation is reasonable because of two important considerations:

- Any patient may be a source of contamination caused by unrecognized bacterial or viral infection.
- The second major source of OR contamination is the personnel who work there.

Rituals applied to dirty cases include placing a germicide-soaked mat outside the OR door, allowing the OR to stand idle for an arbitrary period after cleanup of a dirty procedure, and using two circulating nurses, one inside the room and one outside. None of these practices has a sound theoretical or factual basis.

By tradition, dirty cases are scheduled after all of the clean cases of the day have been completed. This restriction, however, reduces the efficiency with which operations can be scheduled and may unnecessarily delay emergency cases. There are no data to support special cleaning procedures or the closing of an OR after a contaminated or dirty operation has been performed.¹²¹ Mats placed outside the entrance to the OR suite show neither a reduction in the number of organisms on shoes and stretcher wheels nor a reduction in SSI risk.¹²²

Data Management in the OR

Regular analysis of OR data is essential to monitor efficiency and correct deficiency.¹²³ OR efficiency is maximized by adherence to several basic principles:

1. The number of ORs available should be matched to the number required to achieve good use.
2. Nurses and anesthesiologists rather than attending surgeons should control access to the surgical schedule.
3. Surgeons should be allowed to follow themselves.

4. Block time should be provided to surgeons.
5. Systems should be established to enable and enforce efficient turnover between cases.¹²⁴

The distinction between efficiency and effectiveness is important. Measures of effectiveness relate achievements to goals. Measures of efficiency relate achievements to cost. The OR must be both efficient and effective.

Data must be both available and rapidly accessible. Automation of OR data is critical and must integrate with the institutional health information system (HIS).¹²⁵ Hospital-wide data regarding work flow, staffing, referral patterns, and even parking may yield useful information for improvements in OR efficacy and efficiency.¹²⁶

OR SCHEDULING

OR scheduling systems should be designed to track all of the operational aspects of the OR, including patients, resources, rooms, and staff. They should be fully integrated into the institutional HIS while also interfacing with key elements located in other parts of the hospital (or ambulatory center), including finance, materials management, electronic medical records, radiology, pathology, nursing, the emergency room, labor and delivery, the blood bank, and the pharmacy.

One of the most important purposes of a good OR scheduling system is to allow informed case substitution. Informed case substitution is critical because surgical scheduling must contend with frequent last-minute case cancellations.¹²⁷ Different specialties differ widely in their scheduling practices. An understanding of these practices allows the OR to use resources to maximum efficiency.¹²⁸

Information systems that predict and fill unexpected openings already exist in the transportation and manufacturing

industries. In the future, such technology may be a useful adjunct to computerized OR scheduling.¹²⁷

QUALITY IMPROVEMENT

The key to increased OR efficiency is increased productivity. Standardization of internal procedures reduces bottlenecks. Computerization speeds the flow of information so that continuous improvement of the system becomes possible. Before a desired improvement can be implemented, the proposed change must be tested quickly so that its effect can be determined, ideally through a small-scale pilot implementation. This requires a collaborative effort, in which the group involved in the change learns how to “plan, do, check, and act.” These are the elements of the so-called “PDCA cycle,” a classic quality initiative method. During the PDCA cycle, teams are encouraged to strategize and communicate about various solutions and look for changes that can be made. A change is tested, quickly evaluated, and adopted if efficacious. The PDCA cycle depends on integrated surgical teams with open communication and mutual respect. Such teams remain the key to a safe, efficient, and effective OR.⁸⁹

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9 FAST TRACK INPATIENT AND AMBULATORY SURGERY

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Fast track (also known as accelerated recovery, accelerated rehabilitation, enhanced recovery, or multimodal rehabilitation) surgery involves the use of a coordinated, multidisciplinary perioperative care plan to reduce complications, facilitate earlier discharge from the hospital, and permit faster recovery of the ability to carry out daily activities after elective surgery.¹ This approach is the result of advancements in anesthetic techniques, improved understanding of perioperative organ dysfunction, and the introduction of minimally invasive surgery (MIS). Attenuation of the stress response to surgery (endocrine, metabolic and immunologic) and consequent prevention of some of its negative effects (e.g., increased cardiac demands, decreased gastrointestinal [GI] motility, and pain) underlie many of the benefits of fast track surgery.²

A unifying theme in the development and implementation of fast track surgery is the quest to understand and address the factors that keep patients hospitalized after major surgery and impede their return to baseline performance and function.³ These interrelated factors include the need for parenteral analgesia, the requirement for intravenous (IV) fluids, and lack of mobility.⁴ Whereas some of these factors have a physiologic basis (e.g., decreased GI motility from the sympathetic response to surgery), others are related to traditions or cultural aspects of the care of surgical patients (e.g., waiting for GI motility to return before introducing oral intake). The goal is to combine a variety of individual evidence-based elements of perioperative care, each of which may have only modest benefits when used in isolation, into a coordinated effort that can be expected to have a synergistic beneficial effect on surgical outcomes.⁵ The term fast track has contributed to the misconception that the primary goal of this approach is cost containment through the reduction of hospital stay; however, the primary goals are in fact to shorten recovery time, decrease morbidity, and improve efficiency.^{6,7} The principles of fast track surgery are applicable to both outpatient and inpatient procedures: many procedures that once necessitated hospitalization are now routinely performed in an ambulatory or short-stay setting.

A fast track surgery program encompasses preoperative, intraoperative, and postoperative phases. The principal elements are as follows.

1. Preoperative patient education and preparation for surgery (“prehabilitation”).
2. Newer anesthetic, analgesic, and surgical techniques, whose aim is to decrease the surgical stress response, pain and discomfort, and postoperative nausea and vomiting.
3. Aggressive postoperative rehabilitation, including early enteral feeding and ambulation. This also includes changes

in the traditional surgical practice concerning the use of drains, tubes and catheters.

Some of these individual elements may be part of evidence-based modern surgical care, but there remains a great deal of variability among surgeons and institutions.⁸ Introduction of one or more components in isolation may improve some specific outcomes, but the underlying hypothesis in fast track surgery is that a multimodal approach to care will enhance outcomes further.⁴ Although few data are available, the existing evidence is encouraging and suggests that fast track programs are associated with reductions in hospital stay and morbidity.⁶ Successful implementation of a formal fast track program at the institutional level, however, requires significant resources and time and involves an organized and coordinated effort on the part of a motivated multidisciplinary team that includes anesthesiologists, surgeons, nurses, physiotherapists, social workers, nutritionists, and patients. This represents a shift from conventional surgical practice, in which perioperative management is primarily dictated by the surgeon’s preference.

In this chapter, we describe the constituent elements of a fast track surgery program. We review the organizational steps required to set up such a program and provide specific examples of care plans in digestive surgery.

Preoperative Issues

PHYSICAL OPTIMIZATION

Evaluation and Optimization of Preexisting Organ Function

Postoperative complications are related to preoperative comorbid conditions,⁹ including inadequate nutrition.¹⁰ Classification of functional capacity and optimization of organ function are expected to reduce cardiovascular and other complications. The preoperative evaluation is also an opportunity to improve long-term health apart from surgical considerations—for example, by counseling patients who may benefit from long-term beta blockade, smoking cessation, or tightened glycemic control. A substantive discussion of cardiopulmonary risk assessment and reduction is beyond the scope of this chapter; however, various current guidelines and algorithms are available for assessment and reduction of perioperative risk related to cardiac disease,¹¹ pulmonary complications,¹² obesity,¹³ and diabetes.¹⁴

The perioperative period provides smokers with a good opportunity to quit. Smoking increases the risk of cardiac, respiratory, and wound complications,¹⁵ and abstinence reduces complications.^{16,17} Although reduction of pulmonary complications requires an abstinence period of weeks to

months, cardiac and wound complications are reduced after shorter periods.¹⁵ Smokers should be advised to quit and referred to resources that will help them do so.

Assessment and Optimization of Nutritional Status

Poor nutritional status is an independent risk factor for complications after surgery. Patients with moderate and severe preoperative undernutrition benefit from preoperative nutritional support, preferably via the enteral route, for at least 7 days preoperatively.^{10,18} Patients with less severe malnutrition, including those with diminished oral intake as a consequence of their underlying disease, generally benefit from the addition of oral nutritional supplements to their normal diet.

Improvement of Physical Fitness

The perioperative period may be associated with rapid physical deconditioning, requiring a period of recovery during which patients are fatigued and quality-of-life and activities are curtailed. Given that patients with poor baseline exercise tolerance and physical conditioning are at increased risk for serious perioperative complications^{11,19} and prolonged disability,^{20,21} it seems reasonable to hypothesize that improving functional capacity by increasing physical activity before surgery may be protective.²² Physical fitness can potentially be improved significantly while patients are waiting for scheduled procedures: modest improvements in aerobic capacity may be seen in older adults after training only 1 hour a day, four times a week, for 4 weeks.²³ The strategy of augmenting physical capacity in anticipation of an upcoming stressor is termed prehabilitation—as opposed to rehabilitation, which begins only after the injury or operation has taken place.

Preliminary evidence supports the use of exercise prehabilitation before surgery. In one study, adults randomly assigned to exercise for 1 month showed faster healing of a punch-biopsy site than control subjects did.²⁴ In another, a preoperative exercise program carried out by patients awaiting lung cancer surgery improved exercise capacity to a degree that mitigated the expected postsurgical decline.²⁵ In yet another study, patients receiving twice-weekly exercise training while waiting for coronary artery bypass graft surgery (CABGS) had shorter hospital stays and better preoperative and postoperative quality of life than control subjects; the quality-of-life differences remained for up to 6 months after surgery.²⁶ Observational data suggest that simply instructing patients to walk 30 minutes daily in the perioperative period may be beneficial, without the need for a formal individualized exercise program (F. Carli and associates, unpublished data).

Preoperative Fasting

To reduce the risk of tracheal aspiration of gastric contents at the induction of general anesthesia, patients have traditionally had to refrain from oral ingestion of both solids and liquids (nil per os [NPO]) from midnight of the night before the operation. This standard approach is convenient and easy to follow, but it requires patients to spend a long period without hydration or nutrition, especially for operations scheduled in the afternoon. Solids may present a risk, but there is no evidence that oral intake of water and other clear fluids (e.g., tea, coffee, apple juice, and pulp-free orange

juice) up to 2 hours preoperatively increases gastric fluid volume or exacerbates the risk of aspiration in otherwise healthy adults.^{27,28} Current preoperative fasting guidelines for adult patients undergoing elective surgery recommend a 2-hour fast for liquids and a 6-hour fast for solids.²⁹ These recommendations do not apply to patients with delayed gastric emptying (e.g., from gastroparesis, GI obstruction, or upper GI tract malignancy).

Preoperative Ingestion of Oral Carbohydrate Drink

That it is safe to administer fluids up to 2 hours before surgery enables the use of high-carbohydrate drinks immediately before operation. Emerging evidence suggests that it may be beneficial to provide a drink containing 100 g of carbohydrate the evening before surgery and a second drink containing a further 50 g 2 to 3 hours before induction of anesthesia. This measure improves preoperative feelings of thirst, hunger, and anxiety³⁰; reduces postoperative insulin resistance; and reduces the catabolic stress response to surgery.³¹ Compared with control subjects, patients receiving preoperative oral carbohydrate drinks had less muscle loss³² and better whole-body protein balance³³ after major abdominal surgery and had shorter hospital stays after colorectal surgery.³⁴ Preoperative carbohydrate drinks reduced nausea and vomiting after laparoscopic cholecystectomy in one trial³⁵ but not in another.³⁶

PATIENT EDUCATION

Preoperative patient education is an essential component of fast track surgery. For many patients, impending major surgery represents a significant psychological stress. Greater preoperative emotional distress, depression, and anxiety are associated with poorer operative outcomes, including increased pain, higher complication rates, poorer wound healing, longer hospital stays, slower return to normal daily activities, and reduced patient satisfaction.^{37,38} There is evidence that emotional distress delays wound healing by altering endocrine and inflammatory responses.^{39,40} The results from meta-analyses suggest that preoperative patient education and preparation have positive effects on certain outcomes (e.g., pain, psychological distress, and indexes of recovery, including hospital stay), even if the intervention is relatively brief and not individualized.⁴⁰ For example, patients who watched a video involving an actor outlining aspects of perioperative care after inguinal hernia surgery experienced improved quality of life and faster resumption of baseline activities in comparison with control subjects.⁴¹

Patient expectation may also play a role in determining postoperative outcome.⁴² Because the fast track recovery program may differ from patients' and caregivers' expectations for and previous experiences with hospitalization and surgery, it is important to specify the active role the patient is expected to play. Such specification includes providing explicit written information about the benefits of the program, the goals for daily nutritional intake and ambulation in the early postoperative period, the discharge criteria, and the expected hospital stay. Information about sensory experiences (e.g., pain, nausea and vomiting, and fatigue) are included in the discussion and the written materials, as well as guidelines regarding what to expect once they leave the hospital.

PREMEDICATION

In the past, preanesthetic medication was administered with the intent of providing sedation and reducing anxiety. Today, with the advent of same-day admission and fast track surgery, premedication may play additional roles, including modulation of intraoperative hemodynamics and attenuation of postoperative side effects.⁴³

Benzodiazepines are excellent anxiolytics that possess rapid onset of action and are flexible in use, being available in both IV and oral forms. Doses as small as 2 mg effectively reduce anxiety and anxiety-related complications.⁴⁴ They also reduce the amount of anesthetic required and provide comfort. Opioids such as morphine and meperidine are no longer for premedicants in outpatient settings, because of the prolonged duration of action and the high incidence of side effects. Fentanyl has a better profile for fast track surgery and facilitates early hospital discharge. Acetaminophen and cyclooxygenase-2 (COX-2) inhibitors (e.g., celecoxib) can be administered either orally or rectally up to 1 hour before surgery and possess significant perioperative opioid-sparing effects.⁴⁵

Anticholinergics (e.g., atropine and scopolamines) are rarely used today, except for procedures such as laryngoscopy or bronchoscopy, in which reduction of secretions is required. These compounds are not given to elderly patients, because they may trigger delirium; rather, glycopyrrolate (0.3 mg IV), which does not cross the blood-brain barrier, is preferred.

Beta blockers and alpha₂ agonists can be used as adjuvants to fast track anesthetic techniques. With their anesthetic and analgesic-sparing effects,^{46–49} these medications maintain perioperative hemodynamic stability and reduce postoperative pain, thus facilitating the early recovery process. Beta blockers (e.g., propranolol, atenolol, labetalol, esmolol) attenuate the intraoperative rise in circulating concentrations of catecholamines, promote hemodynamic stability during emergence from anesthesia and in the early postoperative period, and prevent perioperative cardiovascular events in elderly patients undergoing noncardiac surgery⁵⁰ and patients with preexisting coronary artery disease.^{51,52} In addition, preliminary evidence that beta blockers possess anticatabolic properties and anesthetic and analgesic-sparing effects suggests that they may play a role in accelerating the recovery process.⁵³ Alpha₂ agonists (e.g., clonidine or dexmedetomidine) have also been used as premedicants with the goal of reducing the need for opioid analgesics and attenuating sympathoadrenergic and hypothalamopituitary responses. Clonidine shortens the duration of paralytic ileus after colorectal procedures⁵⁴ and decreases the incidence of postoperative nausea and vomiting (PONV). Both clonidine and dexmedetomidine have been shown to reduce the incidence of myocardial ischemia.⁵⁵

Antacids and H₂-receptor antagonists can be administered before surgery in subjects at risk for gastric aspiration (e.g., those who are diabetic, obese, or pregnant; have gastroesophageal reflux disease; or have sustained a stroke). H₂-receptor antagonists are given the evening before surgery and in the morning to decrease the volume and acidity of gastric content. A nonparticulate antacid (e.g., sodium citrate) is given 1 hour before surgery to raise the gastric pH.

Administration of anti-PONV medications such as dexamethasone and ondansetron before or during the induction and maintenance of anesthesia is recommended in high-risk

subjects and has been shown to facilitate the recovery period and decrease hospital admission after ambulatory surgical procedures.

Intraoperative Issues

ATTENUATION OF SURGICAL STRESS RESPONSE

Surgery initiates a series of metabolic and inflammatory responses that are involved in the pathogenesis of postoperative morbidity and can slow the recovery process. These responses induce a transient but reversible state of insulin resistance, the magnitude of which is linked to the invasiveness of the surgical procedure. This state is characterized by a decrease in peripheral glucose uptake and a concomitant increase in endogenous glucose production. The magnitude of this noxious response can be reduced by perioperative interventions that modify the catabolic response. These interventions can be classified as pharmacologic (high-dose opioids, neural blockade with local anesthetics, beta blockers, glucocorticoids, alpha₂ agonists, nonsteroidal anti-inflammatory drugs [NSAIDs]), hormonal (insulin, growth hormone, estrogens), physical (normothermia, MIS), and nutritional. Among these interventions, intraoperative and postoperative blockade of afferent neural nociceptive stimuli by epidural and spinal block using local anesthetics has been shown to be the most powerful modulator of the metabolic and endocrine stress response. To be effective, however, the neural blockade must be established before surgery and continued for a minimum of 48 hours.⁵⁶

For postoperative pain relief, epidural block achieved with a mixture of local anesthetics and opioids provides excellent postoperative analgesia at rest and during movement compared with systemic opioids,⁵⁷ thus facilitating resumption of dietary intake and utilization of nutrients,⁵⁸ attenuating the loss of body mass, and allowing earlier resumption of exercise.⁵⁹ Epidural block also affects insulin resistance, attenuating the hyperglycemic response, facilitating the oxidative utilization of exogenous glucose,⁶⁰ and thereby preventing the postoperative loss of aminoacids and saving almost 100 g of lean body mass daily.⁶¹ The extent of protein sparing has been found to be greater than that previously achieved with hormonal and nutritional interventions. Epidural block has anticatabolic effects, and patients can be rendered anabolic with the concomitant administration of glucose and aminoacids⁶² or aminoacids alone; the advantage of the latter is that it is not associated with hyperglycemia.^{63–65} Preoperative oral or IV carbohydrate administration also reduces postoperative insulin resistance, thus decreasing postoperative catabolism and resulting in less fatigue.^{66–68}

A single dose of glucocorticoids given at induction of anesthesia decreases the inflammatory response without causing any significant side effects. Beta blockers also reduce cardiac demands and sympathetic stimulation and have been shown to attenuate catabolism in burn patients.⁵³ MIS attenuates the inflammatory response but not the endocrine one. Although it is not clear to what extent MIS modulates catabolism, the administration of dextrose after laparoscopic colon surgery results in a significant suppression of endogenous glucose production (an index of gluconeogenesis), with no protein-sparing capacity.⁶⁹ This implies enhanced whole-body

glucose uptake and greater utilization and oxidation of exogenous glucose. Insulin, growth hormones, and anabolic steroids have been shown to improve wound healing, directing aminoacids toward anabolic pathways to enhance lean tissue synthesis.

ANESTHETIC TECHNIQUES

General Anesthesia

After general anesthesia for fast track surgery, the patient should be able to walk out of the hospital with minimal side effects. Therefore, the choice of anesthetic agents should include fast-acting IV drugs and less soluble volatile anesthetics, along with adjuvants to minimize the side effects.

Propofol is the IV agent of choice for induction of fast track anesthesia.⁷⁰ For maintenance of anesthesia, highly soluble volatile anesthetic agents, such as desflurane and sevoflurane, offer advantages over propofol and isoflurane, in that they facilitate early recovery.^{71–73} Nitrous oxide (50–70%) remains a popular adjuvant during the maintenance period because of its anesthetic- and analgesic-sparing effects, low cost, and favorable pharmacokinetic profile;⁷⁴ however, it is not recommended in subjects at risk for PONV, nor is it suitable for laparoscopic surgery when the operating time is longer than 1 hour. Prolonged use of nitrous oxide causes bowel distention (the so-called gas effect) and predisposes to PONV. When general anesthesia is maintained with volatile anesthetic agents, there is an increased risk of PONV in the early postoperative period; accordingly, it is suggested that low-dose droperidol (0.625 mg) and dexamethasone (4–8 mg) should be used to provide effective antiemetic prophylaxis.⁷⁵ Titration of both IV and inhaled anesthetics using cerebral monitoring devices may also facilitate the fast track process,^{76–79} except in spontaneously breathing patients.⁸⁰

With regard to opioids, fentanyl remains a good choice, though infusion of the ultra-short-acting opioid remifentanyl (0.05–0.15 µg/kg/min) is an increasingly popular alternative for short and painful conditions. Whereas intraoperatively administered fentanyl can maintain some residual effect during the postoperative period, remifentanyl is rapidly metabolized; thus, one must remember that as soon as the remifentanyl infusion ends, the patient can be in serious pain. Long-acting opioids must therefore be administered in due time. The use of nonopioid analgesics (e.g., NSAIDs, [including COX-2 inhibitors], acetaminophen, alpha₂ agonists, glucocorticoids, ketamine, and local anesthetics in the wound) are recommended as part of a multimodal analgesic regimen aimed at reducing opioid-related side effects.^{81,82} Adjuvants such as beta blockers and lidocaine have had some success in reducing opioid use during and after laparoscopic surgery. These compounds represent an alternative to short-acting opioids in controlling for any associated acute autonomic responses.^{83–85}

Short- or intermediate-acting muscle relaxants are used for fast track surgery because they often do not need to be reversed. A novel agent, sugammadex (a cyclodextrin compound),⁸⁶ has been shown to provide faster reversal of nondepolarizing muscle relaxants without anticholinergic side effects,⁸⁷ thus facilitating earlier tracheal extubation and

reducing postoperative respiratory complications as a result of residual muscle paralysis.

In summary, short-acting anesthetic drugs and adjuvants minimize postoperative side effects and enhance the ability to fast track patients after both ambulatory and major inpatient surgical procedures. Not surprisingly, combining short-acting anesthetic techniques with an educational program has been reported to increase fast tracking significantly in ambulatory centers. Although a majority of adults can be fast-tracked after ambulatory surgery under general anesthesia, minimizing patient discomfort and anxiety is critically important for establishing a successful fast track surgery program for all types of elective surgery.

Regional Anesthesia

Regional anesthetic techniques (spinal, epidural, and peripheral nerve blocks) have several advantages over general anesthesia—including improved pulmonary function, decreased cardiovascular demand, a lower incidence of ileus, and good quality of analgesia at rest and on ambulation—both when used in place of GA and when used as adjuvants. The appropriate combination of a local anesthetic with an adjuvant will facilitate readiness for discharge. Consequently, epinephrine should not be added to spinal local anesthetics, because it might delay time to micturition; however, fentanyl in small doses does not interfere with bladder function.^{88,89} Faster recovery of sensory and motor function results when minidose lidocaine (10–30 mg), bupivacaine (3.5–7 mg), or ropivacaine (5–10 mg) spinal anesthetic techniques are combined with a potent opioid analgesic (e.g., fentanyl [10–25 µg] or sufentanil [5–10 µg]).^{90,91} However, postoperative side effects (e.g., pruritus, nausea) are increased when intrathecal opioids are used.

Thoracic epidural blockade is the most effective technique for postoperative analgesia. Whether in the form of a continuous infusion or of patient-controlled analgesia (PCA), epidural analgesia results in better static and dynamic pain relief than IV opioid-based PCA delivery systems.⁹² Epidural block with local anesthetics reduces the endocrine and metabolic responses to surgery, improves pulmonary outcome after major abdominal and thoracic operations (e.g., aortic surgery⁹³ and thoracoabdominal esophagectomy),⁹⁴ and facilitates the return of bowel function, while resulting in better preservation of perioperative nutritional profiles, higher health-related quality-of-life scores, and improved exercise capacity after colon surgery⁵⁹; however, it has not been found to affect the duration of hospitalization. Over the past 20 years, several randomized controlled studies and meta-analyses have been conducted to study the effect of spinal and epidural block on postoperative outcome. One large meta-analysis reported that morbidity and mortality were significantly lower with spinal and epidural analgesia than with general anesthesia and systemic opioid analgesia,⁹⁵ but these benefits could not be demonstrated in several subsequent randomized, controlled trials. However, these studies were not controlled for factors that might influence the stress response, including hypothermia, immunosuppression, hypoxemia, perioperative surgical and nursing care, infection, and the use of drains and tubes. One might therefore assume that the beneficial effects of regional anesthesia on

postoperative mortality and morbidity are most apparent when it is used as part of a multimodal therapeutic regimen in which all evidence-based therapeutic strategies have been put in place.

With regard to some biologic outcome measures, thoracic epidural analgesia with a local anesthetic and administration of opioids reduce ileus and lead to faster discharge after colonic surgery in patients enrolled in a fast track program (i.e., in patients being treated with multimodal techniques that include preoperative preparation, attenuation of the intraoperative stress response, multimodal analgesia, early oral feeding and mobilization, and early removal of drains and tubes).^{6,96} A role for epidural analgesia as part of a multimodal analgesia technique has also been suggested in the setting of fast track cardiac anesthesia,^{97–100} in which epidural local anesthetics have been associated with earlier tracheal extubation, decreased pulmonary complications and cardiac dysrhythmias, reduced postoperative pain and opioid analgesic requirements, shorter stays in the intensive care unit (ICU), and faster recovery of bowel and bladder function.^{101–103} However, with advances in MIS, the perioperative use of mu-receptor antagonists and other analgesia adjuvants, and the advent of fast track accelerated recovery programs in which all surgical, anesthetic, and nursing care elements are revised according to scientific evidence, the role of thoracic epidural technique in some types of surgery must be reconsidered.¹⁰⁴

Incisional Local Anesthesia

Infiltration of local anesthetics into the surgical wound is an effective analgesia technique for minor surgical procedures (e.g., hernia repair, anal surgery, and breast procedures). When possible, local infiltration should be performed before the surgical incision is made and should be a component of all balanced fast track anesthetic techniques.^{105,106} Better analgesia results when the infiltration of local anesthetics is supplemented with a peripheral nerve block (e.g., ileoinguinal block for inguinal hernia repair).¹⁰⁶ Compared with neuroaxial or general anesthetic techniques, local anesthetic infiltration techniques reduce the risk of postoperative urinary retention associated with anorectal surgery¹⁰⁷ and inguinal herniorrhaphy.^{108,109} The instillation of local anesthetics on the visceral peritoneum during laparoscopy has only weak and short-lasting analgesic effects.¹¹⁰

Continuous wound infusion with local anesthetics has been used for abdominal, gynecologic, and thoracic operations, and many studies have shown it to yield improved analgesia, greater patient satisfaction with pain management, reduced PONV, and shorter hospital stay.¹¹¹ Continuous infusion of bupivacaine at the median sternotomy incision site after cardiac surgery not only provides good postoperative pain relief but also allows patients to ambulate earlier, leading to a shorter hospital stay.^{112,113} A systematic review of randomized trials of the efficacy of continuous wound irrigation with local anesthetics for postoperative analgesia demonstrated good analgesia and opioid-sparing, with reduced side effects.¹¹¹ Nevertheless, the quality of analgesia can be highly variable even in a given patient or a given type of surgery, which highlights the difficulty of interpreting the results.

MAINTENANCE OF NORMOTHERMIA

During major surgery, body temperature falls by approximately 1° to 2°C as a result of loss of body heat and inhibition of the thermoregulatory response. Whereas a small drop in core temperature is not a cause for concern in fit and healthy persons, it can be detrimental in elderly, malnourished, or frail persons with cardiorespiratory and metabolic instability. Mild hypothermia elicits a stress response during the recovery period while the patient attempts to regain normothermia by means of shivering and vasoconstriction. It results in increased cardiovascular demands, elevated oxygen consumption, hypoxia, and impaired coagulation and leukocyte formation. Maintenance of intraoperative normothermia with the use of active and passive warming devices in conjunction with aggressive postoperative management of shivering and residual hypothermia decreases the incidence of wound infections, blood loss, myocardial ischemia, and protein breakdown.¹¹⁴

FLUID MANAGEMENT

Intraoperative fluid management strategy remains controversial, in that adverse outcomes may be associated with both inadequate and excessive fluid administration.^{115–117} Inadequate fluid administration can lead to a reduction in effective circulating volume, with diversion of blood towards the brain and heart and away from the gut, skin, and kidneys. Liberal (as opposed to restrictive) IV fluid administration improves gut perfusion and increases left ventricular stroke volume. In contrast, excessive IV fluid administration may result in adverse effects. Excess fluid in the intravascular compartment leads to increased venous pressure and pulmonary and peripheral edema that may compromise peripheral oxygenation. Two studies have suggested that excessive hydration can increase postoperative morbidity and lengthen the hospital stay after major abdominal surgery.^{118,119} In these studies, perioperative water and salt restriction reduced cardiopulmonary and tissue healing complications and prevented hyperchloremic metabolic acidosis after abdominal surgery. On the other hand, after laparoscopic cholecystectomy, large volumes of intraoperative fluid have been associated with reduced side effects (e.g., pulmonary dysfunction, dizziness, drowsiness, thirst, and PONV) and a shorter hospital stay.¹²⁰ Although aggressive crystalloid administration during colorectal surgery improves tissue oxygenation,¹¹⁷ it does not reduce the risk of surgical site infection (SSI).¹²¹

Perioperative fluid administration should take into account preoperative dehydration resulting from fasting and bowel preparation, replacement of blood loss and secretions, and maintenance hydration. The volume and composition of the fluid, together with the type of surgery performed and the patient's hemodynamic requirements, influence the duration and magnitude of intravascular volume expansion. Intraoperative esophageal Doppler monitoring can facilitate goal-directed fluid administration by targeting specific values for the cardiac index. Several studies have been conducted on different types of surgical procedures, and the outcomes have been positive (shorter length of hospital stay, lower incidence of admission to ICU, and fewer complications) when fluid administration was guided by a predetermined stroke volume and filling pressure.^{122,123} Therefore, strategies that avoid both hypovolemia and postoperative fluid overload are important in facilitating the fast track recovery process.

MINIMIZATION OF INCISION SIZE AND USE OF MIS

The size and orientation of the surgical incision are dictated primarily by the location and extent of the pathology, the need for exposure, the requirement for stoma placement (if applicable), the likelihood of further abdominal surgery, and the patient's body habitus. The incision should be as small as possible while allowing adequate exposure. Transverse incisions are used when possible by some fast track colorectal groups (though not by all). A meta-analysis found clinical outcomes after transverse or midline incisions to be similar overall.¹²⁴

Laparoscopic techniques are used when possible. In comparison with conventional open surgery, laparoscopic surgery is associated with better preservation of systemic immune function,^{125,126} less pulmonary compromise,¹²⁷ a lower incidence of ileus,¹²⁸ a shorter hospital stay, and earlier resumption of regular activities.^{129–134} In addition, the risk of SSI,¹³⁵ incisional hernia,^{136,137} and small-bowel obstruction¹³⁸ may be reduced with laparoscopic approaches.

In the setting of colorectal surgery, it is unclear at present whether the laparoscopic approach further improves on the short-term recovery benefits already seen with multimodal rehabilitation programs; benefits have been reported in some studies^{138,139} but not in others.^{140,141}

Postoperative Issues

PAIN MANAGEMENT

Pain remains the most common reason for delaying discharge after ambulatory surgery,¹⁴² while good analgesia accelerates restoration of function and improves recovery [*see 1:6 Postoperative Pain*].¹⁴³ Although there is no direct relation between analgesic techniques and postoperative morbidity and mortality,¹⁴⁴ optimal pain control, in combination with other interventions, remains a priority for the physician in the perioperative period. The pathophysiology of postoperative pain is characterized by a combination of nociceptive stimuli from the wound, inflammation and sensitization of peripheral somatic and visceral nerve terminals and central neurons, and inhibition of central descending control. It is therefore necessary to approach pain in a multidisciplinary fashion, whereby different treatment modalities complement each other with the aim of improving analgesia while minimizing the side effects associated with each treatment.

Opioids remain the most successful compounds for postoperative pain control, but they are associated with several important side effects (e.g., acute opioid tolerance, hypoventilation, sedation, ileus, nausea and vomiting, and urinary retention), any of which may delay hospital discharge. Accordingly, it is sensible to consider multimodal analgesia as the next step in providing optimal pain control. In this approach, the synergistic or additive effects of a variety of analgesics are exploited, allowing the individual doses to be reduced and thereby minimizing individual drug-related side effects. Intraoperative use of adjuvants such as ketamine, clonidine, dexmedetomidine, adenosine, gabapentine, dexamethasone, lidocaine, beta blockers, magnesium, and neostigmine has an opioid-sparing effect during the whole perioperative period.

The use of peripheral nerve blocks and conduction blockade for major and minor surgical procedures in combination with adjuvants provides excellent analgesia, though not always consistently. One reason for partial analgesic failures might be that too often, the analgesia regimen has not been optimized for a specific procedure. Accordingly, various procedure-specific analgesic regimens have been developed. On the basis of published evidence, the addition of either NSAIDs or regional analgesia and beta blockers to opioids enhances the quality of analgesia and exerts significant opioid-sparing effects.¹⁴⁵ At present, the evidence does not support adding acetaminophen to an opioid; however, the combination of acetaminophen with an NSAID provides better analgesia than either drug alone. More work is needed to verify whether the combination of several nonopioid analgesics could produce good analgesia with minimal side effects.⁸¹ In the meantime, the current strategy for postoperative analgesia involves a combination of regional and local anesthesia, MIS, and nonopioid pharmacologic interventions.

POSTOPERATIVE NAUSEA AND VOMITING

PONV continues to be a common complication of surgery, with an overall estimated incidence of 20 to 30%. PONV delays discharge from the postanesthesia care unit (PACU) and is the leading cause of unanticipated hospital admission in ambulatory surgical patients. Vomiting increases the risk of aspiration and has been associated with suture dehiscence. Nausea and vomiting remain the most common reasons for poor patient satisfaction during the postoperative period. In one study, a simplified risk factor chart was developed that identified four main risk factors for PONV: female sex, nonsmoking status, a history of PONV, and opioid use.¹⁴⁶ The incidence of PONV in patients with none, one, two, three, or all four of these risk factors was approximately 10%, 20%, 40%, 60%, and 80%, respectively. In a large study of 18,000 ambulatory patients, general anesthesia was associated with an 11-fold higher incidence of PONV than regional or local anesthesia was.¹⁴⁷ The risk of PONV has also been shown to increase with longer operating times.

Consensus guidelines for managing PONV recommend intraoperative pharmacologic strategies designed to compensate for baseline risk factors and modify the incidence of this complication. Currently available antiemetics may act at the cholinergic (muscarinic), dopaminergic (D₂), histaminergic (H₁), or serotonergic (5-HT₃) receptors. NK-1-receptor antagonists are also being investigated. A 2000 study introduced the concept of a multimodal approach to management of PONV in high-risk patients, utilizing total IV anesthesia (TIVA) with propofol and remifentanyl, ketorolac, no nitrous oxide, no neuromuscular blockade, IV hydration, ondansetron, droperidol, and dexamethasone.¹⁴⁸ This approach resulted in a 98% complete response rate (i.e., no PONV and no antiemetic rescue). A subsequent study comprising 5,000 patients employed a multifactorial design to evaluate three antiemetic interventions (ondansetron [4 mg], droperidol [1.25 mg], and dexamethasone [4 mg]) and three anesthetic interventions (TIVA with propofol, omission of nitrous oxide, and substitution of remifentanyl for fentanyl) for PONV prophylaxis.¹⁴⁹ Each antiemetic reduced the risk of PONV by approximately 26%. The efficacy of the interventions was dependent on the patient's baseline risk. The greatest

absolute risk reduction from the intervention was achieved in the patients at high risk for PONV. Consensus guidelines for management of PONV do not currently recommend prophylaxis for patients at low risk for PONV. For those at moderate risk, combination therapy with two antiemetic agents is recommended. For those at high risk, combination therapy with three antiemetic agents is recommended. In patients who experience PONV despite receiving prophylaxis, an antiemetic regimen acting at a different receptor should be used for rescue within the first 6 hours after surgery.¹⁵⁰ After 6 hours, PONV can be treated with any of the drugs used for prophylaxis except dexamethasone and scopolamine. Other useful adjuvants to standard antiemetic drugs include beta blockers, α_2 agonists, acupuncture, acupressure, and transcutaneous electrical nerve stimulation (TENS).^{151,152}

ILEUS

Postoperative ileus is defined as a temporary paralysis of the gut after major surgical procedures. It occurs as a consequence of sympathetic reflexes resulting from surgery and pain and of production of local and systemic inflammatory mediators. The effect on bowel motility can last up to 72 hours in the colon. Ileus causes discomfort and delays oral food intake, thereby prolonging recovery and the duration of hospitalization. The most effective technique for reducing ileus is continuous thoracic epidural administration of local anesthetics to block sympathetic visceral innervation and reestablish the balance between vagal and sympathetic neural influence on the gut. Other interventions, such as early feeding, prokinetics like metoclopramide and cisapride (currently unavailable because of a high incidence of cardiac dysrhythmias), prophylactic nasogastric intubation, have only minor effects on the occurrence of ileus. In the past few years, there has been some interest in the mu-receptor antagonist alvimopan, which may reduce the effect of opioids on the gut mucosa, favor the restoration of bowel function, and accelerate hospital discharge.^{153–155}

Within multimodal programs in GI surgery, the combination of epidural analgesia using diluted concentrations of local anesthetics and minimal amounts of opioids, aggressive PONV prophylaxis, and early oral feeding and mobilization has been found to shorten the duration of ileus.⁹⁶ There is also evidence that reduced perioperative sodium administration and avoidance of fluid excess¹⁵³ are associated with earlier return of bowel function after abdominal surgery and a shorter hospital stay.¹⁵⁶ IV infusion of lidocaine during surgery and the first 24 postoperative hours has been shown to minimize ileus and facilitate dietary intake.^{85,157}

POSTOPERATIVE FEEDING

GI motility is predictably decreased after major abdominal surgery, with colonic motility requiring 3 to 5 days to recover. On the assumption that bowel rest shortens the duration of ileus and protects anastomoses, patients have traditionally been kept fasting until peristalsis has returned throughout the entire GI tract, as evidenced by passage of flatus or stool¹⁵⁸; a step-wise progression of oral intake is then allowed, resulting in a planned minimum perioperative starvation period of several days. Yet after abdominal surgery, interruption of oral intake is actually neither necessary nor beneficial in most

patients.¹⁰ After colorectal surgery, feeding before complete return of peristalsis is tolerated by most patients.¹⁵⁹ Meta-analysis of randomized trials comparing early enteral or oral feeding with fasting after various types of elective GI surgery found no obvious advantages to keeping patients on NPO status, with several studies suggesting that early feeding offered benefits, such as decreased overall infectious complications and reduced length of stay. Although the risk of vomiting is somewhat higher with early feeding, the risk of anastomotic dehiscence is not increased.¹⁶⁰ One caveat is that most studies of early oral feeding involve patients undergoing colorectal resection, which means that the results may not be applicable to patients with upper GI anastomoses.

In fast track surgery, the protocol should be tailored in accordance with the procedure being done and by the patient's tolerance (e.g., as evidenced by PONV and abdominal distention). After most types of abdominal surgery, patients are encouraged to take liquids on the night following the operation, with light solids given on the morning of postoperative day 1 and a normal diet initiated on postoperative day 2. Protein-rich drinks are given between meals. This approach allows patients to resume recommended energy and protein intake in just a few days and preserves lean body mass, particularly when combined with thoracic epidural analgesia and early mobilization.¹⁶¹ Setting specific daily goals that are understood by the patients and formulating protocol-based orders for the nursing staff are important for achieving adequate oral intake of calories and protein, given that simply starting clear fluids on postoperative day 1 without a structured, written plan does not prevent negative nitrogen balance.¹⁶²

In patients for whom early oral feeding is not possible (e.g., those who have undergone major head and neck surgery, esophageal or gastric anastomoses, or pancreaticoduodenectomy), especially in those who were undernourished preoperatively, enteral tube feeding should be considered. This is done via a tube placed distal to the anastomosis at the time of surgery; either a nasojejunal tube or a feeding jejunostomy may be employed. Enteral feedings are started at a low rate (10–20 mL/hr) within 24 hours after the procedure and are slowly increased over the next few days as the patient's tolerance permits.¹⁰

In undernourished patients, oral nutritional supplements are continued for 10 weeks after discharge; this approach results in less weight loss, faster weight regain, better preservation of muscle mass and grip strength, and improved quality of life.¹⁶³

MOBILIZATION

Postoperative bed rest should be discouraged. In addition to impairing pulmonary function and predisposing to thrombotic complications,¹⁶⁴ bed rest reduces exercise capacity in a linear fashion¹⁶⁵ and decreases muscle mass¹⁶⁶ and strength¹⁶⁷ (a result that may be related to the development of postoperative fatigue¹⁶⁸). Although the association of early postoperative mobilization with faster recovery and lower pulmonary and thrombotic complications has been acknowledged since the 1940s,¹⁶⁹ modern surgical patients actually spend very little time out of bed in conventional care plans. For example, patients in the control arm of a trial comparing fast track care with conventional care after

colorectal resection spent a median of 8 minutes out of bed on postoperative day 1, despite having been given thoracic epidural analgesia.¹⁷⁰ In an observational study of patients who had undergone upper abdominal surgery, the total median upright mobilization time was only 34 minutes on postoperative day 4, and mobilization time predicted length of stay.¹⁷¹

Structured postoperative mobilization is an important component of fast track surgery protocols, and patients should be given explicit written instructions preoperatively that outline the benefits of early mobilization. These instructions include specific goals for each day, which are also included in the postoperative nursing orders. The nursing culture and the ward environment should encourage and enable patient independence. Adequate pain control using thoracic epidural analgesia with local anesthetics facilitates effective early mobilization.⁴ Asking patients to maintain a diary of the time spent out of bed and walking or suggesting that they use a pedometer to self-monitor their ambulation may help with compliance. Placing a wall chart at the bedside that lists mobilization and diet goals for each day is also helpful.¹⁷²

Because patients in fast track protocols spend significantly more time out of bed in the first postoperative week, the decrease in voluntary muscle strength traditionally seen after major abdominal surgery is prevented.^{173,174} The importance of early mobilization may be independent of other elements of the protocol, in that compliance with “out-of-bed” day 0 has been found to be a significant predictor of hospital stay, even after other fast track elements, patient characteristics, presence of complications, and additional factors have been adjusted for.¹⁷⁵

USE OF DRAINS AND CATHETERS

Routine use of nasogastric tubes and abdominal drains after abdominal surgery is not supported by the evidence; instead, selective use, based on clinical circumstances, is indicated. Drains and catheters impede independent ambulation,¹⁷¹ can be painful, and may pose a psychological barrier to recovery.⁷ A meta-analysis of randomized trials concluded that routine nasogastric decompression after abdominal surgery does not hasten recovery from ileus, increases pulmonary complications after upper abdominal surgery, is uncomfortable, and should be abandoned.¹⁷⁶ With respect to foregut surgery, anastomotic leaks were not increased in two randomized trials of routine versus selective nasogastric decompression after partial or total gastrectomy.^{177,178}

Similarly, reviews of randomized trials do not support the use of routine prophylactic drainage for colorectal anastomoses,¹⁷⁹ thyroid surgery,¹⁸⁰ cholecystectomy,^{181,182} uncomplicated liver resection,¹⁸³ or pancreatic resection.¹⁸⁴ Routine drainage is associated with an increased SSI rate and a longer hospital stay after laparoscopic cholecystectomy,¹⁸¹ an increased hospital stay after thyroid surgery,¹⁸⁰ and increased SSI and chest infection rates after open cholecystectomy¹⁸²; it does not lower the incidence or improve the diagnosis of anastomotic leaks after colon surgery,¹⁸¹ nor does it decrease abdominal sepsis after pancreatic resection.¹⁸⁴

It is common practice to catheterize the bladder just before major operations to monitor postoperative urine output and prevent the development of postoperative urinary retention. Because epidural local anesthetics block the transmission

of afferent and efferent nervous impulses from and to the bladder, it is customary to keep the bladder catheterized for as long as epidural analgesia is in force. However, urinary catheters may cause discomfort and impede mobilization. In addition, the risk of urinary infection increases with the duration of catheterization.¹⁸⁵ Urinary infections prolong the hospital stay, are expensive to treat, and cause unpleasant symptoms. The incidence of urinary retention after epidural analgesia has been reported to be between 18 and 23%.¹⁸⁶ In one study, as part of an accelerated recovery program, bladder catheterization was discontinued 24 hours after colon surgery in 102 patients receiving continuous postoperative epidural analgesia; the incidence of bladder recatheterization was low (only 9%).¹⁸⁷ Accordingly, current practice, unless it is contraindicated by the type of surgery or by the need for ongoing monitoring of urinary volumes, is to remove urinary catheters 24 to 36 hours after the surgical procedure.

DISCHARGE CRITERIA

Patients can be discharged home when their oral intake is adequate, their pain is well controlled with oral analgesics, they are voiding without difficulty, they are passing flatus or stool, they ambulating independently or at baseline levels, they feel ready for discharge, and they are able to care for themselves at home.⁴ Yet even within an enhanced colorectal recovery program, only 30% of patients are actually discharged on the day of functional recovery; thus, it is clear that length of stay is not determined solely by medical factors but is also greatly influenced by social and cultural factors.¹⁷⁵

POSTDISCHARGE FOLLOW-UP

Because of the earlier hospital discharge with fast track programs, it is important that patients be able to contact a team member easily should problems like fever, wound redness or discharge, PONV, or worsening abdominal pain arise. A follow-up telephone call should routinely be made 24 to 36 hours after patients go home. Patients should be seen between postoperative day 7 and 10 so that the wound can be checked and their overall status assessed, then seen again at 1 month after the operation. Depending on the planned discharge day, the risk of readmission after fast track colon surgery ranges from 10 to 20%.

Studies of the duration of convalescence after abdominal surgery report great discrepancies in the time away from regular activities; these discrepancies are partly attributable to variations in how patients are instructed.¹⁸⁸ Very little information is available about the recovery period after surgery, and a standardized approach to measurement of surgical recovery is lacking. After discharge, patients are given specific written instructions outlining the expected recovery course. They are encouraged to continue the exercise program begun preoperatively, with a goal of 30 to 60 minutes of exercise per day. Undernourished patients continue to receive oral nutritional supplements. No specific restrictions are placed on the resumption of specific activities.

OTHER COMPONENTS

The preceding discussion outlines many of the more common components of multimodal perioperative rehabilitation. Specific programs may include a variety of other interventions, such as the administration of probiotics, the avoidance of standard mechanical bowel preparation,¹⁸⁹ and the use of prokinetics and laxatives.^{4,6}

Implementation of Fast Track Surgery Program

ORGANIZATIONAL ISSUES

Implementation of a multimodal rehabilitation requires substantial resources and effort. Success depends on the ability of the leader to interface with numerous stakeholders over time in order to reach a multidisciplinary consensus. Several aspects of perioperative care (e.g., the use of drains, dietary and activity restrictions, and fluid management) that may have been passed down through generations of training are abandoned or significantly revised in fast track protocols. In addition, the differences in patient preparation and education necessitate revision of information given to patients

and expansion of the role played by the surgeon or perioperative caregiver in the preoperative phase. Certain surgical techniques (e.g., the use of transverse incisions or MIS) may require surgeons to hone new skills; similarly, the significant role of thoracic epidural analgesia and pharmacologic modulation of the stress response to surgery may require anesthesiologists to play a dramatically expanded role. Early ambulation, goal-driven protocols for oral nutritional supplementation, the presence of thoracic epidural analgesia, and early withdrawal of urinary catheters significantly change the way nursing care is provided on the postoperative ward. Although guidance from published studies of successful fast track programs is available, especially in the colorectal

Table 1 Organization of Multimodal Perioperative Care Plan for Specific Procedure or Group of Procedures¹

Step	Personnel Involved	Specific Task	Time Line	Comments
1. Develop protocol	Everyone who interfaces with surgical patient: surgery, anesthesia, nursing (preop, postop, postdischarge), nutrition, psychology, physiotherapy, pharmacy	Write pathway	Meetings for 1–2 hr/wk for 1–2 mo	Requires committed leader and team members with ability to reach consensus; requires significant time and energy commitment
2. Outline specifics of preoperative preparation	Surgeon Consulting internist Nutrition Physiotherapy	Evaluate need for routine tests; standardize strategy for prevention of complications; optimize nutrition and fitness	~25 hr	Emphasis on optimization of cardiopulmonary disease, glycemic control, prevention of infectious and thrombotic complications, smoking cessation, alcohol, weight loss
3. Develop anesthesia and analgesia programs	Anesthesiology/pain service Surgery Nursing Pharmacy	Optimize regional techniques to reduce stress response and optimize pain management	1–2 mo	May require special training for thoracic epidural analgesia and other neural blocks; requires postoperative protocol for nursing unit
4. Minimize stress of surgery	Anesthesiology/pain service Surgery Nursing	Optimize anesthetic technique; minimize incision size; prevent hypothermia		Give short-acting opioids or short-acting muscle relaxants; use local anesthetics in thoracic epidural; preferably use vasopressor for hypotension versus overhydration
5. Adjust postoperative care according to evidence	Surgery Nursing Pain service	Modify routine use of nasogastric tubes, drains, and bladder catheters; protocolize feeding and ambulation with specific daily goals		Create standard postoperative orders
6. Develop postoperative nursing care programs	Nursing Physiotherapy Nutrition	Enforce feeding, ambulation and sleeping protocols; determine hospital discharge criteria		Staff may benefit from visiting an established program
7. Determine methods for follow-up	Surgeon Nursing Surgical assistant Pharmacy	Arrange telephone follow-up and office visit		Standardize discharge orders and instructions, including nutrition and physical activity; develop protocols for response to nausea, vomiting, pain, fever, wound problems
8. Develop patient information program	All team members, possibly headed by patient educator	Develop standard oral, written, and electronic material to educate patient before operation		
9. Document results and tabulate problems and patient satisfaction; revise and improve	All team members, perhaps headed by data manager	Choose outcome measures and method of follow-up		Identify methods for reassessment and pathway failure

surgery literature, there are no off-the-shelf protocols, and local differences in expertise, experience, and resources will inevitably shape the development of the protocol for each individual center. To further complicate implementation, each surgical procedure or family of procedures requires an individual protocol with specialized input from a team that is experienced in caring for this subset of patients. Even after the protocol is implemented, compliance remains an important issue that necessitates ongoing monitoring and adjustment, particularly to ensure compliance with the postoperative components.¹⁷⁵ Creating the protocol is necessary for success but not sufficient to ensure it; even within a fast track program, patients cared for by surgeons who are new adopters have longer hospital stays than those cared for by surgeons experienced with the protocol.¹⁷²

The implementation process has been well described¹ and includes the following major steps [see Table 1]:

1. Assemble the relevant stakeholders (the multidisciplinary team).
2. Examine the evidence for components of perioperative care.
3. Interpret the evidence in the light of local experience, patient population, resources, and so forth.

4. Write, circulate, and revise the protocol.
5. Implement the plan.
6. Measure the outcomes with timely feedback.
7. Revise the protocol in the light of the outcomes.

Once the protocol is introduced, there is an adjustment and learning period for the medical and nursing personnel, which is estimated to last about 1 year.¹⁹⁰

Examples of multimodal perioperative care plans for inpatient and outpatient surgical procedures are available [see Table 2, Table 3, Table 4, and Table 5].

CONTRAINDICATIONS

Whether fast track surgery is applicable to a wide variety of patients and procedures has been questioned. Fast track protocols seem to be feasible for most patients undergoing elective colon surgery, as demonstrated by a report from 24 German centers of various sizes and affiliations that voluntarily adopted the same fast track protocol.¹⁹¹ Compliance and outcomes were prospectively documented in more than 1,000 patients with a median age of 66 years. More than 30% of the patients had significant comorbid disease (American Society of Anesthesiologists [ASA] class 3 or 4). Compliance with the protocol was high, with more than 85% of the

Table 2 Sample Multimodal Perioperative Care Plan for Elective Colorectal Resection

Preoperative assessment and optimization Evaluation of medication compliance and control of risk factors: hypertension, diabetes, COPD, smoking, alcohol, asthma, CAD, malnutrition, anemia Psychological preparation for surgery and postoperative recovery: explanation of preoperative bowel preparation, importance of generous clear fluid intake up to 2 hr before surgery, intraoperative and postoperative trajectory and hospital stay (2–4 days for nonrectal surgery, > 4 days for rectal surgery), immediate postoperative mobilization, early oral intake, presence of routine bladder catheter for 24 hr Physical preparation with exercises at home: anaerobic and resistance 1–2 hr/day, gradual increase from 50% to 80% of maximum capacity, breathing exercises Surgical considerations: laparoscopic or laparotomy, risk of SSI, drains, bleeding risk, strategies for blood loss reduction. Familiarization with epidural analgesia: occasional numbness in lower extremities, short spells of hypotension, pain assessment at rest and on coughing and walking, care of the epidural catheter, explanation of possible risks (hematoma and paralysis, pain and abscess) Nutritional preparation: oral nutritional supplements for patients with diminished oral intake or mild undernutrition Intraoperative management <i>Anesthetic management</i> Allay anxiety with midazolam and good hydration. Insert epidural catheter at appropriate intervertebral level (T7–8 for right, transverse, and left hemicolectomy; T9–10 for sigmoid and rectal resection). Use local anesthetics, and test epidural blockade for bilateral spread. Infuse local anesthetics during surgery. Give minimal amount of IV opioids throughout surgery. Administer prophylactic antiemetics, antibiotics, and DVT prophylaxis. Avoid overhydration. Avoid blood replacement in cancer resection. Maintain normothermia. Use BIS to guide anesthesia titration. Avoid neostigmine to reverse muscle relaxants. <i>Surgical care</i> Minimize incision size, and use MIS if possible. Achieve accurate hemostasis and thorough removal of debris. Check integrity of anastomosis. Do not routinely place nasogastric and abdominal drains. Postoperative strategy <i>PACU</i> Discharge criteria: patient alert, cooperative, pain free, warm, normotensive, able to lift legs; urine output > 0.5 mL/kg <i>Surgical ward</i> Day of surgery (0–24 hr): Mobilize patient for 2 hr in chair and 2 hr walking, starting 6 hours after operation, and increase by 50% daily. Have patient drink fluids, including nutritional supplements. Hold oral intake if abdomen distended. Place NG tube for persistent PONV (repeated in subsequent days). Confirm working epidural block with VAS for pain at rest, cough, and mobilization. Check skin site (repeated in subsequent days). Give oral acetaminophen, 1 g q. 4 hr, and NSAID (repeated in subsequent days). Postoperative day 1 (24–48 hr): Remove urinary catheter in the morning. Mobilize patient for at least 6 hr. Institute light oral diet, including nutritional supplement. Postoperative day 2 and later (> 48 hr): Mobilize patient fully. Institute regular diet. Transition from epidural to oral medication (oxycodone + oxycodone + acetaminophen + NSAIDs) if epidural stop test is successful (repeated in subsequent days if epidural stop test is not successful). Enforce criteria for discharge: passing gas or stool, no fever, minimal pain, walking unattended, eating. If five criteria are fulfilled, patient can go home. <i>Post discharge</i> Instructions while recovering at home or on chemotherapy/radiotherapy: normal diet (± supplements), exercise every day for 1–2 hr, no opioids for pain relief, psychological support Clinic visit on postoperative day 14: check wound and overall recovery; discuss pathology and further treatment; plan further follow-up	
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BIS = bispectral index monitor; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; MIS = minimally invasive surgery; NG = nasogastric; NSAID = nonsteroidal antiinflammatory drug; PONV = postoperative nausea and vomiting; SSI = surgical site infection; VAS = visual analog scale.

Table 3 Sample Multimodal Perioperative Care Plan for Ambulatory Laparoscopic Cholecystectomy

Preoperative assessment and optimization

Evaluation of medication compliance and control of risk factors: hypertension, diabetes, COPD, smoking, alcohol, asthma, CAD, malnutrition, anemia
Psychological preparation for surgery and postoperative recovery: explanation of perioperative pathway, postoperative out-of-hospital self-care, expectations about duration of recovery period
Day of surgery: drink clear fluids containing carbohydrate up to 2 hr before operation
Preinduction: give acetaminophen 1 gm and NSAID. Provide DVT prophylaxis.

Intraoperative management

Anesthetic management

Induce with propofol, give short-acting opiates for analgesia (e.g., fentanyl), consider adjuvants for analgesia (beta blockers [propranolol, esmolol] or lidocaine), administer rocuronium or desflurane.
Prevent PONV with dexamethasone, ondansetron, or droperidol.
Give normal saline, 2 L IV, over intraoperative and postoperative time.
Keep patient warm.

Surgical care

Provide incisional anesthesia with local anesthetic at beginning and end of case. Keep abdominal insufflation pressure as low as possible (12 mm Hg or less). Maximize use of small (5 mm) trocars.

Postoperative strategy

PACU

Provide analgesia with strong short-acting opioid (e.g., fentanyl). Manage PONV with ondansetron. Encourage postoperative oral fluid intake as soon as possible; do not wait for voiding to discharge from PACU.

> 6 hr after operation²⁰⁵

Provide nonopioid analgesia with NSAIDs (e.g., ketorolac, naproxen, COX-2 inhibitor) and acetaminophen. Add oxycodone, 5–10 mg q. 4 hr, if pain persists.

Post discharge

Provide written instructions for postdischarge care; no specific activity limitations need be placed. Schedule follow-up visit at 2 wk after surgery.

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DVT = deep-vein thrombosis; NSAID = nonsteroidal antiinflammatory drug; PACU = postanesthesia care unit; PONV = postoperative nausea and vomiting;

patients undergoing epidural analgesia, oral nutrition, and mobilization on the day of the operation. The median length of stay was 8 days, representing a 40% decrease from conventional German data. Readmissions occurred in 4% of cases. A 2001 study enrolled 60 consecutive patients undergoing elective laparotomy and intestinal surgery over a 6-week period, including many reoperative and complex pelvic cases; only two of the 60 patients had to be excluded from the fast track protocol on the basis of operative findings.¹⁹² Fast track colorectal surgery has been successfully performed in older patients,¹⁹³ patients with significant comorbidities (ASA class 3 or 4),^{192,194,195} and patients requiring complex operations.¹⁹⁵ Whether these results are applicable to more complex procedures in general is not known. In a study of fast track Ivor-Lewis esophagectomy, 75% of patients older than 70 years failed the protocol.¹⁹⁶

Readmission is a concern after early discharge from hospital. The rate at which readmission occurs is related to the planned day of hospital discharge, with readmission rates after colon surgery decreasing from 20% to 11% as planned hospital stays increase from 2 days to 3. The difference is mainly attributable to a reduction in readmissions for “social reasons” or observation; no significant differences in complications have been reported.¹⁹⁷ A systematic review of fast track studies in colon surgery found no overall increase in readmission rates over those seen with conventional care.⁶

RESULTS

There remains significant variability in perioperative care among individual surgeons, institutions, and geographic areas, and overall adherence with evidence-based recommendations and guidelines is still suboptimal.⁸ Consequently, it is likely that creation of any standard perioperative care proto-

col (also referred to as a critical pathway or clinical pathway) that multiple surgeons are willing to buy into may improve efficiency and outcomes simply by removing variability and improving compliance with evidence-based care. This phenomenon has been demonstrated not only for colon surgery¹⁹⁸ but also for more complex procedures such as pancreaticoduodenectomy¹⁹⁹ and aortic surgery.²⁰⁰ By themselves, however, pathways often are not effective in decreasing the length of stay.²⁰¹

Fast track surgery represents an extension of the critical pathway that integrates new modalities in anesthesia and nutrition, enforces early mobilization and feeding, and emphasizes reduction of the surgical stress response. It is hoped that this approach will not only improve efficiency by shortening the hospital stay and reducing variability, as any standardized protocol might, but also decrease the physiologic impact of major surgery, thereby reducing organ dysfunction and shortening the recovery time. Experience with fast track programs is accumulating in a number of different areas. Most reports are single-center studies focusing on colorectal surgery. A systematic review of three randomized trials and three additional prospective studies of enhanced recovery programs for colon surgery found that fast track protocols were associated with decreased ileus, duration of hospitalization, and morbidity, without any significant increase in the readmission rate.⁶ Fewer results are available for other types of abdominal surgery. Preliminary reports, however, suggest that it is possible to implement fast track protocols even for debilitated patients undergoing complex procedures. Some studies have reported dramatically low lengths of stay (e.g., a 3-day median length of stay after open aortic aneurysm repair,²⁰² a 2-day median length of stay after colon surgery,⁹⁶ and an 88% discharge rate on postoperative day 1 after laparoscopic donor nephrectomy²⁰³). Even if these results are not widely applicable, they might well stimulate us

Table 4 Sample Multimodal Perioperative Care Plan for Esophageal Resection²⁰⁶⁻²⁰⁸

Preoperative assessment and optimization

Initial evaluation of medication compliance and control of risk factors: hypertension, diabetes, COPD, smoking, alcohol, asthma, CAD, anemia

Psychological preparation for surgery and postoperative recovery: explanation of pathway, diet and mobilization plan, presence of drains, expectations for length of hospital stay (7–8 days) and postdischarge recovery

Physical preparation with exercises at home: anaerobic and resistance 1–2 hr/day, gradual increase from 50% to 80% of maximum capacity, breathing exercises

Surgical considerations: operative approach individualized on basis of tumor characteristics and location, patient comorbidity, previous surgery

Familiarization with epidural analgesia: occasional numbness in lower extremities, short spells of hypotension, pain assessment at rest and on coughing, walking, care of epidural catheter

Nutritional preparation: oral nutritional supplements for patients with diminished oral intake or mild undernutrition; formal nutritional assessment if malnutrition is more severe

Intraoperative management

Anesthetic management

Insert thoracic epidural catheter. Use local anesthetics, and test epidural blockade for bilateral spread. Infuse local anesthetics during surgery. Provide antibiotics and DVT prophylaxis. Give prophylactic antiemetics. Restrict fluids. Avoid blood transfusion. Maintain normothermia. Perform early extubation (preferably in operating room).

Surgical care

Minimize blood loss. Place feeding jejunostomy. Routinely place NG tube and chest tubes.

Postoperative strategy

Day of surgery (0–24 hr)

Admit to ICU or other unit with continuous monitoring of heart rate and pulse oximetry. Apply strict aspiration precautions; place head of bed at 30°, and place NG tube to suction. Restrict fluids postoperatively as dictated by hemodynamics (~1–1.5 mL/kg/hr crystalloid and 20–30 mL/hr urine output if renal function is normal). Place chest tube to suction. Have patient sitting in chair on evening of surgery if possible and ambulating in hall on morning after surgery. Perform incentive spirometry. Monitor chest tube and urinary output q. 4 hr. Obtain hemoglobin level q. 6 hr three times; measure electrolyte concentrations in morning.

Surgical ward

Postoperative day 1: Have patient ambulate 3–4 times daily; obtain physiotherapy consult. Perform incentive spirometry (repeated in subsequent days). Apply strict aspiration precautions; place head of bed at 30°; place NG tube to suction (repeated in subsequent days). Order complete blood count and electrolyte levels in morning (repeated in subsequent days). Obtain chest x-ray (repeated three times in subsequent days). Confirm working epidural block with VAS for pain at rest, cough, and mobilization; check skin site (repeated in subsequent days). Supply jejunal feedings at full concentration, starting at 20 mL/hr.

Postoperative day 2: Increase rate of jejunal feedings by 10 mL/4 hr until achieving target rate is achieved. Request nutritional therapy consult. Remove anterior chest tube. Ambulate a minimum of four times daily until discharge.

Remove bladder catheter unless urinary output is poor.

Postoperative day 3: Remove NG tube if abdomen is not distended and gastric conduit is not dilated on chest x-ray.

Remove last chest tube if drainage < 450 mL/day (reassess in subsequent days if drainage is higher). Transition from epidural to oral/J-tube analgesics (oxycontin + oxycodone + acetaminophen + NSAID) if epidural stop test is successful (repeated in subsequent days if epidural stop test is not successful).

Postoperative day 4 or 5: Transition from epidural to oral/J-tube analgesics (oxycontin + oxycodone + acetaminophen + NSAID) if epidural stop test is successful (repeated in subsequent days if epidural stop test is not successful). Perform sodium amidotrizoate–meglumine amidotrizoate swallow. If there is no leak, advance to full liquid diet with oral supplements. Continue jejunal feedings. Continue aspiration precautions: avoid eating if drowsy, and avoid recumbency within 3 hr of eating.

Postoperative day 5 or 6: Advance to soft diet. If patient is undernourished, start compressing jejunal feedings by increasing rate and turning off for 4 hr/day. Arrange for home nighttime feedings (7 pm to 7 am). Remove central line. Continue physiotherapy and aspiration precautions. Obtain nutritional education from dietitian.

Postoperative day 7: Discharge home on soft diet with aspiration precautions ± nighttime jejunal feedings.

Post discharge

Instructions while recovering at home and/or on chemotherapy/radiotherapy: eating normal diet (± supplements), exercise every day for 1–2 hr, no opioids for pain relief, psychological support

Clinic visit on postoperative day 14 to check wound and overall recovery, discuss pathology and further treatment, and plan further follow-up

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DVT = deep-vein thrombosis; ICU = intensive care unit; NG = nasogastric; NSAID = nonsteroidal antiinflammatory drug.

to question our assumptions about what keeps patients in the hospital after surgery.

More research is required to understand which of the multiple individual components of fast track surgery have the greatest impact.⁶ In addition, it remains unclear whether certain patients are more likely than others to benefit from fast track protocols. Several elements of this approach seem relatively consistent among fast track centers, at least with respect to colorectal surgery (e.g., thoracic epidural analgesia and the philosophy of encouraging early oral feeding and ambulation), whereas several others are more variable (e.g.,

use of probiotics, specific feeding protocols, preoperative carbohydrate administration, bowel preparation, and specific anesthesia protocols). Length of hospital stay is the most common outcome measure used, but this measure can be confounded by nonphysiologic issues: even within fast track programs, only a minority of patients are discharged on the day of functional recovery.²⁰⁴ Yet little research has been undertaken to achieve a better description of the recovery process, and there is no currently accepted outcome measure to define the length of clinical recovery. More research is also needed in the area of implementation.

Table 5 Sample Multimodal Perioperative Care Plan for Laparoscopic Foregut Surgery²⁰⁹

Preoperative assessment and optimization

Initial evaluation of medication compliance and control of risk factors: hypertension, diabetes, COPD, smoking, alcohol, asthma, CAD, anemia

Psychological preparation for surgery and postoperative recovery: explanation of pathway, diet and mobilization plan, expectations for length of hospital stay (1–2 days) and postdischarge recovery

Nutritional preparation: oral nutritional supplements for patients with diminished oral intake or weight loss

Intraoperative management

Anesthetic management

Address aspiration risk. Give short-acting opioids. Use TIVA with propofol to minimize PONV. Provide good muscle relaxation to facilitate surgical repair. Give prophylactic antiemetics to prevent postoperative retching (dexamethasone, 8 mg; droperidol, 0.625 mg; ondansetron, 4 mg). Provide DVT prophylaxis. Initiate active warming.

Surgical care

Use small trocars. Administer preincisional and postoperative local anesthesia. Avoid lithotomy position (use split table and bean bag). Apply pneumatic compression stockings. Do not routinely place Foley catheter or NG tube.

Give sips of water immediately after operation and fluids the morning after surgery. Request nutritional consult for education on posthospital surgery diet on postoperative day 1.

Have patient ambulate the night of the operation.

No routine postoperative investigations are required. Take stepwise approach to analgesia: start with NSAIDs and acetaminophen, avoid opiates if possible, and do not use PCA. Assess for discharge criteria after lunch on postoperative day 1 (fluids tolerated, no fever, pain controlled with oral analgesia).

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DVT = deep-vein thrombosis; NG = nasogastric; NSAID = nonsteroidal anti-inflammatory drug; PCA = patient-controlled analgesia; PONV = postoperative nausea and vomiting; TIVA = total intravenous anesthesia.

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10 FAST TRACK SURGERY

Henrik Kehlet, M.D., Ph.D., F.A.C.S. (Hon.), and Douglas W. Wilmore, M.D., F.A.C.S.

Over the past several decades, surgery has undergone revolutionary changes that are leading to improved treatments (involving lower risk and better outcome) for an increasing number of diseases. These salutary developments are the result of more advanced anesthetic techniques, new methods of reducing the perioperative stress response, wider application of minimally invasive techniques, improved understanding of perioperative pathophysiology, and more sophisticated approaches to the prevention of postoperative organ dysfunction. Currently, many operations that once necessitated hospitalization can readily be performed in the outpatient setting; in addition, many major procedures are now associated with a significantly reduced duration of hospitalization and a shorter convalescence.

Although these anesthetic and surgical developments are the result of basic scientific and clinical research, they have also been influenced by governmental and managed care policies aimed at encouraging more cost-effective treatments. Such extraclinical influences, coupled with new clinical developments, have resulted in novel approaches designed to enhance the cost-effectiveness of health care, such as so-called fast track surgery, critical pathways, and various types of clinical guidelines. To understand the true potential value of such approaches, it is essential to recognize that their aim is not merely to ensure that fewer health care dollars are spent but, more important, to ensure that better and more efficient health care is delivered. Although these novel approaches may reduce cost, their primary purpose is to improve surgical management by reducing complications and providing better outcomes. In what follows, we outline the basic concept, primary components, and current results of fast track surgery, which is a comprehensive approach to the elective surgical patient that is designed to accelerate recovery, reduce morbidity, and shorten convalescence.

Basic Concept

Fast track surgery involves a coordinated effort to combine (1) preoperative patient education; (2) newer anesthetic, analgesic, and surgical techniques whose aim is to reduce surgical stress responses, pain, and discomfort; and (3) aggressive postoperative rehabilitation, including early enteral nutrition and ambulation. It also includes an up-to-date approach to general principles of postoperative care (e.g., use of tubes, drains, and catheters; monitoring; and general rehabilitation) that takes into account the revisions to traditional practice mandated by current scientific findings. It is believed that by these means, fast track surgery can shorten the time required for full recovery, reduce the need for hospitalization and convalescence, and lower the incidence of generalized morbidity related to pulmonary, cardiac, thromboembolic, and infectious complications.¹⁻³

For an accelerated recovery program of this type to succeed, proper organization is essential. In general terms, fast track

surgery must be based on a process of multidisciplinary collaboration that embraces not only the surgeon, the anesthesiologist, the physiotherapist, and the surgical nurse but also the patient. More specifically, fast track surgery depends on the inclusion and integration of a number of key constituent elements (see below).

Constituent Elements

EDUCATION OF THE PATIENT

To obtain the full advantages of a fast track surgical program, it is essential to provide patients with information about their perioperative care in advance of the procedure. Such educational efforts often serve to reduce patients' level of anxiety and need for pain relief, thereby providing a rational basis for collaboration with health care personnel, a process that is crucial for enhancing postoperative rehabilitation.¹⁻³ Patients can supplement the information they receive directly from health care providers by accessing reference sources such as www.facs.org/public_info/operation/aboutbroch.html, a collection of electronic brochures on specific clinical procedures that is provided by the American College of Surgeons.

OPTIMIZATION OF ANESTHESIA

The introduction of rapid-onset, short-acting volatile anesthetics (e.g., desflurane and sevoflurane), opioids (e.g., remifentanyl), and muscle relaxants has enabled earlier recovery from anesthesia and thereby facilitated ambulatory and fast track surgery.⁴ Although use of these newer general anesthetic agents has resulted in quicker recovery of vital organ function after minor surgical procedures, it has not been shown to decrease stress responses or mitigate organ dysfunction after major procedures.

Regional anesthetic techniques (e.g., peripheral nerve blocks and spinal or epidural analgesia), on the other hand, have several advantages in addition to providing anesthesia. Such advantages include improved pulmonary function, decreased cardiovascular demands, reduced ileus, and more effective pain relief. Neural blockade is the most effective technique for providing postoperative pain relief, and it has been shown to reduce endocrine and metabolic responses to surgery [see 1:6 *Postoperative Pain*]. For a pronounced reduction in perioperative stress after a major operation, continuous epidural analgesia for 24 to 72 hours is necessary.^{5,6} A meta-analysis of randomized trials evaluating regional anesthesia (primarily involving patients undergoing operations on the lower body) found that morbidity was 30% lower with regional anesthesia than with general anesthesia.⁷ However, the effect of continuous epidural analgesia on outcome after major abdominal or thoracic procedures has been questioned in the past several years. In three large randomized trials,⁸⁻¹⁰ no beneficial effect on overall morbidity could be demonstrated, except for a slight improvement in pulmonary outcome, and the duration of hospi-

talization was not reduced. It should be remembered, however, that in these studies, either an epidural opioid regimen or a predominantly epidural opioid regimen was employed and that the perioperative care regimens either were not described or were not revised according to current scientific data regarding the use of nasogastric tubes, early oral feeding, mobilization, and other care parameters.³ We believe, therefore, that for further assessment of the role of continuous epidural local analgesic regimens that include local anesthetics in improving outcome, an integrated approach within the context of fast track surgery is required.⁶

Perioperative measures should also be taken to preserve intraoperative normothermia. Hypothermia may lead to an augmented stress response during rewarming, impaired coagulation and leukocyte function, and increased cardiovascular demands. Preservation of intraoperative and early postoperative normothermia has been shown to decrease surgical site infection, intraoperative blood loss, postoperative cardiac morbidity, and overall catabolism.¹¹

REDUCTION OF SURGICAL STRESS

The neuroendocrine and inflammatory stress responses to surgery increase demands on various organs, and this increased demand is thought to contribute to the development of postoperative organ system complications. At present, the most important of the techniques used to reduce the surgical stress response are regional anesthesia, minimally invasive surgery, and pharmacologic intervention (e.g., with steroids, beta blockers, or anabolic agents).¹²

Neural blockade with local anesthetics reduces endocrine and metabolic (specifically, catabolic) activation and sympathetic stimulation, thereby decreasing the demands placed on organs and reducing loss of muscle tissue; however, regional anesthetic techniques have no relevant effect on inflammatory responses.^{5,6}

Minimally invasive surgical techniques clearly decrease pain and lessen inflammatory responses,¹³⁻¹⁵ but they appear to have relatively little, if any, effect on endocrine and metabolic responses.

Pharmacologic intervention with a single dose of a glucocorticoid (usually dexamethasone, 8 mg) given before a minor procedure has led to reduced nausea, vomiting, and pain, as well as to decreased inflammatory responses (interleukin-6), with no observed side effects.^{16,17} This intervention may facilitate recovery from minor (i.e., ambulatory) procedures¹⁸; however, the data from major procedures are inconclusive. The use of perioperative beta blockade to reduce sympathetic stimulation and thereby attenuate cardiovascular demands has been shown to reduce cardiac morbidity,¹⁹ as well as to reduce catabolism in burn patients [see *Elements of Contemporary Practice:6 Risk Stratification, Preoperative Testing, and Operative Planning*].^{20,21} Perioperative beta blockade may therefore become an important component of efforts to facilitate recovery in fast track surgical programs.

For patients whose nutritional status is normal, oral feeding ad libitum is appropriate in the postoperative period. For patients who are elderly or nutritionally depleted, nutritional supplementation, administration of an anabolic agent (e.g., oxandrolone or another anabolic steroid,²²⁻²⁴ insulin,²⁵ or growth hormone [GH]^{26,27}) to enhance deposition of lean tissue, or both may be beneficial. Most of the studies addressing the use of anabolic agents have focused on critically ill catabolic patients, in whom both indirect effects (e.g., improved nitrogen balance²⁶) and direct effects (e.g., improved wound healing and decreased length of stay with GH in burned children²⁷ and decreased mortality with insulin in critically ill patients²⁵) on outcome have been demonstrated. In a study published in 2000, a group of elderly patients undergoing opera-

tions for hip fracture received either low-dose GH (20 mg/kg/day) or placebo.²⁸ Overall, those in the GH group were able to return to their prefracture living situation earlier than those in the placebo group. A 1999 study reported increased mortality when GH was administered to ICU patients,²⁹ but a 2001 meta-analysis failed to confirm this observation.³⁰ More work is necessary before definitive conclusions can be formed in this regard.

Postoperative insulin resistance is an important metabolic factor for catabolism. There is evidence to suggest that preoperative oral or intravenous carbohydrate feeding may reduce postoperative insulin resistance.³¹ Whether this approach yields clinical benefits in terms of improved recovery remains to be determined,^{31,32} but its simplicity, its clear pathophysiologic rationale, and its low cost make it a potentially attractive option.

CONTROL OF NAUSEA, VOMITING, AND ILEUS

The ability to resume a normal diet after a surgical procedure (whether minor or major) is essential to the success of fast track surgery. To this end, postoperative nausea, vomiting, and ileus must be controlled. Principles for rational prophylaxis of nausea and vomiting have been developed on the basis of systematic reviews³³: for example, 5-HT₃ receptor antagonists, droperidol, and dexamethasone have been shown to be effective in this regard, whereas metoclopramide is ineffective. There is some reason to think that multimodal antiemetic combinations may be superior to single antiemetic agents; unfortunately, the data currently available on combination regimens are relatively sparse. In addition, analgesic regimens in which opioids are cut back or eliminated have been shown to decrease postoperative nausea and vomiting.

Paralytic ileus remains a significant cause of delayed recovery from surgery and contributes substantially to postoperative discomfort and pain. Of the various techniques available for managing ileus,^{34,35} continuous epidural analgesia with local anesthetics is the most effective, besides providing excellent pain relief. Now that cisapride has been taken off the market, no effective anti-ileus drugs are available. In a 2001 study, however, a peripherally acting mu opioid receptor antagonist significantly reduced nausea, vomiting, and ileus after abdominal procedures, without reducing analgesia.³⁶ If further studies confirm these findings, use of peripherally acting opioid antagonists may become a popular and effective way of improving postoperative recovery; this treatment is simple and apparently has no major side effects.

ADEQUATE TREATMENT OF POSTOPERATIVE PAIN

Despite ongoing development and documentation of effective postoperative analgesic regimens—such as continuous epidural analgesia in major operations, patient-controlled analgesia (PCA), and multimodal (balanced) analgesia that includes nonsteroidal anti-inflammatory drugs as well as stronger agents³⁷⁻³⁹ [see *1:6 Postoperative Pain*]⁴⁰—postoperative pain still is too often inadequately treated. Improved pain relief, facilitated by an acute pain service,⁴⁰ is a central component of any fast track surgery program and is a prerequisite for optimal mobilization and oral nutrition, as well as a valuable aid in reducing surgical stress responses.³⁷

APPROPRIATE USE OF TUBES, DRAINS, AND CATHETERS

There is substantial support in the literature for the idea that nasogastric tubes should not be used routinely in patients undergoing elective abdominal surgery.^{1,2} Randomized trials indicated that drains offered little benefit after cholecystectomy, joint replacements, colon resection, thyroidectomy, radical hysterectomy, or

pancreatic resection^{1,3,41} but that they might limit seroma formation after mastectomy.^{1,3} Such postmastectomy drainage does not necessarily impede hospital discharge, and the patient generally may be treated on an outpatient basis. Urinary catheterization has been routinely performed after many operations, but scientific documentation of the requirement for this measure is often lacking. In general, catheterization beyond 24 hours is not recommended with colorectal procedures, except with the lowest rectal procedures, for which 3 to 4 days of catheterization may be indicated.³

Although tubes, drains, and catheters may lead to morbidity only when used for extended periods, they do tend to hinder mobilization, and they can raise a psychological barrier to the patient's active participation in postoperative rehabilitation. Therefore, such devices should be used not routinely but selectively, in accordance with the available scientific documentation.

NURSING CARE, NUTRITION, AND MOBILIZATION

Postoperative nursing care should include psychological support for early rehabilitation, with a particular focus on encouraging the patient to resume a normal diet and become ambulatory as soon as possible. Early resumption of an oral diet is essential for self-care; furthermore, according to a 2001 meta-analysis of controlled trials, it may reduce infectious complications and shorten hospital stay after abdominal procedures, without increasing the risk of anastomotic dehiscence.⁴² In addition, early resumption of enteral feeding may reduce catabolism and may be facilitated by the methods used to reduce postoperative nausea, vomiting, and ileus (see above).

Postoperative bed rest is undesirable because it increases muscle loss, decreases strength, impairs pulmonary function and tissue oxygenation, and predisposes to venous stasis and thromboembolism.³ Accordingly, every effort should be made to enforce postoperative mobilization; adequate pain relief is a key adjuvant measure in this regard.

Organization is essential for good postoperative nursing care: a prescheduled care map should be drawn up, with goals for rehabilitation listed for each day.

DISCHARGE PLANNING

Given that a primary result of fast track surgery is reduced length of hospitalization, discharge planning must be a major consideration in the preoperative patient information program, as well as during hospitalization. Careful, detailed discharge planning is essential for reducing readmissions and increasing patient safety and satisfaction. The discharge plan should include (1) detailed information on the expected time course of recovery, (2) recommendations for convalescence, and (3) encouragement of enteral intake and mobilization. For patients with a significant degree of postoperative disability, various acute care facilities are available after hospital discharge. It should be kept in mind, however, that the integrated care approach fundamental to fast track surgery is specifically intended as a way of limiting or preventing such disability, thereby reducing patients' need for and dependence on postdischarge care facilities.

Reported Results

Ongoing efforts to formulate multimodal strategies aimed at improving postoperative outcome have led to the development of a variety of fast track surgical programs [see Table 1]. Most of the studies published to date have been descriptive ones reporting consecutive patient series from single centers, the findings from which have often been confirmed by other groups using the same

or a slightly modified fast track care program. On the whole, the preliminary results from these studies are very positive: fast track surgery is associated with shorter hospital stays, reduced or at least comparable morbidities, and low readmission rates, with no apparent decrease in safety.

Studies of fast track surgery in which organ function was assessed postoperatively and compared with organ function after traditional care found fast track surgery to be associated with earlier ambulation,^{43,44} superior postoperative muscle function,⁴⁴ improved oral nutritional intake,⁴⁵ better preservation of lean body mass,^{43,45} reduced postoperative impairment of pulmonary function,⁴³ earlier recovery of GI motility,⁴⁶ and mitigation of the decrease in exercise capacity and impairment of cardiovascular response to exercise that are usually expected after an operation.⁴³ The few randomized trials performed to date (mostly involving patients undergoing cholecystectomy, colonic resection, or mastectomy) reported that fast track programs increased or at least maintained patient satisfaction while achieving major cost reductions.

Future Developments

The initial promising results from the fast track surgical programs studied suggest that such programs can achieve major care improvements in terms of reducing postoperative stay. At present, however, sufficient scientific documentation is lacking for many commonly performed major operations. Thus, there is a need for additional data—in particular, data on the potential positive effects of fast track surgery on postoperative morbidity. The necessary data would probably be best obtained through multicenter trials using identical protocols. Randomized trials within the same unit that allocate some patients to suboptimal care recommendations for pain relief, mobilization, and nutrition would be difficult to perform, if not unethical, though a few such reports have been published on colon surgery patients.^{44,47}

As yet, it has not been conclusively demonstrated that reducing the duration of hospitalization necessarily reduces morbidity,⁴⁸ though data from studies addressing colonic and vascular procedures suggest that nonsurgical (i.e., cardiopulmonary and thromboembolic) morbidity may be reduced and overall postoperative recovery (assessed in terms of exercise performance and muscle power) enhanced. More study is required in this area. Future trials should also focus on identifying any factors that might be limiting even more aggressive early recovery efforts, so that more effective fast track programs can be designed. Finally, studies are needed to identify potential high-risk patient groups for whom fast track surgery may not be appropriate or who may need to be hospitalized for slightly longer periods to optimize organ function.⁴⁷

There has been considerable interest in whether the use of critical pathways improves postoperative care. Preliminary studies involving coronary artery bypass grafting, total knee replacement, colectomy, thoracic procedures, and hysterectomy suggested that critical pathways may reduce length of hospital stay, but the reduction is no greater than can be observed in neighboring hospitals that do not use critical pathways.⁴⁹ Thus, the initial enthusiasm for critical pathways notwithstanding, conclusive evidence that they have a beneficial effect on postoperative care is still lacking. The continuously decreasing length of stay noted in hospitals without fast track programs may be partly attributable to the intense competition within the health care system, which can lead to changes in care principles even without the formal adoption of critical pathways or similar systems.⁴⁹

All of the studies on the economic implications of fast track surgical programs and critical pathways have documented substantial

Table 1 Results from Selected Fast Track Surgical Programs

Type of Operation	Postoperative Hospital Stay	Comments and Other Findings
Abdominal procedures		
Inguinal hernia repair ⁵⁹⁻⁶¹	1.5–6 hr	Large consecutive series using local infiltration anesthesia in > 95%, with one series ⁵⁹ using unmonitored anesthesia; documented low morbidity, with no urinary retention; patient satisfaction ~90%, cost reduction > \$250 with local anesthesia
Cholecystectomy (laparoscopic, ⁶²⁻⁶⁷ mini-incision ⁶⁸)	> 80% discharge on same day	Large consecutive series, with documented safety and patient satisfaction > 80%; cost reduction of \$750/patient in randomized study ⁶⁴ ; recovery of organ functions within 2–3 days, with <1 wk convalescence ⁶⁷ ; similar results with mini-incision in consecutive series ⁶⁸
Fundoplication ^{69,70}	> 90% < 23 hr	Large consecutive series with documented safety ⁷⁰
Open ^{43,44,46,47,56,71-76} and laparoscopic ^{72,77-79} colorectal procedures	2–4 days	Consecutive series including high-risk patients; reduced cardiopulmonary morbidity, readmission rates 0%–15%; no documented advantages of laparoscopy-assisted colonic resection, though costs may be reduced ⁷² ; ileus reduced to < 48 hr in > 90% of patients, ^{46,56} with improved muscle and pulmonary function in fast track patients and better preservation of postoperative body composition ⁴³ ; one randomized study showed similar morbidity, readmissions, and satisfaction with fast track versus traditional care ⁴⁷
Complex pelvic-colorectal procedures ^{80,81}	3–6 days	Short stay ⁸⁰ (~4–6 days) even with additional stoma; low readmission rate (7%)
Rectal prolapse ⁸²	80% < 24 hr	Consecutive series (N = 63) with Altemeier repair; 5% readmission rate (nonserious indications)
Pancreaticoduodenectomy, ^{83,84} complex biliary tract procedures ⁸⁵	—	Hospital stay decreased by implementation of clinical pathway
Mastectomy ⁸⁶⁻⁹⁰	90% < 1 day	Large cumulative series; documented safety and major cost reduction with high patient satisfaction; no increased morbidity with fast track, but less wound pain and improved arm movement and no increase in risk of psychosocial complications
Vascular procedures		
Carotid endarterectomy ⁹¹⁻⁹⁴	90% < 1 day	Surgery done with local anesthesia; specialized nurses and wards
Lower-extremity arterial bypass ⁹⁵	2–3 days	Large series (N = 130); documented safety
Abdominal aortic aneurysmectomy ^{96,97}	~3 days	Preliminary studies (N = 50 ⁹⁶ and N = 77 ⁹⁷); documented early recovery and safety; one study with epidural analgesia, ⁹⁷ one without ⁹⁶
Urologic procedures		
Radical prostatectomy ⁹⁸	~75% 1 day	Large consecutive series (N = 252); documented safety and patient satisfaction
Laparoscopic adrenalectomy ⁹⁹⁻¹⁰¹	< 1 day	Small series; safety and low morbidity suggested
Cystectomy ^{102,103}	7 days	Improved mobilization, bowel function, and sleep recovery with fast track surgery ¹⁰² ; low mortality; ileus a problem ^{102,103}
Laparoscopic donor nephrectomy ¹⁰⁴	< 1 day	Preliminary study (N = 41); low readmission rate (2%)
Open donor nephrectomy ¹⁰⁵	2 days	—
Pulmonary procedures ¹⁰⁶⁻¹¹⁰	~1 day in some series, ^{106,107} ~4–5 days in others	Shortest stay with fast track protocol including revision of drainage principles ^{106,107} ; safety with very early discharge suggested
Other procedures		
Craniotomy ¹¹¹	~40% < 24 hr	Large consecutive series (N = 241) including tumor surgery; local anesthesia used; low readmission rate; safety suggested
Parathyroid procedures ¹¹²	~90% ambulatory	Selected consecutive series (N = 100); regional anesthesia and intraoperative adenoma localization employed; documented safety
Vaginal procedures ¹¹³	~1 day	Consecutive series (N = 108); surgery done with local anesthesia

cost savings. It should, however, be borne in mind that the last portion of a hospital stay is much less expensive than the initial portion; thus, the cost savings in this area may turn out to be smaller than they would at first appear.⁵⁰⁻⁵² This caveat should not hinder further development and documentation of fast track surgery, because inherent in the concept is the idea that revision and optimization of perioperative care may also reduce morbidity,

thereby achieving additional cost savings. As noted, the large-scale data with detailed patient description and stratification that are needed to clarify the improvements achieved by fast track surgery are, unfortunately, lacking at present, but so far, all indications are that postoperative morbidity is comparable or reduced.

A commonly expressed concern is that fast track surgery might increase the burden on general practitioners and other parts of the

nonhospital care system. The evidence currently available clearly indicates that increased use of ambulatory surgery is safe and is associated with a very low readmission rate.^{53,54} After major procedures such as colorectal surgery, however, readmissions are often unpredictable, and the readmission rate is not significantly reduced by keeping patients in the hospital for an additional 2 to 3 days.^{55,56} Moreover, in some studies of patients who have undergone coronary bypass⁵⁷ and hip replacement,⁵⁸ earlier discharge and hospital cost savings have been offset by increased use of postacute rehabilitation services. Thus, any assessment of the costs associated with fast track surgery should include the total period during which care (including both hospital care and rehabilitation care) is delivered.

Again, however, it should be emphasized that the basic concept of fast track surgery implies control of perioperative pathophysiology with the aim of enhancing recovery and thereby reducing the need for postdischarge care. The relatively few published studies that

addressed patient functional status after fast track colonic surgery suggested that muscle function, exercise capacity, and body composition are better preserved with this approach than with traditional care, in which surgical stress, insufficient nutrition, and prolonged immobilization typically lead to significant deterioration of organ function. Accordingly, an optimal fast track surgery regimen should aim at early recovery of organ function, not just early discharge.

In summary, the basic concept of fast track surgery, which could be expressed as multimodal control of perioperative pathophysiology, seems to be a highly promising approach to improving surgical outcome. We believe that the principles and techniques embodied in this approach will eventually be integrated into the care of all surgical patients. To this end, resources should be allocated for evaluation and documentation of the effects of fast track surgery and related systems on cost, postoperative morbidity, safety, and overall patient well-being.

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1 ORAL CAVITY LESIONS

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Approach to Oral Cavity Lesions

The oral cavity is a complex structure that plays a role in many important functions, including mastication, swallowing, speech, and respiration. It extends from the vermilion border of the lips to the oropharynx and is separated from the oropharynx by the anterior tonsillar pillars, the junction of the hard and soft palates, and the junction between the base of the tongue and the oral tongue at the circumvallate papillae. Subsites of the oral cavity include the lips, buccal mucosa, alveolus, retromolar trigone, tongue, floor of the mouth, and hard palate [see Figure 1].

In most cases, lesions of the oral cavity reflect locally confined processes, but, on occasion, they are manifestations of systemic disease. The cause of an oral cavity lesion can usually be identified by the history and the physical examination; however, it is most often determined definitively by either a response to a therapeutic trial or a biopsy. A systematic classification of oral cavity lesions facilitates the development of a differential diagnosis. One approach to classification is based on the appearance of the lesion (e.g., white, red, pigmented, ulcerative, vesiculobullous, raised, or cystic). Another approach is first to categorize the lesion as either neoplastic or nonneoplastic and then to further divide the nonneoplastic lesions into various subcategories (e.g., infectious, inflammatory, vascular, traumatic, and tumorlike) [see Table 1]. In the following discussion, we adopt the second approach.

Clinical Evaluation

HISTORY

The onset, duration, and growth rate of the oral lesion should be determined. Inflammatory lesions usually have an acute onset and are self-limited, and they may be recurrent. Neoplasms tend to exhibit progressive enlargement; a rapid growth rate is suggestive of malignancy. It is often possible to identify specific events (e.g., upper respiratory tract infection, oral trauma, or medications) that precipitated the lesions. Both malignancies and inflammatory conditions may be associated with various non-specific symptoms, including pain and dysphagia. Symptoms suggestive of malignancy include trismus, bleeding, a change in denture fit or occlusion, facial sensory changes, and referred otalgia. Fever, night sweats, and weight loss may occur in various settings but are particularly associated with lymphomas and systemic inflammatory conditions. Some oral lesions are identified without presenting signs or symptoms as incidental findings noted during a general dental or medical examination.

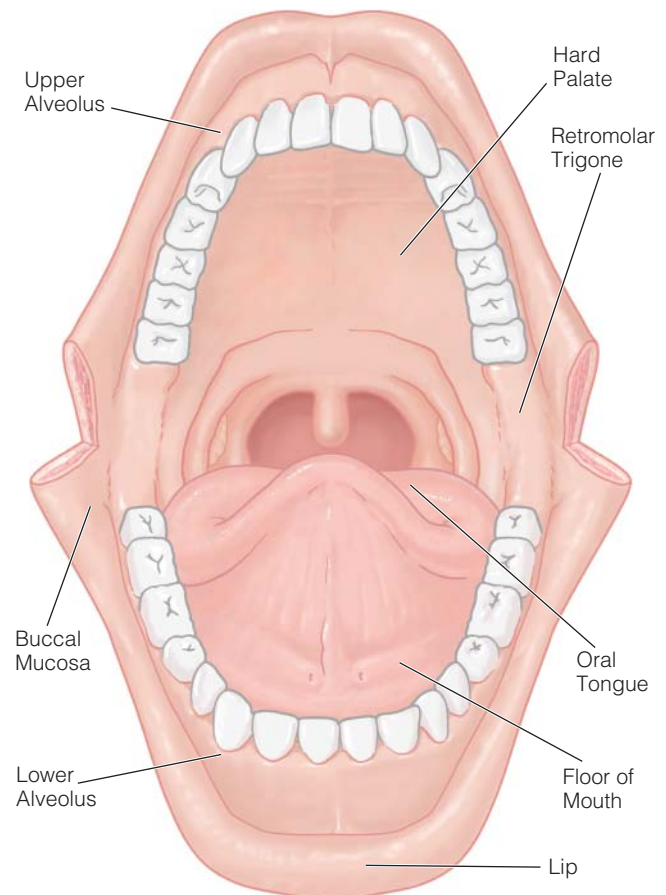
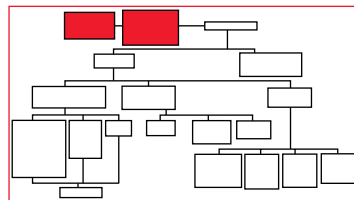
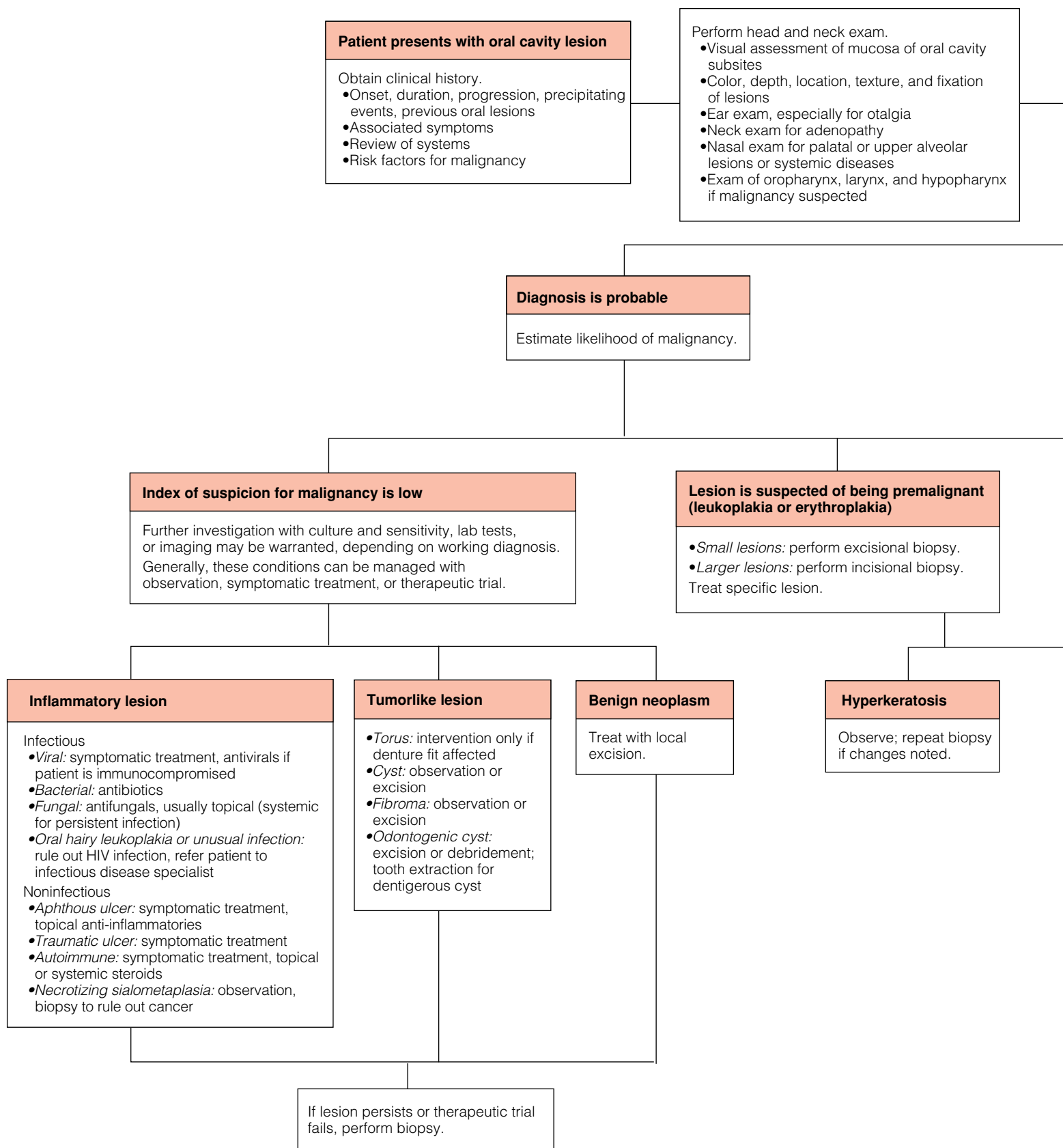


Figure 1 Depicted are the major anatomic subsites of the oral cavity.

A review of systems may uncover signs (e.g., rashes or arthritis) that suggest a possible autoimmune disorder. The medical history should always address previous or current connective tissue diseases, malignancies, radiation therapy, chemotherapy, and HIV infection. It is especially important to elicit a medication history because many classes of medications cause drug eruptions that involve the oral mucosa: for instance, well over 100 medications are associated with lichenoid drug reaction, and even more are associated with xerostomia. Use of alcohol or tobacco is a notable risk factor for the development of oral cavity carcinoma, as is a previous head and neck carcinoma. The quantity of alcohol or tobacco consumed should be determined because a dose-response relationship exists between the level of use and the risk of cancer. Other risk factors for oral cavity carcinoma include sun exposure (lip cancer), human papillomavirus infection, and nutritional deficiencies. Radiation exposure is a risk

Approach to Oral Cavity Lesions



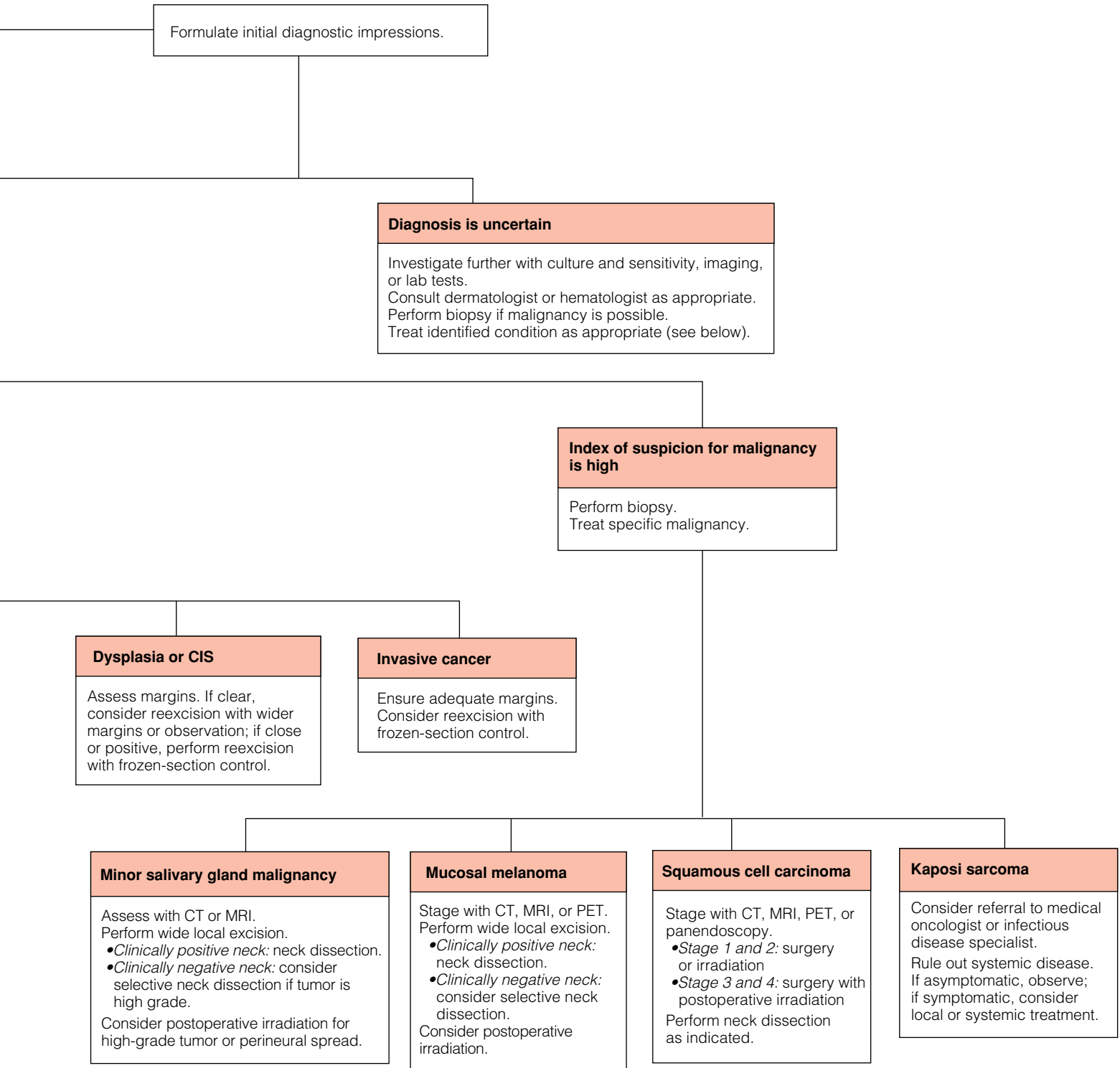


Table 1 Differential Diagnosis of Oral Cavity Lesions Based on Etiology

Inflammatory lesions
Infectious
Viral
Herpes simplex
Herpes zoster
Cytomegalovirus
Herpangina
Hand, foot, and mouth disease
Oral hairy leukoplakia (Epstein-Barr virus)
Bacterial
Mycobacterial infection
Syphilis
Gingivostomatitis
Fungal
Candidiasis
Coccidioidomycosis
Noninfectious
Recurrent aphthous stomatitis
Traumatic ulcer
Autoimmune disorders
Behçet syndrome
Systemic lupus erythematosus
Wegener granulomatosis
Sarcoidosis
Amyloidosis
Pemphigus and pemphigoid
Pyogenic granuloma
Necrotizing sialometaplasia
Lichen planus
Tumorlike lesions
Mucocoele
Ranula
Tori
Fibroma
Odontogenic cysts
Neoplasms
Benign
Squamous papilloma
Minor salivary gland neoplasms
Ameloblastoma
Hemangioma
Granular cell tumor
Brown tumor
Neuroma, schwannoma, neurofibroma
Osteoma, chondroma
Malignant
Squamous cell carcinoma
Verrucous carcinoma
Minor salivary gland malignancies
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Polymorphous low-grade adenocarcinoma
Mucosal melanoma
Kaposi sarcoma
Lymphoma
Osteosarcoma

factor for soft tissue sarcoma, lymphoma, and minor salivary gland tumors, and HIV infection is a risk factor for Kaposi sarcoma.

PHYSICAL EXAMINATION

The head and neck should be examined in an organized and systematic manner. Illumination with a headlight or a reflecting mirror facilitates oral examination by freeing the examiner's hands for use in retracting the cheeks and the tongue.

The mucosa of the oral cavity is evaluated at each of the oral subsites. Any trismus should be noted, as should the general health of the teeth and the gingiva. Percussion of carious teeth with pulpitis often elicits pain, although this is not always the case if caries is shallow or pulpal necrosis is present. Palpation of the tongue, the floor of the mouth, and the oral vestibule is an essential component of oral examination. Palpation of the submandibular and submental regions is best performed bimanually.

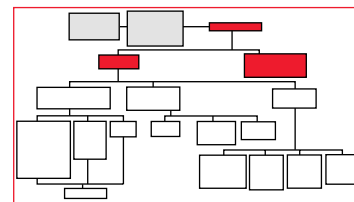
Oral lesions should be characterized in terms of color, depth, location, texture, fixation, and other applicable attributes. When cancer is present, tenderness, induration, and fixation are common. Invasion of surrounding structures (e.g., the mandible, the parotid duct, or the teeth) by a malignant lesion should be noted. Physical examination is not a definitive means of detecting mandibular invasion, because tumor fixation can be secondary to other factors and cortical invasion can occur with minimal fixation.^{1,2} In addition, lesions in some areas of the oral cavity (e.g., the hard palate and the attached gingiva) almost always appear to be fixed.

A history of otalgia warrants otoscopic examination. Otalgia in the absence of any identifiable pathologic condition of the ear often represents referred pain from a malignancy of the upper aerodigestive tract. The presence of otalgia in a middle-aged person should always trigger a search for an underlying cause. The nasal cavity should be examined with a speculum to rule out tumor extension in lesions of the hard palate, and transnasal fiberoptic pharyngoscopy and laryngoscopy should be done if a malignant neoplasm is a possibility or if a systemic condition is suspected that may also affect the nasal or pharyngeal mucosa.

Examination of the neck may reveal enlarged lymph nodes. Lymphadenopathy in an adult should be considered to represent metastatic cancer until proved otherwise. A benign ulcer in the oral cavity may cause a reactive adenopathy as a consequence of the associated inflammation, but in the setting of cervical lymphadenopathy, the initial diagnostic assumptions should emphasize the strong possibility of a primary oral cancer with metastases to the neck. Asymmetrical enlargement of the parotid or submandibular glands may result either from obstruction of the ducts by an oral cavity mass or from enlargement of nodes intimately associated with the glands. Symmetrical enlargement suggests a systemic process (e.g., Sjögren syndrome or HIV infection). The cranial nerves should be examined, with particular attention focused on the trigeminal, facial, and hypoglossal nerves.

Investigative Studies

The history and physical examination should narrow down the differential diagnosis and lead to a working diagnosis. If



a benign local process (e.g., aphthous stomatitis, traumatic ulcer, or viral infection) is suspected, no further investigation, other than reevaluation, may be needed. If the lesion persists or progresses, further investigation is warranted.

LABORATORY TESTS

Laboratory studies are usually not beneficial in the initial workup of oral cavity lesions. If a connective tissue disease

is suspected, serologic tests [see Table 2] and referral to a rheumatologist or another appropriate specialist may be considered.

IMAGING

The value of advanced imaging with computed tomography (CT), magnetic resonance imaging (MRI), or both in the management of oral cavity lesions has not been firmly established. Accordingly, judgment must be exercised. There is evidence to suggest that early oral cavity malignancies can be managed without either CT or MRI. Nevertheless, many clinicians obtain these studies in all cases of malignancy and in most cases of suspected malignancy. CT and MRI can help assess the size and location of the lesion and determine the degree to which surrounding structures are involved. In patients with oral cavity carcinoma, imaging facilitates the staging of tumors and the planning of treatment. In patients with cervical metastases, physical examination augmented by MRI and CT has a better diagnostic yield than physical examination alone. Bone-window CT scans are particularly helpful for assessing invasion of the mandible, the maxilla, the cervical spine, and the base of the skull. CT scans are highly sensitive and specific for detecting mandibular invasion.¹⁻³ MRI provides better soft tissue delineation than CT, with fewer dental artifacts, and therefore is particularly valuable for assessing malignancies of the tongue, the floor of the mouth, and the salivary glands. Loss of the usual marrow enhancement on T₁-weighted MRI images suggests bone invasion, although this is not a specific finding. Chest radiography, CT, or both may be employed to search for lung metastases or a second primary tumor.

Positron emission tomography (PET) is playing an increasingly important role in the workup of patients with head and neck carcinoma or mucosal melanoma. PET is useful for confirming the presence of a malignancy, as well as for assessing cervical and distant metastases; it is particularly valuable for detecting recurrent or persistent disease.⁴⁻⁶ The development of fused PET-CT images has allowed for greater accuracy in anatomically delineating tumors and planning treatment. Drawbacks of PET include frequent false positive results with active inflammation, high cost, and limited availability. In addition, the quality of the images obtained and the level

of technical experience available vary considerably among institutions. The role of PET imaging in the initial management and follow-up of head and neck cancer is still being defined.

BIOPSY

For oral cavity lesions that are suggestive of malignancy or are probably of neoplastic origin, biopsy is usually required. A brief observation period to allow reevaluation, with biopsy withheld, may be warranted if a response to therapy or spontaneous resolution is possible. The potential morbidity associated with a biopsy done in a previously irradiated region should be considered in deciding whether biopsy is advisable. Specimens are usually sent to the pathologist in 10% buffered formalin, but there are notable exceptions. If a lymphoma is suspected, specimens should be sent without formalin for genetic testing and flow cytometry. If an autoimmune disease is suspected, special tests requiring immunofluorescence are indicated, and specimens should be sent either fresh or in Michel solution. In addition, if fungal, mycobacterial, bacterial, or viral infection is suspected, a small portion of a specimen may be sent separately for culture. If there is an associated neck mass, fine-needle aspiration (FNA) may be performed to rule out metastatic disease.⁷ In general, FNA is not useful for biopsy of oral lesions: incisional biopsy is often technically easier and provides more tissue.

EXAMINATION UNDER ANESTHESIA AND PANENDOSCOPY

In patients with oral carcinoma, examination under anesthesia (EUA) and panendoscopy should be performed before definitive resection to assess the extent of the primary tumor and identify any synchronous tumors. Both EUA and panendoscopy are commonly performed in the operating room with the patient under general anesthesia. Panendoscopy involves endoscopic examination of the larynx, the oropharynx, the hypopharynx, the esophagus, and, occasionally, the nasopharynx. As a rule, assessment of the tumor and neck is more accurately performed when the patient is relaxed under a general anesthetic.

Diagnosis and Management of Specific Oral Cavity Lesions

INFLAMMATORY LESIONS

Infectious

Viral stomatitis may be caused by a number of different viruses, including herpes simplex virus (type 1 or type 2), varicella-zoster virus, and coxsackievirus [see Figure 2, a and b].⁸ It is most common in children and immunocompromised patients. The lesions of viral stomatitis are generally vesicular, occur in the oral cavity and the oropharynx, and erupt over the course of several days to form painful ulcers. Eruption may be preceded by local symptoms (e.g., burning, itching, or tingling) or systemic symptoms (e.g., fever, rash, malaise, or lymphadenopathy). The diagnosis is usually established by the history and the physical examination and may be confirmed by means of biopsy or viral culture.

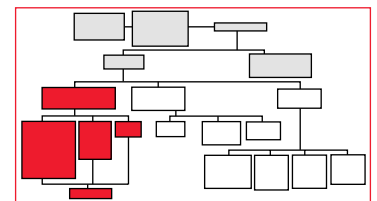


Table 2 Serologic Tests for Diagnosing Connective Tissue Disease

Connective Tissue Disease	Serologic Tests
SLE	CBC, antinuclear antibody, anti-double-stranded DNA antibody, anti-Smith antibody
Sjögren syndrome	Antinuclear antibody, rheumatoid factor, anti-Ro (SS-A) and anti-La (SS-B) antibodies
Wegener granulomatosis	cANCA, serum creatinine level, urine microscopy
Sarcoidosis	Serum calcium and ACE levels

ACE = angiotensin-converting enzyme; cANCA = cytoplasmic antineutrophil cytoplasmic antibodies; CBC = complete blood count; SLE = systemic lupus erythematosus.



Figure 2 Shown are infectious lesions of the oral cavity: (a) primary herpes stomatitis of the buccal mucosa and soft palate; (b) primary herpes stomatitis of the tongue (in the same patient as in frame a); (c) oral candidiasis (pseudomembranous form); and (d) oral candidiasis (erythematous form).

Treatment of viral stomatitis primarily involves managing symptoms with oral rinses, topical anesthetics, hydration, and antipyretics. Systemic antiviral medications may shorten the course of herpetic stomatitis and are indicated in immunocompromised patients.⁹

Candidiasis is a common fungal infection of the oral cavity [see Figure 2, c and d]. *Candida albicans* is the species most commonly responsible; however, other *Candida* species can cause this condition as well, with *Candida glabrata* emerging as a growing problem in immunocompromised hosts. Factors predisposing to oral candidal infection include immunosuppression, use of broad-spectrum antibiotics, diabetes, prolonged use of local or systemic steroids, and xerostomia.¹⁰ Oral candidiasis presents in several different forms [see Table 3], of which pseudomembranous candidiasis (thrush) is the most common. This form is characterized by white, curdlike plaques on the oral mucosa that may be wiped off (with difficulty) to leave an erythematous, painful base (the Auspitz sign). Widespread oral and pharyngeal involvement is common. The diagnosis is based on the clinical appearance of the lesion and on evaluation of scrapings with the potassium hydroxide (KOH) test. Culture is generally not useful, because *Candida* is a common commensal oral organism.¹¹

Ideally, initial management of oral candidiasis is aimed at reversing the underlying condition, although this is not always

Table 3 Clinical Presentation of Oral Candidiasis	
Type of Oral Candidiasis	Presentation
Pseudomembranous	White, curdlike plaques on oral mucosa that when wiped off (with difficulty) leave erythematous, painful base
Hyperplastic	Thick white plaques on oral mucosa that cannot be rubbed off
Erythematous	Red, atrophic areas on palate or dorsum of tongue
Angular cheilitis	Cracking and fissuring at oral commissures

possible. Treatment typically involves either topically administered antifungal agents or, if infection is severe or topical therapy fails, systemically administered antifungals. Patients who are immunocompromised or have xerostomia may benefit from long-term prophylaxis.

Noninfectious

Recurrent aphthous stomatitis Aphthous stomatitis is a common idiopathic ulcerative condition of the oral cavity [see Figure 3, a and b]. The ulcers are typically painful and



Figure 3 Shown are noninfectious inflammatory lesions of the oral cavity: (a) minor aphthous ulcer of the lower lip; (b) minor aphthous ulcer of the upper lip; (c) necrotizing sialometaplasia of the hard palate; (d) resolution of necrotizing sialometaplasia without treatment (in the same patient as in frame c); (e) pyogenic granuloma of the upper alveolus; (f) reticular lichen planus involving the buccal mucosa; (g) lichen planus of the lateral tongue; (h) pemphigus vulgaris of the oral cavity, with an erythematous base after rupture of bullae (involving the left lateral tongue, the buccal mucosa, and the lip); and (i) traumatic ulcer of the tongue secondary to dental trauma.

may occur anywhere in the oral cavity and the oropharynx but are rarely found on the hard palate, the dorsal tongue, and the attached gingiva.^{9,12} Affected patients often have a history of lesions, beginning before adolescence. There are three different clinical presentations of recurrent aphthous stomatitis, of which minor aphthous ulcers are the most common [see Table 4].⁹ The diagnosis is made on the basis of the history and the physical examination; biopsy is reserved for lesions that do not heal or that grow in size.

Numerous therapies have been tried for recurrent aphthous stomatitis, most with only minimal success. The majority of aphthous ulcers heal within 10 to 14 days and require no treatment; however, patients with severe symptoms may require medical intervention. Temporary pain relief can be obtained with topical anesthetic agents (e.g., viscous lidocaine). Tetracycline oral suspension and antiseptic mouthwashes have also been used, with varying success.^{9,12} Topical steroids are the mainstay of therapy and may shorten the duration of the ulcers if applied during the early phase.^{11,12} These agents may be applied either in a solution (e.g., dexamethasone oral suspension, 0.5 mg/5 mL) or in an ointment (e.g., fluocinolone or clobetasol). Ointments work much better in the oral cavity than creams or gels do. Systemic steroids are indicated when the number of ulcers is large or when the outbreak has persisted for a long time.

Necrotizing sialometaplasia Necrotizing sialometaplasia is a rare benign inflammatory lesion of the minor salivary glands that resembles carcinoma clinically and histologically and is readily mistaken for it [see Figure 3c].⁸ This condition most commonly develops in white males in the form of a deep, sudden ulcer of the hard palate. The presumed cause is ischemia of the minor salivary glands resulting from infection, trauma, surgery, irradiation, or irritation caused

by ill-fitting dentures.⁹ Biopsy is usually necessary to rule out squamous cell carcinoma or a minor salivary gland malignancy. Review of the tissue by a pathologist well versed in head and neck pathology is essential. Characteristic histologic findings include coagulation necrosis of the salivary gland acini, ductal squamous metaplasia, preservation of the lobular architecture, and a nonmalignant appearance of squamous nests.¹³

Lesions resolve without treatment within 6 to 10 weeks [see Figure 3d].

Pyogenic granuloma A pyogenic granuloma is an aggregation of proliferating endothelial tissue [see Figure 3e] that occurs in response to chronic persistent irritation (e.g., from a calculus or a foreign body) or trauma.¹⁰ The lesion appears as a raised, soft, sessile or pedunculated mass with a smooth, red surface that bleeds easily and can grow rapidly.¹⁴ Surface ulceration may occur, but the ulcers are not invasive. The gingiva is the most common location, but any of the oral tissues may be involved.

Conservative excision with management of the underlying irritant is the recommended treatment. The classic presentation is in a pregnant woman, and hormonal influences may have an additional influence on recurrence.

Lichen planus Lichen planus is a common immune-mediated inflammatory mucocutaneous disease [see Figure 3, f and g].¹⁵ Clinically, idiopathic lichen planus is indistinguishable from lichenoid drug reaction. The reticular form of lichen planus is the most common one and presents as interlacing white keratotic striae on the buccal mucosa, the lateral tongue, and the palate.¹⁵ Lichen planus is usually bilateral, symmetrical, and asymptomatic.¹⁶ The symptomatic phases may wax and wane, with erythematous and ulcerative changes being the primary signs. Cutaneous lesions occur less frequently and appear as small, violaceous, pruritic papules. The diagnosis is generally made on the basis of the history and the physical examination; biopsy is not always necessary.

For asymptomatic lesions, no treatment is required other than observation. For painful lesions, which are more common with the erosive form of the disease, either topical or systemic steroids are appropriate.¹⁶ There is some controversy regarding the risk of malignant transformation; however, long-term follow-up is still recommended.¹⁶ The main risk posed by lichen planus may be the masking effect that the white striae cause, which can prevent the clinician from observing the early leukoplakic and erythroplakic changes associated with epithelial dysplasia.

Ulcer from autoimmune disease Oral ulcers may be the first manifestation of a systemic illness. The most common oral manifestation of systemic lupus erythematosus (SLE) is the appearance of painful oral ulcers in women of child-bearing age. Patients with Behçet disease present with the characteristic triad of painful oral ulcers, genital ulcers, and associated iritis or uveitis. Patients with Crohn disease or Wegener granulomatosis frequently manifest oral ulceration during the course of the illness. These disorders should be managed in conjunction with a rheumatologist.

Mucous membrane pemphigoid and pemphigus vulgaris are chronic vesiculobullous autoimmune diseases that frequently affect the oral mucosa [see Figure 3h]. In mucous

Table 4 Clinical Presentation of Aphthous Stomatitis

Type of Aphthous Ulcer	Presentation	Time to Resolution
Minor	Multiple painful, well-demarcated ulcers, < 1.0 cm in diameter, are noted, with yellow fibrinoid base and surrounding erythema; typically involve mobile mucosa, with tongue, palate, and anterior tonsillar pillar the most common sites	7–10 days, without scarring
Major (Sutton disease)	Ulcers, often multiple, may range in size from a few millimeters to 3 cm and may penetrate deeply with elevated margins; typically involve mobile mucosa, with tongue, palate, and anterior tonsillar pillar the most common sites	4–6 wk, with scarring
Herpetiform	Small (1–3 mm) ulcers occur in “crops” but are still limited to movable mucosal surfaces; gingival involvement, if present, is caused by extension from nonkeratinizing crevicular epithelium	1–2 wk

membrane pemphigoid, the antibodies are directed at the mucosal basement membrane, resulting in subepithelial bullae.¹⁶ These bullae rupture after 1 to 2 days to form painful ulcers, which may heal over a period of 1 to 2 weeks but often do not display a predictable periodicity. Oral pain is often the chief complaint, but there may be undetected ocular involvement that can lead to entropion and blindness.

Pemphigus vulgaris is a more severe disease than mucous membrane pemphigoid. In this condition, the antibodies are directed at intraepithelial adhesion molecules, leading to the formation of intraepithelial bullae.⁹ The blisters are painful and easily ruptured and tend to occur throughout the oral cavity and the pharynx.¹⁷ The Nikolsky sign (i.e., vesicle formation or sloughing when a lateral shearing force is applied to uninvolved oral mucosa or skin) is present in both pemphigus and pemphigoid. In most cases, biopsy with pathologic evaluation (including immunofluorescence studies) is helpful in establishing the diagnosis. Circulating antibodies may be present in either condition but are more common in pemphigus. Serologic tests may suffice to establish the diagnosis, without any need for biopsy. Management involves administration of immunosuppressive agents, often in conjunction with a dermatologist.

Traumatic ulcer Trauma (e.g., from tooth abrasion, tooth brushing, poor denture fit, or burns) is a common cause of oral mucosal ulceration [see Figure 3i]. The ulcers usually are painful but typically are self-limited and resolve without treatment. Topical anesthetic agents may be beneficial if pain is severe enough to limit oral intake.

Tumorlike Lesions

TORUS MANDIBULARIS AND TORUS PALATINUS

Palatal and mandibular tori are benign focal overgrowths of cortical bone [see Figure 4, a and b].¹⁰ They appear as slow-growing, asymptomatic, firm, submucosal bony masses developing on the lingual surface of the mandible or the midline of the hard palate.¹⁴ When these lesions occur on the labial or buccal aspect of the mandible and the maxilla, they are termed exostosis.¹⁸ Torus mandibularis tends to occur bilaterally, whereas torus palatinus arises as a singular, often lobulated mass in the midline of the hard palate. Surgical management is required only if the tori are interfering with denture fit.

MUCOCELE AND MUCOUS RETENTION CYST

A mucocele is a pseudocyst that develops when injury to a minor salivary gland duct causes extravasation of mucus, surrounding inflammation, and formation of a pseudocapsule [see Figure 4, c and d].¹⁴ Mucoceles are soft, compressible, bluish or translucent masses that may fluctuate in size. They are most commonly seen on the lower lip but also may develop on the buccal mucosa, anterior ventral tongue, and floor of the mouth. Only very rarely do they involve the upper lip; masses in the upper lip, even if they are fluctuant, should be assumed to be neoplastic, developmental, or infectious. Treatment involves excision of the mucocele and its associated minor salivary gland.

A ranula (from a diminutive form of the Latin word for frog) is a mucocele that develops in the floor of the mouth

as a consequence of obstruction of the sublingual duct,¹⁹ secondary either to trauma or to sublingual gland sialoliths. If the ranula extends through the mylohyoid muscle into the neck, it is referred to as a plunging ranula. A plunging ranula may present as a submental or submandibular neck mass. Imaging helps delineate the extent of the mass and may confirm the presence of a sialolith. The recommended treatment is excision of the ranula with removal of the sublingual gland and often the adjacent submandibular gland. Marsupialization is an option but is associated with a relatively high recurrence rate.^{19,20}

A mucous retention cyst (salivary duct cyst) is usually the result of partial obstruction of a salivary gland duct accompanied by mucous accumulation and ductal dilatation [see Figure 4e].¹⁹ It is a soft, compressible mass that may occur at any location in the oral cavity where minor salivary glands are present. Treatment involves surgical excision with removal of the associated minor salivary gland.

FIBROMA

A fibroma is a hyperplastic response to inflammation or trauma [see Figure 4, f and g].⁸ It is a pedunculated soft or firm mass with a smooth mucosal surface that may be located anywhere in the mouth. Such lesions are managed with either observation or local excision.

ODONTOGENIC CYST

A dentigerous cyst is an epithelium-lined cyst that, by definition, is associated with the crown of an unerupted tooth [see Figure 4h]. Such cysts cause painless expansion of the mandible or the maxilla. Treatment involves enucleation of the cyst and its lining and extraction of the associated tooth.²¹

An odontogenic keratocyst is a squamous epithelium-lined cyst that produces keratin. Bone resorption occurs secondary to pressure resorption and to inflammation caused by retained keratin. Management involves either excision or débridement and creation of a well-ventilated and easily maintained cavity.²²

Neoplastic Lesions

BENIGN

Squamous Papilloma

Squamous papilloma is one of the most common benign neoplasms of the oral cavity [see Figure 5, a and b].¹³ It usually presents as a solitary, slow-growing, asymptomatic lesion, typically less than 1 cm in diameter. It is well circumscribed and pedunculated and has a warty appearance.¹⁶ The palate and tongue are the sites most frequently affected¹³; occasionally, multiple sites are involved. The presumed cause is a viral infection, most likely human papillomavirus.²³

Papillomas are managed with complete excision, including the base of the stalk.

Giant Cell Lesions

Central giant cell granulomas, brown tumors of hyperparathyroidism, aneurysmal bone cysts, and lesions associated with genetic diseases (e.g., cherubism) may all be seen in the jaws. Of particular note is the aneurysmal bone cyst that may occur at sites of trauma, which, in theory, is the consequence

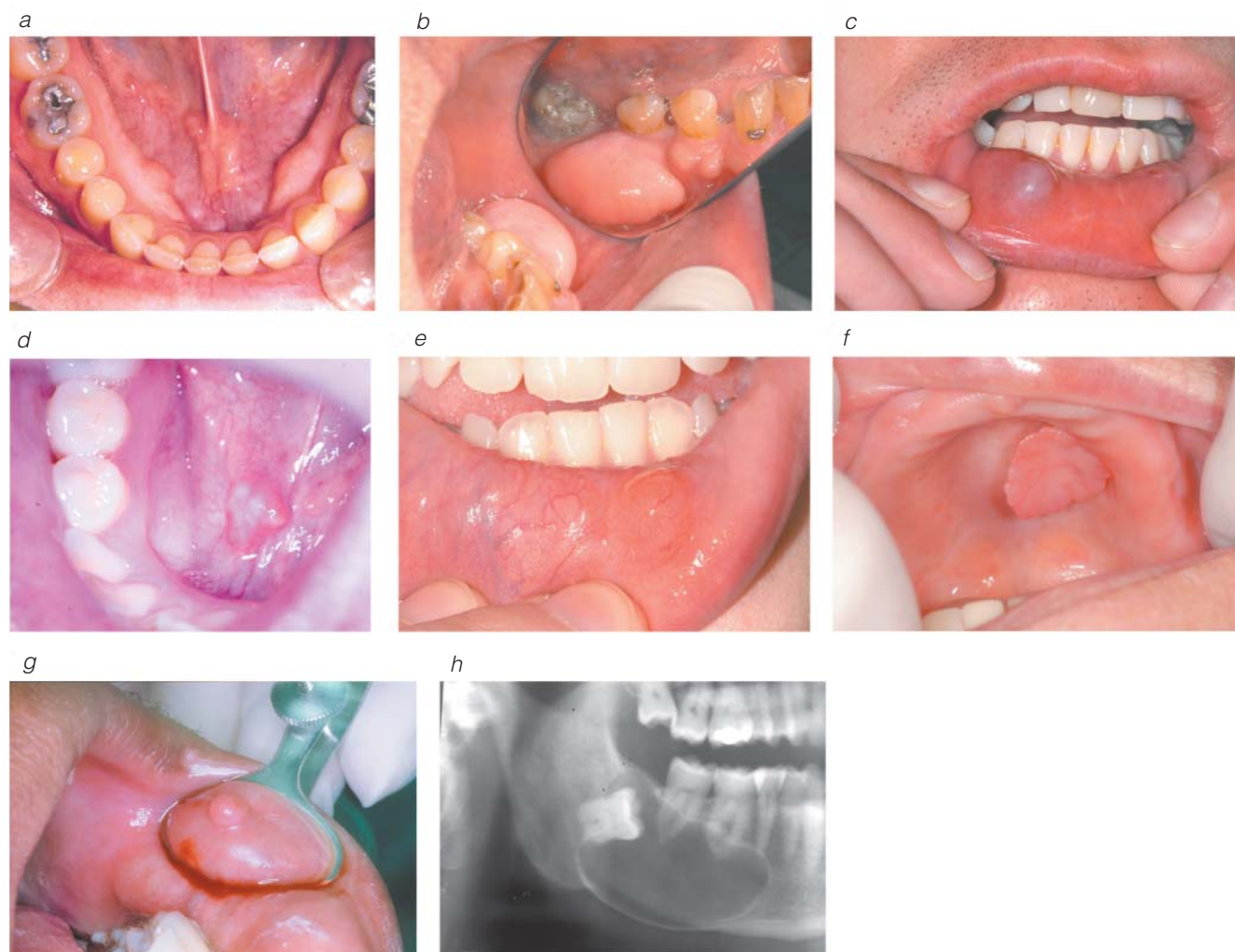


Figure 4 Shown are tumorlike lesions of the oral cavity: (a) torus mandibularis, with bilateral bony protuberances on the lingual surface of the mandible; (b) mandibular exostosis, with a unilateral bony protuberance on the labial-buccal surface of the mandible; (c) mucocele of the lip (note the bluish hue of the cystic lesion; cf. frame e); (d) mucocele of the floor of the mouth associated with the sublingual gland (ranula); (e) mucous retention cyst of the lower lip (presenting much like mucocele but appearing more transparent); (f) fibroma of the hard palate resulting from denture trauma; (g) fibroma of the lower lip; and (h) dentigerous cyst (a unilocular radiolucency surrounding the crown of an unerupted tooth, with no bone destruction).

of an organizing hematoma that leads to bony expansion and giant cell proliferation.²⁴ Eventually, erosion of the buccal cortex may occur with the development of facial swelling.

Management involves enucleation and curettage.^{24,25} The surgeon should be prepared for bleeding during treatment. The use of calcitonin or intralesional steroid injections is gaining popularity.²⁵

Minor Salivary Gland Neoplasms

The minor salivary glands are small, mucus-secreting glands that are distributed throughout the upper aerodigestive tract, with the largest proportion concentrated in the oral cavity. Minor salivary gland neoplasms are uncommon, but when they do occur, they are most likely to develop in the oral cavity. Within the oral cavity, the hard palate and the soft palate are the most common sites of minor salivary gland neoplasms; however, tumors involving the tongue, the lips, the buccal mucosa, and the gingivae have been described.

Approximately 30% of minor salivary gland neoplasms are benign. Of these benign lesions, the most common is pleomorphic adenoma, which presents as a painless, slow-growing submucosal mass [see Figure 5, c and d].^{13,26}

Pleomorphic adenoma is managed with complete surgical excision to clear margins. This tumor exhibits small, pseudopodlike extensions that may persist and cause recurrence if enucleation around an apparent capsule is attempted.

Granular Cell Tumor

A granular cell tumor is a benign neoplasm that is thought to arise from Schwann cells.¹³ It usually presents as a small, asymptomatic, solitary submucosal mass. The lateral border and the dorsal surface of the tongue are the sites where this tumor is most frequently found in the oral cavity.²⁷ Pathologic examination may reveal pseudoepitheliomatous hyperplasia, which is similar in appearance to well-differentiated squamous cell carcinoma.²⁸ This similarity has led to reports of

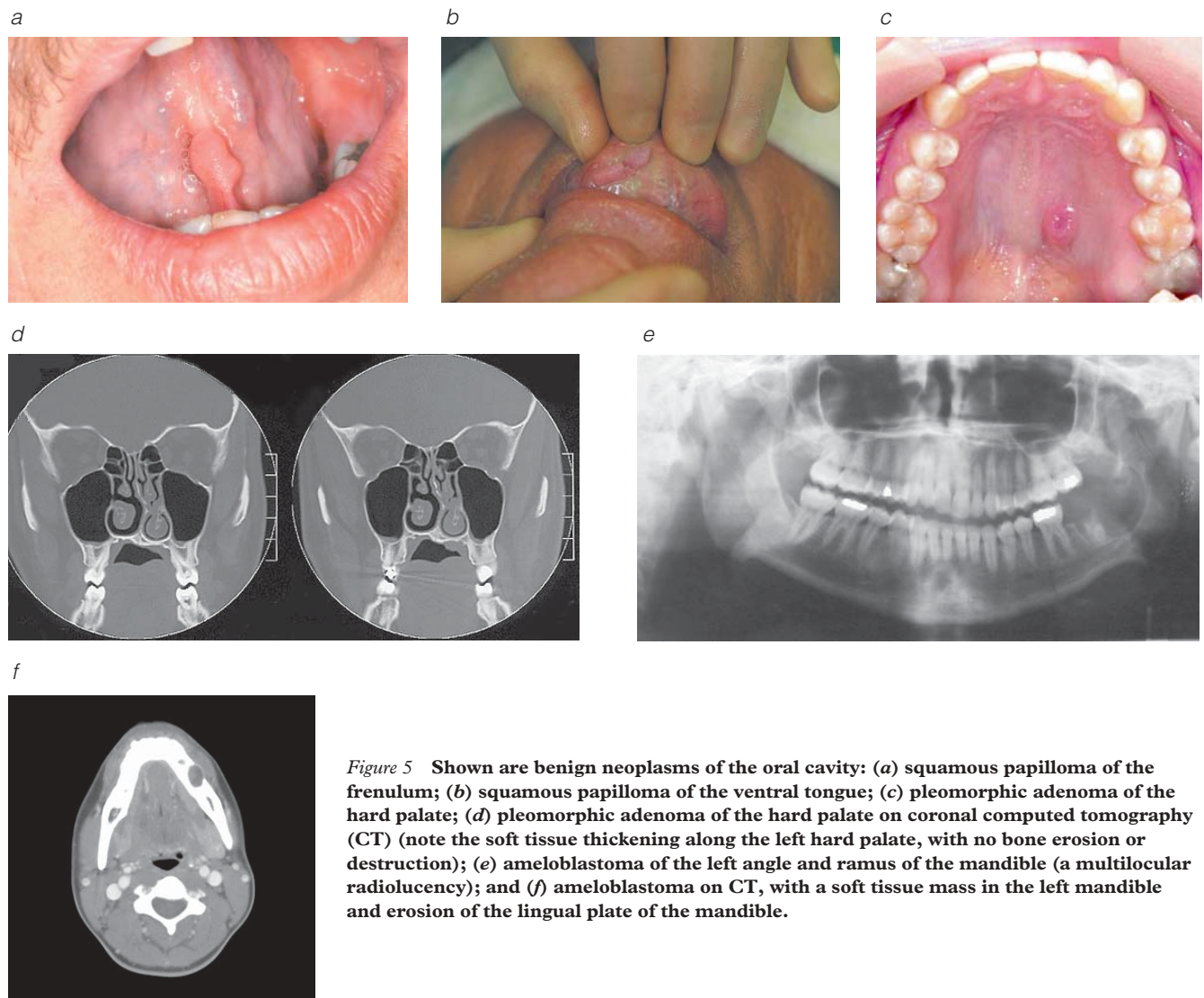


Figure 5 Shown are benign neoplasms of the oral cavity: (a) squamous papilloma of the frenulum; (b) squamous papilloma of the ventral tongue; (c) pleomorphic adenoma of the hard palate; (d) pleomorphic adenoma of the hard palate on coronal computed tomography (CT) (note the soft tissue thickening along the left hard palate, with no bone erosion or destruction); (e) ameloblastoma of the left angle and ramus of the mandible (a multilocular radiolucency); and (f) ameloblastoma on CT, with a soft tissue mass in the left mandible and erosion of the lingual plate of the mandible.

misdiagnosis on histopathologic evaluation. Accordingly, given the known rarity of squamous cell carcinoma of the dorsal surface of the anterior two thirds of the tongue, it may be prudent to obtain a second histopathologic opinion whenever a diagnosis of squamous cell carcinoma is rendered in this location. Treatment consists of conservative excision.²⁷

Ameloblastoma

Ameloblastoma is a neoplasm that arises from odontogenic (dental) epithelium, most frequently in the third and fourth decades of life [see Figure 5, e and f].^{8,26} It often presents as a painless swelling with bony enlargement. Approximately 80% of ameloblastomas involve the mandible and 20% the maxilla²⁹; the mandibular ramus is the most common site.²⁹ Ameloblastomas are usually benign but are often locally aggressive and infiltrative. Malignant ameloblastomas are rare but are notable for being associated with pain, rapid growth, and metastases.¹¹

On CT and panoramic jaw films, ameloblastomas typically appear as multilocular radiolucent lesions with a honeycomb appearance and scalloped borders.³⁰ These tumors are often

associated with an unerupted third molar tooth and, with the exception of the desmoplastic variant, rarely appear radiopaque. They may also appear unilocular on radiographic imaging.³¹ Histologic examination shows proliferating odontogenic epithelium with palisading peripheral cells that display reverse polarization of the nuclei.¹³

Appropriate management of ameloblastomas involves resection to clear margins. For mandibular ameloblastomas, either a marginal or a segmental mandibulectomy is done, depending on the relation of the lesion to the inferior cortical border. Curettage is associated with a high recurrence rate.²⁹ The prognosis for maxillary multicystic ameloblastoma is relatively poor because of the higher recurrence rate and the greater frequency of invasion of local adjacent structures (e.g., the skull base).³²

Most types of mesenchymal neoplasms may be found also in the oral region. Benign mesenchymal neoplasms known to occur in the oral cavity include (but are not limited to) hemangiomas, lipomas, schwannomas, neuromas, and neurofibromas. These are relatively rare lesions but should nonetheless be included in the differential diagnosis of intraoral

masses. The diagnosis is usually made on the basis of histopathologic examination of biopsy specimens. Benign bone tumors, although uncommon, are not unknown. Chondromas, hemangiomas, ossifying fibromas, and osteomas may all present as intraoral masses with bony expansion and normal overlying mucosa.

PREMALIGNANT

Leukoplakia

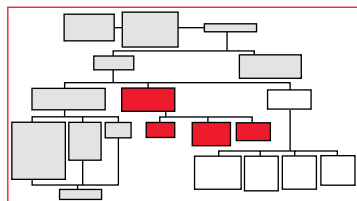
Leukoplakia is defined by the World Health Organization as a whitish patch or plaque that cannot be characterized clinically or pathologically as any other disease and that is not associated with any physical or chemical causative agent (except tobacco).³³ It is therefore a clinicopathologic entity of exclusion. It is often considered a potentially premalignant lesion. Leukoplakic lesions vary in size, shape, and consistency; there is usually no relation between morphologic appearance and histologic diagnosis. Histologic examination may reveal hyperkeratosis, dysplasia, carcinoma in situ (CIS), or invasive squamous cell carcinoma, or other pathologic processes.¹⁶ Dysplasia occurs in as many as 30% of leukoplakic lesions.⁸ Whereas a small percentage of lesions show invasive squamous cell carcinoma on pathologic examination,¹⁴ 60% of oral mucosa carcinomas present as white, keratotic lesions.¹⁶

Because leukoplakias are clinicopathologic entities, a biopsy result of “hyperkeratosis, acanthosis with or without inflammation” must be further interpreted by the clinician as to whether the clinical lesion could represent a frictional injury such as morsicatio mucosae oris, benign alveolar ridge keratosis, or some other less well-defined frictional keratosis. This is because it is well known that some so-called “benign leukoplakias” will develop squamous cell carcinoma when followed. Furthermore, the entity “proliferative verrucous leukoplakia” almost always shows benign histology for many years and the majority if not all of such lesions become invasive cancer when followed over time.

All leukoplakic lesions should undergo biopsy. For small areas of leukoplakia, excisional biopsy is usually appropriate. For larger lesions, incisional biopsy is generally preferable: it is important to obtain an adequate-size biopsy specimen in that varying degrees of hyperplasia and dysplasia may occur within the same specimen. There is no consensus regarding the management of “nondysplastic” leukoplakias that in the clinician’s opinion are not reactive or inflammatory in nature. Some believe that such hyperkeratotic lesions should be followed on a long-term basis, with rebiopsy performed if there are any changes in size or appearance. Others believe that they should be narrowly excised and, if the lesion recurs, more widely excised. Lesions characterized by dysplasia and CIS should be completely excised to clear margins when possible.

Erythroplakia

Erythroplakia is defined as a red or erythematous patch of the oral mucosa. It is associated with significantly higher rates of dysplasia, CIS, and invasive carcinoma than leukoplakia is.⁸ Erythroplakia is managed in much the same fashion as

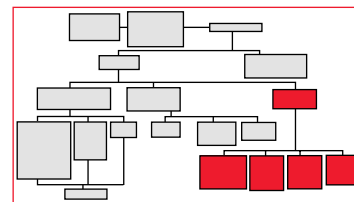


leukoplakia, with biopsy performed to rule out a malignant or premalignant lesion. Complete surgical excision is indicated if either a malignancy or a premalignancy is confirmed, and frequent follow-up is necessary.

MALIGNANT

Minor Salivary Gland Malignancies

The majority (60 to 70%) of minor salivary gland neoplasms are malignant, with adenoid cystic carcinoma, mucoepidermoid carcinoma, and adenocarcinoma [see Figure 6a] being the most commonly encountered cancers.^{26,34} As with benign minor salivary gland neoplasms, the hard and soft palates are the most common sites.³⁴



A minor salivary gland malignancy usually appears as a painless, slow-growing, intraoral mass.³⁵ Nodal involvement at presentation is uncommon.²⁶ Treatment usually involves surgical excision; adequate margins should be obtained with frozen-section control. Because these malignancies—particularly adenoid cystic carcinoma and polymorphous low-grade adenocarcinoma—have a propensity for perineural spread, frozen-section analysis of the nerves within the field of resection is usually obtained at the time of operation. If perineural spread occurs, postoperative irradiation is usually indicated, and distant metastases are likely to develop despite surgery and locoregional radiotherapy. As a result, it is usually best to limit the extent of the operation if major morbidity is anticipated from a radical resection.

Neck dissection is warranted in the treatment of minor salivary gland malignancies only if there is clinical or radiographic evidence of cervical metastases. Postoperative irradiation is indicated for most patients with high-grade malignancies, positive or close surgical margins, cervical metastases, or pathologic evidence of perineural spread or bone invasion.³⁵ Studies suggest that postoperative radiotherapy allows improved local control and may lead to longer disease-free survival.^{36,37}

Local recurrence and distant metastases are common, often developing many years later; regional recurrence is uncommon.³⁴ The survival rate for adenoid cystic carcinoma is relatively high (approximately 80%) at 5 years but decreases dramatically over the subsequent 10 to 15 years.^{34,38} Various factors predictive of poor survival have been identified [see Table 5].³⁸

Mucosal Melanoma

After the sinonasal region, the oral cavity is the site at which mucosal melanoma most often occurs in the head and neck.³⁹ Within the oral cavity, mucosal melanoma is most frequently found involving the upper alveolus and the hard palate.⁴⁰ It is most common in men, usually developing in the sixth decade of life.⁴⁰ No specific risk factors or premalignant lesions have been identified. There may, however, be an increased risk among certain subsets of East Asian patients.

Oral mucosal melanoma typically appears as a flat or nodular pigmented lesion, frequently associated with ulceration. Amelanotic melanoma is, fortunately, rare.⁴¹ Patients usually seek medical attention at an advanced stage of the

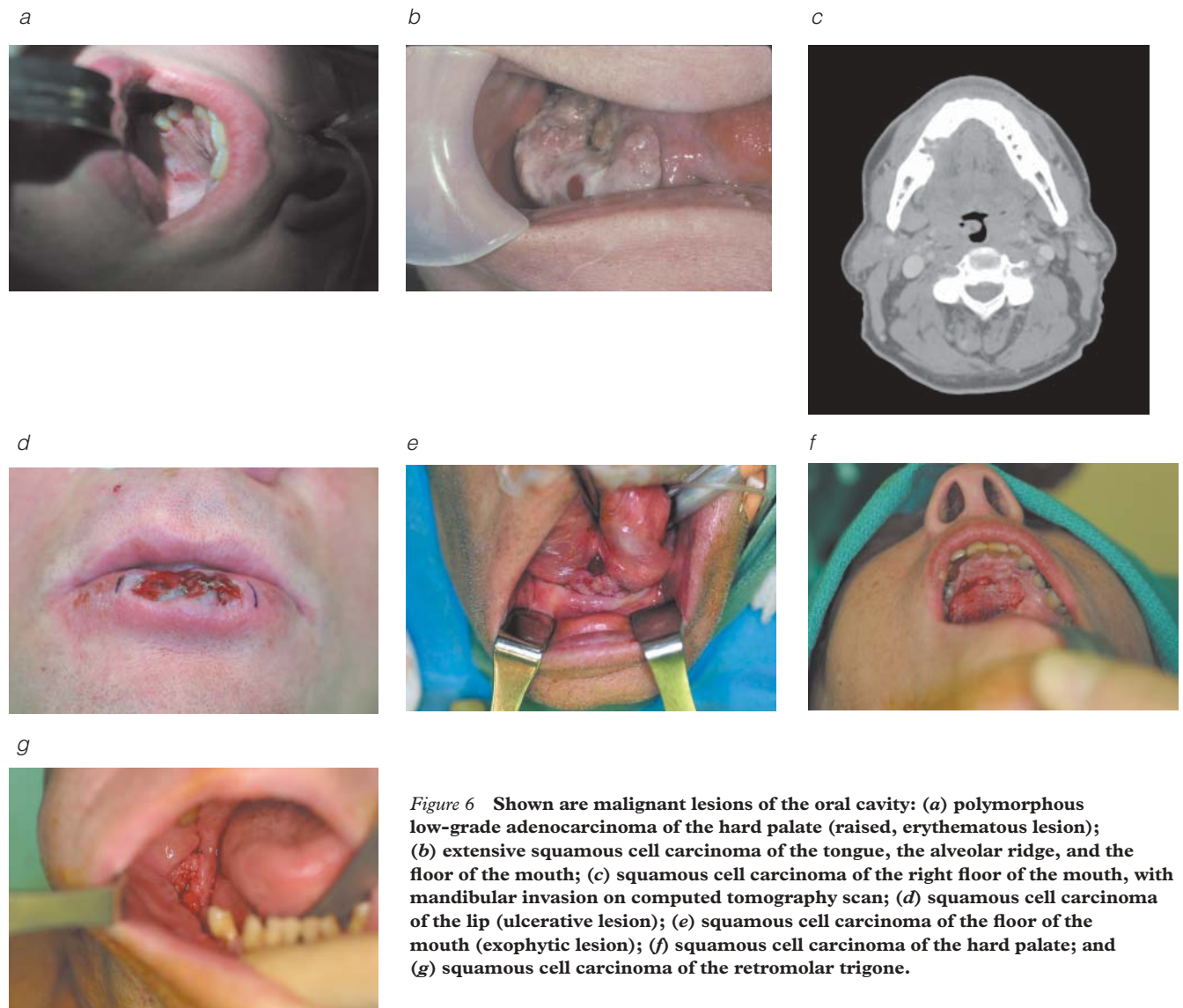


Figure 6 Shown are malignant lesions of the oral cavity: (a) polymorphous low-grade adenocarcinoma of the hard palate (raised, erythematous lesion); (b) extensive squamous cell carcinoma of the tongue, the alveolar ridge, and the floor of the mouth; (c) squamous cell carcinoma of the right floor of the mouth, with mandibular invasion on computed tomography scan; (d) squamous cell carcinoma of the lip (ulcerative lesion); (e) squamous cell carcinoma of the floor of the mouth (exophytic lesion); (f) squamous cell carcinoma of the hard palate; and (g) squamous cell carcinoma of the retromolar trigone.

disease, when pain develops or when they notice a change in the fit of their dentures. Early asymptomatic lesions are usually identified incidentally by either a physician or a dentist. Approximately 25% of patients have nodal metastases at presentation.⁴⁰ Tumors thicker than 5 mm are associated with an increased likelihood of nodal metastases at presentation.⁴²

No formal staging system has been developed for mucosal melanoma. The diagnosis is made by means of biopsy and

immunohistochemical staining (e.g., for HMB-45 antigen, Melan-A, or S-100 protein). Any suspicious pigmented lesion in the oral cavity should undergo biopsy to rule out melanoma. Amalgam tattoos are common in the oral cavity and can often be diagnosed on the basis of the presence of metallic fragments on dental radiographs.

Mucosal melanoma is managed primarily with surgical resection. The role of radiation therapy in this setting remains controversial.³⁹ Some clinicians recommend postoperative radiotherapy for all cases of mucosal melanoma; others recommend it only for patients with close or positive margins. The role of lymph node mapping has not been defined for mucosal melanoma. Because of the high incidence of nodes at presentation and the high regional recurrence rates reported in some studies, consideration should be given to treating the neck prophylactically by extending the postoperative radiation fields to cover this region.^{39,40}

The poor prognosis of mucosal melanoma with conventional treatment employing surgery and irradiation is a strong argument for referring patients to a medical oncologist for

Table 5 Poor Prognostic Factors for Minor Salivary Gland Malignancies

Advanced disease at time of diagnosis
Positive nodes
High-risk histologic type (i.e., high-grade malignancies such as high-grade mucoepidermoid carcinoma, adenocarcinoma, carcinoma ex pleomorphic adenoma, and adenoid cystic carcinoma)
Positive margins
Male sex

potential enrolment in postoperative systemic therapy trials. The survival rate for oral mucosal melanomas at 5 years ranges from 15 to 45%,^{40,41,43} with most patients dying of distant disease. Nodal involvement further reduces survival.⁴¹ Melanoma of the gingiva has a slightly better prognosis than melanoma of the palate.⁴¹ Several factors predictive of poor survival have been identified [see Table 6].⁴⁰ The relation between lesion depth and prognosis is not as clearly defined for oral mucosal melanoma as it is for cutaneous melanoma.

Squamous Cell Carcinoma

The incidence of squamous cell carcinoma increases with age, with the median age at diagnosis falling in the seventh decade of life,^{44,45} and is higher in men than in women. This cancer may be found at any of a number of oral cavity sub-sites [see Figure 6, *b through g*]. Lip carcinoma is the most common oral cavity cancer; 80 to 90% of these lesions occur on the lower lip.¹³ After the lip, the most common sites for oral cavity carcinoma are the tongue and the floor of the mouth. When the primary lesion is on the tongue, the lateral border is the most common location, followed by the anterior tongue and the dorsum.⁸ Approximately 75% of cases of oral cavity squamous cell carcinoma arise from a specific 10% of the mucosal surface of the mouth,¹¹ an area extending from the anterior floor of the mouth along the gingivobuccal sulcus and the lateral border to the retromolar trigone and the anterior tonsillar pillar.¹¹ Verrucous carcinoma is a subtype of squamous cell carcinoma and occurs most frequently on the buccal mucosa, appearing as a papillary mass with keratinization.

Between 80 and 90% of patients with oral cavity carcinoma have a history of either tobacco use (cigarette smoking or tobacco chewing) or excessive alcohol intake.⁴⁶ A synergistic effect is created when alcohol and tobacco are frequently used together.⁴⁶ In Asia, the practice of reverse smoking is associated with a high incidence of palatal carcinoma; betel nut chewing is associated with a high incidence of buccal carcinoma. The incidence of tumors in patients who have never smoked or drunk alcohol is rising, and the role of human papillomavirus in the pathogenesis and prognosis of this disease continues to be defined.⁴⁷

Small lesions tend to be asymptomatic. Larger lesions are often associated with pain, bleeding, poor denture fit, facial weakness or sensory changes, dysphagia, odynophagia, and trismus. Oral intake may worsen the pain, leading to malnutrition and dehydration.

Squamous cell carcinoma of the oral cavity has four different possible growth patterns: ulceroinfiltrative, exophytic, endophytic, and superficial [see Table 7].⁴⁸ Lip and buccal carcinomas tend to appear as exophytic masses. Ulceration is less common early in the course of cancers arising at these sites, but it may develop as the lesion enlarges. Cancers of the floor of the mouth may be associated with invasion of the

Table 7 Growth Patterns of Squamous Cell Carcinoma of Oral Cavity⁴⁸

Growth Pattern	Characteristics
Ulceroinfiltrative	Most common pattern; appears as ulcerated lesion that penetrates deep into underlying structures with surrounding induration
Exophytic	Common on lip and buccal mucosa; appears as papillary mass that may ulcerate when large
Endophytic	Uncommon; extends deep into soft tissue, with only small surface area involved
Superficial	Flat, superficial appearance; may be either a white patch or a red/velvety patch

tongue and the mandible. Decreased tongue mobility as a result of fixation is an indicator of an advanced tumor.^{48,49} Mandibular invasion occurs frequently in carcinomas of the floor of the mouth, the retromolar trigone, and the alveolar ridge as a consequence of the tight adherence of the mucosa to the periosteum in these regions. The risk of mandibular invasion increases with higher tumor stages. The majority (70 to 80%) of alveolar ridge carcinomas occur on the lower alveolus, often in areas of leukoplakia.⁵⁰

Oral cavity carcinoma is generally classified according to the staging system developed by the American Joint Committee on Cancer [see Table 8 and Table 9].⁵¹ Staging is based on clinical examination and diagnostic imaging. The diagnosis is made on the basis of biopsy and immunohistochemical staining (e.g., for cytokeratin and epithelial membrane antigen).

Squamous cell carcinoma of the oral cavity is usually managed with surgery, radiation therapy, or a combination of the two. Chemotherapy is increasingly used in combination with radiotherapy for patients at high risk of local or regional recurrence. For localized disease without bone invasion, the cure rate for radiation therapy is comparable to that of surgery.⁴⁶ The development of free tissue transfer has allowed for the successful cosmetic and functional reconstruction of large surgical defects of the oral cavity, including the mandible. Advanced tumors of the oral cavity are best managed with both surgery and irradiation. Traditionally, in North America, oral cavity cancer is treated primarily with surgery, and postoperative radiotherapy is added if the disease is advanced or if there are pathologic features indicative of a high risk of recurrence (i.e., positive margins on microscopy, extensive perineural or intravascular invasion, two or more positive nodes or positive nodes at multiple levels, or nodal capsular extension). North American practice is reflected in the guidelines developed by the American Head and Neck Society (www.headandneckcancer.org/clinicalresources/docs/oralcavity.php).

Radiation may be delivered to an oral cavity carcinoma via either external beam radiotherapy or brachytherapy, with the former being more commonly employed. Postoperative radiation, if indicated, should be started 4 to 6 weeks after surgery. The total radiation dose depends on the clinical and pathologic findings; the usual range is between 50 and 70 Gy, administered over 5 to 8 weeks. Primary radiation therapy is indicated for patients with stage I and selected stage II oral

Table 6 Poor Prognostic Factors for Mucosal Melanoma

Amelanotic melanoma
Advanced stage at presentation
Tumor thickness > 5 mm
Presence of vascular invasion
Distant metastases

Table 8 American Joint Committee on Cancer TNM Classification of Head and Neck Cancer

Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ
	T1	Tumor 2 cm or less in greatest dimension
	T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
	T3	Tumor more than 4 cm in greatest dimension
	T4a	Tumor invades adjacent structures, extending through cortical bone into deep (extrinsic) muscles of tongue, maxillary sinus, or facial skin
Regional lymph nodes (N)	T4b	Tumor invades masticator space, pterygoid plates, or skull base or encases internal carotid artery
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastases
	N1	Metastases in a single ipsilateral lymph node ≤ 3 cm in greatest dimension
	N2a	Metastases in a single ipsilateral lymph node > 3 cm but ≤ 6 cm in greatest dimension
	N2b	Metastases in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension
	N2c	Metastases in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension
Distant metastases (M)	N3	Metastases in lymph node > 6 cm in greatest dimension
	MX	Distant metastases cannot be assessed
	M0	No distant metastases
	M1	Distant metastases

cavity carcinomas, patients who refuse surgery or in whom surgery is contraindicated, and patients with incurable lesions who require palliative treatment. Radiation therapy is less effective against large or deeply invasive tumors, especially those that are invading bone, and therefore generally is not used alone for curative management of T3 and T4 lesions. For advanced-stage tumors of the oral cavity, surgery with postoperative radiotherapy is performed to decrease recurrence rates. Brachytherapy can be used as an adjunct when close or positive margins are noted. Brachytherapy also has a role in the management of recurrence or previously irradiated patients.⁵²

The decision regarding which treatment is presented to a patient as the first option is often determined by factors other than the extent of the tumor. Patient factors to be considered include desires and wishes, age, medical comorbidities, and performance status. Disease factors to be considered include tumor grade and stage, extent of invasion, primary site, the presence and degree of nodal or distant metastasis, and previous treatment. It is often helpful to discuss each case at a multidisciplinary treatment planning conference to develop a ranked list of options.

Squamous cell carcinoma of the oral cavity tends to spread to regional lymph nodes in a relatively predictable fashion. The primary levels of metastatic spread from oral cavity carcinoma include level I through III nodes and, less frequently, level IV nodes^{53–55}; metastases to level V are infrequent.^{53,55} The likelihood that cervical node metastases will develop varies depending on the location of the primary tumor in the oral cavity and on the stage of the tumor. Cervical metastases from carcinomas of the lip or the hard palate usually occur only in advanced disease⁸; however, cervical metastases from carcinomas of any of the other oral cavity subsites are common at presentation [see Table 10].^{8,11,48,50,51,53,56,57} Larger tumors carry a higher risk of cervical metastasis.

The clinically positive neck is usually managed with either a radical or a modified radical neck dissection, depending on the extent of the disease. Some studies have found that for N1 and some N2a patients, a comparable control rate can be achieved with a selective neck dissection encompassing levels I through IV, with postoperative radiation therapy added when indicated.^{58,59}

The clinically negative neck can occasionally be managed with observation alone, with treatment initiated only when nodal metastases develop. Alternatively, the nodal basins at risk can be managed prophylactically by means of either surgery or radiation therapy (involving levels I through III and, possibly, IV). The rationale for prophylactic neck management is that treatment initiated while metastases are still

Table 9 American Joint Committee on Cancer Staging System for Head and Neck Cancer

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3 T1, T2, T3	N0 N1	M0 M0
IVA	T4a T1, T2, T3, T4a	N0, N1 N2	M0 M0
IVB	Any T T4b	N3 Any N	M0 M0
IVC	Any T	Any N	M1

Table 10 Incidence of Nodal Metastases* at Presentation in Oral Cavity Subsites

Oral Cavity Subsite	Incidence of Metastases (%)
Lip	10
Tongue	30–40
Floor of the mouth	50
Alveoli	28–32
Buccal mucosa	40–52

*Clinically detectable or occult.

occult is thought to be more effective than treatment initiated after the disease has progressed to the point where it is clinically detectable. For this reason, many clinicians advocate prophylactic neck dissection for patients with oral cavity carcinomas who are at moderate (15–20%) risk for occult metastases at presentation. The selective neck dissection not only addresses any occult metastatic nodes but also functions as a staging procedure that helps in determining the prognosis and assessing the need for postoperative radiotherapy.^{60,61} In general, elective neck management is recommended for T2 and higher-stage carcinomas of the tongue, the floor of the mouth, the buccal mucosa, the alveolus, and the retromolar trigone, as well as for advanced (T3 or T4) carcinomas of the lip and the hard palate.^{8,11,48,56,57,62,63} Most surgeons now emphasize the depth of invasion of the primary tumor as a critical determinant of the risk of occult nodal metastases. It has been suggested that elective treatment of the neck with surgery or radiation therapy should be considered on the basis of the depth of tumor invasion rather than the surface diameter of the lesion. The tumor depth that is held to warrant investigation varies among published studies, ranging from 2 to 5 mm.^{64–66} Bilateral neck dissection may be indicated for midline oral cavity cancers.

The prognosis depends on the location of the tumor in the oral cavity. Overall, if all of the oral cavity subsites are considered together, the presence of cervical metastases decreases survival by approximately 50%. Varying 5-year survival rates have been reported for the different subsites of the oral cavity [see Table 11].^{8,11,48,50,51,56,67}

Oral Cavity Manifestations of HIV Infection

Infectious and neoplastic oral cavity lesions are often the first manifestation of HIV infection or the first indication of the progression to AIDS.

INFECTIONS

The same organisms that affect the general population cause most of the oral infections seen in the HIV population; however, oral infections in HIV patients tend to be recurrent, comparatively severe, and relatively resistant to treatment.⁶⁸ Oral hairy leukoplakia, caused by Epstein-Barr virus, is a

common oral infection seen almost exclusively in the HIV population. It presents as an asymptomatic, corrugated, whitish, nonremovable, slightly raised patch on the lateral borders of the tongue. The finding of such a lesion on clinical examination of an HIV patient is suggestive of the diagnosis, but confirmation of the diagnosis requires biopsy. Treatment usually is not necessary. High-dose acyclovir may be given if the patient requests treatment.

Several rare infections of the oral cavity are being seen with increasing frequency in the HIV population, including tuberculosis, syphilis, *Rochalimaea henselae* infection (bacillary angiomatosis), *Borrelia vincentii* infection (acute necrotizing ulcerative gingivitis), cryptococcosis, histoplasmosis, coccidioidomycosis [see Figure 7], and human papillomavirus infection.

NEOPLASMS

The two most common intraoral neoplasms in the HIV population are Kaposi sarcoma and non-Hodgkin lymphoma. Kaposi sarcoma occurs most commonly in patients with HIV, although it is not exclusive to this population. It frequently involves the oral cavity, showing a predilection for the attached mucosa of the palate or the gingiva.⁶⁸ The characteristic lesions are blue, brown, purple, or red exophytic masses that may be either confined to the oral mucosa or systemic. They are usually asymptomatic but may become painful or obstructive with growth or ulceration. Treatment is aimed at palliation of symptoms and may involve sclerotherapy, intralesional chemotherapy, laser ablation, cryotherapy, surgical excision, or radiation therapy.⁶⁹ Systemic chemotherapy may be provided if the disease is systemic.



Figure 7 Shown is coccidioidomycosis of the tongue in an HIV-positive patient.

The risk of non-Hodgkin lymphoma is much higher in the HIV population than in the general population.⁶⁹ It should be suspected in any HIV patient who presents with an intraoral mass or an ulcerated lesion. Non-Hodgkin lymphoma appears as painful lesions that show a predilection for the palate, the retromolar trigone, and the tongue. Associated symptoms include facial paresthesias, loose dentition, fever, night sweats, and weight loss. Local disease is managed with radiation; systemic disease is managed with chemotherapy.

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Table 11 Five-Year Carcinoma Survival Rates for Oral Cavity Subsites

Oral Cavity Subsite	Survival Rate
Lip	80%; > 90% for early-stage disease
Tongue	30–35% (advanced-stage disease); > 80% (early-stage disease)
Floor of the mouth	85% for stages I and II (T1 lesions > 95%); 20–52% for stages III and IV
Alveoli	50–60%
Retromolar trigone	75% for T1 and T2 lesions; approximately 20–50% for T3 and T4 lesions
Buccal mucosa	49–68%
Palate	85% for T1 lesions; 30% for T4 lesions

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Figure 1 Tom Moore

2 PAROTID MASS

*Harrison W. Lin, MD, and Neil Bhattacharyya, MD, FACS**

Demographics

Major salivary gland tumors constitute 3 to 6% of all tumors of the head and neck in adults,¹ and approximately 85% of these salivary gland tumors are found in the parotid gland. Roughly 16% of these neoplasms are malignant.² The spectrum of histopathologic entities encompassed by the term “parotid mass” is exceedingly broad and continues to evolve as our understanding of the origin and clinical behavior of the various tumors arising from the parotid gland expands.

Anatomy

The parotid gland is an irregular, wedge-shaped, unilobular salivary gland residing in the parotid space, a compartment that additionally contains the facial nerve (cranial nerve VII), sensory and autonomic nerves, branches of the external carotid artery and external jugular vein, and lymphovascularity [see *Figure 1*].³ The gland itself resides within the split layers of the superficial layer of the deep cervical fascia and overlies the upper one fourth of the sternocleidomastoid muscle, the ramus of the mandible, and the masseter muscle. Approximately 20% of the gland extends medially through the stylomandibular tunnel, which is formed by the posterior edge of the mandibular ramus, the anterior border of the sternocleidomastoid muscle, and the posterior belly of the digastric muscle. At its lower pole, the parotid gland is separated from the submandibular gland by the stylomandibular ligament, which extends from the tip of the styloid process to the angle and the posterior edge of the mandible.

The seventh cranial nerve artificially divides the parotid gland into two surgical zones: tissue lateral to the facial nerve is designated as the superficial lobe, whereas the medial portion is referred to as the deep lobe. Moreover, each lobe has been described to have variable processes, including the condylar, meatal, and posterior processes of the superficial lobe and the glenoid and stylomandibular processes of the deep lobe. Furthermore, a retromandibular portion of the deep lobe resides in the prestyloid compartment of the parapharyngeal space, anterior to the styloid process and associated musculature, the carotid sheath, and cranial nerves IX through XII. Note that the separation of the parotid gland into superficial and deep lobes is not based on a fascial plane. The parotid isthmus, the portion of the gland between the ramus of the mandible and the posterior belly of the digastric muscle, connects the superficial with the deep lobes of the parotid gland.

The parotid (Stensen) duct originates from the superficial lobe of the gland, courses anteriorly on the lateral surface of

the masseter muscle, and then turns medially to pierce the buccinator muscle at the level of the second maxillary molar tooth and open into the mouth through the parotid papilla. The expected course of the duct is approximated by a line drawn between the tragus and philtrum of the upper lip, midway between the angle of the mouth and the zygomatic arch.

Etiology

Two predominant theories of the neoplastic pathogenesis of parotid masses have been proposed, including the bicellular and multicellular theories. The former, also referred to as the reserve cell theory, suggests that tumors arise from stem cell populations in both the excretory and intercalated ductal systems. Warthin tumor, mixed tumor, oncocytoma, acinic cell carcinoma, adenoid cystic carcinoma, and oncocytic carcinoma are proposed to arise from stem cells of the intercalated duct, whereas squamous cell carcinoma (SCC) and mucoepidermoid carcinoma are thought to derive from excretory duct stem cells. Alternatively, the multicellular theory suggests that the various parotid tumors arise from the fully differentiated cells within the salivary gland unit. Based on this theory, mucoepidermoid and squamous cell carcinomas derive from excretory duct cells, oncocytic tumors from striated duct cells, acinous tumors from acinar cells, and mixed tumors from intercalated duct cells and myoepithelial cells.⁴

Although the true nature of the neoplastic transformation of parotid gland cells is yet to be fully elucidated, these and other classification systems are founded on the understanding that primary parotid tumors are of epithelial origin. The parotid gland also hosts numerous lymph nodes that serve as a basin for metastatic spread of malignancies of the head. Accordingly, parotid masses will not infrequently represent the presenting sign of a cutaneous SCC or melanoma of the temple or scalp, for example.

Differential Diagnosis

NONNEOPLASTIC CONDITIONS

The causes of nonneoplastic parotid masses include congenital, infectious or inflammatory, and lymphoepithelial conditions. Congenital lesions such as hemangiomas and vascular malformations often present in childhood as a swelling in the preauricular region. First branchial cleft cysts can also present in the pediatric population and can be manifest as a mass inferior to the cartilaginous external auditory canal and with a cyst tract that will have a variable relationship with the branches of the facial nerve.

Inflammatory disorders of the parotid gland can be categorized into acute and chronic processes. Moreover, acute infections of the salivary glands can be further subclassified

* The authors and editors gratefully acknowledge the contributions of the previous author, Ashok R. Shaha, MD, FACS, to the development and writing of this chapter.

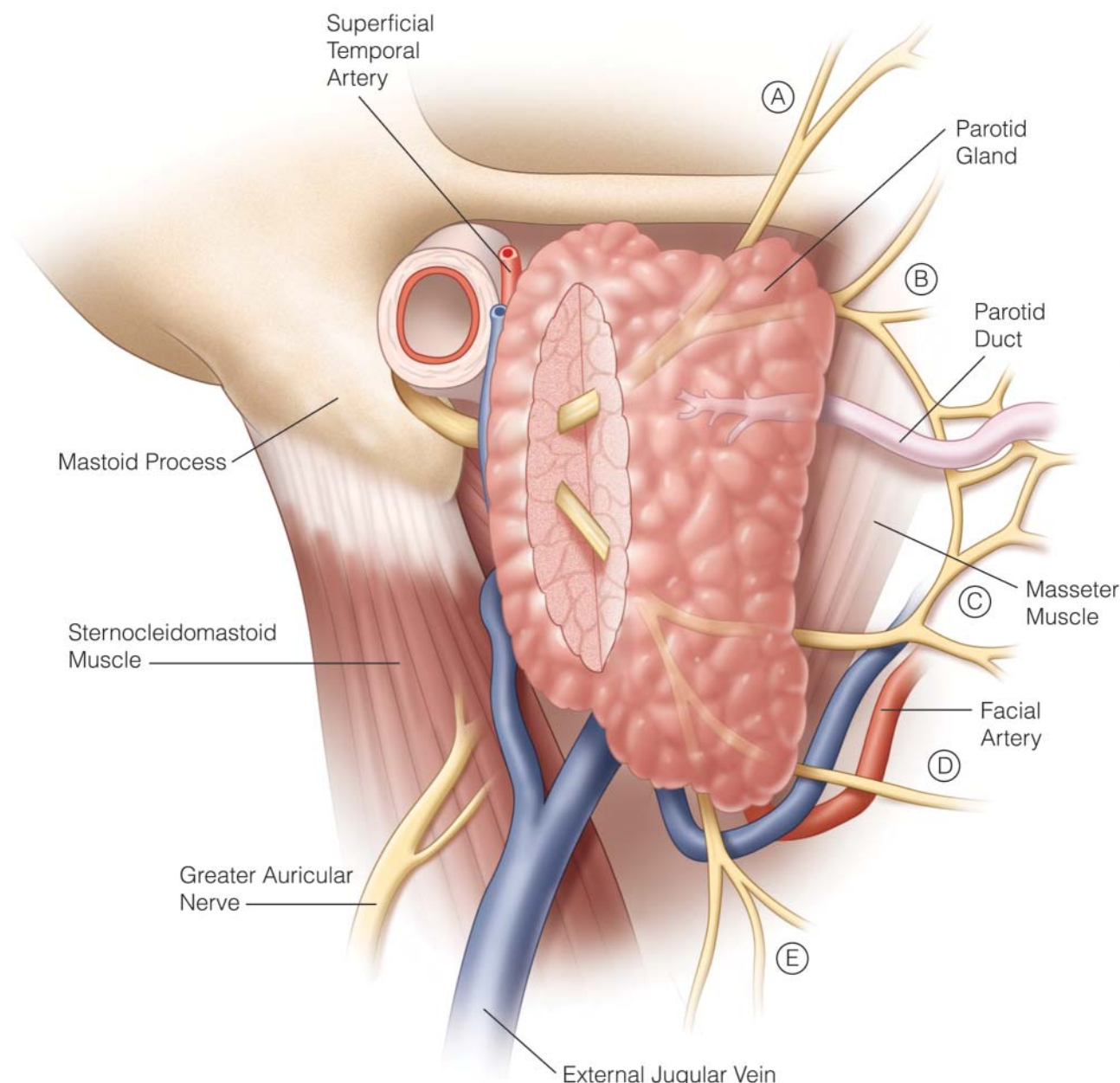


Figure 1 Anatomy of the parotid region. Branches of the facial nerve: A = temporal; B = zygomatic; C = buccal; D = marginal; E = cervical.

into viral and bacterial processes. Although viral parotid infections by the RNA virus paramyxovirus resulting in the mumps syndrome are now exceedingly rare following the introduction of the mumps vaccine in 1967, acute viral parotitis from the influenza, parainfluenza, adenovirus, cytomegalovirus, coxsackievirus, and enteric cytopathic human orphan (ECHO) viruses have been reported in the literature.⁵ Acute bacterial infections of the parotid gland, however, are by far more common and are believed to be the result of retrograde contamination of the salivary ducts and parenchymal tissues by oral flora combined with stasis of salivary flow, often attributable to dehydration. Additionally, the serous composition of the saliva produced by the parotid gland lacks

many of the antibacterial lysosomes, antibodies, and mucins found in the mucinous saliva produced by the other major salivary glands. Accordingly, bacterial sialadenitis most commonly affects the parotid gland. Relatively sudden onset of pain, tenderness, and swelling of the parotid are the most frequent presenting signs and symptoms, and treatment consists of hydration, sialogogues, and systemic antimicrobial therapy. If a discrete abscess is suspected and identified on cross-sectional imaging, surgical or radiologically guided needle drainage may be required.

Chronic inflammatory disorders of the parotid gland are frequently manifested by a mildly painful, recurrent, and gradual enlargement of the gland. Of these disorders, chronic

sialadenitis is the most frequently encountered and is believed to be the result of reduced rates of salivary production and flow, resulting in frequent subacute suppurative infections, sialectasis, ductal ectasia, and progressive acinar cell loss. Initial treatment is similar to that of acute bacterial sialadenitis, and failure to respond to conservative measures may prompt consideration for surgical interventions, including ductal dilation, ductal ligation, and parotidectomy. In sarcoidosis, salivary gland involvement may cause duct obstruction, pain associated with the duct, xerostomia, or enlargement of the gland. The diagnosis is supported by chest films that show bilateral hilar adenopathy and by elevated levels of angiotensin-converting enzyme. Uveoparotid fever (Heerfordt disease), a subtype of sarcoidosis manifested by the triad of uveitis, parotid enlargement, and facial weakness, can persist for months to years and will often resolve spontaneously and without treatment.⁶

Lymphoepithelial lesions of the parotid gland may be divided into lymphocytic infiltrative diseases and lymphomas. In many cases, patients with lymphocytic infiltrative diseases such as Mikulicz disease, sicca complex, and Sjögren syndrome have had their conditions for long periods and simply believe that their chronic enlargement of bilateral parotid glands was normal facial soft tissue changes associated with age. Eighty percent of patients with primary Sjögren syndrome will experience parotid gland swelling; moreover, malignant transformation to high-grade lymphoma is known to occur. Lymphoepithelial cysts are benign cystic lesions that may arise from lymph nodes or from lymphoid aggregates in the salivary gland. These lesions may be associated with HIV infection.

Primary lymphoma of the salivary gland is uncommon, occurring in fewer than 5% of patients with parotid masses. Suggestive clinical features include (1) the development of a parotid mass in a patient with a known history of malignant lymphoma, (2) the occurrence of a parotid mass in a patient with an immune disorder (e.g., Sjögren syndrome, rheumatoid arthritis, or AIDS), (3) the presence of a parotid mass in a patient with a previous diagnosis of benign lymphoepithelial lesion, (4) the finding of multiple masses in one parotid gland or of masses in both parotid glands, and (5) the association of a parotid mass with multiple enlarged cervical lymph nodes unilaterally or bilaterally.⁷

As discussed, infectious or inflammatory diseases involving the parotid, unlike neoplasms, tend to give rise to pain in their early stages. However, certain parotid malignancies may also present with pain attributable to sensory nerve involvement. Most such inflammatory conditions begin with diffuse enlargement of one or more salivary glands rather than with presentation with a discrete, palpable parotid mass. Although parotitis is generally unilateral, it may be bilateral or affect other salivary glands if a systemic causative condition is involved. The pain reported may be related to the presence of a stone in the salivary duct or to diffuse obstructive parotitis. Chronic parotitis may lead to recurrent infection and inflammation. When recurrent swelling of the salivary gland does occur, it may be directly related to eating and increased salivation.

NEOPLASTIC CONDITIONS

Neoplastic masses may be present for years without causing any symptoms and affect both men and women at similar

rates. Benign salivary tumors tend to be more common in younger persons, whereas malignant parotid lesions are more common in the fifth and sixth decades of life.⁸ The classic presentation of a benign parotid tumor is that of an asymptomatic parotid mass that has been present for months to years, often exhibiting slow growth.

Benign Neoplasms

Benign neoplasms of the parotid, which include pleomorphic adenoma, basal cell adenoma, myoepithelioma, Warthin tumor, oncocytoma, and cystadenoma, are typically slow-growing and rarely exhibit malignant transformation. However, the observation of rapid growth in a long-standing pleomorphic adenoma (often 10 to 15 years later) is suggestive of malignant transformation. In a 2005 study of 94 patients with pleomorphic adenoma, malignant transformation to carcinoma ex pleomorphic adenoma was documented in 8.5% of cases.⁹ Rapid tumor growth, metastasis to lymph nodes, deep fixation, and facial nerve weakness are all strongly suggestive of malignant disease and are indicators of a poor prognosis.¹⁰ Although pain is more often experienced by patients with inflammatory or infectious conditions, it is also reported by some patients with infiltrative malignant tumors. In these patients, pain is another indicator of a poor prognosis.^{11,12}

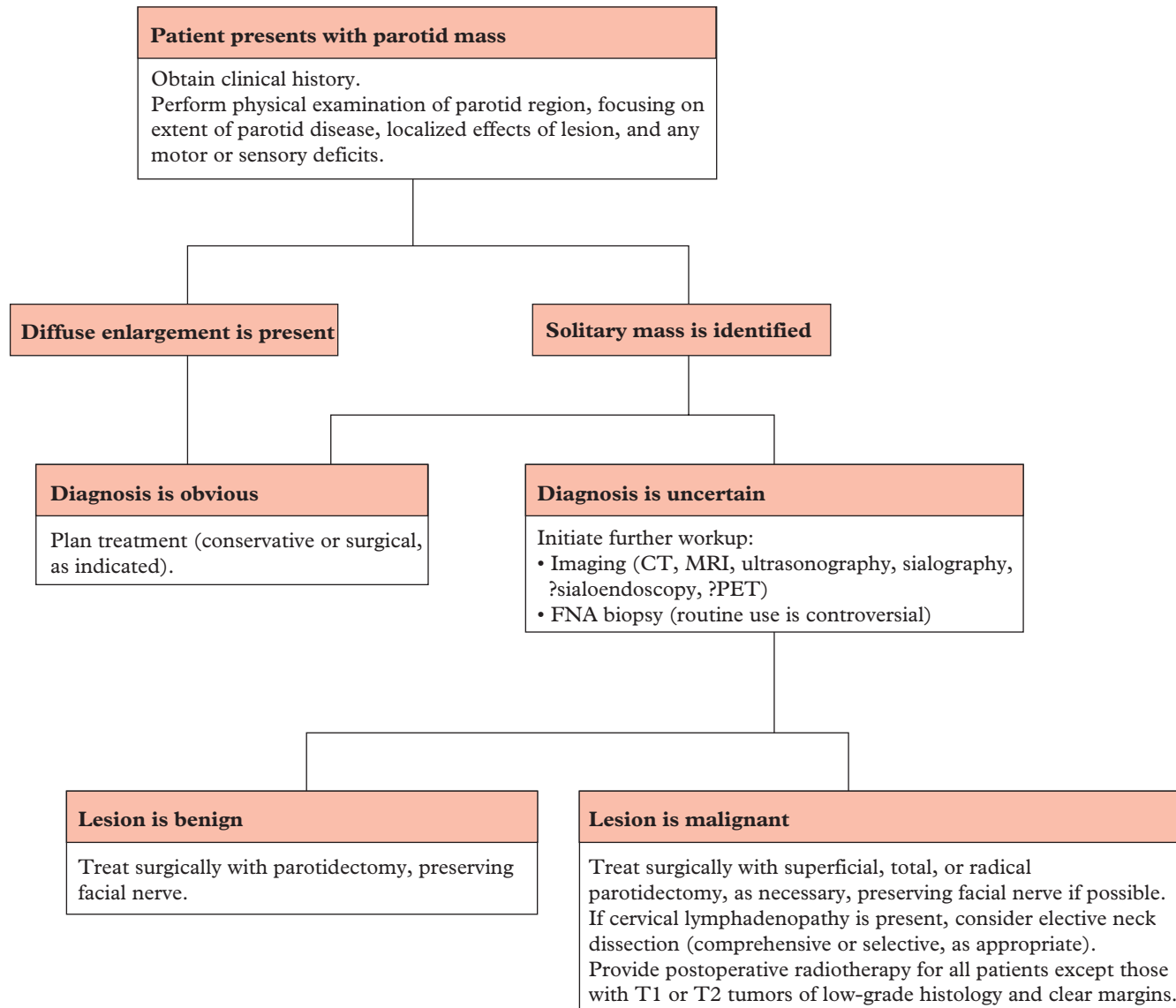
Malignant Neoplasms

Although considerable debate continues to surround the histopathologic classification of malignant parotid tumors, most clinicians currently prefer the classification system of the Armed Forces Institute of Pathology¹³ or that of the World Health Organization.¹⁴ Malignant parotid neoplasms include primary SCC, mucoepidermoid carcinoma, acinic cell carcinoma, adenocarcinoma, adenoid cystic carcinoma, carcinoma ex pleomorphic adenoma, and malignant mixed tumor. The presence of facial nerve palsy should raise the index of suspicion for malignancy. Occasionally, patients present with classic Bell palsy. This condition is usually of viral origin, and most patients recover over time. If Bell palsy persists, however, further investigation is required, including imaging or biopsy studies to rule out an associated parotid lesion.¹⁵

Mucoepidermoid carcinoma is the most common malignant tumor of the parotid gland, comprising roughly one third of all parotid cancers, and is subclassified into low-, intermediate-, and high-grade tumors. For high-grade tumors, selective cervical node dissection may be indicated and postoperative radiation therapy is often required. Combined surgical and radiation therapies for such tumors results in a 5-year survival rate of under 50%. In contrast, low-grade tumors are more circumscribed and contain more mucinous cells. Surgical therapy without radiation yields a 5-year survival rate of 75%.

Adenoid cystic carcinoma is an aggressive salivary gland tumor that exhibits a very high incidence of perineural spread with skip metastasis along the facial nerve and its branches, and the incidence rises with higher tumor stages.¹⁶ The incidence of local recurrence is also very high; therefore, postoperative radiation therapy should be provided to patients who are at high risk for relapse, such as those with close or positive margins and those with perineural invasion. Although

Approach to Evaluation of a Parotid Mass



the incidence of cervical lymph node metastasis in patients with adenoid cystic carcinoma is relatively low, the incidence of distant metastasis (especially pulmonary metastasis) has been reported to be as high as 38%.¹⁷ Long-term follow-up in these patients is essential.

Adenocarcinoma has been considered a shrinking category as advances in electron microscopy and immunohistochemistry have reclassified many of these tumor variants into other subtypes and histopathologies. Adenocarcinomas are exceedingly aggressive tumors with high rates of facial nerve involvement, regional disease, and distant metastases and, accordingly, should be managed as a high-grade parotid tumor with surgical and radiation therapies.

Acinic cell carcinoma is a low-grade tumor with a female predominance and bilateral presentation approximately 3% of the time. Tumors are frequently well circumscribed, but a small percentage of patients will present with cervical nodal metastases. Patients with acinic cell carcinoma are typically managed with surgical therapy alone, although histopathologic findings to suggest a more aggressive, high-grade tumor have been proposed to serve as indicators for postoperative radiation therapy.¹⁸

Primary SCC of the parotid gland is quite rare, and most diagnoses of parotid SCC represent skin cancer that has metastasized to the periparotid lymph nodes. Primary SCC has a high malignant potential, and radical surgical extirpation (with preservation of the facial nerve when possible), followed by planned postoperative radiotherapy, is the treatment of choice.¹⁹

Metastatic Neoplasms to the Parotid

The parotid gland represents the first or second nodal basin for metastatic scalp, temple, and auricular cutaneous malignancies. Although the incidence of metastatic parotid disease is comparatively low in the Northern Hemisphere, it has been reported to be far more common than primary parotid disease in regions of the world with high rates of skin cancers, such as Australia.²⁰ Cutaneous SCC and melanoma are by far the most frequently encountered metastatic parotid malignancies and, despite treatment, will exhibit local or distant failure in 25 to 50% of cases. Other cancers that have been reported to metastasize to the parotid include basal cell, Merkel cell, and small cell carcinomas.

Presentation and Diagnostic Workup

HISTORY

Evaluation of any parotid mass should begin with a detailed clinical history. Comprehensive inquiries regarding the duration of signs and symptoms are paramount as masses resulting in local pain and swelling of recent onset (i.e., within the past few days) are more likely to be infectious or obstructive in nature. If the mass has been present for a longer period (i.e., weeks to months), a neoplasm is more likely. Unfortunately, the

presentations of some nonneoplastic conditions resemble those of neoplasms, and distinguishing one type of condition from the other can be challenging. Accordingly, the history should continue with further questions focusing on local or systemic signs and symptoms, the presence of swelling or other masses in the salivary glands, and previous medical conditions, including cancers of the skin.

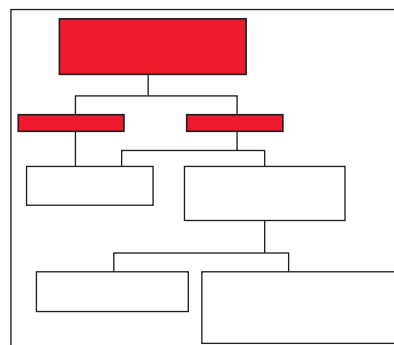
PHYSICAL EXAMINATION

The physical examination begins with an assessment of the extent of the disease in the parotid region, the neck, and the parapharynx. Extension of a tumor to regional compartments can be manifest as trismus or as motor or sensory deficits resulting from neural invasion. Palpation of the mass will reveal whether it is painless or painful; soft, firm, hard, or cystic; and mobile or fixed to deep tissue or skin. The skin of the scalp, ear, and face should be carefully examined for suspicious lesions, and the neck is palpated for adenopathy. In the oral cavity, the Stensen ducts are examined for discharge or saliva with parotid massage. The oropharynx is examined for asymmetries or lateral wall deviation.

The most common presentation of a parotid mass, whether benign or malignant, is an asymptomatic swelling in the preauricular or retromandibular region. Of note, the location of the parotid mass is a very important diagnostic factor. A benign tumor will classically present as a firm, mobile, and marblelike mass in the superficial portion of the gland and not fixed to the deeper structures or to the skin. Parotid tumors that originate in the deep lobe, however, may present as a vague, diffuse swelling behind the angle of the mandible or as a swelling of the parapharyngeal area, resulting in medial displacement of the tonsil, soft palate, or lateral oropharyngeal wall.

Occasionally, patients will present with metastases to one or more of the 17 to 20 intraparotid or periparotid lymph nodes in the substance of the parotid and along its tail. These lymph nodes may be directly affected by metastatic tumors originating from the anterior scalp or the temporal, periocular, or malar regions. It is critical to obtain a detailed history of any previously excised skin lesions, some of which may have been an SCC or a melanoma primary tumor that metastasized to the periparotid nodes. Generally, such metastasis involves multiple superficial lymph nodes and presents as diffuse enlargement of the parotid parenchyma. With massive involvement of the parotid gland, facial nerve palsy is not uncommon in this setting. Although the majority of metastases to the parotid gland derive from cutaneous SCC or melanoma, metastatic spread from the lung, breast, and kidney has also been reported.

As with any patient with an otolaryngologic complaint, a thorough evaluation of the head and neck, including a detailed visualization of the oral cavity and laryngopharynx, is required. Occasionally, a tumor of the oropharynx presents as cervical lymphadenopathy or as metastatic disease in the tail of the parotid. In such cases, it may be difficult to determine whether the patient has a primary salivary gland tumor or a metastatic lesion. The presence of any suspicious pathologic condition in the oropharynx or the base of the tongue is an indication for appropriate endoscopy and biopsy of the suspected primary site.



Physical findings suggestive of malignancy include a large and fixed mass, facial nerve weakness, lymph node metastasis, and skin involvement; patients with advanced parotid malignancies may present with trismus. Although patients with benign parotid tumors rarely exhibit facial nerve weakness, approximately 12 to 15% of patients with parotid malignancies have facial nerve dysfunction at presentation. The most common causes of facial nerve weakness in this setting are adenoid cystic carcinoma, poorly differentiated carcinoma, and SCC.

The presence of cervical lymph node metastasis may direct the clinician’s attention to the parotid mass, although less than 20% of persons with parotid malignancies actually have clinically apparent cervical lymph node metastases at the time of the initial presentation.^{11,21} The parotid tumors most commonly associated with metastatic disease to the lymph nodes at presentation are undifferentiated carcinoma (89%),²² high-grade mucoepidermoid carcinoma (42%),²³ and SCC (44%).²⁴ Lymph node metastases may also derive from high-grade adenocarcinomas (22%) or malignant mixed tumors (16%).²⁵

Some patients will present without any symptoms, with the only significant physical examination finding being an oropharyngeal mass, which is suggestive of either a deep-lobe parotid or parapharyngeal tumor. Given that between 80 and 90% of the parotid tissue is superficial to the facial nerve, the majority of parotid tumors, not surprisingly, develop within the superficial lobe of the parotid. However, approximately 10% of parotid masses will be found within the deep lobe. Most deep-lobe parotid tumors are benign, in which case, surgical treatment generally consists of a superficial parotidectomy with dissection and preservation of the facial nerve, followed by removal of the tumor. Occasionally, however, malignant deep-lobe parotid tumors do occur, and such tumors frequently involve the facial nerve. Surgical treatment may require sacrifice of the facial nerve in select circumstances. Most patients who have undergone surgical treatment of a malignant deep-lobe tumor will require postoperative radiation therapy.

FINE-NEEDLE ASPIRATION CYTOLOGY

Although fine-needle aspiration cytology (FNAC) has been shown to play a vital part in the management of head and neck SCC, the role of FNAC in parotid gland masses has yet to be fully resolved. This is attributable in large part to the perceived minimal impact of FNAC results on therapeutic decision making as most parotid masses, both benign and malignant, will require surgical excision and thereby provide a definitive pathologic diagnosis. Moreover, the variability of histopathologic subtypes, intralesional cellular distribution, and cytopathologist expertise has led some surgeons to question the utility of preoperative FNAC.

However, the ability of FNAC to distinguish masses of benign nature from those of malignant nature, salivary gland origin from those of nonsalivary gland origin (e.g., sarcoma, lymphoma, metastatic melanoma), and, in some cases, low-grade malignancy from high-grade malignancy has been suggested to provide useful guidance for medical and surgical planning [see Table 1]. Preoperative discovery of a non-salivary gland neoplasm in a parotid mass may preclude surgical excision in lieu of medical, radiation, or palliative

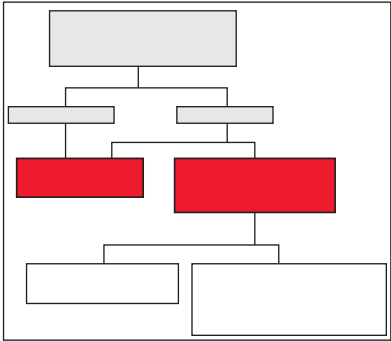
Table 1 Salivary and Nonsalivary Pathologic Processes Distinguished by Fine-Needle Aspiration Biopsy
Salivary processes
Benign
Mixed tumor
Warthin tumor
Oncocytoma
Malignant
Primary salivary gland cancer
Adenoid cystic carcinoma
Acinic cell carcinoma
Adenocarcinoma
SCC
Mucoepidermoid carcinoma
Metastatic disease in salivary gland
Melanoma
SCC
Nonsalivary processes
Lipoma
Sebaceous cyst
Lymph node pathology
Metastatic cancer
Lymphoma

SCC = squamous cell carcinoma.

therapies. Additionally, preoperative knowledge of a parotid malignancy has been shown to significantly impact both surgical planning and surgical results. In one study, patients who underwent parotidectomy for an FNAC-diagnosed parotid malignancy had significantly higher rates of both upfront cervical neck dissections and clear pathologic margins.²⁶ In addition, knowledge of the nature of a parotid mass may greatly influence patient counseling, which may have particular utility in patients who are poor surgical candidates or prefer a watchful-waiting strategy, when appropriate. Accordingly, the use of FNAC in the evaluation of a parotid mass should be strongly considered as it is generally felt to be an excellent investigational tool as long as it is employed in the appropriate clinical context.

IMAGING

Modern imaging of salivary gland pathology predominantly consists of computed tomography (CT) or magnetic resonance imaging (MRI) or both. As with their characteristics in the imaging of other regions of the body,



CT is considered superior to MRI for evaluation of the bony structures, whereas MRI is typically more helpful in soft tissue resolution and in distinguishing between inflammatory conditions and neoplasms. Additionally, MRI may better discern an inferior tail of a parotid mass from an upper cervical mass and detect radiologic signs of malignancy, including irregular, indistinct margins with parotid tissue, low signal intensities on all imaging sequences, and tumor infiltration into muscle, bone, or nerve [see Figure 2].

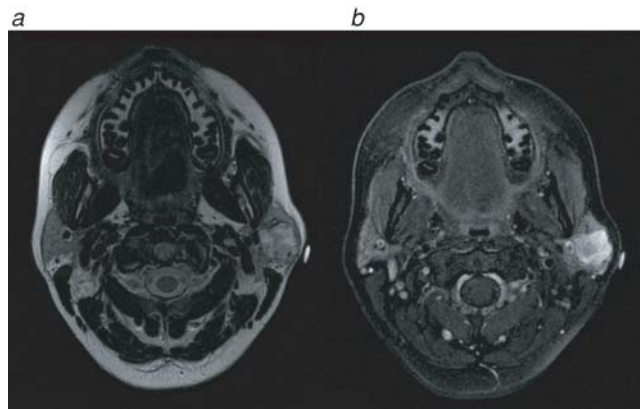


Figure 2 Axial (a) T₁ and (b) T₂ magnetic resonance images of a left superficial parotid pleomorphic adenoma demonstrating the classic irregular, bosselated appearance.

Similar to FNAC, the utility of the various imaging modalities used in the evaluation of a parotid mass continues to be controversial. Many surgeons believe that preoperative ultrasonography, CT, and MRI will provide little to no influence on therapy for a small, mobile, superficial parotid nodule, which would be better assessed with FNAC, surgery, or both. Conversely, management of the more advanced, fixed, aggressive, and deep parotid tumors can be considerably influenced by CT or MRI findings. Patients with diffuse parotid enlargement, tumor extension beyond the superficial lobe, facial nerve weakness, trismus, or deep tumors that are difficult to evaluate clinically should be initially assessed with CT. Fixation to the deeper structures may prompt the need for MRI to evaluate the extent and for parapharyngeal extension or origin. Patients with tumors in close proximity to the facial nerve, external auditory canal, mastoid, mandible, or regional musculature may also benefit from a preoperative MRI, which may influence surgical planning.

Currently, the role of positron emission tomography (PET) in the initial evaluation of a parotid mass remains undefined. This modality may, however, be of some value in the evaluation of suspected recurrent parotid cancers, lymph node metastases, or distant metastases.

Management

BASIC PRINCIPLES

Treatment of a parotid mass depends on the nature and extent of the lesion, which, like most cancers of the body, is categorized and described by a universal staging system. Staging for cancers of the parotid gland is accomplished by means of the familiar tumor-node-metastasis (TNM) system developed by the American Joint Committee on Cancer (AJCC) [see Table 2 and Table 3].

Malignant parotid masses are primarily treated surgically according to established oncologic principles [see Table 4]. An

appropriate parotidectomy with identification and assessment of the facial nerve for tumor involvement is considered the current standard of care. Postoperative radiation therapy is often indicated for more involved and advanced-stage tumors. Moreover, benign parotid masses are frequently managed surgically as well, with exploration of the parotid gland, identification and preservation of the facial nerve, and evaluation of the neoplasm regarded as the customary surgical interventions. Enucleation, once considered an acceptable alternative to superficial parotidectomy for benign pathologies, is now discouraged owing to the possibility of tumor spillage, incomplete removal of the tumor, inadvertent injury to the branches of the facial nerve, and high rates of local recurrence. The need for revision surgery for benign parotid processes is considered unacceptable given the difficulty of surgery on a previously operated tissue bed and consequential increased risk of injury to the facial nerve.

SURGICAL THERAPY

Surgery is the primary treatment modality for nonlymphoid salivary gland neoplasms, both benign and malignant. Optimal surgery for the parotid gland should address both the primary tumor and cervical disease, if present, in a single operation. The minimum surgical intervention for a parotid mass is superficial parotidectomy with identification, dissection, and preservation of the facial nerve, although a subtotal or total parotidectomy and neck dissection may be required for larger tumors that involve the deep lobe of the parotid gland or for patients with clinical or radiologic evidence of regional disease, respectively. If the tumor involves and directly infiltrates the facial nerve, a diagnosis of malignancy, if not previously established preoperatively, should be explored. If a malignant diagnosis is confirmed, a low threshold for nerve sacrifice should be maintained. However, facial nerve preservation despite tumor encroachment on the nerve can be considered as long as all gross disease is removed. With the availability of adjuvant radiation therapy, the surgeon can choose to leave behind microscopic disease, which can be addressed postoperatively. In addition to temporary or permanent facial weakness, patients should be counseled on and consented for other potential complications of parotid surgery, including permanent numbness of the auricle from greater auricular nerve injury and Frey and first-bite syndromes. Frey syndrome, also known as auriculotemporal syndrome or gustatory sweating, is believed to result from misdirected regeneration of cut parasympathetic fibers from the otic ganglion to the parotid gland, leading to the innervation of sweat glands and subcutaneous vasculature. Patients report discomfort, erythema, and perspiration over the parotid bed or neck when eating. First-bite syndrome is a poorly understood complication of surgery in the parapharyngeal space believed to result from injury to the cervical sympathetic chain. A denervation hypersensitivity of parotid myoepithelial cells to parasympathetic neurotransmitters results, leading to supramaximal myoepithelial contraction and consequent pain with the first bite of a meal. Intracutaneous and intraglandular injections of botulinum toxin type A have been shown to provide patients with long-term and effective relief from the symptoms of Frey and first-bite syndromes, respectively.

Table 2 American Joint Committee on Cancer TNM Clinical Classification of Major Salivary Gland Tumors

Primary tumor (T)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T1: Tumor ≤ 2 cm in greatest dimension without extraparenchymal extension
T2: Tumor > 2 cm but ≤ 4 cm in greatest dimension without extraparenchymal extension
T3: Tumor having extraparenchymal extension without seventh nerve involvement and/or > 4 cm but < 6 cm in greatest dimension
T4a: Tumor invades the skin, mandible, external auditory canal, seventh nerve, and/or > 6 cm in greatest dimension
T4b: Tumor invades the base of skull, pterygoid plates, carotid artery
Regional lymph nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension
N2: Metastasis in a single ipsilateral lymph node, > 3 cm but ≤ 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension
N2a: Metastasis in a single ipsilateral lymph node > 3 cm but ≤ 6 cm in greatest dimension
N2b: Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension
N2c: Metastasis in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension
N3: Metastasis in a lymph node > 6 cm in greatest dimension
Distant metastasis (M)
MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

An incision in a preauricular skin crease gently curving 2 mm below the auricular lobule and continuing 2 to 3 cm below the mandible is made down to the level of the parotid fascia to prevent lobular distortion and transection of the marginal mandibular branch of the facial nerve, respectively. An anterior flap above the level of the parotid fascia is elevated with a blade or scissors, whereas a posterior flap is raised to expose the tail of the parotid, sternocleidomastoid muscle, and mastoid tip. Dissection then proceeds deeper to

identify the posterior belly of the digastric muscle. Identification of the tragal pointer is then accomplished with cautious dissection along the tragal cartilage, and the main trunk of the facial nerve is typically found roughly 1 cm anterior and deep to this important landmark at the level of the digastric muscle. After the nerve is identified, the superficial lobe of the parotid is removed with the mass with careful dissection along the nerve branches.²⁷ In certain instances, a retrograde approach to facial nerve identification can be used and has been shown to reduce operative time and blood loss and conserve normal parotid tissue without compromising surgical margin status.²⁸

High-grade tumors involving the deep lobe or with extension to the parapharyngeal space may require a total parotidectomy. Following removal of the superficial portion of the gland, the facial nerve and its branches are carefully raised off the deep parotid tissue or tumor, and this tissue is subsequently elevated off the masseter muscle and removed. A cervical-parotid approach with exposure of the internal and external carotid arteries, internal jugular vein, and vagus, spinal accessory, and hypoglossal nerves may facilitate identification and excision of parapharyngeal space masses posterior to the stylomandibular ligament. A midline mandibulotomy to provide additional exposure and control of vessels can also be added for tumors extending to the skull base or encasing the carotid artery. If the tumor extends beyond the parotid gland and involves the skin, infratemporal fossa, ascending ramus of the mandible, or mastoid process, more extensive surgical procedures (e.g., composite resection, lateral temporal bone resection, or radical parotidectomy) may become necessary.

Table 3 American Joint Committee on Cancer Staging System for Major Salivary Gland Tumors

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3 T1, T2, T3	N0 N1	M0 M0
IVA	T4a, T4b T1, T2, T3, T4a	N0, N1 N2	M0 M0
IVB	T4b Any T	Any N N3	M0 M0
IVC	Any T	Any N	M1

Table 4 Principles of Treatment of Parotid Tumors

Adequate local excision of tumor, based on extent of primary lesion
Preservation of facial nerve if possible
Elective neck dissection reserved for selected patients
Postoperative radiotherapy when indicated (in appropriate fields)
Prognosis determined primarily by stage and grade of tumor

Patients with preoperative facial weakness or paralysis will often require sacrifice of the main trunk of the facial nerve. If the tumor involves only an isolated branch of the facial nerve, the surgeon can elect to selectively sacrifice the involved branch alone. Following nerve sacrifice, nerve grafting should be considered in the same procedure. Reconstruction of the facial nerve can be performed with a nerve graft from the greater auricular nerve, medial or lateral antecubial cutaneous nerve, sural nerve, and ansa hypoglossi, among others. The functional results of nerve grafting vary considerably, depending on the age of the patient, the extent of the disease, and the identification of and appropriate anastomosis to the peripheral branches of the facial nerve. If postoperative radiation therapy is envisioned, its potential deleterious effects on nerve regeneration should be considered.

FACIAL NERVE MONITORING

Postoperative facial weakness is a frequent complication of parotid surgery and is the most feared complication for both the patient and the surgeon. Transient facial dysfunction after parotidectomy ranges from 20 to 40%, whereas permanent paralysis has been reported to be as high as 5%. Continuous visual observation of the patient's ipsilateral face by the assistant surgeon or nurse has historically been the traditional method of facial nerve monitoring during a parotidectomy. More recently, however, facial nerve stimulators and continuous electromyographic neuromonitoring of the facial nerve have been employed by surgeons as a means to assist in nerve identification, to provide additional indication for what is "safe" to cut, and to reduce operative time.

Although a few small retrospective case-control comparisons have noted a significant reduction in the rates of temporary and/or permanent facial weakness with the use of these electrophysiologic devices,²⁹ the vast majority of studies have failed to demonstrate a significant improvement in postoperative facial nerve function outcome.^{30,31} Given the exceedingly low incidence of inadvertent permanent facial paralysis in parotid surgery, however, Eisele and colleagues pointed out that a prospective, randomized study would need, at minimum, 1,000 patients to demonstrate a reduction in permanent facial nerve injury from 2% to 1%.³² Accordingly, the authors suggested that a large, multi-institutional study will be needed to ascertain the benefits and drawbacks of electrophysiologic nerve monitoring technologies and that surgeons who believe that patients will benefit from the information provided should continue to use the devices.

INTRAOPERATIVE FROZEN-SECTION ANALYSIS

The role of intraoperative frozen-section examination in the evaluation of a parotid mass, like that of fine-needle aspiration biopsy, is the subject of considerable debate. Nevertheless, frozen-section examination has been found to be useful for distinguishing salivary processes from nonsalivary processes and benign disease from malignant disease. In 80 to 90% of cases, the findings from intraoperative frozen-section examination correlate with the final pathologic diagnosis.³³ If frozen-section examination shows a benign tumor and confirms the presumed preoperative diagnosis, lateral superficial parotidectomy should be sufficient. If frozen-section examination shows high-grade mucoepidermoid carcinoma in a

patient without evidence of cervical disease, selective neck dissection may be considered for staging purposes. Moreover, if frozen-section examination provides a definitive diagnosis of malignancy, further decisions about the extent of parotidectomy and possible selective neck dissection can be made accordingly. If the pathology is unrevealing, the procedure originally planned can be performed, and any further interventions, if required, can be dictated by the final pathologic diagnosis. Notably, significant caution should be exercised when deciding on facial nerve preservation or sacrifice based solely on frozen-section results as frozen-section classification of the wide variety of parotid tumors (both benign and malignant) is often difficult and will often depend on the experience of the frozen-section pathologist.

NECK DISSECTION

Overall, about 10 to 20% of patients with malignant parotid tumors present with clinically detectable cervical lymphadenopathy, most frequently in levels II and III. Nodal metastasis reduces the survival rate by roughly 50%.^{11,21,34} Patients with clinically or radiologically positive cervical metastases are treated with either a comprehensive, modified radical, or selective neck dissection, depending on the extent of the disease. However, the surgical management of patients with salivary malignancies who have no detectable cervical lymphadenopathy continues to be a matter of debate. Studies have revealed that only 12 to 16% of patients without clinical evidence of cervical disease demonstrated pathologically positive nodes.^{25,35} In view of the low incidence of occult metastases, these investigators do not recommend routine elective treatment of the neck.

Other authors have investigated the patient and tumor factors that may predict the presence of neck disease. Two large population studies identified older age, facial nerve paralysis, extraparotid involvement, higher tumor grade, and perilymphatic invasion as variables predictive of occult cervical disease.^{34,36} In addition, Bhattacharyya and Fried determined that tumor size and histopathologic type were also predictors of regional disease and identified adenocarcinoma and SCC as histopathologies with the highest odds ratios for nodal metastases.³⁴ Similarly, Regis De Brito Santos and colleagues found that the variables that showed the highest correlation with the incidence of lymph node metastasis were the histopathologic type (i.e., adenocarcinoma, undifferentiated carcinoma, high-grade mucoepidermoid carcinoma, SCC, or salivary duct carcinoma) and tumor stage.³⁷

Accordingly, an elective neck dissection may be considered in patients with advanced-stage primary tumors, those whose tumors are of high histologic grades, and those whose tumors are of certain specific histologic types. A selective neck dissection may be performed to remove levels IB, II, III, and the upper part of V for the purposes of staging.³⁸ However, a more comprehensive neck dissection that encompasses levels I through V may be necessary in patients who present with clinically or radiologically apparent cervical metastases.

RADIATION THERAPY

Candidates for postoperative radiation therapy include patients with advanced-stage disease, a large primary tumor, close or positive margins, nodal disease, perineural spread, soft tissue extension, preoperative facial nerve dysfunction, or

Table 5 Indications for Postoperative Radiation Therapy for Parotid Cancer

Aggressive, highly malignant tumor
Invasion of adjacent tissues outside parotid capsule
Regional lymph node metastases
Deep-lobe cancer
Gross residual tumor after resection
Recurrent tumor after resection
Invasion of facial nerve by tumor

Table 6 Prognostic Factors for Salivary Gland Tumors

Increasing age at diagnosis
Pain at presentation
Higher T stage
Higher N stage
Skin invasion
Facial nerve dysfunction
Perineural growth
Positive surgical margins
Soft tissue invasion
Treatment type

high-grade tumors [see Table 5].^{39,40} Accordingly, postoperative radiation therapy is suggested for all patients with parotid malignancy other than those with low-grade T1 or T2 tumors and clear surgical margins. Combined surgical and radiation therapy has been shown to result in 5- and 10-year survivals of as high as 95% and 84%, respectively.⁴¹

A role for radiation therapy for the treatment of an N0 neck in lieu of an elective neck dissection has been proposed, and there is some evidence to suggest that elective irradiation is as effective as elective neck dissection.²⁵ Some authors have proposed that postoperative patients who will already be requiring radiation therapy for additional primary-site sterilization are excellent candidates for elective radiation of the neck.⁴²

Additionally, there is substantial interest in the potential role of neutron radiotherapy as a primary treatment modality for certain parotid malignancies, including advanced inoperable cancers, adenoid cystic carcinomas, and recurrent pleomorphic adenomas, and for poor surgical candidates. Particle radiation may be of particular benefit in adenoid cystic carcinoma to treat perineural extension. Although additional work and further data on survival and related complications await this treatment modality, neutron radiotherapy may be the best option currently available for patients with inoperable parotid cancer.⁴³

Survival

Survival of patients with parotid gland malignancies is influenced by multiple factors [see Table 6]. The various histopathologies with variable aggressiveness will naturally exert different influences on mean survival durations and rates; histopathologic distributions and survival estimates of parotid gland cancers extracted from a national cancer database are provided in Table 7.⁴⁴ In this study, acinar cell carcinomas and mucoepidermoid carcinomas exhibited the best survival, whereas carcinoma ex pleomorphic adenoma, adenocarcinomas, and SCCs displayed substantially poorer survivals. Of note, separate survival analyses of the different grades of mucoepidermoid carcinoma demonstrated statistically significant differences in overall survival according to grade.

In addition to histopathology, increasing age, tumor size, tumor grade, extraglandular extension, and the presence of cervical disease all significantly and negatively impacted survival, whereas the use of external-beam radiation therapy provided a statistically significant survival benefit.^{44,45} Moreover, Lima and colleagues concluded in their institutional experience that the presence of facial nerve dysfunction also negatively influenced prognosis.²¹

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Table 7 Histopathologic Distribution of Major Salivary Gland Malignancies of the Parotid

Histopathology	n	%	Mean Survival (mo)	5-Year Actuarial Survival (%)	10-Year Actuarial Survival (%)
Mucoepidermoid carcinoma	367	40.6	105	81.5	63.5
Primary SCC	191	21.2	60	46.1	27.2
Adenocarcinoma	189	20.9	70	65.9	49.7
Acinar cell carcinoma	95	10.5	108	80.0	77.7
Carcinoma ex pleomorphic adenoma	23	2.5	59	40.2	0.0
Malignant mixed tumor	20	2.2	95	73.3	55.0
Adenoid cystic carcinoma	18	2.0	95	70.7	NA
Total	903	100.0	88	66.6	49.7

NA = not available; SCC = squamous cell carcinoma.

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3 NECK MASS

Christopher Scally, MD, and Gerard M. Doherty, MD*

Assessment of a Neck Mass

Clinical Evaluation

HISTORY

The evaluation of any neck mass begins with a careful history taken with the differential diagnosis in mind [see

Table 1] because directed questions can narrow down the diagnostic possibilities and focus subsequent investigations. For example, in younger patients, one might suspect congenital or inflammatory lesions, whereas in older adults, the first concern is often neoplasia.

The duration and growth rate of the mass are important: malignant lesions are more likely to grow rapidly than benign ones, which may grow and shrink. The location of the mass in the neck can also narrow the list of possibilities. This is particularly important for differentiating congenital masses from neoplastic or inflammatory ones because each type usually occurs in particular locations. In addition, the location of a neoplasm has both diagnostic and prognostic significance. The possibility that the mass is an infectious or inflammatory process should also be assessed. One should evaluate for evidence of infection or inflammation (e.g., fever, pain, or tenderness); a recent history of tuberculosis, sarcoidosis, or fungal infection; the presence of dental problems; and a history of trauma to the head and neck. Masses that appear inflamed or infected are far more likely to be benign.

Finally, factors suggestive of cancer include a history of malignancy elsewhere in the head and neck (e.g., a history of skin cancer, melanoma, thyroid cancer, or head and neck cancer); night sweats (suggestive of lymphoma); excessive exposure to the sun (a risk factor for skin cancer); smoking or excessive alcohol consumption (risk factors for squamous cell carcinoma of the head and neck); nasal obstruction or bleeding, otalgia, odynophagia, dysphagia, or hoarseness (suggestive of a malignancy in the upper aerodigestive tract); or exposure to low-dose therapeutic radiation (a risk factor for thyroid cancer).

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Financial disclosure information is located at the end of this chapter before the references.

PHYSICAL EXAMINATION

The head and neck examination is challenging because much of the area to be examined is not easily seen. Patience and practice are necessary to master the

special instruments and techniques of examination. A head and neck examination is usually performed with the patient sitting in front of the physician. Constant repositioning of the head is necessary to obtain adequate visualization of the various areas. Gloves must be worn during the examination, particularly if the mucous membranes are to be examined. Good illumination is essential. Fiberoptic endoscopy with a flexible laryngoscope and a nasopharyngoscope is a common component of the physical examination for evaluating

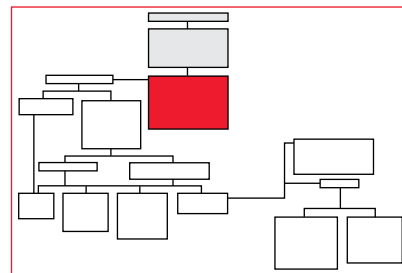
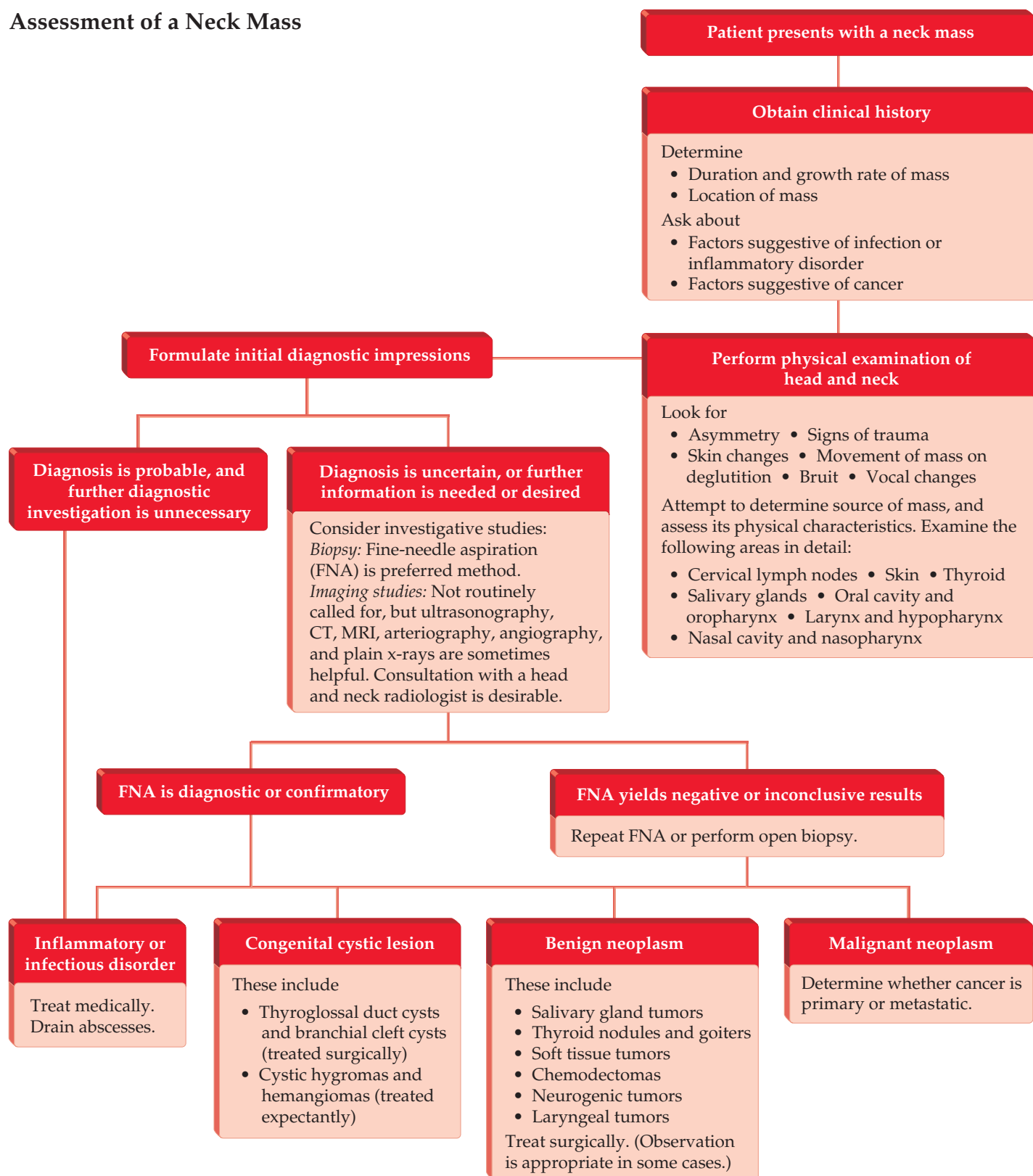
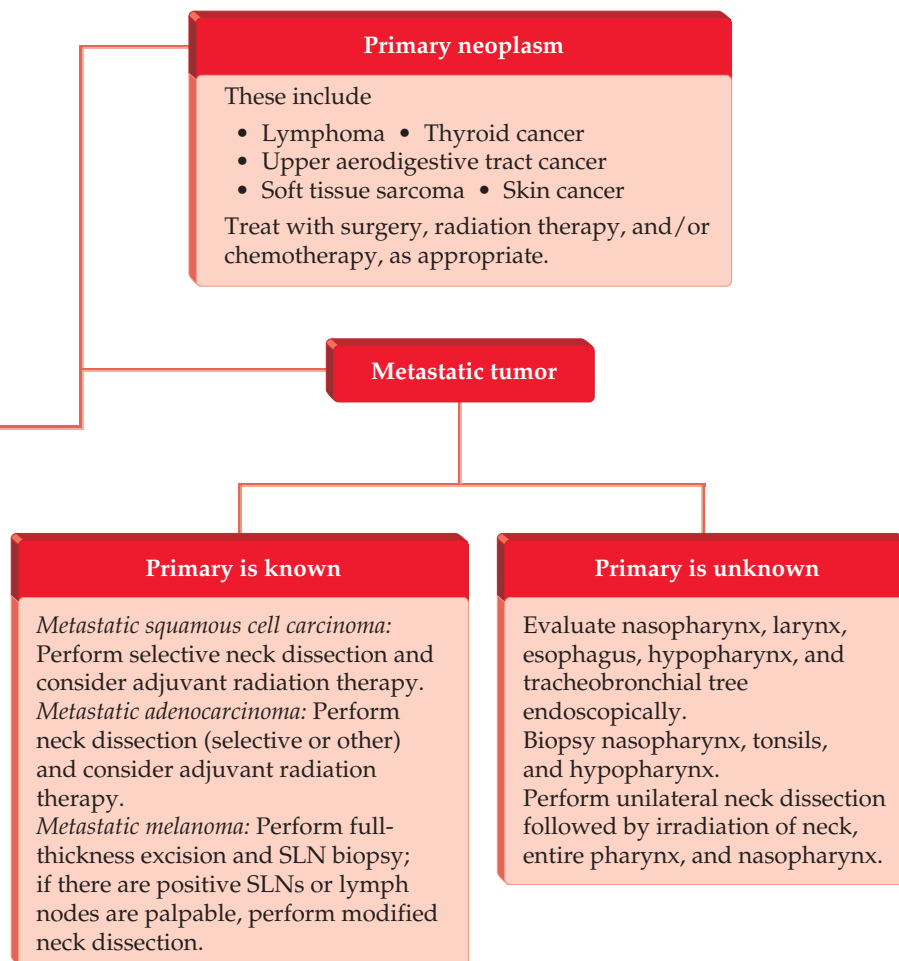


Table 1 Etiology of Neck Mass

Inflammatory and infectious disorders
Acute lymphadenitis (bacterial or viral infection)
Subcutaneous abscess (carbuncle)
Infectious mononucleosis
Cat-scratch fever
AIDS
Tuberculous lymphadenitis (scrofula)
Fungal lymphadenitis (actinomycosis)
Sarcoidosis
Congenital cystic lesions
Thyroglossal duct cyst
Branchial cleft cyst
Cystic hygroma (lymphangioma)
Vascular malformation (hemangioma)
Laryngocele
Benign neoplasms
Salivary gland tumor
Thyroid nodules or goiter
Soft tissue tumor (lipoma, sebaceous cyst)
Chemodectoma (carotid body tumor)
Neurogenic tumor (neurofibroma, neurilemmoma)
Laryngeal tumor (chondroma)
Malignant neoplasms
Primary
Salivary gland tumor
Thyroid cancer
Upper aerodigestive tract cancer
Soft tissue sarcoma
Skin cancer (melanoma, squamous cell carcinoma, basal cell carcinoma)
Lymphoma
Metastatic
Upper aerodigestive tract cancer
Skin cancer (melanoma, squamous cell carcinoma)
Salivary gland tumor
Thyroid cancer
Adenocarcinoma (breast, gastrointestinal tract, genitourinary tract, lung)
Unknown primary tumor

Assessment of a Neck Mass





the larynx, the nasopharynx, and the paranasal sinuses, especially when these areas cannot be adequately inspected with other techniques.

The examination should begin with inspection for asymmetry, signs of trauma, and skin changes. The examiner should ask the patient to swallow to observe whether the mass moves with deglutition and should palpate the neck from both the front and behind. Auscultation can detect audible bruits. One should also both listen to and ask about the patient's voice, changes in which may suggest either a laryngeal tumor or recurrent nerve dysfunction from locally invasive thyroid cancer.

During the physical examination, one should be thinking about the following questions: What structure is the neck mass arising from? Is it a lymph node? Is the mass arising from a normally occurring structure, such as the thyroid gland, a salivary gland, a nerve, a blood vessel, or a muscle? Or is it arising from an abnormal structure, such as a laryngocele, a branchial cleft cyst, or a cystic hygroma? Is the mass soft, fluctuant, easily mobile, well encapsulated, and smooth? Or is it firm, poorly mobile, and fixed to surrounding structures? Does it pulsate? Is there a bruit? Does it appear to be superficial, or is it deeper in the neck? Is it attached to the skin? Is it tender?

The following areas of the head and neck are examined in some detail.

Cervical Lymph Nodes

The cervical lymphatic system consists of interconnected groups or chains of nodes that parallel the major neurovascular structures in the head and neck. The skin and mucosal surfaces of the head and neck all have specific and predictable nodes associated with them. The classification of cervical lymph nodes has been standardized to comprise six levels [see Figure 1]. Accurate determination of lymph node level on physical examination and in surgical specimens not only helps establish a common language among clinicians but also permits comparison of data among different institutions.

The location, size, and consistency of lymph nodes furnish valuable clues to the nature of the primary disease. Other physical characteristics of the adenopathy should be noted as well, including the number of lymph nodes affected, their mobility, their degree of fixation, and their relation to surrounding anatomic structures. One can often establish a tentative diagnosis on the basis of these findings alone. For example, soft or tender nodes are more likely to derive from an inflammatory or infectious condition, whereas hard, fixed, painless nodes are more likely to represent metastatic cancer. Multiple regions of enlarged lymph nodes are usually a sign of systemic disease (e.g., lymphoma, tuberculosis, or infectious mononucleosis), whereas solitary nodes are more often due to malignancy. Firm, rubbery nodes are typical of lymphoma.

The submental and submandibular nodes (level I) are palpated bimanually. The three levels of internal jugular chain nodes (levels II, III, and IV) are best examined by gently rolling the sternocleidomastoid muscle between the thumb and the index finger. The posterior triangle nodes (level V) are palpated posterior to the sternocleidomastoid.

The tracheoesophageal groove nodes (level VI) are then palpated.

Skin

Careful examination of the scalp, the ears, the face, the oral cavity, and the neck can identify potentially malignant skin lesions, which may give rise to lymph node metastases.

Thyroid Gland

The thyroid gland is first observed as the patient swallows; it is then palpated and its size and consistency are assessed to determine whether it is smooth, diffusely enlarged, or nodular and whether one nodule or several are present. If it is unclear whether the mass arises from the thyroid, one can clarify the point by asking the patient to swallow and watching to see whether the mass moves upward with the larynx. Signs of superior mediastinal syndrome (e.g., cervical venous engorgement and facial edema) suggest retrosternal extension of a thyroid goiter. Elevation of the arms above the head can elicit this finding in a patient with a substernal goiter (a positive Pemberton sign). The larynx and trachea are examined, with special attention to the cricothyroid membrane, over which Delphian nodes can be palpated. These nodes can be an indication of thyroid or laryngeal cancer.

Major Salivary Glands

Examination of the paired parotid and submandibular glands involves not only palpation of the neck but also an intraoral examination to inspect the duct openings. The submandibular glands are best assessed by bimanual palpation, with one finger in the mouth and one in the neck. They are normally lower and more prominent in older patients. The parotid glands are often palpable in the neck, although the deep lobe cannot always be assessed. A mass in the region of the tail of the parotid must be distinguished from enlarged level II jugular nodes. The oropharynx is inspected for distortion of the lateral walls. The parotid (Stensen) duct may be found opening into the buccal mucosa, opposite the second upper molar.

Oral Cavity and Oropharynx

The lips should be inspected and palpated. Dentures should be removed before the mouth is examined. The buccal mucosa, the teeth, and the gingiva are then inspected. The patient should be asked to elevate the tongue so that the floor of the mouth can be examined and bimanual inspection performed. The tongue should be inspected both in its normal position in the mouth and during protrusion.

Most of the oropharyngeal contents are easily visualized if the tongue is depressed. Only the anterior two thirds of the tongue are clearly visible on examination, however. The base of the tongue is best inspected using a mirror. In most persons, the tongue base can be palpated, although with some discomfort to the patient. The ventral surface of the tongue must also be carefully inspected and palpated.

The hard palate is examined by gently tilting the patient's head backward, and the soft palate is inspected by gently depressing the tongue with a tongue blade. The movement of the palate is assessed by having the patient say "ahh."

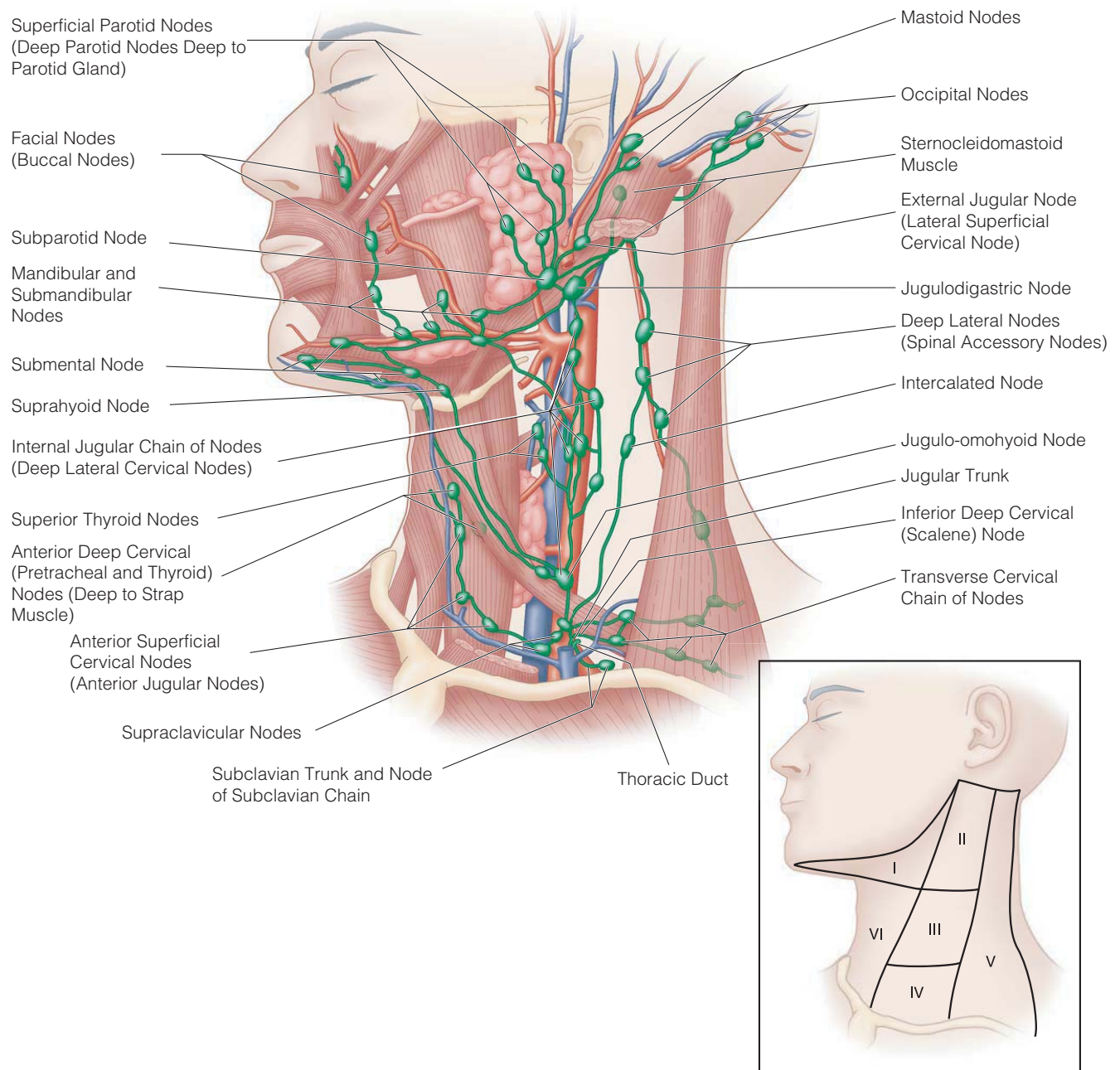


Figure 1 Cervical lymph nodes. Inset: Classification of cervical lymph nodes by anatomic level.

The tonsils are then examined. They are usually symmetrical but may vary substantially in size. For example, in young patients, hyperplastic tonsils may almost fill the oropharynx, but in adult patients, this is an uncommon finding. Finally, the posterior pharyngeal wall is inspected.

Larynx and Hypopharynx

The larynx and the hypopharynx are best examined by indirect or direct laryngoscopy. A mirror is warmed, and the patient's tongue is gently held forward to increase the space

between the oropharyngeal structures. The mirror is carefully introduced into the oropharynx without touching the base of the tongue. The oropharynx, the larynx, and the hypopharynx can be inspected by changing the angle of the mirror.

The lingual and laryngeal surfaces of the epiglottis are examined. Often the patient must be asked to phonate to bring the endolarynx into view. The aryepiglottic folds and the false and true vocal cords should be identified. The mobility of the true vocal cords is then assessed: their resting

position is carefully noted, and their movement during inspiration is recorded. Normally, the vocal cords abduct during breathing and move to the median position during phonation. The larynx is elevated when the patient attempts to say “eeeeee”; this allows one to observe vocal cord movement and to better visualize the piriform sinuses, the post-cricoid hypopharynx, the laryngeal surface of the epiglottis, and the anterior commissure of the glottic larynx. Passage of a fiberoptic laryngoscope through the nose yields a clear view of the hypopharynx and the larynx. This procedure is well tolerated by almost all patients, particularly if a topical anesthetic is gently sprayed into the nose and swallowed, thereby anesthetizing both the nose and the pharynx.

Nasal Cavity and Nasopharynx

The nasopharynx is examined by depressing the tongue and inserting a small mirror behind the soft palate. The patient is instructed to open the mouth widely and breathe through it to elevate the soft palate. With the patient relaxed, a warmed nasopharyngeal mirror is carefully placed in the oropharynx behind the soft palate without touching the mucosa.

The nasal septum, the choanae, the turbinates, and the eustachian tube orifices are systematically assessed. The dorsum of the soft palate, the posterior nasopharyngeal wall, and the vault of the nasopharynx should also be inspected. The exterior of the nose should be carefully examined, and the septum should be inspected with a nasal speculum. Polyps or other neoplasms can be mistaken for turbinates.

Careful evaluation of the cranial nerves is essential, as is examination of the eyes (including assessment of ocular movement and visual activity), the external ear, and the tympanic membrane.

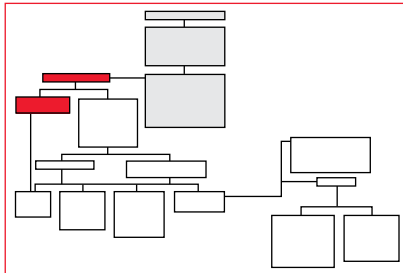
Additional Areas

The remainder of the physical examination is also important, particularly as regards the identification of a possible source of metastases to the neck. Other sets of lymph nodes—especially axillary and inguinal nodes—are examined for enlargement or tenderness. Women should undergo complete pelvic and rectal examination. Men should undergo rectal, testicular, and prostate examinations; tumors from these organs may metastasize to the neck, albeit rarely.

Developing a Differential Diagnosis

Once a comprehensive history and examination have been performed, one is likely to have a better idea of the etiology of the mass.

In some patients, the findings are clear enough to strongly suggest a specific disease entity. For example, a rapidly developing mass that is soft and tender to palpation is most likely a reactive lymph node from an acute bacterial or viral illness. A slow-growing facial mass associated with facial nerve deficits is probably a malignant parotid tumor.

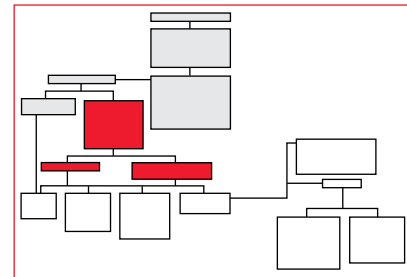


A thyroid nodule with an adjacent abnormal lymph node in a young patient probably represents thyroid cancer. In an elderly patient with a substantial history of smoking and alcohol use, a neck mass may be a metastasis from squamous cell carcinoma in the aerodigestive tract.

The initial diagnostic impressions and the degree of certainty attached to them determine the next steps in the workup and management of a neck mass; options include empirical therapy, ultrasonographic scanning, computed tomography (CT), fine-needle aspiration (FNA), and observation alone. For example, in a patient with suspected bacterial lymphadenitis from an oral source, empirical antibiotic therapy with close follow-up is a reasonable approach. In a patient with a suspected parotid tumor, the best first test is a CT scan: the tumor probably must be removed, which means that one will have to ascertain the relation of the mass to adjacent structures. In a patient with suspected metastatic cancer, FNA is a sensible choice: it will confirm the presence of malignancy and may suggest a source of the primary cancer.

Investigative Studies

Neck masses of suspected infectious or inflammatory origin can be observed for short periods. Most neck masses in



adults, however, are abnormal and are often manifestations of serious underlying conditions. In most cases, therefore, further diagnostic evaluation should be rigorously pursued.

ULTRASONOGRAPHY

Ultrasonography of the neck can be extremely useful in clarifying physical examination findings and supplying additional definitive information. In many clinics, ultrasonography is considered an extension of the physical examination and is applied for nearly all patients with neck masses. Ultrasonography can also be useful to guide tissue sampling and is helpful for mapping of normal or abnormal lymph nodes, for characterizing lesions as cystic or solid, and for defining the risk of some individual lesions (especially thyroid lesions) of being malignant. Ideally, point-of-care ultrasound examination by the treating physician can guide and clarify the subsequent evaluation.

TISSUE SAMPLING

Whether or not the history and the physical examination strongly suggest a specific diagnosis, the information obtained by sampling tissue from the neck mass is often highly useful. In many cases, biopsy establishes the diagnosis or, at least, reduces the diagnostic possibilities. At present, the preferred method of obtaining biopsy material from a neck mass is FNA, which is generally well tolerated and can usually be performed without local anesthesia. Although FNA is, on the whole, both safe and accurate, it is an invasive diagnostic procedure and carries a small but definable risk of potential problems (e.g., bleeding and sampling error). Accordingly, FNA should be done only when the results are likely to influence management.

FNA can be used to sample cystic or solid lesions and can often diagnose malignancy. It has become the standard for making treatment decisions in patients with thyroid nodules and for assessing for suspicious adenopathy for treatment planning. Benign FNA results should not be considered the end point of any search and do not rule out cancer.

Several studies have shown FNA to be approximately 90% accurate in establishing a definitive diagnosis.¹ Lateral cystic neck masses that collapse on aspiration usually represent hygromas, branchial cleft cysts, or cystic degeneration of a metastatic papillary thyroid cancer, although the cystic nature of these lesions is best determined on ultrasonography. Fluid from these masses is sent for cytologic examination. If both cystic and solid components are evident on a sonogram, or if a palpable mass remains after cyst aspiration, then tissue sampling should target the solid component as the morphology of the cells will be better preserved.

If a complete physical examination including ultrasonography has been completed and the FNA is not diagnostic, then an open biopsy may be necessary to obtain a specimen for histologic sections and microbiologic studies. It is estimated that open biopsy eventually proves necessary in about 10% of patients with a malignant mass. For an open biopsy, it is important to orient skin incisions within the boundaries of a neck dissection; the incisions can then, if necessary, be extended for definitive therapy or reexcised if reoperation subsequently proves necessary.

IMAGING

Diagnostic imaging beyond ultrasound studies should be used selectively in the evaluation of a neck mass; imaging studies should be performed only if the results are likely to affect subsequent therapy. Such studies often supply useful information about the location and characteristics of the mass and its relation to adjacent structures. Diagnostic imaging is particularly useful when a biopsy has been performed and a malignant tumor identified. In such cases, these studies can help establish the extent of local disease and the presence or absence of metastases.

CT is useful for differentiating cysts from solid neck lesions and for determining whether a mass is within or outside a gland or nodal chain.² In addition, CT can delineate small tongue base or tonsillar tumors that have a minimal mucosal component. Magnetic resonance imaging (MRI) provides much the same information as CT. T₂-weighted gadolinium-enhanced scans are particularly useful for delineating the invasion of soft tissue by tumor: endocrine tumors are often enhanced on such scans. Fluorodeoxyglucose (FDG) positron emission tomography (PET) is increasingly employed in the diagnosis and staging of both primary and metastatic head and neck malignancies, including squamous cell carcinoma, thyroid cancer, lymphoma, and melanoma.³ FDG-PET is generally reserved for specific situations, however, rather than as a primary imaging modality. FDG-PET-positive, radioiodine-negative, metastatic thyroid cancers are more aggressive than their radioiodine-avid counterparts, for example.

Arteriography is useful mainly for evaluating vascular lesions and tumors fixed to the carotid artery. Angiography is helpful for evaluating the vascularity of a mass, its specific blood supply, or the status of the carotid artery but

provides very little information about the physical characteristics of the mass. Plain radiographs of the neck are rarely helpful in differentiating neck masses, but a chest x-ray can often confirm a diagnosis (e.g., in patients with lymphoma, sarcoidosis, or metastatic lung cancer).

It is important to communicate with the radiologist: an experienced head and neck radiologist may be able to offer the surgeon valuable guidance in choosing the best diagnostic test in a specific clinical scenario. Furthermore, providing the radiologist with a detailed clinical history facilitates interpretation of the images.

Management of Specific Disorders

CERVICAL ADENOPATHY

Anatomy

The lymph nodes of the neck are typically

divided into six levels [see Table 2 and Figure 1], based on common patterns of metastatic spread.⁴ These six levels correspond to the submandibular and submental nodes (level I), the jugular nodes (levels II to IV), the posterior triangle nodes (level V), and the anterior triangle nodes (level VI). The boundaries of level I are the mandible superiorly, the anterior belly of the digastric muscle anteriorly, and the stylohyoid muscle posteriorly. Malignant nodes in this level most commonly contain metastases from cancers of the lips, the oral cavity, or the facial skin.

Level II contains nodes located near the upper third of the internal jugular vein. The anterior boundary of level II is the stylohyoid muscle; the posterior boundary is the posterior border of the sternocleidomastoid. Level II extends inferiorly to the level of the hyoid bone. Level III relates to the middle third of the jugular vein. The superior border is the hyoid bone, the inferior border is the level of the cricoid cartilage, and the anterior and posterior borders are the sternohyoid and sternocleidomastoid muscles, respectively. Level II and level III lymph nodes are common sites for lymph node metastases from primary cancers of the oropharynx, the larynx, and the hypopharynx.

Level IV contains nodes relating to the lower third of the internal jugular vein. Its anterior and posterior borders are the same as those for level III; the superior border is the cricoid cartilage, and the inferior border is the superior edge of the clavicle. Metastases in level IV lymph nodes can arise from cancers of the upper aerodigestive tract, cancers of the thyroid gland, or cancers arising below the clavicle.

Level V consists of the posterior triangle of the neck and contains several nodal groups: the spinal accessory, transverse cervical, and supraclavicular nodes. Nodal metastases in the posterior triangle can arise from nasopharyngeal and thyroid cancers and from squamous cell carcinoma or melanoma of the posterior scalp and the pinna of the ear. The eponymous Virchow node in the left supraclavicular region is a common site of distant metastasis. The anterior border of level V is the sternocleidomastoid; the posterior border is the anterior edge of the trapezius muscle. Level V extends

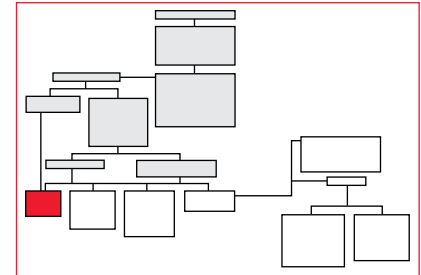


Table 2 Classification of Cervical Lymph Nodes

Level	Nodes	Common Sources of Metastatic Disease
I	Submental nodes Submandibular nodes	Oral cavity and lip, facial skin
II	Upper internal jugular chain nodes	Oropharynx, larynx, hypopharynx
III	Middle internal jugular chain nodes	Oropharynx, larynx, hypopharynx
IV	Lower internal jugular chain nodes	Upper aerodigestive tract, thyroid
V	Spinal accessory nodes Transverse cervical nodes	Remote metastases (Virchow node); posterior scalp
VI	Tracheoesophageal groove nodes	Thyroid, larynx

superiorly from the point at which the sternocleidomastoid and trapezius converge to the clavicle inferiorly.

Level VI contains the lymph nodes of the anterior compartment of the neck. The borders are the hyoid superiorly and the sternal notch inferiorly, and this level extends laterally to the carotid arteries on each side. Nodes in level VI commonly contain metastases from thyroid cancer, as well as from laryngeal cancers.

Investigative and Diagnostic Studies

Lymph node enlargement is a frequent finding with a wide differential diagnosis. Most commonly, lymph node enlargement occurs as a reaction to acute infection; however, given the potential for alternate causes such as malignancy, a benign diagnosis cannot be assumed. A careful history and thorough examination, as well as consideration by the clinician of all potential causes, are essential. Acute infection of the neck (cervical adenitis) is most often the result of dental infection, tonsillitis, pharyngitis, viral upper respiratory tract infection, or skin infection. In this situation, the enlarged lymph nodes are usually just posterior and inferior to the angle of the mandible. Signs of acute infection (e.g., fever, malaise, and a sore mouth or throat) are usually present. A constitutional reaction, tenderness of the cervical mass, and the presence of an obvious infectious source confirm the diagnosis. Treatment should be directed toward the primary disease and should include a monospot test for infectious mononucleosis.

For patients with cervical adenopathy without an obvious acute infection, further investigation is indicated. Various chronic infections (e.g., tuberculosis, fungal lymphadenitis, syphilis, cat-scratch fever, and AIDS) may also involve cervical lymph nodes. Certain chronic inflammatory disorders (e.g., sarcoidosis) may present with cervical lymphadenopathy as well. Because of the chronic lymph node involvement, these conditions are easily confused with neoplasms, especially lymphomas. Biopsy is occasionally necessary; however, skin tests and serologic studies are often more useful for establishing a diagnosis. Treatment of these conditions is primarily medical; surgery is reserved for complications.

In adult patients with cervical adenopathy and no clear infectious etiology, there is a high risk of malignancy, and FNA is recommended. FNA may provide a conclusive diagnosis or further reduce the range of diagnostic possibilities. FNA is also useful in patients with a known distant malignancy in whom confirmation of metastases is needed for

staging and for planning therapy, as well as in patients with a primary tumor of the head and neck who are not candidates for operation but in whom a tissue diagnosis is necessary for appropriate nonsurgical therapy to be initiated. A wide variety of primary tumors may metastasize to the cervical lymph nodes, and therapy depends on the primary site and the type and stage of the tumor.

FNA of an enlarged cervical node does have limitations. Sampling error or an inadequate sample may occur; in these cases, a repeat aspiration or an excisional biopsy may be useful.

When lymphoma and metastatic squamous cell carcinoma are diagnostic possibilities, FNA alone is often incapable of determining the precise histologic subtype for lymphoma, but it is usually capable of distinguishing a lymphoproliferative disease from metastatic squamous cell carcinoma. This is a crucial distinction in that the two neoplasms are treated in drastically different ways.

If a lymphoma is suspected, FNA is typically followed by open biopsy, frozen-section confirmation, and submission of fresh tissue for further pathologic characterization. The intact node is placed in normal saline and sent directly to the pathologist for analysis of cellular content and nodal architecture and identification of lymphocyte markers. If, however, metastatic squamous cell carcinoma is suspected, FNA usually suffices for establishing the diagnosis and formulating a treatment plan, which is specific to the site and size of the primary tumor but often includes chemotherapy and radiation initially. In this setting, performing an open biopsy can lead to significant wound healing complications; there is no need to incur this risk when FNA is sufficient to initiate treatment.

THYROID NODULES: BENIGN AND MALIGNANT THYROID DISEASE

Thyroid disease is a relatively common cause of neck mass. Nearly 4% of the population have a palpable thyroid nodule. The majority of thyroid nodules are benign; however, approximately 5% of these lesions are malignant.⁵ The evaluation of a thyroid nodule begins with a careful history, focusing on both local symptoms (dysphagia, hoarseness, vocal changes, sleep apnea) and systemic symptoms, as well as a family history of thyroid disease and past exposure to radiation [see Figure 2]. A past history of radiation exposure in particular is associated with increased risk of malignancy. After a thorough history and examination, including

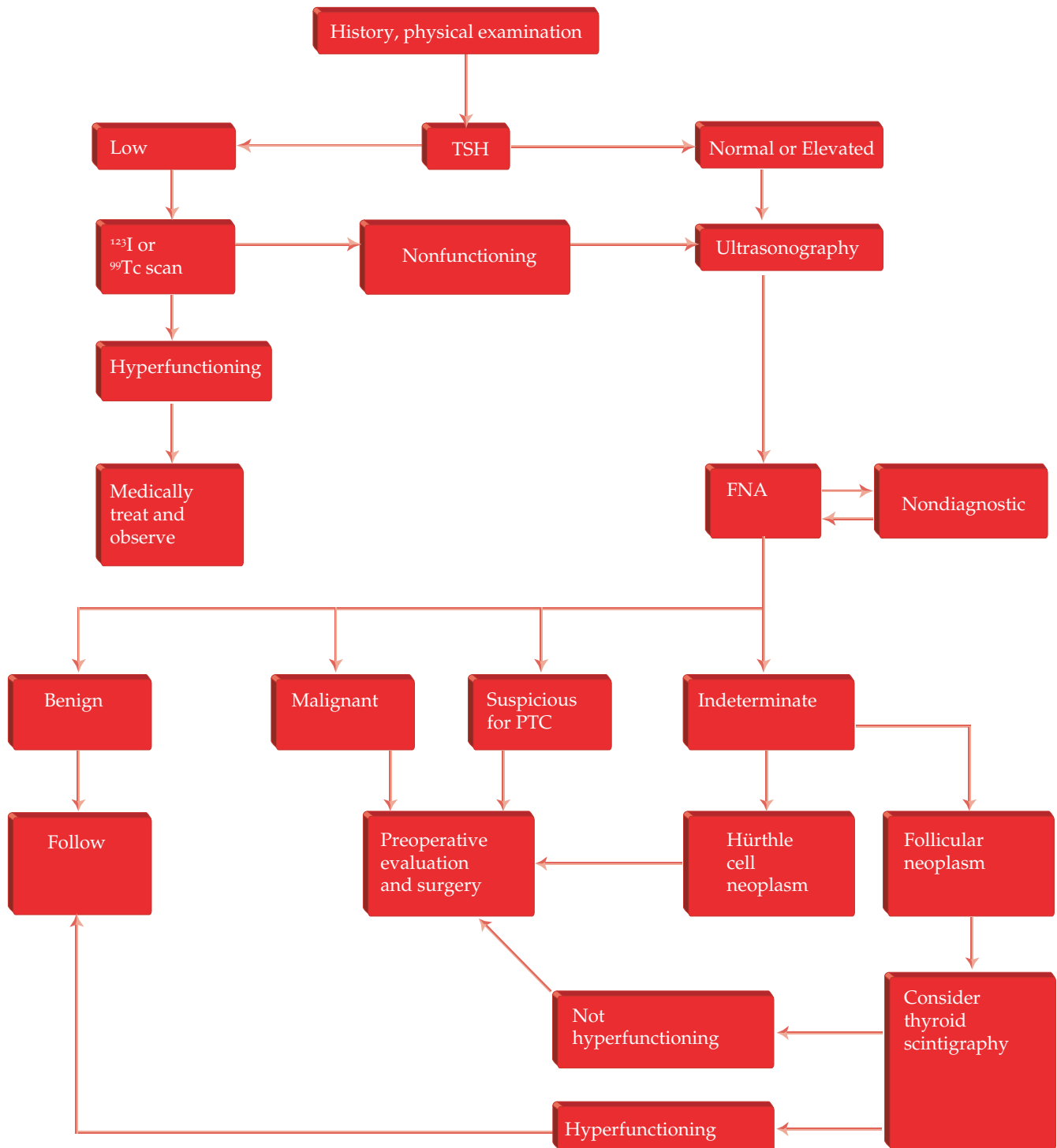


Figure 2 Management algorithm for thyroid nodules. FNA = fine-needle aspiration; PTC = papillary thyroid cancer; TSH = thyroid-stimulating hormone.

ultrasonography, further investigation is usually warranted. This can include laboratory studies, further imaging, and cytologic assessment.⁶

A serum thyroid-stimulating hormone (TSH) level should be obtained on any patient with a palpable thyroid nodule or a nodule detected incidentally on imaging. If the serum TSH is low, then radionuclide scanning should be

performed. If the nodule is hyperfunctioning, then no further evaluation is needed as the risk of malignancy is low. Patients with a hyperfunctioning nodule, a depressed serum TSH, and clinical symptoms may then be evaluated and medically treated for hyperthyroidism. Additionally, an elevated TSH is associated with a small increased risk of malignancy.

Ultrasonography should be performed for any patient with a palpable thyroid nodule as part of the initial evaluation. Sonography can indicate the size of the nodule and its position within the gland; it can identify features that suggest a benign or malignant nodule. A thorough ultrasound examination may also help the practitioner identify suspicious cervical adenopathy, additional nodules not palpated on examination, or other abnormalities. Findings of microcalcifications, irregular margins, and increased vascularity are suggestive of papillary thyroid cancer. Follicular cancers are often iso- or hyperechoic with a peripheral “halo” of decreased echogenicity.

FNA is recommended for the majority of thyroid nodules detected either by palpation or imaging. Table 3 outlines the current recommendations for FNA based on clinical history, size of the nodule, and imaging characteristics. FNA is not routinely recommended for nodules smaller than 1 cm; however, in patients with a higher risk of malignancy, including those with a family history of thyroid cancer or a history of radiation exposure in childhood or adolescence, FNA of a smaller nodule may be indicated. FNA can be performed either by palpation or ultrasound guidance. The latter is recommended for most nodules as it decreases the occurrence of nondiagnostic results but especially for those that are predominantly cystic, located posteriorly in the thyroid lobe, or nonpalpable. FNA is useful in the evaluation of thyroid nodules in children.⁷

Interpretation of FNA Cytology

FNA results can be classified as nondiagnostic, benign, malignant, suspicious for malignancy, or indeterminate.⁸ Nearly 20% of FNAs are nondiagnostic; repeated FNA under ultrasound guidance can lead to a diagnostic cytology specimen in 50 to 75% of these nodules. For nodules that

repeatedly yield nondiagnostic samples, surgical excision should be considered, particularly if the nodule is solid rather than cystic. For nodules with FNA findings diagnostic of malignancy, surgical resection is recommended. For benign nodules, no further investigation is required. However, if a benign nodule continues to grow, as demonstrated on follow-up ultrasonography, repeated biopsy should be performed, and a diagnostic thyroid lobectomy may be indicated.

Nodules with indeterminate cytology are typically reported as “cellular atypia,” “Hürthle cell neoplasm,” or “follicular neoplasm” and are an area of significant debate in terms of management. Many molecular markers and imaging studies have been evaluated for a possible role in improving the diagnostic accuracy in patients with these lesions. Most recently, the role of ¹⁸FDG-PET has been explored as a promising method of determining malignant potential; however, the findings of most studies of FDG-PET utility show low specificity. Currently, for indeterminate lesions interpreted as “suspicious for papillary carcinoma” or “Hürthle cell neoplasm,” surgical resection is recommended.⁶ For the remainder of indeterminate lesions, a radionuclide study can be considered; if the nodule is not hyperfunctioning, then surgical resection may be warranted.

Thyroid Cancer: Overview of Surgical and Medical Management

The procedure of choice for a papillary thyroid cancer that is small (< 1 cm in diameter) and confined to the gland, as well as for minimally invasive follicular thyroid cancer, is a thyroid lobectomy. For the remainder of papillary or follicular cancers, as well as Hürthle cell and medullary thyroid cancer, total or near-total thyroidectomy is preferable. Patients with thyroid nodules and a history of radiation exposure should also undergo a total thyroidectomy as approximately 40% of these patients have at least one additional focus of papillary thyroid cancer. Total thyroidectomy also allows the use of ¹³¹I scanning to monitor for recurrence and increases the sensitivity of thyroglobulin and calcitonin assays in posttreatment surveillance. New information regarding the molecular basis for thyroid neoplasia is gradually informing the individualized care for patients with these tumors.⁹

Patients with medullary thyroid cancer should additionally undergo bilateral central neck dissection, screening for *ret* proto-oncogene mutations, and screening for pheochromocytoma.¹⁰ Anaplastic thyroid cancer is best treated with a combination of chemotherapy and radiation therapy, in conjunction with removal of as much of the neoplasm as can be safely excised. Most patients with thyroid lymphomas should receive chemotherapy, radiation therapy, or a combination of the two.

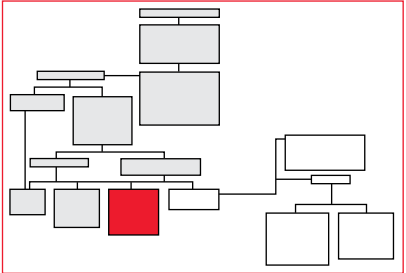
Table 3 Thyroid Nodule Assessment	
Nodule Sonographic or Clinical Features	Recommended Size Threshold for FNA
High-risk history	
Nodule with suspicious sonographic features	> 5 mm
Nodule without suspicious sonographic features	> 5 mm
Abnormal cervical lymph nodes	All
Microcalcifications present in nodule	≥ 1 cm
Solid nodule	
And hypoechoic	> 1 cm
And iso- or hyperechoic	≥ 1.5 cm
Mixed cystic-solid nodule	
With any suspicious sonographic features	≥ 1.5–2.0 cm
Without any suspicious sonographic features	≥ 2.0 cm
Purely cystic nodule	FNA not indicated
Spongiform nodule	≥ 2.0 cm

Adapted from Cooper DS et al.⁶
FNA = fine-needle aspiration.

NEOPLASTIC MASSES

Salivary Gland Tumor

Salivary gland neoplasms usually present as an enlarging solid mass in front of



and below the ear, at the angle of the mandible, or in the submandibular triangle. Benign salivary gland lesions are often asymptomatic; malignant ones are often associated with seventh cranial nerve symptoms or skin fixation. Diagnostic imaging studies (CT or MRI) indicate whether the mass is salivary in origin but do not help classify it histologically. The diagnostic test of preference is open biopsy in the form of complete submandibular gland removal or superficial parotidectomy.

With any mass in or around the ear, one should be prepared to remove the superficial lobes of the parotid, the deep lobes, or both and to perform a careful facial nerve dissection. Any less complete approach reduces the chances of a cure: there is a high risk of implantation and seeding of malignant tumors. Benign mixed tumors make up two thirds of all salivary tumors; these must also be completely removed because recurrence is common after incomplete resection. Malignant lesions may require additional therapy with radiation or chemotherapy.¹¹

Soft Tissue Tumor (Lipoma, Sebaceous Cyst)

Superficial intracutaneous or subcutaneous masses may be sebaceous (or epidermal inclusion) cysts or lipomas. Final diagnosis and treatment usually involve simple surgical excision, often done as an office procedure with local anesthesia.

Chemodectoma (Carotid Body Tumor)

Carotid body tumors belong to a group of tumors known as chemodectomas (or, alternatively, as glomus tumors or nonchromaffin paragangliomas), which derive from the chemoreceptive tissue of the head and neck. Chemodectomas most often arise from the tympanic bodies in the middle ear, the glomus jugulare at the skull base, the vagal body near the skull base along the inferior ganglion of the vagus, and the carotid body at the carotid bifurcation. They are sometimes familial and can occur bilaterally.¹²

A carotid body tumor presents as a firm, round, slowly growing mass at the carotid bifurcation. Occasionally, a bruit is present. The tumor cannot be separated from the carotid artery by palpation and can usually be moved laterally and medially but not in a cephalocaudal plane. The differential diagnosis includes a carotid aneurysm, a branchial cleft cyst, a neurogenic tumor, and nodal metastases fixed to the carotid sheath. The diagnosis is made by CT or arteriography, which demonstrate a characteristic highly vascular mass at the carotid bifurcation. Neurofibromas tend to displace, encircle, or compress a portion of the carotid artery system, events that are readily demonstrated by carotid angiography.

Biopsy should be avoided. Chemodectomas are sometimes malignant and should therefore be removed in most cases to prevent subsequent growth and pressure symptoms. Fortunately, even malignant chemodectomas are usually low grade; long-term results after removal are generally excellent. Vascular surgical experience is desirable in that the tumors are very vascular and intimately involve the carotid artery, and clamping of the carotid artery may result in a stroke. Expectant treatment may be indicated in older or debilitated individuals. Radiotherapy may be helpful for patients with unresectable tumors.

Neurogenic Tumor (Neurofibroma, Neurilemmoma)

The most common neurogenic tumors in the head and neck, neurilemmomas (schwannomas) and neurofibromas, arise from the neurilemma and usually present as painless, slowly growing masses in the lateral neck. Neurilemmomas can be differentiated from neurofibromas only by means of histologic examination.

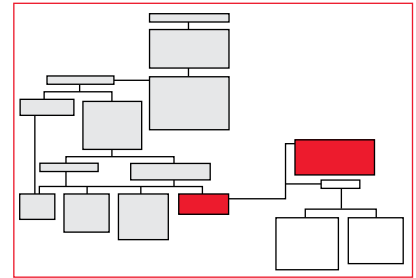
Given the potential these tumors possess for malignant degeneration and slow but progressive growth, surgical resection is indicated. This may include resection of the involved nerves, particularly with neurofibromas, which tend to be more invasive and less encapsulated than neurilemmomas.

Laryngeal Tumor

In rare cases, a chondroma may arise from the thyroid cartilage or the cricoid cartilage. It is firmly fixed to the cartilage and may present as a mass in the neck or as the cause of a progressively compromised airway. Surgical excision is indicated.

Lymphoma

Cervical adenopathy is one of the most common presenting symptoms in patients with Hodgkin and non-Hodgkin lymphoma. The nodes tend to be softer,



smoother, more elastic, and more mobile than nodes containing metastatic carcinoma. Rapid growth is common, particularly in non-Hodgkin lymphoma. Involvement of extranodal sites, particularly Waldeyer tonsillar ring, often occurs in patients with non-Hodgkin lymphoma; enlargement of these sites may provide a clue to the diagnosis. The diagnosis is usually suggested by FNA and then confirmed via excisional biopsy of an intact lymph node. Lymphoma is typically treated by radiation therapy, chemotherapy, or both depending on the disease's pathologic type and clinical stage.

Upper Aerodigestive Tract Cancer

Many localized tumors of the aerodigestive tract can be cured with surgery alone. Treatment of locally advanced squamous cell cancers, however, often necessitates a multimodality approach.¹³ Such an approach has traditionally consisted of surgery followed by radiation therapy, but recent data indicate that concurrent chemoradiotherapy has an additional beneficial effect as an adjuvant measure.^{14,15}

Chemoradiotherapy is also employed for unresectable disease, and induction chemotherapy may be administered preoperatively to reduce operative morbidity. Among the chemotherapeutic agents active against head and neck squamous cell cancers are the taxanes, cisplatin and fluorouracil, and various newer targeted agents (e.g., epidermal growth factor receptor antagonists).

Treatment planning for such patients depends on the tumor's location and stage, the patient's age, and the presence and severity of associated medical conditions, among

other factors.¹⁶ Consultation with a specialist in this field is generally required. Therefore, cancers involving the nose, the paranasal sinuses, the nasopharynx, the floor of the mouth, the tongue, the palate, the tonsils, the piriform sinus, the hypopharynx, or the larynx are best managed by an experienced head and neck oncologic surgeon in conjunction with a radiation therapist and a medical oncologist.

Soft Tissue Sarcoma

Malignant sarcomas are not common in the head and neck. The sarcomas most frequently encountered include rhabdomyosarcoma in children, fibrosarcoma, liposarcoma, osteogenic sarcoma (which usually arises in young adults), and chondrosarcoma. The most common head and neck sarcoma, however, is malignant fibrous histiocytoma (MFH). MFH occurs most frequently in the elderly and extremely rarely in children, but it can arise at any age. It is often difficult to differentiate from other entities (e.g., fibrosarcoma). MFH can occur in the soft tissues of the neck or involve the bone of the maxilla or the mandible. The preferred treatment is wide surgical resection; adjuvant radiation therapy and chemotherapy are being studied in clinical trials.

Rhabdomyosarcoma, usually of the embryonic form, is the most common form of sarcoma in children. It generally occurs near the orbit, the nasopharynx, or the paranasal sinuses. The diagnosis is confirmed by biopsy. A thorough search for distal metastases is important before treatment—consisting of a combination of surgical resection, radiation therapy, and chemotherapy—is begun.

Skin Cancer

Basal cell carcinomas are the most common of the skin malignancies. These lesions arise most commonly in areas that have been extensively exposed to sunlight (e.g., the nose, the forehead, the cheeks, and the ears). Treatment consists of local resection with adequate clear margins. Metastases are rare, and the prognosis is excellent. Inadequately excised and neglected basal cell carcinomas may ultimately spread to regional lymph nodes and can cause extensive local destruction of soft tissue and bone. For example, basal cell carcinoma of the medial canthus may invade the orbit, the ethmoid sinus, and even the brain. Periauricular basal cell carcinoma can spread across the cartilage of the ear canal or into the parotid gland. In such cases of locally advanced basal cell cancer or nodal involvement with tumor, patients may require more extensive surgical treatment (i.e., modified neck dissection). Postoperative radiation therapy is often administered to optimize local control and reduce the risk of recurrence.

Squamous cell carcinoma also arises in areas associated with extensive sunlight exposure; the lower lip and the pinna are the most common sites. Unlike basal cell carcinoma, however, squamous cell carcinoma tends to metastasize to both regional and distant sites. This tumor must also be excised with an adequate margin.

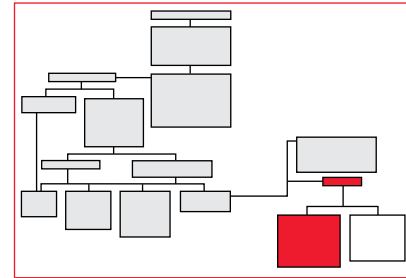
Melanoma is primarily classified on the basis of depth of invasion (as quantified by Clark level or Breslow thickness), location, and histologic subtype, although the prognosis is closely related to the thickness of the tumor [see Metastatic Disease, Metastatic Melanoma, *below*]. In addition to the

typical pigmented, irregularly shaped skin lesions, malignant melanoma can also arise on the mucous membranes of the nose or the throat, on the hard palate, or on the buccal mucosa. The treatment of choice is wide surgical resection. Radiation therapy, chemotherapy, and immunotherapy may be useful in specific situations.

METASTATIC DISEASE

Metastatic Squamous Cell Carcinoma

The basic principle in the management of metastatic squamous cell carcinoma



is wide excision of the primary tumor and treatment of all regional lymph node groups at highest risk for metastases by means of surgery or radiation therapy, depending on the clinical circumstances. Selective lymph node dissection can be performed along with wide excision of the primary tumor at the time of the initial operation. Sentinel lymph node (SLN) biopsy may provide a low morbidity staging opportunity for this as in other diseases.¹⁷ For example, carcinomas of the oral cavity are treated with supraomohyoid neck dissection, and carcinomas of the oropharynx, the hypopharynx, and the larynx are treated with lateral neck dissection. If extranodal extension or the presence of multiple levels of positive nodes is confirmed by the pathologic findings, the patient should receive adjuvant bilateral neck radiation therapy for 4 to 6 weeks after operation.

Metastatic Adenocarcinoma

Adenocarcinoma in a cervical node most frequently represents a metastasis from the thyroid gland, the salivary glands, or the gastrointestinal (GI) tract. The primary tumor must therefore be sought through endoscopic and radiologic study of the bronchopulmonary tract, the GI tract, the genitourinary tract, the salivary glands, and the thyroid gland. Other possible primary sites include breast and pelvic tumors in women and prostate cancer in men.

If the primary site is controlled and the tumor is potentially curable, or if the primary site is not found and the neck disease is the only established site of malignancy, neck dissection is the appropriate treatment. Postoperative adjuvant radiation may also be considered. If the patient has thyroid cancer and palpable nodes, lateral neck dissection (levels II to V) and central neck dissection (level VI) are recommended.

Overall survival is low—about 20% at 2 years and 9% at 5 years—except for patients with papillary or follicular thyroid cancer, who have a good prognosis. Two factors associated with a better prognosis are unilateral neck involvement and limitation of disease to lymph nodes above the cricoid cartilage.

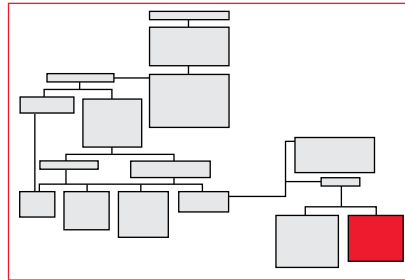
Metastatic Melanoma

If the patient has a thin melanoma (Breslow thickness < 1 mm; Clark level I, II, or III), full-thickness excision with 1 cm margins is adequate treatment for the primary site.

Patients with intermediate-thickness melanomas (Breslow thickness 1 to 4 mm; Clark level IV) should have a full-thickness excision with at least a 1.5 cm margin. These patients also have a definable risk of lymph node spread and thus should be concurrently staged with lymphatic mapping and SLN biopsy. All patients with intermediate-thickness melanomas and positive SLNs and all melanoma patients with palpable lymph nodes should undergo complete staging with full-body CT/PET scans. If no other disease is found, modified neck dissection should be performed to obtain optimal local disease control. Because these tumors may metastasize to nodes in the parotid region, superficial parotidectomy is often included in the neck dissection, particularly in the case of melanoma located on the upper face or the anterior scalp. Consultation with a medical oncologist is indicated for all patients with intermediate-thickness or thick (Breslow thickness > 4 mm; Clark level V) melanomas; immunotherapy or chemotherapy may be considered. Radiation therapy is often considered in patients with extensive local or nodal disease following adequate surgical resection.

Metastasis from an Unknown Primary Malignancy

Management of patients with an unknown primary malignancy is challenging for the surgeon. It is helpful to



know that when cervical lymph nodes are found to contain metastatic squamous cell carcinoma, the primary tumor is in the head and neck about 90% of the time. Typically, such patients are found to have squamous cell carcinoma on the basis of FNA of an abnormal cervical lymph node; this finding calls for an exhaustive review of systems and a detailed physical examination of the head and neck.

If no primary tumor is identified, the patient should undergo endoscopic evaluation of the nasopharynx, the hypopharynx, the esophagus, the larynx, and the tracheobronchial tree under general anesthesia. Biopsies of the nasopharynx, the tonsils, and the hypopharynx often identify the site of origin (although there is some debate on this point). If the biopsies do not reveal a primary source of cancer, the preferred treatment is unilateral neck dissection, followed by radiation therapy directed toward the neck, the entire pharynx, and the nasopharynx. In 15 to 20% of cases, the primary cancer is ultimately detected. Overall 5-year survival in such cases ranges from 25 to 50%.

If a malignant melanoma is found in a cervical lymph node but no primary tumor is evident, the patient should be asked about previous skin lesions, and a thorough repeat head and neck examination should be done, with particular attention to the scalp, the nose, the oral cavities, and the sinuses. An ophthalmologic examination is also required. If physical examination and radiographic studies find no evidence of metastases, modified neck dissection should be performed on the involved side.

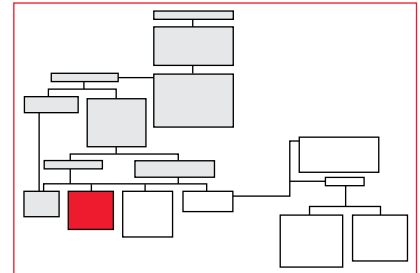
Metastatic adenocarcinoma in a cervical lymph node with no known primary tumor is discussed elsewhere [see

Metastatic Adenocarcinoma, *above*]. The most common primary sites in the head and neck are the salivary glands and the thyroid gland. The possibility of an isolated metastasis from the breast, the GI tract, or the genitourinary tract must also be rigorously investigated. If no primary site is identified, the patient should be considered for protocol-based chemotherapy and radiation therapy, directed according to what the primary site is most likely to be in that patient.

CONGENITAL NECK MASS

Thyroglossal Duct Cyst

Thyroglossal duct cysts are remnants of the tract along which the thyroid gland descended



into the neck from the foramen cecum [see Figure 3]. They account for about 70% of all congenital abnormalities of the neck. Thyroglossal duct cysts may be found in patients of any age but are most common in the first decade of life. They may present as a lone cyst, a cyst with a sinus tract, or a solid core of thyroid tissue. They may be so small as to be barely perceptible, as large as a grapefruit, or anything in between. Thyroglossal duct cysts are almost always found in the midline, at or below the level of the hyoid bone; however, they may be situated anywhere from the base of the

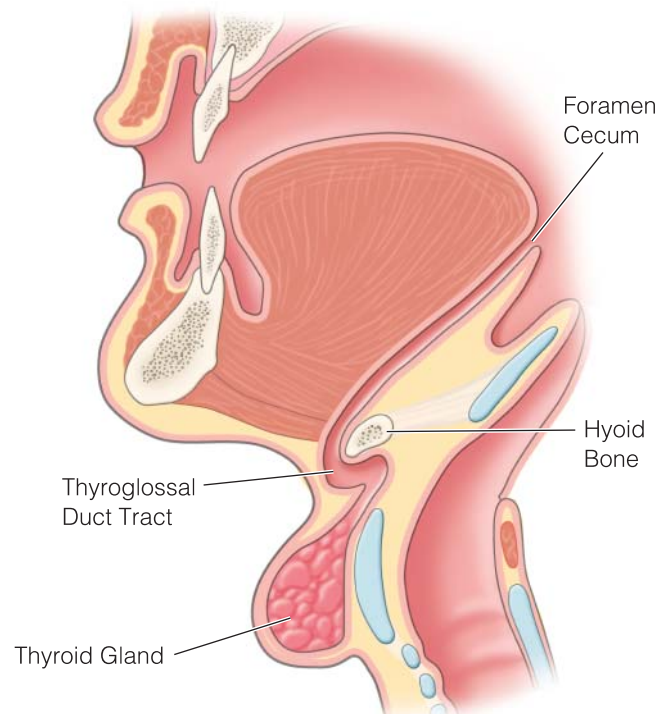


Figure 3 The course of the thyroglossal duct from the foramen cecum to the pyramidal lobe of the thyroid gland. The operative treatment of thyroglossal duct abnormalities includes removal of the central portion of the hyoid bone to ensure complete tract removal, thus limiting the risk of recurrence.

tongue to the suprasternal notch. They occasionally present slightly lateral to the midline and are sometimes associated with an external fistula to the skin of the anterior neck. They are often ballotable and can usually be moved slightly from side to side but not up or down; however, they do move up and down when patients swallow or protrude the tongue.

Thyroglossal duct cysts must be differentiated from dermoid cysts, lymphadenopathy in the anterior jugular chain, and cutaneous lesions (e.g., lipomas and sebaceous cysts). Operative treatment is almost always required, not only because of cosmetic considerations but also because of the high incidence of recurrent infection, including abscess formation. About 1% of thyroglossal duct cysts contain cancer; papillary cancer is the neoplasm most commonly encountered, followed by squamous cell carcinoma. About 25% of patients with papillary thyroid cancer in thyroglossal duct cysts have papillary thyroid cancer in other parts of the thyroid gland as well. About 10% have nodal metastases, which in some cases are bilateral.

Branchial Cleft Cyst

Branchial cleft cysts are vestigial remnants of the fetal branchial apparatus from which all neck structures are derived. Early in embryonic development, there are five branchial arches and four grooves (or clefts) between them. The internal tract or opening of a branchial cleft cyst is situated at the embryologic derivative of the corresponding pharyngeal groove, such as the tonsil (second arch) or the piriform sinus (third and fourth arches). The second arch is the most common area of origin for such cysts. The position of the cyst tract is also determined by the embryologic relation of its arch to the derivatives of the arches on either side of it.

The majority of branchial cleft cysts (those that develop from the second, third, and fourth arches) tend to present as a bulge along the anterior border of the sternocleidomastoid muscle, with or without a sinus tract. Branchial cleft cysts may become symptomatic at any age, but most are diagnosed in the first two decades of life. They often present as a smooth, painless, slowly enlarging mass in the lateral neck. Frequently, there is a history of fluctuating size and intermittent tenderness. The diagnosis is more obvious when there is an external fistulous tract and there is a history of intermittent discharge. Infection of the cyst may be the reason for the first symptoms.

Treatment consists of complete surgical removal of the cyst and the sinus tract. Any infection or inflammation should be treated and allowed to resolve before the cyst and the tract are removed.

Cystic Hygroma (Lymphangioma)

A cystic hygroma is a lymphangioma that arises from lymph channels in the neck. Almost always, this condition is first noted by the second year of life; on rare occasions, it is first diagnosed in adulthood. A cystic hygroma may present as a relatively simple thin-walled cyst in the floor of the mouth or may involve all the tissues from the floor of the mouth to the mediastinum. About 80% of the time, there is only a painless cyst in the posterior cervical triangle or in the supraclavicular area. A cystic hygroma can also occur, however, at the root of the neck, in the angle of the jaw

(where it may involve the parotid gland), and in the midline (where it may involve the tongue, the floor of the mouth, or the larynx).

The typical clinical picture is of a diffuse, soft, doughy, irregular mass that is readily transilluminated. Cystic hygromas look and feel somewhat like lipomas but have less well-defined margins. Aspiration of a cystic hygroma yields straw-colored fluid. They may be confused with angiomas (which are compressible), pneumatoceles from the apex of the lung, or aneurysms. They can be distinguished from vascular lesions by arteriography. On occasion, a cystic hygroma grows suddenly as a result of an upper respiratory tract infection, infection of the hygroma itself, or hemorrhage into the tissues. If the mass becomes large enough, it can compress the trachea or hinder swallowing.

In the absence of pressure symptoms (i.e., obstruction of the airway or interference with swallowing) or gross deformity, cystic hygromas may be treated expectantly. They tend to regress spontaneously; if they do not, complete surgical excision is indicated. Excision can be difficult because of the numerous satellite extensions that often surround the main mass and because of the association of the tumor with vital structures such as the cranial nerves. Recurrences are common; staged resections for complete excision are often necessary.

Vascular Malformation (Hemangioma)

Hemangiomas are usually considered congenital because they either are present at birth or appear within the first year of life. A number of characteristic findings—bluish-purple coloration, increased warmth, compressibility followed by refilling, bruit, and thrill—distinguish them from other head and neck masses. Angiography is diagnostic but is rarely indicated.

Given that most of these congenital lesions resolve spontaneously, the treatment approach of choice is observation alone unless there is rapid growth, thrombocytopenia, or involvement of vital structures.

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Acknowledgment

Figures 1 and 3 Tom Moore

4 HEAD AND NECK DIAGNOSTIC PROCEDURES

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Head and neck diseases can be inflammatory, infectious, congenital, neoplastic, or traumatic. An accurate diagnosis is mandatory and is based on a detailed history and physical examination, as well as ancillary tests. After a detailed history, including the chief complaint, history of present illness, past medical history, current medications, allergies, social history including tobacco and ethanol use, and family history, is obtained, a physical examination should be done.

The physical examination of the head and neck is complicated by the close relationship of structures and the need to examine many of the structures through orifices. The entire mucosal surface of the head and neck needs be examined when evaluating for head and neck cancers. Once a detailed history and physical examination have been done, a differential diagnosis list is created. The correct diagnosis and treatment plan are arrived at with the use of diagnostic procedures including imaging and sampling of the tissue.

Anatomy

The regions of the head and neck are usually divided into the following areas: the ear, the nose and paranasal sinuses, the oral cavity, the pharynx, the larynx, the salivary glands, and the neck, including the thyroid [see *Figure 1*].

EAR

The ear is divided into three parts: the external, middle, and inner ear. The external ear is made of the pinna and external auditory canal. The pinna is the only part of the ear that grows after birth. It is composed of an irregular plate of fibrocartilage tightly covered by skin and a thin layer of subcutaneous tissue. The external auditory canal is a tortuous passage with an average length of 3.7 cm in an adult male. The canal has thicker skin overlying cartilage in the outer half. This skin also has hair and special glands that secrete cerumen. The inner portion of the canal is thin skin over bone. The tympanic membrane is the common wall between the external ear and the middle ear. It is semitranslucent, cone shaped, and concave laterally.

The middle ear is an air-filled chamber that has five bony walls. The sixth wall is the tympanic membrane. Within the middle ear are ossicles. It is connected to the nasopharynx by the eustachian tube. It runs downward and forward and is composed of a cartilaginous segment and a bony segment.

The inner ear is made up of a system of channels and chambers within the otic capsule. It has two parts anatomically and functionally: the vestibular labyrinth and the cochlear. The vestibular system is responsible for balance and the cochlear system for hearing.

Tumors of the ear may present with pain, discharge, decreased hearing, facial nerve involvement, and dizziness.

NOSE AND PARANASAL SINUSES

The external nose is made of two fused nasal bones and four alar cartilages. There are two nasal passages that are separated by a vertical septum composed of cartilage (antero-inferiorly) and bone (the thin perpendicular plate of the ethmoid bone and the vomer). The nose is lined with ciliated respiratory mucoperichondrium, which contains glands and mucus-secreting cells. The cribriform plate forms the roof of the nose, with the hard palate forming its floor. The lateral wall is a partition between the paranasal sinuses and the nasal passages. There are three turbinates on each lateral wall: superior, middle, and inferior. The inferior turbinate is the largest and most vascular. The turbinates divide the nasal passages vertically and create the superior, middle, and inferior meatuses.

There are four paranasal sinuses on each side. The frontal and sphenoid sinuses are midline and frequently are asymmetrical. The ethmoid and maxillary sinuses are placed laterally. The ethmoid sinus is considered the key sinus and can provide access to all the other sinuses [see *Figure 2*]. Its roof is the fovea ethmoidales, which, in conjunction with the cribriform plate, separates the anterior cranial vault from the nose. The sphenoid sinus is the most posterior sinus and has the internal carotid artery, optic nerve, second division of the trigeminal nerve, and vidian nerve all in close proximity.

The symptoms associated with nasal cavity tumors frequently do not occur early in the diseases because much of the nasal cavity and paranasal sinuses is air filled. This can also be a hard area to examine, and the symptoms are usually first attributed to more mundane conditions, such as allergies and sinusitis. The most common symptoms are facial pain, nasal obstruction, epistaxis, nasal discharge, decreased sense of smell, and changes to the orbit.

Oral Cavity

The limits of the oral cavity are the lips anteriorly and the anterior tonsil pillars and circumvallate papillae of the tongue posteriorly. The oral cavity is divided into the vestibules, which is the space between the teeth and cheek; the alveolar ridges, which are the teeth-bearing areas of the maxilla and mandible; the floor of the mouth; the retromolar trigone, which is the triangular area of gum and soft tissue immediately posterior to the lower molars; the buccal mucosa, which

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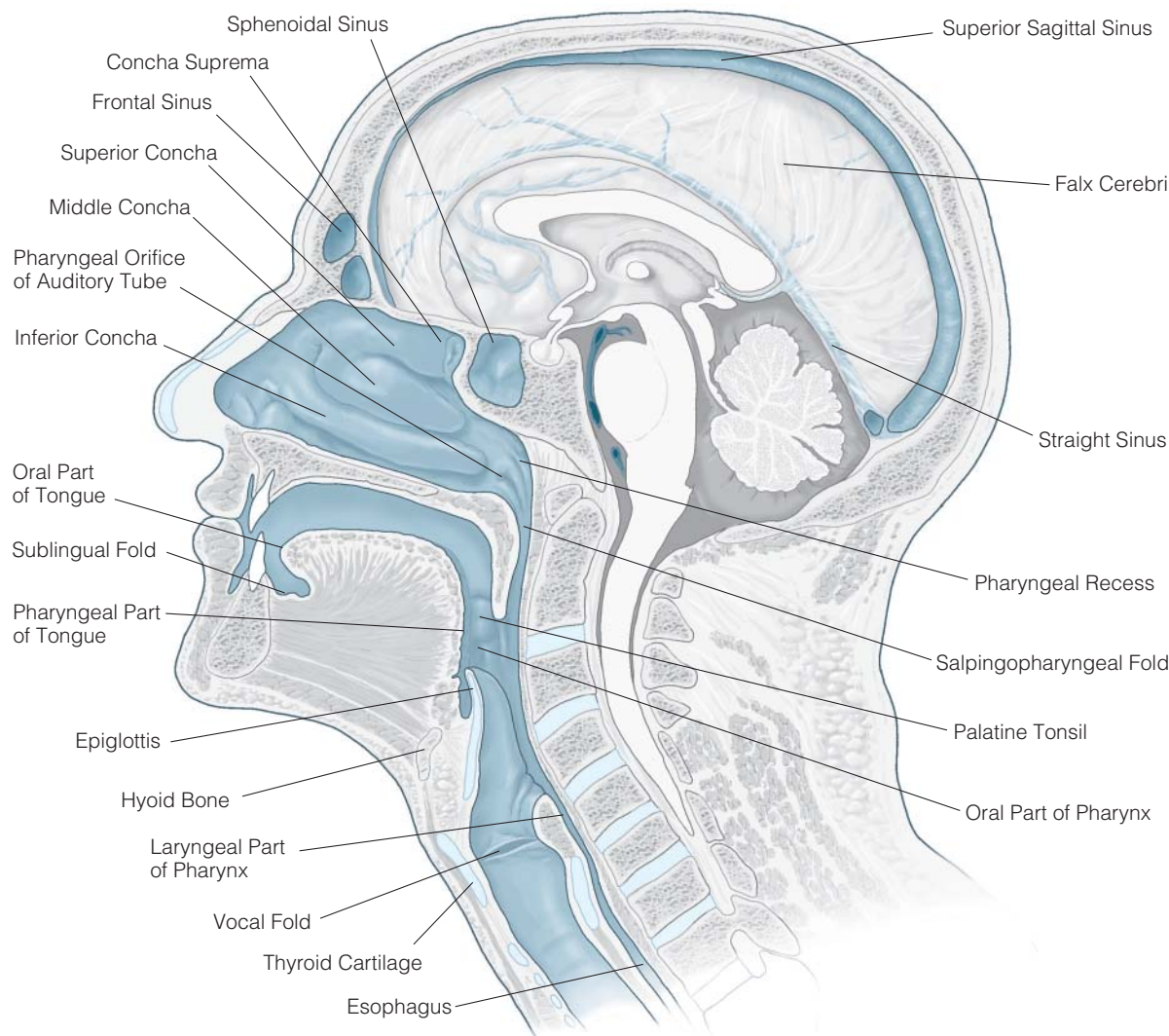


Figure 1 The anatomic structures of the head and neck are shown.

is the mucous membrane lining of the cheek; and the oral tongue, which is the anterior two thirds of the tongue. The posterior limit is the circumvallate papillae.

Salivary Glands

Salivary glands are subdivided into major and minor salivary glands. The major salivary glands consist of the parotid glands, submandibular glands, and sublingual glands. The parotid gland is the largest salivary gland. It is incompletely split by the facial nerve into deep and superficial lobes. The main duct runs horizontal to the zygoma on the lateral surface of the masseter and enters the oral cavity opposite the second maxillary molar. It has serous secretions with low mineral content. Approximately 80 to 85% of the neoplasms in the parotid are benign.

The submandibular gland is below the body of the mandible. It lies on the lateral surface of the mylohyoid muscle. The duct passes upward and medially to the anterior floor of the mouth. Its secretions are mixed serous and mucous, and it has a higher mineral content than the parotid gland. Neoplasms in the submandibular glands are more evenly split between malignant and benign.

The sublingual glands are located in the floor of the mouth and frequently have multiple ducts. The secretion is mucous.

Thousands of minor salivary glands are present throughout the oral cavity, pharynx, and epiglottis. Minor salivary gland neoplasms are usually malignant, with quoted rates around 75%.

Pharynx

The pharynx is an incomplete muscular tube from the base of the skull to the inlet of the esophagus. The pharynx is divided into three parts: the nasopharynx, oropharynx, and hypopharynx. The nasopharynx sits behind the nasal cavity, extending from the choanae to the inferior surface of the palate. Adenoid tissue and the eustachian tubes are present in the nasopharynx. Malignancies of the nasopharynx can present as nasal obstruction, epistaxis, tinnitus, headache, diminished hearing, and facial pain.

The oropharynx extends from the junction of the hard and soft palates and the circumvallate papillae to the valleculae. It includes the soft palate and uvula, base of the tongue, pharyngoepiglottic and glossoepiglottic folds, palatine arch

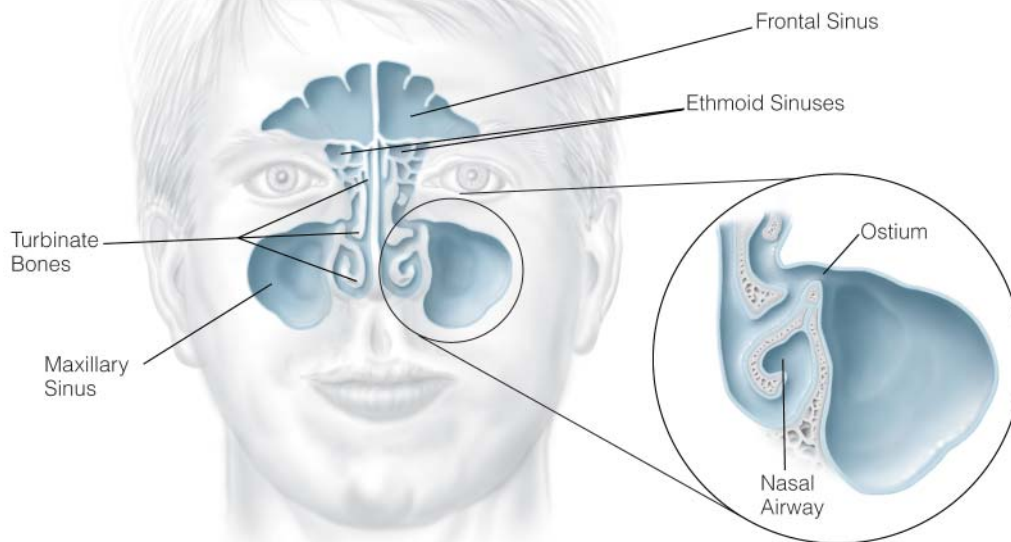


Figure 2 The paranasal sinuses are shown.

(which includes the tonsils and the tonsillar fossae and pillars), valleculae, and lateral and posterior oropharyngeal walls. Carcinomas of the oropharynx can present as pain, sore throat, dysphagia, and referred otalgia.

The hypopharynx extends from the superior border of the hyoid bone to the inferior border of the cricoid cartilage. It includes the piriform sinuses, hypopharyngeal walls, and postcricoid region (i.e., the area of the pharyngoesophageal junction). Malignancies of the hypopharynx can present as odynophagia, dysphagia, hoarseness, referred otalgia, and excessive salivation.

LARYNX

The larynx is subdivided into the supraglottis, glottis, and subglottis. It consists of a framework of cartilages that are held together by extrinsic and intrinsic musculature and lined with a mucous membrane that is topographically arranged into two characteristic folds (the false and true vocal cords). The larynx has the following basic functions: (1) to protect the lower airway; (2) to conduct air to the lungs; and (3) to allow vocalization. Neoplasms of the larynx can present as hoarseness, dyspnea, stridor, hemoptysis, odynophagia, dysphagia, and otalgia.

Supraglottis

The supraglottis extends from the tip of the epiglottis to the junction between respiratory and squamous epithelium on the floor of the ventricle (the space between the false and true cords). Carcinomas of the supraglottis can present as sore throat, odynophagia, dysphagia, and otalgia.

Glottis

The space between the free margin of the true vocal cords is the glottis. This structure is bounded by the anterior

commissure, true vocal cords, and posterior commissure. The most common symptom of carcinoma of the glottis is hoarseness.

Subglottis

The subglottis extends from the junction of squamous and respiratory epithelium on the undersurface of the true vocal cords (approximately 5 to 10 mm below the true vocal cords) to the inferior edge of the cricoid cartilage. The cricoid is the only complete cartilaginous ring in the airway; therefore, it is the only rigid area in the respiratory tree. The most common symptom of carcinoma of the subglottis is hoarseness.

NECK

The neck is divided into different compartments by fascia. The visceral compartment is in the midline and contains the larynx, pharynx, trachea, thyroid, parathyroid glands, recurrent laryngeal nerves, and cervical esophagus. The neurovascular compartment runs the entire length of the neck from the base of the skull to the esophageal inlet. It contains the carotid artery, internal jugular vein, vagus nerve, and jugular lymph nodes. There are two muscular compartments on each side of the neck. Neoplasms in the neck usually present as masses. Most commonly, they are painless. When malignant, they are usually metastatic from primary malignancies in the aerodigestive tract.

The thyroid gland performs a vital role in regulating metabolic function. It is susceptible to benign conditions (e.g., nodule, goiter, and cyst), inflammatory disease (e.g., thyroiditis), and malignancies. Additionally, congenital anomalies of the thyroid, such as a thyroglossal duct cyst, can present later in life. Thyroid lesions can present as pain, hoarseness, dyspnea, or dysphagia.

On the posterior aspect of the thyroid gland reside the four parathyroid glands. These glands play a vital role in maintaining calcium balance. Parathyroid adenomas and, rarely, carcinomas can develop.

Clinical Evaluation

The diagnostic approach to the upper aerodigestive tract begins with a thorough history, starting with a detailed evaluation of the chief complaint. Once a complete history of the chief complaint has been obtained, the physician should elicit a more comprehensive general medical history from the patient, including pertinent past medical history, past surgical history, medications, allergies, social history (tobacco, ethanol, and intravenous drug use), and family history.

The next step is to perform a comprehensive physical examination. This begins with a thorough inspection of the entire surface of the head and neck. The examination should proceed in an orderly fashion. The exact order is not important, but examiners should determine the order with which they are most comfortable and not deviate from that order. This way, they are unlikely to skip an anatomic area. The mucosal surfaces of the aerodigestive tract are inspected. Endoscopic evaluation of the upper aerodigestive tract is crucial in establishing a definitive diagnosis. The equipment used consists of both rigid and flexible laryngoscopes, bronchoscopes, and esophagoscopes. Many of these techniques can be performed in the office setting, providing the surgeon with an array of methods for gaining the information necessary for a working diagnosis and, in some cases, for performing a therapeutic intervention [see Figure 3]. Operative endoscopy is performed to obtain a definitive diagnosis, to stage tumors, and to rule out synchronous lesions. There is no substitute for a thorough examination and biopsy of a lesion with the patient under general anesthesia. Regardless of the endoscopic method used, an adequate biopsy specimen must be obtained for a histologic diagnosis.

An accurate history and a careful physical examination of the head and neck, including the mucosal surfaces, are the most important steps in evaluating a lesion in this part of the body; this clinical evaluation usually provides only a working diagnosis. The head and neck surgeon must then proceed in a stepwise fashion to further clarify the diagnosis and, in the case of a neoplasm, to perform an accurate staging.

Radiographic techniques allow the head and neck surgeon to visualize the mass and determine its characteristics (i.e., to differentiate between solid and cystic lesions), as well as its anatomic associations. Ultrasonography, magnetic resonance imaging (MRI), computed tomography (CT), and dual-modality positron emission tomography (PET)/CT each provide a unique view of the pathology in question and thereby help narrow the differential diagnosis. Acquisition of a tissue specimen for cytologic or histologic analysis, or both, is the next step. Fine-needle aspiration (FNA) is often used at this stage in the workup provided that the location of the mass lends itself to a safe procedure. If the lesion is located deep in the neck near vital structures, image-guided FNA can be attempted before resorting to an open biopsy. If the lesion is on a mucosal surface of the upper aerodigestive tract, an endoscopic biopsy is performed. Often panendoscopy is performed at this point to accurately map the lesion, obtain



Figure 3 Otolaryngology clinic office space with needed equipment, including an examination chair, a headlight, and a fiberoptic rhinolaryngoscope.

a tissue specimen, and, in patients with cancer, assess the rest of the upper aerodigestive tract for a synchronous primary tumor.

After a histologic diagnosis has been made and correlated with imaging, the patient and the physician can have a comprehensive discussion of the pathology, the stage of the disease, and the selection of therapy.

NOSE

Anterior Rhinoscopy

Anterior rhinoscopy is the examination of the nasal cavities with the use of a nasal speculum [see Figure 4]. The speculum is used to spread the ala. When done, the speculum should touch only the parts that are covered with skin. Resting the speculum on the nasal mucosa is painful. Anterior rhinoscopy is best done before and after topical vasoconstriction of the nasal mucosa. A good coaxial light source is needed. The more anterior portions of the nasal cavity are most readily examined.

Posterior Rhinoscopy

Posterior rhinoscopy is used to examine the posterior portion of the nasal cavity and, more importantly, the



Figure 4 Shown is an assortment of nasal specula.

nasopharynx. It is done with a small-angled mirror placed posterior to the palate and uvula. The tongue should be depressed using a tongue blade with the other hand. This examination is limited at times by the patient's gag reflex and the presence of enlarged adenoids.

Rigid Nasal Endoscopy

Rigid nasal endoscopy offers a superior view of the nasal cavity. Topical anesthesia and vasoconstriction are required for a good examination. The image is magnified, and deeper structures are better visualized than with anterior rhinoscopy. The endoscopes come in a variety of lens angles (0, 30, and 90 degrees). This allows inspection of structures that may be blocked from direct line of site. A more complete examination of both the anterior and posterior nasal cavities and nasopharynx is obtained than with anterior and posterior rhinoscopy. Rigid nasal endoscopy has become the examination of choice for a through nasal evaluation.

LARYNX AND PHARYNX

Indirect Laryngoscopy

Indirect laryngoscopy is used to examine the larynx, oropharynx, and hypopharynx. It is done in the clinic under topical or no anesthesia. An angled mirror is used, and the patient needs to be sitting upright with the neck straight and the head thrust slightly forward [see Figure 5]. A bright coaxial light source is used. The patient should relax and breathe



Figure 5 Shown is a laryngeal mirror, which is used for indirect laryngoscopy.

deeply and rhythmically, as if panting like a dog. The non-dominant hand of the examiner grasps the patient's tongue with gauze. The mirror is warmed and placed gently against the soft palate. To optimize the view, the examiner should ask the patient to say "ee." This technique can be performed rapidly and is inexpensive.

Flexible Laryngoscopy

Flexible laryngoscopy is also referred to as flexible rhinolaryngoscopy [see Figure 6]. It has become the most common way to examine the nasopharynx, oropharynx, hypopharynx, and larynx and is superior to indirect laryngoscopy. It allows better visualization and assessment of the structures, and since the tongue is not grasped, it allows better assessment of how structures function. The procedure is better tolerated by the patient, with less gagging. It has the disadvantage of requiring more expensive equipment than indirect laryngoscopy. Topical anesthesia is used. Most commonly, an anesthetic and a decongestant are sprayed into the nasal cavity prior to the procedure. The passage of the scope is best tolerated passing just inferior to the middle turbinate. If the patient has a deviated septum, the side with less obstruction is used.

Fiberoptic examinations in the clinic setting are not tolerated by all patients. Even if this examination is tolerated, an exact diagnosis frequently is not reached or a lesion is seen that cannot be biopsied in the clinic. It is recommended that the patients undergo an examination under anesthesia. This is done to look for an occult synchronous tumor and to more accurately examine and map the known tumor. The advantages of doing this under anesthesia are that it is better tolerated by the patient (gagging is eliminated) and allows deeper digital palpation and biopsies as needed. The disadvantage is that it requires general anesthesia and its possible complications as well as the complications of the procedure.

Direct Laryngoscopy

Direct laryngoscopy requires general anesthesia and therefore is done in the operating room. It is done with hollow, metal, rigid tubes [see Figure 7]. The laryngoscopes used by otolaryngologists differ from those used by anesthesiologists. They are straight and tubular and have distal lighting. There



Figure 6 A small-caliber flexible laryngoscope is used for rhinolaryngoscopy.

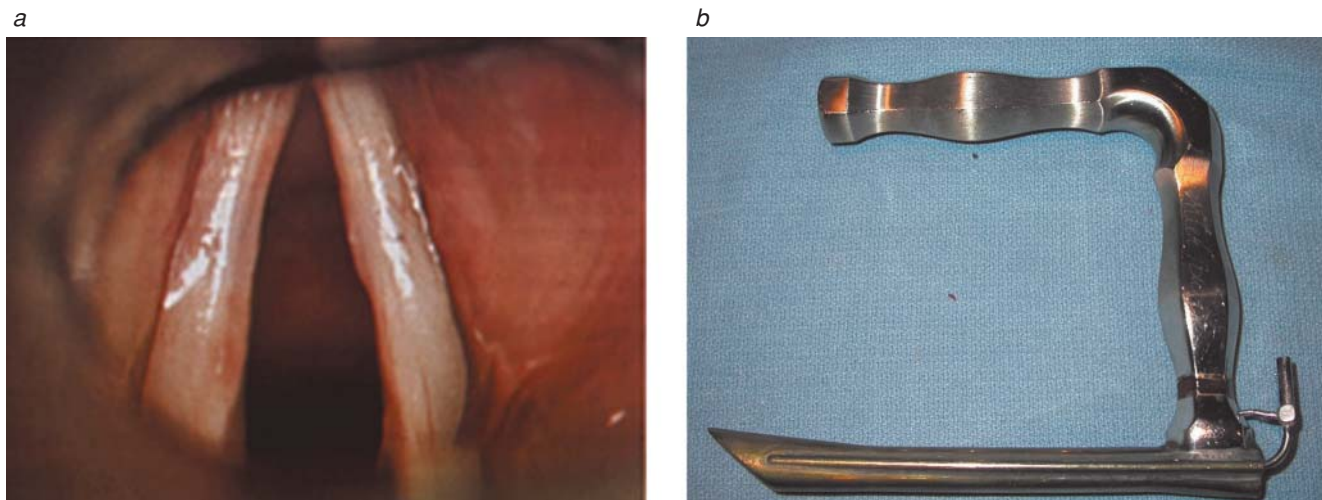


Figure 7 Shown are (a) normal vocal folds directly visualized via (b) a rigid laryngoscope.

are many different laryngoscopes. The sides of the laryngoscope hold surrounding soft tissue out of the way, allowing uninterrupted direct inspection of pharyngeal and laryngeal structures. The teeth are protected with a guard, and the structures in the oral cavity, pharynx, and larynx are all examined. It is best to become accustomed to doing this procedure in a specific order so that it becomes routine and lesions will not be missed. With the use of general anesthesia, palpation of the structures and a lesion can be done. The examination can be improved with suspension of the laryngoscope from a Mayo stand or the use of other suspension devices to allow the surgeon's hands to be free to perform procedures. Increased magnification is possible with the added use of a microscope. This is particularly useful when examining laryngeal lesions and is referred to as suspension microlaryngoscopy. A laser can also be used if needed.

ESOPHAGUS

Esophagoscopy plays an important role in the evaluation of patients with dysphagia, odynophagia, caustic ingestion, trauma, ingested foreign bodies, suspected anomalies, and upper aerodigestive tract malignancies. This procedure may be performed with either a flexible or a rigid scope.

Flexible Esophagoscopy

Flexible esophagoscopy is a diagnostic tool used to examine the esophagus and stomach. It is not well suited to visualizing the pharynx and is usually used in an outpatient setting with sedation and topical anesthesia. It is easier to perform than rigid esophagoscopy in patients who are elderly or have limited neck mobility, short, thick necks, and/or a limited mouth opening. The examination is usually done in the lateral decubitus position with the neck flexed. Air insufflation is important to completely visualize the mucosal surfaces. Tissue sampling is performed with a cup forceps through a working channel or by obtaining a brush biopsy. An endoscopic ultrasound probe can be passed to help define the extent of cancer of the esophagus. It is particularly useful to see the depth to which a tumor has invaded into the wall of the esophagus. If a lesion is found within the esophagus, its location is measured in centimeters from the teeth.

Rigid Esophagoscopy

Rigid esophagoscopy has been used for more than a century [see Figure 8]. It is used to diagnose cancer and remove foreign bodies. Unlike flexible esophagoscopy, it needs to be done under general anesthesia. The esophagoscope is a hollow metal tube of varying lengths and widths. The patient is placed supine and the maxillary teeth are protected with a mouth guard. The scope is passed transorally under direct visualization down the right side of the oral cavity and pharynx. If resistance is met, the scope should never be forced. There is a greater chance of perforation than with a flexible scope. As the scope is advanced, the lumen of the esophagus is kept in the center of the field of vision. The lumen has the appearance of a rosette. When advancing the scope, the left thumb is used. The right hand helps direct the scope and is used to pass instruments through its lumen. With rigid esophagoscopy, the removal of the scope is as important, if not more so, than inserting it. Removal allows better visualization of the mucosal surface as it slips over the tip of the instrument as it is removed.

TRACHEA AND LUNGS

Bronchoscopy is the technique of visualizing the trachea and lungs for both diagnostic and therapeutic reasons. Two basic forms of bronchoscopes are available: rigid and flexible. Each has its own advantages and disadvantages.

Rigid Bronchoscopy

The use of rigid bronchoscopy began in the 19th century with Killian. A rigid bronchoscope is a hollow, metal tube that is available in differing widths and lengths [see Figure 9].



Figure 8 Shown is a rigid esophagoscope.



Figure 9 (a) Rigid bronchoscopes incorporate stainless steel tubes of varying lengths and diameters. The beveled distal end of this Hopkins bronchoscope facilitates mobilization of the epiglottis during intubation; the side ports permit ventilation and use of suction catheters. (b) Illumination is provided by fiberoptic rods that are inserted into the bronchoscope.

It is used to examine the trachea and lungs and requires general anesthesia. It is used to remove foreign bodies and to diagnose and biopsy tumors and is better than flexible bronchoscopes for evaluation of large-volume hemoptysis because it allows suctioning and instruments to be used together. The patient is under general anesthesia with the neck hyperextended.

The bronchoscope is passed into the trachea either directly or through a slotted laryngoscope. Once in the airway, ventilation is usually done through a port on the scope. Venturi jet ventilation is also possible through a rigid bronchoscope. The entire trachea and main bronchi of both lungs are easily examined. Bronchial lavage is also possible.

Flexible Bronchoscopy

In the 1970s, Ikeda introduced flexible bronchoscopy. It is usually performed under sedation and is more common than rigid bronchoscopy. The instrument is thinner and longer than a rigid scope. There is a working channel that allows passage of biopsy forceps and brushes and lavage.

Panendoscopy

When visualization of the entire mucosal surface of the aerodigestive tract is needed, then panendoscopy is performed. Panendoscopy is the term used when direct laryngoscopy (with or without microscopic assistance), esophagoscopy, and bronchoscopy are done in the same setting.

Biopsy

After a thorough physical examination and history, tissue sampling should be considered if a lesion has been present for more than 3 to 4 weeks. To make a diagnosis, an open biopsy is not immediately indicated. Other methods are available to help obtain tissue and make a diagnosis. However, a biopsy is not recommended until after the history and physical examination have been done and appropriate imaging has been obtained. Imaging is important prior to a biopsy because the biopsy may cause a distortion of the tissue, such as occurs when a hematoma develops.

When a biopsy is indicated to establish a diagnosis for a neck mass or lesion, the options include FNA, a core biopsy, and an open biopsy. FNA offers the advantages of being simple and quick and can be done in the clinic.

FNA is possible for lesions that can be palpated. A thin-gauge needle is passed into the lesion, allowing a small number of cells to be sampled. It is a safe procedure that can be done under local or no anesthesia. It has not been shown to have an increased risk of seeding of the tumor spread along its tract. However, there is a risk of sampling error. This occurs if the needle does not collect a representative sample from the lesion. In reality, the test has a high sensitivity and specificity. The benefits of FNA include the rapid availability of results.

To optimize sampling, FNA can be done under guidance with CT or ultrasonography. The use of imaging allows direct visualization of the biopsy and therefore increases the likelihood of obtaining an accurate sample.

The procedure is performed with a thin-gauge needle such as a 23-gauge needle. The needle is attached to a 20 mL syringe, which allows negative pressure to be generated [see Figure 10]. Multiple passes are made through the lesion prior to removing the needle. Just before the needle is removed from the skin, any negative pressure in the syringe is released and the needle is withdrawn. If a cyst is encountered, it should be completely evacuated and the fluid sent for cytologic analysis. Ideally, for FNA, there should be minimal to no fluid or tissue in the syringe. The cells should be in the needle. The sample is then placed on a glass slide. A smear is made by laying another glass slide on top of the drop of fluid and pulling the slides apart to spread the fluid. Fixative spray is then applied. Alternatively, wet smears are placed in 95% ethyl alcohol and treated with the Papanicolaou technique and stains.

When the lesion is not easily palpated or is close to a delicate structure, FNA may need to be done under imaging. The most common imaging techniques used are ultrasonography and CT. When ultrasonography is used, it allows real-time imaging of the needle's passage. This results in an accurate trajectory and avoidance of vital structures. It also provides an image of the mass, allowing its characterization as solid, cystic, or heterogeneous. With cystic or complex masses, the tip of the needle can be placed into the wall to increase specimen yield.

CT guidance also provides visualization of the needle as it is passed through the tissue and into the underlying mass. It has the disadvantage of requiring ionizing radiation.

Core Biopsy

A core biopsy is a percutaneous biopsy done with a large-bore needle. The needle has a cutting tip and a hollow core. The area is infiltrated with local anesthesia prior to the needle being passed. The procedure can be done with image



Figure 10 A 20 mL syringe with a 23-gauge needle attached. The syringe is mounted in a handle to help allow creation of negative pressure.

guidance if needed. It has the disadvantage of causing more bleeding and has an increased risk of seeding the tumor along the needle tract. For most lesions in the neck, FNA is usually the first choice.

Open Biopsy

An open biopsy is indicated when a needle biopsy or core biopsy is unable to give a diagnosis. This can be done in either the clinic or, more commonly, in the operating room. Whenever possible, open biopsy is usually done after other techniques have not yielded a diagnosis. It has the greatest chance of seeding the tumor along the path of the biopsy.

Imaging

Imaging studies are important in the workup of patients with head and neck complaints. This is true because direct visualization of many structures is difficult because most of the structures are examined through orifices. The most common studies ordered are a barium swallow, CT, MRI, ultrasonography, and dual-modality PET with CT.

ULTRASONOGRAPHY

Ultrasonography offers many advantages. It is inexpensive, offers real-time imaging, and is performed without radiation exposure. Ultrasonography is particularly helpful in differentiating between solid and cystic masses. It allows evaluation of surrounding structures such as blood vessels. It is an excellent tool to follow masses to assess for changes in the size or character of the structure. It can also be used to help guide cytologic evaluation with FNA.

Barium Swallow

A barium swallow is used to examine the esophagus and, to a lesser extent, the stomach. Barium sulfate is swallowed and is used to identify tumors, ulcers, diverticula, and strictures. It is done under fluoroscopy to be able to follow the dynamic passage of the barium through the esophagus and stomach.

Computed Tomography

CT of the neck with contrast is the most common test performed to evaluate a mass in the head and neck. It allows

evaluation of the primary tumor and regional metastasis. It is usually used as part of the workup for head and neck malignancies and for surveillance posttreatment.

Magnetic Resonance Imaging

MRI results in superior evaluation of soft tissue compared with CT and does so without ionizing radiation. Instead, its images are attributable to a strong magnetic field that aligns the nuclear magnetization of hydrogen atoms in water. The examination is more difficult for some patients to tolerate compared with CT. The machine can make patients feel more claustrophobic and is noisier during the procedure. It also has the disadvantage that patients with implanted ferromagnetic foreign material are not able to go into the magnetic field. MRI is not as accurate for calcium structures such as bone and teeth.

Positron Emission Tomography/Computed Tomography

PET is a study that measures tissue metabolic activity by using a radioactive tracer. The tracer is fluorodeoxyglucose (FDG), an analogue of glucose. FDG is short acting with a half-life of 110 minutes. The scan works because neoplastic cells have a higher rate of glycolysis; therefore, the tracer is localized in the tissue. Unfortunately, tracer localization is not specific for neoplastic disease and can occur with inflammatory processes as well. Muscle activity will also result in increased uptake of the FDG. The scan is also limited by the inability to identify neoplasms that are smaller than 3 to 4 mm. In this situation, the amount of FDG concentrated is not large enough to stand out from the surrounding structures. The dual-modality scan of PET/CT has, for the most part, replaced the PET scan alone. Performing coregistered scans allows the metabolic activity from the PET scan to be more accurately correlated with the anatomic detail of the CT. PET/CT is most useful in head and neck oncology to look for unknown primary tumors, second primary tumors, and metastatic disease, both regional and distant. In the era of chemoradiotherapy, PET/CT has been used posttreatment to assess for response to treatment. This is most accurately done 2 to 3 months after treatment because the inflammation must resolve first.

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Recommended Reading

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5 ORAL CAVITY PROCEDURES

Carol R. Bradford, MD, FACS, and Mark E.P. Prince, MD, FRCSC

Preoperative Evaluation

Oral cavity procedures are commonly performed to treat malignancies. Tumors should be assessed preoperatively to allow accurate staging of the disease and to facilitate planning of definitive treatment. In most cases, an examination under anesthesia with endoscopy and biopsy is required to stage the primary tumor and to look for synchronous second primary tumors. Except in the case of very superficial lesions, computed tomography (CT) plays an important role in preoperative planning. In selected cases, plain radiographs (e.g., Panorex views) may be useful in evaluating the mandible. When the lesion is located in the tongue, magnetic resonance imaging (MRI) may provide additional information about the extent of the primary tumor.

Wide surgical margins are necessary for adequate treatment of primary squamous cell carcinoma of the head and neck. A margin of 1 to 2 cm should be achieved whenever possible, ideally with frozen-section control. Current evidence clearly indicates that overall patient outcome improves when clear margins are obtained.

Nodal metastases are common with oral cavity tumors. Accordingly, patients should be assessed for cervical adenopathy both clinically and radiographically. A chest x-ray should be obtained in all cases. CT or MRI can provide valuable information regarding the nodal status of the neck. In patients with advanced disease, a more extensive search for distant metastases should be conducted, including a CT scan of the chest. In some circumstances, combining CT with positron emission tomography (PET) may be useful.

Operative Planning

Surgical management of the neck is an evolving field. In general, if the risk of occult metastasis is greater than 20 to 25%, a selective neck dissection is recommended, particularly if postoperative radiation therapy is not planned. Whenever there is clinical evidence of nodal disease, treatment of the neck must be included in operative planning.

The oral cavity is a major component of a number of important functions, including speech and swallowing. Reconstruction of the anticipated surgical defect must be carefully planned to achieve the best results. Several basic considerations must be kept in mind. Tongue mobility and sensation must be maintained to the extent possible. Maintenance of mandibular continuity (especially in the anterior segment of the mandible) is vital for ensuring postoperative oral competence. Separation of the nasal cavity from the oral cavity is critical for the oral phase of swallowing and speech. Maintenance of the gingivobuccal and gingivolabial sulcus is important for oral function and the fitting of dentures.

As a rule, oral cavity defects should be closed primarily whenever possible. Primary closure has the advantage of

using sensate tissue similar in form to the tissue that was excised. With experience and careful judgment, the surgeon can usually determine when a defect is too large for primary closure or when primary closure is likely to cause distortion and tethering of adjacent tissues and result in a significant functional disturbance. In such cases, a flap reconstruction must be considered. In select cases, pedicled flaps may be appropriate. Often, particularly with larger or more complicated defects, free flaps provide the best reconstructive result. Free tissue reconstruction has the advantage of allowing the surgeon to reconstruct the defect with the exact tissue components that were excised, including bone and skin. In addition, free flaps can be reinnervated to achieve a sensate reconstruction.

If the planned surgical procedure involves resection of part of the maxilla or the mandible, appropriate dental consultation should be obtained. If a postoperative splint, obturator, or dental prosthesis is to be placed, it is critical that dental impressions be obtained before operation. Thyroid function should be tested in all patients who have a history of radiation therapy to the neck to confirm that they are euthyroid.

In cooperative patients, small primary lesions of the oral cavity can sometimes be excised with local anesthesia; however, general anesthesia with adequate relaxation is required in the majority of cases. The route of intubation must be carefully considered for each patient. When the planned resection is extensive and when significant postoperative edema is anticipated, a tracheostomy should be performed. Patients with bulky lesions should undergo tracheostomy under local anesthesia before general anesthesia is induced. When a tracheostomy is not planned, nasotracheal intubation is often desirable.

When the excision is limited to the oral cavity, perioperative antibiotics are generally unnecessary. When a graft, a flap, or packing is employed, however, perioperative intravenous administration of antibiotics is advisable. In all cases in which the neck is entered, perioperative antibiotics are recommended. The oral cavity can be prepared preoperatively with chlorhexidine and a toothbrush.

A nasogastric feeding tube should be inserted whenever it is believed that the patient may have a problem maintaining oral nutrition postoperatively. Patients who undergo primary closure or split-thickness skin grafting or whose surgical wound is allowed to heal by secondary intention may be allowed clear liquids in 24 to 48 hours and a pureed diet by postoperative day 3; they can often tolerate a soft diet within 1 week. Patients who undergo flap reconstruction will have to be fed via a nasogastric tube until they have healed to the point where they can resume oral intake.

Patients should be advised to maintain oral hygiene postoperatively by means of frequent irrigation and rinses with either normal saline or half-strength hydrogen peroxide.

Teeth may be gently cleaned with a soft toothbrush until healing has occurred.

Anterior Glossectomy

OPERATIVE PLANNING

Either orotracheal or nasotracheal intubation may be appropriate, depending on the surgical approach and the extent of the planned resection. A tracheostomy should be performed whenever significant postoperative swelling or airway compromise is anticipated.

The depth of the excision and the size of the anticipated defect determine the optimal reconstructive approach. Defects that connect to the neck, unless they are small and can easily be closed primarily, usually necessitate creation of a flap for optimal reconstruction. When the excision extends down to the underlying musculature but there is no connection to the neck, a skin graft may be used. If a postoperative dental splint is planned to hold a skin graft in place, a dental consultation must be obtained before operation.

The patient should be supine in a 20° reverse Trendelenburg position. Turning the table 180° may facilitate access and positioning for the surgeon.

OPERATIVE TECHNIQUE

Step 1: Surgical Approach

Small anterior lesions up to 2 cm in diameter may be approached transorally, as may certain carefully selected larger lesions. Exposure of the tongue is usually achieved with the help of an appropriately sized bite block; alternatively, a specialized retractor (e.g., a Molt retractor) may be used. Retraction of the tongue is facilitated by the use of a piercing towel clip or a heavy silk suture placed through the tip of the tongue.

Access to posterior lesions and most larger lesions is obtained by performing a mandibulotomy through a lip-splitting incision [see Figure 1]. A stair-step incision is made in the lip and extended downward straight through the mentum, and a Z-plasty is done at the mental crease. Alternatively, the incision may be carried around the mental subunit.

The mandibular periosteum is elevated and a plate contoured to the mandible before the mandible is divided; this measure ensures exact realignment of the cut ends of the mandible. When possible, the mandibulotomy should be made anterior to the mental foramen to preserve sensation throughout the distribution of the mental nerve. Repair of the mandibulotomy is greatly facilitated by making a stair-step or chevron-type mandibulotomy [see Figure 2]. A paralingual mucosal incision is made to allow retraction of the mandible and exposure of the posterior oral cavity.

As an alternative, a visor flap may be created [see Figure 3]. Such a flap allows the surgeon to avoid making a lip-splitting incision and provides adequate exposure of small lesions of the anterior oral cavity; however, it is inadequate for exposure of lesions posterior to the middle third of the tongue or in the area of the retromolar trigone. Furthermore, creation of a visor flap results in anesthesia of the lower lip because of the necessity of dividing both mental nerves.

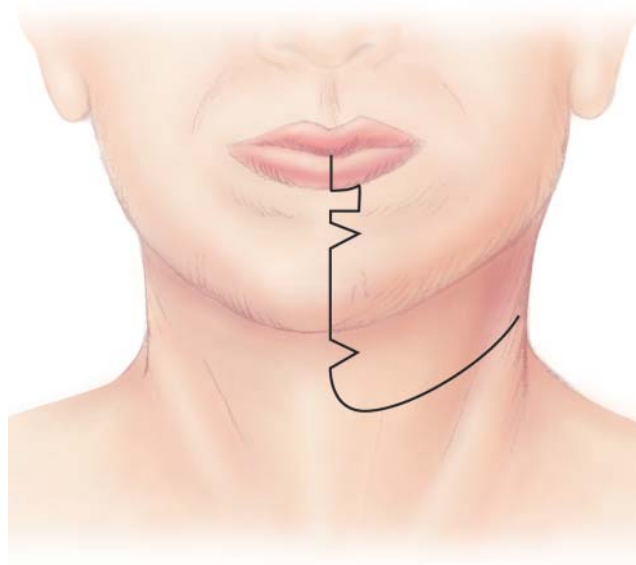


Figure 1 Anterior glossectomy. A lip-splitting incision is made that extends downward straight through the mentum.

To create a visor flap, an incision is made from mastoid to mastoid along a skin crease in the neck, with care taken to remain below the marginal mandibular nerves. The skin flap is elevated in the subplatysmal plane to the level of the mandible. The marginal mandibular nerves are preserved. The flap is elevated from the lateral surface of the mandible, and the two mental nerves are divided. An incision is made in the oral cavity mucosa along the gingivolabial sulcus and

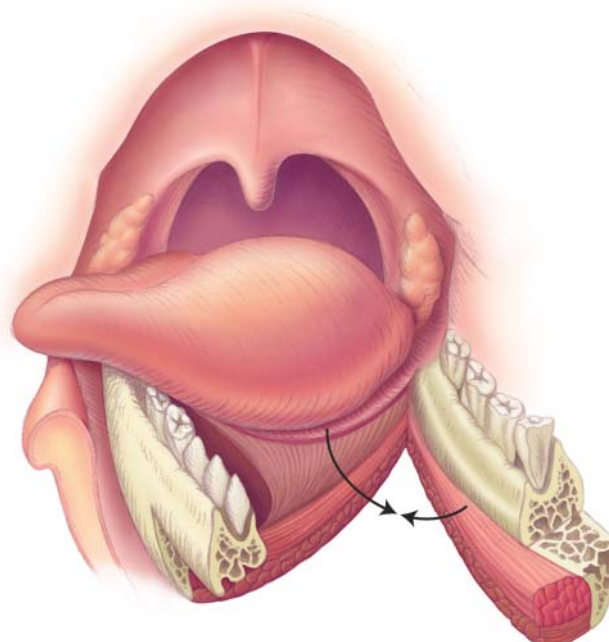


Figure 2 Anterior glossectomy. A stair-step mandibulotomy is made.

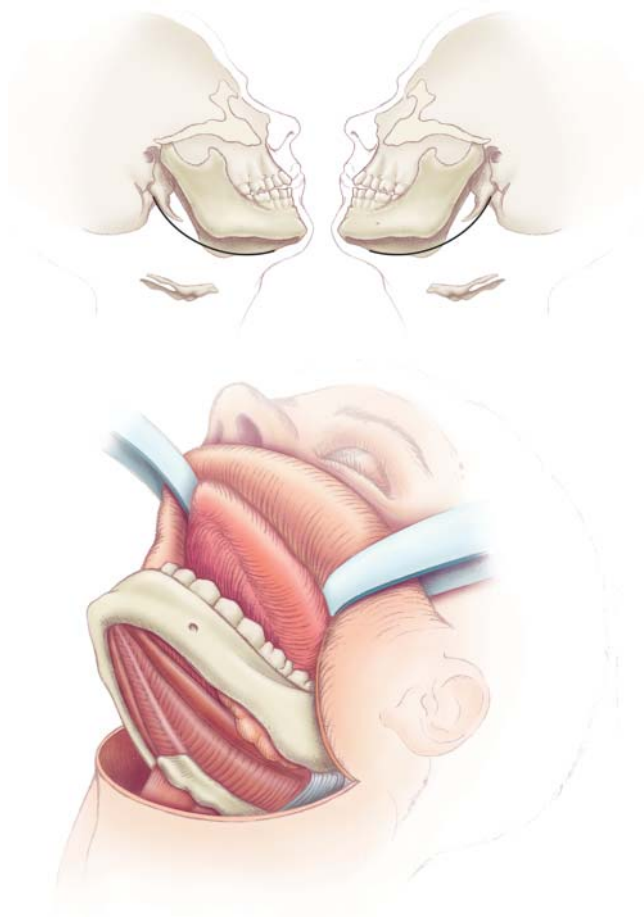


Figure 3 Anterior glossectomy. As an alternative to a lip-splitting incision with mandibulotomy, a visor flap may be employed for exposure.

continued so that it connects to the skin incision. The flap is then retracted superiorly to expose the anterior mandible and the oral cavity.

Step 2: Resection

The excision should include a generous mucosal margin around the visible lesion. A significant amount of the tongue musculature surrounding the lesion should be resected as well. Palpation of the lesion is critical for obtaining adequate deep surgical margins.

Resection may be performed with a monopolar electrocautery, with the cutting current used to incise the mucosa and the coagulation current used to cut the muscle. Alternatively, resection may be performed with a scalpel and scissors. Hemostasis is achieved with a monopolar or bipolar electrocautery. Larger vessels are ligated with chromic catgut or Vicryl ties.

Lesions of the lateral tongue should be wedge-excised in a transverse (rather than horizontal) fashion to facilitate closure and enhance postoperative function. With larger lesions, for which either flap reconstruction or healing by secondary intention is typically indicated, the shape of the defect is contoured so as to obtain wide margins around the lesion, and the flap is designed to fill the contoured defect.

Step 3: Reconstruction

After negative margins are confirmed by frozen-section examination, repair of the surgical defect is initiated. Careful preoperative assessment of the anticipated defect lays the groundwork for optimal reconstruction. Many defects can be either repaired primarily or allowed to heal by secondary intention. Free tissue transfer is an excellent reconstructive option in many cases, allowing the maintenance of tongue mobility and the separation of the tongue from the mandible and making sensate reconstruction possible.

In many patients with wedge-excised lateral tongue lesions, primary closure of the defect yields good results. The deep muscle is carefully reapproximated with long-lasting absorbable sutures. The mucosa is also closed with absorbable sutures. Care should be taken not to strangulate tissues by making the sutures too tight. When complete primary closure is not possible or desirable, the tongue may be allowed to granulate and heal by secondary intention. Split-thickness skin grafts, although useful for relining the floor of the mouth, generally do not take well on the tongue.

For large defects of the tongue and those involving the floor of the mouth, flap reconstruction is appropriate. Defects that connect to the neck, unless they are small and can be closed primarily, should also be closed with a flap. Free tissue transfer is frequently the optimal reconstructive approach. Free fasciocutaneous flaps from the radial forearm, the anterior lateral thigh, or the lateral arm are well suited to reconstruction in this area. Pedicled flaps (e.g., myocutaneous flaps from the pectoral muscle) are also used in this setting but are bulkier and harder to contour to the defects.

If a mandibulotomy was made, it is repaired with the previously contoured plate. The lip-splitting incision is closed in three layers (mucosa, muscle, and skin). Great care must be taken to ensure accurate realignment of the vermilion border and the orbicularis oris muscle.

Alternative Procedure: Laser Vaporization

Very superficial and premalignant lesions of the tongue may be vaporized by using a CO₂ laser. The desired depth of tissue destruction for leukoplakia is approximately 1 to 2 mm.

TROUBLESHOOTING

Larger excisions may lead to airway edema. Whenever this possibility is a concern, a tracheostomy should be performed. A single intraoperative dose of steroids may reduce postoperative tongue edema without adversely affecting wound healing. Using a stair-step incision for the lip-splitting incision facilitates accurate reapproximation of the vermilion border. Excessive tongue movement may result in dehiscence of the closure. Voice rest for 3 to 5 days after operation may be beneficial.

POSTOPERATIVE CARE

Patients who undergo primary closure of the tongue may begin a fluid diet on the day after operation; they should remain on a liquid diet for 7 to 10 days. Patients who undergo skin grafting may also begin a liquid diet on postoperative day 1. If a flap was used to close the defect or if there is some question whether the patient will be capable of adequate oral intake, a nasogastric feeding tube should be inserted and maintained until the suture lines heal.

Bolster dressings may be removed and skin grafts inspected after 7 to 10 days. Patients with skin grafts should stay on a soft diet for 2 weeks. If a tracheotomy was performed, the patient may be decannulated when postoperative edema has settled.

Meticulous and frequent oral hygiene is essential. Mouth rinses and irrigation with normal saline or half-strength hydrogen peroxide should be done at least four times a day and after every meal. Teeth may be gently cleaned with a soft toothbrush.

COMPLICATIONS

The main complications of anterior glossectomy are as follows:

1. Injury to the lingual nerve, which causes numbness and loss of the sense of taste in the ipsilateral tongue
2. Injury to the submandibular and sublingual gland ducts, which causes obstruction of the glands, pain and swelling, and possibly ranula formation
3. Injury to the hypoglossal nerve, portions of which are resected with the lesion. Injury to the main trunk of this nerve leads to paralysis and atrophy of the remaining ipsilateral tongue.
4. Tethering and scarring of the tongue, which can lead to difficulties with speech and swallowing. This problem can usually be avoided by careful preoperative planning of reconstruction.

Excision of Floor-of-Mouth Lesions

OPERATIVE PLANNING

Planning for excision of a lesion from the floor of the mouth is essentially the same as that for anterior glossectomy [see Anterior Glossectomy, Operative Planning, *above*]. If either or both of Wharton ducts are to be transected without excision of the submandibular glands, consideration must be given to the management of these glands.

OPERATIVE TECHNIQUE

Step 1: Surgical Approach

The surgical approach is the same as that described for glossectomy [see Anterior Glossectomy, Operative Technique, Step 1, *above*].

Step 2: Resection

The area to be excised, including adequate margins, is marked. The lesion is then excised with a monopolar electrocautery; as in a glossectomy, the cutting current is used to cut the mucosa and the coagulation current to cut the deeper tissues. Palpation is important for obtaining adequate deep surgical margins.

If the excision cuts across the Wharton duct, the duct should be identified and transected obliquely to create a wider opening. The transected stump is held with a 4-0 chromic catgut suture. Once the resection is complete, the duct is transposed posteriorly to the cut edge of the mucosa of the floor of the mouth and sutured in place with two or three 4-0 chromic sutures. During subsequent reconstruction, care should be taken not to obstruct the orifice of the duct.

Step 3: Reconstruction

After clean surgical margins have been verified by frozen-section examination, repair of the surgical defect is initiated. Small superficial defects of the floor of the mouth may be allowed to heal by secondary intention.

For small defects that do not connect to the neck, reconstruction with a 0.014 to 0.016 inch-thick split-thickness skin graft is appropriate. The graft is cut to size and sutured in place with 4-0 chromic sutures. Several perforations should be made in the graft to allow the egress of blood and serum. A Xeroform gauze bolster is fashioned to fit over the skin graft and sutured in place with 2-0 silk tie-over bolster stitches; alternatively, it may be held in place by a prefabricated dental prosthesis.

For larger defects, particularly those involving the tongue, a flap reconstruction typically yields the best functional results. In select cases, a platysma flap may be used for reconstruction of defects in the floor of the mouth. Other regional flaps tend to be bulky and difficult to shape to the contours of the defect. Free tissue transfer frequently provides the most suitable reconstructive tissue characteristics and the most favorable postoperative results. A free fasciocutaneous radial forearm flap is usually the optimal choice for reconstruction of floor-of-mouth defects when a flap is required.

TROUBLESHOOTING

Special care should be taken to identify the lingual nerve and artery so that these structures are not inadvertently divided. Meticulous hemostasis should be obtained in all cases. Any skin grafts used should be adequately sized and should not “tent up.” Generally, skin grafting and bolsters do not work well on mobile structures. Quilting grafts to the underlying tissues with multiple absorbable sutures can eliminate the need for a bolster and result in acceptable graft take.

POSTOPERATIVE CARE

Postoperative care of patients undergoing excision of floor-of-mouth lesions is virtually identical to that of patients undergoing anterior glossectomy [see Anterior Glossectomy, Postoperative Care, *above*].

COMPLICATIONS

Excision of floor-of-mouth lesions is associated with the same complications as anterior glossectomy [see Anterior Glossectomy, Complications, *above*].

Excision of Superficial or Plunging Ranulas

OPERATIVE PLANNING

Planning for excision of a superficial or plunging ranula resembles that for glossectomy. A Ring-Adair-Elwyn (RAE) tube is inserted orally and taped to the contralateral cheek. Cervical exploration is usually unnecessary because the cervical component of the ranula resolves after removal of the ipsilateral sublingual gland. In select cases, especially those involving disease recurrence after a previous attempt at excision, a transcervical approach should be considered.

OPERATIVE TECHNIQUE

Step 1: Surgical Approach

Ranulas are resected via the transoral approach. A bite block or a Molt retractor is used to gain exposure.

Step 2: Resection

A local anesthetic preparation with epinephrine is infiltrated into the area of the mucosal incisions. A small superficial ranula may be marsupialized and packed with gauze. The ranula is widely unroofed and the contents removed with suction. The margins of the cyst are sutured to the mucosa with 4-0 chromic sutures, and the cavity is packed with iodoform strip gauze. The gauze may be removed in 5 to 7 days.

A plunging ranula is treated with complete surgical excision of the cyst and the sublingual gland [see Figure 4]. A mucosal incision is made directly over the cyst. Careful dissection is carried out around the cyst and the associated gland. Hemostasis is achieved with a bipolar electrocautery, with care taken not to injure the adjacent lingual nerve. The submandibular gland duct is cannulated with a lacrimal probe to help guard against inadvertent injury to this structure. The incision is closed with 4-0 chromic suture.

TROUBLESHOOTING

Efforts should be made to identify the lingual nerve and artery to prevent inadvertent division of these structures.

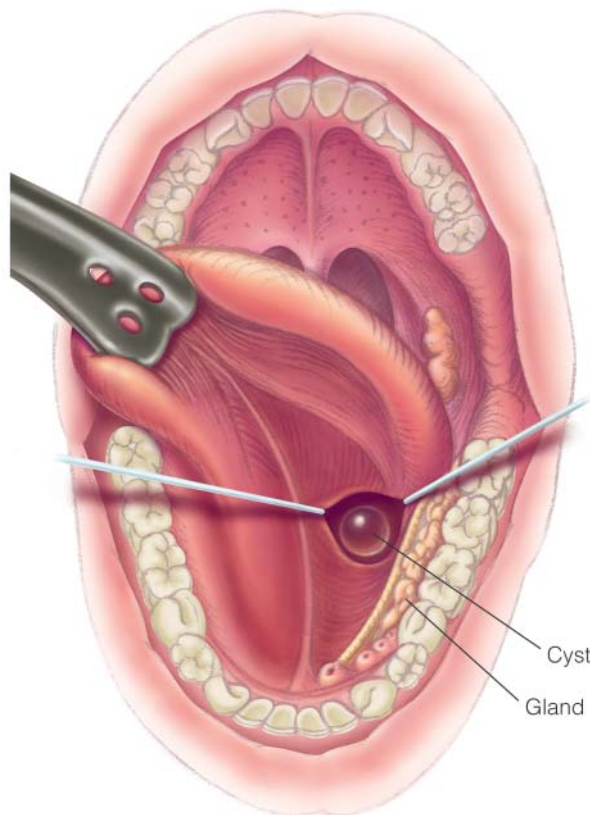


Figure 4 Excision of plunging ranula. A mucosal incision is made over the cyst, dissection is done around the cyst and the associated sublingual gland, and the cyst and gland are completely excised.

Meticulous hemostasis should be obtained in all cases. If the submandibular gland duct is injured, it should be transected and the cut end sutured to the adjacent floor-of-mouth mucosa (sialodochoplasty).

COMPLICATIONS

The three main complications of the procedure for excising a ranula are among those that are also associated with anterior glossectomy and excision of floor-of-mouth lesions: injury to the lingual nerve, injury to the submandibular gland duct, and injury to the hypoglossal nerve [see Anterior Glossectomy, Complications, above].

Removal of Submandibular Gland Duct Stones

OPERATIVE PLANNING

When a submandibular gland duct stone is readily palpable in the floor of the mouth, a transoral approach is appropriate. When the stone is within the hilum of the gland, however, it generally cannot be removed transorally and often must be treated by excising the submandibular gland.

OPERATIVE TECHNIQUE

Step 1: Surgical Approach

The procedure is easily accomplished with local anesthesia in a cooperative patient. The patient is seated upright in the examining chair, and a topical anesthetic is applied to the oral cavity.

Step 2: Resection

A local anesthetic preparation with epinephrine is infiltrated into the floor of the mouth and around the duct in which the stone is palpated. A 2-0 silk suture may be placed around the duct behind the stone to prevent it from migrating back into the hilum of the gland.

A lacrimal probe is inserted into the duct and advanced to the stone in a retrograde manner. A mucosal incision is then made directly over the stone and extended downward to the duct, with the stone and the lacrimal probe serving as guides. The duct is incised and the stone delivered. As a rule, repair of the duct is not required.

TROUBLESHOOTING

Careful dissection directly onto the duct and stone usually serves to prevent inadvertent injury to the lingual nerve.

COMPLICATIONS

The main complications of the procedure are as follows:

1. Injury to the lingual nerve, resulting in numbness and loss of the sense of taste to the ipsilateral tongue
2. Stricture of the submandibular gland duct. This is an unusual complication that can be corrected by transecting the duct posterior to the stricture and suturing it to the mucosa of the floor of the mouth.

Resection of Hard Palate

OPERATIVE PLANNING

Careful evaluation is required to determine whether resection of part of the hard palate will suffice or whether a more

extensive dissection (e.g., maxillectomy) will be required. If it is anticipated that a dental prosthesis will be required, a dental consultation should be obtained before operation. When the lesion to be resected is superficial or only a limited amount of the bony hard palate must be resected, the procedure may be performed via the transoral approach.

OPERATIVE TECHNIQUE

Step 1: Surgical Approach

The patient is supine, with the bed turned 180° to facilitate the surgeons' access to the operative site. An oral RAE tube is inserted and taped in the midline. The lesion is approached transorally, and a Dingman or Crowe-Davis retractor is used to obtain exposure.

Step 2: Resection

An incision is made around the periphery of the lesion in such a way to maintain adequate margins; a monopolar electrocautery with a needle tip is ideal for this purpose. The periosteum is elevated away from the underlying bone, and the lesion is removed [see Figure 5].

When bone must be resected, the periosteum is elevated away from the incision site. A high-speed oscillating saw or an osteotome is used to make the cuts in the bone, after which the specimen is rocked free and removed.

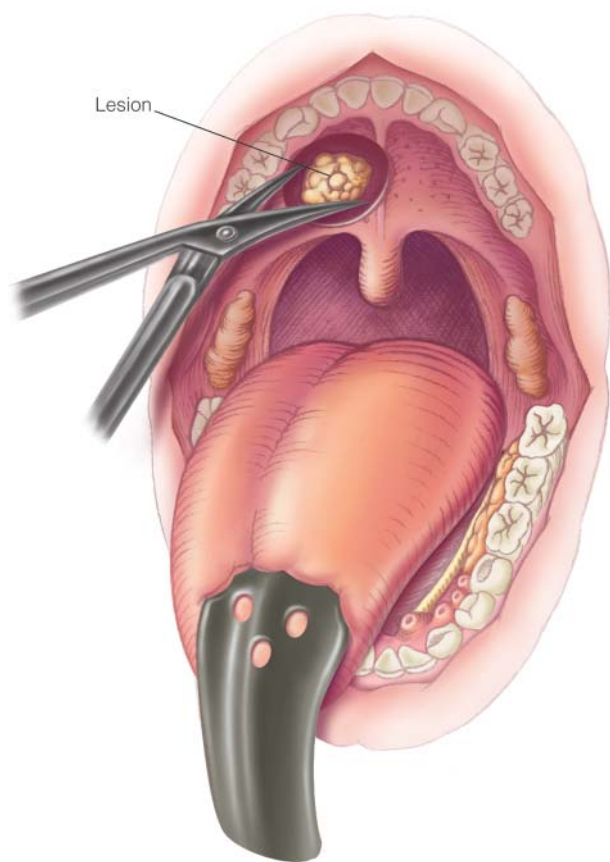


Figure 5 Resection of hard palate. An incision is made around the lesion, with adequate margins maintained, the periosteum is lifted off the bone, and the lesion is removed.

Step 3: Reconstruction

After surgical margins have been verified by frozen-section review, repair of the surgical defect is initiated. Small mucosal defects may be allowed to heal by secondary intention. Small through-and-through resections may be closed by placing relaxing incisions laterally and advancing the mucosa to permit primary closure. Larger defects may be closed with palatal mucosal flaps. Many through-and-through defects can be closed quite satisfactorily with a dental obturator.

POSTOPERATIVE CARE

The patient should be maintained on a soft diet postoperatively. Meticulous oral hygiene is important. Oral rinses and flushes with normal saline or half-strength hydrogen peroxide should be performed at least four times daily and after meals.

COMPLICATIONS

The most significant potential complication of hard palate resection is oral antral or oronasal fistula; careful tissue reconstruction and the use of an obturator can prevent this complication.

Maxillectomy

OPERATIVE PLANNING

General anesthesia with muscle relaxation is essential for all types of maxillectomy. Either orotracheal or nasotracheal intubation may be appropriate, depending on the surgical approach. Skin incisions should be marked before the endotracheal tube is taped in place to avoid distortion of facial structures and skin lines. The patient should be supine in a 20° reverse Trendelenburg position. The eyes should be protected carefully (e.g., with a corneal shield or a temporary nylon tarsorrhaphy suture).

Radiographic evaluation plays a vital role in planning the surgical approach and determining the extent of resection required [see Figure 6]. Lesions of the infrastructure of the maxilla can be excised by means of partial maxillectomy via the transoral route. More extensive lesions usually must be accessed via facial incisions in conjunction with the transoral approach.

In all cases, a dental consultation should be obtained preoperatively so that a dental impression can be taken and an obturator fashioned for intraoperative use. Antibiotics should be given perioperatively and continued until nasal packing is removed.

OPERATIVE TECHNIQUE

Step 1: Surgical Approach

In addition to the transoral approach, maxillectomy usually requires exposure of the anterior face of the maxilla. There are several options for achieving such exposure, including a Weber-Ferguson incision and midface degloving. Midface degloving has the advantage of eliminating the need for visible facial incisions but yields limited exposure in the ethmoid region. The choice of surgical approach is determined by the extent of the planned resection and by the preferences of the patient and the surgeon.

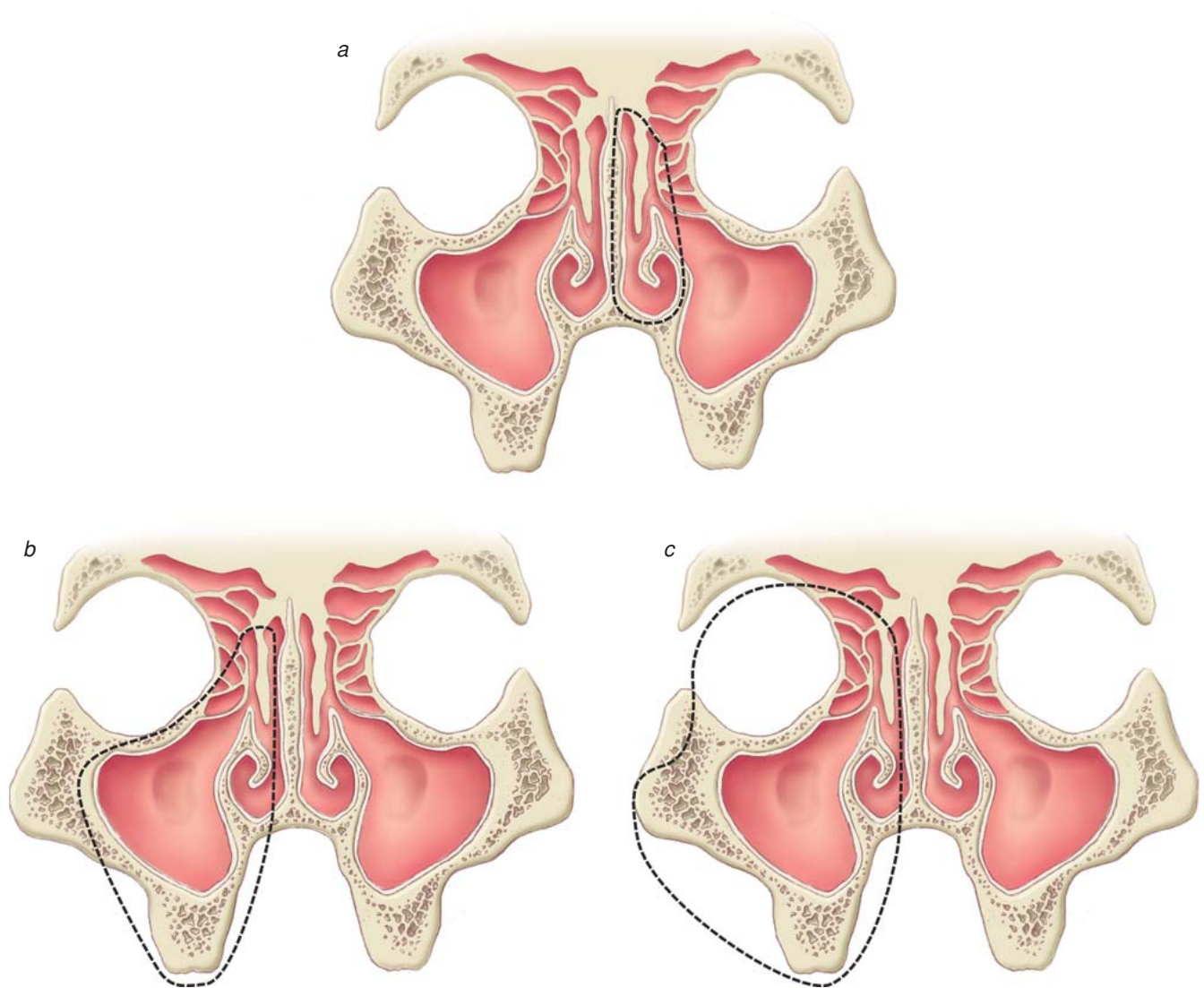


Figure 6 Maxillectomy. Radiographic assessment helps determine the required extent of resection. Depicted are (a) medial maxillectomy, (b) subtotal maxillectomy without orbital exenteration, and (c) total maxillectomy with orbital exenteration.

In the Weber-Ferguson approach, the first step is to mark the path of the incision, which begins in the midline of the upper lip; extends through the philtrum; curves around the nasal vestibule and the ala; continues upward along the lateral nasal wall, just medial to the junction of the nasal sidewall and the cheek; and ends near the medial canthus. For added exposure in the ethmoid region, a Lynch extension, in which the incision is continued superiorly up to the medial eyebrow, may be performed. Alternatively, the Weber-Ferguson incision may be continued laterally in the subciliary crease along the inferior eyelid to the lateral canthus of the eye; this extension yields added exposure of the posterolateral aspect of the maxilla.

The skin incisions should initially be made with a scalpel and then continued with an electrocautery. The upper lip is divided through its full thickness, and the incision is continued in the gingivolabial sulcus laterally until the posterolateral aspect of the sinus is exposed. When possible, the infraorbital nerve is identified and preserved. The soft tissues

are elevated from the anterior wall of the maxillary sinus; if access to the pterygomaxillary fissure is desired, elevation should be continued up to the zygoma.

In a midface degloving, the skin of the lower face and nose is mobilized and retracted superiorly. A standard transfixion incision is made, transecting the membranous septum. Intercartilaginous incisions are then made bilaterally and connected to the transfixion incision. The incision is then continued laterally along the cephalic border of the lower lateral cartilage and across the floor of the nose. To prevent stenosis, a small Z-plasty or triangle is incised medially just before the transfixion incision is joined. The soft tissues are elevated over the nasal dorsum and the nasal tip with Joseph scissors. An incision is made in the gingivolabial sulcus with the monopolar cautery, and this incision is connected to the floor-of-nose incisions by means of gentle dissection. The soft tissues are then elevated from the anterior maxilla as far as the infraorbital rims and laterally as far as the zygoma.

Step 2: Resection

A Molt retractor is placed on the side opposite the side of the planned excision and opened as wide as possible to expose the hard palate and the alveolus.

The infraorbital rim should be preserved if it is possible to do so safely. Often a thin strip of the rim can be preserved even when the rest of the bone must be resected. If the orbital floor must be resected but the orbital contents can be preserved, the periorbital can be dissected away from the bone of the orbital floor and preserved. If the orbital contents are involved, an orbital exenteration must be performed in conjunction with the maxillectomy.

The cut along the infraorbital rim and superior anterior maxillary wall is made with a high-speed oscillating saw with a fine blade. The level at which this superior cut is made is determined by the extent of the resection. Lesions that are confined to the alveolus or the palate and do not invade the maxilla typically can be removed by excising the infrastructure of the maxilla. The line of transection is continued through the nasal process of the maxilla medially and downward through the piriform aperture. Laterally, the cut extends to the zygomatic process of the maxilla and around the posterolateral aspect of the sinus.

If the pterygoid plates are to be preserved, they are cut free by placing a curved osteotome along the posterior wall of the sinus and sharply dividing the plates from the sinus wall. If the pterygoid plates, part of the pterygoid musculature, or both are to be resected, the soft tissue attachments are cut sharply with curved Mayo scissors once the entire maxillary specimen has been mobilized.

The line of transection in the maxillary alveolus can run between two teeth if a suitable gap is evident. In the majority of cases, however, it is advisable to extract a tooth and make the cut through the extraction site. A power saw is used, and the cut is connected to the transection line through the nasal process of the maxilla and the piriform aperture. The hard palate mucosa is then incised lateral to the proposed cut in the hard palate bone to preserve a flap of mucosa that can be used to cover the raw cut bony edge of the palate. This incision is made with a needle-tip electrocautery and carried down to the bone of the hard palate. It should extend from the maxillary tuberosity posteriorly to the cut bone in the maxillary alveolus anteriorly, with care taken to obtain adequate mucosal margins. The mucosa is elevated for a short distance over the hard palate bone to create a short mucosal flap that is wrapped over the cut bony edge of the palate. The mucosal cut is connected around the maxillary tuberosity to the gingivolabial sulcus incision that was made earlier.

The hard palate is then cut with a power saw. Once all the bone cuts are complete, an osteotome may be used to connect them if necessary. The remaining soft tissue attachments are divided along the posterior hard palate with curved Mayo scissors. The surgical defect is packed to control bleeding. Bleeding from the internal maxillary artery is controlled by ligatures or ligating clips.

Step 3: Reconstruction

All sharp spicules of bone are débrided. The flap of hard palate mucosa is brought up over the cut bony edge of the palate and held in place with several Vicryl sutures. The anterior and posterior cut edges of the soft palate are reapproximated with absorbable sutures.

A split-thickness skin graft, 0.014 to 0.016 inches thick, is harvested and used to line the raw undersurface of the cheek flap. The skin graft is sutured to the mucosal edge of the cheek flap with 3-0 chromic sutures. Superiorly, the graft is not sutured but draped into position and retained by a layer of Xeroform packing and strip gauze coated with antibiotic ointment. Gentle pressure is applied to the packing so that it conforms to the defect. The previously fabricated dental obturator is placed to support the packing and to close the oral cavity from the nasal cavity. In a dentulous patient, the obturator may be wired to the remaining teeth; in an edentulous patient, it may be temporarily fixed in place with two screws placed in the remaining hard palate.

The skin incisions are closed in two layers, with interrupted absorbable sutures used for the deep layers and nonabsorbable monofilament sutures for the skin. If a lip-splitting incision was made, care must be taken to ensure exact reapproximation of the orbicularis oris and the vermilion border.

If the infraorbital rim was resected, it should be reconstructed to yield good aesthetic results. A split calvarial bone graft may be used for this purpose when there is adequate soft tissue coverage for the bone grafts available. When soft tissue coverage is inadequate or the orbital floor must be reconstructed, an osteocutaneous radial forearm or scapular flap may be employed, with excellent results.

Alternative Procedure: Peroral Partial Maxillectomy

The oral cavity is exposed with cheek retractors. An incision is made in the gingivobuccal sulcus and the mucosa of the hard palate, with care taken to maintain adequate margins; a monopolar electrocautery, set to use the cutting current, is suitable for this purpose. Incisions are made circumferentially through all the soft tissues up to the anterior wall of the maxilla and the hard palate. The infraorbital nerve should be preserved if it is not involved with the disease process.

The cut in the hard palate mucosa should be made lateral to the planned cuts in the hard palate bone to create a mucosal flap, which will be used to cover the cut bony edge of the hard palate. If necessary, teeth may be extracted to allow the surgeon to make bone cuts through tooth sockets while preserving adjacent teeth. The bone is cut with a high-speed power saw, and an osteotome is used to divide any remaining bony attachments and deliver the specimen. If the mucosa remaining in the maxillary antrum is not diseased, it need not be removed.

A split-thickness skin graft, 0.014 to 0.016 inches thick, is harvested from the anterolateral thigh and used to reline the raw buccal mucosa area. The graft is sutured to the cut edge of the buccal mucosa with 4-0 chromic catgut. Xeroform and strip gauze coated with antibiotic ointment are gently packed into the defect to secure the skin graft. The previously fabricated dental obturator is wired to the remaining teeth to hold the packing in place.

TROUBLESHOOTING

If a lip-splitting incision is planned, lip contraction can be reduced and vermilion border realignment improved by employing a stair-step lip incision and a Z-plasty. A single intraoperative steroid dose reduces facial edema without compromising wound healing. Retention of the obturator is

aided by the band of scar tissue that forms at the junction of the mucosa and the skin graft. Covering the cut edge of the hard palate bone with mucosa eliminates pain caused by pressure from the obturator on thinly covered bone.

If more than a small area of the floor of the orbit is resected, it should be repaired to prevent enophthalmos. Epiphoria is uncommon; when it occurs, it is related to scarring of the nasolacrimal duct. Identifying the duct and transecting it obliquely should reduce the incidence of this complication.

POSTOPERATIVE CARE

A nasogastric tube is placed at the end of the procedure. Many patients are able to begin a liquid diet and advance to a soft diet within a few days after operation. A soft diet should be continued for at least 2 weeks. Oral rinses and flushes with normal saline or half-strength hydrogen peroxide should be performed at least four times daily and after meals.

The obturator and the packing may be removed from the cavity in 7 to 10 days. The obturator should be replaced to maintain oral competence. The prosthodontist makes a final obturator once healing is complete and the cavity has stabilized. Facial incisions are cleaned twice daily and coated with antibiotic ointment. Facial sutures are removed 5 to 7 days after operation.

COMPLICATIONS

The main complications of maxillectomy are as follows:

1. Enophthalmos and hypophthalmos, which create a cosmetic deformity
2. Infraorbital nerve injury, which results in anesthesia or paresthesia of the ipsilateral cheek and upper lip. On occasion, the infraorbital nerve may have to be sacrificed as part of the planned resection.
3. Epiphoria, caused by scarring of the nasolacrimal duct
4. Difficult retention of the dental prosthesis, which can usually be prevented by careful preoperative evaluation and appropriate choice of reconstructive method. In select cases, free tissue reconstruction without a dental prosthesis may be optimal.

Mandibulectomy

OPERATIVE PLANNING

General anesthesia with muscle relaxation is essential for all types of mandibulectomy. Either orotracheal or nasotracheal intubation is appropriate, depending on the surgical approach and the extent of the planned resection. A tracheostomy should be performed whenever significant postoperative swelling or airway compromise is anticipated. Skin incisions should be marked before the endotracheal tube is taped in place.

Preoperative radiographic evaluation is essential for planning the surgical approach and determining the extent of the proposed resection. For lesions without radiographic or clinical evidence of bone invasion, a marginal mandibulectomy is often appropriate. This procedure may also be performed to obtain adequate surgical margins for lesions that are in close proximity to the mandible. When the lesion is small, it is occasionally possible to perform marginal mandibulectomy via the transoral route. For more extensive lesions and those that show evidence of bone invasion, a segmental mandibulectomy is required.

The patient should be supine in a 20° reverse Trendelenburg position. Perioperative antibiotics should be administered.

OPERATIVE TECHNIQUE

Step 1: Exposure

Wide exposure for access to primary tumors of the oral cavity and the mandible may be achieved by means of either a lower-cheek flap or a visor flap. The former is often preferable in that it allows resection of the primary and ipsilateral lymph nodes.

To create a lower-cheek flap, a lip-splitting incision is made through the full thickness of the lower lip and carried down through the chin tissues to the periosteum of the anterior mandible [see Figure 7]. This incision may be made straight through the mental subunit with a Z-plasty placed at the mental crease; alternatively, it may be made around the mental subunit. The incision is continued vertically to approximately the level of the thyrohyoid membrane and then extended laterally to the mastoid along a skin crease. The transverse component of the incision should be made at least two fingerbreadths below the mandible to prevent injury to the marginal mandibular nerve. The cheek flap is fully developed by incising the oral mucosa along the gingivolabial sulcus while maintaining adequate surgical margins around the lesion. The periosteum of the mandible is then elevated and the cheek flap retracted to expose the mandible.

A visor flap [see Figure 3] has the advantage of not requiring a lip-splitting incision and provides adequate exposure for lesions of the anterior oral cavity. However, it is inadequate for exposing lesions posterior to the middle third of the tongue or in the area of the retromolar trigone and may lead to anesthesia of the lower lip as a consequence of the need to divide both mental nerves. The technical aspects of

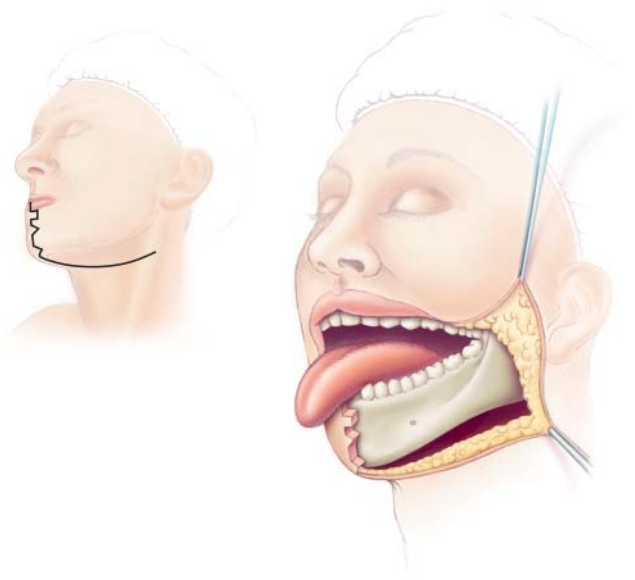


Figure 7 Mandibulectomy. A cheek flap is created by making a lip-splitting incision and extending it down to the level of the thyrohyoid membrane and then laterally to the mastoid along a skin crease.

visor flap creation are summarized elsewhere [see Anterior Glossectomy, Operative Technique, Step 1, *above*].

Step 2: Resection

If a plate is to be used in the reconstruction of the mandible, a template and a reconstruction plate are shaped and conformed to the mandible before resection. The segment of mandible to be resected is marked. The plate is applied to the buccal cortex of the mandible, and screw holes are predrilled in the mandible for gauging of depth. The plate is then set aside until needed for reconstruction.

Mucosal incisions are made around the lesion with the electrocautery, with care taken to maintain adequate surgical margins. The mandibular segment to be removed is cut with a high-speed sagittal saw. The lingual nerve and the hypoglossal nerve are preserved if possible. Muscle attachments to the resected mandibular segment are sharply divided, allowing the surgical specimen to be delivered [see Figure 8].

In some cases, only a marginal mandibulectomy of the lingual or alveolar cortex of the mandible is necessary. The

bone is cut with a high-speed saw in such a way that the cuts are rounded off and lack sharp angles, which are prone to fracturing. Once the bone cuts are made, an osteotome may be used to free the specimen.

Step 3: Reconstruction

When a marginal mandibulectomy has been performed, a plate is sometimes needed to support the mandible. This is especially likely to be the case for a patient with a thin edentulous mandible, in which the remaining bone cannot withstand the forces of mastication.

When the anterior mandible has been resected, it must be reconstructed with vascularized bone. Any of several free flaps may be employed, depending on the tissue requirements for the planned reconstruction. Free tissue flaps from the fibula, the scapula, or the iliac crest can provide bone that is suitable for mandibular reconstruction, as well as soft tissue that is suitable for reconstruction of accompanying mucosal and cutaneous defects.

After lateral mandibular resections, good results can be achieved by using mandibular reconstruction plates with suitable soft tissue reconstruction. There is a significant risk of plate failure, however, especially in dentulous patients. In many cases, replacing the resected portion of the mandible with vascularized bone—especially if the defect is longer than a few centimeters—yields better long-term results than using a reconstruction plate alone.

POSTOPERATIVE CARE

A nasogastric tube is placed at the end of the surgical procedure; most patients will need to be fed through this tube until their incisions are healed. A soft diet should be continued for 6 weeks. Oral rinses and flushes with normal saline or half-strength hydrogen peroxide should be performed at least four times a day and after meals.

Facial incisions are cleaned twice a day and coated with antibiotic ointment. Facial sutures are removed 5 to 7 days after operation.

TROUBLESHOOTING

Contouring the reconstruction plate to the mandible before resecting the mandibular segment will prevent malocclusion and enhance cosmetic results. Preserving the lingual nerve and the hypoglossal nerve, when possible, will improve postoperative swallowing and speech. The marginal mandibular nerve should be identified and protected as well. If a lip-splitting incision is used, performing a stair-step lip incision and a Z-plasty reduces lip contraction and improves vermilion border realignment.

COMPLICATIONS

The main complications of mandibulectomy are as follows:

1. Malocclusion, caused by inaccurate repair of the resected mandibular segment
2. Plate failure or fracture, which can be reduced by reconstructing bony defects larger than 1 to 2 cm with revascularized bone
3. Oral incompetence, caused by inadequate reconstruction of anterior mandibular defects.

Financial Disclosures: None Reported

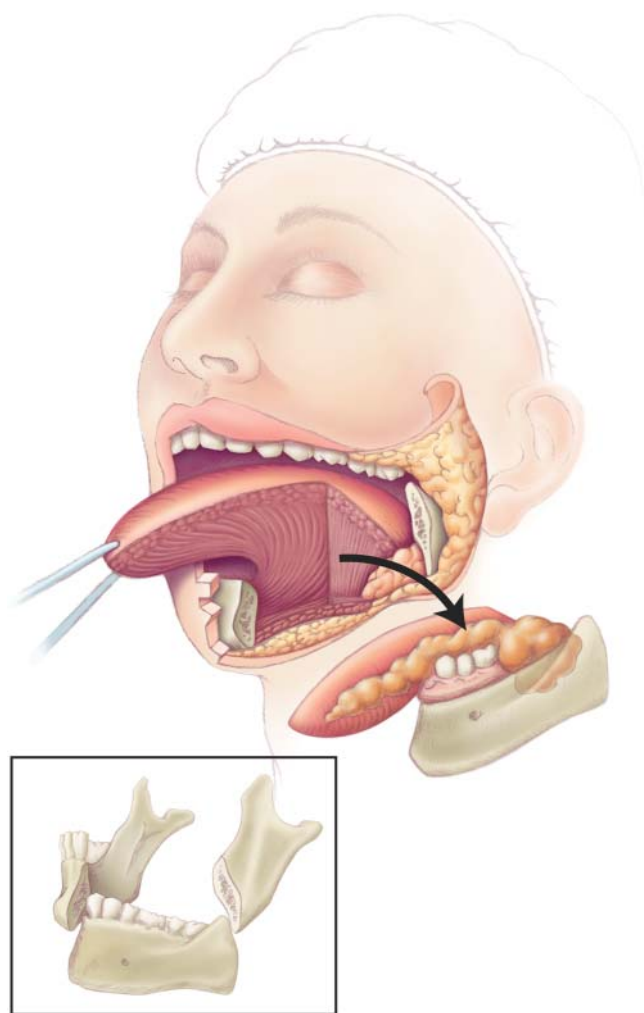


Figure 8 Mandibulectomy. The segment to be removed is cut with a high-speed saw, with care taken to preserve the lingual and hypoglossal nerves if possible, and the muscle attachments to the segment are sharply divided to free the surgical specimen.

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Acknowledgment

Figures 1 through 8 Alice Y. Chen

6 PAROTIDECTOMY

Leonard R. Henry, MD, and John A. Ridge, MD, PhD, FACS

Anatomic Considerations

The parotid (“near the ear”) gland, the largest of the salivary glands, occupies the space immediately anterior to the ear, overlying the angle of the mandible. It drains into the oral cavity via Stensen’s duct, which enters the oral vestibule opposite the upper molars. The gland is invested by a strong fascia and is bounded superiorly by the zygomatic arch, anteriorly by the masseter muscle, posteriorly by the external auditory canal and the mastoid process, and inferiorly by the sternocleidomastoid muscle. The masseter muscle, the styloid muscles, the posterior belly of the digastric muscle, and a portion of the sternocleidomastoid muscle lie deep to the parotid. Terminal branches of the external carotid artery, the facial vein, and the facial nerve are found within the gland. Parasympathetic innervation to the parotid is via the otic ganglion, which gives fibers to the auriculotemporal branch of the trigeminal nerve. Sympathetic innervation to the gland originates in the sympathetic ganglia and reaches the auriculotemporal nerve by way of the plexus around the middle meningeal artery.¹

The facial nerve trunk exits the stylomastoid foramen and courses toward the parotid. Once inside the gland, it commonly bifurcates into superior (temporal-frontal) and inferior (cervicomarginal) divisions before giving rise to its terminal branches. The nerve branching within the parotid can be quite complex, but the common patterns are well known and their relative frequencies well established.^{2,3} The portion of the parotid gland lateral to the facial nerve (about 80% of the gland) is designated as the superficial lobe; the portion medial to the facial nerve (the remaining 20%) is designated as the deep lobe. Deep-lobe tumors often present clinically as retro-mandibular or parapharyngeal masses, with displacement of the tonsil or the soft palate appreciated in the throat.

Operative Planning

Obtaining informed consent for parotidectomy entails discussing both the features and the potential complications of the procedure. It is appropriate to address the possibility of facial nerve injury, but in doing so, the surgeon should not neglect other, far more common sequelae, such as cosmetic deformity, earlobe numbness, and Frey syndrome. Even conditions that are expected beforehand may prove distressing or debilitating for the patient. The risk of complications such as nerve injury is greater in cases involving reoperation or resection of malignant or deep-lobe tumors. The overwhelming majority of parotid tumors, however, are benign and lateral to the facial nerve. Accordingly, in what follows, we focus primarily on superficial parotidectomy, referring to variants of the procedure where relevant.

Excellent lighting, correctly applied traction and countertraction, adequate exposure, and clear definition of

the surgical anatomy are essential in parotid surgery. The use of magnifying loupes and headlights is recommended. General anesthesia without muscle relaxation should be employed.

The patient is placed in the supine position, with the head elevated and turned away from the side undergoing operation and with the neck slightly extended. The table is positioned to allow the first assistant to stand directly above the patient’s head, while the surgeon faces the operative field. A small cottonoid sponge is placed in the external auditory canal, where it remains for the duration of the procedure to prevent otitis externa from blood clots in the external auditory canal. The skin is painted with an antiseptic agent. A single perioperative dose of an antibiotic is administered.

The patient is draped in a fashion that permits the operating team to see all of the muscle groups innervated by the facial nerve. To this end, we employ a head drape that incorporates the endotracheal tube and hose. This drape secures the airway, keeps the tube from interfering with the surgeon, and permits rotation of the head without tension on the endotracheal tube. The skin of the upper chest and neck is widely painted and draped with a split sheet to allow additional exposure in the unlikely event that a neck dissection or a tracheostomy becomes necessary. The nose, the lips, and the eyes are covered with a sterile transparent drape that allows observation of movement during the procedure and permits access to the oral cavity (if desired) [see *Figure 1*].

Operative Technique

STEP 1: INCISION AND SKIN FLAPS

The incision is planned so as to permit excellent exposure with good cosmetic results. It begins immediately anterior to the ear, continues downward past the tragus, curves back under the ear (staying close to the earlobe), and finally turns downward to descend along the sternocleidomastoid muscle [see *Figure 1*]. Either all or part of this incision may be used, depending on circumstances. The incision is marked before draping. Skin creases typically help conceal the resulting scar.

Skin flaps are then created to expose the parotid gland. A tacking suture is placed within the dermis of the earlobe so that it can be retracted posteriorly. Skin hooks are used to apply vertical traction. The anterior flap is created superficial to the parotid fascia to afford access to the appropriate dissection plane. Vertically oriented blunt dissection minimizes the risk of injury to the distal branches of the facial nerve [see *Figure 2*]. The face is observed for muscle motion. The flap is raised until the anterior border of the gland is identified. The facial nerve branches are rarely encountered during flap elevation until they emerge from the parenchyma of the

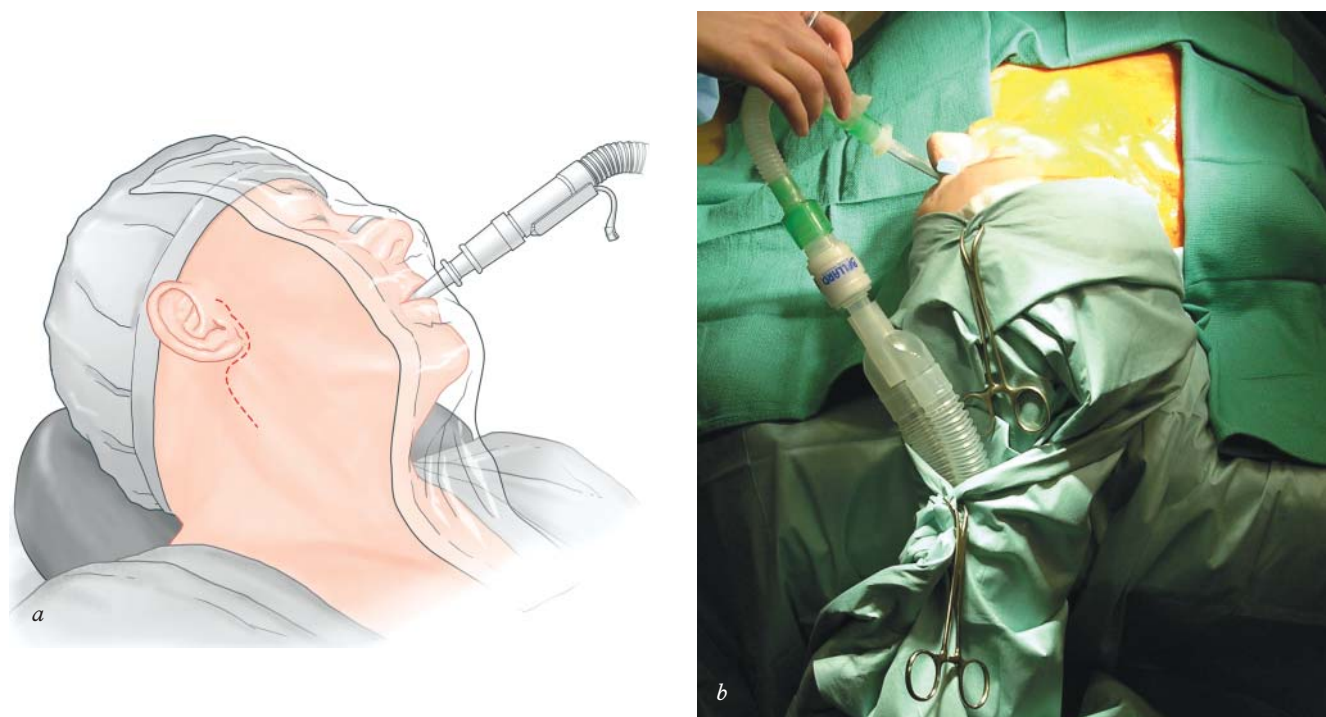


Figure 1 Parotidectomy. (a) Shown are the recommended head position and incision. A transparent drape is placed over the eyes, the lip and oral cavity. (b) The head drape incorporates the hose from the endotracheal tube.

parotid. If muscle movement occurs, the flap has been more than adequately developed. The anterior flap is retracted with a suture through the dermis.

The posterior-inferior skin flap is then elevated in a similar manner. Careful dissection is performed to define the relationship of the parotid tail to the anterior border of the sternocleidomastoid. During this portion of the procedure, the great auricular nerve is identified coursing cephalad and superficial to the sternocleidomastoid muscle. Uninvolved

branches of this nerve should be preserved if possible to prevent postoperative numbness of the earlobe.^{4,5} The parotid tail is dissected away from the sternocleidomastoid muscle. Vertical traction is applied to the gland surface with clamps to facilitate exposure.

Troubleshooting

A favorable skin crease, if available, may be used for the incision to improve the postoperative cosmetic result;

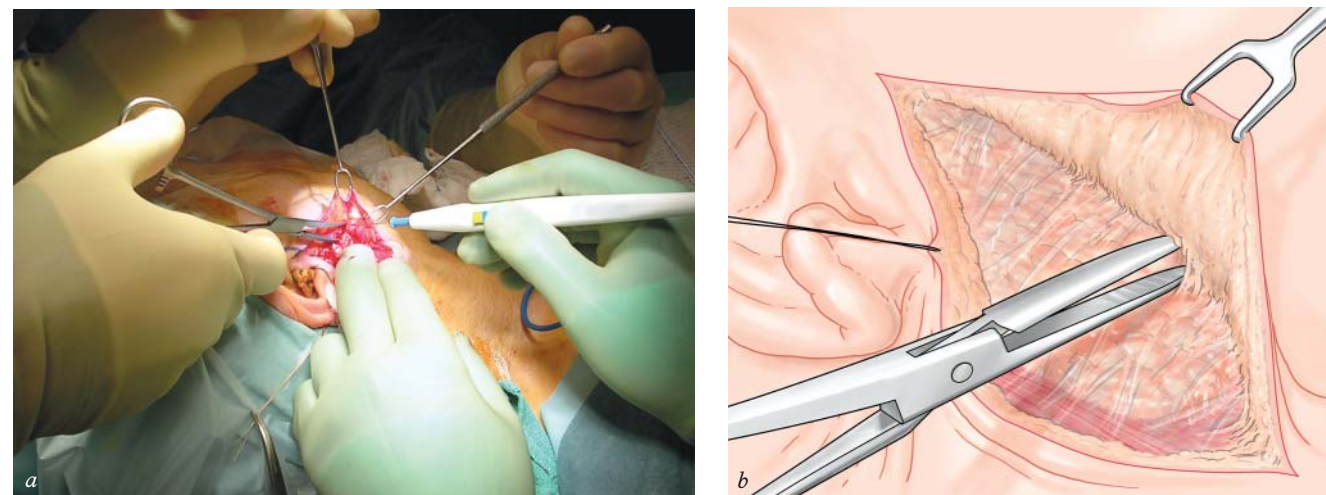


Figure 2 Parotidectomy. (a) Shown is the creation of the anterior skin flap superficial to the parotid gland. (b) Vertically oriented blunt dissection minimizes the risk of injury to facial nerve branches as they exit the gland.

however, it is important to keep the incision a few millimeters from the earlobe itself. A wound at the junction of the earlobe with the facial skin will distort the earlobe and create a visible contour change. An incision behind the tragus may lead to similar problems.

STEP 2: IDENTIFICATION OF FACIAL NERVE

Once the skin flaps have been developed and retracted, the next step is to identify the facial nerve. Usually, the nerve may be identified either at its main trunk (the antegrade approach) or at one of the distal branches, with subsequent dissection back toward the main trunk (the retrograde approach). For a lateral parotidectomy, our preference is to identify the main trunk first (unless it is thoroughly obscured by tumor or scar).

Antegrade Approach

The dissection plane is immediately anterior to the cartilage of the external auditory canal. The gland is mobilized anteriorly by means of blunt dissection. To reduce the risk of a traction injury, tissue is spread in a direction that is perpendicular to the incision and thus parallel to the direction of the main trunk of the nerve [see Figure 3]. The nerve trunk can usually be located underlying a point about halfway between the tip of the mastoid process and the ear canal. In addition, there are several anatomic landmarks that facilitate identification of the nerve, including the tragal pointer, the posterior belly of the digastric muscle, and the tympanomastoid suture. Of these, the tympanomastoid suture is closest to the main trunk of the facial nerve.⁶ The clinical utility of this landmark is limited, however, because the tympanomastoid suture is not easily appreciated in every case. In addition,

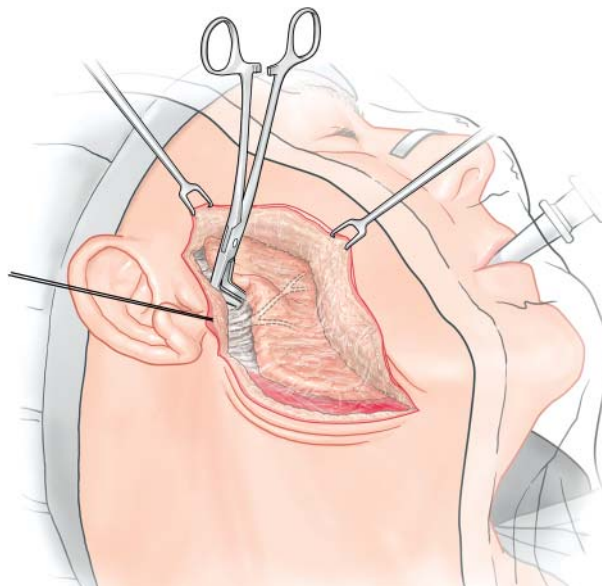


Figure 3 Parotidectomy. Depicted is identification of the facial nerve at its trunk. A wide trough is created anterior to the external auditory canal and deepened by spreading a blunt curved instrument in a direction perpendicular to the incision and parallel to the nerve trunk. Anatomic landmarks assist in identification of the nerve.

deep-lobe tumors may displace the nerve from its normal location. For appropriate and safe exposure of the nerve trunk, it is necessary to mobilize several centimeters of the parotid, thereby creating a trough rather than a deep hole. Small arteries run superficial and parallel to the facial nerve; these must be divided. Use of the electrocautery this close to the nerve is potentially hazardous. Bleeding is typically minor but nonetheless must be controlled.

Retrograde Approach

As noted, when the main trunk cannot be exposed, the most common alternative method of identifying the facial nerve is to find a peripheral branch and then dissect proximally toward the main trunk. Which branch is sought may depend on factors such as the surgeon's comfort with the anatomy and the known consistency of the nerve branch's location. In this setting, tumor bulk is often the deciding factor.

The anatomic relationships between the nerve branches and various landmarks can be exploited for more efficient identification. For example, the marginal mandibular branch of the facial nerve characteristically lies below the horizontal ramus of the mandible.⁷ Often, the facial vein can be traced toward the parotid on the submandibular gland; the nerve branch can then be found coursing perpendicular and superficial to the vein. The buccal branch of the facial nerve has a typical location in the so-called buccal pocket—the area inferior to the zygoma and deep to the superficial musculoaponeurotic layer, which contains the buccal fat pad and Stensen's duct in addition to the buccal branch.⁷ The zygomatic branch of the facial nerve lies roughly 3 cm anterior to the tragus, and the temporal-frontal branch lies at the midpoint between the outer canthus of the eye and the junction of the ear's helix with the preauricular skin.⁷ Nerve branches to the eye should be dissected with particular care: even transient weakness of these branches may have a significant impact on morbidity.

Troubleshooting

Special efforts should be made to ensure that the cartilage of the ear canal is not injured during exposure of the facial nerve trunk. Any injury to this cartilage must be repaired, or else an intense whistling will be heard from the closed suction drain after operation.

The anxiety associated within isolation of the nerve trunk may be alleviated somewhat by keeping in mind that the nerve typically lies deeper than one might expect. In a study of 46 cadaver dissections, the facial nerve was found to lie at a median depth of 22.4 mm from the skin at the stylomastoid foramen (range, 16 to 27 mm). The diameter of the nerve trunk was found to range from 1.1 to 3.4 mm.⁸ In our experience, the facial nerve trunk is slightly larger than the nearby deep vessels.

Some surgeons advocate the use of a nerve stimulator to aid in identifying the facial nerve trunk or its branches; however, we have substantial reservations about whether this measure should be employed on a regular basis [see Complications, Facial Nerve Palsy, below]. Knowledge of the anatomy and sound surgical technique are the keys to a safe parotidectomy; it may be hazardous to rely too much on practices that may diminish them.

STEP 3: PARENCHYMAL DISSECTION

Once identified, the plane of the facial nerve remains uniform throughout the gland (unless the nerve is displaced by a tumor) and serves to guide the parenchymal dissection. Although some surgeons advocate the use of hemostatic devices for parenchymal division,^{9,10} our practice is to divide the substance of the parotid gland sharply and use ligatures as appropriate when bleeding is encountered. Usually, there is no significant hemorrhage: loss of more than 30 mL of blood is rare.

The parenchymal dissection proceeds directly over the facial nerve. We favor using fine curved clamps for this portion of the procedure. To prevent trauma to the nerve, care must be taken to resist the tendency to rest the blades of the clamp on the nerve during dissection. Each division of the gland should reveal more of the facial nerve [see Figure 4]. When this is the case, the surgeon can continue the parenchymal dissection with confidence that the nerve will not be injured. As a rule, if a parenchymal division does not immediately show more of the facial nerve, it is in an improper plane.

We do not regularly resect the entire lateral lobe of the parotid unless the tumor is large and such resection is required on oncologic grounds. The goal in resecting the substance of the parotid is to obtain sound margins while preserving the remainder of the gland. This so-called partial superficial parotidectomy has been shown to reduce the incidence of Frey syndrome without increasing the rate of recurrence of pleomorphic adenoma.¹¹ The plane of dissection is developed along facial nerve branches until the lateral margins have been secured. This is the portion of the procedure during which the risk of nerve injury is highest. Once the lateral margins have been secured, the parenchymal dissection can proceed from deep to superficial for the excision of the tumor.

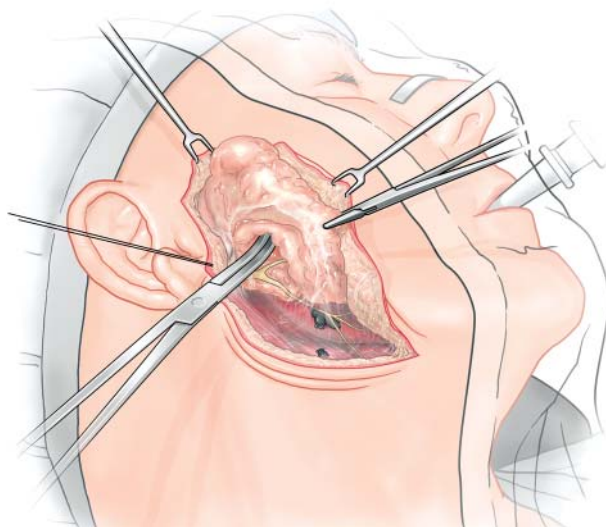


Figure 4 Parotidectomy. Dissection of the gland parenchyma is carried out over the branches of the facial nerve to minimize the risk of nerve injury. Each division of the substance of the gland should reveal more of the facial nerve.

The vertical portion of the dissection seldom poses a threat to the integrity of the facial nerve, but care must be taken to maintain appropriate margins. If division of Stensen's duct is required, the distal remnant may be either left open¹² or ligated.

Caution is appropriate in the resection of deep-lobe tumors. Tumors medial to the facial nerve may displace this structure laterally. Thus, after establishing the plane of the facial nerve, the surgeon must remain careful when dissecting near the tumor to keep from injuring the nerve. Once the substance of the gland obscuring the tumor has been removed, the nerve branches in the area of the tumor are retracted to allow exposure of the deep portion of the gland and facilitate resection. Traction injury to the nerve may still result in transient facial weakness.

Troubleshooting

Complete superficial parotidectomy with full dissection of all facial nerve branches is seldom necessary, though in some cases it is mandated by tumor size or histologic findings. Removal of the entire superficial lobe with the intention of obtaining a larger lateral margin is rarely useful, because the closest margin is usually where the tumor is nearest the facial nerve. Even temporary paresis of the temporal-frontal branch of the facial nerve may have devastating consequences, and dissection near this branch is usually unnecessary in treating a benign tumor in the parotid tail. Any close margins remaining after nerve-preserving cancer treatment can be addressed by means of postoperative radiation therapy, usually with excellent results.¹³

The question of whether to sacrifice the facial nerve almost invariably arises in the setting of malignancy. In our view, this measure is seldom necessary. Benign tumors tend to displace the nerve, not invade it. Sacrifice of the nerve probably does not enhance survival.^{14,15} Although this issue remains a subject of debate, our practice, like that of others,¹⁶ is to sacrifice only those branches intimately involved with tumor. Repair, if feasible, should be performed [see Complications, Facial Nerve Injury, below].

STEP 4: DRAINAGE AND CLOSURE

Before closure, absolute hemostasis is confirmed (including hemostasis during the Valsalva maneuver, which is approximated by transiently increasing airway pressure to 30 cm H₂O¹). We may then assess the integrity of the facial nerve with a nerve stimulator. A 5 mm closed suction drain is placed through a stab incision posterior to the inferior aspect of the ear in a hair-bearing area. The tip of the drain is loosely tacked to the sternocleidomastoid muscle, with care taken to avoid direct contact with the facial nerve). The wound is closed with the drain placed on continuous suction. The skin is closed with interrupted 5-0 nylon sutures. Bacitracin is applied to the wound. No additional dressing is necessary or desirable [see Figure 5].

Troubleshooting

The use of interrupted skin sutures instead of a continuous suture allows the surgeon to perform directed suture removal to drain the rare postoperative hematoma or fluid collection instead of reopening the entire wound.

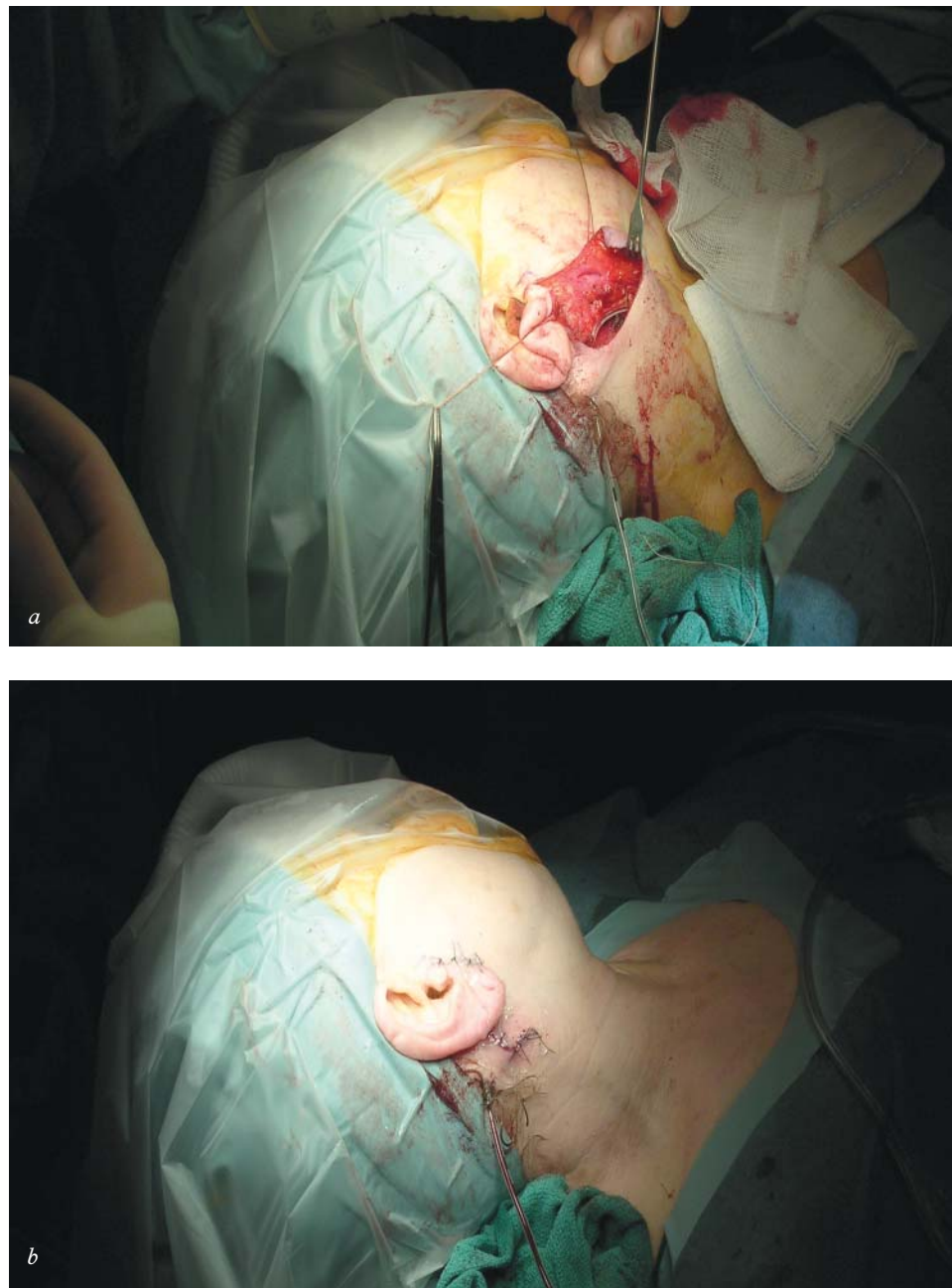


Figure 5 Parotidectomy. Shown is drainage and closure after parotidectomy. (a) A closed suction drain is placed in the operative bed and loosely tacked to the sternocleidomastoid muscle. (b) Interrupted monofilament sutures are used for the skin. Bacitracin is applied. No additional dressings are used.

Postoperative Care

Facial nerve function is evaluated in the recovery room, with particular attention paid to whether the patient is able to close the eyelid. The patient resumes eating when nausea (if any) abates. Pain is generally well controlled by means of oral agents. At discharge, the patient should be warned to protect the numb earlobe against cold injury. The closed suction drain is kept in place for 5 to 7 days (until the first postoperative visit) to minimize the risk of salivary fistula.

Complications

FACIAL NERVE INJURY

Studies have found that transient paralysis of all or part of the facial nerve occurs in 17 to 100% of patients undergoing parotidectomy,^{17–20} depending on the extent of the resection and the location of the tumor. Fortunately, permanent paralysis is uncommon, occurring in fewer than 5% of cases.^{19,21}

Nerve monitoring has been advocated to reduce the incidence or severity of facial nerve injury, particularly in the

setting of surgery for a recurrent parotid tumor.²² To date, however, no randomized trial has demonstrated that intraoperative facial nerve monitoring or nerve stimulators yield any significant reduction in the incidence of facial nerve paralysis after either primary parotidectomy or recurrence surgery. Indeed, indiscriminate use of nerve monitoring and nerve stimulators may imbue the surgeon with a false sense of security and cause him or her to pay insufficient attention to the appearance of nerve tissue. Transient nerve dysfunction may follow inappropriate (or even appropriate and unavoidable) trauma to or traction and pressure on nerve trunks. Nerve monitoring does not prevent such problems; moreover, it adds to the cost of the procedure and lengthens the operating time.²³ Some, in fact, have suggested that nerve stimulators may actually increase transient dysfunction. Accordingly, our use of nerve stimulators is selective.

The management of facial nerve injury depends on when the injury is discovered and on how sure the surgeon is of the anatomic integrity of the nerve. If the injury is discovered intraoperatively, it should be repaired if possible. Primary repair—performed with interrupted fine permanent monofilament sutures under magnification²⁴—is preferred if sufficient nerve is available for a tension-free anastomosis. If both transected nerve ends are identified but tension-free repair is not feasible, interposition nerve grafts may be used. A sensory nerve harvested from the neck (e.g., the great auricular nerve) is often employed for this purpose. If the nerve is injured (or deliberately sacrificed) in conjunction with treatment of malignancy, use of nerve grafts from distant sites may be indicated.²⁴

If unexpected facial nerve dysfunction is identified in the postanesthesia care unit and if the surgeon is unsure of the anatomic integrity of the nerve (ideally, a rare occurrence), the patient should be returned to the operating room for wound exploration so that either the continuity of the nerve can be confirmed or the injury to the nerve can be identified and, if possible, repaired. When the surgeon is certain that the nerve is intact, facial nerve dysfunction can be managed without reoperation, in anticipation of recovery²⁴; however, this may take many months.

Management of enduring facial nerve paralysis (from any cause) is beyond the scope of our discussion and constitutes a surgical subspecialty in itself.²⁴

GUSTATORY SWEATING (FREY SYNDROME)

Gustatory sweating, or Frey syndrome, occurs in most patients after parotidectomy; it has been seen after submandibular gland resection as well. The symptom complex includes sweating, skin warmth, and flushing after chewing food and is caused by cross-innervation of the parasympathetic and sympathetic fibers supplying the parotid gland and the overlying skin. The reported incidence of Frey syndrome varies greatly, apparently depending on the sensitivity of the test used to elicit it. When Minor's starch

iodine test is employed, the incidence of Frey syndrome may reach 95% at 1 year after operation.²⁵ Fortunately, the majority of patients have only subclinical findings, and only a small fraction complain of debilitating symptoms.²⁵ Most symptomatic patients are adequately treated with topical antiperspirants; eventually, however, they tend to become noncompliant with such measures, preferring simply to dab the face with a napkin while eating.²⁵ Despite the relatively low incidence of clinically significant Frey syndrome, there is an extensive literature addressing prevention and additional treatment of this condition.^{11,21,26–34}

SIALOCELE (SALIVARY FISTULA)

Sialocele, or salivary fistula, has been reported to occur after 1 to 15% of parotidectomies.^{11,35} Although this condition is generally minor and self-limited, it may nonetheless be embarrassing for the patient. We believe that the incidence of sialocele can be reduced by maintaining closed suction drainage for 5 to 7 days (to facilitate adhesion of the skin flaps to the underlying parotid parenchyma). Postparotidectomy salivary fistula is usually attributable to gland disruption rather than to duct transection and therefore tends to resolve without difficulty.³⁶ Compression dressings are generally effective.³⁵ Anticholinergic agents have been used in this setting as well.^{37–40} Low-dose radiation,⁴¹ completion parotidectomy, and tympanic neurectomy⁴² have all been employed in refractory cases.

COSMETIC CHANGES

Parotidectomy creates a hollow anterior and inferior to the ear, which may extend behind the mandible and may reach a significant size in patients with large or recurrent tumors. This cosmetic change is a necessary feature of the procedure, not a complication; nonetheless, it should be discussed with the patient before operation. Many augmentation methods, using a wide variety of techniques, have been devised for improving postoperative appearance (as well as alleviating Frey syndrome).^{27–31,43,44} All of these methods have limitations or drawbacks that have kept them from being widely applied and accepted.

Outcome Evaluation

With proper surgical technique, superficial or partial superficial parotidectomy can be performed safely and within a reasonable operating time. The requirement for blood transfusions should be vanishingly rare. Given adequate exposure, good knowledge of the relevant anatomy, limited trauma to the nerve, and appropriate use of closed suction drains (see above), complications should be uncommon. Although patients may tolerate parotidectomy on an outpatient basis, we prefer to keep them in the hospital overnight. Patients should be able to leave the hospital with minimal pain, comfortable with their drain care, by the morning of postoperative day 1.

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7 NECK DISSECTION

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Preoperative Evaluation

In the majority of cases, cancer in the neck is a metastasis from a primary lesion in the upper aerodigestive tract, although metastases from skin, thyroid, and salivary gland neoplasms are also encountered. Lymphomas often present as cervical lymphadenopathy.

When a patient presents with a suspicious lesion in the neck, a careful history and physical examination should be performed, along with a thorough evaluation of the aerodigestive tract aimed at locating the source of possible metastatic disease. Fine-needle aspiration (FNA) of the neck mass should then be done to determine whether the mass is malignant. FNA can often differentiate between epithelial and lymphoid malignancies, and this differentiation will guide subsequent workup. The reported sensitivity of FNA ranges from 92 to 98% and the reported specificity from 94 to 100%.^{1,2}

If FNA reveals the presence of atypical lymphoid cells, an excisional lymph node biopsy may be performed if additional tissue is required for adequate tumor typing. An excisional biopsy may also be performed if the FNA is negative or indeterminate, the surgeon suspects a malignancy, and the rest of the physical examination yields negative results. Routine excisional biopsy of neck masses for diagnostic purposes is not recommended, however, because it may result in tumor spillage into the wound and complicate subsequent definitive resection.

Once the presence of an epithelial malignancy is established, the primary site of the lesion must be determined. The clinical setting provides clues regarding the source of the cancer. For example, in an elderly patient with a previous history of skin cancer, with abnormal cutaneous lesions over the scalp or face and a nontender, enlarging posterior triangle neck mass, a metastasis from a cutaneous cancer is suspected. Alternatively, in a 50-year-old alcohol abuser with an enlarging level II lymph node also complaining of a several-month history of sore throat and otalgia, a metastasis from a pharyngeal primary cancer should be entertained. In any patient with metastatic cervical adenopathy thought to originate in the upper aerodigestive tract, panendoscopy and biopsy with general anesthesia are mandatory for locating and characterizing the primary source of the tumor and ruling out the presence of synchronous lesions. The most common occult primary sites are the base of the tongue, the tonsils, and the nasopharynx. Imaging studies (e.g., computed tomography [CT] and magnetic resonance imaging) may be helpful in locating the source of a cervical metastasis. Positron emission

tomography (PET) detects lesions with increased metabolic activity but has the limitation of being unable to detect lesions smaller than 1 cm in diameter. Primary lesions greater than 1 cm in diameter usually are easily identified on physical examination and other imaging studies; thus, PET scans add little in this setting. In 5 to 10% of patients who present with a metastatic node, the primary lesion is never found despite extensive workup.

INCIDENCE AND IMPACT OF NECK METASTASES

Cutaneous Squamous Cell Carcinoma

The incidence of cervical metastases is governed by many factors. Cervical metastases from cutaneous squamous cell carcinomas are rare, occurring in 2 to 10% of cases. However, certain lesions—those that are greater than 2 cm in diameter; are recurrent; are deeper than 6 mm; involve the ear, the temple, or the classic H zone; occur in an immunocompromised patient; or are poorly differentiated—have a significant occult metastatic rate, ranging from 20 to 60%. The presence of cervical metastases reduces 5-year survival to about 32%,³ which suggests that early intervention for high-risk cutaneous lesions, involving regional lymphadenectomy, sentinel lymph node (SLN) biopsy, or irradiation of at-risk lymph node basins, may be warranted.

Salivary Gland Neoplasms

With salivary gland neoplasms [see 2:1 Oral Cavity Lesions], the incidence of cervical metastases is related to the histopathology and the size of the tumor. The most aggressive salivary gland lesions are squamous cell carcinoma, carcinoma ex pleomorphic adenoma, adenocarcinoma, and salivary ductal carcinoma. Patients with these lesions often have cervical metastases at presentation that warrant a therapeutic neck dissection [see Table 1]. How best to manage occult cervical salivary gland metastatic disease is controversial. The occult metastatic rate for aggressive lesions ranges from 25 to 45%. For such lesions, a selective neck dissection is typically incorporated into the surgical approach.⁴

Metastatic Well-Differentiated Thyroid Cancer

Cervical lymph node metastases are present in 10 to 15% of patients with well-differentiated thyroid carcinoma. The impact of nodal metastases on local recurrence and survival has not been established. Other factors (e.g., age, sex, tumor extent, and distant metastases) appear to have a greater effect on prognosis. Nevertheless, in the presence of clinically

Table 1 Incidence of Cervical Metastases in Selected Head and Neck Cancers

Tumor	Incidence of Cervical Adenopathy (%)
Cutaneous squamous cell carcinoma	2–10
Salivary gland malignancies	30–70
Mucoepidermoid carcinoma (high grade)	
Adenoid cystic carcinoma	8
Malignant mixed tumor	25
Squamous cell carcinoma	46
Salivary duct carcinoma	50
Acinic cell carcinoma	40
Metastatic well-differentiated thyroid cancer	10–15
Squamous cell carcinoma of upper aerodigestive tract	
Alveolar ridge	30
Hard palate	10
Oral tongue	30
Anterior pillar/retromolar trigone	45
Floor of mouth	30
Soft palate	44
Tonsillar fossa	76
Tongue base	78
Bilateral	20

apparent nodal disease, a formal neck dissection is advised: so-called cherry-picking operations or limited lymph node excisions result in higher rates of recurrence.⁵

Squamous Cell Carcinoma of the Upper Aerodigestive Tract

With upper aerodigestive tract squamous cell carcinomas, the incidence of cervical metastases is related to the site of the primary lesion, the size of the tumor, the degree of differentiation, the depth of invasion, and other biologic factors. A significant proportion of head and neck cancer patients who harbor clinically silent primary tumors of the base of the tongue, the tonsils, or the nasopharynx initially present with cervical adenopathy [see Table 1]. These sites lack anatomic barriers that limit tumor spread and are supplied by rich lymphatic networks that facilitate metastasis. In contrast, patients with glottic and lip cancers rarely present with clinical adenopathy.

The presence of cervical metastases negatively affects prognosis and has been associated with increased recurrence rates and reduced disease-free and overall survival. The presence of clinical adenopathy decreases survival by 50%. Metastatic tumors that rupture the lymph node capsule—a process known as extracapsular spread (ECS)—are biologically more aggressive. Patients who have palpable cervical lymphadenopathy with ECS manifest a 50% decrease in survival compared with those who have palpable cervical lymphadenopathy without ECS.⁶ In addition, about 50% of clinically negative, pathologically positive neck specimens exhibit ECS. Clinically negative, pathologically positive, and ECS-positive specimens are

associated with a high risk of regional recurrence and distant metastases.^{7–9} The presence of ECS in lymph node metastases may, in fact, be the single most important prognostic factor in patients with head and neck cancer. Identification of this patient subset may be the most important benefit of elective neck dissection in that it allows these patients to be offered adjuvant therapy. The presence of extracapsular extension is an indication for adjuvant concurrent chemoradiation, which has been shown to decrease the risk of recurrence and improve survival in randomized clinical trials.^{10,11}

Whereas anatomic and pathologic factors (e.g., ECS) have long been known to predict tumor behavior, it is only comparatively recently that the impact of comorbidity has been well characterized. When patients are stratified by tumor stage, those with comorbidities fare worse. In fact, the impact of comorbidity on overall survival is greater than that of tumor stage or treatment type.^{12,13} In addition, comorbidity is associated with both increased frequency and increased severity of surgical complications. These factors may be important in treatment selection and patient counseling. To date, comorbidity has not been incorporated into clinical staging of head and neck cancer patients.

STAGING OF NECK CANCER

Staging of the neck for metastatic squamous cell carcinomas of the head and neck is based on the TNM classification formulated by the American Joint Committee on Cancer (AJCC) [see 2:1 *Oral Cavity Lesions*]. The N classification applies to cervical metastases from all upper aerodigestive tract mucosal sites except the nasopharynx; nodal metastases from cutaneous, sinonasal, and thyroid malignancies have their own staging systems.

The purpose of staging is to characterize the tumor burden of an individual patient. Precise characterization and differentiation of tumors facilitate identification of those patients who are most likely to benefit from treatment. However, the TNM staging system does not include a number of factors that are known to have an impact on prognosis, such as the presence or absence of ECS and the pattern of lymphatic spread. Nonanatomic factors (e.g., comorbidity, immune status, and nutritional status) have a strong impact on survival as well but are also not incorporated in the current staging system. In general, TNM staging may be inadequate for use in clinical trials.¹⁴

The limitations of clinical staging of the neck are well described. In particular, patients with short, thick necks are challenging to stage accurately on physical examination alone. The addition of imaging to clinical examination improves diagnostic sensitivity but not specificity. Pathologic review of neck specimens remains the gold standard for anatomic staging. The addition of ultrasound-guided FNA of neck nodes yields enhanced diagnostic accuracy in cases in which the neck is clinically negative, but the radiologic findings are positive. This approach is employed to select patients for neck dissection in a number of centers, particularly in Europe; whether it provides more accurate staging than alternative methods, such as SLN biopsy, remains to be determined. The results from the First International Conference on Sentinel Node Biopsy in Mucosal Head and Neck Cancer revealed that SLN biopsy of the clinically negative neck has a sensitivity comparable to that of a staging neck dissection.¹⁵ In general, imaging modalities

appear to be neither sufficiently sensitive nor sufficiently specific in the evaluation of the clinically negative neck. Uptake of 2-deoxy-3 [^{18}F] fluoro-D-glucose, as measured by PET scans, is undetectable in small foci of cancer in the clinically negative neck.¹⁶

Proper staging is important for stratification of patients into risk categories on the basis of tumor biology so that high-risk patients may be appropriately selected for clinical trials or offered adjuvant therapy and other patients may be spared unnecessary treatment. Until accurate methods of assessing the clinically negative neck are developed, selective neck dissection will be performed to treat the neck when the occult metastatic rate is expected to be higher than 20%.

INDICATIONS FOR NECK DISSECTION

Neck dissections are considered either therapeutic (performed to remove clinically identifiable cancer in the neck) or elective (performed when the expected incidence of occult metastases from a lesion exceeds 20%). In patients with head and neck cancer, neck dissection may be performed as part of initial definitive treatment, often combined with resection of the primary cancer. Alternatively, neck dissection may be performed in an adjuvant setting to remove residual cancer in the neck following treatment with radiation or chemoradiation. Technically, neck dissections are classified as comprehensive dissections, which incorporate five levels of the neck, or selective dissections, in which only selected lymph node levels are removed according to predicted drainage patterns from specific primary sites. There is also a third technical classification, extended neck dissections, which can be combined with selective or comprehensive neck dissections for removal of additional nodal basins [see Operative Planning, Choice of Procedure, below]. Six lymph node drainage basins in the neck are recognized [see Figure 1]. The extent of neck dissection is determined by the clinical setting.

CONTRAINDICATIONS TO NECK DISSECTION

The only absolute contraindication to neck dissection is surgical unresectability. The determination of unresectability is made by the operating surgeon either preoperatively, on the basis of imaging studies, or in the operating room. Typically, the presence of Horner syndrome, paralysis of the vagus nerve or the phrenic nerve, or invasion of the brachial plexus or the prevertebral muscles indicates that the tumor is unresectable. The involvement of the carotid artery may be predicted on the basis of imaging studies. Encasement of the carotid artery by tumor suggests direct invasion of the vessel; however, studies correlating imaging characteristics and pathologic invasion of the carotid have shown that tumors surrounding 180° or more of the carotid's circumference have a higher incidence of carotid invasion than tumors surrounding less than 180° (75% versus 50%). In the absence of direct invasion of the vessel wall, tumor may be peeled off by means of subadventitial surgical dissection. Tumors surrounding 270° of the vessel have an 83% incidence of carotid invasion, necessitating sacrifice of the artery.¹⁷ However, sacrifice of the carotid artery, with or without reconstruction with a vein graft, has been associated with significant morbidity. The survival of patients with such extensive neck disease is uniformly poor.¹⁸

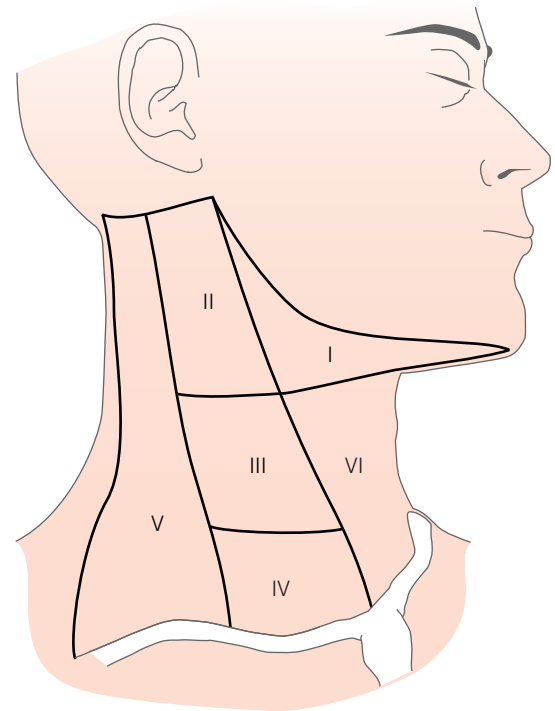


Figure 1 Cervical lymph nodes are divided into six levels on the basis of their location in the neck.

Operative Planning

CHOICE OF PROCEDURE

Comprehensive Dissection: Radical and Modified Radical Neck Dissection

The radical neck dissection was first described in 1906 by George Crile, who based his approach on the Halstedian principle of en bloc resection. The procedure was subsequently standardized by Hayes Martin at Memorial Hospital in New York in the 1930s and 1940s. In this latter version of the procedure, lymphatic structures from the strap muscles anteriorly, the trapezius posteriorly, the mandible superiorly, and the clavicle inferiorly are removed. Nonlymphatic structures in this space are also sacrificed, including the spinal accessory nerve, the sternocleidomastoid muscle, the internal and external jugular veins, the submandibular gland, and sensory nerve roots. The routine sacrifice of the spinal accessory nerve, the internal jugular vein, and the sternocleidomastoid muscle contributes to the significant morbidity associated with radical neck dissection.

Since the 1970s, the necessity of en bloc resection for oncologic cure has been reexamined. Structures once routinely sacrificed are now routinely preserved unless they are grossly involved with cancer. The various functional, or modified, radical neck dissections are classified according to which structures are preserved. Type I dissections preserve the spinal accessory nerve; type II, the spinal accessory nerve and the internal jugular vein; and type III, both of these structures, along with the sternocleidomastoid muscle. Modified radical neck dissections have proved to be as effective in controlling metastatic disease to the neck as the classic radical neck dissection.¹⁹

Selective Neck Dissection

In a selective neck dissection, at-risk lymph node drainage basins are selectively removed on the basis of the location of the primary tumor in a patient with no clinical evidence of cervical lymphadenopathy. Cancers in the oral cavity, for example, typically metastasize to levels I through III and, occasionally, IV; laryngeal cancers typically metastasize to levels II through IV. The rationale for selective neck dissection is based on retrospective pathologic reviews of radical neck dissection specimens from patients without palpable lymphadenopathy. These reviews revealed that lymph node micrometastases were confined to specific neck levels for a given aerodigestive tract site.²⁰

The advantages of selective neck dissection over radical and modified radical neck dissection are both cosmetic and functional. A selective neck dissection involves less manipulation (and thus less risk of devascularization) of the spinal accessory nerve, thereby decreasing the incidence of postoperative shoulder dysfunction. Preservation of the sternocleidomastoid muscle alleviates the cosmetic deformity seen with a radical neck dissection and provides some protection for the carotid artery. Preservation of the internal jugular vein decreases venous congestion of the head and neck and is necessary if the contralateral internal jugular vein is sacrificed.

In the presence of multiple pathologically positive lymph nodes or evidence of ECS, adjuvant therapy is indicated.²¹ Accordingly, selective neck dissection may be viewed as a diagnostic and a therapeutic procedure. To date, however, no randomized clinical trials have demonstrated that selective neck dissection with adjuvant treatment as needed is better than so-called watchful waiting with regard to prolonging survival in patients who present without evidence of cervical metastatic disease. Therefore, it is not yet possible to justify the added cost and morbidity of elective neck dissection in patients without evidence of metastatic disease. SLN mapping may facilitate pathologic staging in this setting and spare low-risk patients from unnecessary interventions; however, its sensitivity and specificity for this purpose are still under investigation.

The growing focus on preservation of function and limitation of morbidity has led some surgeons to promote the use of selective neck dissection to treat node-positive neck tumors. Although retrospective studies have suggested that a selective neck dissection may be adequate in carefully selected node-positive patients,²² the effectiveness of this approach is still unproven, and its application remains subject to individual surgical judgment.

Extended Neck Dissection

Extended neck dissections can be combined with selective or comprehensive neck dissections to remove additional nodal basins, such as the suboccipital and retroauricular nodes. These groups of nodes, which are located in the upper posterior neck, are the first-echelon nodal basins for posterior scalp skin cancers. The retroauricular nodes lie just posterior to the mastoid process, and the suboccipital nodes lie near the insertion of the trapezius muscle into the inferior nuchal line. Cancers of the anterior scalp, the temple, and the preauricular skin drain to periparotid lymph nodes; these lymph nodes are removed in conjunction with a parotidectomy

[see 2:6 Parotidectomy]. Retropharyngeal nodes may be removed in the treatment of selected cancers originating in the posterior pharynx, the soft palate, or the nasopharynx. A mediastinal lymph node dissection may be combined with a neck dissection in the treatment of metastatic thyroid carcinomas.

Bilateral Neck Dissection

With primary lesions located in the midline in the base of the tongue, the supraglottic larynx, or the medial wall of the piriform sinus, bilateral regional metastases are common, and bilateral neck dissections are therefore indicated. Provided that at least one internal jugular vein is preserved, bilateral neck dissection is well tolerated. In contrast, sacrifice of both internal jugular veins is associated with significant morbidity, including increased intracranial pressure, syndrome of inappropriate antidiuretic hormone secretion, airway edema, and death. Bilateral internal jugular sacrifice is managed by staging the neck dissections or by carrying out vascular repair.

NECK DISSECTION AFTER CHEMORADIATION

The indications for neck dissection have been significantly affected by the increasing use of organ preservation protocols for the treatment of head and neck cancer. Nasopharyngeal carcinomas, which are uniquely radiosensitive, are generally treated with irradiation, with or without chemotherapy. Following chemoradiation, neck dissection is reserved for patients with an incomplete clinical response to treatment who are at high risk of cancer recurrence in the neck. Most patients with early nodal disease (N0 or N1) treated according to organ preservation protocols do not require neck dissection. Patients who have advanced neck disease (N2 or N3) are less likely to respond completely to nonsurgical treatment and require a neck dissection. Early surgery (within 8 to 10 weeks) is recommended for a number of reasons. After this period, progressive soft tissue fibrosis develops, resulting in difficult surgical dissection and increased postoperative morbidity. Over time, surgery is also less effective in clearing disease from the neck, and surgical treatment of such so-called neck failures is rarely curative.²³ Observation of necks suspected of harboring residual cancer after chemoradiation is therefore not recommended. Since observation may lead to nonsalvageable regional recurrences, some surgeons recommend that all patients presenting with N2 or N3 cervical lymphadenopathy undergo planned neck dissection, regardless of clinical response to chemoradiation therapy.²⁴ Others recommend that imaging with CT of the neck be used to evaluate clinical response following chemoradiation to determine the need for neck dissection.²⁵ The presence of nodes on CT scan measuring greater than 1.5 cm or any nodes with focal lucency, enhancement, or calcification suggest the presence of residual disease. In their study, only 2 of 34 patients (6%) with a complete radiographic response were found to have residual cancer in the neck dissection specimen, suggesting that this imaging modality is a sensitive means by which to identify patients at high risk for harboring residual disease after chemoradiation.

The required extent of planned neck dissection after chemoradiation is still under investigation. Pathologic reviews of comprehensive neck specimens after chemoradiation reveal that in patients with oropharyngeal cancer, levels I and V are rarely involved in the absence of radiographic abnormalities,²⁶ which suggests that a planned selective dissection involving

levels II through IV may be sufficient for oropharyngeal cancer patients treated with chemoradiation. This more limited approach undoubtedly causes less morbidity, but additional data are required to assess its oncologic efficacy.

For patients in whom no primary site can be identified, neck dissection followed by radiation is usually recommended. This approach has also been used selectively to treat bulky nodal disease in patients with small primary cancers, although this practice is controversial.²⁷ Bulky cervical adenopathy is unlikely to exhibit a complete pathologic response to nonsurgical treatment, and postradiotherapy neck dissections are generally associated with higher rates of surgical complications. A patient who requires dental extractions before radiation therapy may undergo a neck dissection at the same time, proceeding to radiation therapy 10 to 14 days after operation. Early neck dissection decreases the tumor burden, thereby allowing lower adjunctive doses of radiation to be delivered to the neck. Significant delays in initiating treatment to the primary site should be avoided.

RECONSTRUCTION AND RECURRENCE AFTER NECK DISSECTION

The use of microvascular free tissue transfer to reconstruct surgical defects in the head has allowed surgeons to resect large tumors with large margins while simultaneously achieving improved functional results. Preservation of vascular—and, occasionally, neural—structures during neck dissection

may facilitate the reconstructive process. Typically, several vessels, including an artery and one or two veins, are required for inflow and outflow into a free flap. The facial artery, the retromandibular vein, and the external jugular vein, which are preserved during level I and level II dissection, are the vessels that are most frequently used for flap revascularization. If these vessels are unavailable as a consequence of high-volume neck disease, the superior thyroid artery and the transverse artery, with companion veins, are suitable substitutes. To date, there is no evidence in the literature that preservation of vascular structures in the neck predisposes patients to regional recurrence. Caution must, however, be exercised in the setting of pathologic lymphadenopathy.

Operative Technique

RADICAL NECK DISSECTION

Step 1: Incision and Flap Elevation

When a radical or modified radical neck dissection is indicated, appropriate neck incisions must be designed so as to facilitate exposure while preserving blood flow to the skin flaps [see Figure 2]. The incision provides access to the relevant levels of the neck, affects cosmesis, and determines the extent of lymphedema and postoperative fibrosis (“woody” neck), especially in previously irradiated areas. If a biopsy was previously performed, the tract should be excised and incorporated

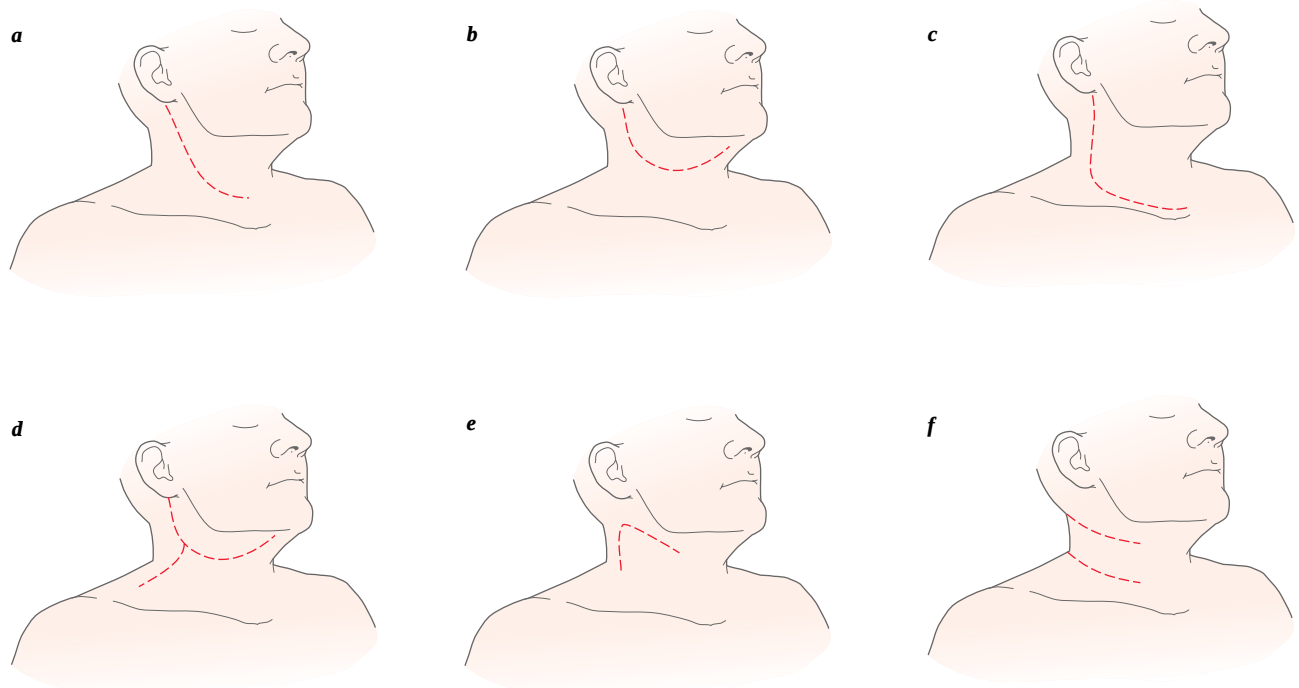


Figure 2 Illustrated are incisions used for neck dissections. Incision design is a critical element of operative planning. Incisions are chosen with the aims of optimizing exposure of relevant neck levels and minimizing morbidity. The incisions depicted in (a) and (b) are useful for selective neck dissections. For the more extensive exposure required in a radical or modified radical neck dissection, a deeper half-apron-style incision (c) may be used, or a vertical limb may be dropped from a mastoid-submental incision (d); the latter incision is less reliable and may break down, exposing vital structures such as the carotid. The incision depicted in (e) is also useful for selective neck dissections. The Macfee incision (f) provides limited exposure and results in persistent lymphedema in the bipedicle skin flap.

into the new incision. When a total laryngectomy is done, the stoma may be fashioned separately from the neck incision; in the event of a pharyngocutaneous fistula, the salivary flow will be diverted away from the stoma.

Once the incision is made, subplatysmal flaps are raised. If there is extensive lymphadenopathy or extension of tumor into the soft tissues of the neck, skin flaps may be raised in a supraplatysmal plane to ensure negative surgical margins. Such flaps, however, are not as reliably vascularized as subplatysmal flaps. Clinical judgment must be exercised in these situations. The flaps are raised to the mandible superiorly, the clavicle inferiorly, the omohyoid muscle and the submental region anteriorly, and the trapezius posteriorly. Radical neck dissection for bulky cervical adenopathy typically necessitates wide exposure of levels I through V. If a vertical limb is used [see Figure 2d], it must not be centered over the carotid artery, because of the risk of potentially catastrophic dehiscence. Deep utility-type incisions yield more limited exposure of level I but provide reliable vascular inflow to skin flaps.

Step 2: Dissection of Anterior Compartment

Embedded within the fascia overlying the submandibular gland is the marginal mandibular branch of the facial nerve, which must be elevated and retracted to prevent lower-lip weakness. The submental fat pad is then grasped, retracted posteriorly and laterally, and mobilized away from the floor

of the submental triangle. The omohyoid muscle is identified inferior to the digastric tendon and followed inferiorly to the sternocleidomastoid muscle. The omohyoid muscle forms the anteroinferior limit of the dissection.

Fat and lymphatic structures are dissected away from the digastric muscle and the mylohyoid muscle. The hypoglossal and lingual nerves lie just deep to the mylohyoid muscle and are protected by it [see Figure 3]. In this region, the distal end of the facial artery can be identified and preserved as needed for reconstructive purposes. Once the posterior edge of the mylohyoid muscle is visualized, an Army-Navy retractor is inserted beneath the muscle to expose the submandibular duct, the lingual nerve with its attachment to the submandibular gland, and the hypoglossal nerve. The submandibular duct and the submandibular ganglion, with its contributions to the gland, are ligated, and the submandibular gland is retracted out of the submandibular triangle.

The posterior belly of the digastric muscle is then identified inferior to the submandibular gland and skeletonized to the sternocleidomastoid muscle posteriorly, where it inserts on the mastoid tip. The specimen must be mobilized off structures just inferior to the digastric muscle. To prevent inadvertent injury, it is essential to understand the relationships among these structures [see Figure 3]. The hypoglossal nerve emerges from beneath the mylohyoid muscle and passes into the neck under the digastric muscle. It then loops around the external carotid artery at the origin of the occipital artery and

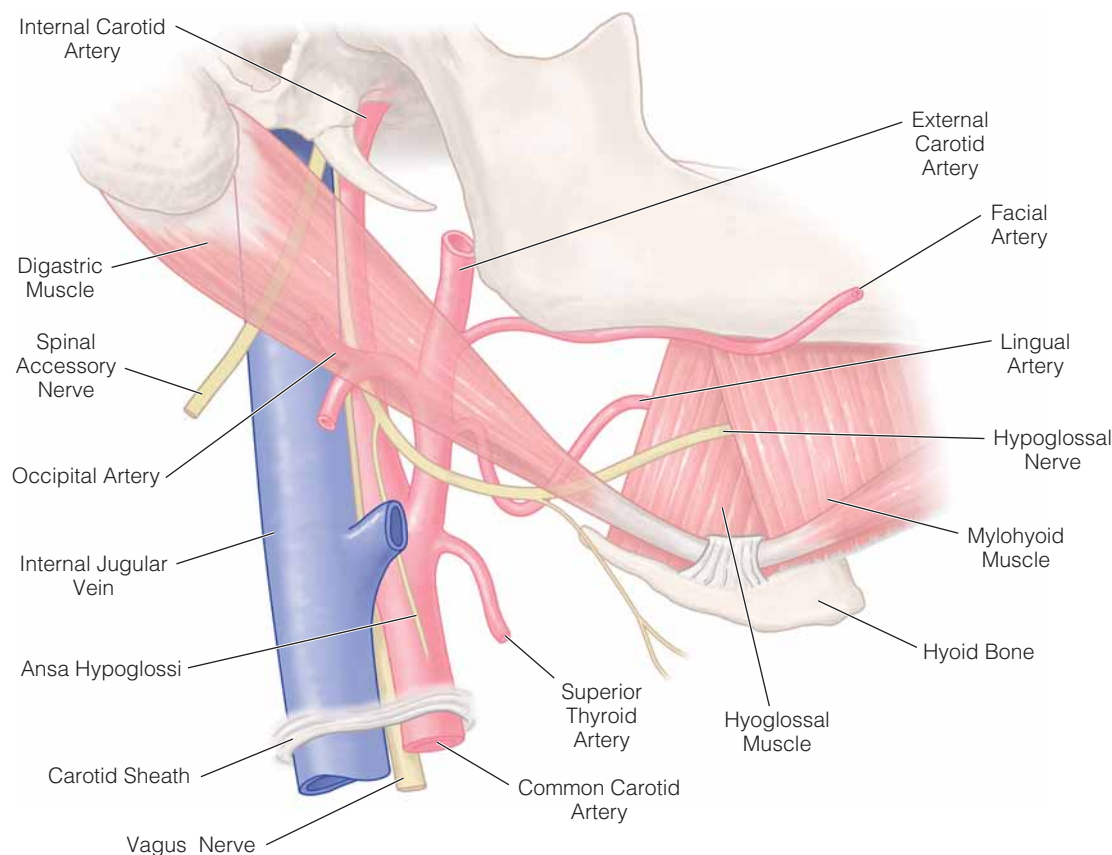


Figure 3 Depicted are the key anatomic relationships in levels I and II that must be kept in mind in performing a neck dissection. View is of the right neck.

ascends to the skull base between the external carotid artery and the internal jugular vein. Often the hypoglossal nerve is surrounded by a plexus of small veins, branching off the common facial vein. Bleeding in this region places the hypoglossal nerve at risk. The jugular vein, located just posterior to the external carotid artery and the hypoglossal nerve, may be isolated and doubly suture-ligated at this point. Frequently, the spinal accessory nerve is identified just lateral and posterior to the internal jugular vein, proceeding posteriorly into the sternocleidomastoid muscle.

In a radical neck dissection, the sternocleidomastoid muscle and the spinal accessory nerve are transected at this point and elevated off the splenius capitis and the levator scapulae to the trapezius posteriorly. The anterior edge of the trapezius is skeletonized from the occiput to the clavicle. In a radical neck dissection, the accessory nerve is again transected where it penetrates the trapezius.

*Step 3: Control of Internal Jugular Vein Inferiorly;
Ligation of Lymphatic Pedicle*

The sternal and clavicular heads of the sternocleidomastoid muscle are transected and elevated to expose the anterior belly of the omohyoid muscle. The soft tissue overlying the posterior belly of the omohyoid muscle is clamped and ligated as necessary. The omohyoid muscle is then transected, and the jugular vein, the carotid artery, and the vagus nerve are exposed. The jugular vein is isolated and doubly suture-ligated. Care is taken not to transect the adjacent vagus nerve and carotid artery. The lymphatic tissues in the base of the neck adjacent to the internal jugular vein are clamped and suture-ligated 1 cm superior to the clavicle. If a chyle leak is encountered, a figure-eight stitch is placed along the lymphatic pedicle until there is no evidence of clear or turbid fluid on the Valsalva maneuver. Care is taken to avoid inadvertent injury to the vagus nerve or the phrenic nerve, which course through this region.

*Step 4: Mobilization of Supraclavicular
Fat Pad ("Bloody Gulch")*

The fascia overlying the supraclavicular fat pad is incised, and the supraclavicular fat pad is bluntly retracted superiorly so as to free the tissues from the supraclavicular fossa. If transverse cervical vessels are encountered, they are clamped and ligated as necessary. Fascia is left on the deep muscles of the neck, which also envelop the brachial plexus and the phrenic nerve.

Step 5: Dissection and Removal of Specimen

Attention is then turned to the posterior aspect of the neck. Fat and lymphatic tissues are retracted anteriorly with Allis clamps, and the specimen is dissected off the deep muscles of the neck with a blade. Again, a layer of fascia is left on the deep cervical musculature: stripping fascia off the deep cervical musculature results in denervation of these muscles, which adds to the morbidity associated with accessory nerve sacrifice. Once the specimen is mobilized beyond the phrenic nerve, the cervical nerves (C1–C4) may be divided. The specimen is peeled off the carotid artery and removed.

Step 6: Closure

The neck incision is closed in layers over suction drains.

MODIFIED RADICAL NECK DISSECTION

The incision is made and flaps are elevated as in a radical neck dissection. Care must be exercised in elevating the posterior skin flap. Typically, the platysma is deficient in this area, and often no natural plane exists. Dissection deep in the posterior triangle may result in inadvertent injury to the spinal accessory nerve, which travels inferiorly and posteriorly across the posterior triangle in a relatively superficial plane to innervate the trapezius.

A type I modified radical neck dissection begins with dissections of levels I and II, as described for a radical neck dissection (see above). The spinal accessory nerve is identified just superficial or posterior to the internal jugular vein and preserved; the distal spinal accessory nerve is then identified in the posterior triangle. Typically, the spinal accessory nerve can be identified 1 cm superior to the cervical plexus along the posterior border of the sternocleidomastoid muscle. Provided that the patient is not fully paralyzed, the surgeon can distinguish this nerve from adjacent sensory branches by using a nerve stimulator.

Once the spinal accessory nerve is identified, it is dissected and mobilized distally. Proximally, the nerve is dissected through the sternocleidomastoid muscle, which is transected over the nerve. The branch to the sternocleidomastoid muscle is divided with Metz scissors, and the nerve is fully mobilized from the trapezius posteroinferiorly to the posterior belly of the digastric muscle anterosuperiorly and then gently retracted out of the way.

The rest of the neck dissection proceeds as described for a radical neck dissection. If the tumor does not involve the internal jugular vein, it may also be preserved; this constitutes a type II modified radical neck dissection. If the spinal accessory nerve, the internal jugular vein, and the sternocleidomastoid muscle are all preserved, the procedure is a type III modified radical neck dissection. In a type III dissection, the sternocleidomastoid muscle is fully mobilized and retracted with two broad Penrose drains, and the contents of the neck are exposed. The spinal accessory nerve is preserved throughout its entire course, including the branch to the sternocleidomastoid muscle. The remainder of the neck dissection proceeds as previously described (see above).

SELECTIVE NECK DISSECTION

Levels I to IV

In a selective neck dissection, the posterior triangle is not removed; thus, there is no need to elevate skin flaps posterior to the sternocleidomastoid muscle. Limited elevation of skin flaps is beneficial, particularly for patients who have previously undergone chemoradiation therapy, in whom extensive flap elevation may contribute to significant persistent lymphedema after operation. Subplatysmal skin flaps are raised sufficiently to expose the neck levels to be dissected, with the central compartment left undisturbed. If level I dissection is planned, the fascia overlying the submandibular gland is raised and retracted so as to preserve the marginal nerve. The submental fat pad is grasped and mobilized away from the floor of the submental triangle (composed of the anterior belly of the digastric muscle and the mylohyoid muscle). Inferiorly, the lymphatic tissues are mobilized off the posterior aspect of the omohyoid muscle, which forms the anteroinferior limit of the neck dissection.

Once the digastric tendon and the posterior edge of the mylohyoid muscle are visualized, the mylohyoid is retracted with an Army-Navy retractor so that the submandibular duct, the lingual nerve with its attachment to the submandibular gland, and the hypoglossal nerve are visualized. The submandibular duct and ganglion are ligated, and the submandibular gland is retracted out of the submandibular triangle.

At this point, the facial artery is encountered and suture-ligated. Because the artery curves around the submandibular gland, the facial artery, if not preserved, must be ligated twice (proximally and distally). If the neck dissection is part of a large extirpative procedure involving free-flap reconstruction, the facial artery is preserved for use in microvascular anastomosis.

The posterior belly of the digastric muscle is then identified inferior to the submandibular gland. This muscle has been referred to as one of several “resident’s friends” in the neck because it serves to protect several critical structures that lie just deep to it, including the hypoglossal nerve, the external carotid artery, the internal jugular vein, and the spinal accessory nerve [see Figure 4]. The posterior belly of the digastric muscle is skeletonized to the sternocleidomastoid muscle,

where it inserts on the mastoid tip. The specimen is then mobilized away from structures just inferior to the digastric muscle. The hypoglossal nerve emerges from beneath the mylohyoid muscle and passes into the neck just below the digastric muscle, looping around the external carotid artery at the origin of the occipital artery and ascending to the skull base between the external carotid artery and the internal jugular vein. Bleeding from small branches of the common facial vein that envelop the hypoglossal nerve places this structure at risk for injury. The spinal accessory nerve is often visualized just superficial or posterior to the internal jugular vein, extending posteriorly to innervate the sternocleidomastoid muscle.

Next, the fascia overlying the sternocleidomastoid muscle is grasped and unrolled medially throughout its length, starting at the anterior edge of the muscle. The fascia is removed until the spinal accessory nerve is identified at the point where it penetrates the muscle. This nerve is dissected and mobilized superiorly through fat and lymphatic tissues to the digastric muscle. Care must be taken not to inadvertently injure the internal jugular vein, which lies in close proximity

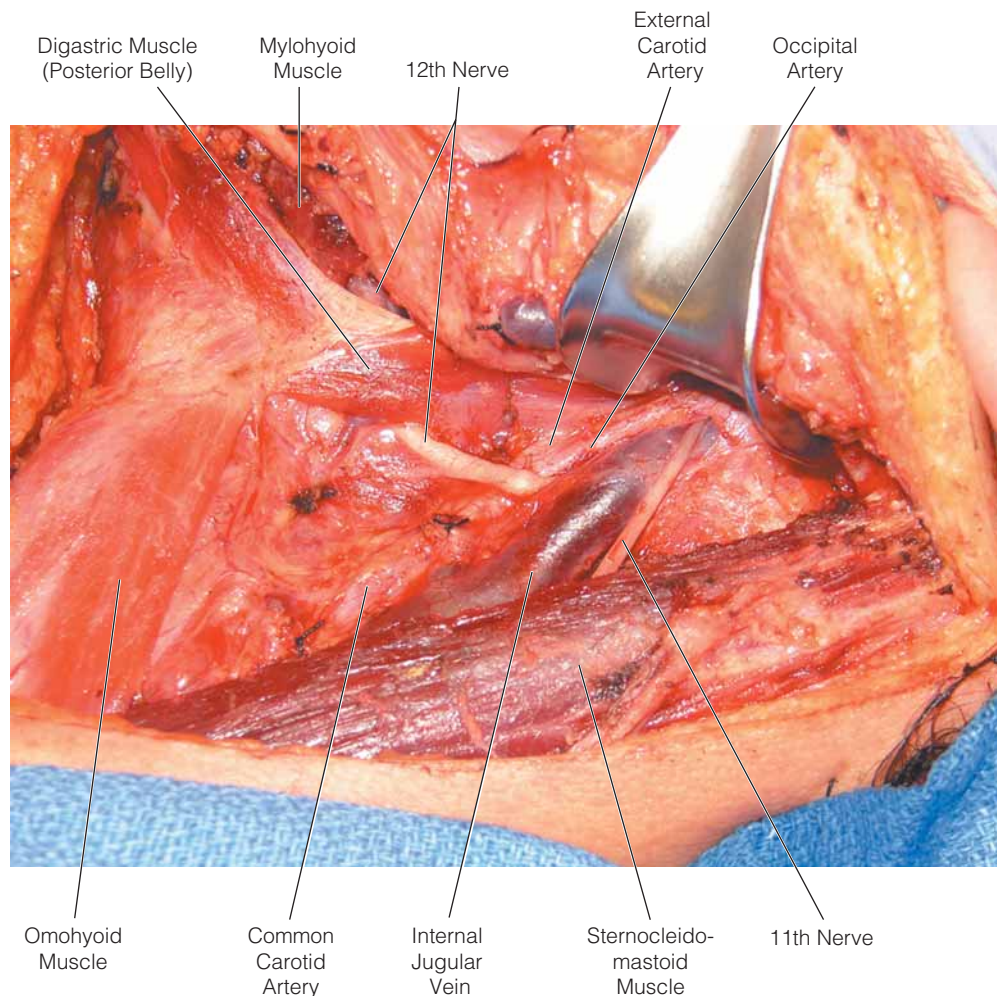


Figure 4 Selective neck dissection. The posterior belly of the digastric muscle is identified inferior to the submandibular gland. This muscle protects several critical structures just deep to it (the hypoglossal nerve, the carotid artery, the internal jugular vein, and the spinal accessory nerve). View is of a left neck dissection.

to the nerve superiorly. Tissue posterior to the accessory nerve is grasped and freed from the deep muscles of the neck, the digastric muscle superiorly, and the sternocleidomastoid muscle posteriorly. The tissue included in so-called level IIB is passed beneath the spinal accessory nerve and incorporated into the main specimen.

The sternocleidomastoid muscle is retracted, and the fascia posterior to the internal jugular vein is incised. Dissection is carried down to the deep cervical musculature and cervical nerves, which form the floor of the dissection. The specimen is retracted anteriorly. A layer of fascia is left on the deep cervical musculature and the cervical nerves to preserve innervation of the deep muscles of the neck and protect the phrenic nerve as it courses over the anterior scalene muscle.

The specimen is peeled off the internal jugular vein and removed. Dissection too far posteriorly behind the vein may result in injury to the vagus nerve or the sympathetic trunk and predisposes to postoperative thrombosis of the vein. Ligation of internal jugular vein branches should be done without affecting the caliber of the vein or giving the vessel a “sausage link” appearance, which would create turbulent flow patterns predisposing to thrombosis. Overall, gentle dissection around all vessels, with care taken to avoid pulling-related trauma, minimizes the risk of endothelial injury.

A level IV dissection may be facilitated by retracting the omohyoid muscle inferiorly or by dividing it for additional exposure. The tissue inferior to the omohyoid is mobilized and delivered with the main specimen. The lymphatic pedicle is clamped and ligated. Care is taken to look for leakage of chyle, particularly when a level IV dissection is performed on the left.

Levels II to IV

When level I is spared, a smaller incision suffices for exposure. Subplatysmal flaps are raised superiorly to the level of the submandibular gland. The inferior flap is raised, exposing the anterior edge of the sternocleidomastoid muscle. Dissection proceeds just inferior to the submandibular gland until the posterior belly of the digastric muscle is identified. The digastric muscle is skeletonized posteriorly to the sternocleidomastoid muscle and anteriorly to the omohyoid muscle, which forms the anterior limit of the dissection. The rest of the neck dissection proceeds as described for a selective neck dissection involving levels I through IV.

Complications

INTRAOPERATIVE

Most intraoperative complications may be prevented by means of careful surgical technique, coupled with a thorough understanding of head and neck anatomy. Injury to the internal jugular vein may occur either proximally or distally. Uncontrolled proximal bleeding endangers adjacent critical structures, such as the carotid artery and the hypoglossal nerve. The bleeding may be initially controlled with pressure, followed by a methodical search for the bleeding source. Internal jugular vein lacerations can often be repaired with 5-0 nylon sutures; if a laceration cannot be repaired, the vein must be ligated. Occasionally, a laceration extends up to the skull base, and the vessel cannot be controlled with clamping

and ligation. In these cases, it is acceptable to pack the jugular foramen for hemostasis.

It is important to gain distal control of the internal jugular vein before repair to prevent air embolism. Harbingers of air embolism include the presence of a sucking sound in the neck, a mill-wheel murmur over the precordium, electrocardiographic changes, and hypotension. Predisposing factors include elevation of the head of the bed and spontaneous breathing, which increase negative intrathoracic pressure and thus promote entry of air into the venous system. Injury to the internal jugular vein is more difficult to control when it occurs distally in the neck or chest at the junction with the subclavian vein. For this reason, ligation of the internal jugular vein in radical and modified radical neck dissection is typically performed 1 cm superior to the clavicle.

Opalescent or clear fluid in the inferior neck suggests the presence of a chyle fistula. Chyle fistulae generally can be prevented by clamping and ligating the lymphatic pedicle at the base of the neck. Those fistulae that occur are repaired at the time of the neck dissection. There is no benefit in isolating individual lymphatic vessels, because these structures are fragile, do not hold stitches, and are prone to tearing. A figure-eight stitch is placed along the lymphatic pedicle until there is no evidence of clear or turbid fluid on the Valsalva maneuver. Care must be taken not to inadvertently injure the vagus nerve or the phrenic nerve during repair of a chyle leak.

POSTOPERATIVE

The best treatment of postoperative complications such as hematoma and chyle leak is prevention. Hematomas, once present, are best managed by promptly returning the patient to the operating room for evacuation. Management of postoperative leakage of chyle depends on the volume of the leak. Low-volume leaks may be managed with packing, wound care, and nutritional supplementation with medium-chain triglycerides.

Wound complications (e.g., infection, flap necrosis, and carotid artery exposure or rupture) share certain interrelated causative factors. Poor nutritional status, advanced tumor stage at presentation, hypothyroidism, and preoperative radiation therapy have all been associated with wound complications. After chemoradiation therapy, the use of smaller incisions and more limited dissection of soft tissues may lower the incidence of postoperative wound problems, including persistent lymphedema and soft tissue fibrosis. Conversely, poor planning of skin incisions may increase the likelihood of wound complications such as wound breakdown, skin flap loss, and exposure of vital structures. Wound complications predispose to carotid artery rupture, the most catastrophic complication of neck dissection.

In some cases, severe edema after planned neck dissections in patients previously treated with chemoradiation may cause respiratory decompensation that necessitates tracheotomy. Postoperative internal jugular vein thrombosis is not uncommon despite preservation at the time of surgery,²⁸ and it may exacerbate facial and upper airway edema. Impaired venous outflow predisposes to increased intracranial pressure.²⁹ This may be a greater concern in patients who require bilateral neck dissections. If a radical neck dissection is performed on one side, the internal jugular vein must be preserved on the

other, or else the neck dissections must be staged. These problems are further exacerbated when the patient has undergone chemoradiation therapy before operation.

Most neck dissections result in some degree of temporary shoulder dysfunction. Patients in whom nerve-sparing procedures are performed can expect function to return within 3 weeks to 1 year, depending on the procedure performed.

Shoulder dysfunction and pain are exacerbated when nerves supplying the deep muscles of the neck are also sacrificed. All patients benefit from physical therapy, which preserves full range of motion in the shoulder while function returns.

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Acknowledgment

Figures 1 through 3 Tom Moore.

8 TRACHEOSTOMY

H. David Reines, MD, FACS, and Elizabeth Franco, MD, MPH&TM

History

The word *tracheotomy* first appeared in *Libri Chirurgiae 12*, published in 1649, but it was not until Laurence Heruter, a German surgeon, reintroduced it that it became part of modern medicine. It was initially performed as a lifesaving procedure to establish an airway. Alexander the Great is reported to have used his sword to open the trachea of a suffocating soldier. The term *tracheotomy* is defined as a surgical creation of an opening in the anterior trachea that can be reversible and temporary, whereas, technically, *tracheostomy* is the formation of an opening into the trachea by suturing the edges of the opening to the skin of the neck. However, over the years, the two terms have been used interchangeably. For this document, we use the term *tracheostomy* to describe the procedure.

Indications

The indication for a tracheostomy has changed over the years. Originally, it was conceived as a method to obtain an airway for obstruction from infections, neoplasm, or trauma. The most common indications for modern tracheostomy are prolonged ventilation for respiratory failure and airway protection following traumatic brain injury with neurologic dysfunction.

Patients requiring tracheostomy or cricothyroidotomy fall into four categories:

1. Emergency for airway control, that is, airway obstruction from the epiglottitis, foreign-body aspiration, laryngeal trauma, or maxillofacial trauma
2. Semielective for patients requiring prolonged intubation or mechanical ventilation for respiratory failure or high spinal cord injury
3. Elective for airway protection, that is, traumatic brain injury, stroke, sleep apnea, or vocal cord problems
4. Elective for long-term airway access. Permanent tracheostomies are used to maintain airway access when patients undergo major head or neck dissection for tumors of the larynx and the base of the tongue.

Patients who arrive with either acute airway compromise from neck trauma or facial burns should first undergo an attempt at oral intubation, and if this fails, an emergent surgical airway is required.

Laryngoscopy should be attempted prior to performing surgical airway. If a patient arrives talking, but there is evidence of hoarseness with increasing airway compromise, the surgeon should be prepared for a surgical airway if

oral intubation is unsuccessful. When an attempt at oral intubation fails and ventilation is a problem, immediate cricothyroidotomy should be performed. A semielective surgical airway should be undertaken in a patient whose injuries may result in progressive laryngeal and cervical soft tissue edema prior to decompensation from respiratory distress. Patients with a Glasgow Coma Scale (GCS) less than or equal to 8 cannot protect their airway, and intubation should be performed immediately. If this is not possible, then a surgical airway should be considered prior to transporting the patient.

Early Tracheostomy

If the patient is ventilator dependent or has severe head injury and will need prolonged airway protection, early tracheostomy should be considered when intracranial pressure is not elevated. Early tracheostomy is defined as occurring at or before 7 days, whereas late tracheostomy occurs after 7 days. Early tracheostomy has been associated with decreased incidence of ventilator-associated pneumonia, decreased days of mechanical ventilation, decreased hospital stay, decreased intensive care unit (ICU) length of stay, and increased patient comfort. Although no study has demonstrated a decrease in overall mortality with early tracheostomy, tracheostomy does provide easier access for suctioning and allows patients to be liberated from the ventilator without the loss of an airway.

Pertinent Anatomy

The trachea lies relatively superficially in the anterior neck covered by the strap muscles midline and the platysma. The first tracheal ring is just below the cricothyroid, whereas the next three rings may lie beneath the thyroid isthmus. The sixth through seventh rings lie low in the neck and into the sternal notch [see Figure 1]. When performing a tracheostomy, knowledge of the normal and potentially abnormal vasculature is imperative. Care must be taken with a horizontal incision to avoid bleeding from injury to the anterior jugular vein. Other potential causes of hemorrhage may arise from injury to a high-riding innominate artery, a medially placed carotid artery, and the thyroid ima vessels in the midline. Tumors, hematoma, and edema can cause tracheal deviation from midline. Other anatomic variants should also be considered. An obese patient may require deeper dissection, longer instruments, and the use of an extra-long tracheostomy tube. The length of the neck and the distance from the jaw to the thyroid cartilage should also be examined. Patients with a known or potential neck injury or with kyphosis must be positioned without extension. Access to the trachea may be compromised, and plans for dissecting the thyroid isthmus should be considered.

* The authors and editors gratefully acknowledge the contributions of the previous author, Ara A. Chalian, MD, FACS, to the development and writing of this chapter.

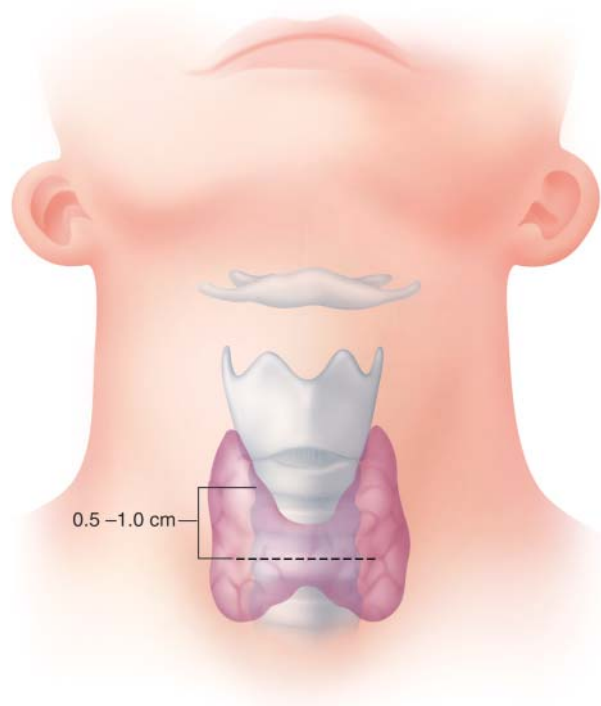


Figure 1 Surgical tracheostomy. A transverse cutaneous incision is made that is approximately 2 to 3 cm long (or as long as is necessary for adequate exposure). The extent of flap elevation may be 1 cm or less.

Physiology

When undergoing a tracheostomy, ideally, the patient should be adequately ventilated and hyperoxygenated in anticipation of a period of apnea during tracheostomy tube placement. An oxygen saturation of 100% and a normal pH and carbon dioxide tension (P_{CO_2}) are desirable at the start of an elective tracheostomy. Use of 100% oxygen during the procedure will help maintain adequate oxygenation throughout the procedure. When an emergency cricothyroidotomy or tracheostomy is necessary, an attempt should be made to preoxygenate and ventilate.

Counseling and Informed Consent

The patient, the family, or both should be advised of the risks and benefits of a tracheostomy. Commonly discussed issues, including pain, mortality, and the range of possibilities of early and late complications (see below), should be on the consent form. A tracheostomy should be proposed as the best option for the patient requiring prolonged mechanical ventilation or airway protection. Tracheostomy contributes to patient comfort, allowing improved oral care, oral alimentation, and speaking as well as the potential for earlier liberation from the ventilator.

Site of the Procedure

Elective open tracheostomy requires good lighting and electrocautery. Some may find open tracheostomy in the ICU

more ergonomically difficult than in the operating room (OR) because the patient is on a hospital bed; however, finding OR time and transporting the patient may be inconvenient. Several studies comparing bedside open to percutaneous tracheostomies find the techniques to be essentially equivalent in outcome with the open technique and possibly lower in cost. Percutaneous tracheostomy is most commonly performed at the bedside, in the ICU, and does not require the same lighting or instrumentation and nursing availability that an open tracheostomy does. A cricothyroidotomy is frequently performed in the trauma bay, although it may be executed anywhere and requires the least amount of instrumentation. Emergency tracheostomy and cricothyroidotomy are frequently not performed in the OR.

Anesthesia

Anesthesia can frequently be given as conscious sedation and/or local anesthesia with epinephrine. Paralysis should be avoided when possible in a patient with any spontaneous breathing.

Patient Positioning

Extension of the neck is desirable; however, if the patient has a known or potential cervical spine injury, operation in the neutral position is necessary. When possible, the patient should be placed on an operating table with a shoulder roll and a foam pad (donut) under the head. When the neck can be extended, the head rest of the surgical bed can be lowered and the patient placed in a 30° head elevation position to decrease venous pressure. Extending the head allows better palpation of the landmarks. If cervical spine precautions are necessary, the posterior portion of the cervical collar should remain in place and the head stabilized by a team member. Another alternative is to stabilize the neck with bilateral head rolls with tape over the forehead and chin extending across the bed.

Operative Techniques

EMERGENT SURGICAL AIRWAY

Cricothyroidotomy

Cricothyroidotomy is generally performed for emergent control of the airway. Inability to secure an airway, especially with severe facial trauma, requires immediate access to the trachea. A cricothyroidotomy can be performed rapidly and does not risk the anatomic problems of a tracheostomy because the cricothyroid membrane is thin and closest to the skin directly under the thyroid membrane. If a #5 or #6 tracheostomy tube is not available, an endotracheal tube can be introduced for immediate airway access.

Transtracheal Needle Ventilation and Oxygenation

Transtracheal needle access also can be used in emergency situations. A large-bore 12- or 14 gauge angiocatheter or a pulmonary artery catheter introducer sheath is placed through the cricoid membrane and attached to oxygen tubing with the capability of providing oxygen at 50 psi. A hole in the tubing is finger-occluded and intermittently opened to allow for ventilation. Adequate ventilation can be provided for

20 to 30 minutes. This method is best used as a bridge while awaiting the proper equipment and support for an orotracheal or surgical airway.

OPEN TRACHEOSTOMY

Steps

1. *Incision of the skin.* The patient should be assessed for a high-riding innominate artery, abnormally placed vessels, and tracheal deviation. Incision can be made either vertically or horizontally. The horizontal scar heals better than the vertical scar. However, visualization, especially if the neck cannot be extended, is frequently easier in a vertical incision. Damage to the anterior jugular veins likewise is less likely with a vertical incision. In an emergency, a longer vertical incision can facilitate exposure while avoiding the subplatysmal anterior jugular veins [see Figure 2]. In general, the incision should be made midway between the cricoid cartilage and the sternal notch. The size of the incision is up to the individual surgeon. However, a minimum of 2 to 2.5 cm is desirable.

Subsequent dissection must be performed perpendicular to the trachea. A common mistake when dividing the subcutaneous tissue is to deflect in a slightly oblique fashion, arriving lower in the trachea than anticipated.

2. *Retracting the strap muscles.* The midline raphe is divided and an assistant with Senn or Army-Navy retractors or with a self-retracting retractor then retracts the strap muscles laterally. Undermining should be minimized to decrease the potential creation of dead-space areas. In the case of a malignant neoplasm overlying the thyroid compartment, the anatomic landmarks may be less clear. In such a case, palpation of the thyroid cartilage and

dissecting caudally are helpful. Care must be taken, especially in women, to palpate the thyroid and not the hyoid cartilage [see Figure 3].

3. *Dissection of the thyroid gland.* The thyroid isthmus frequently lies in the field of dissection. Because its size and thickness vary greatly and can vary from 5 to 10 mm in vertical dimension, dissection of this can be undertaken, and, in many cases, immobilizing the trachea and retracting the isthmus either superiorly or inferiorly to place the tracheal incision in the second or third tracheal interspace can be accomplished [see Figure 4]. However, if the isthmus is a problem, especially in cases where the neck cannot be extended, it can be divided and the edges ligated either with ties or with a Harmonic scalpel. When there is an isthmus nodule, the isthmus should be removed for diagnostic and therapeutic purposes. Recurrent laryngeal nerves should not be directly in the operative field and are rarely at risk as long as one stays in the midline anterior on the trachea. If significant deviation of the trachea is noted, the nerves may be injured. Because the blood supply to the trachea is laterally based, one should not encounter them. However, a thyroid ima vessel is frequently noted in the lower portion of the isthmus, and this may need to be ligated prior to dissection.
4. *Incision of the trachea.* Tracheostomy should be performed with a sharp blade. The pretracheal tissues may be coagulated with a bipolar electrocautery. The opening of the airway may bring volatile gasses into the operative field; therefore, monopolar electrocautery should be avoided if volatile gasses are in use. Several types of incisions are possible:

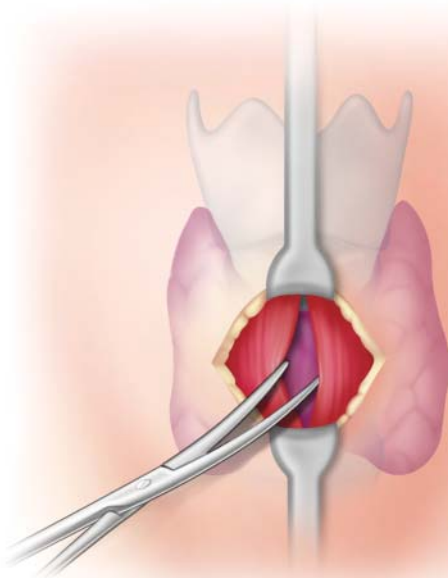


Figure 2 Surgical tracheostomy. Retractors are placed, the skin is retracted, and the strap muscles are visualized in the midline. The muscles are divided along the raphe and then retracted laterally.

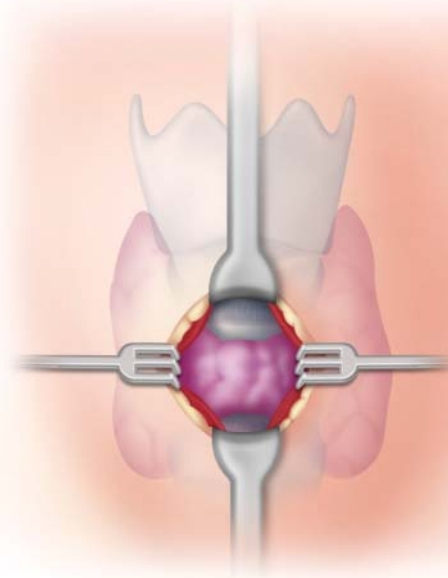


Figure 3 Surgical tracheostomy. With the strap muscles retracted, the thyroid isthmus is visualized, and the inferior (or superior) edge of the isthmus is dissected down to the trachea. The isthmus is then retracted superiorly (or inferiorly) or divided to permit visualization of the trachea before the tracheal incision is made.

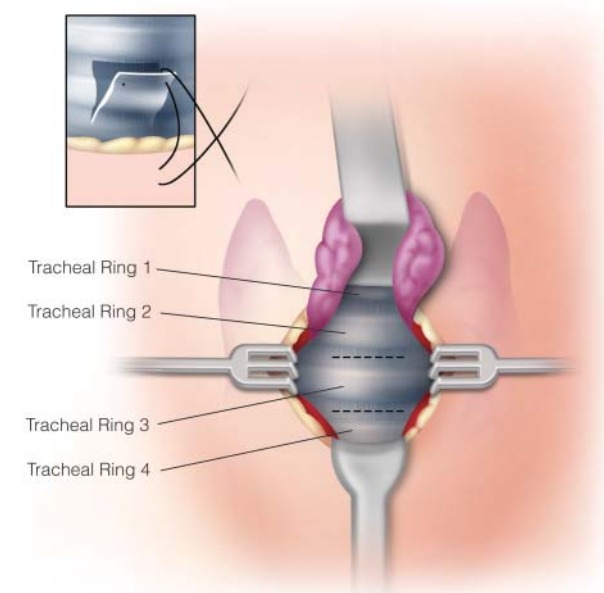


Figure 4 Surgical tracheostomy. A tracheostomy is made either between the second and third tracheal rings or between the third and fourth rings. A Björk flap (*inset*) may be created by extending the ends of the tracheostomy downward through the next lower tracheal ring in an inverted U shape.

- a. *Linear incision.* This transverse incision is made either between the second and third rings or the third and fourth rings. Stay sutures are then placed superiorly and inferiorly around the tracheal rings [see Figure 5].

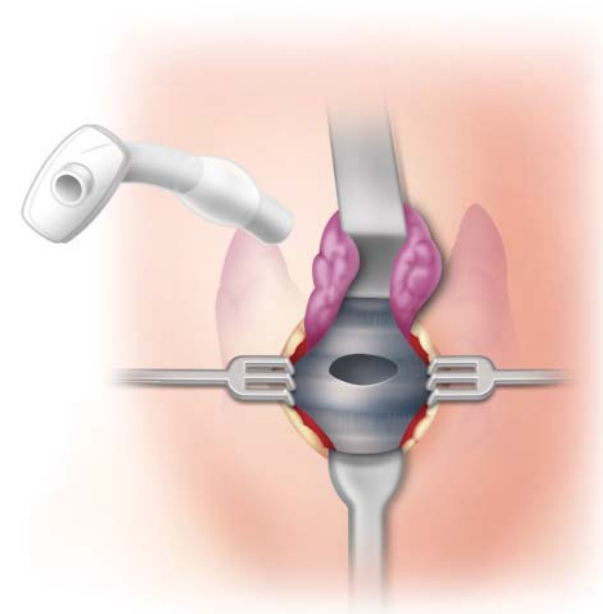


Figure 5 Surgical tracheostomy. The tracheostomy tube is inserted into the tracheal opening from the side, with the faceplate rotated 90° so that the tube's entry into the airway can be well visualized.

- b. *T-type incision.* This incision is a combination of a vertical incision that crosses the second ring and forms a “T” with a transverse incision below the third tracheal ring. Stay sutures are placed laterally and allow for controlled opening of the trachea with a tracheostomy spreader.
- c. *Tracheal window.* Although a tracheal window with removal of a portion of the third tracheal ring has been performed, this is more difficult and may not heal as rapidly as a ring-preserving incision.
- d. *Björk flap.* A Björk flap is an inferiorly based U-shaped flap that incorporates the ring below and the tracheal incision [see Figure 4]. A U-type incision is made from the third tracheal ring through the second tracheal ring, and the second tracheal ring is then retracted inferiorly and sutured with a dissolvable suture as high in the neck as possible to the skin. The theoretical justification for this is to keep the tracheal incision close to the skin edges in the instance of tracheostomy tube displacement, to ensure ease of airway access. This flap suture can be released 3 to 5 days after creation once the tract has been established or after the first tracheostomy change.
5. *Stay sutures.* Stay sutures using a 2-0 nonabsorbable suture on a UR6 needle can be placed either laterally or superiorly and inferiorly. These help stabilize the tracheostomy during the procedure. The sutures are then taped to the chest and labeled so that they will not be inadvertently removed. Stay sutures may provide access to a fresh tracheostomy if the tracheostomy tube becomes dislodged in the immediate postoperative period. These sutures are left in place until the first tube change.

In adults, a number 8(outside diameter [OD]) or 6(OD) tube is preferable. If there is significant edema or obesity, the use of an extra-long tube is desirable. If a tracheostomy tube is not available, a standard endotracheal tube can be used to intubate the neck. Remember when trimming the tube to spare the pilot balloon.

PERCUTANEOUS TRACHEOSTOMY

Percutaneous tracheostomy was first described over 50 years ago, but the availability of a dilational percutaneous tracheostomy kit prompted widespread use in the 1990s. In many centers, this has become the method of choice for tracheostomy. Although initial contraindications included morbid obesity, inability to extend the neck as in potential cervical spine injuries, short neck, enlarged thyroid isthmus, and previous tracheostomy, these have been disproven with increasing experience. A benefit of the percutaneous approach is the ability to perform the procedure at bedside in the ICU, reducing OR costs and scheduling conflicts. The percutaneous approach has been championed for its ease of performance at the bedside in the ICU; however, several studies comparing cost and personnel use demonstrate open bedside tracheostomy to be more cost-effective with equivalent complications and safety outcomes. The long-term cosmetic effects of percutaneous tracheostomy appear to be better than those of the open technique.

The choice between percutaneous and open tracheostomy remains a decision best left to individual centers.

Operative Technique

Equipment and personnel The personnel necessary for the procedure are a respiratory therapist, a critical care nurse, a surgeon, and a bronchoscopist to safely perform a percutaneous tracheostomy. The equipment required is a bronchoscope and a percutaneous dilation tracheostomy kit. Surgical instruments for an open tracheostomy should be readily available. Maximum sterile barriers are employed, including sterile gown, gloves, and drapes. All participating personnel must wear mask and head covers.

Procedure

1. *Incision.* Once conscious sedation is initiated, the subcutaneous tissue is infiltrated with local anesthetic 1 cm caudal to the cricoid cartilage. A 1 to 1.5 cm incision is made either in a horizontal or a vertical fashion. The subcutaneous tissue is then bluntly dissected using a hemostat to spread the tissue down to the level of the trachea.
2. *Bronchoscopy.* The bronchoscope is advanced to the tip of the endotracheal tube. With the surgeon providing one-finger ballottement at the level of the first or second tracheal ring, the endotracheal tube is slowly withdrawn while maintaining the bronchoscope at the tip of the tube until one-to-one ballottement is appreciated. Every step of the procedure involving instrumentation of the trachea is preferably performed under direct bronchoscopic visualization.
3. *Transcutaneous tracheostomy.* The introducer needle is advanced through the incision at the level where one-to-one ballottement was appreciated. Constant aspiration of the syringe and direct bronchoscopic visualization immediately identify the entrance into the trachea. Once the needle is noted to be in a good position, the guide wire is introduced again under direct bronchoscopic visualization.
4. *Dilation.* Using a modified Seldinger technique, the needle is removed and a stiff conical dilator is introduced and removed. The tract is then dilated with the largest conical dilator to the level marked for the skin. The dilator is removed and fully introduced three times. The tracheostomy tube is then introduced over the snugest fitting dilator. Once the tracheostomy tube is in place, the guide wire and dilator are removed. Often the endotracheal tube must be withdrawn a short distance to allow for serial dilation and introduction of the tracheostomy tube.
5. *Confirmation of placement.* Once the tracheostomy tube is in place, the bronchoscope is withdrawn from the endotracheal tube and introduced through the tracheostomy tube to confirm placement within the trachea. The endotracheal tube is kept in place until confirmation is complete. The tracheostomy tube is then secured with sutures from the faceplate to the skin and tied in place.

Tracheostomy Management

Tracheal sutures are removed on postoperative day 7. If the patient is on minimal ventilator settings or liberated from the ventilator, the tracheostomy tube is downsized. Once the patient is liberated from the ventilator, the tracheostomy tube cuff is deflated and the patient is placed on humidified air or oxygen. The humidified air can be delivered via a

tracheostomy collar or tracheostomy tube. A tracheostomy collar allows more patient freedom and less torque than a T tube when frequent suctioning is not required. Speech pathology consultation should be obtained for swallowing evaluation and speaking valve placement versus capping the tracheostomy tube. The approach depends on the patient's mental status and suctioning requirements. Once the patient is tolerating either tracheostomy tube occlusion or a speaking valve for greater than 24 hours and managing his or her own secretions, the tracheostomy is removed. In preparation for decannulation, the patient should be suctioned and a replacement tracheostomy with a stylet should be available in case of sudden respiratory decompensation. An occlusive dressing is left in place for 24 hours. Generally, no further dressing is required afterward.

Complications

Reported complication rates from tracheostomy range from 5 to 31%, with an average of nearly 12%. Major complications range from 2 to 6%. Mortality is extremely low (0.5%).

EARLY COMPLICATIONS

Displacement

The most dangerous complication is early accidental displacement or decannulation. This can occur when moving the patient to the ICU or recovery room and when patients are turned for care or x-rays in the ICU in the first 5 to 7 days after placement. A loosely tied tracheostomy or one placed in a precarious position can be dislodged, resulting in the inability to ventilate and oxygenate. If this is suspected, the patient should immediately be placed supine and an attempt at ventilation should commence. If the patient cannot be ventilated, an attempt to replace the tube should be tried if stay sutures or a Björk flap is present. Emergency oral intubation should be performed if the attempt fails. Multiple attempts to replace the tube can result in a false passage. The tracheostomy can then later be replaced via the same incision with the proper light and proper retraction. A new tracheostomy tube should be available in the room or above the bed for all patients who have had a fresh tracheostomy.

Pneumomediastinum/Pneumothorax

Pneumomediastinum can occur, especially with a low tracheostomy or if a false passage is created. Pneumothorax is a rare (< 2%) complication that can occur especially in children, in whom the cupola of the lung may ride high. Pneumothorax can also occur in patients who require high ventilatory pressures or who cough vigorously during the procedure. A low tracheostomy and deep dissection potentially increase the risk of pneumothorax.

Bleeding

A small amount of blood via the wound or tracheostomy immediately following the procedure is not alarming. However, the persistence of blood around the trachea implies venous bleeding from either the skin, subcutaneous tissues, or thyroid gland. In general, this can be controlled with gentle packing and the use of a bioabsorbable hemostatic agent. If bleeding continues, the patient should be taken to the OR if possible and reintubated under ideal light and retraction;

the tracheostomy should be removed and the bleeding controlled with cautery or sutures if necessary. If hemorrhage is demonstrated via the tracheostomy tube, early careful bronchoscopy should be performed to ascertain the site of bleeding. Significant bleeding from the tracheostomy is usually a late complication and may be related to a tracheoinnominate fistula (see below).

Infection

Tracheostomy infections requiring treatment are much less common than one would imagine, considering the contamination of the bronchial/tracheal tree in many patients who have been intubated for a period of time. The majority of infections can be treated with local wound care, although deep infections from *Staphylococcus aureus* and *Pseudomonas aeruginosa* may require antibiotics and removal of sutures. Placing tracheostomies through burn eschar presents a separate problem.

Acute Obstruction

The most common cause for acute obstruction of a tracheostomy is dislodgment. If that is not the case, the tracheostomy may have accumulated blood or mucus, which can clog the airways. To avoid this, humidified oxygen should always be administered, and gentle careful suctioning should be initiated by experienced personnel. The inner cannula should be removed and examined. Occasionally, bronchoscopy will be necessary to remove and irrigate mucus plugs.

Negative Pressure Pulmonary Edema

A rare complication of upper airway obstruction may occur after a tracheostomy is performed for airway obstruction. Patients generating large negative pressure against resistance, which is suddenly released, can experience a noncardiogenic pulmonary edema. The patient becomes hypoxic, develops rales in the lungs, and can demonstrate pink frothy pulmonary edema via the tube. A chest x-ray may demonstrate bilateral pulmonary edema. This process is usually self-limited and responds to positive end-expiratory pressure (PEEP) and positive pressure ventilation.

LATE COMPLICATIONS

Late complications of tracheostomy are often attributable to the cuff, either from the tracheostomy tube or from the endotracheal tube in place prior to tracheostomy. Complications attributable to cuff injuries are less common now than previously as a result of improvement in technology allowing for lower-pressure cuffs, but they still occur in patients who undergo prolonged endotracheal intubation.

Tracheostomy cuff pressures should be measured daily or more often to prevent tracheal necrosis. X-rays demonstrating a dilated cuff in the trachea require assessment of the tube, cuff, and trachea.



Subglottic Tracheal Stenosis

Tracheal stenosis has a reported incidence of 4 to 18%. Stenosis is associated with a longer hospital stay and prolonged time to tracheostomy. Dyspnea and stridor result when tracheal stenosis is greater than 50% of tracheal diameter. In suspected tracheal stenosis, referral to a specialist for evaluation either by computed tomography (CT) or rigid laryngoscopy is essential for diagnosis. Once the diagnosis is confirmed, treatment may require tracheal reconstruction.

Tracheal Granulation

Tracheal granulation may cause bleeding or occlusion of the tracheostomy tube if a flap of granulation tissue is elevated on exhalation. Granulation tissue may mimic tracheal stenosis. This complication is often easily treatable with removal of the tracheostomy tube. Occasionally, resection of the granulation tissue is necessary.

Vocal Cord Dysfunction

Vocal cord dysfunction occurs in less than 2%, whereas voice changes, including hoarseness and weakness, occur in 10 to 20% of patients. In cases of bilateral vocal cord paralysis, a tracheostomy is necessary until the paralysis resolves. Most complaints of vocal changes are considered minor by patients.

Tracheoesophageal Fistula

Tracheoesophageal fistula occurs in less than 0.3% of patients following tracheostomy. It can occur if a puncture is made into the posterior trachea or a cuff erodes into the esophagus. The combination of a tracheostomy tube and a stiff nasogastric tube in the esophagus increases the risk of this complication. Symptoms include aspiration and persistent cuff leak around the tracheostomy. Persistent tracheobronchitis or pneumonia may also be present. A swallow study with the cuff deflated or CT and panendoscopy will demonstrate the defect. Definitive therapy is usually necessary.

Tracheoinnominate Fistula

Tracheoinnominate fistula has a reported incidence of 0.4 to 4.5% and presents initially as "sentinel bleeding" that usually develops within the first month following the procedure. Mortality between 50 and 75% has been reported. Risk factors include a low (below the third ring) tracheostomy, caudal migration from leverage on the tube, and the presence of a more cephalad-coursing innominate artery. An attempt to visualize the site of bleeding should be undertaken. If hemorrhage is significant, hyperinflate the cuff and try to compress the vessel against the posterior sternum. If this is unsuccessful, oral intubation should be performed. The tracheostomy tube must be removed and replaced with digital pressure through the tracheostomy to tamponade the bleeding en route to the OR. Often the upper extremity of the person responsible for maintaining digital pressure is prepared into the operative field in preparation for median sternotomy.

Tracheocutaneous Fistula

Rarely, the tracheostomy wound does not completely close in 24 to 48 hours. Granulation tissue may be treated topically with silver nitrate with good success. Occasionally, the tracheostomy site must be surgically closed in layers for a nonhealing tracheocutaneous fistula.

Scar

Cosmetic results vary following tracheostomy. Ten to 15% of patients consider scar revision of the tracheostomy site.

Financial Disclosures: None Reported.

Additional Reading

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Acknowledgments

Figures 1 through 5 Thom Graves

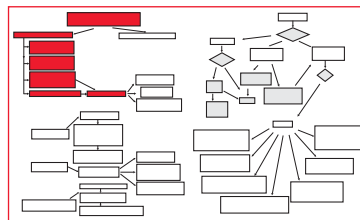
9 THYROID DISEASES

Karen R. Borman, MD, FACS, and Jennifer L. Rabaglia, MD*

Approach to the Patient with Thyroid Disease

The thyroid plays a central role in normal metabolic and homeostatic processes, including thermomodulation, protein synthesis, carbohydrate and lipid metabolism, and modulation of adrenergic activity. A normal thyroid weighs 15 to 25 g and is firm, mobile, and smooth to palpation. The thyroid contains two distinct, physiologically active cell types. Follicular cells are responsible for thyroid hormone synthesis, whereas parafollicular or C cells produce calcitonin. Patients are most often referred to the surgeon for control of hyperthyroidism or for treatment of euthyroid nodular disease.

APPROACH TO THE PATIENT WITH HYPERTHYROIDISM



The symptoms of thyroid hormone overproduction are numerous and often nonspecific, including palpitations, heat intolerance, weight changes (gain or loss), increased appetite, poor concentration, decreased libido, and irregular menses. The diagnosis of hyperthyroidism is definitively established by thyroid function testing (TFT); thyroid-stimulating hormone measurement (TSH, thyrotropin) is the single most useful test. TSH normally ranges between 0.3 and 3.0 mU/L; values less than 0.3 indicate hyperthyroidism (excess thyroid hormone causing decreased TSH secretion), and values > 3.0 suggest hypofunction (low levels of circulating thyroid hormone stimulating increased TSH secretion). Free thyroxine (T_4) and triiodothyronine (T_3) levels can provide further confirmation. Total T_4 and T_3 levels are influenced by serum protein derangements and must be interpreted with caution. Thyroglobulin (Tg) and calcitonin determinations are not useful for diagnosing hyperthyroidism.

DIFFERENTIAL DIAGNOSIS

Potential etiologies for hyperthyroidism are numerous, but relatively few lead to surgical referrals. Thyroidectomy as a treatment option is largely confined to three entities: diffuse toxic goiter (Graves disease), toxic nodular goiter (TNG; Plummer disease), and solitary hyperfunctioning nodule. Other forms of hyperthyroidism most often respond to medical management and/or withdrawal of the inciting agent (e.g., amiodarone) while the underlying thyroiditis resolves [see Table 1].

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Table 1 Etiologies of Hyperthyroidism

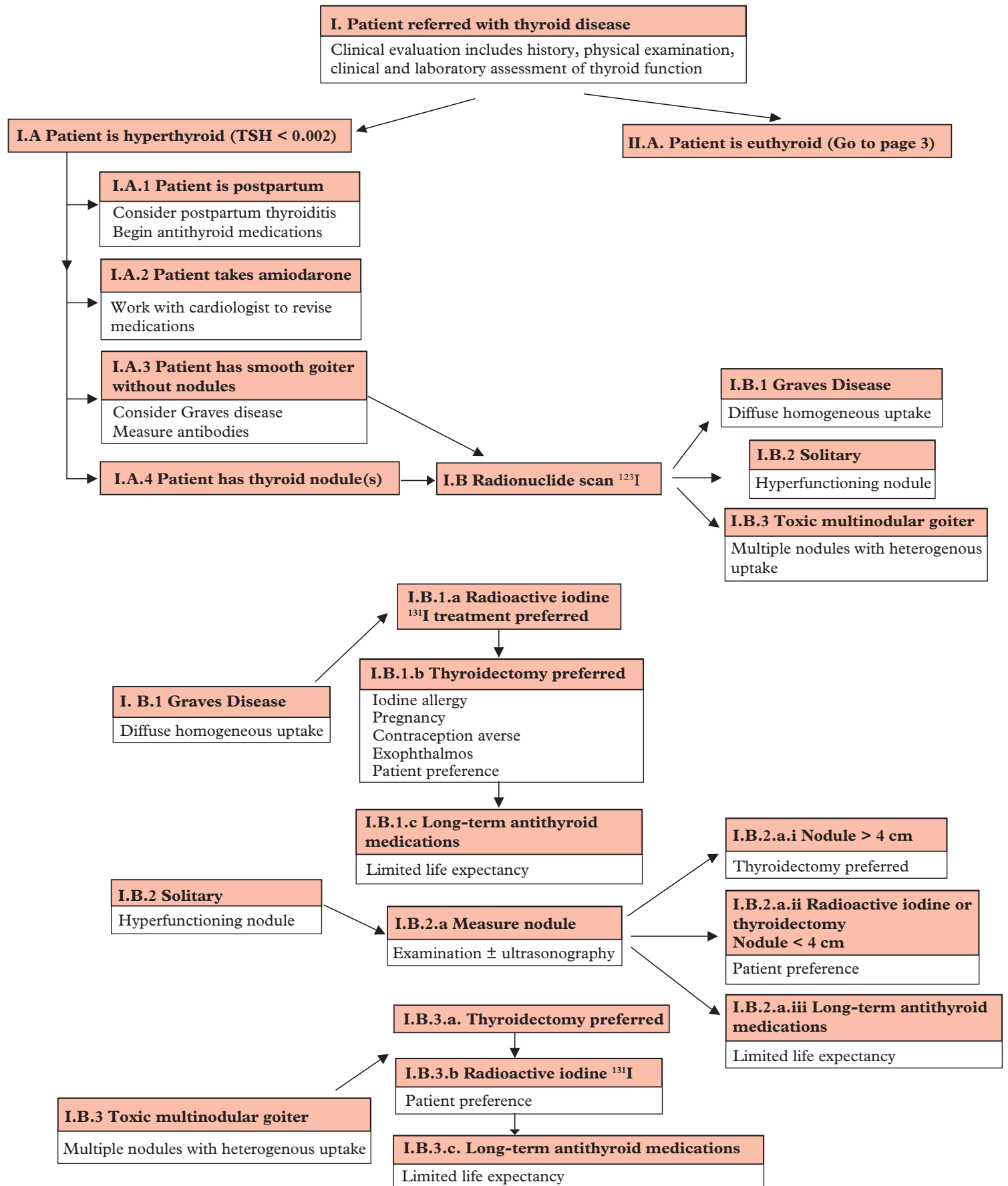
Disease	Predominant Treatment
Iodine induced (jodbasedow)	Medical
Subacute thyroiditis (de Quervain)	Medical
Chronic lymphocytic thyroiditis (Hashimoto thyroiditis)	Medical (surgical for compressive symptoms)
Postpartum thyroiditis	Medical
Drug induced (e.g., amiodarone)	Medical (rarely surgical)
Struma ovarii	Surgical (resect ovarian teratoma)
Graves disease	Medical or surgical
Toxic nodular goiter (Plummer disease)	Surgical or medical
Solitary hyperfunctioning nodule	Surgical; rarely medical

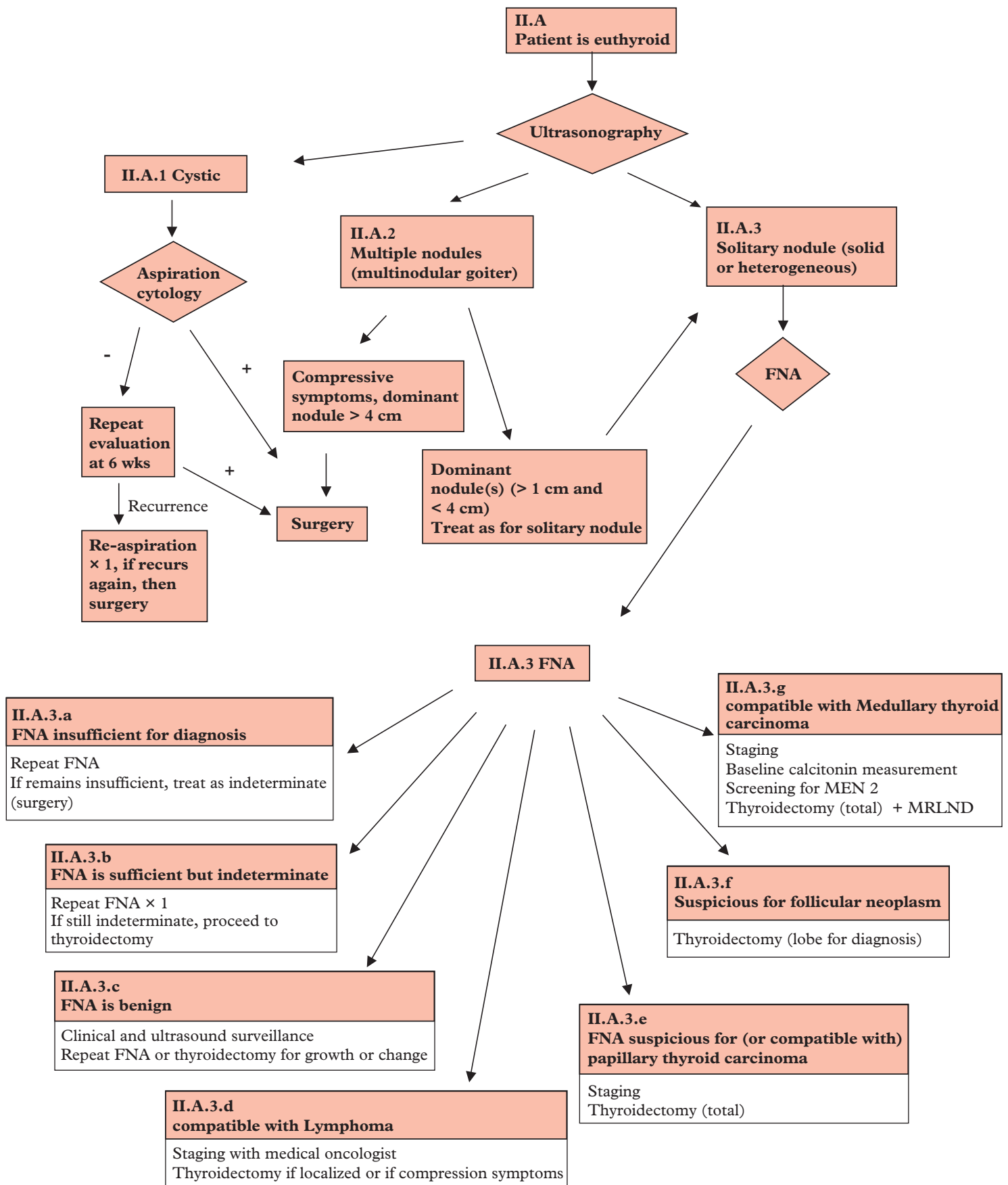
CLINICAL EVALUATION

History and Physical Examination

A thorough history may raise considerations of thyroiditis (e.g., amiodarone, pregnancy, iodinated contrast agents) and lead to reconsideration of nonsurgical management. Previous or ongoing treatment with thyroxine or antithyroid medications (ATMs) is noteworthy, along with review of recent TFT results. Factors that could influence treatment choices (e.g., iodine allergy, comorbid diseases) should be identified. Adrenergic symptoms (e.g., palpitations, tremor) are valuable in assessing antithyroid treatment response and readiness for operation. Compression symptoms (dysphagia, nocturnal dyspnea) are more likely with TNG than Graves disease or solitary toxic nodule (STN). Dysphonia is extremely rare with benign disease and should be definitively evaluated before thyroidectomy is recommended.

Examination of the thyroid begins with observation of the neck for goiter, including size and symmetry. Palpation may discriminate the smooth, soft, diffuse Graves gland from the firm, multinodular toxic goiter or the STN. Tenderness to palpation is most consistent with thyroiditis, as is bilateral lymphadenopathy. Unilateral, hard, or fixed cervical or supraclavicular adenopathy should prompt evaluation as outlined below for euthyroid nodular disease. Substernal extension of the goiter and cervical tracheal deviation should be noted when present. A solitary or dominant nodule should be characterized as to its location, size, and mobility. Physical examination should also focus on other signs of hyperthyroidism, including Graves ophthalmopathy (lid lag, lid retraction, proptosis, exophthalmos) and adrenergic excess (tachycardia, bilateral fine tremor of the hands). General medical status should be assessed as for any potential preoperative patient.





Imaging

Thyroid scintigraphy reliably characterizes the hyperthyroid processes most often referred to surgeons and should precede any other form of imaging. Technetium pertechnetate (Tc-99m) scanning is rapid and produces sharper images at lower cost than iodine-123 (^{123}I). ^{123}I scintigraphy is superior when precise uptake quantification is required (before radioactive ^{131}I treatment) or when better bone penetration is necessary (substernal goiter).¹ Graves disease appears as homogeneous radionuclide uptake. An enlarged, heterogeneous gland with two or more areas of increased uptake surrounded by areas of normal or decreased uptake is typical of TNG. An STN is confirmed when a single, high-uptake (“hot”) focus is seen against a suppressed background. Computed tomography (CT) and magnetic resonance imaging (MRI) have limited utility in hyperthyroidism other than for assessment of substernal goiters, and iodinated contrast administration will interfere with any subsequent ^{131}I treatment. Once the etiology of the hyperthyroidism is established, treatment options may then be considered. TNG and STN are preferentially treated operatively, whereas the algorithm for Graves is a bit more complex; ultrasonography (US) and fine-needle aspiration (FNA) may be indicated to exclude malignancy if nonoperative treatment is chosen.

TREATMENT CONSIDERATIONS

Initial Therapy

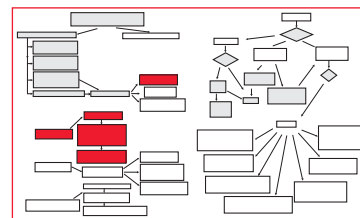
Medical management for control of symptoms and signs of hyperthyroidism precedes surgical treatment. ATMs and beta blockers are the most commonly used agents. The thionamides propylthiouracil (PTU) and methimazole limit thyroid hormone synthesis by disrupting organification of iodine. PTU also inhibits peripheral conversion of T_4 to the metabolically more active T_3 . Minor side effects (pruritis, fever, gastrointestinal disturbances, and arthralgia) occur in 5 to 25% of patients receiving thionamides, and agranulocytosis affects 0.2 to 0.5% of patients receiving either medication.² Rare cases of fulminant hepatic failure and autoimmune vasculitis have been associated with PTU alone.²⁻⁴ Beta blockers (atenolol, propranolol) may be added to ATM for more rapid control of severe adrenergic symptoms when present. Treatment efficacy is monitored by TFTs and clinical evaluation (resolution of tachycardia and tremor). Most patients are rendered euthyroid within 6 weeks of treatment initiation; virtually all are euthyroid at 3 months. PTU is often chosen over methimazole during pregnancy as methimazole is more apt to cross the placenta and has been linked to fetal scalp aplasia cutis.

Preoperative Therapy

Achieving euthyroidism markedly reduces the chance of thyrotoxicosis and thyroid storm intra- or postoperatively. Preoperative treatment goals include normalization of TFTs, a resting heart rate of 60 to 70 beats per minute, and resolution of tremor. In Graves disease patients, inorganic iodine administration in the form of Lugol solution (3 to 5 drops t.i.d.) or saturated solution of potassium iodide (SSKI; 2 to 3 drops t.i.d.) may decrease the size and vascularity of the gland when given for 7 to 10 days immediately preoperatively. Beta blockade alone supplemented by inorganic iodine is somewhat less effective but is rarely used in urgent clinical circumstances or for patients intolerant of thionamides.

Graves Disease

Graves disease is the leading cause of hyperthyroidism in the United States, comprising about 70% of cases. Women between the ages of 20 and 50 years are most commonly affected.³



There are three effective, long-term treatments for Graves disease: prolonged ATM administration, radioactive iodine (RAI), and thyroidectomy. Factors influencing treatment choice include overall patient status (age, gender, comorbidities, life expectancy); thyroid findings (goiter size, dominant nodule, compression symptoms); health care system characteristics (access to physicians, medications, and laboratory testing); and patient preference.

Prolonged ATM administration Although common in Europe and Asia, this treatment is not often chosen in the United States, perhaps linked to the rare but potentially life-threatening side effect profile of thionamides. This approach also requires a prolonged medication trial (12 to 24 months), and patients often find this less palatable when more rapidly acting treatments with higher success rates are available. Remission (euthyroidism for at least 1 year posttreatment) is achieved initially in approximately 50% of cases, but this success rate declines to 30% at 10 years.^{2,3,5} Negative predictors of remission include large goiter, severe biochemical disease, high serum ratio of T_3 to T_4 , male gender, multiple relapses, and very high TSH receptor antibody titers.^{2,5} Remissions are more common in adults than in children. Prolonged ATM administration should be considered when life expectancy is limited. Here methimazole has the advantage of twice-daily dosing versus PTU, which is given three to four times per day. Patients who fail to achieve remission or who relapse can be salvaged with RAI or surgery.

Radioactive iodine RAI is the definitive management of choice for Graves disease in the United States. Approximately 60% of patients are euthyroid within 6 to 8 weeks after a single oral dose of 5 to 15 mCi, and nearly all the remaining patients become euthyroid within several months.⁴ Hyperthyroidism persists or recurs in 5 to 25% of cases and is dose dependent. Posttreatment hypofunction is also dose dependent. The risk of hypothyroidism is 20% within the first year and 3 to 5% per year thereafter. Thus, TFTs must be followed lifelong in all patients treated with RAI. Acute adverse reactions are uncommon after RAI administration. Pain secondary to radiation thyroiditis and nausea are reported most often. Because RAI treatment can trigger thyrotoxicosis, pretreatment with ATM before RAI administration may be appropriate for patients who are elderly or have concurrent heart disease. An exceedingly rare but more serious complication is hypoparathyroidism, which can be detected promptly by monitoring serum calcium.

RAI may not be the preferred treatment for some subgroups of patients with Graves disease. Although little credible evidence supports a generalized oncogenic effect of RAI, parental concerns about future cancers may prompt a choice for prolonged ATM administration or surgery in Graves disease in children and adolescents. RAI may exacerbate eye manifestations in patients with Graves ophthalmopathy,

particularly in smokers or when hyperthyroidism is severe.^{6,7} Concurrent glucocorticoid administration minimizes this risk,^{6,7} although moderate to severe ophthalmopathy remains a relative contraindication to RAI therapy, and surgery may be preferred in cases where eye findings of Graves disease are clinically overt. Pregnancy and lactation are absolute contraindications to RAI because ¹³¹I crosses the placenta and is secreted into breast milk. Women should defer pregnancy for 6 to 12 months after receiving RAI to allow for stabilization of maternal thyroid function and to prevent transplacental passage of residual radioisotope and subsequent fetal hypothyroidism. RAI therapy is also contraindicated in patients who are allergic to iodine.

Surgery Surgical intervention provides rapid normalization of thyroid function with the lowest rate of recurrent hyperthyroidism while avoiding both the potential risks of prolonged ATM administration and the theoretical risk of ionizing radiation. **Surgical treatment is preferred for Graves disease patients with relative or absolute contraindications to RAI, as outlined above, as well as in patients with compressive symptoms and those with concurrent suspicious or indeterminate nodules.** Operation also is favored in patients for whom RAI is less likely to be effective, including patients with large goiters, severe biochemical disease, a high serum ratio of T₃ to T₄, male gender, or very high TSH receptor antibody titers. Graves ophthalmopathy frequently stabilizes and sometimes regresses after operation.^{8,9} In some cases, patients may choose surgery to avoid ionizing radiation, to simplify family planning, or to minimize the duration of thyrotoxicosis.

Recommendations about the optimal extent of thyroidectomy for Graves disease have evolved over time. Bilateral subtotal resection was historically advocated for its safety profile and control of hyperthyroidism with the potential for euthyroidism without medication. However, estimation of tissue remnant size that will avoid hypothyroidism while minimizing recurrent hyperthyroidism may be difficult. **Recent studies suggest similar complication rates following subtotal and total resections, whereas cure rates are substantially higher after total thyroidectomy.^{8,10,11}** When performed by surgeons with appropriately low morbidity (recurrent laryngeal nerve injury less than 1% and permanent hypoparathyroidism less than 3%^{8,10}), total thyroidectomy is now favored over lesser resections.

Toxic Nodular Goiter

Much less prevalent than Graves disease, TNG accounts for about 25% of all cases of hyperthyroidism in the United States. TNG is uncommon in patients under 50 years of age but is the most common cause of hyperthyroidism in the elderly.¹² TFT abnormalities are similar to those in Graves disease, although a higher proportion of patients with TNG will have T₃ thyrotoxicosis. Treatment options include ATM, RAI, and surgery.

Prolonged ATM administration TNG results from thyroid hormone production by multiple autonomously functioning nodules without the potential for spontaneous

remission. Definitive management of TNG by ATM therefore requires lifelong ATM administration. Because of rare but sometimes life-threatening adverse reactions to the thionamides, only TNG patients with limited life expectancies are suitable for primary ATM treatment.

Radioactive iodine Iodine uptake is lower and less uniform in TNG than in Graves disease, making effective RAI dosing less predictable. Substantially higher initial doses are necessary, and up to 20% of patients require at least one additional RAI treatment.² Thus, patients may experience more side effects, including prolonged xerostomia and xerophthalmia, oral ulcers, and sialadenitis.¹³ As with Graves disease, the time to euthyroidism is prolonged, and the risk of posttreatment hypothyroidism remains substantial. RAI shrinks the gland in less than half of patients, and radiation thyroiditis may cause serious, symptomatic thyroid edema. As a result, RAI is particularly unsuited for TNG patients with large or substernal goiters or with pretreatment compression symptoms. RAI for treatment of TNG is typically reserved for patients who are poor surgical candidates or those with small, asymptomatic goiters who refuse surgery.

Surgery Thyroidectomy is the treatment of choice for TNG. Surgery allows for rapid control of hyperthyroidism, relief of compressive symptoms, and histologic examination of any dominant or suspicious nodules and avoids any long-term side effects of ionizing radiation. Total thyroidectomy is favored when performed by surgeons with acceptable complication rates and confers the advantages of easy titration of thyroid replacement and a nonexistent recurrence rate. Inorganic iodine (Lugol, SSKI) generally is not given preoperatively in this setting as the variable and unpredictable iodine uptake by TNG raises the risk of triggering acute thyrotoxicosis.

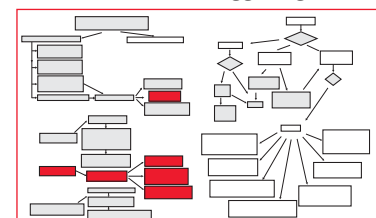
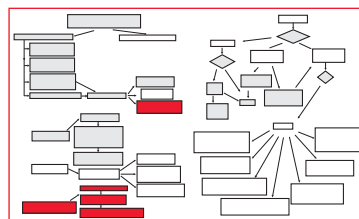
Solitary Toxic Nodule

STN causes less than 5% of all cases of hyperthyroidism in the United States. The frequency of STN is higher in women

and increases with age. STNs are usually palpable on physical examination as thyrotoxicosis is rare when nodules are under 3 cm in diameter.² Like TNG, STN can be associated with T₃ toxicosis and normal T₄ levels. Treatment choices include ATM, RAI, and surgery.

Prolonged ATM administration Excess thyroid hormone secretion by the autonomously functioning STN will recur after ATM withdrawal. Definitive management of STN by lifelong ATM treatment is an option of last resort because of the rare but sometimes life-threatening adverse reactions to the thionamides, and this is indicated only for patients with limited life expectancy.

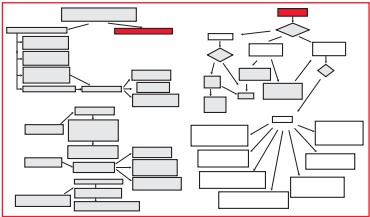
Radioactive iodine RAI can be effective definitive treatment for STN but usually is reserved for very-high-risk surgical candidates and for patients who refuse operation. The differential RAI uptake of the surrounding suppressed gland compared with the STN can confound RAI dosing.



Intense RAI concentration by the STN itself exposes the adjacent normal thyroid to potentially oncogenic levels of ionizing radiation, with subsequent risk of thyroid neoplasia.

Surgery Thyroidectomy is the treatment of choice for STN. Resection of the affected thyroid lobe promptly controls hyperthyroidism in patients with STN and relieves any symptoms associated with these relatively large nodules. The risks of operation are quite low because lobectomy plus isthmusectomy is sufficient in most cases. When the contralateral remaining lobe is normal, long-term T₄ supplementation is usually unnecessary.

Approach to the Patient with Euthyroid Nodular Disease



Thyroid nodules are very common and represent a wide spectrum of thyroid disease, both benign and malignant [see Table 2 and Table 3]. Palpable disease is present in 5 to 7% of women and 1 to 2% of men, whereas cervical US reveals subclinical nodular disease in up to 67% of patients.¹⁴ Most patients with nodules are clinically and biochemically euthyroid. Surgical referral is usually targeted at

symptomatic relief in bulky benign disease, definitive diagnosis for indeterminate lesions, and definitive therapy for malignancy. Although the incidence of thyroid cancer has doubled since 1973,¹⁴ 85 to 96% of palpable and subclinical nodules are benign. The rate of malignancy varies with factors including age, gender, family history, and radiation exposure. Screening for thyroid cancer is not cost-effective in the general population but is appropriate for some high-risk groups (e.g., multiple endocrine neoplasia [MEN] kindreds, after substantial radiation exposure). When considering treatment options, near-total (residual tissue < 1 g) and total (removal all visible thyroid) thyroidectomy will be used interchangeably. Subtotal resection refers to residual tissue more than 1 and less than 5 g.

DIFFERENTIAL DIAGNOSIS

The clinical challenge of euthyroid nodular disease is to reliably identify the small subset of patients with substantial likelihood of malignancy while avoiding the risks of surgery for the vast majority of patients with benign disease. Most thyroid nodular disease is more common in women and occurs in middle age, although anaplastic thyroid cancer (ATC), lymphoma, and sporadic medullary thyroid cancer (MTC) peak somewhat later.¹⁵ Papillary (PTC) and follicular (FTC) thyroid cancers are often grouped together as well-differentiated thyroid cancer (WDTC).

CLINICAL EVALUATION

History and Physical Examination

A palpable solitary or dominant nodule should lead to documentation of duration, changes in size, associated symptoms, exposure to ionizing radiation, prior thyroid disease, or prior therapy with T₄. Recent TFT results should be reviewed. Bearing in mind that most WDTCs are slow-growing and asymptomatic, rapid growth with associated symptoms suggests an aggressive process, such as ATC or lymphoma.¹⁶ Dysphagia and dyspnea are more common with multinodular goiter (MNG), whereas pain and hoarseness should heighten concerns for malignancy. Hashimoto disease raises the chance of lymphoma, and exposure to ionizing radiation, especially in childhood or adolescence, increases the likelihood of PTC. Family history should target a history of familial endocrinopathy or other hereditary tumor syndromes linked to thyroid disease, especially in the setting of suspected MTC¹⁷ [see Table 4]. A history of prior neck surgery or irradiation should be carefully documented.

On examination, the neck is observed for visible nodule or goiter. Voice quality and volume are noted. Palpation defines thyroid size, symmetry, and consistency, as well as the number, size, location, consistency, tenderness, and mobility of nodules; the number, size, location, and mobility of cervical lymph nodes; and the presence of tracheal deviation or substernal extension. A firm, mobile, solitary nodule is most often a colloid nodule or simple cyst but also may represent follicular adenoma; a hard, fixed mass suggests cancer but may represent Hashimoto disease. Central or unilateral adenopathy favors PTC or MTC. Thyromegaly of variable texture and multiple nodules are most common with MNG; substernal extension may produce cervical tracheal deviation or venous engorgement. General medical status should be assessed as for any potential preoperative patient.

Table 2 Benign Etiologies of Euthyroid Nodular Disease		
Disease	Nodularity	Predominant Treatment
Colloid nodule	Solitary or multiple	Observation
Simple cyst	Solitary or multiple	Observation or aspiration if > 4 cm or growing
Follicular adenoma (FA)	Solitary or multiple	Resection (thyroid lobectomy) to exclude malignancy
Multinodular goiter (MNG)	Often with dominant nodule in multinodular gland	Resection for compressive symptoms, dominant nodule > 4 cm, or suspicious dominant nodule
Chronic lymphocytic thyroiditis (Hashimoto disease)	Heterogeneous gland; may have dominant nodule	Resection for compressive symptoms or if suspicious dominant nodule

Table 3 Malignant Etiologies of Euthyroid Nodular Disease	
Disease	Percentage
Papillary thyroid cancer (PTC)	80
Follicular thyroid cancer (FTC)	10
Hürthle cell cancer (HCC)	1
Anaplastic thyroid cancer (ATC)	2
Medullary thyroid cancer (MTC)	5
Lymphoma	1
Metastases	< 1

Table 4 Familial Syndromes of Thyroid Disease

Syndrome	Thyroid Disease	Gene/Tumor Marker
MEN type IIA	Medullary thyroid cancer	<i>ret</i> proto-oncogene/calcitonin
MEN type IIB	Medullary thyroid cancer	<i>ret</i> proto-oncogene/calcitonin
FMTC	Medullary thyroid cancer	<i>ret</i> proto-oncogene/calcitonin
Familial adenomatous polyposis	Papillary thyroid cancer	<i>APC</i>
Carney complex	Well-differentiated thyroid cancer	<i>PRKARIA</i>
Cowden disease (<i>PTEN</i> multiple hamartoma syndrome)	Follicular adenoma/follicular carcinoma	<i>PTEN</i>
Peutz-Jeghers syndrome	Well-differentiated thyroid cancer	<i>STK 11</i> or <i>LKB 1</i>

FMTC = familial medullary thyroid carcinoma; MEN = multiple endocrine neoplasia.

Ultrasonography

Further assessment is accomplished with US, a safe, non-invasive, cost-effective means of imaging thyroid parenchyma and the cervical nodal basins. Patients are categorized as having solitary or multiple nodules, and lesions are subdivided into cystic, solid, or mixed cystic-solid. In a multinodular thyroid, a particularly large or irregular nodule is termed dominant. Benign nodules typically are round, homogeneous, slightly hypoechoic, and easily separable from surrounding tissue. Malignant nodules are more often irregular in shape, heterogeneous, markedly hypoechoic, and poorly demarcated. Tiny, hyperechoic, “comet tail”-shaped lucencies in a nodule favor benignity, whereas fine internal calcifications or hypervascularity suggests malignancy.¹⁸ Thin-walled cysts without internal echoes are overwhelmingly benign; mixed cystic-solid nodules are indeterminate and grouped with solid lesions for further evaluation.

Fine-Needle Aspiration

FNA provides the most accurate, cost-effective assessment of thyroid nodules. Benign lesions comprise 70% of FNA results, whereas roughly 5% of FNA are read as definitively malignant. Most of the remaining lesions are “follicular aspirates,” ranging from hyperplastic nodules to follicular cancer. A benign FNA diagnosis is credible^{19,20} and requires no further intervention other than periodic screening. The sensitivity and specificity of FNA for the diagnosis of malignancy approach 94% and 99%, respectively.²¹ A standardized thyroid FNA reporting system (Bethesda criteria) has recently been advocated.²² There are six general diagnostic categories: nondiagnostic or unsatisfactory, benign, atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), suspicious for follicular neoplasm, suspicious for malignancy, and malignant. Risk of malignancy varies by category [see Table 5]. FNA of solid solitary or dominant nodules greater than 1 cm is appropriate in most cases. Solid lesions 5 to 10 mm may warrant FNA if the nodule is hypoechoic and microcalcifications are present, if the history discloses a high risk for cancer, or if they are found on an

Table 5 Bethesda Classification of FNA Cytology and Associated Malignancy Risk

Bethesda FNA Cytology Class	Risk of Malignancy (%)
Nondiagnostic/unsatisfactory	1–4
Benign	0–3
AUS/FLUS	5–15
Suspicious for follicular neoplasm	15–30
Suspicious for malignancy	60–75
Malignant	97–99

AUS = atypia of undetermined significance; FLUS = follicular lesion of undetermined significance; FNA = fine-needle aspiration.

unrelated fluorodeoxyglucose-positron emission tomographic (FDG-PET) scan.^{14,23} When US confirms MNG and compression symptoms are absent, FNA is indicated for the dominant nodule.

Sequencing of Investigations

US typically precedes FNA as US findings may change the FNA target (e.g., an unsuspected suspicious nodule). “Pure” cystic lesions are rare, are overwhelmingly benign, and can be observed without FNA for diagnosis when asymptomatic. When a mixed nodule has a substantial cystic component, US-guided FNA allows fluid aspiration for cytology and FNA of the residual solid component. For solid nodules, US-guided FNA can reduce the rates of nondiagnostic and false negative results when the likelihood of inadequate material or sampling error is high (difficult to palpate, posteriorly located).¹⁴ Operation without FNA is indicated for a solitary or dominant nodule exceeding 4 cm given the substantial chance of malignancy and the possibility of nonrepresentative sampling by FNA (although many clinicians obtain a biopsy for the purpose of operative planning). FNA is also unnecessary when US confirms MNG in a patient with compression symptoms.

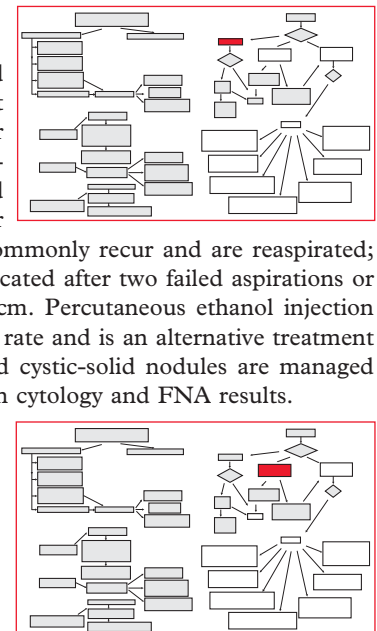
MORPHOLOGY-BASED TREATMENT CONSIDERATIONS

Cystic Lesions

Incidentally discovered simple cysts do not require investigation or treatment. Clinically evident cysts are aspirated dry and the fluid sent for cytology. Benign cysts commonly recur and are reaspirated; thyroid lobectomy is indicated after two failed aspirations or for cysts greater than 4 cm. Percutaneous ethanol injection carries a 20% recurrence rate and is an alternative treatment for smaller cysts.¹⁴ Mixed cystic-solid nodules are managed like solid lesions based on cytology and FNA results.

Multinodular Goiter

Most MNG patients are managed medically with serial clinical evaluations (examination, TFT, and US) unless compressive symptoms

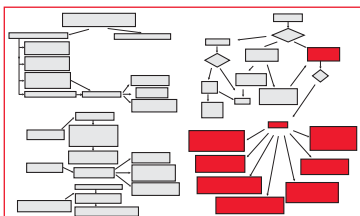


or dominant nodules develop. Thyroidectomy is indicated for patients with US findings of MNG and compressive symptoms. Compressive symptoms are typically associated with markedly asymmetrical goiters or those with substernal extension. When examination or US findings are inconsistent with symptomatology, CT or MRI can help exclude other etiologies. These cross-sectional modalities are also useful to delineate the extent of the mediastinal component if present.

Indications for surgery include compressive symptoms, severe or bothersome cosmetic deformity, any dominant nodule greater than 4 cm, or any nodule greater than 1 cm with FNA results that meet the criteria for removal. Total thyroidectomy is preferred over lesser resections to minimize recurrent disease from remnant hypertrophy and is appropriate for these patients when done by surgeons with low complication rates. Nearly all substernal goiters can be safely removed through a generous collar incision, and the remaining few are reached via partial sternotomy. Patients with tracheal deviation or substernal goiters may present endotracheal intubation challenges; airway management is optimized by preoperative dialogue between the surgeon and the anesthesiologist. Frozen section adds little value except when preoperative FNA was nondiagnostic or not performed or when intraoperative findings suggest unexpected malignancy.

Solitary or Dominant Nodule

The management of a solitary nodule is highly dependent on cytologic diagnosis and can be broken down into six categories based on the Bethesda criteria.²²



FNA nondiagnostic About 10 to 15% of aspirates are nondiagnostic, most often attributable to technical error, inadequate sampling, or a substantial cystic component. Less than 5% of these are malignant. Repeat FNA often yields adequate and definitive material²⁴; US guidance may enhance yields. Persistently insufficient results should prompt lobectomy.

FNA benign A benign diagnosis is rendered in nearly 70% of all specimens, and no intervention is required. The risk of malignancy is 0.5 to 3%.²² Surveillance by serial clinical evaluations (examination, TFT, and US) is done annually and then less often for stable nodules. Enlarging lesions (50% or more increased volume) warrant repeat FNA.

FNA AUS/FLUS Atypia or follicular lesion of undetermined significance is a heterogeneous subset of cytologically indeterminate nodules; roughly 5 to 15% prove to be malignant.²² AUS/FLUS is managed like FNA nondiagnostic: repeat FNA and then lobectomy if a definitive diagnosis remains elusive. Molecular markers (e.g., *braf*, *ras*) hold promise for future use in this patient subset; FDG-PET specificity is too low to add clinically relevant value.

FNA suspicious for follicular neoplasm Cancer is present in 15 to 30% of suspicious for follicular neoplasm (SFN),²² but the distinction between benign follicular

adenoma and follicular carcinoma cannot be made by FNA cytology. Assessment for malignancy is based on capsular or vascular invasion, and lobectomy is indicated for tissue diagnosis. Completion thyroidectomy is performed for final diagnoses of follicular cancer or follicular variant of papillary cancer. Some patients opt for total thyroidectomy initially to avoid the need for reoperation; this strategy is reasonable when complication rates are kept low.

FNA suspicious for malignancy A small number of abnormal cells within a sparsely cellular or more benign-looking background characterizes lesions in this category. Malignancy rates are 60 to 75%.²² Thyroid lobectomy is the minimum adequate treatment, and total thyroidectomy is preferable when complication rates are low.

FNA malignant Roughly 5% of cytologic diagnoses are conclusively malignant, and the positive predictive value of FNA for cancer is 97 to 99%.²² Comments about the cell type are usually provided. Total thyroidectomy is the preferred treatment for WDTC and MTC, whereas lobectomy suffices for unilateral metastases from other primary sites. Resections for primary thyroid lymphoma and ATC are tailored to the extent of disease, although resection for ATC is usually aimed at palliation only.

High-Risk Patients

Patients exposed to ionizing radiation, especially in childhood or adolescence, have a lifetime increased risk of PTC. Whereas FNA is credible for assessing their nodules, total thyroidectomy should be considered once nodules develop. Patients who retain irradiated thyroids require extremely close surveillance, so noncompliant individuals are better served by operation. A contralateral nodule developing after a lobectomy for cancer most often warrants completion thyroidectomy. Close surveillance is acceptable for compliant patients when FNA is clearly benign. Large (> 4 cm) solitary or dominant nodules should be resected to allow complete histopathologic examination; lobectomy is the minimum acceptable procedure. When intraoperative findings suggest malignancy (e.g., adherence to strap muscles), total thyroidectomy is appropriate for surgeons with low complication rates. For less experienced surgeons or when findings are benign, lobectomy suffices, and further resection decisions are based on the final pathology. Frozen section cannot exclude malignancy in these cases because of the potential sampling error.

Additional Studies

Additional laboratory tests are seldom indicated preoperatively. When the history raises the potential for MTC, the cytopathologist should be alerted and special cytologic stains performed. Any suspicion of MTC on FNA should trigger exclusion of pheochromocytoma and assessment for primary hyperparathyroidism prior to thyroidectomy (plasma or urine metanephrine assays, serum parathyroid hormone and calcium levels). Additional imaging is warranted for palpable cervical adenopathy in the setting of any thyroid malignancy; the modality is selected based on local expertise. US avoids iodinated contrast administration (which confounds postoperative ¹³¹I scanning or therapy), but accuracy is more operator dependent than for CT or MRI. FNA is appropriate

when other etiologies for adenopathy are present or when documented nodal metastases would change management (e.g., lobectomy only is planned, tertiary care referral). For nodes detected only on preoperative imaging, image-guided FNA is used similarly. **Preoperative laryngoscopy to document vocal cord function is indicated for patients with vocal complaints, audible vocal abnormalities, and prior neck operation or radiotherapy, although some surgeons perform laryngoscopy routinely.** Vocal cord paralysis or other concerns for tracheal or esophageal invasion should be investigated by endoscopy and imaging. Vocal cord paralysis should also trigger preoperative dialogue about airway management with both the patient and the anesthesiologist. **Radionuclide scanning is not useful, and the role of FDG-PET in preoperative staging remains ill-defined.**

Intraoperative observations may lead to revision of the operative plan. Strap muscle adherence, adjacent soft tissue invasion, and extracapsular tumor extension are consistent with malignancy and favor total thyroidectomy. Contralateral disease palpable through the strap muscles warrants at least FNA (through the muscles) and consideration of total thyroidectomy. To lessen the morbidity of reoperation, the contralateral strap muscles should not be elevated unless resection is planned at the same operative session. **Suspicious nodes may be evaluated by FNA or frozen section. Multiple suspicious central nodes or a positive biopsy result merit central lymphadenectomy [see Figure 1, Level VI].** Central neck dissection also should be considered by surgeons with low complication rates for T3 or T4 WDTC tumors

even though nodal disease is absent. **Proven lateral nodal disease is best treated by level II–IV en bloc functional resection when appropriate surgical expertise is available [see Figure 1].**

DISEASE-SPECIFIC TREATMENT CONSIDERATIONS

Papillary Thyroid Cancer

PTC is the most common thyroid cancer and carries an excellent prognosis when treated appropriately (> 90% 10-year survival overall). Poor prognostic factors include age less than 20 or more than 60 years, tumor greater than 4 cm, extrathyroidal extension, and the presence of distant metastases.^{25,26} Lymphatic spread worsens the prognosis and increases local recurrence risk for patients over 45 years and those with clinically apparent nodal involvement.¹⁴ The tall cell, columnar, diffuse sclerosing, trabecular, and insular variants are more aggressive but uncommon. The follicular variant is more common but behaves more like classical PTC. One quarter of PTCs are multicentric, and lymph nodes are involved at the initial presentation in about one third.²⁷ Distant metastases, usually pulmonary, are present initially in 5% of cases. PTC rates are sharply increased by ionizing radiation, with a lag time of 15 to 25 years. The high long-term survival rates of PTC patients and paucity of large randomized controlled trials have contributed to inconsistent treatment guidelines and to multiple prognostic scoring systems [see Table 6]. Staging should follow the TNM classification [see Table 7]. Most scoring systems correlate with recurrent disease, whereas the TNM system links best to mortality. Recent consensus evaluation and treatment recommendations from the American Thyroid Association are achieving widespread recognition.¹⁴

Total thyroidectomy should be performed for most PTCs exceeding 1 cm²⁸; this procedure addresses multicentricity, maximizes the therapeutic impact of postoperative RAI, and facilitates surveillance for recurrences. Lobectomy suffices for small, intrathyroidal PTC discovered incidentally in glands resected for other diagnoses when radiation exposure, nodal disease, and poor prognostic variants are absent. Central neck dissection is added based on FNA or operative findings suggesting lymphatic spread [see Figure 1, Level VI]. Judicious addition of prophylactic dissection by surgeons with low complication rates is reasonable, particularly for patients over 45 years, larger tumors (T3–T4), and more aggressive histologies.^{14,27} The favorable natural history of PTC and the morbidity of lateral cervical lymphadenectomy suggest that this procedure be added only for pathologically proven lateral nodal disease. An aggressive operative approach should be considered in good operative candidates with PTC invading the trachea or esophagus. A functioning recurrent laryngeal nerve (normal vocal cord function) should seldom, if ever, be sacrificed.

Postoperative administration of RAI for thyroid remnant ablation may also have an adjuvant therapeutic effect on residual microscopic disease in the central neck. RAI ablation is indicated when nodal or distant metastases are known to be present and for T3–T4 tumors.¹⁴ Ablation may also reduce recurrence rates for N1 disease or T2 tumors. Lifelong levothyroxine is given postoperatively at doses sufficient to suppress TSH secretion without causing overt hyperthyroidism. Dose reduction may be required if the osteoporosis risk

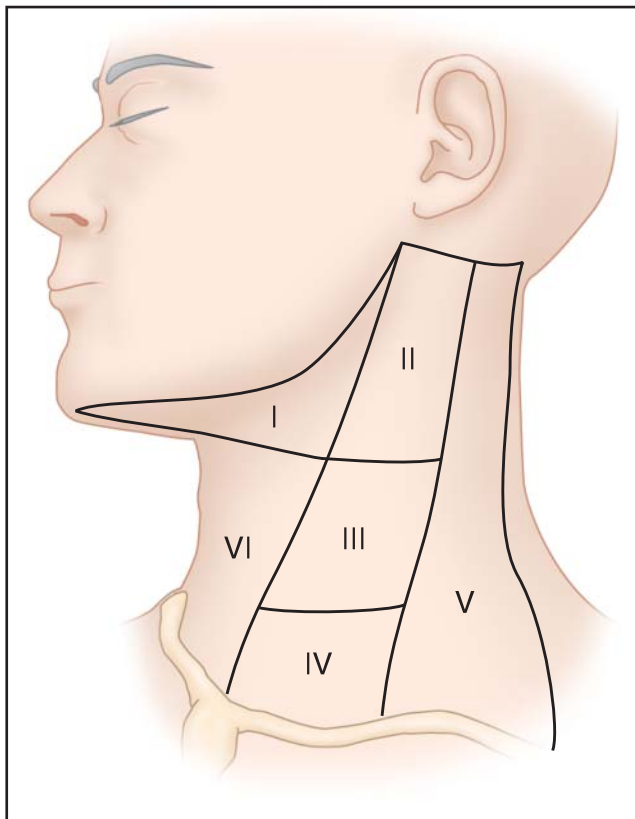


Figure 1 Cervical lymph nodes can be classified into six levels (*inset*) on the basis of their location in the neck.

Table 6 Elements of Common Prognostic Schemes for Well-Differentiated Thyroid Cancer

Prognostic Scheme	Patient Characteristics		Tumor Characteristics						Operative Factors
	Age	Gender	Size	Histologic Grade	Histologic Subtype	Extrathyroidal Extension	Nodal Metastasis	Distant Metastasis	Completeness of Resection
AGES	+	–	+	+	*	+	–	+	–
AMES	+	+	+	–	+	+	–	+	–
MACIS	+	–	+	–	*	+	–	+	+
MSKCC	+	–	+	+	+	+	+	+	–

+ = variable used in defining risk group; – = variable not used; * = only for papillary thyroid carcinoma; AGES = patient age, tumor grade, extent, and tumor size; AMES = patient age, presence of distant metastases, extent, and tumor size; MACIS = metastatic lesions, patient age, completeness of resection, invasion, and size of tumor; MSKCC = Memorial Sloan-Kettering Cancer Center scheme.

Table 7 Staging of Differentiated Thyroid Cancer

Tumor Type	Stage	Patient Age (yr)	Tumor	Node	Metastasis
PTC/FTC	I	< 45	Any T	Any N	M0
	I	45 or older	T1	N0	M0
	II	< 45	Any T	Any N	M1
	II	45 or older	T2	N0	M0
	III	45 or older	T3	N0	M0
	III	45 or older	T1–3	N1a	M0
	IVA	45 or older	T4a	N0–1a	M0
	IVB	45 or older	T4b	Any N	M0
	IVC	45 or older	Any T	Any N	M1

Adapted from Greene FL, editor. AJCC Cancer Staging Manual, Sixth Edition. New York: Springer-Verlag; 2002.
FTC = follicular thyroid cancer; PTC = papillary thyroid cancer.

is high or atrial fibrillation develops. Postoperative surveillance can include RAI whole body scan, serum Tg levels, and cervical US; test combinations and frequencies are individualized based on tumor staging, estimated recurrence risks, and patient compliance. Anti-Tg antibodies should be measured simultaneously with each Tg assay.

Follicular Thyroid Cancer

FTC comprises 10 to 15% of thyroid malignancies. In contrast to PTC, FTC is typically solitary, and metastasis is more often hematogenous than lymphatic, favoring lung and bone. Poor prognostic factors include age over 50 years and tumors over 3.5 cm. An FTC with a limited area of microscopic capsular invasion and no vascular invasion is termed “minimally invasive” and carries no excess mortality when treated by thyroid lobectomy. Total thyroidectomy is indicated for more extensive capsular invasion or for vascular invasion. Central [see Figure 1, Level VI] or lateral lymphadenectomy [see Figure 1, Level II–IV] is performed for clinically evident or palpable nodal disease. Staging follows the TNM classification. RAI ablation is indicated for all FTCs except minimally invasive lesions. Levothyroxine suppression is given, and surveillance is performed as for PTC. Stage for stage, FTC and PTC have equivalent prognoses.

Oncocytic (Hürthle Cell) Carcinoma

Hürthle cell carcinomas (HCCs) comprise less than 5% of WDTCs and are a subset of follicular neoplasms. They

contain at least 75% oncocytes and demonstrate capsular or vascular invasion. Oncocytic cancers are considered more aggressive than classical FTC because extrathyroidal extension and metastases (nodal and distant) are more common and RAI uptake is often minimal.^{15,29} Total thyroidectomy is indicated for nearly all HCCs, although this is often done in a two-stage fashion because FNA cannot provide a definitive diagnosis. Central or lateral lymphadenectomy is performed when nodes are clinically positive. Staging should follow the TNM classification. RAI ablation is indicated for all HCCs, and levothyroxine suppression is given as for FTC. Surveillance includes US and Tg; FDG-PET may be useful when Tg is elevated and a radioiodine whole body scan is negative.

Anaplastic Thyroid Cancer

ATC is rare in the United States, representing less than 2% of thyroid malignancies.^{29,30} The median survival for patients with ATC is approximately 6 months.^{15,30} ATC is suspected when older patients present with rapidly progressive, bulky, fixed tumors. Diagnosis may require core-needle or incisional biopsy when FNA is inadequate. The vast majority of tumors are unresectable at diagnosis because of locoregional spread. Over 40% of patients have extensive nodal involvement, and nearly 50% present with distant metastases (lung, bone, brain, adrenal).³⁰ Surgery has little utility other than for establishing an airway for palliation. External beam radiotherapy plus chemotherapy may transiently shrink the tumor;

palliative debulking is occasionally feasible for the few patients with significant and sustained responses.

Medullary Thyroid Carcinoma

Unlike WDTC, MTC is a neuroendocrine tumor that arises from the calcitonin-secreting parafollicular cells. MTC constitutes about 5% of thyroid cancers; most (75%) cases are sporadic, whereas the remainder are hereditary. Sporadic disease presents as a solitary nodule, often with palpable adenopathy. Cytologic features are characteristic and confirmed by immunostaining for calcitonin. Distant metastases to lung, liver, and bone are frequent. Staging follows the TNM classification [see Table 8]. Preoperative staging includes neck, chest, and abdominal CT or MRI for all but those with small primary tumors and no adenopathy. Liver and lung lesions are often multiple but sometimes small enough to escape detection via CT. A baseline calcitonin should be measured preoperatively. **Testing to exclude pheochromocytoma also is essential because the patient may represent the index case of an unsuspected kindred with MEN. If present, pheochromocytoma must be resected prior to thyroidectomy for MTC.** Overall survival in MTC is considerably lower when compared with WDTC. Poor prognostic features include large tumor size, high preoperative calcitonin, advanced age, and mediastinal adenopathy.²⁸ Surgery is the only effective treatment modality and should consist of total thyroidectomy plus central neck dissection [see Figure 1, Level 6] and ipsilateral modified radical neck dissection [see Figure 1, Levels I–V]. Contralateral lymphadenectomy is added when bilateral thyroid masses or clinically positive nodes are identified. Extrathyroidal or extranodal tumor extension worsens the prognosis. Calcitonin is followed serially as a tumor marker postoperatively. A subset of patients with persistent or recurrent hypercalcitonemia follow a prolonged course, and reoperation may be indicated when tumor masses are detected by imaging and confirmed by FNA. Aggressive cervical reoperation for persistent hypercalcitonemia alone is controversial. Symptomatic hypercalcitonemia is unusual. RAI has no therapeutic role for MTC.

MTC occurs as a component of three familial syndromes: MEN type IIA, MEN type IIB, and familial medullary

thyroid carcinoma (FMTC). MTC associated with MEN type IIB is the most aggressive, followed by MEN type IIA and then FMTC. Hereditary lesions usually are bilateral and are associated with a precursor lesion termed C-cell hyperplasia. MEN type IIA accounts for two thirds of hereditary MTCs. *Ret* proto-oncogene testing is recommended before age 6 within known kindreds. Prophylactic total thyroidectomy and central neck dissection are performed when a *ret* mutation is confirmed, after excluding pheochromocytoma.^{31,32} MTC has an earlier age at onset in MEN type IIB, and genetic screening is conducted shortly after birth. Positive *ret* testing is followed by total thyroidectomy and central neck dissection in the first year of life.³¹ FMTC is defined by the presence of four or more MTC cases within a family in the absence of associated endocrinopathy. The age at onset of FMTC is delayed compared with that of MEN type II, but FMTC survival is optimized by childhood genetic screening and operation (total thyroidectomy and central neck dissection).

Primary Thyroid Lymphoma

Primary thyroid lymphoma (PTL) accounts for approximately 1% of thyroid malignancies and 1% of extranodal lymphomas.^{27,28} The risk of PTL is increased by Hashimoto thyroiditis. FNA is diagnostic in most cases (80%); core-needle or incisional biopsy may be required for diagnosis or for tumor markers. About 75% of PTL are diffuse large B cell lesions and 25% are mucosa-associated lymphoid tissue (MALT) lymphomas, with MALT lesions carrying a better prognosis.¹⁶ Poor prognostic features include size greater than 10 cm, advanced stage, compressive symptoms, mediastinal involvement, and rapid tumor growth. Constitutional symptoms are rare. PTLs are chemo- and radiosensitive, so multiagent chemotherapy is usually combined with external-beam radiation as definitive treatment. Surgery alone may be appropriate for early-stage MALT tumors.^{16,30} If PTL is diagnosed intraoperatively, total thyroidectomy is appropriate.

Metastases

Metastases to the thyroid are rare. Renal cell and breast tumors are common tumors of origin. FNA will suggest metastatic tumor, although perhaps not identify a specific tumor of origin. When the thyroid is the sole site of metastatic disease, thyroidectomy (lobe versus total) may be curative. Palliative resection is seldom, if ever, appropriate. Preoperative evaluation is tailored to the tumor of origin.

Thyroidectomy: Technique, Tips, and Troubleshooting

OPERATIVE TECHNIQUE

Proper Positioning

The first step to a safe thyroidectomy is positioning the patient to optimize operative exposure. A shoulder roll or a sandbag placed between the scapulas allows the neck to be extended and shifted anteriorly. Proper positioning is particularly important in facilitating access to substernal goiters through the cervical approach. Neck extension must be gentle in all patients and should be limited in patients with known cervical disk disease, rheumatoid arthritis, or osteoporosis. The occiput should be stabilized by support with a foam

Table 8 Staging of Medullary and Anaplastic Cancer

Tumor Type	Stage	Tumor	Node	Metastasis
MTC	I	T1	N1	M0
	II	T2–3	N0	M0
	III	T1–3	N1a	M0
	IVA	T4a	N0–1a	M0
	IVB	T1–4a	N1b	M0
	IVC	T4b	Any N	M0
Anaplastic	IVA	T4a	Any N	M0
	IVB	T4b	Any N	M0
	IVC	Any T	Any N	M1

Adapted from Greene FL, editor. AJCC Cancer Staging Manual, Sixth Edition. New York: Springer-Verlag; 2002.
MTC = medullary thyroid cancer.

pillow. Neck hyperextension or poor occipital support can result in significant postoperative muscle spasm and associated headache.

General Technical Principles

The thyroidectomy incision is located in a cosmetically sensitive area, but exposure should not be compromised by an inadequate incision. A larger operative field is generally needed for resections for Graves disease and toxic multinodular goiters, for large nontoxic multinodular goiters producing compression symptoms (particularly those with substernal components), when preoperative evaluation suggests extrathyroidal extension of tumor, and when there is a high likelihood of performing a lymphadenectomy.

Operative complications are best avoided by unhurried dissection in a bloodless field.^{33,34} If encountered, bleeding can and should be controlled first by pressure so that the relationship of the source vessel to the recurrent laryngeal nerve can be clarified. Early identification of the nerve facilitates safe control of vessels. Suture ligatures should be considered for controlling vessel ends that are likely to retract away from the operative field (e.g., cephalad end of the superior thyroid artery at the superior pole, mediastinal end of a thyroidea ima artery). Operating telescopes (2.5 to 3.5 power magnification) are a useful adjunct during delicate dissection around the recurrent nerve and vascular branches supplying parathyroid glands.

When bilateral resection is planned, dissection should nearly always be done first on the side of the suspected tumor or larger goiter. Should a problem be encountered (e.g., parathyroid involvement by tumor or recurrent nerve operative injury), the operative plan can be revised to a subtotal resection on the contralateral side to enhance protection of the parathyroid glands and recurrent nerve on that side. Rarely, when tumors are known or suspected preoperatively to be very extensive, beginning on the “easy” (less abnormal) side may facilitate identification of and access to the trachea and esophagus.

Step 1: Skin Incision and Subplatysmal Flaps

A collar incision paralleling the normal cervical skin lines offers extensile exposure. Typically, the incision is sited about 1 cm caudad to the cricoid cartilage and extends between the sternocleidomastoid muscles [see Figure 2]. Shifting the incision cephalad should be considered when the superior poles are likely to extend significantly upward (e.g., Graves disease) or caudad when a substernal goiter is present. After dividing the platysma, subplatysmal flaps are raised widely in all directions in this bloodless plane, avoiding the anterior jugular veins that may be particularly prominent in patients with Graves disease or substernal goiters.

Tips and troubleshooting Developing the superior flap to 1 to 2 cm above the thyroid cartilage notch will facilitate later access to the superior poles and the pyramidal lobe. Taking the inferior flap until the flat surface of the manubrium is palpable will aid exposure of substernal goiters. A retractor with attachable side-arm blades (e.g., the Mahorner-Hamburger-Brennan) is particularly useful for operations on larger glands but requires a slightly longer skin incision for atraumatic placement into the neck.

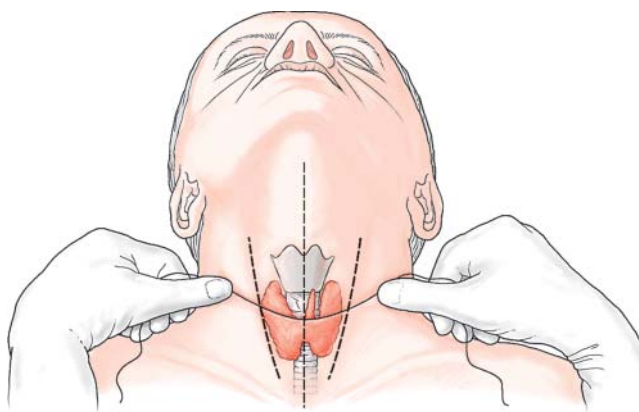


Figure 2 The initial incision in a thyroidectomy is made 1 cm below the cricoid cartilage and follows normal skin lines. A sterile marking pen is used to mark the midline of the neck, the level of the incision, and the lateral borders of the incision. A 2-0 silk tie is pressed against the neck to mark the incision site itself.

Step 2: Mobilization of Strap Muscles

The thyroid gland is exposed by dividing the investing and pretracheal layers of the cervical fascia in the midline. The sternohyoid and sternothyroid muscles can then be elevated as a single unit on each side off the thyroid lobe in what is usually a bloodless plane [see Figure 3]. The dissection is carried laterally until the lateral border of the sternothyroid muscle is easily seen. Partial or complete division of the sternothyroid muscle at its insertion into the thyroid cartilage can significantly improve exposure of the superior pole while avoiding denervation of the muscle. Routine division of both strap muscles is unnecessary in most cases. Once the strap muscle unit is elevated fully, side-arm blades can be inserted and fixed to the self-retracting retractor for lateral retraction of the strap muscles.

In patients operated on to exclude or to treat malignancy, a deliberate pause prior to further dissection is appropriate after the strap muscle unit is fully elevated from the thyroid lobe. The size, location, color, and consistency of the solitary or dominant nodule should be noted, along with the integrity of the overlying thyroid capsule and the presence of fibrosis in or adherence of adjacent soft tissues to the lobe. The characteristics of visible central neck lymph nodes should be assessed.

Tips and troubleshooting The midline fascia should be opened down to the inferior aspect of the sternal notch, where the interclavicular ligament can be palpated, facilitating later mobilization of substernal goiter, identification of inferior parathyroid glands, and central lymphadenectomy.

Tissue attachments or vessels crossing the plane between the thyroid and the midline strap muscles are concerning for malignancy, and any densely adherent portion of strap muscle should be sacrificed and left attached to the underlying thyroid for en bloc resection. This maneuver will also aid the pathologist later in determining extrathyroidal extension of tumor, a finding that is an important predictor of recurrence. Tissue reaction to a preoperative FNA biopsy can simulate tumor adherence. Benign central lymph nodes should be

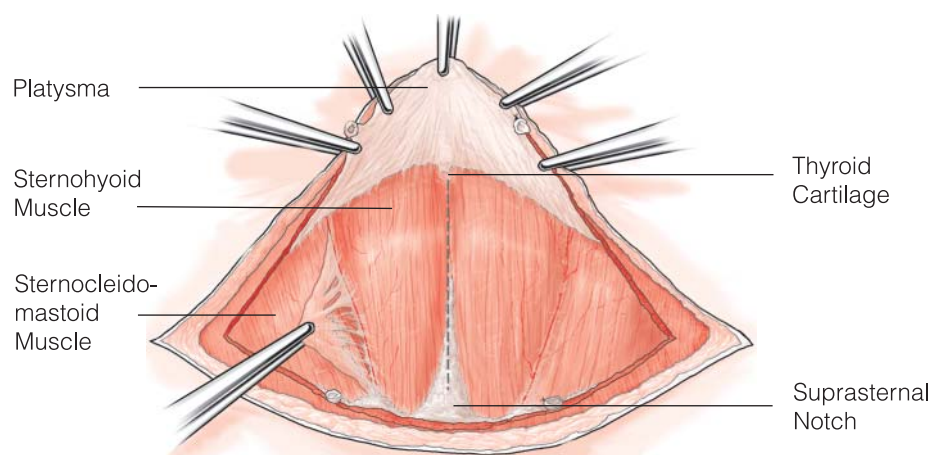


Figure 3 To expose the thyroid, a midline incision is made through the superficial layer of deep cervical fascia between the strap muscles. The incision is begun at the suprasternal notch and extended to the thyroid cartilage.

small, firm but not hard, and mobile and have well-defined capsules; nodes appearing otherwise should be regarded as suspicious, and intraoperative FNA should be considered. Benign lymphadenopathy is most often associated with Graves disease and Hashimoto thyroiditis.

Step 3: Initial Mobilization of the Thyroid Lobe and Superior Parathyroid Gland Identification

SCORE A 2-0 suture is placed deeply through the thyroid lobe for retraction to facilitate exposure. The stitch should not traverse a thyroid nodule as it is more likely to pull loose and may create artifacts that confound later histopathologic interpretation. The lobe is retracted medially while the filmy soft tissue lateral to the lobe is divided close to the gland. Dissection parallel to the usual course of the recurrent laryngeal nerve is safest. The addition of inferior traction facilitates carrying the dissection up to the superior pole. Vessels are controlled and divided near or on the surface of the lobe whenever feasible, limiting risk to the nerve and minimizing the chance of parathyroid devascularization. The superior thyroid artery is best managed by dividing it at the branch level, controlling the individual branches low on the thyroid gland, which minimizes the risk of injury to the external branch of the superior laryngeal nerve [see Figure 4].

Tips and troubleshooting A small sponge applied to the gland surface further facilitates lobar retraction and lessens trauma to the thyroid surface, particularly when the gland is hypervascular (e.g., Graves disease). Palpation of the inferior cornu of the hyoid bone is advisable as the lobe is retracted medially and caudally as a guide to the location of the recurrent nerve, which enters the cricothyroid muscle in close proximity to the cornu. As the lobe is rotated medially and the superior pole branches are divided, the superior parathyroid gland usually is easily seen and should be gently freed from the perithyroidal soft tissue [see Figure 5]. The parathyroid with its adjacent soft tissue and fat is gently swept away from the thyroid.

Step 4: Recurrent Laryngeal Nerve Identification

SCORE It is usually safest to identify the recurrent laryngeal nerve low in the neck and then to follow it to where it enters the

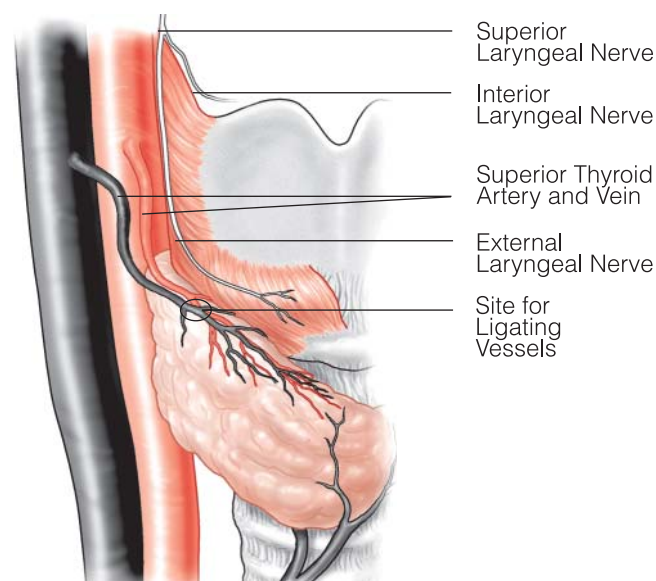


Figure 4 The superior pole vessels should be individually identified and ligated low on the thyroid gland to minimize the chances of injury to the external branch of the superior laryngeal nerve.

cricothyroid muscle through the Berry ligament [see Figure 6]. With the thyroid lobe retracted medially and anteriorly, the nerve is put on stretch and can be palpated as a taut, linear structure (“guitar string”) slightly inferior to the inferior thyroid artery. The filmy soft tissue overlying the nerve can be lifted anteriorly away from the nerve and divided under direct vision, allowing the nerve to be followed to its cricothyroid entry. Sharp, fine-bladed scissors (e.g., tenotomy, Jameson) and fine-tipped hemostats (“mosquito”) are essential instruments for this step. Having looped around the right subclavian artery, the right recurrent nerve follows a more oblique lateral-to-medial course than the left nerve, which follows a straight vertical course somewhat more deeply in the tracheoesophageal groove, having looped around the ductus arteriosus in the mediastinum.

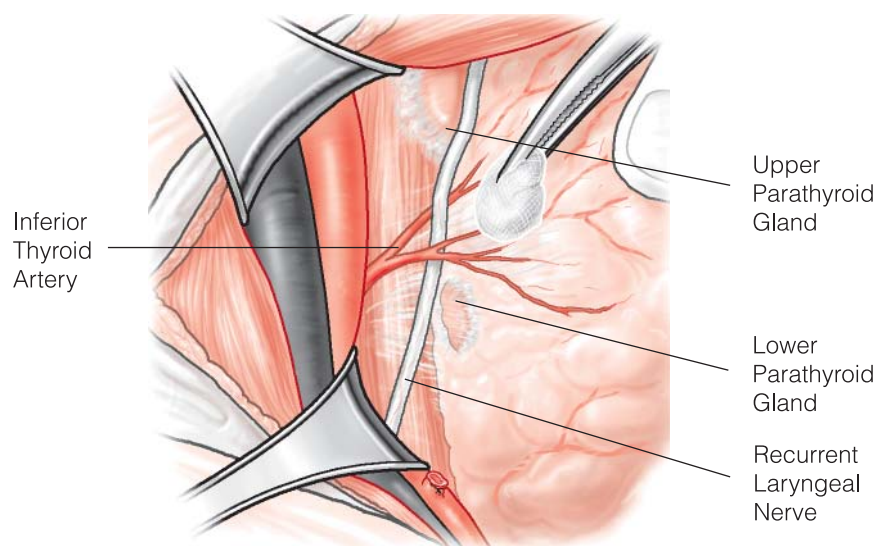


Figure 5 The upper parathyroid glands are usually situated on either side of the thyroid at the level where the recurrent laryngeal nerve enters the cricothyroid muscle. The lower parathyroid glands are usually anterior to the recurrent laryngeal nerve and inferior to where the inferior thyroid artery crosses this nerve.

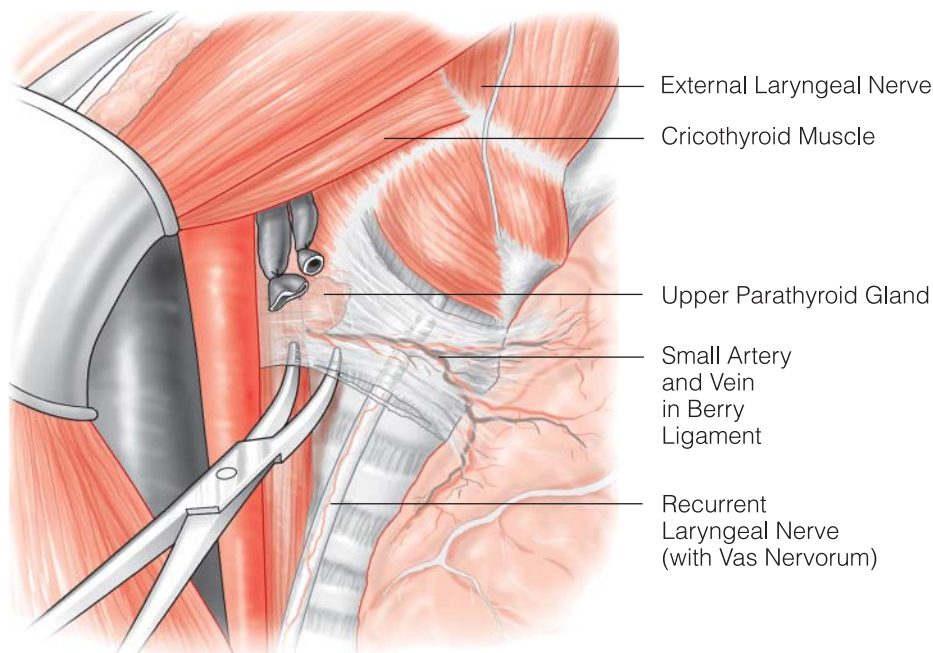


Figure 6 The recurrent laryngeal nerve enters the cricothyroid muscle at the level of the cricoid cartilage, first passing through the Berry ligament.

Tips and troubleshooting In about 0.5% of persons, the right recurrent laryngeal nerve is, in fact, “nonrecurrent,” arising as a direct branch from the vagus in the midneck and coursing toward the thyroid from either laterally or superiorly.¹ Rarely, both a recurrent and a nonrecurrent nerve are present on the right. Branching of the nerve is common on both sides, and all branches must be preserved because all of the motor fibers of the recurrent laryngeal nerve are usually in the most medial branch. Initial identification of the nerve near the level of the inferior thyroid pole rather than

superiorly will usually allow identification of any nerve branches. Some surgeons find intraoperative nerve monitoring to be helpful, but its use is not uniform among endocrine surgeons.³⁵

Step 5: Thyroid Mobilization and Identification of Inferior Parathyroid Glands

Once the course of the recurrent laryngeal nerve has been identified, the lobe can be further rotated medially along its length and around the inferior pole, again controlling vessels



close to the lobar surface. During this dissection, the inferior parathyroid gland is typically seen. Located in a plane anterior to the recurrent nerve, the parathyroid gland often appears attached to the capsule of the inferolateral thyroid pole. The attachment is filmy and easily separated, but care must be taken to avoid injuring the small vessels to the parathyroid.

Tips and troubleshooting Parathyroid glands should be swept from the thyroid gland on as broad a vascular pedicle as possible to prevent devascularization. If the pedicle is injured or if the parathyroid changes from its normal dark mustard color to a dusky purple, a tiny piece of the gland should be sent for frozen section to confirm its identity as parathyroid. Once confirmed, the gland is resected and put on sterile iced slush for autotransplantation into the sternocleidomastoid muscle just prior to closure.

In patients who have invasive tumors or who require reoperation, extensive scarring is often present. It may be preferable to identify the recurrent laryngeal nerve from a superior and medial approach by dividing the isthmus and the superior thyroid vessels. Careful medial to lateral rotation of the thyroid lobe from the trachea allows visualization of the nerve at its most consistent location (i.e., at its entrance into the larynx immediately posterior to the cricothyroid muscle). Alternatively, the nerve can be approached from laterally by identifying the lateral border of the sternothyroid muscle at the level of the inferior thyroid pole and working medially toward the inferior thyroid artery. The approach is modified to maximize dissection through the least scarred plane.

Step 6: Mobilization of the Pyramidal Lobe

A pyramidal lobe is found in about 80% of patients. This embryologic remnant usually arises from the left thyroid lobe near the midline and extends for a variable distance cranially. Inferior traction on the left lobe will bring most if not all of the pyramidal lobe into the operative field. The pyramidal lobe is dissected free medially and laterally from adjacent soft tissue and is transected at its cephalad termination. It is left attached to the main thyroid mass caudally and resected en bloc. As the pyramidal lobe is mobilized, one or more central neck nodes may be encountered overlying the cricothyroid membrane (so-called Delphian nodes) [see Figure 7].

Tips and troubleshooting The pyramidal lobe may extend to the base of the tongue as a thyroglossal duct remnant, but it is often just a fibrotic strand, particularly superior to the hyoid bone. Complete resection of the pyramidal lobe up to the tongue and removal of the middle third of the hyoid bone are important components of the Sistrunk operation for thyroglossal duct cyst. Resection of the pyramidal lobe within the usual thyroidectomy operative field without hyoid excision is sufficient during thyroid resection for other diseases.

Step 7: Completing the Thyroid Resection

Once the lobe has been mobilized superiorly, inferiorly, and laterally, it must be freed from its attachments to the trachea. As the lobe is rolled from lateral to medial, the most challenging part of the dissection involves the thyrotracheal ligament (Berry ligament), connecting the posterior aspect of the lobe to the trachea just caudal to the cricoid cartilage [see Figure 6]. A small branch of the inferior thyroid artery traverses the ligament, as do one or more thyroid veins; controlling bleeding from these vessels risks recurrent nerve injury as the nerve passes through or under the ligament. Should bleeding occur, it should be controlled by applying pressure with a gauze pad, avoiding clamps and ligatures until the course of the nerve through the ligament has been clearly delineated. Irrigating the field to limit blood staining of tissues is helpful. In some patients, a lateral projection of the thyroid (the tubercle of Zuckerkandl) overlies the nerve and ligament. Once the thyrotracheal ligament has been divided, the remaining thyroid attachments to the trachea can be divided through what is usually an avascular plane on the tracheal surface.

Division of the isthmus should be done between clamps and the ends suture ligated. When lobectomy is performed, the point of division should be at the junction of the isthmus with the contralateral lobe that will remain in situ. Division of the isthmus may be done earlier in the dissection when doing so will facilitate thyroid retraction or mobilization.

Tips and troubleshooting If bilateral resection will be performed, the isthmus may be left intact until the contralateral lobe is dissected free and the entire gland delivered as a

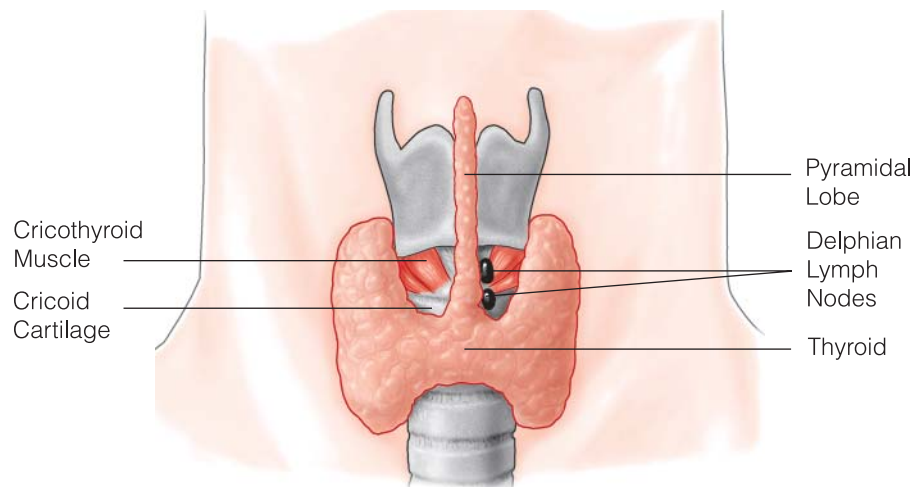


Figure 7 Delphian lymph nodes may be found just cephalad to the isthmus over the cricothyroid membrane.

single specimen The thyroid lobe should be carefully examined after removal. If a parathyroid gland is identified with the specimen, a frozen section biopsy is sent for confirmation and the gland is autotransplanted back into the neck unless the parathyroid appears to be involved by thyroid tumor extension (see above). The resected thyroid should be oriented for the pathologist; marking sutures or clips are helpful for this purpose.

Step 8: Closure

The best strategy to avoid a postoperative neck hematoma is taking time to ensure meticulous hemostasis prior to closure. Thorough irrigation of the field followed by precise identification and control of bleeders should be repeated as necessary until the field is hemostatic and dry throughout. The recurrent nerve should always be reidentified prior to placement of clamps or ligatures. The sternothyroid and sternohyoid muscles are reapproximated as separate layers in the midline. The platysma is closed as a separate layer once the subplatysmal flaps have been released from the self-retaining retractor and verified to be hemostatic. The skin can be closed in several ways, including subcuticular suture, butterfly clips, or tissue adhesive; the key factor in cosmesis is gentle tissue handling, not the closure method.

Smooth emergence from anesthesia with avoidance of coughing and retching can reduce the chance of high pressures being transmitted to the neck veins, and administration of an antiemetic during closure can be helpful, along with spraying the oral cavity with a topical local anesthetic. Endotracheal extubation with the patient still in a relatively “deep” plane of anesthesia is also helpful if not otherwise contraindicated. If postoperative laryngoscopy is contemplated, insertion of a nasal pack containing cocaine or another local anesthetic and decongestant during wound closure will facilitate early flexible fiberoptic endoscopy in the operating room or postanesthesia care unit.

Tips and troubleshooting It is not necessary to reattach a divided sternothyroid muscle to its thyroid cartilage insertion. However, the distal sternothyroid segment should be stretched to full length during closure to allow accurate approximation to the contralateral sternothyroid muscle. When both sternothyroid muscles have been divided superiorly, they can be anchored by including bites of both sternohyoid muscles at the cephalad end of the sternothyroid layer closure.

Drainage of the thyroid bed is no substitute for adequate hemostasis. A drain does not prevent wound hematoma, nor does it provide “early warning” of significant wound hemorrhage. A suction drain placed beneath the midline strap muscle closure may be useful when there is a large dead space in the resected thyroid bed (e.g., after excision of very large goiters). The drain is generally removed on postoperative day 1.

When a subcuticular closure is performed, a patient-friendly wound dressing can be created using a clothlike strip (e.g., roller gauze, Cover Strip II) placed directly over the incision and painted with collodion to render it waterproof. The patient is allowed to shower or wash over the wound beginning on the first postoperative day. The dressing separates from the skin at 7 to 10 days and is easily removed by the patient at that time.

EARLY POSTOPERATIVE CARE

Unilateral Resection (Lobectomy)

Thyroid lobectomy is often accomplished successfully on an outpatient or ambulatory basis, particularly when regional anesthesia is used. Patients with multiple comorbidities or those living in remote areas may be candidates for overnight observation, along with those failing to meet ambulatory surgical unit discharge criteria. The patient is maintained in a gentle head-up position (10° to 20°) for the first 24 hours when nonambulatory to enhance venous drainage and minimize edema formation. After regaining consciousness at a level sufficient to protect the airway, the patient is allowed liquid intake and can be advanced to a regular diet by the following morning. Liberal use of antiemetics during the early postoperative period will minimize retching and emesis. Initial patient-controlled analgesia should be transitioned to oral analgesics as soon as smooth swallowing is observed. Unless there has been neck surgery previously, there is no risk of clinically important hypocalcemia after thyroid lobectomy. It is unnecessary to measure serum calcium levels or to prescribe prophylactic calcium supplementation. The quality of the voice and the adequacy of the airway should be assessed in the postanesthesia care unit and prior to discharge to home. If there is any concern about the integrity of recurrent laryngeal nerve function, flexible fiberoptic laryngoscopy should be performed. Finally, if there is any question of a developing neck hematoma, the patient should be kept hospitalized for airway monitoring. A tray with sufficient instruments to reopen the neck incision urgently is kept at the bedside (e.g., tracheostomy tray).

Bilateral Resection

Patients undergoing bilateral thyroid resections are typically observed overnight or admitted for a brief inpatient stay. Patients undergoing removal of extensive tumors, tracheal or esophageal resections, or lymphadenectomies have longer lengths of stay. Positioning, antiemetics, diet, and patient-controlled analgesia are given as for lobectomy. Severe sore throat may be improved by topical anesthetic spray or solution. **Voice quality and airway adequacy should be assessed in the postanesthesia care unit and periodically thereafter; any concern about the integrity of recurrent laryngeal nerve function should be evaluated promptly with flexible fiberoptic laryngoscopy.** Patients with known coagulation abnormalities or evidence of neck hematoma merit close monitoring in a special care unit for 24 to 48 hours. A tray with sufficient instruments to reopen the neck incision urgently is kept at the bedside (e.g., tracheostomy tray).

Patients undergoing bilateral resections (or completion thyroidectomy after prior lobectomy) are at risk for transient or permanent hypoparathyroidism; the risk is increased with malignancy and by lymphadenectomy. **Strategies for detecting and treating hypocalcemia vary among surgeons.³⁶ Total calcium is more often available and less expensive compared with ionized calcium. In some series, postoperative parathyroid hormone levels are early predictors of hypocalcemia, but parathyroid hormone may not always be available. In the absence of symptoms (perioral tingling, digital paresthesias), there is little reason to measure serum calcium until the morning of postoperative day 1. An exception might be when multiple parathyroid glands have been autotransplanted or when parathyroid tissue is excised deliberately en bloc with**

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tumor. A simultaneous albumin level allows correction of the total calcium level for hemodilution by perioperative fluids; otherwise, ionized calcium alone is the optimal single measurement. An elevated serum phosphate level (> 4.5 mg/dL) denotes an increased risk of parathyroid hypofunction. Magnesium assay is performed when patients are symptomatic because hypomagnesemia can mimic or worsen hypocalcemia. An abnormal calcium value (unexplained by hemodilution) when symptoms are absent merits reassessment in 6 to 8 hours and again on postoperative day 2. Symptomatic patients and those with total calcium values less than 7.5 mg/dL warrant treatment. When symptoms are minimal, oral calcium suffices; calcium citrate is the best absorbed of the calcium salts. Severe symptoms (e.g., dark vision, feelings of doom) or neuromuscular findings (e.g., Trousseau sign or claw hand) merit intravenous calcium; calcium gluconate is the least problematic if extravasated. Calcium is remeasured if treatment is required and reaches a steady state 5 to 6 hours after oral dosing. Vitamin D supplementation is seldom necessary but is useful for patients who have required intravenous calcium or who are marginally controlled by 3 to 4 g calcium citrate total daily doses. 1,25-Dihydroxycholecalciferol is the maximally effective vitamin D agent and is given in one to two doses daily (0.5 to 1.0 μ g total daily dose). Some surgeons use a strategy of routine postoperative oral calcium (1.5 to 3 g daily, with or without vitamin D) for all patients after bilateral resections to facilitate early discharge to home. Serum calcium is measured at the first postoperative visit and weaned as tolerated thereafter.

POSTOPERATIVE THYROID HORMONE MANAGEMENT

The half-life of T_4 is long enough that thyroid hormone replacement can be withheld safely until the final surgical pathology results are available. Awaiting the final diagnosis allows efficient, individualized treatment. Previously euthyroid patients seldom become hypothyroid after lobectomy alone. TFT measurement by the patient's primary care physician at 6 months (sooner if hypothyroid symptoms develop) will detect most patients who need T_4 supplementation. Older patients and those with Hashimoto disease are at greatest risk.

Patients will require T_4 therapy after bilateral resections. For patients with benign disease, levothyroxine can be started as soon as the pathology results are known. For patients with cancer, a decision for or against RAI will guide next steps.

When RAI will be given, efficient preparation with minimal hypothyroid symptoms is accomplished by giving low-dose T_3 (50 μ g b.i.d.) for 3 weeks. One week thereafter, most patients will have a TSH level suitable for RAI administration. Alternatively, patients may be given no thyroid hormone for the 4 weeks prior to RAI administration, but this approach more often results in bothersome symptoms. Patients can also reach appropriately high TSH levels by administration of recombinant human TSH for a brief period prior to giving RAI; this option, however, is very expensive, and the efficacy of RAI using this approach is not conclusively known. A baseline Tg level is most sensitive for the detection of residual thyroid tissue and/or residual WDTC when measured while the patient is thyroprival (TSH is elevated). Anti-Tg antibody assay should be measured along with each Tg level; Tg is unreliable when antibodies are present.

Regardless of the RAI preparation approach chosen, T_4 is started after RAI treatment and/or whole body scan.

Replacement, achieving a TSH level within the normal range, is the treatment goal for patients with benign diagnoses. For patients with WDTC, suppression such that TSH is undetectable is the therapeutic target. Lower T_4 doses (less suppression) should be considered for older patients, those with cardiac disease, when osteoporosis risks are increased, or when clinically important hyperthyroid symptoms develop on full suppression. Some clinicians favor full suppression for the first few years postoperatively and then T_4 dose reduction to replacement levels if there is no evidence of recurrent WDTC. A steady-state TSH level is reached at 4 to 6 weeks after starting T_4 or after a dose adjustment.

Patients with MTC, ATC, or lymphoma are started on replacement doses of T_4 postoperatively because there is no proven benefit to TSH suppression in these diseases.

COMPLICATIONS

Thyroidectomy is well tolerated by most patients. General postoperative complications such as atelectasis and deep vein thrombosis or pulmonary embolism are possible but less common than after intracavitary operations. Thyroidectomy is a clean operation, and wound infection should be rare. If wound infection occurs, however, it is potentially quite serious. Infection-related soft tissue edema can lead to airway compromise, and local infection can progress to mediastinitis since the soft tissues of the thoracic inlet are usually opened during thyroidectomy. Thyroidectomy should be postponed if a patient arrives for operation with a recent history or current symptoms of acute pharyngitis.

Complications specific to thyroidectomy include neck hematoma or seroma, recurrent or external laryngeal nerve injury, and transient or permanent hypoparathyroidism. Postoperative bleeding into the neck can produce life-threatening airway compromise, and any postoperative respiratory distress should raise concern for neck hematoma. Urgent bedside decompression by reopening the wound down through the strap muscles is lifesaving when symptoms are sudden and severe. The patient is then returned to the operating room for wound exploration and reclosure under anesthesia. Neck hematoma development with few or no symptoms merits intensive care unit observation for at least 24 hours. Most bleeding occurs within 4 hours of operation, and virtually all occurs within 24 hours. Neck seroma is particularly likely after resection of very large goiters because of the residual dead space, and subplatysmal fluid is ballotable early postoperatively. In the absence of airway symptoms or persistent dysphagia, reassurance of the patient is the only intervention necessary. Percutaneous aspiration is performed for airway or swallowing symptoms or when preferred by the patient for cosmetic or comfort reasons.

Symptoms or signs of airway compromise not attributable to neck hematoma may indicate injury to the recurrent laryngeal nerves. Prompt performance of flexible fiberoptic laryngoscopy allows assessment of vocal cord position and function along with evaluation for other etiologies of respiratory distress (laryngeal edema, laryngospasm). Diagnostic laryngoscopy should not delay securing the airway of a patient with true stridor. Laryngoscopy may, however, be a useful adjunct to rapid, safe reintubation. Paretic or paralyzed vocal cords warrant reintubation. Symptomatic patients who are maintaining their oxygenation without tachypnea may benefit from inhaling a helium-oxygen admixture. The clinical

response is rapid, and the admixture should be continued for several hours before attempting weaning to supplemental oxygen alone.

The reintubated patient should be kept in a head-up position for 36 to 48 hours. A parenteral dexamethasone bolus may be useful at the time of reintubation and carries little risk. Once the patient has mobilized his perioperative fluids and has minimal neck edema (usually by 48 hours postoperatively), airway reassessment can be undertaken. The patient who can vocalize and move air through the larynx with the endotracheal tube in place but with the cuff deflated is likely to tolerate extubation. Flexible laryngoscopy should be done immediately postextubation to document vocal cord function and adequate airway lumen. Close observation for an additional 24 to 48 hours is appropriate after successful extubation. For the patient failing extubation, laryngoscopic findings should drive the decision for early tracheostomy or for a second extubation attempt. Vocal cord function sufficient to maintain the airway must be documented before tracheal decannulation.

Some hoarseness or other vocal change is fairly common early postoperatively and can represent intubation trauma rather than recurrent nerve injury. Intubation-related vocal changes improve rapidly postoperatively. Hoarseness that persists at the first outpatient office visit deserves diagnostic laryngoscopy. If vocal cord motion is impaired, consideration should be given to confirmation by a second, independent observer. Voice rest and aspiration precautions should be instituted, and the patient is followed carefully. When symptoms resolve or plateau, laryngoscopy is repeated to document the level of functional return. Interventions such as vocal cord injection are not undertaken until function has

clearly stabilized. Nerve dysfunction at 1 year is likely to be permanent.

Superior laryngeal nerve external branch dysfunction typically is more subtle than recurrent nerve injury, and injury rates are not as well established. Referral for comprehensive evaluation of vocal function is appropriate for persistent voice symptoms despite good vocal cord movement or for patients whose livelihoods require normal voices (e.g., a professional singer or storyteller). The impact of routine intraoperative nerve monitoring on recurrent and external branch nerve injury rates is unclear.

Permanent hypoparathyroidism (requirement for calcium supplementation more than 1 year postoperatively) should be uncommon (< 2%) after bilateral thyroid resections. Up to 10% of patients may have transient hypocalcemia that requires treatment, especially with Graves disease or synchronous lymphadenectomy. Resolution is usually fairly rapid (< 6 weeks). Autotransplanted parathyroid tissue is usually functional within 12 weeks postoperatively. Diagnosis and management of hypocalcemia have already been discussed [see Early Postoperative Care, Bilateral Resections, above].

OUTCOME EVALUATION

Surgeons performing thyroidectomies should track their individual rates of nerve and parathyroid injuries along with wound infections and neck hematomas. Participation in a registry system such as the National Surgical Quality Improvement Program (NSQIP) facilitates recognition of nonspecific complications (e.g., urinary tract infection) and system parameters (e.g., length of stay).

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10 PARATHYROID DISEASES AND OPERATIONS

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Anatomy/Embryology



The parathyroid glands arise during the fourth and fifth weeks of gestation from branchial pouches III and IV. The superior glands descend into the neck from branchial pouch IV, whereas the inferior glands descend into the neck from branchial pouch III. In general, the superior glands settle 1 cm superior to the inferior thyroid artery in a posterior position to the thyroid gland, and the inferior glands settle at the lower pole of the thyroid gland in a posterolateral position. The superior and inferior parathyroids are consistently located posterior and anterior to the recurrent laryngeal nerve, respectively.

The parathyroid glands can be found in ectopic locations. Approximately 60% of parathyroids on reoperation are not located in the typical locations. The inferior glands have a higher propensity for this in comparison with the upper glands. Common ectopic locations of the inferior glands at reoperation include the thymus (46%), within the thyroid itself (7%), undescended (4%), and the carotid sheath (1%). Common ectopic locations of the superior glands include the posterior superior mediastinum (40%), the tracheoesophageal groove (17%), within the thyroid (1.5%), and the carotid sheath (1.5%). Of note, the posterior and anterior relation to the recurrent laryngeal nerve is typically preserved in superior and inferior ectopic glands, respectively.

Most commonly, there are four parathyroid glands; however, the incidence of supernumerary glands is around 13%. All four glands derive their blood supply from the inferior thyroid artery. Venous drainage is by the venous network of the thyroid capsule and/or venous pedicles of the thyroid body. The glands are often found embedded in fat. When dissected, normal parathyroid glands have a flat triangular shape with a mustard hue whereas pathologic parathyroids are plump with a reddish-brown hue resembling a grape.

The recurrent laryngeal nerves innervate all intrinsic muscles of the larynx except the cricothyroid muscles. These nerves arise from the vagus nerves in the chest and travel upward on either side of the trachea through the tracheoesophageal groove. They usually cross posterior to the inferior thyroid arteries but can pass anteriorly. They will then cross posterior to or through the Berry ligament to insert into the cricothyroid muscles. Caution should be taken when dissecting this area as the nerve may branch into an anterior motor branch and a posterior sensory branch. One can easily mistake a posterior sensory branch as the only branch and ligate the motor branch causing ipsilateral vocal cord paralysis.

Function

The primary function of the parathyroid glands is to maintain calcium homeostasis within the body. Calcium concentrations in the serum are directly regulated by a sensitive calcium-sensing receptor that is highly expressed on the surface of the parathyroid cells. When ionized calcium is bound within this receptor, release of parathyroid hormone (PTH) is inhibited. In contrast, when ionized calcium levels are low, fewer receptors are bound, and production of PTH is stimulated. PTH is an 84-amino acid protein with multiple effects on calcium homeostasis. PTH increases osteoclast and osteoblast activity, leading to the net release of calcium from bone stores as clastic activity is more affected than blastic activity. Furthermore, PTH increases gastrointestinal absorption and renal calcium retention, primarily in the proximal tubule and the loop of Henle. Lastly, PTH increases renal hydroxylation of 25-hydroxyvitamin D. In addition to increasing serum calcium, PTH also decreases serum phosphate and increases renal bicarbonate excretion.

Dysfunction

Primary hyperparathyroidism (PHPT) results from the inappropriately high secretion of PTH causing hypercalcemia. This is thought to be caused by the spontaneous loss of calcium-sensing receptors in parathyroid tissue. This may be caused by dysfunction in one or multiple parathyroid glands. Approximately 90% of PHPT is caused by adenomas, which can be multiple in approximately 3 to 8% of cases. In contrast, 9% of PHPT is attributable to four-gland hyperplasia and approximately 1% is the result of parathyroid carcinoma. As much as 3% of PHPT is associated with the multiple endocrine neoplasia (MEN) syndromes. PHPT is not caused by renal disease, a history of lithium use, or gastrointestinal malabsorptive syndromes.

Although PHPT has traditionally been considered to manifest itself by hypercalcemia in the setting of excessive PTH secretion, a less common manifestation of PHPT that has only minimal, intermittent, or even the absence of hypercalcemia is now being recognized. As many as 15% of patients with PHPT will have "normocalcemic hyperparathyroidism." As noted, these patients will have elevated PTH levels but will not have persistently elevated calcium levels. In fact, some may have calcium levels that are consistently within a normal range. They will still exhibit, however, the destructive complications of PHPT. Because one cannot use hypercalcemia as a diagnostic tool for this entity, diagnosis is difficult. Typically, PTH levels are inappropriately elevated in the



presence of PHPT complications. Vitamin D deficiency and benign familial hypocalciuric hypercalcemia should be excluded prior to the diagnosis. Additionally, evidence suggests that calcium-loading challenges may assist in identifying these patients. In most normal patients, an oral calcium load has been shown to suppress serum PTH levels by 70% or more, whereas in patients with normocalcemic PHPT, this is usually not the case. Nonetheless, this is not a perfect test and cannot be used alone to identify these patients.

Secondary hyperparathyroidism (SHPT) occurs from the physiologic response to low serum calcium levels of nonparathyroid origin. Although the pathophysiology of SHPT is complex, it is most commonly caused by chronic renal failure, which interferes with vitamin D metabolism, which in turn leads to decreased calcium absorption from nutritional sources. Other causes include “hungry bone syndrome,” sprue, chronic vitamin D deficiency, and aluminum toxicity from hemodialysis. Generally, hypercalcemia is not a characteristic of this disease.

Tertiary hyperparathyroidism (THPT) is the long-term consequence of prolonged SHPT after the cause is corrected. It results in autonomously elevated PTH concentrations as a result of the loss of calcium-sensing receptors in parathyroid tissue. The net result of THPT is elevated serum calcium. The typical scenario is the patient with SHPT attributable to end-stage renal disease who undergoes renal transplantation. In this condition, all four glands are treated as hyperplastic glands.

Parathyroid carcinoma is a very rare cause of hyperparathyroidism. It often results in markedly elevated levels of both PTH and calcium. Complications of hyperparathyroidism are more common with parathyroid carcinoma. The incidence of kidney stones is over 50%, whereas severe bone disease is observed in as many as 90% of patients. These lesions are more likely palpable than benign hypersecreting glands, and on gross inspection, they exhibit invasive features. Histologically, parathyroid carcinoma shows features of capsular and vascular invasion, cellular mitoses, thick fibrous bands separating tumor lobules, and a trabecular pattern. Of course, the hallmark of parathyroid carcinoma is its invasive nature. Thirty percent of patients will have nodal metastases on presentation, and the 5-year survival rate approximates 60% with treatment. Posttreatment, recurrent hypercalcemia is a good marker for local recurrence or new metastases.

Complications of Hypercalcemia

 The normal serum calcium level is 9 to 10.5 mg/dL. Dysregulation of calcium homeostasis has profound effects on patient well-being. On questioning, patients often complain of a general sense of poor physical performance. This includes symptoms of depression, fatigue, muscle weakness, cognitive deficits, and forgetfulness. In addition, patients may present with gastrointestinal complaints, particularly constipation and gastroesophageal reflux.

More seriously, 30% of patients with PHPT will develop nephrolithiasis and 15% of patients will develop osteoporosis. Occasionally, patients can develop severe osteodystrophy, resulting in bone pain, osteomalacia, pathologic fractures, and osteitis fibrosa cystica (brown tumors of bone).

Interestingly, there is now a growing literature implicating hyperparathyroidism in atherosclerotic disease. Evidence for

this includes studies showing increased blood pressure, arterial stiffness, and intima/media thickness in patients with PHPT as well as derangements in a number of metabolic processes leading to the development of cardiovascular disease, including dyslipidemia and impaired glucose metabolism. In fact, cardiovascular complications are the most common cause of death in both treated and untreated patients with PHPT. Estimates of mortality resulting from cardiovascular disease in patients with PHPT range from 53 to 68%. This includes death from myocardial infarction, stroke, and heart failure. Epidemiologic studies suggest that the life expectancy in patients with PHPT is lower than that in matched controls.

Evaluation of Primary Hyperparathyroidism

Although often unrevealing, a thorough history and physical examination should be performed. This may reveal symptoms or complications of hyperparathyroidism that may need to be addressed. Additionally, the information obtained may reveal the need to evaluate patients for familial causes of hyperparathyroidism, particularly the MEN syndromes. Physical examination may reveal a palpable neck mass that may alert the surgeon to the possibility of malignancy. Physical examination findings in chronic PHPT include band keratopathy and intraoral tumors.

Laboratory workup should include serum calcium and PTH levels and 24-hour urinary calcium levels to rule out familial hypocalciuric hypercalcemia. As noted earlier, patients with PHPT typically have elevated serum PTH and serum calcium levels but PTH may fluctuate and near normocalcemic variants have been reported. In these patients, one will see a persistently elevated (as opposed to suppressed) PTH level despite near normal serum calcium or high normal serum calcium levels. Patients with PHPT may have normal but often have high 24-hour urinary calcium levels as the kidneys surpass their threshold for calcium resorption. Patients with benign familial hypocalciuric hypercalcemia will have low 24-hour urinary calcium levels. Additionally, patients with familial hypocalciuric hypercalcemia generally have mildly elevated serum calcium levels. Benign familial hypocalciuric hypercalcemia can be excluded in patients with a history of normal serum calcium levels in the distant past. Hyperparathyroid patients are typically hypophosphatemic, and alkaline phosphatase may predict high-turnover bone disease. 25-Hydroxyvitamin D should be checked to exclude vitamin D deficiency.

Localization studies have improved dramatically over recent years, allowing for progressively fewer invasive surgical options. Because 80% of patients with PHPT have a single adenoma, preoperative localization studies allow far less extensive neck dissection. The mainstays of localization studies are ultrasonography and sestamibi scanning. Ultrasonography has a sensitivity of 79%. Sestamibi scanning has a sensitivity of 88%. When these two modalities are combined, sensitivity increases to greater than 90%. Sestamibi scanning works on the premise that both thyroid and parathyroid absorb tracer but that, as a result of increased blood flow in the thyroid, thyroid tracer washes out more quickly (minutes to 2 hours), allowing for visualization of enlarged parathyroid

glands. When comparing early and delayed sestamibi images persistent uptake may be seen in the delayed images at the location of pathologic parathyroid glands. Occasionally, these imaging modalities are insufficient. The advent of four-dimensional computed tomographic (CT) scanning has allowed for the localization of many allusive parathyroid glands. Other options include venous PTH sampling. Although localization studies are useful for surgical planning, they should not be used to establish the biochemical diagnosis.

Treatment

Treatment algorithms depend on the pathology causing hyperparathyroidism. In general, PHPT is treated surgically with removal of all hyperfunctioning parathyroid tissue. There is agreement that all symptomatic disease should be treated surgically. However, the indications for the treatment of asymptomatic disease are less clear-cut. These indications receive a great deal of scrutiny and are periodically revised by National Institutes of Health consensus conferences in response to evolving data. Currently, surgery is recommended for asymptomatic patients with serum calcium levels 1.0 mg/dL above the upper limit of normal, a glomerular filtration rate less than 60 mL/min, T scores less than -2.5 at any site and/or previous fracture fragility, or age less than 50 years. T score refers to the number of standard deviations above or below the normal bone mineral density a person's own bone mineral density is. Normal is defined by a T score above -1. Osteopenia is defined by a T score between -1 and -2.5. Osteoporosis is defined by a T score less than -2.5. It is expected that these criteria for surgery in the asymptomatic patient may be further revised as new data elucidate other complications of hyperparathyroidism, particularly atherosclerotic disease.

For individuals who cannot undergo surgery, patients with persistent hyperparathyroidism in which hyperfunctioning tissue cannot be found, and patients with hypercalcemic crisis, a number of medical therapies may improve hypercalcemia. These include hydration with normal saline, loop diuretics, bisphosphonates, calcitonin, mithramycin, and calcium receptor agonists. SHPT generally is not considered a surgical disease. Instead, these patients are treated with calcimimetics, calcium, and vitamin D replacement. Rarely, with failure of medical management, surgery may be considered. In this case, indications for surgery may include severe pruritis, musculoskeletal pain, renal osteodystrophy, and calciphylaxis.

Tertiary hyperthyroidism is primarily a surgical disease. Because all parathyroid tissue is hyperfunctioning in these patients, the preferred operation is four-gland parathyroidectomy with autotransplantation of half of a single gland or subtotal parathyroidectomy. In the latter case, a parathyroid remnant roughly the size of a normal parathyroid gland is left in situ.

Parathyroid carcinoma absolutely requires surgery if cure is to be achieved. In this case, the operation of choice is en bloc resection of the malignant parathyroid tumor with the overlying musculature and ipsilateral thyroid lobe. Additionally, local recurrences and localized distant metastases should be treated surgically. Systemic chemotherapy and radiation have

minimal efficacy and are considered palliative interventions in this context.

Surgical Technique

OPERATIVE PLANNING

Patients with profound hypercalcemia (serum calcium ≥ 12.5 mg/dL) or mild to moderate renal failure should be hydrated and given furosemide before operation. On rare occasions, such patients require additional treatment—for example, administration of bisphosphonates, mithramycin, or calcitonin. Bisphosphonates should be used with caution as they can exacerbate postoperative hypocalcemia. Electrolyte abnormalities, such as hypokalemia, should also be corrected prior to this elective surgery. Optimally, patients should have any anticoagulation held perioperatively and should be deemed safe from a cardiopulmonary standpoint for anesthesia.

We recommend either bilateral exploration or focused exploration with intraoperative PTH assay for most patients undergoing initial operations for primary sporadic hyperparathyroidism. The latter approach can be taken only when the abnormal gland has been identified by sestamibi scanning and/or ultrasonography. For patients with familial primary or secondary hyperparathyroidism, bilateral exploration is recommended because most of these patients have multiple abnormal parathyroid glands.

Other preoperative localization studies (e.g., magnetic resonance imaging [MRI] and CT scanning) are generally unnecessary: they provide useful information in about 75% of patients but are often not considered cost-effective, because an experienced surgeon can treat hyperparathyroidism successfully without imaging 95 to 98% of the time. Such studies are, however, essential when reoperation for persistent or recurrent hyperparathyroidism is indicated. High-resolution, four-dimensional CT scanning is particularly useful for patients in this setting. Patients requiring reoperation should be considered for direct or indirect laryngoscopy before operation to evaluate vocal cord function.

Optimum exposure of the parathyroid glands is facilitated by placing a soft roll transversely across the scapula and a support under the occiput; in this way, the neck is gently extended and the thyroid or parathyroids can assume a more anterior position. This positioning also facilitates identification of the recurrent laryngeal nerve by placing it under slight tension. The head must be supported to prevent postoperative posterior neck pain. Care also is taken to ensure that no body parts are exposed to undue pressure. The skin is prepared with betadine or chlorhexidine.

OPERATIVE TECHNIQUE

General Troubleshooting

Safe parathyroid operations require good visualization of central neck structures. Therefore, the field should be bloodless and well illuminated, preferably with the use of a headlamp. Operating telescopes ($\times 2.5$ or $\times 3.5$ magnification) are also recommended because the recurrent laryngeal nerve can be difficult for some to visualize without magnification. If bleeding occurs, surgeons should avoid grasping or clamping a poorly visualized vessel. A bleeding vessel should be clamped only after it is precisely identified and inclusion

of the recurrent laryngeal nerve is excluded. Preoperative localization studies should be available in the operating room to guide the dissection.

Step 1: Incision and Mobilization of Skin Layers

A transverse incision paralleling the normal skin lines of the neck is made approximately 1 cm caudad to the cricoid cartilage [see Figure 1]. Preferably, this incision can be placed completely within a skin crease. Such creases can be marked in the preoperative setting with the patient sitting upright with a neutral neck position. As a rule, the incision should be about 4 to 6 cm long and should extend from the anterior border of one sternocleidomastoid muscle to the anterior border of the other. Either sharp dissection or electrocautery can be used to dissect through the subcutaneous layer and platysma muscle. Straight Kelly or small Kocher clamps are placed on the dermis for retraction, which facilitates the creation of flaps in the avascular plane located just deep to the platysmal muscle and anterior to the anterior jugular veins and their branches. These subplatysmal flaps are made in the cephalad direction up to the level of the thyroid cartilage notch and caudally down to the suprasternal notch. Self-retaining retractors are then applied.

Troubleshooting Placing the incision approximately 1 cm below the cricoid locates it precisely over the thyroid isthmus. The course of the incision should conform to or overlay the natural skin creases. The length of the incision should be modified as necessary for good exposure. Patients with short, thick necks or large, low-lying tumors require longer incisions. The lateral margins of the incision should be at equal distances from the midline, and the overall shape of the incision should be symmetrical. Flaps must be created using anterior traction and taking care not to perforate the skin.

Step 2: Midline Dissection and Mobilization of Strap Muscles and Thyroid

The thyroid gland is exposed via a longitudinal midline incision through the deep cervical fascia between the strap

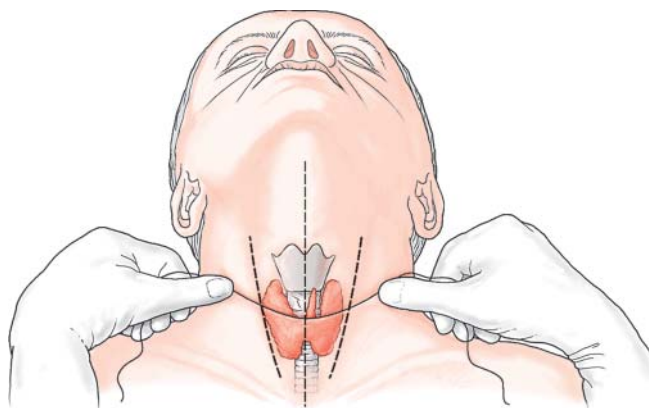


Figure 1 The initial incision is made 1 cm below the cricoid cartilage and follows normal skin lines. A sterile marking pen is used to mark the midline of the neck, the level of the incision, and the lateral borders of the incision. A 2-0 silk tie is pressed against the neck to mark the incision site itself.

muscles. Because the strap muscles are farthest apart low in the neck, the incision is begun at the sternal notch and extended upward to the thyroid cartilage [see Figure 2].

On the side where the suspected parathyroid adenoma is located, the more superficial sternohyoid muscle is separated from the underlying sternothyroid muscle by blunt dissection using a Kitner sponge. This typically does not cause bleeding and should extend posterolaterally until the ansa cervicalis becomes visible on the lateral edge of the sternothyroid muscle and on the medial side of the internal jugular vein. The sternothyroid muscle is then dissected free from the thyroid and the prethyroidal fascia with electrocautery until the middle thyroid vein or veins are encountered laterally.

The thyroid is retracted anteriorly and medially and the carotid sheath laterally; this retraction places tension on the middle thyroid veins and helps expose the area posterolateral to the thyroid, where the parathyroid glands and the recurrent laryngeal nerves are situated. The middle thyroid veins are ligated with sutures or with a hemostatic device to mobilize the thyroid and provide exposure behind the superior portion of the thyroid lobe [see Figure 3].

Troubleshooting Separation of the sternohyoid muscle from the sternothyroid muscle improves exposure of the operative field and does not worsen postoperative morbidity. The middle thyroid veins should be dissected free to prevent injury to the recurrent laryngeal nerve prior to their ligation. It is always safest to mobilize tissues parallel to the recurrent laryngeal nerve rather than transversely across its anticipated course. If the exposure is so limited that the strap muscles have to be divided, this should be done horizontally and high enough in the neck to preserve innervation to the bulk of the muscles. These muscles can be closed with interrupted figure-of-eight 2-0 absorbable sutures, holding the muscle apposed as the sutures are taken to prevent shredding. The neck can be gently flexed or held in a neutral position at this late stage of the operation to facilitate muscle approximation.

Step 3: Identification of Upper Parathyroid Glands

Dissection is continued superiorly, laterally, and posteriorly with a small Kitner sponge on a clamp. This maneuver can be performed with minimal bleeding when done gently. The superior thyroid artery and veins are identified by retracting the thyroid inferiorly and medially. The tissues posterolateral to the upper lobe of the thyroid and medial to the carotid sheath can be mobilized caudally to the cricothyroid muscle; the recurrent laryngeal nerve enters the larynx just posterior to the Berry ligament at this craniocaudal level [see Figure 4]. Berry ligament refers to the lateral ligament suspending the thyroid to the trachea. It is attached to the inferior margin of the cricoid cartilage cornu and extends inferomedially onto the trachea. At the level of the cricoid cartilage, the mean distance between the attachment of the ligament to the cricoid cartilage and the recurrent laryngeal nerve is 1.9 mm. This is the most common location of recurrent laryngeal nerve injury. Caution should be taken when dissecting caudal to the cricoid cartilage in this region, where the recurrent nerve can be encountered.

The tissues posterior and lateral to the superior pole can be easily swept by blunt dissection away from the thyroid gland medially and anteriorly and away from the carotid sheath

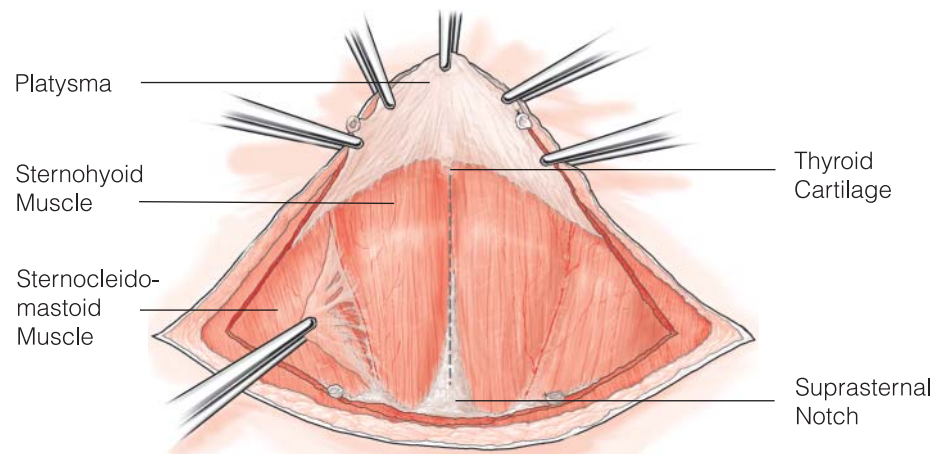


Figure 2 To expose the thyroid, a midline incision is made through the superficial layer of deep cervical fascia between the strap muscles. The incision is begun at the suprasternal notch and extended to the thyroid cartilage.

laterally. The upper parathyroid gland is often identified at this time near the level of the cricoid cartilage situated posterior to the recurrent laryngeal nerve.

Step 4: Identification of Recurrent Laryngeal Nerves and Lower Parathyroid Glands



When the thyroid lobe is further mobilized and retracted anteromedially, the lower parathyroid gland is often found anterior to the recurrent laryngeal nerve and inferior to where the inferior thyroid artery crosses the recurrent laryngeal nerve [see Figure 5]. The carotid sheath is gently retracted laterally, and the thyroid gland is retracted anteriorly and medially. This retraction puts tension on the inferior thyroid artery and consequently on the recurrent laryngeal nerve, thereby facilitating the identification of the nerve. The recurrent laryngeal nerve is situated more medially on the left in

the tracheoesophageal groove and more obliquely on the right. As such, it can be more susceptible to accidental injury on the right side. Dissection should proceed cephalad along the lateral edge of the thyroid. Fatty and lymphatic tissues loosely attached to the thyroid capsule are swept from it with a Kitner sponge on a clamp, and small vessels are ligated. No tissue should be transected until one is sure that it is not the recurrent laryngeal nerve. Some find it helpful to use a nerve monitoring device for this portion of the dissection.

Troubleshooting The upper parathyroid glands are usually situated on each side of the thyroid gland just posterolateral to where the recurrent laryngeal nerves enter the cricothyroid muscle [see Figure 4 and Figure 5]. Because the recurrent laryngeal nerve enters the larynx posterior to the cricothyroid muscle at the level of the cricoid cartilage, caution should be taken when dissecting caudal to this area.

The right and left recurrent laryngeal nerves should be preserved during every parathyroid operation. Although both nerves enter at the posterior medial position of the larynx in the cricothyroid muscle, their courses vary considerably. The right recurrent laryngeal nerve takes a more oblique course than the left recurrent laryngeal nerve and may pass either anterior or posterior to the inferior thyroid artery. In about 0.5% of persons, the right recurrent laryngeal nerve is non-recurrent and may enter the thyroid from a superior or lateral direction. On rare occasions, both a recurrent and a non-recurrent laryngeal nerve may be present on the right. The left recurrent laryngeal nerve almost always runs in the tracheoesophageal groove because of its deeper origin within the thorax as it loops around the ductus arteriosus. Recurrent laryngeal nerves often branch before entering the larynx; the left nerve is more likely to do this. Although all nerve branches should be preserved, the motor fibers of the recurrent laryngeal nerve are usually in the most medial branch.

It is helpful to remember that the recurrent laryngeal nerves are supplied by a small vascular plexus and that a tiny vessel runs parallel to and directly on each nerve, which contrasts with the white color of the nerve [see Figure 4]. In young persons, the artery usually is readily distinguished from the recurrent laryngeal nerve. However, in older persons with

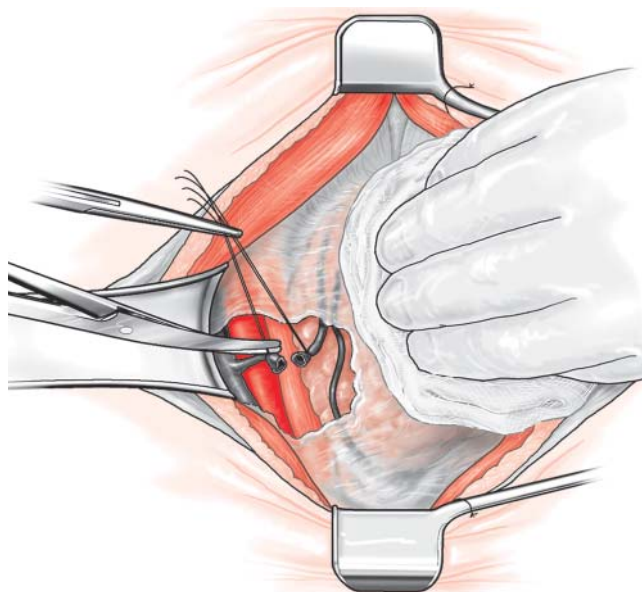


Figure 3 The middle thyroid veins are divided to give better exposure behind the superior portion of the thyroid lobe.

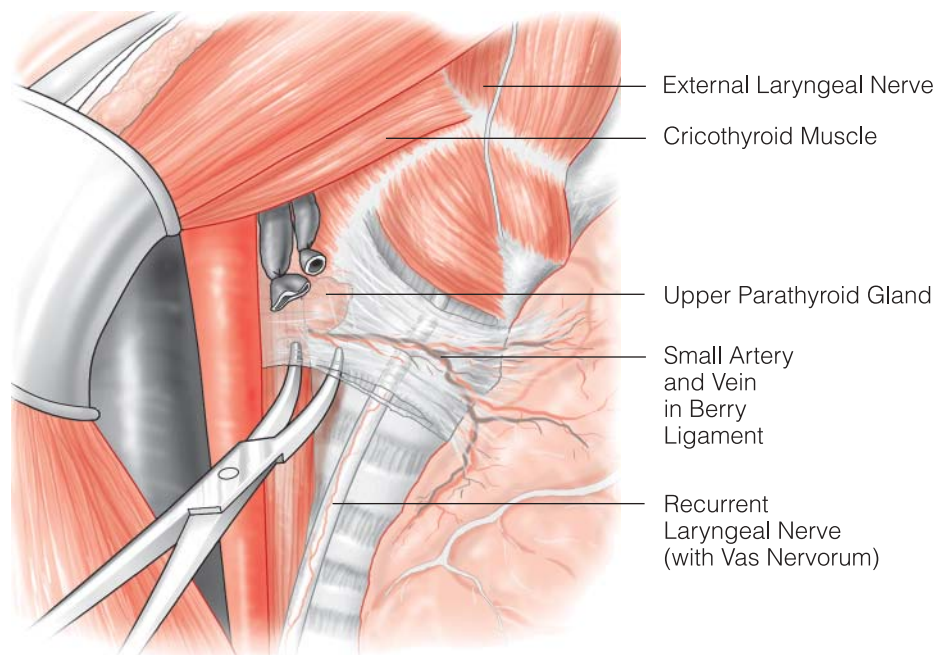


Figure 4 The recurrent laryngeal nerve enters the cricothyroid muscle at the level of the cricoid cartilage, first passing through the Berry ligament.

arteriosclerosis, the white-appearing artery may be mistaken for the nerve, and caution should be taken. Lateral traction on the carotid sheath and medial and anterior traction on the thyroid gland place tension on the inferior thyroid artery; this maneuver often helps identify the recurrent laryngeal nerve where it courses lateral to the midportion of the thyroid gland. It is usually safest to identify the recurrent laryngeal nerve low in the neck and then to follow it to where it enters the cricothyroid muscle through the Berry ligament. Sometimes the recurrent laryngeal nerves can be palpated through

the surrounding tissue in the neck; they feel like a taut ligature of approximately 2-0 gauge.

About 85% of people have four parathyroid glands, and in about 85% of these persons, the parathyroids are situated on the posterior lateral capsule of the thyroid. Normal parathyroid glands measure about $3 \times 3 \times 4$ mm and are light brown in color. The upper parathyroid glands are more posterior and more constant in position (at the level of the cricoid cartilage) than the lower parathyroid glands, which typically are more anterior (on the posterolateral surface of the thyroid

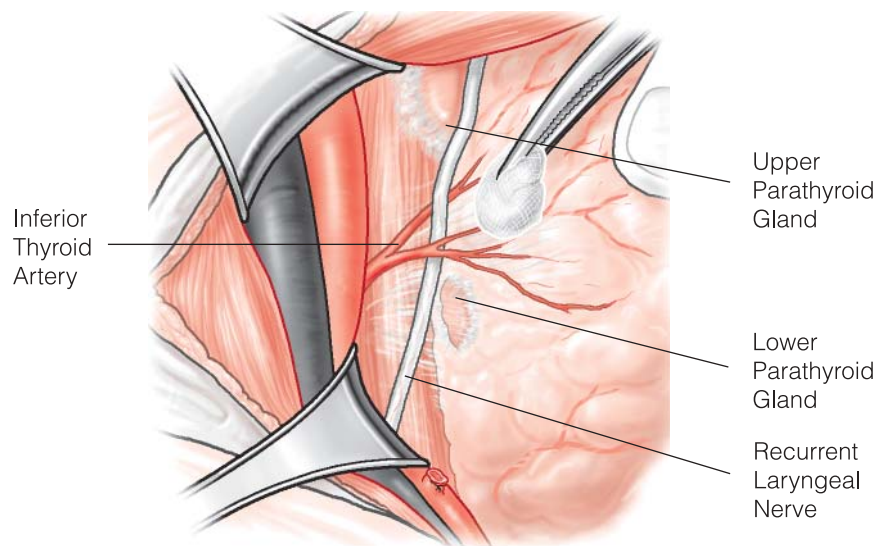


Figure 5 The upper parathyroid glands are usually situated on either side of the thyroid at the level where the recurrent laryngeal nerve enters the cricothyroid muscle. The lower parathyroid glands are usually anterior to the recurrent laryngeal nerve and inferior to where the inferior thyroid artery crosses this nerve.

gland). Both the upper and the lower parathyroid glands are supplied by small branches of the inferior and superior thyroid arteries in most patients. About 15% of parathyroid glands are intrathyroidal, and about 1% are intrathyroidal. Other abnormal sites for the parathyroid glands are (1) the carotid sheath, (2) the anterior and posterior mediastinum, and (3) anterior to the carotid bulb or along the pharynx (undescended parathyroids).

The upper parathyroid glands are usually posterolateral to the recurrent laryngeal nerve at the level of the Berry ligament. When the upper parathyroids are not found at this site, they often can be found in the tracheoesophageal groove or in the posterior mediastinum along the esophagus. The lower parathyroid glands are almost always situated anterior to the recurrent laryngeal nerves and caudal to where the recurrent laryngeal nerve crosses the inferior thyroid artery; they may be surrounded by lymph nodes. When the lower parathyroids are not found at this site, they usually can be found in the anterior mediastinum (typically in the thymus or the perithymic fat).

Step 5: Parathyroid Resection

Abnormal parathyroid glands are then removed. In about 80% of patients with PHPT, one parathyroid gland is abnormal; in about 15%, all glands are abnormal (diffuse hyperplasia); and in about 5%, two or three glands are abnormal and one or two are normal. Parathyroid cancer occurs in about 1% of patients with PHPT.

Troubleshooting In some patients, parathyroid tumors and hyperplastic parathyroid glands are difficult to find. If this is the case, the first step is to explore the sites where the parathyroids are usually located, near the posterolateral surface of the thyroid gland within 1 cm of the point where the inferior thyroid artery crosses the recurrent laryngeal nerve. Typically, the upper and lower parathyroid glands are located posterolateral and anteromedial to the recurrent nerve, respectively. When a lower gland is missing from the usual location, it is often intrathyroidal in the upper mediastinum or lower neck. Approximately 15% of parathyroids are found within the thymus. If an upper parathyroid gland cannot be located, one should look not only far behind the thyroid gland superiorly but also in a paraesophageal position down into the posterior mediastinum. A thyroid lobectomy should be done on the side where fewer than two parathyroid glands have been located and no abnormal parathyroid tissue has been identified, and the preoperative consent should prepare patients for this possibility. The carotid sheath and the area posterior to the carotid, as well as the retroesophageal area, should also be explored for unidentified upper parathyroids. In rare cases, there may be an undescended parathyroid tumor anterior to the carotid bulb.

Although we do not recommend routine biopsy of more than one normal-appearing parathyroid gland, we do recommend taking a small biopsy of all normal parathyroid glands when no abnormal parathyroid tissue can be found. This can be done by placing a small clip across the apex of the gland followed by sharp dissection; this achieves good hemostasis without devascularizing the gland and permanently marks it for future reference. When four normal parathyroid glands are found in the neck, the fifth (abnormal) parathyroid gland

is often in the mediastinum. To minimize the risk of recurrent nerve injury during removal of identified parathyroids, dissection should be directly on the surface of the capsule without disruption. The risk of permanent hypoparathyroidism or injury to the recurrent nerve should be less than 2%.

Step 6: Closure

The strap muscles are approximated with interrupted 3-0 Vicryl sutures, and an opening is left in the midline at the suprasternal notch to make any bleeding that occurs more evident and to allow the blood to exit the central neck. The platysma is reapproximated with interrupted absorbable sutures. The skin is then closed using a deep dermal absorbable stitch, and either a skin adhesive or sterile tape is applied on the epidermis.

SPECIAL CONCERNS

Four-Gland Parathyroidectomy for Hyperplasia

This procedure will render a patient permanently hypocalcemic. We prefer to leave a remnant of the most normal-appearing parathyroid gland in situ. Alternatively, autotransplantation can be done by mincing the most normal parathyroid into 1 mm cubes and placing it in a pocket inside the sternocleidomastoid muscle, subcutaneous tissue, or forearm muscle. Clips can be placed in this location to aid in localization should a second resection become required.

Parathyroid Cancer

Parathyroid lesions that grossly extend into neighboring structures should prompt suspicion of malignancy. Such lesions should be removed en bloc with the ipsilateral thyroid lobe by hemithyroidectomy. On rare occasions, parathyroid cancers may invade the trachea or the esophagus. As much as 5 cm of the trachea can be resected safely, without impairment of the patient's voice. If the invasion is not extensive and is confined to the anterior portion of the trachea, a small section of the trachea that contains the tumor should be excised, and a tracheostomy may be placed at the site of resection. If the invasion is more extensive or occurs in the lateral or posterior portion of the trachea, a segment of the trachea measuring several centimeters long is resected, and the remaining segments are reanastomosed. To prevent tension on the anastomosis, the trachea should be mobilized before resection, the recurrent laryngeal nerves should be preserved and mobilized from the trachea, and the mylohyoid fascia and muscles should be divided above the thyroid cartilage to drop the cartilage. Care must be taken not to injure the internal laryngeal nerves during this dissection, given that these nerves course from lateral to medial just above the lateral aspects of the thyroid cartilage. After resection, the trachea is reapproximated with 3-0 Maxon sutures. One or two Penrose drains should be left near the resection site to allow air to exit. The drains are removed after several days, when there is no more evidence of air leakage.

If the esophagus is invaded by tumor, the muscular wall of the esophagus can be resected along with the tumor, with the inner esophageal layer left in place. If the recurrent nerve is surrounded or invaded by tumor, it is known that it can be dissected free, even with a slight coating of tumor, without adversely affecting the patient's cancer prognosis. However,

preoperative direct laryngoscopy or the use of nerve monitoring can allow the surgeon to determine whether the nerve is still functional prior to this dissection by testing proximal to the point of invasion. Knowledge that the nerve is not functioning can then be used to more aggressively resect the tissue in the ipsilateral paratracheal space, including the nerve. In the absence of nerve testing, careful observation can reveal a full, white nerve proximal to the tumor but a collapsed, gray nerve distal to the tumor, in which case, a complete interruption by the tumor can be inferred. In general, a recurrent laryngeal nerve that is functioning normally preoperatively also should be functioning postoperatively.

POSTOPERATIVE CARE

SCORE Patients with hyperparathyroidism should have values for serum calcium, phosphorus, and PTH checked in follow-up to evaluate for the possibility of persistent or recurrent hyperparathyroidism. Persistent hyperparathyroidism is considered when hypercalcemia in the setting of elevated PTH levels occurs within 6 months of surgery, whereas recurrent hyperparathyroidism is considered when corrected calcium and PTH levels rise again 6 months or more after surgery. As many as 10% of patients will develop recurrent hyperparathyroidism in their lifetime.

In the immediate postoperative days, patients should receive oral calcium and vitamin D as prophylaxis against hypocalcemia that can occur in the early days after parathyroidectomy. Such temporary calcium supplementation allows the remaining, normal, potentially suppressed parathyroid tissue time to upregulate. Serum calcium level checks during this period of supplementation can be used to guide withdrawal. A typical starting dose for calcium supplementation is 5 days' worth of two calcium citrate tablets four times daily.

SCORE COMPLICATIONS

The following are the most significant complications of parathyroidectomy:

SCORE 1. *Hypocalcemia.* Hypocalcemia after parathyroidectomy has a number of causes, including permanent hypoparathyroidism, transient hypoparathyroidism, and a condition referred to as hungry bone syndrome. Whereas the normal serum calcium is 9.0 to 10.5 mg/dL, anything below that would be considered hypocalcemic. Few people, however, will have symptomatic hypocalcemia with only mildly low serum calcium. Symptoms generally do not occur unless serum calcium is less than 8.0 mg/dL. Additionally, it is important to note that symptomatic hypocalcemia may be related to both the actual serum calcium level as well as its rate of fall. It is important to acknowledge how high a patient's serum calcium level was preoperatively when faced with an individual complaining of hypocalcemic symptoms.

Hypocalcemia can have a wide range of severity. Mild hypocalcemia may present with perioral numbness and tingling in the fingertips, whereas severe hypocalcemia may present with muscle cramping, spasm, and tetany. Signs of hypocalcemia include Chvostek sign, a twitching of the facial muscles when the cheek is tapped over the facial nerve. Trousseau sign is elicited by inflating a sphygmomanometer above systolic blood pressure, which causes

muscular contractions with hyperextension of the fingers in some hypocalcemic patients.

Hypoparathyroidism may arise as the result of removal, bruising, ischemic injury, or devascularization of the parathyroid glands. These injuries can be avoided by restricting any dissection to the plane nearest the thyroid capsule and then gently teasing tissue away in a posterolateral direction. As noted, hypocalcemia from hypoparathyroidism may be transient or permanent if all four glands are permanently damaged. If one is concerned about the inadvertent devascularization of normal parathyroid tissue intraoperatively, biopsy should be performed on the gland to confirm its identity and then minced pieces should be autotransplanted into a pocket in the sternocleidomastoid muscle. This tissue should not be expected to function immediately; rather, it will begin to function in a matter of weeks. Only about 50% of autotransplanted parathyroid glands survive.

Laboratory values in postoperative patients with hypoparathyroidism are likely to show low serum calcium, high phosphorus, and low or even undetectable PTH levels. It is also important to note magnesium levels as calcium replacement can be dependent on maintaining normal magnesium levels as well.

Hungry bone syndrome is a phenomenon that occurs after the PTH stimulus for bone resorption has been taken away and the bones suddenly begin to sequester calcium. The consequence of this sequestration is hypocalcemia. Additionally, phosphorus will be absorbed as well, giving low serum phosphorus levels. PTH levels may be slightly elevated here as they begin to respond to the declining serum calcium concentration. This phenomenon may last days or, sometimes, even weeks. A severe manifestation of this condition occurs in patients with osteitis fibrosa cystica. In addition to the profound hypocalcemia that may occur after parathyroidectomy, these patients may have very high alkaline phosphatase levels.

Patients treated for a single adenoma are more likely to have hypocalcemia secondary to hungry bone syndrome. This generally presents 2 to 3 days postoperatively. Patients being treated with four-gland exploration with multiple resections are more likely to experience permanent hypocalcemia. This can present within 2 hours of surgery.

Treatment and prophylaxis for hypocalcemia associated with both problems are similar; in particular, treatment consists of oral calcium, calcitriol, and magnesium when it is also low. It is our practice to give every patient for 5 days after surgery, calcium citrate four times per day and 0.5 mg calcitriol daily. If patients complain of symptoms, we ask them to take double doses. We recommend calcium citrate over calcium carbonate because calcium citrate is better absorbed. Rarely does anyone require intravenous calcium replacement as oral calcium is readily absorbed.

2. *Injury to the recurrent laryngeal nerve.* Unilateral recurrent nerve dysfunction usually results in a hoarse voice and sometimes aspiration when swallowing liquids of thin consistency. If a recurrent nerve is transected during surgery, the ends should be débrided and anastomosed with 6-0 permanent interrupted sutures. This does not restore

vocal cord function but medializes the cord and prevents atrophy. Bilateral injury to the recurrent laryngeal nerve may result in airway obstruction, which often requires tracheostomy.

3. *Bleeding.* Postoperative bleeding can be life threatening in that it can compress the trachea and result in airway obstruction. Any postoperative respiratory distress should be attributed to a neck hematoma until proven otherwise. Most bleeding occurs within 4 hours of operation, and virtually all occurs within 24 hours. Acute airway compromise from hematoma requires that the incision be opened emergently without waiting for reintubation.
4. *Infection.* This complication is exceedingly rare after parathyroidectomy. Any patient with acute pharyngitis or neck cellulitis should not undergo this procedure until the infection resolves.
5. *Seroma.* Most seromas are small and reabsorb spontaneously. Symptomatic seromas can be aspirated. Compression bandages after aspiration are helpful in some cases.
6. *Keloid.* Hypertrophic and keloid scar formation after thyroidectomy is most common in African-American patients and in patients with a history of this problem.

OUTCOME EVALUATION

The patient should have a normal voice and be normocalcemic. The overall complication rate should be less than 2%. Most patients can return to work or full activity in 1 to 2 weeks.

ALTERNATIVE TECHNIQUE

Much has been written and discussed about limiting parathyroid surgery to the exposure and removal of a single parathyroid, with consequent reduced morbidity and improved cosmesis. As experience has been gained with these techniques, we have come to realize that virtually all parathyroid surgery can be performed on an outpatient basis and that the morbidity is independent of the size of the incision or the extent of the exploration. Thus, the advantage of the “limited,” “concise,” “focused,” or “mini” parathyroid exploration may be only to those with cosmetic concerns.

Nonetheless, “mini” parathyroidectomy remains a popular operative method, limiting the necessity for a full four-gland exploration. This uses preoperative ultrasonography and sestamibi scanning to direct a more focused exploration. When both modalities have concordant results suggesting a single abnormal gland, one has a greater than 97% success with a focused parathyroidectomy that avoids bilateral neck dissection. In our experience, we have found it useful to take the time to explore the ipsilateral presumed “normal” parathyroid under these circumstances. On rare occasions, this ipsilateral gland will be abnormal and prompt the appropriate bilateral neck exploration.

Also of utility with this method is intraoperative PTH testing. Because PTH has a half-life of less than 5 minutes, comparison of a predissection PTH level to one obtained 10 minutes after excision of the adenoma should show a 50% or greater drop if all the abnormal parathyroid tissue has been removed. If this does not happen, the surgeon is generally directed to continue exploring the neck. At its inception, this assay received great attention; however, it has become

somewhat controversial whether or not it adds much when there is concordance between operative findings and preoperative imaging. Based on our experience, it does not add significantly when preoperative localization studies are concordant. When ultrasonography, sestamibi scanning, and intraoperative PTH testing are combined, patients have an approximately 98% chance of cure. This is equal in success to the results from bilateral neck surgery and four-gland exploration.

Multiple Endocrine Neoplasia Syndromes



The MEN syndromes are an inherited group of disorders characterized by the propensity for patients to develop tumors and diffuse hyperplasia of endocrine tissues. They are inherited in an autosomal dominant fashion. Because these syndromes can present with simultaneous, different endocrine tumors, treatment algorithms will be influenced by the consequences of the various presenting tumors. Additionally, prophylactic operations in these patient populations may be recommended by the high penetrance of endocrine malignancies.

MEN I is characterized by hyperparathyroidism and pituitary and pancreatic neuroendocrine tumors. Ninety percent of patients with this syndrome will have a mutation in the *MEN1* tumor suppressor gene located on chromosome 11q13. All MEN I cases will present with hyperparathyroidism, two thirds of which will be the initial manifestation of this syndrome. Most cases will occur before age 40 and will exhibit multiglandular disease. About 70% of MEN I patients will have neuroendocrine tumors of the pancreas. In this population, the tumors are usually multiple and are generally benign. Gastrinomas are the most common for MEN I patients as opposed to the general population, which has a higher incidence of insulinomas. The most common pituitary tumor is prolactinoma. The workup for these patients should routinely include serum calcium and gastrin levels, pancreatic polypeptide levels, fasting blood glucose, serum prolactin, visual field testing, and head imaging. Because hypercalcemia often exacerbates the symptoms of pancreatic neuroendocrine tumors, it is preferable to treat the hyperparathyroidism in MEN I patients first. All patients should undergo four-gland parathyroidectomy with autotransplantation of a single remnant to prevent permanent hypocalcemia. Supernumerary parathyroids are common in this group.

MEN IIa is characterized by hyperparathyroidism, medullary thyroid cancer, and pheochromocytomas. These patients generally have a mutation in the *ret* proto-oncogene on chromosome 10. This gene codes for a cell membrane receptor tyrosine kinase. Only about half of these patients will have hyperparathyroidism, again involving multiple glands. Around 70% will have pheochromocytomas, and in this patient population, they are often bilateral, multiple, and extra-adrenal. Only rarely are they malignant. Most patients will present with pheochromocytomas in the third or fourth decade of life. All of these patients will develop medullary thyroid carcinoma. Because these tumors present at a younger age than sporadic medullary thyroid carcinoma, it is recommended that patients have prophylactic total thyroidectomies at 2 years of age. All of these patients should undergo *ret*

proto-oncogene mutation screening as it is 95% sensitive for this syndrome. Additionally, serum calcium levels should be monitored, pentagastrin-stimulated plasma calcitonin can be used to follow patients for recurrence, and urinary catecholamines and their metabolites, as well as metaiodobenzylguanidine (MIBG) testing, should be considered in patients. In patients with concurrent tumors, pheochromocytomas should be treated first as operative management of other tumors may precipitate hypertensive crisis. Patients with hyperparathyroidism should undergo four-gland parathyroidectomy with single-gland remnant autotransplantation. Some kindreds have uniglandular disease and do not require such extensive surgery.

MEN IIb is characterized by medullary thyroid carcinomas (95%), pheochromocytomas (50%), neuromas (100%), and marfanoid habitus (70%). This syndrome is also associated with the *ret* proto-oncogene mutation. In these patients, medullary thyroid carcinoma presents 15 years earlier than in patients with MEN IIa and is more severe, and metastases are almost always found on presentation. The workup is the same as that for patients with MEN IIa. Again, pheochromocytomas should be treated first. Prophylactic total thyroidectomy should be performed as soon as the diagnosis of MEN IIb is made.

Financial Disclosures: None Reported

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Acknowledgment

Figures 1 through 5 Tom Moore

1 BREAST CANCER

*Stephen B. Edge, MD, FACS**

Breast cancer is the most common malignancy in women in the Western world. It is increasingly prevalent in developing countries and leads to the death of hundreds of thousands of women worldwide annually. In the United States, general surgeons treat most breast cancers. It is the responsibility of surgeons to have a thorough understanding of the principles and current practices of breast cancer surgery and care beyond surgery, including the use of imaging and other diagnostic modalities, pathology, radiation, and systemic therapy, so that surgical care is coordinated as a component of comprehensive breast cancer care.

Breast cancer refers primarily to a malignancy of the epithelium of the ductal and lobular epithelial components of the breast. Nonepithelial malignancies of the breast are much less common and include tumors of mesenchymal origin (phylloides tumors, soft tissue sarcomas) and lymphoma.^{1,2} The breast is only rarely the site of metastases from other primary malignancies. This chapter addresses only the treatment of epithelial malignancies.

Investigative Studies

HISTORY AND PHYSICAL EXAMINATION



Most women with breast cancer are asymptomatic at the time of presentation, but a complete history of breast-related symptoms and evaluation for symptoms related to metastatic disease should be performed. Particular attention should be paid to skeletal symptoms and their extent or degree and duration. A prior history of imaging findings and biopsies is important. The history should include the presence of masses or lumps in the breast, any apparent swelling, edema or thickening in the breast tissue or skin, and the presence or absence of discharge from the nipple (character, color, consistency, frequency, and mode of expression—spontaneous or elicited). The patient should be queried regarding any changes in the appearance of the nipple and the areola, the presence of scaling, eczematous changes, or peeling of the skin. The physician should also document factors related to breast cancer risk: age at onset of menarche and menopause, age at first-term pregnancy and hormone use, and a detailed family history, including the type of cancer and age at onset of all first-degree and second-degree relatives with breast cancer and ovarian cancer, on both the maternal and paternal sides of the family. If there is evidence of a syndrome of inherited susceptibility to breast and ovarian cancer or to other inherited syndromes, consideration should be made for referral to

a genetic specialist for genetic counseling and possible genetic testing. Finally, a thorough history of medication use should be recorded. In addition to common prescription medication, the patient should be queried regarding the use of supplements and other alternative medicine because of the potential effect on hormone metabolism and bleeding.

Examination of the breast and chest wall begins maneuvers to accentuate skin puckering or retraction, including extending the arms over the head and/or flexing the pectoral muscles with the hands on the patient's hips. Examination of the axilla is best performed in the sitting position. The key to successful examination of the axilla is relaxation of the muscles of the shoulder girdle. This is best accomplished with the examiner supporting the full weight of the arm abducted from the body at about an angle of 60° while palpating the axilla with the other hand. Care should be taken to examine the axilla fully underneath the pectoral muscles and along the chest wall toward the latissimus muscle. It is important to examine both axillae. The supraclavicular region should be carefully examined for the presence of enlarged lymph nodes.

The most common technique for examining the breast includes accentuating the skin of the breast by placing the patient's hand behind her head. The surgeon should develop a standard manner of examining the breast so that the entirety of both breasts is fully examined. It is generally best to begin the examination with the breast opposite the breast of concern so that this examination is not forgotten. Most examiners use a process of pushing the breast tissue back against the underlying rib cage starting at the areola and working out in a circular motion extending through the entire breast, recognizing that the breast tissues goes into the axilla. The character and size of any masses identified should be noted. The density and glandularity of the breast should be identified. It is important to compare areas of dense glandular tissue with the contralateral side to identify subtle differences in the size and density of breast tissue. Although the primary examination is performed in the supine position, the patient should be queried as to whether she perceives a palpable lesion and should be asked to reproduce the position where the lesion is best examined. Frequently, patients will identify a lesion in a position other than the supine position, and subtle findings may be identified in this way. After examination of the breast, the skin of the nipple and areola should also be carefully examined, and after warning the patient, the nipple may be compressed to elicit a discharge.

Ultrasonography is an excellent adjunct to physical examination to allow the characterization of palpable lesions as solid or cystic and to help define whether there is a specific lesion identified in areas of dense breast. Surgeons who perform ultrasonography in the office need to be fully familiar with its value and limitations and should undergo appropriate training and certification of their skill. Surgeon-performed

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ultrasonography may or may not replace ultrasonography performed as part of the diagnostic breast imaging.

IMAGING

Mammography

The majority of breast cancers are detected by screening mammography. Controversy continues over the exact populations that benefit from screening mammography, but most organizations recommend mammography annually beginning at age 40 and at a younger age for women at substantial risk for increased risk of cancer.³⁻⁵

Concerning findings include new masses, asymmetry, distortion in the architecture of the breast tissue, and the presence of calcifications grouped (“clustered”) in an area of breast tissue. When an abnormality is identified, the mammogram becomes a “diagnostic mammogram,” and supplemental views are obtained in addition to the standard bilateral craniocaudad and mediolateral oblique screening views. These include accentuated positions, localized “spot” compression, and magnified settings. Any finding should be compared with previous mammograms to determine if it is new. Mammogram findings are assigned a score of 0 to 6 using the Breast Imaging Reporting and Data System (BI-RADS), with BI-RADS 4 and 5 findings requiring biopsy.⁶ Mammography detects only 80 to 90% of breast cancers and is less sensitive in women with dense glandular tissue (more common in younger women) and for lobular cancer. Suspicious physical findings (e.g., a lump or discharge) should be evaluated and biopsied even if breast imaging is normal. Mammography also has a relatively low specificity, with about 60 to 70% of all lesions requiring biopsy proving benign.

Ultrasonography

Ultrasonography is an adjunctive imaging tool to define the characteristics of a lesion identified by other imaging modalities. Ultrasonography itself is not a useful screening tool. It primarily defines whether a lesion is cystic or solid. Malignant lesions are solid and tend to have irregular borders and inhomogeneous acoustic shadowing. However, ultrasound features alone are insufficient to define if the lesion is malignant. Ultrasonography may also be used to direct needle biopsy by fine-needle aspiration (FNA), core biopsy, or vacuum-assisted needle biopsy.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) may be used in breast cancer screening and evaluation of breast cancers.⁷ MRI visualization of breast cancers requires contrast enhancement using intravenous gadolinium. Indications for breast MRI continue to evolve. MRI may detect cancers that are occult on mammography but suffers from a substantial rate of false positive findings, which leads to otherwise unnecessary biopsies and significant patient concern. MRI screening is useful in women at defined increased risk of developing breast cancer. Standard criteria in 2009 are to consider MRI screening for women with a lifetime breast cancer risk of at least 20 to 25%.⁸

The use of MRI in women with a known breast cancer has the dual purpose of screening the remainder of breast tissue and providing additional information on the extent of

the known cancer. MRI detects mammographically occult breast cancer in the contralateral breast in as many as 3% of women.⁹

MRI may assist in surgical planning. It is critical to recognize that surgical planning for cancer treatment cannot be based on the MRI finding alone and requires biopsy confirmation of any suspicious findings. Retrospective studies show that the surgical treatment planning is changed by MRI findings in as many as 20% of cases—most commonly, alteration from planned breast conservation to mastectomy. However, every study to date that has examined the question has failed to show any difference in outcomes, including local recurrence in women having presurgical MRI.¹⁰ Use of MRI may, paradoxically, unnecessarily increase the use of mastectomy. Therefore, the use of MRI in treatment planning remains controversial.

MRI may be useful in women with locally advanced breast cancer for whom neoadjuvant chemotherapy is being considered to downsize the tumor to allow breast conservation. In addition, MRI clinical response quantified by changes in enhancement and in reduction in tumor volume may be prognostic of ultimate cancer outcome.

Other Imaging Modalities

Other imaging modalities include sestamibi imaging and positron emission tomography (PET).¹¹⁻¹³ Sestamibi imaging remains investigational. PET scanning is of minimal value in evaluating the primary tumor. Other whole-body imaging of the asymptomatic patient with breast cancer is not useful in stage I and II breast cancer unless there are symptoms suggestive of metastatic disease but may be used in those with advanced disease.

Evaluation of Suspicious Findings

A breast lesion suspicious for malignancy requires tissue biopsy. Percutaneous needle biopsy is preferred over surgical excision in all circumstances. Surgical excision as a diagnostic procedure is not a justifiable alternative simply because of “patient choice” and should be performed only when needle biopsy cannot be performed for specific technical reasons, when a needle biopsy is either nondiagnostic, the result is not concordant with the imaging findings (i.e., the needle biopsy is benign, but the lesion is of high suspicion), or in highly select other cases. Technical reasons that may preclude needle biopsy include anatomic location of the lesion on mammography directly opposed to the chest wall or in the far periphery of the breast so that it cannot be visualized on stereotactic imaging devices.

FNA that provides cytology only, used extensively in the past, has largely been supplanted by core biopsy or vacuum-assisted needle biopsy that provides tissue for histologic examination. The specimens also allow performance of tumor marker studies.

Needle biopsy may be directed by direct palpation or image guidance. Lesions that are clearly palpable may be accurately localized for biopsy by palpation in the office without using imaging equipment. However, it is best to use image guidance if there is any question or if the lesion is not palpable. The choice between ultrasound, stereotactic mammographic, or MRI guidance is based on the character of the lesion

(i.e., calcifications require mammographic guidance) and the expertise and preference of the provider. In a few cases, surgical excision is required for lesions defined as benign by needle biopsy.

In addition to the “nonconcordant” finding, this includes cases where the biopsy shows the benign lesions atypical hyperplasia (ductal or lobular) or lobular carcinoma in situ. Excision is necessary in these cases because there is a small chance that there is cancer in the tissue immediately surrounding the biopsy-sampled tissue.¹⁴

Breast Cancer Management

The treatment of breast cancer requires coordination between multiple disciplines.

Surgical care cannot be done in a vacuum and must be integrated with adjuvant therapies, including radiation and systemic therapy. Although it is not mandatory that every breast cancer patient consult with specialists in each relevant discipline prior to surgery, it is incumbent upon the surgeon to ensure that the surgical care is appropriately coordinated in overall breast cancer care.

Breast cancer management addresses two major issues. The first is the treatment of the local disease in the breast itself. This is generally accomplished through surgical resection with or without radiation. The second is the adjuvant systemic therapy (chemotherapy and endocrine therapy) because any woman with invasive cancer has the risk of harboring occult microscopic metastatic disease that will ultimately lead to clinically apparent metastatic disease and death.

Decisions about treatment require accurate information on the extent of the cancer at the time of diagnosis codified using staging systems. The clinically used staging system is the TNM system of the American Joint Committee on Cancer (AJCC).¹⁵ This classifies the size and extent of the primary tumor (T), the involvement of regional lymph nodes (N), the presence or absence of distant metastases (M), and a “stage group” derived from the T, N, and M. The AJCC TNM system was recently revised for cases diagnosed beginning in 2010.

Stage should be documented in the medical record at two distinct points in treatment.

Clinical stage is the initial cancer stage used in treatment planning and includes information gleaned from the history and physical examination and any available imaging studies prior to surgery or the start of systemic or radiation therapy. Pathologic stage is the clinical stage supplemented with the findings from surgical resection. When neoadjuvant therapy is used, the extent of disease after treatment is the posttreatment stage. The degree of response to neoadjuvant therapy may be prognostic. The rules and specifics of the TNM staging system are presented in detail in the *AJCC Cancer Staging Manual* (seventh edition).¹⁵

Breast cancer management continues to evolve, and no book chapter can remain up to date. Surgeons are urged to remain current with the relevant literature and refer to guidelines in making treatment decisions. The most comprehensive guidelines that are updated at least annually are supplied by the National Comprehensive Cancer Network (NCCN) and are available at www.nccn.org.¹⁶

Noninvasive Cancer

Cancer that is confined to the lumen of the duct or lobule of the breast and has not penetrated the basement membrane is termed in situ cancer. This generally refers to ductal carcinoma in situ (DCIS) but also encompasses a benign entity called lobular carcinoma in situ (LCIS).

LOBULAR CARCINOMA IN SITU

Small uniform cells confined to the lobule of the breast characterize LCIS. It is generally a clinically and mammographically occult lesion that is identified only incidentally when a biopsy is performed for calcifications or a mass that proves to be some other benign lesion. LCIS is actually not cancer but rather is a benign lesion and does not require cancer treatment per se. The primary issue with LCIS is that it conveys an increased lifelong risk of subsequent invasive cancer quantified at 0.5 to 0.75% per year.¹⁷ In addition, when LCIS is identified on a core-needle biopsy, there is a 10 to 20% chance of DCIS or invasive cancer in the surrounding tissue; therefore, surgical excision is warranted.¹⁸

Long-term follow-up shows that the large majority of women with LCIS never develop invasive breast cancer. Therefore, ablative surgical therapy and radiation for LCIS are not necessary. Previously, LCIS was considered in and of itself an indication to consider bilateral mastectomy. However, mastectomy is generally not indicated in women with LCIS and should be performed only in the context of risk reduction for those at very high risk related to factors such as inherited susceptibility.¹⁹

Because women with a diagnosis of LCIS are at increased risk for subsequent invasive cancer, they should be counseled regarding that risk and may benefit from consultation with genetics professionals if they have a family history of breast or ovarian cancer. Women with a biopsy showing LCIS may also consider risk-reducing chemoprevention with one of the selective estrogen receptor modulators (SERM's), tamoxifen or raloxifene. These reduce the risk of subsequent invasive cancer by about 50%, with an acceptable toxicity profile.^{20,21} Raloxifene is the preferred agent in postmenopausal women.

DUCTAL CARCINOMA IN SITU

The histologic hallmark of DCIS is the presence of malignant-appearing cells confined to the lumen of the ductal system in the breast. DCIS is most often diagnosed because of the presence of calcifications clustered in one area of the breast. The calcifications suspicious for DCIS are often linear (not round), growing in a ductal distribution. The DCIS may not be confined to the extent of calcifications, and not all DCIS is manifested by calcification. Therefore, the size or extent of DCIS may not be defined by the mammographic appearance. Although DCIS occasionally presents as a mass, the presence of the mass even in the setting of a biopsy showing DCIS most often signifies that the cancer is primarily invasive.

DCIS is generally considered a precursor to invasive cancer.²² The purpose of treatment of DCIS is to prevent progression to invasive cancer with the sequelae of metastatic disease and death. However, indirect evidence suggests that not all DCIS lesions will progress to invasive cancer. Unfortunately, despite extensive research, there is insufficient

evidence to identify which DCIS lesions will progress to invasive cancer and which will remain clinically occult for the duration of a woman's life.²³ Therefore, all women diagnosed with DCIS should undergo appropriate treatment.

DCIS encompasses a spectrum of histologic subtypes. Malignant-appearing cells confined to the breast duct characterize all of these. However, the appearance ranges from bland, uniform cells growing from the wall of the duct or bridging the duct (papillary; cribriform) to cells filling the entire duct (solid). These cells also vary in nuclear morphology, ranging from low-grade, uniform-appearing nuclei to varying size and shape and large nuclei (high grade) and in the presence or absence of central necrosis within the duct. The combination of high nuclear grade and central necrosis is termed "comedo-DCIS" or "comedocarcinoma." It is possible that these subtypes of DCIS are different disease entities with different potential for progression to invasive cancer, but this is poorly understood. The clinical relevance of the DCIS subtypes is that they may have different potential for local recurrence after breast-conserving surgery, which may impact on the utility of radiation as an adjunct to wide excision. The presence of high-grade cells or comedonecrosis is not an indication of metastatic potential and does not itself warrant systemic therapy or lymph node staging.

Treatment



The overall cancer-specific survival for women with DCIS approaches 100% almost irrespective of the subtype of DCIS and the type of treatment [see Figure 1].²² Mastectomy is effective in DCIS, but in most cases, a breast-conserving approach is possible. Recurrence in the skin of the mastectomy site or on the chest wall muscle ("local recurrence") may occur, but the frequency after mastectomy for DCIS is extremely low (1 to 3%).²⁴ Most women with DCIS may be treated by surgical excision ("lumpectomy" or "wide excision") of the DCIS with some surrounding normal breast tissue to achieve a "negative margin." The choice between breast-conserving surgery (BCS) and mastectomy may be influenced by the size of the area of involvement, the size of the breast, and the location of the DCIS.

There is no specific size above which mastectomy is mandatory. Wide excision ("lumpectomy") with a generous margin of normal breast tissue can be accomplished in most women.

Large-scale randomized clinical trials in North America and Europe have demonstrated the effectiveness of BCT and the role of radiation in DCIS. The National Surgical Adjuvant Breast and Bowel Project (NSABP), the European Organization for Research and Treatment of Cancer (EORTC), and others conducted trials comparing wide excision alone versus wide excision plus radiation therapy.^{25–28} Every study demonstrated long-term overall survival approaching 100% irrespective of treatment. However, women treated with BCT had a substantial risk of recurrence in the same breast, and radiation reduced this risk. The rate of local recurrence in the NSABP study was 30% without radiation and about 12% with radiation. The size and histologic characteristics of the DCIS as well as the extent of the margin of resection also affect the risk of local recurrence.

A key factor in breast-conserving surgery for DCIS is obtaining a negative surgical margin. Because the DCIS may

extend beyond the area of calcifications seen on mammography, the rate of positive margins on the initial excision for DCIS ranges as high as 20 to 25%. Women who have a positive margin on the initial excision for DCIS must undergo repeat surgery to obtain a negative margin. On occasion, even with such "reexcision," the DCIS extends to the new margin, and some of these women ultimately require mastectomy. The definition of a "negative margin" is an area of controversy.^{29,30}

The NSABP studies used the definition of a negative margin as the absence of the ink used to paint the surgical margin on any cancer cells. However, the margin width, measured as the distance from the closest surgical margin to the DCIS, affects the risk of local recurrence, with the lowest rates among women with a full 1 cm margin.³¹ The best current evidence is that a margin of at least 2 mm is required to obtain optimal rates of local recurrence.³²

Substantial research has focused on identification of those women with DCIS who may not require radiation. Some evidence from nonrandomized series suggests that the size of the area of DCIS coupled with the nuclear grade and the width of the resection margin may identify subsets of women with DCIS for whom the risk of local recurrence is so low that radiation is not warranted.^{33,34} However, in randomized trials, there are no subsets that can be identified for whom radiation does not reduce the risk of local recurrence. Therefore, the decision to omit radiation therapy with DCIS requires careful counseling of the patient coupled with multidisciplinary input.

The standard radiation treatment is whole-breast radiation therapy to a dose of about 50 Gy potentially coupled with a 15 Gy boost to the site of the surgical excision. Because most local recurrences occur in the breast tissue close to the original DCIS, it is possible that radiation administered only to the affected region of the breast may be as effective as whole-breast radiation therapy. Techniques for administering so-called accelerated partial-breast irradiation therapy allow treatment to be delivered over a much shorter period of time (as short as 5 days), making it an attractive alternative.³⁵ However, as of 2009, there are no long-term data demonstrating the effectiveness of accelerated partial-breast irradiation in DCIS, and it remains investigational.

The choice between mastectomy and breast conservation may be difficult. It is different for women with DCIS than for those with invasive cancer primarily because those with DCIS do not face the threat of death from metastatic disease. For women with disease treatable by breast conservation, mastectomy remains a reasonable option if selected by the patient. The choice may also be influenced by the risk of developing a subsequent second breast cancer related to family history and biologically defined inherited susceptibility. An initial reaction of "just remove it" is insufficient justification for mastectomy and should be followed by careful counseling and reassurances regarding the long-term outlook for women with DCIS.

Reconstruction of the breast mound is available to most women who require or choose mastectomy for DCIS. Breast reconstruction may be performed at the same time as the mastectomy using implant techniques or tissue transfer using a variety of tissue flaps (see below).

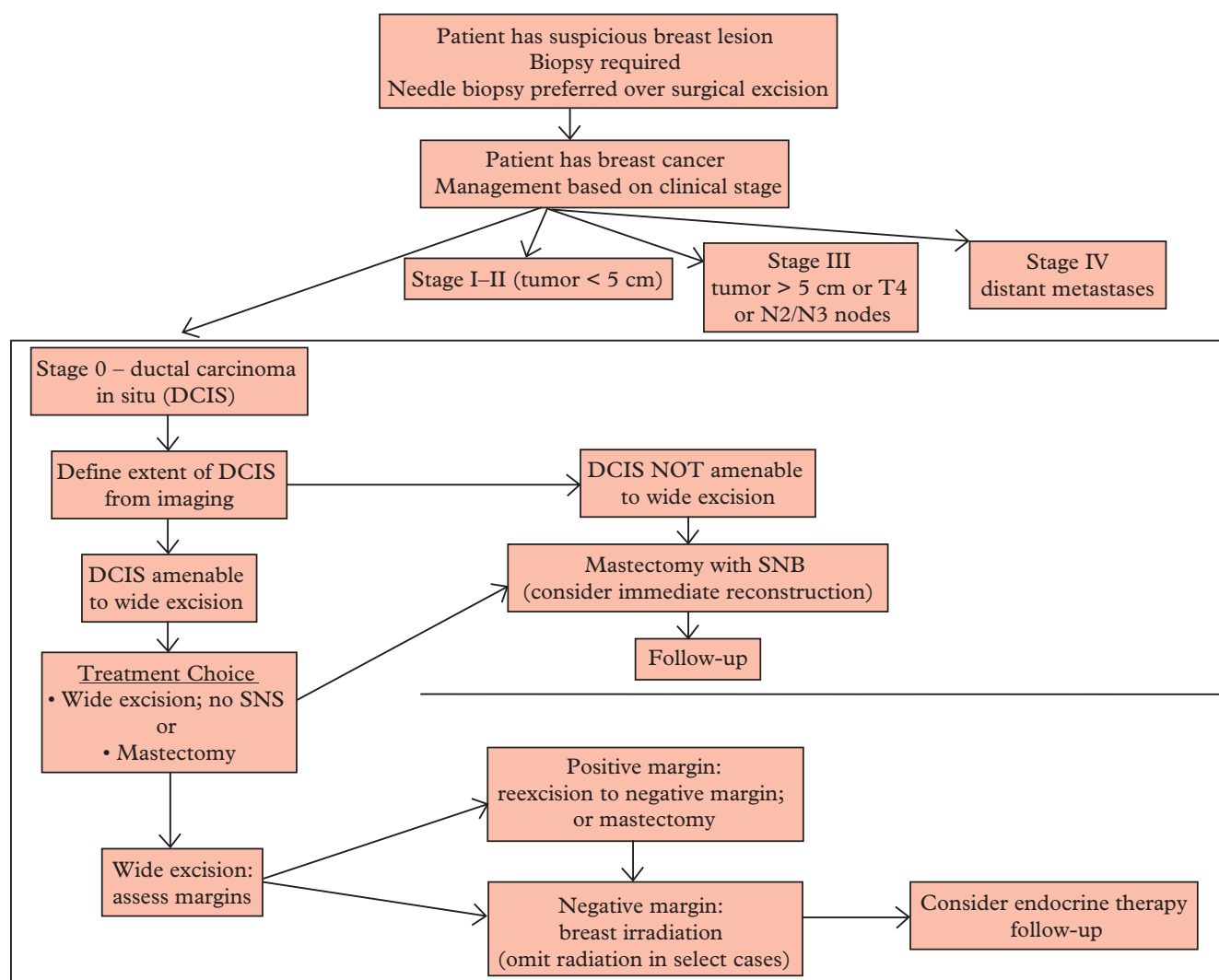


Figure 1 Guidelines for treatment of ductal carcinoma in situ (DCIS). SNB = sentinel node biopsy.

An important issue with DCIS is that there is a risk that invasive cancer is identified in the final surgical specimen in 5 to 20% of women for whom needle biopsy showed DCIS. Invasive cancer is more likely in cases where a mass is present on imaging or physical examination. This leads some surgeons to recommend lymph node surgery in all women with DCIS. However, lymph node surgery is unnecessary in the management of DCIS because it has no metastatic potential. For women undergoing breast-conserving treatment, if an invasive cancer is identified in the final surgical specimen, lymph node staging with sentinel node biopsy (SNB) may be performed at a subsequent surgical procedure with the same level of accuracy as if done at the time of excision. Some surgeons advocate SNB in all women with DCIS, making the argument that it is cost-effective compared with a separate SNB procedure for those with invasive cancer, but there are no high-level data to support this statement. In addition, SNB carries some risk of long-term morbidity; careful evaluation on prospective studies demonstrates that women with SNB have about a 6% risk of at least mild lymphedema.^{36,37} Therefore, with breast-conserving surgery, SNB should not

be performed. Exceptions are the presence of a suspicious mass—indicative of invasive cancer—or when the DCIS is in the axillary tail of the breast, and excision may preclude subsequent SNB because of interruption of lymphatic flow to the axilla. SNB is appropriate when mastectomy is used for DCIS because of the chance that the breast harbors an invasive cancer. Mastectomy may preclude subsequent SNB; therefore, mastectomy without SNB for women with DCIS may commit those women to undergoing a full axillary lymph node dissection if invasive cancer is present.

Women who undergo radiation with DCIS may also benefit from adjuvant endocrine therapy. The NSABP conducted a clinical trial of wide excision plus radiation with or without tamoxifen.³⁸ Tamoxifen reduced the risk of local recurrence by 40%. A subsequent clinical trial not as yet reported in 2010 addresses whether an aromatase inhibitor is effective and comparable or superior to tamoxifen in reducing the rate of local recurrence in DCIS. The use of endocrine treatment in DCIS must be balanced against the toxicity of the selected drug, recognizing that endocrine therapy is not lifesaving in this situation. There are no data supporting the use of

endocrine therapy in women treated for DCIS with mastectomy.

PAGET DISEASE OF THE BREAST



An uncommon presentation of breast cancer is with eczematoid changes directly in the nipple, often with beet red and ulcerated skin in the nipple. This is due to malignant cells with a characteristic “fried egg” appearance occurring in the nipple skin or “Paget cells.” This is Paget disease of the nipple. In most cases of Paget disease, there is a cancer in the underlying breast, and the cells in the nipple may represent intraductal spread of the cancer to the nipple, although this process is poorly understood. In most cases, the underlying cancer is relatively close to the nipple and in most cases is DCIS.

Women with these changes in the nipple are often misdiagnosed as having benign skin conditions and are treated with topical agents, including steroids. If such treatments are used and the lesion does not resolve, or if there is any clinical suspicion, a biopsy of the affected skin is needed. If the biopsy shows Paget disease, then the breast should be carefully imaged by mammography supplemented by MRI if the breast is dense to search for primary tumor in the breast. If a breast lesion is found, it, too, should be biopsied.

Treatment is generally based on the type (in situ or invasive) of primary tumor in the breast and treatment of the nipple. This may be accomplished in many cases with removal of the nipple in continuity with the breast cancer, followed by radiation.³⁹ Mastectomy is still often used but may be reserved for cases with more extensive involvement.⁴⁰ Lymph node surgery is warranted only with invasive cancer. Adjuvant systemic therapy is administered by standard guidelines.

Invasive Breast Cancer

The majority of breast cancers are classified as invasive or infiltrating, characterized by the cancer invading through the basement membrane of the duct or lobule. The same properties allow basement membrane invasion may allow the malignant cells to invade surrounding blood vessels or lymphatic channels and raise a possibility of spread to distant sites. Although most have probably not spread as assessed by long-term survival without distant metastases, the treatment issues for invasive breast cancer include not only the local treatment of the breast but also the potential for distant spread and the role for adjuvant systemic drug therapy.

CLASSIFICATION



The majority of breast cancers arise from the ductal component of the terminal ductal lobular unit and are termed invasive ductal cancer. An additional 10 to 15% arise within the lobule and have a characteristic appearance of small cells infiltrating in a linear fashion through the breast stroma, termed invasive lobular cancer. Invasive lobular carcinoma carries the same risk of distant metastases as ductal carcinoma. However, lobular carcinoma may be more insidious because of the infiltrative nature of the disease, which results in a lesion more difficult to detect by mammographic or clinical means.

Certain subtypes may have a different prognosis than typical invasive ductal cancer. These include tubular carcinoma,

mucinous carcinoma, medullary carcinoma, and metaplastic carcinoma. Tubular and mucinous carcinomas may have a lower propensity for lymphatic metastases and a generally better prognosis than typical ductal cancers.^{41,42}

Medullary cancer was historically considered a cancer with a better prognosis, but the term is overused, and most tumors classified this way are high-grade cancers with a poor prognosis. Standard guidelines do not assign medullary cancer to a good prognosis subgroup.¹⁶ Because of the potential overuse of these subgroup terms, great care should be taken in making treatment decisions based on these subgroups without ensuring with the pathologist that the tumor truly is the special histology.

Inflammatory breast cancer is an infiltrating cancer characterized by skin edema and erythema encompassing over half the breast and associated with an especially high likelihood of subsequent metastases and death. It often correlates with the histologic finding of dermal lymphatics clogged by tumor cells, but the diagnosis of inflammatory cancer is only a clinical diagnosis. Skin biopsy showing dermal lymphatic involvement is not necessary to classify a cancer as inflammatory.¹⁵

Breast cancers may be better classified by biologic characteristics rather than histologic appearance. At the very least, all breast cancers should be analyzed for expression of the hormone receptors for estrogen and progesterone and the level of expression or amplification of the HER-2/*neu* gene.¹⁶ These provide key prognostic information and “predictive” information about sensitivity to specific drugs to treat breast cancer. It is expected that biologic classification of breast cancers beyond these three receptors will ultimately allow a higher degree of personalization of both local and systemic treatment.^{43,44}

The accuracy of testing for estrogen, progesterone, and HER-2 varies, and this variation impacts significantly on patient outcome. To improve this situation, national organizations have established practice standards for laboratories performing this testing.^{45,46} Pathology should be reported using structured documentation according to the templates provided by the College of American Pathologists (www.cap.org). Surgeons should be sure that testing for their patients is performed and reported in accordance with these standards.

LOCAL THERAPY OF T1 AND T2 INVASIVE BREAST CANCER

The primary goal of local therapy of breast cancer is eradication of the primary tumor to prevent progression and further dissemination of the disease [see Figure 2]. In addition, staging of the regional lymph nodes is performed to provide prognostic information and to guide systemic treatment as well as provide regional control in the common regional nodal basins.



Mastectomy versus Breast-Conserving Surgery

Historically, local treatment of breast cancer meant mastectomy. One can argue that the development of the operation of radical mastectomy was the single most important advance in the treatment of breast cancer. At the time it was developed in the late 1800s, most women presented with breast cancers that were locally advanced and were likely to progress to difficult painful and infected local problems. However, the ability to treat breast cancer effectively led to

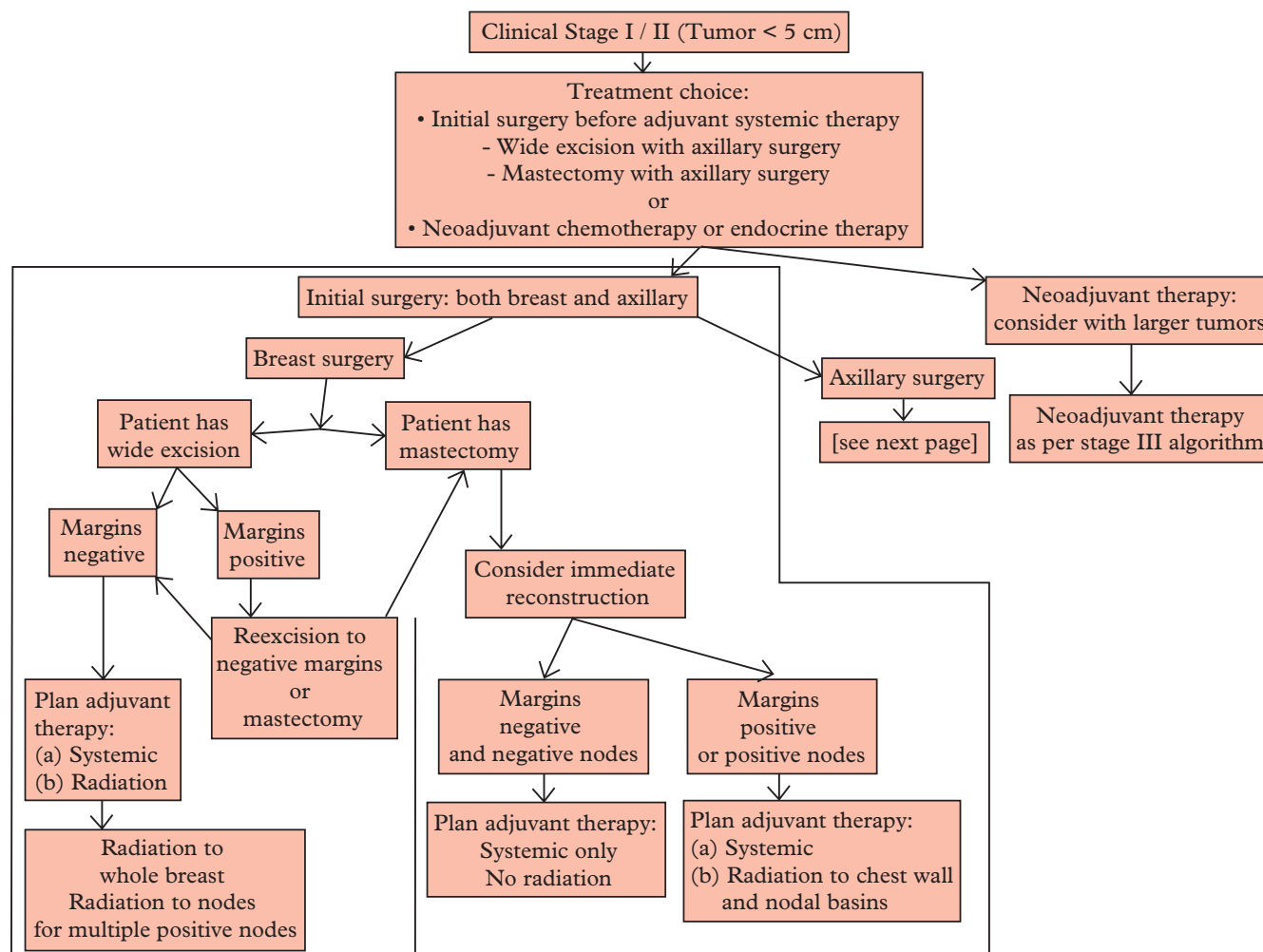


Figure 2 Overview schema for local therapy for stage I/II breast cancer.

women presenting with smaller cancers. However, it was not until the 1970s that the so-called “halstedian” thesis, that breast cancers progressed in a stepwise fashion from the breast (local) to lymph nodes (regional) to distant disease (metastases), was proven incorrect. In the 1970s and 1980s, landmark clinical trials demonstrated that breast cancer is a systemic disease with the possibility of disseminated disease even at the smallest primary tumor and that removal of the tumor without mastectomy provided long-term outcome equivalent to mastectomy. The most significant study was the NSABP B-06 trial comparing mastectomy with lumpectomy alone and with lumpectomy plus radiation therapy.⁴⁷ Long-term follow-up on this trial demonstrated no difference in overall survival between the three groups. However, with lumpectomy alone, the cancer recurred in the same breast in as many as 40% of women. Radiation reduced this rate of local recurrence to approximately 12%. On the basis of this finding, lumpectomy plus radiation therapy became an accepted standard in the late 1980s and became widely used through the 1990s.

Breast-conserving surgery may be performed in a majority of women with invasive breast cancer. Successful BCT requires obtaining negative margins of resection around

the tumor. As with DCIS, major clinical trials testing BCT defined a negative margin as no ink on the tumor. However, in general, a minimum 2 mm margin is optimal. A specific exception may be at the chest wall, where the pectoralis fascia has been taken, and anteriorly at the skin. If a negative margin cannot be obtained with lumpectomy, including with a second or occasionally a third operation for “reexcision,” mastectomy is necessary.

Indications for mastectomy include the presence of multicentric disease in the breast—separate cancers in distinct parts of the breast separated by at least 5 cm of normal breast tissue, occurring in 2 to 5% of cases; a very large tumor in relation to the size of the breast that is not amenable to lumpectomy or does not respond sufficiently to neoadjuvant systemic therapy; and previous radiation treatments to the breast, such as with a prior breast cancer or for treatment of other cancers, such as lymphoma. Radiation may not be administered during pregnancy, but with standard sequencing of systemic and radiation after BCT, radiation is usually timed such that it is administered after delivery of the baby; therefore, BCT is possible for women presenting with breast cancer during pregnancy. In addition, mastectomy is indicated after completion of systemic chemotherapy for

inflammatory breast cancer because of the likelihood of the microscopic extent of disease both in the skin and within the breast beyond the area of known cancer.

An unusual presentation of breast cancer is with axillary lymph node involvement without the presence of a detectable primary cancer in the breast (occult breast primary tumor). If a woman has suspicious lymph nodes in the axilla, biopsy is warranted. If the histology shows an adenocarcinoma (as opposed to lymphoma or melanoma), the primary source of this metastatic deposit is almost invariably the breast, even if the hormone receptors are negative. Mammography usually shows the primary tumor, but MRI may find some of these cancers not seen on mammography.⁴⁸ However, in a few cases, even MRI will be negative, yet the source is invariably the breast. A whole-body search for another source of adenocarcinoma is not indicated. The woman should receive therapy assuming that this is a breast cancer.

In the past, mastectomy was used for all women with an occult breast primary tumor with a positive axillary node. However, recent data show that mastectomy is not necessary.

They should undergo axillary lymph node dissection and then receive adjuvant systemic therapy (chemotherapy and endocrine therapy) as appropriate based on stage and biologic features and then radiation to the breast.^{49,50}

Women who have inherited susceptibility with a mutation known in *BRCA1* or *BRCA2* also often choose mastectomy or bilateral mastectomy. The overall survival for women treated with BCT in this situation is the same as for women without inherited susceptibility.⁵¹ However, they are at increased risk for developing a second primary cancer in the same breast, a chance that approaches 50%, especially in women under age 50 at the initial diagnosis.⁵²

Radiation in Local Therapy

Mastectomy should be supplemented with radiation when the cancer is over 5 cm in size, when surgical resection margins are close or positive, or when multiple lymph nodes are involved.⁵³ The “textbook” standard is that radiation is indicated with four or more positive nodes. However, radiation should be considered even when only one to three nodes are involved based on the findings of randomized clinical trials demonstrating improved survival. Unfortunately, a major American clinical trial addressing the use of radiation after mastectomy for women with one to three positive nodes failed to accrue sufficient numbers of patients to provide an answer to this critical question.

The possible need for radiation after mastectomy may affect decisions regarding the cosmetic outcome of immediate breast reconstruction.⁵⁴ Immediate reconstruction may complicate radiation dosimetry and uniform dose delivery over the entire field and increase the volume of tissue outside the field, including the lung and heart. In addition, radiation may compromise the cosmetic result of immediate reconstruction through contracture of the scar capsule around an implant and/or contracture of tissues within an autologous tissue flap. The potential need for radiation after mastectomy should be discussed with all women having mastectomy for invasive breast cancer.

Radiation is generally administered in all cases with BCT. Radiation reduces the risk of local recurrence by as much as

70%, and this may improve survival.⁵⁵ Subset analysis of large clinical trials and limited clinical trials in women with small cancers failed to identify cancers of sufficiently small size that radiation does not reduce the risk of local recurrence.

One group in whom the omission of radiation is reasonable is women over age 70 with cancers that are hormone receptor positive, 2 cm or smaller, with clinically negative nodes. A clinical trial conducted by Cancer and Leukemia Group B (CALGB) randomized such women to lumpectomy and tamoxifen with or without radiation.⁵⁶ There was no difference in long-term survival. Local recurrence occurred in 1% with and 6% without radiation. However, the same number of women in both groups ultimately underwent mastectomy as those who had not received radiation or were most often treated with lumpectomy and radiation. Therefore, omission of radiation is reasonable in this group. A similar trial conducted in Canada for women age 50 and over demonstrated local recurrence rates of about 15% among women between age 50 and 70, lending caution to omitting radiation for younger women.⁵⁷

The standard radiation treatment after breast-conserving surgery is treatment of the entire breast to a dose of about 50 Gy, with an additional boost of radiation to the primary tumor site of about 15 Gy. Radiation treatment takes about 6 weeks of therapy and is well tolerated. Long-term serious sequelae of whole-breast radiation are uncommon.

Recent clinical research has focused on the potential for limiting the extent and time required to deliver radiation to the breast. This research is based on the finding that most recurrences occur within a short distance from the primary tumor site. Only about 15% of new events in the treated breast occur outside the area of the original tumor area and are most likely a new second primary cancer. It is hypothesized that limitation of radiation treatment only to the site of the primary cancer can provide local control equivalent to whole-breast radiation therapy. So-called accelerated partial-breast irradiation (APBI) has one major advantage: because of the technical issues in radiation dosimetry and tissue tolerance, APBI may be delivered in a much shorter time frame—generally two fractions a day over only 5 days. Another purported advantage is that if there is a second disease event in the affected breast, this may be treated by a repeat lumpectomy rather than mastectomy. However, there are no data to support this thesis.

There are a number of techniques to deliver APBI.⁵⁸ The technique with the longest-term follow-up, albeit in a limited number of patients, is multicatheter brachytherapy. This technique is cumbersome, unsightly, and seldom used. More recent alternative techniques for delivery of APBI include three-dimensional computed tomography (CT)-directed external beam radiation, brachytherapy using a radiation seed in a balloon catheter placed in the lumpectomy site, and a single intraoperative dose of radiation. These are promising technologies, but there are no long-term data from controlled clinical trials demonstrating the safety and effectiveness of these techniques.⁵⁸ Data from noncontrolled series are scant and have very short-term follow-up in a setting where, at the very least, 5-year follow-up is required. Large clinical trials are ongoing, including a study by the NSABP. Therefore, as of 2010, APBI remains investigational and whole-breast radiation therapy remains the standard.^{16,59}

Local Recurrence with Mastectomy or Breast-Conserving Surgery

Local recurrence after surgical treatment of breast cancer occurs with both mastectomy and BCT. The risk of local recurrence after lumpectomy is somewhat lower than reported in the NSABP B-06 trial. When performed by experienced surgeons with careful pathologic control, appropriate radiation, and stage-appropriate adjuvant systemic therapy, the rate of local recurrence with BCT is as low as 1 to 5%. Local recurrences are also a significant issue among women treated with mastectomy. This risk is about 2 to 5% for women with negative lymph nodes and ranges as high as 25% for women with multiple positive lymph nodes.^{60,61}

Local recurrence is a serious event whether it occurs after BCT or mastectomy. These women have a higher risk of developing distant metastases compared with women with similar-stage cancer who do not suffer local recurrence. It has previously been generally cited that radiation impacts only the risk of local recurrence and not overall survival. However, a meta-analysis of all available data for women treated with BCT and mastectomy demonstrated that radiation therapy not only reduces the risk of local failure but also improves survival.⁵⁵ The best estimate is that radiation saves one life for every four local recurrences prevented. Radiation is therefore recommended for women who have a risk of local failure over 10% regardless of the type of primary surgery.

The accepted treatment for local recurrence after BCT is mastectomy. This is because the recurrence may be multifocal and because full-dose radiation cannot be administered safely a second time because of tissue toxicity. Local recurrence after mastectomy is more difficult to treat and carries a more serious prognosis. Treatment usually includes resection of a local recurrence in the skin, muscle, or regional nodes if possible, followed by radiation to the chest wall and regional nodes. The role for additional adjuvant systemic therapy after local recurrence is uncertain, and there are no clinical trial data supporting its use. However, many oncologists will deliver additional systemic treatment based on the type of previous treatment and the nature and extent of the local recurrence.

Selection of Breast-Conserving Surgery versus Mastectomy

The decision between BCT and mastectomy is a complex and difficult one for women with breast cancer. From a technical standpoint, BCT is possible in the large majority of women with breast cancer. More than 90% of women with tumors under 2 cm in size (T1) may undergo BCT given the absolute and relative contraindications to BCT discussed above. However, many other factors in addition to the technical ability to perform BCT affect the decision. Ultimately, the individual patient is the determinant of whether or not she will have mastectomy. Her choice may be influenced by perceptions or values based on personal or family experiences, real or perceived increased risks of recurrent cancer based on family history, and other factors.

Counseling women regarding the choice of surgery is one of the most important tasks for the treating surgeon.⁶² Surgeons need to learn the skills of nondirective counseling and must incorporate other professionals and resources into their practice. Careful study of the decision-making process has shown that physicians are not necessarily fully sensitive to

their patient's concerns or to their styles of decision making.⁶³ This has led to the development of decision assistance and support tools and to the recognition of the need for multidisciplinary counseling, especially in more complex situations or those associated with questions surrounding inherited susceptibility and genetics.⁶⁴

One of the key factors in this process is the recognition that breast cancer treatment is not an immediate emergency. There are no data to support the contention that treatment initiated within a few days of diagnosis improves outcome compared with that delayed a reasonable period of time, measured in a number of weeks or even months. Women should be given the opportunity to seek additional counseling, research information on their own, and obtain second opinions if they so desire. Inclusion of professionals of other disciplines, including radiation oncology, plastic surgery, medical oncology, radiology, psychology and social support, nursing, and genetics, may be warranted.

MANAGEMENT OF THE CONTRALATERAL BREAST

Women with breast cancer have a risk of second malignancies and especially the risk of developing a contralateral primary breast cancer. Outside the setting of inherited susceptibility, the chance of developing a contralateral primary breast cancer is about 10% over 20 to 30 years.⁴⁷ Given that the average woman is in her 50s or 60s and that most of these contralateral breast cancers will be effectively treated, the risk that a woman with a breast cancer will succumb to a new contralateral breast cancer is far outweighed by both the risk of death from the current breast cancer and the long-term risk of death from other causes during the very long-term follow-up in which second cancers occur. Therefore, treatment addressing the other breast is generally not necessary.

Previously, it was believed that women with invasive lobular cancer had a much higher risk of a contralateral breast cancer compared with ductal cancer. The added risk of contralateral cancer with lobular cancer is relatively small and should have little bearing on treatment decisions.

The issues are different for women with inherited susceptibility, most notably those with mutations in *BRCA1* and *BRCA2*. They are generally younger at breast cancer diagnosis and have a higher risk of developing a second cancer. This risk appears dependent on the age at which they are diagnosed with their first breast cancer: 25 to 50% for those under age 50 at the initial diagnosis and 15 to 20% for those over age 50.⁵²

Careful counseling can largely allay a woman's fears of the impact of the risk of a second cancer. However, some women, especially those undergoing mastectomy for the index cancer, may request contralateral mastectomy. Recent observational studies demonstrate that the number of women undergoing prophylactic contralateral mastectomy increased significantly over the last decade. In New York State, about 4% of women treated with mastectomy in 1995 had a contralateral mastectomy compared with 15% in 2005.⁶⁵

LYMPH NODE STAGING IN BREAST CANCER

The presence of metastases in regional lymph nodes is a key prognostic factor used in making treatment decisions, as discussed below [see Figure 3]. In addition, removing lymph

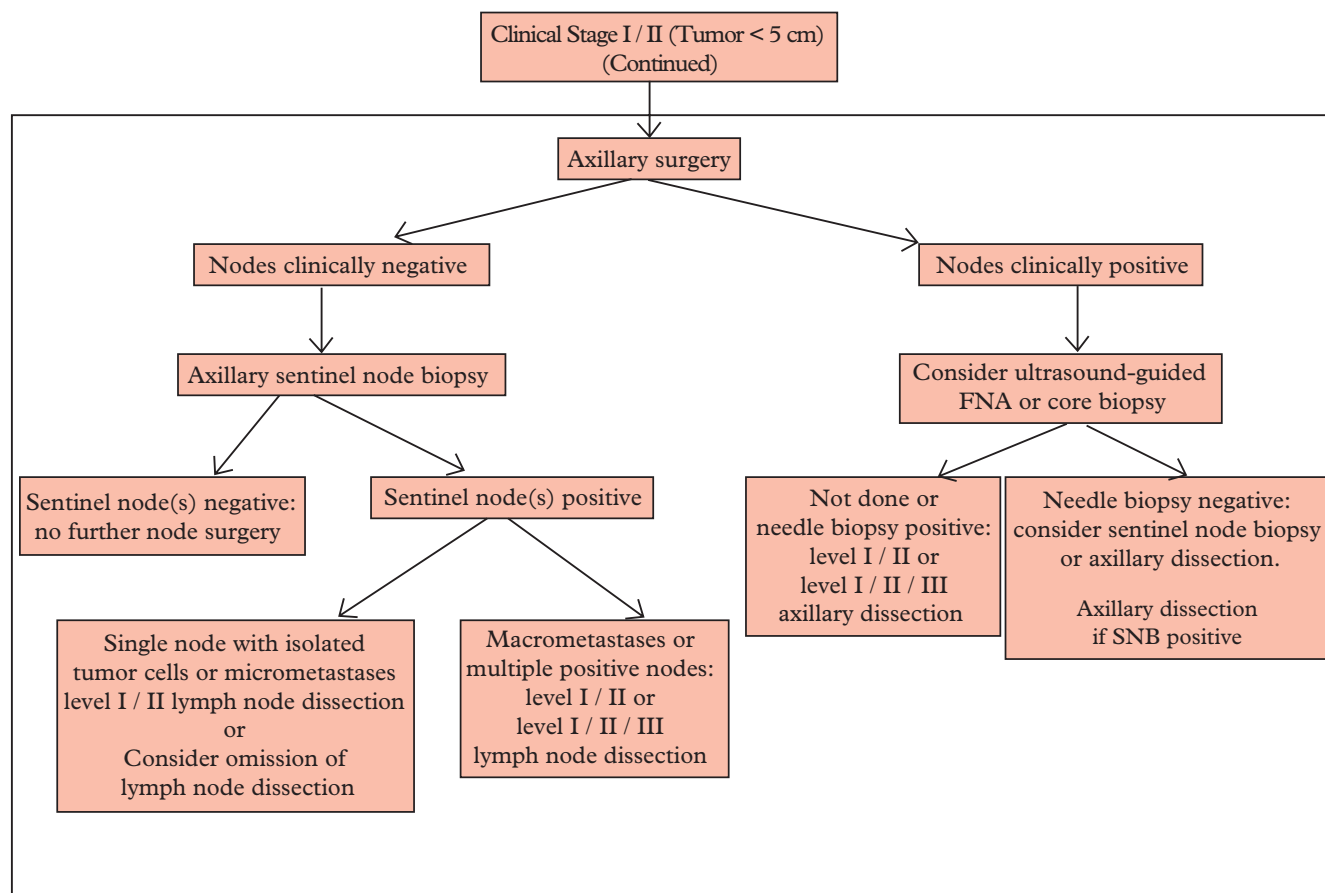


Figure 3 Axillary surgery management schema. FNA = fine-needle aspiration; SNB = sentinel node biopsy.

nodes prevents recurrence risk in the regional lymph node basin. However, treatment of lymph nodes does not itself affect survival. Defining the involvement of regional lymph nodes requires surgical resection. No noninvasive test of the regional lymph nodes has proven insufficient sensitivity and specificity to replace surgical resection. Therefore, surgical evaluation of regional nodes remains a key component of breast cancer treatment.⁶⁶

Lymph fluid from the breast drains primarily through the axillary lymph nodes.⁶⁷ A small fraction of lymph drainage from the breast is through other pathways, including direct drainage through the supraclavicular nodes and via the internal mammary chain.⁶⁸ Because the majority of drainage is through the axilla, and because of potential morbidity of internal mammary lymph node dissection, most surgeons limit surgical evaluation of lymph nodes to the axilla.

The axilla contains an average of 15 to 20 lymph nodes extending under the axillary vein medially toward the thoracic inlet. Until the last decade, evaluating these nodes required dissection of the entire axillary contents. A safe operation, it carries substantial risk of long-term morbidity related to disruption of the lymphatic flow from the arm and permanent swelling, termed lymphedema.^{69–71} Lymphedema is a chronic lifelong condition that ranges from minimal effects to disabling swelling. The risk of lymphedema is about 10% with axillary dissection alone and substantially higher when radiation is also required after node dissection.^{37,72}

During the 1990s, the hypothesis that lymphatic drainage to the axilla could be mapped using radioactive or large colloidal particle tracers and that the first few lymph nodes identified by these mappings would define the status of the lymph nodes was tested and proven accurate.⁷³ Termed the sentinel lymph node, the first few lymph nodes can be identified and full axillary lymph node dissection limited only to those women with proven nodal metastases. Morbidity, including the risk of lymphedema, is lower with SNB than with axillary dissection, but lymphedema still may occur.³⁶

SNB is appropriate for women with clinically negative nodes. Those with clinically positive nodes are not candidates for SNB and should have full axillary lymph node dissection. If there is a question about nodes, involvement of nodes may be confirmed before surgery using ultrasound-guided needle biopsy (core biopsy or FNA).

SNB is performed by injecting radiolabeled tracer and/or vital dyes that drain to and are trapped in the initial lymph nodes in the chain. The injection is generally in the periareolar skin and under the nipple-areola complex. This identifies an average of three lymph nodes, which are then removed and examined for metastases. SNB is appropriate in virtually all women with invasive breast cancer clinically negative nodes. SNB may be performed in women with local recurrence after previous breast-conserving surgery and radiation, although the accuracy of SNB in this setting has never been tested.

BREAST RECONSTRUCTION

Women treated with mastectomy may consider reconstruction of the breast mound performed either at the time of mastectomy (immediate reconstruction) or at a later time (delayed reconstruction).⁷⁴ Immediate reconstruction is reasonable in women with early-stage breast cancer. However, the potential need for postmastectomy radiation must be considered in reconstruction planning.⁵⁴ Although satisfactory cosmetic outcomes may be obtained even with radiation to the implant, radiation increases the rate of painful scar contracture. Decisions regarding immediate breast reconstruction should be made in collaboration with the entire multidisciplinary treatment team. Conversely, delayed reconstruction requires that the woman live without the reconstructed breast for a period of 1 to 2 years and may be more difficult to perform because there is less skin remaining from the original mastectomy to be used in reconstruction.

Options for breast reconstruction include prosthetic reconstruction with an implant or “tissue expander implant” generally placed beneath the pectoralis major muscle or transfer of autologous tissue from another region in the body.⁷⁴ Implant reconstruction is generally simpler and quicker to perform but may not leave as attractive an aesthetic result. Complications of implant reconstruction include contracture around the implant (which may be exacerbated if radiation is necessary) and infection, resulting in loss of the implant. Autologous tissue reconstruction often leaves a superior cosmetic result but at the cost of more complex surgery, longer recovery, and the potential for complications at the site of the donor tissue. The most common donor sites are the rectus abdominus muscle (so-called transverse rectus abdominus myocutaneous [TRAM] flap), the more superficial fat and skin from the abdominal wall (deep inferior epigastric perforator [DIEP] flap), and the latissimus dorsi muscle flap. These flaps may be used in conjunction with complete sparing of all the skin of the breast that provides for an even better cosmetic result. In general, the nipple and areola are resected with mastectomy, but in select circumstances, such as small tumors located in the periphery of the breast, some surgeons have been experimenting with mastectomy that preserves the nipple.^{75–77}

ADJUVANT SYSTEMIC THERAPY



Women with invasive cancer also face the risk of developing distant metastases. These metastases develop from microscopic dissemination of cancer cells prior to diagnosis. Staging studies including CT, PET, and MRI are not insensitive at detecting this microscopic disease. In stage I and stage II cancer, these studies are unnecessary unless there are symptoms such as new skeletal pain or other constitutional symptoms. The chance of identifying metastatic disease is very low, and there is a substantial chance of false positive scans, requiring extensive evaluation and invasive studies.

Therefore, every woman with invasive cancer must consider whether to receive systemic adjuvant therapy to prevent the growth of this microscopic metastatic disease [see Figure 4]. The decision depends on both the estimated risk of developing metastatic disease and the degree of benefit that treatment may provide. These risks are estimated by analysis

Clinical Stage I / II (Tumor < 5 cm) Adjuvant systemic therapy: Consider in all cases: Based on • Primary tumor characteristics • Hormone receptor status • HER-2/<i>neu</i> status • Genomic profiling <u>Principles of Systemic Therapy</u> • ER positive: endocrine therapy and consider adding chemotherapy even with negative nodes • ER negative: consider chemotherapy even with negative nodes • HER-2/<i>neu</i> positive: add trastuzumab to chemotherapy
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Figure 4 Principles of adjuvant systemic therapy.
ER = estrogen receptor.

of features about the cancer, including the size of the invasive component of the cancer, the presence or absence of regional lymph node metastases, the grade of the cancer, and the presence or absence of specific biomarkers associated with prognosis and response to treatment. The three clinically used markers are the estrogen receptor, the progesterone receptor, and HER-2/*neu* protein expression or gene amplification. In making these assessments, it must be recognized that a substantial fraction of women with negative lymph nodes still develop metastatic disease.¹⁵

Treatment entails two major classes of drugs: endocrine drugs, which block the effect of circulating estrogen on breast cancers that express estrogen and progesterone receptors, and systemic cytotoxic chemotherapy. The best available treatments are codified in widely accepted practice guidelines developed and updated annually by the NCCN.¹⁶

Endocrine therapy is effective only for women whose tumors express hormone receptors. This includes premenopausal women and postmenopausal women as they have low levels of circulating estrogens from non-ovarian sources. There are two primary classes of endocrine drugs: SERMs, of which the primary agent used in breast cancer is tamoxifen, and aromatase inhibitors, which block peripheral synthesis of estrogen and are effective only in postmenopausal women.⁷⁸ Recent clinical trials demonstrated that aromatase inhibitors are superior to tamoxifen in preventing the recurrence of breast cancer, with a slightly improved safety profile in postmenopausal women. Aromatase inhibitors are not effective in premenopausal women, for whom tamoxifen remains the drug of choice. These drugs are remarkably safe and effective, with only rare serious side effects.

With only a few exceptions, all women with hormone receptor–positive breast cancers should receive prolonged endocrine therapy. At least 5 years of therapy is warranted.

Ongoing clinical trials are addressing whether prolonged therapy with aromatase inhibitors may be of value.

Women with hormone receptor-positive breast cancers should consider whether to also receive systemic chemotherapy. A large body of evidence from clinical trials shows that survival may be improved by the addition of chemotherapy.^{79,80} However, the magnitude of benefit over the benefit of endocrine therapy alone may be small. For otherwise healthy women who have positive lymph nodes, additional chemotherapy may be strongly considered. For those with negative nodes, the benefit varies according to the characteristics of the cancer. Until recently, many women received chemotherapy for a survival advantage as low as 1%. Recently, genomic profiling of cancers through characterization of the expression of multiple genes has allowed identification of women in this situation with a very high and with a very low risk of distant disease and also has to find which patients benefit from chemotherapy.^{81,82} The most widely used genomic profiling system in breast cancer in 2009 is OncotypeDx. This profiling is validated for use in women with hormone receptor-positive, lymph node-negative invasive breast cancer.

Endocrine therapy is not effective in women with hormone receptor-negative breast cancer. For these women, the only treatment to reduce the risk of distant metastases is cytotoxic chemotherapy.^{79,80} Unless otherwise contraindicated by serious comorbidities, women with cancers over 1 cm and negative hormone receptors should receive chemotherapy.¹⁶ Those with tumors under 1 cm have a lower risk of distant metastases and may derive substantially less benefit from chemotherapy.

Breast cancers that express the HER-2/neu protein have a higher risk of developing distant metastases. However, the monoclonal antibody trastuzumab (Herceptin) directed against HER-2 has proven to be safe and effective when given in combination with chemotherapy. The risk of distant metastatic disease is cut by about half over the benefit of chemotherapy alone when combined with trastuzumab.⁸³

The most difficult situation is when estrogen, progesterone, and HER-2/neu are negative. So-called “triple negative cancers” are more common in younger women, those of African American ancestry, and those with inherited susceptibility. There is active ongoing clinical research to define improved approaches in this setting.

Clinical trials over the last three decades have defined the most effective drugs in breast cancer. Chemotherapy drugs are most effective when used in combination with other drugs. The most effective drugs in breast cancer are the anthracyclines, of which the most widely used agent is doxorubicin (Adriamycin), cyclophosphamide (Cytosan), and the taxanes (paclitaxel and docetaxel). Readers are referred to a large-scale meta-analysis of the value of adjuvant chemotherapy and endocrine therapy and to recent reviews on the subject.^{79,80,84}

Decisions regarding adjuvant systemic therapy are complex for both patients and their physicians. To aid these decisions, there are mathematical models that incorporate relevant prognostic factors and provide individualized risk of distant recurrence and benefit from treatment. The most widely used models are Adjuvant! (www.adjuvantonline.com) and CancerMath.net (<http://cancer.lifemath.net/>).^{85–87}

NEOADJUVANT SYSTEMIC THERAPY AND LOCALLY ADVANCED BREAST CANCER

Locally advanced breast cancer is generally defined as any tumor over 5 cm, involving the skin, or with extensive lymph node involvement [see Figure 5]. In these cases, surgery may be difficult and even standard mastectomy may not be possible. With the advent of chemotherapy in the 1970s, clinical trials investigated the value of systemic treatments, most notably chemotherapy, prior to surgery. These demonstrated that such “neoadjuvant” presurgical therapy with locally advanced breast cancer often reduced the size and extent of the cancer more than 50%, which often allowed standard surgery. Equally interesting was that 15 to 25% had complete disappearance of cancer clinically and half of these women had no viable tumor identified pathologically (pathologic complete response). Neoadjuvant chemotherapy became the accepted standard treatment for locally advanced and inflammatory breast cancer (stage III).

This finding with locally advanced breast cancer led to studies of presurgical chemotherapy with lower-stage cancer.⁸⁸ Large-scale studies, most notably the NSABP B-18 study, demonstrated similar cancer responses with presurgical chemotherapy.⁸⁹ Neoadjuvant therapy did not convey any survival advantage over chemotherapy administered postoperatively. However, women treated with presurgical chemotherapy were more likely to have BCT, and the rate of local recurrence after this treatment was equivalent to that of others receiving BCT. The degree of response to neoadjuvant therapy is itself of significant prognostic importance.^{89–91} Those women who achieve a major response, especially those who achieve a complete pathologic response in the tumor, are more likely to have long-term survival compared with those who do not.⁸⁸ These and other factors have led to an increasing use of neoadjuvant therapy.

Presurgical endocrine therapy may also be of value in select cases.^{92,93} A response to neoadjuvant chemotherapy is most likely among women with high-grade and hormone receptor-negative cancers. Those with endocrine receptor-positive cancers may be somewhat less likely to respond. However, these tumors may also respond to presurgical endocrine therapy, with similar benefits in terms of surgical treatment. With endocrine therapy, the time to maximal tumor response is longer than with chemotherapy; it may take 6 months to achieve maximum tumor response prior to surgery.

It is therefore reasonable to administer neoadjuvant therapy to any woman who would otherwise receive chemotherapy for treatment for breast cancer. In general, neoadjuvant therapy is administered to those with larger T2 cancers (those over three or 4 cm in size) and T3 cancers in an effort to allow breast conservation. In addition, neoadjuvant therapy is the treatment of choice for those with cancer that involves the skin or chest wall (T4), with extensive lymph node involvement clinically, or those who have inflammatory cancer. Regardless of the final surgery type and the degree of tumor response, women with locally advanced breast cancer should receive surgery and radiation.⁹⁴

STAGE IV BREAST CANCER

A small fraction of breast cancers have distant metastases (stage IV) at the time of the initial cancer presentation [see



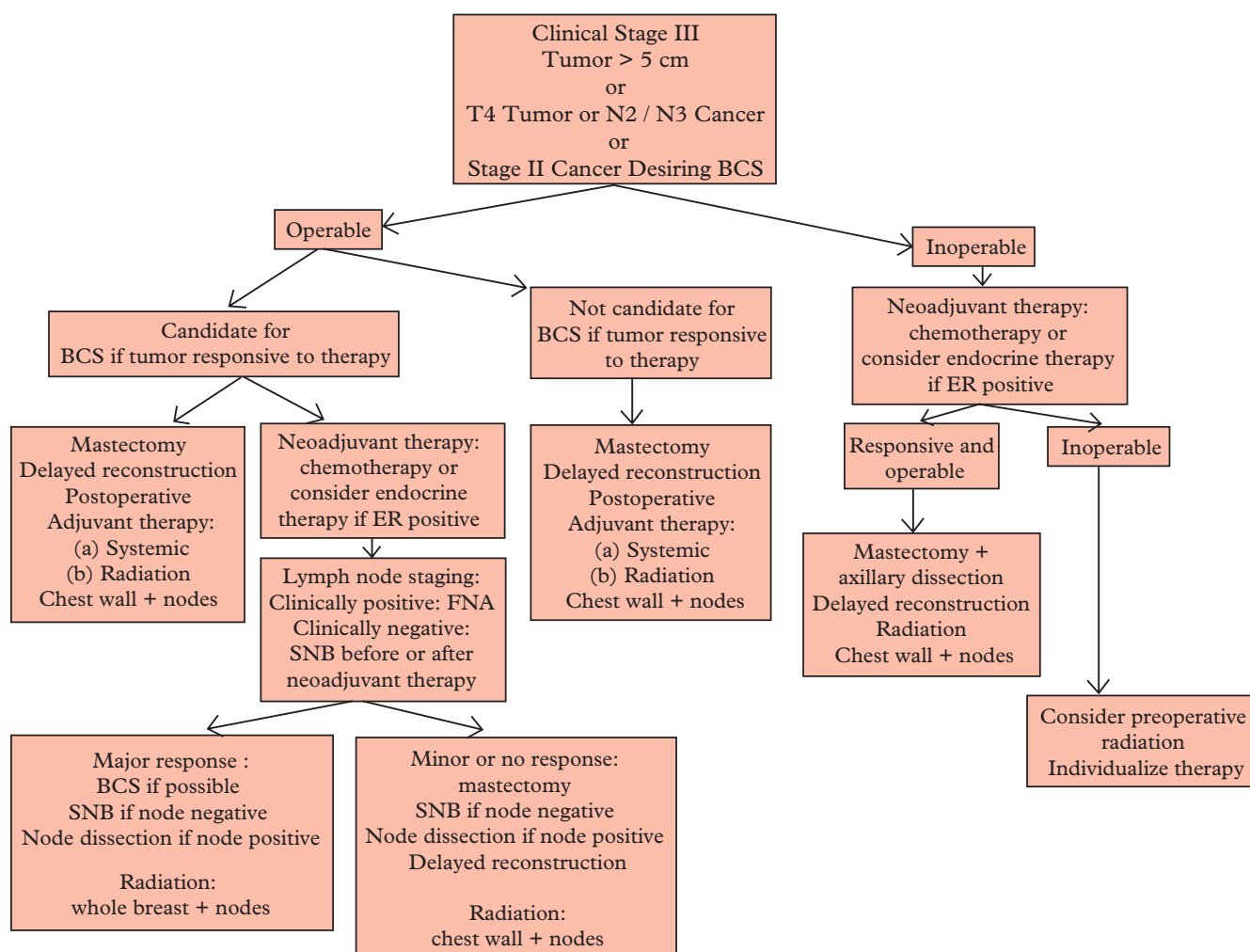


Figure 5 Schema for treatment of locally advanced breast cancer. BCS = breast-conserving surgery; ER = estrogen receptor; FNA = fine-needle aspiration; SNB = sentinel node biopsy.

Figure 6]. This disease is generally incurable, and treatment is targeted at preventing disease progression for the longest time possible while maintaining high quality of life. It is generally necessary to obtain tissue from the primary tumor to obtain hormone receptor and HER-2/neu information, as well as to biopsy a metastatic site if there is any doubt regarding whether the metastatic deposit is truly a metastasis.

First-line treatment is generally systemic therapy.¹⁶ In the absence of symptomatic or aggressive visceral disease, those with endocrine-sensitive tumors are best treated with oral endocrine therapy. Many may achieve a major response and have long, progression-free intervals with high quality of life without significant treatment-related toxicity. Those with hormone receptor-negative cancers may begin with systemic chemotherapy.

For those diagnosed with metastases before the primary tumor in the breast is removed, there is generally no reason to do surgery. Systemic treatment often provides a major response in the breast and achieves sufficient local control for the duration of the woman's life. For those women fortunate enough to have prolonged survival but in whom the primary

tumor does progress, surgery and/or radiation may be used for local control and preserving quality of life.

There is an interesting literature from population cancer registries suggesting that those women who present with metastatic disease who undergo surgery at the time of diagnosis have longer survival than those who do not have surgery.⁹⁵⁻⁹⁷ However, this finding is most likely a selection bias in that women with a lower burden of disease are more likely to have undergone surgery before the discovery of the metastatic cancer and are therefore more likely to survive longer. There are no controlled clinical trial data to support either argument.

Breast Cancer in Pregnancy

Breast cancer is uncommon in young women but may occur during the childbearing years. Therefore, breast cancer may occur during pregnancy and, in fact, is the second most common cancer associated with pregnancy. Women in this age group are generally not undergoing routine breast cancer screening, and changes in the breast associated with pregnancy can mask the presence of a mass. Therefore, breast



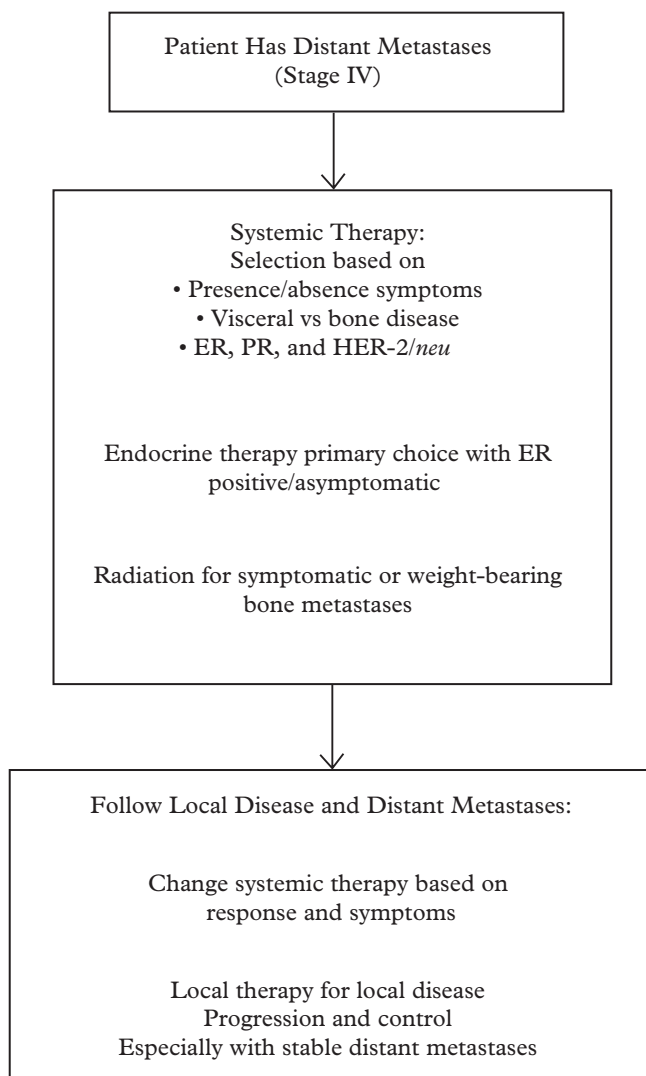


Figure 6 Schema for treatment of women with cancer with distant metastases at presentation (stage IV). ER = estrogen receptor; PR = progesterone receptor.

cancer diagnosis is often delayed in this situation. Women with a suspicious breast mass detected during pregnancy should be evaluated aggressively. Imaging can generally be done with judicious use of mammography, ultrasonography, and biopsy performed as in any woman with a suspicious breast lesion.

The principles of treatment are the same as in any woman with breast cancer.⁹⁸ The only limitations are that chemotherapy cannot be administered during the first trimester and radiation cannot be administered until after delivery. However, neither of these issues limits aggressive treatment of women with breast cancer during pregnancy. Termination of the pregnancy is not necessary, although some women diagnosed early in pregnancy may choose to do so.

Older texts suggested that mastectomy is the preferred treatment in women with breast cancer during pregnancy. However, the same choices are available to women with cancer during pregnancy because the radiation that is administered is generally delayed until after chemotherapy and

therefore is timed to occur after delivery of the child. Therefore, breast conservation can be used safely during pregnancy. Similarly, chemotherapy may be used safely during pregnancy. There are extensive data demonstrating the safety of chemotherapy for both the mother and the fetus. SNB may also be performed during pregnancy using the radioactive tracers. The estimated radiation dose to the fetus is exceedingly low and is considered safe.⁹⁹ The vital dyes isosulfan blue and methylene blue have potential teratogenic effects and are contraindicated during pregnancy.

Women who have breast cancer at a young age or during pregnancy may wish to have additional children. Decades ago, they were advised against this because of concern that hormonal changes associated with pregnancy could promote recurrence. This has been proven incorrect. Women may choose to have children after breast cancer treatment with no additional risk of breast cancer recurrence and death.

Breast Cancer in Men

Breast cancer occurs in men with an incidence less than 1% of that of women. No screening for men is warranted, but a mass in the breast should be fully evaluated. Most masses proved to be gynecomastia. Breast cancer in a younger man may be indicative of inherited susceptibility within that family particularly related to *BRCA2*. Careful family history and counseling regarding this risk should be provided.

The treatment of breast cancer in men follows the same principles as in women.^{100,101}

Surgery is generally mastectomy because of the tumor is directly under the nipple complex. Wide margins should be obtained. Radiation may be administered if the tumor is larger or involves the skin and/or chest wall. SNB and axillary lymph node dissection should be performed using the same indications as in women. Men should also receive adjuvant systemic therapy using the same criteria as women. Most are hormone receptor positive, and endocrine therapy is effective.

Follow-up after Breast Cancer Treatment

Patients who have been treated for invasive breast cancer are at risk for developing distant metastases, local recurrence, and a contralateral or ipsilateral new breast cancer. Most recurrences occur within the first 5 to 10 years, with the peak at 4 to 6 years. Occasionally, women develop distant metastases many years later.

Women with breast cancer often assume that careful screening is warranted to allow early detection of metastases on the assumption that early detection will provide a better chance of a successful outcome. Unfortunately, there is no such entity as early metastatic cancer. Once breast cancer metastases are established to the extent that they are detectable, there is no therapy that is curative, and treatment is largely palliative, as discussed above related to stage IV breast cancer. Because of this, extensive testing for metastatic disease on a periodic basis does not provide any advantage to a woman with breast cancer.¹⁰² This question has actually been tested in randomized clinical trials of extensive testing versus simple follow-up for local recurrence only combined with evaluation of any symptoms suggestive of metastatic disease.

These studies showed no survival advantage despite detection of metastatic disease, and those recurred an average of 3 months earlier in the screened group.

Screening women for evidence of local recurrence with both invasive and in situ cancer may be of value. This should include mammography of the ipsilateral breast in women treated with breast conservation, contralateral mammography for all women, and a careful history and physical examination. Mammography should be done annually, with the history and physical examination done every 6 to 12 months. The role of breast MRI in breast cancer follow-up is unclear. Women should maintain a primary care provider to be sure that other regular medical care is provided.

CANCER SURVIVORSHIP

In addition to covering medical issues in cancer follow-up, surgeons should provide ongoing resources to help women adjust to the cancer diagnosis, deal with psychological issues, address cancer genetic and family concerns, and identify other long-term sequelae of cancer.¹⁰³ Patients should be provided with a written “care plan” for their ongoing care and should be encouraged to seek individual counseling and participate in support groups as they see the need and to gain the value of engagement in the vast array of support and advocacy activities available in most communities.¹⁰⁴

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2 SOFT TISSUE INFECTION

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Approach to the Patient with Soft Tissue Infection

Soft tissue infections are a diverse group of diseases that involve the skin and underlying subcutaneous tissue, fascia, or muscle. Such infections may be localized to a small area or may involve a large portion of the body. They may affect any part of the body, though the lower extremities, the perineum, and the abdominal wall are the most common sites of involvement. Some soft tissue infections are relatively harmless if treated promptly and adequately; others can be life-threatening even when appropriately treated. The symptoms and signs range from subtle or nonspecific indicators (e.g., pain, localized tenderness, and edema without fever) to obvious features (e.g., necrosis, blistering, and crepitus associated with systemic toxicity).

Soft tissue infections were first defined as such more than a century ago. In 1883, Fournier described a gangrenous infection of the scrotum that continues to be associated with his name.¹ In 1924, Meleney documented the pathogenic role of streptococci in soft tissue infection.² Shortly thereafter, Brewer and Meleney described progressive polymicrobial postoperative infection of the muscular fascia with necrosis³ (though the term necrotizing fasciitis was not introduced until more than 25 years later⁴). The association between toxic-shock syndrome and streptococcal soft tissue infection was delineated as this disease reemerged in the 1980s.⁵

Various classification systems and eponyms are used to describe specific forms of soft tissue infection [see Discussion, Etiology and Classification of Soft Tissue Infection, below]. In our view, however, it is more important to develop a common approach to the diagnosis and treatment of these conditions than to refine the minor details of classification. For therapeutic purposes, the primary consideration is to distinguish between necrotizing soft tissue infections and nonnecrotizing infections. Nonnecrotizing soft tissue infections involve one or both of the superficial layers of the skin (epidermis and dermis) and the subcutaneous tissue, and they usually respond to antibiotic therapy alone. Necrotizing soft tissue infections may involve not only the skin, the subcutaneous tissue, and the superficial fascia but also the deep fascia and muscle, and they must be treated with urgent surgical debridement. At times, it is difficult to distinguish between these two categories of infection, especially when obvious clinical signs of necrotizing soft tissue infection are absent.

In this chapter, we review diagnosis and management of the main soft tissue infections seen by surgeons, including both superficial infections (e.g., pyoderma, animal and human bites, and cellulitis) and necrotizing infections involving superficial and deep tissues [see Table 1].

Clinical Evaluation

The diagnosis of soft tissue infection is usually made on the basis of the history and the physical examination. Patients typically seek medical attention because of pain, tenderness, and erythema of recent onset. They should be asked about environmental

factors that may have disrupted the normal skin barrier [see Table 2], as well as about any host factors that may increase their susceptibility to infection and limit their ability to contain it. It is particularly important that they be questioned about specific clinical scenarios associated with unusual pathogens, such as an animal bite (associated with *Pasteurella multocida*), a human bite (*Eikenella corrodens*), chronic skin diseases (*Staphylococcus aureus*), saltwater exposure or ingestion of raw seafood (*Vibrio vulnificus*), and brackish or freshwater exposure (*Aeromonas hydrophila*).

Physical examination usually reveals erythema, tenderness, and induration. Vesicular lesions and honey-colored crusted plaques are seen in patients with impetigo. Intense, sharply demarcated erythema is characteristic of erysipelas. A tender, swollen erythematous papule, often containing a visible hair shaft, is indicative of folliculitis. A single painful, tender, indurated, erythematous skin nodule suggests a furuncle, and the presence of multiple inflammatory nodules with sinus tracts is consistent with a carbuncle. Cellulitis in association with a decubitus ulcer or an ischemic leg ulcer frequently signals a polymicrobial infection with gram-negative organisms. An erythematous linear streak, characteristic of lymphangitis, usually indicates a superficial infection secondary to *Streptococcus pyogenes*; associated lymphadenopathy may be present as well.

Patients with necrotizing soft tissue infections often complain of severe pain that is out of proportion to their physical findings. Compared with patients who have nonnecrotizing infections, they are more likely to have fever, bullae, or blebs [see Figure 1]; signs of systemic toxicity; hyponatremia; and leukocytosis with a shift in immature forms. Physical findings characteristic of a necrotizing infection include tenderness beyond the area of erythema, crepitus, cutaneous anesthesia, and cellulitis that is refractory to antibiotic therapy.⁶ Tenderness beyond the borders of the erythematous

Table 1 Common Soft Tissue Infections

Superficial infections	Pyoderma
	Impetigo
	Erysipelas
	Folliculitis
	Furuncles and carbuncles
	Infections developing in damaged skin
	Animal bites
	Human bites
	Cellulitis
	Nonnecrotizing
Deep necrotizing cutaneous infections	Necrotizing
	Necrotizing fasciitis
	Myonecrosis
	Gas gangrene
	Metastatic gas gangrene

Table 2 Environmental Factors That Disrupt Skin and Alter Normal Barrier Function

Cuts, lacerations, or contusions
Injections from contaminated needles
Animal, human, or insect bites
Burns
Skin diseases (e.g., atopic dermatitis, tinea pedis, eczema, scabies, varicella infection, or angular cheilitis)
Decubitus, venous stasis, or ischemic ulcers
Contaminated surgical incisions

area is an especially important clinical clue that develops as the infection in the deeper cutaneous layers undermines the skin. Early in the course of a necrotizing soft tissue infection, skin changes may be minimal despite extensive necrosis of the deeper cutaneous layers. Bullae, blebs, cutaneous anesthesia, and skin necrosis occur as a result of thrombosis of the nutrient vessels and destruction of the cutaneous nerves of the skin, which typically occur late in the course of infection.

Clinicians should be mindful of certain diagnostic barriers that may delay recognition and treatment of necrotizing soft tissue infections.⁷ In particular, these infections have a variable clinical presentation. Although most patients present with an acute, rapidly progressive illness and signs of systemic toxicity, a subset of patients may present with a more indolent, slowly progressive infection. Patients with postoperative necrotizing infections often have a more indolent course. Moreover, in the early stages, underlying necrosis may be masked by normal-appearing overlying skin. As many as 20% of necrotizing soft tissue infections are primary (idiopathic) and occur in previously healthy patients who have no predisposing factors and no known portal of entry for bacterial inoculation. Finally, crepitus is noted in only 30% of patients with necrotizing soft tissue infections. Overall, fewer than 40% of patients exhibit the classic symptoms and signs described.^{8,9} Accordingly, it is imperative to maintain a high index of suspicion for this disease in the appropriate setting.

Investigative Studies

Diagnostic studies have a low yield in patients with superficial soft tissue infections. They are rarely necessary and are used only in specific clinical circumstances. Either needle aspiration at the advancing edge of erythema with Gram staining and culture or full-thickness skin biopsy and culture may be helpful when cellulitis is refractory to antibiotic therapy or when an unusual causative organism is suspected. Because of their low yield, blood cultures are obtained only in patients with signs of systemic toxicity, those with buccal or periorbital cellulitis, and those with infection suspected of being secondary to saltwater or freshwater exposure; these clinical situations are associated with a higher likelihood of a positive culture.

When the characteristic clinical features of necrotizing soft tissue infection are absent, diagnosis may be difficult. In this setting, laboratory and imaging studies become important [see Figure 2]. In one study, logistic regression analysis showed that an elevated white blood cell (WBC) count ($\geq 15,400/\text{mm}^3$) and hyponatremia (serum sodium level lower than 135 mmol/L) at the time of hospital admission were highly sensitive for the presence of a necrotizing soft tissue infection; however, the positive predictive

value of these findings was only 26%.¹⁰ The absence of these findings in a patient without obvious clinical signs of a necrotizing soft tissue infection had a negative predictive value of 99%. A normal serum creatine kinase (CK) level rules out muscle necrosis.

In a 2004 report, one group of investigators described the development and application of the Laboratory Risk Indicator for Necrotizing fasciitis (LRINEC) score.¹¹ This scoring system assigns points for abnormalities in six independent variables: serum C-reactive protein level ($> 150 \text{ mg/L}$), WBC count ($> 15,000/\text{mm}^3$), hemoglobin level ($< 13.5 \text{ g/dl}$), serum sodium level ($< 135 \text{ mmol/L}$), serum creatinine level ($> 1.6 \text{ mg/dl}$), and serum glucose level ($> 180 \text{ mg/dl}$). With a score of 8 or higher, there is a 75% risk of a necrotizing soft tissue infection. The authors of the report recommended that the LRINEC score be used to determine which patients require further diagnostic testing, given that the negative predictive value of this screening tool was 96%.

A plain x-ray of the involved area demonstrates soft tissue gas in only 15% to 30% of patients with necrotizing infections [see Figure 3].⁶ Computed tomography is more sensitive in identifying soft tissue gas, but other CT findings are seldom diagnostic.

Magnetic resonance imaging is currently the preferred imaging study for documenting deep necrotizing infections [see Figure 4]. The presence of soft tissue gas on MRI is diagnostic of a necrotizing soft tissue infection. T_2 -weighted images demonstrate thickening and increased signal intensity of the deep fascial planes.^{12,13} Increased signal intensity in the subcutaneous tissue and edema of the adjacent muscle are also frequently present. High signal intensity on T_2 -weighted images and tissue enhancement after gadolinium administration are indicative of inflamed tissue and may also occur with certain nonnecrotizing soft tissue conditions (e.g., exertional muscle injury, lymphedema, dermatomyositis, polymyositis, eosinophilic fasciitis, and neoplastic disease).¹³⁻¹⁷ Low or absent signal intensity on gadolinium-enhanced T_1 -weighted images is indicative of necrosis, a finding that is more specific for a necrotizing soft tissue infection.¹⁸⁻²⁰ The reported sensitivity of MRI for diagnosis of necrotizing soft tissue infection ranges from 89% to 100%, and its specificity ranges from 46% to 86%.^{18,20}

A prospective study from 2000 evaluated the use of MRI to differentiate necrotizing from nonnecrotizing soft tissue infection in nine patients.²⁰ The absence of gadolinium enhancement on T_1 -weighted images was indicative of fascial necrosis in all six patients



Figure 1 Lower-extremity necrotizing fasciitis is characterized by bullae, blebs, and discolored skin.

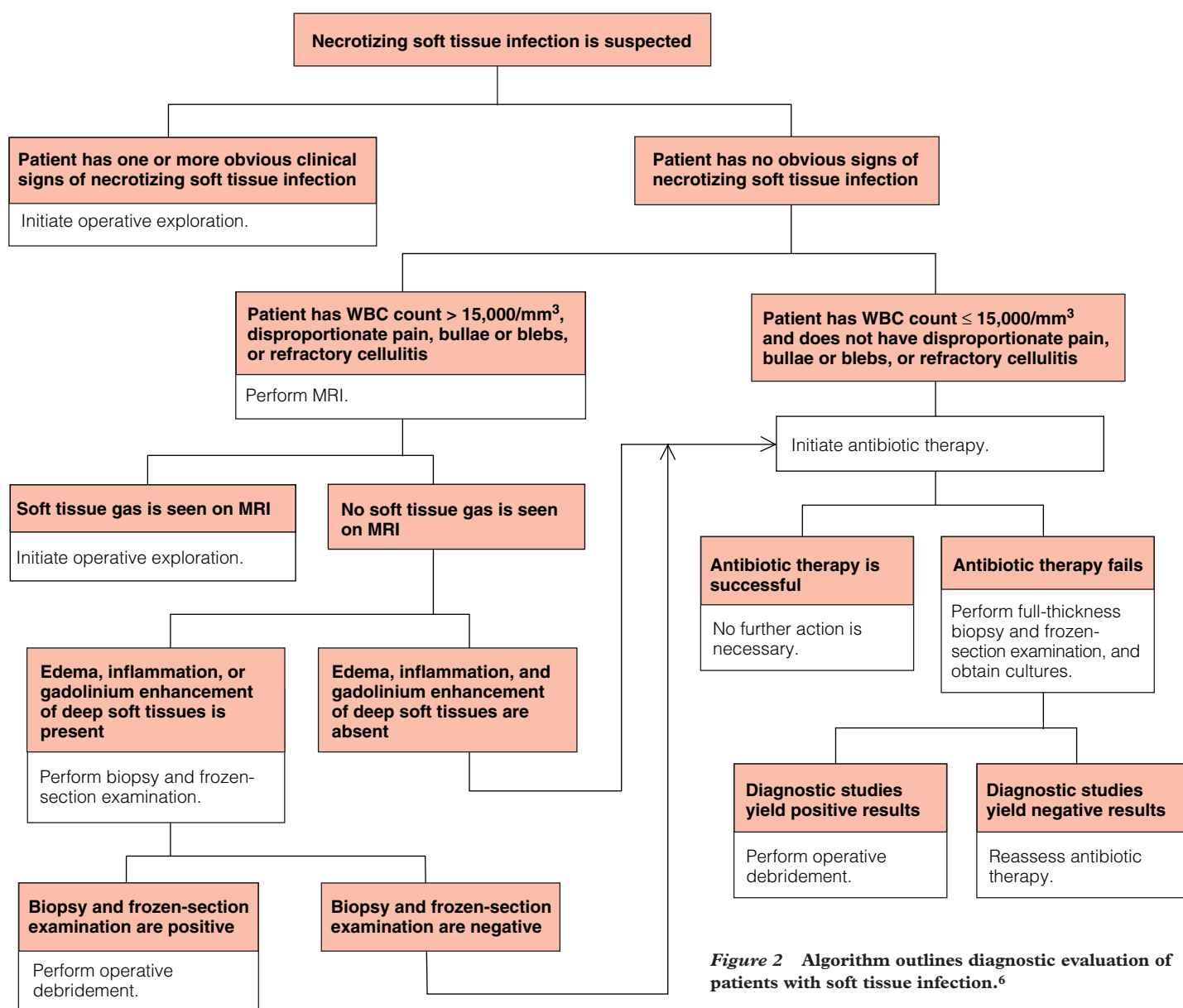


Figure 2 Algorithm outlines diagnostic evaluation of patients with soft tissue infection.⁶

who underwent operative debridement.²⁰ Operation was avoided in two patients who showed no evidence of necrosis on MRI. A third patient without MRI evidence of necrosis underwent operative exploration because of a high degree of clinical suspicion and was diagnosed as having nonnecrotizing cellulitis. In a prospective study from 1998, the investigators successfully employed MRI to differentiate necrotizing from nonnecrotizing infections in 16 of 17 patients (11 of 11 patients with necrotizing fasciitis and five of six patients with nonnecrotizing cellulites).¹⁹

The finding of soft tissue gas on diagnostic imaging warrants immediate operative exploration and debridement. Because of the high sensitivity of MRI, necrotizing infection can be excluded when no involvement of the superficial fascia, subcutaneous tissue, or the deeper cutaneous layers is demonstrated. However, the inflammatory changes seen on MRI when necrotizing soft tissue infection is present may also be seen in patients with nonnecrotizing infections, as well as in those with other inflammatory conditions affecting the deep soft tissues. Because of the relatively low specificity of this study, biopsy of the deeper cutaneous layers, with frozen-section examination and culture, may be needed to diag-

nose or rule out soft tissue infection [see Figure 2]. This procedure may be performed at the bedside with local anesthesia. The observation of necrotic or infected tissue through the biopsy incision indicates that immediate debridement is needed.

General Management of Nonnecrotizing and Necrotizing Soft Tissue Infection

NONNECROTIZING INFECTION

Antibiotic therapy is the cornerstone of treatment for patients with nonnecrotizing infections. Such patients usually require antibiotics that are effective against group A streptococci or *S. aureus*. The prevalence of community-acquired methicillin-resistant *S. aureus* (MRSA) strains has increased significantly. These strains now outnumber methicillin-sensitive strains by a two-to-one margin.²¹ This development has necessitated a change in the empirical treatment of these infections. Topical, oral, or intravenous preparations may be employed, depending on the nature and severity of the disease process [see Management of Specific

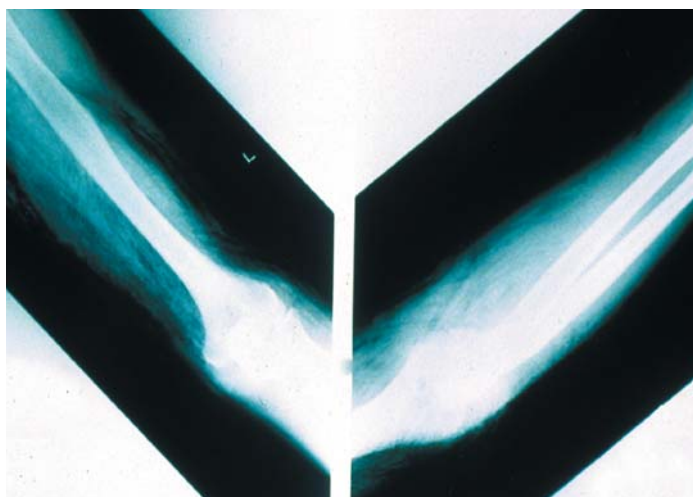


Figure 3 Upper-extremity x-ray of a patient with necrotizing soft tissue infection demonstrates soft tissue gas outlining the muscles.

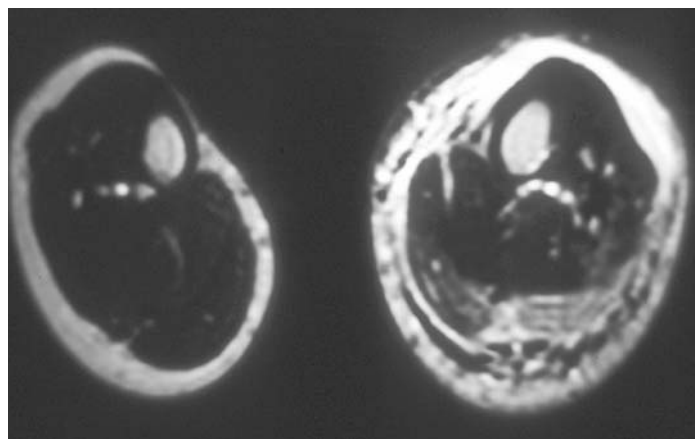


Figure 4 Lower-extremity MRI of a patient with necrotizing fasciitis of the left leg demonstrates inflammatory changes typical of necrosis.

Soft Tissue Infections, *below*]. If polymicrobial infection is suspected, broad-spectrum antimicrobial agents should be given, either alone or in combination.

NECROTIZING INFECTION

Management of necrotizing soft tissue infections is predicated on early recognition of symptoms and signs and on emergency operative debridement. Once the diagnosis of necrotizing soft tissue infection is established, patient survival and limb salvage are best achieved by means of prompt operation; precise identification of the causative bacteria and correct assignment of the patient to a specific clinical syndrome are unnecessary. The delay between hospital admission and initial debridement is the most critical factor influencing morbidity and mortality: a number of reports have demonstrated a strong correlation between survival and the interval between onset of symptoms and initial operation.^{9,22-24}

The components of treatment of necrotizing soft tissue infection are (1) resuscitation and correction of fluid and electrolyte disorders, (2) physiologic support, (3) broad-spectrum antimicrobial therapy, (4) urgent and thorough debridement of necrotic tissue, and (5) supportive care [see *Figure 5*].

Nonoperative Measures

Patients with necrotizing soft tissue infections frequently present with tachycardia and hypotension, reflecting depleted intravascular volume and possible septic shock. Such patients often exhibit extensive extracellular fluid sequestration within the affected area, as well as more generalized sequestration resulting from sepsis. A balanced isotonic electrolyte solution, such as lactated Ringer solution (or 0.9% normal saline, for patients with renal dysfunction), is administered to replace these fluid deficits. The adequacy of intravascular volume repletion is often assessed by monitoring vital signs and urinary output; however, it sometimes proves necessary to use a central venous catheter to monitor central venous or pulmonary arterial pressure in patients with associated myocardial dysfunction, septic shock, chronic pulmonary disease, renal insufficiency, or other severe chronic illnesses.

Hyponatremia is usually corrected by infusing isotonic fluids. Hypocalcemia, which can result from calcium precipitation in patients with extensive fat necrosis, is usually corrected by administering I.V. calcium gluconate. Hyperglycemia is corrected with insulin, given either via subcutaneous injection or, for patients with more severe abnormalities, via I.V. infusion. Lactic acidosis generally responds to fluid administration. Renal function is assessed by measuring blood urea nitrogen (BUN) and serum creatinine concentrations. CK levels should be monitored and a qualitative evaluation of urine myoglobin done if muscle necrosis is suspected or renal failure is present. Myoglobinuria and elevated CK levels are

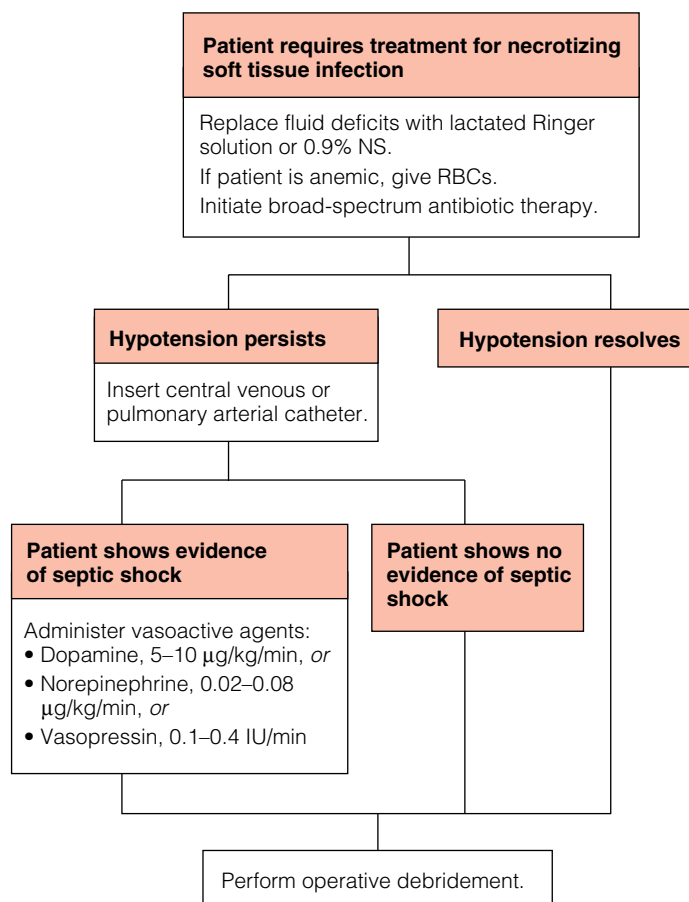


Figure 5 Algorithm outlines treatment of necrotizing soft tissue infection.

Table 3 I.V. Antibiotic Dosages for Adult Patients with Necrotizing Soft Tissue Infection and Normal Renal Function

Single agents	Ampicillin-sulbactam	3 g q. 6 hr
	Imipenem-cilastatin	500–750 mg q. 6 hr
	Meropenem	1–2 g q. 8 hr
	Piperacillin-tazobactam	3.375 g q. 6 hr
	Ticarcillin-clavulanate	3.1 g q. 6 hr
Agents used in combination regimens	Aerobic/facultative coverage	
	Ampicillin	2 g q. 6 hr
	Cefotaxime	1–2 g q. 8 hr
	Ceftazidime	1 g q. 8 hr
	Cefuroxime	1.5 g q. 8 hr
	Ciprofloxacin	400 mg q. 12 hr
	Daptomycin	4 mg/kg q. 24 hr
	Gentamicin	1.7 mg/kg q. 8 hr or 5.1 mg/kg q. 24 hr
	Linezolid	600 mg q. 12 hr
	Moxifloxacin	400 mg q. 24 hr
	Tigecycline	100 mg initially; then 50 mg q. 12 hr
	Vancomycin	1 g q. 12 hr
	Anaerobic coverage	
	Clindamycin	600–900 mg q. 8 hr
	Metronidazole	500 mg q. 6 hr

suggestive of myonecrosis. Anemia is treated with packed red blood cell transfusions.

Patients whose hypotension does not resolve with appropriate intravascular fluid resuscitation often experience septic shock. In these circumstances, low dosages of I.V. dopamine (5 to 10 µg/kg/min), vasopressin (0.1 to 0.4 IU/min), or norepinephrine (0.02 to 0.08 µg/kg/min) are useful for raising blood pressure and improving myocardial function.

Patients with traumatic wounds or other contaminated sites should receive tetanus toxoid or human tetanus immunoglobulin, depending on their immunization status.

Hyperbaric oxygen has been advocated as adjunctive therapy for extensive necrotizing infections, particularly those caused by clostridia.²⁵ The beneficial properties of hyperbaric oxygen include inhibition of bacterial exotoxin production [see Discussion,

Pathogenesis of Soft Tissue Infections, *below*], improved leukocyte function, and attainment of tissue oxygen levels that are bactericidal for *Clostridium perfringens* and bacteriostatic for other anaerobic bacteria. Hyperbaric oxygen does not, however, neutralize exotoxin that has already been released.²⁵ At present, except for some data from retrospective studies, there is little evidence supporting the benefits of hyperbaric oxygen therapy. Such therapy has not been demonstrated to improve survival or to bring about earlier resolution of necrotizing soft tissue infection, and it has been associated with barotrauma, pneumothorax, and oxygen toxicity. Accordingly, we believe that operative debridement should not be delayed to accommodate hyperbaric oxygen therapy and that such therapy should not be considered a substitute for complete debridement of infected nonviable tissues.

I.V. antimicrobial therapy is indicated in all patients with necrotizing soft tissue infections [see Table 3]. Such therapy is important, but it is not a substitute for prompt and adequate operative debridement. Necrotizing soft tissue infections are most often caused by a mixed polymicrobial bacterial flora [see Table 4]. Approximately 25% to 30% of necrotizing soft tissue infections are monomicrobial. Although *S. pyogenes* is the bacterium most frequently involved, the microbiology of the infections often cannot be accurately predicted before final identification of organisms on culture. Thus, the empirical antibiotic regimen chosen should be effective against a diverse group of potential pathogens.²⁶ In addition, because these patients have a high incidence of associated nosocomial infections and even of metastatic infections, it is important to ensure that the dosage is high enough to achieve adequate serum concentrations.^{9,23} Once the results of intraoperative culture and antimicrobial sensitivity testing become available, antibiotic therapy is adjusted accordingly. This adjustment can be challenging, in that all of the pathogens identified must be treated.

I.V. antimicrobial therapy is continued until operative debridement is complete, there is no further evidence of infection in the involved tissues, and signs of systemic toxicity have resolved. Topical antiseptic agents (e.g., Dakin solution and Burrow solution) may help control infection that progresses despite adequate debridement and I.V. antibiotics. Topical application of mycostatin powder may help control progressive fungal infection. When patients are able to resume oral intake, they can often be switched from I.V. to oral antimicrobial therapy. Antimicrobial therapy should not, however, be prolonged merely because oral agents are available.

Operative Treatment

The most critical factors for reducing mortality from necrotizing soft tissue infections are early recognition and urgent operative debridement.^{9,22,24,27} The extent of debridement depends on intraoperative findings and cannot be accurately predicted before operation. Operative intervention helps limit tissue damage by removing necrotic tissue, which serves as a nidus for infection.

Thorough exploration is necessary to confirm the diagnosis of necrotizing soft tissue infection and determine the degree of involvement. Aggressive, widespread debridement of all apparent necrotic, infected tissue is essential; antibiotics will not penetrate dead tissues. The underlying necrosis of subcutaneous tissues, fascia, and muscle typically extends beyond the obvious limits of cutaneous involvement. Operative debridement should therefore be continued until viable tissue is reached. In most instances, the involved tissues are easily separated from their surrounding structures. The presence of “dishwater pus” and noncontracting muscle are additional indicators of necrotizing infection. The presence of arterial bleeding generally indicates that tissues are viable; in the

Table 4 Organisms Causing Necrotizing Soft Tissue Infection

Aerobes	Gram-positive
	Group A <i>Streptococcus</i>
	<i>Enterococcus</i> species
	<i>Staphylococcus aureus</i>
	Group B <i>Streptococcus</i>
	<i>Bacillus</i> species
	Gram-negative
	<i>Escherichia coli</i>
	<i>Pseudomonas aeruginosa</i>
	<i>Enterobacter cloacae</i>
	<i>Klebsiella</i> species
	<i>Serratia</i> species
	<i>Acinetobacter calcoaceticus</i>
	<i>Vibrio vulnificus</i>
Anaerobes	<i>Bacteroides</i> species
	<i>Clostridium</i> species
	<i>Peptostreptococcus</i> species

absence of arterial bleeding, tissues are nonviable even if venous bleeding is present. With deep necrotizing infections, debridement of the necrotic fascia and muscle may create large skin flaps that are poorly perfused. It is best to preserve as much viable skin and subcutaneous tissue as possible because these tissues can be essential for later coverage of the wound. Nonviable skin, however, should be resected.

Wound drainage or exudate should be submitted for Gram staining, as well as for aerobic, anaerobic, and fungal cultures and antimicrobial sensitivity testing. Fasciotomy is rarely required. The presence of subcutaneous gas extending beyond areas of nonviable tissue does not necessitate debridement if the surrounding tissues are viable. It is sometimes helpful to perform an exploratory incision over an area beyond the limits of debridement when it is uncertain whether necrosis is undermining viable skin. If no necrotizing infection is found, the incision may be closed primarily.

Reexploration should be routinely performed within 24 to 48 hours to ensure that all necrotic tissue has been debrided. Debridement is repeated as necessary until the infection is controlled. If repeated debridement does not control infection, if there are persistent, fulminant infections of the extremities, or if an extremity remains nonfunctional after debridement has been completed, amputation can be lifesaving. Amputation is most often required for patients with clostridial myonecrosis and for diabetic patients with necrotizing infections.²⁴ In two large series of patients with necrotizing soft tissue infections, the incidence of amputation was approximately 15% to 25%.^{9,22}

Patients with necrotizing soft tissue infections involving the perineum and perirectal areas may need a diverting colostomy to prevent tissue contamination resulting from defecation and to control local infection. Overall, this measure is required in fewer than 25% of cases.⁹

After debridement, the exposed areas should be treated with 0.9% normal saline wet-to-dry dressings. Once the initial infection has been controlled and debridement is no longer necessary, dressing changes can often be performed at the bedside after sufficient analgesics have been given to achieve adequate pain management. Patient-controlled analgesia is frequently useful early in the course of treatment. Propofol or ketamine can be given in the intensive care unit to facilitate pain control during dressing changes.

Early enteral or parenteral nutritional support should be instituted to optimize recovery. Nutritional support should begin once resuscitation is complete, the infection is adequately controlled, and the signs of sepsis have resolved. Because it frequently proves necessary to return the patient to the operating room, enteral feeding tubes should be placed beyond the pylorus so that enteral nutrition can be provided without interruption. Alternatively, parenteral nutrition may be employed.

Once the localized infection is under control and the patient is recovering, the exposed soft tissues should be covered. This is most commonly done with split-thickness skin grafting, though other reconstructive procedures (e.g., rotational flaps) [see 3:7 *Surface Reconstruction Procedures*] can be effective in this setting as well. Vacuum-assisted closure devices can reduce the exposed surface area and lessen the need for skin graft coverage. Exposed tendons, nerves, or bone often should be covered with full-thickness skin to prevent desiccation and preserve limb function. Premature closure of highly contaminated or persistently infected sites usually fails and leads to recurrence of infection and a greater likelihood of death.

When the abdominal or chest wall has been excised to control infection, reconstruction is necessary. Prosthetic mesh is useful for restoring continuity of the abdomen or the chest wall, and overlying moist dressings can help prevent desiccation of underlying vis-

cera. Some have advocated using biologic materials or absorbable mesh for restoration of abdominal wall continuity; however, we prefer to use permanent mesh in most circumstances, especially when omentum is available for interposition between the mesh and the small intestine.⁹

Mortality from necrotizing soft tissue infection ranges from 21% to 29%.^{9,22,24,27,28} Risk factors for mortality include age greater than 60 years, the presence of associated chronic illnesses, a relatively high percentage of total body surface area involved, and, most important, delays in recognition and treatment.^{9,22,24} Patients with truncal involvement or positive blood cultures also have a higher mortality.^{22,28}

Management of Specific Soft Tissue Infections

Normal skin functions as a protective barrier that prevents microorganisms from causing soft tissue infection. The skin is made up of two layers, the epidermis and the dermis [see Figure 6]. The epidermis, the outer avascular epithelial layer, functions as a permeability barrier for the rest of the body. The dermis, the inner layer, contains blood vessels, lymphatic vessels, sweat and sebaceous glands, and hair follicles. The subcutaneous tissue separates the skin from the deep fascia, muscle, and bone. Typically, soft tissue infections result from disruption of the skin by some exogenous factor; less commonly, they result from extension of a subjacent infection or hematogenous spread from a distant site of infection.

SUPERFICIAL INFECTIONS

Superficial infections constitute the majority of soft tissue infections. They primarily involve the epidermis or dermis (pyoderma)

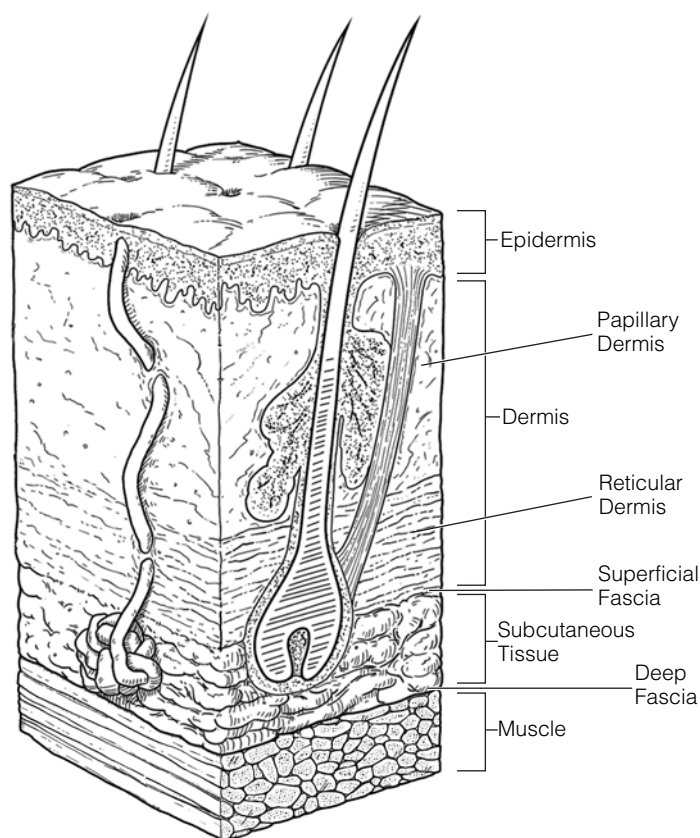


Figure 6 Depicted is the normal anatomy of the skin and the deeper cutaneous layers.⁶

Table 5 Topical and Oral Antibiotic Agents Used for Superficial Soft Tissue Infections*

Mupirocin ointment (2%), applied to affected area t.i.d.†
Erythromycin ointment (2%), applied to affected area b.i.d.†
Clindamycin gel or lotion (1%), applied to affected area b.i.d.†
Gentamicin cream or ointment (0.1%), applied to affected area t.i.d. or q.i.d.
Penicillin V, 250–500 mg q.i.d. (pediatric: 25–50 mg/kg in divided doses q.i.d.)
Amoxicillin, 250–500 mg t.i.d. (pediatric: 20–30 mg/kg/day p.o. in divided doses t.i.d.)
Dicloxacillin, 250–500 mg q.i.d. (pediatric: 12.5–25.0 mg/kg/day in divided doses q.i.d.)
Cephalexin, 250–500 mg q.i.d. (pediatric: 25–100 mg/kg/day in divided doses q.i.d.)
Cefadroxil, 500–1,000 mg b.i.d. (pediatric: 30 mg/kg/day in divided doses b.i.d.)
Erythromycin, 250–500 mg q. 6 hr (pediatric: erythromycin ethyl succinate, 40 mg/kg in divided doses q.i.d.)
Clindamycin, 150–450 mg q.i.d. (pediatric: 20 mg/kg/day in divided doses t.i.d. or q.i.d.)
Trimethoprim-sulfamethoxazole, 160/800 mg b.i.d.
Amoxicillin-clavulanate, 500 mg t.i.d. (pediatric: 40 mg/kg/day in divided doses t.i.d.)
Ciprofloxacin, 500 mg p.o., b.i.d.

*All dosages are for patients with normal renal function.

†Adult dosage and pediatric dosage are the same.

or the subcutaneous tissue (cellulitis) and secondarily occur in skin damaged by animal or human bites. Nonnecrotizing superficial soft tissue infections are principally treated with antibiotics. Necrosis is rare but may develop in superficial infections that are inadequately treated or neglected.

Pyoderma

Pyoderma is a general term referring to a bacterial infection of the skin. It may be divided into several subcategories, including impetigo, erysipelas, folliculitis, and furuncles and carbuncles.

Impetigo Impetigo is a highly contagious bacterial infection that is confined to the epidermis and that usually involves the face or the extremities. It is most common in infants and preschool children and is seen more frequently in patients with preexisting skin conditions (e.g., eczema, atopic dermatitis, varicella infection, angular cheilitis, and scabies). Warm and humid weather, crowded living conditions, and poor hygiene can all contribute to the development of impetigo.²⁹ The dominant pathogen is *S. aureus*, which causes either a bullous or a nonbullous form of the disease; a less common pathogen is *S. pyogenes*, which causes a nonbullous form.³⁰

Impetigo usually occurs in areas of skin breakdown, though *S. aureus* may give rise to de novo infection in normal skin. Bullous impetigo is manifested by numerous blisters or bullae that rapidly become pustules, then rupture within 1 to 2 days to form a thick, honey-colored, crusted plaque that remains for days to weeks. Nonbullous impetigo is characterized by erythema and tiny, less prominent vesicles that progress to crusted erosions in the skin. The skin lesions are intensely pruritic, and local spread may occur as a result of scratching and release of infected fluid from the blisters, bullae, or vesicles. Associated regional lymphadenopathy is common. Glomerulonephritis may complicate streptococcal-induced impetigo.^{30,31}

The diagnosis is established by Gram stain and culture of the vesicular fluid or the crusted plaque. The skin lesions usually resolve spontaneously within 2 to 3 weeks.³¹ Antibiotic therapy accelerates the resolution of these lesions. Mupirocin ointment (2%) is applied topically three times a day until the lesions clear. This agent possesses excellent in vitro activity against both staphylococci and streptococci and achieves high rates of cure in patients with localized disease. Erythromycin and clindamycin ointments are acceptable alternatives [see Table 5]. For patients who have disseminated impetigo or impetigo of the scalp or mouth and those in whom topical therapy fails, an oral antibiotic (e.g., dicloxacillin, cephalexin, cefadroxil, erythromycin, or clindamycin) may be used [see Table 5]. A 7-day course of oral antibiotic therapy is usually sufficient.³¹

Erysipelas Erysipelas is an acute bacterial infection that principally involves the dermis. It is almost invariably caused by *S. pyogenes*. Most cases are preceded by influenzalike symptoms. Infection extends through the dermal lymphatic vessels and is typically manifested by a tender, pruritic, intensely erythematous, sharply demarcated, and raised plaque. Patients complain of pain, often in conjunction with high fever, increased skin warmth, and leukocytosis. Lymphangitis and lymphadenopathy are sometimes present as well. The leg is the most common site of involvement, but erysipelas may also occur on the face, the arms, and the upper thighs.

The factors predisposing to the development of erysipelas of the extremity include local conditions such as tinea pedis (athlete's foot), leg ulcers, and venous stasis dermatitis.³² Erysipelas tends to be more common in the presence of associated conditions such as lymphedema, diabetes mellitus, alcoholism, immunocompromise, and obesity,^{30,32} and it is more likely to recur in patients with these associated diseases and in those whose underlying skin conditions are inadequately treated. Erysipelas recurs in 10% of patients within 6 months of their first episode and in 30% within 3 years.³²

The standard antibiotic treatment for uncomplicated erysipelas is penicillin, which is effective in at least 80% of cases. Oral and intravenous antibiotic regimens are equally efficacious. Amoxicillin appears to work as well as penicillin. Patients with erysipelas of the lower extremity should be placed on bed rest, and the involved leg should be elevated to reduce edema and pain. Once the patient is able to resume normal activities, he or she should be fitted with elastic stockings, which help reduce the occurrence of edema and lower the risk of lymphedema. For patients with tinea pedis, a topical antifungal agent is used to treat the infection and prevent recurrence.

Folliculitis Folliculitis is an infection of the hair follicle that is typically caused by *S. aureus*. It is characterized by a painful, tender, erythematous papule with a central pustule. A shaft of hair is often seen in the center of the pustule. Shaving, plucking, waxing, heat and humidity, the use of corticosteroids or antibiotics, immunosuppression, and occlusion of the skin by clothing, adhesives, or plastics may predispose to folliculitis.²⁹ Single or multiple lesions may occur in the skin of any hair-bearing area. If the pustule ruptures, superficial erosion often ensues. Infection that principally involves the deeper part of the hair follicle is characterized by a tender, swollen papule without an associated pustule at the skin surface.

In rare cases, folliculitis is caused by pathogens other than *S. aureus*, such as *Pseudomonas aeruginosa*, *Klebsiella* species, *Enterobacter* species, *Proteus* species, yeasts, and fungi. *Pseudomonas* folliculitis usually results from exposure to inadequately chlorinated

ed water in swimming pools, hot tubs, or whirlpools. Patients with this infection have multiple papular or pustular lesions on the back, the buttocks, and the extremities, along with fever and malaise appearing 6 hours to 3 days after exposure.^{31,33} Organisms may be cultured either from the pustules or from the infected water. *Klebsiella*, *Enterobacter*, and *Proteus* species can cause folliculitis in patients receiving long-term antibiotic therapy for acne vulgaris.³⁰ Yeast folliculitis and fungal folliculitis tend to occur in immunocompromised patients.³⁰

In most patients, folliculitis resolves spontaneously within 7 to 10 days.³¹ Topical therapy with clindamycin, erythromycin, or mupirocin ointments or benzoyl peroxide in combination with warm soaks may accelerate resolution [see Table 5]. Isotretinoin can be used to treat gram-negative folliculitis. Gentamicin cream may be helpful in drying out the pustular lesions in patients with *Pseudomonas* folliculitis.

In patients with refractory or disseminated follicular infections, oral antibiotic therapy is indicated. When *S. aureus* is considered the most likely pathogen, trimethoprim-sulfamethoxazole, a tetracycline, or clindamycin should be given, in view of the high prevalence of MRSA^{21,34}; an oral quinolone is indicated for the treatment of gram-negative folliculitis [see Table 5]. Elimination of predisposing factors is important for reducing the likelihood of recurrence.

Furuncles and carbuncles Furuncles and carbuncles are deeper infections of the hair follicle that extend beyond the follicle to involve the subcutaneous tissue. For both, *S. aureus* is the usual causative organism.

A furuncle, or boil, is a small abscess, manifested as a firm, tender, erythematous nodule that tends to occur in skin areas exposed to friction (e.g., the inner thighs and the axilla). Furuncles also may occur on the face, the neck, the upper back, and the buttocks. Possible predisposing factors include increased friction and perspiration (as seen in obese individuals or athletes), corticosteroid use, diabetes mellitus, and inherited or acquired defects in neutrophil function.^{29,31}

Initial treatment consists of applying warm compresses to help promote drainage and administering an oral antimicrobial agent that is effective against *S. aureus* (e.g., dicloxacillin, cephalixin, cefadroxil, erythromycin, or clindamycin for infections presumed to be caused by methicillin-sensitive strains; trimethoprim-sulfamethoxazole, a tetracycline, or clindamycin for suspected MRSA infections) [see Table 5]. With time, the furuncle becomes fluctuant, and the pus coalesces at the skin surface. An incision-and-drainage procedure is necessary when these lesions do not drain spontaneously. This procedure should be performed with local anesthesia, and care should be taken to open the abscess cavity completely. Lesions that have drained spontaneously should be examined to confirm that the cavity has been opened sufficiently. Failure to drain these lesions adequately may result in recurrence, as well as in progression to a more serious infection.

A carbuncle is a deep cutaneous infection involving multiple hair follicles that is characterized by destruction of fibrous tissue septa and consequent formation of a series of interconnected abscesses. It is typically manifested by a painful, red, tender, indurated area of skin with multiple sinus tracts. Systemic manifestations (e.g., fever and malaise) are common. Carbuncles occur most frequently on the nape of the neck, the upper part of the back, or the posterior thigh. The thickness of the overlying skin in these areas leads to lateral extension of the infection and loculation. Patients commonly present with relatively large skin lesions that represent a confluence of inflammatory nodules. These lesions are associated with chronic drainage, sinus tracts, and scarring.

Table 6 Risk Factors for Soft Tissue Infection Complicating Animal or Human Bite

Location on the hand or the foot or over a major joint	Immunosuppression
Location on the scalp or the face of an infant	Chronic alcoholism
Puncture wound	Diabetes mellitus
Delay in treatment lasting longer than 12 hr	Corticosteroid use
	Preexisting edema in an affected extremity

An incision-and-drainage procedure is recommended when a fluctuant carbuncle is present. A thorough search for loculated areas should be undertaken to facilitate drainage of deeper accumulations of pus and to ensure adequate treatment. Wide local excision of the involved skin and subcutaneous fat is often necessary to prevent recurrent disease. An oral antistaphylococcal agent should be given. All patients with hair follicle infections should cleanse the site with chlorhexidine or an iodine-containing solution.

Infections Developing in Damaged Skin

Damage to skin as a result of animal or human bites predisposes patients to soft tissue infection. An estimated 50% of all Americans will be bitten by an animal or by another human being during their lifetime.³⁵ Animal and human bites account for approximately 1% of all emergency department visits.³⁵ Soft tissue infection is the most common complication of such bites. The risk of infection depends on the type of bite, the site of injury, the time elapsed from the bite until presentation, host factors, and the management of the wound [see Table 6].

Most animal and human bites produce minor injuries for which patients do not seek medical attention. The overall risk of infection after a bite is estimated to be 5% to 15%³⁶; however, among the subset of patients who seek medical attention, estimated infection rates range from 2% to 20% for dog bites, from 30% to more than 50% for cat bites, and from 10% to 50% for human bites.³⁷ Most patients with an infected bite can be managed on an outpatient basis with oral antibiotic therapy and elevation of the involved site.

Animal bites In the United States, dog bites account for 80% to 90% of all animal bites, cat bites for 3% to 15%.^{37,38} Nondomestic animals are responsible for only 1% to 2% of all animal bites. Patients with infections resulting from animal bites typically present with significant pain, soft tissue swelling, and tenderness; they may also have associated injuries to nerves, tendons, bones, joints, or blood vessels. Bites involving the hand are associated with an increased risk of tenosynovitis, septic arthritis, and abscess formation.³⁷

Infections that occur after a dog or cat bite are usually polymicrobial, involving a mixture of aerobes and anaerobes [see Table 7]. *P. multocida* is the major pathogen, isolated from 50% to 80% of infections related to cat bites and from 25% of those related to dog bites.^{35,37} Infection with *P. multocida* is characterized by the acute onset of severe pain, tenderness, and swelling, usually within 12 to 18 hours of the bite. In rare cases (usually involving immunocompromised patients), *Capnocytophaga canimorsus* causes soft tissue infection after a dog or cat bite. *C. canimorsus* infection can be quite serious, leading to overwhelming sepsis; the associated mortality is 25% to 30%.³⁷⁻³⁹

Wounds resulting from animal bites should immediately be washed with soap and water. When seen early, dog bites should be

copiously irrigated, debrided, and, in most circumstances, closed. Infected wounds, wounds older than 12 hours, cat bites, and bites on the hand should be left open. In all cases of infection related to an animal bite, aerobic and anaerobic cultures should be obtained from the site of infection. Tetanus immune status should be determined, and immunization against tetanus should be provided when appropriate. In cases of bites from nondomestic carnivores (e.g., bats, skunks, raccoons, foxes, or coyotes), wounds should be irrigated with povidone-iodine to reduce the transmission of rabies, and immunization against rabies should be provided.

Patients with established soft tissue infection and patients with noninfected bites who have risk factors for infection should receive antibiotic therapy [see Table 6]. A broad-spectrum antibiotic effective against aerobic and anaerobic organisms should be chosen [see Table 5]. Amoxicillin-clavulanate is the antibiotic of choice because of its broad spectrum of activity against common pathogens; trimethoprim-sulfamethoxazole, doxycycline, and ciprofloxacin are also used [see Table 5]. Infections secondary to *P. multocida* respond to oral treatment with penicillin V, amoxicillin, cefuroxime, or ciprofloxacin.³⁷ Infections secondary to *C. canimorsus* respond to penicillin, ampicillin, ciprofloxacin, erythromycin, or doxycycline. Whether antibiotics are indicated for a fresh animal bite in a patient with a low risk of infection is controversial. Because it is difficult to predict which bite wounds will become infected, some experts advocate routine antibiotic treatment of all dog bites for at least 3 to 5 days.³⁵

Human bites Human bites may be classified as either occlusional bites (in which teeth puncture the skin) or clenched-fist injuries (in which the hand is injured after contact with teeth).^{37,39} Occlusional bites carry roughly the same risk of infection as animal bites, except when they occur on the hand. Clenched-fist injuries and all hand injuries are associated with a higher risk of infection. Clenched-fist injuries typically occur at the third metacarpophalangeal joint. Penetration of the metacarpophalangeal joint capsule may occur, with subsequent development of septic arthritis and osteomyelitis.³⁵

Soft tissue infections resulting from human bites are polymicrobial, involving a mixture of aerobes and anaerobes. On average, five different microorganisms are isolated from a human-bite wound³⁷—significantly more than are usually isolated from an animal-bite wound. In addition, the concentration of bacteria in the oral cavity is higher in humans than in animals. The anaerobic bacteria isolated from human-bite wounds are similar to those that cause infection after dog and cat bites, except that *Bacteroides*

species are more common [see Table 7]. Unlike the anaerobic pathogens in dog and cat bites, however, those involved in human-bite infections often produce β -lactamases.³⁷ The predominant aerobic organisms in human-bite infections are *S. aureus*, *Staphylococcus epidermidis*, α - and β -hemolytic streptococci, *Corynebacterium* species, and *E. corrodens*. *E. corrodens* is a fastidious facultative aerobic gram-negative rod that is cultured from approximately 25% of clenched-fist injuries and frequently causes a chronic indolent infection.³⁷ It typically is susceptible to amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, doxycycline, and ciprofloxacin but resistant to dicloxacillin, nafcillin, first-generation cephalosporins, clindamycin, and erythromycin. Other pathogens may also be transmitted as a result of contact with blood or saliva, including hepatitis B and C viruses, *Mycobacterium tuberculosis*, and, possibly, HIV.

Management of human-bite wounds is similar to that of animal-bite wounds. The wound must be thoroughly irrigated, preferably with 1% povidone-iodine, which is both bactericidal and viricidal. Puncture bite wounds should be irrigated with a small catheter to achieve high-pressure irrigation. If the wound appears infected, aerobic and anaerobic cultures are obtained. Devitalized tissue should be debrided, and the wound should be left open, whether infected or not. The injured extremity should be immobilized and elevated.

Because of the high degree of contamination and local tissue damage associated with human-bite wounds to the hand, antimicrobial therapy is indicated for all such injuries. A prospective, randomized study of 45 patients with human bites to the hand seen within 24 hours after injury and without evidence of infection, tendon injury, or joint capsule penetration demonstrated that infection developed in 47% of the patients who did not receive antibiotics but in none of those who did.⁴⁰ Patients with an uncomplicated human bite to the hand should receive a broad-spectrum oral antimicrobial agent, such as amoxicillin-clavulanate (or doxycycline if they are allergic to penicillins).

Patients with human-bite wounds at sites other than the hand who have risk factors for infection [see Table 6] should also receive antimicrobial therapy. However, minor bite wounds in patients who have no risk factors for infection do not call for antibiotic therapy. As with animal-bite wounds, tetanus immunization status should be determined, and tetanus toxoid, tetanus immunoglobulin, or both should be administered as indicated.

Patients with systemic manifestations of infection (e.g., fever or chills); severe cellulitis; compromised immune status; diabetes mellitus; significant bites to the hand; associated joint, nerve, bone, or tendon involvement; or infection refractory to oral antibiotic therapy should be admitted to the hospital for I.V. antibiotic therapy.³⁷ Appropriate choices for I.V. treatment include cefoxitin, cefotetan, and piperacillin-tazobactam. Tenosynovitis, joint infections, and associated injuries to deep structures must also be treated if present.

Cellulitis

Cellulitis is an acute bacterial infection of the dermis and the subcutaneous tissue that primarily affects the lower extremities, though it can affect other areas as well (e.g., the periorbital, buccal, and perianal regions; the areas around incisions; and sites of body piercing).⁴¹ The most common causes of cellulitis are (1) soft tissue trauma from injection of illicit drugs, puncture wounds from foreign bodies or bites (animal, human, or insect), or burns; (2) surgical site infection; and (3) secondary infection of preexisting skin lesions (e.g., eczema; tinea pedis; and decubitus, venous stasis, or ischemic ulcers). Less common causes include extension of

Table 7 Organisms Most Frequently Isolated from Dog- and Cat-Bite Wounds

Aerobes	<i>Pasteurella multocida</i>
	<i>Corynebacterium</i> species
	<i>Staphylococcus</i> species
	<i>Streptococcus</i> species
	<i>Capnocytophaga canimorsus</i> (rare)
Anaerobes	<i>Bacteroides</i> species
	<i>Prevotella</i> species
	<i>Porphyromonas</i> species
	Peptostreptococci
	<i>Fusobacterium</i> species
	<i>Bacteroides fragilis</i>
	<i>Veillonella parvula</i>

a subadjacent infection (e.g., osteomyelitis) and bacteremia from a remote site of infection. Predisposing factors for the development of cellulitis include lymphatic disruption or lymphedema, interstitial edema, previous irradiation of soft tissue, diabetes mellitus, immunocompromise, and peripheral vascular disease.

Nonnecrotizing The overwhelming majority of patients with cellulitis have a nonnecrotizing form of the disease. Patients typically present for medical attention because of pain and soft tissue erythema, and they often have constitutional symptoms (e.g., fever, chills, or malaise). Physical examination reveals erythema with advancing borders, increased skin warmth, tenderness, and edema. Lymphangitis may also be present, manifested as an erythematous linear streak that often extends to a draining lymph node basin; associated lymphadenopathy, fever, and leukocytosis with a shift to immature forms may be apparent.

Cellulitis is usually caused by a single aerobic pathogen. The organisms most frequently responsible for cellulitis in otherwise healthy adults are *S. pyogenes* and *S. aureus*. Of the two, *S. pyogenes* is the more common and is the usual pathogen in patients with associated lymphangitis. *S. aureus* is usually present in patients with underlying chronic skin disease. Other microorganisms may cause cellulitis on rare occasions but usually only in specific clinical circumstances. *Haemophilus influenzae* sometimes causes cellulitis in children or adults infected with HIV.⁴² *Streptococcus pneumoniae* may cause this condition in patients with diabetes mellitus, alcoholism, nephrotic syndrome, systemic lupus erythematosus, or hematologic malignancies.⁴³ *P. multocida* may cause cellulitis as a complication of dog or cat bites. *S. epidermidis* is a recognized cause of cellulitis among immunocompromised patients, including those with HIV infection and those receiving organ transplants.⁴⁴ *V. vulnificus* occasionally causes cellulitis in patients who have ingested raw seafood or who have experienced minor soft tissue trauma and are exposed to sea water.⁴¹ *A. hydrophila* may cause cellulitis in patients with soft tissue trauma who are exposed to brackish or fresh water, soil, or wood.⁴¹ Cellulitis that complicates decubitus or other nonhealing ulcers is usually a mixed infection that includes gram-negative organisms.

In most situations, cellulitis is treated with empirical antibiotic regimens that include agents effective against *S. pyogenes* and *S. aureus*. Attempts to isolate a causative pathogen are usually unsuccessful; needle aspiration and skin biopsy at an advancing margin of erythema are positive in only 15% and 40% of cases, respectively.⁴⁵ Bacteremia is uncommon, and as a result, blood cultures are positive in only 2% to 4% of patients with cellulitis.^{41,46} Blood cultures are obtained selectively when the patient has high fever and chills, preexisting lymphedema, or buccal or periorbital cellulitis or when a saltwater or freshwater source of infection is suspected. In all of these clinical situations, the prevalence of bacteremia is higher.⁴⁶ Radiologic examination should be reserved for patients in whom it is difficult to exclude a deep necrotizing infection.

In an otherwise healthy adult, uncomplicated cellulitis without systemic manifestations can be treated with an oral antibiotic on an outpatient basis. Because the vast majority of cellulitides are caused either by *S. pyogenes* or by a penicillinase-producing *S. aureus*, one of the following agents is usually given: dicloxacillin, cephalexin, cefadroxil, erythromycin, or clindamycin. When MRSA infection is suspected, trimethoprim-sulfamethoxazole, a tetracycline, or clindamycin should be administered [see Table 5]. The margins of the erythema should be marked with ink to facilitate assessment of the response to treatment. For lower-extremity cellulitis, reduced activity and elevation are important ancillary measures. Appropriate analgesic agents should be given.

Table 8 Suggested Parenteral Antibiotic Regimens for Treatment of Cellulitis in Adults

Agent	I.V. Dosage
Nafcillin	2 g q. 4 hr
Cefazolin	1–2 g q. 8 hr
Clindamycin	600–900 mg q. 8 hr
Vancomycin	1 g q. 8 hr
Ampicillin-sulbactam	3 g q. 6 hr

Patients who are diabetic or immunocompromised and those who have high fever and chills, rapidly spreading cellulitis, or cellulitis that is refractory to oral antibiotic therapy should be admitted to the hospital for I.V. antibiotic therapy [see Table 8]. Nafcillin is the preferred I.V. agent. Cefazolin or piperacillin-tazobactam should be added if gram-negative organisms are suspected pathogens, as when cellulitis complicates a decubitus or a diabetic foot ulcer. Vancomycin, tigecycline, linezolid, or gentamicin should be given to patients with MRSA infections and those with serious penicillin allergies.

Necrotizing Necrotizing cellulitis is similar to nonnecrotizing cellulitis in etiology and pathogenesis but is more serious and progressive. Necrosis generally occurs when the infection is neglected or inadequately treated. The microbiology of necrotizing cellulitis is also similar to that of nonnecrotizing cellulitis, except that *C. perfringens* and other clostridial species may be involved when necrosis is present. In addition to antimicrobial therapy [see Table 8], urgent operative debridement is indicated. In other respects, necrotizing cellulitis is treated in much the same way as deep necrotizing infections are (see below). In some patients with necrotizing fasciitis, the skin is involved secondarily.

DEEP NECROTIZING INFECTIONS

Infections that involve the soft tissues deep to the skin tend to become apparent after necrosis has developed. It is possible that deep necrotizing infections begin without necrosis but progress rapidly as a result of intrinsic factors. Alternatively, such infections may develop as a result of delayed recognition attributable to the tissue depth at which the process takes place and the lack of specific early signs and symptoms. The relatively poor blood supply to subcutaneous fat makes this tissue more susceptible to microbial invasion. Contamination of the deep soft tissues occurs either through neglect or inadequate treatment of cutaneous or subcutaneous infections or through hematogenous seeding of microorganisms in an area of injury.

Most deep necrotizing soft tissue infections are polymicrobial and occur on the extremities, the abdomen, and the perineum.^{9,22,24} Necrotizing infections that involve only muscle are uncommon; therefore, necrotizing fasciitis can be considered the paradigm for these infectious processes.

The early signs and symptoms of deep necrotizing soft tissue infection are localized pain, tenderness, mild edema, and erythema of the overlying skin. These characteristics may be subtle, and this diagnosis may not readily come to mind. Sometimes, there is a history of previous injury to the area of suspected infection, which can lead to confusion about the diagnosis. The more classic findings associated with these infections—skin discoloration, the formation of bullae, and intense erythema—occur much later in the process.

It is important to understand this point so that an early diagnosis can be made and appropriate treatment promptly instituted.

Necrotizing Fasciitis

Necrotizing fasciitis is characterized by angiothrombotic microbial invasion and liquefactive necrosis.⁶ Progressive necrosis of the superficial fascia develops, and the deep dermis and fascia are infiltrated by polymorphonuclear leukocytes, with thrombosis of nutrient vessels and occasional suppuration of the veins and arteries coursing through the fascia; bacteria then proliferate within the destroyed fascia. Initially, tissue invasion proceeds horizontally, but as the condition progresses, ischemic necrosis of the skin develops, along with gangrene of the subcutaneous fat and dermis (characterized by progressive skin necrosis, the formation of bullae and vesicles, and occasional ulceration [see Figure 1]).

Myonecrosis

Myonecrosis is a rapidly progressive life-threatening infection of skeletal muscle that is primarily caused by *Clostridium* species. The classic example of myonecrosis is clostridial gas gangrene, a disease that was common in World War I soldiers who sustained extremity injuries that were contaminated with soil. Delays in definitive treatment and the use of primary closure for these contaminated wounds contributed to the severity and mortality of these infections.⁴⁷ Clostridial myonecrosis may also occur as a deep surgical site infection after contaminated operations, particularly those involving the GI tract or the biliary tract. Devitalized tissue is a per-

fect environment for clostridial proliferation. A rare form of this disease occurs in patients with colon cancer in whom myonecrosis caused by *Clostridium septicum* develops in the absence of tissue damage. Myonecrosis may also result from the spread of contiguous fascial infections.

Clostridial myonecrosis has a notably short incubation period: severe progressive disease can develop within 24 hours of contamination. This condition is characterized by acute catastrophic pain in the area of infection, with minimal associated physical findings. Systemic signs of toxicity (e.g., confusion, incontinence, and delirium) often precede the physical signs of localized infection. The skin initially is pale, then gradually becomes yellowish or bronze. Blebs, bullae, and skin necrosis do not appear until late in the course of the disease. Edema and tenderness occur early, and the absence of erythema distinguishes clostridial infections from streptococcal infection. A thin serosanguineous discharge is present in involved areas and may emanate from an involved incision. Gram stain reveals gram-positive coccobacilli with few leukocytes.

When clostridial myonecrosis is suspected or confirmed, penicillin G, 2 to 4 million U every 4 hours, should be given immediately; clindamycin, 900 mg every 8 hours, should be added. When *C. septicum* is identified on culture, a search for an occult GI tract malignancy should be made. Clostridial myonecrosis is the one soft tissue infection for which hyperbaric oxygen is recommended, though as yet, there is little evidence that this modality improves outcomes. If hyperbaric oxygen therapy is to be used, it should not be given before operative debridement.

Discussion

Etiology and Classification of Soft Tissue Infection

Soft tissue infection commonly results from inoculation of bacteria through a defect in the epidermal layer of the skin, such as may occur with injury, preexisting skin disease, or vascular compromise. Less commonly, soft tissue infection may be a consequence of extension from a subjacent site of infection (e.g., osteomyelitis) or of hematogenous spread from a distant site (e.g., diverticulitis or *C. septicum* infection in patients with colonic carcinoma). It may also occur de novo in healthy patients with normal-appearing skin, often as a result of virulent pathogenic organisms.⁴⁸

Conditions that disrupt the skin and alter its normal barrier function [see Table 2] predispose patients to bacterial contamination. Host factors may increase susceptibility to infection and limit the patient's ability to contain the bacterial inoculum. Clinically occult infection or inadequate treatment of other conditions may also lead to secondary development of soft tissue infection (as is sometimes seen in patients with diverticulitis; perirectal, pilonidal, or Bartholin's cyst abscesses; strangulated hernias; or panniculitis). Delayed or inadequate treatment of superficial infections (e.g., folliculitis, furuncles, carbuncles, cellulitis, and surgical site infections) may lead to more severe necrotizing infections.

Soft tissue infections may be classified as superficial or deep, as nonnecrotizing or necrotizing, as primary (idiopathic) or secondary, and as monomicrobial or polymicrobial. Superficial infections involve the epidermis, dermis, superficial fascia, or subcutaneous tissue, whereas deep infections involve the deep fascia or muscle [see Figure 6]. Necrotizing soft tissue infections are distinguished by the presence of extensive, rapidly progressing necrosis and high mortality. Such infections are termed necrotizing cellulitis, necrotizing fasciitis, or myonecrosis according to whether the deepest tissue layer affected by necrosis is subcutaneous tissue, deep fascia, or muscle, respectively.

Primary (idiopathic) soft tissue infections occur in the absence of a known causative factor or portal of entry for bacteria. Such infections are uncommon and are believed to result from hematogenous spread or bacterial invasion through small unrecognized breaks in the epidermis.^{48,49} Soft tissue infection caused by *V. vulnificus* is an example of a primary soft tissue infection: it is attributed to bacteremia developing after the ingestion of contaminated raw seafood. Only 10% to 15% of all necrotizing soft tissue infections are idiopathic; the remaining 85% to 90% are secondary infections, developing as a consequence of some insult to the skin that predisposes to infection. Secondary soft tissue infections may be further categorized as posttraumatic, postoperative, or complications of preexisting skin conditions.

Soft tissue infections are classified as monomicrobial when they are caused by a single organism and as polymicrobial when they are caused by multiple organisms. Most superficial soft tissue infections are caused by a single aerobe, usually *S. pyogenes* or *S. aureus*. Exceptions to this general rule include infections caused by animal or human bites, cellulitis associated with decubitus or other non-healing ulcers, and infections in immunocompromised patients. These infections are typically polymicrobial, often involving aerobic or facultative gram-negative organisms and anaerobes in addition to aerobic gram-positive bacteria.

Deep necrotizing soft tissue infections are polymicrobial 70% to 75% of the time. They are caused by the synergistic activity of facultative aerobes and anaerobes [see Figure 7].^{50,51} *S. aureus*, *S. pyogenes*, and enterococci are the most common gram-positive aerobes. *Escherichia coli* is the most common gram-negative enteric organism. *Bacteroides* species and peptostreptococci are the most common anaerobes.^{9,27,51} The remaining 25% to 30% of deep necrotizing infections are monomicrobial. Most primary necrotizing soft tissue infections are monomicrobial.⁴⁸ These infections are



Figure 7 Meleney’s ulcer is characterized by central necrosis, erythema, and edema.

more fulminant and are notable for their acute onset, rapid progression, and systemic toxicity. Their characteristic clinical manifestations are related to exotoxin production by the pathogen involved [see Table 9 and Pathogenesis of Soft Tissue Infections, below]. *S. pyogenes* is the pathogen in more than half of monomicrobial infections; *S. aureus*, *C. perfringens*, *V. vulnificus*, and *P. aeruginosa* are less common.

Pathogenesis of Soft Tissue Infections

Soft tissue infections generally induce localized inflammatory changes in the involved tissues, regardless of the species of bacteria involved. As the infection progresses, tissue necrosis occurs as a result of (1) direct cellular injury from bacterial toxins, (2) significant inflammatory edema within a closed tissue compartment, (3) thrombosis of nutrient blood vessels, and (4) tissue ischemia.

The exotoxins produced by gram-positive cocci and some gram-negative bacteria are powerful proteolytic enzymes. *S. pyogenes* produces hemolysins, fibrinolysins, hyaluronidases, and streptolysins. *S. aureus* and *P. aeruginosa* produce coagulases that result in local tissue damage and necrosis. *C. perfringens* produces numerous exotoxins. The α -toxin, a lecithinase enzyme, is highly lethal: it destroys cell membranes, causes hemolysis, and alters capillary permeability. Other clostridial toxins lyse red blood cells and have direct cardiotoxic effects. These toxins also cause platelet aggregation and fibrin deposition, with resultant vascular thrombosis and necrosis. Production of the θ -toxin leads to intravascular leukostasis and inhibits diapedesis of white blood cells into infected tissue. This unique collection of bacterial toxins accounts for the rapid progression of *C. perfringens* infection in a setting of minimal inflammatory changes.

That most necrotizing soft tissue infections involve multiple bacterial species strongly suggests that bacterial synergy plays an important role in their pathogenesis. Toxin-induced cellular necrosis establishes an anaerobic environment that facilitates the growth of both facultative and anaerobic bacteria. These anaerobes elaborate additional enzymes and other by-products that facilitate tissue invasion and destruction.

Preexisting local tissue damage frequently serves as a nidus for soft tissue infection. The reduced oxygen tension of this abnormal environment allows pathogens to proliferate. In addition, various

patient factors predispose susceptible individuals to these infections. Chronic illnesses can contribute to a diminished immunologic response. Peripheral vascular disease impairs the local blood and oxygen supply. Diabetes mellitus inhibits WBC function. Chronic pulmonary disease can result in systemic hypoxemia. Patients with congestive heart failure or significant coronary artery disease may be unable to increase their cardiac output in response to infection. Malnutrition can result in a lack of nutrients and critical enzymatic cofactors involved in the normal cellular response to infection. Each of these patient factors impairs the host response and thereby increases the likelihood that infection will develop.

In the 1920s, Meleney demonstrated that injection of animals with pathogens isolated from patients with infectious gangrene reproduced the characteristics of infection.² Decades later, the importance of bacterial synergy and exotoxins was demonstrated in experiments performed by Seal and Kingston,⁵² who showed that a spreading infection developed in 12% of animals that received an intradermal injection of group A β -hemolytic streptococci. When *S. aureus* was coinjected with β -hemolytic streptococci, spreading infections developed in 50% of animals, and when the α -lysin of *S. aureus* was coinjected with streptococci, spreading infections developed in 75%.

Streptococcal Toxic-Shock Syndrome

Hemolytic streptococci were originally described by Meleney as the cause of a “synergistic gangrene.”² The current resurgence of necrotizing soft tissue infections attributed to so-called flesh-eating bacteria probably represents an adaptation of group A streptococci to the contemporary environment.⁵³ Streptococcal toxic-shock syndrome (STSS) is defined as the isolation of group A streptococci from a normally sterile body site in conjunction with hypotension and either renal impairment, acute respiratory distress syndrome, abnormal hepatic function, coagulopathy, extensive tissue necrosis, or an erythematous rash.⁴⁵ STSS is considered the probable diagnosis when these abnormalities occur in conjunction with isolation of group A streptococci from nonsterile body sites. More than 60% of patients with STSS have bacteremia. STSS has been shown to be a major risk factor for mortality among patients with necrotizing soft tissue infections.⁵⁴

Population-based studies in North America and Europe documented a nearly fivefold increase in group A streptococcal infections between the late 1980s and 1995.⁵⁵ The current incidence of group A streptococcal infections in the population of Ontario, Canada, is estimated to be 1.5 per 100,000.⁵⁵ STSS develops in

Table 9 Major Exotoxins Associated with Organisms Causing Monomicrobial Necrotizing Soft Tissue Infection

Bacterium	Exotoxins
<i>Streptococcus pyogenes</i>	Pyrogenic exotoxins A and B, hemolysin, fibrinolysin, hyaluronidase, streptokinase
<i>Staphylococcus aureus</i>	Hemolysins (intravascular hemolysis and local tumor necrosis), coagulase
<i>Pseudomonas aeruginosa</i>	Collagenase (local tissue damage and necrosis)
<i>Clostridium perfringens</i>	α -Toxin (lecithinase causing tissue necrosis, intravascular hemolysis, hemoglobinemia, and acute renal failure)



Figure 8 Shown is the superficial appearance of streptococcal gangrene of the posterior thigh.

approximately 10% to 15% of these patients, necrotizing fasciitis in about 6%.⁵⁶ It is likely that the rise in serious group A streptococcal infections reflects an antigenic shift that has increased the virulence of these organisms.

Soft tissue infections associated with STSS typically involve an extremity. Approximately 70% of patients will progress to necrotizing fasciitis or myositis and will require operative treatment. Only about 50% of patients with streptococcal soft tissue infections have a demonstrable portal of entry for bacteria.^{48,57}

Severe pain is the most common initial symptom of STSS. It is of sudden onset and generally precedes tenderness or other physical findings. Fever is another common early sign. About 80% of STSS patients show clinical signs of soft tissue infection (e.g., localized swelling, erythema, and tenderness) [see Figure 8]. In approximately 50%, blood pressure is initially normal, but hypotension invariably develops within 4 to 8 hours after presentation.

Hemoglobinuria and an elevated serum creatinine concentration are hallmarks of renal involvement. Even when adequate resuscitation is provided and antibiotics and vasopressors are given, hypotension persists in the overwhelming majority of patients. Renal dysfunction can persist or progress for 48 to 72 hours despite treatment. Hypoalbuminemia and hypocalcemia are common. Mild leukocytosis is present initially; however, the percentage of immature neutrophils is generally 40% or higher.

S. pyogenes can be classified into more than 80 different strains, or M types, on the basis of the M proteins expressed. M proteins impede phagocytosis of streptococci and induce vascular leakage by forming complexes with fibrinogen.⁵⁸ They also cleave nicotinic acid dinucleotide (NAD), thereby interrupting elemental cellular

processes. The M proteins M1 and M3 are associated with the majority of streptococcal necrotizing soft tissue infections.⁵³ Streptococcal pyrogenic exotoxins (SPEs) are produced by most streptococci that cause severe soft tissue infection and can be transmitted by bacteriophages to different M types. They are the cause of the fever, shock, and tissue injury associated with these infections. SPE-A and SPE-B induce the synthesis of tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and IL-6. Peptidoglycan, lipoteichoic acid, and killed organisms also are capable of inducing TNF- α production.

It has been proposed that M proteins or SPEs act as superantigens. These exotoxins, along with certain staphylococcal toxins (e.g., toxic-shock syndrome toxin-1 [TSST-1] and staphylococcal enterotoxins), can stimulate T cell responses through conventional antigen-presenting cells, as well as through direct binding to the V β region of the T cell receptor. Conventional T cell activation through antigen-presenting cells is a multistage process that stimulates a relatively small percentage of T cells and limits the magnitude of the resultant cytokine response. In contrast, superantigens bypass the normal antigen presentation pathway and do not undergo phagocytosis. The superantigen processing pathway can stimulate more than a thousand times more T cells than the conventional antigen pathway and thus can trigger a massive release of cytokines. The idea that T cell stimulation by superantigens can explain the severe degree of illness and exaggerated response seen in these patients is attractive, but at present, there is no definitive proof that this process occurs in humans.

Although *S. pyogenes* is susceptible to penicillin and other β -lactam antibiotics in vitro, clinical treatment failure sometimes occurs when penicillin is used alone against *S. pyogenes* infections.⁵³ Such failure is a particular problem with more aggressive group A streptococcal infections and may be attributable to the large inoculum size (the so-called Eagle effect). These large inocula reach the stationary growth phase very quickly. Penicillin and other β -lactam antibiotics are ineffective in the stationary growth phase because of the reduced expression of penicillin-binding proteins in this phase. Moreover, toxin production is not inhibited by β -lactam antibiotics during the stationary growth phase. In contrast, antibiotics that inhibit protein synthesis have been associated with improved survival after serious group A streptococcal infections.

Clindamycin is more effective than β -lactam agents in managing experimental and clinical infections caused by group A streptococci, particularly when necrosis is present.⁵⁹ Clindamycin inhibits protein synthesis, and its efficacy is unaffected by inoculum size or the stage of bacterial growth. In particular, it suppresses bacterial toxin synthesis and inhibits M-protein synthesis, thus facilitating phagocytosis of *S. pyogenes*. Clindamycin also suppresses synthesis of penicillin-binding proteins, and it can act synergistically with penicillin.

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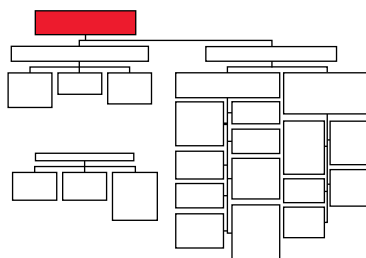
Figure 6 Tom Moore.

3 PRINCIPLES OF WOUND MANAGEMENT AND SOFT TISSUE REPAIR

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Difficult Wounds

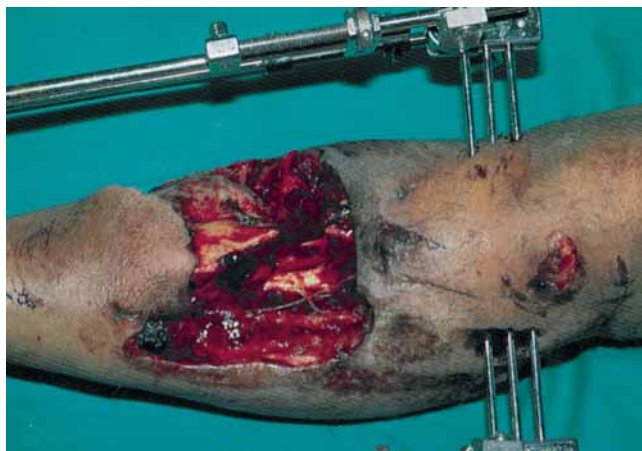
Problem wounds are characterized by one of the following: large size that precludes direct primary closure, gross infection or uncertain bacteriologic status, or threatened loss of critical structures exposed as a result of insufficient



soft tissue coverage. Surgically created wounds, which generally pose less of a problem from a bacteriologic standpoint than traumatic wounds, are best managed by an immediate coverage procedure when direct closure is impossible.

Traumatic wounds are more difficult to evaluate than surgical wounds for several reasons. First, the potential for infection is high because of the environment in which the wound is created, the mechanism of injury, and the time that elapses before operative intervention. Second, the mechanism of injury (e.g., crush, avulsion, or gunshot) may extend the zone of injury beyond what is immediately apparent [see Figure 1]. Serious

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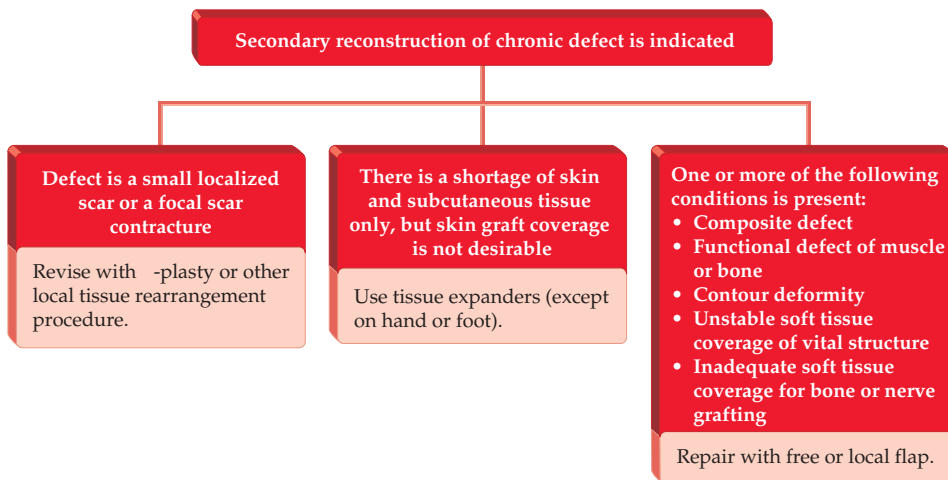
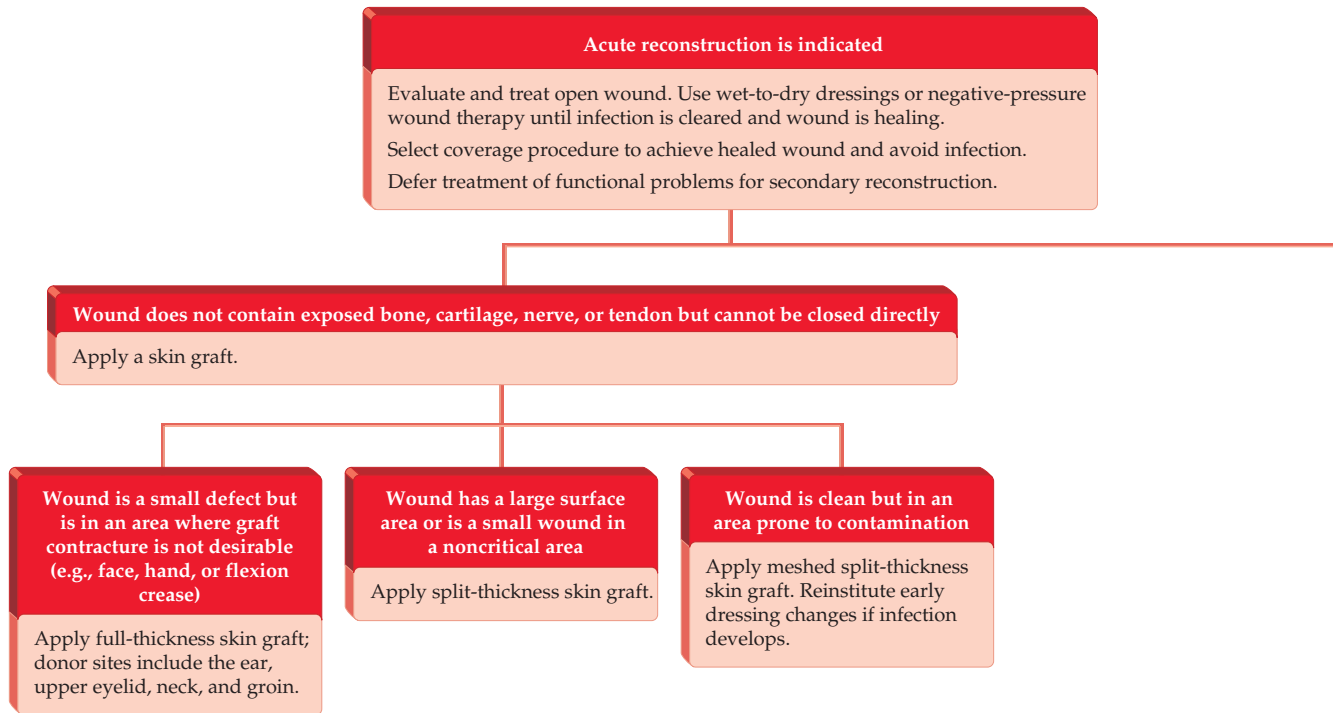
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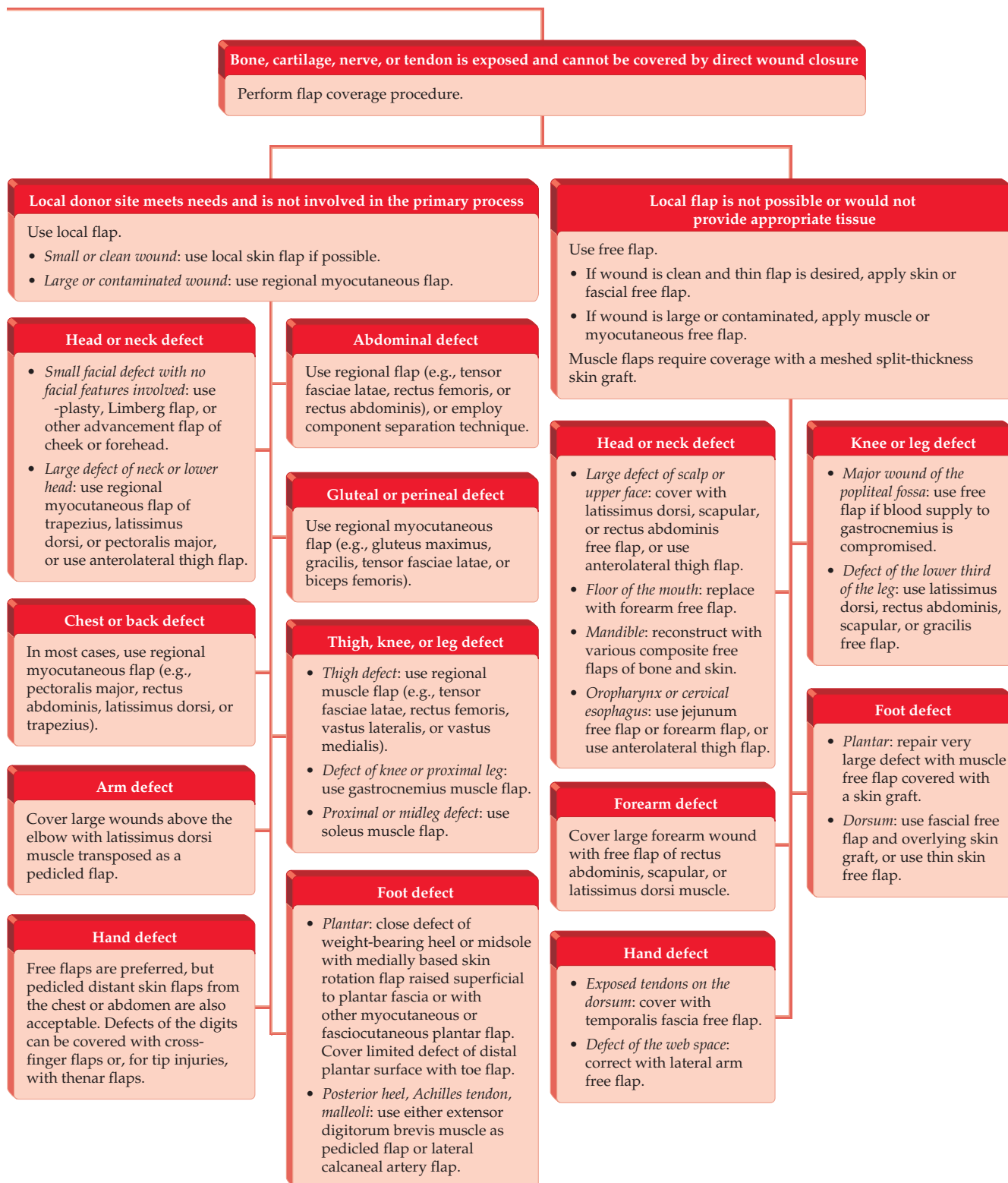
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Figure 1 (a) A so-called bumper injury of the leg is shown after initial débridement and bony stabilization (2 days after injury). (b) After the second débridement, the true extent of devitalization of bone and soft tissue is apparent (4 days after injury). (c) A latissimus dorsi free flap has been used to reconstruct the soft tissue defect (5 days after injury).



Approach to Surgical Reconstruction



postoperative infection may develop in these cases if definitive wound coverage is provided in the absence of adequate débridement. Third, whereas accurate assessment of the chances for recovery of specific structures within the wound is vital for selecting the optimal method of treatment, such assessment is often difficult immediately after injury.

EVALUATION

The initial step in the management of problem wounds is to decide whether the wound is suitable for immediate soft tissue coverage. Wounds that are surgically created during the course of an elective procedure are almost always best treated with primary definitive coverage. Traumatic wounds that present within 1 or 2 hours of injury and have a minimal crush component are also best treated with a primary definitive coverage procedure after thorough débridement (if the patient's hemodynamic status permits).

Injuries with a significant crush component and exposure of critical structures (e.g., nerves, vessels, tendons, or bone) are best treated more aggressively. In these cases, thorough débridement requires considerable surgical experience because the tendency is to débride inadequately. The accuracy with which tissue viability can be assessed varies from one type of tissue to another. For example, skin can be evaluated by its color, the nature of its capillary refill, the quality of its dermal bleeding, or its bleeding response to pinprick. After intravenous fluorescein injection, skin viability can also be assessed qualitatively, with a Wood light, or quantitatively, with a dermofluorometer. Muscle is the most difficult tissue to evaluate. Color, capillary bleeding, and contractile response to stimulation are not always reliable indicators of muscle viability. In severe injuries, they can be misleading. Inadequate débridement may lead to severe consequences resulting from infection. Therefore, serial débridement at 24- to 48-hour intervals is essential for accurately establishing the limits of muscle injury. Efforts should be made during débridement to preserve tissues such as major nerves and blood vessels unless they are severely injured. These structures are vital for function and are of small mass compared with other tissues (e.g., skin, fat, and muscle) at risk for necrosis and subsequent infection.

Wound débridement, therefore, should involve careful analysis of the injury from an anatomic point of view; débridement should not consist of indiscriminate excision of blocks of tissue. Between débridement procedures, the wound should be treated with sterile dressing changes or negative-pressure wound therapy (NPWT) if conditions permit. A definitive soft tissue coverage procedure should then be performed as soon after the initial injury as wound conditions permit. When thorough débridement and definitive coverage can be completed within less than 1 week, the wound will generally heal uneventfully. Inadequate débridement frequently results in the loss of any additional tissue invested to achieve acute soft tissue coverage. The wound becomes grossly infected, and important functional structures within the wound are reexposed.

Infected surgical wounds, neglected wounds, or other complex wounds in which initial wound management fails should be débrided and then treated by open methods. Proper care of these wounds is aimed at converting estab-

lished gross infection to a much lower level of bacterial contamination, which is then compatible with successful secondary wound closure. For example, advances in the use of NPWT [see Initial Treatment, Negative-Pressure Wound Therapy, *below*] have simplified the management of complex lower extremity traumatic wounds, reducing the use of free tissue transfer.¹

INITIAL TREATMENT

Débridement

Devitalized tissue provides an ideal culture medium for bacteria and isolates them from host defense mechanisms. Surgical débridement must be performed aggressively—and on a serial basis if necessary—to remove all necrotic tissue.

High-Pressure Irrigation

A useful adjunct to débridement is high-pressure irrigation, which has been shown experimentally to reduce wound infection rates significantly.^{2,3} Some argue that small particulate materials may get pushed deeper into a wound bed; therefore, this technique should not be used indiscriminately. It is recommended as an adjunct once thorough débridement has been performed manually.

Quantitative Bacteriology

The degree of bacterial wound contamination can be accurately quantified. The standard technique of quantitative bacteriology requires several days to complete and is therefore of somewhat limited utility in the management of acute wounds. In addition to a count, it provides identification and antibiotic sensitivities of the organism. As an alternative, quantitative bacteriology can be performed by using the rapid slide technique, which provides valuable information about the wound within 20 minutes.^{4,5} The level of bacterial contamination has been shown to be a significant predictor of outcome in wound closure by either skin graft or flap coverage techniques. According to the golden period principle of wound closure, a minimum time interval is necessary for bacteria to proliferate to a certain threshold level. Contaminated wounds take a mean time of about 5 hours to reach a bacterial count of 10^5 /g of tissue. Attempts to close wounds that have counts higher than 10^5 /g of tissue will fail 75 to 100% of the time, whereas attempts to close wounds with lower counts are successful more than 90% of the time.⁶ β -Hemolytic streptococci are an exception in that much lower concentrations of these organisms consistently result in failure of wound closure. When a β -hemolytic streptococcus is the dominant isolate, the wound should generally be treated openly until cultures become negative. Good clinical judgment often makes quantitative bacteriology unnecessary, and it is not used frequently. In many modern microbiology laboratories, it is no longer available.

Systemic and Topical Antibiotics

The role of systemic antibiotics in wound management is not clearly defined. Broad-spectrum antibiotics should be given in cases of severe trauma as a prophylactic dose prior to surgery. Certain antibiotics provide broad-spectrum activity when applied topically. Neomycin, 10 mg/mL, or a

combination of bacitracin, 50 U/mL, and polymyxin B, 0.05 mg/mL, kills most common wound pathogens. These solutions can be used when wet dressings are indicated, or as described in the chapter “Management of the Burn Wound” [see 7:15]. In the past few years, numerous antibacterial dressings have been developed, including an antibacterial NPWT sponge. Such dressings may prove useful in the treatment of open, contaminated wounds; however, discussion of these products is outside the scope of this chapter.

Topical Antiseptics

A variety of topical antiseptics have been used empirically in wound care. In the concentrations usually recommended, however, these solutions are detrimental to wound healing. Povidone-iodine (1%), hydrogen peroxide (3%), acetic acid (0.25%), and sodium hypochlorite (0.5%) all have been shown to be lethal to fibroblasts, as well as to bacteria. More dilute concentrations of povidone-iodine (0.001%) and sodium hypochlorite (0.005%) are effective against bacteria while being safe for fibroblasts.⁷ A number of these agents also inhibit normal white blood cell function in the wound.

Damp Dressings

Open wounds can be treated with damp dressings, generally consisting of gauze soaked in saline or an acceptable topical antiseptic, and then wrung out until just damp. Damp-to-damp dressings prevent desiccation of exposed vital structures or freshly placed skin grafts. Damp-to-dry dressings are useful for assisting in daily wound débridement. These dressings are allowed to dry on the wound; when they are removed, adherent fibrinous debris is removed with the dressing. Damp dressings of either type should be changed at least twice a day.

Small wounds can be expected to close by contraction and secondary epithelialization after appropriate open management with the techniques described. Large wounds will improve with aggressive open care but will then stabilize into a chronic state of wound colonization of varying degrees. A soft tissue coverage procedure may then be necessary to complete closure in these cases.

Negative-Pressure Wound Therapy

In the past 10 years, the vacuum-assisted closure (VAC) device (VAC Dressing System, Kinetic Concepts Inc., San Antonio, TX) has gained widespread acceptance for the treatment of open wounds. Because this device does not accomplish débridement to any significant degree, it should be applied only to a clean wound that has no necrotic debris or infection present. If any significant necrotic tissue remains after sharp débridement, wet-to-dry dressings may be employed until the wound is clean and granulating. Dressing changes are typically carried out every 2 or 3 days; this is a significant advantage, given that conventional dressing changes are generally done at least twice daily. Exudate is removed and quantified by the suction device, and more robust wound granulation and contraction can be observed. After treatment with a VAC device, wound closure can be accomplished secondarily with a skin graft, local flaps, or free tissue transfer, depending on the clinical situation. The disadvantages of NPWT include the need for specialized equipment and training and the increased cost.

SELECTION OF COVERAGE PROCEDURE

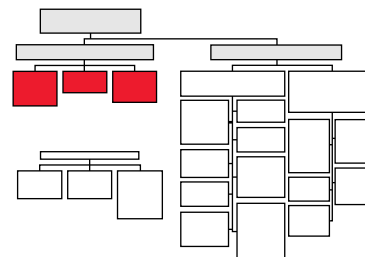
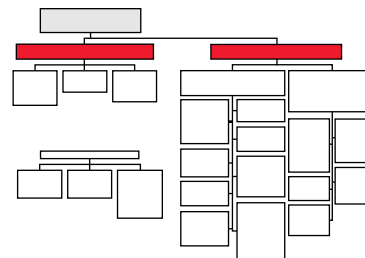
The main goals of coverage procedures in the management of both acute and chronic wounds are (1) to achieve a healed wound and (2) to avoid infection. The treatment of functional problems is generally deferred for secondary reconstruction.

The method of coverage depends on whether vital structures (e.g., vessels, tendons, nerves, and bone) are exposed in the wound. If no vital structures are exposed, skin graft coverage is indicated. Skin grafts can also be used over tendon if the paratenon is intact, over nerve if the epineurium is intact, and over bone if the periosteum is intact. Skin grafts are the most expendable type of soft tissue available for the coverage of open wounds. They allow the wound to heal completely and set the stage for secondary reconstruction, during which more valuable tissue can be used to achieve other goals at minimal risk. When vital structures are exposed in the wound, a flap is preferred because it provides more substantial soft tissue coverage of the structure. The choice of flap depends on the location of the wound and on its overall size, depth, and topographic configuration (see below).

Skin Grafts

Skin grafts may be either partial thickness (i.e., split thickness) or full thickness. Split-thickness grafts are preferred for wounds with a large surface area. Full-thickness grafts are suitable only for small defects because their donor sites must be closed primarily; the most common donor sites for full-thickness grafts are the ears, upper eyelids, neck, and groin. Full-thickness grafts contract less with time than split-thickness grafts and are therefore particularly suitable for wounds of the hands, extremity flexion creases, nose, eyelids, and other areas of the face.

Successful healing of skin grafts requires immobilization of the recipient site to prevent shearing in the plane between the graft and the wound bed. Although complete immobilization is desirable, the required dressings may preclude observation of a wound that is known to be significantly contaminated. In such cases, a meshed split-thickness graft is indicated, and the wound should be treated in an open fashion. A meshed graft can be placed directly over the muscle of a flap and secured over its irregular contour with staples [see Figure 2]. Because the graft is meshed, serum can escape between the interstices and there is little risk of separation from the underlying tissue. A meshed graft is also less vulnerable to disruption by shear forces. An additional advantage of a meshed graft is that it permits the wound to be treated with wet dressings if there is still risk for



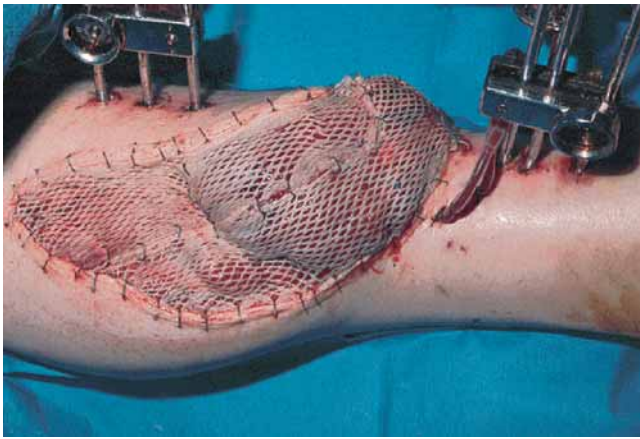


Figure 2 A meshed (1.5:1 ratio) skin graft has been secured to the irregular contour of a muscle free flap with staples. No additional immobilization of the graft is needed. The interstices of the graft allow free drainage of serous exudate from the muscle.

infection. A mesh expansion ratio of 1.5:1 is generally preferred, except when the surface area of the wound is very large and the availability of donor sites is limited.

Flaps

Flaps consist of tissues that have a self-contained vascular system. They permit a more substantial transfer of tissue bulk than do skin grafts and may consist of skin and subcutaneous tissue, fascia, muscle, bone, or a combination of several tissue types. Local flaps consist of tissue that is mostly detached from surrounding tissue but retains enough connection to preserve an adequate blood supply to the entire flap. Local flaps are either transposed, rotated, or advanced into adjacent defects for purposes of reconstruction. Island flaps are local flaps that are based only on their skeletonized axial blood supply. Once created, an island flap is transferred through a subcutaneous tunnel into the defect. The skeletonized pedicle remains in the subcutaneous space while the cutaneous portion of the flap fills the defect. Free flaps, in contrast, are totally detached; their blood supply is reconnected at the recipient site by means of surgically performed microvascular anastomoses between recipient-site blood vessels and the major vessels that supply the flap.

Blood Supply

The earliest flaps in common use were skin flaps that had what is known as a random-pattern type of circulation [see Figure 3a], in which blood is supplied by the subdermal capillary plexus rather than by a named vessel.⁸ The precarious nature of the blood supply of such flaps severely limited flap design and resulted in a preoccupation with suitable length to width ratios. Greater length to width ratios became

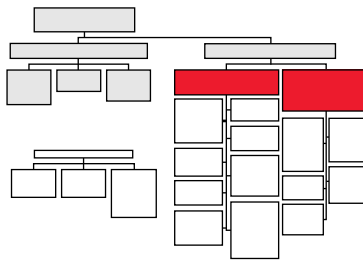
possible after the empirical discovery that a more vigorous circulation develops in flaps raised in stages (the delay phenomenon).⁹ The next flaps to come into common use had an axial-pattern type of circulation, in which a sizable artery coursed directly to a specific cutaneous territory [see Figure 3b]. The groin was the first region where this arrangement was carefully described, and it remains a useful source of flaps for selected applications. Because longer flaps can be made in areas where the blood supply has an axial pattern, the length to width ratio and the delay phenomenon became less important issues.¹⁰ Identification of an axial-pattern blood supply to a given graft allows so-called islanding of the graft from the donor site except for the vascular connection, which is preserved. Such island flaps have greater mobility than flaps with a less attenuated attachment to the donor site.

A third type of flap was based on the myocutaneous blood supply, a network of vessels that perforate muscles vertically and supply the overlying skin [see Figure 3c and Figure 3d]. These vessels are not necessarily the exclusive supply to the skin in a specific region, but they are able to support the skin entirely when other sources of blood supply are eliminated. Investigation of the body musculature showed that there were at least five basic patterns of blood supply to muscle, distinguished by the existence of and balance between primary pedicles and secondary sources of blood supply [see Figure 4]. Some muscles can be rotated or transposed as myocutaneous flaps on the basis of either their dominant or their secondary blood supply (e.g., the pectoralis major and the latissimus dorsi). Some muscles have two dominant supplies and can be transposed on either one (e.g., the rectus abdominis). Other muscles do not reliably support skin territories supplied by minor pedicles (e.g., the gracilis).

Other patterns of cutaneous blood supply are now well recognized. Fasciocutaneous flaps with high length to width ratios can be reliably raised on the trunk, arms, and legs. The blood supply of deep fascia appears to consist of both a deep and a superficial fascial plexus. These vessels connect both to perforating vessels from the underlying muscles and to the subcutaneous tissue vessels above them.¹¹ At least three types of fasciocutaneous flaps may be distinguished on the basis of the fascial blood supply to the skin [see Figure 5].¹²

In some areas, fascia supplies overlying subcutaneous tissue and skin more directly. Such a blood supply is most evident in the extremities, where direct branches from major vessels course through intermuscular septa to reach the deep fascia and supply the overlying skin and subcutaneous tissue. The forearm is a clinically important donor site because thin septocutaneous flaps fed by the radial artery can be raised as either pedicled or free flaps. Other examples of fasciocutaneous flaps include the lateral arm septocutaneous flap, fed by the profunda brachii artery; the scapular flap, fed by the circumflex scapular artery [see Figure 3d]; the fibular osteofasciocutaneous flap, fed by the peroneal artery; and the anterolateral thigh flap, fed by the descending branch of the lateral circumflex femoral artery.

The 21st century has seen the popularization of “perforator” flaps, which are based on musculocutaneous branches (or perforators) of named, axial vessels. In the early years of



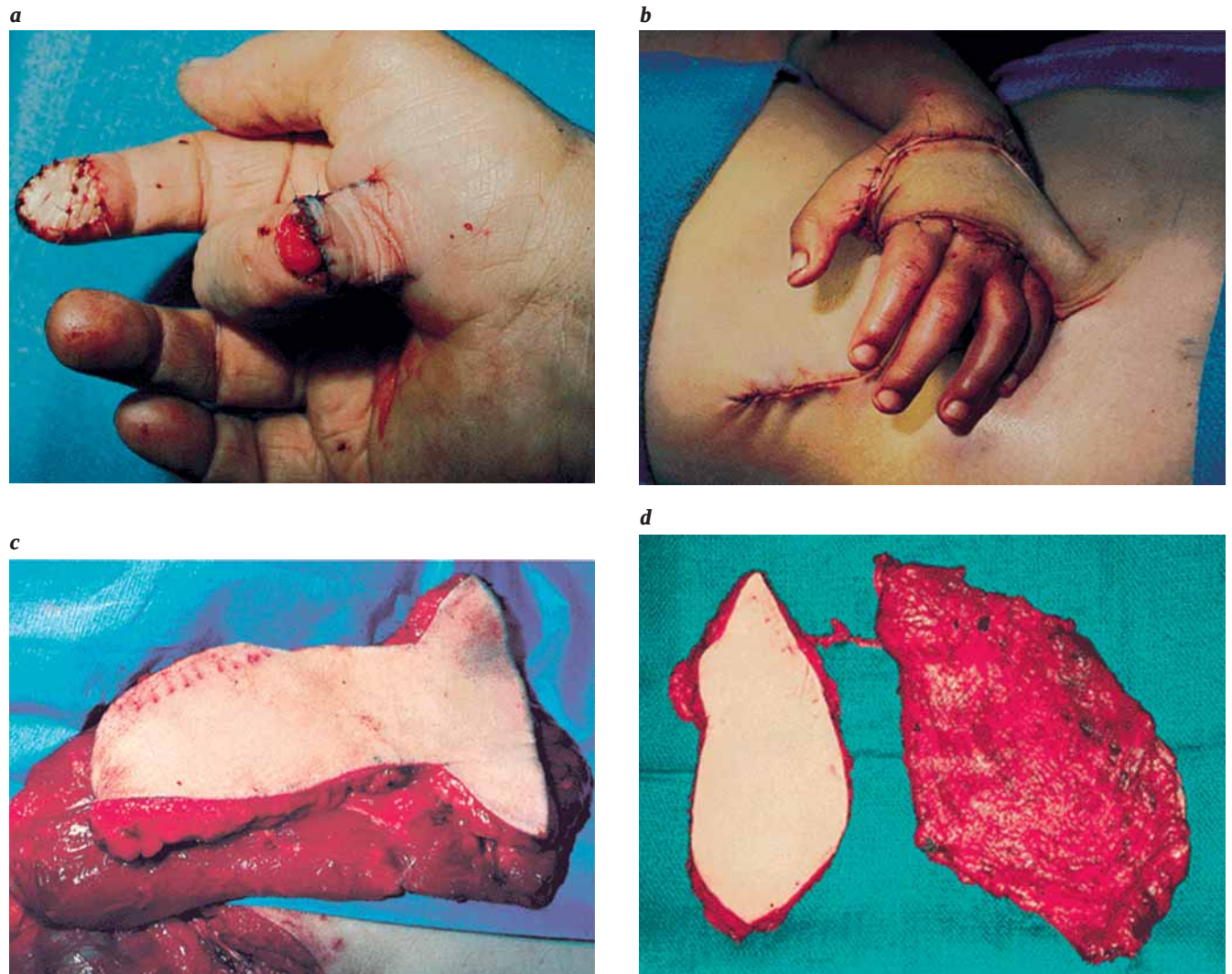


Figure 3 (a) The blood supply of random-pattern skin flaps is limited; only small flaps (e.g., thenar flaps, shown here) are consistently reliable. (b) Shown is an axial-pattern skin flap. (c) The skin and subcutaneous tissue of a myocutaneous flap can exist as a complete island because the blood supply is derived from vertical muscular perforators. (d) Shown are a large free flap of scapular area skin and the entire latissimus dorsi. The subscapular vessels that connect the two will supply both components of the flap after microvascular anastomoses.

microsurgery, success was defined by a lack of microvascular thrombosis. As experience was gained and rates of microvascular anastomotic failure decreased, focus was then turned on limiting donor-site morbidity. Several myocutaneous flaps used primarily for their skin and subcutaneous components were modified such that musculocutaneous perforators supplying the overlying fat and skin were dissected through the muscle down to the pedicle origin, thus preserving muscle and function. Common perforator flaps include the deep inferior epigastric perforator flap, or DIEP flap, and the superior and inferior gluteal artery perforator flaps, or SGAP and IGAP flaps. These flaps are commonly performed for breast reconstruction. The anterolateral thigh flap, or ALT flap, is supplied by a musculocutaneous perforator of the descending branch of the lateral circumflex femoral artery roughly two thirds of the time and by a septocutaneous branch one third of the time.

TYPES OF LOCAL FLAPS

Transposition Flaps

A flap that is moved laterally into the primary defect is called a transposition flap. The essential concept in the design of such a flap is to ensure that the flap is long enough to cover the entire defect, so that the transfer can be done without tension [see Figure 6].

The skin is marked and incised with a scalpel, and dissection is carried through the subcutaneous fat. The flap is retracted with a skin hook, and dissection is performed with blunt scissors until the flap is elevated sufficiently to allow it to be transposed into the defect without tension. The secondary defect is closed primarily; alternatively, depending on the location of the donor area and the degree of skin tension present there, a skin graft may be indicated. As with any local flap, wide undermining of the surrounding tissues may be

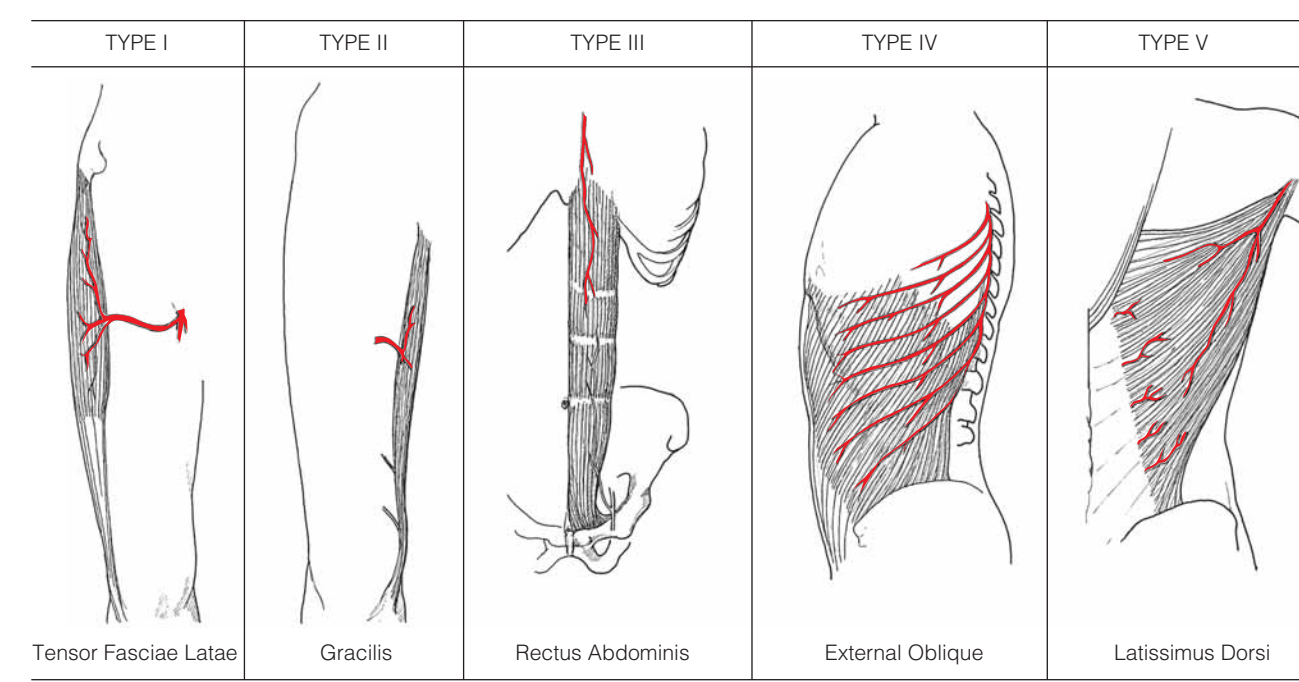


Figure 4 Schematized are the five basic patterns of blood supply to muscle. Individual muscles are classified on the basis of the dominance, number, and size of the vessels that supply them. Type I is supplied by a single dominant pedicle. Type II is supplied by one dominant vessel and several much smaller vessels. Type III is supplied by two dominant pedicles. Type IV is supplied by multiple vessels of similar size. Type V is supplied by one dominant pedicle and several smaller segmental vascular pedicles.

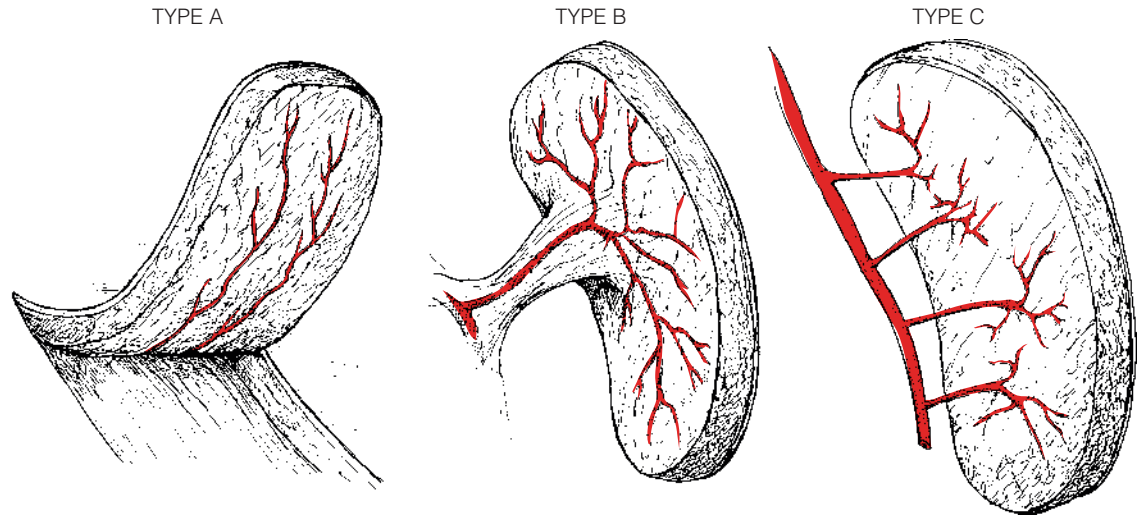


Figure 5 At least three types of fasciocutaneous flaps exist, categorized by blood supply configuration. Type A is supplied by multiple small, longitudinal vessels coursing with the deep fascia. These flaps must retain a base of a certain width and cannot be raised as islands (e.g., longitudinally oriented flaps of skin and fascia on the lower leg). Type B is supplied by a single major vessel within the fascia (e.g., scapular flap). Type C is supplied by multiple perforating segments from a major vessel coursing through intermuscular septa (e.g., forearm flaps).

necessary for closure of the defect and the donor site. Closure is then performed in two layers.

Bilobed flap A bilobed flap is a transposition flap consisting of two lobes of skin and subcutaneous tissue based on a common pedicle [see Figure 7]. It is often used to correct

nasal defects involving the lateral aspect, the ala, or the tip. The keys to a successful bilobed flap are (1) accurate design and (2) wide undermining of the surrounding tissue in the submuscular plane to allow a smooth transposition. The primary lobe is usually at an angle of 45° or less to the defect;

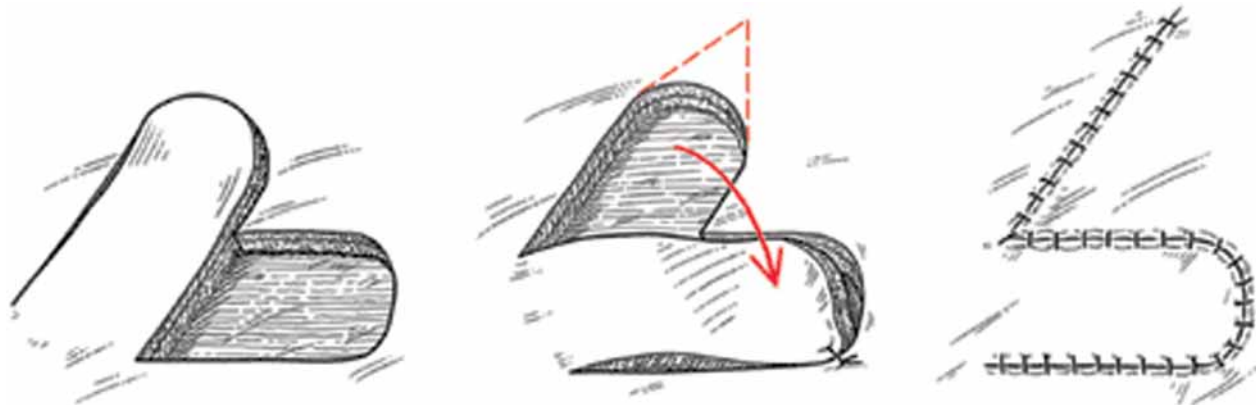


Figure 6 After excision of the defect, a transposition flap of adequate length is designed and elevated in the subcutaneous plane. The flap is moved laterally into the defect and inset. It may be necessary to excise a dog-ear of excess skin at the tip of the flap harvest site.

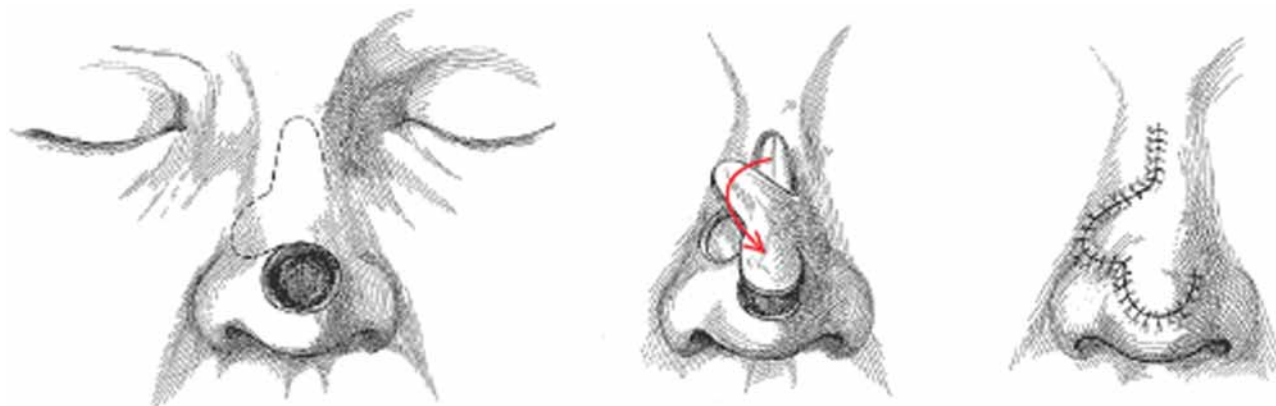


Figure 7 A flap with two lobes is created, with the first lobe the same size as the defect and the second lobe substantially (50%) smaller than the first. The flap is elevated in the submuscular plane. Wide undermining at this level is necessary for tension-free transposition. The first lobe covers the initial defect, and the second covers the defect from the first. The second lobe is placed in an area of loose skin, and its area of origin is closed primarily.

the secondary lobe is designed to achieve closure of the donor defect and is substantially smaller than the primary lobe. The angle between the two is 90° to 100°. Both flaps are raised simultaneously in the submuscular plane. Wide undermining of the area (also in the submuscular plane) minimizes tension. The primary lobe of the bilobed flap is transposed into the initial defect, the secondary lobe is transposed into the donor defect left by the primary lobe, and the defect left by the secondary lobe is closed primarily. Closure is accomplished with 5-0 or 6-0 nylon.

Rhomboid flap (Limberg flap) A rhomboid flap is a transposition flap that is designed in a specific geometric fashion [see Figure 8]. The initial defect is converted to a rhomboid, with care taken to plan the flap in an area with minimal skin tension. The rhomboid must be an equilateral parallelogram with angles of 60° and 120°; this design allows the surgeon to excise less tissue than would be needed for an elliptical flap. One face of the rhomboid constitutes the first side of the flap (YZ). The short diagonal of the rhomboid is then extended outward for a distance equal to its own length.

This extension should be oriented along relaxed skin tension lines, perpendicular to the line of maximum extensibility; it constitutes the second side of the flap (XY). Next, a line parallel and equal in length to YZ is drawn from X to outline the third side of the flap. Correct orientation of the rhomboid is vital for achieving flap repair with minimal tension, particularly with respect to the line of maximum extensibility: it is along this base line that maximum tension results when the donor defect is closed. Once the flap has been correctly designed and elevated, it is transposed into the defect. Closure is done in two layers.

Rhomboid flaps work best on flat surfaces (e.g., the upper cheek, the temporal region, and the trunk). Extra attention to flap design is necessary when an attempt is made to close a defect over a convex surface with a rhomboid flap; improper flap design leads to excessive tension and potential flap necrosis.

Rotation Flaps

A flap that is rotated into the defect is called a rotation flap.^{13,14} This type of flap is commonly used to repair a defect

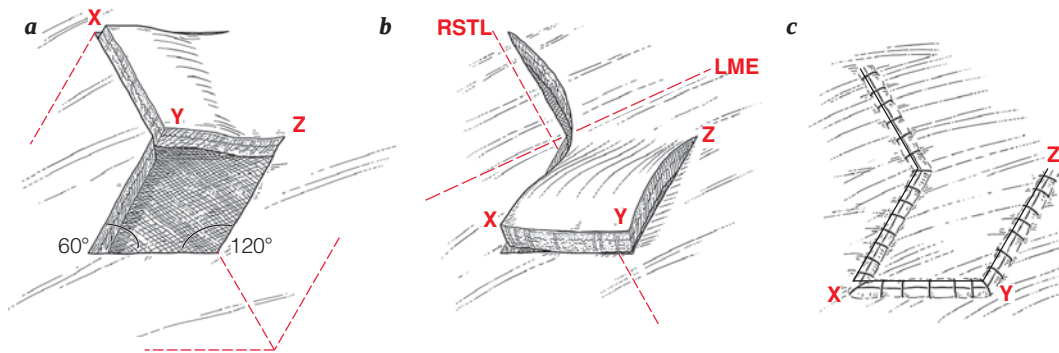


Figure 8 (a) The defect is converted to a rhomboid, with all four sides of equal length and angles of 60 and 120. An extension XY is made that is the same length as the short diagonal of the rhomboid, and a line of equal length is drawn from X paralleling YZ. (b) The flap is oriented so that XY follows the relaxed skin tension lines (RSTL) and YZ the line of maximum extensibility (LME). (c) The flap is inset.

on the scalp, where large flaps must be designed to overcome the inelasticity of scalp tissue. A rotation flap takes the form of a semicircle, of which the defect occupies a wedge-shaped segment [see Figure 9]. The original defect is converted to a triangular shape (ABC). One side of the triangular defect (AC) is extended to a point (D) that will serve as the pivot point for the flap. The distance between A and D should be at least 50% greater than that between A and C. A semicircular line extending from C to D is then defined.

The flap is incised with a scalpel, elevated, and rotated. As with all local skin flaps, wide undermining of the surrounding tissue may be necessary to allow tension-free rotation and wound closure. The flap is secured with a two-layer closure; the secondary defect may be closed primarily. Sometimes a so-called back cut is required to gain adequate rotation. The most common technical error with rotation flaps is improper design: a flap that is too small will not cover the defect adequately.

Advancement Flaps

Advancement flaps are moved directly forward into a defect without either rotation or lateral movement. The single-pedicle advancement flap is a rectangular or square flap of skin and subcutaneous tissue that is stretched forward. The flap is oriented with respect to the local skin tension, with care taken to plan the advancement in an area where the skin is extensible. A rectangular defect is created, and the flap is elevated in an area of loose skin and advanced to cover the defect [see Figure 10]. When closure is performed, some excess skin (dog-ears) at the base of the flap (Burow triangles) may have to be excised.

V-Y advancement flap The -Y advancement flap is a modification of a basic advancement flap [see Figure 11]. The use of a -Y advancement flap eliminates the need to revise the dog-ears that sometimes result with rotation flaps. When possible, the flap should be oriented in accordance with the line of maximum extensibility. Its length should be 1.5 to 2 times that of the defect in the direction of the closure.

Incisions are made completely through skin. As with other flaps, skin hooks are used to retract the skin flap, and blunt

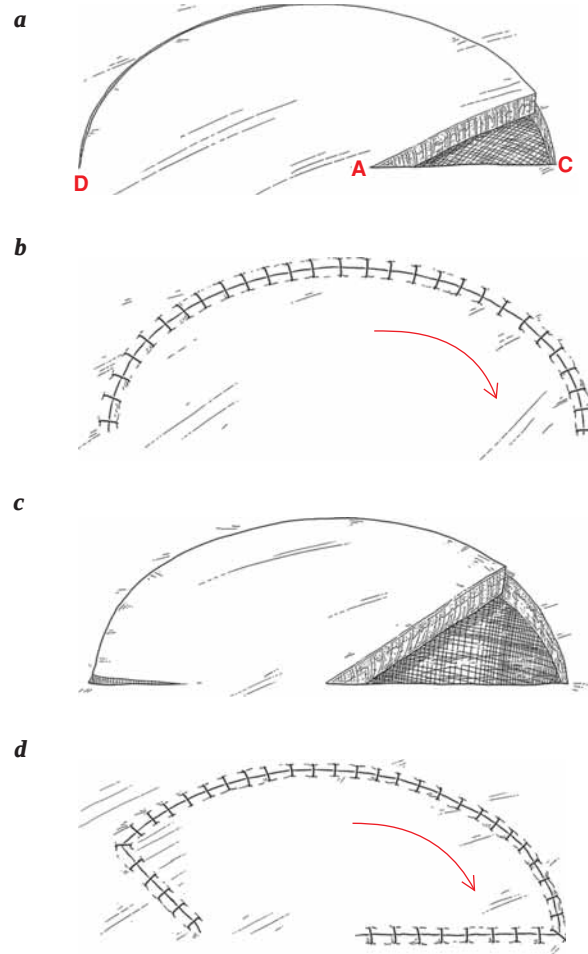


Figure 9 (a) The defect is converted into a wedge. One side (AC) is extended to a pivot point D, so that AD is at least 50% longer than AC. A semicircle from C to D is defined. (b) The flap is elevated, rotated, and inset. (c, d) If there is too much tension, a back cut may be necessary to release the flap and allow rotation. Care is taken not to make the back cut excessively long; to do so could devascularize the flap.

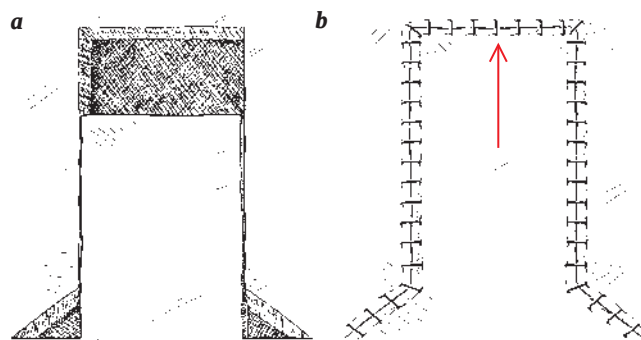


Figure 10 (a) A flap whose shape corresponds to that of the defect is elevated in the subcutaneous plane and advanced into the defect. (b) Excision of Burow triangles (excess skin at the flap base) may be necessary to permit advancement.

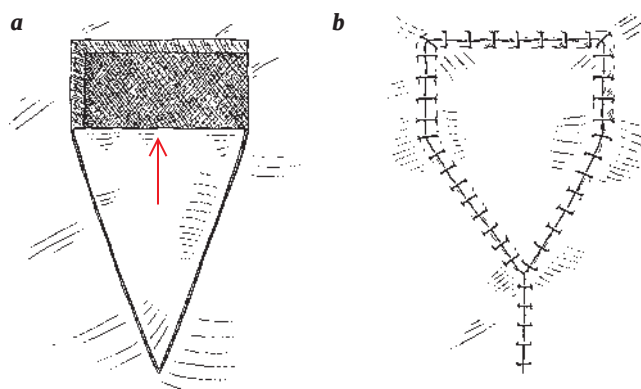


Figure 11 (a) A V-shaped flap is created whose length is 1.5 to 2 times that of the defect. With subcutaneous connections to the skin preserved (because these constitute the blood supply to the flap), the flap is advanced into the defect. (b) The V incision is converted to a Y as the base is closed primarily.

scissors dissection is then performed. The point of the on the flap is the area where tightness is most frequently encountered; this area may have to be released to facilitate advancement. Care must be taken not to undermine the advancing flap excessively: doing so may impair or interrupt the blood supply to the flap and result in necrosis. Once adequately advanced, the flap is sutured at the advancing edge and at the base of the Y.

Z-Plasty

When reconstruction is indicated for small, localized scars, soft tissue coverage is generally sufficient. With such coverage, there is no threat of breakdown leading to exposure of important structures; instead, the reconstructive problem is generally functional. An example is a flexion crease contracture, which is commonly seen after a burn injury. A local procedure that rearranges the existing tissue can relieve the tension by making more tissue available in one direction, even though the amount of tissue in the area is not actually increased.

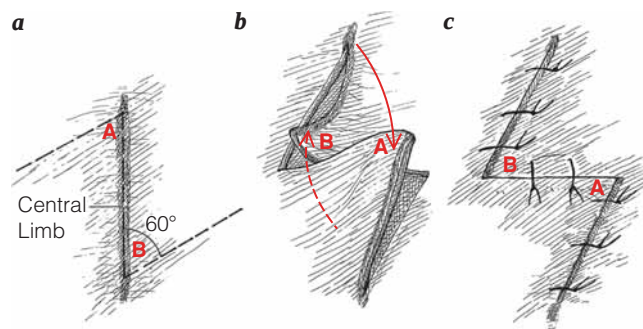


Figure 12 (a) The central limb of the Z is placed along the line of contracture. Incisions diverging from the scar at a 60 angle will yield an increase of approximately 75% in the direction of the central limb. (b) The flaps are transposed. (c) The length has been increased in the desired direction, and the original Z design has been rotated 90 and reversed.

The -plasty [see Figure 12] is an example of such tissue rearrangement.¹⁵ Two triangular flaps are designed so that they have in common a central limb aligned in the direction along which additional length is desired. For example, the limb may be placed along the line of a contracture. Two lines, approximately equal in length to the central limb, are drawn from either end of the limb, diverging from it at equal angles varying from 30° to 90°. The degree of lengthening obtained is determined by the size of this angle [see Table 1]. In theory, maximal length gain is achieved by using the largest angle possible, but in practice, the maximum usable angle is determined by the limits of skin elasticity. A 60° angle, which is commonly used, will result in a 75% gain in length along the central limb. Triangular flaps are elevated, and the fibrous tissue band responsible for the contracture is divided. The triangular flaps are transposed and inset, yielding increased length in the desired direction, with the original rotated 90° and reversed.

Although -plasty is conceptually simple, it is not necessarily easy: experience is necessary for the surgeon to realize the limitations of technique and appreciate the subtleties of proper design. Important considerations in the use of -plasty include appropriate determination of the length of the central limb and correct orientation of the limbs so that the new central limb formed after transposition is parallel to skin tension lines. Multiple -plasties may be useful for some localized scars.

Table 1 Z-Plasty: Incision Angle and Degree of Lengthening Theoretically Possible

Incision Angle (degrees)	Theoretical Amount of Lengthening (%)
30	25
45	50
60	75
75	100
90	120

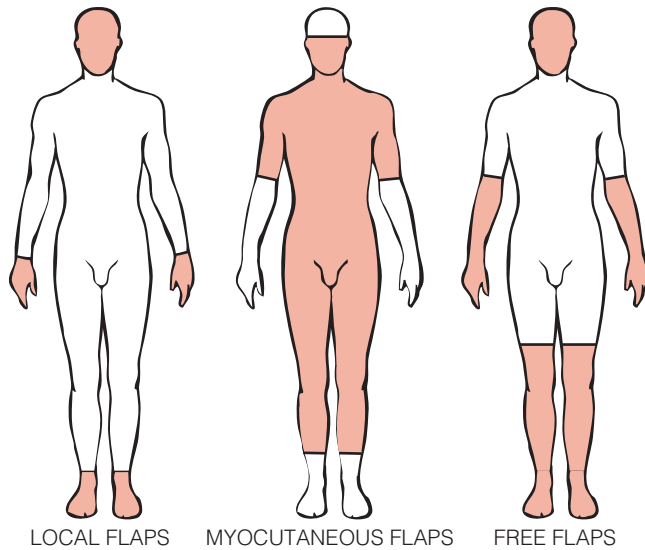


Figure 13 Defects in the central portion of the body are treated with myocutaneous flaps primarily; defects of the peripheral areas are treated with either local flaps or free flaps. In some areas, several options exist, and the choice is influenced by the size of the defect and the specific tissue requirements.

Local flaps versus free flaps The choice between a local flap and a free flap is determined by the amount and the type of tissue needed, as well as by the availability of flaps in the immediate area of the wound [see Figure 13]. The availability of local flaps, in turn, is determined by the nature of the regional blood supply. The vascular anatomy of a particular area determines the availability of arterialized skin flaps, fasciocutaneous flaps, myocutaneous flaps, and other forms of composite flaps. Local flaps can be grouped regionally by the types of tissue that they provide.

A local flap is generally preferred over a free flap if the two provide similar tissue, primarily because of the additional effort required to transfer a free flap. A free flap procedure commonly takes twice as long as a local flap procedure.

Free flaps are indicated in areas where local flaps are unavailable (e.g., the distal third of the leg) or when an extremely large flap is needed but cannot be obtained locally. When regional donor sites are affected by the primary process, free tissue transfer allows healthy, well-vascularized tissue to be brought into the compromised area. Moreover, if free tissue is transferred, the size of the wound is not extended, because the donor site is not contiguous but instead is located at a distance from the wound.

If expertise in microvascular surgery is available, free flaps are frequently a first-line choice. Free flaps allow selection of the appropriate type of tissue in the most suitable size and configuration for the specific reconstructive problem. Compared with free flaps, local flaps are inefficient ways of moving tissue because only a small portion of a local flap actually reaches the defect itself. The choice of donor site is greater with free flaps because the limitations imposed by local availability are avoided.

REGIONAL ALTERNATIVES IN FLAP SELECTION

Head and neck

Facial defects of small to moderate size are best treated with local skin flaps. A variety of flaps are available for reconstruction of limited defects of the eyelids, cheeks, nose, and mouth.^{16–18} Small

facial defects that do not directly involve the facial features can often be closed with any of several types of flaps that rearrange the existing tissue in the area—for example, a Z-plasty or a Limberg flap. Tissues that are difficult to match (e.g., those of the eyelids or lips) can often be reconstructed with flaps that borrow tissue from their opposite, intact counterparts (e.g., the Abbe lip flap).

For coverage of some large defects in the head and neck region, the trapezius, the latissimus dorsi, and the pectoralis major can be used. Each muscle can be raised with an optional skin island. These flaps are generally too bulky to be used on the face, and their reach is limited when used as pedicled flaps. None of them can cover major portions of the scalp or comfortably reach the upper face.

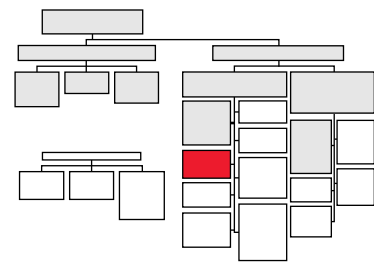
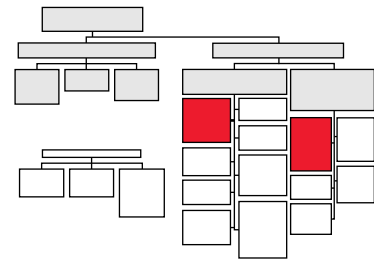
Latissimus dorsi, scapular, and rectus abdominis free flaps are useful for very large defects of the scalp or upper face. Smaller defects of the scalp are best treated with local scalp flaps.

Other free flaps of a specialized nature are superior for reconstruction of the floor of the mouth and mandible, even though local myocutaneous flaps will reach this area. For example, the forearm free flap based on the radial artery is quite thin and pliable and therefore provides an ideal replacement for the floor of the mouth. Composite free flaps that contain both bone and skin (e.g., those taken from the scapula, the ilium, the radius, and the fibula) provide tissue of the appropriate type and proper configuration for defects of the lower face in which the mandible must be reconstructed along with the intraoral lining, the external skin, or both.

Chest and back

Most clean defects of the chest and back are amenable to treatment with local myocutaneous flaps because of the wide arc of rotation of muscles located in these areas.¹⁹ In the presence of contamination,

open wound management is indicated. Traditionally, this has been accomplished with wet-to-dry dressing changes, which are especially effective for superficial débridement. Currently, these wounds are increasingly being managed with NPWT after all necrotic tissue is débrided. A common example is the wound resulting from the treatment



of poststernotomy mediastinitis. After sepsis is eliminated and the wound is granulating, definitive flap closure can be performed.^{20,21} Midline sternal wounds can be covered with pectoralis major, rectus abdominis, or omental flaps; lateral chest defects with latissimus dorsi or pectoralis major flaps; and midline back defects with latissimus dorsi or trapezius flaps. To cover midline defects, the pectoralis major, the latissimus dorsi, and the trapezius can be divided from their primary vascular supply and folded over as local flaps based on their medial segmental intercostal secondary blood supply.

Arm and forearm

Large wounds above the elbow can be covered with a latissimus dorsi myocutaneous flap transposed as a pedicled flap, provided that the vascular pedicle of the muscle has not been affected by the injury.

Forearm wounds that require flap closure are best treated with free flaps. A rectus abdominis, scapular, anterolateral thigh, or latissimus dorsi muscle flap can be used for large defects of the arm or forearm. Although soft tissue coverage with simultaneous functional forearm muscle replacement can be achieved with a single flap (e.g., a gracilis muscle flap), this is generally reserved as a secondary operation. A skin flap (e.g., a scapular free flap) is preferred as a first stage of reconstruction to achieve wound healing.

Hand

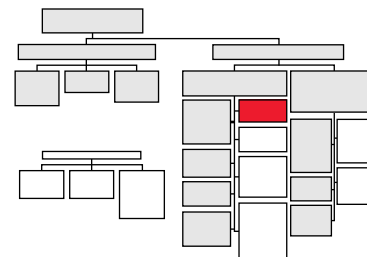
Both free flaps and pedicled skin flaps are useful for soft tissue coverage of hand wounds. A temporalis fascia free flap is particularly thin and is ideal for coverage of exposed tendons on the dorsum of the hand. A lateral arm free flap is ideal for reconstruction of a large defect of the first web space; it has sensory potential because it contains a large sensory nerve. Both of these free flaps are small. Pedicled distant skin flaps from the chest or abdomen are available as an alternative form of coverage for sizable hand defects. However, pedicled skin flaps have major disadvantages: wound care is difficult, edema persists because elevation and movement of the hand are seldom possible while it is attached to the trunk, and a second procedure is needed to divide these flaps.

Digital injuries with exposed tendons can be closed with a variety of cross-finger flaps of skin and subcutaneous tissue raised from either the volar or extensor aspect of an adjacent digit. Because these flaps do not contain a great deal of subcutaneous tissue, they are preferred for coverage of digits proximally, where a thick subcutaneous pad is not essential. A thenar flap is useful for fingertip injuries in which the soft tissue pad of the fingertip is lost and bone is exposed. This

flap provides an ideal pulp replacement, as well as better sensory recovery than skin grafts. Fingertip injuries can also be closed with several types of -Y advancement flaps that can be raised from either the volar surface or the lateral surfaces of the end of the finger.

Abdomen

Clean defects of the abdominal wall that require flap closure are best treated with local muscle flaps such as the tensor fasciae latae and the rectus femoris from the thigh. The rectus abdominis also can occasionally be trans-



posed to cover an abdominal defect. Each of these flaps is harvested along with skin, although a large tensor fasciae latae flap will probably necessitate skin-graft closure of the donor site. The tensor fasciae latae flap has the advantage of including the thickened deep fascia (iliotibial band) of the thigh, which can provide additional strength for abdominal wall closure. Midline defects resulting from previous operation or trauma can often be closed by means of the component separation method. The external oblique fascia is divided lateral to the lateral edge of the rectus sheath, and the bloodless plane between the external and internal oblique muscles is developed. This maneuver mobilizes the recti toward the midline, usually allowing primary closure. Adding a prosthetic mesh reduces the recurrent rate of hernias but is more difficult to manage when exposed or infected.

As a consequence of the growing realization of the benefits of the open abdomen, increasing numbers of patients treated for abdominal trauma, sepsis, and compartment syndrome are presenting for management and closure. With contaminated wounds, the use of permanent meshes for reconstruction is contraindicated, and definitive flap closure is best delayed. In these difficult situations, the wound must be treated in an open manner, with close attention paid to the unique vulnerability of the intestines to fistula formation. Many treatment options are currently available for the open abdomen [see 7:6 *Operative Exposure of Abdominal Injuries and Closure of the Abdomen*]. Important considerations for any treatment modality include whether the method controls abdominal contents, whether it avoids promoting fistula formation, whether it achieves skin and fascial closure, whether it removes and quantifies exudate, whether it controls infection, and whether it promotes wound healing. The VAC device performs well with respect to all of these considerations, perhaps because of reverse tissue expansion and full-thickness wound contraction.^{22,23} Once all acute problems have been addressed and recovery is well under way, an absorbable mesh is commonly applied, followed by dressing changes or NPWT. To protect the underlying bowel, a layer of nonstick gauze should be applied before dressings or NPWT sponges. Once granulation is achieved, a skin graft can be placed. Chronic hernia formation is the rule and can generally be treated as a stable chronic ventral hernia provided that the wound is closed and free of infection.

Gluteal area and perineum

Local muscle flaps with or without skin are indicated for defects in the gluteal area or the perineum. Such flaps are preferable to large, random-pattern advancement skin flaps from the posterior thigh and thoracolumbar rotation skin flaps. The gluteus maximus, for example, can be used as a rotation flap, a -Y advancement flap, or a turnover flap in the treatment of pressure sores. As a turnover flap, it can be proximally or distally based, or it can be split along its longitudinal axis so that only a portion of it is used. Also useful for covering defects in the gluteal area and the perineum is the myofasciocutaneous gluteal thigh flap, which is a combination of a gluteus muscle flap and a fasciocutaneous flap from the posterior thigh that is supplied by an extension of the inferior gluteal artery. Because of its size and location, the gracilis muscle is well suited for coverage of defects of the perineum. The gracilis and the biceps femoris are generally secondary choices for the treatment of pressure sores over the ischium. The tensor fasciae latae is frequently used for treating open wounds over the greater trochanter. The entire quadriceps can be used to close defects resulting from hemipelvectomy.

Thigh

Flaps are rarely required for soft tissue coverage in the thigh area because critical vital structures are located deep within the thigh and are rarely exposed by injury or by surgical procedures. A number of regional muscle flaps are available for coverage in this region, however, including the tensor fasciae latae, the rectus femoris, the vastus lateralis, and the vastus medialis. An anterior defect that involves exposure of the femoral vessels can be covered with a rectus abdominis myocutaneous flap, a rectus femoris flap divided distally and turned over, or a sartorius flap. The sartorius muscle has a segmental blood supply and will not be reliable if more than one to two segmental pedicles are ligated, which limits its utility for larger defects. A number of smaller local skin flaps that are supplied with blood from the deep fascia can be raised over portions of the thigh. The anterolateral thigh flap is the most commonly employed thigh flap for free tissue transfer.

Knee, proximal leg, and midleg

The two heads of the gastrocnemius can be used either together or independently to cover defects of the knee and the proximal third of the leg. The soleus is useful for coverage of defects of the proximal and middle thirds of the leg. Local flaps should not be used for major leg wounds if the extent of the injury suggests involvement of the muscle donor site. Instead, a free flap should be used to bring healthy tissue

into the area. Therefore, free flaps are a first choice, for example, for coverage of major wounds of the popliteal fossa, knee, and proximal leg that involve the sural artery blood supply to the gastrocnemius; they are also highly useful for coverage of defects in the distal third of the leg. Traumatic wounds of the distal lower extremity can also be managed with NPWT. Increased use of this modality has been associated with the performance of fewer free tissue transfers and more delayed local flap procedures for definitive closure.¹

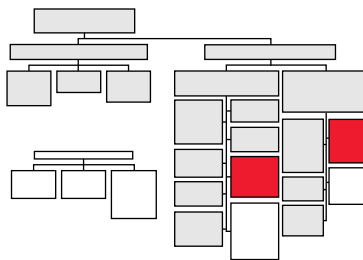
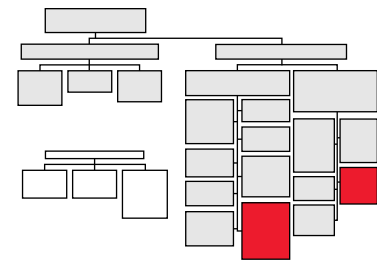
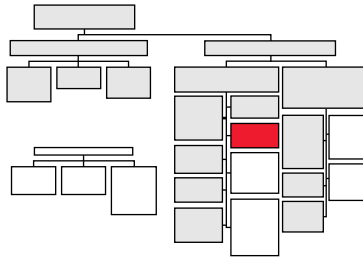
Skin flaps fed by the fascial blood supply can also be raised over the leg.²⁴ A number of fasciocutaneous flaps have been described in this area, but they tend to be smaller than muscle flaps and generally less reliable. These flaps are longitudinally oriented over the course of the anterior tibial artery or the peroneal artery. The maximum length at which such fasciocutaneous flaps are safe and their specific applications have not been well established.

Foot

The foot is as complex as the hand and the face in that it is composed of separate regions, each of which has a unique set of alternatives for reconstruction. These regions include the plantar surface; the dorsum; and the posterior (non-weight-bearing) heel, Achilles tendon, and malleoli.

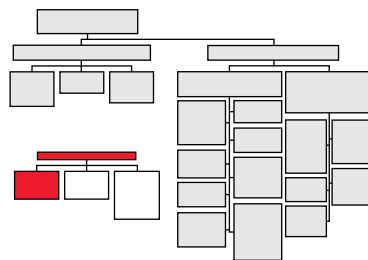
Superficial defects that lie completely within the non-weight-bearing portion of the midsole do not need flap coverage. Defects of the weight-bearing heel and midsole area that are less than 6 cm in diameter can be closed with a medially based skin rotation flap that is raised superficial to the plantar fascia.²⁵ This flap maintains plantar sensation. Limited defects of the distal plantar surface can be treated with local toe flaps that also maintain sensation. Very large plantar defects are best resurfaced with a muscle free flap (e.g., latissimus dorsi, gracilis, or rectus abdominis) covered with a skin graft or thin fasciocutaneous flaps. Although this type of flap lacks sensation, it appears to provide the most durable form of coverage because it resists shear forces well.²⁶

Defects of the dorsum that require flap coverage are best covered either with a fascial free flap (e.g., temporalis fascia) and an overlying skin graft or with a skin free flap that is thin (e.g., from the forearm or the anterolateral thigh). The extensor digitorum brevis can be raised from the dorsum as a pedicled flap fed by the dorsalis pedis artery. This flap, which measures approximately 5 × 6 cm, has an arc of rotation that makes it useful for the coverage of defects of the malleolus or the Achilles tendon area. A narrow transposition skin flap fed by the lateral calcaneal artery is useful for coverage of defects approximately 3 cm in diameter that lie over the Achilles tendon or the non-weight-bearing posterior heel. A distally based reverse sural artery flap transfers skin, subcutaneous fat, and fascia from the proximal posterior calf based on the vasa nervorum of the sural nerve, supplied by a distal branch of the peroneal at the level of the malleolus. This flap can also be used for defects of the ankle; however, it can be prone to venous congestion.



Secondary Reconstruction

Selection of the proper method for secondary reconstruction requires analysis of the type and extent of tissue deficiency that is present and consideration of the functional goals that are involved. Superficial defects may require replacement or supplementation of only skin and subcutaneous tissue, whereas more complex defects may require replacement of several types of tissue. Specialized tissue, such as vascularized nerve or intestine, may be necessary to provide a functional reconstruction in some cases (see below).



SMALL LOCALIZED SCAR

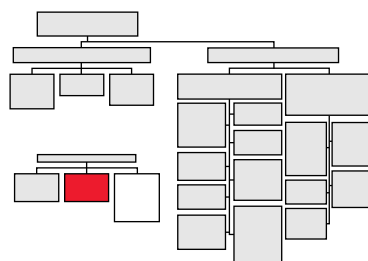
When reconstruction is indicated for a small localized scar, soft tissue coverage is generally sufficient and poses no threat of breakdown leading to exposure of important structures. Instead, the reconstructive problem is generally functional in nature. An example is a tight scar band across a flexion crease, which is commonly seen after a burn injury. A local procedure that rearranges the existing tissue can relieve the tension by making more tissue available in one direction, although the amount of tissue in the area is not actually increased.

The Z-plasty is an example of such tissue rearrangement. Multiple Z-plasties or other procedures, such as W-plasty, may be useful for some localized scars.

SHORTAGE OF SKIN AND SUBCUTANEOUS TISSUE

A shortage of skin and subcutaneous tissue may result from excision of a large scar or a large congenital defect (e.g., a nevus). Mastectomy commonly leaves a shortage of skin that prevents creation of a breast mound. In these cases, extra tissue can be created locally with the use of tissue expanders. These devices are inflatable plastic reservoirs of various shapes and volumes that are implanted under the skin. The skin over the expander is stretched during a period of several weeks as the expander is gradually filled by percutaneously injecting saline into an incorporated or remote fill port. The expander is then removed as a second procedure, and the expanded area of skin is advanced to cover the defect. The process of tissue expansion results in thinning of all layers of tissue overlying the expander—except for the epidermis, which actually thickens.

A number of important principles govern the use of tissue expanders. The expanders must be placed so as to allow expansion only in normal skin adjacent to the defect, not in the defect itself. To ensure adequate expansion, a sufficiently large expander or multiple expanders must be used. Complications associated with the use of tissue expanders include



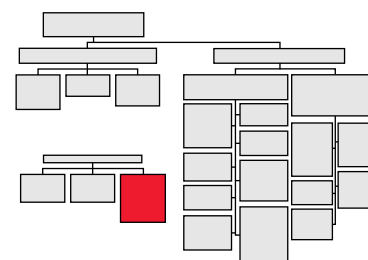
infection, extrusion, deflation, flipped ports (remote type), and hematoma formation.²⁷

Tissue expanders are used in secondary reconstruction only; they play no role in acute wound management. They are not indicated for contour defects (see below), because the tissue they provide is two-dimensional and lacking in bulk. Expanded tissue may not be adequate for coverage of chronically exposed structures (e.g., bone).

The scalp is an ideal location for the use of tissue expanders because no equivalent substitute for this type of hair-bearing tissue exists. Expanders work effectively when implanted over the hard calvarium and are useful in cases of burn alopecia and large nevi involving the scalp. Expanders are also useful for breast reconstruction, for carefully selected large lesions of the face, and for certain scars of the limbs. They are generally not indicated for use in the hands or feet. Although some local flap donor sites (e.g., the forehead) can be expanded before flap transfer, there is a loss of tissue pliability that appears to limit the usefulness of this particular application.

COMPLEX DEFECTS

Certain reconstructive problems require substantial amounts of tissue of one or more types or of a very specialized type. Either local or free flaps are used to meet these tissue requirements.



Composite Defect

A composite defect may result from resection of an intraoral carcinoma with loss of the mandible and either the lining of the mouth or external skin. Another example is a crush injury of the leg with loss of soft tissue and a segment of weight-bearing bone. These defects require that a composite flap be brought to the area to meet more than one type of tissue deficiency. Local flaps generally do not provide the necessary types of tissue or permit the freedom of design possible with free flaps. The wide variety of free flap donor sites that exists allows selection of tissue in the appropriate quantity and configuration for a particular defect [see Figure 14].

Functional Defect

Functional defects require repair with specialized flaps. Free flaps are frequently used because the specific tissue requirements usually cannot be satisfied by a local flap. A functional defect may result, for example, in the cervical esophagus from tumor resection or in the forearm from the Volkmann contracture. A segment of small intestine can repair the esophageal defect; transfer of a vascularized and innervated muscle (e.g., the gracilis) can replace forearm muscle.²⁸

Contour Defect

Contour defects, such as those that result from mastectomy or from trauma to the lower extremity, can be reconstructed with either local or free flaps. A mastectomy defect, because of its location on the chest, is suitable for reconstruction with

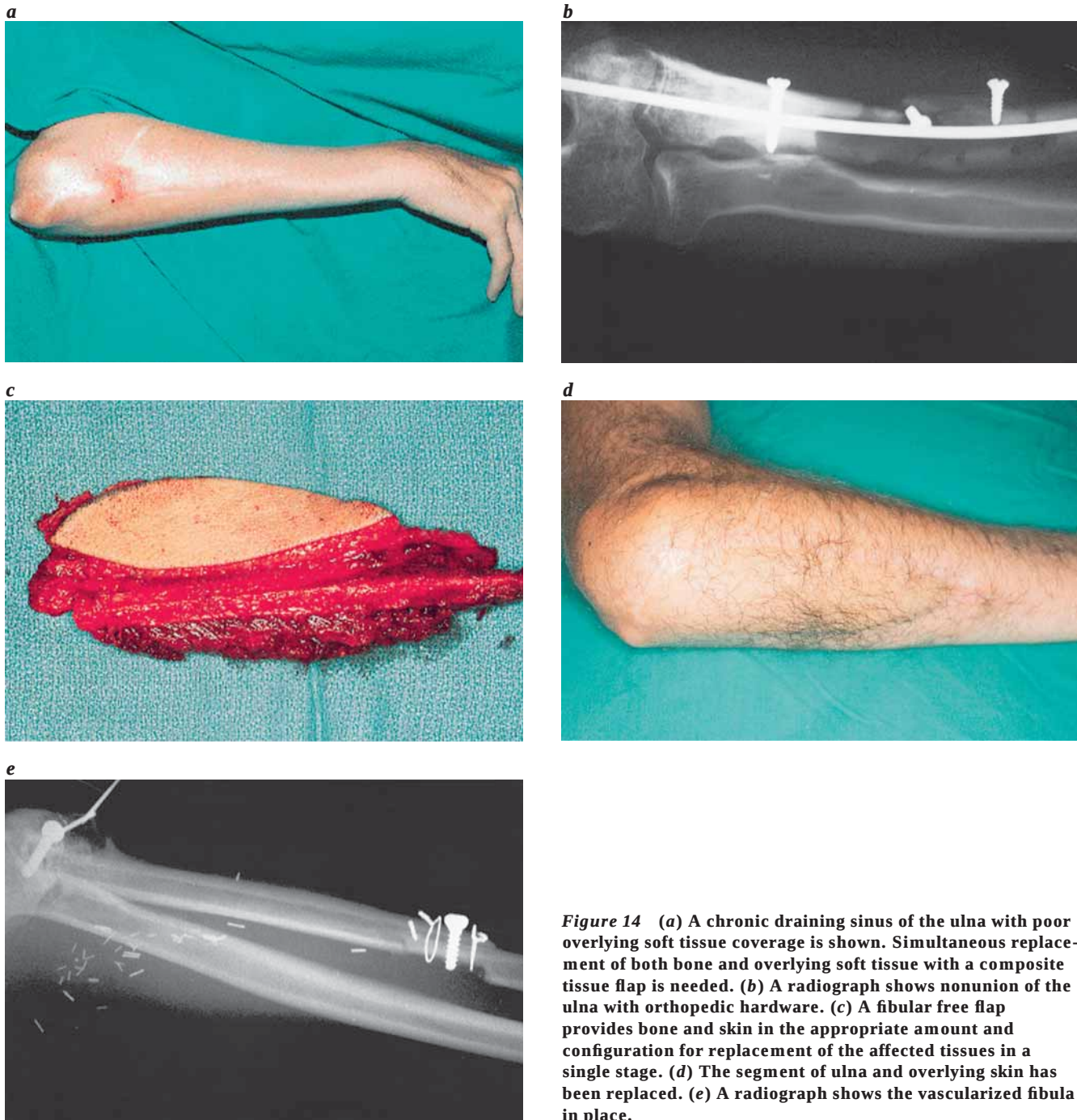


Figure 14 (a) A chronic draining sinus of the ulna with poor overlying soft tissue coverage is shown. Simultaneous replacement of both bone and overlying soft tissue with a composite tissue flap is needed. (b) A radiograph shows nonunion of the ulna with orthopedic hardware. (c) A fibular free flap provides bone and skin in the appropriate amount and configuration for replacement of the affected tissues in a single stage. (d) The segment of ulna and overlying skin has been replaced. (e) A radiograph shows the vascularized fibula in place.

one of several myocutaneous flaps from either the back or the abdomen [see 3:5 *Breast Procedures*]. A free flap from the abdomen or the gluteal area is another alternative. The best reconstructive solution for a particular person is determined by variables such as body habitus and the size and configuration of the contralateral breast.

A contour defect of the lower extremity is best reconstructed with a large myocutaneous free flap that provides tissue of sufficient quantity and flexibility to allow sculpting into the appropriate shape. An excellent example is the latissimus

dorsi free flap, which provides a large volume of thin, pliable muscle, which can be wrapped around orthopedic hardware.

Unstable Soft Tissue Coverage

Marginal soft tissue coverage (e.g., skin grafts) may break down after repeated minor trauma. Bones may become exposed and are then at risk for osteomyelitis. This situation can be avoided by elective replacement of the tissue at risk with a more substantial soft tissue covering. As in acute reconstruction, local flaps are the first choice for lesions of the

trunk or the proximal extremities, whereas free flaps are often more appropriate for lesions of the distal extremities.

Soft tissue coverage is sometimes inadequate even in a healed wound. For example, certain procedures (e.g., nerve or bone grafting) require an ideal soft tissue bed to promote adequate graft revascularization. In some cases, it may initially be necessary to replace the existing soft tissue coverage as a first-stage procedure before grafting a bone or nerve gap. A skin or muscle flap is most commonly used in such cases. Muscle flaps tend to provide superior vascularity (e.g., for bone grafts) but are considered inferior for coverage of tendons that need to glide. This problem is most common in areas such as the distal extremities, where native soft tissue coverage is not overly abundant and is easily lost as a consequence of trauma or tumor resection. Free flaps are usually chosen to provide a healthy, well-vascularized soft tissue bed before further functional reconstruction is undertaken.

POST OPERATIVE CARE AND FLAP MONITORING

Local Flaps

The postoperative care of local flaps is not complex. Flap healing is supported by adequate nutrition and maintenance of a normal hemodynamic state, including normal blood volume. Tension must not be placed on the flap. Tension can develop in flaps on the trunk as a result of changes in patient position or in flaps on the limbs as a result of loss of immobilization. Generally, the tip of any local flap is not only its most valuable portion but also its most vulnerable area. At the tip, the blood supply is the most precarious, and the detrimental effects of tension are magnified. Unfortunately, no pharmacologic agents are of proven benefit in preventing necrosis of a flap with failing circulation. Any flap necrosis that might develop should be minimized by preventing infection of the necrotic tissue. Necrotic tissue must therefore be debrided after the extent of tissue loss becomes clear. Portions of the flap that are undergoing demarcation but do not appear actively infected can be protected by the application of a topical antibiotic (e.g., silver sulfadiazine cream).

Extremities that are recipient sites for flaps, such as those that are recipient sites for skin grafts, should be immobilized and elevated after the operation until satisfactory wound healing has occurred.

Free Flaps

Survival of free flaps, unlike that of local flaps, tends to be an all-or-none phenomenon. Careful postoperative monitoring of flap circulation is essential because flap failure is likely to be the result of a problem at the vascular anastomoses. Flaps are usually monitored for 7 days. However, the most critical time for free flap monitoring is the first 48 hours because the majority of vascular crises usually occur within this period. Early detection and aggressive investigation of such crises generally allow a flap to be salvaged. Maintenance of normal blood volume, treatment of hypothermia, and avoidance of pressors are particularly important in the early postoperative period to prevent vascular spasm. Spasm causes flaps to appear pale and to exhibit a significant temperature drop. There is no cutoff for hemoglobin or transfusion that has proven beneficial for flap survival. It is

recommended that transfusion be reserved for when indicated by other patient factors.

Free flaps exhibit venous engorgement when placed in a dependent position up to several weeks postoperatively. Such engorgement is generally not dangerous, although patients with free flaps below the knee should be gradually mobilized in the same fashion as patients with skin grafts in this location by keeping the lower extremity elevated for at least 10 to 14 days.

Free flaps in the head and neck area require that the patient's head motion be restricted somewhat for the first few days to prevent kinking of the vascular pedicle. It is important that electrocardiographic leads and tracheostomy tube ties not compress the external jugular vein if it was used as a recipient vessel for anastomosis. If central lines are used after operation, they should be placed on the contralateral side of the neck to prevent thrombosis near the microvascular anastomosis.

Free flaps should be monitored on an hourly basis during the early postoperative period. Most free flaps include an exposed skin island, which facilitates evaluation of the flap circulation. The flap is observed for color and for capillary refill—the most important indicators of flap viability. A pale flap generally indicates arterial insufficiency; however, this is not always the case, because certain donor sites, such as the abdomen, are relatively light in color under normal circumstances, which means that a flap from one of these sites may appear pale while still having an adequate arterial supply. Mottling is an indicator of arterial insufficiency in these circumstances. Flaps with venous insufficiency are characteristically blue in color and exhibit rapid capillary refill. In such flaps, an increase in the pink/red color of the skin with brisk capillary refill often precedes the blue discoloration, and it is cause for concern when observed. Bleeding from the edges of a flap and swelling are common in the presence of venous hypertension.

If a skin island is exposed, Doppler ultrasonography should reveal the presence of a triphasic arterial pulse. The site of this pulse should be marked with a suture, staple, or permanent ink to facilitate monitoring by nursing staff. A trained ear can distinguish between triphasic, biphasic, and monophasic pulses, which (in that order) indicate increasing degrees of arterial compromise from arterial thrombosis or increasing venous hypertension. Sometimes a cutaneous venous signal can be found. The venous signal is a multiphasic “whooshing” sound that augments with flap compression and then reduces as the flap fills with blood again. It then returns to its baseline. The signal will also get cut off when the pedicle is compressed. The nontrained ear will not distinguish between static and a normal venous signal, so it is important to train the monitoring staff to assess the venous signal while performing flap or pedicle compressing maneuvers. When the flap is buried, monitoring becomes more difficult. Alternative methods of monitoring buried free flaps are being developed and are being used with increasing frequency. One example is the implantable Doppler monitor. This device is placed in direct contact with the artery or vein distal to the anastomosis to obtain a continuous Doppler signal.²⁹ These devices are useful for buried flaps, when cutaneous signals are not found, when a complicated microanastomosis has been performed, and for monitoring the flap during inseting. Too tight of a closure

will change the venous signal from a multiphasic signal with augmentation on flap compression to a more monophasic signal that does not augment. Tissue oximetry has also been developed to monitor flaps with an external skin island.³⁰ Using this device, a probe is placed on the skin island and attached to a monitor that measures overall tissue oximetry (arterial and venous). A baseline level is reached, and any significant fall below the baseline indicates vascular compromise. The flap can be monitored remotely via the Internet, and when the level falls below a preset point, the machine can notify personnel via a pager.

Surface temperature probes can also be used to monitor free flaps that have a skin island. One probe is placed on the flap and another on a nearby area to serve as a control. The flap surface temperature is generally about 1.0° to 2.5°C lower than the control temperature. A progressive widening of this temperature difference is ominous and calls for critical assessment of the flap circulation. The absolute temperature of the flap probe is also significant: a flap temperature higher than 32°C indicates healthy circulation, whereas a temperature between 30° and 32°C indicates marginal circulation and a temperature lower than 30°C often indicates a vascular problem. In a healthy flap, temperature fluctuations may be caused by a dislodged probe, an exogenous heat source (e.g., a lamp), cooling of one of the probes from an oxygen mist mask, or cleaning of the flap skin with alcohol (which results in a precipitous drop in skin temperature).

To confirm the presence of an anastomotic problem, flap circulation is assessed directly by a full-thickness puncture of the flap skin with a 20-, 22-, or 25-gauge needle. If flap circulation is healthy, a drop of bright red blood should appear at the puncture site within a few seconds, and another drop should appear each time the previous drop is wiped away by an alcohol swab. The failure of blood to appear or the delayed appearance of a clear, serous ooze instead of blood is an indication of arterial insufficiency. Vigorous, dark bleeding confirms a venous problem. Flaps that are pale as a result of vascular

spasm are difficult to assess because their bleeding response to needle puncture is poor despite intact anastomoses.

As a rule, clinical judgment of flap viability on the basis of all of these methods of flap monitoring will be highly predictive. If, however, some uncertainty exists, surgical exploration should be undertaken because the entire flap may be in jeopardy.

Free flaps without skin islands are more difficult to monitor accurately. Muscle flaps can be followed in much the same way as skin free flaps by inserting needle temperature probes directly into the muscle belly. A healthy muscle free flap is red in color and typically has a serous ooze between the interstices of the overlying meshed skin graft. A flap with an arterial problem quickly becomes dry and dark in appearance. A muscle flap with a venous problem becomes dark and engorged with blood and exhibits bleeding from its surface and perimeter. A muscle free flap can be punctured with a needle to assess the quality of the bleeding if its circulatory status is unclear.

Fascial free flaps covered with skin grafts are also difficult to assess. They tend to transmit body core temperature readily because they are quite thin; therefore, needle temperature probes are generally unreliable. It is often possible in these cases either to observe the arterial pulsations in the flap directly or to monitor them with a conventional or implantable Doppler device.

Some free flaps are completely buried beneath the skin. Others, such as intraoral skin free flaps, are equally difficult to monitor postoperatively. Specialized transplants (e.g., jejunal transplants) are particularly vulnerable to short periods of anoxia and are not likely to be salvageable by the time a problem is recognized.

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4 SURGICAL MANAGEMENT OF MELANOMA AND OTHER SKIN CANCERS

Jennifer A. Wargo, MD, and Kenneth Tanabe, MD

The clinical assessment and management of skin lesions can be challenging as the natural history and prognosis of these lesions are widely variable. Surgeons play a pivotal role in the treatment of these lesions, although the initial evaluation of these lesions is often performed by other clinicians. The management of various benign skin lesions is beyond the scope of this review. Evaluation and management of malignant skin conditions are addressed in detail.

The prevalence of malignant skin lesions has increased significantly over the past several years. Approximately 1.2 million cases of nonmelanoma skin cancer are diagnosed per year.¹ More alarming, up to 80,000 cases of melanoma are diagnosed per year,² an incidence that has been rapidly increasing,³ with a lifetime risk of 1 in 75 for the development of melanoma.² The disturbing increase in the incidence of both nonmelanoma skin cancer and melanoma can largely be attributed to the social attitude toward sun exposure.⁴

Assessment of Skin Lesions

HISTORY AND PHYSICAL EXAMINATION

Obtaining a careful history is critical to the evaluation of skin lesions. Particular attention should be paid to a history of sun exposure. Blistering sunburn in childhood or adolescence is a significant risk factor and is present in virtually all Caucasians who develop melanoma.⁵ Patients should also be questioned about any personal or family history of skin cancer as those who report a history of melanoma in a first-degree relative have an 8- to 12-fold risk for the development of melanoma.⁶ In addition, patients should be questioned regarding immunosuppression and a history of transplantation as these put them at a higher risk of developing skin cancer.

A detailed history regarding when the lesion was first noted and changes in the size or the appearance of the lesion is important to elucidate. Generally speaking, lesions are nonsuspicious if they remain stable and uniform in their physical characteristics (e.g., size, shape, color, profile, and texture). An example of a nonsuspicious lesion is a simple nevus, which typically becomes apparent at 4 to 5 years of age, darkens with puberty, and fades in the seventh to eighth decades of life. However, pigmented lesions that demonstrate an irregular border or demonstrate a change in size, color, or texture

are considered to be suspicious. Careful attention should also be paid to constitutional symptoms as patients may present with advanced disease with metastases and systemic or focal complaints, such as headaches or visual changes in the case of melanoma metastatic to the brain.

Physical examination should include a complete skin examination and examination of mucous membranes. Specific attention should be paid to the presence of ulceration in a skin lesion as this significantly affects the prognosis depending on the histology of the lesion. Consideration should be paid to the potential draining nodal basins as lymph node metastases are known to occur in squamous cell cancer and melanoma.

Nonsuspicious lesions may be safely monitored conservatively with regular self-examination by patients and regular follow-up with their health care provider. Any change in a lesion constitutes a criterion for biopsy.

BIOPSY

Any suspicious lesion should be biopsied. This can be performed by excisional biopsy if the lesion is small or incisional biopsy if the lesion is large. Excisional biopsy should be performed incorporating a 1 to 4 mm margin of normal skin surrounding the lesion depending on the clinical characteristics. This may eliminate the need for subsequent reexcision for some types of lesions (e.g., dysplastic nevus). However, no attempt should be made to perform a definitive radical excision until a diagnosis is established by biopsy. Full-thickness excision into the subcutaneous fat should be performed, and margins on the specimen should be marked for orientation. This allows the pathologist to comment on the level of invasion and on margins for possible microscopic involvement with tumor cells. Electrocautery should generally not be used during excisional or incisional biopsy as margins can be distorted significantly by the artifact created by this technique. Shave biopsy for evaluation of pigmented lesions is discouraged as it runs the risk of a positive deep margin, which compromises the ability to determine the true depth of penetration of a melanoma or other malignant skin lesion.

The long axis of an elliptically shaped excisional biopsy should be oriented along the long axis of the extremity, which facilitates subsequent reexcision if necessary. If the lesion is

benign, no further treatment is warranted. If it proves to be malignant, further excision with an appropriate margin is usually necessary, and staging of the tumor becomes important. Adequacy of margins is discussed under each particular tumor type.

EXCISION

If a lesion proves to be malignant, complete excision should be performed with adequate margins as dictated by the type of tumor. An elliptical-shaped excision, with a length approximately 3.5 to 4 times the width, allows for a cosmetic closure without “dog ears.” If an area cannot be closed without significant tension, skin grafting may be necessary to achieve a technically acceptable result. Tissue transfer may also be required for very large lesions or for special areas, such as on the face.

Specific Types of Skin Cancer

BASAL CELL CARCINOMA

Incidence and Epidemiology

Basal cell carcinoma is the most common malignancy in Caucasians⁷ and the most prevalent type of skin cancer. The incidence is widely variable across the globe, with an incidence of 146 per 100,000 in the United States and 726 per 100,000 in Australia.⁸ The lifetime risk for a Caucasian in the United States for developing a basal cell carcinoma is approximately 30%.¹ Although the metastatic potential of these lesions is very low, the economic and social burden remains quite high.

In general, the vast majority of basal cell carcinomas occur on the head and neck. Basal cell carcinoma develops without a known precursor lesion, although it seems to be most closely related to exposure to ultraviolet radiation. Significant sun exposure during childhood and adolescence confers significant risk for the development of these lesions, although studies have failed to demonstrate a significant correlation between the development of basal cell carcinoma and cumulative exposure to ultraviolet light in adulthood.⁹ Several heritable conditions are associated with an increased risk of basal cell carcinoma, including albinism, xeroderma pigmentosum, and Gorlin syndrome. Patients with Gorlin syndrome develop multiple basal cell carcinomas, as well as anomalies of the spine and ribs, jaw cysts, pitting of the palms and soles, and calcification of the falx cerebri. Inheritance is autosomal dominant.¹⁰

Histologic Subtypes of Basal Cell Carcinoma

Several subtypes of basal cell carcinoma exist. Typical patterns seen in more mature lesions include nodular or cystic, superficial, morpheaform, and pigmented. Nodular or cystic basal cell carcinomas typically present as solitary lesions, often on the face, and are usually shiny and red, with central telangiectasias [see Figure 1a]. The classic basal cell carcinoma is the nodular type, which is also known as a “rodent ulcer.” These lesions are characterized by an indurated edge and an ulcerated center. Superficial basal cell carcinomas are typically found on the trunk and appear as an erythematous patch that is often mistaken for eczema or psoriasis and are typically slow-growing.¹⁰ Perhaps the most pertinent of these lesions is the morpheaform basal cell carcinoma [see Figure 1b], which

represents the minority of these lesions but has clinical features that are particularly pertinent to the surgeon. These lesions are often larger than they appear clinically and have a

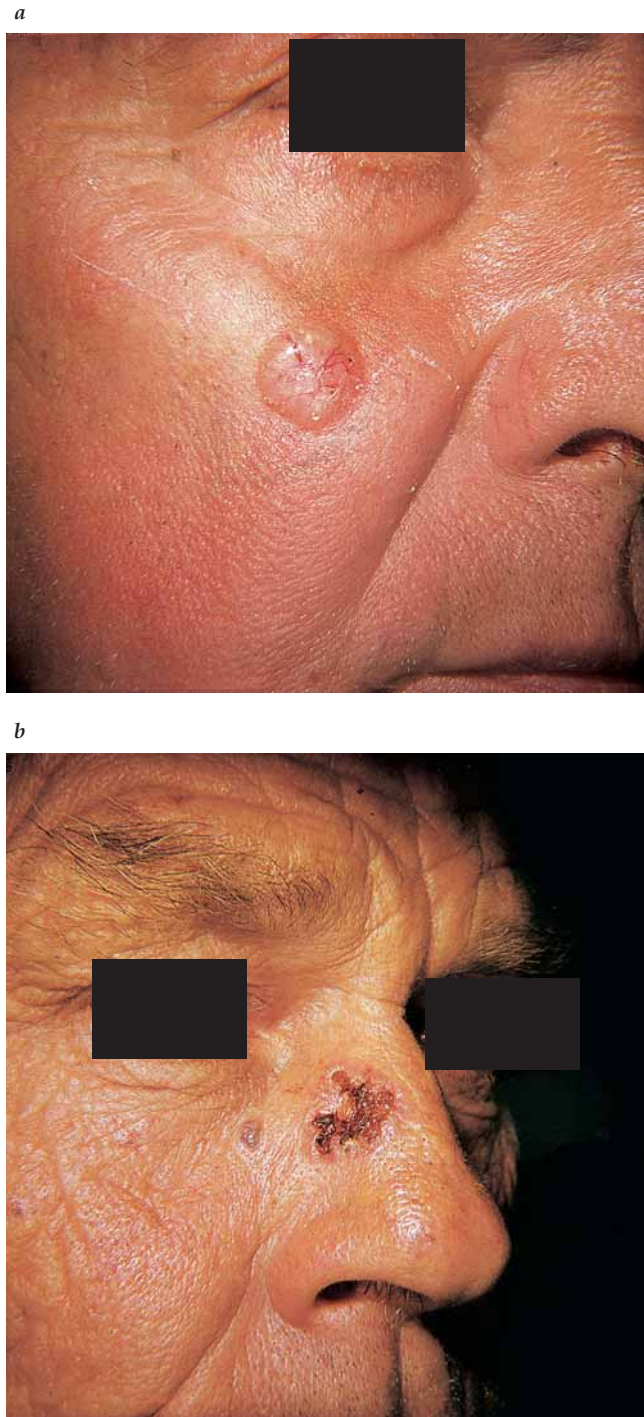


Figure 1 (a) Typical basal cell carcinoma. A pearly luster and telangiectasias are evident in this typical basal cell carcinoma on the cheek of a 43-year-old man. (b) Morpheaform basal cell carcinoma. This sclerosing (morpheaform) basal cell carcinoma on the nose of a 55-year-old man was found to be deeply invasive and exhibited multidirectional growth.

more aggressive natural history, which can make complete excision quite challenging.

Treatment

Surgical excision remains the mainstay of treatment for primary basal cell carcinomas. Typically, a surgical margin of 4 mm is recommended when possible.¹¹ Primary closure is generally possible for small defects, and rotation flaps or skin grafting may be necessary for larger defects. Although present only extraordinarily rarely, lymphatic spread identified in the primary tumor may be an indication for lymphatic mapping.¹²

Other surgical techniques include cryosurgery, curettage and cautery, and Mohs micrographic surgery. Cryosurgery and curettage should generally be avoided in large or morpheiform tumors or in those in high-risk areas (such as the central face) as surgical margins cannot be assessed. Mohs micrographic surgery is a technique involving excision of serial sections with intraoperative histologic examination of frozen sections to control surgical margins. It is particularly useful in morpheiform or recurrent basal cell carcinomas or those in high-risk sites, with 5-year cure rates approaching 95%.¹³

Nonsurgical modalities available for treatment of basal cell carcinoma include radiotherapy, photodynamic therapy, and topical agents such as 5-fluorouracil, imiquimod, or intralesional interferon alfa. Radiation therapy is generally reserved for elderly patients with extensive lesions that preclude excision, with 5-year cure rates approaching 90%.¹⁴ Photodynamic therapy involves the use of -aminolevulinic acid in a 20% emulsion that is applied to the lesion followed by exposure to light in the wavelength range of 620 to 640 nm. This treatment is based on the uptake of the porphyrin metabolite by the tumor with subsequent conversion to protoporphyrin IX, which is subject to destruction in the presence of light.¹⁰ Responses to treatment are somewhat lower, with an overall clearance rate of 87% and a lower clearance rate of 53% in nodular basal cell carcinoma.¹⁵ Fluorouracil 5% cream may also be used in the management of multiple basal cell carcinomas of the trunk and limbs. Imiquimod is an immunomodulatory agent that is used in a 5% cream for basal cell carcinomas, with a clearance rate of 70 to 100%.¹⁶ Intralesional interferon alfa has also been used experimentally, with a 67% cure rate in a series of 140 patients treated in this manner.¹⁷

Patients who have been treated for any skin cancer, including basal cell carcinoma, should perform frequent self-examination to look for suspicious lesions as they are at a greater risk for developing additional skin cancers. Counseling to reduce sun exposure should be undertaken to limit further damage from ultraviolet irradiation. High-risk individuals, such as those with Gorlin syndrome or those who are on immunosuppressive therapy after renal transplantation, are offered oral retinoid treatment in the hope of preventing the development of other nonmelanoma skin cancers.¹⁷

SQUAMOUS CELL CARCINOMA

Incidence and Epidemiology

Squamous cell carcinoma of the skin is the second most common form of nonmelanoma skin cancer, with the majority (50 to 60%) of these lesions occurring on the head and neck. Squamous cell carcinoma is the most common tumor

found in elderly patients, likely representing the result of cumulative doses of sun exposure over the course of their lifetime.

Precursor Lesions

Unlike basal cell carcinomas, squamous cell skin cancers often arise in precursor lesions, such as actinic keratosis.¹⁸ Actinic keratoses, sometimes referred to as solar keratoses, develop in chronically sun-damaged areas of the body. They are generally ill-defined and irregular and may range significantly in size, from only a millimeter to a few centimeters. They have a scaly appearance, are often multiple, and can range in color from dark brown to flesh colored. Biopsy may be necessary to rule out the presence of a squamous cell carcinoma. The rate of malignant transformation of actinic keratosis to squamous cell carcinoma is less than 0.1% per year,¹⁹ although lesions should be treated to decrease the chance of progression. Treatment options include cryotherapy, curettage, and topical agents. Surgical excision of actinic keratoses is rarely necessary but may be indicated if there is a high suspicion for a concurrent squamous cell carcinoma.

Intraepithelial squamous cell carcinoma, carcinoma in situ, is thought to be the next step in the progression from actinic keratosis to invasive squamous cell carcinoma. Another term for this lesion is Bowen disease, and lesions are typically located on sun-exposed areas of the head, neck, trunk, or legs. This lesion is referred to as “erythroplasia of Queyrat” when located on the genitalia. When it occurs on non-sun-exposed areas, it may be associated with internal malignancy.²⁰ These lesions typically appear as erythematous, slightly keratotic plaques and are usually larger than lesions of actinic keratosis. These lesions should be excised with a 5 mm to 1 cm margin.

Diagnosis

Squamous cell carcinomas occur on the head and neck in approximately 50% of cases. Caucasians have nearly a 10% lifetime risk of developing a squamous cell carcinoma. Interestingly, in one series, nearly half of fatal cases of squamous cell carcinoma occurred in patients in whom the lesion arose from the ear.²¹ The mortality rate associated with squamous cell carcinoma is estimated at 1:100,000.²²

As noted, squamous cell carcinomas are most often associated with sun exposure, although they may also be seen in a background of old scars, radiation-damaged skin [see Figure 2a], or chronic open wounds.²³ Chronic inflammation and irritation appear to be the common denominators. Marjolin ulcer is a term for squamous cell carcinoma arising in a burn scar or open wounds such as osteomyelitis draining sites.

These lesions typically appear as keratotic papules, which may ulcerate, and may be reddish-brown, pink, or flesh colored [see Figure 2b]. A cutaneous “horn” may be evident if there is extensive hyperkeratosis.²¹ Symptoms that may suggest malignant transformation of actinic keratosis include pain, erythema, ulceration, or induration. Histologically, these lesions are characterized by nests of atypical keratinocytes that have invaded into the dermis, which may be well or poorly differentiated.

Once a diagnosis of squamous cell carcinoma is suspected, careful attention should be paid to the draining nodal basins

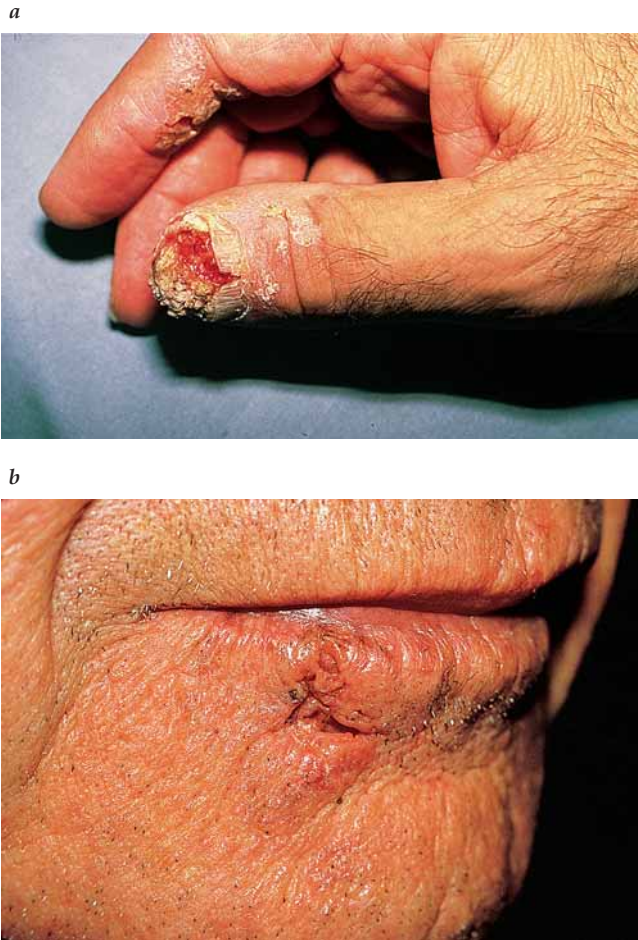


Figure 2 (a) Squamous cell carcinoma related to radiation exposure. This squamous cell carcinoma involving the thumb and index finger of a 72-year-old man, a retired dentist, was related to exposure to occupational hazards; he had subjected these digits to repeated radiation exposures by holding dental x-rays against his patients' teeth. (b) Squamous cell carcinoma related to sun exposure. This squamous cell carcinoma on the lip of a 70-year-old man was related to sun exposure; the patient was a nonsmoker.

as lymph node metastases are possible. Overall, the risk of metastasis is between 2 and 4% and is higher in larger, poorly differentiated lesions and lesions located on the scalp, nose, ear, lip, and extremities. The most common sites of metastasis are regional lymph nodes, the lungs, and the liver. Recurrence or metastases typically occur within 3 years after treatment of the index lesion.

Treatment

Surgical excision remains the mainstay of treatment for primary squamous cell carcinomas as well, although the recommended margin of excision is generally larger than that for basal cell carcinoma, ranging from 0.5 to 2 cm. Primary closure is often possible for smaller lesions, although larger lesions may require rotation flaps or skin grafting. Sentinel lymph node mapping should be considered for patients with large squamous cell carcinomas (e.g., > 2 cm) or those with histologic evidence of lymphovascular invasion. Fine-needle

aspiration of palpable nodal masses should be performed to diagnose metastatic squamous cell cancer, a condition that should be treated by aggressive lymphadenectomy. Adjuvant radiation therapy to the nodal basin is often indicated, based on the extent of nodal metastases.

Other therapies for squamous cell carcinoma are similar to those used to treat basal cell carcinoma and include cryosurgery, curettage and cautery, Mohs micrographic surgery, radiotherapy, photodynamic therapy, and topical agents such as 5-fluorouracil, imiquimod, or intralesional interferon alfa. Squamous cell carcinomas that develop from Marjolin ulcer are characterized by aggressive growth after surgical excision.

Patients who have been treated for squamous cell carcinoma should perform frequent self-examination to look for suspicious lesions as they are at risk for developing other non-melanoma skin cancers. Counselling to reduce sun exposure should be undertaken to limit further damage from ultraviolet irradiation. High-risk individuals, such as those who are on immunosuppressive therapy after renal transplantation, may be offered oral retinoid treatment in the hope of preventing the development of other nonmelanoma skin cancers.¹⁷

MELANOMA

Incidence and Epidemiology

Although it is less common than basal cell or squamous cell carcinoma, melanoma is clearly the most deadly of these cancers. Up to 80,000 cases of melanoma are diagnosed per year,² and it is the sixth leading cause of cancer death in the United States. The lifetime risk is estimated to be 1 in 75 individuals for the development of melanoma.² The incidence of melanoma is increasing significantly at a rate of 4.1% per year, faster than any other malignancy. The incidence is slightly higher in men than in women, and the median age at diagnosis is 57 years.²⁴ An average of 18.8 life-years are lost per melanoma death,²⁵ and it is estimated that one American will die from melanoma every hour.²⁶

Melanoma results from the malignant transformation of melanocytes, which are responsible for pigment production. Both genetic and environmental factors are implicated in the development of melanoma. Genetic susceptibility is important, and patients with melanoma often report a family history. Those who report a history of melanoma in a first-degree relative have an 8- to 12-fold risk for the development of melanoma.⁶ Somatic mutations in the *p16* tumor suppressor gene have been identified in both familial and sporadic cases of melanoma.²⁷ Environmental exposure to ultraviolet radiation also is implicated in the transformation of melanocytes. Risk for the development of melanoma is associated with intermittent, intense sun exposure rather than with a cumulative effect, although the exact mechanism behind the pathogenesis remains unknown.

In one study, six risk factors were identified by multivariate analysis to be important in the development of malignant melanoma and include the following: a family history of melanoma, a history of three or more blistering sunburns before age 20 years, the presence of blonde or red hair, the presence of actinic keratosis, a history of 3 or more years of an outdoor summer job as a teenager, and the presence of marked freckling on the upper part of the back.²⁸ Individuals with one or two of these factors have a 3.5-fold increased risk

Table 1 ABCD Guidelines for Pigmented Lesions	
Asymmetry	Most early lesions grow at an uneven rate, resulting in an asymmetrical pattern
Border irregularity	The uneven growth rate also results in an irregular border
Color variegation	Irregular growth also causes new shades of black and light and dark brown
Diameter	Lesions with ABC features and diameters of > 6 mm should be considered suspicious for melanoma

of developing melanoma, whereas if they have three or more, they have a 20-fold increase in risk.

Screening and Diagnosis

The frequency of screening of patients for melanoma should be based on the above risk factors. Routine screening of low-risk patients using a total body skin examination by health care providers is not supported. Self-screening, however, is clearly recommended, with excellent educational materials provided by the American Academy of Dermatology and the American Cancer Society. Nevertheless, physicians should take every opportunity to screen opportunistically as lesions found by physicians are significantly thinner than those detected by patients or their spouse.²⁹

Early recognition of melanoma is paramount to its effective treatment. The “ABCD” guidelines may be used in the evaluation of pigmented lesions [see Table 1].³⁰ These lesions often occur on sun-exposed areas of the upper trunk and extremities and are typically asymmetrical, with irregular borders and variegated pigmentation [see Figure 3a]. Occasionally, they lack pigmentation or are associated with significant ulceration. Any lesion suspicious for melanoma should be biopsied. Histologically, these lesions are characterized by atypical melanocytes with mitotic figures. Special staining may also be performed, and the most commonly used markers are HMB-45 and S100.

Histologic Subtypes

Melanoma may be further classified into histologic subtypes based on patterns of growth and anatomic location. The significance of these subtypes is generally less important than the pattern of growth (radial versus vertical growth) and depth of penetration.³¹ The most common subtypes include lentigo maligna melanoma, superficial spreading melanoma, acral lentiginous melanoma, and nodular melanoma. Superficial spreading accounts for over 70% of melanomas. These lesions are most common in white adults and typically occur on the back or legs. Nodular melanomas are the second most common, accounting for between 15 and 30% of all melanomas. These lesions often appear dome shaped and may occur anywhere on the body. They typically invade the dermis early in their natural history owing to an early vertical growth phase. Lentigo maligna melanoma accounts for approximately 5% of all melanomas and is thought to arise in a focus of lentigo maligna, or Hutchinson freckle. These lesions demonstrate a prolonged radial growth phase before developing an invasive component. Acral lentiginous melanomas occur on the hands or feet [see Figure 3b], often under the nail bed, where the



Figure 3 (a) Typical melanoma. A halo effect caused by loss of pigmentation is visible along the left margin of this melanoma on the upper back of a 33-year-old white woman; irregularities in shape, contour, and pigmentation are also evident. (b) Acral lentiginous melanoma. This melanoma, on the sole of the foot of a 47-year-old black woman, shows irregularities in shape, contour, and pigmentation.

dermis is thinner (e.g., subungual melanoma). A more rare histologic variant is desmoplastic melanoma, which typically occurs in areas of sun damage and tends more often to recur locally.

Prognostic Factors in Melanoma

An important variable in the prognosis of melanoma is the thickness of the primary tumor as assessed using the Clark or the Breslow system. The Clark system remains of primarily historical interest. In this staging system, levels I to V are defined by the presence of malignant melanocytes in each of the following layers: epidermis, papillary dermis, reticular dermis, and subcutaneous fat [see Figure 4 and Table 2].³² But the Breslow microstaging system has been demonstrated to have more prognostic information than the Clark system. Tumor thickness in the Breslow system is measured in millimeters from the epidermal surface to the deepest point of the tumor with a calibrated ocular micrometer [see Table 3].³³

Extensive research has been done over the past several years regarding prognostic factors in both early and late stage melanoma. Overall, clinical factors shown to have significant prognostic value include patient age, sex, location of the melanoma, number of involved lymph nodes, presence of distant metastasis, and serum lactate dehydrogenase (LDH) level.³⁴ Prognosis is generally better for patients < 65 years of age, women, tumor location on the extremities, absence of lymph node involvement, absence of distant metastasis, and a normal serum LDH level. The American Joint Committee of Cancer (AJCC) approved the latest version of the melanoma staging system in 2002, with changes that were validated via analysis of over 17,000 patients with melanoma [see Table 4].³⁴ Five-year survival rates correlate with stage [see Table 5].³⁴ A new version of staging will be released in 2009, incorporating additional factors such as mitotic rate³⁵ that influence prognosis and survival.

Table 2 Clark's Levels for Staging of Malignant Melanoma

Level		5 yr Survival Rate (%)
I	Malignant melanocytes are confined to the epidermis	99
II	Malignant melanocytes infiltrate the papillary dermis by single cells or small nests of cells	95
III	Malignant melanocytes fill and expand the papillary dermis with extension of the tumor to the papillary-reticular dermal interface (usually signifies vertical growth phase)	82
IV	Malignant melanocytes infiltrate the reticular dermis in a significant fashion	71
V	Malignant melanocytes infiltrate the subcutaneous fat	49

Table 3 Breslow's Microstages for Malignant Melanoma

Stage	5 yr Survival (%)
1: < 0.76 mm	> 98
2: 0.76–1.49 mm	87–94
3: 1.50–3.99 mm	66–83
4: > 4.0 mm	< 50

Stage I and II melanoma Those with localized melanoma represent the vast majority of patients, and several prognostic factors have been identified for risk stratification and prognosis in this heterogeneous group. The most important prognostic factors in early-stage melanoma are tumor thickness (T1 to T4) and the presence or absence of ulceration. These have significant

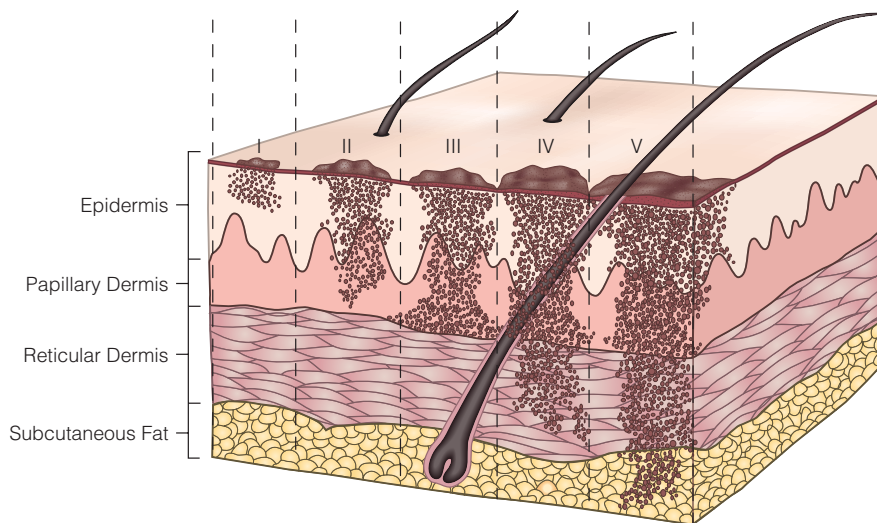


Figure 4 Clark categorized skin tumors according to their level of invasion. Tumors of level I involve the epidermis and are essentially carcinoma in situ. In level II, the tumor has extended into the papillary dermis. Tumor cells at level III are spread along the papillary-reticular dermal interface. Invasion into the reticular dermis occurs at level IV. Level V tumors extend into the subcutaneous tissue. In general, survival decreases as the depth of invasion increases.

Table 4 AJCC Staging of Malignant Melanoma

T classification		
T1	≤ 1.0 mm	A: without ulceration and Clark's level II or III B: with ulceration or Clark's level IV or V
T2	1.01–2.0 mm	A: without ulceration B: with ulceration
T3	2.01–4.0 mm	A: without ulceration B: with ulceration
T4	> 4.0 mm	A: without ulceration B: with ulceration
N classification		
N1	1 lymph node	A: micrometastases B: macrometastases
N2	2–3 lymph nodes	A: micrometastases B: macrometastases C: in-transit metastases, satellite(s) without metastatic nodes
N3	4 or more metastatic lymph nodes, matted lymph nodes, or combinations of in-transit metastases, satellites, or ulcerated melanoma and metastatic lymph node(s)	
M classification		
M1	Distant skin, subcutaneous or lymph node metastases	Normal LDH
M2	Lung metastases	Normal LDH
M3	All other visceral or any distant metastases	Normal LDH Elevated LDH with any M

AJCC = American Joint Committee on Cancer; LDH = lactate dehydrogenase.

Stage 0: Tis, N0, M0; stage IA: T1a, N0, M0; stage IB: T1b, N0, M0; T2a, N0, M0; stage IIA: T2b, N0, M0; T3a, N0, M0; stage IIB: T3b, N0, M0; T4a, N0, M0; stage IIC: T4b, N0, M0; stage IIIA: any T1–4a, N1b, M0; stage IIIB: any T1–4a, N2b, M0; stage IIIC: any T, N2c, M0; any T, N3, M0; stage IV: any T, any N, M1–3.

implications in prognosis as 5-year survival in stage I to II melanomas falls significantly with increasing thickness and dropped from 80% to 55% in the presence of ulceration in a 2006 analysis.³¹ Mitotic rate in the primary tumor has been identified as an important prognostic factor, possibly even surpassing ulceration in importance in early-stage melanoma.^{34,36} The mitotic rate will be incorporated into the new version of the AJCC staging system, which will be released in 2009.

Thin (< 1 mm thick) melanomas in particular have also been studied with great interest because they represent the largest group of patients. A recent publication from the University of Pennsylvania describes a prognostic model using four factors based on multivariate analysis: mitotic rate (0 versus ≥ 1), growth phase (radial or vertical), gender, and tumor-infiltrating lymphocytes.³⁷ Investigators developed an algorithm for risk stratification based on these factors, with minimal- and low-risk patients having a predicted risk for metastasis of less than 4%, whereas those who were considered moderate or high risk had a predicted risk for metastasis of 12 and 30%, respectively.³⁷

Intermediate-thickness (1.0 to 4 mm) melanomas clearly have a worse prognosis, with 5-year survival rates of 89% for nonulcerated T2 lesions (1 to 2 mm) and 77.4% for ulcerated lesions. Patients with ulcerated T3 lesions (2 to 4 mm) have

a predicted 5-year survival of 78.7% for nonulcerated lesions and 63% for ulcerated lesions. Thick (> 4 mm) lesions in node-negative patients have an associated 5-year survival of 67.4%, which drops to 45.1% if the lesion is ulcerated.³⁴

Stage III melanoma Stage III melanoma is characterized by the presence of nodal metastases (micro- or macro-metastases) with or without in-transit or satellite lesions. The presence of lymph node metastases confers a significantly worse prognosis, with less than half of node-positive patients surviving 5 years.³⁴ The number of involved nodes is also of prognostic significance and is reflected in the recent revisions to the AJCC staging system.

In patients with stage III disease, four prognostic factors for survival were identified: number of metastatic lymph nodes, microscopic versus macroscopic tumor deposits in lymph nodes, the presence of in-transit or satellite metastases, and the presence of ulceration in the primary lesion.³⁴ In earlier staging systems, the size of the involved lymph node was thought to be of significance, although this has been disproven.³⁸ However, macroscopic disease (that which is identified clinically and confirmed histologically) does have a significant impact, with a much poorer survival in those with macroscopic as opposed to microscopic disease.³⁴

Table 5 5-Year Survival Rates Based on AJCC Stage

Stage	T, N, M	5 yr Survival (%)
IA	T1a, N0, M0	95.3
IB	T1b, N0, M0	90.9
	T2a, N0, M0	89.0
IIA	T2b, N0, M0	77.4
	T3a, N0, M0	78.7
IIB	T3b, N0, M0	63.0
	T4a, N0, M0	67.4
IIC	T4b, N0, M0	45.1
IIIA	Any T, N1a, M0 (no ulceration, 1 node, micrometastases)	69.5
	N2a, M0 (no ulceration, 2–3 nodes, micrometastases)	63.3
IIIB	N1a, M0 (+ ulceration, 1 node, micrometastases)	52.8
	N2a, M0 (+ ulceration, 2–3 nodes, micrometastases)	49.6
	N1b, M0 (no ulceration, 1 node, macrometastases)	59.0
	N2b, M0 (no ulceration, 2–3 nodes, macrometastases)	46.3
IIIC	N1b, M0 (+ ulceration, 1 node, macrometastases)	29.0
	N2b, M0 (+ ulceration, 2–3 nodes, macrometastases)	24.0
	N3, M0 (+ ulceration, > 4 nodes, micro- or macrometastases)	26.7
IV	Any T, any N, M1a (skin or subcutaneous metastases)	18.8
	Any T, any N, M1b (lung metastases)	6.7
	Any T, any N, M1c (other visceral metastases + LDH)	9.5

AJCC = American Joint Committee on Cancer; LDH = lactate dehydrogenase.

In-transit and satellite metastases represent dissemination of tumor via lymphatic channels, and the 5-year survival rate in patients with these findings is similar to that of those with lymph node metastases. If these findings are present in association with lymph node metastases (N3), the survival rate drops significantly.³⁴

Stage IV melanoma For stage IV melanoma, the site of distant metastasis and serum LDH seem to have the most value in prognosis, with a far more favorable prognosis in those with cutaneous metastases and a normal serum LDH. On analysis, there is a significant difference in 1-year survival rates between those with cutaneous, subcutaneous, or distant nodal metastases (M1) versus those with lung metastases (M2) versus those with any other visceral metastases, or any metastasis with an elevated serum LDH (M3). Predicted 1-year survival rates for patients in these groups are 59%, 57%, and 41%, respectively.³⁴

Initial Evaluation

Recommendations for initial evaluation of patients with melanoma are as follows: all patients should receive a complete

history and physical examination, as well as a comprehensive dermatologic examination. For patients with thin melanomas (< 1.0 mm) or intermediate-thickness melanomas, no routine laboratory or radiologic tests are recommended. Chest radiography is considered optional in patients with stage IB or stage II melanoma as this is unlikely to pick up occult metastatic disease. For patients with stage III disease who present with clinically positive nodes, computed tomography (CT) of the chest, abdomen, and pelvis may be performed to confirm the presence of regional disease and to exclude the possibility of metastatic disease. In a patient with stage III disease defined by a microscopically positive sentinel node, the yield of CT scans is much lower, although current guidelines leave it to the discretion of the treating physician. If inguinal lymphadenopathy is apparent, pelvic CT should be obtained to assess iliac lymph nodes.³⁹ For patients with stage IV disease, a chest radiograph and serum LDH should be obtained. Brain magnetic resonance imaging and CT of the chest, abdomen, and pelvis should be performed before embarking on any surgery. Other imaging will be guided by protocol if the patient is enrolled in a clinical trial.³⁹

Surgical Treatment of Stage I and II Melanoma

Margins of excision Surgical excision remains the mainstay of treatment for melanoma. The width of the recommended surgical margins depends on the thickness of the lesion and has been well defined by a series of prospective randomized clinical trials. The most recent recommendations suggest that a 0.5 cm margin is adequate for in situ melanoma, whereas margins of 1 cm are suggested for melanomas less than 1.0 mm in thickness. Two-centimeter margins should be obtained for lesions measuring 1 to 2 mm in depth. Although a reduction in surgical margin width to 1 cm for melanomas 1 to 2 mm in thickness may slightly increase the risk for local recurrence, it would not reduce overall survival statistics. Two-centimeter margins should be obtained for melanomas greater than 2 mm in thickness.⁴⁰

Sentinel lymph node biopsy Another important issue in the surgical management of melanoma is the use of sentinel lymph node biopsy (SLNB), which has essentially replaced elective lymph node dissection. Sentinel lymph node status is the single most important predictor of survival in patients with melanoma⁴¹ and is considered a standard approach in this country. SLNB is recommended for intermediate-thickness (1 to 4 mm) and thick (> 4 mm) melanomas. It is generally not recommended for thin melanomas (< 1 mm) unless the lesion is of high risk (presence of ulceration, extensive regression, high mitotic rate, Clark level IV, or positive deep margin) or depending on the patient's age (SLNB may be performed in young patients). A positive result is defined as the presence of identifiable melanoma cells on either routine hematoxylin-eosin stains and/or by immunohistochemical staining with S100 or HMB-45. Preoperative lymphatic mapping via lymphoscintigraphy is very helpful in these patients as many lesions have variable drainage basins that cannot be predicted clinically and may even drain to contralateral nodes.⁴² The greatest accuracy is achieved when both radioactive colloid and blue dye are used during SLNB.⁴³ SLNB should not be performed in the setting of clinically positive nodes or in patients who would otherwise not be considered for lymphadenectomy.

The impact of SLNB for melanoma has been impressive. The results are critical to accurate staging and are also important in deciding whether to perform completion lymphadenectomy or offer adjuvant therapy. Several studies have demonstrated increased survival and disease-free interval between sentinel lymph node–negative and –positive patients.^{44,45} One of these studies demonstrated a 3-year disease-free survival of 88.5% versus 55.8% in sentinel lymph node–negative versus –positive patients, with a 58.6% increase in disease-free survival if the SLNB was negative.⁴⁴

Surgical Treatment of Stage III Melanoma

Therapeutic lymph node dissection Therapeutic lymph node dissection is currently recommended for management of the regional lymph node drainage basin in the presence of a positive sentinel node and in clinical stage III disease. Some challenge this recommendation as four randomized trials of elective lymph node dissection failed to demonstrate an overall survival benefit.^{46–49} Yet the majority of patients in these studies did not have nodal disease; thus, the trials were not sufficiently powered to detect a small survival benefit.⁵⁰ Other trials have supported this practice, including the World Health Organization 14 trial, which on subgroup analysis demonstrated a significantly improved 5-year survival rate in patients with occult nodal metastases detected at elective lymph node dissection compared with patients who had delayed lymphadenectomy at the time when they developed palpable nodal metastases (48% versus 27%, respectively; $p = .04$).⁴⁸

Nonetheless, the impact of completion lymphadenectomy on overall survival is still a matter of debate. This has been further addressed since the advent of the use of SLNB in melanoma. The results of the first Multicenter Selective Lymphadenectomy Trial (MSLT-I) suggest that SLNB with immediate completion lymphadenectomy if the sentinel node is positive improves disease-free survival but not overall survival for these patients.⁵¹ In this trial, 1,973 patients were randomized in a 4:6 ratio to wide excision followed by nodal observation (WEO) or to wide excision plus lymphatic mapping and sentinel lymph node biopsy (LM/SLNB) with immediate completion lymphadenectomy if the sentinel node was positive for metastasis. The groups were comparable in regard to age, gender distribution, and location, thickness, and ulceration status of the lesion. Sentinel nodes were analyzed using hematoxylin-eosin stain and immunohistochemistry. Wound complications at the primary site were comparable, although surgical morbidity was significantly greater when the SLNB was followed by completion lymphadenectomy.⁵¹ A follow-up analysis presented at the American Society of Clinical Oncology in 2005 demonstrated a significant difference in 5-year disease-free survival (73% in WEO versus 78% in LM/SLNB); however, there was no difference in 5-year overall survival (86% in WEO versus 87% in LM/SLNB).⁵² Although there were suggestions based on the data that a survival benefit might be gained by LM/SLNB followed by completion lymph node dissection in the event of a positive node, their statistical analysis has been criticized.⁵³ The role of lymphadenectomy will be addressed further in the second Multicenter Selective Lymphadenectomy Trial (MSLT-II), which is designed to evaluate the therapeutic value of completion lymph node dissection versus SLNB alone in patients who have metastasis in the sentinel node.⁵²

An important factor in considering a therapeutic lymph node dissection following a positive SLNB is the likelihood of finding

metastases in the remaining nonsentinel nodes. This was addressed in a recent series of 658 patients, in which 90 (14%) were found to have a positive sentinel node, with 18 (20%) of that group having evidence of metastases in additional nonsentinel nodes.⁵⁴ The number of positive nodes clearly has an impact on prognosis and is included in the AJCC staging system.³⁴ This adds credence to the argument for therapeutic lymph node dissection following a positive SLNB.

Another aspect of this topic that is debated is the extent of lymph node dissection required. Investigators at the John Wayne Cancer Institute recently reviewed their experience with therapeutic lymph node dissection prior to the use of sentinel node biopsy, and concluded that the extent of lymph node dissection is more important with higher tumor burden and less important with a lower tumor burden.⁵⁵ Those with micrometastatic disease in a sentinel node and those with bulky nodal disease are clearly different, and the potential benefits of therapeutic lymph node dissection must be carefully weighed against the morbidity of the procedure.⁵⁶ The role of lymphadenectomy and adjuvant alpha 2B and its impact on survival was addressed in the Sunbelt Melanoma trial,⁵⁷ the results of which were updated at the annual meeting of the American Society of Clinical Oncology in May 2008 (published in abstract form only). In essence, there was no significant difference in disease-free or overall survival among patients randomized to completion lymphadenectomy versus completion lymphadenectomy with adjuvant high dose interferon. There is, however, clearly a role for therapeutic lymph node dissection in patients with bulky nodal disease, and it can be performed with minimal morbidity and good palliation.⁵⁸

Isolated limb perfusion Patients with in-transit metastases have an unfavorable prognosis. This reflects a disseminated stage of disease, with a 5-year survival rate of 25 to 30%. Surgical excision is the mainstay of therapy when the size and the number of lesions permit, although there is no formal recommendation regarding the extent of surgical margin. Amputation is rarely necessary.

Another therapeutic option for patients with extensive in-transit metastases in an extremity involves the use of isolated limb perfusion (ILP). This technique was introduced in 1958 and holds the advantage of achieving high regional concentrations of therapeutic agents while minimizing systemic side effects.⁵⁹ The arterial supply and venous drainage are isolated, and an oxygenated extracorporeal circuit is used to circulate chemotherapeutic agents for 1 to 1.5 hours. A tourniquet is also often used. Melphalan is typically used as a chemotherapeutic agent, and the limb temperature is typically elevated to 39 to 40°C.⁶⁰ In patients who have clinically positive nodes, therapeutic lymph node dissection is performed at the same setting just prior to limb perfusion. The response to isolated limb perfusion can be dramatic. Complete response with melphalan alone is 54%,⁶¹ which is increased to 91% with the addition of tumor necrosis factor.⁶² However, these responses are often short-lived, with recurrence rates of 50% within 1 to 1.5 years after limb perfusion.⁶³ Overall 5-year survival after ILP was 32% in a recent series.⁶³ Recurrences following ILP may be treated with excision, although repeat ILP has also been used with success in patients with extensive disease.⁶⁴

ILP can be very effective for in-transit metastases; however, it is time and resource consuming and can be quite toxic. One

alternative to this approach involves the use of normothermic isolated limb infusion (ILI),^{65,66} a technique in which the artery and vein are isolated percutaneously and the limb is isolated using a tourniquet. Melphalan is typically used as a chemotherapeutic agent. One major difference between the two (ILP versus ILI) is that in ILI, blood is circulated at a much lower rate in the isolated extremity and only for 30 minutes. In addition, a pump oxygenator is not used in ILI; thus, the isolated extremity becomes hypoxic, leading to acidosis. The largest series of ILI reports the use of this approach with melphalan and dactinomycin chemotherapy in 135 patients.⁶⁵ In this series, there was an overall response rate of 85%, with 41% achieving a complete response and 42% achieving a partial response.⁶⁵ No randomized controlled trials compare ILP with ILI, although the results from a single-institution prospective database were recently published, yielding a higher overall and complete response rate for ILP versus ILI (88% versus 44% and 57% versus 30%, respectively).⁶⁶

Adjuvant Therapy

Radiotherapy Radiotherapy has been used with some success in high-risk lesions following therapeutic lymph node dissection, demonstrating a decrease in local recurrence⁶⁷ and a modest survival benefit⁶⁸ compared with historical controls. This modality is typically employed in stage III disease in the setting of poor prognostic pathologic factors, including positive surgical margins, multiple positive nodes, extracapsular spread, or vascular or perineural involvement.⁶⁹

Chemotherapy Adjuvant therapy with interferon alfa 2b is associated with improvement in disease-free survival but is also associated with significant toxicity. In addition, it is unclear whether adjuvant therapy with interferon alfa 2b enhances overall survival. Although initial studies (Eastern Cooperative Oncology Group trial 1684) demonstrated prolongation of relapse-free interval and overall survival with 1 year of high-dose interferon alfa 2b,⁷⁰ a subsequent meta-analysis showed no overall survival benefit.⁷¹ Furthermore, nearly all patients experience adverse effects with interferon therapy, including fatigue, neutropenia, headache, fever, and chills.⁶⁸ Interferon alfa 2b is currently approved by the Food and Drug Administration for adjuvant treatment of stage IIB and stage III melanoma.

Melanoma vaccines Several experimental melanoma vaccines are currently being investigated for use in advanced-stage melanoma and use a variety of strategies to present melanoma antigens to host immune cells in an immunostimulatory context.⁷²⁻⁷⁴ Despite initial optimism, a recent review of the experience at the National Cancer Institute demonstrated a response rate of only 2.6% for cancer vaccines,⁷⁵ which was comparable to the results obtained by others. The authors concluded that this approach may still be viable but will require profound changes to improve the efficacy of these vaccines.

Treatment of Stage IV Melanoma

Metastasectomy A large body of literature supports resection of metastases from melanoma, with the following factors cited as predictive of improved survival: stage of the initial disease, disease-free interval after treatment of the primary melanoma, initial site of metastasis (e.g., visceral versus subcutaneous), extent of metastatic disease (single versus multiple sites), and ability to achieve complete resection.⁵⁸ This approach can be successful as a recent series reported a 5-year survival

rate of 29% following pulmonary metastasectomy and a median survival of 40 months compared with 13 months in those who were not eligible for resection.⁷⁶ Similar results have been demonstrated in metastasectomy for metastatic lesions to the gastrointestinal tract, with a series reporting a median survival of 47.5 months in patients in whom a complete resection was achieved.⁷⁷ This was in sharp contrast to the median survival of 4 weeks in those patients in whom complete resection could not be achieved.⁷⁷ The aforementioned factors are of critical importance in deciding whether to perform metastasectomy, and patient selection is key. To enhance patient selection for curative procedures, some recommend treating patients with a single-site asymptomatic metastasis with 2 to 3 months of chemotherapy prior to resection to assess for disease stabilization or the development of additional metastases.⁵⁸ If there is a response to treatment or disease stabilization with no evidence of further metastases, these authors proceed with resection.

Preoperative imaging is a critical part of the evaluation of a potential metastasectomy patient and may include the use of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) to more accurately detect occult metastatic disease. A recent comparison of FDG-PET with conventional imaging in patients with stage IV melanoma demonstrated a sensitivity and a specificity of 76% and 87%, respectively, for conventional imaging compared with 79% and 87%, respectively, for FDG-PET.⁷⁸ Sensitivity and specificity for combined conventional imaging with FDG-PET were 88% and 91%, respectively.⁷⁸ As with any other modality, it is important to understand the limits of the technology to apply its use properly.

Another important indication for metastasectomy is palliation as the vast majority of patients with stage IV melanoma will not be candidates for metastasectomy for curative intent. The goal of a palliative procedure is to control identifiable symptoms caused by an advanced malignancy while minimizing morbidity.⁵⁸ Classic examples of palliative metastasectomy include resection of bleeding small bowel metastases, resection of ulcerated subcutaneous metastases, and resection of symptomatic brain metastases. A thorough discussion should be held between the surgeon, the patient, and the family to address the goals and expected outcomes and the potential morbidity of the procedure.

Chemotherapy Response rates following adjuvant chemotherapy in the treatment of malignant melanoma have been somewhat disappointing. Dacarbazine (DTIC) is the agent with the longest track record in the treatment of melanoma and offers marginal therapeutic benefit with moderate side effects.⁷⁹ Various combination regimens have been used and include BOLD (bleomycin, Oncovin [vincristine], lomustine [CCNU], and DTIC), CVT (cisplatin, vincristine, and DTIC), and CBDT (cisplatin, BCNU [carmustine], DTIC, and tamoxifen) with response rates ranging from 9 to 55%.⁷⁹ However, the responses are not durable. More recently, temozolamide (an oral alkylating agent) was studied in stage IV melanoma patients, with a modest prolongation of survival compared with DTIC and an acceptable side-effect profile.⁸⁰

Melanoma vaccines Several experimental melanoma vaccines have been used in patients with stage IV melanoma in the context of clinical trials,⁷²⁻⁷⁴ although the results have not been very encouraging. An extensive review of the use of vaccines in advanced cancer suggests that significant improvements must be made to increase vaccine efficacy.⁷⁵

Immunotherapy Perhaps the most promising area of investigation for the treatment of advanced melanoma is immunotherapy. Immunotherapy has a wide range of definitions but is generally considered a form of treatment based on the concept of modulating the immune system to achieve a therapeutic goal.⁸¹ Multiple modalities can be considered immunotherapy, including the use of monoclonal antibodies and interferon-based therapy, although the focus of this review highlights the use of interleukin-2 (IL-2) and adoptive cell transfer.

High-dose IL-2 has been used to treat melanoma, with response rates in early series ranging from 15 to 20%, with complete regression in about half of these patients.⁸² Moreover, in those who achieve a complete response, the result is often durable.⁸³ However, this regimen is noted to be quite toxic.

Another modality under active investigation involves the use of adoptive immunotherapy. Adoptive immunotherapy involves the use of activated cytotoxic T lymphocytes (CTLs) that are generated against particular tumor types. This approach can help break immunologic tolerance by allowing the selection of tumor-specific T lymphocytes that are capable of generating a strong immunologic response. These can be generated using specific tumor-associated antigens or by culture with tumor cells. The addition of nonmyeloablative lymphodepleting chemotherapy prior to autologous transfer of tumor-specific CTLs in conjunction with IL-2 administration results in rapid clonal expansion of tumor-specific T lymphocytes *in vivo*, which is associated with a significant clinical response.⁸⁴ More recently, transfer of a T cell receptor gene from a patient with a significant antitumor response conferred impressive T cell responses.⁸⁵

Despite some advances in therapy, the overall survival for patients with stage IV melanoma has not improved over the past 20 years. Overall 5-year survival is dismal at less than 5%, with a median survival of only 7.5 months. Hope likely lies in treatment of micrometastatic disease via targeted chemotherapy and immunotherapy.

Conclusions

The clinical assessment and management of skin lesions are challenging, and surgeons play a pivotal role in treatment of these lesions. Furthermore, the prevalence of malignant lesions of the skin has increased dramatically over the past several years, with nearly 1.2 million cases of nonmelanoma skin cancer diagnosed per year¹ and close to 80,000 cases of melanoma diagnosed per year.² Thus, it is critical for surgeons to have an astute awareness of these lesions, their workup, and their management.

Specific Procedures

SUPERFICIAL AND DEEP GROIN DISSECTIONS

The inguinal nodes drain the anterior and inferior abdominal wall, perineum, genitalia, hips, buttocks, and thighs. A superficial groin dissection removes the inguinal nodes, whereas a deep groin dissection additionally incorporates the iliac and obturator nodes. Palpable nodes can be marked on the patient before operation.

Superficial Groin Dissection

The patient is placed in a supine position on the operating table, with the hip slightly abducted and supported by a

pillow and with the hip and knee slightly flexed. A Foley catheter is inserted, and the patient is prepared and draped.

The femoral artery, anterior superior iliac spine, pubic tubercle, and femoral triangle apex are marked, and a diagonally oriented skin incision is planned. The incision courses from medial to the anterosuperior iliac spine down to the apex of the femoral triangle. An “S”-shaped incision is used to avoid crossing the thigh flexion crease at a right angle. This incision interferes least with the musculocutaneous and cutaneous vascular territories of the skin, minimizes ischemia to the skin flaps, and avoids a flexion contracture. Flaps are raised to identify the medial border of the sartorius muscle, the lateral border of the adductor longus muscle, and the external oblique fascia on the lower abdominal wall. Fat and nodal tissue are dissected off the external oblique aponeurosis, spermatic cord, and inguinal ligament and are reflected inferiorly [see Figure 5]. The fat and lymph nodes are then dissected from the femoral triangle starting medially at the lateral edge of the adductor longus and proceeding laterally [see Figure 6 and Figure 7]. The femoral vessels are left undisturbed. At the fossa ovalis, the saphenous vein is ligated and divided [see Figure 8]. It is also ligated and divided as it exits the femoral triangle distally. The specimen is then dissected free from the femoral nerve, usually sacrificing branches of the lateral femoral cutaneous nerve, thereby resulting in numbness of the anterolateral thigh. The Cloquet lymph nodes are located medial to the femoral vein

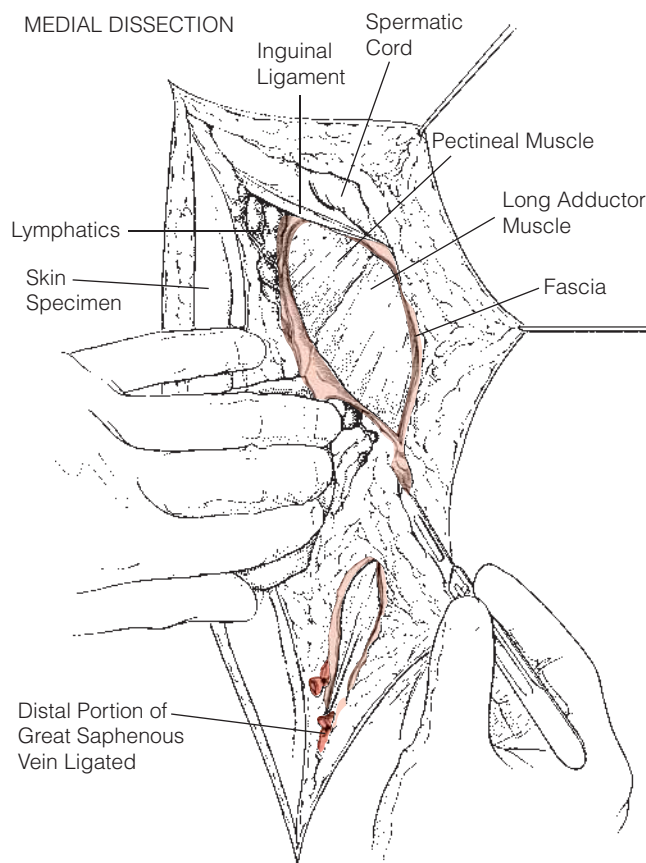


Figure 5 In a superficial groin dissection, the incision is deepened to include the deep muscular fascia.

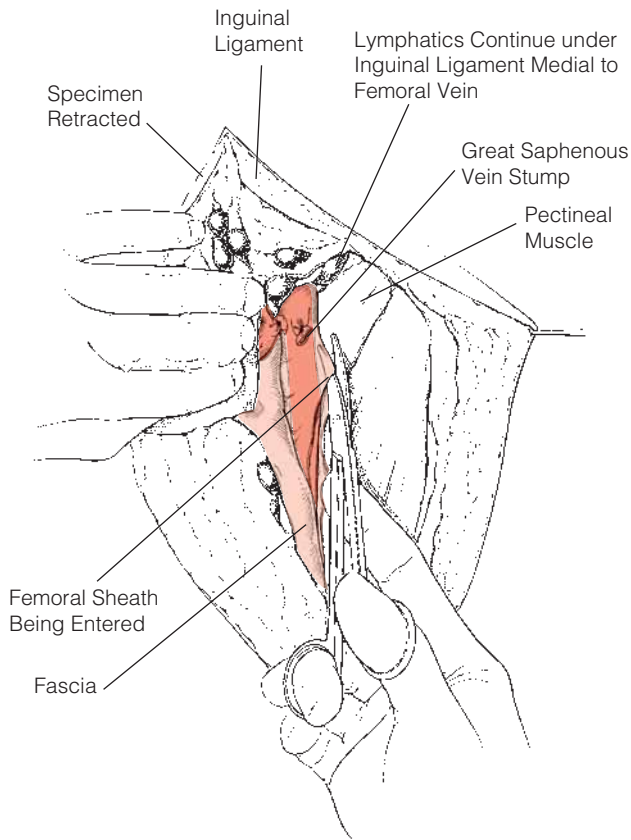


Figure 6 As the superficial groin dissection proceeds, the investing fascia overlying the femoral nerve and vessels is removed.

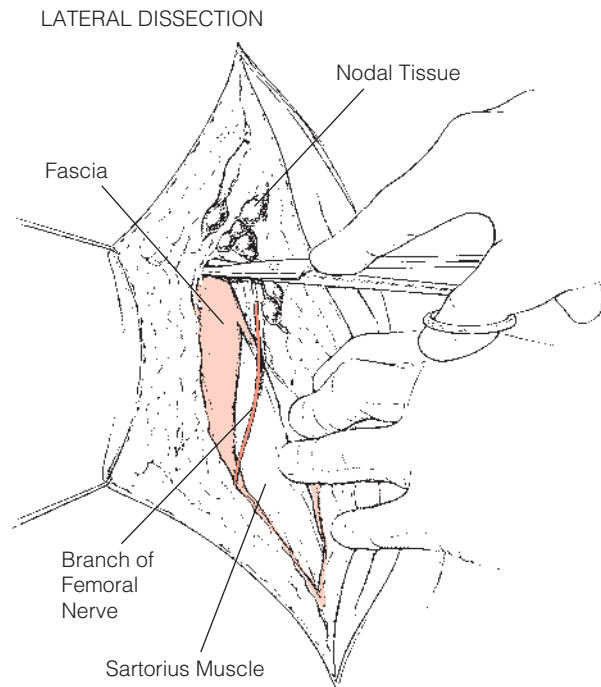


Figure 7 The superficial groin dissection is continued at the same level on the lateral side.

under the inguinal ligament and resected. Following removal of the specimen, these nodes are dissected out and submitted as a separate specimen. If the Cloquet nodes contain melanoma, the risk for iliac nodes with melanoma is high, and a deep groin dissection should be performed.

Deep Groin Dissection

The iliac region is easily approached through a separate incision in the external oblique fascia, parallel to and above the inguinal ligament. The retroperitoneal space is further exposed by separating the internal oblique abdominal muscle fibers and incising the transversus abdominis and fascia transversalis. The deep circumflex iliac vessels are ligated, and blunt finger dissection separates the peritoneum from the retroperitoneal fat and nodes. Alternatively, the inguinal ligament may be divided to allow access to the retroperitoneal space, although reconstruction of the inguinal ligament can be challenging.

Retractors are inserted to widen the retroperitoneal space, and the peritoneum and the abdominal viscera are retracted superomedially. The chain of lymph nodes, areolar tissue, and adventitial tissues along the external iliac vessels is dissected; the dissection proceeds proximally to the origins of the internal iliac vessels (avoiding the ureter) and incorporates the nodes overlying the obturator foramen by removing the internal obturator fascia but carefully avoiding injury to the obturator nerve. The lymph node-bearing specimen is then removed as a unit, oriented, and labeled appropriately with sutures. The space medial to the femoral vein under the inguinal ligament is obliterated to prevent a hernia. The sartorius muscle is detached from the anterior superior iliac spine and the midportion of the inguinal ligament to cover the femoral vessels. The skin and the subcutaneous tissues are then closed in layers over a soft suction drain.

Specific details regarding SLNB are described in a separate ACS chapter [see III:6 Lymphatic Mapping and Sentinel Lymph Node Biopsy].

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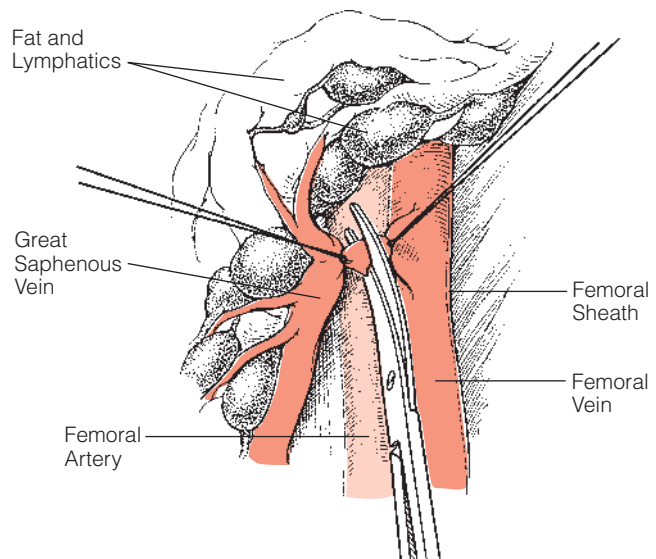


Figure 8 The great saphenous vein is ligated and divided.

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5 BREAST PROCEDURES

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The procedures used to diagnose, stage, and treat breast disease are rapidly becoming less invasive and more cosmetically satisfying while remaining oncologically sound. In particular, percutaneous core biopsy has largely replaced excisional breast biopsy for both palpable and nonpalpable breast lesions and has proved to be an equally accurate, less invasive, and less costly means of pathologic diagnosis.¹ Moreover, in clinically appropriate patients, sentinel lymph node biopsy (SLNB) has proved to be an accurate method of staging the axilla that reduces the incidence of many of the complications associated with traditional axillary node dissection.² Furthermore, breast conservation has largely supplanted mastectomy for definitive surgical treatment of breast cancer; randomized trials continue to demonstrate equivalent survival rates for the two therapies.³ Even in those cases where mastectomy is either required or preferred, advances in reconstructive techniques have been made that yield significantly improved outcomes after breast reconstruction.⁴ Finally, in an effort to eliminate the need for open surgical treatment of breast cancer, various percutaneous extirpative and ablative local therapies have been developed and are being evaluated for potential use in managing breast cancer in carefully selected patients.⁵

A more minimally invasive approach to breast disease will depend to a substantial extent on the availability of accurate and efficient imaging modalities. Adeptness with such modalities is rapidly becoming an essential part of the general surgeon's skill set. In this chapter, we describe selected standard, novel, and investigational procedures employed in the diagnosis and management of breast disease. The application of these procedures is a dynamic process that is shaped both by technological advances and by physicians' evolving understanding of the biology of breast diseases.

Breast Ultrasonography

Breast ultrasonography can be useful for evaluating palpable breast masses or mammographically indeterminate lesions; for carrying out postoperative and oncologic follow-up; for guiding aspiration and biopsy of lesions; and for facilitating intraoperative tumor localization, margin assessment, placement of catheters for partial-breast irradiation, and investigational tumor-ablating techniques.

In the office, breast ultrasonography has become a useful adjunct to the clinical breast examination, particularly in patients with radiographically dense mammograms. It defines breast lesions more clearly than physical examination does and

thus can potentially reduce the number of unnecessary biopsies done for simple cysts or fibroglandular tissue presenting as a palpable nodularity. Whole-breast ultrasonography is not an effective screening tool and therefore should not be a substitute for annual mammography. The American College of Surgeons (ACS) and various surgical subspecialty organizations offer a multitude of courses, at varying skill levels, geared toward training general surgeons in the use of breast ultrasonography.

TECHNIQUE

Most real-time ultrasound imaging is performed with handheld probes generating frequencies between 7.5 and 12 MHz. The procedure is conducted with the patient supine, a pillow behind the shoulder, and the ipsilateral arm extended over the head for maximal spreading of the breast. Sonographic transmission gel is applied between the transducer and the skin to reduce air artifacts, and the transducer is pressed slightly against the skin to improve image quality. The selected breast area is imaged from the nipple outward in a radial pattern.

All lesions should be sonographically characterized with respect to margins, effect on adjacent tissue, internal echo pattern, compressibility, height to width ratio, and presence of shadowing versus posterior enhancement. Classically, simple cysts tend to be oval or lobulated, anechoic, and sharply demarginated; they typically demonstrate posterior enhancement. Benign solid lesions tend to be well circumscribed, hypoechoic, and wider than they are tall; they show homogeneous internal echoes and edge shadowing. Carcinomas are also hypoechoic masses, but they cross tissue planes and therefore tend to be taller than they are wide, with irregular borders; in addition, they can demonstrate heterogeneous interior patterns and broad acoustic shadowing [see *Figure 1*]. A lesion that has a single indeterminate characteristic on ultrasonography or that is clinically suspicious despite appearing benign on ultrasonography is an indication for core or open biopsy. Lesions should be characterized in at least two orthogonal planes, and the image should be saved for future reference.

Ductal Lavage

The majority of breast cancers originate from the epithelium of the mammary ducts. Originally developed to increase the cellular yield after nipple aspiration failed to obtain adequate sampling, ductal lavage is a method of recovering breast duct epithelial cells for cytologic analysis via a microcatheter that is inserted into the duct.⁶ Potential applications include

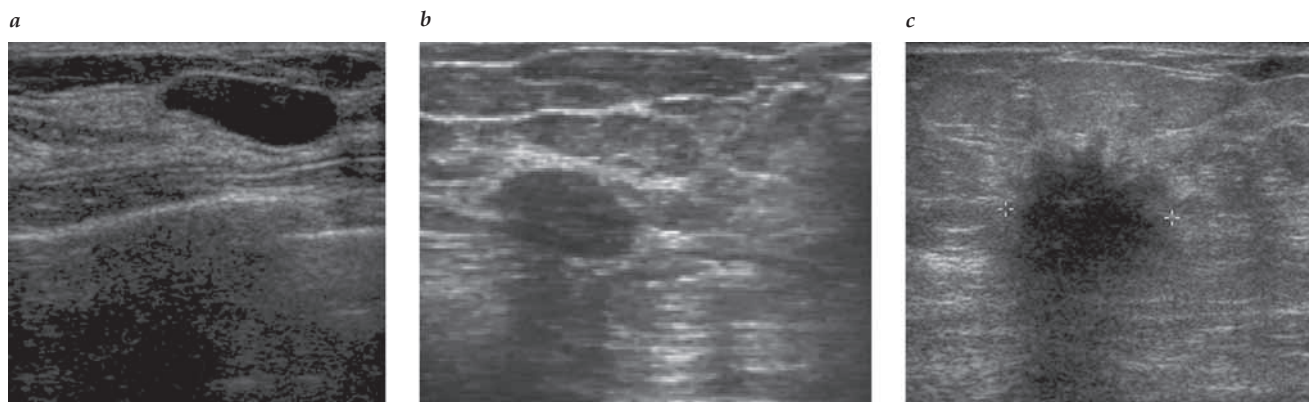


Figure 1 Breast ultrasonography. Shown are (a) a simple cyst that has smooth margins, is anechoic, and shows posterior enhancement; (b) a fibroadenoma that has smooth margins, is hypoechoic, and shows posterior shadowing; and (c) a mammary carcinoma that has irregular borders, is hypoechoic, and shows irregular posterior shadowing.

identifying high-risk women, predicting risk with molecular markers, monitoring the effectiveness of chemopreventive agents, and delivering drugs directly into the ducts. At present, however, ductal lavage remains investigational, and its predictive value and clinical utility await further definition.⁷

TECHNIQUE

The breast duct epithelium may be sampled by means of either nipple fluid aspiration or ductal lavage. For the aspiration of nipple fluid, a topical anesthetic is first applied to the nipple, followed by a mild scrub with a dekeratinizing gel. Suction is then applied to the nipple while the breast is gently massaged. Aspirated fluid is sent for analysis. In ductal lavage, the breast and nipple are similarly prepared. The nipple duct orifice that yields fluid spontaneously or as a result of suction is cannulated, the duct is irrigated with saline, and the effluent is collected for cytologic analysis. Cannulation of the duct is possible in the majority of women. Both nipple fluid aspiration and ductal lavage are generally well tolerated. The former is simpler and less expensive, but the latter retrieves more cells.⁸

Ductoscopy

Advances in endoscopic technology have allowed for visualization and biopsy of the mammary ducts, including those in more peripheral locations.⁹ Mammary ductoscopy is a procedure in which a 0.9 mm microendoscope is employed to visualize the lining of the ductal system directly. Previous studies have revealed ductoscopy to be safe for use in three main areas: (1) evaluation of patients with pathologic nipple discharge,¹⁰ (2) evaluation of high-risk patients, and (3) evaluation of breast cancer patients to determine the extent of intraductal disease and perhaps reduce the rate of positive margins. This is especially important in those patients with in situ disease and benign radiographic findings.¹¹ Current research is aimed at the use of ductoscopy-directed biopsy and ablation techniques. Perforation of the mammary duct is the most commonly reported complication; however, this appears to have minimal sequela. At present, this investigational technology is available at only a few centers, and further study will be required to determine its precise role in the evaluation and management of breast disease.

TECHNIQUE

Ductoscopy can be performed either in the office or in the operating room with minimal discomfort. Before the procedure, a nipple block is usually performed with topical lidocaine cream, supplemented (if necessary) by intradermal injection of 1% lidocaine around the nipple-areola complex or intraductal instillation of lidocaine (or both). The breast is massaged to promote expression of nipple aspirate fluid, which facilitates identification of a ductal orifice. The duct is then gently dilated, and the ductoscope is advanced with the help of insufflation under direct visualization. Most ducts with pathologic discharge can readily be identified and dilated sufficiently to allow passage of the ductoscope.¹² Under direct visualization, the ductoscope is advanced using saline insufflation. An outer air channel on the fiberscope permits instillation and collection of saline solution so that cells can be retrieved for ductal lavage.¹³ Intraductal lesions can be percutaneously localized under direct endoscopic visualization for subsequent biopsy; alternatively, they may be amenable to endoscopic cytologic brushing or to the newly described technique of intraductal breast biopsy.¹²

The procedure is usually well tolerated. It should be noted that duct excision is still regarded as standard practice for pathologic discharge, regardless of endoscopic findings.

Breast Biopsy

Cytologic or tissue diagnosis of a palpable breast mass may be obtained by means of fine-needle aspiration (FNA) biopsy, core-needle biopsy (CNB), or open incisional or excisional biopsy. Currently, most solid lesions are initially diagnosed by means of CNB, which is less invasive, less costly, and more expeditious than open biopsy while achieving comparable accuracy. In select circumstances, however, FNA biopsy and open biopsy may remain suitable options. All minimally invasive biopsy techniques are facilitated when guided by imaging modalities; such guidance enables the physician to perform a more directed biopsy that targets the lesion precisely while avoiding benign-appearing tissue, necrotic tissue, and adjacent structures (e.g., the chest wall, skin, and axillary vessels). Therefore, even when a lesion is palpable, ultrasound-directed

biopsy is preferable to blind biopsy (although not absolutely necessary) and is recommended if the surgeon has a suitable ultrasound device in the office.

The choice of a specific biopsy technique should be individualized on the basis of the clinical and radiographic features of the lesion, the experience of the clinician, and the patient's condition and preference.

FINE-NEEDLE ASPIRATION BIOPSY

FNA biopsy permits the sampling of cells from the breast or the axillary region for cytologic analysis. It is particularly useful for sampling a clinically or sonographically suspicious axillary node and for evaluating cyst fluid that is bloody or that comes from an incompletely collapsed or recurrent cyst. In patients receiving anticoagulants, FNA biopsy is a reasonable alternative to CNB for evaluation of a solid lesion in that there is less potential for hemorrhage if anticoagulation cannot be discontinued. Discrete masses discovered on physical examination may be either cystic or solid. A lesion that is shown by ultrasonography to be a simple cyst need not undergo FNA biopsy unless it is symptomatic.

Technique

The skin of the breast or axilla is prepared, and a local anesthetic is injected superficially via a 25-gauge needle. Although smaller needles may be used, a 21-gauge needle is optimal for FNA biopsy because it can be effectively used both for aspiration of potentially viscous fluid and for procurement of sufficient cellular material from solid masses. To generate adequate suction, a 10 mL or larger syringe should be used. As noted (see above), FNA biopsy ideally is performed under ultrasonographic guidance. If such guidance is unavailable, the lesion is held steady between the thumb and the index finger of the nondominant hand. Before the needle enters the skin, 1 mL of air is introduced into the biopsy syringe. Then, without the application of suction, the needle is advanced into the lesion. Once the needle is in place, strong suction is applied.

If the lesion is cystic, all fluid is aspirated, at which point the mass should disappear. Ultrasonography can confirm the complete collapse of a cyst or help direct the needle to an undrained portion of the cyst. The fluid need not be sent for analysis unless it is bloody or is associated with a residual palpable mass or an incompletely collapsed cyst as seen on ultrasonography. If the fluid is to be sent for analysis, it is injected directly into the pathologic preservative. The patient is reexamined 4 to 8 weeks after successful aspiration. If the same cyst has recurred, aspiration should be repeated and the new aspirate sent for cytologic analysis.

If the lesion is solid, the needle is moved back and forth within the lesion along a 5 to 10 mm tract until tissue is visualized in the hub of the needle. (This oscillation of the needle along the same tract is the most effective way of obtaining a cellular, diagnostic specimen.) Suction is released while the needle is still within the lesion, and the needle is then withdrawn. The contents of the needle are expelled onto prepared glass slides, spread into a thin smear, and fixed according to the preferences of the cytology laboratory. The syringe may be rinsed so that a cellblock can be prepared for further analysis. The lesion should be sampled twice to ensure that a sufficiently cellular sample has been obtained.

Interpretation of Results

Accurate interpretation of FNA requires substantial experience on the part of both the operator and the cytopathologist; only in a few select centers with expert breast cytopathologists has it remained the diagnostic procedure of choice for solid breast masses. Consequently, one must exercise considerable caution about using FNA biopsy rather than CNB as the sole means of confirming a cancer diagnosis before the initiation of definitive operative management or neoadjuvant therapy. FNA biopsy is unable to discriminate carcinoma in situ from invasive carcinoma and therefore is incapable of establishing whether axillary node staging is needed. Furthermore, because of the smaller quantity of tissue extracted, FNA biopsy is a less reliable means of assessing receptor status than CNB is. Finally, in 1 to 2% of cases, FNA biopsy may yield false positive results,¹⁴ potentially leading to an unnecessary cancer operation. For these reasons, it is recommended that malignancies identified by FNA biopsy be confirmed by means of CNB or open biopsy (preferably the former) before definitive therapy is provided.

Cytologic analysis that is diagnostic of a specific benign lesion (e.g., a fibroadenoma) may generally be relied on if it is in concordance with the clinical features of the lesion. However, a negative result from FNA biopsy does not exclude cancer: this procedure fails to diagnose as many as 40% of breast malignancies.¹⁴ Cellular atypia, pathologic discordance, or a nondiagnostic FNA is an indication for tissue diagnosis.

CORE-NEEDLE BIOPSY

As noted (see above), CNB is the diagnostic procedure of choice for breast lesions. Like FNA biopsy, it is easily performed in an outpatient setting. Unlike FNA biopsy, CNB removes a narrow cylinder of tissue that is submitted for pathologic rather than cytologic analysis. Whenever feasible, CNB of both palpable and nonpalpable lesions is performed under ultrasonographic guidance, which permits real-time documentation of the needle's position within the lesion. For lesions not visualized on ultrasonography or for suspicious microcalcifications, stereotactic guidance may be employed instead. A preoperative diagnosis of malignancy obtained via CNB enables the surgeon to perform a single-stage operative procedure. It may also help lower the positive margin rate for patients undergoing breast-conserving therapy (BCT), thereby reducing the need for reexcision and improving the cosmetic outcome.¹⁵

Various automatic, rotational, and vacuum-assisted devices may be employed to perform CNB; in what follows, we briefly discuss these devices [see *Technique, below*]. When CNB is performed with a 14-gauge needle, as is the case with Tru-Cut (Cardinal Health, Dublin, Ohio) devices and spring-loaded guns, up to 30% pathologic upgrading may be seen on subsequent surgical excision.¹ When CNB is done with a larger needle (8 to 11 gauge), as is the case with image-guided vacuum-assisted and rotational devices, a greater volume of tissue is delivered; consequently, less pathologic upgrading is seen.¹⁶ With the vacuum-assisted core biopsy (VACB) devices currently available, it is possible to remove all radiographic evidence of the lesion. It is therefore common practice with all core biopsies to place a titanium clip or another surrogate marker at the biopsy site to facilitate future localization procedures. In addition, a clip should be placed at the biopsy site if the patient has a larger

cancer for which neoadjuvant chemotherapy is required; some such lesions exhibit a complete clinical response to chemotherapy and thus are no longer radiographically visible at the time of definitive operative treatment. Two-view postbiopsy mammography should be performed to confirm accurate placement of the clip and adequate sampling of the lesion at the time of biopsy.

Technique

Palpation-guided biopsy In this setting, a manual Tru-Cut-type device or, more commonly, a spring-loaded semiautomatic biopsy gun is used to obtain the specimen. The skin is prepared, and a local anesthetic is infiltrated superficially via a 25-gauge needle. A nick is made in the skin with a No. 11 blade to permit easy entry of the biopsy needle (usually a 14-gauge needle). As with FNA biopsy (see above), the lesion is held steady in the nondominant hand while the biopsy needle is advanced into the periphery of the lesion. Next, the needle is manually advanced through the center of the lesion (if a manual device is used), or the gun is fired (if a spring-loaded device is used). Finally, the needle is withdrawn to retrieve the core. Four to five cores, each from a separate pass, should be obtained to ensure that the lesion is not undersampled. Pressure is applied over the lesion and the biopsy tract for 10 to 15 minutes to ensure adequate hemostasis. The nick in the skin is closed with an adhesive strip (e.g., Steri-Strip, 3M, St. Paul, Minnesota).

Ultrasound-guided biopsy This technique may be employed for both palpable and nonpalpable lesions. The lesion that is to undergo biopsy is centered on the screen of the ultrasound device. A local anesthetic is injected superficially, first along the anticipated biopsy tract and then both anterior and posterior to the lesion; this latter maneuver helps ensure that there is a safe distance between the lesion and the skin or the chest wall. A nick is made in the skin with a No. 11 blade. The biopsy needle is then inserted through the skin, with care taken to keep it in a plane parallel to the footplate of the ultrasound probe as it passes through the breast tissue. The biopsy itself can be either performed in a freehand manner or directed with a needle guide attached to the probe. The ideal final positions of the tip and shaft vary, depending on the particular biopsy device selected for the procedure [see Figure 2]. Regardless of which device is used, the tip and shaft of the needle should be visualized throughout the entire approach to and biopsy of the lesion. Prefire and postfire images should be obtained that show the needle in proximity to and within the lesion, respectively. Four to five good cores are required for adequate sampling. Once the biopsy is complete, pressure is applied over the lesion and the biopsy tract, and a Steri-Strip is placed. To facilitate closure of larger entry sites, a single subcuticular stitch may be used.

Brisk bleeding may occur during and immediately after the procedure, but it usually can be controlled by the application of direct pressure. Patients are restricted from engaging in strenuous activity for 24 hours after biopsy. Bruising may result, but it typically resolves within days. Other potential complications include hematoma, fat necrosis, a palpable lump, and infection; however, such events are uncommon. Most patients receiving oral anticoagulants can be switched to a subcutaneous alternative that can be stopped on the morning of the procedure.

Semiautomated gun biopsy When a spring-loaded semiautomatic biopsy gun is used, the tip of the needle should abut the lesion in such a way that the biopsy trough will be in the lesion after the device is fired. Ideally, the repeat passes should sample different portions of the lesion and avoid any necrotic areas that have been visualized.

Vacuum-assisted core biopsy Vacuum-assisted rotational cutting devices employ a 7- to 11-gauge probe with a distal sampling trough and an inner rotating cutter. The sampling trough can be placed either in the center of the lesion or directly under it. The probe is attached to a vacuum system, which draws the target tissue into the trough. Once the tissue has been drawn into the trough, the inner rotating cutter is advanced and cuts a core from it. The tissue core is then delivered by the vacuum system through the barrel of the probe and into a proximal collection chamber. The probe can be rotated up to 360° and can retrieve multiple samples through a single insertion in the skin. The larger tissue volumes obtained with these rotational VACB devices have reduced the incidence of atypical ductal hyperplasia or ductal carcinoma in situ (DCIS) upgrades on subsequent excisional biopsies.⁵

Cryoassisted core biopsy In a cryobiopsy, a thin (19-gauge) solid needle is placed in the middle of the targeted tissue. The tip is then cooled to approximately 10°C, a temperature that freezes the tissue to the needle but does not cause tissue necrosis. An outer rotating cutting cannula (10 gauge) is then advanced over the inner localizing needle. The device is removed from the breast, and the single specimen is removed. As with the semiautomatic biopsy gun, multiple passes into the breast are still required. However, the local anesthetic effect of the cooling process, the ability of the device to spear and stabilize a lesion, and the absence of a firing gun-type action make cryobiopsy advantageous, particularly for a mobile lesion that lies close to the skin or the chest wall.

Stereotactic-guided biopsy Lesions that are visible on mammography—including small solid lesions, asymmetrical densities, and suspicious groups of microcalcifications—can often be targeted and subjected to core biopsy under stereotactic guidance.¹⁷ Stereotaxy refers to the use of three-dimensional coordinates to localize and identify the lesion and determine the precise positioning of the tissue to be sampled.¹⁸ This outpatient procedure commonly makes use of a mounted VACB gun, similar to the handheld VACB device previously described (see above). Stereotactic biopsy is appropriate for lesions that are clearly visible on digital images and identifiable on stereotactic projections. Lesions that lie close to the chest wall or in the subareolar region may not be amenable to stereotactic biopsy and are often best approached via open biopsy with needle localization (see below). Likewise, lesions in thinly compressible breasts may not be amenable to stereotactic biopsy, because firing of the needle may result in a through-and-through injury to the breast. Certain stereotactic systems may not be suitable for patients who are unable to lie prone or are morbidly obese. It should be kept in mind that stereotactic biopsy is a diagnostic procedure and is not intended for therapeutic purposes. On the whole, it is safe, and the complication rate is acceptably low.

Depending on the system being employed, the patient either lies prone on the stereotactic table or sits upright. With the breast compressed craniocaudally or mediolaterally, stereotactic digital imaging is then performed to visualize the

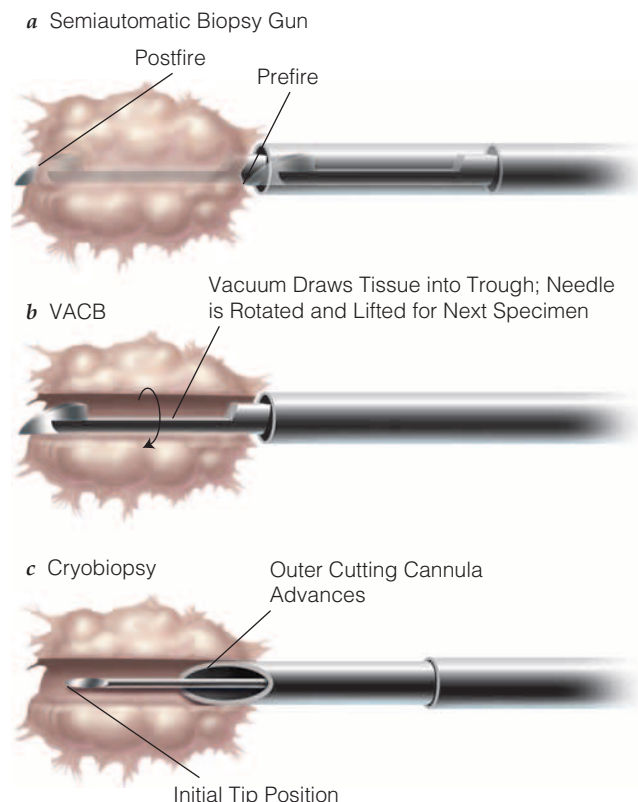


Figure 2 Core-needle biopsy. The positioning of the needle shaft and tip varies with the particular biopsy device being used. (a) For manual or semiautomatic guns that fire through the lesion, the position of the tip before firing should be at the edge of the lesion. Keeping the needle shaft parallel to the chest wall or the skin keeps these structures from being injured when the gun is fired or the core is manually obtained. (b) For most vacuum-assisted devices, multiple cores can be obtained through a single placement of the device within the breast. For diagnostic biopsies performed under ultrasonographic or stereotactic guidance, the needle may be placed in the center of the lesion and rotated up to 360° in specified intervals. (c) For cryobiopsy, the tip of the needle should be advanced through the center of the lesion toward the far edge of the lesion before firing. This step stabilizes the lesion. The outer cutting and rotating cannula is then fired over the inner needle. VACB = vacuum-assisted core biopsy.

targeted lesion and calculate its location in three dimensions, and a suitable probe insertion site is identified. The skin is prepared, and a small amount of buffered 1% lidocaine with epinephrine is administered. The skin at the insertion site is punctured with a No. 11 blade, the probe is manually advanced to the prefire site, and the position of the probe is confirmed by means of stereotactic imaging. The device is then fired, repeatedly cutting, rotating, and retrieving samples until the desired amount has been removed. Targeted removal of suspicious microcalcifications is confirmed with specimen mammography.

Once the biopsy is complete, an inert metallic clip is deployed into the biopsy site through the probe for future localization; deployment and positioning are initially confirmed by

stereotactic imaging. The biopsy device is then removed, the edges of the skin incision are approximated with Steri-Strips, and a compressive bandage is applied. Typically, 1 g of tissue (equivalent to approximately 10 to 12 samples with an 11-gauge probe) is sufficient for diagnosis. Once the procedure is over and the breast has been released from compression, a two-view mammography should be obtained to verify that the clip was accurately placed and to document that the targeted lesion was adequately sampled.

Magnetic resonance imaging-guided biopsy Contrast-enhanced magnetic resonance imaging (MRI) has been found to be a highly sensitive method for detecting breast cancer, especially those that are nonpalpable or are unable to be viewed using conventional radiographic methods. A stereotactic method similar to the one described above has been developed using a VACB to perform an incisional biopsy under MRI guidance. Similarly, the patient is placed prone and the targeted breast undergoes mediolateral compression. Using MRI, a software program calculates the three-dimensional coordinates for the biopsy device. The VACB gun is used outside the magnet, so MRI compatibility is not required. After several tissue samples are removed, the resulting cavity is directly visualized to ensure precise tissue removal. A metallic marking clip can be placed during the procedure to facilitate future surgical excision if a diagnosis of cancer is determined. The procedure is generally well tolerated. Bleeding and hematoma are the most commonly encountered complications. Compared to conventional stereotactic biopsy, MRI-guided biopsy has a significantly higher cost. MRI-guided biopsy is a promising modality but requires further investigation as there are few long-term studies to determine histopathologic correlation and the false negative rate.¹⁹⁻²¹

Interpretation of Results

CNB is a highly accurate diagnostic tool: the false negative rate is only 1 to 2%,²² which is comparable to that of open wire-localized biopsy. When pathologic evaluation reveals fibroadenoma, microcalcifications within benign fibrocystic tissue, or other comparably benign pathologic conditions, there is no need for any special follow-up, and routine screening mammography may be resumed. However, when biopsy of the targeted mass lesion fails to yield a mass diagnosis or a biopsy specimen from a group of clustered calcifications is devoid of microcalcifications on pathologic review, the discordant result should be viewed with some suspicion and should be considered an indication for open biopsy. Subsequent excisional biopsy is also indicated when CNB reveals atypical hyperplasia, radial scar, lobular carcinoma in situ (LCIS), or papilloma. The rationale is that the excisional biopsy may result in a pathologic upgrade to cancer. For example, open biopsy after a CNB indicative of atypical ductal hyperplasia may reveal DCIS in approximately 40% of patients when CNB was performed with a 14-gauge automated gun. The use of larger (e.g., 11-gauge) core biopsy devices has reduced the frequency of this finding to approximately 20%,²³ but it has not eliminated the need for excision. False positive results are rare with CNB; therefore, a diagnosis of malignancy may be believed, and a one-stage definitive surgical procedure may then be planned without further biopsy.

Touch Preparation of Cores

For an immediate but preliminary diagnosis, cytologic touch preparation of fresh cores may be performed in the office.²⁴ The tissue is blotted to remove any gross blood, the core is gently smeared along a glass slide, and the slide is then immediately fixed in 70% ethanol. A layer of cells is left on the surface of the slide for cytologic evaluation, whereas the core is preserved for permanent evaluation. This procedure has a diagnostic accuracy of nearly 90%. Although the false negative rate is approximately 25%, an immediate diagnosis is obtained in 75% of patients.¹⁸ Like all preliminary diagnoses, touch preparation diagnoses should be treated with caution until the final results of histopathologic evaluation are available.

PERCUTANEOUS EXCISIONAL BIOPSY

In some instances, patient preference may dictate complete removal of a mass regardless of its benign appearance. As an alternative to open biopsy (see below), percutaneous excision of small masses may be performed.^{25–27} This procedure can be performed in an outpatient setting with the patient under local anesthesia. Some of the devices used for percutaneous excision are vacuum assisted and remove the mass as multiple cores, whereas others deliver large intact samples in a single pass [see *Figure 3*]. Although such approaches clearly show promise for future surgical treatment of breast cancer, these percutaneous devices are currently approved by the US Food and Drug Administration (FDA) only for excision of benign masses. Lesions found to be harboring cancer should undergo subsequent open surgical reexcision. Excision of lesions that are close to the skin or the chest wall or are larger than 2 to 3 cm in diameter may prove technically challenging with percutaneous techniques; open excisional biopsy [see *Open Biopsy, below*] may be preferable for such lesions.

OPEN BIOPSY

The vast majority of open breast biopsies are now performed with either local anesthesia alone or local anesthesia with intravenous sedation.

Technique

Various options for incisions are available [see *Figure 4*]. If the pathology is unclear, the incision is placed directly over the lesion to minimize tunneling through breast tissue. The incision should be long to ensure that the mass, together with a small rim of grossly normal tissue, can be excised as a single specimen and be oriented so that it can be included within any future lumpectomy or mastectomy incision should the lesion prove malignant. Resection of overlying skin is not necessary unless the lesion is extremely superficial. Historically, surgeons performing open biopsies have generally employed curvilinear incisions placed within the resting lines of skin tension [see *Figure 4, a and b*]. Currently, however, some surgeons are advocating the use of radial incisions, particularly for medial, lateral, and inferior lesions.¹⁵ If a previous CNB proved the lesion to be benign (e.g., fibroadenoma) but the patient still favors excision, it is acceptable to move the incision to a circumareolar position or another less visible site.

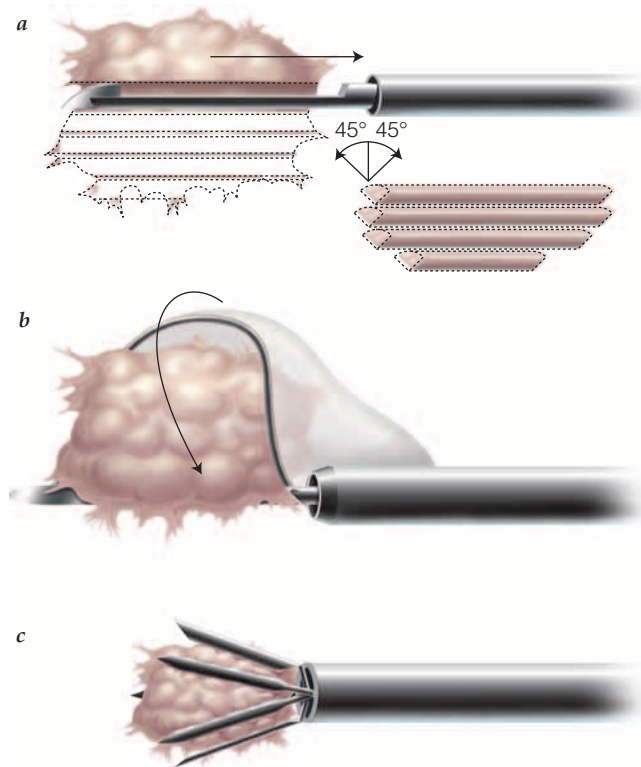


Figure 3 Percutaneous excisional biopsy. This procedure may be performed by means of several different methods. (a) One approach is to employ a vacuum-assisted device, which is placed with the trough under the lesion and the shaft parallel to the posterior aspect of the lesion. The needle is then lifted anteriorly as it is rotated first 45° clockwise, then back to the center position (0°), and finally 45° counterclockwise to remove the entire lesion in multiple cores. (b) Another option is to employ an electro-surgical device such as the Ovation (Rubicon Medical, Inc., Redwood City, California), which circumscribes the mass with a cutting wire loop while concurrently deploying a retractable plastic bag that encapsulates the lesion and retracts it through the skin en bloc. (c) A third option is to employ a device such as the Intact Breast Lesion Excision System (Intact Medical Corp., Natick, Massachusetts), which circumscribes the mass with a radiofrequency wand and delivers it en bloc.

For diagnostic biopsies, the surgeon should orient the specimen, and the pathologist should ink all margins. Meticulous hemostasis should be achieved before closure to prevent the formation of hematomas that could complicate subsequent definitive oncologic resection. A cosmetic subcuticular skin closure is preferred.

NEEDLE (WIRE)-LOCALIZATION BREAST BIOPSY

Lesions that are not amenable to stereotactic core biopsy may be excised by means of needle (wire)-localization breast biopsy (NLBB). Such lesions include those that are close to the chest wall or under the nipple, as well as those occurring in a thin breast, where firing the needle may cause it to pass through the opposite side of the breast. Radiographic evidence of a radial scar is also an indication for NLBB: a core pathologic diagnosis of such a scar would ultimately necessitate

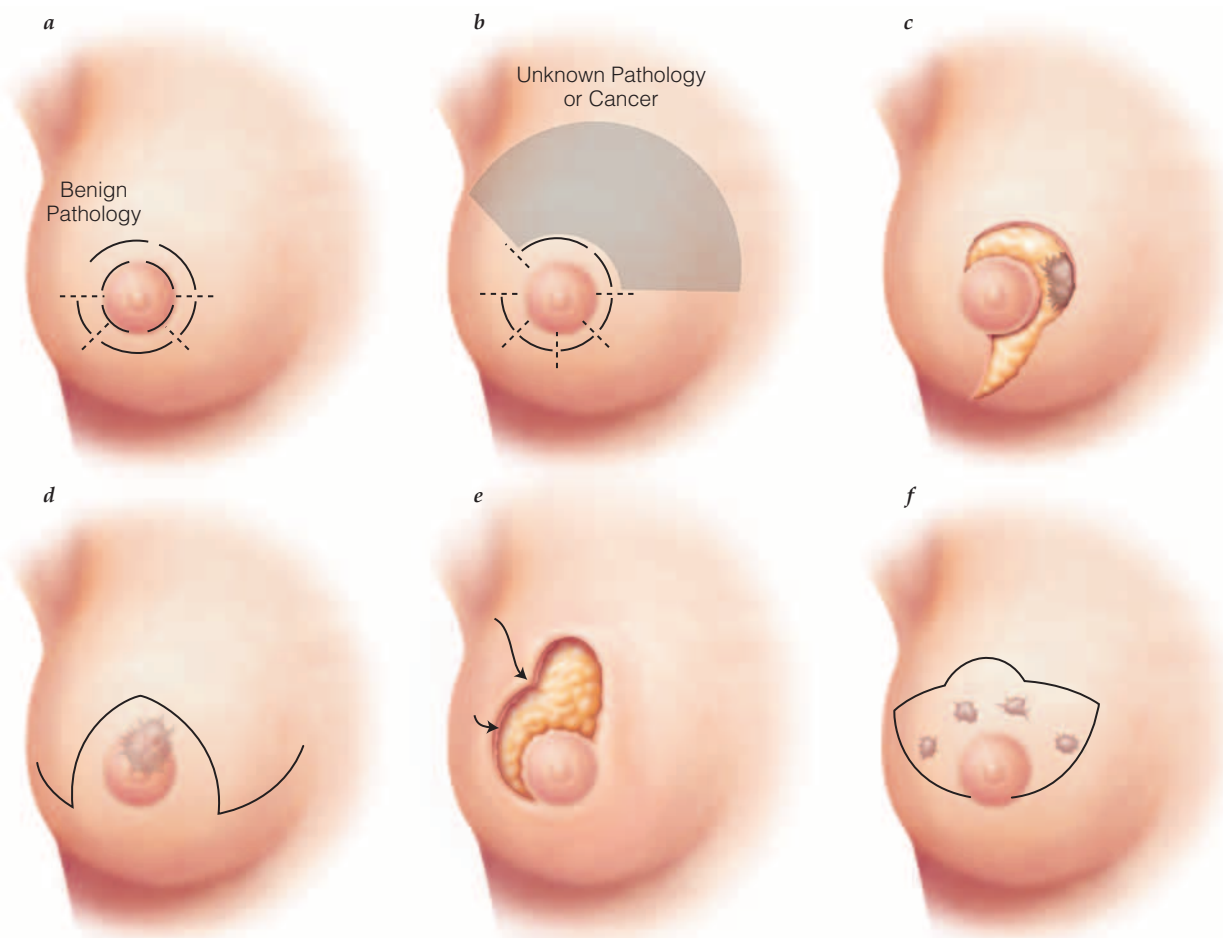


Figure 4 Open biopsy. (a) For biopsy-proven benign masses, a circumareolar incision generally provides excellent cosmesis and a well-hidden scar. If the lesion is too far from the nipple, curvilinear incisions are traditionally employed instead. Alternatively, medial, lateral, and inferior incisions may be placed in a radial fashion. (b) For lesions of unknown pathology, incisions should be placed directly over the lesion and should be oriented so that they will be included within a subsequent mastectomy incision if margins prove positive and mastectomy is indicated. As with benign lesions, either curvilinear or radial incisions may be employed. Circumareolar incisions should be avoided in this setting because reexcision to provide clear margins, as is indicated in the case of malignancy, can necessitate excision of a portion of the nipple-areola complex and can commit the surgeon to a mastectomy. In cases where reexcision is indicated, avoidance of incisions in the so-called no man's land may improve cosmesis in that it allows future reconstructive efforts to include advancement of the nipple-areola complex if desired. Various oncoplastic incisions may be employed as alternatives for (c) medial, (d) central, or (e, f) superior lesions.

open excision. Finally, reexcision is required when stereotactic or ultrasound-guided CNB reveals lesions determined to be high risk on pathologic evaluation (e.g., atypical hyperplasia, LCIS, papilloma, carcinoma, or lesion whose pathologic status is discordant with radiographic findings). In these circumstances, wire localization may be performed on the residual lesion, a clip placed at the time of CNB, or another surrogate marker (see below). To bracket a more extensive area of calcifications, multiple wires may be placed, especially if previous CNB revealed atypia or malignancy in the area.

Technique

The lesion to be excised is localized by inserting a thin needle and a fine wire under mammographic, ultrasonographic, or MR guidance immediately before operation. To facilitate incision placement, images should be sent to the

operating room with the wire entry site indicated on them. The incision is placed as directly as possible over the mass to minimize tunneling through breast tissue. With superficial lesions, the wire entry site is usually close to the lesion and thus may be included in the incision. With some deeper lesions, the wire entry site is on the shortest path to the lesion and so may still be included in the incision. Once the incision is made, a block of tissue is excised around and along the wire in such a way as to include the lesion [see Figure 5, a and b]. This process is easier and involves less excision of tissue if the localizing wire has a thickened segment several centimeters in length that is placed adjacent to or within the lesion. The wire itself can then be followed into breast tissue until the thick segment is reached, at which point the excision can be extended away from the wire to include the lesion in a fairly small tissue fragment.

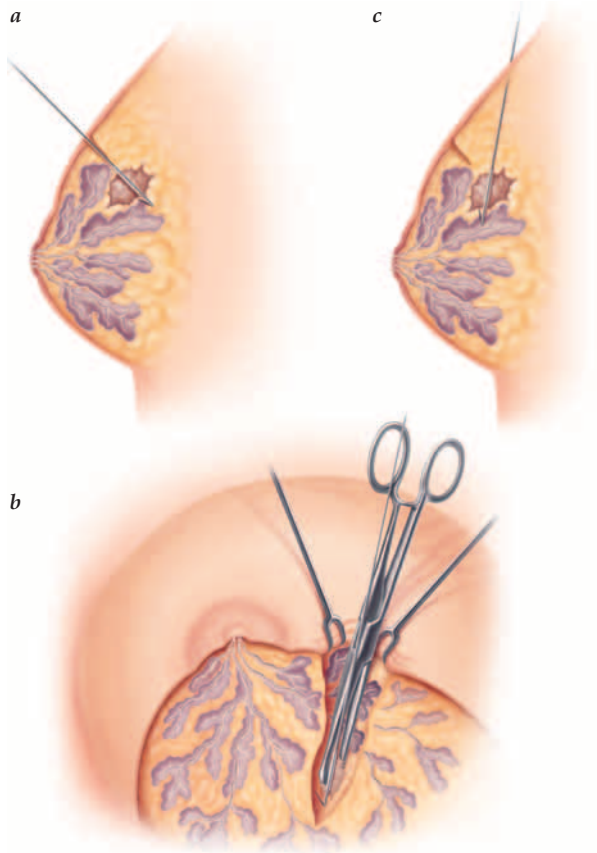


Figure 5 Needle-localization breast biopsy. (a) The mammographic abnormality is localized preoperatively. The relation between the wire, the skin entry site, and the lesion is noted by the surgeon. The skin incision is placed over the expected location of the mammographic abnormality. (b) The tissue around the wire is removed en bloc with the wire and sent for specimen mammography. Tunneling and piecemeal removal are to be avoided. (c) It is sometimes necessary to insert the localizing wire from a peripheral site to localize a deep or central lesion. The incision should be placed directly over the expected location of the lesion, not over the wire entry site. The dissection is extended into breast tissue to identify the wire a short distance from the lesion. The free end of the wire is pulled into the wound, and the biopsy is performed as previously described.⁹⁹

With many lesions, the wire entry site is in a fairly peripheral location relative to the position of the lesion, which means that including the wire entry site in the incision would result in excessive tunneling within breast tissue. In such cases, the incision is placed over the expected position of the lesion [see Figure 5c], the dissection is extended into breast tissue to identify the wire a few centimeters away from the lesion itself, and the free end of the wire is pulled up into the incision. A generous block of tissue is then excised around the wire. Intraoperative ultrasonography may be useful for identifying the tip of the needle and facilitating excision, particularly in the case of a deep lesion or biopsy site in a large breast.

Radiography should be performed intraoperatively on all wire-localized biopsy specimens to confirm excision of the lesion. If the lesion was missed, another tissue sample may be

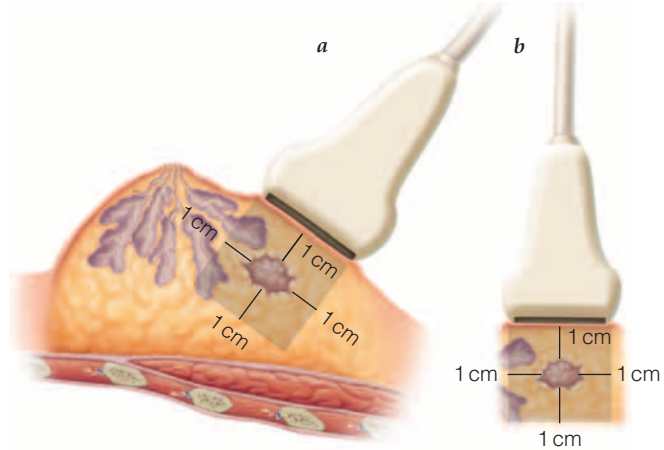


Figure 6 Hematoma ultrasound-guided excision. (a) The hematoma is localized in two planes with intraoperative ultrasonography, and 1 cm margins are marked off around it. Dissection then proceeds down toward the chest wall in a block fashion. Excision of the hematoma is confirmed by ultrasonography of the specimen ex vivo. (b) as well as by direct visualization of the hematoma in the gross specimen.^{31,32}

excised if the surgeon has some idea of the likely location of the missed lesion. If, however, the surgeon suspects that the wire was dislodged before or during the procedure, then the incision should be closed, and repeat localization and biopsy should be performed later. In addition to wire dislocation or transection, wire localization is occasionally associated with vasovagal reactions. Alternatives to wire localization include hematoma ultrasound-guided (HUG) excision (see below), carbon marking,²⁸ use of methylene blue dye,²⁹ and placement of radioactive seeds.³⁰

Hematoma ultrasound-guided excision In patients who have undergone CNB, particularly those who have undergone VACB, the hematoma at the biopsy site can often serve as a physiologic marker that accurately guides intraoperative localization [see Figure 6].^{31,32} This procedure, referred to as HUG excision, renders wire placement unnecessary and can facilitate operative scheduling. The hematoma is localized in two planes using ultrasound guidance and 1 cm margins are marked off around the lesion; dissection is then continued down toward the chest wall in a block fashion. Excision of the hematoma can be confirmed by ultrasonography of the specimen ex vivo, as well as direct visualization of the hematoma in the gross specimen. Another variation of the procedure includes localization of the tumor with MRI and infusion of the patient's own blood into the lesion for future localization and surgical excision.³¹

RADIOISOTOPE-GUIDED OCCULT LESION LOCALIZATION

As widespread mammographic screening programs have been employed, there has been an increase in the detection of nonpalpable breast lesions requiring improved localization techniques for biopsy and/or excision. Radioisotope-guided occult lesion localization (ROLL) is one such modality using an intratumorally injected radiotracer to identify the lesion intraoperatively by use of a gamma probe.³³ Contraindications

to the ROLL procedure include patients with a history of albumin allergy attributed to the injection of a colloid into the breast lesion.³⁴ The ROLL procedure has shown a decrease in the volume of breast tissue excised while preserving surgical margins. Patients have reported less pain and an improved cosmetic result with this procedure.^{34–36} Clinical trials have shown adequate excision rates when compared with the needle-localization technique. Combination with the sentinel lymph node (SLN) mapping procedure has been successfully described in the literature.^{37–39} Further investigation with randomized clinical trials is currently underway.

Technique

Lesions are identified by image guidance using either ultrasonography or stereotactic mammography, and intratumoral injection of a radionuclide-labeled colloid is performed prior to surgery. The procedure can be performed using local anesthesia with or without sedation. Intraoperatively, a handheld gamma-detecting probe is used to identify the area with the maximum radioactivity, and a small incision is made in the skin overlying this site. Determination of excision volume is made by review of preoperative lymphoscintigraphic imaging and decreased detection of radioactivity in the resection bed. Surgical specimens should undergo radiographic evaluation to confirm removal of the lesion.

Terminal Duct Excision

Terminal duct excision is the procedure of choice in the surgical treatment of pathologic nipple discharge.⁴⁰ The goal is to excise the discharging duct with as little additional tissue as possible to maintain cosmesis. To this end, the surgeon should carefully note the precise position of the offending duct at the time of the initial examination. To ensure accurate ductal identification, intraductal injection of methylene blue has been used to aid in visualization of the involved ductal system prior to major duct excision. Other methods used in conjunction with terminal duct excision to limit the volume of tissue removed include ductography and ductoscopy.⁴¹

OPERATIVE TECHNIQUE

The patient is instructed to refrain from manually expressing her discharge for several days before operation. After local anesthesia (with or without sedation) is administered, the surgeon attempts to express the discharge. If this attempt is successful, the edge of the nipple is grasped with a forceps, and a fine lacrimal duct probe (000 to 0000) is gently inserted into the discharging duct. A radial incision is made within the areola at the same clock position as is occupied by the draining duct [see Figure 7]; this incision is preferred to a circumareolar incision because it is believed to preserve more nipple sensation and function.⁴² The nipple skin flap is raised, and the duct containing the wire is excised with a margin of surrounding tissue from just below the nipple dermis to a depth of 4 to 5 cm within the breast tissue. The electrocautery should be employed with particular caution in the superficial portions of the dissection to prevent devascularization of the nipple-areola complex. If it is not possible to pass the lacrimal duct probe into the discharging duct or it is unclear which duct has resulted in the pathologic discharge, the entire

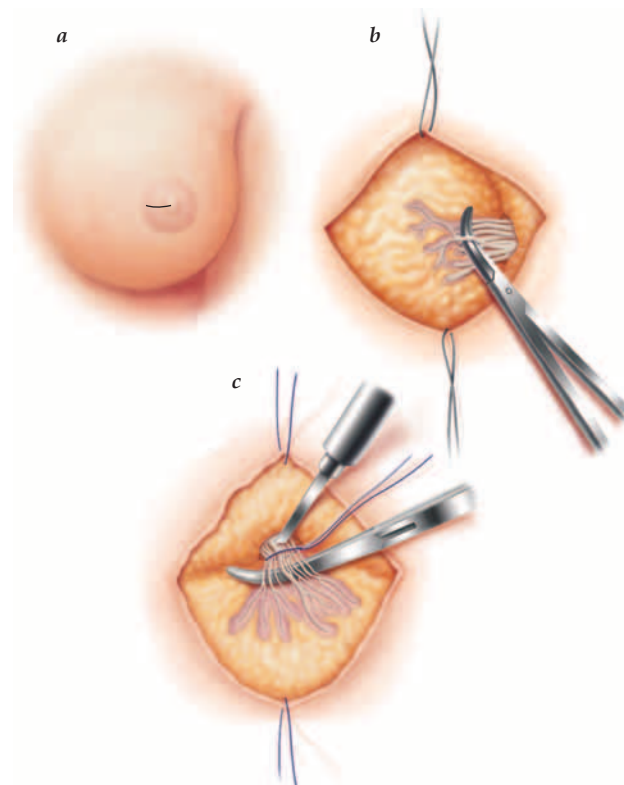


Figure 7 Terminal duct excision. (a) A radial incision is made within the areola. (b) The involved duct is identified by means of blunt dissection and removed along with a core of breast tissue. (c) If no single duct is identified, the entire subareolar ductal complex is excised from immediately beneath the nipple dermis to a depth of 4 to 5 cm within breast tissue.^{40,42}

subareolar duct complex must be excised from immediately beneath the nipple dermis to a depth of 4 to 5 cm within the breast tissue. The breast tissue should be reapproximated beneath the nipple to prevent retraction of the nipple or indentation of the areola.

Minimally Invasive Techniques

The next step in the evolving application of minimally invasive techniques to breast cancer is to determine whether ablative local therapies can safely substitute for standard surgical extirpation. Cryotherapy, interstitial laser therapy, radiofrequency ablation (RFA), microwave ablation, and high-intensity focused ultrasound ablation have all been studied as means of eradicating small breast cancers.⁴³ In most of these techniques, a probe is placed percutaneously into the breast lesion under imaging guidance, and tumor cell destruction is achieved by means of either heat or cold.

To date, experience with ablative breast therapies has been limited, and long-term follow-up has not been carried out. There is some evidence that patients who have small, well-defined, unifocal cancers without an extensive intraductal component may have greater success with these techniques.⁴³ Lesions in close proximity to the pectoralis major muscle or the skin should be isolated by injecting normal saline to prevent thermal injury. Most of the time, these minimally

invasive techniques are well tolerated and can be performed in an outpatient setting. Additionally, superior cosmesis is achieved by leaving the ablated tissue in situ without loss of tissue volume, thus preventing breast deformity and scarring. However, most of the initial studies of ablative breast therapies involved subsequent surgical excision to obtain histologic evidence of cell death. Unfortunately, when ablative therapies are used alone, the benefits of pathologic assessment of the specimen, including evaluation of margin status, are lost. Limiting factors include the ability of current imaging modalities to detect residual disease, thereby identifying patients who may need subsequent surgical intervention. Clearly, minimally invasive ablative approaches to breast cancer are technically feasible and safe, and they do appear to offer some potential advantages; however, it remains to be determined to what extent they are oncologically appropriate.

CRYOABLATION

Cryotherapy has been successfully used in the treatment of nonresectable liver tumors. It destroys targeted tissue by alternately freezing (-40°C) and thawing the lesion. Intracellular ice formation and osmotic and ischemic injury are believed to contribute to the mechanism of tissue destruction. Because of the natural analgesic effect of cold, cryoablation is generally a well-tolerated procedure that can be performed in an outpatient setting using local anesthesia with minimal need for pain-controlling medications.

Patients with a biopsy-proven fibroadenoma who want their mass removed but desire an alternative to open or percutaneous surgical excision may be candidates for cryoablation. Clinically, resorption of the fibroadenoma increases over time, with 12-month follow-up studies reporting a significant reduction in lesion volume. Despite the occasional residual disease noted when cryoablation is used to treat larger masses, both hospital- and community-based studies have reported that patient satisfaction rates are higher than 90% with this procedure.⁴⁴

The role of cryotherapy in the treatment of primary malignant disease has recently been explored. Immunologic activation from the cryoablative technique may provide an effective tumor-specific response.⁴⁵ Early studies reveal the degree of tumor destruction achieved by cryotherapy to be inconsistent.^{46–48} Larger clinical trials are currently in the planning stages, and the efficacy of this treatment for selected patient populations remains investigational.

Use of the cryoprobe has also been explored as an alternative to needle localization for excision of nonpalpable lesions prior to BCT. Theoretically, the ability to palpate previously nonpalpable lesions may reduce reexcision rates for positive margins. Pilot studies have shown decreases in resected tissue volume, improved cosmesis, and improved patient satisfaction with a consistently negative margin status.⁴⁹ Clearly, the use of cryoablation in this role also requires further examination.

Technique

A 12-gauge cryoprobe is inserted into the center of the lesion under ultrasonographic guidance. To freeze the lesion, inert argon gas is delivered through the tip of the probe in such a way as to create a local temperature of -40°C or

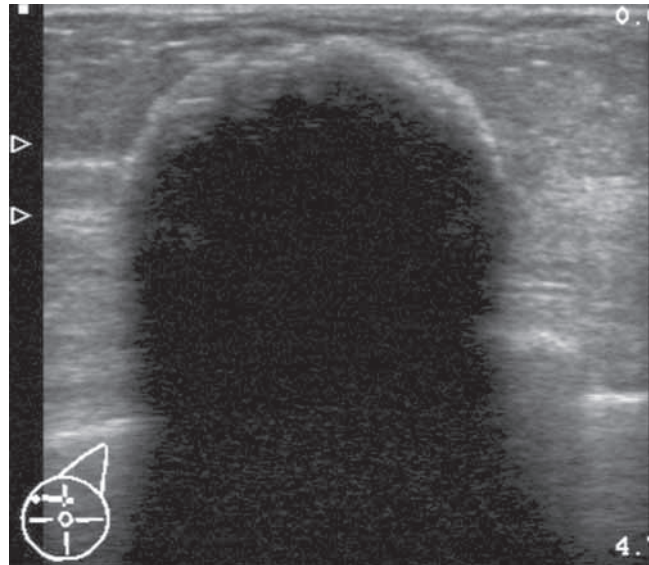


Figure 8 Cryoablation. The needle is placed through the center of the lesion, and argon gas is delivered to create a local temperature of -40°C . The resulting iceball is well visualized by ultrasonography.

lower. An iceball is thereby formed that is well visualized by ultrasonography [see Figure 8]. In a tightly coupled system, helium is then delivered to thaw the lesion. For adequate necrosis to occur, two freeze-thaw cycles must be performed; the exact specifications of these cycles depend on the size of the lesion.

INTERSTITIAL LASER THERAPY

Interstitial laser therapy causes hyperthermic (80°C to 100°C) cell death and coagulative tissue necrosis by delivering energy through a fiberoptic probe. Precise targeting with the use of an MRI-guided laser or stereotactic mammography is required. Benefits of this treatment include the use of local anesthesia only. One reported complication with significant morbidity included gaseous rupture of the tumor.⁴⁶ Small studies employing surgical excision following laser treatment have shown complete ablation to be inconsistent. Smaller tumors were more likely to be completely ablated.^{50,51} Complete tumor destruction has been difficult to ensure with this technique. Further investigation and long-term follow-up are required.

Technique

A 16-gauge needle with a thermal sensor is inserted into the center of the tumor using image guidance. The stylet is then replaced with a laser fiber, and the tissue is heated to 80°C to 100°C . For larger lesions, multiple laser fibers may be placed. A thermal sensor needle is placed 1 cm away from the laser needle to monitor peripheral temperatures and ensure an ablative zone of 2.5 to 3.0 cm. Tumor destruction is confirmed by ultrasonography or MRI.⁵⁰

RADIOFREQUENCY ABLATION

Like cryotherapy, RFA has also been extensively used to treat liver tumors. RFA is a minimally invasive thermal ablation technique in which frictional heat is generated by intracellular ions moving in response to alternating current. It is

currently the most promising ablative method for small breast cancers; however an accurate treatment algorithm remains to be developed.⁵⁰ Complications include superficial skin burning and temporary elevation of body temperature. Early studies with RFA followed by immediate or delayed surgical resection have shown incomplete ablation of tumors.⁴⁶ Incomplete ablations were attributed to large tumor size (> 2 cm) and the presence of multifocal disease.⁴³

Technique

A large-gauge probe is placed into the center of the tumor using image guidance. A star-shaped set of electrodes is deployed from the tip of the probe to deliver heat at a temperature of 95°C, which is maintained for 15 minutes followed by a period of cooling for 1 minute. Postprocedural MRI may help confirm complete tumor destruction after RFA and other ablative techniques.

MICROWAVE ABLATION

Microwave ablation is an investigational technique similar to RFA causing tumor necrosis by generation of frictional heat using two microwave phased array applicators. Because of the higher water content of cancer tissue (compared to adipose and glandular tissue), agitation of intracellular water molecules causes temperature elevation of the breast lesion, leading to tissue necrosis. Image guidance is usually performed to localize the lesion. Complications have included skin flap necrosis and mild skin burns overlying the treatment area. Pilot studies have shown a reduction in the size of the tumor; however, further prospective trials are needed to investigate the use of microwave ablation as a treatment modality for invasive cancer.^{52–55} Current investigations into the added benefit of microwave ablation in conjunction with neoadjuvant chemotherapy are promising.⁵⁴

FOCUSED ULTRASOUND ABLATION

Focus ultrasound ablation (FUS) is a modality used to incur cellular death by thermal injury from an ultrasonic energy source. One of the benefits of FUS is that no implantable device is required, allowing the procedure to be performed through the intact skin. Additionally, larger tumors and lesions with an irregular shape can be ablated using this technique. Image guidance is required to make sure the lesion is adequately ablated including a 2 cm margin, in keeping with the oncologic principles of breast conservation surgery. Short-term follow-up studies ablating smaller tumors have shown contradictory results with FUS regarding complete tumor necrosis. A palpable lump following the procedure is noted by most patients from local tissue edema; however, this is transient and usually resolves within 1 to 2 weeks. Contraindications to FUS include multifocal, deep lesions and tumors in close proximity to the skin and nipple.^{54–56}

Surgical Options for Breast Cancer

There are several surgical options for primary treatment of breast cancer. It should be emphasized that for most patients, partial mastectomy (lumpectomy) to microscopically clear margins coupled with axillary staging and radiation therapy yields long-term survival equivalent to that associated with mastectomy and axillary staging. Currently, indications for

mastectomy include patient preference, the inability to achieve clean margins without unacceptable deformation of the breast, the presence of disease in multiple quadrants (multicentric disease), previous chest wall irradiation, pregnancy, the presence of severe collagen vascular disease (e.g., scleroderma), and the lack of access to a radiation therapy facility.

Partial Mastectomy

Partial mastectomy—also referred to as wide local excision or lumpectomy—involves excision of all cancerous tissue to microscopically clear margins. Although 1 cm margins are the goal, many surgeons consider 2 mm margins to be adequate for reducing the risk of local recurrence.⁵⁷ Hence, reexcision is indicated whenever margins are either positive or too close (< 2 mm). Partial mastectomy is commonly performed with the patient under local anesthesia, with or without sedation. The addition of an axillary staging procedure (a common event) usually necessitates general anesthesia, but in select circumstances, local or epidural anesthesia may suffice.

OPERATIVE TECHNIQUE

An incision is placed directly over the lesion to minimize tunneling through breast tissue; it should be oriented so as to be included within a subsequent mastectomy incision if margins prove positive. As with open biopsy (see above), curvilinear incisions have been the standard, but radial incisions are now being advocated by some surgeons, particularly for upper outer, medial, lateral, and inferior lesions. A radial incision facilitates excision of tumors that extend in a ductal distribution, preserves the contour of the breast, and permits easier reexcision if margins prove positive [see *Figure 4b*]. With current oncoplastic techniques,^{58,59} lesions in the central, medial, or superior portions of the breast can be resected with minimal cosmetic deformity [see *Figure 4, c, d, e, and f*]. Resection of a portion of the overlying skin is not necessary unless the lesion is extremely superficial.

To obtain clear margins, a 1 to 1.5 cm margin of normal-appearing tissue should be removed beyond the edge of the palpable tumor or, if excisional biopsy has already been performed, around the biopsy cavity. In the case of nonpalpable lesions diagnosed by means of CNB, wire localization is performed, and 2 to 3 cm of tissue should be excised around the wire to obtain an adequate margin. Intraoperative ultrasonography may reduce the rate of positive margins by allowing visualization of the tumor edge or the previous biopsy site.⁶⁰

The specimen should be oriented by the surgeon and the margins inked by the pathologist; this orientation is useful if reexcision is required to achieve clean margins. Reexcision of any close (< 2 mm) margins may be performed during the same surgical procedure if the specimen margins are assessed immediately by the pathologist. If the specimen was not oriented, the entire biopsy cavity should be reexcised. Surgical clips may be left in the lumpectomy site to help the radiation oncologist plan the radiation boost to the tumor bed or to direct partial-breast irradiation. In the closure of the incision, hemostasis should be meticulous: a hematoma may delay adjuvant therapy. Deep breast tissue should be approximated only if such closure does not result in significant deformity of breast contours. A cosmetic subcuticular closure is preferred.

Wearing a support bra during the day and night can reduce shearing of fragile vessels.¹⁵

ACCELERATED PARTIAL-BREAST IRRADIATION WITH BALLOON CATHETER

Historically, whole-breast irradiation has been the standard treatment to reduce the risk of local recurrence after BCT. Long-term follow-up of patients who have received BCT demonstrates, however, that only 1 to 3% of recurrences within the breast arise at a significant distance from the primary cancer site (i.e., in other breast quadrants); the remainder develop near the original biopsy site.^{57,61} These data provide the rationale for the approach known as accelerated partial-breast irradiation (APBI), in which a shortened course of high-dose radiation is delivered to the tissue surrounding the lumpectomy cavity (the region theoretically at greatest risk). Decreasing the volume of tissue receiving radiation therapy allows for patients to undergo a shorter course of therapy (approximately 1 week).⁶² Several different APBI techniques have been developed, including placement of interstitial catheters, use of a localized external beam, single-dose intraoperative treatment, implantation of radioactive beads or seeds, and insertion of a balloon catheter into the lumpectomy site. Although long-term follow-up has not been carried out, the short-term results reported for some APBI techniques indicate that in most centers, recurrence rates have been low, with good cosmesis and only mild chronic toxicity.⁶³

The technique of APBI can be illustrated by considering the MammoSite Radiation Therapy System (Cytac Corp., Palo Alto, California), in which a balloon catheter is inserted into the surgical cavity after lumpectomy to provide partial-breast irradiation (see below). Although the catheter may also be inserted at the time of the original operation, it is preferable to wait for final pathologic evaluation to confirm clear margins; if the catheter is inserted and margins are found to be positive, it will have to be replaced (a costly process). The optimal time for insertion of the APBI balloon is within 2 to 3 weeks from the final procedure. Postoperative insertion may be done either percutaneously under ultrasonographic guidance or by means of an open technique. Once the catheter is in place, a radiation source (iridium 192) is delivered into the balloon via a high-dose rate remote afterloader.

Technique

For safe and effective delivery of radiotherapy through the MammoSite balloon catheter, the lumpectomy cavity must be able to conform its shape to that of an ovoid or spherical catheter without significant air pockets, able to accommodate a volume of at least 30 mL (the volume of the smallest available balloon), and able to maintain a minimum distance of 7 mm from the skin with the catheter in place. In addition, if a percutaneous technique is being considered, the surgeon should be comfortable with ultrasonography (which will be employed for initial visualization of the lumpectomy cavity). If the above criteria seem reasonably attainable, one may proceed with a percutaneous approach [see Figure 9].

Percutaneous approach A site peripheral to the scar is chosen as the entry site for the balloon catheter, and a local anesthetic is injected along the proposed catheter tract.

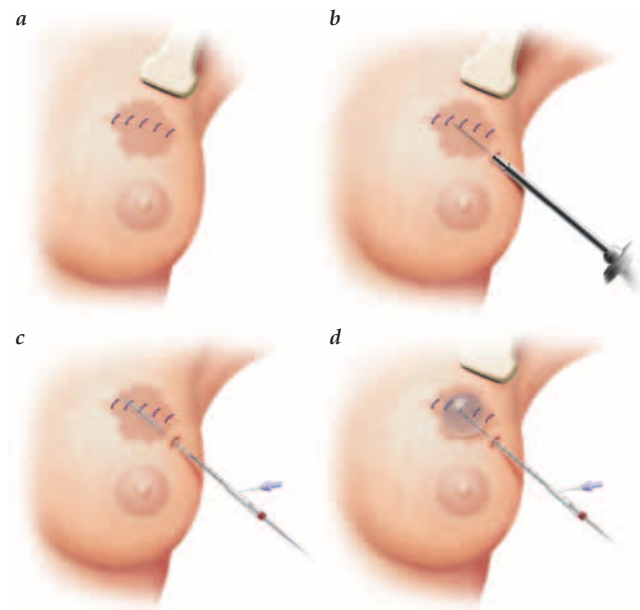


Figure 9 Accelerated partial-breast irradiation with balloon catheter. (a) The lumpectomy cavity is evaluated by means of ultrasonography. (b) The trocar is inserted through a separate entry site under ultrasonographic guidance. (c) The uninflated balloon catheter is advanced through the trocar path. (d) Under ultrasonographic visualization, the balloon is inflated with saline or contrast material. An anterior distance of at least 7 mm between the catheter and the chest wall or skin is confirmed.

A trocar (supplied with the insertion kit) is inserted into the cavity via the peripheral entry site and then removed. Removal of the trocar allows for the evacuation of the postlumpectomy seroma and prevents underdosage of tissue around the cavity. The shape of the cavity and skin-to-cavity distance are visualized by means of ultrasonography, and a catheter of appropriate shape (ovoid or spherical) and volume (30 to 65 mL) is advanced through the newly formed tract. Saline is then infiltrated to inflate the catheter balloon to the maximum volume that the cavity can accommodate. A small amount of radiographic contrast may also be infused to aid in visualization. The cavity is then reimaged to confirm that the catheter is an adequate distance (7 mm) from the skin. If the distance is inadequate, the balloon volume is reduced. If it is not possible to keep the catheter at least 7 mm from the skin while maintaining a balloon volume of at least 30 mL, conversion to an open approach is indicated.

Open approach The cavity is reopened through the original skin incision. Occasionally, a thick rind may form around the residual seroma; this rind may be excised to reduce tension and increase the volume of the cavity. If necessary, the anterior skin may be excised in the form of an ellipse to provide improved anterior coverage of the catheter, and the subcutaneous tissue may be pulled together over the catheter and the cavity to help ensure adequate coverage and sufficient distance from the skin. A peripheral site is chosen for insertion of the catheter. After the skin is closed, ultrasonography is employed to confirm that the distance from the

skin is adequate. A topical antibiotic is applied at the insertion site; no anchoring stitch is necessary. Correct positioning of the catheter is confirmed by a postplacement treatment-planning computed tomographic (CT) scan that is evaluated by the radiation oncologist.

Mastectomy

The goal of a mastectomy is to remove all breast tissue—including the nipple, the areola, and the pectoral fascia—while leaving viable skin flaps and a smooth chest wall for application of prosthesis. This should be the objective whether the mastectomy is performed for cancer treatment or for prophylaxis. Skin-sparing mastectomy (SSM) performed in conjunction with immediate reconstruction is discussed elsewhere [see Breast Reconstruction, *below*]. Proper skin incisions and good exposure are the key components of a well-performed mastectomy. Mastectomy usually calls for general anesthesia, but it may be performed with thoracic epidural anesthesia or local anesthesia in select circumstances.

OPERATIVE TECHNIQUE

The traditional mastectomy incision is an elliptical one that is placed either transversely across the chest wall or at an upward angle toward the axilla. It should be fashioned in such a way as to include the nipple-areola complex and any incision from a previous biopsy [see Figure 10a]. Ideally, the upper and lower skin flaps should be of similar length so that there is no redundant skin on either flap. The outline of the incision may be established by using the following five steps:

1. The lateral and medial end points are marked.
2. The breast is pulled firmly downward.
3. To define the path of the upper incision, a straight line is drawn from one end point to the other across the upper surface of the breast.
4. The breast is pulled firmly upward.
5. To define the path of the lower incision, a straight line is drawn from one end point to the other across the lower surface of the breast.

The outlined incision is then checked to confirm that it can be closed without either undue tension or redundant skin. Dog-ears or lateral skin folds can be prevented by extending the incision medially or laterally to remove all the skin that contributes to the forward projection of the breast. The closure should be fairly snug intraoperatively while the arm is extended; significant slack will be created when the arm is returned to the patient's side. The medial and lateral end points of the incision may be adjusted upward or downward to include any previous biopsy incisions.

As noted [see Partial Mastectomy, *above*], there is increasing acceptance of the use of radial and oncoplastic incisions for BCT. In a small percentage of women, persistently positive margins may dictate conversion from BCT to mastectomy. In large-breasted women with excess breast skin, traditional elliptical incisions can easily incorporate any previous radial or superior-pole oncoplastic incisions that may have been performed [see Figure 10b]. In smaller-breasted women, however, sigmoid, modified Wise, or other oncoplastic mastectomy incisions may be needed to incorporate previous lumpectomy incisions [see Figure 10c].

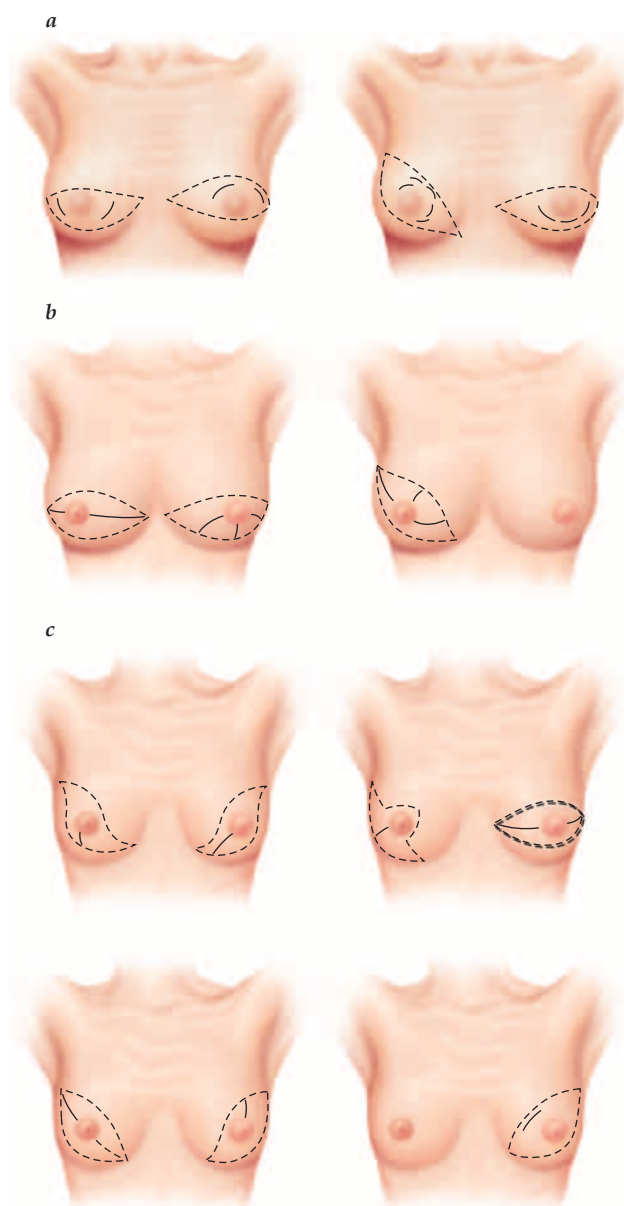


Figure 10 Mastectomy incisions. (a) Elliptical incisions incorporate traditional lumpectomy incisions. (b) In large-breasted women with excess breast skin, traditional ellipses can easily incorporate previous radial and superior-pole oncoplastic incisions. (c) In smaller-breasted women, sigmoid, modified Wise, or other oncoplastic mastectomy incisions may be needed to incorporate previous radial lumpectomy incisions.

Once the incision is made, the next step is to create even and viable flaps. In most patients, there is a fairly well-defined avascular plane between subcutaneous fat and breast tissue. This plane is identified by pulling the edges of the incision upward with skin hooks and beginning a flap that is 8 to 10 mm thick. After an initial release of the skin edge, the desired plane is developed by applying firm tension downward on the breast tissue and away from the skin at a 45° angle. The fine fibrous attachments between breast tissue and subcutaneous fat (Cooper ligaments) are then divided

with the electrocautery or a blade, and crossing vessels are coagulated or ligated as they appear. To protect both arterial supply to and venous drainage from the skin flap, one must refrain from excessive ligation or cauterization of vessels on the flap. For most women, flap viability is not an issue. For diabetics, smokers, and other patients with diffuse small vessel disease, however, it is a serious consideration. In such patients, flaps should be no longer than necessary with no excess tension, and extra care should be taken to preserve flap vessels. Patients should be warned that even with these measures, there may be some skin necrosis along the incision. Such necrosis is best treated with gradual débridement of the eschar.

Flaps are raised superiorly to the clavicle, medially to the sternum, inferiorly to the inframammary fold, and laterally to the border of the latissimus dorsi. The pectoral fascia is incised both superiorly and medially. Inferiorly, the fascia of the abdominal muscles is not divided. The pectoralis major, the abdominal muscles, and the anterior serratus muscle form the deep border of the dissection. The pectoral fascia is removed with the breast specimen and may be separated from the muscle with either the electrocautery or a blade.

In a simple mastectomy, the dissection proceeds around the lateral edge of the pectoralis major but stops before entering the axillary fat pad (unless the procedure is being done in conjunction with SLNB). A single closed suction drain is placed through a separate lateral stab wound in such a way that it extends under the lower flap and a short distance upward along the sternal border of the dissection.

A modified radical mastectomy essentially consists of an axillary node dissection added to a simple mastectomy. At the lateral edge of the dissection, the border of the latissimus dorsi is exposed, as is the lateral border of the pectoral muscle. Retraction of these two muscles provides excellent exposure for the axillary dissection [see Axillary Dissection, *below*]. Some surgeons prefer to remove the breast from the chest wall first, whereas others leave the breast attached to provide tension for the axillary dissection. On completion of the procedure, two closed suction drains are placed, one in the axilla and another under the lower flap and extending to the midline.

After either a simple or a modified radical mastectomy, the skin is closed and a dressing applied according to the surgeon's preference. Early arm mobilization is encouraged.

SKIN-SPARING MASTECTOMY

SSM, which consists of resection of the nipple-areola complex, any existing biopsy scar, and the breast parenchyma, followed immediately by breast reconstruction, has become an increasingly popular approach for women requiring mastectomy.⁶⁴ With this approach, the inframammary fold and contour of the breast are preserved, and a generous skin envelope remains in situ for reconstruction; cosmetic results are thereby optimized. In addition, SSM is oncologically safe and is not associated with an increased incidence of local recurrence.⁶⁵ The recurrences that do occur typically develop below the skin flaps and thus are easily detectable; deep recurrences beneath the reconstruction are comparatively uncommon.

The incision for SSM with immediate reconstruction should be planned in collaboration with the plastic surgeon [see Figure 11], and the inframammary fold should be marked

preoperatively with the patient in a sitting position. Several options are available for SSM. For CNB-diagnosed tumors that are not superficial, a circumareolar incision may be employed, with a lateral extension for exposure if necessary. Different incisions may be used if it proves necessary to incorporate previous incisions or to remove skin anterior to superficial tumors. A separate axillary incision may be useful when axillary dissection or SLNB is being performed. CNB sites generally are not included in the excised skin segment; the surgeon may opt to excise them through a separate skin ellipse. Intraoperatively, flaps are created in a circular fashion to optimize exposure. Although optimal cosmesis is part of the rationale for SSM, cosmetic considerations should never be allowed to compromise the extent of the dissection in any way.

NIPPLE-SPARING MASTECTOMY

Following mastectomy or SSM, many patients report dissatisfaction with the reconstruction of their nipple areolar complex using skin grafting or tattooing. Nipple-sparing mastectomy (NSM) eliminates the need for reconstruction by preservation of the dermis and epidermis of the nipple-areola complex during the initial procedure. Several initial studies have shown NSM to be an oncologically safe procedure in those patients appropriately selected.⁶⁶⁻⁷¹ Contraindications to NSM include larger tumors (> 2 cm), centrally located lesions with a small tumor-to-nipple distance, and lymphovascular invasion.⁷²

Several types of incisions have been described, including periareolar with lateral extension, transareolar with lateral extension, and inframammary fold incisions. These typically allow for good exposure and dissection of the retroareolar structures.⁷³ Elevation of the areola off of the breast parenchyma should be performed with sharp dissection to prevent thermal injury to the nipple from electrocautery. The lactiferous ducts are transected at the base of the nipple papilla. Skin flaps are raised in a manner similar to that of SSM or conventional mastectomy. On removal of the subcutaneous breast, the remaining nipple tissue is removed with sharp dissection. A small (2 to 3 mm) rim of peripheral subcutaneous tissue should be preserved behind the nipple to prevent partial or complete nipple necrosis. Pathologic evaluation of the excised lactiferous ducts for tumor involvement is imperative

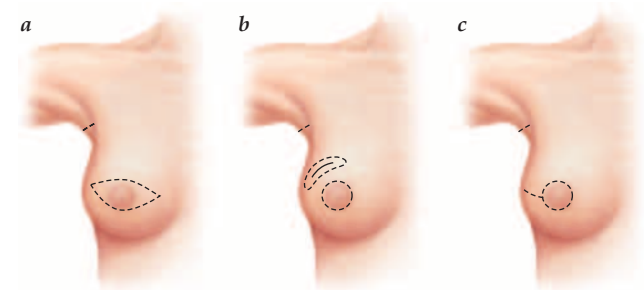


Figure 11 Shown is (a) the recommended placement of the traditional circumareolar incision for skin-sparing mastectomy. (b) Separate incisions may be used to excise previous lumpectomy incisions or to gain access to the axilla. (c) A lateral extension can provide further exposure for flap development or axillary staging.

and mandates complete removal of the nipple if in situ or invasive disease is present.

One of the most concerning complications to NSM includes nipple or areolar necrosis, which not only negatively impacts cosmesis but can cause loss of the reconstructed implant. Additional complications include lack of sensation to the nipple, change in nipple pigmentation, and improper nipple positioning following reconstruction.⁷⁴ Currently, long-term follow-up to investigate local recurrence rates for NSM is lacking. However, NSM appears to be a good option for those patients undergoing prophylactic mastectomy or those with small, peripheral tumors or in situ disease.

Lymphatic Mapping and SLNB

The pathologic status of the axillary nodes is the single most important prognostic factor for outcome after treatment of breast cancer. The growing recognition of the morbidity of traditional axillary dissection (lymphedema and sensory deficits), together with the increased capability of mammography to detect smaller, potentially node-negative invasive breast cancers, has given rise to the development of SLNB as an axillary staging procedure. SLNB is a minimally invasive means of identifying the first node or nodes draining the breast and hence the first node or nodes to which tumor may spread. In experienced hands, a negative SLNB reliably predicts a tumor-free axilla (false negative rate, 5 to 9%); therefore, when such a result is obtained, no further nodes need to be removed and the patient can be spared the morbidity of a traditional axillary node dissection.⁷⁵⁻⁷⁷ Surgeons competent in SLNB should be able to identify the SLN with at least 90% accuracy and a false negative rate lower than 5%.⁷⁸ It is recommended that surgeons first learning the technique use axillary dissection as a backup for the first 20 procedures to gain experience in identifying the SLN. Currently, axillary dissection is recommended for patients who have a positive SLN; however, prospective, randomized trials are required to determine the extent to which this step is necessary in SLN-positive patients.

The most common method of identifying the SLN involves injection of both a vital blue dye and a radionuclide.⁷⁹⁻⁸² The radionuclide is first injected into the subareolar lymphatic plexus, either preoperatively or, in some centers, intraoperatively.⁸⁰ Because the breast and its overlying skin drain to the same few SLNs,⁸² peritumoral, intradermal, and subareolar injections are all acceptable approaches; subareolar injection has the advantage of being expeditious and accurate in cases of multicentric (as well as unicentric) disease.⁷⁹ The vital blue dye is then injected, commonly in the subareolar plexus, and the breast is massaged for 5 minutes to stimulate lymphatic flow. Lymph nodes that are “hot” (i.e., radioactive), blue, or both, as well as palpable nodes, are removed for evaluation by frozen-section analysis or touch-print cytology.

SLNB has also been employed in DCIS patients, but, in general, its use should be limited to patients with extensive DCIS who are undergoing mastectomy (in the event of occult invasive disease). Some investigators recommend SLNB for patients with extensive DCIS who are undergoing BCT (in whom CNB may have missed an area of invasion),⁸³ whereas others caution against this practice.^{84,85} Results from

the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial suggest that in patients undergoing neoadjuvant therapy, SLNB may be performed either before or after therapy, with no significant differences in identification and false negative rates⁸⁶; however, this suggestion is not universally accepted.⁸⁷ Contraindications to SLNB include the presence of clinically positive axillary nodes, previous axillary surgery, and pregnancy or lactation. Large or locally advanced breast cancers commonly give rise to a positive SLN but are not a contraindication to the procedure in that some patients may still be spared the morbidity of a full axillary dissection.

Axillary Dissection

Before the advent of SLNB, axillary dissection was routinely performed in breast cancer patients. It provided prognostic information that guided subsequent adjuvant therapy, afforded excellent local control, and may have contributed a small overall survival benefit.

Axillary dissection includes resection of level I and level II lymph nodes [see Figure 12a].⁸⁸ The superior border of the dissection is formed by the axillary vein; the lateral border of the dissection is formed by the latissimus dorsi; the medial border is formed by the pectoral muscles and the anterior serratus muscle; and the inferior border is formed by the tail of the breast. Level II nodes are easily removed by retracting the pectoralis major and the pectoralis minor medially; it is not necessary to divide or remove the pectoralis minor. Level III nodes are not removed unless palpable disease is present.

Axillary dissection, either alone or in conjunction with lumpectomy or mastectomy, usually calls for general anesthesia, but it may be performed with thoracic epidural anesthesia. To facilitate identification and preservation of motor nerves within the axilla, the anesthesiologist should refrain from using neuromuscular blocking agents. In the absence of neuromuscular blockade, any clamping of a motor nerve or too-close approach to a motor nerve with the electrocautery will be signaled by a visible muscle twitch.

STRUCTURES TO BE PRESERVED

A number of vascular structures and nerves passing through the axilla must be preserved during axillary dissection [see Figure 12b]. These structures include the axillary vein and artery; the brachial plexus; the long thoracic nerve, which innervates the anterior serratus muscle; the thoracodorsal nerve, artery, and vein, which supply the latissimus dorsi; and the medial pectoral nerve, which innervates the lateral portion of the pectoralis major.

The axillary artery and the brachial plexus should not be exposed during axillary dissection. If they are, the dissection has been carried too far superiorly, and proper orientation at a more inferior position should be established. In some patients, there may be sensory branches of the brachial plexus superficial (and, rarely, inferior) to the axillary vein laterally near the latissimus dorsi; injury to these nerves results in numbness extending to the wrist. To prevent this complication, the axillary vein should initially be identified medially, under the pectoralis major. Medial to the thoracodorsal nerve and adherent to the chest wall is the long thoracic nerve of

Bell. The medial pectoral nerve runs from superior to the axillary vein to the undersurface of the pectoralis major, passing through the axillary fat pad and across the level II nodes; it has an accompanying vein whose blue color may be used to identify the nerve. If a submuscular implant reconstruction [see Breast Reconstruction, *below*] is planned, preservation of the medial pectoral nerve is especially important to prevent atrophy of the muscle.

The intercostobrachial nerve provides sensation to the posterior portion of the upper arm. Sacrificing this nerve generally leads to numbness over the triceps region. In many women, the intercostobrachial nerve measures 2 mm in diameter and takes a fairly cephalad course near the axillary vein; when this is the case, preservation of the nerve will not interfere with node dissection. Sometimes, however, the nerve is tiny, has multiple branches, and is intermingled with nodal tissue that should be removed; when this is the case, one should not expend a great deal of time on attempting to preserve the nerve. If the intercostobrachial nerve is sacrificed, it should be transected with a knife or scissors rather than with the electrocautery, and the ends should be buried to reduce the likelihood of postoperative causalgia.

OPERATIVE TECHNIQUE

The incision for axillary dissection should be a transverse or curvilinear one made in the lower third of the hair-bearing skin of the axilla. For cosmetic reasons, it should not extend anteriorly onto the pectoralis major; however, it may be

extended posteriorly onto the latissimus dorsi as necessary for exposure. Skin flaps are raised to the level of the axillary vein and to a point below the lowest extension of hair-bearing skin, either as an initial maneuver or after the initial identification of key structures.

The key to axillary dissection is obtaining and maintaining proper orientation with respect to the axillary vein, the thoracodorsal bundle, and the long thoracic nerve. After the incision has been made, the dissection is extended down into the true axillary fat pad through the overlying fascial layer. The fat of the axillary fat pad may be distinguished from subcutaneous fat on the basis of its smoother, lipomalike texture. There may be aberrant muscle slips from the latissimus dorsi or the pectoralis major; in addition, there may be an extremely dense fascial encasement around the axillary fat pad. It is important to divide these layers early in the dissection. The borders of the pectoralis major and the latissimus dorsi are then exposed, which clears the medial and lateral borders of the dissection.

The axillary vein and the thoracodorsal bundle are identified next. As discussed (see above), the initial identification of the axillary vein should be made medially, under the pectoralis major, to prevent injury to low-lying branches of the brachial plexus. Sometimes, the axillary vein takes the form of several small branches rather than a single large vessel. If this is the case, all of the small branches should be preserved.

The thoracodorsal bundle may be identified either distally at its junction with the latissimus dorsi or at its junction with the axillary vein. The junction with the latissimus dorsi is

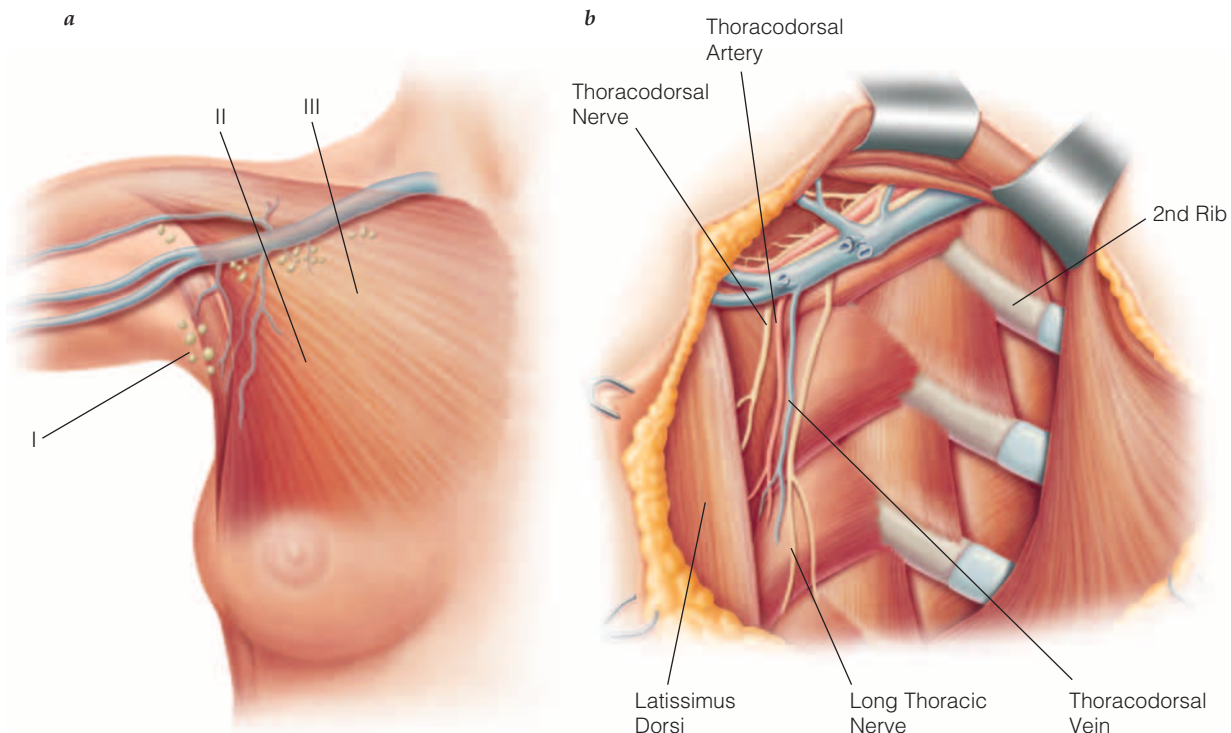


Figure 12 Axillary dissection.⁸⁸ (a) Shown are axillary lymph node levels in relation to the axillary vein and the muscles of the axilla (I = low axilla, II = midaxilla, III = apex of axilla). (b) Shown is a view of the structures of the axilla after completion of axillary dissection.

within the axillary fat pad at a point two thirds of the way down the hair-bearing skin of the axilla, or approximately 4 cm below the inferior border of the axillary vein. Occasionally, the thoracodorsal bundle is bifurcated, with separate superior and inferior branches entering the latissimus dorsi; this is particularly likely if the entry point appears very high. If the bundle is bifurcated, both branches should be preserved. The thoracodorsal bundle may be identified at its junction with the latissimus dorsi by spreading within axillary fat parallel to the border of the muscle and looking for the blue of the thoracodorsal vein. Identification is also facilitated by lateral retraction of the latissimus dorsi. The long thoracic nerve lies just medial to the thoracodorsal bundle on the chest wall at this point and at approximately the same anterior-posterior position. It may be identified by spreading tissue just medial to the thoracodorsal bundle and then running the index finger perpendicular to the course of the long thoracic nerve on the chest wall to identify the cordlike nerve as it moves under the finger. Once the nerve is identified, axillary tissue may be swept anteriorly away from the nerve by blunt dissection along the anterior serratus muscle; there are no significant vessels in this area.

The junction of the thoracodorsal bundle with the axillary vein is 1.5 to 2.0 cm medial to the point at which the axillary vein crosses the latissimus dorsi. The thoracodorsal vein enters the posterior surface of the axillary vein, and the nerve and the artery pass posterior to the axillary vein. Generally, one or two scapular veins branch off the axillary vein medial to the junction with the thoracodorsal vein. These are divided during the dissection and should not be confused with the thoracodorsal bundle.

The axillary vein and the thoracodorsal bundle having been identified, the pectoralis major is retracted medially at the level of the axillary vein, and the latissimus dorsi is retracted laterally to place tension on the thoracodorsal bundle. Once this exposure is achieved, the axillary fat and the nodes are cleared away superficial and medial to the thoracodorsal bundle to the level of the axillary vein. Superiorly, dissection proceeds medially along the axillary vein to the point where the fat containing level II nodes crosses the axillary vein. To improve exposure, the fascia overlying the level II extension of the axillary fat pad should be incised to release tension and expose the lipomale level II fat. As noted [*see Structures to Be Preserved, above*], the medial pectoral nerve passes onto the underside of the pectoralis major in this area and should be preserved. One or more small venous branches may pass inferiorly from the medial pectoral bundle; particular attention should be paid to preserving the nerve when ligating these venous branches.

The next step in the dissection is to reflect the axillary fat pad inferiorly by dividing the medial attachments of the axillary fat pad along the anterior serratus muscle. Care must be taken to preserve the long thoracic nerve. Because there are no significant vessels or structures in the tissue anterior to the long thoracic nerve, this tissue may be divided sharply, with small perforating vessels either tied or cauterized. Finally, the axillary fat is freed from the tail of the breast with the electrocautery or a knife.

There is no need to orient the axillary specimen for the pathologist, because treatment is not affected by the anatomic

level of node involvement. A closed suction drain is placed through a separate stab wound. (Some practitioners prefer not to place a drain and simply aspirate postoperative seromas as necessary.) A long-acting local anesthetic may be instilled into the axilla—a particularly helpful practice if the dissection was done as an outpatient procedure.

Breast Reconstruction

The vast majority of women undergoing a partial or complete mastectomy are candidates for breast reconstruction and should be offered a plastic surgery consultation before undergoing definitive surgical treatment. Reconstruction is covered by insurance and may be done either at the time of the oncologic surgery (immediate reconstruction) or as a delayed procedure (delayed reconstruction). Despite early concerns and debate, studies show that neither mode of reconstruction interferes with detection of recurrent disease nor does it significantly delay subsequent adjuvant therapy.

REPAIR OF PARTIAL MASTECTOMY DEFECTS (ONCOPLASTY)

Recently, there has been an increase in the proportion of breast cancer patients treated with partial mastectomy followed by radiation therapy, an approach referred to as BCT. This trend is in part attributable to increased mammographic screening that has led to the detection of earlier breast cancers and the use of neoadjuvant chemotherapy, where significant clinical responses can obviate the need for a traditional mastectomy. Alarming, 20 to 30% of patients who undergo BCT report having a poor cosmetic result in the treated breast.⁸⁹

The term *oncoplasty* has been used to describe techniques to improve the cosmesis of the breast after oncologic resection. Techniques integral to plastic surgery are often incorporated and include local tissue rearrangement, purse-string defect closure, breast reduction techniques, local pedicled flaps, and lower abdominal flaps.^{89,90} The ultimate goal is to obtain a natural-appearing breast with improved cosmesis compared to partial mastectomy alone.

REPAIR OF MASTECTOMY DEFECTS

Options for breast reconstruction continue to evolve and include, but are not limited to, implants with or without tissue expansion, the transverse rectus abdominis myocutaneous (TRAM) flap, the latissimus dorsi myocutaneous flap, and various other free flaps. Patient preference and lifestyle, the availability of suitable autologous tissue, and the demands imposed by additional cancer therapies are variables that can influence the timing and choice of the optimal reconstructive technique [*see Figure 13*].

If the need for postmastectomy radiation therapy is definite or unclear at the time of mastectomy (i.e., final pathology results are not available), a delayed reconstruction may be chosen because of an increased risk of complications related to the reconstructed breast. An expander is typically placed at the time of mastectomy to preserve the breast skin envelope, and the definitive reconstructive plan is formulated once the final pathologic results have become available and the radiation therapy has been completed.⁹¹

RECONSTRUCTION OPTIONS

Prosthetic Implants

The simplest method of reconstruction is to place a saline- or silicone-filled implant beneath the pectoralis major. However, even after SSM, the pectoralis major is usually so tight that expansion of this muscle and the overlying skin is necessary before an implant that matches the opposite breast can be inserted. A tissue expander is typically placed and serial expansions are performed on an outpatient basis until an appropriate-size breast pocket has been attained. The time required to complete the expansion process usually ranges from 3 to 6 months after mastectomy and is dependent mostly on the desired breast size, the thickness of the mastectomy skin flaps, and the patient's ability to tolerate the expansion.⁹² A second operative procedure is then required to exchange the expander for a permanent implant. The nipple-areolar complex is constructed at a later date. AlloDerm (LifeCell Corp., Branchburg, New Jersey) and Flex HD (MTF, Edison,

New Jersey) are acellular dermal matrices derived from human cadaver skin that may be sewn to the pectoralis muscle and the inframammary fold to reinforce the lower pole of the breast and enlarge the breast pocket so that it may accommodate a tissue expander or implant.⁹³ This measure may reduce postoperative pain and improve cosmesis, as well as facilitate immediate implant placement in smaller-breasted women. Porcine-derived dermal matrices are also available and may be used as an alternative to the aforementioned.

The major advantages of implant reconstruction are reduced operative time, faster recuperation, and a reasonably good cosmetic outcome. These advantages must be weighed against the fact that this method is a two-stage approach and that obtaining symmetry with the contralateral native breast can be difficult and often requires a mastopexy (breast lift) with or without an implant augmentation.⁹⁴ The cosmetic result may also deteriorate over time as a consequence of capsule formation or implant migration, resulting in replacement of the implant each decade.

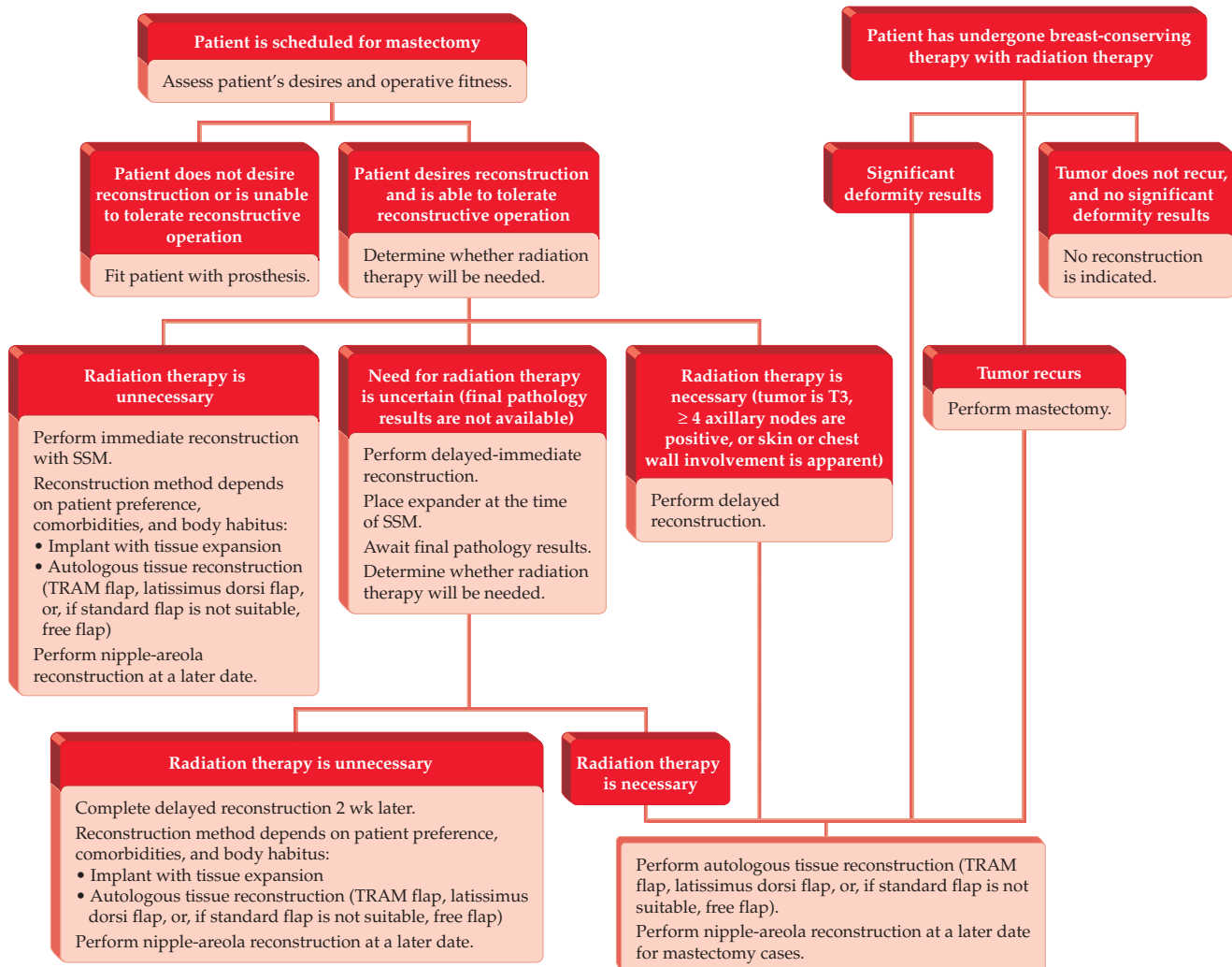


Figure 13 Algorithm outlining the major steps in breast reconstruction after mastectomy. SSM = skin-sparing mastectomy; TRAM = transverse rectus abdominis myocutaneous.

Autologous Tissue

An alternative approach to reconstruction that continues to evolve is the transfer of vascularized muscle, skin, fat, or a combination of these from a donor site to the mastectomy defect. The transferred tissue may be relocated either on a vascular pedicle or as a free tissue transfer requiring a microsurgical anastomosis. Although autologous tissue procedures can be lengthy and are associated with a longer recovery period, they often require fewer revision and symmetry procedures.⁹⁵ With autologous tissue reconstruction, it is possible to create a natural-appearing breast without the need for a breast implant, often sparing the patient a contralateral breast procedure to obtain symmetry.⁹⁴ The most commonly used pedicled myocutaneous flaps are the TRAM flap [see Figure 14] and the latissimus dorsi flap [see Figure 15]. Recent advances have led to the conception of perforator flaps such as the deep inferior epigastric perforator (DIEP) flap and the superficial inferior epigastric artery (SIEA) flap, which allow for safe and reliable tissue transfer with minimal donor-site morbidity.

The major advantage of autologous tissue reconstruction is that it generally yields a superior cosmetic result and provides variability in breast volume and shape⁹⁶; in addition, the reconstructed breast has a softer, more natural texture than a breast that has undergone implant reconstruction. The main drawbacks are the magnitude of the surgical procedure (involving both a prolonged operating time and longer inpatient hospitalization), the potential need for blood transfusion, and the morbidity related to the donor site. Smokers and patients with significant vascular disease may not be ideal candidates for autologous tissue reconstruction. Partial necrosis of the transferred flap may create firm areas; on rare occasions, complete necrosis and consequent loss of the flap can occur.

Pedicled myocutaneous flaps In a pedicled TRAM flap reconstruction, the contralateral rectus abdominis is transferred along with overlying skin and fat based on the superior epigastric vessels to create a breast mound. This procedure yields a flatter abdominal contour but calls for a long transverse abdominal incision and necessitates repositioning of the umbilicus. The major advantages of TRAM flap reconstruction are that it provides enough tissue to match most contralateral breasts and that it offers the option of performing bilateral TRAM flap procedures in healthy candidates who desire or require bilateral reconstruction. Patients who have undergone abdominal procedures that compromise the TRAM flap's vascular supply are not ideal candidates for TRAM reconstruction. Postoperative discomfort is greater with TRAM flap reconstruction than with other flap reconstructions because of the extent of the abdominal wall dissection and defect.

In a pedicled latissimus dorsi myocutaneous flap reconstruction, the ipsilateral latissimus dorsi is transferred along with overlying skin and fat based on the thoracodorsal vessels to create a breast mound. The operative technique for the latissimus dorsi flap reconstruction is complex, requiring intraoperative changes in patient position (unless the oncologic surgeon is willing to perform the mastectomy with the patient in a lateral decubitus position). Patients who have undergone irradiation of the breast, the chest wall, or the axilla (including irradiation of the thoracodorsal vessels) may not be eligible for this procedure. A major advantage of the latissimus dorsi flap is that its donor site is associated with less postoperative discomfort than the abdominal donor site of the TRAM flap. In addition, transfer of the latissimus dorsi results in substantially less functional impairment than transfer of the rectus abdominis. One major drawback is that in many women, the latissimus dorsi is not bulky enough to

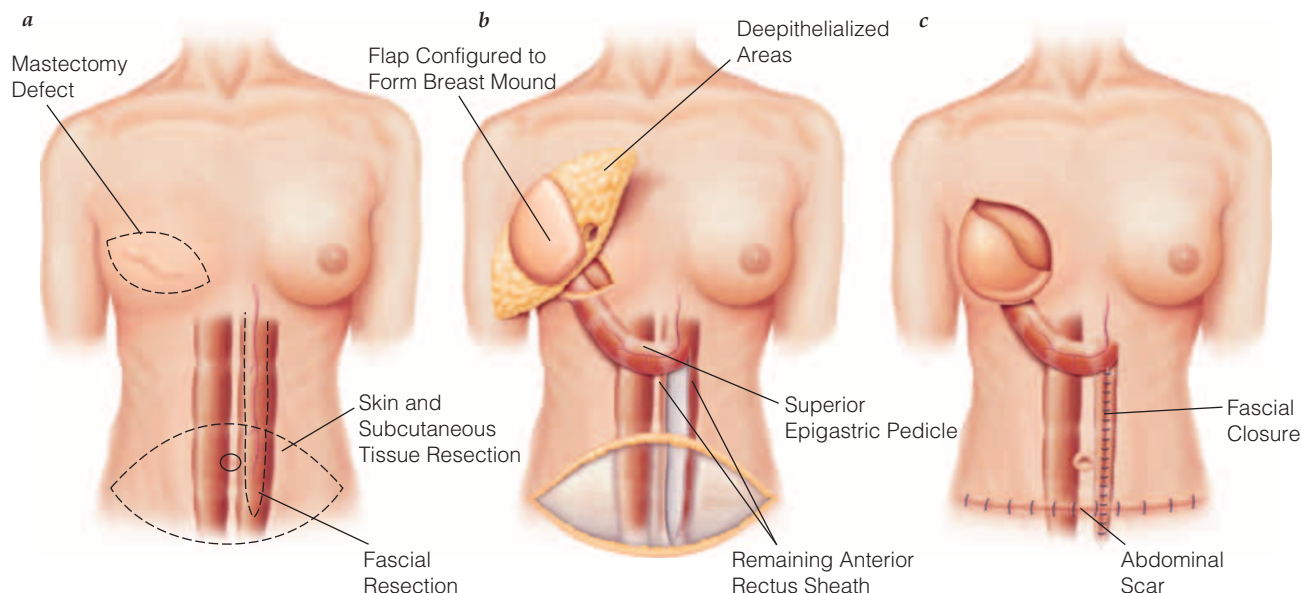


Figure 14 Breast reconstruction after mastectomy: transverse rectus abdominis myocutaneous (TRAM) flap. (a) The infraumbilical flap is designed. The TRAM flap is tunneled subcutaneously into the chest wall cavity. Blood supply to the flap is maintained from the superior epigastric vessels of the rectus abdominis. (b) Subcutaneous fat and deepithelialized skin are positioned under the mastectomy flaps as needed to reconstruct the breast mound. (c) The fascia of the anterior rectus sheath is approximated to achieve tight closure of the abdominal wall defect and to prevent hernia formation. The umbilicus is sutured into its new position.

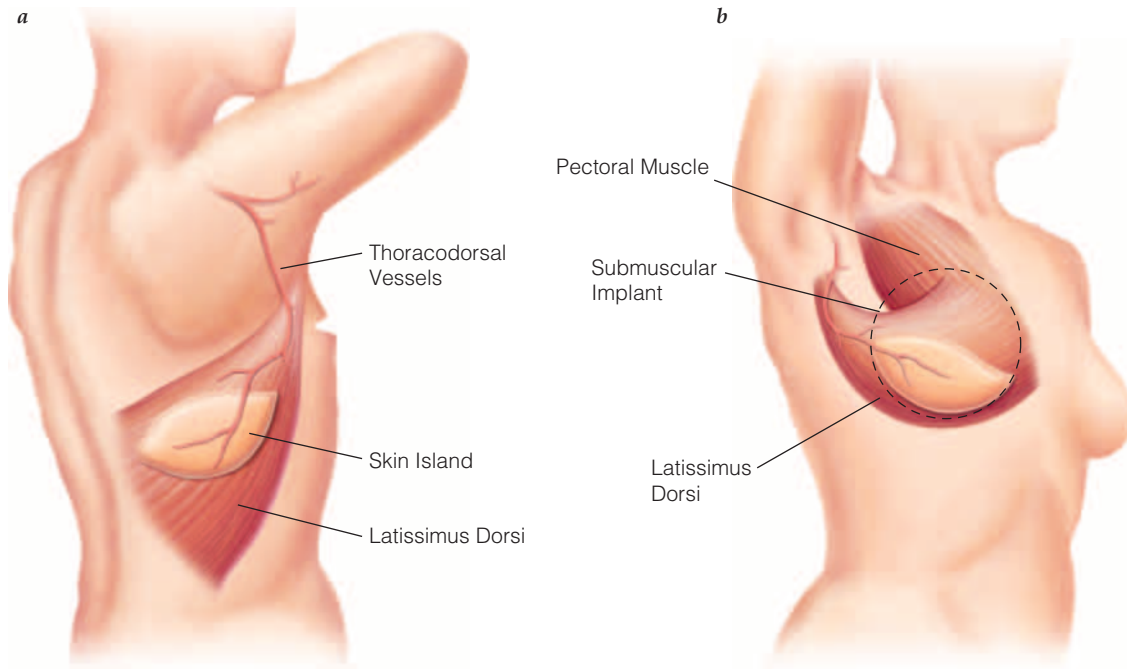


Figure 15 Breast reconstruction: latissimus dorsi flap Breast reconstruction after mastectomy: latissimus dorsi myocutaneous flap with submuscular implant. With this flap, addition of an implant is often required to provide the reconstructed breast with adequate volume and projection. (a) The myocutaneous flap is elevated; it is important to maintain the blood supply to the flap from the thoracodorsal vessels. The flap is tunneled subcutaneously to the mastectomy defect. (b) The latissimus dorsi is sutured to the pectoralis major and the skin of the inframammary fold so that the implant is completely covered by muscle.

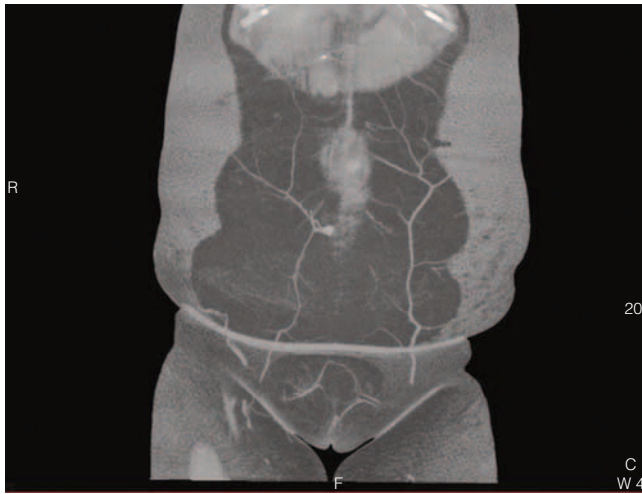


Figure 16 Preoperative computed tomographic angiography of the inferior epigastric arterial system, the basis for free transverse rectus abdominis myocutaneous (TRAM), deep inferior epigastric perforator (DIEP), and superficial inferior epigastric artery (SIEA) flaps, used for autologous breast reconstruction.

provide symmetry with the contralateral breast; consequently, to match the size of the opposite breast, the flap must be supplemented with an implant. Thus, the drawback of the implant's limited life span is added to the drawbacks associated with autologous tissue reconstruction.

Free myocutaneous and perforator flaps Free-flap reconstruction options are used primarily when other autologous and implant reconstruction options are not available, do not provide sufficient tissue volume, or have failed. They are more complex procedures, requiring microvascular anastomoses, and carry a higher risk of total flap loss. Although, historically, the free TRAM flap and the free gluteal artery flap (GAP) have been the most often employed techniques, the introduction of perforator flaps (DIEP, SIEA, superior GAP, inferior GAP) has added options to the reconstructive surgeon's armamentarium. Preoperatively, CT angiography [see Figure 16] has replaced duplex ultrasonography as the gold standard for evaluation of donor vessel caliber and patency.⁹⁶ Perforator flaps are supplied by blood vessels that perforate through or around overlying muscles to vascularize the overlying skin and fat. During flap harvest, these perforators must be meticulously dissected free from the surrounding muscle, which is preserved intact and left in its natural position. The free tissue flap is then anastomosed to recipient vessels, and the donor site is closed without the need of additional support such as mesh or biologics.⁹⁷ Ideally, they provide adequate tissue for reconstruction without the level of donor-site morbidity seen with the free TRAM or other myocutaneous free flaps.⁹⁸ The disadvantages of perforator flaps include the considerable technical expertise and long operating time required, as well as the greater potential for flap loss (because these flaps have a more tenuous blood supply than the standard TRAM flap).

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Figures 2, 3, 5 to 11, and 13 to 15 Alice Y. Chen.

6 LYMPHATIC MAPPING AND SENTINEL NODE BIOPSY

David W. Ollila, MD, FACS, Karyn B. Stitzenberg, MD, MPH, and Nancy Klauber-Demore, MD, FACS*

With an estimated 194,280 new cases in the United States in 2009, breast cancer is among the most common malignancies treated by US surgeons.¹ Meanwhile, the incidence of melanoma is rising faster than for all other solid malignancies. In 2009, there were an estimated 68,720 new cases of invasive melanoma in the United States.

Over the past 25 years, significant strides have been made in the management of these two diseases from the standpoint of both surgical and adjuvant therapy. For both diseases, the presence or absence of lymph node metastases is highly predictive of patient outcome and is the most important prognostic factor for disease recurrence and cancer-related mortality. As a result, nodal staging is a critical component of the staging workup and of treatment planning. The focus of this chapter is the role of nodal staging for both diseases.

No patient with tumor-free regional lymph nodes derives any therapeutic benefit from a complete regional lymphadenectomy. For patients with clinically negative nodal basins, the development of intraoperative lymphatic mapping and sentinel node (SN) biopsy has made it possible to map lymphatic pathway from a primary tumor to the initial draining node(s) (i.e., the SN or SNs) in the regional nodal basin. This is the lymph node most likely to harbor metastatic nodal disease, if any exists. It has been demonstrated in both breast cancer and melanoma that the pathologic status of the SN, when performed by an experienced team, is to be concordant with the pathologic status of the entire nodal basin. Integration of these techniques, along with increasingly detailed and sophisticated pathologic examination of the SN, into the surgical treatment of melanoma and breast cancer offers the potential for more conservative nodal basin operations, lower morbidity, and more accurate disease staging.

Lymphatic Mapping and SN Biopsy for Melanoma

RATIONALE

Assessment of Nodal Status

Approximately 20% of melanoma patients have nodal metastases at the time of diagnosis. The presence of lymph node metastases is the single most powerful predictor of recurrence and survival in melanoma patients. Five-year

survival is approximately 40% lower in patients who have lymph node metastases than in those who do not.² As a result, accurate nodal staging is important for stratifying patients into different risks groups that can be used to direct further therapy.

Elective Lymph Node Dissection

Until the early part of the 1990s, elective lymph node dissection (ELND) was the mainstay of the surgeon's armamentarium for nodal staging of melanoma patients. ELND is the complete surgical removal of the closest nodal basin in patients with clinically negative lymph nodes. In contrast, therapeutic lymph node dissection (TLND) is the complete surgical removal of the draining nodal basin known to have histopathologically confirmed nodal metastases. Three prospective, randomized trials failed to demonstrate better survival in melanoma patients treated with ELND than in patients undergoing wide local excision (WLE) alone as primary surgical therapy.³⁻⁵

With ELND offering no overall survival advantage, a more accurate method to identify the approximately 20% of melanoma patients who presented with nodal metastasis was needed. In the 1970s, Roth and colleagues were attempting to identify the nodal basin at risk by injecting colloidal gold around a patient's primary melanoma site.⁶ This was a very crude technique that identified only the basin at risk and not the specific node at risk. Alternative newer-generation radiopharmaceuticals and improved gamma detection devices were needed.

An alternative method of identifying the node at risk for harboring metastatic disease was first described by Wong and colleagues using a feline model.⁷ They demonstrated that a vital blue dye (Lymphazurin, Hirsch Industries, Inc., Richmond, VA) injected into the dermis of the cat would travel via the dermal lymphatics to the regional nodal basin.

The following year, in human melanoma patients, Morton and colleagues demonstrated the feasibility of lymphatic mapping and SN biopsy using vital blue dye injected.⁸ These investigators showed that the SN is the first node in the regional lymphatic basin into which the primary melanoma consistently drains (although not necessarily the closest to the primary lesion). They harvested the SN separately from the remainder of the regional nodes and found that the pathologic status of the SN was highly accurate at predicting the pathologic status of the entire nodal basin, which was also surgically removed in all of the patients studied. These findings suggested that melanoma patients could be accurately staged with procedures that were far less extensive than complete regional nodal dissections.

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PREOPERATIVE EVALUATION

Selection of Patients

The risk of nodal metastases in any one individual melanoma patient depends on a number of factors, including primary tumor thickness, presence of ulceration, and mitotic rate.^{9,10}

SN biopsy is most likely to alter therapy in patients who have a significant risk of nodal metastases but a low risk of systemic disease. As a result, the subgroup of patients with intermediate-thickness melanomas (1.0 to 4.0 mm) is the group most likely to benefit from SN biopsy. In patients with melanomas between 0.76 and 1.0 mm thick, the risk of nodal metastasis is approximately 5 to 6%,^{11–16} and a balanced discussion should be held with the patient including other factors such as ulceration, mitotic rate greater than 1, male sex, and axial location.¹⁷ Patients with thin melanomas and multiple risk factors may be at high enough risk to warrant SN biopsy.

On the opposite end of the spectrum are patients with thick melanomas (> 4.0 mm). For these patients, the risk of systemic metastases is as high as 50 to 60%, whereas the risk of nodal metastases ranges from 40 to 50%. ELND was not recommended for such patients in the past because of this high risk of systemic disease. However, even among patients with thick melanomas, survival is better for those with negative nodes than for those with microscopic nodal disease.¹⁸ As a result, patients with thick melanomas and no obvious systemic metastases may benefit from SN biopsy to stage the nodal basin. This is particularly important if the presence of nodal metastases will change the adjuvant treatment plan from observation to active systemic therapy.

The available data suggest that lymphatic mapping is applicable to all primary body sites, including the head and neck (the most technically demanding sites).^{19,20} The best results are achieved with a combination mapping approach that employs both a vital blue dye and a radiocolloid. The procedure is associated with slightly higher false negative rates in patients with head and neck melanoma than in those with melanoma of the trunk or extremities (10% versus 1 to 2%). Nevertheless, the false negative rates with head and neck melanoma are still low enough to justify offering lymphatic mapping to patients.

Special Circumstances

The extent of any operation done at the primary site before SN biopsy may affect the success of the biopsy procedure. In patients who have had an appropriate 1 or 2 cm margin resection and then large areas of tissue undermining or have undergone reconstruction with a rotational flap or Z-plasty to close the oncologic resection defect, the normal lymphatic channels may be disrupted. Such disruption may render SN biopsy inaccurate. Nevertheless, there have been reports of SN biopsy being performed successfully after previous WLE.²¹ These patients may have more SNs in more regional nodal basins than patients in whom the primary tumor has not been resected with curative intent, but at present, there is no unequivocal evidence that previous WLE of the primary lesion increases the risk of postoperative nodal relapse.^{22,23}

Increasingly, surgeons are caring for patients who have undergone previous nodal surgery. Over time, patients develop alternate lymphatic drainage pathways after nodal surgery. Although localization rates tend to be lower under these circumstances, the accuracy of the SN for predicting the status of the nodal basin remains high.^{24,25} Preoperative lymphoscintigraphy is critical, even for breast cancer patients, because the altered lymphatic pathways may result in drainage to less common nodal basins. Because development of new drainage pathways takes time, accuracy is related to the amount of time that has elapsed since the first procedure. For patients in whom the previous nodal procedure was performed less than 6 months previously, the reliability of the SN is doubtful.

Breast cancer and melanoma are frequently diagnosed in women of childbearing age, so the safety of lymphatic mapping during pregnancy needs to be discussed. Sentinel lymphadenectomy generally requires general anesthesia, so the risks of surgery during pregnancy need to be considered. In addition, there are potential risks related specifically to the lymphatic mapping. Neither isosulfan blue dye nor methylene blue dye has been tested for safety during pregnancy. In the absence of data, it is recommended that these be avoided. Although radiation is teratogenic, studies suggest that the levels of radiation associated with lymphoscintigraphy are low and safe.^{26–28} No adverse events have been documented in reported case series to date.^{29,30}

OPERATIVE PLANNING: POSITIONING AND ANESTHESIA

Patients should be prepared to undergo wide excision of the primary melanoma site (if not previously performed) and SN biopsy during the same operative session. Depending on the location of the primary lesion, it may be possible to perform the two procedures with the patient in a single position; however, often the patient must be repositioned during the procedure to afford the surgeon adequate access to the different locations. The choice of anesthesia varies, depending on the size and location of the wide excision and the anatomic depth of the SNs. In very selected cases, local anesthesia may be appropriate, but for most lesions, general or regional anesthesia is preferable.

OPERATIVE TECHNIQUE

Although the technical details of lymphatic mapping and SN biopsy for melanoma vary from institution to institution, the reported results of the different approaches have been very similar. Proper performance of these procedures requires close collaboration between the nuclear medicine physician, the surgeon, and the pathologist, with each member playing a critical role in the process.

Step 1: Injection of Radiolabeled Tracer and Lymphoscintigraphy

On the day of the procedure, the patient reports to the nuclear medicine suite for injection of the radiolabeled tracer and preoperative lymphoscintigraphy. It is crucial to have a mechanism in place by which the location of the primary melanoma site can be reliably communicated to the nuclear radiologist. Some melanoma biopsy sites are difficult to locate, particularly if multiple skin biopsies have already been performed.

A radiolabeled agent is then selected; the most common choices are technetium-99m (^{99m}Tc)-labeled sulfur colloid (TSC) and ^{99m}Tc -labeled antimony trisulfide colloid (T-ATC). The dose of the tracer and the volume of the injectate are largely determined by the location and size of the primary tumor site but generally can be kept to 0.5 mCi or less and 1 mL or less, respectively. Injections are made intradermally around the circumference of the lesion or biopsy site, and dynamic scans are taken 5 to 10 minutes after injection. Although the location of the SN may be marked on the skin by the radiologist to assist the surgeon, this location may vary slightly with changes in patient position and should therefore be confirmed by the surgeon with the gamma probe in the operating room. To allow complete and accurate nodal staging, all regional basins at risk should be marked, along with any in-transit nodes that are identified [see Figure 1]. If there is no migration of TSC after approximately 60 to 90 minutes, then a second injection of filtered TSC is performed. If no migration occurs, the nuclear medicine physician communicates this directly with the operating surgeon.

The surgical procedure should be carried out no more than 6 to 8 hours after TSC injection. Activity in the SNs usually reaches its maximum 2 to 6 hours after injection; waiting longer to carry out the procedure may increase the labeling

of secondary nodes. There have, however, been several reports of SN procedures being accurately performed 16 to 24 hours after tracer injection.¹⁹ Because TSC is retained in the SN dendritic cells, the SNs can still be easily identified after 6 hours, whereas the radioactivity at the injection site and resultant background interference may be diminished because of the short half-life of technetium (6 hours).

Step 2: Intraoperative Lymphatic Mapping and Identification of SN

It is our practice to review the lymphoscintigram when the patient arrives in the preoperative holding area. For patients who had either ambiguous drainage or no drainage, we evaluate the patient with the gamma probe before deciding on positioning. Probe evaluation, whether performed in the preoperative holding area or in the operating room, begins by defining the diffusion zone around the primary tumor site, where SN identification is not possible. The area between this diffusion zone and the possible nodal drainage sites is then mapped for possible in-transit nodes by means of a systematic but expeditious evaluation for radioactive “hot spots.” The gamma probe is moved in a linear fashion between the diffusion zone and the nodal basin. It is then shifted medial or lateral to the previous line, and the process is repeated until the entire area is evaluated. The location of a radioactive hot spot is confirmed by identifying a discrete location where the radioactive counts are higher than the counts found in the tissue 1 to 2 cm more proximal to the injection site (the background skin count). The counts from the hot spot and the background are recorded. The hot-spot site is marked on the skin to allow more direct dissection to the SN.

Concomitant use of a vital blue dye is favored by many surgeons and is our preferred method. The blue dye is complementary to the radiolabeled tracer; the combination of the two marking agents improves the chances of identifying the SN and facilitates node retrieval. The blue dye is injected into the dermis immediately adjacent to the melanoma. For lesions on an extremity, the dye may be injected along the proximal margin of the lesion or biopsy site; for lesions on other areas, it should be injected circumferentially. The general recommendation is to wait 5 to 10 minutes after injecting the dye before initiating SN retrieval.

To minimize the dissection required for node resection, the incision for the SN biopsy should be made through the hot spot identified by the gamma probe. The incision should also be situated so that it can be incorporated into a longer incision should the finding of a positive SN necessitate performance of a TLND. The gamma probe is placed in a sterile sheath and used again after the incision is made to guide further dissection. If blue dye was used, the surgeon can visually follow the blue lymphatic channels to the blue-stained SN.

An SN is defined as either (1) all radioactive nodes with an ex vivo node to background ratio greater than 10:1, (2) a node that either is blue or clearly has a blue-stained lymphatic vessel entering it, or (3) a firm palpable node. When an SN is removed, the ex vivo radioactivity count in the node is recorded. This count is then used as a reference for determining which, if any, of the remaining nodes in that basin (some of which may be potential SNs) should be removed. In our

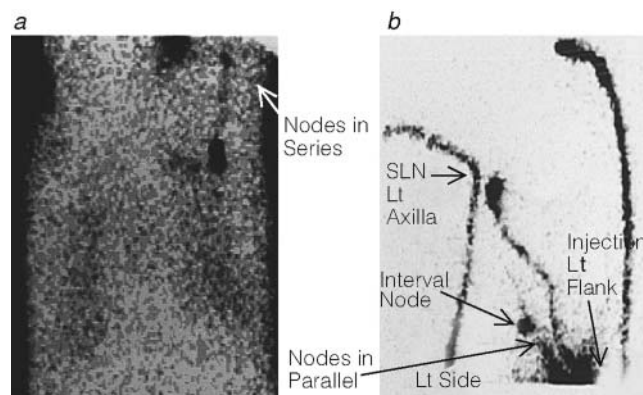


Figure 1 Lymphatic mapping and sentinel lymph node (SLN) biopsy for melanoma. In-transit nodal areas are identified in 5% of melanoma patients; this is the reason why preoperative lymphoscintigraphy is performed for primary sites on either the upper or the lower extremity. In a patient with a melanoma on the left hand (a), the injection site and the left arm are raised above the head, and cutaneous lymphatic flow into an epitrochlear node can be seen. This in-transit node then emits a lymphatic vessel flowing to the left axilla. By definition, the SLN is the first node in the chain that receives primary lymphatic flow. The epitrochlear node and any axillary nodes are nodes in series. Hence, the epitrochlear node is the SLN and thus is the only node that must be harvested. In a patient with a primary melanoma on the left flank (b), there are two separate afferent lymphatics, one leading to an SLN in the left axilla and the other leading to an in-transit node on the left flank. These are nodes in parallel in that they both receive primary lymphatic flow from the skin site. Hence, the two nodes are equally at risk for metastatic disease, and both are considered sentinel nodes and must be harvested.

view, if the radioactivity count in the hottest remaining node in the basin is less than 10% of the ex vivo count in the hottest SN, none of the remaining nodes should be considered SNs.^{19,31} Any nodes with radioactivity counts exceeding this 10% threshold, however, should be removed.

Once an SN is identified, it should be dissected out with as little trauma to the surrounding tissues as possible. Lymphatic channels to the node should be identified and either tied or clipped to reduce the risk of postoperative seroma formation. Because the gamma probe can localize SNs with great accuracy, routine dissection of motor nerves is not required; however, knowledge of the likely location of the motor nerves is critical for preventing inadvertent injury to these structures during dissection.

After SN removal, a final count of the SN biopsy bed is taken to document that all significantly radiolabeled nodes have been accounted for and removed. In addition, the tissues are examined for blue-stained lymphatic channels or lymph nodes regardless of radioactivity. (As noted, blue staining confers SN status even if the node is not radioactive.)

Firm tumor-involved nodes with obstructed afferent lymphatics may divert lymph flow to non-SNs, and such diversion is a significant cause of false negative SN biopsy results. Consequently, the final step is to palpate for grossly suspicious nodes. If grossly suspicious nodes are identified after all relevant SNs have been removed, the suspicious nodes should also be removed.

Step 3: Pathologic Evaluation of SN

The optimal extent of pathologic evaluation of SNs in patients with melanoma has been the subject of some debate. SN biopsy allows pathologists to focus their efforts on one node or a small number of nodes, and this focus has led to a process of ultrastaging. Several good methodology articles describing the handling and processing of SN are available in the literature.^{32,33} Our current institutional protocol has been published.³⁴ Briefly, the SN is bivalved and then serially sectioned at 1 to 2 mm section across both halves. The nodal sections are first evaluated with hematoxylin-eosin (H&E) stain. If no obvious metastases are identified, the immunohistochemical stains are applied, S-100 and MART-1. This enables the pathologist to identify tiny (less than 1 mm) deposits of metastatic melanoma.

COMPLICATIONS

Complications of SN biopsy are quite uncommon. Allergic reactions to the blue dyes occur in less than 1% of patients but can range in severity from mild urticaria to anaphylaxis; thus, the surgical team and the anesthesia team should always be prepared for this uncommon but potentially serious problem.^{35,36} In experienced hands, motor nerve injury is rare. In a series of 47 patients who had head and neck melanomas with SN drainage to the parotid region, there were no permanent injuries to the facial nerve when the SN was removed without formal nerve dissection.³⁷ Similar results have been reported for nodes in the posterior triangle of the neck and in the axilla. The incidence of wound complications is quite low (1.7% wound complication rate; 3.0% seroma rate), as is the incidence of postbiopsy lymphedema (0.7%). In the Sunbelt Melanoma Trial, the complication rate in 2,120 patients

undergoing SN biopsy was 4.6%, compared with 23.2% in 444 patients undergoing completion lymph node dissection (CLND).³⁸

OUTCOME EVALUATION

Ideally, level I evidence from a prospective, randomized, controlled trial would demonstrate that lymphatic mapping and SN biopsy are superior to close nodal observation as the treatment of choice for melanoma patients. The Multicenter Selective Lymphadenectomy Trial (MSLT-1; Donald Morton, principal investigator) was designed to compare WLE and SN biopsy to WLE and close observation in patients with intermediate-thickness melanomas. A detailed description of the trial has been published.³⁹ Briefly, all patients with intermediate-thickness melanomas eligible for the trial (Breslow thickness 1.2 to 3.5 mm) were randomized in a 60:40 ratio to WLE and SN biopsy or to WLE and watchful waiting. All patients with a tumor-involved SN went on to an immediate TLND. For patients in the watchful waiting arm, a delayed TLND was performed if clinically apparent, pathologically confirmed nodal disease was identified.

After the third interim analysis, the Data Safety Monitoring Board insisted that the data be released to the public because several secondary end points had been met. Most importantly, melanoma-specific survival in patients with nodal disease was improved for patients in the SN biopsy arm compared with watchful waiting. Patients with a tumor-involved SN who underwent immediate LND had a 5-year survival advantage compared with those in the watchful waiting arm who developed a nodal basin metastasis: 72.3% versus 52.4% (hazard ratio 0.51, 95% confidence interval 0.32 to 0.81, $p = .004$).³⁹ These results continue to hold up after the fourth interim analysis with 10-year survival advantage of 63.2% versus 36.5% ($p < .001$).⁴⁰

To date, the primary end point, improved overall survival, has not been met. Although this has led some critics to advocate abandoning SN biopsy in melanoma patients,⁴¹ several clarifications need to be emphasized. First, no lymph node-negative patient ever derives a survival benefit from undergoing nodal operation, whether ELND or SN biopsy. Given that the incidence of nodal metastases in patients with intermediate-thickness melanoma, as defined by the MSLT-1, would be expected to be around 20%, 80% of patients enrolled on the trial could not possibly derive a survival advantage. These patients who cannot benefit dilute the observed magnitude of effect for those who do benefit. Second, SN biopsy is not proposed as a therapeutic procedure but rather as a highly sophisticated staging procedure. On MSLT-1, the patients with a tumor-involved SN subsequently underwent a directed TLND. The results of MSLT-1 demonstrate a clear survival advantage in performing the TLND early in an association with a tumor-involved SN as opposed to later, when palpable lymphadenopathy is detected.

Lymphatic Mapping and SN Biopsy in Breast Cancer

RATIONALE: ASSESSMENT OF NODAL STATUS

In early breast cancer, as in melanoma, the pathologic status of the regional lymph nodes is the most important

predictor of outcome. The presence of regional lymph node metastases in breast cancer reduces 5-year survival by 28 to 40%.^{42,43} Prognostic factors related to primary tumor characteristics have consistently been shown to be inferior to nodal status as predictors of overall survival. In addition, axillary lymph node dissection in the setting of breast cancer is superior to observation and at least equivalent to irradiation for regional disease control in clinically node-negative patients.⁴⁴ There is some evidence that adequate regional disease control may confer a small survival benefit.⁴⁵

Invasive breast cancer has a relatively high rate of nodal metastasis in clinically node-negative patients. The risk of metastasis is clearly related to the size of the primary tumor, but it is significant (15% or higher) even in patients with early (T1a) lesions.^{46,47} The primary nodal drainage basin for the breast is the ipsilateral axilla; however, drainage to extra-axillary sites (e.g., the internal mammary lymph node chain, the supraclavicular nodes, and the intramammary nodes) is also reported. Other potential sites of lymphatic drainage notwithstanding, the recommended surgical procedure for evaluating the regional lymph nodes in clinically node-negative breast cancer patients has been level I and II axillary lymph node dissection (ALND). Such dissections are, however, associated with a significant risk of long-term morbidity, primarily related to the risk of lymphedema in the affected arm. For this reason, SN biopsy was developed and investigated as a possible substitute for standard ALND in the treatment of breast cancer patients with clinically uninvolved axillary lymph nodes.

PREOPERATIVE EVALUATION

Selection of Patients

All clinically node-negative patients with a diagnosis of invasive breast cancer are potential candidates for SN biopsy. Ideal candidates are those patients with unifocal lesions less than 5 cm in greatest dimension who have no history of previous axillary surgery or previous cancer treatment. Performing an SN biopsy after a previous excisional biopsy is technically feasible. Patients who have undergone extensive previous breast procedures (e.g., breast reduction, placement of breast implants, or multiple open biopsies) may have significant alterations in the lymphatic pathways; however, accurate identification of the SN can still be accomplished with proper planning of the injection sites. Patients with multifocal tumors or multicentric breast cancers also require thoughtful planning of the injection sites, although there is some evidence suggesting that using periareolar injection sites may allow the procedure to be performed accurately in patients with multifocal disease.⁴⁸ For patients who will be undergoing mastectomy with immediate breast reconstruction, performing SN biopsy as an outpatient procedure prior to the planned mastectomy may facilitate surgical planning depending on the need for postmastectomy radiation or ALND.⁴⁹ However, the false negative rate of SN biopsy may be higher in cases with large additive tumor burden.⁵⁰

For patients who present with inflammatory breast carcinoma or who present with palpable adenopathy and pathologically confirmed metastatic nodal disease, there is absolutely no role for SN biopsy at the time of presentation. The role of SN biopsy in patients who present with large breast cancers and are scheduled to receive neoadjuvant

chemotherapy is highly controversial. Several recent studies have shown a low false negative rate for patients with T3 tumors who have an SN procedure prior to neoadjuvant chemotherapy,^{51–55} as well as those authors advocating the procedure after the neoadjuvant chemotherapy.^{56–58} Several good reviews of the controversy are published.^{59–61} The remainder of this chapter deals with patients who present with unifocal, T1 or T2, clinically node-negative breast cancer.

OPERATIVE PLANNING: POSITIONING AND ANESTHESIA

Patients should be placed in the supine position, with all potential nodal sites within the operative field. Although SN biopsy may be performed with the patient under local anesthesia, we favor general anesthesia for this procedure, particularly when it is done in conjunction with the breast excision.

OPERATIVE TECHNIQUE

Step 1: Injection of Radiolabeled Tracer and Lymphoscintigraphy

In the United States, the radiocolloid most commonly employed for SN biopsy in breast cancer patients is TSC, which may be used either unfiltered or filtered (< 220 nm). The ^{99m}Tc dose generally ranges from 0.45 to 1.0 mCi, and the injectate volume ranges from 4 to 8 mL. Several routes of tracer injection have been investigated for SN biopsy in breast cancer patients, primarily in response to the difficulties sometimes associated with peritumoral injection (e.g., delayed tracer uptake and wide diffusion zones that can overlap the nodal basins). These routes include intradermal or subdermal injection in the area overlying the tumor, subareolar injection, and periareolar injection. The rationale for the development of these alternatives is that there is significant overlap between the lymphatic vessels of the breast skin and those of the breast parenchyma. Multiple studies have confirmed that the use of these injection routes yields high localization rates and results in accurate removal of SNs that reflect the pathologic nodal status of individual patients. A notable deficiency of these techniques, however, has been the low reported rate of tracer migration to nodes outside the axilla, particularly to the internal mammary lymph node chain. This result is thought to be attributable to a unique set of lymphatic channels deep in the breast parenchyma, separate from the overlying skin, that drain to the internal mammary chain.

The various tracer injection methods have not been directly compared; thus, at present, the optimal route of injection can be inferred only by comparing studies from different institutions. The potential importance of the extra-axillary sites is not entirely clear, but it appears that these sites may be the sole locations of metastatic disease in as many as 20% of the node-positive patients from whom they are removed.^{62,63} Most patients in whom SNs are found outside the axilla have additional SNs in the axillary basin.

A thorough literature review on the use of different routes of injection and the associated rates of SN localization by nodal basin, node positivity rates, and false negative rates has been performed. This review included those studies in which a radiolabeled tracer was used for SN identification (either by lymphoscintigraphy or by intraoperative gamma

probe localization) and in which the location of the SN basins and the pathologic status of the SNs could be ascertained. The results of previous reviews of almost 9,000 patients indicated that all of the approaches have acceptable SN retrieval rates but that the rates are slightly higher with the more superficial ones (i.e., the dermal, subareolar, and periareolar techniques).^{62,64–67} There are, however, significant differences in the locations of the SN basins identified with the different methods: with the superficial injection techniques, drainage is essentially confined to the axillary basin, whereas with the deeper injection techniques, as many as 22% of patients are found to have nodal basins outside the axilla. Approximately 16 to 21% of the extra-axillary SNs will be found to have metastatic disease if removed. The clinical ramifications of these findings are that some patients may be understaged if the extra-axillary sites are not evaluated, and such understaging may affect the recommendations for systemic adjuvant therapy.

Whether the breast cancer is palpable or nonpalpable, we prefer that the injection is guided by ultrasonographic evidence. If an excisional biopsy was previously performed, the tracer should be injected into the breast parenchyma rather than into the biopsy cavity; it will not diffuse out of the cavity. This is also best done under ultrasonographic guidance. In addition, injections should not be made into the retromammary fat or the pectoral fascia, because doing so would lead to wide diffusion of tracer throughout the chest area, which would make nodal identification very difficult.

In breast cancer patients, the timing of SN biopsy after tracer injection is not of critical importance. Good results have been obtained with injection-to-biopsy intervals ranging from 30 minutes to 24 hours. The usual recommendation is to wait 1 to 2 hours.

Step 2: Intraoperative Lymphatic Mapping and Removal of SN

Once the patient is asleep, the vital blue dye (Lymphazurin) is injected either peritumorally, into the parenchyma surrounding an excisional biopsy, intradermally, or subareolarly depending on surgeon preference. The breast is gently massaged for 5 to 10 minutes to enhance transport of the dye to the SNs. Our approach begins by performing a primary survey of the potential nodal sites with the handheld gamma detector. Using one of the commercially available handheld gamma probes, an axillary hot spot is identified, and then a small incision is made. The gamma probe, sterile sheathed, is inserted into the wound and guides the dissection to the radioactive node(s). During the dissection, the surgeon looks for blue-stained lymphatic channels and nodes [see Figure 2]. Most of the time, the radiocolloid and the vital blue dye identify the same SNs. The SNs are then carefully removed, and the lymphatic vessels entering them are tied or clipped off whenever possible.

An SN is defined as either (1) all radioactive nodes with an ex vivo node to background ratio greater than 10:1, (2) a node that either is stained blue or clearly has a blue-stained lymphatic vessel entering it, or (3) a firm palpable node. When an SN is removed, the ex vivo radioactivity count in the node is recorded. This count is then used as a reference for determining which, if any, of the remaining nodes in that



Figure 2 Lymphatic mapping and sentinel node (SN) biopsy for breast cancer. A small incision is made in the axilla on the basis of the hot-spot location. The SNs identified are both radioactive and stained blue.

basin (some of which may be potential SNs) should be removed. In our view, if the radioactivity count in the hottest remaining node in the basin is less than 10% of the ex vivo count in the hottest SN, none of the remaining nodes should be considered SNs, and none should be removed.⁶⁷ Any nodes whose radioactivity counts exceed this 10% threshold, however, should be removed.

A final count of the SN biopsy bed is then taken to document that all significantly radiolabeled SNs have been accounted for and removed. In addition, the tissues are examined for blue-stained lymphatic channels or lymph nodes regardless of radioactivity; as noted, blue staining confers SN status even if the node is not radioactive. Finally, when it appears that all relevant SNs have been removed, as confirmed by the final bed count, the tissues are palpated for grossly suspicious nodes. Firm tumor-involved nodes with obstructed afferent lymphatics may divert lymph flow to non-SNs, and such diversion is a significant cause of false negative SN biopsy results.

Once an SN is identified, it should be dissected out with as little trauma to the surrounding tissues as possible. Lymphatic channels to the node should be identified and either tied or clipped to reduce the risk of postoperative seroma formation. Because the gamma probe can localize SNs with great accuracy, routine dissection of motor nerves is not required; however, knowledge of the likely location of the motor nerves is critical for preventing inadvertent injury to these structures during dissection.

Step 3: Pathologic Evaluation of SN

Pathologic SN evaluation in breast cancer patients has two main aspects. The first is intraoperative evaluation of the SN when the pathologic status of the node is being used to determine the need for ALND; the second is permanent evaluation of the nodes to determine whether micrometastatic disease is present. Both have conflicting views in the literature.

Two techniques are commonly employed for intraoperative evaluation of SNs: frozen-section analysis and touch-imprint cytology. Frozen-section histopathology is available in most hospitals, and all surgical pathologists have some experience

with it. This technique has a drawback, however, in that it sometimes uses up a large portion of the SN, leaving a remnant that is insufficient for permanent paraffin-embedded sections. In addition, the sectioning of radioactive nodes on a cryostat raises radiation safety issues for the pathologists.

Studies of frozen-section techniques of evaluating SNs for metastatic breast cancer report false negative rates of 27 and 32%.^{64,68} When 60 frozen sections are made from each SN, the false negative rate can be reduced to about 5%,^{64,69} but at the cost of 45 to 60 minutes of operating time and loss of tissues for permanent histopathologic evaluation. Frozen section is far more effective in detecting macrometastatic disease (sensitivity 92%) than micrometastatic disease (sensitivity 17%), and the volume of nodal metastases is highly correlated with tumor size.⁷⁰ In comparison, touch-imprint cytology consumes much less time and tissue, is far more accurate (false negative rate 0.8%),⁷¹ and does not contaminate the cryostat. It has also been applied to the evaluation of lumpectomy margins [see Figure 3]. The chief limitation of the touch-imprint method is that for optimal results, it requires a pathologist who is highly skilled in the cytologic evaluation of lymph nodes. Some centers use rapid immunohistochemical (IHC) analysis for cytokeratin staining to detect tumor cells in touch-imprint or frozen-section specimens, anticipating that detection of such cells can thereby be improved, particularly in patients with invasive lobular or well-differentiated ductal carcinomas.

The optimal extent of pathologic evaluation of SNs in patients with breast cancer has been the subject of some debate. SN biopsy allows pathologists to focus their efforts on one node or a small number of nodes, and this focus has led to a process of ultrastaging. Several good methodology articles describing the handling and processing of SN are available in the literature.^{32,33} Our current institutional protocol has been published previously.³⁴ Briefly, the SN is bivalved

and then serially sectioned at 1 to 2 mm section across both halves. The nodal sections are first evaluated with H&E stain. In 1999, the College of American Pathologists issued a consensus statement recommending that the staging of SNs be based on routine histologic evaluation of the nodes cut at approximately 2 mm intervals.⁷² Routine use of cytokeratin IHC staining should not be adopted as standard until its significance is demonstrated in clinical trials.

COMPLICATIONS

The complications of SN biopsy in breast cancer patients are similar to those seen in melanoma patients.⁷³ There is a minor (< 1%) risk of allergic reactions to the blue dye.⁷⁴ There is a small risk of sensory or motor nerve injury or lymphedema whenever an axillary node procedure is performed; this risk is substantially reduced, although not entirely eliminated, with SN biopsy.⁷⁵ With an internal mammary SN biopsy, there is a risk of pneumothorax from unintended opening of the parietal pleura. This risk is very small with careful technique, however, and the problem can almost always be corrected by closing the wound around a rubber catheter inserted through a small stab incision and removing it at the end of a positive pressure breath given by the anesthesiologist. Surgical site infections occur in fewer than 1% of cases, and small seromas occur in about 10%.

OUTCOME EVALUATION

The first report of SN biopsy in breast cancer, published in 1993, described the use of the gamma probe localization technique for SN identification.⁷⁶ A second report, published the following year, described the use of the vital blue dye technique for SN identification.⁷⁷ Since these initial feasibility reports, many single-center and multicenter studies have been published that achieved remarkably similar results using either or both of these techniques.

The early studies of SN biopsy tended to use either a radio-labeled tracer or a vital blue dye alone. The first trial in which the two agents were used together was published in 1996.⁶⁵ This study documented an improvement in SN localization and a 0% false negative rate, albeit in a small series of patients. Subsequent multicenter trials incorporating larger study groups yielded more reliable indications of the applicability of these techniques to the overall surgical community. In one such study, surgeons from 11 centers performed SN biopsies and confirmatory axillary dissection in clinically node-negative patients with invasive breast cancer.⁶⁶ The overall success rate for identifying and removing an SN was 93%, the pathologic accuracy rate for predicting the presence of nodal metastases from the SNs removed was 97%, and the pathologic false negative rate was 11.4%. A subsequent multicenter trial, using a combination of blue dye staining and the gamma probe technique in most patients, reported an SN retrieval rate of 88% and a pathologic false negative rate of 7.2%.⁶⁷ A third trial, using the gamma probe technique, reported an SN retrieval rate of 87% and a pathologic false negative rate of 13%.⁷⁸ A fourth trial, using both blue dye staining and the gamma probe technique, reported an SN retrieval rate of 86% and a pathologic false negative rate of 4%.⁷⁹

To evaluate the true efficacy of a new technology, a prospective trial needs to be performed, and the first one completed was by Veronesi and colleagues.⁸⁰ In this trial, 516

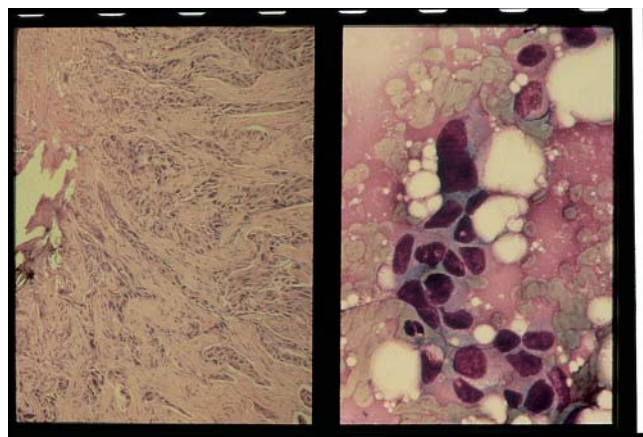


Figure 3 Lymphatic mapping and sentinel node biopsy for breast cancer. In touch-imprint cytology, slides are touched to tissue from a “hot” specimen, and cells on the section or the margin are exfoliated onto the slide for cytologic preparation. Shown are (a) permanent histology of an infiltrating ductal carcinoma extending down to an inked margin and (b) a touch preparation demonstrating bizarre malignant cells from the sampling of the margin. The advantages of this technique are that the entire margin can be sampled and that tissue is not lost in the cryostat.

evaluable patients were randomly assigned to undergo either SN biopsy with confirmatory axillary dissection (257 patients) or SN biopsy with axillary dissection done only if the biopsy yielded positive results (259 patients). At a median follow-up point of 46 months, no significant survival differences were reported, and there were no regional nodal recurrences in either arm. Admittedly, the study size was small and the follow-up relatively short, but still there was no significance in axillary failure in patients who received only an SN biopsy.



The National Surgical Adjuvant Breast and Bowel Project (NSABP) undertook a trial very similar to that of the Milan group, NSABP B-32. Breast cancer patients with clinically node-negative axillae were randomized to undergo SN biopsy with mandatory ALND or SN biopsy with ALND if the SN revealed metastatic breast cancer.⁸¹ Between 1999 and 2004, 5,611 patients were accrued and randomized. The technical details have been published⁸¹; previously, the SN identification on the trial was 97% and the false-negative rate was 9.7%, very consistent with some of the early breast SN reports. At the 2010 meeting of the American Society of Clinical Oncology (ASCO 2010), Krag and colleagues stated for the first time that there was no difference in overall survival, disease-free survival, or locoregional recurrences, thus providing level I evidence that the SN biopsy is an accurate and safe alternative to routine ALND in clinically node-negative breast cancer patients.⁸²

The American College of Surgeons Oncology Group (ACOSOG) undertook an SN trial designed to evaluate the incidence and prognostic significance of SN and bone marrow micrometastases in patients with early-stage breast cancer. ACOSOG Z0010 was a phase II trial in which all patients enrolled underwent a SN biopsy and bilateral iliac crest bone marrow aspirates. If the SNs were negative by H&E stain, then they were submitted to the central laboratory for IHC stains. From April 1999 through May 2003, 5,539 patients were enrolled. At ASCO 2010, Cote and colleagues presented for the first time the unblinded SN IHC results.⁸³ There was no difference in overall survival in patients with IHC-detected metastases compared with tumor-free SN (95.1% versus 95.8%, $p = .53$). Thus, the routine examination of SN with IHC in patients with invasive ductal carcinoma should not be performed.

The advent of the SN has reopened the debate regarding the impact of ALND on overall survival. One of the earliest NSABP studies, B-04, randomized patients to either radical mastectomy, total mastectomy with delayed ALND if necessary, or total mastectomy and radiotherapy.⁴⁴ There was no overall survival difference between the three arms of the trial, but the trial was not powered to detect a small survival advantage. Patients receiving an ALND appeared to have improved the locoregional recurrence rate.

The question in the SN era remains: in patients with H&E-detected metastases, what, if anything, should be done to the remainder of the axillary nodes? Two prospective, randomized trials were designed to answer this very important question. The first is the European Organisation for Research and Treatment of Cancer (EORTC) AMAROS (after mapping of the axilla: radiotherapy or surgery) trial in which patients with an H&E-detected SN metastasis were randomized to axillary radiation versus a completion ALND. The trial finished accrual in 2008 but, because of a lower than expected event rate, had to reopen to accrual. The other important trial is ACOSOG Z0011, in which patients with H&E-detected metastases were randomized to completion ALND or observation. At ASCO 2010, Giuliano and colleagues, for the first time, stated that there was no difference in overall survival between the two groups (completion ALND 91.9% versus observation 92.5%) or disease-free survival (82.2% versus 83.8%, $p = .13$).⁸⁴ Thus, in a large phase III trial, albeit underpowered, there is not even a trend toward a survival advantage in patients receiving ALND. Routine ALND following a positive SN adds nothing to the patient's overall survival.

Radiation Exposure Guidelines and Policies

The amount and type of radioactivity injected in the course of lymphatic mapping and SN biopsy are relatively limited. Typically, from 0.4 to 1.2 mCi of ^{99m}Tc is injected. This agent is a pure gamma emitter with a short half-life (6 hours); thus, the risks of potentially harmful beta radiation are avoided. The total radiation dose used is quite small—only about 5% of that used in common nuclear scanning techniques (e.g., bone scans). It has been estimated that a maximum of 0.45 Gy could be absorbed at the injection site. Of hospital workers, the surgeon is exposed to the highest levels of radiation. A study from Walter Reed Army Medical Center found that the hands of surgeons performing lymphatic mapping and SN biopsy were exposed to an average of 9.4 ± 3.6 mrem per operation.⁸⁵ Therefore, on the basis of skin dosage recommendations set by the Nuclear Regulatory Commission, a surgeon would have to perform more than 5,000 SN procedures a year to incur more than the minimal level of risk.

The low risk notwithstanding, proper handling of radioactive specimens is recommended. All such specimens should be handled as little as possible for at least 24 to 48 hours and should be appropriately labeled. Physicians performing these procedures should develop guidelines for handling and processing specimens in accordance with their institution's radiation safety policies.

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7 EVOLVING MOLECULAR THERAPEUTICS AND THEIR APPLICATIONS TO SURGICAL ONCOLOGY

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Despite advances in both medical and surgical therapy for cancer, the majority of cancer deaths result from metastasis. Traditionally, chemotherapy has been the mainstay of therapy for systemic disease. However, even the most effective chemotherapeutic agents are rarely curative. Moreover, toxicity is common and can be debilitating and dose limiting. It has proven difficult to find an agent that is toxic to cancer cells but does not in some way damage healthy cells. This treatment paradox has prompted a revolution in drug development. Increasingly, research efforts are focusing on the development of agents that target molecules that are specific to tumor cells. The ability of cancer cells to resist apoptosis, proliferate unchecked, and detach and metastasize results from activation and dysregulation of complex signaling cascades that in normal cells are controlled by intrinsic checkpoints and regulatory processes. Better understanding of these pathways, and of their checks and balances, has led to the development of agents that specifically target these processes in tumor cells. Agents are generally classified based on mechanism of action; however, overlap exists, and class lines are often blurred. The following summary describes historic targeted therapies that have laid the groundwork for current investigations and outlines current breakthroughs that are revolutionizing the way cancer is treated. The ultimate goal of molecular therapeutics is to develop agents that are lethal only to tumor cells, that maintain efficacy without developing resistance, and that possess acceptable toxicities that make them well tolerated by patients.

Tyrosine Kinase Inhibitors

BIOCHEMICAL RATIONALE

Tyrosine kinases (TKs) are enzymatic proteins that catalyze the phosphorylation and activation of other signaling proteins.¹ As their name implies, the target of these kinases is the tyrosine residue on a variety of proteins. TKs have long been known to play a role in cancer progression, and as such, inhibition of TKs has been at the forefront of targeted cancer therapy.

TKs are classified as either receptor or nonreceptor kinases. Fifty-eight membrane-spanning receptor tyrosine kinases (RTKs) have been identified.² Structurally, the lipophilic transmembrane domain is flanked by an immunoglobulin-like, ligand-binding extracellular head and an intracellular

tyrosine autophosphorylating carboxy-terminal tail. The majority of RTKs function in pairs, and activation induces dimerization [see Figure 1].^{1,3,4} Dimerization then triggers a phosphorylation cascade involving the cytosolic non-RTKs [see Figure 2]. These non-RTKs relay intracellular signals by additional protein phosphorylation.⁴ Many processes involved in tumor progression and metastasis, including proliferation, angiogenesis, migration, and cell survival, are influenced by dimerization, autophosphorylation, and the resulting downstream signal cascade.^{1,3} Although these processes are necessary for normal cell turnover, mutations can alter the expression or activation of TKs and thereby lead to uncontrolled activation in cancer cells.⁵ To date, the 58 RTKs that have been described are classified into over 20 families based on molecular structure and the sequence of the kinase domain.^{2,5,6} Of these, approximately 30% have been found to be either mutated or unregulated in cancer.⁵ Several RTKs are now known to play important roles in tumorigenesis and have become effective therapeutic targets. For example, c-kit is unregulated in gastrointestinal stromal tumors (GISTs) and acute myelogenous leukemia (AML), HER-2 is elevated in breast cancer, and RET is altered in the multiple endocrine neoplasia (MEN) disorders.⁵ These and other RTKs, therefore, provide potential targets for molecular therapeutics.

TYROSINE KINASE INHIBITORS

Delineating the role of TKs in tumorigenic processes such as invasion, angiogenesis, and proliferation prompted the development of several tyrosine kinase inhibitors (TKIs) that target either the receptor or the ligand that promotes the downstream signal cascade.¹ The resulting flood of TKIs has been variably classified by the target receptor or ligand, the signaling pathway affected, or their molecular structure. For the purposes of this review, TKIs are classified based on molecular structure: (1) monoclonal antibodies, (2) small molecule kinase inhibitors, and (3) multitargeted kinase inhibitors [see Table 1].

Monoclonal Antibodies

TKIs were first introduced to the anticancer armamentarium with the development of imatinib mesylate for the treatment of chronic myelogenous leukemia (CML), and this monoclonal antibody revolutionized therapy for this disease. The majority of patients with CML possess the t(9;22) translocation mutation (Philadelphia chromosome) that fuses the

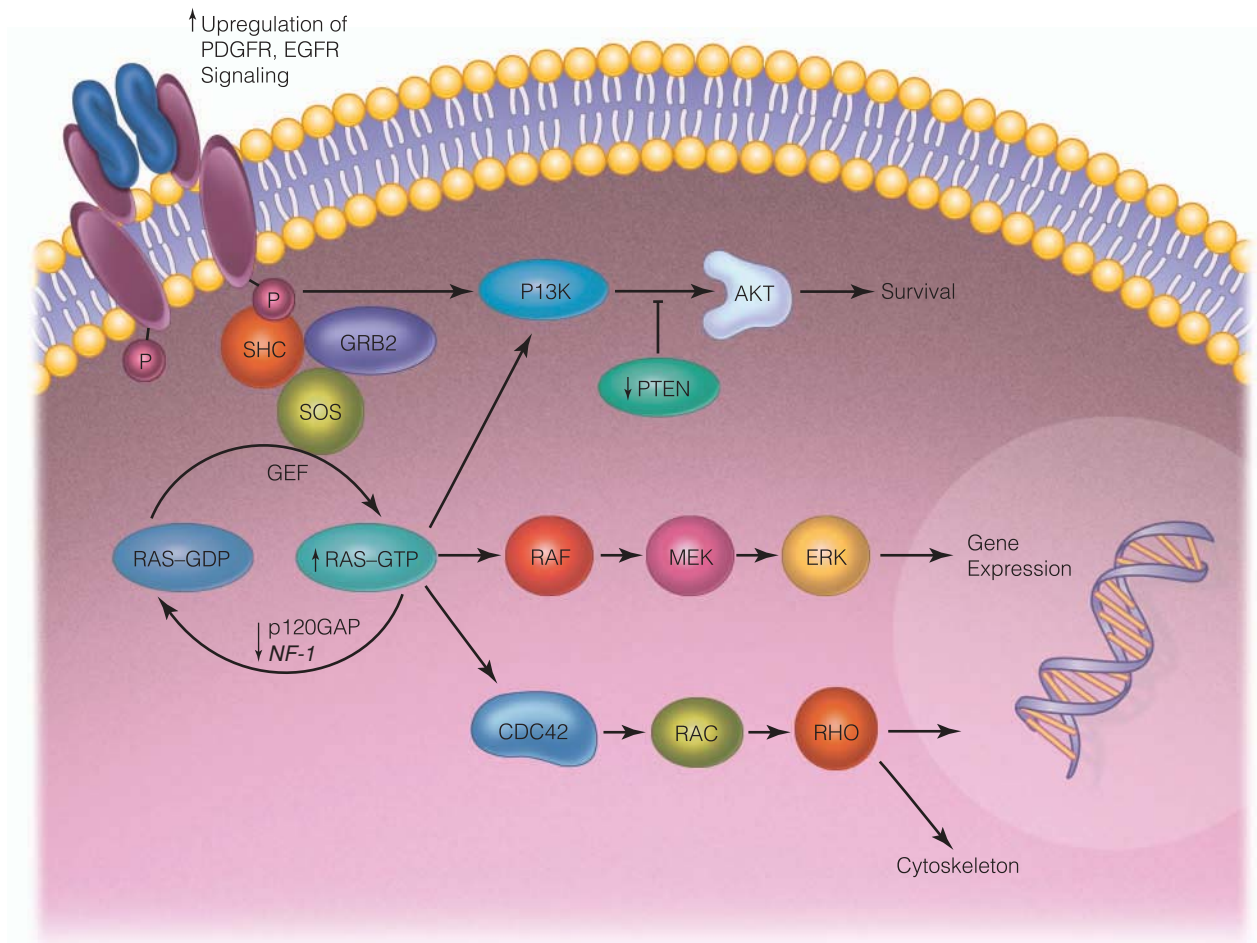


Figure 1 Activation of a receptor tyrosine kinase induces dimerization and downstream phosphorylation of nonreceptor tyrosine kinases. Major signaling cascades include the RAS/RAF/MAPK pathway, MEK pathway, and PI₃ kinase/AKT pathway. Adapted with permission from Zhu Y, Parada LF. The molecular and genetic basis of neurological tumours. *Nat Rev Cancer* 2002;2:616–26. EGFR= epidermal growth factor receptor; ERK= extracellular signal-related kinase; GAP= GTPase-activating proteins; GEF= guanosine exchange factors; MEK= mitogen-activated protein kinase; NF1= neurofibromin gene; PDGFR= platelet-derived growth factor receptor; PI3K= phosphatidylinositol-3 kinase.

Abl TK to the *Bcr* gene on chromosome 22.^{1,7} Transcription and translation of this mutation produce two TKs, p190 and p210, both of which are involved in hematopoietic stem cell proliferation and inhibition of apoptosis.¹ Imatinib blocks the adenosine triphosphate (ATP)-binding site on these proteins, hindering activation and downstream signaling. In clinical trials, this early TKI improved long-term survival in CML by prolonging periods of remission and has been an effective treatment modality for both newly diagnosed patients and those who have failed interferon-alfa therapy.⁸

The success of imatinib in the treatment of CML raised the question of whether this agent might be useful for treating solid tumors. The recognition that imatinib also inhibits the c-kit and platelet-derived growth factor receptor (PDGFR) TKs led to trials treating tumors with mutations in these molecules.⁹ For example, GISTs are well known to express c-kit, and imatinib has been highly successful in treating these

tumors. Currently, there are several clinical trials designed to test the efficacy of imatinib in other solid tumors, including colorectal cancer, ovarian cancer, prostate cancer, and thyroid cancer.¹⁰ Nevertheless, despite successes with this agent, prolonged use of imatinib has resulted in the development of resistant tumors. The most common mechanism of resistance appears to involve mutations in the kinase domain of bcr-abl, which then prevent binding of the drug.¹¹ As a result, current research is focusing on overcoming this limitation.

Another RTK that has been identified as a target for monoclonal antibody inhibition is epidermal growth factor receptor 2 (EGFR2, ErbB2), also known as human epidermal receptor 2 (HER-2).¹² This RTK can bind a wide array of growth factors, thereby inducing dimerization and stimulating downstream activation of either the RAS/MAPK, PI₃ kinase/Akt/mTOR, or other signaling pathways, which promote cell proliferation and migration and inhibit apoptosis.^{12,13} HER-2

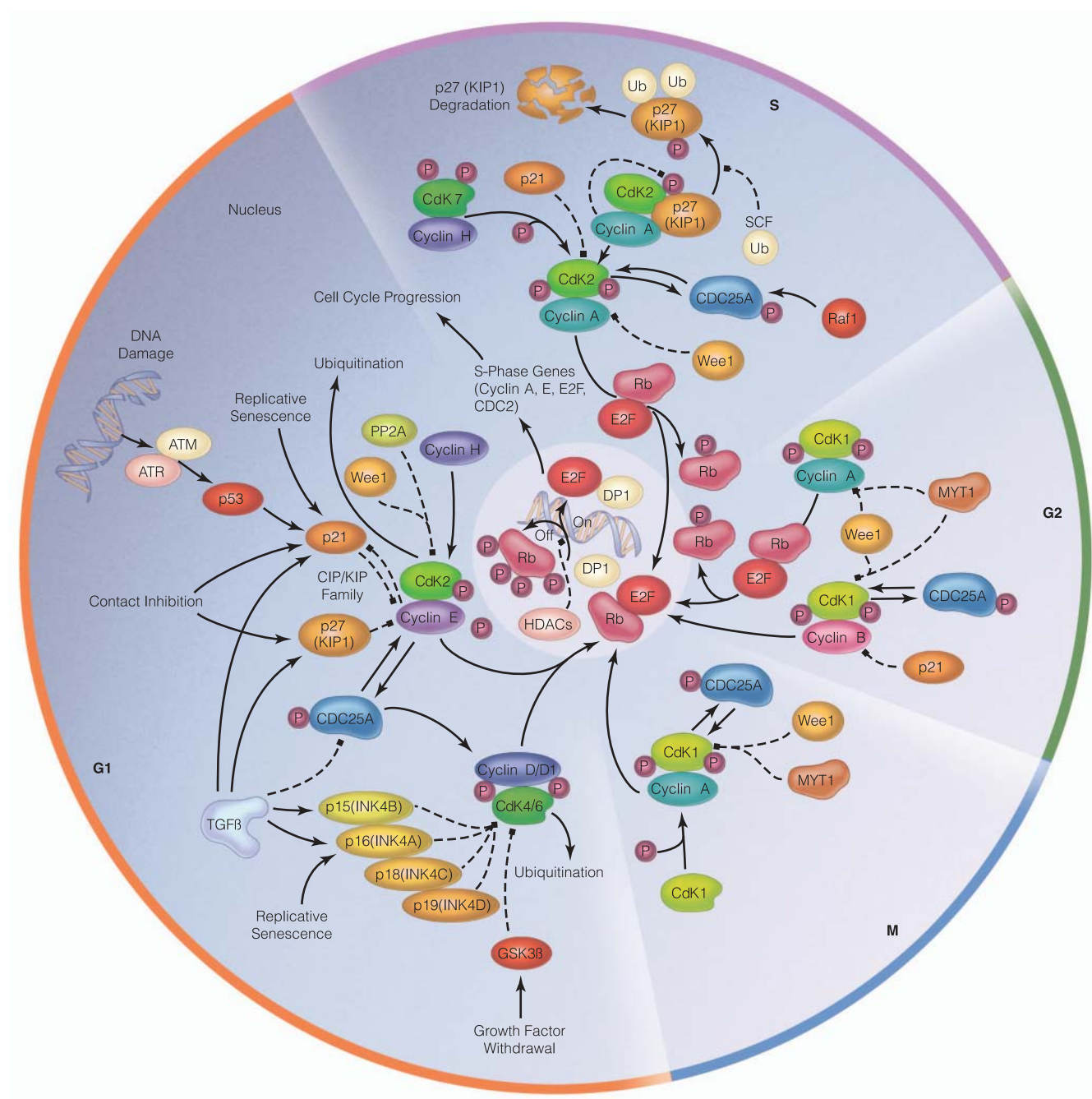


Figure 2 Regulation of the cell cycle involves a highly complex sequence of events. The interaction of cyclin-dependent kinases (CdKs) and cyclins determines progression through different phases of the cell cycle. Adapted from SABiosciences. Cyclins and cell cycle regulation. Available at: www.sabiosciences.com (accessed October 2010).

is overexpressed in many malignancies, and between 20 and 30% of advanced breast cancers express this receptor.^{12,14} Trastuzumab is a humanized monoclonal antibody that inhibits activation of the HER-2 receptor by binding to the extracellular domain and blunting the activation of downstream signaling.¹² In addition, trastuzumab has been shown to affect breast cancer cells by inducing cell cycle arrest at G₁ via upregulation and translocation of p27 from cytosol to nuclei.^{15,16} These findings have led to clinical use of this drug for treating HER-2-positive breast cancer.

Trastuzumab has demonstrated efficacy against both early- and late-stage breast cancer and is currently the standard of care for HER-2-positive tumors.^{17,18} This agent was first used as adjuvant therapy for node-positive or advanced node-negative breast cancer with *HER-2* gene amplification. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and North Central Cancer Treatment Group (NCCTG) N9831 trials, trastuzumab was studied as a conjugate to the established treatment regimen of doxorubicin and cyclophosphamide plus paclitaxel.¹⁹ The Herceptin

Table 1 Tyrosine Kinase Inhibitors

Monoclonal antibodies
Imatinib
Trastuzumab
Cetuximab
Panitumumab
Small molecule inhibitors
Gefitinib
Erlotinib
Multitargeted inhibitors
Lapatinib
Dasatinib
Sunitinib
Axitinib
Vandetanib

Adjuvant (HERA) and Breast Cancer International Research Group (BCIRG) 006 trials then examined the efficacy of adjuvant trastuzumab for 1 or 2 years following different chemotherapy regimens (HERA) or as an addition to the regimen of anthracycline, cyclophosphamide, and docetaxal (BCIRG 006).²⁰ In all four trials, both disease-free survival and overall survival were improved in the groups that received trastuzumab. In addition, patients who received trastuzumab developed fewer metastases and had lower mortality compared with patients who received chemotherapy alone. Unfortunately, side effects observed in these studies and attributed to trastuzumab treatment were congestive heart failure and a measurable decline in left ventricular ejection fraction.^{19,20} Further investigation revealed that the risk of cardiac failure was greatest in patients who received anthracycline, and although there is evidence that this untoward effect was curtailed with the concomitant administration of epirubicin, it remains a real concern for many patients and physicians.²¹ Thus, trastuzumab should not be given with anthracycline, and close monitoring of cardiac function is recommended.

Although trastuzumab has traditionally been administered in conjunction with chemotherapy in advanced HER-2-positive disease, more recent work has focused on using this drug as a single agent in early disease in an effort to delay the use of other, more toxic chemotherapy.¹⁷ In addition, the recent phase III Trastuzumab for Gastric Cancer (ToGA) trial has suggested that trastuzumab may be a reasonable adjunct to capecitabine and cisplatin or 5-fluorouracil (5-FU) and cisplatin for patients with HER-2-positive gastric or gastroesophageal junction cancer. Patients who received trastuzumab experienced 13.8-month median overall survival compared with 11.1 months for those receiving chemotherapy alone, decreasing the rate of death by 26%.^{22,23} Trials are also under way to test the efficacy of trastuzumab in combination with other targeted therapies. For example, trastuzumab-DM1 is a combination of the monoclonal antibody and the maytansine derivative DM1, a drug that interferes with microtubule formation. Preclinical studies demonstrate efficacy in lapatinib and trastuzumab-refractory breast cancer cells, and this combination is currently in phase II clinical trials for the treatment of breast cancer.^{24,25} Preliminary data show an approximately 40% overall response rate in metastatic disease after 6 months.^{26,27}

Like trastuzumab, cetuximab is a monoclonal antibody that targets EGFRs by binding to the extracellular domain.^{3,28} The development of this drug began with the identification of a murine monoclonal antibody (called 225) that could bind EGFR and inhibit activation of the intracellular TK domain of the receptor. The downstream effects of 225 included increased apoptosis and cell cycle arrest in G₁.²⁹ Experimental data were promising; however, concern about the use of a mouse monoclonal antibody in the human population and the potential for antimouse antibody response prompted chimerization of the antibody with human IgG1.^{30,31} The resulting chimeric antibody (C225, cetuximab) performed better than the original 225 antibody in inhibiting tumor growth in vivo.^{31,32} In addition, early studies demonstrated the efficacy of cetuximab in improving progression-free survival and overall response rate in metastatic colorectal tumors that had developed resistance to chemotherapeutic agents such as irinotecan.^{3,33} Moreover, patients with metastatic colorectal cancer refractory to oxaliplatin and fluoropyrimidine (5-FU) experienced prolonged progression-free survival when cetuximab was given in conjunction with irinotecan compared with irinotecan alone. These results established the combination regimen as a standard of care for refractory metastatic colorectal cancer.³ In 2004, cetuximab either in combination with irinotecan or as a single agent was approved by the Food and Drug Administration (FDA) for the treatment of metastatic colorectal cancers that express EGFR and are refractory to irinotecan- or oxaliplatin-based therapies.^{3,34,35}

As cetuximab was increasingly used to treat refractory metastatic colorectal cancer, it became clear that this agent is most effective in a subset of patients.^{33,36–38} Specifically, tumors possessing a mutation in the *K-ras* gene responded poorly to cetuximab, whereas tumors with wild-type *K-ras* responded well.^{39–41} The consensus that *K-ras* status is a predictive marker for response to cetuximab therapy has led to current recommendations that patients be tested for the mutation prior to the initiation of treatment.^{42,43}

In 2001, Shin and colleagues studied the combined effect of cetuximab and cisplatin in patients with recurrent or late-stage squamous carcinoma of the head and neck.³⁰ In this study, 67% of patients demonstrated a major response with the addition of cetuximab.³⁰ This drug also showed efficacy in improving the response rates in patients with head and neck cancer when combined with cisplatin, 5-FU, and radiation.³² As such, in 2006, cetuximab was approved by the FDA for the treatment of squamous cell carcinoma of the head and neck in combination with radiation therapy or as a single agent in cases refractory to platinum-based regimens.⁴⁴ Thus, cetuximab has demonstrated efficacy for the treatment of several cancers that in the past have been difficult to treat, and the recognition of optimal applications is growing. Although still under active investigation for more general use, this agent holds promise for treating a variety of cancers.

Another human monoclonal antibody that targets EGFR, panitumumab, has a different mechanism of action. Panitumumab functions by binding to the site of epidermal growth factor and tumor necrosis factor- α (TNF- α) binding on the EGFR.⁴⁵ The antibody is then internalized and downregulates EGFR production, induces apoptosis, and inhibits tumor growth and cell cycle progression.⁴⁵ Panitumumab has

been approved by the FDA for the treatment of EGFR-expressing metastatic colorectal cancer refractory to fluoropyrimidine-, irinotecan-, or oxaliplatin-based therapies.⁴⁶ Similar to cetuximab, however, several studies have identified *K-ras* mutation as a predictive marker for panitumumab response and thus recommend that *K-ras* status be identified prior to the initiation of treatment.⁴³ Recent work also has identified additional markers that have the potential to predict tumor response to monoclonal antibodies, such as cetuximab and panitumumab. For example, *BRAF*, *N-ras*, and *PIK3CA* have been suggested as potential biomarkers for response to anti-EGFR therapy and hold promise for further personalizing cancer treatment.^{47,48}

Finally, other similar agents, such as pertuzumab, an antibody that prevents dimerization of HER-2 receptors, are being developed and tested.⁴⁹ In vitro, pertuzumab demonstrated synergy with trastuzumab in inhibiting breast cancer cell growth. A phase I trial demonstrated that this drug was well tolerated and produced promising preliminary clinical results.^{49,50}

Small Molecule TKIs

Gefitinib is a small molecule inhibitor that targets the epidermal growth factor receptor 1 (EGFR1/HER-1) by inhibiting autophosphorylation.²⁷ This small molecule binds the intracellular TK domain of the receptor.^{51,52} Gefitinib was originally approved for the treatment of non-small cell lung cancer in 2003. However, in 2005, its use was limited only to patients who had previously benefited from the drug after two clinical trials demonstrated no advantage in patients with non-small cell lung tumors that overexpressed EGFR.⁵³ As clinical testing has continued, the results with gefitinib treatment have been mixed. Recent data from the North-East Japan Study Group indicated that first-line gefitinib prolonged progression-free survival in patients with metastatic non-small cell lung cancer with EGFR mutation(s) compared with carboplatin and paclitaxel.⁵⁴ In contrast, other studies have failed to show any improvement in survival.^{55,56} Interestingly, gefitinib appears to reverse drug resistance in breast cancer cells that overexpress Pgp, a multidrug resistance protein, suggesting that this may also be a therapeutic target for this agent.⁵⁷

Erlotinib is another small molecule inhibitor of EGFR autophosphorylation that binds the kinase domain of the receptor and inhibits cell proliferation and cell cycle progression. In preclinical trials, erlotinib effectively inhibited activation of EGFR in colorectal cancer cells, inhibited in vivo growth of squamous cell head and neck cancer cells that overexpress EGFR, and inhibited in vivo growth of non-small cell lung cancer cells.^{58–60} In a large randomized, placebo-controlled, double-blind trial studying patients with advanced non-small cell lung cancer (stage IIIB or IV), erlotinib therapy prolonged progression-free and overall survival and was subsequently approved as second-line therapy for treating non-small cell lung cancer in 2004.^{61–64} Later, erlotinib was approved in combination with gemcitabine for treating pancreatic cancer (2005) and as maintenance therapy for non-small cell lung cancer (2010).⁶⁴

Multitargeted Inhibitors

Despite the demonstrated efficacy of monoclonal antibodies and small molecule inhibitors of TKIs, the development

of resistance has been a concern and, as such, has led to the development of second-generation TKIs that are capable of inhibiting multiple TKs. These molecules are designed to inhibit not only EGFR/HER-2 activation, for example, but also downstream cell signaling molecules such as the src family of kinases and proteins such as c-kit, HER-2, and PDGFR.⁶⁵

Lapatinib is an EGFR and HER-2 inhibitor that has been extensively studied in the treatment of breast cancer. The unique feature of this inhibitor is the extended binding time to EGFR that prolongs its inhibitory effect. As a single agent, only modest clinical benefit was appreciated in phase II trials. However, lapatinib appears to be effective when used in combination with other agents. For example, in patients with metastatic breast cancer who overexpress HER-2, treatment with lapatinib plus capecitabine markedly improved progression-free survival. Also, patients receiving the combination regimen showed 51% reduction in risk of disease progression, decreased incidence of central nervous system (CNS) metastases, and decreased volume of existing CNS metastases.²⁷ In 2007, lapatinib in combination with capecitabine was approved by the FDA for use in advanced breast cancers that overexpress HER-2. In addition, in 2010, the FDA approved the combination of lapatinib and letrozole in postmenopausal women with advanced breast cancers who overexpress HER-2 and are hormone receptor positive. The combination regimen significantly improved progression-free survival.⁶⁶

Another of the second-generation, multitargeted TKIs, dasatinib, has demonstrated increased inhibitory activity against Bcr-Abl compared with imatinib in vitro and is currently approved for the treatment of CML in patients who have developed resistance to imatinib or are otherwise intolerant of the drug.^{8,65} In the SRC/ABL Tyrosine kinase inhibition Activity Research Trials of dasatinib (START-C) trial, 53% of patients who received dasatinib achieved a complete cytogenetic response and 62% achieved a major cytogenetic response after 24 months.^{8,67} Although this investigation involved the initiation of dasatinib treatment after failure of imatinib, there is speculation and early evidence that it may be effective as a first-line agent. Initial studies have suggested that the rate of remission at 24 months was superior with initial treatment of dasatinib when compared with initial treatment with imatinib.^{8,68}

Additional multitargeted agents are also under development. For example, neratinib inhibits both EGFR (ErbB1), HER-2 (ErbB2), and HER-4 (ErbB4), and in a phase I study for use against solid tumors, the agent was well tolerated and showed promising clinical activity.⁶⁹ A phase II trial of its use against advanced breast cancer supported early findings, and further studies are under way for the treatment of breast cancer and other solid tumors.^{10,70}

Another group of TKIs that target multiple receptors is difficult to classify because these agents affect a variety of kinases and downstream signaling cascades. For example, some of these molecules inhibit angiogenesis by blocking the vascular endothelial growth factor receptor (VEGFR) while also inhibiting TKs such as c-kit and HER-2. One such inhibitor is sunitinib, a molecule that inhibits c-kit, PDGFR- α , CSF-1 receptor, and VEGFR-1, -2, and -3.²⁷ The FDA approved its use in advanced renal cell carcinoma after it demonstrated efficacy by improving progression-free survival

and overall survival compared with interferon alfa.^{71,72} Sunitinib has also been used successfully to treat GISTs that have developed resistance to imatinib and is FDA approved for use in that setting.^{71,73,74}

Other clinical trials test sunitinib's efficacy in a variety of settings, and a phase II study using sunitinib for treating thyroid cancer that was resistant to radioactive iodine showed that 3% of patients had a complete response, 29% showed a partial response, and 46% maintained stable disease.⁷⁵ In addition, for metastatic breast cancer patients who failed treatment with anthracyclines and taxanes, sunitinib treatment helped some (5%) achieve stable disease.⁷⁶ Despite these promising results, toxicity has emerged as a concern with this agent. For example, in the study treating metastatic breast cancer, dose modification was necessary in 56% of patients as a result of adverse effects.⁷⁶ Similarly, in a study combining sunitinib with cyclophosphamide and methotrexate, of the 15 patients studied, three developed neutropenia and five developed mucositis.²⁷ In another phase I dose-escalation study combining sunitinib and capecitabine in patients with solid tumors, five grade 3 adverse effects emerged: abdominal pain, mucosal inflammation, fatigue, neutropenia, and hand-foot syndrome.⁷⁷ Similar side effects have been reported in other clinical trials, and one trial was terminated early because of the high incidence of neutropenia, febrile neutropenia, and fatigue.²⁷ Interestingly, in one study of efficacy against hepatocellular carcinoma, the neutropenia and skin toxicities seemed to correlate with response to therapy, overall survival, and time to tumor progression, suggesting that those toxicities may be a marker for tumor response.⁷⁸

Axitinib is another inhibitor of several RTKs, including all VEGFRs (1, 2, and 3), PDGFR- β , and c-kit.²⁷ This agent has shown promise in phase I studies and was initially thought to have few severe side effects (hypertension was most common). Phase II studies have suggested a benefit to adding axitinib to docetaxel for patients with metastatic breast cancer and in combination with gemcitabine for treating metastatic pancreatic cancer.^{27,79} In the phase II trials, however, toxicity appeared to be greater than suggested in the phase I trials (febrile neutropenia, fatigue, stomatitis, diarrhea, hypertension), and a phase III trial combining the agent with gemcitabine was terminated early because of a lack of improved survival.^{27,80} Clinical trials continue to investigate the use of axitinib for the treatment of a variety of solid tumors, including, but not limited to, renal cell carcinoma, hepatocellular carcinoma, colorectal cancer, lung cancer, and melanoma.¹⁰

Finally, vandetanib is a molecule that inhibits EGFR, the kinase domain of VEGFR2, and ret autophosphorylation that is currently in the early stages of clinical investigation.^{27,81–85} Phase I data suggest that although this agent is well tolerated, it provided no clinical benefit for patients with multiple myeloma.⁸¹ Early clinical trials for use against refractory non-small cell lung cancer, however, were more promising, prompting the initiation of phase III investigations for its use in that disease.^{83,85} The Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC) trial examined the effect of vandetanib with docetaxel on previously treated non-small cell lung cancer; compared with patients who received docetaxel with placebo, patients who received vandetanib had significantly longer progression-free survival and an improved

overall response rate.⁸⁶ Early clinical trials in glioblastoma and medullary thyroid cancer also have shown promising results.^{87,88} At present, the indications for the use of these agents, both alone and in combination with other drugs, are evolving and await the results of clinical trials.

TKIs are the prototype for targeted therapeutics. These agents have been widely studied, and new and increasingly effective molecules are under development. Interestingly, one consistent theme with TKIs is the ability of biomarkers such as *K-ras* mutation and EGFR overexpression to predict response. This improved understanding of the molecular mechanisms underlying carcinogenesis and tumor response to therapy increasingly is leading to a more individualized approach to cancer treatment.

Angiogenesis Inhibitors

BIOCHEMICAL RATIONALE

Angiogenesis is one of the earliest events in tumor growth.⁸⁹ Hypoxic conditions provoke tumor microvascular formation by not only inciting proangiogenic signals but also inhibiting antiangiogenic signals.^{90–92} The proangiogenic factors released include, but are not limited to, vascular endothelial growth factors (VEGFA, -B, -C, -D, and -E), basic fibroblast growth factor (bFGF), interleukin-8, placental growth factors (PLGF-1 and -2), neurophilins (NRP1 and NRP2), transforming growth factors (TGFs), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF).^{3,89,93} The effects of these proangiogenic proteins can be classified based on the mechanism by which they stimulate microvascular formation.⁸⁹ For example, some stimulate new growth of vasculature from preexisting blood vessels, whereas others induce the formation of de novo vascular channels.⁹⁴ VEGFR stimulation activates intracellular phospholipase C γ (PLC- γ), protein kinase C (PKC) and the MAPK pathway, PI $_3$ kinase, Akt/PKB (protein kinase B), nuclear factor κ B (NF- κ B), and endothelial nitric oxide synthases and inhibits proapoptotic proteins, thereby inducing endothelial cell survival, proliferation, and migration and increasing vasodilation, vascular remodeling, and vessel permeability.⁹⁵ In addition, hypoxia-inducible factors (HIFs) are transcription factors that are activated under hypoxic conditions and serve as a major stimulus for angiogenesis.⁸⁹

Folkman's hypothesis suggests that approximately 2 mm³ is the critical tumor size at which further growth and survival depend on an autonomous vascular network.⁹⁶ The resulting neovasculature is tortuous and irregular, and although not efficient enough to satisfy the oxygen needs of the growing tumor, these networks are able to promote growth and metastasis.⁸⁹ The most important cell involved in this process is the vascular endothelial cell, and its growth is primarily regulated by VEGF activation of the VEGFR. In normal tissues, VEGFR2 appears to be the major inducer of angiogenesis, whereas the relatively weak signal cascade of VEGFR1 may actually decrease angiogenesis. VEGFR3 is involved in embryologic and postnatal angiogenesis and lymphangiogenesis. In cancer, VEGFR1 and -2 appear to be the receptors most involved in tumor angiogenesis.³ Both VEGF and VEGFRs have emerged as logical targets for drugs seeking to inhibit angiogenesis.^{42,89}

ANGIOGENESIS INHIBITORS

Bevacizumab is the prototypical angiogenesis inhibitor. This anti-VEGFA antibody reduces the amount of effective circulating VEGFA and thereby prevents VEGFR activation.⁴² Bevacizumab has shown efficacy in suppressing endothelial cell adhesion and proliferation in vitro and suppressing peritoneal dissemination of gastric cancer in a murine model.^{97,98} Clinical efficacy was first demonstrated in colorectal cancer. In stage IV disease, bevacizumab in combination with irinotecan, 5-FU, and folinic acid (leucovorin) (FOLFIRI) induced higher response rates and prolonged progression-free and overall survival compared with traditional chemotherapy.⁹⁹ In 2004, bevacizumab was approved by the FDA as a first-line treatment for metastatic colorectal cancer and in 2006 as second-line treatment in combination with oxaliplatin, folinic acid, and 5-FU (FOLFOX4).^{100,101} The efficacy of bevacizumab has subsequently been tested in other tumor types, including pancreatic and hepatocellular carcinoma, renal cell carcinoma, neuroendocrine tumors, non-small cell lung cancer, and breast, brain, and ovarian cancers.¹⁰

Despite early enthusiasm about bevacizumab, additional experience has met with mixed results. The Bevacizumab Regimens' Investigation of Treatment Effects (BRiTE) study, an observational cohort study of 1,953 patients with metastatic colorectal cancer from 248 United States sites between 2004 and 2005, examined the efficacy of bevacizumab combined with chemotherapy as first-line treatment for metastatic colorectal cancer. At 20 months, progression-free survival was observed in 22% of patients who had received bevacizumab, whereas disease progression was seen in 79% of the patients. In addition, 66% of patients died during the study period, and 12% either withdrew from the study or were lost to follow-up.¹⁰² Similarly, in a phase III study by Stathopoulos and colleagues in 2010, median overall survival did not differ between groups that received bevacizumab with chemotherapy (irinotecan, 5-FU, leucovorin) and groups that received chemotherapy alone as the initial treatment for metastatic colorectal cancer.¹⁰³ Moreover, in a phase II study of bevacizumab with erlotinib for treating recurrent malignant glioma, progression-free survival was not significantly improved in patients who received bevacizumab.¹⁰⁴ Other early studies, however, have suggested efficacy in the treatment of other types of cancer. In non-small cell lung cancer, the effects on overall survival were inconsistent, but the drug appeared to slow the progression of the disease.¹⁰⁵ In vitro data suggest efficacy in combination with docetaxel for treatment of breast and prostate cancers.¹⁰⁶ In combination therapy with paclitaxel for metastatic breast cancer, bevacizumab improved response rates compared with paclitaxel alone.¹⁰⁷

To date, the FDA has approved bevacizumab in combination with carboplatin and paclitaxel for the treatment of non-small cell lung cancer and in combination with interferon for the treatment of metastatic renal cell carcinoma.^{101,108,109} It has also been approved for use as a second-line single agent for the treatment of glioblastoma.¹⁰¹ In 2008, bevacizumab was approved as first-line treatment in combination with paclitaxel for metastatic HER-2-negative breast cancer.¹⁰¹ However, the results of more recent analyses of several clinical trials have failed to show any survival advantage in breast

cancer patients who receive bevacizumab compared with chemotherapy alone. As a result, the Oncologic Drugs Advisory Committee of the FDA has recommended withdrawing the approval of bevacizumab as first-line treatment for metastatic breast cancer.¹¹⁰ The FDA is currently reviewing the data on this drug, and the decision regarding possible revocation of approval is pending.¹¹¹

Toxicity, although not prohibitive, is common, and the most common adverse effects are rash, hepatotoxicity (elevated liver function tests), proteinuria, diarrhea, myelosuppression, fatigue, infection, pain, nausea/vomiting, and hypokalemia.^{104,105,107,112} In addition, the BRiTE study found several rare, but more severe, side effects. New onset or worsening hypertension was seen in 22% of patients, and hypertension was implicated in eight serious adverse events. Additional less common but serious adverse events included postoperative wound healing complications (4%), grade 3 to 4 bleeding (2.2%), arterial thromboembolic events (2%), and gastrointestinal perforation (2%). The majority of bleeding events were gastrointestinal. Significant postoperative wound healing complications occurred following major surgery and in patients in whom surgery was undertaken within 2 weeks of the last bevacizumab dose.¹⁰² This observation has led most surgeons to try to avoid operating on patients within 6 to 8 weeks of bevacizumab therapy. Moreover, the FDA has issued a drug warning and safety labeling update concerning these adverse effects.¹⁰¹

Aflibercept (VEGF Trap) is a molecule in which the ligand-binding domains of the VEGFR1 and VEGFR2 proteins are fused with human IgG1, forming a decoy receptor that binds all VEGFs and placental growth factor.²⁷ Preclinical studies have suggested that this agent is well tolerated but have failed to show significant clinical activity. Definitive recommendations about the use of aflibercept await the results of ongoing trials.²⁷

Angiogenesis inhibitors have demonstrated efficacy in a variety of disease sites; however, they also have limitations. Of particular concern to surgeons are the risk of increased bleeding and inhibition of wound healing. Nevertheless, antiangiogenic compounds have proven to be useful in well-selected patients.

Cell Cycle Inhibitors

BIOCHEMICAL RATIONALE

Regulation of the cell cycle involves a highly complex sequence of events orchestrated by cyclins and cyclin-dependent kinases (CdKs) [see Figure 3]. The interaction of these molecules is regulated by several naturally occurring cyclin-dependent kinase inhibitors (CdKIs) that prevent binding of CdKs to cyclins. Two families of CdKIs have been identified: the INK4/ARF family and the Cip/Kip family. The INK4/ARF family includes p15, p16, p18, and p19, and the Cip/Kip family includes p21, p27, and p57.^{113,114} A cell will exit the quiescent phase, G₀, and enter G₁ following the production of cyclin D, which is the result of activation of the Ras/Raf/MAPK signal cascade by mitogens. Progression through the cell cycle is permitted to occur when the CdKIs do not prevent CdK-cyclin interactions. For example, cyclin E-CdK2 complex formation promotes cell entry into

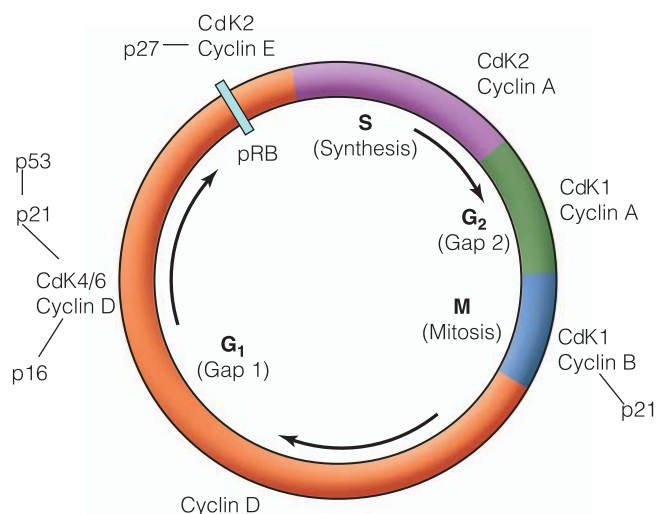


Figure 3 Progression through each phase of the cell cycle is regulated by cyclin-cyclin-dependent kinase interactions. Adapted from www.sysmex-lifescience.com (accessed October 2010).

S phase, and cyclin B–Cdk1 allows mitosis to occur^{115,116} [see Figure 3]. Overall, nine CdKs have been described, and these molecules interact with 20 possible cyclins (A to T).¹¹⁵ Given that cyclins and CdKs play major roles in controlling progression through the cell cycle, they are logically attractive targets for treating cancer. In addition, there is evidence that CdK or cyclin production is disrupted in several malignancies, including melanoma and lung, breast, and colorectal cancers.^{115,117,118} Several cell cycle inhibitors are currently under investigation, but clinical results have been mixed, and it has been suggested that these agents may have more utility as chemosensitizers for other agents.¹¹⁵

CELL CYCLE INHIBITORS

Currently, CdKis include flavopiridol, roscovitine, E7070, AZD5438, SNS-032 (BMS-387032), bryostatin-1, PD 0332991, and SCH 727965. Flavopiridol acts on the G₁ and S phases of the cell cycle via inhibition of CdKs 2, 4, 6, and 9 and has demonstrated early success in vitro by inducing arrest of cellular growth and inducing apoptosis in chronic lymphocytic leukemia (CLL) and colorectal cancer cells.^{119,120} Currently, flavopiridol is useful for treating recurrent CLL, where it has been shown to induce a clinical response in patients with high-risk genomic features.¹²¹ In addition, when given with cytosine arabinoside and mitoxantrone, flavopiridol induced complete remission in 67% of patients with AML who had poor-risk features (older age, unfavorable genetic mutations, or secondary AML).¹²² Phase I trials indicate drug tolerability, and phase II trials continue to test this drug's efficacy in a variety of cancers.¹²³

Roscovitine inhibits cyclin E–Cdk2, cyclin B–Cdk1, cyclin H–Cdk7, and cyclin T1–Cdk9 and prevents progression through the S, G₂, and M phases of the cell cycle.¹¹⁵ In vitro studies also indicate that this drug induces apoptosis by activating p53, suppressing NF-κB, and downregulating Mcl-1 (an antiapoptosis protein) in multiple myeloma cells.^{124–126} It also inhibits mitosis by decreasing production of promoters of cell division, such as Aurora-A/B, CDC25C, pololike kinase,

and WEEL.¹²⁷ Preclinical studies have demonstrated the efficacy of this agent in a variety of cancer cell lines. A phase II clinical trial of roscovitine for treating resistant non-small cell lung cancer has recently been completed, and phase I investigation of its clinical safety in treating any solid tumors resistant to standard treatment is under way.¹⁰

E7070 is a synthetic sulfonamide that inhibits Cdk2 and cyclin E, effectively inhibiting progression through G₁ and S phases.¹²⁸ In vitro, this agent blocked cell cycle progression in non-small cell lung cancer cells, and in vivo, it not only inhibited tumor growth but also induced regression in models of colon cancer and non-small cell lung cancer.^{129,130} Four phase I clinical trials are currently under way evaluating the use of this agent in solid tumors and melanoma. However, the results of phase II trials in other disease sites have been somewhat disappointing. For example, E7070 as a single agent did not show significant response in non-small cell lung cancer.¹³¹ In 2005, Smyth and colleagues reported similar results in metastatic melanoma, with the best response being stable disease in 17% of patients, whereas 58% experienced disease progression.¹³² A phase II study in squamous cell head and neck cancer was terminated because of the 15 patients who were treated, none achieved 4 months of progression-free survival.¹³³ In addition, toxicity was concerning in these trials, prompting some patients to withdraw. Most common problems consisted of gastrointestinal upset (nausea, vomiting, constipation, or diarrhea) and pain at the injection site.¹³¹ However, more severe side effects, such as anemia, thrombocytopenia, bleeding, and one reported death attributable to pulmonary embolus, have also been attributed to E7070 treatment.¹³² Since the conclusion of those trials, pharmacokinetic studies have been initiated in an effort to identify the optimal dose of E7070 in combination with other agents in an attempt to minimize toxicity.^{134,135}

A number of additional cell cycle inhibitors are currently undergoing early clinical evaluation for the treatment of a variety of malignancies [see Table 2]. One such agent is SNS-032, an aminothiazide-based inhibitor that halts cell cycle progression by way of Cdk2 and -7 inhibition, and transcription via Cdk7 and -9 inhibition.^{136,137} Interestingly, the antitumor efficacy of SNS-032 may also result from inhibition of VEGF expression, hindering angiogenesis.¹³⁸ Phase I investigations of oral bioavailability in patients with metastatic solid tumors and lymphomas, as well as previously treated CLL and multiple myeloma patients, indicate that oral administration is feasible, and although neutropenia and thrombocytopenia were the most common side effects, the agent was largely well tolerated.^{137,139}

Bryostatin-1 is a macrocyclic lactone derived from *Bugula neritina*.¹⁴⁰ This natural antineoplastic agent affects protein kinase C levels, inhibits Cdk2, and induces p21.^{115,141} Although promising in preclinical investigations, the results of phase II studies have shown inconsistent efficacy as a single agent or in combination with other agents. Some trials, however, did report disease improvement with bryostatin-1 treatment. Most recently, Barr and colleagues demonstrated that combination bryostatin-1 and vincristine induced an overall response rate of 31% with complete remission of disease in two patients with non-Hodgkin lymphoma.¹⁴² Clinical trials continue to test this agent under myriad conditions.¹⁰

Table 2 Cell Cycle Inhibitors

<i>Cell Cycle Inhibitor</i>	<i>Mechanism of Action</i>	<i>Effects</i>	<i>Clinical Trials*</i>
Flavopiridol	Inhibits Cdk 2, 4, 6, 9	G ₁ /S arrest	Phase I/II (hematologic and several solid tumors)
Roscovitine	Inhibits cyclin E/Cdk2, cyclin B/Cdk1, cyclin H/Cdk7, cyclin T1/Cdk9; p53 activation, nuclear factor κB, decreases Mcl-1	S/G ₂ /M arrest	Phase I/II (solid tumors)
E7070	Inhibits Cdk2, cyclin E	G ₁ /S progression	Phase I/II (several solid tumors, melanoma)
SNS-032	Inhibits Cdk 2, 7, 9, VEGF	Inhibits progression and transcription, angiogenesis	Phase I (advanced B cell lymphomas, several solid tumors)
Bryostatin-1	Affects protein kinase C, Cdk2; induces p21	Cell cycle modulation	Phase I/II (combination therapy for hematologic and several solid tumors)
AZD5438	Inhibits Cdk1, 2, 9	Affects all phases of cell cycle	Trials terminated due to safety concerns

*Adapted from www.clinicaltrials.gov.¹⁰

Cdk = cyclin-dependent kinase; VEGF = vascular endothelial growth factor.

Finally, AZD5438 is one cell cycle inhibitor that exemplifies the difficulty in translating laboratory outcomes to clinical practicality. This agent worked through all phases of the cell cycle by inhibiting Cdk1, -2, and -9.^{115,143} Preclinical data were promising, but the clinical trials yielded less favorable outcomes. The most recent phase I trial published, studying patient tolerance of AZD5438 for the treatment of recurrent solid malignancies, indicated that weekly dosing was more appropriate than continuous. However, safety concerns prompted manufacturer discontinuation of the agent and thus resulted in early termination of clinical trials.¹⁴⁴

Cell cycle inhibitors are in the early stages of evaluation, and some have shown promising initial results in combination with other chemotherapies. However, although tumor cells demonstrate accelerated cell turnover and, as such, should be most sensitive to these agents, the nonspecific targeting of the cell cycle can injure normal tissues. Thus, as is the case with angiogenesis inhibitors, toxicity remains a major concern and has limited the clinical applicability of some of these drugs.

Inducers of Apoptosis

BIOCHEMICAL RATIONALE

Apoptosis is the natural process of programmed cell death, and two pathways are involved in this process. The extrinsic pathway is mediated by death receptors such as Fas, TNF, and TRAIL, among others. The intrinsic pathway is mitochondria and apoptosome mediated and can be activated by radiation and chemotherapy. It includes downstream signaling mediated by bcl-2 and the bcl-2 family of antiapoptotic or proapoptotic proteins (e.g., Bid, Bax, Bak), as well as caspases and cytochrome-c. These pathways are not mutually exclusive; for example, caspases are known to participate in both intrinsic and extrinsic pathways. Naturally occurring apoptosis proteins interact with the caspases to either inhibit or induce the innate process of programmed cell death.^{145,146} Although these molecules balance the proapoptotic/antiapoptotic equilibrium, changes in any number of elements in the signal cascade may disrupt normal apoptosis.

For example, a mutation resulting in the loss of antiapoptotic p53 functions can lead to genomic instability and decreased apoptosis. Cancer therapies that target the inappropriate loss of control over apoptosis have been developed to induce the intrinsic and extrinsic pathways either independently or together. Recent work has focused on inhibition of pathways involving the TRAIL receptor, bcl receptors, and inhibitors of apoptosis proteins (AIPs).¹⁴⁷

APOPTOSIS-INDUCING AGENTS

Apoptosis inducers can be classified based on their mechanism of action. Bortezomib, suberoylanilide hydroxamic acid (SAHA), TLK286, ONYX015, FTI-R115777, and 17AAG target protein kinases, proteasomes, and transcriptional factors. Mapatumumab and lexatumumab target the proapoptotic proteins TRAILR1 and TRAILR2.

Bortezomib is a boronic acid dipeptide and was the first proapoptotic agent used in cancer treatment. Bortezomib promotes apoptosis by inhibiting the 26S proteasome.¹⁴⁸ This proteasome degrades many cellular proteins, including those involved in the cell cycle, transcription, and tumor suppression. Early work suggested that 26S proteasome inhibition promoted apoptosis in multiple myeloma cells and that this molecule stabilized tumor suppressor and cell cycle proteins (p53, p21, and p27).¹⁴⁸ The Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial suggested superior efficacy of bortezomib over dexamethasone for refractory multiple myeloma.¹⁴⁹ Clinical trials also suggest that this agent may effectively augment the antitumor activities of established chemotherapy regimens. For example, the Velcade as Initial Standard Therapy in Multiple Myeloma (VISTA) study was a phase III clinical evaluation of bortezomib in combination with melphalan and prednisone as first-line therapy for multiple myeloma. The addition of bortezomib to the standard melphalan-prednisone regimen slowed time to disease progression, increased the incidence of partial and complete response, and prolonged the duration of response.¹⁵⁰ Further follow-up showed that patients treated with a combination of bortezomib, melphalan, and prednisone had better overall survival at 3 years (69% versus 54%),

and 35% reduced risk of death at 26.7 months when compared with patients who received only melphalan and prednisone.¹⁵¹ The FDA approved bortezomib as a second-line therapy for the treatment of mantle cell lymphoma in 2006 and as first-line therapy for multiple myeloma in 2008.¹⁵²

Several clinical trials have studied the efficacy of bortezomib against solid tumors, such as hepatocellular carcinoma and metastatic rectal cancer.^{153–155} Bortezomib has also been proposed as a radiosensitizer in combination with 5-FU for neoadjuvant treatment of locally advanced (stages II and III) rectal cancer. However, in a small study, only one of nine patients treated had a complete pathologic response, arguably equivalent to 5-FU-based strategies alone.¹⁵⁴ At present, there are no indications for use of this agent in solid tumors, despite its efficacy in hematologic malignancies.¹⁵⁶

SAHA inhibits histone deacetylase, thereby suppressing the expression of genes that can promote tumorigenesis.¹⁵⁷ In vitro and in vivo studies indicated that histone deacetylase inhibitors such as SAHA downregulate TNF- α receptor-1 expression and activation of NF- κ B.¹⁵⁸ Several clinical trials have been completed, and in 2006, the agent was approved by the FDA as a third-line treatment option for cutaneous T cell lymphoma.¹⁵⁹ The trials that led to approval demonstrated that patients who had previously failed treatment benefited from treatment with SAHA. Side effects were tolerable, and the most common adverse effects were fatigue (52%), diarrhea (52%), and nausea (40%). More serious effects (pulmonary embolism, deep vein thrombosis, myocardial infarction) occurred in fewer than 10% of patients.¹⁵⁹ Additional clinical investigations are under way, including a phase III trial of SAHA use against advanced mesothelioma.¹⁶⁰

Several other agents designed to induce apoptosis are under investigation [see Table 3]. TLK286, a modified glutathione analogue, is metabolized by glutathione S-transferase (GST) in the tumor cell cytosol, yielding a molecule that is toxic to the cell. Because GST is overexpressed in many resistant

tumor cells, TLK286 may be an ideal therapeutic option in these refractory tumors.^{161,162} Preliminary data suggest that TLK286 has little efficacy as a single agent, but combination with other agents may be useful.^{163–167} A phase III study comparing TLK286 with doxorubicin or topotecan as a third-line treatment for refractory ovarian, fallopian, or primary peritoneal cancer is currently under way.¹⁶⁸

The adenovirus ONYX015 is an attenuated adenovirus that has also shown antitumor activity, although the mechanism of action remains poorly understood. It was initially thought that the virus selectively invades and replicates in *p53* mutated cells and binds to and inactivates the *p53* gene but has no effect on normal cells.^{169,170} However, other studies have suggested that its efficacy results from more complex interactions and not just mutated *p53*.^{171,172} In 2004, the agent was approved in China for use against squamous cell head and neck cancer, and in the United States, it has shown promise in phase I and II trials as combination therapy for patients with solid tumors such as advanced sarcoma and recurrent head and neck cancer.^{173–175}

Another agent that induces apoptosis is FTI R115777, a methylquinolone farnesyl transferase inhibitor (FTI). Initially thought to inhibit cell growth and induce apoptosis solely by blocking farnesylation of Ras, it now appears that FTI R115777 also induces cell death by disrupting the mitochondrial membrane and inducing caspase-9 activation.¹⁷⁶ Early clinical trials have yielded mixed results. The Children's Oncology Group, however, recently reported that although the pharmacokinetics were more variable in the pediatric population, the agent is well tolerated for the treatment of pediatric hematologic malignancies, and further investigation in solid tumors and neurofibromatosis type 1-related plexiform tumors is warranted.^{177,178}

7AAG is an inhibitor of heat shock protein HSP90, a molecule that is frequently overexpressed in tumor cells.¹⁷⁹ This agent has been thoroughly studied in vitro and in vivo

Table 3 Inducers of Apoptosis

<i>Inducer of Apoptosis</i>	<i>Mechanism of Action</i>	<i>Effects</i>	<i>Clinical Trials*</i>
Bortezomib	Inhibits 26S proteasome	Decreased degradation of cell cycle and transcription proteins	FDA approved as first-line treatment of multiple myeloma and as second-line treatment of mantle cell lymphoma
Suberoylanilide hydroxamic acid (SAHA)	Inhibits histone deacetylase	Suppress tumorigenic gene expression	FDA approved as third-line treatment of cutaneous T cell lymphoma; phase III (advanced mesothelioma)
TLK286	Formation of a toxic metabolite	Induces apoptosis	Phase III (refractory gynecologic malignancies), combination therapy
ONYX015	Adenovirus; invades and replicates in <i>p53</i> mutated cells, inactivates <i>p53</i> gene	Lyses <i>p53</i> mutated tumor cells	Phase I/II (combination therapy for solid tumors)
FTI-R115777	Blocks farnesylation of Ras, disrupts mitochondrial membrane, induces caspase-9 activation	Inhibit cell growth and induce apoptosis	Phase III (colorectal cancer and AML; no significant improvement in progression-free survival or overall survival, respectively); phase I/II (pediatric leukemias, glioma)
17AAG	Inhibits HSP90	Inhibit cell motility and invasion	Phase I/II (multiple myeloma)
Mapatumumab	TRAILR1 agonist	Inhibit TRAIL ligand binding and apoptotic signal cascade	Phase I/II (several solid tumors)
Lexatumumab	TRAILR2 agonist		

*Adapted from www.clinicaltrials.gov.¹⁰
AML = acute myelogenous leukemia; FDA = Food and Drug Administration.

and affects a variety of cancer cell types by inducing apoptosis, decreasing growth, potentiating the effects of known chemotherapeutic drugs, and sensitizing tumors to radiotherapy.¹⁸⁰ Phase I and II trials suggest a tolerable safety profile and disease stability when administered as a single agent or in combination with bortezomib.^{181,182}

Another pathway targeted to induce apoptosis involves TRAILR1 and TRAILR2. TRAILR1 and TRAILR2 are two TRAIL receptors that are believed to be involved in apoptosis via FADD and caspase-8 or -10 recruitment and possibly by activation of other signaling pathways involving NF- κ B, MAPK, PI₃ kinase, and Akt. Initiated by TRAIL ligand binding, this process has been linked to tumorigenesis and is a promising target for anticancer therapy. Mapatumumab (HGS-ETR1) and lexatumumab (HGS-ETR2) are two monoclonal antibodies that agonistically bind the TRAILR1 and TRAILR2 receptors, respectively.¹⁴⁷ The role of mapatumumab and lexatumumab in combination with other agents has been supported by the observation of a synergistic effect with either antibody and cisplatin or bortezomib in non-small cell lung cancer cells and malignant mesothelioma cells or with radiotherapy in colorectal cancer cells.^{183–185} Clinical trials are under way for both mapatumumab and lexatumumab.¹⁰ Although well tolerated, the clinical response at the dose of mapatumumab administered was not significant.¹⁸⁶ Phase I trials also suggested that lexatumumab is safe and well tolerated and has promising clinical efficacy.^{187,188}

Thus, drugs designed to induce apoptosis are showing early promise for the treatment of a variety of cancers. Clinical trials suggest that the side effect profile does not limit use and that these drugs may be most effective as chemo- or radio sensitizers.

Focal Adhesion Kinase Inhibitors

BIOCHEMICAL RATIONALE

Focal adhesion kinase (FAK) is a non-RTK that was identified at adhesion sites between cells and the extracellular environment. The 125 kDa protein is encoded by a gene located on chromosome 8 and houses three domains, the amino-N-terminal domain, the central catalytic domain, and the carboxy-C-terminal domain. FAK activation relies on autophosphorylation of the Y397 site that is found in the N-terminal domain. This is also a binding and activation site for several signaling proteins, such as src, PI₃ kinase, and Grb-7. In addition, this region also binds extracellular matrix and signaling proteins involved in cell motility, invasion, and cytoskeletal changes, as well as EGFR, p53, and other molecules that are critical for carcinogenesis.¹⁸⁹ It is well known that p53 is mutated in many cancers; interestingly, p53 can inhibit FAK expression, and FAK can inhibit p53 expression. In breast cancer cells, p53 mutation is highly correlated with FAK overexpression.¹⁹⁰ Finally, FAK appears to play a key role in motility and migration, invasion, survival, angiogenesis, lymphangiogenesis, and proliferation¹⁸⁹ [see Figure 4].

FAK is upregulated in several types of cancer.¹⁸⁹ The potential role of FAK activation in cancer growth and progression has led to the development of several therapeutic agents targeting this molecule. Initial attempts were focused on downregulation of FAK expression. Subsequently, more

specific targeted therapeutic approaches have been developed using small molecules designed to inhibit FAK kinase activity and activation or to inhibit protein-protein interactions.

FAK INHIBITORS

Initial attempts at FAK inhibition focused on downregulating FAK expression. Early studies demonstrated that transfection of breast cancer cells with dominant negative C-terminal FAK-CD decreased adhesion, colonization, and in vivo tumor growth.¹⁹¹ Moreover, cells transfected with FAK-silenced RNA (FAKsiRNA) showed increased rounding, decreased growth, and decreased in vivo tumorigenesis.¹⁹¹ Combination FAK/src inhibition with adenoviral FAK-CD and the src inhibitor PP2 appeared to have a synergistic effect and functioned by increasing apoptosis.¹⁹² Thus, FAK inhibition via silencing FAK expression seems to decrease tumorigenesis in vitro and in vivo.

Another approach to FAK inhibition involved either activation of p53 or elimination of p53-deficient cells. This indirect approach was studied by introducing retroviruses that express p53 into rapidly dividing p53-deficient cells. A similar tactic was applied in the development of AD5CMV-p53, an adenoviral vector encoding p53 that was subsequently used to replenish p53 deficiency in tumor cells. This approach inhibited lung cancer cell growth in vitro and in vivo.¹⁹³ Clinically, phase I and II trials suggest that this agent is both safe and effective against esophageal squamous cell carcinoma.^{194,195} However, concerns about the safety of a viral vector and about the logistics of production and storage persist.¹⁹⁶

More recent efforts have focused on the development of small molecules to inhibit FAK activity. The first FAK inhibitor that was developed, TAE226, blocks the ATP-binding site and inhibits FAK phosphorylation at both Y397 and Y861, a site that is involved with VEGF signaling. This molecule showed promise in preclinical in vitro and in vivo trials and most recently was found to inhibit angiogenesis in models of human colon cancer.¹⁹⁷ TAE226 has not yet progressed to clinical evaluation.

In addition to TAE226, several other FAK inhibitors have been developed and are currently in phase I clinical trials. Like TAE226, PF-562,271 blocks the ATP-binding site of FAK and of Pyk2 (protein-rich tyrosine kinase 2), another nonreceptor tyrosine kinase known to bind and activate src.^{198,199} PF-562,271 inhibited in vivo breast cancer cell growth and metastasis in a murine model and decreased the in vivo growth of prostate cancer cells and in vitro growth of lung cancer cells.^{198,200–202} It also has exhibited synergy with sunitinib in the inhibition of hepatocellular tumor growth in vivo.²⁰³ Phase I clinical trials employing PF-562,271 for treating prostate, pancreatic, and head and neck cancers have recently been completed. Another inhibitor, PF-573,228, works similarly and has been found to inhibit breast cancer cell migration.²⁰⁰ Interestingly, this agent in combination with tamoxifen decreased proliferation in estrogen receptor-positive breast cancer cells.²⁰⁴ Other FAK inhibitors include PF-04554878, which is currently in phase I clinical trials for the treatment of advanced nonhematologic malignancies, and GSK2256098, which has completed phase I trials.¹⁰

PND-1186 is another FAK inhibitor with a different mechanism of action. PND-1186 likely inhibits ATP activity by substituting a pyridine ring for the pyrimidine ring found in

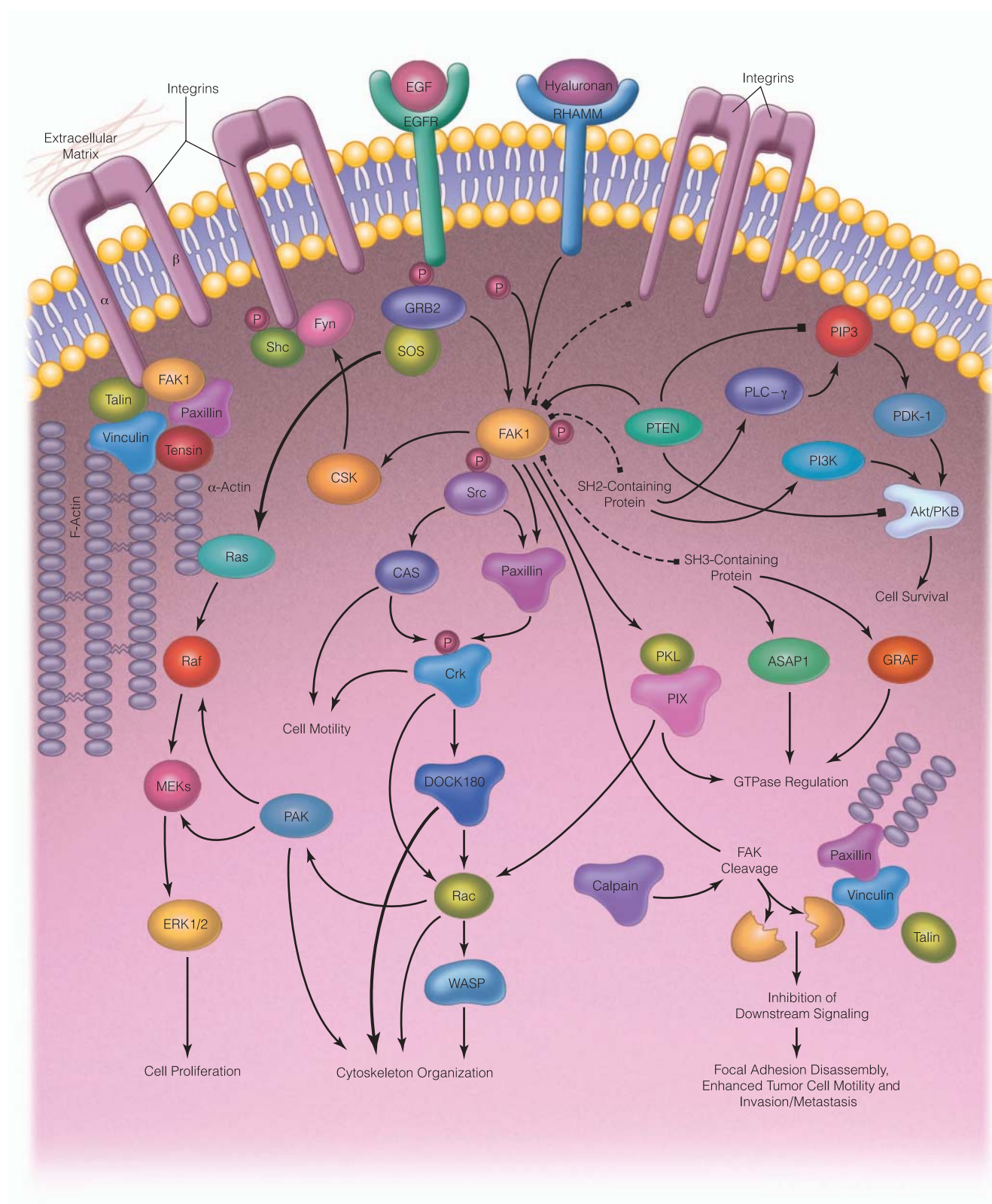


Figure 4 Focal adhesion kinase (FAK) plays a key role in a signaling cascade that can lead to some of the tumorigenic properties of cancer cells. FAK activation induces cell proliferation, motility, survival, invasion, and metastasis. Adapted from SABiosciences. Retrieved from www.sabiosciences.com (accessed October 2010). EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; PLC- γ = phospholipase C γ .

other ATP-binding FAK inhibitors.^{205,206} Early studies show that this molecule increases breast cancer cell apoptosis, inhibits *in vivo* breast cancer cell growth and metastasis, and inhibits ascites and peritoneal seeding in models of ovarian cancer.^{205,207}

An obvious concern with any drug is the potential for toxicity. Theoretically, the more specific the drug, the less potential it has to produce untoward effects. Although inhibiting ATP binding prevents FAK activation, this effect is somewhat nonspecific and, as such, raises concern about potential toxicity. Specific inhibition of the Y397 phosphorylation site, without blocking ATP binding, may offer a more specific target for FAK inactivation. Recently, several small molecule inhibitors that directly target the Y397 autophosphorylation site have been developed.²⁰⁸ One such molecule, 1,2,4,5-benzenetetraamine tetrahydrochloride (Y15), binds specifically to the Y397 site, does not affect ATP binding or Pyk-2, and effectively inhibits FAK activation. *In vitro*, Y15 increased detachment and inhibited adhesion of breast cancer cells and tumorigenesis *in vivo*.²⁰⁸ Additional studies have demonstrated the efficacy of Y15 in inhibiting pancreatic and neuroblastoma tumor growth *in vivo*.^{209–211} In addition, when combined with gemcitabine, these two agents demonstrated synergy in inhibiting pancreatic cancer cell growth.²¹¹ This novel small molecule inhibitor of FAK activation, therefore, holds promise as a potential new therapeutic agent.

FAK inhibition has been a relatively new approach to targeted cancer therapy. This approach is unique, and early studies suggest that FAK inhibition, either alone or in combination with other agents, may provide novel anticancer regimens.

Conclusion

The oncologic arena is changing. As the understanding of the complexities of cell signaling, cell division, apoptosis, and angiogenesis, grows, so does the armamentarium of therapeutic agents against cancer. Some of these agents have been studied extensively and already are used clinically. Others that show promise are at the early stages of development. The objective of studying these molecules is to develop drugs that selectively target malignant cells while sparing normal cells. By doing so, not only can efficacy against cancer be improved, but toxicity can also be minimized. Thus, in addition to more traditional advances in surgical and medical treatment of cancer, targeted therapeutics increasingly will play a role in surgical oncology. This is an exciting area of development with a substantial collection of established regimens and promising new therapies on the horizon.

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8 SOFT TISSUE SARCOMA

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The term *soft tissue sarcoma* (STS) defines cancers that develop from mesenchymal cells and their progenitors. STS is rare; the disease is diagnosed in approximately 10,000 individuals yearly in the United States.¹ This represents approximately 1% of adult malignancies and 15% of pediatric malignancies. We now recognize that, as rare as STS is, it actually represents an umbrella diagnosis encompassing over 50 different histologic subtypes of disease. Histologic subtype, in conjunction with tumor location, largely defines the biologic behavior of a given lesion and the associated clinical prognosis [see Figure 1]. Approximately half of all STSs occur in the extremities and 15% in the retroperitoneum [see Figure 2]. The most common histologic subtype in adults is liposarcoma (24% of extremity STS and 45% of retroperitoneal STS); other common subtypes are malignant fibrous histiocytoma (21% of extremity STS) and leiomyosarcoma (21% of retroperitoneal STS) [see Figure 3].

Unfortunately, the complexity created by diverse tumor characteristics means that treatment of STS is similarly complex. This chapter attempts to simplify the principles of STS therapy, defining an algorithm for patient evaluation and treatment while highlighting common indications for diverging from this strategy as dictated by disease subtype and location.

Etiology

Factors responsible for the development of sporadic STS are poorly understood, and few etiologic relationships have been definitively characterized. The disease is loosely associated with exposure to various herbicides and environmental toxins. The clearest of these connections are associations of vinyl chloride and thorium dioxide (Thorotrast) with hepatic angiosarcoma.² Patients who develop chronic lymphedema, often following surgical lymph node dissection, are also at risk for the development of angiosarcoma, a clinical scenario known as Stewart-Treves syndrome.³

Exposure to therapeutic and environmental radiation is a factor that clearly puts patients at risk for the development of STS. Radiation-induced sarcomas are defined as those occurring within the prior radiation field and having a pathologic confirmation of sarcoma that is histologically distinct from the primary cancer.⁴ In a population-based study of 295,712 patients with solid or hematologic tumors, those treated with radiation therapy had a twofold higher rate of sarcoma development compared with the general population. For patients who received radiation before age 55, the rate was fourfold higher than in the general population.⁵ The median interval between radiation administration and development of radiation-associated STS is 10 years. The most common

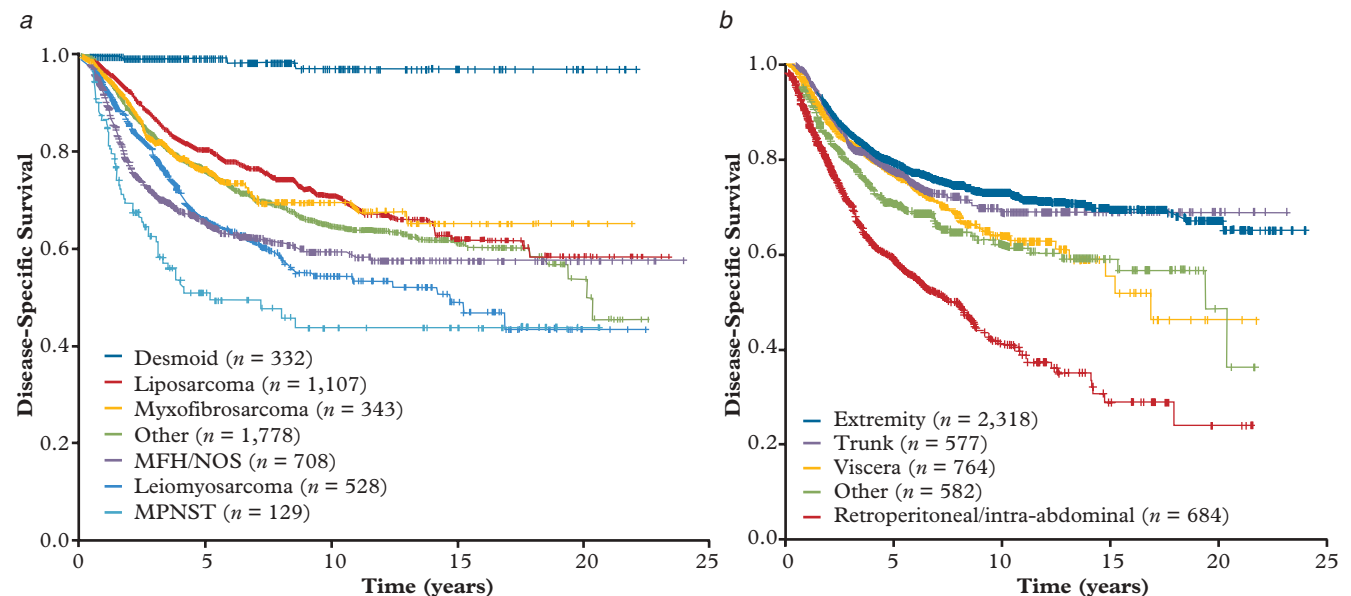


Figure 1 Disease-specific survival stratified by (a) histologic type and (b) tumor location. Data are derived from all cases of soft tissue survival evaluated, treated, and followed prospectively at Memorial Sloan-Kettering Cancer Center over a 25-year period. MFH/NOS = malignant fibrous histiocytoma/sarcoma not otherwise specified; MPNST = malignant peripheral nerve sheath tumor.

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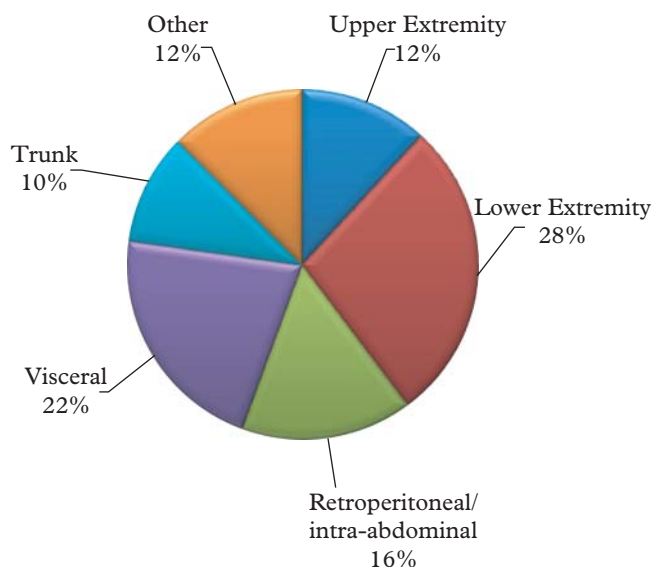


Figure 2 Anatomic distribution of all cases of soft tissue sarcomas evaluated, treated, and followed prospectively at Memorial Sloan-Kettering Cancer Center over a 25-year period ($N = 7,850$).

subtypes of radiation-induced sarcoma are angiosarcoma (27%), high-grade malignant fibrous histiocytoma (26%), and leiomyosarcoma (12%). In retrospective and case-control studies, a sarcoma being radiation associated is an independent risk factor (by multivariate analysis) for disease-specific death.⁶

Although environmental causes for STS are incompletely understood, characteristic molecular changes have been

identified in many histologic subtypes of STS. These include chromosome amplifications, point mutations, and gene translocations. In many tumors, these genomic alterations can be used to identify the histologic subtype. For instance, well-differentiated and dedifferentiated liposarcoma cells have characteristic chromosome 12 amplifications that result in increased levels of MDM2 and CDK4 proteins, which can be stained by immunohistochemistry. In myxoid-round cell liposarcomas and synovial sarcomas, gene fusion products (FUS-CHOP and SSX-SYT, respectively) can be detected by polymerase chain reaction. With gastrointestinal stromal tumors (GISTs), genetic characterization (c-kit overexpression) has been used to identify the tumor; in addition, c-kit overexpression is targeted by imatinib in systemic treatment of the disease.

Germline mutations have also been associated with development of STS. Examples include Li-Fraumeni syndrome (*p53* mutation associated with STS and osteosarcoma), neurofibromatosis type 1 (von Recklinghausen disease; *NF1* mutation associated with progression of neurofibromas to malignant peripheral nerve sheath tumors), and Gardner syndrome (*APC* mutation associated with intra-abdominal desmoid tumors). These syndromes can be inherited. Childhood retinoblastoma, Werner syndrome, Gorlin syndrome, Carney triad, and tuberous sclerosis also carry increased risk of STS.

Tumor Staging and Patient Prognosis

T stage for STS is determined not only by tumor size (T1, 5 cm and below; T2, larger than 5 cm) but also whether the lesion is superficial (T1a or T2a) or deep (T1b or T2b) to the muscle fascia. Nodal disease (N1) is rare in STS patients;

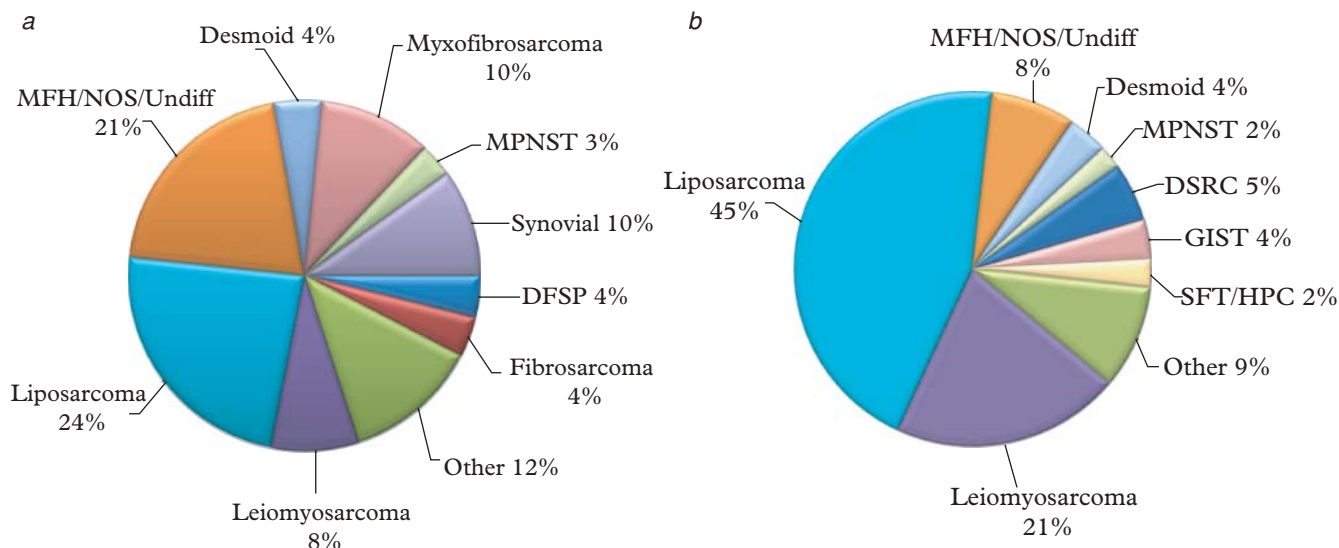


Figure 3 Histopathologic distribution of (a) extremity soft tissue sarcoma ($n = 3,123$) and (b) retroperitoneal/intra-abdominal soft tissue sarcoma ($n = 1,241$). Data are based on all cases of soft tissue sarcoma evaluated, treated, and followed prospectively at Memorial Sloan-Kettering Cancer Center over a 25-year period. DFSP = dermatofibrosarcoma protuberans; DSRC = desmoplastic small round cell tumor; GIST = gastrointestinal stromal tumor; MFH/NOS/Undiff = malignant fibrous histiocytoma/sarcoma not otherwise specified/undifferentiated pleomorphic sarcoma; MPNST = malignant peripheral nerve sheath tumor; SFT/HPC = solitary fibrous tumor/hemangiopericytoma.

it does not confer a prognosis as poor as do distant metastases (M1).

The American Joint Committee on Cancer (AJCC) staging system for STS includes not only tumor size and the presence of nodal and metastatic disease, as in adenocarcinomas, but also tumor grade⁷; it is therefore termed TNGM staging. It should be noted, however, that the traditional AJCC grading system, which is based on differentiation (well, moderate, or poor), is not generally applicable to STS. Most sarcoma grading systems incorporate the histology-specific extent of differentiation, mitotic rate, and necrosis. The most widely accepted system, that of the French Federation of Cancer Centers Sarcoma Group (FNLCC), uses these three factors to classify sarcomas as low (G1), intermediate (G2), or high (G3) grade.

TNGM staging classifies STS into four broad stages.⁷ Stage I includes all localized, low-grade tumors. Stage II is localized intermediate-grade tumors or high-grade, localized tumors that are small and/or superficial. Stage III disease represents large (> 5 cm), high-grade tumors. Stage III disease also includes STS associated with nodal metastases independent of grade and size. Stage IV disease represents all disease associated with distant metastases.

Outcomes based on TNGM staging are shown in Figure 4. Although stage is a strong prognostic factor, there is a significant degree of variability among patients within each of the localized disease stages (stage I, II, or III) as relates to outcome after surgical resection of the primary tumor. One reason for this limitation may be that the AJCC system does not incorporate multiple prognostic factors important in STS. For example, tumor histology is of significant import; malignant peripheral nerve sheath tumors are associated with poorer disease-specific survival than are myxofibrosarcomas [see Figure 1a]. Given these facts, a prognostic nomogram has been developed from retrospective data collected from 2,163 patients treated at Memorial Sloan-Kettering Cancer Center [see Figure 5] and validated using a prospectively enrolled cohort of 929 patients treated at the University of California, Los Angeles.^{8,9} Tumor size, histologic subtype, and site of disease are all used to improve prediction of patient outcome. Prognostic accuracy is further enhanced by the fact that variables such as size and patient age can be considered continuous variables rather than being divided into a few categories, as they are in staging systems and risk category systems. A Web-based version of the STS nomogram is available for general reference (<http://www.mskcc.org/mskcc/html/6181.cfm>).

Evaluation and Treatment of Soft Tissue Sarcoma

Surgical excision of STS is the mainstay of our current treatment algorithm. A multidisciplinary approach to the disease is, however, essential, because of the complexity involved in histology-based treatment. The risks and benefits of radiation and chemotherapy as well as adjuvant and neoadjuvant approaches should be carefully weighed when determining the overall treatment plan for a patient with STS. Prevalence of histologic subtypes, treatment-related morbidities, and patterns of recurrence are very different for primary STS of the extremity or superficial trunk versus the abdomen or retroperitoneum. The sections below separately

describe extremity and truncal STS and abdominal and retroperitoneal STS.

EXTREMITY AND SUPERFICIAL TRUNCAL STS

Diagnosis and Evaluation

Patients with STS of the extremity and superficial trunk most commonly present with a palpable mass sometimes brought to their attention by a minor trauma in the region. After a careful history and physical examination, a magnetic resonance imaging (MRI) or computed tomographic (CT) scan is indicated for all but small (< 2 cm), superficial lesions, which can be evaluated by excisional biopsy. Cross-sectional imaging provides the size and location of the lesion and identifies involvement of adjacent structures. CT is readily available and less expensive, although MRI can provide better soft tissue definition in the extremity. Histologic subtype, which dictates appropriate treatment, is not, in most instances, well defined by CT or MRI. The exception to this rule is well-differentiated liposarcoma (atypical lipomatous tumors). On cross-sectional imaging, these lesions resemble normal fat in their signal intensity, appear encapsulated, and are associated with thick, internal septations.¹⁰ For tumors located deep to the investing fascia, imaging findings are almost pathognomonic for this subtype, and further workup is not warranted. These lesions should be completely excised with, when possible, a margin of normal muscle or fascial tissue to minimize the risk of local recurrence.

If the STS does not appear consistent with an atypical lipomatous mass, biopsy is indicated prior to defining a treatment plan. Performed improperly, the biopsy of an extremity mass can result in significant oncologic and cosmetic consequences when definitive excision is performed. For this reason, the principles of STS biopsy should be part of the core procedural knowledge for all general surgeons. Although incisional biopsy had been the standard method of diagnosis, core biopsy provides adequate tissue for evaluation in almost all cases and often leads to accurate diagnosis of histologic type and grade.¹¹ When performing a core biopsy for suspected STS, the surgeon or radiologist should first consider where the surgical incision will be placed. The biopsy site will be excised at the time of surgery and should, therefore, be placed directly adjacent to the planned surgical incision. If multiple cores are taken, they should be angled serially toward a different region of the tumor but always obtained through a single biopsy site.

In the event that core biopsy is insufficient for diagnosis or the lesion is too small to biopsy in this manner, incisional or excisional biopsy is performed. Again, careful planning of the biopsy is essential. The biopsy incision should always be oriented longitudinally along the limb. This is because the definitive surgery for excision of an STS will require resection of the biopsy incision with circumferential margins between 1 and 2 cm (depending on the histologic subtype of the STS). If a biopsy scar is oriented transversely, the diameter of the surgical specimen must increase dramatically to obtain adequate surgical margins. This often means that primary closure of the defect is impossible, and a skin graft or muscle flap is essential to cover the surgical bed.

All STS patients with high-grade disease should undergo a CT scan of the chest to evaluate for pulmonary metastases.

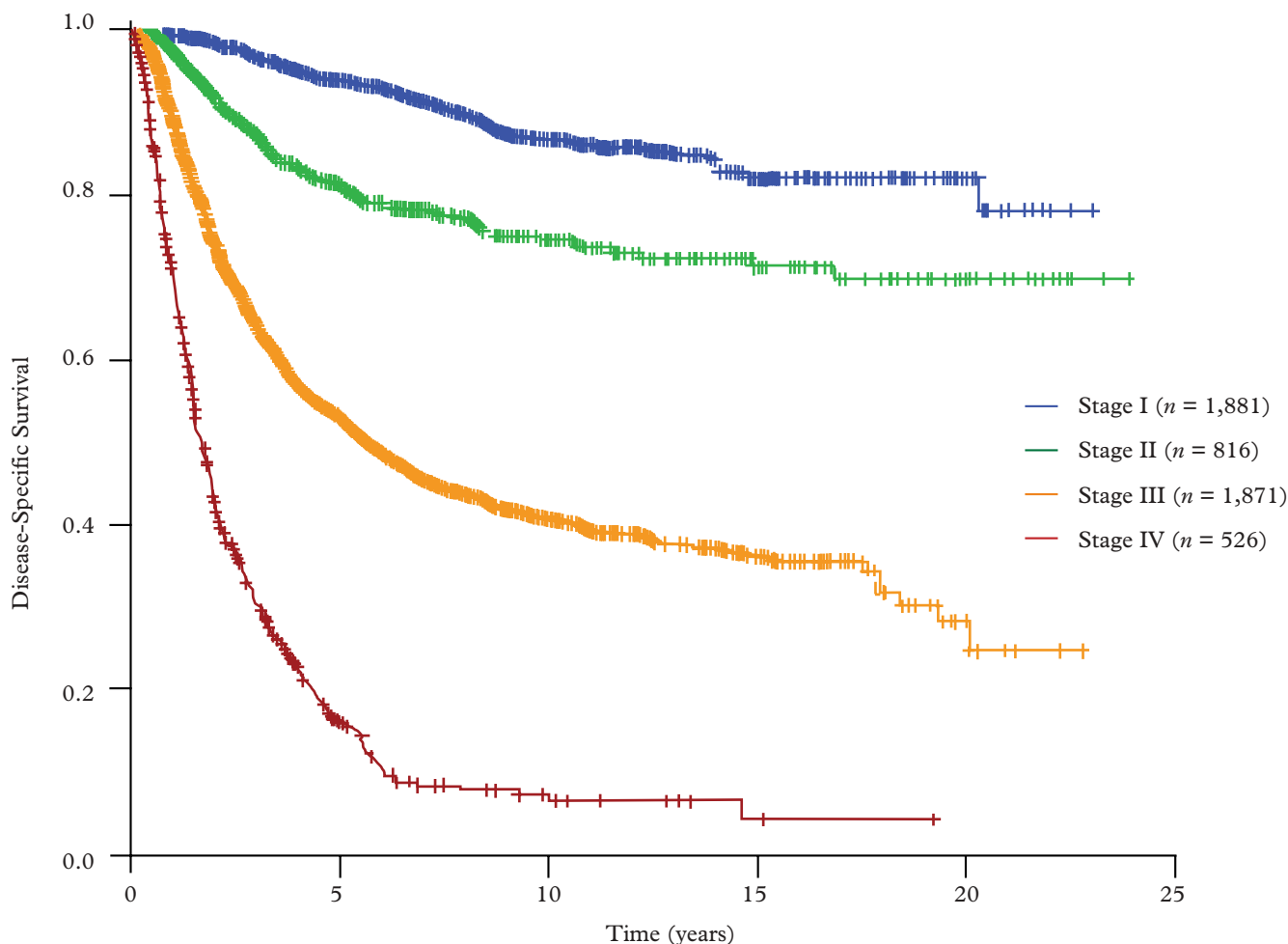


Figure 4 Disease-specific survival according to American Joint Committee on Cancer TNM stage based on all cases of soft tissue survival evaluated, treated, and followed prospectively at Memorial Sloan-Kettering Cancer Center over a 25-year period.

For those with low-grade disease, the risk of metastasis is minimal and chest x-ray is generally adequate and cost-effective. Many STSs are not fluorodeoxyglucose avid; therefore, positron emission tomography (PET) has poor sensitivity for use in the staging of these diseases.

After a pathologic diagnosis of STS has been obtained, the histologic subtype and grade have been identified, and the patient has been assessed for distal metastases, a multidisciplinary treatment plan can be defined. In most cases of localized disease, the primary treatment will be resection or, much less commonly, radiation (discussed below in the context of adjuvant radiation).

Surgical Planning

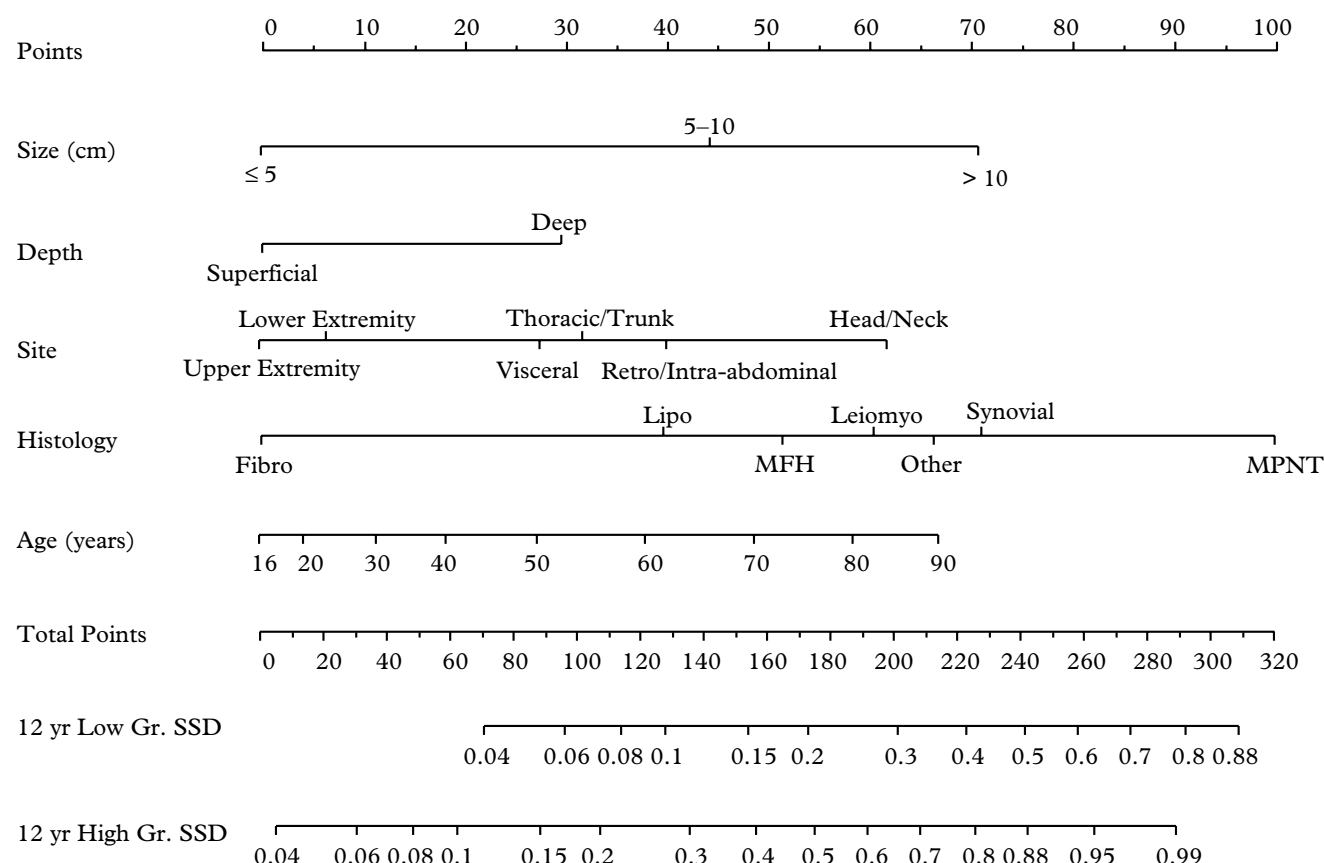
An algorithm for the treatment of extremity STS is shown in Figure 6.

Prior to 1981, the standard surgical approach to STS of the extremity was amputation. A randomized, controlled trial, coordinated at the National Cancer Institute, defined a role for limb-sparing surgery. The trial followed 43 patients with high-grade tumors treated with amputation or limb-sparing resection with adjuvant radiation. Five years after resection, patients undergoing limb-sparing surgery clearly had a higher

incidence of local recurrence, but their disease-free and overall survival rates were no different from those who underwent amputation. Patients experiencing a local recurrence were, in large part, salvaged with additional surgery.¹² Limb-sparing surgery is, therefore, currently considered the standard of care in STS surgery.

Resections should be carefully planned preoperatively to consider functional outcomes and risks of recurrent local disease and distal progression. Importantly, although many extremity lesions are associated with what appears on inspection to be a well-defined pseudocapsule, microscopic disease extends beyond this layer. Therefore, during limb-sparing procedures, a wide margin (1 to 2 cm) of normal tissue should be resected with the specimen to reduce the risk of local recurrence. When the tumor abuts a fascial plane of an adjacent muscle, this layer should be resected with the tumor. When the tumor is superficial, the underlying muscle fascia should always be resected.

When treating extremity STS, the surgeon should consider the relationship between the tumor and nearby neurovascular structures. This will allow him or her to inform the patient about sensory and motor deficits that may be expected after a limb-sparing procedure. It is also vital for surgical planning;



Instructions for Physician: Locate the patient's tumor size on the Size axis. Draw a line straight upward to the **Points** axis to determine how many points toward sarcoma-specific death the patient receives for his tumor size. Repeat this process for the other axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total Points** axis. Draw a line straight down to either the Low Grade or High Grade axis to find the patient's probability of dying from sarcoma within 12 years assuming he or she does not die of another cause first.

Instruction to Patient: "If we had 100 patients exactly like you, we would expect between <predicted percentage from nomogram - 8%> and <predicted percentage + 8%> to die of sarcoma within 12 years if they did not die of another cause first, and death from sarcoma after 12 years is still possible."

Figure 5 Positive nomogram for prediction of sarcoma-specific death (SSD) at 12 years postresection for patients with soft tissue sarcoma. Fibro = fibrosarcoma; GR = grade; Leiomyo = leiomyosarcoma; Lipo = liposarcoma; MFH = malignant fibrous histiocytoma; MPNT = malignant peripheral nerve sheath tumor.

nerves, veins, and arteries often limit the extent of the resection to be performed. Whenever possible, vascular structures are skeletonized and major nerves salvaged by resecting perineurium. This will preserve limb function, and if a high-risk lesion is removed with an R1 margin, adjuvant radiation is an option for reducing rates of local recurrence (see below). To avoid amputation when major neurovascular structures are encased by a high-grade tumor, the surgeon may consider advanced maneuvers such as arterial bypass or resection of the sciatic nerve.¹³ Venous reconstruction is rarely indicated and when performed is often not successful; compression garments are used to control postoperative symptoms.

Preoperative diagnoses of dermatofibrosarcoma protuberans (DFSP) and myxofibrosarcoma are of particular concern in planning local resection. These lesions often have microscopic tentacles that extend laterally from the lesion.¹⁴⁻¹⁶

DFSP should be resected en bloc with margins of 2 cm, including the underlying fascia, but underlying muscle rarely needs to be removed as this subtype generally does not penetrate the fascia. Myxofibrosarcoma, however, often penetrates fascia and invades muscle and is often multifocal with skip areas. Therefore, excision should be not only wide laterally but also deep with significant surrounding muscle; again, margins of 2 cm should be resected en bloc with the tumor. With either of these subtypes, more conservative resection leads to a high risk of local recurrence. Although recurrence of DFSP in the surgical bed is a difficult local problem, it is almost never associated with distant spread (unless there is histologic evidence of sarcomatous degeneration). Local recurrence of myxofibrosarcoma, however, is potentially more dangerous as it is associated with a high-grade phenotype in as many as 54% of cases. High-grade

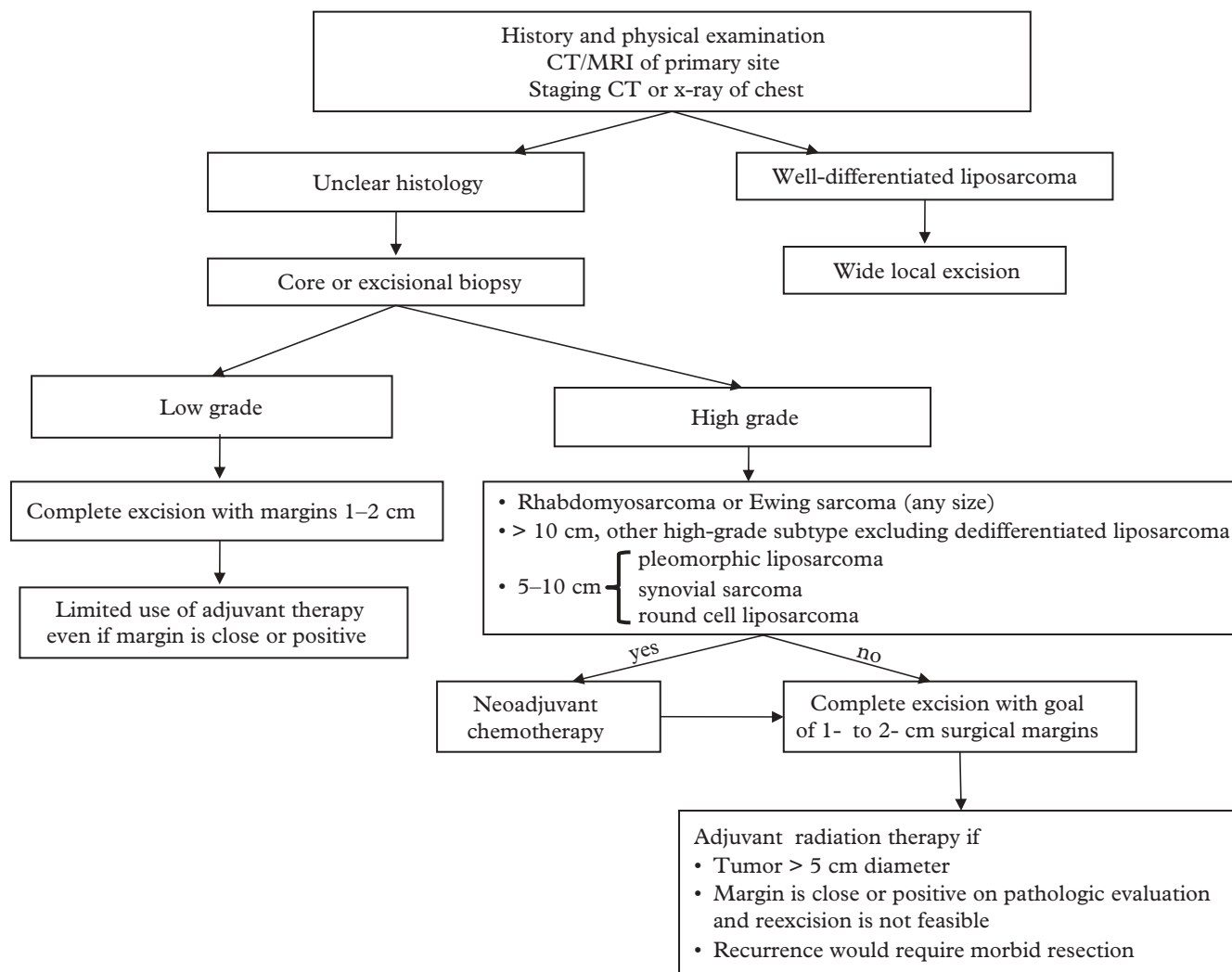


Figure 6 A treatment algorithm for soft tissue sarcoma of the extremity. CT = computed tomography; MRI = magnetic resonance imaging.

recurrence of myxofibrosarcoma places the patient at significant risk for metastatic disease.^{15,16} Therefore, every attempt should be made to resect myxofibrosarcomas with negative margins, even when they appear as low-grade lesions. Multiple procedures may be required to adequately remove all disease, and reconstruction will often require tissue flaps or a skin graft.

SCORE Lymph node metastases are rare in STS and generally occur in the context of epithelioid or clear cell variants of STS.¹⁷ In these cases, sentinel lymph node biopsy has been reported and can give prognostic information as a positive biopsy defines stage III disease. However, this procedure has not been associated with a therapeutic benefit, and no survival advantage has been reported in patients undergoing completion lymph node dissection.¹⁸ For these reasons, the role of sentinel lymph node biopsy in management of STS remains debatable.

Radiation in Extremity STS

SCORE Radiation therapy after limb-sparing surgery for STS appears to increase local control but not survival. This

conclusion comes from three large randomized, controlled trials. In the first trial, 141 patients with STS of the extremity treated with surgery and chemotherapy were randomized to receive postoperative radiation or no radiation.¹⁹ In the context of both high- and low-grade tumors, the addition of adjuvant radiation significantly reduced the risk of local recurrence (risk at 9 years of 33% versus 4% for low-grade tumors and 19% versus 0% for high-grade tumors). However, radiation afforded no benefit in terms of overall survival. Similarly, brachytherapy applied after complete resection of STS in the extremity and superficial trunk improved local control but did not alter disease-specific survival.²⁰ Moreover, local benefit of brachytherapy was restricted to patients who presented with high-grade tumors. Because radiation therapy can have long-term complications such as joint fibrosis and secondary malignancies, the potential risk versus benefit of radiation therapy must be carefully weighed for each patient. Radiation therapy is routinely prescribed for high-risk lesions (> 5 cm and high-grade or recurrent tumors that were not previously treated with radiation) with close margins. Given

the fact that no trial has shown radiation to improve overall or disease-specific survival, it is reasonable to defer adjuvant therapy when the tumor is low grade or the margin is wide, particularly if a local recurrence could be excised without amputation or major functional impairment.

The decision to prescribe radiation therapy is further complicated in that the modality can be administered either preoperatively or postoperatively. A randomized trial compared these strategies by assigning 190 patients with extremity STS to either adjuvant radiation (66 Gy) or neoadjuvant radiation (50 Gy).²¹ This study showed no difference in local control. It did show an increased rate of wound complications in patients treated with radiation prior to resection (35% versus 17%). This difference was most pronounced in patients with STS of the lower extremity. Conversely, patients receiving therapy after resection had a higher risk of long-term fibrotic complications (e.g., joint stiffness), presumably related to the higher dose of radiation.²² Therefore, preoperative radiation therapy can be an excellent choice for patients with tumors adjacent to a joint or tumors located in the upper extremity that are likely to have close or positive margins. In all other settings, the role of radiation therapy is determined from the final assessment of tumor histology, and margin status following resection determines the contribution radiation may play in the multimodality treatment of extremity STS.

Neoadjuvant Chemotherapy

No prospective study has definitively shown a benefit to administration of adjuvant chemotherapy in STS patients. However, three groups of patients should receive neoadjuvant therapy [see Figure 6] because of the high risk of metastasis and/or predicted chemosensitivity of a tumor subtype. The first group includes patients with rhabdomyosarcoma or Ewing sarcoma. Regardless of tumor size, these patients have a high risk of metastasis and are always treated with chemotherapy prior to surgery. The second group encompasses patients with high-grade tumors that are larger than 10 cm. Retrospective studies have demonstrated that neoadjuvant chemotherapy is associated with improved disease-specific survival among these patients.²³ Specifically, neoadjuvant chemotherapy is considered in patients without significant comorbidities and with large, high-grade, round cell liposarcoma, pleomorphic liposarcoma, synovial sarcoma, malignant peripheral nerve sheath tumor, or leiomyosarcoma. However, dedifferentiated liposarcomas, even when they are large and high grade, have a low risk of distant metastasis and are rarely chemosensitive, so initial treatment is surgery when the lesions are resectable.

The third group considered for neoadjuvant chemotherapy includes patients with moderate-size tumors (5 to 10 cm) representing relatively chemosensitive histologies that have a propensity to metastasize. Round cell liposarcoma, pleomorphic liposarcoma, and synovial sarcoma are the most common histologic subtypes treated in this manner.^{24–26}

RETROPERITONEAL AND VISCERAL SARCOMAS

Retroperitoneal Disease

The retroperitoneum is the second most common site of STS, although retroperitoneal lesions are significantly less common than those of the extremity [see Figure 2]. Patients

typically present with a palpable mass or a mass found incidentally on imaging acquired for an unrelated symptom. Patients may have pain and/or symptoms of lower extremity neural compromise. This is particularly true for those with large retroperitoneal tumors, which often remain undetected until they reach sizes greater than 10 cm in diameter. Rarely, patients with retroperitoneal tumors are diagnosed because of paraneoplastic syndromes, such as hypoglycemia related to leiomyosarcoma or solitary fibrous tumor.

A preoperative biopsy is usually needed only if there is suspicion of carcinoma, lymphoma, or germ cell tumor or if the mass appears to be not completely resectable; in other circumstances, biopsy rarely alters the therapeutic plan. Regardless of histologic subtype, the goal of operative intervention is complete gross resection, which can be achieved in 80% of patients. The major hindrance to tumor resectability is involvement of the great or visceral vessels. Retroperitoneal lesions can encase the aorta, vena cava, celiac axis, or porta. In these cases, attempt at resection will leave gross tumor in the surgical bed, and when an R2 resection is anticipated, surgery should be considered only as palliative therapy. Debulking has not been demonstrated to provide survival benefit, and patients with a grossly positive margin have outcomes that are similar to those of patients undergoing no operative intervention [see Figure 7].

Involvement of adjacent organs such as the spleen, pancreas, and bowel does not preclude surgical resection. STS associated with these findings can be managed by en bloc resection to achieve R0 or R1 resection. It should be noted that resection of these organs (excluding the kidney) with STS does increase the morbidity associated with surgery.^{27,28} If the retroperitoneal lesion involves the kidney, adequate resection can often be achieved by removing only the renal capsule with the tumor. This is possible as retroperitoneal tumors rarely invade the renal parenchyma. Involvement of the kidney hilum, however, will require a nephrectomy to obtain adequate margins.

Visceral Disease

The principles that govern surgical resection of visceral sarcomas are similar to those noted above for retroperitoneal tumors. In all instances, a negative resection margin is the goal of operative intervention. The most common subtype of STS in the viscera is GIST; patients present with gastrointestinal bleeding or bowel obstruction. These tumors are generally well circumscribed and can be removed with a 1 cm gross margin; anatomic resection has not been shown to improve outcomes. For example, in most cases, a gastric GIST can be removed with only a small (1 cm) margin of surrounding tissue, preserving the main body of the stomach. Even with large tumors, this approach allows for preservation of visceral organs and minimizes the complexity of reconstruction.

Adjuvant Therapy in Retroperitoneal and Visceral STS

Retroperitoneal lesions are almost exclusively liposarcoma, leiomyosarcoma, or malignant peripheral nerve sheath tumors. These tumors have low rates of response to chemotherapy, and adjuvant chemotherapy has never been demonstrated to improve survival in this patient population. Radiation therapy, however, is more debatable. Several small, retrospective studies have suggested that its use is associated with reduced

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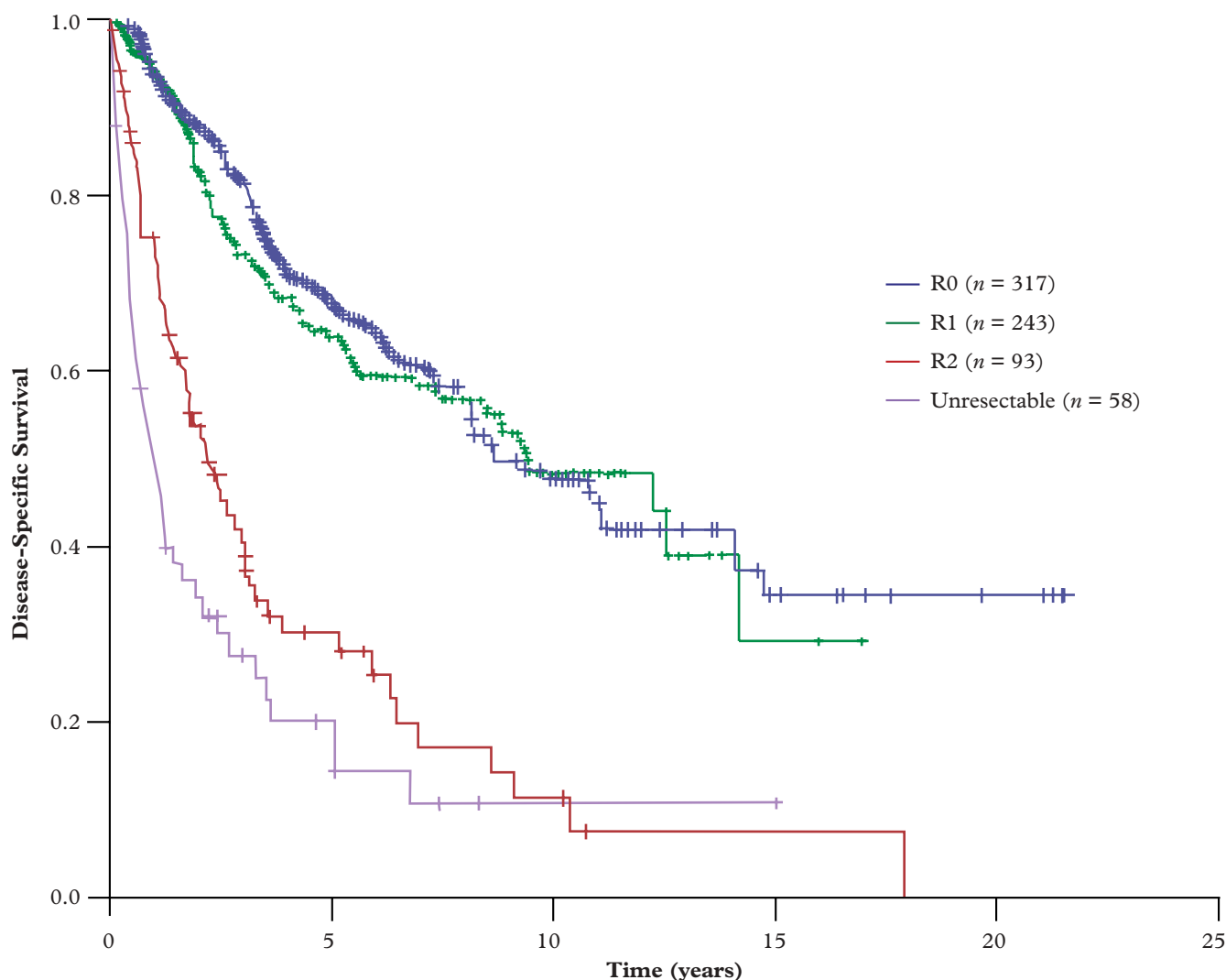


Figure 7 Disease-specific survival according to extent of resection among patients with retroperitoneal soft tissue sarcoma treated at Memorial Sloan-Kettering Cancer Center over a 25-year period. Outcomes were similar for patients undergoing incomplete gross resection (R2; $n = 93$) and for patients with disease judged unresectable at exploration ($n = 58$).

risks of local recurrence following surgical resection.²⁹ Nevertheless, no difference in overall survival has been implied, and selection bias and significant differences in surgical management between institutions remain confounding factors when interpreting the literature. We do understand that adjuvant radiation administered after resection of a retroperitoneal lesion is associated with significant morbidity. Radiation enteritis occurs in up to 60% of patients and can lead to chronic malnutrition, enteric fistulization, and bowel obstruction.³⁰ Given this drawback of adjuvant radiation therapy, neoadjuvant radiation should be considered if surgical resection is likely to result in positive margins and radiation is to be prescribed. The neoadjuvant approach limits the morbidity of treatment because it can target the radiotherapy to the region at highest risk for microscopic residual disease while limiting the dose to surrounding viscera.

GISTs present a unique case for application of adjuvant treatment because many of them are sensitive to imatinib.

This drug targets the c-kit receptor and is a cytostatic reagent. The effect of adjuvant imatinib therapy in high-risk GIST (at least 3 cm in diameter) has been examined in a randomized, controlled trial.³¹ In patients treated with adjuvant imatinib, recurrence-free survival at 1 year was increased from 83 to 98%. For this reason, the drug is generally administered in the adjuvant setting to high-risk patients. Imatinib is also of use in the neoadjuvant setting.³² It can be prescribed in attempt to reduce the size of the tumor and minimize the morbidity of resection when surgical resection of a lesion will prove morbid. Examples of these cases include lesions located at the gastroesophageal junction or rectal lesions. Imatinib can be prescribed in attempt to reduce the size of the tumor and minimize the morbidity of resection.

RECURRENT AND METASTATIC DISEASE

Following surgical resection of STS, the tumor bed is evaluated by cross-sectional imaging every 4 to 6 months,



depending on the grade of the tumor. Local recurrence is observed in approximately 10 to 30% of patients with extremity STS and 50% of patients with retroperitoneal lesions.³³ At the time of recurrence, patients should again be staged to rule out metastatic disease.

In the context of extremity recurrence, local resectability is determined as above. Important considerations are the post-operative morbidity of limb-sparing surgery and the ability to spare the neurovascular bundle. The surgeon should excise not only gross tumor and a margin of normal tissue but also the prior surgical incision, drain site, and resected specimen bed. Adjuvant or neoadjuvant radiation or chemotherapy may be considered if the patient was not previously treated with these modalities. Local recurrence is associated with poor prognosis when lesions are high grade, recurrences are greater than 5 cm in diameter, and the recurrence-free interval is short (less than 16 months).³⁴ Patients whose disease recurs with these features have an increased risk of disease-associated death and should be considered for neoadjuvant chemotherapy or enrolment in clinical trials.

As in the extremity, retroperitoneal recurrence presents a difficult problem and is associated with a poor prognosis. If the lesion is isolated, surgical resection can again be used in an attempt to achieve a cure, and its goal should be negative margins. Neoadjuvant radiation therapy can be considered. As in extremity recurrence, poor prognostic features include large size of tumor recurrence and short disease-free interval, and patients with these features should be considered for neoadjuvant trials. In addition, retroperitoneal liposarcoma patients with local recurrence growth rates exceeding 1 cm per month have an extremely poor prognosis even after aggressive attempts to completely excise all measurable disease. In a retrospective analysis of such patients, surgical resection was not associated with increased survival. Thus, patients with liposarcoma growth rates greater than 1 cm per month should be considered for systemic treatment with novel targeted therapies or conventional chemotherapy.³⁵

Indications for Metastasectomy

In patients with high-grade STS, surveillance of the surgical bed is accompanied by cross-sectional imaging of the lung, the most common site of metastatic disease (44%). In most patients, metastases are treated with chemotherapy. The choice of agents is dependent on disease histology and is beyond the scope of this review. Resection, however, is often recommended when disease at the primary site is well controlled and the patient presents with isolated pulmonary metastases. Patients most likely to benefit from metastasectomy include those with metachronous disease and long disease-free intervals, those with slowly growing metastases, and those with a limited number of lesions (one to three). Patients with metastatic disease have an overall survival of less than 20% at 5 years, but long-term survival is observed in patients carefully selected for metastasectomy.^{36,37} In these patients, surgery alone may be sufficient for cure as no additional increase in survival has been associated with perioperative chemotherapy.³⁸

DESMOID FIBROMATOSIS

Desmoid tumors are rare neoplasms that develop from mesenchymal stem cells.³⁹ The estimated incidence is only

1,000 cases per year in the United States. Standard management of the disease has included wide resection in the past. Such procedures may be associated with significant morbidity; they can result in short bowel syndrome, incisional hernia, or functional impairment of a limb. Desmoids do not metastasize, however, and this has led to a significant shift in treatment algorithms. Current management strategies do not focus solely on complete eradication of local disease but also on improving functional outcomes for patients with desmoid tumors.

Data supporting current treatment recommendations have been collected only over the last two decades. Large retrospective series showed no difference in the rates of local recurrence following R1 versus R0 resection. This fact was the first that suggested clinicians could adopt a function-preserving approach when planning surgical resection.⁴⁰ Subsequently, in the context of recurrent, nonoperable desmoids, it was observed that the growth of tumors was actually self-limited in some cases. An initial period of observation was, therefore, proposed to be a safe treatment option in patients with recurrent disease.⁴¹ The clear benefit thought to be associated with early surgical resection was questioned.

Most recently, an analysis of 142 patients with primary or recurrent desmoid was reported by Fiore and colleagues.⁴² This study examined cases in which a frontline, nonoperative approach was employed. Eighty-three of these patients did not receive surgery, radiation, or medical treatment at presentation. They were instead followed with serial imaging every 3 to 6 months. The 5-year progression-free survival in this cohort was 49%. For patients who progressed, surgical resection was considered. If resection would result in significant functional impairment or was not technically feasible, a course of medical management with targeted therapies or cytotoxic therapy was prescribed in the neoadjuvant setting or for long-term maintenance. Sorafenib, tamoxifen, cyclooxygenase-2 inhibitors, imatinib mesylate (Gleevec), and anthracyclines (Doxil) are currently employed for this purpose.⁴³ No patient with progressive disease was noted in the study by Fiore and colleagues to have unexpected complications or a poor outcome that could be attributed to an initial period of observation. Given these data, many large sarcoma referral centers now uniformly recommend an initial period of observation before undertaking major surgery in the context of desmoid fibromatosis.

Radiation following resection of desmoids has been advocated in both the adjuvant and neoadjuvant settings. Although several analyses have demonstrated an association between radiation and reduced local recurrence after surgery, no difference in overall survival has been observed.^{44,45} The long-term complications associated with radiation in a patient population, which is generally diagnosed during their second through fourth decade of life, limit its utility. In the context of a disease that has no metastatic potential, this modality is, therefore, almost always reserved for intractable cases that are symptomatic and have failed all other therapeutic options.

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Desmoid tumors are rare neoplasms that develop from mesenchymal stem cells.³⁹ The estimated incidence is only

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9 Benign Breast Disease

*Helen Cappuccino, MD, FACS, Ermelinda Bonaccio, MD, and Swati Kulkarni, MD, FACS**

Clinicians should have an understanding of the evaluation and management of breast disorders. One in two women will consult a health care provider for a breast-related complaint during her lifetime.¹ The fundamental task facing a physician who is evaluating a patient with a breast concern is to determine whether the abnormality is benign or malignant. Even though most breast complaints do not result in a diagnosis of cancer, any woman presenting with a breast complaint should receive a comprehensive evaluation. In this chapter, we focus on the evaluation and management of benign breast conditions.

Screening Recommendations

In the absence of a specific breast complaint, breast cancer can be detected by screening. The three main methods of breast cancer screening are breast self-examination (BSE), clinical breast examination (CBE), and screening mammography.² American Cancer Society (ACS) screening guidelines for women aged 40 years and older specify that mammography and CBE should be included as part of an annual health examination.³ In addition, health care providers should tell women about the benefits and limitations of BSE, stressing the importance of promptly reporting any new breast symptoms. There is currently no role for routine screening ultrasonography or screening magnetic resonance imaging (MRI) in the general population.

BREAST SELF-EXAMINATION

In BSE, the patient inspects and palpates both breasts and axillae. One might assume that instruction in BSE would improve breast cancer detection. However there is no conclusive evidence that BSE is of significant value in this regard. Many self-detected tumors are found incidentally, not during BSE. Furthermore, the best technique for BSE and optimal frequency has not been established. The ASC recommends counseling patients on the benefits and limitations of BSE as a part of the breast cancer screening process that also includes mammography and CBE.³

CLINICAL BREAST EXAMINATION

In CBE, a qualified health care professional carries out a complete examination of the breasts and axillae. As with BSE, there is little evidence indicating that annual or semiannual CBE increases breast cancer detection rates.⁴ Nevertheless, it is prudent for the clinician to include CBE as part of the physical examination performed on every female patient.

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SCREENING MAMMOGRAPHY

Screening mammography refers to the imaging of asymptomatic women to detect early, clinically occult breast cancers. Mammography is the only breast imaging modality proven to reduce mortality from breast cancer. The Swedish Two-County Trial updated their data in 2000 and demonstrated a 32% reduction in breast cancer mortality in women invited to screening.⁵ Based on the findings from these trials, women should begin annual screening mammography at age 40. There are subgroups of women at high risk for breast carcinoma who may benefit from screening at a younger age, although no randomized controlled trials support these recommendations.⁶ Currently, there is no accepted upper age limit for mammographic screening; however, the presence of significant comorbidities reducing life expectancy to less than 10 years should be considered when ordering a screening mammogram in women over the age of 70.

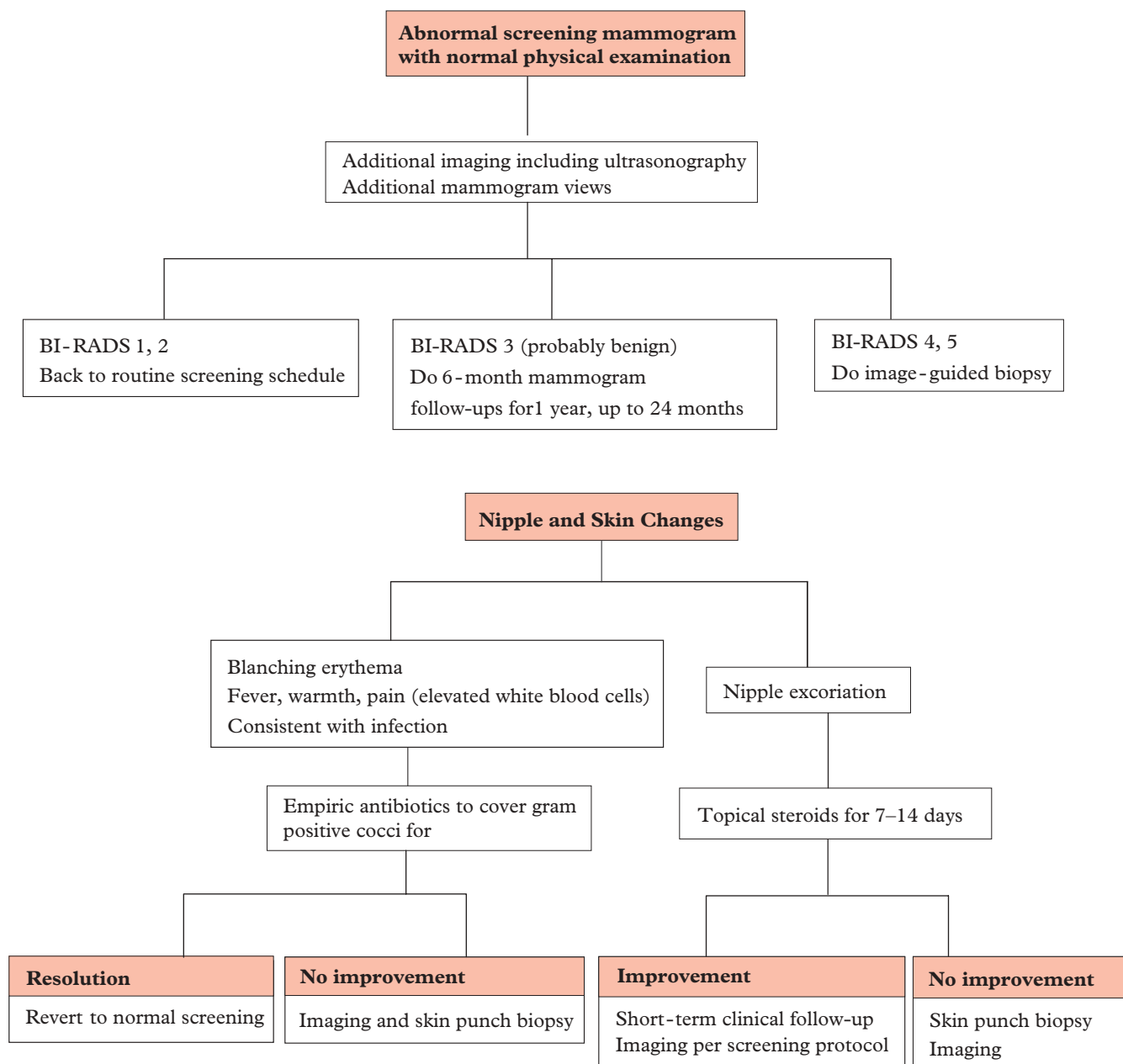
Digital mammography is becoming more common in many centers. Results from a large prospective multicenter trial comparing digital to conventional film mammography demonstrated no significant difference in cancer detection rates.⁷ However, digital mammography was found to be more sensitive than film in three subgroups: women less than 50 years of age, women with radiographically dense breasts, and women who were pre- or perimenopausal.⁸

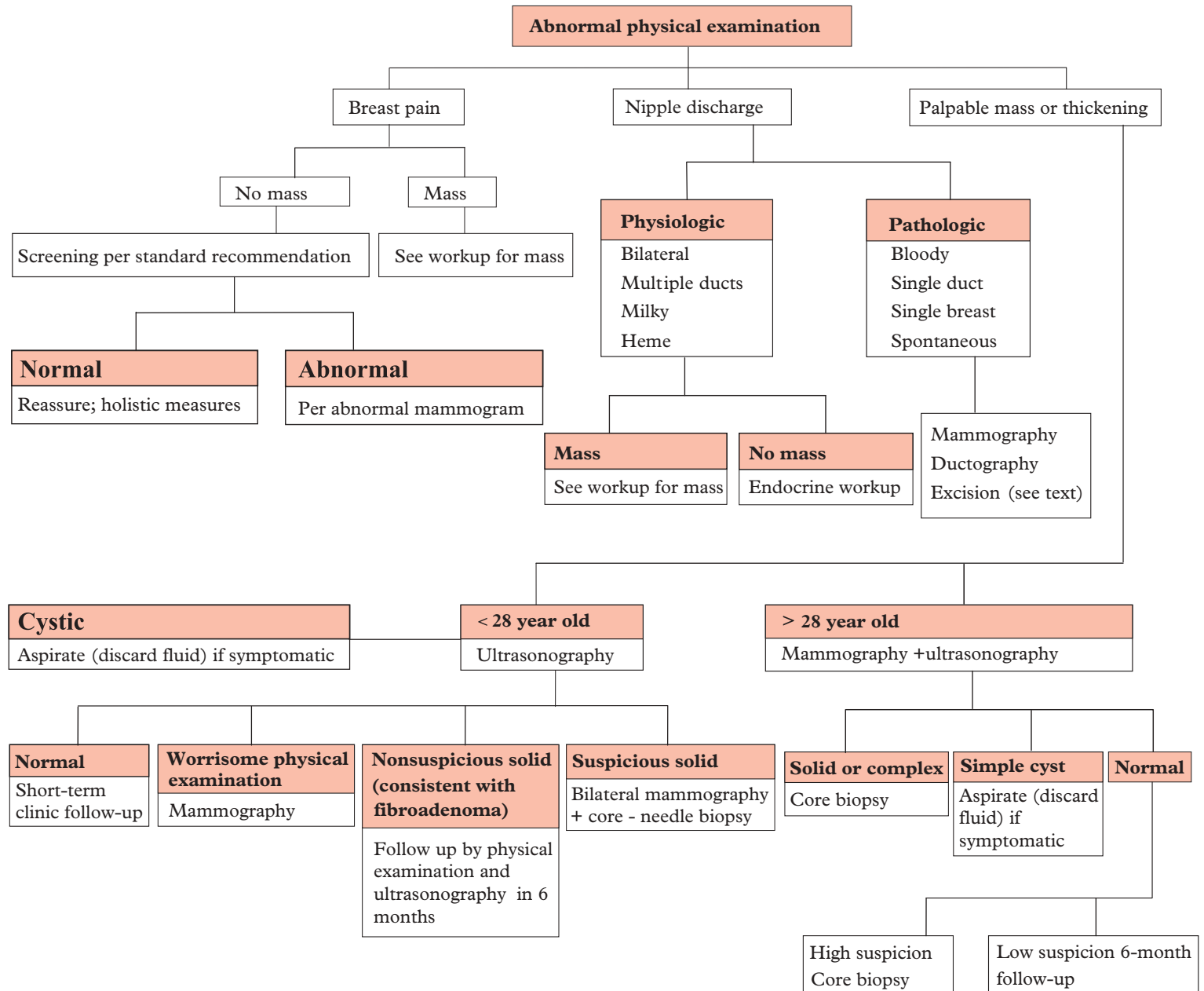
Evaluating Breast Complaints and Masses

HISTORY

Evaluation of a woman with a breast complaint should include a thorough history, a physical examination, and appropriate diagnostic studies. A complete history of the current complaint should include onset, duration, and progression of symptoms. Precipitating and ameliorating factors should be noted, as should the relationship of palpable abnormalities, pain, and tenderness to the menstrual cycle. Recent history of trauma to the breast, prior infections, fine-needle aspirations (FNAs), core biopsies, and surgical biopsies should also be recorded. Medical records, including operative reports and corresponding pathology and radiographic reports, should be reviewed carefully. The treating clinician should obtain and review prior breast imaging as part of the patient's history.

Symptoms or complaints involving the breast should be evaluated in the context of historical breast cancer risk data. Historical risk data include (1) history of the duration and type of hormone use (oral contraceptives and hormone replacement therapy); (2) reproductive history (age at menarche, age at menopause, age at first live birth, number of gestations and completed pregnancies); and (3) complete family history of all malignancies on both the maternal and





SCORE the paternal side, including the age at diagnosis. The remainder of the patient's general history should be evaluated with a focus on significant medical problems that may impact surgical planning. Medications and supplements that may contain estrogen-like substances and social history (especially tobacco, alcohol, work, exercise, and even sexual history as it pertains to breast stimulation) can be relevant.

PHYSICAL EXAMINATION

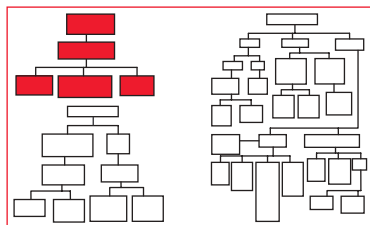
SCORE The breasts should be thoroughly examined in the upright and supine positions. Breast asymmetry and overall appearance of the skin, nipples, and areola should be observed with the patient upright. Any erythema, induration, peau d'orange, nipple retraction, and ulceration should be noted. Occult skin retraction can be demonstrated by having the woman raise her hands above her head and then place them against her hips. Bimanual examination of the breast tissue can facilitate identification of masses in women with dense breast tissue. In the supine position, turning the patient to either side to disperse breast tissue facilitates a more thorough examination for women with larger breasts. For the ptotic breast, palpation of the breast tissue between the thumb and index finger of the same hand may be useful. Location, mobility, and characteristics of masses and thickening should be noted, including size, firmness, presence of smooth or irregular borders, overlying skin changes, consistency, and areas of tenderness. Drawings or digital images can be made to document physical findings. All tissue between the clavicle and costal margins should be palpated, from the lateral sternal border to the posterior axillary line. Patients should also be checked for nipple discharge. Axillary, clavicular, and cervical lymph node basins should also be palpated in the upright and supine positions. The presence of adenopathy, including the size, consistency (hard versus soft), number, laterality, location, and mobility of the lymph nodes, should be documented.

DIAGNOSTIC STUDIES

Diagnostic Mammography and Targeted Ultrasonography

SCORE As mentioned previously, screening mammography refers to imaging of an asymptomatic woman. Diagnostic mammography, on the other hand, refers to imaging a woman with either a clinical complaint (a palpable lump, thickening, focal pain, discharge) or an abnormal screening mammogram. The initial workup of an abnormal screening mammogram involves additional mammographic imaging directed by a radiologist, which determines if the perceived abnormality is a real lesion. Spot and rolled views (with or without magnification) can sometimes demonstrate that the perceived abnormality was actually only the result of overlapping glandular tissue and there is no underlying lesion. The diagnostic mammogram report would then be given a final assessment 1 (negative), and the patient should return to annual screening mammography.

When an abnormality is detected and the patient needs additional mammographic and/or sonographic imaging, the



initial screening mammogram in these patients is given a final assessment 0 [see Table 1]. Women with a Breast Imaging Reporting and Data System (BI-RADS) 1 or 2 should continue to undergo routine annual mammography.⁸ Women with a BI-RADS 3 should undergo short-term follow-up, which typically involves an ipsilateral mammogram in 6 months followed by a bilateral study at 12 and 24 months. A finding in this category should have a less than 2% risk of malignancy based on morphologic and distribution features.^{9,10} Any interval progression at follow-up should prompt a biopsy. Patients with a BI-RADS category 4 or 5 lesion require a tissue diagnosis. As an adjunct to diagnostic mammography, high-frequency breast ultrasonography is often used in the diagnostic workup of a mass and can distinguish between a solid and a cystic lesion. If a solid mass is visualized sonographically, ultrasound-guided core-needle biopsy (CNB) can be performed for pathologic diagnosis.

PERCUTANEOUS CORE BIOPSY

Breast biopsies should be performed percutaneously whenever possible, using stereotactic, ultrasound, or MRI guidance. CNB with an automated gun or vacuum-assisted device has been confirmed in multiple studies to be a reliable alternative to surgical excision.^{11,12} Stereotactic (mammographic) guidance is typically used to biopsy indeterminate or suspicious calcifications as well as masses or densities that are sonographically occult. Ultrasound guidance is used to biopsy masses that can be visualized sonographically and is the most cost-effective type of image-guided core biopsy.¹³ MRI guided CNB is reserved for lesions that are occult to conventional imaging. The benefit of CNB over FNA is that it provides tissue for histologic rather than cytologic evaluation.

With any image-guided approach, it is important to confirm that the pathologic results are concordant with the imaging findings. Treatment decisions should be based on both pathologic findings and the appearance of the abnormality on diagnostic imaging. Discordant imaging and pathologic findings should prompt a surgical biopsy.

OTHER IMAGING MODALITIES

Magnetic Resonance Imaging

MRI is an imaging modality that uses strong magnetic fields to create a cross-sectional image. Breast MRI requires a specific coil and peripheral intravenous injection of a gadolinium-based contrast medium. Contrast-enhanced breast MRI has been shown to have a high sensitivity for detection of invasive breast cancer and can find both invasive and in situ carcinomas that are occult to conventional imaging. In practice, use of breast MRI is predominantly limited to women diagnosed with breast carcinoma and women at increased risk of developing breast cancer.

At present, there is no indication for the use of positron emission tomographic scans in the diagnostic workup of breast diseases outside a clinical trial. A number of new modalities are being investigated, such as positron emission mammography, breast-specific gamma imaging, tomosynthesis, and coned-beam computed tomography. Although some of these modalities are approved by the Food and Drug Administration (FDA), they are not currently standard practice.

Table 1 American College of Radiology Breast Imaging Reporting and Data System (BI-RADS)

Category	Assessment	Description/Recommendation
0	Additional imaging evaluation required	Additional imaging recommended
1	Negative finding	Nothing to comment on; routine screening recommended
2	Benign finding	Negative mammogram, but interpreter may wish to describe a finding; routine screening recommended
3	Probably benign finding	Very high probability of benignity; short-interval follow-up suggested to establish stability
4	Suspicious abnormality	Probability of malignancy; biopsy should be considered
5	Abnormality highly suggestive of malignancy	High probability of cancer; appropriate action should be taken

The report generated after the diagnostic workup is completed will have a final assessment of 1 to 5. The Breast Imaging Reporting and Data System (BI-RADS) lexicon was developed to standardize mammographic reports.⁶ It defines the final assessment categories, which informs the referring physician about the likelihood of malignancy.

General Management of Clinical Findings in the Breast

SCORE+ PALPABLE MASS

A dominant breast mass is defined as a discrete lump that is distinctly different from the surrounding breast tissue. Overall, approximately 10% of dominant breast masses are malignant. The workup and management of a discrete breast mass are governed by the age of the patient, the patient's family and medical history, the physical characteristics of the palpable lesion, and findings on diagnostic imaging.

SCORE+ SOLID MASSES

The likelihood of malignancy is greater when the patient is 40 years of age or older and when the mass is solid, hard, immobile and has irregular borders. Appropriate imaging studies, including mammography and ultrasonography should be done. In women over 30 years of age or with a significant family history of breast cancer, contralateral mammography is indicated to rule out synchronous lesions. If the mass is clinically suspicious, CNB or surgical biopsy should be performed for tissue diagnosis even in the setting of negative imaging.

SCORE+ CYSTIC MASSES

Cysts are a common cause of dominant breast masses, particularly in premenopausal women. They can be differentiated from solid lesions by means of ultrasonography. Sonographically, simple cysts tend to be oval, lobulated, and anechoic, with well-defined borders. Complex cysts with indistinct walls or solid components are more likely to be associated with carcinoma; therefore, imaging-guided aspiration, biopsy, or both should be performed. For asymptomatic simple cysts, no further intervention is required. For symptomatic cysts, FNA is appropriate. If the mass does not disappear completely after aspiration, then biopsy of any residual solid component should be performed. Clear fluid should not be sent for cytologic analysis because of the high likelihood of a false positive result. Bloody fluid obtained from a cyst aspiration should be sent for cytologic examination.

SCORE+ VAGUE THICKENING OR NODULARITY

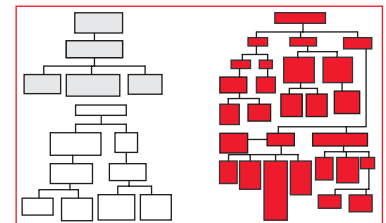
Normal breast texture is often heterogeneous, particularly in premenopausal women. Vague thickening or tender or nontender areas of nodularity are frequently detected by the

patient or the clinician. It is important to distinguish this vague breast thickening or nodularity from a discrete or dominant breast mass. In clinical practice, the first step in evaluating a nodular area is to compare it with the corresponding area of the opposite breast. Symmetrical tender nodularity—for example, in the upper outer quadrant of both breasts—is rarely pathologic. These areas often represent fibrocystic changes that may resolve with time and thus should be followed clinically. Asymmetrical areas of vague thickening in premenopausal women should be reexamined after one or two menstrual cycles. If the asymmetry persists, the patient should undergo mammography if she is 35 years of age or older and has not undergone a mammogram within the last 6 months. If the mass is clinically suspicious, a surgical biopsy for adequate sampling should be performed even in the setting of negative imaging.

Management of Specific Benign Breast Complaints

MASTALGIA

One of the most common complaints for which a woman seeks a doctor's opinion is mastalgia. Mastalgia (breast pain) can be cyclical or noncyclical and may be idiopathic. Often it is related to other common processes that occur in the breast, such as fibrocystic change or infection. Two thirds of women will complain about mastalgia during the course of their lives.¹⁴ Its cause is poorly understood. A history of the onset and course of the pain are important, especially as it relates to a woman's menstrual cycle. Although rarely a presenting complaint of breast cancer, mastalgia often causes considerable concern for patients. Mastalgia resolves spontaneously in 20 to 30% of cases but can recur in up to 60% of women. Some studies suggest a relationship with caffeine intake, premenstrual syndrome, and serum hormone levels.¹⁵ Frequently, after a complete history and physical examination to rule out a malignancy, the clinician is left treating mastalgia of unknown etiology. Many women respond well to reassurance^{14,16} and simple interventions, such as wearing a properly fitted bra and reducing caffeine intake.



Commonly used remedies, including evening primrose oil, vitamin E, and vitamin B₆, have limited evidence supporting their use to relieve symptoms.^{17,18} If simple interventions are not successful, consideration can be given to pharmacologic agents including nonsteroidal antiinflammatory drugs (NSAIDs), danazol, bromocriptine, and tamoxifen.^{15,18,19} In extreme and otherwise nonresponsive cases, surgical excision of the tender area can be used.²⁰

FIBROCYSTIC CHANGE

Fibrocystic change is often referred to by the misnomer fibrocystic disease. It is a common finding in women who are menstruating, occurring almost exclusively between the ages of 30 and 50. Fibrocystic change is characterized by lumpy or “cobblestone” breasts with ridges of tissue appreciated on palpation. The change is considered a normal variant. If a dominant mass is found in a woman with fibrocystic breasts, diagnostic imaging and biopsy should be undertaken to rule out malignancy. Symptoms generally improve with oral contraceptive use and abate with menopause. Treatment is geared toward symptomatic relief using the agents listed above for mastalgia and reassuring the patient that there is no worrisome etiology or increased risk of developing breast cancer.

NIPPLE DISCHARGE: PAPILLOMAS, DUCTAL ECTASIA, AND GALACTORRHEA

Nipple discharge is the third most common breast complaint after mastalgia and breast mass.²¹ In the majority of cases, the discharge is caused by noncancerous processes, including (1) physiologic discharge, (2) ductal ectasia, and (3) intraductal papilloma. However, malignancy should be ruled out as part of the workup for nonphysiologic discharge.²¹

For women presenting with this concern, the clinician should elicit a history that includes the characteristics of the discharge. The initial question to the patient should be whether the discharge is spontaneous or self-induced. If self-induced, the patient should be counseled to stop eliciting the discharge. If spontaneous, the characteristics are important in determining the cause, including whether it is unilateral or bilateral, milky, bloody, clear, posttraumatic, or cyclical. The history should also include questions pertaining to symptoms associated with an endocrine disorder (hypothyroidism) or to an intracranial etiology such as a pituitary tumor (amenorrhea, visual disturbances, and headache). A history of recent medication changes should also be taken because numerous medications are associated with galactorrhea (H₂ receptor antagonists, antihypertensives, antidepressants, and antidopaminergic agents).²¹

To understand physiologic nipple discharge, an understanding of breast physiology is critical. During pregnancy, high circulating levels of estrogen result in development of the breast into a predominantly glandular structure. With parturition, estrogen production decreases, resulting in prolactin secretion and increased secretory activity, whereas oxytocin results in “letting down” or ejection of milk into the ducts. A suckling infant or similar stimuli (i.e., sexual breast stimulation, postthoracotomy syndrome)²² may result in oxytocin release. Any of these conditions can result in physiologic discharge, which is usually milky and bilateral. Pregnancy can result in galactorrhea from the second

trimester to as late as 2 years postpartum. Elevated thyroid-stimulating hormone (TSH) levels can also be associated with elevated prolactin levels.

Nipple discharge characterized as nonbloody but darker green or brown is associated with ductal ectasia, a benign condition characterized by dilated ducts resulting from obstruction with keratin plugs, and subsequent inflammation and secretions. Ductal ectasia can arise in one or multiple ducts. Dilated ducts are visualized on ultrasonography and on ductography. The characteristics of the discharge from ductal ectasia can be similar to those seen with papillomas and ductal carcinoma in situ (DCIS) and are therefore included in the differential diagnosis of pathologic nipple discharge.

Bloody nipple discharge can appear as bright red, rusty, brown, or green and is considered pathologic. It is characteristically unilateral and emanates from a single duct. Although the most common etiology of this remains a solitary intraductal papilloma, DCIS and invasive breast cancer can also present with pathologic discharge. Of patients presenting with such a discharge, 17% have malignancy, 65% have papillomas, and the remainder have other benign lesions.²³

A thorough physical examination that includes a search for signs of an endocrine disturbance should be conducted (e.g., thyromegaly, visual field defects). As part of the breast evaluation, if nipple discharge is not apparent, the clinician should gently squeeze the nipple to determine whether the discharge is coming from a single duct or multiple ducts and whether the discharge is bilateral. The breast should be evaluated for the presence of a discrete mass that may be associated with an underlying carcinoma.

Historical and physical findings suggestive of an endocrine disorder should prompt the clinician to order TSH and prolactin levels. An MRI of the brain should be ordered to rule out a prolactin-secreting tumor of the pituitary if prolactin levels are elevated. In women of childbearing age, a pregnancy test should also be ordered as part of the workup of galactorrhea. Women with medication-induced bilateral discharge should be counseled about the etiology and reassured.

For patients who are found to have pathologic discharge, the diagnostic workup should begin with bilateral diagnostic mammography. If imaging reveals a focal lesion or microcalcifications, tissue diagnosis should be obtained. Ductography may be able to identify an intraductal lesion and guide surgical planning. Ductography involves cannulating the discharging duct with a small catheter and then injecting a small amount of radiographic contrast medium. Magnified mammographic views are then obtained, and lesions within the duct are identified as either a filling defect or an abrupt cutoff. More recently, ductoscopy, which uses a flexible or rigid fibroscopic ductoscope to cannulate the nipple, can be used to isolate areas of pathology for excision. In skilled hands, it can be combined with (brush) cytology for improved accuracy.^{24,25}

The role of cytologic analysis remains controversial. FNA is also unreliable in evaluating patients with drainage and/or papillomatous disease²⁶ (and many feel that even CNB of endoductal lesions remains inadequate for definitive diagnosis of these lesions).^{27–30} Therefore, surgical excision is recommended given the incidence of concomitant premalignant

and malignant disease in the setting of pathologic nipple discharge.^{27,31} When the location of the intraductal pathology is identified prior to surgical resection, a more limited resection (i.e., single duct excision) of the disease is possible.³² If the duct is peripheral in the breast, the duct can be localized via needle localization. When possible, single duct excision is preferred because it preserves nipple sensation and the ability to breastfeed. In cases where the focal pathology cannot be isolated preoperatively, or in the case of multiduct involvement, a major duct excision is more appropriate. This involves removing all of the central lactiferous ducts and sinuses, preventing further discharge. Both procedures can be done on an outpatient basis and require only local anesthesia and intravenous sedation.

FIBROEPITHELIAL LESIONS: FIBROADENOMA AND PHYLLODES TUMOR

Fibroepithelial lesions encompass a spectrum of breast abnormalities ranging from the fibroadenoma (FA) to the phyllodes tumor (PT). FAs are the most common benign breast lesions and occur most frequently in the second and third decades of life. Their natural history is one of stability or slow growth. Patients will often give a history of a solitary nontender nodule. Physical examination will usually demonstrate a well-defined solitary, rubbery, and mobile nodule. Ultrasonography is particularly useful in younger women and demonstrates a well-defined oval or round hypoechoic mass with discrete margins. Mammography should be obtained (in addition to ultrasonography) in women over 35 years of age and typically demonstrates a well-defined radiopaque mass with smooth borders. If the history, physical examination, and imaging are consistent with an FA, careful clinical follow-up is reasonable with ultrasonography and CBE at 6-month intervals to assess the stability of the lesion. When the diagnosis is uncertain, CNB should be performed. For women who request excision of a benign FA, enucleation of the lesion is adequate. Conversely, if the lesion increases in size during clinical follow-up, surgical excision is recommended to rule out a PT.

PTs are unusual, representing only 0.3 to .5% of breast neoplasms.³³ They have the same clinical appearance and imaging characteristics as FAs, but unlike FAs, they are characterized by a clinical history of rapid growth and have larger dimensions. With increased screening, more PTs are being discovered mammographically. Given that these lesions do not have any features on imaging that would be helpful in differentiating them from FAs, CNB is recommended. However, it can be difficult to differentiate between FA and PT on CNB. A pathologic diagnosis of a fibroepithelial lesion on CNB necessitates excision to rule out a PT. Tumors are classified histologically as low, intermediate, or high grade. Although most PTs have minimal metastatic potential, they have a proclivity for local recurrence and should be excised with at least a 1 cm margin. Local recurrence has been correlated with excision margins but not with tumor grade or size.³⁴ The most common site of metastasis from malignant PT is the lungs.

ATYPICAL DUCTAL HYPERPLASIA, RADIAL SCAR, LOBULAR NEOPLASIA, AND LOBULAR CARCINOMA IN SITU

During the course of a patient's workup for a suspicious physical finding or image-detected abnormality, CNB or

FNA may be performed. A pathologic diagnosis demonstrating atypia (on FNA), atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS), or radial scar requires formal surgical excision with needle localization to rule out the presence of invasive carcinoma or DCIS. CNB of these lesions understages findings related to these diagnoses in up to 30% of cases.^{35–39} These lesions may be an independent risk factor for the development of carcinoma³⁸ [see Evaluation of Patients at High Risk for Breast Cancer, *below*].

FAT NECROSIS

Fat necrosis can masquerade as breast cancer. It often presents as a firm, irregular mass within breast tissue, which is occasionally tender. The patient's history is helpful in providing clues to this diagnosis and will often include a history of trauma, reduction mammoplasty, or prior breast surgery. Large cavity size, postoperative hematoma, or infection, as well as adjuvant radiation, can increase the likelihood of fat necrosis. A compromise to the surrounding parenchymal blood supply is thought to be the underlying factor in its development. Diagnostic mammography and ultrasonography can aid in the diagnosis. Loss of speculation, compressibility, oil cysts, and the presence of eggshell calcifications are suggestive of a benign etiology. Review of prior films is necessary to determine the stability of the lesion.⁴⁰ Ultrasonography or stereotactic CNB is appropriate if there is doubt about the diagnosis and will reveal chronic inflammatory cells, lymphocytes, histiocytes, fat necrosis, and saponification. Should the physician opt for short-term clinical follow-up (1 to 2 months) instead of biopsy, it is important to have a patient who will be compliant with keeping follow-up visits.⁴¹

GALACTOCELE

In the pregnant patient with complaints of a mass or tenderness, the clinician should bear in mind the hormonally stimulated status of the breast, resulting in increased tenderness. However, any mass or thickening in the breast requires prompt evaluation in the pregnant patient. Malignancy should always be ruled out, particularly in older, childbearing-age women. A galactocoele, which is a collection of milk within an obstructed, dilated duct, can form during pregnancy, lactation, or recent postlactation. A patient may complain of a tender nodule within the breast tissue. A mammogram will demonstrate a well-circumscribed mixed-density lesion, and ultrasonography will reveal a corresponding partially cystic mass. Simple aspiration can be both diagnostic and therapeutic, providing relief. Malignancy should always be in the differential, particularly in older women of childbearing years.

MONDOR DISEASE

Mondor disease is thrombophlebitis of the superficial veins of the breast. It is characterized by the finding of a tender and often inflamed cord palpated on the patient's breast. After a thorough history and physical examination of the patient's breasts, treatment should consist of NSAIDs, analgesics, and antibiotics. If there is evidence of infection, or should the condition fail to improve, surgical excision is appropriate for definitive management and diagnosis.⁴²

GYNECOMASTIA

SCORE Gynecomastia, or a breast mass in male breast tissue, is usually a benign condition in adolescent males and presents as discoid, subareolar, rubbery thickening of the breast tissue. In the absence of any other findings, such as testicular pathology, or a history of ingestion or use of substances associated with gynecomastia, these patients should be reassured and reexamined. In the case of especially prominent, large, or symptomatic gynecomastia, surgical excision is reasonable. In the mature male population, a physical examination and history are vitally important. Soft, diffuse enlargement is a result of medication in 20 to 25% of cases.⁴³ Gynecomastia can also be due to hormonal, physiologic, or idiopathic factors and can usually be managed nonoperatively and with serial examinations. Many medications resulting in gynecomastia are felt to do so by elevating prolactin levels comparatively. If the gynecomastia is attributable to medication, switching the patient off the medication will often result in regression over the course of a few months. For men who would like to avoid surgery, some success has been noted in treating gynecomastia with tamoxifen, raloxifene, and aromatase inhibitors.^{44,45} However, a finding of a solitary hard mass, especially with findings of adenopathy and skin changes, requires aggressive workup, including mammogram and tissue diagnosis, usually with CNB.

SKIN AND NIPPLE CHANGES

SCORE Common breast skin and nipple changes include bacterial infections (mastitis, cellulitis, with or without underlying abscess), fungal infections, and dermatitis. In lactating women, mastitis is generally the result of poor hygiene. Women will often give a history of an abrasion or crack in the nipple. Symptoms typically include erythema, tenderness, and swelling of the breast. *Staphylococcus aureus* is the most common organism identified. Treatment involves continued breastfeeding and antibiotics. The choice of antibiotics should take into consideration the safety of the breastfeeding infant.⁴⁶

SCORE Nonresolution of the infection with a course of appropriate antibiotics should prompt the surgeon to consider the presence of an underlying abscess or an antibiotic-resistant organism. Fluid from an abscess should be sent for Gram stain and culture to ensure the appropriate choice of antibiotic. If the symptoms persist in the absence of the above causes, inflammatory breast cancer should be considered, followed by appropriate imaging, punch biopsy of the skin, and percutaneous biopsy of any underlying lesion.

SCORE In nonlactating women, cellulitis of the breast typically occurs in the lower half of the breast and is more commonly found in women who are overweight, have large, pendulous breasts, or have poor personal hygiene. Breast abscesses are more frequently seen in women with a history of diabetes, rheumatoid arthritis, chronic steroid use, chronic granulomatous lobular mastitis, and trauma.⁴⁶ Treatment includes antibiotics and identification of an underlying abscess followed by aspiration or drainage. Aspiration should always precede

drainage. Intravenous antibiotics should be considered for women with elevated temperature and white blood cell count. Other skin conditions in the breast include sebaceous cysts and hidradenitis suppurativa. Appropriate antibiotics should be given, and surgical excision is often required for resolution of the symptoms. Fungal (candidal) infections involving the breast are a common complaint in women with large, pendulous breasts. The lower breast and inframammary crease are common locations for the characteristic erythematous moist patches. Treatment includes keeping the area clean and dry and topical antifungal powders or creams.

In nonlactating women, benign processes involving the nipple are often the result of trauma or damage to the nipple or subareolar ducts. Smoking is associated with periductal mastitis, which can present with pain, inflammation, nipple retraction, and discharge. Appropriate antibiotics and abscess aspiration or drainage are the recommended treatments. Trauma, dry skin, or dermatitis can lead to excoriation of the nipple. Allergic or atopic dermatitis frequently occurs as a result of allergies to clothing, dyes, perfumes, and detergents. Treatment is symptomatic, with removal of the offending agent and a course of topical steroids. Short-term clinical follow-up (1 to 2 weeks) is essential to ensure resolution of the symptoms. Breast cancer, including Paget disease of the nipple, can present with these symptoms, and it is vital that the surgeon make an accurate diagnosis. If there is no improvement of the symptoms in 2 weeks, punch biopsy of the nipple should be done.

Evaluation of Patients at High Risk for Breast Cancer

Significant morbidity and cost are associated with breast cancer treatment. Approximately one third of women diagnosed with breast cancer will succumb to the disease. This has led to efforts to provide primary prevention to high-risk women. A number of factors have been identified that increase breast cancer risk [see Table 2].⁴⁷ These risk factors include (1) mutations in genes that confer a predisposition to breast

Table 2 Magnitude of Known Breast Cancer Risk Factors

Relative risk < 2
Early menarche
Late menopause
Nulliparity
Age > 35 first birth
Hormone replacement therapy
Obesity
Alcohol use
Proliferative breast disease
Prior breast biopsies
Relative risk 2–4
One first-degree relative with breast cancer
Radiation exposure
Prior breast cancer
Mammographic density
Relative risk > 4
Two first-degree relatives with breast cancer
Gene mutation
Lobular carcinoma in situ
Ductal carcinoma in situ
Atypical hyperplasia

Adapted from: Morrow M, Jordan VC. Managing breast cancer risk. 1st edition. Hamilton, ON: BC Decker Inc; 2003. p. 302.

cancer⁴⁸; (2) hormonal and reproductive factors^{47,49–51}; (3) environmental factors, including diet and lifestyle characteristics of developed Western nations⁵²; (4) prior radiation to the chest wall as a teenager or young adult⁵³; (5) a history of prior breast cancer, radial scar, or other premalignant lesions^{37,54,55}; and (6) increased mammographic density.⁵⁶ Recognition of factors that increase breast cancer risk facilitates appropriate screening and clinical management of individual patients. It must be recognized, however, that most women have none of the known risk factors for breast cancer, and the absence of these risk factors should never prevent full evaluation or biopsy of a suspicious breast lesion.

Approximately 10% of all breast cancers are hereditary.⁵⁷ Hereditary breast cancer is characterized by early age of onset, bilateral disease and disease in other organ sites. Therefore, an accurate and complete family history, including all malignancies, is essential for quantifying a woman's genetic predisposition to breast cancer. Questions about breast cancer in family members should go back several generations, with age at diagnosis recorded if available. Any personal history of cancer should be recorded, with particular attention paid to breast, ovarian, and endometrial cancers.

BRCA1 and *BRCA2* account for the majority of hereditary breast cancers. The lifetime risk of breast cancer in these individuals can be as high as 85%. Mutations in these genes are associated with other malignancies, most notably ovarian, pancreatic, and prostate cancer. Specific founder mutations in *BRCA1* and *BRCA2* occur within certain ethnic groups (e.g., Ashkenazi Jews).⁵⁷ Surgeons should also be aware of mutations in other genes that are commonly associated with an increased risk of breast cancer, including mutations in *p53* (Li-Fraumeni syndrome), mutations in the *PTEN* gene (Cowden syndrome), and hereditary diffuse gastric cancer syndrome (*CHD1*). Tests that detect mutations in these genes are commercially available. Clinicians should consult a licensed genetic counselor to determine appropriate candidates for testing.

Genetic testing has significantly improved our ability to define breast cancer risk for the subset of women who have a mutation. For women without a known genetic predisposition, the Gail⁵⁸ and Claus models⁵⁹ are two tools that can screen women who may be at increased risk and would therefore benefit from enhanced surveillance and chemoprevention. It should be noted that these mathematical models define population-based risk, not individual risk.

Histologic markers of risk include both ductal and lobular atypia, radial scar, and lobular carcinoma in situ (LCIS). Atypia and radial scar confer a fourfold increased risk of developing breast cancer.^{60,61} LCIS is associated with an increased lifetime risk of subsequent carcinoma between 20 and 25%. Pleomorphic LCIS, a pathologically distinct entity of LCIS, appears to be associated more frequently with invasive cancer.^{62,63} At present, women with these high-risk lesions should be offered screening and chemoprevention.

Currently, there are three options for women to manage their risk: (1) enhanced surveillance, (2) chemoprevention, and (3) prophylactic mastectomy. For women with LCIS or a family history of breast carcinoma, surveillance should include twice-yearly CBE. Mammography should be performed annually after the diagnosis of LCIS or atypical hyperplasia. Women with a family history of breast cancer

should have screening mammography performed annually, beginning 10 years before the earliest age at which cancer was diagnosed in a first-degree relative.⁶⁴ For women with known genetic mutations and other women from families with an autosomal dominant pattern of breast cancer transmission, annual mammographic screening should begin at age 25.⁶⁴ There are several prospective nonrandomized trials which were designed to assess the benefit for adding yearly screening breast MRI for women at high risk for breast cancer.^{65–69} These studies demonstrated that breast MRI is more sensitive than mammography. The ACS recently published recommendations for the use of screening breast MRI as an adjunct to mammography. Annual screening with breast MRI is recommended for the following: (1) *BRCA* mutation carriers; (2) first-degree relatives of a *BRCA* mutation carrier who have never been tested; (3) women with a lifetime risk of 20 to 25% based on risk models that are predominantly dependent on family history; (4) women with a history of radiation to the chest between the ages of 10 and 20 years; (5) women with Li-Fraumeni syndrome (mutations in the *p53* gene) and their first-degree relatives; and (6) women with Cowden and Bannayan-Riley-Ruvalcaba syndromes (mutations in the *PTEN* gene) and first-degree relatives.⁷⁰

It is important to remember that although the sensitivity of breast MRI for cancer is high, the specificity is relatively low and can result in high recall and biopsy rates.⁷⁰ Breast MRI should be used as an adjunct to mammography and not a replacement. Mammography and MRI can be done simultaneously or alternating with each other at 6-month intervals to coincide with the CBE. Given the specificity of breast MRI and the fact that many enhancing lesions seen on breast MRI are occult to conventional imaging modalities, it is essential that any facility performing screening breast MRI should have the capability for MRI-guided breast biopsy.

Chemopreventive strategies are designed either to block the initiation of the carcinogenic process or to prevent (or reverse) the progression of the premalignant cells to an invasive cancer.⁷¹ Only tamoxifen and raloxifene are currently FDA approved for chemoprevention in breast cancer. Both are selective estrogen receptor modulators (SERMs). Large multicenter randomized trials demonstrated the efficacy of these agents in the primary prevention setting for women at increased risk of breast cancer based on a Gail score of 1.67 or a personal history of ADH or LCIS. The overall risk of invasive breast cancer was reduced by 50% after treatment for 5 years and limited to estrogen receptor (ER)-positive breast cancers in these high-risk women. Raloxifene is currently approved only for postmenopausal women and has the added benefit of treating postmenopausal osteoporosis. It is noteworthy, however, that raloxifene was not found to prevent noninvasive breast cancers in this trial.⁷²

The hot flashes, deep vein thrombosis, and endometrial cancer associated with tamoxifen have made it an unattractive option for many women. This has generated interest in identifying other chemopreventive agents. Aromatase inhibitors, which are used to treat ER-positive breast cancers in postmenopausal women, reduce the risk of contralateral cancers and may have a role to play in chemoprevention. In addition, gonadotropin-releasing hormone agonists, monoterpenes, lignans, retinoids, rexinoids, vitamin D derivatives,

and inhibitors of tyrosine kinase are all undergoing evaluation in clinical or preclinical studies with a view to assessing their potential chemopreventive activity. Whether any of these compounds will play a clinically useful role in preventing breast cancer remains to be seen.

For those women at significant risk of breast cancer attributable to genetic predisposition, bilateral prophylactic mastectomy can be considered. High-risk women who underwent this procedure, compared with those who did not, had their breast cancer risk reduced by at least 90%.⁷³ Oophorectomy also confers up to a 50% breast cancer risk reduction in premenopausal women.⁷⁴ The benefits of prophylactic

mastectomy must be weighed against the irreversibility and the psychosocial consequences of the procedure.

Research involving high-risk women is challenging because of the large numbers of women who must be recruited and followed for many years and because of the cost associated with such an undertaking. Improved risk assessment tools that can aid in improved risk stratification are under active investigation.⁷⁵ Current trials are focused on identifying and using intermediate biomarkers of breast cancer risk to test potential chemopreventive agents.

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1 DYSPHAGIA

P. James Villeneuve, MDCM, PhD, FRCSC, and R. Sudhir Sundareshan, MD, FRCSC, FACS*

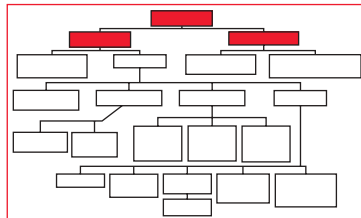
The term *dysphagia*, derived from the Greek *dys-* (with difficulty) and *-phagia* (to eat), describes difficulty in the transfer of food or liquid boluses from the mouth to the stomach. Dysphagia is a common complaint, with at least 35% of patients above the age of 50 complaining of weekly dysphagia and up to 60% of nursing home residents suffering feeding difficulties as a result of dysphagia.^{1,2}

There are two forms of dysphagia. Oropharyngeal dysphagia results from a functional impairment in the initiation of swallowing, including the oral and pharyngeal phases [see *Sidebar Normal Swallowing Mechanism*], and often results from systemic neurologic or myopathic syndromes [see *Table 1*]. Esophageal dysphagia relates to intrinsic functional (motor) and anatomic abnormalities of the esophagus that result in swallowing difficulties [see *Table 2*].^{1,3}

This chapter outlines the basic physiology of the swallowing mechanism and proposes an evaluative and diagnostic approach to difficulties with swallowing. The technical details of specific procedures employed in the definitive treatment of certain causes of dysphagia are described in later chapters of this volume.

Evaluation

A systematic approach to the patient with dysphagia is mandatory. A thorough history and complete physical examination allow for an accurate assessment of likely etiologies. Confounding diagnoses, such as angina pectoris, thyroid goiter, and pharyngitis, should be eliminated.



IMPORTANT ELEMENTS TO ELICIT ON HISTORY

Timing of Dysphagia

Immediate coughing, choking, or regurgitation suggests oropharyngeal causes for dysphagia. A sensation of food “sticking” or getting “caught” or the delayed regurgitation of food suggests esophageal causes of dysphagia.² Patients reporting the constant presence of symptoms not associated with swallowing difficulties may have globus sensation, which is a benign, nonpainful fullness in the neck or throat.⁴

Painful Swallowing

Odynophagia is not typically associated with dysphagia; its presence should prompt consideration of infectious or inflammatory etiologies. Exposure and ingestion of caustic

substances must be sought out as an expedient assessment of severity and consideration of immediate surgery must be made.

Location

Patients will self-localize symptoms to the cervical, retrosternal, or epigastric regions. Studies have demonstrated accurate localization, by patient history, to within 4 cm of the culprit lesion in up to 74% of cases.⁵ Accuracy seems best for proximal lesions.

Solid or Liquid

Intolerance to both liquids and solids suggests a functional or neuromuscular cause of dysphagia. Difficulties with solid food only strongly implicates a mechanical or anatomic causes of dysphagia⁶; a progression from purely solid food dysphagia to both solid and liquid dysphagia suggests narrowing attributable to an evolving mechanical obstruction.

Onset and Progression

The temporal pattern of symptom onset and duration also gives valuable information as to possible causes for dysphagia. Intermittent, nonprogressive symptoms suggest an intrinsic motor dysfunction (such as diffuse esophageal spasm) or a mechanical cause such as a web or ring. If the symptoms have been present for a short period of time or are rapidly progressive, a malignant etiology must be ruled out.

Associated Symptoms

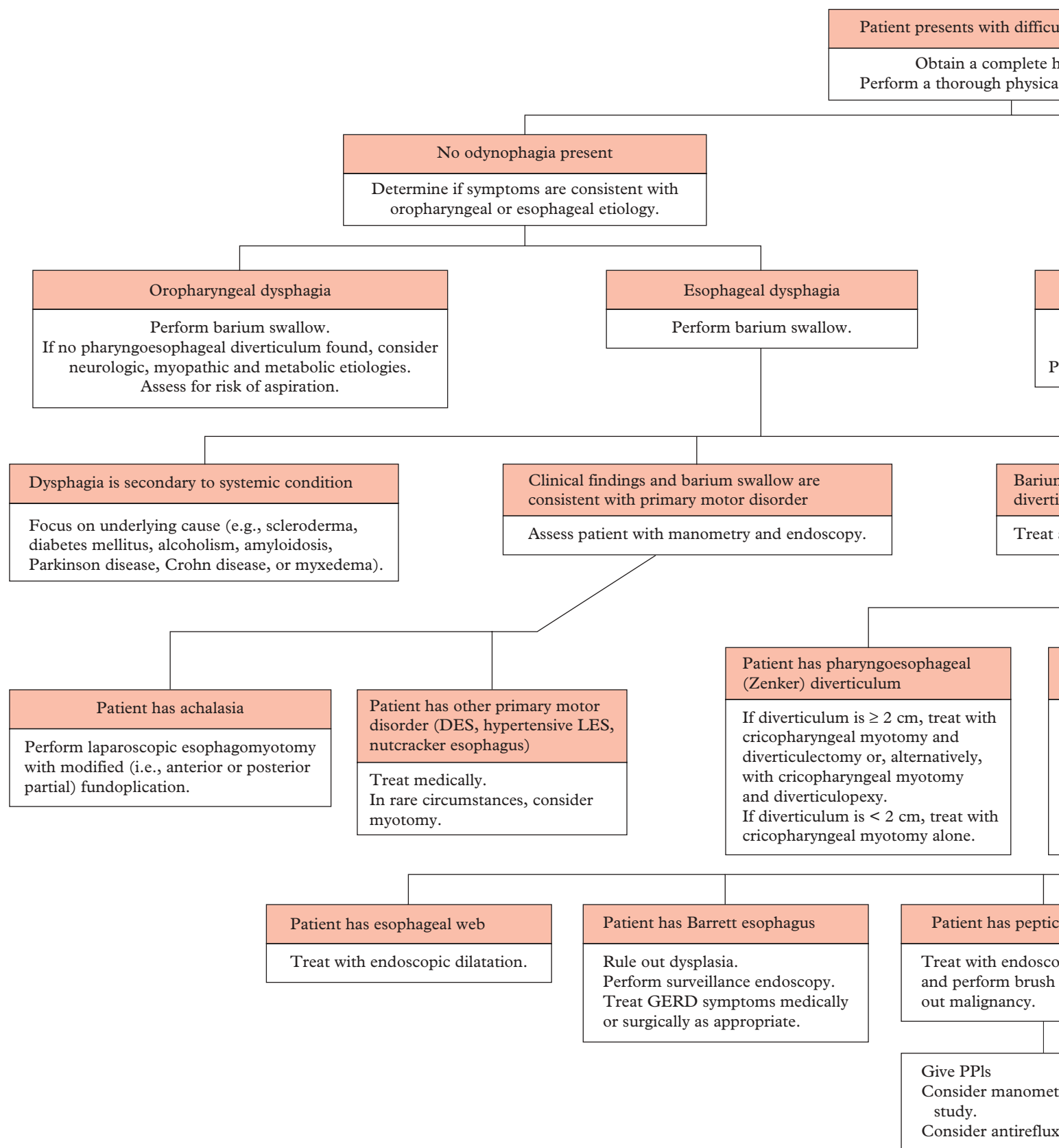
A history of anorexia or weight loss suggests an underlying malignancy. Passive regurgitation of food particles may arise from achalasia or a cricopharyngeal diverticulum. Retrosternal chest pain, once cardiac etiologies have been eliminated, may be present in cases of esophageal spasm or gastroesophageal reflux. However, dysphagia secondary to peptic strictures and adenocarcinoma are without symptoms of gastroesophageal reflux disease (GERD) in up to 25 to 35% of cases.⁷ Medication lists must be examined to rule out culprit medications (alendronate, doxycycline, nonsteroidal antiinflammatory drugs [NSAIDs], and mycophenolate mofetil [MMF]) that may cause drug-induced esophageal injury.⁸

PHYSICAL EXAMINATION

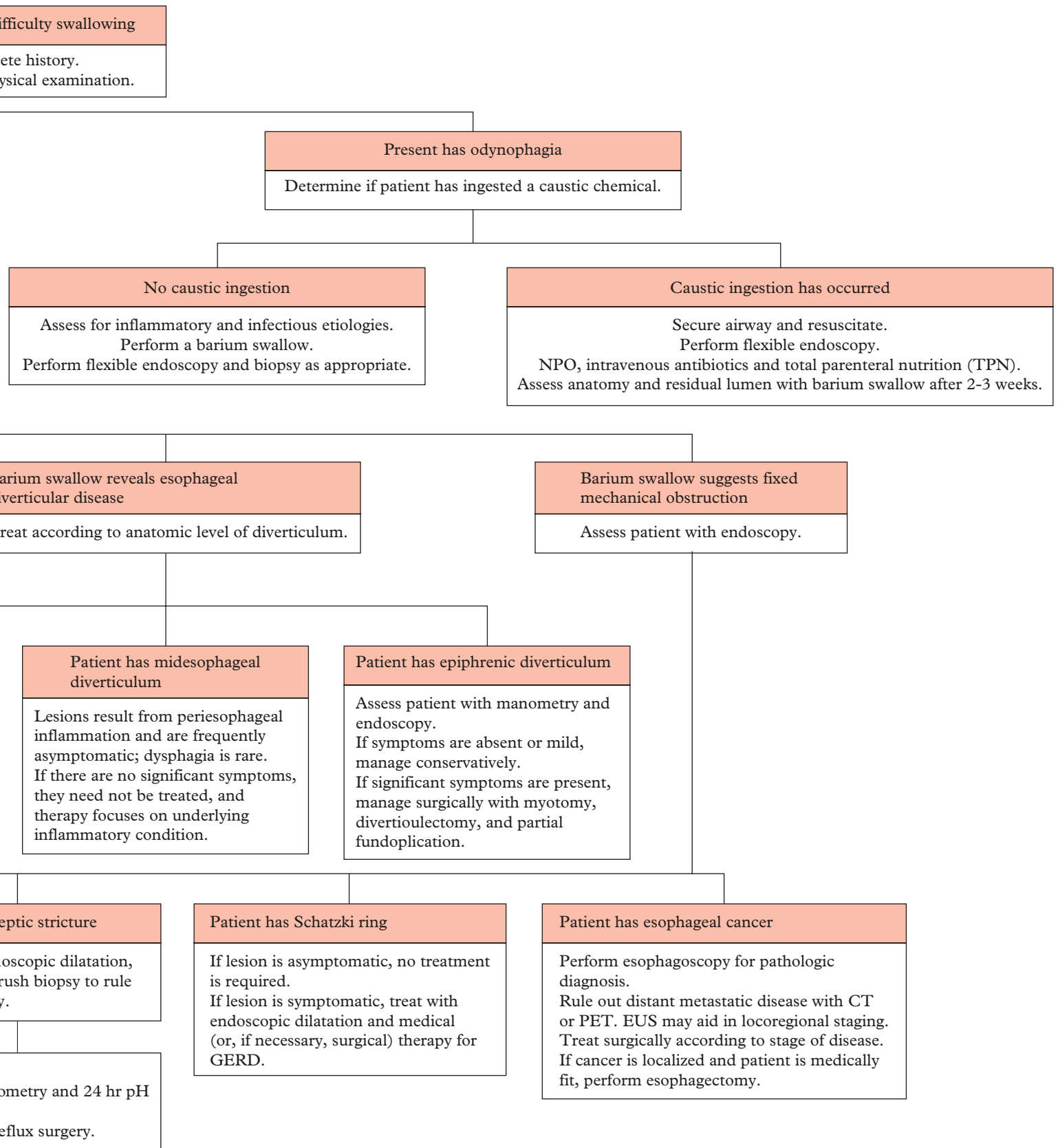
The esophagus is a deep-seated structure that does not lend itself to direct physical assessment. Although a thorough physical examination should follow a complete history, information gathered is useful only in inferring potential diagnoses. A detailed and accurate history is the mainstay of clinical assessment in patients who present with dysphagia.

The head and neck are examined for the size of the thyroid gland, as well as for the presence of any lymphadenopathy or masses. A careful examination of cranial nerves may

* The authors and editors gratefully acknowledge the contributions of the previous author, Ahmad S. Ashrafi, MD, FRCSC, to the development and writing of this chapter.



DES = diffuse esophageal spasm; LES = lower esophageal sphincter; GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor; NPO = nil per os; CT = computed tomography; PET = positron emission tomography; EUS = endoscopic ultrasound.



Normal Swallowing Mechanism adapted from Matsuo and Palmer²⁵

Swallowing was previously described using a three-phase sequential model, whereby the position of the food bolus was used to identify the oral, pharyngeal, and esophageal phases. Later reports expanded this into a four-stage model by dividing the oral phase into preparatory and propulsive stages. These early models accurately depicted liquid swallows but were inadequate to model solid food boluses. The process model accounts for swallowing of solid foods by expanding the oral phase into stage I, transport, food processing, and stage II, transport. The pharyngeal and esophageal phases are common to both liquid and solid transport.

Oral Phases of Liquid Swallowing

Preparatory	Liquid is held against hard palate by tongue and sealed posteriorly by contact between tongue and soft palate
Propulsive	Sequential contact between tongue and hard palate coupled with relaxation of seal between posterior tongue and soft palate squeezes liquid into pharynx

Oral Phases of Solid Swallowing

Stage I transport	Food is positioned against occlusive tooth surfaces by tongue movement.
Oral food processing	Coordinated movements of the jaw, in concert with the tongue, cheek, soft palate, and hyoid bone movement. This results in masticated, moistened food that is optimal for further swallowing.
Stage II transport	Food bolus is positioned on the tongue surface. Sequential contact between the tongue and hard palate coupled with relaxation of seal between posterior tongue and soft palate propels food into the pharynx.

Intraluminal pressure (mm Hg)

Pharynx

Upper Esophageal Sphincter

Upper esophagus

Middle esophagus

Lower esophagus

Lower Esophageal Sphincter

Pharyngeal Phase

This rapid phase must achieve airway protection while facilitating passage of boluses through the upper esophageal sphincter (UES) to the esophagus proper. Airway protection is achieved by concerted closure of the vocal cords and laryngeal movement (anteriorly and superiorly) with concomitant tilting of the epiglottis to seal the laryngeal vestibule. Food propulsion follows: the soft palate rises to block retrograde passage into the nasopharynx. Pharyngeal constrictors sequentially contract from cranial to caudal, shortening the pharynx and propelling the food bolus downward. This “pharyngeal pump” can generate pressures of up to 200 mm Hg. The UES has a resting pressure of between 16 and 118 mm Hg and is closed at rest. Active opening of the UES is achieved by relaxation of the cricopharyngeus, traction by the strap muscles, and distending pressure of the descending food bolus.

Esophageal Phase

Both the UES and the lower esophageal sphincter (LES) remain closed at rest to prevent reflux. Autonomic efferent signals mediate peristalsis; an initial wave of relaxation preceding the food bolus is followed by a wave of contraction, resulting in transit through the esophagus into the stomach. *Primary* esophageal peristalsis is triggered by voluntary swallowing but autonomously propagates at 2 to 5 cm/s through the striated muscles of the upper third of the esophagus, slowing as peristalsis passes into the smooth muscles of the lower esophagus. Secondary esophageal peristalsis is involuntary and arises in response to esophageal distention or irritation. It is thought that these waves of peristalsis serve to keep the esophagus clear. Tertiary esophageal waves can arise normally between swallows but are often nonpropulsive.

The sidebar figure demonstrates normal waveforms and propagation of peristalsis in swallowing. It is evident that coordination between the different anatomic levels of the esophagus is required for effective swallowing. The high-pressure contraction in the pharynx is coordinated with full relaxation of the UES. This allows transfer of swallowed material into the esophagus proper, where peristaltic pressures of up to 80 mm Hg are noted. Orderly progression of moderate-amplitude waves through the esophageal body occurs. The LES relaxes early in response to swallowing and slowly regains its resting pressure of 10 to 25 mm Hg in concert with distal esophageal transport.

demonstrate deficits contributing to oropharyngeal dysphagia, and corresponding neurologic assessment may reveal signs of a cerebrovascular accident (CVA), myasthenia gravis, or Parkinson disease. The chest and abdomen are examined for the presence of subcutaneous nodules or masses that may indicate underlying malignancy. Dermatologic rashes may

indicate a paraneoplastic syndrome or a primary autoimmune disorder. Murmurs or thrills on cardiac auscultation may represent atrial enlargement (secondary to mitral valvular stenosis), causing extrinsic esophageal compression. Refer to *Table 1* and *Table 2* for specific causes of oropharyngeal and esophageal dysphagia.

04/10

Table 1 Etiologies of Oropharyngeal Dysphagia

Systemic conditions
Cerebrovascular accident
Myasthenia gravis
Intrinsic motor disorders
Cricopharyngeal (Zenker) diverticulum
Fixed mechanical obstruction
Oropharyngeal cancer
Webs
Previous surgical/radiation treatment

DIAGNOSTIC TESTS

Many diagnostic tests can be used to assess dysphagia, including endoscopic, radiologic, and manometric modalities. The application of these should be predicated by the history.

In cases of suspected or confirmed caustic ingestion, the first test is emergent upper flexible endoscopy to assess the anatomic extent of damage and to grade the injury.⁹ In all other cases of dysphagia, the barium swallow is the ideal first test as it is readily available, cost-effective, and rapidly performed. Information can be gained from the barium study regarding anatomic relations, esophageal transit patterns, and the presence or absence of mass lesions and diverticulae. The safety and diagnostic yield of subsequent upper endoscopy are enhanced.

Upper endoscopy allows for a visual assessment of mucosa; diagnostic and therapeutic maneuvers such as biopsies, brushings, and dilatations can be performed.

Endoscopic ultrasonography (EUS) is an emerging diagnostic modality that allows for assessment of the esophageal wall and surrounding tissues. This permits the characterization of esophageal masses (depth of invasion, T stage) and an assessment of adjacent lymphadenopathy (N stage), and guides endoscopic fine-needle aspiration biopsies. EUS-guided biopsies have excellent predictive value in the assessment of lymph node involvement in cases of esophageal carcinoma.¹⁰

Table 2 Etiologies of Esophageal Dysphagia

Systemic conditions
Scleroderma
Diabetes mellitus
Intrinsic motor disorders
Secondary to GERD
Achalasia
Esophageal spasms
Fixed mechanical obstruction
Webs
Neoplasms
Extrinsic compression
Inflammatory
Eosinophilic esophagitis
HSV/CMV/ <i>Candida</i>

CMV = cytomegalovirus; GERD = gastroesophageal reflux disease; HSV = herpes simplex virus.

When reflux disease is suspected, extended pH monitoring is invaluable in assessing the presence and severity of GERD. Motility disorders are best diagnosed using manometric techniques.

In cases where extrinsic compression is suspected or demonstrated, cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) may be useful in identification of malignant masses or vascular anomalies (aberrant subclavian vessels, aortic aneurysms, or Kommerell diverticulae).^{11,12} Dysphagia lusoria is a rare entity in which dysphagia results from extrinsic vascular compression of the esophagus from an aberrant right subclavian artery, which arises from the thoracic aorta and typically courses posterior to the esophagus [see Figure 1].

The assessment of esophageal cancer also requires cross-sectional imaging with CT and fluorodeoxyglucose-positron emission tomography (PET). The use of PET is highly sensitive for the detection of unsuspected metastatic lesions in patients deemed candidates for curative resection on the basis of CT alone.¹³

Management of Esophageal Dysphagia

MOTOR DISORDERS

Motility disorders affect the smooth muscle of the distal esophagus and the lower esophageal sphincter (LES). Symptoms typically include dysphagia to solids and liquids; noncardiac chest pain may also be present.

Achalasia

Ninety-eight percent of all cases of achalasia are idiopathic. The disease is thought to result from a loss of inhibitory neurons in the Auerbach

plexus, altering neural input to the LES and preventing normal relaxation.¹⁴ Achalasia affects females and males equally at a rate of 1 per 100,000 individuals per year. The usual presentation is between 20 and 50 years, but it has been described in all age groups. The disease is slowly progressive, and presentation is typically at advanced stages. Symptoms include progressive dysphagia to both solids and liquids, accompanied by regurgitation of food particles, chest pain, and weight loss. GERD-like symptoms were present in up to 48% of patients in a study of 32 patients¹⁵; these symptoms are a consequence of stasis esophagitis (secondarily to fermentation of retained food) rather than reflux of gastric acid.

Plain x-rays may reveal an air-fluid level in the distal esophagus, and a barium swallow will demonstrate a dilated and atonic esophagus with the pathognomonic “bird’s-beak” narrowing of the gastroesophageal junction (GEJ) [see Figure 2]. Long-standing achalasia may manifest with an extremely dilated and tortuous esophagus (often described as a sigmoid esophagus) [see Figure 3]. Manometric findings of aperistalsis and failure of LES relaxation are key in establishing the diagnosis. Resting LES pressures may be normal or elevated. Endoscopic assessment is required to visually assess mucosal appearance to rule out cancer.

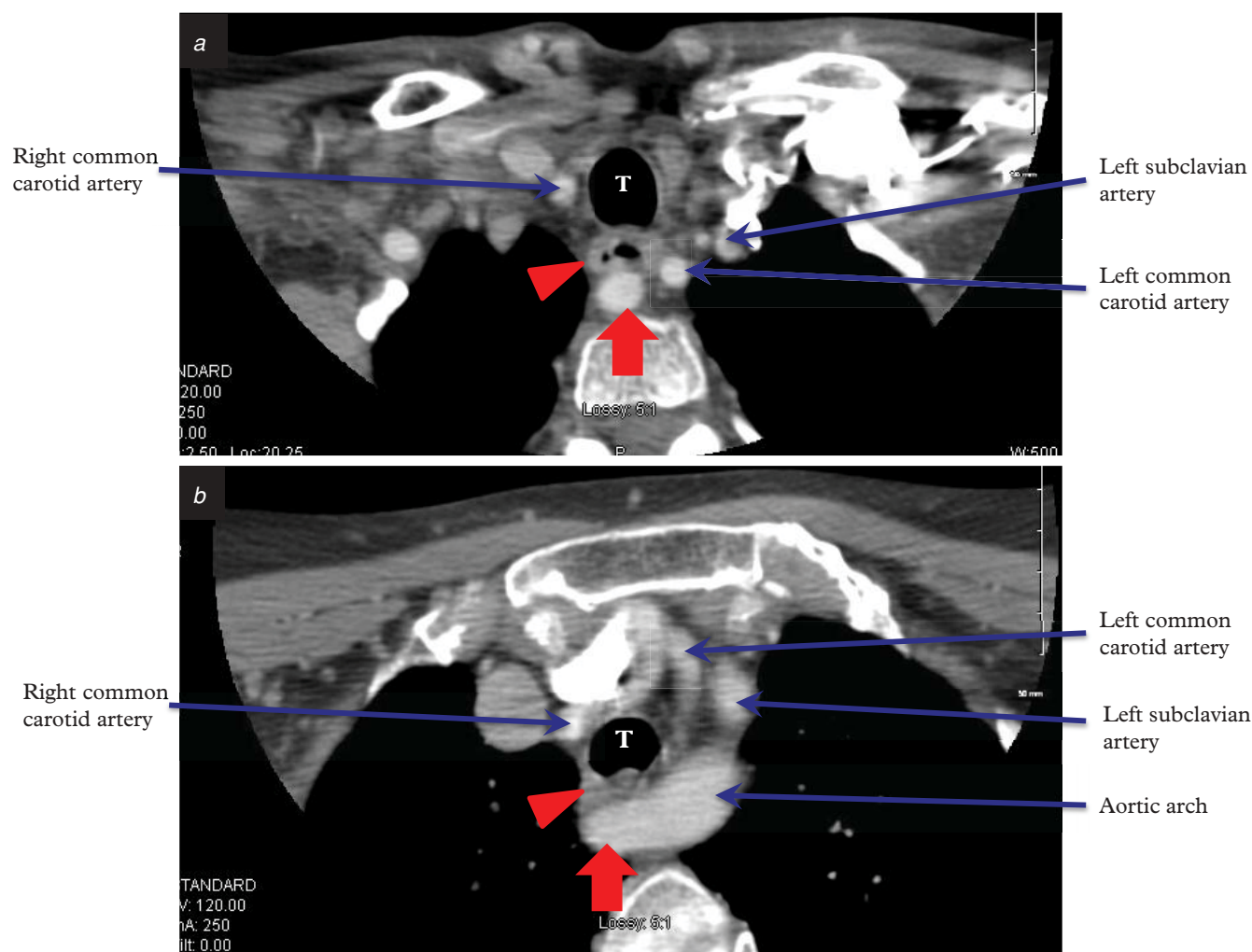


Figure 1 Dysphagia lusoria. Contrast-enhanced CT scan of the upper chest at the level of the clavicular heads (a) and near the carina (b) demonstrating the retroesophageal course of the right subclavian artery (arrow) causing compression of the esophagus (arrowhead) against the trachea (T) and right carotid artery. One can appreciate the idea of a “vascular ring” in such cases causing esophageal compression.

Treatment modalities for achalasia must achieve enhanced LES compliance and lower resting LES pressures. Medical management with calcium channel blockers or nitrates has no meaningful benefit. Endoscopic management includes endoscopically injected botulinum toxin, or balloon dilatation, to mechanically disrupt the lower esophageal muscle fibers. Recurrent dysphagia (up to 50%) has been noted in some studies at 5 years after balloon dilatation, with a 5% periprocedural risk of esophageal rupture.¹⁶ In comparison, a laparoscopically performed Heller esophagomyotomy with partial anterior (Dor) fundoplication is considered to be the standard of care in terms of both durable outcomes (90 to 95% resolution of dysphagia) and low complication rates.¹⁴

Long-standing achalasia is a risk factor for esophageal squamous cell carcinoma, and tumors of the GEJ may present with symptoms similar to those of achalasia.

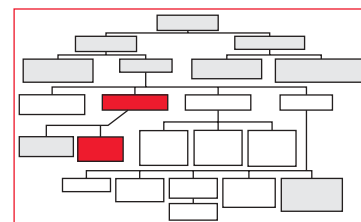
Dysmotility Syndromes

Motility disorders can be considered within a spectrum that includes diffuse esophageal spasm (DES), nutcracker

esophagus, and hypertensive LES. These disorders are traditionally considered separate entities; however, the manometric findings and the mainstays of medical treatment are similar.

DES is a dysmotility syndrome of unknown etiology. It is characterized in 50% of patients by intermittent dysphagia to solids and liquids. Up to 5% of patients with unexplained chest pain are found to have DES on manometric testing.⁷ Evidence for DES on manometry includes periodic prolonged, multi-peaked, high-amplitude contractions in more than one in five wet swallows, with observation of normal peristalsis in intervening periods. Incomplete LES relaxation or hypertensive LES may also be observed. Figure 4 demonstrates the classic corkscrew appearance that is observed in some cases of DES.

Nutcracker esophagus presents more commonly with chest pain rather than dysphagia. Manometry also forms the



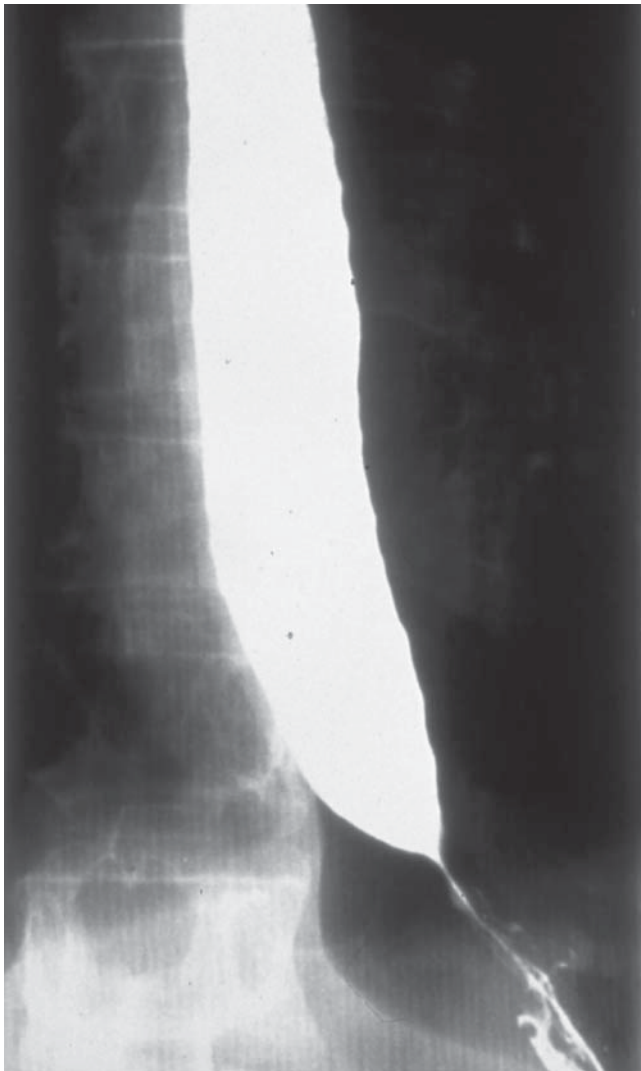


Figure 2 Achalasia. Barium swallow demonstrates the proximal dilatation and classic “bird’s beak” narrowing at the esophagogastric junction, consistent with achalasia, in a 22-year-old woman being evaluated for dysphagia.

mainstay of diagnosis: a normal peristaltic pattern is noted, with extremely increased pressure amplitudes of more than 180 mm Hg. In contrast to DES, normal peristalsis is not observed within trains of high-pressure waves. Barium swallow is of normal appearance.

Hypertensive LES may be found in isolation but often coexists with other dysmotility syndromes. Resting pressures at the LES by manometry are found to be 45 mm Hg or greater.

Treatment for DES, nutcracker esophagus, and hypertensive LES is based on smooth muscle relaxation using nitrates such as isosorbide dinitrate or calcium channel blockers such as diltiazem. Balloon dilatation may be effective for isolated hypertensive LES.

Esophageal Diverticulae

Diverticulae are classified according to the degree to which the esophageal wall is involved in the outpouching: true

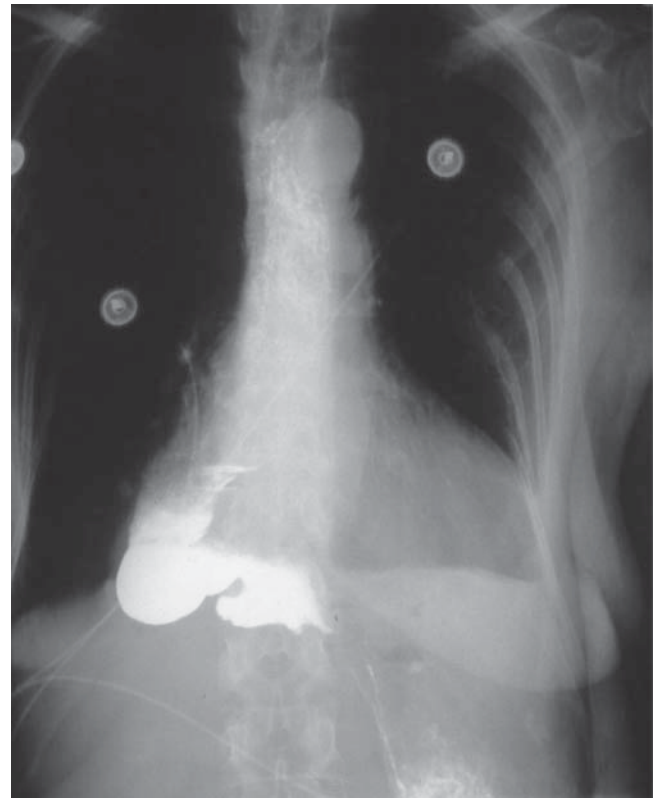
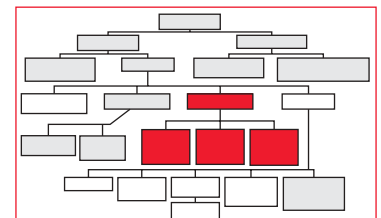


Figure 3 Sigmoid esophagus. Barium study demonstrates dilated esophagus with right-sided deviation and tortuous course of the distal esophagus. Treatment most often involves resection of diseased esophagus with conduit interposition.

diverticulae involve all layers of the esophageal wall, whereas false diverticulae involve only the mucosal layer. Both types of diverticulae can also be classified by the



mechanism underlying their formation: True diverticulae usually form in the midesophagus and are most often related to extrinsic traction from extramural inflammation in adjacent mediastinal lymph nodes. These are also referred to as traction diverticulae. False diverticulae relate to dysmotility and consist of the mucosa being extruded through external muscular layers above a high-pressure zone and are thus pulsion-type diverticulae.

Intramural pseudodiverticulosis is a rare cause of dysphagia characterized by multiple outpouchings of the esophageal wall; these outpouchings represent the dilatation of submucosal glands.¹⁷ Although a benign condition, complications related to infection, inflammation, perforation, stricture, and bleeding have been reported. The mainstay of treatment is reduction of inflammation and dilatation of strictures as necessary.

Pharyngoesophageal diverticulae (Zenker diverticulum) are the most common diverticulae observed. These pulsion-type false diverticulae arise in the Killian triangle and are located just superior to the cricopharyngeus muscle. The

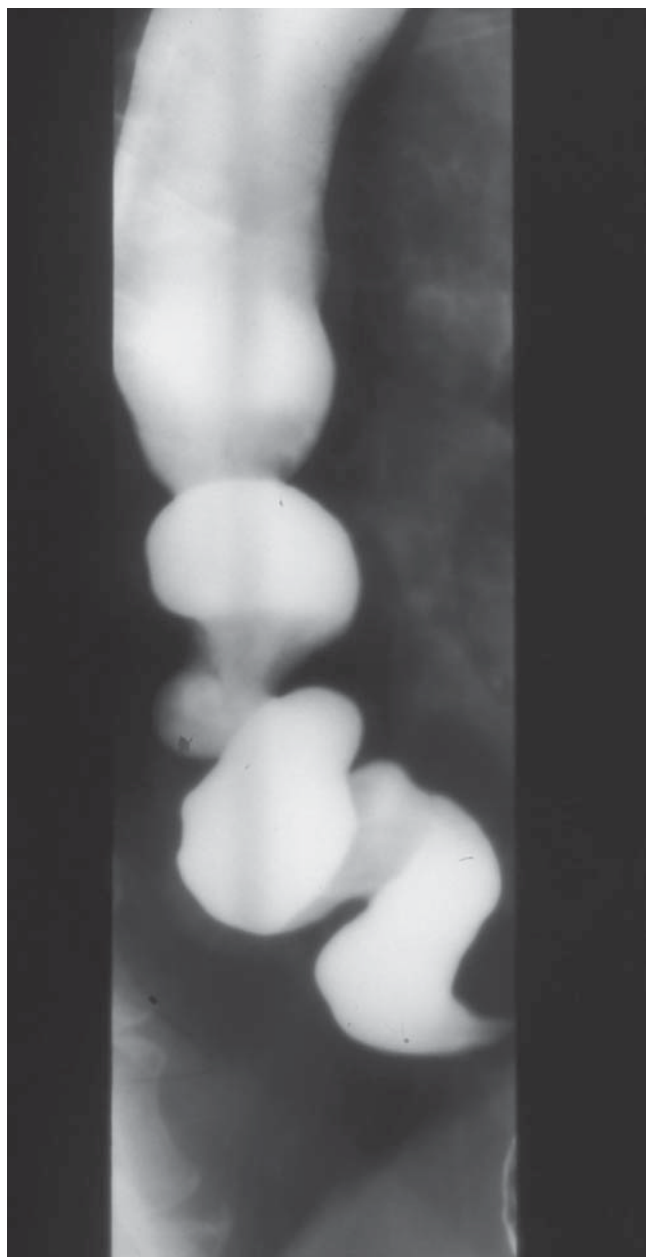


Figure 4 Diffuse esophageal spasm. The classic corkscrew appearance of the esophagus is evident in this barium study in a middle-aged patient presenting with dysphagia and intermittent chest pain.

basis for the formation of a Zenker diverticulum is pharyngo-cricopharyngeal dyscoordination. When the cricopharyngeal sphincter fails to immediately and fully relax during swallowing, the pharyngeal pump mechanism produces extremely high pressures. As a result of these high pressures, progressive bulging of the mucosa occurs in the posterior midline through a potential gap between the pharyngeal constrictors and the cricopharyngeus muscles (the Killian space). There has been a long-standing appreciation of an association between the pathologic severity of gastroesophageal reflux and the development of Zenker diverticulae: it is thought that repeated

exposure of the proximal esophagus and pharynx to low pH refluxate results in cricopharyngeal spasm and loss of normal coordination.

Symptoms of a cricopharyngeal diverticulum include dysphagia, halitosis, throat discomfort, a palpable mass, and regurgitation of undigested food. Some patients may suffer from recurrent aspiration pneumonia and in severe cases may develop lung abscesses.

The first diagnostic test should be a barium swallow [see Figure 5], which will delineate the size and position of the diverticulum. Initial assessment by endoscopic means is not recommended as there is a sizable risk of perforating the pouch with the endoscope.

Treatment is surgical and must include the division of the cricopharyngeus muscle. Smaller pouches may be treated by myotomy alone, whereas those larger than 2 cm should

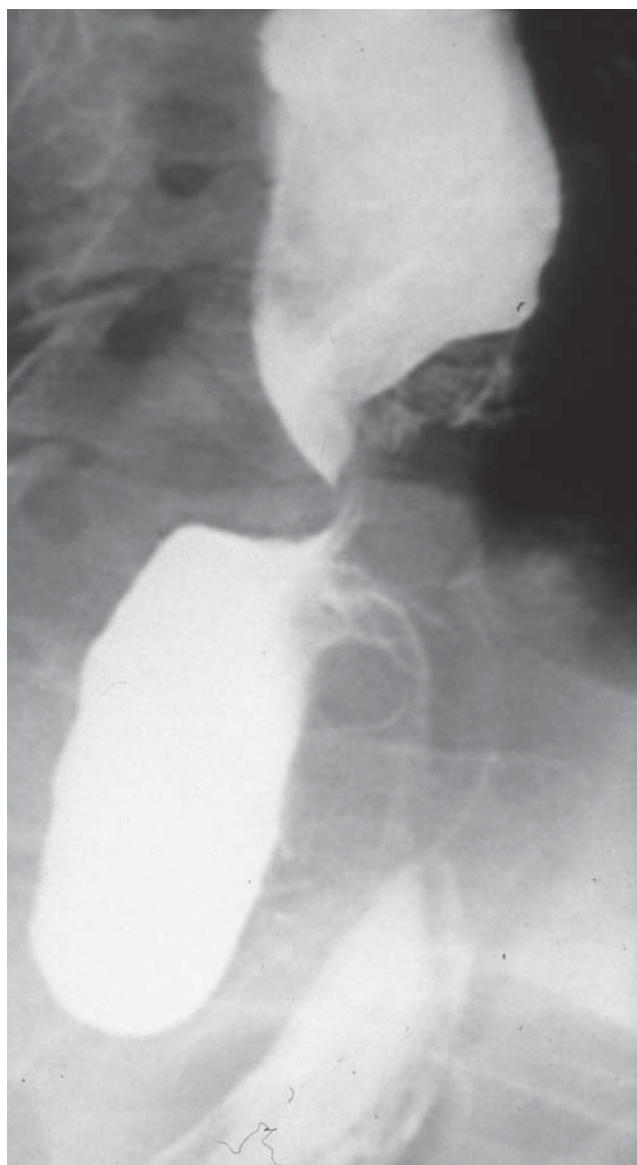


Figure 5 Pharyngoesophageal diverticulum. A large Zenker diverticulum is shown in an elderly patient who presented with dysphagia, recurrent pneumonia, and regurgitation.

be excised.¹⁸ Endoscopic (transoral) approaches to diverticulectomy have also been described.¹⁹

Midesophageal diverticulae are not typically associated with dysphagia. These true diverticulae are formed by traction from extraesophageal inflammation, most often granulomatous disease in subcarinal lymph nodes. Midesophageal diverticulae are usually asymptomatic, and treatment is focused on the underlying inflammatory process.

Epiphrenic diverticulae arise in the distal esophagus. These pulsion-type diverticulae are associated with underlying esophageal dysmotility^{20,21} and are also occasionally an isolated finding [see Figure 6]. In the absence of symptoms, expectant management is appropriate. When dysphagia is present, surgical management is necessary. The surgical approach, understood to incorporate “triple therapy,” must include (1) excision of the diverticulum, (2) an esophageal myotomy, and (3) an antireflux procedure.^{22,23}

Secondary Motor Disorders

In secondary dysmotility syndromes, the esophageal symptoms are a manifestation of a generalized systemic process. The etiology is

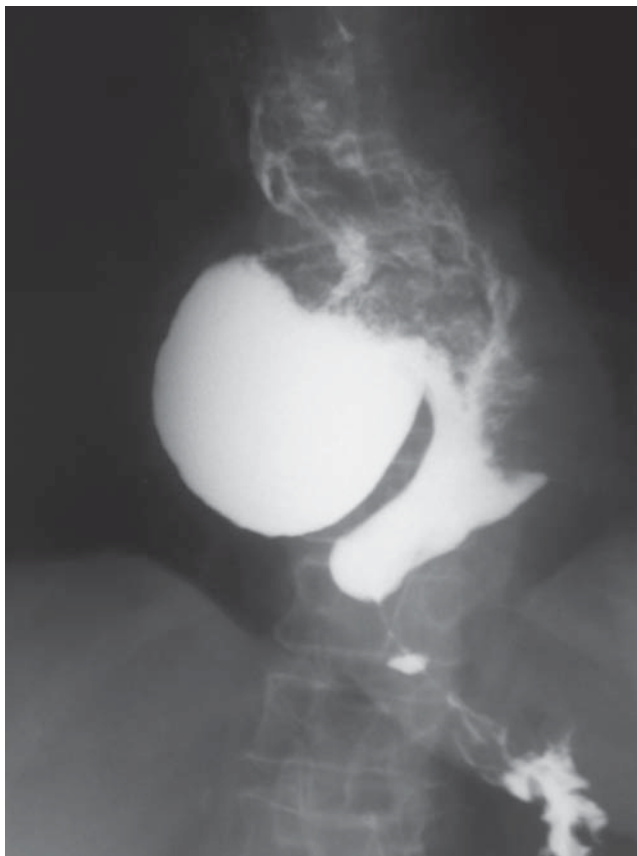
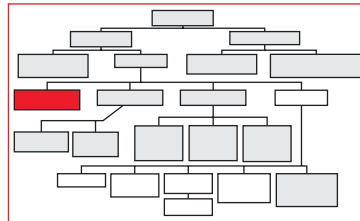


Figure 6 Giant epiphrenic diverticulum. Barium swallow shows an epiphrenic diverticulum in an elderly female with progressive dysphagia and weight loss; cancer was initially suspected.

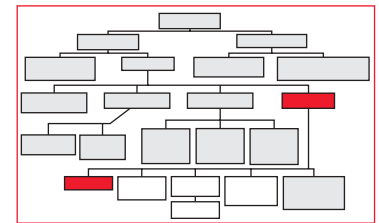
thought to be progressive neuropathy and subsequent fibrosis. Common diseases associated with secondary dysmotility include rheumatologic syndromes, such as scleroderma, and diabetes mellitus.

MECHANICAL OBSTRUCTION

Webs

A web is a thin mucosal fold that protrudes into the esophageal lumen. Congenital webs are rare and usually restricted to the pediatric population. These are located in the middle and lower thirds of the esophagus.⁷ Acquired webs are normally located in the postcricoid cervical esophagus and are mostly asymptomatic. Etiologies for acquired webs include iron deficiency anemias (Plummer-Vinson and Paterson-Kelly syndromes) and dermatologic diseases. Webs are twice as common in female patients.

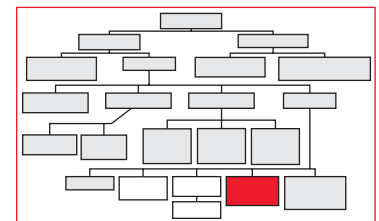
Dysphagia occurs intermittently with solids, and when symptoms arise, the orifice of the web is found to be less than 1.3 cm. Diagnosis is by barium swallow, and treatment involves mechanical dilatation using Savary bougies or endoscopic balloons. Underlying anemias and dermatologic conditions should also undergo assessment and appropriate treatment.



Rings

Esophageal rings are typically located in the lower third of the esophagus. Two types are typically described: muscular rings and mucosal or Schatzki rings.

Muscular rings are rarely associated with dysphagia and are often found incidentally in children undergoing barium swallow for other reasons. Schatzki rings are located at the Z-line (squamocolumnar junction) and are almost always seen in patients with GERD [see Figure 7]; consequently, the upper surface of a Schatzki ring is covered by squamous epithelium, whereas the lower surface is covered by columnar epithelium. Associations with eosinophilic esophagitis and GERD have been proposed. Diagnosis and treatment are as for esophageal webs.



Peptic Stricture

Peptic stricture was previously found in up to 10% of patients with GERD and represents the end stage of reflux-associated ulcerative esophagitis [see Figure 8]. The incidence of peptic strictures has been drastically reduced with the increased use of effective antireflux medications, chiefly the proton-pump inhibitors (PPIs).

Symptoms are described as progressive in nature and involve initial solid food dysphagia, progressing to liquid dysphagia. A history of reflux symptoms will also be elicited.

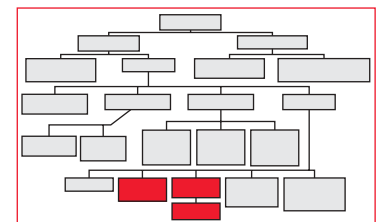




Figure 7 Schatzki ring. Barium swallow demonstrates a ring in a middle-aged man with severe gastroesophageal reflux disease symptoms and recent-onset dysphagia.

Initial assessment is by barium swallow. Peptic strictures are short segment, circumferential, and located at the squamocolumnar junction. A high index of suspicion for concomitant Barrett esophagus or frank cancer at the site of

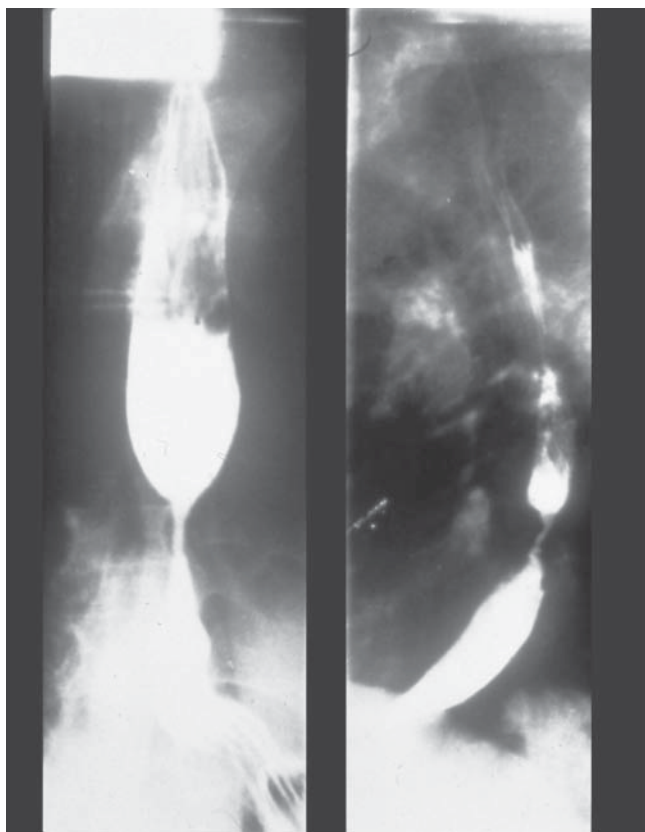


Figure 8 Severe ulcerative esophagitis. Shown is the appearance of severe ulcerative esophagitis, annular stricture, and evidence of esophageal shortening. The caliber of the narrowed segment suggests a benign etiology.

stricture must be kept. Treatment of isolated peptic strictures includes acid suppression and endoscopic dilatation. In the past, peptic strictures were usually an indication for surgical correction; however, recent clinical experience with careful repeated dilatations combined with effective acid suppression



Figure 9 Midesophageal squamous cell carcinoma. Shown is the classic appearance of a midesophageal squamous cell carcinoma. Mucosal irregularity is apparent within the lesion, along with proximal dilatation and shouldering at the upper and lower borders. Bronchoscopy confirmed anterior penetration of tumor into the airway mucosa.



Figure 10 Caustic ingestion. Barium swallow from a 22-year-old patient after ingestion of toilet cleaner showing a long, stringlike lumen spanning the midesophagus to the stomach. Dilatation was impossible, and esophageal resection with colonic interposition was performed.

therapy (using PPIs) has rendered surgical treatment an uncommon occurrence.

Cancer

Dysphagia is the presenting complaint in the majority of patients with esophageal cancer. The temporal course is usually short and rapidly progressive. Weight loss is a prominent feature. Locally advanced cancers causing airway fistulization may present with aspiration (swallow-cough sequence) [see Figure 9]. Evaluation and staging should proceed as per established guidelines.

ODYNOPHAGIC SYNDROMES

Caustic Ingestion

Caustic agents are found in many household cleaning products. Ingestion is typically accidental but may be related to a suicide attempt. The pH of the offending agent (less than 2 or greater than 12), the volume ingested, and the total contact time with the esophageal mucosa are the determinants of the severity of the esophageal injury.⁸ Immediate flexible endoscopy is required to assess the degree and severity of the injury.⁹ Frank perforation or instability mandates immediate surgical exploration and resection. Sites most commonly affected include the distal esophagus and stomach; there is relative sparing of the upper pharynx and esophagus because of rapid transit through these regions.

Injuries will mature into strictures, which require serial assessment by barium studies starting 4 weeks after the initial injury [see Figure 10]. Repeated dilatations are typically required, although these procedures are technically challenging and sometimes dangerous as a result of the intense fibrosis, which virtually obliterates the esophageal lumen. A large majority of these patients do not have satisfactory results with dilatation as a result of an inability to



Figure 11 Dysphagia and odynophagia secondary to tuberculous lymphadenitis in the neck and mediastinum arising in an immunocompromised patient with chronic HIV infection. (a) Computed tomography image showing extensive necrotizing inflammation in the mediastinal lymph nodes (long arrow), air within the esophagus (arrowhead), and a collection of extraluminal air in the mediastinum (short arrow). (b) Contrast swallow study using water-soluble contrast, showing extravasation of contrast into the mediastinum (arrowhead) and fistulization between the esophagus and the right bronchial tree (arrow). Esophagoscopy showed extensive destruction of the esophagus by the mediastinal infection and multiple small fistulae into the airway. A covered self-expanding esophageal stent was inserted to block the fistula, followed by aggressive antituberculous therapy. The fistula healed, and the patient continues to do well clinically.

establish an esophageal lumen or an inability to maintain an adequate lumen despite repeated dilatations. Resection and reconstruction using colonic interposition become necessary.

Eosinophilic Esophagitis

This rare inflammatory condition is characterized by eosinophilic infiltrates isolated to the esophagus.²⁴ Intermittent dysphagia to solid food and pain are commonly noted, and associated manometric abnormalities (hypercontractility) are found in up to 60% of patients. Barium studies and endoscopy are often normal in appearance. Glucocorticoids and leukotriene antagonists represent currently accepted treatment.⁷

Infections

Infectious causes of dysphagia associated with odynophagia include intrinsic infections such as esophageal candidiasis, herpetic infections, and cytomegaloviral illness. Treatment is

based on the infectious agent involved. Rarely, extrinsic infection of the esophagus (originating in neighboring necrotizing mediastinal lymph nodes) can occur, causing dysphagia, odynophagia, and other potentially disastrous complications [see Figure 11].

Conclusion

Evaluation of the patient presenting with dysphagia represents a challenge for the surgeon. A careful history is key in determining likely etiologies. The barium swallow should be the first diagnostic test to be considered, with endoscopy to follow. Esophageal manometry represents the gold standard for diagnosing benign, functional (motor) disorders. Treatment is varied and depends on the etiology of the dysphagia.

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2 COUGH AND HEMOPTYSIS

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Cough is one of the most common symptoms in patients seeking medical attention from the office-based physician.¹ In the United States, it accounts for approximately 30 to 50 million physician visits each year, and more than \$1 billion is spent annually on its workup and treatment.² Despite its massive burden on health care resources, cough is often dismissed as an unimportant irritation rather than a symptom of major socioeconomic importance.³ Hemoptysis, however, may not be as common a presenting complaint, and even mild hemoptysis is distressing to many patients and physicians and calls for prompt attention and diagnosis. It may range in severity from mild blood streaking in sputum to massive hemorrhage that, if left untreated, can lead to shock and rapid death from blood loss and asphyxiation. Every case of hemoptysis warrants a thorough clinical evaluation. Cough and hemoptysis can result from a wide variety of conditions, ranging from fairly non-life-threatening causes (e.g., bronchitis) to life-threatening ones (e.g., lung cancer). Because both cough and hemoptysis may be signs of urgent or life-threatening disease, patients who present with either or both of these symptoms should undergo a thorough, methodical workup consisting of a detailed history, a careful physical examination, and appropriate diagnostic studies.

Cough

DEFINITION

Cough is a forceful release of air from the lungs that can be heard. Coughing protects the respiratory system by clearing it of irritants and secretions. Although people can cough voluntarily, a cough is usually a reflex triggered when an irritant stimulates one or more of the cough receptors found at different points in the respiratory system.

Cough is a reflex defense mechanism that consists of an acute rapid inspiratory phase followed by an equally rapid and forceful expiratory phase against a closed glottis. Rapid opening of the glottis and brisk forceful expulsion result in the clearance of inhaled pathogens, aeroallergens, irritants, particulate matter, secretions, and aspirate.⁴ Impaired cough reflexes significantly increase the risk of pulmonary infection from retained secretions. Cough helps maintain airway function and lung capacity for gas exchange.^{5,6}

The cough reflex is initiated by the irritation of cough receptors that exist not only in the epithelium of the upper and lower respiratory tract but also in the pericardium, lower esophagus, stomach, and diaphragm.^{7,8} These receptors can be triggered by chemical and mechanical stimuli such as foreign bodies, irritant particles, fumes, and extrinsic pressure from masses (e.g., lung cancer), edema from pulmonary parenchymal infection (e.g., pneumonia or abscess), or pulmonary parenchymal fibrosis resulting from any of a variety

of interstitial lung diseases (e.g., idiopathic pulmonary fibrosis or sarcoidosis).

The airway sensory receptors are either primarily mechanically sensitive (low-threshold mechanoreceptors) or primarily chemically sensitive (chemosensors or, alternatively, nociceptors). Mechanoreceptors are of two types: rapidly adapting receptors (RARs) and slowly adapting receptors (SARs). They are sensitive to many mechanical stimuli, including changes in lung volume, airway smooth muscle constriction, and airway wall edema. As their names suggest, RARs display rapid adaptation (i.e., a rapid reduction in the number of action potentials) during sustained lung inflations, whereas SARs adapt slowly to this stimulus. RARs and SARs have different mechanical activation profiles. Thus, RARs may be activated during both inflation and deflation of the lungs (including lung collapse). SARs, on the other hand, display activity during tidal inspirations, peaking just prior to the initiation of expiration. Even though the RARs and SARs are not chemosensitive, they do get activated secondary to airway smooth muscle contraction, mucous secretion, or edema formation caused by bradykinin and capsaicin.

Chemically sensitive airway afferent fibers become recruited during airway inflammation or irritation. They are typically activated by a wide range of chemicals, including capsaicin, bradykinin, adenosine, and prostaglandin E₂. Chemosensors are stereotypically defined by their responsiveness to the irritant chemical capsaicin and, hence, the expression of the capsaicin receptor. The transient receptor potential cation channel, subfamily V, member 1 (TRPV1), also known as the capsaicin receptor, is a protein that, in humans, is encoded by the *TRPV1* gene. This protein is a member of the TRPV group of the transient receptor potential family of ion channels. TRPV1 is a nonselective cation channel that may be activated by a wide variety of exogenous and endogenous physical and chemical stimuli. The best known activators of TRPV1 are heat greater than 43°C and capsaicin, the pungent compound in hot chili peppers. Airway chemosensors are sometimes thought of as high-threshold mechanosensors. Within this group are fibers that are not readily excited by mechanical stimulation (e.g., bronchoconstriction, lung inflations, light touch) but can be activated using severe mechanical manipulations (e.g., lung hyperinflation, forceful punctate stimuli) and one or more chemical stimuli (e.g., capsaicin, bradykinin, adenosine).^{9–12}

Afferent fibers from cough receptors in the airways converge via the vagus nerve on brainstem sites in the nucleus tractus solitarius. The nucleus tractus solitarius is connected to respiratory-related neurons in the central respiratory generator that coordinate the efferent cough response.¹³ Sensation of the cough reflex can also arise in the brainstem neurons. Higher cortical centers can also voluntarily inhibit or produce cough.^{14,15}

CLINICAL EVALUATION

Guidelines from the American College of Chest Physicians distinguish three categories of cough based on duration:

- Acute cough, lasting less than 3 weeks
- Subacute cough, lasting between 3 and 8 weeks
- Chronic cough, lasting more than 8 weeks¹⁶

Cough can be the first indication of serious pulmonary or extrapulmonary pathologic conditions; the differential diagnosis of cough includes infectious, inflammatory, and neoplastic conditions and many pulmonary disorders [see Table 1]. The most common cause of acute, transient cough is the common cold. The most prevailing genesis in a series of 184 patients with subacute cough (lasting 3 to 8 weeks) was postinfectious cough (48%), postnasal drip (33%), and cough-variant asthma (16%).⁴ The most frequent etiology of chronic cough includes asthma, postnasal drip, sinusitis, chronic bronchitis, and reflux disease. The etiology of chronic cough can be multifactorial. For example, in a study of 88 consecutive unselected immunocompetent patients referred to pulmonary outpatient clinic for evaluation of chronic cough, 39% had a single cause of cough, 42% had two causes, and 17% had three causes. The most common causes of chronic cough were gastroesophageal reflux disease (GERD) (71.6%), postnasal drip syndrome (67%), asthma (23.9%), and bronchiectasis (8%). When considering only patients with cough for at least 3 weeks, who are nonsmokers and not on angiotensin-converting enzyme (ACE) inhibitors, with normal or nearly normal and stable chest radiographs, 99.4% will have GERD, postnasal drip syndrome, and/or asthma.¹⁷

Table 1 Differential Diagnosis of Cough

Acute infections
Acute bronchitis
Viral and bacterial pneumonias
Pertussis
Chronic infections
Bronchiectasis
Tuberculosis
Cystic fibrosis
Airway diseases
Asthma
Chronic postnasal drip
Chronic bronchitis
Parenchymal diseases
Emphysema
Chronic interstitial lung fibrosis
Sarcoidosis
Tumors
Primary lung carcinoma
Benign airway tumors
Mediastinal tumors
Cardiovascular diseases
Congestive heart failure
Pulmonary embolism
Other diseases
GERD
Recurrent aspiration
Endobronchial stents
Drugs
ACE inhibitors

ACE = angiotensin-converting enzyme; GERD = gastroesophageal reflux disease.

The cause of cough can be determined from a comprehensive history and physical examination. In fact, some studies estimated that the cause of cough is found in up to 80% of cases from the history and physical examination alone.^{17,18} The initial approach to the diagnosis of cough is a careful and detailed review of the history of the patient's cough, especially its features, including time of occurrence, frequency, duration, precipitating or aggravating factors, whether it is productive or nonproductive, and the color of the expectorant.¹⁹ In the study of 71 immunocompetent patients with chronic cough productive greater than 30 mL of sputum/day, all patients underwent careful evaluation, including chest radiography, and other tests being selectively administered, including sinus x-rays, allergy evaluation, pre- and post-bronchodilator spirometry, methacholine challenge, barium swallow, sputum culture, sputum cytology, fiberoptic bronchoscopy, and studies of cardiac function. A specific cause of chronic cough was determined in 97%: postnasal drainage syndrome (40%), asthma (24%), GERD (15%), acute and chronic bronchitis (11%), bronchiectasis (4%), and left ventricular failure (3%).⁴

MANAGEMENT

Acute Cough

Pneumonia (bacterial, viral, and aspiration) can present with fever, cough, and shortness of breath. Patients may also complain of pleuritic chest pain. Diagnosis is often made on a chest x-ray, sputum, and blood cultures, and treatment is directed toward the causative organism.

Asthmatic patients can develop cough in response to various provoking factors (allergens, cold, and exercise) and may not always be associated with airflow obstruction, wheezing, or dyspnea. The cough is often nocturnal, and the diagnosis is supported by bronchial hyperresponsiveness using a bronchial challenge test using nebulized methacholine or histamine and spirometry flow rates.²⁰ Cough can be the first sign of worsening of asthma; physicians should look for a fall in early-morning peak flows [see Figure 1].

Chronic Cough

Chronic bronchitis Chronic bronchitis accounts for about 10% of cases of chronic cough.²¹ The typical patient is a smoker experiencing productive cough. There is a wide spectrum of the disease, from mild early-morning sputum production to a chronic variety in patients with severe disabling chronic obstructive airway diseases.^{22–28} In a smoker, a chronic cough is not a particularly worrisome symptom; however, if the character of the cough or the quality of the sputum changes, further workup is indicated to look for a possible superimposed infection or neoplasm.²⁷ Any degree of hemoptysis in a former smoker should be taken seriously, especially if it is not associated with an infection. A chest x-ray may not be diagnostic, and evaluation with chest computed tomography (CT) and/or bronchoscopy may be indicated.^{27,28} Treatment consists of cessation of smoking, antibiotics, bronchodilators, and oral or inhaled steroids [see Figure 2].

Postnasal drip Postnasal drip, also known as upper airway cough syndrome, occurs when excessive mucus is produced by the nasal membrane. The excess mucus

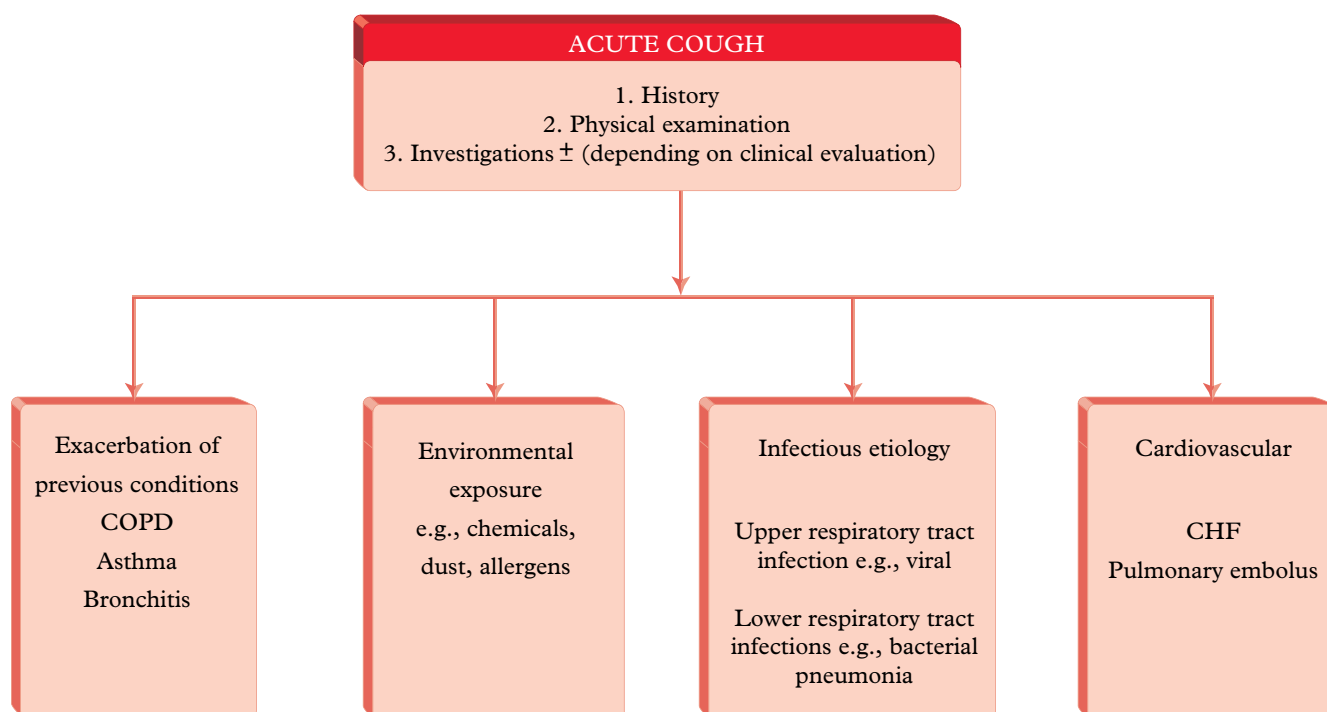


Figure 1 Acute cough algorithm for the management of patients over 15 years of age with cough lasting less than 3 weeks. CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease.

accumulates in the back of the nose and trickles down the throat. It is characterized by a sensation of nasal secretions of a drip at the back of the throat, often accompanied by the frequent need to clear the throat, and is associated with nasal discharge or nasal stiffness. Nasal secretions irritate the larynx and trachea, leading to activation of the cough reflex arc.²⁹ Postnasal drip occurs during the day or night and may be worse at night. Generally, the diagnosis is made on the basis of the history and the symptom complex. The symptoms may be vague at times, and the diagnosis is confirmed only when the patient responds to empirical therapy. In recalcitrant cases, an otolaryngologic examination may be required to exclude sinus disorders. Physical examination may reveal nasal edema, mucopurulent secretions, and the typical cobblestone appearance of the posterior pharyngeal wall.²⁹ CT scanning of the sinuses may be required if the diagnosis is uncertain. Steroid nasal sprays, antihistamines, and nasal irrigations with saline are useful for ameliorating symptoms.

Medications Cough is a well-recognized complication of ACE inhibitor therapy.³⁰ ACE inhibitors are prescribed for the treatment of hypertension and heart failure; 2 to 33% of patients report a dry cough.³¹ The cough can arise within a few hours of taking the drug but can also become apparent after only a few weeks or months; it improves within days or weeks of withdrawal of the drug but can take longer to resolve completely. ACE inhibitor cough can be caused by the accumulation of bradykinin and prostaglandin, which directly sensitize cough receptors. Cough may also result from nonselective beta-blocker therapy or may develop as a consequence of idiosyncratic reactions to a variety of drugs and herbal remedies.

Reflux disease GERD is commonly implicated as a cause of chronic cough. In fact, it may be the only symptom in GERD.³² Typically, symptoms of acid reflux, other than cough, are heartburn, chest pain, a sour taste, and regurgitation. Reflux of gastric contents to the larynx can cause reflux laryngitis with thickening, redness, and edema of the posterior larynx.^{33–35} The diagnosis is difficult to make if the typical symptoms of reflux and heartburn are absent. As awareness of reflux-induced asthma and cough grows, more patients are being evaluated with barium studies and esophageal pH monitoring, which often provide the correct diagnosis when clinical evaluation cannot.

Tumors In smokers, a change in the nature of cough or hemoptysis should alert the physician to an underlying carcinoma.²⁷ There may be associated weight loss and weakness. Malignant central tumors tend to be squamous cell carcinoma or small cell cancers and can have associated mediastinal lymphadenopathy detected as hilar or mediastinal fullness on a chest x-ray and confirmed on CT scans. Carcinoid tumors, for the most part, tend to be central endobronchial lesions, causing obstruction to the lumen of the bronchus, and appear as smooth, round, fleshy, and highly vascular lesions on bronchoscopy. Not uncommonly, patients with a carcinoid tumor of the airway will have been treated with inhalers and steroids for years because of the presumptive diagnosis of asthma. Patients with malignant fistulas between the airway and the esophagus either from the cancers eroding the lumens or as a result of breakdown after radiotherapy present with copious secretions and foul breath. These patients usually have advanced disease and are best palliated with covered stents in the trachea and/or the esophagus.

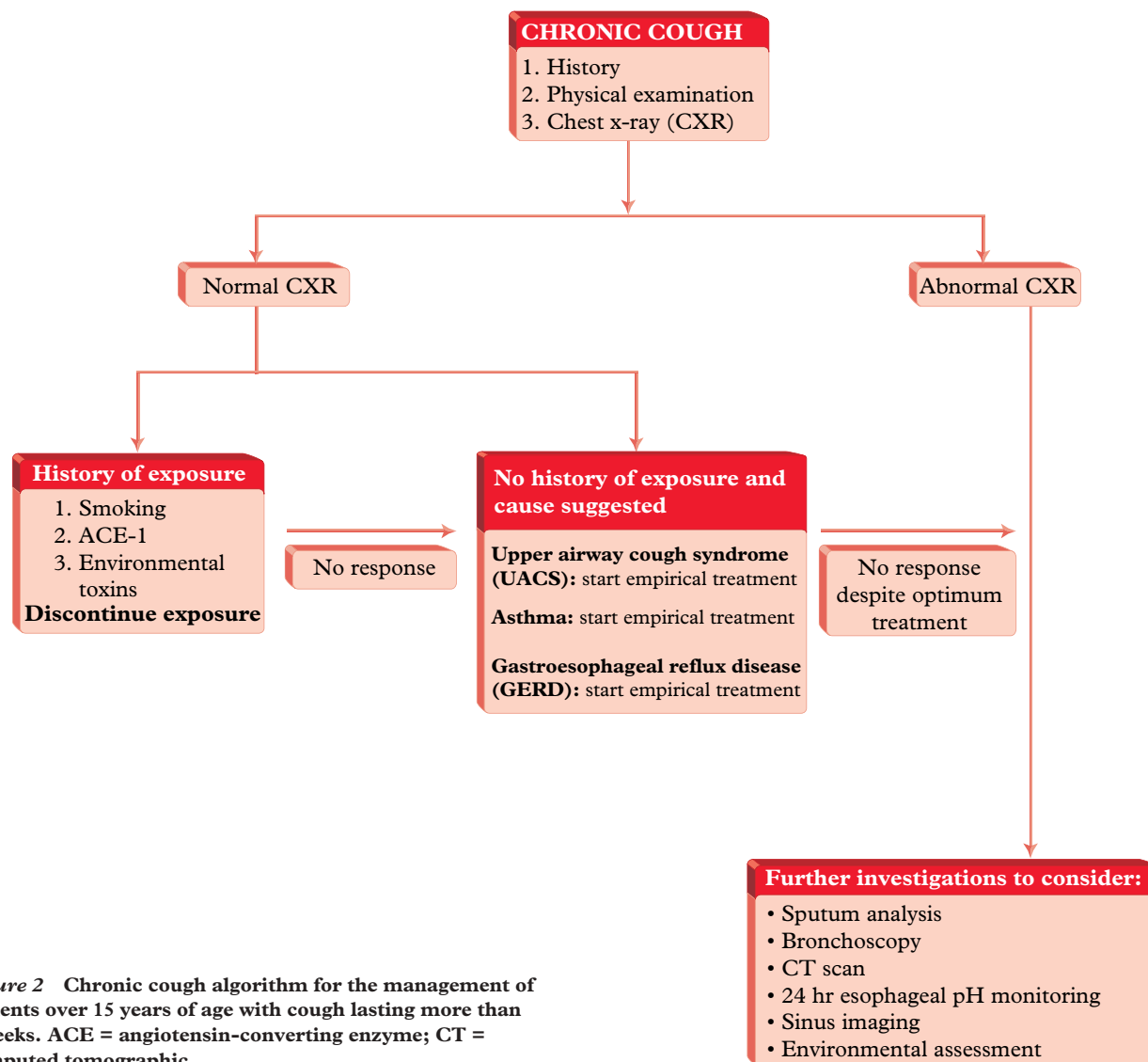


Figure 2 Chronic cough algorithm for the management of patients over 15 years of age with cough lasting more than 8 weeks. ACE = angiotensin-converting enzyme; CT = computed tomographic.

Other conditions associated with cough Bronchiectasis cough is associated with extensive secretions from overproduction, together with reduced clearance, of airway secretions³⁶ The patient produces mucoid or mucopurulent sputum, sometimes accompanied by fever, hemoptysis, and weight loss.³⁶ Cough can be the only presenting symptom. Bronchiectasis can be associated with postnasal drip and rhinosinusitis, asthma, GERD, and chronic bronchitis.³⁷ Bronchiectasis can lead to clubbing of the fingers. Common pathogens cultured from sputum include *Haemophilus influenzae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*.³⁷ Patients with immotile cilia syndrome (Kartagener syndrome) will have other hallmarks of disease, such as situs inversus, sinusitis, and recurrent otitis.³⁸ Diagnosis is made by the delay (over 12 minutes) in the patient's ability to taste the saccharine placed on the anterior nares. Treatment is directed at the recurrent infections in the sinuses, ears, and chest.

A chronic cough may also be a consequence of congestive heart failure (CHF) (from any cause), although this is not a

common occurrence. Mild CHF with symptoms of orthopnea at night may be associated with coughing. The diagnosis is made on the basis of a history of orthopnea and associated cardiac risk factors or valvular disease, followed by cardiac echocardiography. Occasionally, the presence of a small unrecognized tracheobronchial foreign body can lead to chronic irritation of the bronchial epithelium and then to a persistent cough; this presentation is more common in children than in adults.³⁹ The diagnosis is usually made by performing bronchoscopy in a patient who is believed to be harboring a foreign body on the basis of chest imaging.

Eosinophilic bronchitis is a rare cause of chronic cough that may be suspected in patients with no other clearly explainable diagnosis.^{40,41} Patients typically have a history of atopy, and the diagnosis is made on the basis of clinical suspicion and the results of bronchial epithelial biopsy. Steroids are the mainstay of treatment. Chronic cough can be a prominent symptom of occupational exposure in glass workers exposed to low-molecular-weight irritants, hydrochloric acid, and organic oils.^{42,43}

In the occasional patient, a chronic cough may be of psychogenic origin. Such a cough classically occurs during the daytime and is absent when the patient is asleep. This is described as short and explosive and usually has been triggered by a precipitating upper respiratory tract infection that leads to a “sensation of a trickle in the throat” and has subsequently persisted. It can be socially disruptive. The mainstay of treatment is creating an awareness in the patient and encouraging voluntary suppression of the cough and attempts at increasing the time interval between coughs.^{44,45}

Hemoptysis

DEFINITION

Hemoptysis is defined as expectoration of blood originating from the lower airways (tracheobronchial or pulmonary parenchymal). Hemoptysis can be traces or massive, potentially resulting in asphyxia by flooding the airways. By definition, a loss of over 600 mL over 24 hours is considered massive. However, even as little as 150 mL of rapid blood loss in a patient with compromised pulmonary functions can be disastrous because the total dead space of the airway is 150 mL.

HISTORY

Hemoptysis dates back to 400 BC, when Hippocrates described hemoptysis in patients with advanced phthisis (Latin, from Greek, from *phthinein*, to waste away). Greek physicians recognized hemoptysis as being caused by underlying tuberculosis. In 1938, Eloesser suggested lobectomy for hemoptysis.⁴⁶ In 1941, Pitkin performed the first pneumonectomy in a patient with bronchiectasis,⁴⁷ and in 1973, Remy and colleagues reported the first case of bronchial arterial embolization.⁴⁸

SURGICAL ANATOMY

There are two major sources of independent arterial inflow to the lungs: an anatomically consistent pulmonary circuit with the inflow through the pulmonary artery and return via the pulmonary veins and a highly variable and complex bronchial arterial system originating from the arch of the aorta, intercostals, or other arterial branches that supply the esophagus, mediastinal lymph glands, and spinal artery.

A bronchial artery greater than 2 mm is considered pathologic, and the bronchial arteries play the dominant role in hemoptysis as these vessels are subjected to higher systemic pressures.⁴⁹ As a rule, the blood seen in the sputum is derived from either the pulmonary arteries or the bronchial arteries; only rarely does it come from the pulmonary veins.^{50–52} Although the bronchial arteries provide less blood flow than the pulmonary arteries do, they supply the bulk of the blood received by the airways and, accordingly, are the source of the blood in most cases of hemoptysis.

ETIOLOGY

Inflammatory processes, including bronchitis, bronchiectasis, tuberculosis, fungal infections, lung abscess, and cystic fibrosis, account for 60 to 70% of cases of hemoptysis, with tumors being responsible for 23%.^{53,54} In 7 to 34% of patients with hemoptysis, no identifiable cause can be found after careful evaluation.⁵⁵ Acute or chronic bronchitis leads to airway inflammation and is usually minor. Bronchiectasis

[see Figure 3] results in the destruction of the cartilage and is associated with proliferation of bronchial arteries in the smaller bronchi (third and fourth generation), resulting in massive hemoptysis.³⁶ Hemoptysis in tuberculosis results from the development of false aneurysms (Rasmussen aneurysm) of the bronchial or pulmonary artery as they traverse the walls of a tuberculous cavity or occasionally from a broncholith (calcified lymph gland) eroding through the bronchus. Broncholithiasis is also seen in histoplasmosis infections.

Various benign and malignant primary epithelial and soft tissue tumors have been associated with hemoptysis. The majority of primary airway tumors are malignant, with squamous cell carcinoma and adenoid cystic carcinoma being the primary malignancies most frequently seen in the trachea.^{56–62} In the case of primary lung cancers, massive hemorrhage is rare. Terminal bleeding in primary lung cancer is usually associated with a cavitary squamous cell cancer and involves major vessels adjacent to the main tracheobronchial airways.^{63,64} Endobronchial carcinoid tumors are highly vascular and appear as smooth, cherry red endobronchial tumors seen on bronchoscopy. Care must be taken when performing a biopsy of endobronchial tumors such as a carcinoid tumor as serious hemorrhage can result. Tumors arising from adjacent structures such as the esophagus and thyroid can erode the tracheobronchial tree, resulting in hemoptysis.

Trauma from penetrating injuries and iatrogenic injuries caused by the Swan-Ganz catheter and transbronchial biopsies can result in hemorrhage. Granulation tissue in a tracheobronchial stent placed for malignant tracheobronchial

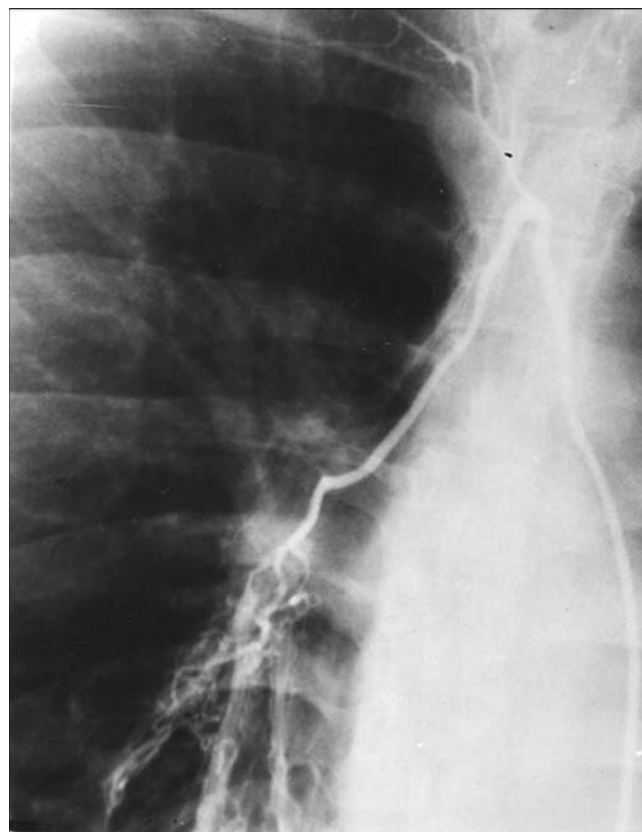


Figure 3 Bronchial angiogram in bronchiectasis.

disease can bleed, requiring bronchoscopy and fulguration. Massive hemoptysis from a tracheostomy should alert the physician to the possibility of a tracheoinnominate fistula.

Mitral stenosis results in pulmonary congestion leading to hemoptysis. Other cardiovascular causes include pulmonary infarction, septic emboli,⁶³ and congenital diseases resulting in pulmonary hypertension, for example, Eisenmenger complex and primary pulmonary hypertension. Arteriovenous fistulas are a rare cause of massive hemoptysis.⁶⁵ Patients with Rendu-Osler-Weber syndrome may have telangiectasis of the skin or superficial mucous membranes.

DIAGNOSIS

History and Physical Examination

Taking a detailed history is essential to differentiate true hemoptysis from other sources of hemorrhage, such as the upper airways or blood being aspirated from the gastrointestinal (GI) tract. A history of coughing must be obtained. A history of spitting, epistaxis or nausea, vomiting, heartburn, and abdominal pain may differentiate other sources of the bleeding, that is, the upper airway or the GI tract. The physician must determine the duration and quantify the bleeding (e.g., a teaspoon, a cupful), the presence of clots, and other respiratory symptoms, such as shortness of breath, chronic cough, and chest pain. Direct observation is sometimes the best way to quantify the bleeding. Obtaining a history of previous cardiac or pulmonary diseases, smoking, and medications, including blood thinners such as aspirin, clopidogrel, or warfarin, is vital. Clinical evaluation may reveal clubbing in patients with chronic disease such as bronchiectasis, calf tenderness, or swelling in deep vein thrombosis, and the presence of telangiectasias, suggesting hereditary telangiectasia, may help narrow the differential diagnosis [see Table 2].

Investigations

Noninvasive investigations Routine chest x-rays are insensitive. Chest CT with contrast can often identify the cause of hemoptysis, especially for parenchymal lesions. CT scanners capable of three-dimensional helical reconstruction are especially useful in this regard. The coagulation profile should be determined and, if abnormal, corrected aggressively.

Table 2 Differential Diagnosis of Hemoptysis

Tracheobronchial disease
Acute or chronic bronchitis
Bronchiectasis
Neoplasms
Foreign bodies
Trauma
Tracheoinnominate fistula
Parenchymal disease
Infection
Interstitial lung disease
Pulmonary embolism
Pulmonary arteriovenous malformations
Miscellaneous conditions
Mitral valve disease
Coagulopathy

Endoscopy: diagnostic and therapeutic The key is to determine the side and site of bleeding, and bronchoscopy is particularly effective if performed within 48 hours of presentation.^{50–52} Bronchoscopy should preferably be carried out in a dedicated suite or the operating room by an experienced bronchoscopist with access to a variety of methods to arrest the hemorrhage using balloon catheters, endobronchial lasers, or endobronchial fulguration. Flexible bronchoscopy can be used for diagnostic purposes when the bleeding is minimal; however, in patients with massive hemoptysis, a rigid bronchoscope will allow not only rapid evacuation of active bleeding but also the use of other modalities to stop the hemorrhage. Selective ventilation with a double-lumen endotracheal tube may be used to temporize a critical situation.

Angiography: diagnostic and therapeutic Failure to identify the source of hemorrhage at bronchoscopy should prompt systematic bilateral angiography of the bronchial, nonbronchial, and pulmonary vascular bed. Direct evidence of extravasation of blood into the bronchi or the lung parenchyma occurs only during active hemorrhage. On occasion, the source of bleeding is a systemic vessel from the subclavian, intercostal, or phrenic vessels.⁶⁶ Most often, we rely on indirect evidence of the bleeding vessel, as suggested by vascular hypertrophy and tortuosity [see Figure 4], and aneurysm formation and collateral circulation [see Figure 5 and Figure 6]. Bleeding from the pulmonary vasculature resulting in hemoptysis is seen in less than 10% of patients with massive hemoptysis, especially in patients with arteriovenous malformations, lung abscess, and Rasmussen aneurysm seen in tuberculosis.⁶⁶ Bronchial arteriography and embolization should be considered in patients in whom resection is contraindicated [see Table 3]. Embolization can result in dramatic relief of hemorrhage. Unfortunately, the majority of patients with massive hemoptysis do not survive, dying of suffocation, and the goal of the treating physician should be to identify and treat these patients before they experience their final bleeding.

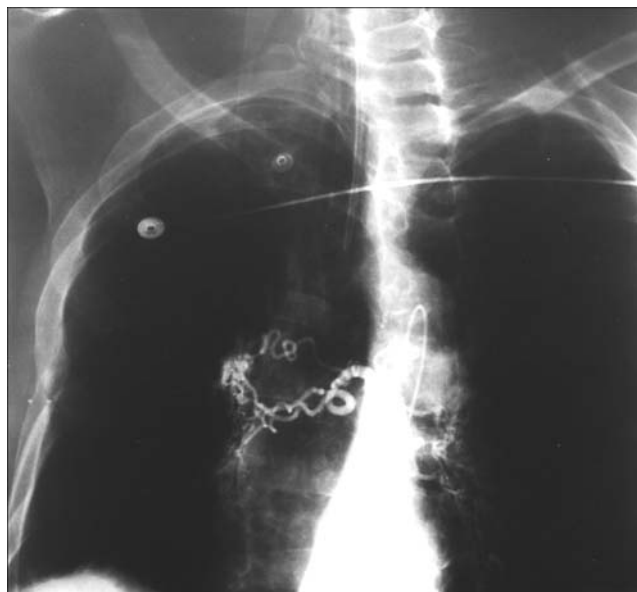


Figure 4 Bronchial arteriogram showing tortuosity.



Figure 5 Collateral circulation from the subclavian artery.



Figure 6 Collateral channels from phrenic artery.

MANAGEMENT

Medical

As with any potentially serious condition, evaluation of the “ABCs” (i.e., airway, breathing, and circulation) is the initial step. The overall goals of management of the patient with

Table 3 Contraindications to Surgical Resection

FEV ₁ < 40% of predicted
Unable to localize site at bronchoscopy
Unresectable cancer
Metastatic disease
Coagulopathy
Systemic disorder
Bilateral lung involvement

FEV₁ = forced expiratory volume in 1 second.

hemoptysis are threefold: aspiration prevention, bleeding cessation, and treatment of the underlying cause. Any patient with significant hemoptysis should be admitted to a monitored unit and evaluated promptly. Initial medical management consists of sedatives, cough suppressants, supplemental oxygen, and bed rest with dependent positioning of the pathologic side. Most cases of minor hemoptysis usually settle down with conservative measures. Patients with massive hemoptysis are, however, best monitored in intensive care units. Interventional techniques described earlier using bronchoscopy (flexible or rigid) and arteriography with embolization as required are used in stabilizing the patient.

Surgical

Surgery is best performed once the acute situation is under control and the site has been identified. There should be no medical contraindications, and the patient must have adequate pulmonary reserve. Pulmonary resection is the most effective method for controlling and preventing recurrent bleeding in most patients. Emergency surgery has a significantly higher morbidity and mortality than elective surgery. Surgical resection prior to hospital discharge must be considered in patients with massive hemoptysis even if the bleeding is stabilized as the recurrence rate is high (> 30%).⁶⁷ Surgical procedures depend on the pathology and pulmonary reserve. For benign disease and in patients with poor reserve, a limited resection may be appropriate, whereas in patients with malignant disease and with better pulmonary functions, a more radical approach with a lobectomy or even a pneumonectomy may be necessary.

SUMMARY

Hemoptysis must always be taken seriously. Death from massive hemoptysis occurs from asphyxiation. Every attempt must be made to localize the site of bleeding. Whenever possible, attempts must be made to control massive hemorrhage by interventional techniques. Elective resection has less morbidity and mortality than emergency surgery.

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3 CHEST WALL MASS

Michael E. Friscia, MD, and John C. Kucharczuk, MD

Chest wall masses are relatively uncommon in clinical practice. Together they encompass a variety of different processes, which may be benign or malignant. Unfortunately, few surgeons have a working knowledge of the etiology, evaluation, treatment, and prognosis of patients with primary or secondary chest wall masses. Often unfamiliarity leads to inappropriate diagnostic studies, delays in treatment, and frustration for the patient and surgeon alike. The intent of this chapter is to review the clinical presentation and diagnostic procedures required to evaluate and treat a patient presenting with a chest wall mass. We begin with the formulation of a clinical algorithm to streamline the evaluation, diagnosis, and treatment of patients with chest wall masses and conclude with a review of the specific causes of chest wall masses.

The chest wall contains a number of distinct tissues, including skin, fat, muscle, bone, cartilage, lymphatics, blood vessels, and fascia. Each of these component tissues has the capability of producing either a benign or a malignant primary chest wall mass. The chest wall is also in intimate proximity to a number of organs, which may cause a mass by extension of a malignancy or infection. These include the breast, the lung, the mediastinum, and the pleura. Additionally, because of the large surface area of the chest wall, it can be the site of metastasis from distant malignancies, including carcinomas and sarcomas. The primary framework for classification of chest wall masses is shown in Table 1.

Clinical Evaluation

The initial evaluation of these patients begins with a careful history noting the symptoms associated with the mass and the history of its growth. A personal history of malignancy should raise concern for a metastatic lesion. A complete physical examination is performed to evaluate other sites of disease and delineate comorbid medical conditions that will impact the patient's candidacy for resection. Previous radiographs, if available, are reviewed to determine the rapidity of the growth. If the mass is palpable, its size and characteristics (hard versus soft, fixed versus mobile) are noted.

A computed tomographic (CT) scan of the chest is required if chest wall involvement of an intrathoracic lesion is suspected. For primary chest wall masses, magnetic resonance imaging (MRI) can be useful for further characterization. An MRI allows delineation of tissue planes and the relationships to major neurovascular structures.¹ Chest radiography is often performed initially but is of little use.

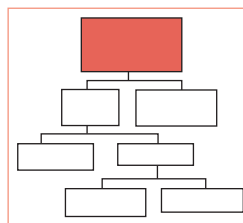


Table 1 Framework for Classification of Primary and Secondary Chest Wall Masses

Primary masses of the chest wall
Benign masses
Infectious masses
Soft tissue neoplasms
Bone and cartilage neoplasms
Malignant masses
Soft tissue malignant neoplasms
Bone and cartilage malignant neoplasms
Secondary masses of the chest wall
Tumor invasion from contiguous organs
Metastasis from distant organs

The next step is to decide whether to pursue a tissue diagnosis prior to proceeding with definitive therapy. For lesions less than 3 cm, whether suspected of being benign or malignant, excisional biopsy is performed for diagnosis and treatment. For lesions greater than 3 cm that can produce significant morbidity with resection, a preoperative tissue diagnosis is obtained.

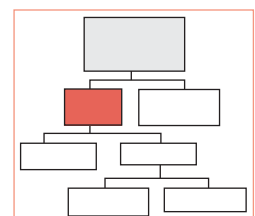
Fine-needle aspirations (FNAs) are technically simple and can be performed in the office at the initial patient evaluation but are best used when metastasis is suspected. Lack of histology and tissue architecture severely limits the use of FNA in distinguishing benign from malignant primary chest wall tumors. In these cases, a core-needle biopsy or incisional biopsy is performed. Both techniques provide tissue for histology, and both must be performed so that the biopsy track will be completely excised at the time of definitive surgery. Given the easy access to most chest wall masses, many patients will tolerate a core-needle biopsy in the office, which can expedite the diagnostic process.²

Benign Primary Masses of the Chest Wall

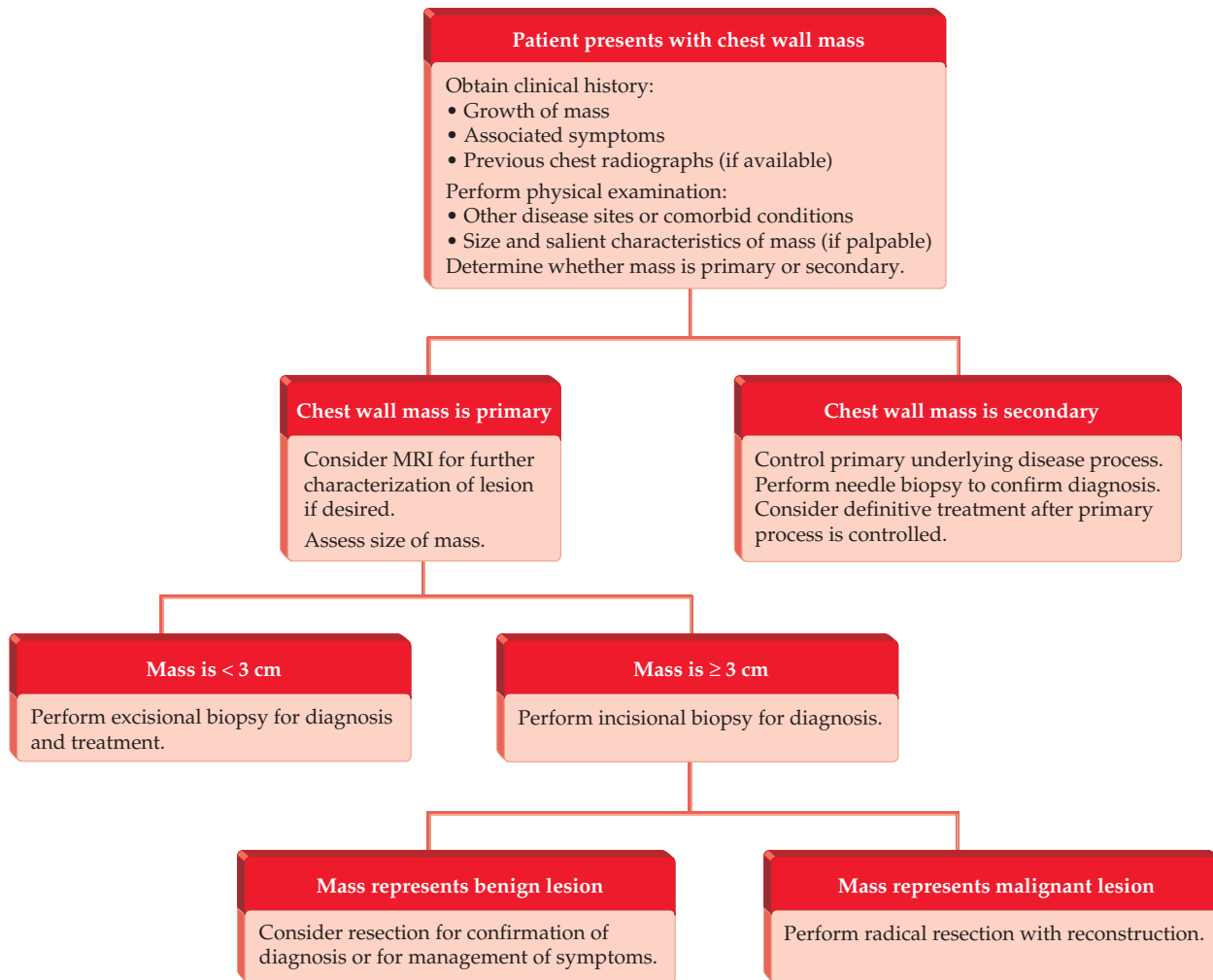
INFECTIOUS MASSES OF THE CHEST WALL

Sternal Infections

Primary sternal osteomyelitis is rare but may be seen in intravenous drug abusers. Much more common is osteomyelitis following median sternotomy. Approximately 1 to 3% of median sternotomies for cardiac surgery are complicated by sternal



Evaluation of Chest Wall Mass



wound infection.² The risk factors for this complication include diabetes, use of bilateral internal mammary arteries, and reoperation.³ These patients present with pain, drainage, and systemic signs of infection. Most of these infections have deep extension into the mediastinum as well as sternal osteomyelitis. When sternal osteomyelitis is suspected, a CT scan of the chest can help determine the extent of mediastinal soilage, but, generally, the patient is taken directly to the operating room for exploration and sternal débridement. Aggressive surgical débridement of the bone and cartilage with flap closure is associated with the best clinical outcomes.⁴

Special mention must be made of the patient who presents after sternotomy with a pulsating sternal mass. These patients have a pseudoaneurysm of the underlying aorta and are at risk for exsanguination. They should undergo an emergent CT angiogram or aortogram to confirm the diagnosis. They must then be taken directly to the operating room, where they are placed on cardiopulmonary bypass through femoral cannulation and are cooled to hypothermia prior to opening the sternum as repair may require circulatory arrest.

Sternoclavicular Joint Infections

Sternoclavicular joint infections present as painful palpable masses overlying the sternoclavicular joint, as shown in Figure 1. These infections are often associated with intravenous drug abuse, infected indwelling subclavian catheters, and trauma. The majority of patients have some underlying risk factor, including diabetes, hepatic or renal insufficiency, or a history of systemic sepsis. The diagnosis is made by a combination of history, physical examination, and MRI of the chest with attention to the sternoclavicular joint. The typical findings include a collection around the joint and abnormal signal intensity in the bone and cartilage [see Figure 2]. Treatment consists of wide resection of the sternoclavicular joint, including the proximal third of the clavicle as well as débridement of the manubrium.⁵ The proximal portion of the first or second ribs can be involved and also requires resection. Immediate reconstruction is performed by rotation of a pectoralis muscle flap into the resection cavity. Postoperatively, the patients are treated with 6 weeks of intravenous antibiotics. Most require intensive postoperative physical therapy to restore strength, function, and mobility in the upper extremity.

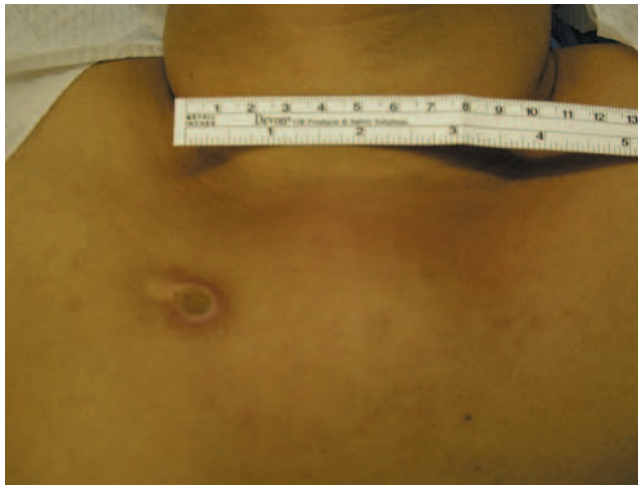


Figure 1 Sternoclavicular joint infections present as painful palpable masses overlying the joint.

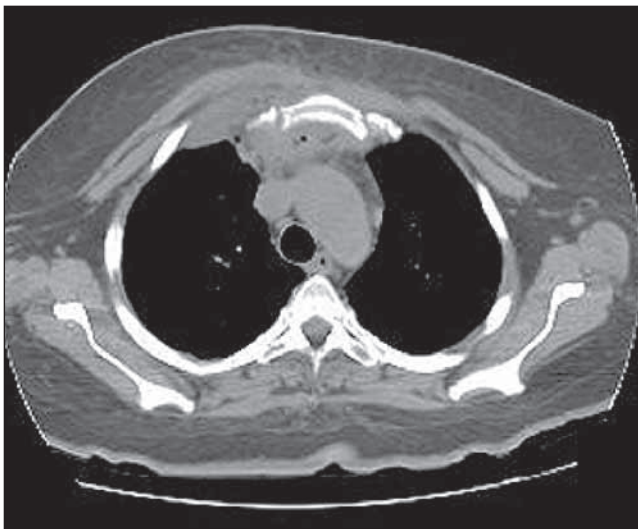


Figure 2 A computed tomographic (CT) scan shows the typical appearance of sternoclavicular joint infection, including fluid collection around the joint and tissue stranding.

Osteomyelitis of the Rib

Osteomyelitis of a rib presents as a painful, swollen mass overlying an infected segment of rib. Often a draining sinus tract is present. The diagnosis is made on a clinical basis. A CT scan of the chest is obtained to rule out underlying intrathoracic pathology such as an empyema. Treatment is resection of the infected bone with soft tissue coverage of the defect. Care is taken to avoid contamination of the underlying pleural cavity during rib resection. In children, the diagnosis can be facilitated by the use of ultrasonography, which demonstrates obliteration of the intermuscular planes adjacent to the infected rib and pericostal edema.⁶ As with adults, the range of pathologic organisms recovered can be quite wide.

BENIGN NEOPLASMS OF THE CHEST WALL

The benign neoplasms of the chest wall are shown in Table 2.

Benign soft tissue neoplasms of the chest wall usually present as slowly growing, painless masses. Often plain radiographs and a CT scan of the chest are obtained, although they are not always necessary.

On examination, benign soft tissue lesions are usually soft and mobile. The CT scan shows a homogeneous mass without necrosis, infiltration of associated soft tissue, or destruction of associated bone. Small (< 3 cm) soft tissue lesions are completely removed by excisional biopsy for definitive diagnosis and treatment. Larger lesions (> 3 cm) are approached with a core-needle biopsy first to rule out a malignant soft tissue neoplasm. If the lesion is confirmed to be benign, it is resected with close negative margins to minimize the size of the surgical defect. If it is determined to be malignant, an aggressive wide excision is performed with immediate reconstruction.

Desmoid tumors deserve special mention in that they are borderline neoplasms.⁷ These tumors generally arise in the muscle and fascia around the shoulder. Although they appear histologically benign, they can infiltrate adjacent structures and have a high tendency for local recurrence, which can make surgical treatment for recurrence morbid and disfiguring. For these reasons, desmoid tumors are best treated with radical surgical excision. The largest current series demonstrates that a positive surgical margin is associated with an 89% recurrence rate, whereas with a negative margin, recurrence is less than 20%.⁸

Benign Bone and Cartilage Neoplasms

Osteochondroma is a benign cartilaginous neoplasm that can occur in any bone that undergoes enchondral bone formation. Essentially, these tumors are hamartomas of the growth plate. The knee is the most common site of occurrence. In the

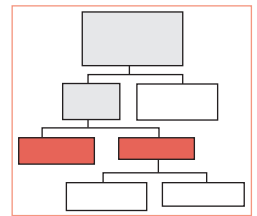


Table 2 Benign Neoplasms of the Chest Wall by Site of Origin

Benign soft tissue neoplasms
Lipoma
Fibroma
Hemangioma
Granuloma
Neurofibroma
Elastoma
Desmoid
Benign bone and cartilage neoplasms
Osteochondroma
Chondroma
Fibrous dysplasia
Eosinophilic granuloma

chest, they arise in the metaphyseal regions of the anterior ribs. Most are asymptomatic and found on a screening chest radiograph where an eccentric growth pattern is noted at the costochondral junction. The diagnosis is made from a characteristic pattern of stippled calcification within the tumor on plain x-ray. In children, they are followed unless causing pain or increasing in size; in postpubescent and adult patients, they are resected to confirm the diagnosis and rule out malignancy.

Chondromas are the next most common benign neoplasm of the chest wall. They occur along the costochondral junctions between the anterior ribs and the sternum. Unfortunately, the distinction between chondroma and chondrosarcoma cannot be made on clinical or radiographic grounds; therefore, excision is required for diagnosis. This results in a significant surgical defect, which usually requires complex reconstruction, including prosthetic material to provide rigid structure and soft tissue coverage.

Fibrous dysplasia is a benign cystic lesion of the medullary cavity of the rib that usually presents as a painless lesion incidentally found on a screening chest x-ray. Medullary replacement by fibrous tissue creates a radiolucent appearance on an x-ray. These lesions are treated conservatively and simply followed. Local resection is indicated if pain develops or the lesion enlarges on serial x-rays.

Malignant Primary Masses of the Chest Wall

Malignant soft tissue lesions of the chest wall constitute a large number of diverse pathologies. The primary malignant masses of the chest wall are listed in Table 3.

SOFT TISSUE

Sarcomas are the most common primary malignant neoplasm of the chest wall. On examination, sarcomas of the chest wall can be quite sizable, as shown in Figure 3. They are painless in half of the patients. The clinical finding is a hard, fixed mass. No calcifications are visible on a CT scan of the chest, but bony invasion is common. The treatment is wide surgical excision. Gordon and colleagues reported the largest surgical series of patients with soft tissue sarcomas of the chest wall in 1991.⁹ The study included 149 patients who had undergone resection at the Memorial Sloan-Kettering Cancer Center in New York. The 5-year survival rate was 66%. Unfortunately, the study also included 32 patients who had desmoid tumors, which are not histologically classified as sarcomas or as malignant. A large retrospective study containing 55 surgically treated patients with soft tissue sarcomas of the chest wall was reported from a single institution in Brazil in 2005.¹⁰ In this series, fibrosarcoma accounted for nearly 53% of the cases. With wide surgical resection, the authors reported disease-free survival rates of 75% at 5 years and 64% at 10 years. The histologic grade of the tumor and the type of surgical resection were found to be independent

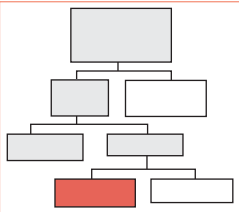


Table 3 Primary Malignant Chest Wall Masses According to Tissue of Origin
Malignant chest wall masses—soft tissue
Liposarcoma
Leiomyosarcoma
Rhabdomyosarcoma
Malignant fibrous histiocytoma
Angiosarcoma
Malignant chest wall masses—cartilage and bone
Solitary plasmacytoma
Chondrosarcoma
Osteosarcoma
Ewing sarcoma
Synovial cell sarcoma



Figure 3 Shown is the appearance of a chest wall sarcoma on physical examination. Such lesions can be quite large.

prognostic factors for disease-free survival. This is consistent with other studies that suggest that age, gender, symptoms, and size do not significantly impact survival.¹¹ The French Sarcoma Group published its retrospective series of soft tissue sarcomas of the trunk wall in 2009, which included 283 patients with chest wall sarcomas treated primarily with surgery.¹² Overall survival at 5 and 10 years was 57% and 52%, respectively. Interestingly, 22% of patients in this study had a previous history of radiation therapy, which adversely affected survival. Currently, no good data are available to recommend neoadjuvant treatment, which has become routine in the treatment of soft tissue sarcomas of the extremities. A single-institution, multidisciplinary experience with primary chest wall sarcomas was reported from The University of Texas M.D. Anderson Cancer Center in 2001.¹³ The retrospective review included patients with sarcomas of soft tissue, cartilage, and bone origin, as well as desmoid tumors. The cumulative 5-year survival was 64%, which is to be expected from surgery alone.

CARTILAGE AND BONE

Solitary plasmacytoma represents an uncommon chest wall mass caused by a localized collection of monoclonal plasma cells. Histologically, the plasma cells are identical to those seen in patients with multiple myeloma; however, unlike patients with multiple myeloma, they are confined to a single site. Patients generally present with pain and often have pathologic rib fractures. With soft tissue involvement, a palpable mass becomes evident. Tissue is required to make the diagnosis either by FNA, core-needle, or small incisional biopsy. The specimen should be sent for flow cytometry, which confirms the clonal nature of the cells.¹⁴ Definitive local radiotherapy is the treatment of choice for solitary bone plasmacytoma.¹⁵ Although local control is achieved in over 90% of patients with radiation alone, about 50% of patient progress to multiple myeloma within 2 years and require systemic treatment.¹⁶

Chondrosarcoma is the most common primary malignant tumor of the chest wall. Chondrosarcomas are found along the anterior sternal border or the costochondral arches and are more common in males than in females. The primary symptom leading to evaluation is pain. The best imaging modality is CT; however, there are no distinguishing radiographic characteristics to provide a definitive diagnosis, and core or incisional biopsy is required.¹⁷ Complete surgical resection with adequate surgical margins and immediate reconstruction is the treatment of choice. The Scandinavian Sarcoma Group published the largest series of patients with chest wall chondrosarcoma.¹⁸ Ninety-seven patients were treated with surgery; wide excision was associated with a 92% 10-year survival and a 4% local recurrence rate, compared with a 47% 10-year survival and a 73% local recurrence rate when margins were positive.

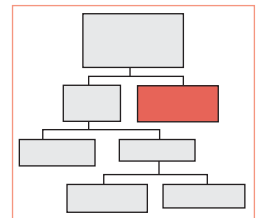
Ewing sarcoma is an aggressive primary malignant bone tumor that presents in children and adolescents with a painful, enlarging mass often associated with fever and malaise. Ewing sarcoma was initially distinguished from osteosarcoma because of its sensitivity to radiation. Although the cellular origin of Ewing sarcoma remains unclear, there appears to be a spectrum of tumors that share the same genetic translocation and are referred to as the Ewing family of tumors.¹⁹ The initial role of surgery in primary chest wall Ewing sarcoma is to obtain tissue for diagnosis. With smaller rib lesions, this may be in the form of an excisional biopsy. Therapeutically, these tumors are best approached with multimodality treatment, including preoperative chemotherapy followed by complete resection of residual disease.²⁰ A review of three multi-institutional trials from the Pediatric Oncology Group in 2003 suggested that the likelihood of a complete resection is improved with neoadjuvant chemotherapy followed by wide resection in patients with Ewing sarcoma and closely related primitive neuroectodermal tumors of the chest wall.²¹ If the resection is complete and the pathologic margins are negative, no radiation therapy is given. The avoidance of radiation therapy may be particularly important in children and adolescents because of the risk (10 to 30%) of developing a radiation-induced malignancy over their lifetime.²² Askin tumors are a small round cell tumor of the thoracopulmonary region and are members of the Ewing family of tumors. They are best managed by diagnostic biopsy and

preoperative chemotherapy followed by complete surgical resection.²³

Synovial sarcomas are rare but may arise on the trunk, where they present as a palpable chest wall mass. Despite the name, these lesions do not arise from synovial cells or joint cavities. They were originally named based on the appearance under light microscopy; however, these tumors are now known to arise from pluripotential mesenchymal cells.²⁴ The most important prognostic factor is tumor size.²⁵ Limited data suggest that although there may be an objective response to neoadjuvant chemotherapy, there is no detectable benefit on survival.²⁶ The current recommendation is aggressive surgical resection. Patients with very large tumors or positive surgical margins receive postoperative adjuvant treatment.

Secondary Masses of the Chest Wall

Secondary chest wall masses arise as direct extensions of a malignancy from a contiguous organ. Breast and lung cancer are the most common. The initial evaluation centers on staging the underlying disease. For example, a patient with a chest wall mass attributable to direct invasion of a primary lung cancer should undergo a staging workup to determine the extent of disease. If the patient is deemed an appropriate candidate for resection and is medically operable, he or she should undergo pulmonary resection with en bloc chest wall resection.²⁷ Following resection, the patient should be referred for adjuvant chemotherapy. The intent is cure, and the outcomes are stage specific.



Unfortunately, most women presenting with a chest wall mass from breast cancer have a local recurrence. Resection with reconstruction can be performed in this situation, but the benefit remains unclear. The Memorial Sloan-Kettering Cancer Center reported on 38 women who underwent extensive chest wall resection for recurrent breast cancer with a 0% operative mortality rate, but the 5-year survival rate was only 18%, and by 5 years, 87% of the patients had local recurrence.²⁸ Currently, chest wall resection of locally recurrent breast cancer must be considered on a case-by-case basis.

A large necrotic ulcer of the chest wall presenting after radiation therapy to the chest wall for previous malignancy should raise the suspicion for osteoradionecrosis. This is a locally destructive lesion characterized by infection and necrosis. The first step is to perform biopsies of the area to ensure that the lesion does not represent tumor recurrence. The preferred treatment is wide excision to healthy tissue and local or free flap coverage of the soft tissue defect, avoiding the use of prosthetic material whenever possible. Close collaboration with a plastic and reconstructive surgeon is critical to operative planning and success.²⁹

Conclusions

Chest wall masses are relatively unusual in clinical practice. Most surgeons have limited experience in diagnosis and

treatment. In general, it is important to move quickly to establish a tissue diagnosis as a physical examination and a radiographic study often cannot distinguish a benign from a malignant chest wall mass. The very unusual tumors will often require consultation with a highly specialized patholo-

gist to make the diagnosis and an oncologist to assist in treatment planning to optimize patient outcome.

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4 PLEURAL EFFUSION

Michael A. Maddaus, MD, FACS, and Rafael S. Andrade, MD, FACS

Approach to the Patient with a Pleural Effusion

Pleural effusion is a common problem in surgical practice. It results from perturbations of normal pleural fluid transport, which are produced by three main mechanisms: abnormalities in Starling equilibrium, increased capillary and mesothelial permeability, and interference with lymphatic drainage. These mechanisms are associated with a variety of different causes [see Table 1].^{1,2} Often more than one mechanism is involved. An inflammatory effusion, for instance, is marked by increases in capillary and mesothelial permeability, which lead to elevated intrapleural oncotic pressure.

Pleural effusion is classified as either transudative or exudative, depending on the chemical composition of the fluid. A transudate is an ultrafiltrate of serum and has a low total protein content (≤ 3 g/dL); an exudate is the result of increased permeability and has a high total protein content. Increased pleural permeability results from complex inflammatory mediator interactions between the mesothelium (whose cells play an active role in inflammation, phagocytosis, leukocyte migration, tissue repair, antigen presentation, coagulation, and fibrinolysis^{3,4}) and the capillary endothelium. The distinction between transudative and exudative pleural effusion is clinically significant in that the two types of effusion have different causes [see Table 2].^{1,4}

Table 1 Pathophysiologic Mechanisms of Pleural Effusion

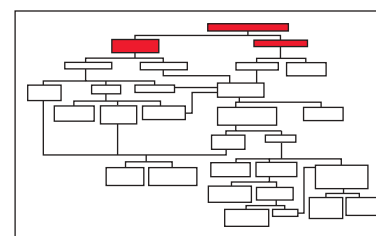
Mechanism	Specific Alteration	Cause
Abnormality in Starling equilibrium	Increased capillary and lymphatic hydrostatic pressure	Increased venous pressure (e.g., biventricular heart failure, renal failure)
	Decreased capillary oncotic pressure	Hypoproteinemia (e.g., nephrotic syndrome)
	Decreased intrapleural hydrostatic pressure	Ex vacuo effusion (e.g., atelectasis)
	Increased intrapleural oncotic pressure	Inflammation (e.g., infection, cancer, autoimmune disease)
Increase in capillary and mesothelial permeability	Increased filtration	Inflammation (e.g., infection, cancer, autoimmune disease)
Interference with lymphatic drainage	Obstruction	Cancer, structural abnormalities

Table 2 Causes of Transudative and Exudative Pleural Effusion

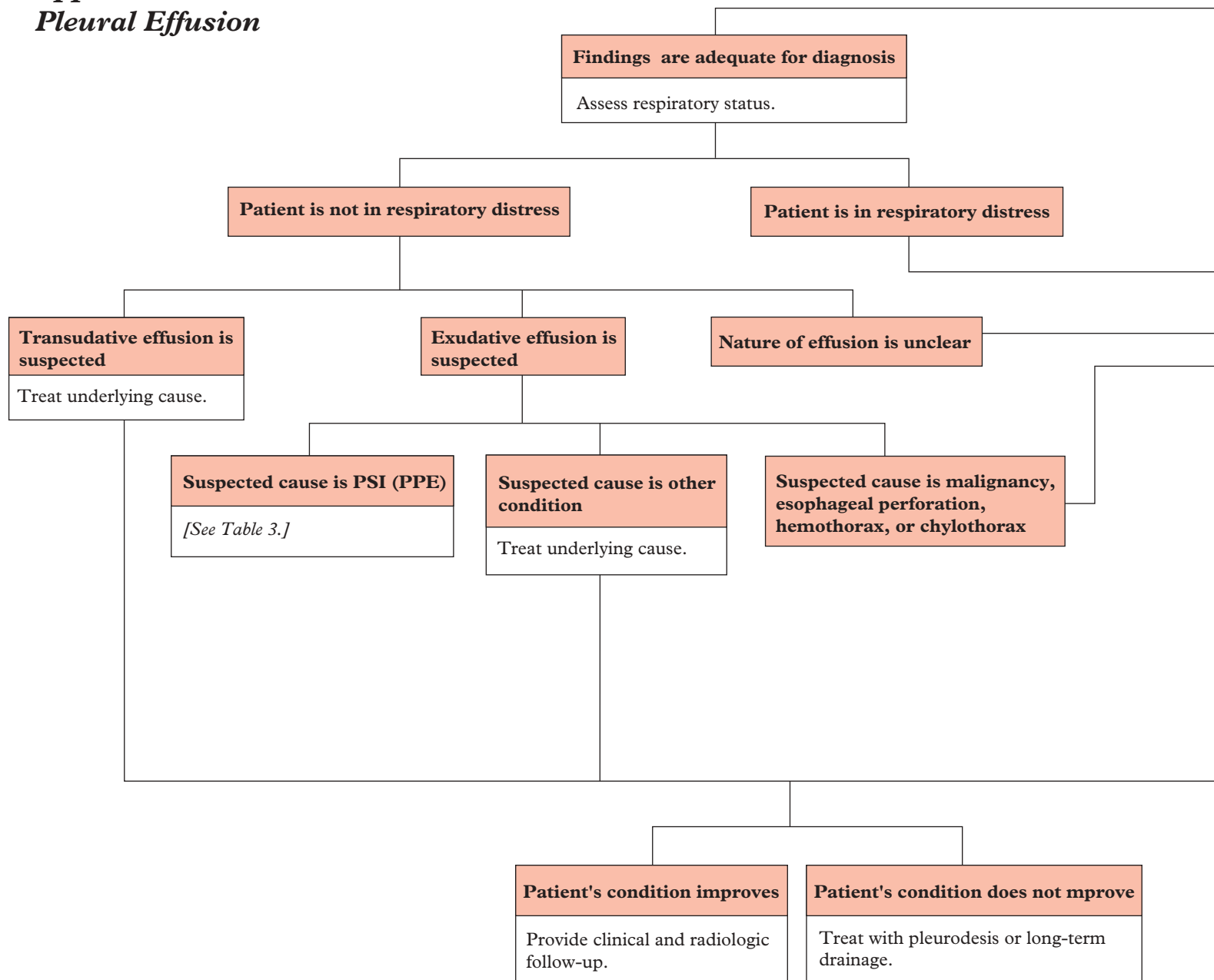
Type of Effusion	Cause
Transudative	Congestive heart failure Cirrhosis Nephrotic syndrome Acute atelectasis Renal failure Peritoneal dialysis Postoperative state Myxedema Postpartum state
Exudative	Pneumonia Malignancy Infection Esophageal perforation Hemothorax Chylothorax Pseudochylothorax Connective tissue diseases Drug-induced pleuritis Pancreatitis Uremia Postmyocardial infarction (Dressler syndrome) Chronic atelectasis Radiation therapy Asbestos exposure Meigs syndrome Ovarian hyperstimulation
Transudative or exudative	Pulmonary embolus

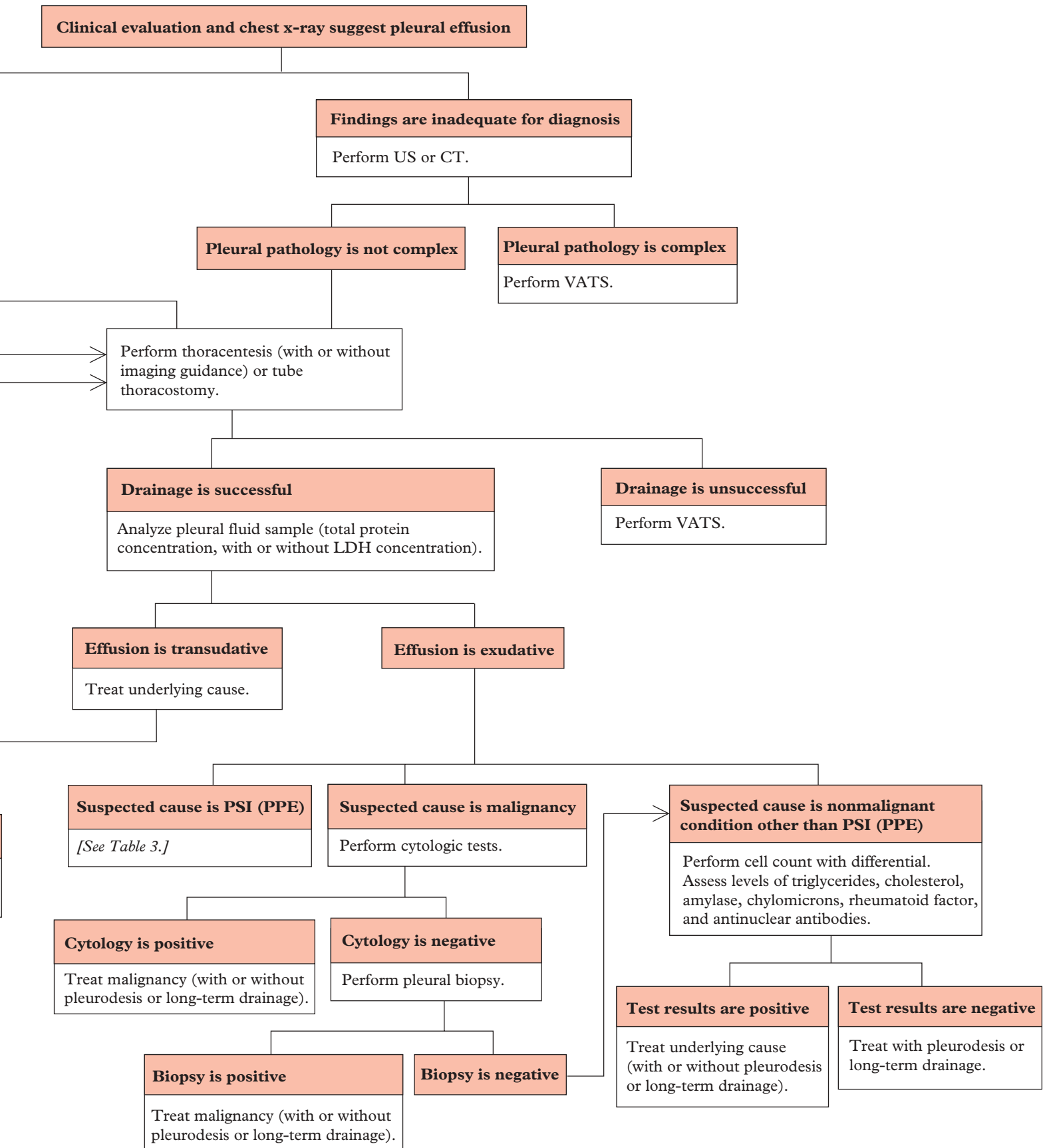
Clinical Evaluation

A complete history, physical examination, and clinical acuity are the initial tools used for diagnosing pleural effusion. Important facts from a patient's history (e.g., respiratory symptoms, pain, extrathoracic symptoms, duration of symptoms, previous medical conditions, and risk factors for cardiopulmonary diseases or cancer) can raise the index of suspicion for an effusion and provide guidance regarding possible causes. Careful physical examination of the chest can detect an effusion, and many physical signs may provide clues to the cause. Physical signs that are particularly useful for diagnostic purposes include jugular venous distention and tachycardia (suggestive of congestive heart failure); lymphadenopathy, digital clubbing, and localized bone tenderness (suggestive of lung cancer); and ascites (suggestive of ovarian tumors or cirrhosis).



Approach to the Patient with a Pleural Effusion





Pleural effusion can occur in a wide variety of clinical situations, however, and it often evades clinical detection by history and physical examination. Consequently, imaging tests are indispensable in the workup of a patient with a possible pleural effusion. Pleural fluid analysis, pleural biopsy, and thoracoscopy may also be required for evaluation.

Investigative Studies

IMAGING

Chest Radiography

To be detectable on a standard upright posteroanterior chest radiograph, an effusion must have a volume greater than 150 mL. If the volume is 150 to 500 mL, the lateral costophrenic angle will be blunted; if the volume is greater than 500 mL, a meniscus will be created.^{5,6} A lateral decubitus chest radiograph can detect minute effusions (< 50 mL), and as a general rule, a layering effusion that is at least 1 cm thick is accessible to thoracentesis.^{6,7} A loculated effusion may appear as a so-called pseudotumor on a chest radiograph and typically will not layer freely on a lateral decubitus radiograph. Subtle changes on an upright chest radiograph (e.g., accentuation of a fissure, elevation of a hemidiaphragm or increased separation between the lung and subdiaphragmatic gas [see Figure 1]) may also signal an effusion. Additional findings on a standard chest radiograph (e.g., laterality, the size of the cardiac silhouette, the position of the mediastinum, pulmonary parenchymal changes, pleural calcifications, and osseous abnormalities) may point to a specific cause.

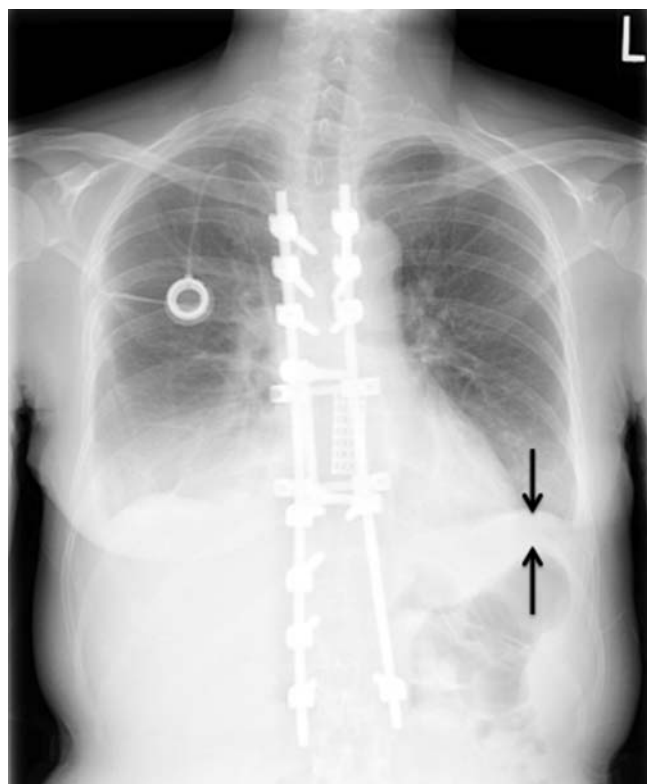


Figure 1 Posteroanterior chest radiograph of a patient with bilateral pleural effusion reveals increased separation between the left lung and subdiaphragmatic gas (arrows).

Supine chest radiographs are less sensitive than other chest radiographs. With these images, suspicion of an effusion is triggered by increased homogeneous density of the lower hemithorax, loss of normal diaphragmatic silhouette, blunting of the lateral costophrenic angle, or apical capping [see Figure 2].⁸

Ultrasonography

Chest ultrasonograms are more reliable for detecting and localizing small (5 to 100 mL) or loculated pleural effusions than chest radiographs are.^{5,9,10} Ultrasonography is particularly helpful for guiding thoracentesis for small-volume effusions and for assessing pleural effusions in critically ill patients.^{6,11}

Computed Tomography of Chest

Computed tomography (CT) of the chest is a very sensitive tool for evaluating pleural effusion. Free-flowing fluid causes a sickle-shaped opacity in the most dependent portion of the thorax, and even small effusions are readily detected [see Figure 3]. CT may also reveal clues to the cause of the effusion, such as a fluid-fluid level (suggestive of acute hemorrhage), pleural thickening and enhancement (suggestive of pleural space infection [PSI] [see Figure 4]), calcified pleural plaques (suggestive of asbestosis), and diffuse irregular nodularity and pleural thickening (suggestive of pleural metastases or mesothelioma). CT is especially useful for characterizing loculated effusions, for differentiating pleural thickening or pleural masses from pleural effusion, for distinguishing between effusion and lung abscess, and for guiding and monitoring closed drainage of effusions.^{6,10,12,13}

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the chest provides no useful information beyond what can be obtained with CT.

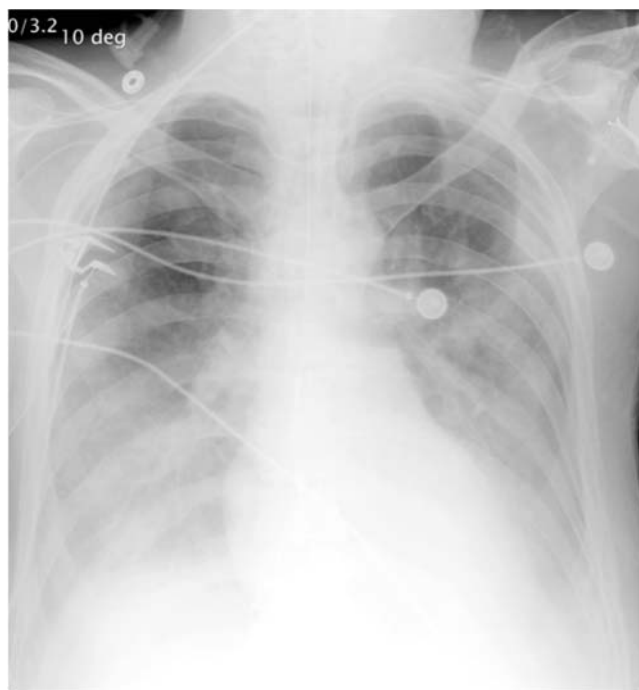


Figure 2 Supine chest radiograph of a patient with bilateral pleural effusion shows increased homogeneous density of the lower hemithoraces.



Figure 3 Computed tomographic scan of the chest shows a free-flowing, sickle-shaped, right-sided effusion.

MRI is neither efficient nor cost-effective in standard evaluation of pleural effusion.^{12,14}

THORACENTESIS

If the cause of a pleural effusion cannot be explained by the clinical circumstances (e.g., congestive heart failure or a recent surgical procedure), diagnostic thoracentesis [see *Sidebar*

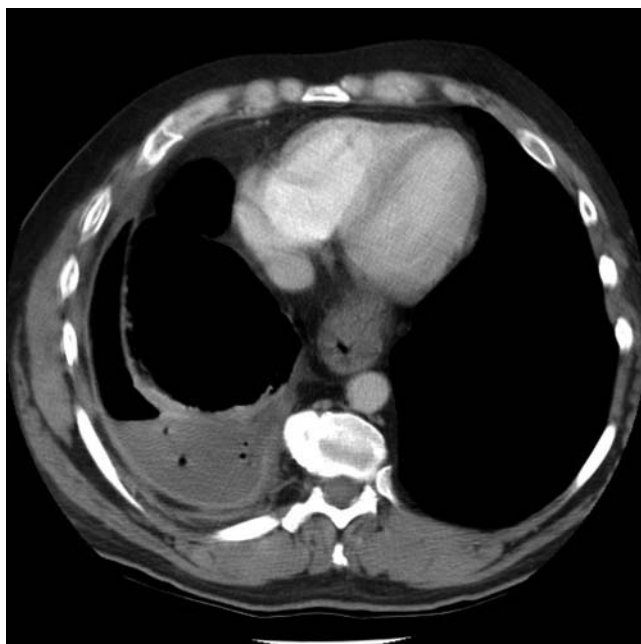
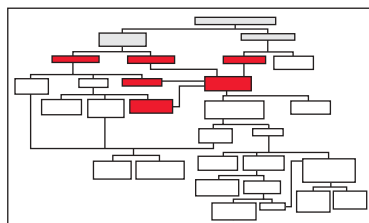


Figure 4 Chest computed tomographic scan of a patient with right-side empyema shows a loculated effusion. The pleura is enhanced with intravenous contrast.

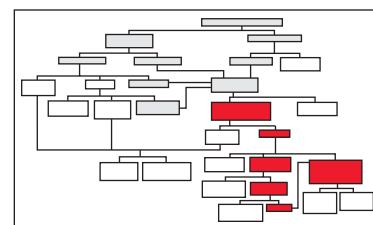
Techniques for Bedside Thoracentesis and Tube Thoracostomy] is indicated. Thoracentesis may also have therapeutic value in that drainage of fluid may relieve dyspnea. Absolute contraindications to thoracentesis include a lack of cooperation on the patient's part, clinical instability with hemodynamic or respiratory compromise, severe coagulopathy, and high-pressure ventilation. Relative contraindications to thoracentesis include a nonlayering effusion, loculations, and previous thoracic trauma, chest tube placement, or surgery.

A large effusion can be drained without any special imaging guidance other than an upright posteroanterior and lateral chest radiograph. Thoracentesis for a small or loculated effusion is best done with ultrasound guidance; success rates are as high as 97%.¹⁵

The incidence of complications associated with thoracentesis varies, depending on the experience of the operator and on the use of imaging guidance. Pneumothorax occurs in 3 to 20% of patients, of whom approximately 20% require tube thoracostomy [see *Sidebar* Techniques for Bedside Thoracentesis and Tube Thoracostomy]. Patients commonly experience pain and cough with lung reexpansion during drainage. Reexpansion pulmonary edema is an uncommon complication that can occur with rapid drainage of a large-volume effusion. It is common practice to drain no more than 1 to 1.5 L at a time, even though no evidence supports this practice. Experimental data suggest that active aspiration of fluid can cause high negative intrapleural pressures, potentially precipitating edema formation; gravity drainage may be preferable to minimize the chance of edema. Additional potential complications include so-called dry tap, vasovagal reaction, hemorrhage, hypovolemia, and PSI.^{10,16–18}

PLEURAL FLUID ANALYSIS

Assessment of a pleural fluid sample is guided, to some extent, by the clinical context in which the pleural effusion occurs. When the cause of the effusion is unknown, evaluation of a pleural fluid sample typically includes measurement of total protein and lactate dehydrogenase (LDH) concentrations, a cell count with differential, cause-specific testing, and microbiologic and cytologic analysis.



Biochemical Analysis of Pleural Fluid

A total protein concentration higher than 3 g/dL is sometimes used as the main criterion for distinguishing a transudate from an exudate; however, the use of this criterion may result in misclassification of as many as 15% of effusions. According to Light and colleagues' criteria,¹⁹ which have a sensitivity of 99% and a specificity of 98% for identifying exudates, an effusion is an exudate if one of the following three findings is present:

1. A pleural fluid-to-serum protein ratio higher than 0.5
2. A pleural fluid-to-serum LDH ratio higher than 0.6
3. A pleural fluid LDH concentration higher than two thirds of the upper limit of the serum reference range

Techniques of Bedside Thoracentesis and Tube Thoracostomy

Bedside Thoracentesis

Bedside thoracentesis should be performed on a bed or an examination table (as a safeguard if hypotension develops). The patient should be upright and seated (provided that he or she is awake and cooperative), with the arms leaning comfortably on a bedside table and the back facing the surgeon.

The proper intercostal space for catheter insertion is determined through physical examination and radiologic evaluation of the effusion; generally, the ninth or 10th intercostal space in the midscapular line is a good choice. The area is prepared and anesthetized with 1% lidocaine, 3 to 5 mg/kg, with care taken not to injure the intercostal bundle. To confirm that the catheter is in the correct location, we recommend drawing a small amount of pleural fluid at the time of local anesthetic infiltration. Several thoracentesis kits with one-way valves are available. Fluid should be allowed to drain by gravity; however, to minimize the risk of reexpansion pulmonary edema, drainage should not exceed 1.5 L. Frequently, a dry cough and pleuritic pain develop as drainage approaches its end. To minimize anxiety, the patient should be warned about this possibility in advance. After the completion of thoracentesis, a chest radiograph should be obtained.

Bedside Tube Thoracostomy

Bedside tube thoracostomy should be performed with the patient supine. The side on which the thoracostomy will be created should be elevated, and the patient's ipsilateral arm should be abducted. Supplemental oxygen should be supplied. Monitoring must include, at the least, continuous oxygen saturation plethysmography and intermittent measurement of blood pressure and heart rate. Tube thoracostomy is potentially very painful; accordingly, in a nonemergency situation, every effort should be made to minimize pain and anxiety. We usually administer intravenous ketorolac about 30 to 60 minutes before the procedure. During preparation for chest tube placement, narcotics and sedatives should be administered intravenously; additional doses should then be administered at the beginning of and during the procedure.

The ideal location for chest tube placement is determined by clinical and radiographic examination. The area is prepared and draped widely, and a local anesthetic is used at a near-maximum dosage, with care taken to anesthetize skin, subcutaneous tissue, muscle, and periosteum. A 1.5 cm skin incision is made, a soft tissue tunnel is created with blunt instrument and finger dissection, the upper edge of the rib is identified clearly, and additional local anesthetic is applied to the periosteum and the intercostal muscles. The subcutaneous tunnel should generally be directed posteriorly so that the chest tube will sit along the posterior chest wall and will not be trapped in a fissure. The intercostal muscle is pierced bluntly, and digital examination of the pleural space is performed to confirm that an intrapleural location has been reached and to search for abnormalities such as adhesions or tumor implants. The chest tube is then directed to the desired location with the aid of a clamp. As with thoracentesis, fluid should be allowed to drain by gravity, but drainage should not exceed 1.5 L. If the effusion exceeds 1.5 L, the chest tube should be clamped and the remaining fluid allowed to drain intermittently in 200 mL aliquots every 2 hours. Immediately after completion of the procedure, a chest radiograph should be obtained to verify lung expansion and confirm the position of the chest tube. When chest tube output falls below 200 mL/day and reexpansion of the lung is verified, pleurodesis should be performed. We recommend that patient-controlled analgesia be employed while the chest tube remains in place.

The size of the chest tube is determined by the suspected cause and by the radiologic characteristics of the effusion. For a free-flowing transudative effusion, a small (20 to 24 French) chest tube or even a pigtail catheter usually suffices; for a thick exudative effusion or a hemothorax, a tube as large as 40 French may be required.

A 1997 meta-analysis of the diagnostic value of tests used to distinguish transudates from exudates did not find any test or combination of tests to be clearly superior.²⁰ The choice of a test for this purpose is therefore a matter of individual preference. If only one test is to be performed, measurement of the total protein concentration is the most practical choice in view of its accuracy and availability.

Assessment of pleural fluid pH and glucose levels may be used adjunctively for risk stratification in patients with PSI, but the clinical utility of these measurements is not well established (see below).²¹

There are numerous substances whose concentrations can be measured to help determine the specific cause of a pleural effusion, such as triglycerides, chylomicrons, and cholesterol (to help diagnose chylothorax); amylase (to help diagnose esophageal perforation or pancreatitis); rheumatoid factor (to help diagnose rheumatoid effusion); antinuclear antibodies (to help diagnose lupus pleuritis); carcinoembryonic antigen (to help diagnose malignancy); and adenosine deaminase (to help diagnose tuberculous pleurisy).^{3,22–25}

Cell Counts

Analysis of the number and type of white blood cells (WBCs) present in pleural fluid is often diagnostically useful. Pleural effusions can be categorized according to the type of WBC that is predominant. Generally, pleural fluid neutrophilia points to acute inflammation (e.g., from PSI or pulmonary infarction) as the underlying cause; however, the

presence of a neutrophilic effusion does not exclude malignancy. Pleural fluid lymphocytosis, in which lymphocytes account for more than 50% of WBCs, most frequently is indicative of malignancy (occurring in 50% of malignant effusions), tuberculosis (occurring in 15 to 20% of tuberculous effusions), or chylothorax.²⁶ Pleural fluid eosinophilia, in which eosinophils account for more than 10% of WBCs, can be caused by a wide variety of benign and malignant conditions—even, in some cases, by the mere presence of air or blood in the pleural space. Approximately one third of eosinophilic effusions are idiopathic. As a rule, the presence of mesothelial cells is of little diagnostic value; the exception to this rule is that if such cells account for more than 5% of WBCs, a tuberculous effusion is unlikely.^{23,27}

Microbiologic Tests

If a PSI is suspected, Gram staining and standard bacterial cultures are indicated. If tuberculous pleurisy is a possibility, acid-fast stains and mycobacterial cultures should be performed. Fungal, viral, and parasitic PSIs are uncommon; accordingly, special stains and cultures for these conditions are indicated only if dictated by a specific clinical setting.²⁸

Cytologic Tests

Cytologic testing of pleural fluid is routinely performed whenever the cause of an effusion is unclear. The diagnostic yield for malignancy varies depending on the stage of the disease, but it generally is in the range of 50 to 60% (higher in

patients with bulky pleural tumors). Repeat cytologic testing may increase the yield to more than 70%,^{10,29} and testing of three or more samples may increase the yield to 90%.³⁰

PLEURAL BIOPSY

In approximately 25% of patients with exudative effusion, the cause remains unknown after clinical evaluation, imaging, and pleural fluid analysis. The next step in the evaluation of such patients is pleural biopsy.

Percutaneous pleural biopsy is an infrequently used tool that has a diagnostic yield of 57% for carcinoma. Its low yield for malignant effusion can be explained by the uneven distribution of pleural metastases. For tuberculous pleurisy, however, the diagnostic yield of percutaneous pleural biopsy is 75%, and the yield rises to 90% when this procedure is combined with pleural fluid culture. In about 10 to 20% of patients with exudative pleural effusion, laboratory analysis of pleural fluid and percutaneous biopsy fail to produce a specific diagnosis.¹⁸ The contraindications and complications associated with percutaneous pleural biopsy are similar to those associated with thoracentesis.³¹

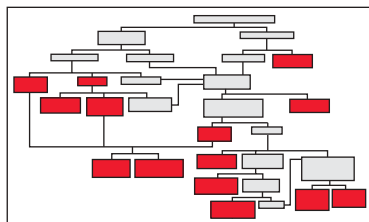
Video-assisted thoracoscopic surgery (VATS) is also employed for pleural biopsy; its diagnostic yield in this setting is 92% for malignancy and nearly 100% for tuberculous pleurisy. VATS is a therapeutic procedure as well, allowing the surgeon to perform pleurodesis, decortication, or pleurectomy if necessary. VATS pleural biopsy is typically performed with the patient under general anesthesia, but if the patient is highly debilitated, it can be done with regional and local anesthesia.³² Procedure-specific complications include hypoxemia, hemorrhage, prolonged air leakage, subcutaneous emphysema, and empyema, each of which occurs at a rate of about 2%. The mortality associated with diagnostic thoracoscopy ranges from 0.01 to 0.09%.^{29,31} When VATS is performed to remove a suspected malignant lesion, a protective plastic device is required to minimize the possibility of tumor seeding. Incisional tumor seeding after a VATS biopsy is rare but can occur at any time after the procedure (reported range 2 weeks to 29 months).³³

If mesothelioma is suspected, pleural biopsy (through a 5 cm incision) is the preferred diagnostic procedure. Ideally, the biopsy incision should be placed at the location of a potential thoracotomy incision so that future excision of the biopsy scar can be accomplished in a manner that minimizes the risk of local tumor recurrence.³⁴

Management

PLEURAL EFFUSION IN THE INTENSIVE CARE UNIT

Pleural effusion develops in as many as 60% of intensive care unit (ICU) patients evaluated with ultrasonography.¹¹ When pleural effusion occurs in the ICU, drainage should be liberally employed to optimize the patient's hemodynamic and respiratory status and to detect PSI early. Thoracentesis can be done in critically ill ventilator-dependent patients with the help of bedside



ultrasonography. Chest tube thoracostomy does not require ultrasonographic guidance and may be a safer choice for patients on high-pressure ventilation.

MALIGNANT PLEURAL EFFUSION

Pleural effusion is associated with malignancy in 30 to 65% of patients, and approximately 75% of patients with malignant effusion have lung or breast cancer.³⁵ The principal aim of therapy is to relieve dyspnea and to limit the number of procedures and hospital days that patients with a limited life expectancy must endure.

Drainage can be achieved by means of thoracentesis, chest tube placement, or VATS. Thoracentesis is a valuable option for initial patient evaluation, particularly in the office setting. Because malignant pleural effusion recurs rapidly unless patients undergo effective systemic or local treatment, repeat thoracentesis is generally not recommended for anything other than urgent relief of symptoms. Chest tubes are placed primarily with the intention of performing bedside pleurodesis.

Small-bore subcutaneously tunneled catheters may be employed for long-term management of malignant pleural effusions. Long-term drainage is preferable in patients with a very short life expectancy (≤ 3 months), patients who have a poor performance status, and patients with a trapped lung.³⁶ Two options are available: the Pleurx catheter (Denver Biomedical, Golden, Colorado) [see Figure 5] and the Tenckhoff peritoneal dialysis catheter. With either device, the procedure is essentially the same: the catheter is inserted with the patient under local or general anesthesia, the patient is discharged on the day of or the day after insertion, and the pleural fluid is drained either according to a schedule or on an as-needed basis. Small-bore tunneled catheters are comfortable, but patients may object to having a permanent catheter or to undergoing home-based procedures. In 20 to 70% of patients with a permanent catheter, pleurodesis develops within 4 to 6 weeks. Patients with malignant pleural effusions secondary to breast or gynecologic cancers are more likely to develop pleurodesis (about 70%) than patients with lung cancer (about 40%).³⁷ Catheter removal is easily done in the office setting with local anesthetic. Technical failures and infection



Figure 5 Shown is a Pleurx catheter after placement and subcutaneous tunneling. The vacuum container is not connected.

may occur in as many as 20% of patients with permanent catheters, but very few patients require operative management.^{38–41}

Pleuroperitoneal shunting has been advocated as an alternative for long-term management of malignant pleural effusions. However, experience with this mode of drainage is limited and the potential for technical complications is high.^{42,43}

Recurrence of malignant pleural effusion is best prevented by using sclerosants to induce pleurodesis. The sclerosant may be instilled either via a bedside tube thoracostomy or thoroscopically; a median hospitalization of 6.5 days is required.³⁸ Of the various sclerosants available, talc is the most efficacious, with an overall success rate of 80 to 96%.^{44–46} The ideal talc dose has not been determined; the usual dose is 4 or 5 g. Talc pleurodesis with a 5 g dose has generally proved efficient and safe. For obvious reasons, simultaneous bilateral talc instillation should be avoided.⁴⁴ A phase III intergroup study (Cancer and Leukemia Group B 9334) that compared bedside talc slurry pleurodesis versus thoroscopic talc insufflation pleurodesis found no difference in outcome at 30 days; however, subgroup analysis revealed that thoroscopic talc insufflation pleurodesis was superior in patients with primary lung cancer or breast cancer.⁴⁷ Thoroscopically guided talc pleurodesis can be performed with an operative mortality of less than 1%.^{48,49}

Pain and fever are frequent side effects of talc pleurodesis, but the main concern is the possible development of acute lung injury (ALI) and respiratory failure. Respiratory failure is reported to occur in approximately 1 to 4% of patients. The cause of respiratory failure secondary to talc pleurodesis is not clear and is probably related to multiple factors (e.g., talc dose, talc absorption, underlying lung disease, reexpansion pulmonary edema, systemic inflammatory response, tumor burden, and lymphatic obstruction). There is no definitive evidence that the talc dose is correlated with the incidence of ALI; respiratory failure has been reported even with a 2 g talc dose.^{44,50–54} Moreover, a recent multicenter prospective cohort study reported a 0% incidence of acute respiratory distress syndrome in 558 patients undergoing talc pleurodesis (4 g dose).⁵⁵

Iodopovidone (10%; 20 mL) is a very effective and inexpensive alternative for chemical pleurodesis that is of value in the setting of limited financial resources.^{56,57}

Treatment of malignant pleural effusion must be individualized. The key factors governing the choice of treatment approach are the (1) patient's performance status, (2) prognosis, (3) patient's choice, (4) ability of the lung to reexpand, and (5) pleural tumor bulk. Patients who have poor performance status (e.g., those with advanced tumors or significant comorbid conditions) or a very poor short-term prognosis should undergo the least invasive treatment—namely, drainage only. Patients who have better functional status and are expected to survive longer should preferably undergo thoroscopically guided talc pleurodesis, but it is not unreasonable for a patient to elect to have long-term drainage in this scenario. Pleural tumor bulk is important in that bulky pleural lesions will interfere with pleurodesis. The lung's ability to reexpand after drainage of a malignant effusion is significant because if the lung is atelectatic as a result of airway obstruction or trapped as a result of pleural seeding, no agent will be able to induce pleurodesis, and the best treatment will be

long-term drainage. Table 3 summarizes practical guidelines for the definitive management of malignant pleural effusion.

PLEURAL SPACE INFECTION

PSI can be caused by a variety of factors, including pneumonia, trauma, and intrathoracic procedures. It has a wide clinical spectrum, ranging from a small parapneumonic effusion (PPE) to a pus-filled pleural space (empyema) with respiratory compromise and sepsis. (The terms PSI and PPE are often used interchangeably.) PSI can be classified according to its pathophysiologic stage (exudative, fibrinopurulent, or organizing) or its anatomic appearance (nonloculated versus loculated or noncomplicated versus complicated). The term empyema is commonly reserved for the most advanced stage of PSI.⁵⁸

The pathophysiology of PSI or PPE can be divided into three stages. The exudative stage is characterized by the development of an exudative effusion secondary to increased pleural permeability; the pleural space is often sterile initially, but if it is left untreated, bacterial infection is likely to ensue. The fibrinopurulent stage is marked by the progressive deposition of fibrin and the increasing presence of WBCs; gradual angioblastic and fibroblastic proliferation leads to extensive fibrin deposits, and the effusion becomes loculated (complicated). The organizing stage starts as early as 1 week after infection, with increasing collagen deposition and lung entrapment; after 3 or 4 weeks, the organized collagen has formed a peel. The pleural fluid is grossly purulent. Eventually, dense fibrosis, contraction, and lung entrapment develop.^{59,60}

In most patients, PSI is caused by bacteria. The most common pathogens are *Staphylococcus aureus*, *Streptococcus pneumoniae*, enteric gram-negative bacilli, and anaerobes. Approximately 30 to 40% of cultures are polymicrobial. In a subgroup of patients, there is sterile pus in the pleural space as a consequence of either previous antimicrobial therapy or bacterial autolysis. The pathogens identified vary according to the cause of PSI. For instance, *S. aureus* and *S. pneumoniae* predominate in PPE, *S. aureus* in postthoracotomy PSI, mixed oropharyngeal organisms in PSI resulting from esophageal perforation,²⁸ and acid-fast bacteria in tuberculous empyema.⁶¹

Parapneumonic Effusion

PPE occurs in as many as 57% of patients hospitalized with pneumonia, and pneumonia accounts for 42 to 73%

Table 3 Practical Guidelines for Definitive Management of Malignant Pleural Effusion

Patient Characteristics	Chemical Pleurodesis	Long-Term Drainage
Performance status		
Good	Yes	Yes
Poor	No	Yes
Life expectancy		
> 6 mo	Yes	Yes
3–6 mo	Individualize	Yes
< 3 mo	No	Yes
Bulky pleural implants	Individualize	Yes
Trapped lung	No	Yes

of cases of PSI. In most cases, early PPE is effectively treated by timely antibiotic therapy aimed at the underlying pneumonia.^{21,28}

In 2000, a panel convened by the Health and Science Policy Committee of the American College of Chest Physicians (ACCP) reviewed the available literature with the aim of developing an evidence-based clinical practice guideline for the treatment of PPE.²¹ The panel formulated a clear and relatively simple classification system that used pleural anatomy and bacteriology to stratify patients according to the risk of a poor outcome [see Table 4]. It then made therapeutic recommendations on the basis of this classification. Some authors have used pleural fluid chemistry test results (e.g., pH and glucose concentration) as additional criteria for categorizing PPE; for example, a pleural fluid pH lower than 7.20 or a glucose level lower than 60 mg/dL has been considered suggestive of moderate risk. To date, however, the clinical utility and decision thresholds of pH and glucose values have not been well defined. Accordingly, the panel omitted pleural fluid chemistry from its guidelines.

The ACCP Health and Science Policy Committee evaluated six primary management approaches: no drainage, therapeutic thoracentesis, tube thoracostomy, fibrinolytic therapy, VATS, and open surgery. Overall, pooled outcomes favored patients treated with fibrinolytics, VATS, and open surgery. However, the success of an approach is related to the patient's risk category. The recommendations for drainage in relation to risk category are general guidelines, based on level C and D evidence (with level C referring to historically controlled series and case series and level D to expert opinion). With these recommendations (and their limitations) in mind, treatment should be tailored to the specific situation of each patient.

Category 1 and 2 PPE PPE in categories 1 (very low risk) and 2 (low risk) can be treated with antibiotic therapy directed at the underlying pneumonia. Some patients with category 2 PPE may require drainage for relief of dyspnea through either thoracentesis or tube thoracostomy.

Category 3 and 4 PPE Drainage options for category 3 (moderate risk) and 4 (high risk) PPE include tube thoracostomy alone, tube thoracostomy with intrapleural fibrinolytic therapy, VATS drainage, and open surgical drainage. These various approaches are not mutually exclusive: in some cases, patient outcomes may be optimized by a combination of treatment modalities.⁶²

Tube thoracostomy alone may be appropriate for category 3 patients with free-flowing effusion. With loculated effusion, however, the key to successful therapy is breaking down the fibrin septations. Evidence from three small randomized, controlled trials suggested that intrapleural fibrinolytic therapy has an advantage over tube thoracostomy alone for patients with category 3 or 4 PPE; a large trial is being conducted to address this specific issue.⁵⁹ To date, only one randomized study, including 20 patients with category 3 or 4 PPE, has compared VATS with fibrinolytic therapy. The primary treatment success rate was significantly higher in the VATS treatment group, the duration of chest tube drainage was less, and the total hospital stay was shorter.⁶³ VATS allows not only adequate drainage and visualization of the pleural space but also decortication of the lung if required; however, if decortication cannot be thoroughly accomplished by means of VATS and satisfactory lung expansion cannot be achieved, a thoracotomy should be performed.^{64,65}

The principles of PPE treatment can be applied to PSI from any cause, but in view of the paucity of reliable data, caution should be exercised.

Posttraumatic PSI

PSI occurs in about 1 to 5% of patients who have sustained blunt or penetrating thoracic injury. The incidence of PSI in the setting of trauma increases with the number of chest tubes placed and with the duration of chest tube drainage. The effect of an undrained hemothorax on the risk of PSI has not been completely defined, and prophylactic antibiotics have not been shown to reduce the incidence of PSI.⁵⁸

As noted (see above), the general guidelines for the treatment of PPE apply to the treatment of posttraumatic PSI.

Iatrogenic PSI

Iatrogenic PSI develops when a preexisting pleural effusion is inoculated with bacteria during an invasive procedure (e.g., thoracentesis or tube thoracostomy). The presence of fluid in the pleural space appears to be a prerequisite for infection.⁵⁸

A bronchopleural fistula (BPF) is by definition a PSI and therefore has a similarly broad spectrum of clinical presentation. The overall incidence of BPF after lobar resection is approximately 1%; it is somewhat higher after resections for inflammatory diseases than after resections for cancer. The incidence of BPF after pneumonectomy varies depending on the side on which the pneumonectomy was done, the indications for surgery, the extent of preoperative irradiation,

Table 4 Categorization of Parapneumonic Effusion by Risk of Poor Outcome

Pleural Space Anatomy	Pleural Fluid Bacteriology	Category	Risk of Poor Outcome	Drainage
Minimal free-flowing effusion (< 10 mm on lateral decubitus x-ray)	Culture and Gram stain results unknown	1	Very low	No
Small to moderate free-flowing effusion (> 10 mm but < 50% hemithorax)	Negative culture and Gram stain	2	Low	No
Large free-flowing effusion (> 50% hemithorax), loculated effusion, or effusion with thickened parietal pleura (as seen on contrast-enhanced CT)	Positive culture or Gram stain	3	Moderate	Yes
	Pus	4	High	Yes

CT = computed tomography.

and the comorbid conditions present. In a report encompassing 464 pneumonectomies for cancer, the incidence of BPF was 8.6% after right pneumonectomy and 2.3% after left pneumonectomy.^{66,67}

Almost every PSI after a lung resection is synonymous with BPF, and operative management is generally required.

Tuberculous PSI

Pleural effusion is common in patients with clinically evident pulmonary tuberculosis. Most cases of tuberculous effusion are secondary to hypersensitivity and resolve spontaneously. Tuberculous empyema is relatively rare; it is typically the result of active pleural infection by acid-fast bacteria.⁶¹

Tuberculous PSI is also treated in accordance with the general treatment guidelines for bacterial PSI. Chronic tuberculous PSI may present specific problems, such as drug resistance and impaired ability (or even inability) to reexpand the lung. Surgical procedures performed to manage chronic tuberculous empyema include VATS, standard open decortication, thoracoplasty, parietal wall collapse, open drainage, myoplasty, and omentopexy.⁶¹

CHYLOTHORAX AND PSEUDOCYLOTHORAX

Chylothorax is the presence of chyle in the pleural space as a consequence of blockage of or damage to the thoracic duct or one of its tributaries. The rate at which chyle flows through the thoracic duct can be higher than 100 mL/hr; thus, large amounts of chyle can leak into the pleural space.⁶⁸ The principal causes of chylothorax are surgical trauma and malignancy (70 to 80% are caused by non-Hodgkin lymphoma).^{49,68,69} Congenital chylothorax is more often attributable to malformation of the thoracic duct than to birth trauma.²⁴

The diagnosis of chylothorax is made by measuring triglyceride levels in pleural fluid. Levels higher than 110 mg/dL are highly suggestive of chylothorax, levels between 50 and 100 mg/dL are equivocal, and levels lower than 50 mg/dL rule out chylothorax.²⁴ A pleura-to-serum triglyceride ratio higher than 1 can be a useful indicator⁷⁰; the presence of chylomicrons is synonymous with chylothorax.²⁵

Treatment of chylothorax depends on its cause and severity. Postoperative chylothorax may be treated initially with conservative measures (e.g., with a nihil per os [NPO] regimen, total parenteral nutrition, and administration of octreotide). However, drainage totaling more than 500 mL/day is considered to predict failure of conservative management. Thoracic duct ligation is the surgical treatment of choice and can often be performed thoracoscopically. To help identify the leak intraoperatively, it may be helpful to administer 100 to 200 mL of heavy cream or olive oil orally 2 to 3 hours before operation.^{71,72} Early surgical intervention is important because the ongoing loss of lymph has significant effects on fluid homeostasis, nutrition, and immunocompetence (secondary to lymphocyte loss). In the early postligation period, medical management should be continued to allow any small leaks to seal. An alternative to surgical ligation that has evoked some interest is transabdominal percutaneous embolization of the thoracic duct. This technique requires significant expertise.⁷³

Lymphoma-related chylothorax is caused principally by obstruction and usually develops on the left side [see *Figure 6*]. In a stiff and infiltrated duct, minor triggers (e.g., a Valsalva maneuver) can lead to duct rupture. Although patients with chylothorax often have extensive disease, supradiaphragmatic disease is not always present. Lymphoma-related chylothorax is best managed with thoracentesis and with therapy directed at the underlying cause. If first-line therapy fails, thoracoscopic talc pleurodesis is recommended; a small series reported 100% resolution of lymphoma-related chylothorax with thoracoscopic talc pleurodesis. If the chylothorax does not respond to any of these approaches, it may respond to thoracic duct ligation or pleuroperitoneal shunting. Chylothorax in the presence of lymphoma-related chylous ascites is a difficult problem that is generally refractory to most forms of therapy (although pleurodesis is occasionally successful).^{49,68,69,74,75}

Pseudochylothorax is a rare disorder associated with the formation of persistent exudates that last for months or years. The most common cause is tuberculosis; the second most common cause is rheumatoid arthritis. Biochemical analysis of pleural fluid from patients with pseudochylothorax reveals very high cholesterol levels (> 200 mg/dL) and the presence of cholesterol crystals. Treatment is generally conservative.^{24,25}

IDIOPATHIC PERSISTENT PLEURAL EFFUSION

In a small percentage of patients, the cause of pleural effusion remains unknown despite extensive diagnostic evaluation. Eventually, most cases of idiopathic effusion turn out to be caused most frequently by tuberculosis and other granulomatous diseases, malignancy, and pulmonary embolism; less common causes include constrictive pericarditis, subphrenic abscess, connective tissue diseases, drug-induced pleuritis, peritoneal dialysis, and cirrhosis.²³ In the management of persistent benign or idiopathic effusion, talc pleurodesis has a high success rate and minimal long-term implications.^{76,77} A chronic drainage catheter (i.e., Pleurx) can be used for refractory pleural effusion in patients with congestive heart failure; however, prolonged use (> 4 months) can lead to empyema.⁷⁸

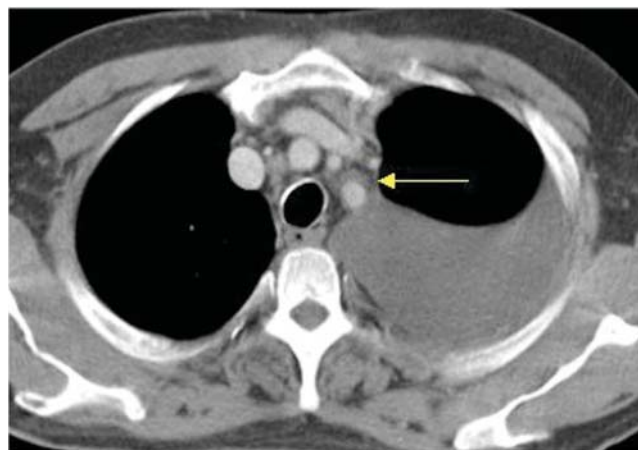


Figure 6 Chest computed tomographic scan shows left-side chylothorax secondary to lymphoma. Subtle mediastinal lymphadenopathy obstructing the thoracic duct (arrow) is apparent.

Hence, in the setting of a benign, refractory pleural effusion, a chronic drainage catheter should be considered only as a last resort.

Pleura: Basic Facts

PLEURAL ANATOMY

The pleura is a continuous membrane that covers the parietal and visceral surfaces of the thorax. In adults, it has an estimated surface area of 2,000 cm².⁷⁹ Light microscopy shows the pleura to have five layers: (1) a mesothelial cell layer; (2) a mesothelial connective tissue layer with basal lamina; (3) a superficial elastic layer; (4) a loose connective tissue layer with adipose tissue, blood vessels, nerves, and lymphatic vessels; and (5) a deep fibroelastic layer. The parietal pleura establishes a pleurolymphatic communication on the diaphragm to allow clearance of large (> 1,000 nm) particles and cells from the normal pleural space. The structure of this pleurolymphatic communication consists of stomata 2 to 12 µm in diameter, which overlie bulblike lymphatic channels (lacunae) separated by a layer of loose connective tissue (the membrana cribriformis).

Electron microscopy reveals microvilli on the mesothelial cell surface of the pleura. The main function of these microvilli is to enmesh glycoproteins rich in hyaluronic acid for

purposes of lubrication. The structure of the intercellular junction in the mesothelial cells of the pleura is similar to that in the endothelial cells of the venules, which suggests that the pleural mesothelial cell layer may be as leaky as the venular endothelium.^{3,4,80}

PLEURAL FLUID PHYSIOLOGY

The amount of pleural fluid in an adult is 1 to 10 mL and forms a 10 µm thick layer.^{1,3,79,80} Fluid exchange across the pleural surface depends on three mechanisms: (1) passive filtration following Starling equilibrium, (2) active solute transport, and (3) lymphatic clearance. In the normal pleura, Starling equilibrium favors the flow of fluid in a parietal-to-visceral direction.⁷⁹ The rate at which fluid traverses the pleura ranges from 20 to 160 mL/day in adults; maximal lymphatic clearance is believed to be approximately 700 mL/day.^{2,79,81–84}

The chemical composition of normal pleural fluid is similar to that of interstitial fluid. The protein concentration is typically 1 to 2 g/dL. The concentration of high-molecular-weight proteins (e.g., LDH) is approximately half that seen in serum. Cell counts in normal pleural fluid range from 1,400 to 4,500 cells/µL; macrophages account for the majority of the cells.^{3,80}

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5 SOLITARY PULMONARY NODULE

Taine T.V. Pechet, MD, FACS*

Assessment of a Solitary Pulmonary Nodule

The solitary pulmonary nodule (SPN) is a common finding that is observed in more than 150,000 persons each year in the United States.¹ An SPN is defined as a single radiographically visible pulmonary lesion that is less than 3 cm in diameter, is completely surrounded by pulmonary parenchyma, and is not associated with atelectasis or adenopathy.² Any pulmonary lesion larger than 3 cm is considered a mass and as such has a greater likelihood of being malignant.^{3,4} SPNs are detected on routine chest radiography at a rate of 1 in 500 x-rays, but with the growing use of computed tomographic (CT) scanning, they are now being diagnosed with increasing frequency.

The differential diagnosis of an SPN is broad and includes vascular diseases, infections, inflammatory conditions, congenital abnormalities, benign tumors, and malignancies [see Table 1]. Although most SPNs are benign, as many as one third represent primary malignancies, and nearly one quarter may be solitary metastases.^{1,5,6} Various approaches have been developed to aid in the characterization and identification of SPNs. Certain clinical characteristics—such as greater age, history of tobacco use, and previous history of cancer—have been shown to increase the likelihood that the SPN is malignant.⁷ Some authors have attempted to use the Bayes theorem, logistic regression models, or neural network analysis to predict the likelihood of malignancy.⁷⁻⁹ Such methods are highly sensitive and specific, but they are cumbersome and of limited clinical applicability.

Clinical Evaluation

Once an SPN has been identified, it is necessary to determine whether the lesion is benign or malignant and what further investigations should be pursued. Evaluation should generally be governed by the dictum “malignant until proven otherwise.” The basis for an initial assumption of malignancy is the observation that the overall 5-year survival rate is low (10 to 15%) once a diagnosis of lung cancer is established.¹⁰ Appropriate evaluation involves careful assessment of the patient’s history and risk factors for malignancy in conjunction with the results of radiographic studies [see Investigative Studies, below] to develop an individualized care plan.

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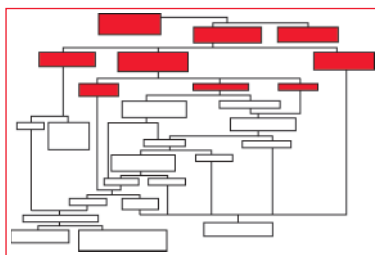


Table 1 Differential Diagnosis of Solitary Pulmonary Nodule

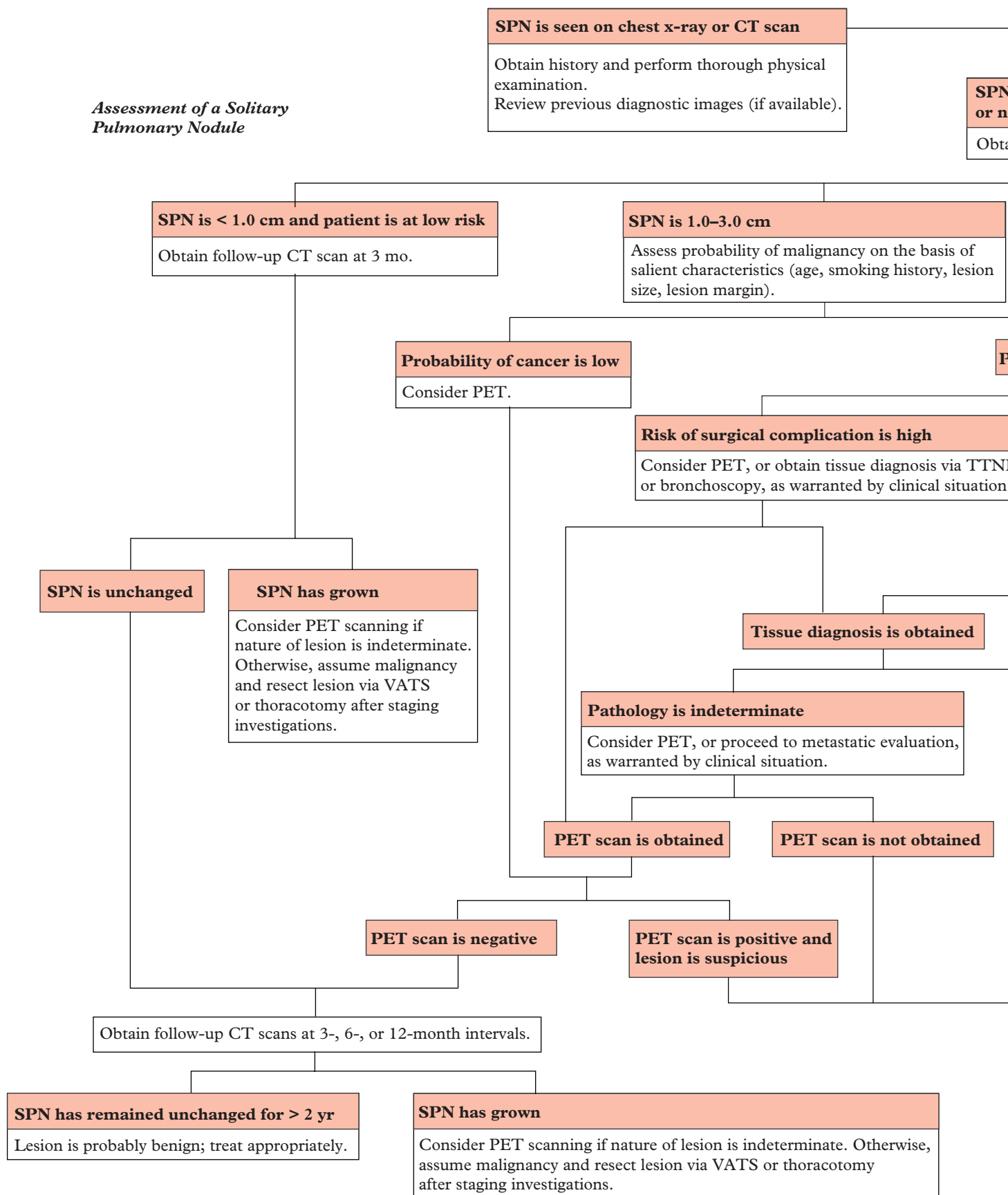
Behavior	Category	Disease
Benign	Vascular disease	Arteriovenous malformations Pulmonary artery aneurysm
	Infection	<i>Mycobacterium avium</i> complex infection Aspergilloma Histoplasmosis Echinococcosis Blastomycosis Cryptococcosis Coccidioidomycosis Ascariasis Dirofilariasis
	Inflammatory condition	Rheumatoid nodule Sarcoidosis Wegener granulomatosis
	Congenital abnormality	Foregut duplication cyst
	Other	Rounded atelectasis Pulmonary amyloidosis
	Benign tumor	Hamartoma Lipoma Fibroma
Malignant	Primary lung cancer	Non-small cell lung cancer Squamous cell carcinoma Adenocarcinoma Large cell cancer Bronchoalveolar carcinoma Small cell lung cancer Carcinoid Lymphoma
	Metastatic cancer	Colon cancer Testicular cancer Melanoma Sarcoma Breast cancer

FACTORS INFLUENCING PROBABILITY OF MALIGNANCY

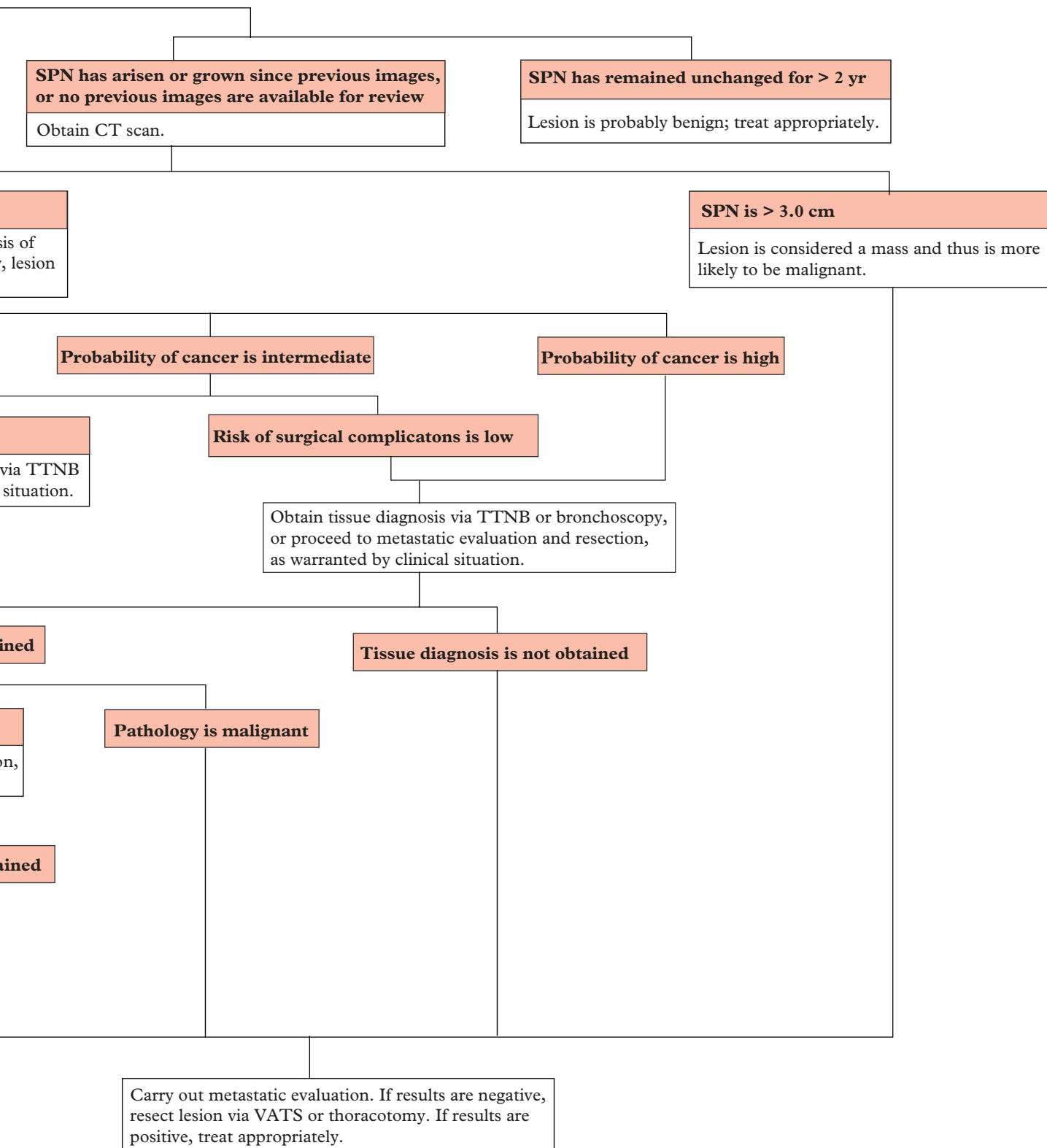
A number of factors influence the probability that an SPN is malignant. Those most strongly associated with lung cancer are age, smoking history, and occupational history. Pulmonary function test results indicative of a severe obstructive ventilatory impairment are also associated with an increased likelihood of malignancy.¹¹ In addition, the presence of endemic granulomatous disease has been shown to increase the probability that an SPN is harboring cancer.⁷

The radiographic appearance of an SPN, particularly on a CT scan, also influences the probability of malignancy

*Assessment of a Solitary
Pulmonary Nodule*



SPN = solitary pulmonary nodule; CT = computed tomography; PET = positron emission tomography; VATS = video assisted thoracic surgery; TTNB = trans-thoracic needle biopsy.



[see Investigative Studies, Imaging, Computed Tomography, below]. The size, contour, internal characteristics, and growth rate of the nodule are all potentially significant indicators of malignant disease [see Table 2].

Age

Lung cancer is rare before the age of 40 years, but its incidence steadily increases from that point until the age of 80.⁵ Above the age of 70, the likelihood that an SPN is malignant increases.⁸ After the age of 80, the incidence of malignancy in an SPN seems to level off or even decrease.¹²

Environmental Exposures

The link between cigarette smoking and lung cancer has been well established since the 1950s, and the incidence of lung cancer in smokers is directly correlated with the number of pack-years of smoking.¹³ The surgeon general's report from 2004 states that "the evidence is sufficient to infer a causal relationship between smoking and lung cancer."¹⁴ There is also ample evidence of a causal relationship between environmental tobacco exposure, termed "secondhand smoke," and lung cancer.¹⁵

Radon exposure is the second leading cause of lung cancer in America, and cigarette smoking further increases the risks associated with radon exposure.¹⁶ Asbestos exposure in combination with cigarette smoking also places patients at significantly increased risk for lung cancer. Patients with a history of workplace exposure to a radioactive substance (e.g., uranium or plutonium) are at increased risk for lung cancer, but this association is not as well documented as the association of lung cancer with tobacco use. Miners of heavy metals (e.g., nickel, cadmium, and silica) are also at increased risk, and a variety of other environmental toxins, from diesel exhaust through vinyl, have been associated with the development of lung cancer.¹⁵ There is some evidence to suggest that patients with idiopathic pulmonary fibrosis and pneumoconiosis are at increased risk for bronchoalveolar cell carcinoma.¹⁷

Table 2 Factors Affecting Malignant Probability of Solitary Pulmonary Nodule⁸

Factor	Likelihood Ratio for Malignancy
Spiculated margins on CT scan	5.54
Age > 70 yr	4.16
Lesion size 2.1–3.0 cm	3.67
Doubling time < 465 days	3.40
History of smoking	2.27
Age 50–69 yr	1.90
Lesion size 1.1–2.0 cm	0.74
Lesion size < 1 cm	0.52
Smooth margins on CT scan	0.30
No history of smoking	0.19
Doubling time > 465 days	0.01

CT = computed tomographic.

Investigative Studies

IMAGING

Chest Radiography (X-Ray)

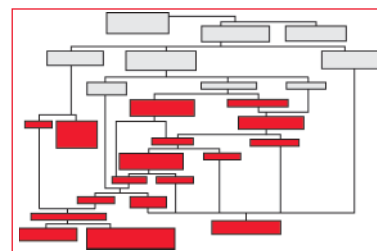
Whereas the prevalence of lung cancer is low in comparison with that of breast or prostate cancer, the mortality for lung cancer exceeds that for breast, prostate, and colon cancer combined. As noted [see Clinical Evaluation, above], the overall 5-year survival rate for lung cancer patients is poor, in part because lung cancer is frequently diagnosed at a more advanced stage than other forms of cancer. Several trials performed before the advent of CT scanning evaluated chest radiography for early screening of lung cancer but were unable to demonstrate that such screening yielded better survival.^{18–20} One explanation for these disappointing results may be that fewer than 10% of lung cancers are stage I at presentation.¹⁸

Although chest radiography is ineffective as a screening tool for early-stage lung cancer, it remains a valuable investigative tool in the evaluation of SPNs. If an SPN's appearance on chest x-rays has not changed for more than 2 years, the SPN will be benign in more than 90% of cases. In such cases, only yearly follow-up is typically required; additional diagnostic tests are usually unnecessary.^{21,22} Therefore, an effort should always be made to obtain old chest radiographs if they are known to exist.

Computed Tomography

The advent of CT scanning has led to an increase in the number of SPNs detected.²³ But, of course, it has also led to an increase in the number of benign SPNs found. Advocates of CT scanning for assessment of SPNs base their argument on two central points. First, as many as 83% of CT-detected stage I malignancies are not visible on chest x-ray.²⁴ Second, non-small cell lung cancer (NSCLC) is the malignancy most commonly identified, and the survival rate for stage I NSCLC is relatively high in comparison with more advanced disease stages. In patients whose SPN proves to be NSCLC, the 5-year survival rate is 67% for stage IA disease. This figure falls rapidly as the disease stage rises: the 5-year survival rate is 55% for stage IIA NSCLC and only 10% for stage IIIA NSCLC with mediastinal nodal metastasis.²⁵

Numerous studies have evaluated the use of screening CT both in the general population and in at-risk groups consisting of older patients with a smoking history.^{24,26,27} The greatest drawback to screening CT is the high false positive rate: nodules are identified on 23 to 66% of all CT scans, depending on the thickness of the slices,^{12,24} and nearly 98% of these nodules are eventually determined to be benign. Sequential CT scanning is often required to determine whether an SPN is benign or malignant. In 10 to 15% of patients, however, this determination cannot be made even when two CT scans are compared. Such patients may be assessed with other imaging modalities (e.g., positron emission tomography [PET]) or may be referred for transthoracic needle biopsy (TTNB) or other invasive diagnostic tests.



Controversy exists in both the literature and in clinical practice around the optimal intervals for follow-up CT scanning after initial identification of an SPN. In the literature, the recommended interval between initial CT scanning and repeat CT scanning has ranged from 1 month to 1 year.^{12,24,27} These varying recommendations are based on what is considered the doubling time for an SPN. In a study from 2000 that included 13 patients with a known diagnosis and lesions less than 10 mm in diameter at initial evaluation, volumetric growth rates were measured to establish the doubling times of the nodules.¹⁰ The doubling times ranged from 51 days to more than 1 year. For malignant lesions, the average doubling time was less than 177 days, whereas for benign lesions, it was more than 396 days. New volumetric modeling methods have been developed that may be capable of detecting conformational changes over much shorter intervals, but they remain infrequently used.²⁸ Because the doubling time is considerably shorter for malignant lesions than for benign lesions, a repeat CT scan should typically be performed for most lesions 3 months after the initial study. If the lesion is visibly larger on the repeat scan, it is likely malignant, and diagnostic evaluation should progress toward presumed resection. If, however, the lesion has neither regressed nor progressed, a follow-up CT scan closer to 12 months is warranted; the precise timing remains controversial and should be determined on the basis of individual patient and SPN characteristics. The Fleischner Society Statement from the Radiological Society of North America provides commonly cited guidelines for the radiographic evaluation of nodules, with recommendations divided into size categories and recommendations that range from 3 to 12 months.²⁹

The morphologic characteristics of an SPN visualized on a CT scan can be extremely helpful in characterizing the probability of malignancy [see Differential Diagnosis, *below*]. Size, margin appearance, cavitation, and attenuation are important criteria. Air bronchograms, ground-glass opacity, and adjacent vascular distortion patterns can also help suggest malignancy. Although an SPN with a spiculated margin is perhaps most suspicious for malignancy, one fifth of lung cancers may have well-defined margins.^{30,31} Within areas of ground-glass opacity, characteristic changes, such as the development of nodularity and solid attenuation, have been identified that increase the probability of malignancy.^{32–34} Other CT characteristics may point more toward a benign condition. For example, although cavitation may occur in either benign or malignant lesions, SPNs with walls thinner than 4 mm are much more likely to be benign, whereas those with walls thicker than 16 mm are more likely to be malignant.³⁵ Intranodular fat is a reliable indicator of a hamartoma, a benign lesion, and is seen in as many as 50% of hamartomas.³⁶ In addition, calcification is most commonly associated with hamartomas and other benign nodules. Unfortunately, between one third and two thirds of benign lesions visualized are not calcified, and as many as 6% of malignant lesions are calcified.^{31,37,38} Finally, increased enhancement (measured in Hounsfield units [HU]) after injection with intravenous contrast is strongly suggestive of malignancy and has been included in the American College of Chest Physicians (ACCP) consensus recommendations.³⁹ Lesions that enhance by less than 15 HU are most likely benign (positive predictive value 99%), whereas lesions that enhance by more than 20 HU

are typically malignant (sensitivity 98%; specificity 73%).⁴⁰ Lesions that enhance by 15 to 20 HU should be considered indeterminate.

Because most SPNs are benign and because the risk of misdiagnosing a malignant lesion is so great, it is important to make use of all of the data obtained from CT scanning in the effort to make cost-effective, logical decisions regarding further evaluation or treatment. Careful evaluation of the size, contours, and internal characteristics of an SPN on successive CT scans, balanced by the patient's risk profile, including age, smoking history, and environmental exposures, provides the framework for developing an individualized evaluation strategy

Positron Emission Tomography

PET is an imaging modality that employs radiolabeled isotopes of fluorine, carbon, or oxygen; the most commonly used isotope is ¹⁸F-fluorodeoxyglucose (FDG). The rationale for FDG-PET scanning in the evaluation of SPNs is based on the higher metabolic rate of most malignancies and the preferential trapping of FDG in malignant cells.⁴¹ However, increased FDG activity can also occur in benign SPNs,^{42,43} especially those arising from active granulomatous diseases^{44,45} or inflammatory processes.⁴⁶ These benign diseases can produce false positive PET scans and thereby reduce the sensitivity of the test. Conversely, some malignancies—bronchoalveolar carcinoma and carcinoid tumors, in particular—have low metabolic activity and commonly produce false negative PET scans.^{47–51} Thus, a negative PET scan is not a particularly helpful result, and it is necessary to follow the lesion with serial CT scans. Accuracy calculations for PET scanning vary widely, with some of the highest sensitivity and specificity figures reported in an early meta-analysis identifying sensitivity of 96% and specificity of 77%.⁵² More recent pooled sensitivity and specificity figures were 87% and 83%, with specificity ranging from 40 to 100%.³⁹

Efforts have been made to improve the sensitivity and specificity of PET scanning in the diagnosis of SPNs. One such effort involves the use of the standardized uptake value (SUV), which is a numerical indication of the activity concentration in a lesion, normalized for the injected dose.⁵³ In many studies, an SPN is considered malignant when its SUV is higher than 2.5. Because of the methodology used to calculate SUV, however, small tumors (< 1.0 cm) may have an SUV lower than 2.5 and still be malignant. Their small volume causes their true activity concentration to be underestimated, with the result that their SUV drops below the threshold value for malignancy. In one prospective study of patients with SPNs, the overall sensitivity of FDG-PET scanning was 79% and the overall specificity was 65%.⁵⁴ When the SPN was smaller than 1.0 cm, however, all of the scans were negative, even though 40% of the nodules were malignant. Another effort involves recent technology combining PET and CT scans. CT-PET fusion imaging is clinically available in many locales, and combination imaging has been found to be particularly important for staging.^{55,56}

In cases where the SPN is larger than 8 mm and no previous radiographs or CT scans are available for comparison, PET scanning can provide information that may facilitate the decision whether to follow the lesion closely or to proceed with tissue acquisition. ACCP consensus recommendations

include the use of PET scanning in select lesions greater than 8 mm identified in patients with low to moderate pretest probability of malignancy.³⁹ Cost analysis is also an important criterion in considering PET scanning. One study that examined the cost-effectiveness of PET in the evaluation of SPNs concluded that it was cost-effective for patients who had an intermediate pretest probability of a malignant SPN and who were at high risk for surgical complications.⁵⁷ In all other groups, PET was not cost-effective, and CT led to similar outcomes (in terms of quality-adjusted life-years) and to lower costs.

BIOPSY

If an SPN displays characteristics suggestive of malignancy, a tissue diagnosis should be obtained. In many cases, the appropriate form of tissue acquisition will be excisional biopsy by wedge resection, often followed by anatomic lung resection. Traditionally, excisional biopsy was performed, accepting the morbidity associated with thoracotomy. Especially for peripheral lesions, however, video-assisted thoracic surgery (VATS) has now supplanted thoracotomy as the procedure of choice. However, several alternative biopsy techniques may be performed in place of resection, including TTNB and bronchoscopy.

Transthoracic Needle Biopsy

Lesions that are between 1.0 and 3.0 cm in diameter should be considered for TTNB. The diagnostic yield of this procedure for SPNs is excellent, reaching 95% in some studies. The reported sensitivity ranges from 80 to 95% and the specificity ranges from 50 to 88%.^{58–60} A study of 222 patients who underwent TTNB for an SPN reported a positive predictive value of 98.6% and a negative predictive value of 96.6%⁶¹; however, several other studies reported false negative rates ranging from 3 to 29%.^{58,62} The complication rate associated with TTNB is relatively high—potentially as high as 30% and rarely lower than 10%, in even the most experienced hands.^{59,63} Most commonly, a pneumothorax results; however, chest tube placement is required only if the patient becomes symptomatic, a situation that occurs in approximately 50% of cases. In the absence of symptoms, observation with serial chest x-rays is generally appropriate. If no increase in the size of the pneumothorax is observed, the patient can be discharged with the expectation that the pneumothorax will resolve.

For lesions smaller than 1.0 cm, the risk-to-benefit ratio of TTNB rises to the point where other techniques are typically preferred. The utility of TTNB depends primarily on the characteristics of the SPN—in particular, its location. Nodules that are central or close to the diaphragm or the pericardium are less well suited to this technique than those at other sites.

Bronchoscopy

Bronchoscopy has a well-established role in the evaluation of central SPNs, which are amenable to direct visualization and biopsy. Most SPNs, however, are not central. Various adjunctive measures, including transbronchial needle biopsy and cytology brushings, are employed to improve the yield of bronchoscopy. For SPNs between 2.0 and 3.0 cm in diameter, the diagnostic yield of bronchoscopy ranges from 20 to

80%, depending on the size of the lesion, the incidence of malignancy in the study population, and the proximity of the lesion to the bronchial tree.^{64,65} For SPNs smaller than 1.5 cm, the yield drops to 10%.⁶⁶ Even though bronchoscopy has a low complication rate (about 5%), its low diagnostic yield for malignancy limits its utility in the evaluation of SPNs.

New technology has allowed the application of guidance techniques to the field of bronchoscopy. Ultrasound transducers affixed to the tip of a bronchoscope, endobronchial ultrasonography (EBUS), has become an important tool in mediastinal staging, with EBUS-transbronchial needle aspiration (EBUS-TBNA) sensitivities in the range of 92% and specificities of 98% reported.⁶⁷ Electromagnetic navigational bronchoscopy (ENB) uses three-dimensional CT reconstructions to provide guidance for bronchoscopic sampling of peripheral lesions. The diagnostic yield for peripheral lesions is in the range of 70%,⁶⁸ and experience within the community is growing. ENB is a technique that can provide tissue from central nodules as well as an alternative to TTNB or VATS for peripheral lesions, and offers the ability to place a fiducial marker for subsequent radiation therapy guidance.

Excisional Biopsy

The decision to proceed to excisional lung biopsy (open or VATS) must be carefully considered. The risk-to-benefit ratio of excisional biopsy for an individual patient is determined by clinical characteristics affecting perioperative morbidity and mortality, as well as by the expected risk of malignancy in the SPN.

Resection is the reference standard for tissue acquisition. The morbidity associated with VATS is less than that associated with thoracotomy; accordingly, when VATS lung biopsy is technically feasible, it is preferable to open lung biopsy. The overall morbidity is lower than 1% for VATS wedge resection, compared with 3 to 7% for the equivalent open procedure. Patients who have undergone VATS resection experience less pain, have shorter hospital stays, and recover sooner than those who have undergone open biopsy.^{69–71}

A technical consideration that must be contemplated when VATS is planned is possible conversion to thoracotomy. The conversion rate for VATS to thoracotomy has been reported to be as high as 33%, but there is evidence to suggest that this rate can be significantly reduced with careful patient selection and increasing experience in minimally invasive techniques.^{72,73} For example, modern experience with VATS techniques has demonstrated a low conversion rate of 2.5% in a series of 1,100 patients undergoing the more complex VATS lobectomy procedure.⁷⁴

Peripheral SPNs more than 1.0 cm in diameter are the lesions best suited to VATS excision. As SPNs become smaller and more central, they become harder to identify, and the rate of conversion to thoracotomy or the need to perform an anatomic resection increases. A wide variety of techniques have been employed to improve the identification of SPNs for VATS, ranging from dye staining through guide-wire localization. One of the more recent developments has been the use of technetium-labeled microalbumin combined with a gamma probe to successfully resect 96% of lesions using thoracoscopic techniques.⁷⁵ Despite demonstrated cost-effectiveness,⁷⁶ however, none of these techniques have

achieved wide acceptance, and most surgeons rely on digital palpation combined with radiographic guidance.

Differential Diagnosis

MALIGNANT LESIONS

Non–Small Cell Lung Cancer

As noted, NSCLC is the malignancy most frequently identified in an SPN. Most lung cancer patients are asymptomatic, and those who are symptomatic usually have advanced disease, including mediastinal lymph node involvement. Arterial invasion has also been shown to have an adverse effect on survival in patients with early-stage NSCLC.⁷⁷ The most common sites of metastases are the lymph nodes, the brain, the bones, and the adrenal glands. Accordingly, it is essential to perform a metastatic evaluation that focuses on these areas before proceeding with resection.

Adenocarcinoma and squamous cell carcinoma remain the most common types of NSCLC, but bronchoalveolar carcinoma is a well-differentiated subtype that has a prolonged doubling time. Because of its slow growth rate, it may be missed by PET scan.⁴⁹ Bronchoalveolar carcinoma may present as an SPN, particularly with a ground-glass appearance, as airspace disease, or as multiple nodules.

Small Cell Lung Cancer

Small cell carcinoma accounts for approximately 20% of lung cancers. Typically, it presents as a central mass in association with significant nodal disease, often accompanied by distant metastases.⁷⁸ Small cell carcinoma typically has a very short doubling time. Paraneoplastic syndromes are more common with small cell lung cancer than with NSCLC.

Pulmonary Carcinoid Tumor

Pulmonary carcinoid tumors are uncommon neuroendocrine neoplasms that account for 1 to 2% of lung cancers.⁷⁹ They are classified as either typical or atypical, depending on their histology, but represent a spectrum of neuroendocrine tumors.⁸⁰ Either type of carcinoid may present as an SPN, usually in the fifth or sixth decade of life. Typical carcinoid tumors have a very long doubling time—up to 80 months—and thus may be mistaken for benign lesions.⁸¹ Atypical carcinoid tumors have a much shorter doubling time and are more likely to show an increase in size on serial CT scans. Typical carcinoid tumors have an extremely low incidence of recurrence and are not usually associated with nodal metastasis.

Metastatic Malignancies

Metastases to the lung frequently appear as smooth, round, well-demarcated lesions. They often are multiple, tend to be found in the better vascularized lower lung zones, and rarely are associated with mediastinal adenopathy. Most pulmonary metastases derive from the lungs, the colon, the testicles, the breasts, melanomas, or sarcomas. Treatment tends to be palliative, based on the diagnosis of the primary tumor, but it may be curative in cases of metastatic sarcoma or testicular carcinoma. In patients with these cancers, limited wedge resection of a metastasis to the lung has been shown to confer a survival advantage; this measure may also be beneficial for

patients with metastatic head and neck cancer and, occasionally, for those with metastatic melanoma.⁸² Recent reports with modern chemotherapeutic strategies and resection have suggested that prolonged survival is possible in colorectal cancer metastatic to the lung, with 5-year survival of 67%.⁸³ Improved outcomes are thought to be more likely in colorectal cancer patients with less than two pulmonary metastases.⁸⁴

BENIGN LESIONS

Pulmonary Hamartoma

Pulmonary hamartomas are the most common benign pulmonary tumors and the third most common cause of SPNs overall. Most (90%) arise in the periphery of the lung, but endobronchial hamartomas are seen as well. Because they are most common in the periphery, hamartomas are usually asymptomatic. When a potential hamartoma appears as an SPN on a chest x-ray, CT scanning is warranted for further evaluation.

Certain typical CT findings suggest that the SPN is likely to be a hamartoma. One such finding is a particular pattern of calcification. Calcification is more common in benign lesions than in malignant tumors. Four patterns of calcification are considered benign: central, diffuse, laminated, and “popcornlike.” The first three patterns are most commonly associated with an infectious condition (e.g., histoplasmosis or tuberculosis). The popcornlike pattern, however, indicates that the lesion is probably a hamartoma. Unfortunately, calcification is present in only about 50% of benign lesions, and only about 50% of hamartomas are calcified.³¹ It is important to remember that pulmonary carcinoid tumors and metastases to the lung (especially those from osteosarcomas, chondrosarcomas, or synovial cell sarcomas) may also have calcifications. Another reliable marker of a hamartoma is the finding of fat within the lesion on a CT scan; however, fewer than 50% of hamartomas demonstrate this characteristic. PET scanning, particularly the correlation between PET and CT findings on PET-CT, has been suggested as a useful diagnostic tool.⁸⁵

Inflammatory Nodules

Sarcoidosis is known as the great mimicker, but it rarely presents as an SPN.⁸⁶ Most commonly, it presents as hilar and mediastinal lymphadenopathy and diffuse parenchymal involvement. When it does present as an SPN, it is almost invariably a solid lesion, hardly ever a cavitary one. The incidence of sarcoidosis is highest in African-American women between 20 and 40 years of age. If sarcoidosis is suspected during the evaluation of an SPN, an elevated angiotensin-converting enzyme level supports the diagnosis, but a normal level does not exclude it. If a biopsy is performed, the presence of noncaseating granulomas on pathologic evaluation helps establish the diagnosis. If a diagnosis of sarcoidosis is suspected, PET scanning has been suggested as an effective method to identify extrathoracic sites of disease to target for pathologic confirmation.⁸⁷

Pulmonary rheumatoid nodules are present in fewer than 1% of patients with rheumatoid arthritis.⁸⁸ They are usually associated with rheumatoid nodules in other parts of the body but may precede any systemic manifestations of the

disease. Pulmonary rheumatoid nodules, although generally asymptomatic in themselves, arise from underlying rheumatoid activity. When the underlying disease is active, the nodules may grow, simulating malignancy. An elevated serum rheumatoid factor level is typical and helps confirm the diagnosis.

Wegener granulomatosis is a necrotizing vasculitis that affects both the upper and the lower respiratory tract, as well as the kidneys. It presents with an SPN in approximately 20% of patients.⁸⁹ If vasculitis is suspected during evaluation of an SPN, laboratory studies should include testing for cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA); a positive result on this test is highly suggestive of Wegener granulomatosis. Treatment includes the cytotoxic drug cyclophosphamide, either alone or in combination with corticosteroids.

Infectious Nodules

An SPN can also represent an infectious granuloma caused by tuberculosis, atypical mycobacterial diseases, histoplasmosis, coccidioidomycosis, or aspergillosis. Such granulomas frequently have a cavitary appearance on CT scans. Occasionally, a chest x-ray taken with the patient in different positions shows shifting of the position of the cavity's contents or a crescent of air around the mass (the Monod sign).⁹⁰ This radiographic finding is characteristic of a mycetoma, usually aspergilloma. Depending on the circumstances—in particular, on whether there has been significant hemoptysis and whether pulmonary function is reasonably well preserved—many of these lesions are best treated with resection. Others are best diagnosed by noninvasive techniques and treated with antimicrobial therapy.

Pulmonary dirofilariasis is a rare but well-attested cause of SPNs that is the consequence of infestation of human lungs by the canine heartworm *Dirofilaria immitis*. This organism is transmitted to humans in larval form by mosquitoes that have ingested blood from affected dogs.⁹¹ Because humans are not suitable hosts for this organism, the larvae die and embolize to the lungs, where they initiate a granulomatous response. Typically, these lesions are pleura based, and the diagnosis is made at the time of resection.⁹² Once the diagnosis is made, no further therapy is required.

Echinococcosis is a hydatid disease caused by the tapeworm *Echinococcus granulosus*. It is endemic to certain areas of the world where sheep and cattle are raised. Normally, it is ingested incidentally; the parasite penetrates the bowel wall and travels to the lungs in 10 to 30% of cases.^{93,94} A complete blood count usually demonstrates peripheral eosinophilia. If echinococcosis is suspected, a hemagglutination test, which has a sensitivity of 66 to 100% and a specificity of 98 to 99% for *Echinococcus*, should be performed. TTNB should not be performed because there is a risk that cyst rupture triggers an anaphylactic reaction to the highly antigenic contents. Patients may be treated with anthelmintic agents, but the incidence of persistent or recurrent disease is high. Accordingly, surgical resection should be considered.

OTHER CONSIDERATIONS

Pulmonary amyloidosis may present in either a diffuse or a nodular form. The prognosis is most favorable when it presents as an asymptomatic SPN. Typically, the nodule is well defined and between 2 and 4 cm in diameter. Unless the

patient exhibits systemic manifestations of amyloidosis, the diagnosis can be confirmed only by biopsy of the nodule.⁴²

Rounded atelectasis usually presents as a pleura-based nodular density that occurs secondary to pleural scarring and thickening. An effort should be made to look for associated pleural plaques resulting from asbestos exposure. The CT scan usually demonstrates an SPN with a “comet tail.” Biopsy is not required unless mesothelioma is strongly suspected or the SPN is seen to have grown on successive CT scans.

Management

The ACCP attempted to provide evidence-based guidelines to direct the evaluation of patients with SPNs 8 to 10 mm in diameter in their 2007 consensus statement.³⁹ Unfortunately, few, if any, randomized controlled trials exist to direct management. Most clinicians rely on a combination of single-institution studies, a few prospective trials, and clinical acumen to assess a given patient's risk profile to inform decisions on invasive and noninvasive testing. The initial step in decision making is to confirm that the lesion is, in fact, new, and to compare current chest x-rays or CT scans with any previous images that are available. An SPN whose size has been stable for 2 years on diagnostic images will be benign 90 to 95% of the time. If no previous images are available for comparison, the patient should undergo a clinical evaluation to determine their risk profile. This evaluation must be individualized according to the characteristics of the patient and the lesion. On the basis of the patient's age, exposure and smoking history, the size of the SPN, and the characteristics of the lesion's borders, an SPN for which no previous diagnostic images are available can be initially classified as having a low, intermediate, or high probability of cancer [see Table 3].^{7,95,96} This classification governs the subsequent workup. Whereas a patient with a high-probability SPN needs a complete evaluation progressing toward resection with minimal delay, the same strategy would not be cost-effective for a patient with a low-probability SPN. It is important not to subject a patient with a high-probability SPN to studies that will not change clinical management or outcome: doing so will delay diagnosis and treatment unnecessarily.

At this point in the evaluation, if the nature of the SPN is still indeterminate and the lesion is larger than 1 cm, there may be a role for PET or PET-CT scanning. If PET scanning yields negative results, the SPN is likely benign, and follow-up CT scanning is appropriate. If PET scanning yields positive results and the patient is at high surgical risk, TTNB, bronchoscopy, or guided bronchoscopy may be performed to

Table 3 Initial Assessment of Probability of Cancer in Solitary Pulmonary Nodule

Characteristics of Patient or Lesion	Probability of Cancer		
	Low	Intermediate	High
Patient age (yr)	< 40	40–60	> 60
Patient smoking history	Never smoked	< 20 pack-yr	≥ 20 pack-yr
Lesion size (cm)	< 1.0	1.1–2.2	≥ 2.3
Lesion margin	Smooth	Scalloped	Spiculated

establish a diagnosis. If, however, the patient is at reasonable surgical risk, proceeding directly to VATS resection (and, potentially, to lobectomy) offers the best chance of cure for a probable carcinoma.

For patients with SPNs smaller than 1.0 cm, the optimal approach may be to perform serial CT scanning at an initial 3-month interval for a minimum of 2 years. The rationale for this approach is based on the difficulty of identifying these lesions with VATS, the low likelihood of establishing a diagnosis with TTNB, and the possibility that the lesion may

be benign. If the lesion has grown visibly between scans, it is probably malignant, and proceeding with resection for diagnosis and treatment is appropriate. The likelihood that nodal metastases will develop in a closely followed SPN smaller than 1.0 cm is low.⁷³ If the SPN proves to be malignant, scanning at 3-month intervals is unlikely to alter the eventual outcome. Society guidelines continue to be refined in an effort to provide helpful recommendations.

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6 PARALYZED DIAPHRAGM

Matthew O. Hubbard, MD, Raymond P. Onders, MD, FACS, and Philip A. Linden, MD, FACS*

Diaphragmatic dysfunction may be unilateral or bilateral, with symptoms ranging from dyspnea only on extreme exertion to ventilator dependence. The etiology, treatment, and prognosis are quite different in unilateral and bilateral paralysis. A paralyzed hemidiaphragm may occur in isolation or as part of a systemic disease, whereas bilateral diaphragmatic paralysis usually occurs as result of a traumatic or neuromuscular degenerative process. The symptoms related to a paralyzed diaphragm are explained by both the loss of muscular action of the diaphragm in respiration and the loss of anatomic domain between the thorax and abdomen.

Unilateral dysfunction usually results from transection, bruising, stretching, or manipulation of one of the phrenic nerves. A paralyzed hemidiaphragm may restrict a patient's vital capacity by almost 20% in a seated position and up to 40% in a supine position. Compression of the lower lobe of the lung may result in ventilation-perfusion mismatch. A small but significant reduction in the arterial oxygenation may be seen, although hypercarbia is usually not present.¹ These alterations are usually well tolerated in a young, healthy patient, with the sole symptom being dyspnea on exertion. A patient at the extremes of life (early childhood or late adulthood) or suffering from underlying lung diseases, obesity, or other systemic disorders may be more adversely affected by unilateral diaphragmatic paralysis.

Bilateral dysfunction may be attributable to central nervous system disorders (central hypoventilation resulting in diminished central triggering of the diaphragms), diffuse nerve dysfunction (disorders such as amyotrophic lateral sclerosis [ALS]), or spinal cord injury (SCI) above C5. Bilateral paralysis causes more severe respiratory symptoms than unilateral paralysis. Vital capacity can be reduced 45 to 50% from predicted in patients with bilateral paralysis.² Arterial hypoxemia can be seen as a result of ventilation-perfusion mismatches at the lung bases, and hypercarbia may result from a decrease in tidal volume and minute ventilation. Assisted ventilation (either noninvasive or invasive) is usually required.

Clinical Evaluation

HISTORY

In adults with a paralyzed hemidiaphragm, the most common complaint is typically dyspnea on exertion. Often there are no symptoms at rest.

Bilateral diaphragmatic paralysis results in more severe symptoms than unilateral paralysis, resulting in profound respiratory compromise. Patients depend on accessory

muscles of inspiration more, may experience dyspnea in the supine position and related sleep disturbances with daytime fatigue, and may suffer from chronic respiratory failure.

Infants and young children depend on the diaphragm to achieve adequate vital capacities because they have a more compliant chest wall, weaker accessory muscles of respiration, and a more mobile mediastinum than adults. Unilateral paralysis may cause severe respiratory compromise requiring mechanical ventilation; bilateral diaphragmatic paralysis almost always requires prompt ventilator support.

COMMON CAUSES OF DIAPHRAGMATIC PARALYSIS

The most common causes of diaphragmatic paralysis are listed in Table 1. The most common causes of unilateral paralysis are neoplastic invasion, idiopathic, and iatrogenic.

Malignancies account for roughly one third of cases of diaphragm paralysis. Neoplasms of bronchogenic origin are most common, although malignancies of the mediastinum, including thymomas, lymphomas, and germ cell tumors, can also result in interruption of the phrenic nerve input to the diaphragm. The phrenic nerve can be damaged by either direct mediastinal invasion of a tumor or metastasis of a tumor to the mediastinal lymph nodes with subsequent lymph node enlargement. Overall, only about 10% of patients with unexplained diaphragmatic paralysis will regain function of the diaphragm.³

Phrenic nerve damage can occur during thoracic and cervical surgery as well as during cervical vein catheter insertion and has even been described as a result of cervical chiropractic manipulation. Injury to the phrenic nerve during cardiac surgery has fallen dramatically with the transition from topical ice slushes to cooling jackets but still may occur as a result of stretching, compression, or sectioning. The use of cautery during high dissection of the internal mammary artery near the first rib may also injure the nerve. Patients with an elevated hemidiaphragm on chest radiographs at the time of discharge after cardiac surgery have a 20% chance at 1 year

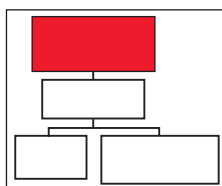


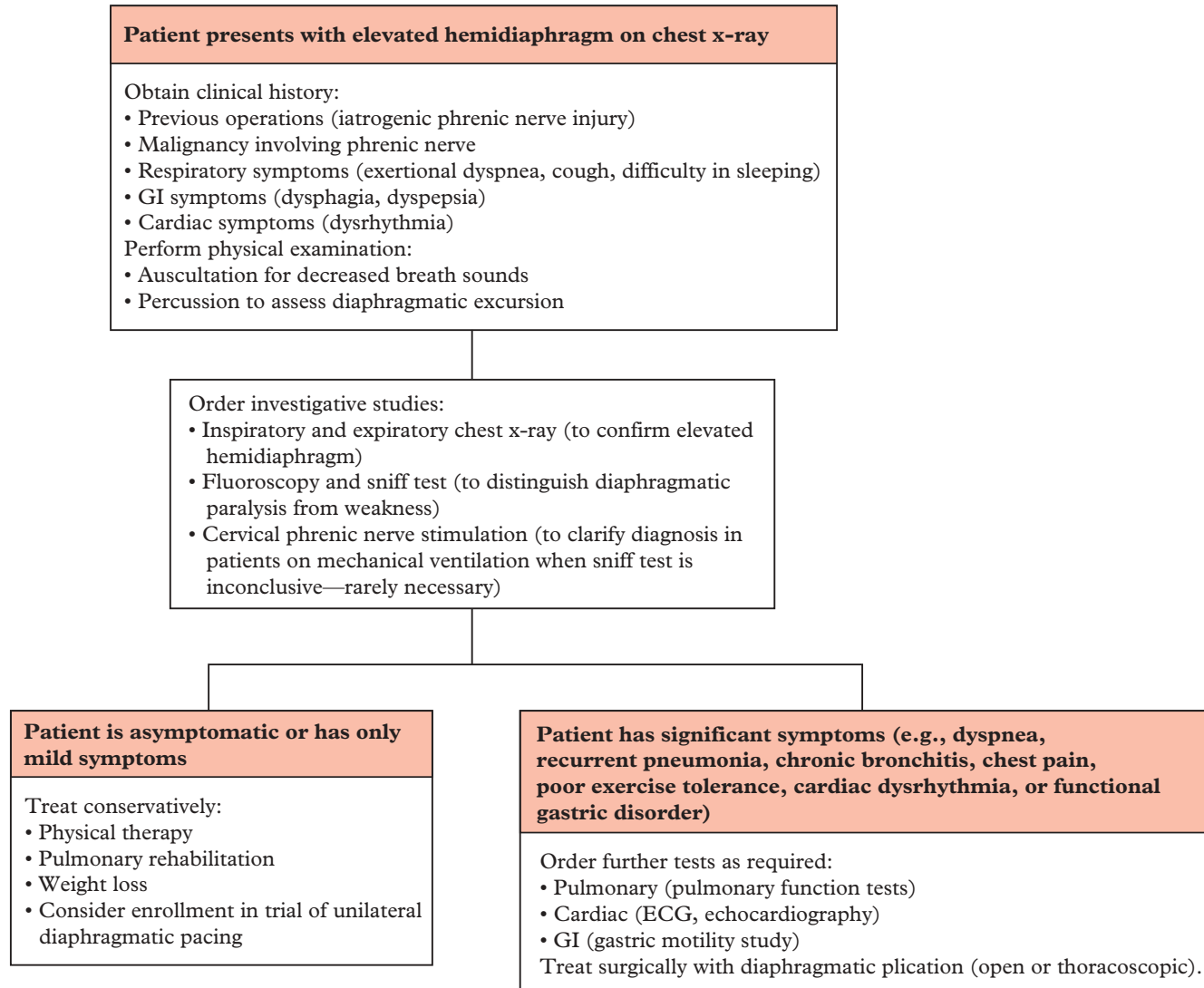
Table 1 General Causes of Unilateral and Bilateral Diaphragmatic Paralysis

Neoplasm invasion
Phrenic nerve injury: surgical section or stretching, cooling, chiropractic cervical manipulation, cervical venipuncture, birth trauma, cervical disk surgery, blunt or penetrating chest trauma
Neuritis: brachial neuritis, herpes zoster infection, mononeuritis multiplex, paraneoplastic neuritis
CNS or spinal cord disorders: neuralgic amyotrophy, stroke, multiple sclerosis, rhizotomy, infantile spinomuscular atrophy, Arnold-Chiari malformation, syringomyelia
Nerve compression: cervical spondylosis, mediastinal lymph node enlargement, substernal goiter
Miscellaneous: diabetes mellitus, carbon monoxide poisoning, upper abdominal surgery, liver transplantation

CNS = central nervous system.

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Evaluation of Elevated Hemidiaphragm



of continued diaphragmatic dysfunction. Injury can occur during dissection of mediastinal vessels during lobectomy. Typically, this is more common on the right than the left (the phrenic nerve courses closer to the hilum on the right than on the left) and may be more commonly injured after upper lobectomies than lower (the nerve courses closer to the superior pulmonary vein than the inferior vein). The phrenic nerve is at risk during a supraclavicular (or scalene) lymph node biopsy as it courses directly anterior to the anterior scalene muscle. The phrenic nerve is also at risk during thymectomy as perithymic tissue often extends bilaterally near both phrenic nerves. If one nerve is invaded by a thymoma, it should be resected en bloc with the thymoma provided that the other nerve is healthy and can be spared. Cautery should generally be avoided within 1 cm of the phrenic nerve. Typically, morbidity surrounding injuries to the phrenic nerves is minimal. Exceptions to this, however, are in pediatric patients undergoing open heart surgery, patients post-lung transplantation, and those adult patients with preexisting respiratory compromise. This may result in a failure to wean from mechanical ventilation after surgery.

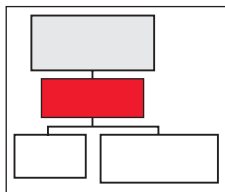
PHYSICAL EXAMINATION

At rest, adult patients with a paralyzed diaphragm may appear asymptomatic or have the nonspecific complaints discussed above. On physical examination, diminished breath sounds are heard on the affected base, with decreased excursion of the diaphragm noted on percussion. Paradoxical inward motion of the ipsilateral abdominal wall may also be seen.⁴

A patient with bilateral diaphragmatic paralysis is much more likely to become symptomatic, complaining of the symptoms above, and is also subject to the neurologic or neuromuscular complaints related to the underlying etiology. Physical examination almost always reveals significant use of accessory inspiratory muscle use. Tachycardia and tachypnea are usually present. Characteristically, paradoxical inward movement of the abdominal wall is seen with inspiration.⁴

Investigative Studies

Diaphragmatic paralysis is usually discovered following an inspiratory chest radiograph, which may demonstrate an elevated diaphragmatic dome with sharpened and deepened costovertebral and costophrenic sulci [see Figure 1]. With left-sided paralysis, the stomach may rotate with the greater curvature facing cephalad and showing two fluid levels corresponding to the inverted fundus and body.⁴



Fluoroscopy or ultrasonography can be used for functional evaluation of the diaphragm in patients with suspected paralysis. Elevation of the diaphragm above the normal range, paradoxical movement with inspiration (especially while sniffing, the “sniff test”), and a mediastinal swing during respiration may all be seen. All of these findings may also be seen in other respiratory ailments and require a good deal of judgment to evaluate. The “sniff test,” rapidly inhaling with a closed mouth, should show a paradoxical upward motion of the diaphragm of at least 2 cm to be considered a positive test



Figure 1 Chest radiograph showing left diaphragmatic paralysis in a breast cancer patient with malignant adenopathy involving the left phrenic nerve near the left main pulmonary artery.

for paralysis. This test may be unobtainable in patients with severe weakness or on mechanical ventilation.⁵

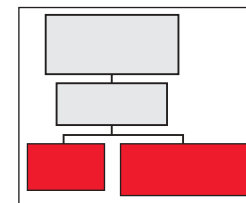
Ultrasound evaluation can also be used to evaluate suspected diaphragmatic paralysis and may be slightly more sensitive than fluoroscopy.⁶ Using ultrasonography, a paralyzed diaphragm fails to increase in thickness during inspiration compared with a normally functioning diaphragm. This was seen in single patients comparing paralytic hemidiaphragms with the contralateral leaflets and also comparing experimental and control patients. Rarely, equivocal noninvasive testing may be augmented with phrenic nerve stimulation with electromyographic measurement of nerve latency; this may be helpful with patients being supported by mechanical ventilation.⁷

Management

CONSERVATIVE VERSUS SURGICAL TREATMENT

Surgical treatment of diaphragmatic paralysis should be reserved for patients with moderate to severe symptoms of respiratory compromise. Adult patients with mild symptoms, such as dyspnea on exertion, would benefit from conservative treatment focusing on physical therapy, pulmonary rehabilitation, and weight loss.

The standard treatment of diaphragmatic paralysis is plication of the affected diaphragm, first performed by Bisgard in 1947 to treat congenital eventration of the diaphragm in an infant with respiratory distress. Several descriptions of plication of the diaphragm exist in the literature for diaphragmatic



paralysis and eventration, varying in suture placement and surgical approach. Developments in phrenic nerve repair and diaphragm plication (DP) have emerged in recent years.

PLICATION OF THE DIAPHRAGM

A posterolateral incision at the seventh or eighth intercostal space provides access to the thoracic cavity for a plication procedure. Four to six parallel rows of nonabsorbable suture with pledgets should be placed in an anteroposterior orientation within the central tendon of the diaphragm. Ideally, these sutures should not strike the phrenic vessels and nerve branches. The phrenic vessels often course under the diaphragm and are not visible from above [see *Figure 2*].

Thoracoscopic approaches to diaphragmatic plication have been described. One study of 25 patients undergoing video-assisted thoracoscopic diaphragm plication showed that forced vital capacity (FVC), forced expiratory volume at 1 second (FEV₁), functional residual capacity (FRC), and total lung capacity (TLC) improved by 17%, 21.4%, 20.3%, and 16.1%, respectively, at 6 months.⁸ Symptomatic dyspnea also improved, and 17 patients were able to return to work.

Radial plication of the muscular portion of the diaphragm, avoiding the mediastinal pleura, has been described through

a transabdominal and transthoracic approach.⁹ This procedure allows for protection of the phrenic nerve branches and vessels. This has also been described through a thoracoscopic approach in children and adults: a three-port technique using anterior and posterior thoracic ports at the sixth and eighth interspaces, respectively, for plication, and a subcostal port used for grasping and displacing the central tendon of the diaphragm through the abdomen.¹⁰

A study of plication in 17 patients (16 men, one woman), with an average age of 54 years, showed subjective improvement in dyspnea score, as well as objective improvement in FVC, TLC, and FRC, as well as arterial oxygenation, at 6 months.¹¹ These results were maintained in the six patients who were followed for more than 5 years. A different study of 15 patients with a mean follow-up of 10 years after plication showed continued improvement in FVC, FEV₁, FRC, and TLC by 11.8%, 15.4%, 26%, and 13.3%, respectively.¹²

Infants and children who suffer from diaphragmatic paralysis are much more susceptible to respiratory compromise. These children are much more likely to require mechanical ventilation and to be exposed to the complications therein. Diaphragmatic plication has been shown to be an effective means to wean children from mechanical ventilation.¹³

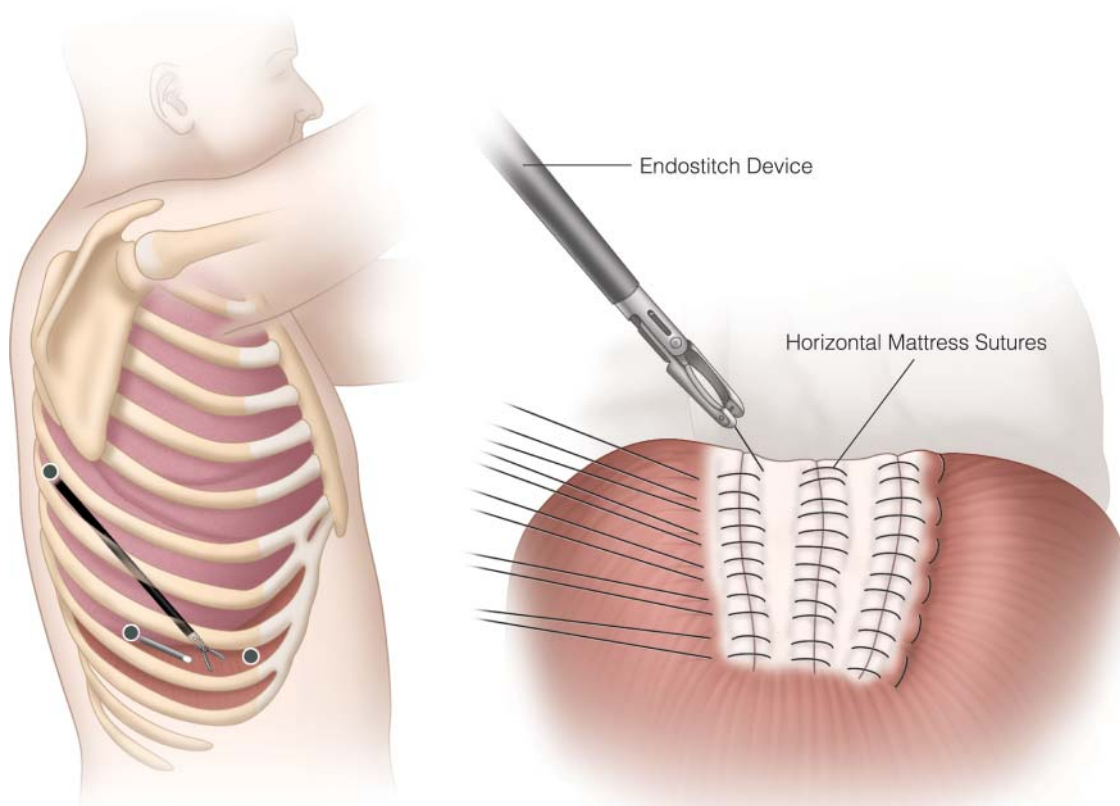


Figure 2 Several parallel rows of sutures are placed in the muscular portion and central tendon of the diaphragm and tied with the aid of a knot pusher. A pledget should be placed at the ends of the suture if the diaphragm is thinned.

REPAIR OF PHRENIC NERVE INJURY

Some cases of diaphragmatic paralysis result from traumatic or iatrogenic severing of the phrenic nerve. Case reports of direct repair of the phrenic nerve using microsurgery techniques have been described in adults and children by end-to-end anastomosis and sural nerve graft techniques; an improvement in diaphragmatic function occurred as early as 6 months after surgery.¹⁴ Repair of the phrenic nerve can be performed for simple transection, whereas sural nerve grafting is used for replacement of phrenic nerve segments that were resected en bloc with tumor. There are no reports of nerve repair in large numbers of patients.

DIAPHRAGMATIC PACING

Indications for Diaphragm Pacing

Direct phrenic nerve pacing and intramuscular DP systems were designed to replace or delay the need for patients requiring long-term positive pressure mechanical ventilation via tracheostomies. In the 1980s, Mortimer and colleagues showed that the diaphragm could be directly stimulated at the motor point (area of phrenic nerve insertion) of the diaphragm to provide ventilation.¹⁵

The initial clinical indications for phrenic nerve or DP have been cervical SCIs and congenital central hypoventilation syndromes. SCI involves the disruption of the signal pathway from the respiratory center in the brain to the respiratory nerves (primarily the phrenic nerves), whereas central hypoventilation syndromes generally involve a decreased respiratory drive. Central hypoventilation is a rare diagnosis, affecting one in 50,000 live births; these children require permanent nighttime positive pressure ventilation unless phrenic nerve pacing is possible.

Of 11,000 new SCIs each year in the United States, slightly more than half are affected by quadriplegia, with only 4% requiring long-term mechanical ventilation. In a prospective worldwide trial of DP in this group, 50 patients were implanted.¹⁶ The average age was 36 years (range 18 to 74 years), and the time from injury to implantation was 5.6 years (range 0.3 to 27 years). Ninety-eight percent of the patients had DP-stimulated tidal volumes above 5 to 7 cc/kg for 4 or more continuous hours, with 50% using DP for continuous 24-hour ventilation. Age and time from injury directly affect the conditioning time needed to achieve independent ventilation, with younger and more recently injured patients weaning from the ventilator faster.¹⁷ In a long-term analysis of 24 patients, 60% reported fewer secretions, and 95% reported greater freedom and independence. This multicenter trial led to approval by the Food and Drug Administration in June 2008.

DP is used in patients with ALS (Lou Gehrig disease), where respiratory insufficiency is the major cause of mortality. There is a significant risk of impending respiratory failure and death when FVC falls below 25 to 30%.¹⁸ In this group of patients, the goal is to delay the need for mechanical ventilation by implanting the DP and stimulating the muscle to maintain diaphragm strength prior to end-stage weakness.

The results of a multicenter prospective trial comparing noninvasive ventilation with DP combined with noninvasive

ventilation in 145 subjects with ALS showed a decreased respiratory decline and improved survival with pacing.¹⁹ After conditioning the diaphragm with the DP, the rate of decline in FVC fell from 2.62% per month to 1.25% per month. Respiratory compliance increased 18% from improving posterior lobe ventilation.

The use of DP for the treatment of ventilator dependence following iatrogenic diaphragmatic paralysis is currently under sporadic investigation

Surgical Technique of Laparoscopic Diaphragm Pacing

For DP to be effective, the phrenic nerve must be intact and able to provide intramuscular conduction pathways. Unfortunately, many patients with tetraplegia have sustained injury to the phrenic motor neurons in the spinal cord and/or phrenic rootlets. Prior to implantation, an assessment of phrenic nerve function should be performed. In patients with ALS or central hypoventilation, fluoroscopy of the diaphragm can also be done to see that volitional diaphragm movement is intact, commonly referred to as a sniff test.

Paralytic agents cannot be used during the pacer insertion procedure as the diaphragm has to be stimulated during the operation. The surgery is described in four phases: exposure, mapping, implantation, and routing. The exposure consists of the setup for the standard laparoscopy with the initial port supraumbilical for adequate visualization of the diaphragm. Two lateral subcostal 5 mm ports are placed for the mapping probe for each side, and these are used initially to completely divide the falciform ligament, which allows easier visualization of the medial aspect of the right diaphragm and easier exit of the pacing electrodes through a 12 mm epigastric port. The epigastric port is used for the diaphragm implant instrument.

Mapping involves finding the point on the abdominal side of the diaphragm where stimulation causes the greatest diaphragm excursion. The mapping instrument has flexible tubing inside a rigid cannula that connects to the operating room suction. The working part of the mapping instrument has a circular electrode that can be stimulated when temporarily attached to the diaphragm by the suction [see Figure 3]. Stimulation is applied in either a twitch or burst mode from the clinical station through a connecting cable. Mapping allows qualitative and quantitative data to be obtained. Quantitatively, changes in abdominal pressures are measured. Qualitatively, observation of the diaphragm contraction is performed. The stronger the stimulated contraction, the closer the mapping probe is to the motor point of the diaphragm. The primary electrode site is identified at the location of maximal pressure change in each hemidiaphragm. A secondary electrode site is identified as either a backup to the primary site or at a location in each hemidiaphragm that recruits another region (e.g., anterior, lateral, or posterior) of the diaphragm at a similar magnitude. On the right diaphragm, the motor point is just lateral to the central tendon, and on the left diaphragm, the motor point tends to be much more lateral because the phrenic nerve travels on the lateral aspect of the pericardium and enters the diaphragm more laterally.

Once the primary and secondary electrode sites are identified in each hemidiaphragm, the implantation phase begins.

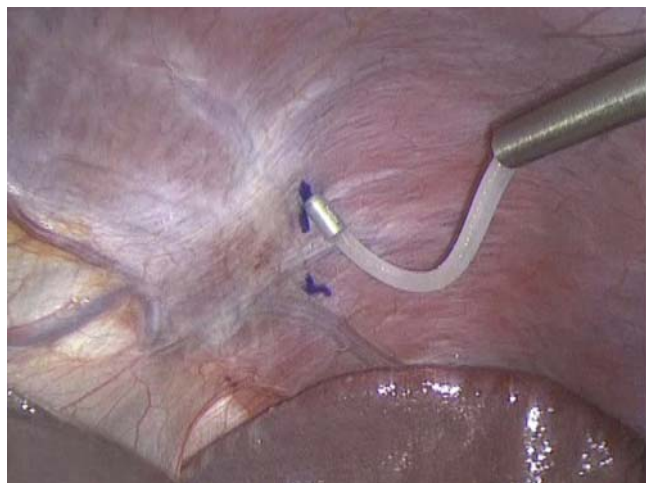


Figure 3 A laparoscopic mapping probe is being held onto the left diaphragm with suction and receives electrical stimuli from an external clinical station. The blue marks were placed at the locations of the strongest contractions.

An intramuscular electrode is introduced into the abdominal cavity with the electrode delivery instrument. The implant instrument needle is inserted into the diaphragm at an angle so that the electrode lead travels parallel to the plane of the diaphragm prior to exit, and the delivery instrument is withdrawn [see Figure 4]. The electrode is then tested to ensure that the desired response to twitch stimuli is achieved, and if the response is not adequate, the electrode may be withdrawn and another implanted. Once all four electrodes are implanted, they are brought out through the epigastric port, keeping the right and left sides separated. Excess electrode length is kept in the abdomen on top of the liver. The



Figure 4 The electrode implant device houses the electrode in the needle and is placed into the diaphragm tangentially. Countertraction can be applied by a second instrument to help deploy the electrode, which has a small barb on the end of it.

electrodes will be tunneled subcutaneously to an area in the upper chest or abdomen at a site deemed appropriate by the surgeon and patient's caregivers. An additional indifferent electrode will be placed subcutaneously through a separate percutaneous exit site.

Electrode evaluation is performed by adjusting individual stimulus parameters (amplitude, pulse width, rate, and frequency) so that a comfortable level of stimulation can be identified for the diaphragm conditioning sessions. The DP system will be set to provide a tidal volume that provides 15% above the basal needs (5 to 7 cc/kg) and that the patient can easily tolerate. For SCI patients and for ALS patients, the highest setting that causes no discomfort will be used.

ALS patients begin conditioning by pacing five 30-minute sessions a day. Continuous positive airway pressure (CPAP) or noninvasive ventilation may still be needed to maintain an upper airway and can be used in conjunction with the DP system. A weaning program for SCI patients is begun where the DP unit is turned on and the ventilator is turned off. The patients are placed back on the ventilator when they feel uncomfortable or if their tidal volumes start dropping because of diaphragm fatigue. Initially, patients may tolerate only 15 minutes of DP. If the DP system is implanted early after an SCI, the patient can be rapidly transitioned from the mechanical ventilator to DP. Figure 5 shows the system attached to a pediatric patient for whom weaning will be started the day of surgery. The diaphragm can recover quite rapidly from training, so patients and their caregivers can repeat a session every hour. The length of time it takes to go more than 4 continuous hours depends on the amount of time the patient and caregivers devote to this process.

The future application for temporary use in the intensive care unit (ICU) has some excellent theoretical possibilities, but well-designed trials will need to be done to identify the actual role of DP in the ICU.

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Figure 5 The diaphragm pacing system has already been programmed for conditioning and is attached via percutaneously placed diaphragm electrodes in this spinal cord-injured child for early conditioning and weaning from the ventilator.

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7 OPEN ESOPHAGEAL PROCEDURES

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The remarkable developments in diagnosis, imaging, and surgical treatment of esophageal diseases over the past 15 years have resulted in markedly better patient outcomes, and the morbidity and mortality associated with surgery of the esophagus have been substantially reduced. In particular, the operative techniques employed to treat esophageal disease have advanced considerably as a result of the successful introduction of minimally invasive approaches to the esophagus. For a number of diseases (e.g., achalasia and routine antireflux surgery), minimally invasive procedures have proved to be as effective as their open counterparts while causing less postoperative morbidity. The growing stature of minimally invasive approaches does not, however, diminish the importance of the equivalent open approaches. In this chapter, we describe common open operations performed to excise Zenker diverticulum, to manage complex gastroesophageal reflux disease (GERD), and to resect esophageal and proximal gastric tumors.

General Preoperative Considerations

METHODS OF PATIENT ASSESSMENT

The functional results achieved with esophageal procedures become more predictable when the approach to preoperative patient evaluation is precise and reproducible. The ciné barium swallow remains the most cost-effective method for initial evaluation of esophageal anatomy and function. It should be employed before endoscopy because the results may direct the endoscopist's attention to particular areas of concern. In addition, endoscopic examination alone is often insufficient for assessing esophageal motility disorders or defining the complex anatomy of a paraesophageal hiatal hernia.

Endoscopic ultrasonography (EUS) is an extension of the visual mucosal examination. The information it can provide about the extension of mass lesions beyond the confines of the esophageal wall is helpful in planning surgical resection. In addition, EUS can differentiate benign stromal tumors from cystic or malignant neoplasms on the basis of characteristic echogenicity patterns. EUS-FNA (fine-needle aspiration) is used to confirm suspected nodal metastases seen during the EUS examination. The combination of EUS and computed tomography (CT) permits highly precise anatomic assessment of esophageal neoplasms, definition of the extent of local invasion, and identification of regional metastases.

Functional imaging with photodynamic or vital staining allows accurate diagnosis of dysplastic or malignant mucosal lesions in their earliest stages. Positron emission tomography (PET) yields similar results by localizing metabolically active tissue regionally or at distant sites. The combination of morphologic data from high-resolution CT and functional data from PET is particularly effective for identifying

occult metastases that would preclude curative resection for esophageal cancer.

Esophageal manometry, 24-hour esophageal pH testing, and nuclear studies for assessment of esophageal and gastric transit provide functional data that can facilitate the diagnosis and treatment of GERD, achalasia, and other disorders of the esophagus. They are useful complements to standard investigations (e.g., ciné barium swallow and endoscopy).

Complete preoperative investigation of all patients, even those with classic histories and physical findings, is mandatory. The data from anatomic and functional testing allow the surgeon to plan the operation more appropriately and effectively (e.g., deciding on the need for esophageal lengthening in patients with paraesophageal hernias or choosing between a complete and a partial fundoplication in patients with hernias associated with varying degrees of esophageal dysmotility).

OPTIMIZATION OF PATIENT HEALTH STATUS

Patients with obstructing esophageal diseases are often elderly, debilitated, and malnourished. Although months of insufficient nutrition cannot be corrected in the space of a few hours, anemia, dehydration, and electrolyte abnormalities can be mitigated by means of intravenous support and appropriate laboratory monitoring. If esophageal obstruction prevents oral intake, endoscopic dilation of the stricture, accompanied by either nasogastric intubation or percutaneous endoscopic gastrostomy (PEG), is often indicated; the patient should then be able to resume at least a liquid diet. Caution should be used when addressing esophageal obstruction in preoperative patients before induction therapy is given. Most surgeons prefer not to have a PEG tube placed in the stomach for fear of compromising its blood supply when an esophagectomy is planned. Alternative options include a nasogastric tube, a jejunostomy tube, or total parenteral nutrition. If weight loss has exceeded 10%, enteral nutrition, comprising at least 2,000 kcal/day of a high-protein liquid diet, should be administered for at least 10 days before the operation. Cardiovascular, renal, hepatic, and respiratory function should be documented and optimized. If the patient is aspirating, the esophagus should be evacuated and the patient should be given nothing by mouth until after the operation. Aspiration pneumonia should always be corrected preoperatively.

Cricopharyngeal Myotomy and Excision of Zenker Diverticulum

PREOPERATIVE EVALUATION

Patients who are candidates for cricopharyngeal myotomy usually present with difficulty initiating swallowing, cervical dysphagia, and a history of pulmonary aspiration. These

symptoms of cricopharyngeal dysfunction may or may not be associated with a Zenker diverticulum. Ciné contrast studies may reveal poor pharyngeal contractility, pulmonary or nasal aspiration, abnormalities of the upper esophageal sphincter, pharyngeal pouches, or other structural abnormalities in the distal esophagus. Barium is the usual contrast agent as it is inert if aspirated.

Zenker diverticulum is a pulsion diverticulum that arises adjacent to the inferior pharyngeal constrictor, between the oblique fibers of the posterior pharyngeal constrictors and the cricopharyngeus muscle. This mucosal outpouching results from a transient incomplete opening of the upper esophageal sphincter. The diverticulum ultimately enlarges, drapes over the cricopharyngeus, and dissects behind the esophagus into the prevertebral space. The pouch usually deviates to one side or the other; accordingly, the side on which the deviation occurs must be determined by means of a barium swallow so that the appropriate operative approach can be selected. Esophageal motility studies (not usually performed) may show either incomplete upper esophageal relaxation on swallowing or poor coordination of the upper esophageal relaxation phase with pharyngeal contractions. Upper gastrointestinal (GI) endoscopy is performed preoperatively to exclude the presence of a pharyngeal or esophageal carcinoma and to assess the upper GI anatomy. If there is evidence of GERD, proton pump inhibitors (PPIs) are given.

In symptomatic patients (e.g., those with dysphagia, nocturnal cough, or recurrent pneumonia from aspiration), surgical therapy is indicated regardless of whether a pouch is present or how large it may be. Such treatment involves correcting the underlying cricopharyngeal muscle dysfunction with a cricopharyngeal myotomy. If there is a diverticulum larger than 2 cm, it should be excised in addition to the cricopharyngeal myotomy. Alternatively, the diverticulum may be managed via endoscopic obliteration of the common wall between the pharyngeal pouch and the esophagus with either a stapler or a laser. Cricopharyngeal incoordination may be temporarily relieved by injecting botulinum toxin into the cricopharyngeus.

OPERATIVE PLANNING

The patient is placed on a clear fluid diet for 2 days before the operation. With the patient under general anesthesia, the trachea is intubated with a single-lumen endotracheal tube. Cricoid pressure is applied to prevent aspiration of diverticular contents. A soft roll is placed behind the shoulders to extend the neck. The patient is placed in a 20° reverse Trendelenburg position, and the legs are wrapped with pneumatic calf compressors to prevent deep vein thrombosis (DVT). With the endotracheal tube placed to the side of the mouth, a preliminary flexible esophagogastroscope is performed to empty the diverticulum of all food and to examine the esophagus and the stomach. The scope is then brought back up into the oropharynx and moved into the pouch. The location of the diverticulum (on the left or the right side) is confirmed by turning off the room lights and noting which side is transilluminated by the gastroscope.

OPERATIVE TECHNIQUE

Step 1: Incision and Dissection of Pharyngeal Pouch

The patient lies with the head turned away from the side on which the incision is made (usually the left). The cricoid

cartilage is palpated and marked. A 6 cm skin incision is made, either obliquely along the sternocleidomastoid muscle [see Figure 1] or transversely in a skin crease at the level of the cricoid. The platysma is divided in the same line. Self-retaining retractors are inserted. The anterior border of the sternocleidomastoid muscle is incised throughout its length. The omohyoid muscle and the sternohyoid and sternothyroid muscles are retracted [see Figure 2]. The sternocleidomastoid muscle is retracted laterally to expose the carotid sheath and the internal jugular vein. The middle thyroid vein is ligated and divided, and the thyroid gland and the trachea are retracted medially by the assistant's finger to minimize the risk of injury to the underlying recurrent laryngeal nerve. There is no need to encircle the esophagus or to dissect in the tracheoesophageal groove. The deep cervical fascia is divided. The inferior thyroid artery is divided as laterally as possible. The carotid sheath is retracted laterally, and dissection is carried down to the prevertebral fascia [see Figure 2]. The endoscope placed in the diverticulum is palpated, and the pouch is dissected away from the cervical esophagus up as far as the pharyngoesophageal junction. The flexible endoscope is then removed from the pouch and advanced into the thoracic esophagus so that it can be used as a stent for the cricopharyngeal myotomy. Dissection of the pharyngeal pouch is then completed.

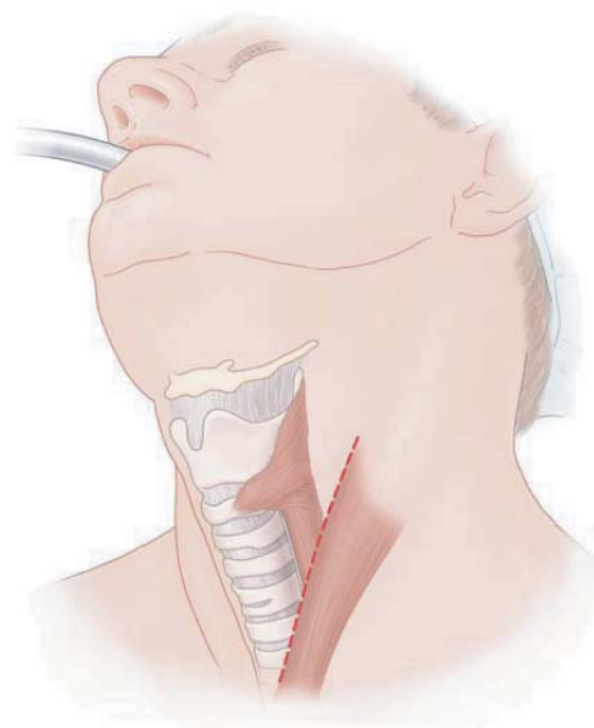


Figure 1 Cricopharyngeal myotomy and excision of Zenker diverticulum. A soft roll is placed behind the shoulders to extend the neck. The head is turned to the side opposite the incision. The cricoid cartilage is palpated and marked. The skin is incised obliquely along the sternocleidomastoid muscle, as shown, or transversely in a skin crease at the level of the cricoid.

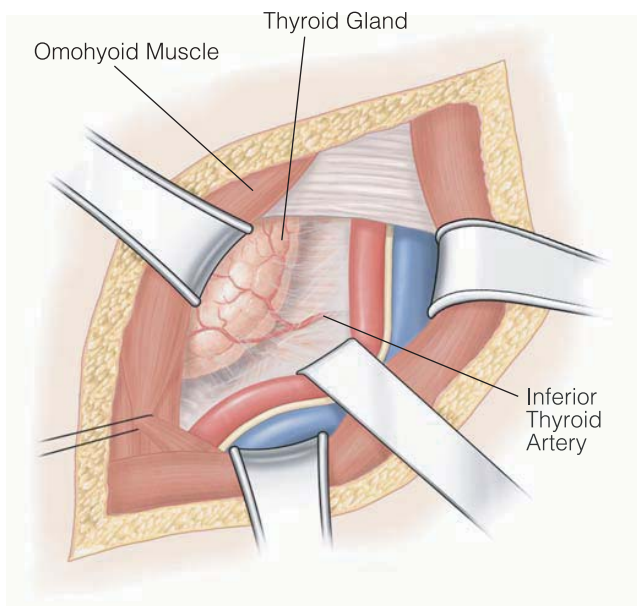


Figure 2 Cricopharyngeal myotomy and excision of Zenker diverticulum. The sternocleidomastoid is incised along the anterior border so as to expose the omohyoid muscle and the sternohyoid and sternothyroid muscles, which are retracted. The thyroid gland and the trachea are retracted medially by the assistant's finger, and the inferior thyroid artery is ligated and divided laterally to avoid injury to the recurrent laryngeal nerve.

Step 2: Myotomy

The esophageal myotomy is started approximately 1 cm below the cricopharyngeus on the posterolateral esophageal wall [see Figure 3a]. The esophageal muscle is divided down to the mucosa, which is recognizable from its bluish coloration with the submucosal plexus overlying it. The esophageal muscle is dissected away from the mucosa with a right-angle dissector and divided with either a knife, scissors, or a low-intensity diathermy unit. The myotomy is then continued proximally through the cricopharyngeus and up into the muscular wall of the hypopharynx for 1 to 2 cm if no diverticulum is present. The hypopharynx is distinguished by a pronounced submucosal venous plexus. The muscle is then swept off the mucosa for 120°.

Step 3: Freeing or Excision of Diverticulum

If there is a diverticulum less than 2 cm in diameter, the cricopharyngeus is transected and the muscularis around the diverticulum is freed. The myotomy is extended onto the hypopharynx for 1 to 2 cm. The diverticulum is then suspended to the back wall of the pharynx to prevent food from easily entering it. It should not be sutured to the prevertebral fascia, because the passage of sutures through the diverticulum can contaminate the fascia or intervertebral disk, leading to an increased risk of infection.

If the diverticulum is more than 2 cm in diameter, it is excised with a linear stapler loaded with 2.5 mm staples, which is placed at the base of the sac and pressed firmly against the esophagoscope [see Figure 3b]. Particular care must be taken at this point so as not to injure the recurrent

laryngeal nerve. The stapler is fired, and the diverticulum is excised. The staple line is cleaned with an antiseptic solution, and the incision is filled with saline. The esophagus is insufflated with air to determine whether mucosal leakage has occurred, and the esophagoscope is removed; any mucosal leaks found are closed with fine absorbable sutures. In the absence of a stapler, the best way of excising the sac is to make a series of short incisions through the neck of the sac with scissors, suturing the edges after each cut with absorbable monofilament sutures (the so-called cut-and-sew technique). The esophagoscope ensures that the esophageal lumen is not narrowed. If an esophagoscope is not used, then a Maloney dilator (50 to 54 French) is used to ensure that excessive esophagus is not removed.

Step 4: Drainage and Closure

Once hemostasis has been achieved, a short vacuum drain is placed through the skin into the retroesophageal space. The platysma is repaired with absorbable sutures, and the skin is closed with a subcuticular absorbable suture. Nasogastric intubation is unnecessary. Prokinetic agents and PPIs are administered to prevent gastroesophageal reflux. A water-soluble contrast study can be done the day after the operation. If the results are normal, the patient is started on a liquid diet, the drain is removed, and the patient is discharged on liquids for 1 week.

COMPLICATIONS

The main complications associated with cricopharyngeal myotomy are recurrent laryngeal nerve trauma (occurring in 1% of cases), fistulas (1%), hematoma formation, infection (2%), aspiration, and recurrence (4%). Hematomas and infections must be drained promptly. Fistulas usually close once the prevertebral space is drained and the associated infection is controlled. Aspiration is the most serious complication after cricopharyngeal myotomy. Gastroesophageal reflux may contribute to oropharyngeal dysphagia. Division of the upper esophageal sphincter in a patient with an incompetent esophagogastric junction may lead to massive tracheobronchial aspiration. Therefore, documented severe gastroesophageal reflux, gastroesophageal regurgitation, and severe distal esophagitis may be relative contraindications to cricopharyngeal myotomy until the lower esophageal sphincter defect has been remedied with an antireflux operation.

OUTCOME EVALUATION

Of patients with a Zenker diverticulum, at least 90% experience excellent results from surgical treatment. Of patients without a Zenker diverticulum, one third experience excellent results, another third show moderate improvement, and the remaining third show no improvement.¹ Patients with poor pharyngeal contractility in conjunction with normal upper esophageal sphincter function show little improvement with cricopharyngeal myotomy. Patients with oropharyngeal dysphagia secondary to neurologic involvement who have intact voluntary deglutination, adequate pulsion of the tongue, and normal phonation may show improvement with cricopharyngeal myotomy. Appropriate selection of patients for cricopharyngeal myotomy leads to better surgical outcomes.

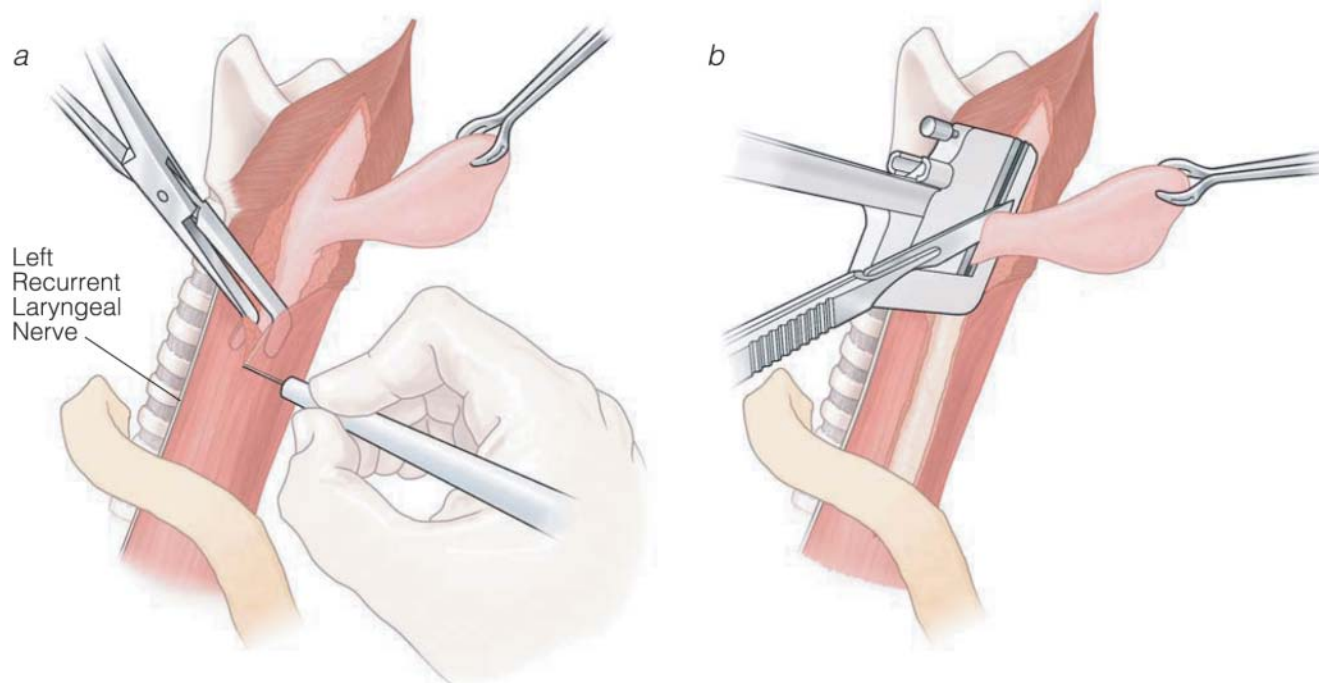


Figure 3 Cricopharyngeal myotomy and excision of Zenker diverticulum. (a) The diverticulum is dissected away from the esophagus, and an esophageal myotomy is started approximately 3 cm below the cricopharyngeus. The myotomy is continued proximally through the cricopharyngeus, and the muscle around the diverticulum is freed. (b) A linear stapler is placed at the base of the sac and pressed firmly against the esophagoscope. The stapler is fired, and the diverticulum is excised.

Transthoracic Hiatal Hernia Repair

Unlike most operations on the esophagus, which are extirpative procedures, hiatal hernia repair with fundoplication is a reconstructive procedure, the aim of which is to restore a high-pressure zone at the esophagogastric junction that prevents reflux but also permits comfortable swallowing. Currently, this repair is usually accomplished via minimally invasive approaches. The degree of tension on the hiatal repair sutures, the length of the esophagus, the quality of the crural tissue itself, and the caliber of the esophageal hiatus after repair all must be assessed. In certain patients, laparoscopic reconstruction of a competent gastroesophageal high-pressure zone may be very difficult and may demand a degree of skill not yet achievable by laparoscopy. The most common indications for transthoracic hiatus hernia repair are a failed previous repair and a hostile abdomen.

The long-term success of antireflux surgery, whether done via the transthoracic approach or by means of laparoscopy, depends on three factors: (1) a tension-free repair that maintains a 4 cm long segment of esophagus in the intra-abdominal position, (2) durable approximation of the diaphragmatic crura, and (3) correct matching of the fundoplication technique according to the peristaltic function of the esophagus. The transthoracic approach should be considered whenever the standard abdominal approaches to hiatal hernia repair carry an increased risk of failure or complication—for example, in patients who have a foreshortened esophagus associated with a massive hernia and an incarcerated intrathoracic stomach, patients with severe peptic strictures of

the esophagus, patients in whom the hiatal hernia coexists with an esophageal motility disorder or morbid obesity, and patients who have undergone multiple previous abdominal operations. The transthoracic repair is particularly useful when a previous open abdominal procedure has failed. In this situation, the reasons for such failure, whether technical or tissue related, should be assessed so that a compensatory strategy can be devised.

PREOPERATIVE EVALUATION

Symptomatic Evaluation

All patients being considered for fundoplication to treat GERD must undergo a comprehensive evaluation to determine whether there is indeed an anatomic substrate for their symptoms and what the most appropriate form of repair is. Specifically, a history of heartburn and effortless regurgitation should be sought. Dysphagia and odynophagia are not typically associated with hiatal hernia unless there is a significant paraesophageal component. Persistent dysphagia may reflect the presence of a stricture or a neoplasm. Reflux-induced esophageal spasm may present with occasional episodes of cervical dysphagia, but the transient nature of the symptoms easily differentiates this condition from dysphagia caused by a fixed obstruction. Chest pain that radiates toward the back after meals and is relieved by nonbilious vomiting may indicate the presence of an incarcerated intrathoracic stomach that is hindering the emptying of the paraesophageal component. Atypical chest pain from cholelithiasis, peptic ulcer, or coronary artery disease may confound the diagnosis.

Imaging

Radiographic investigation should begin with a ciné barium swallow, which will yield valuable information regarding the length of the esophagus, its peristaltic function, and the integrity of the mucosal surface. The gastric views can be used for qualitative assessment of distal emptying. Any paraesophageal component will be clearly demonstrated, along with any associated organoaxial volvulus. A simple barium swallow often yields the most useful information for managing the complex problem of recurrent hiatal hernia and a slipped Nissen fundoplication.

Next, esophagogastroscope should be performed to examine the mucosa for the presence of esophagitis, Barrett mucosa, stricture, or malignancy. The locations of any lesions observed, along with the position of the squamocolumnar junction, should be carefully documented in terms of their distance from the incisors. All strictures must undergo cup or brush biopsy to rule out an occult malignancy. The presence of severe esophagitis raises the possibility of acquired shortening of the esophagus secondary to transmural inflammation and contraction scarring. Every effort should be made to measure the length of the esophagus accurately.

Dilation

If a stricture is found during esophagoscopy, a decision must be made about whether to attempt esophageal dilation. This procedure carries the risk of perforation and should be performed only after careful consideration. If the stricture is diagnosed at the time of the initial endoscopic examination, it is advisable to perform only the brush biopsy at this point, deferring dilation to a subsequent visit. Delaying dilation gives the surgeon time to reassess the anatomy depicted on the barium swallow, to decide whether wire-guided dilation is necessitated by angulation of the esophagus, to obtain informed consent, to assemble the requisite equipment, and to plan sedation for what is often an uncomfortable procedure. If a malignancy is suspected at the time of the initial endoscopic examination, dilation should be avoided. In this situation, repair is impossible; thus, if iatrogenic perforation of a malignant stricture occurs, the surgeon will have to attempt emergency resection in an inadequately prepared patient in whom proper staging is unlikely to have been completed.

The standard flexible adult esophagoscope is approximately 32 French in caliber. In advancing the scope into the stricture, only very gentle pressure should be necessary. As a rule, a mild stricture that is not associated with steep angulation of the esophagus will readily accept passage of the endoscope and will be amenable to subsequent blind dilation with Hurst-Maloney bougies.

After successful passage, the scope is removed, and sequential insertion of progressively larger dilators (starting at 32 French) into the stricture is attempted. The weight of the dilator alone should be sufficient to effect its passage, with little or no forward force applied. Although the patient will be able to swallow comfortably only after satisfactory passage of a dilator at least 48 French in caliber, it is essential never to try to force passage. To this end, the surgeon must take careful note of the subtle signs of increasing resistance transmitted through the dilator. Sequential dilation should be stopped whenever significant resistance is encountered

or blood streaks appear on the dilator. Sudden pain during dilation is an ominous sign and calls for immediate investigation with a swallow study using a water-soluble contrast agent (e.g., Gastrografin, Schering AG, Berlin, Germany). Subcutaneous emphysema in the neck or mediastinal air on a plain chest radiograph may also indicate an injury to the esophagus. Perforation must be definitively ruled out before the patient can be discharged.

Highly stenotic strictures that do not allow the passage of a standard adult endoscope may be associated with a distorted and a steeply angulated esophagus. In such cases, the use of a pediatric endoscope may permit directed placement of a guide wire through the stricture; fluoroscopy is a useful adjunct for this purpose. A series of progressively larger Savary-Gillard dilators may then be passed over the guide wire to enlarge the lumen and allow subsequent endoscopic biopsy. As a rule, less tactile feedback is available during wire-guided dilation than during passage of standard Maloney-Hurst bougies. Increased pressure is required to pass the Savary-Gillard dilators because of the resistance caused by the wire passing through the dilator itself. It is essential that the wire be well lubricated and not be allowed to dislodge proximally between the sequential insertions of progressively larger dilators. The caveats that apply to blind dilation also apply to wire-guided dilation.

Patients whose esophagus can be dilated to 48 French and who are candidates for antireflux surgery may undergo subsequent intraoperative dilation to 54 to 60 French. Patients who cannot be dilated to 48 French and fail to achieve comfortable swallowing should be classified as having a nondilatable stricture and should be considered for transhiatal esophagectomy [see Resection of Esophagus and Proximal Stomach, *below*].

Functional Evaluation

Esophageal manometry permits quantitative assessment of peristalsis, a capability that is critically important for determining which type of fundoplication is most suitable for reconstructing a nonoccluding high-pressure zone at the esophagogastric junction. Stationary pH tests measure the capacity of the esophagus to clear acid, its sensitivity to instilled acid, the relation of reflux episodes to body position, and the correlation between changes in esophageal pH and the subjective symptoms of heartburn. Ambulatory 24-hour pH testing allows further quantification of reflux episodes with respect to duration, frequency, and association with patient symptoms.

OPERATIVE PLANNING

The transthoracic hiatus hernia repair may be completed with either a partial fundoplication (as in the 240° Belsey Mark IV procedure) or a complete fundoplication (as in the 360° Nissen procedure). Acquired shortening of the esophagus may necessitate lengthening of the esophagus by means of a Collis gastropasty, in which the portion of the gastric cardia along the lesser curvature and directly contiguous to the distal esophagus is fashioned into a tube [see Operative Technique, Step 6a, *below*].

A thoracic epidural catheter is placed for regional analgesia. General anesthesia is administered, and flexible esophagocopy is performed by the operating team. Insufflation should

be done with as little air as is practical, particularly in the case of large paraesophageal hernias. The extent of the pathologic condition is documented, and the absence of malignancy is verified. The stomach is decompressed with suction, and the endoscope is removed. A nasogastric tube is placed while the patient is supine.

Tracheal intubation is performed with a double-lumen endotracheal tube. A Foley catheter is placed. Subcutaneous heparin is administered for DVT prophylaxis, and pneumatic calf compression devices are applied. Antibiotic prophylaxis is provided.

The patient is positioned for a left thoracotomy. The table is flexed to distract the ribs. The right leg is bent at the hip and knee while the left leg is kept straight. Pillows are placed between the legs, and all pressure points are padded. The arms are positioned so that the humeri are at right angles to the chest and the elbows are bent 90°.

OPERATIVE TECHNIQUE

Step 1: Incision and Entry into Chest

A standard left posterolateral thoracotomy is performed. The latissimus dorsi is divided. The serratus fascia is incised, but the muscle itself can generally be preserved. For most patients, the sixth interspace is the most appropriate incision site for exposing the hiatus. The seventh interspace can also be used, particularly if the patient is tall or has a hyper-extended chest as a result of chronic pulmonary disease. The paraspinal muscles are elevated away from the posterior aspect of the adjacent ribs, and a 1 cm segment of the rib below the selected interspace is resected to facilitate exposure. The chest is then entered, and the lung and the pleural space are thoroughly inspected. The leaves of the retractor are spread slowly over the course of the next several minutes so as not to cause iatrogenic rib fractures.

Step 2: Mobilization of Esophagus and Excision of Hernia Sac

The inferior pulmonary ligament is divided with the electrocautery to the level of the inferior pulmonary vein [see Figure 4]. The mediastinal pleura overlying the esophagus is longitudinally incised to expose the esophagus from the level of the carina to the diaphragm. Particular care is taken to avoid injury to the vagi. Vessels supplying the esophagus and arising from the adjacent aorta are cauterized and divided. A few larger vessels may have to be ligated with 2-0 silk. The esophagus is encircled just below the inferior pulmonary vein with a wide Penrose drain [see Figure 4]. The two vagi are mobilized and carried with the esophagus. (The right vagus is located along the right anterior border of the descending aorta and can easily be missed.)

The esophagus is then elevated, and mobilization is circumferentially completed in the direction of the diaphragm, starting from the level of the carina. In cases of giant paraesophageal hernia or reoperation for a failed repair, the stomach will have a large intrathoracic component. Dissection continues inferiorly to separate the sac from the pericardium anteriorly and the aorta posteriorly. The right pleura is closely approximated to the esophagus for 2 to 5 cm above the diaphragm; in the presence of a substantial hiatal hernia and its sac, it may be difficult to identify. The right pleura should be gently dissected away from the sac without entry into the

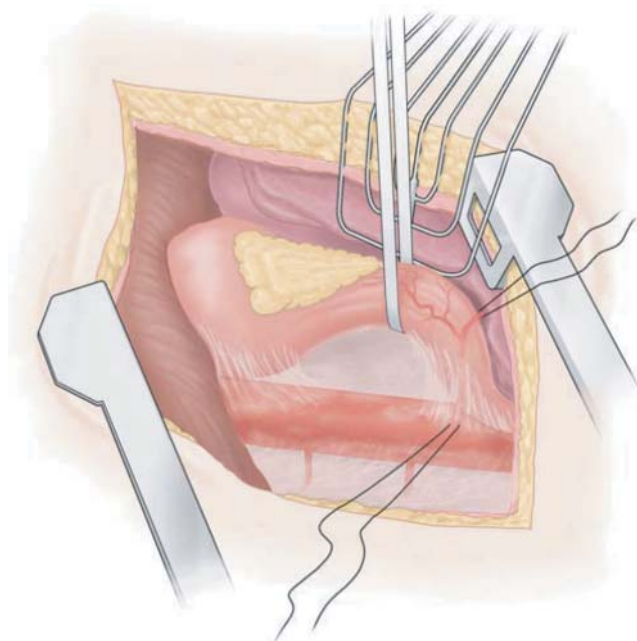


Figure 4 Transthoracic hiatal hernia repair. The lung is retracted, and the inferior pulmonary ligament is divided to the level of the inferior pulmonary vein. The mediastinal pleura overlying the esophagus is incised to expose the esophagus from the level of the carina to the diaphragm. The esophagus and both vagi are encircled just below the inferior pulmonary vein with a Penrose drain. Vessels supplying the esophagus and arising from the adjacent aorta are ligated and divided.

right chest. This can generally be done with a small sponge on a stick. If a tear occurs, it should be closed with absorbable suture material to prevent accumulation of blood and fluid on the right side during the operation.

Dissection is continued inferiorly to expose the right and left crura. The left crus is generally more robust and is certain to be easily seen with this exposure. Its medial fibers may be attenuated and may blend into the hernia sac superiorly. The sac should be incised 1 cm above the muscle fibers because the muscle alone will not hold sutures well for the subsequent repair. Skeletonization of the crural muscle must be avoided; it is the fibroconnective tissue that provides the most tensile strength. The hernia sac is dissected away from the left crus in an anterior-to-posterior direction. The right crus is generally less robust than the left. In the case of a previous failed repair, the right crus may be very difficult to see, being obscured from the operator's view by the intrathoracic stomach. Dissection of the right crus is best accomplished in a posterior-to-anterior direction.

Once the sac is circumferentially freed from the crura, dissection proceeds cephalad along the esophagus. To minimize the risk of vagal injury, the sac should be incised parallel to the esophagus.

Step 3: Division of Phrenoesophageal Membrane and Gastrohepatic Ligament

The esophagus is retracted anteriorly to expose the posteriorly located phrenoesophageal membrane, which is

then divided to yield entry into the lesser sac. The remainder of the phrenoesophageal membrane is elevated with a right-angle clamp as it courses anteriorly, yielding a view of the spleen below. The esophagus and the stomach are thus completely mobilized from the left crus. The esophageal branch of the left phrenic artery, visible near the left vagus, is divided near the crus.

The uppermost portion of the gastrohepatic ligament is found along the undersurface of the right crus. It is divided with the electrocautery. The Belsey artery, a communicating branch between the left gastric artery and the inferior phrenic artery, lies in this area and may have to be ligated directly. It is vital to divide the gastrohepatic ligament down to the level of the left gastric artery. The caudate lobe of the liver must be clearly visible beneath the right crus. This opening is essential for subsequent passage of the fundoplication wrap behind the esophagus.

Step 4: Mobilization of the Stomach

The highest short gastric arteries are ligated between ties to permit mobilization of the fundus. Excessive traction must be avoided to prevent splenic injury. Three or four vessels are usually divided. The esophagogastric junction is elevated well into the chest, and any organoaxial rotation of the stomach is released as the short gastric vessels are divided. It is crucial that ligation be limited to the vessels along the greater curvature. Inadvertent ligation of the vessels along the lesser curvature can easily occur, especially if there was a previous operation. Loss of blood supply from the branches of the left gastric artery along the lesser curvature will lead to ischemia of the Collis gastroplasty tube and will predispose to either leakage at the staple line or subsequent stricture formation.

In the case of a redo repair, the previous fundoplication often will have slipped down onto the cardia or even onto the body of the stomach. Generally, the inner aspect of the previous fundoplication can be freed from the esophagus without any difficulty; rarely will any major dissection have been done in this area during the original operation. The vagi will be found within the wrap and should be specifically visualized. Because of scarring, it may be difficult to see the point at which the previous fundoplication attaches to itself. Not uncommonly, a serosal tear develops on the fundus as the wrap is undone. Any areas of concern can be reinforced with a simple stitch of 4-0 silk. Mobilization is complete when the fundus is restored to its original anatomic position and the greater curvature can be followed down to the left gastroepiploic artery.

Step 5: Closure of Crura

Because the right crus is often quite attenuated, it is crucial to incorporate an adequate amount of tissue into the repair. An Allis or Babcock clamp is placed at the apex of the hiatus and into the central tendon so that both crura can be placed under tension. The esophagus is retracted anteriorly, and a No. 1 silk suture is passed through the most posterior aspect of the left crus, with care taken to avoid the adjacent spleen [see Figure 5]. A notched spoon retractor is placed through the hiatus and into the abdomen behind the left crus. The spleen is thus protected while the suture is brought through the left crus.

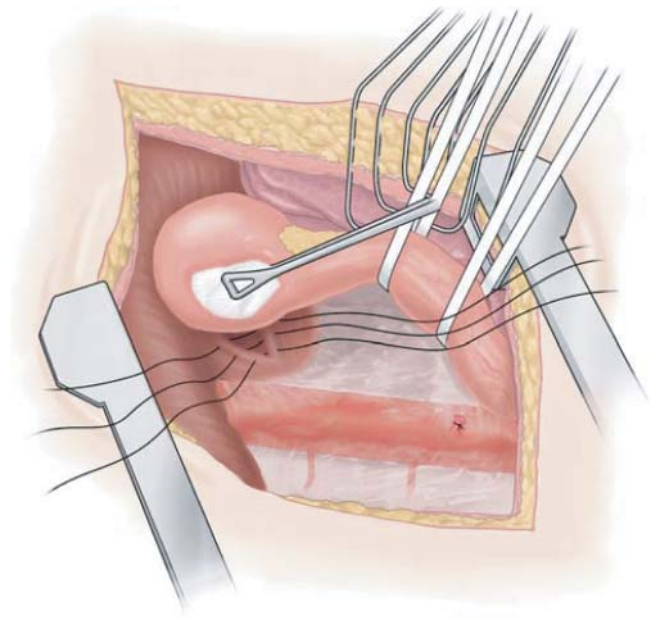


Figure 5 Transthoracic hiatal hernia repair. The esophagogastric junction is mobilized by dividing the phrenoesophageal ligament and some short gastric vessels. No. 1 silk sutures are passed through the exterior aspect of the right crus (with care taken to avoid the adjacent inferior vena cava) and through the left crus.

Next, the suture is brought out through the right crus, with care taken to prevent injury to the aorta or entry through the right pleura. Three to five crural repair stitches are then placed at 1 cm intervals, from posterior to anterior. The sutures should be staggered slightly so that the needle entry points are not all in a straight line; this measure helps prevent longitudinal shredding of the muscle fibers when the sutures are placed under tension. The sutures are held together with hemostats but left untied at this point in the operation.

Placement of traction on the last suture should close the defect while still allowing easy passage of one finger along the esophagus. The final decision on whether to tie this last suture or to cut it out is made later, after construction of the fundoplication. It is better to err on the side of an overly narrow opening; removing a suture is easier than having to place an extra one at a time when exposure is less than optimal.

Step 6: Assessment of Esophageal Length and Removal of Anterior Fat Pad

After placement of the crural stitches, an assessment of the esophageal length is made. Ideally, the stomach can easily be reduced into the abdomen without placing tension on the thoracic esophagus. When esophageal foreshortening is found, a Collis gastroplasty is performed [see Step 6a, below].

If an esophageal stricture is present, the assistant performs dilation by passing a tapered bougie orally while the surgeon supports the esophagus. The anteriorly located esophageal fat pad is removed in anticipation of the gastroplasty, with care taken not to injure the vagi located on either side [see Figure 6].

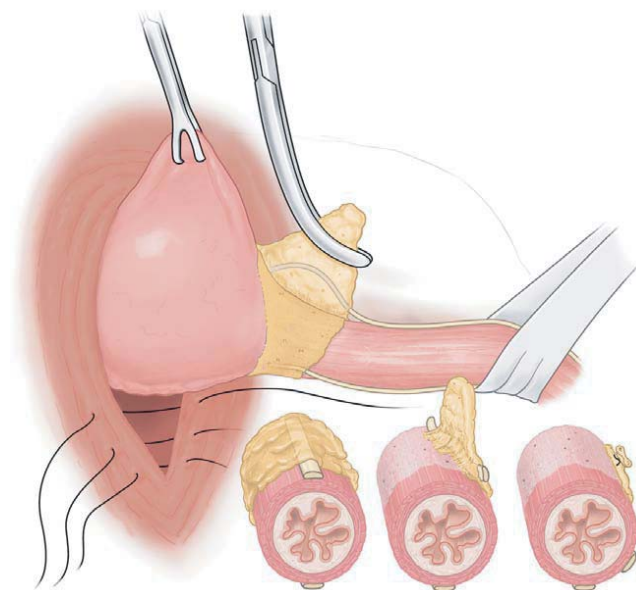


Figure 6 Transthoracic hiatal hernia repair. The anterior fat pad is removed from the esophagus with sharp dissection, with care taken to avoid injury to the vagi.

Step 6a: Collis Gastroplasty

In a Collis gastroplasty for a short esophagus, a stapler is used to form a 4 to 5 cm neoesophagus out of the proximal stomach, thereby effectively lengthening the esophagus and transposing the esophagogastric junction more distally. A large-caliber Maloney bougie (54 French for women, 56 French for men) is placed in the esophagus to prevent narrowing of the lumen as the stapler is fired. The bougie is advanced well into the stomach so that its widest portion rests at the esophagogastric junction. The bougie is held against the lesser curvature, and the fundus is retracted away at a right angle to the esophagus with a Babcock clamp. A 60 mm gastrointestinal anastomosis (GIA) stapler loaded with 3.5 mm staples is applied immediately alongside the bougie on the greater curvature side [see Figure 7a] and fired, simultaneously cutting and stapling the cardia. The staple line is oversewn with nonabsorbable 4-0 monofilament suture material on both sides [see Figure 7b]. Two metal clips are placed to mark the distal extent of the gastroplasty tube, denoting the new esophagogastric junction.

Step 7: Fundoplication and Reduction of Wrap into Abdomen

The fundus is passed posteriorly behind the esophagus and brought up against the anterior stomach, with care taken to avoid torsion of the fundal wrap. The fundus is then wrapped either over the lower 2 cm of the esophagus, if no gastroplasty was done, or over a 2 cm length of the gastroplasty tube while the bougie is in place. The seromuscular layer of the fundus is approximated to that of the esophagus or the gastroplasty tube and that of the adjacent anterior stomach with two interrupted 2-0 silk sutures [see Figure 8]. When tied, the wrap should still be loose enough to accommodate a finger alongside the esophagus. The fundoplication sutures are

again oversewn with a continuous seromuscular nonabsorbable monofilament suture. Two clips are placed at the superior aspect of the wrap. These, along with the previously placed clips, help confirm both the length and the location of the wrap on chest x-ray.

Once the fundoplication is complete, the dilator is removed and the wrap is reduced into the abdomen. Two mattress sutures of 2-0 polypropylene are placed to secure the top of the fundoplication to the underside of the diaphragm. The crural sutures are then sequentially tied, from the most posterior one to the most anterior. When the final suture is tied, one finger should still be able to pass through the hiatus alongside the esophagus.

Step 8: Drainage and Closure

A nasogastric tube is passed into the stomach and secured. Hemostasis is verified, and a single thoracostomy tube is placed. The wound is closed in layers. A chest x-ray is performed to verify the position of the tubes and the location of the clips marking the wrap. The patient is then extubated in the operating room (OR) and transported to the recovery area.

POSTOPERATIVE CARE

Patients typically remain in the hospital for about 5 days. The nasogastric tube is left on low suction and removed on postoperative day 3. Patients then begin liquid oral intake, advancing to a full-fluid diet as tolerated. Early ambulation is encouraged to prevent respiratory complications. Judicious use of analgesics and antiemetics minimizes nausea and vomiting. The thoracostomy tube is removed as drainage subsides. The epidural and Foley catheters are generally removed later the same day. A barium swallow is performed on postoperative day 5 to verify the position of the wrap, to ensure that there is no significant esophageal obstruction, and to provide a qualitative impression of gastric emptying. Gastroparesis secondary to vagal nerve dysfunction may be apparent.

Once patients can tolerate a soft solid diet, they are discharged home with instructions about the gradual resumption of a normal diet at home. Large meals and carbonated beverages should be avoided in the early postoperative period.

COMPLICATIONS

The root causes of the complications arising after transthoracic hiatal hernia repair are often technical; thus, the best prevention, in most cases, is meticulous surgical technique. Mobilization of the stomach with ligation of short gastric vessels may result in injury to the spleen. Injury to the vagi predisposes to gastric dysfunction, early satiety, and so-called gas-bloat syndrome. Poor crural approximation increases the chances that the repair will fail. Dehiscence allows upward migration of the wrap into the chest or the development of a paraesophageal hernia. The gastroplasty may leak at the staple line. Overzealous dissection along the lesser curvature can devascularize the cardia and cause ischemic stenosis of the gastroplasty tube. Torsion of the fundus results in perforation and sepsis. Excessive distraction of the ribs can lead to pain and splinting with subsequent atelectasis or pneumonia. Inadequate mobilization of the fundus may place

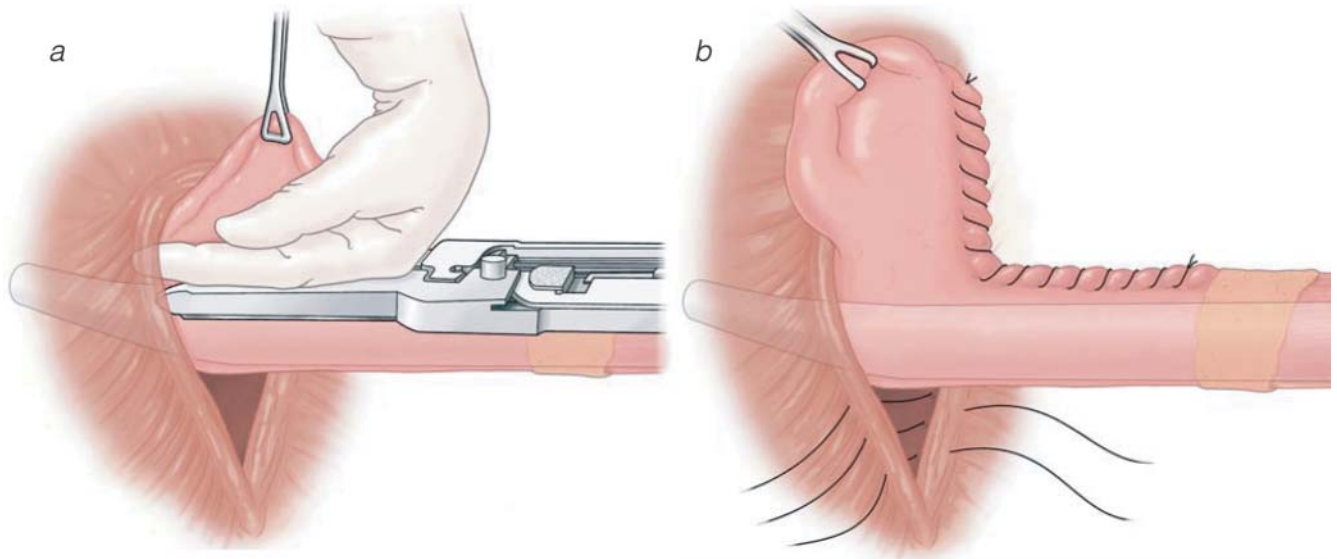


Figure 7 Transthoracic hiatal hernia repair. (a) If esophageal foreshortening is present, a Collis gastroplasty is performed. A 54 French Maloney bougie is inserted through the esophagogastric junction. A 4 to 5 cm neoesophagus is formed with a 60 mm gastrointestinal anastomosis stapler loaded with 3.5 mm staples. (b) Both the fundal staple line and the lesser curvature staple line are oversewn with nonabsorbable monofilament suture.

excessive tension on the wrap and promote later disruption and recurrent reflux. A slipped Nissen can result when the wrap is inadequately fixed to the esophagus or the gastroplasty tube and the stomach telescopes through the intact fundoplication to assume an hourglass configuration. This event leads to varying degrees of heartburn, regurgitation, and dysphagia because the proximal pouch tends to empty

slowly and remain distended after meals. A wrap that is too tight or too long results in persistent dysphagia.

Recurrent heartburn and regurgitation call for evaluation with contrast studies and esophagoscopy. The barium swallow is the most useful test for assessing whether the repair has failed. If there is an anatomic condition that is responsible for recurrent symptoms (e.g., slipping of the fundoplication or disruption of the crural repair), reoperation is usually necessary; continued medical treatment of symptoms related to a structural failure invariably proves to be of little use. A barium swallow may also identify gastroparesis secondary to vagal nerve injury. Nuclear transit studies for gastric emptying will help confirm this diagnosis. Dysphagia that is not related to recurrent reflux, ulceration, or stricture usually responds to dilation; reoperation is not required if the barium swallow shows contrast flowing through the esophagus and an intact wrap beneath the diaphragm. Given that patients with long-standing reflux are at higher risk for Barrett dysplasia and esophageal adenocarcinoma, it is important to perform endoscopy to rule out malignancy.

OUTCOME EVALUATION

Transthoracic hiatal hernia repair yields good to excellent results in more than 85% of patients undergoing a primary repair. Approximately 75% of patients who have previously undergone hiatal hernia repair experience symptomatic improvement.²

Resection of Esophagus and Proximal Stomach

In the remainder of the chapter, we describe the standard open techniques for resection of the esophagus and the esophagogastric junction. The technique of esophagectomy is largely surgeon dependent, with often strong preferences expressed for a particular operative approach. There is a

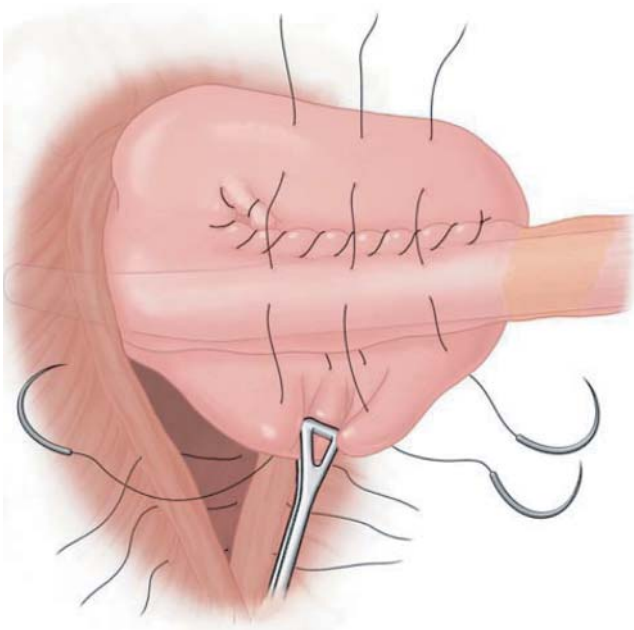


Figure 8 Transthoracic hiatal hernia repair. The fundus is passed behind the esophagus and sewn to the neoesophagus and the anterior stomach over a 2 cm length with interrupted 2-0 silk sutures.

paucity of definitive evidence as to which technique is superior. Transhiatal esophagectomy is commonly performed to treat end-stage benign esophageal disease and carcinomas of the cardia and the lower esophagus. Esophageal resection through a combined laparotomy–right thoracotomy approach (Ivor Lewis esophagectomy) is ideal for cancers of the middle esophagus but is also used by many for lower third cancers. A three-hole esophagectomy (also known as a McKeown esophagectomy) is sometimes preferred for its excellent exposure of all lymph node stations. The gastric conduit may be anastomosed to the cervical esophagus either high in the right chest (as in an Ivor Lewis esophagectomy) or in the neck (as in a transhiatal esophagectomy or three-hole esophagectomy). The left thoracoabdominal approach is less commonly used but may be indicated for resection of the distal esophagus and the proximal stomach in the case of a bulky tumor that is locally aggressive. Although the traditional anastomosis of the gastric conduit is in the left chest, it may also be placed in the neck.

PREOPERATIVE EVALUATION

Thorough preoperative preparation is essential for a good postoperative outcome. Smoking cessation and a graded regimen of home exercise will help minimize postoperative complications and encourage early mobilization. Schematic diagrams have proved useful for educating patients and shaping their expectations about quality of life and ability to swallow after esophagectomy. Illustrations, by emphasizing the anatomic relations, greatly facilitate discussion of potential complications (e.g., hoarseness from recurrent laryngeal nerve injury, pneumothorax, anastomotic leakage, mediastinal bleeding, and splenic injury).

Potential postoperative problems (e.g., reflux, regurgitation, early satiety, dumping, and dysphagia) must be discussed before operation. Such discussion is particularly relevant for patients undergoing esophagectomy for early-stage malignant tumors or for high-grade dysplasia in Barrett mucosa. These patients generally have no esophageal obstruction and may be completely asymptomatic; accordingly, their expectations about postoperative function may be quite different from those of patients with profound dysphagia secondary to near-complete esophageal occlusion. Support groups in which patients with upcoming operations can contact patients who have already undergone treatment have proved to be highly beneficial to all parties. Realistic expectations improve the chances of a satisfactory outcome.

Evaluation of Operative Risk

Preoperative assessment should include a thorough review of the patient's cardiopulmonary reserve and an estimate of the level of operative risk. Spirometry, arterial blood gas analysis, and exercise stress testing should be considered. Even when a transhiatal esophagectomy is planned, patients should be assessed with an eye to whether they can tolerate a laparotomy and a thoracotomy, in case the latter is made necessary by findings that become apparent only at the time of operation. Thoracic epidural analgesia should be administered for pain control. If a transthoracic approach is taken, a double-lumen endotracheal tube should be placed for separate lung ventilation before beginning the chest portion of the resection.

Imaging

Esophagoscopy with biopsy and contrast-enhanced CT of the chest and the upper abdomen are required before esophagectomy. If performed, the esophagogram identifies the location of the tumor and may indicate whether it extends into the proximal stomach. Esophagoscopy allows direct assessment of the mucosa, precise localization of the tumor, and collection of tissue for histologic study. Retroflexion views of the stomach, after distention with air, are particularly important if proximal gastric invasion is suspected, in which case distal esophagectomy and total gastrectomy with reconstruction of alimentary continuity by means of intestinal interposition may be required. In cases of midesophageal cancer, bronchoscopy is mandatory to rule out airway involvement. The carina and the proximal left mainstem bronchus are the sites most at risk for local invasion.

Contrast-enhanced CT scans of the chest and abdomen are standard. Thoracic and abdominal CT scans yield information on the extent of any celiac or mediastinal adenopathy, the degree of esophageal thickening, and the possibility of invasion of the adjacent aorta or tracheobronchial tree. The lung parenchyma is assessed for metastatic nodules, as are the liver and the adrenal glands. When the distal extent of tumor cannot be defined as a result of near-complete obstruction on endoscopy, a prone abdominal CT scan can help differentiate a tumor at the gastric cardia from a collapsed but normal stomach. If the obstruction is not complete, the stomach can be distended with air (through either the ingestion of effervescent granules or the passage of a small-bore nasogastric tube) to improve visualization. A prone CT scan also yields improved imaging of the gastrohepatic and celiac lymph nodes by allowing the stomach to fall away from these adjacent structures. Metastatic cancer in the celiac lymph nodes portends a poor prognosis.

PET is useful for the detection of occult distant metastases that preclude curative resection. Suspicious areas should undergo needle biopsy or laparoscopic or thoracoscopic assessment. Similarly, pleural effusions must be tapped for cytologic evaluation. Invasion of mediastinal structures and the presence of distant metastases are contraindications to esophagectomy.

At present, EUS, although quite sensitive for detection of paraesophageal adenopathy, is incapable of accurately differentiating reactive lymph nodes from nodes invaded by malignancy. EUS-FNA of suspicious lymph nodes should be done if possible. This is often not possible because of intervening tumor in the wall of the esophagus. CT and PET have limitations; thus, locoregional involvement may not be recognized before resection is attempted. In patients who are marginal candidates for surgical treatment and in whom metastatic disease is suspected, laparoscopy has been advocated for histologic evaluation of small superficial liver nodules, peritoneal abnormalities, and celiac nodes. Although this approach adds to the cost of investigation, it can save the patient from having to undergo a major operation for what would later prove to be an incurable condition.

Neoadjuvant Therapy

Patients with esophageal cancer who are candidates for resection may benefit from neoadjuvant chemotherapy and

concurrent radiation therapy. In particular, patients with good performance status and locally advanced disease should be considered for such therapy. To date, no randomized trials have conclusively demonstrated a survival benefit with this approach, but several series have documented a 20 to 30% rate of complete response with no viable tumor found at the time of resection. After chemoradiation, patients are restaged with a CT. PET after treatment may yield spurious results in that inflammatory conditions can mimic the increased tracer uptake seen in malignant tissue. Microscopic disease cannot be assessed, and scarring from radiation may further confound the situation by preventing tracer uptake in areas that actually harbor malignancy.

If there are no contraindications to surgical treatment, resection is scheduled 4 to 6 weeks after the completion of neoadjuvant therapy. This interval allows time for patients to return to their baseline activity level and for any induced hematologic abnormalities to be corrected. Previous chemoradiation therapy does not make transhiatal esophagectomy significantly more difficult or complicated. Many tumors are downstaged and less bulky at the time of resection. In centers with experience in this approach, the rates of bleeding and anastomotic leakage remain low.

OPERATIVE PLANNING

Transhiatal Esophagectomy

In transhiatal esophagectomy, the stomach is mobilized through an upper midline laparotomy, the esophagus is mobilized from adjacent mediastinal structures via dissection through the hiatus without the use of a thoracotomy, and the stomach is transposed through the posterior mediastinum and anastomosed to the cervical esophagus at the level of the clavicles. The main advantages of this approach are (1) a proximal surgical margin that is well away from the tumor site, (2) an extrathoracic esophagogastric anastomosis that is easily accessible in the event of complications, and (3) reduced overall operative trauma. Single-center studies throughout the world have shown transhiatal esophagectomy to be safe and well tolerated, even in patients who may have significantly reduced cardiopulmonary reserve. Long-term survival is equivalent to that reported after transthoracic esophagectomy.

Although transhiatal esophagectomy has been used for resection of tumors at any location in the esophagus, it is best suited for resection of tumors in the lower esophagus and at the esophagogastric junction. It should also be considered for certain advanced nonmalignant conditions of the esophagus. Nondilatable strictures of the esophagus may occur as an end-stage complication of gastroesophageal reflux. Intractable reflux after failed hiatal hernia repair may not be amenable to further attempts at reconstruction of the esophagogastric junction and thus may call for esophagectomy. Because of the high cervical anastomosis, transhiatal esophagectomy is less likely to predispose to postoperative reflux and recurrent stricture formation than transthoracic esophagectomy would be. Achalasia may result in a sigmoid megaesophagus and dysphagia that cannot be managed without removal of the esophagus. Transhiatal esophagectomy permits complete removal of the thoracic esophagus and, in the majority of patients, restoration of comfortable swallowing without the need for a thoracotomy.

Generally, patients are admitted to the hospital on the day of the operation. Thoracic epidural analgesia is administered, both intraoperatively and postoperatively, and appropriate antibiotic prophylaxis is provided. Heparin, 5,000 U subcutaneously, is given before induction, and pneumatic calf compression devices are applied. A radial artery catheter is placed to permit continuous monitoring of blood pressure. Central venous access is rarely required. General anesthesia is administered via an uncut single-lumen endotracheal tube. Flexible esophagoscopy is performed (if it was not previously performed by the surgical team). A nasogastric tube is placed before final positioning and draping.

The patient is placed in the supine position with a small rolled sheet between the shoulders. The arms are secured to the sides, and the head is rotated to the right with the neck extended. The neck, the chest, and the abdomen are prepared as a single sterile field. The drapes are placed so as to expose the patient from the left ear to the pubis. The operative field is extended laterally to the anterior axillary lines to permit placement of thoracostomy tubes as needed. A self-retaining table-mounted retractor is used to facilitate upward and lateral traction along the costal margin.

Ivor Lewis Esophagectomy

At many institutions, Ivor Lewis esophagectomy is preferred because it provides excellent direct exposure for dissection of the intrathoracic esophagus in that it combines a right thoracotomy with a laparotomy. This procedure should be especially considered when there is concern regarding the extent of esophageal fixation within the mediastinum. One advantage of Ivor Lewis esophagectomy is that an extensive local lymphadenectomy can easily be performed through the right thoracotomy. Any attachments to mediastinal structures can be freed under direct vision. Whether any regional lymph node dissection is necessary is highly controversial; no significant survival advantage has yet been demonstrated. Long-term survival after Ivor Lewis resection is equivalent to that after transhiatal esophagectomy.³

The main disadvantages of the Ivor Lewis procedure are (1) the physiologic impact of the two major access incisions employed (a right thoracotomy and a midline laparotomy) and (2) the location of the anastomosis (in the chest). Incision-related pain may hinder deep breathing and the clearing of bronchial secretions, resulting in atelectasis and pneumonia. The use of thoracic epidural catheters for pain management has greatly improved pain-related respiratory complications. Complications of the intrathoracic anastomosis may be hard to manage. Although the anastomotic leakage rate associated with Ivor Lewis esophagectomy has typically been 5% or lower—and thus substantially lower than the rate cited for the cervical anastomosis after transhiatal esophagectomy—intrathoracic leaks are much more dangerous and difficult to handle than intracervical leaks. In many cases, drainage of the leak will be incomplete and empyema will result. Reoperation may prove necessary to manage mediastinitis.

Three-Hole Esophagectomy

Three-hole esophagectomy is performed when the surgeon desires direct exposure to all phases of dissection, extensive lymph node clearance, and an anastomosis in the neck. The

right chest is opened first, and the intrathoracic esophagus and the regional lymph nodes are dissected and mobilized free. The patient is then turned supine for the abdominal and neck phase, very similar to a transhiatal esophagectomy.

Left Thoracoabdominal Esophagogastrectomy

The left thoracoabdominal approach is indicated for large gastroesophageal junction tumors and resection of the distal esophagus and the proximal stomach when removal of the stomach necessitates the use of an intestinal substitute to restore swallowing. This approach can also be used for very obese patients to obtain optimal exposure. If the proximal stomach must be resected for adequate resection margins to be obtained, then the distal stomach may be anastomosed to the esophagus in the left chest. This operation can be associated with significant esophagitis from bile reflux. Consequently, many surgeons prefer to resect the entire stomach and the distal esophagus and then to restore swallowing with a Roux-en-Y jejunal interposition anastomosed to the residual thoracic esophagus. Alternatively, some surgeons use this approach for most cancers and routinely place the anastomosis in the left neck. Similar to other transthoracic approaches, the use of a thoracic epidural catheter for pain control ameliorates pain-related respiratory complications.

OPERATIVE TECHNIQUE

Transhiatal Esophagectomy

Transhiatal esophagectomy is best understood as consisting of three components: abdominal, mediastinal, and cervical. The abdominal portion involves mobilization of the stomach, pyloromyotomy (if performed), and placement of a temporary feeding jejunostomy.

Step 1: incision and entry into peritoneum A midline laparotomy is performed from the tip of the xiphoid to the umbilicus. The peritoneum is opened to the left of the midline so that the falciform and the preperitoneal fat may be retracted en bloc to the right. Body wall retractors are placed at 45° angles from the midline to elevate and distract both costal margins. The retractors are placed so as to lift up the costal margin gently and open the wound. The abdomen is then inspected for metastases.

Step 2: division of gastrohepatic ligament and mobilization of distal esophagus The left lobe of the liver is mobilized by dividing the triangular ligament and then folded to the right and held in this position with a moist laparotomy pad and a deep-bladed self-retaining retractor. Next, the gastrohepatic ligament is divided. Occasionally, there is an aberrant left hepatic artery arising from the left gastric artery [see Figure 9]. The peritoneum over the right crus is incised, and the hiatus is palpated; the extent and mobility of any tumor may then be assessed. The peritoneum over the left crus is similarly divided, and the esophagus is encircled with a 2.5 cm Penrose drain. Traction is applied to draw the esophagogastric junction upward and to the right; this measure facilitates exposure of the short gastric arteries coursing to the fundus and the cardia.

Step 3: mobilization of stomach The greater curvature of the stomach is inspected, and the right gastroepiploic

artery is palpated. The lesser sac is generally entered near the midpoint of the greater curvature. The transition zone between the right gastroepiploic arcade and the short gastric arteries is usually devoid of blood vessels.

Dissection then proceeds along the greater curvature toward the pylorus. The omentum is mobilized from the right gastroepiploic artery. Vessels are ligated between 2-0 silk ties, and great care is exercised to avoid placing excessive traction on the arterial arcade. A 1 cm margin is always maintained between the line of dissection and the right gastroepiploic artery. Venous injuries, in particular, can occur with injudicious handling of tissue. The ultrasonic scalpel is particularly efficient and effective for mobilization of the stomach; again, this instrument must be applied well away from the gastroepiploic arcade. Dissection is continued rightward to the level of the pylorus. It should be noted that the location of the gastroepiploic artery in this area may vary; often it is at some unexpected distance from the stomach wall. Posterior adhesions between the stomach and the pancreas are lysed so that the lesser sac can be completely opened.

The assistant's left hand is then placed into the lesser sac to retract the stomach gently to the right and place the short gastric vessels on tension. The Penrose drain previously placed around the esophagus facilitates exposure by retracting the cardia to the right. Dissection along the greater curvature proceeds cephalad. The vessels are divided well away from the wall of the stomach to prevent injury to the fundus. Clamps should never be placed on the stomach. A high short gastric artery is typically encountered just adjacent to the left crus. Precise technique is required to prevent injury to the spleen. The Penrose drain [see Step 2, above] is exposed as the peritoneum is opened over the left crus. Mobilization of the proximal stomach and liberation of the distal esophagus are thereby completed.

Once the stomach has been completely mobilized along the greater curvature, it is elevated and rotated to the right [see Figure 10]; the left gastric artery and associated nodal tissues can then be visualized via the lesser sac. The superior edge of the pancreas is visible, and the remaining posterior attachments of the stomach are divided along the hiatus and the left crus. These may be quite extensive if there has been a history of pancreatitis or preoperative radiation therapy.

If the operation is being done for malignant disease, a final determination of resectability can be made at this point. Tumor fixation to the aorta or the retroperitoneum can be assessed. Celiac and para-aortic lymph nodes can be palpated and, if necessary, sent for biopsy. The left gastric artery and vein are then ligated proximally, either through the lesser sac or directly through the divided gastrohepatic ligament. All nodal tissue is dissected free in anticipation of subsequent removal en bloc with the specimen.

Step 4: mobilization of duodenum and pyloromyotomy The duodenum is mobilized with a Kocher maneuver. Careful attention to the superior extent of this dissection is critical. Adhesions to either the porta hepatis or the gallbladder must be divided to ensure that the pylorus is sufficiently freed for later migration to the diaphragmatic hiatus.

Gastric drainage can be provided by a pyloromyotomy and is performed by most surgeons. The pyloromyotomy is begun 1 to 2 cm on the gastric side of the pylorus. The serosa and

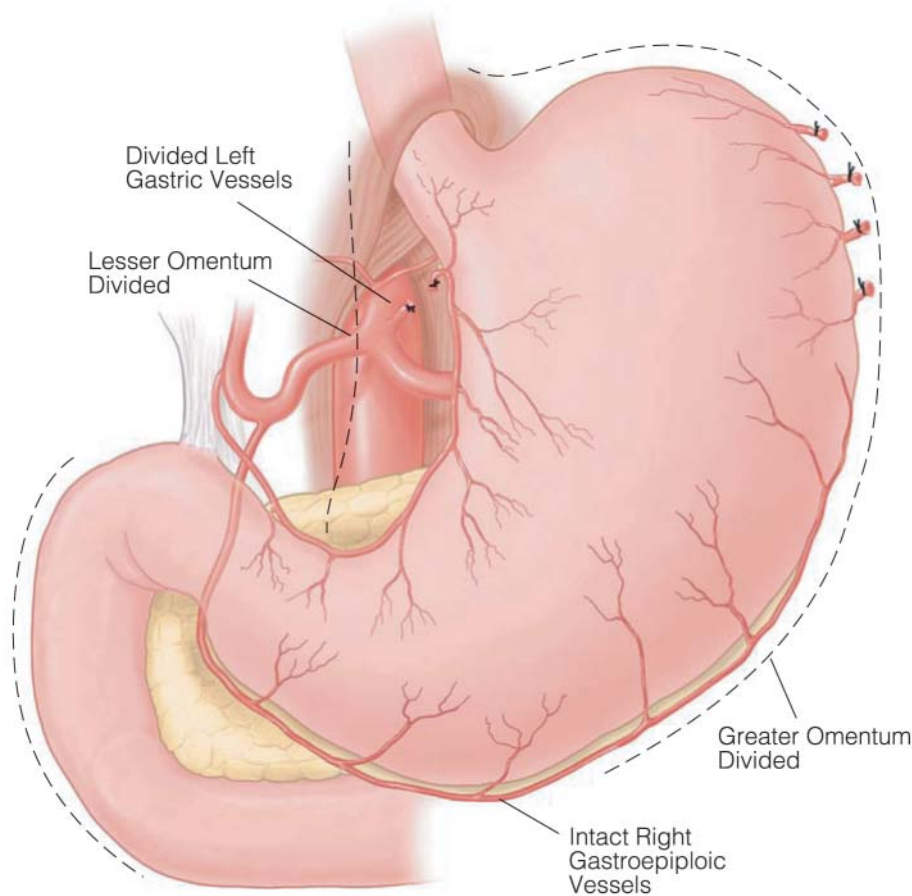


Figure 9 Transhiatal esophagectomy. The duodenum is mobilized, and the gastrohepatic and gastrocolic omenta are divided.

the muscle are divided with a small scalpel to expose the submucosa; generally, these layers of the stomach are robust, making the proper plane easy to find.

Dissection is extended toward the duodenum with the aid of a fine-tipped right-angle or tonsil clamp. The duodenal submucosa, recognizable by its fatty deposits and yellow coloration, is exposed for approximately 0.5 cm. The duodenal submucosa is usually much more superficial than expected, and accidental entry into the duodenum often occurs just past the left edge of the circular muscle of the pylorus. Should entry into the lumen occur, a simple repair using interrupted fine monofilament (4-0 or 5-0 polypropylene) sutures to close the mucosa is performed. Small metal clips are applied to the knots of the traction sutures before removal of the ends; these clips serve to indicate the level of the pyloromyotomy on subsequent radiographic studies. A tag of omentum can be easily sutured over the myotomy site for an added layer of security. My own preference is not to perform a pyloromyotomy primarily to reduce the possibility of postoperative bile reflux, which is very problematic to treat. In addition, I remain unconvinced that pyloromyotomy helps gastric drainage that much. With the availability of balloon dilation, it is now simple to enhance emptying postoperatively if needed. Many studies have confirmed that not performing a pyloromyotomy is safe.

Step 5: feeding jejunostomy Placement of a standard Weitzel jejunal feeding tube approximately 30 cm from the

ligament of Treitz completes the abdominal portion of the transhiatal esophagectomy.

Step 6: exposure and encirclement of cervical esophagus

The cervical esophagus is exposed through a 6 to 8 cm incision along the anterior edge of the left sternocleidomastoid muscle [see Figure 1] that is centered over the level of the cricoid cartilage. The platysma is divided to expose the omohyoid, which is divided at its tendon. The strap muscles are divided low in the neck at their origin on the back of the manubrium. The esophagus and its indwelling nasogastric tube can be palpated.

The carotid sheath is retracted laterally, and blunt dissection is employed to reach the prevertebral fascia. The inferior thyroid artery is ligated laterally; the recurrent laryngeal nerve is visible just deep and medial to this vessel. No retractor other than the surgeon's finger should be applied medially: traction injury to the recurrent laryngeal nerve will result in both vocal cord palsy and uncoordinated swallowing with aspiration. In particular, metal retractors must not be used in this area. The tracheoesophageal groove is incised close to the esophageal wall while gentle finger traction is applied cephalad to elevate the thyroid cartilage toward the right. This measure usually suffices to define the location of the nerve.

The esophagus is then encircled by passing a right-angle clamp posteriorly from left to right while the surgeon's finger remains in the tracheoesophageal groove. The tip of the

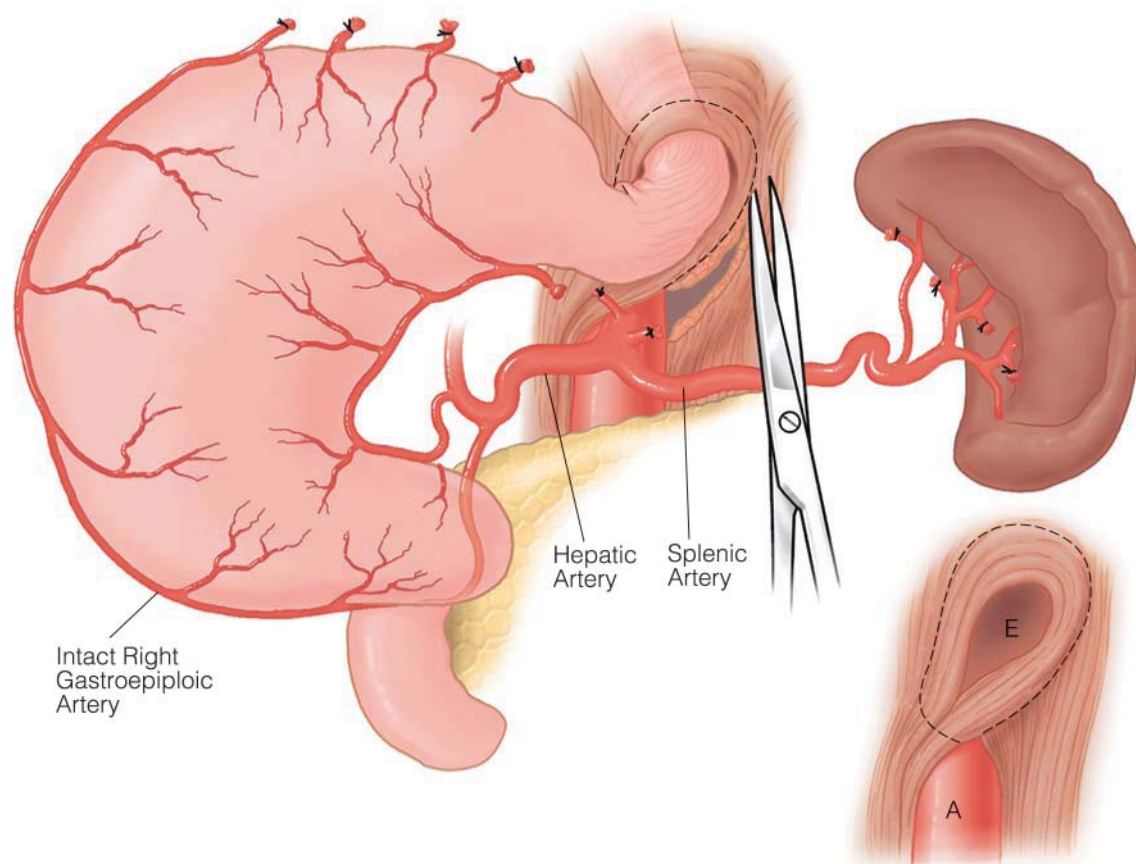


Figure 10 Transhiatal esophagectomy. After the stomach has been completely mobilized along the greater curvature, it is elevated and rotated to the right. The left gastric vessels are suture-ligated and divided. A 1 cm margin of the diaphragmatic crura is taken in continuity with the esophagogastric junction, providing ample clearance of the tumor and improved exposure of the lower mediastinum. *A* denotes the aorta, *E* denotes the esophageal hiatus.

clamp is brought into the pulp of the fingertip. The medially located recurrent laryngeal nerve and the membranous trachea are thereby protected from injury. The clamp is brought around, and a narrow Penrose drain is passed around the esophagus [see Figure 11]. Blunt finger dissection is employed to develop the anterior and posterior planes around the esophagus at the level of the thoracic inlet.

Step 7: mediastinal dissection Some authors describe this portion of the procedure as a blunt dissection, but, in fact, the vast majority of the mediastinal mobilization is done under direct vision. Narrow, long-handled, handheld, curved Harrington retractors are placed into the hiatus and lifted up to expose the distal esophagus. Caudal traction is placed on the esophagus, allowing excellent visualization of the hiatus and the distal esophagus. Long right-angle clamps are used to expose these attachments. Vascularity in this area is often minimal, and hemostasis can easily be achieved with either the electrocautery, ultrasonic scalpel, metal clips, or ties. The left crus can be divided to facilitate exposure. Paraesophageal lymph nodes are removed either en bloc or as separate specimens. Dissection is continued cephalad with the electrocautery and a long-handled right-angle clamp. The two vagi

are divided, and the periesophageal adhesions are lysed. Mobilization of the distal esophagus under direct vision is thus completed up to the level of the carina.

Three specific maneuvers are now carried out. First, the plane posterior to the esophagus is developed [see Figure 12]. The surgeon's right hand is advanced palm upward into the hiatus, with the fingers closely applied to the esophagus. The volar aspects of the fingers run along the prevertebral fascia, elevating the esophagus off the spine. A moist sponge stick is placed through the cervical incision, also posterior to the esophagus. The sponge is advanced toward the right hand, which is positioned within the mediastinum. As the sponge is advanced into the right palm, the posterior plane is completed.

Second, the anterior plane is developed [see Figure 13]. This is often much more difficult than developing the posterior plane because the left mainstem bronchus may be quite close to the esophagus. Again, the surgeon's right hand is placed through the hiatus, but it is now palm down and anterior to the esophagus. The fingertips enter the space between the esophagus and the left mainstem bronchus. The hand is gently advanced, and the airway is displaced anteriorly. A blunt curved suction handle is employed from above as a

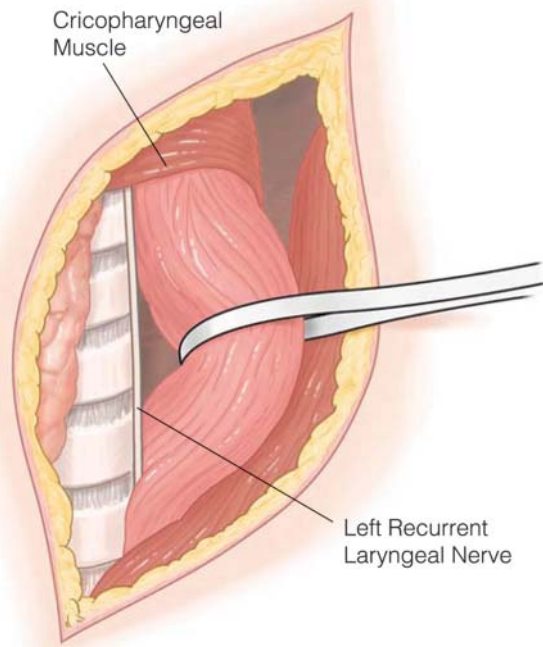


Figure 11 Transhiatal esophagectomy. Once the cervical esophagus is exposed through an incision along the left sternocleidomastoid muscle, strap muscles are divided and retracted, and the cervical esophagus is dissected away from the left and right recurrent laryngeal nerves.

substitute finger. It is advanced along the anterior aspect of the esophagus through the cervical incision. The right hand guides the tip of the suction handle beneath the bronchus. Lateral displacement of the handle allows further mobilization of the bronchus away from the esophagus. Completion of the anterior and posterior planes usually results in a highly mobile esophagus.

Third, the lateral attachments of the upper and middle esophagus are divided. Upward traction is applied with the Penrose drain previously placed around the cervical esophagus, allowing further dissection at the level of the thoracic inlet. Lateral attachments are pushed caudally into the mediastinum, and traction applied to the esophagus from below allows these attachments to be visualized inferiorly through the hiatus and then isolated with long right-angle clamps and divided with the electrocautery. Caution must be exercised so as not to injure the azygos vein. Dissection on the right side must therefore be kept close to the esophagus. Once the last lateral attachment is divided, the esophagus is completely free and can be advanced into the cervical wound.

Close monitoring of arterial blood pressure is maintained throughout. Transient hypotension may occur as a result of mediastinal compression and temporary impairment of cardiac venous return as the surgeon's hand or retractors are passed through the hiatus. Vasopressors are never required for management: simple repositioning of the retractors or removal of the dissecting hand usually results in prompt restoration of normal blood pressure. Placement of the patient in a slight Trendelenburg position is often helpful.

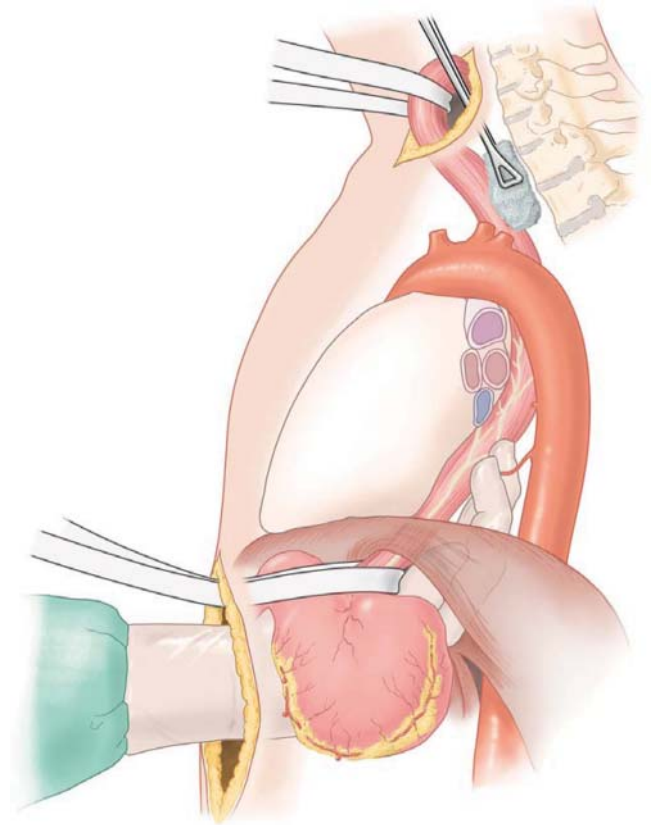


Figure 12 Transhiatal esophagectomy. The plane posterior to the esophagus is developed by placing the surgeon's right hand into the hiatus along the prevertebral fascia. A moist sponge stick is placed through the cervical incision posterior to the esophagus, and the posterior plane is completed.

Step 8: proximal transection of esophagus and delivery into abdomen The nasogastric tube is retracted to the level of the cricopharynx, and the esophagus is divided with a cutting stapler 5 to 6 cm distal to the muscle. The esophagus is then removed via the abdomen [see Figure 14]. Retractors are placed in the hiatus, and the mediastinum is inspected for hemostasis. Both pleurae are inspected. The lungs are inflated so that it can be determined which pleural space requires thoracostomy drainage. The mediastinum is packed with dry laparotomy pads from below. A narrow pack is placed into the thoracic inlet from above. Chest tubes are then placed as required along the inframammary crease in the anterior axillary line. The drainage from these tubes should be closely monitored throughout the rest of the operation to ensure that any bleeding from the mediastinal dissection does not go unnoticed.

Step 9: excision of specimen and formation of gastric tube The gastric fundus is grasped, and gentle tension is applied along the length of the stomach. The esophagus is held at right angles to the body of the stomach, and the fat in the gastrohepatic ligament is elevated off the lesser curvature; all lymph nodes are thus mobilized. A point approximately midway along the lesser curvature is selected. The blood vessels traversing this area from the right gastric artery are

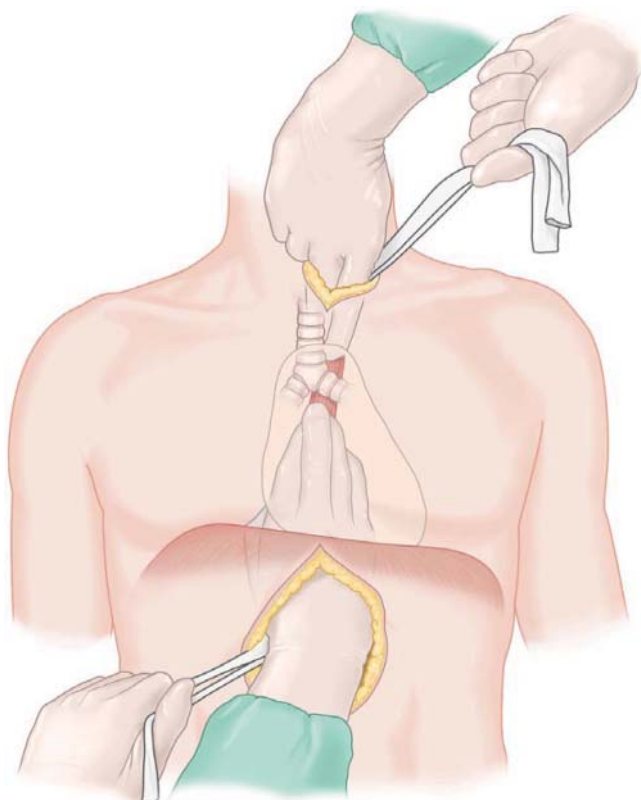


Figure 13 Transhiatal esophagectomy. The anterior plane is developed by placing the surgeon's right hand through the hiatus anterior to the esophagus. The fingertips enter the space between the esophagus and the left mainstem bronchus, to be met by a blunt suction handle passed downward through the cervical incision. The lateral attachments of the esophagus are divided from above downward as far as the aortic arch.

ligated to expose the lesser curvature. The distal resection margin is then marked; it should be 4 to 6 cm from the esophagogastric junction, extending from the selected point on the lesser curvature to a point medial to the fundus. A 60 mm GIA stapler loaded with 3.5 or 4.8 (depending on the thickness of the stomach) mm staples is then used to transect the proximal stomach, proceeding from the lesser curvature toward the fundus [see Figure 15]. Resection of the cardia along with the adjacent portion of the lesser curvature effectively converts a J-shaped stomach into a straight tube and harvests many left gastric territory lymph nodes.

For maximizing the length of the gastric tube, several technical points are critical. Tension must be maintained on the stomach as the stapler is serially applied. The stapler should be simply placed on the stomach and fired: no attempt should be made to telescope tissue into the jaws because to do so would effectively reconstitute the curve of the stomach and diminish its upward reach. Typically, five or six staple loads are required.

The specimen is removed, and frozen-section examination is done on the distal margin. The completed staple line is then oversewn with a continuous Lembert suture of 4-0 polypropylene. Once again, tension is maintained along the stomach to prevent any foreshortening of the lesser curvature. The use of two separate sutures, each reinforcing half of the staple line, is helpful in this regard. Alternatively, interrupted 4-0 sutures can be used.

Step 10: advancement of stomach into chest or neck

The mediastinal packs are removed, and hemostasis is verified in the chest. The stomach is inspected as well. The ends of any short gastric vessels that were divided with the

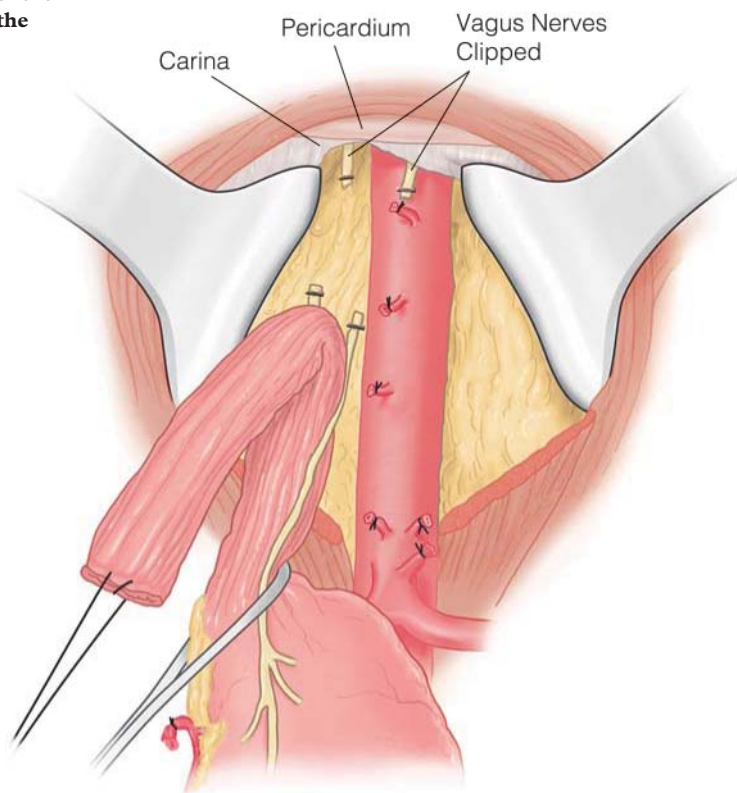


Figure 14 Transhiatal esophagectomy. The esophagus is divided in the neck and delivered into the abdomen. Retractors are placed in the hiatus, and any vessels entering into the esophagus are clipped and divided. The vagi are also clipped and divided.

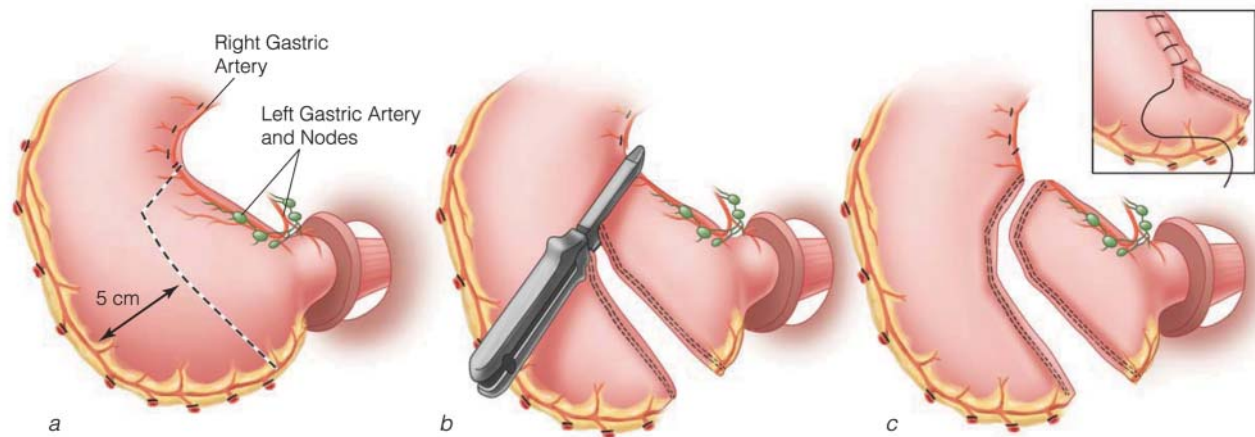


Figure 15 Transhiatal esophagectomy. A gastric tube is formed by stapling along the lesser curvature of the stomach from the junction of the right and left gastric vessels to the top of the fundus. This staple line is oversewn with either an interrupted or a continuous fine suture, with care taken not to foreshorten the gastric tube. The gastric tube is made at least 5 cm wide to avoid undo ischemia.

ultrasonic scalpel are now tied so that subsequent manipulation does not precipitate bleeding. The stomach is oriented so that the greater curvature is to the patient's left. There must be no torsion. The anterior surface of the fundal tip should be marked with ink so that proper orientation of the stomach can be confirmed after its passage into the neck. The stomach can usually be advanced through the posterior mediastinum without any traction sutures or clamps. The surgeon's hand is placed palm down on the anterior surface of the stomach, with the fingertips about 5 cm proximal to the tip of the fundus. The hand is then gently advanced through the chest, pushing the stomach ahead of itself. The tip of the fundus is gently grasped with a Babcock clamp as it appears in the neck. To prevent trauma at this most distant aspect of the gastric tube, the clamp should not be ratcheted closed.

No attempt should be made to pull the stomach up into the neck: the position of the fundus is simply maintained as the surgeon's hand is removed from the mediastinum. Further length in the neck can usually be gained by gently readvancing the hand along the anterior aspect of the stomach. This measure uniformly distributes tension along the tube and ensures proper torsion-free orientation in the chest. The stomach is pushed up into the neck rather than drawn up by the clamp.

A useful alternative approach for positioning the gastric tube involves passing a large-bore Foley catheter through the mediastinum from the neck incision. The balloon is inflated, and a 50 cm section of a narrow plastic laparoscopic camera bag is tied onto the catheter just above the balloon. The gastric tube is positioned within the bag, and suction is applied through the catheter, creating an atraumatic seal between the stomach and the surrounding plastic bag. As the bag is drawn upward through the neck with gentle traction on the Foley catheter, the stomach advances through the mediastinum. The stomach is not secured to the prevertebral fascia in any way.

The feeding jejunal tube is brought out the left midabdomen through a separate stab incision. The hiatus is inspected

for hemostasis, as is the splenic hilum. It may be necessary to reconstitute the hiatus with one or two simple sutures of 1-0 silk placed through the crura. These sutures must be placed with care to ensure that injury to the gastroepiploic arcade does not occur at this late point in the procedure. The hiatus is narrowed, but not so much that three fingers cannot be easily passed alongside the gastric conduit. This reconstitution will help prevent herniation of other abdominal contents alongside the gastric conduit. The liver is returned to its anatomic position, thus also preventing any subsequent herniation of bowel into the chest. The pylorus is generally found at the level of the diaphragm. The laparotomy is then closed in the usual fashion. The viability of the fundus in the neck incision is checked periodically as the abdominal portion of the procedure is completed.

Step 11: cervical esophagogastric anastomosis The construction of the esophagogastric anastomosis is the most important part of the entire operation: any anastomotic complication will greatly compromise the patient's ability to swallow comfortably. Accordingly, meticulous technique is essential.

A seromuscular traction suture of 4-0 polyglactin is placed through the anterior stomach at the level of the clavicle and drawn upward, thus elevating the fundus into the neck wound and greatly facilitating the anastomosis.

The site of the anterior gastrotomy is then carefully selected: it should be midway between the oversewn lesser curvature staple line and the greater curvature of the fundus (marked by the ligated ends of the short gastric vessels). The staple line on the cervical esophagus is removed, and the anterior aspect of the esophagus is grasped with a fine-toothed forceps at the level of the planned gastrotomy. A straight DeBakey forceps is then applied across the full width of the esophagus to act as a guide for division. The esophagus is cut with a new scalpel blade at a 45° angle so that the anterior wall is slightly longer than the posterior wall; the anterior wall then forms the hood of the anastomosis. The fine-toothed forceps is used to maintain orientation of the esophagus throughout. Two

full-thickness stay sutures of 4-0 polyglactin are placed, one at the midpoint of the anterior cut edge of the esophagus and one at the corresponding location posteriorly. The posterior stitch is placed from inside the lumen, and the needle is left on the suture for later use.

A small gastrotomy is then performed with a needle-tipped electrocautery using cutting current. The incision is obliquely oriented, with the cephalad extent proceeding slightly medially. The needle from the stay suture previously placed on the posterior wall of the esophagus is then passed the full thickness of the cephalad aspect of the gastrotomy [see Figure 16a]. Traction on this untied suture brings the esophagus toward the stomach. A 45 mm endoscopic stapler loaded with 3.5 mm staples is used to form the back wall of the anastomosis. The thicker portion of the device (the cartridge) is advanced cephalad into the esophagus, with the narrower portion (the anvil) in the gastric lumen [see Figure 16b]. The tip of the stapler should be aimed toward the patient's right ear. Tension is applied to the stay suture holding the esophagus and stomach together so as to bring tissue into the jaws of the device. The portion of the fundus extending beyond the stapler is then rotated medially to ensure that the new staple line is well away from the one previously placed along the lesser curvature. This is a crucial point: crossing of the two staple lines may create an ischemic area that can give rise to a large leak in the postoperative period.

The stapler is then closed, holding the esophagus and stomach together, but not yet fired. The position of the nasogastric tube should be maintained just at the level of the cricopharyngeus during the construction of the anastomosis. This positioning keeps the tube out of the operative field and protects it from being entrapped by the jaws of the stapler; it also facilitates subsequent passage of the tube into the gastric conduit once the posterior wall of the anastomosis is complete. Two suspension sutures are placed on either side of the closed stapler, one toward the tip and the other near the heel of the jaws. These four sutures alleviate any potential tension on the staple line by approximating the muscular layer of the esophagus to the seromuscular layer of the stomach. The suspension sutures are tied, and the stapler is fired, thereby completing the posterior portion of the anastomosis [see Figure 16c].

The anterior portion of the anastomosis is closed in two layers. The inner layer consists of a continuous 4-0 polydioxanone suture placed as full-thickness inverting stitches, and the second layer consists of interrupted seromuscular Lembert sutures [see Figure 17]. The lateral and medial corners of the anastomosis, where the staple line meets the handsewn portion, merit extra attention. These corners are quite fragile, and excessive traction may result in dehiscence progressing cephalad along the staple line in a zipperlike fashion. The inner layer should therefore be started at each corner, incorporating the last 5 mm of the staple line. Once several stitches have been placed from the two corners, the nasogastric tube can be passed through the anastomosis. The nasogastric tube is properly positioned when the most distal black marker is at the nares. The inner layer is then completed as the two sutures are tied at the midpoint.

Step 12: drainage, closure, and completion x-ray The incision is irrigated. The strap muscles are not reapproximated but are merely attached loosely to the underside of the

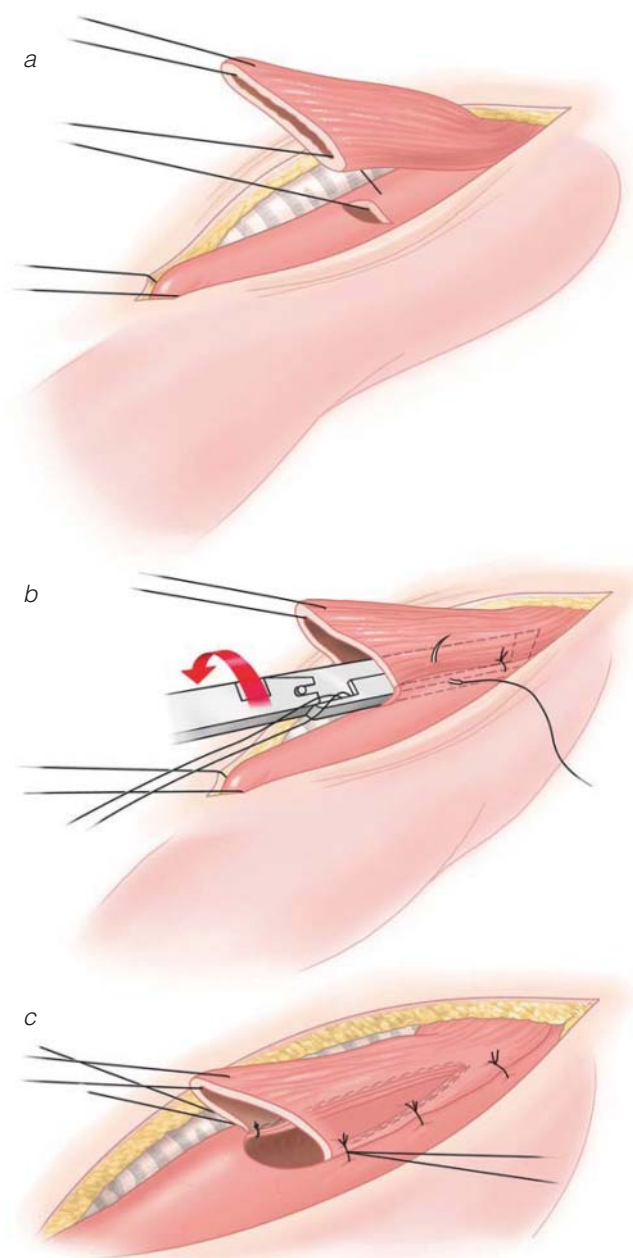


Figure 16 Transhiatal esophagectomy. (a) After the proximal end of the stomach tube is delivered into the neck, the esophagus is cut at a 45° angle so that the anterior wall is longer than the posterior wall. A gastrotomy is placed between the oversewn lesser curvature staple line and the greater curvature of the fundus. A full-thickness suture is placed through all layers of the esophagus and all layers of the gastrotomy. (b) An endoscopic gastrointestinal anastomosis stapler is used to form the back wall of the anastomosis. The thicker portion of the device (the cartridge) is advanced cephalad into the esophagus, with the narrower portion (the anvil) in the gastric lumen. The tip of the stapler should be aimed toward the patient's right ear. The staple line must be well away from the lesser curvature staple line. Two suspension sutures are placed on either side of the closed stapler, one toward the tip and the other near the heel of the jaws. (c) The stapler is fired to complete the posterior portion of the anastomosis.

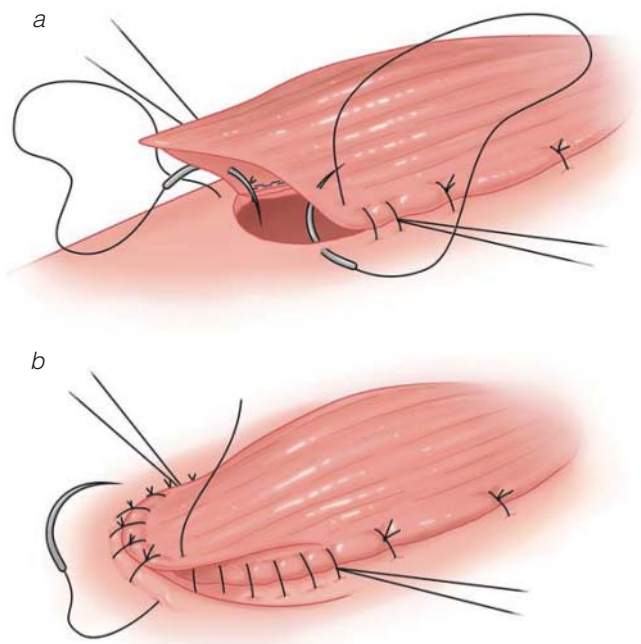


Figure 17 Transhiatal esophagectomy. The anterior portion of the anastomosis is completed with (a) an inner layer consisting of a continuous 4-0 polydioxanone suture and (b) an outer layer consisting of interrupted sutures.

sternocleidomastoid muscle with two interrupted 4-0 polyglactin sutures. The platysma is reconstituted with interrupted 4-0 polyglactin sutures. The nasogastric tube is secured.

A chest x-ray is obtained in the OR to verify the position of the drains and the absence of any abnormal collections in the chest. Patients are extubated in the OR and transported to the anesthetic recovery area. Extubation should be carried out only when the health care team is confident that subsequent reintubation is unlikely to be necessary. Emergency reintubation after a cervical anastomosis is hazardous in that vigorous neck extension may threaten the suture line. Once patients are awake and alert, which is usually 3 to 4 hours after the operation, they are taken to the general ward. As a rule, admission to an intensive care unit is not required unless there are substantial comorbidities or intraoperative concerns. To prevent excessive traction on the anastomosis, the neck should be maintained in a flexed position with two pillows placed behind the head.

In certain patients, a stapled anastomosis may be impractical. In patients with a bull-neck habitus, for example, a partial sternal split may be required for adequate exposure of the cervical esophagus, and a handsewn true end-to-end anastomosis (EEA) may be necessary. In addition, patients who have previously undergone antireflux surgery may have a relatively short gastric tube that will necessitate an end-to-end reconstruction.

Patients should, if possible, begin walking the morning after the operation. An incentive spirometer should be constantly within arm's length of the patient, and hourly use of this device should be encouraged. The nasogastric tube is removed on postoperative day 3, and the patient is allowed

ice chips in the mouth. The thoracic epidural catheter is removed the afternoon after the chest tube is removed. The diet is gradually advanced so that a soft diet is begun on postoperative day 5 or 6. A barium swallow is performed on postoperative day 6 in preparation for hospital discharge on day 7 or 8.

Ivor Lewis Esophagectomy

Steps 1 through 5 Esophagoscopy is performed to confirm the location of the tumor. Steps 1 through 5 of an Ivor Lewis esophagectomy are virtually identical to the first five steps (i.e., the abdominal portion) of a transhiatal esophagectomy. Once complete mobilization of the stomach is verified, the pylorus is manually advanced to the level of the diaphragm to ensure that it is not being tethered by the duodenum or the greater omentum. Although it is possible to form the gastric tube in the chest, it is easier to do in the abdomen. Similar to step 9 in a transhiatal esophagectomy, a 5 to 6 cm wide gastric tube is created. The proximal divided stomach is sewn to a large Penrose drain. The other end of the drain is sutured to the tip of the gastric tube so that it can be pulled into the chest when needed. A jejunostomy is performed, and the laparotomy is closed.

Step 6: exposure and mobilization of esophagus The patient is shifted to the left lateral decubitus position and redraped. Single-lung ventilation is instituted, and the chest is entered through a right fifth interspace thoracotomy. The inferior pulmonary ligament is divided, and the lung is retracted cephalad. The esophagus is mobilized from the level of the diaphragm to a point above the azygos vein [see Figure 18], which can be divided with a vascular stapler. I prefer not to divide the vein as the azygos helps keep the stomach conduit in the midline for comfortable swallowing. The pleura overlying the esophagus is divided to the level of the thoracic inlet, superior to the azygos vein. The esophagus is encircled with a Penrose drain in the retrotracheal region. The pleura is then divided to the level of the diaphragm, with care taken to stay close to the right bronchus and the pericardium and avoid injury to the thoracic duct. The soft tissue between the esophagus and the aorta posteriorly and between the esophagus and the trachea or the pericardium anteriorly is dissected free and maintained en bloc with the esophagus. Periesophageal and subcarinal nodes are thereby mobilized [see Figure 18b].

Step 7: excision and removal of specimen The hiatus is incised, and the abdomen is entered. The stomach is drawn up into the chest, with care taken not to place excessive traction on the gastroepiploic pedicle. The esophagus is divided proximally at least 5 cm away from any grossly evident tumor, typically just below the thoracic inlet. The esophageal specimen is removed from the operative field, and proximal and distal margins are sent for frozen-section examination. [see Figure 19]. The stomach is positioned in the posterior mediastinum with care to avoid any twisting.

Step 8: intrathoracic esophagogastric anastomosis The site of the esophagogastric anastomosis should be about 2 to 4 cm above the azygos vein. Several interrupted sutures are used to secure the transposed stomach to the adjacent pleura. The staple line on the esophagus is removed, and a

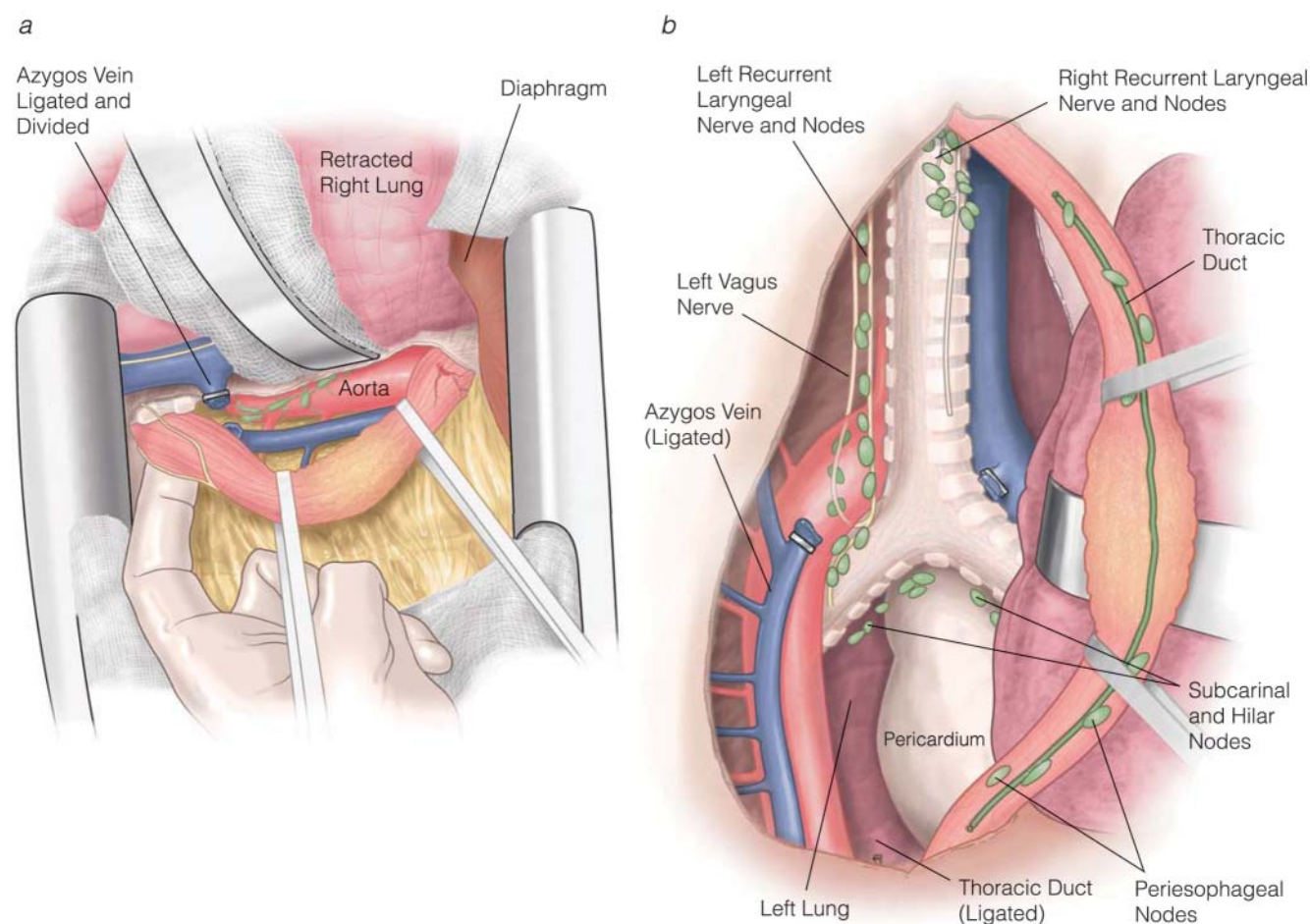


Figure 18 Ivor Lewis esophagectomy. (a) The lung is retracted, and the azygos vein is stapled and divided. The esophagus and the vagi are mobilized from the level of the diaphragm to the thoracic inlet. (b) Dissection en bloc via right thoracotomy of the thoracic duct, the azygos vein, the ipsilateral pleura, and all periesophageal tissue in the mediastinum. The specimen includes the lower and middle mediastinal, subcarinal, and right-side paratracheal lymph nodes.

gastrotomy is performed in preparation for a side-to-side functional EEA [see Figure 20]. With the aid of full-thickness traction sutures, the esophagus is positioned along the surface of the stomach and well away from the oversewn staple line defining the gastric resection margin. The posterior aspect of the anastomosis is completed with an endoscopic GIA stapler as described earlier [see Transhiatal Esophagectomy, Step 11, above, and Figure 16 and Figure 17]. A nasogastric tube is passed, and the anterior wall is completed in two layers. The first layer consists of a full-thickness continuous 3-0 polydioxanone suture; the second consists of interrupted absorbable sutures approximating the seromuscular layer of the stomach to the muscular layer of the esophagus.

Two alternative methods of anastomosis are sometimes used: (1) a totally handsewn end-to-side anastomosis and (2) a totally stapled EEA. I prefer a handsewn anastomosis, although it is no longer in vogue. An outer layer of interrupted 4-0 silk is used followed by a mucosal layer of interrupted inverting 4-0 silk [see Figure 20]. The stapled circular technique involves opening the previously placed gastric staple line and advancing the handle of an EEA stapler

through the stomach. The proximal esophagus is dilated sufficiently to accommodate at least a 25 mm head. The anvil is placed into the distal esophagus and secured with a purse-string suture. The tip of the stapler is brought out through the apical wall of the stomach and attached to the anvil. The stapler is then fired to create the EEA, and the gastrotomy is closed. The advantages of this technique are its relative simplicity and the theoretical security of a completely stapled anastomosis; the main potential disadvantage is the risk of postoperative dysphagia resulting from an overly narrow anastomotic ring.

After completion of the anastomosis, the stomach is inspected for any potential redundancy or torsion in the chest. To prevent torsion, the stomach is anchored to the pericardium and pleura with nonabsorbable sutures. The diaphragmatic hiatus is then inspected: it should allow easy passage of two fingers into the abdomen alongside the transposed stomach. Interrupted sutures may be used to approximate the edge of the crura to the adjacent stomach wall, thereby preventing any later herniation of abdominal contents into the pleural space.

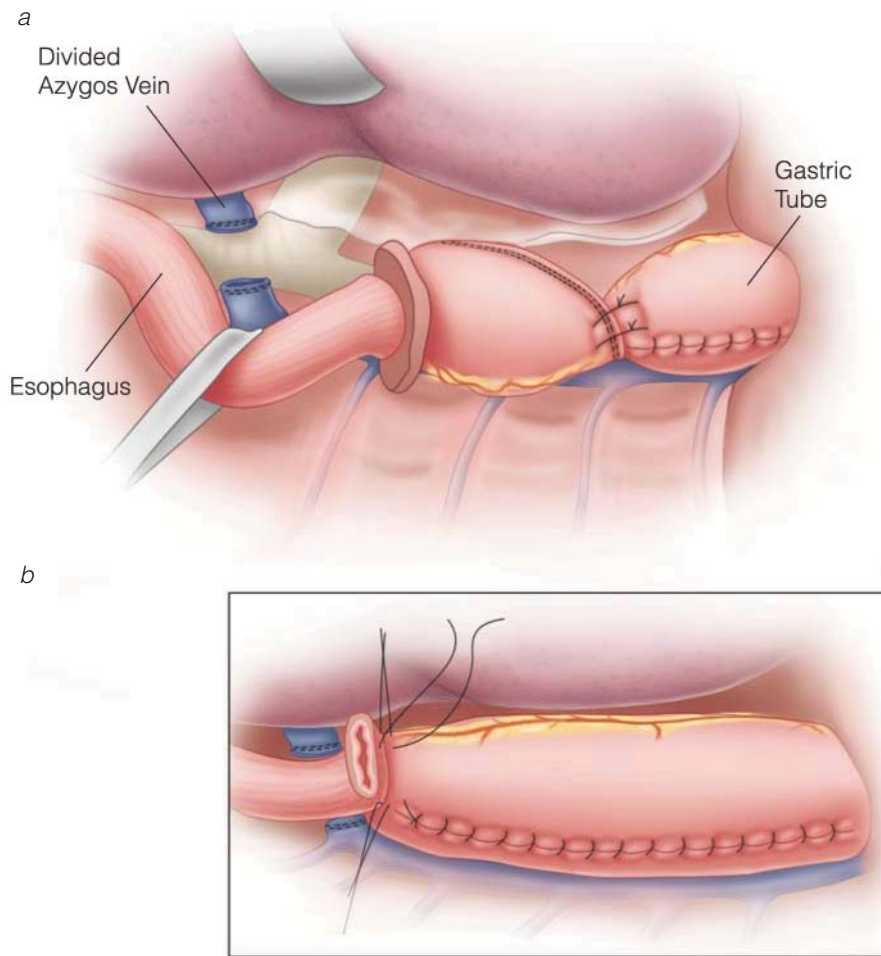


Figure 19 Ivor Lewis esophagectomy. (a) After full mobilization of the esophagus, the gastric conduit (sutured to the divided proximal stomach) is pulled up into the chest. (b) An open anastomosis is begun at or above the level of the azygos vein.

Step 9: drainage and closure A chest tube is placed. The tip of the chest drain is positioned alongside the stomach at the level of the anastomosis. Fine gut sutures secured to the adjacent parietal pleura will help maintain the position of the tube. The thoracotomy is then closed in the standard fashion.

Patients should begin walking on postoperative day 1. The nasogastric tube is generally removed on postoperative day 3. Oral intake is not begun at this point; feeding is accomplished via the temporary jejunostomy. A barium contrast study is performed approximately 5 to 7 days after the operation. If there is no anastomotic leakage, oral intake is initiated and advanced as tolerated. The chest tube and epidural catheter are removed, usually on day 4. Patients are generally discharged from the hospital by postoperative days 8 to 10.

Three-Hole Esophagectomy

Step 1: thoracotomy phase Esophagoscopy is performed to confirm the location of the tumor. A double-lumen endotracheal tube is placed. The first step is a right thoracotomy and mobilization of the esophagus and the regional lymph nodes, similar to step 6 of an Ivor Lewis esophagectomy. The chest is closed after esophageal mobilization is performed.

Step 2: abdominal and cervical phase The patient is turned back to the supine position. The double-lumen

endotracheal tube is replaced by a standard single-lumen tube. Thereafter, the operation proceeds exactly like a transhiatal esophagectomy with steps 1 through 12. The mediastinal phase is, of course, much easier because all of the dissection was done in the thoracotomy phase of the operation.

Patients should begin walking on postoperative day 1. The nasogastric tube is generally removed on postoperative day 3. Oral intake is not begun at this point; feeding is accomplished via the temporary jejunostomy. A barium contrast study is performed approximately 5 to 7 days after the operation. If there is no anastomotic leakage, oral intake is initiated and advanced as tolerated. The chest tube and epidural catheter are removed, usually on day 4. Patients are generally discharged from the hospital by postoperative days 8 to 10.

Left Thoracoabdominal Esophagogastrrectomy

Step 1: incision and entry into peritoneum The patient is placed in the right lateral position, with the hips rotated backward about 30°. An exploratory laparotomy is performed through an oblique incision extending from the tip of the sixth costal cartilage to a point about halfway between the sternum and the umbilicus. The peritoneal cavity is carefully examined to rule out peritoneal and hepatic metastases. The region of the cardia is palpated, and the mobility of the tumor is assessed. If there is minor involvement of the crura or the

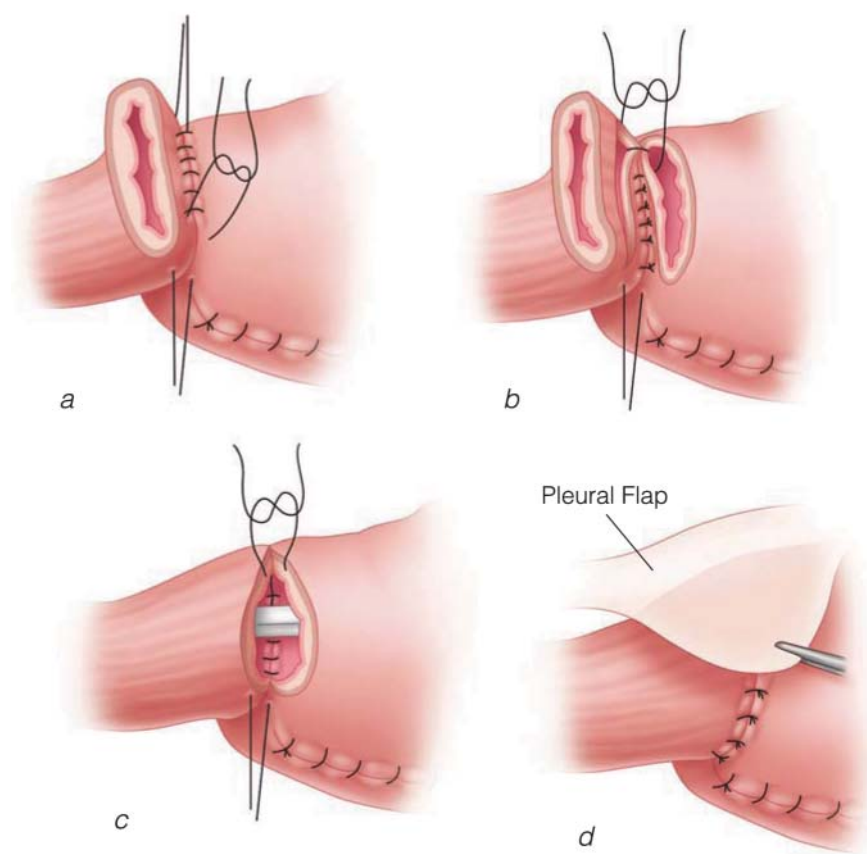


Figure 20 Ivor Lewis esophagectomy. The two-layer anastomosis is performed with fine 4-0 sutures in an interrupted fashion. It is important to locate the gastrostomy away from the turned-in lesser curve suture line to avoid ischemia. (a) Posterior layer. (b) Posterior inner mucosal layer. (c) Anterior mucosal layer. (d) After the anterior seromuscular layer is done, local pleura is used to cover the anastomosis to buttress it and to keep the conduit in the middle of the mediastinum. The anastomosis can also be completed as in a transhiatal esophagectomy or with an end-to-end anastomosis [see Figure 16 and Figure 17].

tail of the pancreas, resection may still be possible; however, if the tumor is firmly fixed or there are peritoneal or hepatic metastases, resection should be abandoned. A feeding jejunostomy, an esophageal stent, or both may be inserted to improve swallowing and allow nutrition.

Step 2: assessment of gastric involvement and incision of diaphragm The extent to which the tumor involves the stomach determines whether a total gastrectomy or a proximal gastrectomy is indicated along with the distal esophagectomy. If no metastases are found, the incision is extended and the chest is opened with a left posterolateral incision through the sixth interspace. If the thoracic component of the tumor appears to be resectable, the costal margin is divided. It is advisable to remove a 1 to 2 cm segment of the costal margin to facilitate repair of the diaphragm at the end of the operation and reduce postoperative costal margin pain. The diaphragm is incised radially. Alternatively, a circumferential incision may be made about 2 cm from the costal margin to reduce the risk of postoperative diaphragmatic paralysis.

Step 3: division of pulmonary ligament and mobilization of esophagus and stomach The pulmonary ligament is divided, and the mediastinal pleura is incised over the esophagus as far as the aortic arch. The esophagus is mobilized above the tumor and is retracted by a Penrose drain. The esophageal vessels are carefully dissected, ligated, and

divided. The tumor is mobilized; the plane of the dissection is kept close to the aorta on the left, and, if necessary, the right parietal pleura is taken in continuity with the lesion. About 1 cm of the crura is taken in continuity with the tumor to provide good local clearance. The stomach is then mobilized in much the same way as in a transhiatal esophagectomy [see Figure 9].

Step 4: assessment of pancreatic involvement and hepatic viability The lesser sac is opened through the greater omentum so that it can be determined whether the primary tumor involves the distal pancreas. If so, it is reasonable to resect the distal pancreas, the spleen, or both in continuity with the stomach; if not, the short gastric vessels are ligated and divided, with the spleen preserved. The lesser omentum is detached from the right side of the esophagus and the hilum of the liver and then divided down to the area of the pylorus, with the right gastric artery and vein preserved. There is often a hepatic branch from the left gastric artery running through the gastrohepatic omentum. If this hepatic branch is of significant size, a soft vascular clamp should be placed on the artery for 20 minutes so that the viability of the liver can be assessed. If the liver is viable, the artery is suture-ligated and divided.

Step 5: division of greater omentum and short gastric vessels The greater omentum is divided, with care taken to

preserve the right gastroepiploic artery and vein. These two vessels are suture-ligated and divided well away from the stomach. Ligation and division of the short gastric vessels allow complete mobilization of the greater curvature of the stomach. Dissection is extended downward as far as the pylorus. The stomach is turned upward, and the left gastric vessels are exposed through the lesser sac [see Figure 10]. The lymph nodes along the celiac axis and the left gastric artery are swept up into the specimen, and the gastric vessels are either suture-ligated or stapled and divided.

Step 6: choice of partial or total gastrectomy At this time, the surgeon determines whether the whole stomach must be resected to remove the gastric part of the cancer or whether a partial (i.e., proximal) gastrectomy will suffice.

If the surgeon decides that resection of the proximal stomach will remove all of the tumor while leaving at least 5 cm of tumor-free stomach, a proximal esophagogastrrectomy is performed [see Figure 21]. A gastric tube is fashioned with a linear stapler [see Transhiatal Esophagectomy, Step 9, above, and Figure 15]. The staple line is oversewn with inverting 3-0 or 4-0 sutures. Because the vagus nerves are divided and gastric stasis may result, a pyloromyotomy may be performed, much as in a transhiatal esophagectomy.

The proximal gastric resection margin is covered with a sponge and turned upward over the costal margin. The stomach tube is then brought up through the hiatus and into the thorax behind the proximal esophageal resection margin [see Figure 21]. The margin should be at least 10 cm from the proximal end of the esophagogastric cancer. If the esophageal resection margin is not adequate, the stomach tube is mobilized and brought to the left neck and then anastomosed

to the cervical esophagus through a left neck incision; alternatively, the left colon is interposed between the gastric stump and the cervical esophagus. If the resection margin is adequate, the tip of the stomach tube is anastomosed to the esophagus by any of the previously described techniques [see Figure 22].

The anastomosis is then performed with the stapling technique previously described for transhiatal esophagectomy [see Figure 16 and Figure 17]. A nasogastric tube is passed down into the gastric remnant. The tube is sewn to the pericardium and the endothoracic fascia to prevent torsion or herniation into the pleural space.

Total gastrectomy with Roux-en-Y esophagojejunostomy If the surgeon decides that a total gastrectomy is necessary, the right gastroepiploic and right gastric vessels are suture-ligated and divided distal to the pylorus. The duodenum is divided just distal to the pylorus with a linear stapler. The staple line is inverted with interrupted 3-0 nonabsorbable sutures and covered with omentum to prevent duodenal stump blowout.

The esophagus is then mobilized up to the level of the inferior pulmonary vein. Two retaining sutures are placed in the esophageal wall. A monofilament nylon purse-string suture is placed around the circumference of the proximal esophagus in preparation for stapling. The resected specimen is sent to the pathologist for examination of the margins.

A jejunal interposition is then fashioned by using the Roux-en-Y technique. One or two jejunal arteriovenous arcades are divided to mobilize enough jejunum to allow anastomosis to the thoracic esophagus [see Figure 23]. A 25 or 28 mm EEA stapler is passed through the jejunum into the

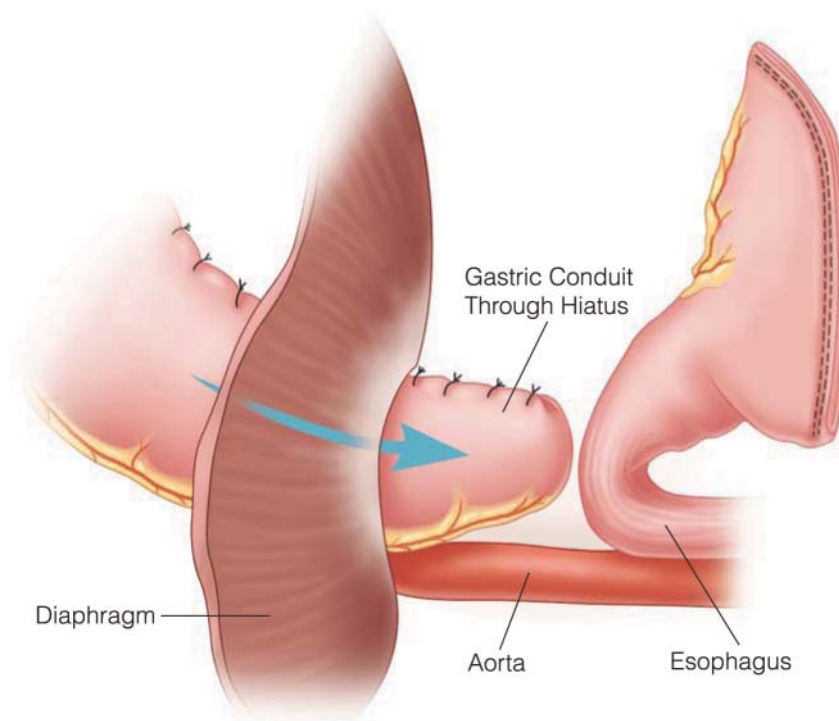


Figure 21 Left thoracoabdominal esophagogastrrectomy. The diaphragm is incised radially sparing major branches of the phrenic nerve. The pulmonary ligament is divided, and the esophagus is mobilized above the tumor and retracted with a Penrose drain. The esophageal vessels are ligated and divided. The tumor and the esophagus are mobilized off the aorta down to the hiatus; 1 cm of the diaphragmatic crura is taken in continuity with the tumor to provide local clearance. The stomach is then mobilized in much the same way as in a transhiatal esophagectomy and brought through the diaphragmatic hiatus [see Figure 9].

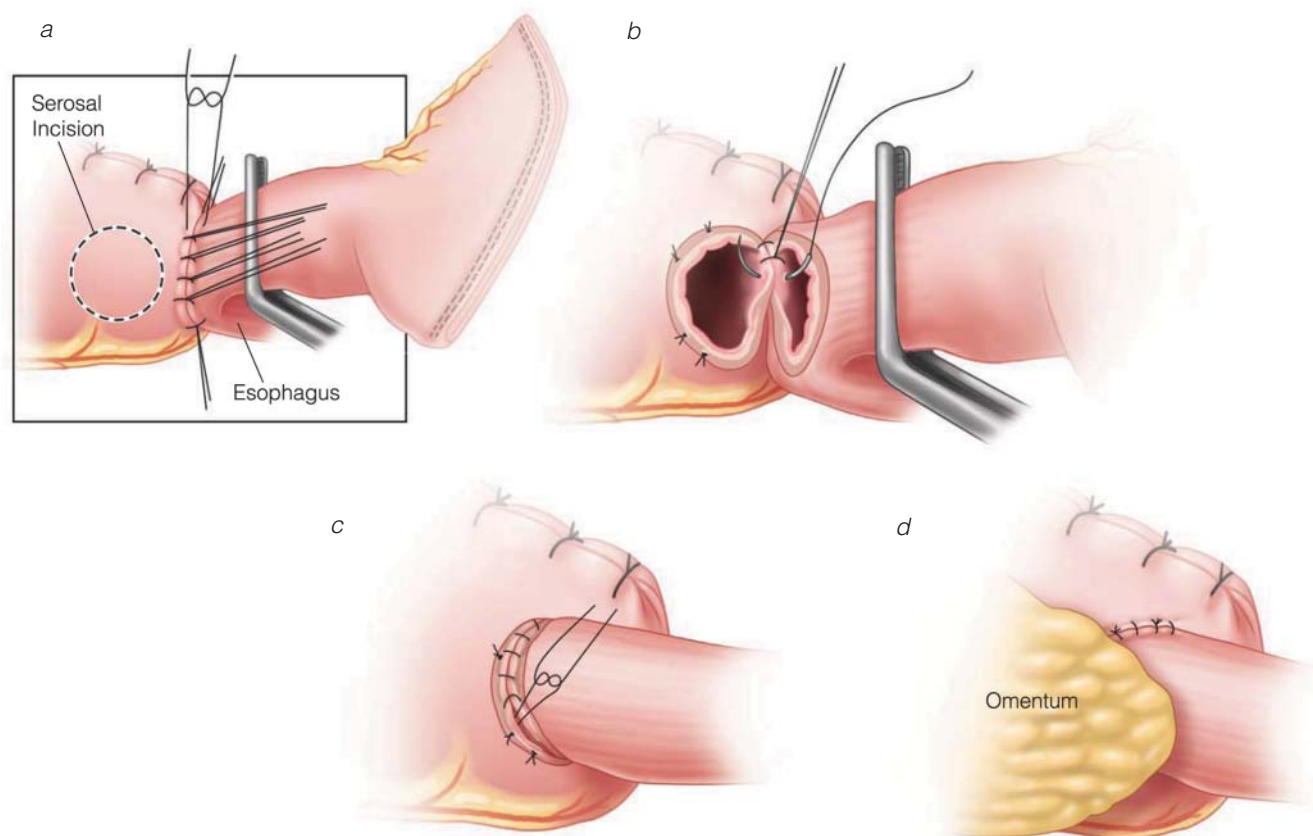


Figure 22 Left thoracoabdominal esophagogastrectomy: proximal esophagogastrectomy with esophagogastrostomy. The esophagus is sewn to the tip of the stomach tube, halfway between the lesser curvature suture line and the greater curvature. (a) The Sweet anastomosis developed at the Massachusetts General Hospital. The outer posterior layer is performed with fine 4-0 silk sutures. A serosal “button” is inscribed with a scalpel down to the level of the submucosal vascular plexus. Fine 4-0 silk sutures are used to ligate these vessels so they do not obscure the anastomosis while it is being performed. (b) The gastric button is excised, and the inner posterior layer is anastomosed with interrupted 4-0 silks. This is continued anteriorly as well. (c) The outer anterior layer is performed also with interrupted 4-0 silks. (d) A tag of omentum from the high greater curve is sutured over the anastomosis to buttress it. Alternatively, an anastomosis can be fashioned with the stapling technique used in transhiatal esophagectomy or with an end-to-end anastomosis [see Figure 16 and Figure 17].

esophagus, fired, and removed. The jejunum is anchored to the pericardium and the proximal esophagus. The duodenal loop is anastomosed to the jejunum at least 45 to 50 cm distal to the esophagojejunal anastomosis to minimize bile reflux [see Figure 23]. The blind end of the jejunal loop is then stapled closed.

After careful irrigation of the chest, the first step in the closure is to repair the diaphragm around the hiatus. The gastric or jejunal interposition is sewn to the crura with interrupted nonabsorbable sutures. The remainder of the diaphragm is closed with interrupted nonabsorbable 0 mattress sutures. A chest tube is placed into the pleural space close to but not touching the anastomosis. The final sutures in the peripheral part of the diaphragm are placed but are not tied until the ribs are brought together with pericostal sutures. The left lung is reexpanded. The costal cartilages are not approximated but are left to float free. If the ends of the costal margin are abutting, another 2 cm of costal cartilage should be removed to reduce postoperative pain. Thoracic and abdominal skin layers are closed with a continuous

absorbable suture. The skin and the subcutaneous tissue are closed in the usual fashion.

POSTOPERATIVE CARE

As a rule, patients are not routinely admitted to the intensive care unit after esophagectomy; however, individual practices depend on the distribution of skilled nursing and physiotherapy personnel. Early ambulation is the mainstay of postoperative care. As a rule, patients are able to walk slowly, with assistance, on postoperative day 1. Patient-controlled epidural analgesia is particularly useful in facilitating good pulmonary toilet and minimizing the risk of atelectasis or pneumonia.

The nasogastric tube is removed on postoperative day 3 or 4; jejunostomy tube feedings are gradually started at the same time. Once bowel function normalizes, patients are allowed small sips of liquids. Chest tubes are removed as pleural drainage subsides. By postoperative day 6, most patients have progressed to a soft solid diet. Dietary education is provided, focusing primarily on eating smaller and more frequent meals,

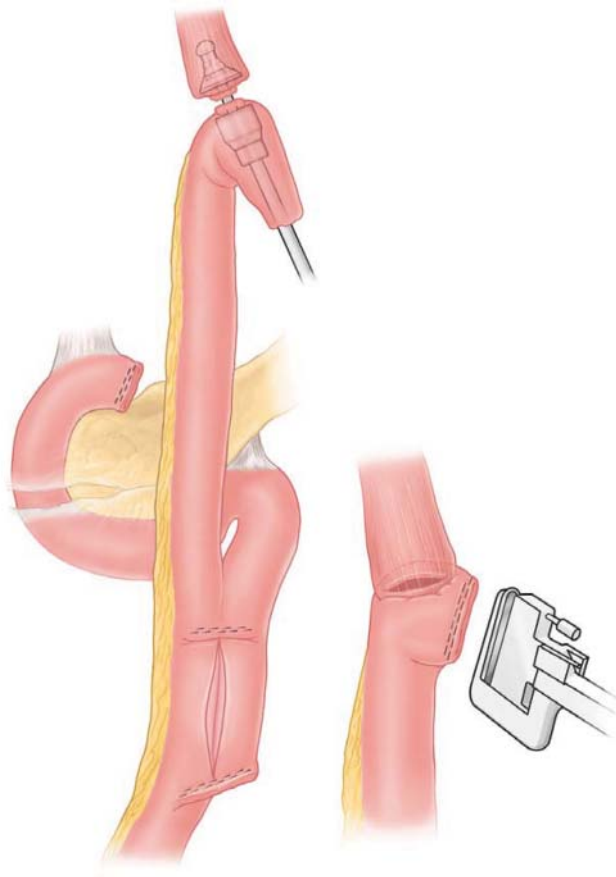


Figure 23 Left thoracoabdominal esophagogastrectomy: total gastrectomy with Roux-en-Y esophagojejunostomy. A jejunal interposition is fashioned with the Roux-en-Y technique. One or two jejunal arteriovenous arcades are divided to mobilize enough jejunum for anastomosis to the thoracic esophagus. A 25 or 28 mm end-to-end anastomosis stapler is passed through the jejunum into the esophagus. The jejunum is anchored to the pericardium and the proximal esophagus. The duodenal loop is anastomosed to the jejunum at least 45 to 50 cm distal to the esophagojejunal anastomosis. The blind end of the jejunal loop is then stapled closed.

avoiding bulky foods (e.g., meat and bread) in the early postoperative period, and taking measures to minimize postprandial dumping. Patients are also taught how to care for their temporary feeding jejunostomy. Consumption of caffeine and carbonated beverages is usually limited during the first few weeks after discharge.

A barium swallow is performed on postoperative day 7 to verify the integrity of the anastomosis and gastric emptying. Patients are usually discharged on postoperative day 7 or 8. The feeding jejunostomy is left in place until the first postoperative evaluation, which usually takes place 2 to 3 weeks after the operation. The feeding tube is removed during that visit if oral intake and weight are stable.

COMPLICATIONS OF ESOPHAGECTOMY

Pulmonary Impairment

Atelectasis and pneumonia should be considered preventable complications of esophagectomy. Patients with

recognized preoperative impairment of pulmonary reserve should be considered for transhiatal esophagectomy. Existing pulmonary function can be optimized through incentive spirometry, use of bronchodilators, and physical rehabilitation. Chronic nocturnal aspiration from esophageal obstruction should be watched for in the postoperative patient; the head of the bed should be elevated 30° to 45° as a preventive measure. Effective pain control is essential to prevent postoperative atelectasis. Routine use of patient-controlled thoracic epidural analgesia should be considered. Deep breathing, early ambulation, and chest physiotherapy encourage the clearing of bronchial secretions. Certain patients will require nasotracheal aspiration or bronchoscopy for pulmonary toilet.

Tracheobronchial Injury

On rare occasions, lacerations of the membranous trachea or the left mainstem bronchus occur during esophagectomy. When such injuries occur during transthoracic resection, management is relatively simple, thanks to the already excellent operative exposure. Direct suture repair and tissue reinforcement with adjacent pleura or a pedicle of intercostal muscle provide safe closure in almost all cases. When tracheobronchial injuries occur during transhiatal esophagectomy, they are less obvious but no less urgent. This rare complication arises during mediastinal dissection. Typically, the anesthetic team notes a loss of ventilatory volume, and the surgeon may detect the smell of inhalational agents in the operative field. Bronchoscopy should be promptly performed to identify the site of the injury. The uncut endotracheal tube is then advanced over the bronchoscope and past the site of the laceration to restore proper ventilation. High tracheal injuries can usually be repaired by extending the cervical incision and adding a partial sternotomy. Injury to the carina or the left mainstem bronchus must be repaired via a right thoracotomy.

Bleeding

Hemorrhage should be rare during esophagectomy. In routine situations, blood loss should amount to less than 500 mL. The blood supply to the esophagus consists of small branches coming from the aorta, which are easily controlled and generally constrict even if left untied. Splenic injuries sometimes occur during mobilization of the stomach. The resultant hemorrhage can be immediate or delayed; blood loss may be significant, and splenectomy is usually required. Precise dissection around the left gastric artery is vital: the bleeding vessels may retract, and attempts at control may result in injury to the celiac artery or its hepatic branches. Similarly, peripancreatic vessels may be difficult to control if inadvertently injured during the Kocher maneuver.

Bleeding that arises during the mediastinal stage of the transhiatal esophagectomy generally subsides with packing if it derives from periesophageal arterial branches. Brisk loss of dark blood usually signifies injury to the azygos vein. The first step in addressing such injuries is to pack the mediastinum quickly so as to allow the anesthetic team to stabilize the patient and restore volume. Chest tubes are immediately placed to allow detection of any free hemorrhage into the pleural space. Precise localization of the bleeding site may then follow. Injury to the azygos vein may be addressed via

an upper sternal split; however, when the exposure is poor, the surgeon should not hesitate to proceed to a full sternotomy. Bleeding from the subcarinal area is usually bright red and may involve bronchial arteries or small periesophageal vessels arising from the aorta, both of which can usually be controlled through the hiatus with a long-handled pistol-grip clip applicator or electrocautery.

Laryngeal Nerve Injury

Injury to the recurrent laryngeal nerve is a major potential complication of transhiatal esophagectomy. Traction neuropraxia may be temporary and require no specific treatment. Permanent injury will lead to hoarseness and impaired protection of the airway during deglutition. Pneumonia from aspiration is a major problem. Meticulous protection of the nerve during the cervical stage should minimize the incidence of this complication. If laryngeal nerve injury becomes apparent in the postoperative period, early medialization of the affected cord should be performed by an otolaryngologist to enhance the ability of the patient to cough and to prevent aspiration.

Of particular concern is the risk of bilateral nerve injury after a transthoracic esophagectomy with a cervical esophago-gastric anastomosis (i.e., a so-called three-hole esophagectomy). Any dissection of the upper esophagus performed through the right chest should be done as close to the esophagus as possible to avoid placing traction on the right recurrent laryngeal nerve; the subsequent left cervical dissection may put the left recurrent laryngeal nerve at risk for damage. Bilateral paralysis of the vocal cords is very poorly tolerated and has a devastating impact on quality of life.

Chylothorax

Thoracic duct injuries typically present by postoperative day 3 or 4. Dyspnea and pleural effusion may be noted if thoracostomy tubes are not in place. Thoracentesis yields an opaque, milky fluid. In patients who already have a chest drain in place, there is typically a high volume of serous drainage in the first 2 postoperative days. As enteral nutrition is established and dietary fat is reintroduced, the fluid assumes a characteristic milky appearance. In most cases, the gross appearance is diagnostic, and there is rarely a need to confirm the diagnosis by measuring the triglyceride level. A thoracostomy drain is placed to monitor the volume of the chyle leak if one is not present. Chest x-rays should be obtained to verify complete drainage of the pleural space and full expansion of the lung.

Patients with chylothorax should be converted to fat-free enteral nutrition. Persistent drainage exceeding 500 mL per day is an indication for early operation and ligation of the thoracic duct; high-volume chyle leaks are unlikely to close spontaneously. Prolonged loss of chyle causes significant electrolyte, nutritional, and immunologic derangements that may prove fatal if allowed to progress. Accordingly, patients with persistent chyle leakage should undergo operation within 1 week of diagnosis. A feeding tube is placed in the duodenum before operation if a jejunostomy tube is not already in place. Jejunal feeding with 35% cream at a rate of 60 to 80 mL/hr is maintained for at least 4 hours before operation. Feeding is continued even during the procedure: the enteral

fat stimulates a brisk flow of chyle and greatly facilitates visualization of any thoracic duct injury.

Right-side chyle leaks are approached via either a thoracotomy or video-assisted thoracoscopy. The magnification and excellent illumination associated with thoracoscopy are partially counterbalanced by the constraints imposed by port placement and limited tissue retraction. The inferior pulmonary ligament is divided, and the posterior mediastinum is inspected for extravasation of milky fluid. Any visible sources of chyle leakage can be controlled with clips or suture ligatures. In some cases, mass ligation of the thoracic duct at the level of the diaphragm, incorporating all of the soft tissue between the aorta and the azygos vein, may be required.

Left-side leaks can be difficult to manage. The subcarinal area is typically involved; this is the level at which the thoracic duct crosses over from the right. Exploration should begin on the left side. If the leak cannot be visualized, a right-side approach may be necessary to control the thoracic duct as it first enters the chest.

Anastomotic Leakage

The consequences of anastomotic complications after esophagectomy vary considerably in severity, depending on their location and cause. The cervical anastomotic leaks that may develop after transhiatal esophagectomy are generally simple to treat. Leaks in the early postoperative period are usually related to technical factors (e.g., excessive tension across the anastomosis). A nonviable stomach may not give rise to obvious signs; thus, any possibility of ischemia in the transposed stomach must be addressed promptly. Tachycardia, confusion, leukocytosis, cervical wound drainage, and neck tenderness may or may not be present.

The morbidity of an open cervical wound is not high—it is certainly lower than that of an untreated leak. Accordingly, any clinical suspicion of a leak should prompt a diagnostic contrast swallow study using dilute barium. Large leaks are manifested as persistent collections of contrast material outside the esophagus. Although such leaks rarely extend into the pleural space, any fluid in the chest must be drained so that its nature can be determined. The neck wound is opened by removing the sutures and performing gentle digital exploration of the prevertebral space behind the esophagus as the finger is advanced into the mediastinum; this is usually done at the bedside and requires little, if any, patient sedation.

Saline-moistened gauze packing is changed three or four times a day. Prolonged or copious cervical drainage may call for supplemental deep wound aspiration with a Yankauer suction handle. Administering water orally during aspiration facilitates removal of any necrotic debris. A fetid, malodorous breath associated with sanguineous discharge from the nasogastric tube and purulent fluid in the opened neck incision are ominous signs that should prompt early esophagoscopy. Diffuse mucosal ischemia may indicate the presence of a nonviable stomach; reoperation with completion gastrectomy and proximal esophagostomy is required to treat this rare catastrophic complication.

Generally, leaks that occur more than 7 days after operation are small and are related to some degree of late ischemic disruption along the anastomosis. They can usually be managed by opening the cervical wound at the bedside and packing the site with gauze. Oral diet is advanced as tolerated. It

may be noted that the volume of the leak is markedly greater or less depending on the position of the head during swallowing. Accordingly, before discharge, patients are taught how to temporarily adjust their swallowing and how to manage their dressing changes. Applying gentle pressure to the neck wound and turning the head to the left may help the patient ingest liquids with minimal soiling of the open neck incision. Dysphagia, even with an opened neck incision, should be treated by passing tapered esophageal dilators orally between 2 and 4 weeks after surgery. When a bougie at least 48 French in caliber can be passed through the anastomosis, the patient can usually swallow comfortably. The size of the leak often decreases after dilation as food is allowed to proceed preferentially into the stomach. To maximize the diameter of the anastomosis and reduce the likelihood of a symptomatic stricture, subsequent dilations should be scheduled at 2-week intervals for the next few months.

When a routine predischarge barium swallow after transhiatal esophagectomy raises the possibility of an anastomotic leak in an asymptomatic patient, the question arises of whether the wound should be opened at all. For small, contained leaks associated with preferential flow of contrast material into the stomach, observation alone may suffice in selected cases. Patients must be closely watched for fever or other signs of major infection. Given the quite low morbidity of cervical wound exploration, the surgeon should not hesitate to drain the neck if the patient's condition changes.

The incidence of anastomotic leakage is low after Ivor Lewis resection, but the consequences are significant. Leaks presenting early in the postoperative period are usually related to technical problems and are difficult to manage; those presenting later are generally related to some degree of ischemic tissue loss. Patients who have received radiation therapy or are nutritionally depleted may be especially vulnerable to problems with anastomotic healing. A contrast swallow with dilute barium is the best method of evaluating the anastomosis. Leaks may be manifested either as a free flow of contrast into the pleural space or as a contained fluid collection.

Small leaks that drain immediately into properly placed thoracostomy tubes can usually be managed by giving antibiotics and withholding oral intake. Local control of infection generally results in spontaneous healing. Anastomotic disruptions that are large or are associated with a major pleural collection typically necessitate open drainage with decortication; percutaneous drainage may be considered as a preliminary approach in selected patients. Persistent soiling of the mediastinum and the pleural space is fatal if untreated.

Early esophagoscopy is strongly advised to evaluate the viability of the gastric remnant. Ischemic necrosis of the stomach necessitates reexploration, decortication, takedown of the anastomosis, gastric débridement, return of any viable stomach into the abdomen, closure of the hiatus, and proximal diversion with a cervical esophagostomy. Repair or revision of the anastomosis in an infected field is certain to fail and should never be considered. In certain cases, diversion via a cervical esophagostomy and a completion gastrectomy may be required.

Late Complications

At every postoperative visit, symptoms of reflux, regurgitation, dumping, poor gastric emptying, and dysphagia must be

specifically sought: these are the major quality-of-life issues for postesophagectomy patients.⁴ Reflux and regurgitation may complicate any form of alimentary reconstruction after esophagectomy, although cervical anastomoses are less likely to be associated with symptomatic reflux than intrathoracic anastomoses are. Reflux symptoms generally respond to dietary modifications, such as smaller and more frequent meals. Regurgitation is usually related to the supine position and thus tends to be worse at night; elevating the bed and avoiding late meals may suffice for symptom control. Dumping is exacerbated by foods with high fat or sugar content. Dysphagia may be related to narrowing at the anastomosis or, in rare instances, to poor emptying of the transposed stomach. Anastomotic strictures are most commonly encountered as a sequel to a postoperative leak. There may be excessive scarring at the anastomosis, associated with local distortion or angulation. Specific tests for gastric atony include nuclear medicine gastric emptying studies using radiolabeled food. A simple barium swallow may indicate an incomplete pyloromyotomy as a cause of poor gastric emptying; balloon dilation often corrects this problem.

Any form of anastomotic leak will increase the incidence of late stricture. Dysphagia may be treated by means of progressive dilation with Maloney bougies. This procedure is performed in the outpatient clinic and often does not require sedation or any other special patient preparation. Complications are rare if due care is exercised during the procedure. As noted [see Transthoracic Hiatal Hernia Repair, Preoperative Evaluation, Dilation, *above*], it is essential that the caliber of the dilators be increased gradually and that little or no force be applied in advancing them. The appearance of blood on a withdrawn dilator signals a breach of the mucosa; further dilation should be done cautiously lest a transmural injury results. Comfortable swallowing, of liquids at least, is usually achieved after the successful passage of a 48 French bougie. It is preferable, however, to advance dilation until at least a 54 French bougie can be passed with ease. For late strictures that are particularly difficult to dilate, endoscopic examination and histologic evaluation may be required to rule out a recurrent tumor. CT of the chest should also be performed whenever there is unexplained weight loss or fatigue late after esophagectomy.

The Savary system of wire-guided dilators has been particularly helpful in the management of tight or eccentric strictures. Patients are generally treated in the endoscopy suite. Temporary sedation with intravenous fentanyl and midazolam is required. Fluoroscopy can be used to confirm proper placement of a flexible-tip wire across the stricture. Serial wire-guided dilation can then be performed with confidence and increased patient safety.

OUTCOME EVALUATION

Transhiatal Esophagectomy

A 2001 study from the University of Michigan presented data on 1,085 patients who underwent transhiatal esophagectomy without thoracotomy, of whom 74% had carcinoma and 26% had nonmalignant disease.⁵ Transhiatal esophagectomy was completed in 98.6% of the patients; the remaining 1.4% were converted to a transthoracic esophagectomy as a result of either thoracic esophageal fixation or bleeding.

Previous chemotherapy or radiation therapy did not preclude performance of a transhiatal esophagectomy. Nine patients experienced inordinate intraoperative blood loss; three died as a result. The overall hospital mortality was 4%. The overall 5-year survival rate for patients undergoing transhiatal esophagectomy is approximately 20% for adenocarcinoma of the cardia and the esophagus and 30% for squamous cell carcinoma of the esophagus.

The stapled anastomosis described earlier [see Operative Technique, Transhiatal Esophagectomy, Step 8, *above*] reflects numerous refinements introduced at the University of Michigan. The endoscopic GIA stapler has a low-profile head that is ideally suited to the tight confines of the neck, enabling the surgeon to fashion a widely patent side-to-side functional EEA with three rows of staples along the back wall. The rate of anastomotic stricture is markedly lower with this anastomosis than with a totally handsewn anastomosis. As regards postoperative function, stomach interposition through the posterior mediastinum after transhiatal esophagectomy is associated with low rates of aspiration and regurgitation. Esophageal reflux and esophagitis—commonly seen with intrathoracic esophagogastric anastomoses—are usually not clinically significant problems with this approach. Patients are advised to elevate the head of their bed and to continue taking acid blockers for about 3 months after the operation. Approximately one third will require esophageal dilation for dysphagia after the operation. Some 7 to 10% experience postvagotomy dumping symptoms, which, in most cases, can be controlled by simply avoiding high-carbohydrate foods and dairy products.

Ivor Lewis Esophagectomy

Ivor Lewis esophagectomy is associated with anastomotic leakage rates and operative mortalities of less than 3%.^{3,6} Approximately 5% of patients will require anastomotic dilation. Again, patients are advised to elevate the head of the bed and to continue taking acid blockers if they have any

reflux symptoms. In some patients, the gastric interposition rotates into the right posterolateral thoracic gutter, resulting in postprandial gastric tension and rendering them more susceptible to aspiration. Compared to transhiatal esophagectomy, extended transthoracic esophagectomy is associated with higher pulmonary morbidity but no difference in operative mortality or in 5-year survival. A post hoc subset analysis did suggest a survival advantage of transthoracic resection with one to eight positive lymph nodes.^{7,8}

Three-Hole Esophagectomy

Three-hole esophagectomy is also associated with low anastomotic leak rates and mortality similar to Ivor Lewis esophagectomy.⁹ Again, patients are advised to elevate the head of the bed and to continue taking acid blockers if they have any reflux symptoms. In some patients, the gastric interposition rotates into the right posterolateral thoracic gutter, resulting in postprandial gastric tension and rendering them more susceptible to aspiration. A special note should be made that cervical leaks with a three-hole esophagectomy can be more problematic than with a transhiatal esophagectomy presumably because of the wide opening of the mediastinum resulting in a greater tendency of leaks to track down into the mediastinum.

Left Thoracoabdominal Esophagogastrectomy

Left thoracoabdominal esophagogastrectomy is also associated with anastomotic leakage rates and operative mortalities of less than 3%.^{3,10} Approximately 5% of patients will require esophageal dilation. Reconstructions involving anastomosis of the distal stomach to the esophagus are associated with a higher incidence of bile gastritis and esophagitis. Of all the operations we have described, this one results in the lowest postoperative quality of life. Accordingly, most surgeons prefer to carry out a total gastrectomy. Swallowing is restored with a Roux-en-Y jejunal interposition.

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Figures 1 through 23 Tom Moore

8 MINIMALLY INVASIVE ESOPHAGEAL PROCEDURES

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The development of laparoscopic surgery over the past 20 years has caused a significant shift in the treatment of benign esophageal diseases.

In the first part of the 1990s, it became clear that treatment of benign esophageal disorders with minimally invasive procedures yielded results comparable to those of treatment with traditional operations while causing minimal postoperative discomfort, reducing the duration of hospitalization, shortening recovery time, and permitting earlier return to work.^{1,2} Consequently, minimally invasive surgery was increasingly considered as first-line treatment for achalasia, and laparoscopic fundoplication was considered more readily and at an earlier stage in the management of gastroesophageal reflux disease (GERD).

Since then, minimally invasive esophageal procedures have continued to evolve, thanks to better instrumentation and improved surgical expertise. In addition, with greater experience and longer follow-up, it has become possible to analyze techniques and their results more rigorously. For instance, whereas a few years ago a left thoracoscopic Heller myotomy was considered the procedure of choice for achalasia, the current procedure of choice is a laparoscopic Heller myotomy with partial fundoplication, which has proved to be better at relieving dysphagia and controlling postoperative reflux.³⁻⁶ Similarly, whereas total fundoplication and partial fundoplication were initially considered equally effective in treating GERD,⁷ total fundoplication is currently used even when peristalsis is weak. Long-term results have, in fact, shown that although the dysphagia rates of the two procedures are similar, total fundoplication achieves better control of reflux than partial fundoplication.⁸

In this chapter, we focus on minimally invasive approaches to the treatment of GERD and esophageal motility disorders. The standard open counterparts of these operations are described elsewhere [see 4:7 *Open Esophageal Procedures*].

Laparoscopic Nissen Fundoplication

PREOPERATIVE EVALUATION

All patients who are candidates for a laparoscopic fundoplication should undergo a preoperative evaluation that includes the following: (1) symptomatic evaluation, (2) an upper gastrointestinal (GI) series, (3) endoscopy, (4) esophageal manometry, and (5) ambulatory pH monitoring.

Symptomatic Evaluation

The presence of both typical symptoms (heartburn, regurgitation, and dysphagia) and atypical symptoms of GERD (cough, asthma, chest pain, dental erosions, and hoarseness)

should be investigated, and symptoms should be graded with respect to their intensity both before and after the operation. Nonetheless, a diagnosis of GERD should never be based solely on symptomatic evaluation. Some assert that the diagnosis can be made reliably from the clinical history,⁹ so that a complaint of heartburn should lead to the presumption that acid reflux is present; however, testing of this diagnostic strategy demonstrates that symptoms are far less sensitive and specific than is usually believed.¹⁰ For instance, a study from the University of California, San Francisco (UCSF), found that of 822 consecutive patients referred for esophageal function tests with a clinical diagnosis of GERD (based on symptoms and endoscopic findings), only 70% had abnormal reflux on pH monitoring.¹¹ Heartburn and regurgitation were no more frequent in patients who had genuine reflux than in those who did not; thus, symptomatic evaluation, by itself, could not distinguish between the two groups.

The response to proton pump inhibitors (PPIs) is a better predictor of abnormal reflux. For example, in the UCSF study just cited, 75% of patients with GERD reported a good or excellent response to PPIs, compared with only 26% of patients without GERD.¹¹ Similarly, a study involving multivariate analysis of factors predicting outcome after laparoscopic fundoplication identified a clinical response to acid suppression therapy as one of three factors predictive of a successful outcome, the other two being an abnormal 24-hour pH score and the presence of a typical primary symptom (e.g., heartburn).¹² In addition, a 2007 report found that patients with a body mass index (BMI) of 35 kg/m² or greater experienced higher failure rates after laparoscopic Nissen fundoplication.¹³ These data support the theory that GERD in morbidly obese patients has a different pathophysiology and may warrant a different therapeutic approach (e.g., laparoscopic Roux-en-Y gastric bypass [see 5:7 *Surgical Treatment of Morbid Obesity*]).¹⁴

Upper Gastrointestinal Series

An upper GI series is useful for diagnosing and characterizing an existing hiatal hernia. The size of the hiatal hernia helps predict how difficult it will be to reduce the esophago-gastric junction below the diaphragm. In addition, large hiatal hernias are associated with more severe disturbances of esophageal peristalsis and esophageal acid clearance.¹⁵ Esophagograms are also useful for determining the location, shape, and size of a stricture and for suggesting the presence of a short esophagus.

Endoscopy

Endoscopy is typically the first test performed to confirm a symptom-based diagnosis of GERD. This approach has two

pitfalls. First, even though the goal of endoscopy is to assess the mucosal damage caused by reflux, mucosal changes are absent in about 50% of GERD patients.¹¹ Second, major interobserver variations have been reported with esophageal endoscopy, particularly for low-grade esophagitis.¹⁶ In one study, for instance, 60 (24%) of 247 patients with negative results on pH monitoring had been diagnosed as having grade I or II esophagitis.¹¹ Endoscopy is also valuable for excluding gastric and duodenal pathologic conditions and detecting the presence of Barrett's esophagus.

Esophageal Manometry

Esophageal manometry provides useful information about the motor function of the esophagus by determining the length and resting pressure of the lower esophageal sphincter (LES) and assessing the quality (i.e., the amplitude and propagation) of esophageal peristalsis. In addition, it allows proper placement of the pH probe for ambulatory pH monitoring (5 cm above the upper border of the LES).

Ambulatory pH Monitoring

Ambulatory pH monitoring is the most reliable test for the diagnosis of GERD, with a sensitivity and specificity of about 92%.¹⁷ It is of key importance in the workup for the following four reasons.

1. It determines whether abnormal reflux is present. In the UCSF study mentioned earlier,¹¹ pH monitoring yielded normal results in 30% of patients with a clinical diagnosis of GERD, thereby obviating the continuation of inappropriate and expensive drugs (e.g., PPIs) or the performance of a fundoplication. In addition, pH monitoring prompted further investigation that in a number of cases pointed to other diseases (e.g., cholelithiasis and irritable bowel syndrome).
2. It establishes a temporal correlation between symptoms and episodes of reflux. Such a correlation is particularly important when atypical GERD symptoms (e.g., cough and chest pain) are present because 50% of these patients experience no heartburn and 50% do not have esophagitis on endoscopy.¹⁸
3. It allows staging on the basis of disease severity. Specifically, esophageal manometry and pH monitoring identify a subgroup of patients characterized by worse esophageal motor function (manifested by a defective LES or by abnormal esophageal peristalsis), more acid reflux in the distal and proximal esophagus, and slower acid clearance. These patients more frequently have Barrett metaplasia and experience respiratory symptoms; thus, they might benefit from early antireflux surgery.¹⁹
4. It provides baseline data that may prove useful postoperatively if symptoms do not respond to the procedure.

Multichannel Intraluminal Impedance and pH Combined multichannel intraluminal impedance and pH testing (MII-pH) has the ability to detect episodes of reflux, regardless of the pH of the refluxate, by identifying changes induced by the presence of a bolus in the esophagus; the episodes are then simply classified as acid or nonacid on the basis of concomitantly recorded pH values. Studies of healthy persons have demonstrated that MII-pH possesses increased sensitivity

and specificity in detecting and characterizing gastroesophageal reflux, and the results have been shown to be highly reproducible.²⁰

Although this technology is still not widely available, it has already been demonstrated to be useful in the workup of patients with GERD refractory to PPIs and patients with respiratory symptoms of unknown origin.²¹

OPERATIVE PLANNING

The patient is placed under general anesthesia and intubated with a single-lumen endotracheal tube. Abdominal wall relaxation is ensured by the administration of a nondepolarizing muscle relaxant, the action of which is rapidly reversed at the end of the operation. Adequate muscle relaxation is essential because increased abdominal wall compliance allows increased pneumoperitoneum, which yields better exposure. An orogastric tube is inserted at the beginning of the operation to keep the stomach decompressed; it is removed at the end of the procedure.

The patient is placed in a steep reverse Trendelenburg position, with the legs extended on stirrups. The surgeon stands between the patient's legs. To keep the patient from sliding as a result of the steep position used during the operation, a bean bag is inflated under the patient, and the knees are flexed only 20° to 30°. A Foley catheter is inserted at the beginning of the procedure and usually is removed at the end. Because increased abdominal pressure from pneumoperitoneum and the steep reverse Trendelenburg position decrease venous return, pneumatic compression stockings are always used as prophylaxis against deep vein thrombosis.

The equipment required for a laparoscopic Nissen fundoplication includes five 10 mm trocars, a 30° laparoscope, a hook cautery, and various other instruments [see Table 1]. In addition, we use a three-chip camera system that is separate from the laparoscope.

OPERATIVE TECHNIQUE

A total fundoplication is the procedure of choice. A partial fundoplication [see Laparoscopic Partial (Guarner) Fundoplication, *below*] is performed only when peristalsis is absent.^{22,23} The operation may be divided into nine key steps as follows.

Table 1 Instrumentation for Laparoscopic Nissen Fundoplication

Five 10 mm trocars
30° scope
Graspers and needle holder
Babcock clamp
L-shaped hook cautery with suction-irrigation capacity
Scissors
Laparoscopic clip applier
LigasSure™ Vessel Sealing System*
Fan retractor
Endo Stitch device†
Penrose drain
2-0 silk sutures
56 French esophageal bougie

* (Valleylab, Boulder, CO)

† (Autosuture, Norwalk, CT)

Step 1: Placement of Trocars

Five 10 mm trocars are used for the operation [see Figure 1]. Port A is placed about 14 cm below the xiphoid process; it can also be placed slightly (2 to 3 cm) to the left of the midline to be in line with the hiatus. This port is used for insertion of the scope. Port B is placed at the same level as port A but in the left midclavicular line. It is used for insertion of the Babcock clamp; insertion of a grasper to hold the Penrose drain once it is in place surrounding the esophagus; or insertion of an instrument to take down the short gastric vessels. Port C is placed at the same level as the previous two ports but in the right midclavicular line. It is used for insertion of the fan retractor, the purpose of which is to lift the lateral segment of the left hemiliver and expose the esophagogastric junction. We do not divide the left triangular ligament. The fan retractor can be held in place by a self-retaining system fixed to the operating table. Ports D and E are placed as high as possible under the costal margin and about 5 to 6 cm to the right and the left of the midline so that they are about 15 cm from the esophageal hiatus; in addition, they should be placed so that their axes form an angle of 60° to 120°. These ports are used for insertion of the graspers, the electrocautery, and the suturing instruments.

Troubleshooting If the ports are placed too low in the abdomen, the operation is made more difficult. If port C is too low, the fan retractor will not retract the left lateral section of the liver well, and the esophagogastric junction will not be properly exposed. If port B is too low, the Babcock clamp will not reach the esophagogastric junction, and when the instrument used to

take down the short gastric vessels is placed through the same port, it will not reach the upper short gastric vessels. If ports D and E are too low, the dissection at the beginning of the procedure and the suturing at the end are problematic.

Other mistakes of positioning must be avoided as well. Port C must not be placed too medially, because the fan retractor may clash with the left-hand instrument; the gallbladder fossa is a good landmark for positioning this port. Port A must be placed with extreme caution in the supraumbilical area: its insertion site is just above the aorta, close to its bifurcation. Accordingly, we initially inflate the abdomen to a pressure of 18 mm Hg just for placement of port A; increasing the distance between the abdominal wall and the aorta reduces the risk of aortic injury. We also recommend directing the port toward the coccyx. Once port A is in place, the intraperitoneal pressure is reduced to 15 mm Hg. A Hasson cannula can be used in this location, particularly if the patient has already had one or more midline incisions. Maintaining the proper angle (60° to 120°) between the axes of the two suturing instruments inserted through ports D and E is also important: if the angle is smaller, the instruments will cover part of the operating field, whereas if it is larger, depth perception may be impaired. Finally, if a trocar is not in the ideal position, it is better to insert another one than to operate through an inconveniently placed port.

If the surgeon spears the epigastric vessels with a trocar, bleeding will occur, in which case we prefer to ligate the vessel under laparoscopic guidance. We favor the Carter-Thomason CloseSure System (Inlet Medical, Inc., Eden Prairie, MN) to ligate the vessel securely with 0 absorbable suture. Once hemostasis is obtained, the surgeon simply repositions the trocar away from the vessels.

Step 2: Division of Gastrohepatic Ligament; Identification of Right Crus of Diaphragm and Posterior Vagus Nerve

Once the ports are in place, the gastrohepatic ligament is divided. Dissection begins above the caudate lobe (segments 1 and 9) of the liver, where this ligament usually is very thin, and continues toward the diaphragm until the right crus is identified. The crus is then separated from the right side of the esophagus by blunt dissection, and the posterior vagus nerve is identified. The right crus is dissected inferiorly toward the junction with the left crus.

Troubleshooting An accessory left hepatic artery originating from the left gastric artery is frequently encountered in the gastrohepatic ligament. If this vessel creates problems of exposure, it may be divided; in our experience, doing so has not caused problems. In dissecting the right crus from the esophagus, the electrocautery should be used with particular caution. Because the monopolar current tends to spread laterally, the posterior vagus nerve may sustain damage simply from being in proximity to the device, even when there is no direct contact. A better alternative is to use a bipolar instrument.

Step 3: Division of Peritoneum and Phrenoesophageal Membrane above Esophagus; Identification of Left Crus of Diaphragm and Anterior Vagus Nerve

The peritoneum and the phrenoesophageal membrane above the esophagus are divided with the electrocautery, and the anterior vagus nerve is identified. The left crus of the diaphragm is dissected downward toward the junction with the right crus.

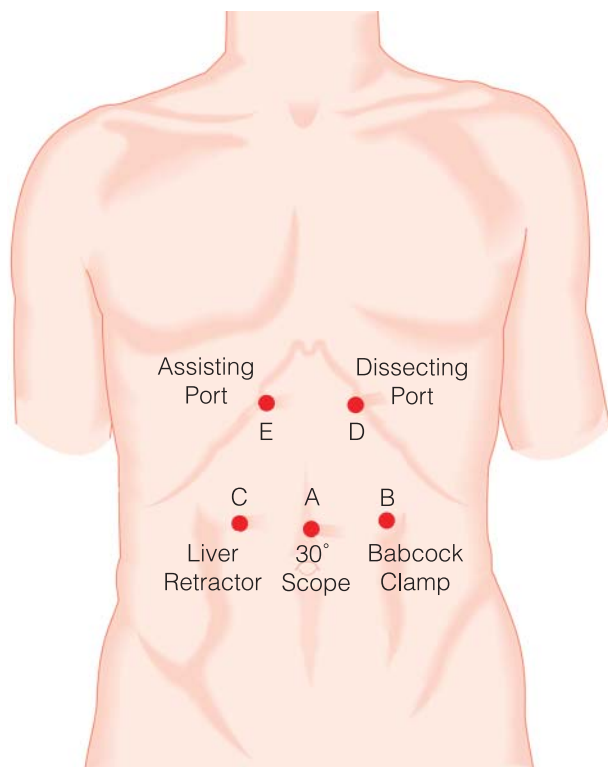


Figure 1 Laparoscopic Nissen fundoplication. Illustrated is the recommended placement of the trocars.

Troubleshooting Care must be taken not to damage the anterior vagus nerve or the esophageal wall. To this end, the nerve should be left attached to the esophageal wall, and the peritoneum and the phrenoesophageal membrane should be lifted from the wall by blunt dissection before they are divided.

Step 4: Division of Short Gastric Vessels

The 5 mm laparoscopic LigaSure Vessel Sealing System (Valleylab, Boulder, CO) is introduced through port B. A grasper is introduced by the surgeon through port D, and an assistant applies traction on the greater curvature of the stomach through port E. Dissection begins at the level of the middle portion of the gastric body and continues upward until the most proximal short gastric vessel is divided.

Troubleshooting There are two problems to watch for during this part of the procedure: (1) bleeding, either from the short gastric vessels or from the spleen, and (2) damage to the gastric wall.

Bleeding from the short gastric vessels is usually caused by excessive traction or by division of a vessel that is not completely coagulated. Vessels up to 5 mm in diameter can be taken down with the LigaSure device. Damage to the gastric wall can be caused by a burn from the electrocautery used to dissect between vessels or by traction applied with the graspers or the Babcock clamp.

Step 5: Creation of Window between Gastric Fundus, Esophagus, and Diaphragmatic Crura; Placement of Penrose Drain around Esophagus

The esophagus is retracted upward with a Babcock clamp applied at the level of the esophagogastric junction. By means of blunt and sharp dissection, a window is created under the esophagus between the gastric fundus, the esophagus, and the left pillar of the crus. The window is enlarged with the LigaSure device, and a Penrose drain is passed around the esophagus. This drain is then used for traction instead of the Babcock clamp to reduce the risk of damage to the gastric wall.

Troubleshooting The two main problems to watch for during this part of the procedure are (1) creation of a left pneumothorax and (2) perforation of the gastric fundus.

A left pneumothorax is usually caused by dissection done above the left pillar of the crus in the mediastinum rather than between the crus and the gastric fundus. This problem can be avoided by properly dissecting and identifying the left pillar of the crus.

Perforation of the gastric fundus is usually caused by pushing a blunt instrument under the esophagus and below the left pillar without having done enough dissection. Care must be exercised in taking down small vessels from the fundus when the area behind the esophagus is approached from the right: the anatomy is not as clear from this viewpoint, and perforation can easily occur. Sometimes, perforation is caused by the use of a monopolar electrocautery for dissection. An electrocautery burn can go unrecognized during dissection and manifest itself in the form of a leak during the first 48 hours after operation.

Step 6: Closure of Crura

The diaphragmatic crura are closed with interrupted 2-0 silk sutures on an Endo Stitch device (Autosuture, Norwalk,

CT); the sutures are tied intracorporeally. Exposure is provided by retracting the esophagus upward and toward the patient's left with the Penrose drain. The lens of the 30° laparoscope is angled slightly to the left by moving the light cable of the scope to the patient's right. The first stitch should be placed just above the junction of the two pillars. Additional stitches are placed 1 cm apart, and a space of about 1 cm is left between the uppermost stitch and the esophagus.

Troubleshooting Care must be taken not to spear esophageal wall with the needle. So as not to limit the space available for suturing, the bougie is not placed inside the esophagus during this part of the procedure.

Step 7: Insertion of Bougie into Esophagus and through Esophagogastric Junction

The esophageal stethoscope and the orogastric tube are removed, and a 56 French bougie is inserted by the anesthesiologist and passed through the esophagogastric junction under laparoscopic vision. The crura must be snug around the esophagus but not too tight: a closed grasper should slide easily between the esophagus and the crura.

Troubleshooting The most worrisome complication during this step is perforation of the esophagus. This can be prevented by lubricating the bougie and instructing the anesthesiologist to advance the bougie slowly and to stop if any resistance is encountered. In addition, it is essential to remove any instruments from the esophagogastric junction and to open the Penrose drain; these measures prevent the creation of an angle between the stomach and the esophagus, which can increase the likelihood of perforation. The position of the bougie can be confirmed by pressing with a grasper over the esophagus, which will feel full when the bougie is in place.

Step 8: Wrapping of Gastric Fundus around Lower Esophagus

The gastric fundus is gently pulled under the esophagus with the graspers. The left and right sides of the fundus are wrapped above the fat pad (which lies above the esophagogastric junction) and held together in place with a Babcock clamp introduced through port B. (The Penrose drain should be removed at this point because it is in the way.) Usually, three 2-0 silk sutures are used to secure the two ends of the wrap to each other. The stitches do not include the esophagus. Two coronal stitches are then placed between the top of the wrap and the esophagus, one on the right and one on the left. Finally, one additional suture is placed between the right side of the wrap and the closed crura.

To avoid the risk of injuring the inferior vena cava at the beginning of the dissection, some surgeons use a different method—the so-called left crus approach.²² In this approach, the operation begins with identification of the left crus of the diaphragm and division of the peritoneum and the phrenoesophageal membrane overlying it. The next step is division of the short gastric vessels, starting midway along the greater curvature of the stomach and continuing upward to join the area of the previous dissection. When the fundus has been thoroughly mobilized, the peritoneum is divided from the left to the right crus, and the right crus is dissected downward to expose the junction of the right and left crura. With this technique, the vena cava is never at risk. In addition, the branches of the anterior vagus nerve and

the left gastric artery are less exposed to danger. This technique can be very useful, particularly for management of very large paraesophageal hernias and for second antireflux operations [see Reoperation for GERD, *below*].

Troubleshooting To determine whether the wrap is going to be floppy, the surgeon must deliver the fundus under the esophagus, making sure that the origins of the short gastric vessels that have been transected are visible. Essentially, the posterior wall of the fundus is being used for the wrap. If the wrap remains to the right of the esophagus without retracting back to the left, then it is floppy, and suturing can proceed. If not, the surgeon must make sure that the upper short gastric vessels have been transected and the posterior dissection completed. If tension is still present after these maneuvers, it is probably best to perform a partial wrap [see Laparoscopic Partial (Guarner) Fundoplication, *below*].

Damage to the gastric wall may occur during the delivery of the fundus. Atraumatic graspers must be used, and the gastric fundus must be pulled gently and passed from one grasper to the other. Sometimes, it is helpful to push the gastric fundus under the esophagus from the left. The wrap should measure no more than 2 to 2.5 cm in length and, as noted, should be done with no more than three sutures. The first stitch is usually the lowest one; it must be placed just above the fat pad where the esophagogastric junction is thought to be.

If the anesthesiologist observes that peak airway pressure has increased (because of a pneumothorax) or that neck emphysema is present (because of pneumomediastinum), the pneumoperitoneum should be reduced from 15 mm Hg to 8 or 10 mm Hg until the end of the procedure. Pneumomediastinum tends to resolve without intervention within a few hours of the end of the procedure. Small pneumothoraces (usually on the left side) tend to resolve spontaneously, rendering insertion of a chest tube unnecessary. Larger pneumothoraces (> 20%), however, call for the insertion of a small (18 to 20 French) chest tube.

Step 9: Final Inspection, Removal of Instruments and Ports from Abdomen, and Closure of Port Sites

After hemostasis is obtained, the instruments and the ports are removed from the abdomen under direct vision. We usually close all port sites with 0 absorbable suture material using the Carter-Thomason CloseSure System.

Troubleshooting If any areas of oozing were observed, they should be irrigated and dried with sponges rolled into a cigarettelike shape before the ports are removed. In addition, if some grounds for concern remain, the oozing areas should be examined after the pneumoperitoneum is decreased to 7 to 8 mm Hg to abolish the tamponading effect exerted by the high intra-abdominal pressure.

All the ports should be removed from the abdomen under direct vision so that any bleeding from the abdominal wall can be readily detected. Such bleeding is easily controlled, either from inside or from outside.

COMPLICATIONS

A feared complication of laparoscopic Nissen fundoplication is esophageal or gastric perforation, which may result either from traction applied with the Babcock clamp or a grasper to the esophagus or the stomach (particularly when the stomach is

pulled under the esophagus) or from inadvertent electrocautery burns during any part of the dissection. A leak will manifest itself during the first 48 hours. Peritoneal signs will be noted if the spillage is limited to the abdomen; shortness of breath and a pleural effusion will be noted if spillage also occurs in the chest. The site of the leak should always be confirmed by a contrast study with barium or a water-soluble contrast agent. Optimal management consists of laparotomy and direct repair. If a perforation is detected intra-operatively, it may be closed laparoscopically.

Almost every patient experiences some degree of dysphagia postoperatively. This problem usually resolves after 4 to 6 weeks, during which period patients receive pain medications in an elixir form and are advised to avoid eating meat and bread. If, however, dysphagia persists beyond this period, one or more of the following causes is responsible.

1. A wrap that is too tight or too long (i.e., > 2.5 cm).²⁴
2. Lateral torsion with corkscrew effect. If the wrap rotates to the right (because of tension from intact short gastric vessels or because the fundus is small), a corkscrew effect is created.
3. A wrap made with the body of the stomach rather than the fundus. The relaxation of the LES and the gastric fundus is controlled by vasoactive intestinal polypeptide and nitric oxide^{25,26}; after fundoplication, the two structures relax simultaneously with swallowing. If part of the body of the stomach rather than the fundus is used for the wrap, it will not relax as the LES does on arrival of the food bolus.
4. Choice of the wrong procedure. In patients who have severely abnormal esophageal peristalsis (as in end-stage connective tissue disorders), a partial wrap is preferable. A 360° wrap may cause postoperative dysphagia and gas bloat syndrome.

If the wrap slips into the chest, the patient may experience dysphagia and regurgitation. The diagnosis is confirmed by means of a barium swallow. This problem can be prevented by using coronal sutures and by ensuring that the crura are closed securely.

Paraesophageal hernia may occur if the crura have not been closed or if the closure is too loose. We believe that closure of the crura not only is essential for preventing paraesophageal hernia but also is important from a physiologic point of view, in that it acts synergistically with the LES against stress reflux. Sometimes, it is possible to reduce the stomach and close the crura laparoscopically. More often, however, because the crural opening is very tight and the gastric wall is edematous, laparoscopic repair is impossible and laparotomy is preferable.

POSTOPERATIVE CARE AND OUTCOME EVALUATION

Postoperative care and outcome evaluation of laparoscopic Nissen fundoplication are considered elsewhere in conjunction with the discussion of partial fundoplication [see Laparoscopic Partial (Guarner) Fundoplication, Postoperative Care and Outcome Evaluation, *below*].

Laparoscopic Partial (Guarner) Fundoplication

PREOPERATIVE EVALUATION AND OPERATIVE PLANNING

Preoperative evaluation and operative planning are essentially the same for partial (Guarner) fundoplication as for Nissen

fundoplication. This operation should be performed only in patients with the most severe abnormalities of esophageal peristalsis: it is less effective than a 360° wrap for long-term control of reflux.⁸ In addition, laparoscopic partial fundoplication may be performed after laparoscopic Heller myotomy for achalasia [see Laparoscopic Heller Myotomy with Partial Fundoplication, below].²⁷

OPERATIVE TECHNIQUE

The first seven steps in a Guarner fundoplication are identical to the first seven in a Nissen fundoplication. The wrap, however, differs in that it extends around only 240° to 280° of the esophageal circumference. Once the gastric fundus is delivered under the esophagus, the two sides are not approximated over the esophagus. Instead, 80° to 120° of the anterior esophagus is left uncovered, and each of the two sides of the wrap (right and left) is separately affixed to the esophagus with three 2-0 silk sutures, with each stitch including the muscle layer of the esophageal wall. The remaining stitches (i.e., the coronal stitches and the stitch between the right side of the wrap and the closed crura) are identical to those placed in a Nissen fundoplication.

POSTOPERATIVE CARE

Currently, our average operating time for a laparoscopic fundoplication is approximately 2 hours. We start patients on a soft mechanical diet on the morning of postoperative day 1 and usually discharge them after 23 to 48 hours. The recovery time typically ranges from 10 to 14 days.

OUTCOME EVALUATION

The initial results of laparoscopic fundoplication obtained in the early 1990s indicated that the operation was effective in controlling reflux but that postoperative dysphagia occurred more often than had been anticipated.⁷ Many experts thought that this problem could be avoided by tailoring the fundoplication to the strength of esophageal peristalsis as measured by esophageal manometry.⁷ Accordingly, partial fundoplication (240°) was recommended for patients with impaired peristalsis, and total fundoplication (360°) was recommended for those with normal peristalsis. The short-term results of this tailored approach were promising.⁷ Gradually, however, it became evident that a partial fundoplication was not as durable as a total fundoplication⁸ and that a total fundoplication was not associated with a higher incidence of postoperative dysphagia even in patients with weak peristalsis.^{28,29}

These findings suggest that the initial problems with postoperative dysphagia were primarily attributable to unknown technical factors that were largely eliminated from the procedure as surgeons garnered more experience with it. As a result, total fundoplication is currently considered the procedure of choice for patients with GERD, regardless of the strength of their esophageal peristalsis.

In a 2007 study, pre- and postoperative manometric results were reviewed in 71 patients who underwent laparoscopic fundoplication. Not only did LES pressure increase after the procedure, but distal esophageal amplitude also increased in patients with abnormal preoperative motility, with normalization of peristalsis occurring in the majority of patients.³⁰ A 2001 report found that 62% of fundoplication patients were using antireflux medications 10 years after the operation, a finding

that raised concerns about long-term durability of the procedure.³¹ This study has been criticized on the grounds that many of the patients were taking PPIs for reasons other than reflux symptoms and that the reflux status was not assessed by pH monitoring. A 2006 study aimed at critically assessing 10-year outcomes reported results from 100 consecutive patients after complete and partial fundoplication.³² In this series, the rate of symptomatic control of reflux symptoms at 5 and 10 years was 90%, with fewer than 10% of patients using antacid medications at 10 years; only one patient required reintervention for persistent dysphagia. Similar results were documented in subsequent studies,^{33,34} confirming laparoscopic Nissen fundoplication as an effective long-term treatment for GERD.

Laparoscopic Heller Myotomy with Partial Fundoplication

Minimally invasive surgical procedures for primary esophageal motility disorders (achalasia, diffuse esophageal spasm [DES], nutcracker esophagus [NE] and hypertensive LES [H-LES]) yield results that are comparable to those of open procedures but are associated with less postoperative pain and with a shorter recovery time.³⁵ Today, laparoscopic Heller myotomy with partial fundoplication has supplanted left thoracoscopic myotomy as the procedure of choice for esophageal achalasia.³⁻⁶ Long-term studies demonstrated that even though left thoracoscopic myotomy led to resolution of dysphagia in about 85% to 90% of patients, it had the following four drawbacks.

1. Gastroesophageal reflux developed postoperatively in about 60% of patients because no fundoplication was performed in conjunction with the myotomy.³ With the laparoscopic approach, in contrast, a partial fundoplication can easily be performed, which prevents reflux in the majority of patients^{3,4} and corrects many instances of preexisting reflux arising from pneumatic dilatation.³ A prospective, randomized, double-blind clinical trial that compared Heller myotomy alone with Heller myotomy and Dor fundoplication clearly demonstrated that the addition of a fundoplication is essential: the incidence of postoperative reflux (as measured by pH monitoring) was 48% in patients who underwent myotomy alone but only 9% in those who underwent myotomy and Dor fundoplication.³⁶
2. The extension of the myotomy onto the gastric wall (clearly the most critical and challenging part of the operation) proved difficult because of poor exposure, with the consequent risk of a short myotomy and persistent dysphagia. With the laparoscopic approach, in contrast, excellent exposure of the esophagogastric junction is easily achieved, and the myotomy can be extended onto the gastric wall for about 2 to 2.5 cm.^{3,37}
3. Double-lumen endotracheal intubation and single-lung ventilation were required, with the patient in the right lateral decubitus position. In contrast, the setting for a laparoscopic myotomy (the same as that for a laparoscopic fundoplication) is much easier for the patient, the anesthesiologist, and the operating room personnel. In addition, most surgeons have by now acquired substantial experience with laparoscopic antireflux procedures and thus are more familiar and comfortable with laparoscopic exposure of the distal esophagus and the esophagogastric junction.

4. The average postoperative hospital stay was about 3 days because of the chest tube left in place at the time of the operation and the discomfort arising from the thoracic incisions. After a laparoscopic Heller myotomy, the hospital stay is only 1 or 2 days; there is no need for a chest tube, and patients are more comfortable.

Although there is now a consensus on the preferred treatment of achalasia, there is no such general agreement on the treatment of the remaining primary esophageal motility disorders (i.e., DES, NE, and H-LES). We reported our experience comparing thoracoscopic and laparoscopic approaches to these disorders and found (1) that laparoscopic myotomy was superior to thoracoscopic myotomy in relieving dysphagia in patients with DES and H-LES, and (2) that the two approaches yielded equally disappointing results with respect to relieving chest pain in patients with NE, the surgical treatment of which remains elusive.³⁸ These results support the view that laparoscopic Heller myotomy should be the standard surgical treatment for achalasia, DES, and H-LES. Accordingly, we would consider surgical intervention (laparoscopic Heller myotomy) in an NE patient only in an attempt at relieving severe dysphagia.

We no longer perform a long myotomy via a right thoracoscopic approach.

PREOPERATIVE EVALUATION

All candidates for a laparoscopic Heller myotomy should undergo a thorough and careful evaluation to establish the diagnosis and characterize the disease.³⁹

An upper GI series is useful. A characteristic so-called bird's beak is usually seen in patients with achalasia. A dilated, sigmoid esophagus may be present in patients with long-standing achalasia. A corkscrew esophagus is often seen in patients with diffuse esophageal spasm. Endoscopy is performed to rule out a tumor of the esophagogastric junction and gastroduodenal pathologic conditions.

Esophageal manometry is the key test for establishing the diagnosis of esophageal achalasia. The classic manometric findings are (1) absence of esophageal peristalsis and (2) an LES that fails to relax appropriately in response to swallowing.

Ambulatory pH monitoring should always be done in patients who have undergone pneumatic dilatation to rule out abnormal gastroesophageal reflux. In addition, pH monitoring should be performed postoperatively to detect abnormal reflux, which, if present, should be treated with acid-reducing medications.³⁹

In patients older than 60 years who have experienced the recent onset of dysphagia and excessive weight loss, secondary achalasia or pseudoachalasia from cancer of the esophagogastric junction should be ruled out. Endoscopic ultrasonography or computed tomography can help establish the diagnosis.⁴⁰

OPERATIVE PLANNING

Patient preparation (i.e., anesthesia, positioning, and instrumentation) is identical to that for laparoscopic fundoplication.

OPERATIVE TECHNIQUE

Many of the steps in a laparoscopic Heller myotomy are the same as the corresponding steps in a laparoscopic fundoplication. The ensuing description focuses on those steps that differ significantly.

Either a Dor or a Guarner fundoplication [see Laparoscopic Partial (Guarner) Fundoplication, *above*] may be performed in conjunction with a Heller myotomy. The Dor fundoplication is an anterior 180° wrap. Its advantages are that (1) it does not require posterior dissection and the creation of a window between the esophagus, the stomach, and the left pillar of the crus; (2) it covers the exposed esophageal mucosa after completion of the myotomy; and (3) it is effective even in patients with GERD.⁴¹ Its main disadvantage is that achieving the proper geometry can be difficult, and a wrong configuration can lead to dysphagia even after a properly performed myotomy.⁴² The advantages of the Guarner fundoplication are that (1) it is easier to perform; (2) it keeps the edges of the myotomy well separated; and (3) it might be more effective than a Dor procedure in preventing reflux. Its main disadvantages are that (1) it requires more dissection for the creation of a posterior window, and (2) it leaves the esophageal mucosa exposed.

Steps 1 through 6

Steps 1, 2, 3, 4, 5, and 6 of a laparoscopic Heller myotomy are essentially identical to the first six steps of a laparoscopic fundoplication. Steps 5 and 6, however, are necessary only if a posterior partial fundoplication is to be performed. Care must be taken not to narrow the esophageal hiatus too much and push the esophagus anteriorly.

Step 7: Intraoperative Endoscopy

At the beginning of a surgeon's experience with laparoscopic Heller myotomy, intraoperative endoscopy is an important and helpful step; however, once the surgeon has gained adequate experience with this procedure and has become familiar with the relevant anatomy from a laparoscopic perspective, it may be omitted.

Troubleshooting The most worrisome complication during intraoperative endoscopy is perforation of the esophagus. This complication can be prevented by having the procedure done by an experienced endoscopist who is familiar with achalasia.

Step 8: Initiation of Myotomy and Entry into Submucosal Plane at Single Point

The fat pad is removed with the LigaSure device to provide clear exposure of the esophagogastric junction. A Babcock clamp is then applied over the junction, and the esophagus is pulled downward and to the left to expose the right side of the esophagus. The myotomy is performed at the 11 o'clock position. It is helpful to mark the surface of the esophagus along the line through which the myotomy will be carried out [see Figure 2]. The myotomy is started about 3 cm above the esophagogastric junction. Before it is extended upward and downward, the proper submucosal plane should be reached at a single point; in this way, the likelihood of subsequent mucosal perforation can be reduced.

Troubleshooting The myotomy should not be started close to the esophagogastric junction, because at this level the layers often are poorly defined, particularly if multiple dilatations or injections of botulinum toxin have been performed. At the preferred starting point, about 3 cm above the esophagogastric junction, the esophageal wall is usually normal. As a rule, we do

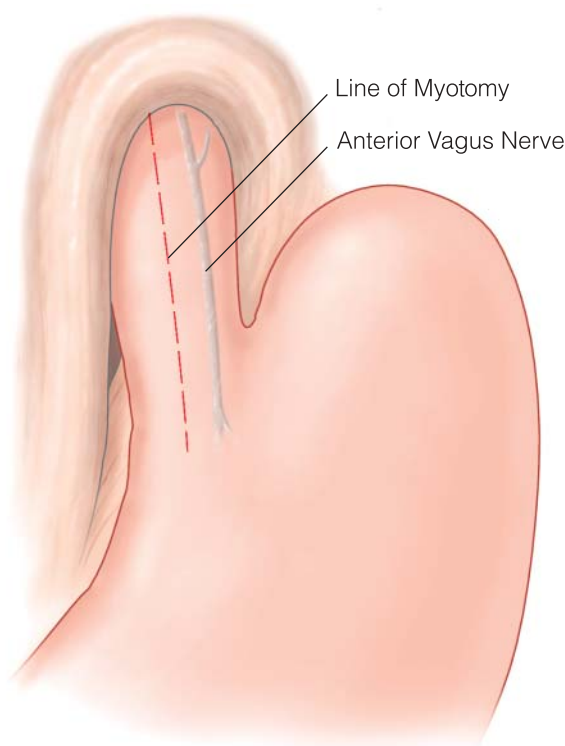


Figure 2 Laparoscopic Heller myotomy with partial fundoplication. The proposed myotomy line is marked on the surface of the esophagus.

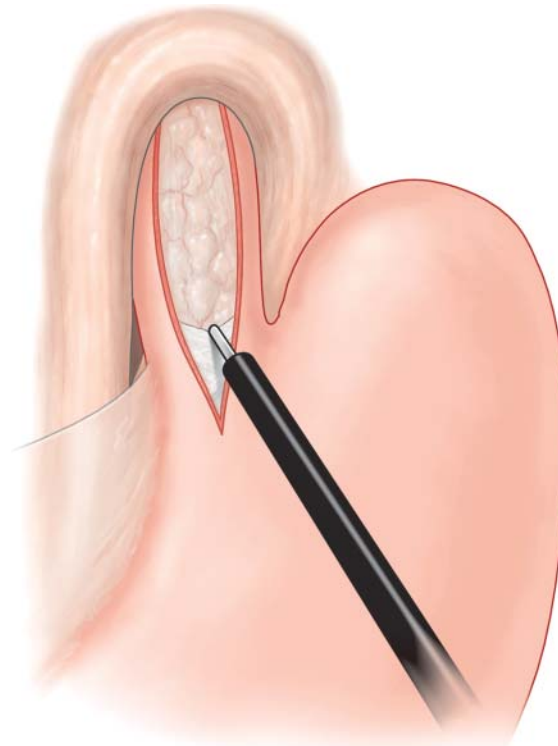


Figure 3 Laparoscopic Heller myotomy with partial fundoplication. The myotomy is extended proximally and distally.

not open the entire longitudinal layer first and then the circular layer; we find it easier and safer to try to reach the submucosal plane at a single point and then move upward and downward from there. In the course of the myotomy, there is always some bleeding from the cut muscle fibers, particularly if the esophagus is dilated and the wall is very thick. After the source of the bleeding is identified, the electrocautery must be used with caution. The most troublesome bleeding comes from the submucosal veins encountered at the esophagogastric junction (which are usually large). In most instances, gentle compression is preferable to electrocautery. A sponge introduced through one of the ports facilitates the application of direct pressure.

Step 9: Proximal and Distal Extension of Myotomy

Once the mucosa has been exposed, the myotomy can safely be extended [see Figure 3]. Distally, it is extended for about 2 to 2.5 cm onto the gastric wall; proximally, it is extended for about 6 cm above the esophagogastric junction. Thus, the total length of the myotomy is typically about 8 to 8.5 cm [see Figure 4]. We find it useful to alternate between a dolphin-nose grasper and using a curved micrograsper during extension of the myotomy; this makes the dissection safer, in that it allows the muscle fibers to be separated from the mucosa before being transected.

Troubleshooting The course of the anterior vagus nerve must be identified before the myotomy is started. If this nerve crosses the line of the myotomy, it must be lifted away from the esophageal wall, and the muscle layers must then be cut under it. In addition, care must be taken not to injure the anterior

vagus nerve while removing the fat pad. Treatment with botulinum toxin occasionally results in fibrosis with scarring and loss of the normal anatomic planes; this occurs more frequently at the level of the esophagogastric junction.

If a perforation seems possible or likely, it should be sought as described earlier [see Step 7: Intraoperative Endoscopy, above]. Any perforation found should be repaired with 5-0 absorbable suture material, with interrupted sutures employed for a small perforation and a continuous suture for a larger one. When a perforation has occurred, an anterior fundoplication is usually chosen in preference to a posterior one because the stomach will offer further protection against a leak.

Step 10 (Dor Procedure): Anterior Partial Fundoplication

Two rows of sutures are placed. The first row (on the left side) comprises three stitches: the uppermost stitch incorporates the gastric fundus, the esophageal wall, and the left pillar of the crus [see Figure 5], and the other two incorporate only the gastric fundus and the left side of the esophageal wall [see Figure 6]. The gastric fundus is then folded over the myotomy, and the second row (also comprising three stitches) is placed on the right side between the fundus and the right side of the esophageal wall, with only the uppermost stitch incorporating the right pillar of the crus [see Figure 7 and Figure 8]. Finally, two additional stitches are placed between the anterior rim of the hiatus and the superior aspect of the fundoplication [see Figure 9]. These stitches remove any tension from the second row of sutures.

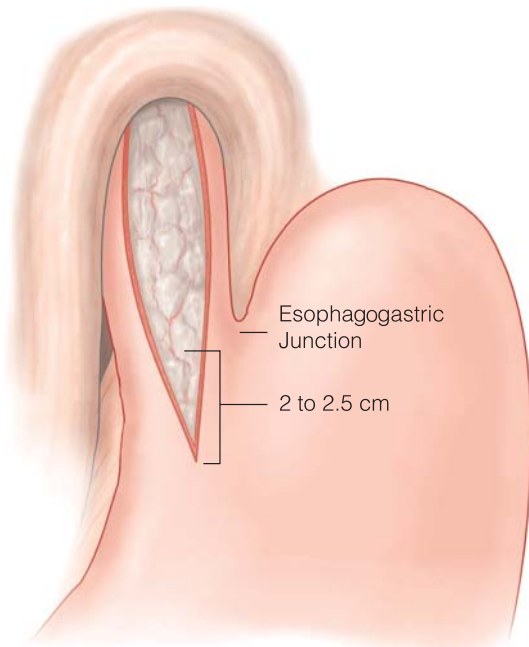


Figure 4 Laparoscopic Heller myotomy with partial fundoplication. The myotomy is approximately 8 cm long, extending distally for about 2 to 2.5 cm onto the gastric wall and proximally for about 6 cm above the esophagogastric junction.

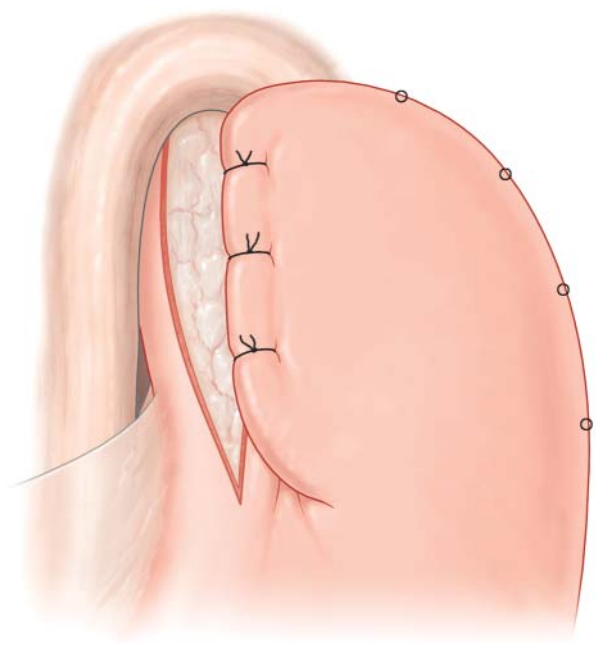


Figure 6 Laparoscopic Heller myotomy with anterior partial fundoplication (Dor procedure). The second and third stitches in the first row incorporate only the fundus and the left side of the esophageal wall.

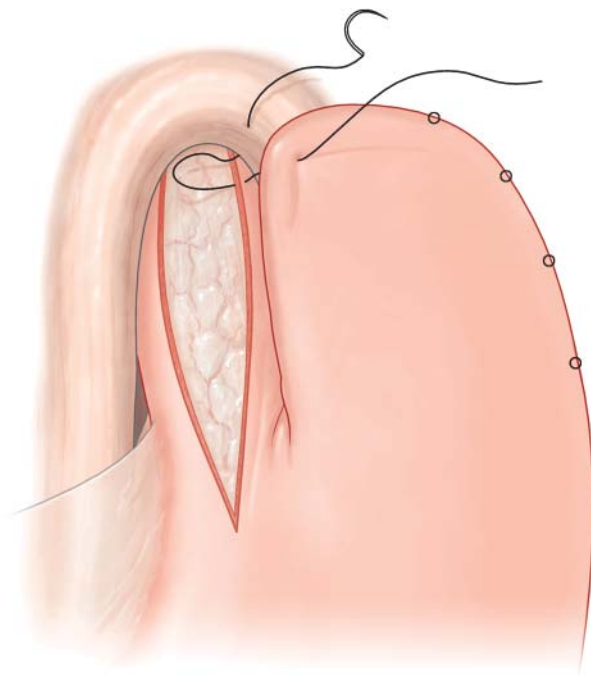


Figure 5 Laparoscopic Heller myotomy with anterior partial fundoplication (Dor procedure). The uppermost stitch in the first row incorporates the fundus, the esophageal wall, and the left pillar of the crus.

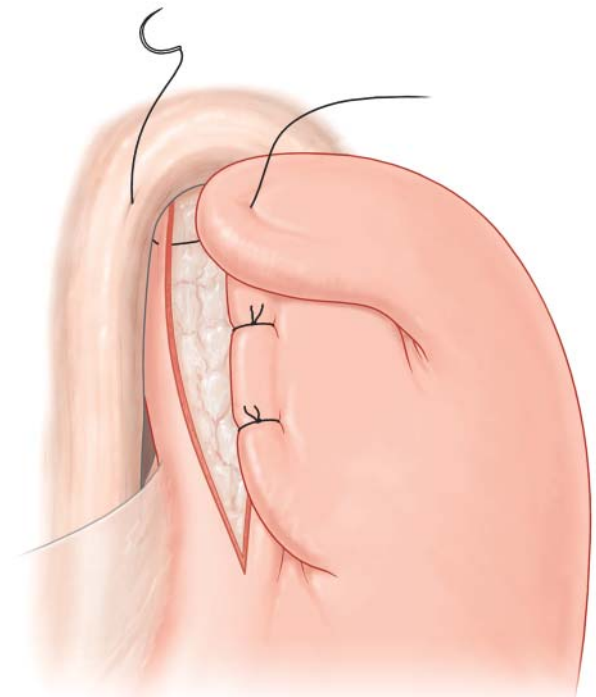


Figure 7 Laparoscopic Heller myotomy with anterior partial fundoplication (Dor procedure). The uppermost stitch in the second row incorporates the fundus, the esophageal wall, and the right crus.

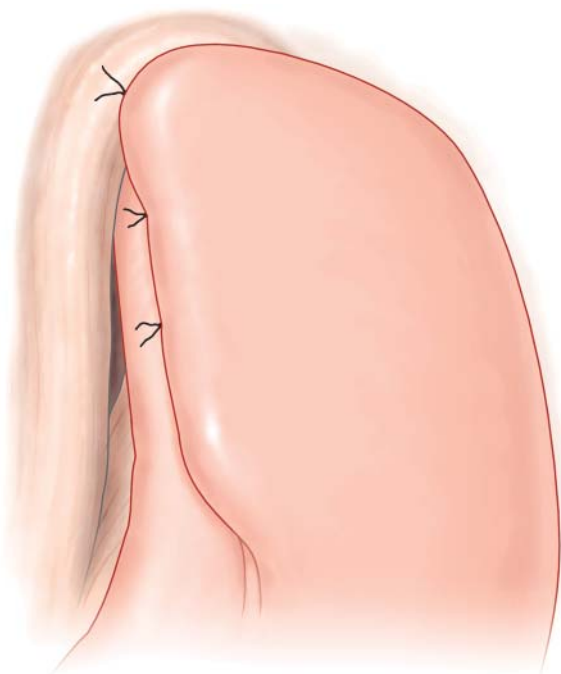


Figure 8 Laparoscopic Heller myotomy with anterior partial fundoplication (Dor procedure). The second and third stitches in the second row incorporate only the fundus and the right side of the esophageal wall.

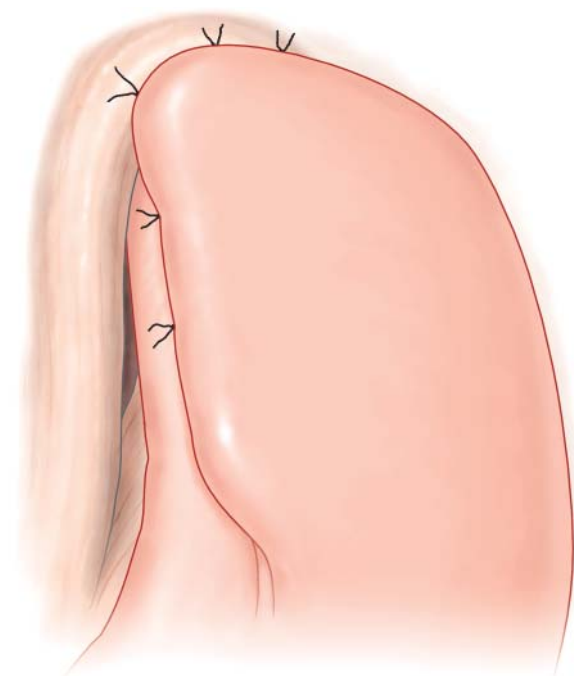


Figure 9 Laparoscopic Heller myotomy with anterior partial fundoplication (Dor procedure). Two final stitches are placed between the superior portion of the wrap and the anterior rim of the hiatus.

Troubleshooting Efforts must be made to ensure that the fundoplication does not become a cause of postoperative dysphagia. Accordingly, we always take down the short gastric vessels, even though some authorities suggest that this step can be omitted.^{4,40} In addition, the gastric fundus rather than the body of the stomach should be used for the wrap, and only the uppermost stitch of the right row of sutures should incorporate the right pillar of the crus.⁴¹

Step 10 (Guarner Procedure): Posterior Partial Fundoplication

Alternatively, a posterior 220° fundoplication may be performed. The gastric fundus is delivered under the esophagus, and each side of the wrap (right and left) is attached to the esophageal wall, lateral to the myotomy, with three sutures [see Figure 10].

Step 11: Final Inspection and Removal of Instruments and Ports from Abdomen

Step 11 of a laparoscopic Heller myotomy is identical to step 9 of a laparoscopic Nissen fundoplication.

COMPLICATIONS

Delayed esophageal leakage, usually resulting from an electrocautery burn to the esophageal mucosa, may occur during the first 24 to 36 hours after operation. The characteristic signs and symptoms are chest pain, fever, and a pleural effusion on the chest x-ray. The diagnosis is confirmed by an esophagogram. Treatment options depend on the time of diagnosis and on the size and location of the leak. Early, small leaks can be repaired directly. If the site of the leak is high in the chest, a thoracotomy

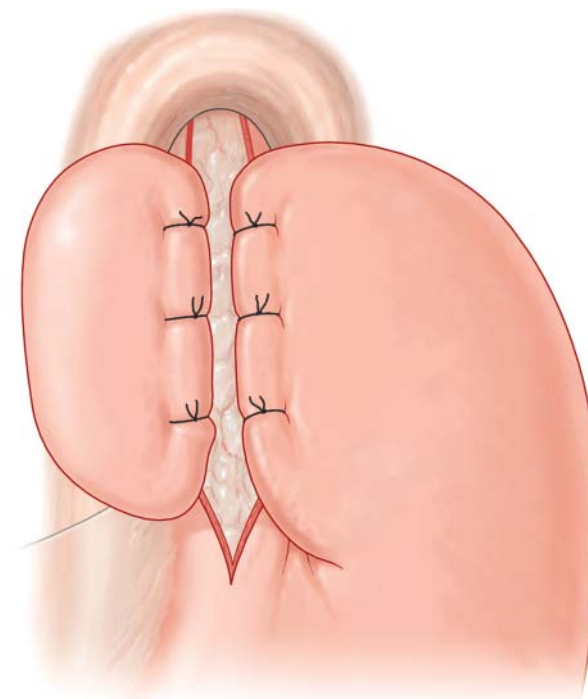


Figure 10 Laparoscopic Heller myotomy with posterior partial fundoplication (Guarner procedure). Each side of the posterior 220° wrap is attached to the esophageal wall with three sutures.

is recommended; if the site is at the level of the esophagogastric junction, a laparotomy is preferable, and the stomach can be used to reinforce the repair. If the damage to the esophagus is too extensive to permit repair, an esophagectomy [see 4:7 *Open Esophageal Procedures*] is indicated.

Dysphagia may either persist after the operation or recur after a symptom-free interval. In either case, a complete workup is necessary, and treatment is individualized on the basis of the specific cause of dysphagia. Reoperation may be indicated [see Reoperation for Esophageal Achalasia, *below*].

Abnormal gastroesophageal reflux occurs in 7 to 20% of patients after operation.^{3,4} Because most patients are asymptomatic, it is essential to try to evaluate all patients postoperatively with manometry and prolonged pH monitoring. Reflux should be treated with acid-reducing medications.

POSTOPERATIVE CARE

We do not routinely obtain an esophagogram before initiating feeding. Patients are started on a soft mechanical diet on the morning of postoperative day 1, and this diet is continued for the rest of the first week. Patients are discharged after 24 to 48 hours and are able to resume regular activities in 7 to 14 days.

OUTCOME EVALUATION

The results obtained to date with laparoscopic Heller myotomy and partial fundoplication are excellent and are generally comparable to those obtained with the corresponding open surgical procedure: dysphagia is alleviated or eliminated in more than 90% of patients.^{3,6,42} These results have been confirmed in long-term follow-up outcome studies. One report from the University of Padua found that at a minimum of 6 years after surgical intervention, 85% of myotomy patients were satisfied.⁴³

In a 2008 report describing our experience with 113 patients treated for achalasia with laparoscopic Heller myotomy and Dor fundoplication, we found that at a median follow-up of 45 months (range, 7 months to 12.5 years), 80% experienced complete relief of dysphagia after the operation.⁴⁴ The remaining 20% required endoscopic dilatation, which was successful in 50% of the cases. We have observed a significant change in the treatment algorithm for this condition: gastroenterologists now typically refer these patients for surgical treatment before any other therapy has been instituted, reserving endoscopic dilatation for cases where operative treatment has failed.⁴⁵ Overall, combined treatment yields a success rate of about 90%.

Historically, the presence of a sigmoid-shaped esophagus has been considered a contraindication to performing a myotomy to treat longstanding achalasia, making esophagectomy the only option. In the study just mentioned,⁴⁴ we subdivided the patients according to the degree of esophageal dilatation and observed the responses to surgery in the various groups. Even in those cases where the esophageal diameter exceeded 6 cm and the esophagus was sigmoid, the outcomes of laparoscopic myotomy were not significantly different.⁴⁴

Left Thoracoscopic Myotomy

Currently, we would consider a left thoracoscopic myotomy for patients in whom multiple previous abdominal procedures (done to treat other diseases) would preclude a laparoscopic approach.

PREOPERATIVE EVALUATION

Preoperative evaluation is essentially the same as that for laparoscopic Heller myotomy.

OPERATIVE PLANNING

The patient is placed under general anesthesia and intubated with a double-lumen endotracheal tube so that the left lung can be deflated during the procedure. As for a left thoracotomy, the patient is placed in the right lateral decubitus position over an inflated bean bag. The instrumentation is similar to that for a laparoscopic Nissen or Guarnier fundoplication. Instead of conventional trocars, four or five thoracoports with blunt obturators are employed, because insufflation of the thoracic cavity is not required. The myotomy can be performed with a monopolar hook cautery, bipolar scissors, or an ultrasonic scalpel. A 30° scope and a 45° scope are essential for thoracoscopic procedures. In addition, an endoscope is used for intraoperative endoscopy.

OPERATIVE TECHNIQUE

Step 1: Placement of Thoracoports

Five ports are usually placed [see *Figure 11*]. Port A, used for the 30° scope, is inserted in the sixth intercostal space about 3.5 to 5 cm behind the posterior axillary line. Port B, used for the lung retractor, is placed in the third intercostal space about 1.25 to 2.5 cm anterior to the posterior axillary line. Port C, used for insertion of a grasper, is placed in the sixth intercostal space in the anterior axillary line. Port D, used for insertion of the instrument employed for the myotomy, is placed in the seventh intercostal space in the midaxillary line. Port E is placed in the eighth intercostal space between the anterior axillary line and the midaxillary line. This port is optional: it is needed in about 30% of cases to allow the surgeon to obtain further exposure of the esophagogastric junction through retraction of the diaphragm.

Troubleshooting A common mistake is to insert port A too anteriorly. This port must be placed well beyond the

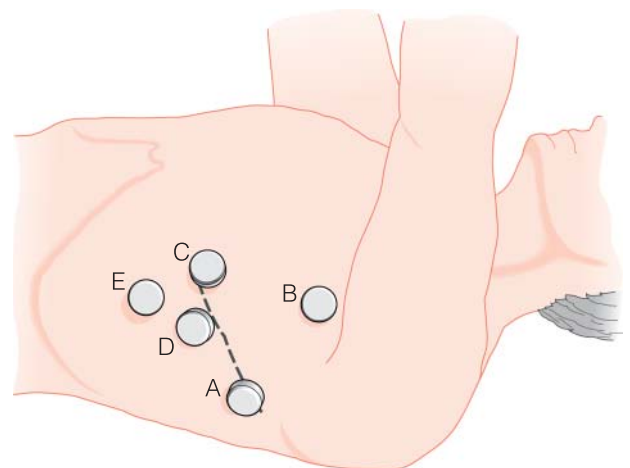


Figure 11 Left thoracoscopic myotomy. Illustrated is the recommended placement of the thoracoports.

posterior axillary line to provide the best angle for the 30° scope. Often, the other ports are placed one or two intercostal spaces too high. This mistake hampers the performance of the most delicate portion of the operation, the myotomy of the distal portion of the esophagus and the stomach.

Sometimes, chest wall bleeding occurs as a consequence of port insertion. This bleeding will obscure the operating field and therefore must be stopped before the intrathoracic portion of the procedure is begun. This is accomplished either by using the cautery from the inside or by applying a stitch from the outside if an intercostal vessel has been damaged.

Step 2: Retraction of Left Lung and Division of Inferior Pulmonary Ligament

Once the ports are in place, the deflated left lung is retracted cephalad with a fan retractor introduced through port B. This maneuver places tension on the inferior pulmonary ligament, which is then divided. After the ligament is divided, the fan retractor can be held in place by a self-retaining system fixed to the operating table.

Troubleshooting Before the inferior pulmonary ligament is divided, the inferior pulmonary vein must be identified to prevent a life-threatening injury to this vessel. If oxygen saturation decreases, particularly in patients with lung disease, the retractor should be removed and the lung inflated intermittently.

Step 3: Division of Mediastinal Pleura and Dissection of Periesophageal Tissues

The mediastinal pleura is divided, and the tissues overlying the esophageal wall are dissected until the wall of the esophagus is visible. This maneuver varies in difficulty depending on the width of the space between the aorta and the pericardium (which sometimes is very small) and on the size and shape of the esophagus. Large (sigmoid) esophagi tend to curve to the right, which makes identification of the wall difficult. If the esophagus is not immediately apparent, it can be easily identified in the groove between the heart and the aorta by means of transillumination provided by an endoscope [see Figure 12].

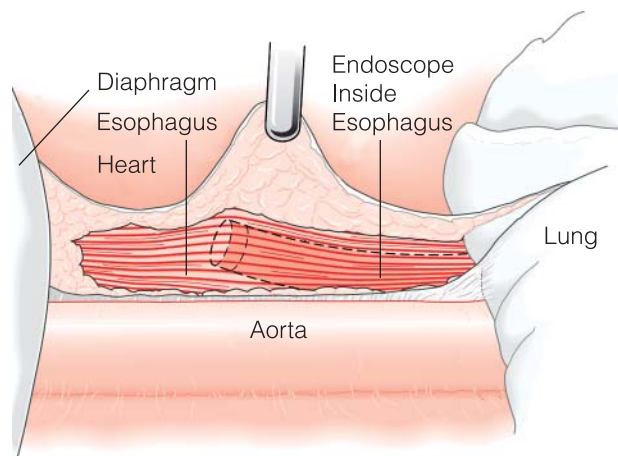


Figure 12 Left thoracoscopic myotomy. The esophagus may be identified by means of transillumination from the endoscope.

Troubleshooting The endoscope placed inside the esophagus at the beginning of the procedure plays an important role. In the early stages of the procedure, it allows identification of the esophagus via transillumination. When the light intensity of the 30° scope is turned down, the esophagus appears as a bright structure. In addition, tilting the tip of the endoscope brings the esophagus into view as it is lifted from the groove between the aorta and the heart.

Step 4: Initiation of Myotomy and Entry into Submucosal Plane at Single Point

As in a laparoscopic Heller myotomy, it is helpful to mark the surface of the esophagus along the line through which the myotomy will be carried out. The myotomy is started halfway between the diaphragm and the inferior pulmonary vein. Again, the proper submucosal plane should be reached at a single point before the myotomy is extended upward and downward.

Troubleshooting Troubleshooting for this step is essentially the same as that for step 8 of a laparoscopic Heller myotomy, with the exception that here the myotomy is started 4 to 5 cm (rather than 3 cm) above the esophagogastric junction.

Step 5: Proximal and Distal Extension of Myotomy

Once the mucosa has been exposed, the myotomy can safely be extended proximally and distally [see Figure 13]. We usually extend the myotomy for about 5 mm onto the gastric wall, without adding an antireflux procedure.^{3,4} Typically, the total length of the myotomy is about 6 cm for patients with achalasia.

Troubleshooting Proximally, the myotomy is extended all the way to the inferior pulmonary vein only in cases of vigorous achalasia (high-amplitude simultaneous contractions associated with chest pain in addition to dysphagia) or diffuse

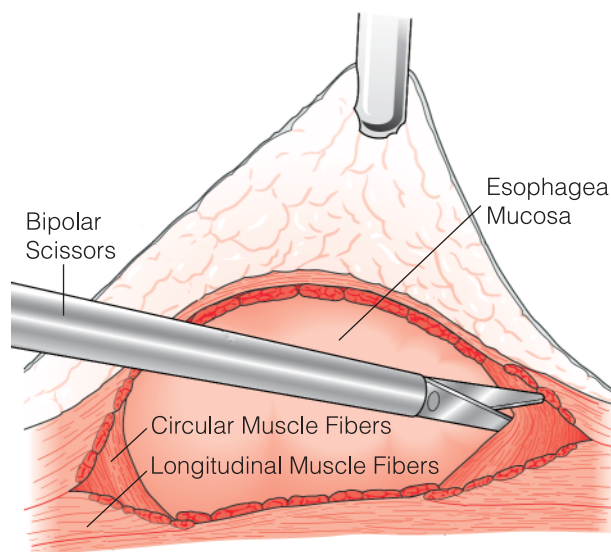


Figure 13 Left thoracoscopic myotomy. Shown are the distal and proximal extensions of the myotomy.

esophageal spasm; otherwise, it is limited to the distal 5 to 6 cm of the esophagus. If a longer myotomy is needed, the lung is displaced anteriorly and the myotomy extended to the aortic arch.

Distally, the myotomy is continued for 5 mm past the esophagogastric junction. The endoluminal view provided by the endoscope is useful for assessing the location of the esophagogastric junction. Often, the stomach is distended by the air insufflated by the endoscope and pushes the diaphragm upward, thereby limiting the view of the esophagogastric junction. If sucking air out of the stomach does not resolve this problem, an additional port (i.e., port E) may be placed in the eighth intercostal space, and a fan retractor may be introduced through this port to push the diaphragm down.

Because the myotomy of the gastric wall is the most challenging part of the operation, good exposure is essential. It is at this level that an esophageal perforation is most likely to occur. The risk is particularly high in patients who have undergone pneumatic dilatation or injection of botulinum toxin, both of which may lead to the replacement of muscle layers by scar tissue and the consequent loss of the regular planes. Perforations recognized in the operating room can be repaired by thoracoscopic intracorporeal suturing or, if this fails, by thoracotomy and open repair. The gastric fundus can be used to buttress the repair. If it is unclear whether a perforation has occurred, the esophagus should be covered with water and air insufflated through the endoscope; bubbling will be observed over the site of any perforation present.

Step 6: Insertion of Chest Tube and Removal of Thoracoports

A 24 French angled chest tube is inserted under direct vision through port D or port E. The ports are removed under direct vision, and the thoracic wall is inspected for bleeding.

COMPLICATIONS

As with laparoscopic Heller myotomy, delayed esophageal leakage is a common postoperative complication, and treatment options are similar.

If the myotomy is not extended far enough onto the gastric wall, residual dysphagia occurs. To prevent this problem, the distal extent of the myotomy should be assessed by means of endoscopy with the goal of including 5 mm of the gastric wall. Patients with residual dysphagia must be evaluated by means of esophageal manometry, which will document the extent of the residual high-pressure zone and the pressure within it. The myotomy can be easily extended by a laparoscopic approach, and a Dor fundoplication can be added.

If, on the other hand, the myotomy is extended too far onto the gastric wall, abnormal gastroesophageal reflux occurs. Some patients present with heartburn; others are asymptomatic. It is essential to evaluate patients postoperatively with manometry and prolonged pH monitoring. Mild reflux can be treated with acid-reducing medications, particularly in elderly patients. In younger patients, abnormal reflux should be corrected with a laparoscopic partial fundoplication (e.g., Dor fundoplication).

POSTOPERATIVE CARE

Patients are started on a liquid diet the morning of postoperative day 1; on postoperative day 2, they are started on a soft mechanical diet, which is continued for the rest of the first week. We do not routinely obtain an esophagogram before starting feedings. The chest tube is removed after 24 hours if the lung is fully expanded and there is no air leak. Patients are discharged after 48 to 72 hours and are able to resume regular activities in 7 to 10 days.

OUTCOME EVALUATION

The results obtained with thoracoscopic myotomy are generally comparable to those obtained with corresponding open surgical procedures. In a 1999 study from UCSF, 26 (87%) of the first 30 patients with achalasia who were treated in this fashion experienced good or excellent results [see Table 2].³ At present, however, this procedure is rarely used to treat esophageal achalasia: laparoscopic Heller myotomy and Dor fundoplication is now the treatment of choice.⁴⁵

Reoperation for GERD

Currently, an increasing number of patients are being seen for evaluation and treatment of foregut symptoms after laparoscopic antireflux surgery. These patients are treated as follows.

PREOPERATIVE EVALUATION

Some degree of dysphagia, bloating, and abdominal discomfort is common during the first 6 to 8 weeks after a fundoplication. If these symptoms persist or heartburn and regurgitation occur, a thorough evaluation (with barium swallow, endoscopy, esophageal manometry, and pH monitoring) is carried out with the aim of answering the following three questions:

1. Are the symptoms attributable to persistent gastroesophageal reflux?
2. Are the symptoms attributable to the fundoplication itself?
3. Can the cause of the failure of the first operation be identified and corrected by a second operation?

Many patients report heartburn after a fundoplication. It is often assumed that this symptom must be the result of a failed operation and that acid-reducing medications should be restarted. In most cases, however, this assumption is mistaken:

Table 2 Results of Thoracoscopic Myotomy in 30 Patients with Achalasia³

Results	Patients (% of Total)
Excellent (no dysphagia)	21 (70)
Good (dysphagia < once/wk)	5 (17)
Fair (dysphagia > once/wk)	3 (10)
Poor (persistent dysphagia)	1 (3)

postoperative pH monitoring yields abnormal results in only about 20% of patients.⁴⁶ The value of manometry lies in its ability to document the changes caused by the operation at the level of the LES and the esophageal body. The pH monitoring assesses the reflux status and determines whether there is a correlation between symptoms and actual episodes of reflux. If abnormal reflux is in fact present, the therapeutic choice is between medical therapy and a second operation.

Other patients complain of dysphagia arising *de novo* after the operation. This symptom is usually attributable to the operation itself and may occur in the absence of abnormal reflux. In addition to manometry and pH monitoring, a barium swallow is essential to define the anatomy of the esophagogastric junction. A study from the University of Washington found that the anatomic configurations observed could be divided into three main types: (1) type I hernia, in which the esophagogastric junction was above the diaphragm (subdivided into type IA, with both the esophagogastric junction and the wrap above the diaphragm, and type IB, with only the esophagogastric junction above the diaphragm); (2) type II hernia, a paraesophageal configuration; and (3) type III hernia, in which the esophagogastric junction was below the diaphragm and there was no evidence of hernia but in which the body of the stomach rather than the fundus was used for the wrap.⁴⁷ In 10% of patients, however, the cause of the failure could not be identified preoperatively.³⁸

Some patients present with a mix of postprandial bloating, nausea, and diarrhea. These symptoms may be the result of damage to the vagus nerves. Radionuclide evaluation of gastric emptying often helps quantify the problem.

OPERATIVE PLANNING

Patient preparation (i.e., anesthesia, positioning, and instrumentation) for a reoperation for reflux is identical to that for the initial laparoscopic fundoplication.

OPERATIVE TECHNIQUE

We do not routinely attempt a second antireflux operation laparoscopically. To provide a stepwise technical description that would be suitable for all reoperations for reflux is impossible, because the optimal procedure depends on the original approach (open versus laparoscopic), the severity of the adhesions, and the specific technique used for the first operation (total or partial fundoplication). The key goals of reoperation for reflux are as follows.

1. To dissect the wrap and the esophagus away from the crura. This is the most difficult part of the operation. The major complications seen during this part of the procedure are damage to the vagus nerves and perforation of the esophagus and the gastric fundus.
2. To take down the previous repair. The earlier repair must be completely undone and the gastric fundus returned to its natural position. If the short gastric vessels were not taken down during the first procedure, they must be taken down during the second.
3. To dissect the esophagus in the posterior mediastinum so as to have enough esophageal length below the diaphragm and avoid placing tension on the repair.
4. To reconstruct the cardia. The same steps are followed as for a first-time repair. If, after extensive esophageal mobilization, the esophagogastric junction remains above

the diaphragm (short esophagus), esophageal lengthening can be accomplished by adding a thoracoscopic Collis gastroplasty to the fundoplication. To date, however, we have never found this step to be necessary.

COMPLICATIONS

Because the risk of gastric or esophageal perforation or damage to the vagus nerves is much higher during a second antireflux operation, the surgeon must proceed with extreme care, making sure to identify structures completely before dividing them. Most perforations are recognized and repaired intraoperatively. Leaks manifest themselves during the first 48 hours. Peritoneal signs are noted if the spillage is limited to the abdomen; shortness of breath and a pleural effusion are noted if spillage also occurs in the chest. The site of the leak should always be confirmed by means of a contrast study with barium or a water-soluble agent. Perforation is best handled with laparotomy and direct repair of the leak.

OUTCOME EVALUATION

Whereas the success rate is around 80 to 90% for a first antireflux operation, it falls to 70 to 80% for a second such operation. In our view, a second operation should be attempted by an expert team only if medical management fails to control heartburn or dilatation has not relieved dysphagia.

Reoperation for Esophageal Achalasia

Laparoscopic Heller myotomy improves swallowing in more than 90% of patients. What causes the relatively few failures reported is still incompletely understood. Typically, a failed Heller myotomy is signaled either by persistent dysphagia or by recurrent dysphagia that develops after a variable symptom-free interval following the original operation.

A complete workup (routinely including barium swallow, endoscopy, manometry, and pH monitoring) is required before treatment is planned. In addition, it is our practice to review the video of the first operation to search for technical errors that might have been responsible for the poor outcome. Such errors typically fall into one of the following three categories.

1. A myotomy that is too short either distally or proximally. If the myotomy is too short distally, a barium swallow shows persistent distal esophageal narrowing and manometry shows a residual high-pressure zone. If the myotomy is too short proximally, it will be apparent from the barium swallow.
2. A constricting Dor fundoplication. Often, manometry and pH monitoring yield normal results, but a barium swallow shows slow passage of contrast media from the esophagus into the stomach. In one study from UCSF,⁴⁰ problems with Dor funduplications occurred in four (4%) of 102 patients. Analysis of the video records of the first operations showed that in three of the four patients, all the stitches in the right suture row had incorporated the esophagus, the right pillar of the crus, and the stomach, thereby constricting the myotomy. In one patient, the short gastric vessels had not been taken down, and the body of the stomach rather than the fundus had been used for the fundoplication.
3. Transmural scarring caused by previous treatment. In patients treated with intrasphincteric injection of botulinum toxin, transmural fibrosis can sometimes be found at the level of the esophagogastric junction. This

unwelcome finding makes the myotomy more difficult and the results less reliable.

There are two treatment options for persistent or recurrent dysphagia after Heller myotomy: (1) pneumatic dilatation and (2) a second operation tailored to the results of preoperative evaluation. In a 2002 study,⁴⁸ pneumatic dilatation was successfully used to treat seven of 10 patients who experienced dysphagia postoperatively; of the remaining three patients, two required a second operation and one refused any treatment.

Reoperation for achalasia is technically challenging. It is of paramount importance to avoid perforating the exposed

esophageal mucosa during the dissection. A small hole can be repaired, but a larger laceration might necessitate an esophagectomy. This option should always be discussed with the patient before the operation. It is our belief that the surgeon attempting a reoperation after a failed attempt at surgical treatment of achalasia should perform a laparotomy, even though several reports have stressed the feasibility of laparoscopic reoperation after a failed myotomy.⁴⁹

Overall, about 10 to 20% of patients experience some degree of dysphagia after a Heller myotomy. Pneumatic dilatation, a second myotomy, or both should always be tried before an esophagectomy is considered.

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Figures 1 through 13 Tom Moore.

9 CHEST WALL PROCEDURES

Bryon J. Boulton, MD, and Seth D. Force, MD

Chest wall procedures are an important component of any thoracic surgeon's practice. The approach to these procedures is somewhat different from the approach to esophageal or pulmonary resections and requires specific knowledge of thoracic musculoskeletal anatomy, as well as of the different types of autologous and artificial grafts available for chest wall reconstruction. Broadly, chest wall procedures may be divided into those performed to treat congenital chest wall disease and those done to treat acquired disease. In what follows, we describe the major surgical techniques in both categories and review the pitfalls that may accompany them.

Procedures for Congenital Chest Wall Disease

Congenital chest wall defects arise from abnormal development of the sternum, the costal cartilages, and the ribs. Such defects include pectus excavatum (funnel chest), pectus carinatum (pigeon chest), cleft sternum, and Poland syndrome (absence of the breast and the underlying pectoralis muscle and ribs). Of these, pectus excavatum is by far the most common, accounting for more than 90% of all congenital chest wall procedures; accordingly, the ensuing discussion focuses on the surgical aspects of pectus excavatum repair.

REPAIR OF PECTUS EXCAVATUM

Preoperative Evaluation

Because pectus excavatum occurs in varying degrees of severity, patients may seek surgical treatment for any of a number of different reasons, such as shortness of breath, early fatigue with exercise, or simple dissatisfaction with their appearance. Thus, one of the most important tasks for surgeons treating pectus excavatum is determining which patients are candidates for operative management. In an attempt to facilitate this determination, the Congenital Heart Surgery Nomenclature and Database Project has developed a classification system for pectus excavatum, in which a deformity less than 2 cm in depth is classified as mild, a deformity 2 to 3 cm in depth is classified as moderate, and a deformity greater than 3 cm in depth is classified as severe.¹ A computed tomography (CT)-based index has also been devised, in which the transverse chest diameter is divided by the anteroposterior diameter; an index greater than 3.2 is considered indicative of severe disease.²

These classification attempts notwithstanding, the precise indications for surgery remain unclear. Many studies have attempted to show that the depressed sternum leads to pulmonary compromise, but, for the most part, these studies have had small sample sizes and have employed differing measures of lung function, both of which have made accurate comparisons difficult. In one study that included 25 US Air Force personnel with symptomatic pectus excavatum, lung volumes were comparable to those in normal persons, but

there was a significant difference in maximum voluntary ventilation.³ In a study that compared 37 patients who had undergone surgical repair of pectus excavatum both with normal persons and with persons who had uncorrected deformities, no differences in physical working capacity among the three groups were noted.⁴ Other studies have reported improvements in exercise tolerance and regional ventilation and perfusion after surgical repair of pectus excavatum.^{5,6} On the other hand, some investigators have reported decreases in pulmonary function in symptomatic patients after corrective surgery. One group attributed this result to overly aggressive resection in very young patients that led to growth restriction of the chest wall; accordingly, they recommended delaying surgical repair until 6 to 8 years of age.⁷

Severe pectus excavatum has also been reported to cause cardiac dysfunction secondary to sternal compression of the right ventricle. Several early studies found stroke volume and cardiac output to be lower in exercising upright patients than in supine patients.^{8,9} However, improvement in cardiac function after pectus excavatum repair has not been universally documented. In one study, first-pass radionuclide angiocardiology failed to show any improvements in left ventricular function after repair of pectus excavatum.¹⁰ At present, there is no consensus on the cardiopulmonary benefits of pectus excavatum repair, and the major reasons for surgical treatment are still patient discomfort and dissatisfaction with appearance.

Operative Technique

A number of different procedures have been employed to treat pectus excavatum, but, for present purposes, we focus on (1) the Ravitch procedure (and variations thereof) and (2) the Nuss procedure. For historical reasons, the turnover technique, originally described by Judet and Judet¹¹ and later employed by Wada and colleagues,¹² warrants a brief mention. Wada and colleagues' series included 199 patients whose deformities were corrected with a version of this technique; good results were achieved in 63% of patients, and there were only three instances of partial sternal necrosis. Today, however, the turnover technique is rarely used because of the good results that can be achieved with techniques that do not carry a risk of sternal necrosis. It is usually reserved for extreme cases of pectus excavatum, which often include deformities of the sternum in addition to abnormalities of the costal cartilages.

Ravitch procedure Repair of pectus excavatum is based on the principle that the deformity is secondary to abnormal growth of the costal cartilages. Accordingly, correction involves (1) resection of the abnormal cartilages, (2) a transverse anterior sternal osteotomy to allow anterior displacement of the sternum, and (3) sternal fixation to

prevent posterior displacement after the repair. Most of the variations in the Ravitch procedure have to do with the use of different sternal fixation techniques.

Step 1: initial incision and exposure Either a midline incision or a bilateral inframammary incision is made [see Figure 1a, b]; the latter incision yields superior cosmetic results, especially in female patients, but necessitates the elevation of large subcutaneous skin flaps to the level of the angle of Louis or the sternal notch superiorly and to the xiphoid process inferiorly. The pectoralis muscles are then mobilized from the chest wall, beginning medially and proceeding laterally until the costal cartilages are exposed [see Figure 1c].

Step 2: resection of abnormal cartilages For each abnormal costal cartilage, the anterior perichondrium is scored with the electrocautery along the length of the cartilage, and the cartilage is dissected from the perichondrium with a periosteal elevator [see Figure 2a]. The posterior plane between the cartilage and the perichondrium is then developed in one area, and the cartilage is divided with a scalpel between the jaws of a right-angle clamp [see Figure 2b]. The cut end of the cartilage is grasped with a clamp, and the rest of the cartilage is dissected from the perichondrium. Once the correct plane is established, the dissection can be facilitated by gently pushing the perichondrium off the cartilage with a finger. The entire cartilage should be removed from the sternum to the rib, with every attempt made to maintain the integrity of the perichondrium. During this part of the procedure, the xiphoid process is also detached from the sternum. The

extent of cartilage removal depends on the individual defect present but usually includes the third rib.

Step 3: sternal osteotomy An osteotomy is made in the upper anterior table of the sternum with either a periosteal elevator or a small reticulating bone saw [see Figure 3a], and the posterior table of the sternum is fractured. The sternum can then be angled anteriorly. When the desired angle is reached, the osteotomy is closed with three interrupted nonabsorbable sutures or with microplates and screws [see Figure 3b, c]. At this point, rotational sternal defects can be corrected by making anterior and posterior lateral osteotomies on either side of the sternum and then closing the osteotomies with sutures or microplates.

Step 4: sternal fixation Sternal fixation can be accomplished by any of several means. Posterior sternal support can be achieved by placing a Kirschner wire or retrosternal bar that is secured to the periosteum of the rib and left in place for approximately 3 months after operation [see Figure 4]. Alternatively, the sternum can be supported with a piece of polypropylene mesh or with two polypropylene sutures sutured to the xiphoid process and then brought around the right and left second ribs.¹³

Step 5: closure and drainage The pectoralis muscles are reapproximated in the midline, closed suction drains are placed in the subcutaneous flaps, and the subcutaneous layer and the skin are closed. To prevent seroma formation, one closed suction drain may be placed posterior to the pectoralis muscles and another between the pectoralis muscles and the subcutaneous layer; the right pleural space may then be

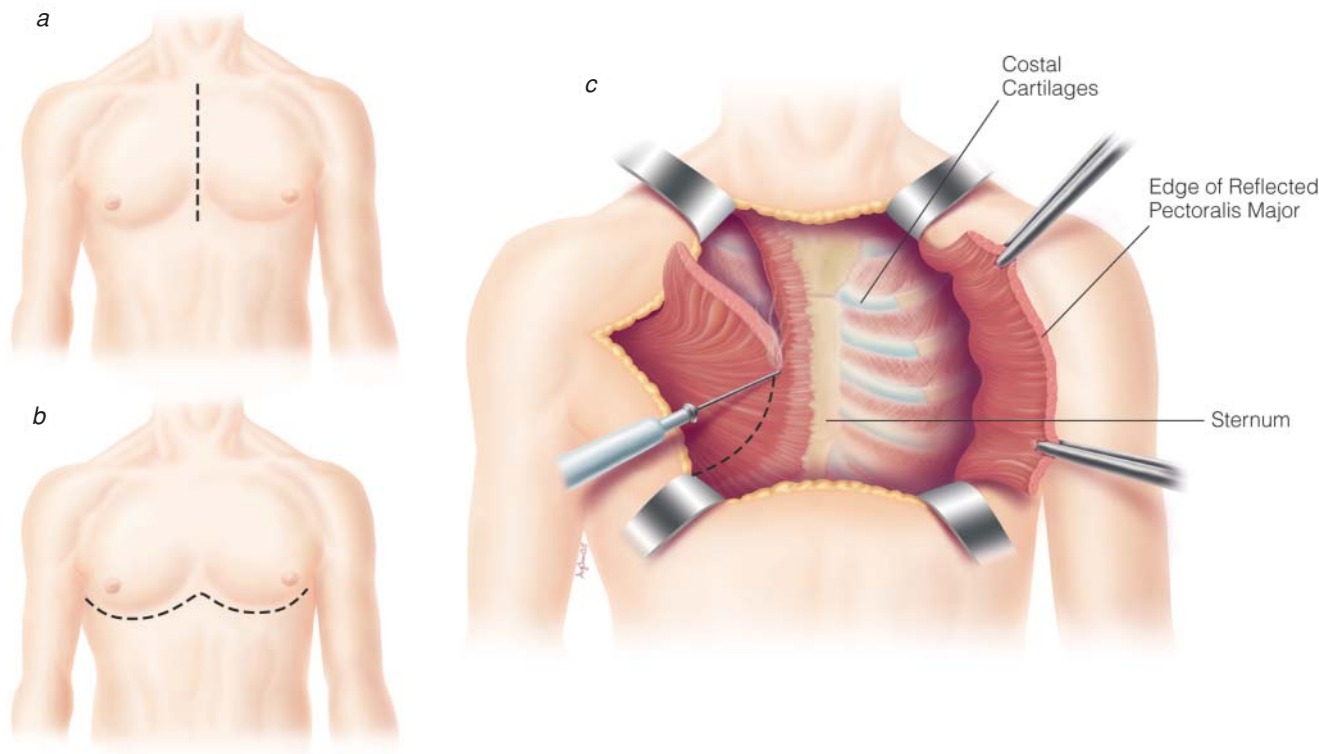


Figure 1 Repair of pectus excavatum: Ravitch procedure. The procedure begins with a midline incision (a) or a bilateral inframammary incision (b). The pectoralis muscles are then dissected off the chest wall (c).

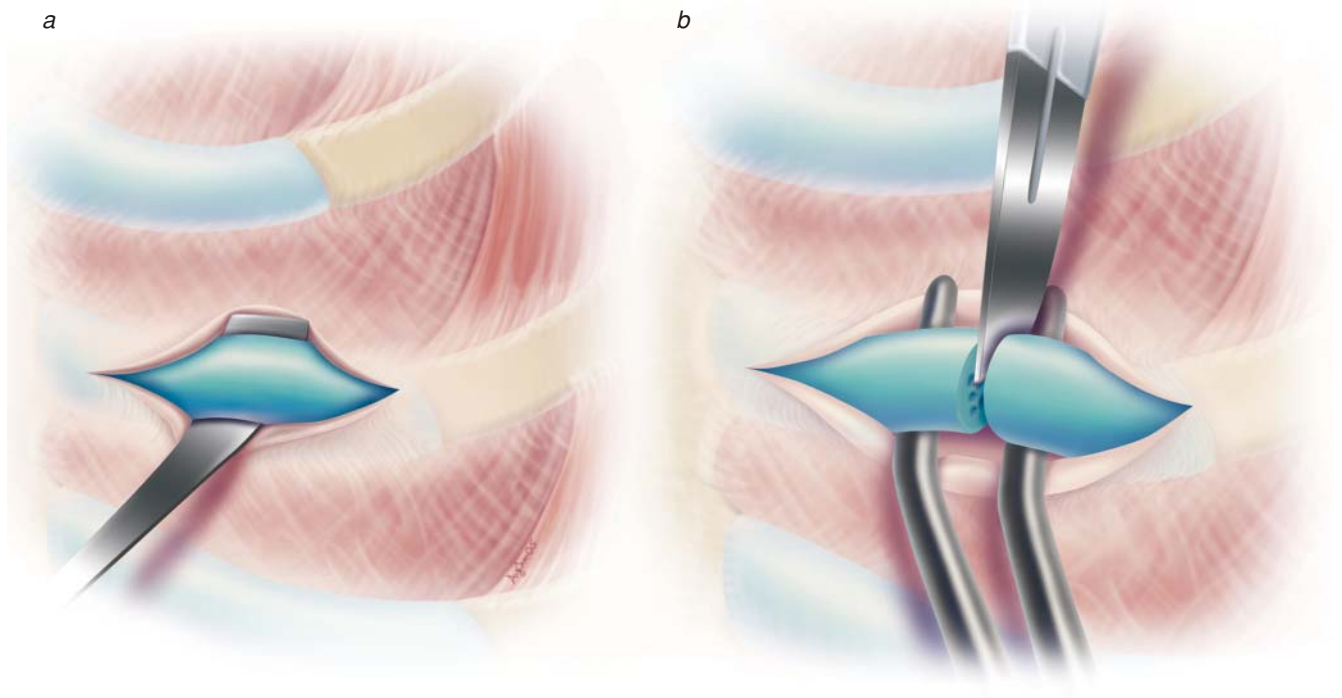


Figure 2 Repair of pectus excavatum: Ravitch procedure. (a) The anterior perichondrium is opened, and the abnormal cartilage is dissected free with a periosteal elevator. (b) The cartilage is divided.

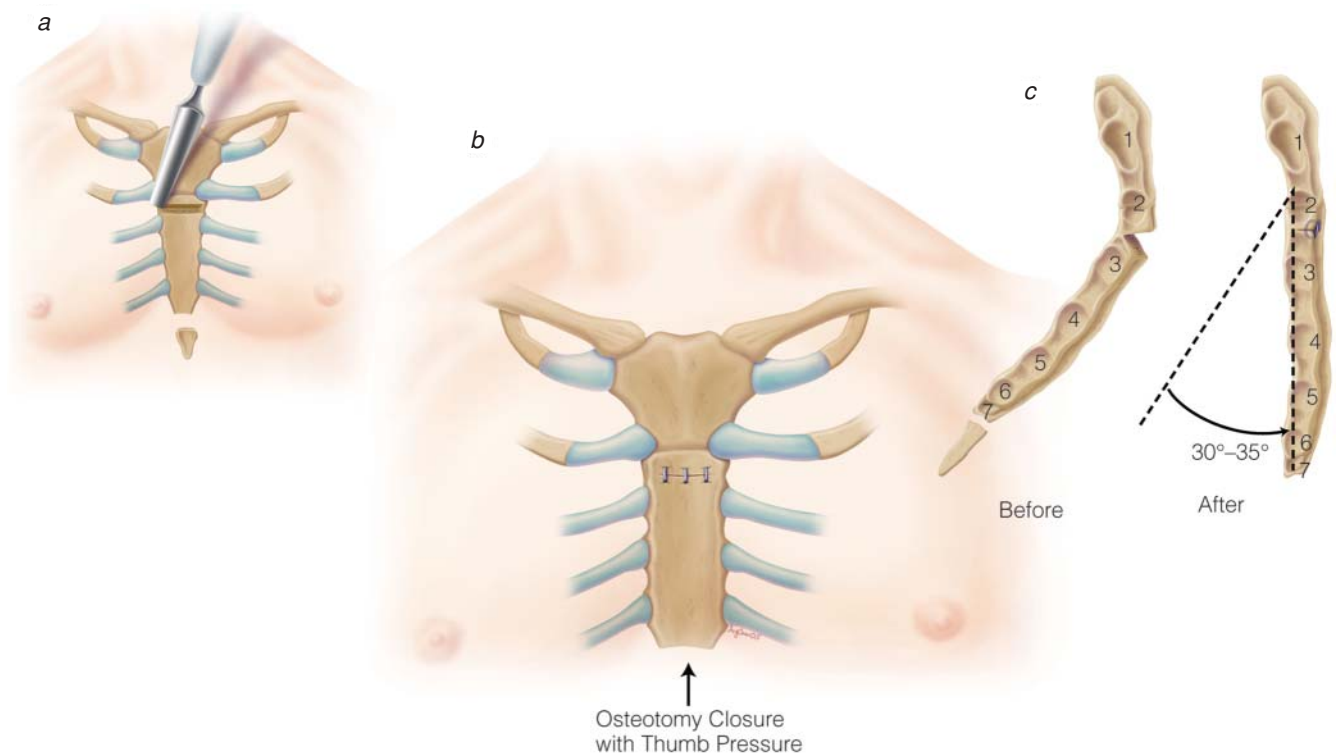


Figure 3 Repair of pectus excavatum: Ravitch procedure. (a) An osteotomy is made in the upper sternum. (b) The sternum is angled anteriorly; when the desired angle is reached, the osteotomy is closed. (c) Shown is a lateral view of the sternal angle before and after correction.

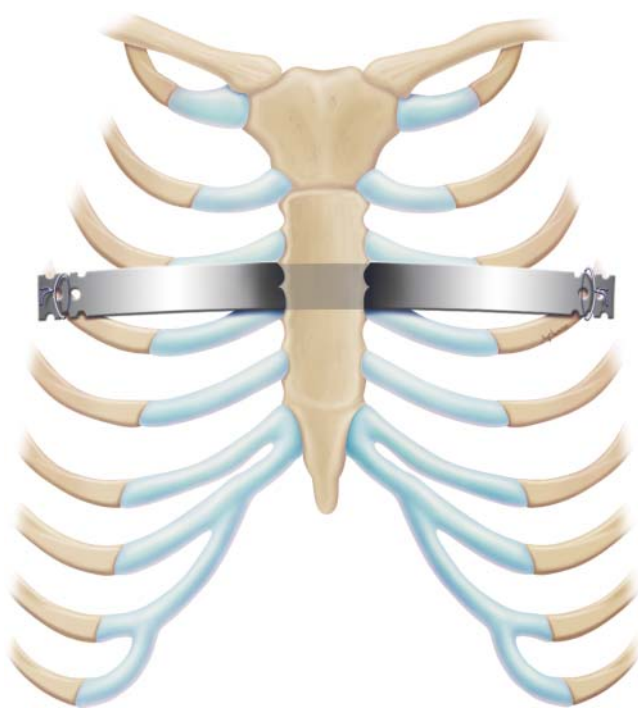


Figure 4 Repair of pectus excavatum: Ravitch procedure. Sternal fixation is accomplished through placement of a retrosternal bar.

opened anteriorly and a right pleural tube placed through a separate incision.¹⁴

Nuss procedure Minimally invasive repair of pectus excavatum, also referred to as the Nuss procedure, has gained popularity over the past decade.

Step 1: configuration of bar The patient is placed in the supine position with the arms abducted, and marks are made on either side of the chest at spots that correspond to the deepest point of the defect. The bar that will be used for the repair is shortened to a length equivalent to the measured distance between the two midaxillary lines minus 1 cm. A complex series of bends are then placed in the bar to match its contours to those of the patient's deformity.

Step 2: initial incisions and creation of intrathoracic tunnel Incisions are made in the right and left midaxillary lines at the level of the marks, and a subcutaneous flap is raised from each incision and extended to the defect. A Crawford vascular clamp or a Lorenz pectus introducer is then placed through the right intercostal space under thoracoscopic visualization and advanced along the posterior sternum and out the corresponding left intercostal space [see Figure 5].

Step 3: placement and fixation of bar An umbilical tape is pulled through the anterior mediastinum and attached to the bar, which is then gently pulled, with the concave side up, through the intercostal space. A Lorenz pectus bar rotator is employed to flip the bar over, and the ends of the bar are positioned in the subcutaneous space [see Figure 6]. Occasionally, for proper alignment, the bar may have to be removed and rebent, or stabilizers may have to be placed alongside it.

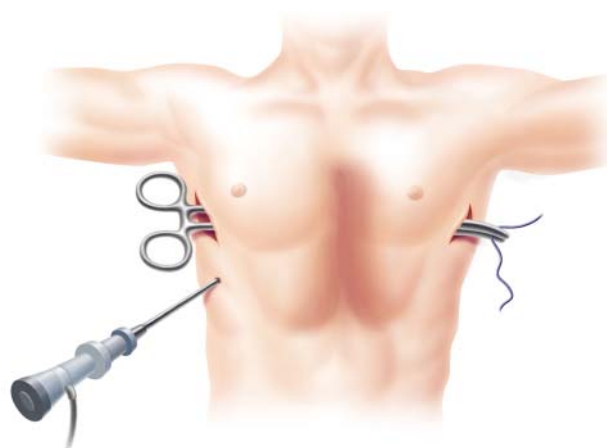


Figure 5 Repair of pectus excavatum: Nuss procedure. Incisions are made on either side of the chest. A Crawford vascular clamp is inserted through the right intercostal space and advanced along the sternum and out the left intercostal space.

When the bar is correctly positioned, it is sutured to the chest wall musculature with an absorbable suture on one end and a permanent suture on the other.

The bar is usually left in place for 2 years. Excellent results have been reported.¹⁵ Significant complications include bar displacement necessitating reoperation (9.2% of procedures), pneumothorax (4.8%), infection (2%), and pleural effusion (2%). Rare complications include cardiac injury, thoracic outlet syndrome (TOS), pericarditis, and sternal erosion caused by the bar.

Outcome Evaluation

In general, the results of pectus excavatum repair are good, and the overall complication rate is low. In one study, 90% of 76 patients operated on over a 30-year period experienced excellent outcomes, and only one patient required reoperation for a recurrent defect.¹⁴ The incidence of complications (pleural effusions, pneumonia, and wound seromas) was 14%.¹⁴ In another study, no operative deaths occurred in more than 800 repairs, and only a few cases of serious infections and bleeding were reported.¹⁶ Other investigators have reported rare complications arising from the migration of sternal support bars and wires.¹⁷

REPAIR OF PECTUS CARINATUM

Operative Technique

Surgical repair of pectus carinatum resembles surgical repair of pectus excavatum in several respects. The same skin incision is employed, and the pectoralis major muscles are elevated in a similar manner. Subperichondrial resection of the abnormal cartilages is then carried out, usually extending to the second costal cartilage. Next, a generous V-shaped osteotomy is made in the upper portion of the sternum at the point of maximal protrusion, which is usually near the insertion of the second cartilage. Occasionally, a second osteotomy is required near the caudal end of the sternum to facilitate elevation of the manubrium and depression of the sternum.

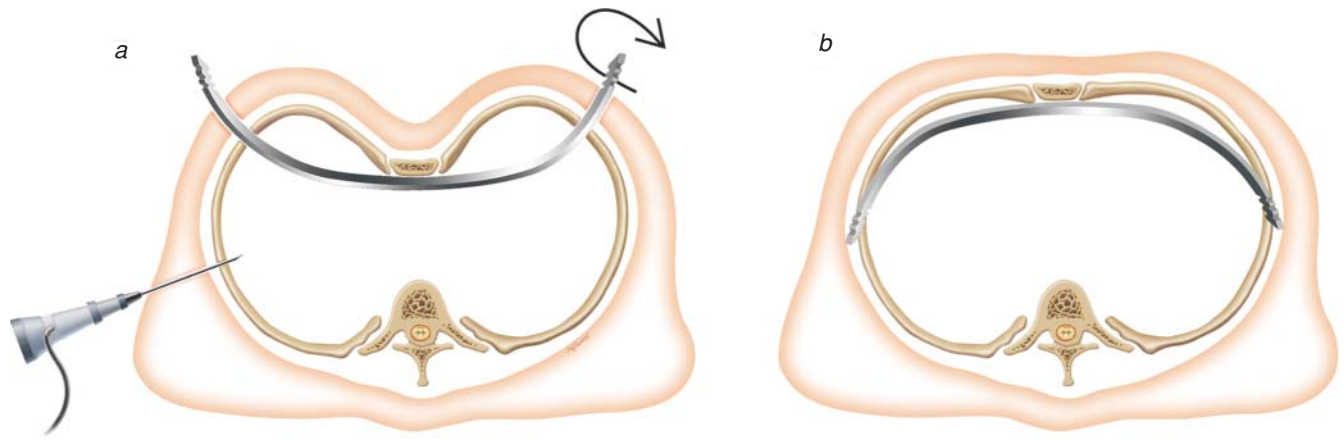


Figure 6 Repair of pectus excavatum: Nuss procedure. (a) The pectus bar is pulled into the tunnel opened by the vascular retractor and then flipped to provide the desired chest contour. (b) The ends of the bar are then sutured to the chest wall musculature.

Finally, the osteotomy is closed with nonabsorbable monofilament sutures, drains are placed, and soft tissue is closed as in a pectus excavatum repair.

Outcome Evaluation

The results of pectus carinatum repair are generally comparable to those of pectus excavatum repair. Most patients experience good outcomes, and operative morbidity is low.

Procedures for Acquired Chest Wall Disease

TRANSAXILLARY FIRST RIB RESECTION FOR THORACIC OUTLET SYNDROME

Preoperative Evaluation

TOS results from compression of the subclavian blood vessels or the brachial plexus as these structures exit the bony thorax. Symptoms may be primarily vascular (e.g., arm swelling or loss of pulse) or neurogenic (e.g., pain and paresthesias). The workup for TOS includes a detailed physical examination, as well as imaging and nerve conduction studies.

Operative Planning

Surgical treatment of TOS typically involves resection of the first rib, which widens the thoracic outlet and relieves the neurovascular impingement. First rib resection can be accomplished via several different approaches, including posterior, supraclavicular, infraclavicular, transthoracic, and transaxillary. I focus here on the transaxillary approach, which provides good exposure of the first rib and allows the surgeon to avoid the subclavian blood vessels and the brachial plexus. Regardless of the specific surgical approach followed, any surgeon embarking on a first rib resection must have a detailed knowledge of the thoracic outlet to keep from injuring the neurovascular structures in the area.

Operative Technique

The patient is placed in the lateral decubitus position, and the affected arm is kept at a 90° angle either by an arm holder or, alternatively, by an assistant. Care must be taken not to hyperabduct or hyperextend the shoulder. The arm, the

axilla, and the chest are prepared and draped into the sterile field.

Step 1: initial incision and exposure An incision is made just below the axillary hair line and extended from the pectoralis major to the latissimus dorsi [see Figure 7]. The subcutaneous tissue is incised down to the chest wall with the electrocautery, with care taken to stay perpendicular to the axis of the chest. Dissection is then begun along the chest wall and carried toward the first rib. The intercostal brachial

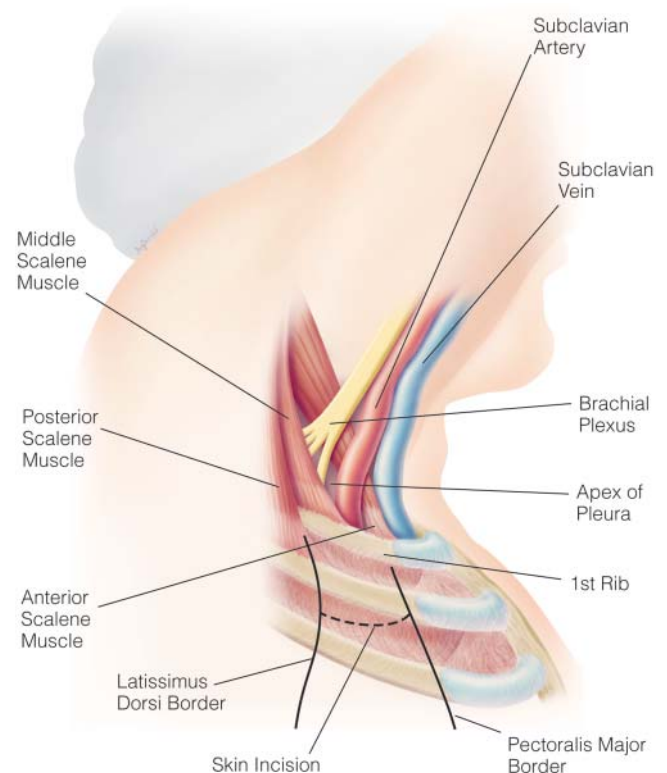


Figure 7 Transaxillary first rib resection. Shown are the transaxillary incision and the thoracic outlet anatomy.

nerve is identified where it exits between the first and second ribs. This nerve should be spared: dividing it leads to numbness of the upper inner biceps region.

Step 2: dissection and division of anterior portion of first rib When the first rib is encountered, it is dissected from the periosteum with a periosteal elevator. Dissection is continued anteriorly along the rib until just past the subclavian vein, at which point a right-angle clamp can be passed around the rib in the subperiosteal plane. A Gigli saw or a first rib cutter is then used to divide the anterior portion of the rib [see Figure 8a].

Next, the first rib is retracted inferiorly to permit visualization of the anterior scalene muscle, which is then divided at its attachment to the rib. To prevent thermal injury to the phrenic nerve, a scalpel rather than an electrocautery is used to divide the muscle [see Figure 8b]. Care should also be taken not to injure the subclavian vein and artery, which lie anterior and posterior to the anterior scalene muscle, respectively. As an alternative, the anterior scalene muscle may be divided before the anterior portion of the rib is cut.

Step 3: dissection and division of posterior portion of first rib The subperiosteal dissection is continued posteriorly, freeing the first rib from the pleura, the subclavian vessels, and the brachial plexus. The posterior portion of the rib is then divided with a first rib cutter as close as possible to the articulation of the rib with the transverse process. Every effort should be made to keep from injuring the C8 and T1 nerve roots.

Step 4: closure The incision is closed without drainage. If the pleura was inadvertently entered, air may be aspirated from the chest with a red rubber tube, which is removed before the subcutaneous tissue is closed. One authority recommends further neurolysis of the C7 to T1 nerve roots and the middle and lower trunks of the brachial plexus, as well as resection of the anterior and middle scalene muscles up into the neck.¹⁸

Complications

Surgical complications include injuries to the subclavian vein and artery (leading to massive blood loss), the brachial plexus, the phrenic nerve, the long thoracic nerve, and the thoracic duct.

Outcome Evaluation

The long-term results of first rib resection appear to be independent of the exposure technique employed. Good results, defined as relief of major symptoms, have been reported in as many of 90% of patients in the first year and in as many as 70% of patients 5 to 10 years after operation. Considerable debate continues over the preferred surgical approach, but, to date, no studies have shown any one approach to have significant advantages over any of the others.

CHEST WALL RESECTION

Chest wall resection has become a critical component of the thoracic surgeon's armamentarium. It may be performed to treat either benign conditions (e.g., osteoradionecrosis, osteomyelitis, and benign neoplasms) or malignant disease.

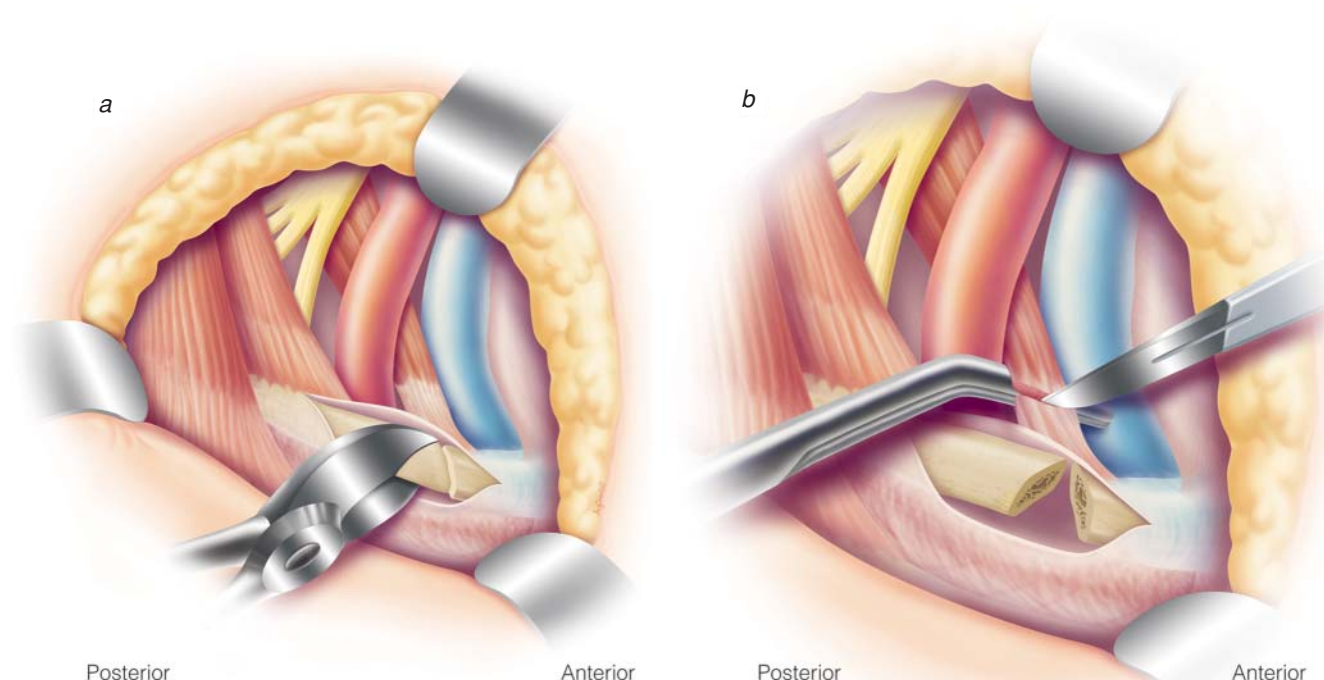


Figure 8 Transaxillary first rib resection. (a) The anterior portion of the first rib is cut. (b) The anterior scalene muscle is then divided.

Preoperative Evaluation

Preoperative imaging studies may include chest x-ray, chest CT [see Figure 9], and magnetic resonance imaging if vertebral involvement is suspected. The other preoperative tests ordered are much the same as those required for any other large thoracic procedure, including pulmonary function testing, nutritional assessment, and cardiac stress testing in patients who are older or have a history of cardiac disease.

Operative Planning

Operative planning for chest wall resection should include establishing the extent of the resection, weighing options for chest wall stabilization, and deciding on the method of tissue coverage to be employed. A multidisciplinary approach, involving the participation of a neurosurgeon and a plastic surgeon, may be required.

The technique of chest wall resection is essentially the same for benign conditions as for malignant ones and is mainly dependent on the location of the lesion. For malignant tumors of the chest wall, a 5 cm margin, or at least resection of one uninvolved rib above and below the tumor, is required. Additionally, any involved skin and any biopsy site must be resected along with the chest wall specimen. For infection or osteoradionecrosis, the resection must include all nonviable skin and underlying bone; if it does not, skin and muscle flaps may not heal properly. Any destroyed lung tissue may also have to be resected along with the chest wall specimen. In addition, recurrent cancer must be ruled out before the operation can proceed. A particular challenge is posed by breast cancer patients who have already had muscle flaps for breast reconstruction; in these patients, tissues other than muscle (e.g., omentum) may be required for tissue coverage after chest wall resection.

Standard Chest Wall Resection

In cases in which a concomitant lung resection is required, the chest wall resection is usually performed first; this measure renders the lung more mobile and facilitates the pulmonary resection. The lateral decubitus position is the best choice for most combined lung–chest wall procedures, whereas the supine position is preferable for isolated anterior chest wall procedures. If a larger chest wall resection is

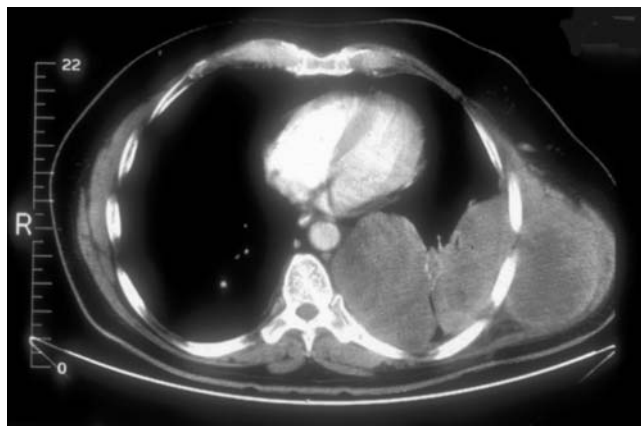


Figure 9 Chest computed tomographic scan reveals a large pulmonary and chest wall mass.

expected, every attempt should be made to spare major muscle groups so that these muscles can be used later to cover any prosthetic material used in reconstruction.

Operative technique

Step 1: initial incision and exposure The usual incision is a standard posterolateral thoracotomy incision through the fifth interspace.

Step 2: determination of extent of required chest wall resection As soon as the pleura is opened, the surgeon should palpate the tumor to evaluate the extent of chest wall involvement, which determines the extent of the resection. Removal of uninvolved ribs may make reconstruction of the chest wall more complicated. For example, posterior resections that do not require removal of the fifth rib are protected by the scapula, so reconstruction is unnecessary. If the fifth rib is removed, however, the tip of the scapula will tend to become stuck under the sixth rib with shoulder movement; this is very uncomfortable for the patient, and chest wall reconstruction will therefore be required at the time of resection.

At this point, the surgeon should also rule out diffuse pleural disease before proceeding with resection. In some cases, the tumor can be removed by means of extrapleural dissection, without any need for chest wall resection. If there is any suspicion of chest wall involvement, however, chest wall resection is mandatory because leaving any tumor behind guarantees a recurrence.

The extent of the chest wall resection is marked with the electrocautery on the outside of the thoracic cavity. At least one grossly uninvolved rib should be included both above and below the tumor.

Step 3: completion of anterior boundary of resection Initially, the periosteum over the lowest rib to be resected is scored, and a periosteal elevator is used to separate the intercostal bundle from the rib. Alternatively, the intercostal bundle can be doubly ligated and divided at the anterior resection margin. Once the intercostal vessels are cleared from the lowest rib, the electrocautery is used to divide the pleura below the rib toward the anterior boundary of the resection. The rib is then divided with a rib cutter, with care taken to ensure a margin of at least 5 cm from the tumor [see Figure 10]. Next, the intercostal bundle of the next higher rib is ligated and divided, the intercostal muscle is divided with the electrocautery, and the rib is cut with a rib cutter in the same manner as the previous rib. This process is repeated until the anterior boundary of resection is completed. A subperiosteal plane is then developed over the highest rib to be resected, the adjacent intercostal bundle is separated from the rib, and the parietal pleura is divided with the electrocautery.

Step 4: completion of posterior boundary of resection If the tumor margin does not involve the vertebrae, the posterior portion of the chest wall resection is identical to the anterior portion [see Step 3, above]. If, however, the tumor appears to encroach on the head of the rib or the transverse process, it will be necessary to disarticulate the rib from the transverse process or, in the latter situation, remove the transverse process entirely.

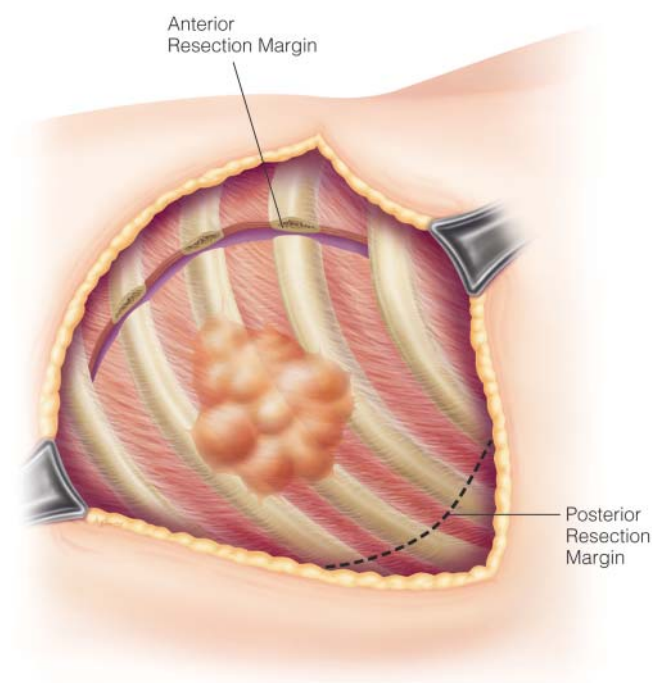


Figure 10 Chest wall resection. The anterior and posterior margins of the required resection are determined. The anterior margin is completed first.

Disarticulation of the rib from the transverse process is performed by dissecting the paraspinal ligament and erector spinae muscles away from the spine with the electrocautery, thereby exposing the joint between the head of the rib and the transverse process. The ligaments attaching the rib to the transverse process are then incised with the electrocautery, and an osteotome is inserted into the joint, which is then levered anteriorly and posteriorly to disarticulate the rib from the transverse process [see Figure 11]. The intercostal neurovascular bundle must be ligated and divided at this point:

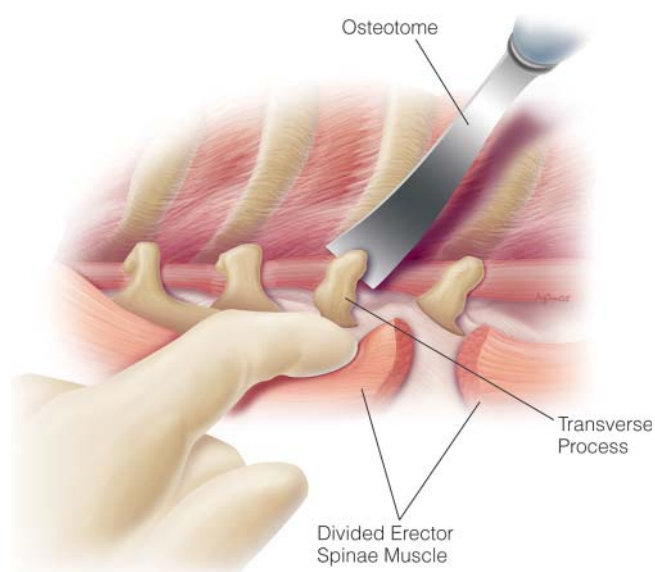


Figure 11 Chest wall resection. Depicted is disarticulation of the rib from the transverse process.

failure to do so will result in bleeding and possibly in leakage of cerebrospinal fluid (CSF). If bleeding occurs, it can be controlled with bipolar electrocauterization and temporary packing with a hemostatic agent. The hemostatic agent must not be left in place permanently, because it may expand or result in a neural foramen hematoma, and either of these events can lead to spinal cord compression and significant neurologic injury. If at any time the surgeon feels uncomfortable about ongoing intercostal bleeding or a possible CSF leak, intraoperative neurosurgical consultation should be obtained. In cases in which the tumor involves the transverse process, this structure must be removed from the vertebral body with an osteotome and a mallet or with a first rib cutter. If the tumor has invaded the vertebral body and resection is still being considered, neurosurgical consultation should be obtained. Generally, if the tumor involves more than one quarter of the vertebral body or extends into multiple vertebral levels, it is considered unresectable.

Step 5: lung resection (if required) Once the posterior chest wall margin has been completed, the lung resection (if required) is performed. The entire lung–chest wall specimen is then submitted for pathologic examination, and histopathologic margins are obtained both on the lung and on the chest wall. If the chest wall margins are positive, the involved area must be trimmed back and a new margin submitted.

Step 6: chest wall reconstruction Chest wall reconstruction is required for all anterior defects and for posterior defects that involve any rib lower than the fourth rib. Reconstruction can be performed either with polypropylene or Gore-Tex (W. L. Gore and Associates, Flagstaff, Arizona) mesh or with a polypropylene-methylmethacrylate sandwich. The latter is employed when rigid reconstruction is warranted (as in anterior reconstruction); it not only provides added protection of pleural and mediastinal structures but also creates a better cosmetic effect by recreating the shape of the chest wall.

To create the polypropylene-methylmethacrylate sandwich, two pieces of polypropylene mesh are cut to the size of the defect. A thin layer of methylmethacrylate cement is spread on one of the mesh pieces, and the other piece is then applied over the methylmethacrylate layer. As this sandwich begins to harden, it is molded to the contours of the chest wall, with care taken to protect the patient's skin against injury from the heat given off by the hardening cement. When the sandwich is sufficiently hardened, it is sewn to the ribs with 0 polypropylene sutures [see Figure 12a]. The sutures may be passed around the uppermost and lowermost ribs and may be placed directly through the anterior and posterior margins [see Figure 12b]. If rib disarticulation was required to complete the posterior margin, holes may be drilled in the transverse processes and the sutures passed through these holes; alternatively, the sandwich may be sutured to the paraspinal ligament.

If polypropylene or Gore-Tex mesh is used without cement, it should be cut to a size smaller than that of the defect. Thus, the mesh will effectively be stretched when it is sutured to the chest wall, and any laxity in the reconstruction will thereby be alleviated.

Step 7: closure and drainage The serratus anterior and the latissimus dorsi are closed in the standard fashion, as

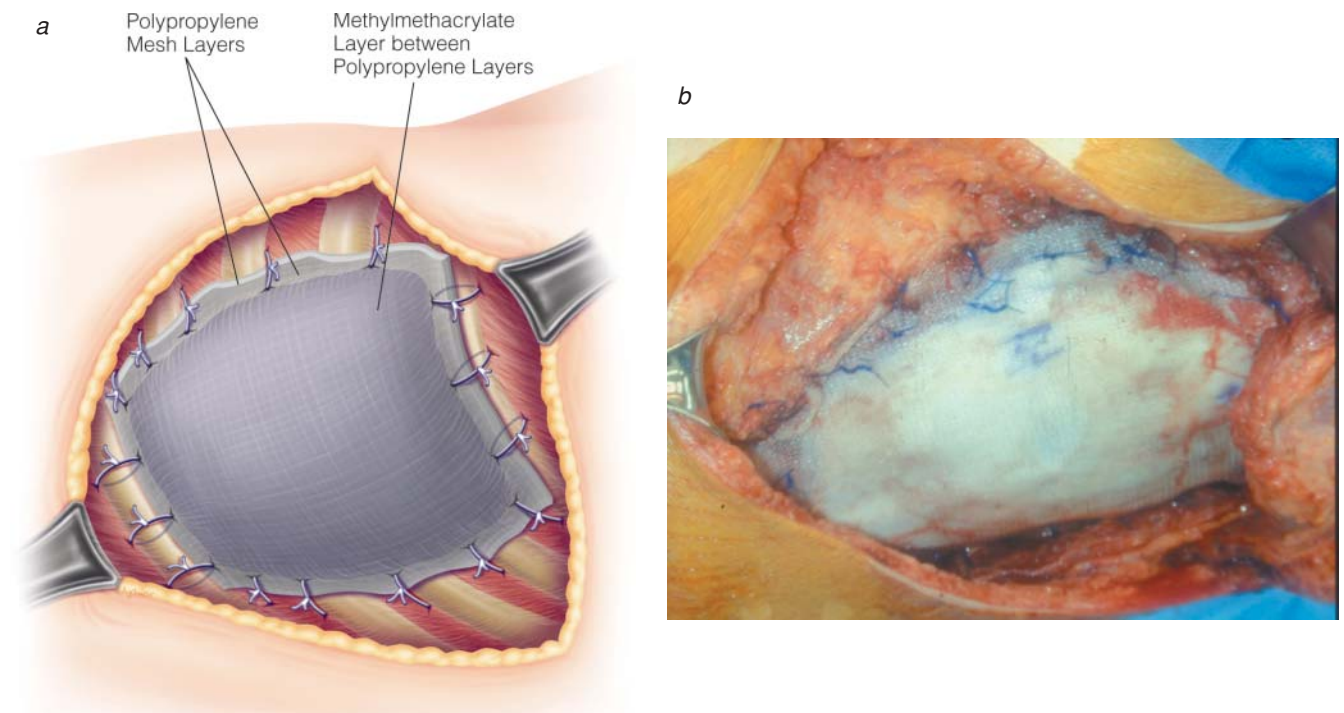


Figure 12 Chest wall resection. (a) A polypropylene-methylmethacrylate sandwich is created by spreading a layer of methylmethacrylate cement between two pieces of polypropylene mesh. When sufficiently hardened, the sandwich is sutured to the ribs. (b) Photograph shows a polypropylene-methylmethacrylate sandwich sutured in place.

are the subcutaneous and skin layers. With the exception of pleural tubes, drains are not routinely used. Special attention should be paid to postoperative analgesia: patients who have undergone extensive resections often experience considerable pain and are therefore prone to atelectasis and pneumonia. Epidural analgesia should be employed routinely in such cases.

Troubleshooting If chest wall infection is a possibility (as with osteoradionecrosis or osteomyelitis), alternative reconstructive techniques are required to obviate concerns about superinfection resulting from the use of synthetic material. In particular, radiation injury may involve all layers of the chest wall, necessitating very large resections [see Figure 13a].

Muscle or omental flaps with split-thickness skin grafts may be required for coverage; thus, preoperative consultation with an experienced plastic surgeon is advisable. A particular concern is what to use to reconstruct the chest wall. Various tissues (e.g., fascia lata and ribs) have been employed, but an easier substitute that works quite well is an absorbable synthetic mesh (e.g., Vicryl). The mesh is sewn to the ribs as previously described [see Step 6, above], and the tissue flap is placed on top of the mesh, followed by a skin graft [see Figure 13b, c]. Alternatively, some authors recommend the use of muscle or myocutaneous flaps without rigid chest wall reconstruction after resection, particularly in infected fields.¹⁹

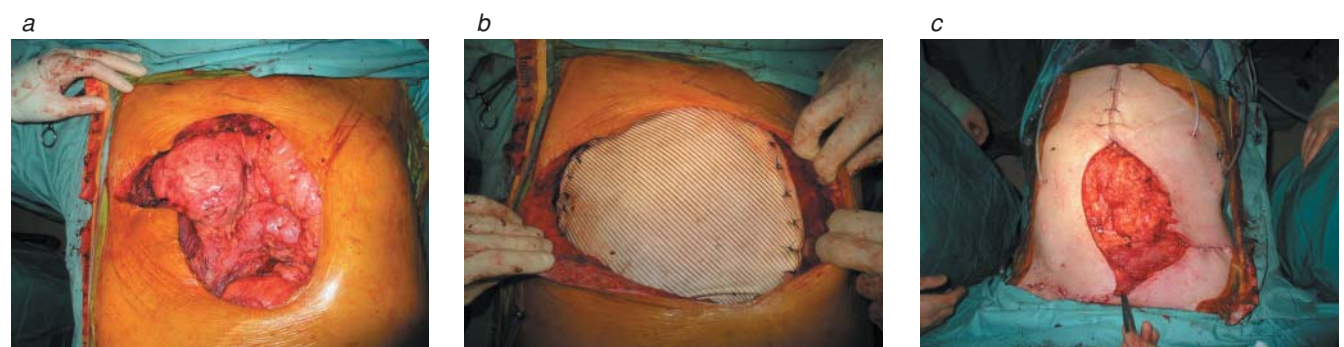


Figure 13 Chest wall resection. The presence of osteoradionecrosis may necessitate very large resections and resulting defects (a). Such defects may be covered with absorbable mesh (b), followed by an omental flap (c) or a muscle flap.

Outcome evaluation The results achieved after major chest wall resection have generally been excellent. One study reviewed 200 patients who underwent resection and reconstruction over a 25-year period.²⁰ The reconstructions ranged from relatively straightforward two-rib resections to more complex forequarter amputations. The indications for resection were lung cancer (38%), osteoradionecrosis (29%), chest wall tumor (27%), and osteomyelitis (16%). Immediate reconstruction was performed in 98% of patients. The major muscle flaps used were latissimus dorsi (20%), rectus abdominis (17%), pectoralis major (16%), and serratus anterior (9%). Free flaps were used in only 9% of cases, and split-thickness skin grafts were required in 12% of patients. Reconstruction was performed with Prolene mesh (25%), Marlex mesh (11%), Vicryl mesh (6%), or a polypropylene-methylmethacrylate sandwich (6%). Operative mortality was 7%, and major morbidity occurred in 24% of patients. Most of the morbidity was accounted for by pneumonia (14%) and acute respiratory distress syndrome (6%).

Manubrial and Clavicular Resection

Resection of the manubrium or the clavicle may be necessary if these structures become infected or involved with tumors. Clavicular and manubrial resections follow the same operative approach as other chest wall resections. Specifically, attention must be paid to how much bone to resect, how to reconstruct the defect, and how to provide tissue coverage.

Resection of sternoclavicular joint for infection

Clavicular resections are rarely performed but may be required to treat tumors, vascular compression from healed fractures, or infection. Occasionally, infections involve the sternoclavicular joint (SCJ). Patients with osteomyelitis of this joint are often immunosuppressed and may have had an indwelling subclavian vein catheter that became infected. In a study of seven patients who underwent SCJ resection for infection, five of six patients initially treated with antibiotics and simple drainage experienced recurrences, whereas six of six patients treated with resection of the joint and pectoralis muscle advancement flaps were cured. None of the patients experienced problems with arm mobility in the course of long-term follow-up.²¹

An incision is made that extends along the distal clavicle and curves down onto the manubrium. The soft tissue is divided with the electrocautery down to the clavicle and the manubrium. The muscular attachments of the pectoralis major and the sternocleidomastoid muscle are dissected off the clavicle and the manubrium with a periosteal elevator. Dissection in the subperiosteal plane is then continued circumferentially around the distal clavicle, with special care taken to keep from injuring the subclavian vessels that lie deep to the clavicle. A Gigli saw is passed around the clavicle with a right-angle clamp and used to divide the distal clavicle. The distal cut end of the clavicle is grasped with a penetrating towel clamp and bluntly dissected away from the deep tissue toward the manubrium. Any pockets of infection encountered should be cultured, drained, and débrided.

At this point, a large separation in the SCJ, caused by the infection, should be apparent. Resection of a small portion of the manubrium is usually required to remove all of the

infected bone. Once the tissue deep to the manubrium has been dissected, a small band retractor is placed beneath the manubrium, and an oscillating sternal saw is used to resect the lateral portion of the manubrium, adjacent to the SCJ. Alternatively, a rongeur may be used to débride infected bone from the manubrium. All tissue should be sent for culture.

Severe infections may necessitate more extensive resection of bone or soft tissue, but if the infection is caught early, simple resection of the SCJ is generally curative. In more extensive resections, muscle flap coverage may be required, but in simple SCJ resections, good results can be obtained by using only deep closed suction drainage, followed by multilayer closure of the wound. To prevent any recurrent osteomyelitis, antibiotics should be continued for several weeks after resection.

Resection of manubrium for cancer Manubrial resections may be required for rare cases of primary or metastatic cancers.

Because of the relative paucity of tissue overlying the manubrium, cancers in this area may involve the dermis. In such cases, it may be necessary to resect skin along with the specimen. Alternatively, if the skin is not involved, an upper midline incision may be employed. The incision is carried down circumferentially to the chest wall, with care taken to maintain a 2 to 3 cm margin from the tumor. The clavicles and ribs are divided in the same fashion as for chest wall and clavicular resections [see Figure 14a]. Associated structures (e.g., the thymus) can be resected along with the manubrium; these tumors rarely involve the innominate vein.

A polypropylene-methylmethacrylate sandwich is useful for reconstruction of this area of the chest wall [see Figure 14b]. The patch is secured to the remaining ribs and clavicles with 0 polypropylene sutures. Coverage is then provided with a pectoralis major advancement flap or, if skin was excised, a pedicled pectoralis myocutaneous flap. A pleural drain may be placed if either pleural space was entered, but this measure is not routinely employed.

Open Chest Drainage (Eloesser Flap)

Open drainage procedures are usually included in discussions of treatment of empyema, but they really represent a type of chest wall resection. Open drainage techniques for empyema were first described in the late 1800s by Poulet and subsequently by Schede. Graham, who headed the Army Empyema Commission during World War I, is credited with the observation that ensuring pleural-pleural symphysis was the key to preventing the often fatal complication of pneumothorax.²² Indications for open chest drainage include postpneumonectomy empyema or bronchopleural fistula, long-standing empyema in a patient who cannot undergo decortication, and chronic bronchopleural fistula in a high-risk patient.

Operative technique The technique currently employed by most thoracic surgeons follows Symbas's modification of Eloesser's open drainage technique.²³ This procedure has come to be known as the Eloesser flap. Preoperative chest CT is essential for identifying the exact location of the empyema, which determines the placement of the incision.

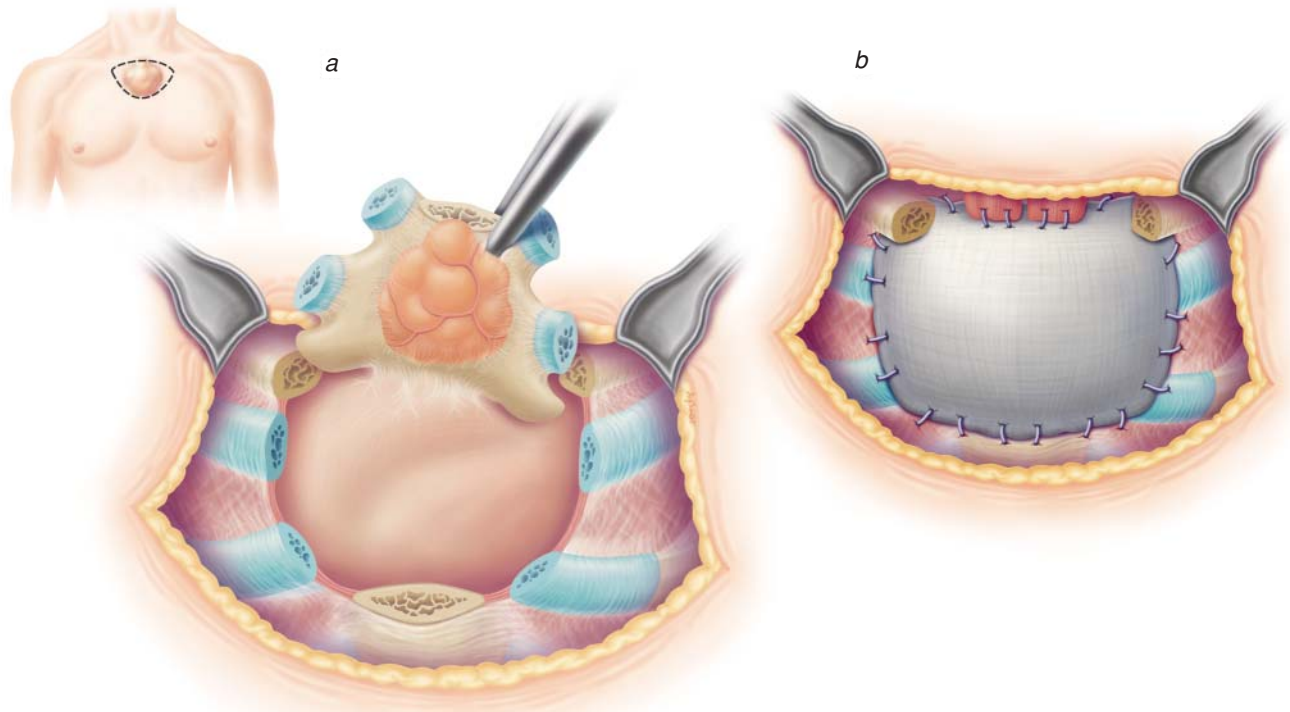


Figure 14 Manubrial resection and reconstruction. (a) The clavicles and ribs are divided as in clavicular and other chest wall resections. (b) A polypropylene-methylmethacrylate sandwich may be used to reconstruct the chest wall.

Step 1: initial incision and exposure The patient is placed in the decubitus position, and a 6 to 8 cm incision is made over the area corresponding to the most dependent area of the infected cavity. Symbas employed a U-shaped incision; however, a simple linear incision can also be used with good results. The subcutaneous tissue and muscle are then divided down to the chest wall with the electrocautery.

Step 2: resection of ribs and creation of thoracostomy The pleural space is opened with the electrocautery, any pus present is drained, and the chest cavity is manually and visually explored. Next, 6 to 8 cm segments of two or three adjacent ribs are resected according to the same principles employed for other chest wall resections. The resulting thoracostomy is large enough to permit drainage and packing. The skin overlying this thoracostomy is then marsupialized to the thickened parietal pleura with absorbable sutures [see Figure 15]. If the pleura does not possess sufficient integrity to hold the sutures, they can be placed through the periosteum of the ribs.

Step 3: packing and drainage The wound is irrigated with normal saline and packed with saline-moistened gauze. Post-operatively, a chest x-ray should be obtained to rule out pneumothorax, and twice- to thrice-daily packing is initiated. Packing is continued on an outpatient basis, and the wound is monitored. The wound will begin to close over the next several weeks. If the empyema or bronchopleural fistula has not healed by the time the wound starts closing, the thoracostomy will have to be revised. In some cases, this can be

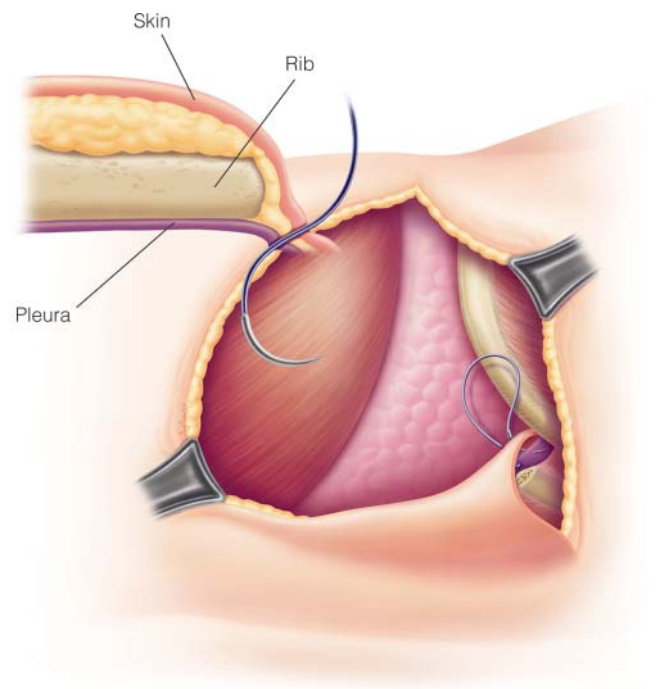


Figure 15 Open chest drainage (Eloesser flap). Once the ribs have been resected, the skin overlying the thoracostomy is marsupialized to the parietal pleura to permit packing and open pleural drainage.

accomplished merely by manually dilating the opening in the operating room; in others, the entire thoracostomy must be revised. In either case, the goal is to maintain a large enough opening to allow adequate packing.

Step 4: closure of thoracostomy Once the lung and the pleural space have healed, the thoracostomy is closed. The procedure for closing the thoracostomy depends on the size and nature of the remaining defect [see Figure 16a]. For small defects, simple closure of the skin will suffice. For larger defects or residual spaces in the pleura, however, muscle flap closure will be required [see Figure 16b]. Improvements in radiographic techniques and greater emphasis on early intervention for empyemas have significantly reduced the need for open chest drainage; however, this technique can still be valuable in the appropriate clinical situation.

PROCEDURES FOR CHEST WALL FRACTURES/TRAUMA

A recent survey of American trauma, orthopedic, and thoracic surgeons found that the majority of polled surgeons had not performed a repair on sternal or rib fractures, nor was there a consensus of surveyed surgeons with agreed upon surgical indications. Also, a large majority were unaware of any published randomized trials addressing rib or sternal fractures.²⁴ Although rib and sternal fracture repairs have been performed for many years, the operative indications remain somewhat controversial. However, there is increasing consensus that operative fixation of these fractures is underused; therefore, basic repair techniques are discussed below.²⁵

Repair of Rib Fractures

Although there are a number of potential indications for operative repair for rib fractures, two recent randomized trials

demonstrate that patients with flail chest can benefit from operative repair in selected scenarios. Flail chest can be defined as three or more consecutive ribs fractured in two or more locations, clinically creating a segment of the chest wall that visibly demonstrates paradoxical motion with respiratory variations. In both of these trials, the operative group demonstrated a reduced number of ventilator days, intensive care unit length of stay, and lower incidence of pneumonia. One of the trials reported that more of the operative group returned to work at the 6-month follow-up compared to the nonoperative group.^{26,27} Retrospective reviews and nonrandomized cohort studies demonstrate that patients with severe flail segments without underlying pulmonary contusion are offered the greatest advantage in surgical repair of rib fractures.²⁸ Opponents to surgical correction of rib fractures suggest that the nonoperative groups were not managed with modern strategies, including epidural anesthesia and chest physiotherapy.²⁹ It is not, however, within the scope of this chapter to argue the merits of the literature surrounding the subject matter but simply to delineate some of the techniques. Other indications include chest wall defect and pulmonary hernia.

Operative planning In preoperative planning, it is useful to define the location and characteristics of all the rib fractures with a CT scan, and three-dimensional reconstruction may provide the surgeon with added information to the fracture geometry. As the main complications of the procedure are infectious in etiology, removal of chest tubes if possible, prior to the operation, is encouraged. The use of an epidural catheter for pre- and postoperative pain management should be considered. Many different techniques have been described, including variations of intramedullary fixation, plate attachment, or wiring, but the most commonly

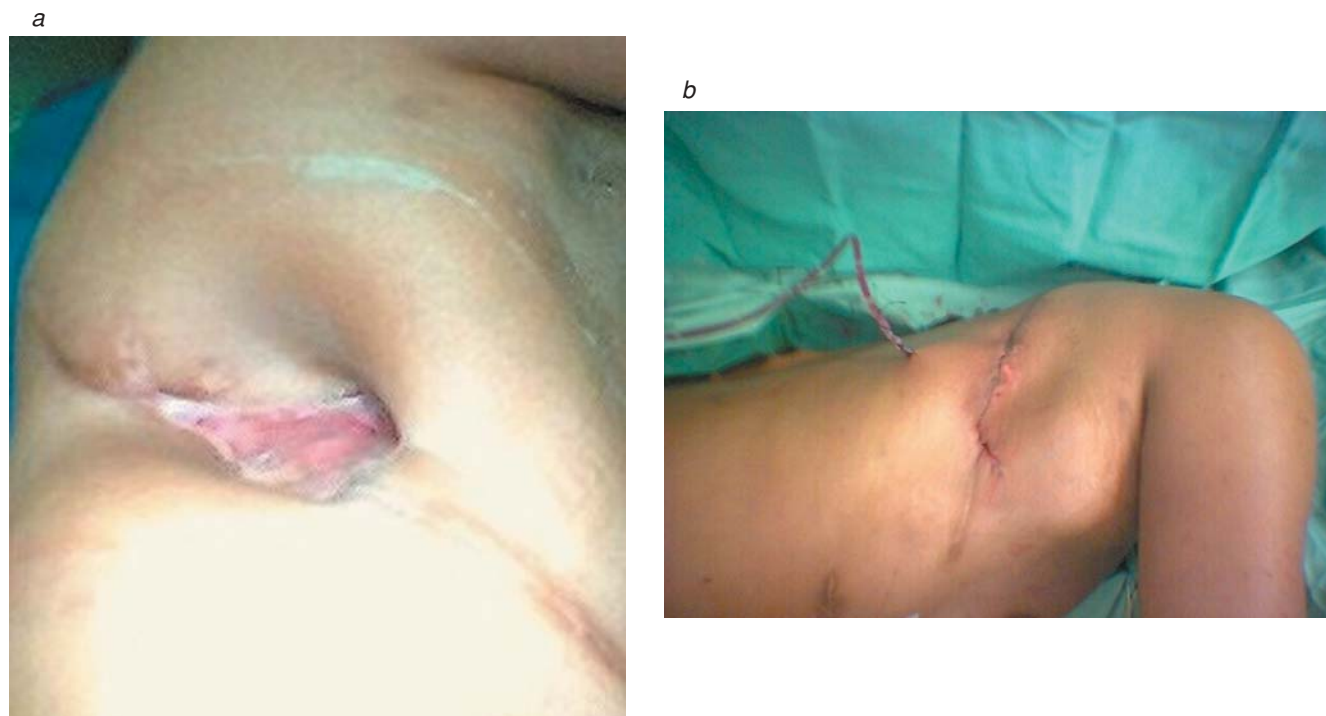


Figure 16 Open chest drainage (Eloesser flap). (a) Photograph shows a right Eloesser flap 8 months after creation. (b) Photograph shows an Eloesser flap that was closed with a muscle flap.

employed technique is anterior plating with bicortical screw fixation.

Operative technique The patient is intubated with a single-lumen endotracheal tube or a double-lumen tube if single-lung ventilation is preferred, but this is not mandatory. The patient is placed in standard lateral decubitus positioning for a posterior lateral thoracotomy. A muscle-sparing thoracotomy incision is used if possible, and the scapulothoracic bursa is incised, giving access to the thoracic cage. This allows for fracture site localization, easily accessing ribs 3 to 9. Soft tissue immediately overlying the fractures is removed with a periosteal elevator, and the ribs are realigned with the use of bone forceps. Plates of the surgeon's selection are secured to the ribs with bicortical screw placement. Careful attention is placed to ensure that the screws are of the appropriate length to prevent screw tips from entering the pleural space. For stabilization of the chest wall, not all the fractured ribs need to be fixed. Depending on the surgeon's comfort, single-lung ventilation can be used, and by inserting a thoracoscope inferior to the fractures, the pleural space can be visualized and monitored during screw placement. Assuming that satisfactory fixation has been accomplished, the pneumothorax can be evacuated on lung reexpansion, and no chest tube would be required.

Complications Postoperative complications are primarily infectious in etiology and include superficial wound infections and empyemas. A postoperative pneumothorax should always be evaluated for on standard postoperative chest x-ray and if there is any respiratory deterioration, even if the pleural space was not entered during the procedure. Other, less frequent complications include fixation failures, chronic pain, reactive pleural effusions, and wound hematomas.

Repair of Sternal Fractures

The diagnosis of sternal fractures is usually suspected because of pain in the precordial area with tenderness and instability on palpation. There is evidence of increased diagnosis of sternal fracture in the trauma literature as a result of the increased use of CT scanning in this patient population.

However, because of the prevalence of median sternotomies in cardiac procedures, more operations for sternal fixation are performed for postoperative chronic sternal nonunion than acute fracture. Sternal fracture nonunion is commonly defined as persistent instability after 6 weeks of nonoperative management and is the most common operative indication. Other indications include fractures that create paradoxical motion with respirations altering respiratory mechanics, and a multitude of anterior plating systems are available for the surgeon to use; other techniques include placement of sternal wires through the fracture fragments.

Operative planning In the preoperative planning of surgical repair, a CT scan with three-dimensional reconstruction provides added geometric insight to the fracture pattern. In an attempt to reduce postoperative infectious complications, mediastinal or chest tubes should be removed if in place. Also, one should consider the use of an epidural catheter for postoperative pain management.

Operative technique The sternum is exposed using a previous surgical incision if present or through a longitudinal or transverse incision depending on the need for exposure. If sternal wires are in place, they are removed, and the fibrous tissue and soft tissue are removed with electrocautery and the periosteal elevator. If there is a fibrous union, this is removed as well. Once all fractures are identified, they are reduced using bone forceps. Plates are selected to allow for at least three screws to be seated on either side of the fracture. Careful attention is placed ensuring that the screws do not penetrate the inner table of the sternum. The pectus muscles are reapproximated and a drain placed to prevent seroma or hematoma formation. The drain is removed on postoperative day 1 or 2 depending on the output.

Complications Postoperative complications have a low incidence for sternal fixation procedures and are similar to rib fixation, including superficial wound infections, wound hematomas and seromas, fixation failures, chronic pain, pleural effusions, and empyemas.

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Alice Y. Chen

10 VIDEO-ASSISTED THORACIC SURGERY

*Marcelo C. DaSilva, MD, and Scott J. Swanson, MD**

Although Sir Francis Richard Cruise has been credited with performing the first thoracoscopy for evacuation of empyema in 1865,¹ Hans Christian Jacobaeus coined the term “thoracoscopy” in an article published in 1910.² In the latter report, Jacobaeus described the use of a cystoscope to examine the chest cavity and to lyse adhesions, allowing the lungs to collapse for the treatment of tuberculosis.³ With the introduction of streptomycin, which revolutionized the treatment of tuberculosis, thoracoscopy was relegated to the occasional case report. It was not until the introduction of laparoscopic procedures in the 1980s that surgeons started to apply this technology to the thoracic cavity. In 1992, Lewis and colleagues reported 100 consecutive patients who underwent video-assisted thoracoscopic surgery, including three lobectomies with anatomic hilar dissection.⁴ From these early studies, minimally invasive video-assisted thoracic surgery (VATS) has emerged as a safe and reliable technique. It has, in many instances, supplanted standard thoracic procedures. Approximately 20% of all lobectomies now are performed thoracoscopically in the United States.⁵

Historical Background

The first single institution prospective randomized trial comparing VATS to the muscle-sparing open technique for lobectomy was published by Kirby and colleagues in 1995.⁶ Sixty-one patients undergoing lobectomy for stage I non-small cell lung cancer (NSCLC) were randomized to VATS or open thoracotomy. There was no significant difference in operating time, intraoperative complications, estimated blood loss, chest tube drainage, length of stay, or postthoracotomy pain between the groups, although it was a small study and many VATS patients had a minithoracotomy. In the early 1990s, the National Institute of Cancer funded an intergroup consortium of thoracic surgeons to investigate the efficacy of thoracoscopy and VATS in the diagnosis, staging, and treatment of intrathoracic malignancies. Cancer and Leukemia Group B (CALGB) 9335 was the first multicenter, clinical research phase II trial to look at the feasibility of treating patients with poor cardiopulmonary reserve and T1 peripheral NSCLC by VATS wedge resection or radiotherapy.⁷ This clinical trial concluded that VATS wedge resection in high-risk patients is safe and feasible. The CALGB 9380 phase II clinical trial was designed to determine the feasibility, morbidity, and mortality for thoracoscopic and/or

laparoscopic staging of esophageal cancer.⁸ One hundred seventeen patients were accrued; 82 patients (70%) met the entry criteria for thoracoscopy. Of those, 57% had positive nodes and 43% had all negative nodes. Node-negative status was confirmed on final pathology in 12 (75%) of 16 patients who underwent surgery, whereas three patients had node-positive status in the specimen (19% false negative rate). The authors concluded that thoracoscopic and/or laparoscopic staging lung and esophageal cancer was feasible and doubled the number of positive lymph nodes identified by conventional surgery.

The first multicenter prospective trial to examine standardized VATS lobectomy was CALGB 39802.⁹ One hundred twenty-eight patients were enrolled for VATS lobectomy as defined by one access incision (4 to 8 cm), two 5 mm port incisions, and no retractor use or rib spreading. The perioperative morbidity was 7.4% and 30-day mortality was 2.7%, both comparable to standards of open thoracotomy in patients with small (≤ 3 cm) peripheral NSCLC. In 1998, CALGB 39803 answered the question of restaging patients with histologic documented stage IIIA NSCLC with VATS on the basis of involved N2 nodes from mediastinoscopy prior to induction therapy.¹⁰ Seventy patients were accrued in 10 institutions. Of those, 47 patients (67%) had radiation therapy and 68 (97%) had chemotherapy. The number of incisions ranged from one to four, with a median of three incisions. VATS restaging criteria were met in 40 patients (57%): four had pleural carcinomatosis, 17 had persistent N2 disease, and 19 had three negative nodal stations. In addition, 13 (18.6%) patients in the VATS group had no evidence of persistent N2 disease attributable to unanticipated obliteration of nodal tissue. VATS was unsuccessful in 17 (24%) patients as a result of adhesions or fibrosis and tumor bulk preventing nodal access. Of the 53 patients who completed VATS restaging, 21 provided cancer tissue and 31 had histologic tissue obtained during thoracotomy; N2 downstaging occurred in 32 patients (46%). The sensitivity of VATS was 75%, the specificity was 100%, and the negative predictive value was 75.8%. No deaths occurred, but one airway injury was directly attributed to VATS. The authors concluded that VATS was feasible and provided pathologic assessment of ipsilateral nodes in treated IIIA (N2) NSCLC.

Eastern Cooperative Oncology Group (ECOG) 2202 was the first multi-institutional phase II trial to assess the feasibility of minimally invasive esophagectomy (MIE) in a multi-institutional setting.¹¹ Of 106 patients enrolled in this study, 99 underwent MIE. Anastomotic leak (7.8%) and pneumonia (4.9%) were the major complications, whereas the mortality rate was 2% (2 of 106), with a mean follow-up

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of 19 months, and the estimated 3-year survival rate for the cohort was 50% (95% confidence interval 35 to 655). The authors concluded that MIE was safe and feasible, with low perioperative mortality and morbidity and with oncologic outcomes similar to those of open esophagectomy.

The era of VATS is sufficiently mature that enough data have accrued to compare the efficacy of VATS with that of open procedures. In this regard, anatomic pulmonary resection by VATS has led to significant reductions in morbidity, mortality, and hospital length of stay, allowing patients a more expeditious return to regular activities. VATS has been used in the treatment of both benign and malignant diseases of the chest. Furthermore, VATS may be used in selected patients with early-stage lung cancer without breaching oncologic surgical principles.

DEFINITION

The terms “VATS” and “thoroscopic” refer to totally thoroscopic approaches, where visualization is dependent on video monitors, and rib spreading is avoided by using a thoracoscope, video monitors, and one to four small (1 to 2 cm) incisions.¹²

INDICATIONS AND CONTRAINDICATIONS

The indications for VATS are the same as for conventional approaches to thoracic surgery. However, tumor size greater than 6 cm, inability to tolerate single-lung ventilation, and previous thoracotomy with obliteration of the pleural space [see Table 1] are considered relative contraindications. The individual experience of the surgeon and the complexity of the operation also influence the procedures that can be performed by VATS.

PREOPERATIVE EVALUATION

The preoperative evaluation of patients undergoing VATS is similar to that of those undergoing open thoracotomy procedures. The risks related to surgical resection include perioperative morbidity and mortality and long-term functional disability. Individual patient circumstances increase or decrease the risks from standard thoracotomy resection and VATS [see Figure 1]. In addition, a discussion of the balance between the risks and benefits of surgical resection by the surgeon and the patient should also include nonstandard treatment options, such as sublobar resections, conventional radiotherapy, stereotactic radiotherapy, and radiofrequency ablation.

A thorough physical examination, past medical history, social history including tobacco smoking and exposure to arsenic and asbestos, radiologic studies (chest x-rays, computed tomographic [CT] scan, positron emission tomographic [PET]-CT scan, magnetic resonance imaging [MRI]), and pulmonary function tests are part of the preoperative preparation. Although thoracoscopic procedures tend to be less stressful than open thoracotomy, with fewer cardiopulmonary complications (e.g., atrial fibrillation or myocardial infarction),¹³ it is important to recognize that risk assessment is a complex process, and the surgeon should focus on determining the individual patient's resectability and operability. Resectability refers to the amount of lung tissue and tumor that can be safely removed without developing respiratory

Table 1 Indications and Relative Contraindications for VATS Procedures

Diagnostic indications
All biopsies: nodules, interstitial lung disease
Pulmonary infection in the immunosuppressed patient
Nodal staging of a primary thoracic tumor
Staging a primary extrathoracic tumor
Trauma: lung laceration, hemothorax diaphragmatic injury
Therapeutic indications
Lung
Spontaneous pneumothorax
Bullous disease/lung volume reduction
Persistent parenchymal airleak
Pleural effusion
Pleural disease: empyema, fibrothorax, decortication
Anatomic resection
Lobectomy
Segmentectomy
Pneumonectomy
Esophageal
Benign
Malignant
Mediastinal
VATS thymectomy for thymoma
Nodal dissection
Pericardial window
Cysts
Chest wall
Rib resection
Sarcoma
First rib for thoracic outlet syndrome
Other
Metastatectomy
Sympathectomy for hyperhidrosis
Ligation of thoracic duct
Repair/plication of the diaphragm
Relative contraindications to VATS pulmonary resection
Intolerance of single-lung ventilation
Tumor size > 6 cm
Anticipated sleeve resection
Hilar lymphadenopathy
Chest wall or mediastinal involvement
Neoadjuvant radiation therapy or chemotherapy

VATS = video-assisted thoracic surgery.

insufficiency. It depends directly on the amount of pulmonary reserve of the patient. Operability, on the other hand, refers to the ability of a patient to survive the proposed procedure and its perioperative complications. It depends on the patient's comorbid conditions. However, neither the operability of an individual patient nor the resectability of a tumor should influence the decision concerning the role of a complete resection on survival.¹⁴

Pulmonary function testing includes pulmonary spirometry, pulmonary hemodynamic response testing, and exercise testing. Pulmonary spirometry is affected by height, age, weight, sex, race, and posture, as well as arterial oxygenation and diffusion capacity. Although pulmonary spirometry and arterial oxygenation help predict mortality, they are not good predictors of postoperative complications. Diffusion capacity of the lung for carbon monoxide (DLCO) is a more sensitive predictor of postoperative complications. DLCO measures the partial pressure difference between inspired and expired carbon monoxide. It relies on the strong affinity and large absorption capacity of erythrocytes for carbon monoxide and thus demonstrates gas uptake by the capillaries that is less dependent on cardiac output.¹⁵ Thus, value is decreased in

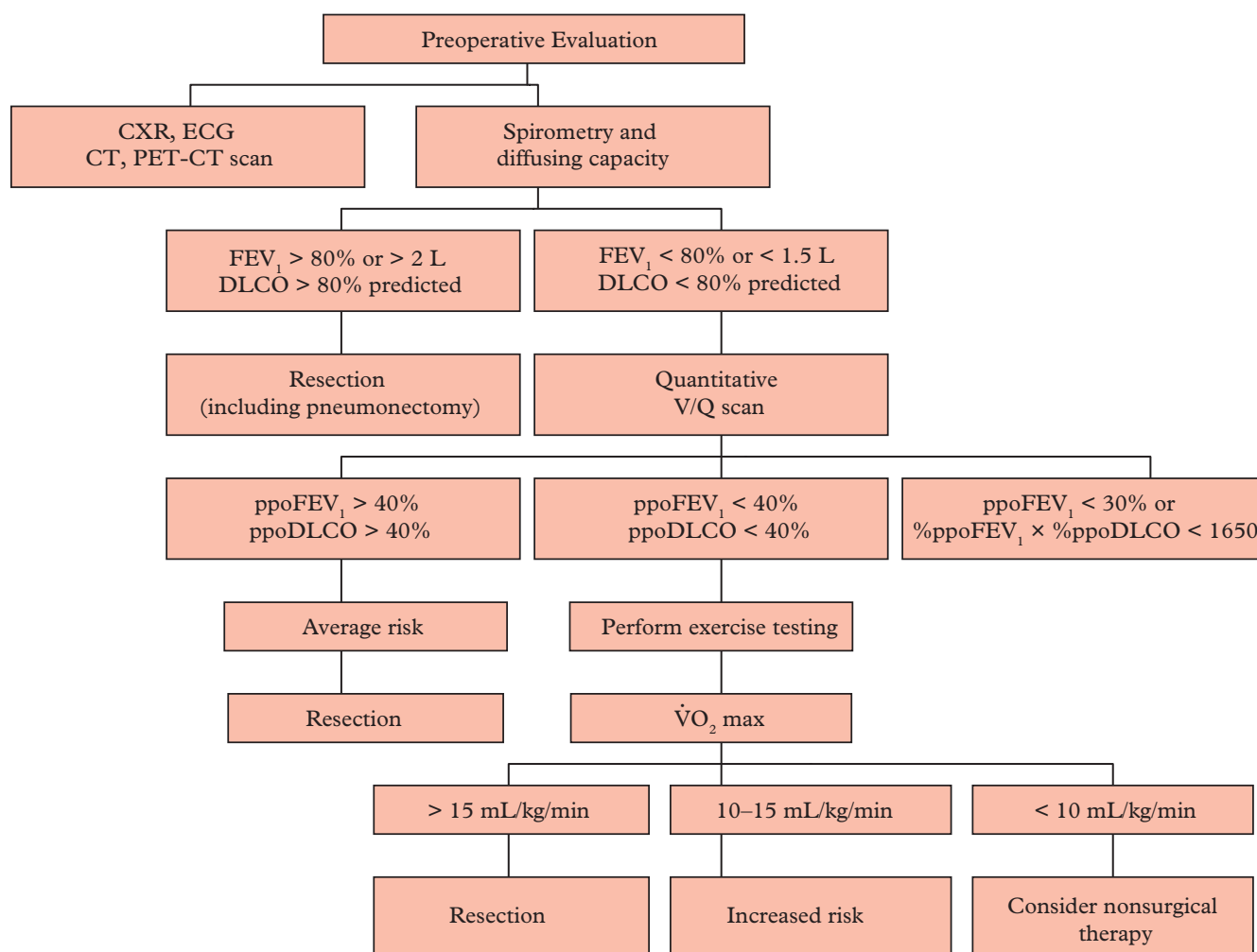


Figure 1 Preoperative evaluation. CXR = chest x-ray; CT = computed tomographic; ECG = electrocardiogram; DLCO = diffusing capacity for carbon monoxide; FEV₁ = forced expiratory volume in 1 second; PET = positron emission tomographic; ppo = postoperative; $\dot{V}O_2$ max = maximum oxygen consumption; V/Q = ventilation-perfusion.

patients with emphysema, chronic pulmonary hypertension, and interstitial lung disease. DLCO is an important and independent predictor of postoperative complications after major lung resection, even in patients without COPD.^{16,17}

Quantitative ventilation/perfusion (V/Q) scan, along with pulmonary spirometry, is useful for predicting postoperative lung function. A calculated predictive postoperative forced expiratory volume in 1 second (ppoFEV₁ of less than 40% is associated with a 50% mortality rate. The absolute minimum ppoFEV₁ in patients undergoing lobectomy is 800 mL. Pulmonary hemodynamic response testing includes the measurement of pulmonary artery pressure and pulmonary vascular resistance. It is an invasive test and requires right heart catheterization. Systolic pulmonary artery pressure greater than 35 mm Hg is associated with a 10-fold decrease in survival rate, and pulmonary vascular resistance greater than 190 dyne is associated with a 90% mortality rate. Maximum exercise testing is concerned with the amount of arterial desaturation that occurs during exercise. Patients

with a maximum oxygen consumption ($\dot{V}O_2$ max) less than 15 mL/kg/min are considered high risk, whereas those with a $\dot{V}O_2$ max of 16 to 20 mL/kg/min could probably undergo surgery.

Flexible bronchoscopy is generally indicated in patients with hemoptysis, wheezing, and evidence of bronchial obstruction. In patients with lung cancer, bronchoscopy is always performed to assess endobronchial invasion. If a mass is found beneath the mucosa or intraparenchyma, endobronchial ultrasonography and electromagnetic navigational bronchoscopy are potential diagnostic tools, but their discussion is beyond the scope of this chapter. Bronchoscopy is also useful for the diagnosis of infectious diseases, such as tuberculosis, fungus, *Pneumocystis* pneumonia, and cytomegalovirus, prior to a thoracoscopic procedure. Finally, a multidisciplinary discussion with medical and radiation oncologists is especially useful in patients who are marginal surgical candidates and serves as a basis for discussing the proposed surgical procedure and treatment options with the patient and appropriate family or surrogates.

The goal of the preoperative evaluation is to identify those patients who can tolerate a thoracic surgical procedure. By integrating the concept of operability and resectability while achieving a complete surgical resection, along with a thorough preoperative evaluation, the surgeon will be able to identify a group of patients who would benefit from VATS.

Operative Planning

ANESTHESIA AND MONITORING

VATS is performed under general anesthesia with single-lung ventilation. A double-lumen endotracheal tube is generally used, but an endobronchial blocker may also be employed to collapse the lung. Alternatively, limited operations such as diagnostic pleuroscopy and pleural biopsy, insertion of pleural drainage catheters, or procedures performed on pneumonectomy patients can be safely done with a single-lumen endotracheal tube and intermittent lung ventilation. The degree of intraoperative monitoring needed depends on the extent of the planned procedure and on the patient's general medical condition. Standard monitoring techniques are used to measure the patient's oxygenation, ventilation, circulation, and temperature.¹⁸ Whenever indicated, a peripheral arterial line, central venous pressure and pulmonary artery (PA) catheters, and transesophageal echocardiography may be used. A Foley catheter is inserted at the beginning of the procedure to monitor urine output. Depending on the pulmonary reserve of the patient, extent of the procedure, and postoperative pain, epidural catheters can provide excellent pain relief, but they are not commonly used for thoracoscopic procedures because of the time required for insertion and frequent side effects, such as hypotension and urinary retention. Alternatively, recent studies have demonstrated the safety and efficacy of continuous infusion pumps delivering local anesthetic through a catheter in the extrapleural pocket during thoracotomy,¹⁹ as well as patient-controlled analgesia for perioperative pain management.

POSITIONING OF THE PATIENT AND PORT PLACEMENT

The general technique for VATS is neither simple nor uniform. Absolute understanding of thoracic anatomy and video orientation is critical. Thoracoscopy is made difficult by paradoxical motion when the camera and instruments are facing each other. Preparation and positioning are the same for all major VATS procedures. The surgeon stands facing the patient, who is placed in the full lateral decubitus position, elevated on pontoons [see Figure 2] designed to protect pressure points. Flexing the operating table to open the intercostal spaces (ICSs) for maneuvering instruments can be used but is not mandatory.

Port placement involves triangulation of the target with trocar ports [see Figure 3]. Alignment of the thoracoscope and positioning of the video monitors in the operating room are of paramount importance. The thoracoscope is usually placed in the seventh or eighth ICS over the mid-to-anterior axillary line [see Figure 4]. Additional 1 cm incisions, usually two, are placed along the line of the standard posterolateral thoracotomy incision approximately on the fifth ICS, one at the anterior axillary line and one at the posterior axillary line. The incisions are placed such that a triangular configuration is achieved. This setup facilitates the most efficient use of the instruments by the surgeon and the assistant. In females, the skin incision can be made in the inframammary fold for



Figure 2 Proper patient position in the operating room, with the patient propped on pontoons.

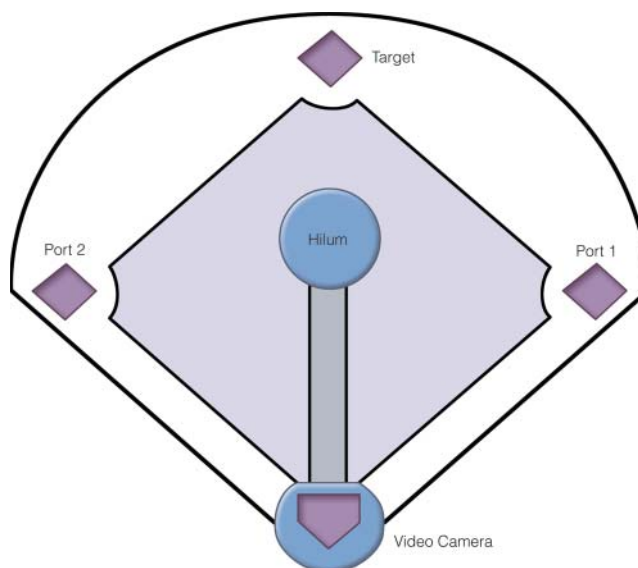


Figure 3 Triangulation technique for port placement in relation to intrathoracic structures and targets.



Figure 4 Thoracoscope and trocar placement.

cosmesis. These incision sites may vary according to the proposed procedure, the location of the pathology, patient body habitus, and previous scars. Alternatively, a ring forceps or endo-Kittner (Ethicon Endo-Surgery, Cincinnati, OH) can be used to inspect the chest cavity and expose the hilum to determine the proper position for the other incisions. The so-called access incision should be placed so as to provide direct access to the hilum. A soft tissue retractor may be used to provide adequate exposure. Intraoperative conversion to a standard thoracotomy will be necessary in approximately 5 to 20% of patients undergoing VATS depending on the level of experience for several reasons, including extensive pleural adhesions and pulmonary lesions that cannot be located thoracoscopically or that necessitate a more extensive resection than can be accomplished by VATS.

INSTRUMENTATION

The equipment used for VATS comprises (1) a video camera and tower; (2) monitors, usually two at 45° from the midline; (3) thoroscopes and ports; (4) staplers; (5) thoracic instruments (e.g., lung clamps and retractors) that have been modified for endoscopic use; (6) various devices for tissue cauterization; and (7) a suction irrigation device [see Figure 5]. A basic open thoracotomy tray and instruments should be available in the event of conversion to open thoracotomy [see Table 2].

Video Equipment

The basic components of all video systems used for thoracoscopy are similar: a large-screen video monitor, a xenon light source, a video recorder, and a printer for still photography. A second video monitor, either mounted on a cart or hanging from the ceiling, is connected by cable to the main monitor and is placed across from it at the head of the operating table. Alternatively, a single monitor can be placed at the head of the operating table. A CO₂ insufflator is used for the combined thoracoscopic/laparoscopic procedures, such as in MIE.

Thoroscopes and Thoracoports

Both rigid and flexible thoroscopes can be used for VATS. Depending on individual surgeon preference, level of expertise, and comfort zone, a 5 or 10 mm 0° or 30° rigid



Figure 5 Video and monitors.

Table 2 Basic Instruments and Equipment Used for VATS Procedures

Standard open thoracotomy set
Standard thoracoscopic instruments set
• Thoracoscope, rigid or flexible
0°, 30°, and 45°
5 or 10 mm (diameter)
• Endoscopic staplers*
Echelon ENDOPATH 45 and 60 mm
Echelon ENDOPATH ETS 35 or 45 mm
• Thoracoscopic endo-Kittner†
• ENDOPATH 5 mm babcocks, graspers, curved dissector and scissors*
• EnSeal (bipolar coagulation, mechanical transection of tissue allows simultaneous sealing and transection of blood vessels up to 7 mm)*
• Harmonic shears (for lymph node dissection only, cut/coagulate vessels up to 5 mm in diameter)*
• Specimen retrieval bags
ENDOPOUCH Retriever 224 mL retrieval bag, polyurethane*
Endo-Catch Gold (10 mm specimen pouch)‡
Endo-Catch II (15 mm specimen pouch)‡
• Endoscopic, surgical irrigation and suction systems

* VATS = video-assisted thoracic surgery. Ethicon Endo-Surgery, Cincinnati, OH

† Aspen Surgical, Caledonia, MI

‡ Covidien, Norwalk, CT

telescope with a forward-viewing scope or a 5 or 10 mm flexible scope can be used. The rigid thoracoscope has an excellent resolution. Placing the video camera at the distal end of a flexible thoracoscope, as in the electronic video-thoracoscope (EVE-L, Fujinon, Wayne, NJ), yields better visualization of some relatively inaccessible areas in the chest. The disadvantages of the flexible thoracoscope include increased expense and complexity and reduced resolution compared with rigid systems.²⁰ For most VATS procedures, a 10 mm 30° rigid telescope is used. This thoracoscope allows better orientation and visualization around structures such as the pulmonary artery and bronchus. Thoracoports are shorter and have a corkscrew configuration on the outside that stabilizes them within the chest wall. The trocar is simply a blunt-tipped obturator that facilitates passage of the cannula through the chest wall. A long laparoscopic trocar may be used in morbidly obese patients. Thoracoports are available in several sizes (5, 10.5, 12, and 15 mm in diameter) to accommodate various instruments.

Staplers

Endoscopic gastrointestinal anastomosis (Endo-GIA) staplers have revolutionized the surgeon's ability to perform minimally invasive pulmonary resections. Furthermore, tissue reinforcements that buttress the staple line with prosthetic materials (Gore-Tex [W.L. Gore & Associates, Newark, DE] or bovine pericardium) are highly reliable and provide excellent hemostasis as well as closure of air leaks reducing post-operative air leakage. The vascular stapler cartridge with six rows of 2.0 or 2.5 mm staples is designed for division of thin vascular tissue such as the pulmonary vessels. Some surgeons are reluctant to use it on hilar vessels because if the stapler fails mechanically (e.g., cuts without applying both staple lines properly), life-threatening hemorrhage can ensue.²¹ Endoscopic staplers that do not cut (transverse anastomosis [TA] staplers) are also available. Some advocate using two applications of the endovascular stapling device to minimize the risk of transecting the vessel as a consequence of a

stapling misfire. In this approach, the stapler is first fired proximally with the knife removed, leaving six rows of staples in place. Next, the stapler is fired again more distally with the cutting mechanism intact to transect the vessel, leaving a total of nine rows of staples on the patient side and three rows of staples on the specimen side.

Instruments

Various types of Pennington and Duval clamps are available. Sponge sticks modified by the introduction of various curves and a line of lung clamps are used for retracting lungs, dissecting hilar structures, and holding lymph nodes. The vein retractor and the fan retractor, which can be opened and closed like a fan by turning a knob on the end, can also be used during VATS. Vein retractors are best suited for gentle retraction of hilar or mediastinal structures (e.g., vessels, bronchi, esophagus, or lymph nodes), whereas the fan retractor can be used to hold the whole lung during MIE.

In major VATS procedures (e.g., VATS lobectomy), the soft tissues of the access incision may be retracted by means of a cerebellar (or Weitlaner [Miltex, Inc, York, PA]) retractor. This allows the surgeon to dissect and encircle hilar vascular structures by using two instruments through the same incision. A Harken clamp (Scanlan, Saint Paul, MN) is useful in that it is long enough to reach behind a vascular structure, pass a silk suture to the tip of the instrument, and tie it to an endoleader to guide the stapler across these delicate arterial branches.²² A long Allis forceps is an excellent instrument for holding and retracting lymph nodes during a mediastinal lymph node dissection. Although biopsy forceps have been specifically created for laparoscopy and thoracoscopy, those used for mediastinoscopy are, in fact, well suited for thoracoscopy. Various curved and right-angle dissecting clamps, needle holders, and scissors have been developed. In addition, standard thoracotomy instruments can be inserted through a minithoracotomy incision and used just as they would be in an open procedure.

Devices for Tissue Cauterization

The standard disposable electrocautery device (Bovie Medical Corporation, Clearwater, FL) with a long tip extension, or the Harmonic Scalpel (Ethicon Endo-Surgery, Cincinnati, OH), the LigaSure vessel sealing system (Covidien, Valleylab, Boulder, CO) and the argon beam electrocoagulator handpiece are narrow enough to pass through a thoracopore. These instruments can be used for dissection and cauterization during VATS. The argon beam electrocoagulator (ConMed Corporation, Utica, NY) is a noncontact form of electrocautery that provides hemostasis on raw surfaces (e.g., denuded pulmonary parenchyma or the chest wall after pleurectomy) and helps seal air leaks from the surface of the lung. Instrumentation for videothoracoscopy continues to evolve. Nevertheless, it may still be necessary to combine disposable and nondisposable instruments from different manufacturers and to use instruments originally designed for other procedures. It is best to maintain a single standard tray that includes the basic instruments required for most operations and to add instruments as needed.

Basic Operative Technique

At our institution, VATS is conducted under general anesthesia using a double-lumen endotracheal tube and

single-lung ventilation. The patient is placed in the full lateral decubitus position, but depending on the location of the target, the patient can be tilted 5° forward or backward. Ventilation to the lung being operated on is stopped as soon as the patient is rotated into the lateral decubitus position, to ensure that the lung will be thoroughly collapsed by the time the videothoracoscope is inserted into the pleural space. The incisions are made on the superior aspect of the ribs to avoid injury to the neurovascular bundle. A standard thoracoscopy is performed with three 10 mm incisions: a camera port is placed in the anterior axillary line in the seventh or eighth ICS; an anterior or access port is placed between the latissimus dorsi and the pectoralis major muscles in the fourth or fifth ICS, and a posterior or working port is placed adjacent to the scapula in the fifth or sixth ICS. Alternatively, a 5 mm incision can be used for a 5 mm camera, and one working port ranging from 3 to 10 mm can be used. It is important to orient the instruments and the thoracoscope such that they face the target within a 180° arc; this positioning prevents mirror imaging and helps the surgery team develop a three-dimensional spatial anatomic orientation in the chest. The incisions should also be placed widely distant from each other so that the instruments do not crowd one another. Should it become necessary to convert to a thoracotomy, the two upper incisions can be incorporated into the thoracotomy incision and the lower incision can be used as a chest tube site. When a patient is being operated on for an apical lesion, the camera port can be placed at the fifth or sixth ICS, and the two instrument ports may also be moved higher, toward the axilla, and the other higher on the posterior chest wall at approximately the third ICS. Also, a fourth port may be helpful for the introduction of additional instruments or to palpate the lesion, depending on its location. An infant Finochietto (Medicon, Bedford, VA) or a Weitlaner retractor is used to keep the soft tissues from falling into the wound without spreading the ribs. These are the basic steps on which modification of the technique will occur depending on the pathology, the location of the target being removed, and the surgeon's skills.

VATS Procedures for Pleural Disease

OPERATIVE TECHNIQUE

One or two 10 mm incisions are made for the videothoracoscope and instruments. The videothoracoscope is inserted through either a 5 or 10 mm thoracopore at the seventh or eighth ICS in the midaxillary line. In cases of pleurodesis, either by mechanical or talc poudrage, the incisions are used for placement of chest tubes, with a right-angle tube inserted over the diaphragm through the lower incision and a straight tube advanced up to the apex of the pleural space through the upper incision. Alternatively, a small 19 French Silastic flexible drain (Blake drain, Ethicon, Somerville, NJ) can be placed in the chest cavity as well, but it has to be looped around the base of the lung and over the diaphragmatic surface and guided posteriorly along the parietal pleura with its tip up in the apex.²³ Special attention must be paid to the placement of the incision in patients with suspected malignant mesothelioma because of the propensity of this tumor to implant in incisions and needle tracks. Once the videothoracoscope has been inserted, pleural fluid is drained with

Yankauer suction tip (Cardinal Health, Dublin, OH) and is sent for cytology, microbiology, and chemistry. Inspection of the cavity is performed, and multiple pleural biopsies are obtained. Fibrinous debris can be removed by irrigating the pleural space with a pulsating water irrigation system. This technique is particularly useful for the débridement and drainage of loculated fibrinopurulent empyema. Talc pouddrage for the treatment of malignant pleural effusion can be accomplished by delivering 2 to 6 g of talc in the pleural cavity with a pneumatic atomizer using 10 L of high-flow O₂.²⁴ At the end of the procedure, an intercostal nerve block is performed under the direct vision of the thoracoscope.

TROUBLESHOOTING

In patients with loculated effusion, the thoracoport placement must sometimes be modified. The preoperative chest CT scan should help ensure that the ports are placed in areas where the lung is not adherent to the chest wall. In some cases, the pleural space is obliterated by adhesions or tumor. This event occurs most frequently in patients who have had severe inflammatory disease (e.g., pneumonia, empyema, or tuberculosis) or extensive pleural malignancy (e.g., locally advanced malignant mesothelioma). In these circumstances, the anterior thoracoport incision can be extended to a length of 5 to 6 cm, the underlying rib section can be resected, and the parietal pleura can undergo biopsy. If thoracotomy is subsequently warranted for therapeutic reasons (e.g., for pleurectomy, decortication, or extrapleural pneumonectomy for mesothelioma), this small incision can be incorporated into the thoracotomy incision.

VATS Pulmonary Wedge Resection

VATS pulmonary wedge resection has become a standard approach to diagnosing small, indeterminate pulmonary nodules and pulmonary infiltrates of uncertain origin, particularly in immunocompromised patients in whom transbronchial biopsy is neither safe nor appropriate. The role of VATS wedge resection is less well defined in the management of primary lung cancers but may be indicated in patients with marginal lung function who otherwise would not tolerate a lobectomy. Although no prospective studies have been performed to clearly assess the benefit of pulmonary metastasectomy, there is an abundance of retrospective data to indicate a long-term survival benefit from complete pulmonary resection. The general criteria in selecting patients for pulmonary metastasectomy include the following: (1) the primary neoplasm must be completely controlled or imminently controllable; (2) metastatic lesions must be limited to the lung without evidence of other distant organ involvement; (3) all metastases must be resectable with adequate pulmonary reserve; and (4) nonavailability of another effective therapy. In cases that meet these resection criteria, long-term survival rates have been reported to be in the range of 30 and 58% for patients with soft tissue and osteogenic sarcomas, respectively. Similar cure rates have been reported with the resection of isolated pulmonary metastases from colon cancer (30.5%), renal cell carcinoma (52.4%), head and neck cancers (48%), and germ cell tumors (59%). Although some melanoma patients with a solitary metastasis may benefit from pulmonary metastasectomy, most patients with this disease do not survive long-term despite aggressive resection of

the metastasis.²⁵ Improved survival in patients with pulmonary metastases appears to be directly linked to the ability to remove all macroscopic tumor. The biology of pulmonary metastases may favor VATS resection based on the following arguments: (1) metastases have been present prior to treatment of the primary lesion and in that sense have been “missed” for a significant period of time already; (2) as noted above, multiple resections do not adversely affect the overall outcome of patients with metachronously detected metastases; (3) patients with unresectable disease who have a recurrence will not be subject to a larger operation, i.e., thoracotomy; (4) VATS resection may be less stressful for patients and therefore result in less immunosuppression, resulting in a more favorable disease course; and (5) VATS may permit patients to return to their regular work or family schedules significantly earlier than an open approach. Other considerations include quality of life and cost of treatment. Historical data, tumor biology, and recent advances in radiologic and surgical techniques support the use of video-assisted surgery in the resection of pulmonary metastases, following the paramount principle of removing all lesions found on a high-resolution CT scan.

Anecdotal reports of port-site recurrence also have raised concerns about VATS as a treatment method in patients with malignancies. However, a 2001 study of 410 patients from a prospective VATS database found only one case of port-site recurrence.²⁶ The authors concluded that the incidence of such recurrences could be kept low if surgical oncologic principles are respected. These principles include (1) reserving VATS for lesions that can be widely excised; (2) conversion to an open thoracotomy for definitive or extensive operations; and (3) meticulous technique for extraction of specimens from the pleural space, with small specimens removed directly through a thoracoport and larger specimens removed in an endo-bag.

OPERATIVE TECHNIQUE

Once general anesthesia has been induced and a double-lumen endotracheal tube inserted, the patient is placed in the full lateral decubitus position. Small subpleural pulmonary nodules are most easily identified in a fully atelectatic lung because they protrude from the surrounding collapsed pulmonary parenchyma. Most pulmonary wedge resections are performed as true videothoroscopic procedures using just three port incisions placed in a triangulated manner [see Figure 4]. The pulmonary nodules to be removed are grasped with an endoscopic lung clamp (Pennington, ring forceps, or Duval) inserted through one instrument port, and wedge resection is done with repeated applications of an endoscopic stapler inserted through the opposite port. An endoscopic lung compression clamp is a linear clamp that can be placed deep to the lesion to ensure a 1 cm margin from the lesion to the staple line [see Figure 6]. As the resection is performed, it is often helpful to introduce the stapler through each of two instrument ports to obtain the correct angle for application to the lung. To prevent tumor implantation in the chest wall, all specimens are placed in a disposable endo-bag and brought out through a slightly enlarged anterior thoracoport incision. At the end of the procedure, intercostal nerve blocks are performed under direct vision of the thoracoscope, and a single chest tube is inserted through the inferior port after the videothoracoscope is withdrawn.

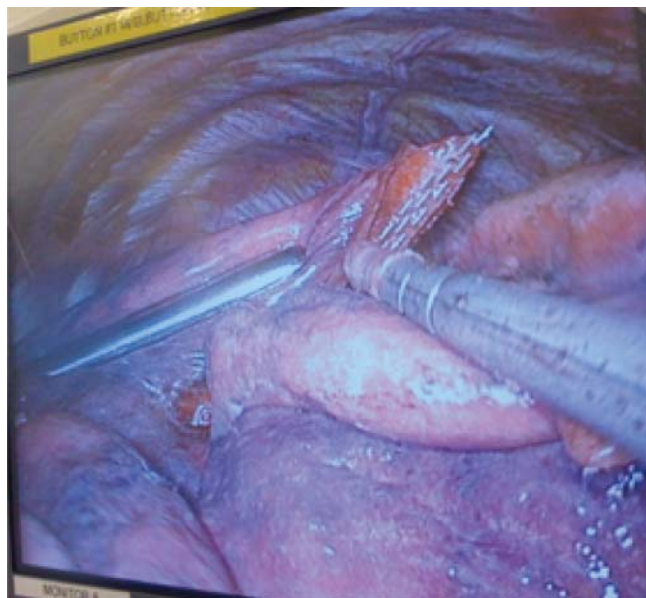


Figure 6 Wedge resection, lung compression clamp.

TROUBLESHOOTING

Several techniques may be used to locate pulmonary nodules that are either too deep or too small to be easily visible on simple inspection of the lung. All of these should be used in conjunction with a high-quality preoperative chest CT scan to identify the lung segment in which the nodule is located. Thoracoscopic examination of the lung nodule can be performed by gently running an endo-Kittner or a ring forceps on the surface of the lung as a surrogate to digital palpation. With experience, one can “feel” a bump and grasp the visceral pleura adjacent to the location. The nodule can be brought up toward the examining finger placed through one of the ports. Alternatively, under prior CT guidance preoperatively, a needle may be inserted into the nodule for intraoperative localization, much like a breast needle localization procedure. Localization is accomplished by injecting methylene blue or by inserting a barbed mammography localization needle, which is then cut off at the skin exit site and later retrieved thoracoscopically. Needle localization techniques are effective, but they also are costly and time-consuming and need to be coordinated with the radiology team and surgeons. Finally, if careful endoscopic examination of the lung fails to reveal the location of a nodule, an access incision is added to the videothoracoscopy. Each lobe of the lung is sequentially rotated up to this non-rib-spreading utility thoracotomy for direct digital palpation. This technique almost always permits identification of a nodule when other techniques fail.

Pulmonary nodules located on the broad surface of the lung may not be amenable to a wedge resection with an endoscopic stapler. Such nodules can be removed by means of electrocauterization, just as in an open thoracotomy. An extension is placed on the handle of the electrocautery device, which is then introduced into the pleural space through either a port or an access incision. Another approach is to resect the pulmonary nodule with a laser in either contact or noncontact mode. To minimize bleeding and air leakage, raw pulmonary

surfaces can be cauterized with either the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser or the argon beam coagulator. Numerous types of absorbable sealant patches or materials are also available to control air leaks from areas of raw pulmonary parenchyma.

Occasionally, after a wedge resection, it is necessary to suture together the pleural edges over an area of raw pulmonary parenchyma. The suturing can be done directly through a non-rib-spreading access incision or through port sites. In the latter case, the ports are removed and a 3-0 polypropylene suture is passed through the anterior port site with a standard needle holder. A second needle holder is introduced via the posterior port site and used in place of a forceps to pick up and reposition the needle as it is passed through the lung. The surgeon and the first assistant work together to oversee the lung, in contrast to the normal practice for an open procedure, in which the surgeon uses a needle holder and a forceps to place the sutures.

VATS Procedures for Spontaneous Pneumothorax and Bullous Disease

OPERATIVE TECHNIQUE

VATS is now frequently performed for the management of recurrent spontaneous pneumothorax and for bullous disease. The approach is similar to that followed in a wedge resection, with three or four port sites being used. The videothoracoscope is inserted at the fifth ICS in the midaxillary line, and two other port sites are added at the fourth ICS in the anterior and posterior axillary lines. In patients with spontaneous pneumothorax, the responsible bulla (which is usually apical in location) is identified, and wedge resection is done with a tissue-reinforced endoscopic stapler. Bullae can be excised by applying the stapler across the base of the area of bullous disease. They also can be ablated with the argon beam coagulator or the Nd:YAG laser and then suture-plicated if necessary.

TROUBLESHOOTING

The placement of port incisions should be determined by the location of the bullae. Because bullous disease is generally apical, port sites are correspondingly higher than for the average wedge resection (i.e., at the fourth and sixth ICSs rather than at the fifth or sixth and eighth ICSs). The precise placement should, however, be determined by determining the exact location of the disease site(s) on the preoperative CT scans. The main problem after resection for bullous disease is prolonged air leak from the staple line. This problem can be minimized by applying commercially available sleeves made of bovine pericardium or with tissue-reinforced staplers and by performing pleurodesis. Mechanical pleurodesis is done with a small gauze sponge passed through a port site. Some surgeons scarify the pleura by cauterizing it with the argon beam coagulator or the Nd:YAG laser, but this is not as effective as mechanical pleurodesis. Chemical pleurodesis by talc poudrage should be reserved for older patients with emphysema and bullous disease and avoided in young patients with spontaneous pneumothorax, who might require a thoracotomy later in life. Another option in younger patients is a limited apical pleurectomy. Special angulated instruments

and blunt dissectors have been designed for this procedure; however, a parietal pleurectomy is also easily performed with combinations of standard blunt and sharp instruments.

VATS Lung Volume Reduction Surgery

OPERATIVE TECHNIQUE

VATS may also be applied to the performance of lung volume reduction surgery (LVRS). If unilateral LVRS is planned, the patient is placed in the lateral decubitus position, and port placement is similar to that for a patient undergoing a wedge resection of the upper lobe. Most patients undergoing LVRS, however, benefit from bilateral LVRS. For this procedure, the patient is placed in the standard supine bilateral lung transplantation position, with shoulder rolls placed vertically in an inverted U fashion behind the back and with the arms positioned above the head. The camera port is placed in the anterior axillary line at the sixth ICS. A lung compression clamp is placed on the area that will be resected. A tissue-reinforced stapler is then inserted into the chest and fired sequentially until the desired area is excised [see Figure 7].

TROUBLESHOOTING

A major cause of morbidity and mortality with this procedure is the occurrence of air leaks, which sometimes are large enough to compromise ventilation significantly. Thus, once LVRS has been done on one side, the lung is reexpanded and any air leaks are carefully assessed. If the leak is small, the other side is operated on in the same setting; if the leak is large, the contralateral procedure is postponed to a later date. The use of fibrin glue or another commercially available pneumostatic sealant along the staple line should be considered to minimize postoperative air leakage.

VATS Lobectomy and Pneumonectomy

Although VATS lobectomy is much less frequently performed than VATS pulmonary wedge resection, standard

techniques have been developed.²⁷ VATS pneumonectomy is performed with less frequency. There are emerging data using VATS, but this approach is experimental at this point in time. These tumors are usually larger and centrally located, making it difficult to assess for the option of a sleeve lobectomy. Therefore, this operation is best performed through an open thoracotomy. However, these operations are done as VATS procedures using an access incision, which facilitates insertion of standard thoracotomy instruments, extraction of the resected specimen from the pleural space, and performance of the technically complex aspects of the procedure, including dissection of the hilar vessels and the mediastinal lymph nodes.

Two approaches to lobectomy have been developed. One involves sequential anatomic ligation of the hilar structures, much as in a standard anatomic lobectomy, and the other involves mass ligation of the pulmonary vessels and the bronchus. The latter is not considered an anatomic lobectomy; therefore, we do not endorse its practice. Both approaches require at least two port incisions in addition to the access incision. The sequential anatomic ligation approach has been well described and follows sound surgical oncologic principles. Accordingly, it is our preferred method of performing VATS lobectomy. In an effort to standardize the approach, we define a VATS lobectomy as an anatomic dissection that is performed entirely under thoracoscopic visualization, proceeds in an anterior-to-posterior fashion, and uses a 4 cm utility incision, two thoracoscopy ports (one for the camera and one for retraction), and no rib spreading. Avoiding rib spreading is the key element in VATS lobectomy to prevent postoperative pain and trauma to the intercostal nerve bundles, which are responsible for the postthoracotomy pain syndrome. A metastatic survey is performed in all patients undergoing VATS lobectomy for malignant disease. The chest is inspected for metastatic pleural and pericardial implants and effusion, chest wall invasion, adhesions, enlarged lymph nodes, and anatomic variations. Radical lymph node dissection includes evaluation of lymph node levels 2, 4, 7, 8, and 9 on the right side. On the left side, it should also include lymph node levels 5 and 6.

OPERATIVE TECHNIQUE

Lobectomy (Sequential Anatomic Ligation)

Correct positioning and port placement are essential for a successful VATS lobectomy. The first port placed is the camera port. It is usually placed through the seventh or eighth ICS and should provide visualization of the anterior and posterior hilum and align with the major fissure in a caudal-cephalic orientation. Whether the port is in the anterior, middle, or posterior axillary line depends on the level of the diaphragm as seen from a review of the preoperative chest x-ray or CT scan, on the location of the target, and on the side of the procedure.

The anterior or utility port (< 4 cm) should be placed right over the hilum. The hilum and the fissures will be dissected through this port. The port usually is created anterior to the latissimus dorsi in the fourth ICS for upper lobectomies and in the fifth ICS for lower lobectomies. A soft tissue retractor may be used to keep the subcutaneous tissue and muscle away from the incision. The third (posterior) port is usually

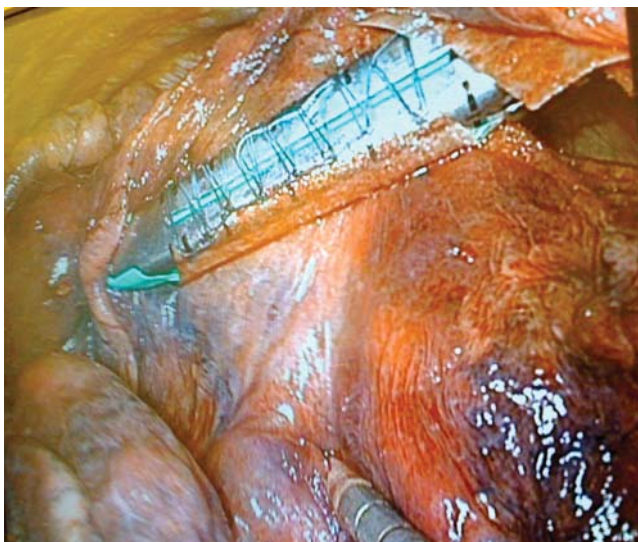


Figure 7 Tissue-reinforced stapler is inserted into the chest.

placed where the edge of the lower lobe touches the diaphragm under the vision of the thoracoscope either inferior or posterior to the scapular tip. This port usually is used for retracting the lung. A ring forceps is placed through the posterior port, and the upper lobe is retracted laterally to permit visualization of the superior pulmonary vein. Table 3 shows the general operative steps for VATS lobectomy.²⁸

Right-Side Resections

Right upper lobectomy The initial dissection is carried out at the anterior hilum. The phrenic nerve is identified, and the mediastinal pleura is opened posterior to it. This plane is developed anteriorly, superiorly, and then posteriorly between the lung and the azygos vein. If any level 10 lymph nodes are found at this location, they are sampled and sent for frozen section. This dissection can, for the most part, be accomplished with blunt dissection using two endo-Kittners. Next, the lung is retracted anteriorly and the posterior hilum is opened to expose the right mainstem bronchus. Further dissection is carried out to expose the bifurcation of the upper lobe bronchus and the bronchus intermedius. The superior pulmonary vein is dissected from the overlying pleura via the access incision with long Pearson or Metzenbaum scissors and DeBakey forceps, similar to an open lobectomy. A Harken clamp is passed behind the superior pulmonary vein after clear identification of the middle lobe vein. The superior pulmonary vein is encircled with an oiled 2-0 silk suture, which is then tied to the endoleader.²⁹ A lung clamp is placed through the utility incision, and the upper lobe is retracted posteriorly. An endovascular stapler is placed through the posterior port and, guided by the endoleader, is passed behind the superior pulmonary vein and deployed [see Figure 8].

Once the pulmonary vein has been divided, the truncus anterior of the pulmonary artery and its variable apical branches are exposed. A Harken clamp is passed around the anterior and apical pulmonary arterial branches, and an oiled 2-0 silk suture followed by the endoleader is passed around these vessels and brought out through the utility incision. The endovascular stapler is passed through the posterior port and used to transect the vessels. Transection of the truncus artery and its branch exposes the right upper lobe bronchus [see Figure 9]. Dissection is performed to separate the ongoing pulmonary artery from the bronchus. An endoscopic 4.8 mm GIA stapler is placed through the posterior port and closed but not fired until the lung is inflated, demonstrating that the middle lobe bronchus is patent. Once the upper lobe bronchus has been divided [see Figure 10], the fissure is completed with the stapler. The upper lobe is then placed in a large surgical tissue endo-bag and removed via the utility incision.

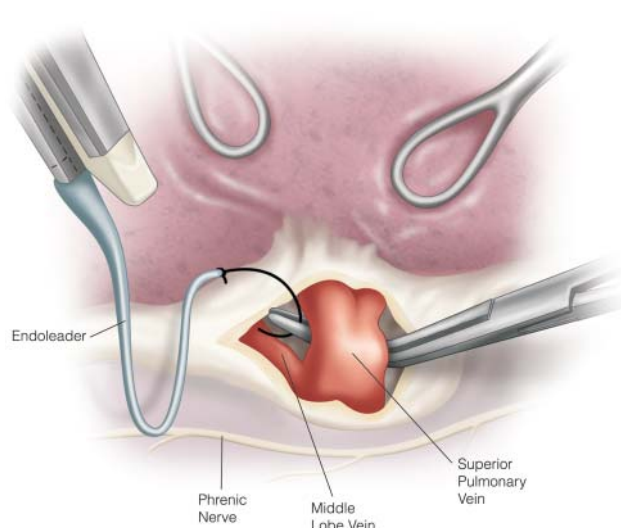


Figure 8 The endoleader looped around the superior pulmonary vein.

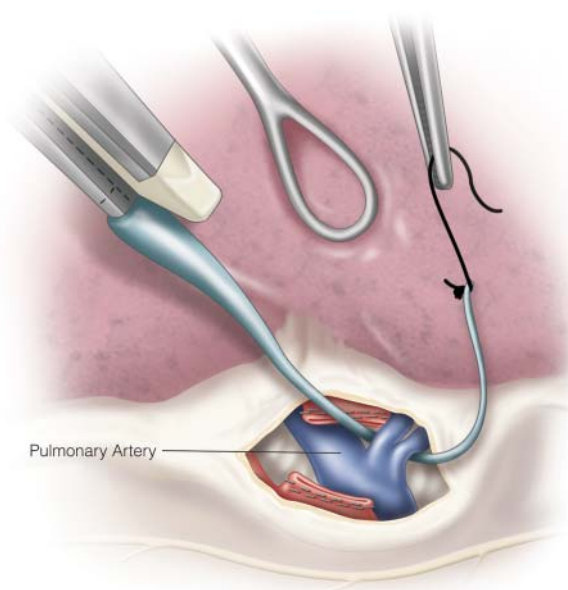


Figure 9 The endoleader looped around the truncus anterior and its branch.

Certain basic surgical concepts—dissection of hilar structures, passage of a monofilament suture around the structure, and transection with a stapler—are similar for all lobectomies. However, the order in which structures are transected and the ports through which staplers are passed differ.

Right middle lobectomy The camera port is placed in the seventh ICS in the midaxillary line. The anterior or access port is placed in the fifth ICS. The posterior or working port is placed either at the scapula tip or posterior to it in the sixth or seventh ICS. The right middle lobe is retracted laterally, and the middle lobe vein is exposed by dissecting it on the anterior hilum. Once the middle lobe vein is dissected free, it is divided using the same maneuvers as described earlier

Table 3 Operative Steps for VATS Lobectomy

Step 1	Positioning and incision/thoracoscopic port placement
Step 2	Lung mobilization
Step 3	Isolation and division of pulmonary arterial and venous branches
Step 4	Fissure completion
Step 5	Bronchial division
Step 6	Lymph node dissection
Step 7	Closure

VATS = video-assisted thoracic surgery.

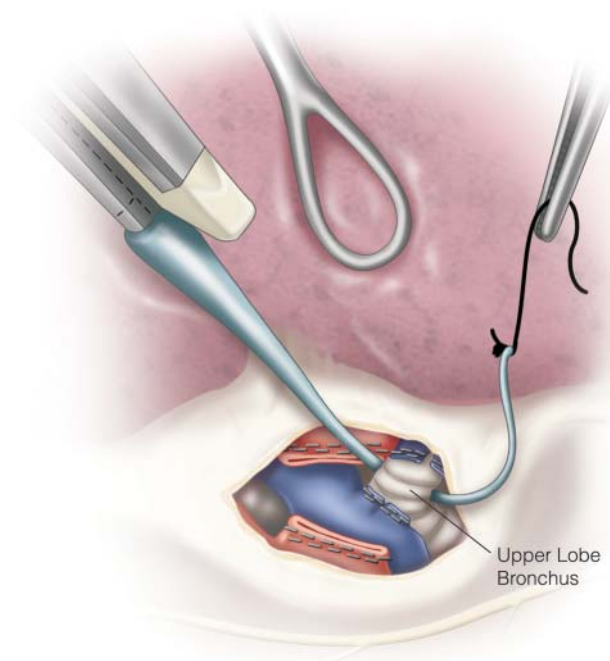


Figure 10 Division of the upper lobe bronchus.

using the endovascular stapler. The middle lobe bronchus is exposed and divided before the artery because it lies anterior to the pulmonary artery to the middle lobe. Caution should be exercised while dissecting around the middle bronchus so as not to injure the arterial branches to the middle lobe. Maciejewski described two arterial branches of the pulmonary artery to the middle lobe in 57% of the patients and a single artery penetrating the middle lobe in 43% of patients.³⁰ The length of arteries can be up to 30 mm and the diameter up to 10.6 mm. The pulmonary artery branches are dissected free, isolated, and divided with the endovascular stapler. The fissure is completed, and the middle lobe is removed in a specimen endo-bag through the access port.

Right lower lobectomy The camera port is inserted in the seventh ICS in the posterior axillary line. The posterior port is placed either at the tip of the scapula or immediately behind it. The access port is placed directly over the fissure between the middle and lower lobe at the level of the inferior pulmonary vein. Ring forceps are used to retract the middle lobe medially and the lower lobe posteriorly. Next, the lower lobe is retracted superiorly and the inferior pulmonary ligament is taken down with either electrocautery device (Bovie) or Harmonic shears (Ethicon Endo-Surgery, Cincinnati, OH). Level 9 lymph nodes are taken during this step of the operation. Next, the posterior mediastinal pleura is opened at the level of the inferior pulmonary vein and the dissection continues posteriorly between the posterior hilum and the esophagus. If a level 8 lymph node is found at this location, it is removed as well. This dissection is carried out to the level of the azygos vein. The lung is then retracted anteriorly toward the anterior mediastinum. Next, level 7 (subcarinal) lymph nodes are dissected with two endo-Kittner dissectors and removed. At this point, most of the pleura along the

hilum has been opened posteriorly and the inferior pulmonary vein dissected. Next, the apex of the lung is gently grasped with a ringed forceps and retracted toward the diaphragm. This maneuver exposes the paratracheal lymph nodes. The pulmonary artery is then identified just under the surface of the pleura at the fissure. The visceral pleura overlying it is opened. A tunnel of visceral pleura is created over the pulmonary artery by gently pulling the visceral pleura toward the chest wall and dissecting it with endo-Kittners. This maneuver allows for identification of the middle lobe bronchus. Once this tunnel is developed, the fissure is completed posteriorly with the endo-stapler. At this point, the lower lobe pulmonary artery is visualized. A Harken clamp is passed under the artery, and the artery is dissected. The flat tip of a 35 mm vascular load stapler (white load) is passed under the pulmonary artery to the lower lobe and the basilar trunk is transected. The lung is retracted upwards and toward the anterior mediastinum. The inferior pulmonary vein is then transected with the same technique as for the pulmonary artery. The vascular stapler is brought in from the access incision toward the back while lifting the lung up with the ring forceps through the posterior port. The lung is then pulled upwards, the lower lobe bronchus is dissected out, and the stapler is applied but not fired. The anesthesiologist should then inflate the middle lobe. Bronchoscopy is also performed, and the orifice to the middle lobe is visualized. Only after these maneuvers have been performed is the bronchus to the lower lobe transected. The lobe is placed in the endo-bag and brought out through the access port incision.

Left-Side Resections

Left upper lobectomy The left upper lobectomy is technically the most challenging approach because of the anatomic variability in the pulmonary artery branches as well as a common pulmonary vein trunk that drains to the back of the left atrium. Maciejewski reported that in most cases of his series, there were four, and, in a few cases, up to seven, branches of the pulmonary artery to the upper lobe, measuring 30 mm in length and 12 mm in diameter.³¹ In about 50% of the cases, the branches were divided in (a) apicoanterior trunk, (b) lingular, and (c) one or two subsegmental branches. In 25% of the cases, almost all segmental branches penetrated into the lobe separately. In 20% of the cases, a single apicoposterior trunk or independent segmental or subsegmental branches were present. Only in 5% of the cases did the branches include the apicoposteroanterior trunk and the remaining segmental and subsegmental branches.

Although port placement is similar to that for right upper lobectomy, the camera port is placed more posteriorly through a seventh or sixth ICS in the anterior axillary line, to avoid obstruction of the camera view by the heart and the pericardial fat pad. Once all ports have been placed, dissection of the anteroposterior window lymph nodes is carried out. This provides information about metastatic nodal spread. It also opens up the space around the artery and vein. The posterior port is placed just behind the tip of the scapula. The lung is retracted posteriorly, the hilum is opened anteriorly, and the superior pulmonary vein is dissected free. Caution must be exercised during this phase of the dissection to avoid injuring the back wall of the vein while it is being dissected off the

airway. The upper lobe is retracted posteriorly and the lower lobe is retracted somewhat anteriorly, toward the pericardium, splaying out the fissure. The pulmonary artery is usually found in the fissure, where it is visualized as a white, shiny structure. Dissection of the pulmonary artery creates a space on the top of the artery, a so-called vascular tunnel that allows one to complete the fissure with a stapler, thereby avoiding problems with air leak. A ringed forceps is placed through the fourth ICS to access the incision anteriorly. The lung is now moved anteriorly. The endo-Kittners are placed through the posterior port to dissect the lymph nodes located above the pulmonary artery as it traverses into the fissure. The first apical branch of the pulmonary artery is dissected free and transected with an endoscopic GIA vascular stapler introduced via the posterior port. The anterior aspect of the fissure is opened with one or two applications of an endoscopic GIA stapler introduced via the access incision. The bifurcation of the left upper and left lower lobe bronchi is identified, and the left upper lobe bronchus is transected with an endoscopic GIA stapler with 4.8 mm staples introduced via the posterior port. A ringed forceps is used to retract the stump of the bronchus laterally, which facilitates exposure of several branches of the pulmonary artery, including the lingular artery. These branches are transected individually via the posterior port. The fissure is completed with an endoscopic GIA stapler with 4.8 mm staples through the posterior port and dividing it. The lobe is placed in the endo-bag and brought out through the access port incision. A 24 French chest tube is placed toward the apex of the lung.

Left lower lobectomy The camera port is placed in the eighth ICS in the posterior axillary line to provide exposure to the posterior hilum and to avoid crowding of the instruments. The access port is placed anteriorly in the fifth ICS. The posterior working port is usually posterior to the scapular tip in the sixth or seventh ICS. First, the lung is retracted superiorly and the inferior pulmonary ligament is identified and level 9 lymph nodes are sampled. The left lower lobe is held superiorly with a ring forceps through the posterior port, with the ligament under tension. A long-tipped electrocautery device, or ultrasonic scalpel, divides the ligament at the base of the inferior pulmonary vein. Next, the inferior pulmonary vein is completely dissected. Once the inferior pulmonary vein has been dissected free, an endoscopic GIA vascular stapler is placed via the utility incision to transect the vessel. The interlobar pulmonary artery is isolated within the fissure. The branches of the pulmonary artery to the left lower lobe are of three types: trunk, segmental, and subsegmental. In 70% of the cases, the branches penetrating the basal segments showed a treelike configuration; in 3% of the cases, the segments had a bushlike configuration; and in 27% of the cases, the branches had an intermediate anatomic configuration.³² The basilar trunk and the artery to the superior segment are identified, dissected, and divided with the endovascular stapler. The superior segmental artery is divided first and the basilar trunk next. This strategy avoids injury to the superior segmental branch with the stapler used to divide the basilar branches. Finally, the bronchus to the lower lobe is dissected and divided with an endo GIA 4.8 mm stapler through the access incision. Attention must be paid

to avoid impingement on the lingular bronchus. In cases of incomplete fissure, the fissure between the lingula and lower lobe should be opened prior to dissection of the pulmonary artery to facilitate subsequent arterial exposure.

Pneumonectomy

This operation is best performed through an open thoracotomy.

VATS Mediastinal Lymph Node Dissection

OPERATIVE TECHNIQUE

For biopsy of the aortopulmonary window nodes or anterior mediastinal masses, VATS mediastinal lymph node dissection is often performed as an alternative to a Chamberlain procedure and is thought by some surgeons to provide better exposure and a superior cosmetic result. The thoracoscope is inserted at the fifth or sixth ICS in the posterior axillary line. Instruments for retracting the lung inferiorly are introduced via a port at the seventh ICS in the midaxillary line. Instruments for dissecting nodes are introduced through ports placed at the fourth ICS in the anterior axillary line and in the auscultatory triangle. The lymph nodes are dissected free with graspers (e.g., curved sponge sticks or polyp forceps), scissors, the electrocautery device, and endoscopic hemostatic clips. A similar approach can be used for biopsy of other mediastinal nodes, including the paratracheal and periesophageal nodes. Dissection of level 4 and level 2 nodes on the right is facilitated by transection of the azygos vein. It is more difficult to do a complete en bloc subcarinal lymph node dissection on the left than on the right with this method, although nodal sampling of this region by means of VATS is certainly feasible, especially when an access incision is used.

TROUBLESHOOTING

Care should be taken not to injure the phrenic nerve as it courses along the superior vena cava on the right and across the anterior aspect of the aortopulmonary window on the left. The vagus nerve should be visualized and the origin of the recurrent laryngeal nerve avoided during dissection. The recurrent laryngeal nerve is easily injured on the left side, where it passes around the ligamentum arteriosum before traveling under the aortic arch; however, it can also be injured on the right side if mediastinal lymph node dissection is carried too high superiorly along the origin of the innominate artery.

It is unwise to perform a VATS mediastinal lymph node dissection after induction chemotherapy or chemoradiotherapy because the lymph nodes will often be densely adherent to surrounding structures. This is especially true on the right side, where the superior mediastinal lymph nodes usually adhere densely to the superior vena cava, the azygos vein, and the right main pulmonary artery. A thoracotomy, with extensive exposure and sharp dissection, is usually required for a safe and complete mediastinal lymphadenectomy.

All lymphatic branches should be ligated during node biopsy or dissection to prevent a chyle leak. There are often large lymphatic branches in the distal right paratracheal area. In addition, the thoracic duct can be injured if periesophageal or posterior mediastinal lymph nodes are being removed.

VATS Esophagectomy

OPERATIVE TECHNIQUE

Transthoracic Approach

The most widely accepted method of performing a thoracoscopic and laparoscopic esophagectomy is the technique developed by Luketich and colleagues.³³ All patients undergo bronchoscopy and on-the-table esophagogastroduodenoscopy (EGD) to make a final assessment of the location of the tumor and the suitability of the gastric conduit for reconstruction. If the EGD, endoscopic ultrasonography, or CT scan findings suggest gastric extension, T4 local extension, or possible metastases, we perform a staging laparoscopy, a thoracoscopy, or both. Patients are intubated with a double-lumen tube and placed in the left lateral decubitus position. The surgeon stands on the right and the assistant on the left. Four thoracoscopic ports are used [see Figure 11]. A 10 mm camera port is placed at the seventh to eighth ICS, just anterior to the midaxillary line. A 5 mm port is placed at the eighth or ninth ICS, posterior to the posterior axillary line, for the Harmonic shears. A 10 mm port is placed in the anterior axillary line at the fourth ICS; this port is used to pass a fan-shaped retractor to retract the lung anteriorly and allow exposure of the esophagus. The last 5 mm port is placed just posterior to the scapula tip; it is used to place instruments for retraction and countertraction. In most patients, a single retracting suture (0-Endostitch, US Surgical, Norwalk, CT) is placed near the central tendon of the diaphragm and

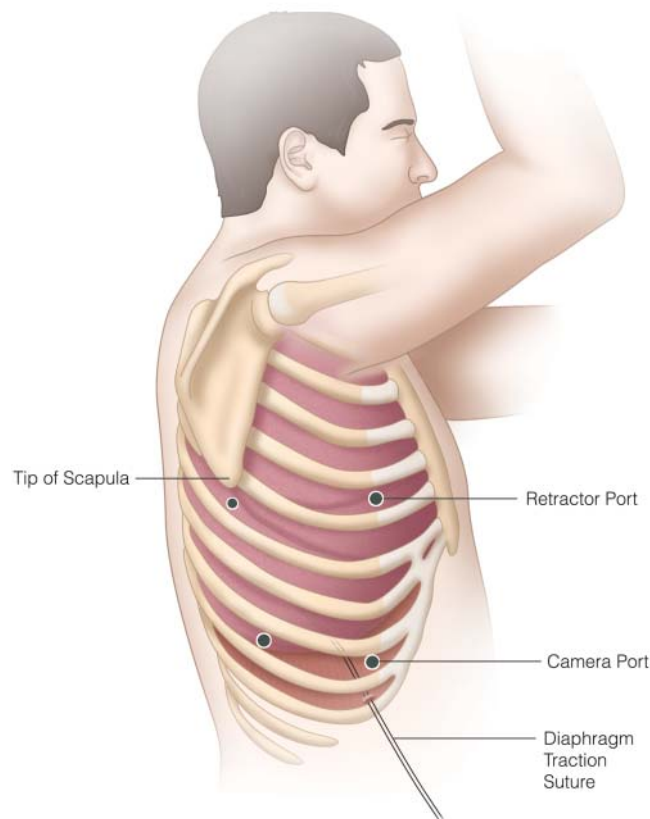


Figure 11 Thoracic port placement for minimally invasive esophagectomy.

brought out through the inferior anterior chest wall through a 1 mm skin incision, providing downward traction on the diaphragm and allowing exposure of the distal esophagus.

The intrathoracic esophagus is exposed by dividing the inferior pulmonary ligament. The mediastinal pleura overlying the esophagus is opened, and dissection is carried out cephalad toward the azygos vein. The azygos vein is divided with an endoscopic stapler [see Figure 12]. Care is taken to preserve the mediastinal pleura above the azygos vein. This maneuver helps to maintain the gastric tube in the posterior mediastinum. By keeping the mediastinal pleura intact near the thoracic inlet, it may help to seal the plane around the gastric tube, preventing downward extension of a cervical leak into the chest. Circumferential mobilization of the esophagus is performed up to the level of 1 to 2 cm above the carina, including all surrounding lymph nodes; periesophageal tissue and fat; the plane along the pericardium, aorta, and contralateral mediastinal pleura up to but not including the thoracic duct; and the azygos vein laterally. Esophageal branches of the aorta are cut with a Harmonic scalpel. No effort is made to find the thoracic duct. A Penrose drain is placed around the esophagus to facilitate traction and exposure [see Figure 12].

The entire intrathoracic esophagus is mobilized from the thoracic inlet to the diaphragmatic reflection. As the dissection proceeds toward the thoracic inlet, care is taken to stay near the esophagus to avoid trauma to the posterior membranous trachea and the recurrent laryngeal nerves. Once the esophagus is completely mobilized in the chest, a single 28 French chest tube is inserted through the most anterior and inferior port and the lung is inflated to search for any air leaks from the trachea and proximal bronchus. The thoracic ports are closed, and the patient is turned to the supine position. The surgeon remains on the patient's right; the patient is positioned in the steep reverse Trendelenburg position.

Five abdominal ports (four 5 mm and one 11 mm) are used for the dissection [see Figure 13]. The gastrohepatic ligament is divided. The right and left crura of the diaphragm are dissected; division of the phrenoesophageal membrane is avoided at this stage of the operation because this may cause loss of the pneumoperitoneum into the chest cavity and lead

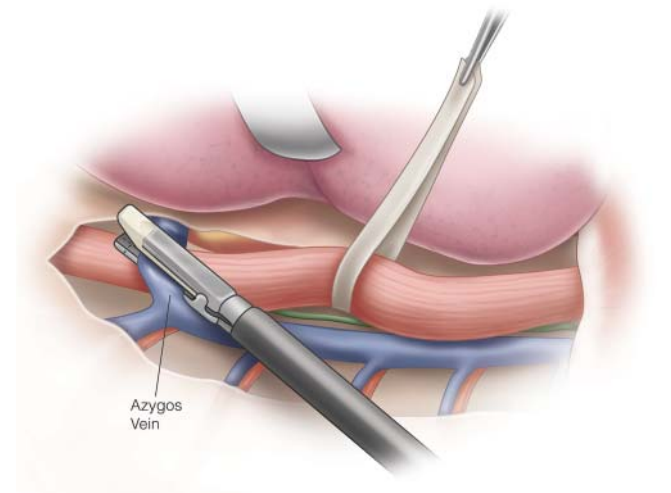


Figure 12 Stapling of the azygos vein.

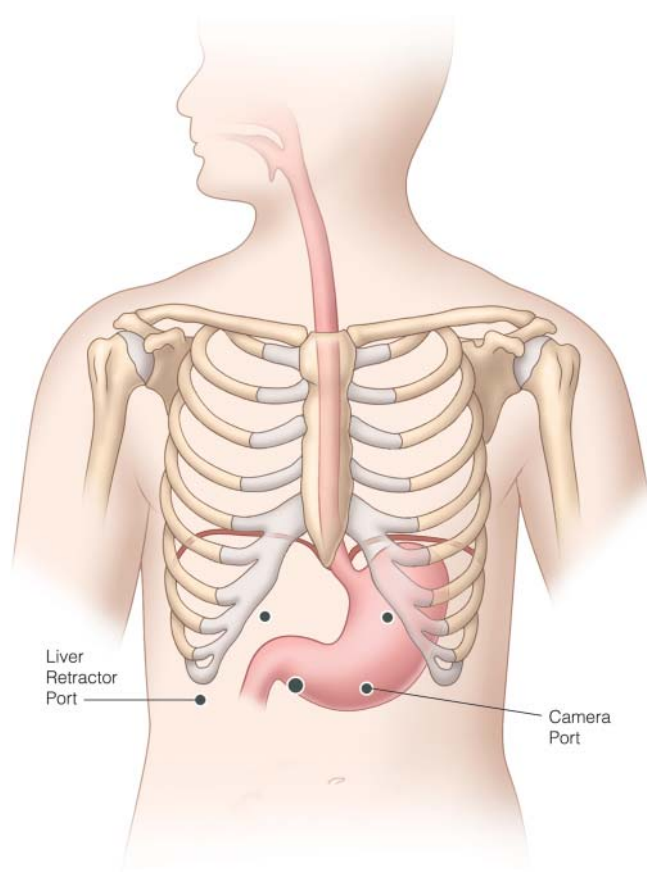


Figure 13 Abdominal port placement.

to technical difficulties. The stomach is mobilized by dividing the short gastric vessels using the Harmonic scalpel. The gastrocolic omentum is divided, with care taken to preserve the right gastroepiploic arcade [see Figure 14]. The stomach is

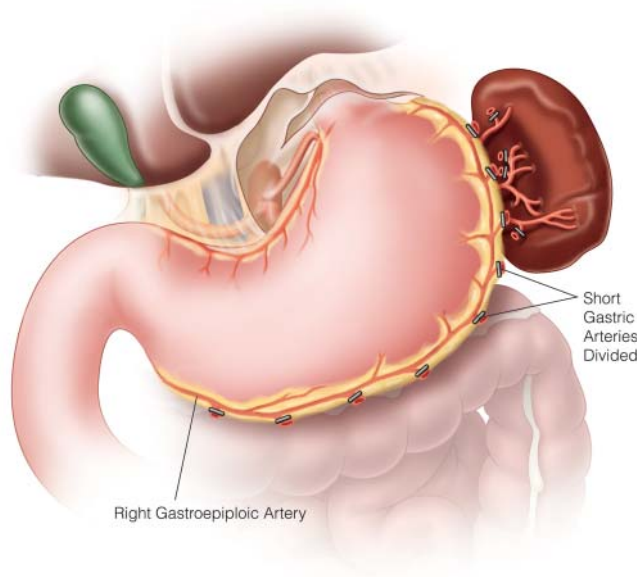


Figure 14 Division of the gastrocolic omentum along the greater curvature of the stomach and dissection of the hiatus.

retracted superiorly, and the left gastric vessels are identified. The left gastric artery and vein can be divided from the retrogastric or lesser curve view, depending on the anatomy, using the Endo-GIA stapler.

PYLOROPLASTY

The Harmonic scalpel is used to open the pylorus, and the Endo Stitch (2.0, US Surgical) is used to close the pylorus transversely [see Figure 15]. A gastric tube is then constructed by dividing the stomach starting at the lesser curvature and preserving the right gastric vessels with the 4.8 mm stapler (Endo-GIA II, US Surgical) [see Figure 16]. There is some variability in the construction of the gastric tube based on the characteristics of the tumor. It may be necessary to construct a slightly more narrow tube or to resect some of the proximal stomach in tumors with significant gastric extension. If gastric extension of the tumor is significant, the resection of the stomach is larger and an intrathoracic anastomosis is performed. Currently, we prefer a gastric tube of 5 to 6 cm in diameter. Extreme caution must be used when manipulating the gastric tube during mobilization and stapling to avoid trauma. The most cephalad portion of the gastric tube is then attached to the esophageal and gastric specimen using two 2-0 endo-sutures. An additional superficial stitch may be placed on the anterior proximal gastric tube to facilitate orientation and prevent twisting as the tube is brought up into the neck [see Figure 17]. A feeding jejunostomy tube is done laparoscopically. First, a proximal limb of jejunum (25 cm distal to the ligament of Treitz) is attached to the anterior abdominal wall in the left lateral quadrant with the endo-stitch. An additional 10 mm port in the right lower quadrant may be inserted to facilitate suturing of the jejunum

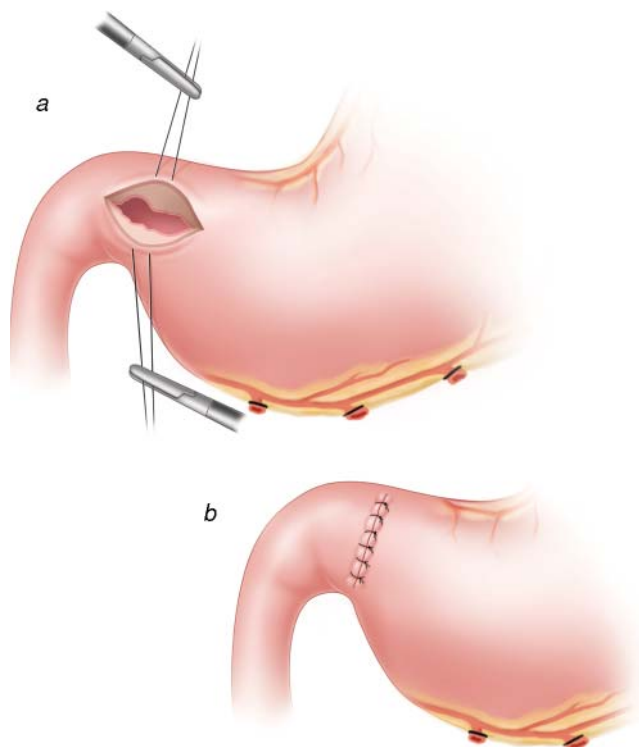


Figure 15 Pyloroplasty. (a) Pyloroplasty is performed using Harmonic shears. (b) Transverse closure of the pyloroplasty with endo-stitch technique.

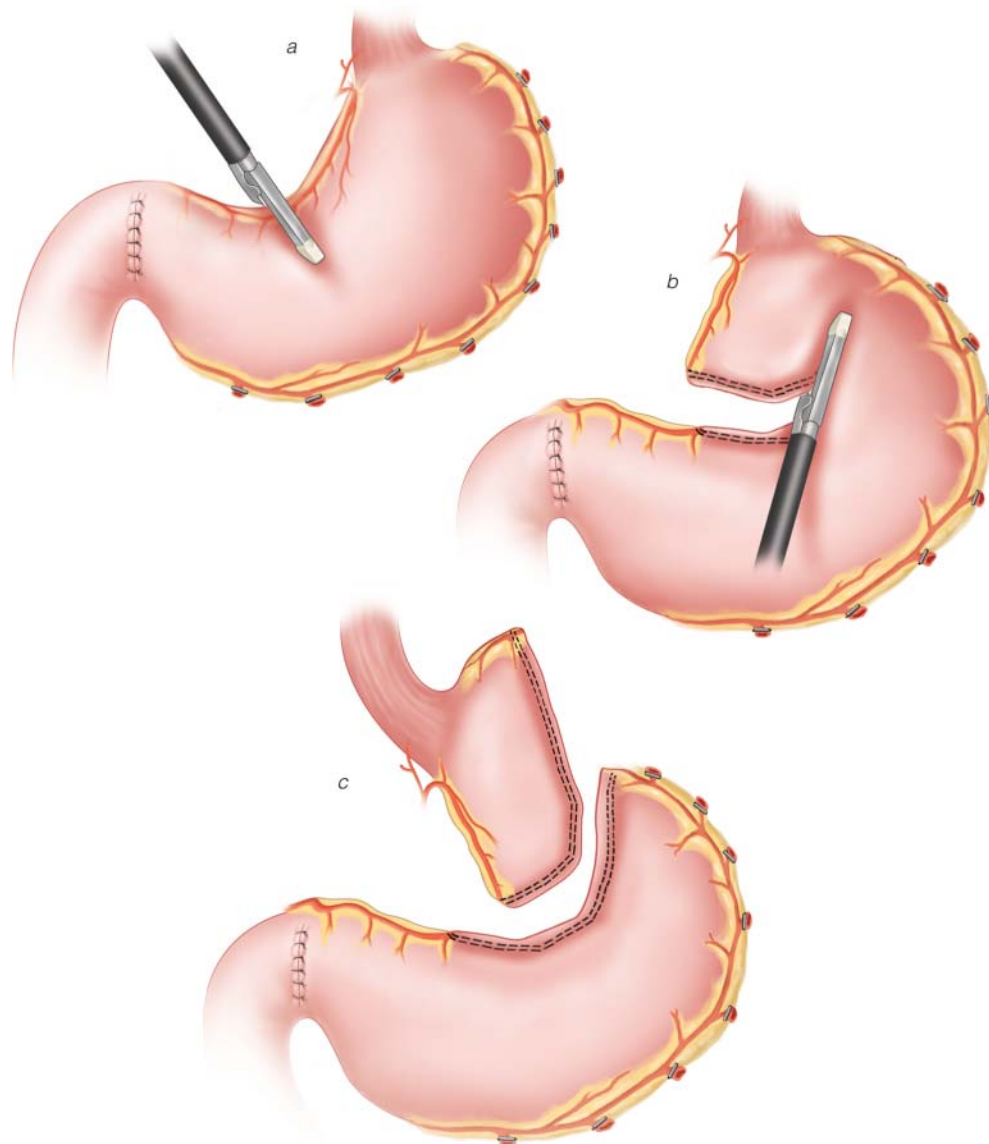


Figure 16 Creation of a gastric tube. (a) The gastric tube is created by dividing the stomach starting at the distal lesser curve, preserving the right gastric vessels. (b) A 5 to 6 cm in diameter gastric tube is preferred. (c) Division of the gastric tube is from the esophagus.

to the anterior abdominal wall. A needle catheter (Compact Biosystems, Minneapolis, MN) is placed percutaneously into the peritoneal cavity. Under direct laparoscopic vision, the guide wire and catheter are directed into the loop of jejunum that has been tacked to the anterior abdominal wall. The entry site of the needle catheter J tube is tacked completely to the anterior abdominal wall for a distance of several centimeters.

The last step in the abdominal operation is the dissection of the phrenoesophageal membrane, which was delayed earlier to minimize the risk of losing the pneumoperitoneum into the mediastinum. The right and left crura are partially divided to permit easy passage of the gastric specimen and tube through the hiatus and to prevent later gastric outlet obstruction.

Next, a 4 to 6 cm horizontal neck incision is made [see Figure 18]. The cervical esophagus is exposed. Careful

dissection is performed inferiorly until the thoracic dissection plane is encountered. This is generally quite easy because the VATS dissection is continued well into the thoracic inlet. In addition, we leave the Penrose drain around the esophagus during the thoracic dissection and push the drain into the periesophageal plane at the thoracic inlet so that it is easily visualized during the neck dissection. This maneuver allows the surgeon to pull the Penrose drain out through the neck to facilitate the neck dissection. The esophagogastric specimen is pulled out of the neck incision and the cervical esophagus is divided high (1 to 2 cm below the cricopharyngeal muscle). The specimen is removed from the field. An anastomosis is performed between the cervical esophagus and gastric tube using a GIA stapler [see Figure 19]. Next, the surgeon returns to the laparoscopic view and gently pulls downward on the pyloroantral area to retrieve any excess gastric tube that may have been pulled up into the chest during the neck

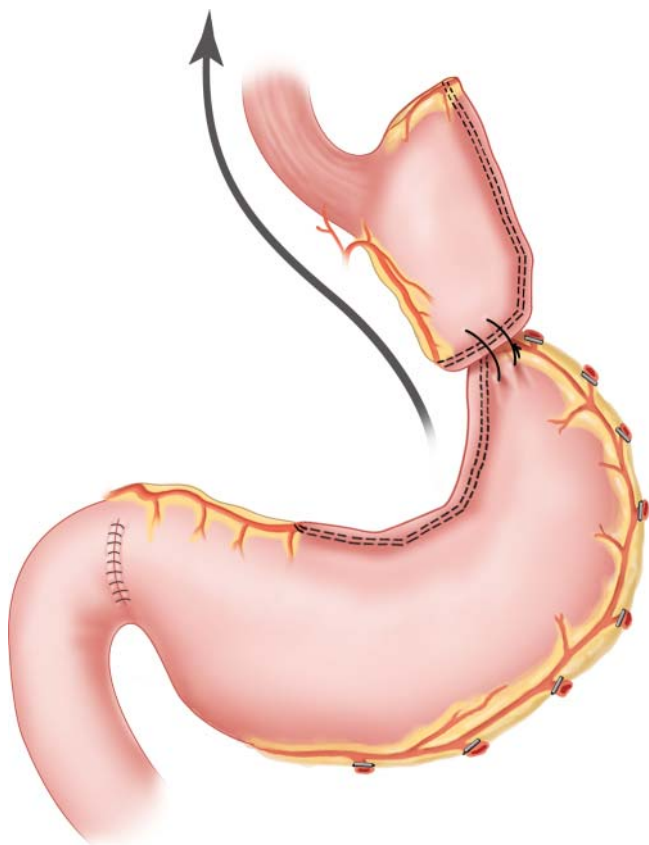


Figure 17 Pulling up the gastric tube for cervical anastomosis.

anastomosis and mobilization. The laparoscopic pull is performed gently and only until the assistant at the neck observes the tube beginning to be pulled down at the level of the anastomosis. The esophagogastric cervical anastomosis is placed high in the neck, just below the level of the cricopharyngeus, to ensure adequate removal of any islands of Barrett and to ensure that any anastomotic leaks will be more likely to drain out via the neck. Three tacking sutures are placed: one between the left crus and stomach just anterior to the greater curve arcade; the second on the right side of the gastric tube just above the right gastric vessels to the right crus; and the third suture anteriorly between the stomach and the diaphragm.

TROUBLESHOOTING

The technical problems associated with VATS esophagectomy are similar to those associated with open thoracic esophagectomy, including thoracic duct injury, recurrent nerve palsy, bleeding from the intercostal vessels, and anastomotic leakage. These problems are best prevented by obtaining good visualization of the superior and posterior mediastinum, which can be achieved by using a 30° angled thoracoscope. The most common reason for conversion to thoracotomy is the presence of a locally advanced tumor that necessitates extensive dissection for safe mobilization away from adjacent mediastinal structures.

To date, comparison of the results of VATS esophagectomy with those of open esophagectomy has not shown VATS to yield a significant decrease in major complications,

especially postoperative respiratory insufficiency and cardiac arrhythmias. As a result, most centers still prefer the standard open transhiatal or transthoracic approaches to esophagectomy. VATS may also be used in the management of postoperative chylothorax. The thoracic duct can be ligated thoracoscopically, although it is sometimes difficult to identify and ligate the primary site of a postoperative lymphatic leak without reopening the thoracotomy.

VATS Pericardial Window

OPERATIVE TECHNIQUE

Some surgeons create a pericardial window by means of VATS as an alternative to taking the subxiphoid approach or the left anterior thoracotomy approach. A double-lumen endotracheal tube is inserted with the patient under general anesthesia, and the patient is rotated into the right lateral decubitus position. Three access sites are used, with the thoracoscope inserted at the seventh ICS in the posterior axillary line and the instruments introduced through two ports, one at the tip of the scapula and the other at the sixth ICS in the axillary line. The pericardium is retracted with a grasper forceps, and scissors are used to resect 8 to 10 cm² areas of pericardium both anterior and posterior to the phrenic nerve. If indicated, talc pleurodesis can be performed to control an associated pleural effusion. One or two chest tubes are then inserted through the port-site incisions.

TROUBLESHOOTING

When a pericardial effusion causes cardiac tamponade, a subxiphoid approach is preferable to VATS for creating a pericardial window because it is safer to perform in a hemodynamically unstable patient. A VATS pericardial window is also inadvisable in patients with constrictive physiology or with intrapericardial adhesions discovered at the time of operation. Conversion to an open procedure with formal pericardiectomy is advisable under these circumstances.

VATS Procedures for Mediastinal Masses

A 1998 multicenter trial aimed at defining the role of VATS in the management of mediastinal tumors suggested that VATS can be used safely to diagnose and resect most middle and posterior mediastinal masses, especially in view of the typically benign nature of these tumors.³⁴

VATS thymectomy has been used to treat myasthenia gravis and thymoma. To date, only anecdotal experience has been reported, and no studies examining long-term outcomes have been published. Although a VATS approach to myasthenia gravis may appear attractive at first, it is not the least invasive approach to the thymus. Transcervical thymectomy is a minimally invasive approach to the thymus that does not require a chest incision, does not violate the pleural space, and allows most patients to be discharged home the next day. There is still a degree of controversy as to whether complete thymic resection, including all ectopic thymic tissue, is necessary to obtain clinical remission in patients with myasthenia gravis. For patients with a thymic mass, we prefer a trans-sternal approach. It is imperative to maintain oncologic surgical principles; accordingly, en bloc resection is emphasized so that pleural seeding is avoided and the risk of incomplete

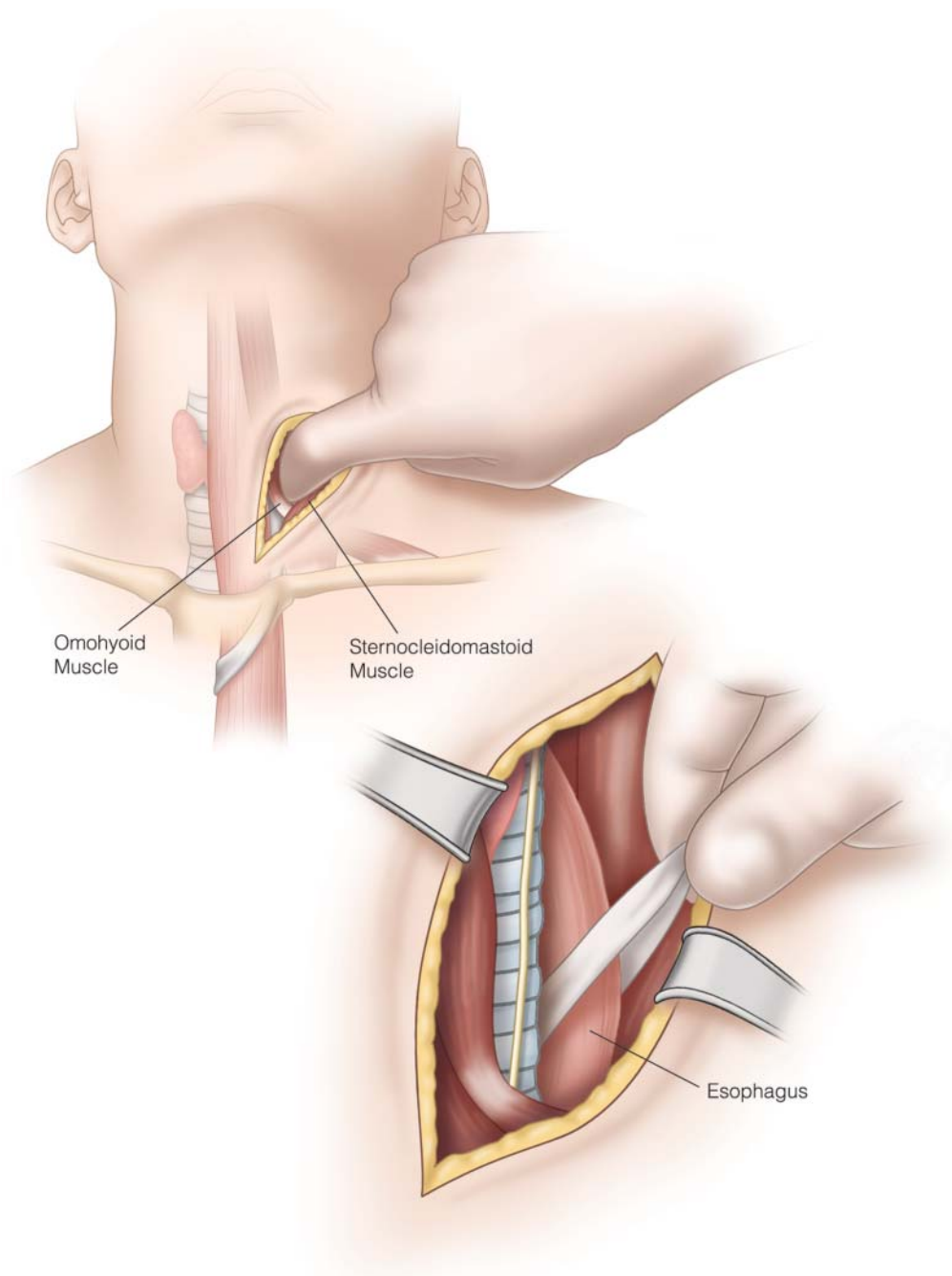


Figure 18 Neck incision.

resection is minimized. For patients with myasthenia gravis who do not have a thymoma, however, there is a need for prospective studies comparing VATS with other surgical approaches to thymectomy.

OPERATIVE TECHNIQUE

VATS has been used to resect masses in all of the mediastinal compartments. VATS resection is an ideal approach to posterior neurogenic tumors that do not extend into the neural foramen or the spinal canal. With the patient in the lateral decubitus position, the operating table is rotated

anteriorly so that the lung falls away from the paravertebral region. The port sites are placed anteriorly: the thoracoscope is inserted at the fifth ICS in the midaxillary line, a lung retractor is inserted at the sixth ICS in the anterior axillary line, and dissecting instruments are inserted at the second and fourth ICSs at the anterior axillary line. The mass is manipulated with a grasper to expose the posteriorly located pedicle, which is then dissected, ligated, and divided with the scissors, clip appliers, and electrocautery device.

For removal of anterior mediastinal masses, the port sites are placed in more posterior locations. The thoracoscope

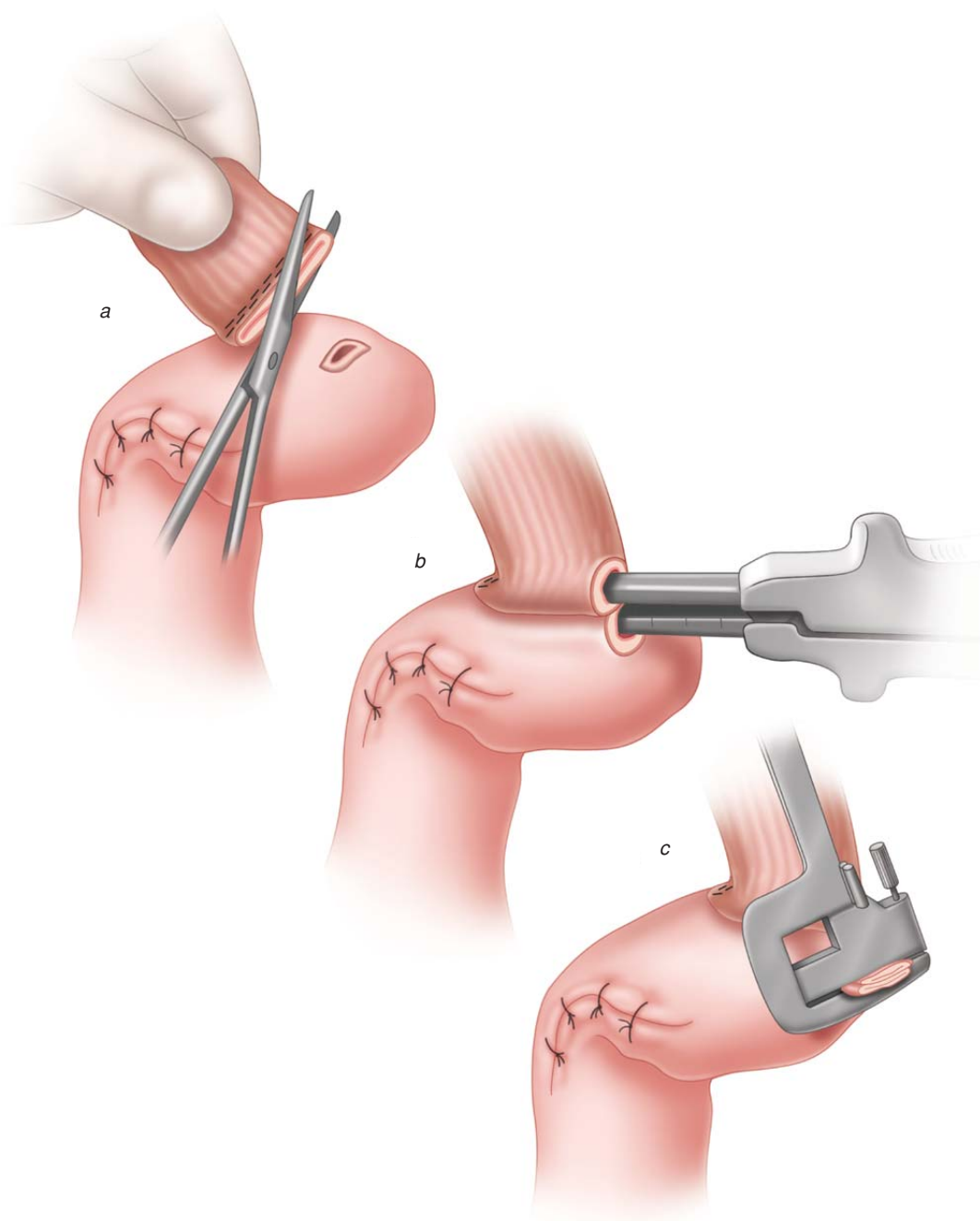


Figure 19 Cervical anastomosis. (a) The cervical esophagus is divided high (1 to 2 cm below the cricopharyngeal muscle). (b) A side-to-side esophagogastric cervical anastomosis is performed using a gastrointestinal anastomosis (GIA) stapler. (c) Closure of the anastomosis by a 45 mm transverse anastomosis stapler.

is introduced at the fifth ICS at the midaxillary or posterior axillary line, and instruments are inserted through two ports, one at the second ICS at the midaxillary line and the other at the fifth or sixth ICS at the anterior axillary line. The mass is retracted with a grasper and dissected free with a combination of sharp and blunt dissection, clip appliers, and the electrocautery device. A similar technique is used to resect middle mediastinal masses, most of which are pericardial or bronchogenic cysts. The access sites should be chosen according to the location of the mass on the preoperative CT scan.

Generally, however, the triangulated site placement used for pulmonary wedge resections provides more suitable exposure than the site placement used for anterior or posterior mediastinal masses.

TROUBLESHOOTING

The placement of the thoracoports and the positioning of the operating team for the resection of posterior mediastinal tumors or for thoracic disectomy differ significantly from the usual practice in most other VATS procedures. In place

of the standard arrangement of trocars in an inverted triangle, the viewing port is placed in the posterior axillary line and the operating ports in the anterior axillary line. The thoracic surgeon and the neurosurgeon both stand on the anterior side of the patient, each viewing a monitor on the opposite side. In addition, a 30° scope is essential for visualizing the intervertebral disk space.

Removal of dumbbell neurogenic tumors can be accomplished thoracoscopically if immediately preceded by posterior surgical removal of the spinal component of the tumor via laminectomy and intervertebral foraminotomy. Preoperative MRI is crucial for defining the extent of the tumor within the spinal canal. Resection of posterior mediastinal tumors is sometimes associated with significant bleeding from intercostal or spinal arteries. If such bleeding occurs, there should be no hesitation in converting to a thoracotomy. Ideally, anterior mediastinal cysts should be resected in toto to prevent recurrence. However, if the cysts are firmly adherent to vital mediastinal structures, partial excision with cauterization of the endothelial lining may be safer.

VATS Management of Thoracic Trauma

The major contraindication to thoracoscopy in thoracic trauma is hemodynamic instability. For major life-threatening injuries involving the great vessels and the mediastinum, thoracotomy is required to obtain expeditious control of injured structures. However, hemodynamically stable patients with certain thoracic problems (e.g., diaphragmatic injury; slow, continued intrathoracic bleeding; persistent air leakage; and empyema) may be diagnosed and often treated by means of VATS.^{35,36}

In the assessment of a trauma patient with a potential diaphragmatic injury, it is important not to ignore the high incidence of associated intra-abdominal injury. If intra-abdominal injury has been ruled out and there is concern about the presence of a diaphragmatic tear, thoracoscopic assessment of the diaphragm is justified. Such assessment allows a more thorough evaluation of the entire diaphragm than the laparoscopic approach, which is limited by the liver on the right side. In the largest series published to date, 60 of 171 patients who underwent thoracoscopy for penetrating chest injuries had diaphragmatic injuries that necessitated repair.³⁷

When a patient has an ongoing intrathoracic problem (e.g., persistent bleeding or a large air leak 24 to 48 hours after a traumatic injury), VATS should be considered before a thoracotomy is done because most problems encountered at this time (e.g., chest wall bleeding and laceration of the lung parenchyma) can be managed endoscopically, without the need for a thoracotomy.

TROUBLESHOOTING

The main pitfall in thoracoscopic evaluation of the diaphragm is failure to assess the abdomen appropriately and consequent failure to recognize an occult intra-abdominal injury. When laparoscopy is performed in a patient with a diaphragmatic injury, insufflation of CO₂ may cause a tension pneumothorax to develop on the side of the diaphragmatic injury. Accordingly, whenever diaphragmatic injury is a

possibility, the chest should be included in the operative field to allow chest tube insertion if required. Because thoracoscopy does not require CO₂ insufflation, it is safer in such situations.

VATS Sympathectomy and Splanchnicectomy

Thoracic sympathectomy is known to be the most effective treatment for upper limb hyperhidrosis, and VATS is now an accepted approach to this operation. The main indication for splanchnicectomy is intractable abdominal pain from unresectable malignancies (e.g., pancreatic or gastric carcinoma) and chronic pancreatitis. The effects of celiac ganglion blocks are transient, and surgical manipulation of this area is usually very difficult because of the primary disease process, previous operations, or both. In the past, thoracotomy was generally considered too invasive an approach to splanchnic denervation in these patients. Currently, however, because of the less invasive nature of thoracoscopy and the quicker recovery time associated with it, thoracoscopic splanchnicectomy is an attractive therapeutic option.

OPERATIVE TECHNIQUE

Sympathectomy

VATS sympathectomy is performed with the patient under general anesthesia and a double-lumen tube in place. Several techniques have been described. Initially, the common practice was to use three port sites: one for the thoracoscope at the third ICS in the midaxillary line, one at the third ICS in the anterior axillary line, and one at the tip of the scapula. Currently, the procedure is most often performed with two incisions: one at the fifth ICS at the border of the pectoralis and one at the fourth ICS in the anterior axillary line. The pleura is incised and divided from T2 to T5, and the sympathetic chain is dissected free with scissors and excised. For complete control of upper limb hyperhidrosis, VATS must be done bilaterally.^{38,39}

A 1998 study reviewed the long-term results in 630 patients who had undergone thoracoscopic sympathectomy for hyperhidrosis (median follow-up 15 years).⁴⁰ Of these patients, 68% were fully satisfied and 26% were only partially satisfied but nevertheless would agree again to the operation. Hyperhidrosis was cured permanently in 93%. Compensatory sweating and gustatory sweating occurred in 67% and 47% of cases, respectively. Overall, patients were well satisfied with the results and considered the compensatory sweating less of a problem than the original hyperhidrosis.

Splanchnicectomy

The technical aspects of VATS splanchnicectomy are quite simple: sound knowledge of the splanchnic anatomy and a basic set of thoracoscopic instruments are all that is needed. Single-lung ventilation is required. Three thoracoports are placed. A silk stitch is placed in the central tendon of the diaphragm and pulled through the most anterior and inferior port to allow better visualization of the splanchnic nerves. The camera is also placed through this port. An endoscopic grasper and an endoscopic scissors with an electrocautery attachment are used to remove the nerve segment from T5 to T9. The greater and lesser splanchnic nerves are resected. The least splanchnic nerve is rarely visualized.

TROUBLESHOOTING

Care should be taken to identify the first and second ribs. Division of the sympathetic trunk at the level of the first rib causes Horner syndrome and does not reduce palmar hyperhidrosis. Division of the rami communicantes rather than the main sympathetic trunk reduces the incidence of undesirable side effects, especially compensatory hyperhidrosis of the trunk, but its overall success rate in controlling upper limb hyperhidrosis is lower. Abolition of only the T2 and T3 ganglia may control palmar hyperhidrosis without being as likely to result in unacceptable compensatory truncal sweating. Some have advocated limited T3 sympathectomy for primary hyperhidrosis to prevent compensatory sweating.⁴¹ Target areas for axillary sweating also include T4 and T5. In addition, an accessory sympathetic nerve fiber that runs lateral to the sympathetic chain (known as the nerve of Kuntz) should be sought and, if identified, divided. Compensatory hyperhidrosis of the inner thighs is a common complication. Neuralgia is frequent after VATS sympathectomy. Some authors advocate a 2-day postoperative course of dexamethasone to reduce the incidence of this problem.⁴²

Miscellaneous VATS Procedures

Several other procedures have been performed by VATS, including ligation of the thoracic duct⁴³ and resection of the adrenal gland.⁴⁴ For adrenal resection, three incisions are placed at the ninth or 10th ICS, extending from the anterior axillary line to the posterior axillary line. A fan retractor is inserted through a radial incision in the diaphragm and used to retract the perirenal fat. The adrenal gland is dissected free and removed, and the associated vessels are clipped or cauterized.

Cost Considerations

It is hard to estimate the cost-effectiveness of VATS procedures because the instrumentation, the types of procedures performed, and the surgical expertise with these operations are all still evolving. Initially, VATS procedures proved expensive for several reasons (e.g., the cost of purchasing video and endoscopic equipment, the cost of disposable instrumentation, and the need for long operating times as surgeons and nursing staff gained experience with the procedures). Soon after VATS was introduced, a study from the Mayo Clinic compared the cost of performing VATS

pulmonary wedge resections with that of the same operation done by thoracotomy.⁴⁵ The VATS approach was associated with substantially shorter hospital stays but also with increased operating room costs; hence, the use of VATS did not result in any significant overall savings. Since that study, however, as some VATS procedures (e.g., pulmonary wedge resection) have become standard operations and more reusable instrumentation has become available, the cost of VATS has undoubtedly decreased. Whether other, more complex VATS procedures (e.g., thoroscopic esophagectomy) are cost-effective remains to be determined.

Within this context, the Society of Thoracic Surgeons (STS) and the American Association for Thoracic Surgery (AATS) formed a joint committee to establish standards and guidelines for training and certification in VATS.⁴⁶ As a result of the educational efforts of this committee, many surgeons were trained within a short time, and VATS was quickly incorporated into thoracic surgical practice and residency training. The important considerations with respect to the training and practice of VATS have been well articulated.^{46,47}

VATS is not minor surgery: it is a minimally invasive, complex intrathoracic procedure that should be performed only by persons who are familiar with intrathoracic anatomy and pathology and are fully competent to manage complications and make intraoperative decisions in such a way as to ensure safe outcomes for thoracic surgical patients. The complications encountered during thoracoscopic operations are potentially immediately life-threatening, whereas those encountered during other endoscopic procedures usually are not. For that reason, VATS procedures should not be performed by anyone—surgeon or nonsurgeon—who lacks the training and experience to perform immediate thoracotomy and repair of intrathoracic injuries.

Conclusion

Since its reintroduction into clinical practice in the early 1990s, VATS has been investigated in a scholarly and academically rigorous manner. It represents a paradigm for the evaluation of surgical innovation, leading to safe and effective application in patients. This chapter describes the most common video-assisted thoracic procedures performed in the current practice of thoracic surgery.

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Acknowledgments

Figures 8–19 Christine Kenney

11 MEDIASTINAL PROCEDURES

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Procedures for Lesions of the Anterior Mediastinum

More than half of all mediastinal masses arise from the anterior compartment. Most primary malignancies of the mediastinum also develop in the anterior mediastinum. Because of the narrowness of the space that makes up the thoracic inlet, as well as the presence of the trachea and esophagus traversing this region, anterior mediastinal masses become symptomatic earlier than their counterparts in other anatomic spaces of the mediastinum. Whereas adults with masses of the middle or posterior mediastinum usually report no significant symptoms, more than 50% of patients with anterior mediastinal masses present with chest pain, fever, cough, dyspnea, dysphagia, or vascular obstruction. Thymic neoplasms and lymphoma, the two most common masses in the anterior mediastinum, may have systemic manifestations (e.g., weakness associated with myasthenia gravis [MG] or symptoms associated with International Working Formulation [IWF] group B lymphoma).

In what follows, we focus on surgical approaches to the diagnosis and treatment of the more common neoplasms of the anterior mediastinum, including thymic tumors, lymphomas, and germ cell tumors. Embryologic anomalies and neoplasms arising from normal structures in this region broaden the differential diagnosis [see Table 1]. Finally, we address thymectomy for MG, a procedure that is frequently performed even in the absence of neoplastic disease.

PREOPERATIVE EVALUATION

In a patient with an anterior mediastinal mass, it is frequently possible to make a strong provisional diagnosis of the tumor type on the basis of clinical evaluation and diagnostic imaging.¹ As noted (see above), the presence of systemic manifestations may be helpful. Physical examination must include examination of peripheral lymph node groups and testes. Computed tomography (CT) yields valuable information about the anatomic location of the tumor, its characteristics (i.e., fatty, solid, or cystic), and its degree of invasiveness (if any) [see Figure 1]. Occasionally, magnetic resonance imaging (MRI) provides useful additional information about the obliteration of normal tissue planes. Positron emission tomography (PET) generally demonstrates strong fluorodeoxyglucose (FDG) uptake in lymphoma; thus, PET and CT may be useful in guiding sites for biopsy in that disease. Several small trials have been conducted evaluating the utility of PET in the evaluation of thymoma.² Uptake of FDG appears to be greater in thymoma than in thymic hyperplasia, and thymic carcinomas appear to have the highest FDG uptake. The reproducibility and thus diagnostic utility of this finding, though, have yet to be clearly elucidated.

Lymphoma is the most likely diagnosis in persons younger than 40 years, and the presence of IWF group B symptoms further raises the level of suspicion. The presence of palpable

remote adenopathy or an elevated serum lactate dehydrogenase level is also suggestive.³ When peripheral nodes are palpable, the diagnosis may be most easily obtained by excising one of them. Patients with suspected lymphoma who have an isolated anterior mediastinal mass should undergo core-needle biopsy or a Chamberlain procedure (anterior mediastinotomy), depending on the pathologists' level of comfort with classifying lymphoma on the basis of small specimens at one's institution. Resection of lymphoma is not indicated; it may be avoided by performing a diagnostic biopsy whenever lymphoma is suspected.

Unlike lymphomas, thymic neoplasms are uncommon before the fourth decade of life. Thymoma [see Figure 1a] may be associated with any of several paraneoplastic syndromes. MG occurs in conjunction with a pathologic condition of the thymus—either thymoma or thymic hyperplasia—in 80 to 90% of cases. Thymoma may also be associated with pure red cell aplasia, agammaglobulinemia, systemic lupus erythematosus, and various autoimmune disorders. The presence of any of these associated syndromes essentially clinches the diagnosis of thymoma. Autoantibodies to the acetylcholine receptor (anti-AChR antibodies) should be measured: their presence is diagnostic of MG, and they are found in nearly 60% of patients who have thymoma without neurologic symptoms.⁴ Once the diagnosis of thymoma has been made, the goal is to proceed to direct resection without preliminary biopsy; these tumors have a predilection for local recurrence once the capsule has been violated.

The majority of germ cell tumors, whether malignant or benign, are diagnosed in the second or third decade of life. Benign teratomas are usually well encapsulated, with frequent recapitulation of one or more tissue elements seen on radiography.⁵ The appearance of the lesions on CT is often diagnostic [see Figure 1b]. Surgical extirpation is the mainstay of treatment for these mature germ cell tumors, and biopsy is not indicated. Malignant germ cell tumors, on the other hand, are treated with primary chemotherapy, radiotherapy, or both; when suspected, these patients should undergo biopsy rather than being taken directly to resection. Characteristic serum tumor markers, including β -human chorionic gonadotropin (β -hCG) and α -fetoprotein (AFP), are elaborated by most malignant germ cell neoplasms but are not found in benign germ cell tumors.⁶ Elevation of the AFP level beyond 500 ng/mL is considered diagnostic of a nonseminomatous component in a malignant germ cell tumor and is usually associated with a concomitant increase in serum β -hCG levels.⁷ In the absence of any marked elevation in the AFP or β -hCG level, percutaneous needle biopsy usually suffices to establish the diagnosis.

OPERATIVE PLANNING

Biopsy versus Resection

Clearly, the decision whether to perform a biopsy of an anterior mediastinal mass is not a simple one. Routine biopsy

Table 1 Differential Diagnosis of Anterior Mediastinal Mass

Neoplastic conditions
Thyroid
Substernal goiter
Ectopic thyroid tissue
Thymus
Thymic hyperplasia
Thymoma
Thymic carcinoma
Thymic carcinoid
Thymic small cell carcinoma
Thymic cyst
Thymolipoma
Teratoma
Mature teratoma
Immature teratoma
Teratoma with malignant component
Lymphoma
Ectopic parathyroid with adenoma
Germ cell tumors
Seminoma
Nonseminoma
Yolk sac tumor
Embryonal carcinoma
Choriocarcinoma
Hemangioma
Lipoma
Liposarcoma
Fibroma
Fibrosarcoma
Cervicomedastinal hygroma
Infectious conditions
Acute descending necrotizing mediastinitis
Subacute mediastinitis
Vascular conditions
Aneurysm of aortic arch with projection in anterior mediastinum
Innominate vein aneurysm
Superior vena cava aneurysm
Dilation of superior vena cava (with anomalous pulmonary venous return)
Persistent left superior vena cava

should be avoided, not only because of the cost and the unnecessary morbidity but also because of the risk that biopsy may spread thymoma. The choice to proceed with biopsy should be made according to which tumor type is believed to be most likely on the basis of the diagnostic workup.

Well-encapsulated lesions that are believed not to represent lymphoma are resected, without a preceding biopsy, for both diagnosis and treatment. Neoplasms that commonly fall into this category include noninvasive thymomas, mature teratomas, mesenchymal tumors, and, occasionally, benign cysts. Most patients with MG should be offered thymectomy whether they have a thymic mass or not.

When lymphoma is suspected, biopsy is required. The technique employed should be minimally invasive while still permitting the acquisition of a sufficient tissue sample. CT-guided core-needle biopsy may be attempted, but, frequently, this technique does not provide enough tissue for the analyses required to classify the tumor.^{8,9} Thus, the Chamberlain procedure (anterior mediastinotomy) is recommended in these situations.

For locally invasive or frankly unresectable anterior mediastinal masses other than those felt likely to represent

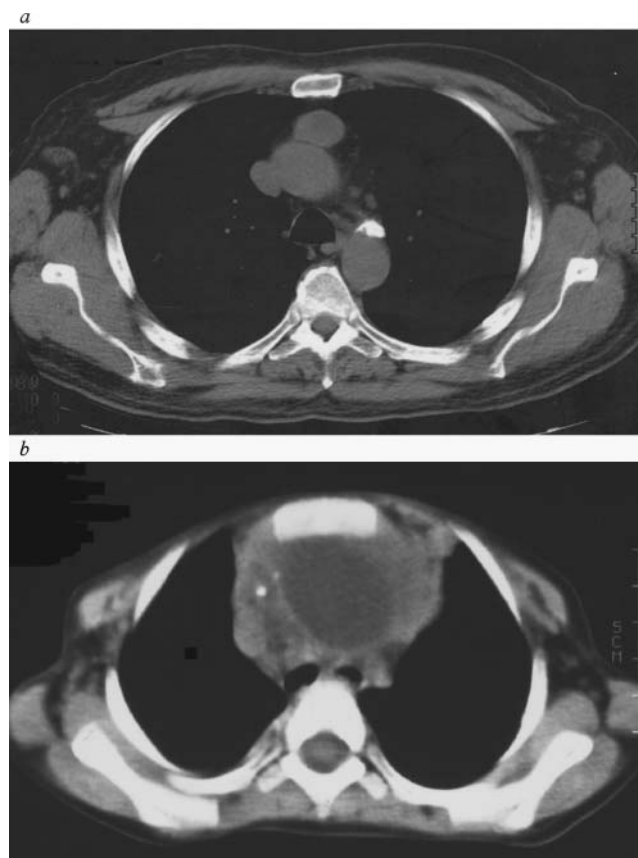


Figure 1 (a) Computed tomography (CT) scan shows a well-encapsulated anterior mediastinal mass—a thymoma. (b) CT scan shows a benign teratoma of the anterior mediastinum; calcification and varying tissue densities may be seen.

lymphoma, biopsy is also preferable to immediate attempt at resection. Such lesions may represent aggressive thymomas that may benefit from neoadjuvant treatment, malignant germ cell tumors, or other rare disease processes. Once the decision has been made to proceed with biopsy rather than resection, selection of a biopsy approach is based on anatomic considerations and patient factors.

BIOPSY OF ANTERIOR MEDIASTINAL MASS

Chamberlain Approach

Anterior parasternal mediastinotomy (the Chamberlain procedure) is favored by most surgeons for biopsy of lesions in the anterior mediastinum and the aortopulmonary window. It is usually done under general anesthesia, although local anesthesia may be used instead, and it does not require single-lung ventilation. This operation affords good exposure and allows generous biopsy specimens to be taken, and it can be performed as an outpatient procedure.

Operative technique *Step 1: initial incision* A 5 cm transverse incision is made over the second costal cartilage on the side to be operated on (the second cartilage is identified by its continuity with the sternal angle). The pectoralis major is separated in a direction parallel to the direction of its fibers,

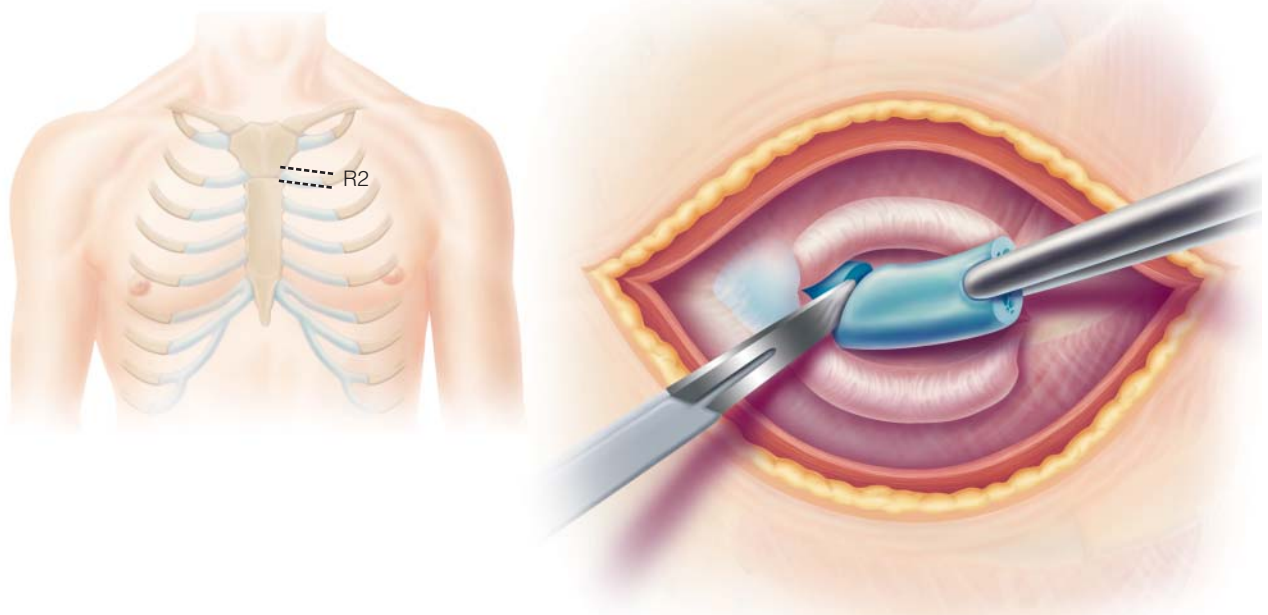


Figure 2 Biopsy of anterior mediastinal mass: Chamberlain approach. Depicted are incision and subperiosteal resection of the second costal cartilage.

and the cartilage is resected in a subperiosteal plane [see Figure 2]. Leaving perichondrium behind facilitates postoperative regrowth of the cartilage.

Step 2: dissection and exposure The posterior perichondrium is incised, and the parietal pleura is bluntly dissected laterally with a peanut sponge; this affords entry into the mediastinal fat and direct access to the tumor mass. Almost invariably, the internal mammary vessels can be mobilized medially and preserved, but, if necessary, they may be ligated to improve exposure.

Step 3: biopsy A generous wedge-shaped portion of the mass is excised with a scalpel. Frozen-section examination is then performed to confirm that diagnostic tissue has been obtained. It is important to remember to request that flow cytometry be performed on the specimen.

Step 4: closure The posterior perichondrium is reapproximated, followed by the pectoralis major, the subcutaneous fat, and the skin.

Troubleshooting If the pleura was entered, a red rubber catheter is used to evacuate the pleural space as the lung is inflated with a large positive pressure breath, and the catheter is withdrawn through the layers of closure. A small postoperative pneumothorax is almost always attributable to residual air rather than to an ongoing air leak.

Sometimes the tumors are fairly vascular and bleed moderately after biopsy is performed. This bleeding can always

be controlled with electrocauterization. We often leave an absorbable hemostatic agent in place as well.

Transcervical Approach

As an alternative to the Chamberlain procedure, a mass of the anterior mediastinum may be approached for biopsy through a cervical incision, exactly as in a transcervical thymectomy [see Resection of Anterior Mediastinal Mass, Transcervical Approach, below]. The use of a Cooper thymectomy retractor (Pilling Company, Fort Washington, Pennsylvania), which elevates the sternum, affords excellent exposure of the anterior mediastinum and sometimes allows direct examination to ascertain the invasiveness of an otherwise uncertain mass. In most cases, general anesthesia is required, but transcervical biopsy can be performed as an outpatient procedure. We have used this technique occasionally and have achieved results comparable to those of anterior mediastinotomy.¹⁰ Proper performance of this procedure does, however, require a level of experience with the technique that is not widely available.

Video-Assisted Thoracic Surgery

Video-assisted thoracic surgery (VATS) has been applied to diagnostic biopsy of anterior mediastinal masses, but VATS biopsy procedures are not widely employed for this purpose. The necessity of single-lung ventilation adds a level of complexity to the procedure beyond what is required for the

Chamberlain procedure or the transcervical approach. Furthermore, intercostal incisions are frequently more painful than transcervical incisions or the incision for an anterior mediastinotomy. VATS does have certain advantages that may be of value in individual cases, such as the capacity to provide simultaneous access to other compartments of the mediastinum and the ability to evaluate the pleural space for evidence of tumor dissemination. Robot-assisted thoracoscopic procedures for anterior mediastinal masses have also been described,¹¹ but their availability does not eliminate the major objection to transpleural approaches to mediastinal masses—namely, the possibility of spreading a disease that had been contained within the mediastinum into the pleural space.

RESECTION OF ANTERIOR MEDIASTINAL MASS

Operative Planning

The most frequent indications for resection (as opposed to biopsy) of an anterior mediastinal mass are (1) thymoma and (2) thymectomy for MG. The principles underlying thymoma resection can be applied to resection of other, rarer anterior mediastinal masses such as thymic carcinoma, thymolipoma, and germ cell tumors. The first successful resection of a thymic mass for MG was described in 1939.¹² Since the introduction of transcervical thymectomy (TCT), there has been ongoing debate regarding the optimal method for thymectomy in patients with nonthymomatous MG. There is little debate, however, regarding the optimal approach to resection of anterior mediastinal malignancies.

For all primary invasive masses of the anterior mediastinum—including invasive thymomas, malignant germ cell tumors (after systemic treatment), thymic carcinomas, and other, less common malignancies—the most important prognostic factor is complete resection. Accordingly, the operative approach must be selected with an eye to providing optimal exposure. There is little doubt that a full median sternotomy is ideal in this regard. However, a less than full sternotomy is a reasonable choice for small (< 3 cm) noninvasive thymomas or other noninvasive mediastinal tumors (e.g., mature teratomas), particularly when the diagnosis of thymoma is in doubt before operation. In such situations, we usually begin with TCT,^{13,14} but we do not hesitate to convert to a sternotomy if unexpected invasion is identified. Some surgeons have employed a partial upper sternotomy in these settings; however, this approach limits exposure, and we do not believe that it actually reduces morbidity in comparison with a full sternotomy. Video thoracoscopic (VATS) and even robotic thymectomy have now been described by a number of groups employing several technical variations and with apparently good results. These approaches have, like TCT, been applied generally to patients with MG without thymoma or those with small, noninvasive thymomas. Studies with longer follow-up reporting myasthenia remission rates and thymoma cure rates will be required before these VATS and robotic approaches can be considered to have a proven role in the management of these diseases.

En bloc resection of malignancies is mandatory, and resection of adjacent serosal membranes (including pleura or pericardium) is required if there is any suggestion of attachment during the operation. Resection of adjacent lung parenchyma

is not uncommon, and resection of the great vessels has been performed with both technical success and good long-term survival. All great vessels resected must be reconstructed, with the exception of the innominate vein, which may be ligated with little deleterious effect. Every effort should be made to preserve the phrenic nerves: damage to even one of these nerves can be disastrous in an already weakened myasthenia patient. In a patient with a malignancy, however, one phrenic nerve may be sacrificed if tumor invasion necessitates this step, provided that the patient's preoperative respiratory status is acceptable and curative resection is likely.

In cases of thymectomy for advanced MG, every effort must be made to optimize the patient's condition preoperatively. To this end, a multidisciplinary approach that includes a neurologist and, possibly, a pulmonologist is necessary. If the disease does not stabilize with medication (e.g., pyridostigmine, low-dose steroids, or intravenous γ -globulin), preoperative plasmapheresis may be required. Patients with moderate or greater generalized weakness despite optimization of medication should certainly undergo plasmapheresis. The question of which MG patients should be offered thymectomy is, at best, difficult to answer. Most studies have found the impact of thymectomy to be greater if it is performed in patients with less severe and shorter-duration disease. Accordingly, our practice is to offer TCT sooner in the course of the disease rather than later; however, we will perform the procedure at any stage, from ocular-only disease to severe, generalized weakness. Because TCT is associated with minimal morbidity, requires only a small incision, and can generally be done as an outpatient procedure, it is a very attractive option for patients with milder disease. At the same time, it is also more easily tolerated by patients with severe disease than is a median sternotomy.

An approach to thymectomy for MG that is favored by a few surgeons is so-called maximal transsternal-transcervical thymic resection, which combines a median sternotomy with an additional neck incision to provide wide access to all areas where thymic tissue has been identified. The rationale for such extensive exposure is the observation that thymic tissue may reside in several extrathymic locations. Proponents of the maximal approach argue that if thymectomy for MG is to provide optimal benefit, it should include removal of all of this extraglandular thymic tissue. This approach has never been compared to TCT in a randomized trial, but, in our view, most of the available data suggest that remission rates after maximal transsternal-transcervical thymic resection are not remarkably different from those after TCT, which is much less invasive. Because we do not personally perform the maximally invasive procedure, we do not describe it in this chapter.

Median Sternotomy Approach

As noted (see above), the standard approach to masses of the anterior mediastinum is via a median sternotomy. Resection of a thymoma of the anterior mediastinum is performed as follows.

Operative technique *Step 1: initial incision and exposure*

The patient is placed in the supine position and intubated with a double-lumen endotracheal tube. The skin incision

typically extends from 2 cm below the jugular notch to the xiphisternal junction; however, depending on the extent of the expected pathologic condition, the incision may be shortened further and the full sternum divided by reaching beneath skin flaps. Finger dissection is performed beneath the sternum to rule out tumor invasion into the posterior sternal table. If the posterior sternal table is clear, the sternum is divided, hemostasis is achieved, and the edges are separated with a sternal retractor.

Step 2: determination of resectability The anterior mediastinum is inspected, the mass is visually identified, and an initial assessment of resectability is undertaken.

Step 3: mobilization of inferior poles of thymus Dissection of the thymus begins at the caudad aspect, with the inferior poles and surrounding mediastinal fat mobilized first from the underlying pericardium and diaphragm by electrocautery dissection. It is difficult to determine by visual means precisely where thymic tissue merges into simple mediastinal fat; accordingly, to ensure complete resection of the thymus, all fatty tissue between the phrenic nerves and down to the level of the diaphragm is removed with the specimen. The mediastinal pleura, to which this fatty and thymic tissue tends to be adherent, is also taken with the specimen [see Figure 3]. This is done by first opening the mediastinal pleura along the entire length of the chest, approximately 1 cm posterior to the sternum.

Step 4: continuation of dissection cephalad From within the pleural space, the phrenic nerves are identified and followed along their entire path up to the point where they course beneath the innominate vein. Sharp dissection is carried close to the nerves, dividing the mediastinal pleura again along this more posterior line, to secure an adequate tumor margin and ensure removal of all thymic tissue that is progressively mobilized medially. It is advisable to clip small vessels near the nerves before dividing them so as to prevent irritating bleeding, which can be difficult to control without compromising the nerve.

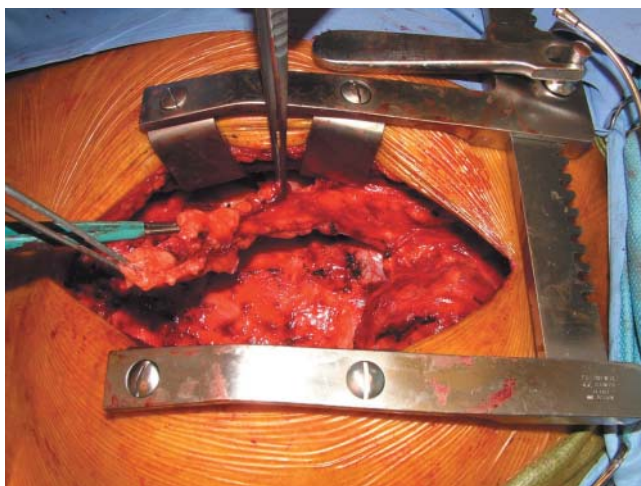


Figure 3 Resection of anterior mediastinal mass: median sternotomy approach. Intraoperative photograph shows dissection of the right inferior thymic pole and associated mediastinal fat.

The small arteries supplying the thymus, which are most often not even clearly seen arising laterally via branches from the internal mammary vessels, are coagulated or ligated and divided as they are encountered. Care must be taken to stay away from the phrenic nerves while controlling the arterial blood supply.

Step 5: mobilization of superior poles of thymus Dissection is then continued in the neck, where the two cervical extensions are isolated by means of gentle traction and blunt dissection and followed until they trail off into the thyrothymic ligament. This ligament is clamped, divided, and ligated superiorly at a point where only a small blood vessel is present and no visible glandular tissue remains.

Step 6: dissection of thymus from innominate vein The cervical poles are followed down over the innominate vein. Sharp dissection is continued onto the surface of the vein, and the two to five veins draining the gland into the innominate vein are ligated and divided [see Figure 4].

Step 7: removal of specimen Once the body of the thymus has been freed from the innominate vein, the H-shaped gland and the associated mass are removed [see Figure 5]. If the

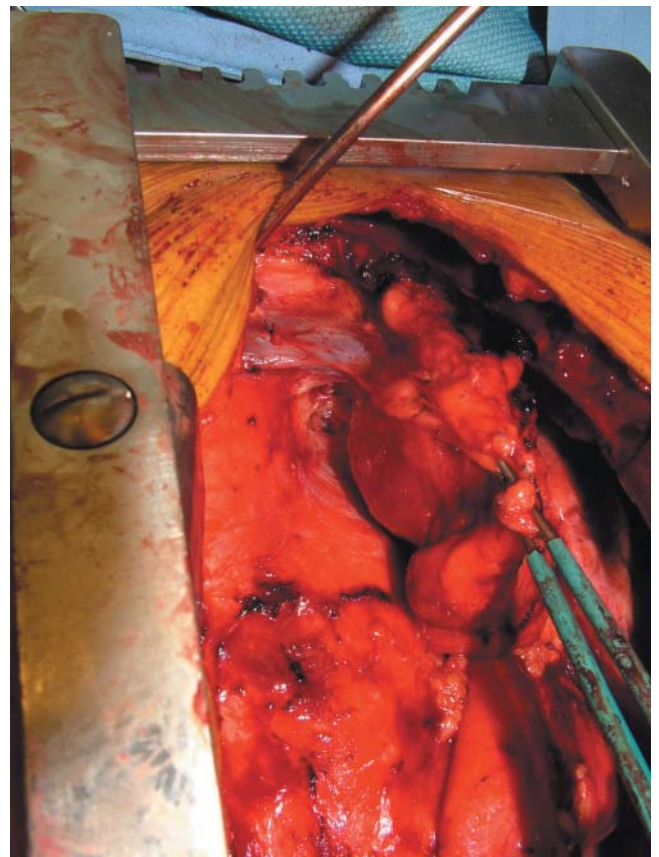


Figure 4 Resection of anterior mediastinal mass: median sternotomy approach. View from feet shows the thymus and tumor mobilized off the innominate vein. The entire right thymus (both the upper and the lower pole) has been fully mobilized.

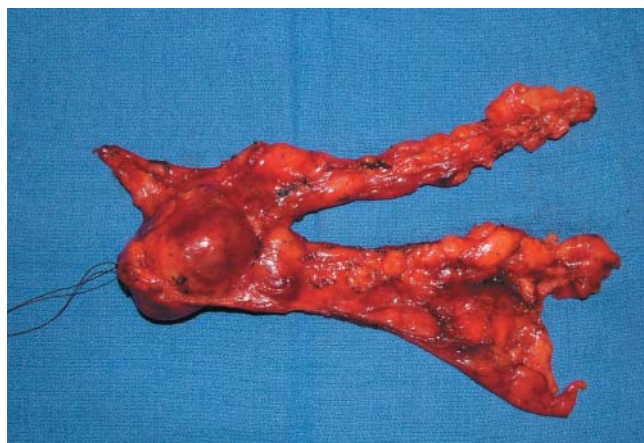


Figure 5 Resection of anterior mediastinal mass: median sternotomy approach. Shown is the resected thymoma specimen.

clean plane between the mass and the underlying pericardium—a plane normally composed of fine, filmy adhesions—is at all compromised, one should not hesitate to resect a portion of the pericardium en bloc with the specimen, with care taken to maintain a gross margin of at least 2 cm at all times.

Step 8: closure Two pleural drains that traverse the mediastinum and reach the apex of each hemithorax are placed, and the sternum and the soft tissues are reapproximated in layers.

Troubleshooting If invasion of great vessels is considered a possibility before the start of the operation, the groin should be prepared and draped into the field to provide access for cardiopulmonary bypass if needed. Giant anterior mediastinal masses may necessitate extension of a partial median sternotomy incision into an ipsilateral intercostal space (usually the fourth space). Such extension may be achieved by making an ipsilateral incision in the neck along the anterior border of the sternocleidomastoid muscle and making a submammary skin incision continuous with the incision over the sternum (a hemiclamshell incision) [see Figure 6].

Transcervical Approach

Although the transcervical approach to thymic resection was the first one used in the early 1900s, it fell into disuse during the middle of the 20th century, when the median sternotomy approach became feasible. During the past 20 years, however, there has been a resurgence of interest in TCT. Today, TCT is used primarily for thymectomy in the setting of MG, although, as noted (see above), a transcervical approach can be useful for biopsy or resection of other anterior mediastinal processes as well. Proponents of TCT have published data establishing that complete remission rates from MG after so-called extended TCT using the sternum-lifting Cooper retractor¹⁵ are very similar to remission rates after the more invasive approaches.^{14,16,17} Because TCT is an outpatient procedure, hospital stay and operative recovery are certainly dramatically shorter than after thymectomy by sternotomy.

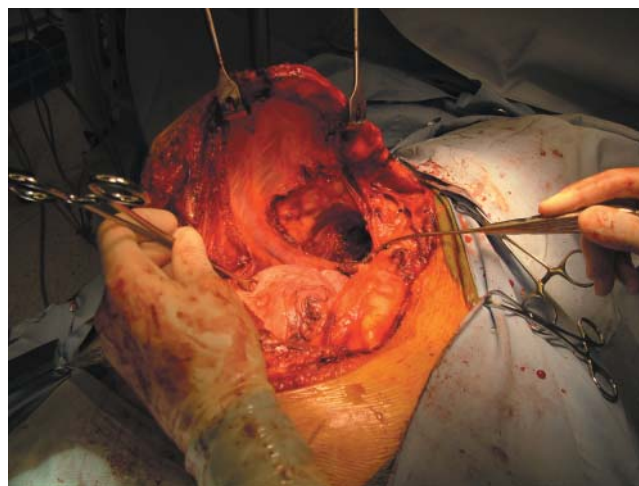


Figure 6 Resection of anterior mediastinal mass: median sternotomy approach. Hemiclamshell incision provides exposure to masses located at the thoracic apex.

TCT should be employed very cautiously in cases in which a neoplasm is suspected or proved on the basis of preoperative studies or is identified during the course of intraoperative exploration. Because thymoma is often an indolent tumor, with recurrence developing many years after resection, long-term follow-up studies are required before TCT can be firmly recommended for treatment of even small thymomas. On the other hand, it is likely that surgeons who have extensive experience with TCT can safely resect small (< 3 cm) thymomas via this approach without risking tumor spillage or incomplete resection.

Operative technique *Step 1: initial incision and exposure*

The patient is placed on the operating table in the supine position, with the head supported by a foam doughnut and an inflatable bag placed horizontally beneath the scapulae. The bag is inflated until the cervical spine is maximally extended. It is important that the top of the patient's head be all the way up to the edge of the table so that the surgeon can easily reach all areas of the mediastinum from a seated position at the head.

A 5 to 6 cm curvilinear incision is made about 2 cm superior to the jugular notch and extending about 1 cm above each clavicular head [see Figure 7]. Electrocautery dissection is continued through the platysma, and subplatysmal flaps are elevated. The strap muscles are separated in the midline, and the interclavicular ligament is divided. Separating a small portion of the attachment of each sternocleidomastoid muscle from the corresponding clavicular head allows the sternum to be elevated somewhat higher, thereby improving exposure.

Step 2: mobilization of superior poles of thymus The superior poles of the thymus are located (usually on the left side first) by means of gentle blunt dissection beneath the strap muscles. After one pole is identified, it is divided between ties at its superior extent. Its medial edge is then followed down to where it meets the medial edge of the opposite superior pole, and this opposite pole can then be similarly traced upward

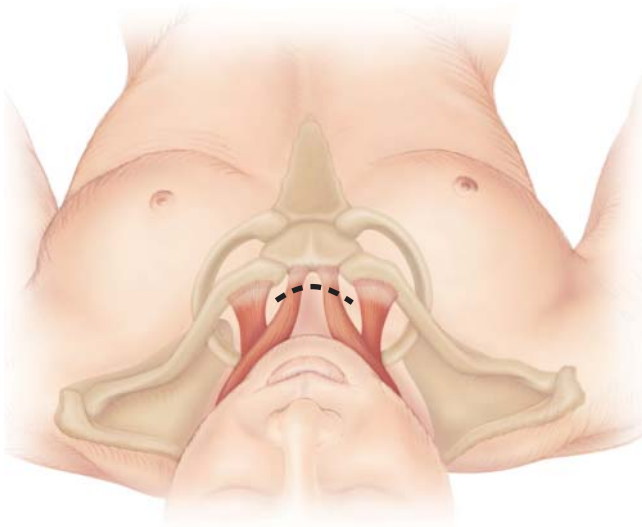


Figure 7 Resection of anterior mediastinal mass: transcervical approach. Shown is the location of the skin incision for transcervical thymectomy in relation to the sternal notch and the heads of the clavicles.

into the neck, ligated, and divided. A very important part of the procedure is the placement of 0 silk ligatures around an area containing strong tissue within each superior pole. These ligatures are left long and clamped. The surgeon or an assistant places traction on them during the remaining course of the dissection to manipulate and progressively mobilize the gland [see Figure 8].

Step 3: continuation of dissection downward into superior mediastinum As traction is being placed on the upper poles, sharp and blunt dissection, staying outside the well-defined capsule of the gland, is extended downward into the superior mediastinum to the level of the innominate vein. The procedure becomes much more difficult if the capsule is violated.

Step 4: elevation of sternum Finger dissection is performed in the substernal plane, and the arm of a Cooper thymectomy retractor is placed into the retromanubrial space to elevate the sternum. The retracting arm is placed under upward tension as the inflatable bag beneath the shoulders is deflated. This step leaves most patients actually hanging from the retractor, thereby opening up a sizable space that allows good visualization and ready passage of dissecting instruments into the anterior mediastinum. Army-Navy retractors are placed in each of the two upper corners of the incision, and their distal ends are tied to the siderails of the table with Penrose drains to provide countertraction and to hold the skin incision open.

Step 5: dissection of venous tributaries to innominate vein With the superior poles gently pulled upward by an assistant (and at times looped over the Cooper retractor), the inferior surface of the gland is dissected until the innominate vein is encountered. The venous tributaries draining the thymus into the innominate vein are isolated sharply, ligated with fine silk sutures, and divided.

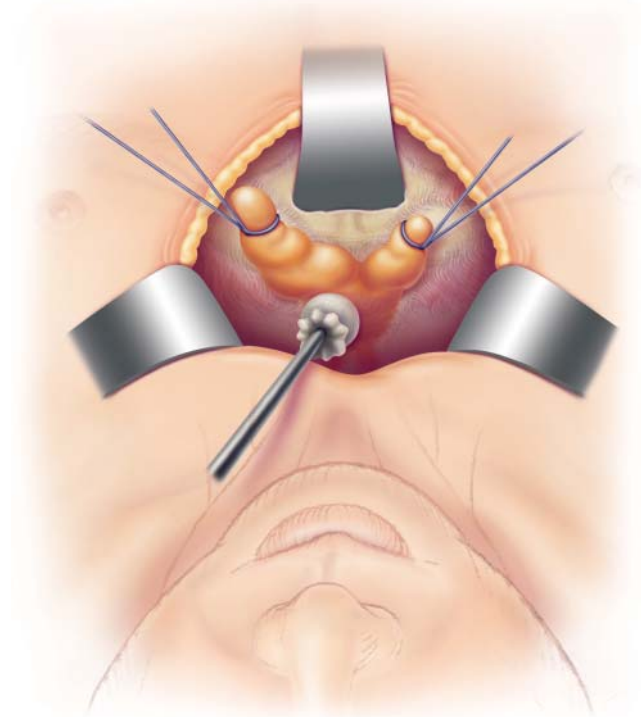


Figure 8 Resection of anterior mediastinal mass: transcervical approach. A Cooper thymectomy retractor is placed beneath the sternum, and retraction on the upper poles of the thymus is maintained with silk sutures.

Step 6: dissection of posterior aspect of thymus Once the thymus is freed from the innominate vein, dissection of the posterior aspect of the gland must be continued directly on the surface of the pericardium. This posterior dissection is carried as far down as possible, primarily in a blunt fashion. Most of the time, the surgeon holds one ring clamp containing a sponge dissector in each hand while an assistant holds the upper poles. Occasionally, the surgeon holds the sutures attached to the upper poles in one hand while employing the sponge dissector in the other hand.

Step 7: removal of specimen When the posterior dissection has been extended as far as possible toward the diaphragm, further mobilization of the thymus is typically accomplished by working the glandular tissue laterally, first off the pleura on one side, then off the sternum anteriorly, and finally off the pleura on the opposite side. In this way, the entire gland is ultimately removed between the phrenic nerves and down to the diaphragm. During this final mobilization, the surgeon periodically asks to have ventilation held temporarily so that the pleura can fall back and thus permit improved visualization. Small feeding vessels from the mammary are doubly clipped and divided as they are encountered.

Often the final stages of blunt dissection may be facilitated by placing a ring clamp on the body of the gland to allow slightly more vigorous retraction than can be achieved by using the upper poles alone. If any suspicious residual tissue is seen in the mediastinum at this point, it can be removed piecemeal; however, this is an unusual occurrence.

Step 8: closure After inspection of the surgical field for hemostasis, the strap muscles and the platysma are closed over a red rubber catheter, to which suction may be applied. The catheter is subsequently removed, and the skin is closed.

Troubleshooting In the course of preoperative evaluation before TCT, it is important to be sure that the patient is able to extend the neck to a reasonable degree. TCT is simplest in young persons who are capable of good extension; it can be difficult or impossible in persons with cervical spine disease that hinders extension.

During the procedure itself, it is important that the branches of the innominate vein be tied rather than clipped; the space anterior to the vein becomes the avenue through which dissecting instruments are passed into and out of the mediastinum, and these instruments often rub against the vein fairly vigorously.

When working laterally, one must take care not to injure the phrenic nerves, and one certainly should not use the electrocautery while working at the lateral extremes of the dissection. If the pleural space is entered while one is working laterally, a red rubber catheter [see Operative Technique, Step 8, *above*] is advanced well into that pleural space, and suction in the form of several large positive-pressure breaths is applied before the catheter is removed.

If a thymoma is encountered during TCT, continuation via this approach may be considered. In our view, most noninvasive thymic lesions less than 3 cm in diameter can be safely and completely resected via the transcervical approach. In addition, it generally is not difficult to resect a portion of the anterior pericardium as well if a tumor or the thymus is adherent to it. However, because the evidence currently available does not conclusively establish that TCT is equivalent to resection via sternotomy for thymoma, some surgeons prefer to convert to a sternotomy if a suspicious mass is discovered during transcervical exploration. Certainly, if any difficulty is encountered that might lead to an incomplete thymectomy or incomplete removal of a thymoma, the incision should be extended.

Approximately 90% of patients are able to go home on the same day as their procedure. The most common cause for hospital admission is a pneumothorax that must be monitored or drained. Occasionally, a seroma develops at the site of the incision, but it almost always resolves either spontaneously or after a single percutaneous drainage procedure in the office.

VATS/Robotic Thymectomy

Although we do not have personal experience with VATS or robotic thymectomy and will therefore not include a discussion on its technique, an increasing number of published reports suggest that these are safe and effective alternatives to transsternal and transcervical approaches. Since the first sporadic case reports of VATS thymectomy in the early 1990s, the popularity of this procedure has increased, likely because of the increased availability of VATS instrumentation, surgeon familiarity with VATS techniques, and

increased awareness of minimally invasive strategies. Proponents of VATS thymectomy cite decreased postoperative pain, decreased length of stay, improved cosmesis, and less morbidity than sternotomy as reasons in support of VATS thymectomy. Most case series report complete stable remission rates from MG^{18,19} comparable to transsternal and transcervical approaches. The data in this area, however, are not nearly as mature as those in support of TCT or sternotomy for thymectomy.

The drawbacks of VATS thymectomy depend on the particular technical approach that is chosen, which include unilateral, bilateral, and substernal approaches. As with any minimally invasive technique, detractors have pointed out that there may be an inability to provide complete clearance of all thymic tissue. It has been suggested that a unilateral VATS approach may provide inadequate access to the portion of the gland approaching the contralateral phrenic nerve. Aside from the question of the completeness of thymectomy, any transthoracic, minimally invasive approach may create a small risk of transpleural seeding in patients with thymoma. Given that “drop metastasis” to the pleural surfaces is the typical mode of spread of thymoma, there is substantial concern that a transpleural, thoracoscopic approach may facilitate this mode of spread.

Procedures for Lesions of the Middle Mediastinum

The majority of masses found in the middle mediastinum in adults are malignant, representing either lymphoma or lymph node metastases from primary lung carcinoma. Accordingly, the procedures performed in this anatomic area primarily involve biopsy for staging or diagnosis rather than curative or palliative resection. On infrequent occasions, however, benign or primary malignant lesions of the middle mediastinum occur for which resection is appropriate. In what follows, we briefly discuss resection of such lesions; for the most part, the principles are the same as those underlying resection of masses in the posterior mediastinum [see Procedures for Lesions of the Posterior Mediastinum, *below*].

Of particular surgical interest in the middle mediastinum are benign cysts, which may arise from the pleura, the pericardium, the airways, or the esophagus. Bronchogenic cysts, which typically develop in proximity to the carina, are probably the middle mediastinal cysts most commonly encountered in clinical practice, with pericardial cysts running a close second. On rare occasions, ectopic remnants from cervical structures (e.g., the parathyroid and thyroid glands) are encountered in this compartment.²⁰

PREOPERATIVE EVALUATION

CT generally provides an accurate preoperative diagnosis of a benign middle mediastinal cyst, as well as information regarding abutment of adjacent structures, the consistency of the mass, and potential invasiveness. MRI may be helpful if there is concern that a cyst might actually represent an aberrant vascular structure or an aneurysm, if the simple nature of the cyst is in doubt, or if clearer delineation of suspected invasion of surrounding structures is required. Radionuclide scans (e.g., with technetium-99m or radioactive iodine) may

be useful if the differential diagnosis includes a parathyroid or thyroid mass. Cystic structures adjacent to the airways and the esophagus are evaluated by means of bronchoscopy, esophagoscopy, barium esophagography, or some combination of these imaging modalities to rule out communication with the lumina.

OPERATIVE PLANNING

Middle mediastinal cysts that are symptomatic should be treated surgically. However, simple cysts of the middle mediastinum that are asymptomatic and meet all radiographic criteria for benignity may be followed. This conservative approach is often more appropriate for asymptomatic middle mediastinal cysts than for asymptomatic posterior mediastinal cysts in that complete cyst resection (at least for bronchogenic cysts) tends to be more complex in the middle mediastinum than in the posterior mediastinum, given the closer proximity to vital structures and the deeper placement within soft tissue. Complete resection of pericardial cysts, on the other hand, typically is easily accomplished by means of VATS; therefore, such cysts are probably best resected when discovered, even if they are asymptomatic. VATS resection of subcarinal bronchogenic cysts is feasible and has been described in published reports.²¹ It is our experience, however, that larger and more chronic cysts in this location may be difficult to remove completely by a VATS approach.

Thus, for a symptomatic, large, or chronic subcarinal bronchogenic cyst (a not uncommon occurrence), one is left to choose between (1) thoracotomy for complete resection and (2) some other approach for incomplete resection. Because this area is easily accessible by means of mediastinoscopy, and because we believe that mediastinoscopy is simpler and causes less morbidity than VATS, we prefer partial resection via mediastinoscopy as the initial approach to these lesions.²² If cysts treated in this manner recur with associated symptoms, one can always perform thoracotomy for complete resection at that time, and little will have been lost in the meantime.

MEDIASTINOSCOPIC PARTIAL RESECTION OF SUBCARINAL BRONCHOGENIC CYST

Operative Technique

Step 1: mediastinoscopy and pretracheal dissection

A standard cervical mediastinoscopy is performed, with dissection in the pretracheal plane down to the level of the carina.

Step 2: freeing of cyst from surrounding tissues With the cyst wall kept intact, as much of the wall as can safely be exposed is visualized by bluntly dissecting it away from the undersurface of the carina and the mainstem bronchi. Next, the mass is dissected away from the soft tissues anterior and posterior to it; obviously, this must be done with caution, given that the right main pulmonary artery and the esophagus are located nearby (anteriorly and posteriorly, respectively).

Step 3: aspiration of cyst contents and excision of exposed cyst wall The contents of the cyst are aspirated for cytologic and microbiologic examination, and the exposed

portion of cyst wall is excised. Typically, approximately 50% of the cyst wall can be removed in this fashion. Some of the remaining cyst wall may be cauterized; this too must be done with caution, given the proximity of the adjacent vital structures.

Procedures for Lesions of the Posterior Mediastinum

The majority of posterior mediastinal masses occurring in adults are benign. These lesions may be usefully classified according to their radiologic appearance—that is, as either cystic or solid. Cystic masses in this region typically are bronchogenic cysts or esophageal duplication cysts, whereas solid masses most frequently are benign neurogenic tumors (e.g., schwannomas, neurofibromas, or ganglioneuromas). Esophageal leiomyomas (benign intramuscular tumors within the esophageal wall) are often grouped with these posterior mediastinal lesions and are managed in a similar fashion. In many cases, posterior mediastinal masses come to light as asymptomatic radiographic abnormalities; however, they may also be associated with signs of infection (in the case of infected cysts), dysphagia, chest pain, or respiratory complaints. At present, because of the growing availability of less morbid, minimally invasive approaches to posterior mediastinal masses, most authors recommend resection even when the lesion is asymptomatic. Although this recommendation remains somewhat controversial, we agree with it.

OPERATIVE PLANNING

VATS versus Thoracotomy

Resection of posterior mediastinal masses may be accomplished by means of either VATS or thoracotomy. The procedure is essentially the same with either approach, and the goal is complete resection. With some exceptions, VATS is considered preferable to thoracotomy in this setting; generally, VATS results in less postoperative pain and quicker functional recovery.^{23,24} Some surgeons argue that a VATS approach may be more likely to leave a patient with microscopic residual disease. In our experience and that of others, however, recurrences of these lesions are very rare after VATS excision.^{25,26} Given the low recurrence rate and the fact that these masses are almost always benign, we believe that the risk-benefit ratio favors VATS in most cases.

There are, however, several circumstances in which thoracotomy is indicated from the outset [see Table 2]. A suggestion of malignancy (in particular, invasion of surrounding structures) on preoperative radiography mandates exploration and resection by thoracotomy; in this situation, the potential consequences of positive margins justify the more aggressive approach. The presence of active infection within a cyst is a relative indication for thoracotomy in that it can cause disruption of normal tissue planes and thereby render VATS dissection more hazardous. Masses larger than approximately 6 cm also call for an open approach: such lesions are typically more difficult to mobilize safely from underlying structures than smaller lesions are, they are more likely to be malignant, and their removal between the ribs is likely to necessitate rib spreading, which may negate some of the benefit of true VATS.

Table 2 Indications for Planned Thoracotomy Approach to Middle or Posterior Mediastinal Mass

Suggestion of malignancy on preoperative radiography
Presence of inflammation or infection, blurring tissue planes
Large mass (> 5–6 cm)
Esophageal duplication cyst believed to communicate with esophageal lumen on the basis of preoperative computed tomography, barium esophagography, or esophagoscopy
Esophageal lesions without evidence of overlying normal esophageal mucosa on preoperative esophagoscopy or endoscopic ultrasonography
Previous ipsilateral thoracotomy with adhesions
Tumor located at apex of the chest, which may necessitate thoracosternotomy

When a cyst is arising from or abutting the esophagus, the possibility of a communication between the cyst and the esophageal lumen should be investigated preoperatively. Such a communication may be suggested on CT scans by the presence of an air-fluid level. To rule out this phenomenon, we perform barium esophagography during the preoperative workup, followed by intraoperative esophagoscopy at the commencement of the operation. If a communication is identified or cannot be ruled out, thoracotomy is performed. After excision of an esophageal duplication cyst with a communication, reapproximation of the esophageal mucosa is a paramount consideration; in our view, this is best done through an open approach.

In cases of suspected leiomyoma of the esophagus, preoperative investigation should be done to confirm the presence of intact overlying mucosa, which is virtually pathognomonic of this disease. Esophagoscopy is done to assess the mucosa; if the mucosa is intact, the possibility of malignancy is essentially ruled out. Simultaneously, endoscopic ultrasonography may be performed to establish the depth to which the esophageal wall is involved. With a preoperative diagnosis of probable leiomyoma, VATS is the approach of choice in our practice.

So-called dumbbell neurogenic tumors (tumors that invade the neural foramen) are special cases. Any solid mass in the costovertebral sulcus should be evaluated by means of MRI to determine whether it is invading the neural foramen if the absence of invasion was not clearly established by CT. Although invasion of the neural foramen by tumor is not in itself an indication for thoracotomy, it does necessitate a combined anterior-posterior approach with neurosurgical involvement for the intraspinal portion of the procedure. Several versions of such an approach have been described.^{27–29} We prefer to perform the posterior neurosurgical resection of the intraspinal component (laminectomy and intervertebral foraminotomy) first and then to reposition the patient and carry out the remainder of the procedure (generally via VATS).³⁰

Although VATS is often an excellent approach to posterior mediastinal lesions, it must be emphasized that one should never hesitate to convert a VATS procedure to a thoracotomy if required. Accordingly, informed consent to undergo thoracotomy should be sought before operation from all patients being treated for posterior mediastinal lesions, even when VATS is the intended approach.

VATS RESECTION OF NEUROGENIC TUMOR OF POSTERIOR MEDIASTINUM

Operative Technique

Resection of a solid neurogenic tumor of the posterior mediastinum that does not invade the neural foramen [see Figure 9] proceeds as follows.

Step 1: intubation and endoscopy The patient is intubated with a double-lumen endotracheal tube to allow single-lung ventilation. Preoperative bronchoscopy (for cystic lesions) or esophagoscopy (for lesions abutting the esophagus) is performed as indicated (see above).

Step 2: patient positioning and placement of ports The patient is placed in the lateral thoracotomy position and stabilized with bean bags so that the operating table can safely be tilted as much as 45° to either side. With this degree of tilt, the lung tends to fall away from the field of vision; thus, there usually is no need to place an additional port for a lung retractor.

The port for the scope is placed through an incision in the midaxillary line at the level of the mass; if it is placed much more anteriorly than the midaxillary line, the surgeon's view of posterior lesions may be obscured by the lung. The two working ports are placed through separate incisions in the posterior axillary line, made as far cephalad and caudad as possible. Sometimes placement of an alternative upper working port posterior to the scapula is advantageous [see Figure 10]. The main working instruments are an endoscopic scissors-cautery, a ring clamp, an endoscopic peanut dissector, a Maryland dissector, a long right-angle clamp, and an endoscopic clip applier.

Step 3: incision of pleura The parietal pleura is incised around the mass, with a margin of approximately 2 cm circumferentially. The pleura is tented up with the aid of

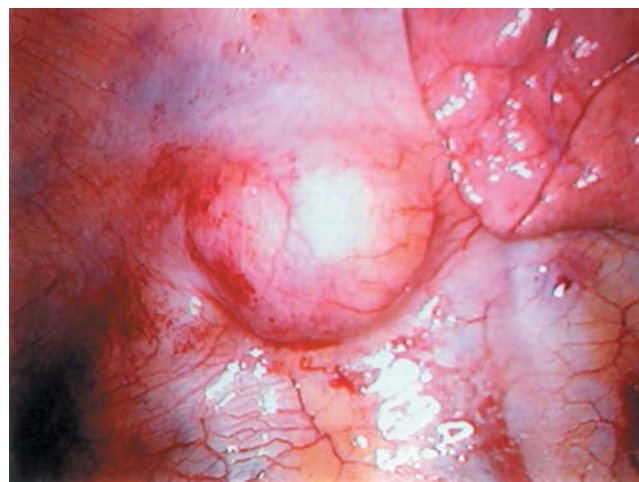


Figure 9 Resection of neurogenic tumor of posterior mediastinum. Intraoperative photograph shows a solid neurogenic tumor of the costovertebral sulcus.

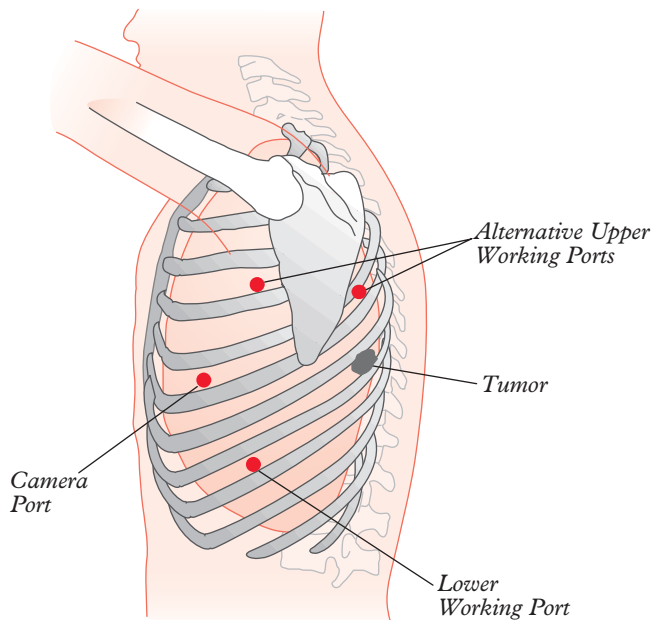


Figure 10 Resection of neurogenic tumor of posterior mediastinum. Shown is typical port placement for video thorascopic resection of a posterior mediastinal mass.

the right-angle clamp or the Maryland dissector to separate it from the underlying structures [see Figure 11]. This separation allows the use of the electrocautery, which provides

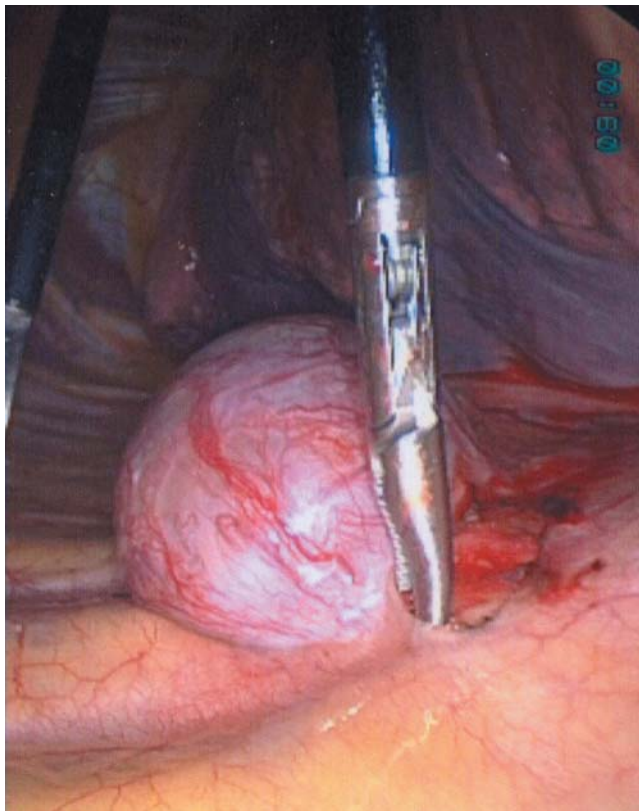


Figure 11 Resection of neurogenic tumor of posterior mediastinum. Shown is circumferential incision of the pleura around a neurogenic mass.

hemostasis while protecting the underlying esophagus, vagus and intercostal nerves, and azygos vein. This dissection and all subsequent work are facilitated by placing gentle traction on the mass with a sponge stick or, for smaller masses, by grasping the entire mass within a ring clamp.

Step 4: dissection of soft tissue attachments Once the pleura has been incised circumferentially, the soft tissue attachments are further dissected bluntly with the endoscopic peanut dissector. Attachments that are relatively thick or vascular are best controlled by double-clipping and division. If the tumor originates from an intercostal nerve, gentle dissection is done beneath the tumor to identify the intercostal bundle that is the source of the lesion.

Step 5: division of source intercostal bundle The source intercostal bundle lateral to the tumor is mobilized, doubly clipped, and divided. Once this has been accomplished, blunt dissection is performed until the nerve root emerging from the neural foramen and the associated intercostal vessels are the last remaining attachments. If the tumor originates from the sympathetic chain, the chain is clipped above and below the tumor, and the intercostal bundle is spared if possible.

Step 6: removal of specimen The remaining stalk is doubly clipped and divided [see Figure 12], and the mass is removed in an endoscopic bagging device.

Step 7: drainage A 24 French chest tube is positioned posteriorly at the apex.

Troubleshooting

Care must be taken to ensure that only very gentle traction is exerted on a mass adjacent to the neural foramen. Overzealous traction can cause tearing of the nerve root proximal to the extraspinal extent of the dura, and this tearing can lead to a cerebrospinal fluid (CSF) leak, which most often becomes evident only postoperatively (in the form of persistent clear

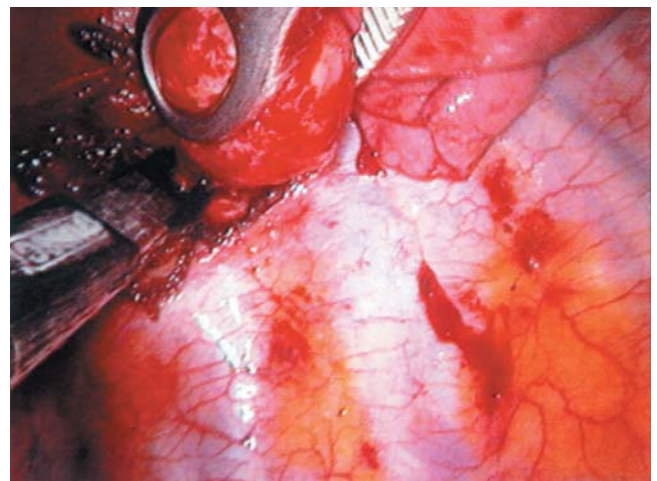


Figure 12 Resection of neurogenic tumor of posterior mediastinum. The final remaining intercostal stalk is divided.

chest tube output). The diagnosis of CSF leakage can be confirmed by measuring the β_2 -transferrin level in the fluid. If CSF leakage is confirmed, reoperation with a neurosurgeon is mandatory; the leak is repaired and buttressed with vascularized tissue.

After resection of a tumor at the costovertebral sulcus, regular neurologic examinations of the lower extremities are indicated. Tamponade with hemostatic agents should never be employed for bleeding at the neural foramen: doing so can result in an intraspinal hematoma with subsequent cord compression. Careful use of the electrocautery at the bony margins of the foramen or watchful waiting is preferable. If hemostasis cannot be achieved with these measures, a neurosurgical consultation should be obtained. In the event of oozing from the vicinity of a foramen that is not easily controlled, there should be no hesitation in converting a VATS procedure to an open procedure.

In a minority of patients, clipping and division of an intercostal nerve result in intercostal neuralgia after the procedure; the possibility that this may occur must be discussed with the patient preoperatively. Many patients who undergo division of a lower thoracic intercostal nerve that supplies an upper abdominal dermatome notice postoperative bulging of the ipsilateral abdomen in the area supplied by that nerve.

RESECTION OF BENIGN CYST OF POSTERIOR MEDIASTINUM

Resection of a benign cystic mass of the posterior mediastinum closely resembles resection of a neurogenic tumor [see Resection of Neurogenic Tumor of Posterior Mediastinum, *above*]; the differences are relatively minor [see Troubleshooting, *below*].

Troubleshooting

In the initial stages of dissection of a benign cyst of the posterior mediastinum, care should be taken not to rupture the cyst; initial mobilization from surrounding structures is easier when the cyst wall is under tension [see Figure 13]. If the area of

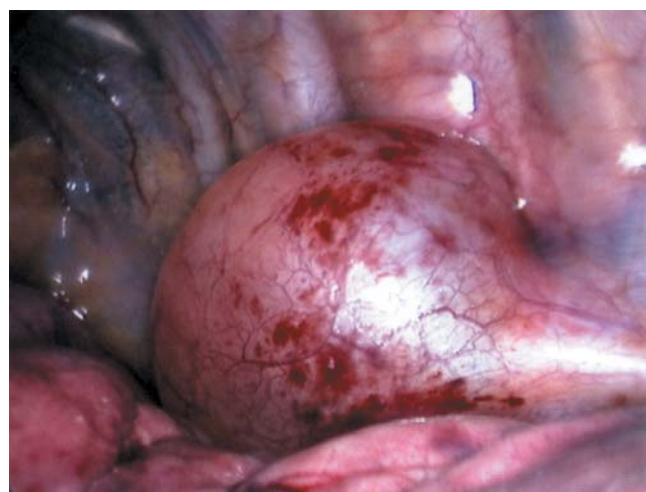


Figure 13 Resection of benign cyst of posterior mediastinum. Intraoperative photograph shows a fluid-filled posterior mediastinal cyst. The tenseness of the cyst wall facilitates initial dissection.

the cyst wall that directly abuts the mediastinum is found to be too adherent to underlying structures to be removed safely, we intentionally rupture the cyst and then remove as much of the cyst wall as possible. As much as 35% of the cyst wall may be left in place. In such cases, we ablate the residual intact cyst wall with the electrocautery to destroy any potential secretory tissue. In our estimation, if more than approximately 35% of the cyst must be left in place, conversion to thoracotomy should be considered.

RESECTION OF ESOPHAGEAL LEIOMYOMA

Operative Technique

In addition to the steps described for resection of a neurogenic mass, there are several special maneuvers that facilitate resection of esophageal intramural masses, such as leiomyomata [see Figure 14a] and duplication cysts:

1. The pleura is incised longitudinally with the electrocautery after it is tented up away from the esophagus, the vagus nerve, and the azygos vein with a right-angle clamp or a Maryland dissector [see Figure 14b].
2. In some cases, exposure is facilitated by dividing the azygos vein with an endoscopic stapler [see Figure 14c].
3. The longitudinal esophageal muscle fibers that overlie the mass are separated bluntly or with the electrocautery in the line of the fibers. These fibers are often markedly attenuated as a result of the expansion of the mass [see Figure 14d].
4. Blunt dissection with an endoscopic peanut dissector allows careful, progressive mobilization of the mass, first from the muscle layer and then from the underlying mucosa. Gentle traction on the mass facilitates exposure at this point in the procedure [see Figure 14e]. A suture may be placed into the tumor to facilitate this retraction. Having an assistant place the endoscope within the esophageal lumen to distend and illuminate the mucosa also may be helpful at this stage. Once the mass has been completely resected, it is sent for pathologic examination [see Figure 14f].
5. The esophagus is distended by insufflating air from above while the distal esophagus is occluded with a sponge stick. The air-filled esophagus is then submerged in saline, and the area of the resection is examined for air leakage.

Troubleshooting

The muscular defect in the esophageal wall must be closed after resection to ensure that an esophageal diverticulum will not develop. Such closure may be accomplished by means of thoracoscopic suturing.

Frequently, duplication cysts are more adherent to the underlying esophageal mucosa than leiomyomata are, and transillumination of the esophageal wall helps define the plane at which blunt dissection should be performed. Where the cyst wall becomes difficult to separate from the mucosa, a small amount of the wall may be left in place if, in the surgeon's judgment, attempting to remove all of it might lead to a breach in the mucosa.

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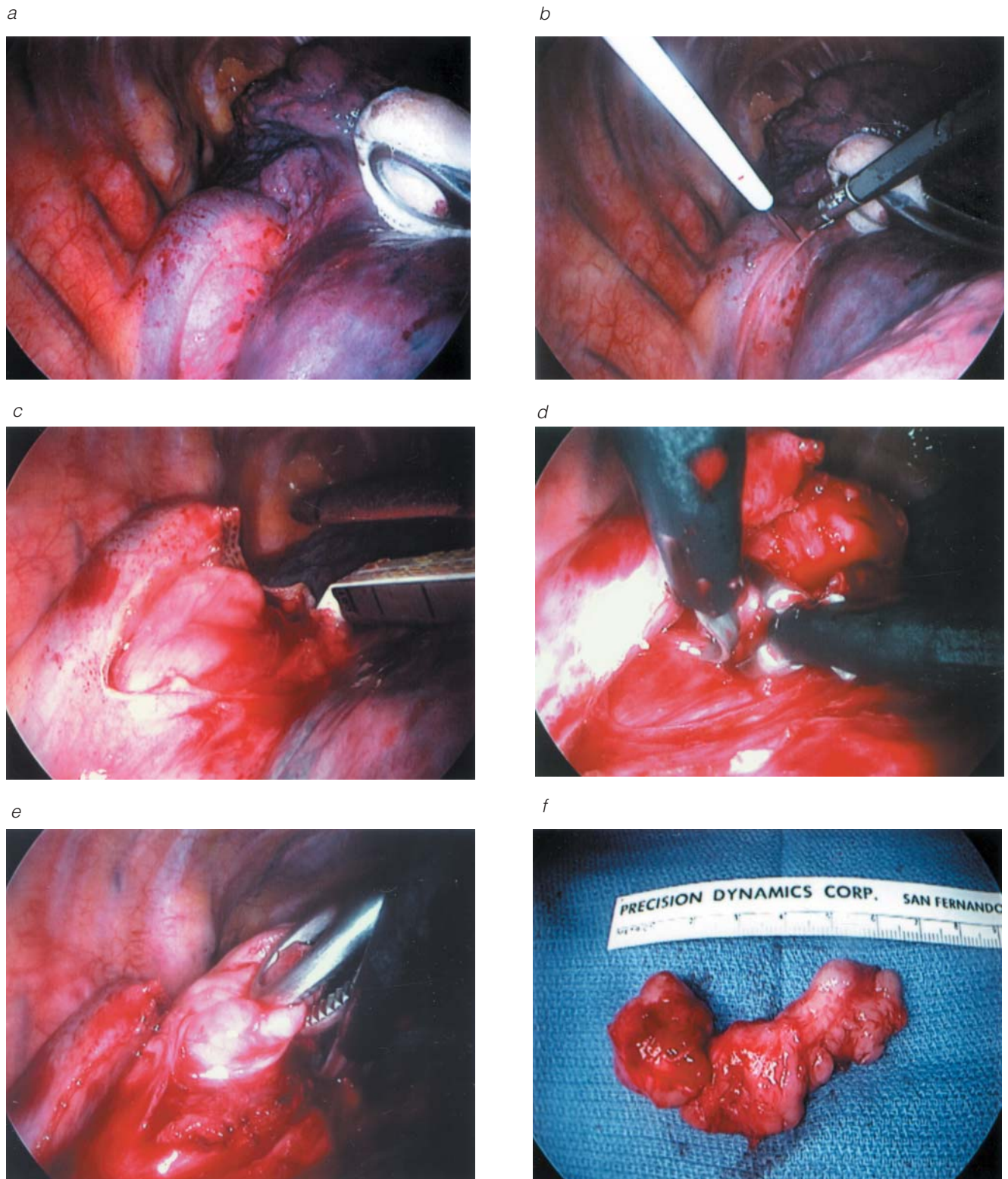


Figure 14 Resection of esophageal leiomyoma. (a) Shown is an esophageal leiomyoma beneath the azygos vein. (b) The mediastinal pleura overlying the leiomyoma is incised. (c) The azygos vein is divided with an endoscopic stapler. (d) The muscle fibers overlying the mass are divided. (e) Gentle traction is applied to facilitate blunt dissection. (f) Shown is a completely resected horseshoe-shaped esophageal leiomyoma.

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Figure 1b Photo courtesy of Wallace T. Miller Sr, MD, University of Pennsylvania School of Medicine
Figures 2, 7, and 8 Alice Y. Chen
Figure 10 Tom Moore

12 PERICARDIAL PROCEDURES

Dawn Emick, MD, and Thomas A. D'Amico, MD

Surgical procedures are performed on the pericardium either for diagnostic purposes or for relief of the hemodynamic consequences of pericardial disease. The pericardial processes for which surgical intervention is required can be divided into two broad categories: pericardial effusion and constrictive pericarditis. Pericardial effusion can either be acute or chronic, and the management of effusion depends largely on the rapidity of fluid accumulation and the risk of cardiac tamponade. The decisions that must be made regarding the selection of patients, the timing of surgery, and the choice of technique or approach often pose substantial challenges to the surgeon. Accordingly, a thorough knowledge of the anatomy, physiology, and pathophysiology of the pericardium is essential for successful management of pericardial disease processes.

Anatomic and Physiologic Considerations

ANATOMY

Like the pleura, the pericardium consists of two layers. The inner layer, the visceral pericardium (or epicardium), is a monolayer of mesothelial cells that is adherent to the heart. The outer layer, the parietal pericardium, is a tough fibrous structure composed of dense bundles of collagen fibers with occasional elastic fibers. The fibrous structure of this layer renders the pericardial sac relatively noncompliant, and this noncompliance plays a significant role in pericardial function and pathophysiology.

The pericardium surrounds the heart and the great vessels [see Figure 1]. Its parietal and visceral surfaces meet superiorly at the ascending aorta and the superior vena cava. From that point, the pericardium continues down the right border of the heart and over the anterior surface of the pulmonary veins to the inferior vena cava. After crossing the inferior vena cava, the inferior pericardium is densely adherent to the diaphragm. Just past the apex of the heart, it turns superiorly again and runs over the pulmonary veins back to the aorta.

Anteriorly, there are normally no connections between the visceral and parietal layers of the pericardium. Posteriorly, the pattern of pericardial reflections around the pulmonary veins and the venae cavae creates two sinuses. The oblique pericardial sinus is the space in the center of the pulmonary veins, directly behind the left atrium. The transverse pericardial sinus is bordered anteriorly by the aorta and the main pulmonary artery and posteriorly by the dome of the left atrium and the superior vena cava.

NORMAL PHYSIOLOGY

The pericardium is normally filled with 15 to 50 mL of serous fluid, which serves as lubrication to facilitate the motion of the heart within this structure. By virtue of its

relative noncompliance, the pericardium exerts an influence on cardiac hemodynamics. This influence can easily be seen in the normal inspiratory variation in systemic arterial pressure. Under normal circumstances, intrapericardial pressure is slightly less than 0 mm Hg, becoming more negative during inspiration and less negative during expiration. Negative intrathoracic pressure during inspiration augments right ventricular filling. Because the pericardium does not allow significant acute right ventricular dilation, the ventricular cavity enlarges by shifting the septum toward the left ventricle. In addition, the noncompliance of the pericardium prevents the free wall of the left ventricle from distending to recapture its normal cavity volume. Thus, the volume ejected from the left ventricle is slightly decreased, resulting in lower systemic arterial pressure. Normally, this effect is exceedingly small. However, it becomes more pronounced when the pericardium is filled with fluid: ventricular distention is restricted even further, and paradoxical pulse becomes clinically apparent.

PATHOPHYSIOLOGY

Although the pericardium is resistant to rapid distention, it is capable of distending over time. If filled slowly, it can expand to contain significant amounts of fluid (sometimes more than 1 L) before hemodynamic consequences develop. In the setting of an acute pericardial effusion (e.g., from trauma), however, devastating hemodynamic consequences may occur with only 100 to 200 mL of blood in the pericardium. When the elastic capacity of the pericardium is exceeded, even small increases in volume cause large increases in intrapericardial pressure and, if untreated, can lead to rapidly fatal cardiac tamponade. Although large, chronic effusions accumulate slowly over time, there is still a point at which the pericardium can no longer accommodate more volume, and tamponade can develop quickly. In a series of 28 patients with large idiopathic pericardial effusions, nearly 30% developed cardiac tamponade unexpectedly.¹ Thus, drainage of large effusions even without signs of tamponade may be appropriate, particularly if there is evidence of right-sided diastolic collapse. A number of different processes can result in the accumulation of fluid in the pericardial space [see Table 1].

Constrictive pericarditis is defined as a chronic fibrous thickening of the pericardium that causes cardiac compression sufficient to prevent normal diastolic filling. It can best be thought of as the chronic sequela of acute pericarditis or of any situation resulting in pericardial irritation and adhesion formation. Almost any cause of acute pericarditis can result in pericardial constriction [see Table 2]. In many patients, there is no clear antecedent event, and the cause of the constrictive pericarditis cannot be determined with certainty.

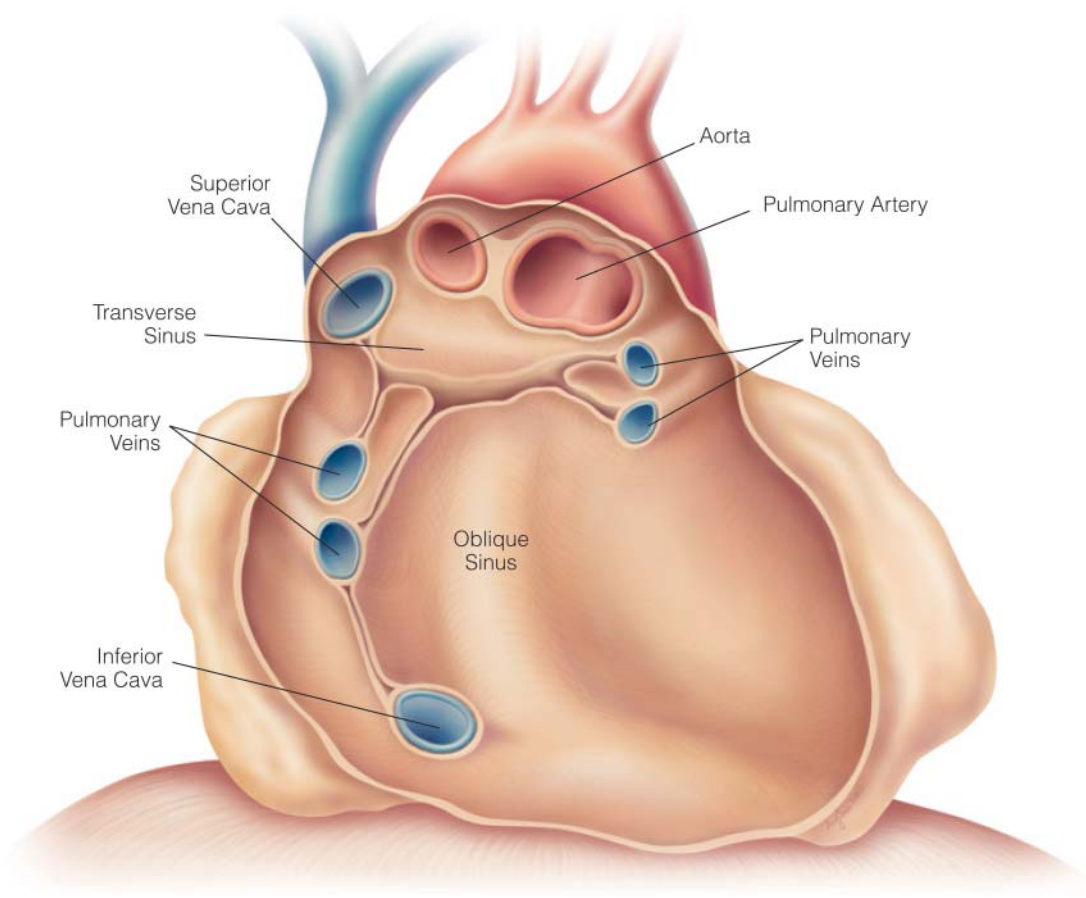


Figure 1 Shown is a view of the pericardium with the heart removed.

Pathologic examination typically demonstrates end-stage fibrosis, and these cases are presumed to be viral in origin. Historically, mycobacterial tuberculosis has been the most common infectious cause of constrictive pericarditis, and it is still the dominant infectious cause in many developing countries today.^{2,3} In the United States, tuberculosis is the cause of constrictive pericarditis in approximately 6% of patients who undergo pericardiectomy.⁴ Constrictive pericarditis also occurs after instrumentation of the pericardium and is seen occasionally (in 0.2 to 0.3% of cases) after cardiac surgery.^{5,6} It also may develop after iatrogenic cardiac perforation in the course of catheterization or pacemaker

Table 1 Common Causes of Pericardial Effusion
Malignancy
Trauma
Uremia
Infection (viral, bacterial, fungal, tubercular)
Autoimmune processes
Cardiac surgery (postoperative complication)
Myocardial infarction
Iatrogenesis (intracardiac procedures)
Aortic dissection
Radiation
Idiopathic origin

Table 2 Causes of Constrictive Pericarditis
Common Causes
Unknown
Infection
Tuberculosis
Viral infection (coxsackievirus B)
Bacterial infection
Fungal infection (histoplasmosis, coccidioidomycosis)
Parasitic infection (amebiasis, echinococcosis)
Cardiac surgery or pacemaker insertion
Penetrating, nonpenetrating, or iatrogenic trauma
Radiation therapy
Connective tissue disorders (rheumatoid arthritis, systemic lupus erythematosus, scleroderma)
Renal failure
Neoplasm
Metastatic disease (breast, lung, lymphatic system, skin)
Primary mesothelioma
Drugs (procainamide, methysergide, hydralazine)
Uncommon Causes
Myocardial infarction
Asbestosis
Amyloidosis
Sarcoidosis
Dermatomyositis
Actinomycosis
Lassa fever
Whipple disease
Mulibrey nanism

placement and after blunt or penetrating trauma—essentially, after any process resulting in an incompletely drained hemopericardium.^{7,8}

The pericardium may harbor metastatic disease or locally advanced disease (e.g., mesothelioma), which may lead to pericardial constriction.^{9,10} Connective tissue disorders (e.g., rheumatoid arthritis and lupus) can cause recurrent acute pericarditis and pericardial effusions, eventually resulting in constrictive pericarditis. A similar situation may arise in patients receiving radiation therapy and patients with renal failure.

The stiffening and thickening of the pericardium have three major physiologic effects. First, the thicker pericardium isolates the heart from changes in intrathoracic pressure. Normally, the pulmonary veins (which are intrathoracic structures) and the cardiac chambers experience the same changes in intrathoracic pressure. In the presence of pericardial constriction, however, the negative intrathoracic pressure generated during inspiration cannot be transmitted to the heart. This isolation of the heart results in decreased flow through the pulmonary veins during inspiration and reduced left-side filling.

Second, the ventricles become interdependent. Because total pericardial volume does not change, the inspiratory decrease in left ventricular filling seen with constriction must be accompanied by an increase in right ventricular filling, with a resultant septal shift toward the left ventricle. During expiration, the opposite occurs: left ventricular filling increases and right ventricular filling decreases, and there is a septal shift toward the right ventricle.

Third, the encasement of the heart impairs the diastolic filling of all cardiac chambers. Elevated atrial pressure causes rapid initial filling of the ventricle (with as much as 75% of the ventricle filled during the first 25% of diastole), but by the middle of diastole, filling abruptly decreases as a result of the rigid pericardium. Because of this limit to diastolic filling, increasing the heart rate becomes the most effective method of increasing cardiac output.¹¹

Other uncommon but potentially significant pericardial diseases include congenital defects and cysts. In one study, congenital defects of the pericardium were found in 1 of 10,000 autopsies.¹² Most commonly, these included partial or total absence of pericardium on the left (70%), right (17%), or total bilateral (rare), and 30% had other associated anatomic anomalies. Most patients with complete absence or large defects are asymptomatic; partial left-sided defects can be complicated by herniation of the heart through the defect and possible strangulation leading to chest pain, shortness of breath, syncope, or sudden death. Surgical pericardioplasty may be indicated in patients with imminent strangulation. Pericardial cysts may be congenital, inflammatory, or echinococcal in origin. Regardless of origin, most cysts are asymptomatic and detected incidentally. Patients with symptoms from compression on the heart are candidates for percutaneous aspiration and ethanol sclerosis, with the addition of pretreatment with albendazole for echinococcal cysts.¹³ Patients with symptomatic inflammatory or congenital cysts who do not respond to aspiration and sclerosis may be candidates for video-assisted thoracotomy or surgical excision.

Pericardial Drainage Procedures for Pericardial Effusion

Pericardial effusion fluid may be transudate, exudate, pyopericardium, or hemopericardium. Regardless of the origin of the fluid accumulation, once the pericardium has reached the limits of its elasticity, the only way in which it can increase its volume is by reducing the volume occupied by the heart within it. Increases in pericardial pressure result in progressive cardiac compression and reductions in intracardiac volumes and myocardial diastolic compliance. This effect is most pronounced in the chambers with the lowest normal intracavitary pressures—namely, the right atrium and the right ventricle.¹⁴ Changes in systemic cardiac output occur as a result of right heart compression, which leads to diminished right ventricular stroke volume, reduced pulmonary blood flow, and decreased left ventricular filling. In the early stages of pericardial effusion, various compensatory changes act to preserve cardiac output. Such changes include an increased ejection fraction, tachycardia, increased intravascular volume via renal conservation of salt and water, increased peripheral vascular resistance, and time-dependent pericardial stretch.^{15,16}

PREOPERATIVE EVALUATION

The presenting symptoms of pericardial effusion may be nonspecific and related to the underlying disorder (e.g., fever, chest pressure, and fatigue). Fluid accumulation that is substantial enough to have hemodynamic consequences is defined as cardiac tamponade. Patients with early tamponade may have dyspnea, tachycardia, mild hypotension, decreased urine output, and paradoxical pulse. As tamponade progresses, patients may manifest signs of end-organ hypoperfusion (e.g., mental status changes, renal insufficiency, and shock). The classic physical findings known as the Beck triad (i.e., jugular venous distention, systemic hypotension, and distant heart sounds) are more common with acute tamponade (such as results from trauma) than with slow-developing tamponade (such as results from medical processes). In patients with slow-developing tamponade, systemic fluid retention is observed, often manifested by peripheral edema or ascites.

Most commonly, pericardial effusion is diagnosed when a patient exhibits new symptoms in the context of an underlying disorder associated with pericardial effusion (e.g., renal failure or malignancy). Chest x-rays may reveal a globular heart or an increasing cardiac silhouette on serial films. Currently, echocardiography is the most commonly employed and most useful modality for the diagnosis of pericardial effusion: it reliably determines the presence, location, and relative volume of fluid accumulations. The size of effusions can be graded based on echocardiographic findings. Grade I effusions are small (echo-free space in diastole <10 mm), grade II effusions are moderate (10 to 20 mm), grade III are large (≥ 20 mm), and grade IV are very large (≥ 20 mm and compression of the heart).¹⁷ In many cases, echocardiography can identify early tamponade, often before symptoms develop. A variety of echocardiographic findings are helpful in diagnosing hemodynamically significant effusions, the most useful being right atrial collapse and right ventricular collapse. Right atrial collapse during late diastole tends to occur early in the development of tamponade because of the normally low right

atrial filling pressures. Right ventricular free wall collapse during early diastole suggests progression of tamponade. Other useful signs are loss of the normal inspiratory collapse of the inferior vena cava and an increase in right ventricular diameter with a reciprocal decrease in left ventricular diameter during inspiration.

In patients who are undergoing invasive hemodynamic monitoring (e.g., those who have just undergone cardiac surgery), hemodynamic findings suggestive of tamponade include elevation of right atrial pressure and equalization of right atrial pressure and pulmonary capillary wedge pressure. It is important to remember, however, that localized tamponade can occur (especially in the postoperative period) without these changes. A common cause is localized clot in the oblique pericardial sinus behind the left atrium, which causes reduced left atrial compliance. Transesophageal echocardiography here may be particularly useful, but it is important to have a high degree of suspicion in these cases as thrombosis does not have the typical echolucent area on echocardiography.

OPERATIVE PLANNING

Choice of Procedure

Three procedures are commonly performed for surgical diagnosis and treatment of pericardial effusion: pericardiocentesis, subxiphoid pericardiostomy (pericardial window), and thoracoscopic pericardiostomy (via either the right or the left pleural space). The choice of a surgical approach to the pericardial space depends on the clinical condition of the patient, the presence or absence of associated pleural effusion or other thoracic process, and the underlying diagnosis (if known). Patients with tamponade may decompensate rapidly during the vasodilatation and positive pressure ventilation associated with general anesthesia. Accordingly, careful consideration must be given to the type of anesthesia employed for pericardial drainage procedures.

Pericardiocentesis is routinely done with local anesthesia only and may be the best choice in an acutely unstable patient with tamponade. If this option is chosen, however, the choice must be made with the understanding that pericardiocentesis, because of its high recurrence rate and its limited diagnostic capacity, is unlikely to constitute definitive therapy. Subxiphoid pericardiostomy is generally done with initial local anesthesia followed by induction of general anesthesia, and most patients with tamponade can undergo this procedure. The subxiphoid approach provides the hemodynamic benefits of pericardiocentesis, offers the enhanced diagnostic capability of pericardial biopsy, and has a low recurrence rate. Consequently, it is the procedure of choice for patients with tamponade who are stable enough to be transported to the operating suite. Thoracoscopic pericardiostomy has the advantage of enabling simultaneous treatment of pleural processes, which are commonly present in these patients [see *Figure 2*]. Ipsilateral pleural and pericardial spaces can be fully explored, pleural effusions can be drained, loculations can be divided, and biopsy specimens can be obtained as needed. The thoracoscopic approach can be especially useful in the case of a known loculated effusion that is limited to one area of the pericardium, in that a pericardial window can be created via either pleural space. This approach also allows resection of a larger segment of pericardium, which may

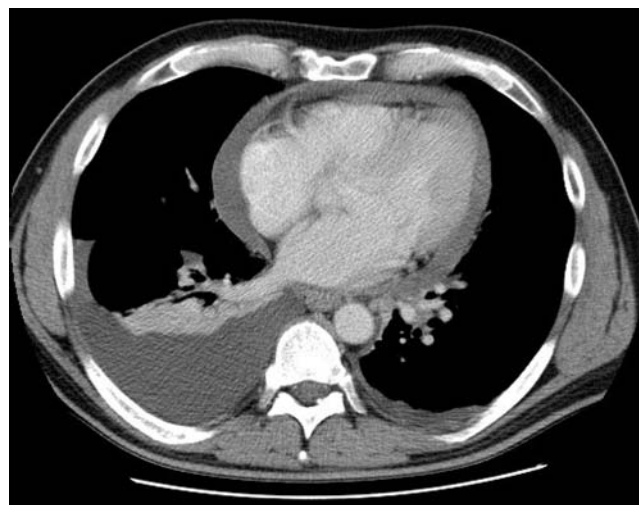


Figure 2 Computed tomography demonstrates right pleural and pericardial effusions, for which a right thoracoscopic approach is ideal.

improve the diagnostic yield and reduce the likelihood of recurrent effusion. The major limitation of thoracoscopic pericardiostomy is the need for lung isolation and lateral positioning, which should not be attempted in patients with evidence of tamponade. By weighing the relative risks and benefits of these three procedures, the surgeon can choose the optimal approach for each patient.

PERICARDIOCENTESIS

Operative Technique

Pericardiocentesis is performed either at the bedside in an urgent situation or, preferably, under echocardiographic or fluoroscopic guidance in a catheterization laboratory. The basic technique is simple.

Step 1: placement of needle A local anesthetic is infiltrated along the left side of the xiphoid. An 18-gauge spinal needle attached to a three-way stopcock and syringe is then advanced into the pericardial space and directed cephalad toward the left shoulder at a 45° angle until fluid is aspirated [see *Figure 3*]; if air is aspirated, the needle is withdrawn and redirected more medially. Once fluid is aspirated freely, it is inspected. If the fluid is bloody, 5 mL is withdrawn and placed on a sponge. If the fluid on the sponge clots, it is fresh blood, probably from a cardiac injury occurring during the procedure or from intracardiac positioning of the needle; blood that has been in the pericardium for even a short time becomes defibrinated and will not clot.¹⁸

Troubleshooting The inherent danger of cardiac injury during pericardiocentesis should be obvious. The risk is highest with small or loculated effusions and patients with coagulation abnormalities. The possibility of cardiac aspiration or injury can be minimized, although not eliminated, by means of various safety measures. Of historical interest, the simplest of these measures was to attach an electrocardiographic (ECG) lead to the needle and employ continuous ECG monitoring. If the needle contacts the epicardium, ST

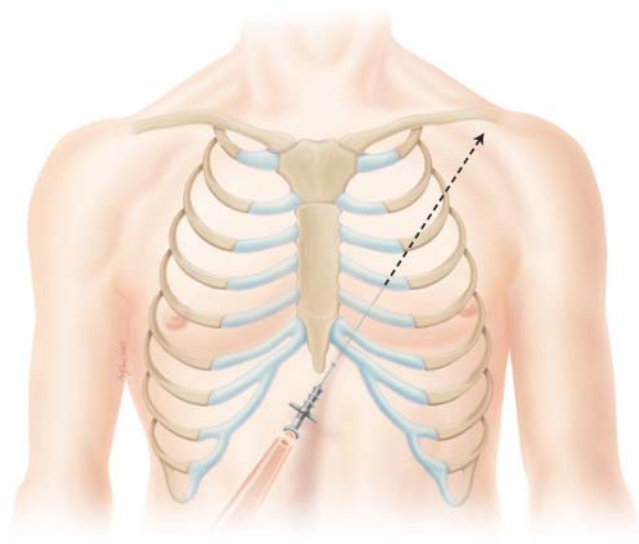


Figure 3 Pericardiocentesis. The needle is angled toward the left shoulder at an angle of 45°.

segment elevation will be observed, in which case, the needle is withdrawn until the ST elevation disappears. This is not considered to be an adequate safeguard anymore, and most experts recommend direct visualization using fluoroscopic or echocardiographic guidance. Fluoroscopy or echocardiography is essential in cases of loculated effusions to help direct aspiration. Simultaneous cardiac catheterization has also been used to locate the right coronary artery and the atrioventricular groove.

Step 2: placement of drainage catheter and aspiration of fluid Once the needle is within the pericardial space, a guide wire is placed through it, and a small-bore drainage catheter is advanced into the effusion by means of a modified Seldinger technique. Fluid is aspirated and sent for laboratory evaluation (including cell count, chemistry, culture, and cytology). The catheter is then connected to a closed drainage system for 24 to 72 hours; this may help reduce recurrence.

Complications

The most serious complications of pericardiocentesis are laceration and/or rupture of the myocardium and coronary vessels. Thankfully, these are rare (<1% when fluoroscopy is used).¹⁹ More common complications of pericardiocentesis include arrhythmias, pneumothorax, air embolism, puncture of the abdominal cavity or abdominal organs, misdiagnosis, and recurrence of pericardial effusion. In every patient undergoing pericardiocentesis, pneumothorax must be ruled out by means of chest x-ray at the completion of the procedure or, if respiratory or hemodynamic changes develop intraoperatively, during the procedure. Cardiac injuries range from minor needle lacerations to the epicardium, which are self-limited in patients with normal coagulation parameters, to potentially fatal injuries to the myocardium or coronary vessels that can lead to acute cardiac tamponade. Incorrect diagnoses based on pericardiocentesis are not uncommon.

Although a diagnosis can be confirmed by positive results from fluid culture or cytology, negative results from cytology do not rule out malignant effusion. Cytologic analysis of pericardial fluid is diagnostic in only 55 to 85% of patients.²⁰ Further diagnostic maneuvers often must be undertaken, usually involving subxiphoid or thoracoscopic approaches with pericardial biopsy. Recurrence of pericardial effusion after pericardiocentesis is extremely common. In a review that included 139 patients with malignant pericardial effusions who were treated with pericardiocentesis, successful fluid removal with symptomatic relief was achieved in 97.1% of cases.²¹ Of the 139 patients, 2.9% experienced complications (e.g., pneumothorax and ventricular laceration) and one (0.7%) died. In all, 45 of the patients received no further therapy, and in 25 (55%) of the 45, recurrent effusions developed that necessitated reintervention.

Several techniques for preventing recurrent pericardial effusion have been tried. Instillation of a sclerosing agent (e.g., tetracycline, thiopeta, or bleomycin) into the pericardium to promote fusion of the two layers of the pericardium has been shown to increase the success rate of pericardiocentesis by as much as 85%.^{22–24} Placement of an indwelling catheter (see above) also has been shown to improve the success rate.^{21,25} Several authors have described creating a pericardial window percutaneously by means of balloon dilation of the tract created by pericardiocentesis, which theoretically allows fluid to drain into the pleural space or the subcutaneous tissues, where it can be absorbed.^{26,27} However, it is unclear how long a window created in this fashion will remain patent. Although pericardiocentesis provides initial symptomatic relief in most patients, the observation that 15 to 45% of patients require a further procedure for diagnosis and as many as 55% require reintervention for recurrence has led some authorities to question its benefit.

SUBXIPHOID PERICARDIOSTOMY (PERICARDIAL WINDOW)

Operative Technique

Subxiphoid pericardiostomy may be performed either to diagnose pericardial effusion or to manage tamponade. For diagnosis, the procedure is usually done with general anesthesia. In an unstable patient with significant tamponade, who would be at risk for hemodynamic collapse with general anesthesia, the procedure may be performed with the patient under local anesthesia and mild sedation and breathing spontaneously. If there is any question of tamponade, the patient is prepared and draped while awake, and anesthesia is induced only when the surgeon is ready to begin. In all patients, the entire chest should be prepared in case a left anterior thoracotomy or median sternotomy is required. Ideally, the patient is sedated and the airway controlled while spontaneous respiration is maintained to minimize hemodynamic effects. If necessary, a local anesthetic may be infiltrated and the incision made before induction of anesthesia.

Step 1: initial incision and exposure of pericardium

A small vertical incision is made from the xiphisternal junction downward to a point slightly below the tip of the xiphoid process [see Figure 4a]. The upper extent of the linea alba is divided, with care taken not to enter the peritoneum. Peritoneal openings are easily repaired but can make the

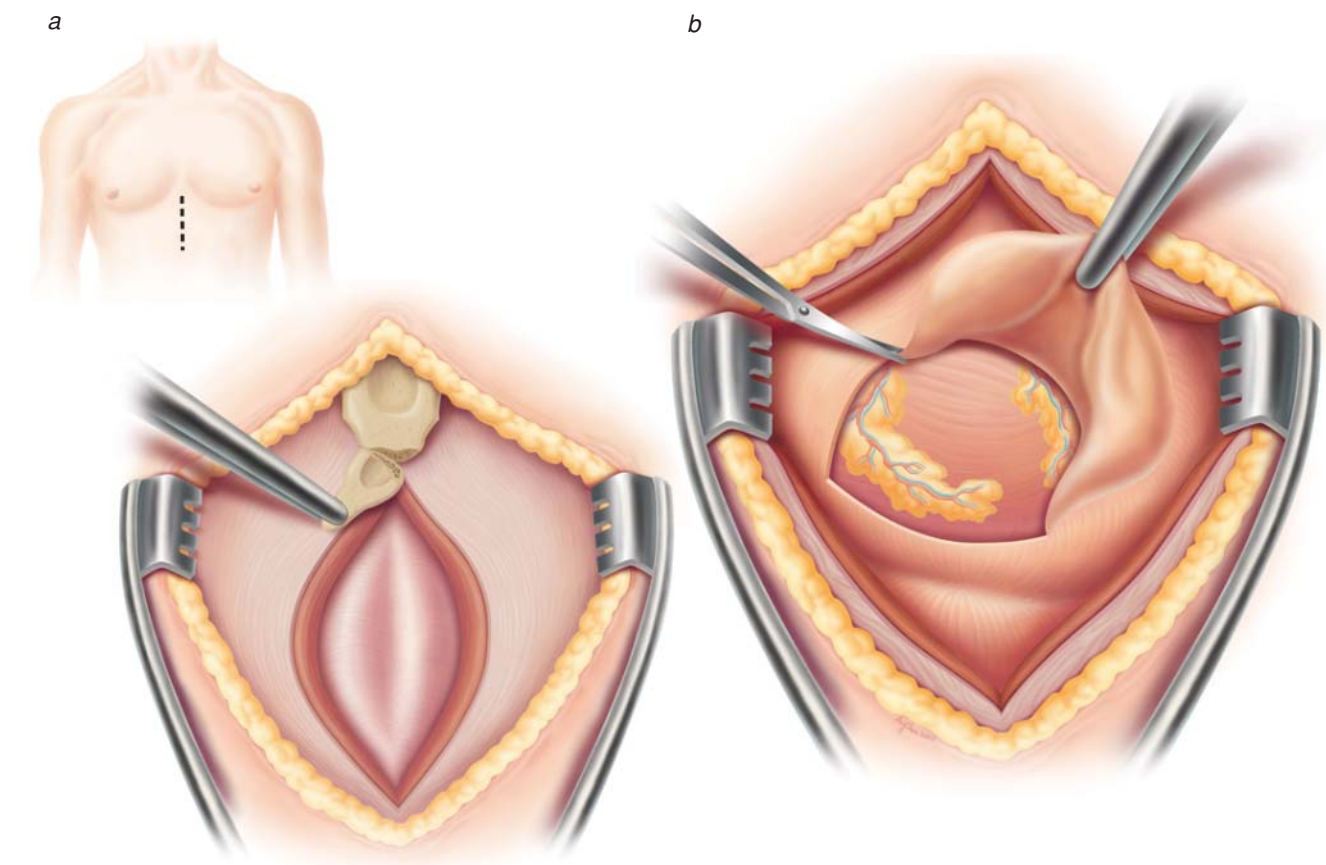


Figure 4 Subxiphoid pericardiostomy. (a) A small vertical incision is made from the xiphisternal junction down to a point just below the tip of the xiphoid, the upper extent of the linea alba is divided, and the xiphoid is removed. (b) The pericardium is opened, and the edge of the opening is grasped and elevated. A pericardial specimen several square centimeters in size is then resected to create the pericardial window.

procedure technically more difficult in that abdominal contents tend to impede visualization, especially in spontaneously breathing patients. Positioning patients with feet down in a reverse Trendelenburg position prior to the procedure may allow the abdominal organs to fall toward the pelvis and out of the way. The soft tissue attachments to the xiphoid are divided, the veins running along either side of the xiphoid are controlled, and the xiphoid process is removed.

The tissue plane behind the lower sternum is developed by means of blunt dissection. This maneuver exposes the retrosternal space to allow visualization of the pericardium. To enhance exposure, the sternum is retracted upward by an assistant. The anterior pericardial surface is then exposed by sweeping away the remaining mediastinal fat. If necessary, the confluence of the pericardium and the diaphragm may be retracted caudally to improve exposure.

Step 2: opening of pericardium The location of the pericardial incision can be confirmed by palpating cardiac motion through the exposed pericardium. The pericardium is then opened with a scalpel; shallow strokes should be employed to reduce the chances of injuring underlying myocardium that may be adherent to the pericardium. Upon entry into the pericardium, there is an initial outrush of fluid. A sanguineous effusion can be difficult to differentiate from

cardiac injury; therefore, the patient's hemodynamics should be carefully monitored during this time. When the pressure placed on the heart by an effusion is released, blood pressure will usually rise and heart rate fall; however, if the heart has been accidentally injured, the opposite will occur. Once hemodynamic stability is achieved, administration of a diuretic (e.g., furosemide) should be considered to reduce the risk of pulmonary edema developing as a result of systemic fluid retention.

Step 3: creation of pericardial window Pericardial fluid is collected for microbiologic and cytologic analysis and for any additional testing suggested by the clinical scenario. The pericardial space is gently explored with the fingers, and all remaining fluid is evacuated. The edge of the pericardial opening is grasped with a clamp and elevated [see Figure 4b]. A pericardial specimen several square centimeters in size—or as large as can safely be managed—is resected and sent for pathologic and microbiologic analysis.

Step 4: drainage and closure A separate stab incision for drain placement is made below and to one side of the lowermost aspect of the skin incision. Bringing the drainage tube out through a separate incision helps prevent incisional complications (e.g., infection and hernia). A 24 to 28 French

chest tube (either straight or right-angle) is tunneled through the fascia at the entry site so that it lies beneath the divided linea alba in the preperitoneal space. The tube is then directed through the pericardial window and into the pericardial space and secured at skin level. The fascia at the linea alba is closed with interrupted sutures to provide secure closure and prevent late hernia; the skin and subcutaneous tissue are closed in the standard fashion. The chest tube is connected to a drainage system with a water seal. Pericardial drainage is maintained for several days postoperatively until the output falls below 100 mL/day. This period allows time for apposition and adhesion formation between the visceral pericardium and the parietal pericardium.

Although some fluid may initially drain into the subcutaneous tissues and be absorbed, the name pericardial window is something of a misnomer. The surgically created window in the pericardium is unlikely to remain patent over the long term, and, in fact, obliteration of the pericardial space has been shown to be the mechanism responsible for the success of this procedure.^{28,29}

Complications

Complications from subxiphoid pericardiostomy are rare; bleeding, infection, incisional hernia, anesthetic complications, and cardiac injury have been reported. In a study that included 155 patients who underwent subxiphoid pericardiostomy over a 5-year period, not a single death was attributable to the operative procedure itself.²³ The 30-day mortality was high but was related to the underlying disease process: 33% in patients with malignant effusions and 5% in those with benign effusions. Recurrent pericardial effusion necessitating additional procedures occurred in four patients (2.5%). In a study that compared 94 patients who underwent subxiphoid pericardiostomy with 23 patients who underwent pericardiocentesis, the rate of recurrent effusion that necessitated reintervention was 1.1% after the subxiphoid window procedure but 30.4% after pericardiocentesis.³⁰ In this series, the rate of major complications after the pericardial window procedure was 1.1% (one patient with bleeding that necessitated reexploration), compared with a major complication rate of 17% after pericardiocentesis (including a mortality of 4%).

Several studies have shown that the most important predictor of long-term outcome is the underlying disease process. In one, the median survival time was 800 days for patients with benign disease, 105 days for patients with known cancer but negative results from pericardial cytology and pathology, and only 56 days for patients with malignant effusions.²⁸ It appears, however, that cancer patients with hematologic malignancies and pericardial effusion survive significantly longer than patients with other malignancies. In another study, the mean survival time after drainage of pericardial effusion was 20 months for patients with hematologic malignancies, compared with 5 months for patients with any other malignancies.³¹ The investigators suggested that this finding may be related to the relative responsiveness of hematologic cancers to systemic chemotherapy. Patients with HIV disease have been shown to have universally dismal outcomes after they present with pericardial effusion. In this population, surgical pericardial drainage generally is not diagnostically revealing and is of little therapeutic value. Several authors

have questioned whether pericardial drainage should even be offered to these patients.³²

THORACOSCOPIC PERICARDIOSTOMY

Operative Technique

Thoracoscopic pericardiostomy is a safe and effective approach to the diagnosis and management of pericardial effusion, especially in patients with a unilateral pleural disease process that can be simultaneously addressed in the course of the procedure. Thoracoscopic pericardial drainage necessitates single-lung ventilation and thus is unsuitable for unstable patients, especially those with tamponade. Such ventilation can be accomplished by means of either a dual-lumen endotracheal tube or a bronchial blocker placed through a standard endotracheal tube.

Once the tube is in place, the patient is turned to the appropriate lateral decubitus position. The side of approach is chosen on the basis of the location of a loculated effusion or the site of any coexisting pathologic condition (e.g., a pleural effusion, pleural nodules or thickening, or pulmonary nodule). If the disease process or processes present do not dictate a particular side of approach, the right side is preferred. It is often easier to operate on the right side because there is more working room within the pleural space; however, operating on the left side usually allows the surgeon to create a larger pericardial window. If tamponade is present in a patient for whom the thoracoscopic approach is desired, pericardiocentesis may be performed before induction of general anesthesia.³³

Step 1: placement of ports and entry into pleural space An initial camera port is placed in the posterior axillary line at the eighth intercostal space [see Figure 5]. The pleural space is entered and explored, and any effusion present is drained. Pleural fluid is sent separately for culture and cytologic analysis. To prevent inadvertent entry into the pericardium, which is often distended, a second incision is created anteriorly at the fifth intercostal space under camera visualization.

Step 2: opening of pericardium On the left side, the phrenic nerve, which runs midway between the hilum and the anterior chest wall, is carefully identified, and an initial pericardial incision is made approximately 1 cm anterior to this nerve. Care must be taken to place this first incision in an area that is free of cardiac adhesions. When grasped, the pericardium should tent outward slightly. Often cardiac motion is visible through the pericardium.

Step 3: creation of pericardial window A pericardial window several square centimeters in area is removed. A similar window may be created posterior to the phrenic nerve—again, with care taken to stay at least 1 cm away from the nerve. The pericardial space is inspected, and any loculations are opened. The procedure is similar when performed on the right side, except that the phrenic nerve on the right runs much closer to the hilum; accordingly, instead of two pericardial windows (anterior and posterior to the nerve), only a single, larger pericardial window is created (anterior to the nerve).

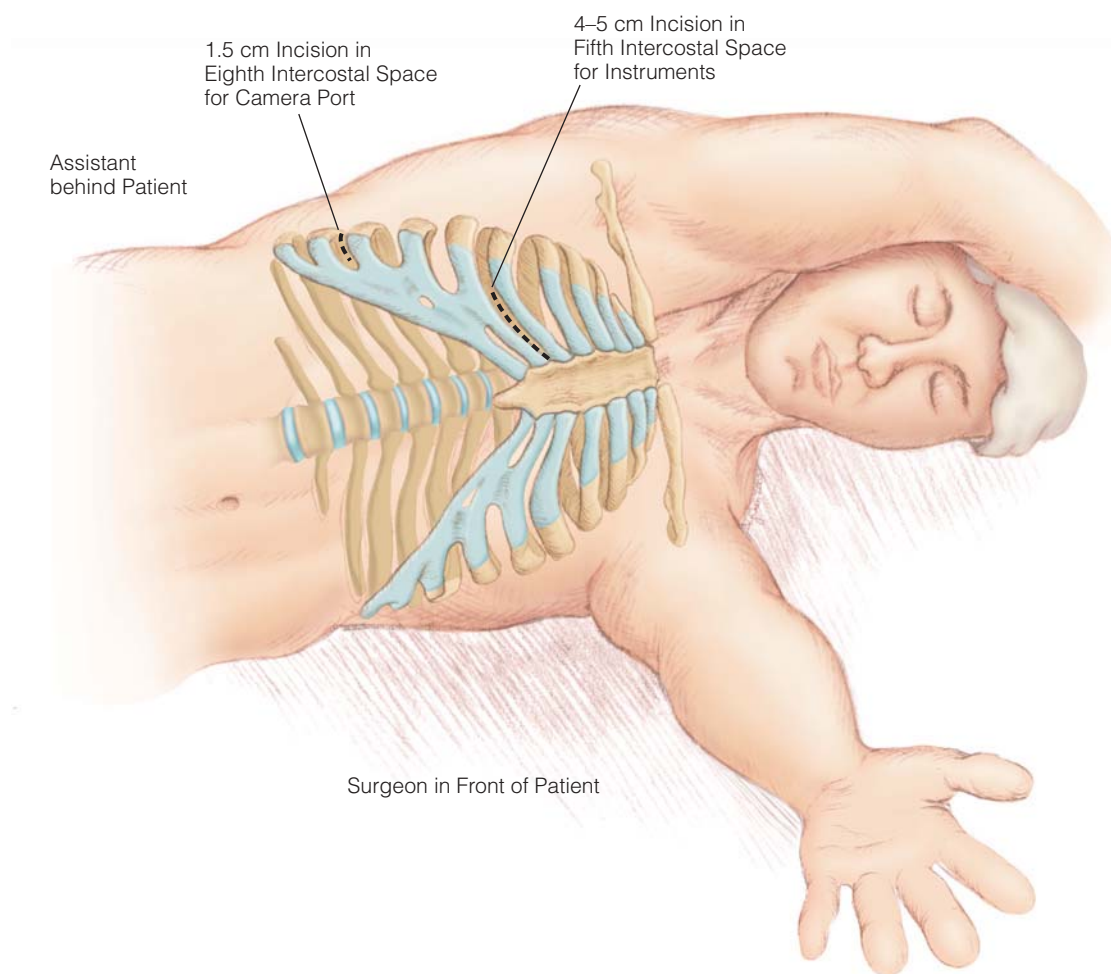


Figure 5 Thoracoscopic pericardiostomy. Shown are the appropriate patient positioning and the proper placement of ports and instruments.

In patients who can tolerate general anesthesia, a pericardial window can be created thoracoscopically with excellent diagnostic yield and relief of symptoms.³⁴ The thoracoscopic approach allows directed access and can be useful in treating effusions that recur after subxiphoid pericardiostomy.³⁵

Complications

Complications from thoracoscopic pericardiostomy occur more frequently than from the subxiphoid approach. Reported complications include bleeding, infection, and cardiac injury similar to the subxiphoid approach, but compared to the subxiphoid approach, patients who undergo thoracoscopic procedures have longer anesthesia times and require single-lung ventilation, which increases the incidence of anesthesia-related complications. Patients who undergo thoracoscopic procedures require pleural tubes in the immediate postoperative period, and various complications related to chest tubes (e.g., recurrent pneumothorax, trapped lung) may occur. One recent study compared subxiphoid to videothoracoscopic pericardial window procedures in 71 patients.³⁶ In this retrospective review, 56 patients underwent subxiphoid pericardiostomy and 15 underwent the procedure thoracoscopically. Nonpericardial procedures were performed in 10 of 15

thoracoscopic procedures (67%) and only 18 of 56 (32%) of the subxiphoid approach. Anesthesia time (117 ± 32 vs 81 ± 26 minutes) and minor procedural morbidity (27% versus 2%) were higher for the thoracoscopic approach, but long-term control of the effusion seemed to be improved in the thoracoscopic approach. Equal percentages of patients had recurrence of their effusions ($\approx 10\%$), but time to recurrence was much longer for the thoracoscopic procedures (36 versus 11 months).

Pericardiectomy for Constrictive Pericarditis

Constrictive pericarditis appears to be about three times as common in males as in females, and it may occur at any point in life from childhood to the ninth decade.³⁷ The symptoms of constrictive pericarditis usually develop progressively over a period of years but may develop within weeks to months after a defined inciting event (e.g., mediastinal irradiation or cardiac surgery). Signs and symptoms are related to pulmonary venous congestion (e.g., exertional dyspnea) and systemic venous congestion (e.g., elevated jugular venous pressure, hepatomegaly, ascites, and peripheral edema).

PREOPERATIVE EVALUATION

The physiologic effects of the thickened pericardium form the basis for the diagnosis of constrictive pericarditis and, more important, for the differentiation of constrictive pericarditis from restrictive cardiomyopathy, which often presents a similar picture. Echocardiography can be employed to rule out other causes of right-side failure. Specific findings that suggest pericardial constriction include septal bounce (a respiratory phase-related septal shift) and decreased transmitral flow velocity during inspiration. Computed tomography and magnetic resonance imaging may demonstrate thickened, often calcified, pericardium; however, the degree of pericardial thickening does not necessarily correlate with the presence of hemodynamic effects.

Cardiac catheterization may demonstrate increases in and equalization of end-diastolic pressure in all four cardiac chambers, a dip-and-plateau pattern (the square-root sign) in the ventricular pressure curves as a result of rapid early filling and limited late filling, and rapid x and y descents in the atrial pressure curves. The most useful information obtainable through cardiac catheterization has to do with the respiratory variation of ventricular pressure. In a patient with a normal heart or a patient with restrictive cardiomyopathy, inspiration causes a decrease in both right ventricular pressure and left ventricular pressure as a consequence of decreased intrathoracic pressure. In a patient with constrictive pericarditis, because of the interdependence of the ventricles, inspiration causes a decrease in left ventricular pressure but an increase in right ventricular pressure.³⁸

OPERATIVE PLANNING

Choice of Approach

Pericardiectomy may be performed via either a median sternotomy or a left anterolateral thoracotomy, with equivalent results. Median sternotomy provides better access to the right atrium and the great vessels, as well as easier access for cannulation if cardiopulmonary bypass is required; left anterolateral thoracotomy allows more complete release of the left ventricle. With either approach, the patient should undergo full monitoring, including radial artery catheterization and central venous catheterization, with consideration given to placement of a pulmonary arterial catheter if there is significant hemodynamic compromise. Because significant blood loss can occur when densely adherent pericardium is resected, large-bore intravenous access should be available as well.

OPERATIVE TECHNIQUE

Median Sternotomy

Step 1: initial incision and exposure The patient is placed in the supine position, and the skin incision is carried down to the level of the sternum. If there is no history of previous pericardial procedures and it is possible to develop the plane behind the sternum bluntly at the superior and inferior aspects, a standard sternotomy saw can be used for the median sternotomy. If, however, there are likely to be adhesions between the sternum and the pericardium or the heart (as in the case of constrictive pericarditis after coronary artery bypass grafting), a careful reoperative sternotomy

should be performed with an oscillating saw. Access to the femoral vessels should be available within the sterile field; placement of a femoral arterial line will facilitate percutaneous cannulation in the event that the heart is injured during sternal reentry.

After the sternum is opened, all adhesions are dissected away from the sternum, with care taken to stay as close to the posterior surface of the sternum as possible. Both pleural spaces are opened, and the left and right phrenic nerves are identified.

Step 2: dissection and resection of pericardium The phrenic nerves define the limits of pericardial resection bilaterally. Small loculated spaces are often present within the pericardium, especially near the great vessels and the diaphragm, and provide good starting places for pericardiectomy. Once an initial flap is raised, it is used to provide retraction to facilitate further dissection. Careful attention must be paid to the coronary artery anatomy: coronary arteries and bypass grafts are vulnerable to injury. If the pericardium is densely adherent in the region of a coronary artery, small islands of pericardium may be left on the heart. Areas of calcification can be addressed with the use of bone-cutting instruments; however, if an island of calcification appears to extend into the myocardium, it should not be removed.

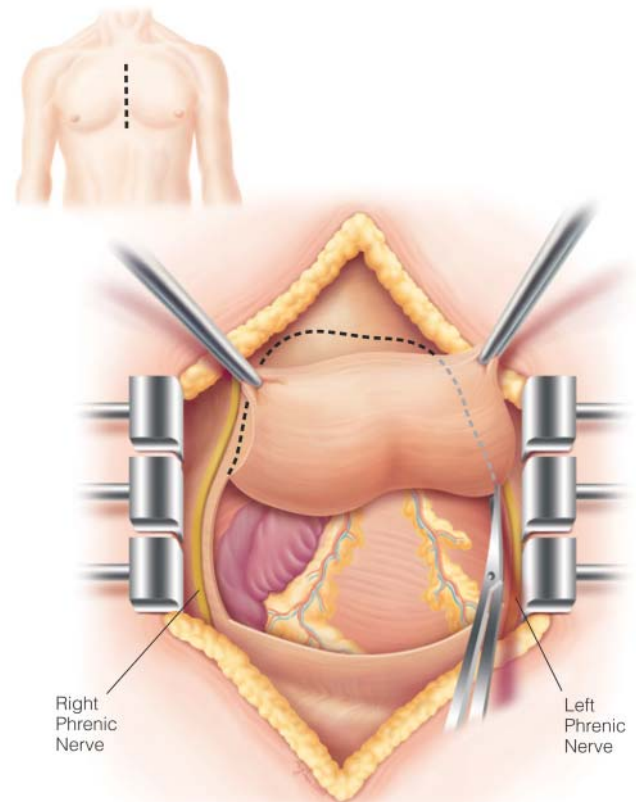


Figure 6 Pericardiectomy: median sternotomy approach. The pericardium is resected from the left phrenic nerve to the right phrenic nerve.

Epicardium can also be involved in the disease process and should be resected or scored until no further restriction to ventricular filling remains. The heart should be dissected free of the left pulmonary veins all the way over to the right pulmonary veins (including the origins of the venae cavae). The pericardium is resected from the left phrenic nerve to the right phrenic nerve [see *Figure 6*].

Cardiopulmonary bypass can make dissection easier, but in view of the greater risk of bleeding and the increased transfusion requirements, it is best avoided if possible. Cardiopulmonary bypass does facilitate repair of cardiac injuries during sternal reentry or dissection and should be used if cardiac procedures are to be performed concomitantly.

Step 3: drainage and closure After completion of the pericardiectomy, mediastinal and pleural drains are placed, and the sternum is closed in the usual fashion.

Left Anterolateral Thoracotomy

Step 1: initial incision and exposure The patient is placed in the supine position, with a roll under the left side of the torso to elevate the left side 45°. It is often difficult to establish cardiopulmonary bypass through the chest via this approach; therefore, the femoral vessels should be available within the sterile field so that femorofemoral bypass can be instituted if necessary. A curvilinear submammary incision is created, and the chest is entered at the fifth interspace.

For improved exposure, the internal thoracic vessels may be divided and the intercostal muscles divided posteriorly. The left phrenic nerve is carefully identified.

Step 2: dissection and resection of pericardium As with the median sternotomy approach, loculated spaces are often present near the great vessels and the diaphragm, and these vessels provide good starting places for dissection. The entire pericardium is dissected free over the left ventricle, and an island of pericardium is left attached to the phrenic nerve along its length [see *Figure 7*]. The pericardium is resected from the pulmonary veins to a point just posterior to the phrenic nerve. Resection resumes anterior to the nerve and continues across the anterior aspect of the heart as far as possible, ideally to the right atrioventricular groove. The same precautions should be taken around the coronary vessels as are taken with the median sternotomy approach.

Step 3: drainage and closure After completion of the pericardiectomy, mediastinal and pleural drains are placed, and the thoracotomy is closed in the usual fashion.

OUTCOME EVALUATION

There is no proven difference between the two approaches to pericardiectomy with respect to outcome. Accordingly, the choice between them is based on whether one option affords better access to the areas believed to be most involved

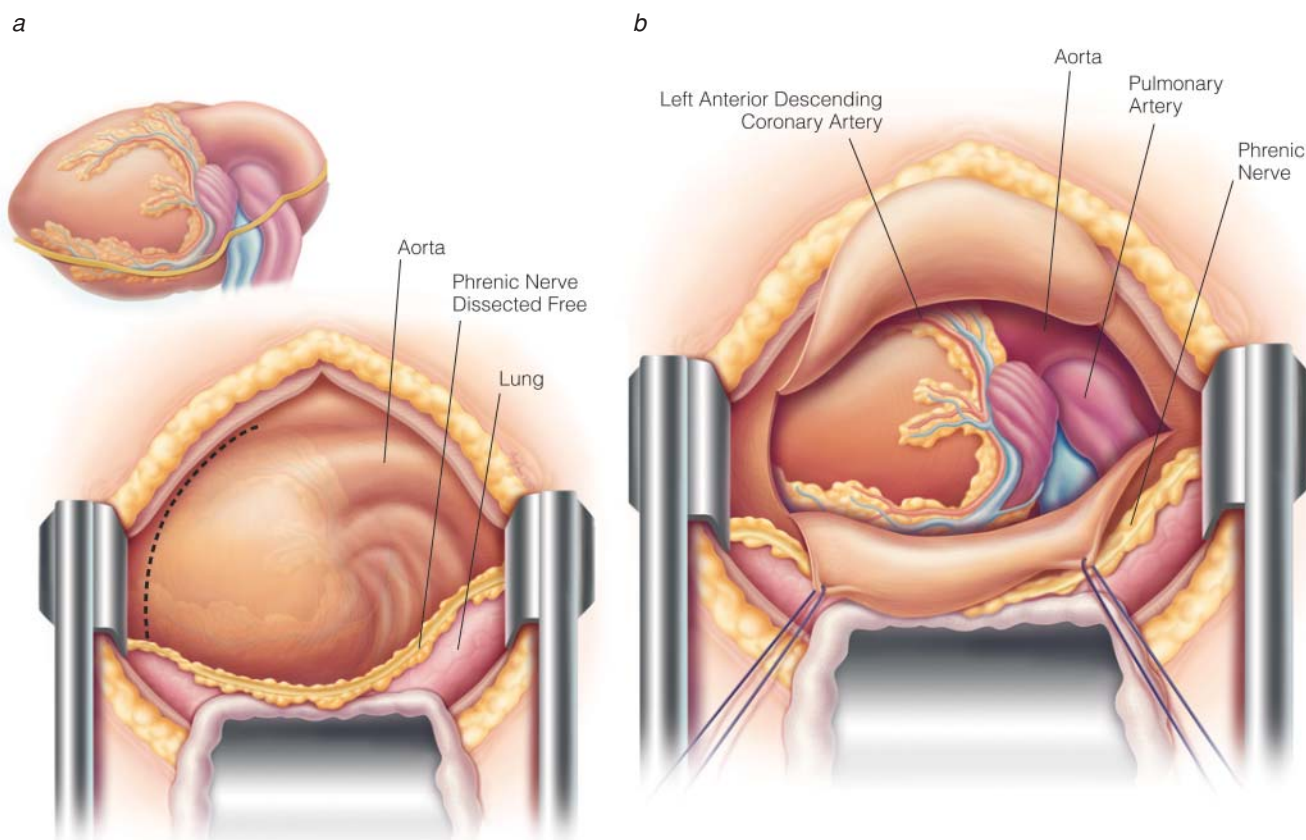


Figure 7 Pericardiectomy: left anterolateral thoracotomy approach. (a) The left phrenic nerve is identified. (b) The entire pericardium is dissected free over the left ventricle, with an island of pericardium left attached to the phrenic nerve along its length. Care must be taken to avoid injuring coronary vessels.

(e.g., a median sternotomy is more effective for releasing the right side of the heart) and whether the surgeon is more comfortable with one approach or the other.

The underlying cause of constrictive pericarditis is a significant predictor of long-term survival. In a study of 163 patients who underwent pericardiectomy, 7-year survival rates were highest in patients with idiopathic constrictive pericarditis (88%), somewhat lower in patients with postoperative constriction (66%), and lowest in patients with radiation-induced constriction (27%).³⁹ Predictors of decreased survival included previous radiation therapy, renal dysfunction, pulmonary hypertension, and abnormal left ventricular systolic function. Perioperative mortality was 6% overall but 21% in patients who had received radiation therapy and 8% in postsurgical patients. The slightly higher mortality recorded in postoperative patients may reflect underlying cardiac dysfunction, as well as the vulnerability of previous bypass grafts to injury. The poor outcomes after

pericardiectomy for radiation-induced constriction indicate that constriction is not the sole factor responsible for cardiac failure in this situation. Although cardiac failure has been attributed to myocardial atrophy caused by prolonged constriction, the excellent outcomes reported after pericardiectomy for idiopathic constrictive pericarditis suggest that constriction is rarely the only cause of cardiac failure.

Another study reported similar findings, with radiation-induced constriction leading to significantly decreased 10-year survival after pericardiectomy.³⁷ The authors also noted that patients who underwent pericardiectomy for radiation-induced constriction had demonstrably worse late functional status. Fifteen of 17 long-term survivors with a history of previous radiation therapy showed New York Heart Association class III or IV symptoms, whereas only 31 of 112 patients without a history of radiation therapy had major symptoms of heart failure.

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13 DECORTICATION AND PLEURECTOMY

Eric S. Lambright, M.D.

In normal circumstances, the pleural space is a potential cavity between the lung and the chest wall—more specifically, between the visceral pleura and the parietal pleura. In the average healthy patient, this space is less than 1 mm thick. There are a number of pathologic processes that can alter the transport of cells and fluid within this space and thus give rise to clinically significant sequelae. One such process is fibrothorax, which is defined as the presence of abnormal fibrous tissue within the pleural space, resulting in entrapment of the underlying pulmonary parenchyma (a state variously referred to as trapped lung, restrictive pleurisy, or encased lung). Decortication is the surgical procedure by which this restrictive fibrous layer is peeled away from the lung; the literal meaning of the term is the stripping away of a rind (from the Latin word *cortex* “bark, rind, shell”). The technical goals of the operation are to reexpand the lung and resolve the pathologic process affecting the pleural space so that pulmonary function and chest wall mechanics will improve and the patient’s symptoms will be relieved.

Successful management of a patient with fibrothorax depends on close adherence to basic surgical tenets: appropriate selection of patients for surgical treatment, preoperative optimization of the patient’s physiologic status, exacting attention to the technical aspects of the procedure, and timely intervention to address perioperative complications. If insufficient attention is paid to any of these important tenets, decortication may fail to achieve any significant improvement in the patient’s symptoms or physiologic status, potentially leaving him or her in an even more debilitated state.

Preoperative Evaluation

PATHOPHYSIOLOGY OF FIBROTHORAX

Although any insult to the pleura can result in an inflammatory response with fibrin deposition,¹ hemothorax and infection (bacterial and mycobacterial) remain the most common causes of fibrothorax [see Table 1]. Typically, empyemas evolve over a 4- to 6-week period as the infection progresses throughout the pleural space. The first (exudative) phase is characterized by a thin, fibrin-containing fluid exudate. The second (fibropurulent) phase is characterized by a heavy fibrin deposit over the pleural surface with the development of loculations and fibrous debris in the thoracic cavity. The third (organizational) phase, which begins at about 3 to 5 weeks, is characterized by the formation of a thick fibrous peel that imprisons the lung and prevents expansion. When fully developed, this peel has three distinct layers: (1) an outer layer consisting of loosely organized vascular tissue, (2) a middle layer consisting of fibrous connective tissue that is relatively avascular and acellular, and (3) an inner layer consisting of necrotic tissue and fibrinoid masses.² Generally, if a hemothorax is small, it will be reabsorbed, provided that the lymphatic system is intact. However, if the hemothorax is relatively large, if there is continued bleeding, or if bacteria are present, there is a high likelihood that a fibrous peel will eventually form.³

HISTORY AND PHYSICAL EXAMINATION

The physiologic consequences of a fibrothorax culminate in pulmonary restriction, manifested by decreased lung volumes, reduced diffusion capacity, and lower expiratory flow rates. Movement of the chest is impaired.⁴ The initial clinical presentation of a fibrothorax depends on its cause and severity, as well as on the presence or absence of underlying parenchymal disease. Typically, dyspnea on exertion is the most common presenting symptom, though cough, fever, pleuritic chest discomfort, malaise, night sweats, weight loss, or chest pressure may also be present. In obtaining the clinical history, it is important to determine whether the condition is chronic and whether there are any other underlying disease processes that may be complicating the pulmonary disease process. Physical examination yields relatively nonspecific findings; typically, decreased breath sounds and decreased chest wall excursion are noted.

DIAGNOSTIC IMAGING AND PHYSIOLOGIC TESTING

Radiographic evaluation is the mainstay of diagnosis [see Figures 1, 2, and 3]. Computed tomography (CT) of the chest is the imaging modality of choice for delineating abnormalities of the pleural space and defining the character of the pleural disease process. CT scanning can assess the extent and thickness of pleural involvement and characterize associated parenchymal disease. It readily identifies parenchymal abnormalities such as fibrosis, bronchiectasis, and malignancy. Such factors play a role in surgical decision making. In particular, malignancy must be included in the differential diagnosis of fibrothorax and ruled out; the management options for malignant disease are quite different from those for benign disease.

Physiologic testing with spirometry and evaluation of diffusing capacity helps define the degree of pulmonary dysfunction and facilitates risk stratification. The results of pulmonary function testing may be quite abnormal preoperatively and are often worse than would have been expected from the radiographic evaluation. Marked abnormalities in physiologic testing should not be considered absolute contraindications to surgical intervention, because some degree of improvement may be anticipated. The improvement in dyspnea, pulmonary reexpansion, and parenchymal function that can realistically be expected after decortication may be

Table 1 Common Causes of Fibrothorax

Chronic empyema
Retained hemothorax (traumatic or iatrogenic)
Pleural effusive disease
Transudative
Chylous
Pancreatic
Sequelae of <i>Mycobacterium tuberculosis</i> infection
Chronic pneumothorax

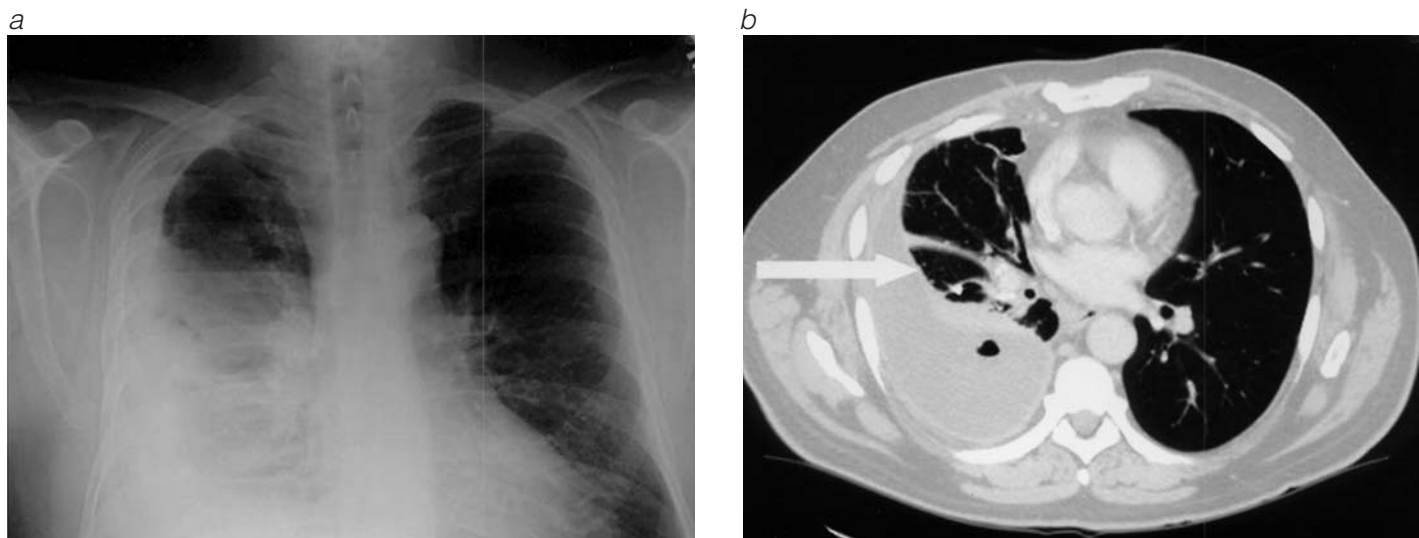


Figure 1 (a) Shown is a chest x-ray from a patient with a 2-month history of dyspnea and cough associated with intermittent fever and night sweats. Treatments included three courses of antibiotics and bronchodilator therapy. (b) A chest CT scan from the same patient shows a large pleural collection containing air and demonstrates pleural thickening (arrow). The findings are consistent with empyema. Thoracentesis was performed, demonstrating white, creamy purulence but failing to achieve reexpansion of the lung. Decortication was performed.

estimated on the basis of the preoperative diagnostic imaging and physiologic testing. Ultimately, the surgeon's judgment plays the key role in deciding for or against surgical intervention.

EXCLUSION OF MALIGNANCY

In the evaluation of a patient with a fibrothorax, it is essential to keep in mind the possibility of a malignant pleural process. If malignancy is a concern, this possibility should be excluded before a decision is made to proceed with decortication. Decortication of a malignant fibrous peel is difficult, and the outcome is not particularly satisfying from the standpoint of lung expansion; accordingly, for a pleural malignancy, a lesser, palliative intervention is generally more appropriate than decortication. Metastatic involve-

ment of the pleura (usually by adenocarcinoma) is far more common than malignant pleural mesothelioma, which is a primary malignancy of the pleural space. Cytologic evaluation of the pleural fluid will establish the diagnosis of metastatic pleural involvement in most cases; however, it tends to be less effective in establishing the diagnosis of malignant mesothelioma. If the presentation of a chronic pleural process is atypical and the etiology is poorly defined, a degree of suspicion for malignancy must be maintained. Appropriate initial pleural biopsies can be useful for ruling out underlying malignancy before decortication. Currently, pleural biopsy is usually performed by means of video thoracoscopy, but closed pleural biopsy is still done occasionally (though it is fast becoming a lost art). If a malignancy is identified, therapeutic alter-

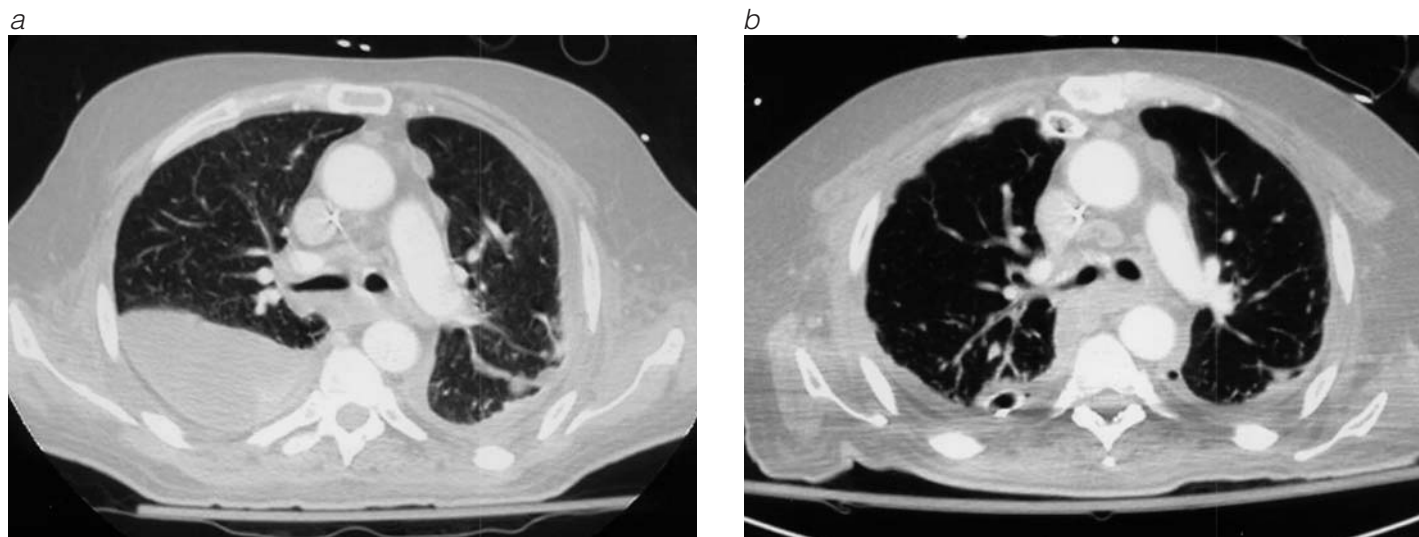


Figure 2 (a) Shown is a preoperative chest CT scan from a patient with a 6-week history of malaise and weight loss who ultimately presented with hypotension and respiratory insufficiency necessitating mechanical ventilatory support. (b) A chest CT scan obtained from the same patient after decortication shows complete reexpansion of the lung.

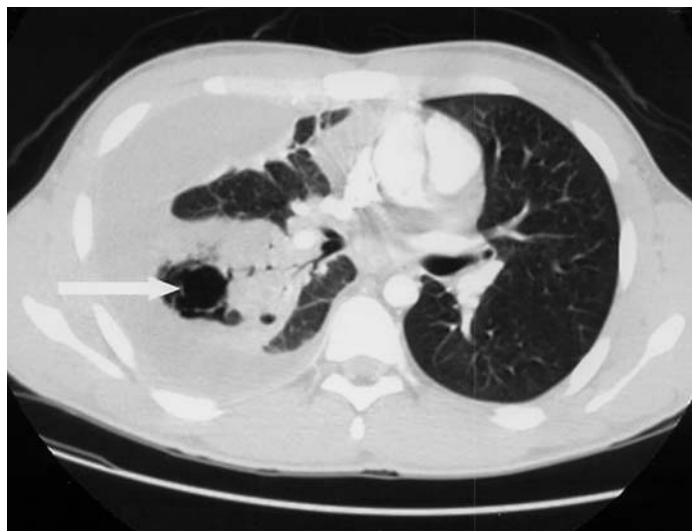


Figure 3 Shown is a chest CT scan from a patient with a pulmonary abscess (arrow) complicated by pleural space infection. The pleural space was drained via a chest tube thoracostomy. The lung did not completely reexpand. Sepsis was controlled with antibiotics. Decortication was not considered, because of the extensiveness of the underlying pulmonary parenchymal process.

natives such as pleurodesis or use of the Pleurx pleural catheter (Denver Biomedical, Golden, Colorado) may be indicated.

Operative Planning

INDICATIONS FOR SURGICAL INTERVENTION

Fibrothorax is a potentially preventable complication. As noted (see above), it is a manifestation of a chronic disease process; thus, the earlier a therapeutic intervention is initiated, the better the chances that fibrothorax can be prevented. In patients with a traumatic hemothorax, early and complete drainage often serves to prevent fibrothorax.⁵ Observational studies have consistently demonstrated that early evacuation of a clotted hemothorax reduces morbidity and mortality and prevents empyema.^{6,7} When parapneumonic effusions are thin, simple aspiration or chest tube drainage may suffice. Often, the fibropurulent stage characterized by loculated empyema or clotted hemothorax can be successfully managed by means of thoracoscopic intervention with debridement of the intrathoracic debris and irrigation; this approach allows the parenchyma to reexpand before a restrictive peel can be formed.⁸

The primary indication for decortication in a patient with fibrothorax is symptomatic pulmonary restriction resulting from the development of a fibrinous peel. The timing of the operation is an important consideration. In many cases, pleuropulmonary processes are self-limiting, and the symptoms resolve over time. As a rule, decortication should be considered (1) if pleural thickening has been present for a substantial period (> 4 to 6 weeks), (2) if respiratory symptoms remain disabling, and (3) if there is radiographic evidence of reversible entrapment of the lung. Decortication is often necessary when lesser interventions have not achieved control of a pleural space infection or have not enabled the lung to reexpand. For tuberculous empyema, drug therapy remains the treatment of choice. Decortication may also be performed to treat pleural effusions that persist despite long-term medical therapy.

A condition that poses a major challenge to the thoracic surgeon is pleural space infection with underlying parenchymal dis-

ease or airway stenosis.^{9,10} In this setting, decortication is destined to fail: the lung parenchyma will not reexpand to fill the pleural space completely, and any surgical intervention carried out on the diseased lung will only aggravate the underlying disease process. Pleuropneumonectomy may be the only option, though it should be considered a last resort, to be used only if there is significant parenchymal destruction. Decortication may be precluded by invasive uncontrolled pulmonary infection, contralateral pulmonary disease, or a chronically debilitated state that results in a significant or even prohibitive level of operative risk. Medical optimization may be required as an initial step. Often, however, the underlying pleural infection process remains unresolved despite optimal medical management, and surgical intervention becomes necessary in a patient who remains medically fragile. Optimally, the patient's nutritional status should be normalized (with forced feedings, if necessary), and sepsis, if present, should be controlled with appropriate antibiotic therapy.

TECHNICAL CONSIDERATIONS

Essentially, pleural cavity infection and fibrosis are problems of residual intrapleural space. The lung cannot expand sufficiently to fill the hemithorax, and as a consequence, the residual space becomes or remains infected. These problems often prove difficult for the thoracic surgeon to address; good surgical judgment is crucial for ensuring optimal outcomes. In planning for decortication, there are a number of technical issues that must be considered, including the timing of intervention (taking into account whether the disease process is chronic or subacute), the quality of the underlying pulmonary parenchyma, the expected ability of the lung to reexpand, the possible need to address residual space issues, and the physiologic status of the patient. The goal of the procedure is to remove the peel from the visceral pleura so as to allow the lung to reexpand and, equally important, to ensure that any potential residual space is obliterated.¹¹

There are few absolute contraindications to pulmonary decortication, other than a patient who is unfit to undergo surgery or the presence of underlying parenchymal or bronchial disease that would prevent lung reexpansion. There are, however, some situations in which a lesser intervention (e.g., chest tube thoracostomy, rib resection, or open window thoracostomy) might yield a better outcome than decortication would from the patient's perspective. In general, decortication is not required for a small, well-defined residual cavity; it is usually reserved for a diffuse pleural process. Whether the disease process is chronic or subacute will also influence the surgeon's choice of approach. For example, in the earlier stages of pleural space infection, when the peel is less organized, a thoracoscopic approach that includes cleansing of the pleural space, removal of the pleural debris, and breaking up of loculations may prove adequate. With a chronic process, however, an attempt at thoracoscopic decortication may do more harm than good.

Operative Technique

The first step in open decortication (which at times includes parietal pleurectomy in addition to decortication) is bronchoscopic evaluation aimed at identifying any endobronchial obstructions that might prevent satisfactory lung expansion. Such evaluation sometimes yields unexpected findings, such as malignancy, bronchial stenosis, or a broncholith.

The chest is entered at the appropriate predetermined interspace (usually the fifth or sixth) via a standard posterolateral thoracotomy [see Figure 4]; alternatively, a vertical axillary thoracotomy may be employed. With either approach, the latissimus dorsi



Figure 4 Decortication. The chest is entered through a posterolateral thoracotomy at the fifth or sixth interspace.

and the serratus anterior should be spared because either or both might subsequently be required for a transposition muscle flap. Because the chest is often rigid and contracted as a result of the underlying inflammatory process, it may be helpful to resect a rib in a subperiosteal fashion. This measure facilitates exposure and helps define the extrapleural plane for the initiation of parietal pleurectomy.

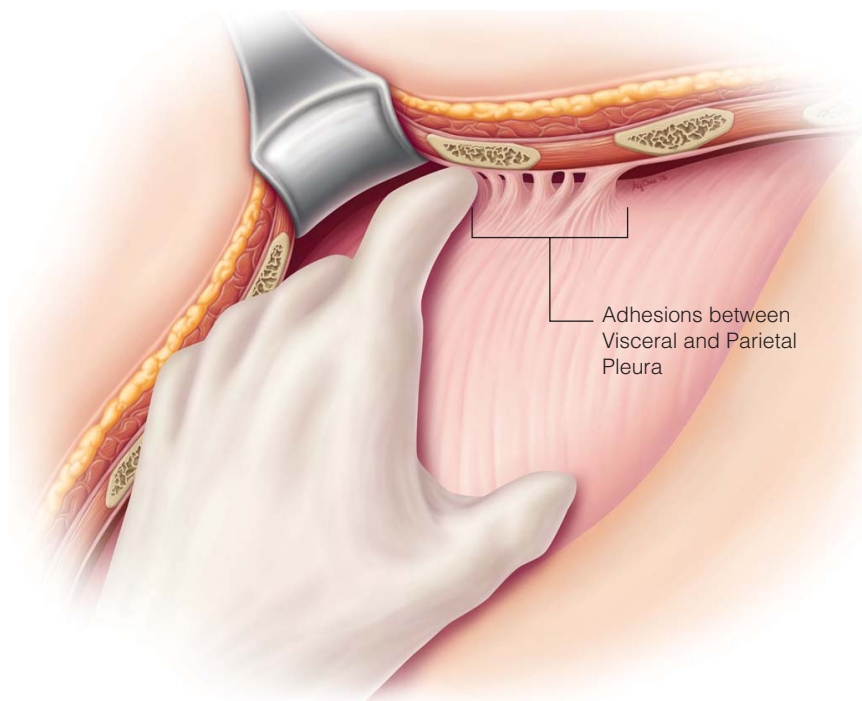
When the disease process is chronic (i.e., has lasted longer than 6 weeks), the parietal pleura and the visceral pleura are often fused. In this situation, one would proceed with pleurectomy. When adhesions are present between the pleural layers but the visceral pleura has not fused with the parietal pleura [see Figure 5], the adhesions may be lysed with a combination of sharp dissection and electrocauterization.

The key to a technically successful decortication is to define the correct plane between the pleural peel and the visceral pleura. If the pleural resection is inadequate, lung expansion will be compromised. If the pleurectomy is too deep, parenchymal injury will result, bleeding and air leakage will occur, and postoperative recovery will be prolonged. Gentle manual ventilation of the lung

operated on, coupled with continuous positive airway pressure (CPAP), should provide appropriate countertraction from the underlying lung parenchyma.

An incision is made in the pleural peel, and the appropriate decortication plane is identified [see Figure 6a]. The pleural peel is then grasped with hemostats, and blunt and sharp dissection is carried out over a broad area to separate the peel from the visceral pleura [see Figure 6b]; a sponge-ball or peanut dissector may be useful for this purpose. Care must be taken to keep from injuring the underlying pulmonary parenchyma, which is fragile; inadvertent injury may result in prolonged and unnecessary air leaks. Some degree of patience is required, in that this operation often becomes tedious. For an optimal surgical outcome, all portions of the lung encased by the peel should be addressed. To this end, it is often necessary to follow the peel into the fissure, down onto the diaphragm, and into the posterior and anterior sulci. At times, a second entry point into the chest through another interspace may be required to achieve an optimal technical result. Should better exposure be deemed necessary, one should not hesitate to proceed with this counterincision.

Figure 5 Decortication. Any adhesions between the visceral pleura and the parietal pleura are lysed with a combination of sharp dissection and electrocauterization.



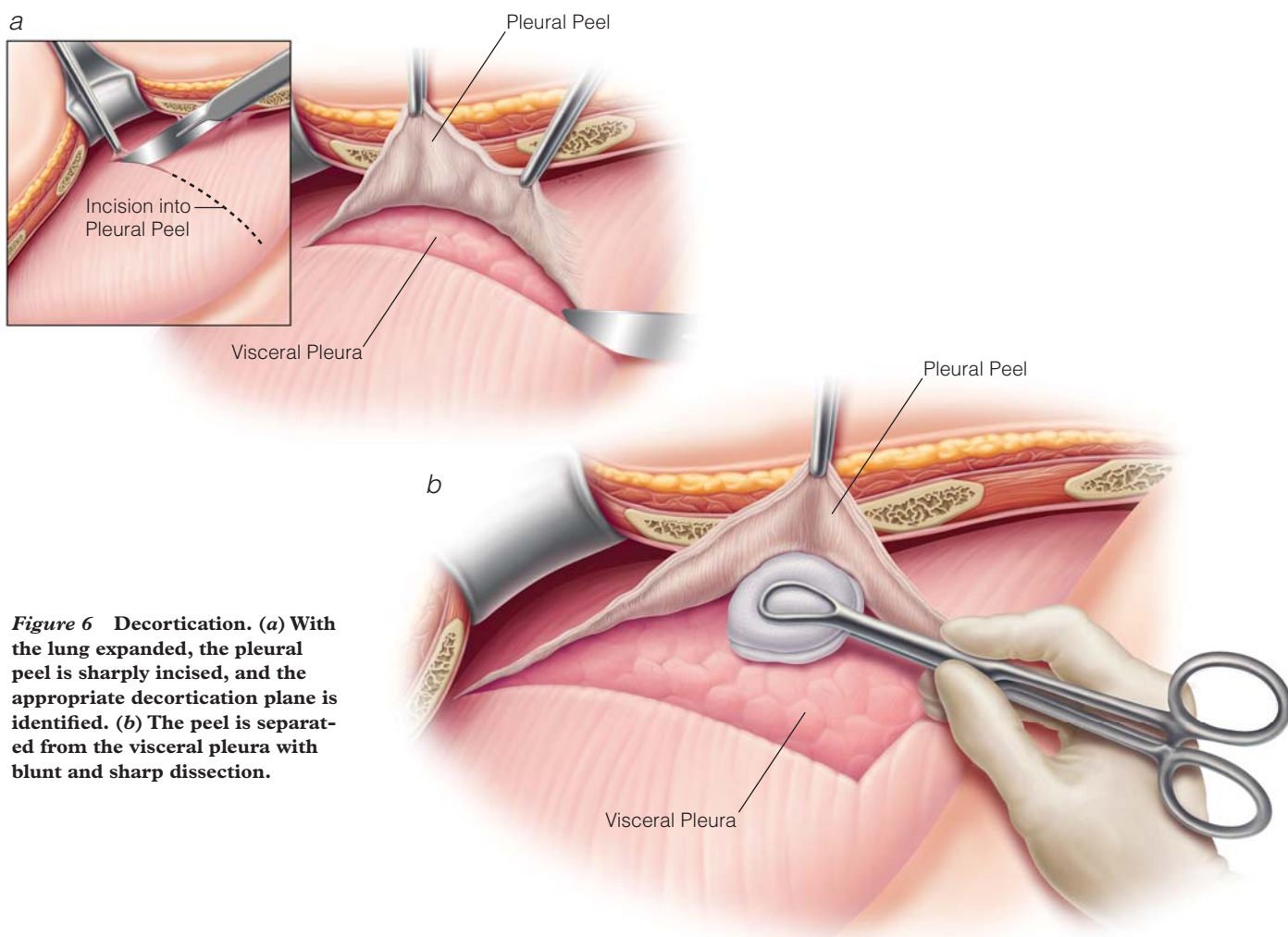


Figure 6 Decortication. (a) With the lung expanded, the pleural peel is sharply incised, and the appropriate decortication plane is identified. (b) The peel is separated from the visceral pleura with blunt and sharp dissection.

Once resected, the peel is sent for pathologic and microbiologic evaluation. The lung is tested to confirm that it is capable of complete reexpansion. Any large parenchymal air leaks that are noted may be oversewn, but this step often is not necessary. The various pulmonary parenchymal sealants now commercially available may reasonably be considered for control of parenchymal air-leaks. Chest tubes are placed—typically, one along the diaphragm, a second anteriorly, and a third posteriorly, toward the apex. Provided that the lung is satisfactorily reexpanded, air leaks will seal promptly. Hemostasis must be ensured: a residual hemothorax in a patient with a pleural space infection will serve as a nidus for ongoing infection.

The role of parietal pleurectomy in this setting remains unclear. Opinions differ, but objective data are sparse. Parietal pleurectomy does result in some improvement of the mechanics of the thoracic cage¹²; however, it also increases the risk of bleeding, prolongs the procedure, and places vital intrathoracic structures (e.g., the phrenic and vagus nerves, the esophagus, the brachial plexus, and certain blood vessels) at risk for injury. In addition, it is often possible that the pleural process will resolve without parietal pleurectomy once the underlying issues are addressed. The technically optimal strategy may be to adopt a compromise approach—that is, to perform a partial parietal pleurectomy and to take extra care when dissecting near the vital mediastinal structures.

Postoperative management of the chest tube is dictated by culture results, intraoperative findings, and the patient's clinical sta-

tus. Concerns related to residual space may be managed by means of open tube thoracostomy, open window thoracostomy, or placement of a muscle flap. On rare occasions, thoracoplasty with multiple rib resection may be considered to obliterate any infection in the residual space by bringing the chest wall down to fill the space.

Outcome Evaluation

The morbidity and mortality to be expected after decortication depend on the severity of the underlying illness and on the occurrence of perioperative complications. In a review from 1985, mortality was less than 8%.¹³ Complications tend to be either infection related (e.g., perioperative sepsis syndrome) or technique related (e.g., bronchopleural fistula, hemorrhage, and persistent air leakage); some of them may necessitate additional surgical intervention. As with all operations in the chest, close attention to detail and meticulous surgical technique are critical for minimizing the incidence of postoperative complications.

The degree of functional improvement attained after decortication depends primarily on the presence and extent of disease in the underlying lung parenchyma.¹⁴⁻¹⁶ If the parenchyma of the lung is normal, complete reexpansion of the lung and obliteration of the pleural space should be achievable. Lung volumes usually improve measurably after decortication, but they generally do not return to normal.^{14,17} Changes within the chest (i.e., mediastinal shift and elevation of the diaphragm, with a resultant decrease in

Table 2 Causes of Failed Decortication

Underlying parenchymal disease	Active tuberculosis or invasive pulmonary infection Bronchial stenosis Chronic lung collapse
Technical considerations	Residual space Inadequate lung expansion Air leakage Postoperative hemothorax

the size of the thorax) may account for this finding. It is unclear to what extent the expected functional improvement is influenced by whether the pleural process is acute or chronic. Some authors have observed an association between shorter durations of pleural disease before treatment and improved outcomes^{18,19}; others have not observed such an association.¹⁴ Failure to achieve improvement after decortication appears to be most strongly related to errors of surgical judgment (in particular, poor patient selection) and to insufficiently meticulous surgical technique (leading to perioperative complications).

Although to date, no studies have dealt specifically with failure after decortication, it is likely that technical difficulties are the most common cause of such failure, with the main problem being inadequate obliteration of the pleural space [see Table 2].

Inability to define the plane of dissection between the peel and the visceral pleura is an especially troublesome technical challenge that can adversely affect results. If visceral pleurectomy is performed, air leakage and postoperative hemorrhage may compromise pulmonary function. Care must be taken throughout the operation to protect the phrenic nerve from injury; fortunately, this usually is not an issue, because the mediastinal pleura is rarely involved in the inflammatory process. Incomplete parietal pleurectomy or inability to free the diaphragm may also compromise results.

If patients are appropriately selected, complete reexpansion of the lung after decortication can usually be achieved. Occasionally, however, an issue related to residual pleural space may arise after an otherwise technically satisfactory decortication. If this space is not obliterated, failure is inevitable. Options for addressing the residual space problem include thoracoplasty and tissue transposition. Either the latissimus dorsi or the abdominal omentum will provide sufficient bulk for obliteration of the residual space.^{20,21} The omentum is preferable when the space is in the inferior hemithorax, whereas the latissimus dorsi is preferable when the space is in the superior hemithorax. At the time of the initial incision, the surgeon should keep in mind the possibility that tissue transposition may eventually prove necessary and should therefore opt for a muscle-sparing thoracotomy if possible.

At present, the use of thoracoscopy to address fibrothorax definitively cannot be recommended.

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Acknowledgment

Figures 4 through 6 Alice Y. Chen.

14 PULMONARY RESECTION

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Anatomic resections of the lung (including pneumonectomy and lobectomy) are the standard operative techniques employed to treat both neoplastic and nonneoplastic diseases of the lung. In neoplastic disease of the lung the disease process can be divided between primary and metastatic lung cancers. In patients with primary lung cancer, the staging of the patient is critical to provide best therapy for the patient. There is no role of pulmonary resection for patients with metastatic disease or stage IV disease. In terms of the nodal stations, pulmonary resection maybe offered in patients with N1 disease or metastatic cancer to ipsilateral hilar lymph nodes (level 10, 11, 12, 13, 14). There is controversy about the role of pulmonary resection in patients with N2 disease or metastatic cancer to ipsilateral mediastinal lymph nodes (on right: level 2R, 4R, 7 and on left: level 2L, 4L, 5, 6, 7). The options include either induction chemotherapy followed by surgery then consolidative radiation to the mediastinum, induction chemoradiotherapy followed by surgery, or chemoradiation therapy without surgery. The final option is most commonly chosen when multiple N2 lymph nodes are involved, the nodal disease is bulky and deemed unresectable, or when the surgical risk is felt to be too high (for example when a right pneumonectomy is required). Finally, there is no role for pulmonary resection in patients with N3 disease or metastatic cancer to contralateral mediastinal lymph nodes. In patients with no nodal or metastatic disease, pulmonary resection is a primary therapy. Any surgeon who intends to operate on the pulmonary system must be keenly aware of the anatomy of the pulmonary vasculature and the bronchi and the relation between the two. There is no substitute for this degree of familiarity. Detailed discussions are available in existing anatomy textbooks. In what follows, we describe several of the more common techniques employed for anatomic resections of the lung.

Preoperative Evaluation

Detailed discussion of the physiologic evaluation of the patient and of the indications for lobectomy or pneumonectomy is beyond the scope of this chapter. In general, the patient must have sufficient pulmonary reserve to tolerate the planned resection. A common contraindication for surgery is an estimated postresectional forced expiratory volume in 1 second (FEV₁) and carbon monoxide diffusion capacity (DLCO) of less than 35 to 40%. The choice of what volume of lung to resect for lung cancer should be a balance between achieving an adequate oncologic outcome and preservation of pulmonary

function. When wedge resection was compared with lobectomy for tumors smaller than 3 cm there was a higher local recurrence rate after a wedge resection compared with a lobectomy. Based on these data the current recommendation is to perform a lobectomy if the patient's pulmonary status will tolerate that volume of resection. A minimally invasive lobectomy can be substituted for an open lobectomy although the presence of hilar nodal involvement by tumor or granulomatous disease is a relative contraindication to this procedure. For metastatic tumors and diagnostic resections of pulmonary nodules a wedge resection, if feasible, is considered adequate. In addition, it is essential to carry out a thorough evaluation of all other systems, especially the cardiac system. In patients who have received preoperative chemotherapy, the hematologic and renal systems should receive particular attention.

Operative Planning

ANESTHESIA

Although pulmonary resections can be performed with bilateral lung ventilation, careful hilar dissection is greatly facilitated by using unilateral lung ventilation. The advent of double-lumen endotracheal tubes and bronchial blockers has made it possible to isolate the ipsilateral lung and has made it easier for surgeons to carry out complex hilar dissections with the required precision. In patients with centrally located tumors, care must be taken with tube placement: inadvertent trauma to an endobronchial tumor during placement of a double-lumen tube can lead to significant bleeding and compromise of the airway. Bronchoscopic confirmation of tube position is recommended after the patient has been positioned.

Requirements for monitoring and intravenous access are determined by the patient's preoperative status and by the complexity of the resection. In most cases, the standard practice is to place a radial arterial catheter, two large-bore peripheral intravenous catheters, and a Foley catheter, with more invasive monitoring employed if mandated by the patient's clinical condition. Thoracic epidural catheters are also commonly employed for postoperative pain control. If carefully placed by an experienced anesthesiologist, these catheters can remain in place for as long as 7 days or until the chest tubes are removed.

PATIENT POSITIONING

Patients are routinely placed in the lateral decubitus position, with the table flexed just cephalad to the superior iliac

crest. This positioning allows sufficient access for most incisions. If an anterior thoracotomy or a sternotomy is planned, the patient may be placed in the supine position, with a pillow placed in such a way as to elevate the area of the thorax that will be operated on.

When the patient is in the lateral decubitus position, several measures should be adopted to guard against injury. Adequate padding should be employed to prevent the development of pressure points on the contralateral lower extremity. A low axillary roll should be used to prevent injury to the contralateral brachial plexus and shoulder girdle. Finally, adequate padding should be placed beneath the head to keep the cervical spine in a neutral position.

GENERAL TECHNICAL CONSIDERATIONS

Incisions

Posterior lateral thoracotomy remains the standard incision for anatomic pulmonary resections; however, safe and complete resections can also be performed through a variety of smaller incisions, including posterior muscle-sparing, anterior muscle-sparing, and axillary thoracotomies. In most cases, the thorax is entered at the fifth intercostal space, an approach that affords excellent exposure of the hilar structures. The anterior muscle-sparing thoracotomy is generally placed at the fourth intercostal space because of the more caudal positioning of the anterior aspects of the ribs. Although a sternotomy may be employed to gain access to the upper lobes, it does not provide good exposure of the lower lobes and the bronchi.

Thoracoscopic lobectomy [see 4:10 *Video-Assisted Thoracic Surgery*] is being performed with increasing frequency, especially for early-stage lesions. This procedure employs two or three 1 cm ports and a utility thoracotomy (frequently in the axillary position) for instrumentation and removal of the specimen. Rib spreading is not necessary, because visualization is achieved via the thoracoscope. The various thoracoscopic lobar resections are generally similar with regard to isolation and division of the hilar vessels and bronchi. Complete nodal dissections are also performed thoracoscopically. The main advantages of this approach seem to be reduced postoperative pain and earlier return to normal activity, but to date, no randomized trials have shown these advantages to be significant. Because of the technical challenges posed by thoracoscopic pulmonary resections, surgeons should have a complete mastery of the hilar anatomy before attempting these procedures.

Special Intraoperative Issues

Upon entry into the thoracic cavity, all benign-appearing filmy adhesions should be mobilized. Any malignant-appearing, broad-based, or dense adhesions should be noted, and a decision whether to perform an extrapleural dissection or a chest wall resection should be made on the basis of the depth of involvement and the preoperative imaging studies. If there is reason to believe that the chest wall or the parietal pleura may be involved, a more aggressive approach may be required to achieve a complete resection. These techniques are beyond the scope of this chapter.

Once the lung is freed of all adhesions, the inferior pulmonary ligament is divided and the lung rendered completely atelectatic. The entire lung and the parietal pleura are

inspected and palpated. In patients with malignant disease, biopsies of any suspicious nodules are performed. The presence or absence of pleural fluid should be noted; if fluid is present, it should be aspirated and sent for immediate cytologic analysis.

Frequently, the fissures are incomplete as a consequence of congenital absence, inflammatory disease, or a neoplasm. If the adhesions within the fissure are filmy, they may be divided sharply or with the electrocautery while the lung is being ventilated. If the adhesions are more densely adherent, the fissures may have to be completed with staplers. During resection for malignancy, any evidence of tumor extension across a fissure or of hilar nodal involvement should be noted. A decision is then made regarding the extent of the required resection. If there is only minor extension, wedge resection of a portion of the additional lobe is indicated. If, however, the involvement is significant, segmentectomy, bilobectomy, or pneumonectomy may be indicated. Often we develop the fissures during ventilation until a dense or incomplete region is encountered, at which point we complete the remainder of the fissure with staples. For this approach to work, the vascular and bronchial anatomy must already have been completely delineated. If the vascular structures cannot be identified in the fissure because the fissure is fused, the pulmonary artery branches will have to be approached from the anterior and posterior hilum.

Traditionally, during a lobectomy, the arterial branches are divided first, followed by the venous branches. However, if conditions exist that limit exposure (e.g., a centrally placed tumor or significant inflammation and scarring), the surgeon should start with the structures that provide the most accessible targets. Veins may be ligated first. Proponents of this approach believe that it may limit the escape of circulating tumor cells (an event that rarely, if ever, occurs); opponents claim that initial vein ligation may lead to venous congestion and retention of blood that is subsequently lost with the specimen, although peribronchial venous channels will frequently prevent this result. The bronchus may also be ligated first. However, two points should be kept in mind if this is done. First, the distal limb of the bronchus (the specimen side) should be oversewn to prevent drainage of mucus into the chest. Second, after division of the bronchus, the lobe is much more mobile; therefore, to prevent avulsion of the pulmonary artery branches, care should be taken not to employ excessive torsion or traction.

The techniques used for dissection, ligation, and division of pulmonary arteries and their branches differ from those used for other vessels. Pulmonary vessels are low-pressure, high-flow, thin-walled, fragile structures. Accordingly, for rapid and safe dissection, a perivascular plane, known as the plane of Leriche, should be sought. This plane may be absent in the presence of long-standing granulomatous or tuberculous disease, after major chemotherapy, after thoracic radiotherapy, and in cases of reoperation. In these situations, proximal control of the main pulmonary artery and the two pulmonary veins may be necessary before the more peripheral arterial dissection can be started. Before any pulmonary vessel is divided, it should be controlled either with two separate suture ligatures proximal to the line of division or with vascular staples; stapling devices are especially useful for larger vessels.

Exposure of the bronchus should not involve stripping the bronchial surface of its adventitia. Aggressive dissection may compromise the vascular supply and lead to impaired healing and bronchial dehiscence. Overlying nodal tissues should be cleared, and major bronchial arteries should be clipped just proximal to the point of division. Bronchial closure has been greatly facilitated by the use of automatic staplers. Because the bronchus is frequently the last structure to be divided before removal of the specimen, we often apply staples only to the proximal side of the bronchus and divide the bronchus distal to the staple line. Once the stapler is applied, every effort should be made to minimize its movement during firing so as to prevent injury to the remaining proximal bronchial segment. With the stapler applied but not yet fired, the remaining lung should be ventilated to determine whether there is any impairment of ventilation secondary to placement of the stapler too close to a proximal lobar bronchus. Only when the absence of ventilatory impairment has been confirmed should the stapler be fired. When bronchial length is limited, one may perform suture closure of the bronchial stump rather than attempt to force a stapler around the bronchus. Whenever there is a high risk of bronchial stump dehiscence (e.g., after chemotherapy, radiotherapy, or chemoradiotherapy; in patients for whom adjuvant therapy is planned; or after right pneumonectomy), a vascularized rotational tissue flap (e.g., from the pericardium, the pericardial fat pad, or intercostal muscle) should be used to reinforce the bronchial closure.

Closure and Drainage

Once the bronchial closure is complete, the next step is to test its adequacy. The bronchial stump is submerged under normal saline, and the lung is inflated to a tracheal pressure of 45 cm H₂O. Any area of hilar dissection and divided fissures should be evaluated in a similar fashion. Significant parenchymal air leaks should be repaired with interrupted fine sutures (e.g., 4-0 polypropylene). If the air leak is from a diffuse raw surface, especially after upper lobectomy, construction of a pleural tent should be considered. Any air leak from the bronchial stump should be assessed very carefully. A simple repair with fine absorbable sutures may suffice, or the entire closure may have to be redone. Strong consideration should be given to reinforcing the stump with vascularized tissue (see above).

The chest is usually drained with two chest tubes that are positioned anteriorly and posteriorly and exit through separate stab incisions in the chest wall. If an epidural or a paravertebral catheter is being employed for postoperative pain management, the chest tubes should exit through an intercostal space that is no more than two spaces below the intercostal space used for entry into the chest. Failure to follow this recommendation is likely to result in pain originating from the chest tube site that will not be adequately addressed postoperatively and will lead to a significant increase in discomfort.

After a pneumonectomy, the chest tubes can be omitted. If this option is chosen, a needle should be used to aspirate 1,000 to 1,200 mL of air from the hemithorax operated on after closure of the skin. If a chest tube is used, a balanced drainage system is employed without suction. At most institutions, suction is employed postoperatively for all other

resections (i.e., lobectomy, segmentectomy, and wedge resection); however, careful use of water seal in selected patients (i.e., those with small air leaks whose lungs do not collapse while on water seal) may allow earlier withdrawal of the tube.

Operative Technique

INITIAL STEPS

After making a posterior lateral thoracotomy and exposing the chest cavity through the fifth intercostal space, the inferior pulmonary ligament is taken down and the hilum is mobilized. A lung grasper is used to provide tension on the lower lobe, and the inferior pulmonary ligament is taken down using a cautery or bluntly to the inferior pulmonary vein. One needs to be very careful not to injure the pulmonary vein. After this is done, the lung is freed of any filmy pleural attachments. Dense attachments may indicate chest wall involvement and should be approached as such.

RIGHT LUNG

Right Hilar Dissection

In the right thoracic cavity, it is important to identify the inferior pulmonary vein draining the right lower lobe, superior pulmonary vein draining the right upper and right middle lobe, the main pulmonary artery, and the truncus anterior branch of the pulmonary artery. In addition, the right main bronchus and the right upper-lobe takeoff and the right bronchus intermedius should be identified. Then the lung is rotated posteriorly, and the pleura is incised posterior to the course of the phrenic nerve, which usually passes close to the base of the superior pulmonary vein. The phrenic nerve is carefully and gently mobilized anteriorly, avoiding the use of cautery. This will expose the superior pulmonary vein and inferior pulmonary vein. The right upper lobe is then rotated more inferiorly to provide a better view of the superior aspect of the hilum. This step allows complete exposure of the truncus anterior branch of the pulmonary artery. Finally, the lung is rotated anteriorly, and the right main bronchus as well as the right upper-lobe bronchus and the bronchus intermedius are exposed.

Right Upper Lobectomy

Pulmonary arteries: truncus anterior and posterior ascending Two branches of the pulmonary artery go into the right upper lobe: the truncus anterior and posterior ascending arteries. The truncus anterior is the first branch coming off the main pulmonary artery and, most of the time, is a large branch that immediately bifurcates to two arteries; however, at times two truncus anterior arteries may be coming off the pulmonary artery. It is imperative that dissection be performed with care. Once the vessel is exposed, it is either suture-ligated and divided or transected with an endovascular stapler.

It is very important to accurately identify all the vessels to prevent inadvertent ligation of the wrong artery. To expose the posterior ascending pulmonary artery, the dissection begins within the interlobar fissure, and the pulmonary artery is exposed at the junction of the major and minor fissures [see *Figure 1*]. In many cases, the artery is partially obscured by a level 11 interlobar lymph node, which should be removed. Also

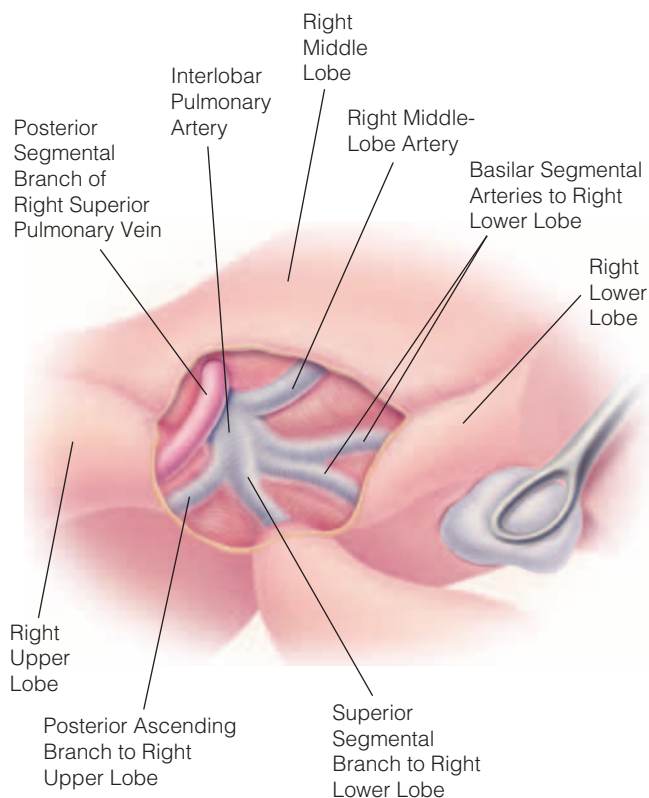


Figure 1 Right upper lobectomy. Shown is the surgeon's view of the right interlobar fissure. The fissures have been completed, and the segmental arteries to the upper, middle, and lower lobes have been identified. The posterior ascending branch to the upper lobe most commonly varies with respect to size and origin. This vessel may be absent or diminutive and may arise from the superior segmental branch to the lower lobe. The posterior segmental vein draining into the superior pulmonary vein (not seen) is clearly visualized in the right upper lobe, lateral to the pulmonary artery branches.

present is the posterior segmental branch of the superior pulmonary vein, which traverses the fissure in a posterior-to-anterior direction. The pulmonary artery lies medial and inferior to this venous branch. Once the pulmonary artery is identified, the branches within the fissure are exposed, including the posterior ascending artery to the right upper lobe. The posterior ascending artery typically comes off the main pulmonary artery opposite to the right middle-lobe pulmonary artery. However, at times there may be no posterior ascending artery or there may be two posterior ascending arteries, or the posterior ascending artery may originate as a branch of the superior segment artery to the right lower lobe. Distal to the posterior ascending artery is the superior segmental artery to the right lower lobe and the basilar branches to the right lower lobe. If the exposure is adequate, the posterior ascending branch can be ligated and divided.

Fissure between the right lower lobe and the right upper lobe If additional length is required to expose the posterior ascending artery, the fissure between the superior segment of the lower lobe and the posterior segment of the upper lobe can be completed. This is accomplished by open-

ing the pleura in the posterior hilum along the lateral edge of the bronchus intermedius. A level 11 lymph node will be encountered between the right upper-lobe bronchus and the bronchus intermedius. Removal of this interlobar node (sometimes referred to as the "sump node") will expose the posterior ascending branch of the pulmonary artery. A right-angle clamp can be passed from the interlobar fissure between the superior segmental branch of the pulmonary artery and the posterior ascending pulmonary artery to the opening between the right upper-lobe bronchus and the bronchus intermedius. A silk can be placed through this opening, which will guide in separation of the right upper lobe and the right lower lobe. The fissure can be completed with gastrointestinal anastomosis (GIA) staplers. The posterior ascending artery can be ligated and divided after completion of the fissure.

Pulmonary vein: right upper-lobe branch of the superior pulmonary vein The superior pulmonary vein is dissected, and the apical, anterior, and posterior branches are encircled [see Figure 2]. Care is taken to preserve the middle-lobe branches. Both the right upper lobe and the middle lobe often drain into the superior pulmonary vein. However, at times the right middle lobe may drain into the inferior pulmonary vein or into both the superior and the inferior pulmonary vein. The right middle-lobe pulmonary vein branch has to be clearly identified prior to taking the right upper-lobe pulmonary vein branches. The branches draining the upper lobe are then ligated and divided or controlled with a vascular stapler. Division of the veins before division of the arterial supply will not cause the lobe to become engorged. Instead, through collateral venous drainage to the middle lobe or via bronchial venous channels, blood will be shunted away from the upper lobe.

Fissure between the right upper lobe and the right middle lobe After the division of the right upper-lobe pulmonary veins, the interlobar (or truncus posterior) branch of the right pulmonary artery will be visible as it courses posterior to the superior pulmonary vein branches. Dissection continues along the lateral surface of the interlobar artery. Once the branches to the middle-lobe artery are identified, the dissection should reach the region previously dissected within the fissure. A right-angle clamp can be used to pass a silk along this opening and keep the right middle pulmonary artery and vein with the right middle lobe. The fissure between the middle lobe and the upper lobe can now be completed through serial application of GIA staplers.

Right upper-lobe bronchus The upper lobe is retracted superiorly and posteriorly, and the interlobar artery is gently retracted anteriorly. The bronchus to the right upper lobe is circumferentially exposed, and all nodal tissue surrounding the right upper-lobe bronchus is swept distally so that it can be included with the specimen. Every effort is made to avoid devascularizing the bronchus. Once an adequate length of the right upper-lobe bronchus is exposed, the lung is rotated anteriorly to allow visualization of the course of the bronchus intermedius. The bronchus is ligated with a transverse anastomosis (TA)-30 stapler loaded with 4.8 mm staples. Care is taken to achieve close apposition of the anterior wall to the posterior membranous wall of the bronchus. With the stapler applied but not fired, the right lung is ventilated to confirm that the bronchus intermedius has not been compromised. The stapler is fired, the bronchus is divided, and the specimen is removed.

To prevent middle-lobe syndrome resulting from torsion of the narrow hilum of the middle lobe after an upper lobectomy, the middle lobe should be secured to the lower lobe. Once the lungs are reexpanded, a small portion of the lower lobe and a comparable portion of the middle lobe are grasped along the major fissure. A single application (or, at most, two applications) of a TA stapler should suffice to secure the lobes to each other at this site and thus prevent middle-lobe torsion.

Right Middle Lobectomy

Pulmonary arteries: one or two right middle-lobe pulmonary arteries The initial steps in a right middle lobectomy are similar to those in a right upper lobectomy. The pulmonary artery and its branches are identified within the fissure. The middle-lobe artery is identified [see Figure 1]. Not infrequently, there are two middle-lobe arteries. When this is the case, the most proximal branch is commonly located across from the posterior ascending branch to the right upper lobe. Once the anatomy has been confirmed, the arterial branches to the middle lobe can be individually ligated and divided. If additional exposure is needed before ligation, the fissures can be completed to yield added exposure of a proximal middle-lobe artery.

Pulmonary vein: right middle-lobe branch of the superior pulmonary vein Once the arteries are divided (or if additional exposure is required), the lung is rotated

posteriorly to expose the superior pulmonary vein [see Figure 2]. The branches to the middle lobe are carefully identified, doubly ligated, and divided. The posterior segmental branch of the superior pulmonary vein should now be easily identifiable, originating just cephalad to the middle-lobe vein and coursing posteriorly (lateral to the interlobar artery) to drain the posterior segment of the right upper lobe. As noted (see above), this venous branch is easily identified during dissection of the interlobar artery within the fissure.

Fissure between the right upper and middle lobes and fissure between the right middle and lower lobes To complete the fissure between the upper and middle lobes, dissection continues along the caudal and lateral surface of the posterior segmental venous branch until the previously performed dissection of the interlobar artery within the fissure is reached. The fissure is then completed through serial application of GIA staplers. When the fissure is complete, the surgeon has a clear view of the posterior segmental branch of the superior pulmonary vein and the interlobar branch of the pulmonary artery coursing posterior and medial to the veins. If the proximal arterial branch to the middle lobe could not be safely ligated from the fissure before, it should be easily accessible now. The fissure between the right middle and lower lobes can be completed using serial application of the GIA staplers by keeping the right middle lobe and the right middle-lobe bronchus to one side and the right lower lobe

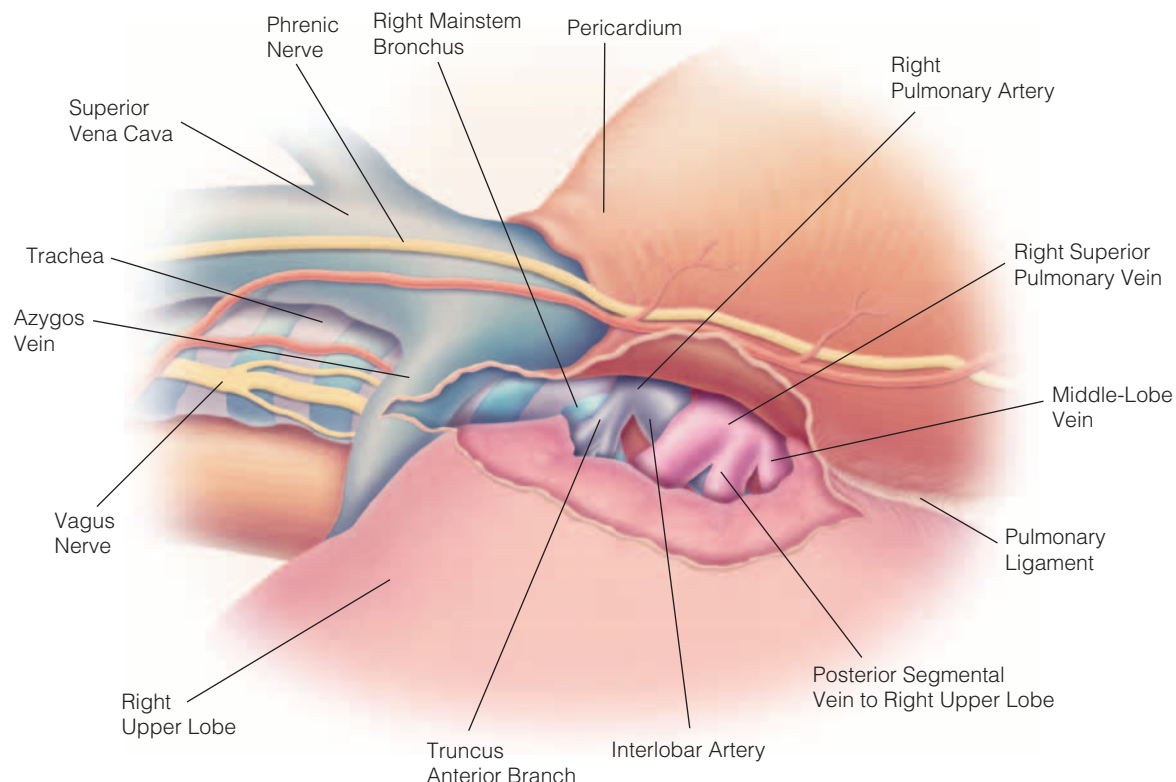


Figure 2 Right upper lobectomy. Shown is the surgeon's view of the anterior right hilum. The apical venous branches of the superior pulmonary vein obscure the interlobar pulmonary artery and, to a lesser degree, the truncus anterior branch. Division of these venous branches during upper lobectomy improves exposure of the truncus anterior. The splitting of the main pulmonary artery into its two main branches may occur more proximally, and care should be taken to identify both branches before either one is divided. Another significant possible variation is a branch of the middle-lobe vein that arises from the intrapericardial portion of the superior pulmonary vein.

with the basilar branches of the pulmonary artery and the right lower-lobe bronchus to the other side.

Right middle-lobe bronchus The middle lobe is then rotated superiorly and posteriorly to expose the right middle-lobe bronchus [see Figure 3], which usually arises anterior and inferior to the right middle-lobe branches of the pulmonary artery. The basilar artery branches to the right lower lobe are gently mobilized posteriorly to expose the bronchus intermedius and the origin of the right middle-lobe bronchus. Peribronchial lymph nodes located in this region should be dissected and removed, with care taken not to injure the bronchial arterial branches. Once the bronchus is free, it is either divided and ligated with an automatic stapler or transected and oversewn as previously described (see above).

Right Lower Lobectomy

Pulmonary artery: superior segmental branch and basilar branches Once again, the pulmonary artery is exposed within the oblique fissure. The pulmonary branches to the superior segment and the basilar segments of the right lower lobe are identified [see Figure 1]. Most of the time, there is one branch to the superior segment of the right lower lobe; however, at times there are two branches, and, rarely, there is a common branch that gives rise to the posterior ascending branch of the right upper lobe and the superior segmental branch of the right lower lobe. Careful identification of the pulmonary artery is important. All branches within the fissure are identified, including the middle-lobe artery and the posterior ascending branch to the right upper lobe. The superior

segmental artery is encircled and doubly ligated, with care taken not to injure the posterior ascending branch if it arises from or close to the origin of the superior segmental branch. The basilar segmental branches are then encircled and doubly ligated, with the same care taken not to injure the middle-lobe branch. Both vessels are then divided.

Fissure between the right upper lobe and right lower lobe The fissure between the superior segment of the lower lobe and the posterior segment of the upper lobe is frequently incomplete. If necessary, it is completed as previously described [see Right Upper Lobectomy, above]. The pleura is incised along the bronchus intermedius, and the lymph node (sump node) just distal to the takeoff of the right upper-lobe bronchus is removed so that the previously dissected pulmonary artery is exposed. Serial application of GIA staplers is employed to complete the fissure.

Fissure between the right middle lobe and right lower lobe The fissure between the middle and lower lobes may also have to be completed (although, in many cases, it is congenitally complete). The pleura is incised within the anterior hilum to allow identification of the superior and inferior pulmonary veins. The basilar segmental bronchi and the middle-lobe bronchus should be exposed. Removal of lymphoid tissue allows easy application of a GIA stapler to complete the fissure.

Pulmonary vein: inferior pulmonary vein The inferior pulmonary vein is then encircled as it exits the pericardium [see Figure 4]. This step is facilitated by dissecting the superior edge of the inferior pulmonary vein with the lung rotated first anteriorly and then posteriorly. Once encircled, the pulmonary vein can easily be ligated and divided with a vascular stapler. An infrequent anatomic variant is a vein draining the posterior segment of the right upper lobe into the inferior pulmonary vein. Although an effort can be made to save this branch, there is adequate collateral venous drainage within the right upper lobe to allow this branch to be sacrificed without consequences.

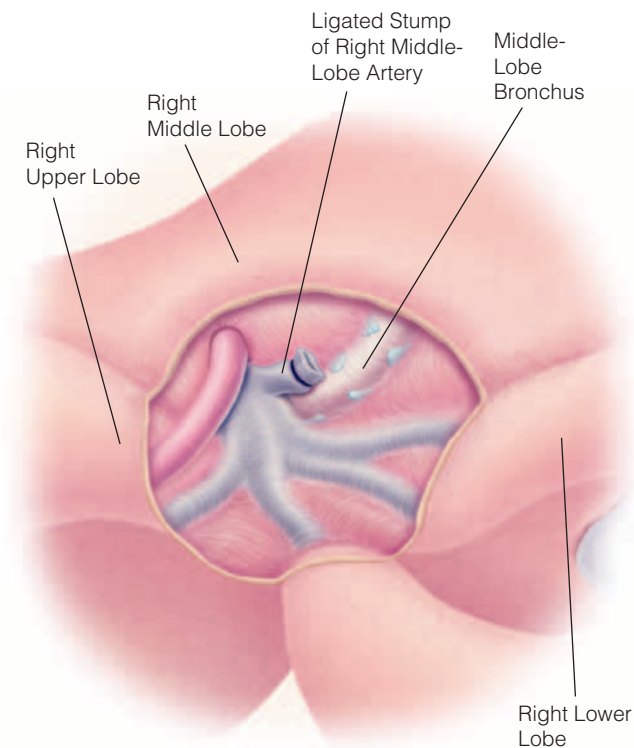


Figure 3 Right middle lobectomy. Shown is the surgeon's view of the right middle-lobe bronchus. Gentle retraction of the basilar segmental artery to the lower lobe posteriorly allows clear visualization of the origin of the middle-lobe bronchus.

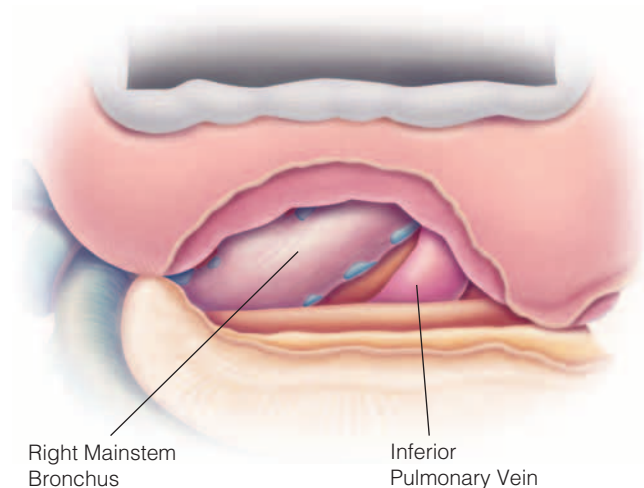


Figure 4 Right lower lobectomy. Shown is the surgeon's view of the right inferior pulmonary vein. For encirclement of this vein, dissection may also have to be performed on its anterior surface. The branch to the superior segment can be seen overlying the origin of the superior segmental bronchus.

Right lower-lobe bronchus Division of the lower-lobe bronchus is best accomplished through the fissure; this approach facilitates identification of the middle-lobe bronchus and helps prevent inadvertent damage to or compromise of the origin of this structure. Level 11 and 12 lymph nodes are cleared distally along the bronchi to expose the origin of the superior segmental bronchus [see Figure 5]. In some patients, there is adequate length to permit oblique placement of a stapler for control of all of the lower-lobe segmental bronchi without compromise of the middle-lobe bronchus. If this step is not possible, separate ligation and division of the superior segmental bronchus and of all the basilar bronchi as a unit should be performed.

The lung is rotated anteriorly, and the bronchus intermedius is dissected distally until the origin of the superior segmental bronchus is identified from this side. The branch of the inferior pulmonary vein draining the superior segment will be encountered and should be mobilized distally to allow adequate exposure of the superior segmental bronchus origin. This bronchus can now be encircled, ligated, and divided with a stapler or divided and oversewn.

Next, the basilar segmental bronchi are encircled at a point where closure will not affect airflow to the middle-lobe bronchus. Appropriate placement is confirmed by asking the anesthesiologist to ventilate the right lung while the stapler or clamp is applied to the base of the basilar bronchi. If placement is adequate, the basilar segmental bronchi are ligated and divided.

Right Pneumonectomy

Pulmonary artery: right main trunk With the pleura incised circumferentially around the hilum, the lung is rotated inferiorly and posteriorly [see Figure 2]. The main trunk of

the right pulmonary artery is exposed as it exits the pericardium posterior to the vena cava. Care is taken not to dissect distally on the vessel and not to encircle only the truncus anterior branch by mistake. Ligation and division of the right pulmonary artery can be accomplished in several different ways; either dividing the vessel between clamps and oversewing it with 3-0 nonabsorbable suture material or using vascular staplers is acceptable.

Pulmonary vein: superior and inferior pulmonary vein Next, attention is directed toward the superior pulmonary vein. The vessel is mobilized on its superior and inferior aspects with blunt and sharp dissection, encircled with blunt dissection, and ligated and divided with either clamps or a vascular stapler. With the lung retracted superiorly, the inferior pulmonary vein is dissected as in a right lower lobectomy [see Figure 4]. Once isolated, this vein is also ligated and divided as previously described (see above).

Right mainstem bronchus With the lung retracted anteriorly, attention is directed toward the right mainstem bronchus. The subcarinal lymph nodes are mobilized, and the bronchial artery on the posterior medial aspect of the right mainstem bronchus is controlled. The remaining peribronchial tissues are then mobilized distally with blunt and sharp dissection. To avoid leaving a long bronchial stump, exposure of the bronchus to within 1 cm of the carina is advisable.

The bronchus can be closed with a TA stapler loaded with 4.8 mm staples. The staples should be oriented so as to allow good approximation of the anterior and posterior membranous walls. If suture closure is selected instead, the bronchus is divided with the clamp placed on the distal bronchus to prevent spillage. The open end of the bronchus is then closed with nonabsorbable simple sutures, with the cartilaginous wall

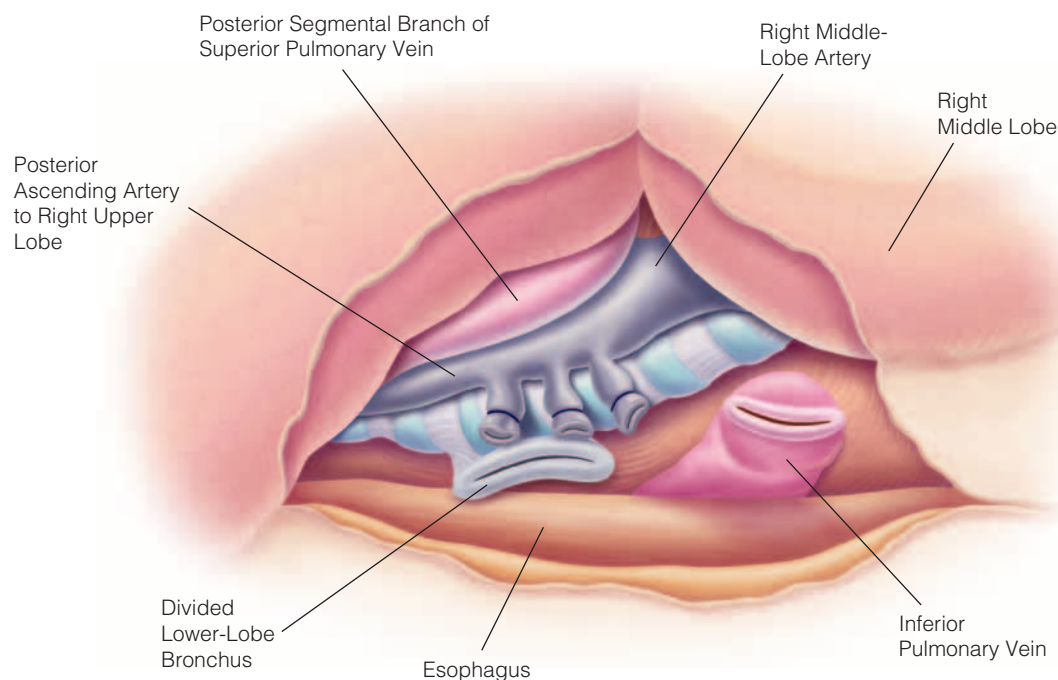


Figure 5 Right lower lobectomy. Shown is the surgeon's view of the right fissure after division of the lower-lobe vessels. The decision whether to divide the bronchi separately or to transect them with a single oblique application of the stapler depends on the proximity of the middle-lobe bronchus to the superior segmental and basilar bronchi.

approximated to the membranous wall. To guard against necrosis of the bronchus, care should be taken not to tie the sutures too tightly. Coverage of the pneumonectomy stump with viable tissue is preferred, especially if the patient has received or will receive chemotherapy, radiation therapy, or both. The ideal choice for this purpose is either a rotated intercostal muscle flap or a pericardial fat pad rotational flap. The flap is secured with carefully placed 4-0 polypropylene sutures.

In the preceding description, the artery is divided first, followed by the individual veins and, finally, by the bronchus; however, the steps of this operation can be carried out in any order. The position of the tumor may make the approach we describe difficult. For example, an anteriorly placed tumor may hinder exposure of the anterior hilum. In this situation, the bronchus can be divided first, and the pulmonary artery can be approached from the posterior hilum. As another example, if the tumor is very proximal, the pericardium can be entered via a U-shaped incision along the anterior, caudal, and posterior hilum. The pulmonary veins can then be divided en masse as they originate from the left atrium, and the pulmonary artery can be divided as it courses posterior to the ascending aorta.

LEFT LUNG

Left Hilar Dissection

In the left chest cavity, it is important to identify the inferior pulmonary vein, pulmonary artery, bronchus, and superior pulmonary artery. Retract the lung anteriorly and take down the mediastinal pleura to expose the inferior pulmonary vein and continue superiorly to expose the left main bronchus and the pulmonary artery. With the lung retracted inferiorly, dissection continues proximally along the pulmonary artery. The pleura is incised under the arch of the aorta to expose the left main pulmonary artery. A variable number of small vessels and vagal branches to the lung are encountered that must be ligated and divided. Care is taken not to injure the recurrent laryngeal nerve as it branches from the vagus and travels under the arch just distal to the ligamentum arteriosum. With the lung now retracted posteriorly, the mediastinal pleura is opened parallel to and posterior to the course of the phrenic nerve [see Figure 6]. This will expose the main trunk of the left pulmonary artery and the superior pulmonary vein.

Left Upper Lobectomy

Pulmonary artery: apicoanterior, posterior, and lingular The interlobar fissure is developed with a combination of sharp and electrocautery dissection. The posterior aspect of the fissure, between the apicoposterior segment of the left upper lobe and the superior segment of the left lower lobe, is completed (with a linear stapler if necessary) to expose the proximal portion of the pulmonary artery. The left upper lobe is then retracted anteriorly and superiorly to expose the pulmonary arteries supplying the lobe [see Figure 7]. The left upper-lobe pulmonary artery anatomy is most variable among the lobes. The most common anatomy is three branches from the pulmonary artery: apicoanterior, posterior, and lingular branches. However, not infrequently, multiple posterior apical branches are encountered; in fact, as many as seven vessels supplying the left upper lobe may be identified. Typically, the posterior segmental branch frequently arises directly opposite the superior segmental branch to the lower lobe, as well as a

more distally situated lingular branch. These vessels should be identified, individually ligated, and divided.

Next, the whole lung is retracted inferiorly to expose the aortic arch. A large arterial branch supplying the apicoposterior aspect of the upper lobe is usually encountered. Although the superior and posterior aspects of this artery are easily dissected, the anterior aspect is frequently obscured by an apical branch of the superior pulmonary vein; division of this venous branch may improve exposure and facilitate control of the artery. Once the artery is encircled, it is ligated and divided. To prevent avulsion of this vessel from the main pulmonary artery, care must be taken not to exert excessive traction on the lung.

Pulmonary vein: superior pulmonary vein The superior pulmonary vein can then be identified easily. If the apical branch was not previously ligated, the surgeon should make every effort not to damage the pulmonary artery branches that lie posterior to this portion of the vein. The majority of the superior pulmonary vein lies anterior to the left upper-lobe bronchus. Once this vein is encircled, it is ligated and divided.

Left upper-lobe bronchus Attention is then redirected toward the fissure, and the peribronchial nodal tissue surrounding the left upper-lobe bronchus is swept distally with blunt and sharp dissection. The fissure between the lingula and the lower lobe is completed with serial application of GIA staplers [see Figure 8]. The left upper-lobe bronchus is encircled and either clamped or controlled with a TA stapler. To prevent inadver-

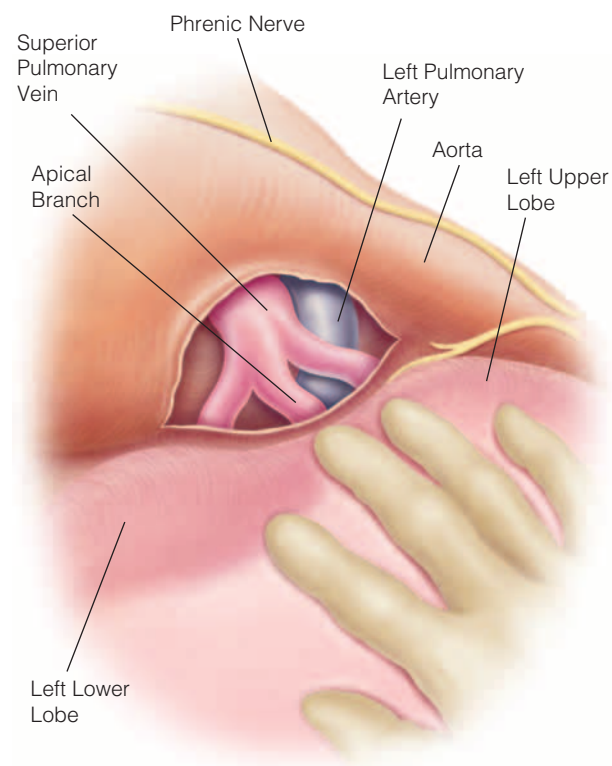


Figure 6 Left upper lobectomy. Shown is the surgeon's view of the anterior left hilum. The apical branches of the superior pulmonary vein course anterior to the apicoposterior branches of the pulmonary artery. If additional vessel length is needed because of the presence of a central tumor, the pericardium may be entered and the vein divided at that location.

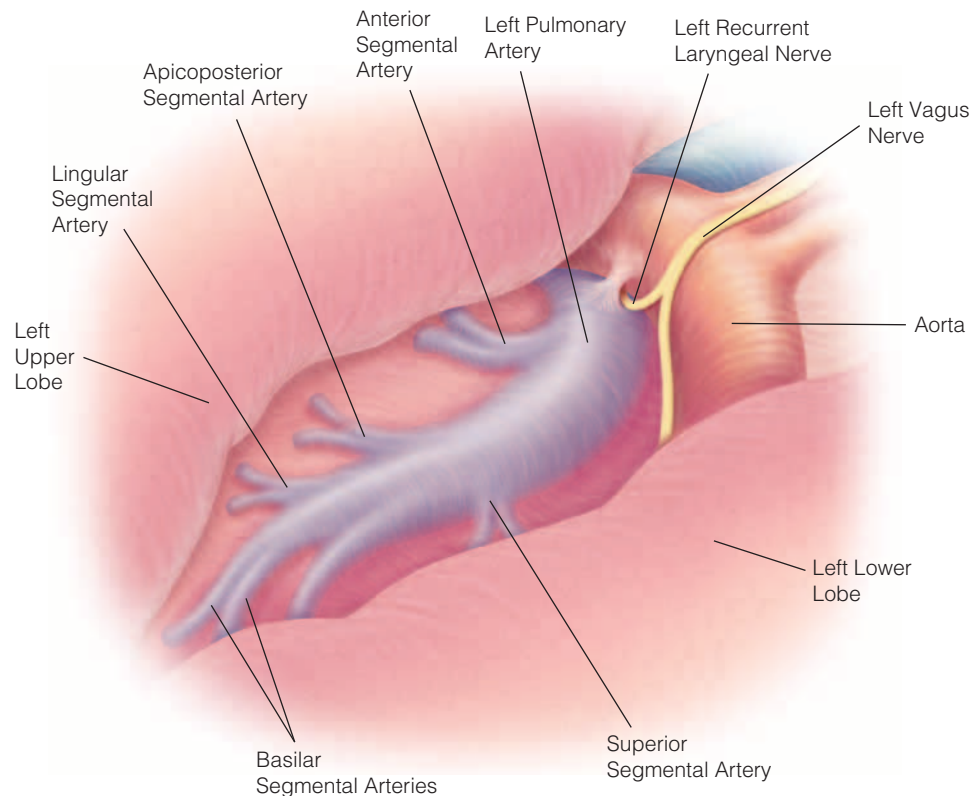


Figure 7 Left upper lobectomy. Shown is the surgeon's view of the left interlobar fissure. The recurrent laryngeal nerve can be seen coursing lateral to the ligamentum arteriosum. The arterial branches supplying the left upper lobe between the apicoposterior segmental branch and the lingular branch can vary substantially in number and size. Another frequently encountered variation is a distal lingular branch that arises from a basilar segmental branch.

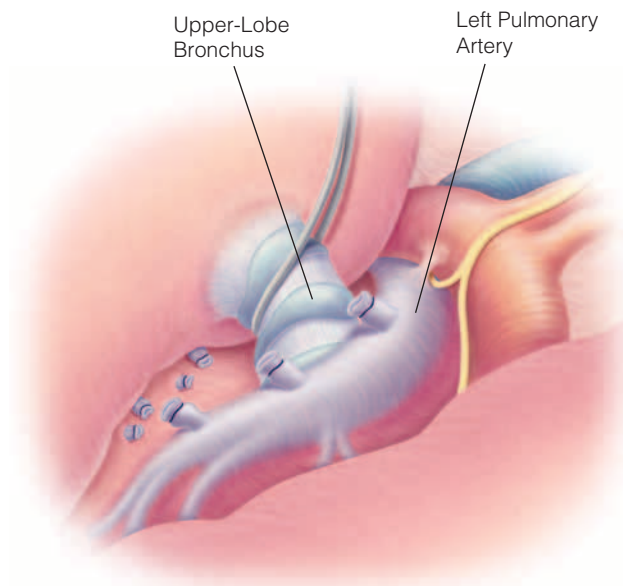


Figure 8 Left upper lobectomy. Shown is the surgeon's view of the left fissure after division of the upper-lobe arteries. Care should be taken not to injure the pulmonary artery inadvertently when applying a stapler.

tent injury, the pulmonary artery branches to the lower lobe should be gently retracted posteriorly during stapler placement. With the stapler applied (or the clamp in place), the anesthesiologist ventilates the left lung to verify that air is flowing freely to the entire left lower lobe. Once unobstructed airflow is confirmed, the stapler is fired and the bronchus is divided.

Left Lower Lobectomy

Pulmonary artery: superior segmental and basilar

As in a left upper lobectomy, dissection begins within the interlobar fissure. The pulmonary artery is identified, and the branches to the upper and lower lobes are dissected [see Figure 7]. The superior segmental artery is encircled first and is ligated and divided; not uncommonly, there are actually two separate superior segmental arteries. The basilar segmental arteries are then encircled distal to the origin of the lingular artery. These vessels are also ligated and divided, with care taken not to encroach on the blood flow to the lingula.

Pulmonary vein: inferior pulmonary vein The lung is rotated superiorly to expose the inferior pulmonary vein. As in a right lower lobectomy, the vein is encircled by dissecting first on its anterior surface with the lung rotated posteriorly, then on its posterior surface with the lung rotated anteriorly [see Figure 9]. Once the vein is encircled, it is ligated and divided.

Left lower-lobe bronchus Attention is then redirected toward the interlobar fissure, and the left lower-lobe bronchus

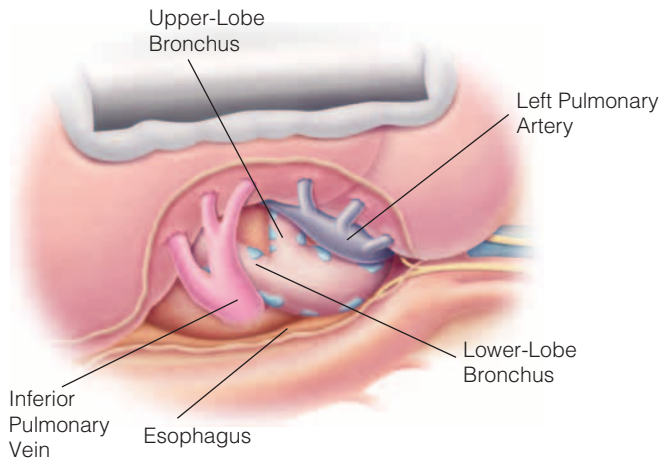


Figure 9 Left lower lobectomy. Shown is the surgeon's view of the left inferior pulmonary vein. The left side, unlike the right side, affords only limited access to the subcarinal space. However, the length of the inferior pulmonary vein outside the pericardium is greater on the left side than on the right.

is identified [see Figure 10]. The origin of the bronchus is cleared by sweeping nodal tissue distally with blunt and sharp dissection. The upper-lobe branches of the pulmonary artery are gently retracted superiorly to allow placement of a TA stapler on the bronchus. With the stapler applied, the anesthesiologist ventilates the left lung to confirm the adequacy of airflow to the upper lobe. The stapler is fired, and the bronchus is divided distal to the staple line.

Left Pneumonectomy

Pulmonary artery: left main pulmonary artery The initial steps of a left pneumonectomy are similar to those of a left upper lobectomy. The lung is retracted caudally, and the pleura is incised along the course of the aortic arch [see Figure 7]. The superior and posterior surfaces of the pulmonary artery are dissected as it enters the thorax under the aortic arch. Once the perivascular space is entered, the entire vessel can usually be encircled with blunt dissection. If the superior pulmonary vein's apical branch limits access to the anterior surface of the pulmonary artery, the branch may be ligated and divided first to improve exposure of the artery; alternatively, the superior pulmonary vein itself may be ligated and divided first to facilitate arterial exposure (see below).

Once the pulmonary artery is encircled, the vessel can be ligated and divided. Our preferred method is to use an endovascular GIA stapler, the advantages of which include its rapidity of use, its consistently reproducible results, and its ability to control the vessel along a broad surface. Mass ligation is not advisable, because the risk of dislocation of the tie is too great. When the length of exposed artery is too short or a stapler cannot be placed safely, the surgeon may apply vascular clamps to the proximal and distal portions of the vessel instead. Once the vessel is divided, the proximal end may be oversewn with a continuous polypropylene suture.

If additional vessel length is required because of the presence of a proximal tumor, the ligamentum arteriosum may be divided. The recurrent laryngeal nerve should be identified and preserved. In dividing the left pulmonary artery proximal

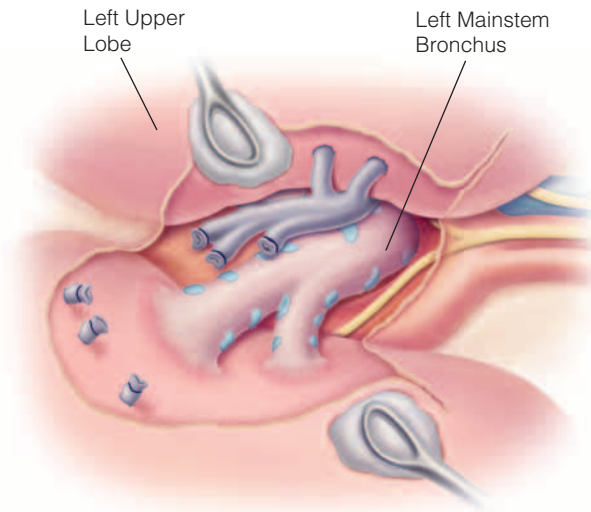


Figure 10 Left lower lobectomy. Shown is the surgeon's view of the left fissure after division of the lower-lobe vessels. In this procedure, a single oblique transection of the entire left lower-lobe bronchus can be employed without any concern that a proximal bronchus will be compromised; this step would not be feasible in a right lower lobectomy, in that the right middle-lobe bronchus arises from the bronchus intermedius.

to the ligamentum arteriosum, care should be taken not to narrow the main pulmonary artery and thereby reduce right-side blood flow. For maximal safety, systemic blood pressures and oxygenation should be evaluated for 15 to 20 seconds after application of the clamp or stapler but before ligation.

Pulmonary vein: superior and inferior pulmonary vein With the lung retracted posteriorly, the pleura is incised posterior to the course of the phrenic nerve, and the superior pulmonary vein is identified [see Figure 6]. The vein is encircled with blunt dissection, then ligated and divided. As noted (see above), the apical branch usually travels across the apical branch of the pulmonary artery, and care should be taken not to injure this vessel during dissection.

The lung is then retracted superiorly to expose the inferior pulmonary vein. Dissection is performed on the anterior and posterior aspects of the inferior pulmonary vein, and blunt dissection is used to achieve complete encirclement of the vein [see Figure 9], which is ligated and divided.

Left main bronchus Next, the lung is retracted anteriorly and superiorly. Complete dissection of the subcarinal lymph nodes is performed, facilitated by division of one or two pulmonary branches of the left vagus nerve and both bronchial arteries. Gentle traction is applied in conjunction with blunt dissection to allow encirclement of the proximal left mainstem bronchus [see Figure 11]. An effort should be made to encircle the bronchus within 1 cm of the carina. A TA stapler is then passed around the left mainstem bronchus and applied at this point. If excessive traction is required to achieve this placement, the bronchial stump can be left slightly longer: 1 to 1.5 cm, as measured from the carina. The stapler is fired, and the bronchus is divided distal to the staple line.

Frequently, the position of the bronchial stump under the aortic arch and deep within the mediastinum renders coverage of the stump unnecessary. If the surgeon is concerned about

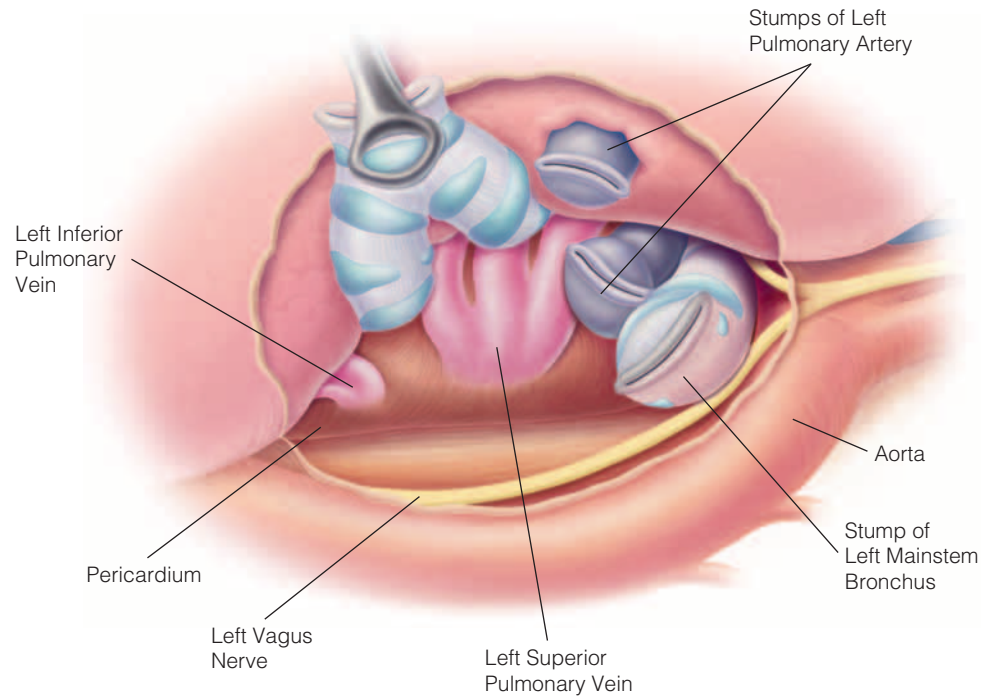


Figure 11 Left pneumonectomy. Shown is the surgeon's view of the posterior left hilum. The carina is located deep under the aortic arch. A left-side double-lumen tube or bronchial blocker may have to be withdrawn to afford better exposure of the proximal left mainstem bronchus. The orientation of the superior pulmonary vein and the pulmonary artery (anterior and superior to the bronchus, respectively) should be noted.

possible stump dehiscence (e.g., in a patient who has undergone high-dose preoperative radiotherapy), coverage with a flap from the pericardial fat pad or intercostal muscle is appropriate.

Postoperative Management

A key to successful postoperative management after pulmonary resection is pain control, pulmonary toilet and chest tube management. Thoracic epidural can provide great pain relief after the operation. If this modality is not available or not efficacious, patient controlled analgesia with or without continuous local anesthetic to the thoracotomy incision can be a good alternative. Although adequate pain control is one of the key elements of good pulmonary toilet it is not sufficient by itself. Patient education should begin preoperatively with clear explanation of the goals of pulmonary toilet and the methods used to achieve this. This includes coughing, deep breathing, usually assisted with an incentive spirometer, ambulation, bronchodilators, and, if necessary, nasotracheal suctioning or even flexible bronchoscopy. An x-ray is obtained after the operation to evaluate for appropriate lung expansion, shift of the mediastinum and the diaphragm. After a lobectomy or any lesser resection, the chest tube is usually placed on suction at -20 cm H_2O then transitioned to a water seal once there is a minimal air leak. Although there are wide variations in chest tube management most surgeons will

remove the tube when the air leak has resolved and the output is less than 300–400 cc in 24 hours. Patients are then transitioned to oral pain medication and discharged home.

Min P. Kim, MD, owns stock, stock options, or bonds in ATSI, General Electric, and Johnson & Johnson Inc.

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Acknowledgment

Figures 1, 2, and 3 through 11 Alice Y. Chen.

15 DIAPHRAGMATIC PROCEDURES

Ayesha S. Bryant, MSPH, MD, and Robert James Cerfolio, MD, FACS, FCCP

Although the diaphragm is sometimes thought of as little more than a partition between the thoracic organs and the abdominal organs, it is, in fact, a dynamic anatomic structure that plays a pivotal role in the physiology of respiratory mechanics. For example, paralysis of just one hemidiaphragm can lead to the loss of 50% of a patient's vital capacity.¹ Like any other anatomic structure, the diaphragm may be affected by either benign or malignant conditions. Overall, benign diseases of the diaphragm (e.g., paralysis) are far more common than malignant ones. With either type of condition, however, the development of a safe surgical treatment strategy depends on a solid knowledge of diaphragmatic anatomy and physiology. Accordingly, we begin with a brief review of the embryology and anatomy of the diaphragm. We then describe the main procedures performed to treat the more common congenital diseases (e.g., congenital diaphragmatic hernia [CDH]) and acquired pathologic conditions (e.g., paralysis and tumor) that affect this structure.

Anatomic Considerations

DEVELOPMENTAL ANATOMY

The diaphragm is a modified half-dome of musculo-fibrous tissue that lies between the chest and the abdomen and serves to separate these two compartments. It is formed from four embryologic components: (1) the septum transversum, (2) two pleuroperitoneal folds, (3) cervical myotomes, and (4) the dorsal mesentery. Development of the diaphragm begins during week 3 of gestation and is complete by week 8. Failure of the pleuroperitoneal folds to develop, with subsequent muscle migration, results in congenital defects.

CLASSICAL ANATOMY

The diaphragmatic musculature originates from the lower six ribs on each side, from the posterior xiphoid process, and from the external and internal arcuate ligaments. A number of different structures traverse the diaphragm, including three distinct apertures (foramina) that allow the passage of the vena cava, the esophagus, and the aorta [see Figure 1]. The aortic aperture is the lowest and most posterior of the diaphragmatic foramina, lying at the level of the 12th thoracic vertebra. Besides the aorta, the thoracic duct and, sometimes, the azygos and hemiazygos veins also pass through this aperture. The esophageal aperture is the middle foramen; it is surrounded by diaphragmatic muscle and lies at the level of the 10th thoracic vertebra. The vena caval aperture is the highest of the three foramina, lying level with the disk space between T8 and T9.

VASCULAR SUPPLY

The diaphragm is supplied by the right and left phrenic arteries, the intercostal arteries, and the musculophrenic

branches of the internal thoracic arteries. Some blood is supplied by small branches of the pericardiophrenic arteries that run with the phrenic nerve, mainly where the nerves penetrate the diaphragm. Venous drainage occurs via the inferior vena cava and the azygos vein on the right and via the suprarenal and renal veins and the hemiazygos vein on the left.

INNERVATION

The diaphragm receives its muscular neurologic impulse from the phrenic nerve, which arises primarily from the fourth cervical ramus but also has contributions from the third and fifth rami. The phrenic nerve originates around the level of the scalenus anterior and runs inferiorly through the neck and thorax before reaching its terminal point, the diaphragm. Because the phrenic nerve follows such a long course before reaching its final destination, a number of processes can disrupt the transmission of neurologic impulses through the nerve at various points and thereby cause diaphragmatic paralysis.

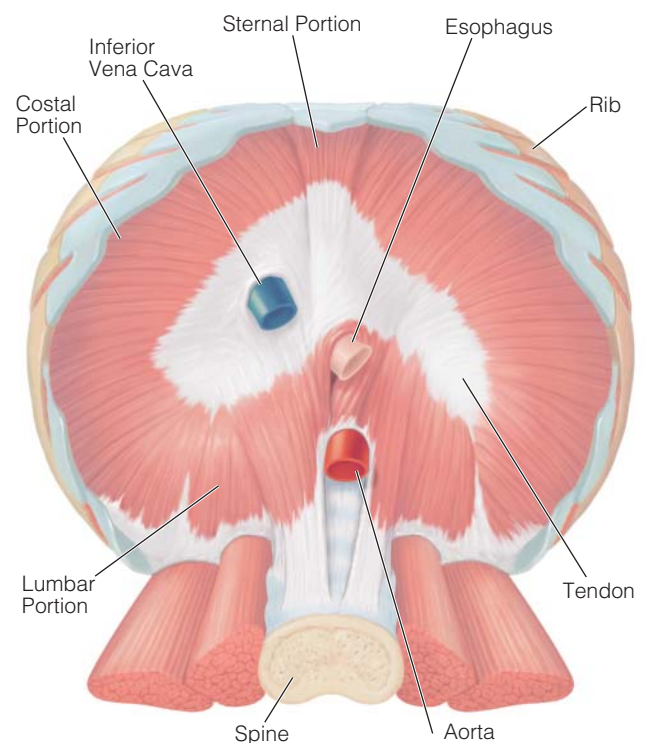


Figure 1 Shown is an inferior view of the diaphragm.

Procedures for CDH

REPAIR OF BOCHDALEK HERNIA

Bochdalek hernia, named after the Czech anatomist Vincent Alexander Bochdalek, is the most common form of CDH and is also the most common surgical emergency in neonates.¹ It involves an opening on the left side of the diaphragm. The stomach and intestines usually herniate into the thoracic cavity. The usual presenting symptoms are severe respiratory distress and a scaphoid abdomen. The primary pathologic condition is the presence of posterolateral defects of the diaphragm, which result either in maldevelopment of the pleuroperitoneal folds or in improper or absent migration of the diaphragmatic musculature.

Bochdalek hernias occur in approximately one of every 2,500 live births and are twice as common in male neonates as in female neonates. Mortality ranges from 45 to 50%. The bulk of the morbidity and mortality of CDH is attributable to the resultant hypoplasia of the lung on the affected side and to various associated abnormalities (e.g., malrotation of the gut, neural tube defects, and cardiovascular anomalies).

Preoperative Evaluation

Prenatal ultrasound examination accurately diagnoses CDH in 40 to 90% of cases.² In most instances, the examination is performed to rule out polyhydramnios. It is noteworthy that polyhydramnios is present in as many as 80% of pregnant women whose fetuses have CDH.³ In neonates with CDH, besides the upper gastrointestinal tract, parts of the colon, the spleen, the kidneys, and the pancreas may herniate, and the abnormal position of these organs can be identified by means of ultrasonography. Malrotation and malfixation of the small bowel should be ruled out. Once the diagnosis is confirmed, additional radiographic, echocardiographic, and ultrasonographic studies should be performed to rule out associated anomalies.

Operative Technique

As a rule, neonates with Bochdalek hernias are taken to the operating room immediately after birth. Some studies, however, have shown that delayed surgical repair yields improved survival rates.⁴

For left-side hernias, a transabdominal subcostal approach is generally preferred, whereas for right-side hernias, a thoracic approach may be more useful. The herniated organs are returned to the peritoneal cavity. The lung is inspected, but no attempt to expand the hypoplastic lung should be made. If any extralobar pulmonary sequestration is present (as is occasionally the case), it should be excised. Most of the defects may be closed primarily with interrupted nonabsorbable sutures; particularly large defects may be closed with a prosthetic patch. The left pleural space is drained with a chest tube, which should be placed on water seal.

Some surgeons have attempted surgical correction of severe Bochdalek hernias in the prenatal period. The safety and feasibility of this therapeutic approach continue to be debated. Prenatal correction of these hernias poses a risk to both the mother and the fetus, with possibly fatal results for both.⁵

REPAIR OF MORGAGNI HERNIA

Morgagni hernias, named after the Italian anatomist and pathologist Giovanni Battista Morgagni, are related to maldevelopment of the embryologic septum transversum and to failed fusion of the sternal and costal fibrotendinous elements of the diaphragm.⁶ The Morgagni hernia involves an opening on the right side of the diaphragm. The liver and intestines usually herniate into the thoracic cavity. These hernias are generally asymptomatic⁷ and are usually detected as incidental findings on radiographs. Accordingly, the average age at diagnosis is typically greater for Morgagni hernia than for Bochdalek hernia: in one report, the mean age at which the former was diagnosed was 45 years.⁸ Morgagni hernias are most commonly seen on the right side. The hernia sac usually contains omentum, but it may also contain part of the transverse colon or, less commonly, parts of the stomach, the liver, or the small bowel; almost any upper abdominal structure may herniate in this setting.

Preoperative Evaluation

On chest radiography, a Morgagni hernia appears as a mass at the right cardiophrenic angle [see Figure 2]. Computed tomography (CT) of the chest and abdomen, liver scintigraphy, and multiplanar magnetic resonance imaging (MRI) are occasionally helpful in the diagnostic process.

Operative Technique

Morgagni hernias can be repaired via a subcostal, a paramedian, or a midline incision. We prefer to use an upper midline abdominal incision. Once the peritoneal cavity is entered, the hernia sac is identified just posterior to the xiphoid and the posterior sternal border and then opened. The herniated abdominal viscera are restored to their normal abdominal anatomic positions, and the sac is ligated. The entire hernia sac is defined, resected, and closed. The diaphragmatic defect may be repaired in several different ways, depending on its size and position. Because there is weak tissue in the area of the defect, we generally use a prosthetic patch for the repair. Either polypropylene mesh (e.g., Marlex; C. R. Bard, Inc., Murray Hill, New Jersey) or polytetrafluoroethylene (PTFE) mesh (e.g., Gore-Tex; W. L. Gore and Associates, Newark, Delaware) may be used for this purpose. We prefer PTFE because it may cause fewer adhesions to the underlying abdominal structure, which may be an important consideration if further abdominal surgery subsequently proves necessary. The prosthetic patch is sewn to the midline abdominal fascia, with wide bites taken to prevent an abdominal incisional hernia. The rest of the patch is sewn to the thickened investing fascia that made up the edges of the hernia sac. As noted, the frequently marginal quality of this tissue is the reason why a patch repair is almost always required.

Repair of a Morgagni hernia via a thoracic incision follows the same basic principles. The hernia sac is entered, the visceral contents are mobilized and reduced into the abdomen, the sac is resected, and the diaphragm is repaired. Again, the closure should be completed without tension. If the defect cannot be closed with horizontal mattress sutures, a prosthetic patch should be used.

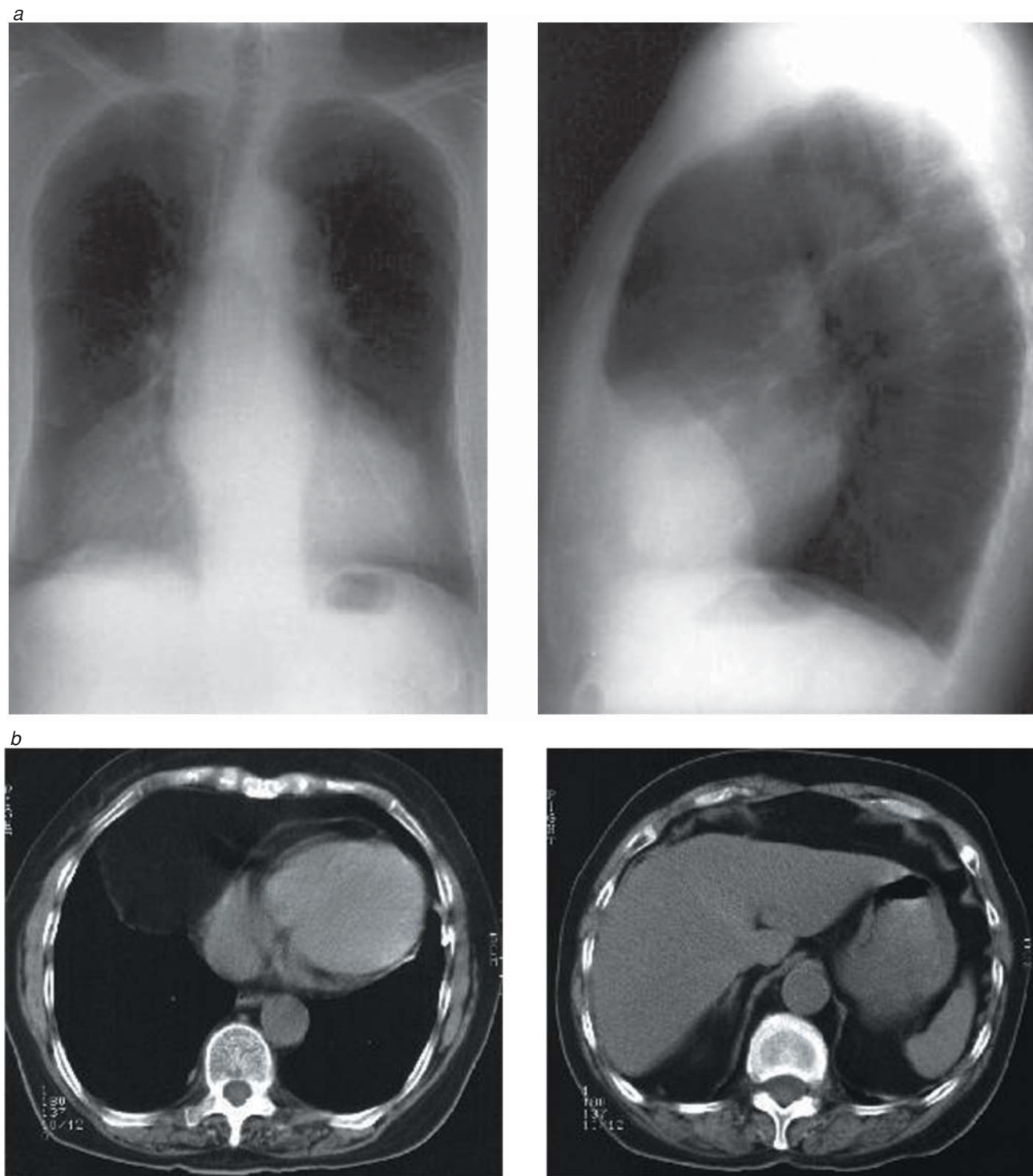


Figure 2 Repair of Morgagni hernia. The differential diagnosis of a cardiophrenic-angle mass includes pericardial fat, a lipoma, a pericardial cyst, a Morgagni hernia, and a thymoma. Shown are (a) chest x-rays and (b) chest computed tomographic scans from a 33-year-old man with an incidental finding of a Morgagni hernia.

Complications

The potential complications of surgical treatment of Morgagni hernia depend to an extent on the type of procedure undertaken to repair the defect. Laparoscopy may result in failure to reduce the contents of the hernia sac, which

necessitates conversion to an open procedure. Laparotomy has been associated with postoperative pleural effusion,⁹ wound infection,¹⁰ deep vein thrombosis,¹¹ and pulmonary embolism.¹² Thoracotomy has been associated with pneumonia, sepsis, and bowel obstruction in the postoperative period.¹³

Outcome Evaluation

Most patients do not have any significant postoperative limitations after repair of a Morgagni hernia, nor are such hernias likely to recur. In one study, 16 patients who underwent transthoracic repair of a Morgagni hernia were followed for 5.7 years; no recurrences or symptoms related to the operation were reported.¹⁴

Procedures for Diaphragmatic Paralysis

The diaphragm is the most important of the respiratory muscles: diaphragmatic contraction decreases intrapleural pressure during inspiration, expands the rib cage, and thereby facilitates the movement of gases into the lungs. Accordingly, paralysis of the diaphragm can have a major adverse effect on respiratory function. Diaphragmatic paralysis may involve either the whole diaphragm (bilateral paralysis) or only one leaflet or hemidiaphragm (unilateral paralysis). The possible causes of diaphragmatic paralysis are numerous [see Table 1]; the most common causes are phrenic nerve trauma related to a surgical procedure (e.g., stretching, crushing, or transection) and invasion by a malignant neoplasm.

DIAPHRAGMATIC PPLICATION FOR UNILATERAL PARALYSIS

Preoperative Evaluation

With unilateral diaphragmatic paralysis, the paralyzed hemidiaphragm paradoxically moves upward on inspiration and downward on expiration, passively following changes in intrapleural and intra-abdominal pressure. Patients with a paralyzed hemidiaphragm who are otherwise healthy usually have no symptoms at rest but experience dyspnea during exertion and show a decrease in exercise performance.

Table 1 Common Causes of Diaphragmatic Paralysis

Neurologic conditions
Spinal cord transection
Multiple sclerosis
Amyotrophic lateral sclerosis
Cervical spondylosis
Poliomyelitis
Guillain-Barré syndrome
Phrenic nerve dysfunction
Compression by tumor
Cardiac surgery cold injury
Blunt trauma
Idiopathic phrenic neuropathy
Diabetes mellitus
Postviral phrenic neuropathy (herpes zoster)
Radiation therapy
Cervical chiropractic manipulation
Myopathic conditions
Limb-girdle dystrophy
Hyperthyroidism/hypothyroidism
Malnutrition
Acid maltase deficiency
Connective tissue disease
Systemic lupus erythematosus
Dermatomyositis
Mixed connective tissue disease
Amyloidosis
Idiopathic myopathy
Muscular dystrophy
Multiple sclerosis

Physical examination may reveal dullness to percussion and an absence of breath sounds over the lower chest on the involved side.

In most cases, the diagnosis of hemidiaphragmatic paralysis is suspected on the basis of incidental findings on a chest x-ray. Typically, the roentgenogram reveals an elevated hemidiaphragm, diminished lung volume, and basilar atelectasis. Fluoroscopy may also be performed. The diagnosis is confirmed by performing a fluoroscopic sniff test, in which paradoxical elevation of the paralyzed diaphragm is observed with sniffing.¹⁵ The sniff test is the gold standard for the diagnosis of this condition. In certain patients, a chest CT scan may be indicated for evaluating the potential cause of the paralysis. If an obvious cause is not apparent from the history or a previous evaluation, CT scanning of the chest should be performed to ensure that no pathologic process is compressing or invading the phrenic nerve. Similarly, MRI of the neck or the spine may be indicated in certain patients to look for conditions that might be causing the diaphragmatic paralysis.

Two other tests that are also (albeit less commonly) used for the diagnosis of unilateral diaphragmatic paralysis are electromyography and transdiaphragmatic pressure assessment. In the first, the phrenic nerve is electrically stimulated in the neck in an effort to distinguish between neuropathic and myopathic causes of paralysis. In the second, transdiaphragmatic pressures are measured by placing a thin-walled balloon transnasally at the lower end of the esophagus in such a way as to reflect changes in pleural pressure; a second balloon manometer is then placed in the stomach in such a way as to reflect changes in intra-abdominal pressure. The difference between the two pressures is the transdiaphragmatic pressure. Measurement of transdiaphragmatic pressure can help differentiate diaphragmatic paralysis from other causes of respiratory failure.

Yet another test involves measurement of maximal inspiratory pressures. Patients with diaphragmatic dysfunction and paralysis show a decrease in their maximal inspiratory pressures. These patients cannot generate high negative inspiratory pressures; thus, their maximal inspiratory pressures will be less negative than -60 cm H₂O.

Operative Planning

Surgical treatment of hemidiaphragmatic paralysis is reserved for symptomatic patients who, after a follow-up period of at least 6 months, have persistent shortness of breath with exertion that is sufficiently pronounced to interfere with lifestyle. For a patient to be considered for operation, the sniff test should show significant paradoxical motion.

The basic principle of the surgical procedure is to “reef” (i.e., reduce the surface area of) the redundant floppy diaphragm by plicating it. This measure lowers the resting position of the hemidiaphragm and thus affords the lung the opportunity to expand fully. The effective result is an increase in the functional vital capacity of the ipsilateral lung. The results of plication have been shown to be better in children compared to adults. Plication is of limited benefit in weaning ventilated adults; however, it still results in lifetime improvement in nonventilated adults.¹⁶ A couple of studies have found

that plication of the diaphragm led to long-term improvements in pulmonary function test results, as well as reduced dyspnea.^{17,18}

Operative Technique

Diaphragmatic plication may be performed with either sutures or staples; we prefer sutures for this procedure. The chest is entered through a thoracotomy in the seventh or eighth intercostal space. Horizontal mattress sutures buttressed with Teflon pledgets are then placed in a lateral-to-medial direction [see Figure 3]. We typically use monofilament nonabsorbable sutures that pass easily through the muscle and can be tightened without dragging through tissue. To distribute the tension, multiple sutures must be placed; this is especially important on the right side, where the diaphragm must be pulled down against the upward force exerted by the presence of the right hemiliver. When the sutures are tied, the hemidiaphragm should be almost back to its normal anatomic location. Care must be taken to ensure that the repair is not under undue tension: excessive tension is likely to result in early dehiscence. Occasionally, a prosthetic patch may be used to buttress the repair further, but in the majority of cases, this measure should be unnecessary. If the choice is made to use staples rather than sutures, care must be taken to ensure that the underlying abdominal contents are not caught in the staple line.

Diaphragmatic plication can also be performed via video-assisted thoracoscopic approach. Some studies have shown that the minimally invasive approach reduces the risk and the recovery time when compared to a thoracotomy.¹⁹

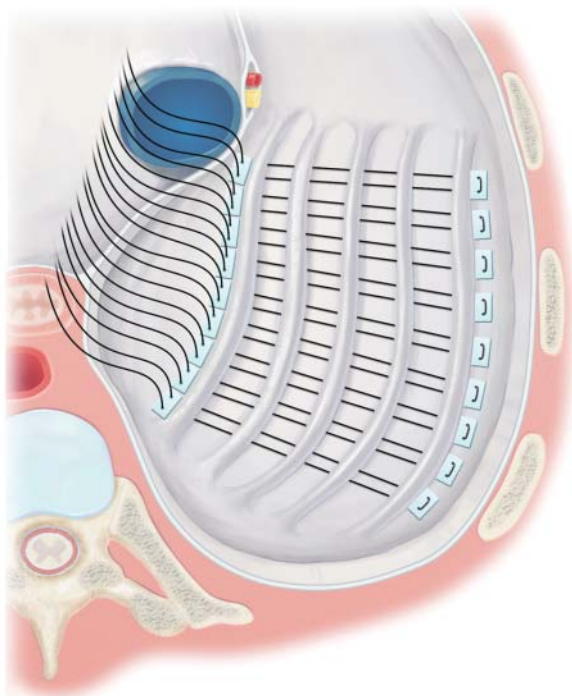


Figure 3 Diaphragmatic plication. Shown is suture plication of the right hemidiaphragm. Placement of sutures buttressed with pledgets extends anteriorly to the level of the vena cava.

DIAPHRAGMATIC PACING FOR BILATERAL PARALYSIS

Preoperative Evaluation

In patients with bilateral diaphragmatic paralysis, the respiratory accessory muscles assume all the work of breathing by contracting more intensely. Both hemidiaphragms move upward on inspiration, concomitant with inward (rather than the normal outward) movement of the abdominal wall.²⁰ Patients typically present with severe respiratory failure or with dyspnea (sometimes misinterpreted as a sign of heart failure) that worsens in the supine position, and they generally exhibit tachypnea and rapid, shallow breathing when in the recumbent position. Increased expenditure of effort in the struggle to breathe may fatigue the accessory muscles and lead to ventilatory failure. Patients also report anxiety, insomnia, morning headache, excessive daytime somnolence, confusion, fatigue, poor sleep habits, and signs of cor pulmonale.²¹

During physical examination, auscultation of the chest reveals limitation of diaphragmatic excursion and bilateral lower-chest dullness with absent breath sounds. The finding that establishes the diagnosis is a paradoxical inward movement of the abdomen with inspiration. As with unilateral diaphragmatic paralysis, however, it is more common for the diagnosis to be suspected on the basis of a chest roentgenogram that shows bilateral diaphragmatic elevation and then confirmed by means of the sniff test.

Operative Planning

Treatment depends on the cause and severity of the diaphragmatic paralysis. Most patients are treated with ventilatory support, but some are treated with bilateral plication or with pacing (as shown in Figure 4). Plication for bilateral paralysis is performed in the same way as plication for unilateral paralysis [see Diaphragmatic Plication for Unilateral Paralysis, above], except that both hemidiaphragms are lowered.

There are patients who have suffered high cervical injuries and are either quadriplegic or have loss of the C3, C4, and C5 anterior horn cells in the nerve roots. These patients are on ventilators for life and usually nonambulatory. To date, two pacing devices have been approved by the Food and Drug Administration: the Mark IV Breathing Pacemaker System (Avery Biomedical Devices, Commack, New York) uses an electrode that is placed on the skeletonized phrenic nerve, and the NeuRx (Synapse Biomedical, Cleveland, Ohio) uses electrodes placed directly in the diaphragm fibers either video-assisted thoracoscopically or laparoscopically. Both are connected to a small receiving electrode unit placed under the skin. A battery-powered external transmitting box connected to an antenna is taped over the surface of the skin, just above the subcutaneous receiver. This transmitting box permits adjustment of pulse duration, pulse train duration, respiratory rate, pulse frequency, and current amplitude. In most patients, the only parameters that the clinician adjusts are current amplitude and respiratory rate.

Implantation of a diaphragmatic pacer requires experience on the part of the surgeon—not so much because of any particular technical demands imposed by the implantation itself but because of the procedures for diaphragm training that must be carried out in the postoperative period.

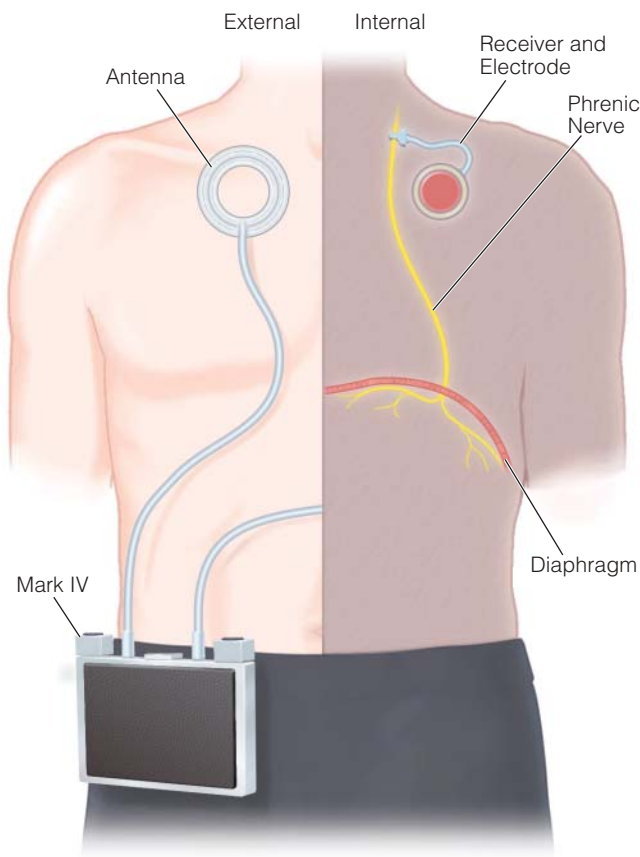


Figure 4 Diaphragmatic pacing. Shown are internal and external pacer connections.

Surgical implantation of a diaphragmatic pacer can be done via either a cervical approach or a thoracic approach. The primary advantage of the cervical approach is that it avoids the morbidity associated with bilateral thoracotomies, which may not be well tolerated in patients who have marginal pulmonary function or a history of severe pulmonary contusions. However, there are other ways of avoiding this morbidity, either laparoscopically, by video-assisted thoracoscopic surgery (VATS), or with a small muscle-sparing, rib-sparing, nerve-sparing thoracotomy.²² One disadvantage of the cervical approach is that in a small percentage of patients, the current amplitude necessary to stimulate the phrenic nerve results in transmission of the current through the soft tissues. The transmitted current stimulates the functioning portions of the brachial plexus, causing rhythmic jerking motions of the upper extremities. Another disadvantage is that a number of accessory nerve branches arise distal to the neck.

One advantage of the thoracic approach is that inadvertent stimulation of portions of the brachial plexus (as sometimes occurs with the cervical approach) may be avoided. Another advantage is that there is some neuroanatomic evidence that a small branch of the phrenic nerve joins the main nerve trunk only after it enters the chest cavity; thus, the thoracic approach may stimulate a larger portion of the phrenic nerve

than the cervical approach would. The disadvantage of the thoracic approach is the preconceived notion that entry into the chest is associated with a higher morbidity than entry into the neck.

Operative Technique

Cervical placement In the neck, the phrenic nerve runs between the scalenus anterior and the scalenus medius. A transverse skin incision is made in the midportion of the neck, just lateral to the sternocleidomastoid muscle, and the borders of the two scalene muscles are dissected. The scalene muscles are then divided, and the phrenic nerve is identified lying in a layer of fascia just anterior to the anterior surface of the scalenus medius. Identification of this nerve is often facilitated by the use of a handheld nerve stimulator. Intraoperative fluoroscopy allows observation of diaphragmatic contraction in response to phrenic nerve stimulation, which confirms that pacing is successful.

Once the phrenic nerve is identified, it is carefully dissected free of its investing fascia, and the Y-shaped electrode is placed under it and secured with sutures. Care must be taken to ensure that the nerve is not injured during this step. The connecting wire from the electrode is then tunneled subcutaneously to a subcutaneous pocket that is created just below the ipsilateral clavicle. The connections are made and sealed, and the small incisions are closed.

Thoracic placement In the thoracic approach, the chest is entered through a high thoracotomy (usually over the fourth interspace), and the proximal phrenic nerve is identified. On the right side, the nerve lies along the mediastinum, situated just anterior to the vena cava and coursing along the pericardial surface. On the left side, it lies on the pericardium for most of its length. The proximal nerve is freed of its fibrous investments, and the electrode is placed under it and secured with sutures. The electrode is connected to the receiver, which is placed in a subcutaneous pocket.

As noted (see above), there are alternative approaches to pacer implantation that avoid the cervical approach but also do not involve standard thoracotomies. For example, there is limited (but growing) experience with thoracoscopic placement of phrenic nerve pacing leads.²³ In addition, laparoscopic implantation of intramuscular pacing electrodes onto the inferior aspect of the diaphragm has been reported.²⁴

Taking into account all the advantages and disadvantages of each approach to pacer implantation, we generally prefer the thoracic approach, either via VATS or via a thoracotomy.^{23,25} The evolution of less invasive surgical techniques may allow the thoracic approach to be employed in patients who are unable to tolerate thoracotomy.

Complications

Besides the usual complications associated with any thoracic procedure (i.e., infection, bleeding, atrial fibrillation, and pneumonia), several specific complications are associated with diaphragmatic pacing. The most common of these are dislodgment of the pacer electrode, transmission of pacer impulses to the brachial plexus with resultant rhythmic jerking of the upper extremity (seen with cervical placement of the electrode), and hardware malfunction.

Outcome Evaluation

Retrospective analysis of the collective experience at a single center between 1981 and 1987 suggested that long-term pacing did not lead to progressive diaphragmatic dysfunction.²⁶ Six of the 12 patients in this cohort continued to undergo diaphragmatic pacing on a full-time basis for a median period of more than 14 years. Pacing was well tolerated in this group; the reasons for discontinuance included intercurrent medical illness and lack of social support. Concerns have been raised that prolonged diaphragmatic pacing might damage the phrenic nerve. In the series cited, however, the ability to pace the phrenic nerve was not lost in any of the patients, and the mean threshold currents for pacing did not change significantly over time.

Resection of Diaphragmatic Tumors

Primary tumors of the diaphragm are extremely rare. Benign tumors (e.g., lipomas and cystic masses) are more common than malignant tumors, which mostly are sarcomas of fibrous or muscular origin. Thoracic and abdominal tumors (e.g., bronchogenic carcinomas, pleural malignancies, and chest wall malignancies) may involve the diaphragm secondarily through direct extension. Malignant pleural mesothelioma represents a different scenario and is not discussed here. Schwannomas, chondromas, pheochromocytomas, and endometriomas have all been reported. Bilateral occurrence,

calcification, sharp margins, and flattened contours are indicative of a malignant process, such as pleural metastases, mesothelioma, or a primary diaphragmatic tumor.

The most common indication for diaphragmatic resection is mesothelioma. This remains true even though mesothelioma is relatively uncommon in comparison with bronchogenic malignancy and even though few patients with mesothelioma are actually candidates for resection. Again, resection of a mesothelioma is not addressed here. The ensuing operative description focuses on diaphragmatic resection to treat either a lung cancer invading the diaphragm or a primary diaphragmatic tumor [see Figure 5].

OPERATIVE TECHNIQUE

Once the decision is made to resect a tumor involving the diaphragm, the key considerations are (1) the surgical approach to be taken and (2) the placement of the incision in the diaphragm. We prefer a skin incision that is lower and slightly more anterior than a normal posterolateral thoracotomy; such an incision allows easy entry over the top of the seventh rib. After entry into the chest, the lung, the pericardium, and the pleural surface are carefully visualized and palpated to search for any signs of metastatic disease.

Next, the incision in the diaphragm is planned. Ideally, the incision should be made anterior or lateral to the tumor so that a hand can be placed easily into the peritoneal cavity [see Figure 5a]. Intra-abdominal palpation confirms that the tumor

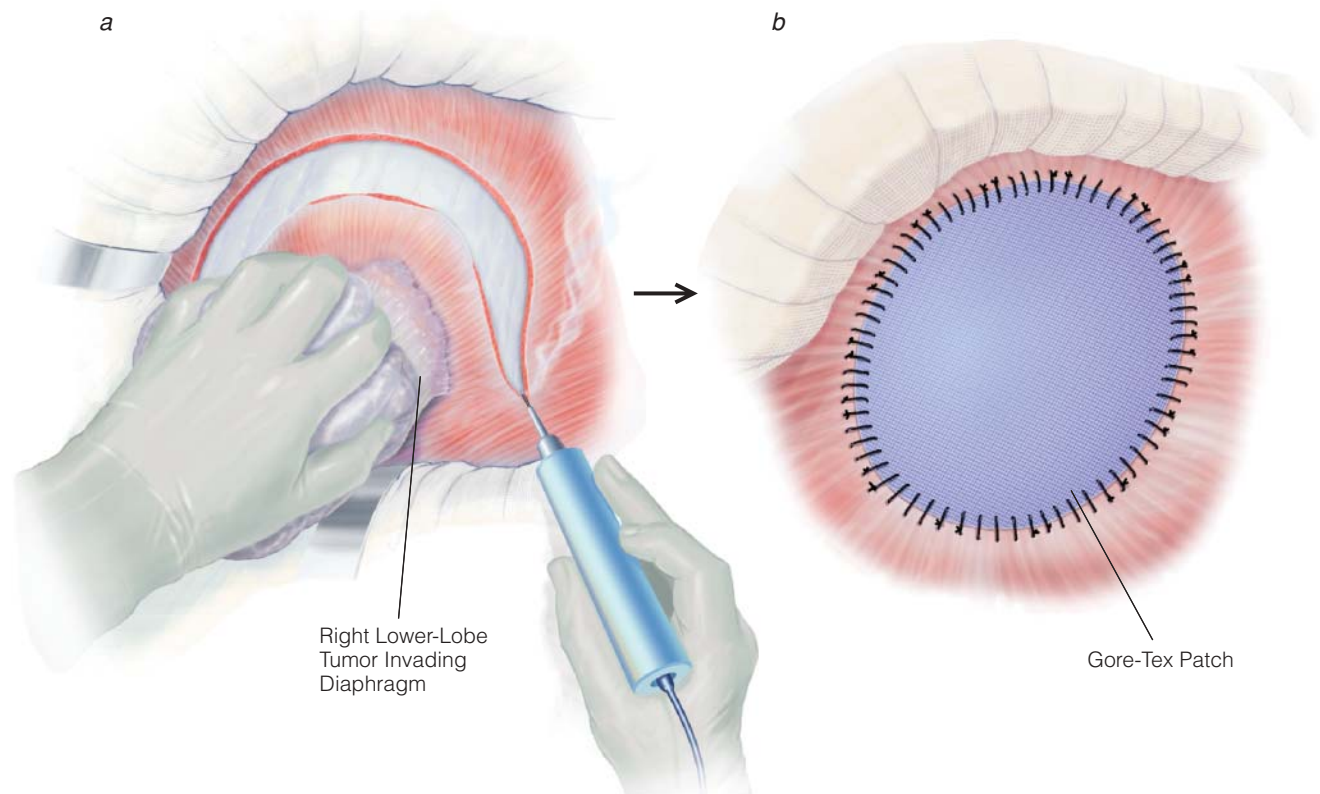


Figure 5 Resection of diaphragmatic tumor. The patient has a right lower-lobe bronchogenic malignancy with erosion into the right hemidiaphragm. (a) The tumor is resected en bloc with the diaphragmatic fibers; the electrocautery is used to achieve clear surgical margins and hemostasis. (b) The defect in the right hemidiaphragm is closed with a mesh patch.

has not extended into underlying structures. This information is almost always gleaned from the preoperative CT scan, but if any uncertainty remains after the scan, diagnostic laparoscopy may be performed before the thoracotomy to look for possible tumor extension.

The tumor is then resected with 2 to 4 cm margins. The large arteries that course through the diaphragmatic fibers are ligated. It is our practice also to place a few silk sutures (stay stitches) in the edges of the defect; this prevents the edges from retracting, helps keep the defect as small as possible, and keeps abdominal contents from interfering with the resection. In addition, we place clips on the edges for guidance purposes in case adjuvant radiotherapy is delivered after the operation. If adequate margins are obtained, which is usually relatively easy in a diaphragmatic resection, postoperative radiotherapy should be unnecessary. If, however, the tumor abuts vital structures (e.g., the suprahepatic vena cava), postoperative radiotherapy may have a useful role to play.

Once the entire tumor has been resected and clear margins have been confirmed by frozen-section examination, the diaphragm is reconstructed. Primary repair is rarely indicated because in most cases, the defect is too large and the tension on the repair would be too great. Moreover, the tissue in the anterior aspect of the diaphragm is thin and is likely to tear

under tension. Accordingly, repair with a prosthetic patch is the usual choice. Infection of such a patch is exceedingly rare, and with the exception of the cost, there is little downside to the use of prosthetic material in this setting. As in the repair of a CDH, we prefer PTFE mesh [see Figure 5b] to polypropylene mesh because it is less likely to adhere to underlying abdominal structures.

The mesh patch is sewn to the edges of the defect (preferably with nonabsorbable suture material, such as 0 polypropylene), starting at the most anterior and inferior portions of the opening and continuing toward the surgeon [see Figure 5]. The inferior half of the repair is done with a continuous suture. The repair is completed with two or three sutures, which are tied circumferentially. To prevent paradoxical motion, the diaphragm must not be too redundant or floppy. It should remain in the normal anatomic position so that the remaining lung can expand completely. In general, however, it is best to keep the repair taut so as to optimize pulmonary mechanics after the procedure.

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Acknowledgment

Figures 1 and 3 through 5 Tom Moore

16 THORACIC DIAGNOSTIC AND STAGING PROCEDURES

Farzaneh Banki, MD and Larry R. Kaiser, MD, FACS

Thoracic diagnostic and staging procedures can be divided into those that involve the lungs, pleural space, mediastinum, and esophagus. Surgeons must be familiar with the TNM staging system for each major thoracic disease to decide on appropriate treatment. A general principle is to proceed with the diagnostic modality that will potentially yield or rule out the highest stage. As an example, in a patient with presumed non-small cell lung cancer and a pleural effusion, there is no reason to proceed with mediastinoscopy to assess lymph node involvement prior to interrogating the pleural space with video-assisted thoracoscopy (VATS). In this chapter, we review the diagnostic and staging procedures that relate to the most common thoracic malignancies that occur in the thoracic cavity that have relevance to the general surgeon.

Clinical Diagnosis and Staging

The diagnosis and staging of intrathoracic disease have major implications for treatment planning, especially in light of recent advances in both neoadjuvant and adjuvant treatment regimens in both lung cancer and esophageal cancer. These two malignancies account for the majority of the pathology seen within the chest cavity and treated by thoracic surgeons. TNM staging for both lung cancer and esophageal cancer recently has undergone revision as noted in the seventh edition of the American Joint Committee on Cancer (AJCC) cancer staging manual, effective since January 2010.¹ It is mandatory for every surgeon who treats these diseases to be intimately familiar with the staging classification as mentioned in the latest edition of this manual. The surgeon needs to be familiar with clinical staging based on preoperative imaging studies and pathologic staging that result from either preoperative invasive staging techniques or the findings that are generated by the pathologist who reviews the histology of the material obtained at the time of definitive resection. Optimal surgical resection that results in definitive information detailing the final clinical stage includes complete removal of the primary tumor as well as, ideally, a systematic dissection or, at minimum, sampling of the regional lymph nodes. Any procedure that is not this inclusive results in partial information that makes a decision regarding postoperative treatment significantly more difficult and may result in a poorer outcome for the patient.

Clinical staging of intrathoracic disease, specifically intrathoracic malignancies, relies on imaging modalities that range from plain chest radiography to positron emission tomography (PET). Most commonly, patients with intrathoracic complaints obtain a chest radiograph that may or may not delineate the relevant pathology. Computed tomographic

(CT) scans of the chest most commonly performed following the injection of intravenous contrast are the mainstay of thoracic imaging procedures. These scans are the most sensitive for defining parenchymal lung lesions and can detect lesions down to a size of several millimeters.

The appearance of a parenchymal lung nodule does not necessarily indicate malignancy. The only definitive information that can be obtained regarding a lung nodule seen on a CT scan is its size. There are no specific defining characteristics that are accurate in delineating a benign from a malignant nodule. If previous CT scans are available for comparison, an increase in the size of a nodule points toward malignancy but, again, is not definitive. The presence of a new nodule on a CT scan may mandate nothing more than a repeat scan in 3 months to assess whether the nodule is changing in size. An increase in the size of a nodule should mandate further diagnostic procedures to define the nodule. The size increase alone may be an indication for resection or, depending on the clinical setting, may mandate a needle aspiration biopsy to obtain material for cytologic analysis. However, one must be aware that only a positive result is helpful, as with any diagnostic test. A “negative” biopsy is of no use because a sampling error may account for the negative result and we are still faced with a nodule that has increased in size. Thus, prior to obtaining a needle aspiration biopsy, the surgeon should know how the information will be used. One recognizes intuitively that if the biopsy is positive for malignancy and there is no evidence of locally advanced or distant disease, the patient is a candidate for resection unless that option is precluded because of other underlying medical problems. But if operation is also indicated in the presence of a negative result on biopsy, one has to think seriously as to whether the risk of a needle biopsy is warranted.

CT scans are also excellent for demonstrating enlargement of mediastinal and hilar lymph nodes, but, once again, an increase in size alone does not necessarily translate into malignancy. By convention, we define mediastinal lymph nodes larger than 1 cm on short axis as pathologic, although some prefer to use 1.5 cm as the definition for pathologic.² Many surgeons have used CT scans to identify those patients without pathologic lymph nodes as defined by size criteria so that certain patients may proceed to resection without the need for invasive mediastinal staging. It has been reported that only 3 to 16% of patients with mediastinal lymph nodes less than 1 cm in size on a CT scan are found to have tumor involvement at mediastinoscopy.^{3,4} Sensitivity and specificity will vary depending on what size criteria for positivity one chooses to use. A meta-analysis looking at CT scans in assessing mediastinal lymph node involvement in bronchogenic carcinoma found an overall sensitivity and specificity of

79% and 78%, respectively.⁵ McLoud and colleagues reported even lower sensitivity and specificity of 64% and 62%, respectively.⁶ The bottom line here is that the presence of enlarged lymph nodes should prompt additional staging studies, including ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET and most likely mediastinoscopy to document the presence or absence of malignancy before deciding that a patient is not an operative candidate.⁷

PET is highly sensitive in the detection of mediastinal lymph node involvement in patients with bronchogenic carcinoma, with a lower limit of detection reported at 4 mm.⁸ It has been estimated to have a sensitivity as high as 91 to 96% and a specificity as high as 86 to 93% in staging of mediastinal lymph nodes.^{9–13} PET has also been found to be quite useful in differentiating benign from malignant parenchymal lung nodules. A nodule with positive ¹⁸F-FDG uptake on PET has a better than 90% likelihood of being malignant. Figure 1a demonstrates a right upper lobe nodule seen on a CT scan, whereas Figure 1b shows the same nodule on a PET scan. Increased metabolic activity is suggestive of malignancy, as seen in the hilar lymph node. The use of combined PET-CT is growing, and several studies suggest that the use of integrated PET-CT improves anatomic localization of lymph nodes compared with PET alone.¹¹ This study provides both the anatomic localization and size information when looking at the mediastinal lymph nodes, as well as the metabolic information obtained from the PET scan, which provides additional information useful in determining benign from malignant tumors. The same applies to parenchymal lesions.

Diagnostic and Staging Procedures for the Lungs, Pleura, and Mediastinum

BRONCHOSCOPY

Bronchoscopy is the standard diagnostic modality used for the assessment of disease that involves the airway, lungs, and pleura. The use of the fiberoptic bronchoscope has, for the most part, supplanted the use of rigid bronchoscopy for all but lesions thought to involve the trachea or proximal mainstem bronchi. It is safe, although sad, to say that rigid bronchoscopy is a dying art except for the few thoracic surgeons and interventional bronchoscopists who continue to use it for certain indications. Flexible bronchoscopes allow for visualization of the entire tracheobronchial tree out to the level of subsegmental bronchi, and lesions may be sampled via the working channel of the instrument. Techniques for sampling include brushings, washings, and use of a flexible biopsy forceps to obtain tissue samples. The procedure may easily be performed with the patient awake and lightly sedated with the instrument passed either via the nares or through the mouth using topical anesthetic to attenuate the gag reflex. Use of an endotracheal tube is not required to place the bronchoscope but may be used to secure the airway if necessary.

Once the instrument is passed, the vocal cords are visualized and traversed, with inspection then carried out of the entire airway. Topical anesthetic may be injected through the instrument as needed to prevent the patient from coughing. Orientation is secured by visualizing the origin of the right upper lobe bronchus, which is the most proximal orifice

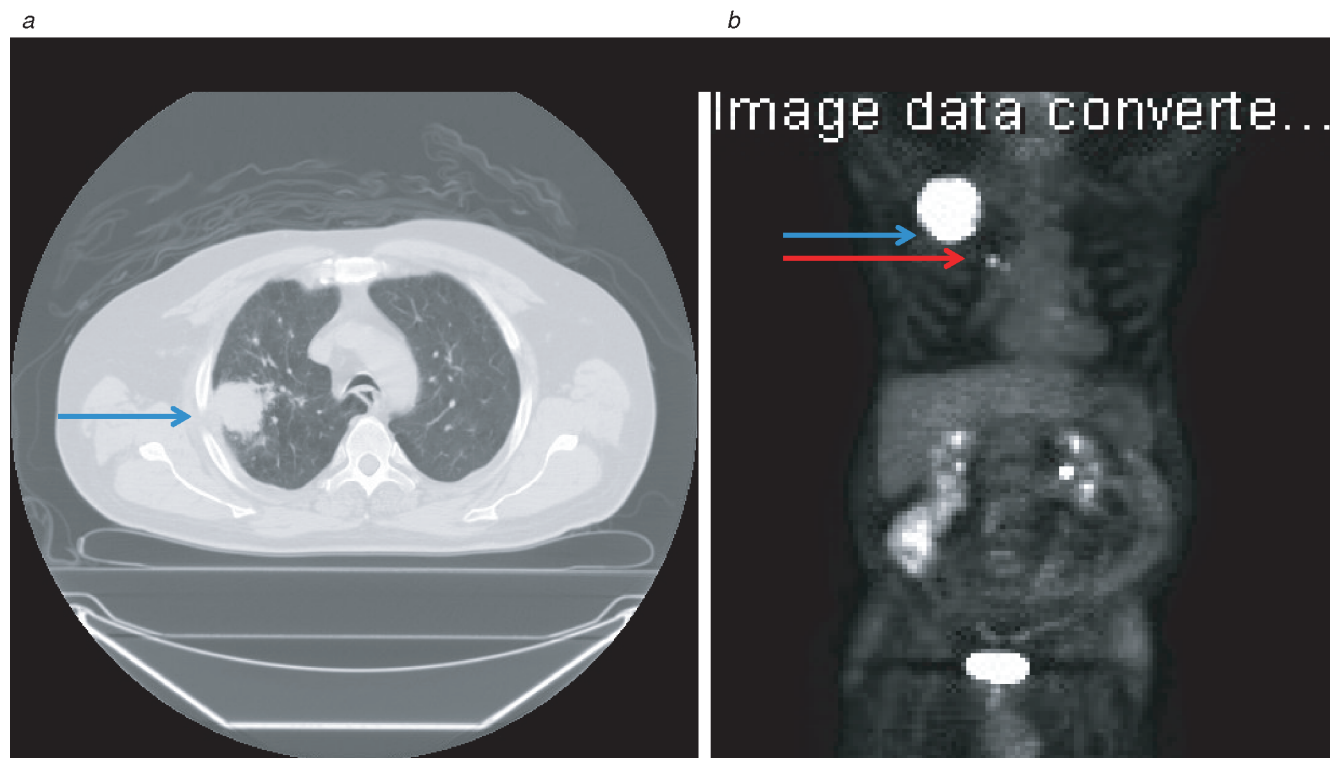


Figure 1 (a) Right upper lobe non-small cell lung cancer on a computed tomographic scan. (b) Positron emission tomographic scan. The blue arrows indicate the primary tumor, and the red arrow indicates the hilar lymph node.

visualized when one proceeds beyond the carina and takes off at an acute angle [see *Figure 2*]. Proceeding down the right mainstem bronchus, the bronchus intermedius is entered distal to the right upper lobe takeoff, and the origin of the middle lobe and lower lobe bronchus can be seen. The takeoff of the superior segment of the lower lobe is visualized heading posteriorly. Next, the left main bronchus is entered and both upper and lower lobe bronchi are interrogated. Any endobronchial lesions seen may be sampled with the cup biopsy forceps. Parenchymal lesions may also be sampled via a transbronchial approach using fluoroscopy for precise localization of the biopsy forceps. Special alligator forceps are passed distally into the airway via the appropriate segmental bronchus, and either a discrete lesion or diffusely involved parenchyma may be sampled. Bleeding, if encountered, usually only requires saline lavage and tamponade with the

bronchoscope. Occasionally, epinephrine in saline is used to control bleeding after a transbronchial lung biopsy.

Transbronchial Needle Aspiration

Transbronchial needle aspiration (TBNA) is another diagnostic technique that may be used to assess regional lymph nodes and is performed via the flexible bronchoscope. A needle catheter is passed through the working channel of the instrument and guided to the area of the tracheobronchial tree adjacent to the mediastinal lymph node of interest. The needle catheter is advanced through the tracheal or carinal wall into the mediastinal lymph node, and a syringe is connected to aspirate cellular material. Several passes may be necessary until an adequate specimen is confirmed by the cytopathologist, who, ideally, is present. On-site cytopathologic examination of needle aspiration specimens significantly improves the yield of TBNA.

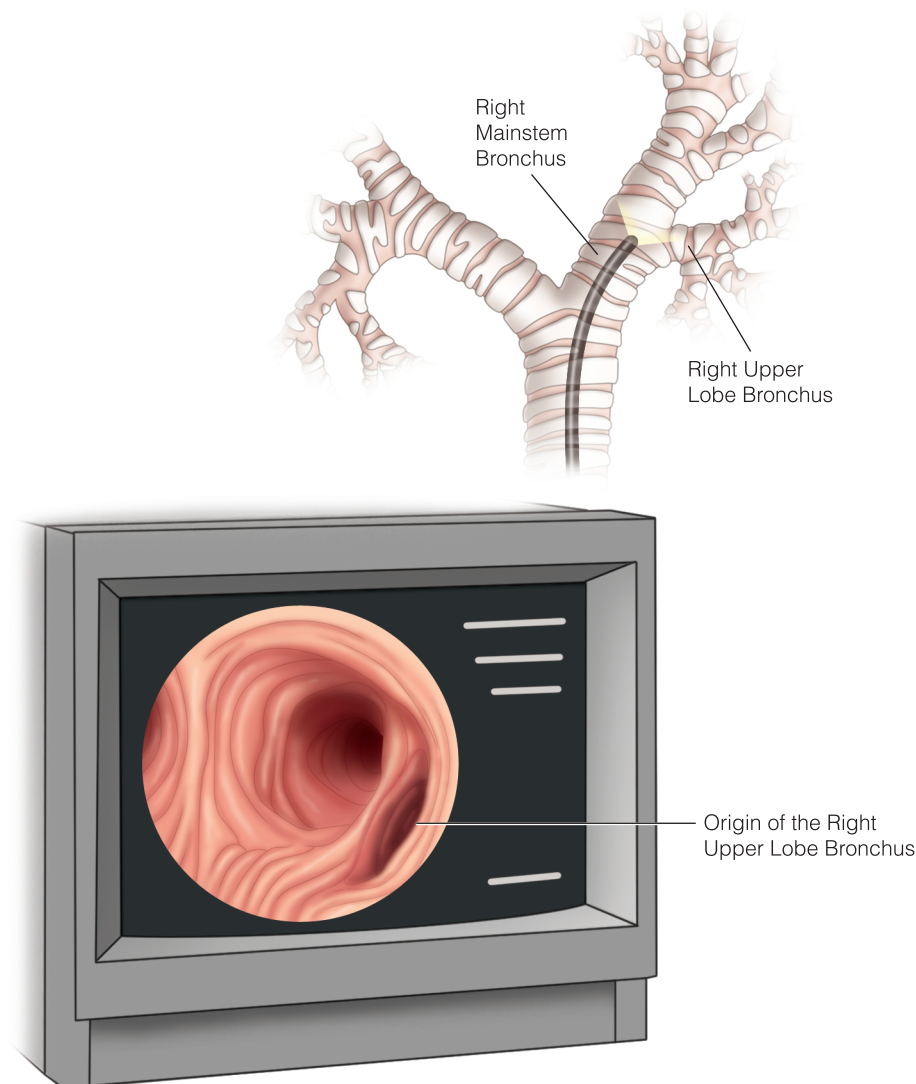


Figure 2 Diagrammatic representation of the right mainstem bronchus and the origin of the right upper lobe bronchus. Note the position of the upper lobe takeoff. This is the point of orientation for bronchoscopy. Reproduced with permission from Kaiser LR et al.²⁵

TBNA is used most frequently to assess subcarinal lymph nodes. Paratracheal lymph nodes may also be sampled with TBNA, but these are somewhat more difficult to access mainly because of the technical difficulty of sufficiently angulating the bronchoscope containing the needle catheter.¹⁴ It has been reported that it is feasible to obtain adequate specimens via TBNA in approximately 80 to 90% of cases.¹⁵ Results achieved for lymph nodes less than 1 to 1.5 cm may be substantially reduced but may improve up to 90% for nodes of greater than 1.5 cm.^{16–18}

Endobronchial Ultrasound-Guided Needle Aspiration

Endobronchial ultrasound-guided needle aspiration (EBUS-NA) is a procedure similar to conventional TBNA that also uses local anesthesia and sedation. However, the patient is intubated because of the larger external diameter of the EBUS-NA bronchoscope. EBUS-NA is a relatively new technique for mediastinal staging and employs a bronchoscope with a convex ultrasound probe that allows for real-time ultrasound-guided TBNA [see Figure 3]. EBUS-NA can be used to sample the highest mediastinal, upper and lower paratracheal, and subcarinal lymph nodes, as well as hilar lymph nodes. The overall reported sensitivity is 90%, with values ranging from 79 to 95%. The average reported false negative rate is 24% but varies significantly among reported series.^{19–21}

Rigid Bronchoscopy

Rigid bronchoscopy, when indicated, is performed with the patient anesthetized and in the supine position. The head should be placed in the “sniffing” position, and using the operator’s thumb as a fulcrum, the instrument tip is used to elevate the epiglottis. Once the vocal cords are visualized, the

instrument is turned so as to facilitate passage into the airway. The rigid instrument cannot be passed beyond the lobar level and is directed by turning the head. Rigid forceps may be used for sampling proximal lesions, and larger specimens may be obtained than can be using the flexible instrument. The rigid bronchoscope may also be used as a therapeutic tool to remove foreign bodies, dilate strictures, or debulk tumor that may be occluding proximal airways. It remains a very useful tool for those who have the expertise to use it.

MEDIASTINOSCOPY

This procedure remains the gold standard for assessing the status of the mediastinal lymph nodes whether for patients with a parenchymal lung lesion or for those who simply present with mediastinal adenopathy of unknown etiology. The CT scan of the chest is used to identify enlarged mediastinal lymph nodes, and the PET scan may be highly suggestive or even “definitive” that these nodes may harbor malignancy, but until there is histologic proof from tissue obtained, some doubt remains. Even with a positive PET scan, at least a 10 to 20% chance of a false positive result attributable mainly to inflammatory disease remains.

In 2007, Detterbeck and colleagues published evidence-based clinical practice guidelines for invasive mediastinal staging of lung cancer that concluded the following¹⁴:

1. In patients with discrete mediastinal nodal enlargement, staging by CT or PET scan is not sufficiently accurate. The sensitivity of various techniques is similar in this setting, although the false negative rate of needle techniques is higher than that for mediastinoscopy.
2. In patients with a stage II or central tumor, invasive staging of the mediastinal nodes is necessary.

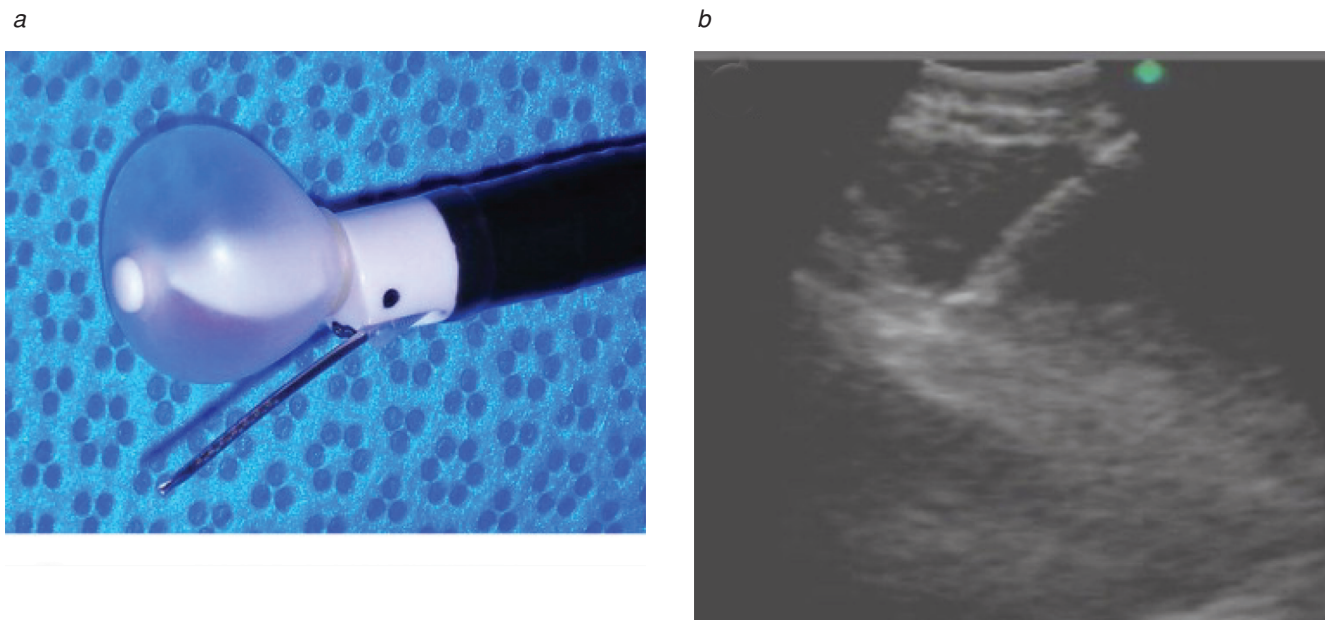


Figure 3 (a) Endobronchial ultrasound probe with the inflated balloon. (b) Ultrasound image with the tip of the needle in the mediastinal lymph node. Reproduced with permission from Yasufuku K et al.²⁰

3. Mediastinoscopy is generally preferable because of the higher false negative rates of needle techniques in the setting of normal-sized lymph nodes.
4. Patients with a peripheral clinical stage I non-small cell lung cancer do not usually need invasive confirmation of mediastinal nodes unless a PET scan finding is positive in the nodes.
5. The staging of patients with left upper lobe tumors should include an assessment of the aortopulmonary window lymph nodes.

Mediastinoscopy is performed with the patient under general anesthesia and positioned supine with the neck hyperextended. A small cervical incision is made approximately 2 cm above the sternal notch, and the strap muscles are separated in the midline. The pretracheal fascia is incised, and the mediastinal plane is defined with finger dissection [see Figure 4]. In most patients, the carina may be palpated with the back of the finger at the distal extent of the defined plane. The innominate artery is palpated anteriorly, as is the arch of the aorta. Thus, the mediastinoscope is passed in a plane with the trachea immediately posterior and the brachiocephalic vessels immediately anterior. Both the right and left upper and lower paratracheal nodal locations may be accessed, as well as the subcarinal space. The mediastinoscope is passed posterior to the right main pulmonary artery as the artery traverses the carina. Recognizing the major vascular structures that are within the field, the operator can see the potential for causing havoc if he or she is not intimately familiar with the performance of this diagnostic procedure [see Figure 5]. Mediastinoscopy is not for the occasional operator; it is a difficult procedure to teach and difficult to perform well. The advent of the video-assisted mediastinoscope has helped advance the teaching of the technique.

It is difficult to overestimate the value of this procedure and the significance of the information in guiding therapy, especially for patients with non-small cell lung cancer. The presence of ipsilateral nodal, or N2, disease portends a somewhat dismal prognosis but also indicates the need for multimodality therapy to achieve optimal results. If at the time of mediastinoscopy, contralateral nodal, or N3, disease is found, this rules out the possibility of surgical resection adding anything to the overall outcome and the patient is, in most circumstances, considered inoperable. The finding of contralateral nodal disease is most common with tumors that arise in the left lower lobe.

This points out the importance of performing a complete and thorough examination of the mediastinum with appropriate specimens taken. This includes sampling the right upper and lower paratracheal locations (levels 2 and 4), left lower paratracheal locatoin (level 4; it is unusual to find upper paratracheal nodes on the left, likely because of the position of the aortic arch), and the subcarinal space (level 7) [see Figure 6]. Finding left level 4 lymph nodes can be challenging, especially for the inexperienced operator, and exploration in this location puts the left recurrent nerve at risk. Complete sampling is not required if contralateral nodal disease is identified first or for those patients who present simply with mediastinal adenopathy but without a lung lesion where the differential diagnosis includes malignancy, sarcoidosis, and other inflammatory or infectious disease. In the latter situations,

a single sample from the most easily accessible location suffices, but adequate tissue for diagnosis must be confirmed by the pathologist on frozen section at the time of the procedure prior to terminating the operation.

The possibility of a major injury to the azygos vein, innominate artery, or pulmonary artery is very real if the surgeon should inadvertently attempt to obtain a specimen from what appears to be a lymph node but is actually a vessel. Often the azygos vein looks very much like an enlarged lymph node, but palpation with the suction or cautery gives the tactile sense of something other than a solid structure. The development of this tactile sense often comes only with significant experience with this procedure. Injury to a vessel may also occur if a lymph node is adherent, unbeknownst to the surgeon, who encounters significant bleeding after sampling a node.

Anyone performing this procedure should know how to manage a potentially lethal complication should a major vascular injury occur. The initial maneuver should be to tamponade the bleeding either with a finger or preferably by packing. Vaginal packing should be on the field just for such use. Only if the bleeding appears minimal should any attempt be made to control it through the mediastinoscopy with clips or electrocautery. Bleeding is common following sampling of the subcarinal space and is easily controlled with minimal packing. When the bleeding is such that the field becomes dark, it is time to pack the mediastinum and prepare for median sternotomy. Once the bleeding has been stopped by packing, the anesthesiologist should have blood in the room and fluids given to optimize perfusion while preparations are made for median sternotomy. The sternotomy approach allows access to any potential bleeding site and because the patient already is supine obviates the need to turn the patient to the lateral decubitus position. The azygos vein is also accessible and can be controlled via this approach as well.

Also vulnerable to injury during mediastinoscopy, as discussed above, is the left recurrent laryngeal nerve. This can be injured with electrocautery if used too close to the nerve or by the biopsy forceps. Unfortunately, this is an all too common complication that results in significant morbidity. The hoarseness or breathy voice that results is one issue, but the major one is the possibility of aspiration on swallowing that can result because of the incomplete glottic closure that is a consequence of the left vocal cord being in the abducted position.

PARASTERNAL MEDIASTINOTOMY

This procedure is related to mediastinoscopy but usually does not require the use of a mediastinoscope. Originally referred to as a Chamberlain procedure, this technique was formerly used most commonly to sample enlarged lymph nodes (level 5) located in the aortopulmonary window on the left side. Currently, most surgeons employ VATS to sample that area if indicated to make a treatment decision. This procedure is most commonly used to obtain tissue from an anterior mediastinal mass to establish a diagnosis. The most common lesion to occur in this location is a lymphoma, either Hodgkin disease or non-Hodgkin lymphoma. Adequate tissue is necessary not only to establish a diagnosis but also to aid in typing the lymphoma. As mentioned above, the procedure most commonly is performed on the left side but may also be

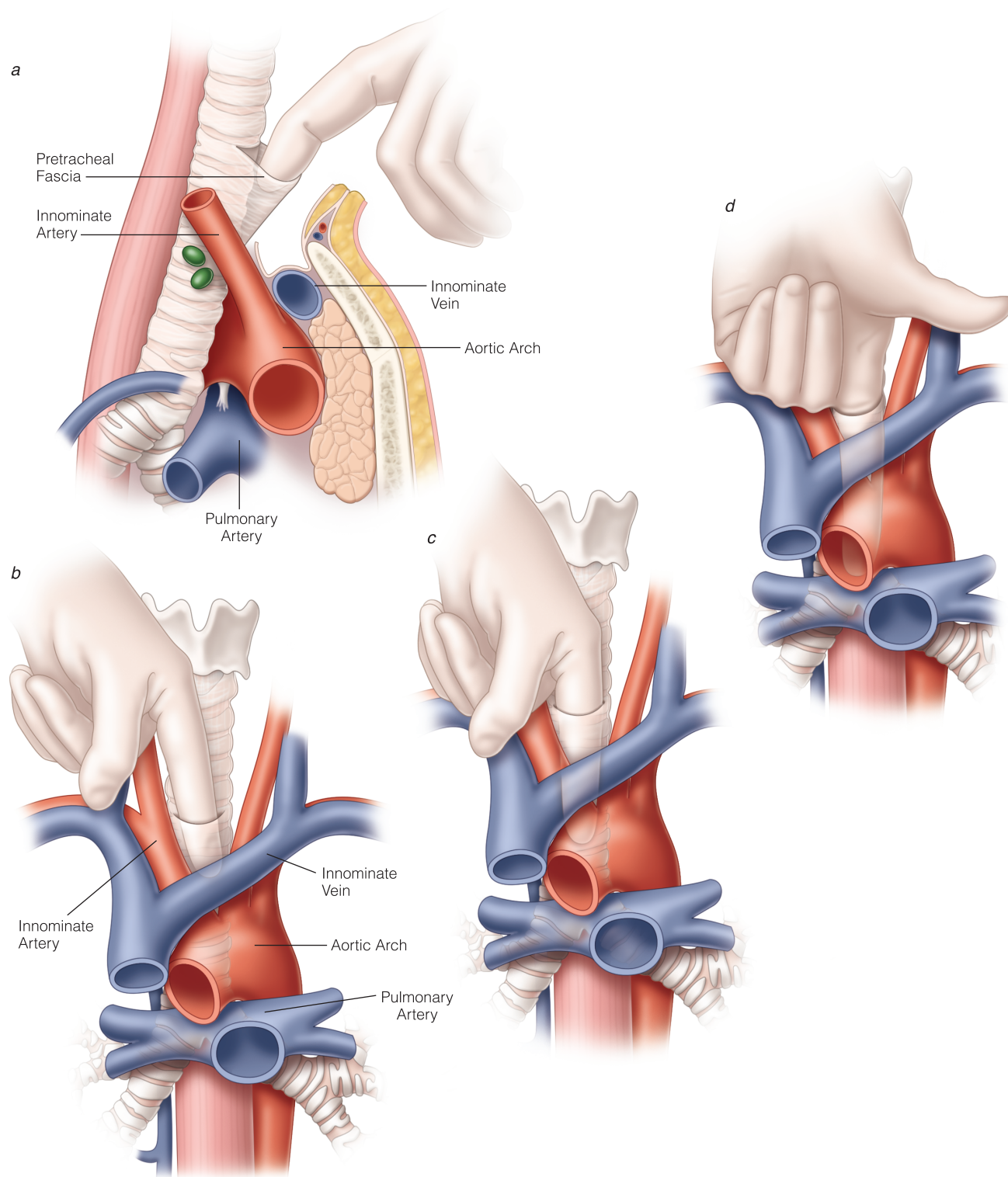


Figure 4 Development of the mediastinal plane prior to introducing the mediastinoscope. (a, b) Oblique and anterior views of the finger entering the pretracheal space after the fascia has been incised. The finger goes along the anterior aspect of the trachea, and the innominate artery is palpated anteriorly. (c) The finger is passed beyond the innominate artery, and both the right and left paratracheal areas are palpated. (d) The finger now is at the level of the carina, which, in most cases, can be palpated. The mediastinal space is now ready for insertion of the mediastinoscope. Reproduced with permission from Kaiser LR et al.²⁵

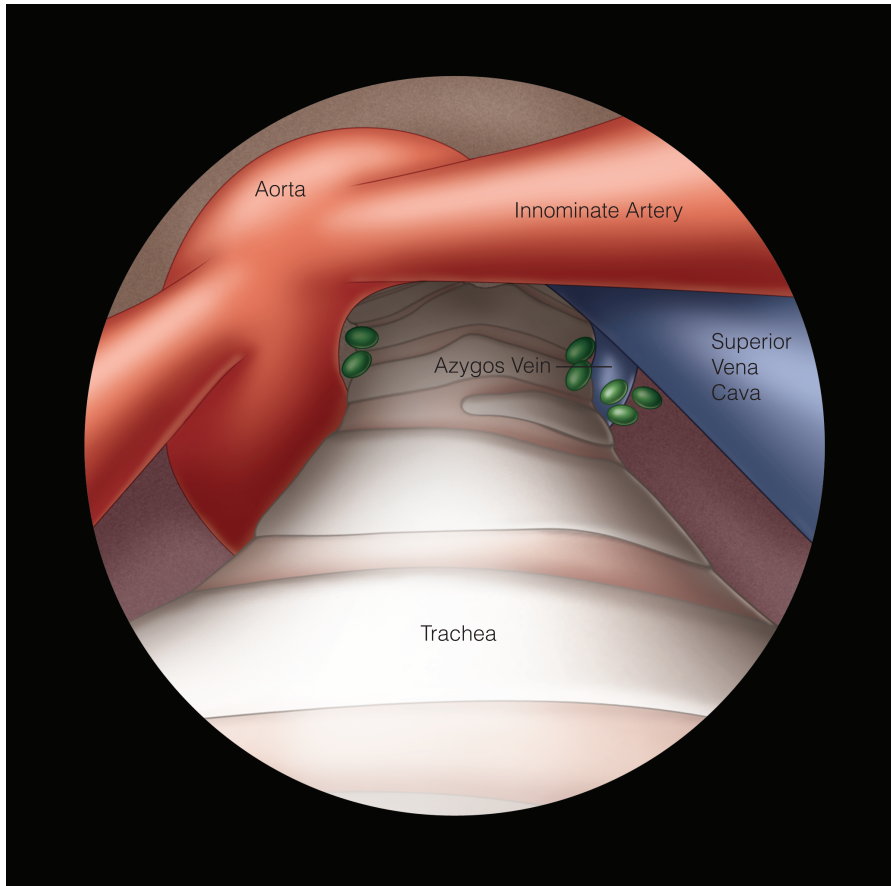


Figure 5 Schematic representation of blood vessels in the superior mediastinum also showing the location of lymph nodes at the tracheobronchial angle. The mediastinoscope is inserted into this space, anterior to the trachea and posterior to the innominate artery. The trachea is always the reference point for location during the conduct of the procedure. Reproduced with permission from Mentzer SJ.²⁶

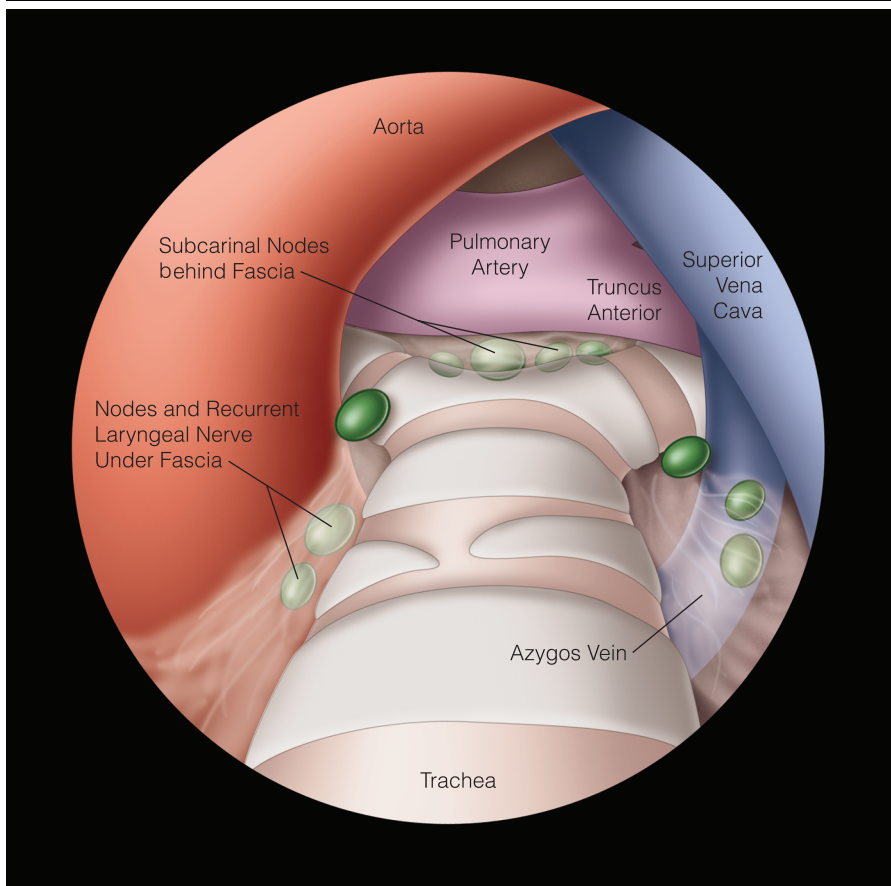


Figure 6 View as seen through the mediastinoscope of the carina and subcarinal space. Note the location of the right main pulmonary artery as it traverses the carina and its proximity to the subcarinal space. Note also the location of the azygos vein. Reproduced with permission from Mentzer SJ.²⁶

carried out on the right side depending on the location of the anterior mediastinal mass.

A small incision is made over the second rib cartilage immediately adjacent to the sternum [see Figure 7]. Resecting the second costal cartilage in a subperichondrial plane

facilitates entry into the mediastinum without breaching the pleural reflection. Some surgeons choose not to resect the costal cartilage and either attempt to stay out of the pleural space or routinely enter it. In any case, care must be taken to avoid the internal thoracic artery pedicle, which usually may

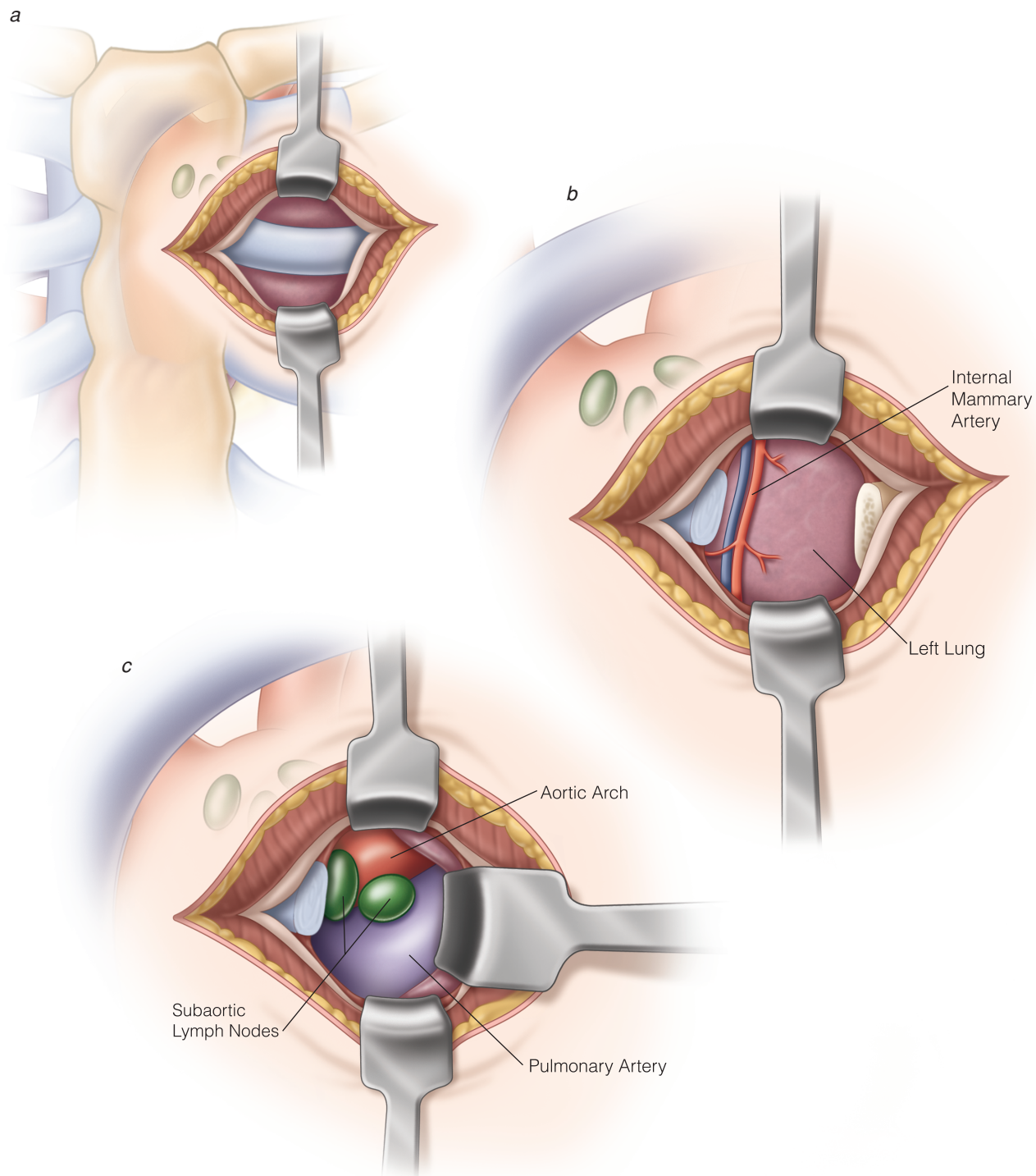


Figure 7 Diagrammatic representation of a left anterior mediastinotomy. (a) An incision is made immediately adjacent to the sternum over the left second costal cartilage. (b) The second costal cartilage is removed, allowing access to the mediastinum without entering the pleural space, or the pleura may be incised. Note the location of the internal mammary vessels. (c) Enlarged lymph nodes in the aortopulmonary window. Reproduced with permission from Kaiser LR et al.²⁵

be identified and reflected out of the way. The endothoracic fascia is incised, the pleural reflection is swept laterally, and the mass is encountered. Multiple samples of the mass may be taken with a biopsy forceps, and frozen section will determine if adequate material has been obtained. If the pleural space is entered, simply placing a red rubber catheter prior to closure and removing it just prior to skin closure following a Valsalva maneuver removes any air from the pleural space. Given that there is no ongoing air leak from lung parenchyma, this is all that is required. Some have warned of the possibility of “seeding” the pleural space when sampling what turns out to be a thymoma, but staying out of the pleural space renders that concern moot.

VIDEO-ASSISTED THORACIC SURGERY

There are multiple uses for VATS procedures in the diagnosis and staging of intrathoracic pathology. As mentioned above, its use for mediastinal staging, for the most part, is confined to accessing the aortopulmonary window to sample the level 5 lymph nodes, if indicated [see Figure 8]. By far the most common use is to assess the pleural space, especially when a pleural effusion is present and there is a question of pleural involvement. Not all pleural effusions indicate pleural space involvement by tumor. In a patient who presents with a pleural effusion for which there is no plausible explanation, thoracentesis is first performed. If positive, the patient is staged M1a and no further invasive diagnostic or staging procedure is necessary. If negative and the patient has a

parenchymal lung lesion, a VATS procedure may be performed to visually examine the parietal and visceral pleural surfaces and sample any abnormal areas seen. Not all malignancies that involve the pleura will shed cells; thus, false negative thoracenteses are not uncommon, especially with certain histologies. If the VATS procedure fails to detect any pleural involvement, then resection can proceed assuming that there is no other evidence of metastatic disease.

In addition to the diagnosis of pleural involvement, VATS has been used routinely to resect parenchymal nodules for diagnosis prior to proceeding with resection. A wedge excision of a pulmonary nodule confirms the diagnosis prior to proceeding with lobectomy, and resection may then be carried out completely via VATS or open thoracotomy. Finding a benign nodule saves the patient a lobectomy and the attendant morbidity. In addition, VATS has been particularly useful in obtaining lung parenchyma in those patients with diffuse interstitial lung disease where a diagnosis guides therapy. For interstitial disease, samples are taken from at least two locations, ideally in different lobes, to fully assess the process. Most commonly, VATS is performed with three incisions placed in a triangulated fashion, which allows for the scope to be placed in one port, leaving the other two for instrument placement. Thus, the lung parenchyma may be grasped via one port and an endoscopic stapler placed in the other to perform the excision. The presence of diagnostic material should be confirmed by the pathologist prior to terminating the procedure.

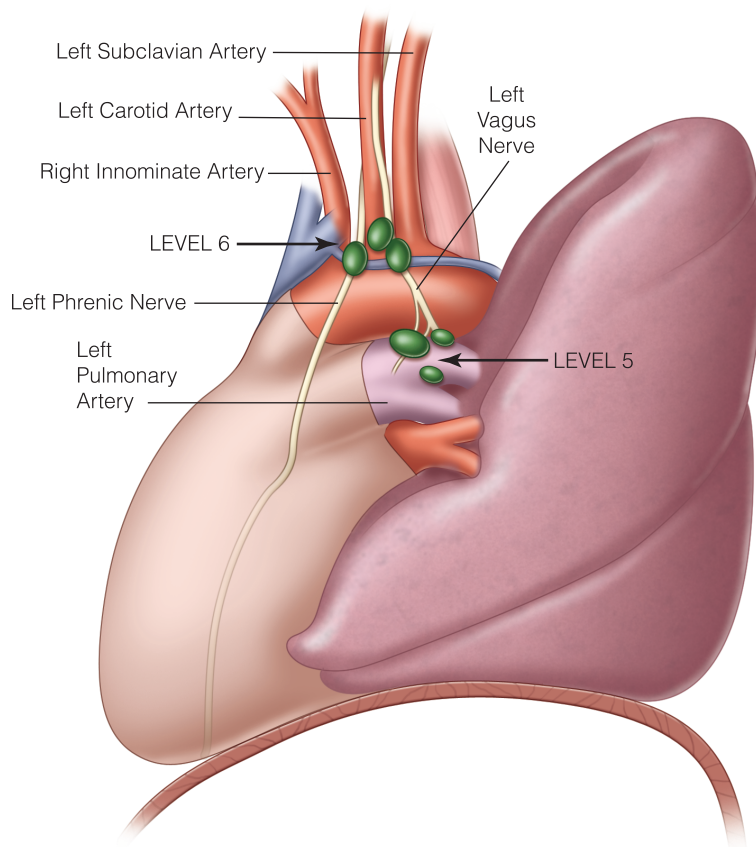


Figure 8 Video-assisted thoracoscopic view of the aortopulmonary window. The third and seventh intercostal space access ports are placed. The lung is reflected posteriorly. The phrenic nerve is traced to the level 6 lymph nodes at the base of the innominate artery. The arrows show the level 5 aortopulmonary window and level 6 para-aortic lymph nodes. Reproduced with permission from Mentzer SJ.²⁶

MEDIASTINAL LYMPH NODE DISSECTION: CRITICAL TO A COMPLETE OPERATION FOR LUNG CANCER

An anatomic pulmonary resection, in most cases lobectomy, remains the standard and definitive operation for lung cancer. As part of the standard operation, a systematic lymph node dissection or, at minimum, lymph node sampling should be performed in all cases to gain maximal information regarding staging. The optimal lymph node dissection consists of excision and examination of mediastinal, hilar, and lobar lymph nodes in a systematic fashion as defined at an international workshop held in 1996 and supported by the International Association for the Study of Lung Cancer. Hilar and lobar lymph nodes are removed with the lobectomy specimen, whereas a separate procedure is required to either sample or systematically dissect the mediastinal lymph nodes. On the right side, the superior mediastinal lymph node packet is defined anteriorly by the superior vena cava, posteriorly by the trachea, superiorly by the subclavian artery, and inferiorly by the azygos vein. In addition, the entire contents of the subcarinal space are taken. On the left side, there is no well-defined lymph node packet, but nodes are removed from the aortopulmonary window and periaortic position as well as from the subcarinal space. The lower paratracheal nodes (left level 4) may also be removed by dissecting inferiorly to the aortic arch, but care must be taken to avoid damage to the left recurrent laryngeal nerve. Because of the difficulty in accessing the left lower paratracheal lymph nodes, there should be a low threshold for performing mediastinoscopy for left lung lesions if there is any suspicion of lymph node involvement based on preoperative imaging studies. There is no definitive evidence that mediastinal lymph node dissection is a therapeutic procedure, but there is no question that it provides the most accurate staging information. Improved survival has been associated with the number of lymph nodes removed, with 11 to 16 being the optimal number.²²

Diagnostic and Staging Procedures for the Esophagus

ESOPHAGOSCOPY

For presumed structural lesions of the esophagus, flexible esophagoscopy is the procedure of choice. Topical anesthetic for the pharynx with minimal intravenous sedation is all that is necessary for this examination. The patient is placed in the left lateral decubitus position, with the tip of the instrument placed posterior to the tongue, and is asked to swallow to allow passage through the cricopharyngeus. Once beyond that point and aided by insufflation, the lumen of the esophagus is easily visualized to facilitate passage of the instrument into the stomach. The pylorus is observed, and the endoscope is passed into the duodenum. The major part of the examination is carried out as the instrument is withdrawn. The entire stomach is examined, and the endoscope is retroflexed to examine the gastroesophageal junction. Continued withdrawal into the esophagus allows for complete visualization back up to the cricopharyngeus. Flexible biopsy forceps are available to be passed through the working channel if a lesion is seen, and multiple samples may need to be taken because of the small cup size of the forceps.

A specialized dedicated endoscope equipped with an ultrasound probe allows the operator to visualize the depth of

invasion of an esophageal tumor as well as provide a look at the regional lymph nodes. The esophageal wall is able to be visualized as a five-layered structure, and the T stage assessed by endoscopic ultrasonography is approximately 80% accurate when compared with the ultimate pathologic stage. The ultrasound signal obtained from an involved lymph node may be diagnostic and provides information that guides a treatment decision, specifically the need for preoperative chemotherapy with or without radiation therapy. Endosonographic criteria most specific for malignancy are an echo-poor pattern and width greater than 10 mm. The sensitivity and specificity for detecting celiac lymph node metastases were 85% (95% CI 72 to 99) and 96% (95% CI 92 to 100), respectively. Sensitivity and specificity for other regional lymph node metastases were 80% (95% CI 75 to 84) and 70% (95% CI 65 to 75), respectively.²³

To further improve the diagnostic capability of endoscopic ultrasonography, fine-needle aspiration (EUS-FNA) of visualized lymph nodes may be performed. The sensitivity, specificity, and accuracy of EUS-FNA for locoregional lymph nodes are all over 85%.²⁴

The use of the rigid esophagoscope is confined to the diagnosis of proximal esophageal neoplasms and has no role in staging. This instrument provides a large working channel and allows for the use of a rigid biopsy forceps that enables the collection of large tissue fragments for histologic analysis. The rigid instrument is a skill that must be learned to pass the instrument safely. If not passed correctly, the rigid instrument can perforate the cervical esophagus. Like the rigid bronchoscope, the thumb is used as a fulcrum on which the instrument rests and the cricopharyngeus is visualized by lifting anteriorly. Once the lumen is seen, the instrument is passed and advanced. With the longer instruments, the entire esophagus may be visualized down to the level of the gastroesophageal junction, but the primary area of interest is the proximal esophagus.

Conclusion

The evaluation of a patient who presents with a question of intrathoracic pathology should begin with appropriate imaging studies, usually beginning with plain chest radiography followed by CT scanning of the chest done with intravenous contrast. Comparison with a previous film may be all that is necessary to avoid further testing if the lesion in question was present on the old film and remains unchanged. Following appropriate imaging that may include a PET scan, a decision needs to be made as to which diagnostic procedure should be performed. Bronchoscopy is the procedure of choice for the diagnosis and staging of pulmonary pathology, and endobronchial as well as transbronchial sampling of tissue may be carried out with this instrument. Staging procedures need to be done in a thoughtful and systematic manner because accurate staging has prognostic implications in patients with lung cancer and guides both initial and subsequent therapy. When these imaging modalities indicate suspicion for mediastinal lymph node involvement, such as an enlarged mediastinal lymph node (> 1 cm) on a CT scan or increased ¹⁸F-FDG uptake in mediastinal lymph nodes on a PET scan (standard uptake value > 2.5) or evidence of distant organ metastasis, tissue biopsy is required for accurate

staging. In the absence of suspicious mediastinal lymph nodes on imaging studies, the choice of diagnostic procedures depends on the location and size of the tumor and the presence of abnormal hilar lymph nodes (N1 disease), a finding that is associated with a higher likelihood of mediastinal nodal involvement.

The classic technique for staging of mediastinal lymph nodes has been standard cervical mediastinoscopy, which allows inspection and sampling of bilateral paratracheal locations and the subcarinal space. Transtracheal needle aspiration of suspicious mediastinal lymph nodes may be carried out through the bronchoscope, but in the presence of abnormal lymph nodes on imaging studies, a negative needle aspiration biopsy should lead to mediastinoscopy (for levels 2, 4, and 7) to ensure that the result was not a false negative. Decisions regarding operability or resectability should not be based solely on abnormalities seen on imaging studies. Pathologic confirmation based on tissue sampling should be the gold standard and offers the patient the best opportunity for a favorable outcome. A systematic mediastinal lymph node dissection should be part of every resection for primary lung cancer. Without the information gained from a node dissection or, at minimum, systematic sampling, staging is

incomplete, and this could result in the patient being overtreated. Although not conclusive, there may also be a therapeutic benefit to mediastinal lymph node dissection.

Unexplained pleural effusions should be evaluated using VATS to assess the pleural surfaces if thoracentesis yields a negative result. VATS may also be used for the diagnosis of either diffuse interstitial lung disease or discrete pulmonary nodules. Assessment of lymph nodes present in the aortopulmonary window on the left side may also be successfully carried out using VATS.

Esophageal pathology is assessed and staged with the flexible esophagoscope and endoscopic ultrasonography. In addition to imaging studies, esophageal motility studies and 24-hour pH monitoring are used to assess benign esophageal pathology, specifically motor disorders.

The surgeon who deals with intrathoracic pathology must be facile with all of the modalities available for diagnosis and staging and should proceed in a logical sequence so that sufficient information is gathered to allow appropriate decision making regarding treatment.

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17 THORACIC OUTLET SYNDROME

Mark W. Fugate, MD, and Julie A. Freischlag, MD

Thoracic outlet syndrome (TOS) is a condition caused by compression of the neurovascular structures leading to the arm passing through the thoracic outlet. The incidence of TOS is reported as 0.3 to 2% in the general population.¹ There are three distinct types of TOS: neurogenic (95%), venous (4%), and arterial (1%). Treatment algorithms depend on the type of TOS. Arterial and venous TOS often present urgently with arterial or venous thrombosis, which is fairly easily identified by thorough history taking and a physical examination. Diagnosis is also aided by duplex ultrasonography. Restoration of arterial or venous flow can often be readily accomplished by thrombolysis. More important, however, is the diagnosis of the underlying structural component involved in the development of symptoms. Although statistically the most common, neurogenic TOS is often the most difficult to diagnose and treat. There are good data indicating that appropriately selected patients benefit from surgical therapy for neurogenic TOS as well. To prevent recurrence of symptoms, patients must undergo first rib resection and anterior scalenectomy, as well as resection of any rudimentary or cervical ribs. Regardless of the type of TOS encountered, proper therapy requires a thorough diagnostic evaluation and multidimodal treatment.

History

Historically, TOS has been a controversial syndrome in terms of its causes, diagnosis, and management. Galen first described a cervical rib in human cadaver dissections.² As his work had fallen out of favor during the Dark Ages, Vesalius, who revived much of Galen's work, again described the cervical rib among human cadavers.² In 1821, Sir Astley Cooper observed that a subclavian artery occlusion was caused by compression from a cervical rib, which came to be known as cervical rib syndrome.³ In 1927, the first rib was implicated in neurogenic TOS.⁴ In 1935, Ochsner and colleagues described the scalenus anticus syndrome, and an association was first made with trauma.⁵ Compression of the subclavian artery and vein was termed costoclavicular syndrome in 1943.⁶ The term thoracic outlet syndrome was first introduced in 1956 by Peet and colleagues, who also described a therapeutic exercise regimen in the management of the syndrome.⁷ This was an important contribution as physical therapy continues to be one of the mainstays of therapy for neurogenic TOS.

As the views of the anatomic causes of TOS evolved over the years, so did the surgical approaches to its management. In 1861, Coote completed the first successful cervical rib resection for relief of arterial compression.⁸ Murphy performed a first rib resection in 1910 for neurogenic TOS.⁹ Adson and Coffey performed the first scalenectomy in 1927, without first rib resection.¹⁰ Later, it was realized that the

division of the muscle alone led to recurrent symptoms. The posterior approach to first rib resection was described by Clagett in 1962,¹¹ and the transaxillary approach to first rib resection was described by Roos in 1966.¹² Other surgical approaches include supraclavicular as well as combined techniques using transaxillary first rib resection and transcervical scalenectomy.^{1,13}

Anatomy and Predisposing Factors

TOS is divided into three distinct subtypes: neurogenic, venous, and arterial. Symptoms are produced relative to which of the neurovascular structures is compressed in the thoracic outlet [see Table 1]. In this regard, the scalene triangle is the most important anatomic space in the thoracic outlet. The anterior and middle scalene muscles comprise the sides of the scalene triangle, with the first rib forming the base of the triangle. The anterior and middle scalene both arise from the lower cervical spine. Through this relatively small space pass the subclavian artery and vein, as well as the five nerve roots of the brachial plexus. These muscles can potentially scar and/or hypertrophy with repetitive motion or trauma, further contributing to compression of the neurovascular structures. The subclavius muscle, which is found between the clavicle and the first rib, also may compress the subclavian vein, contributing to venous TOS. This muscle is frequently found to be hypertrophied in patients presenting with effort thrombosis.¹⁴

A combination of congenital anatomic predispositions and acquired extrinsic factors results in the spectrum of symptoms associated with TOS. Cervical ribs, which are congenital, can predispose to all three types of TOS. They have an incidence of approximately 1% in the general population with 50% bilaterality.^{15,16} Although most cervical ribs are asymptomatic, they occur in up to 11% of patients undergoing surgical decompression for TOS.^{17,18} A long C7 transverse process or bifid first rib may also predispose to TOS, but these are even less common. Particularly in neurogenic TOS, congenital fibromuscular bands often are observed—in more than 80% of patients, according to some authors.¹⁹ These congenital bands and ligaments have been categorized into nine different types by Roos.²⁰ Anatomic variation in the size and insertion points of the scalene muscles has also been implicated.

In addition to these predisposing anatomic factors, trauma and repetitive motion also play a role in the development of TOS. Some authors have reported that up to 80% of TOS patients have a history of trauma to the neck or shoulder area.²¹ Repetitive motion attributable to athletic activity (e.g., swimming or weight lifting) or occupational environment (e.g., poor posture and/or prolonged computer use) also may contribute to the development of TOS.

Table 1 Thoracic Outlet Syndrome: Types and Characteristics

Characteristic	Neurogenic Most Common Form of TOS	Venous Subclavian Vein Thrombosis	Arterial Subclavian Artery Thrombosis
Sex	Female (3.5:1)	Male	Female/male equally
Age (yr)	20–40	20–30	20–30
Risk factors	Repetitive movements Previous trauma	Strenuous work Athletics	Vigorous arm activity
Symptoms	Pain down arm, forearm, ring finger, and little finger Paresthesias (pain, numbness) at night Arm/hand weakness Arm/hand swelling Loss of dexterity Cold intolerance Headache	Pain in affected arm often associated with strenuous work Arm/hand swelling Veins of shoulder and chest appear more visible Hand/arm appears blue in color	Pain Claudication Hand appears white in color Hand/arm cool Decreased pulse
Laboratory studies	None	Hypercoagulable studies	Hypercoagulable studies
Imaging studies	Chest x-ray	Chest x-ray Duplex ultrasonography Venography	Chest x-ray Duplex ultrasonography Arteriography
Other studies	Nerve conduction study	Nerve conduction study	Nerve conduction study
Consultations	Vascular surgeon Physical therapy (PT) Pain management	Vascular surgeon Hematologist	Vascular surgeon Hematologist
Treatment	Physical therapy (PT) Lidocaine blocks Botulinum toxin blocks* Surgical intervention† Postoperative PT	Anticoagulant Surgical intervention Venography/venoplasty Postoperative PT	Anticoagulant Surgical intervention Arteriography/arterioplasty Postoperative PT
Prognosis	Good	Good	Good
Recovery time	Longer period of time (time needed is dependent on duration of symptoms prior to treatment and commitment to PT)	Quick	Quick

TOS = thoracic outlet syndrome.

*Brand of botulinum toxin type A manufactured by Allergan (Irvine, CA).

†Not all neurogenic TOS patients need or are candidates for surgery.

Preoperative Evaluation

NEUROGENIC THORACIC OUTLET SYNDROME

Symptoms attributable to neurogenic TOS are caused by compression of the roots of the brachial plexus and are much the same as those experienced with nerve compression in other parts of the body. Pain, paresthesias, and weakness in the pattern of the affected nerve roots are common. Pain and/or point tenderness in the anterior or posterior shoulder region, as well as the neck and occipital or mastoid region, is also a common finding. Headaches may also be present. On physical examination, there is often tenderness over the scalene muscles and/or the supraclavicular fossa on the involved side. Radiation of pain or paresthesias in the symptomatic arm can often be reproduced by deep palpation of the scalene muscles or other provocative maneuvers, such as abducting the arms to 90° in external rotation. With the arms in the same position, the patient can be asked to repeatedly open and close the hands for several minutes, the so-called Roos stress test. Reproduction of the patient's symptoms with this maneuver may be an indication of neurogenic TOS. During the Adson maneuver, the arm on the affected side is

abducted and the head is rotated toward the same side. Disappearance of the radial pulse is a nonspecific finding, but reproduction of the patient's symptoms may again be an indication of neurogenic TOS. Decreased grip strength and mild to moderate sensory abnormalities in the affected hand are common findings. Atrophy of the intrinsic muscles of the hand is a late and uncommon finding. A chest x-ray to rule out bony abnormalities is mandatory. Magnetic resonance imaging, nerve conduction studies, and electromyography can be helpful. However, as there is no definitive diagnostic test for neurogenic TOS, the diagnosis is typically clinical. Prior to considering surgery for neurogenic TOS, nerve conduction studies should be obtained as they are the best objective test for this condition.

VENOUS THORACIC OUTLET SYNDROME

The most common presentation of venous TOS is acute effort thrombosis of the axillosubclavian vein, also known as Paget-Schroetter syndrome. This is characterized by the sudden onset of swelling, pain, and discoloration of the affected upper extremity. Edema is nonpitting and involves the entire arm. Additionally, superficial veins of the upper

arm, shoulder, and chest wall may be distended and visible. Typically, these patients are young and healthy and often quite athletic. Swimmers, weight lifters, and volleyball players are particularly common. Again, the diagnosis is typically clinical but can be confirmed with duplex ultrasonography. If ultrasonography is for some reason unavailable or equivocal, contrast venography will confirm the diagnosis. Again, chest x-ray to rule out bony abnormalities should be performed.

ARTERIAL THORACIC OUTLET SYNDROME

Symptoms attributable to arterial TOS are commonly the result of thromboemboli from intimal lesions or post-stenotic arterial aneurysms. Patients present with varying degrees of arm or hand ischemia. Ischemia may manifest with many signs and symptoms, including weakness, paresthesias, pain and pallor, and diminished pulses distally, especially with activity or positional changes. A positive Adson test aids in the diagnosis but is not pathognomonic. Chest x-ray is extremely important in the diagnosis as cervical ribs are often present in cases of arterial TOS. Duplex ultrasonography is also essential to assess the presence and degree of arterial stenosis and to detect subclavian artery aneurysm.²² Arteriography is not mandatory but can be quite useful in identifying arterial lesions caused by extrinsic compression or post-stenotic aneurysms.

Treatment

NEUROGENIC THORACIC OUTLET SYNDROME

Initial therapy for neurogenic TOS is always conservative. This consists of two broad categories, lifestyle modification and physical therapy. Lifestyle modification includes posture training for proper posture when walking, sitting, and standing, which promotes relaxation of the neck muscles and may help decompress the thoracic outlet. It also includes modification of daily activities, including minimization of repetitive motion, overhead work, and weight lifting, if applicable. Exercises directed toward improved range of motion and flexibility also may provide symptomatic improvement. Physical therapy is TOS specific [see Table 2] and consists of three sessions per week for 8 weeks before surgery is considered. If the patient proceeds to surgical treatment, physical therapy is also used postoperatively for the same frequency and duration to include increased range of motion, strengthening exercises, and soft tissue or scar tissue massage.

If lifestyle modification and physical therapy are unsuccessful, a computed tomography (CT)-guided anterior scalene block is performed with local anesthetic. The block causes relaxation of the anterior scalene muscle, allowing the first rib to drop, which should relieve tension on the brachial plexus. Symptomatic relief as the result of a scalene muscle block is a reasonable procedure to give some indication as to whether a first rib resection and anterior scalenectomy will be beneficial. CT-guided scalene muscle block is used by some investigators for diagnosing neurogenic TOS.²³ We have also found that CT-guided botulinum toxin type A (Botox, Allergan, Irvine, CA) injections provide symptomatic relief for at least 1 month and often up to 3 months.²⁴ These treatments may be used as a bridge to surgery or as an adjunct to nonoperative treatment with physical therapy. We do not offer more

Table 2 Thoracic Outlet Syndrome: Specific Physical Therapy Protocol

Weeks 1–3 Manual therapy: - Soft tissue mobilization (STM) of scar when closed - STM of anterior thorax, intercostal spaces, diaphragm - Joint mobilization of sternoclavicular (SC) and costosternal joints and acromioclavicular joint (AC) - Positioning and mobility of the ribs - Mobilization of the thoracic and cervical spine - Usually thoracic extension and cervical flexion - Focus of occiput-atlantis (OA) flexion - Brachial plexus and peripheral neural mobility - Teasing stretch or pain sensation—with caution to avoid exacerbating symptoms Therapeutic exercise and neuromuscular reeducation: - Diaphragmatic breathing - OA flexion - Gentle scapular posterior depression exercises - Use prolonged holds > 45" to retain position and movement with gentle manual resistance - Gentle neural mobility Posture training: - Activity restriction education, patient self-care education - Sleep position and transfers - Lifting and reaching related to activities of daily living (ADL)
Weeks 4–6 (build-off gains made in weeks 1–3) Manual therapy: - STM to pectoralis, serratus anterior, and latissimus dorsi - STM to neck and along track of brachial plexus (neck to hand) - Gentle mobility of glenohumeral joint and AC joint separation - Focus on inferior glide of humeral head and mobility of the posterior rotator cuff Therapeutic exercise and neuromuscular reeducation: - Continue with prolonged holds of OA flexion with manual and self-progressive resistance exercise - Continue with prolonged holds of scapular posterior depression - Add mild resistance with Thera-Band or weights - Train scapular stability in prone or elbow position before progressing to quadruped - Supine shoulder flexion exercises with wand - Add gentle manual resistance in flexion when patient can perform full flexion without scapular substitution, thoracic extension, or sternum elevation Posture training - Focus on sitting posture and assumption of work position while holding proper posture
Weeks 7–8 Manual therapy: - Moderate to aggressive glenohumeral mobilizations (specifically Mulligan glenohumeral mobilizations with movement) - Continue neural mobilization until patient can reach full tension position without complaints of pain/stretch symptoms - Address other limitations in soft tissue and joint mobility as needed Therapeutic exercise and neuromuscular reeducation: - Scapular posterior depression exercises against resistance as tolerated - Still focus on prolonged hold of postural muscles - Plank exercises maintaining scapular neutral position - Add weight shifts, walking out with a Thera-Ball, and pushups from the knees - Independent maintenance of neural mobility - Progress to resisted exercises of shoulder flexion against gravity if patient is able to perform without scapular substitution - Perform exercises until fatigue or substitution Posture training: - Lifting crates/boxes with full squat while maintaining scapular neutral position - Mimic work-related activities

than two injections because the muscle and surrounding tissues tend to scar and the long-term effects of repeated botulinum toxin injections are not known.

Surgical treatment consists of first rib resection and anterior scalenectomy, and our favored approach is transaxillary (see below). When neurogenic TOS patients are appropriately selected for surgical intervention, we have shown good outcomes in terms of quality-of-life improvements.²⁵

VENOUS THORACIC OUTLET SYNDROME

Traditionally, treatment of secondary axillosubclavian vein thrombosis has consisted of conservative measures: systemic anticoagulation with rest and elevation of the affected extremity. However, in primary axillosubclavian vein thrombosis, conservative treatment alone leaves most patients with residual symptoms attributable to venous outflow obstruction. As most of these patients are young and active, more aggressive therapy is required. Once the diagnosis of thrombosis as a result of venous TOS is suspected, the patient should undergo contrast venography. Once thrombosis is confirmed, catheter-directed thrombolysis should be performed. Once the thrombosis has been cleared, venography should be repeated to confirm extrinsic compression of the subclavian vein. Compression and narrowing of the vein at the costoclavicular junction are almost universally present in cases of venous TOS. Angioplasty and stenting should not be performed in the initial setting until the patient has undergone thoracic outlet decompression via first rib resection and anterior scalenectomy. This can be performed days to weeks after the initial thrombolysis. Again, our preferred approach is transaxillary. To avoid bleeding complications, no anticoagulation is given until 3 days after surgery. Therapeutic low-molecular-weight heparin injections are given until 2 weeks later, when repeat venography is performed. At this time, residual stenotic areas can be percutaneous and dilated effectively as extrinsic compression has been relieved. If the vein has remained patent and no intervention is required, anticoagulation is discontinued. If the vein has rethrombosed, repeat thrombolysis may be performed and anticoagulation continued with warfarin, with an international normalized ratio of 2 to 3. The patient is followed long term with duplex ultrasonography monthly, and anticoagulation is continued as long as areas of increased velocities in the subclavian vein are visualized during arm abduction, up to 6 months. In our series of more than 80 patients with venous thrombosis secondary to venous TOS, we found that after 6 months, all remained patent. Therefore, we do not anticoagulate beyond this time.

The final important consideration is a thorough hypercoagulable workup. We have observed an increased frequency of hypercoagulable disorders in patients with Paget-Schroetter syndrome. Therefore, we now perform a hypercoagulable workup in all our venous TOS patients, as well as in arterial thrombosis patients. If the patient presents acutely, these laboratory values will be assessed initially. If the patient presents from another institution where he or she has already undergone thrombolysis and is being maintained on warfarin therapy, the hypercoagulable evaluation is done 6 months after discontinuation of warfarin. These laboratory tests include protein C and S levels, factor V Leiden mutation, prothrombin gene mutation 20210, antithrombin III level,

antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies), homocysteine levels, and methylene tetrahydrofolate reductase (MTHFR) 677T variant. If the patient is confirmed to have a hypercoagulable disorder, then he or she is continued on lifelong anticoagulation.

ARTERIAL THORACIC OUTLET SYNDROME

The timing and sequence of therapy for arterial TOS depend on the degree and acuteness of ischemia. The majority of patients with arterial TOS present chronic ischemic symptoms and a nonthreatened limb. In this situation, the proximal embolic source is eliminated first. This is typically accomplished by direct arterial reconstruction, preferably with an autologous vein. This can be undertaken at the same time of resection of the commonly found cervical or rudimentary rib, depending on the surgical approach. In arterial TOS, a transaxillary approach may be employed for rib resection and scalenectomy, but arterial reconstruction is not possible from this approach. This typically requires a supraclavicular approach. If the patient presents with acute and limb-threatening ischemia, distal thromboemboli must be cleared first, either surgically or via thrombolysis, before rib resection and arterial reconstruction.

TRANSAXILLARY APPROACH TO FIRST RIB RESECTION AND ANTERIOR SCALENECTOMY

A detailed description of the multiple approaches to thoracic outlet decompression is beyond the scope of this chapter. Our preferred approach is transaxillary because it allows for safe exposure and excellent visualization of the major structures through a cosmetically acceptable, low-morbidity incision. First and cervical ribs, as well as rudimentary ribs, are all readily removed via this approach. The vast majority of patients are easily treated through transaxillary thoracic outlet decompression. As previously mentioned, direct arterial reconstruction is the only task not amenable to this technique.

The patient undergoes general anesthesia with a short-acting neuromuscular blockade such as succinylcholine, allowing for safer dissection around the brachial plexus, as well as easier identification of the long thoracic nerve. The patient is placed in the lateral decubitus position and prepared from the neck to beyond the nipples. An adjustable arm support, the Machleder retractor [see Figure 1], is attached to the operating room table and allows for elevation of the arm. This elevation is vital for adequate exposure of the axilla during dissection. Prior to placement on the retractor, the arm is well padded to prevent injury to the median and ulnar nerves at the elbow. The skin incision is made at the lower border of the axillary hair line between the latissimus dorsi and pectoralis major muscles. Dissection with cautery proceeds down to the flimsy areolar tissue superficial to the chest wall. Gentle blunt dissection is then used in an anterior and cephalad direction. Manual palpation is used to identify the first rib as it approaches the clavicle. A self-retaining retractor is then placed and the Machleder retractor is elevated to facilitate exposure in the axilla. The soft tissue overlying the subclavian vessels and the scalene muscles is swept away with a Kittner blunt dissector. Frequently, a small branch of the subclavian artery must be ligated and divided to fully mobilize the artery. The first rib is identified and the



Figure 1 Machleder retractor used for positioning during transaxillary first rib resection. The patient is placed in a decubitus position with the nonoperative side down. Ample sterile towels are used for padding, and the arm is secured in the retractor with a combination of gauze and elastic wraps.

intercostal muscle attachments are bluntly cleared from the lower edge using a Kittner blunt dissector followed by a flat periosteal elevator [see Figure 2]. The first rib is separated from the underlying pleura by gently sliding a small periosteal elevator beneath the first rib. The pleura is pushed away from the rib, and this mobilization extends from behind the brachial plexus posteriorly to in front of the subclavian vein anteriorly. The subclavius muscle, which has a crescent-shaped ligamentous attachment on the first rib adjacent to the subclavian vein, is sharply divided with scissors, taking care not to injure the subclavian vein. Division of the subclavius muscle provides greater anterior mobilization of the first rib, allowing for more anterior resection, which is of particular importance in venous TOS. The scalene medius fibers are dissected bluntly using a periosteal elevator. Sharp dissection

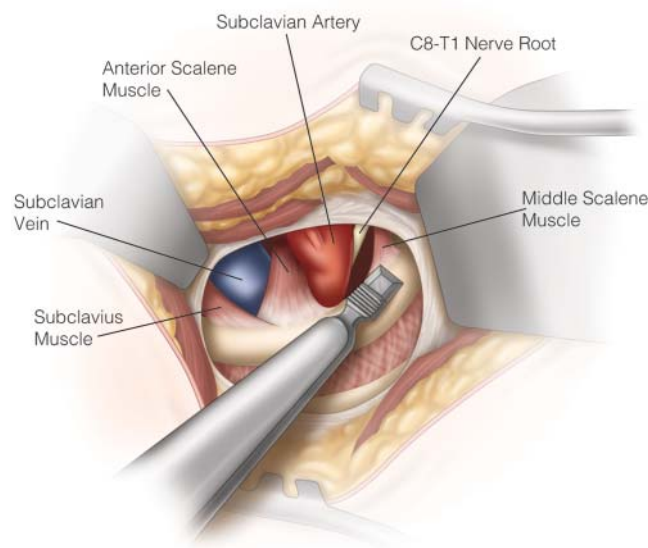


Figure 2 Gentle dissection of the first rib with a periosteal elevator.

is avoided because of the adjacent course of the long thoracic nerve. The anterior scalene muscle must be clearly visualized between the subclavian artery and vein. A right-angle clamp is then placed behind the anterior scalene muscle, lifting it away from the adjacent artery. The muscle is divided sharply with scissors, leaving as much length as possible attached to the rib [see Figure 3]. This maneuver is performed with care and may need to be repeated multiple times to divide the muscle safely. A bone cutter is then placed anteriorly and the first rib is divided adjacent to the subclavian vein. The posterior division of the rib occurs once the remainder of the rib is mobilized. This allows for optimal visualization of the brachial plexus to prevent injury when cutting the rib posteriorly. The rib cutter is gently applied to the rib just anterior to the brachial plexus. The nerve must be visualized prior to making any cut [see Figure 4]. The rib is divided and removed. The rib is always cut in front of the nerve so that posterior nerve roots are not unintentionally damaged. The remainder of the rib anteriorly and posteriorly is trimmed with a rongeur. The nerve root is pushed away and protected with a Roos retractor as the posterior remnant of the rib is rongeuired. The bone edges should be fairly uniform, and there should be no impingement on the neurovascular structures [see Figure 5]. Saline is then instilled into the axillary cavity, and the patient is given several positive pressure ventilations to check for tears in the parietal pleura. If a pneumothorax is present, a 12 French chest tube is placed in the second intercostal space through a separate stab incision. This is applied to 20 cm of water suction after the arm is lowered and the wound is closed in two layers.

Outcomes

The most common complication of transaxillary thoracic outlet decompression is pneumothorax, occurring in approximately 10% of patients. Fortunately, this is easily dealt with intraoperatively by placement of a small chest tube, which is

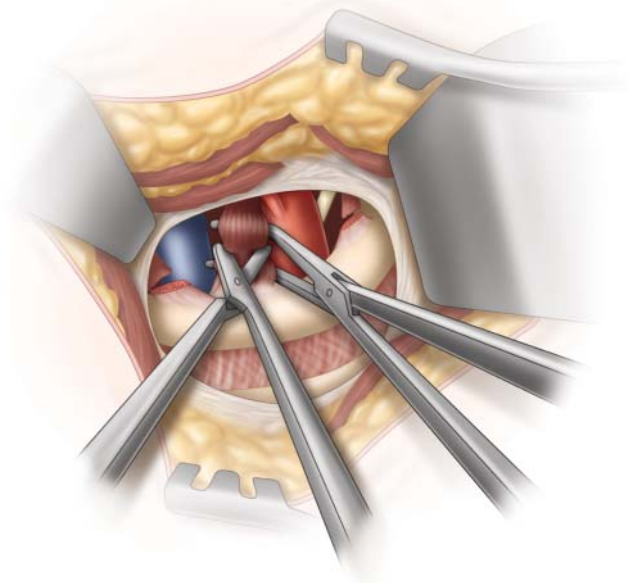


Figure 3 Anterior scalene muscle isolated by a right-angle clamp prior to dissection.

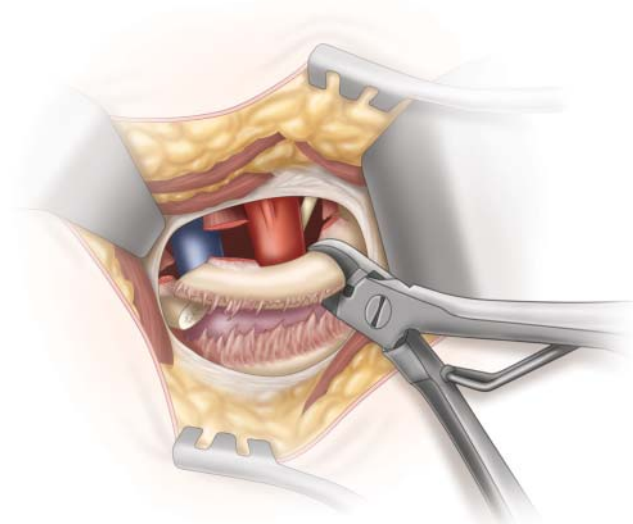


Figure 4 Bone cutter used to remove the first rib.

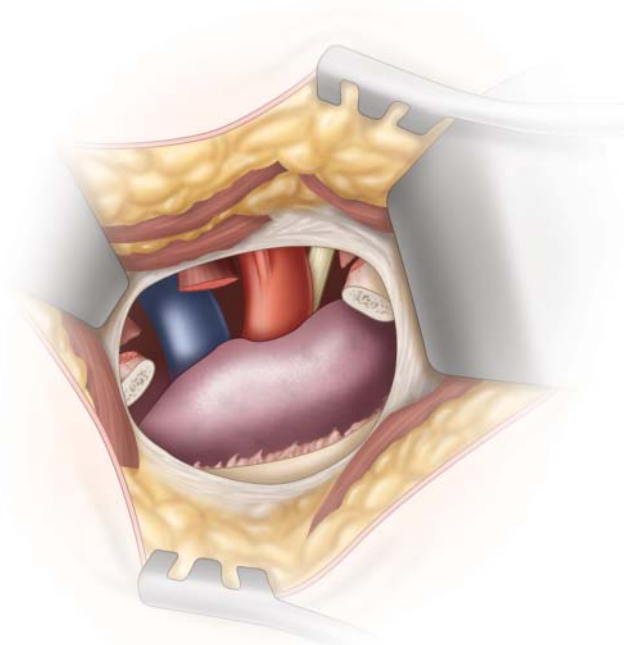


Figure 5 Anatomic space immediately prior to closure. The neurovascular structures are no longer restricted following rib resection.

removed the following day. More serious complications of major vascular or brachial plexus injuries are much less common, occurring in less than 1%. Recurrence of symptoms occurs in up to 10%, and reoperation for recurrent TOS provides other challenges outside the scope of this chapter. There are few objective criteria for measuring success in thoracic outlet decompression. Obviously, the patient's ability to return to normal daily activities, including work, is a good indication of successful therapy. At Johns Hopkins, a prospective study of over 100 patients undergoing thoracic outlet decompression showed statistically significant improvement in quality of life. This was evaluated through the use of

a novel survey instrument.²⁵ The majority of patients in this study were able to return to work or activity within 6 months. Ultimately, successful outcomes depend on thorough diagnostic evaluation, carefully selected and often multimodal therapy, and long-term follow-up.

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Acknowledgments

Figures 2–5 Christine Kenney

1 ACUTE ABDOMINAL PAIN

Alex Nagle, MD, FACS

Acute abdominal pain generally refers to previously undiagnosed pain that arises suddenly and is of less than 48 hours' duration.¹ It may be caused by a great variety of intraperitoneal disorders, many of which call for surgical treatment, as well as by a range of extraperitoneal disorders,² which typically do not call for surgical treatment [*see Clinical Evaluation, Tentative Differential Diagnosis, below*]. Abdominal pain that persists for 6 hours or longer is usually caused by disorders of surgical significance.³ The primary goals in the management of patients with acute abdominal pain are (1) to establish a differential diagnosis and a plan for confirming the diagnosis through appropriate imaging studies, (2) to determine whether operative intervention is necessary, and (3) to prepare the patient for operation in a manner that minimizes perioperative morbidity and mortality.

In many cases, these goals are easily accomplished. On occasion, however, the evaluation of patients with acute abdominal pain can be one of the most difficult challenges in clinical surgery. It is essential to keep in mind that most (at least two thirds) of the patients who present with acute abdominal pain have disorders for which surgical intervention is not required.^{2,4,5} In addition, most clinicians depend on recognition of specific patterns and sequences of symptoms and signs to determine the need for further testing and to make decisions regarding the timing of operation; however, at least one third of patients with acute abdominal pain exhibit atypical features that render pattern recognition unreliable.^{2,5} Finally, it is not clear that individual clinicians always or even usually agree on presenting symptoms and physical signs. In one study of abdominal pain in children, agreement between individual observers was reached 50% of the time for the physical sign of rebound tenderness; however, for five other signs (abdominal distention, abdominal tenderness to percussion, abdominal tenderness to palpation, abdominal guarding, and bowel sounds), interobserver agreement was not reached in more than one third of patients. These findings highlight the difficulties inherent in evaluation and management of acute abdominal pain. In addition, they emphasize the importance of integrating care among different providers to minimize loss of information and maximize continuity of care.

Clinical Evaluation

HISTORY

A careful and methodical clinical history should be obtained. Key features of the history include the dimensions of pain (i.e., mode of onset, duration, frequency, character, location,

chronology, radiation, and intensity), as well as the presence or absence of any aggravating or alleviating factors and associated symptoms. Often such a history is more valuable than any single laboratory or x-ray finding and determines the course of subsequent evaluation and management.

Unfortunately, when the ability of clinicians to take an organized and accurate history has been studied, the results have been disappointing.⁶ For this reason, the use of standardized history and physical forms, with or without the aid of diagnostic computer programs, has been recommended.⁷⁻¹⁰ A large-scale study that included 16,737 patients with acute abdominal pain demonstrated that integration of computer-aided diagnosis into management yielded a 20% improvement in diagnostic accuracy.⁷ The study also documented statistically significant reductions in inappropriate admissions, negative laparotomies, serious management errors (e.g., failure to operate on patients who require surgery), and length of hospital stay, as well as statistically significant increases in the number of patients who were immediately discharged home without adverse effects and the promptness with which those requiring surgery underwent operation. Although many factors may have contributed to the observed benefits of computer-aided decision making, it is clear that the use of structured and standardized means of collecting clinical and laboratory data was crucial. An example of such a structured data sheet is the pain chart developed by the World Organization of Gastroenterology (OMGE) [*see Figure 1*]. Because this pain chart is not exhaustive and does not cover all potential situations, individual surgeons may want to add to it; however, they would be well advised not to omit any of the symptoms and signs on the OMGE data sheet from their routine examination of patients with acute abdominal pain.¹¹

The patient's own words often provide important clues to the correct diagnosis. The examiner should refrain from suggesting specific symptoms, except as a last resort. Any questions that must be asked should be open-ended—for example, "What happens when you eat?" rather than "Does eating make the pain worse?" Leading questions should be avoided. When a leading question must be asked, it should be posed first as a negative question (i.e., one that calls for an answer in the negative) because a negative answer to a question is more likely to be honest and accurate. For example, if peritoneal inflammation is suspected, the question asked should be "Does coughing make the pain better?" rather than "Does coughing make the pain worse?"

The mode of onset of abdominal pain may help the examiner determine the severity of the underlying disease. Pain that has a sudden onset suggests an intra-abdominal catastrophe, such as a ruptured abdominal aortic aneurysm (AAA), a

ABDOMINAL PAIN CHART			
NAME _____		REG. NUMBER _____	
MALE _____ FEMALE _____		AGE _____	
MODE OF ARRIVAL _____		DATE _____	
TIME _____			
PAIN	Site of Pain	Aggravating Factors	Progression of Pain
	At Onset	movement coughing respiration	better same worse
	At Present	food other none	Duration Type intermittent steady colicky
HISTORY	Radiation	Relieving Factors	Severity moderate severe
		lying still vomiting antacids food other none	
EXAMINATION	Nausea yes no	Bowels normal constipation diarrhea blood mucus	Previous Similar Pain yes no
	Vomiting yes no	Micturition normal frequency dysuria dark hematuria	Previous Abdominal Surgery yes no
	Anorexia yes no		Drugs for Abdominal Pain yes no
EXAMINATION	Indigestion yes no		Female-LMP pregnant vaginal discharge dizzy/faint
	Jaundice yes no		
EXAMINATION	Temp. _____ Pulse _____	Location of Tenderness	Initial Diagnosis & Plan
	BP _____	Rebound yes no	Results amylase blood count (WBC) urine x-ray other
	Mood normal upset anxious	Guarding yes no	
EXAMINATION	Color normal pale flushed jaundiced cyanotic	Rigidity yes no	Diagnosis & Plan after Investigation
	Intestinal Movement normal poor/nil peristalsis	Mass yes no	(time)
	Scars yes no	Murphy's Sign Present yes no	
EXAMINATION	Distention yes no	Bowel Sounds normal absent increased	Discharge Diagnosis
		Rectal-Vaginal Tenderness left right general mass none	

History and examination of other systems on separate case notes.

Figure 1 Shown is a data sheet modified from the abdominal pain chart developed by the World Organization of Gastroenterology (OMGE). Adapted from American College of Emergency Physicians.¹⁰ BP = blood pressure; LMP = last menstrual period; Temp. = temperature; WBC = white blood cells.

perforated viscus, or a ruptured ectopic pregnancy; a near loss of consciousness or stamina associated with sudden-onset pain should heighten the level of concern for such a catastrophe. Rapidly progressive pain that becomes intensely focused in a well-defined area within a period of a few minutes to an hour or two suggests a condition such as acute cholecystitis or pancreatitis. Pain that has a gradual onset over several hours, usually beginning as slight or vague discomfort and slowly progressing to steady and more localized pain, suggests a subacute process and is characteristic of processes that lead to peritoneal inflammation. Numerous disorders may be associated with this mode of onset, including acute appendicitis, diverticulitis, pelvic inflammatory disease (PID), and intestinal obstruction.

Pain can be either intermittent or continuous. Intermittent or cramping pain (colic) is pain that occurs for a short period (a few minutes), followed by longer periods (a few minutes to one half-hour) of complete remission during which there is no pain at all. Intermittent pain is characteristic of obstruction of a hollow viscus and results from vigorous peristalsis in the wall of the viscus proximal to the site of obstruction. This pain is perceived as deep in the abdomen and is poorly localized. The patient is restless, may writhe about incessantly in an effort to find a comfortable position, and often presses on the abdominal wall in an attempt to alleviate the pain. Whereas the intermittent pain associated with intestinal obstruction (typically described as gripping and mounting) is usually severe but bearable, the pain associated with obstruction of small conduits (e.g., the biliary tract, the ureters, and the uterine tubes) often becomes unbearable. Obstruction of the gallbladder or the bile ducts gives rise to a type of pain often referred to as biliary colic; however, this term is a misnomer in that biliary pain is usually constant because of the lack of a strong muscular coat in the biliary tree and the absence of regular peristalsis.

Continuous or constant pain is pain that is present for hours or days without any period of complete relief; it is more common than intermittent pain. Continuous pain is usually indicative of a process that will lead, or has already led, to peritoneal inflammation or ischemia. It may be of steady intensity throughout, or it may be associated with intermittent pain. For example, the typical colicky pain associated with simple intestinal obstruction changes when strangulation occurs, becoming continuous pain that persists between episodes or waves of cramping pain.

Certain types of pain are generally held to be typical of certain pathologic states. For example, the pain of a perforated ulcer is often described as burning, that of a dissecting aneurysm as tearing, and that of bowel obstruction as gripping. One may imagine that the first type of pain is explained by the efflux of acid, the second by the sudden expansion of the retroperitoneum, and the third by the churning of hyperperistalsis. Colorful as these images may be, in most cases, the pain begins in a nondescript way. It is only by carefully following the patient's description of the evolution and time course of the pain that such images may be formed with confidence.

For several reasons—atypical pain patterns, dual innervation by visceral and somatic afferents, normal variations in organ position, and widely diverse underlying pathologic states—the

location of abdominal pain is only a rough guide to diagnosis. It is nevertheless true that in most disorders, the pain tends to occur in characteristic locations, such as the right upper quadrant (cholecystitis), the right lower quadrant (appendicitis), the epigastrium (pancreatitis), or the left lower quadrant (sigmoid diverticulitis) [see Figure 2]. It is important to determine the location of the pain at onset because this may differ from the location at the time of presentation (so-called shifting pain). In fact, the chronological sequence of events in the patient's history is often more important for diagnosis than the location of the pain alone. For example, the classic pain of appendicitis begins in the periumbilical region and settles in the right lower quadrant. Another example is the pain from a perforated ulcer which can shift to the right lower quadrant as escaping gastroduodenal content tracks down the right gutter.

It is also important to take into account radiation or referral of the pain, which tends to occur in characteristic patterns [see Figure 3]. For example, biliary pain is referred to the right subscapular area, and the boring pain of pancreatitis typically radiates straight through to the back. Obstruction of the small intestine and the proximal colon is referred to the umbilicus, and obstruction distal to the splenic flexure is often referred to the suprapubic area. Spasm in the ureter often radiates to the suprapubic area and into the groin. The more severe the pain is, the more likely it is to be associated with referral to other areas.

The intensity or severity of the pain is related to the magnitude of the underlying insult. It is important to distinguish between the intensity of the pain and the patient's reaction to it because there appear to be significant individual differences with respect to tolerance of and reaction to pain. Pain that is intense enough to awaken the patient from sleep usually indicates a significant underlying organic cause. Past episodes of pain and factors that aggravate or relieve the pain often provide useful diagnostic clues. For example, pain caused by peritonitis tends to be exacerbated by motion, deep breathing, coughing, or sneezing, and patients with peritonitis tend to lie quietly in bed and avoid any movement. The typical pain of acute pancreatitis is exacerbated by lying down and relieved by sitting up. Pain that is relieved by eating or taking antacids suggests duodenal ulcer disease, whereas diffuse abdominal pain that appears 30 minutes to 1 hour after meals suggests intestinal angina.

Associated gastrointestinal symptoms (e.g., nausea, vomiting, anorexia, diarrhea, and constipation) often accompany abdominal pain; however, these symptoms are nonspecific and therefore may not be of great value in the differential diagnosis. Vomiting in particular is common: when sufficiently stimulated by pain impulses traveling via secondary visceral afferent fibers, the medullary vomiting centers activate efferent fibers and cause reflex vomiting. Once again, the chronology of events is important in that pain often precedes vomiting in patients with conditions necessitating operation, whereas the opposite is usually the case in patients with medical (i.e., nonsurgical) conditions.^{5,12} This is particularly true for adult patients with acute appendicitis, in whom pain almost always precedes vomiting by several hours. In children, vomiting is commonly observed closer to the onset of the pain, although it is rarely the initial symptom.

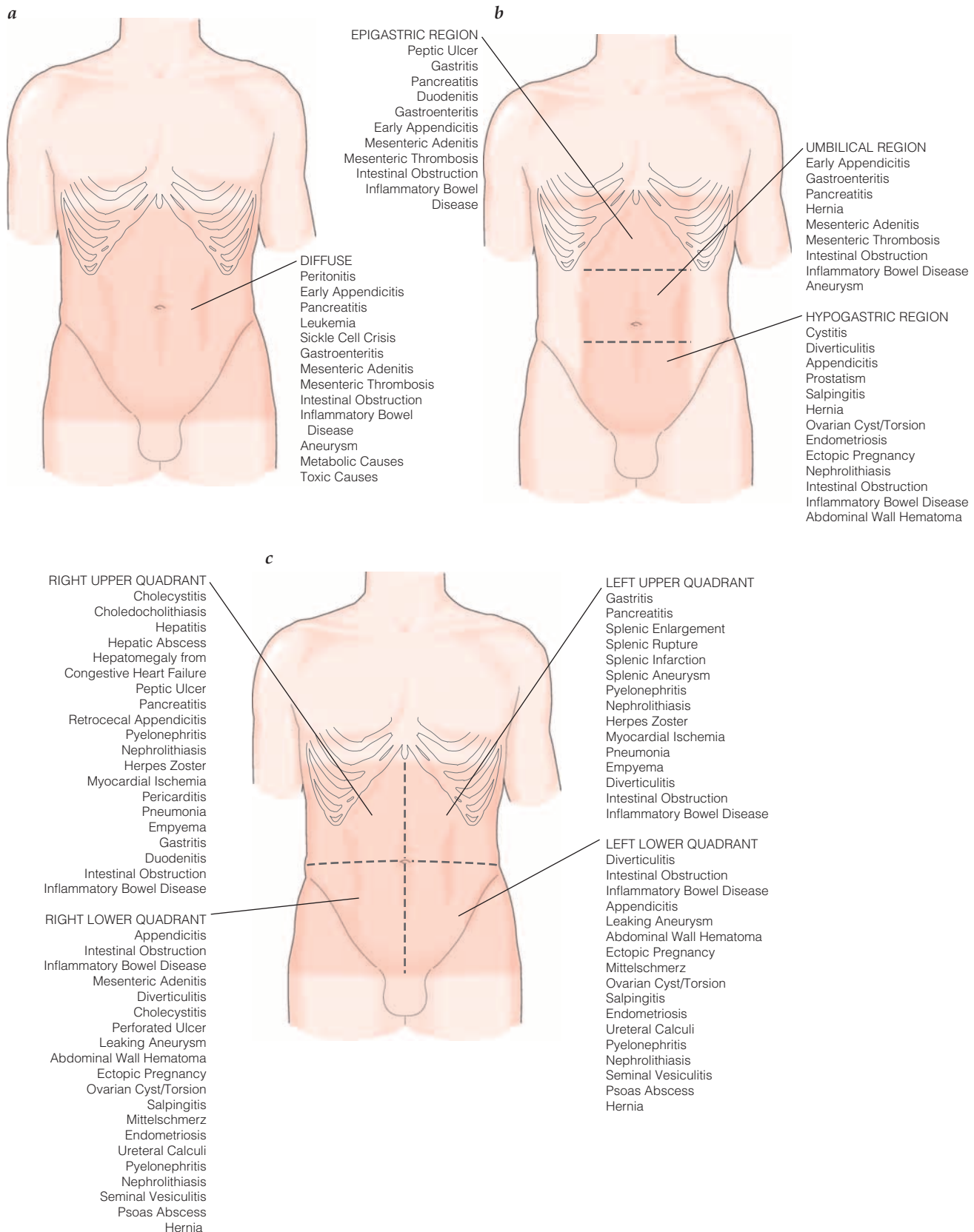


Figure 2 In most disorders that give rise to acute abdominal pain, the pain tends to occur in specific locations. (a) Diffuse pain suggests a certain set of diagnostic possibilities. (b) Differing groups of disorders give rise to abdominal pain in the epigastric, umbilical, and hypogastric regions. (c) Disorders that give rise to acute abdominal pain may be grouped according to the quadrant of the abdomen in which pain tends to occur.

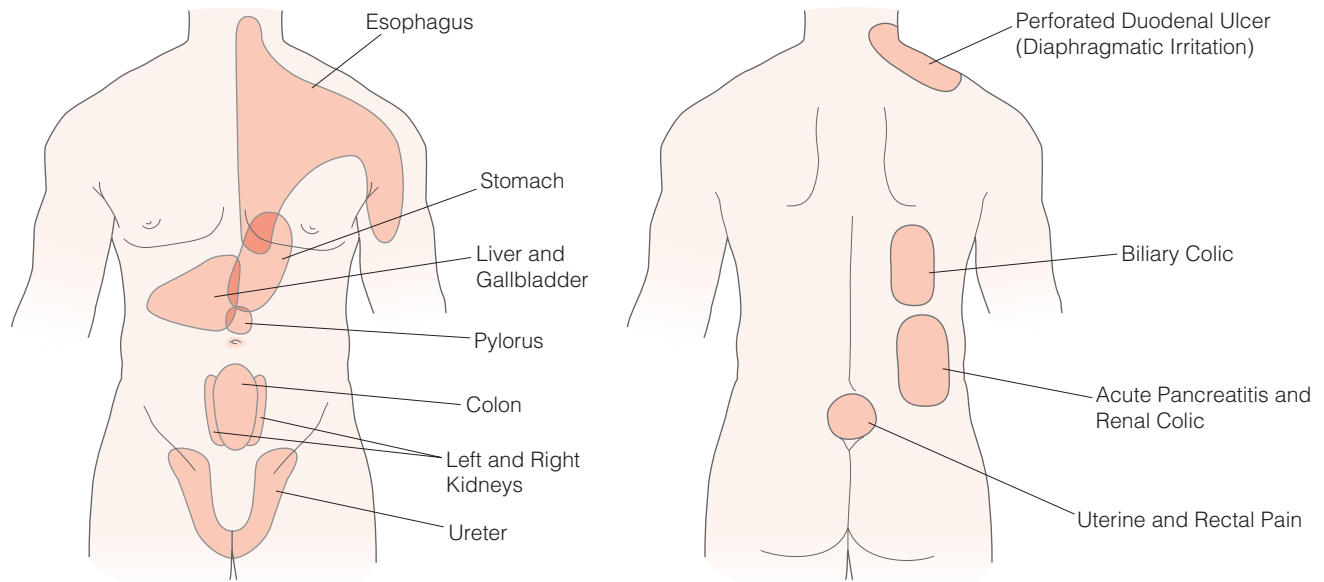


Figure 3 Pain of abdominal origin tends to be referred in characteristic patterns.⁸⁰ The more severe the pain is, the more likely it is to be referred. Shown are anterior (*left*) and posterior (*right*) areas of referred pain.

Similarly, constipation may result from a reflex paralytic ileus when sufficiently stimulated visceral afferent fibers activate efferent sympathetic fibers (splanchnic nerves) to reduce intestinal peristalsis. Diarrhea is characteristic of gastroenteritis but may also accompany incomplete intestinal or colonic obstruction. More significant is a history of obstipation because if it can be definitely established that a patient with acute abdominal pain has not passed gas or stool for 24 to 48 hours, it is certain that some degree of intestinal obstruction is present. Other associated symptoms that should be noted include jaundice, melena, hematochezia, hematemesis, and hematuria. These symptoms are much more specific than the ones just discussed and can be extremely valuable in the differential diagnosis. Most conditions that cause acute abdominal pain of surgical significance are associated with some degree of fever if they are allowed to continue long enough. Fever suggests an inflammatory process; however, it is usually low grade and often absent altogether, particularly in elderly and immunocompromised patients. The combination of a high fever with chills and rigors indicates bacteremia, and concomitant changes in mental status (e.g., agitation, disorientation, and lethargy) suggest impending septic shock.

A history of trauma (even if the patient considers the traumatic event trivial) should be actively sought in all cases of unexplained acute abdominal pain; such a history may not be readily volunteered (as is often the case with trauma resulting from domestic violence). The history may be particularly relevant in a patient taking anticoagulants and presenting with acute onset of abdominal pain accompanied by tenderness but no clear signs of inflammation. Hematoma within the rectus muscle sheath can easily be mistaken for appendicitis or other lower abdominal illnesses; hematoma

elsewhere can produce symptoms of obstruction or acute bleeding into the peritoneum and the retroperitoneum. In female patients, it is essential to obtain a detailed gynecologic history that includes the timing of symptoms within the menstrual cycle, the date of the last menses, previous and current use of contraception, any abnormal vaginal bleeding or discharge, an obstetric history, and any risk factors for ectopic pregnancy (e.g., PID, use of an intrauterine device, or previous ectopic or tubal surgery). Pregnancy should be excluded in all women of childbearing age with abdominal pain.

A complete history of previous medical conditions must be obtained because associated diseases of the cardiac, pulmonary, and renal systems may give rise to acute abdominal symptoms and may also significantly affect the morbidity and mortality associated with surgical intervention. The use of regular and as needed medications must also be obtained. Weight changes, past illnesses, recent travel, and environmental exposure to toxins or infectious agents used should also be investigated. A history of previous abdominal operations should be obtained but should not be relied on too heavily in the absence of operative reports. A careful family history is important for detection of hereditary disorders that may cause acute abdominal pain. A detailed social history should also be obtained that includes any history of tobacco, alcohol, or illicit drug use, as well as a sexual history.

TENTATIVE DIFFERENTIAL DIAGNOSIS

Once the history has been obtained, the examiner should generate a tentative differential diagnosis and carry out the physical examination in search of specific signs or findings that either rule out or confirm the diagnostic possibilities.

Given the diversity of conditions that can cause acute abdominal pain [see Table 1 and Table 2], there is no substitute for general awareness of the most common causes of acute abdominal pain and the influence of age, gender, and geography on the likelihood of any of these potential causes. Although acute abdominal pain is the most common surgical emergency and most non-trauma-related surgical admissions (and

1% of all hospital admissions) are accounted for by patients complaining of abdominal pain, little information is available regarding the clinical spectrum of disease in these patients.¹³ Nevertheless, detailed epidemiologic information can be an invaluable asset in the diagnosis and treatment of acute abdominal pain. Now that patients from different parts of the world are increasingly being seen in North American

Table 1 Intraperitoneal Causes of Acute Abdominal Pain

Inflammatory	Mechanical (obstruction, acute distention)
Peritoneal	Hollow visceral
Chemical and nonbacterial peritonitis	Intestinal obstruction
Perforated peptic ulcer/biliary tree, pancreatitis, ruptured ovarian cyst, mittelschmerz	Adhesions, hernias, neoplasms, volvulus
Bacterial peritonitis	Intussusception, gallstone ileus, foreign bodies
Primary peritonitis	Bezoars, parasites
Pneumococcal, streptococcal, tuberculous	Biliary obstruction
Spontaneous bacterial peritonitis	Calculi, neoplasms, choledochal cyst, hemobilia
Perforated hollow viscus	Solid visceral
Esophagus, stomach, duodenum, small intestine, bile duct, gallbladder, colon, urinary bladder	Acute splenomegaly
Hollow visceral	Acute hepatomegaly (congestive heart failure, Budd-Chiari syndrome)
Appendicitis	Mesenteric
Cholecystitis	Omental torsion
Peptic ulcer	Pelvic
Gastroenteritis	Ovarian cyst
Gastritis	Torsion or degeneration of fibroid
Duodenitis	Ectopic pregnancy
Inflammatory bowel disease	Hemoperitoneum
Meckel diverticulitis	Ruptured hepatic neoplasm
Colitis (bacterial, amebic)	Spontaneous splenic rupture
Diverticulitis	Ruptured mesentery
Solid visceral	Ruptured uterus
Pancreatitis	Ruptured graafian follicle
Hepatitis	Ruptured ectopic pregnancy
Pancreatic abscess	Ruptured aortic or visceral aneurysm
Hepatic abscess	Ischemic
Splenic abscess	Mesenteric thrombosis
Mesenteric	Hepatic infarction (toxemia, purpura)
Lymphadenitis (bacterial, viral)	Splenic infarction
Epiploic appendagitis	Omental ischemia
Pelvic	Strangulated hernia
Pelvic inflammatory disease (salpingitis)	Neoplastic
Tubo-ovarian abscess	Primary or metastatic intraperitoneal neoplasms
Endometritis	Traumatic
	Blunt trauma
	Penetrating trauma
	Iatrogenic trauma
	Domestic violence
	Miscellaneous
	Endometriosis

Adapted from McFadden DW et al.⁸¹

Table 2 Extraperitoneal Causes of Acute Abdominal Pain

Genitourinary	Neurogenic
Pyelonephritis	Herpes zoster
Perinephric abscess	Tabes dorsalis
Renal infarct	Nerve root compression
Nephrolithiasis	Spinal cord tumors
Ureteral obstruction (lithiasis, tumor)	Osteomyelitis of the spine
Acute cystitis	Abdominal epilepsy
Prostatitis	Abdominal migraine
Seminal vesiculitis	Multiple sclerosis
Epididymitis	Inflammatory
Orchitis	Schönlein-Henoch purpura
Testicular torsion	Systemic lupus erythematosus
Dysmenorrhea	Polyarteritis nodosa
Threatened abortion	Dermatomyositis
Pulmonary	Scleroderma
Pneumonia	Infectious
Empyema	Bacterial
Pulmonary embolus	Parasitic (malaria)
Pulmonary infarction	Viral (measles, mumps, infectious mononucleosis)
Pneumothorax	Rickettsial (Rocky Mountain spotted fever)
Cardiac	Hematologic
Myocardial ischemia	Sickle cell crisis
Myocardial infarction	Acute leukemia
Acute rheumatic fever	Acute hemolytic states
Acute pericarditis	Coagulopathies
Metabolic	Pernicious anemia
Acute intermittent porphyria	Other dyscrasias
Familial Mediterranean fever	Vascular
Hypolipoproteinemia	Vasculitis
Hemochromatosis	Periarteritis
Hereditary angioneurotic edema	Toxins
Endocrine	Bacterial toxins (tetanus, <i>Staphylococcus</i>)
Diabetic ketoacidosis	Insect venom (black widow spider)
Hyperparathyroidism (hypercalcemia)	Animal venom
Acute adrenal insufficiency (Addisonian crisis)	Heavy metals (lead, arsenic, mercury)
Hyperthyroidism or hypothyroidism	Poisonous mushrooms
Musculoskeletal	Drugs
Rectus sheath hematoma	Withdrawal from narcotics
Arthritis/diskitis of thoracolumbar spine	Retroperitoneal
Psychogenic	Retroperitoneal hemorrhage (spontaneous adrenal hemorrhage)
Hypochondriasis	Psoas abscess
Somatization disorders	
Factitious	
Munchausen syndrome	
Malingering	

emergency rooms, it is important to consider endemic diseases, including tuberculosis,^{14,15} parasitic diseases,^{16–18} bezoars from unusual dietary habits,^{19,20} and unusual malignancies.^{21,22}

The value of detailed epidemiologic knowledge notwithstanding, it is worthwhile to keep in mind the truism that common things are common. Regarding which things are common, the most extensive information currently available comes from the ongoing survey begun in 1977 by the Research Committee of the OMGE. As of the last progress report on this survey, which was published in 1988, more than 200 physicians at 26 centers in 17 countries had accumulated data on 10,320 patients with acute abdominal pain [see Table 3].²³ The most common diagnosis in these patients was nonspecific abdominal pain (NSAP)—that is, the retrospective diagnosis of exclusion in which no cause for the pain can be identified.^{24,25} NSAP accounted for 34% of all patients seen; the four most common diagnoses accounted for more than 75%. The most common surgical diagnosis in the OMGE survey was acute appendicitis, followed by acute cholecystitis, small bowel obstruction, and gynecologic disorders. Relatively few patients had perforated peptic ulcer, a finding that confirms the current downward trend in the incidence of this condition. Cancer was found to be a significant cause of acute abdominal pain. There was little variation in the geographic distribution of surgical causes of acute abdominal pain (i.e., conditions necessitating operation) among

developed countries. In patients who required surgery, the most common causes were acute appendicitis (42.6%), acute cholecystitis (14.7%), small bowel obstruction (6.2%), perforated peptic ulcer (3.7%), and acute pancreatitis (4.5%).²³ The OMGE survey's finding that NSAP was the most common diagnosis in patients with acute abdominal pain has been confirmed by several studies^{12,13,25}; the finding that acute appendicitis, cholecystitis, and intestinal obstruction were the three most common diagnoses in patients with acute abdominal pain who require operation has also been amply confirmed [see Table 3].^{1,12,13}

The data described so far provide a comprehensive picture of the most likely diagnoses for patients with acute abdominal pain in many centers around the world; however, this picture does not take into account the effect of age on the relative likelihood of the various potential diagnoses. It is well known that the disease spectrum of acute abdominal pain is different in different age groups, especially in the very old^{4,26,27} and the very young.^{28–30} In the OMGE survey, well over 90% of cases of acute abdominal pain in children were diagnosed as having acute appendicitis (32%) or NSAP (62%).²⁸ Similar age-related differences in the spectrum of disease have been confirmed by other studies,¹⁶ as have various gender-related differences.

This variation in the disease spectrum is readily apparent when the 10,320 patients from the OMGE survey are segregated by age [see Table 4]. In patients 50 years of age

Table 3 Frequency of Specific Diagnoses in Patients with Acute Abdominal Pain

Diagnosis	Frequency in Individual Studies (% of Patients)					
	OMGE ²³ (N = 10,320)	Wilson et al ⁸² (N = 1,196)	Irvin ¹³ (N = 1,190)	Brewer et al ¹² (N = 1,000)	de Dombal ¹ (N = 552)	Hawthorn ⁸³ (N = 496)
Nonspecific abdominal pain	34.0	45.6	34.9	41.3	50.5	36.0
Acute appendicitis	28.1	15.6	16.8	4.3	26.3	14.9
Acute cholecystitis	9.7	5.8	5.1	2.5	7.6	5.9
Small bowel obstruction	4.1	2.6	14.8	2.5	3.6	8.6
Acute gynecologic disease	4.0	4.0	1.1	8.5	—	—
Acute pancreatitis	2.9	1.3	2.4	—	2.9	2.1
Urologic disorders	2.9	4.7	5.9	11.4	—	12.8
Perforated peptic ulcer	2.5	2.3	2.5	2.0	3.1	—
Cancer	1.5	—	3.0	—	—	—
Diverticular disease	1.5	1.1	3.9	—	2.0	3.0
Dyspepsia	1.4	7.6	1.4	1.4	—	—
Gastroenteritis	—	—	0.3	6.9	—	5.1
Inflammatory bowel disease	—	—	0.8	—	—	2.1
Mesenteric adenitis	—	3.6	—	—	—	1.5
Gastritis	—	2.1	—	1.4	—	—
Constipation	—	2.4	—	2.3	—	—
Amebic hepatic abscess	1.2	—	1.9	—	—	—
Miscellaneous	6.3	1.3	5.2	15.5	4.0	8.0

OMGE = World Organization of Gastroenterology.

Table 4 Frequency of Specific Diagnoses in Younger and Older Patients with Acute Abdominal Pain in the OMGE Study

Diagnosis	Frequency (% of Patients)	
	Age < 50 yr (N = 6,317)	Age ≥ 50 yr (N = 2,406)
Nonspecific abdominal pain	39.5	15.7
Appendicitis	32.0	15.2
Cholecystitis	6.3	20.9
Obstruction	2.5	12.3
Pancreatitis	1.6	7.3
Diverticular disease	< 0.1	5.5
Cancer	< 0.1	4.1
Hernia	< 0.1	3.1
Vascular disease	< 0.1	2.3

OMGE = World Organization of Gastroenterology.
Adapted from de Dombal FT et al.²³ and Telfer S et al.²⁷

or older,²⁷ cholecystitis was more common than either NSAP or acute appendicitis; small bowel obstruction, diverticular disease, and pancreatitis were all approximately five times more common than in patients younger than 50 years. Hernias were also a much more common problem in older patients. In the entire group of patients, only 1 in every 10 instances of intestinal obstruction was attributable to a hernia, whereas in patients 50 years of age or older, 1 in every 3 instances was caused by an undiagnosed hernia. Cancer was 40 times more likely to be the cause of acute abdominal pain in patients 50 years of age or older; vascular diseases (including myocardial infarction, mesenteric ischemia, and ruptured AAA) were 25 times more common in patients 50 years of age or older and 100 times more common in patients older than 70 years. What is more, outcome was clearly related to age: mortality was significantly higher in patients older than 70 years (5%) than in those younger than 50 years (< 1%). Whereas the peak incidence of acute abdominal pain occurred in patients in their teens and twenties,²⁸ the great majority of deaths occurred in patients older than 70 years.²⁷

PHYSICAL EXAMINATION

In the physical examination of a patient, as in the taking of the history, there is no substitute for organization and patience; the amount of information that can be obtained is directly proportional to the gentleness and thoroughness of the examiner. The physical examination begins with a brief but thorough evaluation of the patient's general appearance and ability to answer questions. The degree of obvious pain should be estimated. The patient's position in bed should be noted. A patient who lies motionless with flexed hips and knees is more likely to have generalized peritonitis. A restless patient who writhes about in bed is more likely to have colicky pain.

The area of maximal pain should be identified before the physical examination is begun. The examiner can easily do this by simply asking the patient to cough and then to point

with two fingers to the area where pain seems to be focused. This allows the examiner to avoid the area in the early stages of the examination and to confirm it at a later stage without causing the patient unnecessary discomfort in the meantime.

The physical examination should be directed, in the sense that it should address critical findings that would confirm or exclude the likeliest disorders in the differential diagnosis. In this context, however, it should be complete. Some processes that can cause abdominal pain occur within the chest (e.g., pneumonia, ischemic heart disease or arrhythmia, esophageal muscular disorders); thus, auscultation of the lungs and the heart is integral to the examination. A pelvic examination should be performed in women, and an examination of the rectum and the groin should be performed in all patients. It should not be assumed that advanced imaging technology (e.g., computed tomography [CT], magnetic resonance imaging [MRI], or ultrasonography [US]) will provide the diagnosis most quickly or with the highest level of confidence. The sensitivity and specificity (not to mention the cost-effectiveness) of any laboratory or imaging study are grounded in the intelligent gathering and categorization of signs and symptoms.^{31,32}

Before attention is directed to the patient's abdomen, signs of systemic illness should be sought. Systemic signs of shock (e.g., diaphoresis, pallor, hypothermia, tachypnea, tachycardia with orthostasis, and frank hypotension) usually accompany a rapidly progressive or advanced intra-abdominal condition and, in the absence of extra-abdominal causes, are indications for immediate laparotomy. The absence of any alteration in vital signs, however, does not necessarily exclude a serious intra-abdominal process.

Examination of the abdomen begins with the patient resting in a comfortable supine position. A right-handed examiner should stand on the patient's right side, and the patient's abdomen should be level with the elbow at rest. In some cases, to make sure that the examination is unhurried and the patient's anxiety is allayed, the examiner may find it useful to sit at the bedside. The examination should include inspection, auscultation, percussion, and palpation of all areas of the abdomen, the flanks, and the groin (including all hernia orifices) in addition to rectal and genital examinations (and, in female patients, a full gynecologic examination). A systematic approach is crucial: an examiner who methodically follows a set pattern of abdominal examination every time will be rewarded more frequently than one who improvises haphazardly with each patient.

The first step in the abdominal examination is careful inspection of the anterior and posterior abdominal walls, the flanks, the perineum, and the genitalia for previous surgical scars (possible adhesions), hernias (incarceration or strangulation), distention (intestinal obstruction), obvious masses (distended gallbladder, abscesses, or tumors), ecchymosis or abrasions (trauma), striae (pregnancy or ascites), an everted umbilicus (increased intra-abdominal pressure), visible pulsations (aneurysm), visible peristalsis (obstruction), limitation of movement of the abdominal wall with ventilatory movements (peritonitis), or engorged veins (portal hypertension).

The next recommended step in the abdominal examination is auscultation. Although it is important to note the presence (or absence) of bowel sounds and their quality, auscultation

is probably the least rewarding aspect of the physical examination. Severe intra-abdominal conditions, even intra-abdominal catastrophes, may occur in patients with normal bowel sounds, and patients with silent abdomens may have no significant intra-abdominal pathology at all. In general, however, the absence of bowel sounds indicates a paralytic ileus; hyperactive or hypoactive bowel sounds often are variations of normal activity; and high-pitched bowel sounds with splashes, tinkles (echoing as in a large cavern), or rushes (prolonged, loud gurgles) indicate mechanical bowel obstruction.

The third step is percussion to search for any areas of dullness, fluid collections, sections of gas-filled bowel, or pockets of free air under the abdominal wall. Tympany may be present in patients with bowel obstruction or hollow viscus perforation. Percussion can be useful as a way of estimating organ size and of determining the presence of ascites (signaled by a fluid wave or shifting dullness). Gentle percussion over the four quadrants of the abdomen can also be used to elicit a sign of peritoneal irritation, and patients tolerate this maneuver reasonably well. Pain associated with mild levels of percussion is a good indicator of peritonitis if the maneuver is performed in the same way each time. In general, however, maneuvers associated with palpation are best for determining whether peritonitis is present.

The last step, palpation, is the most informative aspect of the physical examination. Palpation of the abdomen must be done very gently to avoid causing additional pain early in the examination. It should begin as far as possible from the area of maximal pain and then should gradually advance toward this area, which should be the last to be palpated. The examiner should place the entire hand on the patient's abdomen with the fingers together and extended, applying pressure with the pulps (not the tips) of the fingers by flexing the wrists and

the metacarpophalangeal joints. It is essential to determine whether true involuntary muscle guarding (muscle spasm) is present. This determination is made by means of gentle palpation over the abdominal wall while the patient takes a long, deep breath. If guarding is voluntary, the underlying muscle immediately relaxes under the gentle pressure of the palpating hand. If, however, the patient has true involuntary guarding, the muscle remains in spasm (i.e., taut and rigid) throughout the respiratory cycle (so-called boardlike abdomen). True involuntary guarding is indicative of localized or generalized peritonitis. It must be remembered that muscle rigidity is relative: for example, muscle guarding may be less pronounced or absent in debilitated and elderly patients who have poor abdominal musculature. In addition, the evaluation of muscle guarding is dependent on the patient's cooperation.

Palpation is also useful for determining the extent and severity of the patient's tenderness. Diffuse tenderness indicates generalized peritoneal inflammation. Mild diffuse tenderness without guarding usually indicates gastroenteritis or some other inflammatory intestinal process without peritoneal inflammation. Localized tenderness suggests an early stage of disease with limited peritoneal inflammation. Rebound tenderness is elicited by applying gentle but deep pressure to the region of interest and then letting go abruptly. As a means of distraction, the examiner may use the stethoscope to apply the pressure. The main difficulties associated with palpation are that the deep pressure may increase anxiety and that the surprise of the sudden withdrawal may elicit pain where peritoneal irritation is not the cause.

Careful palpation can elicit several specific signs [see Table 5], such as the Rovsing sign (pain in the right lower quadrant when the left lower quadrant is palpated deeply), which is associated with acute appendicitis, and the Murphy sign (arrest of inspiration when the right upper quadrant is

Table 5 Common Abdominal Signs and Findings Noted on Physical Examination

Sign or Finding	Description	Associated Clinical Condition(s)
Aaron sign	Referred pain or feeling of distress in epigastrium or precordial region on continued firm pressure over the McBurney point	Acute appendicitis
Ballance sign	Presence of dull percussion note in both flanks, constant on left side but shifting with change of position on right side	Ruptured spleen
Bassler sign	Sharp pain elicited by pinching appendix between thumb of examiner and iliacus muscle	Chronic appendicitis
Beevor sign	Upward movement of umbilicus	Paralysis of lower portions of rectus abdominis muscles
Blumberg sign	Transient abdominal wall rebound tenderness	Peritoneal inflammation
Carnett sign	Disappearance of abdominal tenderness when anterior abdominal muscles are contracted	Abdominal pain of intra-abdominal origin
Chandelier sign	Intense lower abdominal and pelvic pain on manipulation of cervix	Pelvic inflammatory disease
Charcot sign	Intermittent right upper quadrant abdominal pain, jaundice, and fever	Choledocholithiasis
Chaussier sign	Severe epigastric pain in gravid female	Prodrome of eclampsia
Claybrook sign	Transmission of breath and heart sounds through abdominal wall	Ruptured abdominal viscus
Courvoisier sign	Palpable, nontender gallbladder in presence of clinical jaundice	Periampullary neoplasm
Cruveilhier sign	Varicose veins radiating from umbilicus (caput medusae)	Portal hypertension

Table 5 (continued) Common Abdominal Signs and Findings Noted on Physical Examination

Sign or Finding	Description	Associated Clinical Condition(s)
Cullen sign	Periumbilical darkening of skin from blood	Hemoperitoneum (especially in ruptured ectopic pregnancy)
Cutaneous hyperesthesia	Increased abdominal wall sensation to light touch	Parietal peritoneal inflammation secondary to inflammatory intra-abdominal pathology
Dance sign	Slight retraction in area of right iliac fossa	Intussusception
Danforth sign	Shoulder pain on inspiration	Hemoperitoneum (especially in ruptured ectopic pregnancy)
Direct abdominal wall tenderness	—	Localized inflammation of abdominal wall, peritoneum, or an intra-abdominal viscus
Fothergill sign	Abdominal wall mass that does not cross midline and remains palpable when rectus muscle is tense	Rectus muscle hematoma
Grey Turner sign	Local areas of discoloration around umbilicus and flanks	Acute hemorrhagic pancreatitis
Iliopsoas sign	Elevation and extension of leg against pressure of examiner's hand causes pain	Appendicitis (retrocecal) or an inflammatory mass in contact with psoas
Kehr sign	Left shoulder pain when patient is supine or in the Trendelenburg position (pain may occur spontaneously or after application of pressure to left subcostal region)	Hemoperitoneum (especially ruptured spleen)
Kustner sign	Palpable mass anterior to uterus	Dermoid cyst of ovary
Mannkopf sign	Acceleration of pulse when a painful point is pressed on by examiner	Absent in factitious abdominal pain
McClintock sign	Heart rate > 100 beats/min 1 hr postpartum	Postpartum hemorrhage
Murphy sign	Palpation of right upper abdominal quadrant during deep inspiration results in inspiratory arrest	Acute cholecystitis
Obturator sign	Flexion of right thigh at right angles to trunk and external rotation of same leg in supine position result in hypogastric pain	Appendicitis (pelvic appendix); pelvic abscess; an inflammatory mass in contact with muscle
Puddle sign	Alteration in intensity of transmitted sound in intra-abdominal cavity secondary to percussion when patient is positioned on all fours and stethoscope is gradually moved toward flank opposite percussion	Free peritoneal fluid
Ransohoff sign	Yellow pigmentation in umbilical region	Ruptured common bile duct
Rovsing sign	Pain referred to the McBurney point on application of pressure to descending colon	Acute appendicitis
Subcutaneous crepitation	Palpable crepitus in abdominal wall	Subcutaneous emphysema or gas gangrene
Summer sign	Increased abdominal muscle tone on exceedingly gentle palpation of right or left iliac fossa	Early appendicitis; nephrolithiasis; ureterolithiasis; ovarian torsion
Ten Horn sign	Pain caused by gentle traction on right spermatic cord	Acute appendicitis
Toma sign	Right-sided tympany and left-sided dullness in supine position as a result of peritoneal inflammation and subsequent mesenteric contraction of intestine to right side of abdominal cavity	Inflammatory ascites

Adapted from Hickey MS et al.⁶

deeply palpated), which is associated with acute cholecystitis. These signs are indicative of localized peritoneal inflammation. Similarly, specific maneuvers can elicit signs of localized peritoneal irritation. The psoas sign is elicited by placing the patient in the left lateral decubitus position and extending the right leg. In settings where appendicitis is suspected, pain on extension of the right leg indicates that the psoas is irritated and thus that the inflamed appendix is in a retrocecal position. The obturator sign is elicited by raising the flexed right leg and rotating the thigh internally. In settings where appendicitis is suspected, pain on rotation of the right thigh indicates that the obturator is irritated and thus that the inflamed

appendix is in a pelvic position. The Kehr sign is elicited when the patient is placed in the Trendelenburg position. Pain in the shoulder indicates irritation of the diaphragm by a noxious fluid (e.g., gastric contents from a perforated ulcer, pus from a ruptured appendix, or free blood from a fallopian tube pregnancy). Another useful maneuver is the Carnett test, in which the patient elevates his or her head off the bed, thus tensing the abdominal muscles. When the pain is caused by abdominal wall conditions (e.g., rectal sheath hematoma), tenderness to palpation persists, but when the pain is caused by intraperitoneal conditions, tenderness to palpation decreases or disappears (the Carnett sign).

Rectal, genital, and (in women) pelvic examinations are essential to the evaluation of all patients with acute abdominal pain. The rectal examination should include evaluation of sphincter tone, tenderness (localized versus diffuse), and prostate size and tenderness, as well as a search for the presence of hemorrhoids, masses, fecal impaction, foreign bodies, and gross or occult blood. The genital examination should search for adenopathy, masses, discoloration, edema, and crepitus. The pelvic examination in women should check for vaginal discharge or bleeding, cervical discharge or bleeding, cervical mobility and tenderness, uterine tenderness, uterine size, and adnexal tenderness or masses. Although a carefully performed pelvic examination can be invaluable in differentiating nonsurgical conditions (e.g., pelvic inflammatory disease and tubo-ovarian abscess) from conditions necessitating prompt operation (e.g., acute appendicitis), the possibility that a surgical condition is present should not be prematurely dismissed solely on the basis of a finding of tenderness on a pelvic or rectal examination.

Investigative Studies

Laboratory tests and imaging studies rarely, if ever, establish a definitive diagnosis by themselves; however, if used in the correct clinical setting, they can confirm or exclude specific diagnoses suggested by the history and the physical examination.

LABORATORY TESTS

In all patients except those in extremis, a complete blood count, blood chemistries, and a urinalysis are routinely obtained before a decision to operate. The hematocrit is important in that it allows the surgeon to detect significant changes in plasma volume (e.g., dehydration caused by vomiting, diarrhea, or fluid loss into the peritoneum or the intestinal lumen), preexisting anemia, or bleeding. An elevated white blood cell (WBC) count is indicative of an inflammatory process and is a particularly helpful finding if associated with a marked left shift; however, the presence or absence of leukocytosis should never be the single deciding factor as to whether the patient should undergo an operation. A low WBC count may be a feature of viral infections, gastroenteritis, or NSAP. Other tests, such as C-reactive protein assay, may be useful for increasing confidence in the diagnosis of an acute inflammatory condition. An important consideration in the use of any such test is that derangements develop over time, becoming more likely as the illness progresses; thus, serial examinations might be more useful than a single test result obtained at an arbitrary point. Indeed, for the diagnosis of acute appendicitis, serial observations of the leukocyte count and the C-reactive protein level have been shown to possess greater predictive value than single observations.³³

Serum electrolyte, blood urea nitrogen, and creatinine concentrations are useful in determining the nature and extent of fluid losses. Blood glucose and other blood chemistries may also be helpful. Liver function tests (serum bilirubin, alkaline phosphatase, and transaminase levels) are mandatory when abdominal pain is suspected of being hepatobiliary in origin. Similarly, amylase and lipase determinations are mandatory when pancreatitis is suspected, although it must be remembered that amylase levels may be low or normal in patients with pancreatitis and may be markedly elevated in patients

with other conditions (e.g., intestinal obstruction, mesenteric thrombosis, and perforated ulcer).

Urinalysis may reveal red blood cells (RBCs) (suggestive of renal or ureteral calculi), WBCs (suggestive of urinary tract infection or inflammatory processes adjacent to the ureters, such as retrocecal appendicitis), increased specific gravity (suggestive of dehydration), glucose, ketones (suggestive of diabetes), or bilirubin (suggestive of hepatitis). A pregnancy test should be obtained in any woman of childbearing age who is experiencing acute abdominal pain.

Electrocardiography is mandatory in elderly patients and in patients with a history of cardiomyopathy, dysrhythmia, or ischemic heart disease. Abdominal pain may be a manifestation of myocardial disease, and the physiologic stress of acute abdominal pain can increase myocardial oxygen demands and induce ischemia in patients with coronary artery disease.

IMAGING

Until relatively recently, initial radiologic evaluation of the patient with acute abdominal pain included plain films of the abdomen in the supine and standing positions and chest radiographs.³⁴ Currently, CT scanning (when available) is generally considered more likely to be helpful in most situations.^{35,36} Still, some situations remain in which plain films may be a more useful and safe form of investigation—as, for example, when a strangulating obstruction is thought to be the most likely diagnosis and plain films are used for rapid confirmation. If the diagnosis of strangulating obstruction is in doubt, however, CT scanning—particularly with the newer generations of scanning instruments—is useful for making a definitive diagnosis and for identifying clinically unsuspected strangulation.^{37–39}

When performed in the correct clinical setting, imaging studies may confirm diagnoses such as pneumonia (signaled by pulmonary infiltrates); intestinal obstruction (air-fluid levels and dilated loops of bowel); intestinal perforation (pneumoperitoneum); biliary, renal, or ureteral calculi (abnormal calcifications); appendicitis (fecalith); incarcerated hernia (bowel protruding beyond the confines of the peritoneal cavity); mesenteric infarction (air in the portal vein); chronic pancreatitis (pancreatic calcifications); acute pancreatitis (the so-called colon cutoff sign); visceral aneurysms (calcified rim); retroperitoneal hematoma or abscess (obliteration of the psoas shadow); and ischemic colitis (so-called thumbprinting on the colonic wall).

Although in most settings, CT is the preferred modality for primary evaluation of acute abdominal pain, there are certain settings in which US should be considered. When gallstones are considered a likely diagnosis, US is more apt to be diagnostic than CT is, given that about 85% of gallstones are not detectable by x-rays. In disorders of the female genitourinary tract, US is also quite sensitive and specific for diagnoses such as ovarian cyst, fallopian tube pregnancy, and intrauterine pregnancy. Although there are reassuring reports that the risks of radiation from CT scanning can be managed in children and pregnant women with abdominal pain,^{40,41} theoretical concerns remain regarding the teratogenicity of the radiation dose.⁴² Accordingly, it would seem prudent to consider US the preferred initial imaging test for such patients. In these circumstances, CT is employed only if the diagnosis

remains unresolved and if the potential delay in diagnosis (from not obtaining a CT scan) is likely to cause harm.

Working or Presumed Diagnosis

The tentative differential diagnosis developed on the basis of the clinical history is refined on the basis of the physical examination and the investigative studies performed, and a working or presumed diagnosis is generated. Once a working diagnosis has been established, subsequent management depends on the accepted treatment for the particular condition believed to be present. In general, the course of management follows four basic pathways [see Management: Surgical versus Nonsurgical Treatment, *below*], depending on whether the patient (1) has an acute surgical condition that necessitates immediate laparotomy, (2) is believed to have an underlying surgical condition that does not necessitate immediate laparotomy but does call for urgent or early operation, (3) has an uncertain diagnosis that does not necessitate immediate or urgent laparotomy and that may prove to be nonsurgical, or (4) is believed to have an underlying nonsurgical condition.

It must be emphasized that the patient must be constantly reevaluated (preferably by the same examiner) even after the working diagnosis has been established. If the patient does not respond to treatment as expected, the working diagnosis must be reconsidered, and the possibility that another condition exists must be immediately entertained and investigated by returning to the differential diagnosis.

Management: Surgical versus Nonsurgical Treatment

ACUTE SURGICAL ABDOMEN

A thorough but expeditious approach to patients with acute abdominal pain is essential because in some patients, action must be taken immediately and there is not enough time for an exhaustive evaluation. As outlined (see above), such an approach should include a brief initial assessment, a complete clinical history, a thorough physical examination, and targeted laboratory and imaging studies. These steps can usually be completed in less than 1 hour and should be insisted on in the evaluation of most patients. In most cases, it is wise to resist the temptation to rush to the operating room with an incompletely evaluated, unprepared, and unstable patient. Sometimes, the anxiety of the patient or the impatience of the health care providers requesting the surgeon's consultation creates an unwarranted feeling of urgency. Often, however, the anxiety or impatience is on the part of the surgeon and, if indulged, may be a cause of subsequent regret.

Very few abdominal crises mandate immediate operation, and even with these conditions, it is still necessary to spend a few minutes on assessing the seriousness of the problem and establishing a probable diagnosis. Among the most common of the abdominal catastrophes that necessitate immediate operation are ruptured AAAs or visceral aneurysms, ruptured ectopic pregnancies, and spontaneous hepatic or splenic ruptures. The relative rarity of such conditions notwithstanding, it must always be remembered that patients with acute abdominal pain may have a progressive underlying intra-abdominal disorder causing the acute pain

and that unnecessary delays in diagnosis and treatment can adversely affect outcome, often with catastrophic consequences.

SUBACUTE SURGICAL ABDOMEN

When immediate operation is not called for, the physician must decide whether urgent laparotomy or nonurgent but early operation is necessary. Urgent laparotomy implies operation within 4 hours of the patient's arrival; thus, there is usually sufficient time for adequate resuscitation, with proper rehydration and restoration of vital organ function, before the procedure. Indications for urgent laparotomy may be encountered during the physical examination, may be revealed by the basic laboratory and radiologic studies, or may not become apparent until other investigative studies are performed. Involuntary guarding or rigidity during the physical examination, particularly if spreading, is a strong indication for urgent laparotomy. Other indications include increasing severe localized tenderness, progressive tense distention, physical signs of sepsis (e.g., high fever, tachycardia, hypotension, and mental status changes), and physical signs of ischemia (e.g., fever and tachycardia). Basic laboratory and radiologic indications for urgent laparotomy include pneumoperitoneum, massive or progressive intestinal distention, signs of sepsis (e.g., marked or rising leukocytosis, increasing glucose intolerance, and acidosis), and signs of continued hemorrhage (e.g., a falling hematocrit). Additional findings that constitute indications for urgent laparotomy include free extravasation of radiologic contrast material, mesenteric occlusion on angiography, endoscopically uncontrollable bleeding, and positive results from peritoneal lavage (i.e., the presence of blood, pus, bile, urine, or gastrointestinal contents). Acute appendicitis, perforated hollow viscera, and strangulated hernias are examples of common conditions that necessitate urgent laparotomy.

If early operation is contemplated, it may still be prudent to obtain additional studies to obtain information related to the site of the lesion or to associated anatomic pitfalls. In deciding whether to order such studies, it is important to consider not only whether the additional information obtained will increase confidence in the diagnosis but also whether the extra time, expense, and discomfort involved will be justified by the quality and usefulness of the information.⁴³ During a short, defined period of resuscitation, it may be possible to employ CT scanning to identify the location of the inflamed appendix in difficult (i.e., retrocecal or pelvic) locations. Knowing the location of the appendix and its morphology can be helpful in directing the incision in an open operation or determining the most expeditious exposure in a laparoscopic procedure. CT scanning may also be used to identify an atypical site of a visceral perforation (e.g., the proximal stomach, the distal or posterior wall of the duodenum, or the transverse colon), thereby guiding placement of the incision and obviating needless dissection of tissue planes. In the setting of distal bowel obstruction, an expeditious Gastrografin (Bracco Diagnostics, Princeton, NJ) enema or CT scan may alert the surgeon to the possibility of an otherwise undetectable malignancy (e.g., cecal carcinoma causing distal bowel obstruction). In cases in which ischemic bowel is suspected, the site of vascular blockage can be localized by using a CT angiogram imaging protocol. In each of these examples, the information gained may permit the

surgeon to plan the operation, to optimize time spent under anesthesia, and to minimize postoperative discomfort after laparotomy.

The use of preoperative imaging has become increasingly important as an operative planning tool, particularly when laparoscopic approaches are contemplated for management of acute abdominal emergencies. In the 1990s and the first few years of the 21st century, a number of trials were performed to determine whether laparoscopy or open operation should be the approach of choice when the primary clinical diagnosis is acute appendicitis. This topic has been reviewed extensively in the literature^{44–46} and in a 2004 update of a Cochrane meta-analysis.⁴⁷ In some environments, the answer to this question remains unclear.^{48,49} In many settings, however, the current consensus is that uncomplicated appendicitis can be treated laparoscopically, with a clear expectation of less postoperative pain, a shorter hospital stay, and an earlier return to work and regular activities. These advantages, although significant, do not indicate that a laparoscopic approach is to be preferred in all or most clinical settings or that it is necessarily more cost-effective than an open approach.⁴⁷ Laparoscopic appendectomy requires a high level of organization with respect to operating room resources, and this level of organization may be difficult to achieve in institutions where the procedure is not performed regularly (particularly in the middle of the night). In addition, it is not clear whether patients with appendicitis that is complicated by a well-established abscess or bowel obstruction benefit from laparoscopic approaches.

Anatomic considerations also enter into the decision whether to perform the procedure laparoscopically. For instance, it can be very difficult to separate a perforated retrocecal appendix from adherent colon in a safe manner. In many cases, it is prudent not to persist in attempting to extract the appendix without a standard open incision, excellent exposure, and controlled technique. The importance of anatomic considerations underscores the usefulness of preoperative CT in identifying pathologic anatomy, associated abnormalities, and potential pitfalls for either open or laparoscopic approaches.

The advantages of laparoscopy in the management of other abdominal emergencies are less clear-cut. It is important that the surgeon determine not only whether the particular clinical scenario is amenable to a laparoscopic approach but also whether the experience of the entire team and that of the institution as a whole are sufficient for what may be an advanced procedure performed in an acute situation. With this caveat in mind, various investigators have demonstrated that laparoscopy can be employed safely and with good clinical results in selected patients with perforated peptic ulcers.^{50–54} Two prospective, randomized, controlled trials comparing open repair of perforated peptic ulcers with laparoscopic repair found that the latter was safe and reliable and was associated with shorter operating times, less postoperative pain, fewer chest complications, shorter postoperative hospital stays, and earlier return to normal daily activities than the former.^{52,54}

ACUTE ABDOMINAL PAIN REQUIRING OBSERVATION

It is widely recognized that of all patients admitted for acute abdominal pain, only a minority require immediate or urgent operation.^{2,12} It is therefore both cost-effective and prudent to adopt a system of evaluation that allows for thought and investigation before definitive treatment in all

patients with acute abdominal pain except those identified early on as needing immediate or urgent laparotomy. The traditional wisdom has been that spending time on observation opens the door for complications (e.g., perforating appendicitis, intestinal perforation associated with bowel obstruction, or strangulation of an incarcerated hernia). However, clinical trials evaluating active in-hospital observation of patients with acute abdominal pain of uncertain origin have demonstrated that such observation is safe, is not accompanied by an increased incidence of complications, and results in fewer negative laparotomies.⁵⁵ Many institutions now employ CT scanning liberally in patients with uncertain diagnoses; this practice should greatly minimize the incidence of diagnostic failures or delays in patients with acute conditions necessitating surgical intervention.³²

The initial resuscitation and assessment are followed by appropriate imaging studies and serial observation. Specific monitoring measures are chosen (e.g., examination of the abdomen, measurement of urine output, a WBC count, and repeat CT scans), and end points of therapy should be identified. Active observation allows the surgeon to identify most of the patients whose acute abdominal pain is caused by NSAP or by various specific nonsurgical conditions. It must be emphasized that active observation involves more than simply admitting the patient to the hospital and passively watching for obvious problems: it implies an active process of thoughtful, discriminating, and meticulous reevaluation (preferably by the same examiner) at intervals ranging from minutes to a few hours, complemented by appropriately timed additional investigative studies.

A major point of contention in the management of patients with acute abdominal pain is the use of narcotic analgesics during the observation period. The main argument for withholding pain medication is that it may obscure the evolution of specific findings that would lead to the decision to operate. The main argument for giving narcotic analgesics is that in a controlled setting where patients are being observed by experienced clinicians, outcomes are not compromised and patients are more comfortable.⁵⁶ It has also been suggested that providing early pain relief may allow the more critical clinical signs to be more clearly identified⁵⁷ and that severe pain persisting despite adequate doses of narcotics suggests a serious condition for which operative intervention is likely to be necessary.

In my view, the decision whether to provide or withhold narcotic analgesia must be individualized.⁵⁸ The current consensus is that for most patients undergoing evaluation and observation for acute abdominal pain, it is safe to provide medication in doses that would “take the edge off” the pain without rendering the patient unable to cooperate during the observation period. It may be especially desirable to provide medication in a manner that allows the patient to be comfortable while lying in the CT scanner. In these cases, the goal of pain relief is to make it easier to obtain accurate information that will facilitate and expedite the diagnosis and the development of a treatment plan. Given the high diagnostic yield and accuracy of the new generation of CT scanners, it is generally safe to provide pain medication while obtaining the diagnosis.

On occasion, however, reflex administration of pain medication solely with the aim of relieving pain may be undesirable or even harmful. For example, in situations for which advanced

imaging is unavailable, physical examination may be so crucial to decision making that any risk of obscuring important physical findings is deemed unacceptable; therefore, pain medication should be withheld. In addition, narcotic analgesia should be used cautiously in patients with acute intestinal obstruction when strangulation is a concern.⁵⁹ These patients present with abdominal pain that is out of proportion to the physical findings, a syndrome whose differential diagnosis includes acute intestinal ischemia, pancreatitis, ruptured aortic aneurysm, ureteral colic, and various medical causes (e.g., sickle cell crisis and porphyria). A period of resuscitation and evaluation, in conjunction with advanced imaging studies (e.g., CT), may then yield a tentative diagnosis of intestinal obstruction caused by adhesions (e.g., if the patient has a history of abdominal surgery and no evidence of herniation or obturation) without evidence of bowel ischemia. In this setting, the decision whether to admit the patient for observation rather than immediate operation depends on the extent to which the surgeon is confident that the obstruction is not a “closed loop.”⁵⁹ However, within a relatively short period (perhaps 4 to 24 hours), the surgeon must determine whether any indications for operation will arise, and the main parameters for observation include the WBC count, the urine output, and the development of peritoneal findings. In such cases, it may well be prudent to withhold pain medication until there is a high level of confidence that the timing of surgery will not be delayed.

A final point is that over the course of a 24- to 48-hour observation period, the patient’s condition may neither deteriorate nor improve, and supplemental investigation may be considered. Diagnostic laparoscopy has been recommended in cases in which surgical disease is suspected but its probability is not high enough to warrant open laparotomy.^{60,61} It is particularly valuable in young women of childbearing age, in whom gynecologic disorders frequently mimic acute appendicitis.^{62–64} A 1998 report showed that diagnostic laparoscopy had the same diagnostic yield as open laparotomy in 55 patients with acute abdomen; 34 (62%) of these patients were safely managed with laparoscopy alone, with no increase in morbidity and with a shorter average hospital stay.⁶³ Diagnostic laparoscopy has also been shown to be useful for assessing acute abdominal pain in acutely ill patients in the intensive care unit.^{60,65}

In patients with AIDS,^{66,67} a number of unusual diagnoses may be related to or coincident with an episode of abdominal pain. The differential diagnosis includes lymphoma, Kaposi sarcoma, tuberculosis and variants thereof, and opportunistic bacterial, fungal, and viral (especially cytomegaloviral) infections. Laparoscopy has been used for the purposes of diagnosis, biopsy, and treatment in patients with an established AIDS diagnosis who manifest acute abdominal pain syndrome.^{66,67} The complication rate and mortality associated with surgery are related to the underlying illness, and outcomes have improved steadily over the years.⁶⁸ It is important to note that patients who are infected with HIV but have no clinical manifestations of AIDS are evaluated and managed in the same fashion as patients without HIV infection when they present with acute abdominal pain. The differential diagnosis and the outcomes are essentially no different, unless there are reasons to think that the new onset of pain in an HIV-infected patient is a manifestation of AIDS.^{58,68}

Subacute or Chronic Relapsing Abdominal Pain: Role of Outpatient Evaluation and Management

For every patient who requires hospitalization for acute abdominal pain, at least two or three others have self-limiting conditions for which neither operation nor hospitalization is necessary. Much or all of the evaluation of such patients, as well as any treatment that may be needed, can now be completed in the outpatient department. To treat acute abdominal pain cost-effectively and efficiently, the surgeon must be able not only to identify patients who need immediate or urgent laparotomy or laparoscopy but also to reliably identify those whose condition does not present a serious risk and who therefore can be managed without hospitalization. The reliability and intelligence of the patient, the proximity and availability of medical facilities, and the availability of responsible adults to observe and assist the patient at home are factors that should be carefully considered before the decision is made to evaluate or treat individuals with acute abdominal pain as outpatients.

SUSPECTED NONSURGICAL ABDOMEN

Numerous disorders cause acute abdominal pain but do not call for surgical intervention. These nonsurgical conditions are often extremely difficult to differentiate from surgical conditions that present with almost indistinguishable characteristics.² For example, the acute abdominal pain of lead poisoning or acute porphyria is difficult to differentiate from the intermittent pain of intestinal obstruction in that marked hyperperistalsis is the hallmark of both. As another example, the pain of acute hypolipoproteinemia may be accompanied by pancreatitis, which, if not recognized, can lead to unnecessary laparotomy. Similarly, acute and prostrating abdominal pain accompanied by rigidity of the abdominal wall and a low hematocrit may lead to unnecessary urgent laparotomy in patients with sickle cell anemia crises. To further complicate the clinical picture, cholelithiasis is also often found in patients with sickle cell anemia.

In addition to numerous extraperitoneal disorders [see Table 2], nonsurgical causes of acute abdominal pain include a wide variety of intraperitoneal disorders, such as acute gastroenteritis (from enteric bacterial, viral, parasitic, or fungal infection), acute gastritis, acute duodenitis, hepatitis, mesenteric adenitis, salpingitis, Fitz-Hugh–Curtis syndrome, mittelschmerz, ovarian cyst, endometritis, endometriosis, threatened abortion, spontaneous bacterial peritonitis, and tuberculous peritonitis. As noted (see above), acute abdominal pain in immunosuppressed patients or patients with AIDS is now encountered with increasing frequency and can be caused by a number of unusual conditions (e.g., cytomegalovirus enterocolitis, opportunistic infections, lymphoma, and Kaposi sarcoma), as well as by the more usual ones.

Although such disorders typically are not treated by operative means, operation is sometimes required when the diagnosis is uncertain or when a surgical illness cannot be excluded with confidence. In such cases, laparoscopy can be very helpful, permitting relatively complete and systematic exploration without involving the potential morbidity or the longer postoperative recovery and rehabilitation period associated with open exploration.^{69–72} From the surgeon’s point of view, an optimal outcome for laparoscopic exploration in these settings is one in

which a diagnosis is established by means of visualization, with or without biopsy, and in which symptoms improve as a consequence of a therapy directed by the laparoscopic findings. Overall, candidate lesions—including appendiceal pathology (e.g., chronic appendicitis or carcinoid tumor), adhesions, hernias, endometriosis, mesenteric lymphadenopathy—are identified in about 50% of cases, with pelvic adhesions being the most common finding. From the patient's point of view, however, establishing a precise diagnosis may not be particularly critical, and symptomatic improvement, by itself, may suffice to render the outcome successful. Indeed, a number of reports have emphasized that laparoscopy often leads to improvement in symptoms even if no lesion is identified or treated.^{69,70} This point may be illustrated by considering pelvic adhesions.

Given the frequency with which laparoscopic exploration identifies pelvic adhesions, adhesiolysis might be expected to alleviate abdominal pain in many cases. However, it is unclear whether adhesiolysis is therapeutically beneficial when there is no firm evidence that the adhesions are contributing to the pain syndrome. In one prospective, randomized trial, 100 patients with laparoscopically identified adhesions were randomly allocated to either a group that underwent adhesiolysis or one that did not.⁷³ Both groups reported substantial pain relief and a significantly improved quality of life, but there were no differences in outcome between them, which suggested that the benefit of laparoscopy could not be attributed to adhesiolysis. Longer-term studies also failed to support the hypothesis that pelvic adhesions are responsible for chronic pelvic pain.⁷⁴ However, in a study conducted concurrently with the aforementioned randomized trial, 224 consecutive patients underwent laparoscopically assisted adhesiolysis, and 74% of the 224 obtained short-term relief.⁷⁵ Factors that contributed to a successful outcome were gender, age, and adhesions severe enough to have led to inadvertent

enterotomy and a consequent need for open exploration. It may, therefore, be possible to identify specific subgroups that would benefit from the addition of adhesiolysis to exploratory laparoscopy.

A similar issue arises with respect to pathologic conditions of the appendix—namely, whether appendectomy should be performed when no other source of the abdominal pain can be identified. Early enthusiasm for appendectomy in patients with chronic right lower quadrant pain was sparked by observations of acute or chronic inflammation in specimens that seemed visibly normal.^{76,77} In subsequent reports, however, this enthusiasm was tempered by the recognition that these pathologic findings were not very prevalent and that appendectomy did not always reduce the pain.^{78,79} No randomized trial of appendectomy for chronic abdominal pain has been performed in a clearly defined patient group, as has been done for adhesiolysis.⁷³

At present, the surgeon can only use his or her best judgment as to the likelihood that a given episode of abdominal pain may originate from a set of visible adhesions or a visually normal appendix. It should be remembered that unnecessary or potentially meddlesome interventions are always best avoided; however, it should also be remembered that failure to alleviate chronic relapsing abdominal pain will lead to a program of chronic pain management, including long-term management with potentially addictive and enervating agents. Thus, if adhesiolysis or appendectomy can be performed with the expectation of low morbidity and without conversion to laparotomy, it seems reasonable to perform these procedures during laparoscopy if no other source of pain can be identified.

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2 ABDOMINAL MASS

Wilbur B. Bowne, M.D., and Michael E. Zenilman, M.D., F.A.C.S.

Evaluation of an Abdominal Mass

Abdominal masses are commonly addressed by surgeons, as well as by members of many clinical subspecialties. In terms of clinical importance, abdominal masses cover a broad spectrum: some have few or no apparent consequences, others significantly impair quality of life, and still others represent severe conditions that are associated with poor outcomes and high mortalities. For each patient, therefore, it is essential to formulate a management approach that is tailored to the particular clinical situation. Effective decision-making in this regard involves establishing the correct diagnosis, introducing an effective treatment plan, eliminating risks and complicating factors, initiating preventive measures, and determining the prognosis.

The history of the abdominal mass in the medical literature is ancient, dating back to the Egyptians. The varied differential diagnosis of such masses was discussed in the Papyrus Ebers (ca. 1500 B.C.).¹ Egyptian medical scholars kept detailed notes chronicling conditions encountered and describing methods of abdominal examination that were based on studies of basic anatomy and embalming practices. Centuries later, in his *Book of Prognostics*, the Greek physician Hippocrates (ca. 400 B.C.) discussed the prognostic significance of various types of abdominal masses:

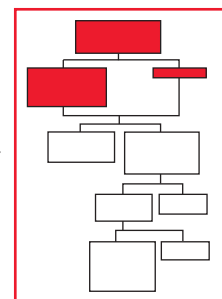
The state of the hypochondrium is best when it is free from pain, soft, and of equal size on the right side and the left. But if inflamed, or painful, or distended; or when the right and left sides are of disproportionate sizes; all of these appearances are to be dreaded. A swelling in the hypochondrium, that is hard and painful, is very bad.... Such swellings at the commencement of disease prognosticate speedy death. Such swellings as are soft, free from pain, and yield to the finger, occasion more protracted crises, and are less dangerous than others.²

Along with the basic methods of clinical evaluation known since antiquity, the modern surgeon has an armamentarium of sophisticated diagnostic studies that aid in the detection, diagnosis, and appropriate treatment of abdominal masses.

In this chapter, we begin with essential definitions and anatomic considerations and then outline our fundamental approach to evaluating patients with an abdominal mass, which integrates the clinical history, the physical examination, and various investigative studies. In particular, we address current developments in investigative techniques, including radiographic and molecular imaging studies that facilitate anatomic evaluation, diagnosis, and determination of the biologic significance of the abdominal mass; we also address minimally invasive diagnostic interventions. Throughout, we emphasize an algorithmic, evidence-based approach to detection and evaluation of abdominal masses. Specific perioperative and operative strategies for addressing particular diagnoses are outlined in other chapters.

Clinical Evaluation

In general, the term abdominal mass refers to a palpable mass that lies anterior to the paraspinal muscles in a region bordered by the costal margins, the iliac crests, and the pubic symphysis. One method of description divides the abdomen into nine areas: epigastric, umbilical, suprapubic, right hypochondriac, left hypochondriac, right lumbar, left lumbar, right inguinal, and left inguinal.³ Our preferred method

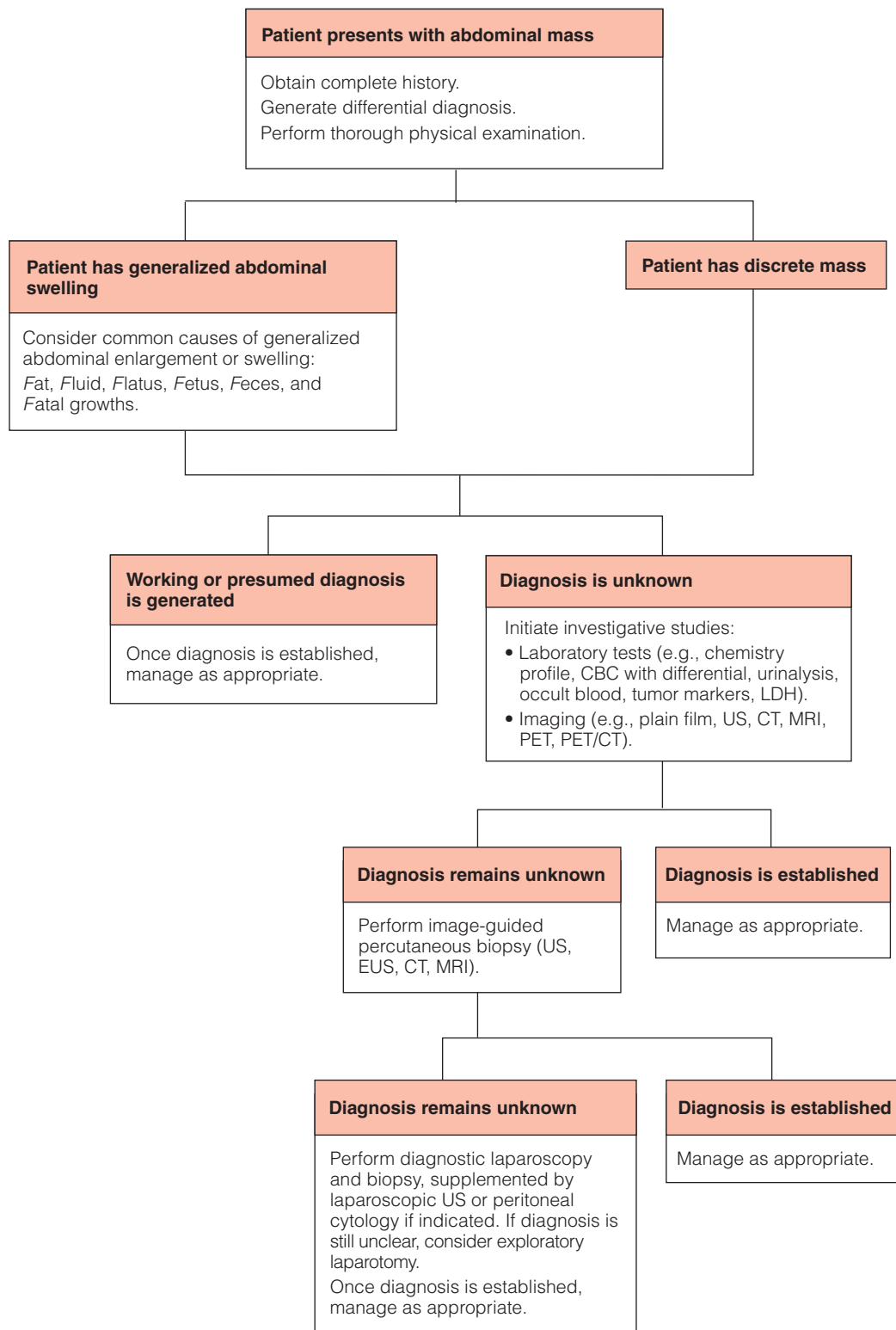


divides the abdominal cavity into four quadrants—right upper, right lower, left upper, and left lower—and makes specific reference to the epigastrium and the hypogastrium as necessary. This method of description also includes masses discovered within the retroperitoneum and the abdominal wall. For practical purposes, the abdominal wall begins from the diaphragm superiorly and continues inferiorly to the pelvic cavity through the pelvic inlet. The anterior, posterior, and lateral boundaries of the abdominal wall should be familiar to surgeons. Further anatomic detail is available in other sources.^{4,5}

A sound understanding of the normal anatomy in each abdominal quadrant is essential for the evaluation of the abdominal mass. Particular abnormalities tend to be associated with particular regions or quadrants of the abdomen, and these associations should be considered first in the differential diagnosis. Commonly, an abnormal enlargement or mass in the abdomen comes to the clinician's attention in one of three ways: it is detected and reported by the patient, it is discovered by the clinician on physical examination, or it is noticed as an unrelated incidental finding on a radiographic study. Subsequent clinical decision making is then influenced by whether the lesion is intra-abdominal, pelvic, retroperitoneal, or situated within the abdominal wall. In certain cases, a prompt diagnosis can be made after the physical examination, with no further investigation required; obesity, ascites, pregnancy, hernias, infection or abscess, cysts, and lipomas are examples of conditions that can generally be diagnosed at this point.

Of the various factors that go into making the diagnosis and implementing therapy, clinical experience is undoubtedly paramount. Nevertheless, even the most experienced physicians are subject to some degree of clinical inaccuracy. A randomized study from 1981 found that even when experienced clinicians were certain about the presence of a mass, there was still an appreciable (22%) chance that further investigation would not reveal any abnormality.⁶ The evaluation of abdominal masses continues to pose many clinical challenges for the surgeon. There is no magical

Evaluation of an Abdominal Mass



formula for mastering the necessary diagnostic skills; the closest thing to such a formula is an approach that combines knowledge and application of fundamental anatomic principles with continuous development and appropriate utilization of new diagnostic modalities. For accurate assessment of the origin and character of the abdominal mass, it is essential to possess a thorough understanding of the normal anatomy, the anatomic variations that may be observed, and the distortions that may be caused by the various potential disease processes. As has been said of many professions besides surgery, "You must know the territory." Ultimately, whether a correct diagnosis calls for further intervention or for referral to colleagues with complementary technical expertise depends on the experience of the practitioner.

Fundamental to the successful diagnosis of any abdominal mass are a detailed medical and surgical history and a meticulous physical examination (see below).

HISTORY

Establishing a solid surgeon-patient relationship is vital for building patient trust and confidence, particularly during a period of great uncertainty and vulnerability in the patient's life. Accordingly, our philosophy in dealing with an abdominal mass is to evaluate the patient first and then consider radiographic and laboratory studies if the initial assessment does not yield a diagnosis. A careful and methodical clinical history should be taken that includes all factors pertaining to the lesion. Information about the lesion's mode of onset, duration, character, chronology, and location should be obtained, as well as confirmation of the presence or absence of associated symptoms.

Interviewing strategies for collecting clinical data may vary from surgeon to surgeon.⁷ For example, some prefer to conduct a clinical history while sitting rather than standing because this posture tends to suggest the absence of undue haste and the presence of appropriate concern and empathy. A focused, comprehensive interview usually provides all the information necessary for making the correct diagnosis. Our practice is to start by asking nondirective questions—for example, "When did you first notice the mass on your left side?" or "How long did you experience this pain in your abdomen?" It is important to allow patients to describe the history in their own words. It is also important to avoid questions with a built-in degree of bias—for example, "Didn't you know the mass was on your left side?" or "The pain must have been there for some time?" Such questions can lead to biased answers that may misrepresent the chronology or the true natural history of the disease. In most cases, we then proceed to ask questions designed to elicit more specific information (e.g., previous operations, previous medical conditions or therapies, family medical history, or recent travel). It is sometimes necessary to fill in the details by asking direct questions about particular points not already mentioned by the patient. For example, an inquiry regarding gastrointestinal symptoms associated with the abdominal mass may be either non-specific (e.g., concerned with nausea, vomiting, diarrhea, or constipation) or specific (e.g., concerned with jaundice, melena, hematochezia, hematemesis, hematuria, or changes in stool caliber). Non-GI symptoms (including urologic, gynecologic or obstetric, vascular, and endocrinologic symptoms) should not be overlooked. A history of surgery, trauma, or neoadjuvant or adjuvant cancer therapy may be diagnostically important.⁸ For instance, the presence of an abdominal mass representing recurrent cancer raises important clinical questions concerning the advisability of additional therapy or palliative measures, which may carry significant morbidity and mortality.⁹⁻¹²

DIFFERENTIAL DIAGNOSIS

For practical purposes, the differential diagnosis for an abdominal mass is divided into categories corresponding to the anatomic divisions of the abdomen (i.e., the four quadrants, the epigastrium, and the hypogastrium) [see *Figure 1*]. The challenge for the modern surgeon is how to narrow down the diagnostic possibilities while avoiding needlessly extensive and expensive evaluations. To accomplish this goal with efficiency, the surgeon must draw both on his or her own reservoir of fundamental knowledge and on the available patient data (e.g., age, gender, associated symptoms, and comorbidities).

After obtaining a thorough clinical history, the surgeon should be able to generate a differential diagnosis. The physical examination may then help confirm or rule out diagnostic possibilities. For example, the presence or absence of pain or tenderness may distinguish an inflammatory or nonneoplastic process from a neoplastic one (e.g., cholecystitis from Courvoisier gallbladder or, perhaps, diverticulitis from carcinoma of the colon). Likewise, the acuteness of the condition may help eliminate diagnostic possibilities, as when an incarcerated abdominal wall hernia is distinguished from a lipomatous mass. So too may the nature of the process, as when a pulsatile mass such as an aneurysm is distinguished from a nonpulsatile one such as a hematoma or a cyst.

Masses of the abdominal wall commonly are subcutaneous lipomas, and care should be taken to differentiate them from neoplastic lesions such as desmoid tumors,¹³ dermatofibrosarcoma protuberans (DFSP),¹⁴ and other related¹⁵ or nonrelated tumors.^{16,17} When an abdominal mass is associated with uncommon or unexpected findings, the surgeon must be alert to the possibility of an uncommon or unexpected disease process.^{18,19} It remains true, however, that knowledge of the most common disease processes associated with region-specific abdominal masses, combined with familiarity with the characteristic signs and symptoms, is the foundation of the clinical assessment of such masses.

PHYSICAL EXAMINATION

The physical examination plays an essential role in the evaluation and workup of an abdominal mass. Current investigative studies are also important in this setting, but all too often, clinicians become overly reliant on various imaging modalities, sometimes overlooking the importance of a careful and thorough examination. Such overreliance can increase the chances of missing subtle physical findings—such as an enlarged lymph node, subcutaneous irregularity, or referred pain—that could have a significant effect on the management of the abdominal mass. Our practice in examining patients with an abdominal mass is to follow an organized, systematic approach consisting of inspection, auscultation, percussion, and palpation, in that order. More detailed discussions of these specific maneuvers are available elsewhere.²⁰

The physical examination has three main objectives. First, the examiner must evaluate the patient's condition as it directly or indirectly relates to the mass (e.g., by noting associated systemic illness, pain, malaise, or cachexia). Second, the examiner must assess the acuteness of the patient's condition (e.g., by determining whether a left upper quadrant mass is likely to be a ruptured spleen or simply a long-standing mass in the abdominal wall), which will dictate whether the next step is immediate treatment or further evaluation. Third, the examiner must carefully examine each abdominal quadrant, assessing both normal and abnormal anatomic relations as possible sources of the presumed mass.

How to distinguish a normal abdominal mass or swelling from an abnormal one remains a common challenge for the surgeon.

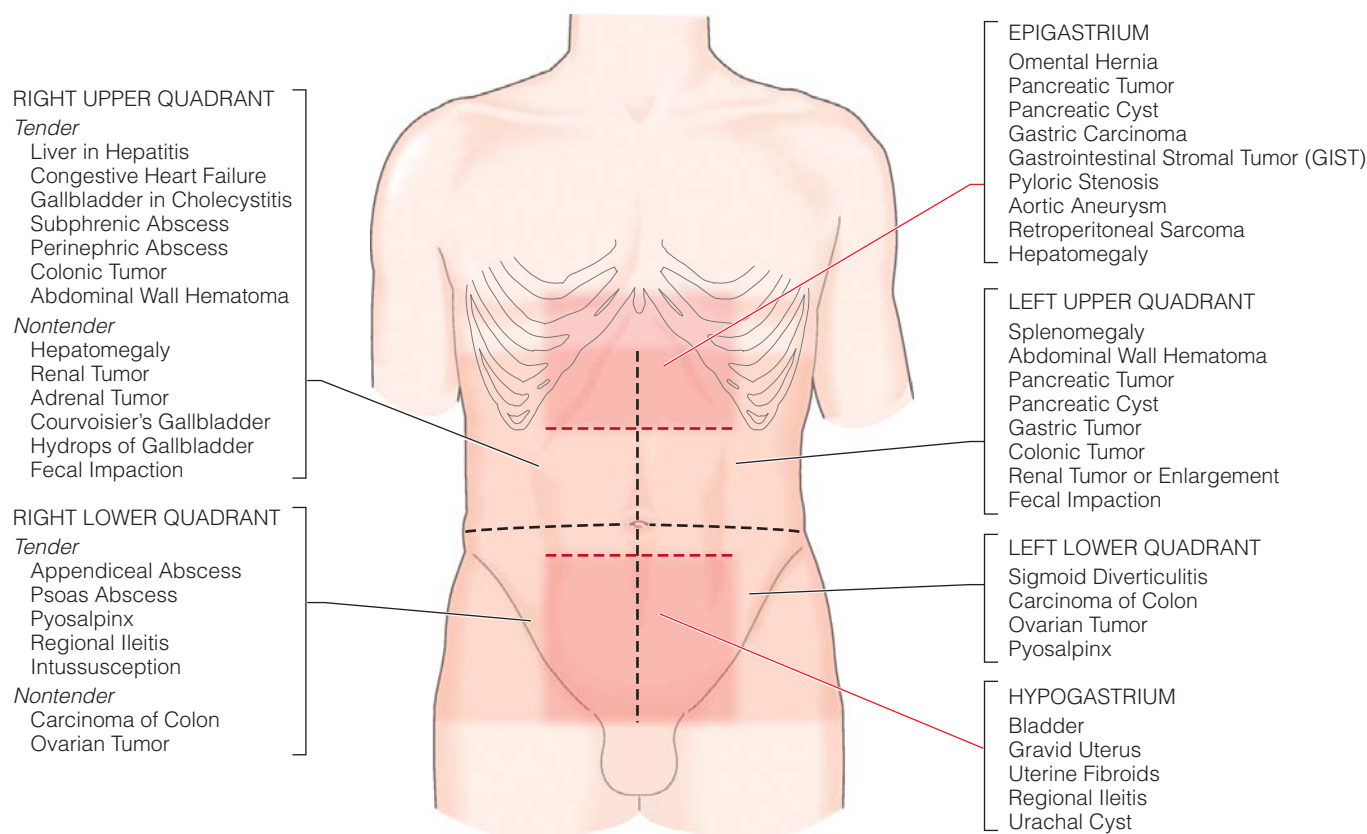


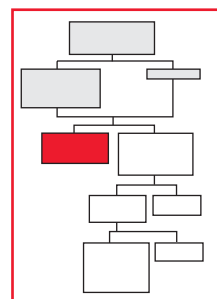
Figure 1 Schema represents differential diagnosis of an abdominal mass by quadrant or region. Fundamental knowledge of normal anatomy and clinical presentations is the basis for distinguishing the various disease processes. Abdominal wall hernia is considered a possibility in every region or quadrant.

Physical findings on examination are sometimes variable and can be affected by factors such as obesity, body habitus, associated medical conditions, and the patient's ability to cooperate. For example, the normal aorta is often palpable within the epigastrium and may be slightly tender; in elderly, asthenic patients, the normal aorta may be mistaken for an aneurysm. Likewise, the cecum and the descending colon, both of which are usually palpable in thin patients (especially when they contain feces), sometimes masquerade as a cancerous mass; subsequent disimpaction causes such "masses" to resolve. Obesity may preclude evaluation of a potential abdominal mass: it can be difficult to identify discrete palpable masses amid the often remarkable adiposity present within the abdominal wall and the surrounding structures. Ascites may also obscure abdominal masses, making examination more problematic. Transient gaseous distention or intestinal bloating occasionally presents a similar problem, but it usually resolves spontaneously, except in cases of intestinal obstruction. Either gastric dilatation or intestinal obstruction may lead to abdominal distention that is severe enough to necessitate nasogastric decompression. Not uncommonly, in women of childbearing age, a lower abdominal mass may represent a gravid uterus. In such cases, a gynecologic examination must be conducted and a pregnancy test performed before further studies are ordered. The multiplicity of potential benign causes notwithstanding, the possibility of a neoplasm (single or multiple) clearly remains a matter of considerable concern in the evaluation of any patient with abdominal distention. A convenient method of recalling the main causes of generalized enlargement or distention of the abdomen is to use the so-called "six Fs" mnemonic device: *Fat, Fluid, Flatus, Fetus, Feces, and Fatal growths.*²¹⁻²³

Palpable or discrete masses should always be localized with respect to the previously described landmarks (see above), and they should, if possible, be described in terms of size, shape, consistency, contour, presence or absence of tenderness, pulsatility, and fixation. Knowledge of the location of the mass in the abdomen shortens the list of structures or organs to be considered and may give insight into the nature and extent of the pathologic process. Frequently, however, the mass's location can only be vaguely outlined, particularly when fluid is present, when the abdomen is tender or tense, or when the patient is obese. Gastric neoplasms, pancreatic neoplasms, colonic neoplasms, sarcomas, pancreatic cysts, and distended gallbladders may be palpable, typically at advanced stages of disease. Recognition of such masses can be facilitated by repeating the abdominal examination after analgesics have been administered or after the patient has been anesthetized in preparation for a procedure.

Working or Presumed Diagnosis

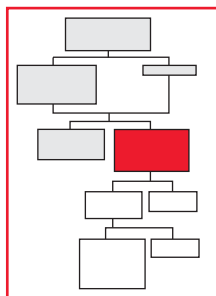
Once a thorough clinical history has been obtained and a careful physical examination conducted, it is usually possible to generate a working diagnosis. Once the working diagnosis has been established, subsequent management is considered in light of its appropriateness for the presumed condition. Sometimes, however, the diagnosis remains unknown even after a comprehensive clinical history and physical examination; in such cases, further studies are required. A wide range of laboratory and imag-



ing studies are now available for establishing the diagnosis. If these studies do not resolve the diagnostic uncertainty, additional procedures, including image-guided percutaneous biopsy, diagnostic laparoscopy, and exploratory laparotomy, may be employed as necessary.

Investigative Studies

Surgeons are in a unique position to care for patients presenting with an abdominal mass and should guide the collaborative management effort and the choice of appropriate investigative studies. It is therefore essential that surgeons be familiar with every available method for efficient and cost-effective diagnosis of an abdominal mass. For any given situation, the selection of investigative studies should be based on the preferences of the patient, the knowledge and judgment of the surgeon, and the capabilities of the institution. In this way, surgeons who practice outside large, specialized referral centers will still be able to provide integral leadership for most disease management efforts arising from the diagnosis of an abdominal mass.



LABORATORY STUDIES

The diagnostic workup of an abdominal mass usually includes laboratory evaluation. If the cause of the mass remains unknown, preliminary laboratory analysis should include a chemistry profile (electrolyte, blood urea nitrogen [BUN], and creatinine concentrations, as well as liver function tests), a complete blood count (CBC) with differential, and urinalysis. An abnormal laboratory value sometimes plays an important role in establishing the identity or pathogenesis of an abdominal mass. For example, an elevated alkaline phosphatase or liver transaminase level may suggest metastasis to the liver. Likewise, an elevated serum amylase concentration may be suggestive of a pancreatic pseudocyst rather than a cystic neoplasm or an adenocarcinoma; however, an elevated total serum bilirubin level (i.e., > 10 mg/dl) may be more suggestive of a malignant process secondary to adenocarcinoma of the pancreatic head or cholangiocarcinoma. Routine testing for occult blood in the stool should not be overlooked. Tumor markers (e.g., carcinoembryonic antigen [CEA], the cancer antigens CA 19-9 and CA 125, and α -fetoprotein [AFP]) may also help differentiate between benign disease processes and malignant ones, distinguish high-level disease from low-level disease, and, in some cases, establish a disease diagnosis (e.g., elevated AFP levels in patients with hepatocellular carcinoma). Similarly, an elevated serum lactate dehydrogenase (LDH) level may prove invaluable in the staging and prognosis of certain diseases (e.g., melanoma) connected with an abdominal mass.²⁴ Furthermore, the ability to distinguish between functional abdominal masses and nonfunctional ones (e.g., adrenal tumors) also has important implications for evaluation and management.

In some cases, when the type of mass remains unknown, needless and expensive laboratory analysis can and should be avoided if it appears that other studies may prove more beneficial.

IMAGING

Diagnostic radiology is a dynamic specialty that has undergone rapid change in conjunction with the ongoing evolution of imaging technology. Not only has the number of imaging modalities increased, but each modality continues to be

improved and refined for use in evaluating abdominal masses. In particular, advances in cross-sectional imaging techniques, such as ultrasonography (US), computed tomography, magnetic resonance imaging, and positron emission tomography (PET), have made it possible to assess these lesions more precisely. Consequently, whenever the surgeon is confronted with the scenario of a clinically suspected or palpable abdominal mass, accurate diagnostic imaging is of paramount importance. The appropriate use of different imaging modalities in the evaluation of the palpable abdominal mass is well described by the American College of Radiology guidelines,^{25,26} which are updated every 6 years.

The use of noninvasive US and CT as first-line procedures for the evaluation of palpable masses has received considerable clinical attention.^{6,27-30} Investigators have found both US and CT to be excellent for affirming or excluding a clinically suspected abdominal mass, with sensitivity and specificity values exceeding 95%. This finding is particularly noteworthy because in only 16% to 38% of patients referred for a suspected abdominal mass will the diagnosis be corroborated by an imaging study.³¹ Both US and CT are also capable of visualizing the organ from which the mass arises: US successfully determines the organ of origin approximately 88% to 91% of the time, and CT does so approximately 93% of the time. Prediction of the pathologic diagnosis of an abdominal mass, however, remains a challenge for both modalities. US correctly predicts the pathologic diagnosis in 77% to 81% of cases, whereas CT suggests the diagnosis in 88% of cases. Further advancements in cross-sectional imaging (e.g., multidetector CT [MDCT] with three-dimensional reconstruction and magnetic resonance angiography [MRA]) and the addition of molecular and functional imaging modalities (e.g., PET) will undoubtedly improve the predictive abilities of CT and US. At any rate, the current state of imaging technology affords clinicians the ability to distinguish benign from malignant processes, to assess tumor biology, and to detect lesions that impose a minimal disease burden. As a consequence, clinicians are more likely to detect clinically occult disease or discover it incidentally.

Employing an integrative assessment approach (which includes clinical history, physical examination, and investigative studies) should lead to more targeted, efficient, and cost-effective strategies for evaluating abdominal masses. For example, the surgeon can correlate the clinical location of the abdominal mass with pertinent findings from the history and laboratory studies to determine which imaging modality is the most expeditious and cost-effective for a given circumstance. Each imaging modality has unique strengths and weaknesses.

Plain Abdominal Radiographs

By definition, a plain film is a radiograph made without the use of an artificially introduced contrast substance.³² Commonly employed for initial surveillance of the abdomen, the plain film still has an important place within the investigative armamentarium. Otherwise known as a KUB (kidney-ureter-bladder) study, this low-cost technique may reveal nonspecific or indirect evidence of an abdominal mass, such as variations in the size and density of an organ or displacement of normal structures or fat planes. Furthermore, the radiolucency of air within the bowel may also prove helpful for recognizing worrisome displacement of viscera as a result of a large abdominal mass. Occasionally, a simple plain radiograph can assist the surgeon in making a specific diagnosis, such as calcified aortic aneurysm, acute gastric distention, fecal impaction, porcelain gallbladder, and certain malignancies [see Figure 2].



Figure 2 Plain abdominal radiograph shows a 10 cm functional left adrenocortical carcinoma. Calcifications creating a rim enhancement are easily identified. The diagnosis was confirmed by means of laboratory analysis and abdominal CT.

Conventional Gastrointestinal Imaging

As a consequence of the technical advances in cross-sectional imaging and endoscopy, conventional GI contrast studies are now largely relegated to more adjunctive roles in the evaluation of abdominal masses. In the upper and middle portions of the abdomen, we occasionally use upper GI studies, small bowel follow-through (SBFT), or enteroclysis to evaluate inflammatory masses (e.g., lesions arising from Crohn disease), masses that are inaccessible to endoscopy, or unusual masses with uncertain diagnoses. For such lesions, we employ single- or double-contrast barium protocols to ensure that significant pathology is not missed; however, these studies are notoriously insensitive and do not provide an opportunity for tissue diagnosis. In the lower portion of the abdomen, barium studies still play a significant role in the evaluation of masses whose history includes GI symptoms (e.g., anemia and weight loss) suggestive of a colonic neoplasm, as well as for evaluating inflammatory masses arising from diverticular disease. In certain cases, we employ a single-contrast barium enema for masses that are causing near-complete obstruction; this study is also helpful for assessing the remaining large bowel for synchronous disease. For small lesions (masses < 1 cm), we typically favor a double-contrast barium enema.

Currently, in the evaluation of an abdominal mass, barium studies are used mainly to complement colonoscopy and CT.

Novel approaches (e.g., CT virtual colonoscopy), in conjunction with advances in cross-sectional imaging, may eventually render conventional GI imaging unnecessary.

Ultrasonography

Compared with other modalities, US has several advantages in the evaluation of suspected abdominal masses, including widespread availability, speed of use, the absence of ionizing radiation, low cost, and the ability to document the size, consistency (solid or cystic), and origin of a mass with real-time images.^{27,33} When directed at solving a specific clinical problem, US generally provides more diagnostic information. Moreover, the necessary equipment can easily be transported to the patient's bedside or another clinical setting; thus, no patient preparation is required, and only minimal patient cooperation is needed.

We consider US indispensable in the assessment of abdominal masses. At the same time, we acknowledge that one disadvantage of US is the extent to which the quality of the results depends on the technical proficiency and diligence of the operator or technician (though this disadvantage can actually become an advantage when personnel are well trained and experienced). In the hands of an inexperienced operator, US may yield inconclusive or untrustworthy results that contribute to delayed diagnosis or even misdiagnosis. In an effort to help minimize this problem, we encourage the surgeons at our institution (who are trained in US) to perform their own studies in the clinic and the operating room. This approach further expedites recognition of disease [see Figure 3], positively influences management, and facilitates operative decision making regarding abdominal masses [see Figure 4].

Another disadvantage of US is its inability to visualize the entire abdominal cavity as a consequence of the acoustic barriers presented by gas-containing structures (e.g., the bowel) and the absorptive interfaces (acoustic shadowing) provided by soft tissue and bone. For optimal visualization of abdominal masses, US should be performed through "acoustic windows" that allow adequate transmission of sound. Accordingly, US is most effective as a tool for evaluating masses in those regions of the abdomen where an acoustic window exists (e.g., the right and left upper quadrants and the



Figure 3 Sagittal ultrasonogram of the pancreas demonstrates a large mass in the pancreatic head of a 71-year-old patient referred for "gallstones" after experiencing a 10 lb weight loss. The mass lies anterior to the inferior vena cava.

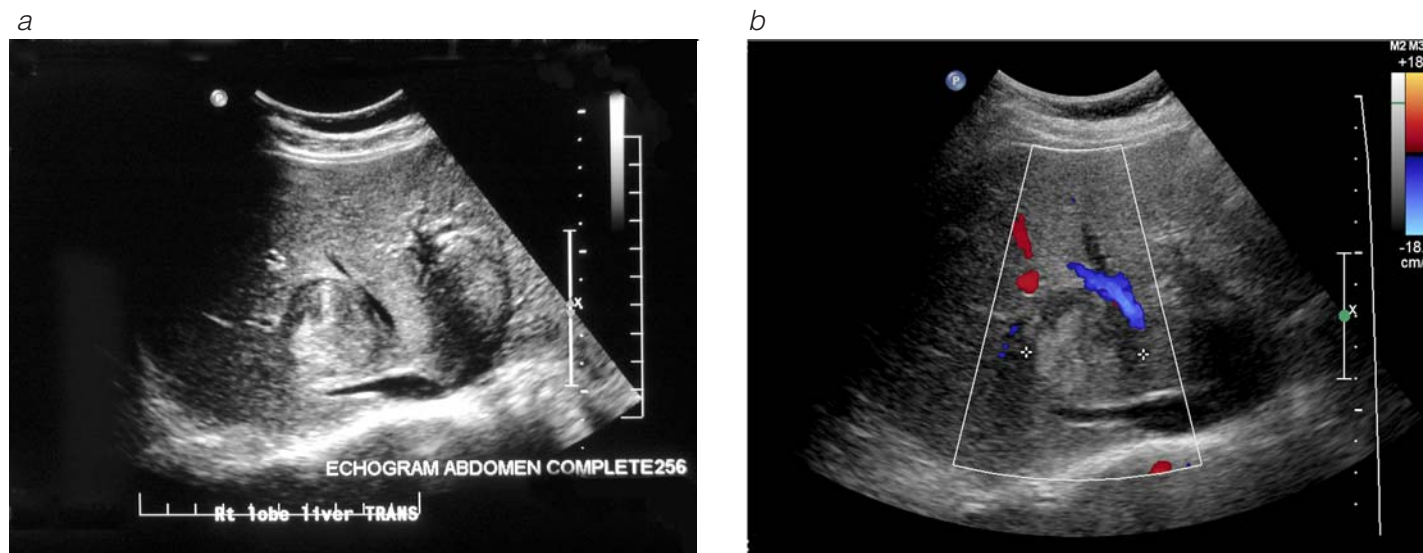


Figure 4 (a) Transverse ultrasonogram of the liver of a 72-year-old cirrhotic patient with a hepatitis C infection shows a 4.0 × 3.5 cm hepatoma, nestled between the right and middle hepatic veins and closely apposed to the inferior vena cava. (b) Color Doppler ultrasonogram from the same patient displays blood flow in the middle hepatic vein and the surrounding liver parenchyma. Blood flow toward the transducer is usually displayed in shades of red, whereas blood flow away from the transducer is displayed in shades of blue. Color Doppler ultrasonography allows evaluation of the patency and flow characteristics of the hepatic circulation as it relates to the mass.

pelvis). Fortunately, the shortcomings of US can be compensated for by employing other cross-sectional imaging modalities.

Computed Tomography

At present, helical (spiral) CT is the most efficient and cost-effective imaging modality for the evaluation of abdominal masses.^{6,27,34,35} Unlike US, CT provides cross-sectional images with excellent spatial resolution and exquisite density discrimination that are unaffected by bowel gas, bone, or excessive abdominal fat. CT routinely visualizes the abdominal wall, the viscera, the mesentery, and the retroperitoneum, clearly defining important tissue planes

and delineating the relations between the abdominal mass and adjacent structures [see Figure 5]. Such data are essential for guiding diagnostic procedures, determining whether operative management is indicated, and selecting the optimal operative approach. Although modalities such as MRI, PET, and endoscopic ultrasonography (EUS) have advantages over CT in one area or another, CT continues to be superior overall for assessing abdominal masses and remains our preferred imaging method for this purpose.

The use of contrast during the acquisition of CT scans is vital. Opacification of the bowel enables the examiner to distinguish the abdominal mass from surrounding viscera or other adjacent structures. Contrast-enhanced scans also allow delineation of the relevant vascular anatomy; in fact, CT angiography has now relegated conventional angiography to a minimal role in the evaluation of certain abdominal masses.^{36,37} Triple-phase or multiphase scanning that includes noncontrast images is now recommended. Such scans achieve optimal definition and characterization of liver and pancreatic masses. This achievement is of significant clinical value: state-of-the-art CT imaging of malignant pancreatic masses, as well as of other malignancies, has the potential to improve outcome not only by correctly detecting the mass but also by accurately assessing the extent of disease, thereby helping determine which patients may benefit from surgical management or neoadjuvant therapy [see Figure 6].

The advent of MDCT technology offers the possibility of even better imaging of abdominal masses than standard contrast CT provides. MDCT scanners can image specific organs or masses with 1 mm slices in less than 20 seconds, and the resultant data can be displayed not only as an axial image but also in a three-dimensional representation that includes detailed vascular mapping.³⁵ Studies suggest that MDCT may be the most useful modality for preoperative assessment of the resectability of pancreatic and other abdominal masses.³⁶ MDCT has a sensitivity of 90% and a specificity of 99%, respectively, and it is not observer dependent.

Currently, although MRI (see below) offers unique tissue contrast and inherent multiplanar capabilities for imaging abdominal

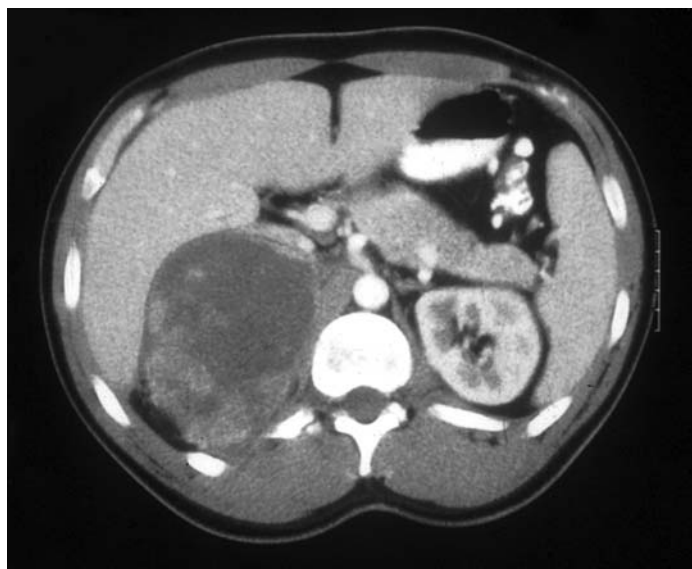


Figure 5 CT scan of a 65-year-old man with a large retroperitoneal leiomyosarcoma clearly demonstrates close association of this mass with the right hemiliver, as well as displacement of the inferior vena cava.

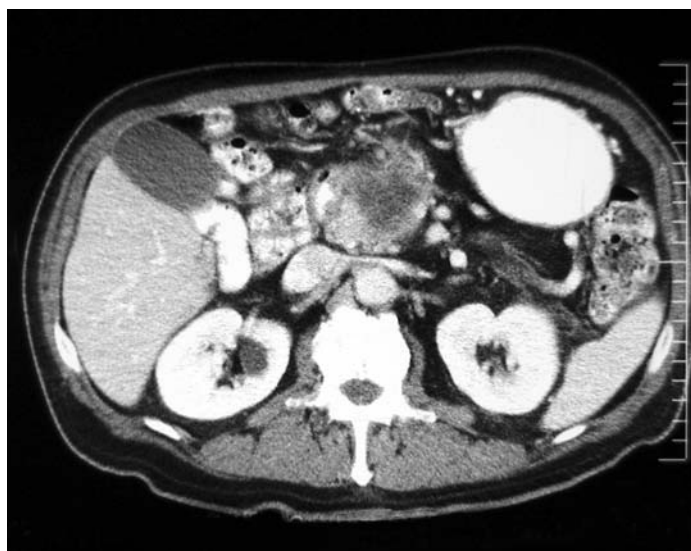


Figure 6 CT angiography performed to evaluate vascular invasion in a 58-year-old patient with a pancreatic mass demonstrates nearly complete encasement of the superior mesenteric vein. The superior mesenteric artery is not involved with the mass.

masses, CT has several advantages—high resolution, short scan times, and fast patient throughput—that make it a more widely preferred imaging modality for this purpose.

Magnetic Resonance Imaging

Since its introduction in the mid-1980s, MRI has become one of radiology's great success stories (though, because it still is not as widely available as US or CT, its cost-effectiveness has yet to be determined). Few would dispute the enormous impact MRI has had on our ability to diagnose pathologic conditions of the brain, the spine, and the musculoskeletal system. Whereas MRI has clear advantages over CT in these areas of the body, this is not the case in the abdomen. Nevertheless, there are situations in which MRI

is a better choice than CT for evaluating an abdominal mass. An example is a case in which the use of iodinated contrast material is contraindicated. The extracellular gadolinium chelates used in MRI are very safe and can be given to patients with mild to moderate azotemia without causing renal impairment. MRI has unique characteristics that can be effectively employed to distinguish normal from pathologic tissue in a patient with an abdominal mass.³⁸

Detailed information about the principles and practices of abdominal MRI is beyond the scope of this chapter and is readily available elsewhere.³⁹ A brief technical summary may, however, be worthwhile. The abdomen and its contents are subjected to a momentary radiofrequency pulse, then allowed to return to a state of equilibrium. During the return to equilibrium, the nuclei within each specific tissue will emit specific radiofrequency signals. The strength and type of the emitted signal determine the image intensity. The way in which the different tissues are visually rendered depends on (1) the longitudinal relaxation time (T_1) and the transverse relaxation time (T_2) of the nuclei in the tissues and (2) the method of image weighting employed. By convention, tissues with short T_1 values (such as solid structures) appear bright on T_1 -weighted images, whereas structures with long T_2 values (e.g., fluid-containing tissues) appear bright on T_2 -weighted images. The tissue contrast and multiplanar capabilities of MRI allow surgeons and radiologists to distinguish not only obvious but also subtle differences between abdominal masses and normal anatomy. For example, T_1 -weighted images may be valuable for detecting abdominal masses that contain fluid (e.g., cystic masses or masses containing necrotic tissue), whereas T_2 -weighted images may be useful for characterizing these masses as either benign or malignant [see Figure 7]. Similarly, magnetic resonance cholangiopancreatography (MRCP) uses T_2 -weighted images to distinguish masses with different signal intensities in the pancreas, the liver, and the biliary tract.⁴⁰

Positron Emission Tomography

In 1930, Warburg reported that cancer cells show higher rates of glycolysis than normal cells do.⁴¹ This discovery has stood the

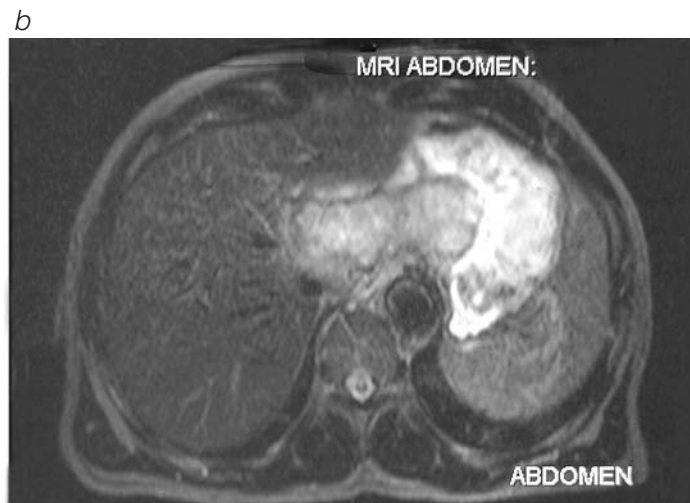


Figure 7 (a) Gadolinium-enhanced, T_1 -weighted MRI shows a large mass that appears dark and well-circumscribed in comparison with the normal-appearing enhanced liver and spleen. This abnormal mass clearly contains some fluid. The fluid-filled stomach also appears dark. (b) T_2 -weighted MRI of the same patient details subtle inhomogeneities characteristic of a malignant mass (less organized appearance with an enhanced necrotic component). Subsequent biopsy showed this mass to be a poorly differentiated adenocarcinoma from recurrent colon cancer.



Figure 8 ^{18}F FDG PET scan demonstrates a large metabolically active non-Hodgkin lymphoma giving rise to an abdominal mass.

test of time and now serves as the theoretical rationale for the use of ^{18}F -fluorodeoxyglucose (^{18}F FDG) PET imaging to assess abdominal masses caused by cancer. Briefly, ^{18}F FDG is a glucose analogue that crosses the cell membrane by sharing the glucose transporter molecules used by glucose. Like glucose, it undergoes phosphorylation by the enzyme hexokinase. The resulting molecule, ^{18}F FDG-6-phosphate, is polar and is unable to cross cell membranes or serve as a substrate for metabolism. The net effect is that ^{18}F FDG both accumulates in and is retained by cancer cells.

The molecular information obtained from PET, as measured by standard uptake values (SUV), allows identification of hypermetabolic (^{18}F FDG-avid) abdominal masses (typically arising from lymphomas, melanomas, or certain GI malignancies [see Figure 8]).⁴² PET may also prove to be an important surrogate modality for distinguishing malignant abdominal masses from benign ones.⁴³ When PET is used alone, it has the disadvantage of being unable to provide sufficient anatomic information to guide biopsy or further therapy. When PET is used with CT in PET/CT fusion imaging, however, the functional advantages of PET and the structural advantages of CT combine to enhance the detection rate for abdominal masses.⁴² If a mass is anatomically evident but metabolically inactive, it will be detected by CT. If it shows increased glycolysis but few or no CT abnormalities, it will be detected by PET. The apparent advantages of PET/CT notwithstanding, prospective, randomized validation is necessary before the widespread application of this approach to the evaluation of abdominal masses can be justified. At present, the use of PET/CT is mostly restricted to large tertiary referral centers.

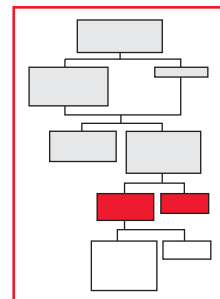
BIOPSY

In many cases, the pathologist is the surgeon's greatest teacher. Despite the surgeon's most strenuous efforts, the biology of the disease or lesion will inevitably dictate the outcome. Nowhere is this statement more true than in the evaluation of the abdominal mass, and its truth becomes increasingly evident as ongoing refinements in molecular diagnosis permit ever more sophisticated discrimination among different tumor types and their respective behaviors.⁴⁴ Aside from the treatment of lymphoma, in which the surgeon is frequently called on to provide technical assistance in obtaining tissue for diagnosis, the decision whether to perform a biopsy (as well as when and how to do so) rests on the surgeon's understanding of the probable disease. For example, surgeons who treat pancreatic cancer usually proceed to surgery without biopsy if the evidence for malignancy is strong. In other cases, biopsy is performed to confirm what is already suspected on the basis of clinical and radiographic findings. Moreover, establishing the type of tumor or mass present has important implications for the use of neoadjuvant or adjuvant therapy, as well as for the planning of the surgical approach. We view the biopsy of an abdominal mass as the first stage of surgery. This procedure, though seemingly innocuous, has the potential to contaminate tissue planes and must therefore be performed carefully. Accordingly, in order to make the appropriate choice when confronted with an abdominal mass, the surgeon must possess a thorough understanding of the various methods of obtaining an accurate and safe biopsy. Factors related to the size and location of the abdominal mass, as well as factors related to institutional preference and experience, may influence the choice of biopsy technique.

Image-Guided Percutaneous Biopsy

The value of image-guided percutaneous biopsy in the evaluation of the abdominal mass is well established.^{45,46} In practice, the procedure begins with identification of the mass by means of a cross-sectional imaging modality such as US, CT, or MRI. Often, three-dimensional imaging reconstructions are generated to detail the relations of the abdominal mass to the surrounding anatomy. Once the mass is identified, decisions are made regarding the safest approach and the most appropriate technique. The biopsy needle is then inserted percutaneously under the guidance of US, CT, or MRI. The choice among the different modalities depends on several factors, including the size and location of the mass, the surgeon's judgment regarding which method is best in the circumstances, and the availability of the various modalities at a particular institution. The most important consideration, however, is the personal preference and experience of the radiologist performing the biopsy. We favor either US or CT, both of which yield good results.

In general, we prefer US-guided biopsy for large, superficial, and cystic masses. This technique is also appropriate for lesions lying at moderate depths in thin to average-size persons. In some cases, US can be employed to guide biopsy of small, deep, and solid abdominal masses; however, US-guided biopsy of these deep-seated masses (as well as of masses in obese patients) often proves difficult because of inadequate visualization resulting from sound attenuation in the soft tissues. Similarly, lesions located within or behind bone or gas-filled bowel cannot be easily visualized (a consequence of the nearly complete reflection of sound from bone or air interfaces).



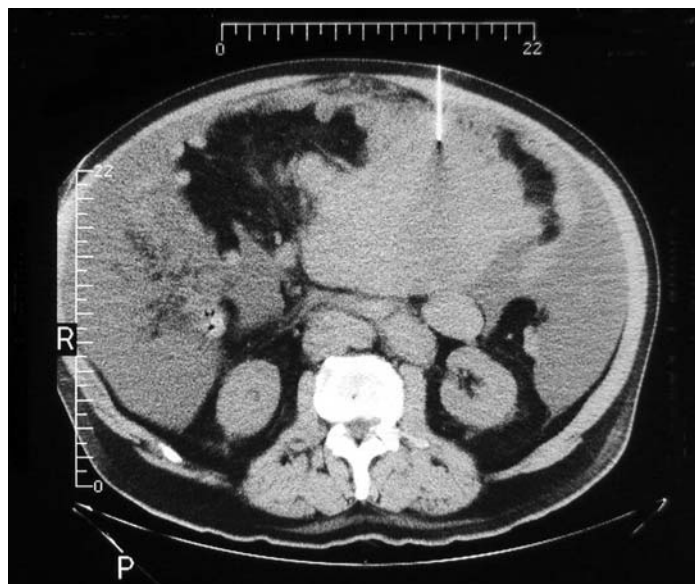


Figure 9 In a percutaneous biopsy of a large abdominal mass, CT guidance is a reliable means of determining the direction and depth of the needle.

US possesses several strengths as a guidance modality for percutaneous biopsy. It is readily available, inexpensive, and portable, and it provides guidance in multiple transverse, longitudinal, or oblique planes. Moreover, it offers real-time visualization of the needle tip as it passes through tissue planes into the target area,⁴⁷ thereby allowing the surgeon to place the needle precisely and to avoid important intervening structures. In addition, color flow Doppler imaging can help prevent complications of needle placement by identifying the blood vessels involved with the mass, as well as any vessels lying within the needle path. Because of its real-time capabilities, US guidance has the potential to allow quicker, more accurate, and less expensive biopsies than CT guidance does.⁴⁸ In theory, any mass that is well visualized with US should be amenable to US-guided biopsy. In practice, however, this modality remains best suited for superficial to moderately deep abdominal masses and for patients with a thin to average body habitus.

The utility of US notwithstanding, CT remains indispensable at our institution as a guidance method for percutaneous biopsy of most regions in the body. It is particularly useful when an abdominal mass is in a location that is inaccessible to US as a result of bowel gas or body habitus. In the abdomen, CT provides excellent spatial resolution of all structures between the skin and the mass, regardless of body habitus or lesion depth, and it provides an accurate image of the needle tip. We favor CT guidance for abdominal masses that are located deep in the abdomen or in the retroperitoneum. The only limitation of CT in this setting is that it does not offer continuous visualization of the needle during insertion and biopsy. In most cases, however, CT guidance can reliably establish the direction and depth of the needle [see Figure 9].

Numerous different needles, covering a broad spectrum of calibers, lengths, and tip designs, are commercially available for use in percutaneous image-guided fine-needle aspiration (FNA) biopsy. For convenience, these needles can be grouped into two main size categories: small caliber (20 to 25 gauge) and large caliber (14 to 19 gauge). Small-caliber needles are used primarily for cytologic analysis but may also be employed to obtain small pieces of tissue for histologic analysis. The flexible shaft of small-caliber needles allows them to be passed with minimal risk of tissue or organ

laceration or of damage from tearing. Such needles are often used to confirm tumor recurrence or metastasis in patients with a pathologically confirmed primary malignancy. Large-caliber needles are typically used to obtain greater amounts of material for histologic or cytologic analysis.⁴⁹ In practice, the choice of a biopsy needle is often influenced by whether the suspected pathology is benign or malignant. For example, large-caliber needles may be necessary to obtain a sufficiently large histologic specimen when certain types of malignancies (e.g., lymphoma) are suspected. When an inflammatory mass is suspected and material is needed for culture, however, a small-caliber needle may be preferred.

Additional considerations for image-guided biopsy include the accuracy, safety, and potential complications of the proposed technique. These considerations are essential for an evidence-based approach to diagnosis of an abdominal mass.

The reported accuracy of US-guided biopsy ranges from 66% to 97%. The location, size, and histologic origin of the abdominal mass appear to influence the diagnostic accuracy of the procedure.⁴⁷ In a series that included 126 consecutive small (< 3 cm) solid masses distributed among various anatomic locations and histologic types, US-guided biopsies showed an overall accuracy of 91%.⁴⁷ Biopsy results improved as the size of the mass increased: accuracy rose from 79% in masses 1 cm or less in diameter to 98% in masses 2 to 3 cm in diameter. The accuracy of US-guided biopsy in the liver, where most of the biopsies were performed, exceeded 96%. Another study found US-guided biopsy to be 91% accurate for abdominal masses less than 2.5 cm in diameter.⁵⁰ Two organ-specific reviews concluded that US-guided biopsy of hepatic masses had an accuracy of 94%⁵¹ and that US-guided biopsy of pancreatic masses had an accuracy of 95%.⁵²

The reported accuracy of CT-guided biopsy ranges from 80% to 100%. As with US-guided biopsy, the size, location, and histologic origin of the mass influence the results.⁵³⁻⁵⁵ In a study of 200 consecutive CT-guided needle biopsies, the overall accuracy for all sites biopsied was 95%. The reported organ-specific accuracy was as follows: kidneys, 100%; liver, 99%; retroperitoneum, 87.5%; and pancreas, 82%.⁵⁶ In a prospective study of 1,000 consecutive CT-guided biopsies, the reported sensitivity was 91.8% and the specificity 98.9%.⁵⁵ At our institution, as well as others, CT-guided biopsy is now considered a reliable tool for the diagnosis and classification of malignant abdominal lymphomas.⁵⁷

The safety of image-guided percutaneous biopsy is well documented. Several large multi-institutional reviews reported major complication rates ranging from 0.05% to 0.18% and mortalities ranging from 0.008% to 0.031%.⁵⁸⁻⁶⁰ A large prospective study of 3,393 biopsies (1,825 US-guided; 1,568 CT-guided) documented an overall mortality of 0.06%, a major complication rate of 0.34% (0.3% with US; 0.5% with CT), and a minor complication rate of 2.9% (2.4% with US; 3.3% with CT).⁴⁷ Procedure-related morbidity and mortality appear to be largely unaffected by whether a small-caliber or a large-caliber biopsy needle is used. A review of 11,700 patients who underwent percutaneous abdominal biopsy with 20- to 23-gauge needles found an overall complication rate of only 0.05% and an overall mortality of only 0.008%.⁵⁸ A single-institution review of 8,000 US-guided needle biopsies performed with both small- and large-caliber needles reported equivalent results: a major complication rate of 0.187% and a mortality of 0.038%.⁶¹ Of the rare major complications that occur, hemorrhage is the most frequently reported; pneumothorax, pancreatitis, bile leakage, peritonitis, and needle track seeding may also develop.

Needle-track seeding remains an important theoretical consideration when an abdominal mass appears likely to be malignant. According to some investigators, percutaneous needle biopsy has

the potential to seed between 10^3 to 10^4 tumor cells into the needle track.^{62,63} Nevertheless, tumor dissemination after percutaneous biopsy remains exceedingly rare: with fewer than 100 cases reported in the world literature, it has an estimated frequency of 0.005%,⁶⁴⁻⁶⁶ mostly occurring after biopsy of pancreatic, hepatic, or retroperitoneal masses. Poorly planned biopsies of malignant abdominal masses have the potential to exert adverse effects on subsequent surgery and to compromise local tumor control; fortunately, such negative consequences remain rare.

EUS-Guided Imaging and Biopsy

EUS provides unique imaging information because it involves the close apposition of a high-frequency ultrasound transducer, called an echoendoscope (whereby image resolution is directly related to frequency), to the structures being studied. As a result, it can delineate abdominal masses and associated structures with greater anatomic detail than standard transcutaneous ultrasonography can. In general, EUS-guided biopsy is well suited for abdominal masses that are too small for visualization by means of other cross-sectional imaging modalities or that are inaccessible to percutaneous biopsy.⁶⁷ The most frequently used EUS device is the radial echoendoscope, which creates a 360° tomographic image perpendicular to the scope. The circumferential view obtained with this instrument facilitates orientation and therefore is more efficient for diagnostic imaging. Alternatively, the linear-array echoendoscope, which generates an image parallel to the shaft of the scope, may be used. This instrument produces high-quality gray-scale images, as well as color and duplex images. EUS-guided biopsy with a linear scanning system offers clear and consistent visualization of the biopsy needle along its entire path in real time, with excellent delineation of intervening tissues and without any interference from intestinal gas.

EUS has proved to be superior to other cross-sectional imaging modalities for detection and staging of pancreatic, gastric, and esophageal masses.⁶⁸⁻⁷¹ For instance, in a patient with a pancreatic mass, EUS not only identifies the size of the mass and the peripancreatic lymph nodes but also delineates the relations of these structures to major blood vessels. EUS has also proved to be helpful in selecting patients for various neoadjuvant protocols. Furthermore, the availability of high-frequency catheter-based intraductal ultrasonography (IDUS) now enables surgeons to visualize masses within the biliary tree and obtain biopsy specimens from them.⁷²

Advantages notwithstanding, EUS technology has several important limitations. As with all forms of ultrasonography, a substantial period is required before the operator achieves proficiency. EUS is highly operator dependent; when it is done by an inexperienced operator, the potential exists for serious misinterpretations. For example, if an operator obtains only one view of a mass in the head of the pancreas, the mass may appear to be invading vascular structures when it is not actually doing so. In the evaluation of pancreatic masses around vessels, the operator should always obtain multiple views. It cannot be overemphasized that EUS and EUS-guided biopsy require personnel with sufficient experience and skill in both ultrasonography and endoscopy.

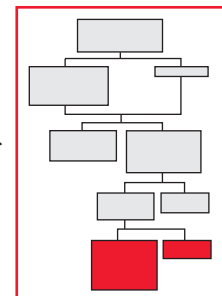
EUS is frequently employed for diagnosis and staging of upper GI malignancies. In a large single-institution study of 267 pancreatic masses that were sampled by means of EUS-guided biopsy and subsequently resected, the overall diagnostic accuracy was 95.6%, the sensitivity was 94.6%, and the specificity was 100%.⁷³ In studies of gastric and esophageal masses, diagnostic accuracy was related to the location of the biopsy,⁷⁴ the histology of the dis-

ease,⁷⁵ and the number of samples obtained. In one series that included more than 200 patients with esophageal or gastric masses, a diagnosis was made in 70% of patients after the first biopsy, 95% of patients after the fourth biopsy, and 98.9% of patients after the seventh biopsy.⁷⁶ Several other studies have confirmed the high sensitivity and specificity of EUS-guided biopsy (especially for the diagnosis of extraluminal abdominal masses) and verified the safety of the procedure (reported complication rates range from 0.3% to 2%).^{68-71,77} It is worth noting that in the resection of a potentially curable abdominal mass, concern about needle-track contamination is obviated when the path of the needle is removed as part of the surgical specimen (as in pancreaticoduodenectomy for a pancreatic head mass or gastrectomy for a stomach mass).

We consider EUS-guided biopsy for the diagnosis of masses that are not readily accessible to percutaneous biopsy, on the grounds that it can obviate more invasive procedures (e.g., laparoscopy and laparotomy). In a 10-year study of the impact of EUS on patient management, 86% of patients required no further imaging, and 25% were able to avoid unnecessary laparotomy.⁷⁷ Overall, EUS changed clinical management significantly in as many as one third of the 537 patients studied.⁷⁷ Nevertheless, despite the high diagnostic yield achieved with EUS-guided biopsy, results that are negative for tumor should not always be interpreted as proving that no tumor is present; laparoscopic or open biopsy may still be indicated.

DIAGNOSTIC LAPAROSCOPY

The available evidence now clearly supports the role of laparoscopy in the diagnosis and management of abdominal masses. We and others advocate the liberal use of laparoscopy as a primary staging tool for upper and lower GI malignancies, believing it to be a safe, cost-effective tool that offers a clear benefit in more than 20% of patients with these diseases.^{78,79} Preventing unnecessary laparotomy in selected patients by performing diagnostic laparoscopy is associated with shorter hospital stays and earlier initiation of locoregional or systemic therapy. Moreover, laparoscopic ultrasonography⁸⁰ and peritoneal cytology⁸¹ are known to provide added value in the staging of disease. Furthermore, diagnostic laparoscopy can safely provide tissue samples from suspected lymphomatous masses for full diagnostic analysis.⁸² With the growth of dedicated minimally invasive fellowships and the improved quality and availability of laparoscopic training for general surgery residents and related subspecialties, the skill sets required for diagnostic laparoscopy are coming to be more widely mastered, and the concerns once commonly expressed regarding intra-abdominal adhesions and effective biopsy techniques for abdominal masses now appear to be less problematic.



Indications for Exploratory Laparotomy

Advances in diagnostic imaging, endoscopy, and minimally invasive surgery have nearly eliminated the need for open exploration for the sole purpose of establishing a diagnosis in patients with an abdominal mass. In selected cases, however, exploratory laparotomy may still help in the assessment of abdominal masses that were initially misinterpreted on preoperative evaluation. In general, exploratory laparotomy should be reserved for those rare instances in which other modalities have failed to yield crucial information needed for evaluation and diagnosis of an abdominal mass.

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Acknowledgments

Figure 1 Tom Moore.

Figure 2 Courtesy of Bimal C. Ghosh, M.D., F.A.C.S.

3 JAUNDICE

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Approach to the Jaundiced Patient

The term “jaundice” refers to the yellowish discoloration of skin, sclerae, and mucous membranes that results from excessive deposition of bilirubin in tissues. It usually is unmistakable but, on occasion, may manifest itself subtly. Jaundice develops when serum bilirubin levels rise above 34.2 mmol/L (2 mg/dL)¹; however, the appearance of jaundice also depends on whether it is conjugated or unconjugated bilirubin that is elevated and on how long the episode of jaundice lasts.

In what follows, we outline a problem-based approach to the jaundiced patient that involves assessing the incremental information provided by successive clinical and laboratory investigations, as well as the information obtained by means of modern imaging modalities. We also propose a classification of jaundice that stresses the therapeutic options most pertinent to surgeons. We have not attempted a detailed review of bilirubin metabolism and the various pediatric disorders that cause jaundice; such issues are beyond the scope of this chapter. Finally, we emphasize that modern decision making in the approach to the jaundiced patient includes not only careful evaluation of anatomic issues but also close attention to patient morbidity and quality-of-life concerns, as well as a focus on working up the patient in a cost-effective fashion. For optimal treatment, in our view, an integrated approach that involves the surgeon, the gastroenterologist, and the radiologist is essential.

Clinical Evaluation and Investigative Studies

HISTORY AND PHYSICAL EXAMINATION

When a patient presents with a skin discoloration suggestive of jaundice, the first step is to confirm that icterus is indeed present. To this end, the mucous membranes of the mouth, the palms, the soles, and the sclerae should be examined in natural light. Because such areas are protected from the sun, photodegradation of bile is minimized; thus, the yellowish discoloration of elastic tissues may be more easily detected. Occasionally, deposition of a yellowish pigment on skin may mimic jaundice but may, in fact, be related to the consumption of large quantities of food containing lycopene or carotene or drugs such as rifampin or quinacrine. In these cases, the skin is usually the only site of coloration, and careful inspection of

sclerae and mucous membranes generally reveals no icteric pigmentation. In certain cultures, long-term application of tea bags to the eyes may lead to a brownish discoloration of the sclerae that can mimic jaundice (M. Jabbari, personal communication, 1994).

DIRECT VERSUS INDIRECT HYPERBILIRUBINEMIA

Once the presence of jaundice has been confirmed, further clinical assessment determines whether the hyperbilirubinemia is predominantly direct or indirect. This distinction is based on the division of bilirubin into conjugated and unconjugated fractions, which are also known, respectively, as direct and indirect fractions on the basis of their behavior in the van den Bergh (diazo) reaction.² If the patient has normal-colored urine and stools, unconjugated bilirubin [see *Sidebar Unconjugated (Indirect) Bilirubin*] is predominant [see *Table 1*]. If the patient has dark urine, pale stools, or any other signs or

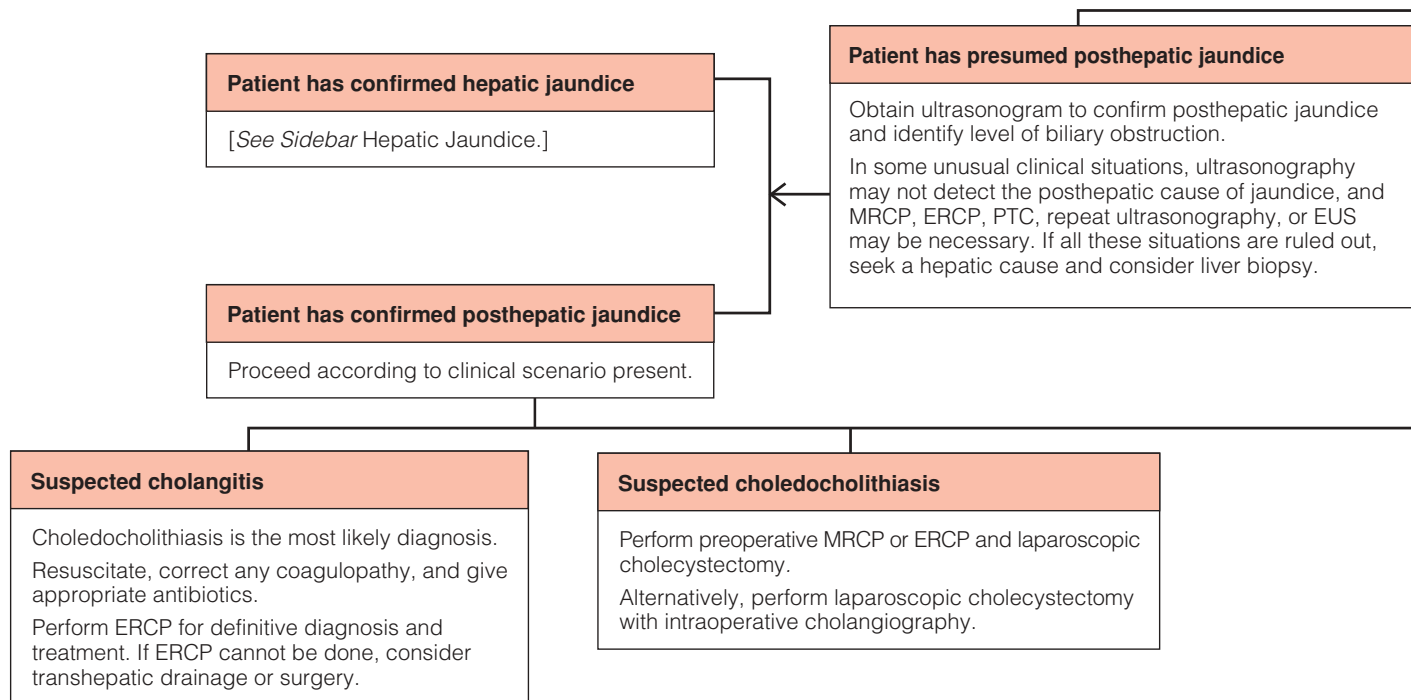
Unconjugated (Indirect) Bilirubin

The breakdown of heme leads to the production of unconjugated bilirubin, which is water insoluble, is tightly bound to albumin, and does not pass into the urine. Excessive production of unconjugated bilirubin typically follows an episode of hemolysis. In the absence of concomitant liver disease or biliary obstruction, the liver can usually handle the extra bilirubin, and only a modest rise in serum levels is observed. There is a substantial increase in bile pigment excretion, leading to large quantities of stercobilinogen in the stool. A patient with hemolysis may therefore be slightly jaundiced with normal-colored urine and stools. Blood tests reveal that 60 to 85% of bilirubin is indirect.¹²⁷

Possible causes of indirect hyperbilirubinemia include a variety of disorders that result in significant hemolysis or ineffective erythropoiesis. The diagnosis of indirect hyperbilirubinemia attributable to hemolysis is confirmed by an elevated serum lactate dehydrogenase (LDH) level, a decreased serum haptoglobin level, and evidence of hemolysis on microscopic examination of the blood smear.

Disorders associated with defects in hepatic bilirubin uptake or conjugation can also produce unconjugated hyperbilirubinemia. The most common of these, Gilbert syndrome, is a benign condition affecting up to 7% of the general population.^{128,129} It is not a single disease but a heterogeneous group of disorders, all of which are characterized by a homozygosity for a defect in the promoter controlling the transcription of the UDP glucuronyl transferase I gene.¹³⁰ The consequent impairment of bilirubin glucuronidation presents as a mild unconjugated hyperbilirubinemia. The elevated bilirubin level is usually detected on routine blood testing, and affected patients may report that their skin turns yellow when they are fatigued or at stressful times (e.g., after missing meals, after vomiting, or in the presence of an infection). Other causes of an unconjugated hyperbilirubinemia are beyond the scope of this chapter.

Approach to the Jaundiced Patient



MRCP = magnetic resonance cholangiopancreatography; ERCP = endoscopic retrograde cholangiopancreatography; PTC = percutaneous transhepatic cholangiography; EUS = endoscopic ultrasonography; CT = computed tomography; MRI = magnetic resonance imaging; MRA = magnetic resonance angiography.

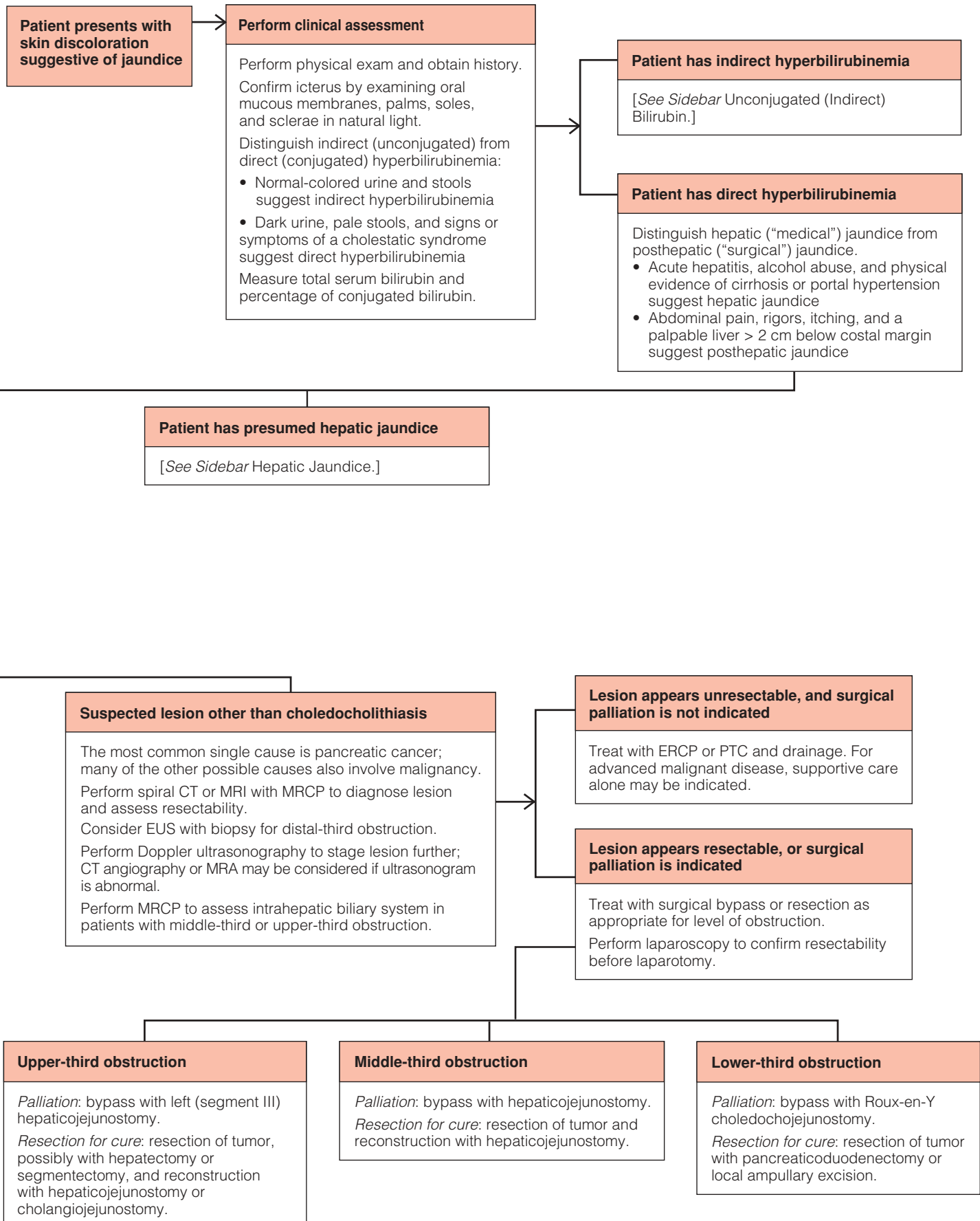


Table 1 Causes of Unconjugated Hyperbilirubinemia

Increased RBC breakdown
Acute hemolysis
Chronic hemolytic disorders
Large hematoma resorption, multiple blood transfusions
Gilbert syndrome
Decreased hepatic bilirubin conjugation
Gilbert syndrome
Crigler-Najjar syndrome types I and II
Familial unconjugated hyperbilirubinemia

RBC = red blood cell.

symptoms of a cholestatic syndrome (see below), the serum bilirubin fractionation usually indicates that conjugated bilirubin is predominant. Rarely, the clinical picture may be secondary to a massive increase in both direct and indirect bilirubin production after the latter has overcome the ability of the hepatocytes to secrete conjugated bilirubin.

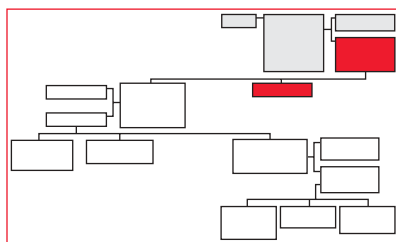
It is nearly always possible to distinguish between direct and indirect hyperbilirubinemia on clinical grounds alone.³ Our emphasis here is on direct hyperbilirubinemia, which is the type that is more relevant to general surgeons.

Cholestatic Syndrome

The term “cholestasis” refers to decreased delivery of bilirubin into the intestine (and subsequent accumulation in the hepatocytes and in blood), irrespective of the underlying cause. When cholestasis is mild, it may not be associated with clinical jaundice. As it worsens, a conjugated hyperbilirubinemia develops that presents as jaundice. The conjugated hyperbilirubinemia may derive either from a defect in hepatocellular function (hepatic jaundice, also referred to as nonobstructive or medical jaundice) or from a blockage somewhere in the biliary tree (posthepatic jaundice, also referred to as obstructive or surgical jaundice). In this chapter, we refer to hepatic and posthepatic causes of jaundice, reserving the term cholestasis for the specific clinical syndrome that is attributable to a chronic lack of delivery of bile into the intestine. This syndrome is characterized by signs and symptoms that are related either to the conjugated hyperbilirubinemia or to chronic malabsorption of fat-soluble vitamins (i.e., vitamins A, D, E, and K): jaundice, dark urine, pale stools, pruritus, bruising, steatorrhea, night blindness, osteomalacia, and neuromuscular weakness.⁴

HEPATIC VERSUS POSTHEPATIC JAUNDICE

Once the presence of direct hyperbilirubinemia is confirmed, the next step is to determine whether the jaundice is hepatic or posthepatic. A number of authors have studied the reliability of clinical assessment for making this determination.^{5–16} The sensitivities of history, physical examination, and blood tests alone range from 70 to 95%,^{5–10} whereas the specificities are approximately 75%.^{9,10} The overall accuracy of clinical assessment of hepatic and posthepatic causes of jaundice ranges from 87 to 97%.^{7,11} Clinically,



hepatic jaundice is most often signaled by acute hepatitis, a history of alcohol abuse, or physical findings reflecting cirrhosis or portal hypertension¹²; posthepatic jaundice is most often signaled by abdominal pain, rigors, itching, or a palpable liver more than 2 cm below the costal margin.¹³

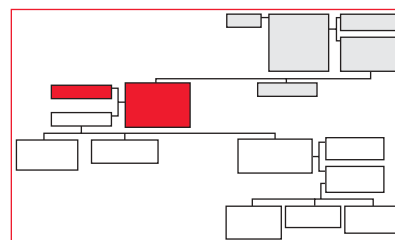
By using discriminant analysis in a pediatric patient population, two investigators were able to isolate three biochemical tests that differentiated between biliary atresia and intrahepatic cholestasis with an accuracy of 95%: total serum bilirubin concentration, alkaline phosphatase level, and γ -glutamyltranspeptidase level.¹⁴ Serum transaminase levels added no independent information of significance to the model. Another multivariate analysis model demonstrated that patients with posthepatic jaundice were younger, had a longer history of jaundice, were more likely to present with fever, and had greater elevations of serum protein concentrations and shorter coagulation times than patients with hepatic jaundice.¹⁵ This model, however, despite its 96% sensitivity (greater than that of any single radiologic diagnostic modality), could not accurately predict the level of a biliary obstruction. Other investigators have reported similar findings,^{7,11,12} and most agree that strategies that omit ultrasonography are clearly inferior.¹⁶

In summary, a clinical approach supported by simple biochemical evaluation displays good predictive ability to distinguish hepatic from posthepatic jaundice; however, a clinical approach alone does not accurately identify the level of biliary obstruction in a patient with posthepatic jaundice.

The remainder of this chapter focuses primarily on management of posthepatic jaundice; hepatic jaundice is less often seen and dealt with by general surgeons [see Table 2 and Sidebar Hepatic Jaundice].

IMAGING

Once the history has been obtained and bedside and laboratory assessments have been completed, the next step is imaging, the goals of which



are (1) to confirm the presence of an extrahepatic obstruction (i.e., to verify that the jaundice is indeed posthepatic rather than hepatic), (2) to determine the level of the obstruction, (3) to identify the specific cause of the obstruction, and (4)

Table 2 Causes of Hepatic Jaundice¹³¹

Hepatitis
Viral
Autoimmune
Alcoholic
Drugs and hormones
Diseases of intrahepatic bile ducts
Liver infiltration and storage disorders
Systemic infections
Total parenteral nutrition
Postoperative intrahepatic cholestasis
Cholestasis of pregnancy
Benign recurrent intrahepatic cholestasis
Infantile cholestatic syndromes
Inherited metabolic defects
No identifiable cause (idiopathic hepatic jaundice)

Hepatic Jaundice

Hepatic jaundice may be either acute or chronic and may be caused by a variety of conditions [see Table 2].

Acute hepatic jaundice may arise de novo or in the setting of ongoing liver disease. Historical clues may suggest a particular cause, such as medications or viral hepatitis. Physical examination usually reveals little. In the presence of preexisting chronic liver disease, bedside stigmata (e.g., ascites, spider nevi, caput medusae, palmar erythema, gynecomastia, or Dupuytren contracture) may be present. Although specific therapies exist for certain clinical problems (e.g., acetylcysteine for acetaminophen ingestion and penicillin plus silibinin for *Amanita phalloides* poisoning), treatment in most cases remains supportive. Patients in whom encephalopathy develops within 2 to 8 weeks of the onset of jaundice are usually classified as having fulminant hepatic failure. Evidence of encephalopathy, renal failure, or a severe coagulopathy is predictive of poor outcome in this setting.¹²⁶ The most common causes of fulminant hepatic failure are viral hepatitis and drug toxicity. The mortality from fulminant hepatic failure remains high even though liver transplantation has favorably affected the prognosis.¹²⁷

In cases of chronic hepatic jaundice, the patient may have chronic hepatitis or cholestasis, with or without cirrhosis. The cause usually is determined on the basis of the history in conjunction with the results of serology, biochemistry, viral DNA analysis, and, occasionally, histology. Causes include viral infection, drug-induced chronic hepatitis, autoimmune liver disease, genetic disorders (e.g., Wilson disease and α_1 -antitrypsin deficiency), chronic cholestatic disorders, alcoholic liver disease, and steatohepatitis.¹²⁸ Physical examination reveals the stigmata of chronic liver disease and occasionally suggests a specific cause (e.g., Kayser-Fleischer rings on slit-lamp examination in Wilson disease). Treatment, once again, is usually supportive, depending on the clinical presentation; whether more specific therapy is needed and what form it takes depend on the cause of liver disease. Although physiologic tests have been developed to quantify hepatic reserve, the most widely used and best-validated prognostic index remains the Child-Pugh classification (see below), which correlates with individual survival and has been shown to predict operative risk.¹²⁹ Liver transplantation is the treatment of choice in most cases of end-stage liver disease.

The Child-Pugh Classification¹²⁹ Numerical Score (points)

Variable	1	2	3
Encephalopathy	Nil (0)	Slight to moderate (1, 2)	Moderate to severe (3–5)
Ascites	Nil	Slight	Moderate to severe
Bilirubin, mg/dL (mmol/L*)	< 2 (< 34)	2–3 (34–51)	> 3 (> 51)
Albumin, g/dL (g/L*)	> 3.5 (> 35)	2.8–3.5 (28–35)	< 2.8 (< 28)
Prothrombin index	> 70%	40–70%	< 40%

Modified Child-Pugh risk grade (depending on total score): 5 or 6 points, grade A; 7 to 9 points, grade B; 10 to 15 points, grade C.

*Système International d'Unités, or SI units.

The Model for End-Stage Liver Disease (MELD) score is now used to prioritize the allocation of organs for liver transplantation by the United Network for Organ Sharing.¹³⁰ This score is based on the serum bilirubin and creatinine concentrations, the international normalized ratio (INR), and the presence of hepatocellular carcinoma; it does not make use of some of the more subjective components of the Child-Pugh score (e.g., ascites and encephalopathy).

to provide complementary information relating to the underlying diagnosis (e.g., staging information in cases of malignancy).

Of the many imaging methods available today, the gold standard for defining the level of a biliary obstruction before operation in a jaundiced patient remains direct cholangiography, which can be performed either via endoscopic retrograde cholangiopancreatography (ERCP) or via percutaneous transhepatic cholangiography (PTC). Unlike other imaging modalities, direct cholangiography poses significant risks to the patient: there is a 4 to 7% incidence of pancreatitis or cholangitis after ERCP,^{17,18} and there is a 4% incidence of bile leakage, cholangitis, or bleeding after PTC.¹⁹ There are also several risks that are particular to the manipulation of an obstructed biliary system (see below). For these reasons, the role of ERCP and PTC is increasingly a therapeutic one: therefore, it is important to gather as much imaging information as possible on the likely cause of the jaundice before performing either investigation.²⁰ We have found the following approach to be an efficacious, cost-effective,²¹ and safe way of obtaining such information in a patient with presumed posthepatic jaundice.

The presence of ductal dilatation of the intrahepatic or extrahepatic biliary system confirms that a posthepatic cause is responsible for the jaundice. Ultrasonography detects ductal dilatation with an accuracy of 95%, although the

results are to some extent operator dependent.²² If ultrasonography does not reveal bile duct dilatation, it is unlikely that an obstructing lesion is present. In some cases, even though ductal dilatation is absent, other ultrasonographic findings may still point to a specific hepatic cause of jaundice (e.g., cirrhosis or infiltration of the liver by tumor).

There are a few specific instances in which ultrasonography may fail to detect a posthepatic cause of jaundice. For instance, very early in the course of an obstructive process, not enough time may have elapsed for biliary dilatation to occur. In this setting, a hepatoinodiacetic acid (HIDA) scan has often helped identify bile duct blockage.²³ The yield from this test is highest when the serum bilirubin level is lower than 100 mmol/L.¹ Occasionally, the intrahepatic biliary tree is unable to dilate; possible causes of such inability include extensive hepatic fibrosis, cirrhosis, sclerosing cholangitis, and liver transplantation. If one of these diagnoses is suspected, ERCP, magnetic resonance cholangiopancreatography (MRCP), or PTC will eventually be required to confirm the diagnosis of biliary obstruction. Occasionally, the biliary tree dilatation may be intermittent; possible causes of this condition include choledocholithiasis and some biliary tumors. In a patient with gallstones, transient liver test abnormalities by themselves may suggest an intermediate to high likelihood of common bile duct (CBD) stones, even if there is no biliary ductal dilatation.^{24,25} If one of these diagnoses is

suspected, ultrasonography may be repeated after a short period of observation (when clinically applicable); biliary ductal dilatation then generally becomes apparent. If all of these unusual clinical situations have been ruled out, a hepatic cause for the jaundice should be sought [see Table 2] and a liver biopsy considered.^{26,27}

Besides being able to identify the presence of extrahepatic ductal obstruction with a high degree of reliability, ultrasonography can accurately determine the level of the obstruction in 90% of cases.²⁸ For example, a dilated gallbladder suggests that the obstruction is probably located in the middle third or the distal third of the CBD.

Some centers prefer computed tomography (CT) to ultrasonography as the initial imaging modality,²⁹ but we, like a number of other authors,³⁰ find ultrasonography to be the most expedient, least invasive, and most economical imaging method for differentiating between hepatic and posthepatic causes of jaundice, as well as for suggesting the level of obstruction.³¹ Traditional imaging techniques, such as oral or intravenous (IV) cholangiography, have a negligible role to play in this setting because of their very poor accuracy and safety, especially in jaundiced patients.

MRCP [see Figure 1] and endoscopic ultrasonography (EUS) have been used to visualize the biliary and pancreatic trees in various populations of patients with obstructive jaundice.^{32–36} Compared with direct cholangiography, both appear to be excellent at diagnosing biliary obstruction and establishing its location and nature.^{37,38} MRCP exhibits more modest detection rates when diagnosing small CBD stones.^{39,40} Spiral (helical) CT scanning is also useful in diagnosing biliary obstruction and determining its cause, although concomitant oral or IV cholangiography is required to detect choledocholithiasis.^{41–43}

In addition to their ability to detect choledocholithiasis, spiral CT, EUS, and MRCP in combination with abdominal magnetic resonance imaging (MRI) (e.g., of the pancreas) are very useful in diagnosing and staging biliopancreatic tumors.^{44–46} Cytology specimens are readily obtained via fine-needle aspiration (FNA) during CT or EUS.⁴⁵

It is our current practice to employ these modalities as second-line tests after the initial abdominal ultrasonographic examination. To obtain a diagnosis, we favor EUS for periampullary pathologic conditions and MRI with MRCP for more proximal diseases of the biliary tree.

In making the choice among the various available second-line tests, local expertise and cost-effectiveness become important considerations. Unfortunately, the reports on cost-effectiveness published to date have suffered either from limited assumptions (when the methodology involved decision modeling) or from the lack of an effectiveness-type design (when the methodology involved allocation of patients).

Workup and Management of Posthepatic Jaundice

Once ultrasonography has confirmed that ductal obstruction is present, there are three possible clinical scenarios:

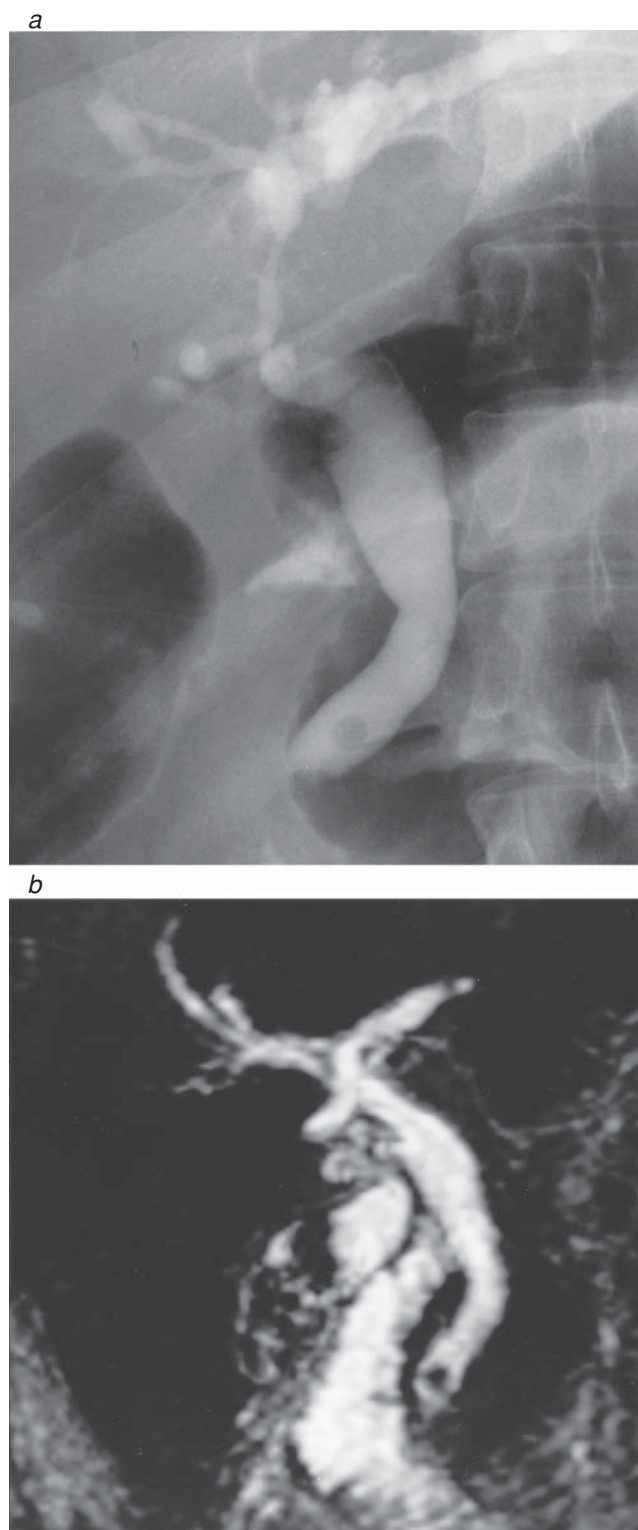
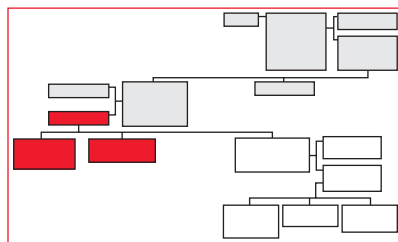


Figure 1 Endoscopic retrograde cholangiopancreatography (a) and corresponding magnetic resonance cholangiopancreatography (b) demonstrate the presence of a stone in the distal common bile duct.

suspected cholangitis, suspected choledocholithiasis without cholangitis, and a suspected lesion other than choledocholithiasis. The direction of the subsequent workup depends on which of the three appears most likely.

SUSPECTED CHOLANGITIS

If a jaundiced patient exhibits a clinical picture compatible with acute suppurative cholangitis (Charcot triad),^{47,48} the most likely diagnosis is choledocholithiasis. After appropriate resuscitation, correction of any coagulopathies present, and administration of antibiotics, ERCP is indicated for diagnosis and treatment.⁴⁹ If ERCP is unavailable or is not feasible (e.g., because of previous Roux-en-Y reconstruction), trans-hepatic drainage or surgery may be necessary. It is important to emphasize here that the mainstay of treatment of severe cholangitis is not just the administration of appropriate antibiotics but rather the establishment of adequate biliary drainage.

SUSPECTED CHOLEDOCHOLITHIASIS WITHOUT CHOLANGITIS

Choledocholithiasis is the most common cause of biliary obstruction.^{12,13} It should be strongly suspected if the jaundice is episodic or painful or if ultrasonography has demonstrated the presence of gallstones or bile duct stones. Patients with suspected choledocholithiasis should be referred for laparoscopic cholecystectomy with either preoperative ERCP, intraoperative cholangiography, or intraoperative ultrasonography.⁵⁰ We favor preoperative ERCP in this setting of jaundice because its diagnostic yield is high,⁵¹ it allows confirmation of the diagnosis preoperatively (thus obviating intraoperative surprises), and it is capable of clearing the CBD of stones in 95% of cases. Decision analyses appear to confirm the utility of this strategy when laparoscopic CBD exploration is not an option.^{52–56} Many authors, however, favor a fully laparoscopic approach, in which choledocholithiasis is detected in the operating room by means of intraoperative cholangiography^{57,58} or ultrasonography^{59–61} and laparoscopic biliary clearance is performed when choledocholithiasis is confirmed. Given that both the ERCP approach and the fully laparoscopic approach have advantages and limitations, the optimal approach in a particular setting should be dictated by local expertise.

SUSPECTED LESION OTHER THAN CHOLEDOCHOLITHIASIS

If no gallstones are identified, if the clinical presentation is less acute (e.g., constant abdominal or back pain), or if there are associated constitutional symptoms (e.g., weight loss, fatigue, and long-standing anorexia), the presence of a lesion other than choledocholithiasis should be suspected. In such cases, another imaging modality besides the ultrasonography already performed must be considered before the decision is made to proceed to cholangiography or operation.

Possible causes of posthepatic obstruction (other than choledocholithiasis) may be classified into three categories, depending on the location of the obstructing lesion (as suggested by the pattern of gallbladder and biliary tree dilatation on the ultrasonogram): the upper third of the biliary tree, the middle third, or the lower (distal) third [see Table 3]. Once it has been determined that choledocholithiasis is unlikely, the

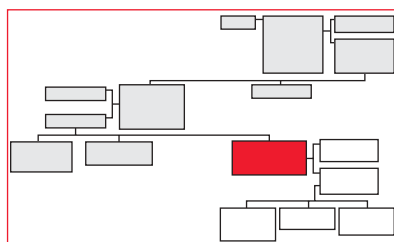


Table 3 Causes of Posthepatic Jaundice

Upper-third obstruction
Polycystic liver disease
Caroli disease
Hepatocellular carcinoma
Oriental cholangiohepatitis
Hepatic arterial thrombosis (e.g., after liver transplantation or chemotherapy)
Hemobilia (e.g., after biliary manipulation)
Iatrogenic bile duct injury (e.g., after laparoscopic cholecystectomy)
Cholangiocarcinoma (Klatskin tumor)
Sclerosing cholangitis
Papillomas of the bile duct
Middle-third obstruction
Cholangiocarcinoma
Sclerosing cholangitis
Papillomas of the bile duct
Gallbladder cancer
Choledochal cyst
Intrabiliary parasites
Mirizzi syndrome
Extrinsic nodal compression (e.g., from breast cancer or lymphoma)
Iatrogenic bile duct injury (e.g., after open cholecystectomy)
Cystic fibrosis
Benign idiopathic bile duct stricture
Lower-third obstruction
Cholangiocarcinoma
Sclerosing cholangitis
Papillomas of the bile duct
Pancreatic tumors
Ampullary tumors
Chronic pancreatitis
Sphincter of Oddi dysfunction
Papillary stenosis
Duodenal diverticula
Penetrating duodenal ulcer
Retroduodenal adenopathy (e.g., lymphoma, carcinoid)

most common cause of such obstruction is pancreatic cancer.^{12,13} In adults, many of the other possible causes also involve malignant processes. Consequently, the next step in the workup of the patient is typically the assessment of resectability and operability.

Diagnosis and Assessment of Resectability

Assessment of the resectability of a tumor usually hinges on whether the superior mesenteric vein, the portal vein, the superior mesenteric artery, and the porta hepatis are free of tumor and on whether there is evidence of significant local adenopathy or extrapancreatic extension of tumor. Unfortunately, the majority of lesions will be clearly unresectable, either because of tumor extension or because of the presence of hepatic or peritoneal metastases.

Many imaging modalities are currently used to determine resectability, and several of these have been established as effective alternatives to direct cholangiography because they involve little, if any, morbidity. Their accuracy varies according to the underlying pathology and the expertise of the user. They have been studied mostly with respect to the staging and diagnosis of pancreatic, periampullary, and biliary hilar cancers.

For determining resectability and staging lesions before operation, we rely mainly on spiral CT. The advent and

widespread availability of multidetector CT have made this modality the dominant second-line imaging method in cases of suspected pancreatic masses. For optimal evaluation of the pancreas, a fine-cut dual-phase (arterial phase and portal venous phase) scan should be obtained. Oral administration of water allows better evaluation of the duodenum and the ampulla.^{62,63} At present, spiral CT is considered to be superior for the diagnosis and staging of lesions such as pancreatic cancer.^{44,64,65} It exhibits a high negative predictive value and has a false positive rate of less than 10%; its sensitivity is optimal for pancreatic lesions larger than 1.5 cm in diameter. Ascites, liver metastases, lymph nodes larger than 2 cm in diameter, and invasion into adjacent organs are all signs of advanced disease.⁶⁶ On the basis of these criteria, spiral CT can predict that a lesion will not be resectable with an accuracy approaching 95%; however, as many as 33% of tumors that appear to be resectable on CT are found to be unresectable at operation.⁶⁵

MRI-based staging, along with MRCP, can further dictate the subsequent choice of therapy.^{66–69} MRI may be particularly useful for following up patients in whom clip artifacts interfere with a CT image.⁶⁶ It also appears to be successful in detecting cholangiocarcinoma spreading along the proximal biliary tree.⁷⁰ Given the renewed interest in biliary contrast media and the availability of software optimized for multidetector scanners, CT cholangiography may soon rival MRCP for evaluation of the biliary tree in cases of suspected malignancy.⁷¹

Only in a few very rare instances is traditional angiography used to assess resectability or stage a hepatobiliary or pancreatic neoplasm. Increasingly, it is being replaced by CT angiography or duplex Doppler ultrasonography, which can confirm the presence of flow in the hepatic arterial or portal venous systems and occasionally can demonstrate invasion of these vessels by tumor.⁷² Magnetic resonance angiography (MRA) has also been used, with excellent results. As yet, none of these noninvasive modalities have been shown to be clearly superior to any of the others.⁷³

EUS is a highly sensitive method of imaging the pancreas and the duodenum.^{45,74,75} In two large studies, it was found to be superior to CT and standard ultrasonography in staging pancreatic and ampullary cancers.^{76,77} Subsequent studies indicated that whereas EUS is superior to CT for detection and staging, it provides similar information regarding nodal status and overall assessment of resectability.^{62,78} From a cost-minimization point of view, the optimal strategy is to begin with a dual-phase CT scan and to follow up with EUS only in cases in which further information or a tissue diagnosis is required.^{79,80} In another large series, EUS was reported to be more accurate than CT in the comparative staging of pancreatic and ampullary cancers. It has also been found useful for identifying small (< 2 cm) pancreatic tumors, which may be suspected in a patient who has an obstruction of the distal third of the bile duct and whose CT scan is normal.⁷⁵ Furthermore, EUS is currently the dominant technique for staging ampullary tumors.⁸¹

In patients with a suspected pancreatic tumor, direct FNA of the lesion at the time of EUS has become the gold-standard method for obtaining a tissue diagnosis. In the case of potentially resectable lesions, however, this measure adds very little to the decision-making process. The limited data

currently available suggest that assays of tumor markers in serum and pancreatic fluid are useful, particularly for cystic lesions of the pancreas.⁸²

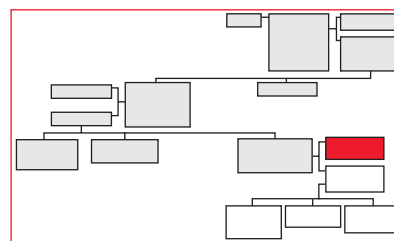
At this point in the evaluation, patients can be referred either for cholangiography (ERCP or MRCP) to clarify a still unclear diagnosis or for biliary decompression (see below). MRI of the pancreas with MRCP continues to improve rapidly. It is a noninvasive modality that evaluates the pancreas, vasculature, and pancreatobiliary ductal system in a single examination, with the additional benefit of avoiding ionizing radiation and iodinated contrast agents.⁸³ MRCP remains our test of choice for evaluation of middle- and upper-third lesions in cases in which decompression is not required.

In the event that none of these modalities point to a diagnosis, the use of ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) may be considered to help differentiate benign pancreatic conditions from malignant ones.^{84,85} Besides facilitating diagnosis, FDG-PET provides information regarding occult metastases and can be useful in detecting recurrent disease. Experience with FDG-PET is growing rapidly as this imaging modality becomes more readily accessible.

When a biliary stricture is detected at cholangiography, brush cytology or biopsy is mandatory. Biliary cytology, however, has been disappointing, particularly at ERCP: diagnostic accuracy ranges from 40 to 85%,^{86,87} mostly because the negative predictive value is poor. Accuracy improves with multiple sampling and when a biliary rather than a pancreatic malignancy is detected. In addition, biopsy tends to be more accurate than brush cytology.⁸⁶

Nonoperative Management: Drainage and Cholangiography

In the majority of patients with malignant obstructions, treatment is palliative rather than curative. It is therefore especially important to recognize and minimize the iatrogenic risks related to the manipulation of an obstructed biliary system; this is why staging and cholangiography are currently being performed with EUS and MRCP.



It is therefore especially important to recognize and minimize the iatrogenic risks related to the manipulation of an obstructed biliary system; this is why staging and cholangiography are currently being performed with EUS and MRCP.

Cholangiography and decompression of obstructed biliary system As a rule, we favor ERCP, although PTC may be preferable for obstructions near the hepatic duct bifurcation. Whichever imaging modality is used, the following four principles apply:

1. In the absence of preexisting or concomitant hepatocellular dysfunction, drainage of one half of the liver is generally sufficient for resolution of jaundice.⁸⁸
2. Because of its external diameter, a transhepatic drain, once inserted, does not necessarily permit equal drainage of all segments of the liver, particularly if there are a number of intrahepatic ductal stenoses. Accordingly, some patients with conditions such as sclerosing cholangitis or a growing tumor may experience persistent sepsis from an infected

excluded liver segment even when the prosthesis is patent [see Figure 2]. An excluded segment may even be responsible for severe persistent pruritus.

3. Any attempt at opacifying an obstructed biliary tree introduces a significant risk of subsequent cholangitis, even when appropriate antibiotic prophylaxis is provided. Accordingly, when one elects to perform direct cholangiography, there should be a plan for biliary drainage either at the time of ERCP or PTC or soon thereafter.
4. Even though jaundice is believed to be associated with multiple adverse systemic effects (e.g., renal failure, sepsis, and impaired wound healing),^{89,90} routine preoperative drainage of an obstructed biliary system does not benefit patients who will soon undergo resection.^{91,92} A growing body of evidence suggests that in patients with either pancreatic^{93,94} or hepatic⁹⁵ malignancies, routine preoperative direct cholangiography with decompression is associated with a higher incidence of postoperative complications when tumor resection is ultimately carried out.

When direct cholangiography is ordered, it should be thought of as more than just a diagnostic test: it is the ideal setting for cytology, biopsy, or even drainage of the obstructed bile duct via a sphincterotomy, a nasobiliary tube, or a catheter or stent. Accordingly, it is essential that the surgeon, the gastroenterologist, and the radiologist discuss the possible need for drainage well before it is required. Early, open communication among all members of the treating team is a hallmark of the modern management of biliary obstruction.

Palliation in patients with advanced malignant disease

When a patient has advanced malignant disease, drainage of the biliary system for palliation is not routinely indicated, because the risk of complications related to the procedure may outweigh the potential benefit. Indeed, the best treatment for a patient with asymptomatic obstructive jaundice and liver metastases may be supportive care alone.⁹⁶ Biliary decompression is indicated if cholangitis or severe pruritus interferes with quality of life.

We, like others,²¹ consider a stent placed with ERCP to be the palliative modality of choice for advanced disease, although upper-third lesions may be managed most easily through the initial placement of an internal or external catheter at the time of PTC. Metal expandable stents remain patent longer than large conventional plastic stents^{97,98} and are becoming the standard of care.^{99,100} Whether plastic biliary stents should be replaced prophylactically or only after obstruction has occurred remains controversial; however, results from a randomized, controlled trial (RCT) favor the former approach.¹⁰¹ In another RCT, the use of prophylactic ciprofloxacin did not prolong stent patency but did reduce the incidence of cholangitis and improve quality-of-life scores.¹⁰²

RCTs suggest that surgical biliary bypass should be reserved for patients who are expected to survive for 6 months or longer because bypass is associated with more prolonged palliation at the cost of greater initial morbidity.¹⁰³

The role of prophylactic gastric drainage at the time of operative biliary drainage remains controversial,^{104,105} although two RCTs demonstrated a reduced incidence of subsequent clinical gastric outlet obstruction when this measure was employed. Jaundiced patients with unresectable lesions who also present with duodenal or jejunal obstruction should be referred for gastrojejunostomy at the time of biliary bypass surgery. There is evidence to suggest that when a pancreatic malignancy is present, intraoperative celiac ganglion injection should be performed for either prophylactic or therapeutic pain control.¹⁰⁶

Operative Management at Specific Sites: Bypass and Resection

Surgical treatment of tumors causing biliary obstruction is determined primarily by the level of the biliary obstruction.

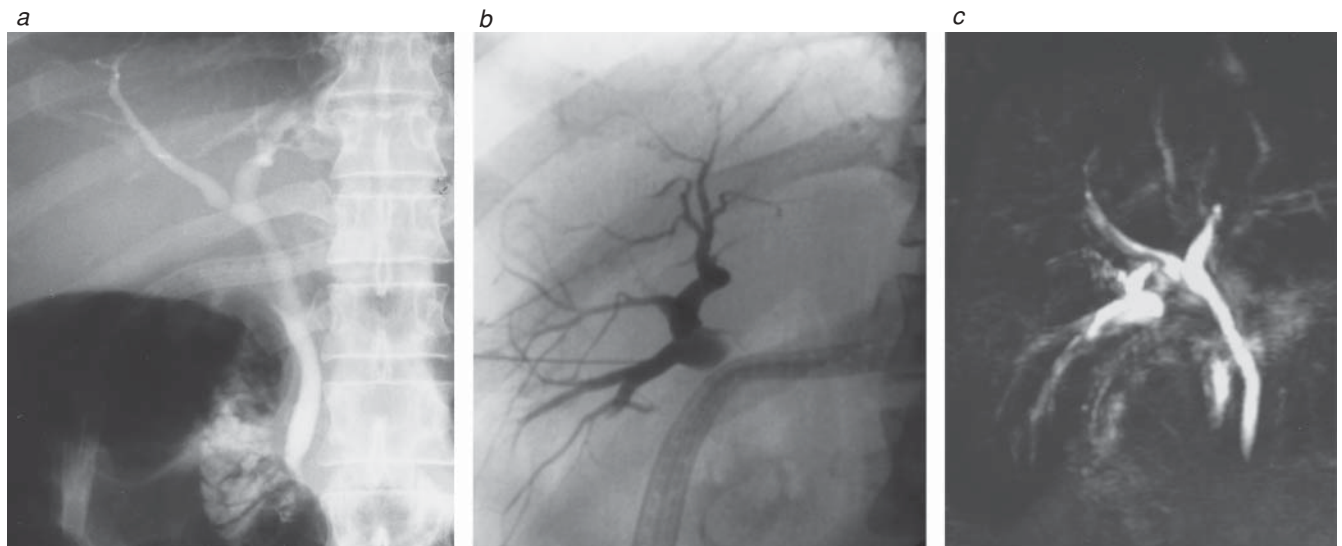
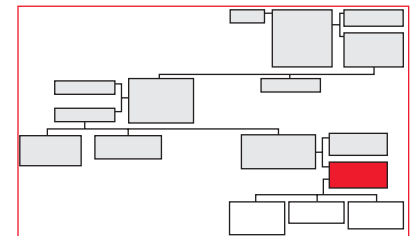


Figure 2 (a) Endoscopic retrograde cholangiopancreatography demonstrates missing liver segments. (b) Transhepatic cholangiography of segment 6 reveals the excluded liver ductal system. (c) Magnetic resonance cholangiopancreatography shows the excluded liver segments, as well as the biliary system, which still communicates with the common hepatic duct.

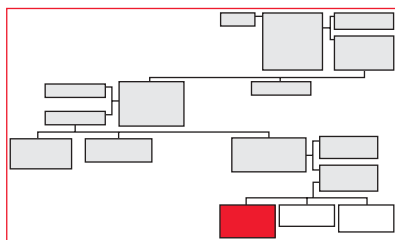
Current evidence indicates that modern surgical approaches are resulting in lower postoperative morbidity and, possibly, improved 5-year survival¹⁰⁷; however, the prognosis is still uniformly poor, except for patients with ampullary tumors. In fact, the surgical procedure rarely proves curative, even after meticulous preoperative patient selection.

At one time, there was considerable enthusiasm for routine use of staging laparoscopy; at present, however, selective use is recommended.¹⁰⁸ The benefits of staging laparoscopy include more accurate assessment of resectability and prevention of the prolonged hospital stay and convalescence associated with an unnecessary laparotomy. Laparoscopy is used mostly to detect peritoneal carcinomatosis, liver metastases, malignant ascites, and gross hilar adenopathy.^{109,110} The main limitation of laparoscopy in this setting appears to be that it does not accurately detect the spread of tumors to lymph nodes or the vascular system.¹¹¹ In several studies, a combined approach that included both laparoscopy and laparoscopic ultrasonography was associated with shorter hospital stays and lower costs.^{108,110–112}

In what follows, only the general principles of resection or bypass at each level of obstruction are discussed; operative technical details are addressed elsewhere. Our preferred method of biliary anastomosis, for either reconstruction or bypass, involves the fashioning of a Roux-en-Y loop, followed by a mucosa-to-mucosa anastomosis. In all cases, a cholecystectomy is performed to facilitate access to the biliary tree.

Upper-third obstruction

Palliation Because the left hepatic duct has a long extrahepatic segment that makes it more accessible, the preferred



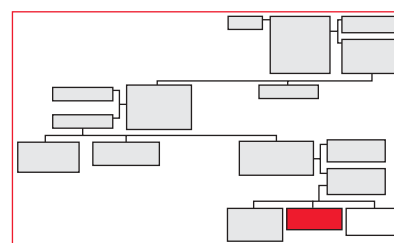
bypass technique for an obstructing upper-third lesion is a left (or segment 3) hepaticojejunostomy. This operation has superseded the Longmire procedure because it does not involve formal resection of liver parenchyma. Laparoscopic bypass techniques that make use of segment 3 have been developed, but their performance has yet to be formally assessed, and they cannot yet be incorporated into a management algorithm.^{113,114}

Resection for cure The hilar plate is taken down to lengthen the hepatic duct segment available for subsequent anastomosis. Often a formal hepatectomy or segmentectomy is required to ensure an adequate proximal margin of resection. If the resection must be carried out proximal to the hepatic duct bifurcation, several choledochojejunostomies will have to be done to anastomose individual hepatic biliary branches. Frozen-section examination of the proximal and distal resection margins is important because of the propensity of tumors such as cholangiocarcinoma to spread in a submucosal or perineural plane.

The results of aggressive hilar tumor resections that included as much liver tissue as was necessary to obtain a negative margin appear to justify this approach.¹¹⁵ In cases of left hepatic involvement, resection of the caudate lobe (segments 1 and 9) is indicated as well.^{116,117}

Middle-third obstruction

Palliation Surgical bypass of middle-third lesions is technically simpler because a hepaticojejunostomy can often be performed distal to the



hepatic duct bifurcation, which means that exposure of the hilar plate or the intrahepatic ducts is unnecessary.

Resection for cure Discrete tumors in this part of the bile duct, although uncommon, are usually quite amenable to resection along with the lymphatic chains in the porta hepatis. Resection of an early gallbladder cancer may, on occasion, necessitate the concomitant resection of segment 5, although the value of resecting this segment prophylactically has not been conclusively demonstrated.¹¹⁸ Sometimes jaundice from a suspected middle-third lesion is, in fact, caused by a case of Mirizzi syndrome [see Figure 3]. In such cases, a gallstone is responsible for extrinsic obstruction of the CBD, either by causing inflammation of the gallbladder wall or via direct impingement. Proper treatment of this syndrome may involve hepaticojejunostomy in addition to cholecystectomy if a cholecystocholedochal fistula is present.¹¹⁹

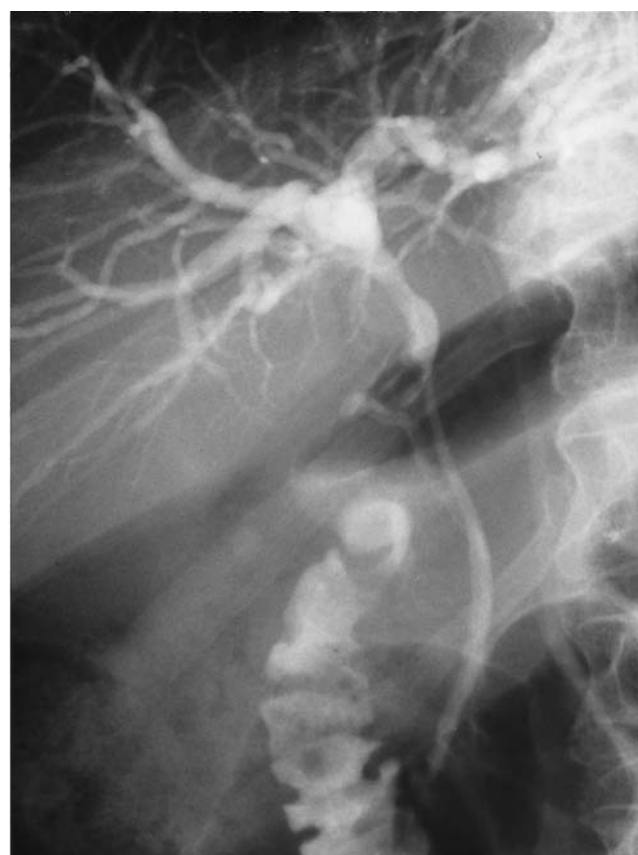
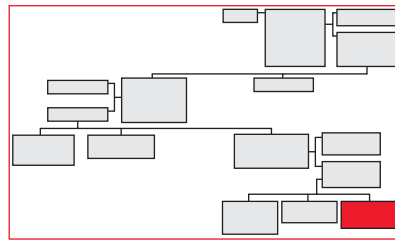


Figure 3 Endoscopic retrograde cholangiopancreatography demonstrates extrinsic compression of the common hepatic duct by a stone in the Hartmann pouch. A biliary stent has been inserted for drainage.

Lower-third obstruction

Palliation The preferred bypass technique for lower-third lesions is a Roux-en-Y choledochojejunostomy. Cholecystojejunostomy carries a



higher risk of complications and subsequent development of jaundice¹²⁰; this remains true even when it is performed laparoscopically. Occasionally, it may be done as a temporizing measure before a more definitive procedure in the context of an upcoming transfer to a specialized center.

Resection for cure Occasionally, an impacted CBD stone at the duodenal ampulla mimics a tumor and is not clearly identified preoperatively. Because of the growing use of EUS and MRCP, such a situation is increasingly uncommon. Resection of a lower-third lesion usually involves a pancreaticoduodenectomy, although transduodenal ampullary resection may be an acceptable alternative for a small adenoma of the ampulla; local duodenal resection without removal of the head of the pancreas has also been described.¹²¹ For optimal results, pancreaticoduodenectomy is best performed in specialized centers.¹²²

It has been suggested that postoperative adjuvant therapy may improve the prognosis after resection of a pancreatic adenocarcinoma,¹⁰⁷ but this debate falls outside the scope of our discussion.

Postoperative Jaundice

A clinical scenario of particular pertinence to surgeons that we have not yet addressed is the development of jaundice in the postoperative setting.

Jaundice develops in approximately 1% of all surgical patients after operation.¹²³ When jaundice occurs after a hepatobiliary procedure, it may be attributable to specific biliary causes, such as retained CBD stones, postoperative biliary leakage (through reabsorption of bile leaking into the peritoneum) [see Figure 4], injury to the CBD, and the subsequent development of biliary strictures. In most instances, however, the jaundice derives from a combination of disease processes, and only rarely is invasive testing or active treatment required.¹²⁴

A diagnostic approach similar to the one outlined earlier (see above) is applicable to postoperative jaundice. However, as the possible causes of postoperative jaundice vary depending on the time interval between the operation and the development of jaundice, the following diagnostic approach may also be useful:

- Jaundice may develop within 48 hours of the operation; this is most often the result of the breakdown of red blood cells, occurring in the context of multiple blood transfusions (particularly with stored blood), the resorption of a large hematoma, or a transfusion reaction. Hemolysis may also develop in a patient with a known underlying hemolytic anemia and may be precipitated by the administration of specific drugs (e.g., sulfa drugs in a patient who has glucose-6-phosphate dehydrogenase deficiency).¹²⁵ Cardiopulmonary bypass or the insertion of a prosthetic



Figure 4 Jaundice has occurred after laparoscopic cholecystectomy as a result of bile leakage from a distal biliary tributary. A stent has been inserted to decrease bile duct luminal pressure and foster spontaneous resolution.

valve may be associated with the development of early postoperative jaundice as well. Gilbert syndrome [see Sidebar Hepatic Jaundice] may first manifest itself early in the postoperative period. Occasionally, a mild conjugated hyperbilirubinemia may be related to Dubin-Johnson syndrome, which is an inherited disorder of bilirubin metabolism. This condition is usually self-limited and is characterized by the presence of a melaninlike pigment in the liver.

- Intraoperative hypotension or hypoxemia or the early development of heart failure can lead to conjugated hyperbilirubinemia within 5 to 10 days after operation. The hyperbilirubinemia may be associated with other end-organ damage (e.g., acute tubular necrosis). In fact, any impairment of renal function causes a decrease in bilirubin excretion and can be responsible for a mild hyperbilirubinemia.
- Jaundice may develop 7 to 10 days after operation in association with a medication-induced hepatitis attributable to an anesthetic agent. This syndrome has an estimated incidence of 1 in 10,000 after an initial exposure.¹²⁵ More commonly, the jaundice is related to the administration of antibiotics or other medications used in the perioperative setting.¹²⁵

- After the first week, jaundice associated with intrahepatic cholestasis is often a manifestation of a septic response and usually presents in the setting of overt infection, particularly in patients with multiple organ dysfunction syndrome. Gram-negative sepsis from an intra-abdominal source is typical; if it persists, the outcome is likely to be poor. Jaundice may occur in as many as 30% of patients receiving total parenteral nutrition (TPN). It may be attributable to steatosis, particularly with formulas containing large amounts of carbohydrates. In addition, decreased export of bilirubin from the hepatocytes may lead to cholestasis, the severity of which appears to be related to the duration of TPN administration. Acalculous cholecystitis or even ductal obstruction may develop as a result of sludge in the gallbladder and the CBD. An elevated postoperative bilirubin level at any time may also result from unsuspected hepatic or posthepatic causes (e.g., occult cirrhosis, choledocholithiasis, or cholecystitis). A rare cause of postoperative jaundice is the development of thyrotoxicosis.

Another entity to consider (as a diagnosis of exclusion) is so-called benign postoperative cholestasis, a primarily cholestatic, self-limited process with no clearly demonstrable cause that typically arises within 2 to 10 days after operation. Benign postoperative cholestasis may be attributable to a combination of mechanisms, including an increased pigment load, impaired liver function resulting from hypoxemia and hypotension, and decreased renal bilirubin excretion caused by varying degrees of tubular necrosis.¹²⁶ The predominantly conjugated hyperbilirubinemia may reach 40 mg/dL and remain elevated for as long as 3 weeks.¹²⁵

- In the late postoperative period, the development of non-A, non-B, non-C viral hepatitis after transfusion of blood products will usually occur within 5 to 12 weeks of operation.

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Acknowledgment

Figure 2c From *MRI of the Abdomen and Pelvis: A Text-Atlas*, by R.C. Semelka, S. M. Asher, and C. Reinhold. John Wiley and Sons, New York, 1997. Used with permission.

4 INTESTINAL OBSTRUCTION

Fuad Alkhoury, MD, and W. Scott Helton, MD, FACS

Intestinal obstruction is a common medical problem and accounts for a large percentage of surgical admissions for acute abdominal pain [see 5:1 *Acute Abdominal Pain*].¹ It develops when air and secretions are prevented from passing aborally as a result of either intrinsic or extrinsic compression (i.e., mechanical obstruction) or gastrointestinal (GI) paralysis (i.e., nonmechanical obstruction in the form of ileus or pseudo-obstruction). Small intestinal ileus is the most common form of intestinal obstruction; it occurs after most abdominal operations and is a common response to acute extra-abdominal medical conditions and intra-abdominal inflammatory conditions [see Table 1].² Mechanical small bowel obstruction is somewhat less common; such obstruction is secondary to intra-abdominal adhesions, hernias, or cancer in about 90% of cases [see Table 2]. Mechanical colonic obstruction accounts for only 10 to 15% of all cases of mechanical obstruction and most often develops in response to obstructing carcinoma, diverticulitis, or volvulus [see Table 3]. Acute colonic pseudo-obstruction occurs most frequently in the postoperative period or in response to another acute medical illness.

There are several different methods of classifying mechanical obstruction: acute versus chronic, partial versus complete, simple versus closed loop, and gangrenous versus nongangrenous. The importance of these classifications is that the natural history of the condition, its response to treatment, and the associated morbidity and mortality all vary according to which type of obstruction is present.

When chyme and gas can traverse the point of obstruction, obstruction is partial; when this is not the case, obstruction is complete. When the bowel is occluded at a single point along the intestinal tract, leading to intestinal dilatation, hypersecretion, and bacterial overgrowth proximal to the obstruction and decompression distal to the obstruction, simple obstruction is present. When a segment of bowel is occluded at two points along its course by a single constrictive lesion that occludes both the proximal and the distal end of the intestinal loop and traps the bowel's mesentery, closed-loop obstruction is present. When the blood supply to a closed-loop segment of bowel becomes compromised, leading to ischemia and eventually to bowel wall necrosis and perforation, strangulation is present. The most common causes of simple obstruction are intra-abdominal adhesions, tumors, and strictures; the most common causes of closed-loop obstruction are hernias, adhesions, and volvulus.

One of the most difficult tasks in general surgery is deciding when to operate on a patient with intestinal obstruction. The purpose of the following discussion is to outline a safe, efficient, and cost-effective stepwise approach to making this often difficult decision and to optimizing the management of patients with this problem. Absolutes are few and far between: treatment must always be highly individualized. Consequently, the

following recommendations are intended only as guidelines, not as surgical dicta.

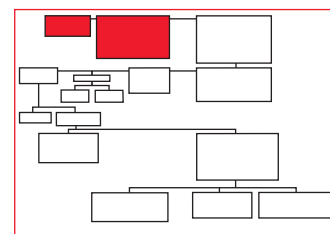
Clinical Evaluation

HISTORY AND CLINICAL SETTING

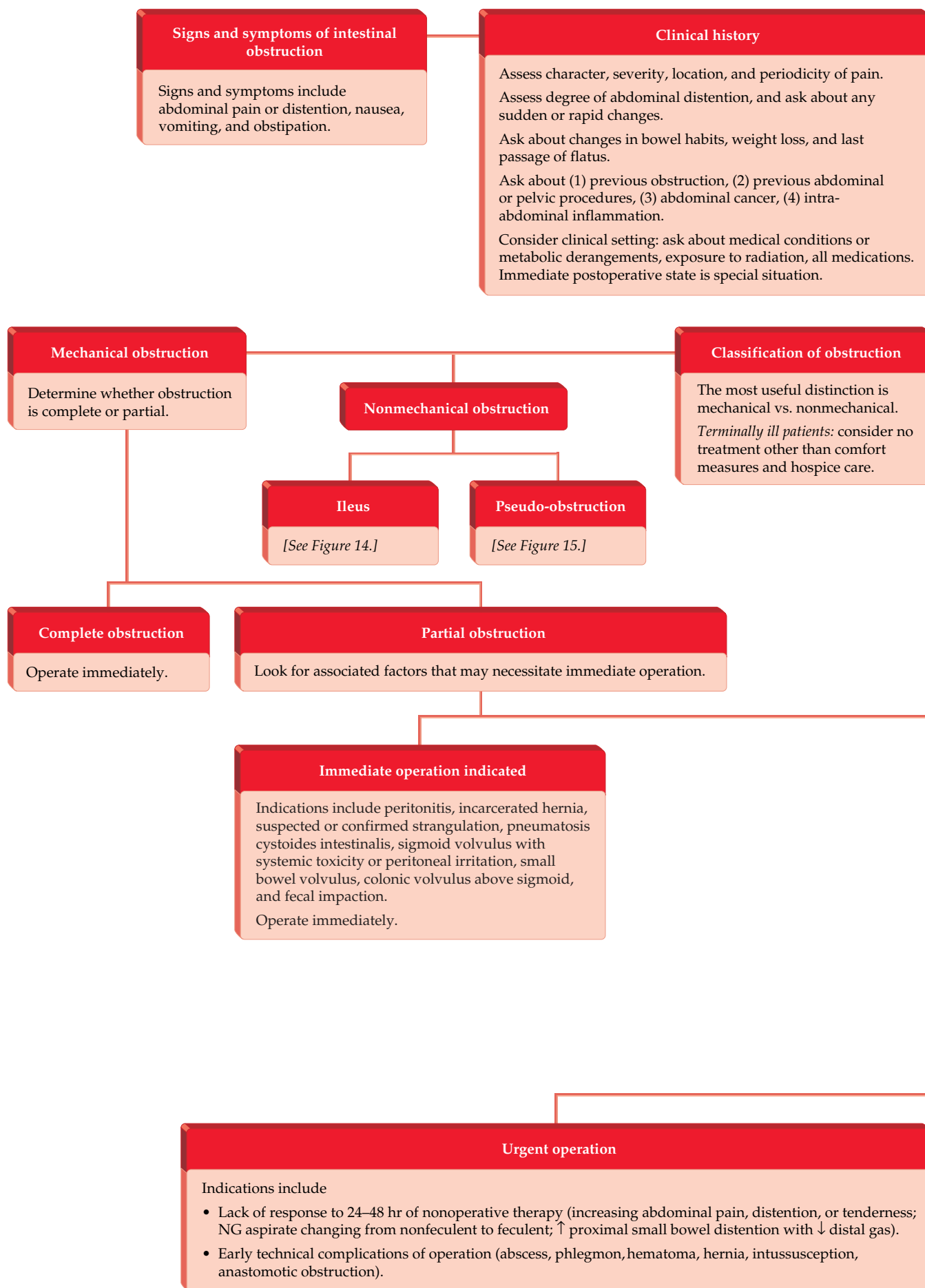
When a patient complains of acute obstipation, abdominal pain and distention, nausea, and vomiting, the probability that either mechanical bowel obstruction or ileus is present is very high.³ Mechanical obstruction can often be distinguished from ileus or pseudo-obstruction on the basis of the location, character, and severity of abdominal pain. Pain from mechanical obstruction is usually located in the middle of the abdomen, whereas pain from ileus and pseudo-obstruction is diffuse. Pain from ileus is usually mild, and pain from obstruction is typically more severe. In general, pain increases in severity and depth over time as obstruction progresses; however, in mechanical obstruction, pain severity may decrease over time as a result of bowel fatigue and atony. The periodicity of pain can help localize the level of obstruction: pain from proximal intestinal obstruction has a short periodicity (3 to 4 minutes), and distal small bowel or colonic pain has longer intervals (15 to 20 minutes) between episodes of nausea, cramping, and vomiting.

Abdominal distention, nausea, and vomiting usually develop after pain has already been felt for some time. The patient should be asked what degree of abdominal distention is present and whether there has been a sudden or rapid change. Distention developing over many weeks suggests a chronic process or progressive partial obstruction. Massive abdominal distention coupled with minimal crampy pain, nausea, and vomiting suggests long-standing intermittent mechanical obstruction or some form of chronic intestinal pseudo-obstruction. The combination of a gradual change in bowel habits, progressive abdominal distention, early satiety, mild crampy pain after meals, and weight loss also suggests chronic partial mechanical bowel obstruction. If the patient has undergone evaluation for similar symptoms before, any previous abdominal radiographs or contrast studies should be reviewed. The patient should be asked when flatus was last passed: failure to pass flatus may signal a transition from partial to complete bowel obstruction. Patients with an intestinal stoma (ileostomy or colostomy) who present with signs and symptoms of obstruction often report abdominal distention and pain after a sudden change in stomal output of stool, liquid, or air.

The patient should also be asked about (1) previous episodes of bowel obstruction, (2) previous abdominal or pelvic



Assessment of Intestinal Obstruction



Physical exam and resuscitate as necessary

Develop gestalt of patient's illness, and assess patient's vital signs, hydration, and cardiopulmonary system.

Place NG tube, Foley catheter, and IV. line immediately.

Assess volume and character of NG aspirate, and measure urine output.

Replace lost fluid with isotonic saline or lactated Ringer solution.

Look for signs of abscess, pneumonia, or myocardial infarction, and be alert for dyspnea, labored breathing, or jaundice.

Perform systematic abdominal examination: observation → auscultation → palpation and percussion. Look for abdominal masses, tenderness, incisions, and hernias; assess bowel sounds; examine rectum for masses, fecal impaction, and occult blood.

Investigative studies

Obtain chest x-rays and abdominal films.

If uncertainty about presence or nature of colonic obstruction remains, perform sigmoidoscopy and barium enema examination.

Measure serum electrolytes and creatinine, determine hematocrit, and order coagulation profile. If ileus is suspected, measure serum magnesium and calcium and order urinalysis.

Perform CT (with oral or IV contrast agents), fast MRI, or abdominal ultrasonography.

Immediate operation not indicated

Manage initially with nonoperative measures.

Reassess patient every 4 hr.

For partial obstruction, administer oral diatrizoate meglumine.

Look for changes in pain, abdominal findings, and volume and character of NG aspirate.

Repeat abdominal x-rays, and look for changes in gas distribution, pneumatosis cystoides intestinalis, and free intraperitoneal air.

Classify patient's condition as improved, unchanged, or worse.

Decide whether operative treatment is necessary and, if so, whether it should be done on urgent or elective basis.

Arrival of contrast agent in right colon within 24 hr is highly predictive of successful resolution of adhesive obstruction without operation.

No operation

Conditions that typically resolve with nonoperative therapy include adhesive obstruction (unless it does not improve in 12 hr), early postoperative obstruction (unless it does not improve in 2 wk), and various inflammatory conditions (IBD, radiation enteritis, diverticulitis, acute Crohn disease).

Elective operation

Indications include nontoxic, nontender sigmoid volvulus with sigmoidoscopically managed obstruction; recurrent adhesive or stricture-related small bowel obstruction; partial colonic obstruction unresponsive to 24 hr of nonoperative therapy; development and resolution of small bowel obstruction in patient who has never undergone abdominal operation.

Table 1 Causes of Ileus

Intra-abdominal causes
Intraperitoneal problems
Peritonitis or abscess
Inflammatory condition
Mechanical: operation, foreign body
Chemical: gastric juice, bile, blood
Autoimmune: serositis, vasculitis
Intestinal ischemia: arterial or venous, sickle cell disease
Retroperitoneal problems
Pancreatitis
Retroperitoneal hematoma
Spine fracture
Aortic operation
Renal colic
Pyelonephritis
Metastasis
Extra-abdominal causes
Thoracic problems
Myocardial infarction
Pneumonia
Congestive heart failure
Rib fractures
Metabolic abnormalities
Electrolyte imbalance (e.g., hypokalemia)
Sepsis
Lead poisoning
Porphyria
Hypothyroidism
Hypoparathyroidism
Uremia
Medicines
Opiates
Anticholinergics
Alpha agonists
Antihistamines
Catecholamines
Spinal cord injury or operations
Head, thoracic, or retroperitoneal trauma
Chemotherapy, radiation therapy

Table 2 Causes of Small Bowel Obstruction in Adults

Extrinsic causes
Adhesions*
Hernias (external, internal [paraduodenal], incisional)*
Metastatic cancer*
Volvulus
Intra-abdominal abscess
Intra-abdominal hematoma
Pancreatic pseudocyst
Intra-abdominal drains
Tight fascial opening at stoma
Intraluminal causes
Tumors*
Gallstones
Foreign body
Worms
Bezoars
Intramural abnormalities
Tumors
Strictures
Hematoma
Intussusception[see Figure 3]
Regional enteritis
Radiation enteritis

*Approximately 85% of all small bowel obstructions are secondary to adhesions, hernias, or tumors.

Table 3 Causes of Colonic Obstruction

Common causes
Cancer (primary, anastomotic, metastatic)
Volvulus
Diverticulitis
Pseudo-obstruction
Hernia
Anastomotic stricture
Unusual causes
Intussusception
Fecal impaction
Strictures (from one of the following)
Inflammatory bowel disease
Endometriosis
Radiation therapy
Ischemia
Foreign body
Extrinsic compression by a mass
Pancreatic pseudocyst
Hematoma
Metastasis
Primary tumors

operations, (3) a history of abdominal cancer, and (4) a history of intra-abdominal inflammation (e.g., inflammatory bowel disease, cholecystitis, pancreatitis, pelvic inflammatory disease, or abdominal trauma). Any of these factors increases the chance that the obstruction is secondary to an adhesion or recurrent cancer. Obstructive symptoms that come and go suddenly over several days in a patient older than 65 years should increase the index of suspicion for gallstone ileus.⁴ If the patient has experienced episodes of obstruction before, one should ask about the etiology and the response to treatment. If the patient has ever undergone an abdominal operation, one should try to obtain and read the operative report, which can provide a great deal of helpful information (e.g., description of adhesions, assessment of their severity, and evaluation of intra-abdominal pathology and anatomy). If abdominal cancer was present, one should find out what operation was performed and attempt to determine the likelihood of intra-abdominal recurrence.

The clinical setting often provides clues to the cause and type of bowel obstruction. In hospitalized patients, there is likely to be an associated medical condition or metabolic derangement that led to obstruction. A thorough review of the patient's medical history and hospital course should be undertaken to identify precipitating events that could have led to intestinal obstipation. One should ask the patient about any previous abdominal irradiation and should note and take into account all medications the patient is taking, especially anticoagulants and agents with anticholinergic side effects. Patients who are receiving chemotherapy or have undergone abdominal radiation therapy are prone to ileus. Severe infection, fluid and electrolyte imbalances, narcotic and anticholinergic medications, and intra-abdominal inflammation of any origin may be implicated. Acute massive abdominal distention in a hospitalized patient usually results from acute gastric distention, small bowel ileus, or acute colonic pseudo-obstruction. Excessive anticoagulation can lead to retroperitoneal, intra-abdominal, or intramural hematoma that can cause mechanical obstruction or ileus. Finally, there are specific problems that tend to arise in the postoperative period; these are discussed more fully elsewhere [see Urgent

Operation, Early Postoperative Technical Complications, No Operation, and Early Postoperative Obstruction, *below*].

PHYSICAL EXAMINATION AND RESUSCITATION

The initial steps in the physical examination are (1) developing a gestalt of the patient's illness and (2) assessing the patient's vital signs, hydration status, and cardiopulmonary system. A nasogastric tube, a Foley catheter, and an intravenous (IV) line are placed immediately while the physical examination is in progress. The volume and character of the gastric aspirate and urine are noted. A clear, gastric effluent is suggestive of gastric outlet obstruction. A bilious, nonfeculent aspirate is a typical sign of medial to proximal small bowel obstruction or colonic obstruction with a competent ileocecal valve. A feculent aspirate is a typical sign of distal small bowel obstruction. Volume replacement, if necessary, is initiated with isotonic saline solution or lactated Ringer solution. Urine output must be adequate (at least 0.5 mL/kg/hr) before the patient can be taken to the operating room (OR); supplemental potassium chloride (40 mEq/L) is administered once this is achieved.

Fever may be present, suggesting that the obstruction may be a manifestation of an intra-abdominal abscess. Signs of pneumonia or myocardial infarction should be sought: these conditions, like intestinal obstruction, can have upper abdominal pain, distention, nausea, and vomiting as presenting symptoms. Dyspnea and labored breathing may occur secondary to severe abdominal distention or pain, in which case, immediate relief should be provided by placing the patient in the lateral decubitus position and offering narcotics as soon as the initial physical examination is performed. Jaundice raises the possibility of gallstone ileus or metastatic cancer.

Examination of the abdomen proceeds in an orderly manner from observation to auscultation to palpation and percussion. The patient is placed in the supine position with the legs flexed at the hip to decrease tension on the rectus muscles. The degree of abdominal distention observed varies, depending on the level of obstruction: proximal obstructions may cause little or no distention. Abdominal scars should be noted. Abdominal asymmetry or a protruding mass suggests an underlying malignancy, an abscess, or closed-loop obstruction. The abdominal wall should be observed for evidence of peristaltic waves, which are indicative of acute small bowel obstruction.

Auscultation should be performed for at least 3 to 4 minutes to determine the presence and quality of bowel sounds. High-pitched bowel tones, tingles, and rushes are suggestive of an obstructive process, especially when temporally associated with waves of crampy pain, nausea, or vomiting. The absence of bowel tones is typical of intestinal paralysis but may also indicate intestinal fatigue from long-standing obstruction, closed-loop obstruction, or pseudo-obstruction.

Approximately 70% of patients with bowel obstruction have symmetrical tenderness, whereas fewer than 50% have rebound tenderness, guarding, or rigidity.³ The traditional teaching is that localized tenderness and guarding indicate underlying strangulated bowel; however, prospective studies have demonstrated that these physical findings are neither specific nor sensitive

for detecting underlying strangulation⁵ or even obstruction.³ Nevertheless, most surgeons still believe that guarding, rebound tenderness, and localized tenderness reflect underlying strangulation and therefore are indications for operation. Patients with ileus tend to have generalized abdominal tenderness that cannot be distinguished from the tenderness of mechanical obstruction. Gentle percussion is performed over all quadrants of the abdomen to search for areas of dullness (suggestive of an underlying mass), tympany (suggestive of underlying distended bowel), and peritoneal irritation.

A thorough search is made for inguinal, femoral, umbilical, and incisional hernias. The rectum is examined for masses, fecal impaction, and occult blood. If the patient has an ileostomy or a colostomy, the stoma is examined digitally to make sure that there is no obstruction at the level of the fascia.

Investigative Studies

IMAGING

One should obtain a chest x-ray in all patients with bowel obstruction to exclude a pneumonic process and to look for subdiaphragmatic air. In most cases, supine, upright, or lateral decubitus films of the abdomen can distinguish the type of obstruction present (mechanical or nonmechanical, partial or complete) and establish the location of the obstruction (stomach, small bowel, or colon). A useful technique for evaluating abdominal radiographs is to look systematically for intestinal gas along the normal route of the GI tract, beginning at the stomach, continuing through the small bowel, and, finally, following the course of the colon to the rectum. The following questions should be kept in mind as this is done:

- Are there abnormally dilated loops of bowel, signs of small bowel dilatation, or air-fluid levels?
- Are air-fluid levels and bowel loops in the same place on supine and upright films?
- Is there gas throughout the entire length of the colon (suggestive of ileus or partial mechanical obstruction)?
- Is there a paucity of distal colonic gas or an abrupt cutoff of colonic gas with proximal colonic distention and air-fluid levels (suggestive of complete or near-complete colonic obstruction)?
- Is there evidence of strangulation (e.g., thickened small bowel loops, mucosal thumb printing, pneumatosis cystoides intestinalis, or free peritoneal air)?
- Is there massive distention of the colon, especially of the cecum or sigmoid (suggestive of either volvulus or pseudo-obstruction)?
- Are there any biliary or renal calculi, and is there any air in the biliary tree (suggestive of gallstone ileus⁶ or a renal stone that could be causing ileus)?

It is important to be able to distinguish between small and large bowel gas. Gas in a distended small bowel outlines the valvulae conniventes, which traverse the entire diameter of the bowel lumen [see Figure 1]. Gas in a distended colon, on the other hand, outlines the colonic haustral markings, which cross only part of the bowel lumen and typically interdigitate

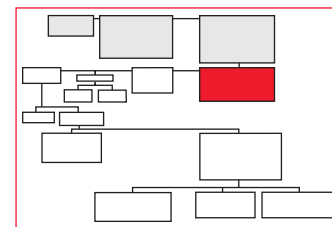
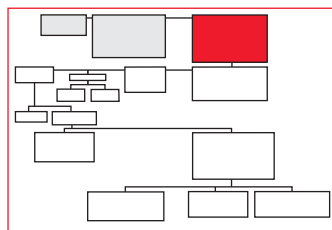




Figure 1 Supine radiograph from a patient with complete small bowel obstruction shows distended small bowel loops in the central abdomen with prominent valvulae conniventes (small white arrow). The bowel wall between the loops is thickened and edematous (large white arrow). No air is seen in the colon or the rectum. Note the presence of an isolated small bowel loop in the right lower quadrant (black arrow), which is seen fixed in the same location on upright films, as shown in Figure 4.

[see Figure 2 and Figure 3]. Distended small bowel loops usually occupy the central abdomen [see Figure 1], whereas distended large bowel loops are typically seen around the periphery [see Figure 2]. In patients with ileus, distention usually extends uniformly throughout the stomach, the small bowel, and the colon [see Figure 3], and air-fluid levels may be found in the colon and the small intestine.

Patients with gastric outlet obstruction or gastric atony typically have a giant gastric bubble if no nasogastric tube has been placed, with little or no air in the small bowel or the colon. Patients with mechanical small bowel obstruction usually have multiple air-fluid levels, with distended bowel loops of varying sizes arranged in an inverted U configuration [see Figure 4]. A dilated loop of small bowel appearing in the same location on supine and upright films suggests obstruction of a fixed segment of bowel by an adhesion or an internal hernia [see Figure 1 and Figure 4]. Small bowel obstruction is often accompanied by a paucity of gas in the colon. The complete absence of colonic gas is strongly suggestive of complete small bowel obstruction; however, the presence of colonic gas

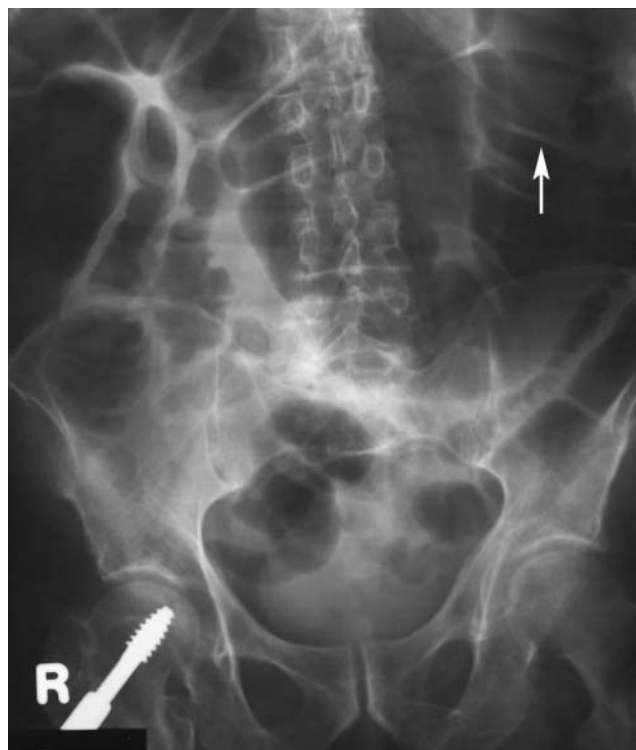


Figure 2 Radiograph from a patient with acute colonic pseudo-obstruction shows a dilated colon with haustral markings (white arrow) and edematous small bowel loops (black arrow). Air extends down to the distal sigmoid. This picture is also consistent with rectal obstruction, which could have been excluded by rigid sigmoidoscopy.

does not exclude complete small bowel obstruction in that there may have been unevacuated gas distal to a point of complete obstruction before the radiograph was taken. On the other hand, if repeat radiographs demonstrate decreased or absent colonic or rectal gas in a patient with small bowel obstruction who previously had more colonic or rectal gas, it is probable that partial obstruction has become complete, and immediate operation is almost always indicated. High-grade obstruction of the colon with an incompetent ileocecal valve may manifest itself as distended small bowel loops with air-fluid levels, thereby mimicking small bowel obstruction. Hence, it is sometimes necessary to perform a barium enema to exclude colonic obstruction.

Massive gaseous distention of the colon is usually secondary to distal colonic or rectal obstruction, volvulus, or pseudo-obstruction [see Figure 2, Figure 5, Figure 6, and Figure 7]. There are well-defined radiographic criteria that are highly sensitive and specific for sigmoid volvulus.⁶ If there is any uncertainty regarding the presence, type, or level of colonic obstruction, immediate sigmoidoscopy followed by barium enema is diagnostic.

LABORATORY TESTS

Serum electrolyte concentrations, the hematocrit, the serum creatinine concentration, and the coagulation profile (prothrombin time [or international normalized ratio] and platelet count) are helpful in determining the severity of

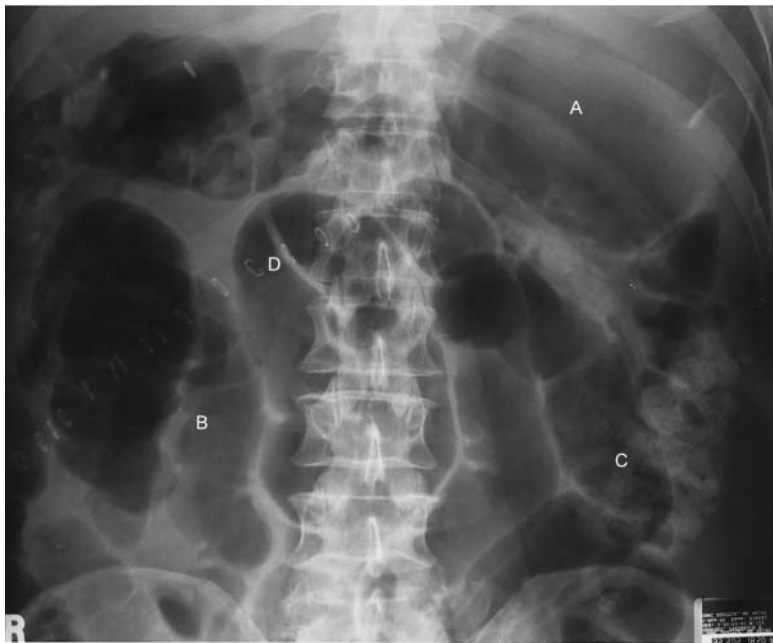


Figure 3 Radiograph from a patient with postoperative ileus shows massive gastric distention (A), distended small bowel loops (B), air throughout the colon, mild dilatation of the sigmoid colon (C) with air mixed with stool, and a haustral fold in the apex of the sigmoid colon (D).

volume depletion and guiding resuscitative efforts. If ileus is suspected, serum magnesium and calcium levels should be measured, and urinalysis should be done to check for hematuria.

Determination of Need for Operation and Classification of Obstruction

The combination of a thorough history, a carefully performed physical examination, and correctly interpreted abdominal radiographs usually allows an experienced surgeon to identify the type of bowel obstruction present and to decide whether a patient requires immediate, urgent, or delayed operation [see Table 4] or can safely be treated initially with nonoperative measures. On the other hand, experienced surgeons may also have difficulty in properly identifying the cause and in deciding when to operate on a patient with intestinal obstruction. Given the importance of establishing a timely and accurate diagnosis on patient outcomes, it is strongly recommended that all patients suspected of having intestinal obstruction be admitted to a surgical hospital service; failure to do so can increase patient morbidity and mortality.⁷ To this end, it is particularly important and useful to stratify patients into those with mechanical obstruction and those with nonmechanical obstruction. In patients with mechanical bowel obstruction, an effort should be made to determine whether the obstruction is complete or partial. Except for a few clinical situations, patients with complete bowel obstruction require immediate operation; conversely, patients with partial bowel obstruction rarely do.

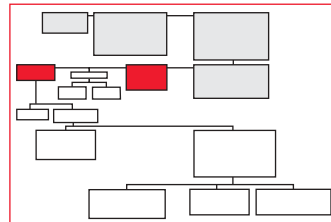


Figure 4 Upright radiograph from the same patient as the supine radiograph in Figure 1 shows multiple air-fluid levels of varying size arranged in inverted Us. In the right lower pelvis, a loop of small bowel is seen in exactly the same location as on the supine abdominal film (black arrow), a finding suggestive of adhesive obstruction.

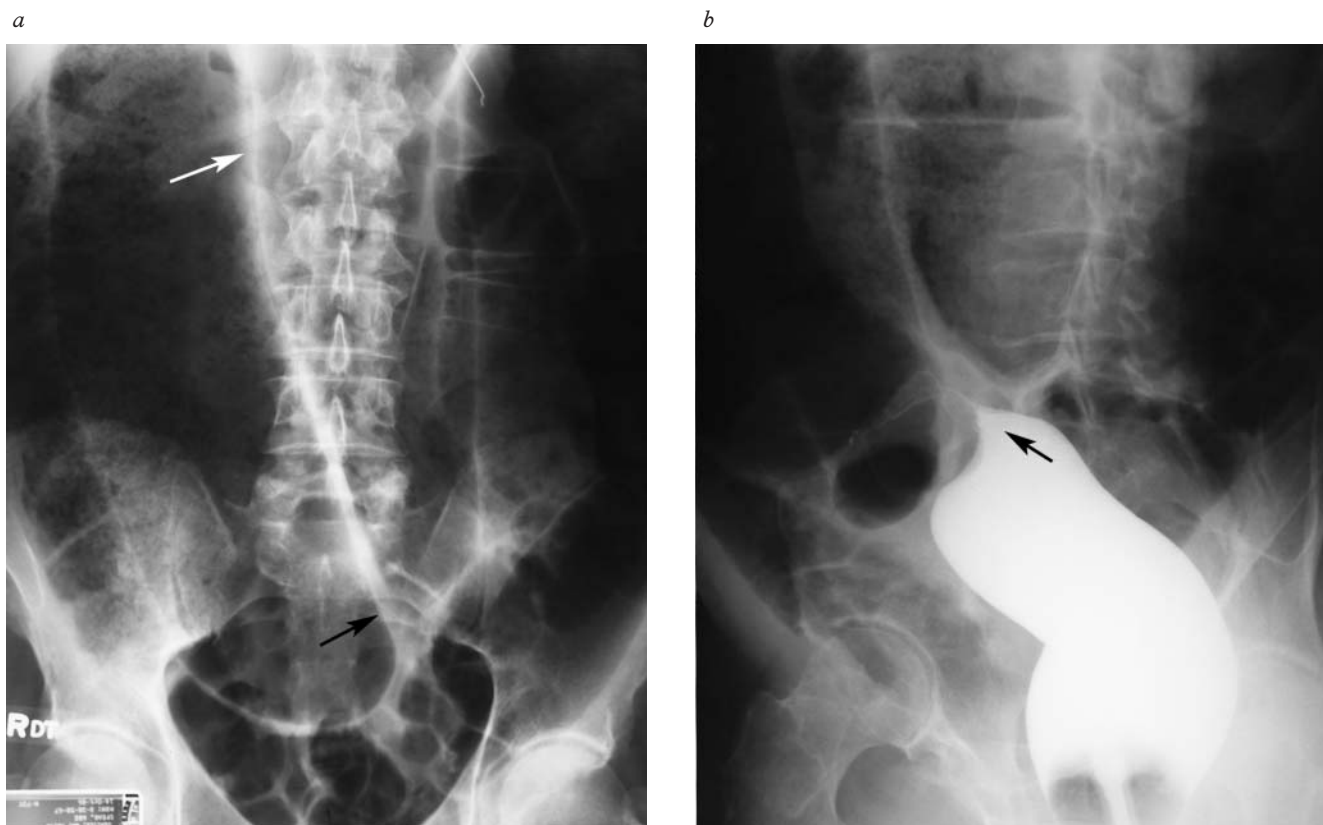


Figure 5 (a) Radiograph from a patient with massive sigmoid volvulus shows a distended ahastral sigmoid loop (*white arrow*), inferior convergence of the walls of the sigmoid loop to the left of the midline, and approximation of the medial walls of the sigmoid loop as a summation line (*black arrow*). (b) Barium enema of the colon shows a tapered obstruction at the rectosigmoid junction with a typical bird's beak deformity (*black arrow*).

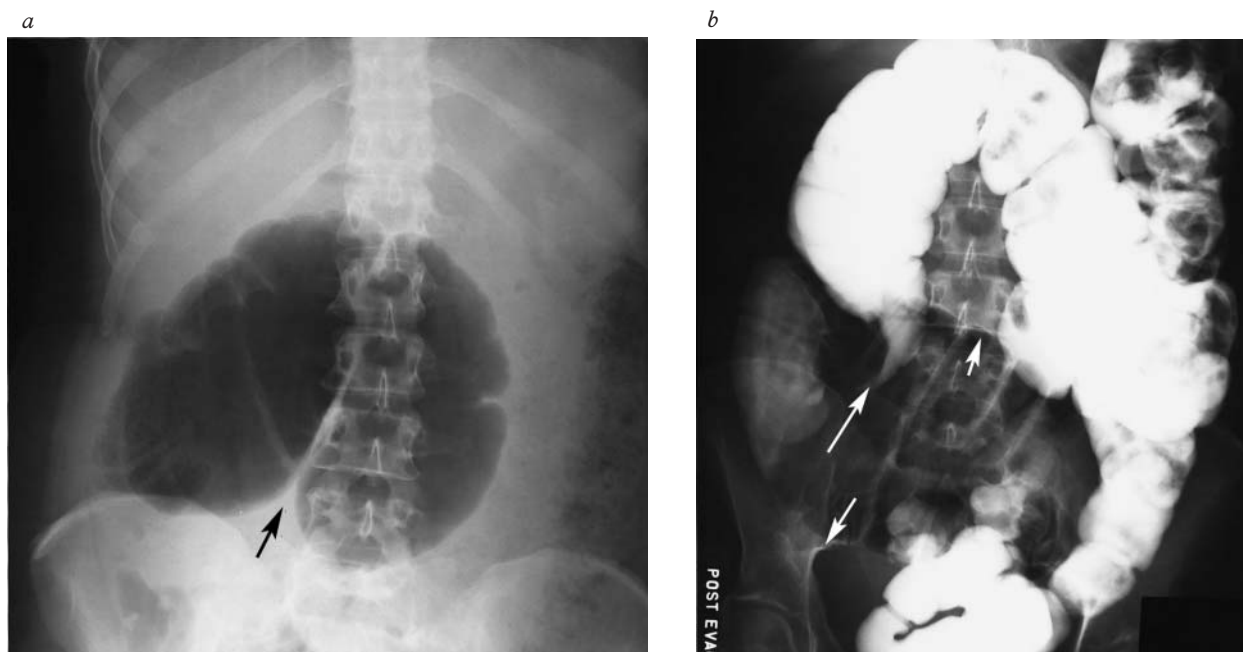


Figure 6 (a) Radiograph from a patient with cecal volvulus shows a dilated cecum with no air distally in the colorectum. Convergence of the medial walls of the loop (*black arrow*) points to the right, a typical finding in cecal volvulus. (b) Barium examination demonstrates a bird's beak deformity tapering at the point of volvulus (*large white arrow*). Note walls of dilated cecum (*small white arrows*).



Figure 7 Radiograph from a patient with complete colonic obstruction from an obstructing carcinoma in the descending left colon with proximal air-fluid levels. The absence of air distally in the rectum or the sigmoid is suggestive of complete obstruction. The ileocecal valve is competent; thus, there is no small bowel air.

Finally, an effort should be made to establish the level and cause of obstruction because these factors often help guide therapy and affect the probability of success in response to specific therapeutic intervention. Patients with nonmechanical obstruction, which derives from ileus or pseudo-obstruction [see Ileus and Pseudo-obstruction, below], do not require immediate operation.

Table 4 Guidelines for Operative and Nonoperative Therapy

Situations necessitating emergent operation
Incarcerated, strangulated hernias
Peritonitis
Pneumatosis cystoides intestinalis
Pneumoperitoneum
Suspected or proven intestinal strangulation
Closed-loop obstruction
Nonsigmoid colonic volvulus
Sigmoid volvulus associated with toxicity or peritoneal signs
Complete bowel obstruction
Situations necessitating urgent operation
Progressive bowel obstruction at any time after nonoperative measures are started
Failure to improve with conservative therapy within 24–48 hr
Early postoperative technical complications
Situations in which delayed operation is usually safe
Immediate postoperative obstruction
Sigmoid volvulus successfully decompressed by sigmoidoscopy
Acute exacerbation of Crohn disease, diverticulitis, or radiation enteritis
Chronic, recurrent partial obstruction
Paraduodenal hernia
Gastric outlet obstruction
Postoperative adhesions
Resolved partial colonic obstruction

ADJUNCTIVE TESTS FOR EQUIVOCAL SITUATIONS

Sigmoidoscopy

When one is uncertain whether or not the obstruction is mechanical on the basis of the information in hand, additional diagnostic measures are immediately indicated. When large amounts of colonic air extend down to the rectum, flexible or rigid sigmoidoscopy will readily exclude a rectal or distal sigmoid obstruction. Care must be exercised to avoid insufflating large amounts of air during endoscopy: excessive insufflation can cause overdistention of the colon above the level of the possible obstruction, which can be counterproductive and harmful. If sigmoidoscopy yields normal findings but partial colonic obstruction seems to be the correct diagnosis, a water-soluble contrast enema should be administered.⁸

Barium studies may be harmful in patients with acute obstruction when they are performed before the nature of the obstruction (complete or partial) is determined. Abdominal ultrasonography, although not as definitive as a contrast examination, is also able to diagnose suspected colonic obstruction in 85% of patients.⁹

Ultrasonography, Computed Tomography, and Fast Magnetic Resonance Imaging

Abdominal radiographs can be entirely normal in patients with complete, closed-loop, or strangulation obstruction.⁹ Therefore, if the patient's clinical profile and the results of physical examination are consistent with intestinal obstruction despite normal abdominal radiographs, abdominal ultrasonography, computed tomography (CT), or fast magnetic resonance imaging (MRI) should be performed immediately.^{10–19} All three modalities are highly sensitive and specific for intestinal obstruction when performed properly and interpreted by experienced clinicians. Two prospective clinical trials found ultrasonography to be as sensitive as and more specific than abdominal radiography in diagnosing intestinal obstruction.^{20,21} Ultrasonography, CT, and fast MRI are all capable of detecting the cause of the obstruction, as well as the presence of closed-loop or strangulation obstruction.^{9,11,16–19,22–25}

Sonographic criteria have been established for small bowel and colonic obstruction^{9,22,23}: (1) simultaneous observation of distended and collapsed bowel segments, (2) free peritoneal fluid, (3) inspissated intestinal contents, (4) paradoxical pendulating peristalsis, (5) highly reflective fluid within the bowel lumen, (6) bowel wall edema between serosa and mucosa, and (7) a fixed mass of aperistaltic, fluid-filled, dilated intestinal loops. One group of authors has recommended that when abdominal radiographs are inconclusive or normal in patients with suspected colonic obstruction, ultrasonography, rather than CT or barium enema, should be the next diagnostic step.⁹ Ultrasonography is well suited to critically ill patients: because it can be performed at the bedside, the risk associated with transport to the radiology suite is avoided. Given that ultrasonography is relatively inexpensive, is easy and quick to perform, and often can provide a great deal of information about the location, nature, and severity of the obstruction, it should be employed early in the evaluation of all patients with intestinal obstruction.²⁰

Several authors have recommended that patients with suspected small bowel obstruction and equivocal plain abdominal films undergo CT before a small bowel contrast series is



Figure 8 Computed tomography scan from a patient with partial small bowel obstruction shows distended, fluid-filled loops of small bowel with air-fluid levels, hyperemia, and bowel wall thickening (large white arrow). Note the discrepancy in caliber between dilated small bowel and decompressed small bowel (dashed white arrow) and the stranding (small black arrow) in the small bowel mesentery. Air in a decompressed descending colon (large black arrow) is indicative of partial obstruction.

ordered.^{12–15} CT has several advantages over a small bowel contrast examination in this setting: (1) it can ascertain the level of obstruction, (2) it can assess the severity of the obstruction and determine its cause, and (3) it can detect closed-loop obstruction and early strangulation [see Figure 8, Figure 9, Figure 10, and Figure 11]. CT can also detect

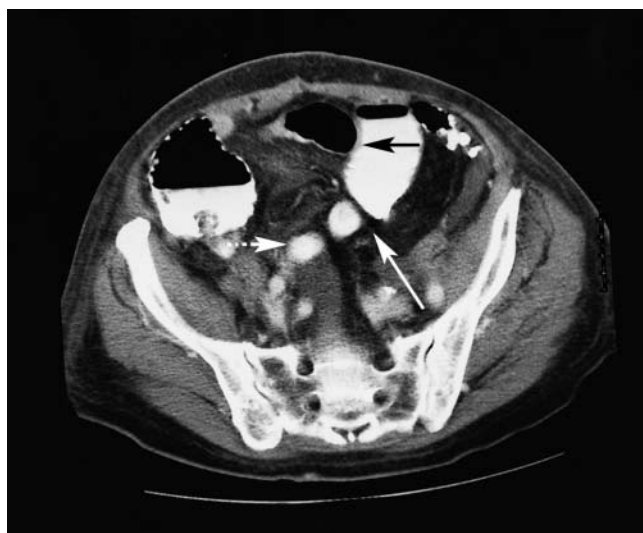


Figure 9 Computed tomography scan from a patient with adhesive partial small bowel obstruction shows a massively dilated small intestine (black arrow) proximal to a thick adhesive band (large white arrow) and decompressed small bowel distal to the adhesion (dashed white arrow). The patient was operated on because of the low probability that this obstruction would resolve with conservative management.



Figure 10 Computed tomography (CT) scan from a patient with partial small bowel obstruction from cancer shows a distended small bowel (dashed white arrows) proximal to a mass (small white arrow). There is air in the cecum (black arrow), the transverse colon, and the descending colon (large white arrow). The small bowel is maximally dilated, with a hyperemic, edematous bowel wall (B) just proximal to an obstructing recurrent colon carcinoma. Even though plain radiographs showed partial small bowel obstruction, this CT scan led to early operation because continued nonoperative management would not resolve the problem.

inflammatory or neoplastic processes both outside and inside the peritoneal cavity and can visualize small amounts of intra-peritoneal air or pneumatosis cystoides intestinalis not seen on conventional films [see Figure 10]. Prospective studies have demonstrated that the accuracy of CT in diagnosing bowel obstruction is higher than 95% and that its sensitivity and



Figure 11 Early closed-loop small bowel obstruction computed tomography (CT) scan from a patient with early closed-loop obstruction of the small intestine shows a markedly edematous, hyperemic small bowel, a finding indicative of early strangulation (white arrow). The patient had minimal symptoms, and there was air in the transverse colon and the descending colon (a finding indicative of partial small bowel obstruction); however, the finding of a gangrenous, nonperforated small bowel on this CT scan led to an early operation.

specificity are each higher than 94%.^{24,25} CT distinguishes colonic mechanical obstruction from pseudo-obstruction more accurately than conventional films do and thus is the preferred modality in many cases.²⁶

There is evidence to indicate that fast MRI with T₂-weighted (spin-spin relaxation time) images is more sensitive, specific, and accurate than contrast-enhanced helical CT in establishing the location and cause of bowel obstruction.¹⁸ The advantages of fast MRI over helical CT are (1) that the image acquisition time is short (1 to 2 seconds per slice), which means that the image can be acquired in the space of a single held breath; (2) no contrast agents are required; and (3) the avoidance of ionizing radiation. In addition, because of its multiplanar capability, MRI is also more effective at demonstrating the transition point of the obstruction and the ability to provide real-time and functional evaluation.²⁷ When helical CT is nondiagnostic in a patient with suspected bowel obstruction and fast MRI is not available, a small bowel follow-through examination with dilute barium is often useful.¹⁵

Contrast Studies

Enteroclysis (direct injection of BaSO₄ into the small bowel) is generally considered the most sensitive method of distinguishing between ileus and partial mechanical small bowel obstruction: it has a diagnostic sensitivity of 87% for adhesive obstruction.^{28,29} Many surgeons are concerned that injection of barium might cause partial obstruction to progress to complete obstruction; however, there is no evidence that this ever occurs, and one therefore should not refrain from using barium to diagnose partial small bowel obstruction.^{30–33} If complete obstruction is identified, the patient should undergo immediate operation. If partial obstruction is identified in either the small or the large bowel, the patient is treated accordingly. If (1) mechanical obstruction is not identified and (2) a point of obstruction, as evidenced by the finding of both dilated and decompressed intestinal loops, cannot be identified through abdominal ultrasonography, CT, or fast MRI, then the diagnosis is almost certainly ileus, in which case, one's attention is directed toward identifying and correcting the underlying precipitating cause [see Table 1 and Mechanical Obstruction, No Operation, and Adhesive Partial Small Bowel Obstruction, below].

Mechanical Obstruction

MALIGNANT BOWEL OBSTRUCTION

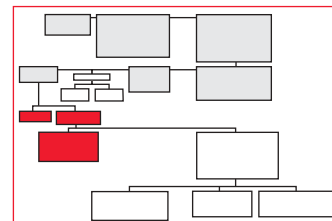
Malignant bowel obstruction (MBO) is a serious complication and most commonly affects patients with abdominal and pelvic tumors. Some patients will present with advanced disease for which curative surgical intervention is not feasible. For those patients, palliative efforts should focus on controlling gastrointestinal symptoms and restoring or preserving quality of life. Avoidance of operation in these patients is desirable. Etiologies for MBO include extrinsic occlusion of the lumen, malignant infiltration of mesentery and intestinal muscle and serosal surfaces, and intraluminal obstruction. Intestinal immobility secondary to opioids, certain antiemetics, and secondary adrenal insufficiency³⁴ may all play a role in MBO. Early and intensive pharmacologic treatment

with a combination of antisecretory drugs, analgesics, and antiemetics has been shown to be effective in controlling GI symptoms and even reverse functional MBO.³⁵ Three prospective, randomized clinical trials demonstrated that octreotide significantly attenuated the severity of nausea and vomiting and the degree of subjective discomfort in patients with inoperable obstruction and permitted the discontinuance of nasogastric tube decompression.^{36–38} One of these studies also demonstrated that octreotide significantly reduced the degree of fatigue and anorexia experienced.³⁸ One trial demonstrated the safety and efficacy of intramuscular long-acting octreotide once a month in patients with advanced cancer in relieving the symptoms of bowel obstruction.³⁹ Some patients with proximal or distal high-grade MBO may be successfully treated by endoscopic deployment of intraluminal stents and thus avoid laparotomy.^{40–42} This treatment option not only provides a better quality of life for patients with colorectal obstruction without the psychological repercussions of a colostomy but also appears to be cost-effective.⁴³ When long-term gastric decompression is required for palliation in a terminally ill patient with gastroduodenal obstruction, percutaneous endoscopic gastrostomy or jejunostomy should be considered [see 5:18 Gastrointestinal Endoscopy].⁴⁴ Patients who do not wish to die of MBO in a hospital should be offered hospice care or home visiting nurse services with continuous octreotide infusion, IV rehydration, and gastrostomy decompression.^{45,46} Attention must always be paid to quality-of-life issues and to the patient's potential interest in pursuing nonoperative forms of palliation. For many terminally ill or incurable patients with bowel obstruction, the most humane and sensible treatment comprises nothing more than instituting comfort measures, including continuous morphine infusion, rehydration, and administration of antisecretory agents.^{36,37,47}

IMMEDIATE OPERATION

All patients with complete bowel obstruction, whether of the small or large intestine, should undergo immediate operation unless extraordinary circumstances (e.g., diffuse carcinomatosis, terminal illness, or sigmoid volvulus that responds to sigmoidoscopic decompression) are present. If one attempts to manage complete intestinal obstruction nonoperatively, one risks delaying definitive treatment of patients with intestinal ischemia and subjecting them to significantly increased morbidity and mortality should perforation or severe infection develop.^{5,48}

Immediate operation is also indicated when bowel obstruction is associated with peritonitis; incarcerated strangulated hernias; suspected or confirmed strangulation; pneumatosis cystoides intestinalis; sigmoid volvulus accompanied by systemic toxicity or peritoneal irritation; colonic volvulus above the sigmoid colon; or fecal impaction. These conditions will not resolve without operation and are associated with increased morbidity, mortality, and cost if diagnosis and treatment are delayed. The only time one would not operate immediately on any patient with one of these diagnoses is when the patient requires cardiopulmonary stabilization,



additional resuscitation, or both. Whenever there is any doubt as to the presence of any of these conditions, additional diagnostic tests (e.g., ultrasonography, CT, fast MRI, or contrast studies) are indicated to confirm or exclude them.

Strangulation and Closed-Loop Obstruction

Morbidity and mortality from intestinal obstruction vary significantly and depend primarily on the presence of strangulation and subsequent infection. Strangulation obstruction occurs in approximately 10% of all patients with small intestinal obstruction. It carries a mortality of 10 to 37%, whereas simple obstruction carries a mortality of less than 5%.^{5,30,49,50} Early recognition and immediate operative treatment of strangulation obstruction are the only current means of decreasing this mortality. Strangulation obstruction occurs most frequently in patients with incarcerated hernias, closed-loop obstruction, volvulus, or complete bowel obstruction; hence, identification of any of these specific causes of obstruction is an important and clear indication for immediate operation. Radiographic evidence of pneumatosis cystoides intestinalis or free intraperitoneal air in a patient with a clinical picture of bowel obstruction is indicative of strangulation, perforation, or both and constitutes an indication for operation. High-quality abdominal CT with IV contrast can detect advanced strangulation and identify early, reversible strangulation [see Figure 11].^{14,16,17}

Abdominal ultrasonography can also identify edematous, hemorrhagic loops of intestine. Accordingly, whenever one is concerned about possible strangulation or closed-loop obstruction but is not yet committed to taking the patient immediately to the OR, an ultrasonogram or a CT scan should be obtained. In fact, given that ultrasonography, CT, and fast MRI are the only well-established means of diagnosing strangulation obstruction short of exploratory laparotomy or laparoscopy, an argument can be made that one of these modalities should be performed in all patients who have been admitted to the hospital with bowel obstruction and are initially being treated nonoperatively.

Many surgeons base the decision of whether to operate on patients with bowel obstruction on the presence or absence of the so-called classic signs of strangulation obstruction—continuous abdominal pain, fever, tachycardia, peritoneal signs, and leukocytosis—and on their clinical experience. Unfortunately, these classically taught signs, even in conjunction with abdominal x-rays and clinical judgment, are incapable of reliably detecting closed-loop or gangrenous bowel obstruction.^{5,30,48,51} In fact, one prospective clinical trial concluded that the five classic signs of strangulation obstruction and experienced clinical judgment were not sensitive for, specific for, or predictive of strangulation⁵: in more than 50% of the patients who had intestinal strangulation, the condition was not recognized preoperatively. Such findings suggest that early nonoperative recognition of intestinal strangulation is not feasible without ultrasonography, CT, or fast MRI. On the other hand, CT findings consistent with intestinal obstruction, when combined with the above clinical stigma (tenderness, tachycardia, fever, and leukocytosis), improve the diagnostic accuracy of CT scan to detect strangulated small bowel obstruction.⁵²

Incarcerated or Strangulated Hernias

A hernia that is incarcerated, tender, erythematous, warm, or edematous is an indication for immediate operation.

Primary or incisional hernias may not be palpable in obese patients, in which case, ultrasonography, CT [see Figure 12], or fast MRI should be performed.

Nonsigmoid Volvulus and Sigmoid Volvulus with Systemic Toxicity or Peritoneal Signs

All intestinal volvuli are closed-loop obstructions and thus carry a high risk of intestinal strangulation, infarction, and perforation. Patients typically present with acute, colicky abdominal pain, massive distention, nausea, and vomiting. Sigmoid volvulus is the most common form of colonic volvulus, followed by cecal volvulus. Abdominal radiographs are fairly diagnostic for colonic volvulus [see Figure 5 and Figure 6]. In contrast, small bowel volvulus may not be visualized on plain radiographs, because the closed loop fills completely with fluid and no air-fluid level can be seen. Small bowel volvulus is readily detected by ultrasonography or CT; one or both of these procedures should be performed in patients presenting with signs and symptoms of bowel obstruction and normal abdominal radiographs. Small bowel volvulus is an indication for immediate operation.

If one observes signs of systemic toxicity, a bloody rectal discharge, fever, leukocytosis, or peritoneal irritation in a patient with sigmoid volvulus, the patient should undergo immediate operation; if all of these signs are absent, the patient should undergo sigmoidoscopy. When there are no signs of peritonitis or generalized toxicity, sigmoidoscopic decompression is safe and effective in more than 95% of patients with sigmoid volvulus.⁵³ If mucosal gangrene or a bloody effluent is noted at the time of sigmoidoscopy, immediate operative intervention is necessary even in the absence of any clinical signs or symptoms of strangulation. After sigmoidoscopy, the patient can undergo elective bowel preparation and a single-stage sigmoid resection before being discharged from the hospital. If, however, clinical toxicity, a bloody rectal discharge, fever, or peritoneal irritation arises at any time after sigmoidoscopic decompression while the patient is being prepared for an elective procedure, immediate operation is indicated.

Patients with volvulus proximal to the sigmoid colon should undergo immediate operation regardless of whether peritoneal irritation is present. The incidence of strangulation infarction is high in such patients, and nonoperative therapy often fails. If the diagnosis of nonsigmoid colonic volvulus is in doubt, a barium enema is indicated to exclude colonic pseudo-obstruction.

Fecal Impaction

Complete colonic obstruction secondary to fecal impaction in the rectum can sometimes be successfully relieved through disimpaction at the bedside; however, this can be difficult and extremely uncomfortable for the patient. The most expeditious and successful method of relieving the obstruction is to disimpact the patient while he or she is under general or spinal anesthesia. In one study, the pulsed-irrigated enhanced-evacuation procedure, which can be performed at the bedside, successfully resolved fecal impaction in approximately 75% of geriatric patients.⁵⁴ In another study, administration of a polyethylene glycol 3350 solution over 3 days successfully resolved intestinal obstruction from fecal impaction in 75% of pediatric patients.⁵⁵

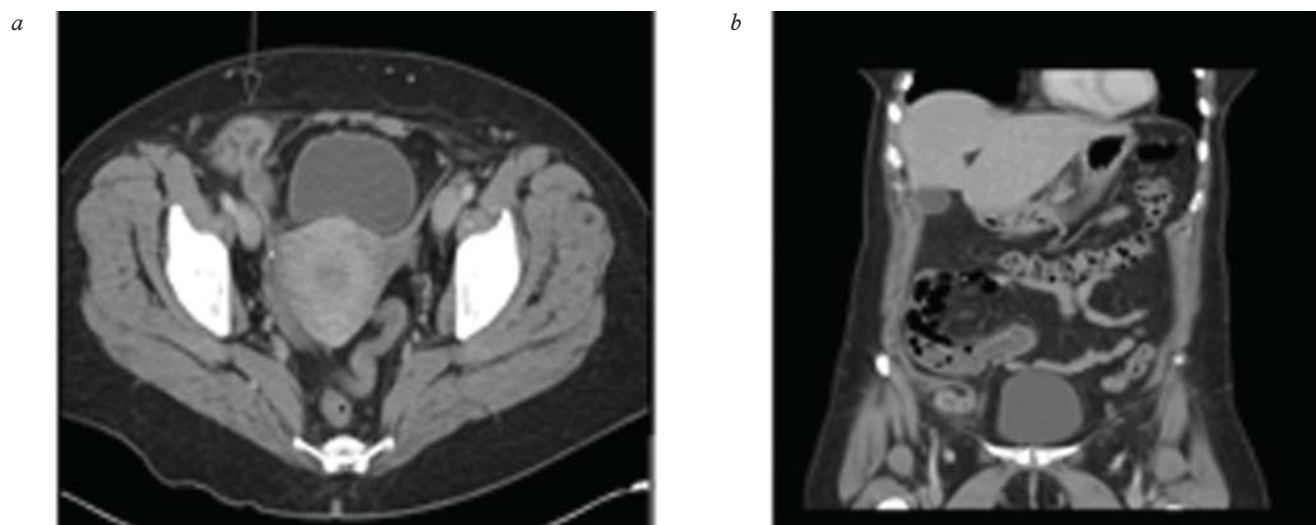


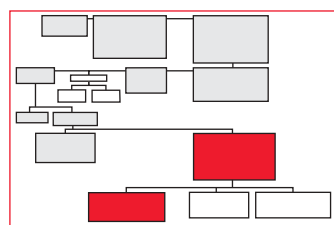
Figure 12 Sagittal (a) and coronal (b) views demonstrate an incarcerated/strangulated bowel in the right inguinal hernia.

URGENT OPERATION

Lack of Response to Nonoperative Therapy within 24 to 48 Hours

It is usually safe to manage partial bowel obstruction initially by nonoperative means: a nil per os (NPO) regimen, nasogastric decompression, analgesics, and octreotide. Such therapy is successful in most cases, especially if the cause of obstruction is postoperative adhesions, but there is always the risk that complete bowel obstruction or strangulation already exists but is undetected. Furthermore, there is the risk that while the patient is being observed, partial obstruction will progress to complete obstruction, or strangulation and perforation will develop. It is therefore crucial to be alert to changes in the patient's condition.

Repeated examination of the abdomen by the same clinician is the most sensitive way of detecting progressive obstruction. Examinations should be performed no less frequently than every 3 hours. If abdominal pain, tenderness, or distention increases or the gastric aspirate changes from nonfeculent to feculent, abdominal exploration is usually indicated. Abdominal radiographs should be repeated every 6 hours after nasogastric decompression and reviewed by the surgeon who is following the patient. If proximal small bowel distention increases or distal intestinal gas decreases, nonoperative therapy is less likely to be successful; in these circumstances, early operative intervention should be seriously considered. Conversely, if the patient's condition appears stable or improved and x-rays indicate that the obstruction either has resolved somewhat or at least is no worse, it is generally safe to continue nonoperative care for another 12 to 24 hours. If the clinical picture is stable after 24 hours of observation, one must decide whether to operate or to continue nonoperative therapy. Clinical judgment and experience, coupled with a thorough and accurate assessment of the patient's underlying



diagnosis and clinical condition, have traditionally been the most reliable guides for making this decision. Currently, however, it appears that the decision whether to operate can be made more cost-effectively and reliably on the basis of abdominal imaging studies [see No Operation and Adhesive Partial Small Bowel Obstruction, below].

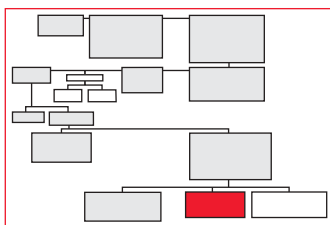
Early Postoperative Technical Complications

When normal bowel function initially returns after an abdominal operation but then is replaced by a clinical picture suggestive of early postoperative mechanical obstruction, the explanation may be a technical complication of the operation (e.g., phlegmon, abscess, intussusception, a narrow anastomosis, an internal hernia, or obstruction at the level of a stoma). An early, aggressive diagnostic workup should be performed to identify or exclude these problems because they are unlikely to respond to nasogastric decompression or other forms of conservative management. It is critical to know exactly what was done within the abdomen in the course of the operation. To this end, one should try to speak directly with the operating surgeon rather than attempt to deduce the needed information from the operative report.

If the patient had peritonitis or a colonic anastomosis at the initial operation, one should order a CT scan to look for an intra-abdominal abscess. An abscess or a phlegmon at the site of an anastomosis is usually secondary to anastomotic leakage and is an indication for reoperation. CT can also identify intra-abdominal hematomas, which should be evacuated through early reoperation. In patients recovering from a proctectomy, herniation of the small bowel through a defect in the pelvic floor is a common cause of intestinal obstruction. Oral contrast studies can help identify patients with an internal hernia, intussusception, or anastomotic obstruction and should be performed after the CT scan. A retrograde barium examination should be performed in patients thought to have a problem related to a stoma or an intestinal anastomosis. When none of the above factors appear to be the cause of the postoperative obstruction, it is reasonable for the surgeon to assume that the obstruction is secondary to postoperative adhesions, which are best treated conservatively (see below).

NO OPERATION

In selected patients, non-operative management of partial small bowel obstruction is highly successful and carries an acceptably low mortality. Such patients include those whose partial obstruction is secondary to intra-abdominal adhesions, occurs in the immediate postoperative period, or derives from an inflammatory condition (e.g., inflammatory bowel disease, radiation enteritis, or diverticulitis).



Adhesive Partial Small Bowel Obstruction

Adhesions are the major cause of bowel obstruction. Obstruction resulting from adhesions can occur as early as 1 month or as late as 20 years after operation.⁵⁶ Adhesive partial small bowel obstruction is treated initially with nasogastric decompression, IV rehydration, and analgesia. Parenteral nutrition should be begun if one believes that oral or enteral nutrition will not be adequate within 5 days. Non-operative therapy leads to resolution of adhesive partial obstruction in as many as 90% of patients^{57,58}; however, such resolution is followed by recurrence of obstruction in approximately 50% of cases.^{59,60} When operative adhesiolysis is performed, the mortality is less than 5% for patients with simple obstruction but may be as high as 30% for patients with strangulation or a necrotic bowel necessitating intestinal resection.⁵⁶ In view of this substantial difference in mortality, it is extremely important to be able to confidently distinguish obstruction that is likely to resolve with nonoperative treatment from obstruction that is not. Patients with adhesive partial obstruction that can be accurately predicted to resolve with medical therapy can and should be treated nonoperatively.

Some studies suggest that the nature of the previous abdominal operation or the type of adhesions present may influence the probability that the obstruction will not respond to medical therapy.^{61–65} Operations associated with a lower likelihood of response to medical therapy include those performed through a midline incision; those involving the aorta, colon, rectum, appendix, or pelvic adnexa; and those done to relieve previous carcinomatous obstruction. Matted adhesions, which are more common in patients who have undergone midline incisions or colorectal procedures, are less amenable to conservative management than a simple obstructive band is.⁶¹ In the context of this kind of operative history, strong consideration should be given to surgical intervention if the obstruction does not resolve within 24 hours—unless comorbid medical conditions tip the risk-benefit balance in the direction of nonoperative therapy.

There is an ongoing debate regarding how long patients with partial adhesive obstruction should be treated conservatively. After 48 hours of nonoperative management, the risk of complications increases substantially, and the probability that the obstruction will resolve diminishes.⁵⁰ Generally, if the obstruction is going to resolve with nonoperative therapy, there will be a fairly prompt response within the first 8 to 12 hours. Therefore, if a patient's condition has deteriorated or has not significantly improved by 12 hours after nasogastric decompression and resuscitation, exploratory laparotomy

is advisable. During this observation period, the patient must be constantly reevaluated, ideally by the same examiner. Analgesics can be safely administered, and repeat abdominal examinations should be performed at 3-hour intervals when the influence of narcotics has waned. Repeat abdominal x-rays should be obtained no later than 6 hours after nasogastric decompression, and the pattern of gas distribution should be compared with that seen on the admission films. A decrease in intestinal gas distal to a point of obstruction coupled with an increase in proximal dilatation suggests that the obstruction is worsening; conversely, a decrease in intestinal distention coupled with the appearance of more gas distally in the colon suggests that the obstruction is being reduced. The degree of abdominal distention, the passage of flatus, and the nature of the nasogastric aspirate should be evaluated periodically. If abdominal distention does not decrease or the gastric aspirate changes from bilious to feculent, the patient should be operated on.

Experimental and clinical studies suggest that patients undergoing nonoperative treatment of bowel obstruction may benefit from the administration of somatostatin analogues as a result of the potent effects these substances exert on intestinal sodium, chloride, and water absorption.⁶⁵ In one study, animals with either complete or closed-loop partial small bowel obstruction were given either long-acting somatostatin or saline; the treatment group had significantly less intestinal distention, less infarction, and longer survival than the control group.^{65,66} In a prospective, randomized clinical trial evaluating the use of somatostatin in patients who had complete small bowel obstruction without clinical or radiologic evidence of strangulation, the treatment group was less likely to need operation, had less proximal intestinal distention, and exhibited decreased mucosal necrosis proximal to the point of obstruction.⁶⁷ In other trials, long-acting somatostatin analogues and other nonsecretagogues significantly decreased the amount of gastric contents aspirated and alleviated the symptoms of intestinal obstruction in terminally ill patients with nonoperable malignant disease.^{36,38–47}

It should be possible to determine with a high degree of accuracy and safety which patients will require an operation for adhesive small bowel obstruction within 24 to 48 hours of admission to the hospital. As a rule, patients with closed-loop or complete bowel obstruction, who require an immediate or urgent operation, can be readily identified by means of abdominal CT or MRI.^{13–15,18,19} For the remaining patients, who have some degree of partial obstruction, the success or failure of conservative management can be predicted with high accuracy by recording the arrival of contrast material (either a water-soluble agent or a mixed barium preparation) in the right colon within a defined time.^{15,32} One prospective study documented the arrival of diatrizoate meglumine–diatrizoate sodium in the colon within 24 hours and found this measure to have a sensitivity of 98%, a specificity of 100%, an accuracy of 99%, a positive predictive value of 100%, and a negative predictive value of 96% as a predictor of successful nonoperative treatment.⁶⁸ Other studies achieved comparable results with shorter arrival times (e.g., 4 or 8 hours).^{15,69,70}

Several prospective, randomized clinical trials have addressed the issue of whether administration of contrast

material can itself be therapeutic with respect to resolving adhesive small bowel obstruction. Two such studies examined small bowel follow-through with barium, either alone or mixed with diatrizoate meglumine.^{32,33} Both found that the intervals between admission and operation were shorter for patients randomized to the contrast arm than for those in the control group but that contrast examination did not lead to more expeditious resolution of obstruction. Both studies also demonstrated that barium could be administered to patients with small bowel obstruction safely and without complications.

Meta-analysis investigating the effect of administering water-soluble hyperosmolar contrast agents to patients with small bowel obstruction revealed that the appearance of water-soluble contrast agent in the colon on an abdominal radiograph within 24 hours of its oral administration predicts the resolution of obstruction with a sensitivity of 97% and a specificity of 96%. Although a Gastrografin dose not reduce the need for an operation, it appears to shorten the hospital stay for those who do not require surgery [see Figure 13].⁷¹

By accelerating the resolution of partial small bowel obstruction and ileus, administration of water-soluble contrast agents can shorten the expected hospital stay and thereby reduce the cost of care. Thus, it is reasonable that the first step in managing suspected partial small bowel obstruction from adhesions or postoperative ileus should be to administer water-soluble contrast material intragastrically. When bowel function does not return within 24 hours and the obstruction is demonstrated to be partial, continued observation is safe and resolution without operation is still highly probable.



Figure 13 The presence of contrast in the colon after 4 hours of its administration predicts resolution of small bowel obstruction with a sensitivity of 97% and a specificity of 96%.

Eventually, however, there will be a point beyond which continued observation is no longer cost-effective in comparison with operative adhesiolysis (especially laparoscopic adhesiolysis). Additional prospective trials are necessary to determine precisely how long the waiting period before operative treatment should be.

Laparoscopic adhesiolysis Several clinical reports have demonstrated that laparoscopic adhesiolysis for acute small bowel obstruction is both feasible and safe.^{72–77} Laparoscopic or laparoscopic-assisted lysis of adhesions relieves bowel obstruction in more than 50% of patients and is associated with lower morbidity, earlier return of bowel function, quicker resumption of a normal diet, and a shorter hospital stay than open operative lysis.^{68–76,78} To minimize the risk of bowel injury at the beginning of the operation, the first trocar is inserted under direct vision by means of an open technique, and the incision is placed well away from any previous scars.^{79,80}

At present, there are no prospective, randomized, controlled clinical trials comparing laparoscopic with open adhesiolysis. In a retrospective, matched-pair analysis that used an intention-to-treat analysis, 52% of the patients in the laparoscopic group underwent conversion to open lysis of adhesions either for completion of adhesiolysis or for management of complications.⁷⁶ No perforations or recurrent obstructions were missed. Perforations were more common overall in the laparoscopic group than in the open group, although this difference was largely eliminated when patients from the laparoscopic group who underwent conversion to open lysis were not considered. Patients with two or more previous laparotomies had a higher incidence of intraoperative complications than those with fewer laparotomies. Accordingly, the authors recommended against laparoscopic adhesiolysis in patients with two or more previous laparotomies. The high conversion rate in this study notwithstanding, the laparoscopic group as a whole (including conversions) experienced an overall reduction in postoperative complications.

Another potential advantage of laparoscopic adhesiolysis is that it results in fewer intra-abdominal adhesions than open laparotomy^{81,82} and thus may reduce the risk of recurrent bowel obstruction. However, one study found that despite a reduction in the median length of stay, patients treated laparoscopically were at increased risk for an early unplanned reoperation as a consequence of either incomplete relief of obstruction or complications.⁷⁵ In fact, bowel perforation in the course of laparoscopic adhesiolysis often is not detected during the procedure and presents in a delayed fashion.⁸⁰ Many such injuries are attributable either to insertion of the initial trocar or to delayed perforation of a thermal injury. When laparoscopic adhesiolysis fails to identify and relieve an obvious point of obstruction or when adhesiolysis is inadequate or unsafe, conversion to an open approach is indicated. At present, the laparoscopic approach appears best suited to those patients who have undergone less than three previous operations or who have been seen early after the onset of obstruction, especially if they have undergone appendectomy only, as well as those in whom the probable cause of obstruction is from adhesive bands.⁸³

Early Postoperative Obstruction

Early postoperative mechanical small bowel obstruction is not uncommon: it occurs in approximately 10% of patients undergoing abdominal procedures.⁸⁴ Postoperative bowel obstruction is often difficult to diagnose because it gives rise to many of the same signs and symptoms as postoperative ileus: obstipation, distention, nausea, vomiting, abdominal pain, and altered bowel sounds. In most cases, there are roentgenographic signs indicative of small bowel obstruction rather than ileus; however, in some cases, abdominal x-rays fail to diagnose the obstruction.⁸⁵ Traditionally, when plain radiographs are equivocal, an upper GI barium study with follow-through views is the next test performed to distinguish ileus from partial or complete small bowel obstruction⁸⁶; however, such studies may yield the wrong diagnosis in as many as 30% of cases.^{27,85,87} A number of authorities believe that abdominal ultrasonography is excellent at distinguishing postoperative ileus from mechanical obstruction and recommend that it be done before any contrast study.²³

Early postoperative obstruction is caused by adhesions in about 90% of patients.^{85,88} When there are no signs of toxicity and no acute abdominal signs, such obstruction can usually be managed safely with nasogastric decompression.^{84,85,87,88} As many as 87% of patients respond to nasogastric suction within 2 weeks. About 70% of the patients who respond to nonoperative treatment do so within 1 week, and an additional 25% respond during the following 7 days. If postoperative obstruction does not resolve in the first 2 weeks, it is unlikely to do so with continued nonoperative therapy, and reoperation is probably indicated^{85,88}; about 25% of patients whose postoperative obstruction was initially treated nonoperatively eventually require reoperation. An exception to this guideline arises in patients known to have severe dense adhesions (sometimes referred to as obliterative peritonitis) in response to multiple sequential laparotomies. These patients may have a combination of mechanical obstruction and diffuse small bowel and colonic ileus. The risk of closed-loop obstruction, volvulus, or strangulation in this group of patients is low. Repeat laparotomies and attempts to lyse adhesions may lead to complications, the development of enterocutaneous fistulae, or exacerbation of the adhesions. Often the best approach to managing these patients is observation for prolonged periods (i.e., months). Total parenteral nutrition (TPN) is indicated. The addition of octreotide to the TPN solution may be helpful and may make patients more comfortable.

Because the risk of intestinal strangulation in patients with postoperative adhesive obstruction is extremely low (< 1%),^{85,89} one can generally treat these patients nonoperatively for longer periods. In fact, the conservative approach is often the wise one: reoperation may do more harm than good (e.g., by causing enterotomies and inducing denser adhesions). The traditional indications for operation in patients with early postoperative obstruction include (1) deteriorating clinical status, (2) worsening obstructive symptoms, and (3) failure to respond to nonoperative management within 2 weeks. With the rising cost of hospitalization, it might, in fact, be more cost-effective to reoperate on patients who have persistent obstruction after 7 days. This speculation would have to be tested by a well-organized cost-benefit study conducted in a prospective fashion.

Some physicians have maintained that long intestinal tubes are beneficial in the management of postoperative bowel obstruction.⁵⁸ However, there is no convincing evidence that long intestinal tubes are any better for resolving bowel obstruction than conventional nasogastric tubes are. In fact, some authorities have reported that the use of such tubes increases morbidity.^{30,50,51} One prospective, randomized clinical trial that addressed this issue found no differences between the two types of tube with respect to the percentage of patients who were able to avoid operation, the incidence of complications, the time between admission and operation, or the duration of postoperative ileus.⁹⁰

Inflammatory Conditions

Partial bowel obstruction secondary to inflammatory bowel disease, radiation enteritis, or diverticulitis usually resolves with nonoperative therapy. Bowel obstruction accompanying an acute exacerbation of Crohn disease usually resolves with nasogastric suction, IV antibiotics, and antiinflammatory agents. If, however, CT detects an intra-abdominal abscess, there is evidence of a chronic stricture, or the patient exhibits persistent obstructive symptoms, an operation may be necessary. Similarly, bowel obstruction arising from acute enteritis caused by radiation exposure or chemotherapy usually resolves with supportive care. Chronic radiation-induced strictures are problematic; astute clinical judgment must be exercised to determine when operative treatment is the best option.

Patients with acute diverticulitis typically present with a history of altered bowel movements, fever, leukocytosis, localized pain, tenderness, and guarding in the left lower quadrant of the abdomen. Approximately 20% of patients with colonic diverticulitis also present with signs and symptoms of partial colonic obstruction. A CT scan should be obtained early in all patients with diverticulitis to ascertain whether there is a pericolic abscess that could be drained percutaneously.⁹¹ Partial colonic obstruction in these patients usually resolves with antibiotic therapy, an NPO regimen, and nasogastric decompression. If obstructive symptoms persist for more than 7 days or if obstructive symptoms from a documented stricture recur, operation is indicated.

ELECTIVE OPERATION

Nontoxic, Nontender Sigmoid Volvulus

Patients with nontoxic, nontender sigmoid volvulus whose bowel obstruction is initially treated successfully with sigmoidoscopic decompression are at risk for recurrent colonic obstruction. Accordingly, these patients should undergo elective sigmoid resection after complete bowel preparation.



Recurrent Adhesive or Stricture-Related Partial Small Bowel Obstruction

Many patients whose adhesive bowel obstruction resolves experience no further obstructive episodes. If a patient does present with recurrent obstruction from presumed adhesions, either a contrast examination of the bowel or CT is indicated

to determine whether there is a surgically correctable point of stenosis. A strong argument can be made that non-high-risk patients should undergo elective operation after presenting with their second episode of mechanical obstruction. Similarly, patients with recurrent obstruction from strictures of any sort should undergo elective operation given that these lesions are unlikely to resolve.

Partial Colonic Obstruction

The most common causes of partial colonic obstruction are colon cancer, strictures, and diverticulitis. Cancer and strictures usually must be managed surgically because they generally go on to cause obstruction later. Strictures from ischemia or endometriosis usually call for elective colonic resection. Inflammatory strictures from diverticulitis may resolve; however, if obstructive symptoms persist or if barium enema examination continues to yield evidence of colonic narrowing, elective resection is warranted.

When abdominal x-rays suggest distal colonic obstruction, digital examination and rigid sigmoidoscopy are performed to exclude fecal impaction, tumors, strictures, and sigmoid volvulus. If obstruction is proximal to the sigmoidoscope, barium contrast examination is indicated. If barium examination does not demonstrate mechanical obstruction, a presumptive diagnosis of colonic pseudo-obstruction is made.

The morbidity and mortality associated with elective colectomy procedures are significantly lower than those associated with emergency colonic surgery. Furthermore, immediate operation for left-side colonic obstruction almost always necessitates the creation of a diverting colostomy. If a colostomy takedown subsequently proves necessary, the overall cost of caring for the patient will be significantly higher than it would have been had a single-stage procedure been performed. For these reasons, one should initially treat partial colonic obstruction with nasogastric suction, enemas, and IV rehydration in the hope that the obstruction will resolve and that the patient thus can undergo mechanical and antibiotic bowel preparation and a single-stage procedure comprising resection and primary anastomosis. Patients who do not respond to nonoperative measures within 24 hours should undergo operation within 12 hours with the aim of preventing perforation.

In patients with partially obstructing rectal or distal sigmoid tumors or strictures that can be traversed with a radiologic guide wire, balloon dilatation can be performed and a self-expanding stent deployed.^{92–95} Clinical improvement and resolution of obstruction occur in more than 90% of patients within 96 hours.⁹⁴ With restoration of the bowel lumen, patients can be prepared for elective surgery, can be spared the creation of a diverting colostomy, and can avoid the extra expense and morbidity associated with the performance of two operations.^{94,95} In a recent prospective trial, the management of acute colonic obstruction using endoscopic stent decompression prepared patients for laparoscopic resection and primary anastomosis with good results.⁹⁶

Bowel Obstruction without Previous Abdominal Operation

When partial small bowel obstruction develops and resolves in a patient who has not previously undergone an abdominal operation, a diagnostic workup should be performed to identify the cause of the obstruction; there may be an underlying condition that is likely to cause recurrent obstruction (e.g., an

internal hernia, a tumor, malrotation, or metastatic cancer). The first diagnostic test to be ordered should be a CT scan, followed by an upper GI barium study with follow-through views and a barium enema.⁹⁷ If a pathologic lesion is identified, elective operation is indicated. An argument can be made that no additional diagnostic tests should be performed in these patients and that diagnostic laparoscopy should be performed instead to enable laparoscopic surgery in case a cause of obstruction is identified that can be treated with a minimally invasive procedure. If no cause of obstruction is found at laparoscopy, open laparotomy is performed.

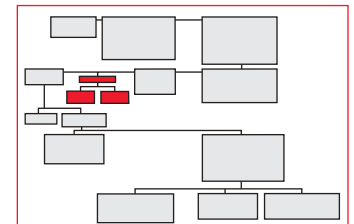
Paraduodenal hernia, a congenital defect resulting from intestinal malrotation, is probably more common than was once thought. It accounts for approximately 50% of internal hernias. Patients with paraduodenal hernia may present with a catastrophic closed-loop obstruction; more often, however, they exhibit mild, nonspecific GI symptoms such as nausea, vomiting, esophageal reflux, and abdominal pain. Duodenogastric reflux and prominent bile gastritis in the absence of a previous operation or diabetic gastroparesis are indirect signs of a paraduodenal hernia. The diagnosis is established by means of either an upper GI contrast study with small bowel follow-through or CT scanning. When a paraduodenal hernia is identified, operative treatment is indicated. Such treatment is usually successful in alleviating symptoms and preventing strangulation obstruction.⁹⁸

Nonmechanical Obstruction

ILEUS

Ileus, or intestinal paralysis, is most common after abdominal operations but can also occur in response to any acute medical condition or metabolic derangement [see Table 1]. The pathophysiologic mechanisms that cause ileus are incompletely understood but appear to involve disruption of normal neurohumoral responses.⁹⁹ Ileus may be classified into two broad categories: postoperative ileus and ileus without antecedent abdominal operation. Postoperative ileus is manifested by atony of the stomach, small intestine, and colon and usually resolves spontaneously within a few days as normal bowel motility returns. Typically, the small bowel regains its motility within 24 hours of operation, followed 3 to 4 days later by the stomach and colon. Initial therapy of ileus is directed at identifying and correcting the presumed cause [see Figure 14]. If the patient experiences abdominal distention, abdominal pain, nausea, or vomiting, then nasogastric decompression, placement of a Foley catheter, and IV rehydration are indicated. In postoperative patients, it is best not to use strong narcotics for analgesia and instead to rely on epidural anesthesia and nonsteroidal anti-inflammatory drugs. When ileus develops in patients who have not recently undergone an operation, a thorough history, a careful physical examination, and well-chosen laboratory tests are necessary to identify the possible causes.

When ileus persists for what is, in one's best clinical judgment, an inordinate length of time for the operation performed (typically, longer than 3 to 4 days), the possibility of partial mechanical obstruction, possibly associated with an



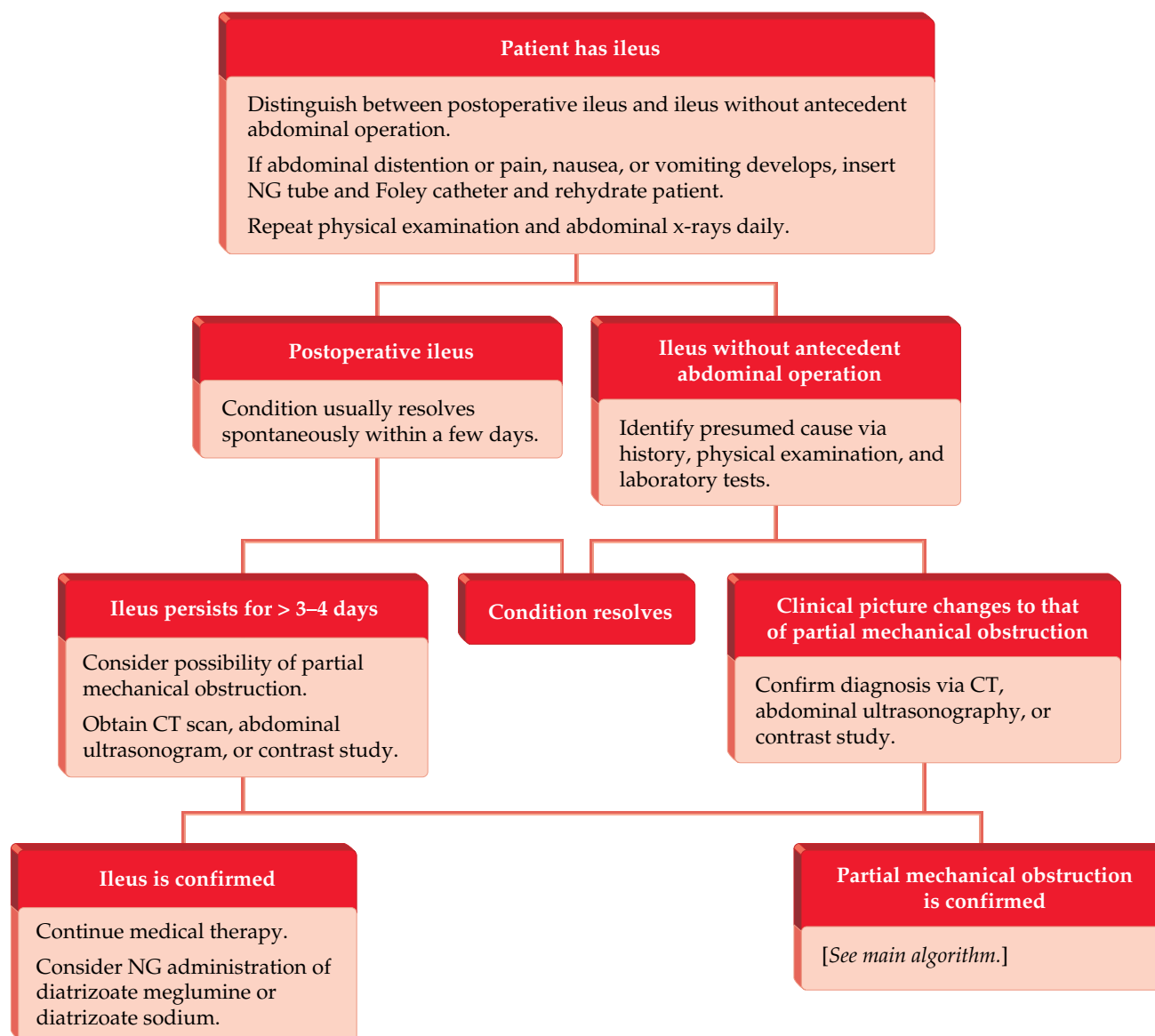


Figure 14 An algorithm outlining an approach to management of ileus. CT = computed tomography; NG = nasogastric.

intra-abdominal abscess or another source of infection, must be considered. If an abscess is suspected, an abdominal CT scan should be obtained. Abdominal ultrasonography has been reported to distinguish postoperative ileus from mechanical obstruction reliably.²³ A small bowel contrast examination with barium identifies partial mechanical small bowel obstruction in about 75% of patients.^{27,30} CT distinguishes ileus from obstruction in about 80% of patients.

Intragastric administration of a water-soluble contrast agent has shown great potential in the treatment of ileus.^{100,101} In one study, administration of 120 mL of diatrizoate meglumine or diatrizoate sodium via a nasogastric tube to 40 adults with postoperative small bowel ileus led to restored intestinal motility within 6 hours in all 40, allowing them to resume oral alimentation within 24 hours.¹⁰⁰ Given these results, a prospective, randomized trial that addresses cost-management end points is warranted.

PSEUDO-OBSTRUCTION

Pseudo-obstruction [see Figure 15] can exist in the small bowel or colon and can be either acute or chronic. Acute colonic pseudo-obstruction, also known as Ogilvie syndrome, is the most common form. Colonic pseudo-obstruction occurs most commonly in hospitalized patients in the postoperative period or in response to a nonsurgical acute illness (e.g., pneumonia, myocardial infarction, hypoxia, shock, intestinal ischemia, or electrolyte imbalance). The pathophysiologic mechanisms underlying idiopathic pseudo-obstruction appear to be related to an imbalance in the parasympathetic and sympathetic influences on colonic motility.

The presenting symptoms of acute colonic pseudo-obstruction are massive dilatation of the colon (with the cecum more dilated than the distal colon), crampy pain, nausea, and vomiting.¹⁰² If peritoneal irritation or systemic toxicity is present, immediate laparotomy is indicated; if not,

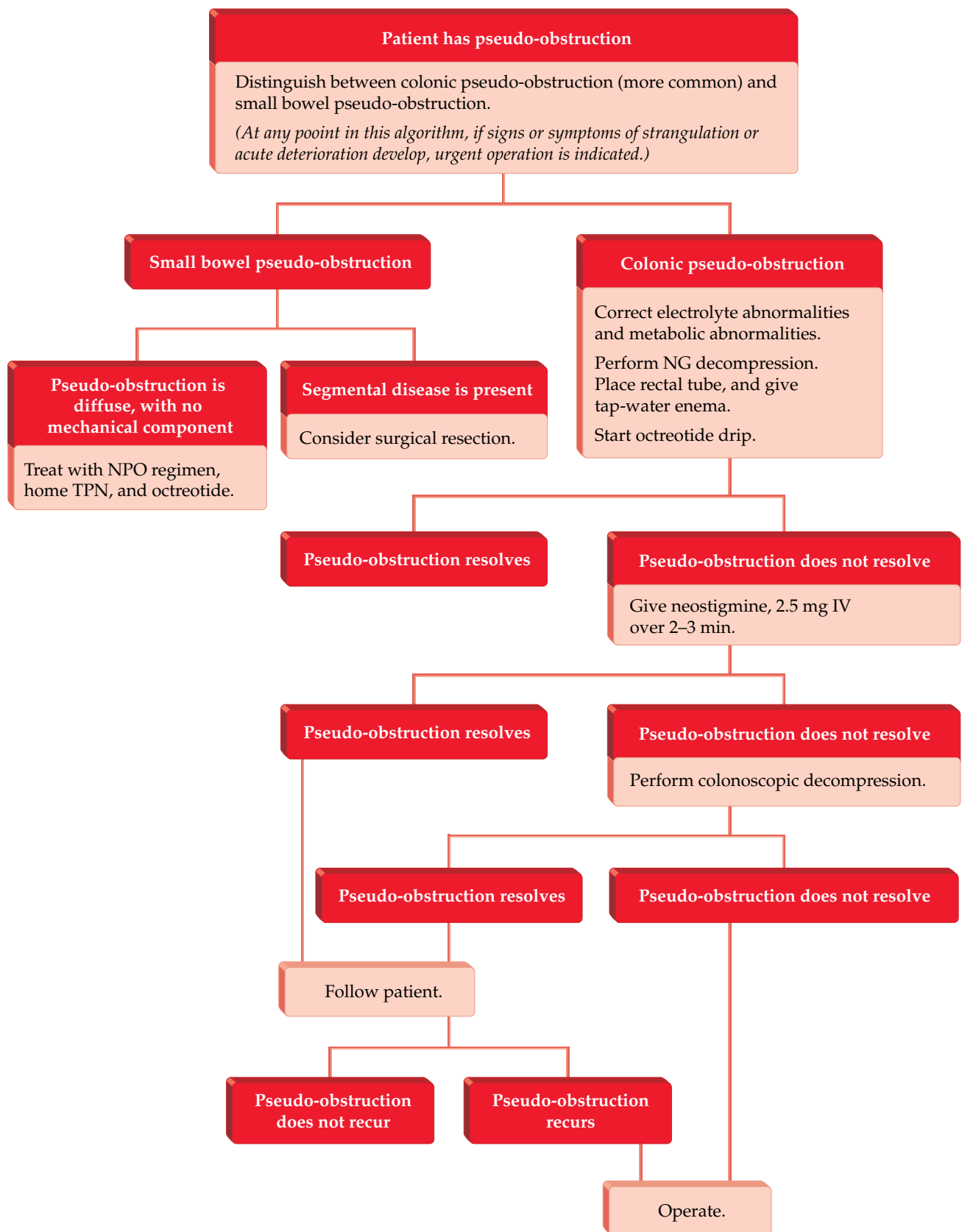


Figure 15 An algorithm outlining an approach to management of pseudo-obstruction. IV = intravenous; NG = nasogastric; NPO = nothing by mouth; TPN = total parenteral nutrition.

treatment involves nasogastric decompression, placement of a rectal tube, tap-water enemas, correction of any underlying metabolic disturbances, and avoidance of narcotic and anticholinergic medications. With conservative management, acute colonic pseudo-obstruction resolves within 4 days in more than 80% of cases.¹⁰³ Colonoscopy was previously the method of choice for decompression in this setting.¹⁰⁴ It has been shown, however, that IV administration of neostigmine, 2.5 mg over 2 to 3 minutes, leads to prompt resolution of acute colonic pseudo-obstruction within minutes in nearly all cases.^{105,106} Now that this previously difficult and potentially lethal problem can readily be treated pharmacologically, colonoscopic decompression and surgical intervention should be reserved for cases in which pharmacologic measures fail.

Chronic intestinal pseudo-obstruction is a rare acquired disorder that is caused by various diseases involving GI smooth muscle, the enteric nervous system, or the extrinsic autonomic nerve supply to the gut.¹⁰⁷ These disorders are treated with an NPO regimen, home TPN, and octreotide. Patients with chronic intestinal pseudo-obstruction should be followed closely for long periods and should undergo repeat contrast studies: a condition occasionally develops that can cause mechanical obstruction and that may be surgically correctable.^{108,109}

Cost Considerations

Cost considerations are exerting an ever-growing influence on surgical care in general and on the decision whether to operate in particular. A large percentage of the high total cost of caring for patients with ileus or mechanical intestinal obstruction is accounted for by the cost associated with hospitalization or the need for laparotomy. Bed stay for these admissions represents the equivalent of almost one surgical bed per year and at least 2 days of OR time.¹¹⁰

Strategies for reducing the overall cost of managing patients with bowel obstruction may take several forms: the development of diagnostic and therapeutic methods that lead to more rapid diagnosis and resolution of ileus and partial small bowel obstruction; the development of techniques for rapid identification of patients with complete or closed-loop obstruction and early reversible strangulation, which would permit earlier operative intervention and thereby reduce the incidence of

complications; the development of therapeutic approaches that prevent postoperative ileus, including the use of selective postoperative inhibition of gastrointestinal opioid receptors,¹¹¹ the use of a well-defined postoperative care program including continuous thoracic epidural analgesia and enforced early mobilization and enteral nutrition,¹¹² gum chewing,¹¹³ and avoiding positive salt and water balance¹¹⁴; and the development of methods for preventing intra-abdominal adhesions, which would significantly reduce the overall incidence of bowel obstruction. Two prospective, randomized clinical trials demonstrated that placement of a bioresorbable membrane composed of sodium hyaluronate and carboxymethylcellulose underneath abdominal fascial closures significantly reduced the severity and density of postoperative adhesions,^{115,116} and in one randomized controlled trial, the use of 4% icodextrin lavage plus instillation was well tolerated and reduced adhesion formation and reformation following laparoscopic gynecologic surgery.¹¹⁷ In theory, use of such a product should reduce the incidence of adhesion-related bowel obstruction; however, longer-term studies are required to determine whether this will actually be the case.

From a management viewpoint, if a specific diagnostic test, medication, or approach (e.g., laparoscopy) costs less than a day of hospitalization does, it immediately becomes cost-effective if it reduces complications and shortens length of stay by 1 day. Intra gastric administration of a water-soluble contrast agent to relieve small bowel ileus or partial adhesive obstruction is an example of an innovative, cost-effective therapeutic strategy. Diagnostic laparoscopy, abdominal ultrasonography, CT, and fast MRI have all been successfully used to make earlier definitive management decisions and to prevent gangrenous obstruction. Laparoscopic adhesiolysis also leads to earlier hospital discharge. On the basis of the collective experience reported in a substantial number of studies (see above), a logical proposal for cost-effective management of patients with bowel obstruction would be to perform ultrasonography or abdominal CT immediately after initial resuscitation and then to perform laparoscopic surgery on those patients in whom the contrast agent does not arrive in the right colon within 24 hours. However, prospective, randomized clinical trials are needed to evaluate the cost-effectiveness of this and other newer management strategies.

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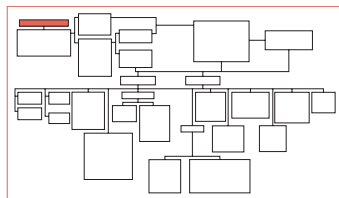
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5 GASTROINTESTINAL BLEEDING

Eric S. Hungness, MD, FACS

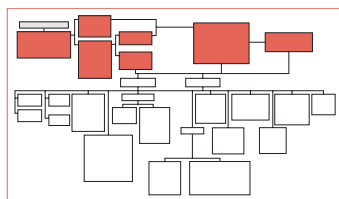
Despite recent advances in therapeutic endoscopy and the widespread use of anti-secretory medications, upper gastrointestinal bleeding (UGIB)—defined as bleeding that occurs proximal to the ligament of Treitz—continues to be one of the more common reasons for surgical consultation. It also remains a significant source of mortality for both emergency admissions (11%) and inpatients (33%).¹ The most common causes of UGIB are esophageal (varices and Mallory-Weiss tears), gastric (acute hemorrhagic gastritis, varices, ulcers, and neoplasms), and duodenal (ulcers) [see Discussion and Management of Specific Sources of UGIB, below]. Less common causes include various other gastrointestinal (GI) conditions and certain hepatobiliary and pancreatic disorders.



Lower gastrointestinal bleeding (LGIB)—defined as abnormal hemorrhage into the lumen of the bowel from a source distal to the ligament of Treitz—usually derives from the colon; however, the small bowel is identified as the source of bleeding in as many as one-third of cases,² and UGIB is identified as the source in as many as 11% of patients presenting with hematochezia.³ The most common causes of LGIB are colonic, with diverticular disease being the most common and accounting for 30 to 40% of all cases.⁴ Arteriovenous malformations (AVMs), although extensively described in the literature, are considerably less common causes, accounting for 1 to 4% of cases.⁵ Other significant causative conditions are inflammatory bowel disease (IBD), benign and malignant neoplasms, ischemia, infectious colitis, benign anorectal disease, coagulopathy, use of nonsteroidal antiinflammatory drugs (NSAIDs), radiation proctitis, AIDS, and small bowel disorders.

Presentation and Initial Management

Gastrointestinal bleeding (GIB) may present as severe bleeding with hematemesis (UGIB), hematochezia (UGIB or LGIB), and hypotension; as gradual bleeding with melena (UGIB); or as



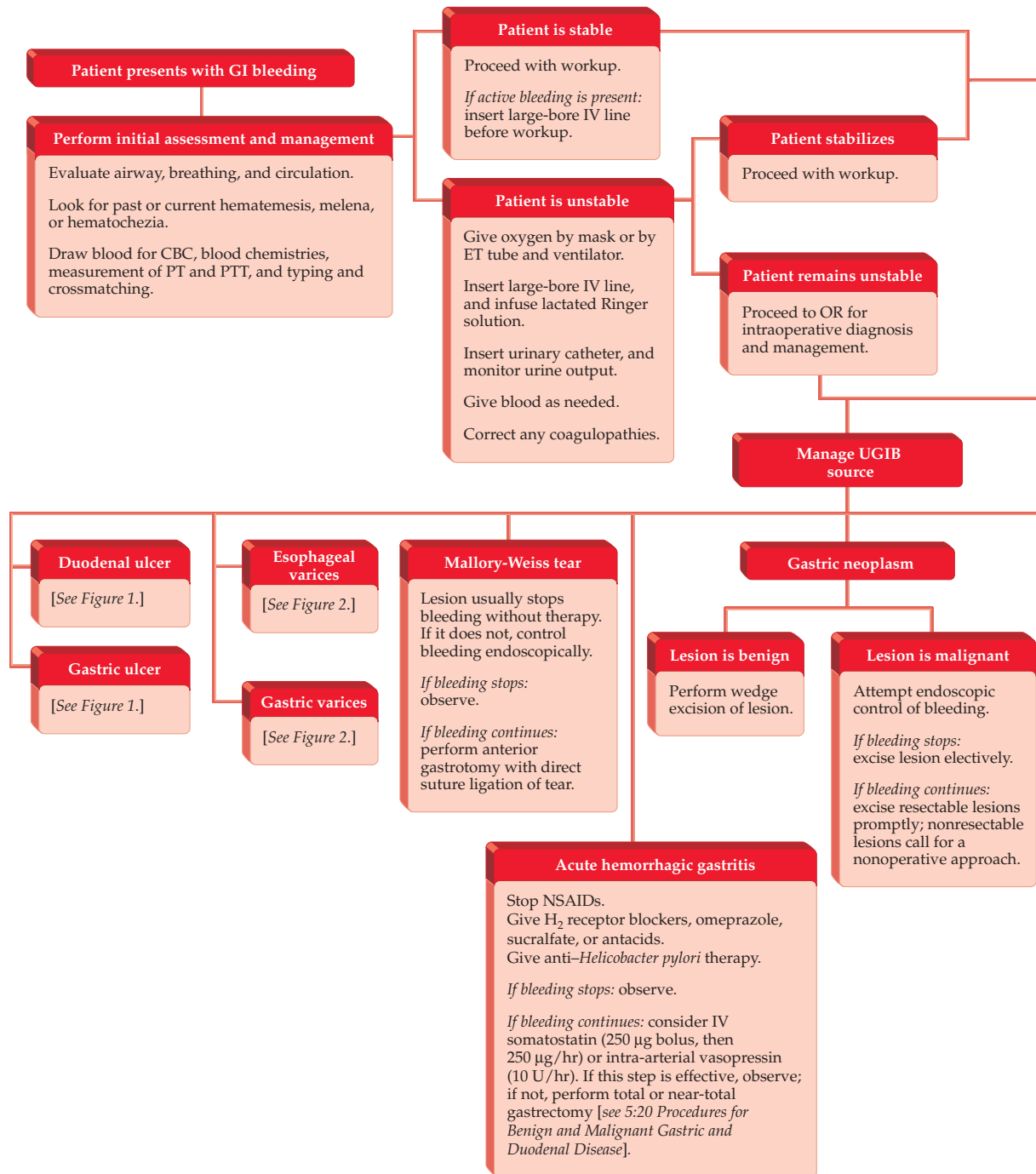
occult bleeding detected by positive tests for blood in the stool. The initial steps in the evaluation of patients with GIB are based on the perceived rate of bleeding and the degree of hemodynamic stability. Hemodynamically stable patients who show no evidence of active bleeding or comorbidities and in whom endoscopic findings are favorable may be treated on an outpatient basis,⁶ whereas patients who show evidence of serious bleeding should be managed aggressively and hospitalized.

The airway, breathing, and circulation should be rapidly assessed, and the examiner should note whether the patient has a history of or currently exhibits hematemesis, melena, or hematochezia. Blood should be drawn for a complete blood count, blood chemistries (including tests of liver function and renal function), and measurement of the prothrombin time and the partial thromboplastin time. Blood should be sent to the blood bank for typing and crossmatching.

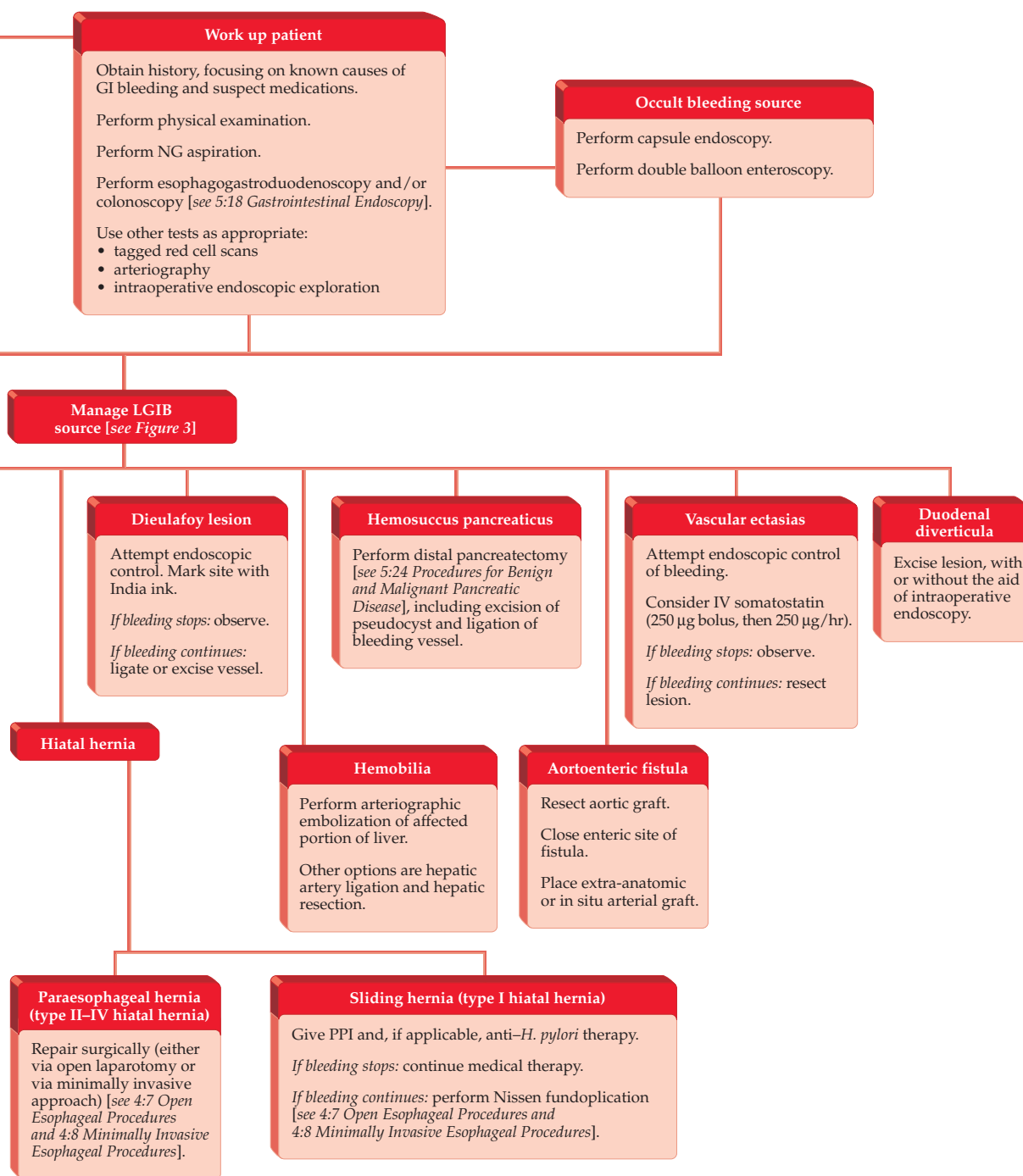
If the patient is stable and shows no evidence of recent or active hemorrhage, the surgeon may proceed with the workup. If, however, the patient is stable but shows evidence of recent or active bleeding, short, large-bore intravenous lines should be placed before workup is begun to ensure that immediate intravenous (IV) access is possible should the patient subsequently become unstable.

If the patient is unstable, he or she should be taken to an intensive care unit and resuscitated immediately. Resuscitation of an unstable patient is begun by establishing a secure airway and ensuring adequate ventilation.⁷ Oxygen should be given, with a low threshold for endotracheal intubation. Much as in trauma resuscitation, either short, large-bore, peripheral IV lines or a single-lumen 8 French catheter in the femoral vein should then be placed, through which lactated Ringer solution or 0.9% normal saline should be infused at a rate high enough to maintain tissue perfusion. A urinary catheter should be inserted and urine output monitored. Blood products should be given as necessary, and any coagulopathies should be corrected. It is all too easy to forget these basic steps in a desire to evaluate and manage massive GI hemorrhage.

Every effort should be made to resuscitate and stabilize the patient sufficiently to allow clinical evaluation and diagnostic testing to help determine the cause of the bleeding and direct subsequent care. Only if the patient remains unstable and continues to bleed despite maximal supportive measures should he or she be taken to the operating room for intraoperative diagnosis as a last resort. If UGIB is the etiology, the



Assessment and Management of Gastrointestinal Bleeding



abdomen should be opened through an upper midline incision, and an anterior gastrotomy should be performed. If inspection does not reveal the source of the bleeding or if bleeding is observed beyond the pylorus, a duodenotomy is made, with care taken to preserve the pylorus if possible. Bleeding from the proximal stomach may be difficult to verify, but it should be actively sought if no other bleeding site is identified. Intraoperative endoscopy should be considered in this situation.

For LGIB, intraoperative options for bleeding-site localization include colonoscopy (to allow for this option, patients should always be placed in the lithotomy position), esophagogastroduodenoscopy (EGD), and transoral passage of a pediatric colonoscope for enteroscopy with simultaneous intraperitoneal assistance for small bowel manipulation [see 5:18 *Gastrointestinal Endoscopy*]. If the bleeding site is identified, directed segmental resection is the procedure of choice: it is associated with rebleeding rates less than 10% and low mortality rates ranging from 0 to 13%.⁸ Blind segmental colectomy should never be performed; it is associated with rebleeding rates as high as 75% and mortality rates as high as 50%.⁹ If the bleeding site still cannot be accurately localized, subtotal colectomy is the procedure of choice. This procedure is associated with high morbidity,¹⁰ which underscores the importance of accurate preoperative localization of bleeding before surgical intervention.

Clinical Evaluation

Only after the initial measures to protect the airway and stabilize the patient have been completed should an attempt be made to establish the cause of the bleeding. The history should focus on known causes of GIB (e.g., previous GIB, peptic ulcer disease, diverticulosis, AVM, esophageal varices, and IBD) and on the possible use of medications that interfere with coagulation (e.g., warfarin, aspirin, and NSAIDs) or alter hemodynamics (e.g., beta blockers and antihypertensive agents). Of particular importance in taking the history is to ascertain the nature and duration of the bleeding, including stool color and frequency. The patient should also be asked about any associated symptoms of potential significance (e.g., abdominal pain, changes in bowel habits, fever, urgency, tenesmus, or weight loss). Knowledge of the patient's cardiac history is useful to assess the patient's ability to withstand varying degrees of anemia.

The physical examination is seldom of much help in determining the exact site of bleeding, but determination of postural vital signs can accurately estimate intravascular volume status. A drop in the orthostatic blood pressure greater than 10 mm Hg or an increase in the pulse rate greater than 10 beats/min indicates that more than 800 mL of blood (> 15% of the total circulating blood volume) has been lost. Marked tachycardia and tachypnea in association with hypotension and depressed mental status indicate that more than 1,500 mL of blood (> 30% of the total circulating blood volume) has been lost. A complete abdominal examination, including digital rectal examination and anoscopy, should be performed as it may reveal jaundice, ascites, or other signs of hepatic

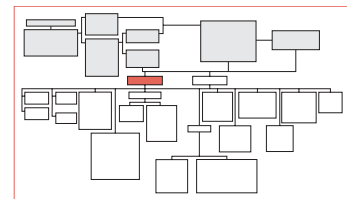
disease; a tumor mass; or a bruit from an abdominal vascular lesion.

A nasogastric tube should be placed for gastric lavage. If lavage yields positive results (i.e., the aspirate contains gross blood or so-called coffee grounds), EGD is indicated. An aspirate that contains copious amounts of bile is strongly suggestive of an LGIB, and the workup proceeds accordingly. The choice is less clear-cut with a clear aspirate. In the absence of bile, such an aspirate cannot rule out a duodenal source for the bleeding. Accordingly, there is some degree of latitude for clinical judgment: depending on the overall clinical picture, the surgeon may choose either to perform EGD to rule out a duodenal bleeding source or to proceed with colonoscopy on the assumption that the source of the bleeding is in the lower GI tract.

UGIB Investigative Tests

ESOPHAGOGASTRODUODENOSCOPY

EGD [see 5:18 *Gastrointestinal Endoscopy*] almost always reveals the source of UGIB; its utility and accuracy have been well documented in the literature.¹¹ Performance of this procedure requires con-



siderable skill: identification of bleeding sites in a blood-filled stomach is far from easy. Hematemesis is an indication for emergency EGD, usually within 1 hour of presentation. If the rate of bleeding is high, saline lavage may be performed to clear the stomach of blood and clots. If the rate of bleeding is moderate or low, as is often the case in patients with melena, urgent EGD is indicated.

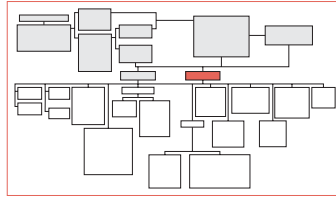
EGD is not only an excellent diagnostic tool but also a valuable therapeutic modality. Indeed, most UGIBs may be controlled endoscopically, although the degree of success to be expected in individual cases varies according to the expertise of the endoscopist and the specific cause of the bleeding. Therapeutic endoscopic maneuvers include injection, thermal coagulation, and mechanical occlusion of bleeding sites (clip application or variceal banding). The choice of therapy depends on the cause, the site, and the rate of bleeding.

OTHER UGIB IMAGING

Tagged red blood cell (RBC) scans may confirm the presence of an active bleeding site; however, scans are fairly non-specific with respect to determining the anatomic location of the bleeding.¹² Arteriography may demonstrate that a lesion is present, but it cannot reliably identify a bleeding site unless the bleeding is brisk (> 1 mL/min). Occasionally, arteriography reveals the cause of the bleeding even if the bleeding has stopped. Angiography may also be considered as a therapeutic modality for high-risk surgical patients.⁶ These tests, in conjunction with EGD, should allow the surgeon to establish the cause of UGIB more than 90% of the time.

LGIB Investigative Tests

A number of diagnostic techniques are available for determining the source of LGIB, including colonoscopy [see 5:18 *Gastrointestinal Endoscopy*], radionuclide scanning, computed tomography (CT), and angiography (in the form of selective mesenteric arteriography), enteroscopy, and capsule endoscopy (CE). The goal of these tests is to locate the site of bleeding accurately so that definitive therapy can be properly directed as the potential source ranges from the ligament of Treitz to the anus. Which diagnostic test is chosen for a specific patient depends on several factors, including the hemodynamic stability of the patient, the bleeding rate, patient comorbidities, therapeutic options, and local expertise available. Unlike radionuclide and CT scanning, arteriography and colonoscopy provide a therapeutic option. Arteriography has a lower diagnostic yield and a higher complication rate than colonoscopy does; therefore, it is reasonable to attempt colonoscopy first and to reserve angiography for patients in whom the volume of bleeding is such that colonoscopy would be neither safe nor accurate.¹³



COLONOSCOPY

Several large series that evaluated the diagnostic utility of colonoscopy in patients with LGIB found this modality to be moderately to highly accurate, with overall diagnostic yields ranging from 53 to 97%.^{3,14,15} Those studies that reported morbidity found colonoscopy to be safe, with an average complication rate of 0.5%. Colonoscopy has both a higher diagnostic yield and a lower complication rate than arteriography in this setting and thus would appear to be a more attractive initial test in most circumstances.^{3,16} An argument has been made that colonoscopy should be considered the procedure of choice for structural evaluation of LGIB and that arteriography should be reserved for patients with massive, ongoing bleeding in whom endoscopy is not feasible or colonoscopy fails to reveal the source of the hemorrhage.¹⁷

The merits of colonic purging have been extensively debated in the literature.^{3,18} Although no firm conclusion has been reached, adequate colonic purging may improve both the diagnostic yield and the safety of colonoscopy. Given the absence of any definitive data suggesting that colonic purging either reactivates or increases bleeding, one should consider administering an oral purge after the patient has been adequately resuscitated.

If the entire colon has been adequately visualized and no source for the bleeding has been identified, the ileum should be intubated; fresh blood in this region suggests a possible small bowel source. If no active bleeding is observed in the ileum, upper GI endoscopy should be performed to rule out a UGIB site.

When colonoscopy identifies a bleeding source, endoscopic treatment may be an option [see 5:18 *Gastrointestinal Endoscopy*]. Endoscopic modalities used to treat LGIB include use of thermal contact probes, laser photocoagulation,

electrocauterization, injection of vasoconstrictors, application of metallic clips, and injection sclerotherapy. The choice of a specific modality often depends on the nature of the offending lesion and on the expertise and resources available locally. A 1995 survey of members of the American College of Gastroenterology found that endoscopic therapy was used in 27% of patients presenting with LGIB.¹⁹

RADIONUCLIDE SCANNING

Radionuclide scanning is highly sensitive for lower LGIB, capable of detecting bleeding at rates as slow as 0.1 to 0.4 mL/min.²⁰ The patient's RBCs are labeled with technetium-99m (^{99m}Tc), which can be detected on images as long as 24 to 48 hours after injection [see Figure 1]. The high sensitivity of ^{99m}Tc-labeled RBC scanning—80 to 98%—is well attested, but there is considerable disagreement in the literature with regard to its specificity in identifying the anatomic site of bleeding.^{21,22} For example, on the one hand, a 1997 study found radiolabeled RBC scanning to be 97% accurate for localizing bleeding in 37 patients undergoing surgical resection²²; on the other hand, a 1990 study reported a 42% rate of incorrect resection when surgical therapy was based solely on this modality.²¹ In 2005, one group retrospectively reviewed 127 bleeding scans in an effort to identify factors that might predict a positive scan.²³ The investigators found that tagged RBC scans were 48% accurate in localizing bleeding sites later confirmed by endoscopy, surgery, or pathologic evaluation. Multivariate analysis demonstrated that both the number of units of blood transfused in the 24 hours preceding the scan and the lowest recorded hematocrit differed significantly between patients with positive scans and those with negative scans. However, the clinical significance of a positive scan was unclear in this study in that the rate of endoscopy was not significantly different between patients who had positive scans and those who did not.

To date, no prospective, randomized trials have compared radionuclide scanning with colonoscopy as the initial diagnostic procedure for patients with lower GI hemorrhage. Given that radionuclide scanning has no therapeutic intervention capabilities, its best use is in patients with non-life-threatening LGIB as a prelude and a guide to mesenteric angiography after active hemorrhage has been confirmed.

Radionuclide scanning is also useful for diagnosing Meckel diverticulum, a rare cause of LGIB. Patients are injected with ^{99m}Tc pertechnetate, which is taken up by the ectopic gastric mucosa. Although studies in the pediatric population have demonstrated high diagnostic accuracy, the sensitivity of the scan is only 60 to 70% in the adult population.²⁴

ANGIOGRAPHY

Selective mesenteric arteriography is somewhat less sensitive than radionuclide scanning for lower GI hemorrhage: bleeding must be occurring at a rate of at least 1.0 to 1.5 mL/min to be detectable with this test.²⁵ The procedure involves percutaneous placement of a transfemoral arterial catheter for evaluation of the superior mesenteric, inferior mesenteric, and celiac arteries. A positive test result is defined as extravasation of contrast into the lumen of the bowel. Once the bleeding vessel has been localized angiographically, the area

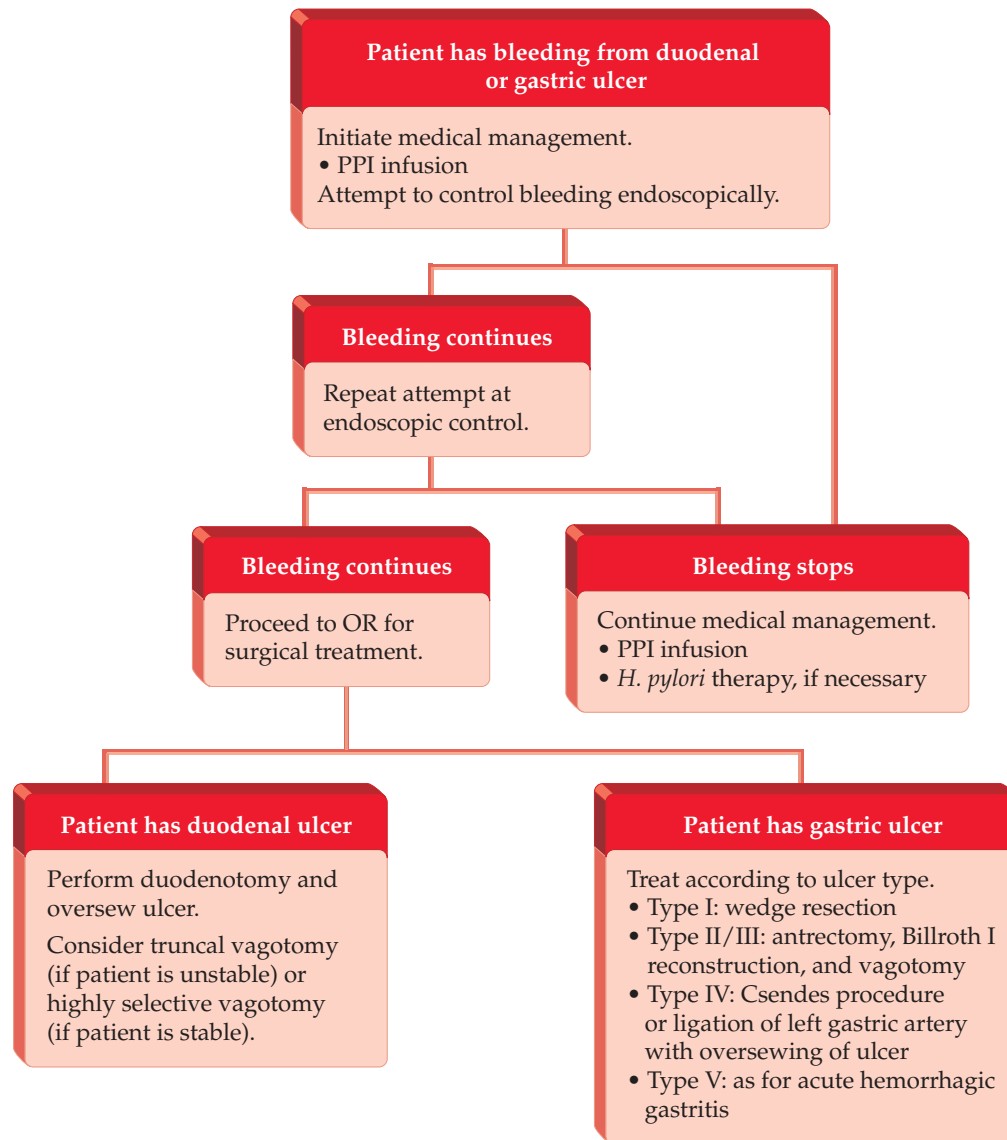


Figure 1 An algorithm for management of bleeding from duodenal or gastric ulcers. OR = operating room; PPI = proton pump inhibitor.

must be marked so that it can be successfully identified intra-operatively; this is commonly accomplished by infusing methylene blue into the bleeding artery [see Figure 2].²⁶

In several large series, the overall diagnostic yield of arteriography ranged from 27 to 67%.^{8,22,27,28} The complication rate for arteriography performed for LGIB ranges from 2 to 4%.^{2,26} Reported complications include contrast allergy, renal failure, bleeding from arterial puncture, and embolism from a dislodged thrombus.¹⁷ Diagnostic use of angiography in patients with LGIB can often be followed by angiographic therapy. The two main angiographic treatment options are intra-arterial injection of vasopressin and transcatheter embolization.

Vasopressin acts to control bleeding by causing arteriolar vasoconstriction and bowel wall contraction. Once the bleeding site has been localized angiographically, the catheter is positioned in the main trunk of the vessel. Infusion of

vasopressin is initiated at a rate of 0.2 U/min and can be increased to a rate of 0.4 U/min. Within 20 to 30 minutes, angiography is performed again to determine whether the bleeding has ceased. If the bleeding is under control, the catheter is left in place and vasopressin is continuously infused for 6 to 12 hours. If the bleeding continues to be controlled, infusion is continued for an additional 6 to 12 hours at 50% of the previous rate. Finally, vasopressin infusion is replaced by continuous saline infusion, and if bleeding does not recur, the catheter is removed.²⁹

The vasoconstrictive action of vasopressin can have deleterious systemic side effects, including myocardial ischemia, peripheral ischemia, hypertension, dysrhythmias, mesenteric thrombosis, intestinal infarction, and death. Occasionally, simultaneous intravenous administration of nitroglycerin is necessary to counteract these systemic effects. The reported success rate of vasopressin in controlling LGIB ranges from

60 to 100%, and the incidence of major complications ranges from 10 to 20%.^{30–32} Rebleeding rates as high as 50% have been reported.^{30,31}

An alternative for patients with coronary vascular disease, severe peripheral vascular disease, or other comorbidities that prevent safe administration of vasopressin is transcatheter embolization. In this technique, a catheter is superselectively placed into the identified bleeding vessel and an embolizing agent (e.g., a gelatin sponge, a microcoil, polyvinyl alcohol particles, or a balloon) is injected. Several small series found this technique to be 90 to 100% successful at stopping bleeding.^{32–34} Equally impressive was the finding that the rebleeding rates in these series were 0%. The complication rates of this procedure are generally reasonable as well; however, intestinal infarction has been reported.^{8,35}

The use of small microcatheters and the ability to superselectively embolize individual vessels have reduced the potential for ischemic perforation. It is possible that as more experience is gained with these techniques, superselective embolization may replace catheter-directed vasoconstrictive therapy, thus obviating the potential deleterious systemic effects of vasopressin administration. Some researchers have suggested that with the exception of cases of diffuse bleeding lesions or cases whose demands exceed the technical limitations of superselective catheterization, embolization therapy should be the first choice for angiographic treatment of LGIB.^{35,36}

In a minority of patients, obscure bleeding persists despite negative findings from endoscopy, mesenteric arteriography, and radiolabeled RBC scanning. This obscure bleeding presents a considerable diagnostic challenge, which some investigators have proposed addressing by means of so-called provocative angiography.³⁷ Provocative angiography involves the use of short-acting anticoagulant agents (unfractionated heparin, vasodilators, thrombolytics, or combinations thereof) in association with angiography. Once the bleeding point has been localized (in up to 89% of cases in a recent study),³⁸ superselective embolization can be attempted or methylene blue is injected and the patient is immediately brought to the operating room (OR) for surgical treatment.

COMPUTED TOMOGRAPHY

With the ongoing improvements in high-speed abdominal CT scanning, interest has been growing in the evaluation of GIB with CT.³⁹ Helical CT scanners can provide direct or indirect evidence of the source of GIB. Typical findings that can facilitate localization of bleeding sites include spontaneous hyperdensity of the peribowel fat, contrast enhancement of the bowel wall, vascular extravasation of the contrast medium, thickening of the bowel wall, polyps, tumors, and vascular dilatation.

CT evaluation of GIB has several noteworthy advantages: the scanners typically are readily available, mobilization of special teams or units is not required, the scans can be completed rapidly in the emergency department, and bowel preparation is unnecessary. In one experimental study, CT scanners were able to detect arterial bleeding at rates as low as 0.07 mL/min, which suggests that CT scanning is more sensitive than angiography for this purpose.⁴⁰ In addition, CT scans are noninvasive and carry little morbidity. Unfortunately, like radionuclide scanning, CT has no therapeutic capability.

A 2003 study of 19 patients with GI hemorrhage compared triphasic helical CT evaluation with colonoscopy and surgery for localization of bleeding sites.⁴⁰ In this series, 5 patients had small bowel bleeding sites, and 14 patients had colonic sites. Helical CT scanning correctly identified 4 of the 5 small bowel lesions and 11 of the 14 colonic lesions. These findings, although preliminary, suggest that CT is a potentially valuable evaluation method in certain cases of GIB. Perhaps CT scanning can eventually replace radionuclide scanning, which is often inaccurate. One potential drawback to the use of CT in this setting is the excessive dye load if angiography is employed as well.

ENTEROSCOPY

When other tests fail to locate a bleeding source, enteroscopy may be helpful to localize the LGIB. This procedure can be carried out in several ways. It can be performed purely endoscopically with a pediatric colonoscope. Termed “push” enteroscopy, this approach generally requires a high level of skill on the part of the endoscopist in that the lack of retroperitoneal attachments of the small intestine makes endoscopic navigation extremely challenging. In most cases, only the proximal 150 cm of the small intestine can be evaluated in this way. Depending on the indication and on the technique employed, the diagnostic yield from push enteroscopy has ranged from 13 to 78%.⁴¹ Typically, yields are highest (40 to 60%) in patients with significant GI hemorrhage.

Recently, double-balloon enteroscopy (DBE) has evolved as an effective method of identifying and endoscopically treating occult LGIB. Using this technique, the entire length of the small intestine can be examined in up to 50% of cases using combined antegrade (transoral) and retrograde (transanal) insertion by milking the bowel in a push/pull technique between two balloons.⁴² A recent study demonstrated that 66% of occult bleeding sources were identified using DBE. DBE should be considered the first choice in stable patients with occult active bleeding.

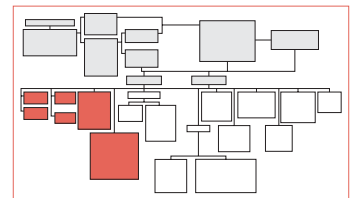
CAPSULE ENDOSCOPY

Another option for stable patients with occult GIB is CE, in which a miniature camera is swallowed and intermittent images are taken along the entire length of the GI tract as the capsule advances. Recent studies, including a prospective, blinded trial and several meta-analyses, have demonstrated that the diagnostic yield of CE is similar to that of DBE, although CE does not allow for therapeutic intervention.^{42–44} Because it is less invasive, however, CE should be considered the first choice in stable patients in whom occult bleeding has stopped.

Discussion and Management of Specific Sources of UGIB

DUODENAL ULCER

The development of effective medical regimens for controlling uncomplicated duodenal ulcers has led to a drastic reduction in the number of elective surgical procedures performed for this purpose. Nevertheless, the incidence of bleeding from duodenal ulcers that is



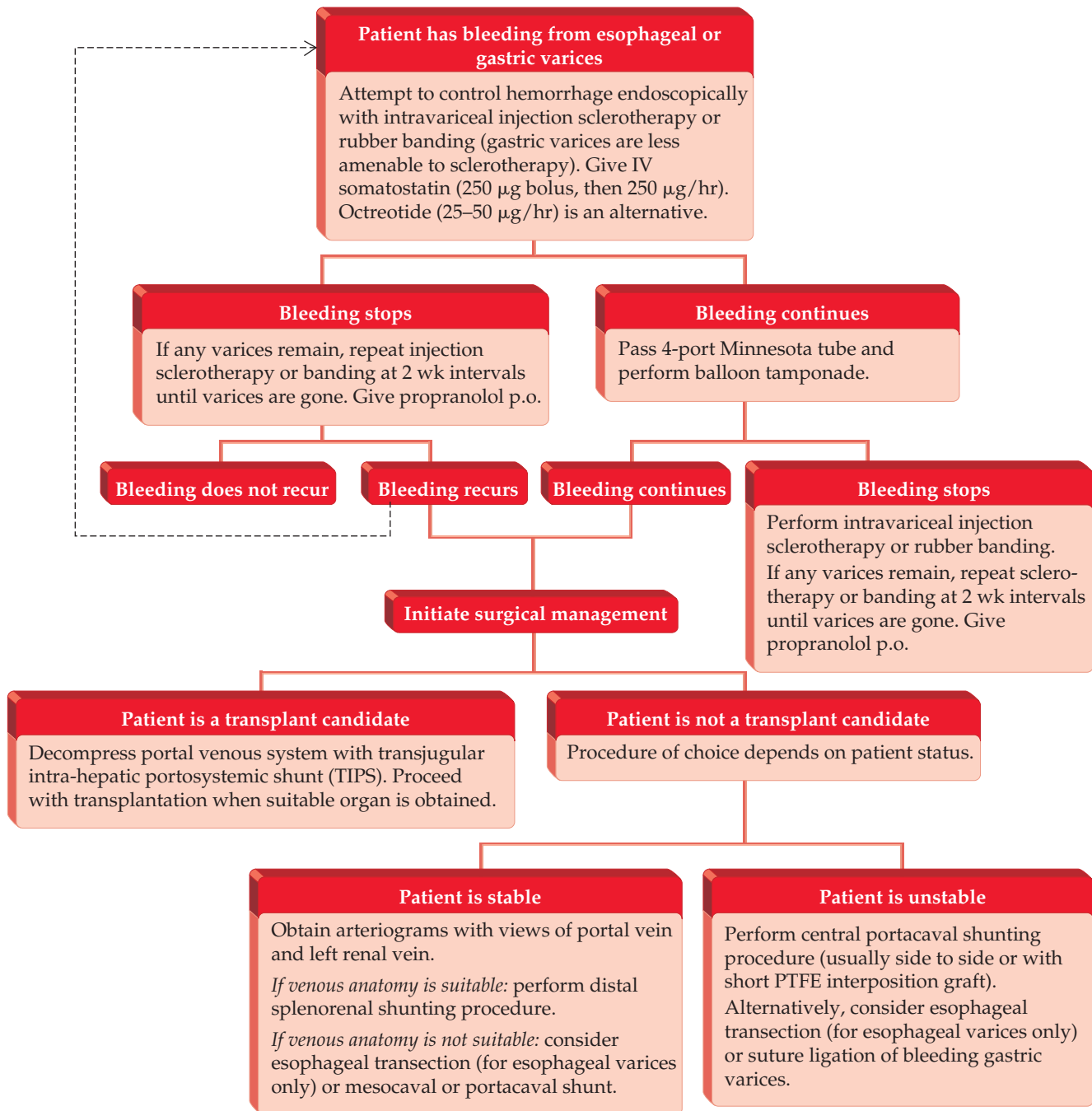


Figure 2 An algorithm for management of bleeding from esophageal or gastric varices.
IV = intravenous; PTFE = polytetrafluoroethylene.

severe enough to necessitate emergency endoscopic or operative intervention has not decreased over the past decade.⁴⁵

Once EGD has demonstrated that a duodenal ulcer is the source of the bleeding, the first question that must be addressed is whether active bleeding is present. If it is, an attempt should be made to control the hemorrhage endoscopically [see Figure 1]. Because ongoing blood loss eventually leads to coagulopathies, the surgeon must exercise good judgment in deciding how long to pursue endoscopic treatment before concluding that such treatment has failed and that surgical treatment is necessary. In general, substantial bleeding (6 units or more) or bleeding that is not controlled

endoscopically is an indication for surgical intervention. Likewise, ongoing hemorrhage in a hemodynamically unstable patient (especially an elderly one) calls for immediate surgical therapy. In addition, certain patients whose bleeding is controlled endoscopically (e.g., those with a visible vessel, active bleeding, or an adherent clot,⁴⁶ as well as those with giant ulcers) should be strongly considered for surgical therapy.

If bleeding is controlled endoscopically, then a proton pump inhibitor (PPI), such as pantoprazole, should be given intravenously, either in a bolus twice daily or by continuous infusion.⁴⁷ In addition, antibiotic therapy directed against *Helicobacter pylori* (e.g., a 14-day course of metronidazole,

500 mg p.o., t.i.d.; omeprazole, 20 mg p.o., b.i.d.; and clarithromycin, 500 mg p.o., b.i.d.) should be considered if the organism is present; such therapy has been shown to reduce rebleeding rates after antacid medication has been stopped.⁴⁸ Food need not be withheld unless the likelihood of rebleeding is high, because resumption of oral feeding does not appear to affect rebleeding rates.⁴⁹ If bleeding recurs despite medical and endoscopic therapy, a second attempt at endoscopic control should be made. Repeat endoscopic treatment reduces the need for surgery without increasing the risk of death and is associated with fewer complications than is surgery.⁵⁰

Surgical management may be accomplished either laparoscopically or via an open approach [see 5:20 *Procedures for Benign and Malignant Gastric and Duodenal Disease*]. The latter begins with an upper midline incision. The duodenum is mobilized, and an anterior longitudinal duodenotomy is performed over the site of the ulcer. The bleeding vessel, which is usually on the posterior wall of the first portion of the duodenum, is ligated with nonabsorbable sutures at sites proximal and distal to the bleeding point. A third stitch is placed posterior to the bleeding vessel. Pains must be taken to avoid injury to the common bile duct during the placement of these sutures. The duodenotomy is then closed. If a truncal vagotomy is to be performed, the duodenotomy should extend through the pylorus and be closed transversely to perform a pyloroplasty. Frozen section to confirm the presence of nerve tissue is helpful for ensuring that the vagotomy is complete.

The recommendation for truncal vagotomy is based on data from studies done before PPIs and *H. pylori* therapy came into use. Subsequent studies and a 2004 Cochrane review that evaluated rebleeding rates with current medical regimens demonstrated much lower rebleeding rates.⁵¹ Furthermore, it seems probable that long-term PPI therapy (the medical equivalent of vagotomy), in conjunction with eradication of *H. pylori* and avoidance of NSAIDs, should reduce rebleeding rates significantly. Studies from the United States⁴⁵ and the United Kingdom⁵² have shown that a vagotomy is performed less than 50% of the time during surgical treatment of an acute bleeding duodenal ulcer. Therefore, although there are no prospective, randomized studies to support it, one may consider an alternative treatment approach in patients who have not been receiving ulcer therapy before the bleeding began—namely, ligation of the bleeding vessel, postoperative administration of PPIs, and *H. pylori* therapy. This approach avoids the complications associated with truncal vagotomy.

Another option for preventing postvagotomy symptoms when operating on stable patients for bleeding duodenal ulcer is to perform a highly selective vagotomy (HSV) [see 5:20 *Procedures for Benign and Malignant Gastric and Duodenal Disease*]. This procedure is considered preferable to truncal vagotomy because of the decreased incidence of gastric atony, alkaline reflux gastritis, dumping, and diarrhea; however, HSV is associated with a higher recurrence rate than is truncal vagotomy and takes significantly longer to perform.⁵³

GASTRIC ULCER

Gastric ulcers are classified according to their location and to the role (if any) that gastric acid hypersecretion plays in their development. Type I ulcers are located on the lesser curvature and are not associated with acid secretion. Type II ulcers are associated with high acid secretion and are located

on the lesser curvature, occurring in synchrony with duodenal ulcers. Type III ulcers are also associated with acid hypersecretion but occur in the prepyloric region. Type IV ulcers are not associated with acid secretion and are located in the cardia near the esophagogastric junction. Type V ulcers are diffuse and are related to the use of medications (e.g., NSAIDs) [see *Acute Hemorrhagic Gastritis, below*].

Bleeding is less common than with duodenal ulcers, but initial management of a bleeding gastric ulcer is the same as that of a duodenal ulcer (i.e., endoscopic control) [see *Figure 1*]. To prevent aggravation of the bleeding, early biopsy generally is not recommended; repeat endoscopy and biopsy are done at a later date. The indications for emergency surgical intervention for gastric ulcers are the same as those for duodenal ulcers.

Bleeding gastric ulcers that necessitate operative intervention should be treated with resection. For type I ulcers, wedge resection is typically performed. For type II and III ulcers, the usual approach consists of antrectomy with Billroth I reconstruction and truncal vagotomy [see 5:20 *Procedures for Benign and Malignant Gastric and Duodenal Disease*]. Type IV ulcers can pose a technical challenge as a consequence of their close proximity to the esophagogastric junction. A distal gastrectomy with a tongue-shaped extension upward along the lesser curvature to incorporate the ulcer, followed by a Roux-en-Y reconstruction (the Csendes procedure), is often required.⁵⁴ Another option is ligation of the left gastric artery, followed by biopsy and oversewing of the ulcer.

ESOPHAGEAL VARICES

The value of endoscopy in the diagnosis and management of variceal bleeding cannot be overemphasized. Even in patients with known varices, the site of bleeding is frequently nonvariceal; endoscopy is therefore essential.⁵⁵ If bleeding varices are identified, rubber banding or intravariceal sclerotherapy with a sclerosing agent (1.5% sodium tetradecyl sulfate, ethanolamine, sodium morrhuate, or absolute alcohol) is performed [see *Figure 2*].⁵⁶ If these measures do not control the hemorrhage, balloon tamponade is indicated.⁵⁷ Patients who are to undergo this procedure require an endotracheal tube. The preferred tube to use for balloon tamponade is the four-port Minnesota tube, although the Sengstaken-Blakemore tube is also acceptable. The Minnesota tube has a gastric balloon, an esophageal balloon, and aspiration ports for the esophagus and the stomach. The gastric balloon is inflated first and placed on traction. If the bleeding is not controlled, the esophageal balloon is then inflated to a set pressure. The pressure in the balloons should be released in 24 to 48 hours to prevent necrosis of the esophageal or the gastric wall. Successful balloon tamponade is followed by endoscopic variceal injection or variceal banding.

Intravenous somatostatin (250 µg bolus, followed by infusion of 250 µg/hr) should be administered in conjunction with the above-mentioned steps. Vasopressin (10 U/hr) may also be given; however, it causes diffuse vasoconstriction, and nitroglycerin may be required to alleviate cardiac side effects. Somatostatin has proved superior to placebo in controlling variceal hemorrhage when used in conjunction with endoscopic sclerotherapy.⁵⁸ It is as effective as vasopressin while giving rise to fewer side effects. Octreotide, a synthetic analogue of somatostatin, shares many of the properties of

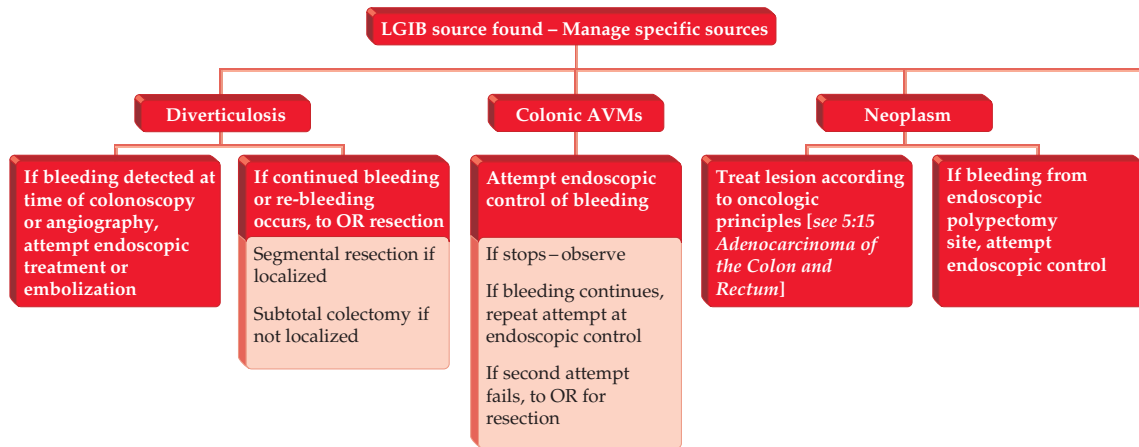


Figure 3 An algorithm for management of lower gastrointestinal bleeding (LGIB). AVM = arteriovenous malformation; IV = intravenous; OR = operating room; TIPS = transjugular intrahepatic portosystemic shunt.

somatostatin but perhaps not all. Both agents decrease secretion of gastric acid and pepsin; however, the decreased gastric blood flow observed with somatostatin administration has not been reported with octreotide administration. Nevertheless, some clinicians in the United States elect to use octreotide (25 to 50 µg/hr) in place of IV somatostatin because the former tends to be more widely available. Several prospective, randomized trials showed that propranolol (40 mg b.i.d., p.o.) decreased the incidence of first-time variceal bleeding and the incidence of recurrent variceal bleeding.^{59,60} Propranolol should not be used during active bleeding but should be started once bleeding stops.

After the acute variceal bleeding has been controlled, any remaining varices should be subjected to injection sclerotherapy or banding at 2-week intervals until they too are obliterated.

The main indications for surgical intervention in patients with bleeding esophageal varices are uncontrolled hemorrhage and persistent rebleeding despite endoscopic and medical therapy. When such intervention is considered, it is essential to determine whether the patient is a transplant candidate. If so, operation should be avoided and bleeding managed by decompressing the portal venous system with a transjugular intrahepatic portosystemic shunt (TIPS) [see 5:10 Portal Hypertension]. TIPS significantly reduces rebleeding rates, but it poses a risk of encephalopathy.⁶¹

If the patient is not a transplant candidate and is not actively bleeding, a distal splenorenal shunt (DSRS) is preferable.⁶² Arteriograms with views of the portal vein and the left renal vein are obtained to assess for suitable anatomy. Alternatively, CT angiography with three-dimensional reconstruction may be performed. If the venous anatomy is suitable—that is, if the diameter of the splenic vein is greater than 0.75 cm (preferably greater than 1.0 cm) and the vein is within one vertebral body of the renal vein on venography—a DSRS procedure should be feasible. If the venous anatomy is not suitable, then esophageal transection, a mesocaval venous graft, or a portacaval shunt is required.

In the emergency setting, a central portacaval shunt, usually in a side-to-side orientation or with a short polytetrafluoro-

ethylene (PTFE) interposition graft, may be placed. Esophageal transection is also a reasonable choice. This procedure is associated with a lower incidence of encephalopathy than a portacaval shunting procedure; however, it is associated with higher rates of rebleeding (particularly late rebleeding), and it can be difficult to perform when active bleeding is present. Suture ligation of the bleeding varices with devascularization (the Sugiura procedure) [see 5:10 Portal Hypertension] should also be considered.

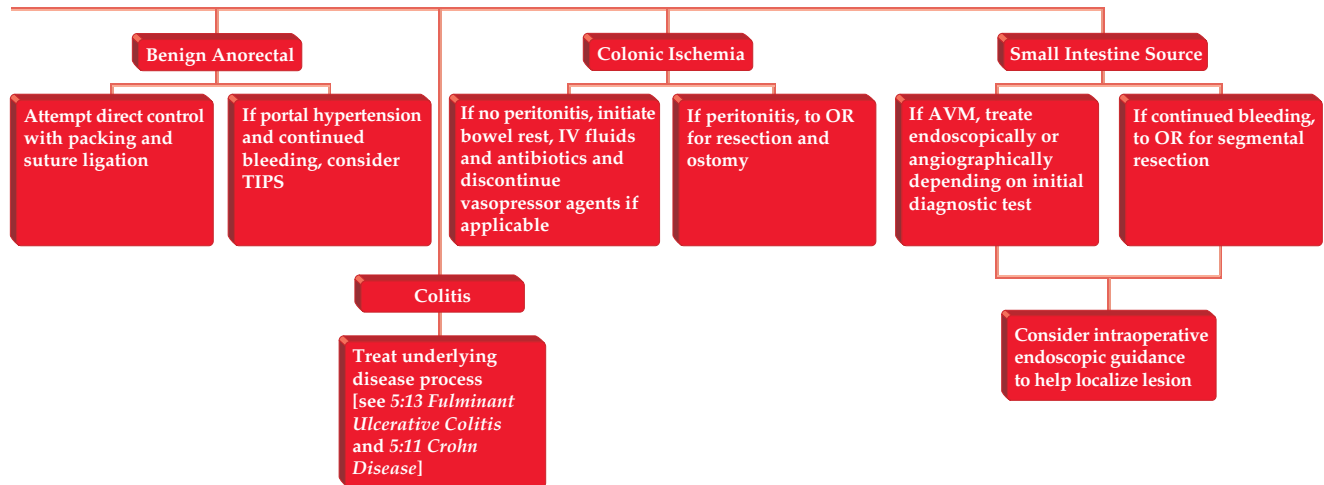
In general, prognosis is related to the underlying liver disease. For example, patients with varices that are secondary to chronic extrahepatic portal venous or splenic venous occlusion generally have a much better prognosis than those whose portal hypertension is secondary to hepatic parenchymal causes. The severity of the cirrhosis also determines short-term and long-term survival and may influence the decision whether to perform a shunting procedure. For varices that are secondary to splenic vein thrombosis (sinistral portal hypertension), splenectomy is usually curative; the procedure may be performed laparoscopically [see 5:25 Splenectomy].⁶³

GASTRIC VARICES

Gastric varices are managed in much the same way as esophageal varices [see Figure 2], although they are less amenable to sclerotherapy.⁶⁴ Other endoscopic treatments (e.g., ligation or sclerotherapy plus ligation) and interventional radiologic treatments (e.g., TIPS or intravascular balloon occlusion) should be considered before surgical management (i.e., DSRS, portosystemic shunting, or suture ligation with gastric devascularization). If the patient is a suitable candidate, liver transplantation may be performed as an alternative to shunting.

MALLORY-WEISS TEARS

Mallory-Weiss tears are linear mucosal tears at the esophagogastric junction that are usually caused by vomiting. Any patient who presents with vomiting that initially is not bloody but later turns so should be suspected of having a Mallory-Weiss tear. As a rule, these lesions stop bleeding without



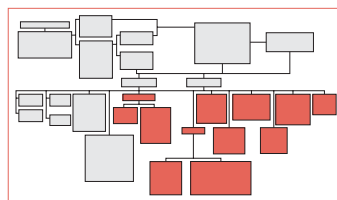
therapy. If bleeding is substantial or persistent, however, endoscopic injection, clipping, banding, or coagulation may be necessary.^{65,66} In rare instances, the tear will have to be oversewn at operation. This is accomplished via an anterior gastrotomy and direct suture ligation of the tear.

ACUTE HEMORRHAGIC GASTRITIS

Bleeding from gastritis is virtually always managed medically with H₂ blockers, PPIs, sucralfate, or antacids (either alone or in combination), along with antibiotics if *H. pylori* is present.⁶⁷ Somatostatin may be beneficial. Sometimes, administration of vasopressin via the left gastric artery is needed to control bleeding. In rare cases, total or near-total gastrectomy [see 5:20 *Procedures for Benign and Malignant Gastric and Duodenal Disease*] is required; however, the mortality associated with this operation in this setting is high. Stress ulcer prophylaxis in severely ill or traumatized patients is essential to prevent this problem.⁶⁸ The gastric pH should be kept as close to neutral as possible. If the gastritis is relatively mild, a biopsy specimen should be obtained and tested for *H. pylori*. Treatment consists of acid reduction and *H. pylori* therapy.

NEOPLASMS

Benign tumors of the upper GI tract (e.g., gastrointestinal stromal tumors [GISTs], hamartomas, and hemangiomas) occasionally bleed [see 5:8 *Tumors of the Stomach, Duodenum, and Small Bowel*]. Wedge excision of the offending lesion is the procedure of choice. GISTs (previously classified as leiomyomas or leiomyosarcomas) run the gamut from benign to highly aggressive. They typically present as a submucosal mass that may cause bleeding as a result of mucosal ulceration. The bleeding may be treated with wedge excision of the tumor,



which can be challenging when the GIST is located in the gastric cardia. Such excision can often be accomplished laparoscopically [see 5:20 *Procedures for Benign and Malignant Gastric and Duodenal Disease*] or even through a laparoscopic intragastric approach.⁶⁹ Some surgeons now perform full-thickness wedge resections endoscopically with the use of a flexible stapler.⁷⁰

Bleeding from malignant neoplasms, whether early stage or late stage, generally can be controlled initially by endoscopic means; however, rebleeding rates are high.⁷¹ If the lesion is resectable, it should be excised promptly once the patient is stable (provided that it has been appropriately staged). If disease is advanced, however, surgical options are limited, and a nonoperative approach, although necessarily imperfect, is preferable.

HIATAL HERNIA

Not infrequently, the source of chronic enteric blood loss is a hiatal hernia. Major bleeding is rare in this condition but may occur as a result of linear erosions at the level of the diaphragm (Cameron lesions),⁷² gastritis within the hernia, or torsion of a paraesophageal hernia. Endoscopy is generally diagnostic, although the sources of chronic blood loss are not always obvious. Recognition that the bleeding derives from a Cameron lesion should incline the surgeon toward operative intervention [see 4:7 *Open Esophageal Procedures* and 4:8 *Minimally Invasive Esophageal Procedures*]; this lesion is usually mechanically induced and therefore tends to be less responsive to antacid therapy.

Chronic bleeding from a type I hiatal hernia should be treated initially with a PPI. *H. pylori* therapy should be added if biopsy shows this organism to be present. Operative management (i.e., laparoscopic Nissen fundoplication [see 4:8 *Minimally Invasive Esophageal Procedures*]) should be considered for fit patients who have complications associated with their hiatal hernia and for all symptomatic patients with type II, III, or IV hiatal hernias (laparoscopic paraesophageal hernia repair).⁷³

DIEULAFOY LESION

A Dieulafoy lesion is the rupturing of a 1 to 3 mm bleeding vessel through the gastric mucosa without surrounding ulceration. This lesion is most commonly found high on the lesser curvature, but it can also occur anywhere throughout the GI tract. Histologic studies have not revealed any intrinsic abnormalities either of the mucosa or of the vessel.

Initial treatment consists of either endoscopically based coagulation of the bleeding vessel with a heater probe or mechanical control with clips or rubber bands; local injection of epinephrine may help control acute hemorrhage while this is being done. In skilled hands, endoscopic therapy has a 95% success rate, and long-term control is excellent. If endoscopic therapy fails, surgical options, including ligation or excision of the vessel involved, come into play.⁷⁴ Having the endoscopist mark the site with India ink is helpful for localization.

HEMOBILIA

Hemobilia should be suspected in all patients who present with the classic triad of epigastric and right upper quadrant pain, GIB, and jaundice; however, only about 40% of patients with hemobilia present with the entire triad. Endoscopy demonstrating blood coming from the ampulla of Vater points to a source in the biliary tree or the pancreas (hemosuccus pancreaticus).

Arteriography may provide the definitive diagnosis: a bleeding tumor, a ruptured artery from trauma, or another cause. Arteriographic embolization of the affected portion of the liver is the preferred treatment option; hepatic artery ligation (selective if possible) or hepatic resection [see 5:23 *Hepatic Resection*] may be required.

HEMOSUCCUS PANCREATICUS

Bleeding into the pancreatic duct, generally from erosion of a pancreatic pseudocyst into the splenic artery, is signaled by upper abdominal pain followed by hematochezia.⁷⁵ If endoscopy is performed when hematochezia is present, the bleeding site may not be seen; however, if endoscopy is performed when pain is first noted, blood may be seen coming from the ampulla of Vater. The combination of significant GIB, abdominal pain, a history of alcohol abuse or pancreatitis, and hyperamylasemia should suggest the diagnosis. If there are no pancreatitis-related indications for surgery, angiographic embolization can be definitive treatment.⁷⁶ If there are pancreatitis-related indications for operation, angiographic embolization may allow an elective operative procedure based on the structural changes observed in the pancreas. If embolization fails, pancreatic resection is usually required, often on an emergency basis [see 5:24 *Procedures for Benign and Malignant Pancreatic Disease*].

AORTOENTERIC FISTULA

Aortoenteric fistulas may occur spontaneously as a result of rupture of an aortic aneurysm or perforation of a duodenal lesion (primary); more often, they arise after aortic surgery (secondary).⁷⁷ A common initial manifestation of an aortoenteric fistula is a small herald bleed that is followed a few days later by a massive hemorrhage. Patients often present with the triad of GI hemorrhage, a pulsatile mass, and infection; however, not all of these symptoms are invariably present.

A high index of suspicion facilitates diagnosis. Endoscopy may show an aortic graft eroding into the enteric lumen, but this is an uncommon finding. CT scanning is the procedure of choice for diagnosis. The finding of air around the aorta or the aortic graft is diagnostic and is an indication for emergency exploration. The preferred surgical treatment is resection of the graft with extra-abdominal bypass. Some authorities, however, advocate resection of the graft with in situ graft replacement.⁷⁸ Some now advocate endovascular stent repair for high-risk patients without evidence of infection.⁷⁹

VASCULAR ECTASIAS

Vascular ectasias (also referred to as vascular dysplasia, angiodysplasia, angiomas, telangiectasia, and AVMs) may bleed briskly. As a rule, gastric lesions can be readily identified and the bleeding controlled by endoscopic means.⁸⁰ Lesions that continue to bleed, either acutely or chronically, despite endoscopic measures should be excised. Some patients have multiple and extensive lesions that necessitate resection of large portions of the stomach. Pharmacotherapy and hormone therapy have been tried; the results have been mixed.

DUODENAL DIVERTICULA

Duodenal diverticula are rare causes of UGIB. Accurate identification of a bleeding site within a given diverticulum is difficult, but an attempt should be made to accomplish this by means of per oral enteroscopy or video-CE. Excision is the preferred treatment and is accomplished by means of segmental resection.⁸¹ Great care must be taken in the treatment of duodenal diverticula in the region of the ampulla of Vater to ensure that the pancreatic duct and the bile ducts are not injured during excision.

Discussion and Management of Specific Sources of LGIB

DIVERTICULOSIS

The vast majority of colonic diverticula are actually false diverticula (pseudodiverticula) that contain only serosa and mucosa [see 5:12 *Diverticulitis*]. They occur at weak points in the colonic wall where the vasa recta penetrate the muscularis to supply the mucosa; as the diverticulum expands, these vessels are displaced. A 1976 anatomic study of colonic specimens from patients with diverticular bleeding used angiography to demonstrate that in all cases, the vasa recta overlying the diverticulum ruptured into the lumen of the diverticulum, not into the peritoneum.⁸²

It has been estimated that approximately 17% of patients with colonic diverticulosis experience bleeding, which may range from minor to severe and life-threatening. Fortunately, most diverticular hemorrhages stop spontaneously. In one series, surgery was unlikely to be necessary if fewer than 4 units of packed RBCs were transfused in a 24-hour period, whereas 60% of patients receiving more than 4 units of packed RBCs in a 24-hour period required surgical intervention.⁸³ Semielective surgical therapy is usually offered after a second diverticular bleeding episode because once a second such episode has occurred, the risk that a third will follow exceeds 50%. In a series of 83 conservatively managed cases of

diverticular disease, the predicted yearly recurrence rates were 9% at 1 year, 10% at 2 years, 19% at 3 years, and 25% at 4 years.⁸⁴

In general, patients who require more than 4 units of blood in a 24-hour period to remain hemodynamically stable, who have not stopped bleeding after 72 hours, or who experience rebleeding within 1 week after an initial episode should undergo surgery.¹⁸

Endoscopic treatment of diverticular hemorrhage can be difficult because of the high bleeding rate and the location of the bleeding point within the diverticulum. In 2000, one group of investigators reported their experience with endoscopic therapy for severe hematochezia and diverticulosis in a prospective series of 121 patients.⁸⁵ In this series, none of the patients treated endoscopically with epinephrine injections, bipolar coagulation, or both required surgery and none experienced recurrent bleeding episodes. A 2001 study from another group, however, reported high rates of recurrent bleeding episodes in both the early and the late posttreatment periods.⁸⁶ In the absence of prospective, randomized trials, it is difficult to draw definitive conclusions about the utility of endoscopic therapy in treating diverticular hemorrhage.

COLONIC AVMS

The term *arteriovenous malformation* includes vascular ectasias, angiomas, and angiodysplasias. AVMs are ectatic blood vessels seen in the mucosa and submucosa of the GI tract. They are degenerative lesions of the GI tract, occurring more frequently with advancing age.¹⁸ In patients older than 50 years, the incidence of colonic AVMs is estimated to range from 2 to 30%.⁸⁷

Colonic AVMs are believed to derive from chronic colonic wall muscle contraction, which leads to chronic partial obstruction of the submucosal veins, causing the vessels to become dilated and tortuous. This process eventually renders the precapillary sphincters incompetent, resulting in direct arterial-venous communication. Colonic AVMs are most commonly found in the cecum. They have been associated with several systemic diseases, including atherosclerotic cardiovascular disease, aortic stenosis, chronic renal disease, collagen vascular disease, von Willebrand disease, chronic obstructive pulmonary disease, and cirrhosis of the liver; to date, however, no definite causal relationship to any of these conditions has been established.²¹

The diagnosis of a colonic AVM is made at the time of angiography or colonoscopy. During angiography, visualization of ectatic, slow-emptying veins, vascular tufts, or early-filling veins establishes the diagnosis.⁸⁸ During endoscopy, angiodysplasias appear as red, flat lesions about 2 to 10 mm in diameter, sometimes accompanied by a feeding vessel.^{4,21}

Typically, the bleeding caused by colonic AVMs is chronic, slow, and intermittent. Although these lesions can cause severe lower GI hemorrhage, they are a relatively uncommon cause. The bleeding stops spontaneously in 85 to 90% of cases,⁸⁸ but it recurs in 25 to 85%.⁸⁹ Accordingly, definitive surgical or colonoscopic treatment should be rendered once the lesion has been identified.

Colonic AVMs are usually amenable to endoscopic treatment. That these lesions are frequently found in the right colon makes perforation a concern; this complication is reported in approximately 2% of patients. Good success rates

have been reported with both injection and thermal methods.⁹⁰ In one series, endoscopic fulguration was successful in 87% of patients, and no rebleeding episodes occurred over a 1- to 7-year follow-up period.⁹⁰ Bleeding from multiple telangiectatic lesions in the distal colon resulting from radiation injury can be treated with thermal contact probes, lasers, or noncontact devices such as the argon plasma coagulator.

NEOPLASIA

Significant GIB from colorectal neoplasia [see 5:15 *Adenocarcinoma of the Colon and Rectum*] accounts for 7 to 33% of cases of severe lower GI hemorrhage.^{3,18} Such bleeding is believed to result from erosions on the luminal surface. Adenomatous polyps are implicated in 5 to 11% of cases of acute LGIB.⁹¹

LGIB, either immediate or delayed, is the most common reported complication after endoscopic polypectomy, occurring in 0.2 to 6% of cases.^{3,84} Immediate postpolypectomy bleeding is believed to result from incomplete coagulation of the stalk before transection. Delayed bleeding has been reported as long as 15 days after polypectomy and is thought to be secondary to sloughing of the coagulum; it is less common than immediate bleeding, occurring in only 0.3% of cases.⁹² Postpolypectomy hemorrhage can often be successfully treated by endoscopic means. Methods used include simple resnaring of the stalk while pressure is maintained⁹²; electrocauterization, with or without epinephrine injection; endoscopic band ligation; and placement of metallic clips.

BENIGN ANORECTAL DISEASE

Hemorrhoids, ulcer or fissure disease, and fistula in ano [see 5:17 *Benign Rectal, Anal, and Perineal Problems*] must not be overlooked as causes of GI hemorrhage: in one review comprising almost 18,000 cases of LGIB, 11% were attributable to anorectal pathology. It is therefore imperative to perform a digital rectal examination and anoscopy in all patients with LGIB. However, identification of a benign anorectal lesion does not eliminate the possibility of a more proximal cause of hemorrhage. Patients with hemorrhoids identified on physical examination should therefore still undergo thorough endoscopic evaluation of the colon to rule out other pathologic conditions. For patients whose bleeding is attributable to benign anorectal causes, endoscopic therapy may include epinephrine injection, sclerosant injection, or band ligation of internal hemorrhoids.⁹³

Portal hypertension [see 5:10 *Portal Hypertension*], congestive heart failure, and splenic vein thrombosis can cause colonic or anorectal varices, which can result in massive lower GI hemorrhage. The reported incidence of anorectal varices in patients with portal hypertension ranges from 78 to 89%.⁹⁴ If local measures fail to control hemorrhage, some form of portosystemic shunting is indicated.

COLITIS

The broad term *colitis* includes IBD, infectious colitis, radiation colitis, and idiopathic ulcers. IBD, in turn, includes Crohn disease [see 5:11 *Crohn Disease*] and ulcerative colitis [see 5:13 *Fulminant Ulcerative Colitis*]. Patients with IBD usually present with bloody diarrhea that is not life-threatening; however, 6 to 10% of patients with ulcerative colitis have

LGIB severe enough to necessitate emergency surgical resection,⁹⁵ and 0.6 to 1.3% of patients with Crohn disease have acute life-threatening LGIB.⁹⁵ In one review, 50% of patients with intestinal hemorrhage from IBD experienced spontaneous cessation of bleeding.⁹⁵ Approximately 35% of patients whose bleeding stops without intervention will have another bleeding episode. Because of this high recurrence rate, semielective surgery is recommended after the first episode of severe GIB secondary to IBD.

Colitis caused by various infectious agents (e.g., typhi, *Escherichia coli* O157:H7, *Clostridium difficile*, and cytomegalovirus) can result in severe LGIB, but this is a relatively rare occurrence.

Increasing use of radiation therapy to treat pelvic malignancies has led to a corresponding increase in the incidence of chronic radiation proctitis. Radiation therapy damages bowel mucosa, resulting in the formation of vascular ectasias that are prone to bleeding. From 1 to 5% of cases of acute LGIB from radiation-induced proctocolitis are severe enough to necessitate hospitalization.⁸⁴ In a survey of patients with prostate cancer who underwent pelvic irradiation, 5% of the patients reported hematochezia daily.⁹⁶ Initial therapy for clinically significant hematochezia related to radiation proctitis should include some form of endoscopic treatment (e.g., argon-beam coagulation). Surgery should be reserved for unstoppable hemorrhage or other major complications, such as fistulas and strictures.

COAGULOPATHY

LGIB can be a presenting symptom for both patients with iatrogenic coagulopathy from heparin or warfarin therapy and patients with a hematologic coagulopathy from thrombocytopenia [see *1:4 Bleeding and Transfusion*]. It is unclear, however, whether severe coagulopathy leads to spontaneous hemorrhage or whether it predisposes to bleeding from an existing lesion.⁹⁷ In an early series of leukemic patients with thrombocytopenia and severe GI hemorrhage, 50% of bleeding patients had platelet counts lower than 20,000/ μ L without any identifiable mucosal lesions; furthermore, when the platelet count rose above 20,000/ μ L, the incidence of bleeding decreased to 0.8%.⁹⁷ The investigator concluded that severe thrombocytopenia led to spontaneous GI hemorrhage. Other investigators subsequently challenged this conclusion, arguing that spontaneous bleeding from coagulopathy is, in fact, rare. In one report, the distribution of pathologic lesions in patients with GIB who were taking heparin or warfarin was essentially equivalent to that in the general population.⁹⁸ Regardless of what the precise relation between coagulopathy and GI hemorrhage may be, a thorough investigation for an anatomic lesion is imperative in the workup of patients with LGIB even in the face of coagulopathy or thrombocytopenia.

COLONIC ISCHEMIA

Acute LGIB can also be a presenting symptom of colonic ischemia. In several large series, colonic ischemia accounted for 3 to 9% of cases of acute lower GI hemorrhage.^{84,91} Other

vascular diseases reported as potential causes are polyarteritis nodosa, Wegener granulomatosis, and rheumatoid vasculitis. The resultant vasculitis can cause ulceration, necrosis, and, ultimately, hemorrhage.

More than 80% of patients with colonic ischemia respond to bowel rest, IV fluids, and antibiotics and do not require surgical intervention.⁹⁹ When exploration is indicated because of peritonitis or recalcitrant disease, all questionable bowel should be resected with stoma creation unless a second-look operation is planned.

SMALL INTESTINAL SOURCES

Small intestinal sources account for 0.7 to 9% of cases of acute LGIB.^{3,84} About 70 to 80% of cases of small bowel hemorrhage are attributable to AVMs; other, less common causes are jejunoileal diverticula, Meckel diverticulum, neoplasia, regional enteritis, and aortoenteric fistulas. Accurate localization of a bleeding site in the small intestine can be highly challenging: the length and the free intraperitoneal position of the small bowel make endoscopic examination difficult, and the nature of the overlying loops makes angiographic localization imprecise. For these reasons, the small intestine is usually left for last in the attempt to localize the source of LGIB and is examined only after sources in the colon, upper GI tract, and anorectum have been ruled out.

AIDS

The etiology of LGIB in patients with AIDS differs from that in the general population. In AIDS patients, LGIB is caused predominantly by conditions related to the underlying HIV infection. Cytomegalovirus colitis is the most common cause of such bleeding in this population, occurring in 39% of cases. AIDS patients with hemorrhoids or anal fissures often experience significant bleeding as a result of HIV-induced thrombocytopenia. A 1998 study reported that in 23% of AIDS patients hospitalized for LGIB, benign anorectal disease was the cause.¹⁰⁰ Other significant causes of lower GI hemorrhage in this population are colonic histoplasmosis, Kaposi sarcoma of the colon, and bacterial colitis.¹⁰⁰

NSAIDS

The association between NSAID use and UGIB is well known. Current data suggest that NSAIDs have a toxic effect on colonic mucosa as well. An epidemiologic study estimated the incidence of NSAID-associated large bowel bleeding to be 7 in 100,000.¹⁰¹ A retrospective review found that patients who had experienced LGIB were twice as likely to have taken NSAIDs as those who had not.¹⁰² NSAIDs have also been linked to diverticular hemorrhage. The exact mechanism of NSAID-induced colonic injury is unknown.

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6 LOWER GASTROINTESTINAL BLEEDING

Michael J. Rosen, M.D., and Jeffrey L. Ponsky, M.D., F.A.C.S.

Approach to Lower GI Bleeding

Lower gastrointestinal bleeding is defined as abnormal hemorrhage into the lumen of the bowel from a source distal to the ligament of Treitz. In the majority of cases, lower GI bleeding derives from the colon; however, the small bowel is identified as the source of bleeding in as many as one third of cases,^{1,2} and the upper GI tract is identified as the source in as many as 11% of patients presenting with bright-red blood per rectum.³

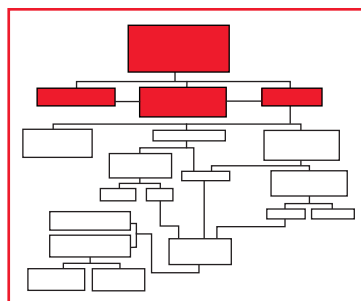
Lower GI bleeding is more common in men than in women. The incidence rises steeply with advancing age, exhibiting a greater than 200-fold increase from the third decade of life to the ninth. This increase is largely attributable to the various colonic disorders commonly associated with aging (e.g., diverticulosis and angiodysplasia).⁴⁻⁶ The exact incidence of lower GI bleeding is not known, because there is no standardized technique for localizing it. Several investigators, however, estimate the incidence to be in the range of 20 to 27 cases per 100,000 adults.^{4,7} A 1997 survey of GI bleeding from the American College of Gastroenterology found that lower GI hemorrhage accounted for 24% of all GI bleeding events.⁸ Another study published the same year found that 0.7% of 17,941 discharges from a Veterans Affairs hospital were for patients who had had lower GI bleeding.⁹

The basic components of management are (1) initial hemodynamic stabilization, (2) localization of the bleeding site, and (3) site-specific therapeutic intervention. There are many conditions that can cause lower GI hemorrhage [see Discussion, Etiology of Lower GI Bleeding, *below*]; accordingly, successful localization depends on timely and appropriate use of a variety of diagnostic tests. Despite the abundance of diagnostic modalities available, attempts to localize the source of the hemorrhage fail in as many as 8% to 12% of patients.^{10,11} Once the bleeding site is localized, the appropriate therapeutic intervention must be carried out as expeditiously as possible.

Lower GI bleeding can be acute and life-threatening, chronic, or even occult. In what follows, we focus on severe, life-threatening hematochezia, reviewing the wide array of possible causes of lower GI bleeding and outlining the diagnostic and therapeutic modalities available for treating this difficult clinical problem.

Initial Evaluation and Resuscitation

Initial evaluation of a patient with lower GI bleeding should include a focused history and physical examination, to be carried out simultaneously with resuscitation. Of particular importance in taking the history is to ascertain



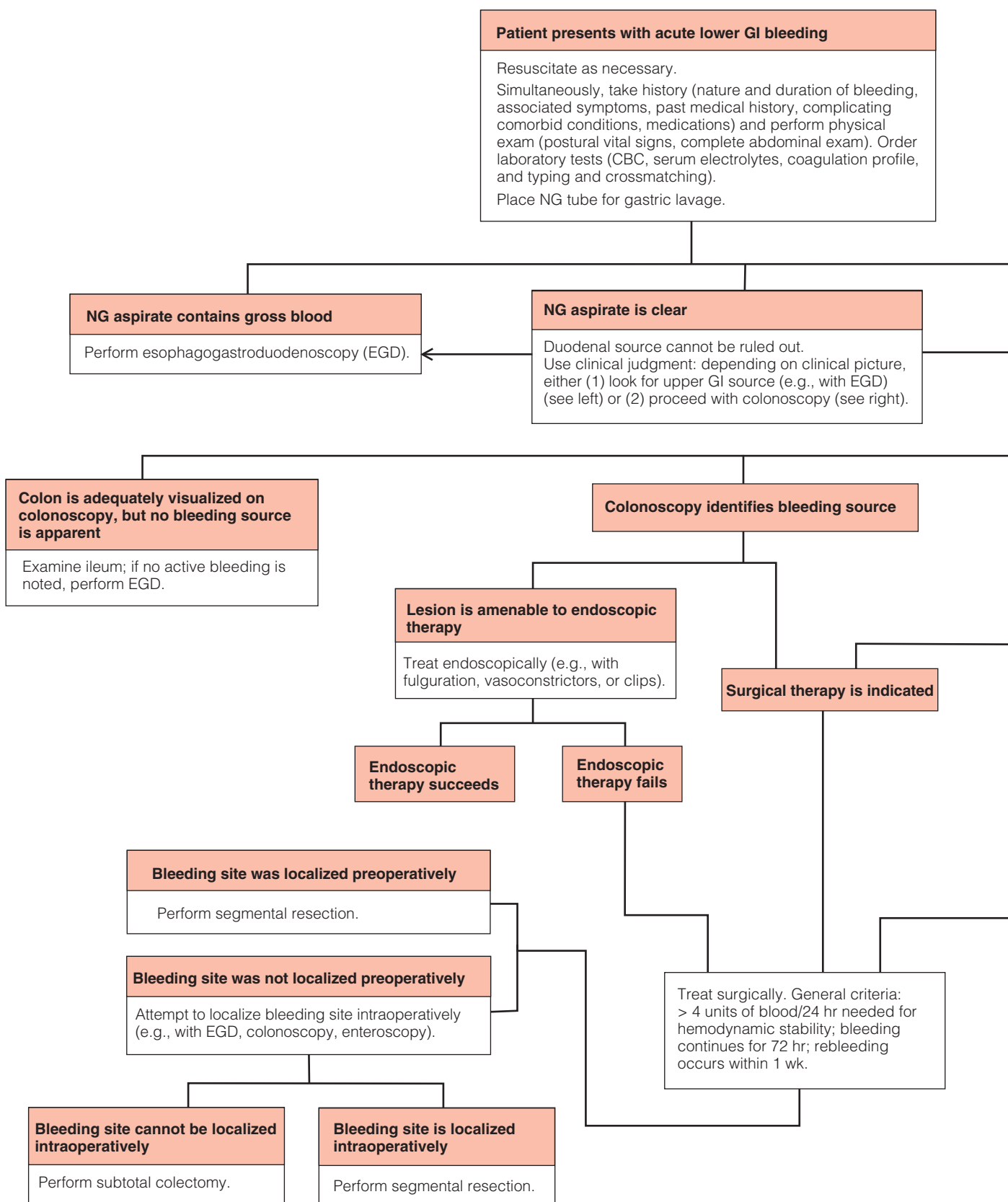
the nature and duration of the bleeding, including stool color and frequency. The patient should also be asked about any associated symptoms of potential significance (e.g., abdominal pain, changes in bowel habits, fever, urgency, tenesmus, or weight loss), as well as about relevant past medical events (e.g., previous GI bleeding episodes, injuries, surgical procedures, peptic ulcer disease, inflammatory bowel disease [IBD], and abdominal or pelvic irradiation). Any complicating comorbid conditions (e.g., heart or liver disease and clotting disorders) should be investigated. A comprehensive review of medications—in particular, nonsteroidal anti-inflammatory drugs (NSAIDs) and anticoagulants—is mandatory.¹²

The physical examination should include determination of postural vital signs so that intravascular volume status can be accurately estimated. A drop in the orthostatic blood pressure greater than 10 mm Hg or an increase in the pulse rate greater than 10 beats/min indicates that more than 800 ml of blood (> 15% of the total circulating blood volume) has been lost. Marked tachycardia and tachypnea in association with hypotension and depressed mental status indicates that more than 1,500 ml of blood (> 30% of the total circulating blood volume) has been lost. A complete abdominal examination, including digital rectal examination and anoscopy, should be performed.

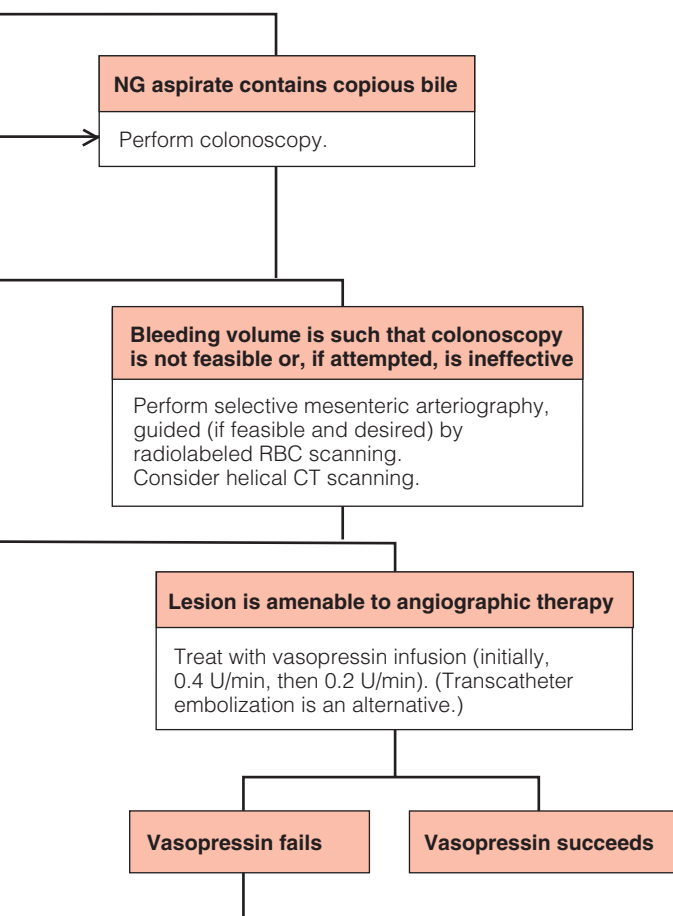
Laboratory evaluation should include a complete blood count, measurement of serum electrolyte concentrations, a coagulation profile (prothrombin time and partial thromboplastin time) [see 1:4 *Bleeding and Transfusion*], and typing and crossmatching.

A nasogastric tube should be placed for gastric lavage. If lavage yields positive results (i.e., the aspirate contains gross blood or so-called coffee grounds), esophagogastroduodenoscopy (EGD) is indicated [see 5:18 *Gastrointestinal Endoscopy*]. An aspirate that contains copious amounts of bile is strongly suggestive of a lower GI source of bleeding, and the workup proceeds accordingly [see Investigative Studies, *below*]. The choice is less clear-cut with a clear aspirate. In the absence of bile, such an aspirate cannot rule out a duodenal source for the bleeding. Accordingly, there is some degree of latitude for clinical judgment: depending on the overall clinical picture, the surgeon may choose either to perform EGD to rule out a duodenal bleeding source or to proceed with colonoscopy on the assumption that the source of the bleeding is in the lower GI tract.

Resuscitative efforts should begin immediately, with the aim of maintaining the patient in a euvolemic state. Two large-bore peripheral intravenous catheters should be inserted and isotonic I.V. fluid administered. A Foley catheter should be placed to facilitate monitoring of intravascular volume status. Whether and in what form to administer blood products is determined on an individual basis, with appropriate weight given to the presence or absence of comorbid conditions, the rate of blood loss, and the



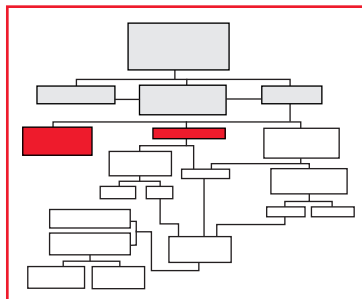
Approach to Lower GI Bleeding



degree of hemodynamic stability. Severe hemodynamic instability may necessitate monitoring in the intensive care unit.

Investigative Studies

A number of diagnostic techniques are available for determining the source of lower GI hemorrhage, the most useful of which are colonoscopy [see 5:18 *Gastrointestinal Endoscopy*], radionuclide scanning, computed tomography, and angiography (in the form of selective mesenteric arteriography). The goal of these tests is to locate the site of bleeding accurately so that definitive therapy can be properly directed. Which diagnostic test is chosen for a specific patient depends on several factors, including the hemodynamic stability of the patient, the bleeding rate, the comorbid conditions present, and the local expertise available at the physician's hospital.



COLONOSCOPY

Several large series that evaluated the diagnostic utility of colonoscopy in patients with lower GI bleeding found this modality to be moderately to highly accurate, with overall diagnostic yields ranging from 53% to 97% [see Table 1].^{3,13-17} Those studies that reported morbidity found colonoscopy to be safe as well, with an average complication rate of 0.5%. Colonoscopy has both a higher diagnostic yield and a lower complication rate than arteriography in this setting and thus would appear to be a more attractive initial test in most circumstances.^{3,18} An argument has been made—one with which we agree—that colonoscopy should be considered the procedure of choice for structural evaluation of lower GI bleeding and that arteriography should be reserved for patients with massive, ongoing bleeding in whom endoscopy is not feasible or colonoscopy fails to reveal the source of the hemorrhage.¹²

The merits of colonic purging have been extensively debated in the literature.^{3,11,14} Although no firm conclusion has been reached, we feel that adequate colonic purging can improve both the diagnostic yield and the safety of colonoscopy. Given the absence of any definitive data suggesting that colonic purging either reactivates or increases bleeding,¹² it is our practice to administer an oral purge after the patient has been adequately resuscitated.

If the entire colon has been adequately visualized and no source for the bleeding has been identified, the ileum should be intubated; fresh blood in this region suggests a possible small bowel source. If no active bleeding is observed in the ileum, upper GI endoscopy should be performed to rule out an upper GI bleeding site.

When colonoscopy and routine upper GI endoscopy fail to locate a bleeding source, push enteroscopy may be helpful. This procedure can be carried out in several ways. It can be performed purely endoscopically with a pediatric colonoscope. This approach generally requires a high level of skill on the part of the endoscopist, in that the lack of retroperitoneal attachments of the small intestine makes endoscopic navigation extremely challenging. In most cases, only the proximal 150 cm of the small intestine can be evaluated in this way. Alternatively, push enteroscopy can be performed in the operating room at the time of exploratory laparotomy. The surgeon can manually “milk” the small bowel over the scope to evaluate its distal portion. In addition, an enterotomy can be made, and the scope can be passed in both a retrograde and an antegrade fashion so that the entire small intestine can be evaluat-

ed. Depending on the indication and on the technique employed, the diagnostic yield from push enteroscopy has ranged from 13% to 78%.¹⁹ Typically, yields are highest (40% to 60%) in patients with significant GI hemorrhage.

RADIOLABELED RED BLOOD CELL SCANNING

Radionuclide scanning is highly sensitive for lower GI hemorrhage: it is capable of detecting bleeding at rates as slow as 0.1 to 0.4 ml/min.²⁰ Two imaging tracers, both labeled with technetium-99m (^{99m}Tc), are currently available for radionuclide scanning in this setting: ^{99m}Tc-labeled sulfur colloid (^{99m}Tc-SC) and ^{99m}Tc-labeled red blood cells (RBCs). ^{99m}Tc-SC requires no preparation time and can be injected immediately into the patient; however, its rapid absorption into the liver and the spleen can often hinder accurate localization of overlying bleeding sites.⁹ At our institution, we prefer to use ^{99m}Tc-labeled RBCs. This agent requires some preparation time, but it has a much longer half-life than ^{99m}Tc-SC does, it is not taken up by the liver and spleen, and it can be detected on images as long as 24 to 48 hours after injection [see Figure 1].^{21,22}

One study directly compared these two techniques and found ^{99m}Tc-labeled RBC scanning to have an accuracy of 93%, compared with an accuracy of only 12% for ^{99m}Tc-SC scanning.²³ The high sensitivity of ^{99m}Tc-labeled RBC scanning—80% to 98%—is well attested, but there is considerable disagreement in the literature with regard to its specificity in identifying the anatomic site of bleeding.²⁴⁻²⁷ For example, on one hand, a 1996 study found radiolabeled RBC scanning to be 97% accurate for localizing bleeding in 37 patients undergoing surgical resection²⁷; on the other hand, a 1990 study reported a 42% rate of incorrect resection when surgical therapy was based solely on this modality.²⁶ In 2005, one group retrospectively reviewed 127 bleeding scans in an effort to identify factors that might predict a positive scan.²⁸ The investigators found that tagged RBC scans were 48% accurate in localizing bleeding sites later confirmed by endoscopy, surgery, or pathologic evaluation. Multivariate analysis demonstrated that both the number of units of blood transfused in the 24 hours preceding the scan and the lowest recorded hematocrit differed significantly between patients with positive scans and those with negative scans. However, the clinical significance of a positive scan was unclear in this study, in that the rate of endoscopy was not significantly different between patients who had positive scans and those who did not.

To date, no prospective, randomized trials have compared radionuclide scanning with colonoscopy as the initial diagnostic procedure for patients with lower GI hemorrhage. In our view,

Table 1 Diagnostic Accuracy of Colonoscopy in Localizing Source of Lower GI Hemorrhage

Study	No. of Patients	Diagnostic Yield (%)
Richter ¹³	78	70 (90%)
Jensen ³	80	68 (85%)
Rossini ¹⁴	409	311 (76%)
Goenka ¹⁵	166	141 (85%)
Ohyama ¹⁶	345	307 (89%)
Chaudhry ¹⁷	85	82 (97%)
Total	1,163	979 (84%)

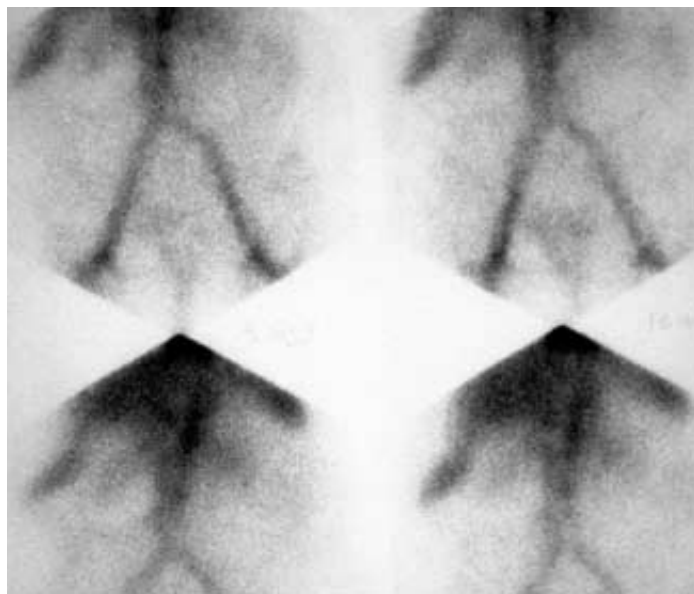


Figure 1 ^{99m}Tc -labeled RBC scan demonstrates collection of tracer at hepatic flexure.

however, given that radionuclide scanning (unlike colonoscopy and angiography) has no therapeutic intervention capabilities, its best use is in patients with non-life-threatening lower GI bleeding as a prelude and a guide to mesenteric angiography after active hemorrhage has been confirmed.

COMPUTED TOMOGRAPHY

With the ongoing improvements in high-speed abdominal CT scanning, there has been growing interest in the evaluation of GI bleeding with CT.²⁹ Helical CT scanners can provide direct or indirect evidence of the source of GI bleeding. Typical findings that can facilitate localization of bleeding sites include spontaneous hyperdensity of the peribowel fat, contrast enhancement of the bowel wall, vascular extravasation of the contrast medium, thickening of the bowel wall, polyps, tumors, and vascular dilatation.



Figure 2 Angiographic study documents extravasation of contrast into small bowel.

CT evaluation of GI bleeding has several noteworthy advantages: the scanners typically are readily available, mobilization of special teams or units is not required, the scans can be completed rapidly in the emergency department, and bowel preparation is unnecessary. In one experimental study, CT scanners were able to detect arterial bleeding at rates as low as 0.07 ml/min, which suggests that CT scanning is more sensitive than angiography for this purpose.³⁰ In addition, CT scans are noninvasive and carry little morbidity. Unfortunately, like radionuclide scanning, CT has no therapeutic capability.

A 2003 study of 19 patients with GI hemorrhage compared triphasic helical CT evaluation with colonoscopy and surgery for localization of bleeding sites.³⁰ In this series, five patients had small bowel bleeding sites, and 14 had colonic sites. Helical CT scanning correctly identified four of the five small bowel lesions and 11 of the 14 colonic lesions. These findings, though preliminary, suggest that CT is a potentially valuable evaluation method in certain cases of GI bleeding. Perhaps CT scanning can eventually replace radionuclide scanning, which is often inaccurate. One potential drawback to the use of CT in this setting is the excessive dye load if angiography is employed as well.

ANGIOGRAPHY

Selective Mesenteric Arteriography

Selective mesenteric arteriography is somewhat less sensitive than radionuclide scanning for lower GI hemorrhage: bleeding must be occurring at a rate of at least 1.0 to 1.5 ml/min to be detectable with this test.³¹ The procedure involves percutaneous placement of a transfemoral arterial catheter for evaluation of the superior mesenteric, inferior mesenteric, and celiac arteries. A positive test result is defined as extravasation of contrast into the lumen of the bowel [see Figure 2]. Once the bleeding vessel has been localized angiographically, the area must be marked so that it can be successfully identified intraoperatively; this is commonly accomplished by infusing methylene blue into the bleeding artery [see Figure 3].^{32,33}

In several large series [see Table 2], the overall diagnostic yield of arteriography ranged from 27% to 67%.^{27,34-38} The complication rate for arteriography performed for lower GI bleeding ranges from 2% to 4%.^{2,38} Reported complications include contrast allergy, renal failure, bleeding from arterial puncture, and embolism from a dislodged thrombus.¹²

Unlike radionuclide scanning, arteriography provides several therapeutic options, including vasopressin infusion and embolization of bleeding vessels. Nonetheless, given that arteriography has a lower diagnostic yield and a higher complication rate than colonoscopy does, it is reasonable to attempt colonoscopy first in patients with lower GI hemorrhage and to reserve angiography for patients in whom the volume of bleeding is such that colonoscopy would be neither safe nor accurate.

Provocative Angiography for Continued Obscure Bleeding

In a minority of patients, obscure bleeding persists despite negative findings from endoscopy, mesenteric arteriography, and radionuclide RBC scanning. This obscure bleeding presents a considerable diagnostic challenge, which some investigators have proposed addressing by means of so-called provocative angiography.^{39,40}

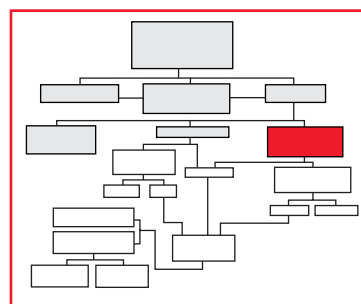




Figure 3 Intraoperative examination of the bowel is aided by injection of methylene blue dye, which facilitates localization of the bleeding site and thereby helps direct surgical resection.

Provocative angiography involves the use of short-acting anticoagulant agents (unfractionated heparin, vasodilators, thrombolytics, or combinations thereof) in association with angiography. Once the bleeding point has been localized, methylene blue is injected and the patient is immediately brought to the OR for surgical treatment. To date, unfortunately, little has been published on this technique, but it does appear to be a promising approach to this difficult problem.

Management

Although, in the majority of cases, lower GI bleeding stops spontaneously, in a significant number of cases, hemorrhage continues and necessitates therapeutic intervention. Treatment options include endoscopic therapy, angiographic therapy, and surgical resection.

ENDOSCOPIC THERAPY

When colonoscopy identifies a bleeding source, endoscopic treatment may be an option [see 5:18 *Gastrointestinal Endoscopy*]. Endoscopic modalities used to treat lower GI bleeding include use of thermal contact probes,^{41,42} laser photocoagulation,⁴³ electrocauterization,⁴⁴ injection of vasoconstrictors, application of metallic clips,⁴⁵ and injection sclerotherapy.⁴⁶ The choice of a specific modality often depends on the nature of the offending lesion and on the expertise and resources available locally. A 1995 survey of members of the American College of Gastroenterology found that endoscopic therapy was used in 27% of patients presenting with lower GI bleeding.⁸

Diverticular hemorrhage can be difficult to treat endoscopically because of the high bleeding rate and the location of the bleeding point within the diverticulum. In 2000, one group of investigators reported their experience with endoscopic therapy for severe

hematochezia and diverticulosis in a prospective series of 121 patients.⁴⁷ In this series, none of the patients treated endoscopically with epinephrine injections, bipolar coagulation, or both required surgery and none experienced recurrent bleeding episodes. A 2001 study from another group, however, reported high rates of recurrent bleeding episodes in both the early and the late post-treatment periods.⁴⁸ In the absence of prospective, randomized trials, it is difficult to draw definitive conclusions about the utility of endoscopic therapy in treating diverticular hemorrhage.

Angiodysplasias resulting in GI hemorrhage typically are amenable to endoscopic treatment. That these lesions are frequently found in the right colon makes perforation a concern; this complication is reported in approximately 2% of patients.⁴⁹ Good success rates have been reported with both injection and thermal methods.⁵⁰ In one series, endoscopic fulguration was successful in 87% of patients, and no rebleeding episodes occurred over a 1- to 7-year follow-up period.⁵⁰ Bleeding from multiple telangiectatic lesions in the distal colon resulting from radiation injury can be treated with thermal contact probes, lasers, or noncontact devices such as the argon plasma coagulator.⁵¹

Postpolypectomy hemorrhage can often be successfully treated by endoscopic means. Methods used include simple resnaring of the stalk while pressure is maintained⁵²; electrocauterization, with or without epinephrine injection; endoscopic band ligation; and placement of metallic clips. For patients whose bleeding is attributable to benign anorectal causes, endoscopic therapy may include epinephrine injection, sclerosant injection, or band ligation of internal hemorrhoids.⁵³

ANGIOGRAPHIC THERAPY

Diagnostic use of angiography in patients with lower GI bleeding can often be followed by angiographic therapy. The two main angiographic treatment options are intra-arterial injection of vasopressin and transcatheter embolization.

Vasopressin acts to control bleeding by causing arteriolar vasoconstriction and bowel wall contraction.⁹ Once the bleeding site has been localized angiographically, the catheter is positioned in

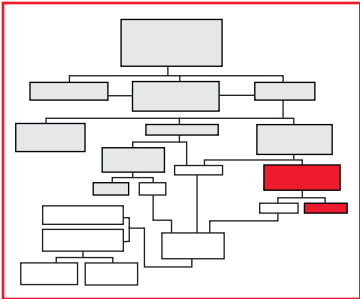


Table 2 Diagnostic Accuracy of Mesenteric Angiography in Localizing Source of Lower GI Hemorrhage

Study	No. of Patients	No. of Positive Angiograms (%)
Pennoyer ³⁴	131	37 (28%)
Ng ²⁷	49	22 (45%)
Rantis ³⁵	30	8 (27%)
Leitman ³⁶	68	27 (40%)
Casarella ³⁷	69	46 (67%)
Colacchio ³⁸	98	40 (41%)
Total	445	180 (40%)

the main trunk of the vessel. Infusion of vasopressin is initiated at a rate of 0.2 U/min and can be increased to a rate of 0.4 U/min. Within 20 to 30 minutes, another angiogram is performed to determine whether the bleeding has ceased. If the bleeding is under control, the catheter is left in place and vasopressin is continuously infused for 6 to 12 hours. If the bleeding continues to be controlled, infusion is continued for an additional 6 to 12 hours at 50% of the previous rate. Finally, vasopressin infusion is replaced by continuous saline infusion, and if bleeding does not recur, the catheter is removed.^{54,55}

The vasoconstrictive action of vasopressin can have deleterious systemic side effects, including myocardial ischemia, peripheral ischemia, hypertension, dysrhythmias, mesenteric thrombosis, intestinal infarction, and death.^{9,36} Occasionally, simultaneous I.V. administration of nitroglycerin is necessary to counteract these systemic effects. The reported success rate of vasopressin in controlling lower GI bleeding ranges from 60% to 100%, and the incidence of major complications ranges from 10% to 20%.⁵⁶⁻⁵⁸ Rebleeding rates as high as 50% have been reported.^{57,58}

An alternative for patients with coronary vascular disease, severe peripheral vascular disease, or other comorbidities that prevent safe administration of vasopressin is transcatheter embolization. In this technique, a catheter is superselectively placed into the identified bleeding vessel and an embolizing agent (e.g., a gelatin sponge, a microcoil, polyvinyl alcohol particles, or a balloon) is injected. Several small series found this technique to be 90% to 100% successful at stopping bleeding.⁵⁹⁻⁶³ Equally impressive was the finding that the rebleeding rates in these series were 0%. The complication rates of this procedure are generally reasonable as well; however, intestinal infarction has been reported.^{36,64}

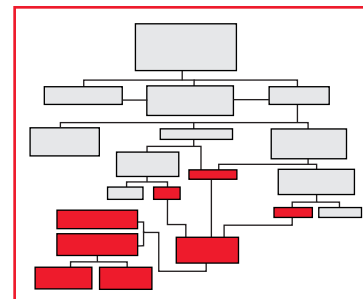
The use of small microcatheters and the ability to superselectively embolize individual vessels have reduced the potential for ischemic perforation. It is possible that as more experience is gained with these techniques, superselective embolization may replace catheter-directed vasoconstrictive therapy, thus obviating the potential deleterious systemic effects of vasopressin administration. Some researchers have suggested that with the exception of cases of diffuse bleeding lesions or cases whose demands exceed the technical limitations of superselective catheterization, emboli-

zation therapy should be the first choice for angiographic treatment of lower GI bleeding.^{65,66}

SURGICAL THERAPY

Although there are no absolute criteria for surgical treatment of lower GI bleeding, there are several factors—including hemodynamic status, associated comorbidities, transfusion requirements, and persistent bleeding—that are instrumental in making an appropriate and timely decision whether to operate. In general, patients who require more than 4 units of blood in a 24-hour period to remain hemodynamically stable, whose bleeding has not stopped after 72 hours, or who experience rebleeding within 1 week after an initial episode should undergo surgery.⁹

If the patient's hemodynamic status permits, surgical treatment should be undertaken after accurate localization of the bleeding site. When possible, directed segmental resection is the procedure of choice: it is associated with rebleeding rates ranging from 0% to 14% and mortality rates ranging from 0% to 13%.^{10,36,67} Blind segmental colectomy should never be performed: it is associated with rebleeding rates as high as 75% and mortality rates as high as 50%.⁶⁸ If hemodynamic compromise and ongoing hemorrhage make it necessary to perform surgical exploration before the bleeding site can be localized, every effort should be made to identify the source of bleeding intraoperatively before embarking on resection. Intraoperative options for bleeding-site localization include colonoscopy (to allow for this option, patients should always be placed in the lithotomy position), EGD, and transoral passage of a pediatric colonoscope for enteroscopy with simultaneous intraperitoneal assistance for small bowel manipulation.⁹ If the bleeding site still cannot be accurately localized, subtotal colectomy is the procedure of choice. This procedure is associated with mortality rates ranging from 5% to 33%,^{69,70} which underscores the importance of accurate preoperative localization of bleeding before surgical intervention.



Discussion

Etiology of Lower GI Bleeding

As noted, lower GI bleeding has a wide array of possible causes [see Table 3].^{9,71} Of these, diverticular disease is the most common, accounting for 30% to 40% of all cases.⁷² Arteriovenous malformations (AVMs), though extensively described in the literature, are considerably less common causes, accounting for 1% to 4% of cases.^{73,74} Other significant causative conditions are IBD, benign and malignant neoplasms, ischemia, infectious colitis, anorectal disease, coagulopathy, use of NSAIDs, radiation proctitis, AIDS, and small bowel disorders.

DIVERTICULAR DISEASE

The reported prevalence of colonic diverticulosis in Western societies is 37% to 45%.⁷⁵ The vast majority of colonic diverticula are actually false diverticula (pseudodiverticula) that contain only serosa and mucosa [see 5:12 Diverticulitis]. They occur at weak points in the colonic wall where the vasa recta penetrate the mus-

cularis to supply the mucosa⁹; as the diverticulum expands, these vessels are displaced. A 1976 anatomic study of colonic specimens from patients with diverticular bleeding used angiography to demonstrate that in all cases, the vasa recta overlying the diverticulum ruptured into the lumen of the diverticulum, not into the peritoneum [see Figure 4].⁷⁶

It has been estimated that approximately 17% of patients with colonic diverticulosis experience bleeding, which may range from minor to severe and life-threatening.⁷⁷ As many as 80% to 85% of diverticular hemorrhages stop spontaneously.⁷⁸ In one series, surgery was unlikely to be necessary if fewer than 4 units of packed RBCs were transfused in a 24-hour period, whereas 60% of patients receiving more than 4 units of packed RBCs in a 24-hour period required surgical intervention.⁵ The risk of a second bleeding episode is approximately 25%.³ Semielective surgical therapy is usually offered after a second diverticular bleeding episode because once a second such episode has occurred, the risk that a

Table 3 Common Causes of Lower GI Hemorrhage

Cause of Bleeding	Frequency
Diverticulosis	17%–40%
Arteriovenous malformation	2%–30%
Colitis	9%–21%
Neoplasia (including postpolypectomy bleeding)	7%–33%
Benign anorectal disease	4%–10%
Upper GI source	0%–11%
Small bowel source	2%–9%

third will follow exceeds 50%.⁷⁹ In a series of 83 conservatively managed cases of diverticular disease, the predicted yearly recurrence rates were 9% at 1 year, 10% at 2 years, 19% at 3 years, and 25% at 4 years.⁴

COLITIS

The broad term colitis includes IBD, infectious colitis, radiation colitis, and idiopathic ulcers. IBD, in turn, includes Crohn disease [see 5:11 *Crohn Disease*] and ulcerative colitis [see 5:13 *Fulminant Ulcerative Colitis*]. Patients with IBD usually present with bloody diarrhea that is not life-threatening; however, 6% to 10% of patients with ulcerative colitis have lower GI bleeding severe enough to necessitate emergency surgical resection,^{80,81} and 0.6% to 1.3% of patients with Crohn disease have acute life-threatening lower GI bleeding.^{80,82} In one review, 50% of patients with intestinal hemorrhage from IBD experienced spontaneous cessation of bleeding.⁸⁰ Approximately 35% of patients whose bleeding stops without intervention will have another bleeding episode. Because of this high recurrence rate, semielective surgery is recommended after the first episode of severe GI bleeding secondary to IBD.

Colitis caused by various infectious agents (e.g., *Salmonella typhi*,^{83,84} *Escherichia coli* O157:H7,⁸⁵ *Clostridium difficile*,⁸⁶ and

cytomegalovirus) can result in severe lower GI bleeding, but this is a relatively rare occurrence.

Increasing use of radiation therapy to treat pelvic malignancies has led to a corresponding increase in the incidence of chronic radiation proctitis.⁸⁷ Radiation therapy damages bowel mucosa, resulting in the formation of vascular telangiectases that are prone to bleeding.⁸⁸ From 1% to 5% of cases of acute lower GI bleeding from radiation-induced proctocolitis are severe enough to necessitate hospitalization.^{4,14} In a survey of patients with prostate cancer who underwent pelvic irradiation, 5% of the patients reported hematochezia daily.⁸⁹ Initial therapy for clinically significant hematochezia related to radiation proctitis should include some form of endoscopic treatment (e.g., argon-beam coagulation). Surgery should be reserved for unstoppable hemorrhage or other major complications, such as fistulas and strictures.⁸⁷

NEOPLASIA

Significant GI bleeding from colorectal neoplasia [see 5:15 *Adenocarcinoma of the Colon and Rectum*] accounts for 7% to 33% of cases of severe lower GI hemorrhage.^{3,11,14,36,90} Such bleeding is believed to result from erosions on the luminal surface.⁹¹ One report identified ulcerated cancers as the cause in 21% of cases of hematochezia.¹⁴ Adenomatous polyps are implicated in 5% to 11% of cases of acute lower GI bleeding.^{7,8,14,92,93} Lower GI hemorrhage, either immediate or delayed, is the most common reported complication after endoscopic polypectomy, occurring in 0.2% to 6% of cases.^{3,4,94,95} Immediate postpolypectomy bleeding is believed to result from incomplete coagulation of the stalk before transection.⁵² Delayed bleeding has been reported as long as 15 days after polypectomy and is thought to be secondary to sloughing of the coagulum; it is less common than immediate bleeding, occurring in only 0.3% of cases.^{14,52}

COAGULOPATHY

Lower GI bleeding can be a presenting symptom both for patients with iatrogenic coagulopathy from heparin or warfarin therapy and for patients with a hematologic coagulopathy from thrombocytopenia [see 1:4 *Bleeding and Transfusion*]. It is unclear, however, whether severe coagulopathy leads to spontaneous hemorrhage or whether it predisposes to bleeding from an existing lesion.^{96,97} In an early series of leukemic patients with thrombocytopenia and severe GI hemorrhage, 50% of bleeding patients had platelet counts lower than 20,000/mm³ without any identifiable mucosal lesions; furthermore, when the platelet count rose above 20,000/mm³, the incidence of bleeding decreased to 0.8%.⁹⁶ The investigator concluded that severe thrombocytopenia led to spontaneous GI hemorrhage. Other investigators subsequently challenged this conclusion, arguing that spontaneous bleeding from coagulopathy is in fact rare.⁹⁸ In one report, the distribution of pathologic lesions in patients with GI bleeding who were taking heparin or warfarin was essentially equivalent to that in the general population.⁹⁸ Regardless of what the precise relation between coagulopathy and GI hemorrhage may be, a thorough investigation for an anatomic lesion is imperative in the workup of patients with lower GI bleeding even in the face of coagulopathy or thrombocytopenia.

BENIGN ANORECTAL DISEASE

Hemorrhoids, ulcer/fissure disease, and fistula in ano [see 5:17 *Benign Rectal, Anal, and Perineal Problems*] must not be overlooked as causes of GI hemorrhage: in one review comprising almost 18,000 cases of lower GI bleeding, 11% were attributable to anorectal pathology. It is crucial to remember that identification of

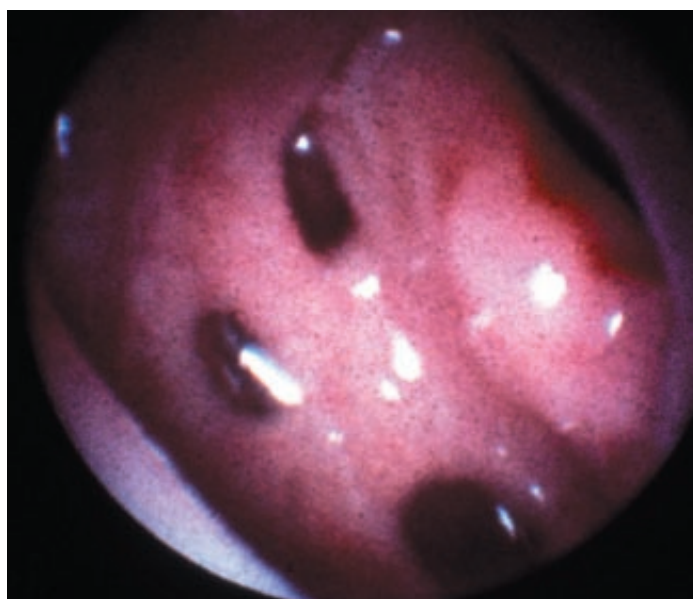


Figure 4 Shown is the appearance of a bleeding diverticulum on colonoscopy.

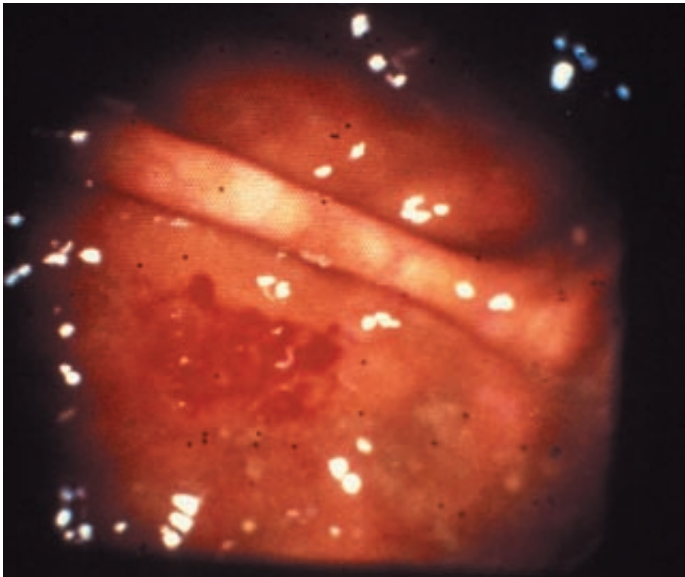


Figure 5 Shown is the appearance of an arteriovenous malformation on colonoscopy.

a benign anorectal lesion does not eliminate the possibility of a more proximal cause of hemorrhage. In general, patients with hemorrhoids identified on physical examination should still undergo thorough endoscopic evaluation of the colon to rule out other pathologic conditions.

Portal hypertension [see 5:10 Portal Hypertension], congestive heart failure, and splenic vein thrombosis can cause colonic or anorectal varices, which can result in massive lower GI hemorrhage.⁹⁹ The reported incidence of anorectal varices in patients with portal hypertension ranges from 78% to 89%.^{100,101} If local measures fail to control hemorrhage, some form of portosystemic shunting is indicated.

COLONIC ARTERIOVENOUS MALFORMATIONS

The term arteriovenous malformation includes vascular ectasias, angiomas, and angiodysplasias. AVMs are ectatic blood vessels seen in the mucosa and submucosa of the GI tract. They are degenerative lesions of the GI tract, occurring more frequently with advancing age.⁹ In autopsy series, the reported incidence of colonic AVMs is 1% to 2%.¹⁰² In patients older than 50 years, the incidence of colonic AVMs is estimated to range from 2% to 30%.¹⁰³⁻¹⁰⁶ In healthy asymptomatic adults, the prevalence is estimated to be approximately 0.8%.¹⁰⁷

Colonic AVMs are believed to derive from chronic colonic wall muscle contraction, which leads to chronic partial obstruction of the submucosal veins, causing the vessels to become dilated and tortuous. This process eventually renders the precapillary sphincters incompetent, resulting in direct arterial-venous communication.^{108,109} Colonic AVMs are most commonly found in the cecum.¹⁰ They have been associated with several systemic diseases, including atherosclerotic cardiovascular disease, aortic stenosis, chronic renal disease, collagen vascular disease, von Willebrand disease, chronic obstructive pulmonary disease, and cirrhosis of the liver; to date, however, no definite causal relationship to any of these conditions has been established.^{6,21,44,110}

The diagnosis of a colonic AVM is made at the time of angiography or colonoscopy. During angiography, visualization of ectatic, slow-emptying veins, vascular tufts, or early-filling veins estab-

lishes the diagnosis.¹¹¹ During endoscopy, angiodysplasias appear as red, flat lesions about 2 to 10 mm in diameter, sometimes accompanied by a feeding vessel [see Figure 5].^{6,41,44,72}

Typically, the bleeding caused by colonic AVMs is chronic, slow, and intermittent.⁹ Although these lesions can cause severe lower GI hemorrhage, they are a relatively uncommon cause: in most large series, they account for only about 2% of cases of acute bleeding.^{74,104} The bleeding stops spontaneously in 85% to 90% of cases,¹⁰ but it recurs in 25% to 85%.¹¹² Accordingly, definitive surgical or colonoscopic treatment should be rendered once the lesion has been identified.

COLONIC ISCHEMIA

Acute lower GI bleeding can also be a presenting symptom of colonic ischemia. In several large series, colonic ischemia accounted for 3% to 9% of cases of acute lower GI hemorrhage.^{4,7,8,14,92} Other vascular diseases reported as potential causes are polyarteritis nodosa, Wegener granulomatosis, and rheumatoid vasculitis.^{113,114} The resultant vasculitis can cause ulceration, necrosis, and ultimately hemorrhage.¹¹⁵

SMALL INTESTINAL SOURCES

Small intestinal sources account for 0.7% to 9% of cases of acute lower GI bleeding.^{3,4,116-118} About 70% to 80% of cases of small bowel hemorrhage are attributable to AVMs; other, less common causes are jejunoileal diverticula, Meckel's diverticulum,¹¹⁹ neoplasia, regional enteritis, and aortoenteric fistulas [see Figure 6].^{90,120,121}



Figure 6 Shown are intraoperative specimens of small bowel tumors causing lower GI hemorrhage.

Accurate localization of a bleeding site in the small intestine can be highly challenging: the length and the free intraperitoneal position of the small bowel make endoscopic examination difficult, and the nature of the overlying loops makes angiographic localization imprecise. For these reasons, the small intestine is usually left for last in the attempt to localize the source of lower GI bleeding and is examined only after sources in the colon, the upper GI tract, and the anorectum have been ruled out.⁹

AIDS

The etiology of lower GI bleeding in patients with AIDS differs from that in the general population.⁹¹ In AIDS patients, lower GI bleeding is caused predominantly by conditions related to the underlying HIV infection. Cytomegalovirus colitis is the most common cause of such bleeding in this population, occurring in 39% of cases.¹²² AIDS patients with hemorrhoids or anal fissures often experience significant bleeding as a result of HIV-induced thrombocytopenia.¹²² A 1998 study reported that in 23% of AIDS

patients hospitalized for lower GI bleeding, benign anorectal disease was the cause.¹²³ Other significant causes of lower GI hemorrhage in this population are colonic histoplasmosis, Kaposi sarcoma of the colon, and bacterial colitis.^{123,124}

NSAID USE

The association between NSAID use and upper GI hemorrhage is well known.¹²⁵ Current data suggest that NSAIDs have a toxic effect on colonic mucosa as well.¹²⁶ An epidemiologic study estimated the incidence of NSAID-associated large bowel bleeding to be 7/100,000.¹²⁷ A retrospective review found that patients who had experienced lower GI bleeding were twice as likely to have taken NSAIDs as those who had not.¹²⁸ NSAIDs have also been linked to diverticular hemorrhage: in one study, 92% of patients with diverticular bleeding were taking NSAIDs.¹⁰⁷ The exact mechanism of NSAID-induced colonic injury is unknown; nevertheless, heightened clinical awareness of this potential cause of lower GI bleeding is warranted.⁹¹

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7 SURGICAL TREATMENT OF MORBID OBESITY

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It is clear that severe obesity is associated with a significant increase in morbidity¹ and a decreased life expectancy.² Morbid obesity—defined as (a) a body weight that exceeds the ideal body weight by 100 lb or more or (b) a body mass index (BMI) greater than 35 kg/m²—has been shown to have a significant genetic basis.^{3,4} To date, attempts to manage morbid obesity with medical weight reduction programs have met with an unacceptably high incidence of recidivism.⁵ The approach that has had the greatest and longest-lasting success in achieving weight loss is bariatric surgery.

Preoperative Evaluation

Many surgeons are afraid to operate on the morbidly obese patient because they presuppose a marked increase in perioperative morbidity and mortality. It is now possible, however, to stratify the mortality risk for patients undergoing gastric bypass (GBP) by using a scoring system known as the Obesity Surgery Mortality Risk Score (OS-MRS), which includes five independent variables that can be identified preoperatively: (1) BMI greater than or equal to 50 kg/m², (2) male gender, (3) hypertension, (4) pulmonary embolus risk (including previous thrombosis, pulmonary embolus, inferior vena cava [IVC] filter, right-side heart failure, and obesity hypoventilation syndrome [OHS]), and (5) patient age greater than or equal to 45 years. These factors were associated with a greater 90-day mortality in a prospective study of 2,075 patients who underwent GBP at a single institution,⁶ which was the basis for the initial proposal of this scoring system. The OS-MRS was subsequently validated in a multicenter study involving four institutions and 4,431 patients.⁷ With the presence of each variable equal to 1 point, each patient's potential score ranged from 0 to 5. Patients with a score of 0 or 1 had a low mortality risk (group A; mortality, 0.2%); those with a score of 2 or 3 had an intermediate mortality risk (group B; mortality, 1.1%); and those with a score of 4 or 5 had a high mortality risk (group C; mortality, 2.4%). These findings suggest that the OS-MRS is a valuable tool that can be effectively used to stratify risk and facilitate surgical decision making and patient discussion regarding bariatric surgery.

Although the morbidly obese patient is certainly at greater risk, this risk can be markedly reduced by paying careful attention to detail in preoperative and postoperative care. The increased risks encountered in these patients include wound infection, dehiscence, thrombophlebitis, pulmonary embolism (PE), anesthetic calamities, acute postoperative asphyxia in patients with obstructive sleep apnea syndrome (SAS), acute respiratory failure, right ventricular or biventricular cardiac failure, and missed acute catastrophes of the abdomen (e.g.,

anastomotic leakage). The ensuing discussion begins by focusing on issues that the surgeon should carefully consider when operating on an extremely overweight patient.

MORBIDITY ASSOCIATED WITH CENTRAL FAT DEPOSITION

Much has been written about the increased health risks inherent in central (android) fat deposition as compared with peripheral (gynoid) fat deposition. It is thought that in the former, the increased metabolic activity of mesenteric fat is associated with increased metabolism of amino acids to sugar, which leads to hyperglycemia and hyperinsulinism. Hyperinsulinism gives rise to increased sodium absorption and hypertension. Furthermore, central obesity has been linked to hypercholesterolemia. Hence, these patients have a significantly higher incidence of diabetes, hypertension, hypercholesterolemia, and gallstones⁸—which explains the higher mortality of the apple distribution of body fat in comparison with the pear distribution. In the past, fat distribution was measured on the basis of the waist-to-hip ratio; however, computed tomographic scanning has shown that abdominal circumference is a more accurate measurement of central fat distribution.⁹ Morbidly obese women have significantly increased intra-abdominal pressure (IAP), and this increase is associated with stress and urge overflow urinary incontinence.¹⁰ With weight loss comes a significant decrease in bladder pressure and correction of incontinence. IAP, as reflected in bladder pressure, appears to be closely correlated with sagittal abdominal diameter and waist circumference but not with waist-to-hip ratio (many morbidly obese patients have both central and peripheral obesity). The increased IAP associated with central obesity may give rise to other comorbid factors as well, including venous stasis ulcers, OHS [see Respiratory Insufficiency of Obesity, *below*], gastroesophageal reflux, and inguinal and incisional hernias.

RESPIRATORY INSUFFICIENCY OF OBESITY

Obese patients are at risk for respiratory difficulties, which may be present before operation or may be exacerbated by an operation. The term pickwickian syndrome (which derives from *The Posthumous Papers of the Pickwick Club*, by Charles Dickens) was resurrected from the late 1800s to describe a morbidly obese 52-year-old man who fell asleep in a poker game while holding a hand containing a full house.¹¹ He was taken to the hospital by friends who presumed he was ill. The pickwickian syndrome is now known to comprise two pulmonary syndromes associated with morbid obesity: SAS and OHS.¹²

Sleep Apnea Syndrome

SAS is a potentially fatal complication of morbid obesity. A diagnosis of SAS should be suspected when there is a

history of loud snoring, frequent nocturnal awakening with shortness of breath, and daytime somnolence. It is estimated that 2% of middle-aged women and 4% of middle-aged men in the US workforce have SAS, and the incidence is markedly higher in the severely obese.¹³ Patients will often admit to falling asleep while driving and waking up with their car on the road's median strip or bumping its guardrail. It is extremely important that trauma surgeons be aware of the relation between obesity and somnolence should a morbidly obese patient be seen in the emergency department after an automobile accident in which he or she fell asleep at the wheel. Patients with SAS suffer from repeated attacks of upper airway obstruction during sleep. The cause is probably related to a large, fat tongue, as well as to excessive fat deposition in the uvula, pharynx, and hypopharynx. The normal genioglossus reflex is depressed, but this depression may be secondary to the excessive weight of the tongue. These patients are notorious snorers. As a result of inadequate stage IV and rapid eye movement (REM) sleep, they are markedly somnolent during the day.

Patients with SAS are at high risk for acute upper airway obstruction and respiratory arrest when undergoing an operation and general anesthesia. Therefore, any patients with suspected SAS should undergo preoperative polysomnography at a sleep center to confirm the diagnosis. Medications are usually ineffective. Stimulants, such as methylphenidate hydrochloride (Ritalin), should not be used. If a patient has a respiratory disturbance index (RDI) greater than 25—indicating more than 25 apneic or hypopneic episodes per hour of sleep—or has cardiac dysrhythmias in association with apnea, treatment by nocturnal nasal continuous positive airway pressure (nasal CPAP) should be provided. With this technique, air flowing through a nasal mask against a constant airway resistance enters the nasal pharynx and pushes the tongue forward to prevent recurrent obstruction.¹⁴ The pressure can be adjusted for each patient. Unfortunately, many patients cannot tolerate the device, because it is cumbersome and noisy and tends to dry out the upper airway, though dryness can be prevented with an inexpensive room humidifier. If the patient has severe SAS with an RDI greater than 40 and does not respond with elimination of the apneic episodes or cannot tolerate nasal CPAP, a tracheostomy should be considered. An extra-long tracheostomy tube is usually necessary because of the depth of the trachea in the morbidly obese patient.

Obesity Hypoventilation Syndrome

OHS is a condition associated with morbid obesity in which a person suffers from hypoxemia and hypercapnia when breathing room air while awake but resting.¹⁵ Spirometry reveals decreases in forced vital capacity, residual lung volume, expiratory reserve volume, functional residual capacity, and maximum minute volume ventilation, usually without obstruction of airflow [see Figure 1]. The most profound decrease is that in expiratory reserve volume; it is probably secondary to increased IAP and a high-riding diaphragm. Thus, these patients have a restrictive rather than an obstructive pulmonary disease. The decreased expiratory reserve volume implies that many alveolar units are collapsed at end-expiration, which leads to perfusion of unventilated alveoli, or shunting. Patients with OHS often are heavy smokers

or have additional pulmonary problems, such as asthma, sarcoidosis, idiopathic pulmonary fibrosis, or recurrent PE. One study of patients who underwent operation for morbid obesity showed no statistically significant difference in weight between those who had OHS and those who did not.¹²

Chronic, severe hypoxemia is associated with three complications that put patients with OHS at risk: polycythemia, pulmonary arterial vasoconstriction, and pulmonary hypertension. The polycythemia further increases the already significant risk of venous thrombosis and PE. If the hemoglobin (Hb) concentration is 16 g/dl or greater, phlebotomy to a concentration of 15 g/dl should be performed to reduce the postoperative risk of venous thrombosis. If the pulmonary arterial pressure (PAP) is 40 mm Hg or higher, consideration should be given to prophylactic insertion of an IVC filter because of the high risk of a fatal pulmonary embolism in these patients.¹⁶ Placement of an IVC filter can be a challenge because the appropriate landmarks cannot be identified in the operating room with fluoroscopy. It is necessary, before operation, to tape a quarter to the patient's back over the second lumbar vertebra with the aid of fixed radiographs and then, during operation, to aim for the quarter with the insertion catheter, using fluoroscopy. Because these patients are usually too heavy for angiography tables, the filter usually cannot be inserted percutaneously in the radiology department.

Chronic hypoxemia also leads to pulmonary arterial vasoconstriction and severe pulmonary hypertension and eventually to right-side heart failure or cor pulmonale with neck vein distention, tricuspid valvular insufficiency, right upper quadrant tenderness secondary to acute hepatic engorgement, and massive peripheral edema.^{17,18} Such patients may also have a significantly elevated pulmonary artery wedge pressure (PAWP), which suggests left ventricular dysfunction.¹⁷ Morbidly obese patients with a history of pulmonary disease or a BMI greater than 50 kg/m² should have preoperative determinations of blood gas values. If arterial blood gas (ABG) measurement reveals severe hypoxemia (i.e., arterial oxygen tension [P_{aO_2}] ≤ 55 mm Hg), severe hypercapnia (arterial carbon dioxide tension [P_{aCO_2}] ≥ 47 mm Hg), or both, the patient should undergo Swan-Ganz catheterization. If the PAWP is 18 mm Hg or greater, intravenous furosemide should be administered for diuresis before elective operation. However, some patients may require a high ventricular filling pressure. A low cardiac output and hypotension may follow diuresis, necessitating volume reexpansion.

It is highly probable that some of the elevated PAP and PAWP measurements are caused by the increased IAP in the morbidly obese patient [see Figure 2].^{19,20} The high IAP leads to an elevated diaphragm, which in turn increases intrapleural pressure and thereby PAP and PAWP; if the pleural pressure is measured with an esophageal transducer, the transmycardial pressure can be estimated. For this reason, these patients may require a markedly elevated PAWP to maintain an adequate cardiac output, and excessive diuresis may lead to hypotension. The same reasoning may be applied to a patient with a distended abdomen resulting from peritonitis and pancreatitis in whom what seem to be unusually high cardiac filling pressures are necessary. Therefore, one must rely on relative changes in cardiac output in response to either

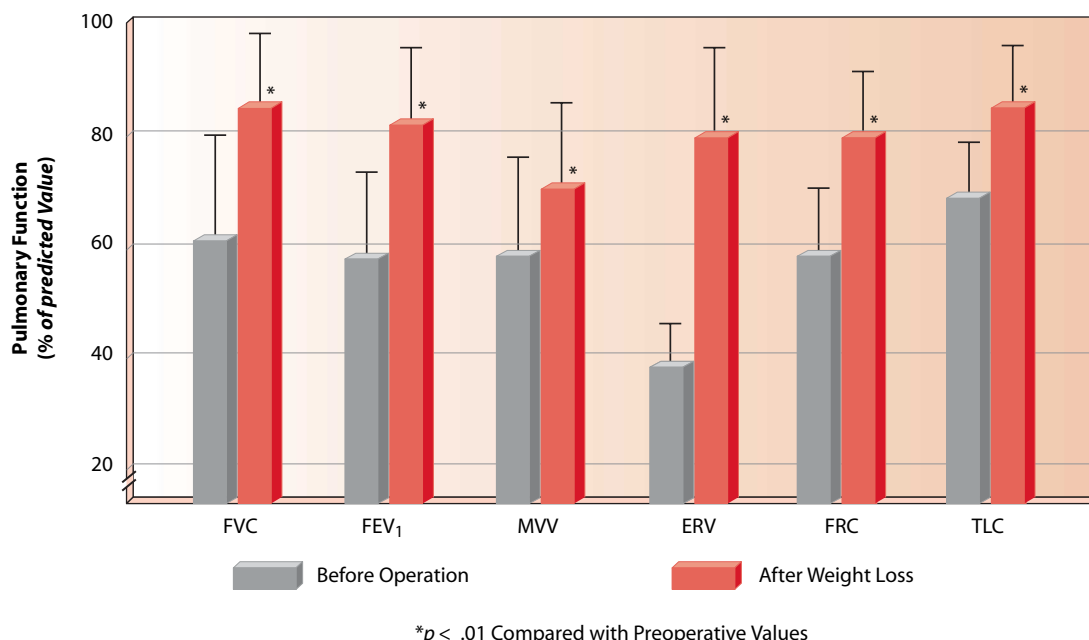


Figure 1 Impaired pulmonary function in the morbidly obese improved significantly after weight loss induced by gastric operation.¹² ERV = expiratory reserve volume; FEV₁ = forced expiratory volume in one second; FRC = functional residual capacity; FVC = forced vital capacity; MVV = maximal voluntary ventilation; TLC = total lung capacity.

volume challenge or diuresis to determine the optimal PAWP in morbidly obese patients.

Patients with OHS respond rapidly to supplemental oxygen. However, oxygen administration is occasionally associated with significant CO₂ retention, which necessitates intubation and mechanical ventilation. Because their pulmonary disease is restrictive rather than obstructive, these patients are usually easy to ventilate without high peak airway pressures. ABG measurements need not return to normal values before extubation; it is only necessary that they return to their preoperative values. These values are achieved early after laparoscopic procedures and, on average, 4 days after major

open upper abdominal operations, when patients experience a decrease in incisional pain.²¹

It is important to emphasize that morbidly obese patients, especially those with respiratory insufficiency, should be placed in the reverse Trendelenburg position to maximize diaphragmatic excursion and to increase residual lung volume.²² These patients will often complain of air hunger and respiratory distress when they lie supine. So-called breaking of the bed at the waist may exacerbate the problem by pushing the abdominal contents into the chest, thereby raising the diaphragm and further reducing lung volumes. Placing these patients in the leg-down position may predispose them to venous stasis, phlebitis, and PE; this tendency should be offset with intermittent venous compression boots [see Thrombophlebitis, Venous Stasis Ulcers, and Pulmonary Embolism, below].²³

Both SAS and OHS can be completely corrected with weight reduction after gastric operation for morbid obesity: the nocturnal apneas resolve, the P_aO₂ rises, and the P_aCO₂ falls to normal as lung volumes improve.¹²

CARDIAC DYSFUNCTION

Morbidly obese patients are at significant risk for coronary artery disease as a result of an increased incidence of systemic hypertension, hypercholesterolemia, and diabetes. Because of this increased risk for cardiac dysfunction, preoperative electrocardiography should be performed on all obese patients 30 years of age or older.

Cardiac dysfunction in the morbidly obese patient is usually associated with respiratory insufficiency of obesity, especially OHS.¹¹ An elevated PAP in these patients may be secondary to hypoxemia-induced pulmonary arterial vasoconstriction, to elevated left atrial pressures secondary to left ventricular dysfunction, or to a combination of these; it may also be secondary to the increased pleural pressures arising from an elevated diaphragm secondary to increased IAP.^{17,20,23} It is unusual for morbidly obese patients without respiratory

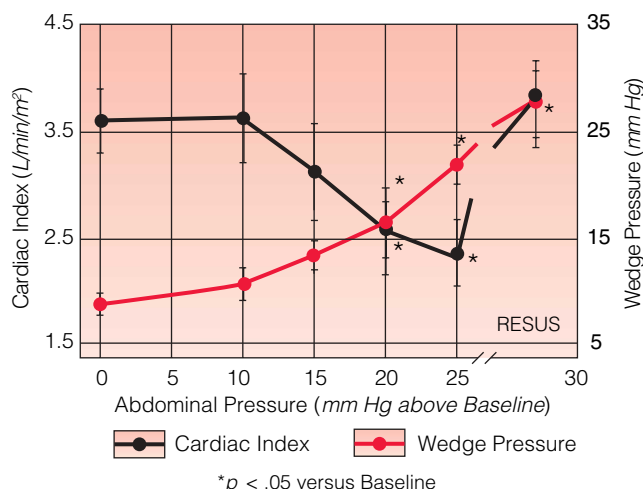


Figure 2 In a porcine model, raising intra-abdominal pressure (IAP) caused cardiac index to fall and pulmonary artery wedge pressure (PAWP) to rise. At an IAP of 25 mm Hg, saline was given to restore intravascular volume; cardiac index returned to baseline levels, but PAWP remained elevated.²⁰

insufficiency to experience significant cardiac dysfunction in the absence of severe coronary artery disease. Morbidly obese patients often have systemic hypertension, which can aggravate left ventricular dysfunction; however, mild left ventricular dysfunction can be documented in many morbidly obese patients in the absence of systemic hypertension.^{24,25} Circulating blood volume, plasma volume, and cardiac output increase in proportion to body weight.²⁵ Massively obese patients may occasionally present with acute heart failure: it is reasonable to assume that the enormous metabolic requirements of such patients can present a greater demand for blood flow than the heart can provide. Vigorous diuresis often corrects such acute heart failure. Significant weight loss corrects pulmonary hypertension [see Figure 3], as well as the left ventricular dysfunction associated with respiratory insufficiency.^{17,26}

THROMBOPHLEBITIS, VENOUS STASIS ULCERS, AND PULMONARY EMBOLISM

Morbidly obese individuals have difficulty walking, tend to be sedentary, have a large amount of abdominal weight resting on their IVC, and have increased intrapleural pressure (which impedes venous return).^{18,20} All of these conditions increase the tendency toward phlebothrombosis. Patients are most at risk when immobilized in the supine position for long periods in the OR. These patients have been shown to have low levels of antithrombin, which may increase their tendency toward venous thrombosis.²⁷ It has also been suggested that starvation, particularly in the postoperative period, may be associated with high levels of free fatty acids, which may predispose to perioperative thrombotic complications.²⁸ Patients with severe OHS often have a noticeably elevated PAP, which can lead to right-side heart failure and can increase the risk of venous stasis and thrombosis. Investigators have noted that patients with primary idiopathic pulmonary hypertension are at significant risk for fatal PE.¹³

The risk of deep vein thrombosis (DVT) increases with a prolonged operation or a postoperative period of immobilization, and it increases even further in the morbidly obese patient. Standard or low-molecular-weight heparin should be administered subcutaneously 30 minutes before operation

and at appropriate intervals thereafter (depending on the type of heparin used) for at least 2 days or until the patient is ambulatory. Because respiratory function in the morbidly obese patient is greatly enhanced with the reverse Trendelenburg position, intermittent sequential venous compression boots should be used to counteract the increased venous stasis and the propensity for clotting. It is important that the intermittent venous compression boots be used before induction of anesthesia and throughout the operative procedure. Such boots are usually part of a standard preoperative protocol in gastric procedures for weight control; their use should not be unintentionally neglected in preparation for other elective or emergency procedures on morbidly obese patients. Patients with severe venous stasis disease (e.g., pretibial stasis ulcers or bronze edema) are at significantly increased risk for fatal PE.²⁹ Prophylactic insertion of an IVC filter should be considered in these patients (as for patients with OHS and a high PAP). All patients should make every attempt to walk during the evening after operation. Bariatric surgery-induced weight loss will correct the venous stasis disease in most cases.²⁹

Venous stasis ulcers can be quite difficult to treat in a thin person; they are almost impossible to cure in a patient with morbid obesity [see Figure 4]. The most important goal in the management of these ulcers is weight loss, which almost invariably leads to healing of the ulcer, probably as a result of decreased IAP.²⁹

GALLSTONES

Approximately one third of morbidly obese patients either have had a cholecystectomy or may have had gallstones noted at the time of another intra-abdominal operative procedure (e.g., a gastric operation for morbid obesity). Preoperative evaluation of the gallbladder may be technically quite difficult in morbidly obese patients because ultrasonography may fail to visualize gallstones. Intraoperative ultrasonography is probably much more accurate. Should symptomatic gallstones be present in a patient undergoing a gastric procedure for obesity, the gallbladder should be removed if the surgeon judges it safe to perform this additional procedure. If

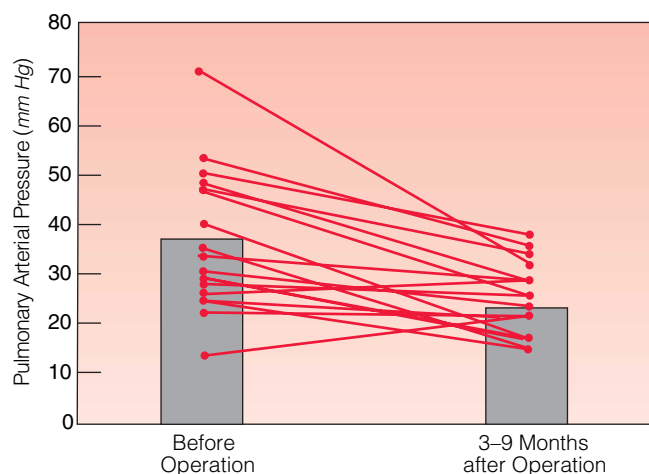


Figure 3 Mean pulmonary arterial pressure was significantly improved in 18 patients 3 to 9 months after gastric surgery-induced weight loss of $42\% \pm 19\%$ of excess weight.



Figure 4 This chronic venous stasis ulcer was present for several years in a morbidly obese patient. Healing followed weight loss induced by a gastric operation.

placement of an adjustable gastric band is contemplated, the cholecystectomy should be undertaken first and the indwelling device placed only in the absence of intra-abdominal bile spillage during the procedure.

In past studies, rapid weight loss led to the development of gallstones in 25 to 40% of patients who underwent GBP. The risk of cholelithiasis in this setting can be reduced to 2% by administering ursodeoxycholic acid, 300 mg orally twice daily.³⁰ Laparoscopic cholecystectomy at the time of laparoscopic gastric bypass can be technically challenging; consequently, many surgeons prefer to take an expectant approach to the gallbladder rather than complicate the bariatric procedure with a simultaneous cholecystectomy (unless cholecystectomy is clearly indicated in a particular patient).

PSEUDOTUMOR CEREBRI

Pseudotumor cerebri is an unusual complication of morbid obesity that is associated with benign intracranial hypertension, papilledema, blurred vision, headache, and elevated cerebrospinal fluid pressures.³¹ It has been our experience that patients with pseudotumor cerebri are not at any additional perioperative risk and that CSF need not be removed before anesthesia and major abdominal operations. There is some theoretical concern that gastrointestinal contamination during GBP may cause shunt infection in patients who have been previously treated with indwelling shunts to relieve elevated CSF pressures. Successful weight reduction cures pseudotumor cerebri.^{32,33}

DEGENERATIVE OSTEOARTHRITIS

Degenerative osteoarthritis of the knees, hips, and back is a common complication of morbid obesity. Weight reduction alone may greatly reduce the pain and immobility that afflict these patients. In some cases, the damage may be so extensive that a total joint replacement is desirable; however, joint replacement in patients who weigh more than 250 lb is associated with an unacceptable incidence of loosening.³⁴ Weight reduction by means of a gastric bariatric operation may be the most sensible initial approach, to be followed by joint replacement after weight loss if pain and dysfunction persist.

Operative Planning

ANESTHESIA IN PATIENTS WITH RESPIRATORY INSUFFICIENCY

Morbidly obese patients can be intimidating to the anesthesiologist because they are at significant risk for complications from anesthesia, especially during induction. The risk is particularly great for obese patients with respiratory insufficiency. An obese patient often has a short, fat neck and a heavy chest wall, which make intubation and ventilation a challenge. If endotracheal intubation proves difficult, however, such a patient can usually be well ventilated with a mask. Awake intubation can be performed, with or without fiberoptic aids, but is quite unpleasant and rarely necessary.

It is extremely important that at least two anesthesia personnel be present during induction and intubation for patients with respiratory insufficiency of obesity. An oral airway is inserted after muscle paralysis with succinylcholine

and sodium pentobarbital induction. One person elevates the jaw, hyperextends the neck, and ensures a tight fit of the mask, using both hands. To ensure adequate oxygen delivery, a second person compresses the ventilation reservoir bag, using two hands because of the resistance to air flow from the poorly compliant, heavy chest wall. After ventilation with 100% oxygen for several minutes, intubation is attempted. If difficulties are encountered within 30 seconds, the steps above should be repeated until the patient has been successfully intubated. A volume ventilator is required during operation. Placing the patient in the reverse Trendelenburg position expands total lung volume and facilitates ventilation²²; however, the reverse Trendelenburg position increases lower-extremity venous pressure and therefore mandates the use of intermittent sequential venous compression boots. It is helpful to monitor blood gases through a radial arterial line or a digital pulse oximeter.

LAPAROSCOPIC VERSUS OPEN APPROACH TO BARIATRIC SURGERY

Bariatric surgical procedures, like most other general surgical procedures, have undergone a transition from an open approach to one that places more emphasis on minimally invasive or laparoscopic techniques. Laparoscopic GBP was first described in 1994 and became widely accepted in 1999, though it was not until 2004 that, according to a national audit of bariatric surgery performed at academic centers, the number of laparoscopic GBP procedures performed exceeded the number of open GBP procedures.

At present, the laparoscopic approach to GBP is favored because it achieves a comparable degree of weight loss while possessing some notable advantages over its open counterpart.²¹ Open GBP is performed through an upper midline incision, whereas laparoscopic GBP is performed through five or six small incisions. Abdominal wall retractors and mechanical retraction of the abdominal viscera, which are necessary for adequate exposure during an open procedure, are not required during a laparoscopic procedure, which makes use of gas insufflation (for pneumoperitoneum) and the effects of body positioning and gravity to facilitate intraoperative exposure. With the elimination of the large surgical incision and mechanical retraction, the laparoscopic GBP patient experiences less operative trauma, less postoperative pain, and fewer wound-related complications. In addition, laparoscopic GBP yields less impairment of immediate postoperative pulmonary function and a lower systemic stress response. A 2007 study of 22,422 patients who underwent Roux-en-Y GBP for treatment of morbid obesity compared the outcomes of laparoscopic procedures ($n=16,357$) with those of open procedures ($n=6,065$).³⁵ The mean length of hospital stay was significantly lower in the laparoscopic group (2.7 days versus 4.0 days), as were the overall complication rate (7.4% versus 13.0%), the 30-day readmission rate (2.6% versus 4.7%), the in-hospital mortality (0.1% versus 0.3%), and the mean cost (\$13,743 versus \$14,585 [US]).

CHOICE OF SURGICAL PROCEDURE

The gastric operations performed for morbid obesity include both GBP procedures and gastric restrictive procedures (i.e., gastropasty and gastric banding). Randomized, prospective trials have conclusively shown that GBP is as

effective for weight control as the malabsorptive jejunioileal (JI) bypass is, while resulting in significantly fewer complications.^{36,37} JI bypass is associated with a substantial incidence of both early complications (e.g., acute cirrhosis, electrolyte imbalance, and fulminant diarrhea)³⁸ and late complications (e.g., cirrhosis, interstitial nephritis, arthritis, enteritis, nephrocalcinosis, and recurrent oxalate renal stones).³⁹ If evidence of cirrhosis, renal failure secondary to interstitial nephritis, or other complications mandates reversal of a JI bypass, the patient, if not extremely ill, should be converted to a GBP; otherwise, all the lost weight is sure to be regained, and the obesity-related comorbidity will return. Admittedly, however, some patients have done well after JI bypass and do not need to have the operation reversed.

Several randomized, prospective trials have found that horizontal gastroplasty yields poorer results than GBP.⁴⁰⁻⁴² Failure of horizontal gastroplasty has generally been attributed to technical causes (e.g., enlargement of the proximal pouch or the stoma or disruption of the staple line). Vertical banded gastroplasty (VBG) was developed in the hope that it would solve these technical problems and yield weight loss comparable to that seen after GBP without incurring the significant risk of iron, calcium, and vitamin B₁₂ deficiencies associated with GBP. In the 1990s, a procedure known as adjustable silicone gastric banding was developed, which involved placement of a restrictive ring around the proximal stomach to create a small gastric pouch. In this restrictive procedure, which can be done laparoscopically in the vast majority of patients, weight loss can be enhanced and vomiting minimized by adjusting the ring diameter via transcutaneous access to the subcutaneous reservoir.

Although VBG and, presumably, other restrictive procedures appear to be excellent from a technical point of view,⁴³ multiple randomized, prospective trials have found such approaches to be significantly less effective than standard GBP. In one comparison trial, patients addicted to sweets lost much more weight after GBP than after VBG because they experienced symptoms of dumping syndrome when ingesting sweets.⁴⁴ The failure rate was high after VBG because these patients experienced no difficulties when eating candy or drinking nondietetic sodas. Subsequent randomized, prospective trials confirmed the superiority of GBP.^{45,46} Furthermore, maintenance of successful weight loss after GBP appears to continue for as long as 14 years after operation: in the average patient, weight loss amounts to about two-thirds of excess weight at 1 to 3 years after operation, three-fifths at 5 years, and more than half in years 5 through 10.^{47,48} It has been suggested that standard (i.e., proximal) GBP will fail in 10 to 15% of patients because these patients will frequently nibble on high-fat snacks (e.g., corn chips, potato chips, and buttered popcorn). Such patients may have to be converted to a combined restrictive and malabsorptive procedure, such as partial biliopancreatic diversion (BPD).⁴⁹

The original BPD procedure involves hemigastrectomy and anastomosis of the distal 250 cm of intestine to the stomach; the bypassed small intestine is reanastomosed to the ileum 50 cm from the ileocecal valve. BPD with duodenal switch is a variant of the original procedure in which a linear gastric tube based on the lesser curvature is created (sleeve gastrectomy), with the pylorus left intact, and an ileal Roux limb is brought up for anastomosis to the proximal duodenum. BPD

has been associated with a high incidence of deficiencies of fat-soluble vitamins, hypocalcemia-induced osteoporosis, and protein-calorie malnutrition.⁵⁰ These nutritional deficiencies may be more common in the United States, where fat intake is high, than in many other countries. In Italy, for example, starch intake (as in pasta) probably outstrips fat intake; still, a number of Italian patients have had to be readmitted for parenteral nutrition and extension of the common absorptive intestinal tract because of refractory malnutrition. In some patients, it might be possible to convert a failed proximal GBP into a modified BPD with a 150 cm absorptive ileal limb (a procedure often referred to as distal GBP); however, these patients must also be monitored carefully for deficiencies of fat-soluble vitamins, for osteoporosis, and for malnutrition.

Superobese patients—defined as those whose weight is 225% of ideal body weight or greater or whose body mass index (BMI) is 50 kg/m² or higher—will lose, on average, only about half of their excess weight, rather than two-thirds, after standard GBP. In these patients, a 150 cm proximal Roux-en-Y procedure (so-called long-limb GBP [see Open Proximal Gastric Bypass, Operative Technique, below]) may increase weight loss in the first few years after operation without causing an increase in nutritional complications.⁵¹

In choosing the appropriate surgical approach, it is important to take into account the tremendous surgical revolution that laparoscopy has brought about in the treatment of morbid obesity. Now that every operation performed to treat obesity can be done laparoscopically, laparoscopic bariatric surgery is not only common but, in many centers, predominant. For this reason, as well as because laparoscopic obesity treatment requires advanced technical skills, minimally invasive bariatric procedures have become a cornerstone of training for surgeons now learning laparoscopic surgery.

Vertical Banded Gastroplasty

OPERATIVE TECHNIQUE

The first step in VBG is to make a circular stapled opening in the stomach 5 cm from the esophagogastric junction. A 90 mm bariatric stapler with four parallel rows of staples is then applied once between this opening and the angle of His. (At this point, according to Mason, the originator of the procedure, the volume of the pouch should be measured by means of an Ewald tube placed by the anesthetist; ideally, pouch volume should be 15 mL.)

Next, a strip of polypropylene mesh is wrapped around the gastrogastic outlet on the lesser curvature and sutured to itself—but not to the stomach—in such a way as to create an outlet with a circumference of 5 cm for the small upper gastric pouch [see Figure 5a]. Some surgeons have used a stomal outlet 4.5 cm in circumference, but this smaller outlet has not led to better weight loss; in fact, many patients with the 4.5 cm outlet exhibit maladaptive eating behavior, drinking high-calorie liquids because meat tends to get caught in the small stoma.

Silastic ring gastroplasty [see Figure 5b] is a variant of VBG that uses a vertical staple line and a stoma reinforced with Silastic tubing.

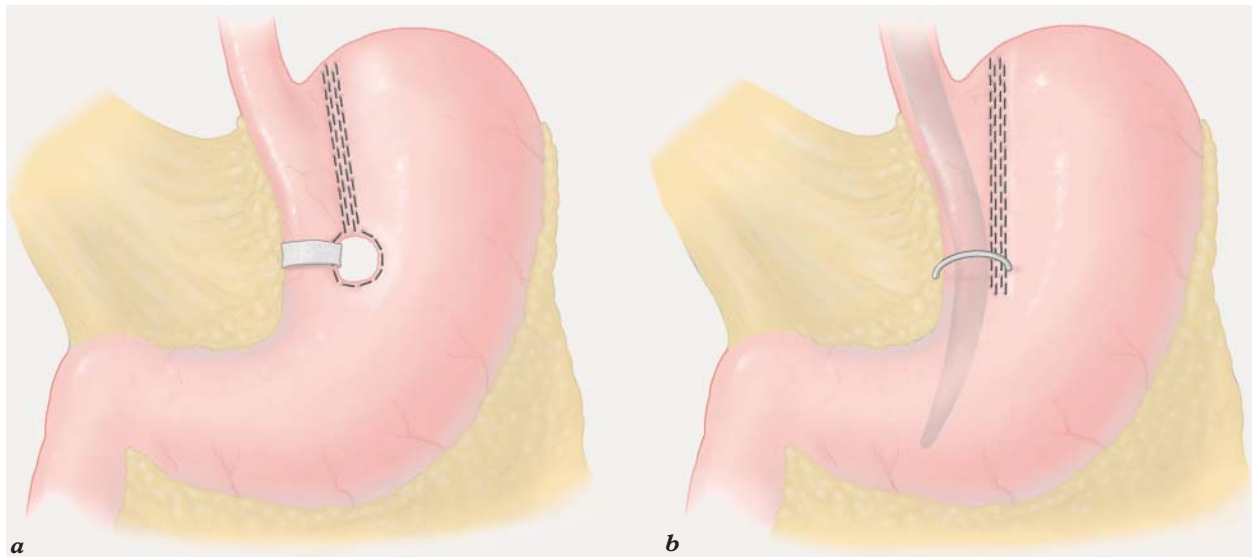


Figure 5 Vertical banded gastroplasty (VBG). Depicted are (a) standard VBG and (b) Silastic ring gastroplasty, a variant of VBG in which the stoma is reinforced with a Silastic tube.

COMPLICATIONS

Complications of VBG include erosion of the polypropylene mesh used to restrict the gastroplasty stoma into the gastric lumen, enlargement of the pouch, stomal stenosis, reflux esophagitis, and mild vitamin deficiencies.⁵² To date, mesh erosion has been infrequently observed after VBG. Pouch enlargement is fairly common with horizontal gastroplasty but is much less likely to occur with VBG, in which the vertical staple line is placed in the thicker, more muscular part of the stomach. In addition, stomal diameter remains fixed with the mesh band. If mesh erosion, pouch enlargement, stomal stenosis, disabling GI reflux, or recurrent vomiting occurs, it is probably best to convert the patient to GBP. In particular, patients with a Silastic ring VBG may exhibit intractable vomiting of solid foods with no evidence of mechanical obstruction. In our experience, conversion of these patients to GBP yields good results and eliminates the vomiting problem. Finally, vitamin deficiencies can usually be prevented by having VBG patients take a standard multivitamin daily for life.

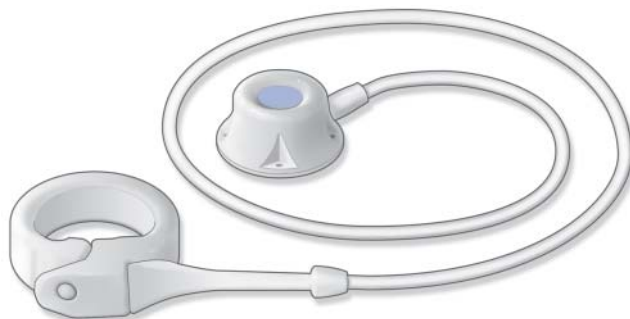


Figure 6 Laparoscopic adjustable gastric banding. Shown is the adjustable gastric banding device used in the procedure.

Laparoscopic Adjustable Gastric Banding

Gastric banding is another form of gastroplasty, in which a synthetic band is placed around the stomach just below the esophagogastric junction. In several series, gastric banding has yielded markedly variable results with respect to achievement of weight loss. Furthermore, it has been associated with slipping or kinking of the banded stoma, obstruction at the band, and intractable vomiting.

Laparoscopic adjustable gastric banding (LAGB) is significant advance over open gastric banding procedures, primarily because of the adjustability of the band. Open gastric banding procedures have used a variety of materials to constrict the gastric lumen and carry a recognized risk of postoperative nausea and vomiting that do not respond to any treatment short of reoperation. The adjustable gastric bands available for use in LAGB [see Figure 6] are silicone devices with an inflatable reservoir that can be inflated or deflated postoperatively through a subcutaneous port placed deep in the abdominal wall for percutaneous access. Saline is injected into or withdrawn from the reservoir to adjust gastric luminal diameter. These diameter changes can be measured by means of barium contrast evaluation, but currently, most adjustments are made without x-ray guidance. If intractable vomiting develops, saline can be removed from the band to alleviate the problem; similarly, if the patient fails to lose weight after operation, additional saline may be injected into the band to narrow the gastric lumen further.

Use of the laparoscopically placed adjustable gastric band (Lap-Band, Allergan Corp., Irvine, CA) was approved by the US Food and Drug Administration in June 2001. Key data on safety and effectiveness were provided by a prospective, single-arm trial involving 299 patients at eight centers in the United States. In this study, patients who completed 36 months of follow-up achieved a mean reduction in BMI of 39% and a mean overall loss of 18% of baseline body weight. However, 28% of patients lost less than 10% of their initial

body weight (a clear definition of failed weight loss). More than half (62%) of these patients lost more than 25% of their excess weight. Most patients (76%) experienced at least one adverse event, and 33% of patients required removal of the banding system.

Subsequent studies have yielded similar results. A 2007 review of two multicenter prospective, single-arm surgical trials evaluating a total of 485 patients who underwent placement of a gastric band (92% laparoscopically) between June 1995 and June 2001 suggested that the procedure was as effective as was previously believed.⁵³ The change in mean BMI (kg/m²) was 38 to 47% at 1 year and 39% at 3 years. The percentage of initial body weight lost was 17 to 18% at 1 year and 18% at 3 years. Similarly, most patients (66 to 76%) experienced upper GI symptoms at 1 year. In one of the trials, 33% of the patients (96/292 patients) had had their bands removed at 9 years, either because of complications or because of inadequate weight loss.⁵³

In a 2006 study comparing outcomes, LAGB proved to be just as safe as, cheaper than, and almost as effective as laparoscopic Roux-en-Y gastric bypass (LRYGB).⁵⁴ This retrospective review of 590 bariatric procedures (120 LRYGB, 470 LAGB) performed between November 2000 and July 2004 suggested that both operating time and duration of hospitalization were significantly shorter in LAGB patients. Complication rates and reoperation rates were similar in the two groups. Patients who underwent LRYGB initially lost weight more rapidly: their mean percentage of excess body weight lost (%EBWL) was 65% during postoperative year 1, compared with 39% for LAGB patients. Thereafter, weight loss slowed, remaining nearly unchanged at 3 years (63%). Patients who underwent LAGB initially lost weight more slowly, but the ongoing weight loss was continuous, eventually approaching that of LRYGB. At 3 years, the %EBWL for LAGB patients was 55%.

OPERATIVE TECHNIQUE

LAGB is performed by using a five-port technique. Initial abdominal access is obtained via a supraumbilical trocar, and the remaining ports are placed sequentially along the right and left costal margins. The liver is retracted via the subxiphoid port, and the proximal stomach is visualized with a laparoscope inserted through the umbilical port.

Subsequent steps are done according to the pars flaccida technique. A retrogastric tunnel for band insertion is created at the posterior confluence of the diaphragmatic crura in a plane of dissection that is easily developed with minimal blunt dissection after electrocauterization of the peritoneal membrane. This tunnel is placed cephalad to the posterior peritoneal reflection, so that the free space of the lesser sac posterior to the stomach is not entered. Additional dissection is then carried out laterally at the angle of His to open the peritoneum and start clearing a plane behind the proximal stomach.

A specially designed implement is inserted behind the stomach from the lesser curvature to the angle of His and used to grasp the tubing of the banding device and pull it around the stomach. The banding device is then locked into place at the chosen location on the proximal stomach [see Figure 7]. Gastrogastric sutures are placed to create a tunnel of stomach overlying the banding device—but not the

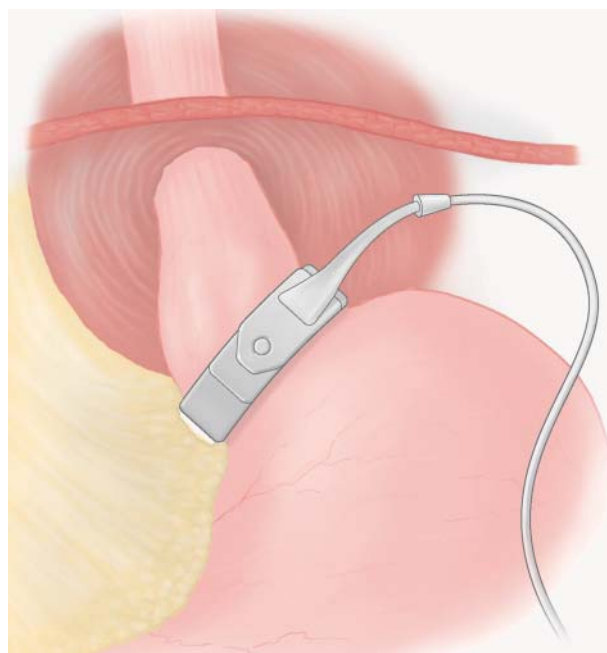


Figure 7 Laparoscopic adjustable gastric banding. Once in the correct position on the proximal stomach, the adjustable band is locked into place.

buckle—so as to hold the device in position. The band tubing is brought through the left midclavicular trocar port, which is placed via the left midclavicular line subcostal trocar incision and fixed to the abdominal wall fascia with sutures. The tubing is connected to the reservoir, which is filled with saline.

TROUBLESHOOTING

It is essential to place the band properly during the initial procedure. The results to date suggest that the proximal pouch must be very small to optimize weight loss. In addition, proper placement minimizes—though it does not eliminate—the risk of band slippage and the complications thereof.

Several techniques have been suggested for posterior fixation of the band, but they are more difficult than anterior fixation techniques. With the pars flaccida technique, posterior fixation of the band is not necessary to prevent band slippage. Anterior fixation, however, is routinely performed, with interrupted sutures of nonabsorbable material placed between the distal and the proximal stomach to allow tissue to be apposed over the band and held in place.

Although LAGB appears easier than many of the procedures done to treat obesity, there is a definite learning curve. A number of surgical misadventures have been reported, including gastric perforation, splenic injury, and malpositioning of the band.

COMPLICATIONS

Band slippage (anterior, posterior, or concentric) may occur even after proper placement, resulting in intolerance of oral intake and vomiting. Such complaints are an indication

for an upper GI series, which usually reveals dilatation of the proximal pouch and rotation of the band [see Figure 8]. Initial treatment consists of evacuating all saline from the band. Frequently, however, the proximal pouch does not return to its normal size, and symptoms recur or fail to resolve. Laparoscopic or open revision of the banding procedure is then required; if the patient also has not lost a sufficient amount of weight, conversion to GBP may be recommended. It is noteworthy that band erosion into the stomach, a not infrequent complication of the use of mesh in VBG or in the Angelchik prosthesis for gastroesophageal reflux treatment, has not been frequently reported. Longer follow-up is necessary to evaluate the true extent of this risk.

As after any form of gastroplasty, the patient may fail to lose weight or may regain lost weight. Inappropriate eating behaviors (e.g., intake of high-calorie sweets) are the most likely cause. If obesity-related comorbid conditions persist, conversion to proximal GBP is appropriate.

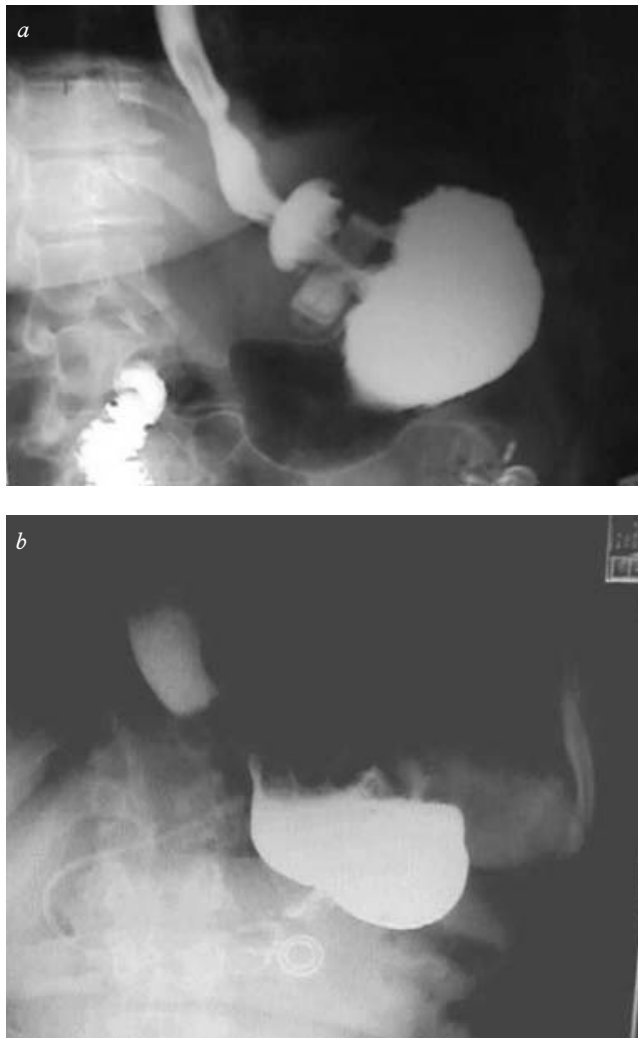


Figure 8 Laparoscopic adjustable gastric banding. Contrast studies illustrate (a) a normally positioned laparoscopic adjustable gastric band and (b) a slipped band.

OUTCOME EVALUATION

How successful LAGB is at achieving weight loss over the long term remains unclear. The adjustability and reversibility of the operation, as well as the decreased disability that results, make it attractive to both patients and physicians. The procedure appears to avoid some of the major postoperative complications associated with open GBP (e.g., incisional hernia, marginal ulcer, and stomal stenosis). Band slippage remains a major postoperative concern, however, though the incidence of slippage does appear to decrease as the surgeon's experience with the procedure increases. More significant, there appears to be a high frequency of failed weight loss—as high as 15 to 20% of all patients undergoing the procedure and possibly even higher. European data confirm that there is a significant failure rate but also suggest that the remaining patients achieve a degree of weight loss approaching that seen with proximal GBP. Whether these reports will withstand the scrutiny of long-term follow-up remains to be seen.

Open Proximal Gastric Bypass

Proximal GBP results in greater weight loss than the gastric restrictive procedures (see above) and carries a lower incidence of weight regain; consequently, it is often considered the gold standard for bariatric surgery. Compared with the version of GBP performed at our institution, the original GBP created a much larger proximal gastric pouch and a much wider anastomotic opening, and it was often associated with inadequate weight loss. In the later version, three superimposed 55 or 90 mm staple lines are placed across the proximal stomach in such a way as to create a gastric pouch no larger than 30 ml with a Roux limb at least 45 cm long and a stoma no larger than 1 cm [see Figure 9]. This anatomic situation is largely replicated when GBP is done laparoscopically, but an isolated gastric pouch is created with stapled transection of the stomach.

OPERATIVE TECHNIQUE

Step 1: Initial Incision and Abdominal Exploration

Once the patient is anesthetized, the abdomen receives a thorough, careful cleansing with povidone-iodine and is draped in a sterile fashion. An upper midline incision is made and extended through the fascia alongside the xiphoid process to facilitate cephalad exposure. The incision is routinely carried down to the supraumbilical area. The deep layer of subcutaneous fat can often be separated bluntly with aggressive lateral traction applied by the surgeon and the assistant, and the midline usually can then be identified for fascial incision. The electrocautery is used to enter the abdominal cavity, and a thick layer of subfascial preperitoneal fat is often encountered before entry into the peritoneal cavity. Abdominal exploration is undertaken in every patient, including examination of the liver for possible signs of liver disease. Other incidental findings may become apparent as well.

Troubleshooting Unexpected significant liver disease is occasionally discovered at the time of operation. If the patient has cirrhosis without portal hypertension, one should perhaps



Figure 9 Open proximal gastric bypass. Depicted is the completed procedure.

proceed with bypass if the patient's comorbid conditions make it mandatory; liver transplantation carries increased risk in morbidly obese patients. The gallbladder should be palpated for gallstones, which, if found, may be an indication for cholecystectomy at the time of the bypass procedure. If there are no visual or palpable gallbladder abnormalities, intraoperative ultrasonography may be used to examine the gallbladder.

It is not unusual to discover other previously unrecognized conditions during GBP, primarily because symptoms may not be obvious in morbidly obese patients and because their large size tends to make radiologic imaging difficult or even impossible. For example, intraoperative discovery of pelvic cysts and tumors is not uncommon in obese female patients. Such lesions may be excised during GBP; on occasion, if they appear benign and their location prevents safe excision, they may be managed with careful follow-up.

Step 2: Mobilization of Esophagus

The bypass procedure itself is begun by mobilizing the distal esophagus and encircling it with a soft rubber drain 0.5 in. in diameter. The gastrohepatic omentum is bluntly entered at a point overlying the caudate lobe, with care taken to look for and avoid injury to an aberrant left hepatic artery. The phrenoesophageal ligament overlying the anterior and lateral distal esophagus is sharply incised to facilitate subsequent blunt mobilization of the distal esophagus. To prevent esophageal injury, the nasogastric tube is carefully palpated within the lumen of the esophagus during mobilization, and blunt dissection proceeds widely around this important landmark. Laterally, dissection must be at the level of the esophagus or higher.

Troubleshooting If dissection is too low laterally, it may result in blunt injury to the short gastric vessels, bleeding, and the need for urgent splenectomy, which is no easy task in a morbidly obese patient. In addition, it may lead to creation of an inappropriately large pouch by keeping the surgeon from recognizing that some of the stomach is above the level at which the encircling rubber drain is placed.

Step 3: Division of Mesentery and Dissection around Stomach

Once the esophagus is mobilized, the assistant's left hand is placed through the gastrohepatic omental opening behind the stomach wall on the lesser curvature. The space between the first and second branches of the left gastric artery is then identified as a landmark for location of the gastric staple line, both to ensure that the pouch created is no larger than 30 ml and to prevent injury to the left gastric artery, which usually runs cephalad to this location. With the surgeon's posterior finger pressing anteriorly to place tension on the tissue, a fine-tip right-angle clamp and the electrocautery pencil are used to divide the mesentery carefully at this level immediately alongside the stomach wall so as to create a mesenteric opening that will admit a large right-angle clamp.

The avascular tissue on the posterior wall of the stomach is then bluntly dissected between the opening in the gastrohepatic omentum and the lateral angle of His, which is identified by the encircling rubber drain. The blunt tip of a large 28 French red rubber tube is placed behind the stomach in a medial-to-lateral direction along this dissected path to encircle the stomach [see Figure 10]. The open end of the red rubber tube is subsequently brought through the previously created mesenteric opening with a large right-angle clamp. The stomach is now ready for stapling, and the red rubber tube serves as a guide for introduction of the stapler. At this point, all intraluminal tubes and devices (e.g., the nasogastric tube and the esophageal stethoscope) are removed from the esophagus by the anesthetist.

Troubleshooting When a tube is inadvertently stapled within the stomach, excising it from the nontransected

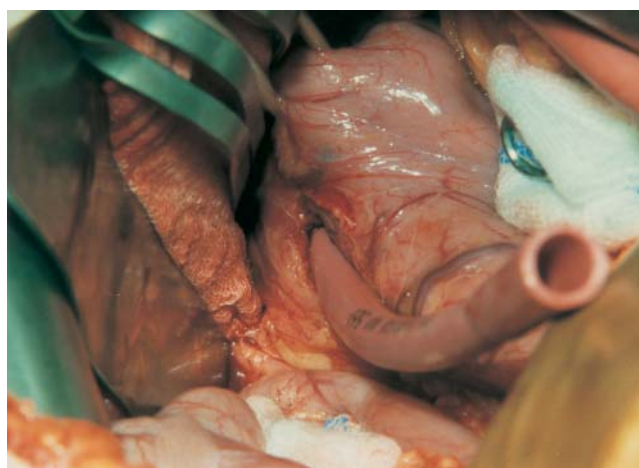


Figure 10 Open proximal gastric bypass. After dissection of the avascular tissue on the posterior gastric wall, a red rubber catheter is passed through the resulting space to encircle the stomach.

gastric staple line can be a technical challenge. To remove the stapled tube, it is generally necessary to use a stapler to transect the stomach, thereby creating the potential for significant injury to the gastric tissue unless the transection is precisely superimposed over the previous staple line. The tube can then be excised from each side (proximal and distal) of the divided gastric staple lines.

Step 4: Creation and Mobilization of Roux Limb and Jejunojejunostomy

The ligament of Treitz is identified, and the jejunum is measured to a point 45 cm beyond the ligament—or somewhat more distally to enhance mobilization of what will become the Roux limb if the mesentery appears foreshortened—at which point the jejunum is divided with a stapler. An 8 to 12 cm segment of jejunum may be resected at this point to create a larger mesenteric defect, which should facilitate mobilization of the limb to the proximal stomach. Mesenteric dissection is carried posteriorly in fat with the sequential application of clamps until further dissection appears either unnecessary for mobilization or unwise (i.e., likely to cause mesenteric vascular injury or ischemia of the Roux limb).

A side-to-side jejunojejunostomy is then created with a 60 mm linear stapler at least 45 cm beyond the initial point of jejunal division for standard proximal GBP. Some surgeons perform this anastomosis 150 cm downstream for the long-limb modification of the procedure used in superobese patients [see Operative Planning, Choice of Surgical Procedure, above] or even further distally for the distal GBP modification, which greatly enhances malabsorption. It is important not to narrow the efferent lumen at the jejunojejunostomy site, particularly with the longer-limb modifications, in which the lumen at the distal end of the Roux limb may be quite small. The enterotomies made to allow placement of the stapler can usually be closed with a 55 mm stapler loaded with 3.5 mm staples; however, if stapling would cause undue narrowing of the lumen, the closures should be handsewn instead.

Troubleshooting It may be preferable to mobilize the Roux limb before committing to stapling the stomach so that it can be determined whether the limb can be extended to reach the proximal stomach without being placed under tension. In those rare cases in which the mesentery is too foreshortened to permit the limb to reach the proximal stomach, it is advisable to change the procedure to VBG or gastric banding rather than create a gastrojejunal anastomosis under tension and thereby incur the increased risk of leakage.

Step 5: Gastric Stapling and Gastrojejunostomy

The Roux limb is brought through the mesentery of the transverse colon with blunt dissection and then brought up to the proximal stomach. The 55 or 90 mm stapler, loaded with 4.8 mm staples, is guided behind the stomach by inserting its open-mouthed end into the lumen of the previously positioned red rubber tube. Once it is determined that the staple line will reach completely across the stomach and that the stomach is not folded on itself, the stomach is stapled three times in such a way that the three staple lines are superimposed [see Figure 11].

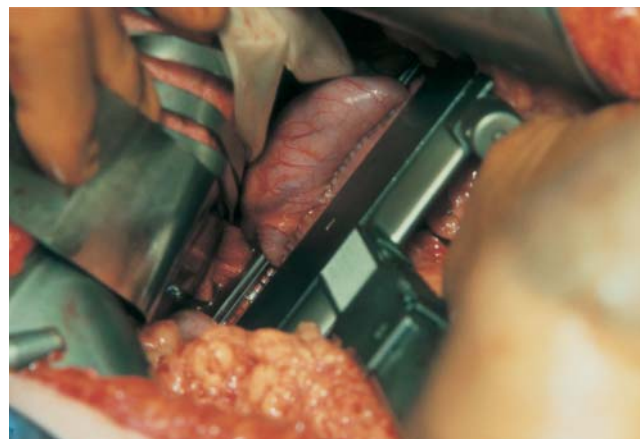


Figure 11 Open proximal gastric bypass. The stomach is stapled to create the small proximal pouch. The stapler is fired three times to create three superimposed staple lines, thereby decreasing the risk of staple line disruption.

A 1 cm anastomosis is created between the proximal stomach pouch and the Roux limb. We prefer a handsewn anastomosis for this procedure, using an outer layer composed of interrupted 2-0 or 3-0 silk sutures and an inner layer composed of a continuous absorbable 3-0 polyglycolic acid (Dexon) suture. When the posterior aspect of the anastomosis is complete, a 30 French dilator is placed orally by the anesthetist and is guided through the anastomosis by the surgeon to ensure that the stoma has the appropriate diameter [see Figure 12]. The anterior aspect of the anastomosis is then completed.

Troubleshooting A significant concern for many bariatric surgeons has been a high incidence of staple line disruption causing failed weight loss or weight regain; in one series, the incidence of such disruption was 35%. To minimize this risk, some surgeons advocate transecting the stomach. Currently, this step is routinely carried out as part of a

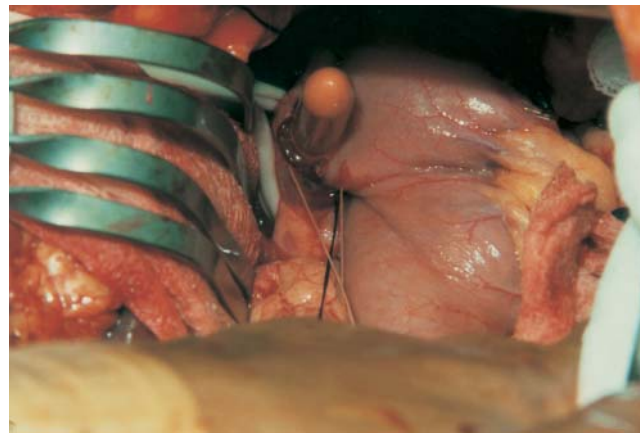


Figure 12 Open proximal gastric bypass. When the posterior aspect of the gastrojejunal anastomosis has been completed, a 30 French dilator is placed through the stoma to confirm that the opening is correctly sized.

laparoscopic GBP. In an open GBP, one may transect the stomach either by applying a linear cutting stapler with 3.5 or 4.8 mm staples (depending on the estimated gastric wall thickness) or by inserting two parallel noncutting transverse anastomosis (TA)-90 staplers and cutting between them with a scalpel after the staplers are fired. Other surgeons, however, prefer to leave the stomach undivided and oversew the staple line. In our version of open GBP, we find that placing three or four precisely superimposed staple lines reduces the incidence of staple line disruption to less than 2%.

Another advantage of gastric transection besides reduction of staple line disruption is that it allows the Roux limb to be brought up to the gastric pouch via a retrocolic and retrogastric tract, which is substantially shorter and places less tension on the limb. This approach is particularly helpful in severely obese patients with a fatty and foreshortened mesentery, in whom it is difficult to free the Roux limb sufficiently to reach the proximal stomach without tension. The possibility that gastric transection may prove helpful in a specific patient is another reason why it is advisable to delay stapling the stomach until the Roux limb has been mobilized.

Step 6: Assessment of Anastomosis

When the entire anastomosis is complete, the dilator is removed and an 18 French nasogastric tube is advanced by the anesthetist while the tip is carefully guided through the anastomosis by the surgeon. The Roux limb is occluded with the assistant's left hand or with an atraumatic intestinal clamp, and the esophagus is occluded by placing tension on the rubber drain surrounding it while the anesthetist injects a series of 10 ml aliquots of methylene blue dye through the nasogastric tube to determine whether the anastomosis is leaking. A total of 30 to 60 ml of methylene blue must usually be injected; lesser amounts will not stress the suture line enough to constitute an adequate test. Alternatively, the anastomosis can be tested by performing intraoperative gastroscopy. If leakage is present, the air insufflated during the procedure will be visible bubbling from the leaking areas when the air-distended anastomosis is submerged in irrigation fluid.

Troubleshooting When an intraoperative leak is identified, the area of leakage should be oversewn with silk sutures until injection of additional methylene blue dye via the nasogastric tube yields no further leakage. The most difficult area to repair is the posterior suture line, which is quite close to the gastric staple line. Posterior leaks are usually repaired by reinforcing the posterior suture line with additional sutures between the excluded stomach and the jejunal limb; often, the entire posterior suture line is oversewn. In addition, a viable pedicle of omentum may be mobilized and placed around the anastomosis for further reinforcement. Closed suction drains may also be placed in this area, both to detect possible postoperative leakage and to control a postoperative leak or fistula.

Finally, a gastrostomy tube may be placed in the excluded portion of the stomach. This measure provides postoperative decompression, which should prevent the development of undue tension on the Roux limb as a result of gastric distention. In addition, it establishes a route for enteral

feeding if a fistula develops. Fortunately, such fistulas are rare. When they do occur, they often heal if (1) they are well drained, (2) there is no distal obstruction or local abscess, and (3) the patient is receiving nutritional support with no oral intake. A gastrostomy tube should also be placed in the distal gastric pouch when extensive adhesions from a previous procedure or a difficult gastric reoperation increase the risk of postoperative gastric distention.

Step 7: Closure

When the absence of leakage is confirmed or when any leaks identified have been controlled, the tip of the nasogastric tube may be positioned further down in the Roux limb and left to continuous suction overnight. All mesenteric defects—at the jejunojejunostomy, at the mesocolon, and behind the Roux limb (Peterson hernia)—are then closed to prevent an internal hernia. The abdominal fascia is reapproximated with a continuous double-looped No. 2 suture, subcutaneous tissues are irrigated with a crystalloid solution, and the skin is closed with skin staples. No subcutaneous sutures or drains are used in routine cases.

COMPLICATIONS

Proximal GBP is associated with a significant incidence of stomal stenosis and with marginal ulcer.⁵⁵ The former responds to endoscopic stomal dilatation, and the latter usually responds to proton pump inhibitor (PPI) therapy. Addition of sucralfate to this regimen may be helpful. The risk of marginal ulcer appears to be increased in smokers and in patients who consume nonsteroidal anti-inflammatory drugs (NSAIDs). We routinely discourage NSAID use after GBP. Perforation of the proximal gastric pouch, probably arising from perforation of a deep ulcer, has been seen with administration of high-dose NSAIDs or with untreated ulcer diathesis.

Iron, vitamin B₁₂, and folic acid deficiencies may occur but can usually be corrected with oral supplementation³²; accordingly, GBP patients, like VBG and gastric banding patients, should be advised to take a multivitamin daily for life. Compared with gastropasty and gastric banding, GBP results in significantly lower serum hemoglobin and iron concentrations. This is primarily a problem in menstruating women. All menstruating women who have undergone GBP should be treated prophylactically with supplemental oral ferrous sulfate, 325 mg/day. As many as six iron tablets a day may be required if menstrual bleeding is heavy. Hormonal therapy to control or temporarily eliminate menses may be helpful. On occasion, intramuscular iron injections or, rarely, hysterectomy may be necessary. The risk of vitamin B₁₂ deficiency is higher after GBP than after gastropasty or gastric banding, but this condition can be prevented with supplemental oral vitamin B₁₂, 500 mg/day. A few patients may require (or prefer) monthly B₁₂ injections, which they can learn to administer themselves.

Concerns have been expressed that GBP can lead to other divalent cation deficiencies. Our group has not encountered zinc deficiencies 5 to 9 years after GBP, though we have observed calcium deficiencies leading to osteoporosis, which may take many years to become manifest and may not be biochemically evident because of normal serum calcium levels. It is therefore recommended that all GBP patients

take oral calcium supplements. Some may require vitamin D supplementation. Magnesium deficiencies should be treated with MgSO_4 supplementation.

Although nutritional deficiencies do not appear to be a greater problem with long-limb GBP than with standard proximal GBP, monitoring patients for possible malabsorption of the fat-soluble vitamins A, D, and E after long-limb GBP is advisable.

BPD may be associated with all of the complications seen after GBP. In addition, patients who undergo BPD may experience diarrhea, severe protein malnutrition (manifested as hypoalbuminemia), and deficiencies of vitamins A (manifested as severe night blindness), D (manifested as severe osteoporosis), and E.⁵⁰ Hypoalbuminemia may respond to oral pancreatic enzymes but often must be treated with total parenteral nutrition. In some patients, it may prove necessary to lengthen the absorptive intestinal tract from 50 cm to 200 cm.

OUTCOME EVALUATION

A series of 672 open proximal GBP procedures reported a 1.2% incidence of anastomotic leakage with peritonitis, a 4.4% incidence of severe wound infections (defined as infections serious enough to delay hospital discharge), an 11.4% incidence of minor wound infections and seromas (which were easily treated at home), a less than 1% incidence of gastric staple line disruption with the use of three superimposed applications of a 90 mm linear stapler, a 15% incidence of stomal stenosis, a 13% incidence of marginal ulcer, a 16.9% incidence of incisional hernia, and a 10% incidence of cholecystitis necessitating cholecystectomy.⁴⁷ Gallstones developed in 32% of the GBP patients who had a normal intraoperative gallbladder sonogram within 6 months of surgery, and sludge was observed in another 10%. In a multicenter randomized, prospective trial, the incidence of gallstones within 6 months of GBP was reduced from 32% to 2% by giving patients ursodeoxycholic acid, 300 mg twice daily.⁵⁶ Gallstone formation beyond 6 months is uncommon. The operative mortality in this series was less than 1%. Patients with respiratory insufficiency of obesity had an operative mortality of 2.2%, whereas those without pulmonary dysfunction had an operative mortality of 0.4%.

Neither the data from this randomized, prospective trial nor the data from selective studies support the contention that VBG is safer than GBP. Although GBP includes one more anastomosis than VBG, complications such as leaks and peritonitis occur with both operations. A common criticism of GBP is that it is difficult to evaluate the distal gastric pouch and duodenum after the operation. Such evaluation, however, can be done in 75% of patients by means of retrograde passage of an endoscope into the duodenum and the stomach and in other patients by means of percutaneous distal distention gastrography. Bleeding from either the distal gastric pouch or a duodenal ulcer is rare. Gastric mucosal metaplasia of the bypassed portion of the stomach may occur in some 5% of patients after retrograde endoscopy, a finding that has raised concerns regarding the risk of carcinoma arising at that location. To date, however, although many thousands of these procedures have been performed over the past four decades, few cases of cancer in the bypassed stomach have been reported.

Laparoscopic Gastric Bypass

Laparoscopic GBP is currently the most popular bariatric procedure in the United States, both because of the rapid weight loss it achieves and because of the strong overall surgical trend toward minimally invasive approaches. As noted [see Operative Planning, Laparoscopic versus Open Approach to Bariatric Surgery, *above*], laparoscopic GBP achieves the same weight-loss results as open GBP but yields less pain, reduced disability, and a shorter duration of hospitalization. Physiologically, laparoscopic GBP results in less operative trauma than open GBP, less impairment of pulmonary function, and a less pronounced stress response. In addition, the laparoscopic technique is associated with lower incidences of major wound infections and incisional hernias. Accordingly, we recommend laparoscopic GBP over any other bariatric procedure.

Laparoscopic GBP poses significant technical challenges, even for surgeons with advanced laparoscopic skills. Most of the variations seen at different institutions are related to various techniques for creation of the gastrojejunal anastomosis, with some groups using a circular stapler, others a linear stapler, and still others a handsewn technique. The anvil of the circular stapler may be placed within the proximal gastric pouch either by means of flexible upper GI endoscopy, through an approach similar to the snare-and-wire technique used for placement of a percutaneous endoscopic gastrostomy (PEG) tube [see 5:18 *Gastrointestinal Endoscopy*], or by means of a gastrotomy of the stomach before pouch creation for intra-abdominal anvil placement, followed by staple closure of the gastrotomy. Peroral placement of the stapler's anvil can be problematic: even the small 21 mm anvil is hard to pass through the proximal esophagus in some patients. To facilitate esophageal passage, a "flip-top" anvil design has been introduced. With this design, a 25 mm anvil can generally be passed without undue difficulty, thereby lowering the risk of postoperative stenosis. We routinely use the linear stapling method to create the gastrojejunal anastomosis; it is easier than circular stapling in this setting, and there is no risk of esophageal trauma from anvil passage.

OPERATIVE TECHNIQUE

Step 1: Initial Access and Trocar Placement

Initial access to the abdomen is obtained through a small left subcostal incision. Gas is insufflated into the abdomen via a Veress needle to a pressure of 15 mm Hg; on occasion, a pressure of 18 to 20 mm Hg may be necessary. A dilating 5 mm trocar is then placed in this location. Many surgeons use commercially available trocars that allow direct vision through the scope during passage of a 12 mm trocar. We encourage preinsufflation of the abdominal cavity before such a device is employed so as to enhance identification of the peritoneal sac and avoid organ injury. Additional trocars are placed in specific locations [see *Figure 13*]. The liver is retracted with a metal Nathanson liver retraction device anchored to the bed, which is inserted after a 5 mm sharp trocar is used to develop a tract into the abdominal cavity in the subxiphoid position and removed. If the left lateral section of the liver is very large (as in patients with steatosis), additional liver retractors may be necessary.

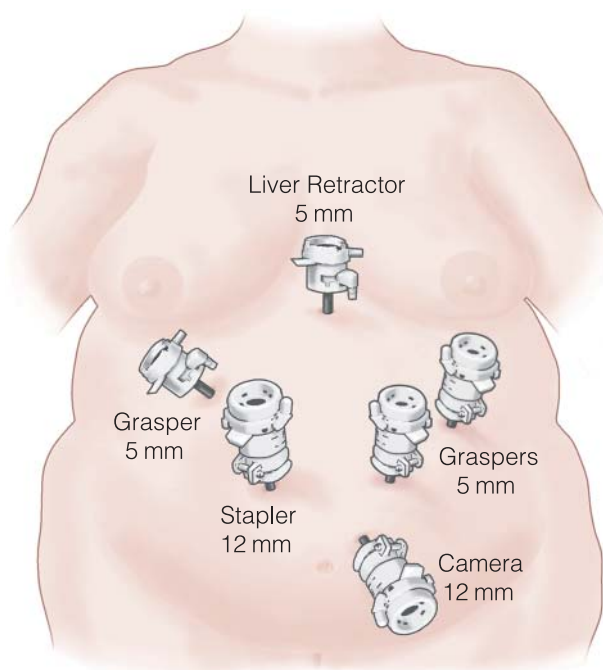


Figure 13 Laparoscopic gastric bypass (GBP). Shown are the trocar incision sites for laparoscopic GBP.

On occasion, the enlarged fatty falciform ligament must be dissected from the anterior abdominal wall with an ultrasonic scalpel or a bipolar cautery device. The advent of long laparoscopic graspers, staplers, and energy dissectors has facilitated operating on the proximal stomach and allows the use of trocar locations away from the abdominal midline. A 12 mm port placed in the right paramedian position serves as the surgeon's primary operative port; two lateral subcostal 5 mm ports allow both surgeon and assistant to employ two-handed techniques for the entire procedure. In most patients, a 45° angled viewing 5 mm laparoscope is inserted via a supraumbilical 5 mm trocar. A longer 10 mm scope may enhance visibility, particularly for especially heavy or tall patients, in whom a 5 mm scope may be subject to damage from excessive torque. High-definition imaging improves visualization during the procedure.

Step 2: Creation of Roux Limb and Jejunojunctionostomy

In most reports of laparoscopic GBP, regardless of how the gastrojejunostomy is done, the approach to creating the Roux limb is essentially the same. The patient is placed in a supine position, and graspers are used to bring the omentum upward into the upper abdomen so that the transverse colon and the underlying mesocolon are exposed. Graspers are then placed on the transverse mesocolon and used to elevate it anteriorly so that the ligament of Treitz is exposed. The position of the ligament of Treitz is confirmed by careful manipulation and verification that the bowel is attached to the retroperitoneum at this location; this may be a more difficult task in patients who have previously undergone abdominal procedures.

With the help of a measuring instrument, the small bowel is measured to a point 50 cm from the ligament of Treitz, where it is transected with the endoscopic gastrointestinal

anastomosis (GIA) stapler, loaded with 2.5 mm staples. A 0.5 in. Penrose rubber drain may be sutured to the cut end of the Roux limb so that it is not confused with the other cut end of the bowel. The Roux limb is then measured to a length of 45 to 60 cm. (As in open GBP, the Roux limb should be significantly longer—up to 150 cm—if the long-limb modification is being performed.) The afferent side of the previously transected small bowel is then attached with a simple absorbable suture to the proposed jejunojunctionostomy site on the Roux limb. Intracorporeal suturing is facilitated by using an automatic suturing device. Positioning is important: the afferent limb should be kept toward the mesocolon (toward the left side of the surgeon's field of view), with the Roux limb brought toward the surgeon (visualized on the right side of the operative field of view).

Two holding sutures are placed, one proximal to the proposed site of the enterotomy for the anastomosis and the other distal to this site, to help manipulate the bowel onto the stapler. A small (1 cm) enterotomy is made with the electrocautery in each of the two adjacent bowel limbs in preparation for passage of the linear stapler, loaded with 2.5 mm staples in a 60 mm cartridge, into the bowel. The stapler is then fired, creating a 60 mm side-to-side anastomosis. A suture is placed at the staple line to elevate the corner of the anastomosis for subsequent stapled closure of the defect, and a third holding suture is placed at the midpoint of the enterotomy. The three sutures are grasped to facilitate closure of the enterotomy by another application of the linear stapler, with great care taken to avoid narrowing at the junction of the Roux limb and the large common channel of the anastomosis. To facilitate closure without obstruction, all three knots should be visible above the stapler, but tissue amputation should be minimal. Once completed, the anastomosis is inspected both for integrity and for possible narrowing. At this point, cephalad traction is applied to the remaining suture (in the medial position) to facilitate placement of a continuous suture to close the mesenteric defect.

Some surgeons prefer to create a loop gastrojejunostomy, thereby avoiding the technical challenges associated with creating a Roux limb laparoscopically. This approach was abandoned years ago in open GBP because of the unacceptably high incidence of postoperative bile reflux and the increased severity of complications resulting from high output of digestive juices when leakage occurred at the gastrojejunal anastomosis; it should be abandoned in laparoscopic GBP as well. The practice of using such suboptimal methods for the purpose of performing this complex operation more expeditiously is poorly conceived.

Step 3: Passage of Roux Limb

Next, the greater omentum is divided from its free edge to its junction with the transverse colon so that the limb can be brought up in an antecolic fashion between the divided halves of the omental "apron," which reduces tension on the limb. Alternatively, a retrocolic, retrogastric tunnel may be created so that the Roux limb can be advanced to the proximal stomach for anastomosis. The retrocolic, retrogastric approach is superior if the antecolic approach appears to be placing undue tension on the limb as it is advanced to the proximal pouch. For retrocolic passage, the ligament of Treitz is identified

by lifting the transverse mesocolon anteriorly, and a spot 1 to 2 cm anterior and to the left of the ligament is chosen as the starting point for electrocautery dissection. The middle colic artery should be medial to this point of entry into the mesocolon. The goal of the dissection is to identify the posterior wall of the stomach, which may be difficult in patients who are extremely obese, have a fatty, foreshortened mesocolon, or have previously undergone abdominal surgery.

Once the stomach is visible, it is grasped and elevated through the mesocolic window, and the end of the Penrose drain is grasped and brought through the mesocolic defect into the lesser sac. When the Penrose is in place in the lesser sac, the omentum is pulled down from the epigastrium to allow visualization of the stomach, and the patient is placed into a steep reverse Trendelenburg position. The Penrose drain will be exposed when the cutting stapler is employed to create the proximal gastric pouch, and care must be taken to avoid stapling the drain.

There has been some controversy regarding the relative merits and deficiencies of antecolic and retrocolic techniques for passage of the Roux limb. The original open GBP often made use of a retrocolic, antegastric approach. The subsequent evolution of gastric transection methods led to a retrocolic, retrogastric approach to limb passage, which decreased the distance the limb had to travel to reach the proximal stomach and reduced the tension placed on the gastrojejunal anastomosis. Eventually, the antecolic, antegastric technique was introduced; this approach became popular with laparoscopic surgeons because it usually made the procedure faster to perform. The advantages of this technique were confirmed by a study that prospectively compared 33 consecutive patients who underwent retrocolic LRYGB with 33 who underwent antecolic LRYGB over a 3-year follow-up period.⁵⁷ The results suggested a similar decrease in BMI (from 45 kg/m² before operation to 34 kg/m² at 36 months) and a similar incidence of complications (e.g., internal hernias and strictures). Operating time was significantly shorter for the antecolic procedure (mean, 188 minutes) than for the retrocolic procedure (mean, 219 minutes).

Other issues that have been raised in comparing the two techniques include the risk of internal hernias through mesenteric defects and the various risks inherent in an anastomosis performed under tension (e.g., leakage, ischemic stricture, and ulceration). In addition, retrocolic passage of the Roux limb during LRYGB leaves a short segment of the limb that is not easily visualized; unrecognized twisting of this segment may occur and lead to postoperative obstruction. A 2007 study that evaluated 754 LRYGB patients (300 retrocolic, 454 antecolic) over a median follow-up period of 16 months found that the rate of complications (e.g., surgical exploration for intestinal obstruction and internal hernias) was higher after the retrocolic procedure.⁵⁸ Another 2007 study that evaluated 353 LRYGB patients (218 retrocolic, 135 antecolic) over a mean follow-up period of 28 weeks found that the incidence of postoperative gastrojejunal leakage was higher after the antecolic procedure.⁵⁹ These varying study outcomes suggest that a prospective, randomized trial will ultimately be required to determine whether antecolic Roux limb passage is superior or inferior to retrocolic passage with respect to outcomes or complication rates.

Both techniques continue to be employed today, and the current evidence is not sufficient to support a blanket recommendation favoring one over the other. We would maintain, however, that if undue tension is evident when the Roux limb is passed via the antecolic pathway, it is advisable to switch to the shorter route available via the retrocolic, retrogastric pathway.

Step 4: Dissection around Stomach and Creation of Gastric Pouch

The mesentery of the lesser curvature is transected with a bipolar electrocautery device to provide hemostasis. Despite the potential for problems with transection of the neurovascular bundle, no clear evidence of such problems has been found in hundreds of procedures performed with this access technique. Dissection posterior to the stomach is performed in the avascular free plane of the lesser sac. Additional dissection along the lesser curvature is not recommended, because it may increase the devascularization of the pouch. Further dissection is done at the angle of His to create a connection with the posterior gastric space. A linear endoscopic GIA stapler loaded with 3.5 mm staples in 60 mm cartridges is then employed in sequential firings to transect the stomach and create the proximal gastric pouch; three or four firings are usually necessary [see Figure 14]. When revisional bariatric surgery is performed on the previously operated-on stomach or when buttressing materials are used to reinforce the staple line, a staple height of 4.8 mm is usually required.

Step 5 (Circular Stapling): Placement of Stapler in Gastric Pouch

As noted (see above), surgeons use several different techniques to complete the gastrojejunal anastomosis. If a linear stapler is used, the next step is gastrojejunostomy [see Step 6b (Linear Stapling), below]. With the technique reported in Wittgrove's original description of the procedure,⁶⁰ however, in which the anvil of a circular stapler is passed down the

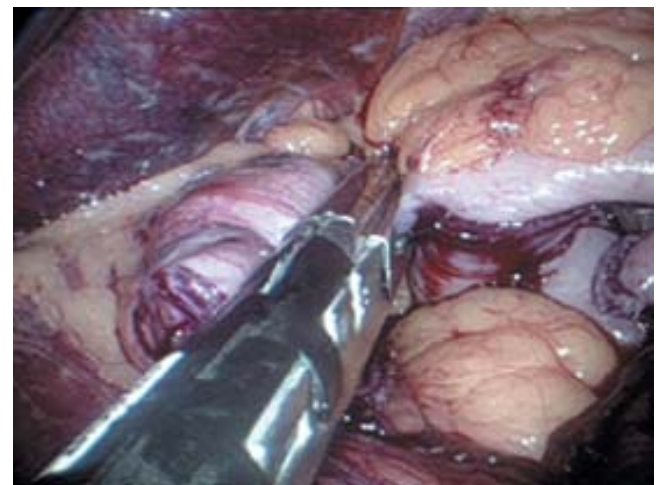


Figure 14 Laparoscopic gastric bypass (GBP). Much as in open GBP, a linear endoscopic gastrointestinal anastomosis (GIA) stapler is fired three times to transect the stomach and create the gastric pouch.

patient's esophagus, the next step in the procedure is to have an assistant perform flexible upper GI endoscopy of the gastric pouch. The pouch wall is transilluminated by the endoscope light, and a site is chosen for the gastrojejunostomy. The endoscopist then places an endoscopic snare, which can be seen pressing against the tissue of the pouch wall. A small opening is made in the pouch with the electrocautery scissors so that the snare can be pushed through the gastric wall at this location. The snare is then used to grasp a wire placed through a needle across the abdominal wall in the left abdomen, and snare and wire are withdrawn through the mouth along with the scope.

The anvil of the stapler is attached to the end of the wire that was drawn through the mouth, and the surgeon pulls on the other end of the wire to deliver the anvil through the mouth, down the esophagus, and into the gastric pouch, where it can be visualized. The electrocautery is used to enlarge the opening in the gastric wall slightly, and the stem of the stapler is then brought through the gastrotomy. To prevent anastomotic leakage after stapling, the gastrotomy should be no larger than the diameter of the stem; if it is too large, it can be closed around the stem by placing one or two simple sutures.

An alternative technique for anvil placement in the pouch involves making a gastrotomy distal to the planned staple line before transection of the stomach. After the anvil is introduced into the abdomen via a dilated trocar site, a long sharpened dissector is employed to grasp a suture tied to the anvil stem. The dissector is then passed into the lumen of the stomach and used to perforate the future pouch in location that is appropriate for the eventual anastomosis. Once the anvil stem has been advanced through the perforation, the dissector is withdrawn. Stapling of the stomach may include amputation of the gastrotomy site. The pouch is created by stapling around the anvil and thus can be made very small.

Troubleshooting Difficulty in passing the anvil perorally may arise at the level where the trachea separates from the esophagus in the deep pharynx. This difficulty can usually be overcome either by having the endoscopist perform a jaw-thrust maneuver or by placing a large laryngoscope blade deep in the pharynx to make the anvil visible in the proximal esophagus and then nudging the anvil forward with either the tip of the blade or a McGill forceps. Transiently deflating the endotracheal tube balloon may also help. Occasionally, a large, blunt esophageal dilator is used to place pressure on the top of the anvil. Given the potential for esophageal injury if the anvil will not advance, it is important not to apply excessive force. In one case from our experience, the anvil became lodged in the proximal esophagus beyond the laryngoscopic view, and the long suture holding it broke; retrograde passage of an esophageal dilator placed via a gastrotomy in the pouch was required to dislodge the anvil. Other surgeons who use wire to draw the anvil down the esophagus have identified nontransmural esophageal injuries on postoperative contrast studies or have seen subcutaneous emphysema in the neck after operation. There is at least one case report describing an esophageal perforation with this technique.

Step 6a (Circular Stapling): Gastrojejunostomy

In the circular stapling technique, the stapled end of the Roux limb is opened to permit introduction of the stapler. A

12 mm trocar site in the left upper quadrant is dilated so that the circular stapler can be inserted through the abdominal wall without the need for a trocar. Lubrication is helpful for this step, and covering the device with a sterile plastic bag helps to protect the wound from contamination when the device is extracted. The transabdominal stapler then cannulates the Roux limb. The stapler is advanced 3 to 4 cm down the limb, and the spike on the body of the device is brought through the antimesenteric portion of the bowel by unscrewing the stapler under direct vision. Once the stapler has been opened completely, it is laparoscopically joined to the anvil protruding from the gastric pouch, then closed and fired.

Once fired, the stapler is removed from the abdominal wall, and a balloon trocar device is used to close the dilated abdominal wall opening. A single firing of the endoscopic GIA stapler, loaded with 2.5 mm staples, is often all that is required to close the enterotomy left from passage of the stapler. Interrupted or continuous absorbable sutures are then placed around the stapled anastomosis to provide added security and reduce tension on the staple line.

Step 6b (Linear Stapling): Gastrojejunostomy

Initially, a continuous posterior row of nonabsorbable suture material is placed to secure the Roux limb to the posterior gastric pouch. An enterotomy and a gastrotomy are performed that are large enough to admit the jaws of the endoscopic GIA stapler, which is loaded with 3.5 mm staples in a 45 mm cartridge for a side-to-side anastomosis [see Figure 15] by means of the same techniques employed



Figure 15 Laparoscopic gastric bypass. A 30 French dilator is placed into the proximal gastric pouch before closure of the gastrojejunal anastomosis with the endoscopic gastrointestinal anastomosis (GIA) stapler.

in creating the jejunojejunostomy. The cartridge is inserted to its full length and fired to create an inner stapled layer [see Figure 16]. We use the full length of the staple cartridge because we have found that our technique (a complete two-layer anastomosis that includes 360° oversewing of the anastomosis over a 30 French dilator or a flexible 9 to 11 mm gastroscope) can lead to obstruction if the full cartridge length is not employed. The remaining gastroenterotomy defect is closed in two layers with continuous sutures (absorbable for the inner layer, nonabsorbable for the outer).

In our experience, using the linear stapler for the gastrojejunostomy simplifies the procedure, reduces operating time, and eliminates the concerns about injury to the body of the esophagus that arise with passage of the circular stapler.

Step 6c (Handsewn Anastomosis): Gastrojejunostomy

Some surgeons employ laparoscopic suturing techniques to create a handsewn gastrojejunostomy, usually with a single layer of continuous nonabsorbable suture material. In particular, robotic surgery techniques usually include hand suturing, using the robotic effectors to grasp the tissue and the needle and, ultimately, to tie the suture. Robotic techniques are hampered by the setup time required for placement of the robotic arms, but they have been touted as being particularly useful for operating on superobese persons, in whom manipulation of traditional laparoscopic instruments is made difficult by the extreme thickness of the abdominal wall, which interferes with the trocar's fulcrum effect. In such cases, use of a robotic technique appears to improve the ergonomics of the procedure and relieve the surgeon's hand and arm fatigue.

Step 7: Assessment of Anastomosis

In every case, regardless of which anastomotic technique is employed, flexible upper GI endoscopy is performed to assess the anastomosis. The Roux limb is occluded with an intestinal clamp to prevent excessive bowel and distal gastric dilatation. The patient is placed in the supine position, and



Figure 16 Laparoscopic gastric bypass. The gastrojejunal anastomosis is closed with the linear endoscopic gastrointestinal anastomosis (GIA) stapler.

the area around the anastomosis is irrigated with saline; the presence of air bubbles, easily detectable in the irrigant, indicates that the anastomosis is leaking. In most cases, the pouch and the Roux limb can be distended tightly, and even tiny air leaks are reinforced with additional sutures. The anastomosis and the staple lines are visualized, and the endoscope is navigated through the anastomosis into the Roux limb whenever possible. After adequate visualization and testing, the gas is suctioned from the intestine, the Roux limb is unclamped, and the endoscope is removed. Alternatively, some surgeons prefer to distend the anastomosis with methylene blue dye to exclude leakage.

Step 8: Closure

Finally, a 10 mm closed suction drainage tube may be placed adjacent to the anastomosis to permit monitoring for postoperative leaks. In our program, we no longer do this on a routine basis. If a drain is placed, it is usually removed after the patient begins oral intake. Selected patients undergo upper GI series to evaluate for postoperative leakage [see Figure 17]. This radiographic study is considered mandatory in patients with equivocal postoperative signs and symptoms of leakage, though surgical reexploration may be preferable and is a more definitive assessment in such patients.

In antecolic Roux-en-Y procedures involving division of the greater omentum, the lateral tongue of greater omentum may be wrapped in a lateral-to-medial direction posteriorly around the gastrojejunostomy, then sutured to the anterior pouch tissue so as to reinforce the anastomosis. We do not do this routinely—only when we have technical concerns about the integrity of the anastomosis. We also sometimes use the distal gastric remnant as a live tissue patch over areas of concern in a difficult anastomosis. The liver retractor is removed under direct vision to ensure that no bleeding occurs. When dilating trocars have been employed, the trocar

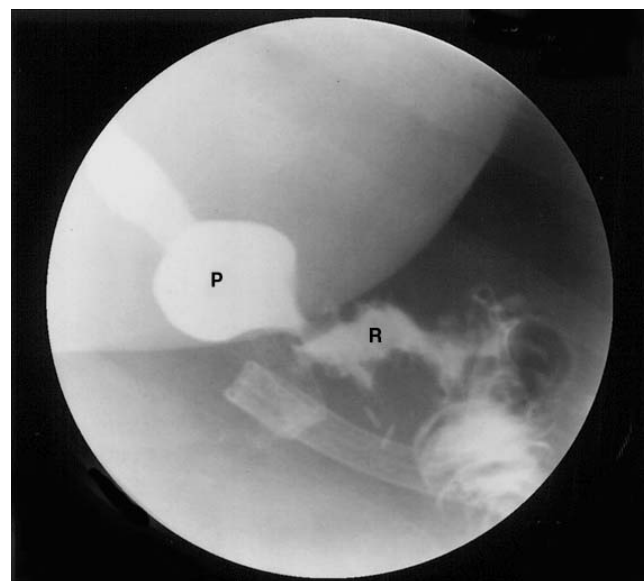


Figure 17 Laparoscopic gastric bypass. Flexible upper gastrointestinal endoscopy is performed to assess the completed anastomosis.

sites are not routinely closed. Trocar sites manually dilated to permit extraction of a specimen (e.g., gallbladder) or passage of a circular stapler should be closed with sutures to avoid risk of hernia formation; we have found that such closure increases postoperative incisional pain at these sites. Skin wounds are closed with minimal subcuticular sutures, and the epidermis is reapproximated with commercially available skin closure adhesives.

HAND-ASSISTED LAPAROSCOPIC GASTRIC BYPASS

Because total intracorporeal laparoscopic GBP is such a challenging technical adventure, a hand-assisted version of the procedure was developed.⁶¹ This technique served as a bridge to the total intracorporeal approach, in that it made it possible to learn the technical aspects of a difficult, highly advanced laparoscopic procedure while enjoying the security provided by the presence of a hand within the abdomen for palpation and manipulation during the procedure. This added security is the major advantage of the hand-assisted approach. The major disadvantage is the potential for complications at the incision used for manual access. The complications seen at this site are reminiscent of those seen after open GBP, including major wound infection, dehiscence, and hernia formation.

In a series of hand-assisted laparoscopic GBP procedures from our institution, there was one major wound infection in the hand incision and one instance of postoperative fascial dehiscence. Subsequent study suggested that the hand-assisted procedure did not reduce the incidence of wound-related complications and incisional hernias and that it significantly increased the cost of surgical treatment when compared with open GBP. It appears, therefore, that the primary role of hand-assisted laparoscopic GBP may be in helping surgeons to negotiate the steep learning curve associated with total laparoscopic GBP. Some surgeons, however, have persisted with hand-assisted techniques, and large series have been published.

COMPLICATIONS

The complications observed to date after laparoscopic GBP include the usual problems that occur in some patients after open GBP, including marginal ulcer and stenosis at the gastrojejunal anastomosis necessitating dilatation. On rare occasions, a gastrogastic fistula may lead to a treatment-resistant marginal ulcer. The major advantage of laparoscopic GBP over open GBP is likely to be reduced wound complications (e.g., major wound infection and incisional hernia). We have seen several relatively minor trocar site infections after laparoscopic GBP but none that carried the long wound-care disability characteristic of a major wound infection after open GBP. Intermediate-term weight loss with laparoscopic GBP appears to be identical to that with open GBP.

Postoperative Management

After operation, the obese patient should be kept in the reverse Trendelenburg position and should not be extubated until he or she is fully alert and showing evidence of adequate ventilatory effort [see 8:6 *Mechanical Ventilation*]. In the absence of respiratory insufficiency, most obese patients can

be extubated in the OR or the recovery room and returned to a standard hospital room.

Patients with obstructive SAS may have to be managed with overnight mechanical ventilation in the ICU, particularly if an open bariatric procedure was performed. Patients who were receiving ventilatory support with nasal CPAP before operation should have this treatment reinstituted after operation; monitoring for prolonged apnea should be continued in the ICU or in a stepdown unit with digital oximetry. If apnea occurs, simply waking the patient should correct the problem.

Patients with OHS may require prolonged mechanical ventilation until the pain of breathing resolves, particularly after open procedures. Such patients cannot be expected to manifest normal ABG values, and they should be weaned to their preoperative values—hence the value of obtaining baseline ABG values before operation in these patients. The weaning process may require several days. It is important that these patients remain in the reverse Trendelenburg position to maximize diaphragmatic excursion by reducing the pressure on the chest cavity that may result from the often very large and heavy abdominal cavity. Swan-Ganz catheters, inserted preoperatively in patients with severe OHS, are useful in monitoring postoperative intravascular volume and oxygen delivery status. Excessive diuresis or restriction of fluids should be avoided.

It is extremely important to encourage early postoperative ambulation for the morbidly obese patient. These patients often experience less pain than one might expect, and it is frequently possible to get motivated patients up and walking in the afternoon or early evening after a major abdominal procedure. If the patients have been advised preoperatively of the merits of early postoperative ambulation and know it is for their own welfare, they may be more willing to cooperate.

These basic principles of postoperative management generally apply to laparoscopic cases as well, but with some differences. Unlike patients who have undergone open GBP, those who have undergone laparoscopic GBP usually do not have a nasogastric tube left in place. The bariatric surgical patient may begin to drink small amounts of liquids on postoperative day 1 and may be kept on a liquid diet with liquid protein supplementation for several weeks. Alternatively, many programs advance postoperative patients to a pureed diet with no sugar or concentrated sweets as soon as they can tolerate it. We have found that when patients consume only liquids during the edematous healing phase of the anastomosis, there is less need for urgent dietary counseling during the first few weeks after surgery. Discharge usually takes place between 1 and 3 days after operation. Vitamin administration should be initiated early after operation; chewable tablets may be used if necessary. Thiamine deficiency is very uncommon but can be quite serious if it progresses to the Wernicke-Korsakoff syndrome of neurologic damage. Such deficiency may develop within weeks in patients who are kept on a liquid-only diet without multivitamins but appears to be more common in patients who experience persistent vomiting. Any postoperative bariatric surgical patient with unexplained neurologic symptoms (e.g., visual changes, confusion, sensory changes in the extremities, or gait disturbance) should

be considered for evaluation of potential nutritional causes, including thiamine deficiency and vitamin B₁₂ deficiency.

The basic principles of postoperative management apply to both laparoscopic and open cases.

General Complications of Surgery in the Morbidly Obese Patient

The following are some of the main complications that may be associated with any abdominal operation (open or laparoscopic GBP, VBG, or LAGB) in a severely obese patient.

ABDOMINAL CATASTROPHE

It may be very difficult to recognize an abdominal catastrophe in patients who are very young, very old, or morbidly obese or who are receiving high doses of steroids. For example, the obese patient may present in the ED with a perforated duodenal ulcer or a ruptured diverticulum, complaining of abdominal pain, and yet on abdominal examination have no evidence of peritoneal irritation (i.e., no guarding, tenderness, or rigidity). This situation has been well documented in patients in whom an anastomotic or gastric leak has developed after operation for morbid obesity.⁶² Symptoms include shoulder pain, pelvic or scrotal pain, back pain, tenesmus, urinary frequency, and, of great importance, marked anxiety. Signs of infection (e.g., fever, tachypnea, and tachycardia) may be absent, though tachycardia is often the first sign of a significant problem. Patients with peritonitis often have clinical symptoms and signs suggesting a massive pulmonary embolus: severe tachypnea, tachycardia, and sudden hypotension. Such acute pulmonary failure is probably secondary to sepsis-induced acute respiratory distress syndrome (ARDS). Thus, peritonitis must be suspected in any morbidly obese patient with acute respiratory failure. One advantage of the laparoscopic approach to bariatric surgery is that if there is concern about a possible leak, reexploration can be carried out without the need to reopen a large abdominal incision.

Because a high index of suspicion of peritonitis is required to detect the condition in morbidly obese patients, radiographic contrast studies with water-soluble agents such as diatrizoate meglumine may be indicated even when there are few clinical signs. If a perforated viscus is suspected, exploratory laparoscopy or laparotomy may be necessary despite normal findings on radiographic contrast study.

INTERNAL HERNIA

GBP places patients at risk for internal hernia with a closed-loop obstruction, leading to bowel strangulation. There are three typical locations for these internal hernias: the jejunojejunostomy anastomosis, the opening in the transverse mesocolon through which the retrocolic Roux limb is brought, and the Petersen hernia (located posterior to the Roux limb between the Roux mesentery and the transverse mesocolon). The primary symptom of an internal hernia is periumbilical pain, usually in the form of cramping consistent with visceral colic. These internal hernias may be very difficult to diagnose. Upper GI radiographic series and abdominal CT scans are often normal, providing a false sense of security. The resulting assumption that no problem exists may be devastating for the patient should bowel infarction occur as a consequence of closed-loop obstruction. The plain abdominal

radiograph should always be carefully inspected for abnormal placement or spreading of the staples in the Roux-en-Y anastomosis. The safest course of action in patients with recurrent attacks of cramping periumbilical pain is abdominal surgical exploration. The frequency of this complication seems to have increased with the advent of laparoscopic GBP, presumably because of the difficulty of closing the potential hernia spaces completely. Some attribute the problem to the decreased tendency toward adhesion formation after laparoscopic surgery or to reduction of the intra-abdominal fatty tissue in the mesentery after successful weight loss surgery. We have seen one patient who had a patent mesenteric defect despite an intact suture; the apparent cause of the defect was a dramatic reduction in the mesenteric fat incorporated in the closure.

ACUTE GASTRIC DISTENTION

After GBP, massive gaseous distention occasionally develops in the distal bypassed stomach, sometimes leading to a gastric perforation or disruption of the gastrojejunostomy. The primary symptoms of this complication are hiccups and a bloated sensation reported by the patient. Massive gastric dilatation can lead to severe left shoulder pain and shock. During the era when open GBP was predominant, gastric paralytic ileus was a known cause of this complication, particularly in patients requiring extensive adhesiolysis at the time of the bypass. Currently, with the advent of laparoscopic GBP, the problem is usually secondary to transient edema or to mechanical obstruction at the jejunojejunostomy anastomosis. The diagnosis is made by means of an urgent upright abdominal radiograph, which reveals the markedly dilated and air-filled bypassed stomach. Occasionally, the stomach is filled with fluid, and the diagnosis may be more difficult; in such cases, CT scanning may be helpful. Percutaneous transabdominal skinny-needle decompression can aid in the management of this complication and allow time for tissue edema at the jejunojejunostomy to resolve. If the dilatation recurs or the patient experiences serious difficulty, an emergency laparotomy should be performed, a gastrostomy tube inserted, and the jejunojejunostomy evaluated.

ALTERED INSULIN REQUIREMENTS IN DIABETIC PATIENTS

Patients with type 2 diabetes may require large amounts of insulin for blood glucose control because of significant insulin resistance. It is not unusual, however, to note a complete absence of the requirement for insulin in the immediate postoperative period in morbidly obese patients. Therefore, insulin should be withheld on the morning of operation. In morbidly obese patients who have undergone GBP, there is often a marked reduction in the requirement for insulin throughout the postoperative period and even at discharge, possibly because of increased release of gastric inhibitory peptide (GIP) from the proximal small bowel. Therefore, regular subcutaneous insulin should be administered to GBP patients according to a sliding scale after operation until insulin requirements can be determined. Before discharge, the patient should be taking an appropriate dose of insulin, but afterward, he or she must perform frequent finger-stick blood glucose determinations, given that the need for insulin will decrease progressively with weight loss.

In one study of 23 patients with diabetes mellitus who underwent gastric bariatric operation, the average

requirement for insulin decreased from 74 units/day before operation to 8 units/day after operation.⁶³ Fourteen of the 23 patients were able to discontinue insulin completely, 11 by the time of discharge from the hospital 1 week after operation. These benefits were maintained during long-term follow-up to 39 months and were a result of a major decrease in insulin resistance that was associated with decreased food intake, as well as with weight loss.

Failed Weight Loss and Weight Regain

A postoperative problem that deserves special mention is the risk of failed weight loss or weight regain. This is one of the most difficult problems associated with bariatric surgery and may arise after any gastric procedure for morbid obesity. Patients who have undergone gastroplasty or gastric banding may have difficulty with solid foods and come to exhibit maladaptive eating behavior involving frequent ingestion of high-calorie liquid carbohydrates (a common reason for failure of a bariatric procedure). Conversion to GBP appears to be a successful management strategy for these patients. In a study in which 53 VBG patients were converted to GBP, the average loss of excess weight after VBG was $31 \pm 5\%$; 2 years after conversion to GBP, the average loss of excess weight increased to $67 \pm 2\%$, a value virtually identical to that in the primary GBP group.⁶⁴

Inadequate weight loss is also seen in GBP patients. In some, stomal dilatation eventually develops after the procedure; however, no correlation between stomal size and weight loss has been demonstrated for GBP patients, and reoperation to make the pouch or the stoma smaller has not yielded any benefit over time when the initial procedure has failed.

New techniques for narrowing the dilated gastrojejunostomy stoma endoscopically are currently being tested, but there remains the larger question as to whether such interventions are of any real value for long-term weight control. In a small percentage of patients, the failure of GBP may be attributable to either the loss or the absence of dumping syndrome symptoms, which leads to resumed ingestion of high-calorie sweets or, more commonly, to frequent ingestion of high-fat junk foods (e.g., potato or corn chips, microwave popcorn, and peanut butter crackers) that crumble easily and empty quickly from the pouch, thereby keeping the patient from feeling full. Repeated dietary counseling over a period of years is required to educate patients to eat low-calorie, high-fiber foods (e.g., raw carrots, broccoli, cauliflower, apples, and oranges) that stay in the small gastric pouch longer and provide a sensation of early satiety.

We make clear to patients, well in advance of the operation, that bariatric surgery is designed to provide them with a tool that will assist them in behavior modification and thereby help them help themselves. Obesity can be beaten by surgical treatment, but patients must continue to make good food choices. Patients who begin to ingest more than 1,100 kcal/day often begin to gain weight; even if the weight gain is only 0.5 lb/month, this amounts to 6 lb/year, or 60 lb in 10 years. Bariatric surgical patients may need lifelong nutritional counseling to optimize the results of surgical management of morbid obesity. In addition, appropriate regular physical exercise is an important adjunct to surgical treatment, and patients who comply with exercise treatment not only lose more weight but also are better able to maintain their weight loss. Accordingly, we recommend that patients follow a suitable exercise regimen for the rest of their lives.

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8 TUMORS OF THE STOMACH, DUODENUM, AND SMALL BOWEL

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Gastric Adenocarcinoma

The incidence of gastric carcinoma exhibits significant geographic variability. The disease is most common in Japan and China, and high rates of occurrence have also been reported in Central and South America, eastern Europe, and parts of the Middle East.¹ In most of the more developed nations, however, gastric carcinoma is relatively uncommon. The overall incidence of this condition has decreased in the past few decades, but gastric carcinoma remains the second leading cause of cancer death worldwide. The reported reductions in gastric cancer mortality appear to be linked to better refrigeration and a concomitant decrease in the intake of salted, pickled, smoked, and chemically preserved foods. An inverse association with the consumption of fresh fruits and vegetables has also been noted.²

Gastric cancer occurs 1.5 to 2.5 times more frequently in males than in females. It is rarely diagnosed before the age of 40, and its incidence peaks in the seventh decade of life. African Americans, Hispanic Americans, and Native Americans are two times more likely to have gastric cancer than white Americans are.³

In the United States in particular, the incidence of stomach cancer has fallen substantially over the past 70 years.⁴ Whereas this disease was once a leading cause of cancer-related death in the United States, it now ranks 13th among major causes. Unfortunately, the decline in incidence has not translated into an improvement in the 5-year survival rate.⁵ Across all races, the 5-year relative survival was 23% for the period extending from 1992 to 1999.³ This result is probably related to the advanced stage at which most patients present. A 2000 study from the National Cancer Data Base found that 55% of patients with gastric cancer presented with locally advanced or metastatic disease.⁶ Resection rates ranged from 40 to 60%, and 5-year survival rates after resection with curative intent were directly related to stage at presentation. For stage IA disease, the survival rate was 78%; for stage IB, 58%; for stage II, 34%; for stage IIIA, 20%; for stage IIIB, 8%; and for stage IV, 7%.

Another relevant change in the epidemiology of gastric cancer is a shift in the distribution of primary lesion sites within the stomach. In the first quarter of the 20th century, two thirds of gastric cancers were located in the antrum and the prepyloric area and only 10% arose in the cardia or the esophagogastric junction. Since the 1970s, however, adenocarcinoma of the proximal stomach has become increasingly common. In one study, the incidence of adenocarcinoma of the gastric cardia rose from 29.1 to 52.2% in the period between 1984 and 1993.⁷ In another study, which included

18,365 gastric cancer patients from Commission on Cancer–approved hospitals, 31% of tumors were found to be in the proximal stomach, compared with only 26% in the distal third.⁸ In the United States, carcinoma of the cardia occurs primarily in whites, with a male-to-female ratio of approximately 2:1. Cancer of the cardia appears to be distinct from adenocarcinoma of the distal esophagus, which frequently arises in the setting of Barrett esophagus.⁹ Associations have also been reported between cancer of the gastric cardia and infection with *Helicobacter pylori* or Epstein-Barr virus.^{10,11}

CLASSIFICATION

Adenocarcinoma of the stomach may be divided into two histologic subtypes, intestinal and diffuse.¹² Each subtype has unique pathologic, epidemiologic, etiologic, and prognostic features. The intestinal (or glandular) subtype usually arises in the distal stomach (often after a long precancerous phase), is more common in elderly patients, and has been closely associated with atrophic gastritis and diets high in nitrates and nitrose compounds.¹³ The characteristic histologic finding is cohesive neoplastic cells that form glandlike tubular structures. The diffuse subtype occurs more frequently in younger patients and has no identifiable precursor lesion. It may develop in any part of the stomach but shows a predilection for the cardia. Cell cohesion is absent; thus, individual cancer cells infiltrate and thicken the stomach wall without forming a discrete ulcer or mass.

In general, the prognosis for the diffuse subtype is worse than that for the intestinal subtype. Whereas intestinal lesions are seen more frequently in regions with a high incidence of gastric cancer, the incidence of diffuse lesions is constant among various populations throughout the world.¹⁴ Accordingly, the overall decline in gastric cancer over the past century has been attributed to a decline in intestinal lesions and to a decline in the incidence of *H. pylori* infection (see below).

RISK FACTORS

Historical studies of specimens obtained during operation or at autopsy suggest that gastric carcinoma, especially of the intestinal subtype, frequently develops in the presence of chronic atrophic gastritis and associated intestinal metaplasia. It has generally been assumed that adenocarcinoma of the distal stomach progresses from chronic gastritis to metaplasia through the teratogenic influence of environmental factors. The most commonly studied environmental factors are the nitrates and nitrose compounds present in high levels in salted, smoked, or pickled foods consumed in areas where gastric cancer is endemic.¹⁵ To date, however, no prospective

studies have conclusively demonstrated that modern refrigeration practices and the subsequent decline in the salting, smoking, and pickling of food have been responsible for the relative decline in intestinal gastric cancer. Furthermore, the intestinal subtype may arise in the absence of metaplasia. Finally, the emergence of chronic infection with *H. pylori* as the dominant risk factor for gastric adenocarcinoma has challenged the paradigm of the atrophic gastritis–intestinal metaplasia–gastric cancer sequence.

Epidemiologic studies across various populations worldwide have consistently demonstrated a strong association between *H. pylori* infection and gastric cancer.¹⁶ Prospective serologic studies have confirmed that persons with evidence of such infection are three to six times more likely to have gastric cancer than persons who are seronegative.¹⁷ Still, only a very small fraction of infected persons develop gastric cancer. It has been estimated that more than half of the world's inhabitants may be infected with *H. pylori*—a number that dwarfs the actual incidence of gastric cancer. What is clear is that *H. pylori* infection of the gastric mucosa leads to a state of chronic active inflammation that lasts for decades. This inflammatory process appears to be modulated by multiple forces, including genetic and environmental factors.¹⁸ Inherited traits may confer susceptibility or resistance to carcinogenesis. Indeed, first-degree relatives of gastric cancer patients have a two to three times higher relative risk of contracting the disease.¹⁹ Gastric irritants may act as promoters, and antioxidants may have a protective effect (which may be part of the reason for the reduced risk of gastric cancer associated with diets rich in fruits and vegetables).²⁰

Unlike intestinal cancers, diffuse cancers appear not to be associated with *H. pylori* infection. Diffuse adenocarcinoma of the stomach is more common in young patients and has no known precursor lesion.⁹ The incidence of genetically associated diffuse cancers is estimated to be in the range of 5 to 10%.¹⁹ Familial cases of diffuse gastric cancer occur at an average age of 38 years and are inherited in an autosomal dominant fashion with 70% penetrance.²¹ Patients with blood group A have a 16 to 20% increased risk of gastric cancer.²²

CLINICAL EVALUATION

In high-risk areas (e.g., Japan), mass screening programs have been successful in identifying early gastric cancer, which is generally amenable to surgical cure.²³ In fact, in some Japanese studies, as many as 40% of newly diagnosed patients had early gastric cancer. Unfortunately, in Western countries, the disease is almost always diagnosed relatively late, when it is locally advanced or metastatic. When it is superficial, gastric cancer typically produces no symptoms. As it progresses, however, a constellation of vague, nonspecific symptoms may develop, including anorexia, fatigue, weight loss, and epigastric discomfort. Dysphagia, early satiety, vomiting, and hematemesis also are seen, albeit rarely; when present, they often indicate advanced disease. Indeed, early gastric cancer has no characteristic physical findings, and many patients are not diagnosed until they present with jaundice, ascites, or a palpable mass, all of which signal incurable disease. Although rare, certain physical examination findings are indicative of metastases, including the Virchow node (left supraclavicular lymph node), Sister Mary Joseph nodule (periumbilical metastasis), Irish node (axillary lymph

node), and Blumer shelf (metastases palpable on a rectal examination in the rectouterine or rectovesical space).

INVESTIGATIVE STUDIES

Until comparatively recently, an upper gastrointestinal (GI) series was often the first diagnostic test ordered to evaluate symptoms related to the upper GI tract. However, even with double-contrast techniques, which allow improved visualization of mucosal detail, false negative rates as high as 25% were reported, especially with small lesions (i.e., 5 to 10 mm).²⁴ Accordingly, in most large series, fiberoptic endoscopy with biopsy has replaced contrast radiography as the primary diagnostic technique.²⁵ Upper GI endoscopy with biopsy has been reported to have a diagnostic accuracy of 95%.²⁰ However, false negatives have been reported, especially in the context of inadequate biopsies. Thus, it is recommended that at least four biopsies be taken from the region of any atypical findings.²⁶

STAGING

Two major classification systems are available for staging gastric cancer. The first is the one used in Japan, where gastric cancer is staged according to the general rules for gastric study in surgery and pathology published by the Japanese Research Society for Gastric Cancer (JSGC).²⁷ This elaborate system focuses on the anatomic involvement of specifically numbered lymph node stations. The second system is the one generally used in Western countries—namely, the familiar tumor-node-metastasis (TNM) system developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) [see Table 1 and Table 2].²⁸ The AJCC/UICC staging system is based on a gastric cancer database and classifies lesions according to the depth to which the primary tumor penetrates the gastric wall, the extent of lymph node involvement, and the presence or absence of distant metastases.

The primary goal in the evaluation of gastric cancer patients is to stratify them into two clinical stage groups: those with locoregional disease (AJCC stages I to III) and those with systemic disease (AJCC stage IV).²⁹ The National Comprehensive Cancer Network (NCCN) has developed consensus guidelines for the clinical evaluation and staging of patients with possible gastric cancer. These guidelines are accessible to any practitioner via the Internet (<http://www.nccn.org/>) and are updated annually. Multidisciplinary evaluation is recommended for all patients. A careful history is obtained and a thorough physical examination is performed, with special attention paid to performance status and to comorbid conditions that might preclude operative intervention. Initial laboratory studies include a complete blood cell count with a platelet count; determination of serum electrolyte, blood urea nitrogen, creatinine, and glucose concentrations; and a liver function panel. Chest radiography is performed, along with computed tomography (CT) of the abdomen and pelvis.

Whereas CT is invaluable for detecting ascites, bulky adenopathy, and significant visceral metastases, its overall accuracy in staging tumors is modest: only 70% for advanced lesions and 44% for early lesions.³⁰ CT assesses lymph node involvement primarily on the basis of node size. Thus, its sensitivity for N1 and N2 disease is low, ranging from 24 to 43%; however, its specificity is high, approaching 100%.

Table 1 American Joint Committee on Cancer TNM Clinical Classification of Gastric Carcinoma, 7th Edition⁹⁶

Primary tumor (T)	TX Primary tumor cannot be assessed T0 No evidence of primary tumor Tis Carcinoma in situ: intraepithelial tumor without invasion of lamina propria T1 Tumor invades lamina propria, muscularis mucosae, or submucosa T1a: Tumor invades lamina propria or muscularis mucosae T1b: Tumor invades submucosa T2 Tumor invades muscularis propria T3 Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures T4a Tumor invades serosa (visceral peritoneum) T4b Tumor invades adjacent structures
Regional lymph nodes (N)	NX Regional lymph node(s) cannot be assessed N0 No regional lymph node metastasis N1 Metastasis in 1–2 regional lymph nodes N2 Metastasis in 3–6 regional lymph nodes N3 Metastasis in 7 or more regional lymph nodes N3a: Metastasis in 7–15 regional lymph nodes N3b: Metastasis in 16 or more regional lymph nodes
Distant metastasis (M)	M0 No distant metastasis M1 Distant metastasis

Technical advances, such as spiral (helical) CT with intravenous contrast plus appropriate gastric distention with 600 to 800 mL of water (a negative contrast agent), have allowed modest improvements in overall staging with CT [see Figure 1]. Although improving, CT is still limited in its ability to evaluate peritoneal disease and liver metastases smaller than 5 mm.³¹

Given the limitations of CT, in the absence of obvious metastatic disease, locoregional staging with endoscopic ultrasonography (EUS) is vital for accurately assessing tumor penetration through the gastric wall (T stage) and ascertaining whether regional nodes (N stage) or even mediastinal or

para-aortic lymph nodes may be involved [see Figure 2]. EUS is unique among imaging modalities in its ability to image the gastric wall as a five-layer structure, with each layer correlating with an actual histologic layer.³² The overall accuracy of EUS in determining the extent of infiltration ranges from 67 to 92%.³³ EUS features that suggest lymph node metastasis include a rounded shape, hypoechoic patterns, and a size larger than 1 cm. In one study comparing preoperative findings from EUS with pathologic findings at operation, EUS was 100% sensitive for N0 disease and 66.7% sensitive for N1 disease.³⁴ EUS also allows identification and aspiration of small-volume ascites. If cytologic study of the ascitic fluid so obtained confirms the presence of malignant cells, the patient is considered to have metastatic disease and therefore is not eligible for curative-intent surgery. For all of these reasons, EUS is now widely accepted as superior to conventional CT in the regional staging of gastric cancer.⁹

The ultimate goal of any staging evaluation is to ensure that patients with metastatic disease are not treated with nontherapeutic laparotomy or other local therapies (e.g., radiation therapy), which are generally ineffective against advanced disease. Even small-volume metastatic disease identified on the surface of the liver or the peritoneum at laparotomy is associated with poor survival: in one study, patients with such disease had a life expectancy of only 6 to 9 months.³⁵ In these situations, there is little to be gained from attempts at palliative resection.

Staging laparoscopy has proved to be highly relevant to the evaluation of patients with gastric cancer. In a study from the Memorial Sloan-Kettering Cancer Center (MSKCC), the investigators performed laparoscopic exploration on 110 of 111 patients with newly diagnosed gastric cancer.³⁶ Of these 110 patients, 94% were accurately staged, with a sensitivity of 84% and a specificity of 100%, and 37% were found to have subclinical metastatic disease. Hospital stay was substantially shorter in the 24 patients who underwent diagnostic laparoscopy with biopsy only (average 1.4 days) than in comparable patients who underwent exploratory laparotomy

Table 2 American Joint Committee on Cancer Staging of Gastric Carcinoma, 7th Edition⁹⁶

Stage	Tumor	Node	Metastasis
0	Tis	N0	M0
IA	T1	N0	M0
IB	T1 T2	N1 N0	M0 M0
IIA	T1 T2 T3	N2 N1 N0	M0 M0 M0
IIB	T1 T2 T3 T4a	N3 N2 N1 N0	
IIIA	T2 T3 T4a	N3 N2 N1	M0 M0 M0
IIIB	T3 T4a T4b T4b	N3 N2 N1 N0	M0
IIIC	T4a T4b T4b	N3 N2 N3	
IV	Any T	Any N	M1

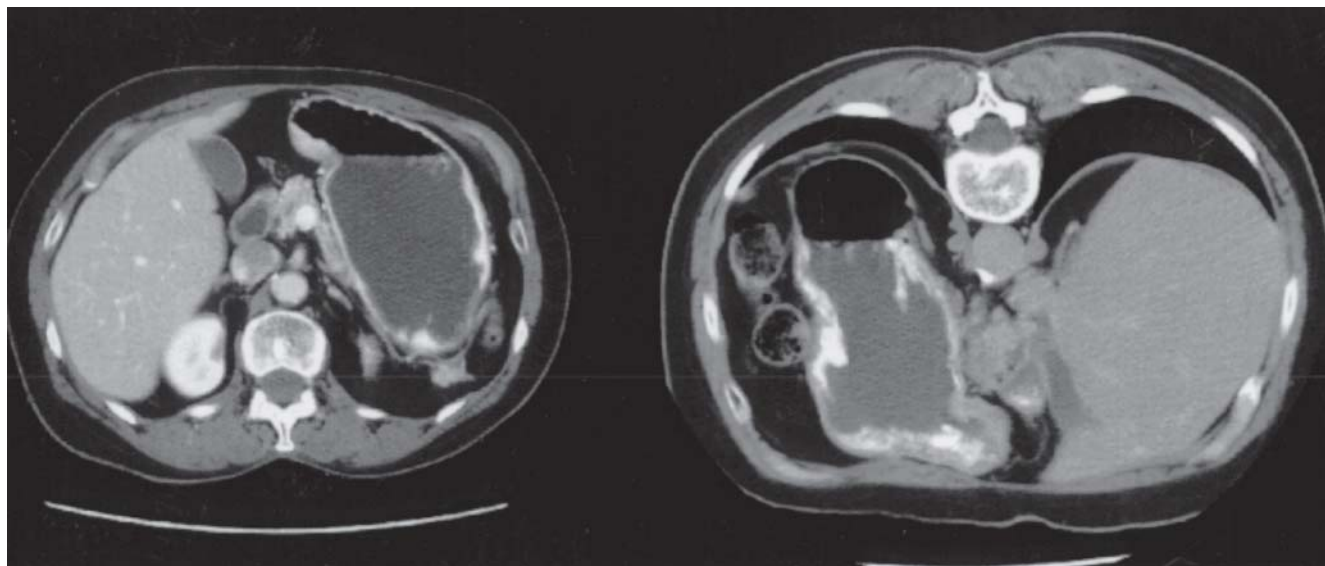


Figure 1 Shown is a computed tomographic scan of a patient with advanced gastric carcinoma. Water (a negative contrast agent) has been used to distend the stomach. The images were acquired with the patient in the prone position to allow the stomach to fall away from the retroperitoneum and to define the interface between the stomach and pancreas.

without resection (average 6.5 days). Finally, at the time the data were reported, none of the patients who underwent laparoscopy had required palliative surgery. Subsequent single-institution series confirmed the utility of staging laparoscopy, reporting accuracy rates ranging from 95 to 97% and occult M1 disease rates approaching 30%.^{37,38} Taken as a whole, the data are compelling and have led the NCCN to encourage laparoscopic staging strongly, either before or at the time of the planned resection.³⁹

MANAGEMENT

Surgical Therapy

Surgical resection remains the only potentially curative therapy for localized gastric cancer [see Figure 3]. Cure requires removal of all gross and microscopic disease. More specifically, a margin-negative (R0) resection entails wide local excision of the primary tumor with en bloc removal of all associated lymphatic vessels and any local or regional

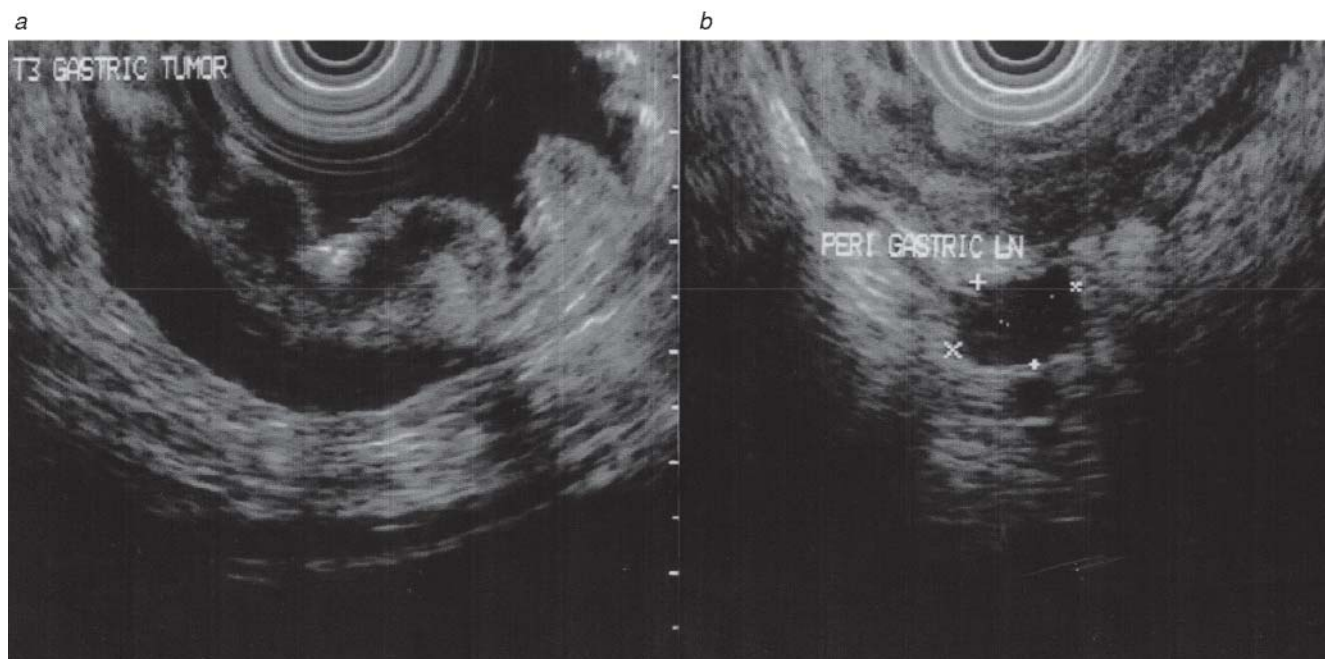


Figure 2 (a) Shown is an endoscopic ultrasonographic (EUS) image of a T3 gastric neoplasm. (b) EUS reveals the presence of suspicious perigastric (N1) nodes, later confirmed as malignant at operation.

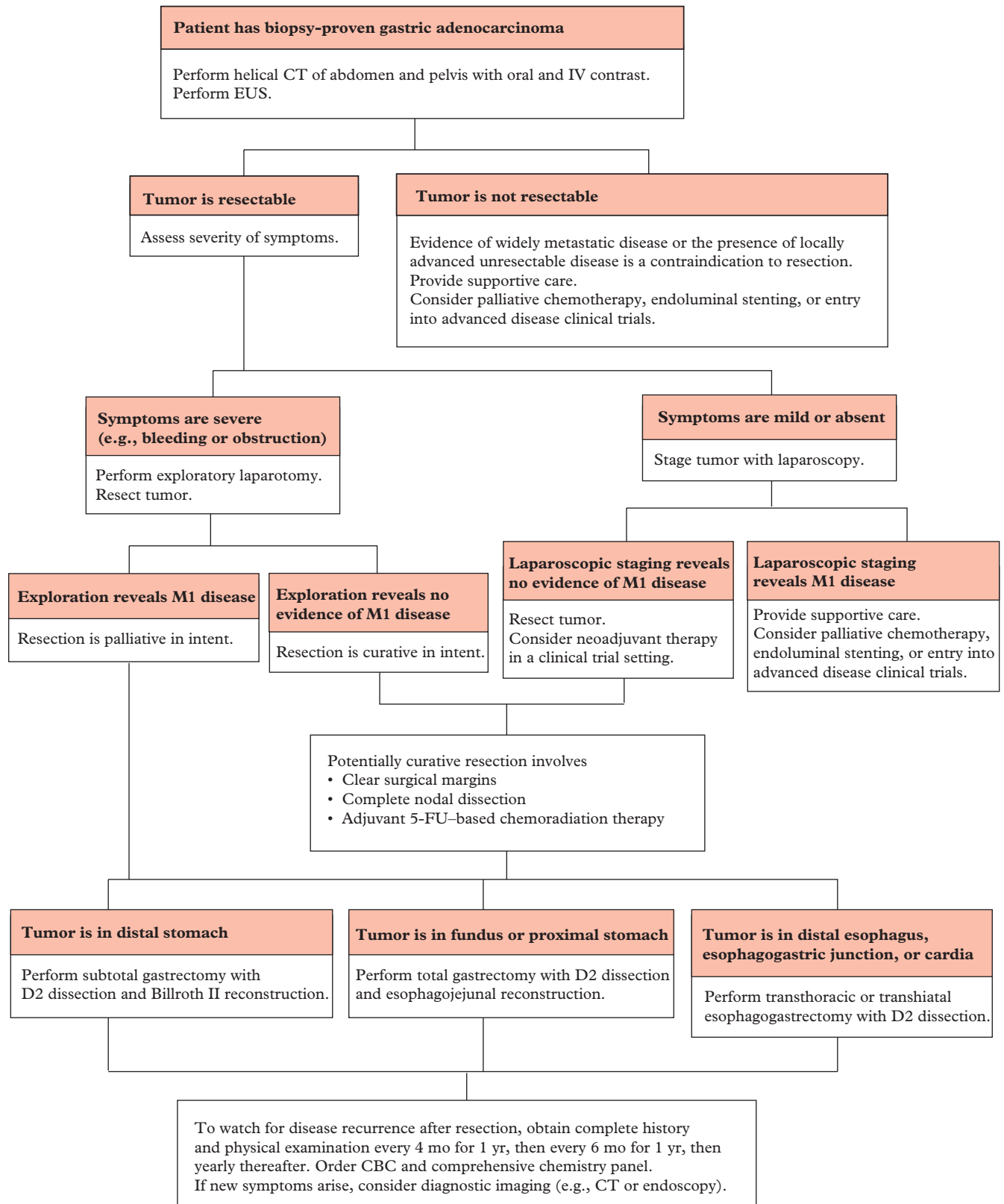


Figure 3 Algorithm illustrating the workup and treatment of a patient with gastric carcinoma. CBC = complete blood cell count; CT = computed tomography; EUS = endoscopic ultrasonography; 5-FU = 5-fluorouracil.

extension of disease. The downside of surgical resection as a sole modality of therapy is that it has a high rate of relapse. Consequently, several areas of surgical treatment of stomach cancer remain subject to controversy. In particular, the extent of gastric resection, the extent of lymph node dissection, the optimal approach to proximal stomach lesions, and the role of splenectomy and adjacent organ resection continue to generate significant debate. Moreover, recent single-center studies have demonstrated the feasibility of laparoscopic resection, although this approach is still investigational and not considered the standard of care in the United States.^{40,41}

Extent of gastric resection R0 resection (i.e., resection of all gross disease with microscopically negative margins) has been shown to have a clear impact on overall survival after potentially curative surgery. In the German Gastric Cancer Study, a prospective multicenter observational trial, the calculated 10-year survival rate in the entire population was 26.3%, compared with 36.1% in patients who underwent an R0 resection.⁴² In a large multi-institution adjuvant therapy trial, 19% of patients underwent an R1 resection (i.e., had resection-line involvement); only 9% of patients with stage I, II, or III disease and resection-line involvement survived beyond 5 years, compared with 27% of those who underwent an R0 resection.⁴³ Given the propensity of tumor for submucosal spreading, many authors consider proximal margins of 5 to 6 cm, with routine frozen-section analysis, to be optimal.^{44,45} A nomogram has been constructed and validated that predicts disease-specific survival, accounting for various clinicopathologic features after an R0 resection for gastric cancer.⁴⁶

In an effort to lower the positive margin rate, some surgeons have proposed that total gastrectomy be considered the operation of choice for all operable gastric cancers. This approach, originally based on historical data from single institutions, has been tested in three clinical trials. In the first trial, elective total gastrectomy was compared with subtotal gastrectomy as curative-intent therapy for adenocarcinoma of the antrum.⁴⁷ Elective total gastrectomy did not increase mortality, but it also did not improve 5-year survival (which was 48% in both treatment arms). In the second trial, patients with antral cancer were randomly assigned to undergo either subtotal gastrectomy or total gastrectomy with extended lymph node dissection (ELND) and en bloc distal pancreatectomy and splenectomy.⁴⁸ Total gastrectomy was associated with increased operative time, greater transfusion requirements, and longer hospital stay; however, median survival was significantly better in the subtotal gastrectomy group (1,511 days versus 922 days). In the third trial, the investigators concluded that subtotal gastrectomy should be the procedure of choice for cancer of the distal half of the stomach, provided that an adequate negative proximal margin can be achieved.⁴⁹ This conclusion was based on their finding that 5-year survival was essentially equivalent in the two groups studied (65.3% in the subtotal gastrectomy group versus 62.4% in the total gastrectomy group).

Options for proximal gastric cancer As noted (see above), adenocarcinoma of the gastric cardia and the esophagogastric junction appears to be clinically distinct from adenocarcinoma of the distal stomach,⁵⁰ and its incidence is

currently escalating across all races and age groups. Accordingly, it is imperative that surgeons understand the surgical options for treatment of proximal gastric cancer.⁵¹

For tumors originating from the distal esophagus, esophagectomy—either transhiatal esophagectomy with a cervical anastomosis or transthoracic (Ivor-Lewis) esophagectomy with a thoracic anastomosis—is clearly the procedure of choice. For tumors of the cardia, it has been suggested that esophagogastrectomy might offer a survival advantage over total gastrectomy with an esophagojejunal anastomosis. This suggestion was evaluated in a study of 1,002 patients with adenocarcinoma of the esophagogastric junction.⁵² The investigators divided tumors into three types on the basis of the location of the tumor center—cancers of the distal esophagus (type I), cancers of the cardia (type II), and cancers of the subcardial fundus (type III)—and analyzed the demographic and long-term survival data. Operative mortality proved to be higher with esophagogastrectomy than with extended total gastrectomy. Furthermore, R0 resection and lymph node status were found to be the dominant prognostic factors influencing survival. Finally, in patients with type II lesions, the pattern of lymphatic spread was primarily to paracardial, lesser curvature, and left gastric node groups. These data, taken together, led the authors to conclude that total gastrectomy is preferable to esophagogastrectomy in this setting if a margin-negative resection can be achieved.

An alternative approach to treating proximal gastric cancer is to perform a proximal subtotal gastrectomy. To date, no prospective studies have compared this method with total gastrectomy or transhiatal esophagogastrectomy for esophagogastric junction tumors, but surgeons from the MSKCC have published their retrospective experience with 98 patients who underwent either total gastrectomy or proximal subtotal gastrectomy for proximal gastric cancer over a 10-year period.⁵³ There were no significant differences between the groups with respect to morbidity, mortality, or 5-year survival in selected patients. It remains to be seen whether such excellent results can be achieved at other centers.

Thus, the evidence at present does not support routine performance of total gastrectomy for lesions of the distal fundus or antrum, provided that histologically negative margins are achievable without compromise of the gastric inlet. Our current practice is to perform a subtotal gastrectomy with Billroth II reconstruction for tumors of the distal stomach, a total gastrectomy with Roux-en-Y esophagojejunostomy for most cancers of the fundus and the proximal stomach, and either a transthoracic esophagogastrectomy or a transhiatal esophagogastrectomy with gastric interposition for tumors of the esophagogastric junction and the cardia.

Extent of lymph node dissection Over the past two decades, few topics in the surgical literature have generated more debate than the optimal extent of regional lymphadenectomy for gastric cancer. In Japan, where radical surgery for gastric cancer is now universally accepted, the JRS GC has codified the extent of lymphatic dissection according to the level of nodes dissected.⁵⁴ A D1 lymph node dissection involves resection of the perigastric lymph nodes along the greater and lesser curvature of the stomach. A D0 dissection is anything less than a D1 dissection. A D2 dissection entails resection of the D1 nodes in addition to nodes along the

common hepatic artery, the left gastric artery, the celiac axis, and the splenic artery. A D3 lymph node dissection adds resection of nodes in the hepatoduodenal ligament and the root of the mesentery. Finally, a D4 resection calls for a D3 dissection plus resection of the retroperitoneal para-aortic and paracolic lymph nodes.⁵⁵ The JRS GC defines a curative operation as a gastric resection that includes lymph nodes one level beyond the level of pathologic nodal involvement. Thus, in Japan, a D2 lymph node dissection is considered the standard resection for even relatively early cancers, and numerous studies have cited the benefits of D3 and even D4 lymphadenectomy for advanced carcinoma.^{56–58}

Western surgeons have been reluctant to embrace radical lymphadenectomy, arguing that it has yet to demonstrate an unequivocal survival advantage in any prospective, randomized trial from a Western institution or cooperative group. Detractors further argue that the survival advantage associated with more radical procedures simply reflects stage migration, a higher incidence of early gastric cancers, and differences in tumor biology and body habitus between Japanese and Western populations and point to the increases in operating time and morbidity that often accompany extended gastric resections. One retrospective review of the tumor registries of over 2,000 hospitals in the United States found that D2 lymph node dissection had no survival advantage over D1 lymph node dissection in terms of either the median survival time or the 5-year survival rate.⁵⁹

Two prospective trials from Western Europe examined this issue further in an effort to evaluate the safety and efficacy of ELND. In the Dutch Gastric Cancer Group trial, 711 patients were randomly assigned to undergo either D1 or D2 lymphadenectomy as part of a potentially curative gastrectomy for biopsy-proven adenocarcinoma.⁶⁰ This trial was unique in its use of extensive quality control measures, which included instruction and operative supervision by an expert gastric cancer surgeon from Japan (who also assisted with the processing and pathologic examination of the surgical specimens). Patients without evidence of disseminated metastases underwent either total gastrectomy or, if 5 cm proximal margins could be obtained, distal gastrectomy. In this study, a D2 lymph node dissection entailed distal pancreatectomy and splenectomy. Both morbidity and mortality were significantly higher in the D2 group than in the D1 group, and D2 dissection conferred no demonstrable survival advantage at a median follow-up of 72 months.

In a trial from the Medical Research Council in the United Kingdom, 400 patients with stage I to IIB disease were randomly assigned to undergo either a D1 or a D2 lymph node dissection.⁶¹ There was no significant difference in overall 5-year survival between the two arms, but multivariable analysis demonstrated that clinical stages II and III, advanced age, male sex, and removal of the pancreas and the spleen were independently associated with poor outcome. The authors concluded that the classic Japanese D2 dissection offered no survival advantage over D1 dissection. However, they hypothesized that D2 dissection with preservation of the distal pancreas and the spleen might lead to decreased morbidity and mortality within the extended resection group and thus potentially to superior outcomes.

Further support for this hypothesis was provided by two nonrandomized trials from specialized centers. The Italian

Gastric Cancer Study Group (IGCSG) completed a phase II multicenter trial designed to evaluate the safety and efficacy of pancreas-preserving D2 lymph node dissection.⁶² Quality control measures included supervision by a surgeon who had studied the technique of D2 lymph node dissection at the National Cancer Center Hospital in Tokyo. At a median follow-up time of 4.38 years, the overall morbidity rate for D2 dissection in the 191 patients enrolled was 20.9% and the in-hospital mortality was 3.1%. The 5-year survival rate among eligible patients was 55%. In a prospective series of 125 patients undergoing standardized D2 lymph node dissection at a single Western center, the investigators reported a mortality of 1.37% and an overall morbidity rate of 33.5%.⁶³ As in the IGCSG study, distal pancreatectomy was avoided in all cases, except when direct extension was suspected on the basis of macroscopic findings (5.5% of cases). Overall 5- and 10-year survival rates for this highly selected cohort were 52.3% and 40%, respectively. These studies suggest that D2 lymph node dissection may be safely performed in Western centers when accompanied by careful selection of patients, strict standardization of technique, and a strategy of pancreatic preservation.

Current AJCC guidelines state that pathologic examination of at least 15 lymph nodes is required for adequate staging.²⁸ Specifically, examination of at least 15 nodes is required to confidently deem a patient free of nodal metastases. However, multiple studies have demonstrated inadequate nodal assessment that is somewhat related to hospital type.⁶⁴ In an effort to confirm the benefit of this staging system, investigators from the MSKCC reviewed their experience with 1,038 patients who underwent R0 resection for gastric cancer.⁶⁵ The location of positive lymph nodes (within 3 cm of the primary tumor versus more than 3 cm away) did not significantly affect median survival; however, the number of positive lymph nodes had a profound effect on survival. Furthermore, in cases in which at least 15 nodes were examined (27% of the total), the median survival for patients with metastasis in one to six regional lymph nodes, metastasis in seven to 15 regional lymph nodes, and metastasis in more than 15 regional lymph nodes was significantly longer than the median survival reported in cases in which 14 or fewer nodes were resected with the specimens. These findings are consistent with published data from our own institution (Northwestern University Feinberg School of Medicine), which indicate that the number of positive lymph nodes is a highly significant predictor of survival.⁶⁶ In our series of 110 patients, those with seven or more positive lymph nodes had a median disease-free survival (DFS) of 17.6 months, whereas those with six or fewer positive nodes had a median DFS of 44 months. Data from other centers support this view as well.

It is our current practice to perform a D2 lymph node dissection with resection of all perigastric lymph nodes along the greater and lesser curvatures of the stomach, as well as those along the common hepatic artery, the left gastric artery, the celiac axis, and the splenic artery. We make every attempt to preserve the tail of the pancreas and spleen, with multivisceral resection reserved for cases of overt direct extension of malignant disease in the absence of disseminated metastasis. This strategy should provide adequate staging in terms of the AJCC guidelines, minimize morbidity, and possibly confer a

survival advantage on certain patient subgroups, as suggested by the results of the trials mentioned.

Role of splenectomy Routine splenectomy has been proposed as a means of facilitating clearance of metastatic nodes along the splenic artery and in the splenic hilum, but there is little evidence to support this practice in the treatment of proximal gastric cancers. Indeed, numerous studies have documented the deleterious effect of splenectomy when it is performed as part of an extended gastric resection.

In a retrospective study of 392 patients who underwent curative gastrectomy at a high-volume cancer center, the impact of splenectomy on survival and postoperative morbidity was evaluated.⁶⁷ Splenectomy was not predictive of death on multivariable analysis, but complications were far more frequent in patients who underwent splenectomy as part of surgical treatment than in those who did not (45% versus 21%). Specifically, the incidence of infectious complications was far higher in the splenectomy group than in the nonsplenectomy group (75% versus 47%).

In a review of data from an American College of Surgeons Pattern of Care Study, the investigators reported that the operative mortality was 9.8% in patients who underwent splenectomy during gastric resection, compared with 8.6% for those who did not.⁶⁸ More significantly, the 5-year observed survival rate was 20.9% in the splenectomy group, compared with 31% in the nonsplenectomy group.

In a randomized, prospective trial, early and late results of total gastrectomy alone were compared with those of total gastrectomy plus splenectomy in patients being treated for cancers of the upper third of the stomach.⁶⁹ All patients underwent a D2 lymph node dissection. The operative mortalities and the 5-year survival rates were similar in the two groups, but the splenectomy group had more infectious complications. Specifically, the splenectomy group had higher incidences of pulmonary complications, postoperative fever higher than 38°C (100.4°F), and subphrenic abscess formation. We agree with the conclusions of the authors of this study: routine splenectomy does not increase survival and should be reserved for situations in which the gastric tumor directly invades the splenic hilum or there is evidence of gross nodal metastases along the splenic artery.

Nonsurgical Therapy

Adjuvant therapy As noted (see above), the majority of patients who present with gastric carcinoma and undergo potentially curative surgical treatment will experience locoregional failure, distant metastasis, or both and will succumb to their disease. Accordingly, numerous adjuvant approaches—including chemotherapy, radiotherapy, chemoradiation, immunochemotherapy, and intraperitoneal chemotherapy—have been tried in gastric cancer patients with the aim of improving overall survival and DFS. The results, for the most part, have been disappointing.

The results from prospective, randomized, controlled trials of adjuvant radiation therapy in this setting have failed to establish a survival benefit. In a multi-institutional trial from 1994, patients were randomly assigned to undergo surgery alone, surgery plus adjuvant radiation, or surgery plus adjuvant multiagent chemotherapy.⁷⁰ There was no significant

benefit to either adjuvant regimen: overall 5-year survival was 20% for surgery alone, compared with 12% for surgery plus radiation therapy and 19% for surgery plus chemotherapy.

The results from trials of chemotherapy alone have been equally unsatisfactory. Because of the established inefficacy of single-agent 5-fluorouracil (5-FU) therapy, combination chemotherapy regimens have been employed. Such regimens have included nitrosourea compounds, mitomycin C, anthracyclines, and members of the cisplatin family.²³ In a meta-analysis of 13 trials comparing adjuvant chemotherapy with observation in non-Asian countries, the odds ratio for death in the treated group was 0.8, corresponding to a relative risk of 0.94.⁷¹ This result did not, however, reflect a statistically significant improvement. Most oncologists have now abandoned the use of chemotherapy by itself in the adjuvant setting.

In an effort to derive greater therapeutic benefit than can be achieved with either radiation therapy or chemotherapy alone, combination chemoradiation therapy has been used in the adjuvant setting. In Intergroup Trial 0116, 556 patients who had undergone R0 resection of adenocarcinoma of the stomach or the esophagogastric junction were randomly assigned to treatment with either surgery alone or surgery plus postoperative chemoradiotherapy.⁷² Patients with tumors ranging from stage IB to stage IVM0 were included; the majority had T3 tumors and node-positive disease. The therapeutic regimen consisted of 5-FU and leucovorin therapy administered concomitantly with 45 Gy of external-beam irradiation over a period of 5 weeks. Median overall survival in the surgery-only group was 27 months, compared with 36 months in the surgery-chemoradiation group. In addition, the 3-year survival rate was 41% in the surgery-only group, compared with 50% in the chemoradiotherapy group. The hazard ratio for death in the surgery-only group compared with the chemotherapy group was 1.35.

In the United States, the results of Intergroup Trial 0116 have led to the acceptance of combined chemoradiation therapy as standard adjuvant therapy for patients who have undergone curative-intent resection of gastric cancer. Nonetheless, numerous criticisms of this trial have been expressed. Specifically, a review of the operative and pathology reports of 453 of the patients revealed a lack of surgical standardization.⁷³ When the extent of lymphadenectomy was categorized, the majority (54.2%) of the patients were found to have undergone a D0 resection; 38.1% underwent a D1 resection, and only 7.5% underwent a D2 or D3 lymph node dissection. These findings suggest that the main effect of the chemoradiation therapy may have been simply to compensate for inadequate surgery. This suggestion is supported by the observation that the number of patients with local and regional recurrences was higher in the surgery-only group (178 versus 101), whereas the number of patients with distant failure was slightly higher in the adjuvant therapy arm (40 versus 32). Furthermore, when the Maruyama Index of Unresected Disease (a computer model developed for accurate prediction of nodal station involvement in gastric cancer) was applied to the 556 patients eligible for the Intergroup trial, the median Maruyama Index was 70.⁷⁴ This value was far above the level considered to represent optimal surgical therapy (i.e., Maruyama Index < 5) and led the authors to conclude that the vast majority of patients in the trial had been surgically undertreated.

Currently, physicians, especially in Europe, generally avoid adjuvant therapy after R0 resection of gastric cancer, except under the auspices of a clinical trial.⁹ The Radiation Therapy Oncology Group has initiated a phase II trial of adjuvant chemoradiotherapy using 45 Gy of external beam radiation therapy with cisplatin and paclitaxel, with or without 5-FU. If promising results are found, a phase III trial will follow. It is hoped that ongoing trials will shed further light on this complex management issue.

Neoadjuvant therapy As a response to the disappointing results of adjuvant therapy and the inability of many patients to regain adequate performance status after radical gastric surgery to undergo systemic therapy, neoadjuvant protocols have been proposed.⁷⁵ The theoretical benefits of a neoadjuvant treatment strategy include treatment-induced tumor downstaging, which may enhance resectability, and early administration of systemic therapy, which allows almost all patients to receive and complete the prescribed treatment. Furthermore, because treatment is administered when measurable disease is present, the response to therapy may be assessed and continued only in patients who are likely to benefit. Finally, patients found to have rapidly progressive disease during preoperative chemotherapy may be spared having to undergo a nontherapeutic gastrectomy.⁷⁶

In a report of three phase II trials from the M.D. Anderson Cancer Center encompassing 83 patients who received neoadjuvant chemotherapy before planned surgical resection, the clinical response rates ranged from 24 to 38%, with three patients (4%) exhibiting a complete pathologic response.⁷⁶ Sixty-one patients (73%) were able to undergo a curative-intent resection, and the response to chemotherapy was the only significant predictor of survival on multivariable analysis.

Preoperative chemoradiation therapy has also been shown to be feasible in phase II trials. In a 2001 trial that included 23 patients, 96% of the study population received combined modality therapy.⁷⁵ Nineteen patients (83%) were able to undergo surgical resection with D2 lymphadenectomy; four patients (17%) had progressive disease and did not undergo resection. Morbidity and death rates were acceptable (32% and 5%, respectively), and 11% of patients exhibited complete pathologic responses. Overall, 63% of patients showed pathologic evidence of a significant treatment effect.

Newer neoadjuvant strategies employ multiagent induction chemotherapy followed by chemoradiotherapy and planned gastric resection in patients with locally advanced but potentially resectable gastric cancer.⁷³ Based on the results of the Intergroup Trial 0116, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial was developed to determine whether neoadjuvant epirubicin, cisplatin, and infused fluorouracil (ECF) resulted in improved outcomes compared with surgery alone.⁷⁷ Postoperative morbidity and mortality were comparable between the two groups, but overall survival (5-year survival 36% versus 23%; hazard ratio 0.75) and progression-free survival (hazard ratio 0.66) were improved in patients who received neoadjuvant ECF. Thus, the NCCN now recommends neoadjuvant therapy for locally advanced (T3 or node positive based on EUS) gastric cancer.

FOLLOW-UP AND MANAGEMENT OF RECURRENT DISEASE

Even after gross resection of all disease with microscopically negative margins (R0 resection), recurrence of gastric carcinoma is common. Adenocarcinoma of the stomach may spread through direct extension, via lymphatic channels to regional and distant lymph nodes, or via the bloodstream to distant sites. Furthermore, once tumors have penetrated the serosa (T3), peritoneal metastasis becomes a possibility. Through autopsy series and clinical studies, certain definite patterns of locoregional failure and distant metastasis have been established. Locoregional recurrences are common in the gastric bed and the adjacent lymph nodes. Clinical and reoperative evaluation have documented recurrent disease at the anastomosis, in the retroperitoneum, or in the regional lymph nodes in 3 to 69% of patients; the incidence of recurrence may vary, depending on whether the patients had received adjuvant therapy.²³ One autopsy series documented a locoregional recurrence rate of 94% in patients treated with surgery alone. The peritoneum is ultimately involved in 17 to 50% of all patients. The most common sites of visceral metastases are the liver and the lungs.

In view of the high recurrence rates, all patients who have undergone resection should be seen for routine surveillance examinations. Currently, the NCCN recommends that a complete history and physical examination be conducted every 3 to 6 months for 1 to 3 years, every 6 months for 3 to 5 years, and then annually thereafter.³⁹ A complete blood count, serum electrolyte concentrations, imaging studies (e.g., CT), and endoscopy should be done if clinically indicated, usually in response to new symptoms. In addition, long-term vitamin B₁₂ supplementation should be initiated for patients who have undergone a proximal or subtotal gastrectomy.

Nonadenocarcinomatous Gastric Malignancies

GASTRIC LYMPHOMA

Gastric lymphoma is the second most common malignancy of the stomach, accounting for 2 to 9% of gastric tumors in the United States. Lymphomas of the stomach are of the non-Hodgkin type. The stomach is the most common site of extranodal involvement of non-Hodgkin lymphoma (NHL) and accounts for nearly 50% of all such cases.⁷⁸

Clinical Evaluation

The presenting symptoms of gastric lymphoma, like those of gastric adenocarcinoma, are nonspecific and include loss of appetite, weight loss, vomiting, and bleeding. B symptoms (e.g., fever and night sweats) are relatively rare: in one multicenter trial concerned with primary gastric lymphoma, they occurred in fewer than 12% of patients enrolled.⁷⁹ Risk factors for gastric lymphoma include *H. pylori* infection, immunosuppression after solid-organ transplantation, celiac disease, inflammatory bowel disease, and HIV infection.⁸⁰

Investigative Studies

The diagnosis is most frequently established by means of endoscopy with biopsy. Staging studies include a comprehensive blood count, a lactate dehydrogenase level, and a comprehensive chemistry panel; CT of the chest, abdomen, and pelvis; and, often, a bone marrow biopsy. All pathology slides should be reviewed by an experienced hematopathologist.⁸¹

Staging and Prognosis

Numerous staging systems have been employed to stage NHL of the GI tract. Of these, the one most commonly applied is a modification of the Ann Arbor staging system for lymphoma.⁸⁰ For surgeons, the most important determination is often whether the NHL (1) is confined to the stomach and the perigastric nodes (stage I and II disease), (2) involves other intra-abdominal nodes and organs (stage III), or (3) extends outside the abdomen (stage IV).⁸²

Management

Over the past decade, the management of patients with gastric lymphoma has undergone significant changes. Generally, there has been a shift away from surgical management, even in relatively localized cases (stages I and II).⁸³ This shift is the result not only of the documented success of chemotherapy alone for more advanced cases (stages III and IV) but also of a better understanding of the etiology of gastric lymphoma.⁸⁴ Approximately 45% of all gastric lymphomas are low-grade mucosa-associated lymphoid tissue (MALT) lymphomas.⁷⁹ The gastric mucosa is normally devoid of lymphoid tissue. It is hypothesized that MALT develops in the stomach in response to chronic *H. pylori* infection.⁸⁵

Nonsurgical therapy Low-grade MALT lymphoma usually presents as stage I or II disease and has an indolent course. Since 1993, when regression of low-grade MALT lymphoma after eradication of *H. pylori* was first reported, numerous trials have documented the efficacy of anti-*H. pylori* therapy, with complete remission rates ranging from 50 to 100%.⁷⁹ In the German MALT Lymphoma Study, the complete remission rate was 81%; 9% of patients exhibited partial responses, and 10% showed no response.⁸⁶ Low-grade lymphomas that are more advanced or do not regress with antibiotic therapy may be treated with combinations of *H. pylori* eradication, radiation, and/or combination chemotherapy.⁸⁷ For localized persistent disease, modest doses of radiation, on the order of 30 Gy, may be employed. When chemotherapy is required, multiagent regimens, such as cyclophosphamide-vincristine (Oncovin)-prednisolone (COP), are often used.

Approximately 55% of gastric lymphomas are high-grade lesions, which can occur with or without a low-grade MALT component.⁷⁹ These lymphomas are treated with chemotherapy and radiation therapy according to the extent of the disease. The cyclophosphamide-doxorubicin-vincristine (Oncovin)-prednisolone (CHOP) regimen is the one most frequently employed. In some studies, the anti-CD20 monoclonal antibody rituximab has been either added to standard therapy or used alone, with encouraging results.⁸⁸

Surgical therapy Surgical resection, once thought to be essential for the diagnosis, staging, and treatment of early-stage gastric lymphoma, now is used mainly in patients who experience bleeding or perforation. In the German Multicenter Study Group trial, 185 patients with stage I or II gastric lymphoma were treated either with gastrectomy followed by radiation or (in the case of high-grade lesions) chemotherapy plus radiation or with chemotherapy and radiotherapy alone.⁷⁹ There was no significant difference in

survival between the group receiving surgical treatment and the group receiving nonoperative therapy: overall 5-year survival rates were 82.5 and 84%, respectively. There were no perforations and only one hemorrhage (in a patient treated with chemotherapy alone). Similarly, in a single-institution, prospective, randomized trial comparing chemotherapy alone with chemotherapy plus surgery for stage I and II lymphoma, there were no instances of perforation and only three instances of GI bleeding in the chemotherapy group, compared with two bleeding episodes in the surgery plus chemotherapy group.⁸³

Currently, patients with early-stage high-grade gastric lymphomas are treated primarily with chemotherapy or radiation therapy; only rarely do they require surgical intervention for complications encountered during therapy. Patients with locally advanced (stage III) or disseminated (stage IV) gastric lymphoma are clearly best treated with chemotherapy, with or without radiation. Occasionally, surgery is indicated in such patients to treat residual disease confined to the stomach or to palliate bleeding or obstruction that does not resolve with nonoperative therapy. Primary surgical therapy is to be avoided in these patients because of the significant risk of complications and the delay in initiating systemic therapy.

GASTROINTESTINAL STROMAL TUMOR

Gastrointestinal stromal tumor (GIST), although relatively rare in absolute terms, is the most common sarcoma of the GI tract,⁸⁹ with approximately 6,000 cases reported each year in the United States alone. The stomach is the most common site of involvement, accounting for 60 to 70% of cases⁹⁰; the small intestine (25%), the rectum (5%), the esophagus (2%), and a variety of other locations account for the remainder. On the basis of their appearance on light microscopy, GISTs were once thought to be of smooth muscle origin, and most were classified as leiomyosarcomas.⁹¹ Thus, extended gastric resection, often including contiguous organs, was advised. Recurrence developed after R0 resection in approximately 50% of cases.⁹² With the advent of immunohistochemistry and electron microscopy, it became clear that GIST has both smooth muscle and neural elements, and the cell of origin is now believed to be a precursor of the interstitial cells of Cajal, an intestinal pacemaker cell.⁹³ The diagnosis of GIST is secured by immunohistochemical staining for the tyrosine kinase receptor KIT (CD 117), which highlights the presence of interstitial cells of Cajal. More than 95% of GISTs exhibit unequivocal staining for KIT.⁹⁰ Approximately two thirds of GISTs also express CD34. Histologically, these tumors may exhibit a spindle cell pattern, an epithelioid pattern, or a mixed subtype.

Clinical Evaluation

The median age of incidence is 63 years, and tumors are generally between 0.5 and 44 cm in diameter at the time of diagnosis (median diameter 6 cm).⁹⁰ Mass-related symptoms (e.g., abdominal pain, bloating, and early satiety) may be present. Melena or anemia from overlying mucosal ulceration may be present as well. A small subset of patients have peritonitis as a consequence of tumor rupture and subsequent hemorrhage. Finally, many GISTs are discovered incidentally during operation, abdominal imaging, or endoscopy.

Investigative Studies

When a GIST is suspected, abdominal and pelvic imaging with either CT or magnetic resonance imaging (MRI) is indicated. Chest imaging is performed as well. Endoscopy, with or without EUS, may occasionally help with surgical planning, but because of the infrequency of mucosal involvement, it is rarely diagnostic.⁹⁴ Surgical consultation should be obtained to determine whether the lesion can be resected. If the tumor is resectable, biopsy should not be performed, because of the risk of tumor rupture and intra-abdominal dissemination. Biopsy may be required, however, if the patient has widespread disease or may be enrolling in a trial of neoadjuvant therapy. In such cases, biopsy may be performed percutaneously or at the time of EUS.

Staging and Prognosis

Although the majority of gastric GISTs have a benign course, a wide spectrum of biologic behavior has been observed. Of the prognostic factors examined to date, tumor size and mitotic rate appear to be the most valuable. If the tumor is less than 2 cm in diameter and the mitotic count is lower than five per high-power field (HPF), the risk of an aggressive disease course is considered to be very low. Conversely, if the tumor is larger than 10 cm, if the mitotic count is higher than 10/HPF, or if the tumor is larger than 5 cm with a mitotic count higher than 5/HPF, the risk of aggressive clinical behavior is considered to be high. For all other tumors, the risk of aggressive disease is considered to be intermediate.⁹⁰ The site of the primary tumor has also been shown to be important, with gastric GISTs having a better prognosis compared with small bowel GISTs of comparable size and mitotic rate.⁹⁵ In addition, the most recent version of the AJCC Cancer Staging Manual (7th Edition) has an added staging system for GISTs (*Table 3 and Table 4*).⁹⁶

Management

Surgical therapy The role of surgery in the treatment of a GIST is to resect the tumor with grossly negative margins and an intact pseudocapsule. Lymph node involvement is rare with GISTs; thus, no effort is made to perform ELND. The tumor must be handled with care to prevent intra-abdominal rupture. Formal gastric resection is rarely required: as a rule, it is indicated only for lesions in close proximity to the pylorus or the esophagogastric junction. The NCCN has

Table 3 American Joint Committee on Cancer TNM Clinical Classification of Gastrointestinal Stromal Tumors, 7th Edition⁹⁶

Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ
	T1	Tumor 2 cm or less
	T2	Tumor 2–5 cm
	T3	Tumor 5–10 cm
Regional lymph nodes (N)	T4	Tumor > 10 cm in greatest diameter
	NX	Regional lymph node(s) cannot be assessed
	N0	No regional lymph node metastasis
Distant metastasis (M)	N1	Regional lymph node metastasis
	M0	No distant metastasis
	M1	Distant metastasis

Table 4 American Joint Committee on Cancer Staging of Gastric and Small Bowel GISTs, 7th Edition⁹⁶

Stage	Tumor	Node	Metastasis	Mitotic Rate
Gastric				
IA	T1, T2	N0	M0	Low
IB	T3	N0	M0	Low
II	T1 T3 T4	N0	M0	High High Low
IIIA	T3	N1	M0	High
IIIB	T4	N0	M0	High
IV	Any T	N1	M1	Any rate
Small intestine				
I	T1, T2	N0	M0	Low
II	T3	N0	M0	Low
IIIA	T1 T4	N0	M0	High Low
IIIB	T2 T3 T4	N0	M0	High High High
IV	Any T	N1 Any N	M0 M1	Any rate

GIST = gastrointestinal stromal tumor.

guidelines updated annually specifically for the management of GISTs.⁹⁷

Nonsurgical therapy If the tumor has metastasized or has advanced locally to the point where surgical therapy would result in excessive morbidity, the patient is treated with the tyrosine kinase inhibitor imatinib mesylate. Imatinib is a selective inhibitor of a family of protein kinases that includes the KIT receptor tyrosine kinase, which is expressed in the majority of GISTs. Originally indicated for the treatment of chronic myelocytic leukemia, imatinib was approved for the treatment of KIT-positive GIST in 2002, when phase II clinical trials documented sustained objective responses in a majority of patients with advanced unresectable or metastatic GIST.⁹⁸ Patients with borderline resectable lesions should be treated with imatinib until they exhibit a maximal response as documented by CT and positron emission tomography (PET); surgery may then be undertaken to resect any residual foci of disease. Similarly, although patients with metastatic disease are unlikely to manifest a complete response to imatinib therapy, they should be periodically reevaluated and considered for resection should surgical treatment become technically feasible.⁹⁴

In 2009, the results of the American College of Surgeons Oncology Group (ACOSOG) phase III trial (Z9001) were reported. After resection of intermediate-risk GIST, patients were randomized to treatment with 1 year of imatinib (400 mg/day) versus placebo. Adjuvant imatinib was well tolerated. After a median follow-up of 19.7 months, patients treated with imatinib had a considerably better recurrence-free survival compared with the placebo group (98% versus 83%, $p < .0001$; hazard ratio 0.35). After resection of a

GIST, adjuvant imatinib is recommended for patients with moderate-to-high risk of recurrence.

GASTRIC CARCINOID

Gastric carcinoid tumors are rare, but this incidence is increasing. These tumors now account for approximately 10% of all GI carcinoids and 2% of all gastric tumors.^{99–101} The median age at diagnosis is 64, and the tumors are somewhat more common in women than in men.

Clinical Evaluation and Investigative Studies

Gastric carcinoid tumors are often discovered during endoscopic examination of patients experiencing chronic abdominal pain; patients may also complain of vomiting and diarrhea. These tumors are rarely associated with symptoms of the carcinoid syndrome. Diagnosis is usually confirmed by endoscopic biopsy, and EUS is helpful in determining the extent of gastric wall penetration and the degree of regional lymph node involvement.

Gastric carcinoid tumors have been divided into three types, primarily on the basis of their association (or lack thereof) with hypergastrinemia. Type I tumors are associated with chronic atrophic gastritis, are generally small (< 1 cm), and are often multiple and polypoid. They grow slowly and only rarely metastasize to regional nodes or distant sites. Type II tumors are associated with the Zollinger-Ellison syndrome and multiple endocrine neoplasia type I and, like type I tumors, are usually small and multiple. They also grow slowly but are more likely to metastasize than type I gastric carcinoids are. Type III (sporadic) gastric carcinoid tumors are the most biologically aggressive type. They are often large (> 1 cm) at the time of diagnosis and are not associated with hypergastrinemia. Type III lesions frequently metastasize to regional nodes (54%) or the liver (24%).⁹⁹

Management

For patients with small, solitary type I tumors, endoscopic polypectomy or open resection via gastrotomy (local excision) is the procedure of choice. For patients with multiple or recurrent tumors, antrectomy is indicated to remove the source of the hypergastrinemia. For patients with type II lesions, treatment is similar to that for patients with type I lesions, with the extent of gastric resection determined by the size and number of lesions. For patients with type III lesions, however, either distal or total gastrectomy with ELND is required.¹⁰² All patients undergoing a less than total gastrectomy should be followed with serial endoscopy at regular intervals.¹⁰³

Small Bowel Malignancies

Malignant tumors of the small intestine are rare, accounting for fewer than 5% of all GI tract malignancies. In the United States, approximately 6,000 new cases of small bowel cancer are reported each year.³ The majority of small bowel malignancies are carcinoid tumors, adenocarcinomas, or lymphomas,¹⁰⁴ although GISTs are being noted with increasing frequency in the small intestine. Although adenocarcinomas had traditionally been the most common tumor of the small bowel, a recent report from our group has shown that the incidence of carcinoid tumors has increased over the past

20 years and carcinoids are now the most common tumor of the small intestine.¹⁰⁵ Treatment of lymphomas, carcinoid tumors, and GISTs in the small bowel is nearly identical to treatment of the same lesions in the stomach [see Nonadenocarcinomatous Gastric Malignancies, *above*] and thus are not covered further in this chapter. Our focus here is on the presentation, diagnosis, and treatment of adenocarcinoma of the small bowel (*Table 5 and Table 6*).

CLINICAL EVALUATION

Between 46 and 55% of small bowel adenocarcinomas occur in the duodenum and approximately 13% occur in the ileum.^{97,98,104–106} Patients frequently present with nausea, vomiting, abdominal pain, weight loss, and GI bleeding; occasionally, they present with iron deficiency anemia or a positive fecal occult blood test result. In rare cases, small bowel obstruction, often with the tumor serving as a lead point for intussusception, is the first manifestation of the disease.¹⁰⁶

INVESTIGATIVE STUDIES

When an adenocarcinoma is located in the duodenum, the diagnosis is often made by means of esophagogastroduodenoscopy (EGD). Lesions within the first 100 cm of the small bowel may be evaluated with push enteroscopy. When the adenocarcinoma is situated elsewhere in the small bowel, it is localized with small bowel radiographs. Some authors consider enteroclysis to be superior to the more commonly used small bowel follow-through in this setting in that enteroclysis is better able to demonstrate fine mucosal detail.¹⁰⁷ In experienced hands, enteroclysis may therefore be more sensitive.¹⁰⁸ Some lesions are identified when CT or MRI is performed to evaluate complaints of abdominal pain. Furthermore, abdominal imaging may yield complementary staging information (e.g., the presence of regional adenopathy or metastatic disease). One new method for the identification of small bowel tumors is wireless capsule endoscopy.¹⁰⁹ This minimally invasive technique may be particularly useful in identifying small lesions in the distal jejunum and ileum that cannot be identified radiographically.

MANAGEMENT

Aggressive surgical resection remains the cornerstone of therapy for adenocarcinoma of the small intestine.¹¹⁰ For periampullary lesions, pancreaticoduodenectomy is typically required to achieve a margin-negative resection. For lesions in the distal duodenum, a segmental sleeve resection with a duodenojejunostomy is appropriate. For lesions in the jejunum or the ileum, segmental resection may be performed with a wide mesenteric resection to encompass potentially involved regional lymph nodes. Contiguous organs are resected en bloc as necessary.⁹⁹

Because the presenting signs and symptoms are often vague and nonspecific, diagnosis is often delayed. In one series, only six (11%) of the 53 patients were suspected of having a small bowel tumor at admission.¹¹⁰ In a retrospective review of patients with small bowel tumors treated at our institution, the mean duration of symptoms before surgical management was 110 months, and more than 50% of the patients were found to have stage III or IV disease.¹¹¹ In our work with the National Cancer Data Base, we found that only 24% of patients presented with metastatic disease.¹⁰⁵

Table 5 American Joint Committee of Cancer TNM Clinical Classification of Small Bowel Carcinoma, 7th Edition⁹⁶

Primary tumor (T)	TX Primary tumor cannot be assessed T0 No evidence of primary tumor Tis Carcinoma in situ T1a Tumor invades lamina propria T1b Tumor invades submucosa T2 Tumor invades muscularis propria T3 Tumor penetrates the muscularis propria into the subserosa or into the nonperitonealized perimuscular tissue (mesentery or retroperitoneum) with extension of 2 cm or less T4 Tumor perforates the visceral peritoneum or directly invades other organs or structures (includes other loops of small intestine, mesentery, or retroperitoneum > 2 cm and abdominal wall by way of serosa; for duodenum only, invasion of pancreas or bile duct)
Regional lymph nodes (N)	NX Regional lymph node(s) cannot be assessed N0 No regional lymph node metastasis N1 Metastasis in 1–3 regional lymph nodes N2 Metastasis in 4 or more regional lymph nodes
Distant metastasis (M)	M0 No distant metastasis M1 Distant metastasis

Table 6 American Joint Committee on Cancer Staging of Small Bowel Carcinoma, 7th Edition⁹⁶

Stage	Tumor	Node	Metastasis
0	Tis	N0	M0
I	T1, T2	N0	M0
IIA	T3	N0	M0
IIB	T4	N0	M0
IIIA	Any T	N1	M0
IIIB	Any T	N2	M0
IV	Any T	Any N	M1

The 5-year survival rate continues to be low (24 to 37%).^{105,111–113} Significant predictors of good overall survival include location in the jejunum, complete (R0) resection, low-grade tumors, and low AJCC tumor stage.^{105,111–113} The available evidence indicates that all patients with small bowel neoplasms should be offered an oncologically sound surgical resection. In one series, curative (R0) resection was accomplished in 51% of cases.¹¹³ No prospective data are available regarding adjuvant therapy, but the treatments and results for colon adenocarcinoma are often extrapolated to small bowel adenocarcinomas.

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9 TUMORS OF THE PANCREAS, BILIARY TRACT, AND LIVER

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Several different types of tumors affect the pancreas, the biliary tree, and the liver. Each year, hundreds of articles are published regarding pancreatic, biliary, and hepatic cancers. Accordingly, this chapter concentrates on essential principles. In particular, it focuses on common malignant tumors, addressing benign tumors and uncommon tumors only insofar as they are important in differential diagnosis.

When a patient presents with an apparent cancer of the pancreas, the biliary tree, or the liver, the surgeon must attempt to answer the following three important questions:

1. What is the diagnosis?
2. What is the surgical stage of the disease—that is, is the tumor resectable?
3. What is the operative rationale that will encompass the disease and produce a margin-free resection (and, for pancreatobiliary cancers, an N1 resection)?

These questions form the underpinning for the process of investigation and management. In what follows, we describe our approach to each of the cancers in these terms.

Pancreatic Cancer

DUCTAL ADENOCARCINOMA

Ductal Adenocarcinoma of the Head of the Pancreas

Adenocarcinoma of the pancreatic head is one of the most common gastrointestinal malignancies and, because of its aggressive nature, one of the hardest cancers to cure. The safety of surgical procedures for cancers of the pancreas has improved dramatically, but 5-year actual survival rates of patients who have undergone resection are still low (about 15%).¹ Cancer of the head of the pancreas is the prototypical tumor that causes painless jaundice; however, other cancers that obstruct the bile ducts also cause jaundice, including extrahepatic bile duct cancer, ampullary malignancy, duodenal cancer, and gallbladder cancer. Some of the following discussion is generalized to determining the diagnosis in patients presenting with obstructive jaundice [see 5:3 *Jaundice*].

Clinical evaluation *History* The classic presentation of cancer of the head of the pancreas is unremitting jaundice, usually accompanied by dark urine, light stool, and pruritus. Darkening of the urine or pruritus is often the first symptom, and scleral icterus frequently is first noted by family members

or coworkers. The pruritus is often severe. The jaundice sometimes is painless but more frequently is associated with epigastric pain, which is often mild. Severe acute pain is more often associated with other conditions that may cause jaundice (e.g., choledocholithiasis and pancreatitis). Back pain suggests that the tumor has invaded tissues outside the pancreas and is unresectable. Significant weight loss (> 10% of body weight) is common even when the pancreatic cancer is resectable.

In some patients, the presenting symptom is steatorrhea or diarrhea from obstruction of the pancreatic duct, weight loss, pain, or a combination of these rather than jaundice. Steatorrhea or diarrhea in the absence of jaundice is usually the result of a tumor in the uncinate process that obstructs the pancreatic duct but not the bile duct. Often these symptoms are overlooked until the tumor extends and causes jaundice. About 5% of patients have a history of diabetes of recent onset. Migratory thrombophlebitis (Trousseau sign) is uncommon and usually signifies metastatic disease. Pancreatobiliary malignancies cause biliary obstruction, but such obstruction is not commonly associated with biliary tract infection unless instruments have been employed in the biliary tree. Therefore, other diagnoses should be suspected in patients presenting with cholangitis who have not undergone biliary tract instrumentation. Patients with pancreatic cancer may also present with acute pancreatitis as the first manifestation. Vomiting and gastrointestinal (GI) bleeding are uncommon presenting symptoms and suggest the presence of advanced tumors that are obstructing or eroding the duodenum.

Physical examination Examination reveals scleral icterus. In some cases, the distended gallbladder may be palpable. In advanced cases, signs of metastatic disease (e.g., hepatomegaly and ascites) may be detected.

Investigative studies *Laboratory tests* Liver function tests (LFTs) are of limited value in diagnosis. The serum bilirubin level is elevated in jaundiced patients, with the direct fraction exceeding 50%. The serum alkaline phosphatase level is almost always elevated when the bile duct is obstructed, and levels three to five times normal are common. Aminotransferase levels usually are moderately elevated as well. Very high aminotransferase levels suggest a hepatocellular cause of jaundice, usually viral, although impaction of a stone in the bile duct can cause transient rises in serum aspartate aminotransferase to levels higher than 1,000 IU/mL. By themselves, LFTs cannot effectively distinguish among jaundice arising

from a hepatocellular cause (e.g., viral hepatitis or drug-induced cholestasis), jaundice resulting from a disease of microscopic bile ducts (e.g., primary biliary cirrhosis), or jaundice caused by any of the malignancies that obstruct the major bile ducts. To make this distinction, radiologic imaging tests are required [see *Imaging, below*].

Serum concentrations of the tumor marker CA 19-9 are often elevated in patients with pancreatic or biliary adenocarcinomas.² The upper limit of the normal range is 37 U/mL. Concentrations higher than 100 U/mL are highly suggestive of malignancy, but elevations between 37 and 100 U/mL are less specific. Serum levels generally reflect the extent of the tumor: small tumors (1 cm in diameter) are rarely associated with levels higher than 100 U/mL, whereas very high concentrations (> 1,000 U/mL) suggest metastatic disease. High levels may also accompany cholangitis, but these levels should subside to normal with relief of obstruction or infection, when malignancy is absent. Measurement of CA 19-9 concentrations may be employed to detect recurrences. In patients who have elevated CA 19-9 levels that return to normal after tumor resection; a second rise in the CA 19-9 level in the follow-up period is indicative of recurrence.

Imaging Several different diagnostic imaging tests may be used in jaundiced patients, including computed tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), and transabdominal ultrasonography. The technical advances in imaging achieved over the past few years are remarkable. CT and MRI can now provide high-quality images of blood vessels and ducts and their anatomic relation to tumors. These images can even be projected in three dimensions if desired, although, to date, no high level studies have shown an advantage for this type of display.

Selection of appropriate imaging tests in a jaundiced patient is influenced by patient characteristics and by the symptoms observed. For instance, the type and order of investigations appropriate for an older patient presenting with obstructive jaundice, who is likely to have a malignancy, differ from those appropriate for a young woman with severe pain, who is more likely to have choledocholithiasis. The best initial imaging test in a patient in whom malignancy is suspected is either a fine-cut (3 mm between slices) three-phase (no-contrast phase, arterial phase, and venous phase) helical (spiral) CT scan or a high-quality MRI scan. Although MRI has the advantage of being able to provide a cholangiogram (i.e., magnetic resonance cholangiopancreatography [MRCP]), small and medium-sized radiologic facilities currently tend to be more skilled at CT than at MRI; this difference should be taken into account when the first test is ordered. High-quality MRI scanners and the very latest generation of CT scanners are capable of providing cholangiograms and angiograms, as well as axial images.

The typical pancreatic cancer appears as an area of reduced attenuation (darker zone) in the pancreatic head [see *Figure 1*], associated with upstream dilatation of bile ducts and the gallbladder. Often the pancreatic duct is also obstructed. As a result, the pancreatic duct may be dilated in the tail, body, and neck of the pancreas, with dilatation terminating sharply at the edge of the tumor. Pancreatic duct dilatation is often accompanied by atrophy of the body and the tail of the pancreas [see *Figure 2*].

When a jaundiced patient is discovered to have a typical-appearing localized cancer of the pancreatic head on CT scanning, no further diagnostic tests are needed, and operative management should be the next step. Tissue diagnosis is unnecessary. Negative biopsy results rarely change the therapeutic approach, and in that they may be falsely negative, they are



Figure 1 Shown is a typical hypoattenuating cancer of the pancreatic head. The tumor (arrow) is invading the right side of the portosplenic confluence, as evidenced by the “beaking” of the vein at that point.

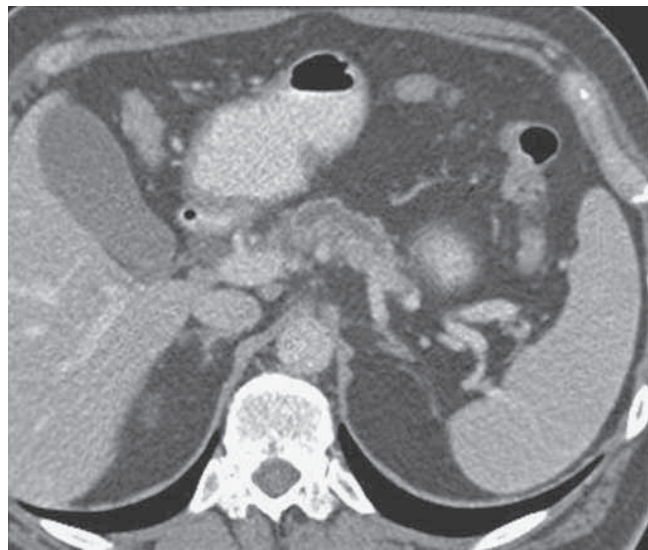


Figure 2 In the same patient as in Figure 1, pancreatic duct dilation is apparent in the body of the pancreas, with atrophy of the parenchyma.

potentially misleading. Furthermore, omitting biopsy eliminates the small risk of tumor implantation in the needle tract. Selection of axial imaging as the first test often renders diagnostic ERCP, which is a more invasive test, unnecessary as well. Cholangiography also is not required for staging pancreatic head tumors [see Surgical Staging, below]. The advantages of starting with axial imaging in jaundiced patients with suspected cancer are discussed in greater detail elsewhere [see Biliary Tract Cancer, Extrahepatic Cholangiocarcinoma, Upper Duct Cholangiocarcinoma, Investigative Studies, below].

Additional diagnostic imaging for atypical CT or MRI findings In many patients with adenocarcinoma of the pancreatic head, the typical CT findings described above are absent and additional diagnostic imaging is required. Such patients may be categorized into two groups: those with an *atypical mass* and those with *no mass* on axial imaging. In either case, before ordering additional tests, it is appropriate to determine whether the CT scan is of adequate quality. The scan may have been performed without contrast, the arterial and venous phases may not have been captured appropriately, or the slice thickness may have been too great for precise visualization of the head of the pancreas. Small adenocarcinomas may be missed when the venous phase is poorly timed, especially if slice thickness is 5 mm or greater, and masses that initially appear atypical may exhibit a typical appearance when the CT scan is optimized. Neuroendocrine cancers commonly display arterial-phase enhancement, which will be missed if the scan is mistimed. In our experience, about 40% of referred patients who underwent CT scanning before arrival require a so-called pancreas protocol CT scan (i.e., a fine-cut three-phase helical scan) when they are first seen; in many of these cases, the second CT scan yields important diagnostic findings.

When no mass is present in a jaundiced patient with a periampullary tumor or another focal obstructing process (e.g., pancreatitis), the CT scan usually shows bile duct dilatation extending down to the intrapancreatic portion of the duct. The dilatation may terminate anywhere from the upper border of the pancreas to the duodenum, depending on the site of the tumor and the nature of the process obstructing the bile duct. In these conditions, ERCP is a good choice as the second test.

ERCP provides an endoscopic view of the duodenum that allows identification and biopsy of ampullary and duodenal tumors, which may be blocking the bile duct and producing jaundice. It confirms the presence of a bile duct stricture and displays its form, which is helpful in diagnosis. Focal strictures, especially those with shoulders, suggest malignancy. Long, tapering strictures limited to the intrapancreatic portion of the bile duct suggest chronic pancreatitis. Concomitant narrowing of the pancreatic duct in the head of the pancreas (the double-duct sign) suggests the presence of a small pancreatic cancer that is not visible on the CT scan. Longer or multiple pancreatic strictures suggest chronic pancreatitis. A single focal bile duct stricture in the absence of pancreatic duct abnormalities is the hallmark of cancer of the lower bile duct. Infiltrating cancers of the bile duct may cause more than one stricture along the bile duct, but when more than one stricture is present, other diagnoses (e.g., primary sclerosing cholangitis) should be considered. Both pancreatic and bile ducts may be assessed with brush cytology. This test

has a 45 to 50% sensitivity for cancer³; therefore, only a positive test result is significant.

ERCP findings in a patient with no mass must be evaluated in the light of findings from other investigations. Patients with the classic double-duct sign or single focal shouldered bile duct strictures are likely to have small pancreatic or bile duct tumors. Further diagnostic support is usually not needed before laparotomy, although such support may be reassuring when the CA 19-9 concentration is lower than 100 U/mL. When doubt persists, EUS often helps resolve it. EUS may identify a small mass that was not seen on the CT scan, and biopsies may then be done. Occasionally, EUS reveals enlarged lymph nodes, which may also undergo biopsy. However, negative EUS-guided biopsy results in patients who present with painless jaundice do not exclude malignancy. When such patients have an identifiable mass on EUS and a presentation in keeping with the diagnosis of cancer, pancreaticoduodenectomy is recommended, even if EUS-guided biopsy yields negative results. If a nonoperative approach is taken, short-term follow-up at 4 to 6 weeks with repeat imaging and biopsy is mandatory. If the findings persist, laparotomy is advisable.

Occasionally, preoperative testing reveals no mass, but a mass is subsequently discovered by intraoperative palpation or intraoperative ultrasonography (IOUS). A mass palpated in the head of a pancreas that is otherwise normal or near normal in texture in the remainder of the gland is highly suggestive of malignancy and constitutes sufficient justification for resection. The same is true of a mass detected by IOUS if the mass has characteristics of malignancy (i.e., is hypoechoic). If the IOUS findings are inconclusive, biopsy with frozen-section examination is a reasonable approach. In many such cases, the whole pancreas is diffusely firm or hard, and IOUS demonstrates a diffuse change in the normal texture of the gland. When the pancreas is diffusely firm and no localized process is seen on IOUS, biopsies should be directed toward the stent in the bile duct at the point where the bile duct narrows (as seen on ultrasonography).

The ultimate diagnostic test is pancreaticoduodenectomy. If there is a strong suspicion of cancer before laparotomy or the findings at laparotomy are strongly suggestive, this procedure should be performed without preliminary biopsy. When this approach is followed, a small number of patients with suspected malignant disease will be found to have benign disease; this possibility should be explained to patients who do not undergo confirmatory tissue diagnosis before operation. Because of the limited negative predictive value of currently available tests, pancreaticoduodenectomy is sometimes still required to make a definitive diagnosis.

The finding of an atypical pancreatic head mass on a CT scan poses an additional challenge. Atypical masses may take different forms. In some cases, they exhibit attenuation that differs only slightly from that of the surrounding pancreas; in others, they have a ground-glass appearance. They may extend into the body and tail of the pancreas, or they may be localized to the head. With atypical masses, the most common problem is how to differentiate focal pancreatitis from adenocarcinoma. This differentiation can be very difficult. Pancreatitis may be present without antecedent acute attacks; without a history of alcoholism, gallstones, or hyperlipidemia; without diabetes or steatorrhea; and without calcifications in the

gland. Cancer appears to be more common in patients who have had chronic pancreatitis, and the diseases may coexist. Therefore, one cannot feel confident that cancer is absent simply because chronic pancreatitis is present. Cancer should be suspected in patients with an established diagnosis of chronic pancreatitis who undergo a rapid change in status (e.g., weight loss). Diabetes is common in patients with chronic pancreatitis, but it may also be the first sign of pancreatic cancer in patients without chronic pancreatitis. Chronic pancreatitis can cause painless jaundice. A rare immune form of chronic pancreatitis, known as lymphoplasmacytic sclerosing pancreatitis, has been recognized that is particularly hard to differentiate from cancer.⁴ However, in these patients, the serum IgG4 level is characteristically elevated.

EUS is becoming increasingly important in the management of patients with atypical pancreatic head masses.⁵ When jaundice is present, EUS with or without ERCP is our usual approach; when it is absent, EUS alone is performed. EUS-guided biopsy is superior to CT-guided transabdominal biopsy in that access to the head of the pancreas is easier and the chance of needle tracking is reduced (because the biopsy is taken through the duodenal wall, which is resected if a Whipple procedure is done).

At the conclusion of all of the preceding investigations, it still may not be clear whether a malignancy is present. Clinical judgment must be exercised in deciding whether to operate or to repeat investigative studies after an interval of 2 to 3 months. Operation is favored in patients who are jaundiced, who have less pain, who have elevated CA 19-9 levels, and whose mass is suspicious for cancer. Elevation of the CA 19-9 concentration beyond 100 U/mL should be regarded as a very important finding. When EUS is inconclusive, ultrasound-guided diagnostic laparoscopy may be performed to obtain core tissue biopsies from several areas of the mass. This technique is especially useful when chronic pancreatitis is strongly suspected⁶ in that the multiple long core biopsies obtainable with this procedure provide a greater degree of assurance against false negative findings for cancer. Even this test, however, is not 100% accurate. The penultimate diagnostic test is laparotomy with mobilization of the pancreatic head and IIOUS-guided transduodenal core biopsies of the mass. The ideal outcome with this approach is to perform pancreaticoduodenectomy in all patients who actually have cancer while reducing to a reasonable minimum resection in patients with benign disease, who in most cases are better served by biliary bypass. Fortunately, today, because of improved axial imaging and EUS, a definitive preoperative diagnosis is usually available.

Surgical staging The term “staging” is currently used to denote the process by which the surgeon determines whether a tumor is resectable. We prefer to use the term “surgical staging” for this process so as to distinguish it from those staging classifications that define the life history and prognosis of tumors and provide the basis for comparison of results—namely, the TNM classifications developed by the American Joint Committee on Cancer (AJCC). These latter systems are also of great importance to the surgeon dealing with pancreatic tumors.

Surgical staging is started preoperatively and completed intraoperatively. Preoperative staging tests determine operability—that is, whether the tumor appears resectable after preoperative testing. However, the final decision regarding

resectability is made only during the operation, on the basis of intraoperative staging. A tumor of the head of the pancreas is deemed unresectable when it is determined to have extended beyond the boundaries of a pancreaticoduodenectomy. Common reasons for unresectability include (1) vascular invasion (i.e., invasion of the superior mesenteric vein, the portal vein, the superior mesenteric artery, or, less commonly, the hepatic artery); (2) lymph node metastases that fall outside the scope of a pancreaticoduodenectomy (e.g., metastases to para-aortic and celiac lymph nodes); (3) hepatic metastases; (4) peritoneal metastases; and (5) extra-abdominal metastases (usually pulmonary). Limited vascular invasion of the superior mesenteric vein and the portal vein may be overcome by resection and reconstruction and thus is only a relative contraindication to resection. This is especially true when the tumor is small and has arisen in the vicinity of the veins. In a series from our institution (Washington University in St. Louis), about 27% of resections done for pancreatic cancer involved resection of these veins.⁷ Recently, the term “borderline” has been introduced to describe tumors that are unresectable by standard criteria but that can be encompassed by extending the zone of resection.⁸ Usually, such tumors are first treated with chemoradiation. Attempts are also being made to downsize more advanced pancreatic tumors to a resectable state by chemotherapy and radiation. To date, no long-term studies have evaluated either approach. However, given the aggressive nature of this tumor, it is likely that chemotherapy and radiation will effectively downsize tumors in only a small number of patients, at least until much more effective chemotherapeutic agents are available.

The tests used to establish the diagnosis and those used to accomplish surgical staging go hand in hand. Abdominal CT scans, abdominal MRI, thoracic CT scans, and chest radiographs are obtained to detect hepatic metastases, vascular invasion, and pulmonary metastases. To assess vascular invasion, fine-cut three-phase helical CT scans or MRI scans are required. These tests may also detect enlarged lymph nodes, but it should be remembered that nodes may be enlarged for reasons other than cancer. Sometimes intraperitoneal fluid collections or peritoneal or omental nodules are identified; fluid may be sent for cytologic analysis, and omental nodules may undergo ultrasound-guided biopsy. Invasion of the mesentery, the mesocolon, or retroperitoneal tissues may also be detected by CT scanning. In the view of some surgeons, such invasion may render the tumor unresectable, but in our experience, this is rarely the case in the absence of concomitant vascular invasion: the resection may still be accomplished with clear margins by resecting the portion of the mesocolon or the mesentery that is locally invaded.

EUS may be used to guide biopsy of suspicious lymph nodes when these lie outside the planned resection zone. It has also been employed to assess vascular invasion, but in our experience, it has no advantage over CT in this regard; moreover, it is more operator dependent than CT. Staging laparoscopy is particularly effective at finding small hepatic and peritoneal nodules. About 20% of patients thought to have resectable pancreatic adenocarcinoma of the head of the pancreas before staging laparoscopy are found to have liver or peritoneal metastases at laparoscopy.⁹ Staging is completed intraoperatively by carefully inspecting the intra-abdominal

contents, including the lesser sac, mobilizing the head of the pancreas, performing biopsies of suspicious nodules or nodes outside the planned resection zone, and attempting dissection of the superior mesenteric vein or the portal vein. Formal clinicopathologic staging according to the AJCC's TNM system is useful for establishing the prognosis and planning additional treatment [see Table 1 and Table 2].

All authorities agree that axial imaging of the abdomen and chest (or roentgenography of the chest) is standard practice for staging pancreatic cancer; however, not all agree on the value of other staging tests. Many authorities advocate omission of staging laparoscopy or EUS-guided biopsy of nodes on the grounds that patients are better served by palliative surgery than by endoscopic stenting of the bile duct. There is no advantage in knowing preoperatively whether small liver metastases or celiac node metastases are present if laparotomy is to be undertaken anyway. Trials examining whether better palliation is offered by surgical bypass or endoscopic stenting report conflicting results; on balance, surgical bypass is still a very good treatment for localized unresectable tumors in younger patients without serious comorbidities. We no longer perform staging laparoscopy in patients with adenocarcinoma of the pancreas except in patients who are suspected to have liver or peritoneal metastases on axial imaging. Finally, ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful in staging pancreatic cancer. Given that inflammation is frequently confused with cancer, the major role of this modality will probably be in the detection of distant metastases.

Management *Preoperative preparation* All jaundiced patients should receive vitamin K, a fat-soluble vitamin whose absorption is reduced by biliary or pancreatic duct obstruction. Routine preoperative bile duct decompression is unnecessary, except when jaundice has been prolonged or operative

treatment will be delayed (e.g., for correction of cardiac or other comorbid conditions). Several studies have shown that surgical outcome is not improved by routine preoperative decompression in jaundiced patients. In fact, stent placement may increase the incidence of postoperative infection.¹⁰

Rationale for pancreaticoduodenectomy The technical details of pancreaticoduodenectomy are discussed more fully elsewhere [see 5:24 *Procedures for Benign and Malignant Pancreatic Disease*]. Therapeutic decision making necessarily includes consideration of the extent of the procedure. The operative goal is to remove the tumor with clear margins, as well as the N1 regional lymph nodes. Attempts have been made to improve results by extending the operation, either through more extensive lymph node dissections¹¹ or through resections of superior mesenteric, hepatic, or celiac arteries.¹² Four randomized trials have now shown no advantage for extended lymph node dissection. Resection of celiac or superior mesenteric arteries has also not been successful in improving overall survival. The lesson seems to be that invasion of additional lymph node regions (N2) or the superior mesenteric or celiac arteries signals an aggressive tumor biology that is unlikely to be overcome by wider resections. Except for resection of the portal vein or the superior mesenteric vein and perhaps short segments of the hepatic artery to address invasion of these structures by otherwise favorable tumors, extended resections are generally unsuccessful. Even these recommended vascular resections are probably best restricted to tumors that have arisen close to the particular vessels and involved them while still small; resections of large adenocarcinomas that have grown over time to involve long stretches of the veins are best avoided. These comments do not apply to tumors that initially might have required resection of the celiac or superior mesenteric arteries but that have been downsized by chemotherapy or chemoradiation so that they can be resected without such vascular resections.

There is also continuing controversy regarding the respective merits of the standard version of the operation and its pylorus-preserving variant. There is no evidence that the two procedures differ with respect to overall survival. Pylorus preservation is associated with gastric-emptying problems in the postoperative period, but, overall, it may be associated with slightly less postoperative GI dysfunction.¹³ We employ pylorus preservation selectively in older, thinner patients, with the aim of minimizing disruption of GI function.

Adjuvant therapy is often given in resected patients; however, there is controversy regarding the role of chemotherapy

Table 1 American Joint Committee on Cancer TNM Clinical Classification of Pancreatic Cancer¹

Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ
	T1	Tumor limited to pancreas, ≤ 2 cm in greatest dimension
	T2	Tumor limited to pancreas, > 2 cm in greatest dimension
	T3	Tumor extends beyond pancreas but without involvement of celiac axis or SMA
	T4	Tumor involves celiac axis or SMA
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Regional lymph node metastasis
Distant metastasis (M)	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	No distant metastasis

SMA = superior mesenteric artery.

Table 2 American Joint Committee on Cancer Staging System for Pancreatic Cancer

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1, T2, T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

versus chemoradiation. Randomized trials have shown that chemotherapy is beneficial and have questioned the role of radiotherapy. The latter may be helpful when an R1 resection has been performed.

Adenocarcinoma of Body and Tail of the Pancreas

Adenocarcinoma of the body and tail of the pancreas is less common than adenocarcinoma of the head. Because it does not produce jaundice, it tends to be recognized relatively late. Accordingly, patients are often in an advanced stage of disease at presentation. Tumors of the midbody tend to invade posteriorly to involve the superior mesenteric artery or the celiac axis, even when these lesions are only 2 to 3 cm in diameter. As a result, tumors of the tail are more likely to be resectable than tumors of the midbody when they are discovered. Many resectable tumors are discovered incidentally; by the time the tumors give rise to symptoms, they are frequently unresectable.

Clinical evaluation Symptoms are nonspecific, consisting of abdominal and back pain (which is usually relieved by sitting up and leaning forward), weight loss, and diabetes of recent onset.

Investigative studies The CA 19-9 concentration may be elevated. CT usually shows a lucent (hypoattenuating) mass [see Figure 3], often with extension outside the pancreas and dilatation of the distal pancreatic duct, when the tumor is proximal to the tail of the gland. EUS is very useful for assessing indeterminate lesions.

Surgical staging Surgical staging of cancers of the body and the tail is similar to that of cancers of the pancreatic head and is based primarily on CT scanning of the abdomen and the thorax. Unresectability by reason of local invasion is usually attributable to the involvement of the superior mesenteric artery, hepatic artery, or the celiac artery and less commonly to the involvement of the portal vein, the superior mesenteric

vein, or the aorta. Another indicator of unresectability is enlarged para-aortic nodes. Invasion of the spleen, the stomach, the left adrenal gland, the mesocolon, the colon, the retroperitoneum, or even the left kidney is not a contraindication to resection provided that clear margins may be expected.¹⁴ Staging laparoscopy is of great value: between 20 and 50% of patients with these tumors are found to have unresectable tumors with this modality, usually due to small liver or peritoneal implants.¹⁵ Cancer of the body and the tail differs from cancer of the head in that there is no effective palliation and therefore no rationale for laparotomy if the lesion is unresectable. Celiac nerve block, which is very helpful in reducing the use of narcotics for pain control, may also be performed laparoscopically or endoscopically.

Management *Rationale for radical antegrade modular pancreatosplenectomy* Logically, the goal of resection of tumors of the body and tail should be the same as that of resection of tumors of the head—namely, excision of the tumor with clear margins, along with the N1 lymph nodes. In practice, this goal generally is not achieved by the traditional retrograde distal pancreatectomy, in which the spleen is taken first and which is not based on the lymph node drainage of the pancreas. Lymph node counts have been low with the traditional procedure, and positive posterior margin rates have been high. As an alternative, we have developed a technique referred to as radical antegrade modular pancreatosplenectomy (RAMPS), which accomplishes the desired goals by performing the resection in an antegrade manner from right to left and which is based on the established lymph node drainage of the gland [see Figure 4].¹⁶ Negative tangential margin rates of 90% have been achieved with this approach. RAMPS also allows early control of the vasculature.

Mucinous Adenocarcinoma

Mucin-producing cancers are special variants of adenocarcinoma of the pancreas that often arise in preexisting lesions. The two main types of premalignant lesions are mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN) (also referred to as intraductal papillary mucinous tumor).¹⁷ A complete discussion of pancreatic cyst disease is beyond the scope of this chapter. Accordingly, we briefly address such disease as it relates to cancer of the pancreas, omitting discussion of less common cystic malignancies of the pancreas.

Mucinous cystic neoplasm MCN occurs most often in middle-aged women, typically in the body or tail of the pancreas. MCNs are unilocular or septated cysts whose diameter ranges from subcentimeter size to 15 cm or larger. Occasionally, calcium is present in the wall. Excrescences may be present on the inner wall; if so, malignancy is more likely. Most symptomatic MCNs are between 4 and 7 cm in diameter.

Clinical evaluation and investigative studies Patients with MCNs typically present with left-sided abdominal pain, often in the flank and the back. These lesions also are frequently discovered incidentally. Pancreatitis is rare and jaundice is uncommon, even when the lesions are situated in the head of the pancreas. MCNs must be differentiated from pseudocysts and from serous cystadenomas (SCAs), which are benign cysts. Differentiation between MCNs and pseudocysts is based on the history, imaging studies, and cyst fluid analysis. The diagnosis of pseudocyst is supported by a history of pancreatitis,

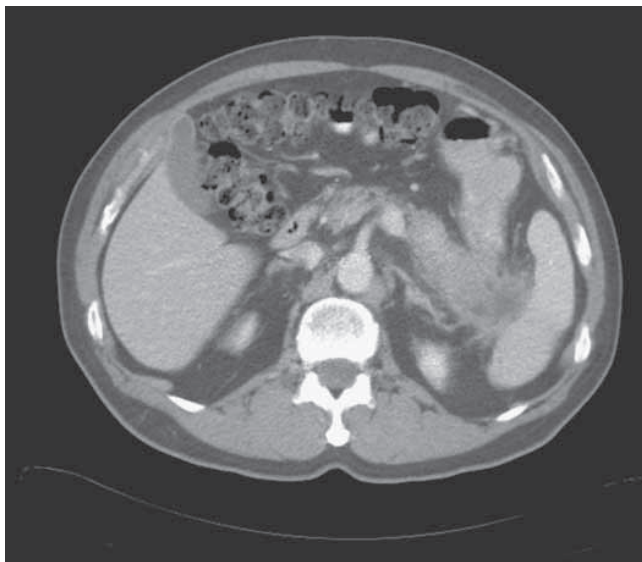


Figure 3 Shown is a typical hypoattenuating cancer of the tail of the pancreas with invasion of the hilum of the spleen and the splenic flexure of the colon. Peritumoral stranding suggests inflammation or invasion of peripancreatic fat.

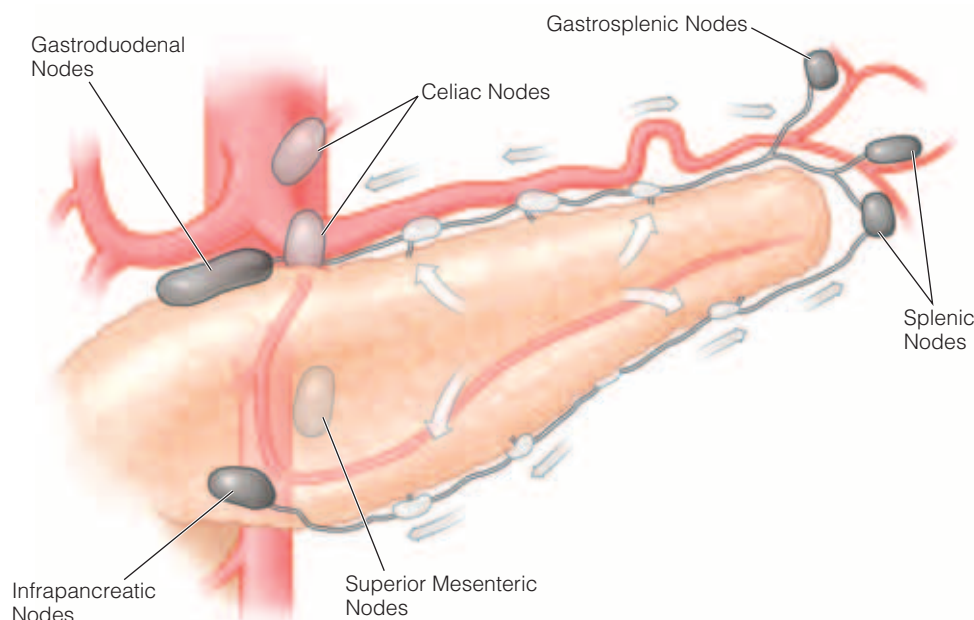


Figure 4 Illustrated is the pattern of lymphatic drainage of the pancreas. The darker nodes are N1 nodes for the body and tail of the pancreas. The lighter nodes on the aorta to the left side of the celiac artery and the superior mesenteric artery are N1 for the central part of the pancreas and N2 for other regions.

a thick-walled, uncalcified cyst with associated radiologic signs of pancreatitis and often cholelithiasis, as well as cyst fluid containing high levels of amylase and lipase and a relatively low level of carcinoembryonic antigen (CEA) (< 500 ng/mL).

SCAs have the same clinical presentation as MCNs. SCAs are more frequently polycystic than MCNs, but this difference is not a certain means of discriminating between the two. In a minority (25%) of cases, SCAs have a pathognomonic central calcification with radiating arms ringed by multiple grape-sized cysts. When the individual cysts are tiny (honeycomb pattern), there are many cyst walls within the lesion, and then SCAs may be mistaken for solid tumors. Unlike pseudocysts and IPMNs, neither MCNs nor SCAs communicate with the pancreatic duct, although they may compress it. Measurement of the CEA level in cyst fluid is a good means of distinguishing MCN from SCA. SCAs have very low levels of CEA, with the cutoff being 5 ng/mL.¹⁸ The cyst fluid obtained from MCNs is often mucinous, and cytologic assessment may show mucin-producing cells; typically, the fluid is high in CEA. The CA 19-9 concentration may also be used to distinguish MCNs from SCAs, but it is not as reliable as the CEA concentration for this purpose.¹⁸

Surgical staging Surgical staging is required when investigations suggest that MCNs are malignant. Essentially, the same methods are used as for any pancreatic adenocarcinoma (see above). Malignancy is suggested by a solid intracystic or extramural component. Sometimes a mucinous tumor is frankly malignant with a large or dominant solid component. Such a tumor is better termed a mucinous cystadenocarcinoma, and it should be evaluated and treated from the outset in the same manner as other adenocarcinomas of the pancreas.

Management In symptomatic patients, preoperative differentiation between MCNs and SCAs is unnecessary because

resection is the treatment for both. In asymptomatic patients, MCNs more than 4 cm in diameter should be excised because of the possibility of malignant degeneration.¹⁹ MCNs associated with internal excrescences or associated with a local solid mass should be removed independent of the size of the cyst.¹⁹ The standard procedure has been open distal pancreatectomy with splenectomy, although lesser procedures, such as spleen-sparing distal pancreatectomy, central pancreatectomy, and enucleation, have all been used as well. Recently, laparoscopic distal pancreatectomy with or without sparing of the spleen has emerged as the procedure of choice because of the advantages of reduced postoperative pain and shortened length of stay.²⁰ These procedures appear to be reasonable choices provided that there is no suggestion of invasive malignancy on imaging (i.e., that there are no excrescences on the inner lining and that the surrounding pancreas appears normal). In these cases, a more formal resection that obeys oncologic goals such as a RAMPS procedure should be employed. Enucleation may be associated with a higher incidence of postoperative fistula. If invasive cancer is not detected in the resected specimen, the chances that the malignancy will recur are small; in fact, we have never seen such a recurrence.

The 4 cm cutoff for surgical treatment of MCNs in asymptomatic patients¹⁹ without other signs associated with malignant degeneration is reasonable, but recommendations could change based on additional studies of natural history. Furthermore, it is still possible that malignant degeneration could occur in smaller cysts, although the probability is low. Many cysts smaller than 2 cm are found in the course of axial imaging performed for other reasons. Such cysts are difficult to diagnose because of the small volume of cyst fluid present, and the benefit to be gained from performing a large number of pancreatectomies for these small cysts is questionable, even

when they are diagnosable as MCNs. Occasionally, MCNs or symptomatic SCAs are located in the head of the pancreas and require pancreaticoduodenectomy. Some authorities feel that very large asymptomatic SCAs should also be excised because of rare instances of malignant degeneration.

Intraductal papillary mucinous neoplasm IPMN begins as a metaplastic change in the cells lining the pancreatic ducts altering from a low cuboidal serous type of cell to a mucin-producing type. These cells are prone to progress to dysplasia and eventual malignant transformation. Overall, IPMNs appear to undergo malignant transformation more frequently than MCNs. There are two recognized types of IPMN, which may occur either separately or together.^{19,21} The more common type affects the main pancreatic duct [see Figure 5] and is called “main duct IPMN.” In this type, the main pancreatic duct becomes dilated and filled with mucin. As the disease progresses toward malignancy, papillary processes may project into the lumen. The less common type, called “side-branch IPMN,” affects the smaller ducts and presents as multiple (usually small) pancreatic cysts. In either type of IPMN, the disease may be either diffuse or focal; when it is focal, the head of the pancreas is the site of disease in the majority (60%) of cases. About 20% of IPMN patients have a malignancy at the time of diagnosis, although the cancer may not be evident until the specimen is examined pathologically.

Clinical evaluation and investigative studies^{19,21} IPMN occurs predominantly in males and usually affects patients in their sixties. Pain (usually attributable to pancreatitis arising as a result of mucous obstruction of the pancreatic duct) is a common presenting symptom. Another common presentation is pancreatic insufficiency with diabetes or steatorrhea. Accordingly, it is not surprising that, formerly, many IPMN patients were diagnosed as having chronic pancreatitis. IPMN may also be discovered incidentally or may present as a cancer with signs and symptoms similar to those of other pancreatic cancers, depending on the part of the gland in which they arise. On rare occasions, cholangitis from obstruction of the common channel by mucus is the presenting problem.

The diagnosis is made on the basis of the presentation and the findings from axial imaging and ERCP. The characteristic ERCP findings are a dilated papillary orifice (“fish mouth”) with mucus bulging from the orifice and a dilated pancreatic duct when contrast is injected. Sometimes, mucus prevents complete filling of the duct with dye. In this situation, CT scans or MRI with MRCP may be quite useful for detecting ductal dilatation and atrophy of the pancreas. MRCP is best at detecting excrescences projecting from the wall of the duct into the lumen. These signal progression of the disease toward neoplasia. In side-branch IPMN, ERCP (and often MRCP) typically demonstrates communication between the cysts and the main duct, which is often normal in size; this finding is not present in MCN or SCA and is very useful for distinguishing side-branch IPMN from these other types of cysts.

Management Knowledge of this entity is evolving, and recommendations are the current ones.^{19,21–23}

Large duct IPMN As this entity is highly premalignant, resection is indicated once the diagnosis is made. Pancreatoduodenectomy is usually required as the disease affects the duct in the head of the pancreas in most cases. Although the duct in the body and tail of the gland may be dilated, this does not mean that it is involved in dysplastic changes as dilation may be secondary to obstruction caused by the viscous mucus in the proximal duct.²¹ Therefore, the decision of whether to perform a complete pancreatectomy is made at the time of pancreatoduodenectomy, based on frozen section of the transected pancreatic neck. In most cases, the frozen section will show normal ductal epithelium or only mild or moderate dysplasia. Such patients do not require more pancreas to be resected. Occasionally, carcinoma, carcinoma in situ, or severe dysplasia is found, necessitating the resection of part or all of the remaining pancreas.²¹

Small duct IPMN This entity is less likely to degenerate into malignancy, and the probability of malignant degeneration is related to size.²² Current indications for resection are cysts exceeding 3 cm in diameter or smaller cysts that are

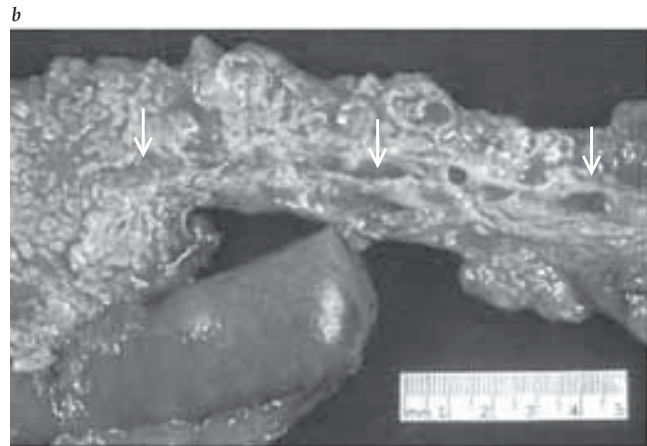
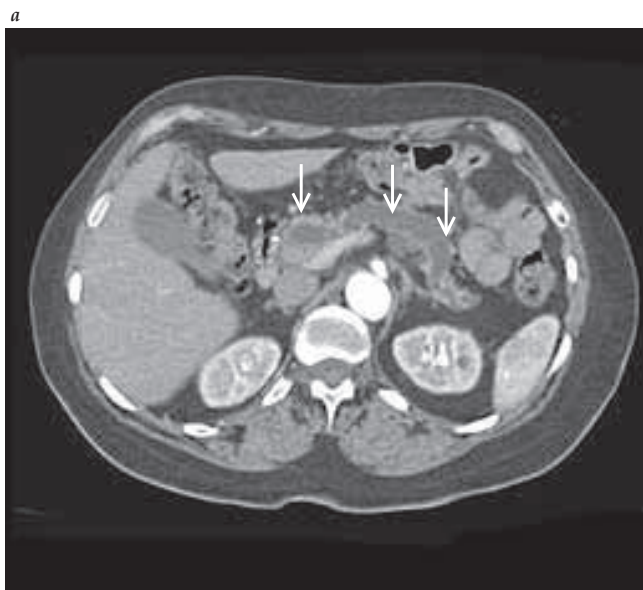


Figure 5 (a) Computed tomographic scan of a patient with main duct intraductal papillary mucinous neoplasm involving the entire length of the pancreatic duct (arrows) reveals substantial distention of the duct. (b) Shown is a cross section through the resected specimen.

associated with symptoms, internal excrescences, pericyst solid tumor, or pancreatic duct obstruction manifested as a dilation of the duct distal to the cyst.

With either type of IPMN, lifelong follow-up with axial imaging is needed.²¹ This problem should be thought of as a field defect in the pancreas. Large duct and small duct IPMNs may coexist, and pancreatic intraepithelial neoplasia (PanIN) lesions (dysplastic lesions of the duct) may coexist with IPMN.

Most patients who require total pancreatectomy tolerate the procedure well when they are enrolled in a program keyed to this operation. Frank mucinous cancers may appear in patients with IPMN as well; they should be managed in much the same fashion as other adenocarcinomas, with the additional requirement that the resection should encompass the entire IPMN-bearing portion of the pancreas. The mucinous cancers associated with IPMN have a better prognosis than ductal adenocarcinomas do.^{21,23}

NEUROENDOCRINE CANCERS

Neuroendocrine cancers account for fewer than 5% of surgically treated pancreatic malignancies. Some of these cancers are functional tumors, which produce hormones that lead to paraneoplastic syndromes. Examples include insulinoma, gastrinoma, glucagonoma, and vasoactive intestinal polypeptide-secreting tumor (VIPoma), all of which are associated with characteristic clinical syndromes. These syndromes are often produced while the tumors are still small. A detailed discussion of functional neuroendocrine tumors is beyond the scope of this chapter.

Other neuroendocrine tumors are nonfunctional and, as a result, reach a larger size before giving rise to symptoms. These lesions present with symptoms caused by mass effect and must be differentiated from ductal adenocarcinomas. Nonfunctional neuroendocrine cancers are relatively slow-growing tumors that tend to push rather than invade structures but are capable of metastasizing to lymph nodes, as well as to the liver and other organs. Pain is the most common presenting symptom. Jaundice, pancreatitis, and systemic symptoms (e.g., weight loss) are less common with these tumors than with adenocarcinoma of the pancreas. Because of the propensity of neuroendocrine tumors to deflect rather than invade the bile duct, jaundice may be absent even when tumors are located in the head of the gland.

Diagnosis, surgical staging, and treatment rationale are essentially the same for neuroendocrine cancers as for ductal adenocarcinomas. On CT scans, these lesions characteristically show enhancement in the arterial phase and are seen to push on bile ducts and vascular structures rather than encase them. Complete resection by means of pancreatoduodenectomy or distal pancreatectomy [see 5:24 *Procedures for Benign and Malignant Pancreatic Disease*] is indicated. Given the slow growth rate of neuroendocrine cancers and their relatively favorable prognosis (a 50 to 60% 5-year survival rate), removal of the primary lesion and any hepatic secondary lesions is justified if all tumor tissue can be removed with clear margins.

Biliary Tract Cancer

Cancers of the biliary tract (cholangiocarcinomas) may arise at any level of the biliary tree from the smallest, most

peripheral intrahepatic bile duct to the termination of the common bile duct. The lesions may be subdivided into intrahepatic and extrahepatic cholangiocarcinomas. The former are described below under “Liver Tumors.” Cholangiocarcinomas may grow in one of three phenotypic forms, a mass, a stricture, or an intraluminal polyp or excrescence, although combinations of these forms in different parts of the tumor may be present. The formal designations are “mass forming” (MF), periductal infiltrating (PI), and intraductal growth (IG). The type of growth pattern may affect the clinical presentation.

EXTRAHEPATIC CHOLANGIOCARCINOMA

Extrahepatic cholangiocarcinoma (CCA) may be subdivided into lower duct CCA and upper duct CCA, with the former arising in the intrapancreatic or retroduodenal portion of the bile duct and the latter arising above it. In practice, most upper duct CCAs (also referred to as hilar CCAs or Klatskin tumors) arise just below the union of the right and left hepatic ducts, at the union of the ducts, or in the main right or left hepatic ducts. Cancer of the midportion of the bile duct at the usual insertion point of the cystic duct is more likely to be an extension of a gallbladder cancer than a primary CCA. AJCC staging criteria for these tumors are useful for establishing the prognosis and planning further treatment [see Table 3 and Table 4].

Table 3 American Joint Committee on Cancer TNM Clinical Classification of Extrahepatic Bile Duct Cancer

Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ
	T1	Tumor confined to bile duct histologically
	T2	Tumor invades beyond wall of bile duct
	T3	Tumor invades liver, gallbladder, pancreas, or unilateral branches of portal vein or hepatic artery
	T4	Tumor invades any of the following: main portal vein or branches bilaterally, common hepatic artery, or other adjacent structures (e.g., colon, stomach, duodenum, or abdominal wall)
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Regional lymph node metastasis
Distant metastasis (M)	MX	Distant metastases cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis

Table 4 American Joint Committee on Cancer Staging System for Extrahepatic Bile Duct Cancer

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1, T2, T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

Lower Duct Cholangiocarcinoma

Clinical evaluation and investigative studies Much of what the surgeon needs to know about lower duct CCA has already been addressed elsewhere [see Pancreatic Cancer, Adenocarcinoma of the Head of the Pancreas, *above*]. By far the most common presentation is painless jaundice with its constellation of associated symptoms (especially pruritus). Laboratory tests reveal the characteristic pattern of obstructive jaundice. A serum CA 19-9 concentration higher than 100 U/mL facilitates the diagnosis. Axial imaging reveals dilation of the intrahepatic bile ducts, the gallbladder (in most cases), and the extrahepatic bile ducts down to the level of the pancreatic head, where the dilatation terminates abruptly. Usually, no mass is visible. ERCP or MRCP shows a focal stricture, and ERCP brushings are positive in about 50% of cases. EUS may be helpful in that it is more sensitive for small tumors than CT. Needle biopsy is directed toward the mass or, if no mass is visible, toward the narrowest segment of the bile duct. A negative biopsy result does not rule out a small bile duct cancer. “Spyglass” cholangioscopy, in which a small endoscope is directed into the biliary tree along a catheter placed by duodenoscopy, facilitates direct biopsy of the bile duct wall and lesions that project into the lumen.

The differential diagnosis includes other potential causes of focal strictures of the bile duct.²⁴ The most common cause of a benign stricture of the intrapancreatic bile duct is pancreatitis, which may be diffuse or focal. Other causes of benign stricture include iatrogenic injury, choledocholithiasis, sclerosing cholangitis, and benign inflammatory pseudotumors [see Upper Duct Cholangiocarcinoma, Investigative Studies, Imaging, *below*]. Iatrogenic injuries rarely involve the intrapancreatic portion of the bile duct, although such injuries can occur in this area as a consequence of forceful instrumentation. Sclerosing cholangitis may affect this section of the bile duct but usually affects other areas of the biliary tree as well. The diagnostic steps for differentiating benign neoplasms from malignant tumors are essentially the same for lower duct CCA as for pancreatic cancer. As noted, resection may be required to make the diagnosis. In any patient presenting with jaundice and a focal stricture of the bile duct, lower duct CCA should be strongly suspected. Mass-forming bile duct cancers may also arise in the lower bile duct, but, for obvious reasons, they are difficult to differentiate from pancreatic adenocarcinomas. Perhaps in the future genetic profiling will permit this to be done. The surgical workup and management are identical.

Surgical staging Surgical staging of lower duct CCAs is usually straightforward. These tumors are usually remote from major vascular structures and thus are not subject to the same local staging considerations as adenocarcinomas of the pancreatic head are. The exception is a tumor that extends to the top of the retroduodenal portion of the bile duct. At this point, the bile duct is apposed to the portal vein and the hepatic artery, and these structures may be invaded by bile duct tumors in this location.

Management The treatment for resectable lesions is pancreaticoduodenectomy, and the rationale for the extent of the resection is the same as for adenocarcinoma of the head of the pancreas.

Upper Duct Cholangiocarcinoma

Upper duct (or hilar) CCA is a sporadically occurring tumor that may also be seen in patients with primary sclerosing cholangitis, ulcerative colitis, or parasitic infestation. It is characteristically slow growing and locally invasive, and it metastasizes more readily to lymph nodes than systemically, although intrahepatic and peritoneal metastases are not uncommon. Most hilar CCAs are cicatrizing diffusely infiltrating cancers (PI tumors), but some form masses (MF type), and others present as papillary ingrowths (IG type). These tumors are also subdivided by the upper level of the tumor in the biliary tree according to the Bismuth classification [see Figure 6].²⁵

When the CCA originates in one of the hepatic ducts, that duct may be obstructed for a considerable period before the tumor causes jaundice by growing into the other hepatic duct or the common bile duct. Such prolonged unilateral obstruction before the onset of the presenting symptom of jaundice may result in atrophy of the obstructed side of the liver, which may affect subsequent management. For example, because the disease is more advanced on the obstructed side, the atrophied half of the liver will be removed in almost all cases in which resection is indicated. In addition, when one side of the liver undergoes atrophy, the other side undergoes hypertrophy. These changes may lead to rotation of the liver, which, in turn, may cause the structures in the hepatoduodenal ligament to be rotated out of their normal anatomic location. For instance, if hypertrophy of the left hemiliver develops, the hepatic artery may come to lie directly in front of the bile duct.

Clinical evaluation The usual presentation of hilar CCA consists of painless jaundice with its accompanying symptoms (especially pruritus), although some pain may be present. Cholangitis before instrumentation of the bile duct is uncommon. In patients who present in the late stages of the disease, general manifestations of cancer (e.g., malaise, weight loss, or ascites) may be noted. In patients with primary sclerosing cholangitis, the presence of CCA is often suggested by a rapid deterioration in the patient’s general condition. It is not unusual for patients with hilar CCA to have undergone a cholecystectomy in the recent past; the symptoms of pain and jaundice may be mistaken for symptoms of gallbladder disease in patients who happen also to have gallstones.

Investigative studies *Laboratory tests* Laboratory testing follows the pattern previously described for obstructive jaundice [see Pancreatic Cancer, *above*]. Again, the most helpful diagnostic laboratory test is the serum CA 19-9 concentration: levels higher than 100 U/mL are strongly suggestive of cancer.

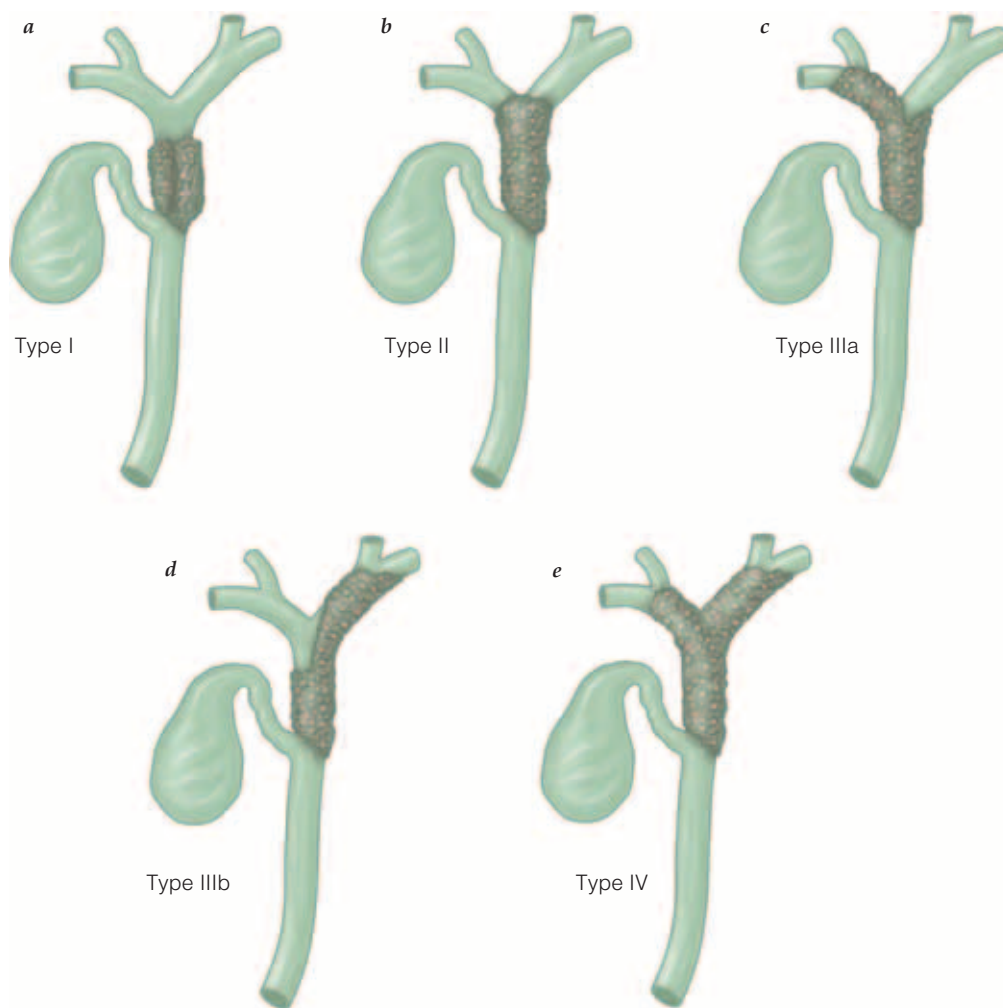


Figure 6 Depicted is the Bismuth classification of hilar cholangiocarcinoma (a through e).

Imaging Earlier [see Pancreatic Cancer, Ductal Adenocarcinoma, Adenocarcinoma of the Head of the Pancreas, *above*], the point was made that it is preferable to employ axial imaging rather than ERCP as the first imaging test in the jaundiced patient because doing so will often render ERCP, an invasive test, unnecessary. This point carries even more force in the setting of hilar CCA. Injection of dye above the malignant stricture is an integral part of ERCP. Once the dye has been injected, stents must be placed to prevent post-ERCP cholangitis. This process may involve insertion of bilateral stents, including a stent in the atrophic hemiliver. Bilateral stenting is disadvantageous because the aim is to encourage atrophy of the hemiliver to be resected and hypertrophy of the hemiliver to be retained, and insertion of a stent in the atrophic side negates that aim. Starting with CT or MRI rather than with ERCP allows detection of any hilar CCA present simultaneously with detection of atrophy. At this point, the patient can be evaluated by a multidisciplinary team with expertise in this disease, and a decision can be made regarding which side of the biliary tree to decompress (if either). Whether stents should be employed in treating hilar CCA is debatable, but if a stent is inserted, only the side

to be retained should be intubated. MRCP now provides resolution that is close to that obtained with direct cholangiography [see *Figure 7*].

ERCP does have one significant advantage in that it allows brushings to be obtained. Standard brushing techniques at this high level in the biliary tree are even less sensitive than those at lower levels, but spyglass technology (see *above*) has opened this area of the biliary tree to direct biopsy on a routine basis. EUS has been employed to obtain diagnostic tissue, with some degree of success; however, because the biopsy needle passes through the peritoneal cavity, concerns have been expressed regarding possible tumor seeding. Such seeding has not been an issue with lower duct cancers, because the biopsy tract is entirely within the future resection specimen. In many cases, a tissue diagnosis cannot be obtained preoperatively, and the diagnosis is based on the presence of a focal hilar stricture that causes jaundice.

Focal strictures of the upper bile ducts are strongly suggestive of cancer, but CCAs must also be differentiated from benign inflammatory tumors (also referred to as hepatic inflammatory pseudotumors and benign fibrosing disease).²⁶ These inflammatory masses mimic upper duct CCAs but

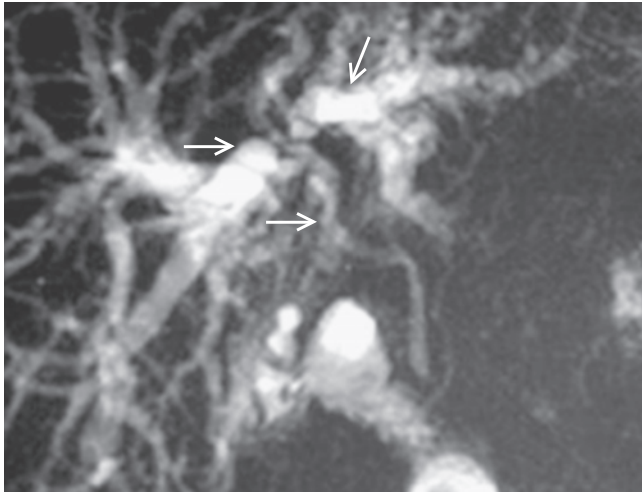


Figure 7 Shown is Bismuth type II cholangiocarcinoma. The right and left hepatic ducts are dilated (*upper arrows*), whereas the common hepatic duct is normal sized.

consist of chronic inflammatory cells and fibrous material. One distinguishing characteristic is that they do not involve blood vessels. Even today, they are very difficult to distinguish from cancers before pathologic examination of a resected specimen. Benign inflammatory tumors appear to occur most frequently in extrahepatic upper ducts, but they also occur intrahepatically and, less commonly, in lower ducts.

Gallbladder cancer may invade the porta hepatis and appear as a CCA, especially on ERCP. Gallstones are usually present. Axial imaging usually shows thickening of the gallbladder wall or the presence of a mass involving the infundibulum. Mirizzi syndrome is another cause of a focal stricture of the middle or upper bile duct. This syndrome results from compression of the bile duct by a large gallstone in the infundibulum and is usually associated with severe inflammation of the gallbladder and the characteristic signs and symptoms of acute cholecystitis. The duct is typically bowed to the left rather than focally narrowed, as in cancer. Iatrogenic causes should be considered if the patient has had a cholecystectomy. On occasion, a stricture appears years after the operation. In these cases, the probable cause of the stricture is ischemic injury to the bile duct. The presence of clips close to or indenting the duct is a clue that such injury is a possibility. Choledocholithiasis may also cause strictures, especially if cholangitis has occurred. Strictures are also frequent with recurrent pyogenic (oriental) cholangitis. Other rare tumors of the bile duct (e.g., neuroendocrine tumors) may mimic cholangiocarcinoma.

Surgical staging Often the first axial imaging test reveals only the presence of intrahepatic bile duct dilatation, which stops abruptly as the ducts merge in the hepatic hilum. This finding, however, leads to MRI or CT aimed at providing high-quality cholangiograms and angiograms of the hepatic arteries and the portal veins. Surgical staging of hilar CCA, unlike that of lower duct CCA, requires exact knowledge of the macroscopic upper extent of the tumor in the bile duct. Furthermore, invasion of hepatic arteries and portal veins is common and frequently affects resectability. Thus, surgical staging also requires accurate determination of the extent of

hepatic arterial or portal venous invasion and assessment of the degree of atrophy.

Bismuth type IV tumors are not resectable, except by liver transplantation. Type I through III tumors are resectable provided that the main portal vein and the proper hepatic artery, as well as the portal vein and the hepatic artery to the side of the liver to be retained, are not invaded by tumor and that the side to be retained is not atrophic. Involvement of the main portal vein or the hepatic artery is a relative rather than an absolute contraindication; lesser degrees of involvement can be handled by means of vascular resection and reconstruction in specialized centers. Unusual combinations of events may preclude resection (e.g., atrophy on one side of the liver and invasion of the hepatic artery supplying the other side, or invasion of the portal vein to one side and the bile duct on the other side to the level of the secondary biliary branches).

MRI (with MRCP and magnetic resonance angiography [MRA]) or CT with the latest generation of scanners can provide complete information regarding the extent of bile duct involvement and the degree of vascular invasion. Doppler ultrasonography is also excellent for evaluating vascular invasion. In our experience, the combination of these two investigations usually provides more useful staging information than either individually. Both are dependent on highly experienced radiologists. ERCP may be used for additional assessment of the extent of the tumor on the side to be retained if a stent on that side is deemed necessary. The use of percutaneous cholangiography is controversial, the main concern being the risk of tumor seeding along the tube, into the peritoneal cavity, and onto the surface of the liver or the abdominal wall. Nevertheless, this procedure is used extensively in Japan, where surgeons have considerable experience with selective decompression of parts of the liver as a preoperative strategy.²⁷

Assessment of distant metastases is achieved by means of axial imaging of the chest and the abdomen. Staging laparoscopy identifies 10 to 15% of cancers that are unresectable because of peritoneal or liver metastases. FDG-PET identifies about 15% of patients with distant metastases. At present, neither of these tests is routinely employed in this setting. Staging laparoscopy has provided a good yield of unresectable cases in some studies but not in others.

Management *Preoperative preparation* Unlike cancers of the lower bile duct, cancers of the upper bile duct usually necessitate major liver resection [see 5:22 *Procedures for Benign and Malignant Biliary Tract Disease*]. Consequently, it has been argued that the risk of postoperative hepatic failure may be lowered by preoperative decompression, especially decompression of the side to be retained, which has the dual purpose of allowing that side to recover function and of actually encouraging hypertrophy. On the other hand, stents may introduce bacteria and cause cholangitis. As noted (see above), selective percutaneous decompression is an accepted strategy in Japan; often multiple stents are inserted.²⁸

A reasonable strategy is to proceed to operation if (1) the patient is relatively young (< 70 years), (2) there are no serious comorbid conditions, (3) the jaundice has been present for less than 4 weeks, (4) the serum bilirubin concentration is lower than 10 mg/dL, (5) the future remnant liver will include more than 35% of the total liver mass, and (6) the patient has not undergone biliary instrumentation (which

always contaminates the obstructed biliary tract). In all other cases, we routinely decompress the side of the liver to be retained and wait until the serum bilirubin concentration falls to 3 mg/dL. When the future remnant liver will include less than 30 to 35% of the total liver mass, portal vein embolization (PVE) of the side to be resected may be performed to induce hypertrophy of the remnant. Because resection for hilar CCA is a major procedure in a somewhat compromised liver, it is contraindicated in patients who are in poor general condition or who have major organ dysfunction.

Rationale for surgery Patients with upper duct CCA are candidates for resection if they have no distant metastases (including intrahepatic metastases) and if the tumor can be removed in its entirety by means of bile duct resection [see 5:22 *Procedures for Benign and Malignant Biliary Tract Disease*] combined with liver resection [see 5:23 *Hepatic Resection*]. The goal of resection of upper duct CCA is to achieve clear resection margins by removing the tumor, the portal and celiac lymph nodes, the side of the liver in which the ductal involvement is greater (via hemihepatectomy or trisectionectomy), and the caudate lobe. (The caudate lobe is resected because cholangiocarcinomas tend to invade along the short caudate bile ducts, which enter the posterior surfaces of the main right and left bile ducts at the bifurcation of the common hepatic duct.) Recently, some surgeons have extended the portal dissection to include the portal vein when the right side of the liver is to be resected.

Table 5 American Joint Committee on Cancer TNM Clinical Classification of Gallbladder Cancer

Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ
	T1	Tumor invades lamina propria or muscle layer
	T1a	Tumor invades lamina propria
	T1b	Tumor invades muscle layer
	T2	Tumor invades perimuscular connective tissue; no extension beyond serosa into liver
	T3	Tumor perforates serosa (visceral peritoneum) and/or directly invades one adjacent organ or structure such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
	T4	Tumor extends > 2 cm into liver or invades two or more adjacent organs (e.g., duodenum, colon, pancreas, omentum, or extrahepatic bile ducts)
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Regional lymph node metastasis
Distant metastasis (M)	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis

This provides a wide resection zone and removes an area that is frequently involved by microscopic tumor.²⁸

Liver transplantation has been used successfully to manage Bismuth type IV tumors and is usually performed after neoadjuvant chemoradiation therapy and staging laparotomy in highly selected patients.²⁹ Liver transplantation for Bismuth tumors of lesser Bismuth grades is highly controversial.

Gallbladder Cancer

The incidence of gallbladder cancer in the United States is about 9,000 cases a year. This cancer almost always arises in patients with preexisting gallstones and is most often seen in elderly patients. Like ductal adenocarcinoma of the pancreas, it is highly malignant and tends to spread at an early stage to lymph nodes, to peritoneal surfaces, and to areas of the liver distant from the gallbladder fossa. AJCC staging criteria are helpful for planning management of this cancer [see Table 5 and Table 6].

Clinical Evaluation

Gallbladder cancer is discovered either incidentally during performance of cholecystectomy for symptomatic cholelithiasis or when the tumor causes symptoms related to invasion of the bile duct or to the effects of metastatic disease. In early stages of the disease in which the tumor is confined to the wall of the gallbladder, the symptoms are usually those of the associated stones—that is, the patient has biliary colic, and the cancer is silent. In later stages of disease, jaundice, weight loss, a palpable right upper quadrant mass, hepatomegaly, or ascites may develop. Jaundice occurs in about 50% of patients. It is a poor prognostic sign because it signifies extension of the tumor beyond the gallbladder and obstruction of the extrahepatic bile ducts. Consequently, most gallbladder cancer patients with jaundice have unresectable tumors. Because the signs and symptoms of gallbladder cancer are nonspecific, delays in diagnosis are common. As a result, most gallbladder cancers are not diagnosed until they have reached stage III or IV; thus, most of these aggressive tumors are unresectable at presentation, even when the patient is not jaundiced.

Investigative Studies

Laboratory tests In stages I and II, LFTs usually yield normal results. In later stages, laboratory test abnormalities may be noted that are not diagnostic but are consistent with bile duct obstruction. Elevated alkaline phosphatase and bilirubin levels are common. An elevation in the serum CA 19-9 concentration is the most helpful diagnostic indicator.

Table 6 American Joint Committee on Cancer Staging System for Gallbladder Cancer

Stage	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1, T2, T3	N1	M0
III	T4	Any N	M0
IVB	Any T	Any N	M1

Imaging Because gallbladder cancer is most curable in its early stages and because the symptoms in those stages are those of cholelithiasis, it is important for surgeons to be aware of subtle signs of gallbladder cancer that are occasionally present on sonograms. These signs include asymmetrical thickening of the gallbladder wall, thickening of the wall in a patient without a history of biliary colic, a mass projecting into the lumen, multiple masses or a fixed mass in the gallbladder, calcification of the gallbladder wall (so-called porcelain gallbladder), and an extracholecystic mass. Displacement of a stone to one side of the gallbladder should also be viewed with suspicion.

In later stages of disease, CT scans usually show a gallbladder mass with or without invasion of the liver or other adjacent organs. Obstruction of the bile duct produces the usual features associated with obstructive jaundice. Percutaneous CT-guided biopsy is a useful technique for confirming the diagnosis in patients with unresectable tumors.

Porcelain gallbladder is a premalignant condition, although there is some evidence that the incidence of cancer depends on the pattern of calcification: selective mucosal calcification apparently carries a significant risk of cancer, whereas diffuse intramural calcification does not.³⁰ It seems reasonable to resect only tumors with the former pattern, but whenever there is a question about the pattern of calcification, one should err on the side of resection.

Surgical Staging

Staging of gallbladder cancer requires knowledge of the extent of direct invasion into the liver and other adjacent organs and tissues (especially the bile duct, the portal veins, and the hepatic arteries). As in hilar CCA, this information may be obtained by means of MRCP and MRA or CT with the latest generation of scanners. Staging laparoscopy is very helpful in managing gallbladder cancer. As many as 50% of patients with this disease are found to have peritoneal or liver metastases on staging laparoscopy,⁸ and as with carcinoma of the body of the pancreas, no useful palliative measures can be undertaken at laparotomy.

Management

Rationale for surgery When early-stage gallbladder cancer is suspected on the basis of diagnostic imaging, open cholecystectomy, rather than laparoscopic cholecystectomy, is probably the procedure of choice [see 5:21 *Cholecystectomy and Common Bile Duct Exploration* and 5:22 *Procedures for Benign and Malignant Biliary Tract Disease*]. Intraoperatively, if there is no evidence of spread outside the gallbladder, we recommend performing an extraserosal cholecystectomy, in which the fibrous liver plate is excised along with the gallbladder so that bare liver is exposed. It is possible to perform an extraserosal resection laparoscopically; however, in our opinion, this should not be attempted, because gallbladder perforation and bile spillage are more common with the laparoscopic version of the procedure. The negative consequences of tumor implantation or incomplete excision far outweigh any benefit that a minimally invasive approach might confer.

The excised specimen should be inked and a frozen section obtained. If there is gallbladder cancer in the specimen but the resection margins are clear and the tumor is a T1 lesion (i.e., has not penetrated the muscularis), the procedure is considered complete in that lymph node metastases are uncommon

with T1 tumors (incidence < 10%). However, lymph node metastases are present in 50% of patients with T2 lesions (i.e., tumors that have invaded the muscularis). Therefore, if margins are positive or the tumor is a T2 lesion, resection of segments 4b and 5 of the liver and dissection of the portal and celiac lymph nodes are recommended. Resection of the extrahepatic bile duct and hepaticojunostomy may be needed in some cases to obtain a complete node clearance, but this is being done less frequently as experience with portal node clearance has been obtained. If it is already clear at the commencement of the operation that the tumor is T2, one should proceed directly to liver, lymph node, and bile duct resection.

In more advanced stages of disease (T3 and T4), the aim is still excision with clear margins and resection of portal and celiac lymph nodes. To obtain clear local margins with these tumors, in addition to what is required for T2 tumors, more extensive hepatic resections—up to a trisectionectomy (resection of segments 4 through 8) [see *Liver Cancer, Anatomic Considerations, below*]³¹—may be necessary, as well as resection of adjacent organs.

Incidentally discovered gallbladder cancer Gallbladder cancer may be an incidental finding at laparoscopic cholecystectomy, as it has been at open cholecystectomy. The incidence of this finding ranges from 0.3 to 1.0%. A concern that has arisen in the current era, in which the laparoscopic approach to cholecystectomy is dominant, is the risk of port-site implantation of tumor. Port-site implantation is the result of contact between the malignancy and the tissues surrounding the port site at the time of gallbladder extraction. Therefore, when evidence of gallbladder wall thickening is noted intraoperatively, the gallbladder should be extracted in a sac. The gallbladder should be inspected at the time of extraction, and any questionable areas should undergo biopsy.

If a gallbladder cancer is discovered at the time of operation, it should be treated without delay according to the principles stated earlier (i.e., depending on whether the margins on the excised gallbladder are clear and on the T stage of the tumor). From an oncologic viewpoint, it would seem ideal to resect the tissue around all trocar port sites. From a technical viewpoint, however, it would be very difficult and impractical to excise the full thickness of the abdominal wall circumferentially around four port sites, especially because the tract of the port site often is not at a 90° angle to the abdominal wall. If the gallbladder was extracted through a port site without having been placed into a bag, it is reasonable to attempt excision of that one port site.

Sometimes cancer is suspected, but frozen-section examination is inconclusive, and the definitive diagnosis of cancer is not made until the early postoperative period. More often, cancer is not suspected intraoperatively, and the diagnosis is made only when permanent sections of the gallbladder are examined. In these situations, patients with completely excised T1 lesions require no further therapy, and patients with higher-stage lesions should undergo reoperation in accordance with the principles outlined earlier (see above). Other appropriate reasons for not performing the additional surgery at the time of the cholecystectomy are (1) the desire to discuss the management scheme with the patient and (2) a lack of experience with the procedure for T2 tumors. Not infrequently, patients are referred to hepatic-pancreatic-biliary centers 10 to 14 days after surgery, which is an

inopportune time for reoperation, especially if the first procedure was difficult. Surgery may then be delayed for 3 to 4 weeks. We restage patients with abdominal CT scans when they are referred with this diagnosis, and it is not unusual to find hepatic metastases when this is done. The survival rate is much higher after radical resection than after cholecystectomy, even when cholecystectomy was the first procedure.³²

Gallbladder polyps Benign gallbladder polyps may be adenomas or more commonly a focal form of cholesterolosis. Multiple polyps are most often due to cholesterolosis. Gallbladder polyps are discovered incidentally on ultrasonograms or CT scans or are diagnosed when they cause biliary colic. They may be malignant but are rarely so when less than 1 cm in diameter, especially when they are multiple. Most gallbladder polyps are less than 0.5 cm in diameter; these are almost always benign cholesterol polyps and may be followed if they are not giving rise to symptoms. Single polyps between 0.5 and 1 cm in diameter should probably be removed by means of cholecystectomy. Multiple asymptomatic polyps in this size range should be followed because they are more likely to be due to cholesterolosis. About one quarter of all single gallbladder polyps more than 1 cm in diameter are malignant, and such polyps should be treated as malignant as a matter of policy. Almost all polyps

more than 1.8 cm in diameter are malignant.³³ Gallbladder sludge and stones may be mistaken for polyps. They are differentiated by using Doppler ultrasonography to determine if the lesion has internal blood flow. If internal blood flow is absent, the lesion is unlikely to be a polyp.

Liver Cancer

ANATOMIC CONSIDERATIONS

A long-standing problem in discussing any surgical liver disease, especially liver cancer, has been the confusing terminology applied to liver anatomy and the various hepatic resections. Fortunately, a lucid and cogent terminology has emerged that is sanctioned by both the International Hepato-Pancreato-Biliary Association (IHPBA) and the American Hepato-Pancreato-Biliary Association (AHPBA).³¹ This terminology has been widely adopted around the world and translated into many languages. It may be briefly summarized as follows.

The fundamental principle is that the anatomic divisions of the liver are based on vascular and biliary anatomy rather than on surface markings [see Figure 8]. This is an important point because surgical resection is a process of isolating specific liver volumes serviced by specific vascular and biliary

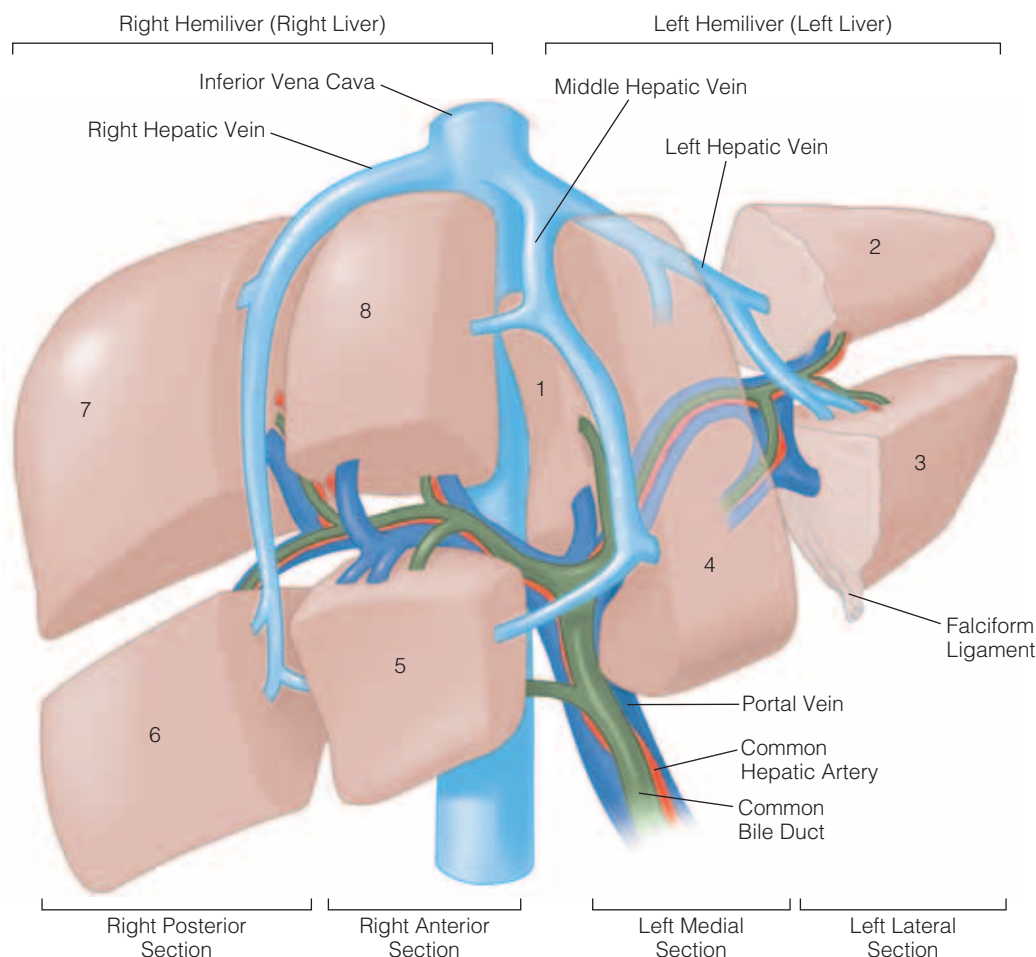


Figure 8 Illustrated are the anatomic divisions of the liver according to IHPBA/AHPBA-sanctioned terminology, including first-order divisions (hemilivers), second-order divisions (sections), and third-order divisions (segments).

structures. The anatomic ramifications of the hepatic artery and the bile duct are regular and virtually identical. Liver anatomy is best understood by first following these structures through a series of orderly divisions. The branching of the portal vein on the right side is similar to that of the bile duct and the hepatic artery, but its branching on the left side is unusual as a result of the need in the fetus that the umbilical portion of the portal vein acts as a conduit carrying blood in the reverse direction to that postnatally.

The first-order division of the proper hepatic artery and the common hepatic duct into the right and left hepatic arteries and the right and left hepatic ducts, respectively, results in

division of the liver into two parts (or volumes), referred to as the right and left hemilivers (or the right and left livers) [see *Figure 8 and Table 7*]. In this system of terminology, the term “lobe” is never used to denote a hemiliver, because it bears no relation to the internal vascular anatomy. The right hepatic artery supplies the right hemiliver, and the left hepatic artery supplies the left hemiliver. The right and left hepatic ducts drain the corresponding hemilivers. The plane between these two zones of vascular supply is called a watershed. The border or watershed of the first-order division is a plane that intersects the gallbladder fossa and the fossa for the inferior vena cava and is called “the midplane of the liver.”

Table 7 Brisbane 2000 Terminology for Hepatic Anatomy and Resections of the IHPBA

Level of Division	Preferred Anatomic Term	Corresponding Couinaud Segments (Sg)	Preferred Term for Surgical Resection*	Comments
First order (hemiliver)	Right hemiliver or Right liver	Sg 5–8 ($\pm$ caudate lobe)	Right hepatectomy or Right hemihepatectomy (stipulate $\pm$ caudate lobe)	The border or watershed separating the two hemilivers is a plane that intersects the gallbladder fossa and the IVC fossa; this plane is referred to as the midplane of the liver
	Left hemiliver or Left liver	Sg 2–4 ($\pm$ caudate lobe)	Left hepatectomy or Left hemihepatectomy (stipulate caudate lobe)	
Second order (section)	Right anterior section	Sg 5, 8	Right anterior sectionectomy	The borders or watersheds separating the sections within the hemilivers are planes referred to as the right intersectional plane (for which there is no surface marking) and the left intersectional plane (which passes through the umbilical fissure and the attachment of the falciform ligament)
	Right posterior section	Sg 6, 7	Right posterior sectionectomy	
	Left medial section	Sg 4	Left medial sectionectomy	
	Left lateral section	Sg 2, 3	Left lateral sectionectomy	
	—	Sg 4–8 ($\pm$ caudate lobe)	Right trisectionectomy (preferred) or Extended right hepatectomy or Extended right hemihepatectomy (stipulate $\pm$ caudate lobe)	
	—	Sg 2, 3, 4, 5, 8 ($\pm$ caudate lobe)	Left trisectionectomy (preferred) or Extended left hepatectomy or Extended left hemihepatectomy (stipulate $\pm$ caudate lobe)	
Third order (segment)	Segments 1–8	Any Sg	Segmentectomy (stipulate Sg—e.g., segmentectomy 7)	The borders or watersheds of the segments are planes referred to as the intersegmental planes
	Two contiguous segments	Any two Sg in continuity	Bisegmentectomy (stipulate Sg—e.g., bisegmentectomy 7, 8)	

IHPBA = International Hepato-Pancreato-Biliary Association; IVC = inferior vena cava.

*It is also permissible to refer to any resection in terms of its third-order components. Thus, a left hemihepatectomy may be referred to as a resection Sg 2–4 (or 1–4).

The second-order division divides each of the hemilivers into two parts [see *Figure 8 and Table 7*], referred to as sections. The right hemiliver comprises the right anterior section and the right posterior section. These sections are supplied by a right anterior sectional hepatic artery and a right posterior sectional hepatic artery and are drained by a right anterior sectional hepatic duct and a right posterior sectional hepatic duct. The left hemiliver comprises the left medial section and the left lateral section. These sections are supplied by a left medial sectional hepatic artery and a left lateral sectional hepatic artery and are drained by a left medial sectional hepatic duct and a left lateral sectional hepatic duct.

The third-order division divides the liver into nine segments, each of which has its own segmental artery and bile duct [see *Figure 8 and Table 7*]. The caudate lobe, a unique portion of the liver that is separate from the right and left hemilivers, is also referred to as segment 1. The left lateral section comprises segments 2 and 3; the left medial section comprises segment 4 (which is sometimes further divided into segments 4a and 4b); the right anterior section comprises segments 5 and 8; and the right posterior section comprises segments 6 and 7.

PRIMARY CANCERS

Hepatocellular Cancer

Hepatocellular cancer (HCC), or hepatoma, is the fifth most common cancer in the world. About 90% of cases arise in patients with chronic liver disease, especially when the disease has progressed to cirrhosis. Although any condition that produces cirrhosis may lead to HCC, the most common cause is viral hepatitis. In the United States, some 3 million people are infected with hepatitis C virus (HCV), and more than 1 million people have liver disease associated with hepatitis B virus (HBV). HCV infection is much more likely

Table 8 American Joint Committee on Cancer TNM Clinical Classification of Adult Primary Liver Cancer

Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	T1	Solitary tumor without vascular invasion
	T2	Solitary tumor with vascular invasion; multiple tumors, none > 5 cm in greatest dimension
	T3	Multiple tumors > 5 cm in greatest dimension or tumor involving major branch of portal or hepatic vein
	T4	Tumor or tumors with direct invasion of adjacent organs (other than gallbladder) or visceral peritoneum
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Regional lymph node metastasis
Distant metastasis (M)	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis

Table 9 American Joint Committee on Cancer Staging System for Adult Primary Liver Cancer

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IIIC	Any T	N1	M0
IV	Any T	Any N	M1

to lead to HCC than HBV infection is. AJCC staging criteria are useful for planning the management of liver cancer [see *Table 8 and Table 9*].

Clinical evaluation The usual presentation of sporadic HCC consists of pain, mass, and systemic symptoms of cancer, although the disease may also be discovered incidentally. HCC occurring as a complication of liver disease may present similarly, but it is often manifested first as a deterioration of liver function with the onset of jaundice, ascites, or encephalopathy.

Investigative studies Screening programs are employed in high-risk populations. These programs, which use α -fetoprotein (AFP) levels and ultrasonographic examination of the liver to detect early HCC, may detect asymptomatic tumors.

The diagnosis of sporadic HCC is based on elevation of AFP levels (an indicator with 50 to 60% sensitivity) and the presence of a hepatic mass on axial images. HCCs typically demonstrate hypervascularity, which is best seen on arterial-phase images [see *Figure 9*]. A pseudocapsule is often visualized, which is best seen on portal venous-phase images. MRI has been found to be more sensitive than CT in the detection of HCC. The characteristic findings are those of a hypervascular tumor on the arterial phase with washout of contrast in the venous phase. These findings also help differentiate HCC from cirrhotic

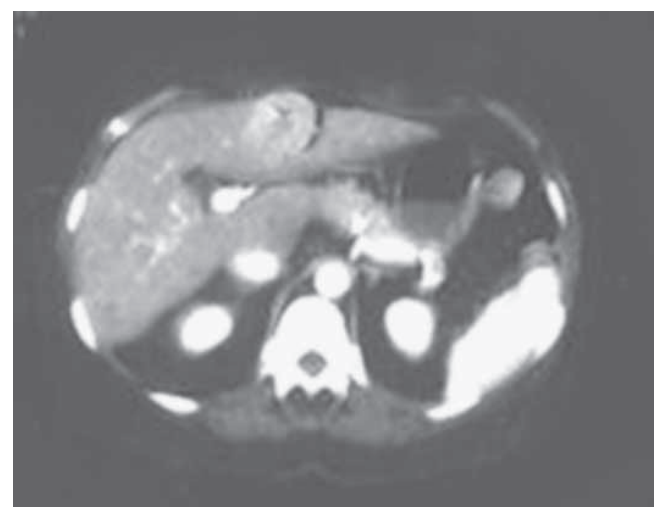


Figure 9 Computed tomographic scan shows a hypervascular hepatocellular carcinoma of the left liver.

nodules, which typically do not show washout. Multifocality is also common in HCC, unlike other hepatic neoplasms. Routine biopsy is not indicated in patients with a characteristic mass, those who have a mass and an elevated AFP level, or those who are symptomatic and require treatment for pain. HCC may be very well differentiated and difficult to distinguish from hepatic adenoma and focal nodular hyperplasia on biopsy. It may also be hard to distinguish from cirrhotic nodules. Biopsy is associated with a small risk of bleeding or tumor seeding.

Surgical staging Staging of sporadic HCC requires axial imaging of the abdomen and imaging of the chest. FDG-PET scanning is only marginally useful: HCCs are typically well differentiated, and, as a result, only 50% of the tumors are visualized. Staging laparoscopy is helpful: additional tumors are found in about 15% of patients.³⁴

Staging also requires evaluation of the extent of liver disease. The Child-Pugh classification is used to determine operability. With few exceptions, resection is limited to Child-Pugh class A patients with near-normal bilirubin levels (< 1.5 mg/dL), a normal or marginally raised prothrombin time, and no or minimal portal hypertension. The extent of resection must be tailored to the severity of the liver disease. For instance, resection of more than two segments is limited to patients with normal liver function. Too extensive resection puts the patients at risk for liver failure in the postoperative period. In Japan and China, indocyanine green clearance is used in Child-Pugh class A patients to determine the possible extent of resection.

Management *Rationale for surgery* The rationale for surgery is clear in patients without liver disease or in Child-Pugh class B or C patients with chronic liver disease. The rationale for surgery in Child-Pugh class A patients, however, remains controversial.

Partial liver resection [*see 5:23 Hepatic Resection*] is the procedure of choice for sporadic HCC in patients with normal livers. In Child-Pugh class B or C patients with chronic liver disease, liver resection can be hazardous, and orthotopic liver transplantation (OLT) is the procedure of choice. To justify the use of donor organs, however, it is necessary to select patients with HCC so that the long-term outcome of OLT for HCC is similar to that of OLT for benign conditions. To achieve this goal, OLT is restricted to patients with a single tumor less than 5 cm in diameter or to patients with as many as three tumors, none of which are more than 3 cm in diameter (the Milan criteria). These criteria have been shown to be associated with OLT outcomes comparable to those for benign conditions.³⁵

In Child-Pugh class A patients with liver disease, hepatic resection and OLT are options if the Milan criteria are met. The optimal therapeutic approach in this situation has been the subject of considerable debate, with proponents arguing for one of two strategies—namely, (1) primary OLT or (2) resection followed by OLT if HCC recurs,^{36,37} provided that the patients still meet the criteria for OLT (so-called salvage OLT). A complete discussion of this controversy is beyond the scope of this chapter. Currently, it would seem that the best strategy in patients who meet the criteria for OLT is to perform resection followed by transplantation if disease recurs.^{36,37} There is a trend toward liberalizing the OLT criteria to include single tumors 6 or 7 cm in diameter, especially if the source of the organ is a living donor.

When OLT is to be performed, it is important that the waiting time be short; these tumors progress over a timescale

of a few months, and when viewed on an intention-to-treat basis, the results of OLT deteriorate significantly if the waiting time is long.³⁸ In the United States, this concern has been dealt with by the introduction of the Model for End-stage Liver Disease (MELD) scoring system, which gives priority to recipients with HCC. It is common in the United States—and even more usual in countries with longer waiting times—to inhibit the growth of the HCC with various bridging-to-transplantation strategies during the waiting period for OLT. Such strategies include systemic chemotherapy, local treatments (e.g., radio-frequency [RF] ablation and alcohol injection), transarterial chemoembolization (TACE), and even resection of the HCC (so-called bridge resection). TACE may also be used to downsize tumors so that they meet transplant criteria.

In patients with nondiseased livers, the extent of resection depends on the size and position of the tumor. As much as 75% of the liver may be safely excised when normal liver function is present. The size of the future hepatic remnant may be determined by means of imaging. PVE of the side of the liver to be resected may be performed preoperatively to increase the size of the future remnant. It may also be used for this purpose in patients with liver disease. In these patients, PVE functions as a test of the liver's ability to regenerate. Failure to respond to PVE is itself a contraindication to surgery in patients with chronic liver disease.

As a rule, liver resections for HCC should be anatomic [*see 5:23 Hepatic Resection*]. Recurrence rates are higher with nonanatomic resections because HCCs grow along portal veins and metastasize locally within segments, sections, or hemilivers, depending on how far they reach back along the portal veins. When a nonanatomic resection is performed, the resection margins should be 2 cm or greater. When HCC reaches the main portal vein, resection is generally contraindicated; the results are very poor in this situation.

Intrahepatic Cholangiocarcinoma

Clinical evaluation Intrahepatic CCAs arise from intrahepatic bile ducts. The three phenotypic types, MF, PI, and IG, are described above. The MF type is by far the most common. Intrahepatic CCA tumor usually occurs in normal livers. The presentation is similar to that of sporadic HCC.

Investigative studies The appearance of intrahepatic CCA on CT is suggestive of a secondary tumor [*see Figure 10*]. Unlike HCC, diagnosis of intrahepatic CCA often requires biopsy, which reveals an adenocarcinoma that is indistinguishable from a hepatic metastasis. Special stains may be helpful in differentiating this tumor from a true secondary malignancy, but the differentiation is rarely certain. An elevated CA 19-9 concentration is strongly suggestive of this diagnosis if it is higher than 100 U/mL. To make the diagnosis of intrahepatic CCA, primary tumors in other sites must be excluded by means of axial imaging of the chest, the abdomen, and the pelvis; upper and lower GI endoscopy; and mammography. FDG-PET scanning is another helpful method by which an extrahepatic primary tumor may be identified.

Surgical staging FDG-PET scanning appears to be a promising staging tool for identifying portal lymph node and distant metastases when the primary tumor is actually an intrahepatic CCA. Portal lymph node metastases are a relative contraindication to resection in patients with MF tumors; the results of resection in this situation are poor. Left-side tumors

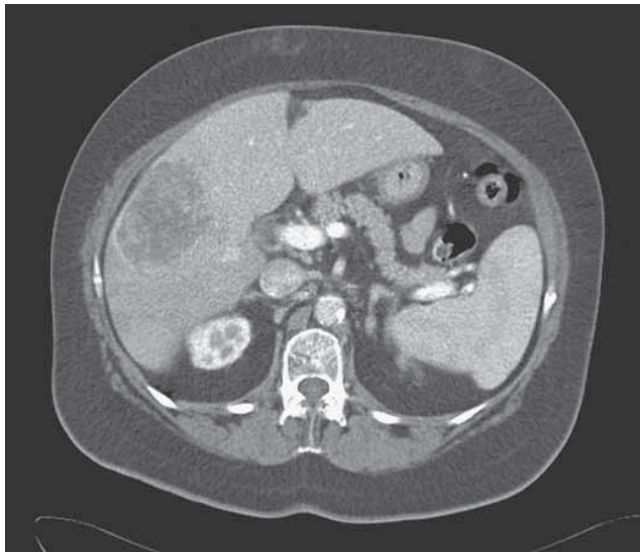


Figure 10 Computed tomographic scan shows a mass-forming intrahepatic cholangiocarcinoma.

may metastasize to lymph nodes at the cardia of the stomach and along the lesser curvature or to the mediastinum.

Management The considerations related to resection for intrahepatic CCA are similar to those for sporadic HCC (see above). Liver transplantation generally is not performed for this tumor, because of the typically poor results.

SECONDARY CANCERS

Colorectal Metastases

Clinical evaluation and investigative studies About 50% of the 150,000 patients who are diagnosed with colorectal cancer annually in the United States either have or will

have liver metastases. About 10% of patients with these colorectal metastases (CRMs) are eligible for liver resection. CRMs may be diagnosed either at the time of treatment of the primary colorectal cancer (synchronous tumors) or at a later stage (metachronous tumors).

Synchronous tumors are diagnosed by means of either preoperative CT scanning [see Figure 11] or intraoperative palpation. LFTs may show elevations (especially of the serum alkaline phosphatase level), but these results are not specific. CEA levels are not helpful as long as the primary tumor is in place. Metachronous tumors are most often diagnosed in the course of a postcolectomy surveillance program, either by imaging the liver with CT or FDG-PET scans or by detecting a rise in the CEA level. When synchronous metastases are discovered preoperatively, a FDG-PET scan should be done to complete the staging.

Surgical staging In about 25% of patients, FDG-PET scans change management as a result of detecting unsuspected extrahepatic or intrahepatic disease. Sometimes it demonstrates that apparent metastases are actually benign lesions. Second primary tumors are not uncommon in patients with metachronous lesions; accordingly, such patients should also be staged by means of colonoscopy, if this procedure was not done in the preceding 6 months, as well as FDG-PET scanning. Staging laparoscopy adds little to staging if an FDG-PET scan has been done.

Intraoperative staging consists of careful palpation of intra-abdominal structures, including hepatic and portal venous lymph nodes. In patients with metachronous lesions, however, palpation of the entire abdomen may be limited by adhesions from previous operations. IOUS of the liver may also detect unsuspected lesions, although this is less likely if the patient has already been staged by means of FDG-PET.

The main value of FDG-PET in this setting is its ability to discover unsuspected extrahepatic disease. In so doing, it helps eliminate futile hepatic resections. If a patient

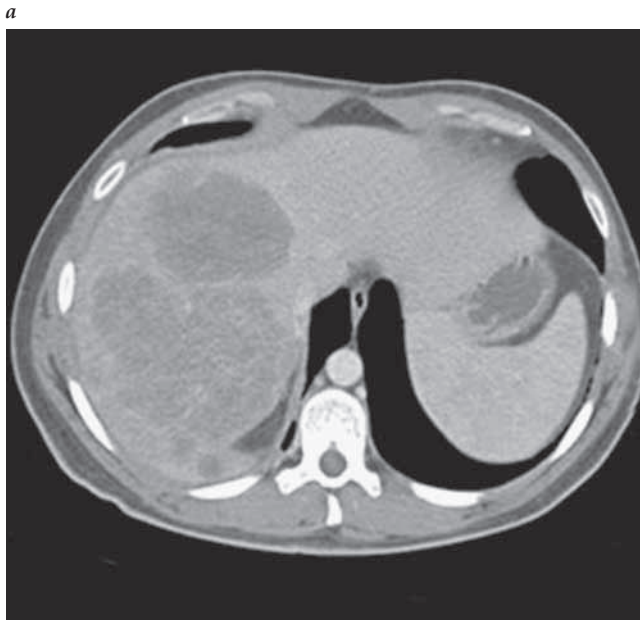


Figure 11 Colorectal metastasis. (a) Computed tomography shows a single large tumor in right hemiliver; (b) is the resected specimen.

with extrahepatic disease is treated with hepatic resection, a “recurrence” is inevitable. Elimination of pointless resections has a positive effect on survival: a 2004 study from our institution found that the overall 5-year survival rate after FDG-PET was about 60%, compared with 40% after conventional imaging.³⁹ Furthermore, after FDG-PET scanning has been done, the most important prognostic factors determining long-term outcome are the grade of the primary colorectal tumor and whether the primary tumor had metastasized to lymph nodes.⁴⁰ FDG-PET-scanned patients with poorly differentiated primary tumors do poorly in terms of overall survival after hepatic resection.³⁹ In recent years, standard PET scanners have been replaced with CT-PET scanners, which fuse the images and provide superior diagnosis and staging. For planning surgical extirpation, however, the level of detail provided by high-quality contrast-enhanced CT or MRI is also required.

Management *Rationale for surgery* The classic criteria that determined eligibility for resection are (1) that the primary tumor has been or can be completely resected, (2) that (with uncommon exceptions) there is no extrahepatic tumor (other than the primary tumor), and (3) that it is possible to resect all tumors in the liver while leaving enough of a hepatic remnant to ensure that hepatic failure does not develop postoperatively. The considerations governing the extent of the resection and the use of PVE are similar to those for sporadic HCC.

Treatment of multiple tumors is much more common with CRMs than with HCC. However, nonanatomic resections are as effective as anatomic resections as long as the resection margin is microscopically clear. The traditional view has been that resection margins of 1 cm are mandatory and lesser margins lead to poorer results. This view has been challenged in several studies that claim that margins as narrow as 1 mm are satisfactory and are probably as effective as traditional margins provided that they are free of microscopic and gross cancer. This issue must be considered to still be unsettled, and, certainly, 1 cm margins should be the goal whenever feasible. When close margins are expected, transection of the liver with a saline-linked RF ablation device may be useful in that this device leaves a margin of devitalized tissue in the patient and in the specimen.⁴¹ When the margin is very close, it may be extended by painting the cut surface of the hepatic remnant with the RF device.

Synchronous resection of the primary tumor and the liver metastases has proved to be safe⁴² and is desired by many patients. The decision to proceed with hepatic resection should not be made until resection of the primary tumor has been completed and it has been determined that the margins are clear and the patient is stable. Some patients with a small number of lung lesions in addition to liver lesions have been cured by resection.

The classic criteria for resection have been challenged and extended by new surgical approaches and the advent of much improved chemotherapy, including oxaliplatin and irinotecan, as well as the targeted monoclonal antibodies bevacizumab and cetuximab. These agents have demonstrated the ability to downsize colorectal tumors both in the liver and at extrahepatic sites. Thus, many formerly unresectable patients can now have liver resection after downsizing with chemotherapy. It is generally agreed that the best time for surgery is when the size and the position of tumors are such that liver resection can be done safely.⁴³ Continuing chemotherapy

until maximal effect is undesirable because irinotecan has been associated with the development of steatohepatitis⁴⁴ and oxaliplatin with endotheliolitis.⁴⁵ These injuries can make liver resection hazardous. Furthermore, continued downsizing may make tumors difficult to locate. This is important because although tumors may show a complete radiologic response on CT and FDG-PET scans, this is infrequently associated with a complete pathologic response. The ability to resect multiple large tumors from the liver has been enhanced by PVE and two-stage hepatectomy. In this approach, one side of the liver is cleared of tumor and the portal vein on the other side is occluded. At a second stage, the atrophied side containing the bulk of the disease (usually the right hemiliver) is excised.

Extrahepatic disease in patients with hepatic metastases Good results have been obtained in patients with recurrent disease in the primary colorectal site and liver metastases, as well as liver and lung metastases.⁴⁶ With the advent of the new chemotherapy, it may be warranted to extend this approach to patients with liver and portal lymph node metastases but not with positive lymph nodes in the celiac or para-aortic regions.⁴⁷ Peritoneal metastases have been treated successfully by resection combined with hyperthermic intraperitoneal chemotherapy. Whether this approach combined with liver resection would be effective in patients with liver and peritoneal metastases is uncertain. Its application seems warranted in selected well-followed cases.

Ablation of colorectal metastases In situ destruction of tumors with cryotherapy or RF ablation may expand the surgeon's ability to eradicate CRMs localized to the liver.⁴⁸ RF ablation has largely supplanted cryotherapy in this context as a result of its lower incidence of complications and greater ease of use. Ablation may be used either as an adjunct to operative management or as the sole treatment when there are many metastases (but usually < 10). The efficacy of RF ablation as an adjunct to surgery remains to be determined. It is doubtful, however, that using this modality alone to eradicate multiple lesions will improve overall survival significantly because the tumor biology in such cases is likely to be that of an aggressive tumor. Recent data suggest that the preceding statement is correct.⁴⁹ FDG-PET scans should be performed in all such patients; the likelihood of discovering extrahepatic tumors increases as the number of hepatic tumors increases.³⁹

RF ablation is not recommended for treatment of resectable metastases: it is not approved for this purpose, and using it in this way would mean substituting an unproven therapy of unknown efficacy for a proven therapy of known value. Again, based on recent publications, it is highly likely that RF ablation results in poorer long-term survival than liver resection.⁴⁸ If a consenting patient with resectable metastases nevertheless insists on this less invasive therapy, the surgeon should document that the preceding considerations have been explained. RF ablation may be applied by means of open, laparoscopic, or percutaneous methods. There is good reason to believe that targeting ability is degraded as one moves to less invasive methods. This consideration should also be explained to patients, although, undoubtedly, there are some patients who, because of comorbid conditions, are candidates only for percutaneous or laparoscopic approaches.

Neuroendocrine Metastases

Neuroendocrine metastases are characteristically slow growing. Some are functional, especially if they arise from the ileum; metastatic liver disease from this source may produce carcinoid syndrome. ¹¹¹In-pentetreotide imaging (OctreoScan, Mallinckrodt Inc., Hazelwood, Missouri) provides staging information comparable to that provided by FDG-PET in patients with CRMs.

The aims of surgical treatment are (1) to eradicate the cancer and (2) to reduce hormonal symptoms. The considerations regarding tumor eradication for neuroendocrine metastases are similar to those for CRMs—that is, resection should be performed if all cancer can be removed and no extrahepatic cancer is detectable. In highly symptomatic patients in whom conservative therapy with octreotide has failed, debulking the tumor by means of either chemoembolization or surgery may provide relief. The former is more suitable for patients with multiple small, diffuse metastases, whereas the latter is preferred for patients with large localized tumors. RF ablation may also be employed, either combined with surgical treatment or alone; this is an excellent use of this procedure in that the aim is cytoreduction rather than eradication. Debulking tumors in asymptomatic patients with the intention of extending survival is controversial. It is not recommended when more than 10% of the tumor will remain.

Noncolorectal, Non-neuroendocrine Metastases

Occasionally, liver metastases from other primary sites behave like CRMs in that they are localized to part of the liver in the absence of extrahepatic disease. Such patients can be managed according to the same approach employed for CRMs, although the outcome is somewhat less satisfactory. Tumors that have been treated in this way with acceptable results include breast cancers, renal cell cancers, gastric cancers, acinar cell cancers of the pancreas, and ovarian cancers. Liver resection for more aggressive malignancies (e.g., metastases from gallbladder cancer and pancreatic ductal adenocarcinomas) can be expected to yield very poor results.

INCIDENTALLY DISCOVERED ASYMPTOMATIC HEPATIC MASS

Now that transaxial imaging of the abdomen is commonly performed for a variety of complaints, the problem of the incidentally discovered asymptomatic hepatic mass is being encountered with increased frequency. Generally, cysts are

easily distinguished from solid tumors; the main diagnostic issue is differentiation of the various solid lesions.

The differential diagnosis of the benign solid hepatic mass includes hepatic adenoma, focal nodular hyperplasia (FNH), focal fatty infiltration, cavernous hemangioma, and other rare neoplasms (e.g., mesenchymal hamartoma and teratoma)—all of which must be distinguished not only from one another but also from malignant tumors. In the past, several diagnostic tests (e.g., ultrasonography, CT, sulfur colloid scanning, and angiography) were used to differentiate these neoplasms. Currently, our usual practice is to perform MRI with gadolinium contrast enhancement, which generally allows accurate differentiation among benign tumors with a single test. Cavernous hemangiomas are usually easy to distinguish because they have a characteristic appearance on MRI (hypointense on T₁-weighted images, very intense on T₂-weighted images, and filling in from the periphery with gadolinium injection); if they are asymptomatic, they need not be resected. It is important to distinguish asymptomatic FNHs from hepatic adenomas: whereas resection is recommended for adenomas because of their potential for hemorrhage or malignant degeneration, asymptomatic FNHs can safely be observed. An FNH is nearly isointense on T₁- and T₂-weighted images; it shows slightly more enhancement than normal liver parenchyma in the early phase after contrast injection and then becomes isointense. A central scar is often, but not always, seen. Conversely, a hepatic adenoma exhibits strong early-phase enhancement with contrast administration and tends to be hyperintense on T₁-weighted images.

Given that a symptomatic hepatic mass is usually treated with resection, preoperative biopsy for tissue diagnosis is rarely necessary or desirable. Modern noninvasive radiologic tests, in conjunction with a careful patient history, are often quite accurate in predicting histologic diagnosis. Biopsy of hepatic lesions should not be performed indiscriminately, because there is a small risk of complications or tumor tracking and because biopsy results often do not change management. As a rule, biopsies should be performed when definitive surgical intervention is not planned and when pathologic confirmation is necessary for institution of nonsurgical therapy.

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Figures 4, 6, and 8 Tom Moore.

10 PORTAL HYPERTENSION

Patrick S. Kamath, MD and David M. Nagorney, MD

Portal hypertension is diagnosed when the hepatic vein pressure gradient (HVPG), which reflects hepatic sinusoidal pressure, is more than 6 mm Hg. The elevation in portal pressure results in development of portosystemic venous collaterals, ascites, and hepatic encephalopathy. Each year, approximately 40,000 deaths within the United States are related to complications of cirrhosis, and the vast majority of these patients will die because of complications of either hepatocellular carcinoma or portal hypertension.

Pathogenesis of Portal Hypertension

As in all vascular systems, portal pressure is a product of portal blood flow and resistance to portal flow.¹ Portal hypertension may, therefore, result from increases in portal blood flow, increases in portal vascular resistance, or a combination of these factors.² The initiating event in portal hypertension secondary to cirrhosis is increased resistance to portal blood flow. The site of increased portal resistance depends on the etiology of portal hypertension. Although the site of increased portal resistance has been classified broadly as presinusoidal, sinusoidal, and postsinusoidal, this scheme oversimplifies the actual sites of resistance. In fact, multiple levels of resistance exist for various causes of cirrhosis.³ In alcoholic cirrhosis and cirrhosis secondary to viral hepatitis, the increase in resistance is at the level of hepatic sinusoids, whereas cirrhosis secondary to primary biliary cirrhosis has, in addition, a presinusoidal component. In schistosomiasis, which is arguably the most frequent cause of portal hypertension worldwide, the site of increased resistance is in the presinusoidal portal venules. In extrahepatic portal vein obstruction, the increased resistance is in the portal vein and its tributaries, whereas in Budd-Chiari syndrome, increased resistance is at the level of the hepatic venous outflow tract.⁴ In contrast to most patients who develop portal hypertension from chronic liver disease, the initial stage of portal hypertension in patients with an arteriovenous fistula is secondary to increases in portal blood flow. Increased portal blood flow, however, is an uncommon cause of portal hypertension.

In cirrhosis, increased resistance to vascular flow may be secondary to mechanical or vascular factors. Mechanical factors include fibrosis and nodularity, which distort the portal vasculature. Vascular factors that contribute to increased intrahepatic vasoconstriction include an elevation in the vasoconstrictor endothelin and a decrease in vasodilator substances such as nitric oxide.⁵ These vasoactive substances are potential targets for the development of drugs to decrease portal pressure. The increase in portal venous flow is secondary to splanchnic vasodilatation and an increase in the cardiac output.

Development of Collateral Circulation and Varices

The portosystemic collateral circulation develops in response to the elevation of portal pressure. Under normal circumstances, there is minimal perfusion of these collaterals and blood flow in these vessels is toward the liver. In portal hypertension, when portal pressure exceeds systemic venous pressure, flow is reversed in these collaterals, which then gradually expand. The sites of these collaterals are where the splanchnic circulation is closely apposed to the systemic circulation. Collaterals develop typically in the distal esophagus and proximal stomach; in the rectum, where the inferior mesenteric vein connects with the pudendal vein; around the umbilicus, where the vestigial umbilical vein communicates between the left portal vein and epigastric veins; and in the retroperitoneum in women, between the mesenteric and the ovarian veins.

The development of gastroesophageal varices requires a portal pressure gradient of at least 10 mm Hg as determined by the HVPG. Moreover, an HVPG of at least 12 mm Hg is required before variceal bleeding occurs. Variceal bleeding is related to variceal wall tension, which is directly proportionate to the transmural pressure gradient between the variceal lumen and the lumen of the esophagus, and the variceal radius and is inversely proportionate to variceal wall thickness. Varices are most likely to bleed at the lower end of the esophagus because at this site, the varices are of larger diameter and thin walled. The transmural pressure gradient is higher in the esophagus compared with the stomach because intrathoracic pressure is negative. Moreover, the varices lack tissue support in the lower end of the esophagus and are thin walled.

Diagnosis of Portal Hypertension

Portal hypertension is suspected clinically in a patient with stigmata of chronic liver disease such as jaundice, spider nevi, palmar erythema, Dupuytren contractures, gynecomastia, testicular atrophy, and splenomegaly. Caput medusae, which are dilated veins around the umbilicus, suggest an intrahepatic cause of portal hypertension. The presence of ascites with splenomegaly makes the presence of esophageal varices even more likely. A bruit may be heard in the left or right upper quadrant in patients with a splanchnic arteriovenous fistula as a cause of portal hypertension, whereas a venous hum in the epigastrium represents collateral flow in the falciform ligament. Alterations in mental status and asterixis, although rarely presenting findings, may be evident also.

Laboratory studies usually reveal evidence of hepatic dysfunction. Hypersplenism associated with cirrhosis is characterized by a mild to moderate thrombocytopenia and

leukopenia. Anemia may be present from recent hemorrhage, hemolysis, or malnutrition. Electrolyte abnormalities, including hyponatremia, hypokalemia, azotemia, and acid-base derangements, may also be present. As hepatic dysfunction progresses, coagulation factors synthesized by the liver are reduced, and, consequently, the prothrombin time and international normalized ratio increase. Similarly, a degree of hyperbilirubinemia occurs with either chronic or acute hepatic decompensation. Serum aminotransferases are elevated variably and partially reflect a degree of hepatocellular necrosis with the underlying liver process.

Determination of the Severity of Liver Disease

The two most commonly used methods to assess the severity of liver disease are the Child-Turcotte-Pugh (CTP) class and the Model for End-stage Liver Disease (MELD) score (<http://www.mayoclinic.org/meld/mayomodel5.html>). The components of the CTP class and the CTP score are shown in Table 1. The MELD score is currently used to prioritize allocation of organs for liver transplantation within the United States and many other countries. The advantages of the MELD score over the CTP score are that it uses only objective variables (the CTP score includes ascites and hepatic encephalopathy, which have a subjectivity in determination), has no ceiling or floor effects (e.g., in the CTP system, a serum bilirubin level of > 3 mg/dL and a bilirubin level of 30 mg are both given the same score, and albumin levels of 2.8 g/dL and 1.8 g/dL are also given the same score), and has extensive prospective validation. However, the CTP score is used more commonly in stratifying perioperative risk, especially as it relates to surgery for portal hypertension. Importantly, both the CTP class and MELD score are predictive of operative risk of death in patients with cirrhosis undergoing any major operation.⁶ However, only the MELD score is predictive of long-term survival.⁷

The most accurate method of diagnosing portal hypertension is measuring the HVP, which is the gradient between the wedged hepatic vein pressure (WHVP) and the free hepatic vein pressure (FHVP).⁸ Measurement of the HVP requires passage of a balloon catheter under fluoroscopic

guidance into the hepatic vein. Measurement of the pressure with the balloon inflated and occluding the hepatic vein represents the WHVP, and the pressure with the balloon deflated represents the FHVP. The HVP may be used to monitor portal pressure in patients on pharmacologic treatment, as a prognostic marker; to assess the risk of hepatic resection in patients with cirrhosis; and to determine the cause of portal hypertension, that is, presinusoidal, sinusoidal, or postsinusoidal.

In selected circumstances, direct pressure of the portal vein may be carried out through a percutaneous transhepatic route when HVP cannot be measured, as in patients with Budd-Chiari syndrome, in whom the hepatic veins are occluded, or in patients with an intrahepatic presinusoidal cause of portal hypertension where the HVP is normal.

Detection of Varices

Upper gastrointestinal endoscopy is the most common method used to detect varices. All patients with cirrhosis of the liver who are potential candidates for prophylactic treatment with either endoscopic variceal ligation or nonselective beta blockers should be screened for esophageal varices by upper endoscopy. Large varices are seen in about 15 to 20% of patients with cirrhosis screened by endoscopy. If no varices are detected at the initial endoscopy, then a repeat endoscopy should be carried out in 2 to 3 years. On the other hand, if only small esophageal varices are noted, then the procedure should be repeated in 1 to 2 years. Endoscopic grading of varices is subjective. The most acceptable classifications of varices at endoscopy are small (< 5 mm in diameter) and large (≥ 5 mm in diameter). In patients with large esophageal varices, Child-Pugh class C, and red-colored signs on varices, the risk of bleeding within 1 year is the highest.

Ultrasound examination has been used to confirm splenomegaly and detect thrombosis in the portal venous system. Fibroelastography, using either ultrasonography or magnetic resonance imaging, is a new technique to study liver stiffness⁹ and may be helpful in detecting portal hypertension but cannot be used to monitor changes in portal pressure. Multi-detector row computed tomography is an emerging modality for the detection of esophageal varices, as is capsule endoscopy.¹⁰ However, liver biopsy is still the gold standard for the diagnosis of cirrhosis,¹¹ and upper endoscopy is the standard for grading of varices.

Table 1 Child-Turcotte-Pugh Classification of Severity of Liver Disease

Parameter	Points Assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	< 2 mg/dL	2–3 mg/dL	> 3 mg/dL
Albumin	> 3.5 g/dL	2.8–3.5 g/dL	< 2.8 g/dL
Prothrombin time			
Seconds over control	< 4	4–6	> 6
INR	< 1.7	1.7–2.3	> 2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

INR = international normalized ratio.

A total score of 5 to 6 is graded as class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease).

Modalities for Treatment of Portal Hypertension-Related Bleeding

Treatment of portal hypertension is traditionally aimed at decreasing portal pressure by decreasing portal blood flow with pharmacologic agents or through the creation of porto-systemic shunts, using radiologic or surgical techniques as a means of decreasing resistance to portal blood flow. Treatment may also be focused directly on the varices using endoscopic techniques for ablation. Rarely, surgical devascularization is used in isolated segments of the gastrointestinal tract with varices to control bleeding when other alternatives have been exhausted. Currently, there are no pharmacologic agents that can decrease intrahepatic resistance to portal blood flow.

PHARMACOLOGIC THERAPY

The pharmacologic agents that decrease splanchnic blood flow are vasopressin and its analogues, somatostatin and its analogues, and nonselective beta-adrenergic blockers. Vasopressin and somatostatin and their analogues are given parenterally and are used only in the acute situation. Vasopressin, a splanchnic vasoconstrictor, can control acute bleeding in nearly half of patients but is not currently used because of an increased risk of cardiovascular ischemia. The semisynthetic analogue of vasopressin, terlipressin, has been used extensively in Europe because of its superior safety profile but is not currently available in the United States. The agent most commonly used within the United States is the somatostatin analogue octreotide because of its safety profile. Octreotide reduces portal pressure by decreasing portal blood flow through arteriolar splanchnic vasoconstriction. Octreotide is administered intravenously as a bolus of 50 mg followed by a continuous infusion at the rate of 50 µg/hr.

Nonselective beta-adrenergic agents are the preferred treatment for long-term use in decreasing portal pressure. A nonselective beta blocker is essential because blockade of beta₁-adrenergic receptors in the heart decreases cardiac output, whereas blockade of beta₂-adrenergic receptors results in decrease in portal blood flow. Of the two nonselective beta blockers, nadolol is preferred to propranolol because it is excreted predominantly by the kidney and has lower lipid solubility, which is associated with a lower risk of central nervous system side effects. The initial starting dose of nadolol is 20 mg daily and that of propranolol is 40 mg daily as a long-acting preparation. The dose of the agents is titrated upward every 3 to 5 days until a target heart rate of 55 to 60 beats per minute is reached or a decrease in resting heart rate by 25% is achieved. Nitrates act by causing venous dilatation and decreased portal blood flow because of the resulting reflex splanchnic vasoconstriction. Nitrates are seldom used within the United States because of the inability of most patients to tolerate the medication for prolonged periods because of headaches.

ENDOSCOPIC THERAPY

Endoscopic therapy is the only modality that can be used to prevent variceal bleeding, control variceal bleeding, and prevent variceal rebleeding. The preferred technique is endoscopic variceal ligation. Multiband devices are available that can apply several bands without withdrawal of the endoscope. The procedure involves suctioning of the varix into the device at the end of the endoscope. A band is then deployed around the varix, which strangulates the vessel and causes thrombosis. Banding the varices is started at the gastroesophageal junction and, moving more proximally in a spiral fashion, banding varices at approximately 2 cm intervals. Care should be taken to avoid applying the bands at the same level because of the risk of triggering esophageal strictures. Complications of variceal ligation include esophageal ulceration and esophageal strictures. Pulmonary aspiration may also occur.

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNTS

A transjugular intrahepatic portosystemic shunt (TIPS) functions effectively as a side-to-side portocaval shunt [see Figure 1]. The technique involves creating a communication in the intrahepatic portion of the liver between the hepatic vein and a portal vein. Because TIPS functions like a side-to-side portocaval shunt, it may be used to treat not only acute or recurrent variceal bleeding but also refractory ascites, Budd-Chiari syndrome, and hepatic hydrothorax. The TIPS placement is usually performed with the patient under sedation. A platelet count of more than $60 \times 10^3/\mu\text{L}$ and an international normalized ratio less than 1.4 are usually recommended. The hepatic vein is cannulated through a transjugular approach by an interventional radiologist. Using a Rosch needle, the portal vein is cannulated through the intervening liver from the hepatic vein. The tract is dilated over a guidewire, and an expandable metal stent is placed across the tract to reduce the portocaval pressure gradient to below 12 mm Hg. The stent may be balloon dilated to reduce the pressure so that the target pressure of less than 12 mm Hg

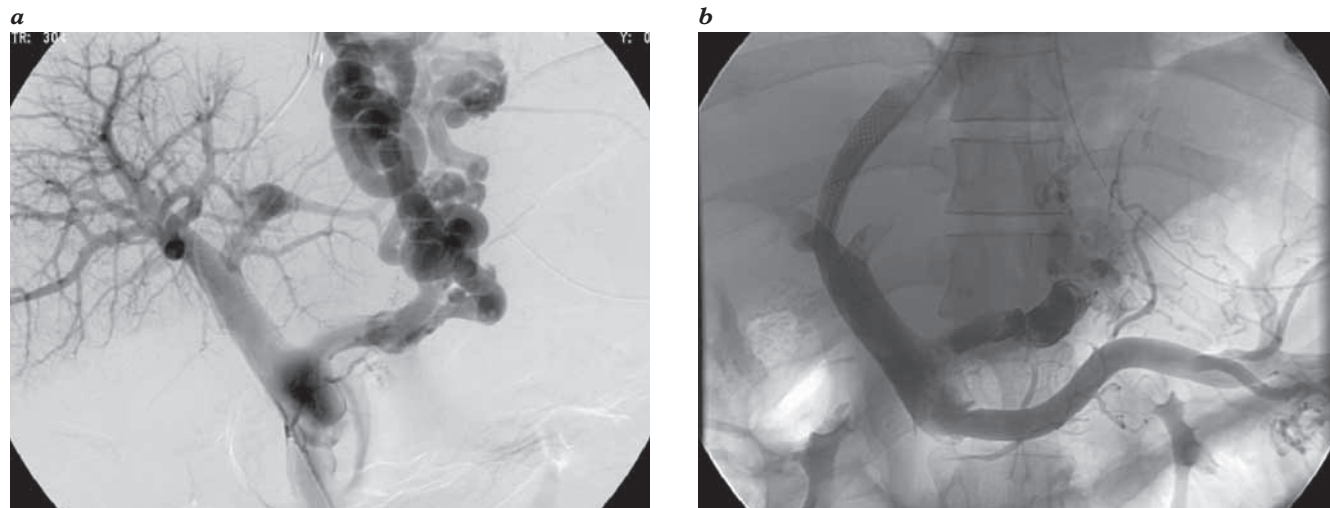


Figure 1 Transjugular intrahepatic portosystemic shunt (TIPS). (a) Portogram demonstrating gastroesophageal varices and portal perfusion of the liver. (b) Portogram following creation of TIPS. Note the absence of portal hypertension.

is reached. A coated stent is preferred nowadays. The uncoated portion anchors the stent to the portal vein, whereas the polytetrafluoroethylene-coated portion lines the tract within the liver. Shunt stenosis is reduced when coated stents are used. TIPS can be placed successfully in over 95% of patients and is associated with a procedure-related mortality of approximately 1%.¹² Complications may occur early or late. Intra-abdominal bleeding is the most serious immediate complication. Long-term complications are related to shunt stenosis. Survival of patients following placement of a TIPS may be determined using the MELD score.¹³ Follow-up ultrasonography at 6-month intervals is recommended as surveillance for shunt patency. The patency of TIPS can usually be maintained through repeated radiographic intervention.

Surgery for Portal Hypertension

Surgical treatment for portal hypertension includes portosystemic shunts, nonshunt procedures, and liver transplantation. Nowadays, surgical procedures are used infrequently for patients with portal hypertension from cirrhosis because of the efficacy of orthotopic liver transplantation. In fact, all patients with variceal bleeding who meet minimal listing criteria for liver transplantation, that is, a CTP score of 7 or greater, should be evaluated for liver transplantation before any nontransplant surgical procedure is undertaken. Portal hypertensive bleeding should be managed preferably by nonoperative alternatives as a bridge to transplantation, and only failure of nonoperative management should prompt consideration of operative intervention. Patients who are CTP class A are the best candidates for nontransplant operations for portal hypertension from cirrhosis. However, patients with portal hypertension and variceal bleeding from portal vein thrombosis should be evaluated for nontransplant procedures. The choice of nontransplant procedure is dependent on the presence or absence of underlying liver disease, the patency of the portal venous system, the acuity of the variceal hemorrhage and its response to nonsurgical therapy, and candidacy for liver transplantation.

NONSHUNT SURGICAL PROCEDURES

Nonshunt procedures include esophageal transection and gastroesophageal devascularization. These procedures are generally reserved for patients whose underlying portal venous anatomy precludes portosystemic shunting.

Esophageal Transection

Esophageal transection involves division and reanastomosis of the esophagus, usually by stapling, to disrupt esophageal varices. Often splenectomy is performed to further reduce portal blood flow. The Sugira procedure has been the primary transection procedure employed and is usually coupled with selective vagotomy. Importantly, this operation attempts to maintain patency of paraesophageal collaterals to permit the development of additional portoazygous collaterals, thus diverting the hypertensive portal blood flow from the esophagogastric junction. This procedure has reportedly been safe and highly effective in controlling variceal bleeding and is associated with a lower risk of encephalopathy than that for portosystemic shunts in the East but not in the West. Patient

selection and modifications in the originally described technique likely account for the differences in outcome. Esophageal transection typically has been undertaken when patients continued to bleed from esophageal varices despite two endoscopic sessions within a 24-hour period. With the increasing use of emergency TIPS to control acute variceal bleeding, esophageal transection is seldom used.

Devascularization Procedures

Devascularization procedures are performed to prevent recurrent variceal bleeding in patients with CTP class A in whom a portosystemic shunt is precluded, either surgically or radiologically. Typically, these procedures are employed in patients with extensive splenic and portal venous thrombosis. As originally described by Sugira, combined thoracotomy and laparotomy approach was required, but, subsequently, the operation has been carried out through an abdominal approach combined with a splenectomy.¹⁴ Total devascularization of the greater curvature of the stomach and the upper two thirds of the lesser curvature of the stomach and circumferential devascularization of the lower 7.5 cm of the esophagus are required [see Figure 2]. The rate of recurrent bleeding following this procedure depends a great deal on the extent of devascularization and may be as high as 40% if devascularization is incomplete.

PORTOSYSTEMIC SHUNTS

Surgical portosystemic shunts are divided into selective shunts, partial shunts, and total portosystemic shunts.

Selective Shunts

Selective shunts isolate and decompress only a portion of the portal venous system, that is, only the gastroesophageal junction, proximal stomach, and spleen. The most widely used selective shunt is the distal splenorenal shunt or Warren shunt [see Figure 3]. Portal hypertensive blood flow is maintained to the liver through the uninterrupted superior mesenteric and portal veins; therefore, selective shunts are ineffective in treating ascites. The distal splenorenal shunt is constructed by anastomosing the distal end of the splenic vein from the preserved spleen to the side of the left renal vein. The right and left gastric and right epiploic veins and greater curve perforating branches to the gastroepiploic vein are ligated, but the short gastric veins are preserved to decompress the gastroesophageal junction through the shunt. Additionally, all pancreatic branches to the splenic vein from the splenic hilus to the portal vein are divided to prevent the late loss of selectivity of this shunt. In expert hands, the distal splenorenal shunt can prevent variceal bleeding in more than 90% of patients with low operative mortality and morbidity and a low risk of hepatic encephalopathy.

Partial Portosystemic Shunts

A partial portosystemic shunt is actually a type of side-to-side portocaval shunt, but the shunt is calibrated by the size of the synthetic interposition graft placed between the portal vein and the inferior vena cava. Shunt diameters of 8 mm usually reduce the portal pressure to less than 12 mm Hg and maintain most antegrade portal blood flow to the liver. Construction of a partial shunt is technically simpler than

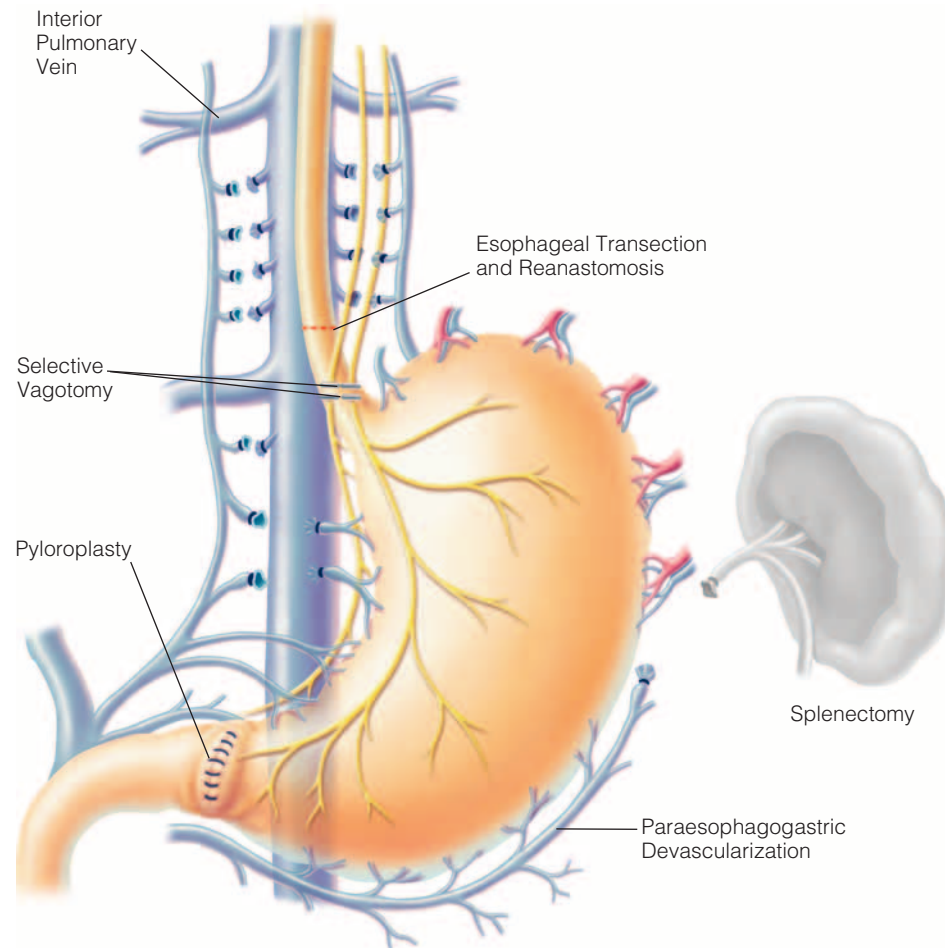


Figure 2 By extensively devascularizing the esophagogastric junction, this procedure may provide a means of interrupting esophagogastric varices without portosystemic shunting.

construction of a distal splenorenal shunt. Although partial shunts are nonselective because they do not selectively decompress an isolated portion of the portal system, their efficacy in terms of reduction of variceal bleeding and the rate of encephalopathy are similar to that seen with a distal splenorenal shunt.

Nonselective Portosystemic Shunts

Nonselective shunts effectively decompress the entire portal venous system and divert portal blood flow from the liver to a significant degree. Nonselective portosystemic shunts include the end-to-side and side-to-side portocaval shunts, the central splenorenal shunt [see Figure 4a]), and the meso-caval shunt [see Figure 4b)]. The end-to-side portocaval shunt [see Figure 4c)], which was an excellent procedure for preventing variceal bleeding but which could not be used to treat ascites because hepatic sinusoidal pressure was maintained, is no longer used. Nowadays, the side-to-side portocaval shunt is used predominantly [see Figure 4d)]. Any portocaval shunt more than 12 mm in diameter results in almost total shunting of portal blood flow. These shunts are very effective in

controlling bleeding and ascites because the hepatic sinusoids are decompressed, but hepatic encephalopathy occurs in about 40% of patients followed long term. Moreover, these shunts may be associated with increased morbidity and intra-operative transfusion requirements in those patients who undergo liver transplantation.

Management of Specific Causes of Portal Hypertension–Related Bleeding

ESOPHAGEAL VARICES

Large esophageal varices are seen in approximately 20% of patients with cirrhosis screened by upper endoscopy. In patients who do not have esophageal varices at the initial endoscopy, the annual rate of development of new varices is approximately 5%. In patients in whom small varices are noted at initial endoscopy, progression to large varices occurs at a rate of about 10% per year. The rate of progression in variceal size is related to increases in portal pressure related to changes in liver fibrosis in liver function. On the other

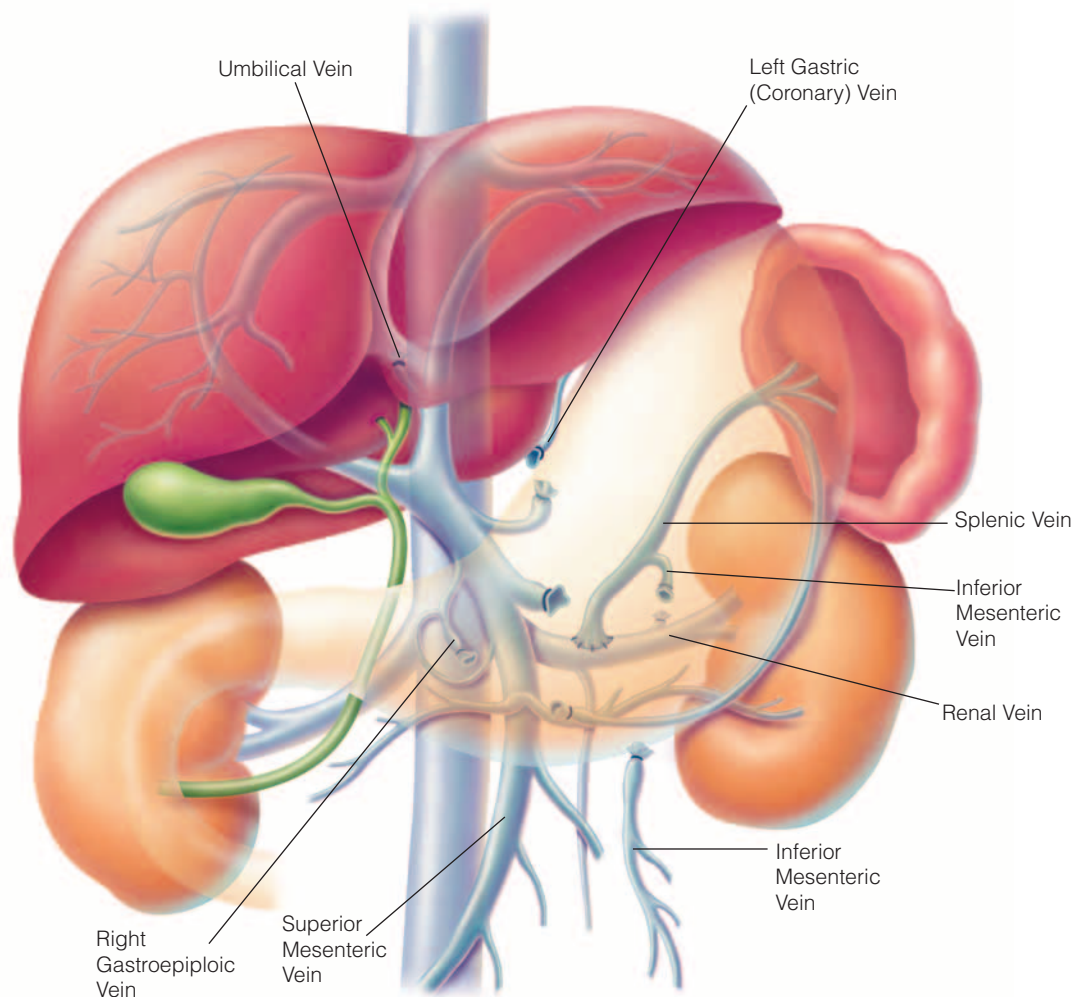


Figure 3 The distal splenorenal shunt (DSRS) diverts portal flow from the spleen and short gastric veins into the left renal vein. The DSRS provides selective shunting by preserving portal flow from the mesenteric circulation. Potential sites of collateralization (e.g., the left gastric vein, the gastroepiploic vein, and the umbilical vein) are routinely interrupted to preserve hepatopedal portal flow.

hand, improvement in liver function in patients with alcoholic liver disease may be associated with a decrease in or even disappearance of varices. Without prophylactic treatment, the risk of bleeding in patients with small varices is 7% at 2 years, whereas the risk of bleeding in patients with large varices is 30% at 2 years. Bleeding is virtually absent when the HVPG is below 12 mm Hg. In patients who bleed, the risk of death with acute variceal bleeding is 5 to 8% at 1 week and about 20% at 6 weeks. Patients with a higher MELD score and those who require greater than 4 units of packed red blood cell transfusions are at the highest risk of death.¹⁵

Treatment of esophageal variceal bleeding is classified as either (a) primary prophylaxis to prevent the first bleeding [see Figure 5]; (b) control of acute variceal bleeding [see Figure 6]; or (c) secondary prophylaxis to prevent rebleeding in patients in whom the initial bleeding is controlled [see Figure 7].¹⁶

Primary Prophylaxis

Either nonselective beta blockers or endoscopic variceal ligation should be considered in patients with large varices.

In patients with CTP class C cirrhosis, small varices should also be considered for treatment with a beta blocker. The benefit of primary prophylaxis is greatest in patients with large varices, with the prevention of variceal bleeding in approximately one of 10 patients treated. Either nadolol or a long-acting preparation of propranolol may be used. In approximately 15% of patients, the drug is discontinued because of side effects. The physiologic goal of treatment with beta blockers is a resting heart rate of between 55 and 60 beats per minute, provided that the systolic blood pressure is more than 90 mm Hg. If patients are started on pharmacologic treatment, follow-up endoscopy is not required unless gastrointestinal bleeding occurs.

Endoscopic variceal ligation is an alternative treatment. Variceal ligation is associated with a lower risk of bleeding and bleeding-related mortality than therapy with beta blockers, but overall mortality is similar. Complications of variceal ligation include esophageal ulcers and strictures, which may be severe but are infrequent with careful technique. Beta blockers are cheaper and convenient to use and may also reduce the

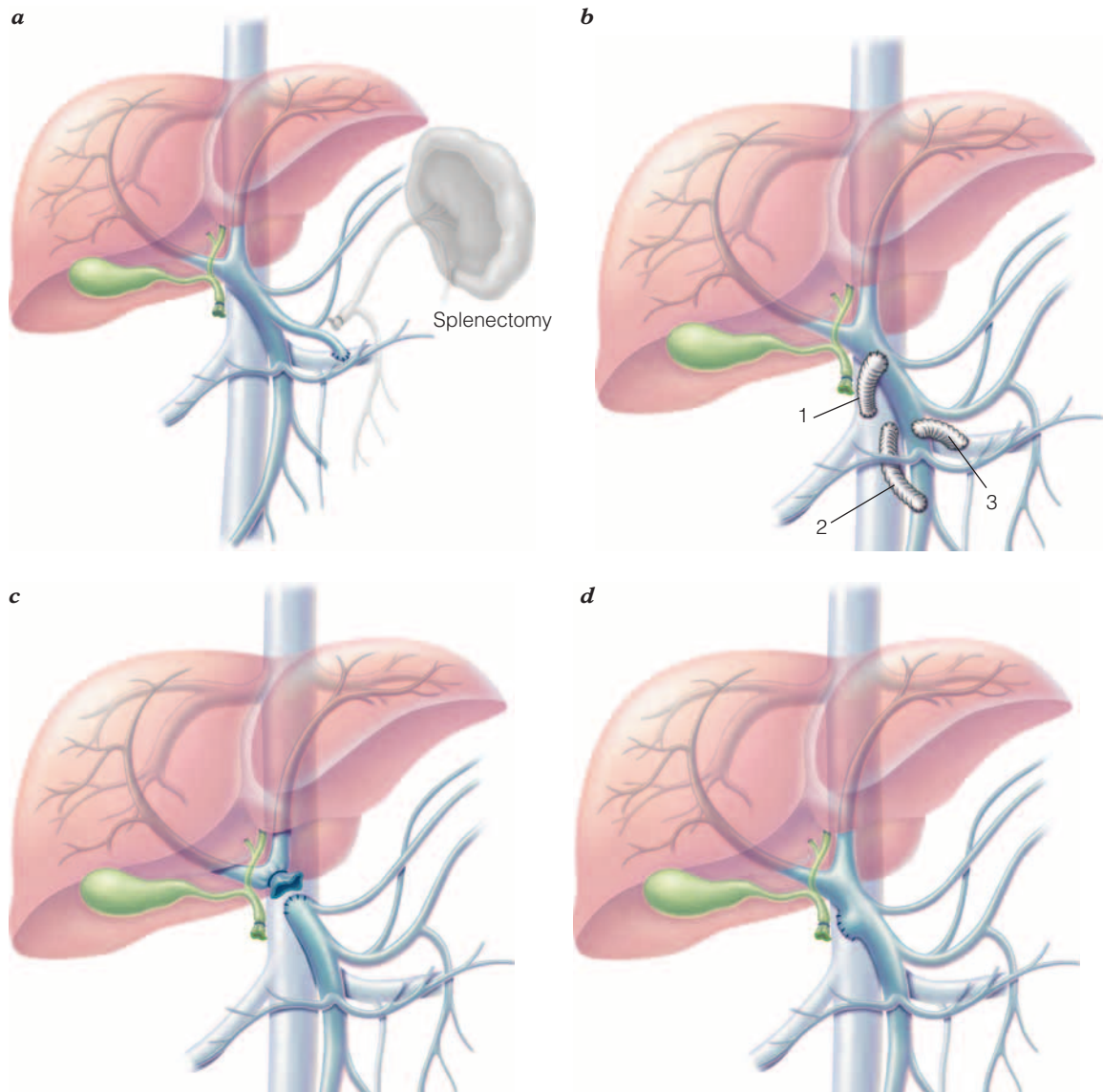


Figure 4 Nonselective portosystemic shunts either immediately or eventually divert all portal blood flow from the liver into the systemic venous circulation. Shown are the four main variants: (a) conventional (proximal) splenorenal shunt, (b) interposition shunt (portacaval [1], mesocaval [2], and mesorenal [3]), (c) end-to-side portacaval shunt, and (d) side-to-side portacaval shunt.

risk of bleeding from gastric varices and portal hypertensive gastropathy, but the side effects are more frequent. Therefore, the choice of therapy should be individualized.

Control of Acute Esophageal Variceal Bleeding

The aims of treatment in a patient with active esophageal variceal bleeding are resuscitation of the patient, control of hemorrhage, and prevention of complications such as infections and liver-specific conditions such as ascites and hepatic encephalopathy. Two large-caliber intravenous access catheters should be inserted as the patient is evaluated. Red blood cells are transfused with the goal of maintaining the hematocrit around 25% and coagulopathy is corrected as indicated.

Endotracheal intubation is advisable in the presence of active bleeding. Antibiotics should be administered to all patients to prevent bacteremia. Norfloxacin 400 mg orally twice daily, intravenous ciprofloxacin 400 mg every 12 hours, ceftriaxone 1 g every 24 hours, or levofloxacin 500 mg every 24 hours for 7 days is recommended. Pharmacologic therapy with vasoactive agents should be started as early as possible. Within the United States, the vasoactive agent most commonly used is octreotide. Endoscopic treatment is undertaken as soon as the patient is hemodynamically stable and the vasoactive agent has been infused for at least 30 minutes. Esophageal variceal bleeding is confirmed if active bleeding is seen from the varices or a white fibrin plug or red blood clot is noted

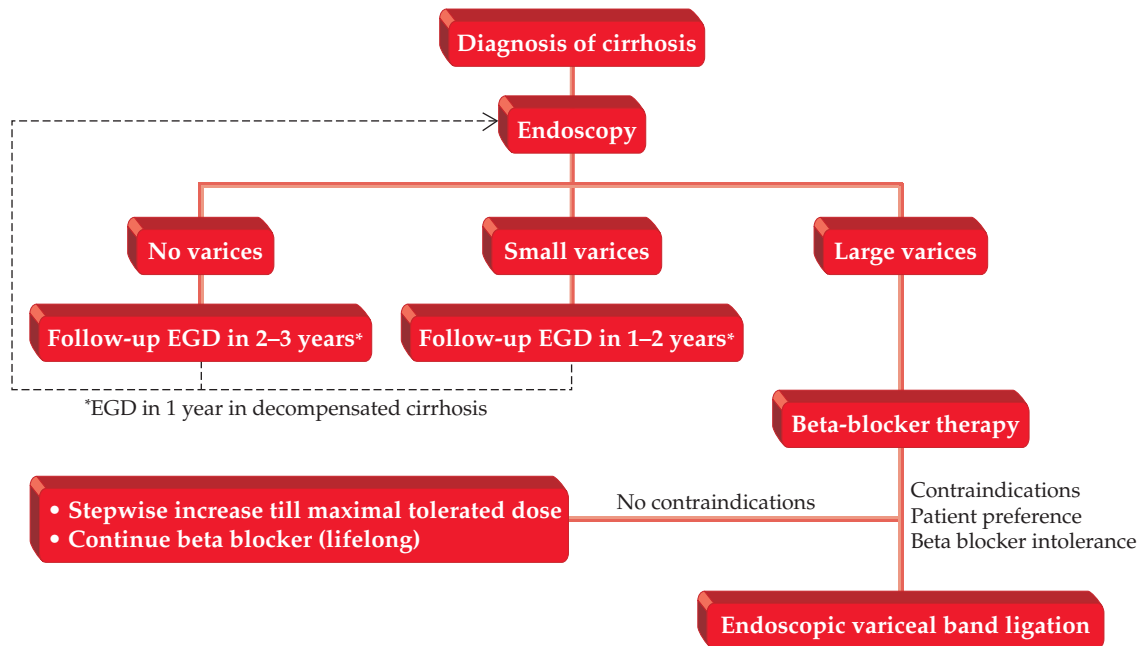


Figure 5 Esophageal variceal bleeding: primary prophylaxis. EGD = esophagogastroduodenoscopy.

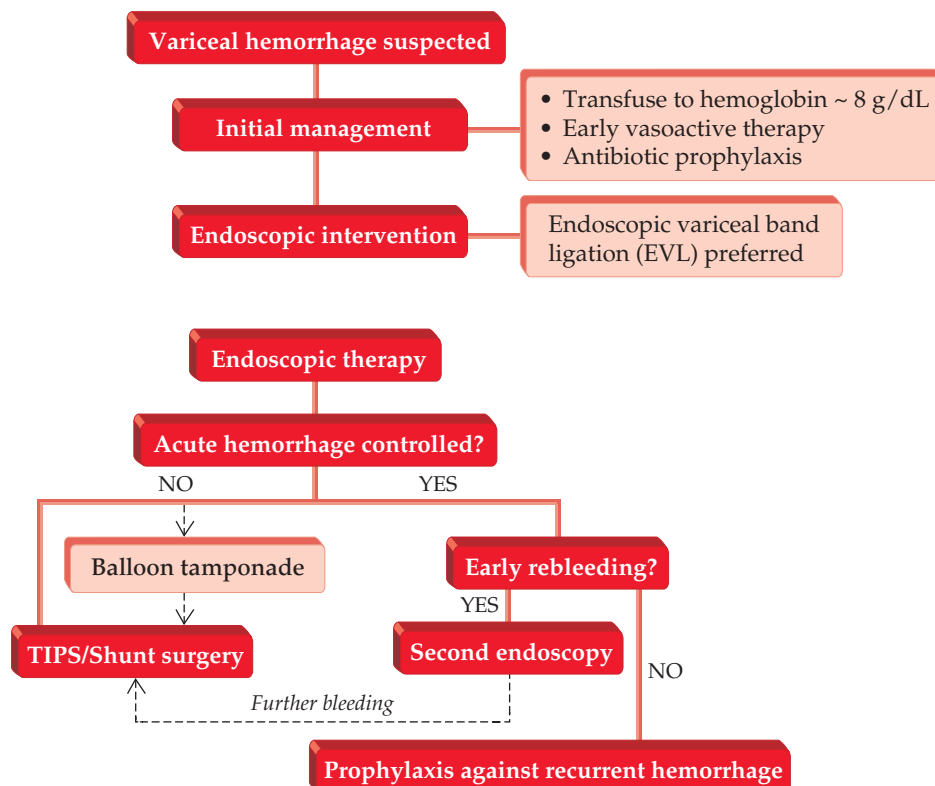


Figure 6 Management of acute variceal bleeding. TIPS = transjugular intrahepatic portosystemic shunt.

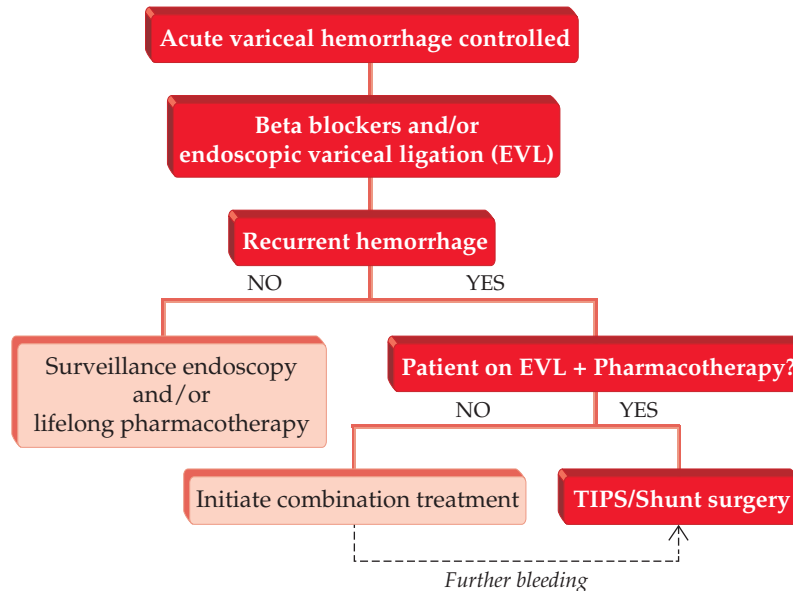


Figure 7 Esophageal variceal bleeding: secondary prophylaxis.
TIPS = transjugular intrahepatic portosystemic shunt.

over a varix. Esophageal varices are considered the site of bleeding if blood is seen in the stomach and no other bleeding source is identified.

Acute variceal bleeding cannot be controlled by endoscopic variceal ligation and pharmacotherapy in approximately 10% of patients. When two endoscopic sessions within a 24-hour period fail to control variceal bleeding, TIPS should be considered. Balloon tamponade with either a Minnesota tube or a Sengstaken-Blakemore tube may be used to control bleeding until TIPS is undertaken. Emergency surgical shunts have largely been abandoned.

Secondary Prophylaxis

All patients who have had even a single episode of esophageal variceal bleeding should receive prophylactic therapy to reduce the risk of recurrent bleeding from esophageal varices. In the absence of prophylactic therapy (secondary prophylaxis), nearly 80% of these patients will have recurrent variceal bleeding at 2 years. Pharmacologic therapy with nonselective beta blockers, endoscopic therapy, and portosystemic shunts (both surgical and TIPS) either alone or in combination have been used for secondary prophylaxis.¹⁷

The preferred initial treatment to prevent variceal rebleeding is a combination of endoscopic variceal ligation and a nonselective beta blocker. Isosorbide mononitrate is seldom used in the United States as patients typically are intolerant of this medication after beta blockade. Endoscopic variceal ligation alone is carried out in patients who are intolerant of beta blockers. Following control of the acute variceal bleeding with variceal ligation, the next session of endoscopic variceal ligation is carried out at 7 to 14 days. Subsequent sessions are repeated every 3 to 4 weeks until esophageal varices are ablated. If patients have recurrent bleeding after endoscopic variceal ligation alone, beta blockers are added. Conversely, if patients are initially started on nonselective beta blockers alone and have recurrent bleeding, endoscopic

variceal ligation is added. For those patients with recurrent bleeding after a combination of endoscopic variceal ligation and beta blocker therapy, an evaluation for a portosystemic shunt is recommended. TIPS is the preferred modality in patients with Child-Pugh class B and C cirrhosis. Even in patients with Child-Pugh class A cirrhosis, the TIPS procedure may be as effective as a distal splenorenal shunt,¹⁸ but the choice of therapy depends on local expertise.

GASTRIC VARICES

The two classes of gastric varices are gastroesophageal varices (GOVs) and isolated gastric varices (IGVs). Gastric varices are classified as type 1 gastroesophageal varices (GOV1), which extend below the gastroesophageal junction and are in continuity with esophageal varices, and type 2 gastroesophageal varices (GOV2), which extend into the cardia and fundus of the stomach but are in continuity with the esophageal varices. Varices in the fundus of the stomach in the absence of esophageal varices are called isolated gastric varices. GOV1 varices comprise approximately 70% of all gastric varices. Type 1 isolated gastric varices (IGV1) are in the fundus, whereas varices that occur elsewhere in the stomach in the absence of esophageal varices are termed IGV2. Although splenic vein thrombosis usually causes IGV1, the most common cause of fundic varices overall is probably cirrhosis. Gastric varices occur in association with advanced portal hypertension, and bleeding is more common in patients with GOV2 and IGV1. Gastric varices that bleed tend to be larger than esophageal varices and are likely to bleed only when their diameter is greater than 1 cm.

Primary Prophylaxis

No studies have evaluated pharmacologic or endoscopic treatment for primary prophylaxis of gastric variceal hemorrhage. In patients with CTP class C with large gastric varices,

pharmacologic treatment with nonselective beta blockers may be started to prevent variceal bleeding. Endoscopic therapy is not currently recommended as primary prophylaxis for gastric variceal bleeding.

Control of Bleeding

The principles of treatment for patients with gastrointestinal bleeding from gastric varices again include volume resuscitation, antibiotic prophylaxis, and a vasoactive agent such as octreotide [see Figure 8].¹⁹ Endoscopic treatment is performed only after endotracheal intubation because these patients typically have large-volume bleeding. A diagnosis of gastric variceal hemorrhage is sometimes difficult because blood pools in the fundus of the stomach. Gastric variceal hemorrhage is suspected whenever bleeding is noted from a gastric varix; if blood is found in the stomach and gastric varices with a white nipple sign are noted; if active bleeding is seen at either the gastroesophageal junction or in the gastric fundus; or if blood is seen in the stomach and gastric varices are noted in the absence of other lesions in the esophagus and stomach.

The preferred endoscopic treatment for fundal gastric variceal bleeding is injection of cyanoacrylate polymers, usually N-butyl-2-cyanoacrylate in the United States.²⁰ These cyanoacrylate tissue adhesives are not licensed for use in the United States for variceal injection. Varices are obliterated when the cyanoacrylate adhesives harden on contact with blood. Cyanoacrylate glue injection is superior to both endoscopic variceal ligation and alcohol sclerotherapy in the treatment of gastric fundal varices. Pulmonary and cerebral emboli have been reported, especially in patients with spontaneous large portosystemic shunts or intrapulmonary shunts, and may even be associated with mortality.

If endoscopic and pharmacologic therapies have failed to control gastric variceal hemorrhage, TIPS is performed. A Linton-Nachlas tube with a 600 mL volume gastric balloon may be used temporarily to tamponade bleeding from gastric varices in patients requiring TIPS. The Minnesota tube and the Sengstaken-Blakemore tube with only 250 mL gastric balloons are not as effective.

Secondary Prophylaxis

No control trials have determined the preferred therapy for the prevention of recurrent gastric variceal bleeding. Cyanoacrylate glue injection for secondary prophylaxis has been used with excellent results. Alternatively, transvenous obliteration of gastric varices can also be undertaken in patients with demonstrable spontaneous splenorenal shunts. This technique requires considerable radiologic skill and is currently popular only in some centers in the Far East. TIPS is effective in preventing gastric variceal rebleeding in patients with cirrhosis. However, TIPS does not always result in a decrease in the size of gastric varices; therefore, the target HVPG in these patients is not clear.

ECTOPIC VARICES

Varices that occur at a site other than the gastroesophageal junction and stomach are termed ectopic varices.²¹ Ectopic varices account for fewer than 5% of all variceal-related bleeding. Depending on the site of rupture of the varices, clinical manifestations include melena, hematemesis, hemobilia, hematuria, and retroperitoneal or intraperitoneal bleeding. Ectopic varices occur in patients with both extrahepatic portal vein obstruction and cirrhosis.

The most common site of ectopic varices is the duodenum. The site of gastrointestinal stomas, particularly in patients with

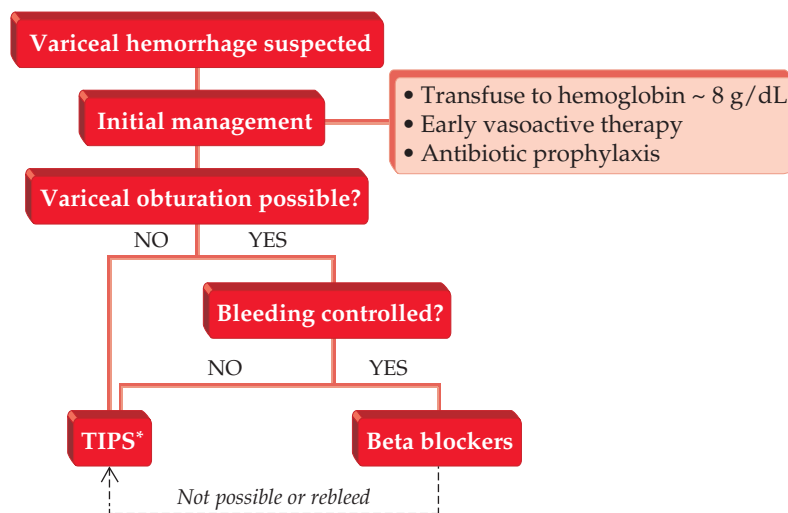


Figure 8 In patients with acute gastric variceal bleeding, initial management consists of transfusion to a hemoglobin of 8 g/dL, pharmacotherapy with vasoactive agents, and antibiotic prophylaxis. Endoscopic treatment is carried out, but if acute hemorrhage is not controlled, transjugular intrahepatic portosystemic shunt (TIPS) is recommended. If the acute hemorrhage is controlled and cyanoacrylate is available, obliteration of the gastric varices is attempted with cyanoacrylate. If cyanoacrylate is not available, then TIPS is recommended.

*A surgical shunt may be considered in patients with Child-Turcotte-Pugh class A cirrhosis.

inflammatory bowel disease and primary sclerosing cholangitis who have had an ileostomy following proctocolectomy, is the next most frequent. Peristomal varices present as a bluish halo surrounding the stoma. Anorectal varices are noted in about 10 to 40% of patients with cirrhosis who undergo colonoscopy.

In patients with suspected ectopic variceal bleeding, vasoactive drugs may be used initially. If the ectopic varices are visualized endoscopically, as in the duodenum or colon, they are treated with band ligation or glue injection. Colonic varices may require application of hemostatic clips. Stomal varices are initially treated with local compression, but, subsequently, patients require either transhepatic embolization of the stomal varices or TIPS.

Ectopic varices that present as intraperitoneal hemorrhage are associated with a poor outcome because the diagnosis is often made late and patients may require a laparotomy.

PORTAL HYPERTENSIVE GASTROPATHY AND GASTRIC VASCULAR ECTASIA

Portal hypertensive gastropathy is common in patients with cirrhosis and is characterized by a cobblestone appearance of the gastric mucosa on endoscopy. If red spots are superimposed on the cobblestone appearance, the patients are said to have severe portal hypertensive gastropathy. Gastric vascular ectasia is an entity in which there are ectatic vessels in the absence of a background mosaic pattern. When these vascular aggregates occur in the antrum of the stomach arranged in a linear pattern, the term *watermelon stomach* is used. If the aggregates are more widely dispersed, the term used is *gastric antral vascular ectasia*. Portal hypertensive gastropathy responds to beta blockers or TIPS. However, vascular ectasia may require thermoablative therapy and, occasionally, antrectomy. TIPS does not reduce the risk of bleeding from gastric vascular ectasia.²²

ASCITES

The initiating event in the formation of ascites is sinusoidal portal hypertension. The resulting splanchnic vasodilatation results in a decrease in the effective arterial blood volume. As a means of increasing the circulating intravascular volume, there is activation of the renin-angiotensin-aldosterone system, vasopressin, and the sympathetic nervous system. The net result of these actions is renal retention of sodium and water and renal vasoconstriction. The excess fluid is compartmentalized into the peritoneal space because of portal hypertension. Spontaneous bacterial peritonitis (SBP) is caused by infection of ascites in the absence of a perforated viscus. As cirrhosis progresses, there is further splanchnic vasodilatation and renal vasoconstriction. Ultimately, refractory ascites and hyponatremia, both of which are associated with decreased survival, occur. When renal vasoconstriction occurs and the serum creatinine is greater than 2.5 mg/dL, the condition is termed type 1 hepatorenal syndrome, which is associated with a median survival of only 2 weeks without treatment. When the serum creatinine rises above 1.5 mg/dL, patients are said to have type 2 hepatorenal syndrome, the major manifestation of which is refractory ascites. The median survival in patients with refractory ascites is 6 months. Another manifestation associated with increased renal retention of sodium and water is hepatic hydrothorax, that is, pleural effusions in the presence of ascites.

Treatment of ascites is aimed toward maintaining a negative sodium balance.²³ Specifically, renal sodium losses should exceed sodium intake because extrarenal losses of sodium via perspiration and stooling are more limited and difficult to control. Patients with ascites are typically placed on a 2 g sodium restricted diet (88 mEq of sodium). Spironolactone is the preferred diuretic because it is an aldosterone antagonist. The maximum dose of spironolactone is 400 mg per day. Spironolactone alone can achieve adequate renal sodium losses in 60 to 70% of patients. Furosemide is added in escalating doses if sodium restriction and spironolactone alone do not result in a daily weight loss of more than 500 g per day. The goal of treatment with diuretics is to achieve a daily weight loss of 500 g per day in the absence of lower limb edema and 1 kg a day in the presence of edema. The dose of diuretics is increased every 3 to 5 days if weight loss is less than 200 g per day.

If, in spite of sodium restriction and diuretics, a weight loss of more than 200 g per day is not achieved, the patient has refractory ascites. Most of these patients have diuretic-intractable ascites; that is, ascites persists because further increases in the dose of diuretics are associated with complications such as hyponatremia, renal insufficiency, and hepatic encephalopathy. Patients in whom ascites cannot be adequately immobilized in spite of 400 mg of spironolactone and 160 mg of furosemide per day have diuretic resistance ascites.

When ascites is refractory to diuretic treatment, large-volume paracentesis is recommended. Albumin is infused in a dose of 6 to 8 g per liter of ascitic fluid removed to prevent renal dysfunction and rapid reaccumulation of ascites. If more than two to three large-volume paracenteses are required every month in spite of optimal sodium restriction and maximal diuretics, TIPS is performed. TIPS results in better control of ascites in more than 80% of patients, but it is associated with an increased risk of hepatic encephalopathy and no change in overall survival. A peritoneovenous shunt should be considered in patients with refractory ascites in whom venous anatomy precludes TIPS. Peritoneovenous shunts are avoided in patients who are candidates for liver transplantation because of the risk of procedure-related mortality and, potentially, peritoneal fibrosis around the catheter. Peritoneovenous shunts are associated with frequent shunt occlusion and disseminated intravascular coagulation. The Denver shunt is the only peritoneovenous shunt currently on the market.

SBP is suspected clinically in patients with ascites who develop fever and, sometimes, abdominal tenderness with associated hepatic and renal deterioration without an obvious abdominal source of infection. The diagnosis of SBP is confirmed by an absolute neutrophil count over 250/ μ L and a positive bacterial culture of the ascites. Unlike secondary bacterial peritonitis, SBP is typically monomicrobial and associated with low ascitic fluid total protein, most often less than 1 g/dL. Treatment for SBP is initiated promptly because the mortality risk approaches 25%. SBP is treated with intravenous cefotaxime 2 g every 8 hours for 5 days and infusion of albumin 1.5 g/kg on day 1 of treatment and 1 g/kg on day 3 of treatment. A repeat paracentesis is carried out in 48 hours to confirm a decrease in the absolute neutrophil count. If the absolute neutrophil count has not decreased by 25%, peritonitis secondary to a perforated viscus or diverticulitis should be suspected. Secondary bacterial peritonitis is also suspected

if the cultures are polymicrobial, anaerobic, or fungal. Computed tomography of the abdomen with oral contrast may be required for diagnosis in such patients. Following the resolution of SBP, norfloxacin 400 mg once daily is given indefinitely to prevent recurrence. Fluoroquinolones may also be used to prevent SBP in patients with low-protein ascites who have not previously had SBP.²⁴

HEPATIC ENCEPHALOPATHY

The neuropsychiatric manifestations of portal hypertension are termed hepatic encephalopathy. Hepatic encephalopathy requires a combination of portosystemic shunting and altered liver function. When hepatic encephalopathy occurs in the absence of significant hepatic dysfunction (MELD score < 15), a large portosystemic shunt should be suspected.

Precipitating factors for hepatic encephalopathy include gastrointestinal bleeding, infection, hypokalemia, dehydration, and excessive intake of animal proteins. Ammonia has been implicated in the pathogenesis of hepatic encephal-

opathy, but there is a poor correlation between circulating levels of ammonia and the severity of hepatic encephalopathy.

Hepatic encephalopathy is treated initially with oral lactulose given in a dose to produce two to three semiformal stools per day. Antibiotics such as neomycin, metronidazole, or rifaximin may be used in those patients who are intolerant of lactulose or in whom encephalopathy cannot be controlled in spite of optimal lactulose dosing. Dietary protein restriction is no longer recommended, but some patients may benefit from conversion to a predominantly vegetable protein diet. When a large portosystemic shunt can be demonstrated and liver dysfunction is not advanced (MELD < 15), occlusion of the portosystemic shunt can be carried out either radiologically or surgically.

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11 CROHN DISEASE

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The role of surgery in the management of Crohn disease has undergone a dramatic evolution over the past 50 years. Currently, surgical treatment of Crohn disease is seldom performed in the emergency setting; it is nearly always performed after failed medical therapy. The decision to proceed with operative management is based on careful patient evaluation, with full awareness of the potential complications and ramifications of treatment. In particular, attention must be paid to the risk of recurrent disease, the possible surgical complications and knowledge of the side effects of medical therapy.

Classification

There are many systems for classifying Crohn disease. One of the simplest is the classification developed by Farmer and colleagues, which categorizes the disease on the basis of disease location alone (ileocolic, purely colonic, small bowel, and perianal).¹ A more elaborate system is the Vienna classification, which categorizes the disease on the basis not only of location but also of age at onset and disease behavior.² In this system, there are four categories for disease location: terminal ileum (L1), colon (L2), terminal ileum and colon (L3), and any location proximal to the terminal ileum (L4). There are two categories for age at onset: less than 40 years of age (A1) and 40 years of age or older (A2). Finally, there are three categories for disease behavior: nonstricturing and nonpenetrating (B1), stricturing (B2), and penetrating (B3).

Given that there are as many types and combinations of Crohn disease as there are patients with this condition, the most sensible approach is probably to use some combination of these two classification schemes. Careful evaluation of the specifics of each case will yield the best treatment results; however, general classification of the disease can help guide therapy. Broadly speaking, Crohn disease of the small bowel has the highest recurrence rate. Because of the important function of the small bowel in digestion, surgeons tend to emphasize conserving small bowel length during operative treatment of Crohn disease. Currently, however, there is an increasing focus on colon conservation with the aims of maintaining water absorption in patients and delaying (or perhaps eliminating) the need for a stoma.

Roles of Medical Therapy and Surgical Therapy

In planning treatment of Crohn disease, it is important not to make the use of medical therapy or surgical therapy an either/or issue. Just as one tool cannot be expected to fill every household need, operative management cannot be expected to solve every problem related to Crohn disease. Overall, careful use of medical therapy, appropriately combined with surgical therapy, provides the best treatment of Crohn disease. Single-minded reliance on either therapy to

the exclusion of the other often leads to inadequate patient care.

Generally speaking, except in the case of a free perforation, cancer, or dysplasia, one should not operate on a patient with Crohn disease without first attempting medical therapy. With the dramatically improved medical treatment options currently available, surgery can be avoided in many cases. This is often a desirable result, given the known risk of disease recurrence after surgical treatment of Crohn disease and the significant associated operative morbidity. In one single-center study, the reoperation rate for Crohn disease was 34% at 10 years.³ The agents used to treat Crohn disease can be divided into several broad groups: probiotics, antibiotics, antiinflammatory drugs, immunosuppressive drugs, and biologic agents. These can be used alone or in combination to treat disease and to maintain remission [see Table 1].

Few good studies have been done on the cost-effectiveness of medical or surgical therapy^{4,5} versus that of timely surgery followed by maintenance medical therapy. There is clearly a need for such studies. The use of potent and expensive immunomodulator therapy (e.g., maintenance infliximab) for simple ileocolic disease is questionable, especially in the light of studies indicating that such treatment is not at all

Table 1 Medical Treatment of Crohn Disease

Category	Example	Application Form	Expense
Probiotics	<i>Lactobacillus</i> , <i>Bifidobacterium</i>	Food, capsules, pills, powders	\$–\$\$
Antibiotics	Metronidazole, ciprofloxacin, rifaximin	p.o., IV	\$–\$\$
Antiinflammatories	Sulfasalazine	p.o.	\$
	5-ASA products	p.o., suppositories, enemas	\$\$
Immunosuppressives	Conventional steroids	p.o., IV	\$
	Budesonide	p.o.	\$\$
	Antimetabolites	p.o.	\$\$
	Methotrexate	p.o. or IM	\$
	Cyclosporine	p.o. or IV	\$\$
Biologics	Infliximab		\$\$\$\$
	Adalimumab		\$\$\$\$
	Certolizumab pegol		\$\$\$\$

5-ASA = 5-aminosalicylic acid. Expense range shows from least expensive (\$) to most expensive (\$\$\$\$).

innocuous.^{6,7} It is essential for the surgeon to be knowledgeable regarding the patient's medical therapy, particularly as there have recently been multiple reports of increased post-operative complications in patients receiving biologics prior to surgery.⁸⁻¹⁰

CHANGING CONCEPTS IN SURGERY FOR CROHN DISEASE

Although first described in the beginning of the 19th century, Crohn disease was not recognized as a discrete clinical entity until the first part of the 20th century.¹¹ At one point, it was treated surgically in much the same way as cancer, with frozen-section margins obtained at the time of resection. This approach did not yield any substantial reduction in the recurrence rate.¹² In fact, overzealous resections often resulted in Crohn patients' requiring lifelong parenteral nutritional support.¹³ Accordingly, conservative surgery is now the rule: only gross macroscopic disease is resected into palpably normal margins (in particular, a palpably normal mesenteric border of the bowel).

General Indications for Surgical Treatment

SIDE EFFECTS OF MEDICAL THERAPY

Significant side effects of medical therapy include those associated with failure to wean from prednisone (e.g., cataract formation, aseptic necrosis of the femoral head, and weight gain). Side effects of antimetabolite therapy include pancreatitis, neutropenia, and opportunistic infections. Side effects of biologic therapy can include reactivation of tuberculosis or histoplasmosis¹⁴ and, as with antimetabolite therapy, an increased risk of non-Hodgkin lymphoma.

COMPLICATIONS OF DISEASE

Lack of Response to Medical Therapy

Many patients with so-called toxic colitis do not respond satisfactorily to medical treatment. In severe cases of refractory disease, if surgery is not performed, colonic perforation, peritonitis, and multiple organ failure may ensue. Such cases are much less frequent now than they once were.

Obstruction

In many patients with Crohn disease, the behavior of the disease changes over time, from a more inflammatory and edematous process to one characterized more by fibrosis and scarring. Whereas antiinflammatory drugs are ideal for treating the former, surgery is frequently necessary for the latter. Failure to refer for surgical treatment of obstruction is, unfortunately, a common error among gastroenterologists. Severe abdominal pain is always a warning sign of obstruction and should be taken seriously. The importance of this point is illustrated by a case from my experience involving a patient who had obstructing ileocolic Crohn disease with gross proximal distention of the terminal ileum [see Figure 1]). This patient lost 20 lb, was experiencing severe abdominal pain, and was treated for more than a year with 6-mercaptopurine before being referred for operative management. Ileocolic resection led to rapid resolution of the symptoms.

Symptomatic Fistulas

Enterointestinal fistulas, by themselves, are no longer considered an absolute indication for operation in the absence of



Figure 1 Shown is an example of stenotic ileocolic Crohn disease resulting in obstructive symptoms that were not relieved by medical therapy.



Figure 2 Shown is an enterocutaneous fistula that persisted for more than 1 year after an ileocolic resection. The choice of parallel incisions by the previous surgeon made selection of a temporary stoma site much more difficult.

other complicating factors. Symptomatic fistulas, such as those associated with obstruction or those associated with disabling symptoms (e.g., rectovaginal fistulas or enterocutaneous fistulas [see Figure 2]), may have to be treated surgically. Ileosigmoid fistulas, which effectively bypass the entire colon, may be associated with profound and refractory diarrhea (i.e., > 20 bowel movements/day) and may also have to be treated operatively.

Abscess Formation

Abscesses are particularly common with ileocolic Crohn disease. If they cannot be controlled by means of computed tomography (CT)-guided drainage, surgical therapy may be indicated.

Cancer or Dysplasia

The risk of colorectal cancer is approximately three times higher in patients with Crohn disease than in the general population.¹⁵⁻¹⁷ Screening recommendations for patient's with long-standing Crohn colitis are similar to those for ulcerative colitis.¹⁸ In Crohn disease, cancer may also arise in long-standing fistula tracts.

Failure to Grow

In children, failure to grow and develop normally is one of the main indications that medical therapy for Crohn disease has been unsuccessful. Timely surgical therapy will permit normal development. On occasion, when bone age lags significantly behind chronological age, treatment with recombinant human growth hormone is required.

Special Considerations

PREGNANCY

Persons who have Crohn disease may be less fertile than healthy age-matched persons. One possible explanation for this difference is that feeling ill may result in reduced sexual desire or decreased sexual activity. Another is that pelvic inflammation caused by Crohn disease or by scarring and adhesion formation resulting from surgery may impair fertility. To reduce the chances of the latter, hyaluronic acid sheets may be placed around the tubes and ovaries; alternatively, the ovaries may be tacked to the undersurface of the anterior abdominal wall with absorbable sutures and thereby prevented from entering the pelvis and being trapped in scar tissue.

There is no evidence that pregnancy exacerbates Crohn disease; however, there are some specific concerns that apply to pregnant patients with this condition. Because patients with Crohn disease often have bowel movements that are more liquid, they have a particular need for a well-functioning anal sphincter. If there is any chance of an obstetrics-related injury (e.g., from a large baby in a primagravida or from a breech presentation), a cesarean section is advisable to minimize the risk of sphincter trauma. The same is true in the presence of severe perianal Crohn disease. During pregnancy, prednisone and 5-aminosalicylic acid (5-ASA) medications are safe, whereas drugs such as metronidazole are not.¹⁹ If imaging studies are needed, magnetic resonance imaging and ultrasonography are the modalities of choice.

MARKING OF STOMA SITES AND CHOICE OF INCISION

When a patient with Crohn disease is expected to need an ileostomy, it is extremely important to mark the site preoperatively. What looks flat when the patient is on the operating table may not be flat when he or she is upright. The patient must be asked to sit and lean over to confirm that the marked stoma site is in an area without folds, creases, or previous incisions. Stoma appliances do not adhere well to areas of previous scarring, and these should be avoided whenever possible.

Patients with Crohn disease do not react to intra-abdominal infection in a typical fashion. It is not unusual to find unsuspected abscesses that were not revealed by preoperative CT scans and other imaging studies. If there is even a remote chance of an unsuspected abscess (particularly in cases of obstructing ileocolic Crohn disease), the possibility of a temporary stoma should be raised with the patient and the proposed stoma site marked preoperatively.

A key point is the necessity of planning for the future. Many patients with Crohn disease will eventually require a stoma. Operating through a midline abdominal incision preserves all four quadrants for possible future stoma sites (if needed). Similarly, when surgery is performed laparoscopically, specimen retrieval sites should be kept away from potential stoma sites.

LAPAROSCOPY

Laparoscopic surgical techniques have gained acceptance in the treatment of Crohn disease. In performing a laparoscopic operation for Crohn disease, it is essential to adhere to the same technical standards that apply to corresponding open procedures. Careful intraoperative exploration of the abdomen is important in that many patients have multifocal disease. Without such exploration, patients may experience persistent postoperative symptoms as a consequence of persistent proximal pathologic states that were not addressed. As with other treatment modalities, there are some circumstances in which laparoscopy is particularly useful and others in which it should not be used. For example, a laparoscopic approach may not be suitable for fixed mesenteric abscesses associated with complex fistulae.

Ileocolic resection for Crohn disease also lends itself particularly well to a laparoscopically assisted approach; compared with open resection, laparoscopic resection has been reported to result in shorter hospital stays and reduced costs.^{20,21} The ileocolic vessels originate centrally, and they lie only over the retroperitoneum. Once the lateral peritoneal attachments are divided, the colon and the small bowel mesentery can be exteriorized, and the mesentery can be divided and the anastomosis performed extracorporeally.

Many studies have shown that even fistulizing Crohn disease can be safely addressed laparoscopically, depending on the skill of the surgeon. A hand-assisted approach is often useful with cases of dense fixation, in which fistulas are common and finger dissection may facilitate definition of the anatomy. If in doubt, one should not hesitate to convert to an open procedure. Typically, most areas that feel fibrotic or contain fibrotic adhesions are actually areas of fistulizing disease and should be treated as such until proved otherwise. In one study, patients with recurrent disease, those older than 40 years, and those with an abdominal mass were more likely to require conversion to an open procedure.²²

Surgical Management of Crohn Disease at Specific Sites

ESOPHAGEAL, GASTRIC, AND DUODENAL DISEASE

Crohn disease of the upper alimentary tract can be difficult to diagnose, largely because it is relatively uncommon. Obstructing strictures as a result of Crohn disease in this area are unusual; the unsuspected finding of noncaseating granulomas in biopsies of erythematous areas in a patient with Crohn disease in other locations is diagnostic.

Occasionally, a patient with Crohn disease of the distal esophagus requires dilatations, but this is uncommon. Surgical treatment for Crohn disease of the upper alimentary tract is almost exclusively reserved for disease affecting the duodenum. Diagnosis of duodenal Crohn disease can be difficult and requires a certain amount of suspicion. Frequently, the diagnosis is not made until relatively late because diagnostic imaging tends to focus on endoscopy and because the degree of duodenal obstruction is often not evident except on barium studies. The rigidity and luminal narrowing of the second portion of the duodenum are typically much more readily apparent on contrast studies than on endoscopy. Duodenal Crohn disease can lead to gastric outlet obstruction. In children, it can be mistaken for annular pancreas.

When duodenal Crohn disease does not respond to medical therapy, gastrojejunostomy with vagotomy is the preferred surgical treatment.^{23,24} Failure to perform a vagotomy may result in marginal ulcer formation and obstruction. Some surgeons have performed duodenal strictureplasty to treat duodenal Crohn disease. The results have been conflicting^{25,26}; the feasibility of this operative approach is limited by the pliability of the duodenum. Many patients experience prompt and full recovery of normal gastric emptying after operation, but some patients with long-standing gastric outlet obstruction continue to experience impaired emptying. The latter may benefit from administration of a prokinetic agent (e.g., metoclopramide or erythromycin).

JEJUNOILEAL DISEASE

Short Bowel Syndrome

Although Crohn disease of the small bowel is not common and accounts for a relatively small proportion of all cases, disease in this area is associated with one of the highest overall recurrence rates. Resection of large portions of the small bowel can result in short bowel syndrome. For this reason, before proceeding with any type of small bowel or ileocolic resection, one should measure the length of the existing small bowel to determine the patient's "bowel resource." One naturally would more readily perform a resection in a patient who has 400 cm of normal small bowel than in one who has only 200 cm.

Resection versus Strictureplasty

The major advance in the surgical treatment of Crohn disease over the past quarter-century has been the technique of small bowel strictureplasty, first proposed by Lee and subsequently popularized by Williams, Fazio, and others.²⁵ Currently, the two most prevalent strictureplasty techniques are Heineke-Mikulicz strictureplasty [see Figure 3] and Finney strictureplasty [see Figure 4]. The former is best suited for

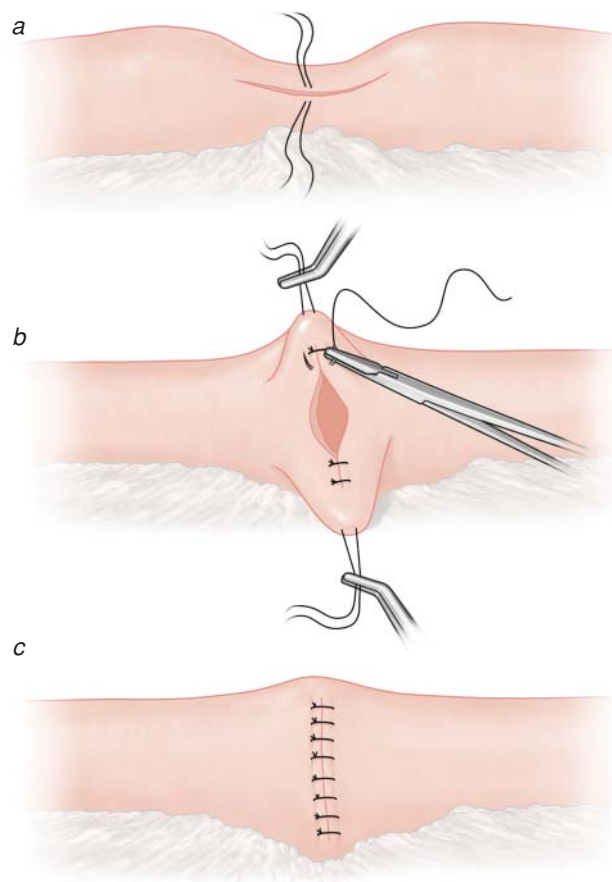


Figure 3 Heineke-Mikulicz strictureplasty. Stay sutures are placed parallel to each other on the antimesenteric border of the bowel over the area of the stricture. (a) The antimesenteric border of the bowel is then opened with the electrocautery over the area of the stricture, and the opening is extended for approximately 1 to 2 cm on either side of the stricture. (b, c) Traction is placed on the stay sutures, and the original longitudinal enterotomy is closed in a horizontal fashion in one or two layers.

strictures up to 5 to 7 cm long [see Figure 5] and the latter for strictures up to 10 to 15 cm long. The side-to-side strictureplasty described by Michelassi and colleagues²⁷ is suitable for longer areas of stricture; however, this technique involves longer suture lines and is mainly considered for patients who already have, or are at high risk for, short bowel syndrome.

The short, isolated strictures characteristic of diffuse jejunoileal Crohn disease are more frequently described in patients with long-standing Crohn disease. It has been postulated that over time, Crohn disease progresses from an edematous condition to a more fibrotic, stricturing condition.²⁸ The fibrotic strictures characteristic of the later stage of the disease are amenable to treatment with strictureplasty. Patients with these short fibrotic strictures typically have obstructive symptoms and often are unable to tolerate solid food, experiencing dramatic weight loss as a result. Although strictureplasty leaves active disease in situ, it usually leads to prompt resolution of obstructive symptoms, regaining of lost body weight, and restoration of normal nutritional status.

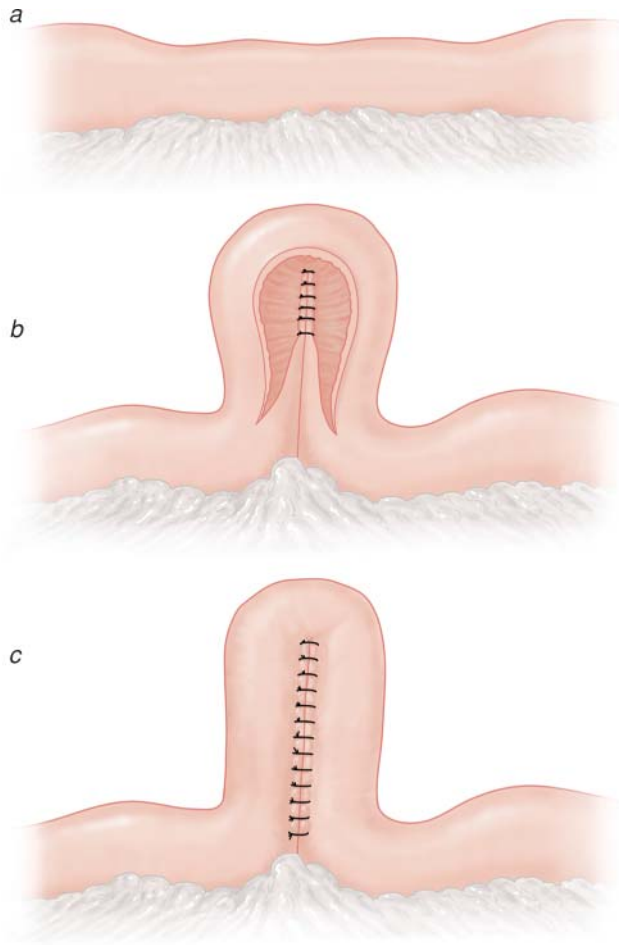


Figure 4 Finney strictureplasty. (a) This procedure is suitable for longer areas of stricture (up to 10 to 15 cm). (b) The strictured bowel is bent into the shape of an inverted U. Stay sutures are placed at the apex of the U, which is at the midpoint of the stricture, and at the far ends, which lie 1 to 2 cm proximal and distal to the stricture. A longitudinal enterotomy is made on the antimesenteric border of the bowel with the electrocautery. A side-to-side anastomosis is then performed, with the posterior wall done first. (c) Shown is the completed anastomosis.

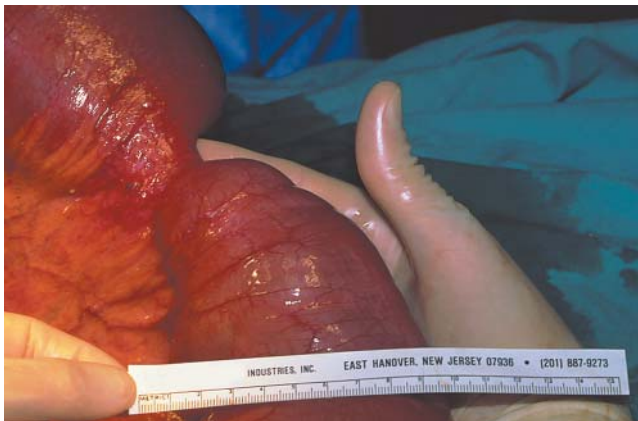


Figure 5 Shown is a short fibrotic stricture that is ideally suited to treatment with Heineke-Mikulicz strictureplasty.

A significant concern with strictureplasty is the possibility that small bowel adenocarcinoma may develop; several cases have been reported.^{29,30} I have treated a patient in whom a poorly differentiated jejunal adenocarcinoma developed at the site of a strictureplasty that had been performed 10 years earlier. Accordingly, many surgeons advocate routine biopsy of the active ulcer on the mesenteric side of the bowel at the time of strictureplasty [see Figure 6]. Another concern has to do with the number of strictureplasties that can safely be performed in a single patient in the course of a single operation. As many as 19 strictureplasties have been performed during one procedure without increased morbidity.³¹

Strictureplasty can be performed with either a single-layer or a double-layer anastomosis. It should not be performed in the presence of an abscess, a phlegmon, or a fistula, and like any other anastomosis, it should not be performed proximal to an existing obstruction that is not treated at the time of operation.

Areas of small bowel Crohn disease that are too long to be treated with strictureplasty can be treated with segmental resection. The area to be resected should be as short as possible. There is no need to obtain frozen-section margins to determine the extent of resection; doing so leads to

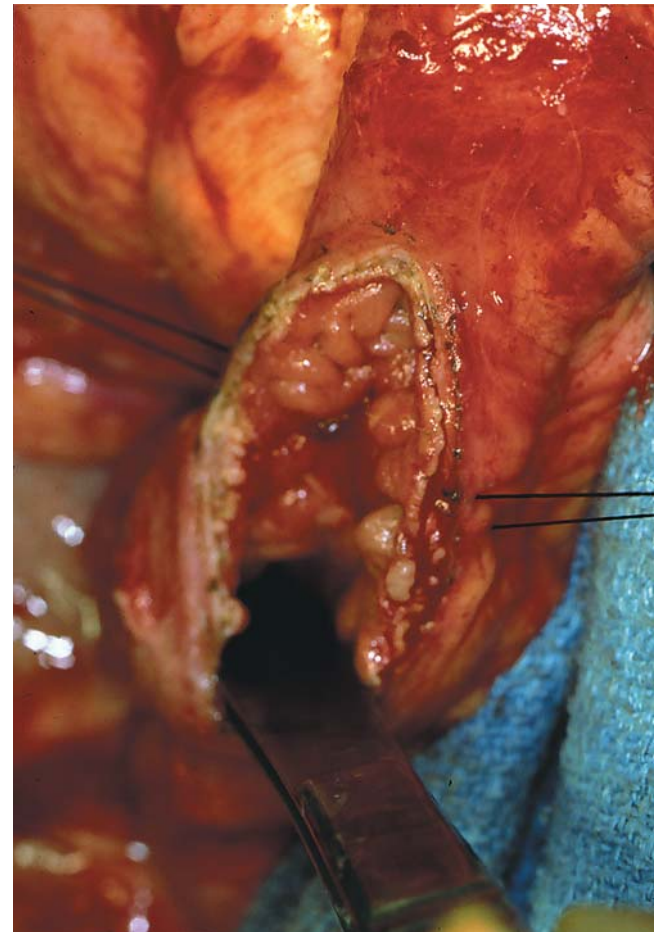


Figure 6 A large ulcer is nearly always present on the mesenteric luminal border of small bowel strictures.

unnecessary loss of small bowel length.³² The resection should extend into palpably normal areas of small bowel. The easiest way of determining the area to be resected is to feel the mesenteric margin of the bowel until palpably normal tissue is reached. Because Crohn disease is generally more severe on the mesenteric side of the bowel, palpation in this area gives the most accurate impression of the intraluminal character of the bowel. Because it is not uncommon for patients to have multifocal Crohn disease, the entire small bowel should always be inspected at the time of operation. Operating on one area of disease while failing to treat a more proximal lesion is clearly not in the patient's interest.

Because of the high rate of recurrence in patients with isolated small bowel disease, postoperative chemoprophylaxis should be strongly considered. In these patients, I prefer to use a more potent agent, such as an antimetabolite, rather than a 5-ASA agent.

ILEOCOLIC DISEASE

Approximately half of those diagnosed with Crohn disease have ileocolic disease. Ileocolic resection is, in fact, the operation most frequently performed to treat Crohn disease. Currently, there is a trend toward more aggressive medical management of Crohn disease; at the same time, surgeons are seeing more complicated disease at the time of operation. These developments have implications for management. In the large Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) Registry, prednisone therapy was associated with increased mortality with medical treatment, and narcotic use and therapy were both associated with serious infections with medical therapy, in this case most often infliximab.¹⁴ These are both often given for amelioration of symptoms in patients with obstructing ileocolic disease. An easy ileocolic resection is an experience that a patient generally tolerates well and recovers from very quickly; however, delaying operative management with years of aggressive medical therapy can lead to more complicated disease associated with enteroenteric fistulas, which can be difficult to treat. Ileosigmoid fistulas are among the most common fistulas associated with ileocolic Crohn disease, along with fistulas between the terminal ileum and the ascending colon and fistulas between the terminal ileum and adjacent loops of small bowel.

Disease recurrence is common after ileocolic resection. Colonoscopy is the most accurate modality for postoperative surveillance and the easiest to use; it is more sensitive than either small bowel follow-through or air-contrast barium enema. For this reason, I favor an end-to-end anastomosis after ileocolic resection. In the event of recurrent disease, an end-to-side, side-to-end, or side-to-side anastomosis may be difficult to intubate. There is some evidence in the literature to suggest that the postoperative recurrence rate may be lower with a wider anastomosis.³³ The anastomosis can be performed in either one or two layers. If the bowel is thicker, a handsewn anastomosis is preferred to a stapled one.

The incidence of reoperation for recurrent disease after ileocolic resection is high and increases with the number of resections.³⁴ Postoperative chemoprophylaxis with mesalazine can significantly reduce the recurrence rate.³⁵ Patients who smoke should be strongly encouraged to stop: the rate and severity of recurrence are increased in smokers.²⁶

Special Circumstances

Ileocolic Crohn disease is often associated with intra-abdominal abscesses or fistulas. If an associated abscess is known to be present, CT-guided drainage should be done preoperatively so that a single-stage procedure can then be performed. If an unsuspected abscess is identified at the time of operation, the safest approach is to proceed with bowel resection, perform the posterior wall of the anastomosis, and exteriorize the anastomosis as a loop ileostomy. This loop ileostomy can then be safely closed, often without a formal laparotomy, 8 weeks after operation if there are no signs of ongoing sepsis. If the abscess or the terminal ileal loop is adherent to the sigmoid colon, an ileosigmoid fistula may be present. The decision whether to resect the sigmoid colon is dictated by the appearance and feel of the sigmoid in the involved areas. If only a portion of the anterior colon wall is involved, that portion can be excised in a wedgelike fashion and the excision site closed primarily. If the entire circumference of the sigmoid colon at that point is indurated and woody feeling, a short segmental resection with anastomosis is the best option.

COLONIC DISEASE

Colonic involvement is present in 29 to 44% of patients with Crohn disease.³⁶ One of the challenges in treating colonic Crohn disease is obtaining the correct diagnosis. Whereas Crohn disease of the small bowel is fairly easy to diagnose, colonic disease often is not. Because granulomas are not present in most cases of colonic Crohn disease and because this condition can look very similar to ulcerative colitis both endoscopically and macroscopically, differentiation between Crohn colitis and ulcerative colitis can be difficult in the absence of small bowel or anal disease. Colonic Crohn disease appears to be more frequently associated with cutaneous manifestations (e.g., pyoderma gangrenosum) [see Figure 7].

Indications for Surgical Treatment

The main indications for operative management of colonic Crohn disease are stricture [see Figure 8], malignancy, side effects of medical therapy, and failure of medical therapy. In children, failure to recognize and treat this condition promptly may result in growth retardation. It is important to monitor both bone age and insulinlike growth factor-1 levels. If these are abnormal, timely institution of human growth hormone therapy, operative management of inflammatory bowel disease, or both may still permit normal growth and development.

Side effects of medical therapy can be substantial. They may include such varied complications as aseptic necrosis of the femoral head and cataract formation (both related to steroid use), as well as an increased incidence of opportunistic infections (from immunosuppression secondary to antimetabolite or biologic therapy).³⁷

Failure of medical therapy can refer to continuing severe disease activity or, at worst, to so-called toxic megacolon. The term *toxic megacolon* is actually a misnomer in that not all patients with this condition actually have a true megacolon [see Figure 9a]. In common usage, the term *toxic megacolon* refers to any condition associated with colitis that is severe enough to result in sloughing of the colonic mucosa; such



Figure 7 (a) Shown is pyoderma gangrenosum affecting the peristomal and incisional area 6 months after creation of a loop ileostomy in a 16-year-old girl who had undergone colectomy with ileal pouch-anal anastomosis for a presumed initial diagnosis of ulcerative colitis. (b) Shown is peristomal gangrenosum of the breast in an otherwise asymptomatic patient with Crohn colitis and perianal Crohn disease who had a diverting loop ileostomy.

sloughing permits endotoxins to enter the circulatory system and evoke a septic response. The signs and symptoms of toxic megacolon include those characteristic of sepsis-leukocytosis, fever, tachycardia, and hypoalbuminemia. These patients are very ill and often manifest ileus, which is an ominous

development that frequently signals impending perforation. Emergency surgical intervention is required. At operation, the colon is often distended, and when the specimen is opened, the colon may appear almost autolytic [see Figure 9b]. In this state, the bowel frequently does not hold staples well; accordingly, it is often helpful to sew the distal Hartmann stump between the left and right halves of the anterior inferior rectus fascia at the lower abdominal incision and then to close the skin over it.³⁸ Thus, if the staple line is disrupted, the result is essentially a surgical site infection that can be opened and drained rather than the pelvic abscess [see Figure 9c] that could develop if the rectal stump were located deep within the pelvis.

Types of Disease

Segmental disease In a 2003 review of 92 consecutive cases of patients with Crohn colitis, the number of patients with segmental colonic Crohn disease and the number of those with pancolonic disease were nearly equal.³⁶ Approximately 63% of those with segmental colitis had other disease involvement as well (e.g., jejunoileal, ileocolic, or perianal), compared with only 12% of those with pancolitis. The recurrence rate, however, was higher in patients with segmental colitis than in those with pancolitis. In addition, the risk of recurrence was higher in patients who had granulomatous disease than in those who did not.

Pancolonic disease In cases of pancolonic Crohn disease with associated perianal, jejunoileal, or ileocolic



Figure 8 Shown is a sigmoid colon stricture secondary to Crohn disease that caused obstructing symptoms refractory to medical therapy.

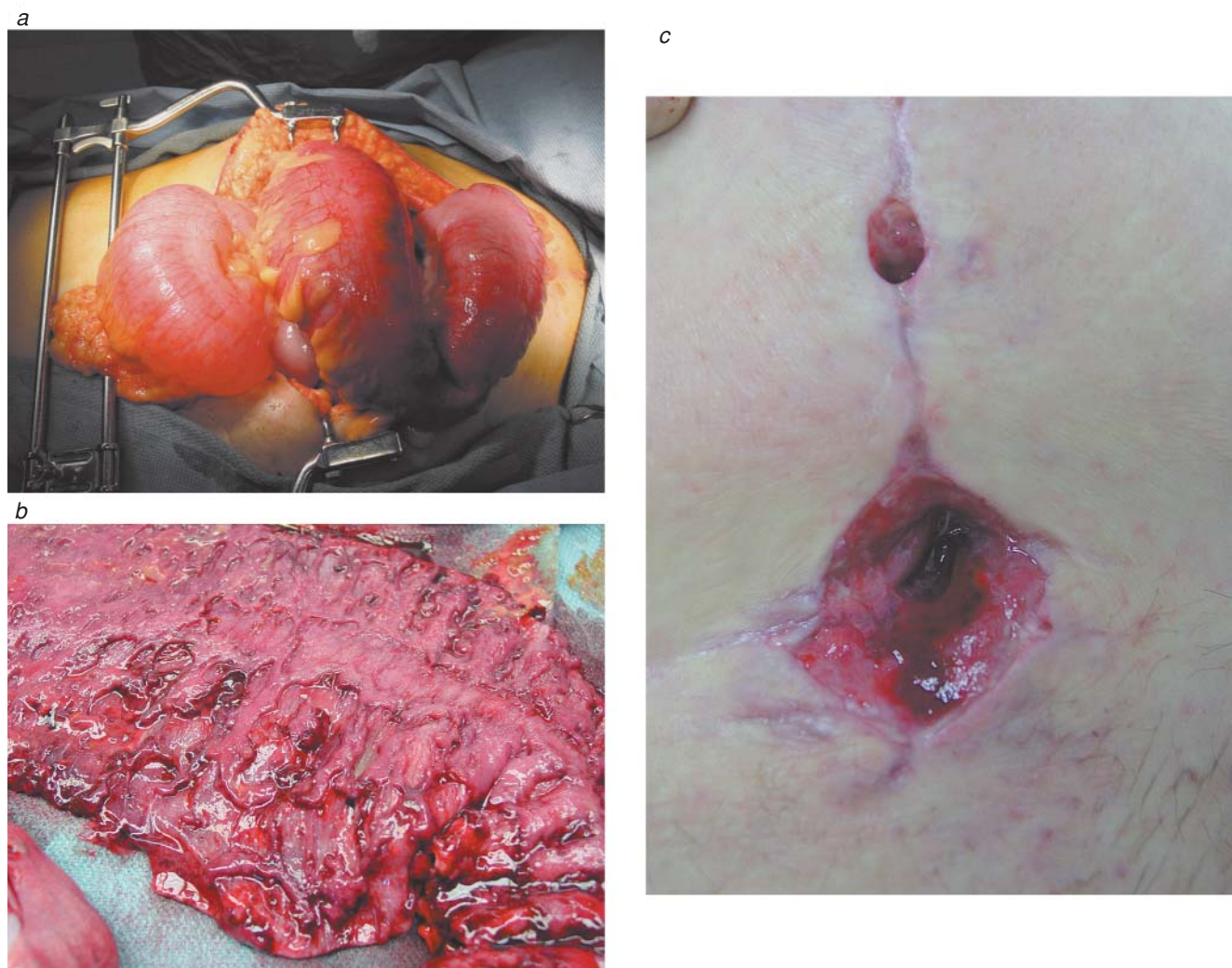


Figure 9 (a) Shown is toxic megacolon in a 17-year-old girl with Crohn colitis. The colon is massively distended and near perforation at the time of operation. (b) When the specimen is opened, it is apparent that large segments of the mucosa have sloughed off, leaving denuded muscle wall. (c) The distal rectosigmoid is incorporated between the left and right halves of the anterior inferior rectus fascia at the lower abdominal incision and placed underneath the skin, which is then closed over it. Thus, in the event of disruption of the distal stump, the contents drain harmlessly through the wound rather than resulting in a pelvic abscess.

involvement, diagnosis is not difficult. However, most patients with Crohn pancolitis do not have other sites of disease involvement, nor do they have granulomas.³⁶ Consequently, differentiation of Crohn pancolitis from ulcerative colitis can be very difficult. Many patients with Crohn disease have been subjected to colectomy with ileal pouch-anal anastomosis (IPAA) because they were initially presumed to have ulcerative colitis.

Operative Procedures

Total proctocolectomy with end ileostomy The traditional procedure for colonic Crohn disease is total proctocolectomy with end ileostomy, which is associated with an 8 to 15% rate of recurrence in the small bowel proximal to the stoma.^{39–41} This operation remains the best choice in patients with severe rectal and anal Crohn disease (e.g., those

with so-called watering-can perineum [see Figure 10a]) and carries the lowest risk of disease recurrence. In contrast to the approach taken in patients with rectal cancer, which involves excising the external anal sphincter and a large portion of the levator muscles, the approach taken in those with colonic Crohn disease is intersphincteric, with dissection performed in the plane between the internal and external anal sphincters to reduce the size of the perineal wound and facilitate healing [see Figure 10b]. Even with the intersphincteric approach, delayed healing of the perineal wound is common, occurring in as many as 30% of patients.

Subtotal colectomy with ileorectal or ileosigmoid anastomosis Because many patients with Crohn disease are young, surgeons have long been interested in operations that do not involve an ileostomy. In the absence of significant

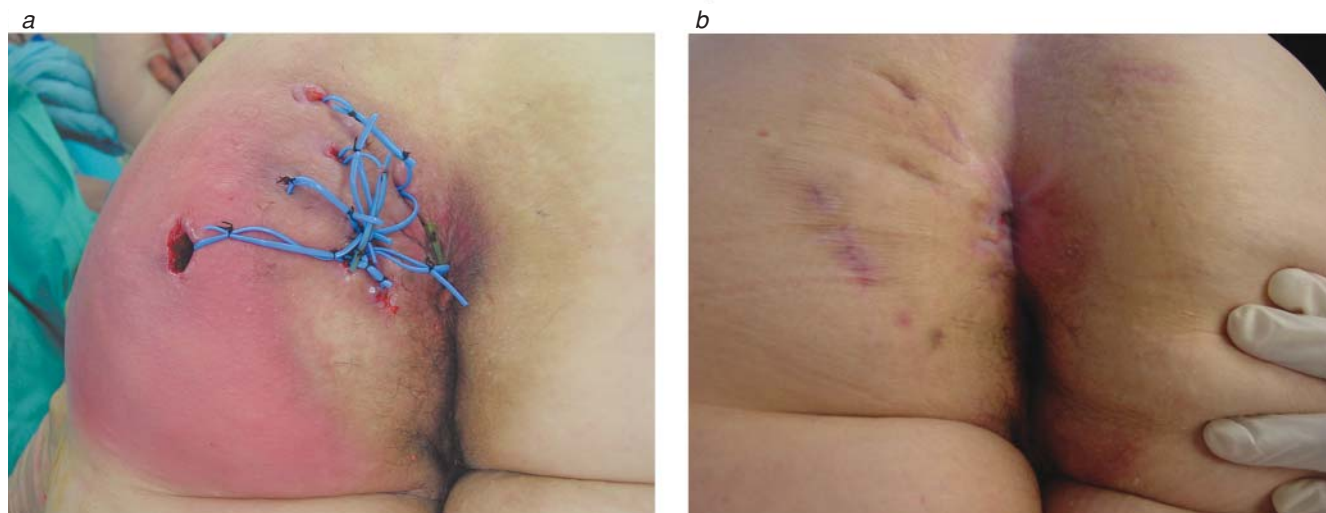


Figure 10 (a) Vessel loops can be used as setons for drainage of abscesses caused by perianal Crohn disease. They can be left in as long as necessary and help prevent recurrent abscess formation. (b) Same patient 6 months following total proctocolectomy.

rectal and anal disease, subtotal colectomy with ileorectal or ileosigmoid anastomosis is an option. Unfortunately, this operation is associated with high recurrence rates (up to 70%)⁴²; however, with the advent of more effective immunosuppressive and biologic therapy, it is hoped that these rates can be reduced. As much palpably normal distal rectum and colon as possible should be spared. The anastomosis can be stapled, although if the bowel wall is thickened, many surgeons would feel more secure with a handsewn anastomosis in either one or two layers.

Segmental resection Currently, more surgeons are advocating colon-sparing procedures for Crohn disease. Although this is a relatively new approach, there have already been some reports documenting the safety of segmental resection in cases of limited disease.⁴³ In patients with colonic strictures resulting in obstruction, segmental resection into palpably normal areas of the bowel yields prompt resolution of symptoms. Because the colon performs an important water-absorbing function, many patients with a limited amount of small bowel can still live without intravenous supplementation if a significant segment of the colon is left in situ. However, patients with segmental Crohn disease appear to have a higher recurrence rate than those with pancolitis, as do patients with granulomas.³⁶ Surgical treatment of Crohn disease continues to undergo reevaluation and reassessment of results on the basis of the availability of newer medical therapies.

Colectomy with IPAA Although colectomy with IPAA is usually not an operation that one would knowingly perform in a patient with Crohn disease, every year many patients undergo this procedure as treatment of colonic inflammatory bowel disease that initially is incorrectly presumed to be ulcerative colitis but later is diagnosed as Crohn disease (on the basis of either final pathologic analysis of the resected specimen or the disease's clinical behavior). Generally

speaking, in the absence of fistulizing disease, most of these patients are able to maintain their pouch, but they require medical therapy for disease control.^{36,44–47} Some surgeons, after very careful patient counseling regarding the real risks of fistulizing disease and other adverse sequelae, will consider IPAA for select patients with Crohn colitis with no evidence of other sites of involvement.⁴⁸

ANAL DISEASE

Types of Disease

With stenosis For patients with anal strictures that are not regularly dilated, the outlook is poor. Such strictures pose functional obstructions and typically lead to continuing problems with fistulas and suppurative disease. They frequently become more and more fibrotic over time and often extend proximally. Most of these patients eventually require fecal diversion. Management generally involves self-dilation, which can often be done with Hegar dilators. If the stenosis is not dealt with, all other treatment of the Crohn disease is doomed to failure; obstruction at the level of the anal canal inevitably results in the persistence of anorectal disease.

Without stenosis Anal Crohn disease without stenosis is much easier to treat medically. Long-term oral metronidazole therapy is often helpful; other medications (e.g., anti-tumor necrosis factor antibody) may be useful as well. Broad fissures are usually asymptomatic. Surgical treatment should be avoided unless the lesions are causing symptoms. Because they tend to have more liquidy bowel movements, patients with Crohn disease need an optimally functioning anal sphincter; hence, fistulotomies, which divide portions of the sphincter, should be avoided if at all possible. Placement of setons through fistula tracts can often prevent abscess formation, provide drainage, and thereby prevent perianal pain while minimizing sphincter trauma. Silk sutures, vessel loops, or Penrose drains also can be used as setons [see

Figure 10]. Although some have reported good results with a collagen fistula plug for Crohn disease,⁴⁹ others, including the author, have not had similarly favorable experiences.^{50,51} Rectovaginal fistulas pose a particular challenge. In the presence of active Crohn disease, advancement flap repair of such fistulas has a low success rate.⁵² Laparoscopically assisted loop ileostomy improves the success rate, but, unfortunately, the fistulas may recur when intestinal continuity is reestablished.

CHEMOPROPHYLAXIS

In 1995, a prospective, randomized study showed that patients who underwent ileocolic resection and were given mesalamine postoperatively had a significant reduction in both the symptomatic and the endoscopic rate of recurrence.³⁵ Not all of the work done since then has confirmed these results, but several studies and a meta-analysis have indicated that mesalamine does reduce the postoperative recurrence rate of Crohn disease.⁵³ Many patients undergoing surgical treatment of Crohn disease are advised to take some type of postoperative preventive medical therapy, either a 5-ASA derivative (e.g., mesalamine) or a stronger immunosuppressive agent (e.g., 6-mercaptopurine or azathioprine). Better studies are required to document the efficacy of the latter agents in preventing recurrence. It is hoped that chemoprophylaxis will reduce the anticipated recurrence rates by 30 to 40%.

SURVEILLANCE

At present, there are no clear guidelines for surveillance after operative treatment of Crohn disease. In my opinion, however, given the increased risk of colorectal cancer in this setting, patients with Crohn disease who retain some colon should undergo colonoscopy every 2 years, not only to detect any development of colonic neoplasia but also to identify any recurrence of disease in a timely manner. If recurrent Crohn disease is detected, appropriate medical therapy should be promptly instituted, with the aim of avoiding subsequent operation if possible.

BEHAVIORAL MODIFICATION

Exposure to cigarette smoke is known to exacerbate the symptoms of Crohn disease. Smoking has been reported to affect the overall severity of the disease, with smokers having a 34% higher recurrence rate and a higher rate of reoperation than nonsmokers.^{54–56} A 1999 study of 141 Crohn disease patients who had undergone ileocolic resection, of whom 79 were nonsmokers and the remainder were smokers, found that the respective 5- and 10-year recurrence-free rates were 65% and 45% in smokers and 81% and 64% in nonsmokers. The recurrence rates were higher in heavy smokers (≥ 15 cigarettes/day) than in moderate smokers.⁵⁷

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12 DIVERTICULITIS

John P. Welch, MD, FACS, Jeffrey L. Cohen, MD, FACS, FASCRS, and Rafal Barczak, MD

Diverticula are small (0.5 to 1.0 cm in diameter) outpouchings of the colon that occur in rows at sites of vascular penetration between the single mesenteric taenia and one of the antimesenteric taeniae. At the sites of most diverticula, the muscular layer is absent [see Figure 1]. Technically, such lesions are really pseudodiverticula; true diverticula (which are much less common than pseudodiverticula) involve all layers of the bowel wall. Nevertheless, both pseudodiverticula and true diverticula are generally referred to as diverticula.

The sigmoid colon is the most common site of diverticula: in 90% of patients with diverticulosis, the sigmoid colon is involved.¹ If a diverticulum becomes inflamed as a result of obstruction by feces or hardened mucus or of mucosal erosion, a localized perforation (microperforation) may occur—a process known as diverticulitis. The incidence of diverticulitis has been estimated to be about 10 to 25% in patients with colonic diverticula.¹ Limited prospective data suggest that the risk of developing diverticulitis is low in patients with symptomatic diverticulosis.² Both diverticulosis and variants of diverticulitis may be subsumed under the more encompassing term *diverticular disease*.

The incidence of diverticular disease increases with age. Diverticula are quite common in elderly patients, being

present in more than 80% of patients older than 85 years. Consequently, as the population of the United States continues to age, the overall risk of diverticular complications continues to increase. Before the 20th century, diverticular disease was rare in the United States. By 1996, however, 131,000 patients were being admitted to hospitals with diverticulitis each year.³

A diet containing refined carbohydrates and low-fiber substances, such as is currently widespread in many developed countries (especially in the West), has been associated with the emergence of this disease entity. A low-residue diet facilitates the development of constipation, which can lead to increased intraluminal pressure in the large bowel. In addition, elevated elastin levels are commonly noted at colon wall sites containing diverticula,⁴ and this change causes shortening of the taeniae.¹ High-pressure zones or areas of segmentation may develop [see Figure 2], usually in the sigmoid colon, and diverticula begin to protrude at these locations.⁵ If microperforation of a thin-walled diverticulum takes place, local or, uncommonly, widespread contamination with fecal organisms may ensue. The pericolic tissue (typically, the mesentery and the pericolic fat) thus becomes inflamed, whereas the mucosa tends to remain otherwise normal.

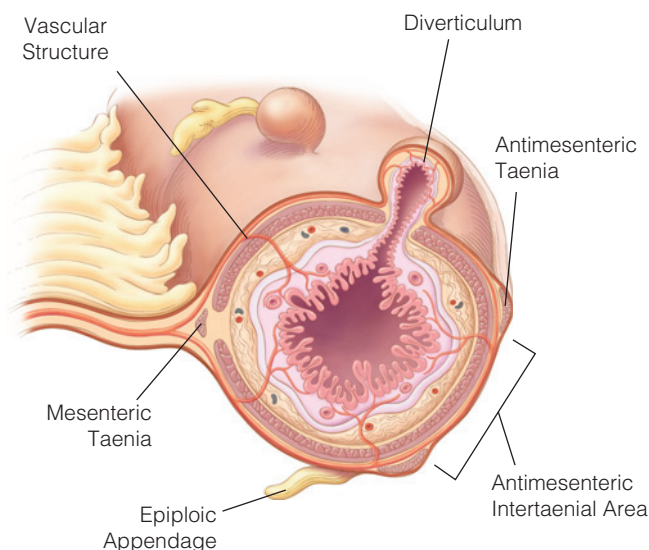


Figure 1 Illustrated are anatomic findings in a segment of colon containing diverticula. Diverticula are located at sites where blood vessels enter the colonic wall.⁸⁷

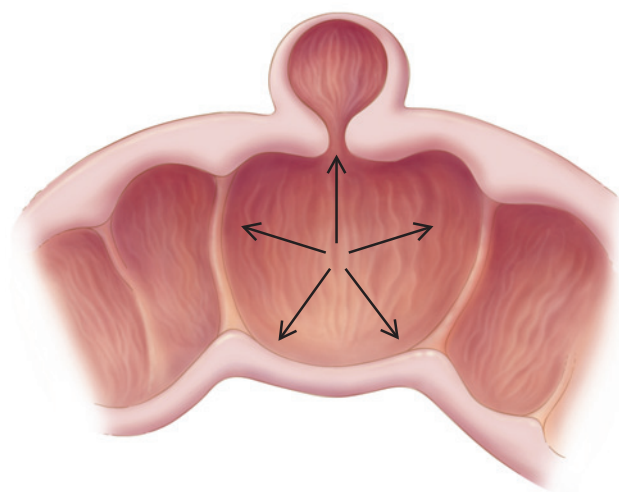


Figure 2 Depicted is a schematic representation of the process termed segmentation in the colon. It has been theorized that high-pressure compartments lead to the development of diverticula.⁸⁸

Several factors appear to promote the development of diverticular disease and its complications, including decreased physical activity,⁶ obesity,⁷ intake of nonsteroidal antiinflammatory drugs (NSAIDs),⁸ smoking,⁹ and constipation from any cause (e.g., diet or medications). The well-known Western afflictions cholelithiasis, diverticulosis, and hiatal hernia frequently occur together (the Saint triad). Obesity has been associated with the intake of low-fiber diets,¹⁰ and growing numbers of young, obese patients with diverticulitis are being seen by physicians. Consumption of nuts, corn, or popcorn does not increase the incidence of diverticulitis or diverticular bleeding.¹¹

Clinical Evaluation

HISTORY

Uncomplicated (Simple) Diverticulitis

The classic symptoms of uncomplicated acute diverticulitis are left lower quadrant abdominal pain, a low-grade fever, irregular bowel habits, and, possibly, urinary symptoms if the affected colon is adjacent to the bladder. If the sigmoid colon is highly redundant, pain may be greatest in the right lower quadrant. Diarrhea or constipation may occur, together with rectal urgency.

The differential diagnosis includes gynecologic and urinary disorders, perforated colon carcinoma, Crohn disease, ischemic colitis, and, sometimes, appendicitis. Chronic diarrhea, multiple areas of colon involvement, perianal disease, perineal or cutaneous fistulas, or extraintestinal signs are suggestive of

Crohn disease. Rectal bleeding should raise the possibility of inflammatory bowel disease, ischemia, or carcinoma; such bleeding is uncommon with diverticulitis alone. Given the prevalence of diverticula, it is not surprising that colon carcinoma may coexist with diverticular disease [see Figure 3].

Complicated Diverticulitis

Some cases of diverticulitis are classified as complicated, meaning that the disease process has progressed to obstruction, abscess or fistula formation, or free perforation [see Figure 4]. Complicated diverticulitis may be particularly challenging to manage,¹² especially because patients may have no known history of diverticular disease. Lower gastrointestinal (GI) bleeding is also a complication of diverticular disease in 30 to 50% of cases; in fact, diverticula are the most common colonic cause of lower GI bleeding. When diverticular hemorrhage occurs [see 5:6 *Lower Gastrointestinal Bleeding*], it is usually associated with diverticulosis rather than with diverticulitis. Approximately 50% of diverticular bleeding originates in the right colon, despite the low incidence of diverticula in

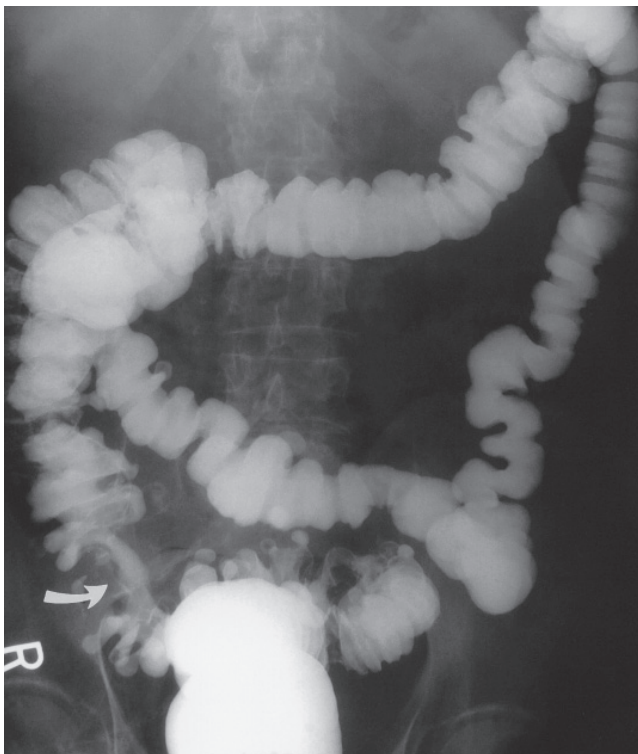


Figure 3 Barium enema shows a napkin-ring carcinoma (arrow) in the middle of multiple diverticula in a redundant sigmoid colon.

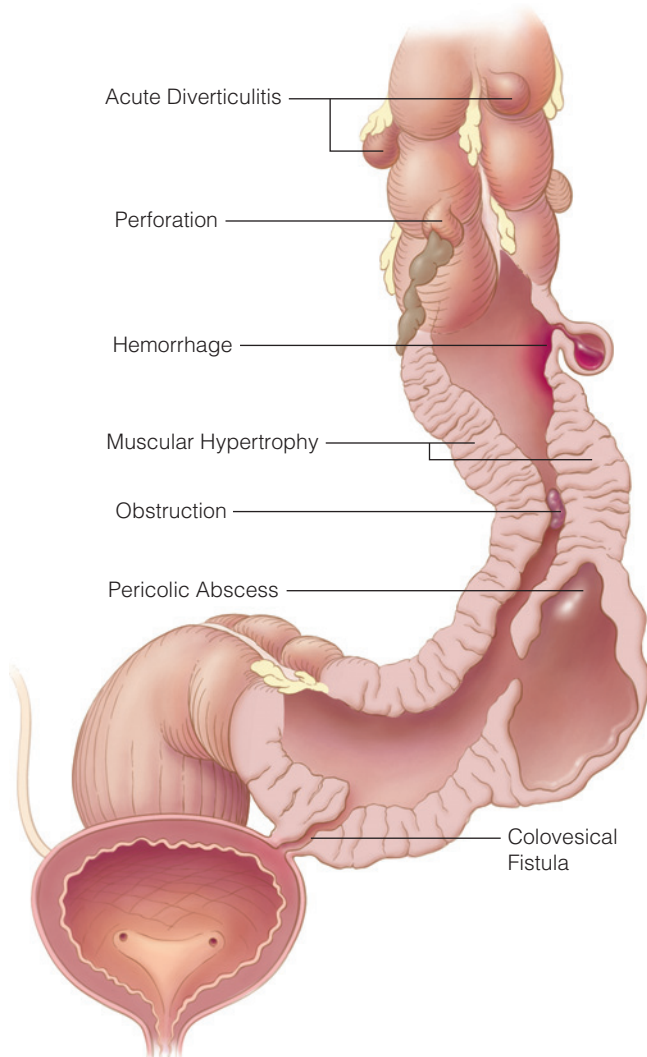


Figure 4 Shown are major complications of diverticular disease of the sigmoid colon.⁸⁹

this segment of the colon. Patients tend to be elderly and to have cardiovascular disease and hypertension. Regular intake of NSAIDs may increase the risk of this complication. Although patients may lose 1 to 2 units of blood, the bleeding usually ceases spontaneously,¹³ and expeditious operative treatment generally is not necessary.

The most common form of complicated diverticulitis involves the development of a pericolic abscess, typically signaled by high fever, chills, and lassitude. Such abscesses may be small and localized or may extend to more distant sites (e.g., the pelvis). They may be categorized according to the Hinchey classification of diverticular perforations,¹⁴ in which stage I refers to a localized pericolic abscess and stage II to a larger mesenteric abscess spreading toward the pelvis [see Figure 5]. On rare occasions, an abscess forms in the retro-peritoneal tissues, subsequently extending to distant sites such as the thigh or the flank. The location of the abscess can be defined precisely by means of computed tomography (CT) with contrast.

Some abscesses rupture into adjacent tissues or viscera, resulting in the formation of fistulas. The fistulas most commonly seen in this setting (50 to 65% of cases) are colovesical fistulas. This complication is less common in women because of the protection afforded by the uterus.

Symptoms of colovesical fistulas tend to involve the urinary tract (e.g., pneumaturia, hematuria, and urinary frequency). Fecaluria is diagnostic of colovesical or enterovesical fistulas. Colovaginal fistulas (which account for 25% of all diverticular fistulas) are usually seen in women who have undergone hysterectomies. The diseased colon is adherent to the vaginal cuff. Most commonly, patients complain of a foul vaginal discharge; however, some patients present with stool emanating from the vagina.

About 10% of colon obstructions are attributable to diverticulitis. Acute diverticulitis can cause colonic edema and a functional obstruction that usually resolves with antibiotic infusion and bowel rest. Stricture formation is more common, usually occurring as a consequence of recurrent attacks of diverticulitis. Circumferential pericolic fibrosis is noted, and marked angulation of the pelvic colon with adherence to the pelvic sidewall may be seen. Patients complain of constipation and narrowed stools. Colonoscopy can be difficult and potentially dangerous in this setting. Differentiating a diverticular stricture from carcinoma may be impossible by any means short of resection.

The term *malignant diverticulitis* has been employed to describe an extreme form of sigmoid diverticulitis that is characterized by an extensive phlegmon and inflammatory

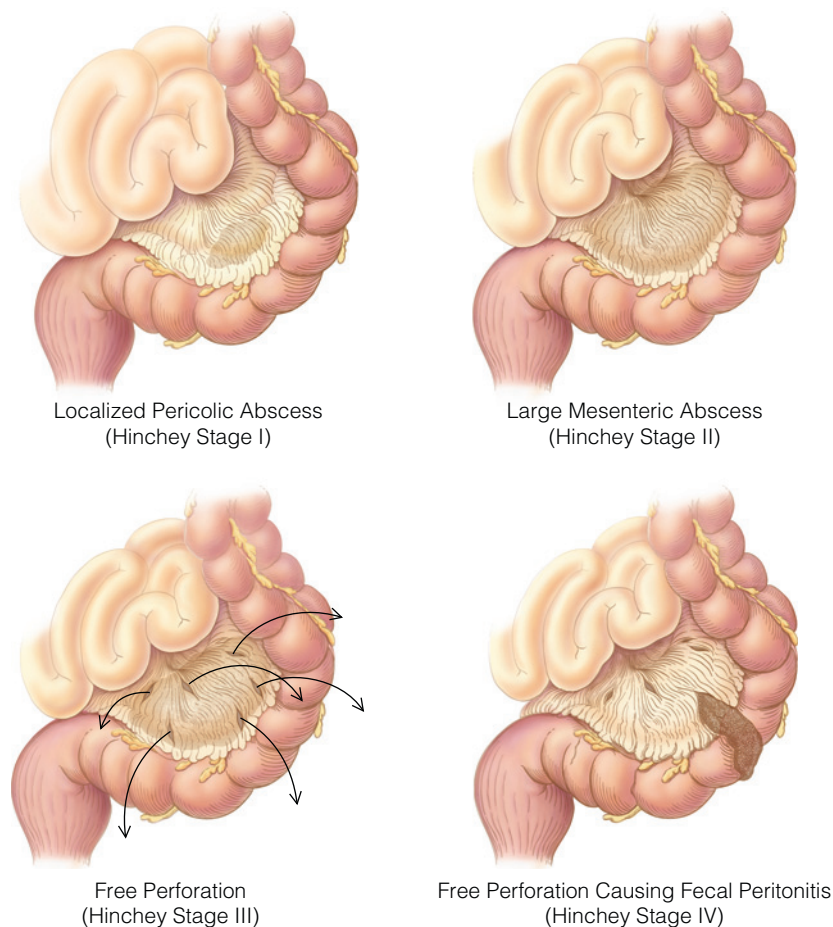


Figure 5 The Hinchey classification divides diverticular perforations into four stages. Mortality increases significantly in stages III and IV.¹⁸

reaction extending below the peritoneal reflection, with a tendency toward obstruction and fistula formation.¹⁵ Malignant diverticulitis is seen in fewer than 5% of patients older than 50 years who are operated on for diverticulitis.¹⁵ The process is reminiscent of Crohn disease, and CT scans demonstrate extensive inflammation. In this setting, a staged resection might be preferable to attempting a primary resection through the pelvic phlegmon. The degree of pelvic inflammation may subside significantly after diversion.¹⁵

A dangerous but rare complication of acute diverticulitis (occurring in 1 to 2% of cases) is free perforation,¹⁶ which includes both perforation of a diverticular abscess throughout the abdomen leading to generalized peritonitis (purulent peritonitis; Hinchey stage III) and free spillage of stool through an open diverticulum into the peritoneal cavity (fecal peritonitis; Hinchey stage IV). The incidence of free perforations may be increasing, at least in the southwestern United States.¹⁷ The overall mortality in this group is between 20 and 30%, that for purulent peritonitis is approximately 13%, and that for fecal peritonitis is about 43%.¹⁶

PHYSICAL EXAMINATION

Uncomplicated Diverticulitis

Physical examination reveals localized left lower quadrant abdominal tenderness with variable degrees of guarding and rebound tenderness. A mass is occasionally felt. The stool may contain traces of blood, but gross bleeding is unusual. Localized inflammation of the perforated diverticulum and the adjacent mesentery is present, and a phlegmon may be seen as well. Depending on the severity of the physical findings, patients may be managed either as inpatients or outpatients.

Complicated Diverticulitis

In a patient with a pericolic abscess, a mass may be detectable on abdominal, rectal, or pelvic examination. In a patient with a colovaginal fistula, a site of granulation tissue and drainage is seen at the apex of the vaginal cuff. In a patient with obstruction, there may be marked abdominal distention, usually of slow onset; abdominal tenderness may or may not be present, but if tears develop in the cecal taeniae, right lower quadrant tenderness is typically seen. In a patient with a free perforation, there is marked abdominal tenderness, usually commencing suddenly in the left lower quadrant and spreading within hours to the remainder of the abdomen. Hypotension and oliguria may develop later. Patients with rectal bleeding usually have no complaints of abdominal pain or tenderness, and they may be hypovolemic and hypotensive, depending on the rapidity of the bleeding.

Investigative Studies

IMAGING

The most useful diagnostic imaging study in the setting of suspected diverticulitis is a CT scan with oral and rectal contrast.¹⁸ Localized thickening of the bowel wall or inflammation of the adjacent pericolic fat is suggestive of diverticulitis; extraluminal air or fluid collections are sometimes seen together with diverticula [see Figure 6]. The most frequent findings (seen in 70 to 100% of cases) are bowel wall thickening, fat stranding, and diverticula.¹⁹ In some cases, small abscesses in the mesocolon or bowel wall are not detected.

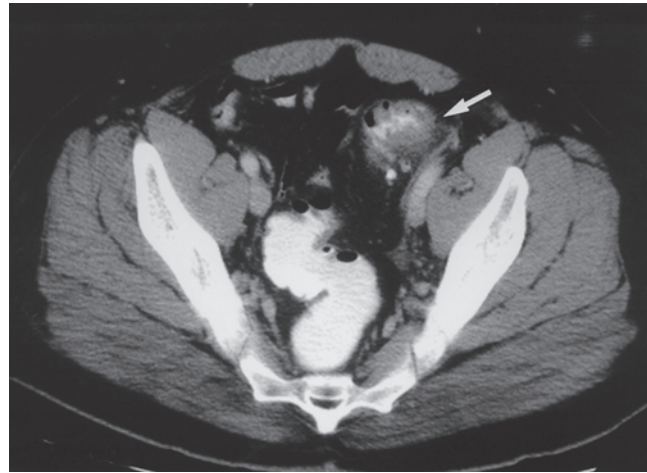


Figure 6 Computed tomographic scan shows thickening of the sigmoid colon (arrow) caused by acute diverticulitis.

The diagnosis of carcinoma cannot be excluded definitively when there is thickening of the bowel wall [see Figure 7]. Limited studies show that magnetic resonance imaging has high sensitivity and specificity for acute diverticulitis, and this technique does not expose the patient to ionizing radiation.²⁰

Although CT has tended to replace contrast studies in the evaluation of diverticulitis,¹⁹ the latter may be more useful in differentiating carcinoma from diverticulitis. A contrast study can also be complementary when the CT scan raises the suspicion of carcinoma.¹⁸ When diverticulitis is suspected, water-soluble contrast material should be used instead of barium because of the complications that follow extravasation of barium [see Figure 8 and Figure 9]. Furthermore, in the acute setting, only the left colon should be evaluated. Carcinoma is suggested by an abrupt transition to an abnormal mucosa over a relatively short segment; diverticulitis is usually characterized by a gradual transition into diseased colon over a longer segment, with the mucosa remaining intact. If the contrast study reveals extravasation of contrast outlining an abscess cavity [see Figure 9], an intramural sinus tract, or a fistula, diverticulitis is likely.¹

Colonoscopy is avoided when acute diverticulitis is suspected because of the risk of perforation. It may, however, be done 6 to 8 weeks after the process subsides to rule out other disorders (e.g., colon cancer) [see Figure 10]. When a patient does not respond to therapy, gentle flexible sigmoidoscopy may detect a carcinoma or some other abnormality.^{21,22} If diverticular disease is advanced, the endoscopic procedure may be difficult; the diverticular segment must be fully traversed for the examiner to be able to exclude a neoplasm with confidence. When major lower GI bleeding occurs, colonoscopy is done to search for polyps, carcinoma, or a site of diverticular bleeding. In the case of massive bleeding, selective arteriography is useful for localizing the source, and superselective embolization frequently quells the hemorrhage. The actual risk of bowel ischemia is low when superselective techniques are employed. Bleeding at the time of arteriography may be facilitated by the infusion of heparin or urokinase; however, this is a risky approach that should be taken only

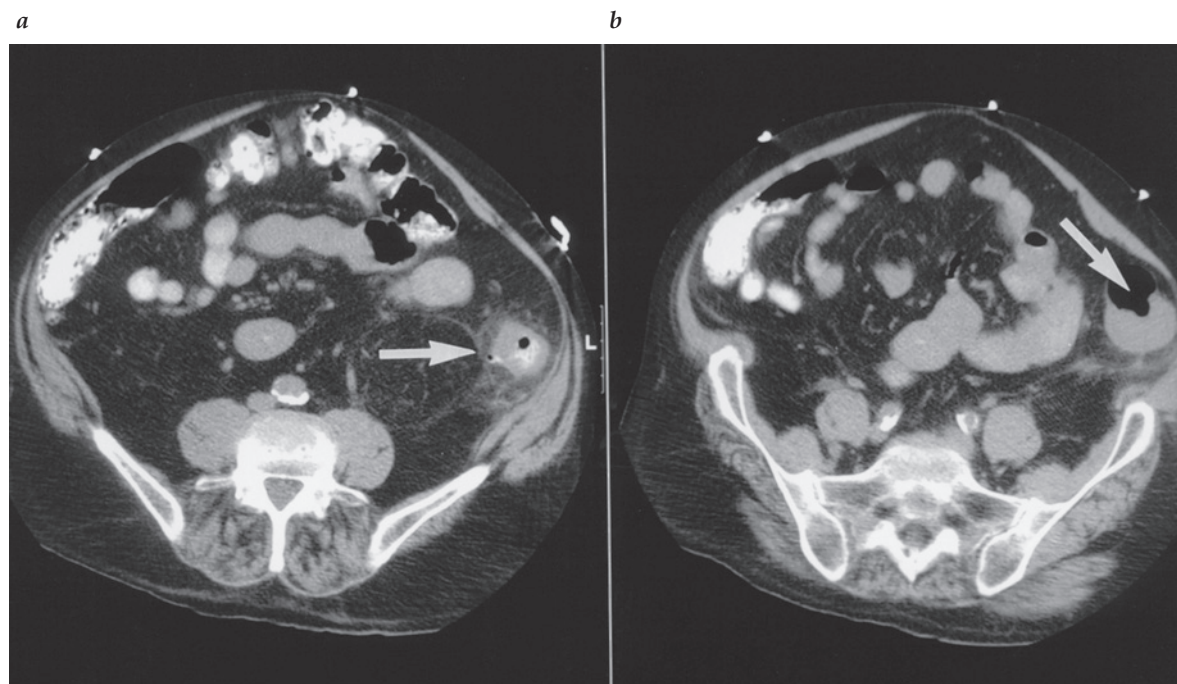


Figure 7 (a) Computed tomographic (CT) scan shows a thickened left colonic wall and diverticulum (arrow). Diverticulitis was considered the most likely diagnosis. (b) CT scan through an adjacent plane shows deformity of the mucosa, suggesting a possible apple-core lesion (arrow). Subsequent endoscopy revealed a carcinoma that was obstructing the colon almost completely.

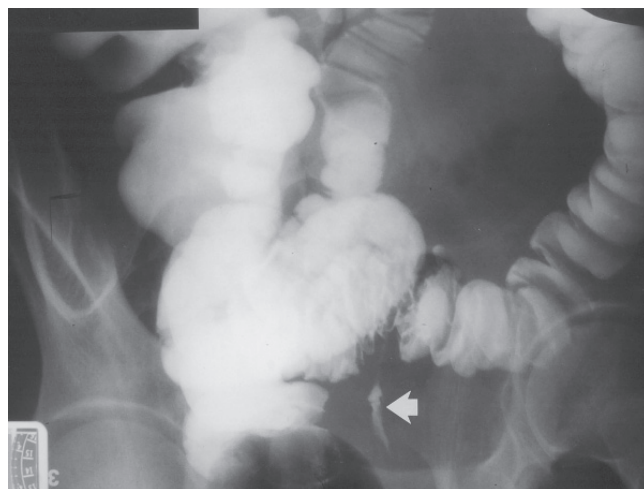


Figure 8 Contrast study shows local extravasation from the sigmoid colon (arrow); a diverticulum is visible.

when other attempts at localization have failed and recurrent bouts of bleeding have occurred.

When a colovesical fistula occurs, contrast CT with narrow cuts in the pelvis can be very helpful. The classic findings are sigmoid diverticula, thickening of the bladder and the colon, air in the bladder, opacification of the fistula tract and the bladder, and, possibly, an abscess [see Figure 11]. Cystoscopy is less specific, showing possible edema or erythema at the site of the fistula. A contrast enema helps rule out malignant



Figure 9 Shown is extravasation into an abscess cavity (arrow) from diverticulitis at the sigmoid colon–descending colon junction in a postevacuation film.



Figure 10 Colonoscopic view of several sigmoid diverticula reveals no evidence of active diverticulitis (e.g., edema or narrowing).

disease. The diagnostic tests that are most useful for detecting colovaginal fistulas are contrast CT and vaginography via a Foley catheter. Charcoal ingestion helps confirm the presence of colovesical or colovaginal fistulas. On rare occasions, colocutaneous fistulas may develop, causing erythema and breakdown of the skin. Colouterine fistulas may occur as well; these are also quite rare.

Management

MEDICAL

Uncomplicated diverticulitis is usually managed on an outpatient basis by instituting a liquid or low-residue diet and administering an oral antibiotic combination that covers

anaerobes and gram-negative organisms (e.g., ciprofloxacin with metronidazole or clindamycin) over a period of 7 to 10 days. Provided that symptoms and signs have subsided, the colon may be evaluated more fully several weeks later with a contrast study or colonoscopy if the diagnosis of diverticular disease has not already been established. If symptoms worsen, hospitalization should be considered. Over the long term, patients should be maintained on a high-fiber diet, although it may take months for the diet to have an effect on symptoms. Limited trials suggest that other substances such as probiotics and antiinflammatory agents such as mesalazine may help prevent recurrent attacks.^{23,24}

If more significant physical findings and symptoms of toxicity develop, hospitalization is warranted [see Figure 12]. Patients are placed on a nihil per os (NPO) regimen, and intravenous fluids and antibiotics are administered (e.g., a third-generation cephalosporin with metronidazole) until abdominal pain and tenderness have resolved and bowel function has returned. As a rule, resolution occurs within several days. If there is clinical evidence of intestinal obstruction or ileus, a nasogastric tube is placed. In most cases, ileus-related symptoms resolve with antibiotic treatment. CT scans are useful for establishing the correct diagnosis in the emergency department²⁵; furthermore, the severity of diverticulitis on CT scans predicts the risk of subsequent medical failure. Following the sedimentation rate may be helpful in assessing the effectiveness of treatment. Most patients recover with conservative management alone. By observing early trends in the leukocyte count and the maximum temperature in patients with acute diverticulitis, one can predict whether they will recover quickly as expected or if they will likely require prolonged intravenous antibiotics and/or an operation.²⁶ It has been estimated that 15 to 30% of patients admitted with acute diverticulitis will require surgical treatment during the same admission.¹

If fever and leukocytosis persist despite antibiotic therapy, the presence of an abscess should be suspected. Small (< 5 cm) abscesses may respond to antibiotic infusion and bowel rest. Larger abscesses that are localized and isolated may be accessible to percutaneous drainage [see Figure 13].²⁷ Generally, this technique is reserved for abscesses greater than 5 cm in

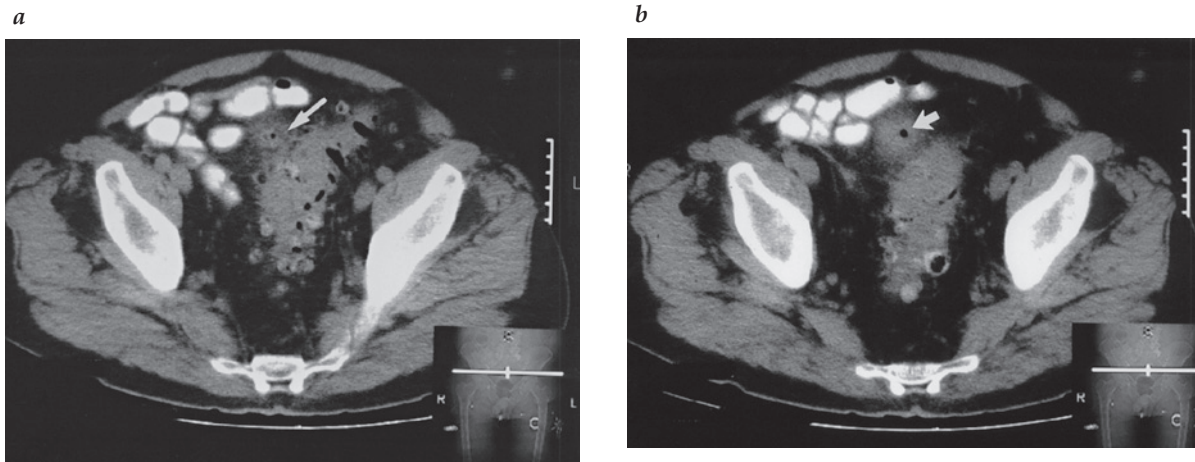


Figure 11 (a) Computed tomographic (CT) scan in a patient with a colovesical fistula shows air in the thickened tract (arrow) adjacent to the sigmoid colon. (b) CT scan through an adjacent plane shows air in the bladder (arrow) as a result of the fistula. No contrast is present in the bladder.

diameter in low-risk patients who are not immunocompromised. It often leads to resolution of sepsis and the resulting symptoms and signs (e.g., abdominal pain and tenderness and leukocytosis), usually within 72 hours, thereby facilitating subsequent elective surgical resection of the colon. In addition, percutaneous drainage offers cost advantages in that it reduces the number of operative procedures required and shortens hospital stay.²⁸ Patients with severe comorbidities at times can be managed with drainage alone.²⁹

Access to a pelvic collection may be difficult to obtain, and the drainage procedure typically must be done with the patient in a prone or lateral position. If the catheter drainage amounts to more than 500 mL/day after the first 24 hours, a fistula should be suspected. Before the catheter is removed, a CT scan is done with injection of contrast material through the tube to determine whether the cavity has collapsed. If this approach fails (as it usually does in patients with multiple or multiloculated abscesses), an expeditious operation may be necessary.¹⁷ An initial surgical procedure is required in about 20% of cases.

SURGICAL

Overall, approximately 20% of patients with diverticulitis require surgical treatment.³⁰ Most surgical procedures are reserved for patients who experience recurrent episodes of acute diverticulitis that necessitate treatment (inpatient or outpatient) or who have complicated diverticulitis. The most common indication for elective resection is recurrent attacks—that is, several episodes of acute diverticulitis documented by studies such as CT. Rerrecurrences may be more common than recurrences.³¹ In 2000, a task force of the American Society of Colon and Rectal Surgeons recommended sigmoid resection after two attacks of diverticulitis.³² A subsequent cost analysis using a Markov model suggested that cost savings could be achieved if resection was done after three attacks.³³ There is a growing tendency to question arbitrary guidelines for surgical management of recurrent attacks, with the exception of certain groups, such as immunocompromised patients.^{34,35} Current practice guidelines state that the recommendation to perform elective sigmoid resection after recovery from uncomplicated acute diverticulitis should be made on a case-by-case basis. The decision-making process should be influenced by the age and medical condition of the patient, the frequency and severity of attacks, and the presence of symptoms after the acute attack. Elective resection is generally recommended after an episode of complicated diverticulitis.³⁶ Efforts are made to time surgical treatment so that it takes place during a quiescent period 8 to 10 weeks after the last attack. Barium enema or colonoscopy may be employed to evaluate the diverticular disease and rule out carcinoma. The bowel can then be prepared mechanically and with antibiotics (e.g., oral neomycin and metronidazole on the day before operation).

Elective resection is a common sequel to successful percutaneous drainage of a pelvic abscess in an otherwise healthy, well-nourished patient.³⁷ The timing of surgery may be guided by the extent of the inflammatory changes (as documented by CT scanning) and the patient's clinical course. Most patients can be operated upon within 6 weeks. Elective resection is the preferred approach to diverticular fistulas as well. Colovesical fistulas are usually resected because of the risk of urinary sepsis and the concern that a malignancy might be overlooked.

Preferably, the operation is done when the acute inflammation has subsided.

Elective resection is done via either the open route or, increasingly, the laparoscopic route.³⁸ The learning curve for laparoscopic colectomy is 20 to 50 cases.³⁹ Obese patients with severe colonic inflammation are poorer candidates for laparoscopic resection.³⁸ In our institution, the development of hand-assisted procedures has widened the opportunities for using minimally invasive surgery [see 5:32 *Procedures for Diverticular Disease*], allowing all types of diverticular resections to be performed more safely.^{40,41} Hand-assisted laparoscopic sigmoidectomy for diverticular disease is associated with lower conversion rates and shorter operative times when compared with purely laparoscopic surgery.⁴² In addition, the hand-assisted approach affords a better opportunity to complete complicated cases in a minimally invasive fashion.^{2,43} Minimally invasive procedures have several advantages over conventional procedures: decreased intraoperative trauma, fewer postoperative adhesions, reduced postoperative pain, shorter duration of ileus, quicker discharge from the hospital, and earlier return to work.⁴⁴ Such procedures can be done safely in obese patients,⁴⁴ and the conversion rate is now low.^{39,44,45} The technical details of the procedures are addressed elsewhere [see 5:32 *Procedures for Diverticular Disease*].

Some patients with complicated diverticulitis require emergency resection because of free perforation and widespread peritonitis. In such patients, the American Society of Anesthesiologists (ASA) physical status score and the degree of preoperative organ failure may be significant predictors of outcome.⁴⁶ Unfavorable systemic factors (e.g., hypotension, renal failure, diabetes, malnutrition, immune compromise, and ascites) play a vital role in determining patient outcome,⁴⁶ as does the severity of the peritonitis (i.e., extent, contents, and speed of development). One of the unfortunate limitations of the Hinchey classification is that it does not take comorbidities into account. Because the bowel is not prepared before operation, the surgeon may feel uncomfortable doing an anastomosis. On-table lavage may be considered if contamination is minimal, but it adds to the time spent under anesthesia during an emergency procedure.

As a general rule, resection and immediate anastomosis (open or laparoscopic)⁴⁵ are suitable for Hinchey stage I and perhaps stage II diverticular perforations, whereas resection with diversion (the Hartmann procedure) is the gold standard for stage III and especially stage IV.⁴⁷ This recommendation is based on the finding that an anastomosis involving the left colon is risky when performed under emergency conditions.⁴⁸ The once-popular three-stage procedures are now of historical interest only. There are some reports of successful outcomes for type III and type IV cases after extensive abdominal lavage and two-layer anastomoses⁴⁹ or after on-table lavage of the colonic contents to allow primary anastomosis.⁵⁰ There have been a number of recent reports of laparoscopic peritoneal lavage and intraperitoneal drainage for the treatment of purulent peritonitis (Hinchey III) scenarios. Morbidity has been low, and a delayed laparoscopic sigmoid resection has been possible.^{51,52} Grading of comorbidities with classification systems such as APACHE II or the Mannheim peritonitis index can facilitate decision making with respect to the question of anastomosis versus diversion.^{53,54} The surgeon's decision must be individualized on the basis of each patient's

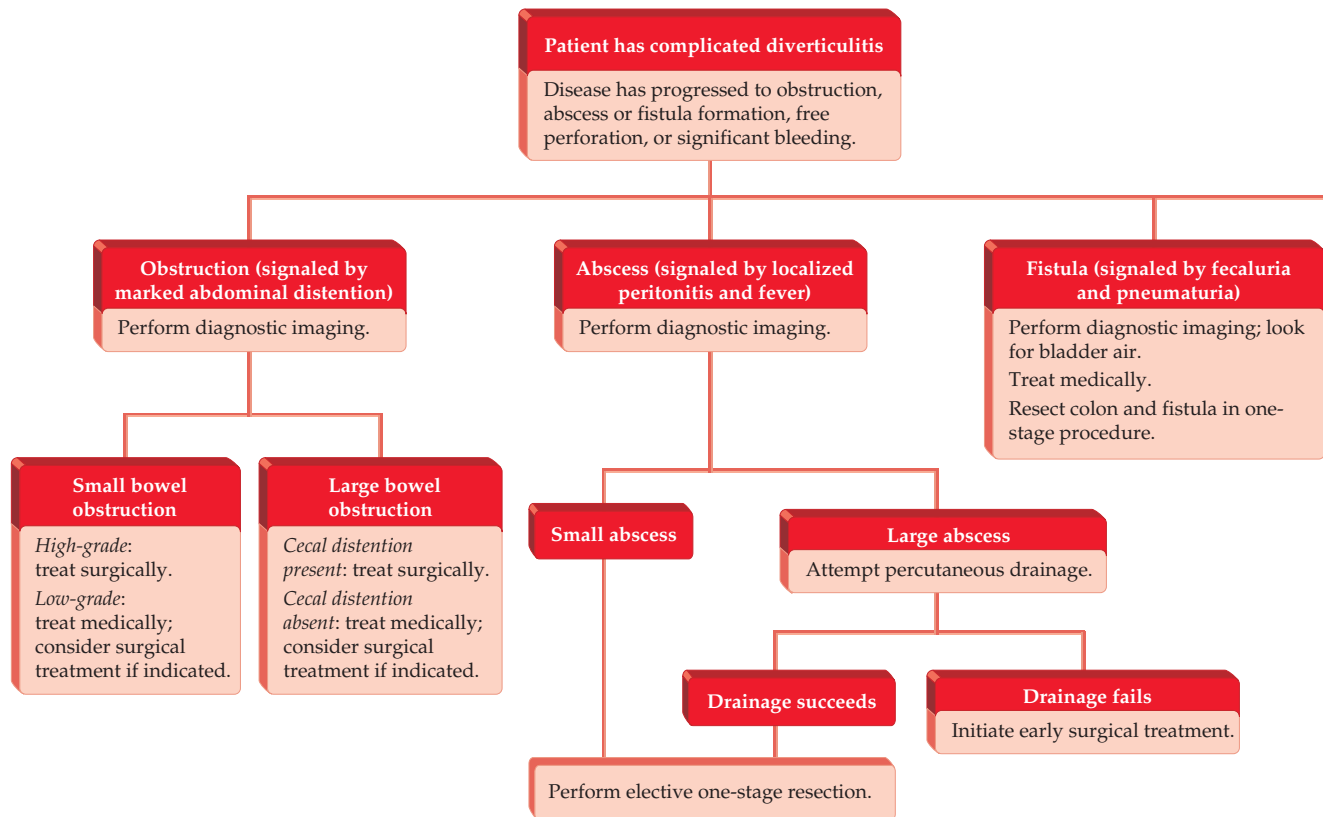


Figure 12 Algorithm outlining treatment options for complicated diverticulitis. GI = gastrointestinal; RBC = red blood cell.

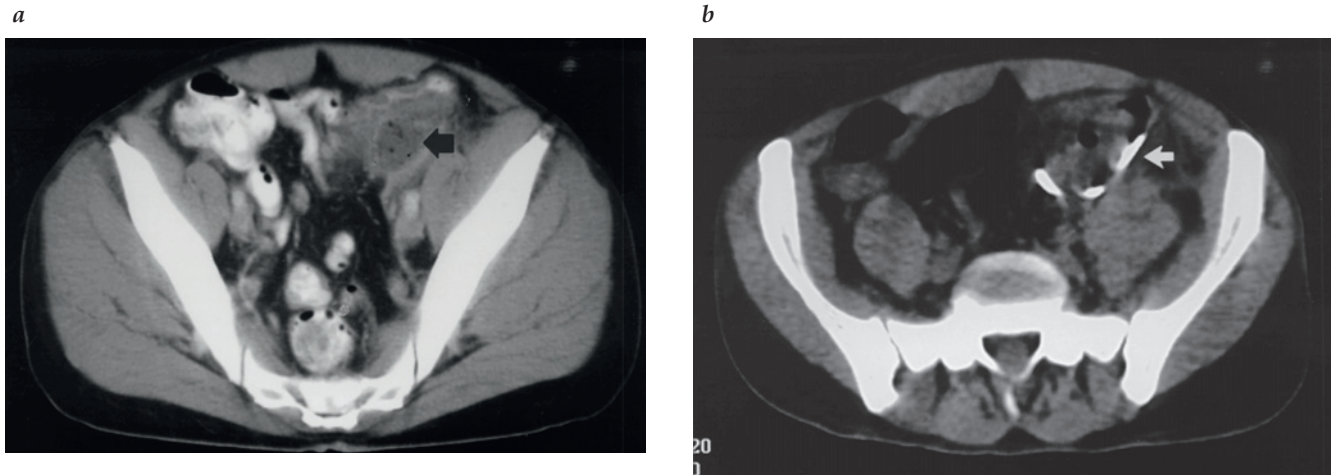
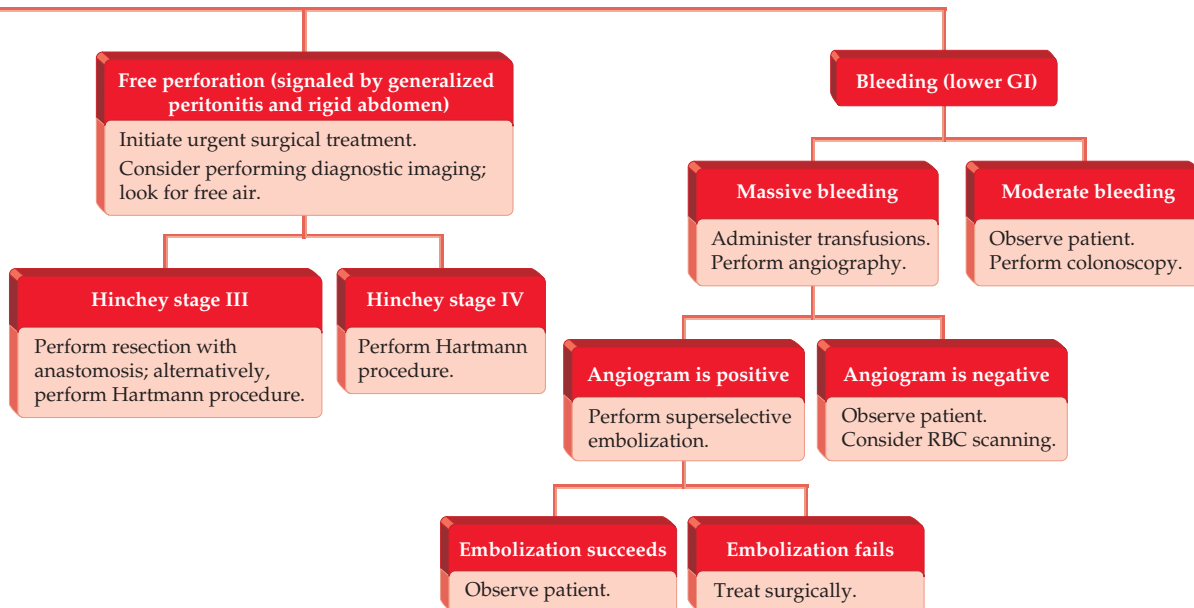


Figure 13 (a) Computed tomographic scan shows a pericolic abscess (arrow) caused by a contained perforation arising from sigmoid diverticulitis. (b) A pigtail catheter (arrow) has been placed into the abscess cavity by the interventional radiologist.

condition and needs. The literature on this topic is confusing in that most of the published reports are small and retrospective, with only limited classification of disease severity.

Currently, surgeons encountering acute diverticulitis are more likely to do one-stage resections, as opposed to Hartmann procedures, than they once were.^{46,55,56} The advantage of the

one-stage approach is that the colostomy takedown, frequent postoperative complications,⁵⁷ and attendant 4% mortality are avoided.⁵⁸ Furthermore, at least 30% of patients who undergo a Hartmann procedure never return for colostomy closure. A primary anastomosis can be protected with a proximal ileostomy as well.^{47,59} Transverse colostomy and loop ileostomy



appear to be equally safe, although skin changes may be more problematic after a colostomy,⁶⁰ and an ileostomy closure tends to be less complex than a colostomy closure. On-table lavage may also be used as an adjunct to anastomosis.

The risk of complications inherent in operations on the colon should always be kept in mind, especially in the relatively few patients undergoing emergency procedures.^{61,62} In this setting, the bowel is unprepared and systemic sepsis may be present. Potential complications include ureteral injuries; anastomotic leakage, anastomotic stricture, and postoperative intra-abdominal abscesses; perioperative bleeding involving the mesentery, adhesions, the splenic capsule, or the presacral venous plexus; postoperative small bowel obstruction; stomal complications; wound infection, wound dehiscence, and abdominal compartment syndrome; acute respiratory distress syndrome; and multiple organ dysfunction syndrome. Even after successful operations, some patients continue to have abdominal pain attributable to factors such as irritable bowel syndrome.^{63,64}

Large bowel obstruction secondary to diverticulitis can lead to considerable morbidity and may necessitate surgical intervention.⁵⁹ The obstruction is usually partial [see Figure 14 and Figure 15], allowing preparation of the bowel in many cases. High-grade obstruction represents a complex problem. If the cecum is dilated to a diameter of 10 cm or greater and there is tenderness in the right lower quadrant, expeditious surgery is necessary because of the risk of cecal necrosis and perforation. High-grade obstruction with fecal loading of the colon is usually

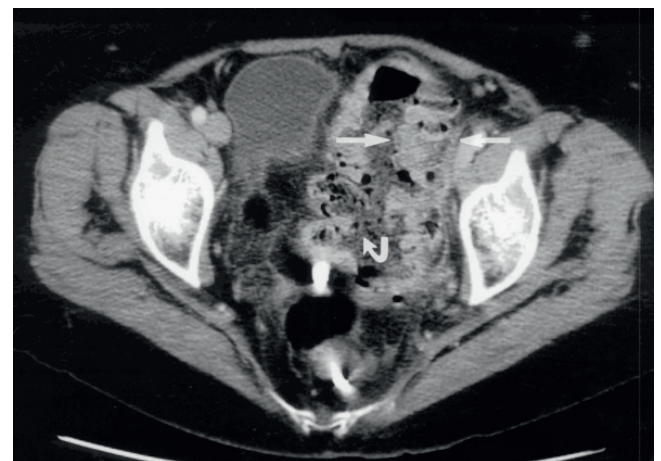


Figure 14 Computed tomographic scan shows marked thickening of the sigmoid wall (arrows) in a patient with diverticular disease who presented with symptoms of intractable constipation. No contrast is present in the lumen (curved arrow).

managed by performing a Hartmann procedure, although on-table lavage may be considered.¹⁷ A survey of GI surgeons in the United States indicated that 50% would opt for a one-stage procedure in low-risk patients with obstruction, whereas 94% would opt for a staged procedure in high-risk patients.⁶⁵

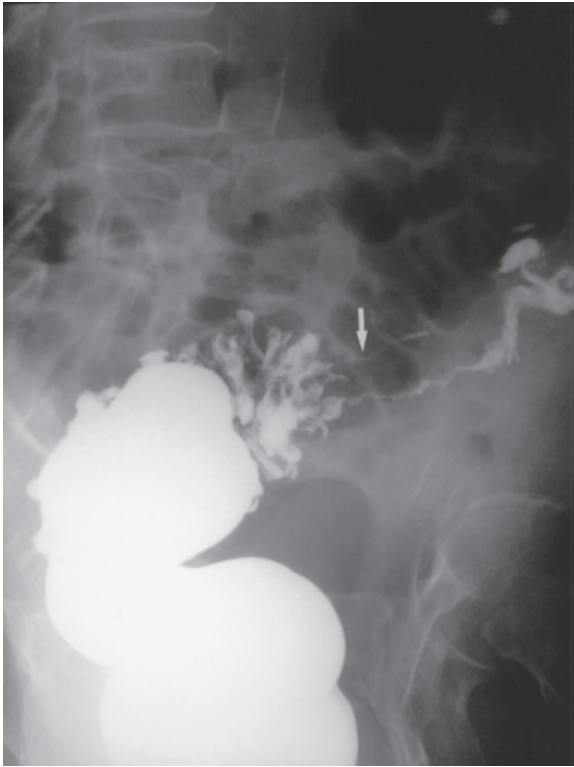


Figure 15 Contrast study shows high-grade retrograde obstruction, multiple diverticula, and a long proximal sigmoid stricture. A tiny extraluminal tract (possibly intramural) from a diverticulum (arrow) is seen.

Small bowel obstruction may also complicate the clinical picture. Mechanical small bowel obstruction may occur as a consequence of adherence of the small bowel to a focus of diverticulitis, especially in the presence of a large pericolic abscess. Whereas small bowel obstruction tends to cause periumbilical crampy abdominal pain and vomiting, these characteristic manifestations may be obscured in part by pain attributed to diverticulitis. The concern in this situation is that ischemic small bowel may be ignored, with potentially disastrous consequences. Diarrhea should trigger the suspicion of colonic disease, and formation of a fistula into the small bowel should raise the possibility of Crohn disease. CT scanning often helps the surgeon differentiate between primary and secondary small bowel obstruction, but, ultimately, exploratory surgery may be required for both diagnosis and treatment.

Lower GI bleeding caused by diverticular disease rarely calls for emergency resection because the bleeding is self-limited in most patients (80 to 90%). Furthermore, active diverticulitis is rare when active bleeding is the presenting symptom. Attempts are made to establish the active bleeding site by means of colonoscopy,⁶⁶ tagged red blood cell nuclear scans, or angiography; barium contrast studies have no role to play in this situation. Emergency resection is indicated if the bleeding is life-threatening and if colonic angiography and attempted superselective embolization prove unsuccessful. In an unstable patient, total abdominal colectomy is necessary if the site of bleeding is unknown, although identification of the bleeding site with intraoperative colonoscopy has been reported. In a stable patient with ongoing bleeding, repeat

angiography at a later time is appropriate, or so-called phar-macoangiography (infusion of heparin) can be employed in an attempt to induce bleeding.

Special Types of Diverticulitis

CECAL DIVERTICULITIS

In the United States, diverticulitis rarely involves the cecum or the right colon. Right-side diverticula occur in only 15% of patients in Western countries, compared with 75% in Singapore.¹ The incidence of cecal diverticulitis appears to be related to the number of diverticula present.⁶⁷ A classification system has been proposed that divides cecal diverticulitis into four grades [see Figure 16] to facilitate comparisons between different clinical series and to help surgeons formulate treatment plans in the operating room.⁶⁷ Some cecal diverticula are true diverticula, containing all layers of the bowel wall, but the majority are pseudodiverticula. Diverticulitis of the hepatic flexure and the transverse colon is even less common and can present with symptoms suggesting appendicitis.⁶⁸

Patients with right-side disease tend to be younger and to have less generalized peritonitis than patients with left-side diverticulitis.^{67,68} Because they typically present with right lower quadrant pain, fever, and leukocytosis, acute appendicitis is usually suspected. CT scans are helpful for differentiating cecal diverticulitis from appendicitis or colon cancer [see Figure 17].⁶⁹ If cecal diverticulitis is suspected (as in a patient who has previously undergone appendectomy or in a patient with known right-side diverticulosis who has experienced similar attacks in the past), medical management with observation and antibiotics is generally the favored strategy, just as with simple sigmoid diverticulitis. In Japan, where right-side diverticulitis is more common, medical treatment has been successfully used for recurrent attacks of uncomplicated right-side diverticulitis.⁷⁰ After a few weeks, colonoscopy should be performed to rule out a colonic neoplasm.

If the patient has significant peritonitis or the diagnosis is unclear, laparoscopy or laparotomy is indicated. It is important that one or the other be done because the mortality associated with delayed treatment of perforated cecal diverticulitis is high. In our institution, laparoscopy is usually employed; if the diagnosis is unclear, laparotomy is recommended. When inflammation is localized and minimal, colectomy is unnecessary, and incidental appendectomy should be considered if the cecum is uninvolved at the base of the appendix.⁷¹ If desired, the diverticulum may be removed as well.

Diverticulectomy should be done only if (1) carcinoma can be ruled out, (2) the resection margins are free of inflammation, (3) the ileocecal valve and the blood supply of the bowel are not compromised, and (4) perforation, gangrene, and abscess are absent.⁶⁷ Localized diverticulectomy, in general, should be reserved for grade I and grade II disease.⁶⁷ Sometimes, the ostium of the inflamed diverticulum is palpable if the cecum is mobilized surgically. On-table cecocolonoscopy through the appendiceal stump has also been helpful in establishing the diagnosis in the operating room.⁷¹ Grade III and IV cecal diverticulitis may be difficult to differentiate from carcinoma; resection is favored for these lesions. An anastomosis may be created if contamination is limited, but, generally, primary resection, ileostomy, and a mucous fistula are favored for treatment of grade IV disease.

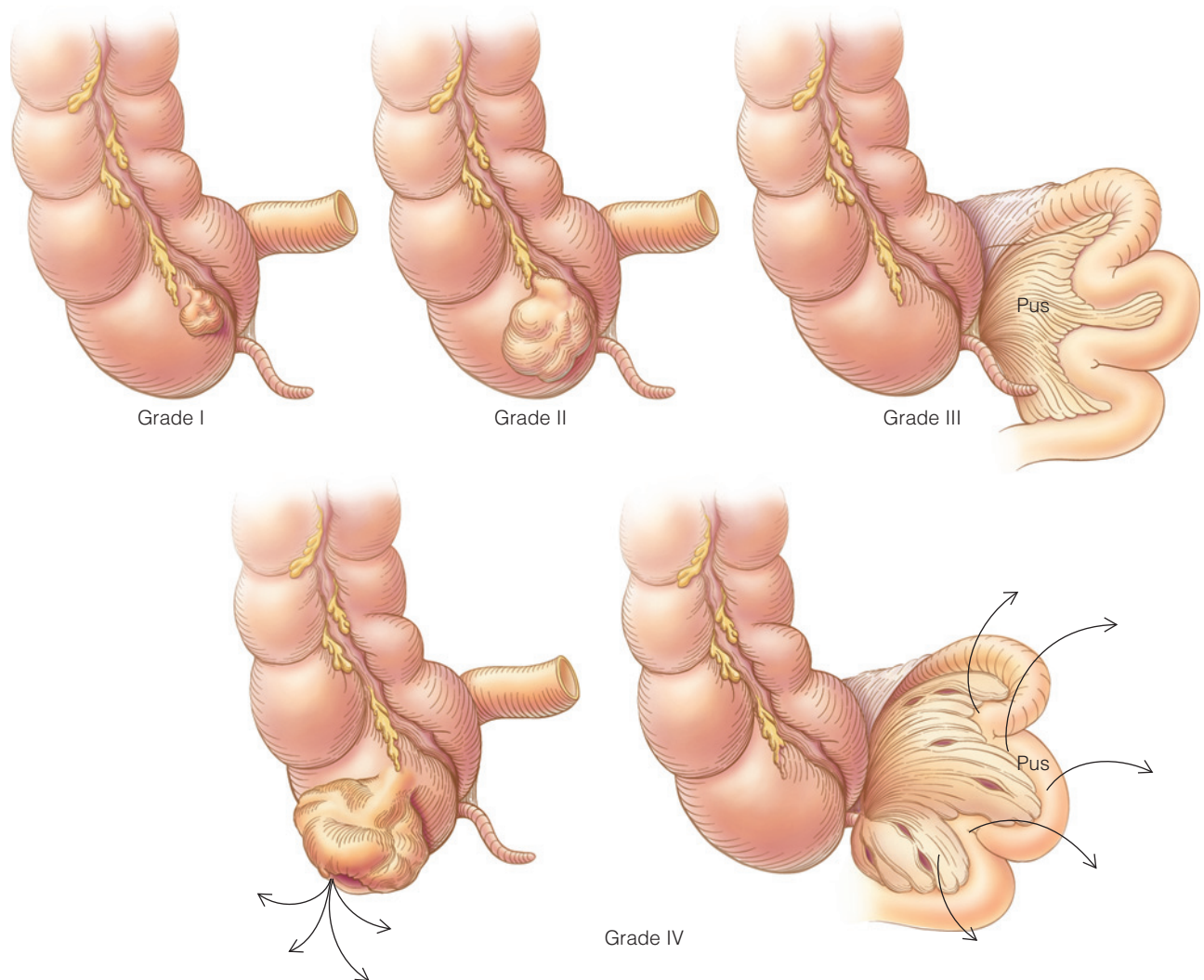


Figure 16 Illustrated is a proposed classification of pathologic types of cecal diverticulitis. Grade I is a specific inflamed diverticulum; grade II is a cecal mass; grade III is characterized by a localized abscess or fistula; and grade IV represents a free perforation or a ruptured abscess with peritonitis.⁵⁹

DIVERTICULITIS IN YOUNG PATIENTS

Diverticulitis in patients younger than 40 years has been a focus of considerable attention in the literature, although this group represents only about 2 to 5% of the patients in large series.³² The incidence of diverticulitis in young patients may be increasing, and obese Latino men appear to be at particular risk.⁷² This predominance in males reflects a tendency to underdiagnose acute diverticulitis in young women.⁷³ Some authors have asserted that diverticulitis is particularly virulent in young patients; however, current data tend not to support this concept, suggesting that patients with mild diverticulitis are misdiagnosed when hospitalized or are treated as outpatients. The high rate of early operation in young patients probably reflects misdiagnosis of diverticulitis as acute appendicitis rather than the development of particularly severe forms of diverticulitis.⁷² Patients found to have uncomplicated acute diverticulitis may, if desired, undergo incidental appendectomy in conjunction with medical treatment of diverticulitis.

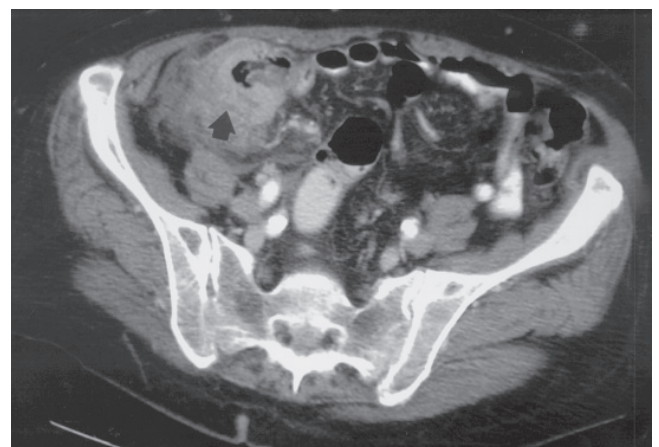


Figure 17 Computed tomographic scan shows inflammation in the pericecal area (arrow) and cecal edema, which could represent cecal diverticulitis. Because the appendix is not clearly visualized, appendicitis cannot be ruled out.

Unlike elderly patients, hospitalized young patients with diverticulitis tend to have few comorbidities other than obesity. Furthermore, young patients hospitalized for diverticulitis tend to have relatively advanced disease, perhaps as a consequence of delayed diagnosis, whereas elderly patients hospitalized with an admitting diagnosis of diverticulitis tend to exhibit a wider spectrum of disease severity. Young patients appear not to have a higher rate of recurrent diverticulitis than older patients do; thus, aggressive resection is not necessary at the time of the first attack.⁷² However, a finding of advanced diverticulitis on CT scans is a predictor of subsequent disease complications in this population.⁷⁴

In general, diverticulitis should be approached in the same fashion in younger patients as in older patients.⁷⁴ The pathophysiology of the disease is probably identical. As in the elderly, elective resection is recommended after recurrent attacks, not after a single attack; with follow-up, the majority of patients hospitalized with acute diverticulitis do not require operation.^{34,74–76}

DIVERTICULITIS IN IMMUNOCOMPROMISED PATIENTS

In view of their known predisposition to infection, immunocompromised patients (e.g., chronic alcoholics, transplant patients, and persons with metastatic tumors who are receiving chemotherapy) with diverticulitis are at particular risk.⁷⁷ There is no evidence that the incidence of diverticulitis is higher in this population than in the general population, but it is clear that immunocompromised patients have higher rates of operation once diverticulitis develops and that their postoperative mortality is higher.⁷⁸ Corticosteroid intake causes a number of significant problems, such as thinning of the colonic wall, lessening of the physical findings with diverticulitis, and an attenuated inflammatory response.

Any immunocompromised patient with abdominal pain should be evaluated aggressively. Contrast-enhanced CT is the imaging study of choice. The risk of perforation is increased in this setting, as is the risk of postoperative complications such as wound dehiscence. For an immunocompromised patient who has recovered from an episode of symptomatic diverticulitis, elective surgical treatment is recommended. A renal transplant patient with asymptomatic diverticulosis, however, need not undergo prophylactic colectomy. Pretransplantation colonic screening of patients older than 50 years does not reliably predict posttransplantation colonic complications.⁷⁹

ATYPICAL PRESENTATIONS

Diverticulitis may give rise to various unusual manifestations involving multiple organ systems [see Table 1]. Not surprisingly, immunocompromised patients are at particular risk.

Retroperitoneal abscesses can track into anatomic planes (e.g., along the psoas muscle) or through the obturator foramen to areas such as the neck, the thigh, the knee, the groin, and the genitalia. CT scanning is essential to outline the extent of such abscesses. Contrast enemas show the diverticula along with a sinus tract into the abscess cavity. Cultures of the abscess demonstrate the presence of colonic organisms

Table 1 Unusual Extra-Abdominal Presentations of Diverticulitis⁹⁰

Dermatologic	Pyoderma gangrenosum
Urinary	Ureteral obstruction Coloureteral fistula
Soft tissue	Thigh abscess Necrotizing fasciitis
Orthopedic	Osteomyelitis Arthritis
Gynecologic	Colouterine fistula Ovarian tumor/abscess
Genital	Epididymitis Pneumoscrotum
Neurologic	Coloepidural fistula
Vascular	Femoral vein thrombosis Mesenteric vein thrombosis Pylephlebitis Colovenous fistula
Perineal	Fournier gangrene Complex anal fistula

such as *Bacteroides fragilis*. Definitive treatment consists of wide abscess drainage and colon resection. Without aggressive surgical management, mortality is high.

The protean manifestations of diverticulitis also include pylephlebitis (which causes liver abscesses), arthritis, and skin changes. Diverticulitis has, in fact, replaced appendicitis as the most common source of liver abscesses of portal origin. Simple abscesses may be drained percutaneously if they are not too large, and multiple loculated abscesses may be managed with open drainage. The main risk factors for mortality from liver abscesses are immunosuppression, underlying malignancy, the presence of multiple organisms, and liver dysfunction. If the decision is made to perform a colectomy, the procedure may be done after drainage of the liver abscess or simultaneously with drainage during an open procedure.

GIANT DIVERTICULA

An anatomic curiosity sometimes encountered in patients with diverticular disease is a giant diverticulum, also termed a giant gas cyst or a pneumocyst of the colon.⁸⁰ These lesions, which may reach diameters of 40 cm, are believed to develop as a consequence of a ball-valve mechanism created by intermittent occlusion of the neck by fecal material that traps air in the diverticulum. Most giant diverticula are minimally symptomatic, causing only mild abdominal pain, and perforation is rare. A mobile mass may be palpable, and the gas-filled cyst can be seen on plain abdominal films. As many as two thirds of giant diverticula are opacified during a barium enema and can thereby be differentiated from other abnormalities (e.g., a mesenteric cyst, emphysematous cholecystitis, or a colon duplication) [see Figure 18]. The cyst tends to adhere densely to adjacent structures (e.g., the bladder and the small bowel). The treatment of choice is resection of the colon and the cyst; performing diverticulectomy alone can lead to the development of a colocutaneous fistula.



Figure 18 Giant sigmoid diverticulum opacified during a barium enema examination.⁸⁰

RECURRENT DIVERTICULITIS AFTER RESECTION

Recurrent diverticulitis is rare after a colectomy for diverticulitis, occurring in 1 to 10% of patients.⁸¹ As many as 3% of patients who have undergone resection for diverticulitis will require repeat resection. The differential diagnosis includes Crohn disease, irritable bowel syndrome, carcinoma, and ischemic colitis. CT and colonoscopy should be carried out. Particular care should be taken to review pathologic specimens for evidence of Crohn disease.

The only significant determinant of recurrent diverticulitis is the level of the anastomosis; the high pressure in the sigmoid colon distal to the anastomosis appears to be responsible.

In one study, the risk of recurrence was four times greater in patients with a colosigmoid anastomosis than in those with a colorectal anastomosis.⁸² Reoperation requires a dissection that commences in noninflamed tissue. Dissection may be particularly difficult near the pelvic sidewall because of fibrosis; ureteral stenting may facilitate identification of the ureters.

SUBACUTE AND ATYPICAL DIVERTICULITIS

A small number of patients experience recurrent episodes of left lower quadrant abdominal pain that are not accompanied by the classic findings of acute diverticulitis (e.g., fever and leukocytosis). The inflammatory changes associated with diverticula in this subgroup have been referred to as atypical, subacute, or smoldering diverticulitis.^{83,84} In this setting, there is not always a direct association between endoscopic and clinical findings; endoscopic evidence of diverticular inflammation has been seen in asymptomatic patients.⁸⁵ It has been suggested that there is a relation between diverticular disease and colitis.⁸⁶ Patients with chronic lower abdominal pain should undergo imaging studies and endoscopic evaluation, and other disorders (e.g., irritable bowel syndrome, inflammatory bowel disease, drug-induced symptoms, and bowel ischemia) should be excluded. In most cases of atypical diverticulitis, endoscopic findings are normal.⁸⁴ In carefully selected patients, colectomy often eliminates the abdominal pain, and many of these patients are eventually found to have histologic signs of acute and chronic mucosal inflammation.⁸⁴

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13 FULMINANT ULCERATIVE COLITIS

Roger Hurst, MD, Sharon L. Stein, MD, and Fabrizio Michelassi, MD

Fulminant ulcerative colitis is a potentially life-threatening disorder that requires expert management to allow for optimal outcomes. Once associated with very high mortality,¹ the medical and surgical treatment of fulminate ulcerative colitis has greatly improved such that mortality from fulminant ulcerative colitis currently is less than 3%.^{2,3} Optimal management necessitates coordination between medical and surgical therapy; hence, multidisciplinary strategies are required.

Disease Definition

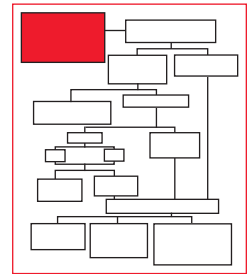
The most commonly applied classification for the severity of ulcerative colitis was described by Truelove and Witts, who identified clinical parameters to categorize mild, moderate, and severe colitis.⁴ The Truelove-Witts classification, however, does not specify a unique category for fulminant disease. Hanauer modified this classification scheme to include the designation of fulminant colitis [see Table 1].⁵ There is, however, no universally agreed-upon distinction between severe and fulminant ulcerative colitis.⁶ Some authors use the

terms “severe” and “fulminant” interchangeably, whereas others, concerned over the lack of a clear definition, recommend that the term “fulminant ulcerative colitis” be avoided.⁷ This recommendation aside, the term “fulminant ulcerative colitis” is an established component of the medical vernacular even if the term itself is not clearly defined.^{8–10} Fulminant ulcerative colitis is certainly a severe condition associated with systemic deterioration related to progressive ulcerative colitis. Most would agree that a flare of ulcerative colitis can be considered fulminant if it is associated with one or more of the following: high fever, tachycardia, profound anemia requiring transfusion, dehydration, low urine output, abdominal tenderness with distention, and profound leukocytosis with left shift, severe malaise, or prostration. Patients with these symptoms should be hospitalized for aggressive resuscitation while clinical assessment and treatment are initiated.¹¹

Clinical Assessment

Patients admitted with severe or fulminant ulcerative colitis require a complete history and physical examination. Fulminant ulcerative colitis is rarely the initial presentation of ulcerative colitis, and most patients will have a prior diagnosis. The abdominal examination should focus on signs of peritoneal irritation that may suggest perforation or abscess formation. Any patients admitted with severe ulcerative colitis may have already received substantial doses of corticosteroids, which can mask the physical findings of peritonitis.

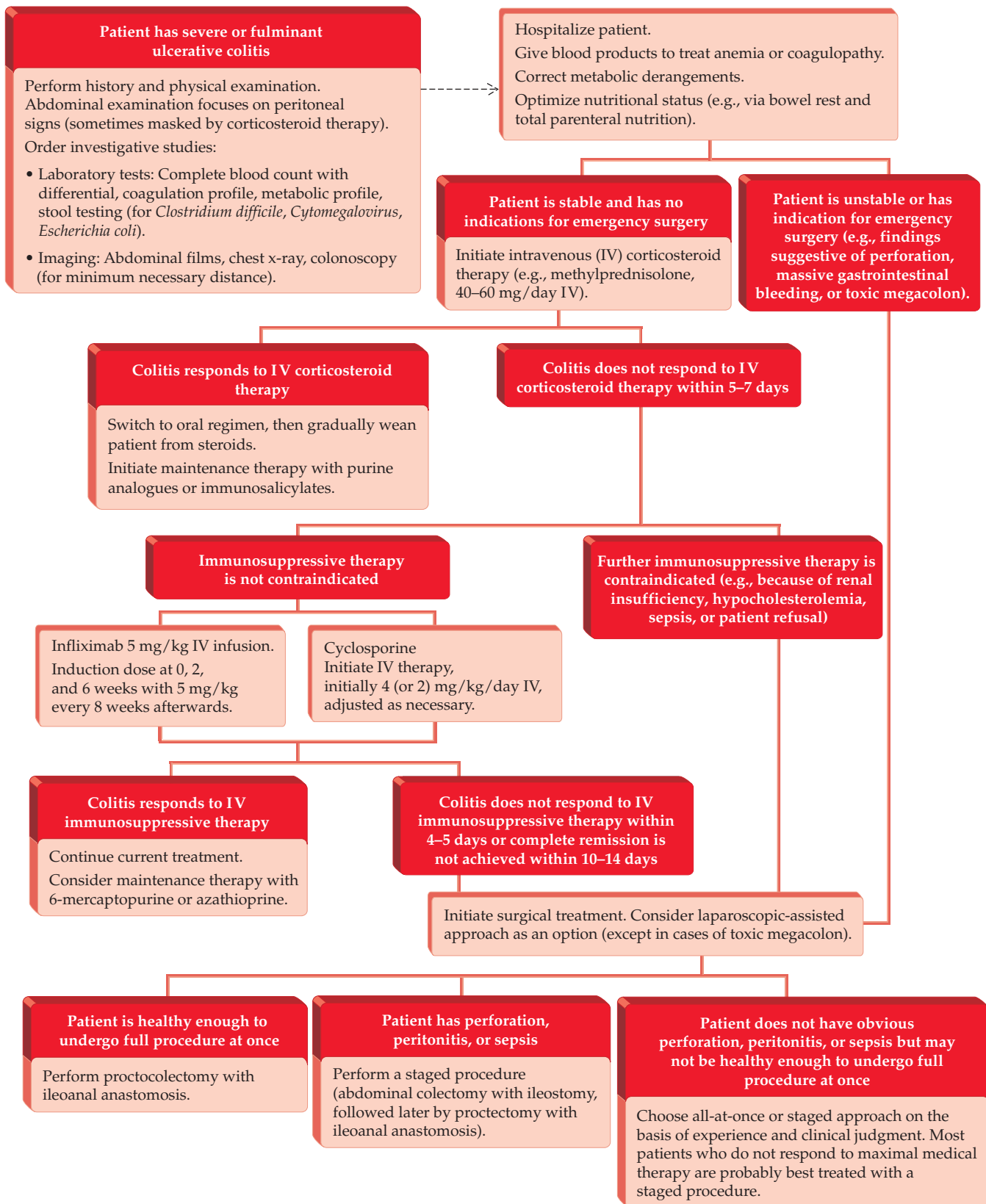
Initial laboratory studies should include a complete blood count with differential, a coagulation profile, and a complete metabolic profile with assessment of nutritional parameters such as the serum albumin. Abdominal films and an upright chest x-ray should be obtained to assess for colonic distention indicating toxic megacolon and to assess for the presence of pneumoperitoneum indicating perforation. Infectious agents should be ruled out by multiple stool specimens sent for *Clostridium difficile*, cytomegalovirus, and *Escherichia coli* O157:H7.^{12,13} It is important to identify the presence of opportunistic infections, particularly *C. difficile*, even in patients with an established diagnosis of ulcerative colitis, as superinfection with *C. difficile* in ulcerative colitis patients is common. Assessment with endoscopic examination of the



Variable	Mild Disease	Severe Disease	Fulminant Disease
Stools (no./day)	< 4	> 6	> 10
Blood in stool	Intermittent	Frequent	Continuous
Temperature (°C)	Normal	> 37.5	> 37.5
Pulse (beats/min)	Normal	> 90	> 90
Hemoglobin	Normal	< 75% of normal value	Transfusion required
Erythrocyte sedimentation rate (mm/hr)	≤ 30	> 30	> 30
Colonic features on radiography	—	Air, edematous wall, thumb printing	Dilatation
Clinical signs	—	Abdominal tenderness	Abdominal distention and tenderness

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Management of Fulminant Ulcerative Colitis



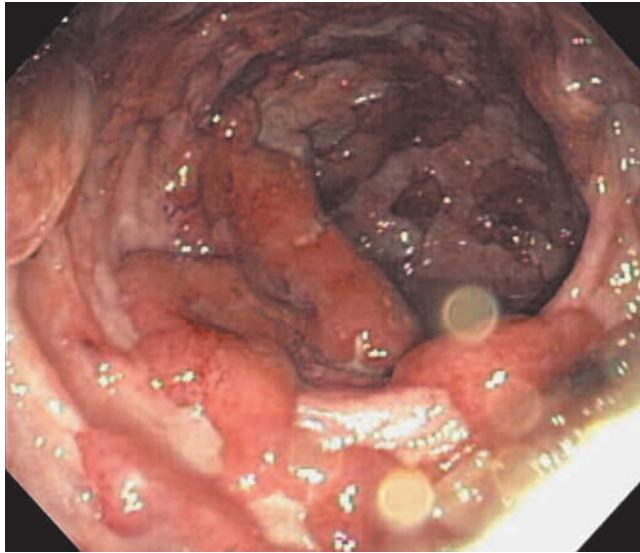


Figure 1 Sigmoidoscopy demonstrating deep ulcerations in a patient suffering from fulminant ulcerative colitis.

colon and rectum in the face of fulminant ulcerative colitis is controversial.¹⁴⁻¹⁶ Colonoscopy with biopsy can provide useful diagnostic information. Reports indicate that in experienced hands, colonoscopy can be performed in patients with severe colitis with little risk.^{14,15} In general, however, it is recommended that endoscopic examination be limited to the minimum distance necessary to confirm severe colitis. If an endoscopic examination is to be performed, it is important to minimize the amount of air insufflation as overdistention of the colon may lead to perforation or the development of megacolon. Typical endoscopic findings in fulminant ulcerative colitis are severe inflammation, ulcerations, and mucosal sloughing. Colitis typically is worst in the rectum and continues proximally in a contiguous fashion. Occasionally, the distal rectum may be spared secondary to the use of topical medications such as steroid suppositories. Although these findings help differentiate ulcerative colitis from Crohn disease and indeterminate colitis, the differentiation is probably not important in the setting of fulminant disease, where maximal medical therapy or surgical treatment with subtotal colectomy will be the same regardless of diagnosis. Beyond the diagnostic information, endoscopy can provide useful prognostic information. Carbonell and colleagues noted that the presence of deep extensive colonic ulcerations indicates a low probability for successful medical treatment of fulminant ulcerative colitis, with less than 10% of patients with deep ulcers responding to medical treatment.¹⁴ Such an endoscopic finding thus may assist in the decision to proceed with early surgery if medical therapy does not show rapid and significant improvement [see Figure 1].

General Care

All patients with fulminant ulcerative colitis require hospitalization. Blood products should be administered to treat significant anemia or coagulopathy. Metabolic derangements should be corrected.¹⁷ Patients with perforation or massive lower gastrointestinal hemorrhage need emergent operative treatment. More stable patients are initially managed with

medical therapy. Narcotics, antidiarrheal agents, and other anticholinergic medications should be avoided as they can precipitate toxic dilation of the colon. Bowel rest typically reduces the volume of diarrhea, but it is not yet clearly established if bowel rest affects the clinical course of the fulminant colitis.^{18,19} McIntyre and colleagues reported no significant change in outcome in patients with acute flares of ulcerative colitis managed with total parenteral nutrition (TPN) and bowel rest compared to patients taking enteral nutrition.¹⁹ This study, however, involved varying degrees of severity of colitis such that only a small number of patients with fulminant ulcerative colitis appear to have been included in the study. Conversely, Mikkola and Jarvinen reported a potential clinical advantage to bowel rest and TPN in patients suffering from fulminant ulcerative colitis.¹⁸ The most common approach is to initially place these patients on bowel rest with hyperalimentation. Oral feedings are initiated once symptoms of the fulminant attack begin to improve. Whether patients are maintained on bowel rest or given oral feeds, each patient should always receive adequate nutritional support; hence, TPN should be maintained until the patient is tolerating full enteral feedings.

Medical Therapy

The main standard medical therapy for fulminant ulcerative colitis involves the induction of remission with intravenous (IV) corticosteroids or biologics followed by long-term maintenance treatment in the form of purine analogues or biologics for those patients who achieve remission. Cases that are unresponsive to IV steroids are considered for IV cyclosporine and, more recently, infliximab.

STERIODS

Steroid treatment has been the frontline therapy for acute flares of ulcerative colitis for almost 50 years. Response rates for cases of fulminant ulcerative colitis fall in the range of 50 to 60% when steroids are given over a 5- to 10-day course of treatment.^{20,21} Methylprednisolone in a dose of 40 to 60 mg per day, given as a continuous IV infusion, is a common regimen.^{5,22-24} The duration of treatment to allow for response from IV steroid therapy has been controversial. Truelove and Witts in 1955 recommended urgent surgery after 5 days if the patient has not responded to IV steroid therapy.⁴ This 5-day rule has been widely adopted, but experience suggests that courses up to 7 to 10 days can be safely administered under careful observation to allow for further time for response.¹² Patients who respond to IV steroid therapy are converted to oral steroids, typically prednisone. Corticosteroids, however, should never be used as a long-term maintenance therapy.^{5,25} The toxic effects of corticosteroids are related to both the dose and duration of treatment. Severe complications, including diabetes, osteoporosis, mood

disturbances, and weight gain, are common with extended use of even modest doses of steroids. Patients should be slowly but completely weaned from steroid therapy. Because recurrence of symptomatic colitis occurs in between 40 and 50% of initial responders to IV therapy, maintenance therapy with either purine analogues, immunosalicylates, or biologics should be administered.^{5,20} Unfortunately, dependency on corticosteroids is often encountered in patients with ulcerative colitis. In these cases, the dose of steroids cannot be tapered without an increase in disease activity and symptoms. When such patients cannot be taken off steroids within 3 to 6 months, then surgical treatment is indicated.

CYCLOSPORINE

Nonresponders to IV steroid treatment, once universally referred for surgery, may be treated with IV cyclosporine. Cyclosporine is an immunosuppressant macrolide that suppresses the production of interleukin-2 by activated T cells through a calcineurin-dependent pathway.²⁶ Originally applied as a means of preventing tissue rejection following transplantation, cyclosporine has become the standard for the treatment of steroid-refractory severe ulcerative colitis. The first report of the use of cyclosporine for the treatment of ulcerative colitis was by Gupta and colleagues in 1984.²⁷ It was not until 10 years later that a randomized placebo-controlled trial of cyclosporine for steroid-refractory ulcerative colitis by Lichtiger and colleagues demonstrated the effectiveness of this agent.²⁸ This revealed a response rate of 82% with 4 mg/kg of cyclosporine in patients with steroid-refractory ulcerative colitis compared to zero response with continued IV steroid therapy alone. Since this initial report, response rates of 56 to 91% have been reported in the medical literature, confirming cyclosporine as a major advance in the treatment of severe and fulminate ulcerative colitis.^{29–31} Dosing and monitoring of cyclosporine are complicated and cumbersome for both physicians and patients, limiting its use. In addition, recurrence of disease after initial remission with cyclosporine is high, with as many as 60% of patients developing recurrent disease.³² Recurrence rates can be substantially lowered with maintenance therapy with mercaptopurine or azathioprine. With appropriate maintenance therapy, early recurrence of symptoms after successful IV cyclosporine treatment have been recorded as low as 22%.^{30,33} Even if disease activity recurs and surgery is necessary, cyclosporine therapy can allow for elective surgical management when the patient is in better general health. This is a clear advantage as urgent surgery for ulcerative colitis carries a much higher risk for complications when compared with surgery performed in a more elective setting.^{18,34,35}

Major side effects associated with cyclosporine treatment include renal insufficiency, opportunistic infections, and seizures. The risk for seizures appears to be highest in patients with hypocholesterolemia. As such, patients with significant (less than 100 mg/dL) hypocholesterolemia should not receive cyclosporine treatment. Hypomagnesemia is commonly seen in patients with fulminant ulcerative colitis undergoing

cyclosporine treatment; hence, serum magnesium levels should be closely followed.

Dosing regimens for cyclosporine vary, but patients are typically started on 4 mg/kg per day of IV cyclosporine, with the dose then adjusted to achieve a whole blood level between 150 and 400 ng/mL as measured by high-performance liquid chromatography or radioimmunoassay.^{36,37} Higher levels up to 800 ng/mL in whole blood have been cited as acceptable by some investigators.²⁸ If the patient does not show any improvement within 4 to 5 days or if complete remission is not achieved by 10 to 14 days, surgery is then advised.¹² Most of the side effects from cyclosporine are dose dependent, and some studies have shown that an initial dose of 2 mg/kg per day of IV cyclosporine can also be effective in achieving a remission.^{38–40}

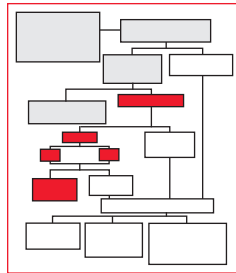
INFLIXIMAB

Infliximab is a chimeric monoclonal antibody directed against human tumor necrosis factor (TNF). Infliximab has been used to treat Crohn disease for over 10 years. It was not until 2005, however, that infliximab was approved for use in patients with ulcerative colitis. Potential adverse effects from infliximab include activation of tuberculosis, infusion reactions, hypersensitivity reactions, the development of lymphoma, and infectious complications.⁴¹ Additionally, recent accumulating data suggest that infliximab may significantly increase the risk for postoperative infection and healing complications following surgery for ulcerative colitis.^{42,43}

The use of infliximab therapy in the setting of fulminant colitis is controversial. **Whereas the data supporting infliximab in the treatment of moderate to moderately severe disease are convincing, the data demonstrating safety and efficacy in the setting of fulminant colitis are limited. Based on the current data, some experts have supported the initiation of infliximab treatment in patients with fulminant colitis who have failed IV steroid therapy.**⁴⁴ On the other hand, others have advocated the avoidance of infliximab therapy in patients with fulminant colitis.⁴¹ With wider use of anti-TNF therapy for ulcerative colitis, a greater percentage of patients admitted to the hospital with fulminant colitis are likely to already be on infliximab therapy; hence, the decision whether or not to initiate therapy is often moot. Because of the risk of severe complications, infliximab therapy should not be given in combination with cyclosporine therapy.⁴⁵

Because of the increased risk for anastomotic leak and pelvic sepsis in patients undergoing the ileoanal procedure while on anti-TNF therapy, patients with fulminant or severe ulcerative colitis should have a staged abdominal colectomy prior to the ileoanal procedure if they are being treated with infliximab. The negative effect of infliximab on wound healing and infection is prolonged and appears to persist beyond 3 to 4 months after the last dose given.^{42,43}

The prolongation of medical therapy in patients with severe disease who have already received high doses of corticosteroids has caused concerns that those patients who fail both steroid and subsequent cyclosporine or infliximab therapy may be at high risk for perioperative morbidity and mortality. Current experience, however, has not identified an increased risk for perioperative complications in patients who fail to respond to cyclosporine therapy and thus does not appear to compromise surgical results.⁴⁶ Yet recent data on infliximab



in ulcerative colitis do demonstrate a trend toward increased number and severity of septic complications.^{42,43,46}

Surgical Therapy

INDICATIONS FOR SURGERY

The indications for surgery in a patient suffering from fulminant ulcerative colitis are listed in Table 2. When the options for appropriate medical treatment have been exhausted, surgery will, of course, be required. Because most patients suffering from fulminant ulcerative colitis will respond to aggressive medical therapy, an attempt at medical treatment is warranted in almost all cases. Care must be exercised, however, not to overtreat the patient with fulminant ulcerative colitis who is unresponsive or shows minimal response to medical treatment. The immunosuppressive effects of high-dose corticosteroids and IV cyclosporine or infliximab, along with the debilitation of prolonged severe disease, can place the patient at high risk for perioperative complications. **If the patient fails to show significant improvement with IV steroids in 5 to 7 days, then the patient should be started on IV cyclosporine or infliximab or referred for surgery.¹² For patients who fail to show improvement on second-line medications within 4 days or fail to achieve remission of major symptoms by 2 weeks, surgery should be undertaken.** If symptoms progress during the course of IV therapy or if no sign of improvement occurs, then the patient should be considered for early surgery. Additionally, patients known to have deep longitudinal ulcerations may also be referred for early surgery, given that these patients are more likely to fail IV medical therapy. The decision when best to abandon medical therapy in favor of surgery for patients with fulminant ulcerative colitis is difficult and requires experience and special expertise. Thus, patients with fulminant ulcerative colitis are best managed in a center specializing in inflammatory bowel disease.

Patients with perforation or severe bleeding require urgent surgery.⁴⁷ Debilitation from disease and immunosuppression from intensive medical therapy can mask the signs and symptoms of sepsis and peritonitis associated with perforation. When perforation occurs, the risk for perioperative mortality is up to 10 times greater compared to cases of fulminant colitis without perforation.⁴⁸ **For these reasons, patients with high fever, marked leukocytosis, and persistent tachycardia should**

be referred for early surgery, independent of other indications of perforation or peritonitis.

Toxic megacolon is an uncommon complication of severe ulcerative colitis. Associated with impending colonic perforation, toxic megacolon requires aggressive management. Two specific parameters are required to confer the diagnosis of toxic megacolon.⁴⁹ **First, there must be colonic dilatation. Second, the patient should appear “toxic.”** Patients with mild symptoms of ulcerative colitis can experience colonic dilatation, perhaps associated with a colonic ileus. This is distinctly different from patients with fulminant ulcerative colitis, some degree of generalized toxicity, and colonic dilatation. **Patients with fulminant ulcerative colitis should have an abdominal x-ray to assess for colonic dilatation [see Figure 2].** Additionally, patients with fulminant ulcerative colitis who develop abdominal distention or have a sudden decrease in the number of bowel movements without signs of significant clinical improvement should also be assessed radiographically for colonic dilatation.

As noted, patients with toxic megacolon should be treated aggressively. Individuals who are otherwise stable may undergo a brief trial of conservative management consisting of eliminating narcotics and anticholinergic agents. Changing the patient’s position from side to side, supine to prone, and into the knee-elbow prone position is thought to assist in the expulsion of colonic gas.⁵⁰ Patients should be kept NPO, and broad-spectrum IV antibiotics are advocated. Attempts at endoscopic decompression are to be avoided, and blind placement of rectal tubes is ineffective and may be harmful. **Patients with**

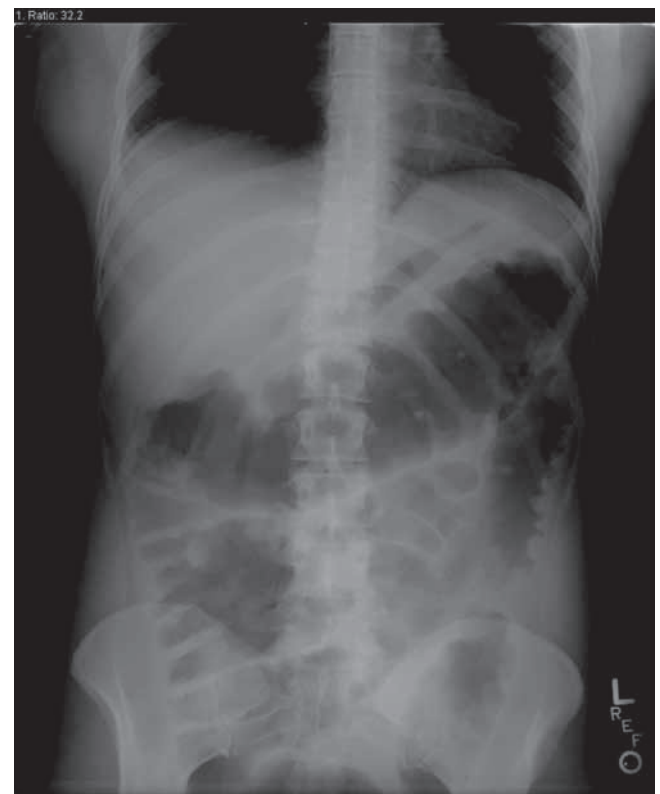
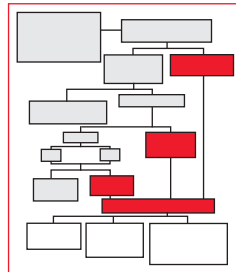


Figure 2 Abdominal radiograph of a patient with toxic megacolon. Printed with permission of University of Chicago Department of Surgery Archives.

Table 2 Indications for Operation
Perforation
Peritonitis
Progressive signs of sepsis
Failure to respond to medical treatment
Inability of tolerate medical treatment
Severe hemorrhage
Toxic megacolon

toxic megacolon who do not rapidly respond to conservative management and those who show signs of peritonitis are otherwise unstable and should undergo urgent surgery.⁵¹

PREPARATION FOR SURGERY

Patients with fulminant ulcerative colitis who are stable but not responding to medical therapy may have time to prepare for surgery. Patients who are not NPO should be maintained on clear liquids and then kept NPO for 6 to 8 hours prior to surgery. Usually, these patients do not require any form of bowel preparation as they have multiple bloody, liquid bowel movements and will require an emergent colectomy with diversion. If used, bowel preparations may be limited to a rectal washout at the time of surgery. If time allows, patients should be provided with a consultation with an experienced enterostomal therapist and an optimal site for the ostomy should be marked on the abdomen. Prophylactic antibiotics should be given prior to the creation of the surgical incision, and appropriate stress-dose steroids should also be administered.

SURGICAL STRATEGIES

The operative strategies for the treatment of fulminant ulcerative colitis are controversial. Ultimately, almost all patients will end up with a restorative proctocolectomy and an ileoanal anastomosis. Most patients with fulminant ulcerative colitis, however, will have the final surgical goal achieved in multiple steps. The safety of performing an extensive resection with a prolonged and delicate reconstructive procedure in an acutely ill patient is questionable. It has thus been the practice of many to first perform a total abdominal colectomy with an ileostomy, leaving the rectum as a stapled stump or a mucous fistula.^{47,48} This approach allows the patient to recover from the acute illness, to wean off the immunosuppressive agents, and to improve the nutritional status. Although the remaining rectal stump will be affected by ulcerative colitis, the activity of disease is greatly diminished with the fecal diversion, and almost all patients can be completely weaned from steroids and other immunosuppressive medications. A subsequent restorative proctectomy with ileoanal anastomosis can then be performed in a more controlled situation.

The benefits of undergoing a staged procedure may be multiple; some studies have demonstrated a reduced risk of anastomotic leak, but findings are not universal. Ziv and colleagues reported excellent long-term results and acceptable short-term morbidity in 12 patients undergoing immediate restorative proctocolectomy with ileal pouch-anal anastomosis.⁵² The authors used a liberal definition for fulminant colitis that included patients who may not have been as acutely ill and represent an extraordinarily small proportion of the total number of ileoanal procedures performed at their institution. Harms and colleagues reported on 20 patients undergoing restorative proctocolectomy with ileal pouch-anal anastomosis for the urgent treatment of ulcerative colitis and also reported excellent long-term results and exceptional perioperative morbidity.⁵³ However, Heyvaert and colleagues

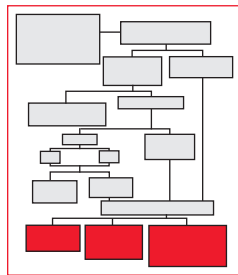
reported on 12 patients also undergoing urgent restorative proctocolectomy with ileoanal procedure for ulcerative colitis and noted a 41% anastomotic leak rate compared to an 11% leak rate in patients undergoing ileoanal anastomosis under more controlled conditions.⁵⁴ Based on these results, Heyvaert and colleagues counseled against ileoanal anastomosis in the urgent setting. Fukushima and colleagues also noted a higher risk for anastomotic leak (36%) in patients undergoing urgent restorative proctocolectomy with ileoanal anastomosis.⁵⁵ This group likewise advised against performing an ileoanal anastomosis in the urgent setting.

Precise parameters under which it is best to stage the procedure with an initial abdominal colectomy have not been clearly defined. It is universally accepted that patients with perforation, peritonitis, or sepsis require a staged procedure. Any patient with suspicion of Crohn colitis or indeterminate colitis should undergo subtotal colectomy to allow for further diagnostic evaluation prior to creation of ileal pouch-anal anastomosis. Beyond this, there is no clear consensus. The available studies addressing this issue unfortunately involve a small number of patients, do not clearly define what is meant by “fulminant” colitis, or do not directly compare results between the two alternative strategies of staged colectomy versus immediate ileoanal anastomosis. Clearly, there is a small subset of patients with symptoms severe enough to require hospitalization who are healthy enough to safely undergo a primary ileoanal anastomosis. On the other end of the spectrum, severely ill patients, that is, most patients with fulminant colitis, should have a staged procedure. Because specific criteria to quantify the risk have not been defined, the decision to stage or not to stage ultimately rests with the clinical judgment of the experienced surgeon. It has been the author’s experience, however, that a large majority of patients who fit the criteria of fulminant colitis as noted in Table 1 and have failed maximal medical therapy are best managed with a staged approach.

If the procedure is staged and the proctectomy delayed, there are several advantages to the patient in terms of having time to fully consider lifestyle and reproductive options. Living with an ileostomy for 2 to 4 months ensures that the patient understands the relationship between the timing and quality of oral intake and the frequency and consistency of ileostomy output. This knowledge is extremely helpful to the patient in affecting the frequency, timing, and consistency of bowel movements after completion of all stages associated with a restorative proctectomy and ileoanal pouch procedure. Further, it gives the patient confidence that life with an ileostomy is manageable, a notion that may be important if complications of an ileoanal procedure escalate to the point of considering reversal.

All patients who undergo proctectomy face the risk of decreased fertility and sexual function postoperatively, and consideration of timing of surgery is appropriate. If the rectum is acutely inflamed, dissection may be more difficult and injuries to pelvic nerves and formation of adhesions and abscesses may be greater. As a large percentage of the population with ulcerative colitis are in their reproductive prime, preoperative consideration of issues is appropriate.

In males, erectile dysfunction appears to be altered after damage to the parasympathetic nerves, whereas ejaculatory dysfunction results from sympathetic nerve injury. It is estimated that between 0 and 10% of males experience some



degree of sexual dysfunction postoperatively.^{56,57} Although studies demonstrate that dysfunction may be transient and relieved with pharmaceutical agents such as sildenafil, this is a significant consideration for males in the peak of their reproductive years.⁵⁸ Subtotal colectomy has not been associated with decreased function; therefore, males in need of an urgent procedure may defer the proctectomy to a later time and consider cryopreservation prior to the removal of the rectum.

In women, causes of sexual dysfunction are more difficult to determine, but infertility rates are significantly elevated following proctocolectomy. Fecundity rates, or the percentage of women who become pregnant per unit time, are reduced to one third of baseline populations after proctectomy for ulcerative colitis.^{59,60} Adhesions and occlusion of fallopian tubes have been noted in a large number of postoperative patients obstructing normal ovulation and fertilization.^{61,62} Although it would be simple to blame surgery alone, patients requiring ileal pouch-anal anastomosis for familial adenomatous polyposis do not experience this radical decrease in fertility postoperatively.⁶³ Although in vitro fertilization has been highly successful in this group, consideration of postponement of proctectomy for family planning may be reasonable in these patients.⁶⁴

SURGICAL TECHNIQUE

Surgical exploration can be performed with a midline or transverse incision. The abdomen should be carefully examined with particular attention given to the small intestine looking for signs of Crohn disease. The colon often shows the changes of colitis with serosal hyperemia, corkscrew vessels, and edema [see Figure 3]. Colectomy can be performed in the standard fashion with mesenteric division occurring at a convenient distance from the bowel. Wide mesenteric resection is not necessary.

If a staged colectomy is performed, an ileostomy is created in the standard fashion at the site selected as least inconvenient for the patient preoperatively, and the rectum is left behind either stapled or brought up to the abdominal wall as a mucous fistula. When stapled, it is important that the stump be of the appropriate length. Too short of a pouch can lead

to a very difficult proctectomy at the next stage of the procedure sequence. Too long of a stump can run the risk of complications related to persistent disease in the rectum, including bleeding, discharge, and tenesmus. In most cases, the rectum can be safely stapled at the level of the sacral promontory [see Figure 4]. When performing the colectomy, the sigmoid branches of the inferior mesenteric artery are divided, whereas the terminal branches of the inferior mesenteric artery are preserved. This will ensure a good blood supply to the remaining rectal stump and aid in the healing of the stapled closure. Preservation of the terminal branches of the inferior mesenteric artery and the superior rectal artery also simplifies the subsequent proctectomy by keeping the pelvic sympathetic nerves free of surrounding scar tissue and by providing a key anatomic landmark that will assist in the location of the appropriate presacral dissection plane at the time of the proctectomy. To staple the proximal rectum safely, the mesenteric and pericolic fat are removed from the bowel wall. Approximately 2 cm of bowel is prepared in such a manner, and the bowel is then closed with a transverse anastomosis stapler (TIA stapler) using 4.8 mm staples. The bowel is then divided proximal to the staple line. It is important to closely examine the staple line to ensure that the staples are formed properly into two rows of well-formed “B’s.” The staple line should also be examined to make sure that individual staples are not cutting into the muscularis propria of the bowel. To provide extra assurance against dehiscence, the staple line can be oversewn with interrupted Lembert sutures [see Figure 4]. If used, these sutures should be carefully placed so that the anterior and posterior serosal surfaces are approximated without undue tension. In a well-constructed rectal pouch, placement of pelvic drains is not necessary and can be harmful as their placement close to the suture line may promote dehiscence.

In some cases, the colon at the level of the sacral promontory will be affected by deep ulcerations and severe inflammation such that the closure of the rectum at this level may be at high risk for dehiscence [see Figure 5]. If the severity of the disease precludes safe closure of the rectal stump, then creation of a mucous fistula should be considered. The mucous fistula does require a longer segment of bowel and thus is

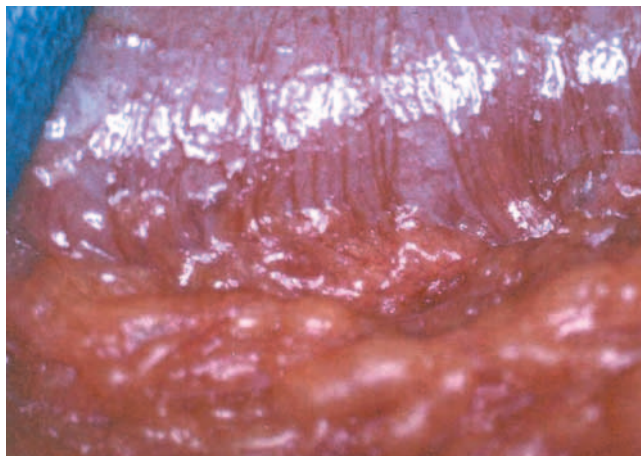


Figure 3 Intraoperative photograph of colon affected by fulminant ulcerative colitis. Changes on the serosal aspect are typically subtle. Serosal hyperemia with small “corkscrew” vessels is present.

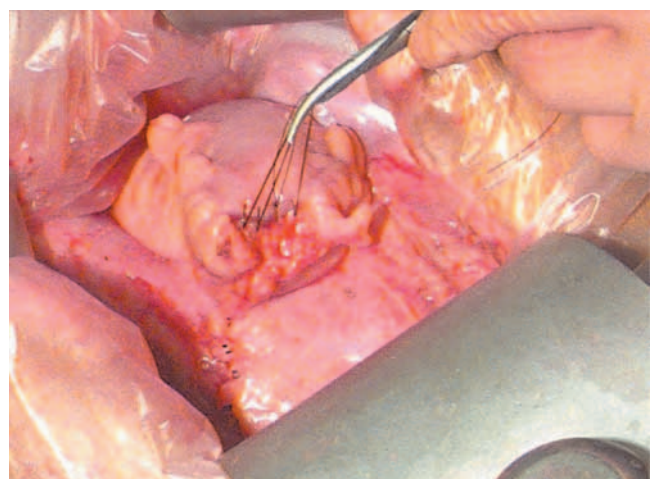


Figure 4 Hartmann pouch constructed at the level of the sacral promontory. The transverse anastomosis stapler line is reinforced with interrupted silk Lembert sutures.

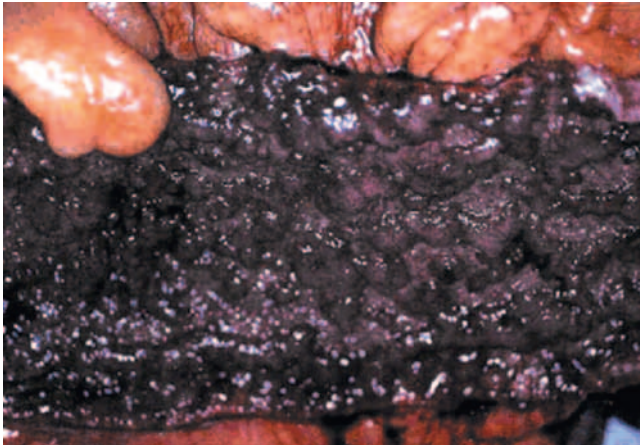


Figure 5 Surgical specimen showing severe ulceration and inflammation seen with fulminate ulcerative colitis.

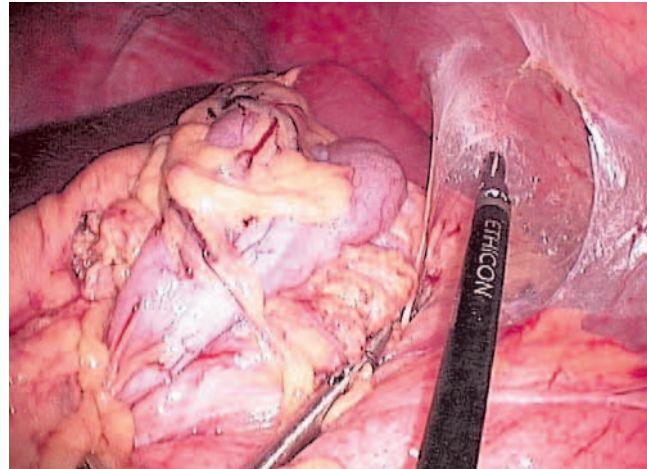


Figure 6 Laparoscopic colectomy for fulminant ulcerative colitis. Mobilization of the splenic flexure.

associated with a greater risk of bleeding from the retained segment. Additionally, a mucous fistula is unsightly and often generates a very foul odor. As a compromise approach, some surgeons have advocated stapling the rectosigmoid and placing the proximal end of the stump through the fascia at the lower edge of the midline incision. The end of the stump is then left buried in the subcutaneous tissue. The benefit of this approach is that should dehiscence of the staple line occur, then sepsis should be limited to the subcutaneous space rather than result in an intra-abdominal or pelvic abscess.

If attempts to fashion a secure rectal closure fail, and the remaining rectal stump is too short to bring out as a mucous fistula, then two options remain: an additional inch or two of proximal rectum can be resected and closure of the rectal stump performed lower, sometimes just below the peritoneal reflection. In this situation, closed suction drains should be placed in the deep pelvis and, if possible, the peritoneum closed over the rectal stump. Such a short rectal stump, however, will make finding it during subsequent completion restorative proctectomy and ileoanal anastomosis more difficult. Alternatively, a large Malecott drain, inserted through the lower abdominal wall, can be placed in the proximal rectum and the opening of the rectum can be synched around it with a purse-string suture. In this case, as well as in any case where the closure of the rectal stump seems precarious, transanal placement of a rectal tube to drain rectal secretions and blood may be beneficial in reducing the risk of intra-abdominal spillage of rectal contents or of dehiscence of the stapled rectal stump.

LAPAROSCOPY

Experience with laparoscopic-assisted approaches has demonstrated that abdominal colectomy can be performed safely in patients suffering from ulcerative colitis using these minimally invasive approaches.⁶⁵⁻⁶⁷ Mobilization of the colon and

division of the mesentery can be accomplished laparoscopically with the specimen being removed through a small Pfannenstiel incision [see Figure 6]. An end ileostomy is also fashioned with the aid of inspection through the Pfannenstiel incision. Alternatively, the Pfannenstiel incision can be made early on in the procedure and used as a hand assist port and the colon removed using a hand-assisted laparoscopic approach. The clinical advantages of a laparoscopic-assisted approach in the management of fulminate ulcerative colitis have not been fully defined. However, increasing experience with this approach indicates that laparoscopic-assisted colectomy is a safe and reasonable alternative that may well result in shorter hospital stays, decreased postoperative pain, decreased complication rates, and possible reduced adhesions.^{68,69} The laparoscopic-assisted approach thus appears to be a reasonable option for most patients suffering from fulminant ulcerative colitis.

Patients suffering from toxic megacolon, however, should be managed with an open surgical approach as the laparoscopic instruments used to grasp the bowel are likely to cause perforation in the severely thinned walls of the dilated colon.

Summary

The optimal management of fulminate ulcerative colitis is challenging. Most patients will respond to medical therapy such that long-term control of disease can be achieved or at least surgery can be undertaken at later, safer, elective conditions. Surgical strategies must be tailored to account for each individual patient's overall physical condition, with most patients who fail medical therapy requiring an abdominal colectomy as the first step in a staged surgical approach.

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14 HEREDITARY COLORECTAL CANCER AND POLYPOSIS SYNDROMES

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The majority of cases of inherited colorectal cancer (CRC) are accounted for by two syndromes: hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP). In both, the predisposition to disease is a germline mutation transmitted in an autosomal dominant fashion. Although the two syndromes are similar in some respects, differences in their phenotypic expression and in the certainty of disease development mandate distinctly different surgical approaches, including the timing and extent of prophylactic procedures in carefully selected patients. In the management of FAP, the role of prophylactic surgery is clearly defined, though the optimal procedure for an individual patient depends on a number of factors. In the management of HNPCC, the indications for prophylactic procedures are emerging, particularly for unaffected mutation-positive patients.

Two less common polyposis syndromes, Peutz-Jeghers syndrome (PJS) and juvenile polyposis syndrome (JPS), are also inherited in an autosomal dominant fashion and are associated with a significant risk of CRC. Carefully selected persons affected by these syndromes may also benefit from prophylactic surgical procedures. Current evidence supports a role for prophylactic colectomy in JPS but not in PJS.

Finally, there are a few other, less common, inherited hamartomatous polyposis syndromes, such as Cowden disease and Ruvalcaba-Myhre-Smith syndrome. At present, these syndromes appear to be associated with an exceedingly low risk of CRC; accordingly, prophylactic surgery is not indicated.¹

Familial Adenomatous Polyposis

FAP is caused by mutations in the tumor suppressor gene *APC*, located at 5q21. Nearly 80% of FAP patients belong to known FAP kindreds; 10% to 30% have new mutations.¹ More than 300 distinct mutations have been identified within the *APC* gene locus in persons manifesting the FAP phenotype. More than half of the known germline mutations associated with the classic FAP phenotype are concentrated in the 5' region of exon 15.¹ Genotype-phenotype correlative studies have revealed a wide range of phenotypic heterogeneity, ranging from the relatively mild presentation associated with attenuated FAP, which is caused by mutations in the 3' and 5' ends of the *APC* gene,² to the severe presentation associated with mutations downstream from codon 1250, particularly those in codon 1309. It has been reported that as many as 7.5% of patients with a classic FAP phenotype and no demonstrable *APC* mutation may have biallelic germline mutations in the base excision repair gene *MYH*.³

CLINICAL EVALUATION

FAP, which accounts for less than 1% of the annual CRC burden, is characterized by the presence of more than 100 adenomatous polyps of the colorectum, virtually 100% penetrance, and a nearly 100% risk of CRC by the age of 40 if prophylactic colectomy is not performed.^{1,4} Extracolonic manifestations are common and include desmoid tumors, osteomas,

odontomas, sebaceous and epidermoid cysts, congenital hypertrophy of the retinal pigment epithelium, and periampullary neoplasms.¹

INVESTIGATIVE STUDIES

Pathologic Findings

The polyps, which develop by the age of 20 years in 75% of cases, are typically less than 1 cm in size. In severe FAP, they may carpet the entire surface of the colorectal epithelium or, alternatively, may spare portions of the epithelial lining (e.g., the rectum). Adenomas may be either pedunculated or sessile and may have tubular, villous, or tubulovillous histology. Microscopic evaluation may reveal innumerable microadenomas within grossly normal-appearing colorectal mucosa. Foci of carcinoma in situ and invasive carcinoma may be found within larger polyps, and the incidence of invasive cancer is proportional to the extent of polyposis. Unlike CRC in the setting of HNPCC, CRC in the setting of FAP is more commonly located on the left side.¹

Screening and Surveillance

Screening (genetic testing or annual or biennial flexible sigmoidoscopy) for at-risk family members should begin around puberty (i.e., at 10 to 12 years of age) [see Table 1]. In families with a demonstrated *APC* mutation, informative genetic testing can be carried out with the protein truncation test [see Table 2]. This test, which detects foreshortened proteins resulting from truncating *APC* mutations, is approximately 80% sensitive⁵; however, the test results are commonly misinterpreted, even by physicians.⁶ Patients with normal protein truncation test results and a previously identified mutation in the family may be discharged from further screening with a nearly 100% certainty that the mutation is absent, but they should still undergo CRC screening starting at the age of 50 years, as is recommended for average-risk persons. When an *APC* mutation has not previously been identified in the family of an affected person, the patient should be tested first to identify the causative mutation. In families in which the protein truncation test fails to provide conclusive information on carrier status, at-risk individuals should continue with the recommended endoscopic surveillance program. Other options for detecting *APC* mutations include linkage analysis, single-stranded confirmation polymorphism, and direct sequence analysis.¹

Genetic counseling is an essential component of the evaluation of patients for FAP. Patients who have a positive genotype or who have adenomatous polyps on sigmoidoscopy should undergo full colonoscopy to establish the extent of polyposis.

MANAGEMENT

Medical Therapy

A number of nonsteroidal anti-inflammatory drugs, including sulindac, celecoxib, and the sulindac metabolite exisulind, have been shown to reduce the number and size of polyps in FAP

Table 1 Genetic Basis, Clinicopathologic Features, Diagnosis, Surveillance, and Surgical Management of Hereditary CRC and Polyposis Syndromes

Syndrome	Genetic Basis	Diagnosis	GI Manifestations	Extracolonic Manifestations	Pathologic Features	CRC Screening and Surveillance	Surgical Management
FAP	APC, 5q21 (> 90%); MYH (8%)	≥ 100 adenomatous polyps of colorectum or APC mutation demonstrated	Adenomatous polyps of colon and rectum 100% risk of colorectal cancer by age 40 without colectomy	Desmoids Osteomas Odontomas Sebaceous and epidermoid cysts CHRPE Periampullary neoplasms	Tubular, villous, or tubulovillous histology	Consider genetic counseling/testing Carry out early surveillance with sigmoidoscopy (at age 10–12 yr) ^{98,99} For at-risk untested individuals, perform FS every 1–2 yr	If polyposis is confirmed, colectomy is indicated Options include the following: TPC with ileostomy TAC with IRA TPC with IPAA
HNPCC	MMR genes: MLH1 and MSH2 (90%), MSH6 (10%), PMS1, PMS2, MLH3, MSH3	MMR mutation demonstrated or Family meets Amsterdam I or II criteria ^{50,51}	Possibly few or no colorectal polyps Right-side tumor (60%–70%) MSI-high tumor (80%–90%) Synchronous/metachronous tumors 80% lifetime risk of CRC	Associated tumors of endometrium, small bowel, ureter, or renal pelvis	Adenocarcinoma, frequently mucinous or signet-ring cell histology Solid or cribriform growth pattern Tumor-infiltrating or peritumoral lymphocytes	Consider genetic counseling/testing If patient is mutation positive or is untested but meets criteria, perform colonoscopy at 20–25 yr (or 10 yr earlier than youngest affected individual), then every 1–2 yr, then annually after age 40 ^{98,99}	<i>Affected patient with identified mutation or meeting Amsterdam criteria:</i> Colon cancer or advanced adenoma: perform TAC with IRA or segmental colectomy with annual colonoscopy Rectal cancer: perform TPC with IPAA or LAR and annual colonoscopy <i>Unaffected patient with identified mutation or meeting Amsterdam criteria:</i> Consider TAC with IRA or colonoscopy every 1–3 yr
PJS	LKB1/STK11, 19p13.3 (18%–63%)	Hamartomas of GI tract and At least two of the following: Small bowel disease Mucocutaneous melanin Family history of PJS	Hamartomatous polyps throughout entire GI tract (small intestine, 90%; colon, 50%) Relative risk of CRC = 84	Mucocutaneous pigmentation (perioral and buccal areas, 95%)	Hyperplasia of smooth muscle of muscularis mucosa Arborization Pseudoinvasion	Consider genetic counseling/testing Perform colonoscopy starting between puberty and age 25, then every 2–3 yr ⁸⁸	Perform operative or laparoscopy-assisted polypectomy or segmental colectomy for polyps > 1.5 cm that are not amenable to endoscopic resection Perform segmental bowel resection for invasive cancers In the setting of laparotomy, perform intraoperative endoscopy (peroral or via enterotomy) <i>Prophylactic colectomy has no role⁸⁸</i>
JPS	SMAD4/DPC4, 18q21.1 (50%); BMPR1A, 10q22.3	≥ 3 juvenile polyps of colon and juvenile polyps throughout GI tract or Any number of polyps with family history of JPS	Multiple hamartomatous polyps throughout gastroduodenum 15% risk of CRC by age 35, 68% risk by age 65	Tumors of stomach, pancreas, duodenum	50–200 polyps Cystic, mucus-filled spaces with epithelial lining Attenuated smooth muscle layer Focal epithelial hyperplasia and dysplasia	Consider genetic counseling/testing Perform colonoscopy in middle to late teenage years, with EGD and SBS; if results are negative, repeat in 3 yr, then every 3 yr if results remain negative; if results are positive, perform biopsy of polyps and intestinal mucosa	<i>Disease is local, and no significant symptoms are present:</i> Manage endoscopically, with colonoscopic surveillance every 1–3 yr <i>Disease is diffuse or significant symptoms are present:</i> Perform TAC with IRA, and carry out rectal surveillance every 1–3 yr

CHRPE—congenital hypertrophy of retinal pigment epithelium CRC—colorectal cancer EGD—esophagogastroduodenoscopy FAP—familial adenomatous polyposis FS—flexible sigmoidoscopy HNPCC—hereditary nonpolyposis colorectal cancer IPAA—ileal pouch–anal anastomosis IRA—ileorectal anastomosis JPS—juvenile polyposis syndrome LAR—low anterior resection MMR—mismatch repair MSI—microsatellite instability PJS—Peutz-Jeghers syndrome SBS—small bowel series TAC—total abdominal colectomy TPC—total proctocolectomy

patients.^{7–10} However, long-term use of chemopreventive agents for primary treatment of FAP is not recommended.¹¹ In a randomized, placebo-controlled, double-blind study of genotype-positive, phenotype-negative patients, the use of sulindac had no effect on the subsequent development of colorectal polyposis.¹² Furthermore, the development of rectal cancer has been reported in patients whose rectal polyps were effectively controlled with sulindac.¹⁰ Finally, these medications necessitate continued com-

pliance⁹ and may be associated with significant side effects. Chemopreventive agents may be useful for reducing polyp load and facilitating endoscopic management of polyps in patients who have an ileal pouch or in patients who have an ileorectal anastomosis, are at high risk for polyp development, and refuse proctectomy. In such cases, however, it is still necessary to perform careful surveillance of the residual rectum or the ileoanal pouch every 6 months.¹¹

Surgical Therapy

The timing of surgical treatment depends to some degree on the extent of polyposis, in that the risk of CRC is partially dependent on the number of polyps present.¹³ Patients with mild polyposis (and thus a lower cancer risk) can undergo surgery in their midteens.¹¹ Practically speaking, the best time is usually the summer between high school and college. Patients with severe polyposis, dysplasia, adenomas larger than 5 mm, and significant symptoms should undergo surgery as soon after diagnosis as is practical.¹¹

There are three basic surgical options for treating FAP: (1) total proctocolectomy (TPC) with permanent ileostomy, (2) total abdominal colectomy with ileorectal anastomosis (IRA), and (3) proctocolectomy with ileal pouch–anal anastomosis (IPAA) [see 5:33 *Procedures for Ulcerative Colitis*]. The optimal procedure for a given patient is determined on the basis of a number of factors, including disease characteristics, differences in postoperative functional outcome, preoperative anal sphincter status, and patient preference.

TPC TPC with permanent ileostomy is rarely chosen as a primary procedure. More commonly, it is considered as an option for patients in whom a proctectomy is required but an IPAA is contraindicated (e.g., those with rectal tumors involving the sphincters or the levator complex or those with poor baseline sphincter function) or for patients in whom an IPAA is not technically feasible (e.g., those with desmoid disease and foreshortening of the small bowel mesentery). Occasionally, however, TPC is chosen as a primary procedure in patients whose lifestyle would be compromised by frequent bowel movements.

IPAA versus IRA The choice between IPAA and IRA is generally more challenging. The main considerations to be taken

into account are the risk of rectal cancer development if the rectum is left in situ and the differences in functional outcome (and associated quality of life) between procedures.

It has been estimated that the risk of rectal cancer after IRA may be as high as 4% to 8% at 10 years and 26% to 32% at 25 years.^{14,15} The true risk, however, may be somewhat lower. Most of the studies from which these figures were derived were completed before IPAA became available; thus, patients and physicians might have been more likely to choose IRA even in the setting of more extensive rectal disease, given that TPC and permanent ileostomy was the only other option at the time. The magnitude of risk in an individual patient is related to the overall extent of colorectal polyposis. IRA may be an option for patients with fewer than 1,000 colorectal polyps (including those with attenuated FAP) and fewer than 20 rectal adenomas, because these patients appear to be at relatively low risk for rectal cancer.^{11,13,16} Ideally, patients with severe rectal (> 20 adenomas) or colonic (> 1,000 adenomas) polyposis, an adenoma larger than 3 cm, or an adenoma with severe dysplasia should be treated with IPAA.^{11,13}

The risk of secondary rectal excision as a consequence of uncontrollable rectal polyposis or rectal cancer may be estimated on the basis of the specific location of the causative *APC* mutation.¹⁵⁻¹⁷ In a study of 87 FAP patients with an identified *APC* mutation who underwent IRA, those with a mutation located downstream from codon 1250 had an approximately threefold higher incidence of secondary rectal resection than those with a mutation located upstream of codon 1250.¹⁴ Furthermore, patients with a mutation located between codons 1250 and 1464 had a 6.2-fold higher risk of rectal cancer than those with a mutation before codon 1250 or after codon 1464.¹⁵

The risk of polyp and cancer development after index surgery is not limited to patients undergoing IRA. In patients undergoing IPAA, the pouch–anal anastomosis may be either handsewn after

Table 2 Availability of Commercial Genetic Testing for Autosomal Dominant Inherited CRC Syndromes

Test	Approximate Time Frame	Approximate Cost	Clinical Availability (in United States)
Protein truncation test	4–6 wk	\$1,100; if mutation known, \$475	Mayo Clinic, Rochester, Minn.; (800) 533-1710 Washington University, St. Louis, Mo.; (314) 454-7601
DNA sequencing, germline <i>APC</i>	3 wk	\$1,475	Baylor College of Medicine, Houston, Tex.; (800) 411-GENE Huntington Medical Research Institute, Pasadena, Calif.; (626) 795-4343 Myriad Inc., Salt Lake City, Utah; (800) 469-7423 University of Pennsylvania, Philadelphia, Pa.; (215) 573-9161
MSI analysis	2–4 wk	\$350–850	ARUP Laboratories, Salt Lake City, Utah; (801) 583-2787 Baylor College of Medicine, Houston, Tex.; (800) 411-GENE Mayo Clinic, Rochester, Minn.; (800) 533-1710 Memorial Sloan-Kettering Cancer Center, New York, N.Y.; (212) 639-5170 Ohio State University, Columbus, Ohio; (614) 293-7774
MSI and IHC	2–3 wk	\$750	Mayo Clinic, Rochester, Minn.; (800) 533-1710
DNA sequencing, germline MMR mutation (<i>MLH1</i> , <i>MSH2</i>)	3 wk	\$1,950; if mutation known, \$350	Baylor College of Medicine, Houston, Tex.; (800) 411-GENE Huntington Medical Research Institute, Pasadena, Calif.; (626) 795-4343 Myriad Inc., Salt Lake City, Utah; (800) 469-7423 Quest Diagnostics, Inc., San Juan Capistrano, Calif.; (949) 728-4279 University of Pennsylvania, Philadelphia, Pa.; (215) 573-9161
<i>LKB1</i> / <i>STK11</i> testing	6–12 wk	\$1,176–1,400; if mutation known, \$200–350	Ohio State University, Columbus, Ohio; (614) 293-7774 GeneDx Inc., Gaithersburg, Md.; (301) 519-2100
<i>SMAD4</i> / <i>BMPR1A</i> testing	3 mo	\$1,234–1,260; if mutation known, \$200	Ohio State University, Columbus, Ohio; (614) 293-7774

IHC—immunohistochemistry MMR—mismatch repair MSI—microsatellite instability

complete anal mucosectomy or stapled to a 1 to 2 cm anal transition zone. Neoplasia may occur at the site of the anastomosis, and the incidence appears to be higher after stapled anastomosis (28% to 31%) than after mucosectomy and handsewn anastomosis (10% to 14%).^{18,19} Function, however, may be better after stapled anastomosis.¹⁹ In the case of anal transition zone neoplasia after stapled anastomosis, transanal mucosectomy can often be performed, followed by advancement of the pouch to the dentate line. Of additional concern is the development of adenomatous polyps in the ileal pouch itself, which occurs in 35% to 42% of patients at 7 to 10 years.²⁰⁻²²

With respect to postoperative bowel function and associated quality of life, IPAA has been associated with a higher frequency of both daytime and nocturnal bowel movements, a higher incidence of passive incontinence and incidental soiling, and higher postoperative morbidity than IRA.²³ Accordingly, some authors recommend IRA for patients with mild rectal polyposis. Other authors, however, have found the two approaches to be equivalent in terms of functional results²⁴ and quality of life²⁵ and therefore recommend IPAA for most patients because of the risk of rectal cancer associated with IRA.

Regardless of which procedure is performed, however, lifetime surveillance of the rectal remnant (after IRA) or the ileal pouch (after IPAA) is required.¹¹ Endoscopic surveillance of the bowel at intervals of 6 months to 1 year after index surgery is recommended.^{5,11} After IRA, small (< 5 mm) adenomas may be safely observed, with biopsy performed to rule out severe dysplasia. If adenomas increase in number, the frequency of surveillance should be increased, and polyps larger than 5 mm should be removed. When fulguration and polypectomy are repeated over a period of many years, subsequent polypectomy may become difficult, rectal compliance may be reduced, and flat cancers may be hard to identify against a background of scar tissue. The development of severe dysplasia or a villous adenoma larger than 1 cm is an indication for proctectomy.¹¹

Extracolonic Disease

After total abdominal colectomy with IRA and regular surveillance, the risk of death appears to be three times higher for FAP patients than for an age- and sex-matched control population.²⁶ The main causes of death after IRA are desmoid disease and upper gastrointestinal malignancy.

Desmoid disease Desmoids are histologically benign tumors that arise from fibroaponeurotic tissue and occur in 12% to 17% of FAP patients.^{11,27,28} Unlike those in the general population, desmoids in FAP patients tend to be intra-abdominal (up to 80% of cases) and mainly occur after abdominal surgical procedures.^{27,28} Patients with *APC* mutations located between codons 1310 and 2011 are at increased risk for these tumors.²⁹ Desmoids often involve the small bowel mesentery (> 50% of cases),²⁸ making complete resection difficult or impossible, and they may also involve the ureters.²⁷ Not uncommonly, patients present with small bowel obstruction.^{27,28} Morbidity after attempted resection, which often involves removal of a significant length of small bowel, is substantial. The recurrence rate after attempted resection is also high, and the recurrent disease is often more aggressive than the initial desmoid.^{27,28}

Intra-abdominal desmoid formation may be more common after IRA than after IPAA, and the disease may be more severe after IRA as well.^{28,30} When desmoid tumors involve the small bowel mesentery, the mesentery may become foreshortened and thereby render IPAA impracticable, especially in patients under-

going a subsequent completion proctectomy after an initial IRA.¹¹ This possibility should be considered in making the choice between IRA and IPAA as the initial procedure for FAP.

Medical therapy. When desmoid tumors are clinically inert, they may be treated with sulindac.¹¹ Tamoxifen or other antiestrogens may be added for slow-growing or mildly symptomatic tumors.^{11,31,32} More aggressive desmoid tumors may be treated with chemotherapy. Vinblastin and methotrexate achieve some degree of response in 40% to 50% of patients.³³ For more rapidly growing desmoids, antineoplastic agents, such as doxorubicin and dacarbazine, may be administered.^{34,35} Radiation therapy may also be effective, but it can result in substantial small bowel morbidity.

Surgical therapy. Surgical treatment of intra-abdominal desmoid tumors should be reserved for small, well-defined lesions with clear margins.¹¹ When intra-abdominal desmoids involve the small bowel mesentery, they should be treated according to their initial presentation and rate of growth. In patients with desmoid lesions that are refractory to all medical treatment and call for surgical treatment with extensive small bowel resection, small bowel transplantation may be feasible in selected cases.³⁶

Periampullary neoplasms In approximately 80% to 90% of persons with FAP, duodenal adenomas, periampullary adenomas, or both will develop.³⁷ Of these patients, 14% to 50% will eventually exhibit advanced polyposis, and as many as 6% will eventually have invasive cancer.^{1,38-42} Although the risk of periampullary or duodenal cancer in FAP patients is relatively low, it is still several hundred times higher than that in the general population. Among FAP patients, those with *APC* mutations between codons 976 and 1067 appear to have the highest incidence of duodenal adenoma.

Surveillance should begin with side-viewing esophagogastroduodenoscopy (EGD) and biopsy of suspicious polyps either at the age of 20 years or at the time of prophylactic colectomy, whichever is earlier.¹¹ The purpose of screening is not to remove all disease but to watch for the development of high-grade dysplasia. Small, tubular adenomas without high-grade dysplasia may be biopsied and observed; adenomas that are larger than 1 cm or that exhibit high-grade dysplasia, villous changes, or ulceration should be removed. Surgical options include endoscopic removal and transduodenal excision, but both approaches have drawbacks: endoscopic ablation generally requires multiple settings,³⁸ and recurrence is high after either procedure.^{38,43} Endoscopic ablation is a reasonable initial approach for most patients without invasive cancer and is an attractive alternative for patients who are unfit for duodenal resection. For patients with persistent or recurrent high-grade dysplasia in the papilla or duodenal adenomas and for patients with Spigelman stage IV disease, pancreas-preserving duodenectomy or pancreaticoduodenectomy is recommended.¹¹ The results reported for duodenal resection in patients with premalignant lesions are encouraging, with good local control and low morbidity.^{38,44,45} Duodenectomy also greatly reduces the need for upper GI surveillance.

Hereditary Nonpolyposis Colorectal Cancer

HNPCC, which accounts for 5% to 7% of CRCs, results from a mutation in one of the DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS1*, *PMS2*, *MLH3*, and *MSH3*).^{46,47} Two genes (*MLH1*, *MSH2*) may be responsible for as many as 90% of causative germline MMR mutations. However, only 50%

to 70% of patients meeting clinical criteria for HNPCC have an identifiable germline MMR mutation, which suggests that one or more unidentified genes may be involved. A significant percentage of cases may be attributable to large germline deletions that are difficult to detect by means of direct sequencing. It appears that genomic deletions may account for as many as 7% of HNPCC cases defined on the basis of clinical criteria.⁴⁸

CLINICAL EVALUATION

HNPCC is characterized by early-onset CRC, a predominance of lesions proximal to the splenic flexure (60% to 70% of cases), benign and malignant extracolonic tumors, and a predilection for synchronous and metachronous colorectal tumors.⁴ Microsatellite instability (MSI), reflecting a deficiency in DNA repair secondary to a mutation in the MMR genes, is noted in approximately 80% to 90% of HNPCC-related tumors.⁴ The lifetime risk of CRC in HNPCC patients is approximately 80%.^{11,49}

Establishing a clinical diagnosis of HNPCC is much more challenging than establishing a clinical diagnosis of FAP, in that it requires a careful and detailed family history. The Amsterdam II criteria [see Table 3] require that there be three relatives (of which one must be a first-degree relative of the other two) with an HNPCC-related cancer (of the colorectum, the endometrium, the small bowel, the ureter, or the renal pelvis), that two or more successive generations be involved, and that at least one relative have a CRC diagnosed before the age of 50.^{50,51} Finally, FAP should be excluded. CRC occurs in 78% to 80% of MMR mutation-positive patients at a mean age of 46 years.^{1,49,52} Endometrial cancer occurs in 43%, gastric cancer in 19%, urinary tract cancer in 18%, and ovarian cancer in 9%.⁵³

INVESTIGATIVE STUDIES

Pathologic Findings

Adenomas in HNPCC patients show high-grade dysplasia and villous changes more frequently than adenomas in sporadic CRC patients.¹ Adenomas may also appear at an earlier age and are often larger than those found in the general population. Other pathologic features reported to be more common in HNPCC-related cancers include a mucinous or poorly differentiated histology, a solid or cribriform growth pattern, signet-ring cell tumors, and the presence of tumor-infiltrating and peritumoral lymphocytes. HNPCC-related CRCs have also been shown to have a lower rate of lymph node involvement.⁵⁴

Screening and Surveillance

CRC patients who belong to known HNPCC kindreds, who have a pedigree suggestive of HNPCC, or who meet the Bethesda criteria [see Table 4]⁵⁵ should be offered screening by MSI testing. MSI evaluation will yield positive results (i.e., an MSI-high tumor) in 80% to 90% of patients belonging to families that meet the Amsterdam criteria. Patients with MSI-high tumors should undergo testing for germline MMR mutations (tests for *MSH2* and *MLH1* are available commercially [see Table 2]). If tumor tissue is not available, initial germline testing may be considered. As in FAP, a mutation in an affected individual must first be established for testing in at-risk individuals to be informative.⁵

Recommended surveillance for HNPCC includes colonoscopy, initially every 1 to 2 years beginning at the age of 20 to 25, then annually after the age of 40.⁵⁶ Given the increasing evidence of an accelerated adenoma-carcinoma sequence in HNPCC, annual colonoscopy should be strongly considered.⁴ Female patients should undergo annual transvaginal ultrasonography and mea-

Table 3 Clinical Criteria for Diagnosis of HNPCC

Amsterdam criteria I ⁵⁰	Three or more relatives with CRC One first-degree relative of the other two One CRC diagnosed at age < 50 yr Two or more successive generations FAP excluded
Amsterdam criteria II ⁵¹	Three or more relatives with an HNPCC-associated cancer (in colorectum, endometrium, small bowel, ureter, or renal pelvis) One first-degree relative of the other two Two or more successive generations One CRC diagnosed at age < 50 yr FAP excluded

surement of CA125 levels starting at 25 to 35 years of age, as well as annual endometrial aspiration.⁵⁶ Annual EGD is recommended for patients belonging to kindreds with a history of gastric cancer. Finally, ultrasonography and urine cytology every 1 to 2 years may be considered to screen for urinary tract malignancy.

MANAGEMENT

Surgical Therapy

Although the development of CRC in persons with HNPCC is not a certainty, the 80% lifetime risk,¹ the 45% rate of metachronous tumors, and the possibility of an accelerated adenoma-carcinoma sequence⁴ mandate consideration of prophylactic surgical options. Patients who have HNPCC as defined by their genotype or the Amsterdam criteria [see Table 3] and who have a colon cancer or more than one advanced adenoma should be offered either (1) prophylactic total abdominal colectomy with IRA or (2) segmental colectomy with yearly colonoscopy [see 5:34 Segmental Colon Resection].^{11,57,58} (The first option, however, is open only to patients with normal rectal and anal sphincter function.) Although the risk of metachronous colon cancers may be higher after partial colectomy than after total colectomy with IRA, intensive colonoscopic surveillance and polypectomy may minimize the number of metachronous cancers in the remaining colon.^{52,59} Careful surveillance is also necessary after total colectomy and IRA, given that the risk of metachronous rectal cancer after total colectomy is approximately 12% at 10 to 12 years.⁶⁰

HNPCC patients with an index rectal cancer that is amenable to a sphincter-preserving resection should be offered either (1) total proctocolectomy with IPAA [see 5:33 Procedures for Ulcerative Colitis] or (2) low anterior resection (LAR) with primary reconstruction [see 5:35 Procedures for Rectal Cancer].^{11,58} The rationale

Table 4 Revised Bethesda Guidelines for Testing CRC Patients for MSI⁵⁵

CRC diagnosed at age < 50 yr
Presence of synchronous or metachronous CRC or other HNPCC tumors (regardless of age)
CRC with HNPCC-like histology at age < 60 yr
CRC in one or more FDR with an HNPCC-related tumor (one diagnosed at age < 50 yr)
CRC in two or more first- or second-degree relatives with HNPCC-related tumors (regardless of age)

FDR—first-degree relative

for total proctocolectomy is based on the 17% to 45% rate of metachronous cancer in the remaining colon associated with an index rectal cancer in HNPCC patients.⁶¹ The decision between the two procedures depends in part on the patient's willingness to undergo intensive surveillance of the retained proximal colon, as well as on the level of bowel function.

Mutation-positive patients with a normal colorectum may also be offered prophylactic colectomy in selected cases.^{56,62} This approach is supported by the similarity of lifetime cancer risk between patients with germline *APC* mutations and those with MMR mutations, as well as by the observation that total abdominal colectomy with IRA yields less functional disturbance than the prophylactic procedure recommended for FAP (total proctocolectomy with IPAA).^{56,62} An alternative strategy in these patients is to carry out colonoscopic surveillance at 1- to 3-year intervals. This strategy has proved to be cost-effective⁶³ and to reduce both the rate of CRC development and overall mortality.^{52,64,65} There is a risk that CRC may develop in the intervals between colonoscopies^{64,66}; however, when the surveillance interval is shorter than 2 years, tumors tend to be found in their early stages and to be curable when found.^{52,64}

A study using a decision-analysis model suggested that prophylactic total abdominal colectomy at the age of 25 might offer a survival benefit of 1.8 years when compared with colonoscopic surveillance. The benefit of prophylactic colectomy decreased when surgery was delayed until later in life and became negligible when it was performed at the time of cancer development.⁶⁵ However, surveillance provided a greater benefit with respect to quality of life (measured in quality-adjusted life years).⁶⁵ On the basis of this evidence, some surgeons recommend that prophylactic colectomy be performed only in highly selected situations (e.g., when colonoscopic surveillance is not technically possible or when a patient refuses to undergo regular surveillance). Thus, the decision between prophylactic surgery and surveillance for gene-positive unaffected patients is based on many factors, including the penetrance of disease in a family, the age of cancer onset in family members, functional and quality-of-life considerations, and the likelihood of patient compliance with surveillance.

Extracolonic Disease

Management of extracolonic cancers in HNPCC patients is not yet well defined. Female patients with a family history of uterine cancer should be offered prophylactic total abdominal hysterectomy (TAH) if their childbearing is complete or if they are undergoing abdominal surgery for other conditions.¹¹ This recommendation is based on the high (43%) rate of endometrial cancer in mutation-positive persons,⁵³ particularly those with *hMSH2* mutations, and on the inefficacy of screening in some studies.⁶⁷ Oophorectomy should be added to TAH because of the high (9%) incidence of ovarian cancer in HNPCC patients⁵³ and the frequent coexistence of endometrial cancer with ovarian cancer.⁶⁸ The optimal timing for prophylactic TAH is unclear; however, endometrial cancer has been reported in HNPCC patients before the age of 35. At present, it seems reasonable to begin surveillance at the age of 25 and delay prophylactic surgery until childbearing is complete.¹¹

Peutz-Jeghers Syndrome

Like FAP and HNPCC, PJS follows an autosomal dominant pattern of inheritance with variable penetrance. It is caused in part by mutations in the gene *LKB1/STK11*, which maps to the telomeric region of chromosome 19p13.3. This gene, which codes for

a multifunctional serine-threonine kinase, is thought to function as a tumor suppressor gene.⁶⁹⁻⁷² Germline mutations in *LKB1/STK11* can be demonstrated in 18% to 63% of PJS patients, which suggests the existence of additional PJS loci.⁷²⁻⁷⁵ Genetic testing for PJS can be accomplished through direct sequencing of the *LKB1/STK11* gene [see Table 2]; however, such testing is not widely available. In families with an established mutation, genetic testing of at-risk individuals is informative, with a reported accuracy of 95%.⁷⁶

CLINICAL EVALUATION

PJS is a hereditary polyposis syndrome characterized by hamartomas of the GI tract, as well as by mucocutaneous melanin pigmentation. Hamartomatous polyps may occur throughout the GI tract but are most frequently found in the small intestine (90%). Other common sites of hamartomas in PJS are the large intestine (50%) and the stomach; less common sites are the renal pelvis, the bile ducts, the urinary bladder, the lungs, and the nasopharynx.^{1,77,78} Mucocutaneous pigmentation generally appears during infancy. The perioral and buccal areas are involved in 95% of cases; the periorbital and facial areas, the genital region, and the acral areas (including the hands and feet) may be involved as well.¹ The average age of diagnosis of PJS is 22 years in men and 26 years in women.

In as many as 86% of cases, the initial presentation of PJS is small bowel obstruction secondary to intussusception of hamartomas. Other presentations include acute or chronic GI bleeding, biliary and gastric outlet obstruction, and anal protrusion of polyps. The diagnosis of PJS is established by the presence of histologically confirmed hamartomas of the GI tract plus two of the following three criteria: (1) small bowel polyposis, (2) mucocutaneous melanotic pigmentation, and (3) a family history of PJS [see Table 1].⁷⁹

Patients with PJS are at significantly increased risk for both intestinal and extraintestinal malignancies. A meta-analysis found that in comparison with the general population, PJS patients were at a relative risk of 15.2 for the development of any malignancy.⁸⁰ The relative risks for the development of specific cancers were as follows: small bowel, 520; gastric, 213; pancreatic, 132; colorectal, 84; esophageal, 57; ovarian, 27; lung, 17; endometrial, 16; and breast, 15. The cumulative risk for the development of any cancer between the ages of 15 and 64 was 93%.⁸⁰ Other cancers associated with PJS are cholangiocarcinomas, testicular neoplasms, and duodenal tumors.¹

Although the relative risk for the development of CRC was high in this study,⁸⁰ the reported magnitude of risk in the individual studies included in the meta-analysis varied considerably. Previous studies also reported a wide range of CRC incidences in these patients.¹ Thus, the true incidence of CRC in PJS patients remains unclear.

INVESTIGATIVE STUDIES

Pathologic Findings

The polyps seen in PJS are hamartomas characterized by hypertrophy or hyperplasia of the smooth muscle of the muscularis mucosa. Smooth muscle extends into the superficial epithelial layer of the bowel wall in a treelike fashion (a process referred to as arborization). Epithelial cells may become entrapped within the muscle layer, and this "pseudoinvasion" can be mistaken for malignant transformation. Therefore, to diagnose a malignancy in a PJS polyp, cellular atypia or an elevated mitotic rate must be documented.⁸¹ Sporadic PJS polyps do occur, generally secondary

to somatic *LKB1/STK11* mutations in one or both alleles, and are histologically identical to their hereditary counterparts. These sporadic polyps appear not to be associated with an increased risk of GI cancer.⁸²

Histologically, areas of cutaneous pigmentation reveal an increased number of melanocytes at the dermal-epidermal junction, with elevated melanin levels in the basal cells. These lesions do not appear to have any malignant potential.

Screening and Surveillance

Clinical screening of asymptomatic persons is facilitated by the appearance of perioral hyperpigmentation during early childhood. Once the diagnosis of PJS is made, patients generally enter a surveillance program. Recommended surveillance for GI disease includes annual serum hemoglobin measurement and EGD every 2 to 3 years, beginning between the ages of 10 and 25.^{79,83-85} Contrast radiography is employed to examine the remainder of the small bowel, beginning at the age of 10 and repeated every 2 to 3 years.^{79,85} The frequency of surveillance examinations may be modified in individual circumstances. Colonoscopic surveillance is also important, commencing between puberty and the age of 25 and repeated every 2 to 3 years.^{83,85} Sigmoidoscopy should not be employed for surveillance, because the rectum may be spared in some patients with more proximal disease. Organ-specific surveillance for other associated malignancies should also be initiated in accordance with current high-risk recommendations.

MANAGEMENT

Medical Therapy

Cyclooxygenase-2 (COX-2) is known to be overexpressed in the hamartomatous tissue of PJS patients, and there is a correlation between expression of the COX-2 protein and expression of the *LKB1/STK11* protein in PJS polyps and cancers.^{86,87} These findings suggest that COX-2 may be a potential target for chemoprevention of PJS.

Surgical Therapy

Indications for surgical management of PJS include the presence of polyps larger than 1.5 cm that cannot be removed endoscopically, incomplete removal of polyps with adenomatous changes, the development of polyp-associated complications (e.g., obstruction, intussusception, and bleeding), and the management of malignant disease.⁸⁸

Endoscopic polypectomy is generally employed as initial therapy when it is technically feasible. For some polyps, however, operative polypectomy performed through an enterotomy is required. Segmental resection should be avoided. In the context of a laparotomy, intraoperative endoscopy (either peroral or via an enterotomy) allows direct visualization of the remainder of the small bowel and endoscopic clearance of any synchronous polyps. This procedure significantly reduces the need for subsequent laparotomy. The St. Mark's Hospital group in London found that none of 25 patients who underwent enteroscopy during laparotomy required subsequent laparotomy within a 4-year period, whereas 17% of historical control patients who did not undergo intraoperative enteroscopy required repeat laparotomy within a 1-year period.⁸⁹

Laparoscopy-assisted polypectomy and laparoscopic management of small bowel intussusception are additional surgical options.

Given the risk of CRC development in PJS patients, careful colonoscopic surveillance is clearly warranted. However, the role of prophylactic colectomy in patients who are at risk or are mutation

positive is unclear. Because the true risk of CRC in these patients is unknown and genetic testing for PJS is not widely available, no recommendations can be made at present regarding the role of prophylactic colectomy in the PJS population.⁸⁸

Juvenile Polyposis Syndrome

Initial evidence suggested that mutations in the *PTEN* gene were responsible for JPS⁹⁰; however, subsequent evidence implicated *SMAD4/DPC4* at 18q21.1 as a more common cause, accounting for as many as 50% of familial cases.⁹¹⁻⁹³ Mutations in *BMPRI1A* at 10q22-q23 have also been reported to cause JPS but display variable penetrance [see Table 2].^{94,95} Clonal genetic alterations are detected in stromal rather than epithelial cells, which suggests that the genetic changes in juvenile polyps originate in the nonepithelial component of the polyps.

CLINICAL EVALUATION

Like PJS, JPS is characterized by the development of multiple hamartomas throughout the GI tract. Isolated juvenile polyps are common in children and are found in approximately 1% of persons younger than 21 years. Juvenile polyposis, however, is much less common. A family history of juvenile polyposis is present in 20% to 50% of patients.¹ Although JPS is an autosomal dominant disorder, its variable penetrance results in a less obvious pattern of inheritance than is seen with FAP or HNPCC.

JPS affects the two sexes equally and generally manifests itself during the first or second decade of life (mean age at diagnosis, 18.5 years).¹ Common presenting symptoms include chronic anemia, acute GI bleeding, prolapse of rectal polyps, protein-losing enteropathy, and intussusception with or without obstruction.¹

Extracolonic manifestations of JPS include gastroduodenal and small bowel polyps, malrotation of the midgut, and mesenteric lymphangiomas. Extraintestinal manifestations include clubbing, hypertrophic pulmonary osteoarthropathy, hydrocephalus and macrocephaly, alopecia, cleft lip and palate abnormalities, supernumerary teeth, porphyria, congenital cardiac and arteriovenous malformations, psoriasis, vitelointestinal duct abnormalities, renal structural abnormalities, and bifid uterus and vagina. JPS is also part of the phenotype for Ruvalcaba-Myhre-Smith syndrome and Gorlin syndrome. Cowden disease, which is characterized by hamartomatous polyposis and is associated with breast and thyroid cancer, may be a phenotypic variant of JPS.^{1,95}

The diagnostic criteria for JPS are as follows: (1) the presence of three or more juvenile polyps of the colon; (2) the presence of juvenile polyps throughout the entire GI tract; or (3) the presence of any number of polyps in a patient with known family history of JPS [see Table 1].⁸⁵ The clinical presentation of JPS can be divided into three main clinical variants: (1) JPS of infancy, which is a non-sex-linked recessive condition characterized by failure to thrive, susceptibility to infections, protein-losing enteropathy, bleeding, diarrhea, rectal prolapse, intussusception, and death by the age of 2 years in severe cases; (2) generalized JPS, which occurs in the first decade of life and is characterized by juvenile polyps throughout the GI tract; and (3) JPS of the colon, the most common presentation, which is characterized by colonic polyposis only.¹

Patients with JPS appear to be at increased risk for GI malignancies, especially CRC. One study estimated the risk of CRC to be 15% by age 35 and 68% by age 65.⁹⁶ In another study, GI malignancies (mostly CRC) were diagnosed in 36 (17%) of 218 JPS patients at a mean age of 33 years.⁹⁷ Associated gastric, pancreatic, and duodenal cancers have also been reported. CRCs are thought to arise from malignant transformation of dysplastic

polyps.¹ Adenocarcinomas occur, on average, 15 years after diagnosis of JPS and generally are poorly differentiated or mucinous tumors with a poor prognosis.¹

INVESTIGATIVE STUDIES

Pathologic Findings

The number of polyps seen in JPS patients varies but typically ranges from 50 to 200. The polyps are usually smaller than 1.5 cm but can be as large as 3 cm. Grossly, they appear as red-brown, smooth, pedunculated lesions with lobulated or spherical heads and superficial ulceration; the cut surface demonstrates cystic spaces corresponding to mucus-filled glands. Histologically, polyps are characterized by an inflammatory infiltration of the lamina propria, an attenuated smooth muscle layer, and cystically dilated mucus-filled glands lined by columnar epithelium. Focal epithelial hyperplasia and dysplasia may be present.

Screening and Surveillance

Initial evaluation of the proband and the first-degree relatives, which ideally would be done in the middle to late teenage years, should include colonoscopy, EGD, and a small bowel series. If the

initial evaluation yields negative results, a repeat evaluation should be performed in 3 years, then every 3 years thereafter as long as the results remain negative. If disease is encountered, random biopsies of polyps and intervening mucosa should be performed to detect adenomatous and dysplastic changes. Management depends on the presence of symptoms and on the extent and severity of polyposis. When polyposis is mild, endoscopic management may be feasible. Continued annual surveillance after endoscopic management is required; the surveillance interval may be lengthened to 3 years if subsequent evaluations reveal no disease.^{1,85}

MANAGEMENT

Surgical Therapy

When polyposis is severe or significant symptoms are apparent, prophylactic colectomy with IRA may be considered for suitable surgical candidates. Although rectal polyposis can generally be managed with rigid or flexible proctoscopy, IPAA may be considered if the polyposis is extensive. Continued annual surveillance of the rectal remnant (after IRA) or the ileal pouch (after IPAA) is required initially. Surveillance intervals may be increased to 3 years if subsequent evaluations find no evidence of disease.^{1,85}

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15 ADENOCARCINOMA OF THE COLON AND RECTUM

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Colorectal cancer (CRC) remains a major public health problem throughout the world. In the United States, CRC is the third most frequently diagnosed cancer in both men and women and the second most common fatal cancer (behind lung cancer).¹ During 2008, there were an estimated 108,000 cases of colon cancer and 41,000 cases of rectal cancer in the United States, resulting in 50,000 total deaths.¹ The cost of treating CRC in the United States is believed to be between 5.5 and 6.5 billion dollars a year.² Worldwide, the risk of death from CRC is highest in developed countries and especially low in Asia and Africa.³

Data from the Surveillance, Epidemiology, and End Results (SEER) program and the National Center for Health Statistics indicate that the overall incidence of and mortality from CRC have been continuously decreasing in the United States since the 1980s among both men and women.⁴ They remain generally higher among men than women. Overall, the incidence of and mortality from CRC are highest among African Americans, somewhat lower among European Americans, and lowest among Asian and Hispanic Americans [see Table 1].⁴ Most CRCs still occur in the distal colon (beyond the splenic flexure), but the incidence of proximal adenocarcinomas relative to that of distal adenocarcinomas has been increasing over the past 30 years [see Figure 1].⁵ The cause of this shift is not known.

Genetics

The development of CRC involves a progression from normal mucosa through adenoma to carcinoma.⁶ A genetic model of colorectal carcinogenesis was first proposed in the early 1990s that describes a sequence of key mutations driving

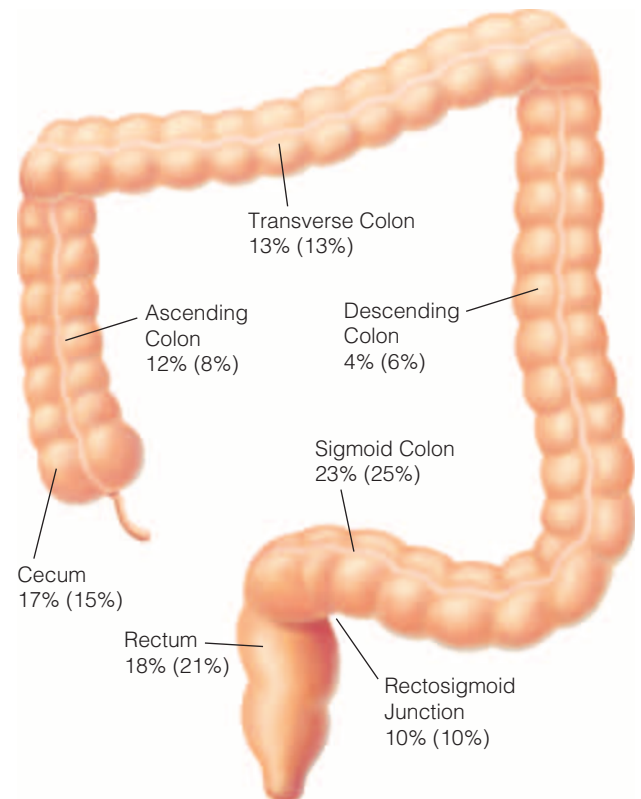


Figure 1 Shown are the relative frequencies of colorectal cancer for various anatomic subsites of the colon in 1996. For comparative purposes, figures for 1976 are provided in parentheses.

Table 1 Incidence and Mortality of Colorectal Cancer by Race and Sex[†]

Race	Incidence* and APC		Mortality* and APC	
	Male	Female	Male	Female
White	60.6 (−2.2)	44 (−1.8)	22.7 (−2.7)	15.3 (−2.6)
African American	69.4 (−1.0)	52.4 (−1.0)	31.8 (−1.6)	22.4 (−1.9)
Asian/Pacific Islander	45.5 (−2.2)	33.6 (−1.4)	14.4 (−2.1)	10.2 (−2.1)
Hispanic	51.5 (−1.0)	36.2 (−1.2)	16.5 (−2.0)	10.9 (−0.9)

*No./100,000.

APC = annual percentage change.

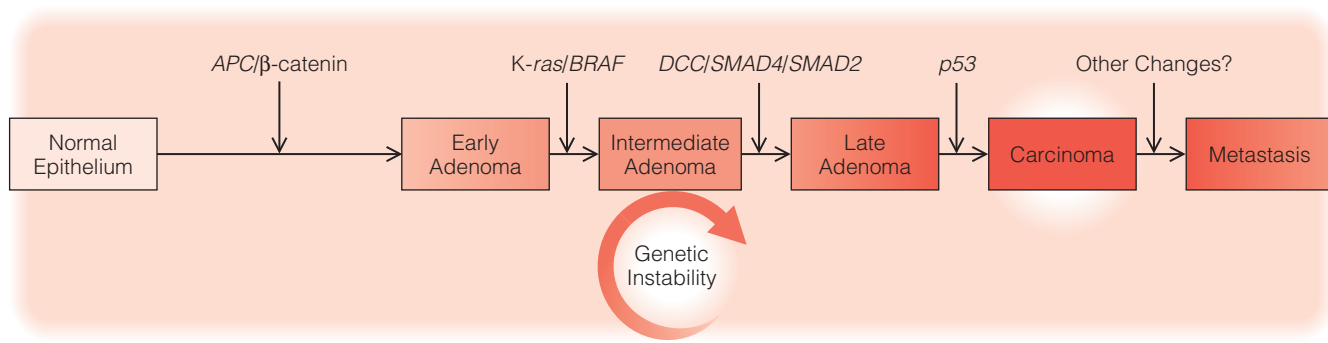


Figure 2 Diagram illustrates genetic model of colorectal tumorigenesis.⁸

the process of colorectal carcinogenesis [see Figure 2].⁷ This progression was recently reevaluated using large-scale genetic sequencing of multiple lesions from an individual patient.⁸ Using this “comparative lesion sequencing” approach, it is estimated that it takes approximately 17 years for a large adenoma to progress to invasive malignancy but less than 2 additional years to develop the capacity to metastasize.

The process of colorectal carcinogenesis may involve the accumulation of mutations in both tumor suppressor genes and proto-oncogenes, as well as epigenetic phenomena such as DNA hypermethylation or hypomethylation.⁹ The onset of genomic instability increases the mutation rate and accelerates this progression. Inactivation of the adenomatous polyposis coli (*APC*) gene on chromosome 5q is thought to be one of the earliest mutations in sporadic cancers and is seen as a germline mutation in patients with familial polyposis. Mutations in other tumor suppressor genes play an important role in this pathway as well, including mutations in *DCC*, *SMAD2*, and *SMAD4* on chromosome 18q and *p53* on chromosome 17p; these events are thought to occur at a later stage of tumor progression. Mutations in the *K-ras* and *BRAF* oncogenes occur at an intermediate stage. The accumulation of additional mutations (as yet poorly defined) allows metastases to develop.

Microsatellite instability (MSI) is an alternative pathway to genomic instability and subsequent colorectal carcinogenesis. This phenomenon arises from defects in mismatch repair genes, which cause significantly increased mutation rates in comparison with those in normal cells. MSI in hereditary nonpolyposis colorectal cancer (HNPCC) [see Risk Factors, below] is most commonly attributable to germline mutations in the *hMLH1* and *hMSH2* genes.¹⁰ MSI in sporadic CRC is most frequently associated with hypermethylation of the promoter region of the *hMLH1* gene,¹¹ which leads to inactivation of the gene and loss of expression of the hMLH1 protein.

Risk Factors

A number of risk factors for CRC have been described, including a family history of cancer or adenomatous polyps, familial CRC syndromes, inflammatory bowel disease (both ulcerative colitis and Crohn’s disease), and dietary and lifestyle factors.^{12,13} The vast majority of CRCs worldwide are

sporadic—that is, they are not associated with known genetic syndromes. In the United States, no more than 5% of CRCs are associated with known genetic syndromes.

In a meta-analysis of studies addressing CRC risk and family history, the relative risk of CRC in those with an affected first-degree relative was 2.25; this figure rose to 4.25 if more than one relative was involved and to 3.87 if CRC was diagnosed before the age of 45.¹⁴ The National Polyp Study found that the relative risk of CRC was 1.78 in first-degree relatives of patients with adenomatous polyps.¹⁵ In another study, the relative risk of CRC was 1.74 in first-degree relatives of patients with adenomatous polyps and was especially high (4.36) in those diagnosed with polyps at or before the age of 50.¹⁶

The most common of the genetic syndromes known to be associated with CRC is HNPCC, which accounts for the majority of patients with familial CRC. MSI is the characteristic finding of HNPCC, although it is also present in approximately 15% of all sporadic CRCs. HNPCC can be diagnosed clinically on the basis of what are known as the Amsterdam Criteria.¹⁷ Polyposis syndromes (e.g., familial polyposis and juvenile polyposis) account for the remainder of patients with familial CRC syndromes.

As determined by a 2001 meta-analysis, the lifetime risk of CRC for patients with ulcerative colitis is 3.7%, which increases to 5.4% for patients with pancolitis and rises further with greater duration of disease.¹⁸ Despite the common misconception, Crohn’s disease may be associated with a similarly increased risk of CRC.¹⁹

Numerous lifestyle and dietary factors have been put forward as potential causes of increased CRC risk. Lower levels of physical activity and increased body mass are associated with an increased risk of CRC in both men and women.²⁰ The Western-style diet, which is high in calories and fat and low in fiber, is associated with high rates of CRC. There is evidence that increased dietary intake of calcium may confer some protection against the development of CRC and adenomatous polyps. The Calcium Polyp Prevention Study, a large randomized trial done in the United States, reported a small but statistically significant reduction in the incidence of recurrent colorectal adenomas with dietary calcium supplementation.²¹ To date, the evidence from randomized trials has not shown dietary fiber supplementation to have a similar effect. In Japan, where the incidence of CRC has traditionally been

low, CRC has become considerably more common in the past few decades.²² This increased incidence is believed to be the result of post–World War II lifestyle changes (e.g., increased consumption of animal fat and decreased expenditure of energy) that mirror Western habits.

Screening

Early diagnosis of colorectal neoplasms at a presymptomatic stage is important for improving survival. Polypectomy has consistently been shown to decrease the subsequent development of CRC: the National Polyp Study found that the incidence of CRC in patients who underwent colonoscopic polypectomy was as much as 90% less than would otherwise have been expected.²³ Identifying patients with early-stage disease that has not yet metastasized can prevent many CRC-related deaths. Detection of adenomatous polyps prior to the development of invasive cancer has become the focus of screening recommendations. Early detection of and screening for CRC have become important components of routine care and public health programs both in the United States and abroad. The benefits of screening for CRC are especially substantial in patients who are at high risk for CRC (e.g., those with affected first-degree relatives), but even average-risk patients derive significant benefit.

There is no ideal method of screening for CRC that is applicable to all patients. Physical examination is generally not helpful in making the diagnosis; various investigative tests are used instead. In patients at increased or high risk for CRC, colonoscopy is the only recommended screening modality. For average-risk patients, current recommendations divide these tests into those that detect both cancers and premalignant adenomas and those that primarily detect cancer and possibly advanced adenomas.²⁴ Recommended modalities for CRC screening that are also effective in detecting adenomas include colonoscopy, flexible sigmoidoscopy, double-contrast barium enema (DCBE), and virtual colonoscopy (computed tomographic [CT] colonography). Those that are predominantly effective in detecting cancers and some large adenomas include fecal occult blood testing (FOBT) with guaiac-based or immunochemical tests and stool DNA testing.

Only a limited number of randomized trials have evaluated the above screening modalities. Sigmoidoscopy has been shown to decrease both CRC incidence and mortality, but only in case-control studies,²⁵ and colonoscopy detects many CRCs in asymptomatic patients that would not be detected by this procedure.²⁶ FOBT is the sole modality that has consistently been shown to decrease CRC mortality in randomized trials.^{27,28} Few studies directly compare different types of FOBT, but fecal immunochemical tests appear to have a higher sensitivity than guaiac-based tests. The specificity may be slightly lower, however, resulting in more patients requiring follow-up colonoscopy.

Virtual colonoscopy, which uses high-resolution CT scanning to image the colon, has been evaluated in at least two multicenter trials in the United States, with varying results.^{29,30} One of the studies reported a sensitivity and a specificity of 89% and 80%, respectively, for polyps larger than 6 mm and up to 94% and 96%, respectively, for polyps larger than

10 mm.²⁹ The sensitivities were equivalent to those of optical colonoscopy in this group of asymptomatic average-risk patients. The second study, however, found that virtual colonoscopy had a sensitivity of only 39% for lesions larger than 6 mm and 55% for lesions larger than 10 mm.³⁰ Given these divergent findings, it appears that there are issues related to equipment, software, training, and overall sensitivity of the study that remain to be addressed before virtual colonoscopy can be recommended as a routine screening modality. Another consideration is that patients with lesions detected by means of virtual colonoscopy must still undergo optical colonoscopy for treatment or tissue diagnosis.

Fecal DNA assays have been developed to test for mutations in multiple genes known to be involved in colorectal neoplasia and are currently being evaluated in clinical trials.³¹ A study comparing fecal DNA testing with a commercially available multigene panel to guaiac-based testing in asymptomatic patients showed both to have a poor sensitivity in detecting cancers and advanced adenomas detected by screening colonoscopy.³² DNA testing was significantly better, but still only detected 52% of cancers and 18% of advanced adenomas.

Colonoscopy has been consistently shown to be a safe and effective method of CRC screening in asymptomatic, average-risk patients. CT colonography has replaced barium enema as the radiologic screening test of choice but has not been clearly demonstrated to be equivalent to colonoscopy. FOBT and DNA testing are less sensitive and specific than colonoscopy in addition to being relatively ineffective in detecting premalignant polyps. These other modalities may be useful in patients who are unable or unwilling to comply with endoscopic screening.

Many groups have advocated CRC screening, and published guidelines are available from several organizations, including a collaborative guideline published by the American Cancer Society, the US Preventive Services Task Force, and the American College of Radiology.³³ Others include the American College of Gastroenterology³⁴ and the National Comprehensive Cancer Network (NCCN).³⁵ All of these guidelines recommend that screening begin at age 50 for average-risk patients with colonoscopy at 10-year intervals. The recommended screening options in patients unwilling or unable to undergo colonoscopy are fairly consistent among the various organizations and include (1) FOBT yearly, (2) flexible sigmoidoscopy every 5 years, (3) yearly FOBT and flexible sigmoidoscopy every 5 years, (4) DCBE every 5 years, and (5) CT colonography every 5 years. In high-risk patients (e.g., those with a family history of CRC), screening may begin at an earlier age—generally at age 40 or 10 years younger than the age of the affected first-degree relative and with shorter, 5-year intervals. There are also specific intensive screening and follow-up regimens for patients with known or suspected familial cancer syndromes.

Clinical Evaluation

As a consequence of the use of screening modalities, patients with CRC are often asymptomatic at diagnosis. Some CRC patients present with occult gastrointestinal bleeding and anemia. Many patients do not exhibit symptoms

until relatively late in the course of the disease. The duration of symptoms, however, is not necessarily associated with the stage of the tumor.³⁶

The most common symptoms of CRC are bleeding per rectum, abdominal or back pain, and changes in bowel habits or stool caliber. Other symptoms are fatigue, anorexia, weight loss, nausea, and vomiting. Some patients present with acute bowel obstruction or perforation.

Staging and Prognosis

Accurate staging of CRC is extremely important for determining patient prognosis and assessing the need for adjuvant therapy. Traditionally, staging of CRC has been based on modifications of the Dukes classification, which was initially developed as a prognostic tool for rectal cancer in the 1930s.³⁷ Since this classification was first implemented, it has undergone multiple modifications, of which the most widely used is the modified Astler-Collier system, initially introduced in the 1950s.³⁸ Currently, the TNM classification, developed by the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC), is the preferred staging system [see Table 2 and Table 3].³⁹ This system takes into account the depth of penetration into the bowel wall (T) [see Figure 3], the presence and number of involved mesenteric nodes (N), and the presence of distant metastases (M).

CLINICAL STAGING

Clinical staging is based on the history and the physical examination, endoscopic findings, and biopsy results. If colonoscopy cannot be completed, an air-contrast barium enema study should be performed to evaluate the remainder of the colon. Additional staging information may be obtained by means of imaging studies (e.g., roentgenography, CT, magnetic resonance imaging [MRI], and positron emission tomography [PET]). A chest x-ray is routinely obtained to rule out metastases and prepare for operation.

There is some debate regarding the utility of preoperative CT scans in the management of primary colon cancer. The rationale for obtaining these scans includes evaluation of potential metastatic disease and assessment of the local extent of disease. In a 2002 study of preoperative CT in patients

Table 2 American Joint Committee on Cancer TNM Clinical Classification of Colorectal Cancer

Primary tumor (T)	
T0	No evidence of primary tumor
Tis	Carcinoma in situ, intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria
T4	Tumor invades other organs or perforates visceral peritoneum
Regional lymph nodes (N)	
N0	No regional lymph node metastases
N1	Metastases in 1 to 3 regional lymph nodes
N2	Metastases in 4 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 3 American Joint Committee on Cancer Staging of Colorectal Cancer³⁹

Stage	T	N	M
0	Tis	N0	M0
I	T1, T2	N0	M0
IIA	T3	N0	M0
IIB	T4	N0	M0
IIIA	T1, T2	N1	M0
IIIB	T3, T4	N1	M0
IIIC	Any T	N2	M0
IV	Any T	Any N	M1

with intraperitoneal colon cancer, however, the results of the imaging changed management in only 19% of patients, and CT had a sensitivity of only 78% for all metastatic disease.⁴⁰ Nonetheless, many surgeons routinely perform staging CT in

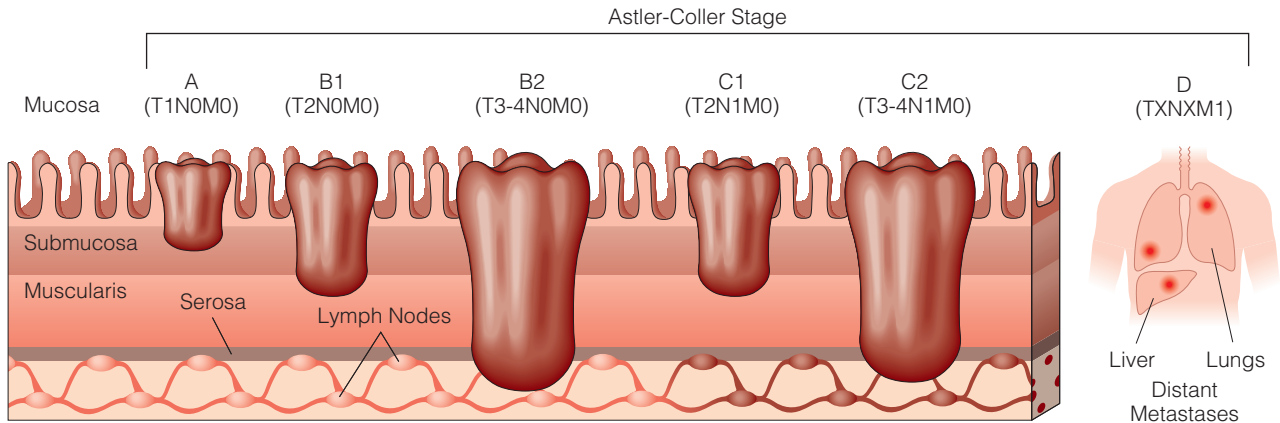


Figure 3 Classification of colorectal cancer takes into account the depth of tumor penetration and involvement of lymph nodes.

patients with primary colon cancer. PET is a sensitive study, but its routine use for staging primary CRC is not generally recommended. PET may be considered for high-risk patients in whom the detection of metastases would change initial management.⁴¹

In cases of rectal cancer, locoregional staging may significantly affect therapeutic decision making. Such staging includes determination of the depth of invasion of the rectal wall and the degree of regional node involvement. Modalities commonly used include CT, MRI, and endoscopic ultrasonography (EUS). In a 2004 meta-analysis that examined the relative utility of each of these studies in rectal cancer staging, EUS proved to be the most accurate technique for evaluating muscularis propria involvement and perirectal tissue invasion.⁴² The various techniques were equally accurate in assessing lymph node involvement, with none of them being highly sensitive.

PATHOLOGIC STAGING

Definitive pathologic staging is carried out after surgical exploration and examination of the resected specimen. The final stage of the cancer is then determined on the basis of the TNM system [see Table 2 and Table 3]. Survival is correlated with the stage of the tumor [see Figure 4 and Figure 5]. In the current (sixth) edition of the AJCC staging system, stage II is subdivided into stages IIA and IIB, and stage III is subdivided into stages IIIA, IIIB, and IIIC on the basis of both the extent of wall penetration and the number of nodes involved.³⁹ These changes were implemented as a result of studies demonstrating differences in survival among these subgroups [see Figure 6].⁴³

Numerous other criteria have been evaluated as additional prognostic factors in CRC. The degree of lymphatic invasion and the extent of vascular invasion are important adjuncts to the TNM staging system and are incorporated in the current schema.³⁹ Certain histologic types, including signet-ring and mucinous carcinomas, are associated with poor outcomes. The preoperative serum carcinoembryonic antigen

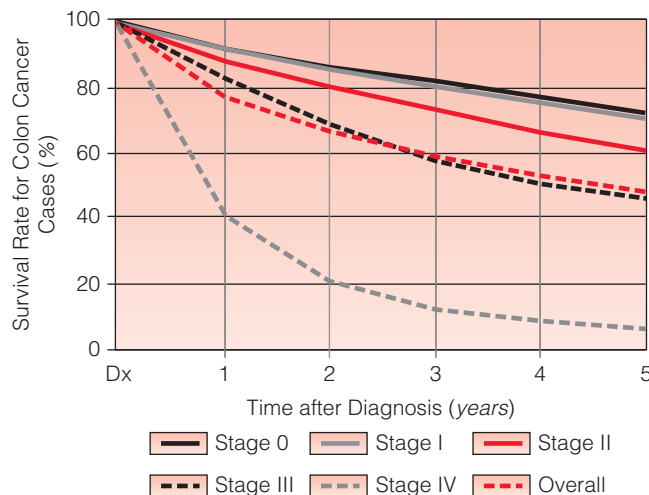


Figure 4 Shown are 5-year survival rates for cases of colon cancer diagnosed in 1,735 US hospitals in 1995 and 1996.

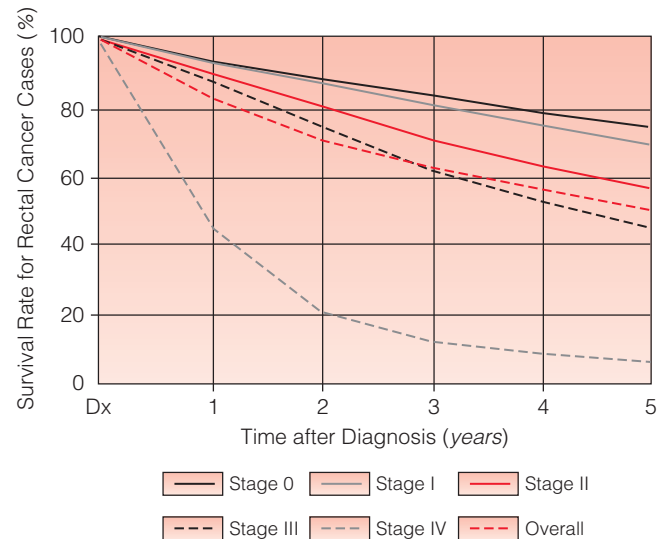


Figure 5 Shown are 5-year survival rates for cases of rectal cancer diagnosed in 1,683 US hospitals in 1995 and 1996.

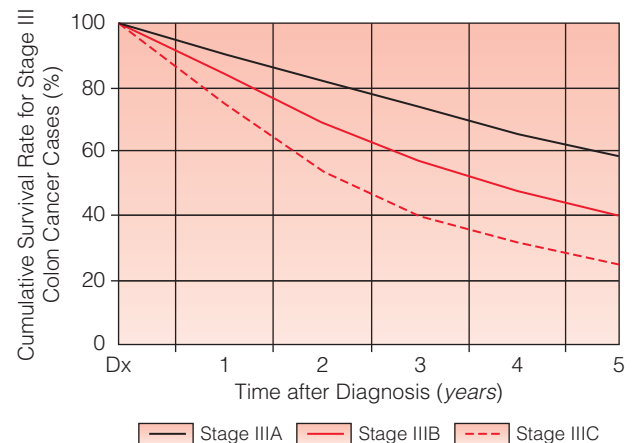


Figure 6 Shown are 5-year survival rates for cases of stage III colon cancer diagnosed between 1987 and 1993, stratified according to stage III subgroups established by the 6th edition of the AJCC Staging Manual.³⁹

(CEA) level may be an independent prognostic factor that is predictive of resectability and the presence of distant metastases.⁴⁴

MOLECULAR MARKERS

Various molecular markers have been investigated with respect to prognosis and response to therapy in CRC patients. Unfortunately, there are conflicting data on the prognostic impact and clinical utility of most of these markers. As noted [see Risk Factors, above], MSI is seen in as many as 15% of patients with sporadic CRC. Patients with MSI typically have proximal, poorly differentiated tumors with mucinous or signet-ring components, but they usually exhibit improved overall survival.⁴⁵ These patients may be less sensitive to 5-fluorouracil (5-FU)-based chemotherapy.⁴⁶

The long arm of chromosome 18 (18q) harbors at least three candidate tumor suppressor genes, including *DCC*, *SMAD2*, and *SMAD4*. Deletions of chromosome 18q in CRC patients are associated with decreased survival. One study found that patients with stage II cancers and 18q allelic loss had a prognosis similar to that of patients with stage III disease.⁴⁷ In addition, *p53* mutations and overexpression are associated with poor outcomes in CRC.⁴⁸ Thymidylate synthase is an enzyme active in DNA synthesis that is targeted by 5-FU and similar chemotherapeutic agents. Overexpression of this enzyme is associated with a poor prognosis but also with improved sensitivity to 5-FU-based chemotherapy.⁴⁹

All of these molecular alterations, as well as others (e.g., *K-ras* mutations and 5q deletions), are commonly observed in CRC patients, but further study is required to establish their real prognostic significance.

Management of Colon Cancer

SURGICAL THERAPY

Surgery with curative intent remains the mainstay of therapy for colon cancer [see Figure 7]. Complete R0 resection (leaving no gross or microscopic disease) with wide margins along the bowel wall, coupled with regional lymphadenectomy, is the standard of care. The major arterial vessels supplying the segment of the colon containing the tumor should be excised at their origins. A minimum margin of 5 cm of normal bowel on each side of the tumor is considered adequate.

Extent of Resection

The standard extent of resection for various colon cancers has been defined. For tumors of the cecum and the ascending colon, a right hemicolectomy that includes the right branch of the middle colic artery at its origin should be performed. For tumors of the hepatic flexure, an extended right colectomy that includes the entire middle colic artery is indicated. For tumors of the transverse colon, an extended right or left colectomy or a transverse colectomy may be performed. For tumors of the splenic flexure region, a left hemicolectomy is performed, and for sigmoid tumors, a sigmoid colectomy is performed.

In patients who have small or flat tumors or who are undergoing resection after a polypectomy, intraoperative identification of the tumor may be difficult. This is especially true with laparoscopic procedures, in which the bowel often cannot be palpated. If the lesion is in the cecum, the ileocecal valve and the appendiceal orifice are visualized endoscopically, and localization of the tumor is simple. If the lesion is at another location, endoscopic measurements of the distance from the anus or estimates of the location of the tumor may be inaccurate. Endoscopic tattooing, a process in which an agent is injected into the bowel wall submucosally at or near the site of the lesion, has been employed to facilitate intraoperative identification of the tumor site. India ink is the agent most commonly used for this purpose and generally yields excellent results.⁵⁰ As an alternative, many institutions use a commercially available sterile suspension of carbon particles, which is also very safe and effective.⁵¹ Intraoperative endoscopy is another option for locating these lesions.

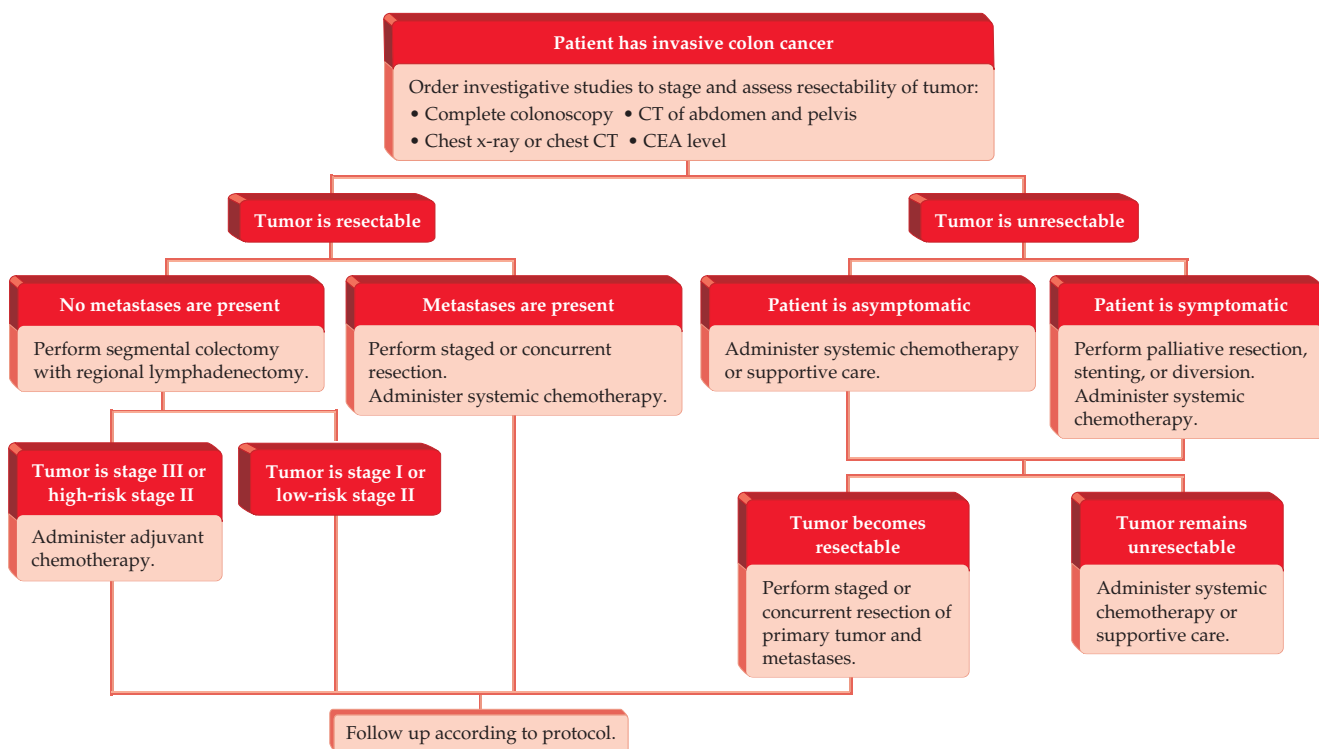


Figure 7 Algorithm outlines treatment of colon cancer. CEA = carcinoembryonic antigen; CT = computed tomography.

Surgical Staging

The selection of patients for adjuvant therapy relies heavily on accurate staging. A significant percentage of patients with early-stage node-negative disease present with recurrences or metastases; such a presentation implies that the patients had occult metastatic disease at the time of operation. Surgical resection of CRC should include division of the appropriate mesenteric vessels at their origins, along with resection of the regional nodes. Optimal staging of CRC patients, especially with regard to nodal status, remains controversial. One area of debate is the number of nodes that must be examined to confirm node negativity. This number depends both on the surgeon's technique (i.e., how many nodes were resected) and on the pathologist's efforts to harvest nodes from the specimen. Most groups recommend analysis of at least 12 nodes to confirm node negativity.⁵²

Because of the importance of nodal status, ultrastaging of harvested nodes with techniques such as serial sectioning, immunohistochemistry (IHC), and reverse transcriptase polymerase chain reaction (RT-PCR) has been proposed as a means of detecting micrometastases. All of these techniques may result in upstaging of patients who are node negative on standard pathologic analysis, which involves only bivalving the nodes and examining a limited number of sections. The prognostic impact of micrometastases that are detected only by IHC or RT-PCR and are not verified by hematoxylin-eosin staining remains unclear. It is impractical to perform these assays on all nodes harvested; accordingly, the use of lymphatic mapping to identify sentinel lymph nodes (SLNs) has been proposed as a means of selecting a small number of nodes for further analysis.

SLN biopsy in the setting of CRC remains investigational. Lymphatic mapping may be done with either in vivo or ex vivo injection of tracer dye. The dye rapidly diffuses through the lymphatic vessels, and SLNs can be identified and marked in the mesocolon within minutes. This procedure has been shown to be feasible in a number of studies⁵³; however, its sensitivity and false negative rates have been variable. In a 2004 multicenter trial, SLN biopsy with serial sectioning had a false negative rate of 54% in patients with node-positive colon cancer.⁵⁴ In a large single-institution trial, both SLNs and non-SLNs were studied with serial sectioning and IHC in patients who were node negative on routine pathologic analysis⁵⁵; 19.5% of patients were upstaged by the combination of serial sectioning and IHC of SLNs. These results imply that the main role of this technique may be in upstaging patients who are node negative on routine pathologic analysis. Further study is required before the use of SLN techniques in the context of CRC becomes standard clinical practice.

Occult metastatic disease may also be present in the peritoneal cavity or systemically in the blood or bone marrow at the time of operation. The presence of tumor cells in the peritoneum may be detected by performing cytologic analysis of washings done at the time of operation. In one study, disseminated tumor cells were identified in peritoneal washings or blood in 25% of patients, and their presence was found to be an independent prognostic factor for survival.⁵⁶ In another study, patients with positive peritoneal washings had significantly higher rates of local recurrence and peritoneal carcinomatosis but manifested no differences in survival.⁵⁷ Again,

further study is required before these assays can be routinely used for staging CRC.

Laparoscopic versus Open Colectomy

At present, open colectomy remains the most widely used treatment of resectable colon cancer. Initially, there were concerns about port-site recurrences,⁵⁸ but current data suggest that these concerns are unfounded.⁵⁹ With respect to comparative cost, data from a subset of patients in the European Colon cancer Laparoscopic or Open Resection (COLOR) trial demonstrated that although the total cost to society from laparoscopic colectomy is similar to that from open colectomy, the costs to the health care system are significantly higher with the former.⁶⁰ The Clinical Outcomes of Surgical Therapy (COST) study group, a large, randomized, multicenter trial conducted in the United States, found that laparoscopic-assisted colectomy conferred only minimal (although statistically significant) short-term quality-of-life benefits when compared with open colectomy.^{61,62} Cancer-specific outcomes (e.g., recurrence rates, wound recurrences, and overall survival rates) were similar at 3 years with the two approaches, leading to the conclusion that laparoscopic colectomy is an acceptable alternative to open colectomy.⁶² This finding was confirmed at 7 years of median follow-up with no difference demonstrated in disease-free or overall survival.⁶³ The COLOR trial could not rule out a small difference in disease-free survival at 3 years in favor of open colectomy, but the authors concluded that this is "clinically acceptable."⁶⁴ The CLASSIC trial from the United Kingdom showed equivalent disease-free and overall survival at 3 years of follow-up.⁶⁵ Based on these and other studies, laparoscopic colectomy has become accepted as equivalent to open colectomy for the treatment of colon cancer.

Special Situations

Obstructing and perforated cancers Obstructing and perforated colon cancers are associated with a poor prognosis and with increased surgical morbidity (as a consequence of the need for emergency surgery). Perforation can occur either via direct erosion of the tumor through the wall of the colon or secondary to obstruction with resultant bowel distention proximal to the tumor. Patients with perforated colon cancer are managed with emergency laparotomy, washout, and resection of the primary lesion to prevent further soilage. A diverting stoma is usually indicated, with either a Hartmann pouch or a mucous fistula constructed distally. Select patients may be managed by means of primary anastomosis, with or without a proximal diverting colostomy or ileostomy.

Obstructing right-side cancers (up to the splenic flexure) can usually be treated with resection and primary anastomosis. The traditional emergency treatment of obstructing left-side colon cancers is a diverting colostomy, with or without resection of the lesion. In many such cases, the stoma is never taken down. Some surgeons advocate emergency treatment of these lesions with total abdominal colectomy and ileorectal anastomosis as a means of improving outcomes.⁶⁶ Another treatment option is primary resection and anastomosis, with or without on-table intestinal lavage. Yet another option for managing obstructing left-side colon and rectal cancers is the use of colorectal stents with the aim of avoiding emergency

surgery. Stents can serve as a bridge to definitive resection by decompressing the colon and thereby allowing subsequent bowel preparation. In patients with advanced disease, stents may also be employed for palliation as an alternative to surgical resection or a diverting stoma.

Synchronous primary colorectal cancers The incidence of synchronous CRCs is reported to range from 3 to 5%^{67,68} but may be as high as 11%.⁶⁹ Stage for stage, there appear to be no differences in survival between synchronous cancers and single primary cancers.^{70,71} Synchronous adenomatous polyps are present in as many as 35% of patients undergoing surgical treatment of CRC.^{68,71} In one study, the presence of synchronous lesions made the surgical procedure more extensive than was initially planned for resection of the primary tumor in 11% of patients.⁶⁸

Most synchronous polyps are identified on preoperative colonoscopy, and the colon can often be cleared of these lesions before operation. Management of adenomas not amenable to endoscopic resection and management of synchronous cancers are more challenging. Each primary cancer must be managed surgically according to sound oncologic principles. One option is to perform multiple segmental resections with multiple anastomoses. Another is to perform an extended resection that encompasses all of the lesions or even total abdominal colectomy if needed. The presence of a rectal cancer and a second synchronous lesion makes surgical treatment even more challenging, especially if sphincter preservation and a low rectal or coloanal anastomosis are contemplated.

ADJUVANT THERAPY

Significant progress in systemic adjuvant therapy for patients undergoing resection of a colorectal adenocarcinoma has been made in the past 20 to 30 years, primarily through a series of phase III randomized trials and the development of new drugs. The evolution of adjuvant therapies is likely to continue for the foreseeable future, and surgeons will play a pivotal role as the primary entrance point for standard adjuvant therapy and new phase III randomized trials. Surgeons' awareness of past accomplishments, current study findings, and future phase III trials is crucial for improving the survival of potentially cured patients.

The 5-year survival rate after resection of colon cancer is inversely correlated with the pathologic stage [see *Figure 4*]. The diminishing 5-year survival rates for stage II and III colon cancer became the basis of several phase III randomized trials designed to test the hypothesis that postoperative systemic adjuvant chemotherapy would significantly improve survival in patients with resected but high-risk cancers. Multi-institutional, cooperative cancer group trials were necessary to obtain populations large enough to test this hypothesis. The North Central Cancer Treatment Group (NCCTG) initiated a randomized trial of postoperative systemic adjuvant 5-FU plus levamisole for Dukes stage B and C (AJCC stage II and III) colon carcinomas.⁷² Patients were randomly assigned to receive either levamisole alone or 5-FU plus levamisole. Overall survival was significantly improved in stage C patients treated with 5-FU plus levamisole. This was

the first randomized trial to demonstrate the efficacy of systemic adjuvant therapy.

The NCCTG trial led to second-generation trials of adjuvant therapy for patients with resected colon cancers. In one such study, patients with high-risk stage II or stage III colon cancer were randomly assigned to receive either 5-FU plus leucovorin and levamisole or 5-FU plus levamisole.⁷³ Survival rates after 12 months of adjuvant chemotherapy were no better than those after 6 months of chemotherapy; however, 5-FU plus levamisole proved to be inferior to 5-FU plus leucovorin and levamisole with respect to survival.

National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol C-04 randomly assigned Dukes stage B and C colon cancer patients to receive (1) postoperative 5-FU plus leucovorin, (2) 5-FU plus levamisole, or (3) 5-FU plus leucovorin and levamisole.⁷⁴ A slight improvement in 5-year disease-free survival was noted with 5-FU plus leucovorin, but overall 5-year survival did not differ significantly among the three treatment arms. Accordingly, 5-FU plus leucovorin became the standard adjuvant regimen.

Intergroup Trial 0089 randomly assigned patients with high-risk stage II and III disease to receive either 5-FU plus high-dose leucovorin or 5-FU plus low-dose leucovorin. The investigators concluded that (1) the high-dose and low-dose regimens were equivalent, (2) a regimen consisting of four cycles of 5-FU with high-dose weekly leucovorin was equivalent to the low-dose leucovorin Mayo Clinic regimen, and (3) the addition of levamisole to the 5-FU plus leucovorin regimen did not improve survival.

These clinical trials established 5-FU plus leucovorin as standard therapy for patients with high-risk stage II and stage III colon cancer. A new series of studies has now provided data regarding newer agents such as oxaliplatin, irinotecan, bevacizumab, and cetuximab. The MOSAIC trial, a large multinational trial,⁷⁵ and the NSABP C-07 trial⁷⁶ both demonstrated improved outcomes with the addition of oxaliplatin to 5-FU-based regimens. In the MOSAIC trial, the addition of oxaliplatin resulted in a 5.9% increase in disease-free survival at 5 years.⁷⁷ There was also a statistically significant 4.6% improvement in overall survival seen in stage III patients with a 6-year median follow-up. Oxaliplatin is now considered a standard component of adjuvant therapy protocols for CRC. Irinotecan has not been shown to improve survival in the adjuvant setting and is associated with increased toxicity⁷⁸ and is therefore not generally used. Addition of targeted agents such as bevacizumab, which is a vascular endothelial growth factor antibody, and cetuximab, which is an epidermal growth factor receptor antibody, is currently being studied in trials.

Routine use of systemic adjuvant therapy for stage II colon cancer remains controversial. Patients with stage II colon cancers, including those at high risk (e.g., those who present with large bowel obstruction or perforation), are typically included in adjuvant chemotherapy trials. A meta-analysis of stage II patients included in NSABP colon cancer trials demonstrated that adjuvant chemotherapy did confer a survival benefit at this disease stage.⁷⁹ This study was criticized, however, for having included patients from trials that lacked a surgery-only arm, as well as from trials that employed outmoded chemotherapeutic regimens.⁸⁰ Another meta-analysis, which included only trials that compared 5-FU plus leucovorin with observation after

curative resection in stage II patients, found no statistically significant survival benefit with chemotherapy.⁸¹ A 2004 meta-analysis formulated recommendations on this controversial topic and provided a Web-based tool for calculating risk.⁸² This report included data from seven randomized trials that compared surgery alone with surgery plus chemotherapy. Patients with node-negative disease derived a much lower reduction in risk and no statistically significant improvement in overall survival. The authors concluded that the use of postoperative adjuvant chemotherapy for stage II colon cancer patients should be individualized on the basis of the estimated prognosis and the potential treatment benefit. In the MOSAIC trial, there was no long-term overall survival benefit in stage II patients receiving oxaliplatin compared to 5-FU and leucovorin alone.⁷⁷

In summary, postoperative systemic adjuvant therapy is the standard of care in patients with stage III disease. In stage II colon cancer patients who have undergone complete surgical resection, the relative risk of recurrence is small enough that adjuvant chemotherapy yields relatively little benefit in terms of survival. There is, however, a subgroup of patients who have recognized prognostic factors that significantly reduce survival and in whom adjuvant therapy is therefore more likely to be beneficial. These risk factors include (1) bowel obstruction, (2) colonic perforation, (3) high-grade or lymphovascular invasion, and (4) the presence of fewer than 12 lymph nodes in the resected specimen. Additional risk factors such as chromosome 18 deletions and MSI continue to be evaluated.

Management of Rectal Cancer

Rectal cancer presents special management issues with respect to local recurrence after surgical resection. With cancer of the intraperitoneal colon, local recurrence is rare. With rectal cancer, however, surgical treatment alone results in recurrence rates of 16.2% after low anterior resection (LAR) and 19.3% after abdominoperineal resection (APR).⁸³ Higher stages are associated with higher recurrence rates: 8.5% for Dukes stage A, 16.3% for stage B, and 26% for stage C.⁸³ Multimodality management, including adjuvant radiation therapy or chemotherapy (or both) in combination with appropriate operative therapy, can reduce local recurrence rates significantly.

SURGICAL THERAPY

Extent of Resection

Sphincter preservation has become a major goal in the multimodality treatment of rectal cancer. Surgical procedures are chosen and performed with this goal firmly in mind.

Radical resection Traditionally, tumors of the rectum have been treated with either LAR or APR [see Figure 8]; in numerous series, APR rates of 60% or higher have been reported. Surgical techniques such as stapled or handsewn coloanal anastomoses, when combined with total mesorectal excision (TME), have led to excellent cancer-related outcomes without the need for permanent colostomy. The use of preoperative chemoradiation therapy for tumor downstaging may also reduce the need for APR.⁸⁴

The morbidity associated with radical rectal resection can be substantial. Anastomotic leakage rates vary widely, ranging from less than 10% to more than 30% after resection with anastomosis. Leaks can lead to substantial morbidity and mortality and can necessitate reoperation. Such concerns have prompted the use of temporary diverting ileostomies or colostomies in patients with low rectal anastomoses. Defunctioning stomas may be overused, however, thereby increasing the cost of care in low-risk patients.⁸⁵ Preoperative chemoradiation therapy has not been shown to increase anastomotic leakage rates. Urinary and sexual dysfunction are also fairly common after radical resection of rectal cancer. Autonomic nerve preservation in conjunction with TME may improve the functional results of these procedures.⁸⁶ The use of local resection techniques (see below) is another means of reducing surgical morbidity and mortality in rectal cancer patients.

Local excision Local excision—including transanal, transsphincteric, and transcoccygeal techniques, as well as transanal endoscopic microsurgery (TEM)—is another option for curative resection of low rectal cancers with preservation of sphincter function. These procedures were initially implemented for local control in patients who were medically unfit for or unwilling to undergo major resections. Transsphincteric and transcoccygeal resections have been associated with an increased incidence of complications, including fecal fistulas and incontinence, and have largely been abandoned now that other, better techniques are available.

Local excision with curative intent is generally reserved for the treatment of early-stage (T1-2N0) lesions and remains controversial even in these patients. Selection of patients for these procedures is critical and is based on preoperative staging and on the probability of harboring nodal metastases, which increases with the T stage. EUS and endorectal coil MRI have become an important staging procedure in these patients, both for assessing the depth of tissue invasion and for detecting the presence of nodal disease. CT is generally performed to rule out distant metastases. Palliative procedures (e.g., fulguration and endocavitary irradiation) may also be considered in patients who are unfit for major surgery.

Several criteria have been established to identify patients who may be candidates for transanal excision (TAE) (NCCN guidelines).⁸⁷ According to guidelines published by the NCCN, the lesion must be no more than 3 cm in diameter, must encompass no more than 30% of the circumference of the rectum, and must be less than 8 cm from the anal verge. With the advent of TEM, these criteria have been expanded to include patients with higher lesions. Poorly differentiated tumors and the presence of lymphovascular invasion may also be associated with increased nodal involvement and higher recurrence rates. At least two prospective trials have reported their results with TAE.^{88,89} Local recurrence rates ranged from 5 to 7% for T1 lesions treated with surgery alone. The results were not as promising for T2 lesions: local recurrence rates ranged from 14 to 16%, even when adjuvant radiation or chemoradiation therapy was provided. Long-term follow-up data were recently published for one of these studies, showing local recurrence rates of 8 and 18% for T1 and T2 lesions, respectively, with a median follow-up of 7 years.⁹⁰ In a recent nationwide cohort study using National Cancer Data Base

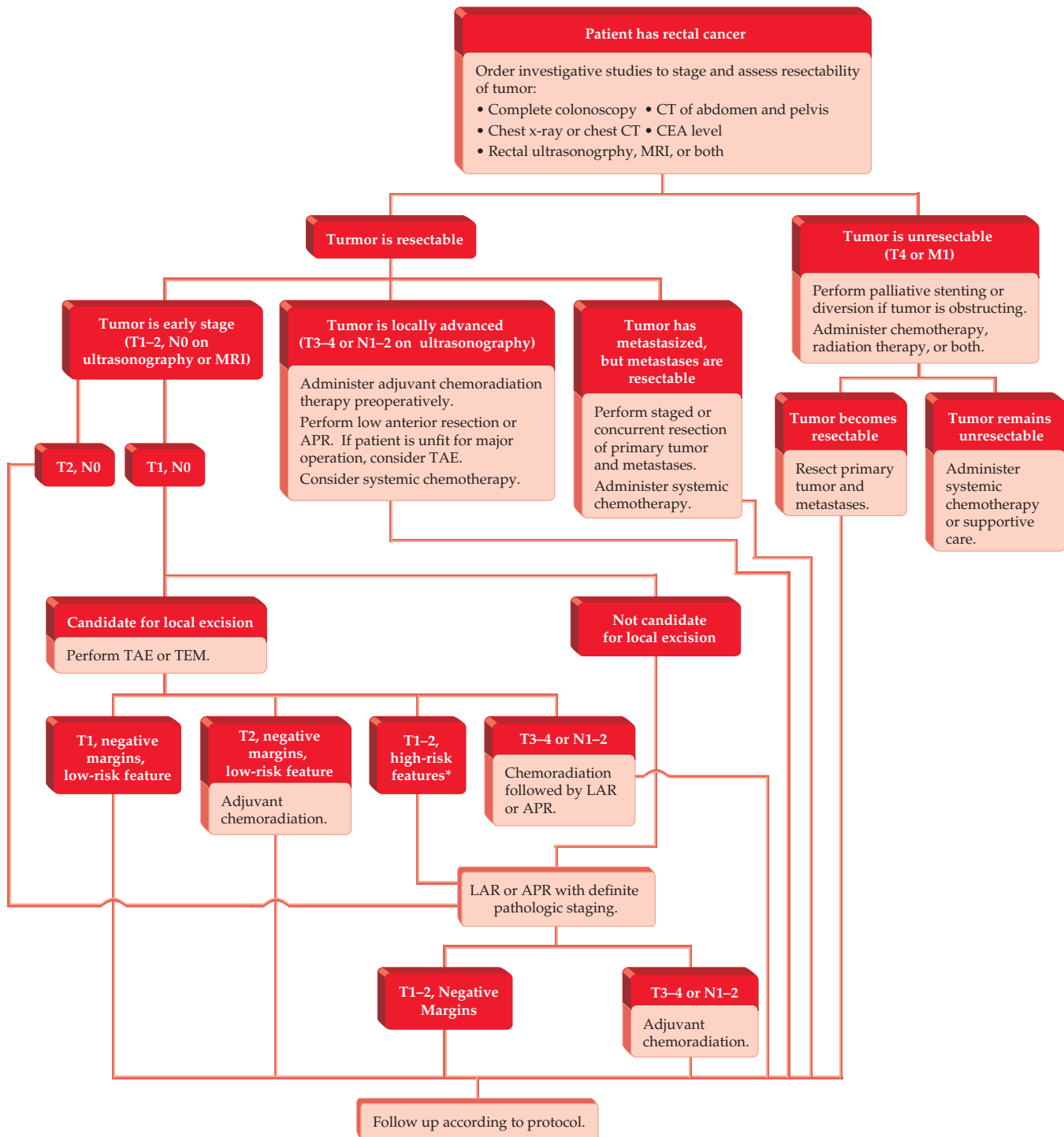


Figure 8 Algorithm outlines treatment of rectal cancer. APR = abdominoperineal resection; CEA = carcinoembryonic antigen; CT = computed tomography; LAR = low anterior resection; MRI = magnetic resonance imaging; TAE = transanal excision; TEM = transanal endoscopic microsurgery. *High-risk features include a positive margin, lymphovascular invasion, and poorly differentiated or mucinous histopathology.

data, local excision resulted in significantly higher local recurrence rates than radical surgery for both T1 (12.5 versus 6.9%) and T2 (22.1 versus 15.1%) tumors.⁹¹ Five-year overall survival rates were not significantly different, however.

The use of local excision in patients with more locally advanced disease is even more controversial. Such patients

are at considerably greater risk for nodal metastases and thus for local recurrence even after adequate resection of the primary lesion. Traditionally, local excision in patients with locally advanced disease has been associated with unacceptably high recurrence rates. Some authors advocate combining chemoradiation therapy with local excision to manage these

patients. In a 2004 retrospective series, the results of local excision were comparable to those of radical resection in T3 patients who had a good response to preoperative chemoradiation therapy and who refused or were medically unfit for major surgery.⁹² The role of local excision in these patients remains poorly defined.

Patients undergoing local resection must receive careful follow-up, including digital examination, measurement of CEA levels, proctoscopy, and, possibly, transanal ultrasonography. A subset of these patients with local-only recurrences who are medically fit for surgery may be candidates for resection. At present, few good data are available on the results of salvage surgery for local recurrence after local excision of rectal cancer, but it is unlikely that outcomes are equivalent to those of initial radical resection.⁹³

Importance of Radial and Distal Resection Margins

There has been a great deal of debate about what constitutes an adequate margin of resection in surgical treatment of rectal cancer. With respect to distal margins, 2 to 5 cm has traditionally been considered to be the minimum necessary for curative resection. Growing interest in sphincter preservation has led investigators to consider smaller distal margins (i.e., < 2 cm). Studies have shown that clear margins smaller than 2 cm are not associated with higher local recurrence rates or reduced survival.⁹⁴ Subsequent reports have suggested that even smaller histologically negative margins (i.e., < 1 cm) may be adequate in patients receiving adjuvant chemoradiation therapy.^{95,96}

The importance of radial margin involvement after rectal cancer resection was not recognized until comparatively recently.⁹⁷ Radial margins are assessed by means of serial slicing and evaluation of multiple coronal sections of the tumor and the mesorectum.⁹⁷ Involvement of radial margins is a predictor of both local recurrence and survival after potentially curative rectal cancer surgery⁹⁸ and may be associated with an increased risk of distant metastases.⁹⁹ Radial margins smaller than 2 mm are associated with increased local recurrence rates.⁹⁹ Adjuvant radiation therapy does not compensate for the adverse impact of positive margins on local recurrence rates.¹⁰⁰

ADJUVANT AND NEOADJUVANT THERAPY

Adjuvant therapy for rectal cancer has focused on both locoregional control of disease and treatment of systemic disease. Several large studies have evaluated local recurrence of disease after surgical resection alone. Local failure rates of 30 to 40% for T2N0 disease and 50 to 70% for node-positive disease strongly suggested that postoperative adjuvant therapy was needed.^{101–103} In distinct contrast to these data, however, other series in which TME was performed reported extremely low local recurrence rates with surgery alone.^{104,105}

A series of randomized trials were conducted to assess adjuvant therapy for rectal cancer. Initial studies reported a decrease in local recurrence rates with postoperative radiation therapy.^{106,107} In a multi-institutional trial conducted by the NCCTG, the combination of 5-FU with radiation therapy led to improvements in local control rates and in survival.¹⁰⁸ These results were confirmed in large intergroup trials, the results of which indicated that continuous infusion of 5-FU during radiation therapy resulted in significantly better disease-free survival and overall survival than bolus infusion of 5-FU.

Simultaneously with the ongoing development of postoperative locoregional adjuvant therapy for rectal cancer, interest in preoperative (neoadjuvant) therapy has been growing. Preoperative radiation therapy has been associated with excellent local control of disease, sphincter preservation, and acceptable postoperative recovery. There is evidence that rectal adenocarcinoma is sensitive to preoperative radiation therapy, with or without 5-FU. Pathologic complete response rates of 10 to 20% have been noted in resected rectal specimens¹⁰⁹; pathologic complete response is associated with improved outcomes.¹¹⁰

Perhaps the strongest reason to consider preoperative therapy for rectal cancer is its potential for inducing significant tumor regression before surgical resection. Such regression makes clear radial and distal margins easier to obtain. Moreover, tumor regression with preoperative therapy may result in higher sphincter preservation rates. In many published series, the APR rate in rectal cancer patients is between 40 and 60%; more aggressive preoperative efforts to induce regression may give surgeons a better chance to achieve sphincter preservation without compromising local control of disease.¹⁰⁹ One advantage of the postoperative approach is that the disease is more accurately staged before adjuvant therapy begins; thus, patients with early-stage disease are less likely to be overtreated. Data continue to accumulate on the relative merits of preoperative versus postoperative adjuvant treatment of rectal cancer.

Two Swedish studies considered the role of preoperative radiation therapy in treating rectal cancer. The first demonstrated that a short course of preoperative radiation therapy (2.5 Gy in five fractions) was comparable to high-dose postoperative radiation therapy (60 Gy over a period of 8 weeks). The local recurrence rate was significantly lower with the short-course preoperative regimen (12% versus 21%), and there was no overall survival difference between the two regimens.¹¹¹ In the second trial, patients received either a short course of preoperative radiation therapy or surgery alone.¹¹² The local recurrence rate at a median follow-up of 13 years was 9% for preoperative therapy plus surgery compared with 26% for surgery alone. The combined regimen also resulted in significantly better overall survival (38% versus 30%).

The relative benefits of preoperative versus postoperative radiation therapy have been elucidated by the findings from more recent trials. A 2004 German trial randomly assigned patients to receive either preoperative or postoperative 5-FU plus radiation followed by systemic 5-FU therapy.⁸⁴ This study was limited to patients with locally advanced disease, including those who had T3 or T4 disease or were node positive on ultrasonography. TME was performed in all patients and was done 6 weeks after treatment in patients receiving preoperative chemoradiation therapy. The primary end point of this study was overall survival; secondary end points included disease-free survival, local and distant control of disease, sphincter preservation, toxicity of adjuvant therapy, surgical complications, and quality of life. There was no difference between the preoperative group and the postoperative group with respect to 5-year survival, but the local recurrence rate was significantly lower with the former (6% versus 13%), as were both the short-term and the long-term toxicity of adjuvant therapy.

Although, overall, the rates of complete (R0) resection and sphincter preservation were similar in the two groups, the APR rate was significantly lower in patients determined by the surgeon to require APR before randomization.

A large multinational trial of preoperative radiation versus selective postoperative chemoradiation demonstrated a significantly decreased local recurrence rate and improved disease-free survival in the preoperative radiation group.¹¹³ Overall survival was not significantly different. A French trial studied the benefits of adding chemotherapy to preoperative radiation.¹¹⁴ The addition of 5-FU-based chemotherapy at any point in the patients' treatment resulted in a significant improvement in local recurrence but no difference in survival.

The use of adjuvant 5-FU-based chemotherapy and radiation, particularly in the preoperative setting, in the treatment of rectal cancer has demonstrated clear benefit in multiple trials. Studies are currently in progress, including the NSABP R-04, to evaluate the benefits of additional chemotherapeutic agents in combination with preoperative radiation.

Special Considerations

SYNCHRONOUS METASTATIC (STAGE IV) DISEASE

As many as 20% of CRC patients have metastatic disease at the time of initial presentation. The need for surgical intervention in this group of patients is not well defined. Clearly, surgical resection or diversion is indicated in patients who present with significant bleeding, perforation, or obstruction. In asymptomatic patients with unresectable metastatic disease, the role of surgical resection of the primary lesion remains controversial. In patients with resectable metastatic disease (e.g., isolated liver or lung metastases), curative resection may be undertaken.

In a retrospective review of patients presenting with unresectable stage IV CRC, there was no difference in survival between those who were initially managed surgically and those who were initially managed nonoperatively.¹¹⁵ In the surgical group, the morbidity was 30% and the mortality was 5%. Only 9% of the nonoperative patients subsequently required surgical intervention for bowel obstruction. In another retrospective series, patients managed surgically had significantly better overall survival than those managed nonoperatively but had a lesser tumor burden¹¹⁶; 29% of the nonoperative patients eventually required surgery for bowel obstruction. When prognostic factors were evaluated in the surgical arm of this series, the only factor associated with improved outcomes was a less than 25% extent of liver involvement. On the basis of these and other studies, asymptomatic patients with unresectable metastatic CRC should be managed selectively: those with limited tumor burdens may benefit from surgical treatment, whereas those with more extensive disease (especially extensive liver involvement) may initially be managed nonoperatively.

Management of patients with synchronous resectable isolated liver metastases continues to evolve. Many studies have documented improved survival after liver resection in patients with metastatic disease that is confined to the liver. Patients presenting with synchronous lesions have a worse prognosis than those presenting with metachronous lesions.¹¹⁷ Many of these patients have been managed with staged resections of the

primary cancers and the liver metastases. Several groups have reported that such combined procedures do not substantially increase surgical morbidity and mortality or compromise cancer survival.^{118,119} These combined procedures should be done only in carefully selected patients at specialized centers with significant experience in resection of both CRC and liver tumors.

PERITONEAL CARCINOMATOSIS

Peritoneal carcinomatosis develops in approximately 13% of all CRC patients.¹²⁰ The survival rate of patients who present with peritoneal carcinomatosis from CRC is dismal. In patients with stage IV CRC, the presence of carcinomatosis is associated with a significant reduction in survival (from 18.1 months to 6.7 months).¹²¹ Treatment has traditionally included systemic chemotherapy, with surgery reserved for palliation of symptoms such as bowel obstruction. Newer chemotherapy regimens that include agents such as oxaliplatin may improve survival, but they certainly are not curative.

Peritoneal carcinomatosis is often associated with hematogenous metastases, but in some 25% of patients, the peritoneal cavity is the only site of disease. Several groups have advocated the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) as a means of improving survival in these patients.¹²² This treatment, however, is associated with significant morbidity and mortality.¹²³ A randomized trial from the Netherlands that compared cytoreduction surgery plus HIPEC with systemic chemotherapy plus palliative surgery found that patients in the former group exhibited a statistically significant improvement in median survival (22.3 months versus 12.6 months).¹²⁴ At 8 years of follow-up, a significant improvement in median disease-specific survival was maintained.¹²⁵ Cytoreductive surgery plus HIPEC seems to be a viable option for the treatment of peritoneal carcinomatosis. Patient selection for these aggressive procedures remains a major issue given the substantial morbidity and mortality associated with them.

Follow-Up and Management of Recurrent CRC

The goal of any CRC follow-up regimen should be to detect any recurrences or metachronous lesions that are potentially curable. In a large, multicenter trial, the incidence of second primary CRCs in patients with resected stage II and III lesions was found to be 1.5% at 5 years.¹²⁶ Between 40 and 50% of patients experience relapses after potentially curative resection of CRC. Detection and treatment of recurrent disease before symptom development may improve survival. The time to recurrence is critical in that as many as 80% of recurrences occur within the first 2 years and as many as 90% within the first 4 years. Patterns of recurrence should also be taken into account—for example, the markedly increased risk of local recurrence in rectal cancer patients compared with that in colon cancer patients. Even when recurrent CRC is detected, only a small percentage of patients are candidates for reoperation, and resection in these patients may not improve overall survival. Systemic therapy may improve survival in some patients who have unresectable recurrent lesions.

Various modalities are available for follow-up after surgical treatment of CRC. The history and the physical examination continue to be useful in that a significant percentage of patients

present with symptomatic recurrences. Measurement of serum CEA levels has proved effective in detecting asymptomatic recurrences. More recent studies have shown a survival benefit for CT scanning as part of routine follow-up in patients at a high risk of recurrence. One study that evaluated routine CEA measurement and CT scanning of the chest, abdomen, and pelvis for follow-up of stage II and III CRC demonstrated that both modalities were able to identify asymptomatic patients with resectable disease.¹²⁷ Colonoscopy is valuable for detecting metachronous cancers and polyps. Other studies, such as liver function tests (LFTs), complete blood count (CBC), and chest x-ray, have not been consistently shown to detect asymptomatic resectable recurrences.

Some authorities advocate so-called intensive follow-up. However, this term lacks a standard definition, and such follow-up has not been conclusively shown to be beneficial. In a meta-analysis that compared an intensive follow-up regimen (including history, physical examination, and CEA measurement) with no follow-up, the former detected more candidates for curative re-resection and led to improvements in both overall survival and survival of patients with recurrences.¹²⁸ Three other meta-analyses have been published that assessed the value of intensive follow-up of CRC patients.^{129–131} These meta-analyses included only randomized, controlled trials, and all documented a survival advantage with intensive follow-up. Some caution is required in interpreting these results, however, because the meta-analyses included trials with vastly different follow-up regimens in their baseline and intensive groups.

At present, the ideal follow-up regimen for CRC patients remains to be determined. Intensive follow-up regimens obviously are more costly. Patients with stage I disease are at very low risk for recurrence and therefore do not generally require intensive follow-up.¹³² Patients with stage II and III disease are at significantly higher risk for recurrence and therefore need more specific cancer-related follow-up, but how intensive such a follow-up regimen should be is still a matter of debate.

Several organizations, including the American Society of Clinical Oncology¹³³ and the American Society of Colon and Rectal Surgeons,¹³⁴ have developed algorithms for postoperative surveillance of CRC patients. Their recommendations generally apply to patients with stage II or III disease (and sometimes patients with T2 lesions) who are candidates for resection of recurrent disease. The recommendations vary somewhat among groups, but the following are generally agreed on:

1. Measurement of CEA levels every 2 to 3 months for 2 years, then every 3 to 6 months for 3 years, then annually
2. Clinical examination every 3 to 6 months for 3 years, then annually
3. Colonoscopy perioperatively, then every 3 to 5 years if the patient remains free of polyps and cancer (some guidelines also recommend colonoscopy 1 year after primary therapy)
4. CT of the chest and abdomen for 3 years; pelvic CT should also be done in patients with rectal cancer

Other imaging studies (e.g., PET and chest x-ray) are not routinely recommended, nor are other blood tests (e.g., CBC and LFTs).

A complete review of the treatment of recurrent CRC is beyond the scope of this chapter. The primary aim of postoperative surveillance is the detection of treatable recurrences or metastatic disease. The most common sites of metastasis in CRC patients are the liver and the peritoneal cavity. Surgery is the only potentially curative therapy for recurrent CRC. Only a select group of patients with isolated peritoneal, liver, or lung metastases are candidates for surgical resection. As noted [see Special Considerations, Peritoneal Carcinomatosis, *above*], cytoreductive surgery and HIPEC improve survival in patients with peritoneal carcinomatosis and may lead to long-term survival in a very select group of patients.

Numerous studies have addressed the treatment of patients with isolated liver metastases from CRC. Resection of isolated hepatic metastases has been reported to yield 5-year survival rates higher than 30%, with acceptable surgical morbidity and mortality. Investigators from the Memorial Sloan-Kettering Cancer Center developed a staging system known as the clinical score in an attempt to predict which patients are likely to benefit from aggressive surgical resection.¹³⁵ This system used five factors that were found to be independent predictors of poor outcome: (1) node-positive primary disease, (2) a disease-free interval shorter than 12 months, (3) the presence of more than one hepatic tumor, (4) a maximum hepatic tumor size exceeding 5 cm, and (5) a CEA level higher than 200 ng/mL. Patients who met no more than two of these criteria generally had good outcomes, whereas those who met three or more were recommended for inclusion in adjuvant therapy trials.

PET scanning has also been used to detect occult metastatic disease and thus to aid in the selection of patients for surgical resection. In one series, a 5-year overall survival of 58% was reported after resection of CRC liver metastases in patients screened with PET.¹³⁶ When combined with the clinical risk score, PET was found to be helpful only in patients with a score of 1 or higher.¹³⁷

Modalities for treating unresectable disease confined to the liver include cryotherapy, radiofrequency (RF) ablation, microwave ablation, hepatic artery infusion of chemotherapeutic agents, and hepatic perfusion. Of these, RF ablation is the one most commonly employed. It may be performed via an open approach, percutaneously, or laparoscopically; it may also be combined with resection and with local or systemic chemotherapy. The survival benefit (if any) associated with use of these modalities has not been well established.

Patients with isolated lung metastases from CRC may also benefit from surgical resection. Because there are relatively few of these patients, treatment of such metastases has not been studied as well as treatment of liver metastases. Some series have reported 5-year survival rates higher than 40% after complete resection. Patient selection remains a major issue. Several prognostic factors that may predict poor outcomes have been identified, including (1) a maximum tumor size greater than 3.75 cm, (2) a serum CEA level higher than 5 ng/mL, and (3) pulmonary or mediastinal lymph node involvement.^{138,139} Patients with both pulmonary and hepatic metastases may also be considered for surgical resection.

Pelvic recurrences of rectal cancer present another difficult management issue. These tumors may cause significant pain and disability, and if they are not treated, survival is measured in months. Radiation and chemotherapy provide symptomatic

relief and yield a modest increase in survival. Surgery may provide excellent palliation and is potentially curative in patients who do not have distant metastases.

Multimodality therapy has been advocated as a means of improving the chances of cure. In one study, a 37% 5-year survival rate was reported in patients who underwent multimodality therapy, including resection with negative margins.¹⁴⁰ A subgroup of patients in whom complete resection was impossible underwent intraoperative radiation therapy; the 5-year survival in this subgroup was 21%. Several predictors of poor outcomes were identified, including incomplete resection, multiple points of tumor fixation, and symptomatic pain. In another series, hydronephrosis was associated with the presence of unresectable disease.¹⁴¹ Selection of appropriate

patients for curative surgery remains a major issue in the management of locally recurrent rectal cancer.

Chemotherapy is the mainstay of palliative treatment for patients with CRC and unresectable recurrent or metastatic disease. Combinations of 5-FU and leucovorin with newer agents such as irinotecan, oxaliplatin, and bevacizumab define the current standard. Patients in whom these regimens fail may be considered for treatment with other agents such as cetuximab or other targeted therapies.

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Figure 1 Alice Y. Chen.

16 MOTILITY DISORDERS

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The term “motility disorder” is commonly used to describe conditions in which symptoms are assumed or proven to result from abnormal contractile activity of the gastrointestinal (GI) tract, although from a purist perspective, several thus described disorders also have a sensory component. Surgeons frequently encounter such patients who have challenging problems but in the main no overt structural cause. In what follows, we discuss two of the most common motility disorders, constipation and fecal incontinence, accepting that other rarer disorders where dysmotility is a cardinal feature, for example, achalasia, intestinal pseudo-obstruction, and gastroparesis, may also reach the surgeon’s attention.

Although constipation is infrequently treated surgically, surgeons regularly see patients with constipation in ward and ambulatory settings. It is therefore critical that surgeons have a practical approach to the patient with constipation with respect to diagnosis, investigation, and management. Furthermore, recent pharmacologic and surgical advances are leading to new hope for some patients with disabling chronic symptoms.

Fecal incontinence is an understudied and undertreated condition that can have a dramatic impact on quality of life. Effective treatment of incontinence has a dramatic positive influence on patients’ lives; thus, it is important for surgeons to have both an effective approach to diagnosis and an informed awareness of the various therapeutic options available (including experimental treatments).

Constipation

OVERVIEW AND TAXONOMY

Constipation is a very common digestive complaint in both adults and children, with as much as 20% of the population self-reporting this symptom¹ and with increased reporting over the age of 50.² The definition of the term “constipation” varies greatly between patients and between clinicians, the latter problem emphasized by the confused taxonomy in this field.³ Thus, patients who self-report constipation may refer to defecatory symptoms such as decreased stool frequency, reduced stool volume, altered stool consistency, and difficulty with evacuation or abdominal symptoms such as pain and bloating.⁴ Others may describe even more diverse symptoms, such as general discomfort, nausea, lethargy, and back pain. Given the diversity of potential causes of constipation, the surgeon can be aided by a classification framework [see Table 1]. Using this approach, constipation may broadly be considered primary (often termed idiopathic), encompassing simple and chronic constipation, or secondary, where a defined local structural or systemic cause is evident.

Considering the scope of the chapter (motility disorders), the following text focuses principally on the evaluation and

management of chronic constipation. Although the exact definition of “chronic constipation” has varied in the literature, most would now agree on a simple working definition of more than 6 months of defecatory symptoms that are non- or only partially responsive to standard laxative therapy. This pragmatic definition has been supported by recent large drug trials.⁵ The reader should note that in choosing this approach, several terms introduced as part of the Rome classification of functional GI disorders⁶ have been excluded from this classification. This deliberate exclusion is worthy of some explanation because terms such as “constipation-predominant irritable bowel syndrome (IBS)” and “functional constipation” may be encountered by surgeons (particularly when communicating with internal medical colleagues). In brief, a succession of consensus committees (meeting in Rome over the past 20 years) have attempted to carefully define various diagnoses (now actually 44 entities from mouth to anus) based on specific combinations of symptoms. For instance, a patient meeting a list of criteria for defecatory symptoms and abdominal pain could be defined as having constipation-predominant IBS. Such criteria may be useful for research-related activity, for example, drug trials (although this is itself debatable), but have little practical value in the diagnosis or management of patients with chronic constipation. Furthermore, there is very poor epidemiologic concordance between the Rome definitions, self-reported constipation, and constipation as defined by physiologic measurement.^{7–9}

CLINICAL EVALUATION

History

Figure 1 is an algorithm for the workup and management of constipation. When a patient presents with a complaint of constipation, a thorough history of the presenting illness is essential. Probably first and foremost is the determination of whether constipation represents a new complaint, that is, one that may be indicative of a change in bowel habit. The patient should be asked specifically about the frequency and consistency of bowel movements and the progress of such changes over time (as well as other alarming symptoms, such as rectal bleeding, anorexia, and weight loss). On this basis, with additional information regarding family history, previous colon cancer screening, and other GI investigations, an informed decision can be made as to whether structural intraluminal investigation of the colon is required. Other organic causes of constipation may be deduced by appropriate history taking and biochemical investigation. With the exclusion of treatable secondary causes, if the history is short and multiple previous therapies have not already been tried, then the patient may be first considered to have “simple” constipation that can be managed with reassurance and lifestyle advice (fiber, fluids, and exercise). However, some patients will have attended many

Table 1 Classification System for Constipation

Secondary constipation
Gastrointestinal causes
Colorectal
Malignant neoplasms, inflammatory strictures, diverticular disease
Megacolon or megarectum
Idiopathic
Hirschsprung disease
Neurologic
Chagas disease
Anorectal
Anal atresia or malformation
Hereditary internal anal sphincter hypertrophy
Anal stenosis
Extragastrintestinal causes
Metabolic and endocrine
Hypothyroidism, diabetes, hypercalcemia, chronic renal failure, pregnancy
Neurologic
Degenerative CNS diseases
Spinal lesions
Damage to sacral parasympathetic nerves
Autonomic neuropathy
Drugs
Opioids
Anticholinergics
Antidepressants
Anticonvulsants
Psychological
Severe endogenous depression
Eating disorders
Other
Scleroderma, Chagas disease, amyloidosis
Primary (idiopathic) constipation
Simple (reversible) constipation
Lifestyle
Exercise, mobility
Diet
Fiber, hydration
Chronic idiopathic constipation*
Evacuation disorder (ED) (40%)
Dynamic structural abnormalities, e.g., rectocele, intussusception
Pelvic floor dyssynergia
Poor defecatory effort
Slow-transit constipation (STC) (10%)
Colonic inertia
Both ED and STC (35%)
No physiologic abnormality evident (15%)
Normal transit constipation†

CNS = central nervous system.

*Approximate percentages have been included based on the experience of over 1,000 consecutive patients at the Royal London Hospital.

†This rather confusing term has become popular in the literature. Note that this group does not equate with “constipation-predominant irritable bowel syndrome.”⁹⁹

physicians already, with various therapies already exhausted. In such patients, a workup for chronic constipation may be indicated.

In reality, it is usually evident whether a patient with chronic symptoms is one in whom a secondary cause should be sought or one in whom the focus should shift to the investigation and management of idiopathic constipation. This decision is helped by overwhelming epidemiologic evidence that patients with chronic idiopathic constipation are usually female (90% or more)^{10,11} and often have symptoms from early childhood or puberty (at least 50%)¹¹ or problems that

start after pelvic surgery, for example, hysterectomy or childbirth.¹² Thus, the history should ascertain the duration and mode of onset of symptoms. In relation to onset, it may sometimes be necessary to tactfully seek a history of physical or sexual abuse because this can sometimes precipitate defecatory problems.¹³ A history of other family members with either severe constipation or Hirschsprung disease should also be sought. Furthermore, it is helpful at this stage to systematically document the spectrum of symptoms that in the patient's mind constitute a problem because this has some bearing on treatment decisions and subsequent monitoring of effectiveness. Several questions form detailed scoring systems to systematically facilitate this in a research context, for example, Cleveland Clinic Constipation¹⁴ and Knowles-Eccersley-Scott-Symptom¹⁵ scores, but in routine practice, it is sufficient to list in the patient record the presence or absence (with some indication of degree) of each symptom. We specifically ask about the following, with and without laxatives (if relevant):

- Frequency of spontaneous or assisted bowel opening
- Painful defecation
- Stool consistency
- Digitation (vaginal or anal)
- Straining
- Abdominal pain
- Incomplete evacuation
- Bloating
- Unsuccessful evacuation with or without toilet revisiting

The remaining history should document prescribed and self-administered laxatives (and the therapeutic benefit thereof) and gain an impression of the quality of diet with respect to fiber and fluid intake.

Physical Examination

During the physical examination, it is important to make a quick assessment of the patient's nutritional status. In general, patients with idiopathic constipation should not appear malnourished; the appearance of malnutrition should prompt a more extensive search for a secondary cause, including occult carcinoma, more widespread dysmotility syndromes such as chronic intestinal pseudo-obstruction, and eating disorders. An abdominal examination should be conducted to look for scars, any significant abdominal distention, tenderness, or masses. Bloating is a common and expected finding with idiopathic constipation, but significant distention, tenderness, or masses should prompt a full investigation.

All patients presenting with constipation should undergo a rectal examination. The perineum and anus should be examined for evidence of fecal incontinence that may indicate impaction and overflow. Fecal incontinence and chronic constipation coexist to some degree in 40% of patients¹⁶; marked soiling of the underwear is especially associated with the rarer diagnosis of megarectum. Scarring, for example, from an episiotomy, sentinel pile formation secondary to underlying fissure, external hemorrhoids, or prolapse may also be present. The degree of perineal descent on straining, which is indicative of pelvic floor weakness, should also be determined. A digital rectal examination should be done to diagnose impaction, gain a rough measure of anal tone at rest and on

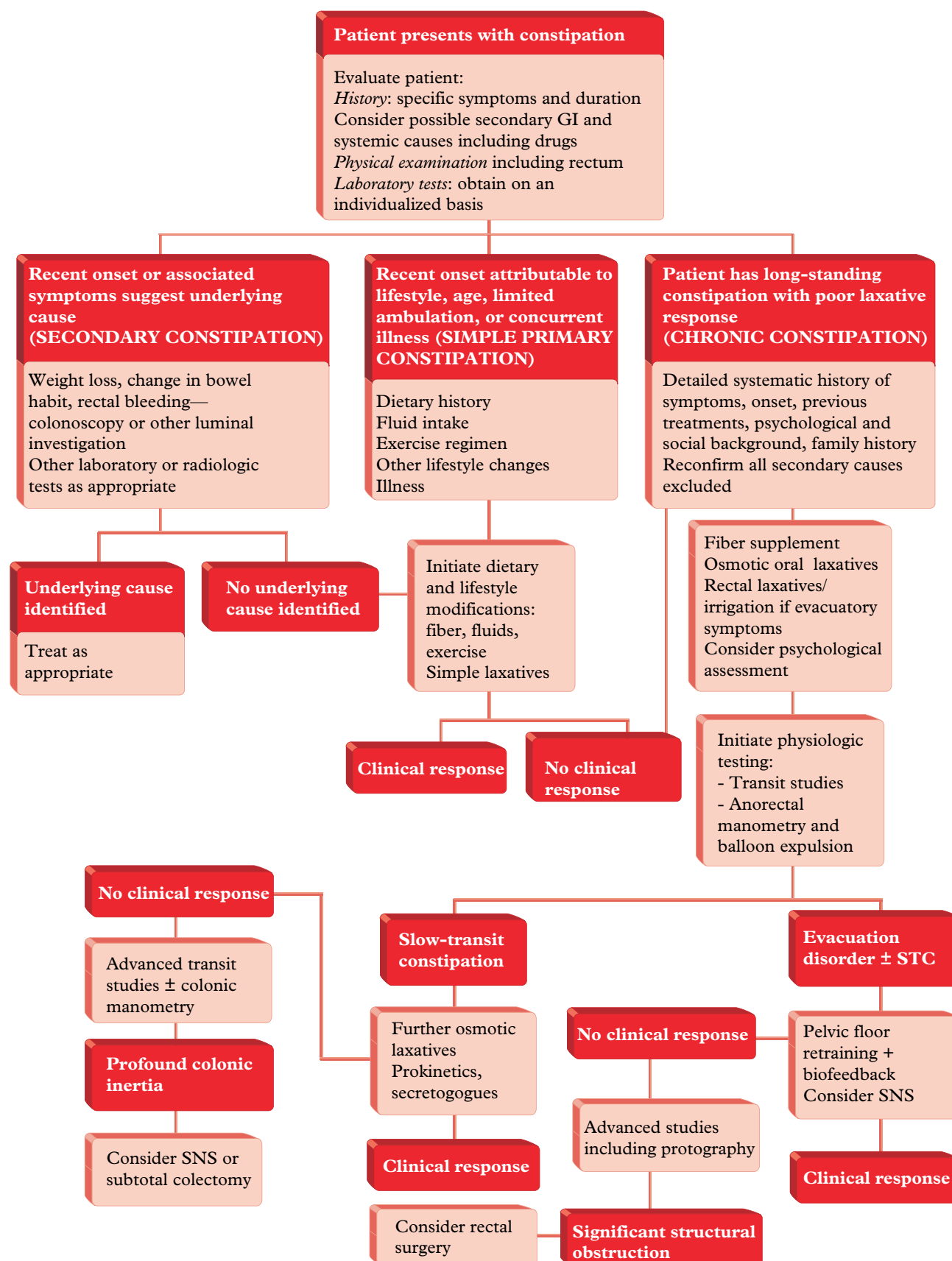


Figure 1 Algorithm outlining the workup and management of constipation. GI = gastrointestinal; SNS = sacral nerve stimulation; STC = slow-transit constipation.

squeezing, and ascertain obvious sphincter defects. Furthermore, an effort should be made to look for any anterior defect in the rectovaginal septum leading to a rectocele (your digit will appear within a pouch visible in the posterior vagina). On removing the digit from the anus, it is sometimes possible to appreciate the presence of an intra-anal intussusception or mucosal prolapse that “drags” out with the examining digit.¹⁷ It is unlikely that a digital examination can give useful information on paradoxical puborectalis contraction (dyssynergia), although the experienced examiner can sometimes have the impression of pelvic floor contraction during straining. The finding of a rectal mass warrants further investigation. Anoscopy and proctoscopy should be performed if there is any history of rectal bleeding and may indicate fissure or internal piles.

INVESTIGATIVE STUDIES

In general, diagnostic studies can be divided into those conducted to rule out an underlying cause of secondary constipation (e.g., partially obstructing colon cancer, metabolic or endocrine cause) and those used to diagnose specific anorectal or colonic physiologic abnormalities associated with chronic idiopathic constipation.

Investigations for Secondary Causes of Chronic Constipation

Although the findings from the history or physical examination may indicate a possible secondary cause of constipation, making further investigation mandatory (e.g., for a change in bowel habit), it is also typical practice in patients with chronic constipation to exclude certain secondary causes by investigation even though the diagnostic utility of such investigations is acknowledged to be low (the most common undiagnosed systemic disease is hypothyroidism). Thus, serum calcium concentrations, thyroid function tests, hemoglobin concentrations, glucose levels, serum electrolyte levels, and creatinine concentrations are usually performed. The approach taken to structural investigation of the colon when patients have no suspected intraluminal pathology varies internationally and on the basis of available resources. In the United States, for patients older than 50 years, the baseline risk of colorectal cancer is sufficiently high that screening colonoscopy is recommended even in the absence of alarming symptoms. These older patients should therefore undergo routine colonoscopy, and many authors recommend that patients younger than 50 years undergo routine flexible sigmoidoscopy. Routine biopsies have no benefit however. In Europe, this approach is being increasingly adopted. At some stage, it is worth assessing the rectum and colon so that subsequent management (which may be protracted or unsuccessful) can start with a baseline of reassurance that no organic disease is present. Barium enema can still be a useful investigation in this instance because it yields more information on colonic diameter (for rarer cases of megacolon) and the distribution and severity of diverticular disease, which may coexist and be responsible in part for symptomatology.

Investigations for Primary (Idiopathic) Chronic Constipation

In patients with chronic constipation in whom basic laxatives have failed, further specialist investigative tests are usually warranted. These tests are conducted to provide information on the underlying pathophysiologic abnormalities

of the colon and/or anorectum on the basis that the results will guide further management. Most opinion leaders agree that such tests are of value, although opinions differ on how rigorous such investigations should be and when in the algorithm they should be performed. Although there is a general lack of evidence that targeted management strategies are superior to empirical stepwise treatments in earlier pharmacologic and behavioral interventions, it is at least generally agreed that such tests are mandatory if surgery is considered.^{18,19} Finally, it should be noted that all are dependent on adequate normative data (sex and age relevant), the expertise of the investigator, and correct interpretation in the context of the clinical information.

These investigations also vary in their availability and complexity internationally. Table 2 lists standard and advanced tests. An additional, often-neglected investigation that can be performed and reviewed immediately in the ambulatory setting is plain abdominal radiography. This is particularly useful as a screening tool for determining whether the symptoms volunteered by patients correlate with a colon loaded with feces and may be shown to the patient to aid discussion.

The mainstay for the rapid evaluation of colonic transit is the radiopaque marker study. Although variations in technique exist in terms of the number of markers, the interval to radiography and definition of slow transit (in the United Kingdom, typically 50 markers, 100 hours, and > 20% remaining),²⁰ the basic premise is that a number of markers (small pieces of plastic tubing, prepackaged in gelatin capsules) are ingested, and an abdominal x-ray (which includes the pelvis) is taken at an interval. The patient abstains from laxatives for the duration of the study. In patients with significant numbers of retained markers (based on control data), slow transit is diagnosed [see Figure 2a]. Alternatively, transit can be measured by radioscintigraphy^{21,22} [see Figure 2b] or a wireless motility capsule²³ [see Figure 2c]. These techniques are valid but not yet widely available. On the basis of radiopaque marker studies, approximately 40% of patients with chronic constipation will have delayed transit.^{18,24} Abnormal transit may be demonstrated either throughout the colon or within a limited portion thereof (most commonly, the sigmoid and the rectum).²¹ In the latter, it is unresolved whether such markers represent a primary disturbance of rectosigmoid motility or are retained secondary to a primary problem of evacuation,²⁵ which is also present in more than half of the slow-transit constipation (STC) group.

Figure 3 schematically shows the normal process of defecation [see Figure 3, a–c] and the three most common causes of evacuation disorder (ED) [see Figure 3, d–f]. Pelvic floor studies are valuable for determining the presence and pathophysiology of ED and are best conducted in a pelvic floor laboratory with a specific interest in anorectal function. The balloon expulsion test can be performed in the office as an initial screening measure. A balloon filled with 50 mL of water is attached to tubing and placed in the rectum. Patients with an evacuation disorder are then defined as those who cannot expel the balloon from the rectum in 1 minute while sitting on a commode. It should be kept in mind, however, that as many as 12% of patients with normal pelvic floor function will have difficulty with balloon expulsion in this setting.²⁴ Furthermore, the literature has become confused by

Measure	Standard	Advanced
Colonic transit	Radiopaque marker study	Colonic isotope scintigraphy
Colonic contractile activity	—	Colonic manometry
Anal sphincter contraction	Anal manometry (water perfused)	High resolution anal manometry
Rectal sensory testing and distention	Simple balloon distention	Rectal barostat
Rectoanal inhibitory reflex	Balloon and anal manometry	Integrated barostat-manometry
Rectal expulsion (defecation)	Balloon expulsion test	Integrated proctography
	Evacuation proctography	Integrated proctography

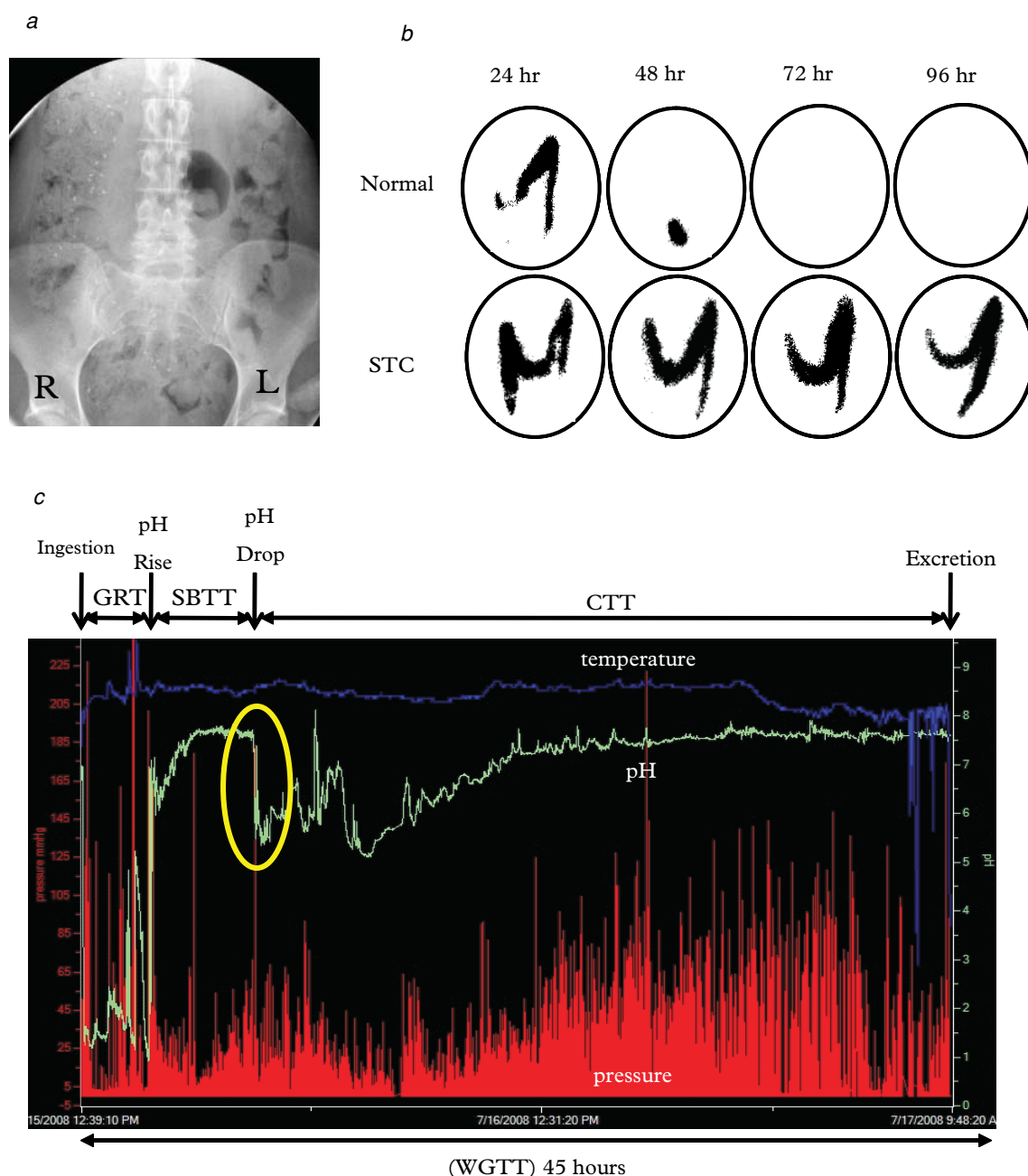


Figure 2 (a) Slow colonic transit: radiopaque marker study—all markers remain in the proximal colon. (b) ^{111}In isotope scintigraphy showing normal progression of isotope in a healthy control and generalized slow-transit delay. (c) SmartPill study measuring whole gut transit: progression of the capsule is determined by changes in pH and impedance. This patient has a normal colonic transit of less than 48 hours. CTT = colonic transit time; GRT = gastric retention time, SBT = small bowel transit time, WGTT = whole gut transit time.

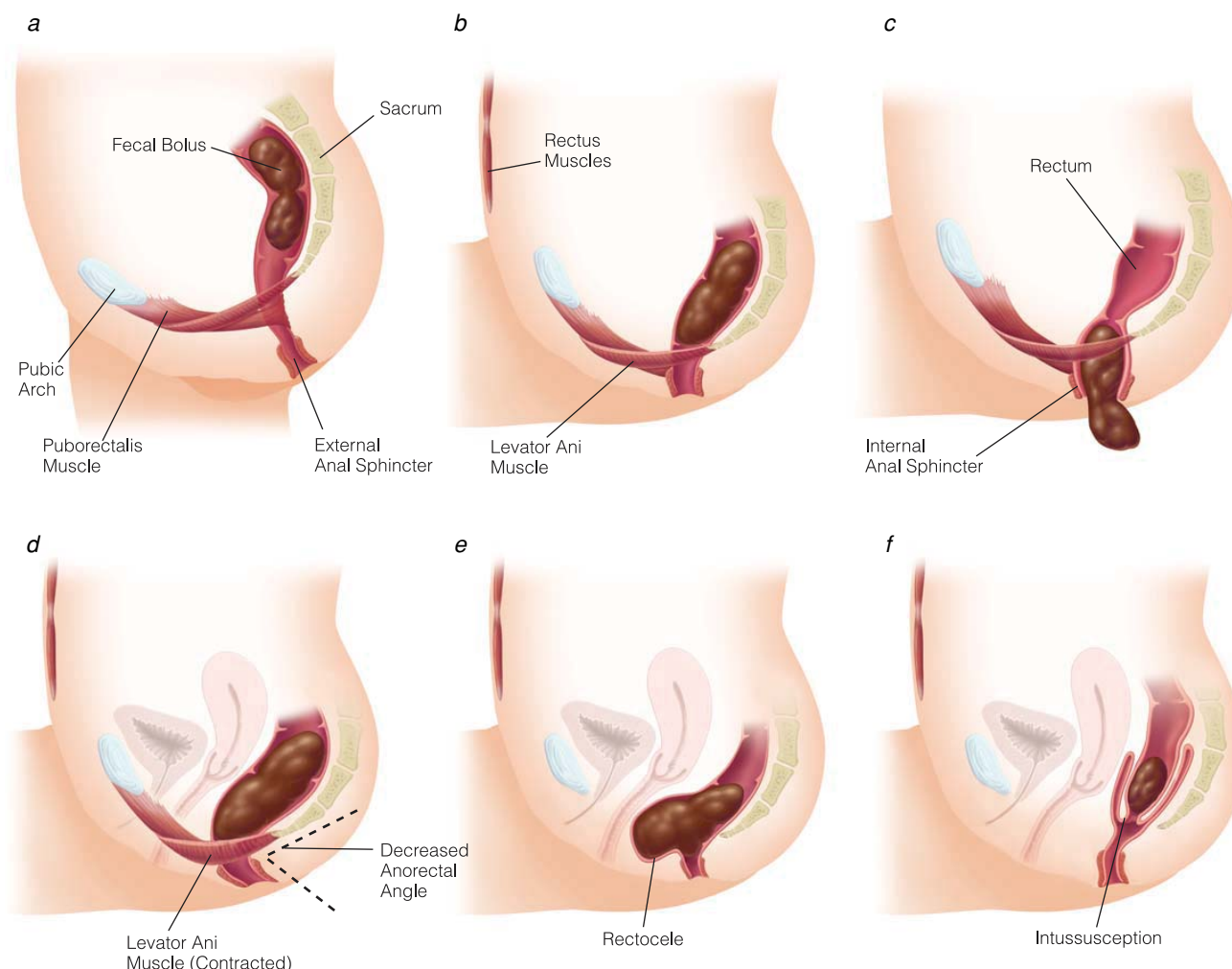


Figure 3 Schematic representation of normal defecation and common causes of evacuation disorder: (a) pelvic floor muscles at rest with preservation of the normal anorectal angle; (b) contraction of abdominal muscles and relaxation of puborectalis and external sphincter muscles leading to straightening of the anorectal angle; (c) relaxation of internal sphincter and evacuation of stool with rectal contraction; (d) puborectalis dyssynergia: the puborectalis sling has paradoxically shortened during straining, leading to exaggeration of the anorectal angle and obstruction of fecal progression; (e) rectocele: feces is pushed during straining into the vagina, which then retains feces at defecation, leading to incomplete evacuation; and (f) rectal intussusception: the rectum has internally prolapsed, leading to obstructed defecation during straining.

the assumption that this test is automatically diagnostic of an entity known as puborectalis dyssynergia (also sometimes termed pelvic floor dyssynergia, paradoxical puborectalis contraction syndrome, or “anismus”).^{24,26} The nonspecialist reader need not become too embroiled in the semantics of this diagnosis, but it suffices to mention that the balloon expulsion test can de facto determine only the ability to expel, not the underlying mechanism leading to failed expulsion. Thus, in patients who remain refractory to therapy, more advanced tests of evacuation may be indicated. Many specialist centers use defecography (also known as evacuation proctography) to evaluate evacuation. Barium paste is formulated so as to simulate a fecal bolus and is placed in the rectum. The patient is asked to defecate on a radiolucent commode, and the event is recorded with fluoroscopy. During normal defecation, the puborectalis and the anal sphincter muscles relax, and the rectum assumes a more

vertical position with respect to the anal canal, facilitating evacuation of stool. In a patient with puborectalis dyssynergia, defecography typically demonstrates failure to open the anorectal angle and persistence of the puborectalis impression during defecation, as well as failure to empty completely.²⁷ Other important findings that may also be noted include rectocele, internal intussusception, and rectal prolapse. There are pros and cons to both approaches, including pelvic radiation dose for defecography (often in young women).

In addition to the balloon expulsion test, pelvic floor evaluation generally involves manometry. Anal canal pressures are recorded at 1 cm intervals throughout the anal canal during rest and squeeze. A balloon is then expanded within the distal rectum and to assess reflexive relaxation of the internal sphincter to rectal distention. The presence of this reflex rules out adult Hirschsprung disease (a very rare cause of

constipation). In many centers, the ability of the patient to sense rectal balloon distention is also determined because loss of the urge to defecate may be caused by blunted rectal sensation (rectal hyposensation).²⁸ In patients with suspected puborectalis dyssynergia, manometry can be employed during straining to demonstrate either failure to relax to enable expulsion or paradoxical contraction.^{24,29} Similar findings during straining can also (if required) be documented by means of electromyography (EMG) with a sponge electrode in the anal canal.²⁹

MANAGEMENT

Chronic Idiopathic Constipation

Figure 1 illustrates that many treatments can be initiated without prior physiologic testing. Following detailed history taking, the patient's past drug use will be documented and can guide further therapy. The evidence base for an exact protocol of laxative use is poor,³⁰ with only polyethylene glycol (PEG)-based osmotic laxatives having been rigorously subjected to trials in the modern randomized, controlled trial age.³¹ Nevertheless, stool softeners (e.g., docusate), stimulant laxatives (e.g., senna and bisacodyl), and osmotic laxatives (e.g., PEG, lactulose, and magnesium salts) may be used alone or in combination with good effect. Bulking agents often cause further abdominal pain and bloating in patients with chronic constipation. Furthermore, attempts to prescribe such products (such as encouraging further dietary fiber intake, exercise, and fluids) will in general be met with hostility by patients who have exhausted such measures many years before and lead to an erosion of trust. In the absence of evidence, we make the following practical suggestions:

- Reassure the patient that modern laxatives do not damage the bowel.
- Try to stop all current laxatives, that is, do something definite (this is referred to as “switching” in the psychiatric literature).
- Consider use of rectal laxatives ($\pm$ oral purgatives) in patients with defecatory symptoms; these have often not been tried.
- Consider laxative dose titration (e.g., magnesium salts).
- Prescribe and monitor the chosen therapy at a fixed interval, for example, 3 months.
- Warn of side effects but emphasize the need for compliance.
- Rotate the laxative type at regular intervals to avoid tolerance.

Other drugs acting on secretion and motility are discussed under Slow-Transit Constipation (see below) but may equally be employed for patients with chronic constipation that has not been further physiologically defined. Similarly, there is some evidence that behavioral treatments may benefit all patients with chronic constipation³² rather than just those with pelvic floor dyssynergia. However, for clarity and better understanding, further discussion of these has been separated by subtypes of chronic constipation.

Slow-Transit Constipation

Medical treatment Patients with STC are primarily treated by addressing the transit disturbance of the colon

(although ED commonly coexists). In this group, the mainstay of therapy is the use of osmotic and stimulant laxatives (alone or in combination) to effect changes in transit^{33,34} with benefit proven in controlled trials.³⁵ A theoretical problem with all classic laxative therapies is their bioavailability in the colon. All require transport to the colon for site of action, and some require metabolism via the enteral flora to produce active products, for example, hydrolysis of stimulant laxatives. Furthermore, laxatives are often poorly tolerated because of pain (mainly stimulant) or unpredictable diarrhea with or without incontinence (mainly osmotic). Given the burden of disease, much investment has been made to find newer classes of drug to treat chronic constipation. To date, two classes of drug are being developed: colonic prokinetics, based on activity at serotonin receptor subtype 4 (5-HT₄ agonists), and intestinal secretagogues.

The main development in the 5-HT₄ agonist class is prucalopride. This drug has much greater selectivity to the 5-HT₄ receptor than the now withdrawn 5-HT₄ agonists such as tegaserod and cisapride. In particular, it has no proven effect on QTc interval caused by activation of the cardiac conducting system channels that led to arrhythmias with less selective drugs. Prucalopride has been the subject of three rigorously conducted phase III pivotal trials with pooled data available on over 2,000 patients.⁵ Abundant cross-species data (including humans) show that prucalopride leads to increases in propagated colonic contractile activity, leading to coordinated mass movements and spontaneous defecation.³⁶ It has an acceptable side-effect profile and is currently licensed in Europe for women with chronic constipation; it has some effect in approximately 50% of patients.⁵ In particular, it has a significant advantage over laxatives in terms of reducing rather than increasing abdominal pain and bloating.

Two drugs, lubiprostone (a chloride channel activator) and linaclotide (a guanylate cyclase C receptor activator), accelerate colonic transit in humans by mediating luminal secretion. Lubiprostone has a phase III portfolio and is approved by the Food and Drug Administration (FDA) for chronic constipation but is reported to cause problematic nausea in approximately 20% of patients.³⁷ Linaclotide is at an earlier developmental stage and has proved effective in phase II trials.³⁸

Surgical treatment Until very recently, colonic excision was the only popularized form of surgery to address STC. It is a fact that colectomy has a “finality” that separates it not only from medical treatments but also from most other invasive interventions for constipation. The results of colectomy have been extensively reviewed previously,^{19,39} with overall success rates varying between 40 and 100%. It is probable that colectomy peaked in popularity in the mid-1990s but has seen a gradual decline in application since publications of more modest longer-term results became available and the potential for serious complications and poor functional outcomes was realized.⁴⁰ Nevertheless, most would agree that colectomy continues to have a limited role as a treatment option for highly selected patients with proven STC (probably < 5% chronic constipation) who have failed all nonsurgical interventions and in whom symptoms are sufficiently severe to contemplate major surgery. Such surgery should be undertaken only in specialized centers where the techniques

required for selection are available. Subtotal colectomy with ileorectal anastomosis has the best results, leading to a median stool frequency of three (range one to five) per day. Unfortunately, surgery may not satisfactorily alleviate other symptoms (e.g., abdominal discomfort or bloating),⁴¹ and patients should be made aware of this possibility before operation. Overall, the majority of well-selected patients are satisfied with the results of surgical treatment^{42,43}; however, long-term postoperative complications, particularly small bowel obstruction, are common. In addition, patients may manifest symptoms of a more global GI dysmotility disorder in the long term.

The role of sacral nerve stimulation (SNS) is being critically evaluated following the very recent publication of a multicenter European trial showing the beneficial effect of SNS in 39 of 62 (63%) chronic constipation patients who predominantly had STC⁴⁴ and other studies with less encouraging results.⁴⁵ Mechanistically, SNS increases pancolonic anterograde propagated sequences in patients with STC.⁴⁶ Controlled studies are required particularly because SNS is not cheap. However, the attraction of this minimally invasive treatment and possibility of pretesting patients prior to stimulator implantation make it a promising tool for patients who might otherwise progress to colectomy.³⁹

A stoma may be used as a definitive procedure, as a guide to further treatment, or as salvage from previously failed or complicated surgical intervention. There are few published data to support an evidence-based use; however, an ileostomy may be employed as a guide to colectomy, with subsequent resection avoided if the ileostomy output is unsatisfactorily high or symptoms such as pain and bloating are untouched by diversion.⁴⁷ As a definitive procedure, both colostomy and ileostomy have been described for a diversity of disorders characterized by constipation, including spinal cord injury, megacolon, and ED. There is little evidence in adults to guide the choice of ileostomy or colostomy⁴⁸; however, some report high complication rates of ileostomy,⁴⁹ and STC may be unsatisfactorily treated by colostomy.

The Malone anterograde continent enema technique may also be an option for refractory STC but has been employed more frequently in patients with severe ED [see Evacuation Disorder, *below*].

Evacuation Disorder

Patients with evidence of ED can be subdivided broadly into those with an obvious structural cause, such as a large rectocele or intussusception, and those in whom no such cause is found but in whom defecation is still ineffective. Depending on the definition and methods used to diagnose, 20 to 75% of the latter will be found to have puborectalis dyssynergia^{24,29}—the term used to describe paradoxical or noncontraction of the pelvic floor during straining. The evidence base for ED management is fraught with semantic differences; however, a few key management strategies have general agreement:

- All patients may benefit from nurse-led bowel retraining and rectal laxatives and/or anal irrigation.
- Patients with large rectoceles in whom clinical (the patient can successfully effect evacuation by digital pressure in the vagina) and radiologic findings concur should have these

repaired by one of the numerous transvaginal, transperineal, or transanal approaches.^{50,51} However, the optimal operation for rectocele remains a matter of debate.

- Patients with proven or suspected puborectalis dyssynergia should undergo behavioral retraining incorporating biofeedback.

Behavioral therapy The predominant behavioral treatment is biofeedback. This (usually nurse-led) therapy retrains the patient to appropriately contract her abdominal and relax her pelvic floor muscles during defecation, with the patient receiving feedback of anal and pelvic floor muscle activity as recorded by surface EMG, anal pressure sensors, or digital examination by the therapist. Several controlled trials and meta-analyses provide data on biofeedback outcomes in comparison with sham or alternative treatments.¹⁸ Opinions vary on which patient groups most benefit, with some favorable³² and some unfavorable⁵² results for patients with STC. However, most would agree that this treatment is best targeted at those with ED, particularly those with proven puborectalis dyssynergia. The results range from approximately 70 to 90% success rates in adults with ED,^{52–54} with a recent meta-analysis of three randomized, controlled trials giving an odds ratio of success over placebo of 3.7 (95% CI 2.1 to 6.3).⁵⁵ Training may have to be reinforced at intervals but is generally sustained in the longer term.

Anorectal surgery The repair of large rectoceles has been noted above and can be performed by urogynecologists who are more familiar with approaches that avoid the rectal lumen.⁵¹ Much more contentious are the numerous surgical approaches for smaller rectoceles, intussuscepta, or both (these frequently coexist). An “industry” of operations that either hitch, reinforce, or excise rectal tissue have been described.³⁹ All are beset with the following problems in relation to the treatment of ED:

1. Anatomic abnormalities such as rectocele and intussusception are detectable in significant proportions (at least 40%) of asymptomatic subjects.⁵⁶
2. Such abnormalities often belie a complex multifactorial problem with several contributing etiologies that cannot be corrected by surgery alone.^{57,58}
3. Promising early success in case series (e.g., 90%⁵⁹) often becomes less encouraging in the longer term (approximately 50%).^{60,61}
4. There are no bona fide data from randomized, controlled trials for any procedure.³⁹
5. Although many procedures have generally low morbidity, none are without the risk of serious complications in at least a minority of patients.⁶²

Two procedures require specific mention as a result of their current popularity.

Laparoscopic ventral rectopexy was first described for full-thickness rectal prolapse⁶³ but has been applied to the treatment of intussusception since 2008.⁶⁴ The rectum is mobilized anteriorly to the pelvic floor and a mesh is sutured to the ventral rectum, posterior vagina, and vaginal fornix and secured to the sacral promontory. Excellent short-term results have recently been published for this procedure⁶⁵; however,

longer-term data are lacking, and complications have also been recorded.⁶⁴

With the advent of suitable staple devices and widespread introduction of stapled hemorrhoidopexy, a currently popularized intervention is that of stapled transanal rectal resection (STARR), in which the internally prolapsed rectum is excised with the aim of improving anatomy and function.⁶² STARR is applicable for both intussusception and small rectoceles; however, controversial results are reported, ranging between 90% success in the short term to 55% persistence of symptoms after 18 months.⁶⁶ Furthermore, reported complications of STARR include bleeding, fecal incontinence, excruciating anal pain, rectal diverticulum, rectovaginal fistulas, and even fatal pelvic sepsis. Painful defecation, possibly attributable to retained staples in the puborectalis muscle, affects 20% of patients 1 year postsurgery, and chronic proctalgia requires reintervention in approximately one third of patients.⁶² This “trade-off” between satisfaction in the majority and serious complications in the minority is one that might be deemed acceptable by some surgeons but not by others (including the authors).

Other surgical approaches Anterograde enema can be considered an alternative to stoma in patients with severe ED when conservative methods with or without anorectal procedures have failed or are contraindicated.⁶⁷ In patients with previous appendectomy or in whom the appendix cannot be satisfactorily employed, cecostomy may be effected using a percutaneously placed Chait tube or surgically by more complex techniques.⁶⁸ In general, success rates have been lower in adults^{67,68} than in children: approximately 50 versus 80%. In the long term, complications such as stomal stenosis and leakage, or failure to effectively treat symptoms commonly (> 50% at 3 years), lead to revision, reversal, or conversion to stoma.⁶⁸

Currently, there are few specific data on the efficacy of SNS for ED. Indeed, although numerous data exist on functional changes in anorectal physiologic functions with SNS,⁶⁹ its effect on evacuation has remained relatively unstudied. There is, however, a good rationale for its use in such patients based on the fecal incontinence literature [*see Fecal Incontinence, below*], and studies are ongoing.

Fecal Incontinence

OVERVIEW AND TAXONOMY

Fecal incontinence may be defined as the involuntary loss of rectal contents through the anal canal. It is a relatively common condition, occurring in an estimated 2.2% of persons in the United States.⁷⁰ Its exact prevalence is unknown, however, and appears to vary with the population being studied. For example, nearly 50% of nursing home patients are incontinent to stool.⁷⁰ Fecal incontinence is often treated inadequately, either because of underreporting of symptoms to the physician⁷¹ or because of ignorance or disinterest on the physician's part.

Fecal incontinence makes a significant contribution to medical morbidity (e.g., urinary tract infections and decubitus ulcers), but its main impact is on quality of life. Affected patients experience embarrassment and shame, and

many dramatically alter their lifestyle in an effort to avoid accidents.

Normal continence depends on a chain of interdependent processes, and disruption of any of the links in the chain can lead to incontinence. Frequently, a combination of factors is responsible for the incontinence.

Individuals must have adequate mental function to care about continence and must have an intact neurologic arc from the brain to the anal sphincter to maintain normal continence. A wide array of neurologic disorders can lead to incontinence, including dementia, strokes, spinal cord injury, multiple sclerosis, and diabetic autonomic neuropathy. So-called idiopathic fecal incontinence is caused by pelvic floor denervation resulting from traction injury to the pudendal nerves.⁷² The injury is usually caused by straining and consequent pelvic floor descent during obstetric delivery or by chronic straining at stool.

Conditions characterized by abnormal GI function, especially diarrheal states, can cause or exacerbate incontinence. Common causative conditions include infectious diarrhea and inflammatory bowel disease. Diarrhea-predominant IBS can contribute to incontinence in patients with other associated disorders. Fecal impaction is an important cause of incontinence, particularly in older and institutionalized populations.⁷³

Abnormalities of the pelvic floor are frequent causes of incontinence. Some such abnormalities are congenital malformations (e.g., imperforate anus, rectal agenesis, and cloacal defect). More often, abnormalities are attributable to acquired sphincter injuries. Common causes of sphincter injury include obstetric injury, pelvic fracture, and traumatic impalement [*see Figure 4*]. One of the most frequent causes is an anorectal procedure, such as fistulotomy,⁷⁴ sphincterotomy,⁷⁵ or anal dilatation.⁷⁶ Sphincter-sparing rectal resections can also lead to incontinence as a consequence of both the loss of the normal rectal reservoir and the sphincter injury caused by transanal introduction of intraluminal staplers.

CLINICAL EVALUATION

History

A careful patient history and a directed physical examination are the most important elements of clinical evaluation for a patient with fecal incontinence [*see Figure 5*]. The patient should be asked about the onset and nature of the incontinence (e.g., whether the stool is liquid or solid and whether flatus is present), any associated changes in stool consistency or bowel habits, and the frequency of incontinence. A pertinent but thorough medical, surgical, and obstetric history should be obtained, and any underlying contributory conditions (e.g., colitis) should be treated. The impact of the incontinence on the patient's quality of life should be assessed, at least qualitatively.

Physical Examination

The physical examination should focus primarily on the perineum. Seepage and secondary perineal skin breakdown should be noted, as should scars from previous surgical treatment or trauma. Perineal body deformity is an important sign of obstetric injury, and gaping of the anus with traction on the buttocks is suggestive of rectal prolapse. When prolapse



Figure 4 Shown is an obstetric sphincter injury.

is suspected but not evident, the patient should be asked to strain while seated on a commode. Digital rectal examination is useful for detecting low rectal tumors and fecal impaction; it also provides a qualitative assessment of both resting sphincter tone and voluntary squeeze pressure.

INVESTIGATIVE STUDIES

Endoscopy should be performed on all incontinent patients to exclude a neoplastic or inflammatory condition. In most cases, flexible sigmoidoscopy is adequate, but if the patient has unexplained diarrhea, bleeding, or changed bowel habits, a complete colonoscopy should be performed.

Anorectal testing is indicated for most patients with significant incontinence, particularly if operative treatment is being considered. The most important test is endoanal ultrasonography (EAUS), which yields a highly accurate assessment of sphincter integrity [see Figure 6].⁷⁷ At some centers, magnetic resonance imaging (MRI) has become the test of choice for evaluating the pelvic floor. Anal manometry

provides a quantitative assessment of resting and squeeze anal pressures, which serve as indicators of internal anal sphincter function and external anal sphincter function, respectively. EMG may be used to diagnose neuropathic injury of the pelvic floor. Although concentric-needle EMG is the most accurate technique, most centers employ a glove-mounted intra-anal electrode to measure pudendal nerve conduction time (i.e., pudendal nerve terminal motor latency [PNTML]). The practical utility of PNTML testing is debatable, however, and opinions vary regarding the test's ability to predict successful outcomes after anal sphincter repair.^{78,79} When the cause of incontinence is uncertain, dynamic imaging of the pelvic floor with defecography or MRI may reveal an occult pathologic state (e.g., occult rectal prolapse).

MANAGEMENT

Conservative Management

Minor incontinence should be treated first with conservative measures. Dietary changes (e.g., avoidance of foods that cause diarrhea or urgency), fiber supplementation, and bowel habit training are helpful for most patients, as is regular use of loperamide. Perianal skin excoriation should be treated with a barrier cream, and seepage may be controlled either with placement of a small cotton wick at the anal orifice or, occasionally, with rectal washouts.

Biofeedback

Biofeedback appears to be an effective therapy for fecal incontinence in a high percentage of patients.^{80,81} It is an inherently attractive approach because it is simple, painless, and risk-free. However, the biofeedback literature consists mostly of small, uncontrolled, retrospective studies, and its specific efficacy has been questioned. A randomized, controlled trial from 2003 found that biofeedback had no advantages over standardized medical and nursing care (i.e., advice) or advice plus sphincter exercises.⁸² In contrast, a more recent randomized trial showed that manometric biofeedback with pelvic floor exercises was more effective than pelvic floor exercises alone in treating fecal incontinence that had failed conservative management.⁸³

Sphincteroplasty

Anal sphincter repair is the most widely accepted operation for fecal incontinence [see Figure 7]. In acute situations (e.g., when an obstetric sphincter injury is recognized), immediate direct repair is generally recommended. Unfortunately, as many as 75% of women have persistent external anal sphincter defects after primary repair, and about 60% have some degree of incontinence.⁸⁴ If immediate repair is not attempted, surgical treatment should be delayed at least 3 to 6 months to permit resolution of local tissue inflammation and edema.

For incontinent patients with established sphincter defects, overlapping sphincteroplasty is the procedure of choice. Complete bowel preparation is carried out before the procedure, and prophylactic antibiotics are administered.

Operative technique *Step 1:* initial dissection The patient is placed in the prone jackknife position, with the buttocks taped apart and a large roll beneath the hips. A

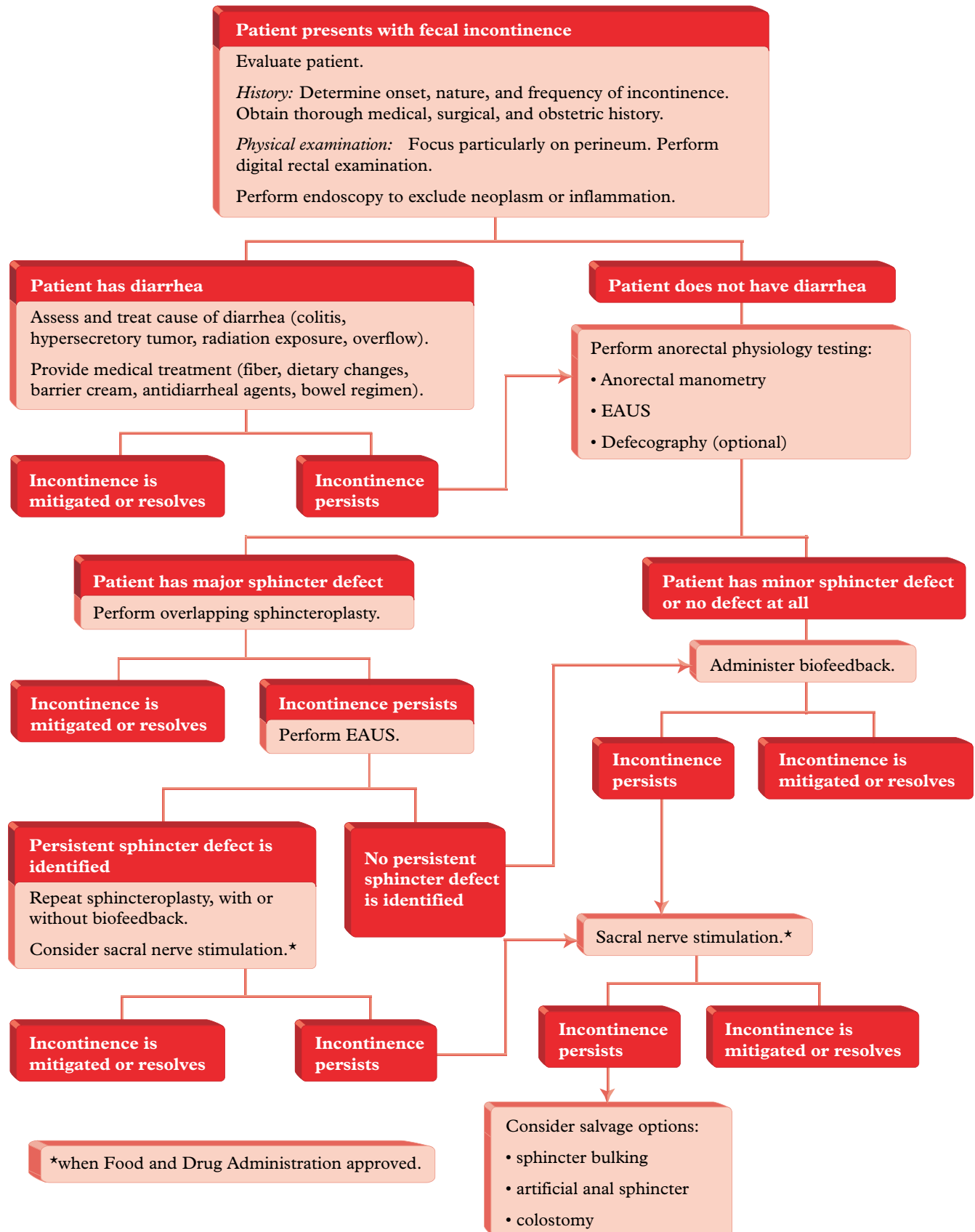


Figure 5 Algorithm outlining the workup and management of fecal incontinence. EAUS = endoanal ultrasonography.

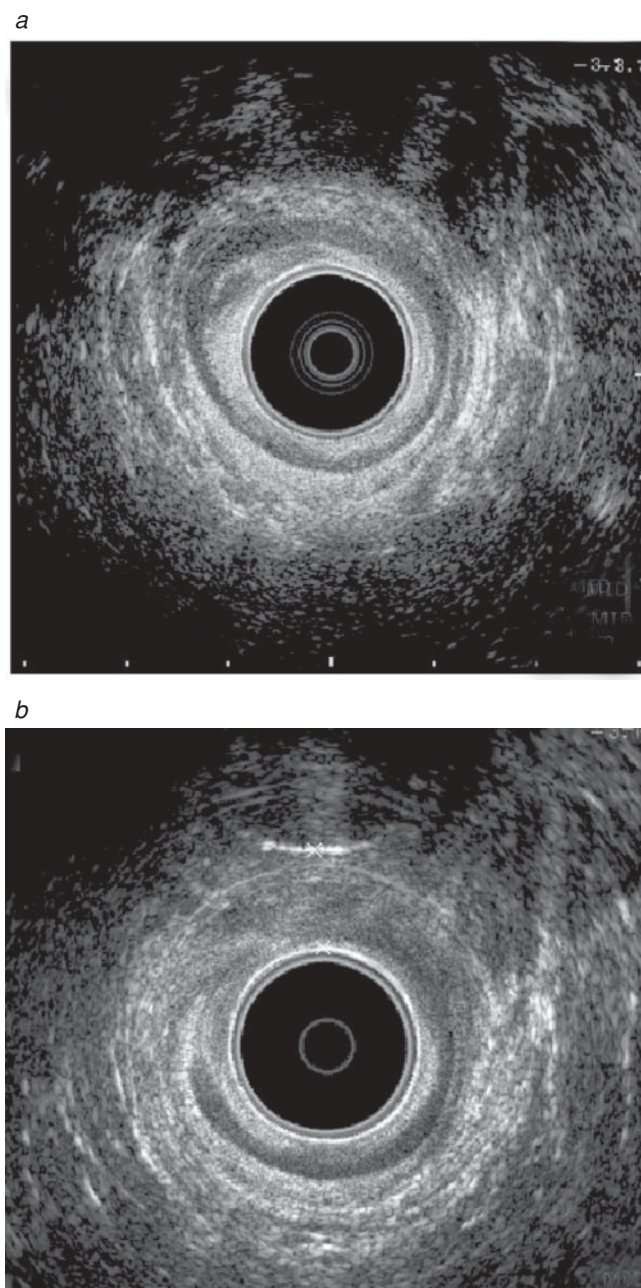


Figure 6 Endoanal ultrasonograms show (a) a normal anal sphincter and (b) a sphincter defect.

curvilinear incision is made over the perineal body, and the anoderm and the anal canal mucosa are raised as an endodermal flap [see Figure 7a]. The vaginal wall is mobilized anteriorly.

Step 2: mobilization of sphincter muscle It is often easiest first to identify normal muscle laterally in the ischiorectal fossa and then to work medially toward the attenuated tissue in the midline. Lateral dissection is extended back on either side until enough healthy muscle is mobilized to allow overlapping without tension. Generally, however, lateral dissection should not extend beyond the midcoronal line so as not to risk injury to the inferior rectal branches of the pudendal

nerves, which cross the ischiorectal fossae posterolaterally. Dissection is then carried out cranially in the rectovaginal septum to the level of the puborectalis. The muscle is divided through its midline scar, but the scar is preserved to help prevent the sutures from tearing through.

Step 3: overlapping repair The tapes on the buttocks are then released, and an overlapping sphincter repair is performed with mattress sutures [see Figure 7, b and c]. A snug plication is universally advocated, but, unfortunately, there are no generally accepted objective criteria to define exactly what “snug” means in this context. Many authorities advise plication of the puborectalis (so-called levatorplasty) at the cranial aspect of the repair to maximize the length of the anal canal.⁸⁵ Others favor individual dissection and repair of the internal and external sphincter muscles, but at present, there is no compelling evidence for the superiority of this approach.

Step 4: restoration of perineal body The skin incision is closed in a V-Y configuration to restore the perineal body and maximize the distance between the anus and the vaginal introitus. The wound is left partially open or closed loosely over small Penrose drains to minimize the risk of surgical site infection [see Figure 7d]. A diverting stoma is not generally indicated but may be considered in special situations (e.g., multiple previous failed repairs, Crohn disease, or various chronic diarrheal states).

Outcome evaluation Overlapping sphincteroplasty yields substantial clinical improvement in approximately 65 to 80% of patients.^{86,87} Unfortunately, current data indicate that the results deteriorate significantly over time.^{88–90} When sphincteroplasty fails, repeat EAUS evaluation should be done to confirm that the muscle wrap is intact, and another repair should be performed after 6 to 12 months if a significant defect persists.⁹¹ If the muscle wrap is intact, the functional outcome can often be improved by means of biofeedback.⁹²

Various surgical options are available for patients in whom sphincteroplasty has failed or who are not candidates for the procedure (e.g., those with pudendal neuropathy and an anatomically intact sphincter). A number of these options are investigational, and further study is needed to determine their eventual role (if any) in incontinence therapy.

Postanal Repair

Sir Alan Parks devised the postanal repair in 1975 to treat patients with incontinence and intact sphincters. The initial results were encouraging but tended to deteriorate over time. Consequently, despite evidence of lasting improvement in some patients, this operation is rarely performed today.^{93,94}

Injectable Biomaterials

A number of studies have explored the use of injectable biomaterials to provide bulk around the anal sphincter and thereby improve continence. The materials employed have included autologous fat, cross-linked collagen, silicone, and carbon-coated beads.^{95,96} Several small, uncontrolled studies have reported promising results, but the sole randomized, controlled trial⁹⁷ identified in a recent systematic review⁹⁸ showed no difference between control and placebo arms. Additional randomized trials with longer follow-up times are needed.

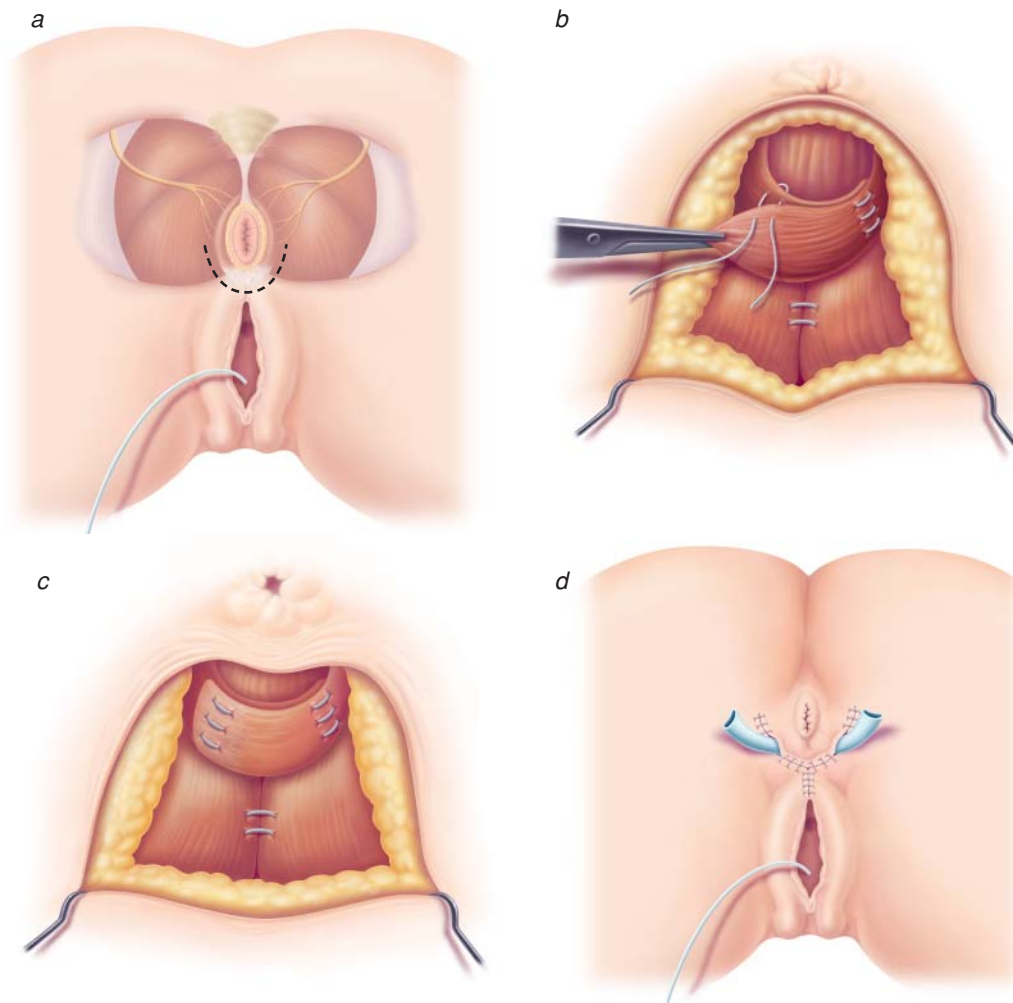


Figure 7 Sphincteroplasty. (a) With the patient in the prone jackknife position, a curvilinear incision is made. Inferior rectal nerves cross the ischiorectal fossa posterolaterally. (b) Anterior levatorplasty is performed, and overlapping sphincter repair is then initiated. (c) Sphincter repair is completed. (d) The incision is closed, with drains in place (optional), and V-Y plasty is done to restore the perineal body.

Nonstimulated Muscle Transposition

Attempts to restore continence by creating a neosphincter from transposed skeletal muscle date back to the early 20th century. Most such attempts have made use of either the gluteus maximus⁹⁹ or the gracilis.¹⁰⁰ Good results have frequently been reported, but many authorities believe that the quality of the resulting continence is poor. One of the main limitations of nonstimulated muscle transposition is that patients are typically unable to maintain voluntary contraction of the transposed muscle over the long term.

Stimulated (Dynamic) Graciloplasty

Successful electrical stimulation of a transposed gracilis by means of an implantable pulse generator was first reported in 1988.¹⁰¹ Such stimulation has two main effects. First, it converts the fast-twitch, rapidly fatigable gracilis to a slow-twitch, fatigue-resistant muscle that is capable of tonic contraction for prolonged periods.¹⁰² Second, electrical stimulation maintains tonic muscle contraction without the need for continuous voluntary control on the part of the patient. A

small number of centers with particular expertise in dynamic graciloplasty and high patient volumes have reported good results with acceptable morbidities¹⁰³; however, three large multicenter trials have reported less encouraging results with prohibitive morbidities.^{104–106} In the United States, dynamic graciloplasty is not available, because it has not been approved by the FDA. Elsewhere in the world, the operation can be considered a salvage option at centers with the requisite expertise and experience.

Artificial Anal Sphincter

The artificial anal sphincter is an implantable system consisting of three parts: an inflatable perianal cuff, a pressure-regulating balloon, and a control pump that is implanted in the scrotum or the labia majora [see Figure 8]. Good results have been reported in individual case series,¹⁰⁷ but device infection has been a problem.^{108,109} In a large multicenter trial, 46% of patients required surgical revision of the device, including 25% who required revision or explantation because of infection.¹⁰⁸ Of the patients who underwent implantation,

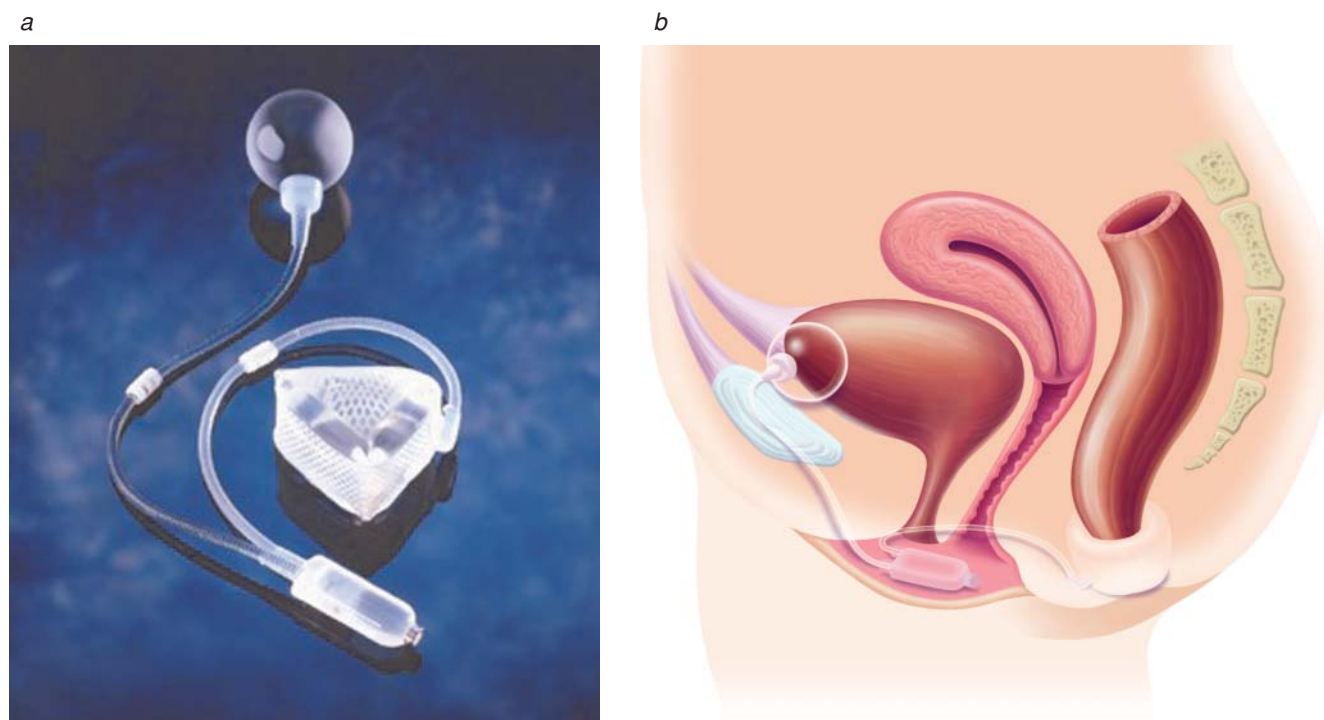


Figure 8 Artificial anal sphincter. (a) A three-part implantable system is used (shown is Acticon, American Medical Systems, Minneapolis, MN). (b) Depicted is the recommended placement of the artificial sphincter device in the patient.

53% had successful results; among those with a functioning device in place, the success rate was 85%.

Sacral Nerve Stimulation

In SNS, an electrode is inserted through a sacral foramen and used to stimulate the sacral nerves. The procedure was originally used exclusively in patients with intact anal sphincters (including those with intact repairs), but more recent studies have shown efficacy in those with sphincter defects as well. SNS has recently been approved for the treatment of fecal incontinence in the United States by the FDA.

SNS is generally carried out in two stages. The first stage, peripheral nerve evaluation (PNE), is performed to confirm a muscular response to stimulation of the sacral nerves, to identify the optimal site for stimulation (S2, S3, or S4), and to determine the clinical response to stimulation with an external pulse generator. In most cases, stimulation of the S3 nerves provides the optimal response.

PNE is performed with the patient prone and under local anesthesia, with or without sedation. The sacral foramina are located by means of bony landmarks; S3 is typically about 1.5 cm off the midline at the level of the sciatic notch.¹¹⁰ Lead placement is optimally performed under fluoroscopic guidance. Initial testing is performed with an insulated spinal needle and an external pulse generator. Stimulation of each foramen leads to a typical response: S3 causes a bellows-type contraction of the pelvic floor and dorsiflexion of the ipsilateral great toe. Usually, several levels are tested until the optimal site is identified. A temporary pacing wire or a permanent quadripolar lead is then inserted and connected to an external stimulator [see Figure 9].

Patients are asked to provide a baseline continence diary, and a second diary is recorded during the test stimulation period. If continence is significantly improved (e.g., by 50% or more), the second stage of SNS, implantation of a permanent lead (if not already in place) and a pulse generator, is carried out. This second stage is also performed with the patient prone, under local anesthesia, and sedated. The pulse generator is implanted in a subcutaneous pocket on the same side as the stimulating electrode.

Both stages of SNS are performed as outpatient procedures. The pulse generator is activated and its stimulation parameters are set by means of a telemetric programmer. If problems (e.g., pain) develop or if the results of stimulation are inadequate, the system can be reprogrammed in a variety of ways: stimulation frequency can be altered, voltage can be increased or decreased, and the configuration of the stimulating electrodes can be modified.

SNS has been shown to be a highly effective treatment for fecal incontinence.^{111–113} Unlike dynamic graciloplasty and the artificial anal sphincter, SNS is associated with only minimal morbidity. In a multicenter prospective trial, the frequency of incontinent events dropped from 16.4/wk at baseline to 3.1/wk at 12 months after SNS and 2.0/wk at 24 months.¹¹⁴ Fecal incontinence–related quality of life was significantly improved. A more recent multicenter prospective trial showed that 83% of patients experienced a greater than 50% decrease in incontinent episodes per week compared with baseline at 12 months following SNS; 41% of patients attained full continence.¹¹⁵

Because of its high success rate and excellent safety profile, many authorities now consider SNS the salvage procedure of

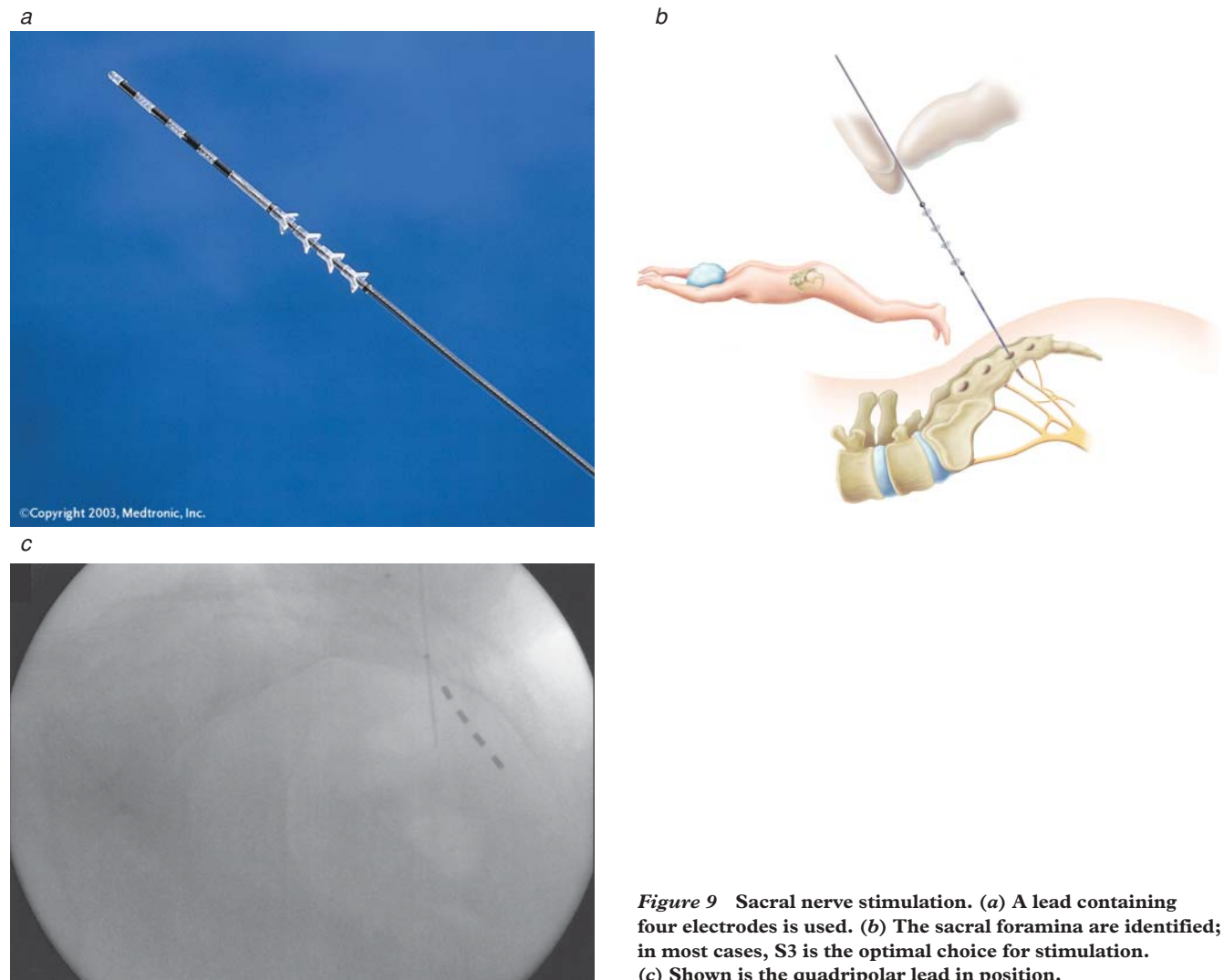


Figure 9 Sacral nerve stimulation. (a) A lead containing four electrodes is used. (b) The sacral foramina are identified; in most cases, S3 is the optimal choice for stimulation. (c) Shown is the quadripolar lead in position.

choice for patients with refractory incontinence. If SNS fails, more aggressive treatments may still be tried at a later time.

Colostomy

Although creation of a colostomy does not restore continence, it does provide a degree of bowel control in a manner that allows patients to resume their normal activities without fear of accidents. Surprisingly few data are available regarding colostomy for incontinence; however, one questionnaire study of patients who underwent colostomy for incontinence

reported extremely high levels of patient satisfaction and marked improvements in subjective quality of life.¹¹⁶ In most cases, a simple end sigmoid colostomy with a Hartmann pouch is the appropriate procedure and can often be performed with relatively little operative trauma by using a laparoscopic or minilaparotomy technique. Patients should receive preoperative counseling from an enterostomal therapist, and the optimal stoma site should be marked before the procedure is initiated.

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17 BENIGN AND MALIGNANT RECTAL, ANAL, AND PERINEAL PROBLEMS

David E. Beck, MD, FACS, FASCRS

Problems of the rectum, anus, and perineum are common, and an understanding of the anatomy is essential to properly diagnose and treat anorectal conditions.¹ As shown in Figure 1, the dentate line divides the rectal mucosa above (generally insensate and lined with columnar mucosa) and the anoderm below (highly sensitive because of somatic enervation provided by the inferior hemorrhoidal nerve and lined with modified squamous mucosa). The anal canal is surrounded by two muscles. The internal anal sphincter, innervated by the autonomic nervous system, maintains the resting anal tone and is under involuntary control. The external sphincter, innervated by somatic nerve fibers, generates the voluntary anal squeeze and is most important in maintaining anal continence. The area surrounding the anorectum is divided into four spaces, which are particularly important when evaluating perirectal abscesses and fistulas.

This chapter briefly reviews the evaluation and management of benign and malignant conditions of the anus and rectum, as well as retrorectal tumors. Rectal cancer is covered in another chapter of this text.

Benign Conditions

HEMORRHOIDS

Hemorrhoids are fibromuscular cushions that line the anal canal and are classically found in three locations: right anterior, right posterior, and left lateral.^{2,3} Smaller secondary cushions may occasionally lie between these main cushions. Contrary to popular belief, hemorrhoids are not related to the superior hemorrhoidal artery and vein, to the portal vein, or to portal hypertension.⁴ Hemorrhoids are part of normal

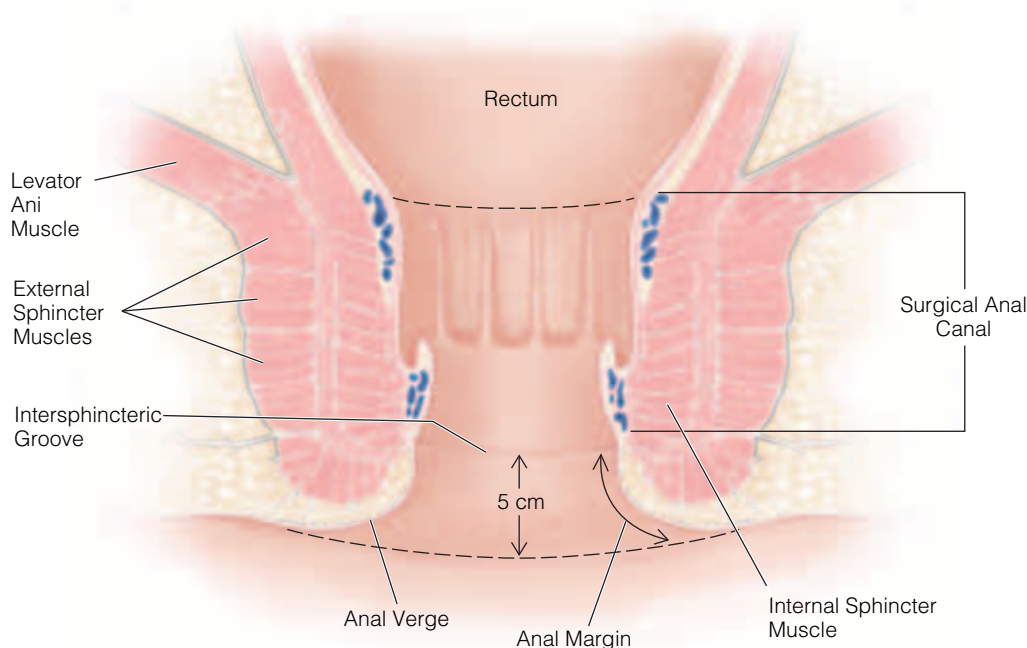


Figure 1 Depicted is the anatomy of the anal canal.⁵³

anatomy and become engorged during straining or performance of the Valsalva maneuver as a component of the normal mechanism of fecal continence. Hemorrhoidal engorgement most likely completes the occlusion of the anal canal and prevents the stool loss associated with nondefecatory straining. However, when the term “hemorrhoid” is used in the medical literature, it almost exclusively refers to pathologic hemorrhoids, and it will be used as such in the following paragraphs.

Hemorrhoids are divided into internal and external components. Internal hemorrhoids are found proximal to the dentate line, whereas external hemorrhoids occur distally [see Figure 2]. External hemorrhoids are redundant folds of perianal skin generally related to previous anal swelling; they remain asymptomatic unless they are thrombosed and are treated entirely differently from internal hemorrhoids.

Internal Hemorrhoids

Evaluation Internal hemorrhoidal disease is demonstrated by two main symptoms: painless bleeding and protrusion.⁴ Pain is rarely associated with internal hemorrhoids because they originate above the dentate line in insensate rectal mucosa. The most popular etiologic theory states that hemorrhoids result from chronic straining at defecation (upright posture and heavy lifting may also contribute). This straining not only causes hemorrhoidal engorgement but also creates forces that decrease the fixation between the hemorrhoids and the anal muscular wall. Continued straining causes further engorgement and bleeding, as well as hemorrhoidal prolapse. Internal hemorrhoids are categorized into four grades based on clinical findings and symptoms: 1, bleeding without prolapse;

2, prolapse that spontaneously reduces; 3, prolapse requiring manual reduction; and 4, irreducible prolapse.

Questioning often reveals a long history of constipation and straining at defecation. Patients with internal hemorrhoids are commonly extensive bathroom readers, spending many hours in the bathroom each week. Symptoms start with painless bleeding and may progress to anal protrusion. Hemorrhoidal prolapse must be distinguished from true full-thickness rectal prolapse. The physical examination begins with visual inspection and may reveal prolapsing hemorrhoidal tissue as a rosette of three distinct pink-purple hemorrhoidal groups. If prolapse is not present, anoscopy reveals redundant anorectal mucosa just proximal to the dentate line in the classic locations.

Surgical treatment of hemorrhoids in a patient whose main disease process is Crohn disease, a pelvic floor abnormality, or fissure disease invariably yields imperfect results. It is especially important to recognize anal pain and spasm and fissure in ano because in patients with this problem, excision of the hemorrhoids without concomitant management of the fissure leads to increased postoperative pain and poor wound healing. Not uncommonly, patients are treated for hemorrhoids when the true primary condition is fissure disease.

Treatment Treatment for symptomatic internal hemorrhoids varies from simple reassurance to operative hemorrhoidectomy [see Table 1]. Treatments are classified into three categories: (1) dietary and lifestyle modification; (2) nonoperative or office procedures; and (3) operative hemorrhoidectomy. All patients with grade 1 or 2 hemorrhoids and most patients with grade 3 hemorrhoids should be

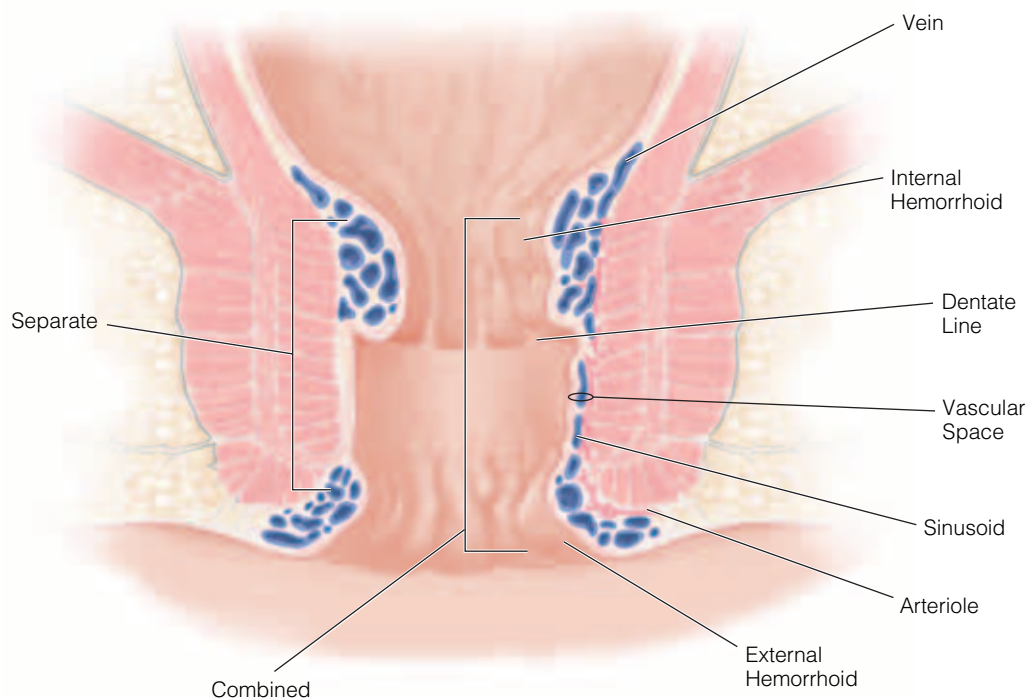


Figure 2 Separate external and internal hemorrhoids are seen on the left and a combined internal-external hemorrhoidal complex is seen on the right.

Table 1 Treatment Alternatives for Hemorrhoids

Treatment	Internal (Grade)				External
	1	2	3	4	
Diet modification	X				
Sclerotherapy	X	X			
Infrared coagulation	X	X	(X)		
Rubber band ligation	(X)	X	X		
Stapled anoplasty (PPH)		X	X		
Excisional hemorrhoidectomy		(X)	X	X	X

PPH = procedure for prolapsing hemorrhoids; (X) = selected patients.

treated initially with efforts to correct their constipation. Recommendations should include a high-fiber diet; liberal water intake (six to eight 8-ounce glasses of water daily); fiber supplements such as psyllium, methylcellulose, calcium polycarbophyl, or gum; or stool modifiers such as polyethylene glycol. Sitz baths are recommended for their soothing effect and ability to relax the anal sphincter muscles. Topical creams may reduce some associated symptoms but do not affect the hemorrhoids themselves. Suppositories are avoided as they deliver medication to the rectum and not the anus. Patients are instructed to avoid prolonged trips to the bathroom, and reading should be performed only when sitting atop the toilet lid. If these initial measures are not effective,

a number of nonoperative therapies are available. Current recommended options include rubber band ligation, infrared photocoagulation, and sclerotherapy.

Rubber band ligation is currently the most common method in use for the outpatient treatment for hemorrhoids.⁵ One to three bands are applied. Complications of hemorrhoid banding include bleeding, pain, thrombosis, and life-threatening perineal sepsis.^{5,6} The cardinal signs of perineal sepsis are significant pain, fever, and difficulty urinating. Patients developing any of these symptoms require urgent evaluation and treatment with broad-spectrum antibiotics and selective débridement of any anal necrotic tissue.

Hemorrhoidal banding is successful in two thirds to three quarters of all individuals with first- and second-degree hemorrhoids.² Repeated banding may be necessary to resolve all symptoms. Rarely, individuals fail to respond whatsoever or cannot tolerate banding. Some of these patients will respond to infrared coagulation, whereas others may require formal hemorrhoidectomy.

The infrared photocoagulator generates infrared radiation, which coagulates tissue protein and evaporates water from cells.⁷ The amount of destruction depends on the intensity and the duration of application. An anoscopic examination is performed, and the infrared coagulator is applied to the apex of each hemorrhoid at the top of the anal canal [see Figure 3]. A duration of 1 to 1.5 seconds is used to treat each hemorrhoid bundle three to four times. The infrared coagulator was designed to decrease blood flow to the region and is less

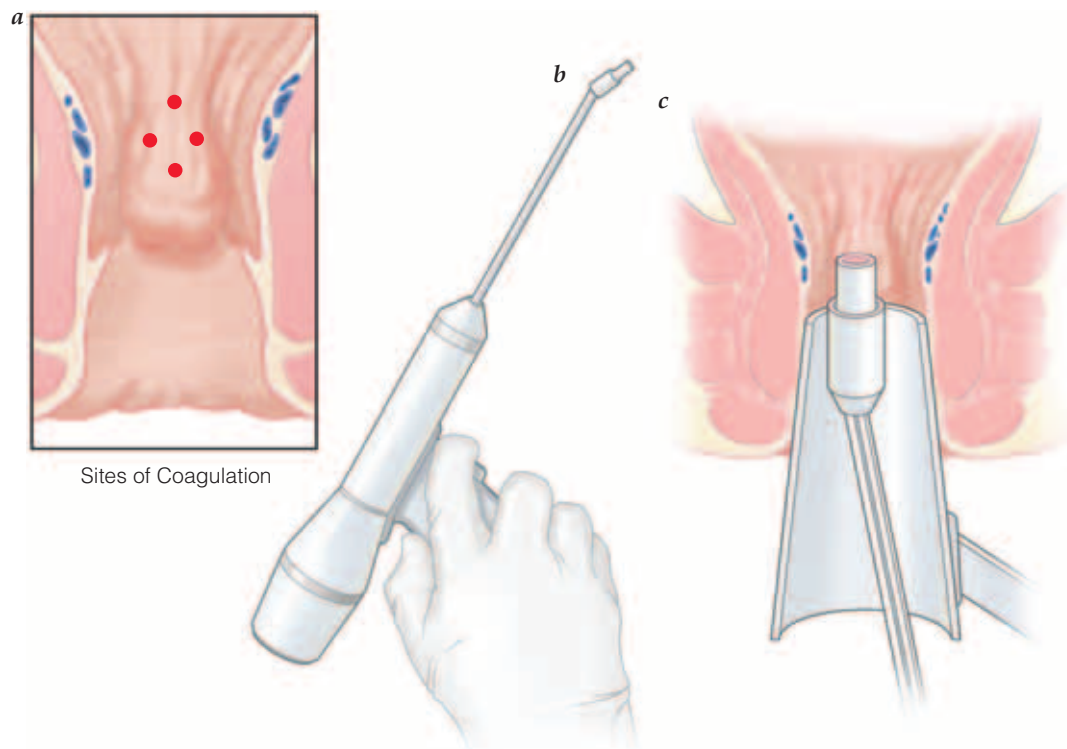


Figure 3 The infrared coagulator is applied to each hemorrhoid bundle three or four times for 1 to 1.5 seconds at a time.⁴

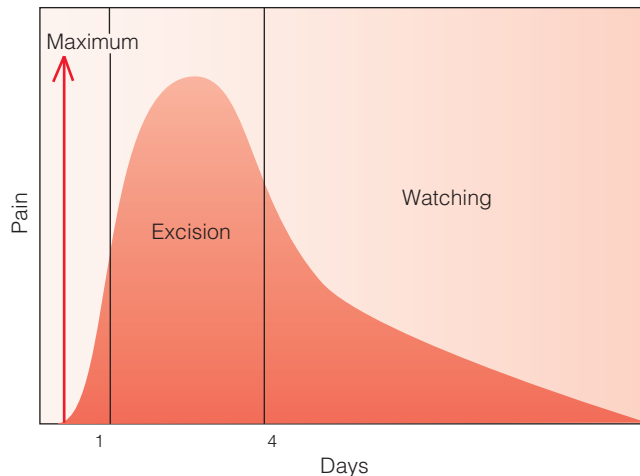


Figure 4 The infrared photocoagulator creates a small thermal injury. Thus, several applications are required for each hemorrhoidal column.⁴

effective in treating large amounts of prolapsing tissue. It is most beneficial in grade 1 and small grade 2 hemorrhoids. It is slightly less painful than rubber banding. This technique is especially useful in patients who fail banding secondary to pain or have symptomatic internal hemorrhoids that are too small to band.

Sclerotherapy was common in the past but with the advent of rubber band ligation is currently less popular. The technique involves injection of an irritating material into the anorectal submucosa to decrease vascularity and increase fibrosis. Injecting agents include phenol in oil, sodium morrhuate, or quinine urea.² The hemorrhoids are identified with an anoscope, and the injecting agent is infiltrated at the apex of the hemorrhoid (proximal anal rectal ring). This occasionally produces a dull ache lasting 24 to 48 hours but rarely results in significant bleeding or other complications. There have been rare reports of misplacement of the sclerosing agent resulting in significant perianal infection and fibrosis.

A meta-analysis comparing a variety of modalities used to treat hemorrhoids found that rubber band ligation was better than sclerotherapy for grade 1 to 3 hemorrhoids.⁸ Patients who were treated with sclerotherapy or infrared coagulation were more likely to require further treatment than those treated with rubber band ligation. Hemorrhoidectomy should be reserved for patients in whom rubber band ligation or infrared coagulation fails or who have associated external hemorrhoidal disease.

Various types of hemorrhoidectomies have been developed throughout the years, but they are all associated with similar basic principles. These include decreasing blood flow to the anorectal ring, removing redundant hemorrhoidal tissue, and fixation of redundant mucosa and anoderm.⁹ Details of the various procedures (Milligan and Morgan [open], Ferguson [closed], or procedure for prolapsing hemorrhoids) are described elsewhere [see 5:37 *Anal Procedures for Benign Disease*].^{10,11}

External Hemorrhoids

External hemorrhoids are asymptomatic except when secondary thrombosis occurs. Thrombosis may be the result of

defecatory straining or extreme physical activity, or it may be a random event.¹ Patients present with acute onset of constant anal pain and often report a sensation of sitting on a tender marble. The physical examination identifies the external thrombosis as a purple mass at the anal verge. The treatment is dependent on the patient's symptoms [see Figure 4].⁴ In the first 24 to 72 hours following the onset of thrombosis, the pain increases, and excision is warranted. After 72 hours, the pain generally diminishes, and expectant treatment is all that is necessary. Patients should be advised that some drainage may occur. If operative treatment is chosen, the entire thrombosed hemorrhoid is excised under local anesthesia. Incision and drainage of the clot is avoided as this often results in rethrombosis and worsening symptoms.

ANAL FISSURE

An anal fissure is a tear or split in the anoderm just distal to the dentate line.¹² Fissures are characterized as acute or chronic. An acute fissure is generally caused by the mechanical force of a large, hard bowel movement being passed through an anal canal too small to accommodate safe, easy passage (although diarrhea can also cause anal fissures). These forces usually cause a split to occur in the posterior midline (90% of the fissures in females and 99% of fissures in males are located posteriorly). Decreased local blood flow or increased mechanical stress may account for these fissures' propensity to occur posteriorly.¹³ Repeated injury (e.g., from hard or watery bowel movements) can result in development of a chronic fissure.

Symptoms associated with anal fissures include anal pain and bright red rectal bleeding associated with bowel movements. The pain is usually described as a knifelike pain or tearing sensation, and the associated anal sphincter spasm may persist for several hours following each bowel movement. The bleeding is usually minor, red in color, and seen mainly on the toilet paper. Physical examination is difficult because the patient has an extremely tender anus and is fearful. Often visual inspection with gentle eversion of the anoderm in the posterior midline is all that is required. Physical findings include an approximately 1 cm split in the anoderm in the posterior midline just distal to the dentate line. In

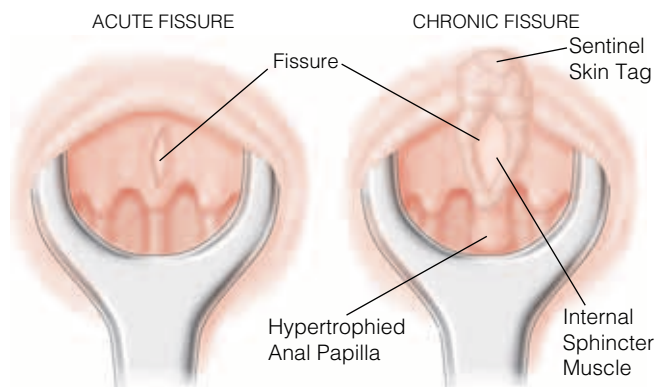


Figure 5 Chronic anal fissures, as opposed to acute fissures, are characterized by hypertrophy of the anal papilla, a sentinel skin tag, rolled skin edges, and exposed internal anal sphincter muscle.

chronic fissures, the classic triad may be present: hypertrophy of the anal papilla, anal fissure, and sentinel skin tag [see Figure 5]. Once an anal fissure has been diagnosed, further examination is very painful, unrewarding, and unnecessary. More extensive investigations can be performed after the fissure has healed.

Multiple fissures, or fissures occurring away from the anterior or posterior midline, are unusual and should raise suspicion for other problems as described in Figure 6.

Acute fissures are usually present for less than 4 to 6 weeks and are usually treated nonoperatively. Fiber supplements, stool softeners, and generous intake of water, along with sitz baths and local anesthetic ointments, improve symptoms rapidly and usually result in complete healing. Anal suppositories are avoided as they are painful and rest in the rectum rather than the anal canal.

Chronic fissures have been present for longer periods (greater than 4 to 6 weeks) and usually have an associated hypertrophied papilla and skin tag, rolled skin edges, and exposed internal anal sphincter muscle at the base of the fissure. Chronic fissures respond less successfully to nonoperative measures. The most common surgical procedure is a lateral internal anal sphincterotomy.¹⁴ In this procedure, the internal sphincter distal to the dentate line is cut in a lateral aspect of the anal canal. This allows for relaxation of the forces keeping the fissure from healing and results in cure in 95 to 98% of patients. Complications of sphincterotomy include incontinence to flatus (0 to 18%), soiling (0 to 7%), fecal incontinence (0 to 0.17%), and miscellaneous (0 to 7%).¹⁴

To avoid an operation and the possibility of complications, several alternatives have been proposed.¹⁵ On the theory that a fissure is actually an ischemic ulcer of the anoderm, topical

nitroglycerin (0.2% NTG) ointment has been used with success rates varying from 48 to 78%. The actual dosing is limited by its side effects, which may occur in up to 88% of patients. Headaches are the predominant complaint, but dizziness, lightheadedness, and hypotension may also occur. Caution must be exercised with this therapy in patients on cardiac medications and those with sensitivities to nitrates. A meta-analysis comparing topical NTG with sphincterotomy demonstrated that sphincterotomy is superior to topical NTG in the healing of chronic fissures.¹⁶

Nifedipine, a calcium antagonist, has been applied topically in a 2% nifedipine ointment, with results similar to those of NTG but with fewer side effects. Caution is recommended for cardiac patients. One multicenter study reported a 95% complete healing rate after 21 days of treatment.¹²

Botulinum toxin has been reported to facilitate the healing of fissures in 78 to 90%, with an 8% recurrence rate in 6 months.^{15,17} The toxin, produced by the bacterium *Clostridium botulinum*, acts by inhibiting the release of acetylcholine at the presynaptic membrane. As a result of blocked neurotransmission, spasms and contractions of the sphincter mechanism are diminished or eliminated. Injections of 2.5 to 50 units are administered in two to four sites in the internal sphincter at the level of the dentate line.¹⁸ Although it still takes days for the fissure to heal, pain relief is generally noted within 24 hours. Postinjection incontinence is rare, but an 8% recurrence rate has been reported.¹² The major drawback is the cost of the toxin, which may be \$400 per 100-unit vial.

None of these alternatives has received a Food and Drug Administration indication for the treatment of anal fissures. An algorithm for the management of anal fissures is presented in Figure 7.

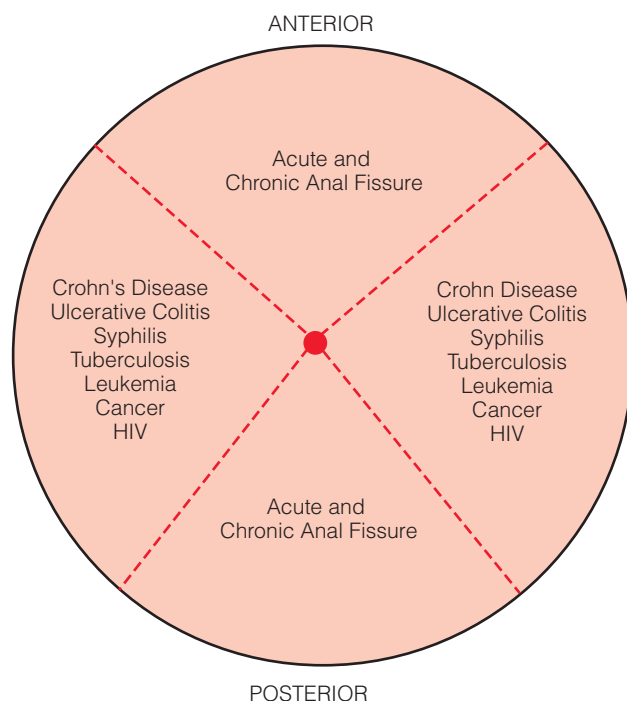


Figure 6 The location of anal fissures suggests their cause.⁴

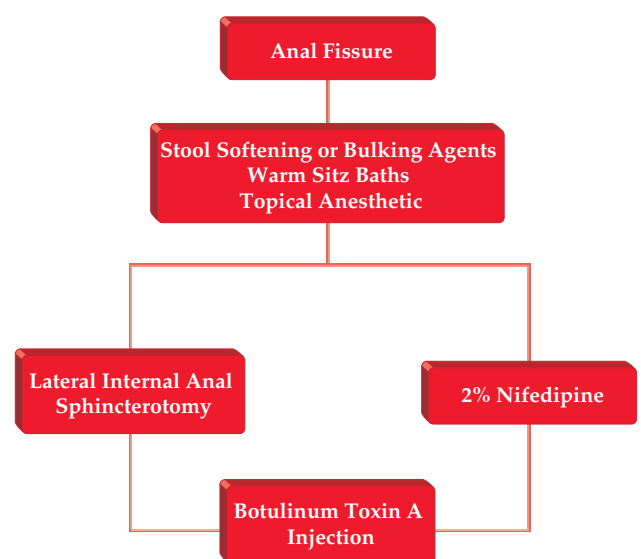


Figure 7 Algorithm for the management of anal fissures.

ANORECTAL ABSCESS

Anorectal abscesses are the result of local, walled-off infections of a cryptogenic origin.^{18,19} That is, they begin as infections in the anal glands that surround the anal canal and empty into the anal crypts at the dentate line. The ducts leading to and from these glands are thought to become obstructed as a result of feces or trauma, and a secondary infection develops that follows the path of least resistance, resulting in an anorectal abscess.

Abscesses are characterized as perianal, ischiorectal, supralevator, or intersphincteric [see Figure 8]. Perianal abscesses are the most common; together with ischiorectal abscesses, they account for more than 90% of perianal infections. Perianal abscesses occur in the perianal space immediately adjacent to the anal verge. Ischiorectal abscesses are larger and often more complex than their perianal counterparts, and they usually present as a tender buttock mass. Supralevator abscesses occur above the levator ani muscles, present with poorly localized pain, and are exceedingly rare. Intersphincteric or intermuscular abscesses occur in the plane between the internal and external sphincters, high within the anal canal. The location of an abscess is important as it dictates subsequent therapy.²⁰

Regardless of their location, anorectal abscesses are associated with constant perianal pain. Accompanying symptoms may include fever, chills, and malaise. In rare cases, systemic toxicity may be evident. History reveals a gradual onset of rectal pain that progressively increased until the time of presentation. Occasionally, spontaneous drainage decompresses the abscess, and the patient presents with a purulent discharge.

Again, visual inspection of the perineum often clinches the diagnosis. A fluctuant, erythematous, tender area identifies the abscess. In the rare case of a supralevator or intersphincteric abscess, there may be no external manifestations, and a tender mass on digital examination above the anal canal, adjacent to the rectal ampulla (supralevator abscess), or within the anal canal (intersphincteric abscess) provides the clue to diagnosis.

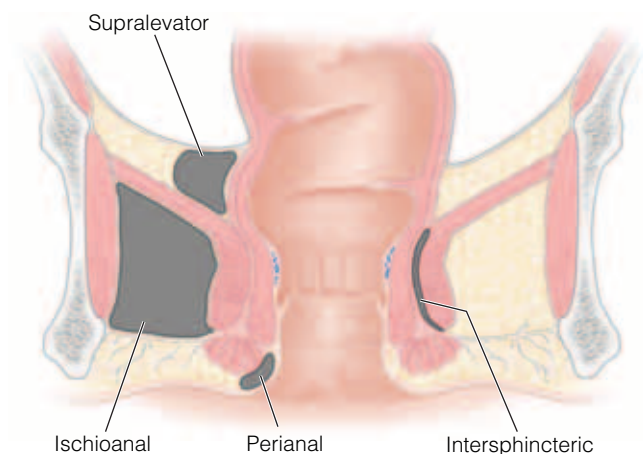


Figure 8 Anorectal abscesses are classified according to the space in which they develop.

The treatment for anorectal abscesses is adequate drainage performed either in the office, the emergency room, or the operating room.¹⁸ Most abscesses can be drained in the office, but recurrent or complex abscesses, abscesses in immunosuppressed hosts (including some diabetics), and intersphincteric or supralevator abscesses are more appropriately drained in the operating room.

Adequate drainage is essential and may be established in several ways. One method is to place a catheter (such as a 10 to 16 French de Pezzer catheter) through a small stab incision.¹⁸ This allows the pus to drain through the catheter as the cavity closes down. After the cavity closes down, the catheter is removed, and the small remaining cavity heals. The incision for the catheter is placed over the fluctuant area, as close to the anal canal as possible. This results in a shorter fistula tract if the abscess does not heal completely. A second drainage option involves creating a larger elliptical incision.²⁰ Unroofing the abscess cavity allows it to heal without the need for packing. A small incision should be avoided as it requires painful packing to keep the skin open until the abscess cavity heals.

The most difficult and potentially quite serious abscess to diagnose and manage is a deep postanal space abscess. Deep postanal space abscesses are caused by fistulization from the posterior anal canal, usually in the bed of a chronic posterior fissure. The patient is impressively uncomfortable and febrile, but there is no apparent sign of a problem perianally. A simple digital examination pushing posteriorly toward the coccyx and deep postanal space is extremely uncomfortable and leads one to suspect the diagnosis. The patient should be taken to the operating room and anesthetized. The deep postanal space is often felt on digital examination to be bulging. The diagnosis is confirmed by aspirating this space with an 18-gauge needle. Once the diagnosis is confirmed, then an incision is made in the perianal skin posterior to the anal verge and deepened into the space. The space is adequately drained. In selected patients, a cutting seton is placed from the primary site in the posterior anal canal directly into the deep postanal space abscess. Any horseshoeing is dealt with using counterincisions.

Following adequate drainage, antibiotics are rarely needed. Patients should be discharged with fiber supplements (stool softeners), pain medication, and instructions for sitz baths two to three times daily.

FISTULA IN ANO

An anal fistula is a communication from the anal canal to the perianal skin. The fistula usually begins in a crypt at the dentate line and follows a course between the internal and external sphincters (the most common location), resulting in an ischiorectal abscess, or above the sphincters, leading to a supralevator abscess.^{18,20} Following acute drainage of an abscess, one of three things may occur if a fistula is present: (1) the fistula will heal spontaneously, and the patient will experience no further symptoms; (2) the abscess may heal only to recur in the future; or (3) the abscess may heal, leaving a chronic draining anal fistula or fistula in ano. Only the third scenario is discussed here.

Following drainage of one or more abscesses, a fistula is usually associated with chronic serosanguineous to

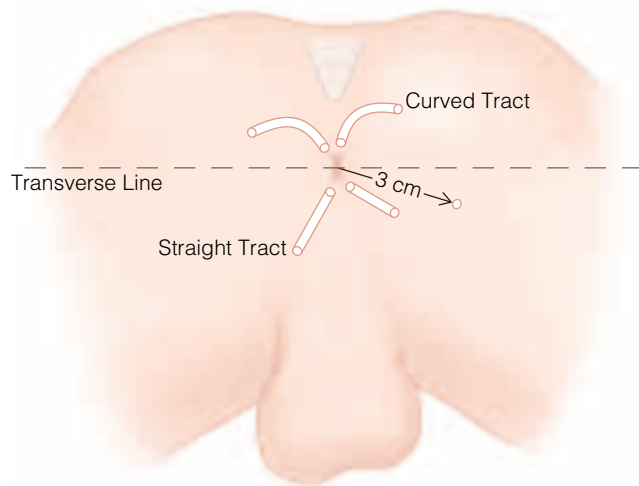


Figure 9 Goodsall's rule. An external opening seen posterior to a line drawn transversely across the perineum will originate from an internal opening in the posterior midline. An anterior opening will originate in the nearest crypt (for fistulas within 23 cm of the anus).⁴

seropurulent drainage. As long as the fistula remains open and draining, patients report little pain. But should the fistula close externally, an anorectal abscess may develop. Physical examination reveals a 2 to 3 mm opening in the perianal skin, with surrounding induration. Often a fistula tract may be palpated as a firm cord running between the external opening and the anal canal. The relationship of the external opening to the internal opening is suggested by Goodsall's rule [see Figure 9]. Fistulas are classified according to their relation to the anal sphincters [see Figure 10].²¹

Essentially, all chronic fistulas require surgical treatment. The most common option consists of unroofing the entire fistula tract (fistulotomy) and leaving the wound open to heal secondarily. Fistulas that course through significant amounts of sphincter muscle, are anterior in women, or are associated with inflammatory bowel disease or weakened sphincter muscles cannot be opened entirely because incontinence will result. These fistulas may be partially opened, leaving the anal musculature intact, which is encircled with a seton.²⁰ A seton is a nonabsorbable suture (e.g., 0 silk) or elastic suture (Silastic vessel loop) that is inserted into the fistulous tract, and the ends of the suture or elastic are tied with multiple knots to

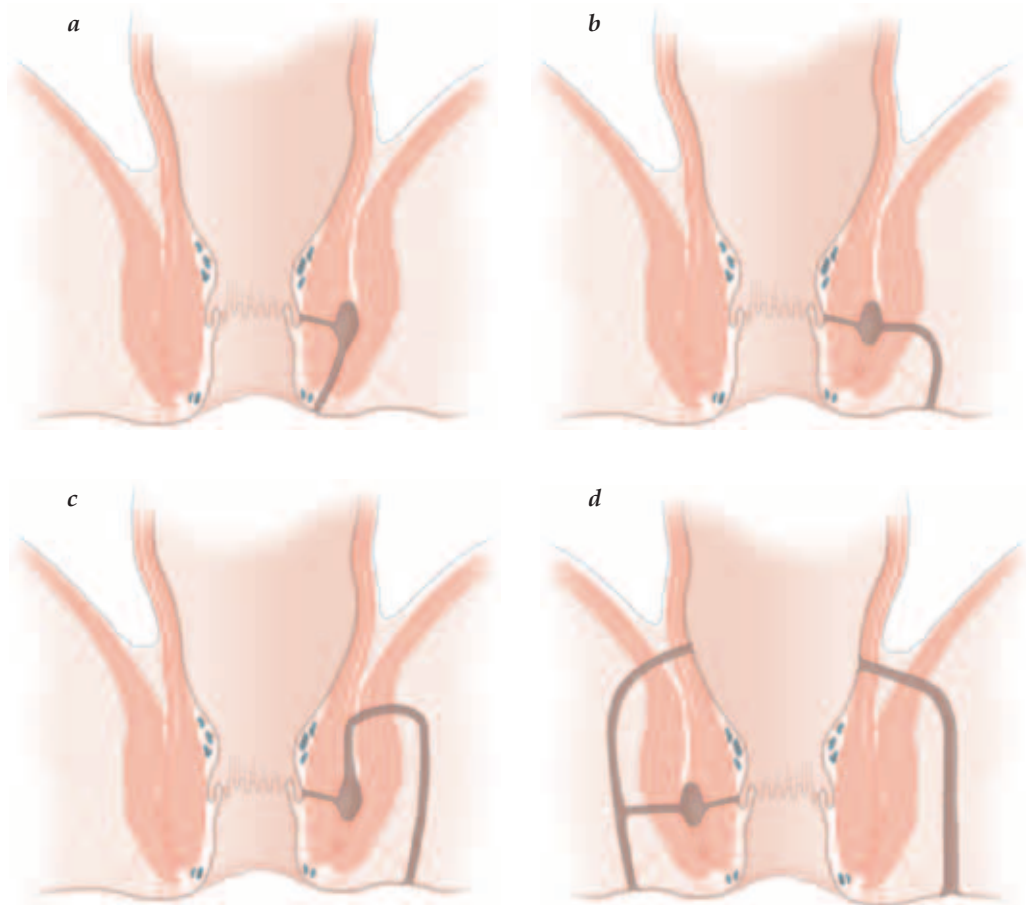


Figure 10 Fistula in ano is classified on the basis of its relation to the anal sphincter muscles. Shown are (a) intersphincteric fistula, (b) transsphincteric fistula, (c) suprasphincteric fistula, and (d) extrasphincteric fistula.

create a handle for manipulation. The seton may serve to facilitate drainage or stimulate fibrosis adjacent to the sphincter muscle to prevent gaping of the sphincter at a secondary stage repair. The seton allows delineation of the amount of remaining muscle. Although some surgeons sequentially tighten the seton (cutting seton), the author avoids this technique because of the resultant patient discomfort. A third option involves closing the internal fistula opening with an advancement flap.²² Advancement flap repairs result in high success rates, with minimal effects on continence. Additional, newer options include an anal fistula plug or a lateral internal anal fistula transaction (LIFT) procedure.²³

PILONIDAL DISEASE

The term *pilonidal disease* is derived from the Latin “pilus” (hair) and “nidus” (nest).²⁴ The term denotes a chronic subcutaneous infection and foreign body reaction to hairs embedded in the skin or abnormalities of hair follicles in the natal cleft.²⁴

Pilonidal disease is more common in men, between puberty and 40 years of age, and obese patients.²⁴ Pilonidal disease has three common presentations. Nearly all patients have an episode of acute abscess formation. When this abscess resolves, either spontaneously or with medical assistance, many patients will develop a pilonidal sinus. Although most sinus tracts resolve, a small minority of patients will develop chronic disease or recurrent disease after treatment.

Physical examination typically reveals one or more small (1 to 2 mm) dermal pits at the base of the intergluteal cleft [see Figure 11]. Tracking from the pits (usually in a cranial and lateral direction) will appear as areas of induration. With an associated abscess, the diseased area may be tender and erythematous, and draining pus may be evident. The more

extensive the disease is, the more prominent the findings are. Treatment methods vary for each stage in pilonidal disease.

Abscesses must be drained. Incision and drainage in an office setting using local anesthesia resulted in healing in 60% of patients.²⁵ Up to 40% of acute pilonidal abscesses treated by incision and drainage form a chronic sinus that requires additional treatment. A review of articles published in the last 30 years on the treatment of pilonidal disease divided the procedures and analyzed them by broad category.²⁶ Closed techniques (coring out follicles and brushing the tracts) required shaving of the area but could be performed on an outpatient basis. The mean healing time was about 40 days, and recurrence rates were slightly higher than with other forms of treatment. Laying open (unroofing) the tracts with healing by granulation resulted in average healing times of 48 days and required frequent outpatient dressing changes. The incidence of recurrent sinus formation was less than 13%. Wide and deep excision of the sinus alone resulted in an average healing time of 72 days and recurrent rates similar to those for simple laying open of the sinus with wound granulation. Excision and primary closure resulted in wound healing within 2 weeks in successful cases (19 days overall). However, up to 30% of patients failed primary wound healing, and the average recurrence rate for these experienced authors was 15%. A nonoperative or conservative approach has been suggested as an alternative to conventional excision.²⁷ In this approach, meticulous hair control by natal cleft shaving, improved perineal hygiene, and limited lateral incision and drainage for treatment of abscess have resulted in a significant reduction in the number of excisional procedures and occupied-bed days.

Even with proper treatment, a small subgroup of patients are left with persistent, nonhealing wounds. A number of more aggressive treatments have been described to treat complex or recurrent disease, including wide excision and split-thickness skin grafting, cleft closure, and excision and closure with various types of flaps.^{25,28} These flap techniques as a group have resulted in primary healing in less than 15 days in 90% of cases.²⁵ There are, however, disadvantages to these aggressive approaches. Nearly all of these techniques require hospitalization and general anesthesia. In addition, up to 50% of those procedures requiring skin flaps for wound coverage or closure develop loss of skin sensation or flap tip necrosis.

The author recommends drainage of acute abscesses followed by measures to keep the cleft free of hair. Chronic disease is managed by unroofing or excision and closure in selected patients. Flap procedures are reserved for extensive, recurrent, and complex disease.²⁴

HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa is a chronic, recurrent inflammatory process involving the apocrine glands of the axilla, groin, perineal, and perianal regions.²⁹ The disease can become quite painful and debilitating, resulting in chronically draining wounds and sinus tracts.³⁰ Occlusion of follicles and abnormalities of apocrine ducts are considered etiologic factors.

Medical management may afford temporary relief of symptoms; however, most patients will eventually require surgical therapy.³¹ Incision and drainage or unroofing of sinuses may provide relief in selected patients but should be reserved for

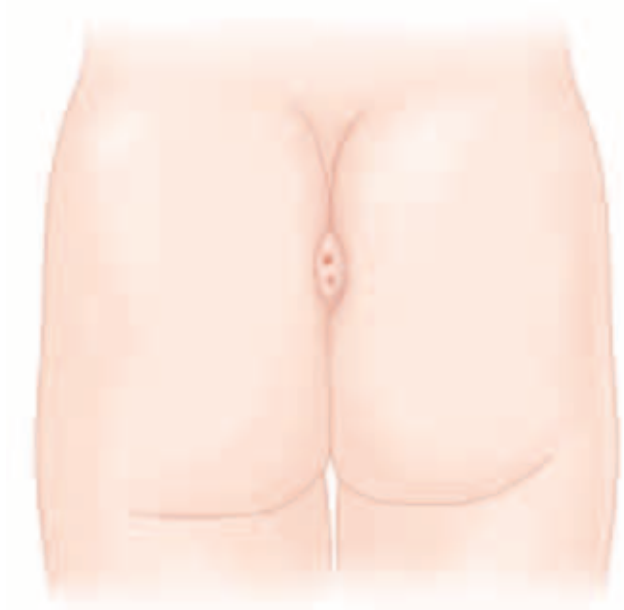


Figure 11 Patients with pilonidal disease generally have one or two dermal pits in the intergluteal cleft, often associated with a sinus and an abscess.

early and acute disease. Local excision will provide adequate control of symptoms; however, greater than 50% recurrence can be anticipated. Wide excision with secondary granulation of perineal wounds will provide the most definitive therapy and can be accomplished safely.³⁰ Perianal disease can more often be managed with local excision alone as recurrence rates of perianal disease are considerably lower than for perineal disease.

PRURITUS ANI

Pruritus ani is a dermatologic condition of the perianal skin characterized by a symptom complex of uneasiness or itching in the perianal area.^{31,32} Factors predisposing the anal area to irritation are poor perianal hygiene (incontinence, diarrhea, excessive hair), excessive moisture, irregularities of the perianal skin (hemorrhoids, fistula, previous surgery), skin hypersensitivity, diet, decreased resistance to infection, and injury to the perianal skin.³² These multiple possible etiologic factors are what can make pruritus ani refractory to treatment. Some patients improve only after the offending agent or agents are identified and specific therapy is instituted. Fortunately, many patients' symptoms improve by the application of non-specific treatments.

A thorough history and physical examination are necessary to suggest possible causes of pruritus. Initial inspection of the perianal skin should be conducted with bright lighting and gentle retraction of the buttocks. Characteristic findings include erythematous or thickened perianal skin [see *Figure 12*].



Figure 12 A characteristic finding in idiopathic pruritus ani is erythematous or thickened perianal skin.⁴

The thickening results in a pale, whitish appearance with accentuation of the radial anal skin creases. In addition, the skin may be excoriated or ulcerated, which, when combined with thickening, is referred to as lichenification. Occasionally, the skin may be so excoriated as to present as a large, coalescing, weeping ulcer. Digital rectal examination should be performed to assess anal sphincter competence both at rest and during maximal squeeze. Anoscopy and proctosigmoidoscopy can be performed following the administration of an enema.

The principles of treating pruritus ani are simple. If an inciting cause can be identified, it should be eliminated or corrected. Frequently, the cause of pruritus is elusive, but most patients can be managed using several simple principles. Patients should keep the perianal area dry and avoid further trauma to the perianal area. The perianal area should be gently washed, never scrubbed. After showering, the area should be patted dry or dried using a hair dryer on a low heat setting. Following bowel movements, the anus should be cleaned using moistened toilet paper. Excessive rubbing or wiping should be discouraged. Scratching or rubbing the anal area damages the perianal skin, making it more susceptible to irritation.

Patients should be instructed to avoid irritating foods and drinks such as tomatoes, peppers, citrus fruits and juices, coffee, colas, beer, alcoholic beverages, milk, nuts, popcorn, or any other foodstuffs found to be associated with increased gas, indigestion, or diarrhea. After 2 weeks, eliminated food items can be reintroduced one at a time in an attempt to identify the offending agent more specifically.

A regular bowel habit should be maintained using fiber supplementation or a high-fiber diet. Patients should be instructed to eschew all proprietary creams, lotions, or emollients. If prescribed and supervised by a physician, a hydrocortisone cream may be applied sparingly to the affected area for a period of a week or less to initiate control of symptoms. Occasionally in refractory cases, a candidal yeast infection exists, and a trial of antifungal lotion, solution, or powder is worthwhile. In general, the principles of treating pruritus ani are to establish and maintain an intact, healthy, clean, and dry perianal skin. In cases that fail to improve, fungal and viral cultures and even biopsy may be necessary to exclude an infectious or neoplastic cause.

SOLITARY RECTAL ULCER SYNDROME

Solitary rectal ulcer syndrome (SRUS) is a clinical condition characterized by rectal bleeding, copious mucous discharge, anorectal pain, and difficult evacuation.³² Despite its name, with this condition, patients can have single, multiple, or no rectal ulcers.³³ When present, the ulcers usually occur on the anterior rectal wall just above the anorectal ring. Less commonly, they may occur from just above to 15 cm above the dentate line. Ulcers usually appear as shallow with a "punched out" gray-white base surrounded by hyperemia.³⁴

Cystica profunda (CCF) is a related benign condition characterized by mucin-filled cysts located deep to the muscularis mucosae. CCF is a pathologic diagnosis whose most important aspect is to differentiate it from colorectal adenocarcinoma. The etiology of these conditions remains unclear, but a common feature is chronic inflammation and/or trauma (internal intussusception or prolapse of the rectum, direct digital trauma, or the forces associated with evacuating a hard stool).

An endoscopic evaluation of the distal colon and rectum will reveal the lesions described above. The differential diagnosis of both CCF and SRUS includes polyps, endometriosis, inflammatory granulomas, infectious disorders, drug-induced colitides, or mucus-producing adenocarcinoma. Differentiation among these entities is possible with an adequate biopsy.

Treatment is directed at reducing symptoms or preventing some of the proposed etiologic mechanisms. Conservative therapy (high-fiber diet, lifestyle changes, and biofeedback) will reduce symptoms in most patients and should be tried first. Patients without rectal intussusception are offered biofeedback to retrain their bowel function. Pharmacologic therapy (antiinflammatory enemas or suppositories) has had limited success but is reasonable to try before embarking on surgery. If symptoms persist, a localized resection may be considered in selected patients. Patients with prolapse are considered for perineal procedures (mucosal or perineal proctectomy) and abdominal procedures (fixation or resection and rectopexy). Patients without prolapse may be offered excision, which varies from a transanal excision to a major resection with coloanal pull-through. Surgeons have been understandably hesitant to offer surgical therapy for this benign condition, and the results are often unsatisfactory.^{35,36}

Malignant Conditions

Anal neoplasms are uncommon, with an incidence one twentieth that of rectal adenocarcinoma or 1.5 to 4% of large bowel cancers.²⁸ Current statistics indicate that this incidence is increasing, and the management of these tumors has recently undergone significant changes.

ANATOMY

For clinical purposes, the anus can be divided into two areas: the anal canal and the anal margin [see Figure 1]. The anal canal runs from the anorectal junction (top of the anal sphincter muscles) to the intersphincteric groove (approximately 2 cm distal to the dentate line). Thus, it corresponds to the internal sphincter. The lining of this portion of the anus is formed by transitional epithelium, which contains elements of both columnar and squamous epithelium above the dentate line and squamous epithelium distal to the dentate line.

The anal margin runs from the intersphincteric groove to approximately 5 cm on the perineum. This area is covered by nonkeratinizing squamous epithelium, which changes to keratinizing squamous epithelium at the anal margin's outer border with the perineal skin.

ANAL CANAL

Epidermoid Carcinoma

Epidermoid carcinomas are the most common forms of anal canal neoplasms.³⁷ On histologic review of these neoplasms, 70% are found to be squamous cell neoplasms, 25% are basaloid neoplasms, and 5% are mucoepidermoid. Clinically, the different histologic types act in a similar manner.

The lymphatic drainage of the anus follows the arterial vessels. Thus, metastatic anal disease can spread in three different directions. Superiorly, this includes the pararectal and superior hemorrhoidal nodes; laterally, the internal iliac

nodes; and inferiorly, the inguinal and external iliac nodes. For prognostic purposes, anal canal cancers have been grouped into four stages: stage 1 tumors are confined to the sphincteric mechanism, stage 2 have extended into the perirectal fat, stage 3 have involved lymph nodes, and stage 4 have distant metastases. Other staging systems have been described, and the TNM system has been adopted by the American Joint Committee on Cancer [see Table 2]. Unfortunately, lymph node involvement is difficult to determine in the absence of surgical specimens.

Diagnosis Patients with anal cancer usually present with bleeding per rectum and pain. The bleeding is red and usually more constant than that associated with hemorrhoids.³⁸ The pain is less severe than with an acute fissure and more constant. An occasional patient will also complain of an ulcerated or mass lesion of the anus. Additional questions help evaluate these symptoms and exclude other differential diagnoses.

The physical examination is helpful in making the diagnosis and is essential to determine the clinical stage of disease. Anal cancers are within reach of the examining finger and are hard, irregular, and usually ulcerated [see Figure 13]. The exact location and size of the lesion must be documented. This includes the vertical and horizontal diameters of the lesion and the height above the anal verge. The anatomic location (e.g., anterior versus posterior and right or left) should also be noted. An assessment of the lesion's fixity, relation to other structures, and status of the sphincteric muscles completes the perineal examination. In addition to an evaluation of the lesion, the patient should be examined for the presence of inguinal adenopathy.

Direct visualization of the anus and rectum is essential to exclude other lesions and allows biopsy of the lesion to confirm the clinical diagnosis. Anoscopy provides good exposure and is the least expensive method to examine the anal canal. After identification, the lesion should undergo biopsy. Several specimens should be obtained from the edges of the lesion. A local anesthetic is usually not required.

Table 2 Tumor Node Metastasis (TNM) Staging System for Anal Cancer

Stage	Description
T1	Carcinoma < 2 cm in diameter
T2	> 2 and < 5 cm in diameter
T3	> 5 cm in diameter
T4	Invading adjacent organ
N0	No regional node involvement
N1	Metastasis in perirectal lymph nodes
N2	Metastasis in unilateral iliac or inguinal nodes
N3	Metastasis in bilateral iliac or inguinal nodes
M0	No distant metastasis
M1	Distant metastasis



Figure 13 Anal cancer.

To assist in clinical staging, several modalities are currently available. Anorectal ultrasonography is being used with increased frequency and is helpful in assessing the depth of anal tumors and in identifying the presence and characteristics of lymph nodes. The difficulty remains with the identification of suspicious nodes. The quality of the examination depends on the operator, and further widespread experience is necessary.

Computed tomographic (CT) scans help assess the extent of the primary tumor and the presence of enlarged lymph nodes. A scan can determine the size and location of lymph nodes but, again, cannot accurately determine if the nodes contain tumor. This study can also evaluate the liver to exclude the presence of large hepatic metastases (greater than 1 cm). Magnetic resonance imaging (MRI) is also being used to stage anal cancer.

Treatment Anal cancer is currently treated by surgery and chemoradiotherapy. Surgical options include transanal excision and abdominoperineal resection (APR). For early lesions, local excision (transanal excision) is a valid consideration but must be limited to lesions that are well differentiated, less than 2 cm in diameter, and located in the distal anal canal. The procedure is similar to that described for early rectal cancers. Using this procedure in selected patients, the reported 5-year survival has ranged from 45 to 100%.^{39,40} An APR performed for anal cancer is similar to that described for rectal cancer, with the exception that a slightly wider margin of perineal skin is removed. This

procedure is used in patients who cannot undergo chemoradiotherapy or fail this therapy. The 5-year survival rate after this form of treatment averaged 50%, with a published range of 30 to 70%, and local recurrence ranged from 11 to 40%.^{39,41}

Inadequate results from surgery or radiotherapy alone led Nigro at Wayne State University to propose initial chemotherapy (5-fluorouracil [5-FU], mitomycin C) and radiotherapy followed by APR.³⁷ Subsequent experience demonstrated that chemoradiotherapy was curative in most patients, and the subsequent APR has been abandoned unless the tumor persists or recurs.

The reported experience with multimodality treatment for anal carcinoma continues to expand.^{37,42} The radiotherapy entails 30 to 60 Gy (given over 3 to 5 weeks) using apposed fields. Chemotherapy is given at the same time as the radiotherapy according to the following scheme: 5-FU (1,000 mg/m²/day) on days 1 to 5 and days 31 to 35 and mitomycin C (15 mg/m²) on day 1. Using an anoscope, the lesion site is inspected 4 to 6 weeks after the radiotherapy is completed, and a biopsy is performed on any abnormalities. Some providers will allow additional time after therapy to confirm complete clinical regression of the tumor before embarking on additional therapy. An APR, local excision, or additional chemoradiotherapy is offered to patients with residual disease following combined therapy.

Melanoma

Anorectal melanomas are rare; they account for 1% of all melanomas and 0.25 to 1% of anorectal tumors.⁴³ The mean age at occurrence is in the fifth decade; females are affected more frequently than males. The most frequent presenting symptom is bleeding, followed by an anal mass or pain. The lesions are usually elevated, and 34 to 75% will be pigmented.

These tumors are locally invasive and have a high metastatic potential. Because many patients present late, the reported 5-year survival rates range from 0 to 12%. The prognosis is related to tumor size, thickness, and clinical stage. Evaluation should include a biopsy and a search for metastatic disease (by CT of the abdomen, pelvis, and chest; liver function tests; chest x-ray evaluation; and bone scans). Special stains or electron microscopy may be required to confirm the diagnosis.

Surgery provides the only hope for cure. However, the small chance for cure and limited experience have led to controversy about the appropriate procedure. An APR has significant morbidity and mortality. Local excision has less associated morbidity. Reports have shown little difference in the mean survival rates following either procedure. Prophylactic lymphadenectomy is not indicated for clinically negative nodes but is helpful for clinically suspicious nodes. Radiotherapy and chemotherapy have demonstrated little benefit in this disease.

ANAL MARGIN

Premalignant Lesions

Premalignant lesions of the anal margin are uncommon and include Bowen disease and Paget disease. Bowen disease is an intraepithelial squamous cell carcinoma, and a few hundred

cases have been reported in the literature.⁴⁴ Paget disease is an even rarer intraepithelial adenocarcinoma, with approximately 300 cases of perianal disease reported in the surgical literature.⁴⁵ Patients with perianal Bowen or Paget disease commonly present with nonspecific complaints of anal itching, burning, or bleeding. Examination of the perineum in symptomatic patients usually reveals raised, irregular, scaly, brownish-red plaques with eczematoid features in perianal Bowen disease. In Paget disease, the lesions are well-demarcated eczematoid plaques that are either ulcerative and crusty or papillary. Less commonly, these lesions may have a gross appearance similar to that of other diseases (e.g., leukoplakia, squamous cell cancer, condylomata acuminata, dermatitis, eczema, downward spread of rectal carcinoma, or prolapsed hemorrhoids), making the diagnosis by inspection alone difficult. A significant percentage of patients will be diagnosed after pathologic evaluation of operative specimens.

The microscopic appearance of these perianal lesions is characteristic and readily confirms the diagnosis. An accurate diagnosis is important for prognostic and therapeutic reasons. The clinical course of Bowen disease has been relatively benign, with progression toward invasive carcinoma in 2 to 6% of cases. The incidence of subsequent nonsquamous malignancy is low. In Paget disease, progression into an invasive carcinoma has been reported to be as high as 40% in untreated lesions.⁴⁵ The incidence of associated malignancies in the reported series averaged 50 to 73%, and the mortality was high from this cancer despite aggressive therapy. The small number of reported patients with these perianal lesions has limited our understanding about prognosis.

Patients with Bowen disease are younger (average age 48 years) than those with Paget disease (average age 66 years). The sex distribution is equal for Paget disease patients, whereas in Bowen disease, there is a higher proportion of women. The incidence of an associated invasive malignancy is higher with Paget disease, and the prognosis is worse.⁴³

Patients with anal lesions that appear suspicious or fail to respond to conventional therapy within a month should undergo a biopsy. An adequate biopsy is essential both to confirm the diagnosis and to exclude an invasive carcinoma. A proper biopsy technique entails three or four full-thickness biopsies (i.e., including subcutaneous tissue) from the central portion and edges of the lesion. This can be easily accomplished with local anesthesia, a sharp punch biopsy, and fine-pointed scissors or a scalpel. If pathologic evaluation identifies a premalignant or potentially malignant lesion, the patient should undergo an evaluation to exclude an associated invasive cancer.

If evaluation demonstrates an invasive carcinoma without metastases, an aggressive approach is warranted to improve the historically poor prognosis associated with these diseases. For adenocarcinoma of the lower rectum, the author recommends an APR, and for an epidermoid anal cancer, chemoradiotherapy is suggested.

In the absence of invasive cancer, a local excision with clear margins has been recommended. The wound defect is either closed primarily, covered with a split-thickness skin graft (either at the initial operation or 3 to 4 days later), or allowed to heal by secondary intention. Wide excision of lesions, especially very large ones, can produce significant morbidity.

Therefore, the morbidity of large, wide excisions must be balanced against the low incidence of cancer development in patients who are monitored closely. In selected patients, the author currently recommends excision of gross lesions, followed by close follow-up.⁴⁶

Long-term follow-up is recommended to prevent recurrence of both perianal Bowen and Paget disease. However, the limited experience with this disease has hindered the development of a standardized follow-up regimen. An annual complete physical examination, proctosigmoidoscopy, and punch biopsy of any new lesion are performed. If a recurrence is found, it is excised with adequate clear margins using the methods described above.

Malignant Lesions

Squamous cell carcinoma of the anal margin acts in a manner similar to that of lesions occurring in other cutaneous areas of the body. The lesions appear as raised, hard, flat masses that may ulcerate. The appropriate therapy is wide local excision with clear margins.

Basal cell cancers of the anal margin are rare and appear as ulcerated masses. Nonspecific complaints include bleeding and pruritus. Wide local excision with clear margins is the treatment of choice.⁴⁶

Retrorectal Tumors

The retrorectal space is bounded by the rectum anteriorly, the sacrum and investing sacral fascia posteriorly, and the ureters, internal iliac arteries, and rectal stalks laterally.⁴⁴ The space extends cranially to the peritoneal reflection. Various classification schemes have been reported for retrorectal tumors. Most commonly, these tumors are broadly categorized as inflammatory, congenital, neurogenic, osseous, and miscellaneous [see Table 3]. Others have proposed benign versus malignant and congenital versus acquired.⁴⁷ With improved preoperative imaging and the widespread use of colonoscopy, most modern series exclude metastatic and/or locally advanced colorectal and genitourinary carcinomas from the category of retrorectal tumors. Likewise, inflammatory conditions that mimic primary tumors can usually (although not always) be diagnosed prior to surgical exploration. The most common or unique retrorectal tumors are discussed below.

LESIONS

Developmental Cysts

These lesions result from abnormal closure of the ectodermal tube (dermoid and epidermoid cysts) or sequestration of the developing hindgut (enterogenous cysts and cystic hamartomas).⁴⁸ Developmental cysts are always lined with epithelium, either squamous epithelium with (dermoid) or without (epidermoid) skin appendages or cuboidal, transitional, or columnar epithelium (enterogenous cysts and cystic hamartomas). Most often they are multilocular, and disorganized smooth muscle fibers can be identified surrounding their thin walls. The more common developmental cysts include dermoid, epidermoid, and enterogenous cysts (rectal duplication cysts). These lesions are usually benign and more common in females.

Table 3 Differential Diagnosis of Retrorectal Tumors

Congenital
Developmental cyst (epidermoid, dermoid)
Cystic hamartoma (rectal duplication)
Teratoma
Teratocarcinoma
Chordoma
Adrenal rest tumor
Anterior sacral meningocele
Inflammatory
Perineal or pelvirectal abscess
Endometriosis
Foreign body granuloma
Infectious granulomas
Diverticulitis
Crohn disease
Neurogenic
Neurofibroma
Neurilemoma
Ependymoma
Ganglioneuroma
Neurofibrosarcoma
Osseous
Osteoma
Osteogenic sarcoma
Ewing tumor
Chondromyxosarcoma
Giant cell tumor
Aneurysmal bone cyst
Miscellaneous
Metastatic carcinoma
Lipoma/liposarcoma
Hemangioendothelial sarcoma
Extra-abdominal desmoid
Plasma cell myeloma
Fibrosarcoma
Leiomyoma/leiomyosarcoma
Hemangioma
Endothelioma
Pelvic ectopic kidney

Teratoma and Teratocarcinoma

By definition, teratomas contain cellular elements derived from all three germ layers. They originate from totipotential cells that are abnormally sequestered during in utero development. Although the sacrococcygeal area is the most common

site for teratomas in newborns, de novo lesions in this region are rare in adults. Teratomas are classified as mature, immature, or malignant (teratocarcinoma). Mature teratomas contain recognizable epithelial and/or mesenchymal cells, whereas immature tumors are composed of primitive endoderm, mesoderm, or ectoderm. Malignant teratomas contain neoplastic cells of germ cell origin (e.g., choriocarcinoma, germinoma), as opposed to teratomas with malignant transformation, which contain malignant cells of somatic origin that have presumably degenerated. Only 4% of teratomas diagnosed at birth are malignant, whereas those found later in childhood tend to be very aggressive and associated with a poor prognosis.⁴⁹ Approximately 30% of adult teratomas harbor malignancy at the time of resection.

Chordoma

Chordomas arise from remnants of the embryologic notochord, a primitive streak running from the skull base to the pelvis and represented by the nucleus pulposus in normal adults. These are rare bony tumors, but approximately 50% of all chordomas are located in the pelvis and retrorectal space. They are the most common malignant tumor of this region. Chordomas are lobulated, gelatinous tumors that tend to be slow-growing but locally destructive. Intratumoral hemorrhage can create a cystic appearance, and a pseudocapsule is commonly present. The pathognomonic feature on microscopy is the presence of “physaliferous” cells, which are vacuolated and filled with mucous droplets. Although they may occur at any age, chordomas typically present in the sixth and seventh decades and are much more common in men.⁵⁰ Despite the rare tendency to metastasize, chordomas are difficult to treat for cure. Symptoms are typically delayed until the tumor reaches a large size, making resection with uninvolved margins extremely difficult.

Anterior Sacral Meningocele

These rare tumors consist of a congenital herniation of the dural sac through the sacrum. The lesions are commonly associated with other developmental abnormalities, such as spina bifida, tethered spinal cord, and genitourinary tract malformations. The sac communicates with the spinal canal and is filled with cerebrospinal fluid. Symptoms result either from local compression of other organs (e.g., the rectum, producing constipation) or by straining maneuvers causing sudden increases in the intracranial pressure (e.g., onset of headache with bowel movements). Treatment involves ligation of the neck of the dural sac prior to resection and typically can be accomplished through a posterior approach. Large anterior meningoceleles require an anterior approach with resection of the tumor followed by closure of the dural sac.

Neurogenic and Osseous Tumors

Tumors arising from pelvic nerve roots, peripheral nerves, or primary bony tumors can occur in the retrorectal space. Taken together, neurogenic and osseous tumors comprise between 20 and 30% of primary retrorectal tumors.⁵⁰ Two thirds of neurogenic tumors in this region are benign; however, even benign tumors that arise from the spinal cord can

produce devastating neurologic morbidity. The most common malignant neurogenic lesions are neuroblastomas, schwannomas, and ependymomas, whereas benign tumors include neurilemmomas and ganglioneuromas. Osseous tumors can derive from cartilage, bone, or fibrous tissue. They behave similarly to bony tumors in other anatomic locations, with sarcomas having a predilection for hematogenous spread to the lungs.

Miscellaneous

Carcinoid tumors of the retrorectal space are rare but have been described. Most represent direct extension or metastatic spread from rectal carcinoids. Retrorectal carcinoid tumors may also arise from the glandular cells present in rectal duplication or tailgut cysts.⁵¹ These lesions are potentially malignant and should be treated by local excision, typically using a perineal approach.

CLINICAL PRESENTATION

Retrorectal tumors are frequently asymptomatic, and they are often found incidentally during evaluation for unrelated physical complaints. Furthermore, even patients with symptoms directly referable to a retrorectal tumor may be initially misdiagnosed as having fistulae in ano; pilonidal cysts; perianal abscesses; psychogenic, posttraumatic, or postpartum pain; or proctalgia fugax. Patients may initially complain of constipation, paradoxical diarrhea, and frequent urge to defecate as the tumor causes compression of the adjacent rectum or pain (either pelvic discomfort or sciatic symptoms). Malignant tumors that invade the sacral plexus or nerve roots can lead to bowel and bladder incontinence or urinary retention.

In most cases, these lesions are palpable on digital rectal examination.⁵² The presence of a postanal skin dimple is suggestive of a developmental cyst. Most retrorectal tumors will feel soft and compressible, whereas teratomas may contain abnormal calcifications that are palpable. A tender mass is suggestive of either an infected developmental cyst or a primary perirectal abscess with supralelevator extension.

All patients with suspected retrorectal tumors should undergo complete colonoscopy. The rectal mucosa overlying a retrorectal tumor will appear normal, and larger lesions will demonstrate extraluminal compression of the rectum.

EVALUATION

Plain radiographs of the pelvis are typically normal unless a malignant tumor has produced bony destruction of the sacrum or rare, benign, bone-based lesions such as aneurysmal bone cysts, giant cell tumors, and osteochondromas are present. Teeth or small bone fragments may be visible in presacral teratomas. The “scimitar sign” (a concave sacral deformity suggestive of the curved sword) is characteristic of anterior sacral meningocele. Normal transrectal ultrasonography (TRUS) performed by an experienced surgeon effectively rules out a retrorectal tumor.

CT or MRI is the standard for the preoperative evaluation of retrorectal tumors. Either modality will demonstrate whether the lesion is cystic or solid and the extent of the lesion, but radiologists have difficulty in differentiating benign from malignant lesions.⁵⁰ Sixty percent of solid tumors are

malignant, whereas 90% of cystic lesions are benign. Thus, although certain characteristics on imaging may be suggestive of a benign pathology, imaging alone cannot obviate the need for surgical resection.

TREATMENT

In appropriate surgical candidates, all retrorectal tumors should be resected, even if asymptomatic.⁴⁸ A multidisciplinary approach involving colorectal surgeons, neurosurgeons, and possibly orthopedists is important. In general, preservation of at least unilateral S3 nerve roots typically allows normal bowel and bladder function following sacral resection.⁵¹ The surgical approach is based on preoperative imaging and expected extent of resection.

Biopsy of a retrorectal tumor prior to surgical resection should be avoided. Transrectal biopsy can lead to superinfection of cystic lesions, produce rapidly fatal meningitis in patients with anterior sacral meningocele, and seed needle tracts.⁴⁸

Perhaps the only indication for biopsy is to make a diagnosis in the patient who is not a candidate for surgery but may benefit from palliative radiation or chemotherapy.

Abdominal- or Perineal-Only Approaches

The perineal-only approach is typically reserved for smaller retrorectal tumors that lie mostly caudal to the S4 level, which are typically palpable on digital rectal examination. An abdominal-only approach may be used for high retrorectal tumors that do not involve the sacrum and lie above S4; however, most large lesions are best treated with a combined abdominoperineal approach, as discussed below.

For the perineal approach, the patient is placed in the prone jackknife position with the buttocks retracted laterally with tape. Either a transperineal or parasacral incision may be used. After the incision is made and muscular attachments to the coccyx and lower sacrum are divided, the coccyx can be dislocated and resected to facilitate further exposure and resection.

Once the coccyx has been disarticulated, the presacral space is readily accessible, and dissection of the tumor from the posterior wall of the rectum can proceed. Alternatively, further sacral disarticulation can be performed as needed. Extensive involvement of the rectal wall can necessitate en bloc proctectomy. Following tumor excision, a closed suction drain is placed in the retrorectal space and the muscles are reapproximated. For large tumors, closure of the pelvic floor with a gluteal flap (often in conjunction with a plastic surgeon) can aid in filling the residual tissue defect.

Combined Abdominoperineal Approach

For the combined approach, the procedure begins with the patient in either the supine or the modified lithotomy position, and the abdomen is opened using a low midline incision. The sigmoid colon is mobilized medially, and the inferior mesenteric artery is identified. Both ureters and the hypogastric nerves are also identified, swept laterally, and preserved. The retrorectal space is entered by incising the peritoneum in the posterior midline at the sacral promontory. The areolar plane between the mesorectal fascia and presacral fascia is

then sharply dissected, proceeding caudally until the tumor is encountered. The middle sacral vessels can be ligated, as can branches from the hypogastric arteries, to gain vascular control of the tumor and reduce bleeding during the deeper portions of the pelvic dissection and the subsequent perineal phase of the operation. The upper aspect of the tumor is then carefully dissected from the surrounding structures, typically, the presacral fascia posteriorly, the levators laterally, and the posterior wall of the rectum anteriorly. If the tumor is adherent to the rectum, an en bloc proctectomy should be performed, with most patients able to undergo restoration of intestinal continuity by coloanal or low-colorectal anastomosis. Once vision becomes limited in the deep pelvis and accurate planes of dissection can no longer be defined, the abdomen is closed, and the patient is either repositioned in

the prone jack-knife position or left in the modified lithotomy position for the perineal phase of the operation, which then proceeds as previously described. If en bloc proctectomy has been necessary and the resection completed in the prone jackknife position, the patient can be returned to the modified lithotomy position for creation of the anastomosis.

Adjuvant Therapy

The rarity and heterogeneity of retrorectal tumors make it difficult to demonstrate the efficacy of adjuvant treatment. Radiation therapy may have a role in palliation of unresectable presacral tumors.

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18 UPPER GASTROINTESTINAL ENDOSCOPY

*Jeffrey Marks, MD, FACS, and Jeffrey L. Ponsky, MD, FACS**

Since the beginning of the 1970s, flexible endoscopy of the gastrointestinal tract has been the dominant modality for the diagnosis of gastrointestinal disease. Over the same period, developments in technology and methodology have made possible the use of endoscopy to treat a host of conditions that once were considered to be manageable only by means of open surgical procedures. The concept of performing endoscopic surgery has become a reality with the advancement of endoscopic therapies to perform mucosal ablation, resection, and tissue approximation. In addition, investigation into intra-abdominal therapy has begun with the progression of natural orifice transluminal endoscopic surgery (NOTES). The tools created for both intraluminal and transluminal interventions will allow the endoscopist to continue to supplant surgical therapies for numerous gastrointestinal diseases. The integration of flexible endoscopic techniques into the armamentarium of the gastrointestinal surgeon permits a more multidimensional approach to the treatment of digestive disease. The modern surgeon must continue to stay abreast of these endoscopic advances to provide appropriate patient care.

Endoscope History

The flexible endoscope was initially developed in 1957 as an imaging device dependent on the delivery of light and transmission of the image along multiple bundles of chemically treated glass fibers. The image undergoes a series of internal reflections within each fiber, which are coated with low optical density glass to prevent escape of light as it is transmitted up the bundle. The endoscopist views the image through an eyepiece at the top of the instrument handle.¹ A teaching head could be fixed onto this eyepiece, allowing a second person to view the endoscopic image. With the advancement of early video camera systems, a video camera could be affixed to the scope eyepiece to transmit an image to a video monitor. Eventually, the video system was imbedded into the scope, allowing the progression from fiberoptic scopes to the videoendoscopes we use today. This has been the key component in the advancements in our ability to perform more involved therapies, educate physicians and endoscopic assistants, and obtain static and dynamic recorded data images for improved clinical management.

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Endoscope Structure

Although the basic structure of the endoscope is unchanged, there are now a wide variety of lengths and diameters of scopes, with an assortment of channel numbers and sizes and adjunct imaging modalities. By knowing the differences among available scopes, the skilled endoscopist is better able to match his or her tools to the desired procedure. The knobs for controlling scope tip manipulation are located on the right side of the headpiece and provide quadridirectional movement. The inner control knob is for up/down and the outer knob for left/right. The two buttons on the front of the scope provide lens cleaning, air insufflation, and suction.

The suction channel also functions as the biopsy channel so that any endoscopic tools placed into the biopsy channel will limit the ability to suction fluids through the endoscope. A small button on the front of the handpiece above the suction button allows for freezing of the image and digital recording by pressing the image capture button on the back of the handpiece.

Advancements in Imaging Technology

There have been many recent advances in endoscopic imaging techniques with the goal of improving immediate detection of dysplasia and other mucosal abnormalities. The ability to perform an “optical biopsy” at the time of the endoscopic procedure would enhance directed tissue sampling and resection as well as overall endoscopic therapy. It should be noted that these techniques can be used for both upper and lower endoscopic procedures.

CHROMOENDOSCOPY

This technique is based on the staining of mucosal surfaces to differentiate different cellular activities and subtle mucosal abnormalities. Liquids commonly used as topical mucosal agents include Lugol (potassium iodide) solution, methylene blue, indigo carmine, and Congo red. Diseases, including Barrett esophagus and squamous cell carcinoma of the esophagus, have been detected with the use of Lugol solution. Normal keratinized squamous epithelium stains a deep brown as a result of a reaction between the potassium iodide and glycogen, but inflammation, dysplasia, and carcinoma do not stain because of a lack of glycogen. Staining of the esophagus with methylene blue may be useful in the search for Barrett mucosa: the blue dye is avidly absorbed by the intestinal absorptive cells of the columnar epithelium. Darkly stained areas may be biopsied for confirmation.²

NARROW-BAND IMAGING

Most endoscopes now have the ability to switch the bandwidth of projected light just by pressing a button on the scope handle. Narrow-band imaging (NBI) can differentiate squamous from nonsquamous epithelium to help identify Barrett esophagus [see *Figure 1* and *Figure 2*]. The use of white light as well as NBI has also enabled endoscopists to provide an immediate assessment of small colonic and gastric lesions without histopathologic evaluation.³

OPTICAL COHERENCE TOMOGRAPHY

This technique uses reflection of near-infrared light to produce real-time two-dimensional cross-sectional images of the gastrointestinal tract. A small probe similar to an endoscope ultrasound probe that does not require tissue contact is passed through the scope. Optical coherence tomography produces a high-resolution image of the layers of the gastrointestinal

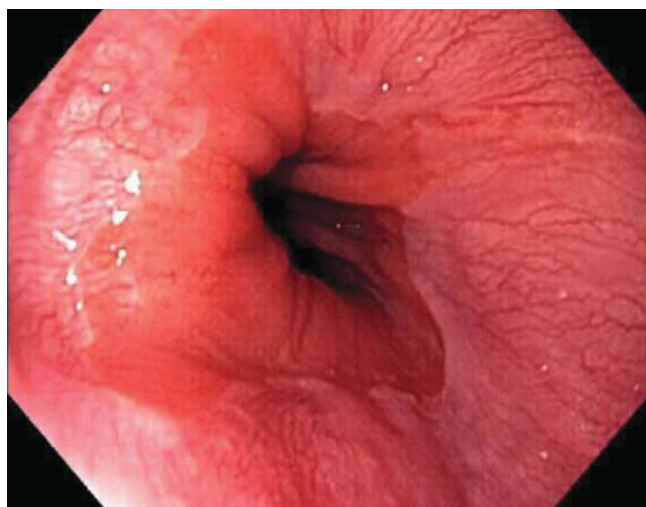


Figure 1 The squamocolumnar junction seen with routine white light.

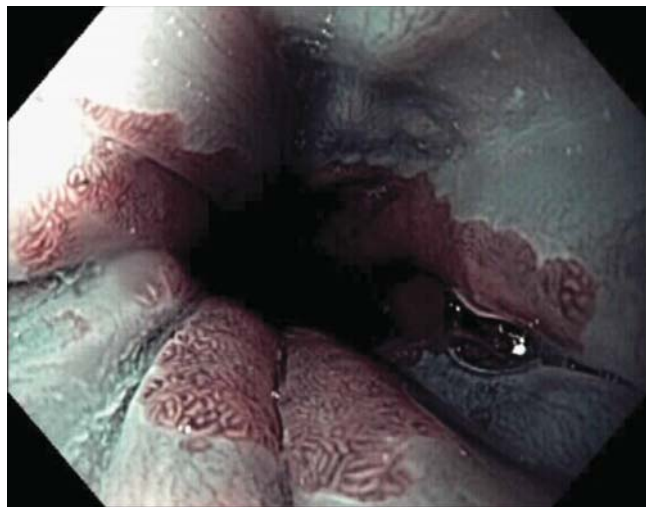


Figure 2 The squamocolumnar junction as seen with narrow-band imaging.

tract. Although not yet in widespread use, investigation into the accurate identification of diseases such as Barrett esophagus is ongoing.

Basic Upper Endoscopy

INDICATIONS

Upper endoscopy, or esophagogastroduodenoscopy (EGD), is indicated when a patient has abnormal findings on traditional gastrointestinal x-ray series or one of the “alarm symptoms,” such as weight loss, early satiety, hematemesis, dysphagia, odynophagia, epigastric pain that does not respond to medical therapy, persistent heartburn, suspected foreign body, or iron deficiency anemia. It is also indicated for surveillance of patients at high risk for malignancy and for sampling of gastrointestinal tissue or fluid. Unsedated transnasal endoscopy with slim endoscopes can also be performed in patients with suspected esophageal or gastric pathology. Biopsies can be performed, but no therapeutic interventions can be provided because of the limitation of the biopsy channel.

CONTRAINDICATIONS

Contraindications to EGD include underlying patient comorbidity and inability to tolerate conscious sedation. Recent surgery or anastomosis is not a contraindication to an EGD, and the risks and benefits of any procedure must be weighed before proceeding.

ASSESSMENT AND MONITORING

Following initial patient evaluation, including American Society of Anesthesiologists classification and Mallampati scoring to assess risk for airway compromise, the patient is placed in a left-side-down decubitus position. One prepares for the examination by ensuring the patient’s hemodynamic stability, having the patient fast for 6 to 8 hours beforehand, and then proceeding with the delivery of medications to provide conscious sedation, which generally involves applying a topical anesthetic to the posterior pharynx and administering a narcotic and a benzodiazepine intravenously. Monitoring of arterial blood pressure and oxygen saturation throughout the procedure is now standard practice.

TECHNIQUE OF UPPER ENDOSCOPY

With the patient in the left lateral decubitus position, a topical anesthetic may be applied to the posterior pharynx and an intravenous sedative administered. The forward-viewing panendoscope—a small-caliber instrument that is long enough to permit examination of the foregut from the mouth to the third portion of the duodenum—is employed. The endoscope is held in the left hand regardless of the individual physician’s hand dominance. The internal upward and downward deflection knob is controlled by the left thumb while the air, water, and suction knobs are controlled by the left index and middle fingers. The smaller left/right knob then is usually manipulated by the right hand.

The endoscope should be introduced under direct visualization rather than using two-handed techniques, which increase the risk for both the patient and the physician. The instrument is advanced slowly until the epiglottis and vocal cords are visualized [see *Figure 3*]; it is then angled posteriorly



Figure 3 Normal appearance of the vocal cords and arytenoid cartilages.

to the esophageal introitus and gently advanced as the patient is asked to swallow. Insufflation of air is begun to distend the esophagus, which appears as a long, round tube. Frequent peristaltic waves are seen; these are normal. Mucosal surfaces must be closely inspected for signs of ulceration, stricture, tumor, or Barrett (columnar) epithelium, which manifests itself as orange patches in otherwise pale salmon-pink esophageal (squamous) mucosa. When abnormalities are noted, biopsy, brushing for cytologic evaluation, or both should be performed [see Figure 4]. As the endoscope is advanced, insufflation is continued, and the curve of the lumen is followed to the left as the esophagus traverses the diaphragm to enter the stomach. If the lumen is not fully visualized, the endoscope is withdrawn and the examination resumes. The distance from the incisors to the esophagogastric junction must be identified and recorded. The diaphragmatic incursion is next identified as it “pinches” on the esophageal lumen. Increased length between these two markers is classic



Figure 4 Evidence of severe *Candida* esophagitis.

for sliding or type I hiatal hernia, as is the presence of gastric folds above this pinched area. The pinching may be better visualized when the patient sniffs.

When the stomach is entered, the tip of the endoscope is elevated so as to center it within the gastric lumen. It should be noted that with the patient lying in the left lateral decubitus position, the stomach is also on its side, with the greater curvature at 6 o'clock, the lesser curvature at 12 o'clock, the posterior wall at 3 o'clock, and the anterior wall at 9 o'clock. Air should be insufflated to distend the stomach fully and permit careful inspection of all mucosal surfaces [see Figure 5 and Figure 6].

After the stomach has been viewed, the instrument is advanced under direct vision through the pylorus and into the duodenal bulb. Insufflation of air should continue as the scope is pressed against the pylorus to facilitate passage of the instrument [see Figure 7]. The scope tends to pop into the duodenal bulb rather than slide smoothly; it should be pulled

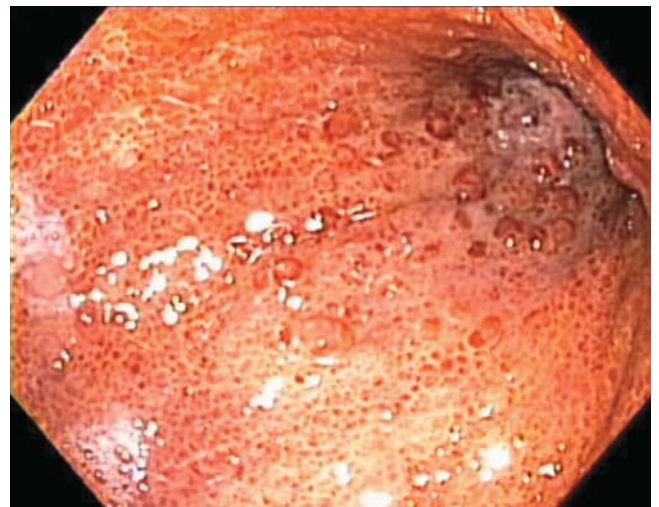


Figure 5 Esophagogastroduodenoscopy revealing linitis plastica of the stomach.

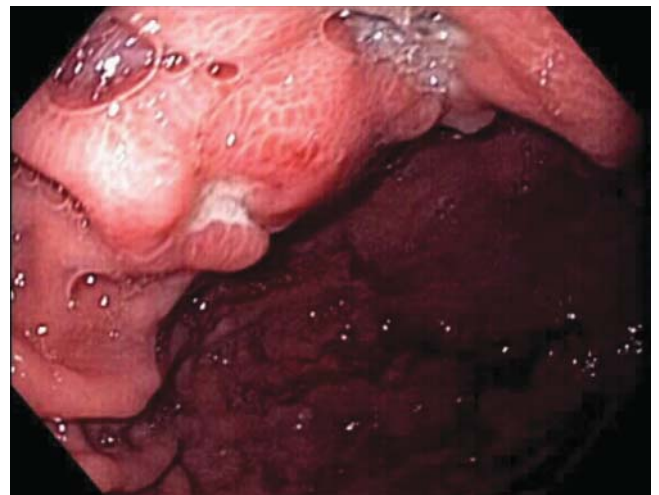


Figure 6 Esophagogastroduodenoscopy revealing a small, nonbleeding, gastric ulcer.

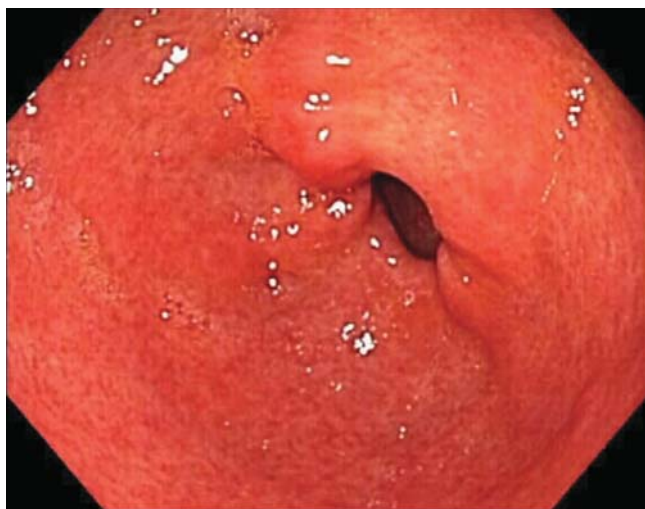


Figure 7 Normal-appearing pylorus and antrum.

back slightly to allow one to observe the mucosal surfaces of the bulb before moving ahead. Unlike the rest of the small bowel, the duodenal bulb has no semicircular folds [see Figure 8]. The tip of the scope must be rotated slightly to permit examination of the walls of the bulb. It is advisable to pull the instrument back into the stomach while observing the walls of the bulb and the pyloric channel for lesions; several such withdrawals may be required for full assessment of this area.

Once the duodenal bulb has been examined, the endoscope is advanced just past the bulb to the point where the first duodenal folds are observed. Here, the duodenum turns sharply to the rear and downward as it becomes retroperitoneal. Advancement of the scope into the second portion of the duodenum is one of the few endoscopic maneuvers that cannot be accomplished under direct vision [see Figure 9]. Because of the sharp angle of the turn, one will experience a moment of so-called “red-out” as the tip of the endoscope touches the mucosa during the turn. To ensure that the



Figure 8 Normal appearance of the duodenal bulb.

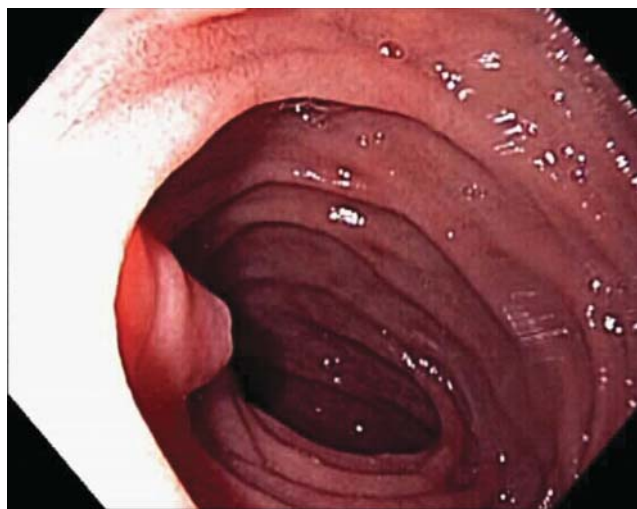


Figure 9 Normal appearance of the second portion of the duodenum. The major papilla is seen at the 9 o'clock position, along the medial wall of the duodenum.

turn is accomplished safely, the instrument is advanced as far through the bulb as is possible under direct vision. The control handle of the scope is then rotated approximately 90° to the right as the tip of the scope is turned to the right and angled first upward and then downward. As the second portion of the duodenum appears, the scope is rotated back to its neutral position. When done correctly, the turn is actually quite easy. It should never be forced: if the instrument does not proceed easily into the descending duodenum, the scope should be pulled back and the attempt repeated. Pushing against resistance may result in perforation.

Entering the descending duodenum causes the scope to form a large loop in the stomach. Therefore, once the second portion of the duodenum is successfully entered, the shaft of the instrument is pulled back. Paradoxically, as this movement straightens the gastric loop, it also advances the tip of the instrument deeper into the duodenum. Further advancement of the instrument under direct vision often permits entry into the third or even the fourth portion of the duodenum. Once the distal limit of intubation is reached, the scope is withdrawn and the luminal surfaces are carefully examined. Rotating the scope with small right-left movements of the controls and side-to-side movements of the control handle itself will help demonstrate the more subtle details of duodenal anatomy. The endoscope is then withdrawn back into the gastric lumen and full upward deflection is performed as the scope is inserted. This allows a retroflex view of the cardia and fundus [see Figure 10]. Often the upper gastrointestinal tract is inspected more completely while the instrument is being withdrawn than while it is being advanced.

COMPLICATIONS OF DIAGNOSTIC EGD

Complications of diagnostic EGD are divided between those related to the actual performance of the procedure and those related to the delivery of conscious sedation. Perforation secondary to EGD can occur related to scope tip or elbow trauma, or barotrauma, which is the insufflation of air. In the cervical esophagus, anatomic alterations such as Zenker

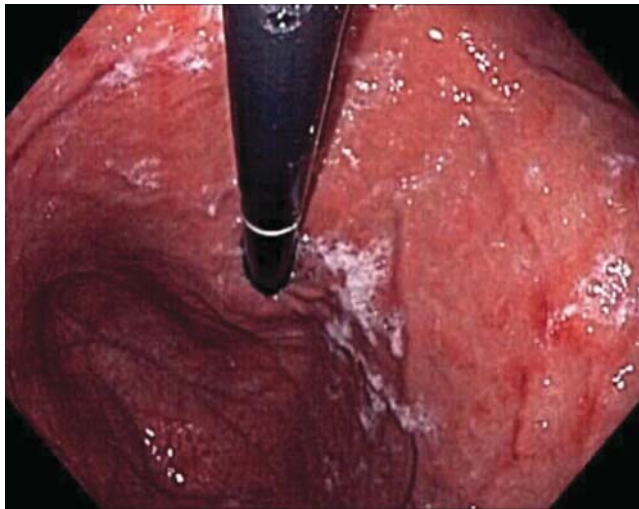


Figure 10 Retroflex view of the gastric fundus. The angularis is seen at the 2 o'clock position along the lesser curvature.

diverticulum, vertebral osteophytes, and cervical ribs can contribute to the occurrence of perforation. Cervical esophageal perforation can usually be managed conservatively with observation and antibiotics but rarely requires cervical drainage of abscess formation. Perforation of the mid- or distal esophagus is very rare with diagnostic EGD. In the stomach and duodenum, perforation is also very rare. Other rare complications include bleeding and infection.

The delivery of conscious sedation can lead to cardiac and pulmonary complications. The presence of an endoscope across the upper esophageal sphincter can increase the risk for airway compromise and aspiration. Cardiac events such as arrhythmias and hypotension are usually the result of primary respiratory compromise such as hypoventilation and resultant hypoxia.⁴ Oxygen saturation is closely monitored throughout the procedure, and if there is a noticeable drop, jaw thrust, increased supplemental oxygen, and verbal communication can all be used to improve the patient's respiratory status. If this is not effective, the procedure should be aborted immediately with scope removal and consideration given to delivery of reversal agents. Appropriate drugs must always be readily available to reverse sedative effects, and a suction apparatus must be ready for use at all times.

Therapeutic Esophagogastroduodenoscopy

ENDOSCOPIC TISSUE SAMPLING

Sampling of tissue is most frequently obtained by passage of a spiked forceps via the endoscope's biopsy channel. Multiple biopsies should usually be obtained. For ulcers, one should biopsy the edge of the lesion in at least four quadrants. Standard biopsy techniques are quite superficial; however, if deeper biopsies are desired, these can be obtained by using either a jumbo forceps or the practice of repetitive biopsies at the same site, which will lead to a deeper sampling. Tissue and lesions can also be sampled by the use of brush cytology.

ENDOSCOPIC TECHNIQUES FOR MANAGEMENT OF BLEEDING

Endoscopy plays a direct role in the evaluation and treatment of upper gastrointestinal bleeding (UGIB). The timing for endoscopy should be based on each individual clinical scenario, understanding that EGD has both a diagnostic and a therapeutic potential. Prior to EGD, the patient must be stabilized with transfusion of blood products for correction of anemia and coagulopathy as needed, and endotracheal intubation for airway protection if warranted. Techniques of providing endoscopic hemostasis can be divided into thermal and nonthermal categories. It is also possible to treat bleeding with combined modalities such as coagulation and injection or clipping and injection. Given the relatively high success rates of controlling UGIB by endoscopic means, it is appropriate to pursue EGD initially before considering surgical or interventional radiology options.⁵

Thermal Endoscopic Tools

Thermal therapies control hemorrhage by inducing tissue coagulation, collagen contraction, and vessel shrinkage. Thermal energy tools are divided between contact and noncontact categories. These techniques overall are easy to use, although perforation may occur with an extensive delivery of energy in areas of thinner viscus walls, such as the duodenum or cecum.

Contact thermal tools Contact or coaptive techniques involve the use of probes passed via the biopsy channel, which allow for pressure tamponade of the bleeding point with simultaneous application of thermal energy for coagulation. The firmer one applies the device to the tissue, the greater the depth of energy penetration. The heat generated, which can reach several thousand degrees, is sufficient to cause full-thickness tissue damage, so care is required when using this modality.

Noncontact thermal tools Energy delivered to the mucosal without direct contact is referred to as a noncontact thermal tool. Argon plasma coagulation (APC) is an example of this technique in which thermal energy is applied to tissue via ionized argon gas. The energy is actually "sprayed" rather than delivered via direct contact. APC is particularly well suited for settings where large mucosal areas require treatment, such as gastric antral vascular ectasia (GAVE), or where the risk of deeper thermal injury leading to perforation is of heightened concern, for example, in the duodenum or cecum⁶ [see Figure 11 and Figure 12].

NONTHERMAL ENDOSCOPIC HEMOSTASIS TOOLS

Injection Sclerotherapy

The delivery of hemostatic agents is performed by passage of a needle catheter system via the biopsy channel of the endoscope. The 5 mm needle can be advanced into the adjacent tissues and withdrawn as needed. The sclerosant agent is routinely injected submucosally at three or four sites surrounding a bleeding. The amount injected varies with different agents, and it must be remembered that systemic absorption will occur. The affect of hemostasis occurs secondary to direct tamponade and to vasoconstriction. Dilute

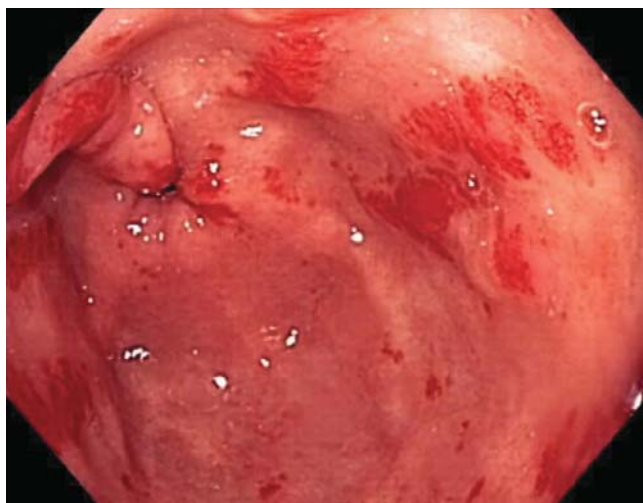


Figure 11 Esophagogastroduodenoscopy revealing gastric antral vascular ectasia.

1:10,000 epinephrine solution is the most commonly used agent and should be limited to less than 10 cc total volume. For esophageal varices, injections are begun just above the gastroesophageal junction. Sclerosants can be injected either directly into the varix or alongside it, intravariceal or paravariceal.

Endoscopic Band Placement

Endoscopic rubber band ligating devices can be used with most standard endoscopes and provide an alternative for management of variceal and nonvariceal bleeding. This technique is based on the ability to suction tissue into a cap placed at the tip of the endoscope and then, with the turning of a control knob, fire a small, tightly constricting rubber band. Applications for endoscopic banding include treatment of internal hemorrhoids, Dieulafoy ulcers, esophageal and

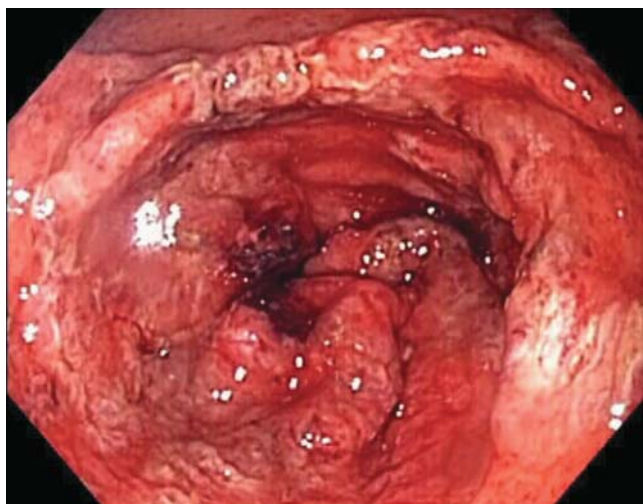


Figure 12 Appearance of gastric antral vascular ectasia following treatment with argon plasma coagulation.

gastric varices, and mucosal neoplasia in conjunction with endoscopic mucosal resection.⁷

Endoscopic Clip Placement

Endoscopic clip placement is an effective method to control bleeding and can be used safely at multiple sites throughout the gastrointestinal tract in conjunction with other endoscopic therapies. The clips are created with different characteristics but routinely provide only a very superficial tissue approximation. The clips will usually slough off within 2 weeks and pass spontaneously through the gastrointestinal tract.⁸

Endoscopic Loop Placement

Pretied endoscopic loops can also be applied through a standard endoscope biopsy channel and can be used for ligation of pedunculated structures before or after endoscopic resection. These single-application devices are similar to laparoscopic endoloops, although they are nylon sutures, and instead of an actual slip knot, a plastic cinching device holds the loop in place once deployed.

ENDOSCOPIC DILATION TECHNIQUES

Endoscopic dilation can be performed for any enteral stricture that can be reached by endoscopic means. Stenoses and anastomotic strictures secondary to ischemia, inflammation, radiation, and neoplasm are all amenable to endoscopic dilation. The use of fluoroscopy as an adjunct to endoscopic dilation is believed to decrease the risk of perforation, although this has not been fully proven in randomized prospective trials. The two most common dilators available are the guide wire–driven type, which applies both axial and radial forces, and the balloon type, which applies only radial forces. Fluoroscopic guidance allows the endoscopist to gauge several components of the procedure. First, it ensures the positioning of the balloon or the guide wire in the viscus lumen. Second, if contrast is injected in the balloon as the dilating fluid, expansion of the balloon can be fully appreciated. This is termed “waist ablation” and refers to the full dilation of the balloon at the site of the stricture [see Figure 13 and Figure 14]. Fluoroscopy also can monitor the position of the guide wire as Savary-type dilators are advanced over the wire in a trolley system fashion. Long, complex strictures may be less responsive to endoscopic dilation, and many strictures may also require repeat treatments. Aggressive biopsying of the mucosa after dilation is necessary in cases of unclear etiology. Complications secondary to endoscopic dilation include bleeding, perforation, mucosal tears, and recurrent structuring.

ENDOSCOPIC ENTERAL STENT PLACEMENT

Endoscopic stents can be used for the treatment of strictures, leaks, fistulae, and obstructing neoplasms. The delivery system is dependent on the type of stent and the location for deployment. Endoscopic stent deployment is either through-the-scope (TTS) or wire guided using fluoroscopic guidance. TTS stents are delivered through the endoscope channel, are routinely a 10 French system, and require a therapeutic scope. Non-TTS stents are limited to the esophagus, including the esophagogastric junction or the rectosigmoid region. In patients following gastric resection, these systems can also traverse a gastrojejunostomy anastomosis.



Figure 13 Enteroscopy revealing small bowel stricture secondary to inflammatory bowel disease.

The characteristics of endoscopic stents are quite diverse, including different lengths, widths, and morphologies. In addition, stents can be uncovered, partially covered, or fully covered. Covered endoscopic stents have been created for the sole purpose of temporarily bridging esophageal and proximal anastomotic leaks and fistulae.⁹ These stents are considered removable as there is minimal tissue ingrowth, which occurs usually at the proximal and distal ends. The greatest problem with these stents is the high risk of migration. Bleeding, perforation, and obstruction are far less common complications.

Uncovered enteral stents, using TTS deployment systems, are not intended for removal and can be placed for temporary

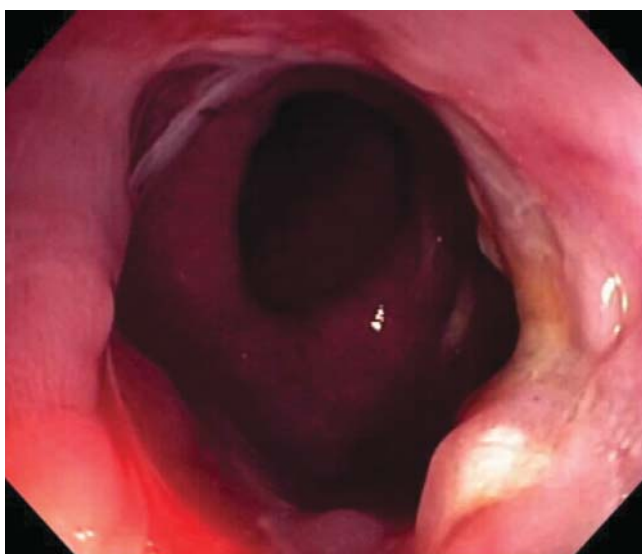


Figure 14 Appearance of small bowel stricture following balloon dilation.

relief of benign and malignant strictures throughout the gastrointestinal tract.¹⁰ They are associated with tissue ingrowth and occasional occlusion if they are left in place, but they have a lower rate of migration. In unresectable disease states, palliation of obstruction with enteral stents can provide an alternative to surgical bypass procedures.

RETRIEVAL OF FOREIGN BODIES

Many ingested foreign bodies pass through the gastrointestinal tract uneventfully, but a good number must be removed by endoscopic means—in particular, foreign bodies in the esophagus, sharp objects that are likely to perforate the bowel, and objects that do not progress from the stomach.

If the ingested object is of an unfamiliar type, it is an extremely good idea to practice with a similar object outside the patient before attempting endoscopic retrieval. This preparatory step allows one to select the most appropriate accessory and technique for removing the object.

Technique

Objects with sharp edges should be removed with the sharp end trailing to prevent perforation. In some cases, this means that the object must be pushed into the stomach and turned around before being removed. If multiple foreign bodies are present or if it is highly likely that the foreign body will injure the esophagus if removed in the standard manner, an overtube should be placed over the scope before insertion. The overtube enables one to pass the instrument several times and retrieve any sharp objects without injuring the esophagus; it also helps ensure that the object is not aspirated into the airway. If the patient is a child or there is concern for airway compromise or aspiration, general endotracheal anesthesia may be advisable.

Multiple tools have been used for foreign-body extraction, including snares, nets, biopsy forceps, tripod forceps, suction caps, and baskets. Meat boluses that form in the esophagus or proximal to a gastric band may be extremely difficult to dislodge; the use of a variceal ligator cap to produce a suction chamber can be helpful in such situations. It is imperative to evaluate the site of foreign-body impaction after removal to rule out underlying pathology or resultant trauma, such as ischemic perforation.¹¹

Complications

Endoscopic removal of foreign bodies is extremely safe and effective. Care must be taken to ensure that the esophagus is not injured during removal of the object. If the object is deeply embedded or refractory to removal, a surgical approach is preferred.

PERCUTANEOUS ENDOSCOPIC GASTROSTOMY

Since 1980, endoscopically guided placement of a tube gastrostomy has been widely employed to provide access to the gastrointestinal tract for feeding or decompression. Indications for percutaneous endoscopic gastrostomy (PEG) include various disease processes that interfere with swallowing, such as severe neurologic impairment, oropharyngeal tumors, and facial trauma. PEG has also been employed to establish a route for recycling bile in patients with malignant biliary obstruction, to provide supplemental feeding in selected patients with inflammatory bowel disease, and to

accomplish gastric decompression in patients with conditions such as carcinomatosis, radiation enteritis, and diabetic gastropathy.

Technique

The patient fasts for 8 hours beforehand, and a single prophylactic dose of an antibiotic is administered just before the procedure is begun. The patient is placed in the supine position, a topical anesthetic is applied to the posterior pharynx, and intravenous sedation is begun. A forward-viewing endoscope is passed into the esophagus and advanced into the stomach. The abdomen is prepared in a sterile fashion and draped. The stomach and the duodenum are then inspected.

The room lights are dimmed, and the light of the endoscope is used to transilluminate the abdominal wall so as to indicate a point where the gastric wall and the abdominal wall are in close proximity. Finger pressure is applied to various areas of the abdomen until a spot is identified at which such pressure produces clear indentation of the gastric wall. An endoscopic snare is deployed through the biopsy channel of the endoscope to cover this spot, and a local anesthetic is infiltrated into the overlying skin [see Figure 5]. A 1 cm skin incision is made at the chosen spot, and a needle is passed through the incision and into the gastric lumen. The endoscopic snare is tightened around the needle, and a wire is passed through the needle and into the gastric lumen. The snare is moved so as to surround the wire, which is then pulled out of the patient's mouth. The gastrostomy tube is fastened to the wire and pulled in a retrograde manner down the esophagus and into the stomach. The gastroscope is subsequently reinserted to ensure that the head of the catheter is correctly positioned against the gastric mucosa and there is no evidence of bleeding [see Figure 6].

An outer crossbar is put in place to prevent inward migration of the tube and to hold the stomach in approximation to the abdominal wall. The crossbar should remain several millimeters from the skin to prevent excessive tension, which would cause ischemic necrosis of the underlying tissue.

Complications

Local wound infections are the most common complications of PEG. They can be minimized by administering preoperative antibiotics and ensuring that excessive tension is not applied to the crossbar at the end of the procedure. When such infections do occur, they can usually be treated via simple drainage and local wound care; sacrifice of the gastrostomy is rarely necessary. Several other complications, such as early extrusion of the tube, progressive enlargement of the tract, and separation of the gastric and abdominal walls with leakage of feedings into the abdominal cavity, are also most often attributable to excessive crossbar tension and subsequent ischemia. Gastrocolic fistula can occur after PEG. This problem may not be obvious for months afterward, but severe diarrhea after feedings is grounds for suspicion. Once the PEG tract is mature, gastrocolic fistulae usually close quickly after simple removal of the gastrostomy tube.

PEG with Jejunostomy Tube Extension

In patients who fail to tolerate gastric feedings as a result of severe gastroesophageal reflux or gastroparesis, transpyloric

feeding can be provided via a jejunostomy tube passed through an existing PEG. PEG-J placement is achieved by passing a jejunal feeding tube through the PEG lumen (a 24 French PEG tube accommodates up to a 12.5 French J tube; a standard 20 French PEG tube accommodates an 8.5 French J tube). Endoscopically, the jejunal tube is guided into the duodenum under direct vision with either a biopsy forceps or an endoscopic clip.

DIRECT PERCUTANEOUS ENDOSCOPIC JEJUNOSTOMY TUBE

Feedings beyond the ligament of Treitz using direct percutaneous endoscopic jejunostomy (PEJ) are associated with a lower incidence of gastroesophageal-induced aspiration compared with simple postpyloric feeding but are associated with increased procedural risks, including bleeding, inadvertent viscus injury, and leakage.¹² Performance of direct PEJ requires both endoscopic and fluoroscopic guidance. Abdominal wall depression with a hemostat is performed at this site to try to identify a loop of small bowel adjacent to the abdominal wall. Safe tract techniques are then used to access the identified bowel, and a "pull" PEJ is performed with either a 16 French or a 20 French tube.

ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY

Endoscopic retrograde cholangiopancreatography (ERCP) is an advanced procedure that is technically more challenging than standard upper gastrointestinal endoscopy; however, it can be mastered by most endoscopists who are willing to dedicate sufficient time to learning the method. ERCP yields a radiologic image of the pancreatic and biliary trees and, in many cases, provides access for therapy. Indications for ERCP include suspected benign or malignant maladies of the common bile duct (CBD), the ampulla of Vater, or the pancreas. Cholelithiasis per se is not an indication for ERCP unless choledocholithiasis is suspected. Diagnostic ERCP is rarely performed because of the high risks of this procedure. MRCP provides safer radiographic imaging of the pancreaticobiliary trees.¹³ The therapeutic potential of ERCP is quite extensive and has supplanted surgical intervention for many diseases of the pancreas and biliary systems.

Technique

As with standard upper gastrointestinal endoscopy, the patient fasts for 6 to 8 hours beforehand. Intravenous sedation is administered, and prophylactic antibiotics are given when biliary obstruction is suspected. The patient is initially placed in the left lateral decubitus position but is later rotated to the prone position after the scope is in place in the second portion of the duodenum. A side-viewing endoscope is employed because it allows the best visualization of the ampulla of Vater. The instrument is passed into the esophagus and maneuvered through the stomach, across the pylorus, and into the duodenum.

Once the endoscope is in the second portion of the duodenum, it is pulled back so that the gastric loop is straightened and the tip of the scope occupies a better position with regard to the papilla. This so-called short scope position is generally best for work in the CBD. The papilla of Vater (also known as the major duodenal papilla) appears as a small, longitudinal nubbins crossing the horizontal semicircular folds of the duodenum, generally in the 12 to 1 o'clock position [see Figure 15].

At its tip, a small, soft, reticulated area may be noted; this is the papillary orifice. Often a small mucosal protuberance is seen just proximal and to the right of the papilla of Vater; this is the minor duodenal papilla.

A small plastic cannula is passed through the channel of the endoscope and introduced into the ampullary orifice, and contrast material is injected under fluoroscopic control to provide visualization of the CBD and the pancreatic duct. The two may share a single orifice within the ampulla or may have separate orifices. The CBD exits the papilla in a cephalad direction, tangential to the duodenal wall. The bulge of the ampulla within the duodenum represents the intramural segment of the duct. The orifice of the CBD is typically found at the 11 o'clock position in the ampulla. The pancreatic duct leaves the papilla in a perpendicular fashion. Its orifice is usually in the 1 o'clock area of the papilla.

Therapeutic interventions that may be accomplished at the time of ERCP include sphincterotomy for ductal access, sphincter of Oddi dysfunction, ampullary stenosis, removal of CBD stones, dilation of benign and malignant biliary strictures, and insertion of stents to maintain ductal patency [see Figure 16]. Pancreatic duct interventions include removal of stones, bridging of ductal disruptions, and drainage of pseudocysts.

All therapeutic applications of ERCP must begin with selective cannulation of the duct being treated. Frequently, a guide wire is then introduced deep into the duct to provide a means of obtaining access to the duct on an ongoing basis and to ensure correct positioning for intraductal manipulations. After electrosurgical division of the papilla, biliary stones are retrieved with balloons or baskets [see Figure 17]. Often



Figure 16 Electrosurgical division of the ampullary sphincter with a pull-wire sphincterotome.

large stones can be captured within the duct in mechanical lithotripsy baskets and crushed before removal.

Strictures should be brushed for cytologic evaluation once they have been traversed by a wire, although this carries a very low yield of sensitivity. They may then be dilated with



Figure 15 The appearance of the major papilla with a side-viewing endoscope. A periampullary diverticulum is seen and an endoscopic retrograde cholangiopancreatography catheter is selectively cannulating the common bile duct.



Figure 17 Following sphincterotomy, stone extraction is performed by withdrawing an extraction balloon.

hydrostatic balloons under fluoroscopic guidance and stented. Plastic stents are used for most benign and many malignant strictures; however, self-expanding metal stents are now being used more frequently for malignant strictures because they remain patent longer¹⁴ [see *Figure 18*, *Figure 19*, and *Figure 20*].



Figure 18 The appearance of a transpapillary positioned plastic biliary stent.



Figure 19 The appearance of a transpapillary positioned self-expanding metal biliary stent.

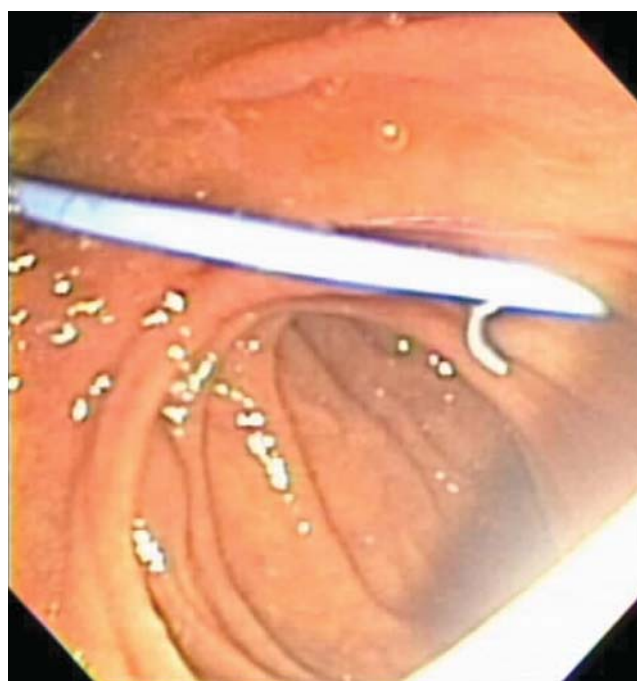


Figure 20 The appearance of a transpapillary positioned plastic pancreatic stent.

Complications

Perforation can occur during endoscopic sphincterotomy as a result of extension or tearing of the papilla beyond the junction of the CBD with the duodenal wall. Retroperitoneal or free intraperitoneal air may be seen. In many cases, intravenous antibiotics, hydration, and avoidance of oral intake are sufficient to manage such complications. If the patient's condition deteriorates, surgical exploration is indicated. Bleeding may also occur with endoscopic sphincterotomy at the time of the procedure or in a delayed fashion up to 1 to 2 weeks later. It is usually controllable at the time of the procedure with balloon tamponade, injection sclerotherapy, thermal coagulation, or endoscopic clip placement. If unsuccessful, interventional radiology may be able to provide embolization of the gastroduodenal artery to provide hemostasis.

Pancreatitis is the most common complication and can occur related to contrast injection with overfilling or acinarization of the ducts or rupture of the small ductules, with extravasation of contrast material into the pancreatic parenchyma; pancreatitis is a frequent consequence of acinarization. In addition, sphincterotomy and ampullary dilation are also associated with post-ERCP pancreatitis. Cholangitis may result when contrast is injected proximal to an obstruction of the biliary tree. When obstruction is demonstrated, drainage of the system by means of stone extraction, stenting, or nasobiliary intubation is important to prevent cholangitis.

DEEP SMALL BOWEL ENTEROSCOPY

The small bowel up until recently had been an elusive part of the gastrointestinal tract in terms of diagnostic and therapeutic endoscopic intervention. The advent of capsule endoscopy has permitted the endoscopist to obtain recorded

images of the lumen of the small bowel for identification of obscure sites of bleeding, inflammatory changes, and neoplasia, and more recently, specially designed endoscopes have allowed direct access to the entire small bowel via either an antegrade or retrograde fashion. Diagnostic and therapeutic small bowel procedures for processes such as bleeding, obstruction, and occult neoplasia have now been described using double-balloon endoscopy and single-balloon endoscopy. In addition, in select patients following surgical resection and reconstruction (i.e., Roux-en-Y bypass, long afferent limb), balloon enteroscopy can allow access into the desired segment of the small bowel.¹⁵

Both systems use the principle of scope fixation with a soft balloon that is serially inflated and deflated as the scope is advanced. This permits the endoscopist to pleat the bowel over the endoscope. The use of fluoroscopy is also helpful in guiding the endoscopist through the small bowel.

ENDOSCOPIC MUCOSAL RESECTION

The treatment of premalignant as well as superficial cancers can now be managed by endoscopic resective techniques. Endoscopic mucosal resection (EMR) has been employed for adenomas, dysplastic lesions, and early-stage carcinomas, including lateral spreading tumors. Multiple technical variations of EMR for the upper and lower tract have been developed, including submucosal injection, “suck-and-cut,” “suck-and-ligate,” and strip biopsy.

Saline Lift EMR

The most commonly performed EMR technique employs submucosal injection of a fluid followed by electrosurgical polypectomy. The most commonly used fluid is saline with or without epinephrine, although hyaluronic acid, glycerol, and dextrose have all been described. A bleb is created with the submucosal injection, creating space between the line of resection and the muscularis propria of the organ, and the lesion is resected. One caveat to this technique is that if the submucosal injection does not result in elevation, one must consider that this mass is an invasive lesion and should not be resected endoscopically.

“Suck-and-Cut” EMR

The “suck-and-cut” technique uses a specially designed cap attached to the tip of the endoscope. A submucosal injection may be created initially as with the saline lift EMR, and the lesion is sucked into the cap. A snare affixed inside the cap is used to encircle the lesion and is then resected by application of electrocautery similar to snare polypectomy. Similar to any thermal technique, the risk of perforation exists.

“Suck-and-Ligate” EMR

The “suck-and-ligate” technique transforms a sessile or nodular lesion into an artificial pedunculated polyp, which can then be resected with standard polypectomy techniques. A band ligating device is attached to the tip of the endoscope, the tissue is sucked into the cap, and a band is placed at the base of the lesion. This is done with or without saline lift injections prior to banding. The site is then resected with a snare similar to routine snare polypectomy.

The most frequent complications of EMR are bleeding and perforation. Immediate bleeding can be controlled

with endoscopically placed clips or injection of dilute epinephrine. Electrocautery should be used judiciously after EMR because the thin submucosa and serosa are susceptible to full-thickness injury with cautery. Delayed bleeding often requires repeat endoscopy with injection therapy or clip application, although angiography and embolization may be an alternative. Perforations can also be managed endoscopically with endoscopic clips as well as temporary enteral stent placement to cover the site of perforation.

ENDOSCOPIC SUBMUCOSAL DISSECTION

An extension of EMR that has been recently reported for endoscopic resection of more extensive lesions is endoscopic submucosal dissection (ESD). Using a combination of needle cautery and blunt endoscope cap dissection, large segments of tissue can be resected. The potential advantage of ESD is that it represents a more classic oncologic procedure compared with the piecemeal resection that occurs with other EMR techniques in that margins as well as lesion depth can be more accurately pathologically evaluated. Complications may be higher for ESD than for the other EMR techniques, including bleeding, perforation, and stricture formation.

ENDOSCOPIC MUCOSAL ABLATION

Endoluminal therapies for ablation of mucosal based diseases such as Barrett esophagus have recently seen great advances. Endoscopic radiofrequency ablation is a relatively new technology that has recently gained acceptance for treatment of intestinal metaplasia, as seen in Barrett esophagus.¹⁶ A balloon-based system, as well as a directed planar electrode device implementing this technology, has been used in this form of therapy. Several studies have proven feasibility and safety for this novel therapy, with very few documented cases of postprocedural structuring, as had been seen with photodynamic therapy. Further studies documenting the long-term effects of this therapy, as well as the absence of buried submucosal metaplastic glands or cancer, are still necessary.

ENDOSCOPIC ULTRASONOGRAPHY

The 1980s saw the introduction of endoscopic ultrasonography (EUS). Extracavitary ultrasonographic methods have been hampered by the presence of air within the gastrointestinal tract, which precludes high-resolution imaging. Consequently, they had been relegated to gross estimates of disease and detection of displacement of other tissues or fluid accumulation proximal to stenoses, such as ductal dilation in patients with CBD stones.

Three advances have proven invaluable in allowing EUS to carve out a niche in the field of gastrointestinal diagnosis. First is the improvement in endoscopes that allows transducer and receiver channels to traverse a tortuous path. Second is the development of multiple-frequency options in conjunction with circumferential visualization. Higher frequencies provide higher resolutions, allowing useful differentiation of the various layers of the intestinal tract. Third is the evolution of treatment protocols keyed to the accurate staging of tumors—information that is sometimes unobtainable from other imaging techniques.¹⁷

This technology has now been firmly established as an accurate way to identify carcinoma. More recent developments are allowing EUS to expand from the field of diagnosis

into the realm of intervention. Examples of EUS-guided procedures include fine-needle aspiration, lymph node sampling, and drainage of pancreatic pseudocysts.¹⁸

EUS devices come in both linear and radial transducers.¹⁹ Radial transducers have the advantage of providing circumferential visualization that parallels the standard modes of perceiving the gastrointestinal tract. Linear images allow EUS-directed biopsies and have the potential to provide color and pulsed Doppler imaging. Probes can be mounted on the top of an oblique-viewing fiberoptic scope or come in an over-the-wire format for use in the pancreaticobiliary tree. A series of frequencies are available, with the higher frequencies providing greater resolution but less tissue depth penetration. Lower-frequency probes allow deeper tissue assessment and a broader view, but at the price of reduced resolution. Nevertheless, any form of EUS will provide better resolution than transcutaneous ultrasonography, allowing markedly improved two-point discrimination and hence more accurate tissue diagnosis.

The benefits of accurate staging of gastrointestinal tumors paved the way for EUS development. Tissue sampling techniques are further benefited by this technology. The sensitivity of EUS makes it one of the best modalities for the evaluation and detection of pancreatic tumors. Its sensitivity, which is in excess of 95%, contrasts favorably with those of other modalities, including ultrasonography (75%), computed tomography (CT) (80%), and angiography (89%). The accuracy of T staging by EUS in esophageal cancer (80 to 90%) is greater than that of staging determined by CT scanning (50 to 60%). This finding has led to the development of several staging schemes that are based solely on EUS findings. EUS has established a role in the identification of early pancreatitis; the detection of CBD stones and mediastinal masses; and the assessment of anastomotic strictures, thickened gastric folds, and the integrity of the anal sphincter. It has also proved a useful adjunct in the determination of whether a tumor is amenable to EMR techniques or is better served by adjuvant therapies or surgical interventions.

The sensitivity of EUS is rooted in its ability to delineate the various layers of the alimentary canal. Experienced endoscopists can easily evaluate the submucosa and differentiate intramural from extrinsic masses. Characteristic patterns are readily learned and rapidly recognized, obviating tissue diagnoses in straightforward cases. Criteria have also been established to aid in the differentiation of benign and malignant lesions. With the continued use of this technique, additional algorithms will be established in conjunction with more

innovative interventional adjuncts. However, two limitations have caused many practitioners to remain skeptical: cost and training issues. Other imaging modalities, such as CT and magnetic resonance imaging, have also made tremendous strides recently. Although these various modalities are often considered competitors—a view arising from the perceived need for a single imaging modality—the issue of which is superior to the others pales in comparison with the benefits that can be gained from combining imaging techniques in appropriate circumstances.

Future of Endoscopy

The future in endoscopy will be based on advancements of both the tools and the applications available to endoluminal therapy. Intraluminal and transluminal endoscopic techniques are being proposed as potential surgical alternatives, taking on an increasingly more invasive and therapeutic role. Recent interest in NOTES united surgeons and gastroenterologists with the desire to access the abdominal cavity via naturally existing orifices, including the stomach, colon, bladder, and vagina.²⁰ An appropriate application for this approach is still yet to be elucidated. It is theorized that NOTES may have distinct advantages over laparoscopy in that NOTES may not necessarily require a sterile working environment to perform, and it possibly could also be completed under conscious sedation, similar to other endoscopic procedures.²¹

The obvious limitations to NOTES were based on the lack of adequate and appropriate endoscopic equipment. It was apparent early on that stable platforms would be necessary as well as endoscopic tools for cutting, hemostasis, and tissue manipulation. Transoral and transvaginal multichannel platforms with internal capability for manipulation and fixation are now becoming available. Scissors, suturing devices, bipolar forceps, and grasping devices are a few of the novel instruments soon to be added to the endoscopist's armamentarium.

These tools, however, will have a more likely impact on other endoscopic therapies, including intraluminal endoscopic surgery. Full-thickness resection, intraluminal anastomoses, and closure of perforations are all likely procedures to be seen in the very near future, and it is imperative that surgeons stay attentive to the advancements in these technologies.

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19 LOWER ENDOSCOPY

Brian J. Dunkin, MD, FACS, and Rohan A. Joseph, MD

The lower endoscopy revolution began in 1967 with the development of the first flexible fiberoptic sigmoidoscope by Bergein F. Overholt.¹ Although the idea for fiberoptic examination of the colon was first conceived by Robert Turell in 1963, he failed to pursue it because of skepticism over its potential for success. The breakthroughs in flexible fiberoptic technology by Harold Hopkins and the invention of the first flexible gastroscope by Basil Hirschowitz in 1958 convinced Dr. Overholt of the possibility of endoscopic examination of the colon and enabled him to develop the device for which he is now credited. In 1970, a longer version of the Overholt sigmoidoscope was devised with four-way tip deflection that enabled navigation of the colonic flexures. Between 1970 and 1973, colonoscopy started gathering increased acceptance across the United States as more diagnostic and therapeutic procedures were demonstrated to be safely performed.¹

Definition

Lower endoscopy includes rigid and flexible sigmoidoscopy, colonoscopy, endoscopic ultrasonography (EUS), and anoscopy. This chapter focuses on the diagnostic and therapeutic maneuvers performed using a colonoscope. A separate section is included at the end to give special attention to the other modalities.

Indications

The indications for performing colonoscopy can be classified into two categories: diagnostic and therapeutic [see Table 1]. The most common diagnostic indication is for screening or surveillance of colorectal neoplasms and evaluation of colonic lesions. Investigation of gastrointestinal (GI) blood loss and unexplained abdominal pain are also frequent indications. Therapeutic indications include the removal of

polyps, treatment of bleeding, decompression, and stenting. Contraindications to colonoscopy include disease states that increase the risk of perforation, such as recent diverticulitis (within 2 to 4 weeks), suspected perforation, or gangrenous ischemic colitis.

Diagnostic and Screening Colonoscopy

Colon cancer is the third most common cause of cancer death among men and women in the United States, with approximately 50,000 deaths annually.^{2,3} Most cancers arise from adenomatous polyps less than 1 cm in size and take almost 10 years to become invasive cancer. Screening programs have resulted in a decreased incidence of colon cancer as revealed in multiple cohort studies comparing them with patients without any form of screening.^{2,3} Interestingly, no current studies have examined whether screening reduces colon cancer–related mortality. The ability of colonoscopy to thoroughly visualize the lower GI mucosa, detect lesions, and remove them while obtaining tissue for histologic diagnosis makes it an effective tool for screening and surveillance.

The risk for colon cancer increases with age. Patients who only have age as a risk factor are considered to be at “average risk” [see Table 2]. Individuals with personal and familial risk factors are considered to be at “high risk” [see Table 2]. The recommendations by the US Multi-Society Task Force for screening and surveillance in colorectal cancer (CRC)² are highlighted in Table 2.

A newer technique called virtual colonoscopy (VC) or computed tomographic (CT) colography is finding more acceptance and popularity among providers and patients alike. This technique employs CT, rapid volumetric imaging, and three-dimensional image rendering made possible by contrast differences between intraluminal air, the colonic wall, and the surrounding soft tissues. Patients have to undergo a standard bowel preparation, and images are acquired in the supine and prone positions. Prior to the examination, a soft rubber catheter attached to a bulb syringe is then inserted into the rectum and the bowel is insufflated with either room air or carbon dioxide. The patient’s subjective assessment of abdominal discomfort and fullness is a good indicator of bowel distention. Analyses of reports indicate a sensitivity and specificity of 75% and 90%, respectively, for adenomatous polyps larger than 10 mm in diameter, 66% and 63% for adenomas larger than 5 mm, and 45% and 80% for polyps smaller than 5 mm.⁴ There are currently no studies that demonstrate a decrease in CRC incidence or mortality using VC, and concerns over radiation exposure have been expressed. VC may be recommended for patients who refuse colonoscopy or have an inadequate bowel preparation but is not currently endorsed by the American Society for

Table 1 Indications for Colonoscopy

Diagnostic
Screening and surveillance of GI neoplasms
GI blood loss
Iron deficiency anemia
Altered bowel habits
Unexplained abdominal pain
Surveillance of inflammatory bowel disease
Intraoperative identification of a lesion
Therapeutic
Removal of GI neoplasms
Treatment of bleeding
Decompression
Dilation of stricture
Placement of stent
Foreign body removal

GI = gastrointestinal.

Table 2a Recommendations for Screening and Surveillance in Colorectal Cancer (Average-Risk)

Average-Risk Individual	Preferred Modality	Alternative
Begin screening at 50 yr	Colonoscopy every 10 yr	Annual fecal occult blood test (FOBT) Flexible sigmoidoscopy every 5 yr Annual FOBT and flexible sigmoidoscopy every 5 yr

Table 2b Recommendations for Screening and Surveillance in Colorectal Cancer (High-Risk)

High-Risk Individual with	Screening Strategy
FAP	Annual sigmoidoscopy beginning at 10–12 yr of age followed by colectomy when polyps develop
HNPCC	Colonoscopy beginning at 20–25 yr of age and repeated every 1–2 yr or colonoscopy performed 10 yr earlier than the first known diagnosis of cancer in the family, whichever is earlier Annual colonoscopy is recommended after 40 yr
IBD	Colonoscopy every 1–2 yr after 8–10 yr of the disease
CRC in a first-degree relative younger than 60 yr or two first-degree relatives of any age	Colonoscopy at 40 yr or performed 10 yr earlier than the affected relative, whichever is earlier If screening colonoscopy is normal, follow-up screening examinations are done every 5 yr subsequently
CRC in a first-degree relative older than 60 yr or two second-degree relatives of any age	Colonoscopy at 40 yr If screening colonoscopy is normal, follow-up screening examinations are done every 10 yr subsequently
Personal history of adenomas on previous endoscopy	1–2 tubular adenomas < 1 cm in size: perform surveillance in 5 yr 3 or more adenomas: perform surveillance in 3 yr Advanced adenomas (> 1 cm, high-grade dysplasia or villous elements): perform surveillance in 3 yr
Adenomatous polyp in a first-degree relative younger than 60 yr	Screening colonoscopy at 40 yr or performed 10 yr earlier than the affected relative, whichever is earlier If normal, screening colonoscopy is carried out every 3–5 yr subsequently
Adenomatous polyp in a first-degree relative older than 60 yr	Screening colonoscopy at 40 yr If normal, perform surveillance as for an average-risk individual
After curative surgery for colon cancer	Repeat colonoscopy at 1 and 3 yr and then at 5 yr intervals if normal
After curative surgery for rectal cancer	Repeat colonoscopy at 1 and 4 yr and then at 5 yr intervals if normal

Recommendations by the US Multi-Society Task Force. CRC = colorectal cancer; FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colon cancer; IBD = inflammatory bowel disease.

Gastrointestinal Endoscopy (ASGE) as a standard screening modality.² Patients with lesions detected on VC must undergo a complete colonoscopic examination.

Bowel Preparation for Colonoscopy

A critical element to safe and accurate colonoscopy is the proper cleansing of the colon. To date, no ideal agent has been identified, and the evolution of agents for cleansing reveals a significant transformation with respect to methods used in the past. High-volume gut lavage and rectal pulsed irrigation are only of historic importance today. All patients are advised to take a clear liquid diet on the day prior to the procedure in combination with a bowel cleansing regimen. The use of diet modifications and enemas alone is insufficient to obtain optimal preparation, but they are used as adjuncts to the agents listed below. A joint consensus statement on bowel preparation prior to colonoscopy was published in 2006 by the American Society of Colon and Rectal Surgeons (ASCRS), ASGE, and Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and is summarized in Table 3.⁵

Patients who present for the procedure without completing their bowel regimen are best managed by rescheduling the

procedure for another day. Options for those who have completed the recommended preparation but failed to achieve adequate cleansing include increasing the duration of the dietary modifications, using an alternate compound, and using adjuncts such as bisacodyl and magnesium citrate in combination with the main compound.⁵ Pregnant patients may be administered a polyethylene glycol (PEG) solution in the face of data not favoring one agent over another.⁵ In pediatric patients, clear data are lacking. A widely used preparation consists of low-volume PEG dosed at 1.25 mg/kg/day for 4 days with the addition of a clear liquid diet on the last day.

Special Considerations for Patients on Anticoagulants and Antiplatelet Agents

Patients on anticoagulant and antiplatelet/antithrombotic therapy for cardiovascular conditions present the usual challenge of balancing the risk of bleeding incurred during the procedure and the risk of thromboembolism from withdrawing these medications. Tailoring of therapeutic strategies to manage these medications must be based on the procedure and patient risk factors to optimize outcomes. The commonly used anticoagulants include warfarin, heparin, and low-molecular-weight heparin. The commonly used antiplatelet

Table 3 Agents for Bowel Preparation Prior to Colonoscopy

Agent	Commercial Name	Comments
Polyethylene glycol electrolyte lavage solution (PEG-ELS)	Colyte GoLYTELY	Passes through the colon with no net absorption or secretion Is faster and more effective than diet combined with cathartics, high-volume gut lavage, or mannitol (grade 1A) Is safer than osmotic laxatives/sodium phosphate in patients with fluid and electrolyte disturbances and hence is the preferred agent for patients with cardiac, renal, or liver disease (grade 1A) Is the proven and preferred method for cleansing in infants and children In adults, it is administered as 240 cc every 10 min until rectal output is clear or 4 L is consumed
Sulfate-free ELS	NuLYTELY TriLyte	Safety, effectiveness, and tolerance are comparable to those of PEG-ELS An alternative to PEG-ELS when a PEG-based solution needs to be used (grade 2B)
Low-volume PEG and delayed-release bisacodyl tablets	HalfLyte MiraLAX	Is better tolerated by patients because of the lower volume of fluid consumed and reduces cramping and bloating associated with consumption of 4 L of solution Combining it with bisacodyl improves the efficacy of bowel preparation (grade 1A)
Aqueous sodium phosphate	Fleet	Hyperosmotic bowel preparation that draws plasma water into the colon to induce bowel preparation Can cause fluid shifts and electrolyte derangements such as hyponatremia, hypokalemia, hypocalcemia, and hyperphosphatemia Can also induce phosphate neuropathy and nephrocalcinosis in renal patients In light of the possible fluid and electrolyte derangements, it must be used with caution in pediatric cases, geriatric populations, and patients with cardiac, renal, and hepatic insufficiency Induces mucosal ulcerations and hence must be avoided in patients with ulcerative colitis and Crohn disease Is dosed in 45 cc volumes every 12 h, with the last dose taken the morning of the procedure (grade 2B) Produces cleaning comparable to PEG-ELS (grade 1A)
Enemas	Tap water Soap suds Fleet—bisacodyl Fleet—mineral oil	Does not increase quality of preparation Used today for patients with a poor quality of preparation and those in whom the distal colonic segment is dysfunctional
Bisacodyl and magnesium citrate		Bisacodyl increases colonic motility, whereas magnesium citrate is a hyperosmotic laxative Adjuncts used in combination with PEG to reduce volume of preparation required for cleansing Does not improve quality of the preparation

agents include aspirin, clopidogrel, ticlopidine, dipyridamole, and glycoprotein inhibitors. Screening procedures and the use of “cold” biopsy techniques are considered to be at low risk for bleeding. This risk increases to 1 to 2.5% with snare polypectomies and to approximately 6% with the use of cautery devices and laser ablation. As the population ages, we find more of our patients on anticoagulant and antiplatelet medications. This has prompted the ASGE to publish guidelines for managing anticoagulant and antiplatelet medications based on the patient’s risk for developing a thrombotic complication.^{6–8} Given that the nature of the procedure to be undertaken is not known a priori, patients may require cessation of their medications for varying lengths of time. These guidelines and treatment strategies are summarized below in Table 4.

Aspirin has been shown to increase mucosal bleeding times, but the significance of this has not been demonstrated clinically. No randomized trials currently exist, and several case

control and retrospective analyses have not demonstrated an adverse outcome to continuing aspirin during a procedure. Therefore, the current recommendation is to continue aspirin in the absence of a preexisting bleeding disorder. Those patients taking a combination of clopidogrel and aspirin may be at increased risk for bleeding, and in these circumstances, withholding the clopidogrel while continuing the aspirin may reduce this risk. This increased risk for bleeding, however, is not seen in patients taking the antiplatelet agent dipyridamole either as monotherapy or in combination with aspirin; however, the safety of this combination has not been evaluated in high-risk procedures.^{6–8}

An important consideration must be given to those patients who have drug-eluting stents placed for coronary artery disease. The current guidelines advocate continuing dual-antiplatelet therapy (e.g., aspirin and clopidogrel) for a minimum of 1 month after placement of a bare metal stent and 1 year after placement of a drug-eluting stent to allow

Table 4 Guidelines and Strategies for Managing Anticoagulant and Antiplatelet Medication for Lower Endoscopy

Patient	High-Risk Procedure*	
	Warfarin	Antiplatelet Agents
High risk 1. Mechanical valve [†] in the mitral or aortic position 2. Those with atrial fibrillation and underlying cardiac or valvular disease	Stop warfarin 3–5 days prior. Use heparin (UFH/LMWH) as a bridge to maintain therapeutic anticoagulation. Stop heparin 4–8 hr before the procedure Resume heparin 2–6 hr after the procedure and gradually reinstitute warfarin until INR is in therapeutic range	Consider discontinuation at least 7–10 days before the procedure Reinstitution should be individualized
Low risk 1. Mechanical valves [†] in other sites 2. Atrial fibrillation without underlying cardiac or valvular disease 3. DVT	Stop warfarin 3–5 days prior and resume within 24 hr postprocedure	Individualize need for therapy based on risk and work with patient's cardiologist
Patient	Low-Risk Procedure [‡]	
	Warfarin	Antiplatelet Agents
High risk 1. Mechanical valve [†] in the mitral or aortic position 2. Those with atrial fibrillation and underlying cardiac or valvular disease	Continue warfarin. Delay procedure while INR is supratherapeutic.	No change in therapy as long as there is no previous issue of bleeding or Individualize therapy based on risk and work with patient's cardiologist
Low risk 1. Those with mechanical valves [†] in other sites 2. Those with atrial fibrillation without underlying cardiac or valvular disease 3. Those with DVT	Continue warfarin. Delay procedure while INR is supratherapeutic.	No change in treatment regimen required or Individualize therapy based on risk and work with patient's cardiologist

DVT = deep vein thrombosis; INR = international normalized ratio; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

*High-risk procedures: polypectomy, pneumatic or bougie dilation, laser ablation, and coagulation.

[†]Patients with caged-ball or disk valves have a higher risk than those with bileaflet, tilting, or bioprosthetic valves.

[‡]Low-risk procedures: screening/surveillance colonoscopy ± biopsy.

reendothelialization and preventing stent thrombosis from premature drug cessation. Elective and semielective procedures should be delayed during this time. At the time of endoscopy, the patient is usually maintained on one agent, usually aspirin because more data are currently available on the safety of aspirin during procedures compared with clopidogrel.

Endocarditis Prophylaxis

It was originally believed that colonoscopy increased the risk of endocarditis as a result of the resulting bacteremia that occurred during the procedure. Contemporary studies cite the risk of bacteremia during colonoscopy to be between 0 and 25%, with a mean frequency of 4.4%.⁹ Updated guidelines regarding the indications for antibiotics in patients with prosthetic devices have been published and are based on the American Heart Association (AHA) guidelines. Patients with a history of bacterial endocarditis, vascular grafts placed within 1 year of the procedure, prosthetic cardiac valves including bioprosthetic and homograft valves, and surgically created pulmonary or systemic conduits are considered to be at higher risk for bacterial seeding. These patients may be given antibiotics at the discretion of the endoscopist while undergoing a colonoscopy with or without biopsy or polypectomy. However, antibiotics are recommended should these

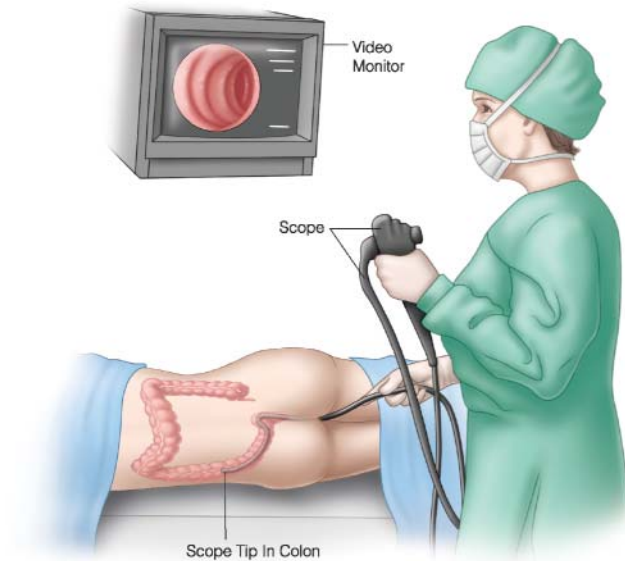
patients require a dilation of a stricture during colonoscopy.⁹ All other subgroups of patients who have prosthetic devices such as joint prostheses, penile prostheses, pacemakers, and implanted defibrillators are considered to be at low risk for infection, and antibiotic prophylaxis is discouraged.⁹ Prophylactic antibiotics should be administered as follows: a single dose of 2 g of ampicillin IV and gentamicin (1.5 mg/kg to a maximum of 80 mg) administered 30 minutes prior to the procedure. In the case of a penicillin allergy, vancomycin 1 g IV can be substituted and should be given together with gentamicin.

General Technique

Colonoscopy begins with the proper selection and preparation of the patient. Informed consent should be obtained and a complete history and physical examination done with particular emphasis on the cardiopulmonary system. It is also important to be aware of previous abdominal surgery such as hysterectomy or colon resection as these can alter the anatomy of the colon.

The setup for colonoscopy is depicted in Figure 1a. The procedure is performed with the patient in the left lateral position and with intravenous sedation to increase patient comfort. An adult or pediatric colonoscope may be used. The adult colonoscope has a slightly increased diameter in

a



b

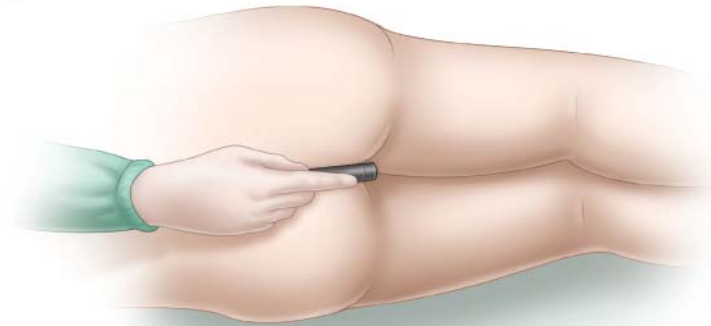


Figure 1 (a) Room setup and patient positioning for colonoscopy. (b) Technique for insertion of a colonoscope.

comparison with the pediatric scope but provides a larger instrument channel and increased shaft stiffness, which may reduce looping. The pediatric scope's smaller diameter may be more comfortable for the patient and allows easier traversal through narrow or angulated areas. It may also improve the endoscopist's ability to traverse the ileocecal valve. The procedure begins with a digital rectal examination to relax the sphincter muscles and screen for anal canal lesions. The well-lubricated colonoscope is then inserted into the anal canal by holding it approximately an inch from the tip and placing it against the patient's perineal body while sliding back and applying pressure toward the anus [see Figure 1b]. This maneuver causes the tip of the endoscope to gradually dilate the anus and reduces mechanical trauma to the anal canal during insertion. As the instrument is passed into the rectum, small amounts of air are insufflated and debris is washed from the lens. Traversing the colon expeditiously requires the endoscopist to use the minimum amount of insufflation to maintain visualization while managing the deflection wheels with the left hand and the endoscope shaft with the right.

Overinsufflation during entry stretches and elongates the colonic flexures and makes traversal more difficult and uncomfortable. The rectal mucosa is identified by its prominent reticular vascular markings and the semilunar valves of Houston that appear in an alternating fashion [see Figure 2a]. As the endoscope is advanced into the sigmoid colon, a combination of tip deflection and shaft torque is used to negotiate this tortuous part of the colon. The long, floppy, and mobile character of the sigmoid colon makes it a common site for loop formation. Further, in patients with previous pelvic surgery, dense peritoneal adhesions to the sigmoid can increase the difficulty of traversal. The endoscope should not be advanced blindly if possible or with excessive force as bowing of the shaft can risk colonic wall perforation. Failure of the tip of the scope to advance while more shaft is introduced transanally is called paradoxical motion and suggests loop formation [see Figure 2b]. Such loop formation may be reduced by pulling back on the shaft of the endoscope so as to straighten it. A jiggling motion while pulling back may cause

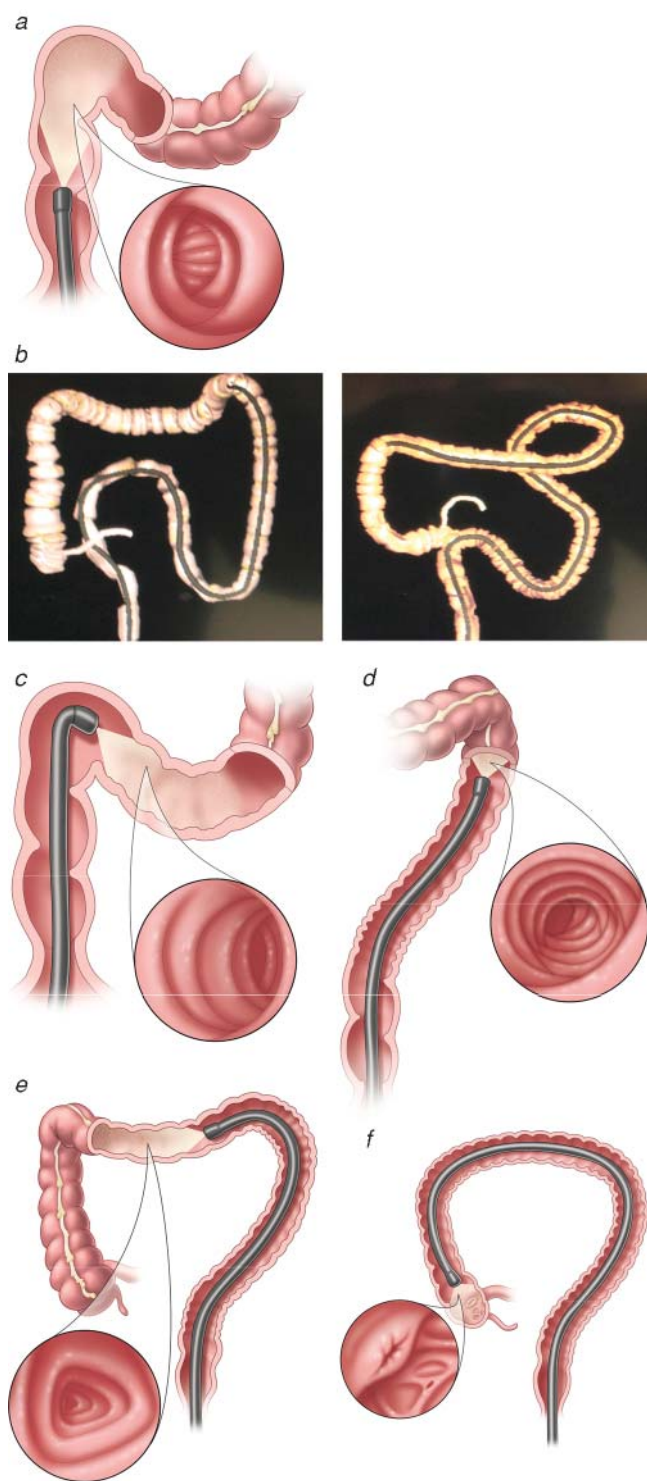


Figure 2 (a) Endoluminal view of rectum with semilunar valves. (b) Loop formation during scope advancement. (c) Direction of lumen indicated by mucosal concavity. (d) Endoluminal view of descending colon. (e) Endoluminal view of transverse colon. (f) Endoluminal view of cecum.

the colon to telescope over the instrument and further helps with loop reduction. The scope is then traversed through the sigmoid colon with the direction of the lumen identified by the concavity of the mucosal folds [see Figure 2c].

The descending colon is identified by the concentric circular pattern of the mucosa, and traversal to the splenic flexure is usually straightforward [see Figure 2d]. The splenic flexure is identified by pooling of fluid and a sharp angulation into the transverse colon. Occasionally, the bluish hue of the spleen can be seen through the colon wall. The transverse colon is identified by the triangular appearance of the lumen formed from omental traction on the tenia [see Figure 2e]. The transverse colon is relatively easy to maneuver through, and the appearance of a bluish hue over the mucosa suggests entry into the hepatic flexure. Commonly, entry into the ascending colon must be accompanied with scope withdrawal and left-hand torque to straighten all flexures and allow traversal into the cecum. Moving the patient into a supine position and applying external pressure to the sigmoid colon are adjuncts that can aid cecal intubation. The cecum is identified by the appearance of the convergence of the colonic tenia at the appendiceal orifice, the appearance of which is often called the “Mercedes” sign. Further, the central appendicular orifice and the liplike mucosal folds of the ileocecal valve are seen [see Figure 2f]. The valve can be intubated to gain access to the lumen by deflecting toward it while pulling back on the endoscope and insufflating gently. Not all endoscopists intubate the ileum routinely, but it should certainly be done when there are specific indications such as possible inflammatory bowel disease or unexplained iron deficiency anemia.

After successful cecal intubation, the colonic mucosa is carefully inspected during withdrawal of the endoscope. Care is taken to flatten the mucosa and look behind each fold and flexure. Obscuring fluid should be aspirated or the patient position changed to move debris out of the way. Evidence from a study by Barclay and colleagues suggests that scope withdrawals done in less than 8 minutes have an increased propensity to miss subtle adenomas that may harbor neoplasia.¹⁰ The procedure ends with retroflexion in the rectum to inspect the anal canal and area of the dentate line, followed by evacuation of insufflation.

Diagnostic and Therapeutic Techniques during Colonoscopy

During inspection of the colonic mucosa, pathology is often identified that requires sampling, marking, or a therapeutic maneuver such as excision. What follows is a description of techniques available to the endoscopist.

BIOPSY

The most common technique of tissue sampling during colonoscopy is to perform a pinch biopsy. This entails delivering a biopsy forceps to the desired target and taking a sample without applying any electrocautery. Many biopsy forceps have a spike at their base that holds the first “bite” in place and allows obtaining a second “bite” before withdrawing the device [see Figure 3a].

POLYPECTOMY

Polypectomy is by far the most common therapeutic procedure performed during colonoscopy. Several techniques have been developed to improve the safety and efficacy of the procedure, and polyps are excised using either a snare or a “hot” biopsy forceps.

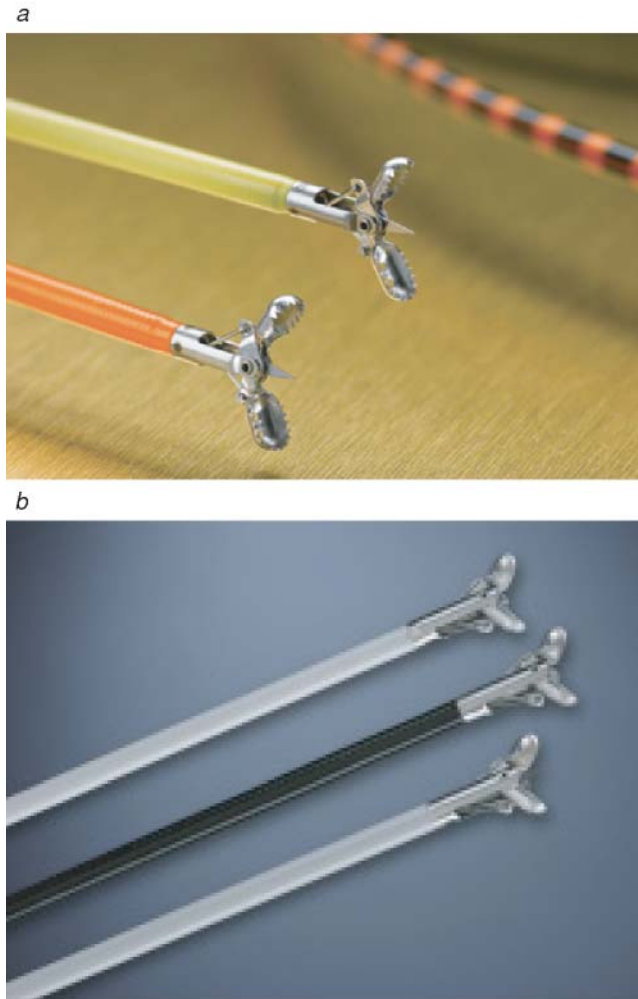


Figure 3 (a) Pinch biopsy forceps. (b) Hot biopsy forceps.

Hot Biopsy

For those polyps less than 3 mm in size, excision with a “hot” biopsy forceps [see Figure 3b] can be sufficient. A hot biopsy forceps differs from that used during regular biopsy in that it delivers monopolar electromechanical energy to the jaws to enable tissue destruction. During hot biopsy, the lesion is grasped with the forceps and distracted away from the underlying submucosa. Brief applications of electrocautery are then applied until a white zone of coagulum at the base of the polyp is seen. In theory, this technique allows sampling of the lesion to determine its pathology while destroying any remaining tissue to minimize recurrence or continued growth. Although still practiced, there is controversy about the efficacy of the hot biopsy technique. Gilbert and colleagues reported that hot biopsy techniques failed to reduce the incidence of CRC and were not associated with complete obliteration of the lesion.¹¹ Further, the procedure risks deep tissue injury, with the consequent complications of bleeding, perforation, and postpolypectomy syndrome [see Postpolypectomy Complications, *below*]. In 1992, Tappero and colleagues described a “cold” biopsy technique as an alternative to hot biopsy in 210 consecutive patients in whom 288 polyps less than 5 mm were excised without diathermy.¹²

They reported this alternative to be safe and comparable to the conventional hot biopsy technique in adequacy of tissue acquisition for histopathology.

A prospective study by Mönkemüller and colleagues in 2004 asked pathologists blinded to the fashion in which the specimen was acquired (hot versus cold biopsy) to evaluate the specimen quality and found a significant rate of architectural distortion and tissue fragmentation in samples acquired by hot biopsy.¹³

Sessile or pedunculated lesions between 3 mm and 2 cm are snare excised. For pedunculated polyps, it must be borne in mind that the stalk represents an extension of normal mucosa and does not need to be excised completely. The snare is advanced beyond the polyp such that the sheath of the snare rests over the lesion. Gentle drawing back of the snare brings it into position over and around the polyp. Once the snare is tightened, brief bursts of cautery are applied while distracting the lesion away from the submucosa so as to prevent transmural thermal injury [see Figure 4a]. The excised polyp must then be retrieved for pathologic examination either by suctioning it through the colonoscope and into a specimen trap (small polyps) or retrieving it directly by attaching it to the tip of the scope (by suction, snare, or basket) and removing it.

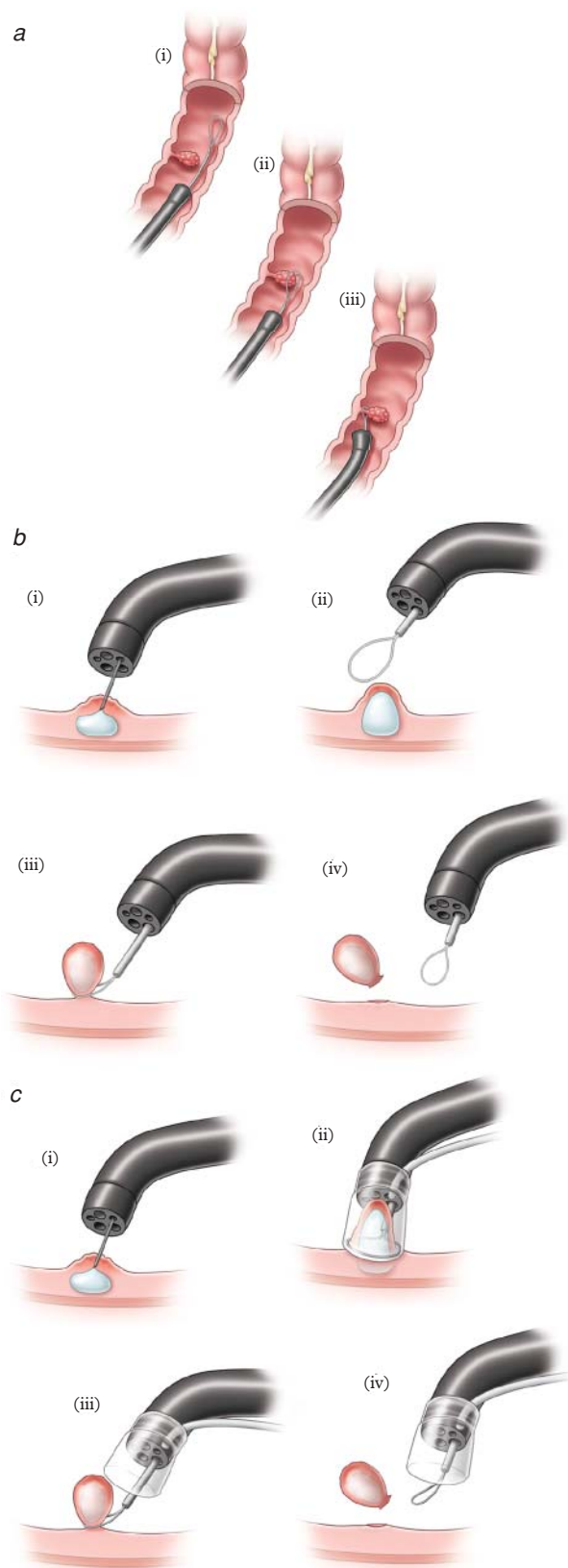


Figure 4 (a) Snare polypectomy of a pedunculated polyp. (b) Endoscopic mucosal resection (EMR) of a sessile polyp using the lift and cut technique. (c) EMR of a sessile polyp using a suction cap.

Sessile polyps greater than 2 cm may not be amenable to simple snare excision without risking injury to the colonic wall. This risk can be reduced by resecting the polyp in a piecemeal fashion using endoscopic mucosal resection (EMR). EMR was first described by Tada in 1984 for dealing with giant sessile lesions in the stomach.¹⁴ It has been safely and effectively applied to similar lesions in the colon. EMR begins with a simple saline lift of the submucosa followed by a piecemeal resection of the lesion using a polypectomy snare [see Figure 4b].

Alternately, EMR can be performed by mounting a transparent suction cap (EMR-C) to the distal end of the endoscope. After a saline lift is performed, a portion of the lesion is aspirated into this cap, and then an open snare is passed around the base of the lesion. These steps are repeated several times until the entire lesion is excised in a piecemeal fashion [see Figure 4c]. EMR affords a greater amount of tissue for resection, thereby optimizing histologic evaluation. Furthermore, lesions located tangentially and those within interhastral folds are better approached with this technique. EMR-C is a painstaking yet rewarding procedure, with an overall complication rate of 10%, which is comparable to standard snare polypectomy techniques.^{15,16}

The treatment strategies for pedunculated polyps excised at polypectomy are best governed by the Haggitt classification.¹⁷ This stratification of treatment depending on the degree of invasiveness of the lesion has demonstrated prognostic importance [see Figure 5]. This classification is depicted in Table 5.

Lesions from levels 0 to 2 are treated with polypectomy alone. For a level 3 lesion, polypectomy is adequate as long as a 2 mm negative margin is present, the cancer is not poorly differentiated, and no lymphatic or vascular invasion is present. Level 4 lesions are treated with segmental colectomy because of the higher risk of lymphatic invasion.

It is usually a wise strategy to tattoo lesions that appear suspicious for malignancy. This is often done with a permanent carbon-based dye injected into the submucosa circumferentially in an area proximal to the lesion. These markings are usually visible from the outside of the lumen during surgery. This is an invaluable tool that enables the surgeon to locate the lesion and acquire appropriate operative margins.

Novel approaches to polypectomy using laparoscopic assistance have been described for those polyps that are hard to access endoscopically and for giant sessile polyps. A review of cases done by Franklin and colleagues described the advantages of laparoscopy-assisted endoscopic polypectomy to include the ability to laparoscopically mobilize the colon so as to enable better access to polyps along flexures, the ability to laparoscopically repair a transmural injury should that occur during excision of giant sessile polyps, or the opportunity to perform a colectomy during the same procedure should the frozen section be positive for an invasive carcinoma.¹⁸

Postpolypectomy Complications

The Munich Polypectomy Study (MUPS), a large, multicenter, prospective trial evaluating risks and complications in 4,000 snare polypectomies, found that the risk of complication increases when polyps are located in the right colon and greater than 1 cm in diameter or located in the left colon and greater than 2 cm in diameter or if multiple polyps are resected.¹⁶ The overall complication rate in this study

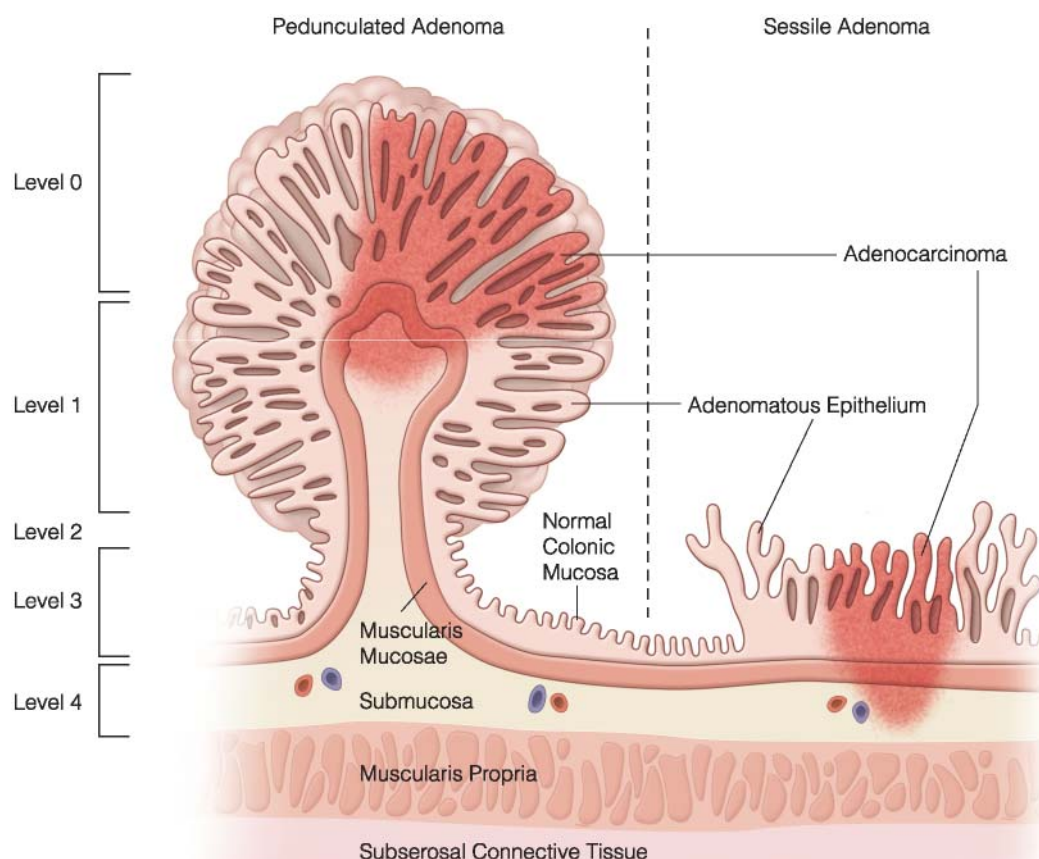


Figure 5 Haggitt classification of tissue invasion in a pedunculated polyp.

was 9.7%, with a bleeding risk of 8.6% and a perforation risk of 1.1%.

Postpolypectomy syndrome occurs in 2 to 3% of patients undergoing polypectomy and is the result of a transmural thermal injury with subsequent serosal inflammation. Most patients present with abdominal pain and fever. Workup includes an abdominal and pelvic CT scan to look for evidence of colonic perforation. If there is none, the patient is managed by avoiding oral intake and the administration of

parenteral antibiotics along with serial abdominal examinations. Most patients can be managed nonoperatively in this fashion. Those patients who develop signs of peritonitis require surgical exploration and primary repair of the injury. This is usually sufficient because the colon has been recently cleansed and contamination is usually minimal.

HEMOSTASIS

Lower endoscopy as a diagnostic and therapeutic tool for management of colonic bleeding is indicated in patients with spontaneous cessation as well as those with ongoing hemorrhage. Although, traditionally, radionuclide scans and angiography in concert with surgery were the first-line treatments, there is now greater advocacy and acceptance of the use of colonoscopy to manage these cases at the outset. Of course, good clinical judgment should be exerted to identify those patients with massive hemorrhage and hemodynamic instability who would benefit from angiography and/or an early trip to the operating room.

Historically, the role of urgent colonoscopy (defined as a procedure within 12 to 48 hours of admission) for lower GI bleeding has been questioned. This arose due to concerns of inadequate visualization and the fact that most bleeding stops spontaneously. However, several studies have demonstrated that colonoscopy under urgent conditions is safe and feasible after prior rapid cleansing, with a diagnostic yield of between 74 and 90%. This is higher than both radionuclide scans

Table 5 Haggitt Classification of Tumor Invasiveness in an Adenomatous Polyp	
Level	Histology Findings
0	Carcinoma in situ or intramucosal carcinoma. Not invasive.
1	Carcinoma invading through muscularis mucosa into submucosa but limited to the head of the polyp
2	Carcinoma invading the level of the neck of the adenoma
3	Carcinoma invading any part of the stalk
4	Carcinoma invading into the submucosa of the bowel wall below the stalk of the polyp but above the muscularis propria

and angiography, although no studies have compared these procedures head to head in a randomized fashion.¹⁹

The bowel preparation for the procedure is undertaken simultaneously with the resuscitation efforts and consists of 1 L of PEG administered orally or via a nasogastric tube every 30 to 45 minutes until the stool effluent is relatively clear. The administration of metaclopramide improves gastric emptying and may be a useful adjunct.

The tools for acquiring hemostasis include the following:

- *Vasoconstricting agents.* The most common method of gaining initial hemostasis is by injection of epinephrine, typically in a 1:10,000 concentration. It is injected into the submucosal layer to gain temporary hemostasis and as an adjunct to thermal therapy. Common side effects are transient tachycardia and hypertension. When bleeding obscures the field of view, irrigation with blind injection around an area of clot is considered safe.¹⁹
- *Thermal devices.* Applying thermal energy to a bleeding lesion either alone or in combination with injection therapy is another common strategy for gaining endoscopic hemostasis. Thorough knowledge of the principles of electrosurgery is critical for this technique. A comprehensive review of this topic is beyond the scope of this chapter, but a basic understanding of the types of electrosurgical energy is reviewed. Cauterizing a lesion with electromechanical energy (electrocautery) is simply the act of applying an alternating electrical current via a device to the desired tissue. Patients are not “shocked” by this energy the way they would be if they came in contact with a common wall outlet because it is delivered at a very high frequency in the radiowave spectrum (radiofrequency). All electrocautery requires a complete circuit to be delivered to the desired tissue. There are essentially two ways to complete this circuit. Monopolar electrocautery completes the circuit by the electrical current passing through the patient. Bipolar electrocautery passes through the affected tissue only. Monopolar electrocautery can penetrate deeply into tissues and is effective for hemostasis but risks deep thermal injury and possible perforation in thin-walled structures. Bipolar energy does not penetrate as deeply but may be less effective in gaining hemostasis. Thorough knowledge of these principles, along with proper energy settings on the generator used for electrocautery, is critical for the safe application of this technology. Argon plasma coagulation (APC) is a special version of monopolar electrocautery that requires additional understanding. Argon gas, when “electrified,” is converted to plasma, which conducts monopolar electricity. This principle is very useful in situations where it is desirable to apply electrocautery to large surface areas without risking deep tissue penetration. An additional benefit of the APC probes is that they enable the application of electrocautery without actually touching the tissue, which prevents the buildup of debris on the probe tip and allows for the expeditious “painting” of large surface areas. Understanding the unique energy settings and argon gas flow rates for operating an APC probe is essential. Being mindful to constantly aspirate the argon gas from the GI tract is also important. Another method of applying thermal energy to tissue in the GI tract is through use of a Teflon-tipped probe that is heated to a

desired level. This “heater probe” does not apply electrocautery to the tissue but simply cauterizes it by generating heat at its tip. Understanding the energy settings available on this probe and the conformity of its tip is important for its proper use.

- *Endoscopic clips.* Endoscopically placed clips [see Figure 6] are an excellent technology used to manage bleeding from discrete sources, such as the mouth of a diverticulum or postpolypectomy bleeding site, and can be applied multiple times. These clips are also excellent for controlling bleeding from a fresh anastomosis when injection and thermal application are undesirable.

DECOMPRESSION

Colonoscopic decompression has been performed in unprepared bowel for sigmoid volvulus and colonic pseudo-obstruction (Ogilvie syndrome). This nonsurgical approach may serve as an invaluable bridge to surgery in those critically ill and elderly patients who may not be able to withstand a surgical operation.

For sigmoid volvulus, the endoscope is advanced beyond the point of torsion gently, without excessive force and while keeping the lumen in sight at all times. Once the bowel is detorsed, contents from the proximal bowel are suction evacuated to decompress it [see Figure 7, a, b]. The decompressed state of the colon is maintained by placing a long rubber catheter in the proximal colon using endoscopic guidance [see Figure 7c].

STENTING

The first reported use of colonic stenting for treatment of large bowel obstruction was by Spinelli and colleagues in 1992.²⁰ Several subsequent studies have further validated its efficacy, and indications for their use are as follows:

- *Preoperative decompression.* In patients who present with acute obstruction from a primary colorectal malignancy, use of a stent to relieve the obstruction decreases the likelihood of requiring emergent surgery and the need for a colostomy. A one-stage en bloc resection of the cancer can be performed subsequently once the obstruction is relieved and the patient’s condition has optimized. Several prospective and retrospective studies have confirmed this. A large study by Dauphine and colleagues examining the role of stents used for preoperative decompression from 1990 to 2000 revealed that stenting was a successful bridge to surgery in 85% of cases and 95% of patients benefitted from a single-stage procedure.²¹ However, data from prospective studies randomizing patients to a stenting versus emergent surgery arm are lacking.
- *Palliation of obstruction.* In those patients with primary or recurrent CRC who are not operative candidates, endoscopic stents can be used as a means of palliation. In the same study by Dauphine and colleagues, stenting averted a colostomy in 90% of the patients.²¹
- *Palliation of malignant fistulas.* Sealing a colovesical or colovaginal fistula for palliation is another indication for stenting, although firm evidence to support this treatment modality is lacking.

Stenting is contraindicated in the presence of a perforation, and this must be definitely excluded prior to the procedure.

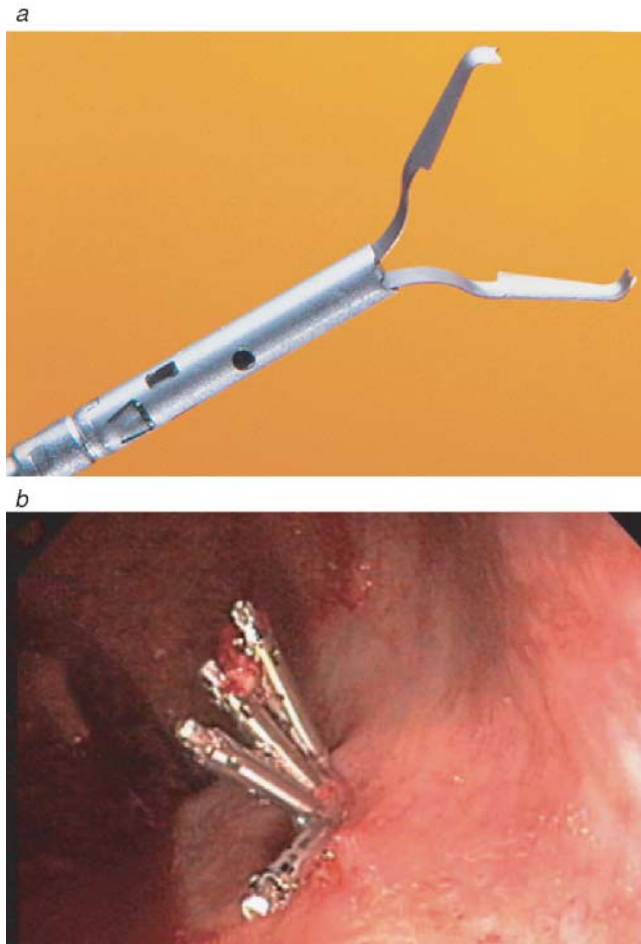


Figure 6 (a) Endoscopic clips. (b) Endoscopic clip application.

Similarly, benign strictures are a relative contraindication, although stents have been deployed in these circumstances.

Colonic stents are referred to as self-expanding metal stents and are made of woven, knitted, or laser-cut metal mesh cylinders that exert radially expansive forces when deployed, which helps keep them in position [see Figure 8a]. Some stents designed for the esophagus or bile duct are covered with a plastic membrane to prevent tumor ingrowth, but colonic stents are uncovered to allow better fixation and prevent migration. These stents usually foreshorten after deployment, which is an important consideration while choosing the length of stent to be deployed. A variety of stents are available, and their salient features are summarized in Table 6.

These stents are passed over a guide wire and are deployed with or without through-the-scope (TTS) assistance, usually with fluoroscopic guidance. The stents are mounted on delivery systems that differ with regard to the design of their handles and the release of the constricting mechanism. Most delivery systems release the stent at the distal end first.

Prior to stenting a patient with an obstruction, it is important to rule out any other proximal source of obstruction and to characterize the degree and length of the obstruction. An enema may be given prior to the procedure, although most patients with a high-grade obstruction have already evacuated stool below the lesion.

For non-TTS stent placement, a guide wire is passed through the endoscope, across the lesion, and as proximal as possible. The endoscope is withdrawn, and the nondeployed stent is advanced over its delivery system and across the stricture. The endoscope is reinserted to verify optimal positioning of the distal end of the stent and then deployed under direct vision. Positioning of the waist of the stent across the middle of the obstruction indicates optimal placement.

For TTS stent placement, a guide wire is passed across the obstruction and up to 20 cm proximally. The nondeployed stent is placed under direct endoscopic guidance and deployed after confirming optimal positioning [see Figure 8, b, c, and d].

Reported complications from stenting include perforation, migration, and bleeding. Perforation is the most devastating complication and negates the reason for the procedure in the first place, which was to avoid a colostomy and facilitate a one-stage resection. The risk of intraprocedural perforation may be reduced by limiting insufflation.²¹ Stent migration can be asymptomatic or present with rectal pain, bleeding, tenesmus, or fecal incontinence if the stent migrates distally. Typically, as long as the stent remains 2 cm above the anal canal, it does not produce symptoms and can be easily removed. Obstruction of the stent by tumor ingrowth is usually managed by placement of new stents across the old one. The study by Dauphine and colleagues alluded to earlier in

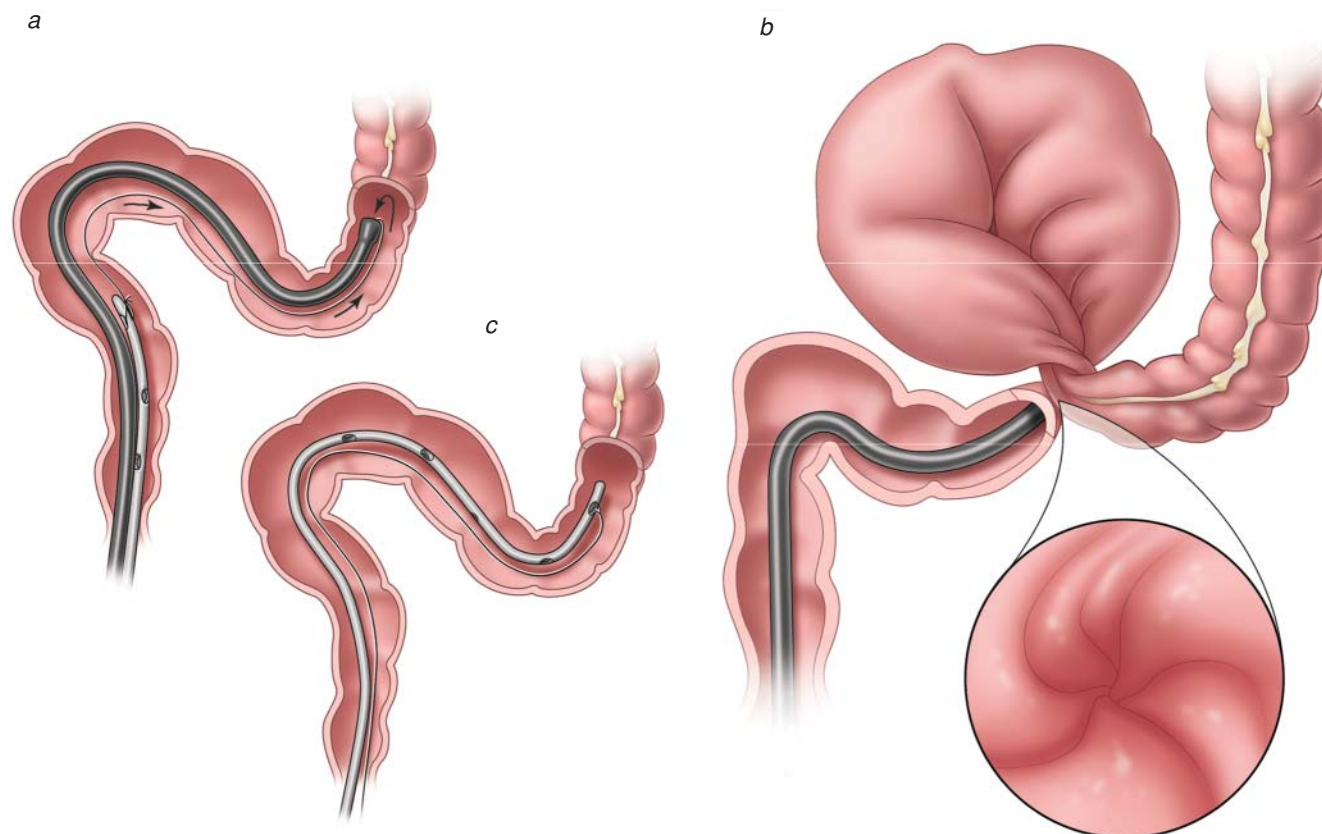


Figure 7 Colonoscopic decompression.

this chapter examined all cases of stent placement from 1990 to 2000 and reported a mortality of 1%, a perforation rate of 0 to 7%, a migration rate of 3 to 22%, bleeding in 0 to 5%, and a reobstruction rate of 0 to 15%.²¹

BALLOON DILATION

The endoscopic management of anastomotic and other benign strictures by balloon dilation provides a relatively non-invasive method to a problem that was long managed surgically. Similar to their role in upper endoscopy, endoscopic balloon dilation lends itself well to the management of benign colonic strictures. The procedure is optimally performed under fluoroscopic guidance, and a gentle bowel preparation to cleanse the colon distal to the stricture is recommended. The deflated balloon is passed through the working channel of the endoscope and positioned across the stricture. Under endoscopic and fluoroscopic guidance, the balloon is inflated to its full diameter and left in position for 1 to 2 minutes. It is then deflated and withdrawn, and the area of dilation is endoscopically inspected for evidence of bleeding or perforation. The procedure may be repeated at 2- to 4-week intervals as necessary, and patients should be advised that multiple sessions are frequently required to obtain maximum therapeutic benefit. Although reports indicate a median number of approximately 2.6 dilations to maintain long-term patency, a retrospective review by Araujo and Costa on patients after low anterior resection did not find a relation between the number of dilation sessions and recurrence.²²

Sigmoidoscopy

The advent of the sigmoidoscope was the first breakthrough in lower endoscopy. Although less in favor and less frequently performed today, it is still a valuable diagnostic and therapeutic tool for conditions of the lower colon and rectum. Indications for its use today include evaluation of a change in bowel habits, bleeding, and lower abdominal pain and as a screening tool for CRC. It is usually performed in the doctor's office after an enema and requires no sedation. Although no prospective studies exist that demonstrate a reduction in CRC mortality from sigmoidoscopy, case control studies have suggested a decrease in the incidence of CRC in the examined areas, with benefits lasting up to 10 years.²³ However, the risk of cancer in the colon beyond the reach of the sigmoidoscope is not reduced, and multiple studies have confirmed that advanced proximal adenomas may exist even in the absence of more distal lesions.^{6,23,24} Flexible sigmoidoscopy is currently recommended as an alternative screening tool to colonoscopy every 5 years.

Certain findings on sigmoidoscopy predict a higher risk for proximal advanced neoplasia and warrant a more complete colonoscopic examination. These include villous histology of the distal adenoma, adenomas greater than 1 cm, and multiple adenomas. Adenomas less than 1 cm may be excised using a cold snare technique and can be histologically distinguished as hyperplastic or inflammatory in nature. Electromechanical energy should not be used in the unprepared bowel to avoid explosion.

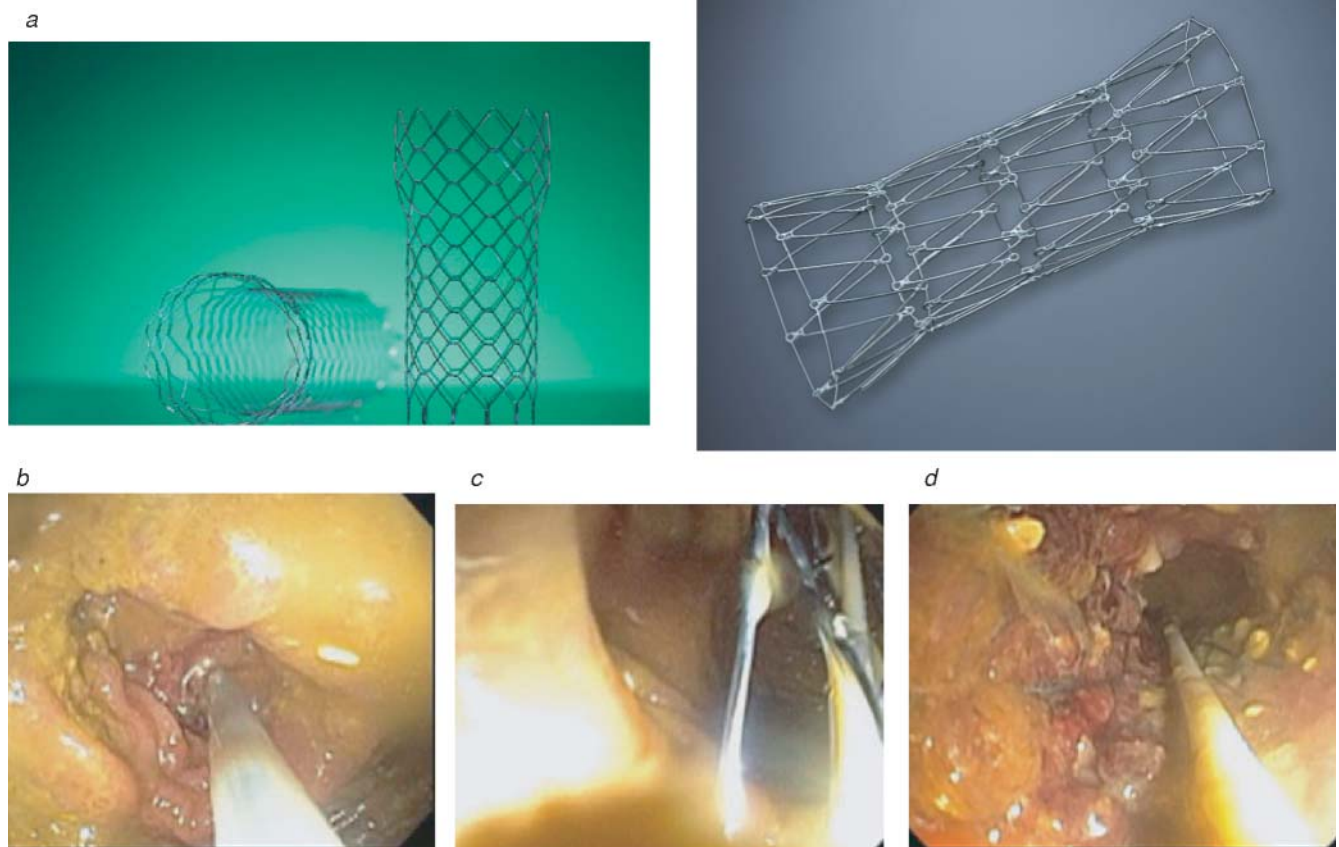


Figure 8 (a) Self-expanding uncovered metal stents. (b, c, d) Self-expanding uncovered metal stent being deployed in a patient with a malignant obstruction. A guide wire is passed through the obstruction. The collapsed stent is passed over the guide wire and across the obstruction. Once optimal position of the stent is confirmed, it is deployed. Luminal caliber is restored once the stent is in position.

Anoscopy

Anoscopy employs a lubricated speculum [see *Figure 9*] to visually inspect and examine the anal canal. It is performed in the doctor's office or emergency department and may be used to diagnose hemorrhoids, anal fissures, fistulas, abscesses, tumors, and bleeding from the anal canal. Maneuvers such as banding of prolapsed hemorrhoids, biopsies of tumors, fulguration of warts, drainage of small superficial abscesses,

and application of silver nitrate to bleeding points may also be safely carried out using anoscopy. Anoscopy requires a minimal preparation such as an enema and produces minimal discomfort. It should be performed carefully after recent anal or rectal surgery.



Figure 9 Anoscope.

Table 6 Colonoscopic Stents and Features	
Material	Comments
Nitinol	A nickel, titanium alloy that is flexible enough to allow stenting across sharply angulated areas at the cost of reduced radially expansive forces Decreased incidence of migration by creating wider flare at its proximal end Foreshortens by 23% when deployed
Elgiloy	A cobalt, chromium, and nickel alloy that is corrosion resistant and exerts high radial forces when deployed Allows through-the-scope deployment Foreshortens by 39–49% when deployed
Stainless steel	Does not foreshorten when deployed

Endoscopic Ultrasonography

The scope of EUS is more limited in lower endoscopy when compared with its application during esophagogastroduodenoscopy (EGD) and endoscopic retrograde cholangiopancreatography (ERCP). EUS uses rigid endorectal probes [see Figure 10a], flexible radial and longitudinal ultrasonographic echoendoscopes, and catheter miniprobe that can be passed through the working channel of the endoscope. A schematic of the endoluminal anatomy as visualized during EUS is depicted in Figure 10b.

Endorectal ultrasonography is an invaluable tool for preoperative staging in rectal cancer [see Figure 10, c and d] and helps stratify those patients who would benefit from local excision versus radical resection as well as the need for neoadjuvant chemoradiation. It is also used for surveillance after surgery to detect local recurrence of tumor.

EUS is also used to guide the management of complicated fistulas [see Figure 10e] in patients with perianorectal inflammatory bowel disease. Patients with complex perineal fistulas from Crohn disease usually undergo a protracted course of medical and surgical therapy, which is dictated by the clinical discretion of the surgeon. With EUS, superior anatomic delineation of the fistula in relation to the sphincter and identification of occult internal openings and abscesses can guide the surgeon in deciding the optimal course of treatment for these complex problems. A retrospective study by Schwartz and colleagues in 21 patients with complex perineal fistulas treated by a combination of medical and surgical therapy guided by serial EUS revealed that 86% of patients had initial cessation of drainage, whereas 76% had long-term cessation.²⁵ Furthermore, a small, randomized, prospective study by the same group demonstrated that when EUS was used to guide treatment, 80% of patients responded completely compared with 20% of patients in the control arm, whose management strategy was solely at the clinical discretion of their provider.²⁶ At this time, the ASCRS recommends the use of EUS as a beneficial adjunct in the management of these patients.²⁷ The use of EUS requires special training and knowledge of the principles of ultrasonography to avoid misinterpretation.²⁸

Lower Endoscopy Training and Innovations on the Horizon

There is currently a deficiency of consistent and curriculum-driven endoscopy training for general surgeons. This has made it difficult for surgeons in training to gain adequate experience in colonoscopy so that they feel confident in performing the procedure. In fact, rural surgeons perform flexible endoscopy more frequently than any other procedure but report a lack of confidence in doing so at the beginning of their practice as a result of either inadequate exposure to the endoscopic platform or lapsed time periods between their rotation as a junior resident and use of the endoscope as a senior resident.²⁹

The American Board of Surgery acknowledges the importance of learning colonoscopy during residency and, as part of this acknowledgment, has recently increased the required number of cases for general surgery board certification. Although it is logical to believe that doing more procedures

results in better performance, there is considerable debate about what numbers to use and if numbers by themselves are an adequate indicator of competency. Some believe that the real underlying problem in endoscopy training is the lack of a validated assessment tool for measuring procedural competence. Recently, Vassillou and colleagues reported on a score card to measure endoscopic proficiency. This Global Assessment of Gastrointestinal Endoscopic Skills (GAGES) provides the first validated objective measure of specific parameters required for proficiency in flexible GI endoscopy. Preliminary testing using this score card indicates that it is a consistent, reliable, and valid measure of endoscopic skill.³⁰ Such a score card may eventually replace numbers as a measure of proficiency in endoscopy.

Recognizing the challenges in learning flexible GI endoscopy, the SAGES has worked to develop a validated training and assessment program for GI endoscopy called the Fundamentals of Endoscopic Surgery (FES). This program provides Web-based didactic material on the essentials of flexible GI endoscopy, as well as a validated written examination of knowledge and a hands-on test of skill. FES may become the first “off-the-shelf” validated training and assessment tool for GI endoscopy, and it is hoped that this program will become an integral part of both surgery residency and GI fellowship training.

Over the past decade, the ultimate therapeutic endoscopic procedure has been pioneered, called natural orifice transluminal endoscopic surgery (NOTES). This type of surgery uses a flexible endoscopic platform passed into a natural orifice and across the wall of the GI tract to gain access to the peritoneal cavity. With this approach, all manner of abdominal surgery have been accomplished in animate and cadaver models, and clinical trials are currently under way for NOTES appendectomy and cholecystectomy. The transcolonic route has been described for peritoneoscopy and staging of cancer, drainage of pelvic abscesses, and urologic and gynecologic procedures. Current experiments in NOTES procedures have described using a combination of transgastric, transvaginal, and transcolonic access for full-thickness polyp resection, colostomy, and ileostomy creation, as well as right and left colon resection.³¹ These achievements, although exciting, have been limited by inadequacy of instrumentation for retraction, hemostasis and suturing, ergonomic challenges, and the inadequacy of the flexible GI endoscopic platform to perform complex surgical procedures. Lack of definitive closure devices for the colotomy also leaves many surgeons wary of pursuing these new techniques, although novel devices for endoscopic suturing are quickly becoming available, as recently reviewed in an article by Swain.³² Some of these devices have been used in small clinical trials with success.

Most reports of NOTES procedures are in animal and cadaver models, with few human case reports and even fewer case series. However, some surgeons have used the advent of NOTES to reexamine their practice and try to develop less invasive laparoscopic procedures. One example is the development of a “hybrid” NOTES approach to colon resection, where the dissection and anastomosis are performed laparoscopically, but specimen extraction is done either transanally or transvaginally.³³ Transanal endoscopic microsurgery, a procedure that uses special laparoscopic instrumentation introduced via the anus and into the rectum for transluminal

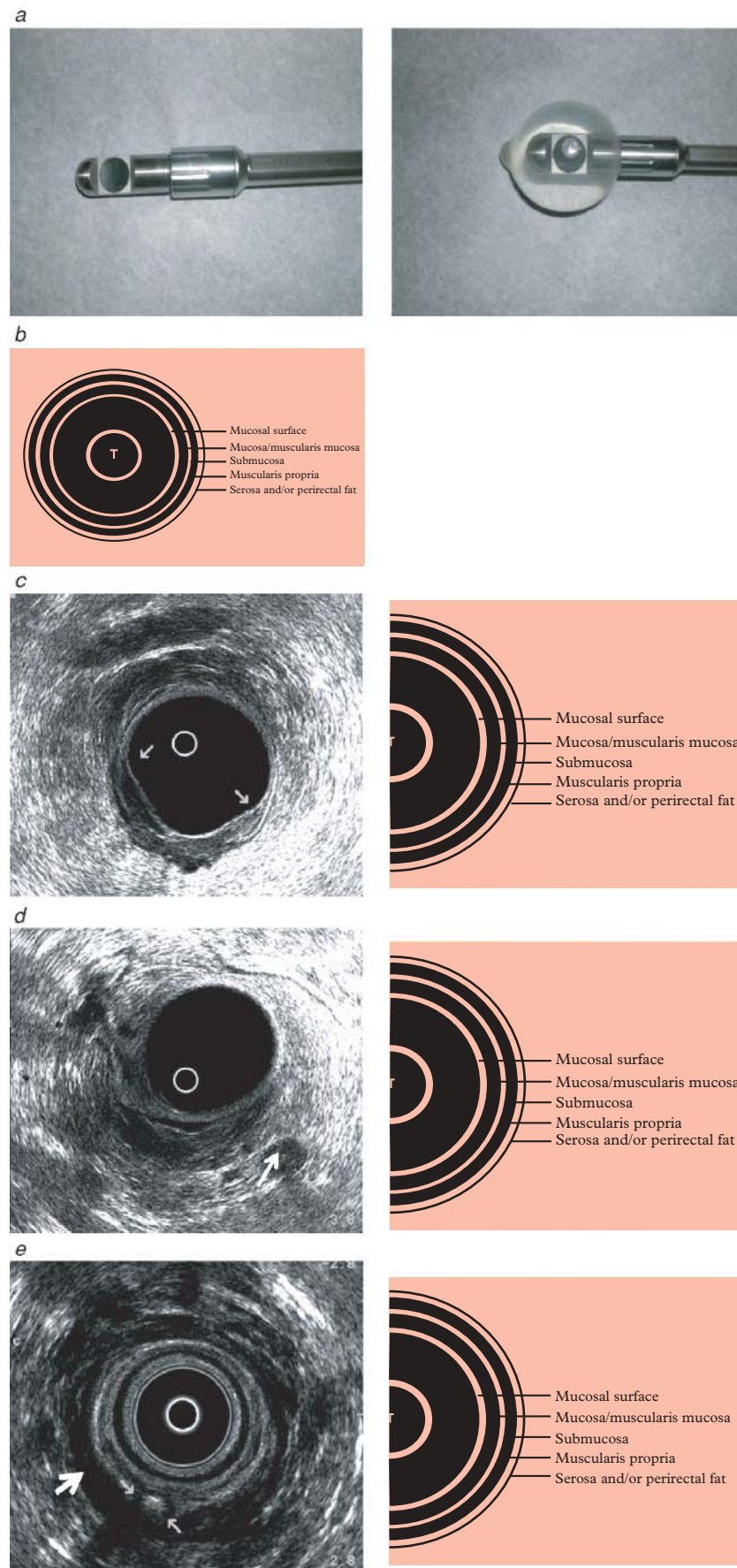


Figure 10 (a) Rigid endorectal probes for endoscopic ultrasonography (EUS). (b) Schematic of the endoluminal anatomy visualized on EUS. (c) T3 cancer invading the pericolic fat. Arrows indicate lateral limits of tumor extension. (d) Presence of lymph node enlargement in a patient with rectal cancer. The arrow indicates a 1 cm lymph node. (e) Transsphincteric fistula as visualized on EUS. The larger, thicker arrow indicates the sphincter complex. The two smaller arrows indicate the site of the fistulous opening.

full-thickness excision of rectal cancer and suture repair of the resultant defect, has been studied as a portal for NOTES surgery on the colon. In a preclinical study on porcine and cadaver specimens, Denk and colleagues demonstrated the feasibility of this platform for colonic excision and extraction using the transrectal route.³⁴ Technical challenges remain, however. Innovative redesign of instrumentation and the endoscope is currently under way to overcome these ergonomic obstacles and advance its acceptance in the surgical community.

Summary

Whether surgeons perform colonoscopy as part of their practice or work in collaboration with a gastroenterologist to provide the service, it is critical to have a thorough understanding of the technique, the indications and contraindications for its use, and potential complications. Such knowledge will allow surgeons to better use the procedure to the maximum benefit of their patients.

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20 PROCEDURES FOR BENIGN AND MALIGNANT GASTRIC AND DUODENAL DISEASE

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Procedures for Benign Gastric and Duodenal Disease

Advances in the medical management of peptic ulcer disease, including the use of effective acid-suppressing medications (e.g., histamine receptor antagonists and proton pump inhibitors [PPIs]) and the treatment of *Helicobacter pylori*, have led to a dramatic decrease in the need for elective surgical management of uncomplicated duodenal and gastric ulcers. In the past, surgery was the only effective long-term option for peptic ulcer disease, but over the past two decades, it has become an increasingly rare choice.¹ Currently, operative therapy for peptic ulcer disease is largely reserved for the management of complications such as hemorrhage, perforation, and obstruction. The recognition that medical management successfully prevents ulcer recurrence in most patients has caused surgical management of complicated ulcer disease to evolve into a more minimalist strategy that favors damage control surgery for complications and only infrequently resorts to acid-reducing operations.²

In this section of the chapter, we focus primarily on procedures performed to treat peptic ulcer disease, although we also briefly address diverticulectomy for duodenal diverticular disease. Other gastroduodenal procedures for nonmalignant disease are described in more detail elsewhere: gastric restrictive procedures and gastric bypass are discussed in the context of bariatric surgery [see 5:7 *Surgical Treatment of Morbid Obesity*]; choledochoduodenostomy and transduodenal sphincteroplasty are discussed in the context of biliary tract surgery [see 5:22 *Procedures for Benign and Malignant Biliary Tract Disease*]; cystogastrostomy for intractable pancreatic pseudocysts is discussed in the context of pancreatic surgery [see 5:24 *Procedures for Benign and Malignant Pancreatic Disease*]; and duodenal diverticularization is discussed in the context of pancreatic and duodenal trauma [see 7:9 *Injuries to the Pancreas and Duodenum*].

PREOPERATIVE EVALUATION

The appropriate extent of preoperative evaluation for a patient undergoing surgery for a benign gastroduodenal disorder is dictated primarily by the nature of the presenting problem. In the case of gastric outlet obstruction or a rare condition such as intractable peptic ulcer disease that is refractory to medical management, the preoperative workup may be extensive and include detailed endoscopy, contrast studies of the upper abdomen, cross-sectional imaging with computed tomography (CT), and full laboratory panels. In

most cases of complicated peptic ulcer disease, however, the emergency nature of the situation necessarily renders an extensive preoperative workup impractical. For instance, patients with perforated duodenal ulcers typically present in distress with an acute abdomen. A chest x-ray that demonstrates free intraperitoneal air is all that is needed before the patient is taken to the operating room; the decision to proceed to operation should not be delayed by waiting for further images (e.g., CT scans).

Patients who are experiencing upper gastrointestinal (GI) hemorrhage secondary to peptic ulcer disease should undergo endoscopy to identify the source of bleeding [see 5:5 *Gastrointestinal Bleeding*]. In many cases, endoscopic management of bleeding ulcers is possible, rendering surgical management unnecessary. Definitive surgical management is indicated, however, if bleeding leads to hemodynamic instability, an extensive transfusion requirement (i.e., more than 6 units), or rebleeding after initial endoscopic management. Objective criteria for surgery must be determined on a patient-by-patient basis. Precise preoperative localization of the bleeding source is essential; a bleeding posterior duodenal ulcer, for example, cannot be managed in the same way as hemorrhage from diffuse severe gastritis. Endoscopy should therefore be performed whenever possible. Alternatively, if brisk bleeding prevents clear intraluminal visualization of a bleeding site, angiographic localization may be attempted.

Occasionally, patients present for surgery with refractory gastric ulcers. If the ulcer has not healed after 12 weeks of optimal medical therapy, resection is indicated to rule out an occult gastric malignancy. In such cases, the preoperative workup should include endoscopic biopsies of the ulcer base and the surrounding gastric mucosa so that a preoperative diagnosis of malignancy can be made if possible. In view of the concern about a possible gastric malignancy, it is reasonable to obtain a preoperative chest x-ray and a CT scan of the abdomen so as to detect possible nodal or distant metastases.

OPERATIVE PLANNING

Patients undergoing gastroduodenal procedures should receive general anesthesia and have a nasogastric tube and Foley catheter in place. The supine position is preferred. The operation is usually done via an upper midline incision or, occasionally, via a bilateral subcostal incision, with fixed retractors used in either case.

The choice of procedure is primarily dictated by the indication for operation. Usually, several options are available. The first priority is to manage complications (e.g., bleeding and perforation); whether an accompanying acid-suppressing procedure is indicated and which one should be done depend on the clinical setting. Most commonly, duodenal perforation is treated with closure and omental patching, with or without an acid-reducing procedure. A bleeding ulcer is treated with oversewing of the bleeding vessel, with or without an acid-reducing vagotomy and pyloroplasty. Gastric outlet obstruction may be managed with several different approaches, including vagotomy with antrectomy and vagotomy with drainage via pyloroplasty or gastroenterostomy. In the rare cases of intractability, highly selective vagotomy (HSV) is the procedure of choice.

An important component of preoperative evaluation is determination of the severity and duration of disease. If symptoms are long-standing or recurrent—particularly when the patient has already received acid-reducing or anti-*H. pylori* therapy—a definitive acid-reducing procedure should be considered. As has been demonstrated,³ however, ulcer recurrence is significantly reduced even without an acid-reducing procedure when perforated ulcers are managed with anti-*H. pylori* agents in conjunction with a PPI. Therefore, a compliant patient who is presumed to be infected with *H. pylori* may not need to undergo an additional acid-reducing procedure. The evidence for this strategy is less clear with respect to bleeding or obstructing ulcers.

OMENTAL PATCH FOR DUODENAL PERFORATION (GRAHAM PATCH)

Operative Technique

Perforated duodenal ulcers are typically treated by oversewing the perforation and then placing a portion of the greater omentum over the suture line. The duodenal ulcer wall is carefully débrided and closed with three or four interrupted silk sutures; the tails of the sutures may be used to hold the omentum in place. Alternatively, if the ulcer edges are edematous and not expected to close easily, the perforation may be closed with a true Graham patch, which involves plugging the defect with a well-vascularized omental pedicle [see Figure 1]. Care should be taken to avoid tying sutures too tightly; this can lead to devascularization of the omental pedicle. Once the operation has been completed, the abdomen is generously irrigated to remove any contamination, and a search is made for occult collections in the subphrenic space and the pelvis.

Troubleshooting

To avoid placing excessive tension on the repair, primary closure should not be attempted if the duodenal wall is overly edematous and thickened. For large perforations that are expected to result in gastric outlet obstruction if closed, consideration should be given to incorporating the closure into a pyloroplasty.

There is some controversy regarding whether an acid-reducing operation should be added to the omental patch procedure. If the patient is stable and has a history of peptic ulcer disease, a definitive ulcer operation is included; HSV may be preferable to truncal vagotomy and pyloroplasty in that it is less likely to give rise to dumping syndrome and postvagotomy diarrhea. If the patient has no history of peptic ulcer disease, has a severe medical illness, is hemodynamically unstable, has a long-standing perforation, or exhibits gross abdominal contamination, a definitive ulcer operation is omitted. In cases

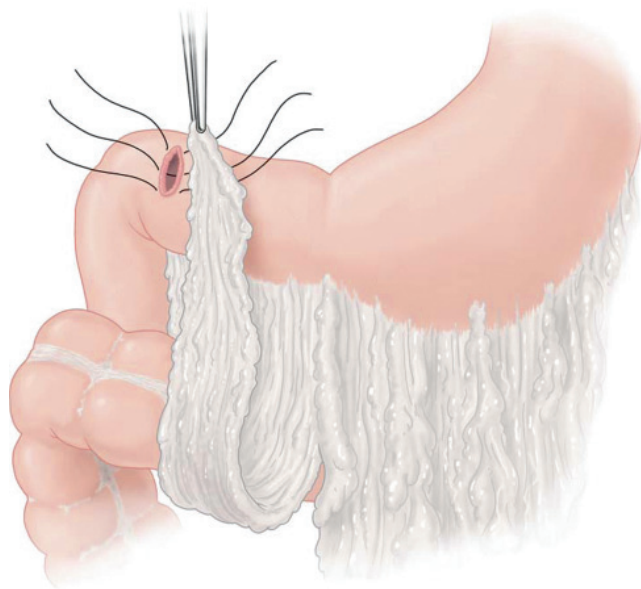


Figure 1 Omental (Graham) patch. Three or four interrupted sutures are placed along the ulcer edge. If possible, the ulcer is closed primarily and reinforced with omentum. Primary closure may be difficult; in a true Graham patch, primary closure is not attempted, and omentum is used to cover the tissue defect.

of gross contamination of the abdomen, it is probably inappropriate to divide the peritoneum over the esophagus during vagotomy and thereby expose the mediastinum to infection.

Complications

Persistent leakage should be uncommon after adequate closure. Duodenal scarring at the area of perforation and repair may lead to gastric outlet obstruction. Incomplete exploration and irrigation of the abdomen may result in late infection.

Outcome Evaluation

With adequate acid suppression and anti-*H. pylori* therapy, symptoms of duodenal ulcer are unlikely to recur. The 1-year recurrence rate after omental patching is substantially lower when both therapies are employed than when only a PPI is given (5% versus 38%).³

VAGOTOMY AND PYLOROPLASTY FOR BLEEDING DUODENAL ULCER

Truncal vagotomy with pyloric drainage via pyloroplasty is rarely employed as primary therapy for peptic ulcer disease, but it does play a role in emergency management of bleeding duodenal ulcers. This approach to acid suppression fits well with the proximal duodenotomy used to control the hemorrhage. Exposure of the first portion of the duodenum via a longitudinal incision in the pylorus is combined with truncal vagotomy; the pylorus is then closed in a transverse fashion to prevent the development of gastric outlet obstruction.

Operative Technique

Step 1: exposure and pyloric division A Kocher maneuver is performed. The pylorus is identified through palpation and through identification of the pyloric vein as it courses anteriorly. Two traction sutures are placed in the anterior aspect of the pylorus, one superiorly and one inferiorly.

A longitudinal incision is made that extends approximately 2 to 3 cm on either side of the pylorus.

Step 2: ligation of bleeding vessel The bleeding ulcer bed is directly oversewn with at least three sutures. Figure-eight sutures are placed on the superior and inferior borders of the ulcer bed to ligate the gastroduodenal artery proximal and distal to the ulcer, and a third figure-eight suture is placed medially to control the transverse pancreatic branch [see Figure 2].

Step 3: pyloroplasty Tension is applied to the previously placed traction sutures to convert the longitudinal incision to a transverse one. The incision is then closed transversely in two layers with full-thickness bites of 3-0 or 2-0 nonabsorbable suture material (Heineke-Mikulicz pyloroplasty) [see Figure 3]. Tension-free closure is facilitated by adequate duodenal mobilization (by means of the Kocher maneuver) and lysis of surrounding adhesions.

Step 4: vagotomy To perform the vagotomy, further exposure may be needed, including mobilization of the left lateral section of the liver and division of the triangular ligament. Downward traction on the greater curvature of the stomach is essential to apply gentle tension to the esophagogastric junction and the proximal vagi. The peritoneum over the esophagus is divided transversely with the electrocautery; exposure may be facilitated by surrounding the distal esophagus with a Penrose drain for downward traction. The left (anterior) vagus is best identified by applying traction to the right and posteriorly so that the nerve can be traced into the posterior mediastinum. All fibers entering the distal esophagus are divided. The main nerve trunk is clipped proximally and distally, and a 2 cm long segment is excised. The right (posterior) vagus is exposed by applying traction to

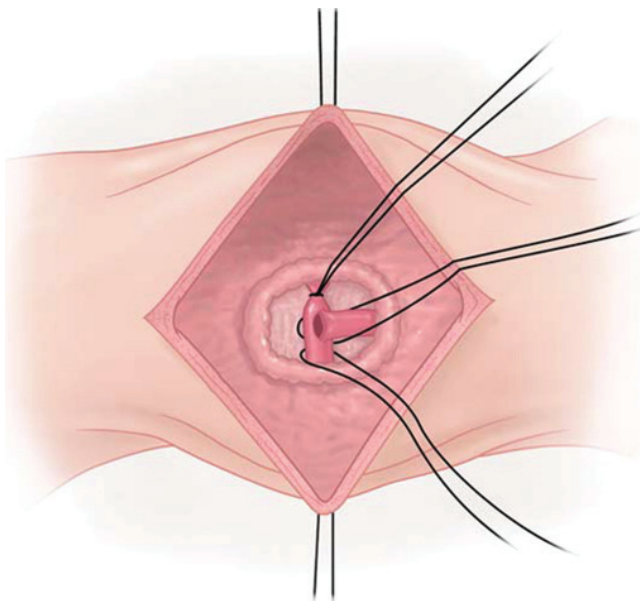


Figure 2 Vagotomy and pyloroplasty: sutures. To control a bleeding duodenal ulcer, traction sutures are placed along the cephalad and caudad borders of a longitudinal incision across the pylorus. Figure-eight sutures are placed at the cephalad and caudad portions of the ulcer to occlude the gastroduodenal artery. An additional U-stitch is placed to control small transverse pancreatic branches that may cause late bleeding. Care should be taken to avoid the underlying common bile duct.

the left and anteriorly; the nerve can then be palpated as a taut cord and divided in much the same manner as the anterior vagus. For a complete vagotomy, the distal esophagus must be skeletonized for approximately 5 cm [see Figure 4].

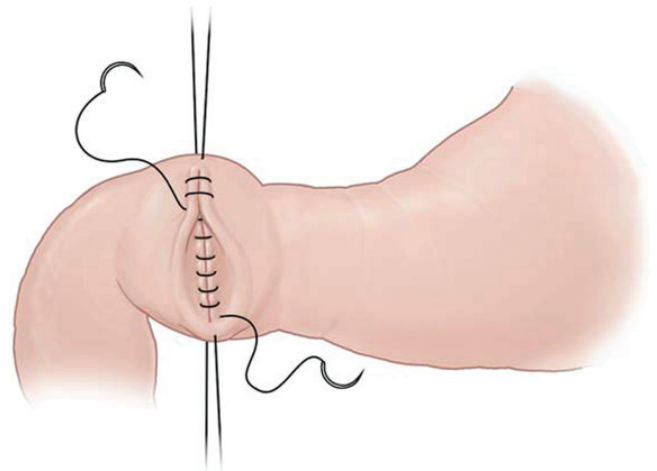


Figure 3 Vagotomy and pyloroplasty. For a Heineke-Mikulicz pyloroplasty, a full-thickness longitudinal incision is made that extends from a point 1 cm proximal to the pylorus to a point 1 to 2 cm distal to the pylorus. The incision is closed transversely in two layers. Superior and inferior stay sutures help align the incision for closure.

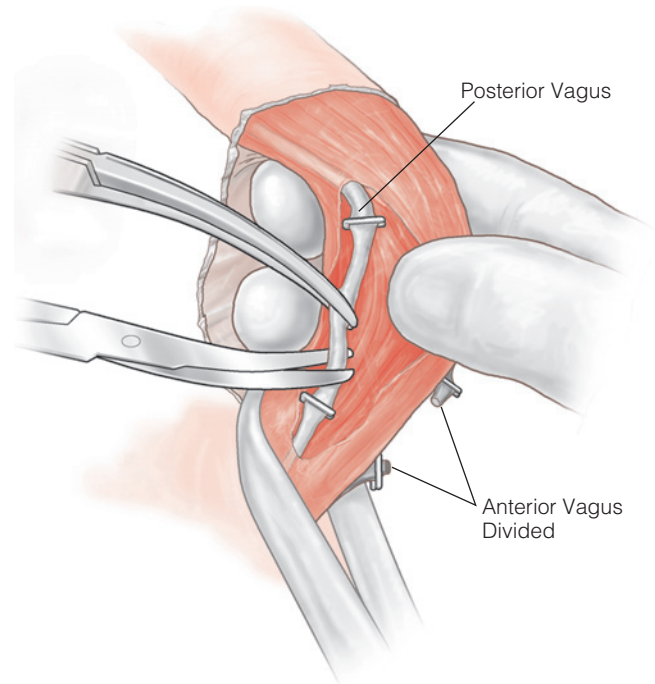


Figure 4 Vagotomy and pyloroplasty. For the truncal vagotomy, the peritoneum over the esophagogastric junction is opened wide to afford exposure. Gentle downward traction is applied to the stomach to facilitate identification of the two vagus nerves. Surgical clips are applied to each nerve in turn, and a 2 to 3 cm nerve segment is removed between the clips. These segments should be inspected to confirm removal of neural tissue.

Troubleshooting

As this procedure becomes less frequent and surgeons' experience with it dwindles, location of the vagus nerves may prove an increasingly troublesome task. In most cases, complete skeletonization of the distal esophagus in conjunction with appropriate traction should allow palpation of the main vagal trunks.

If substantial duodenal scarring is present, a tension-free Heineke-Mikulicz pyloroplasty may not be possible, and a Finney pyloroplasty may be preferable. The Finney procedure is essentially a side-to-side anastomosis that is created in two layers between the distal stomach and the proximal duodenum [see Figure 5]. Complete mobilization of the duodenum, including adhesiolysis and a generous Kocher maneuver, is required.

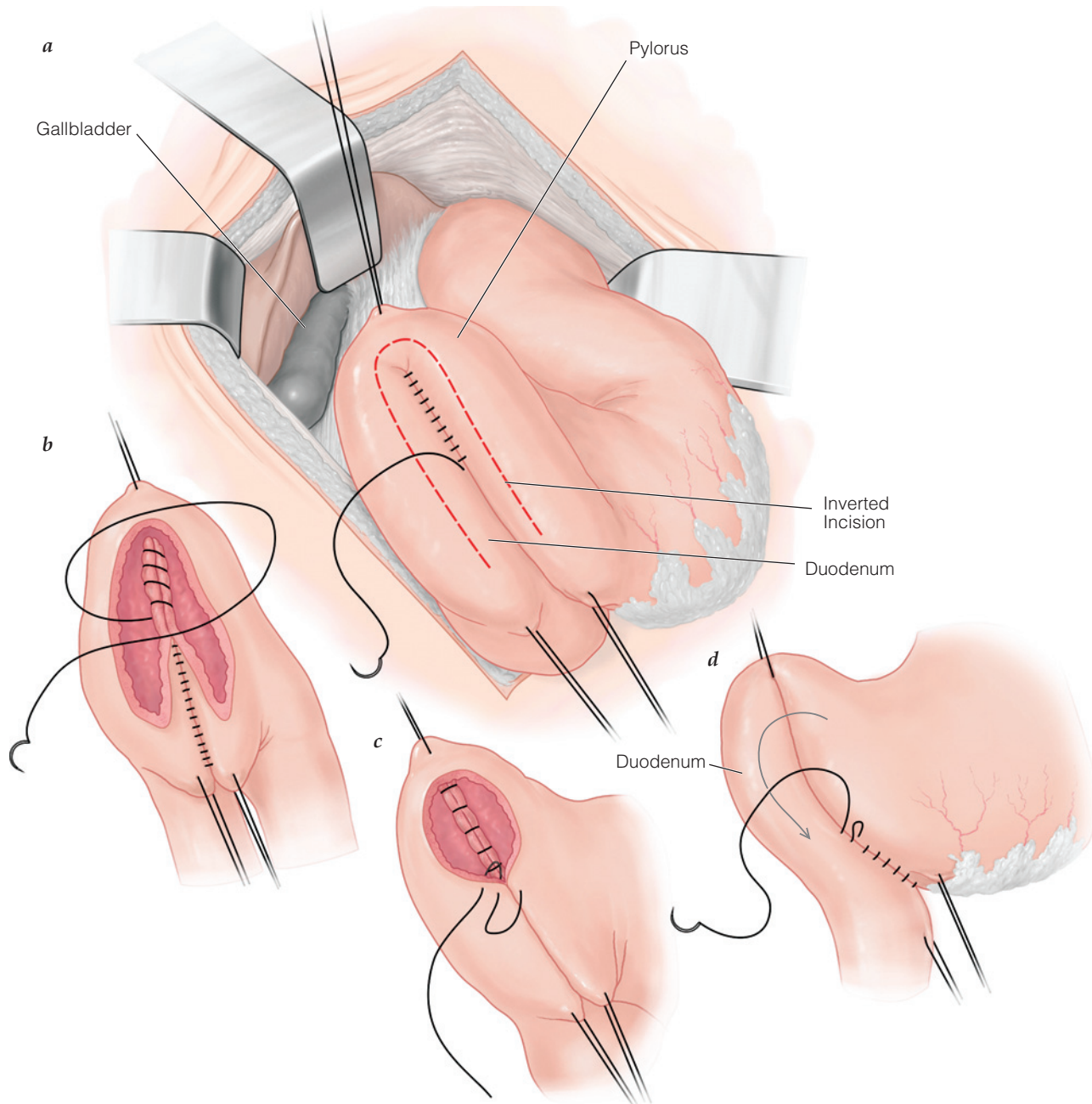


Figure 5 Finney pyloroplasty. If a tension-free Heineke-Mikulicz pyloroplasty is not feasible, a Finney pyloroplasty may be performed instead. (a) The distal stomach and the proximal duodenum are aligned with stay sutures; meticulous lysis of surrounding adhesions is essential. An inverted U-shaped incision is made. (b) The pyloroplasty is created in two layers. The posterior portion of the outer layer, consisting of seromuscular Lembert sutures, is placed first, followed by an inner layer constructed with a continuous full-thickness absorbable suture. (c) The anterior portion of the inner layer is closed with a continuous full-thickness suture. Some surgeons prefer a Connell suture at this site. (d) The anterior portion of the outer layer, consisting of silk Lembert sutures, is placed.

Care should be taken to keep from injuring the common bile duct (CBD), particularly when the vascular inflow to a deeply penetrating duodenal ulcer is being sutured.

Complications

Leakage from a pyloroplasty is rare. Gastric outlet obstruction may occur secondary to either scarring or edema at the operative site; often it is relieved by nasogastric decompression and conservative management. The incidence of ulcer recurrence and rebleeding is quite low with adequate anti-*H. pylori* treatment.

ANTRECTOMY

The primary indication for gastric resection in the setting of peptic ulcer disease is chronic obstruction caused by scarring, typically from a pyloric channel ulcer. Antrectomy removes the gastrin-secreting portion of the stomach. In addition, antrectomy may be required for recurrent bleeding after an adequate vagotomy and pyloroplasty for a bleeding duodenal ulcer. Alternatively, antrectomy may be the elective operation of choice for intractable type I, II, and III gastric ulcers, as well as a primary emergency surgical option for perforated or bleeding gastric ulcers. Historically, a primary Billroth I gastroduodenostomy has been the preferred procedure, but surrounding scar tissue may limit the mobility of the duodenum, in which case, a Billroth II gastrojejunostomy may be required for a tension-free anastomosis. Antrectomy is typically combined with truncal vagotomy.

Operative Technique

Step 1: exposure The lesser sac is entered via the avascular plane in the greater omentum, the plane between the stomach and the pancreas is developed, and the lesser omentum is divided. The proximal border of the antrum must be identified before the stomach is divided. On the greater curvature, the antrum extends to a point between the pylorus and the fundus; on the lesser curvature, it extends to a point just above the incisura. Distally, the dissection is carried past the pylorus. Along the lesser curvature, dissection necessitates division of the descending branch of the left gastric artery, as well as the right gastric artery. Dissection along the pylorus must be meticulous to ensure that the pancreas is not damaged. If a Billroth I anastomosis is planned, dissection should continue 1 cm beyond the pylorus to expose a sufficient length of duodenum for the anastomosis. If a Billroth II reconstruction is planned, dissection need extend only far enough to allow division of the duodenum past the pylorus.

Step 2: division of stomach A gastrointestinal anastomosis (GIA) stapler is used to divide the stomach at the estimated borders of the antrum. The antrum is gently retracted anteriorly and to the patient's left. The right gastroepiploic artery and vein are divided just distal to the pylorus. The duodenum is then divided distal to the pylorus with a transverse anastomosis (TA) stapler.

Step 3: reconstruction When feasible, a Billroth I reconstruction (primary gastroduodenostomy) may be performed to maintain physiologic antegrade flow (although there are no data establishing that this maintenance of antegrade flow is beneficial). In addition, this reconstruction avoids the complications associated with a Billroth II reconstruction (e.g., afferent and efferent loop syndromes and

duodenal stump leaks). A generous Kocher maneuver, if not already performed, is necessary to minimize tension on the anastomosis. The lower portion of the staple line is removed for the width of the duodenal stump, and the anastomosis is performed in two layers or fashioned with a GIA stapler through a gastrotomy [see Figure 6].

If a primary gastroduodenostomy is not possible, a Billroth II reconstruction (gastrojejunostomy) is indicated. This procedure involves a number of technical considerations: management of the duodenal stump, the length and placement of the afferent limb, and the placement and method of the anastomosis. If the duodenum is not scarred or inflamed, simple staple closure will suffice; if closure proves difficult, a lateral duodenostomy tube may help decompress the stump. The duodenal stump should be covered with an omental patch.

The segment used for the anastomosis should be as short as possible while still being able to reach the stomach without tension; approximately 20 cm of proximal jejunum should be sufficient to serve as the afferent limb. Passing the jejunum through a retrocolic window places less tension on the mesentery than an antecolic approach does, although gastric emptying will occur with either method. If a retrocolic approach is used, a window is created for the jejunum; this must be closed and fixed to the small bowel.

The gastrojejunostomy may be constructed either to the posterior wall of the stomach or to the inferior portion of the excised staple line. If the anastomosis is placed at the gastric staple line, the inferior portion of the staple line is excised, often together with a wedge of stomach behind the staple line. A two-layer anastomosis is created with an outer layer of Lembert sutures and an inner layer of absorbable full-thickness

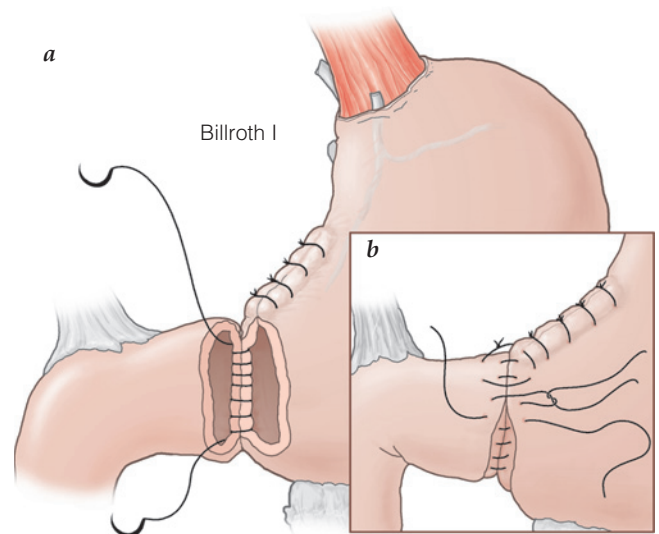


Figure 6 Antrectomy: Billroth I reconstruction (gastroduodenostomy). (a) The anastomosis is done in two layers. The inner layer is constructed by placing a continuous full-thickness suture. (b) The outer layer is constructed with silk Lembert sutures. The junction of the anastomosis and the gastric staple line has been referred to as the angle of sorrow, a term that reflects the common complication of leakage at the intersection of suture or staple lines. This junction may be reinforced with additional Lembert sutures.

sutures; the gastric staple line may be oversewn [see Figure 7]. Alternatively, the gastrojejunostomy may be created by means of stapling. A GIA stapler is introduced via a gastrotomy and a small enterotomy, and the defect is subsequently closed with a TA stapler. Additional reinforcement is not necessary for this staple line.

Some authors recommend the use of a Braun enteroenterostomy between the efferent and afferent limbs to reduce bile reflux and decompress the duodenal stump [see Figure 8a]. Staple closure of the afferent limb above the enteroenterostomy may also be performed to limit bile reflux into the stomach; this measure creates a configuration referred to as an uncut Roux-en-Y [see Figure 8b]. Enteroenterostomy at this site may also be performed on an emergency basis to treat afferent limb syndrome. Staple closure of the afferent limb may discourage bile reflux, with the effect of limiting bile reflux gastritis and esophagitis.⁴

Troubleshooting

In most instances, a noninflamed duodenum can readily be closed with a TA stapler. However, the thickened and inflamed tissue present in the setting of inflammation with duodenal perforation is not amenable to easy closure. Furthermore, poor afferent limb drainage can lead to increased pressure in the afferent limb, thus contributing to leakage. Lateral duodenostomy tubes may be used for decompression. The duodenum should be sutured to the abdominal wall in a Stamm fashion at the exit site of the tube. Alternatively, if the duodenum cannot be closed without significant tension, closure may be accomplished around a red rubber or mushroom

catheter. For especially thick tissue, primary suture closure is preferable to staple closure. Inversion of the duodenal suture line with Lembert sutures is not necessary. In addition, omental patch reinforcement of the duodenal stump may be desirable.

Some surgeons report success with a retrograde duodenostomy tube. If sufficient afferent limb of jejunum is available to reach the abdominal wall prior to the gastrojejunostomy, a soft duodenostomy tube may be passed from this site in a retrograde manner past the ligament of Treitz to the second portion of the duodenum. Although this tube is potentially more difficult to place than a lateral duodenostomy tube, eventual removal and closure are thought by some to be easier and may avoid persistent duodenal fistula.

Complications

Leakage from the duodenal stump is a potentially devastating complication that necessitates prompt reoperation, wash-out, and drainage. The diagnosis of duodenal stump leakage is confirmed by aspirating bilious fluid from a right upper quadrant fluid collection or by performing a technetium-99m—labeled hepatiminodiacetic acid scan.

Duodenal leaks can rarely be closed primarily. Duodenostomy may be indicated to further decompress the afferent limb and prevent continuous leakage. The goals are to create a controlled fistula to the skin and to prevent the accumulation of biliary fluid in the abdomen.

Delayed gastric emptying after gastrojejunostomy may occur and is generally managed conservatively. On rare occasions, reoperation is required for delayed anastomotic function.

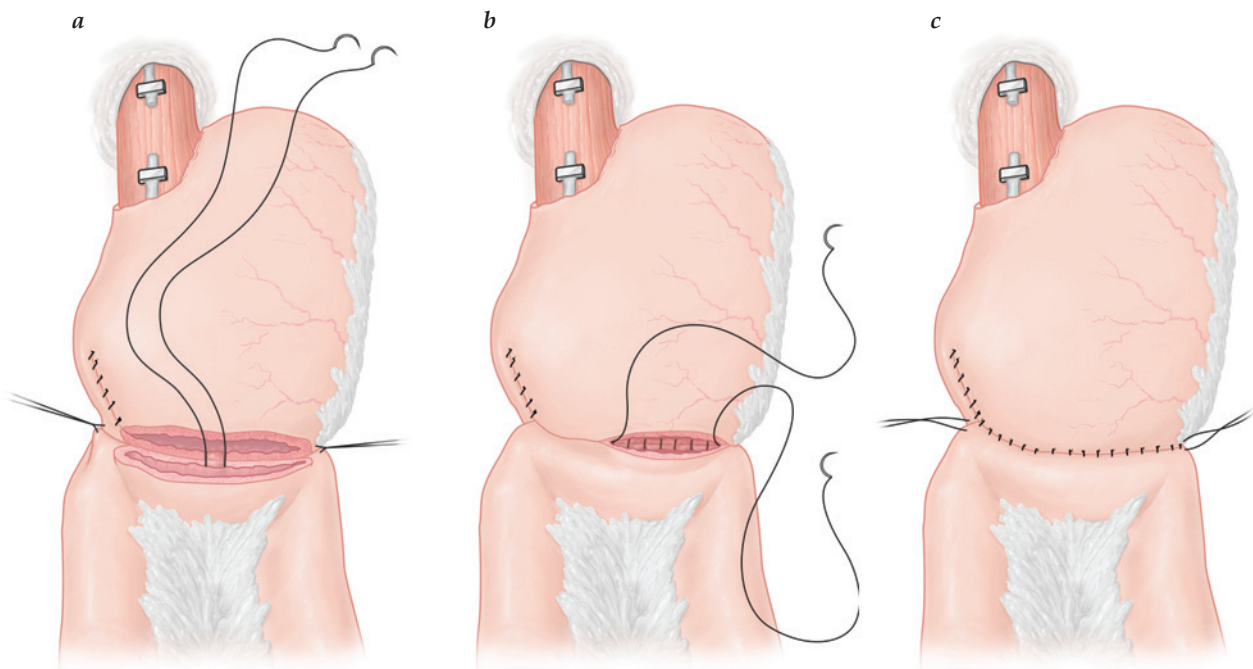


Figure 7 Antrectomy: Billroth II reconstruction (gastrojejunostomy). (a) The inferior portion of the gastric resection line is excised, along with a small wedge of the stomach. (b, c) A two-layer anastomosis is created, with an outer layer of Lembert sutures and an inner layer of full-thickness absorbable sutures. The upper gastric staple line may be oversewn with interrupted Lembert sutures.

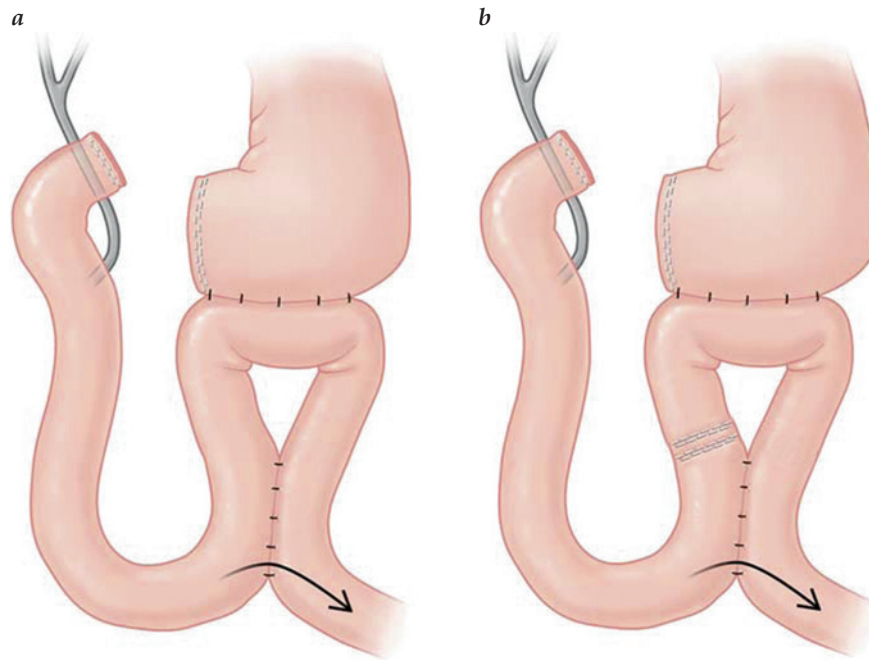


Figure 8 Braun enteroenterostomy. Antrectomy: Billroth II reconstruction (gastrojejunostomy). (a) A Braun enteroenterostomy facilitates decompression of the afferent limb in a Billroth II gastrojejunostomy. It may be done as either a sutured or a stapled anastomosis. (b) An option is to close the afferent limb above the enteroenterostomy with a transverse anastomosis stapler (so that the jejunal lumen is occluded but not divided). This configuration, often referred to as an uncut Roux-en-Y, temporarily discourages, but does not prevent, reflux of bile into the stomach.

In the case of a Billroth I reconstruction, takedown of the anastomosis is associated with devascularization and duodenal stump leakage. It is therefore preferable to leave the anastomosis in place and perform a gastrojejunostomy along the greater curvature of the stomach. In the case of a Billroth II reconstruction, revision may be required for better positioning of the anastomosis.

Afferent limb obstruction may occur as a consequence of adhesions, internal herniation, volvulus, or a kink at the angle formed with the gastric remnant. Obstruction to outflow of the afferent limb creates a closed-loop obstruction, with persistent secretion of bile and pancreatic fluids into the loop. Such obstruction often presents as recurrent pancreatitis. The diagnosis is facilitated by CT scanning; if it is confirmed, prompt exploration is mandated. Correction of the obstruction may necessitate conversion to a Roux-en-Y reconstruction, shortening of the afferent limb, or a side-to-side enteroenterostomy with the efferent limb (see above).

Bleeding, generally in the form of intraluminal blood loss, is a frequent occurrence after gastrectomy. A bloody aspirate from the nasogastric tube is a common presentation. If bleeding persists for more than 5 days after the initial operation, endoscopy with endoscopic coagulation or epinephrine injection may be considered. Endoscopic approaches should be undertaken with care to minimize the risk of distending the new anastomosis.

Alkaline reflux gastritis is one of the most common long-term complications of gastrectomy, developing in 5 and 15%

of patients after gastric surgery.⁵ This complication is most frequently associated with Billroth II reconstructions. Although reflux is common, symptoms (e.g., epigastric pain, nausea, and bilious emesis) are relatively rare. Medical management is generally ineffective. If surgery is required, conversion of the Billroth II reconstruction to a Roux-en-Y reconstruction is indicated. In those patients who have a Roux-en-Y rather than a Billroth II reconstruction, the preferred treatment is to divert alkaline contents to a location 45 to 60 cm beyond the gastric remnant.

HIGHLY SELECTIVE VAGOTOMY

Although both vagotomy with antrectomy and vagotomy with pyloroplasty drainage provide relief from duodenal ulcers, they are also associated with significant complications, including dumping syndrome, diarrhea, bile reflux, and poor gastric emptying. Highly selective vagotomy, also referred to as parietal cell vagotomy, was developed with these complications in mind; the idea was to avoid vagal denervation of viscera other than the parietal cell mass while keeping the pylorus mechanically and functionally intact.^{6,7} HSV was found to reduce post-vagotomy diarrhea and dumping dramatically; however, it was also found to be associated with a much higher rate of recurrent ulceration (greater than 10% at 5 years). Today, in an era characterized by greatly improved medical management of peptic ulcer disease, most GI surgeons rarely perform HSV, if at all. One possible use for this procedure in the current context might be to treat intractable ulcer disease in young patients.

Operative Technique

Step 1: exposure and gastric mobilization Wide exposure is obtained with the help of upward retraction on the costal margin. The gastrocolic omentum is entered outside the gastroepiploic vessels to preserve the blood supply to the greater curvature. Adhesions to the peritoneum over the pancreas are divided sharply, and the stomach is rotated upward to allow visualization of the posterior leaf of the lesser omentum and the posterior nerve of Latarjet, which runs adjacent to the descending branch of the left gastric artery.

Step 2: dissection of anterior and posterior nerve branches to lesser curvature The distal branches of the nerve of Latarjet are defined, with care taken to preserve the so-called crow's foot, which is typically located near the incisura angularis, approximately 6 to 7 cm proximal to the pylorus. Gentle downward traction is applied to the stomach, the left gastric vascular arcade is identified, and all tissue between this arcade and the lesser curvature is divided and ligated. The dissection therefore includes individual branches of the vagus nerve to the stomach. It should proceed upward as far as the esophagogastric junction. The posterior branches are approached either by rotating the stomach or by proceeding directly through the lesser omentum [see Figure 9].

Step 3: dissection of esophagogastric junction The distal esophagus is cleared of all nerve fibers for a distance of approximately 5 cm above the esophagogastric junction. The dissection must stay close to the lesser curvature and the esophagus, avoiding the tissues to the right of the esophagus,

where the main vagal trunks lie. The posterior esophagogastric junction is exposed by means of gentle traction and slight rotation of the distal esophagus. Exposure is facilitated by downward traction provided by a Penrose drain placed around the esophagogastric junction.

Troubleshooting

Incomplete denervation of the parietal cell mass is prevented by paying meticulous attention to dissection, particularly at the esophagogastric junction. The left side of the distal esophagus must be manually stripped so that the so-called criminal nerve of Grassi can be identified and ligated. About 4 to 5 cm of the distal esophagus should be stripped of vagal input.

Complications

The primary complication of HSV is recurrent ulceration. The reported rates vary, but the general view is that the 5-year ulceration recurrence rate may be higher than 10%.⁸ Most recurrent ulcers occur in the setting of incomplete vagal denervation. Given the small number of patients for whom HSV is indicated, few GI surgeons are likely to have accumulated sufficient experience with this technique to be proficient at it. Fortunately, most recurrent ulcers can now be managed medically, and few call for surgical management.

LAPAROSCOPIC TREATMENT OF PEPTIC ULCER DISEASE

Numerous reports of laparoscopic approaches to truncal vagotomy and HSV have been published over the past two decades. The laparoscopic versions of these procedures proceed in much the same way as the traditional open versions. In a laparoscopic HSV, the ultrasonic shears are frequently used to divide the anterior and posterior vagal branches to the lesser curvature from the crow's foot to the esophagogastric junction. Mixed procedures that combine posterior truncal vagotomy with more selective anterior gastric denervation are common. In the Taylor procedure, an anterior seromyotomy is performed from the angle of His to the crow's foot, and the seromuscular layers are subsequently closed primarily.⁹ A variant of the laparoscopic Taylor procedure includes an anterior linear gastrectomy, in which a linear strip of the stomach wall is removed parallel to the lesser curvature with an endoscopic GIA stapler. This procedure seems to be functionally equivalent to HSV. The majority of the studies of laparoscopic vagotomy, however, have been individual case series that do not compare the laparoscopic approach with a traditional open approach. Undoubtedly, the scarce comparative data reflect the declining indications for vagotomy for intractable peptic ulcer disease. Thus, although laparoscopic HSV has been well described, it is by no means clear that it should be recommended over open HSV for those rare patients in whom this procedure is indicated.

More data are available on laparoscopic treatment of perforated duodenal ulcers. A meta-analysis of 13 studies comparing laparoscopic and open approaches to perforated peptic ulcers found that laparoscopic repair yielded excellent results, albeit with a small but insignificant increase in the reoperation rate.¹⁰ The laparoscopic approach is therefore considered as safe and effective as open Graham patch repair.

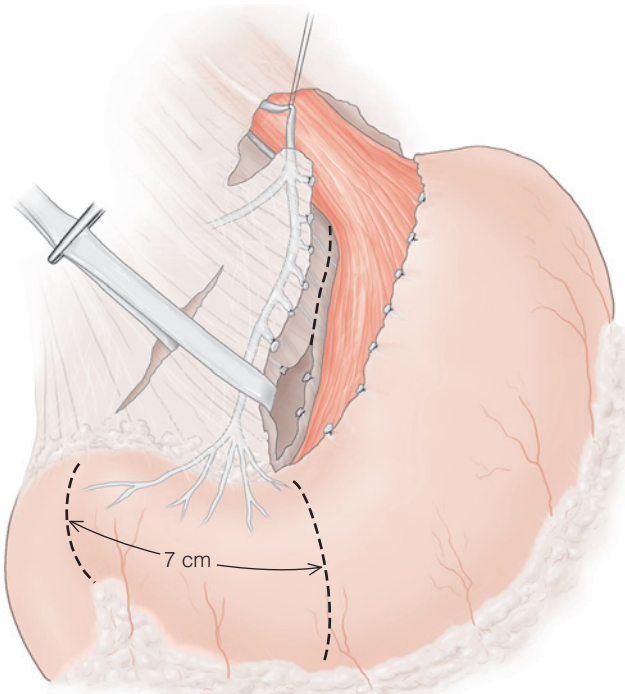


Figure 9 Highly selective vagotomy. Anterior and posterior branches of the nerve of Latarjet to the lesser curvature are ligated and divided. The distal branches, comprising the so-called crow's foot, are left intact. The posterior branches may be approached via the lesser omentum.

The procedures generally involve either suture closure of the perforation followed by omentopexy or omentopexy alone and should be attempted only by surgeons with advanced laparoscopic skills. The threshold for conversion to an open procedure should be low if the ulcers are particularly large ulcers or prove difficult to localize.

DUODENAL DIVERTICULECTOMY

Incidental duodenal diverticula are common. Such diverticula consist of a sac that includes only mucosa and submucosa, and most occur within 2 cm of the ampulla of Vater. Complications include ulceration and bleeding, compression of the CBD with cholangitis or pancreatitis, and, in cases of perforation, abscess formation with peritonitis. CT scanning is useful for differentiating this condition from cholecystitis or pancreatitis. Surgery is rarely required; it is indicated primarily for complications such as bleeding, perforation, and biliary or duodenal obstruction.

Operative Technique

The main surgical options are simple diverticulectomy with drainage and transduodenal diverticulectomy (as described by Iida¹¹). If the duodenum is free of inflammation, the transduodenal approach is preferred because it minimizes the need for dissection of the diverticulum from the surrounding pancreas. However, if the diverticulum does not involve the pancreas, simple excision flush with the duodenal wall, followed by closure in two layers, may be sufficient. The ensuing technical description focuses on transduodenal diverticulectomy.

Step 1: exposure and duodenotomy A generous Kocher maneuver is performed to elevate the head of the duodenum. The duodenum is then opened by making a 4 cm longitudinal incision along the antimesenteric border, and the ampulla is either visualized or palpated. To identify the ampulla, it may be necessary to place a catheter into the CBD via a separate choledochotomy.

Step 2: diverticulectomy The orifice of the diverticulum is identified, and the mucosa is inverted into the lumen of the duodenum. The neck of the diverticulum is transected 2 mm from the junction with the duodenal wall. The diverticular opening is then closed with interrupted seromuscular Lembert sutures of 3-0 silk and interrupted mucosal sutures of 4-0 polyglactin. The duodenum is closed in two layers, also with an inner layer of 4-0 polyglactin and an outer layer of seromuscular Lembert sutures of 3-0 silk. Closed-suction drainage adjacent to the duodenum is indicated.

Special case: perforated duodenal diverticulum In the setting of acute inflammation, duodenotomy is avoided. Instead, the abscess is evacuated, and the diverticulum is excised along with just enough of the adjacent duodenal wall to ensure that only healthy tissue is left. If the resulting duodenal defect is large, either sleeve resection of the duodenum or drainage of the open duodenal defect into a Roux-en-Y jejunal limb may be required.

Troubleshooting

Inadvertent closure of the CBD may be prevented by inserting a catheter into the duct. If the duodenum is markedly inflamed, suture line breakdown is likely, eventually leading to a duodenal fistula. The area can be isolated by means of

pyloric exclusion or antrectomy with Billroth II reconstruction. In addition, bile flow can be diverted by performing a choledochojejunostomy to a Roux-en-Y intestinal limb to prevent combined leakage of pancreatic fluid and bile.

Diverticula arising from the third or the fourth portion of the duodenum may be approached via the transverse mesocolon and may be excised either primarily or via a transduodenal approach. Inverting the diverticulum without excising it is not recommended, because it may lead to duodenal obstruction.

Procedures for Gastric Cancer

Surgical resection remains the primary therapeutic modality for gastric cancer [see 5:8 *Tumors of the Stomach, Duodenum, and Small Bowel*]. The diagnosis of gastric cancer is primarily made by means of endoscopy with biopsy. Numerous considerations must be addressed before operation, including the stage of the cancer on diagnostic imaging, the use of staging laparoscopy, the extent of the planned gastrectomy, the extent of the planned lymphadenectomy, the placement of feeding enterostomies, and the patient's overall medical fitness for surgery.

PREOPERATIVE EVALUATION

Endoscopy, with or without endoscopic ultrasonography (EUS), is essential for diagnosis. Preoperative biopsy is helpful for confirming the suspected pathologic process, particularly because the extent of resection will be different if a less common lesion, such as a gastrointestinal stromal tumor (GIST), is identified. Endoscopic localization is critical because the extent of the gastrectomy will depend on the precise location of the tumor. It should be noted, however, that the true location of the tumor, as determined at laparotomy, may differ significantly from the preoperative estimate made on the basis of endoscopy. Abdominal CT and chest radiography are indicated to rule out obvious metastatic disease, which would be an indication for a more conservative surgical approach or even for nonoperative therapy. The preoperative physical examination should also focus on the detection of occult metastatic disease, concentrating on such sites as the supraclavicular lymph nodes and the pouch of Douglas. A bone scan is indicated if metastasis to bone is suspected. Laparoscopic staging (see below) may be performed to identify occult metastatic disease (and, possibly, to prevent an unnecessary laparotomy in an otherwise ill patient).¹² If the tumor is not bleeding or causing an obstruction, palliative resection might be avoided. Generally, curative surgery should be attempted only when the tumor is believed to be limited to the stomach and the perigastric lymph nodes. On occasion, however, curative intent surgery may be considered for tumors that involve nearby resectable structures (e.g., the transverse colon), provided that these structures can be removed en bloc with the primary lesion.

In Japan, where gastric cancer is among the leading causes of cancer-related death, screening endoscopy is widespread and early gastric cancer is identified with some frequency. In Western countries, however, screening endoscopy has not been implemented because of the lower incidence of gastric cancer and hence the lower utility of screening. It is therefore not uncommon for patients to present with more advanced

cancers. Accordingly, although procedures such as wedge resection for early gastric cancer have been described, most gastric cancer patients in the United States require formal gastrectomy and lymphadenectomy.

OPERATIVE PLANNING

Extent of Resection

The extent of the resection required for treatment of a gastric malignancy is determined primarily by the preoperative pathologic diagnosis and the site of the tumor. Considerably smaller surgical margins are required for rare mesenchymal tumors (e.g., GISTs) than are necessary for gastric adenocarcinomas, which tend to spread microscopically well beyond the gross extent of the tumor. Most mesenchymal tumors can be adequately treated with a wedge resection or partial gastrectomy that achieves a 1 cm gross margin. Laparoscopic approaches to such tumors have been described that employ either the endoscopic GIA stapler or excision with suture closure [see Laparoscopic Resection of Malignant Gastric Tumors, *below*]. Such approaches may be facilitated by endoscopic tattooing of an appropriate margin or by intraoperative endoscopic guidance. For adenocarcinomas, a margin of at least 5 cm is recommended.

A 5 cm margin may be particularly difficult to achieve when the tumor is located along the lesser curvature. In many such cases, although the tumor appears to be distal and possibly amenable to a subtotal gastrectomy, a 5 cm negative margin along the lesser curvature would place the proximal resection margin far above the incisura angularis and near the esophagogastric junction, thus necessitating total or near-total gastrectomy. For lesser-curvature tumors whose location allows adequate margins to be obtained, distal gastrectomy with Billroth II gastrojejunostomy is preferred; for more proximal tumors, total gastrectomy with esophagojejunostomy may be required.

Special consideration must be given to tumors of the esophagogastric junction. In the classification scheme described by Siewert and Stein,¹³ such tumors are defined as lying within 5 cm of the anatomic esophagogastric junction in either direction along the craniocaudal axis of the esophagus and the stomach. They are classified into three types as follows:

1. Type I: the center of the tumor lies 1 to 5 cm proximal to the esophagogastric junction
2. Type II: the center of the tumor lies within 1 cm of the esophagogastric junction proximally or within 2 cm distally
3. Type III: the center of the tumor lies 2 to 5 cm distal to the esophagogastric junction

It is generally agreed that total esophagectomy is required for type I esophagogastric junction tumors [see 4:7 *Open Esophageal Procedures*]. The necessary extent of resection for type II and III esophagogastric junction tumors has been more controversial. A microscopically negative (R0) surgical margin is closely associated with survival after resection of esophagogastric junction adenocarcinomas, although R0 resection can be quite difficult to achieve, given the propensity of these tumors for intramural spreading. In our experience, positive margins have not been found in patients with T1 or T2 tumors, even when the margins are smaller than

4 cm. In patients with T3 or T4 tumors, however, proximal margins of at least 6 cm have proved necessary. For T1 and T2 tumors, total gastrectomy without thoracotomy may yield adequate margins. For T3 and T4 tumors, however, extended gastrectomy with thoracotomy or esophagectomy may be required.¹⁴ It is well documented that the margin lengths measured on prefixed esophageal specimens are only about 50% of the corresponding lengths measured in situ before completion of resection.¹⁵ Accordingly, intraoperative decisions about the extent of resection should be based on margin length requirements that may be considerably greater than those derived from resection specimens.

Extent of Lymphadenectomy

The extent of lymphadenectomy with gastrectomy, in terms of not only the gross number of lymph nodes examined but also the particular nodal basins sampled, has been the subject of considerable debate. Regional nodes are classified as N1 (perigastric), N2 (along the splenic and left gastric arteries and at the celiac axis), N3 (along the hepatoduodenal ligament and the root of mesentery), and N4 (para-aortic and middle colic nodes). Alternatively N2 nodes have been variously reported as groups N2–N4 above, including splenic, left gastric, celiac, hepatoduodenal, mesenteric, and para-aortic nodes. Since the 1960s, Japanese surgeons have advocated extended dissection of lymph nodes to improve outcomes in gastric cancer.¹⁶ Whereas a D0 resection represents incomplete dissection of the N1 nodes, D1 resection involves complete resection of the N1 nodes, and D2 involves complete resection of both N1 and N2 nodes. Western and European authors, however, have not demonstrated the benefit of extended lymphadenectomy in gastric cancer.¹⁷ Outside Japan, surgeons have therefore typically limited lymphadenectomy to the perigastric (D1) lymph nodes. Surgeons in Japan, however, have tended to prefer a much more radical lymph node dissection that includes the second-order (D2) nodes [see Figure 10]. It has not been clear whether more extensive lymph node dissection actually provides a survival benefit or simply improves surgical staging. To date, four randomized, controlled trials have failed to show any significant benefit from extended lymph node dissection. In the largest such study, performed by the Dutch Gastric Cancer Group, more than 700 patients were randomly assigned to undergo either D1 or D2 lymphadenectomy.¹⁸ The 5-year survival rate was essentially the same in the two groups; perioperative morbidity and mortality were significantly higher after D2 lymphadenectomy.

A subsequent study from the same group found that at 10 years after operation, D2 lymphadenectomy provided a benefit (in terms of lower local recurrence) only in the subgroup with positive second-order nodes; however, these patients could not be identified preoperatively.¹⁹ For the cohort as a whole, extended lymph node dissection generated no long-term survival benefit. Therefore, although some surgeons extend the lymphadenectomy to include lymph nodes along the left gastric, celiac, and common hepatic arteries (a so-called D1+ dissection), the standard of care for surgeons in the United States continues to be a D1 lymphadenectomy that includes all perigastric lymph nodes and the greater omentum.

Furthermore, the minimum number of lymph nodes for gastric cancer staging has been evaluated. It has been suggested

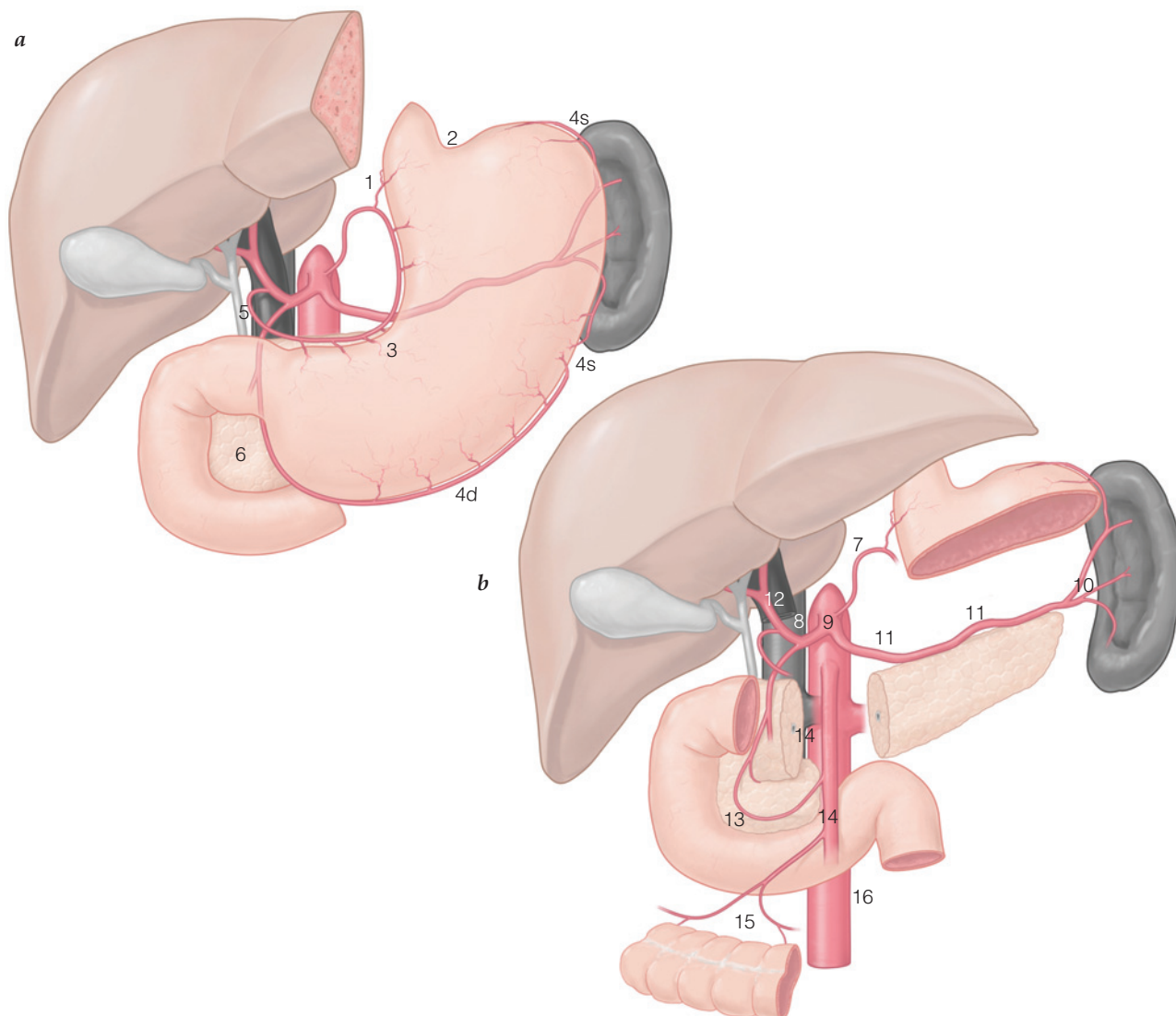


Figure 10 Illustrated are the differences between a D1 lymphadenectomy and a D2 lymphadenectomy for gastric cancer. (a) A D1 lymphadenectomy is accomplished by removing the perigastric lymph nodes with the resection specimen; these nodes include those along the right and left cardia (1, 2), those along the lesser curvature (3), those along the greater curvature (4), the suprapyloric nodes (5), and the infrapyloric nodes (6). (b) A D2 lymphadenectomy involves a more radical resection specimen, which includes nodes along the left gastric artery (7), the common hepatic artery (8), the celiac artery (9), the splenic hilum (10), the splenic artery (11), the hepatoduodenal ligament (12), the posterior pancreas (13), the root of the mesentery (14), the transverse mesocolon (15), and the aorta (16).

that a minimum of 15 lymph nodes must be removed during gastrectomy. In a study published in 2000, 5-year survival rates were significantly lower in patients with fewer than 15 lymph nodes sampled than in those with 15 or more lymph nodes examined.²⁰ This decreased survival with fewer sampled lymph nodes was attributed primarily to understaging as the result of inadequate lymphadenectomy.

TOTAL GASTRECTOMY

Operative Technique

Step 1: incision and exposure The abdomen is entered via a midline or bilateral subcostal incision. If a subcostal incision is used, it may have to be extended past the xiphoid process in the midline for optimal exposure. Thorough

exposure of the peritoneal cavity (including the liver, all peritoneal surfaces, and, in women, the ovaries) is undertaken to search for signs of metastatic disease. If the patient has a proximal lesion near the gastric cardia, a thoracotomy may be needed if the distal thoracic esophagus is to be included in the resection specimen. If an incision into the thoracic cavity is being considered, the left chest should be surgically prepared at the time of initial draping to allow extension of the incision across the lower left costal margin if desired. In this setting, if thoracotomy is possible, preoperative placement of a double-lumen endotracheal tube should be considered. The abdominal portion of a thoracoabdominal incision should be performed first to allow assessment of resectability.

Step 2: dissection of omentum from colon The omentum is separated from the colon with an electrocautery or scissors through the relatively avascular plane. Gentle upward traction is placed on the omentum to facilitate entry into the correct surgical plane [see Figure 11]. If the procedure involves a formal D2 lymph node dissection, this is also a convenient time to enter the anterior leaf of the transverse mesocolon, which is resected with the anterior covering of the pancreas. (As noted, most US surgeons perform a D1 resection or some modification thereof and thus do not dissect the anterior peritoneal surface of the mesocolon and pancreas.)

With the dissection starting on the right side, the right gastroepiploic artery is identified and ligated where it originates from the gastroduodenal artery. The short gastric vessels are divided as the dissection proceeds along the greater curvature. The lesser omentum is also divided near the liver and is included with the specimen; care should be taken to identify an aberrant left hepatic artery in the lesser omentum (if present). The dissection is continued onto the peritoneal surface of the distal esophagus.

Step 3: division of duodenum The duodenum is divided just distal to the pyloric ring either with a GIA stapler or with a TA stapler applied twice [see Figure 12]. The right gastric artery is identified and ligated near its base. Division of the duodenum allows elevation and rotation of the stomach, thereby facilitating access to the left gastric artery and the surrounding node-bearing tissue.

With the stomach gently retracted upward and anteriorly, dissection identifies the celiac axis and the left gastric artery [see Figure 13]. The origin of the left gastric artery is ligated and divided, and a suture ligature is placed on the proximal end.

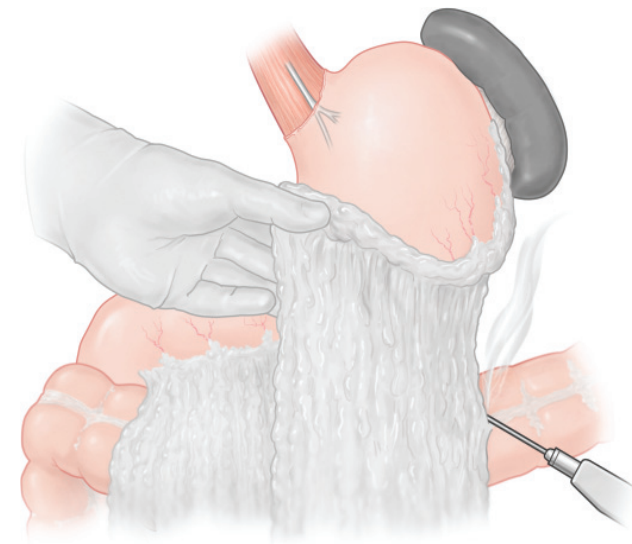


Figure 11 Total gastrectomy: dissection. The omentum is dissected from the transverse colon with scissors or the electrocautery. In the course of this dissection, the right gastroepiploic artery is encountered near the pylorus and divided near its base at the gastroduodenal artery. The dissection continues along the greater curvature, including ligation of the short gastric vessels. In a formal D2 lymphadenectomy, the anterior leaf of the transverse mesocolon and the anterior capsule of the pancreas are dissected. In a D1 lymphadenectomy, these structures are left intact.

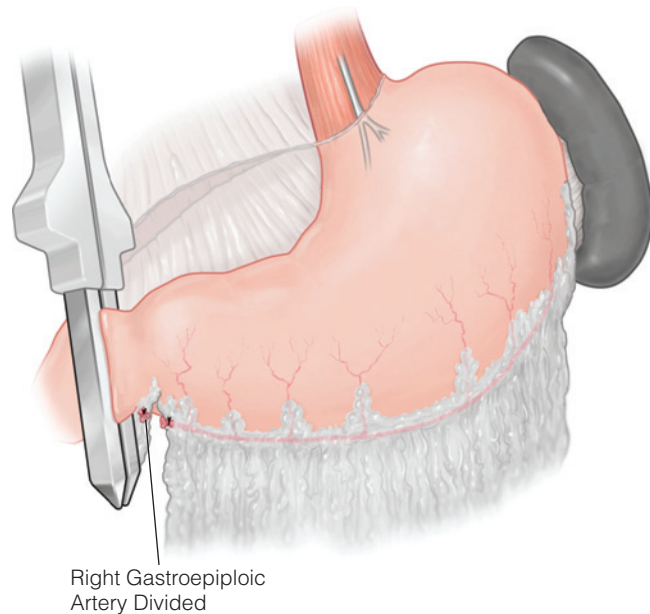


Figure 12 Total gastrectomy: division of duodenum. The duodenum is divided just beyond the pylorus with a gastrointestinal anastomosis or transverse anastomosis stapler. The duodenal staple line may be reinforced with interrupted Lembert sutures.

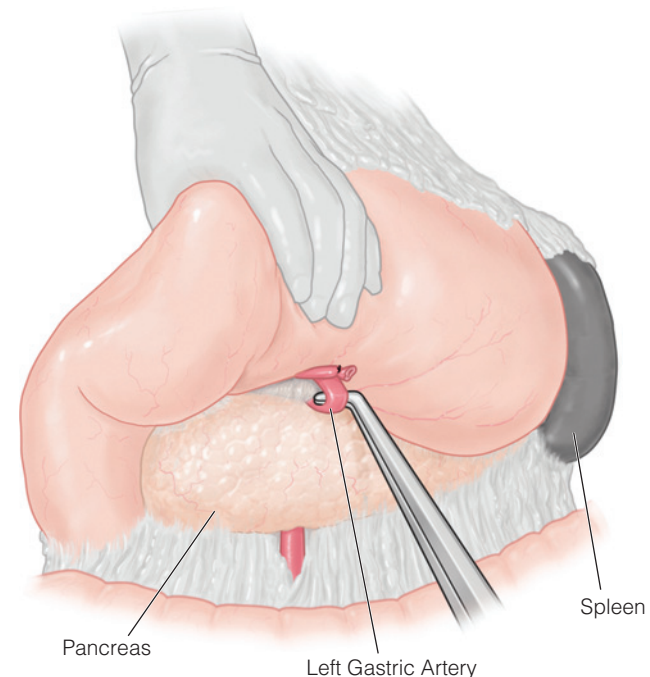


Figure 13 Total gastrectomy: division of left gastric vessels. The stomach is retracted cephalad to expose the left gastric vessels, which may be divided and suture-ligated on the proximal side. Division of the distal esophagus should be preceded by placement of several stay sutures on the proximal esophagus to prevent it from retracting into the posterior mediastinum.

A standard D1 lymphadenectomy does not include splenectomy and distal pancreatectomy. The spleen and pancreas are left in situ and are separated from the resection specimen by dividing and ligating the short gastric vessels (see above). The D2 lymphadenectomy as originally described includes stripping the peritoneum along the anterior pancreas, as well as removing nodes along the splenic artery and, if needed, performing splenectomy and distal pancreatectomy to sample the splenic hilar lymph nodes.

Troubleshooting Leakage from the duodenal stump is a potentially disastrous complication. If the stapled duodenum appears to be ischemic, the staple line may be inverted with Lembert sutures of 3-0 silk.

Step 4: inclusion of necessary lymph nodes The degree of dissection to be performed in the porta hepatis depends on the extent of the planned lymphadenectomy. A D1 lymphadenectomy does not require any of the lymph nodes in this area, but a D1+ lymphadenectomy includes lymph nodes along the common hepatic artery. Gentle left lateral traction is placed on the stomach before division of the left gastric artery to apply some tension to the hepatic artery. The dissection proceeds along the celiac and hepatic arteries to the porta hepatis. The tissue surrounding the common hepatic artery and the left gastric artery is swept medially with the specimen. To sample splenic artery nodes, the peritoneum over the anterior border of the pancreas is divided if not previously removed as part of a planned D2 dissection. Nodal tissue along the splenic artery is visualized and sampled.

Step 5: division of esophagus The peritoneum is divided over the anterior esophagus, and the esophagus is completely dissected free of surrounding tissue. The esophagus is then divided either with a TA stapler or with a scalpel after the placement of a noncrushing bowel clamp. To keep the stump from retracting too far proximally, stay sutures of 2-0 silk should be placed in the proximal esophagus before division. Alternatively, the specimen may be left attached and used as a handle to retract the proximal esophagus inferiorly. The esophagus may then be divided after placement of the posterior suture line. Evaluation of the proximal resection margin with frozen-section analysis is advisable.

Troubleshooting The proximal margin may be found to harbor malignancy; if so, reresection of the proximal margin should be performed. Placement of stay sutures in the proximal esophagus is important; if this is not done, the retracting esophagus may migrate into the posterior mediastinum.

Step 6: reconstruction via esophagojejunostomy The options for reconstruction after gastrectomy include stapled end-to-side esophagojejunostomy, hand-sewn end-to-side esophagojejunostomy, side-to-side esophagojejunostomy, and anastomosis to a jejunal pouch. A Roux-en-Y jejunal limb is fashioned; to prevent biliary reflux, it should be at least 40 to 50 cm long. The Roux limb is then brought up behind the colon to the esophagus. Some authors recommend antecolic placement of the Roux limb to prevent obstruction in the setting of recurrent disease; however, retrocolic placement may facilitate a more tension-free anastomosis.

For a stapled end-to-side esophagojejunostomy, a purse-string suture of 3-0 or 2-0 polypropylene is placed in the esophagus and used to secure the anvil of an end-to-end

anastomosis stapler. The body of the stapler is placed into the Roux limb, with the tip protruding through the end, and the esophagojejunostomy is created on the antimesenteric border of the jejunum [see Figure 14a]. The open end of the Roux limb is then closed with a TA stapler. To reduce tension on the anastomosis, the staple line may be reinforced with interrupted Lembert sutures of 3-0 silk.

A hand-sewn end-to-side esophagojejunostomy is created in a similar fashion at a point near the end of the Roux limb on the antimesenteric border. The posterior row is placed first, with interrupted 3-0 silk sutures as the outer layer and interrupted full-thickness 3-0 absorbable sutures as the inner layer [see Figure 14b]. The knots are tied on the inside of the bowel. The anterior row is then placed, with an inner layer of interrupted full-thickness 3-0 absorbable sutures and an outer layer of interrupted 3-0 silk sutures. Some surgeons prefer a single-layer anastomosis, either with a continuous suture or with interrupted full-thickness sutures. The available data do not favor either single- or two-layer anastomosis in this setting.

Side-to-side esophagojejunostomy requires a substantial length of intra-abdominal esophagus and necessitates extensive mobilization of the distal esophagus. The jejunum may be sutured to the underside of the diaphragm to relieve tension on the anastomosis.

Some authors report improved postoperative quality of life with a jejunal pouch reconstruction. Although straight esophagojejunostomy is known to be related to intestino-esophageal reflux, the creation of a gastric reservoir has intrinsic appeal but has not been widely accepted. A recent randomized controlled trial comparing straight Roux-en-Y esophagojejunostomy with a jejunal J-pouch, however, suggested significant benefit to creating a gastric reservoir.²¹ Whereas functional results were similar in the first year after surgery, function in years 3 to 5 was significantly improved in patients with a jejunal pouch. For a jejunal pouch, the proximal limb of the Roux-en-Y jejunal limb is folded back on itself for a distance of 10 to 15 cm. The pouch is constructed with an enteric stapling device; esophageal anastomosis may then be constructed via a hand-sewn or stapled technique [see Figure 14c].

Drains are not routinely placed after esophagojejunostomy as drain placement may increase the rate of leakage from the esophagojejunostomy.

Troubleshooting Without a sufficient length of intra-abdominal esophagus, primary reconstruction can be difficult. Full mobilization of the intra-abdominal esophagus is essential. Because the esophagus lacks a serosa, transversely oriented Cushing-type sutures may be preferable to Lembert sutures on the anterior and posterior outer layers of a hand-sewn anastomosis.

Step 7 (optional): feeding enterostomy Many patients with gastric adenocarcinoma become significantly malnourished after gastrectomy. The loss of the gastric pouch may adversely affect their ability to fulfill their caloric requirements in the early postoperative period. To prevent further malnutrition, some authors recommend creating a feeding jejunostomy at the time of total gastrectomy with esophagojejunostomy. The jejunostomy should be placed downstream from the jejunoesophagojejunostomy (i.e., more than 50 cm distal to

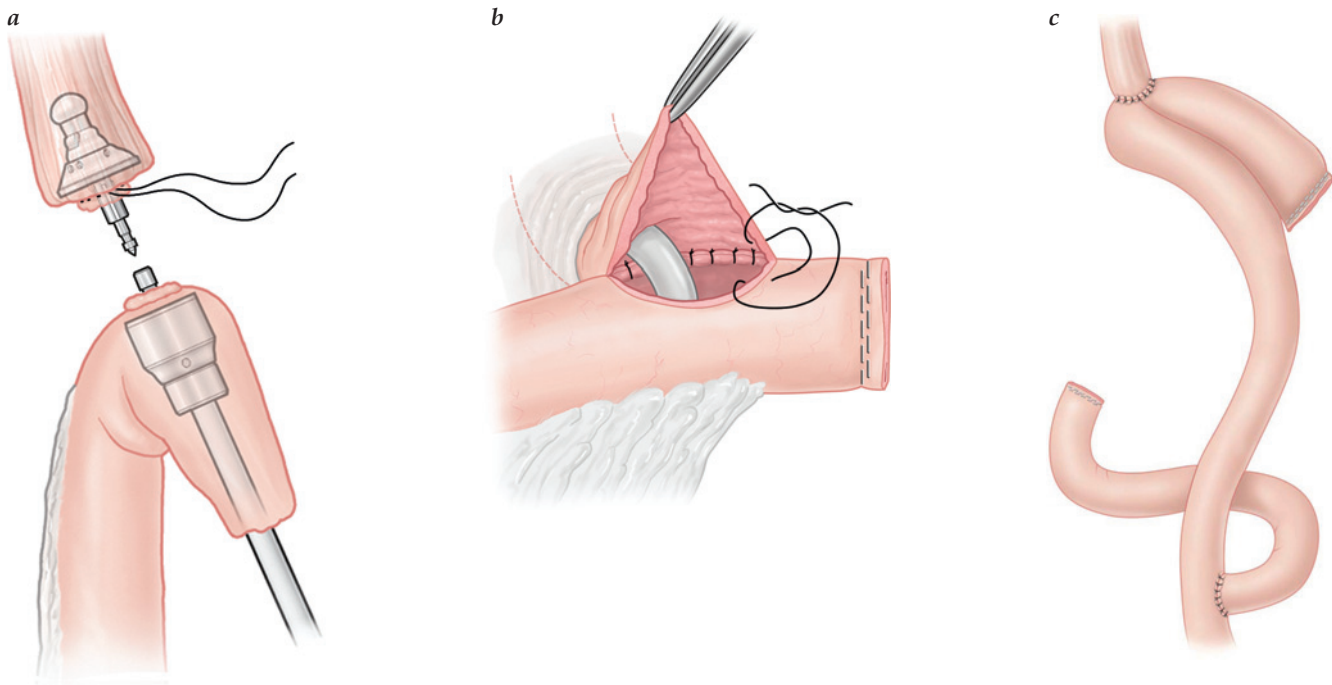


Figure 14 Total gastrectomy: reconstruction via esophagojejunostomy. Reconstruction via esophagojejunostomy; options include stapled end-to-side esophagojejunostomy, hand-sewn end-to-side esophagojejunostomy, side-to-side esophagojejunostomy, and anastomosis to a jejunal pouch. (a) In a stapled esophagojejunostomy, the anvil is secured in the esophagus with a purse-string suture, an end anastomosis stapler is inserted through the distal end of the Roux limb, and the anastomosis is created to the antimesenteric side of the bowel. Once the anastomosis is complete, the end of the Roux limb is amputated with a single firing of a gastrointestinal anastomosis stapler. (b) A hand-sewn esophagojejunostomy may be fashioned with interrupted full-thickness sutures (as shown), with a continuous full-thickness suture, or as a two-layer anastomosis. After completion of the posterior row, a sump tube may be placed across the anastomosis into the proximal jejunum. After completion of the anterior row, several reinforcing seromuscular sutures may be placed to reduce tension on the anastomosis. (c) Roux-en-Y jejunal pouch. Roux-en-Y reconstruction using a jejunal J pouch is depicted. The antimesenteric sides of two jejunal loops are connected with linear stapling devices for a distance of 10 to 15 cm. The enterotomy is closed with either a hand-sewn or stapled technique. The jejunal pouch may be used for reconstruction via either stapled or hand-sewn esophagojejunostomy.

the anastomosis). When a feeding enteroenterostomy is indicated, we prefer a Witzel jejunostomy.

Complications

D2 lymphadenectomy has been associated with numerous complications, including increased blood loss, longer operating time, colonic devascularization, pancreatitis, and pancreatic leakage. Although complication rates appear to be acceptably low when the procedure is done by an experienced surgeon, there is still the potential for the benefits of extensive lymphadenectomy to be outweighed by the additional complications. Complications may be reduced by omitting distal pancreatectomy and splenectomy while sampling common hepatic, celiac, and splenic artery nodes (D1+ resection).

Anastomotic leakage at an esophagojejunostomy may lead to postoperative infection. Intra-abdominal leaks may be managed by drainage via percutaneous drains or laparotomy, as well as by proximal nasogastric drainage. High anastomotic leaks may result in contamination of the posterior mediastinum or the pleural space, and thoracotomy or tube thoracostomy may be necessary to achieve external drainage.

Occasionally, bleeding may be substantial enough to necessitate reoperation. In this situation, the gastric remnant may be entered via a transverse incision just proximal to the

anastomosis. As a rule, the bleeding can be successfully controlled by placing simple figure-eight sutures.

DISTAL OR SUBTOTAL GASTRECTOMY

Cancers of the distal stomach or antrum may be addressed by means of a distal gastrectomy. Particular attention should be paid to tumors on the lesser curvature, where obtaining an adequate proximal margin may be a problem [see Operative Planning, Extent of Resection, *above*]. The dissection proceeds as in a total gastrectomy, but without division of the short gastric vessels. The omentum is separated from the transverse colon with the electrocautery, and the entire omentum is taken with the specimen. A 5 cm proximal margin is ideal. Commonly, the stomach is divided at a point inferior to the short gastric vessels and proximal to the incisura angularis.

Additional operative details and comments on postgastrectomy complications are available elsewhere [see Procedures for Benign Gastric and Duodenal Disease, Antrectomy, *above*].

LAPAROSCOPIC STAGING FOR GASTRIC CANCER

The goal of laparoscopic staging before attempted curative resection of gastric carcinoma is to detect occult metastatic disease, the presence of which may affect management. For

example, if laparoscopy reveals peritoneal studding in a patient who does not have symptoms such as bleeding or obstruction, a decision may be made to forgo attempts at resection. In the setting of T2 or T4 tumors, laparoscopic staging has been shown to detect occult metastases in 20 to 30% of patients.¹²

The abdomen is explored with a 30° laparoscope inserted via an umbilical port. To facilitate exposure, additional 5 mm ports may be placed in the right upper and left upper quadrants. If laparoscopic ultrasonography is available, one of the port sites should be 10 mm to allow passage of the ultrasound probe. Any suspicious lesion encountered is sampled and sent for frozen-section analysis.

LAPAROSCOPIC RESECTION OF MALIGNANT GASTRIC TUMORS

Laparoscopic gastrectomy is being performed with increasing frequency. The principles of laparoscopic gastric resection are similar to those of the corresponding open procedure, although extensive lymph node dissections may be considerably more difficult with the minimally invasive approach. In the last several years, laparoscopic distal gastrectomy has been described with increasing frequency for early-stage distal gastric cancers, with early results suggesting equivalent outcomes compared with standard “open” techniques.²²

LAPAROSCOPIC DISTAL GASTRECTOMY

Operative Technique

Step 1: positioning Patients are positioned on a split-leg table to allow one surgeon between the patient’s legs. A 30° laparoscope is preferred. It is useful to include intraoperative gastroscopy to confirm the location of the tumor.

Step 2: exposure The omentum is separated from the colon and divided at the splenic flexure with a laparoscopic energy device such as the Harmonic shears or Ligasure device. The greater omentum is divided medial to the short gastric vessels. Medially, the right gastroepiploic artery and vein are divided individually near their roots using hemoclips.

Step 3: division of duodenum and lesser omentum The duodenum is divided 1 cm distal to the pylorus using an endoscopic stapling device. The right gastric artery is divided at its origin using hemoclips. The lesser omentum and pars flaccida are divided at the border of the liver.

Division of the left gastric artery and vein is described at this point, with perfusion of the stomach via the short gastric arteries. Division of the left gastric artery facilitates laparoscopic dissection lymph nodes along the celiac axis. Division of the left gastric artery is not routinely performed for distal gastrectomy in Western centers.

Step 4: division of stomach and reconstruction The stomach is divided using an endoscopic stapler or alternatively via a standard gastrointestinal stapler via a minilaparotomy. Laparoscopic Billroth II anastomosis is performed with an endoscopic stapler, using laparoscopic suture techniques to close the gastrotomy and enterotomy for this anastomosis.

LAPAROSCOPIC WEDGE RESECTION

Laparoscopic wedge resection may be appropriate for small lesions that are potentially benign or for malignant lesions for which extensive surgical margins are not required

(e.g., GISTs [see Figure 15]). The lesion is visualized intraoperatively by means of endoscopy or marked preoperatively with India ink. Laparoscopic sutures are placed in the tissue surrounding the lesion and then retracted upward so that the portion of the gastric wall containing the lesion is elevated. A wedge resection is then performed with an endoscopic stapler. Intraoperative assessment of the surgical margin by a pathologist is useful to ensure that the margin is negative.

Procedures for Duodenal Cancer

LOCAL RESECTION OF DUODENAL TUMORS

Small duodenal tumors (e.g., polyps, villous adenomas, small GISTs, and neuroendocrine tumors) are occasionally amenable to local surgical resection. The diagnosis must be confirmed by endoscopic biopsy before resection. Endoscopy is also useful for localization of the lesion with respect to the ampulla and pancreatic head. Lateral lesions are removed by local resection far more easily than lesions on the medial wall are.

Operative Planning

Endoscopic confirmation of the diagnosis and localization of the lesion are crucial for operative planning. In addition, appropriate patient selection is essential. Local resection may be inappropriate for lesions close to the ampulla of Vater, for large duodenal lesions, for carcinomas, or for lesions on the medial aspect of the duodenum abutting the pancreas. For lesions in the second or third portion of the duodenum that are not amenable to local excision, pancreaticoduodenectomy may be required. Exposure may be achieved through an upper midline or right upper quadrant incision.

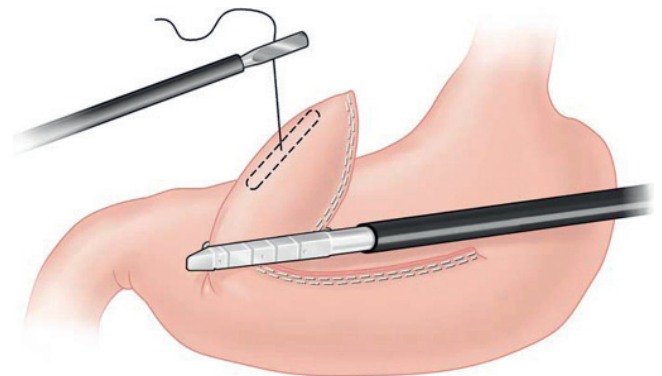


Figure 15 Laparoscopic resection of gastrointestinal stromal tumor. The tumor is visualized preoperatively and marked with India ink; alternatively, the tumor may be identified intraoperatively by means of endoscopy and its location marked with a suture. Traction sutures may be employed to “tent up” the lesion, thereby isolating it from the remainder of the stomach. The tumor is then resected with several firings of an endoscopic linear stapler. For lesions higher along the greater curvature near the cardia, wedge resection should be performed with an esophageal bougie in place to prevent inadvertent narrowing of the esophagogastric junction.

Operative Technique

The duodenum is mobilized with an extensive Kocher maneuver. The tumor is palpated and approached via a longitudinal duodenotomy. The tumor is grasped and everted, and a full-thickness portion of the duodenal wall is resected with the mass. Stay sutures are placed at the ends of the duodenotomy, and the duodenotomy is closed transversely, either with a TA stapler or with sutures. If a transverse closure would place too much tension on the suture line, a longitudinal closure is undertaken. If possible, omentum is placed over the duodenal closure.

Troubleshooting

Intraoperative endoscopy may be required to locate small duodenal lesions that cannot be palpated. During dissection, the location of the ampulla can be determined by passing a Fogarty catheter into the cystic duct, down the CBD, and through the ampulla. This measure requires that a cholecystectomy be done.

RESECTION OF DISTAL DUODENAL TUMORS

Lesions of the distal duodenum (e.g., GISTs, carcinoids, and, rarely, adenocarcinomas) are occasionally amenable to sleeve resection. Preoperative CT and endoscopy are essential to the workup of such lesions. Endoscopic biopsy should be performed if it is technically feasible.

Operative Technique

Step 1: exposure of duodenum Operative access to the distal duodenum is limited by the presence of the superior mesenteric vessels and the transverse mesocolon. The third and fourth portions of the duodenum may be approached either by moving the duodenum under the mesenteric vessels or by temporarily mobilizing the mesenteric vessels. In the first approach, the distal duodenum and the proximal jejunum are mobilized upward by dissecting the ligament of Treitz away from its mesenteric attachments. The proximal jejunum is divided with a stapler. After extensive mobilization, the duodenum is passed under the superior mesenteric vein and artery and moved to the right side of the abdomen.

In the second approach, the superior mesenteric vessels are mobilized upward to expose the third portion of the duodenum. The right colon is mobilized cephalad by incising the peritoneum along the white line of Toldt from the hepatic flexure to the cecum [see Figure 16a]. Division of the peritoneum is then continued along the cecum and medially to liberate the terminal ileum. The avascular attachments between the small bowel mesentery and the retroperitoneum are divided by means of cauterization and gentle blunt dissection [see Figure 16b].

Step 2: resection and anastomosis The duodenum is divided with the stapler approximately 1 cm proximal to

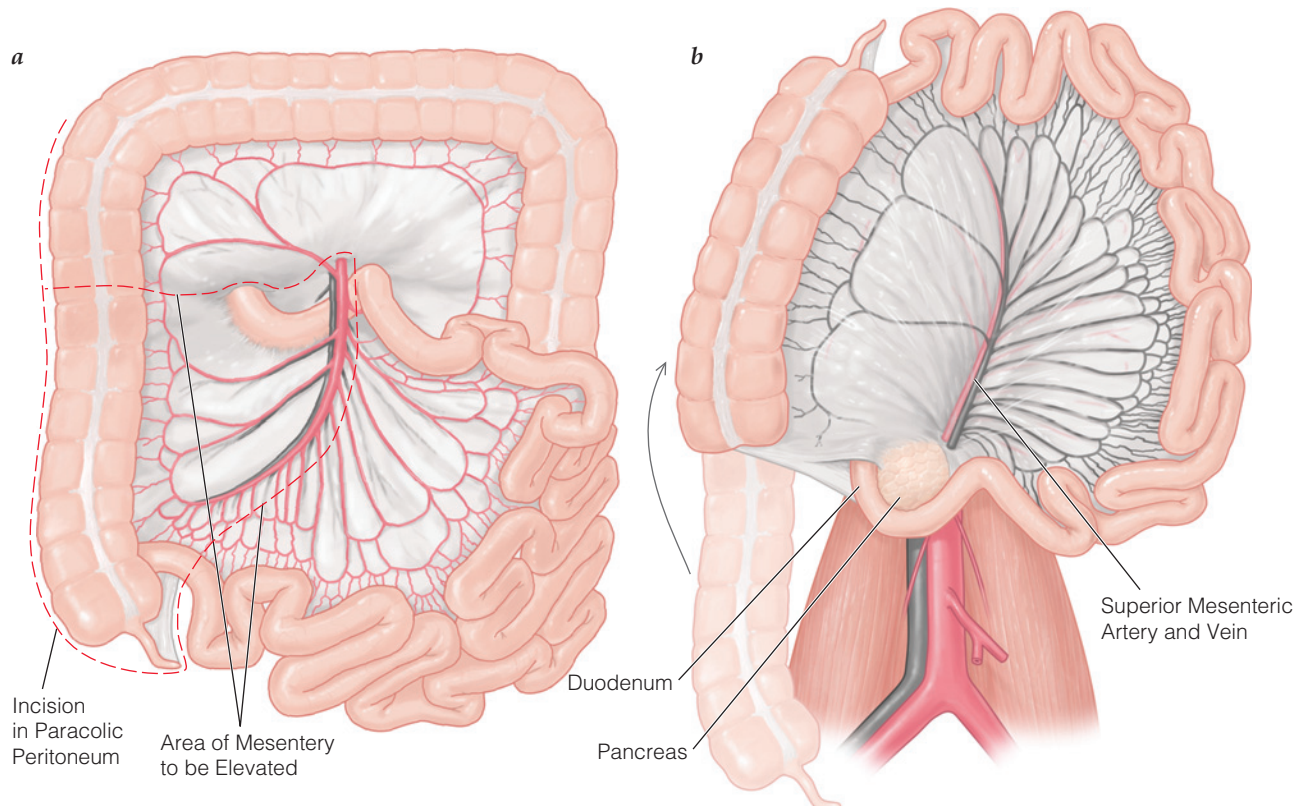


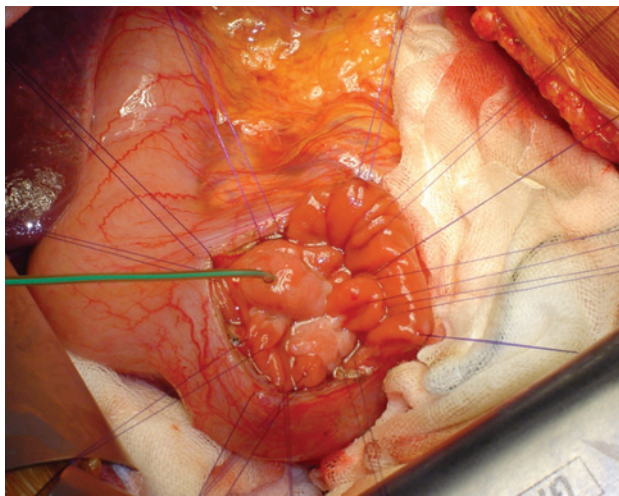
Figure 16 Local resection of duodenal tumors. Mobilization of the right colon and upward retraction of the small bowel mesentery allow direct access to the third and fourth portions of the duodenum. Sleeve resection of the duodenum with subsequent duodenojejunostomy can then be performed. (a) Avascular peritoneal attachments of the right colon are divided, as well as avascular attachments underneath the small bowel mesentery. Dotted lines enclose the area of mesentery to be elevated from posterior attachments. (b) Cephalad retraction of the right colon, the small bowel, and the mesenteric vessels allows exposure of the third and fourth portions of the duodenum.

the tumor. If pancreatic invasion is identified, pancreaticoduodenectomy should be considered. The distal bowel is brought through the transverse mesocolon, and a side-to-side duodenojejunostomy is created with an outer layer of 3-0 silk and an inner layer of 3-0 polyglactin. Alternatively, the anastomosis may be performed to the second portion of the duodenum.

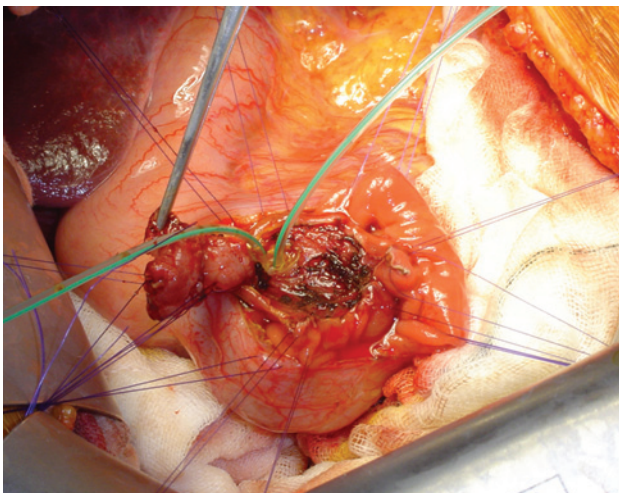
Troubleshooting

The blood supply to the third portion of the duodenum arises from numerous branches of the inferior pancreaticoduodenal arcade, each of which must be meticulously dissected, divided, and ligated to prevent pancreatic trauma. The distal duodenum receives its blood supply from branches of the superior mesenteric artery.

a



b



The duodenum should not be simply closed distally and drained via a gastrojejunostomy; if this is done, the proximal duodenum will not be properly decompressed.

Complications

Delayed gastric emptying is common with duodenojejunostomy; it generally responds to prolonged conservative therapy. A delay in the return of bowel function should generally be treated with nasogastric suction; on occasion, a percutaneous gastrostomy is required for proximal decompression. Postoperative pancreatitis may occur secondary to operative trauma; conservative management is usually sufficient.

AMPULLECTOMY

Local periampullary resection is indicated primarily for rare benign lesions, small neuroendocrine tumors of the pancreas, and small adenomatous or villous polyps. The likelihood of occult malignancy in an adenomatous periampullary tumor is significantly higher when the lesion is larger than 2 cm; caution is therefore indicated in attempting local resection of lesions of this size. The recurrence rate is high after local resection of any periampullary adenocarcinoma. The preoperative workup should include endoscopy with biopsy, EUS or transabdominal ultrasonography, CT scanning, and endoscopic retrograde cholangiopancreatography.

Operative Technique

The ampulla of Vater is resected together with the distal CBD and the distal pancreatic duct [see Figure 17]. A Kocher maneuver is performed, and a longitudinal duodenotomy is made to expose the ampulla. Identification of the ampulla may be facilitated by placing a Fogarty catheter in the CBD via the cystic duct after a cholecystectomy. If the ampulla is identified during exploration, it may simply be cannulated. Circumferential stay

c

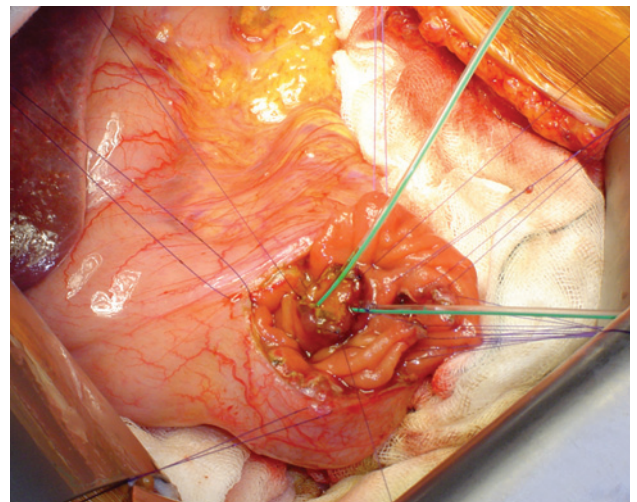


Figure 17 Ampullectomy. (a) After a longitudinal duodenotomy is made, the common bile duct (CBD) is cannulated. Circumferential stay sutures of 4-0 polydioxanone are placed in the duodenal mucosa. A 2 cm periampullary tumor is visualized. (b) The ampullary tumor is removed from the underlying duodenum with the electrocautery. The CBD and the pancreatic duct are entered and separately cannulated. The CBD is typically seen at the 11 o'clock position, and the pancreatic duct is typically encountered at the 3 o'clock position. (c) The duodenal mucosa is sutured directly to the CBD and the pancreatic duct with 4-0 polydioxanone. In addition, the CBD and pancreatic duct are carefully connected with 4-0 polydioxanone sutures.

sutures are placed in the mucosa. The CBD is entered at approximately the 11 o'clock position, and duodenal mucosa is reattached to the duct with 4-0 polydioxanone sutures. The pancreatic duct is encountered at approximately the 3 o'clock position; it may be cannulated separately to facilitate identification. The pancreatic duct is approximated to the CBD, and the inferior pancreatic duct is sewn to the duodenal wall. The duodenum is closed transversely in two layers.

Troubleshooting

Frozen-section analysis may identify invasive adenocarcinoma, which is an indication for pancreaticoduodenectomy. This possibility should be carefully considered before the operation.

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Figures 1 through 15 Tom Moore.
Figure 16 Courtesy of Dr. John Windsor and Dr. Yatin Young, Auckland Hospital, Auckland, New Zealand.

21 CHOLECYSTECTOMY AND COMMON BILE DUCT EXPLORATION

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and Dennis R. Klassen, MD, FRCS(C), FACS*

Cholecystectomy is the treatment of choice for symptomatic gallstones because it removes the organ that contributes to both the formation of gallstones and the complications ensuing from them.¹ The morbidity associated with cholecystectomy is attributable to injury to the abdominal wall in the process of gaining access to the gallbladder (i.e., the incision in the abdominal wall and its closure) or to inadvertent injury to surrounding structures during dissection of the gallbladder. Efforts to diminish the morbidity of open cholecystectomy have led to the development of laparoscopic cholecystectomy, made possible by modern optics and video technology.

Carl Langenbuch performed the first cholecystectomy in Berlin, Germany, in 1882. Erich Mühe performed the first laparoscopic cholecystectomy in Germany in 1985,² and by 1992, 90% of cholecystectomies in the United States were being performed laparoscopically. Compared with open cholecystectomy, the laparoscopic approach has dramatically reduced hospital stay, postoperative pain, and convalescent time. However, rapid adoption of laparoscopic cholecystectomy as the so-called gold standard for treatment of symptomatic gallstone disease was associated with complications, including an increased incidence of major bile duct injuries.

Since the early 1990s, considerable advances have been made in instrumentation and equipment, and a great deal of experience with laparoscopic cholecystectomy has been amassed worldwide. Of particular significance is the miniaturization of and improvement in optics and instruments, which have reduced the morbidity of the procedure by making possible ever-smaller incisions. With proper patient selection and preparation, laparoscopic cholecystectomy is being safely performed on an outpatient basis in many centers.³

The primary goal of cholecystectomy is removal of the gallbladder with minimal risk of injury to the bile ducts and surrounding structures. Our approach is designed to maximize the safety of both routine and complicated cholecystectomies. In what follows, we describe our approach and discuss current indications and techniques for imaging and exploring the common bile duct (CBD).

Laparoscopic Cholecystectomy

PREOPERATIVE EVALUATION

To plan the surgical procedure, assess the likelihood of conversion to open cholecystectomy, and determine which patients are at high risk for CBD stones, the surgeon must

obtain certain data preoperatively. Useful information can be obtained from the patient's history, imaging studies, and laboratory tests.

Preoperative Data

History and physical examination A good medical history provides information about associated medical problems that may affect the patient's tolerance of pneumoperitoneum. Patients with cardiorespiratory disease may have difficulty with the effects of CO₂ pneumoperitoneum on cardiac output, lung inflation pressure, acid-base balance, and the ability of the lungs to eliminate CO₂. Most bleeding disorders can also be identified through the history. A disease-specific history is important in identifying patients in whom previous episodes of acute cholecystitis may make laparoscopic cholecystectomy more difficult, as well as those at increased risk for choledocholithiasis (e.g., those who have had jaundice, pancreatitis, or cholangitis).⁴⁻⁹

Physical examination identifies patients whose body habitus is likely to make laparoscopic cholecystectomy difficult and is helpful for determining optimal trocar placement. Abdominal examination also reveals any scars, stomas, or hernias that are likely to necessitate the use of special techniques for trocar insertion.

Imaging studies Ultrasonography is highly operator dependent, but in capable hands, it can provide very useful information. It is the best test for diagnosing cholelithiasis, and it can usually determine the size and number of stones.⁴ Large stones indicate that a larger incision in the skin and the fascia will be necessary to retrieve the gallbladder. Multiple small stones suggest that the patient is more likely to require operative cholangiography (if a policy of selective cholangiography is practiced) [see Operative Technique, Step 5, below]. A shrunken gallbladder, a thickened gallbladder wall, and pericholecystic fluid on ultrasonographic examination are significant predictors of conversion to open cholecystectomy. The presence of a dilated CBD or CBD stones preoperatively is predictive of choledocholithiasis. Other intra-abdominal pathologic conditions, either related to or separate from the hepaticobiliary-pancreatic system, may influence operative planning.

Preoperative imaging studies of the CBD may allow the surgeon to identify patients with CBD stones before surgery. Such imaging may involve endoscopic retrograde cholangiopancreatography (ERCP) [see 5:18 *Gastrointestinal Endoscopy*],¹⁰ magnetic resonance cholangiopancreatography

(MRCP) [see Figure 1],^{11,12} or endoscopic ultrasonography (EUS). These imaging modalities also provide an anatomic map of the extrahepatic biliary tree, identifying unusual anatomy preoperatively and helping the surgeon plan a safe operation. Endoscopic sphincterotomy (ES) is performed during ERCP if stones are identified in the CBD. MRCP has an advantage over ERCP and EUS in that it is noninvasive and does not make use of injected iodinated contrast solutions.¹¹ Most surgeons would probably recommend that preoperative cholangiography be performed selectively in patients with clinical or biochemical features associated with a high risk of choledocholithiasis. The specific modality used in such a case varies with the technology and expertise available locally.

Laboratory tests Preoperative blood tests should include liver function, renal function, electrolyte, and coagulation studies. Abnormal liver function test results may reflect choledocholithiasis or primary hepatic dysfunction.

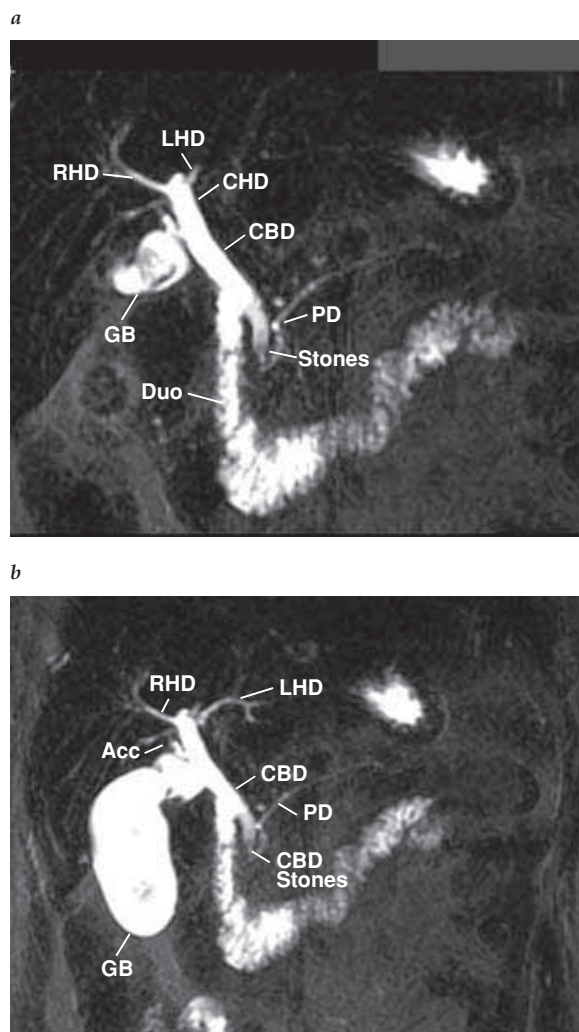


Figure 1 Laparoscopic cholecystectomy. (a) and (b) Preoperative magnetic resonance cholangiopancreatography alerts the surgeon to abnormal anatomy and the presence of stones in the distal common bile duct (CBD). Acc = accessory duct entering the common hepatic duct near the neck of the gallbladder; CHD = common hepatic duct; Duo = duodenum; GB = gallbladder, containing stones; LHD = left hepatic duct; PD = pancreatic duct; RHD = right hepatic duct.

Selection of Patients

Patients eligible for outpatient cholecystectomy

Patients in good general health who have a reasonable amount of support from family or friends and who do not live too far away from adequate medical facilities are eligible for outpatient cholecystectomy, especially if they are at low risk for conversion to laparotomy [see Special Considerations, Conversion to Laparotomy, below].³ These patients can generally be discharged home from the recovery room 6 to 12 hours after surgery provided that the operation went smoothly, their vital signs are stable, they are able to void, they can manage at least a liquid diet without vomiting, and their pain can be controlled with oral analgesics.

Technically challenging patients Before performing laparoscopic cholecystectomy, the surgeon can often predict which patients are likely to be technically challenging. These include patients who have a particularly unsuitable body habitus, those who are highly likely to have multiple and dense peritoneal adhesions, and those who are likely to have distorted anatomy in the region of the gallbladder.

Morbidly obese patients present specific difficulties [see Operative Technique, Step 1, Special Considerations in Obese Patients, below].¹³ Small, muscular patients have a noncompliant abdominal wall, resulting in a small working space in the abdomen and necessitating high inflation pressures to obtain reasonable exposure.

Patients with a history of multiple abdominal operations, especially in the upper abdomen, and those who have a history of peritonitis are likely to pose difficulties because of peritoneal adhesions.¹⁴ These adhesions make access to the abdomen more risky and exposure of the gallbladder more difficult. Patients who have undergone gastroduodenal surgery, those who have any history of acute cholecystitis, those who have a long history of recurrent gallbladder attacks, and those who have recently had severe pancreatitis are particularly difficult candidates for laparoscopic cholecystectomy. These patients may have dense adhesions in the region of the gallbladder, the anatomy may be distorted, the cystic duct may be foreshortened, and the CBD may be very closely and densely adherent to the gallbladder. Such patients are a challenge to the most experienced laparoscopic surgeon. When such problems are encountered, conversion to open cholecystectomy should be considered early in the operation.^{14,15}

Predictors of choledocholithiasis CBD stones may be discovered preoperatively, intraoperatively, or postoperatively. The surgeon's goal is to clear the ducts but to use the smallest number of procedures with the lowest risk of morbidity. Thus, before elective laparoscopic cholecystectomy, it is desirable to classify patients into one of three groups: high risk (those who have clinical jaundice or cholangitis, visible choledocholithiasis, or a dilated CBD on ultrasonography), moderate risk (those who have hyperbilirubinemia, elevated alkaline phosphatase levels, pancreatitis, or multiple small gallstones), and low risk.

In our institution, where MRCP and EUS are available and reliable and where ERCP achieves stone clearance rates higher than 90%, we recommend the following approach: (1) preoperative ERCP and sphincterotomy (if required) for high-risk patients and (2) MRCP, EUS, or intraoperative fluoroscopic cholangiography for moderate-risk patients. Patients at low risk for CBD stones do not routinely undergo cholangiography [see Figure 2]. Laparoscopic CBD exploration

and postoperative ERCP appear to be equally effective in clearing stones from the CBD.

Ultimately, surgeons and institutions must establish a reasonable approach to choledocholithiasis that takes into account the expertise and equipment locally available.

Contraindications There are few absolute contraindications to laparoscopic cholecystectomy. Certainly, no patient who poses an unacceptable risk for open cholecystectomy should be considered for laparoscopic cholecystectomy, because it is always possible that conversion will become necessary. Of the relative contraindications, surgical inexperience is the most important.

Neither ascites nor hernia is a contraindication to laparoscopic cholecystectomy. Ascites can be drained and the gallbladder visualized. Large hernias may present a problem, however, because with insufflation, the gas preferen-

tially fills the hernia. Patients with large inguinal hernias may require an external support to minimize this problem and the discomfort related to pneumoscrotum. Patients with umbilical hernias can have their hernias repaired while they are undergoing laparoscopic cholecystectomy. For such patients, the initial trocar should be placed by open insertion according to the Hasson technique [see Operative Technique, Step 1, *below*], with care taken to avoid injury to the contents of the hernia. The sutures required to close the hernia defect can be placed before insertion of the initial trocar. For patients with small incisional hernias, laparoscopic cholecystectomy can proceed as usual. The hernia may be repaired at the same operation if the cholecystectomy goes smoothly and there is no peritoneal contamination. For large incisional hernias, we would proceed with laparoscopic cholecystectomy, limiting adhesiolysis to that

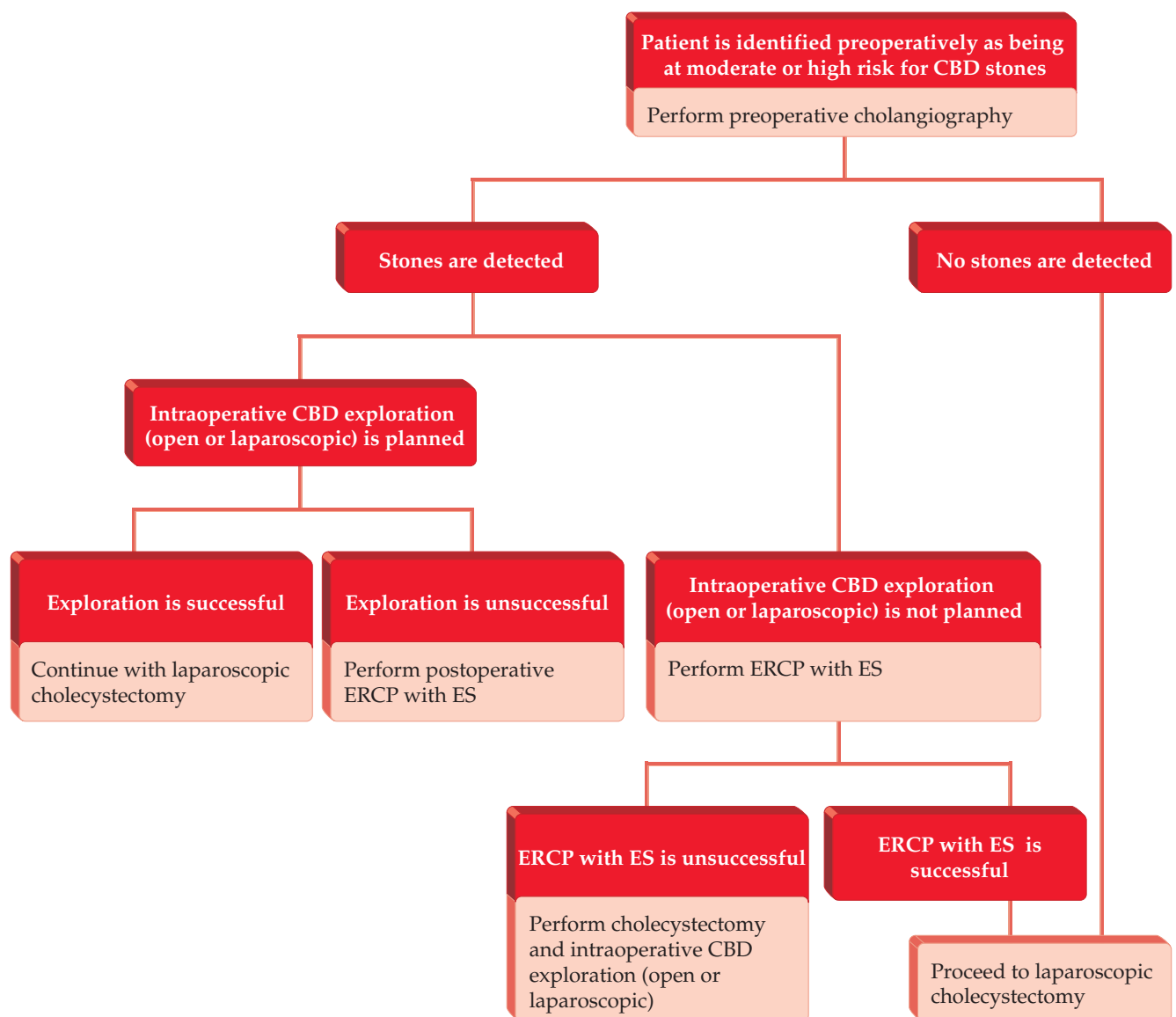


Figure 2 Laparoscopic cholecystectomy. Shown is an algorithm outlining the use of preoperative cholangiography in patients at moderate or high risk for common bile duct (CBD) stones. ERCP = endoscopic retrograde cholangiopancreatography; ES = endoscopic sphincterotomy.

required to safely perform the procedure. Patients with stomas may also undergo laparoscopic cholecystectomy provided that the appropriate steps are taken to prevent injury to the bowel during placement of trocars and division of adhesions.

Patients with cirrhosis or portal hypertension are at high risk for morbidity and mortality with open cholecystectomy.^{16,17} If absolutely necessary, laparoscopic cholecystectomy may be attempted by an experienced surgeon. The risk of bleeding can be minimized by rigorous preoperative preparation, meticulous dissection with the help of magnification available through the laparoscope, and use of electrocautery and enabling hemostatic devices.

Patients with bleeding diatheses, such as hemophilia, von Willebrand disease, and thrombocytopenia, may undergo laparoscopic cholecystectomy. They require appropriate preoperative and postoperative care and monitoring, and a hematologist should be consulted.

Questions have been raised about whether laparoscopic cholecystectomy should be performed in pregnant patients; it has been argued that the increased intra-abdominal pressure may pose a risk to the fetus. Because of the enlarged uterus, open insertion of the initial trocar is mandatory, and the positioning of other trocars may have to be modified according to the position of the uterus. Inflation pressures should be kept as low as possible, and prophylaxis of deep vein thrombosis (DVT) is recommended. Despite these potential problems, safe performance of laparoscopic cholecystectomy and other laparoscopic procedures in pregnant patients is increasingly being described in the literature. If cholecystectomy is necessary before delivery, the second trimester is the best time for it.^{18–21}

Patients in whom preoperative imaging gives rise to a strong suspicion of gallbladder cancer should probably undergo open surgical management.

OPERATIVE PLANNING

Antibiotic Prophylaxis

Some surgeons recommend routine preoperative administration of antibiotics to all patients undergoing cholecystectomy, on the grounds that inadvertent entry into the gallbladder is not uncommon and can lead to spillage of bile or stones into the peritoneal cavity. Other surgeons do not recommend routine prophylaxis. Resolution of this controversy awaits appropriate prospective trials. We recommend selective use of antibiotic prophylaxis for patients at highest risk for bacteria in the bile (including those with acute cholecystitis or CBD stones, those who have previously undergone instrumentation of the biliary tree, and those older than 70 years) and for patients with prosthetic heart valves and joint prostheses.

Prophylaxis of DVT

The reverse Trendelenburg position used during laparoscopic cholecystectomy, coupled with the positive intra-abdominal pressure generated by CO₂ pneumoperitoneum and the vasodilatation induced by general anesthesia, leads to venous pooling in the lower extremities. This consequence may be minimized by using antiembolic stockings or by wrapping the legs with elastic bandages. Subcutaneous heparin and pneumatic compression devices may be employed

for patients at increased risk for DVT [see 6:6 *Venous Thromboembolism*]. As yet, however, there is no convincing evidence that the incidence of DVT is higher with laparoscopy than with open surgery.

Patient Positioning

Typically, the patient is positioned supine and the surgeon stands to the patient's left side [see Figure 3].

The camera operator usually stands on the patient's left and to the left of the surgeon, while the assistant stands on the patient's right. The video monitor is positioned on the patient's right above the level of the costal margin. If a second monitor is available, it should be positioned on the patient's left to the right of the surgeon, where the assistant can have an unobstructed and comfortable view. Exposure can be improved by tilting the patient in the reverse Trendelenburg position and rotating the table with the patient's right side up. Gravity pulls the duodenum, colon, and omentum away from the gallbladder, thereby increasing the working space available in the upper abdomen.

The operating room (OR) table should allow easy access for a fluoroscopic C arm to facilitate intraoperative cholangiography. The table cover should be radiolucent.

Equipment

The equipment required for laparoscopic cholecystectomy includes an optical system, an electronic insufflator, trocars (cannulas), surgical instruments, and hemostatic devices [see Table 1].

Optical system The laparoscope can provide either a straight, end-on (0°) view or an angled (30° or 45°) view. Scopes that provide an end-on view are easier to learn to use,

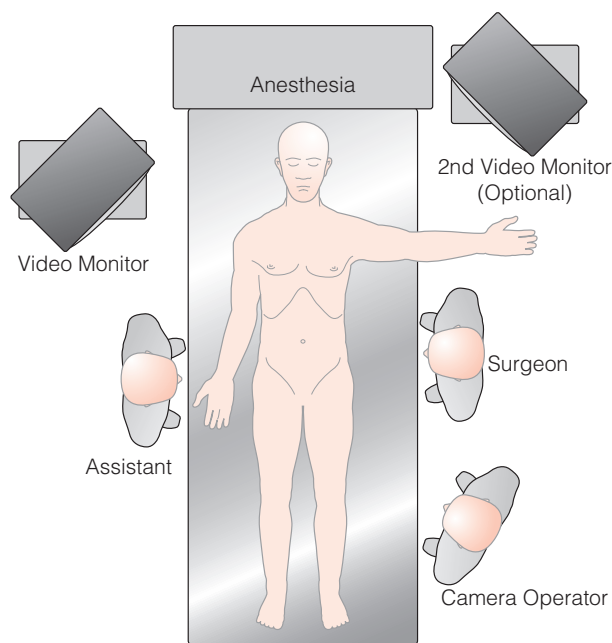


Figure 3 Laparoscopic cholecystectomy. A patient undergoing laparoscopic cholecystectomy should be positioned so as to allow easy access to the gallbladder and a clear view of the monitors. Shown are the positions of the surgeon, the camera operator, and the assistant in the operating room.

but angled scopes are more versatile. Scopes with a 30° angle cause less disorientation than those with a 45° angle and are ideal for laparoscopic cholecystectomy. Excellent 30° scopes are currently available in diameters of 10, 5, and 3.5 mm.

Fully digital flat-panel displays are now available that yield better resolution than analog video monitors, take up less

space, are less subject to signal interference, and require less power. The introduction of high-definition optics has further improved the quality of the image. The associated 16:9 display increases the width of the field of view.

The resolution and quality of the final image depend on (1) the brightness of the light source; (2) the integrity of the

Table 1 Equipment for Laparoscopic Cholecystectomy

Instrument/Device	Number	Size	Comments
Laparoscopic cart High-intensity halogen light source (150–300 watts) High-flow electronic insufflator (minimum flow rate of 106 L/min) Laparoscopic camera box Videocassette digital video and still image recorder (optional) Digital still image capture system (optional)			
Laparoscope	1	3.5–10 mm	Available in 0° and angled views; we prefer to use a 30° 5 mm diameter laparoscope
Atraumatic grasping forceps	2–4	2–10 mm	Selection of graspers should allow surgeon choice appropriate to thickness and consistency of gallbladder wall; insulation is unnecessary
Large-tooth grasping forceps	1	10 mm	Used to extract gallbladder at end of procedure
Curved dissector	1	2–5 mm	Should have a rotatable shaft; insulation is required
Scissors	2–3	2–5 mm	One curved and one straight scissors with rotating shaft and insulation; additional microscissors may be helpful for incising cystic duct
Clip appliers	1–2	5–10 mm	Either disposable multiple clip applier or 2 manually loaded reusable single clip appliers for small and medium-to-large clips; 5 and 10 mm diameter
Dissecting electrocautery hook or spatula	1	5 mm	Available in various shapes according to surgeon's preference; instrument should have channel for suction and irrigation controlled by trumpet valve(s); insulation required
High-frequency electrical cord	1		Cord should be designed with appropriate connectors for electrosurgical unit and instruments being used
Suction-irrigation probe	1	5–10 mm	Probe should have trumpet valve controls for suction and irrigation; may be used with pump for hydrodissection
10-to-5 mm reducers	2		Allow use of 5 mm instruments in 10 mm trocar without loss of pneumoperitoneum; these are often unnecessary with newer disposable trocars and may be built into some reusable trocars
5-to-3 mm reducer	1		Allows use of 2–3 mm instruments and ligating loops in 5 mm trocars
Ligating loops			
Endoscopic needle holders	1–2	5 mm	
Cholangiogram clamp with catheter	1	5 mm	Allow passage of catheter and clamping of catheter in cystic duct
Veress needle	1		Used if initial trocar is inserted by percutaneous technique
Allis or Babcock forceps	1–2	5 mm	Allow atraumatic grasping of bowel or gallbladder
Long spinal needle	1	14 gauge	Useful for aspirating gallbladder percutaneously in cases of acute cholecystitis or hydrops
Retrieval bag	1		Useful for preventing spillage of bile or stones in removal of inflamed or friable gallbladder; facilitates retrieval of spilled stones

fiberoptic cord used to convey the light; (3) clean and secure connections between the light source and the scope; (4) the quality of the laparoscope, the camera, and the monitor; and (5) correct wiring of the components. The distal end of the scope must be kept clean and free of condensation: bile, blood, or fat will reduce brightness and distort the image. Lens fogging can be prevented by immersion in heated water or by antifogging solutions.

Insufflator CO₂ is the preferred insufflating gas for laparoscopic procedures because it is highly soluble in water and does not support combustion when electrocautery is used. The CO₂ should be insufflated with an electronic pump capable of a flow rate of at least 10 L/min; most current systems have a maximum flow rate of 20 L/min or higher. The insufflator is connected to one of the trocars by means of a flexible tube and a stopcock.

Trocars For cholecystectomy, at least one trocar site must be large enough to allow passage of the gallbladder and any stones removed. Most surgeons prefer to use a 10/12 mm trocar at the umbilicus for this purpose. The other trocars can range from 2 to 12 mm, depending on the size of the instruments to be placed through them. The conventional approach is to use a 10/12 mm trocar at the operating port site and 5 mm trocars for the other instruments; however, if a 5 mm laparoscope and a 5 mm clip applier are used, the operating port size can be reduced to 5 mm. Although 2 mm instrumentation is also available, it must be remembered that, as a rule, the smaller the working port, the less versatile the instruments. In our experience, the combination of a 10 mm umbilical trocar, a 5 mm operating port, and 2 mm ports for grasping forceps is a good one: optical quality is maintained, little flexibility is lost with respect to selecting operating instruments, trocar size is minimized, and the cosmetic result is excellent.

Hemostatic devices Hemostasis can be achieved with monopolar or bipolar electrocauterization. A monopolar electrocautery can be connected to most available instruments; however, bipolar electrocauterization may eventually prove safer. With a monopolar electrocautery, depth of burn is less predictable, current can be conducted through noninsulated instruments and trocars, and any area of the instrument that is stripped of insulation may conduct current and result in a burn. Caution is essential when the electrocautery is used near metallic hemostatic clips because delayed sloughing may occur.

Electrocauterization should be avoided near the CBD because delayed bile duct injuries and leaks may occur as a result of sloughing from a burned area and devascularization of the duct. Care must be exercised when cautery is employed near the bowel and when intra-abdominal adhesions are being taken down. The electrocautery can be used with a forceps, scissors, hooks (L or J shaped), a spatula, and other instruments. Some cautery probes incorporate nonstick surfaces to prevent buildup of eschar. The use of hand-activated cautery probes and the presence of a channel that allows suction and irrigation through the cautery probes are especially convenient.

More advanced energy sources and instruments are also available. Bipolar devices designed to weld tissues have proved capable of achieving superb hemostasis. Ultrasonic dissecting shears can also be used to dissect and coagulate tissues effectively and precisely. For laparoscopic cholecystectomy, however, such advanced—and costly—devices are rarely needed.

OPERATIVE TECHNIQUE

Step 1: Placement of Trocars and Accessory Ports

Placement of initial trocar The first step in laparoscopic cholecystectomy is the creation of pneumoperitoneum and the insertion of an initial trocar through which the laparoscope can be passed. This step is critical because complications resulting from improper placement may cause serious morbidity and death. The surgeon may use either a percutaneous technique or an open technique. We prefer the open technique, which eliminates the risks inherent in the blind puncture [see Figure 4].^{22,23}

Scars Patients who have previously undergone abdominal surgery may have adhesions, both to the undersurface of the abdominal wall and intra-abdominally. Adhesions to the undersurface of the abdominal wall make access to the abdominal cavity potentially hazardous, particularly when the percutaneous method is used for placement of the initial trocar. Scars from previous operations may affect insertion of the initial trocar, depending on its orientation and location. If a patient has a scar in the lower abdomen (e.g., from a Pfannenstiel incision or an incision in the right lower quadrant for an appendectomy), the position of the initial trocar need not be changed. If the scar is in the upper abdomen, the initial trocar may be inserted below the umbilicus in the midline. If there is a long midline scar that is impossible to avoid, careful dissection of the peritoneum through a vertical incision that is somewhat longer than usual affords safe access to the peritoneum in most cases.

An alternative is to insert the initial trocar high in the epigastrium or in the right anterior axillary line, where bowel adhesions are less common. The laparoscope is inserted through this trocar and used to examine the undersurface of the old scar for a clear site near the umbilicus, where a 10 mm trocar can be placed. Previous laparoscopy, which rarely creates significant intra-abdominal adhesions, rarely necessitates modification of trocar insertion.

The surgeon should also consider the reason for the previous surgery. For example, a patient who underwent an appendectomy for perforated appendicitis may have had diffuse peritonitis and may have adhesions well away from the old scar.

Placement of accessory ports In most cases, four ports are necessary. The first port is for the laparoscope; the remaining ports are for grasping forceps, dissectors, and clip appliers. The precise position of the accessory ports depends on the surgeon's preference, the patient's body habitus, and the presence or absence of previous scars or intra-abdominal adhesions [see Figure 5]. A rigid approach to port placement is inappropriate: trocar placement determines operative exposure, and improper placement will haunt the surgeon throughout the procedure. In some cases, a fifth trocar is required to elevate a floppy liver or to depress or retract the omentum or a bulky hepatic flexure of the colon [see Figure 5].

Most surgeons elect to place one of the grasping forceps on the fundus of the gallbladder through an accessory port placed approximately in the anterior axillary line below the level of the gallbladder. Because the level of the gallbladder varies from patient to patient, the placement of this accessory port should not be decided on until the gallbladder is visualized. If the gallbladder is low lying and the trocar is placed too high, the surgeon will have difficulty achieving the appropriate angle

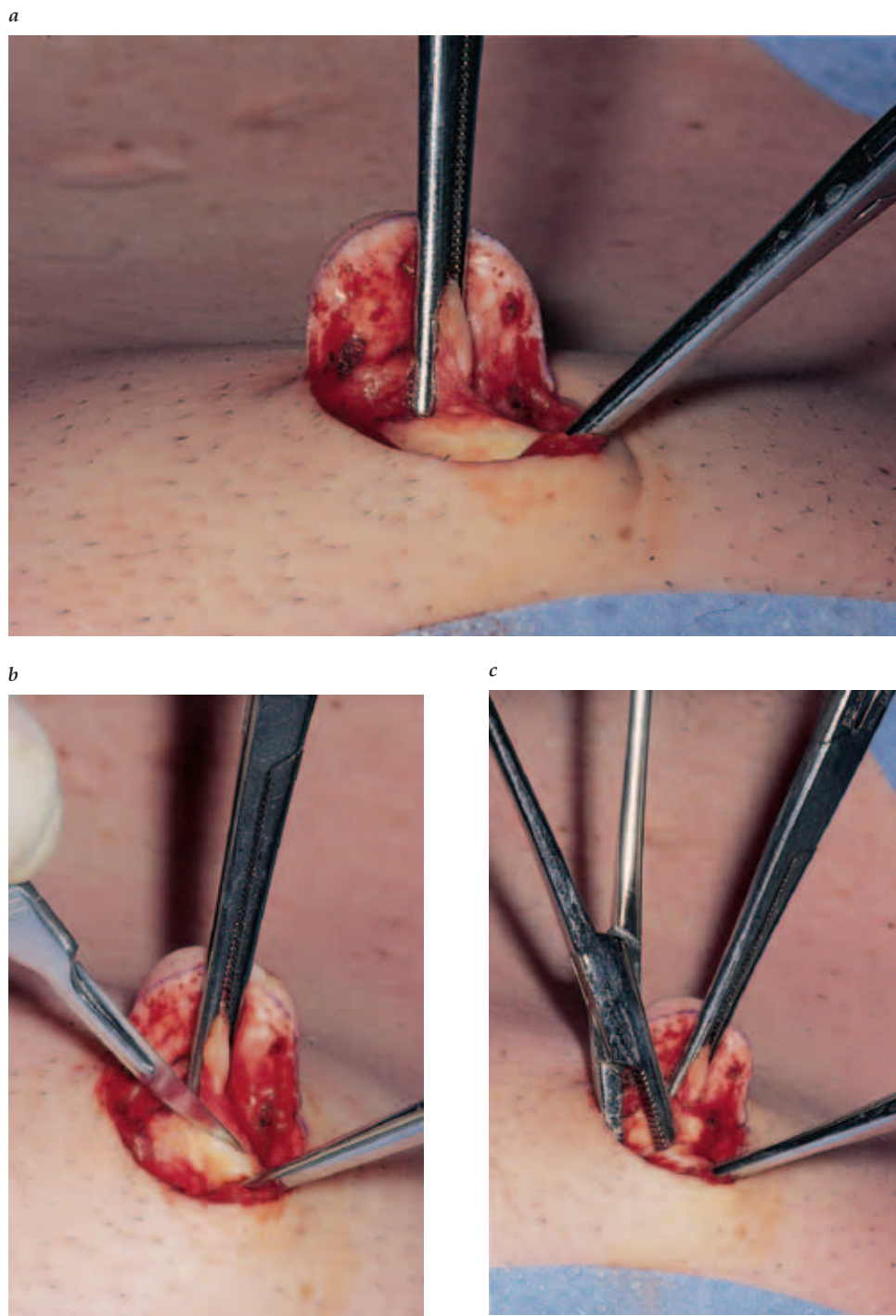


Figure 4 Laparoscopic cholecystectomy. With the open insertion technique, the initial trocar is placed under direct vision. (a) The umbilical skin is elevated with a sharp towel clip. A curvilinear incision is made in the inferior umbilical fold. The skin flap is elevated, and the raphe leading from the dermis to the fascia is thereby exposed. (b) The fascia is grasped in the midline between forceps and elevated. The fascia and the underlying peritoneum are incised under direct vision. (c) A blunt instrument is placed into the peritoneum to ensure that the undersurface of the peritoneum is free of adhesions. The opening can be enlarged sufficiently to allow placement of a blunt 10/11 mm trocar.

of retraction. As a general rule, positioning the trocar in the anterior axillary line approximately halfway between the costal margin and the anterosuperior iliac spine provides the appropriate exposure. A 2 to 5 mm port usually suffices at this site

because its only likely function is to allow retraction of the gallbladder. In some cases of acute cholecystitis, however, a larger port may be preferable so that a larger grasper can be inserted and used to hold the gallbladder without tearing it.

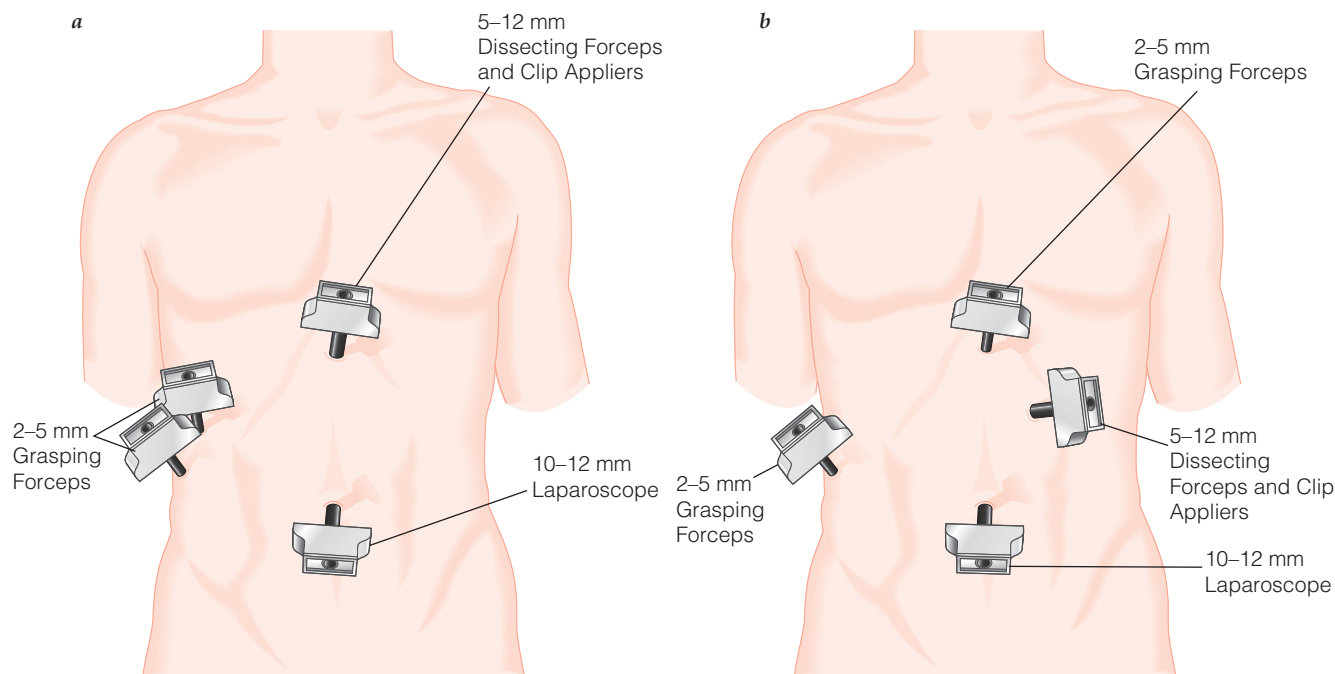


Figure 5 Laparoscopic cholecystectomy. (a) and (b) are two popular options for trocar positioning and instrument placement.

A second accessory port (also 2 to 5 mm) allows the surgeon to grasp the gallbladder in the area of the Hartmann pouch for retraction. This port is usually positioned just beneath the right costal margin. Some surgeons prefer it to be approximately at the midclavicular line; others prefer it to be higher and more medial, just to the right of the falciform ligament.

The main operating port should be 5 or 10 mm in diameter so that clip appliers can be readily placed through it and the laparoscope can be moved to this port at the end of the procedure. The positioning of this port is determined by the surgeon's preference and, in particular, by the patient's body habitus. The optimum placement is at about the same horizontal level as the gallbladder or slightly higher so that during the operation, the laparoscope and the operating instrument form an angle of about 90°. Some surgeons prefer to place the operative port in the midline, to the right of the falciform ligament; others prefer to place it to the left of the falciform ligament, passing the trocar underneath the ligament and elevating it with the trocar.

Surgeons should be encouraged to use both hands when performing laparoscopic cholecystectomy. One hand should control the grasping forceps holding the Hartmann pouch so that the gallbladder can be moved to provide the best possible exposure. The other hand should control the dissecting instruments placed through the operating port.

Special considerations in obese patients Port placement in obese patients may be complicated by the thick abdominal wall, the large amount of intra-abdominal fat, or both. A thick abdominal wall makes it more difficult to rotate the trocar around the normal fulcrum point in the abdominal wall. Consequently, the trocar must be placed at the angle most likely to be used during the procedure. When a trocar is tunneled through the abdominal wall, more of the cannula

is within the abdominal wall than if the trocar had been placed perpendicularly; accordingly, the trocar is less mobile. If the trocars are not easily rotated, the instruments placed through them will be difficult to manipulate smoothly. Thus, in the patient with a very thick pannus, a standard-length trocar may be too short. Displacement of trocars can lead to insufflation into the abdominal wall and consequently to subcutaneous emphysema, which further thickens the abdominal wall and hinders exposure.

To prevent such problems, special extra-length trocars designed for morbidly obese patients have been developed. It may also be necessary to place the trocars closer to the area of the gallbladder to ensure that the operating instruments can reach the gallbladder. For example, the initial port may have to be placed above the umbilicus.

In obese patients, the bulky falciform ligament and the large omentum may adversely affect exposure. A 30° laparoscope may help the surgeon see over the omentum and the high-lying hepatic flexure of the colon. In some cases, it is useful to place a fifth port so that the surgeon can retract the hepatic flexure downward. Fat may envelop the cystic duct and artery and the portal structures, obscuring normal anatomic landmarks. When the electrocautery is used, the heat melts the fat and causes it to sizzle and spray onto the lens of the laparoscope, resulting in a blurry image. To prevent this, the camera operator should pull the scope slightly away from the operative field during electrocauterization and then advance the scope during dissection. This should also be done when an ultrasonic dissector is being used.

Given that obese patients are more difficult candidates for open cholecystectomy and have a higher complication rate with laparotomy, the advantages of laparoscopic cholecystectomy in these individuals justify the effort needed to overcome the technical problems.

Step 2: Exposure of the Gallbladder and Calot Triangle

Dissection of adhesions Adhesions must be dissected to provide an unimpeded view of the gallbladder through the laparoscope. Not all intra-abdominal adhesions must be taken down, just enough to allow entry of accessory trocars under direct vision and thus permit access to the gallbladder. This process is facilitated by pneumoperitoneum, which provides traction on adhesions to the abdominal wall, and by the magnification provided by the optical system, which allows identification of the avascular plane of attachment.

The most difficult problem is positioning the dissecting instruments so that they can reach the undersurface of the anterior abdominal wall. A rigid trocar inserted through the anterior abdominal wall cannot be rotated enough to allow scissors passed through this port to cut adhesions to the anterior abdominal wall. In such cases, one or two trocars should be placed laterally, near the anterior axillary or midaxillary line. Instruments passed through these ports can easily be angled parallel to the anterior abdominal wall, and the adhesions can then be dissected without difficulty.

Bowel adhesions should be taken down with endoscopic scissors at their insertion to the abdominal wall, where they are least vascular. Electrocauterization, which is generally unnecessary, should be avoided because of the risk of thermal injury to the bowel. Interloop adhesions, which rarely interfere with exposure of the gallbladder, need not be dissected. Frequently, adhesions to the gallbladder occur as a reaction to inflammatory attacks [see Figure 6]. They are usually relatively avascular. Dissection of these adhesions should begin at the fundus of the gallbladder and should then proceed down toward the neck of the gallbladder. The best way to take them down is to grasp the gallbladder with one grasping forceps at the site where the adhesions attach and gradually place traction on the adhesions with the other hand. Usually, the adhesions peel down in an avascular plane. Dissection should continue until all adhesions to the inferolateral aspect of the gallbladder have been taken down. It is not necessary to divide adhesions between the superior surface of the liver and the undersurface of the diaphragm unless they impede superior retraction of the liver.

Exposing the Calot triangle Obtaining adequate exposure of the Calot triangle is a key step. First, the patient is placed in a reverse Trendelenburg position, with the table rotated toward the left side. Next, the fundus of the gallbladder and the right lobe of the liver are elevated toward the patient's right shoulder. One grasping forceps, inserted through the most lateral right-side port and held by an assistant, is placed on the fundus of the gallbladder [see Figure 7], and the gallbladder is retracted superiorly and laterally above the right hepatic lobe. This maneuver straightens out folds in the body of the gallbladder and permits initial visualization of the area of the Calot triangle. If the Calot triangle is still obscured, the patient can be placed in a steeper reverse Trendelenburg position, and the stomach can be emptied of air via an orogastric tube inserted by the anesthetist, or, if necessary, a fifth trocar can be inserted on the patient's right side to push down the duodenum.

In some patients, such as those with acute cholecystitis and hydrops of the gallbladder, the gallbladder is tense and distended, making it difficult to grasp and easy to tear. In these

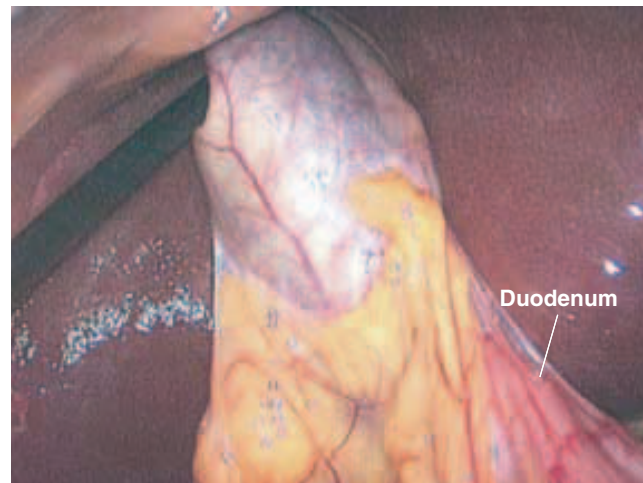


Figure 6 Laparoscopic cholecystectomy. Adhesions of the duodenum and omentum to the gallbladder wall obscure the view of structures of the Calot triangle.

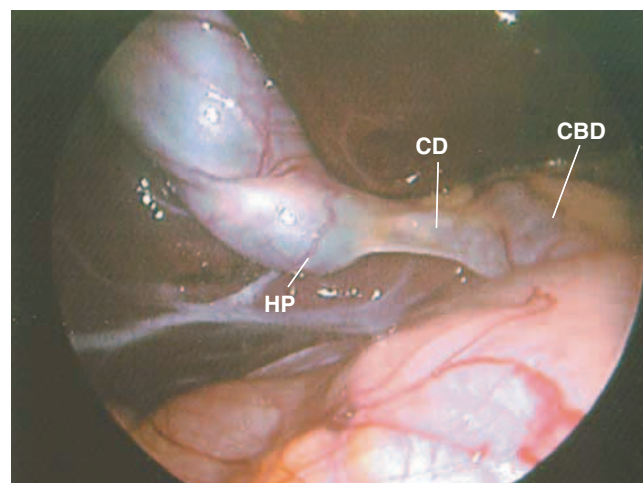


Figure 7 Laparoscopic cholecystectomy. Initial view of the gallbladder and related structures is facilitated by appropriate tilting of the operating table. The Hartmann pouch (HP), cystic duct (CD), and common bile duct (CBD) can be readily identified before any dissection.

patients, retraction of the fundus is difficult, and exposure of the Calot triangle is unsatisfactory. This problem is best managed by aspirating the contents of the gallbladder either percutaneously with a 14- or 16-gauge needle inserted into the fundus of the gallbladder under laparoscopic vision or by using the 5 mm trocar in the right upper abdomen to puncture the fundus and then aspirate with the suction irrigator. After the needle is withdrawn, a large atraumatic grasping forceps can be used to hold the gallbladder and occlude the hole; a 10 mm forceps may be preferred if the wall is markedly thickened. An alternative is to place a stitch or a ligating loop around the fundus of the collapsed gallbladder; the tail of the suture can then be grasped with a forceps to achieve a secure grip and prevent further leakage of gallbladder contents from the needle hole.

Once the fundus of the gallbladder is retracted superiorly by the assistant, the surgeon places a grasping forceps in the area of the Hartmann pouch. Using both hands, the surgeon controls the grasper on the Hartmann pouch and the operating instrument. The surgeon maneuvers the Hartmann pouch to provide various angles for safe dissection of the Calot triangle. Initially, lateral and inferior traction are placed on the Hartmann pouch, opening up the angle between the cystic duct and the common ducts [see Figure 8], avoiding their alignment [see Figure 9].

A large stone impacted in the gallbladder neck may impede the surgeon's ability to place the forceps on the Hartmann pouch. This problem can usually be managed by dislodging the stone early in the operation, as follows: the gallbladder is grasped as low as possible with one grasping forceps; a widely opening dissecting instrument, such as a right-angle dissector, a Babcock

forceps, or a curved dissector, is used to dislodge the stone and milk it up toward the fundus; with the same forceps or another large grasper, the stone is held up and away from the neck of the gallbladder, and appropriate retraction is provided.

If the stone cannot be disimpacted, an instrument can be used to elevate the infundibulum of the gallbladder superiorly, allowing exposure of the Calot triangle. Alternatively, one can attempt to crush the stone, but small pieces of the stone may fall into the cystic duct. A third option is to place a stitch in the Hartmann pouch and grasp the end of the stitch to provide exposure.

Step 3: Stripping of the Peritoneum

The key to avoiding injury to the major ducts during laparoscopic cholecystectomy is accurate identification of the junction between the gallbladder and the cystic duct [see Figure 10]. Unless the gallbladder–cystic duct junction is immediately obvious on examination of the Calot triangle anteriorly, our approach is to begin dissection of the Calot triangle posteriorly [see Figure 11]. From this approach, the insertion of the gallbladder neck into the cystic duct is usually more clearly identified, especially with the aid of a 30° laparoscope. Exposure is obtained by retracting the Hartmann pouch superomedially and is facilitated by looking from below with a 30° scope.

Dissection should always start high on the gallbladder and hug the gallbladder closely until the anatomy is identified clearly. Using a curved dissector, the surgeon gently teases away peritoneum attaching the neck of the gallbladder to the liver posterolaterally to visualize the funneling of the neck of the gallbladder into the cystic duct [see Figure 12]. Only the posterior layer of peritoneum is dissected; care must be taken not to dissect deeply in this area because of the risk of injury to the cystic artery [see Figure 13].

In some problem cases, edema, fibrosis, and adhesions make identification of the gallbladder–cystic duct junction very difficult. An anatomic landmark on the liver known as the Rouvier sulcus may be helpful in such circumstances [see Figure 11]. This sulcus, or the remnant of it, is present in

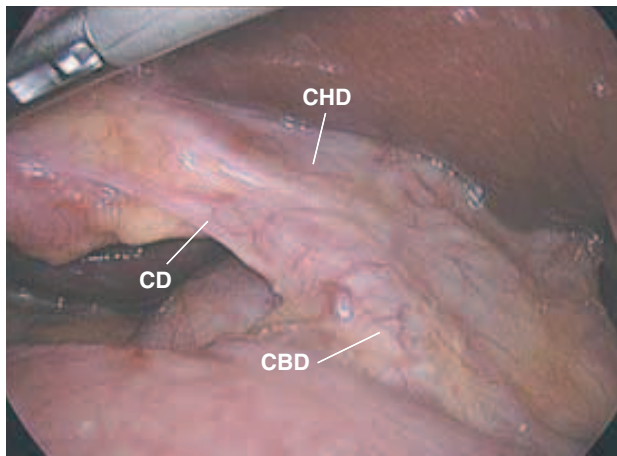


Figure 8 Laparoscopic cholecystectomy. The area of the Hartmann pouch is retracted laterally. The cystic duct (CD) is seen at an angle to the common hepatic duct (CHD) and the common bile duct (CBD).

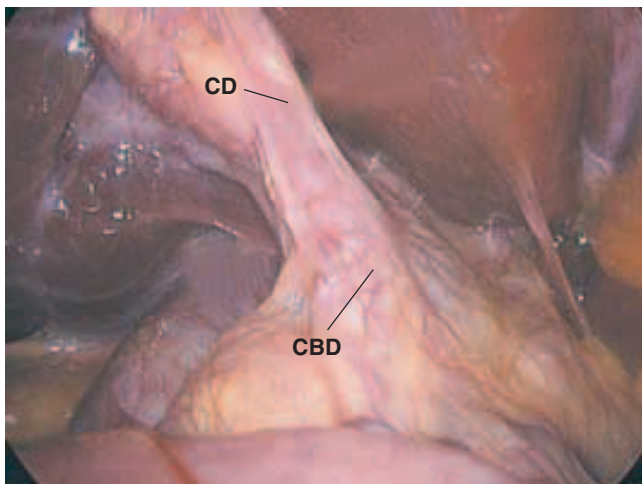


Figure 9 Laparoscopic cholecystectomy. In this case, the gallbladder is retracted cephalad. The cystic duct (CD) can be seen running in the same direction as the common bile duct (CBD). The CBD may be misinterpreted as being the cystic duct and consequently is at risk for injury.

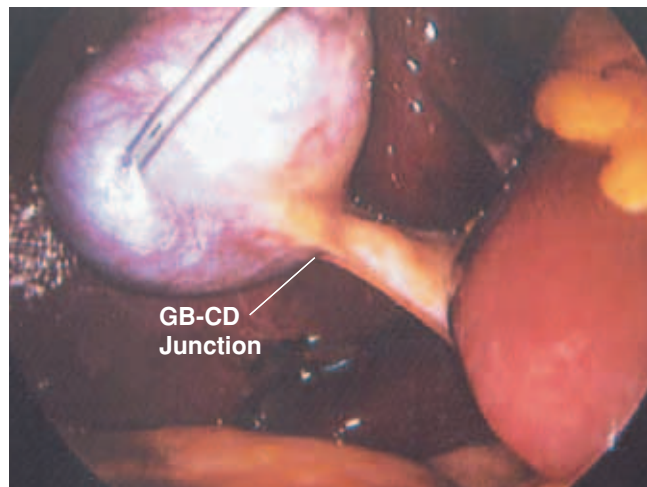


Figure 10 Laparoscopic cholecystectomy. The gallbladder–cystic duct (GB-CD) junction is clearly seen. This should be dissected circumferentially, allowing a 360° view.

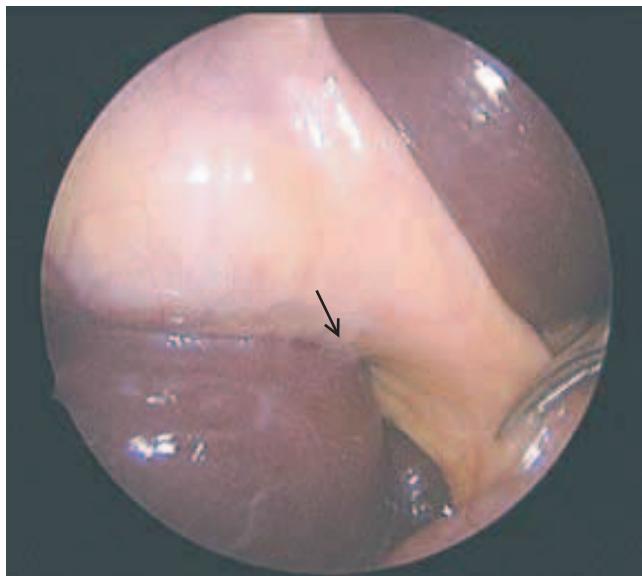


Figure 11 Laparoscopic cholecystectomy. A view from below with a 30° laparoscope demonstrates the point for beginning dissection (arrow), where the gallbladder funnels down to its junction with the cystic duct. Just below this point can be seen a cleft in the liver known as the Rouvier sulcus. This cleft, present in 70 to 80% of livers, reliably indicates the plane of the common bile duct.

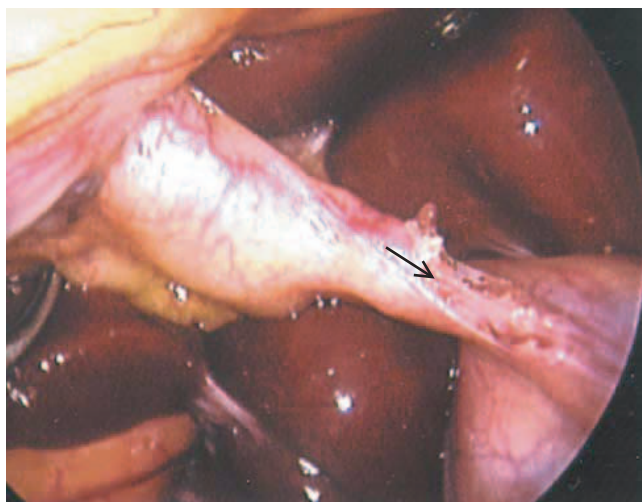


Figure 12 Laparoscopic cholecystectomy. The peritoneum is dissected from the gallbladder–cystic duct junction (arrow), as seen from below through a 30° angled laparoscope.

70 to 80% of livers and usually contains the right portal triad or its branches. Its location is consistently to the right of the hepatic hilum and anterior to the caudate process (Couinaud segment 1). This landmark reliably indicates the plane of the CBD. Therefore, dissection dorsal to it should be done with caution. Once the funneling of the gallbladder into the cystic duct has been identified, the area of the Hartmann pouch should be again pulled laterally and inferiorly so that the anterior peritoneum can be dissected while the 30° scope is angled to view the area. The two-handed technique facilitates

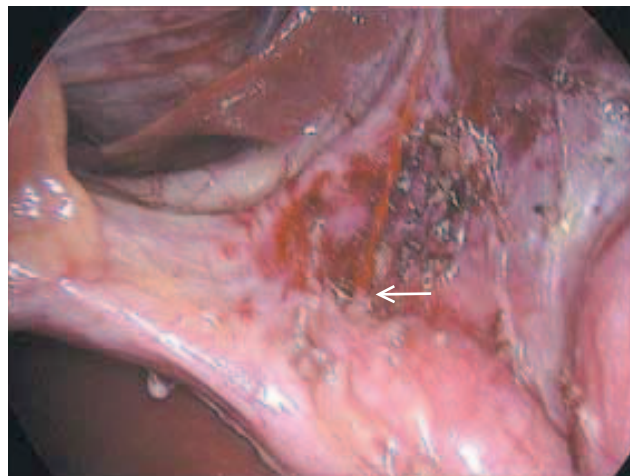


Figure 13 Laparoscopic cholecystectomy. Arterial bleeding can be seen (arrow) from a branch of the cystic artery injured during dissection from the posterior approach.

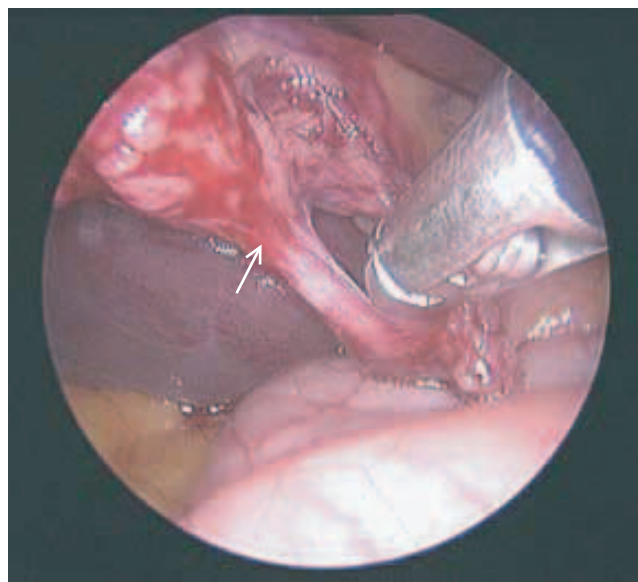


Figure 14 Laparoscopic cholecystectomy. The superior border of the cystic duct has been dissected. Funneling of the gallbladder into the cystic duct is clearly seen (arrow).

the surgeon's movement between the posterior and anterior aspects of the Calot triangle, providing complete visualization. Dissection should always take place at the gallbladder–cystic duct junction, staying close to the gallbladder to avoid inadvertent injury to the CBD. A curved dissecting forceps is used to strip the fibroareolar tissue just superior to the cystic duct. The superior border of the cystic duct can then be identified and the cystic duct gently and gradually dissected [see Figure 14]. The cystic duct lymph node is a useful landmark at this location and may facilitate identification of the gallbladder–cystic duct junction.

When traction is placed as described, the cystic artery tends to run parallel and somewhat cephalad to the cystic duct. This artery can often be identified by noting its close relation

to the cystic duct lymph node. Complete dissection of the area between the cystic duct and the artery develops a window through which the liver should be visible. The cystic duct is then encircled with a curved dissecting instrument or an L-shaped hook. Downward traction should be applied to the cystic duct to open this window and ensure that there is no ductal structure running through this space in the Calot triangle to join the cystic duct (i.e., the right hepatic duct).

Dissection of the Calot triangle should be completed before the cystic duct is clipped or divided. This is best accomplished by dissecting the neck of the gallbladder from the liver bed. Unequivocal identification of the gallbladder–cystic duct junction is imperative.^{24,25} The cystic duct should be dissected for a length sufficient to permit secure placement of two clips; it is not necessary, and indeed may be hazardous, to attempt to dissect the cystic duct–CBD junction.

The cystic artery is exposed next [see Figure 15]. A small vein can usually be identified in the space between the cystic duct and the cystic artery; it can usually be pulled up anteriorly and cauterized. Because dissection is done near the gallbladder, it is not unusual to encounter more than one branch of the cystic artery. Each of these branches should be dissected free of the fibroareolar tissue. Care should also be taken to ensure that the right hepatic artery is not inadvertently injured as a result of being mistaken for the cystic artery.

Step 4: Control and Division of the Cystic Duct and Cystic Artery

At this point, the cystic duct is clipped on the gallbladder side, and a cholangiogram is obtained if desired [see Step 5, below]. If a cholangiogram is not desired, three or four clips should be placed on the cystic duct and the cystic duct divided between them. Two or three hemostatic clips are placed on the cystic artery, and the vessel is divided. It is prudent to incise the artery partially before transecting it

completely to ensure that the clips are secure and that there is no pulsatile bleeding. Once the artery is completely divided, the proximal end will retract medially, making it more difficult to expose and control the artery safely if bleeding occurs. Electrocauterization should be avoided near the cystic duct and all metallic clips. Electric current will be conducted through metallic clips and may result in delayed sloughing of the duct or a clip. Delayed injuries to the CBD may be caused by a direct burn to the duct or by sparking from noninsulated instruments or clips during dissection. An alternative is to use locking polymer clips that fit through 5 mm ports, clip across a greater width of tissue, and do not conduct electricity.

Control of the short or wide cystic duct Edema and acute inflammation may lead to thickening and foreshortening of the cystic duct, with subsequent difficulties in dissection and ligation. If the duct is edematous, clips may cut through it; if the duct is too wide, the clip may not occlude it completely. A modified clipping technique can be employed, with placement of an initial clip to occlude as much of the duct as possible. The occluded portion of the duct is then incised, and a second clip is placed flush with the first so as to occlude the rest of the duct. Alternatively, wider polymer clips may be used.

Because this technique is not always possible, the surgeon should be familiar with techniques for ligating the duct with either intracorporeal or extracorporeal ties. It is extremely helpful to know how to tie extracorporeal ties so that the cystic duct can be ligated in continuity before it is divided. In some cases, the duct can be divided, held with a forceps, and controlled with a ligating loop. If there is concern about secure closure of the cystic duct, a closed suction drain may be placed. If inflammation, as in cholecystitis, has caused the duct to be shorter than usual, dissection must be kept close to the gallbladder to avoid inadvertent injury to the CBD. A short cystic duct is often associated with acute cholecystitis. Patient blunt dissection with the suction-irrigation device may be the safest technique.

Cystic duct stones Stones in the cystic duct may be visualized or felt during laparoscopic cholecystectomy. Every effort should be made to milk them into the gallbladder before applying clips. Placing a clip across a stone may push a fragment of the stone into the CBD and will increase the risk that the clip will become displaced, leading to a bile leak. If the stone cannot be milked into the gallbladder, a small incision can be made in the cystic duct (as is done for cholangiography), and the stone can often be expressed and retrieved. Given that cystic duct stones are predictive of CBD stones, cholangiography or intraoperative ultrasonography is indicated.²⁶

Step 5: Intraoperative Cholangiography

Whether intraoperative cholangiography should be performed routinely is still controversial. Advocates believe that this technique enhances understanding of the biliary anatomy, thus reducing the risk of bile duct injury^{27,28}; at present, however, there are no objective data to confirm this impression. Cholangiography is not a substitute for meticulous dissection, and injuries to the CBD can occur before cystic duct dissection reaches the point at which cholangiography can be performed. Catheter-induced injuries and perforations of the biliary tree have been reported, and cholangiograms have been misinterpreted. On the other hand, one of the main advantages of cholangiography is that injuries can be

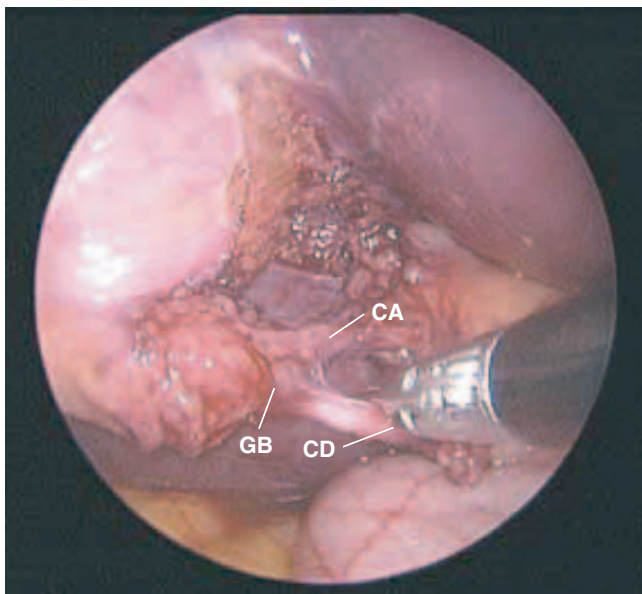


Figure 15 Laparoscopic cholecystectomy. Dissection of the Calot triangle further exposes the cystic duct (CD) and the cystic artery (CA) near their entry into the gallbladder (GB) in preparation for clipping and division.

recognized during the operation and promptly repaired. Another advantage of routine cholangiography is that it helps develop the skills required for more complex biliary tract procedures, such as transcystic CBD exploration.

The two methods of laparoscopic cholangiography differ in their technique for introducing the cholangiogram catheter into the cystic duct. In both approaches, a clip is placed at the gallbladder–cystic duct junction and a small incision is made in the anterior wall of the cystic duct. In the first technique, a specially designed 5 mm cholangiogram clamp (the Olsen clamp) with a 5 French catheter is inserted via a subcostal trocar. For easy guidance of the catheter into the incision in the cystic duct, the catheter should be parallel, rather than perpendicular, to the cystic duct. This angle is facilitated by placing the subcostal port directly below the costal margin, near the anterior axillary line. A fifth trocar may occasionally be needed if exposure is lost when one of the grasping forceps is removed to allow passage of the cholangiogram clamp. The clamp and the catheter are then brought to the cystic duct under direct vision, and the catheter is steered into the duct [see Figure 16]. The clamp is then closed, holding the catheter in position and sealing the duct to avoid extravasation of dye.

In the second method, the cholangiogram catheter is introduced percutaneously through a 12- to 14-gauge catheter, inserted subcostally as described (see above). The surgeon then grasps the cholangiogram catheter and directs it into the cystic duct. A hemostatic clip is applied to secure the catheter in place. If passage of the catheter into the cystic duct is prevented by the Heister valve, a guide wire can be passed initially.

If the cystic duct is tiny and cannulation is expected to be difficult or impossible, the gallbladder can be punctured, bile aspirated, and contrast material injected through the gallbladder until the biliary tree is filled.

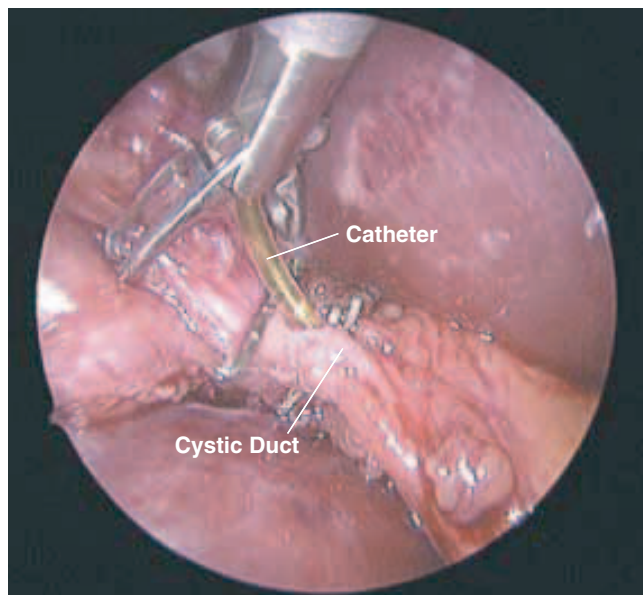


Figure 16 Laparoscopic cholecystectomy. The cystic duct has been clipped, a small incision has been made for placement of the cholangiogram catheter, and the catheter has been advanced through the specialized cholangiogram clamp into the cystic duct.

The cannulas and operating instruments should be positioned so as not to obstruct the view of the biliary tree. If the cannulas cannot be positioned outside the x-ray window, radiolucent cannulas should be used, or the cannulas should be removed and replaced after the cholangiogram. A cholangiogram that does not visualize the biliary tree from the liver to the duodenum is inadequate.

Fluoroscopic cholangiography [see Figure 17] may be performed either with hard-copy film or with digital imaging and storage. After the C arm is positioned, with the operating staff protected behind a lead screen, full-strength contrast is slowly injected under fluoroscopic control. The goal is to visualize the biliary tree in its entirety, including the right and left hepatic ductal systems as well as the distal duct. Once the cholangiogram is obtained, the catheter is removed, and the cystic duct is double-clipped and transected.

Laparoscopic ultrasonography Evaluation of the biliary tree with intraoperative laparoscopic ultrasonography appears to be as accurate as intraoperative fluorocholangiography in identifying biliary stones.^{28,29} This modality has several advantages over conventional cholangiography: it does not expose patients and staff to radiation; contrast agents are unnecessary; there is no need to cannulate the cystic duct; significantly less time is required; the capital cost of most ultrasound units is less than that of fluoroscopic equipment; and disposable cholangiogram catheters are not needed.

Most of the laparoscopic ultrasound devices in use at present are 7.5 MHz linear-array rigid probes 10 mm in diameter. Flexible probes capable of multiple frequencies are also available, and it is likely that future probes will be increasingly versatile. The probe is inserted through a 10/12 mm port (usually a periumbilical or epigastric port) and placed directly on the porta hepatis, perpendicular to the structures of the hepatoduodenal ligament. The probe is then moved to the cystic duct–CBD junction. The transverse image obtained



Figure 17 Laparoscopic cholecystectomy. Shown is a normal intraoperative cholangiogram.

should show the three tubular structures of the hepatoduodenal ligament in the so-called “Mickey Mouse head” configuration: the CBD, the portal vein, and the hepatic artery [see Figure 18]. As the probe is moved distally, it is rotated clockwise to allow identification of the distal CBD and the pancreatic duct where they unite at the papilla. Instillation of saline into the right upper quadrant can enhance acoustic coupling and improve visualization.

Because of its many advantages, intraoperative laparoscopic ultrasonography may eventually replace fluorocholangiography in this setting, particularly for surgeons who practice routine intraoperative evaluation of the CBD.³⁰ Although the learning curve for effective performance of laparoscopic ultrasound examination is not long, surgeons should receive expert mentoring and formal instruction in ultrasonography before attempting it. During the first few attempts, it may be instructive to perform intraoperative laparoscopic ultrasonography in conjunction with fluorocholangiography. It should be emphasized that intraoperative laparoscopic ultrasonography is not a replacement for intraoperative cholangiography if the purpose of the examination is to define an anomalous anatomy or to evaluate a suspected injury or leak.

Step 6: Dissection of the Gallbladder from the Liver Bed

The gallbladder is grasped near the cystic duct insertion and pulled down toward the right anterosuperior iliac spine, placing the areolar tissue between the gallbladder and liver anteriorly under tension. The areolar tissue is cauterized with an L-shaped hook dissector or spatula, and dissection is carried upward as far as possible for as long as there is sufficient exposure. When exposure begins to diminish, the cystic duct end of the gallbladder should be pulled up toward or over the left lobe of the liver to expose the posteroinferior attachments of the gallbladder. A two-handed approach by the surgeon

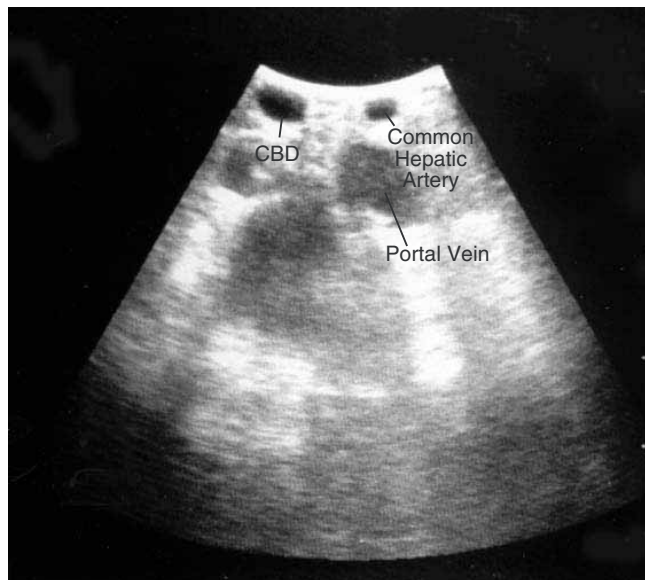


Figure 18 Laparoscopic cholecystectomy. A transverse intraoperative ultrasound scan of the hepatoduodenal ligament reveals a typical “Mickey Mouse head” appearance. Visible are the common bile duct (CBD), the common hepatic artery, and the portal vein.

facilitates this dissection. It is sometimes helpful to apply downward and lateral traction on the forceps grasping the fundus. Bleeding during this stage generally indicates that the surgeon has entered the wrong plane and dissection has entered the liver. Bleeding can usually be readily controlled with the electrocautery. In some difficult cases (e.g., an intrahepatic gallbladder), it may be prudent to leave some of the posterior wall of the gallbladder in situ and cauterize it rather than persist with an excessively bloody dissection.¹⁶

Dissection continues until the gallbladder is attached only by a small piece of peritoneum at the fundus. Before the last attachment to the gallbladder is completely divided, the vital clips are reinspected to ensure that they have not slipped off, and the operative field is checked for hemostasis and the presence of any bile leakage. The final attachment to the gallbladder is then divided. The gallbladder is placed over the right lobe of the liver and laterally so that it can be found again to be retrieved. The grasping forceps on the gallbladder should not be removed.

Perforation of the gallbladder The gallbladder may be accidentally breached at some point in the operation, with the result that bile and stones spill into the peritoneal cavity.^{31,32} Efforts should be made to suction the spilled bile, which accumulates in the suprahepatic space, the right subhepatic space, and the lower abdomen because of the patient's position. Each of these areas should be irrigated and the effluent aspirated until it is clear. Stones should be located and removed whenever possible. An effective way of removing small stones is to irrigate the subhepatic space copiously. Cholesterol stones usually float on the irrigation fluid and can then be suctioned through a 10 mm suction probe or through a 32 French chest tube passed through the 10 mm operating port. Unfortunately, small stones may be lost in the omentum or between bowel loops. In such cases, it is probably appropriate to leave the stones within the peritoneum rather than perform a laparotomy to attempt to retrieve them. However, there have been reports of serious morbidity, including intra-abdominal abscess, fistula, empyema, and bowel obstruction, resulting from lost stones.

If the gallbladder is perforated and it seems likely that multiple stones will be spilled, the surgeon should introduce a sterile bag into the peritoneal cavity, placing it close to the perforation. Spilled stones can then be transferred immediately into the bag. After the gallbladder is removed from the liver bed, it, too, is placed in the bag, affording some protection to the wound when it is removed from the abdominal cavity.

Step 7: Extraction of the Gallbladder

The laparoscope is moved to the epigastric port, and a large-tooth grasping forceps is inserted through the umbilical port to grasp the gallbladder at the area of the cystic duct. Under direct vision, the gallbladder is then retrieved and pulled out as far as possible through the umbilical port. If the gallbladder is small enough, it can be drawn right into the trocar sleeve, and it and the trocar can then be removed together. It is sometimes necessary to stretch the fascial opening with a Kelly clamp or to aspirate bile from the gallbladder. It is far preferable to enlarge the incision than to have stones or bile spill into the abdominal cavity from a ripped gallbladder. Enlargement of this incision is easier if initial access was obtained via the Hasson technique. All of

the other ports are then removed from the abdominal wall under direct vision to ensure that there is no bleeding. All residual CO₂ should be removed to prevent postoperative shoulder pain. The fascial opening at the umbilicus should be sutured closed to prevent subsequent herniation, and all skin incisions should be closed.

Need for drainage The decision to place a drain after laparoscopic cholecystectomy should be governed by the same principles applied to patients undergoing open cholecystectomy. There are two main indications for drainage: (1) the cystic duct was not closed securely, and (2) the CBD was explored by either a direct or a transcystic approach.

Drain placement is easily accomplished. A closed suction drain is inserted intra-abdominally through the 10 mm operative port. A grasping forceps placed through the right lateral port is used to pull one end of the drain out through the abdominal wall. The other end is then positioned according to the surgeon's preference, usually in the subhepatic space.

COMPLICATIONS

Intraoperative Complications

Veress needle injury A syringe must always be attached to the Veress needle, and fluid must be aspirated before insufflation is initiated: failure to do so may lead to insufflation into a vessel and consequently to massive gas embolism. If the aspirate from the syringe attached to the Veress needle contains copious amounts of blood, a major vascular injury may have occurred, and immediate laparotomy is indicated. Because the problem at this point is a needle injury, it can usually be repaired easily and without serious sequelae.

Puncture of the bowel by a Veress needle is usually signaled by aspiration of bowel contents through the needle. If this occurs, the needle should be withdrawn and the approximate course and direction of the puncture remembered. The initial trocar should then be inserted by means of the open technique, under direct vision, to ensure that the undersurface of the abdominal wall is free of adherent bowel. Once pneumoperitoneum is created, careful examination of the abdomen through the laparoscope is undertaken. In most cases, either further leakage of bowel contents, staining of the serosal surface with bowel contents, or an ecchymosis on the serosal surface of the bowel helps the surgeon locate the site of the bowel injury. If ecchymosis is present without spillage of bowel contents, the bowel loop should be marked with a suture and reinspected at the end of the procedure. If ongoing leakage of bowel contents is noted, the injured loop of bowel can be either repaired by means of laparoscopic suturing or grasped with an atraumatic forceps and gently withdrawn through an enlarged umbilical incision for suture repair. The bowel is returned to the peritoneal cavity, and the laparoscopic cholecystectomy is completed.

Improper placement of the Veress needle into the omentum, the retroperitoneum, or the preperitoneal space may be signaled by high inflation pressures, uneven distribution of the gas on percussion, or marked subcutaneous emphysema. If such misplacement goes unrecognized, creation of a safe intraperitoneal space is impossible, and subsequent blind insertion of the trocar may result in injury to an intraperitoneal structure.

Trocar injury Trocar injury to blood vessels or bowel is much more dangerous than Veress needle injury to the same structures. Major vascular injuries virtually never occur when trocars are placed under direct vision; however, they remain a potentially lethal—although rare—complication of percutaneous trocar insertion. If active bleeding follows removal of the trocar from the cannula, prompt laparotomy is mandatory; if bleeding passes unnoticed and insufflation begins, massive air embolism will result. At the time of laparotomy, both the anterior and the posterior wall of the vessel must be examined after proximal and distal control of the vessel have been obtained.

Bowel injuries can result from either percutaneous or open insertion of the initial trocar. With open insertion, the bowel injury should be immediately obvious and can be repaired after the injured bowel is pulled through an enlarged umbilical incision; laparoscopic cholecystectomy can then proceed. Bowel injuries caused by percutaneous insertion may occur even in the absence of abdominal wall adhesions and can be managed in the same way as those caused by open insertion. The one caveat is that it is possible to spear the bowel in a through-and-through fashion so that when the laparoscope is inserted through the trocar, the view is normal and the injury is not recognized. This type of injury can be diagnosed only if the laparoscope is repositioned to the operating port at some time during the procedure and the undersurface of the umbilical site is carefully examined. This step is mandatory during the course of the operation, preferably early.

Bleeding *Abdominal wall* Bleeding from the abdominal wall can usually be prevented by careful trocar placement. The abdominal wall should be transilluminated before percutaneous trocar insertion and the larger vessels avoided. If a vessel is speared, the cannula usually tamponades the bleeding reasonably effectively during the procedure.

Once the procedure is completed, each trocar is removed under direct vision. If bleeding follows the removal of a trocar, the puncture hole can be occluded with digital pressure to maintain pneumoperitoneum and the bleeding controlled by cauterization or suture repair. Alternatively, the surgeon may place a Foley catheter through the trocar site with a stylet, inflate the balloon, and place traction on the catheter for 4 to 6 hours; however, tissue ischemia can make this technique quite painful.

Omental or mesenteric adhesions Generally, omental adhesions can be bluntly teased from their attachments to the gallbladder, with the plane of dissection kept close to the gallbladder, where the adhesions are less vascular. Adhesions to the liver should be taken down with the electrocautery to prevent capsular tears. Persistent bleeding from omental adhesions is unusual but can be managed by means of electrocauterization (with care taken to avoid damage to the duodenum or colon) or the application of hemostatic clips or a pretied ligating loop.

Cystic artery branch Arterial bleeding encountered during dissection in the Calot triangle is usually from loss of control of the cystic artery or one of its branches. Biliary surgeons must be aware of the many anatomic variations in the vasculature of the gallbladder and the liver. Because the main cystic artery frequently branches, it is common to find more than one artery if dissection is maintained close to the gallbladder. If what seems to be the main cystic artery is small, a posterior

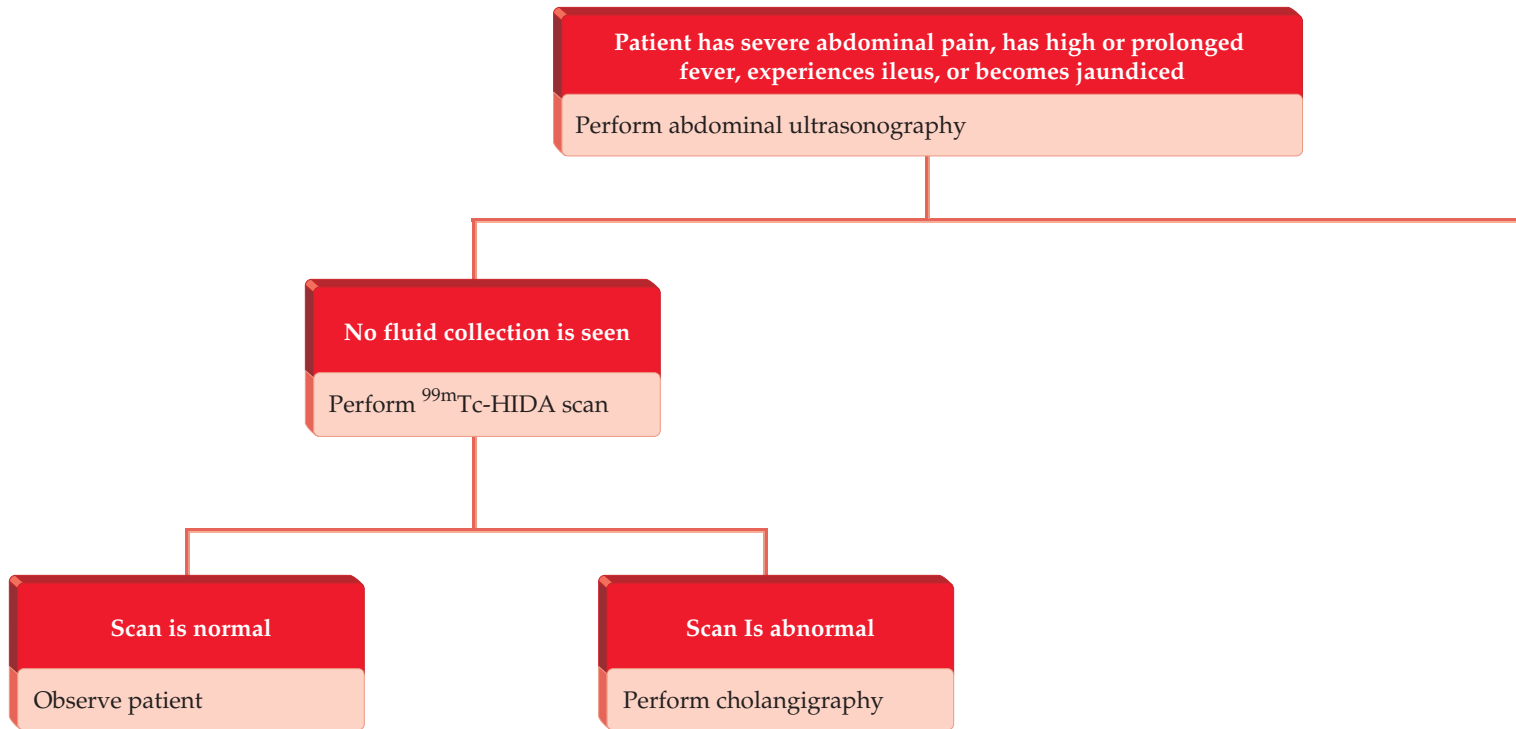


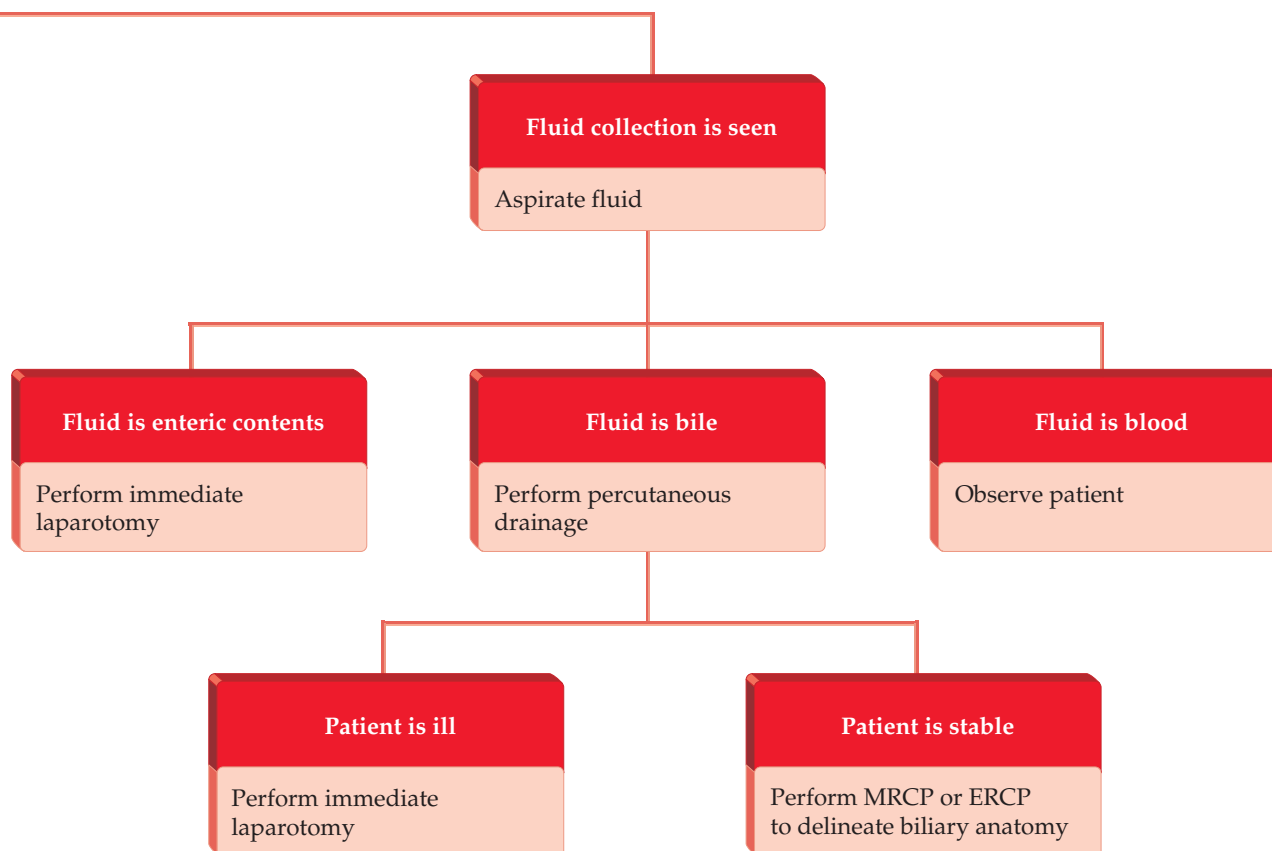
Figure 19 Laparoscopic cholecystectomy. Shown is an algorithm outlining a screening approach that is often useful when the patient shows signs (e.g., pain, fever, or ileus) that are suggestive of a postoperative intra-abdominal complication, such as fluid collection or bile leakage. ERCP = endoscopic retrograde cholangiopancreatography; MRCP = magnetic resonance cholangiopancreatography.

cystic artery may be present and may have to be clipped during the dissection.

Prevention of arterial bleeding begins by dissecting the artery carefully and completely before clipping and by inspecting the clips to ensure that they are placed completely across the artery without incorporating additional tissue (e.g., a posterior cystic artery or right hepatic artery). When arterial bleeding is encountered, it is essential to maintain adequate exposure and to avoid blind application of hemostatic clips or cauterization. The laparoscope should be withdrawn slightly so that the lens is not spattered with blood. The surgeon should then pass an atraumatic grasping forceps through a port other than the operating port and attempt to grasp the bleeding vessel. An additional trocar may have to be inserted for simultaneous suction-irrigation. Once proximal control is obtained, the operative field should be suctioned and irrigated to improve exposure. Hemostatic clips are then applied under direct vision; in addition, a sponge may be introduced

to apply pressure to the bleeding vessel. Conversion to open cholecystectomy is indicated whenever bleeding cannot be promptly controlled laparoscopically.

Liver bed Bleeding from the liver bed may be encountered when the wrong plane is developed during dissection of the gallbladder. Patients who have portal hypertension, cirrhosis, or coagulation disorders are at particularly high risk. Control of bleeding requires good exposure, accomplished via lateral and superior retraction of the gallbladder; hence, bleeding is most easily controlled before the gallbladder is detached from the liver bed. Most liver bed bleeding can be controlled with the electrocautery, and it should be controlled as it is encountered to allow exposure of the specific bleeding site. Either a hook-shaped or a spatula-shaped coagulation electrode is effective. If oozing continues, oxidized cellulose can be placed as a pack through the operative port and pressure applied on the raw surface of the liver. If needed, fibrin glue can be applied to the bleeding raw surface.



Postoperative Complications

If a patient (1) complains of a great deal of abdominal pain necessitating systemic narcotics, (2) has a high or prolonged fever, (3) experiences ileus, or (4) becomes jaundiced, an intra-abdominal complication may have occurred. Blood should be drawn for assessment of the white blood cell count, hemoglobin concentration, liver function, and serum amylase level. Abdominal ultrasonography may help diagnose dilated intrahepatic ducts and subhepatic fluid collections [see Figure 19].

Fluid collection or bile leakage When a significant fluid collection is seen, it should be aspirated percutaneously under ultrasonographic guidance. If the fluid is blood and the patient is hemodynamically stable and requires no transfusion, observation of the patient and culture of the fluid are usually sufficient. If the fluid is enteric contents, immediate laparotomy is indicated. If the fluid is bile and the patient is ill, immediate laparotomy should be considered; if the patient is stable and the appropriate facilities are available, MRCP or ERCP may

be performed to identify the site of bile leakage, determine whether obstruction is also present, and assess the integrity of the extrahepatic biliary tree. If the bile ducts are in continuity and the bile is coming from the cystic duct stump or a small lateral tear in the bile duct, ES, with or without stenting, usually controls the leak. Percutaneous placement of a drain under ultrasonographic guidance allows control of the bile leakage and measurement of the quantity of fluid present.

Fever Postoperative fever is a common complication of laparoscopic cholecystectomy. As noted, it may be indicative of a complication such as bile collection or bile leakage. Other common reasons for postoperative fever (e.g., atelectasis) should also be considered.

Abnormal liver function When postoperative blood tests indicate significantly abnormal liver function, possible causes include injury to the biliary tree and retained CBD stones [see Figure 20].³³ Cholangiography is required, even if it was performed intraoperatively. If MRCP or ERCP yields

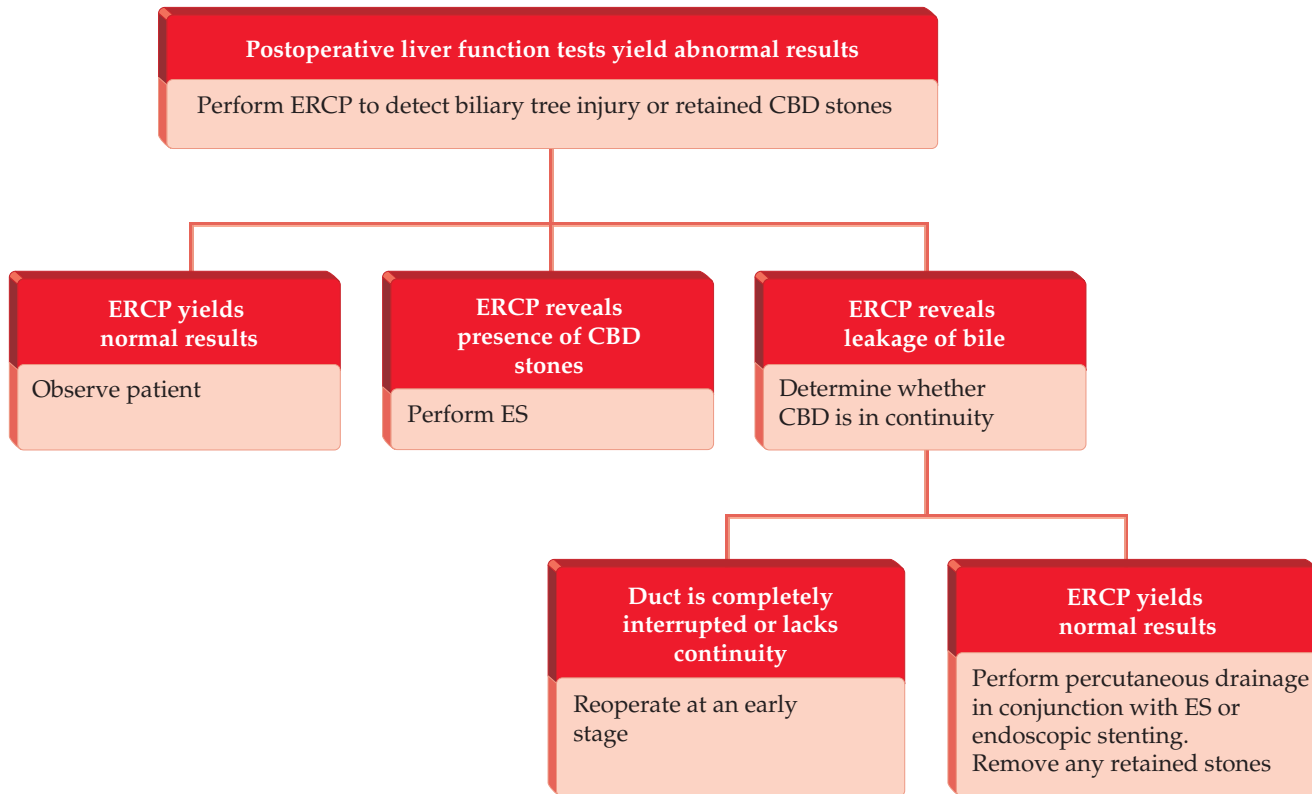


Figure 20 Laparoscopic cholecystectomy. Shown is an algorithm outlining an approach to abnormal liver function test results after laparoscopic cholecystectomy. CBD = common bile duct; ERCP = endoscopic retrograde cholangiopancreatography; ES = endoscopic sphincterotomy.

normal results, observation is sufficient; the abnormalities may be attributable to a passed stone or drug-related cholestasis. If stones are present, ES can usually solve the problem. If ERCP demonstrates extravasation of bile, it is important to establish whether the CBD is in continuity. If the duct is interrupted, early reoperation, ideally at a specialized center, is the best option. If the duct is in continuity, endoscopic and radiologic techniques may successfully resolve the problem without substantial morbidity.^{34,35} Percutaneous drainage is instituted to control the fistula, and sphincterotomy or stenting is useful to overcome any resistance at the sphincter of Oddi. Any retained stones causing distal obstruction should also be removed. Major ductal injuries usually call for operative repair. When such an injury is identified at operation, the surgeon must decide whether to attempt repair immediately; this decision should be based on the surgeon's experience with reconstructive biliary surgery and on the local expertise available. At a minimum, adequate drainage must be established. Most major ductal injuries are not, in fact, identified intraoperatively. When such an injury is identified postoperatively, adequate drainage must be established and the anatomy of the injury clarified as well as possible before repair. MRCP or transhepatic cholangiography may be required to delineate the anatomy of the proximal biliary tree when ERCP does not opacify the biliary tract above the injury. If surgical repair is indicated, it should be performed by a surgeon experienced in complex biliary tract procedures. Often referral to a specialized center is the most appropriate decision, especially in the case of more proximal biliary injuries.

SPECIAL CONSIDERATIONS

Conversion to Laparotomy

Conversion from laparoscopy to laparotomy may be required in any laparoscopic cholecystectomy, in accordance with the judgment of the surgeon. The most common reason for such conversion is the inability to identify important anatomic structures in the region of the gallbladder. Distorted anatomy may be the result of previous operations, inflammation, or anatomic variations. Conversion may also be required because of an intraoperative complication [see Postoperative Complications, *above*]. Ideally, the surgeon would wish to convert before any complication occurs. It must be emphasized that conversion to open surgery should not be considered a failure or a complication. Rather, it should be considered a prudent maneuver for achieving the desired objective—namely, safe removal of the gallbladder. Accordingly, every patient consent obtained for a laparoscopic cholecystectomy must explicitly allow for the possibility of conversion to an open procedure. Attempts have been made to predict the probability of conversion on the basis of preoperative information.^{36,37} It is clearly useful to stratify patients according to the likelihood of conversion. This information is helpful in selecting patients for laparoscopic cholecystectomy in an outpatient versus hospital setting, in determining the resources required in the OR, and in assisting patients in planning their work and family needs around the time of surgery.

Factors found to be predictive of an increased probability of conversion include acute cholecystitis, either at the time of

surgery or at any point in the past; age greater than 65 years; male sex; and thickening of the gallbladder wall to more than 3 mm as measured by ultrasonography. Other factors more variably associated with an increased likelihood of conversion are obesity, previous upper abdominal operations (especially gastroduodenal), multiple gallbladder attacks over a long period, and severe pancreatitis. Factors not associated with an increased likelihood of conversion are jaundice, previous ES, previous lower abdominal procedures, stomas, mild pancreatitis, and diabetes.

On the basis of our data, a 45-year-old woman with no history of acute cholecystitis and no gallbladder wall thickening has a probability of conversion lower than 1%; such a patient is a good candidate for laparoscopic cholecystectomy in an outpatient setting. Conversely, a 70-year-old man with acute cholecystitis and ultrasonographic evidence of gallbladder wall thickening has a probability of conversion of about 30%; such a patient would be better managed in a traditional hospital environment.

Acute Cholecystitis

Laparoscopic cholecystectomy has been shown to be safe and effective for treating acute cholecystitis.^{38,39} There are, however, several technical problems in this setting that must be addressed if the procedure is to be performed with minimal risk. It should also be recognized that the probability of conversion to laparotomy is greatly increased in these circumstances. There appears to be no advantage to delaying surgery in patients with acute cholecystitis, even if rapid improvement is noted with nonoperative management.^{40,41} Many patients return within a short time with recurrent attacks, and delaying surgery does not reduce the probability of conversion.

Technical difficulties associated with cholecystectomy for acute cholecystitis include dense adhesions, the increased vascularity of tissues, difficulty in grasping the gallbladder, an impacted stone in the gallbladder neck or the cystic duct, shortening and thickening of the cystic duct, and close approximation of the CBD to the gallbladder wall.

The surgeon should not hesitate to insert additional ports (e.g., for a suction-irrigation apparatus) if necessary. Because the tense, distended gallbladder is difficult to grasp reliably, it should be aspirated through the fundus early in the procedure, as previously described. If the graspers fail to grasp the wall or cause it to tear, exposure of the Calot triangle can be achieved by propping up or levering the neck of the gallbladder and the right liver with a blunt instrument. A sponge can be used for this purpose, thereby reducing the potential trauma of the retraction. This maneuver is also useful when an impacted stone in the neck of the gallbladder prevents the surgeon from grasping the gallbladder in the area of the Hartmann pouch. Dense adhesions that may be present between the gallbladder and the omentum, duodenum, or colon should be dissected bluntly (e.g., with a suction tip). Because the tissues are friable and vascular, oozing may be encountered. Electrocauterization should be only sparingly employed until the vital structures in the Calot triangle are identified. Instead, the surgeon should move to another area of dissection, allowing most of the oozing to coagulate on its own. Liberal use of suction and irrigation will keep the operative field free of blood.

In the identification of anatomic structures, it is important to keep dissection close to the gallbladder wall, working down

from the gallbladder toward the Calot triangle. Dissection of the lower part of the gallbladder from the liver bed early in the operation may aid in identification of the gallbladder neck–cystic duct junction (analogous to an open, retrograde dissection). The surgeon should be aware that edema and acute inflammation may cause foreshortening of the cystic duct. If the anatomy cannot be identified, preliminary cholangiography through the emptied gallbladder may indicate the position of the cystic duct and the CBD.

Often the obstructing stone responsible for the acute attack is in the neck of the gallbladder; thus, the cystic duct will be normal and easily secured with clips. If the stone is in the cystic duct, it must be removed before the duct is clipped or ligated. A thickened, edematous cystic duct is better controlled by ligation with an extracorporeal tie or a ligating loop than by clipping. If closure of the cystic duct is tenuous, closed suction drainage is advisable. Obviously, conversion to open cholecystectomy is indicated if the anatomy remains obscure. Conversion should also be considered if no progress is made after a predesignated period (e.g., 15 minutes) because at this point, the surgeon is unlikely to make any headway.

CBD Stones

Identification of patients at risk About 10% of all patients undergoing cholecystectomy for symptomatic gallstones will also have choledocholithiasis. To select from the various diagnostic and therapeutic options for managing choledocholithiasis, it is helpful to know preoperatively whether the patient is at high, moderate, or low risk for stones. Patients with obvious clinical jaundice or cholangitis, a dilated CBD, or stones visualized in the CBD on preoperative ultrasonography are likely to have choledocholithiasis (risk > 50%). Patients who have a history of jaundice or pancreatitis, moderately elevated preoperative levels of alkaline phosphatase or bilirubin, or ultrasonographic evidence of multiple small gallstones are somewhat less likely to have choledocholithiasis (risk 10 to 50%). Patients with large gallstones, no history of jaundice or pancreatitis, and normal liver function are unlikely to have choledocholithiasis (risk < 5%).

Diagnostic and therapeutic options One argument for routine intraoperative cholangiography is that it is a good way of identifying unsuspected CBD stones. However, more selective approaches to diagnosing choledocholithiasis make use of preoperative cholangiography via MRCP, EUS, or, more invasively, ERCP [see 5:18 *Gastrointestinal Endoscopy*]. Preoperative identification of choledocholithiasis allows the surgeon to attempt preoperative clearance of the CBD by means of ES or intraoperative clearance during laparoscopy, depending on his or her expertise. Preoperative cholangiography is suggested when the patient's history and the results of laboratory and diagnostic tests suggest that there is a moderate or high risk of CBD stones. It is our practice to have patients at high risk for CBD stones undergo ERCP and ES if warranted. For patients at moderate risk, MRCP or EUS is done first, followed by therapeutic ERCP if CBD stones are identified. Intraoperative cholangiography can also be used to identify choledocholithiasis. ERCP with ES may result in pancreatitis, perforation, or bleeding and carries a mortality of approximately 0.2%.

When stones are detected during the operation, the options include laparoscopic transcystic duct exploration,

laparoscopic choledochotomy and CBD exploration, open CBD exploration, and postoperative ERCP with ES.^{10,42} If a single small (≈ 2 mm) stone is visualized, it can probably be flushed into the duodenum by irrigating the CBD via the cholangiogram catheter and administering glucagon, 1 to 2 mg intravenously, to relax the sphincter of Oddi. Even if a stone of this size does not pass intraoperatively, it will usually pass on its own postoperatively.

Laparoscopic transcystic CBD exploration *Access to the biliary tree* The cholangiogram is reviewed; the size of the cystic duct, the site where the cystic duct inserts into the CBD, and the size and location of the CBD stones all contribute to the success or failure of transcystic CBD exploration.^{43–45} For example, transcystic exploration is extremely challenging in a patient who has a long, spiraling cystic duct with a medial insertion. The size of the stones to be removed dictates the approach to the CBD: stones smaller than 4 mm can usually be retrieved in fluoroscopically directed baskets and generally do not necessitate cystic duct dilatation; larger stones (4 to 8 mm) are retrieved under direct vision with the choledochoscope.

A hydrophilic guide wire is inserted through the cholangiogram catheter into the CBD under fluoroscopic guidance. The cholangiogram catheter is then removed. If the largest stone is larger than the cystic duct, dilatation of the duct is necessary, not only for passage of the stone but also to allow passage of the choledochoscope, which may be 3 to 5 mm in diameter.

Dilatation is accomplished with either a balloon dilator or sequential plastic dilators. Because plastic dilators may cause the cystic duct to split, balloon dilatation is recommended. A balloon 3 to 5 cm in length is passed over the guide wire and positioned with its distal end just inside the CBD and its proximal end just outside the incision in the cystic duct. The balloon is then inflated to the pressure recommended by the manufacturer and observed closely for evidence of shearing of the cystic duct. The cystic duct should not be dilated to a diameter greater than 8 mm. Larger stones in the CBD may be either fragmented with electrohydraulic or mechanical lithotripsy, if available, or removed via choledochotomy.

Once dilatation is complete, the guide wire may be removed or left in place to guide passage of a choledochoscope or baskets. When the choledochoscope is used, a second incision in the cystic duct, close to the CBD, avoids the Heister valves and allows removal of the guide wire. If baskets are used, a 6 French plastic introducer sheath may be inserted through the trocar used for cholangiography into the cystic duct. This sheath is especially useful if multiple stones must be removed.

Fluoroscopic wire basket transcystic CBD exploration Stones smaller than 2 to 4 mm that do not pass with irrigation through the cholangiograph catheter after injection of glucagon can usually be retrieved by using a 4 French or 5 French helical stone basket passed into the CBD over a guide wire under fluoroscopic guidance. The baskets can be passed alongside the cholangiograph catheter or inserted via a plastic sheath replacing the cholangiograph catheter. The basket is opened in the ampulla of Vater, pulled back into the CBD, and rotated clockwise until the stone is entrapped. The stone and basket are then removed together. A Fogarty catheter should not be used, because the stones are likely to be pulled up into the hepatic ducts, where they are much more difficult to remove.

Endoscopic transcystic CBD exploration When stones are 4 to 8 mm in diameter, the helical stone basket wires are generally too close together to permit retrieval. Hence, choledochoscopic basketing is used. A videocholedochoscope with a working channel is either passed over the guide wire or inserted directly into the cystic duct. Because the usual laparoscopic grasping forceps may damage the choledochoscope, forceps with rubber-covered jaws should be used. The image from the choledochoscope can be displayed on the monitor by means of an audiovisual mixer (i.e., a picture within a picture) or displayed on a separate monitor.

Once the choledochoscope enters the cystic duct, warm saline irrigation is begun under low pressure to distend the CBD and provide a working space. The choledochoscope usually enters the CBD rather than the common hepatic duct. When a stone is seen, a 2.4 French straight four-wire basket is inserted through the operating port. The stones closest to the cystic duct are removed first by advancing the closed basket beyond each stone, opening the basket, and pulling the basket back, thereby trapping the stone. The basket is then closed and pulled up against the choledochoscope so that they can be withdrawn as a unit. Multiple passes may be required until the duct is clear. A completion cholangiogram is done to ensure that the duct is clear and to rule out proximal stones. The dilated, traumatized cystic duct is ligated with a ligating loop rather than a hemostatic clip. If drainage is required, a red rubber catheter can be inserted into the CBD via the cystic duct.

Because of the angle created by the cephalad and superior retraction of the gallbladder, it may be difficult to pass the choledochoscope into the proximal ducts. If a common hepatic duct stone is seen on the cholangiogram, the patient is placed in a steep reverse Trendelenburg position. In this position, any nonimpacted stones may fall into the distal duct for retrieval. It may be possible to pass the choledochoscope into the proximal ducts by applying caudal traction to the cystic duct so as to align it with the common hepatic duct. An additional access port in the right upper quadrant may be needed. If the cystic duct is long or spiraling or inserts medially, this measure may not be feasible, in which case, access must be obtained by means of choledochotomy.

Laparoscopic CBD exploration Large stones (> 1 cm), as well as most stones in the common hepatic ducts, are not retrievable with the techniques described above. Ductal clearance can be achieved via choledochotomy if the duct is dilated and the surgeon is sufficiently experienced.^{46,47} The anterior wall of the CBD is bluntly dissected for a distance of 1 to 2 cm. When small vessels are encountered, it is preferable to apply pressure and wait for hemostasis rather than use the electrocautery in this area. Adrenaline-soaked gauzes placed through the 12 mm umbilical port are very effective for this purpose. Two stay sutures are placed in the CBD. An additional 5 mm trocar is placed in the right lower quadrant for insertion of an additional needle driver. A small longitudinal choledochotomy (a few millimeters longer than the circumference of the largest stone) is made with curved microscissors on the anterior aspect of the duct while the stay sutures are elevated. A choledochoscope is then inserted, and warm saline irrigation is initiated. In most cases, baskets should suffice for stone retrieval; however, lithotripter probes and

lasers are available for use through the working channel of the choledochoscope. The choice of approach depends on availability and individual surgical experience.

Subsequently, a 12 or 14 French latex T tube is fashioned with short limbs, placed entirely intraperitoneally to prevent CO₂ from escaping, and positioned in the CBD. The choledochotomy is then closed with fine interrupted absorbable sutures. The first suture is placed right next to the T tube, securing it distally, and the second is placed at the most proximal end of the choledochotomy; lifting these two sutures facilitates placement of additional sutures. Intracorporeal knots are preferred to avoid sawing of the delicate tissues. The end of the T tube is then pulled out through a trocar, and cholangiography is performed after completion of the procedure.

Open Cholecystectomy

Open cholecystectomy is usually reserved for patients in whom the laparoscopic approach is not feasible or is contraindicated. As such, it is typically performed only in the most difficult situations or when additional maneuvers such as CBD exploration are anticipated. Conversion from the laparoscopic to the open approach is not considered a complication and does not represent failure. Rather, conversion to this time-honored and effective procedure represents the prudent judgment of a safe surgeon.

OPERATIVE TECHNIQUE

The choice of incision depends on the surgeon's experience and preference, along with patient factors such as previous surgical procedures and body habitus. Typically, open cholecystectomy is performed through a right subcostal (Kocher) incision, but it can also be approached through an upper midline incision or, less commonly, through a right paramedian or transverse incision. A mechanical retraction system should be used, if available, so that the hands of the participating surgeons are free; there is no good rationale for struggling to perform difficult biliary surgery with handheld retractors.

The abdomen is opened and then explored; the abdominal viscera are inspected and palpated, and a retraction system is put in place. Long curved or angled clamps, such as Kelly or Mixer, are placed on the gallbladder fundus and infundibulum for the application of gentle traction. The fundus is elevated and the infundibulum is pulled laterally and away from the liver [see Figure 21]. If the gallbladder is not too inflamed and edematous, the procedure may be performed similarly to the typical laparoscopic approach: the surgeon identifies and ligates the cystic duct and artery and then removes the gallbladder from the liver bed.

With more difficult open cases, the above technique may not be possible. In such cases, a retrograde or so-called fundus down approach is usually employed. Staying as close to the gallbladder wall as is possible, the surgeon uses electrocautery or sharp and digital blunt dissection to remove the gallbladder from the liver bed, continuing downward to the cystic duct and artery [see Figure 22]. Anatomic variations of the duct and artery must always be anticipated. These structures can be very difficult to identify and safely dissect in cases of severe inflammation and markedly edematous tissues. In such cases, palpation and gentle digital blunt dissection of the duct and artery between the thumb and index finger is useful [see Figure 23]. Opening the gallbladder to remove stones or aspirate bile or pus may be necessary when it is tense and distended or necrotic and gangrenous. As with laparoscopic cholecystectomy, it is critical to identify the cystic duct and artery and their anatomic relations to the gallbladder and CBD before division and to avoid injury to the CBD or common hepatic duct. The cystic duct and artery may be suture ligated or divided between clips. Stones found in the cystic duct should be gently milked back into the gallbladder.

SPECIAL CONSIDERATIONS

Cholangiography

The indications for cholangiography are the same as for laparoscopic cholecystectomy. Several techniques for the performance of cholangiography can be used. Usually, the same

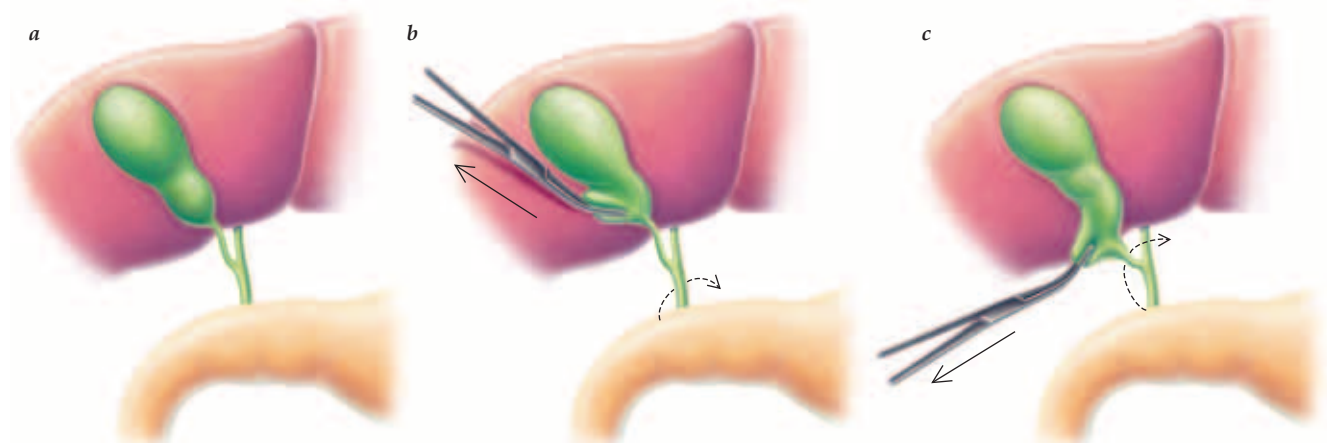


Figure 21 Open cholecystectomy. (a) Shown are the resting positions of the cystic duct and the common bile duct (CBD) (with the Calot triangle closed). (b) Improper upward retraction of the Hartmann pouch lines up the CBD and the cystic duct so that one can easily encircle the CBD or clamp the cystic duct and the CBD. (c) Correct downward and rightward retraction opens the Calot triangle; dissection proceeds lateral to the CBD.

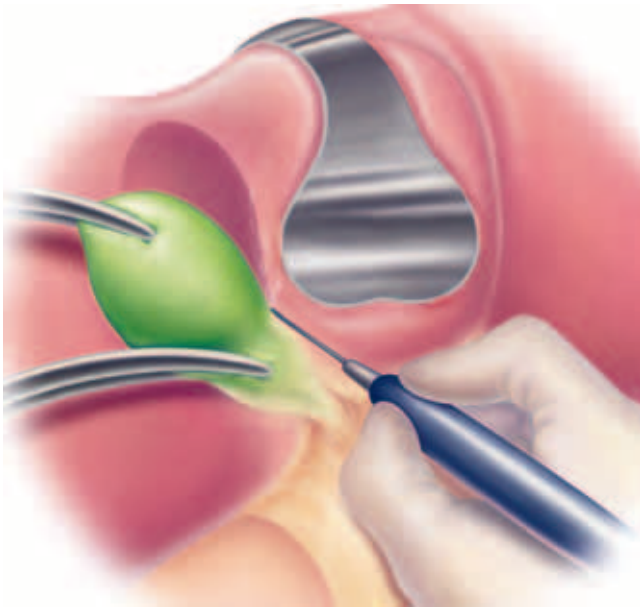


Figure 22 Open cholecystectomy. In so-called fundus down dissection, the fundus and infundibulum are retracted up and away from the liver while dissection is performed with electrocautery. Sharp dissection with scissors or scalpel and blunt digital dissection all may be used, at the surgeon's discretion.

technique as for laparoscopic cholecystectomy is employed; the cystic duct is ligated or clipped high near the infundibulum and incised just below this point for insertion of a cholangiography catheter, which is secured against leakage by another clip or ligature. Alternatively, the cystic duct can be divided near the infundibulum and the gallbladder removed; then the cystic duct is cannulated. Needle puncture cholangiography can also be performed via the cystic duct or the common duct. Once cholangiography is complete, the gallbladder is removed and sent for pathologic examination. The operative field is inspected for hemostasis and irrigated. Any bile leak is identified. Drains are not routinely placed but can be used at the surgeon's discretion. If drains are used, a closed suction Jackson-Pratt or similar drain is recommended; the drain should be brought out through a separate stab incision.

Open CBD Exploration

Open CBD exploration has become a rare procedure, but it remains a skill that surgeons require. If ERCP has failed or is not possible, if the surgeon does not have the experience and necessary tools to perform laparoscopic duct exploration, or if laparoscopic efforts have failed, then open exploration becomes necessary. Ductal stones are identified either preoperatively or intraoperatively by ultrasonography, cholangiography, or palpation.

Appropriate retraction and exposure are crucial. The anterior aspect of the duct is exposed over a distance of 1 to 2 cm, avoiding electrocautery during dissection. Two stay sutures of a 3-0 monofilament are placed lateral to the midline of the duct. The common hepatic duct is sharply opened with a No. 11 or No. 15 scalpel and longitudinally incised further with a Potts arteriotomy or similar scissors. When performing these maneuvers, the surgeon must respect the arterial blood

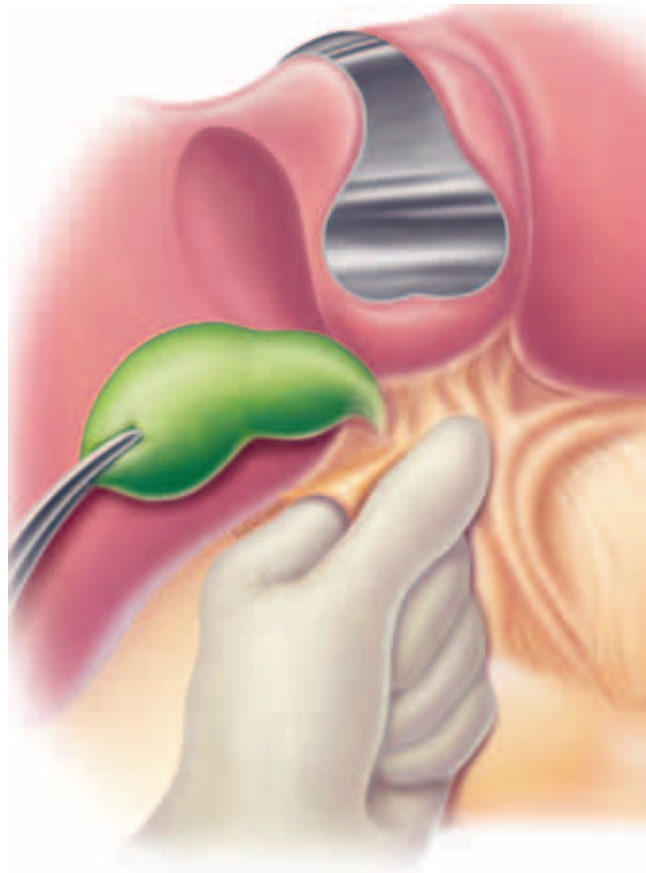


Figure 23 Open cholecystectomy. In patients with severe inflammation and edema, the surgeon must be cautious when approaching the Calot triangle during fundus down dissection. In such circumstances, digital palpation can be very helpful in safely identifying the cystic duct and artery.

supply of the duct, which courses laterally on either side of the duct in the 3 o'clock and 9 o'clock positions [see Figure 24]. In some cases, stones are immediately visible and can simply be plucked from the duct once it is opened. Flushing the duct with saline, proximally and then distally, through a 12 or 14 French Foley or red rubber catheter may also clear the duct of stones. The intravenous administration of 1 to 2 mg of glucagon will relax the sphincter of Oddi, which may help in the flushing of stones from the duct. In some cases, stones will be impacted within the duct and will require additional maneuvers. The Kocher maneuver (liberally mobilizing the lateral duodenum and head of the pancreas) will allow the surgeon to hold and palpate the duodenum, the head of the pancreas, and stones within the duct, facilitating instrumentation. Stone retrieval forceps, biliary Fogarty catheters, and wire baskets can all be employed to retrieve stones. A choledochoscope can also be used, either at the outset of exploration or for stone retrieval, if simpler maneuvers are not successful.

Either T tube cholangiography or choledochoscopy may be employed to confirm clearance of ductal stones. If no stones are present, primary closure of the choledochotomy has been successfully employed, although most surgeons will leave in place a 12 or 14 French T tube, which is brought out through a separate stab incision in the right lateral abdominal wall [see Figure 25]. If stone clearance is not achieved, a T tube is

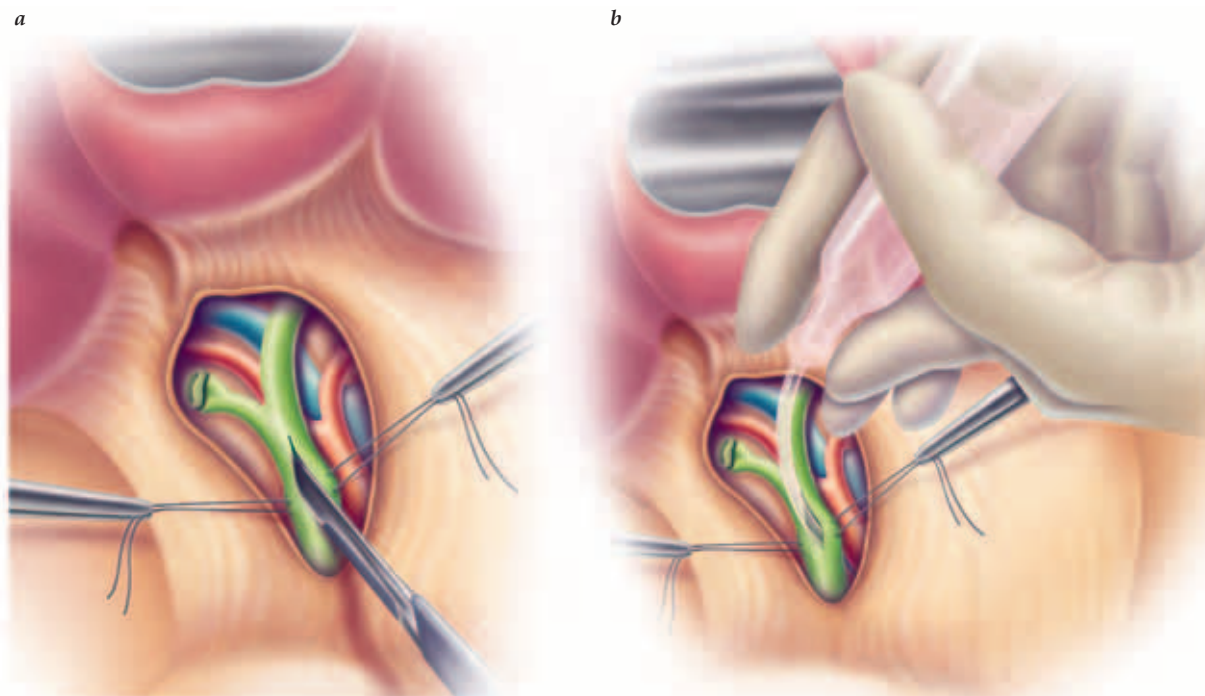


Figure 24 Open common bile duct exploration. (a) The common bile duct is opened vertically between laterally positioned stay sutures. (b) A catheter is then used to irrigate and flush stones from the duct. If stones are impacted within the duct, they can be retrieved with Fogarty catheters, wire stone retrieval baskets, or stone retrieval forceps. The choledochoscope can be used if any of these methods fail or as the initial method of exploration.

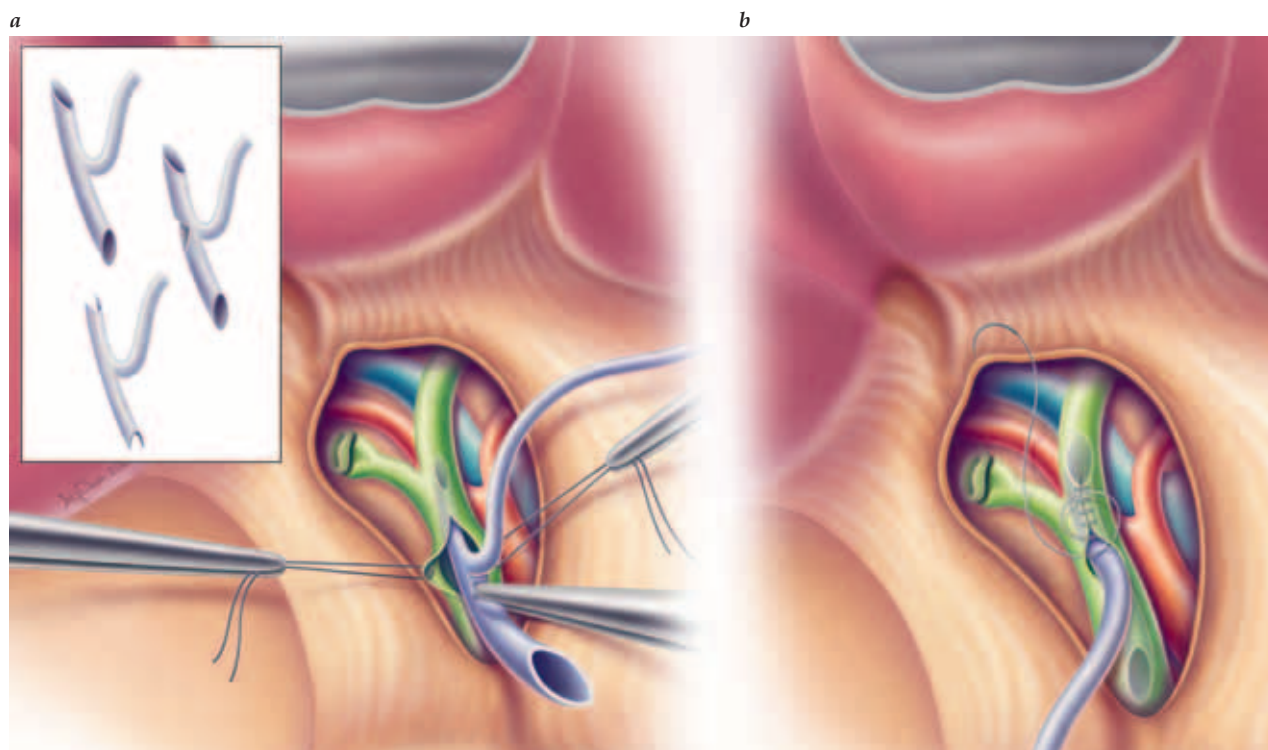


Figure 25 Open common bile duct exploration. (a) After common bile duct exploration, a T tube is fashioned and is placed into the duct. (b) Interrupted 4-0 absorbable sutures are used to close the choledochotomy snug around the tube. Completion cholangiography may then be performed. The tube is brought out through the right abdominal wall, through a separate stab incision, and secured to the skin.

mandatory for decompression of the biliary tract and to provide a route for future duct instrumentation. The T tube is connected to a bag for free drainage. Several days later, cholangiography is repeated. If it shows good flow into the duodenum without obstruction, the tube may be clamped and removed at the 2-week mark. If there are retained stones, a more mature tract must be allowed to develop over 4 to 6 weeks for future instrumentation and stone retrieval. Retained

stones may require ERCP, percutaneous transhepatic instrumentation, T tube tract instrumentation, or combinations of these for removal.

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Figure 18 Courtesy of Nathaniel J. Soper, MD,
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22 PROCEDURES FOR BENIGN AND MALIGNANT BILIARY TRACT DISEASE

Susan Logan, MD, MPP, and David Linehan, MD, FACS

Over the past several decades, advances in imaging technology have been made that allow more accurate diagnosis of biliary tract diseases and better planning of surgical procedures and other interventions aimed at managing these conditions. Operative techniques have also improved as a result of a better understanding of biliary and hepatic anatomy and physiology. The role of endoscopists and interventional radiologists in the management of benign conditions, as well as palliation of malignant disease, is also expanding. Accordingly, biliary tract surgery, like many other areas of modern surgery, is constantly changing.

In this chapter, we describe common operations performed to treat diseases of the biliary tract, emphasizing details of operative planning and intraoperative technique and suggesting specific strategies for preventing common problems. Complex biliary tract procedures should be performed only in specialized centers where experienced multidisciplinary teams, including hepatobiliary surgeons, endoscopists, interventional radiologists, and intensivists, collaborate to manage the special problems and requirements of patients undergoing such procedures.

Preoperative Evaluation

ANATOMY

Before embarking on any operation on the biliary tract, the surgeon must accurately define the relevant anatomy and extent of disease. Familiarity with the numerous variations of ductal anatomy is crucial [see *Figure 1a*]. In the prevailing pattern, the segment 6 and 7 ducts coalesce to form the right posterior sectional bile duct, and the segment 5 and 8 ducts join to form the right anterior sectional duct. The right anterior duct is usually oriented vertically, whereas the right posterior duct tends to follow a more horizontal course. The right anterior and posterior sectional ducts unite to form the right hepatic duct. Note that the posterior sectional duct crosses in front of the right anterior portal vein before joining the right anterior bile duct (Hjortsjo crook) [see *Figure 1b*]. Division of the right anterior portal pedicle too close to its origin may result in injury to the right posterior bile duct. The right hepatic duct runs a short extrahepatic course before joining the left hepatic duct at the hepatic confluence, forming the common hepatic duct. Similarly, in the prevailing pattern, the ducts draining segments 2 and 3 join to form the left lateral sectional duct. This duct then crosses behind the ascending portion of the left portal vein and joins the duct from segment 4 (also called the medial sectional bile duct) to form the left hepatic duct. The left hepatic duct runs a longer, usually horizontal, extrahepatic course at the base of segment 4b.

The above description is of the prevailing pattern of biliary anatomy, but the surgeon must be aware of several common variations, particularly those involving the right-sided ducts [see *Figure 1c*]. Not infrequently, one of the right sectional ducts crosses the midplane of the liver to drain directly into the left hepatic duct. If this variation is present and the surgeon performs a standard left hepatectomy, the right-sided duct(s) may be injured. The segment 8 duct may also drain into the posterior sectional duct. Other important variations include a low insertion of the right hepatic duct or an anomalous low insertion of a right sectional, segmental, or subsegmental duct directly into the common hepatic duct, the common bile duct, or even the cystic duct. Variations to the left ductal system most frequently involve variable numbers and sites of insertion of the segment 4 duct(s). Rarely, the segment 4 duct(s) may drain directly into the common hepatic duct or confluence.^{1,2}

Finally, familiarity with the plate-sheath system is essential to performing safe dissection at the hepatic hilum [see *Figure 1d*]. This system is composed of four thick, fibrous plates—hilar, umbilical, cystic, and arantian—of which the hilar plate is most important to the liver surgeon. The hilar plate lies mainly in the coronal plane, at the base of segment 4 and posterior to the vasculobiliary structures in the porta. Superiorly, however, the hilar plate curves anteriorly, along the posterior aspect of the quadrate lobe, and here it is superior to all structures in the porta hepatis, including the right and left bile ducts. As the three vasculobiliary structures pass through the hilar plate, they are “sheathed” within the same fibrous tissue and become a single unit above the plate. Identification of these structures as a single unit above the hilar plate is much simpler and safer than individually isolating each structure lower in the porta hepatis. To gain access to these sheathed pedicles above the hilar plate, the surgeon must dissect the upper border of the hilar plate away from the liver, a technique referred to as “lowering the hilar plate.”³

IMAGING STUDIES

High-quality ultrasonography is useful for confirming the presence of biliary dilatation, and duplex ultrasonography is excellent for assessing vascular involvement. However, ultrasonography is very user dependent and, even in experienced hands, is less helpful for determining resectability or the level or cause of obstruction. Multidetector computed tomography (MDCT) is noninvasive and provides excellent information regarding mass lesions, the presence or absence of ductal dilatation, the extent and level of duct obstruction, and the extent of vessel involvement. Multiphase computed tomography (CT) generates precise and reliable images of the relevant arterial, portal, and venous anatomy. Therefore, conventional

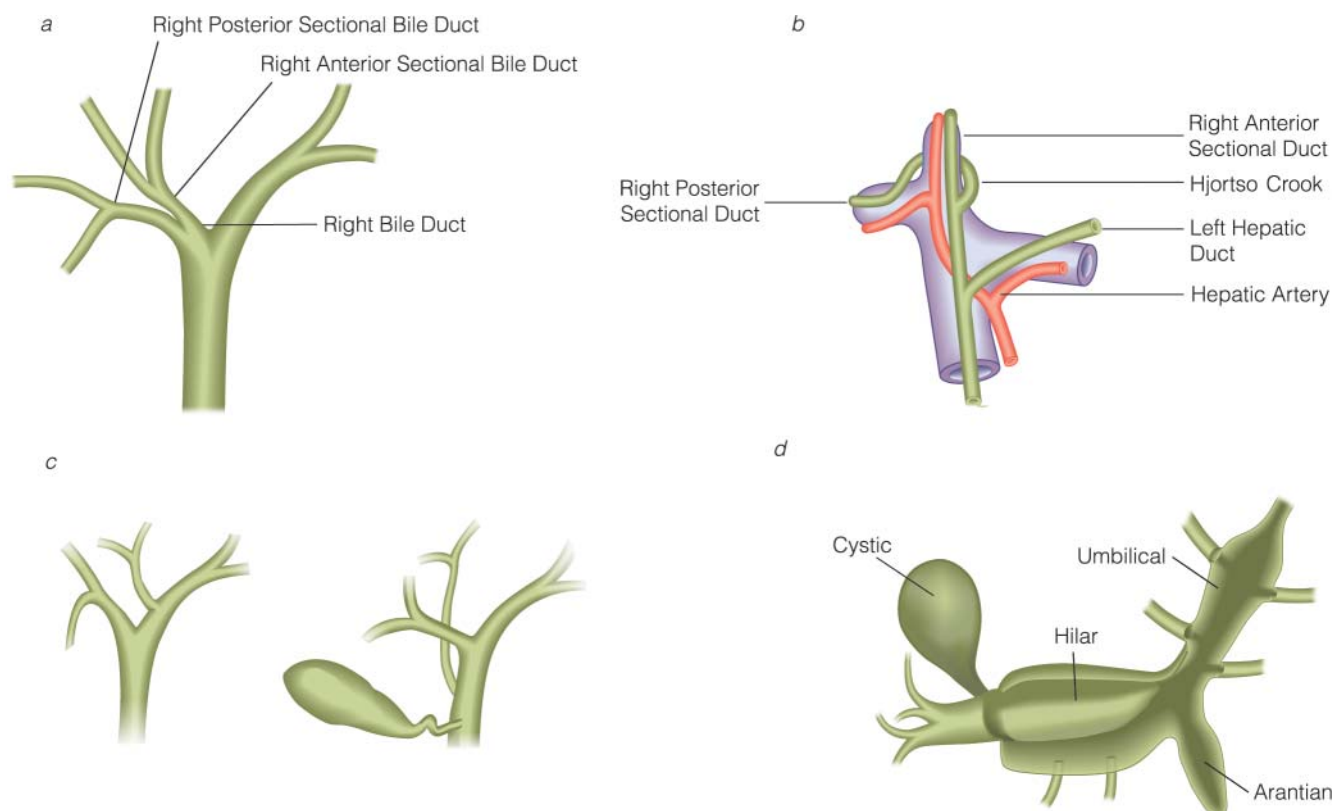


Figure 1 (a) The most common pattern of bile duct anatomy. (b) Hjortso crook. (c) Common variations of right hepatic duct anatomy: (left) right anterior or right posterior duct draining into left hepatic duct; (right) low insertion of right sectional duct. (d) Plate-sheath system of the liver.

angiography is no longer used to determine resectability. Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) can provide detailed images of biliary anatomy and have reported accuracy rates of 100% and 95%, respectively, for determining the location and cause of biliary obstruction. Direct cholangiography—percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP)—may supply additional information about ductal anatomy, is useful for providing tissue (e.g., brush cytology) for diagnosis, and allows drainage of the biliary tree prior to operation. When major liver resection is anticipated, liver volumetric analysis using three-dimensional reconstruction of axial CT images should also be performed to confirm adequate size of the future remnant liver.⁴

In the case of malignant diseases of the biliary tract, evidence of distant organ metastases remains a contraindication to operation. The resectability of locally advanced hilar cholangiocarcinoma depends on the extent of vasculobiliary involvement, the presence or absence of contralateral lobar atrophy, and the predicted size of the future remnant liver.⁵ Repair of biliary injuries should be deferred in the setting of cholangitis, intra-abdominal infection, and sepsis [see Repair of Biliary Injuries, below].

MANAGEMENT OF BILIARY OBSTRUCTION

Jaundice by itself does not increase operative risk, and we do not routinely perform preoperative biliary drainage in all

patients with jaundice.⁶ However, long-standing biliary obstruction has secondary effects that may increase perioperative morbidity and mortality. In the presence of these secondary effects, we recommend elective preoperative biliary decompression.

Infection

Patients with cholangitis, whether spontaneous or induced by duct instrumentation (via PTC or ERCP), should be treated with biliary drainage and appropriate antibiotics until they are infection free. We recommend antibiotic treatment and postponement of operation for at least 3 to 4 weeks. Rarely, antibiotics and endoscopic or transhepatic drainage are not immediately effective, and patients with biliary tract infection (e.g., associated with choledocholithiasis) may require urgent surgical decompression. Broad-spectrum antibiotics, including coverage of anaerobic organisms, should be administered preoperatively.

Renal Dysfunction

The pathogenesis of renal failure in the setting of obstructive jaundice is multifactorial. Extracellular water depletion, increased plasma renin and aldosterone activity, a paradoxical increase in atrial natriuretic peptide, and myocardial dysfunction are all thought to contribute to renal insufficiency in jaundiced patients.⁷ Because the combination of a high bilirubin level and hypovolemia is a significant risk factor for acute renal failure, patients with biliary obstruction should be well hydrated before receiving intravenous contrast agents or

undergoing operative procedures. In patients with acute renal dysfunction secondary to biliary obstruction, decompression of the bile duct until renal function returns to normal is advisable before any major elective procedure for malignant disease.

Impaired Immunologic Function and Malnutrition

In patients with long-standing biliary obstruction, absence of bile salts in the gut lumen may lead to severe malnutrition and contribute to impaired immune function.⁸ Decompression of the bile duct until immune function and nutritional status are restored to normal is indicated before any major elective procedure is undertaken. This may take as long as 4 to 6 weeks.

Coagulation Dysfunction

Prolonged bile duct obstruction may lead to significant deficits in vitamin K–dependent clotting factors. These deficits should be corrected with fresh frozen plasma and vitamin K before an operative procedure is begun. Even if there is no measurable coagulation dysfunction, vitamin K should be given to all patients with obstructive jaundice at least 24 hours before operation to replenish their depleted vitamin K stores.

Projected Major Liver Resection

If resection of an obstructing bile duct tumor is likely to necessitate major liver resection (e.g., a right trisectionectomy), we recommend unilateral decompression of the liver segments that are to be retained. Unilateral drainage is usually sufficient to normalize serum bilirubin and allows atrophy of the undrained segments to occur, along with concomitant hypertrophy of the future liver remnant.

Operative Planning

GENERAL TECHNICAL CONSIDERATIONS

Place the patient in the supine position on an operating table that can be rotated, tilted, and elevated. Equipment for fluoroscopy, intraoperative ultrasonography and choledochoscopy should be available during major resections. Access to a pathology department that can perform cytologic or frozen-section examination of tissue is essential in operations for malignant disease.

A right subcostal incision with vertical midline extension provides excellent exposure for most open procedures on the liver and biliary tract. For more extensive resections or reconstructions, the right subcostal incision can be extended laterally below the costal margin and across the midline to the left as a chevron incision. A vertical midline incision may give sufficient exposure in very thin persons. In any case, the incision must be long enough to allow sufficient visualization and as much mobilization of the liver as is necessary for safe performance of the procedure.

Adequate exposure and lighting are essential. The best retractors are those that can be fixed to the table while remaining flexible in terms of placement and angles of retraction. Retractor blades should be positioned to lift the ribcage anteriorly and cephalad and to pull the right abdominal wall laterally.

Locating the hepatoduodenal ligament and dissecting the structures in the porta hepatis are straightforward in patients who have never had an abdominal operation. However, in patients who have undergone previous operations, there may be considerable obliteration of planes. The following are suggestions for gaining access to the subhepatic space in patients who have had previous abdominal procedures:

1. Use the falciform ligament as a landmark. In reoperative surgery, the key to opening up the upper abdomen is the falciform ligament. This structure should be found immediately after the opening of the abdominal wall and retracted superiorly. The omentum, the colon, and the stomach are then dissected inferiorly, and a plane that leads to the hepatoduodenal ligament and the porta hepatis is thereby opened.
2. Take the right posterolateral approach. When the colon and the duodenum are densely adhered to the undersurface of the right liver, separation may be difficult. In most patients, an open space remains that can be approached by sliding the left hand posteriorly to the right of these adhesions and into the (usually open) subhepatic space in front of the kidney and behind the adhesions. Anterior retraction allows identification of the adherent structures by palpation and permits dissection of the adhesions in a lateral-to-medial direction. The undersurface of the liver is thus cleared, and the hepatoduodenal ligament can be approached.
3. Take the lesser sac approach. Ordinarily, the foramen of Winslow is open, and the left index finger can be passed through it from the right subhepatic space. When the foramen of Winslow is obliterated, however, one should approach it from the left, dividing the lesser omentum and passing an index finger from the lesser sac behind the hepatoduodenal ligament to reopen the foramen of Winslow by blunt dissection.

For a discussion of techniques to aid in the safe exposure of the porta hepatis in patients who have sustained a bile duct injury or have had previous biliary operations, refer to the section below on repair of biliary injuries: exposure of the porta hepatis.

General Guidelines for Biliary Anastomoses

As a rule, biliary anastomoses, whether of duct to bowel or of duct to duct, heal very well provided that the surgeon adheres to the following principles: (1) preservation of adequate blood supply, (2) avoidance of tension, (3) accurate placement of sutures with mucosa-to-mucosa apposition, and (4) construction of anastomoses of adequate caliber. In preparing the bile duct for anastomosis, it is essential to define adequate margins while avoiding excessive dissection that might compromise the blood supply to the duct. In repairs that follow acute injuries, it is important to resect crushed or devascularized tissue; however, in late repairs, it is not necessary to resect all scar tissue as long as an adequate opening can be made in the proximal obstructed duct through normal healthy tissue and as long as mucosa, rather than granulation tissue, is present at the duct margin. The length of the corresponding opening in the jejunal loop should be significantly smaller than the bile duct opening because the bowel opening tends to enlarge during the procedure.

Certain principles of suture placement apply to all biliary anastomoses. Mucosa-to-mucosa apposition is essential for good healing and the prevention of late stricture.⁹ Sutures should be of an absorbable, synthetic monofilament material and should be as fine as is practical (e.g., 5-0 for a normal duct and 4-0 for a thickened duct). Because the bile duct wall has only one layer, biliary anastomoses should all be single layer. Sutures should pass through all layers of the bowel, taking sizable bites of the seromuscular layer and much smaller bites of the mucosa, and should take moderate-sized (1 to 3 mm, depending on duct diameter) bites in the bile duct. Interrupted sutures are used when access is difficult or the duct is small; continuous sutures are used when access is easy and the duct is larger. Sutures should be securely placed but should not be so tight as to injure the tissues. Magnification with loupes is useful when anastomosing small ducts. With the exception of repair of high, complex bile duct injuries, we do not routinely place stents for biliary anastomoses. Some studies suggest that placement of drains is not necessary after biliary operations.^{10,11} Nevertheless, it is currently our practice to place a drain at the time of the operation and to remove the drain within 2 to 3 days if the output does not show evidence of a bile leak.

When the bile duct opening has a vertical configuration (as in side-to-side choledochoduodenostomy or choledochojejunostomy), we place stay sutures inferiorly and superiorly in the duct and at corresponding points in the intestine. Traction is placed on these sutures to line up the adjacent walls. One side of the anastomosis is done first; the bowel is then rotated 180°, and the other side is completed [see Figure 2]. This maneuver may be facilitated by retracting the first interrupted posterior stitch to the opposite side to serve as a pivotal stitch. We recommend sewing about two thirds of the first wall and two thirds of the second, leaving the anterior third of the circumference (the easiest part) to be closed last. For end-to-side choledochojejunostomy, or when the bile duct opening lies transversely, as in bifurcation reconstruction, lateral stay sutures are placed first, and the posterior wall stitches are placed from inside the lumen. If interrupted sutures are used, they are all placed individually before any of them are tied, with the untied tails carefully clamped and arranged in order. When the posterior wall sutures have been tied, the anterior wall can then be sutured with either continuous or interrupted sutures [see Figure 3].

When the intended anastomosis will be to a very small-caliber or intrahepatic duct, and access is particularly difficult because of some combination of an unfavorable position, a previous scar, or a stiff liver that is difficult to retract, another technique may be useful. Beginning left to right, place all of the anterior wall stitches (inside to outside) into the duct. Clamp each suture and place them in order on a single retracting forceps with the needles left attached. Retract the sutures superiorly to expose the posterior wall of the duct [see Figure 3c]. Again, working left to right, place the posterior stitches inside to outside through the bowel wall and outside to inside into the duct. Remove the needles at the completion of each stitch, clamp each suture, and keep them in order as described for the anterior row. When all of the posterior stitches have been placed, carefully appose the bowel wall to the bile duct, tie all but the two corner stitches in order, and

cut the sutures. Leaving the corner stitches (at 3 and 9 o'clock) loose facilitates accurate placement of the lateral and medial stitches of the anterior wall. Finally, place the anterior wall stitches inside to outside on the bowel, sequentially clamp the stitches until the last stitch is placed, and then tie the stitches in order and cut the sutures.⁹

When the duct is very small, three additional techniques may be useful for increasing the size of the lumen:

1. An anterior longitudinal incision can be made in a small common bile duct (CBD) and the sharp corners trimmed to enlarge the opening [see Figure 4a].
2. If the cystic duct is present alongside a divided CBD, an incision can be made in the shared wall to create a single larger lumen [see Figure 4b].
3. If the bifurcation has been resected, two small ducts can be brought together and sutures placed into their adjoining walls to form a single larger lumen as long as the space between the ducts is small and the ducts can be brought together without tension [see Figure 4c]. If the ducts cannot be brought together without tension, more than one anastomosis must be created.

Construction of a Roux Loop

When the jejunum is used for long-term biliary drainage, we prefer a 60 cm Roux loop to prevent reflux of small bowel contents into the biliary system. In the creation of the loop, it is important to select a segment of jejunum with a well-defined vascular arcade that will be long enough to support a tension-free anastomosis. If access to the biliary system will be required in the future (e.g., in an operation for recurrent intrahepatic stones), the loop should be long enough to allow one to place a tube jejunostomy, fixing the loop to the abdominal wall with nonabsorbable sutures. The site of attachment should be marked with metallic clips to facilitate future percutaneous puncture, cannulation, and removal of recurrent or persistent stones. The tube can be removed after postoperative imaging studies confirm that the biliary tree is free of stones.

Choledochoduodenostomy

Choledochoduodenostomy is a relatively straightforward end-to-side (or sometimes side-to-side) biliary-enteric bypass procedure that is useful in certain restricted circumstances. It is most commonly used in patients with multiple bile duct stones when there is concern about leaving residual stones at the time of CBD exploration, as well as in patients with recurrent bile duct stones when endoscopic papillotomy either cannot be done or has been unsuccessful. Choledochoduodenostomy has the advantage of being simpler and safer than transduodenal sphincteroplasty. It is also used in patients with benign distal biliary obstruction (e.g., from chronic pancreatitis or a very low bile duct injury) and occasionally in patients with malignant distal CBD obstruction whose life expectancy is limited. Choledochoduodenostomy works best if the CBD is at least 1 cm in diameter.

CONTRAINDICATIONS

Choledochoduodenostomy should not be used in patients with actual or potential duodenal obstruction.

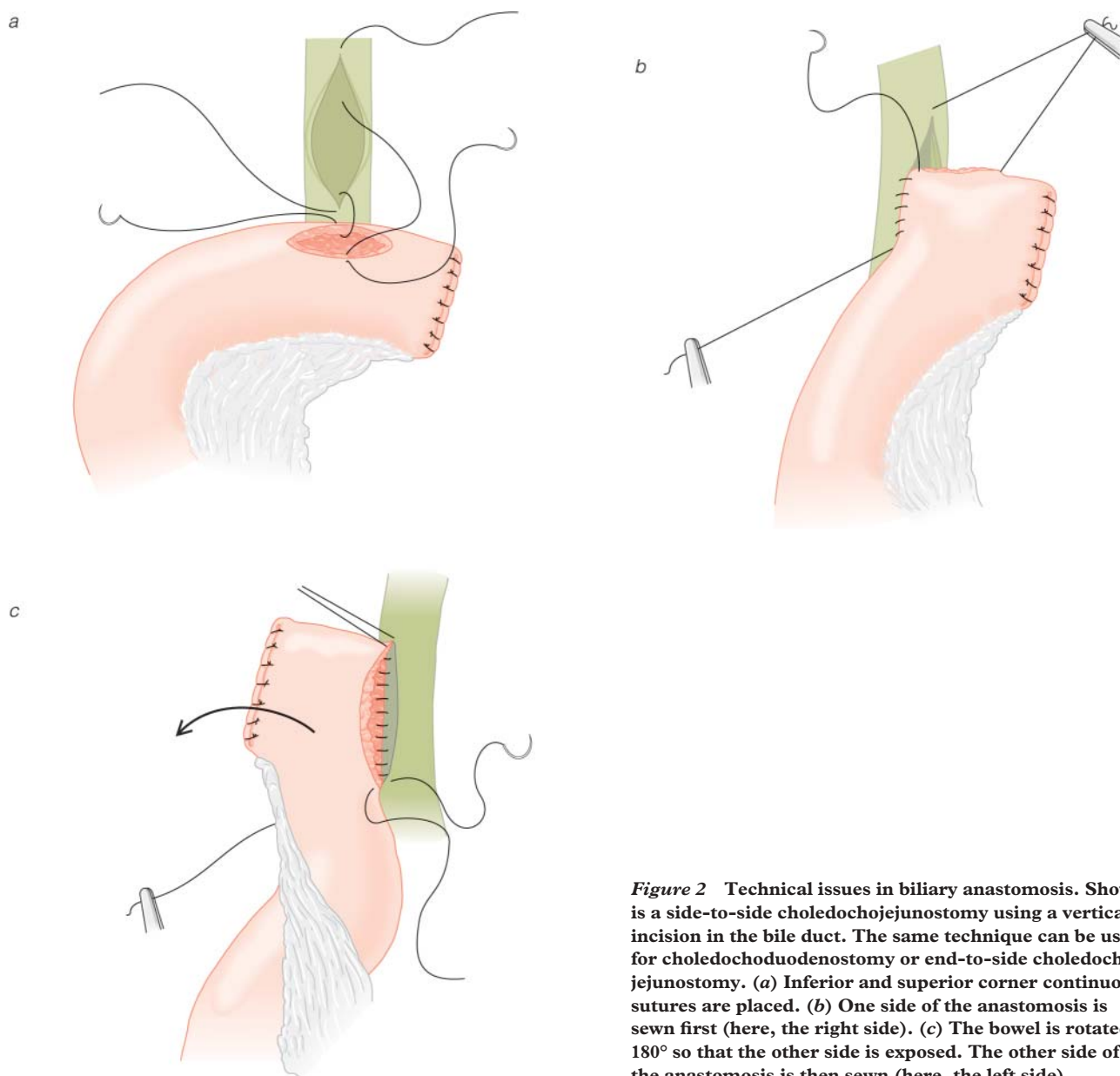


Figure 2 Technical issues in biliary anastomosis. Shown is a side-to-side choledochojejunostomy using a vertical incision in the bile duct. The same technique can be used for choledochoduodenostomy or end-to-side choledochojejunostomy. (a) Inferior and superior corner continuous sutures are placed. (b) One side of the anastomosis is sewn first (here, the right side). (c) The bowel is rotated 180° so that the other side is exposed. The other side of the anastomosis is then sewn (here, the left side).

OPERATIVE TECHNIQUE

Mobilize the duodenum to allow approximation to the CBD without tension. Ordinarily, the first part of the duodenum can easily be rolled up against the CBD; however, in patients who have chronic pancreatitis or have previously undergone an abdominal procedure, extensive Kocherization may be required. If satisfactory approximation is not achieved with this maneuver, a choledochojejunostomy should be performed instead.

Expose the CBD as described elsewhere. Make longitudinal incisions in both the duodenum and the duct [see Figure 2] and create the anastomosis as described previously [see Operative Planning, General Technical Considerations, General Guidelines for Biliary Anastomoses, above].

COMPLICATIONS

Late closure or stricture of the anastomosis may occur if the CBD is small, has inadequate blood supply, or malignant

disease is present. Consider alternative methods of biliary decompression in these situations.

Cholangitis related to the presence of food in the CBD distal to the anastomosis (so-called sump syndrome) is an uncommon occurrence. The larger the anastomosis, the smaller is the likelihood that this complication will occur.

Cholecystojejunostomy

Cholecystojejunostomy may be performed to treat malignant biliary obstruction in selected patients whose lesions are found to be unresectable at operation and whose life expectancy is short.

CONTRAINDICATIONS

Absolute contraindications to this drainage procedure include obstruction above the cystic duct entry point, evidence of cholecystitis, and benign causes of biliary

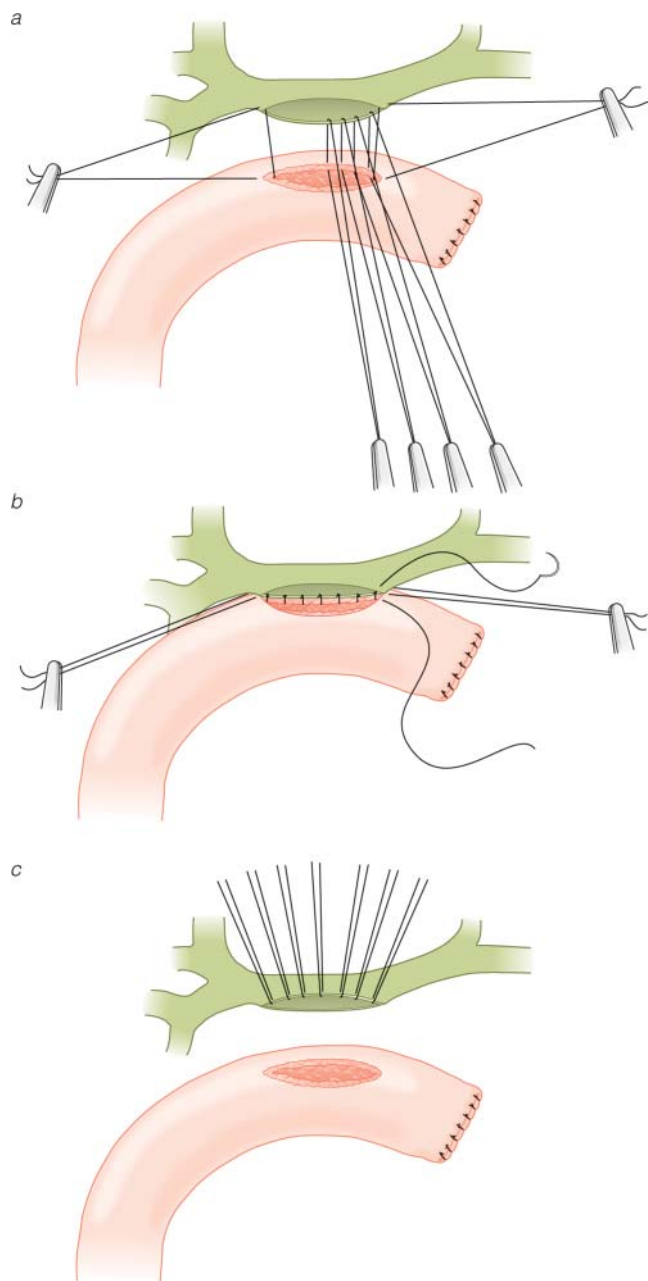


Figure 3 Technical issues in biliary anastomosis. Shown is an end-to-side choledochojejunostomy using a transverse opening in the bile duct. This technique can be used at any level. (a) Corner sutures and posterior wall sutures are all placed before being tied. (b) The posterior wall is completed, and the anterior wall is sewn. (c) In difficult cases, the anterior wall sutures may be placed first and then retracted superiorly.

obstruction (i.e., patients with normal life expectancy). This operation is not the preferred procedure for long-term decompression.

OPERATIVE TECHNIQUE

Step 1: Verification of Feasibility of Procedure

The cystic duct must be patent. Its junction with the CBD must be at least 1 cm above the tumor obstruction [see

Figure 5]. The suitability of the anatomy for cholecystojejunostomy should have been verified by preoperative cholangiography; if not, intraoperative cholangiography via the gallbladder or the CBD is mandatory. If one still cannot be certain that the operation is feasible, the CBD should be opened and a choledochoenterostomy performed. The finding of a bile-filled gallbladder is not sufficient evidence that the patient is a suitable candidate for a cholecystojejunostomy. The gallbladder must be normal: there should be no evidence of cholecystitis or stones. Verify normal status by inspection, palpation, and, if necessary, needle cholecystography.

Step 2: Preparation for Anastomosis

Select a site near the fundus for the anastomosis and anchor an appropriate, tension-free segment of proximal jejunum to the gallbladder with two fine stay sutures. Between the two stay sutures, make a 2 cm transverse opening in the gallbladder and a corresponding longitudinal incision in the antimesenteric border of the bowel.

Step 3: Anastomosis

Create a single-layer anastomosis using a continuous monofilament absorbable suture or a stapler.

COMPLICATIONS

Bile leakage may occur if there is excessive tension on the anastomosis. In addition, jaundice may persist if there is unrecognized cystic duct obstruction resulting from inflammation or an unnoticed stone in the cystic duct or the gallbladder. Recurrent jaundice is usually the result of extension from an obstructing tumor that has involved the cystic duct–CBD junction.

Choledochojejunostomy

Choledochojejunostomy, one of the most commonly performed biliary tract procedures, is done to provide biliary drainage after CBD resection, repair of ductal injury, or relief of obstruction caused by a benign or malignant stricture. To reduce the likelihood of reflux of intestinal contents into the biliary tract, we prefer to use a 60 cm Roux-en-Y jejunal limb for the anastomosis [see Operative Planning, General Technical Considerations, Construction of a Roux Loop, above].

When the operation is performed after CBD resection, an end-to-side choledochojejunostomy using the proximal transected duct is preferred as long as adequate vascularization of the transected bile duct is confirmed. When the operation is performed for bile duct obstruction resulting from tumor or stricture and no resection has been performed, a side-to-side anastomosis is constructed.

OPERATIVE TECHNIQUE

Step 1: Preparation for Anastomosis

Preparation for an end-to-side anastomosis includes resection of any crushed or devitalized bile duct tissue. The CBD should be trimmed back to healthy, viable, bleeding duct wall.

If a side-to-side anastomosis is being performed for stricture or tumor, the proximal duct is almost always dilated and

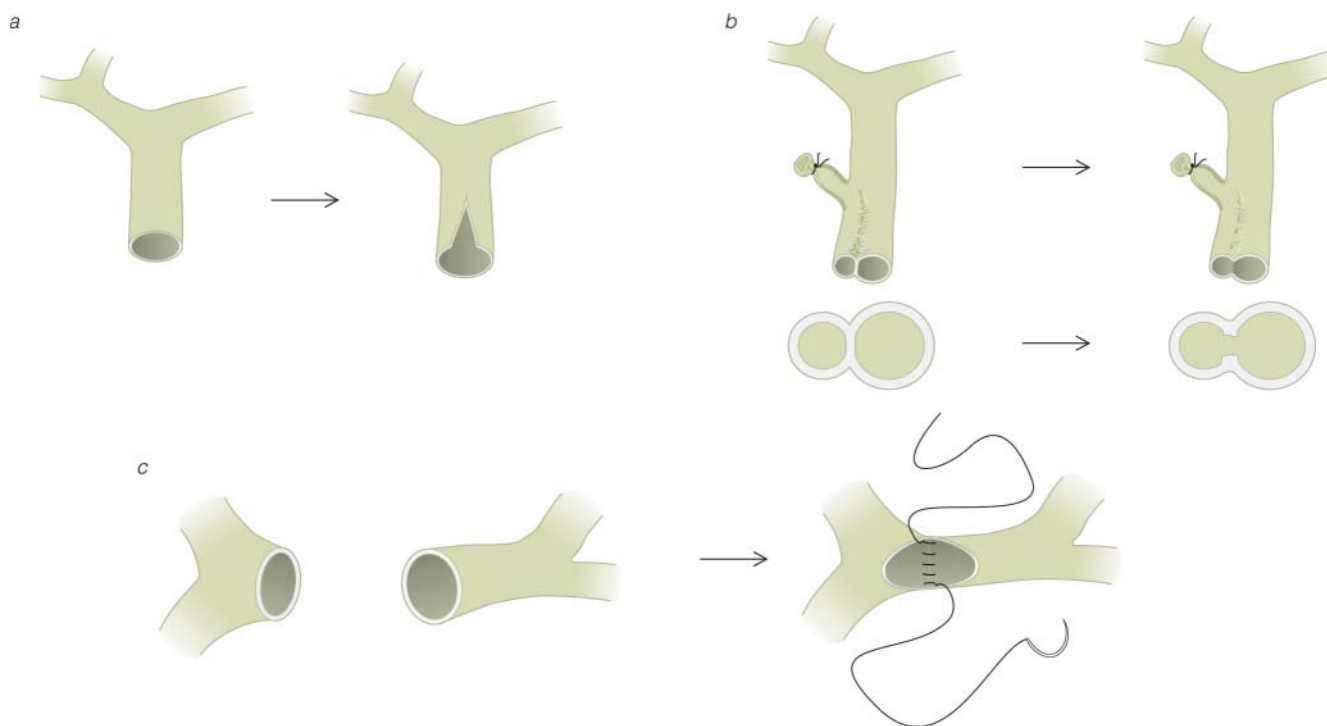


Figure 4 Technical issues in biliary anastomosis. Shown are three methods of enlarging a small duct. (a) An anterior longitudinal incision can be made in the duct wall. (b) A wall shared by the common bile duct and the cystic duct can be divided. (c) Adjoining walls of two small ducts can be sutured together to make a single opening for anastomosis.

has thicker walls, facilitating a vertical incision on the anterior surface. When the procedure is being done for malignant disease, the incision should be made as high as possible above the malignancy to delay the eventual obstruction of the anastomosis by tumor growth.

Step 2: Anastomosis

When the duct is large, a secure, tension-free anastomosis is easily constructed by means of the techniques previously illustrated. When the duct is small, extra effort must be made to place sutures carefully to prevent narrowing of the lumen.

TROUBLESHOOTING

Injured ducts must be adequately débrided, even if this means extending the resection of the duct to the bifurcation. However, preservation of the blood supply to the CBD is essential. Avoid extensive mobilization of the duct from the surrounding tissues to prevent injury to the ductal blood supply. Finally, longitudinal incisions should not be made in the medial or lateral (3 and 9 o'clock) portions of the CBD, where the major longitudinal blood supply is located.

Meticulous surgical technique is critical for ensuring good healing and preventing stricture. Use the finest suture material that will do the job and employ magnifying devices to facilitate accurate placement of sutures. Routine postoperative stenting is unnecessary, but stents may be helpful in those very rare cases in which mucosal apposition cannot be accomplished. In these situations, sutures may have to be placed in surrounding liver or scar tissue in much the same way as in a Kasai procedure.¹² In difficult cases of proximal

stricture, the surgeon may be forced to incise and lower the liver plate and seek out viable intrahepatic ducts for anastomosis [see Repair of Biliary Injuries, *below*].

COMPLICATIONS

The main complications of a choledochojejunostomy are bile leakage, late stricture, and recurrent jaundice as a result of tumor extension [see Cholecystojejunostomy and Choledochoduodenostomy, *above*].

Choledochal Cyst Resection

Choledochal cysts are generally categorized according to the Todani classification [see Figure 6]. More than 80% are type I cysts that involve the CBD in its accessible portion. The following discussion addresses the resection of type I cysts and those type IV cysts that include the proximal right or left hepatic ducts.

Most choledochal cysts are associated with an abnormal junction of the pancreatic duct and the distal CBD. Preoperative cholangiography to clarify the anatomy is important for preventing injury to the pancreatic duct, especially when an intrapancreatic resection is required. Occasionally, intraoperative cholangiography is needed to clarify abnormal anatomy. Patients may be symptomatic as a result of stones within the cyst, infection, or malignancy, any of which is an indication for operation. The increased risk of bile duct malignancy associated with choledochal cysts, and the high mortality associated with cholangiocarcinoma, is justification for prophylactic cyst resection even in asymptomatic patients.

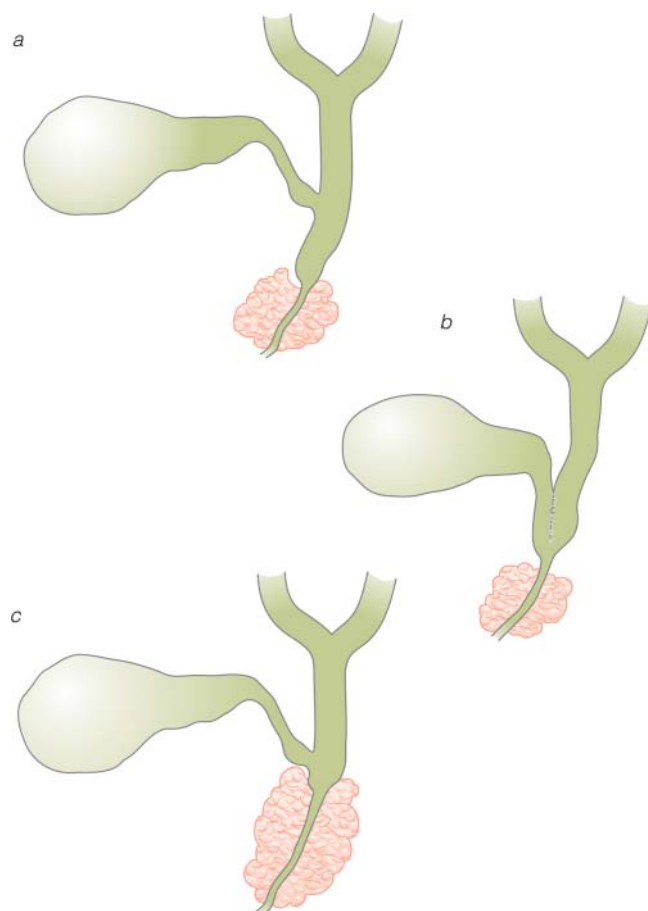


Figure 5 Cholecystojejunostomy. Cholangiography is essential for determining whether the anatomy is suitable (a) or unsuitable (b, c) for the procedure.

The objectives of treatment are (1) to remove the cyst completely, along with the gallbladder and any stones that remain in the bile ducts proximal to the cyst, and (2) to restore biliary-enteric drainage. Resection of a choledochal cyst may be made more difficult by several factors, such as previous operations, recurrent bouts of infection and inflammation in the cyst, and portal hypertension, which may develop as a result of long-standing cholangitis or portal vein thrombosis.¹³

OPERATIVE TECHNIQUE

Resection of a choledochal cyst may be difficult, especially if inflammation is present. In addition, dissection of a choledochal cyst in its intrapancreatic portion is hazardous because of the vascularity of this region and the difficulty identifying anatomic structures.

Step 1: Clarification of Anatomy

The proximal and distal extent of the cyst and the presence or absence of stones or tumor may be determined preoperatively, as noted, but in many cases, intraoperative verification of the findings is necessary. Intraoperative cholangiography can be carried out by inserting a catheter through the gallbladder, by directly needling the cyst, or both. If cholangiography does not yield an accurate definition of the anatomy of the cyst, the cyst may then be opened anteriorly and digital exploration and choledochoscopy used to clarify the proximal and distal extent of the cyst.

Step 2: Mobilization of the gallbladder

If the gallbladder is still in place, dissect it free of the liver, leaving it attached to the cyst via the cystic duct, and retract the gallbladder to the right.

Step 3: Distal Dissection

Early distal division of the cyst facilitates the posterior dissection and allows mobilization of the duct to better define the proximal extent of the cyst. Dissect distally along the wall of the cyst until the junction of the cyst with the normal portion of the CBD is reached. If the intrapancreatic portion of the CBD is involved, the cyst must be separated from pancreatic tissue. A number of small vessels must be individually identified and ligated to minimize the risk of early or delayed bleeding. If the cyst is close to the pancreatic duct junction, one must exercise considerable care not to injure the pancreatic duct. Transect the distal bile duct. Place a clamp on the proximal cut end of the duct to assist with retraction and oversew the distal cut end using fine monofilament absorbable suture, being careful not to injure the pancreatic duct.

Step 4: Mobilization of Cyst

Vascularity in the region and the presence of inflammation may render dissection difficult. Rather than cleaning off the hepatic artery and the portal vein and dissecting them off the cyst, find a plane immediately adjacent to the wall of the

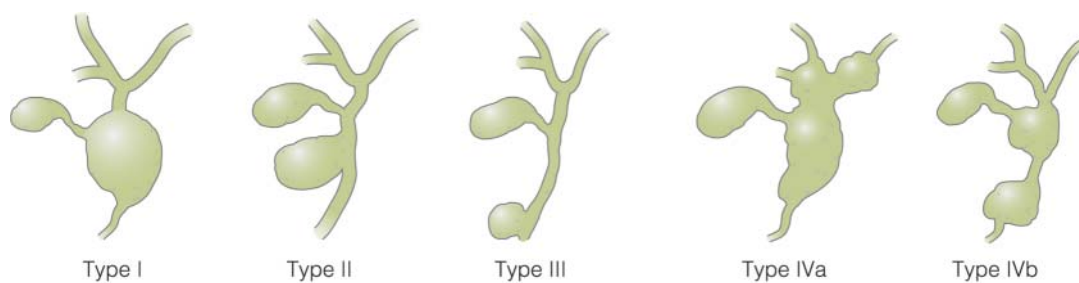


Figure 6 Choledochal cyst resection. Illustrated is the Todani classification of choledochal cyst.

cyst and remain close to it [see Figure 7]. This approach differs significantly from the corresponding approach in resection of a bile duct malignancy [see Resection of Middle-Third and Proximal Bile Duct Tumors, Operative Technique, below]. If necessary, open the cyst with a vertical anterior cystotomy and continue the dissection with direct visualization of the inside of the cyst to yield a more accurate definition of its boundaries. Clear the cyst circumferentially, separating the cyst from the hepatic artery, the portal vein, and any remaining soft tissue in the hepatoduodenal ligament.

Step 5: Proximal Dissection

If the proximal common hepatic duct is normal (as in a type I cyst), transect the duct above the cyst. If the cystic dilatation includes the bifurcation (as in a type IVa cyst), a small button of proximal cyst is usually left attached to the intrahepatic ducts [see Figure 8].

Step 6: Reconstruction

Reconstruction is accomplished via an end-to-side anastomosis to a Roux jejunal loop to minimize the likelihood of reflux of enteric contents into the biliary tract. Stenting is not required, but we recommend draining the area with closed suction drains, especially if an intrapancreatic resection has been done.

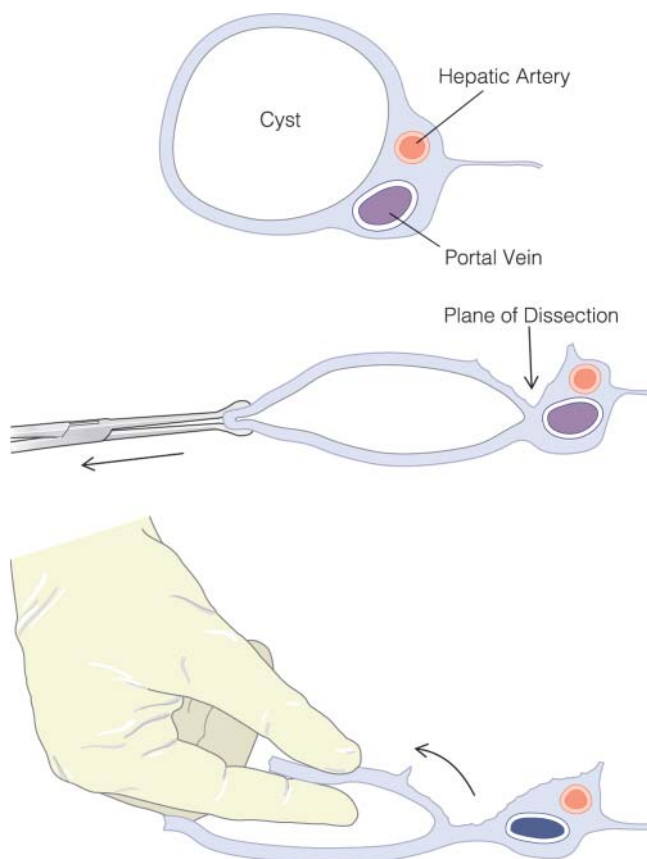


Figure 7 Choledochal cyst resection. Illustrated is the proper plane of dissection in removal of a choledochal cyst. If necessary, dissection can be done with a finger inside the cyst.

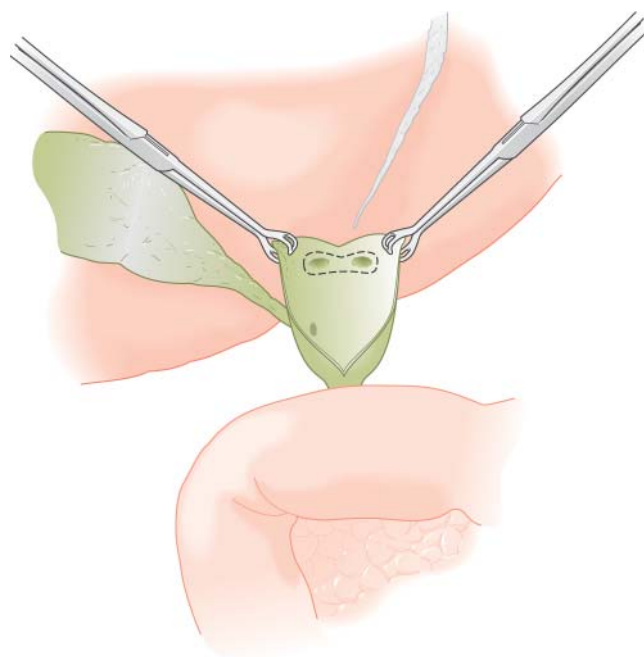


Figure 8 Choledochal cyst resection. If a cyst extends proximally past the bifurcation (e.g., a type IVa cyst), it may be necessary to open the cyst widely to identify the hepatic duct orifices. A small button of cyst wall is left attached to the hepatic ducts.

TROUBLESHOOTING

If dissection of the cyst is carried distally into the pancreas, care must be taken to keep from injuring the pancreatic duct. Transect the cyst as distally as possible and carefully oversew the end with absorbable sutures. Intraoperative cholangiography and/or preoperative MRCP are useful to confirm the relationship of the cyst and the CBD to the pancreatic duct.

If the cystic process extends to include the bifurcation (type IVa), the hepatic ducts should be identified from within the cyst and their orifices preserved by leaving a small button of cyst wall in situ; this is preferable to performing an intrahepatic dissection to remove the entire cyst. The presence of this button simplifies and facilitates the anastomosis to the Roux loop. Note that liver resection for choledochal cyst is rarely justified unless there is evidence of a solid mass or papillary excrescence emanating from the cyst mucosa.

COMPLICATIONS

Bleeding and pancreatitis are the main early complications of cystectomy. These can be largely prevented by meticulous dissection and ligation of all fine bleeding vessels as well as tissue adjacent to an intrapancreatic cyst. Late stricture of the anastomosis is an uncommon complication but may occur, especially if a small button of proximal cyst is left in place for the anastomosis; this particular complication is considered an acceptable hazard in a difficult situation.

OUTCOME EVALUATION

The immediate expected outcome is the relief of pain, jaundice, and cholangitis and the return of liver function to normal. The long-term expected outcome is the absence of

any recurrence of symptoms of stone disease, cholangitis, or malignancy. Because of the rarity of this condition, no good data on the recurrence rate of problems are available, but in our experience, the need for reintervention is rare.

Resection of Middle-Third and Proximal Bile Duct Tumors

The most common bile duct tumor is adenocarcinoma. Because this tumor responds poorly to irradiation and chemotherapy, surgical resection offers the best opportunity for cure. Unfortunately, many patients present with unresectable local disease and distant metastasis, and only palliative interventions are warranted. The appropriate operative approach depends on the location and extent of the tumor [see Figure 9]. Tumors in the distal third of the CBD (the pancreatic portion) are treated by means of a pancreaticoduodenectomy that includes bile duct and periductal tissues right up to the bifurcation. Those in the middle third or the proximal third are treated by means of bile duct resection, often with concurrent liver resection.

Certain basic principles underlying bile duct resection for tumor must be followed. First, the proximal extent of the tumor must be identified so that the correct procedure can be planned. Preoperative PTC is usually not required for staging if high-quality MRI and MRCP are available. With the exception of the clinical circumstances outlined previously [see Management of Biliary Obstruction, *above*], we do not routinely place preoperative biliary drainage tubes.

Second, given that bile duct tumors spread by local extension to lymphatics, along perineural spaces, and along the biliary radicles directly into the liver, wide local excision beyond the visible edges of the tumor is required in the performance of curative resections. In proximal tumors, such excision necessitates resection of the adjacent segments of the liver. The principles of en bloc resection beyond tumor margins must be closely adhered to: dissection into or even close to the tumor must be avoided.¹⁴

Third, intraoperative biopsy of the tumor is unreliable because of the difficulty of making a firm pathologic diagnosis on the basis of frozen-section examination.

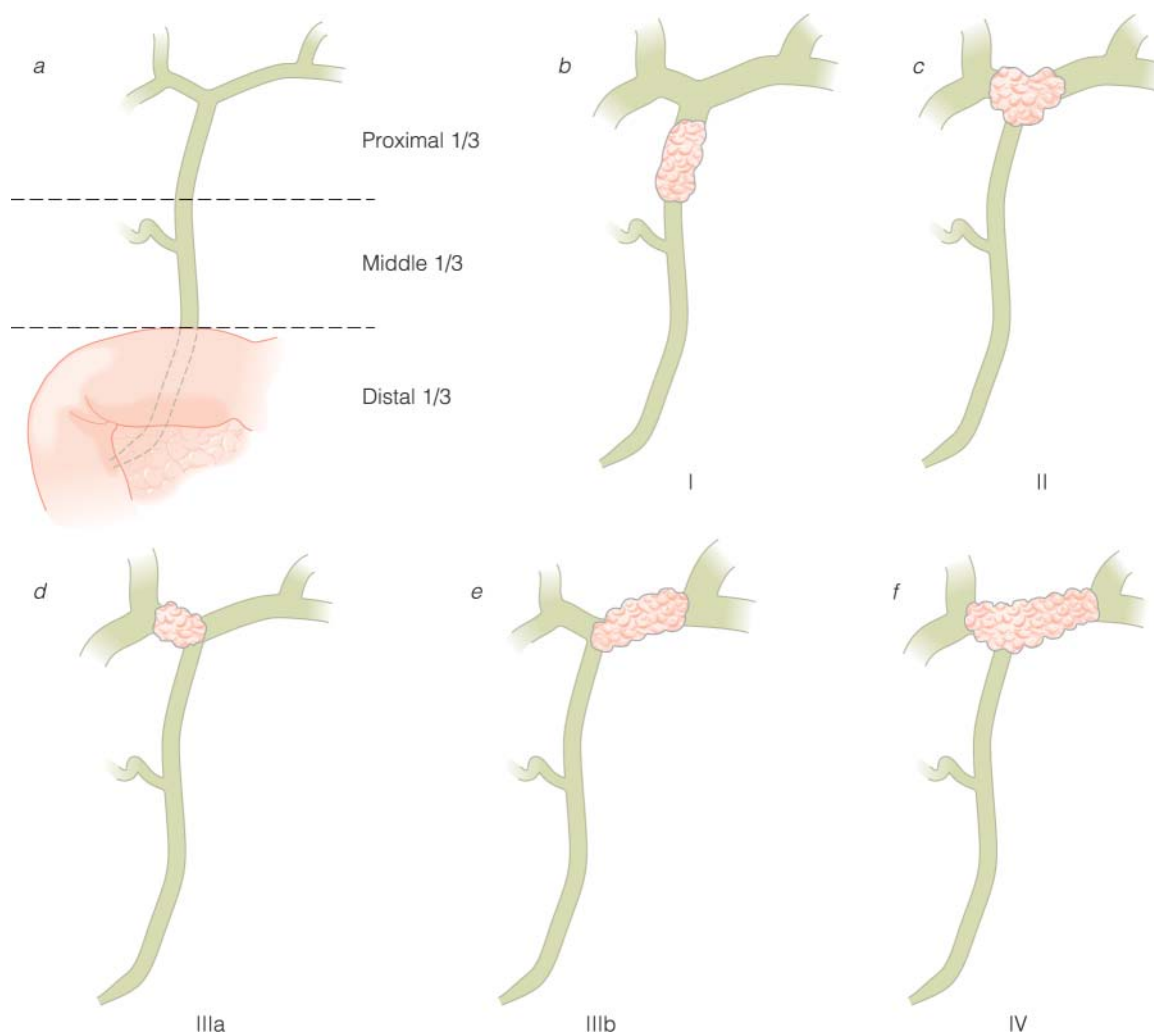


Figure 9 Resection of middle-third and proximal bile duct tumors. The appropriate operation depends on the location and extent of the tumor. (a) Broadly, tumors may be localized to the proximal third, the middle third, or the distal third of the biliary tract. (b through f) Proximal tumors may be further categorized according to the Bismuth classification.

Finally, given that liver resection is required in most cases, one must be careful to preserve enough healthy liver tissue to allow regeneration of the remnant.¹⁵ If there has been long-standing obstruction, biliary drainage on the side to be preserved is important for recovery of function in that portion of the liver. Some surgeons advocate preoperative portal vein embolization on the contralateral side to stimulate hepatic regeneration in the segments to be preserved, especially if the future remnant is marginal in size. Often this is unnecessary, however, because of lobar atrophy attributable to ipsilateral portal vein involvement and compensatory contralateral hypertrophy.

On the whole, we are aggressive in treating proximal tumors for two main reasons: (1) the accompanying liver resection can now be done with low morbidity, and (2) this more radical approach has been shown to yield improved long-term results.⁵ For middle-third or type I proximal tumors, we favor resection of the bifurcation in conjunction with intrahepatic cholangiojejunostomy. For types II, III, and IV, we recommend additional liver resection: a right trisectionectomy (resection of segments 4, 5, 6, 7, and 8, along with the caudate lobe) for types II, IIIa, and IV and a formal left hepatectomy (resection of segments 1, 2, 3, and 4) for type IIIb. There is some controversy as to whether patients with these complex proximal biliary tumors have a better chance of long-term survival with liver transplantation than with radical resection because of the high incidence of positive microscopic margins. This controversy has yet to be resolved, but we prefer radical resection when feasible. Transplantation for hilar cholangiocarcinoma should be performed only in the context of an approved clinical trial.

OPERATIVE TECHNIQUE

Step 1: Assessment of Resectability

Assessment of resectability begins with an evaluation of the patient's fitness and exclusion of underlying liver disease (i.e., cirrhosis and portal hypertension). The next step is to confirm the radiographic appearance of resectability. Radiographic evidence of metastatic disease is an absolute contraindication to resection. In the absence of metastatic disease, the resectability of hilar cholangiocarcinoma is predicted by the extent of vasculobiliary involvement and the presence or absence of contralateral lobar atrophy. In general, if the tumor involves only the ipsilateral portal vein and/or bile ducts, it may be resectable; if the tumor involves the contralateral portal vein and/or contralateral secondary bile ducts, it is generally not resectable.⁵ Finally, if curative resection requires major hepatectomy, the future remnant liver must be of adequate size to prevent postoperative liver failure.

Before any dissection of the tumor or the CBD is done, conduct a careful search for peritoneal metastases. Evaluate spread within the liver by palpation. Palpate for suspicious lymph nodes in the immediate and secondary drainage areas. Biopsy any suspicious areas outside the planned resection margins and send this for frozen-section analysis. If the frozen section confirms that tumor is present outside the planned resection area, palliative stenting or a bypass procedure is indicated.

During dissection, determination of resectability is often difficult, especially with respect to assessment of tumor extension into the liver and the degree of vessel involvement.

Therefore, the surgeon should defer any firm commitment to resection (e.g., dividing the blood supply) until resectability is confirmed.

Dissect the gallbladder off the gallbladder fossa, taking care to leave the cystic plate on the liver. The gallbladder can be left attached to the CBD and used as a retractor. Follow the cystic plate down to the hilar plate and lower the hilar plate by dividing its attachment to segment 4B all the way to the umbilical fissure. This allows palpation and inspection of the hilum to determine the extent of tumor involvement into the left and right hepatic ducts.

Dissection is then begun from below. Identify the common hepatic artery and the portal vein just above the neck of the pancreas and circumferentially clear these of all tissue. Continue the dissection proximally, retracting the hepatic artery to the left and the portal vein to the right. Adjacent areolar tissue, nerve trunks, and lymph nodes should be left in place around the CBD and the tumor [see Figure 10]. As noted, this approach differs from that used in resection of choledochal cysts [see Choledochal Cyst Resection, Operative Technique, above].

Step 2: Division of CBD

Once resectability is confirmed, divide the CBD at the level of the pancreas. Place a clamp on the end of the divided duct and use this as a retractor to facilitate the most proximal dissection of the CBD and the tumor away from the hepatic artery and the portal vein [see Figure 11].

Step 3: Proximal Dissection

With middle-third tumors or Bismuth type I proximal tumors, it is usually possible to palpate the proximal tumor margin and identify uninvolved right and left hepatic ducts. If this is not the case, the surgeon should consider the possibility of a type II or III tumor and be prepared to completely excise the bifurcation, with or without part of the liver.

Dissect the hepatic artery by retracting the vessel anteriorly and to the left, dividing and ligating the cystic artery where it originates from the right hepatic artery, and clearing all tissue off the right and left branches at least 1 cm proximal to the proximal margin of the tumor. Involvement of the right or left hepatic artery by tumor is a sign of extensive spread on the corresponding side and an indication for resection of that half of the liver.

Dissect the portal vein by retracting the bile duct and the tumor anteriorly and the hepatic artery to the left. All tissue should be cleanly dissected away from the portal vein to expose the bifurcation and the region proximal to it [see Figure 11]. At this point, the duct may be tethered down to the caudate lobe. Bile ducts from the caudate lobe may drain into the right or left duct and tumor may extend along these caudate ducts. Therefore, whether or not there is gross tumor in this area, the caudate lobe should be included in the resection.¹⁶

The level at which the proximal bile ducts are transected depends on the proximal extent of the tumor. For all middle-third or proximal tumors that are at least 1 cm beyond the bifurcation, proximal resection should be above the level of the bifurcation. For type I or type II proximal tumors, proximal resection should always include all of the bifurcation along with the proximal right and left bile ducts out as far as

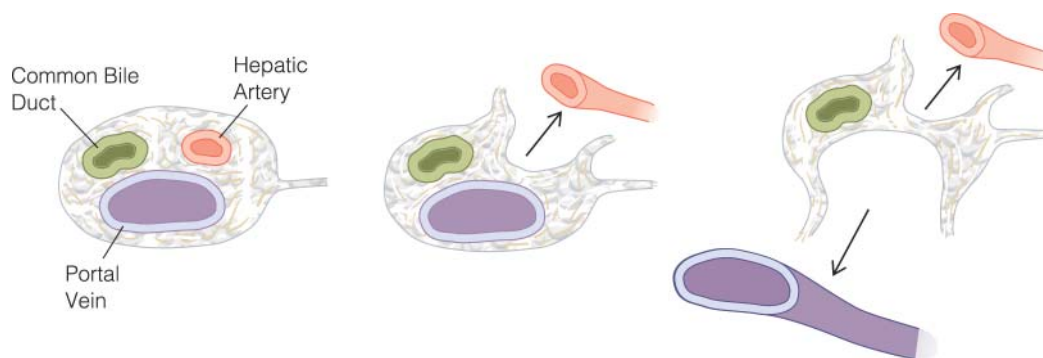


Figure 10 Resection of middle-third and proximal bile duct tumors. Shown is the proper plane of dissection in the removal of a bile duct cancer. Except for the hepatic artery and the portal vein, all tissue stays with the common bile duct to be resected.

the first major branch [see Figure 12]. With type III or IV proximal tumors, the proximal extent of the tumor cannot be determined in both right and left ducts unless the main pedicles are dissected out of the liver. Because these tumors tend to infiltrate locally, such dissection is not advisable. Instead, concurrent hepatectomy should be performed to optimize the likelihood of curative resection. Intraoperative ultrasonography may help verify the extent of tumor at this point in the operation. Any major liver resection for type III

or IV bile duct cancer should include the caudate lobe [see Figure 13].

Before committing to a major hepatectomy (i.e., before dividing the blood supply), the tumor must be dissected away from the hepatic artery and portal vein branch supplying the segments of the liver to be preserved. Once this has been accomplished, the hepatic artery and the portal vein branch to the side to be resected can be divided. This allows the tumor to be retracted further and provides better exposure of the duct to the side to be preserved [see Figure 14 and Figure 15]. In selected cases, resection of an involved portal vein bifurcation may be carried out at this point [see Figure 16]; an end-to-end primary venorrhaphy (without the need for an interposition conduit) can usually be fashioned.

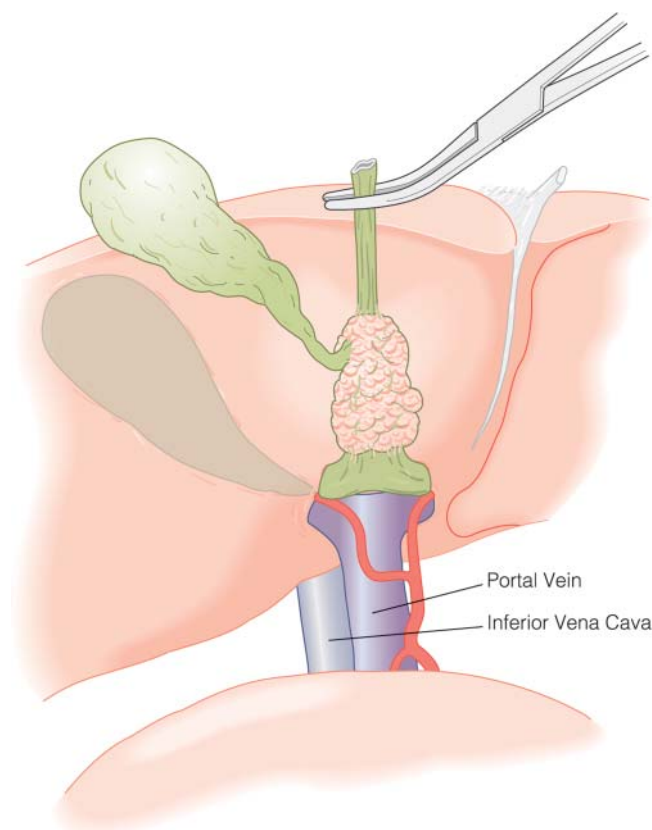


Figure 11 Resection of middle-third and proximal bile duct tumors. When resectability is confirmed, the common bile duct (CBD) is transected at the duodenum. The proximal portion of the divided duct is retracted anteriorly, and the CBD is cleaned off the portal vein up to a point above the bifurcation.

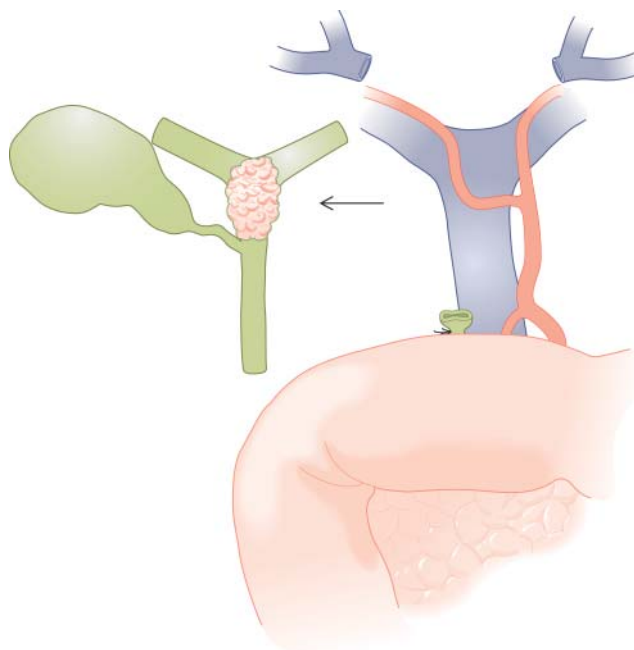


Figure 12 Resection of middle-third and proximal bile duct tumors. Illustrated is the level of resection for middle-third and type I proximal tumors. The common bile duct is resected from the pancreas to a point above the bifurcation. Reconstruction is accomplished via Roux-en-Y hepaticojejunostomy (involving either one or two separate anastomoses).

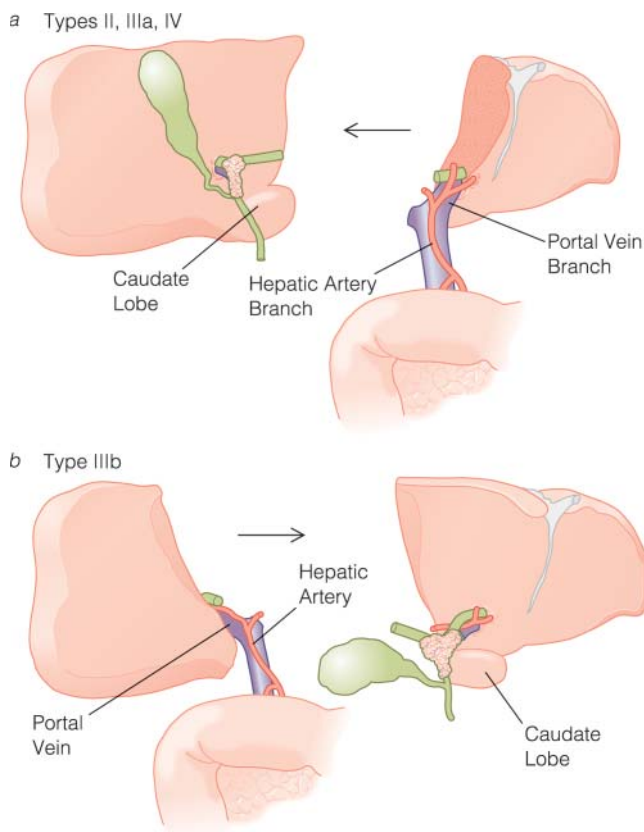


Figure 13 Resection of middle-third and proximal bile duct tumors. Illustrated are (a) a right trisectionectomy (extended right hepatectomy) for type II, IIIa, and IV tumors and (b) a left hepatectomy (including the caudate lobe) for type IIIb tumors.

The point at which the hepatic parenchyma will be divided is marked, and the parenchymal transection is performed. Division of the hepatic duct (or ducts) to the part of the liver being preserved is done as far from the tumor as possible.

Step 4: Reconstruction

After resection of the bifurcation or intrahepatic bile ducts, an intrahepatic cholangiojejunostomy is performed. The duct tissue is usually healthy enough and the duct lumen large enough to allow mucosa-to-mucosa repair without stenting.

Step 5: Closure and Postoperative Care

Close the abdomen in the standard fashion and place closed suction drains. In the early postoperative period, particularly when a major liver resection has been performed, mild abnormalities in coagulation test results are common. In the absence of active bleeding or severe coagulopathy, we do not administer fresh frozen plasma. Drains are removed 2 to 3 days postoperatively if there is no evidence of a bile leak.

COMPLICATIONS

Bile leakage, bleeding, and infection are the most important complications of bile duct resection for tumor. Following major hepatectomy, expect a transient rise in liver function

studies. A moderate increase in coagulation studies is also common, and we do not transfuse fresh frozen plasma for an international normalized ratio of 2.0 or less unless clinical bleeding is evident. Nevertheless, these laboratory values should be monitored closely in the early postoperative period as persistent elevation of liver function tests or coagulation studies is an indication of hepatic insufficiency. Parahepatic collections are treated with percutaneous drainage, and significant early postoperative bleeding is usually best managed by reexploration.

Repair of Biliary Injuries

Biliary injuries during laparoscopic cholecystectomy are estimated to occur in only 0.4 to 0.6% of cases, but with approximately 500,000 procedures yearly in the United States, this seemingly low injury rate translates into significantly increased cost, resource use, morbidity, and mortality.^{17–21} In as many as 50% of cases, the injury may be discovered at the time of operation, and depending on the type of injury, the surgeon may attempt an immediate repair.^{22,23} General surgeons who perform laparoscopic cholecystectomies should be adequately trained to repair Strasberg type A and D injuries [see Figure 17]. Strasberg type A injuries include cystic duct stump leaks or leakage from small ducts in the liver bed (e.g., duct of Luschka). If a type A injury is detected during laparoscopic cholecystectomy, oversew the offending duct (laparoscopically or open) and place a drain. A type D injury is a lateral injury to a major duct. One may safely perform a primary repair of the duct at the time of operation under the following conditions: (1) less than 25% of the circumference of the duct is involved, (2) the injury is not thermal (i.e., from a cautery burn), and (3) the duct is of sufficient caliber to allow insertion of a T tube. Place a T tube across the injury (via a separate incision in the duct) and perform a primary repair using fine absorbable monofilament suture. If any one of the above conditions is absent, the surgeon should instead perform a choledochojejunostomy as previously described or refer the patient to a hepatobiliary surgeon if necessary. Type B injuries usually involve ligation of an aberrant right hepatic duct and are rarely detected at the time of surgery. Type C injuries involve transection, but not ligation, of an aberrant (usually right hepatic) duct. If discovered at the time of operation, such injuries are best repaired immediately with cholangiojejunostomy. Strasberg type E injuries parallel the Bismuth classification system of biliary strictures. These injuries occur higher on the biliary tree, may be very complex, and are often accompanied by a vascular component. When such injuries are noted at the time of cholecystectomy, the surgeon must honestly assess his or her expertise in the repair of complex biliary injuries and do nothing that might worsen the injury. In general, this means that once any hemorrhage is carefully controlled, a drain should be placed, the wound should be closed, and the patient should be transferred without delay to the nearest specialty center with provider teams experienced in the management of complex biliary injuries.²⁴

Injuries not discovered at the time of initial operation may present days, weeks, or even years later.^{25,26} Signs and symptoms of delayed presentation vary depending on the nature of the injury and whether obstruction or bile leakage

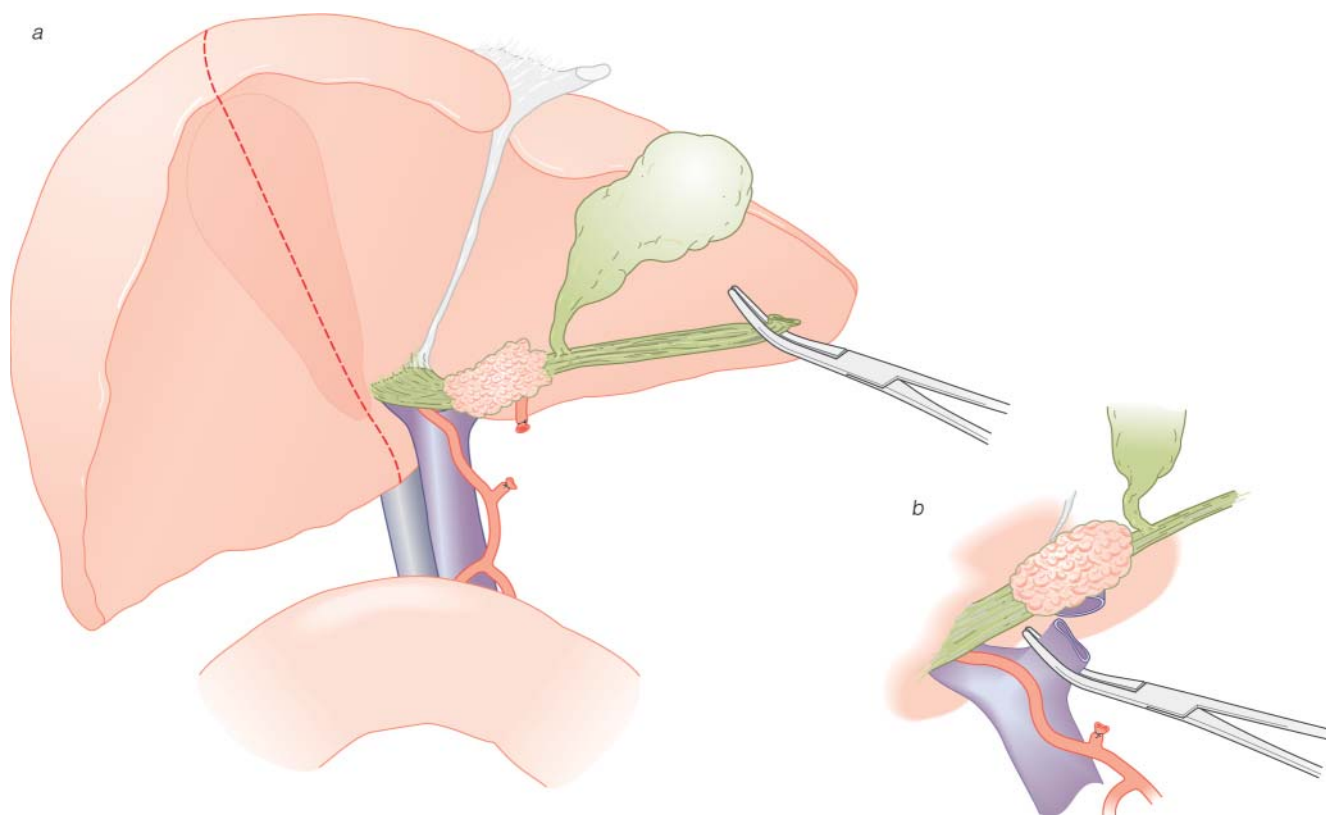


Figure 14 Resection of middle-third and proximal bile duct tumors. Shown is the resection of type IIIb proximal tumors. (a) The common bile duct is retracted upward and to the left; the left hepatic artery is divided; and the right portal vein and the right hepatic artery, which are to be saved, are exposed. (b) The left portal vein is divided.

is the dominant pathology at the time. Persistent but usually mild, unexplained pain and malaise in the postoperative period are the most common initial symptoms, and the non-specific nature of these symptoms may lead to further delay in diagnosis.²⁷ Patients may also present with nausea, anorexia, elevated white blood cell count and liver function studies, fever, jaundice, cholangitis, or sepsis. Initial management depends on the clinical state of the patient. Correct any fluid and electrolyte derangements, administer appropriate analgesia to control the pain associated with bile peritonitis, and initiate broad-spectrum antibiotic coverage in any patient with infection. High-quality cross-sectional imaging—multi-phase CT, MRI/MRCP, or both—is essential to evaluate the extent of injury and detect abdominal fluid collections or major vascular injury. Patients with signs or symptoms of cholangitis or sepsis should undergo percutaneous drainage of any biloma or abscess seen on imaging, followed by PTC with placement of an external biliary drainage catheter (or bilateral catheters for type E4 injuries). No attempt should be made to internalize the biliary drainage catheter(s) until the patient becomes clinically stable.²⁸ Stable patients with jaundice and/or biloma may also undergo ERCP, and if a type A injury is clearly demonstrated, then drainage of the biloma and temporary biliary stenting until the leak ceases will usually solve the problem. To adequately define anatomy and plan repair of most other injuries, specifically those

involving excluded ducts, requires imaging of both the upper and lower bile ducts with both ERCP and PTC. Failure to adequately define the biliary anatomy and extent of injury by cholangiography predicts eventual failure of any repair.²⁴ Although there is no level 1 evidence to guide the timing of repair, we generally complete the necessary perioperative imaging studies and repair injuries within 24 hours of transfer under the following conditions: (1) the transfer occurs within 0 to 3 days of the injury, (2) peritoneal contamination is minimal and well drained, (3) the patient has no signs or symptoms of cholangitis or sepsis, and (4) there is no radiographic evidence of major vascular injury. Patients with bile peritonitis, abscesses, and cholangitis are managed as described above, and definitive repair is delayed for at least 3 months. Likewise, repair is delayed 3 months in patients with major vascular injuries to better establish the level of associated ductal ischemia and resulting stricture.

OPERATIVE TECHNIQUE

Step 1: Exposure of the Porta Hepatis

In patients who have sustained a biliary injury, particularly those who have already undergone attempted repair, local inflammation may obliterate the normal tissue planes and lead to significant distortions of the normal portal anatomy. The following are some useful techniques for safely

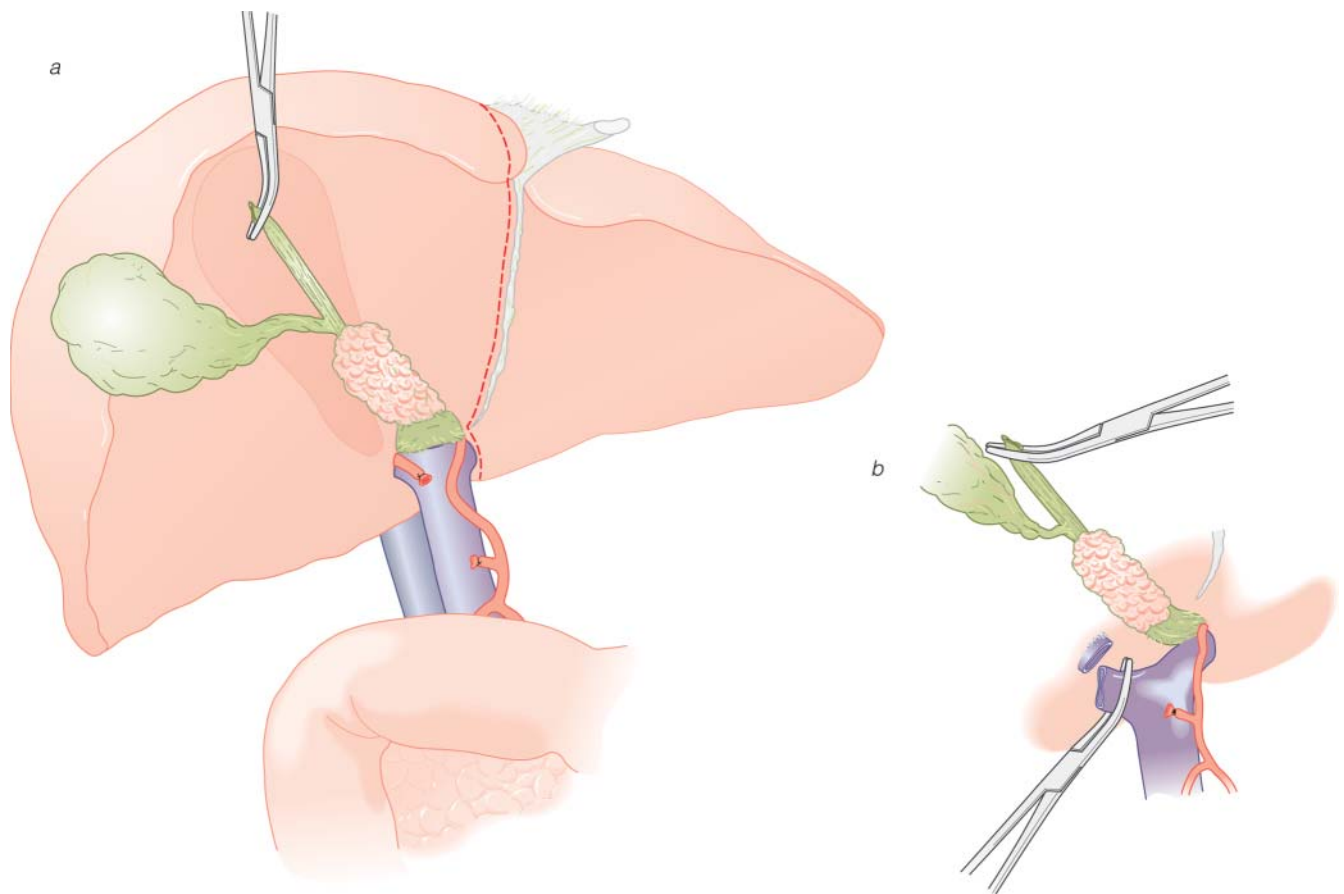


Figure 15 Resection of middle-third and proximal bile duct tumors. Shown is the resection of type II, IIIa, and IV proximal tumors. (a) The CBD is retracted upward and to the right; the right hepatic artery is divided; and the left portal vein and the left hepatic artery, which are to be saved, are exposed. (b) The right portal vein is divided.

defining the anatomy and avoiding potentially devascularizing dissection within the porta hepatis.

1. Use the round ligament to find the true porta hepatis. Patients who have already undergone one or more operations on the bile duct often have adhesions between the hepatoduodenal ligament and segment 4 of the liver. If one dissects this area via the anterior approach, one may think that the actual porta hepatis has been reached but notice that the hepatoduodenal ligament appears unusually short. In most cases, one can safely find the true porta by tracing the round ligament to the point where it joins the left portal pedicle and the umbilical portion (or ascending branch) of the left portal vein. To completely expose the umbilical fissure, the bridge of liver tissue between segment 4b and the left lateral section must first be divided. This tissue is devoid of any major vascular or biliary structures and may be safely divided with electrocautery. One may then follow the pedicle toward the right along the true porta. The adhesions between the hepatoduodenal ligament and segment 4b are more easily divided from the left than from the front.

2. Use aids to dissection. Usually, structures in the hepatoduodenal ligament can be identified by inspection and palpation, especially if a biliary stent is in place. When repairing complex, high biliary injuries (e.g., types E4 and E5), we routinely place percutaneous stents preoperatively for this purpose. Intraoperative Doppler ultrasonography may be useful in identifying the hepatic artery and the portal vein. Intraoperative ultrasonography may also be helpful in identifying the bile duct, and needle aspiration may be used before the duct is incised if there is any doubt about its location. Either blunt or sharp dissection is effective in this area. Our preference is to use a long fine right-angle clamp to obtain exposure in a layer-by-layer fashion. We then carefully cauterize or ligate and divide the exposed tissue.

Step 2: Defining the Duct

Carefully débride crushed, cauterized, or devitalized tissue back to normal healthy tissue. When performing a delayed repair, it is not necessary to resect all scar tissue around the duct. Just be certain that the anastomosis is constructed to healthy duct mucosa proximal to the injury and not to granulation tissue at the opening in the duct.

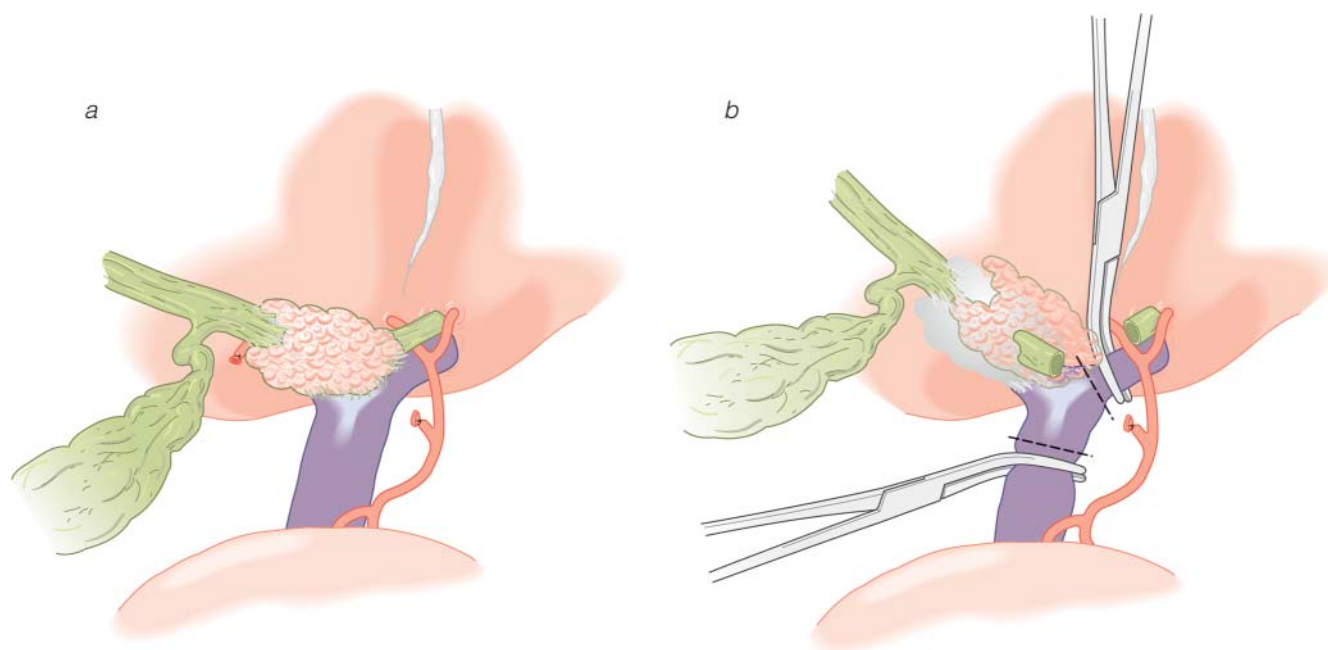


Figure 16 Resection of middle-third and proximal bile duct tumors. (a) Occasionally, a type III or IV proximal tumor will involve the portal vein bifurcation. (b) Shown is the resection of an involved portal vein bifurcation. Reconstruction is accomplished in an end-to-end fashion.

Step 3: Anastomosis

For all types of repair, construct a Roux-en-Y loop of sufficient length to make a tension-free anastomosis and perform a biliary-enteric anastomosis as previously described.

INJURY-SPECIFIC REPAIRS

E1- and E2-Type Injuries

Make a longitudinal incision in the anterior portion of the exposed duct and perform a vertical side-to-side anastomosis.

E3-Type Injuries

It is very rare for the left duct to be injured during a laparoscopic cholecystectomy; therefore, the left duct is also

less involved in the ensuing inflammatory processes that affect the common and right hepatic ducts. The surgeon can take advantage of this fact when repairing an E3-type injury. This injury is at the level of the confluence, but the confluence remains intact, and drainage of the left hepatic duct alone is sufficient to establish drainage for the entire liver. Using the techniques described above, identify and expose the extrahepatic left duct at the base of segment 4, make a longitudinal incision in the duct, and perform a transverse side-to-side bilioenteric anastomosis [see Figure 18]. This technique,

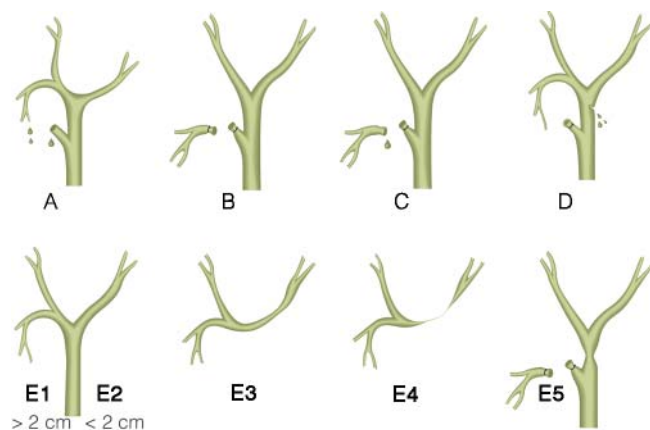


Figure 17 Strasberg classification of biliary injuries.

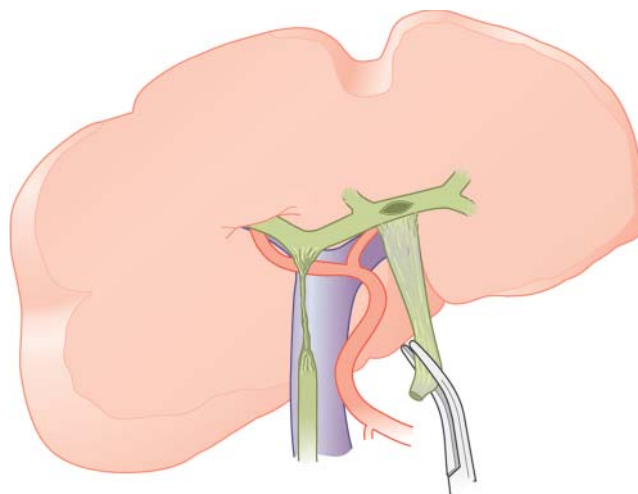


Figure 18 Hepp-Couinaud approach to repair of a Type E3 bile duct injury.

described by Hepp and Couinaud in 1956,²⁹ is known as the Hepp-Couinaud technique. We recently published our experience with this technique, which provides excellent long-term results.³⁰

E4- and E5-Type Injuries

In these types of injuries, all (E4) or some portion (E5) of the right ductal system is isolated from the left ductal system. Therefore, the Hepp-Couinaud approach provides adequate drainage only for those segments of liver with bile ducts in continuity with the left hepatic duct. The excluded right side must be drained separately, but inflammation and scar tissue make exposing the right duct more challenging. Rather than attempting to dissect out the right duct directly, begin the dissection along the left hepatic duct and under the base of

segment 4, rolling the base of segment 4 upward (lowering the hilar plate). The takeoff of the right duct is located within the same coronal plane as the left duct, so keep the dissection in this same plane, continuing to the right until encountering the attachment of the cystic plate to the right portal pedicle. Divide this fibrous tissue band and then elevate and dissect the liver at the base of segment 5, exposing the sheath of the right portal pedicle. Palpate the previously placed stent to confirm the position of the right bile duct within the sheath. Intrahepatic exposure of the right pedicle is usually possible and a well-vascularized, uninjured duct can be identified for anastomosis. In extremely rare cases of very proximal right-sided injuries, hepatic resection may be required.³¹

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Figures 1 to 17 Elizabeth Hayden
Figure 18 Christine Kenney

23 HEPATIC RESECTION

*Clifford S. Cho, MD, and Yuman Fong, MD, FACS**

Although first described centuries ago, the majority of liver resections were performed for management of trauma or infection until the latter half of the 20th century. Today, partial hepatectomy is performed not only for treatment of acute emergencies but also as potentially curative therapy for a variety of benign and malignant hepatic lesions.^{1–5}

The first planned anatomic resection of a lobe of a liver is credited to Lortat-Jacob, who performed a right hepatic lobectomy in 1952 as treatment for metastatic colon cancer.⁶ However, it was not until the 1980s that major hepatectomies became commonplace. Since that time, the safety of hepatic resection has improved dramatically; moreover, as the safety of the operation has improved, the indications for hepatic resection have broadened. Currently, resection of as much as 85% of functional liver parenchyma is being performed at numerous centers with an operative mortality of less than 2%. The duration of hospitalization is typically well less than 2 weeks, and nearly all patients regain normal hepatic function postoperatively.⁷

In this chapter, we focus on the technical aspects of hepatic resection, emphasizing efficiency and safety and taking into account recent developments, current controversies, and special operative considerations (e.g., the cirrhotic patient and repeat liver resection). Detailed discussions of the indications for hepatic resection are available elsewhere.^{8–10}

Hepatic Anatomy

Safe operative conduct during partial hepatectomy demands a close familiarity with the surgical anatomy of the liver.¹¹ In 1998, in response to the confusion created by various anatomic nomenclatures applied to the liver, the International Hepato-Pancreato-Biliary Association (IHPBA) appointed a committee charged with establishing a universal terminology for hepatic anatomy and hepatic resections. In 2000, the recommendations of this committee were accepted at IHPBA's biannual meeting in Brisbane. Accordingly, this system for naming the anatomic divisions of the liver and their corresponding resections has come to be known as the Brisbane 2000 terminology.¹²

In the Brisbane 2000 system, the anatomy of the liver may be thought of in terms of first-order, second-order, and third-order divisions, all of which are based on the underlying vascular and biliary anatomy and not on surface features [see Figure 1]. At the first level, the liver is divided into two hemilivers (right and left). At the second level, it is divided into four sections (right posterior, right anterior, left medial, and left lateral). At the third level, it is divided into nine

segments, each of which is a discrete anatomic unit that possesses its own nutrient blood supply and venous and biliary drainage.

The right hemiliver consists of segments V through VIII and is nourished by the right hepatic artery and the right portal vein; the left hemiliver consists of segments II through IV and is nourished by the left hepatic artery and the left portal vein. (The caudate lobe, a portion of the liver that is separate from the two hemilivers, consists of segments I and IX.) The anatomic division between the right hemiliver and the left hemiliver is not at the falciform ligament (the most readily apparent visual landmark on the anterior liver) but follows the principal scissura (or Cantlie line) that runs posterosuperiorly from the medial margin of the gallbladder to the left side of the inferior vena cava.

The venous drainage of the liver consists of multiple small veins draining directly from the back of the right hemiliver and the caudate lobe to the inferior vena cava, along with three major hepatic veins. These major hepatic veins occupy three planes, known as portal scissurae. The three scissurae divide the liver into the four sections, each of which is supplied by a portal pedicle; further branching of the pedicles subdivides the sections into their constituent segments. The right hepatic vein passes between the right anterior section (segments V and VIII) and the right posterior section (segments VI and VII) in the right scissura. This vein empties directly into the vena cava near the atriocaval junction. The middle hepatic vein passes between the right anterior section and the left medial section (segment IV, sometimes subdivided into segments IVa and IVb) in the principal scissura that divides the right and left hemilivers. The left hepatic vein runs in the left scissura between segments II and III (which together comprise the left lateral section). In most persons, the left and middle hepatic veins join to form a common trunk before entering the inferior vena cava. Occasionally, a large inferior right hepatic vein is present that can provide adequate drainage of the right hemiliver after resection of the left even when all three major hepatic veins are ligated.¹³

The portal vein and hepatic artery divide into left and right branches below the hilum of the liver. Unlike the major hepatic veins, which run between segments, the portal venous and hepatic arterial branches, along with the hepatic ducts, typically run centrally within segments [see Figure 1]. On the right side, the hepatic artery and the portal vein enter the liver substance almost immediately after branching. The short course of the right-sided extrahepatic vessels and the variable anatomy of the biliary tree make these vessels vulnerable to damage during dissection.¹⁴ In contrast, the left branch of the portal vein and the left hepatic duct take a long extrahepatic course after branching beneath the undersurface of segment IV. When these vessels reach the base of the umbilical fissure, they are joined by the left hepatic artery to form a triad, which

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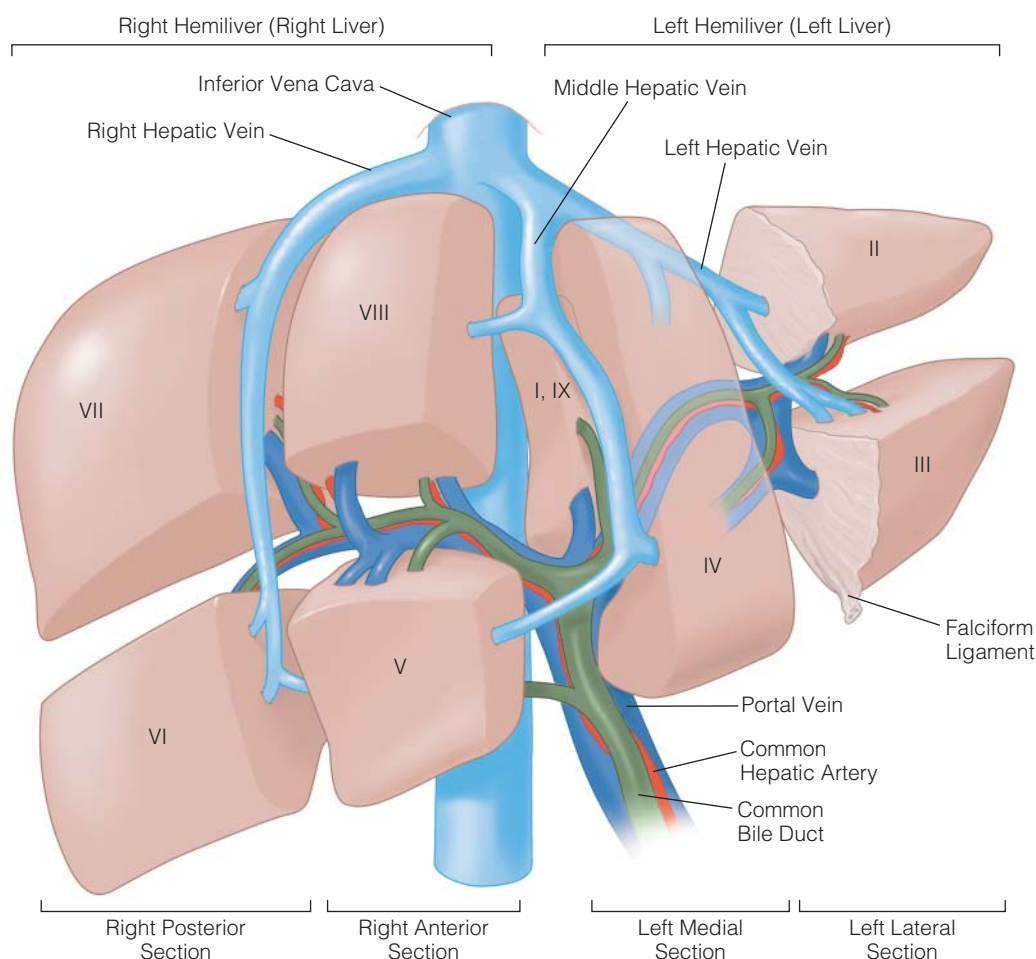


Figure 1 The liver is separated into nine anatomic segments, each with an independent nutrient blood supply and venous and biliary drainage. Appreciation of this segmental anatomy is the basis of anatomic resection of the liver.

then enters the substance of the left hemiliver. Importantly, the left-sided structures are not a triad proximal to the base of the umbilical fissure. This long extrahepatic course makes operative exposure of the left-sided structures far easier than on the right. A surgical consequence of this anatomy is that when a choice exists between extended right hepatectomy and extended left hepatectomy [see Operative Technique, *below*] for resection of tumors involving the hepatic hilum (e.g., Klatskin tumors), most surgeons choose the former because of the greater ease of dissection and preservation of the left-sided structures. Knowledge of the relative anatomic courses of the portal veins, hepatic arteries, and hepatic ducts is the basis of the classic extrahepatic dissection for control of hepatic inflow [see Operative Technique, Right Hepatectomy, Step 6 (Extrahepatic Dissection and Ligation): Control of Inflow Vessels, *below*].

The fibrous capsule surrounding the liver substance was described by Glisson in 1654.¹⁵ It was Couinaud, however, who demonstrated that this fibrous capsule extends to envelop the portal triads as they pass into the liver substance.¹⁶ Thus, within the liver parenchyma, the portal vein, hepatic artery, and hepatic duct running to each segment of the liver lie within a substantive sheath. This dense sheath facilitates rapid control of inflow vessels to specific anatomic units

within the liver and permits en masse ligation of these vascular structures in a maneuver known as pedicle ligation [see Operative Technique, Right Hepatectomy, Step 6—Alternative (Intrahepatic Pedicle Ligation): Control of Inflow Vessels, *below*].¹⁷

Preoperative Evaluation

Cross-sectional imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography play important roles in enhancing the safety and efficacy of hepatic resection. These modalities, along with biologic scanning techniques such as positron emission tomography (PET), are also invaluable for staging malignancies so as to improve patient selection and thereby optimize long-term surgical outcomes.³

At a minimum, all candidates for hepatic resection should undergo either CT or MRI. These imaging tests not only identify the number and size of mass lesions within the liver but also delineate the relationships of the lesions to the major vasculature—data that are crucial for deciding whether to operate and which operative approach to employ.

Use of contrast enhancement during CT scanning is vital for accurate definition of the vascular anatomy. Data from

thin-slice (1 to 2 mm) images captured by current spiral (helical) CT scanners can be reconstructed to provide angiographic images whose level of detail rivals that of direct angiograms [see Figure 2]. Triple-phase scans (including a noncontrast phase, an arterial phase, and a venous phase) are recommended as these permit optimal definition and characterization of intrahepatic lesions. For example, some vascular tumors become isodense with liver parenchyma after contrast injection. By first obtaining noncontrast scans and then obtaining contrast scans at two different times after contrast injection, the likelihood of detecting such tumors is enhanced.

For small tumors, CT portography may be employed. In this technique, contrast material is injected through the superior mesenteric artery, and images are obtained during the portal venous phase. The normal liver receives the majority of its nutrient blood from the portal vein and is therefore contrast enhanced in this phase. Tumors, on the other hand, usually derive their nutrient blood from the hepatic artery and therefore appear as exaggerated perfusion defects. For this reason, CT portography is highly sensitive for identifying small hepatic tumors.¹⁸

MRI may also be valuable for characterizing lesions and defining their relationships with the vasculature. It is particularly helpful in diagnosing benign lesions such as hemangioma, focal nodular hyperplasia, and adenoma. Whenever any of these benign lesions is suspected, MRI is typically indicated. With regard to surgical planning, magnetic resonance angiography is useful for identifying the major hepatic veins and clarifying their relationship to tumors.¹⁹

Over the past decade, biologic imaging in the form of ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET), has emerged as an invaluable technique for preoperative staging of patients with hepatic malignancies. In patients with hepatic metastases being considered for resection, FDG-PET can identify occult foci of disease not detected by other modalities that may represent contraindications to operative

intervention. In this way, incorporation of FDG-PET into the diagnostic regimen of these patients can decrease the incidence of nontherapeutic laparotomy²⁰ and improve long-term survival among cases where resection is indicated.²¹ Of note, the role of FDG-PET in the evaluation of patients with primary hepatocellular carcinoma (HCC) is less clear in that many HCC tumors cannot be distinguished from the surrounding liver through assessment of glucose metabolism alone.

To summarize imaging recommendations, a triple-phase CT scan should be obtained for most patients being considered for hepatic resection. If diagnostic doubt remains after CT, particularly if the differential diagnosis includes an asymptomatic benign tumor, MRI should be performed. If questions remain after CT as to the extent of hepatic venous or major biliary involvement, MRI or duplex ultrasonography should be considered.²² If small tumors are encountered, CT portography may be helpful for further characterization. By demonstrating the vascular hilar structures, hepatic veins, and inferior vena cava, duplex ultrasonography obviates the need for angiography in many cases.^{19,23} For patients with liver metastases from colorectal cancer,⁴ breast cancer, or melanoma, FDG-PET imaging should be performed before hepatic resection. Direct hepatic angiography is rarely required, and inferior vena cavography is almost never necessary.

Operative Planning

PREPARATION

In general, preparation for hepatic resection is similar to preparation for any other major abdominal procedure. Patients with a history of cardiopulmonary disease undergo a full cardiopulmonary assessment. It was once believed that patients over the age of 70 years were poor candidates for major liver resection,^{24,25} but this notion has been dispelled by

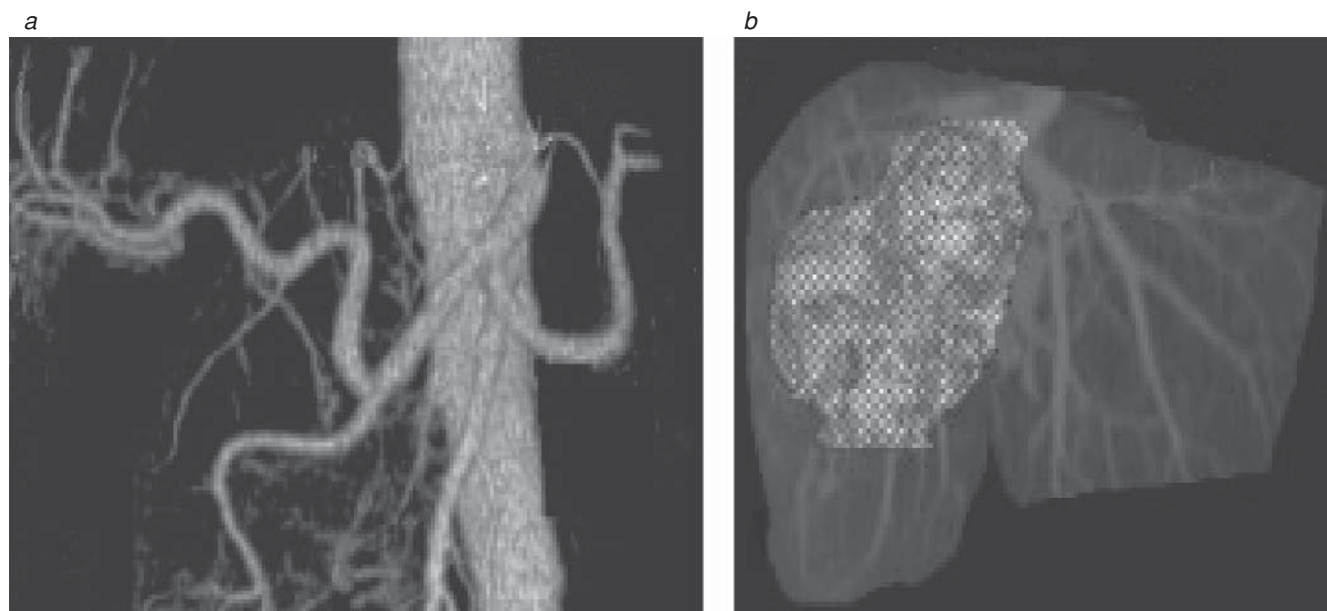


Figure 2 (a) The arterial anatomy of the celiac axis is reconstructed from thin-slice computed tomographic images. (b) The hepatic venous anatomy is similarly reconstructed, with the tumor superimposed on the vascular reconstruction.

more recent data^{26–28}; advanced chronologic age is not an absolute contraindication to partial hepatectomy.

If present, anemia and coagulopathy are corrected in the preoperative period. If feasible, patients may be encouraged to donate two units of autologous blood before undergoing major partial hepatectomy. Alternatively, hemodilution, in which a portion of the patient's blood volume is withdrawn intraoperatively and reinfused immediately after the completion of the hepatectomy, may be considered.

Appropriate single-dose antibiotic prophylaxis is administered in the immediate preoperative period.

ANESTHESIA

Considerations regarding anesthesia should account for the possibilities of baseline hepatic dysfunction from underlying liver disease, as well as postoperative hepatic dysfunction resulting from resection of large portions of hepatic parenchyma. The most important consideration, however, is the possibility of major intraoperative hemorrhage. Suitable hemodynamic monitoring and sufficient vascular access to permit rapid transfusion must be established prior to liver resection. In the past, fluid resuscitation and blood transfusions were often initiated early in the course of resection to increase intravascular volume as a buffer against sudden blood loss. The opposite approach is currently favored, in which a low central venous pressure is intentionally maintained before and during hepatic parenchymal transection. The rationale for this approach is that most hemorrhage encountered during hepatic resection is a result of venous back-bleeding from major hepatic veins or the inferior vena cava.^{29,30} Maintenance of central venous pressures below 5 mm Hg combined with elevation of liver tissue results in less back-bleeding from the hepatic venous radicles during dissection. Reduction of intrahepatic venous pressure can be facilitated by placing the patient in a 15° Trendelenburg position, which increases venous return to the heart and enhances cardiac output. Central venous pressure is maintained at the desired level through a combination of anesthesia and early intraoperative fluid restriction.

The need for intraoperative blood transfusion can be minimized by accepting hematocrit levels of 24% in patients without antecedent cardiac disease and 29% in patients with significant cardiac disease. If blood loss is estimated to reach or exceed 20% of total volume, or if the patient becomes hemodynamically unstable, transfusion is warranted.^{29,30}

PATIENT POSITIONING

The patient should be placed in a supine position; even for patients with very large tumors, we have not found a left lateral decubitus position to be necessary. Electrocardiographic leads should be kept clear of the right chest wall and the presternal area in the event that a thoracoabdominal incision becomes necessary because of difficulties with liver mobilization or intraoperative hemorrhage. Preparation and draping should therefore also allow for satisfactory exposure of the lower chest and the entire upper abdomen down past the umbilicus. A crossbar or a similar device that holds self-retaining retractors should be used to elevate the costal margin in an anterosuperior direction. Ring-based self-retaining retractors are also adequate for most resections; however, particularly in large patients, the rings can restrict

lateral access during posterior dissection, particularly when mobilizing the right hemiliver off the diaphragm and inferior vena cava.

ANATOMIC VERSUS NONANATOMIC RESECTION

A key decision when planning partial hepatectomy is whether to undertake an anatomic or nonanatomic resection. In the treatment of malignant disease, anatomic resection is generally favored as the long-term outcome appears to be improved. Anatomic resections result in the excision of parenchymal areas distal to the index tumors, where vascular micrometastases may reside. In addition, they are significantly less likely to result in positive resection margins. In a large series of partial hepatectomies performed for metastatic colorectal cancer, wedge or nonanatomic resections were associated with a 19% rate of positive margins.³¹ In another analysis, wedge resections were associated with a 16% rate of positive margins compared with a 2% rate seen with anatomic resections.³²

Importantly, there are two oncologic settings in which nonanatomic resections are favored. In patients with HCC, viral hepatitis and cirrhosis are often complicating underlying factors. Cirrhotic patients do not tolerate resection of more than two segments of functional parenchyma well; for these patients, the smallest resection that will achieve complete tumor excision is favored even if it involves a nonanatomic wedge resection. In patients with hepatic neuroendocrine metastases, for whom resections are cytoreductive procedures often designed to alleviate symptoms, nonanatomic resections are acceptable because the likelihood of cure is very small.³³

Hepatic resections for benign tumors are usually performed for one of three reasons: (1) symptom alleviation (e.g., pain or early satiety), (2) diagnostic uncertainty, or (3) prevention of malignant transformation.³⁴ One goal of these resections should be to spare as much normal parenchyma as possible. Consequently, lesions such as hemangiomas, adenomas, complex cysts, and focal nodular hyperplasia are commonly excised by means of enucleation or other nonanatomic resections with limited margins.

Operative Technique

In theory, any hepatic segment may be resected in isolation. For practical purposes, however, there are six major types of anatomic resection. As stated earlier, we employ the Brisbane 2000 terminology for hepatic resection [see *Figure 3*].

The core principles of all anatomic hepatic resections are the same: (1) control of inflow vessels, (2) control of outflow vessels, and (3) parenchymal transection. To illustrate these principles, we begin by outlining the steps involved in right hepatectomy [see *Figure 3a*] in some detail, describing both extrahepatic vascular dissection and ligation and the alternative intrahepatic pedicle ligation approach to inflow control. Left hepatectomy [see *Figure 3b*] and other common anatomic resections [see *Figure 3, c, d, e, f*] share a number of steps in common with right hepatectomy; accordingly, we discuss them in less detail. Further detail on these procedures is available in other sources.^{35,36}

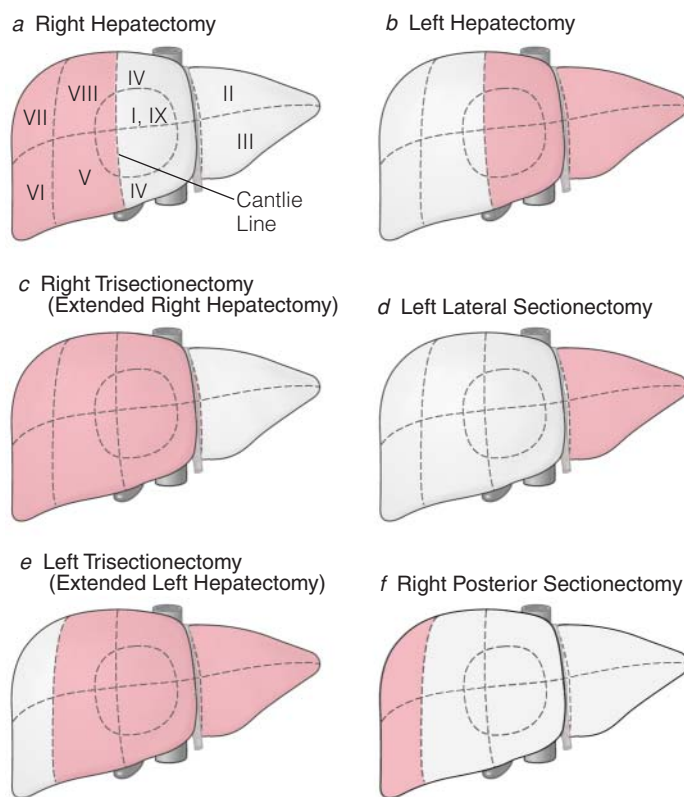


Figure 3 Shown are schematic illustrations of standard hepatic resections, with the shaded areas representing the resected portions: (a) right hepatectomy, (b) left hepatectomy, (c) right trisectionectomy (extended right hepatectomy), (d) left lateral sectionectomy, (e) left trisectionectomy (extended left hepatectomy), and (f) right posterior sectionectomy.

RIGHT HEPATECTOMY (RIGHT HEMIHEPATECTOMY)

Step 1: Laparoscopic Inspection

Laparoscopic examination of the peritoneal cavity can detect unresectable metastases that cannot be visualized by cross-sectional imaging, thereby preventing the morbidity associated with a nontherapeutic laparotomy.^{37–40} We generally perform laparoscopy immediately before laparotomy during the same period of anesthesia. The laparoscopic port sites are placed in the upper abdomen along the line of the intended incision [see Step 2, below]. The first two ports are usually 5 or 10 mm ports placed in the right subcostal area along the midclavicular line and along the anterior axillary line. These ports allow inspection of the abdomen and of the entire liver, including the dome and segment VII. A 10 mm port along the right anterior axillary line is particularly suitable for laparoscopic ultrasound devices. If additional ports are necessary, a left subcostal midclavicular port is usually the best choice.

Step 2: Incision

If no evidence of distant or unresectable metastasis is identified at the time of laparoscopy and an open hepatic resection is planned, an incision that will afford optimal exposure of the liver is made. For most hepatic resections, many surgeons use a bilateral subcostal incision extended vertically to the xiphisternum [see Figure 4]. Our preference is to use an upper midline incision extending to a point approximately 2 cm above the umbilicus, with a rightward extension to a point in the midaxillary line halfway between the right costal margin and the right anterior superior iliac spine [see

Figure 4]. This incision provides superb access for both right- and left-sided resections and avoids the wound complications often encountered with trifurcated incisions (e.g., ascites leak, incisional hernia). On rare occasions (e.g., resection of large and rigid posterior tumors of the right hemiliver), a right thoracoabdominal incision may be required. However, in a series of nearly 2,000 resections performed at Memorial Sloan-Kettering Cancer Center, a thoracoabdominal incision was necessary in only 3% of cases, with the most common indication being repeat liver resection after previous right hepatectomy [see Repeat Hepatic Resection, below].

Step 3: Abdominal Exploration and Intraoperative Ultrasonography

Exploration commences with bimanual palpation of the entire liver. Intraoperative ultrasonography (IOUS) is then performed systemically to identify all lesions and their relation to the major vascular structures. IOUS is capable of identifying small lesions that preoperative imaging studies and palpation of the liver may miss.⁴¹ The lesser omentum is incised to allow examination of the caudate lobe and inspection of the celiac axis nodal metastases. A finger is passed from the lesser sac inferior to the caudate lobe through the foramen of Winslow to permit identification of the portal vein and palpation of the portocaval lymph nodes. The hilar lymph nodes are palpated, and any suspicious nodes may be excised and submitted for frozen-section pathologic analysis. If the operation is being undertaken for malignancy, the entire abdomen is also inspected for evidence of extrahepatic tumors.

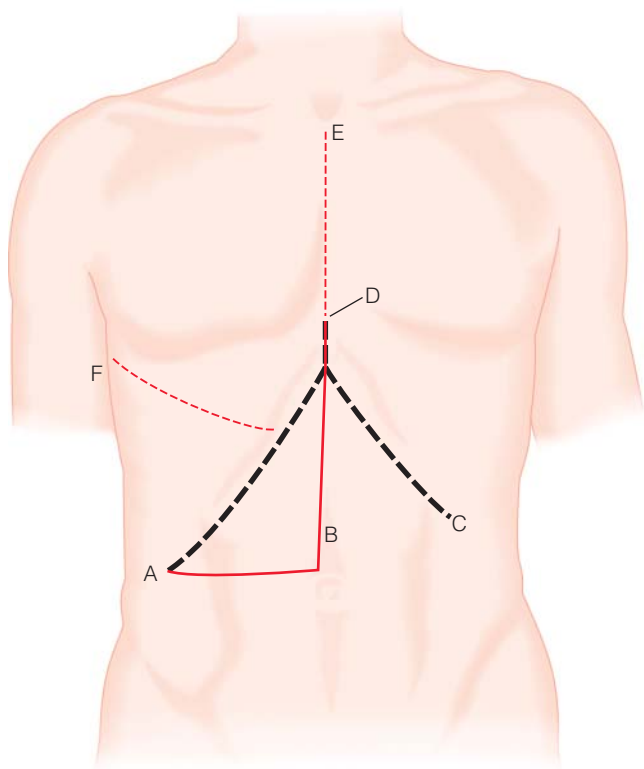


Figure 4 Right hepatectomy. A right subcostal incision (A) with a midline extension to the xiphoid (D) is the most common choice; an extension to the left subcostal area (C) is sometimes added to provide further operative exposure. We prefer a long midline incision from the xiphoid (D) to a point approximately 2 to 3 cm above the umbilicus (B) along with a rightward extension (A) because this incision provides superb exposure of both the right side and the left without the wound complications of a trifurcated incision. The chest can be entered through either a median sternotomy (E) or an anterolateral right thoracoabdominal incision (F).

Step 4: Mobilization of Liver

Once the decision is made to proceed with hepatic resection, the liver is fully mobilized by detaching all ligamentous attachments on the side to be resected. (Some surgeons defer completion of mobilization to a later stage in the procedure.) In particular, the falciform ligament is divided and the suprahepatic inferior vena cava and the hepatic veins above the liver are dissected to facilitate the subsequent approach to the hepatic veins [see Step 7: Control of Outflow Vessels, below]. Early mobilization of the liver will facilitate additional bimanual palpation to detect small lesions that may have been obscured during the initial examination. This additional palpation is particularly important on the right side as the right posterior section cannot be effectively examined prior to mobilization, and IIOUS may fail to detect small lesions in this area.⁴¹

During the course of mobilization, if tumor is found to be attached to the diaphragm, the affected area of diaphragm may be excised and subsequently repaired.

Step 5: Identification of Arterial Anomalies

The presence of possible hepatic arterial anomalies should be verified before resection is initiated. With contemporary

imaging techniques, the arterial anatomy can usually be defined with sufficient exactitude prior to laparotomy. However, it is also possible to clarify the arterial anatomy intraoperatively with several simple maneuvers that do not involve major dissection.

The lesser omentum should be examined to determine whether there is a vessel coursing through its middle to the base of the umbilical fissure, and the hepatoduodenal ligament should be palpated with an index finger within the foramen of Winslow to determine whether there is an artery in the gastropancreatic fold along its medial aspect. The usual bifurcation of the hepatic arteries occurs low and medially within the hepatoduodenal ligament, and the left hepatic artery normally travels on the medial aspect of the ligament to reach the base of the umbilical fissure. Therefore, an artery palpable in the medial upper portion of the hepatoduodenal ligament is the main left hepatic artery. If the main left hepatic artery is identified in this manner, any vessel identified in the lesser omentum must be an accessory left artery. If no arterial structure is found in the medial upper portion of the hepatoduodenal ligament, the vessel in the lesser omentum must be a replaced left hepatic artery. The right hepatic artery typically travels transversely behind the common bile duct (CBD) to reach the base of the cystic plate. An artery traversing vertically along the lateral hepatoduodenal ligament must therefore be either a replaced or an accessory right hepatic artery, likely arising from the superior mesenteric artery.

Step 6 (Extrahepatic Dissection and Ligation): Control of Inflow Vessels

The classic approach to controlling the inflow vessels during right hepatectomy involves extrahepatic dissection and ligation [see Figure 5]. The cystic duct and the cystic artery are ligated and divided. The gallbladder may be either removed or left attached to the right hemiliver, according to the surgeon's preference. A common practice is to first ligate the right hepatic duct, then the right hepatic artery, and finally the right portal vein, working from anterior to posterior. However, our preference is to work from posterior to anterior.

The sheath of the porta hepatis is opened laterally. Dissection is performed in the plane between the CBD and the portal vein. To facilitate this dissection, the CBD is elevated by applying anterior traction to the ligated cystic duct. The portal vein is followed in a cephalad direction until its bifurcation into the left and right portal veins is visible. Visualization of this bifurcation is critical because the left portal vein arises from the right anterior branch of the portal vein in a small percentage of patients. If the main right portal vein is ligated in a patient with this anatomic variant, portal flow to the entire liver, including the remnant left hemiliver, will be lost. There is usually a small portal branch that passes from the main right portal vein to the caudate process; ligation of this branch will untether an additional 1 to 2 cm of the right portal vein, allowing safer dissection and ligation. The right portal vein can be occluded with vascular clamps, divided, and oversewn with nonabsorbable sutures. Once divided, the right hepatic artery becomes readily visible behind the CBD and can be easily secured and ligated with nonabsorbable sutures. Because of the multitude of biliary anatomic variations, we typically leave the right hepatic duct intact until

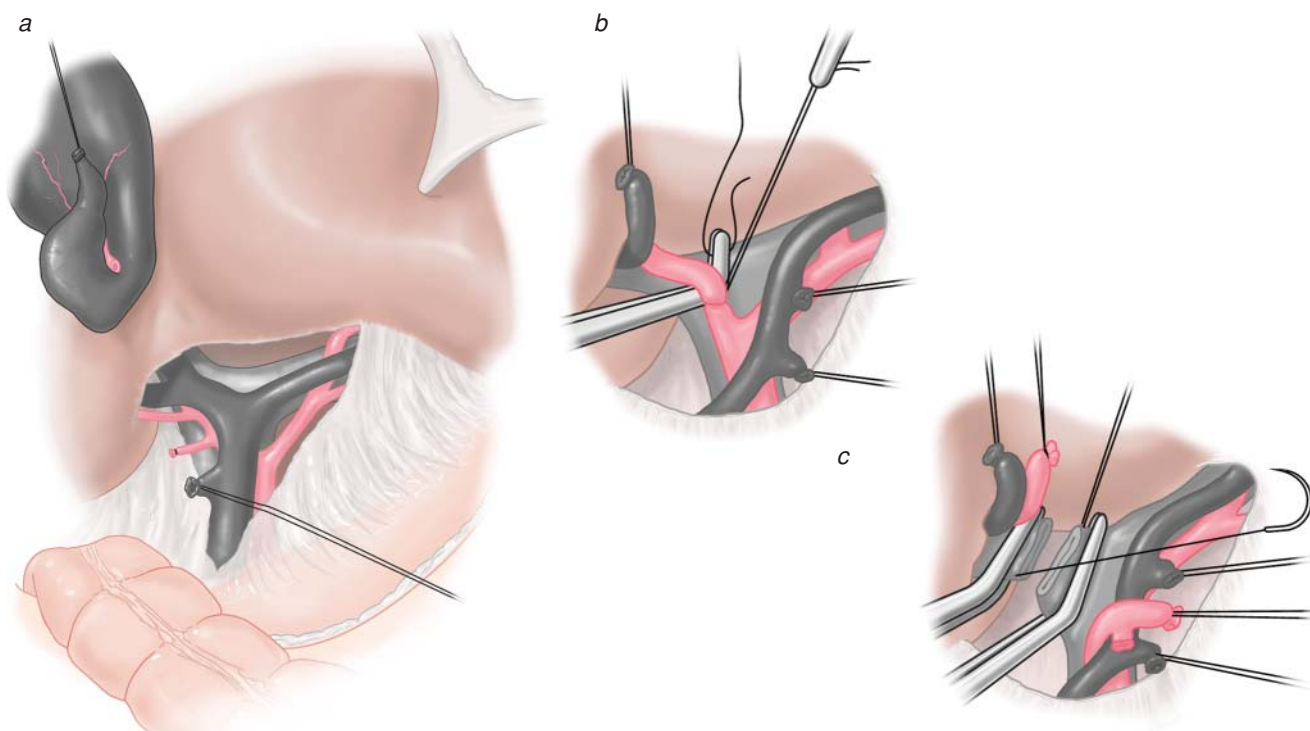


Figure 5 Right hepatectomy. For control of the inflow vessels of the right hemiliver, the liver is retracted cephalad to allow exposure of the porta hepatis. (a) The gallbladder is resected to allow access to the bile duct and hepatic vessels. (b) The right hepatic duct is ligated to allow access to the hepatic artery and the portal vein. (c) After the right hepatic artery is divided, the right portal vein is controlled and divided. Alternatively, the vessels may be approached from a posterolateral direction and the portal vein and hepatic artery may be divided first, with the hepatic duct left intact until the parenchymal transection.

parenchymal dissection [see Step 8: Parenchymal Dissection, below] is begun; this structure can then be divided higher within the hepatic parenchyma to minimize the likelihood of injury to the left ductal system. Once the portal vein and hepatic artery are divided, a clear line of ischemic demarcation of the right hemiliver will be visible along the Cantlie line.

Staple ligation Alternatively, vascular staplers may be used to divide the right or the left portal vein during extrahepatic vascular dissection^{42,43}; in most cases, suture ligation of the extrahepatic portal veins is such a straightforward technical exercise that staplers add little except cost.

Step 6—Alternative (Intrahepatic Pedicle Ligation): Control of Inflow Vessels

As stated above, Glisson and Couinaud observed that the nutrient vessels to the liver are contained within a thick connective tissue capsule [see Figure 6]; this was the basis for the initial proposal by Launois and Jamieson that intrahepatic vascular pedicle ligation could serve as an alternative to extrahepatic dissection and ligation for controlling vascular inflow to the liver.¹⁷ This alternative technique has the advantages of being rapid and less likely to cause injury to the vasculature or the biliary drainage of the contralateral liver. Using this technique, one can readily access and isolate the major pedicles to the areas of liver to be resected using simple combinations of hepatotomies at specific sites along the inferior surface of the liver [see Figure 7].

In this approach, the right hemiliver is completely mobilized from the retroperitoneum. The most inferior small hepatic veins are ligated, and the inferior right hemiliver is mobilized off the vena cava. Incisions are made in the liver capsule at hepatotomy sites A and B [see Figure 7]. The first incision is made through the caudate lobe. The full thickness of the caudate lobe is divided with a combination of diathermy, crushing, and ligation. The second incision is made almost vertically in the medial part of the gallbladder bed. Both incisions must be fairly substantive and reasonably deep. Care must be taken to avoid the terminal branches of the middle hepatic vein, particularly along hepatotomy site B, as this is the most common source of bleeding. Using either finger dissection or passage of a large curved clamp (e.g., a renal pedicle clamp), a tape is placed around the right main sheath [see Figure 8]. This tape can be pulled medially to provide better exposure of the intrahepatic right pedicle and to retract the left-sided structures away from the area to be clamped and divided. Vascular clamps are applied, the right pedicle is divided, and the stumps are suture-ligated.

In practice, for right hepatectomy, we prefer to isolate the right anterior and posterior pedicles separately [see Figure 8] and ligate them individually. By dividing the right inflow structures higher within the liver, this measure ensures that the left-sided structures cannot be injured. Any minor bleeding from a hepatotomy usually ceases spontaneously or with application of Surgicel into the wound.

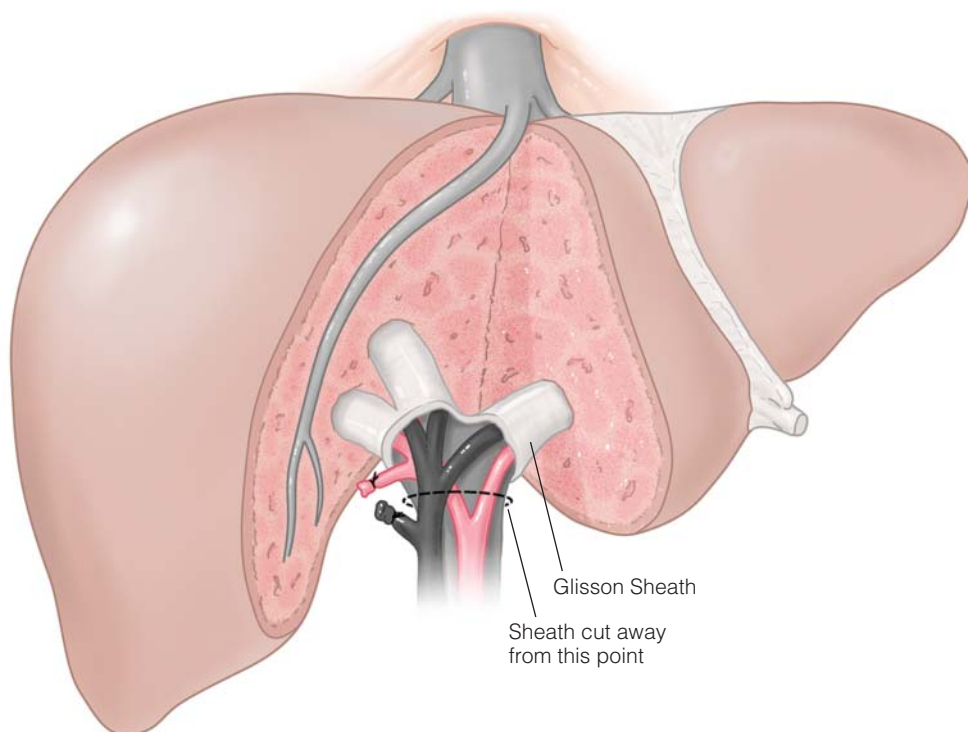


Figure 6 Right hepatectomy. The Glisson sheath is a vascular and biliary pedicle that contains the portal triad. If this sheath is not violated, the entire pedicle can be suture-ligated or staple-ligated with confidence and safety.

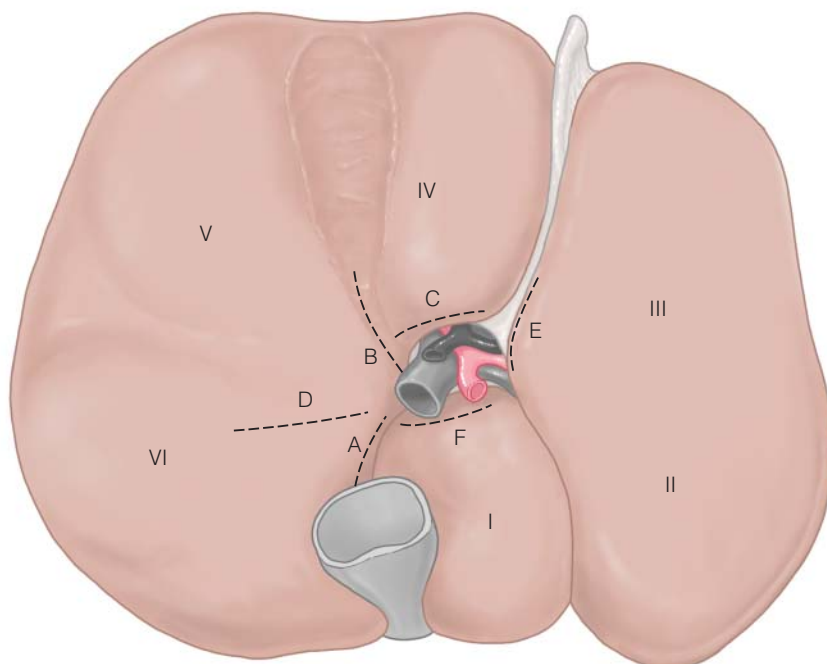


Figure 7 Right hepatectomy. Depicted are sites where hepatotomies can be made to permit isolation of various vascular pedicles. Incisions at sites A and B allow isolation of the right main portal pedicle. Incisions at sites A and D allow isolation of the right posterior portal pedicle. Incisions at sites B and D allow isolation of the right anterior pedicle. Incisions at sites C and E allow isolation of the left main portal pedicle; if the caudate lobe is to be removed, incisions are made at sites C and F. The Roman numerals refer to the hepatic segments.

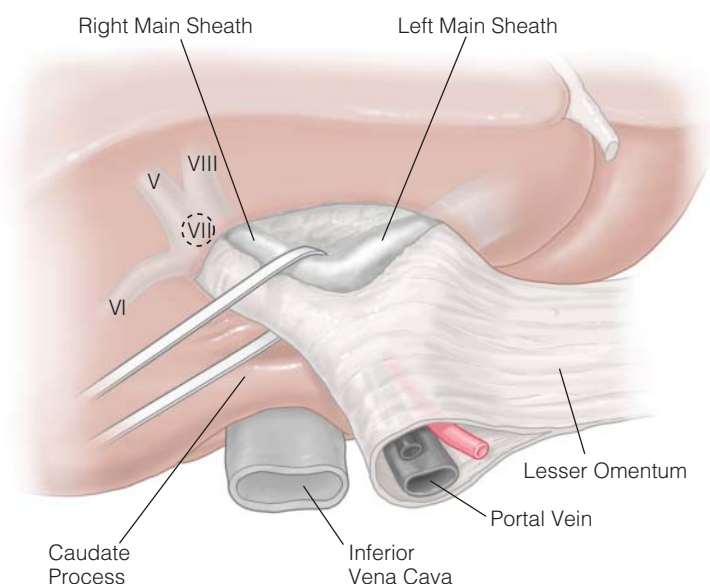


Figure 8 Right hepatectomy. Depicted is isolation of the main right portal pedicle. The pedicle is controlled with a vascular tape and retracted from within the liver substance. This tape can be used for countertraction when a vascular clamp or stapler is applied. The main right portal pedicle has anterior and posterior branches. The right anterior pedicle consists of pedicles to segments V and VIII. The right posterior pedicle usually consists of only the segment VI pedicle but may also give rise to the segment VII pedicle.

Staple ligation The use of staplers is now well established for liver resections^{42–47}; we have found that staple ligation greatly increases the speed with which intrahepatic portal pedicle ligations can be performed. To control the intrahepatic portal pedicles for a right hepatectomy, incisions are made at hepatotomy sites A and B [see Figure 7]. Ultrasonography directed from the inferior aspect of the liver helps determine the depth at which the right pedicle lies, which is usually 1 to 2 cm from the inferior surface. The right main pedicle is secured and encircled with an umbilical tape [see Figure 9a]. The hilar plate along the base of segment IV is lowered via an incision at hepatotomy site C [see Figure 7] to ensure that the left-sided vascular and biliary structures are mobilized well away from the area of staple ligation. A transverse anastomosis (TA) vascular stapler is applied to the right main pedicle while firm countertraction is applied to the umbilical tape to pull the hilum to the left [see Figure 9a]. The stapler is fired, and the pedicle is divided [see Figure 9b].

Troubleshooting Several important principles should be followed when considering intrahepatic pedicle ligation. The most important is that intrahepatic pedicle ligation should not be undertaken when resection is being performed for a tumor located within 2 cm of the hepatic hilum. In these cases, extrahepatic dissection should be performed to avoid potential violation of the tumor margin.

From a technical standpoint, removal of the gallbladder greatly facilitates isolation and control of right-sided vascular pedicles in a right hepatectomy. Application of the Pringle maneuver decreases bleeding during hepatotomy and isolation of the pedicle. Also, the lowest hepatic veins behind the liver should be dissected before any attempt is made to isolate the right-sided portal pedicles as incising the caudate lobe without first dividing the small hepatic veins draining this portion of the liver to the inferior vena cava can lead to troublesome hemorrhage.

Step 7: Control of Outflow Vessels

Control of the outflow vessels begins with division of the hepatic veins passing from the posterior aspect of the right hemiliver directly into the inferior vena cava. After the right hemiliver is completely mobilized off the retroperitoneum by dividing the right triangular ligament, it is carefully dissected off the vena cava. Dissection proceeds in a cephalad direction from the inferior border of the liver until the right hepatic vein is exposed. Complete mobilization of the right hemiliver is particularly critical for tumors close to the vena cava. Exposure of the right hepatic vein usually requires division of the inferior vena caval ligament, which connects the right hemiliver to the diaphragm along the right lateral aspect of the right hepatic vein. The right hepatic vein is then isolated, cross-clamped, divided, and oversewn [see Figure 10]. Unless the lesion to be resected involves the middle hepatic vein close to its junction with the vena cava, the middle hepatic vein usually is not controlled extrahepatically for right-sided resections and can be easily secured during parenchymal transection.

In cases where a large tumor resides at the dome of the liver, control of the hepatic veins and the vena cava may prove very difficult. In this circumstance, one should not hesitate to extend the incision into the chest with a right thoracoabdominal extension. The morbidity of a thoracoabdominal incision is preferable to the potentially catastrophic hemorrhage that may be encountered when the right hepatic vein is torn during mobilization of a rigid right hemiliver containing a bulky tumor.

Staple ligation Staple ligation has proven very useful for outflow control during partial hepatectomy. When the tumor is in proximity to the hepatic vein–inferior vena cava junction, extrahepatic control of the hepatic veins is essential for excision of the tumor with clear margins, and limits blood loss during parenchymal transection.⁴⁸ Ligation of the hepatic veins, particularly when an adjacent large and rigid tumor is

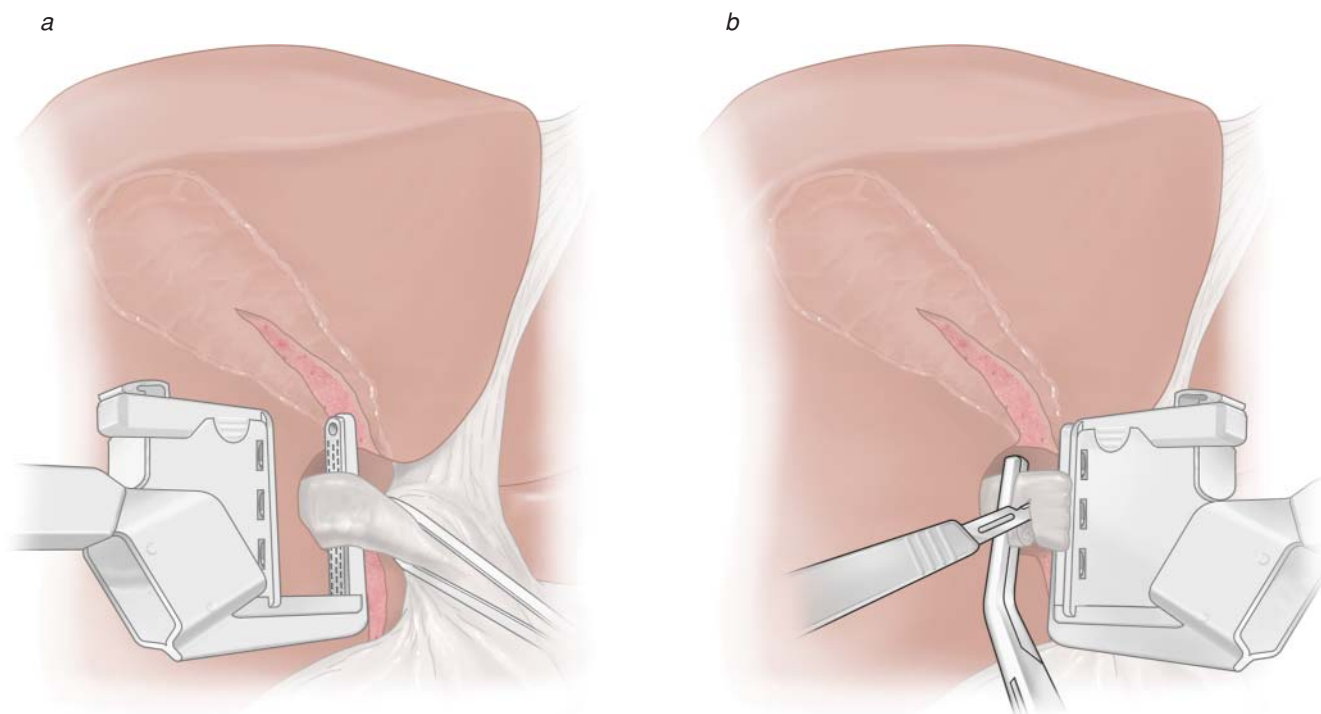


Figure 9 Right hepatectomy. Shown is staple ligation of the right portal pedicle. (a) After the liver is incised across the caudate lobe and along the gallbladder bed, the right main pedicle is isolated and held with an umbilical tape. Countertraction is placed on the umbilical tape while a transverse anastomosis vascular stapler is placed across the pedicle, allowing the left hepatic duct and the left vascular structures to be retracted away from the line of stapling. (b) After the stapler is fired, the pedicle is clamped and divided.

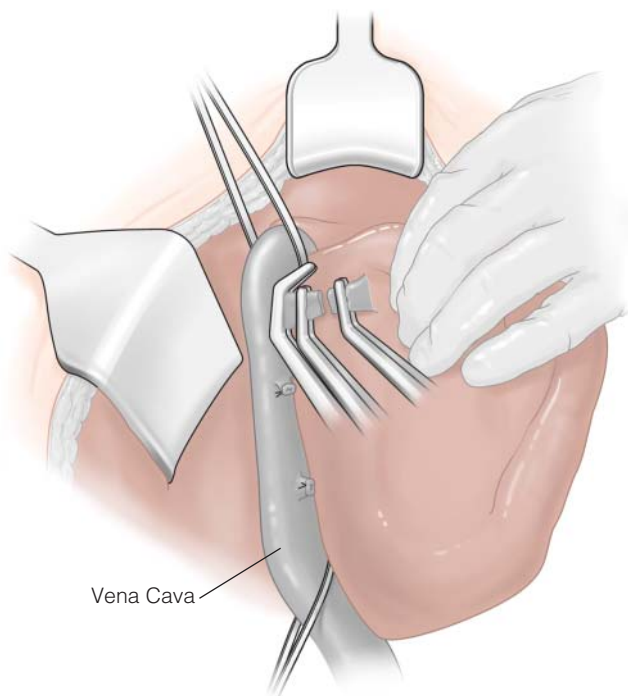


Figure 10 Right hepatectomy. Once the small perforating vessels to the vena cava have been ligated, further dissection cephalad leads to the right hepatic vein. This vessel is controlled with vascular clamps and divided.

present, can be a technically demanding and dangerous exercise. Tearing the hepatic vein or the inferior vena cava during this maneuver is the most common cause of major intraoperative hemorrhage.³⁶ The linear cutting stapler is well suited for ligation of the major hepatic veins because of its low profile and ability to seal the hepatic vein on the inferior vena cava and resection specimen sides simultaneously.

For staple ligation of the right hepatic vein, the right hemiliver is mobilized off the vena cava. Any large accessory right hepatic vein encountered can also be staple-ligated, as can the tongue of liver tissue that often passes from the right hemiliver behind the vena cava to the caudate lobe. The right hepatic vein is then identified and isolated. Although some surgeons introduce the stapler from the top of the liver downward,⁴³ we find that the location of the liver high in the surgical wound can make this angle of introduction difficult. Rather, we typically introduce the stapler parallel to the vena cava and direct it from below upward [see Figure 11]. To ensure that the stapler does not misfire, care should be taken to confirm that no vascular clips are present near the area where the stapler is to be applied.

Step 8: Parenchymal Transection

Inflow to the left hemiliver can be temporarily interrupted by clamping the hepatoduodenal ligament (the Pringle maneuver). The safety of temporary occlusion of the vessels supplying the hepatic remnant is well documented. Even in patients with cirrhosis, the warm ischemia produced by

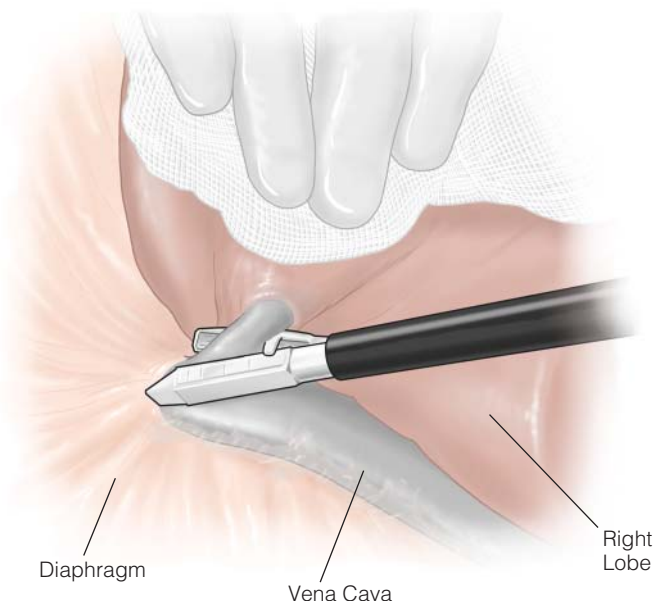


Figure 11 Right hepatectomy. As an alternative to clamping and division, the right hepatic vein may be staple-ligated. Once the small perforating tributaries from the right hemiliver to the vena cava have been divided, the right hepatic vein is isolated and ligated with an endoscopic gastrointestinal anastomosis (GIA) vascular stapler. The safest method for introducing this stapler is to retract the liver cephalad and to the left while advancing the stapler cephalad in the direction of the vena cava.

continuous application of the Pringle maneuver is well tolerated for as long as 1 hour.⁴⁹ Our practice is to apply the Pringle maneuver intermittently for periods of 10 minutes, with 2 to 5 minutes of perfusion between applications to allow for intestinal venous decompression.

Parenchymal division is then initiated along the line demarcated by devascularization of the right hemiliver. The line of transection along the principal plane is marked with the electrocautery, and the Glisson capsule is cut with scissors. Stay sutures of 0 chromic catgut are placed on either side of the plane of transection and used for traction, separation, and elevation as dissection proceeds.

Many special instruments have been proposed for use in parenchymal transection, including electrocautery, ultrasonic dissectors, and water-jet dissectors. For the majority of hepatic resections, we find that blunt clamp dissection is the most rapid method and is quite safe. In this technique, a large Kelly clamp is used to crush the liver parenchyma [see Figure 12]. The relatively soft liver substance dissects away, leaving behind the vascular and biliary structures, which are then ligated with vascular clips. Using this technique, the principal plane of the liver can usually be transected in less than 30 minutes.

In cirrhotic patients, the clamp-crushing technique may not work well because the vessels will often tear before the firm liver parenchyma does. Accordingly, ultrasonic dissectors that coagulate while transecting the parenchyma may be a better choice for cirrhotic patients. Water-jet dissectors may be useful in defining the major intrahepatic vascular pedicles or the junction of the hepatic vein and the vena cava, particularly when the tumor is in close proximity.

After the specimen is removed, the raw surface of the hepatic remnant is carefully examined for hemostasis and bile leakage. Any oozing from the raw surface may be controlled with the argon beam coagulator. Bile leaks should be controlled with clips or suture ligation. The retroperitoneal

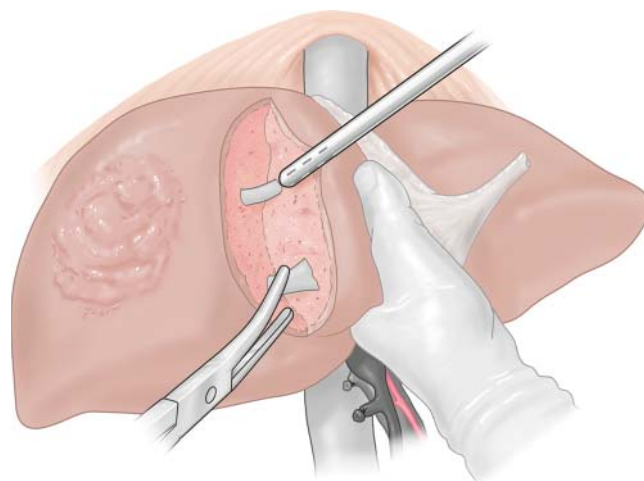


Figure 12 Right hepatectomy. The parenchyma can be quickly and safely transected by means of the clamp-crushing technique. Large vessels and biliary radicles are visualized and ligated or clipped. This is usually done in tandem with inflow occlusion (i.e., the Pringle maneuver). Alternatively, the parenchyma can be bluntly dissected away by means of the finger-fracture technique.

surfaces should be examined carefully for hemostasis, and the argon beam coagulator can be used where necessary.

Step 9: Closure and Drainage

The abdominal wall is closed in one or two layers with continuous absorbable monofilament sutures. The skin is closed with staples or subcuticular sutures. Drains are unnecessary in most routine cases⁵⁰; in fact, they may introduce harmful effects by promoting ascending infection or fluid management problems if ascites develops postoperatively. We

reserve use of drains for four clinical scenarios: (1) evidence of a clear bile leakage, (2) an infected operative field, (3) operations involving a thoracoabdominal incision (in which a drain is used to ensure that any bile leakage does not develop into a peritoneopleural fistula), and (4) operations involving biliary reconstruction.

LEFT HEPATECTOMY (LEFT HEMIHEPATECTOMY)

Steps 1 through 5

Left hepatectomy involves removal of segments II, III, and IV and sometimes I and IX as well. The first five steps of the procedure are much the same as those of a right hepatectomy, except that the left hemiliver is mobilized by dividing the falciform ligament and left triangular ligaments.

Step 6 (Extrahepatic Dissection and Ligation): Control of Inflow Vessels

Extrahepatic control of vascular inflow vessels can be achieved in essentially the same fashion as in a right-sided resection. Our preference is to start the dissection at the base of the umbilical fissure, dividing the left hepatic artery first. The left portal vein is then easily identified at the base of the umbilical fissure. The point at which the left portal vein is to be divided depends on the extent of the planned parenchymal resection [see Figure 13]; if the caudate lobe is to be preserved, the left portal vein is divided just distal to its caudate branch (line B); if the caudate lobe is to be removed, the left portal vein is divided proximal to the origins of the portal venous branches to the caudate lobe (line A).

Step 6—Alternative (Intrahepatic Pedicle Ligation): Control of Inflow Vessels

If a left hepatectomy is undertaken to treat benign disease or to remove a malignancy that is remote from the base of the umbilical fissure, we recommend performing stapler-assisted intrahepatic pedicle ligation in preference to extrahepatic dissection and ligation.

The left portal pedicle is identified at the base of the umbilical fissure. The hilar plate is lowered through an

incision at hepatotomy site C [see Figure 7], and a second incision is made along the back of segment II at hepatotomy site E [see Figure 7], permitting isolation of the left portal pedicle with minimal risk of injury to the right-sided inflow vessels at the hilum. If the caudate lobe is to be removed as well, incisions should be made at hepatotomy sites C and F [see Figure 7] to allow isolation of the main left portal pedicle proximal to the vessels nourishing the caudate. The portal pedicle is isolated and encircled with an umbilical tape. In the course of dividing the left portal pedicle, the middle hepatic vein, which lies immediately lateral to the left portal pedicle, may be injured. To minimize this risk, firm downward traction is applied to the umbilical tape, and a TA-30 vascular stapler is placed across the left portal pedicle [see Figure 14], which is then stapled and divided.

Step 7: Control of Outflow Vessels

The left hemiliver is reflected to the right, and the entire lesser omentum is divided. The ligamentum venosum is identified between the caudate lobe and the back of segment II and is divided near its attachment to the left hepatic vein; this greatly facilitates identification and dissection of the left and middle hepatic veins anterior to the inferior vena cava. The left and middle hepatic veins are isolated in preparation for division.

Control of the left hepatic vein is quickly and safely accomplished with staple ligation. In approximately 60% of patients, the left and middle hepatic veins join to form a single trunk before entering the vena cava. In a left hepatectomy, the middle hepatic vein may be left intact, in which case, it must be protected while ligating the left. After the left hepatic vein is identified, an endoscopic gastrointestinal anastomosis (GIA)-30 vascular stapler is directed from above downward [see Figure 15] to divide this vessel. The liver is retracted to the right to permit visualization of the junction of the left and middle hepatic veins. If ligation of the middle hepatic vein is desired as well, as is the case when there is tumor in proximity to the vessel, this can be accomplished with a stapler directed along the same path used for left hepatic vein ligation.

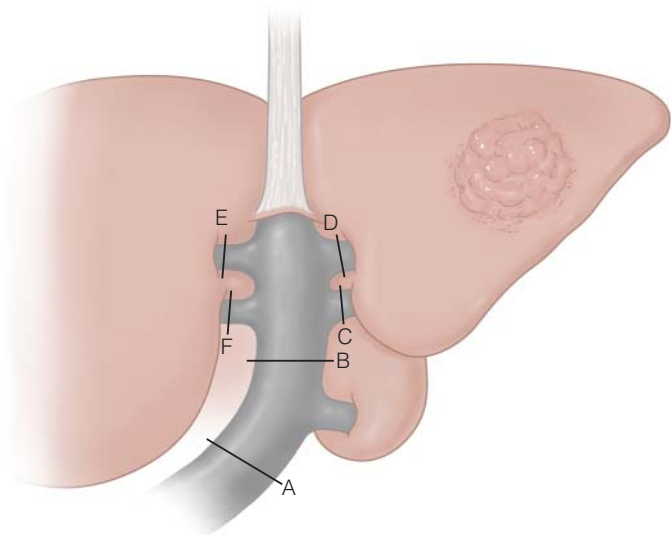


Figure 13 Left hepatectomy. Ligation of vascular pedicles at specific sites in the left hemiliver interrupts inflow to specific areas. Ligation at A interrupts inflow to the entire left hemiliver, as well as the caudate lobe. Ligation at B interrupts blood flow to the left liver while sparing the caudate lobe. Ligation at C devascularizes segment II, and ligation at D devascularizes segment III. Ligation at E and F devascularizes segment IV.

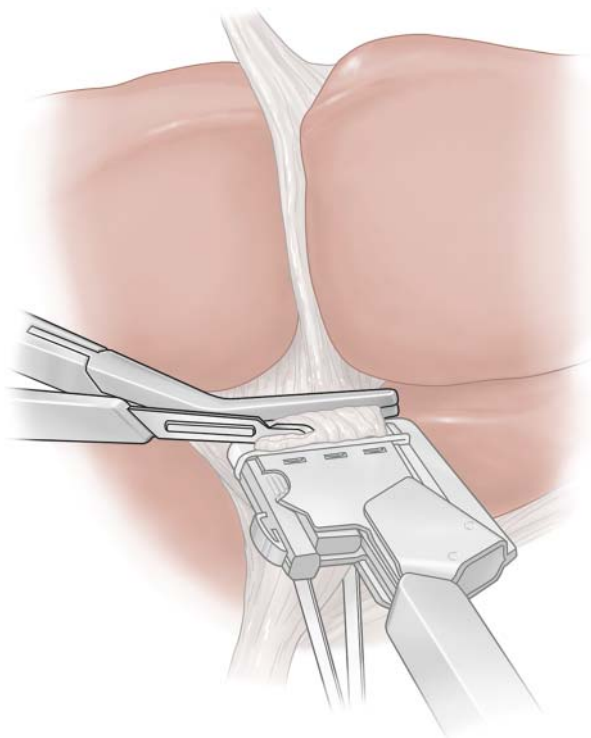


Figure 14 Left hepatectomy. After hepatotomies in segment IV and in the back of segment II, the left portal pedicle is isolated, stapled, and divided.

Steps 8 and 9

Parenchymal transection and closure are accomplished in much the same manner in a left hepatectomy as in a right hepatectomy (see above).

OTHER ANATOMIC RESECTIONS

In the following reviews of the other types of major anatomic resections, we focus primarily on the ways in which they differ from right and left hepatectomy. More detailed discussions of these operations are available in specialty texts on liver resection.^{35,36}

Right Trisectionectomy (Extended Right Hepatectomy)

Right trisectionectomy (extended right hepatectomy) involves removal of the right hemiliver along with segment IV, thereby resecting all liver tissue to the right of the falciform ligament [see Figure 3c]. The initial steps of this operation are the same as those for right hepatectomy, up through division of the right inflow vessels and the right hepatic vein.

The next step is devascularization of segment IV. The umbilical fissure is dissected to permit identification of the vascular pedicles to segments II, III, and IV, which lie within this fissure [see Figure 13]. In most patients, the lower part of the umbilical fissure is concealed by a bridge of liver tissue fusing segments II and III to segment IV. After this tissue bridge is divided with diathermy, the ligamentum teres is retracted caudally to reveal the vascular pedicles from the umbilical fissure to segment IV (lines E and F [see Figure 13]). We generally suture-ligate these pedicles before dividing them.

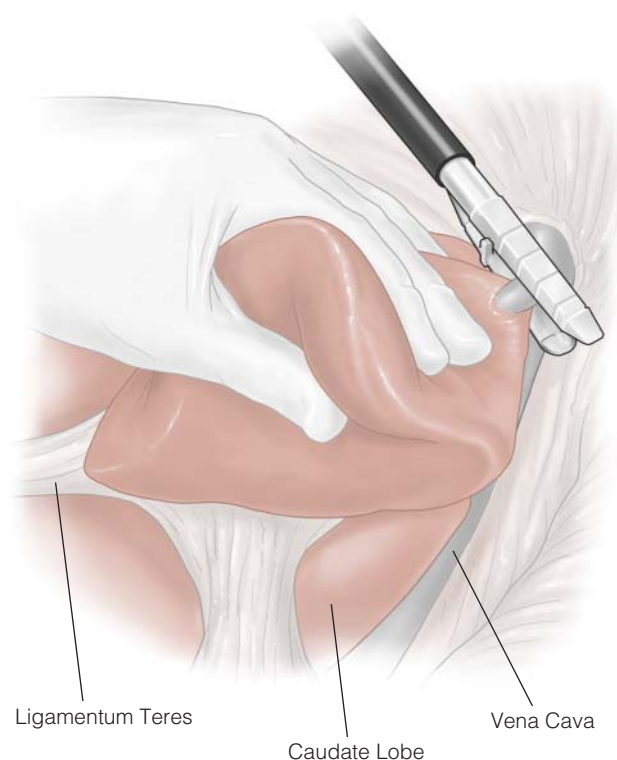


Figure 15 Left hepatectomy. Staple ligation of the left hepatic vein. After the left hemiliver is completely mobilized through division of the left triangular ligament and the lesser omentum, the left hepatic vein is isolated and ligated with an endoscopic GIA vascular stapler. The best angle for introducing the stapler is from the xiphoid posteriorly and caudad.

The liver tissue is then transected immediately to the right of the falciform ligament, from the anterior surface back toward the divided right hepatic vein. The middle hepatic vein is generally left intact until it is encountered in the upper part of the parenchymal transection, at which point it is either suture- or staple-ligated.

Left Lateral Sectionectomy

A left lateral sectionectomy involves removal of only segments II and III, thereby resecting all liver tissue to the left of the falciform ligament [see Figure 3d]. These segments are mobilized by dividing the falciform ligament and left triangular ligaments. As this is done, care is taken to avoid injury to the left hepatic and phrenic veins, which run along the medial portion of the left triangular ligament.

The falciform ligament is retracted caudally, and the bridge of liver tissue between segment IV and segments II and III is divided with diathermy. Dissection is performed along the left of the umbilical fissure. The vascular pedicles to segments II and III are readily dissected and controlled (lines C and D [see Figure 13]). Control of these pedicles within the umbilical fissure is particularly important for tumor clearance if tumor is in proximity to the umbilical fissure: if the condition is benign or if tumor is remote from the umbilical fissure, the liver may be split anteroposteriorly just to the left of the ligamentum teres and the falciform ligament, and the vascular

pedicles may be identified and ligated as they are encountered during the course of parenchymal transection.

Once the inflow vessels have been ligated, the left hepatic vein is identified and divided either before parenchymal transection or as the vessel is encountered near the completion of parenchymal transection. If there is tumor near the dome, it is particularly important for tumor clearance that the left hepatic vein be controlled and ligated early and outside the liver.

Left Trisectionectomy (Extended Left Hepatectomy)

A left trisectionectomy (extended left hepatectomy) involves resection of segments II, III, IV, V, and VIII and sometimes segments I and IX [see Figure 3e]. This is effectively a left hepatectomy combined with a right anterior sectionectomy, with or without resection of the caudate lobe. This complex resection is usually undertaken to excise large tumors occupying the left hemiliver and crossing the principal scissura into the right anterior section.

Throughout this procedure, it is imperative that the right hepatic vein be preserved as it represents the sole venous drainage of the intended hepatic remnant. However, parenchymal transection must often be performed along the course of this vein; therefore, the major risk in the operation is injury to the right hepatic vein, which could result in hemorrhage or hepatic failure from venous congestion of the hepatic remnant. In addition, because the blood supply to segment VII often arises from the right anterior portal pedicle or from the junction of the right anterior and posterior pedicles [see Figure 8], there is a risk of devascularization of a large portion of the hepatic remnant. Finally, the enormous variability of biliary anatomy and the extensive intrahepatic dissection required in this procedure increase the risk of biliary complications.⁵¹ For these reasons, left trisectionectomies are rarely performed outside major centers.⁵²

When planning a left trisectionectomy, particularly close attention must be paid to preoperative imaging investigations so that the right-sided intrahepatic vessels and biliary structures may be accurately delineated. Thin-slice CT and MRI in the form of arterial, portal venous, and hepatic venous reconstructions [see Figure 2] are quite helpful in this regard. For large tumors encroaching on the hepatic hilum or on the junction of the right anterior and posterior pedicles, direct angiography may be helpful on occasion.

The liver is fully mobilized by dividing the peritoneal attachments of the left and right hemilivers. This is essential for identifying the correct plane of parenchymal dissection and for ensuring safe dissection along the right hepatic vein.

The initial dissection is the same as for a left hepatectomy. The liver is turned to the right, the inflow vessels to the left hemiliver are divided, and the left hepatic vein and the subdiaphragmatic inferior vena cava are dissected free. The left and middle hepatic veins are controlled and divided extrahepatically.⁵² The left hemiliver is thus freed, facilitating dissection of the right hemiliver.

Next, the plane of transection within the right hemiliver is defined. This plane runs horizontally and lies lateral to the gallbladder fossa and just anterior to the main right hepatic venous trunk in the right scissura, halfway between the right anterior pedicle and the right posterior pedicle. The plane can be approximated by drawing a line from just anterior to

the right hepatic vein at its insertion into the vena cava to a point immediately behind the fissure of Gans. This line can also be accurately defined by clamping the portal pedicle to the right anterior section of the liver.⁵² If the tumor is remote from the junction of the right anterior and posterior portal pedicles, the anterior pedicle is controlled as outlined earlier [see Right Hepatectomy, Step 6—Alternative (Intrahepatic Pedicle Ligation): Control of Inflow Vessels, *above*]. A vascular clamp is placed on the pedicle and the line of demarcation on the liver surface is carefully inspected before the pedicle is divided. If segment VII appears to be ischemic as well, further dissection must be done to identify and protect the origins of the vessels supplying segment VII.

Parenchymal dissection is carried out from below upward, with bleeding controlled by means of low central venous pressure anesthesia and intermittent application of the Pringle maneuver. If the caudate lobe is to be removed as part of the total resection, the veins draining the caudate must be controlled before parenchymal transection.

Segment-Oriented Resection

Each segment of the liver can be resected independently. In addition, right posterior sectionectomy (removal of segments VI and VII) [see Figure 3f] and right anterior sectionectomy (removal of segments V and VIII) are not uncommon. Extensive descriptions of so-called segment-oriented hepatic resection are available elsewhere.^{53,54}

Postoperative Care

Intravenous fluids administered postoperatively should include phosphorus for support of liver regeneration. For large-volume hepatic resections, electrolyte levels, blood count, and prothrombin time (PT) are checked after the operation and then daily for 3 to 4 days. Packed red blood cells may be administered if the hemoglobin level falls to 8 mg/dL or lower, and fresh frozen plasma may be given if the PT is longer than 17 seconds. Postoperative pain control is best achieved with patient-controlled analgesia or epidural analgesia. Because of the decreased clearance of hepatically metabolized drugs after a major liver resection, selection and dosing of pain medications should be adjusted accordingly. An oral diet can be resumed as early as postoperative day 1 or 2 unless a biliary-enteric anastomosis was performed.

Peripheral edema is common after major hepatic resections and may be treated with spironolactone. Unexplained fevers or isolated hyperbilirubinemia with otherwise normal liver enzymes raises the suspicion for an intra-abdominal biloma, for which CT imaging should be obtained. If a biloma is identified, percutaneous drain placement usually brings about resolution of these collections after a few days, and reoperation is rarely necessary.

Special Considerations

TOTAL VASCULAR ISOLATION FOR CONTROL OF BLEEDING

For control of bleeding during liver parenchymal transection, a technique known as total vascular isolation can be used as an alternative to the Pringle maneuver. In this technique, the liver is isolated by controlling the inferior vena

cava (both above and below the liver), portal vein, and hepatic artery. This approach is based on techniques developed for liver transplantation and on the observation that the liver is capable of tolerating total normothermic ischemia for as long as 1 hour.⁵⁵ Its primary advantage is that while the liver is isolated, little or no bleeding occurs. It does, however, have disadvantages as well. In some patients, temporary occlusion of the inferior vena cava causes hemodynamic instability resulting from reduced cardiac output coupled with increased systemic vascular resistance.⁵⁶ Cardiac failure with marked hypotension, arrhythmia, and even cardiac arrest may ensue. In addition, when hepatic perfusion is restored, the sudden return of stagnant potassium-rich blood to the systemic circulation can aggravate hemodynamic instability. For these reasons, and because bleeding is generally well controlled with low central venous pressure anesthesia, total vascular isolation is useful only in very rare cases. Indeed, one prospective analysis found that total vascular isolation had no major advantages over the approaches described earlier [see Operative Technique, Right Hepatectomy, Step 8: Parenchymal Transection, *above*] and was actually associated with greater blood loss.⁴⁸

The one setting in which total vascular isolation may have a significant role is in the resection of very large tumors that compromise the vena cava or the hepatic veins. To extend the duration of vascular isolation in this setting, venovenous bypass that vents the splanchnic blood into the systemic circulation may be used.⁵⁷ To further minimize parenchymal injury during vascular isolation, the liver may be perfused with cold organ preservation solutions. For extensive vascular invasion that necessitates major vena cava or hepatic venous reconstruction, some authors have suggested that the liver can be removed during venovenous bypass, with resection and reconstruction performed extracorporeally.⁵⁸

Although there are clinical situations that may call for these measures, they are very rarely necessary. Resection and reconstruction of short lengths of inferior vena cava can be performed quite safely without resorting to them. In fact, involvement of the retrohepatic vena cava at a level below the major hepatic veins can generally be treated with simple excision of the affected segment without replacement,⁵⁹ particularly if complete obstruction at this level has already led to established collateral venous circulation.

HANGING MANEUVER IN MAJOR HEPATECTOMY

The classic technique for a right hepatectomy (see above) involves complete mobilization of the right hemiliver before vascular control and parenchymal transection. However, in cases where the tumor has invaded the retroperitoneum or diaphragm, such mobilization may prove exceedingly difficult. Moreover, in cases where the tumor is large, soft, and vascular (e.g., HCC), early mobilization of the right hemiliver may increase the risk of tumor rupture. Finally, division of the vascular inflow and outflow vessels before manipulation of the tumor has the theoretical advantage of preventing vascular dissemination of cancer cells caused by compression of the tumor. For these reasons, some authors have proposed an anterior approach wherein the liver parenchyma is transected first, with ligation of the inflow and outflow vessels performed before mobilization of the right hemiliver.⁶⁰ This approach is now widely followed for resection of HCC.

Subsequently, other authors proposed a modification of this technique, whereby blunt dissection performed along the anterior surface of the vena cava permits passage of a tape that may be used to lift the liver and facilitate parenchymal transection [see Figure 16].⁶¹ The first step in this so-called “hanging maneuver” is to dissect the space between the right and middle hepatic veins in a downward direction for approximately 2 cm. Next, dissection is performed between the vena cava and the caudate lobe on the left side of the inferior right hepatic vein. A clamp is then passed along this plane in the notch between the right and middle hepatic veins, and an umbilical tape is passed for suspension of the liver. Transection of the parenchyma is performed in an anterior-to-posterior direction until the vena cava is reached. The right side of the vena cava is then dissected, and the right hepatic vein and the inferior hepatic veins are ligated. The triangular ligament and the retroperitoneal attachments are transected, and the specimen is removed.

THE CIRRHOTIC PATIENT

The reduction in hepatic functional capacity and reserve present in patients with cirrhosis places them at higher risk for posthepatectomy complications. As a result, the cirrhotic patient requires a very careful assessment of liver function, appropriate selection for surgery, possible alteration of operative technique, and closer attention to perioperative care.

Operative Planning

Selection of patients Hepatic failure is the major cause of hospital death and long-term morbidity after hepatic resection in cirrhotic patients.^{62–66} Consequently, determination of

SCORE

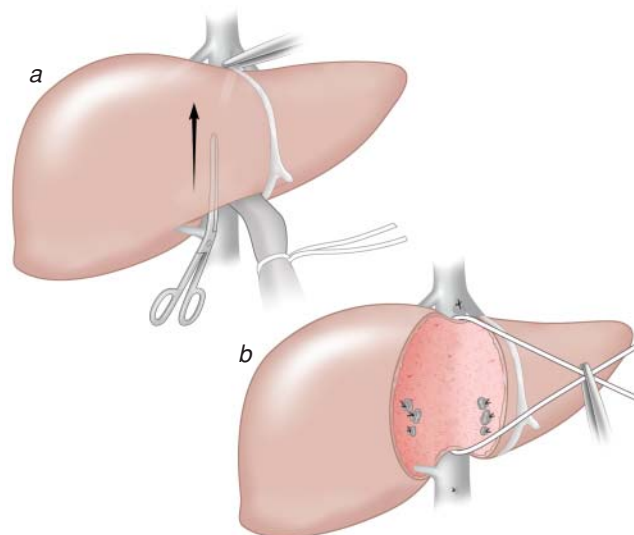


Figure 16 Illustrated is clamp dissection in preparation for the hanging maneuver. (a) A long vascular clamp is passed between the vena cava and the caudate lobe. This clamp is directed at the notch between the right and middle hepatic veins, which has been dissected from above. (b) An umbilical tape is then passed to suspend the plane of parenchymal transection.

a cirrhotic patient's candidacy for hepatectomy is based on a preoperative assessment of baseline liver function.

A variety of tests have been proposed for assessment of hepatic reserve, including measurement of clearance of various dyes and metabolic substrates.^{62,65,67–69} Measurement of elevated hepatic portal venous pressure gradients via invasive radiologic techniques and noninvasive Doppler ultrasonography have also been found to predict postoperative hepatic failure.^{70,71}

Currently, none of these functional tests are routinely performed at most major liver resection centers. In practice, the Child-Pugh score remains the most commonly employed clinical tool for selection of surgical candidates, with Child-Pugh scores higher than 8 being generally accepted as contraindications to major hepatic resection.^{64,66,72–75}

Operative approach The appropriate extent of resection for cirrhotic patients may be quite different from that which may be reasonable for patients without cirrhosis. A guiding principle for hepatectomy in cirrhotic patients is to favor limited resections that spare as much functional parenchyma as possible. In general, even for patients with well-compensated Child class A cirrhosis, we work to limit resections to less than two segments of functional liver. Major hepatic resections involving removal of at least one hemiliver are now reported to carry an operative mortality of less than 10% in cirrhotic patients.^{76,77} However, these procedures are usually performed in cirrhotic patients who have large tumors replacing most of one hemiliver, acceptable liver function, and no atrophy of the uninvolved hemiliver. Patients with large and peripheral tumors are more likely to tolerate a major resection because relatively little functional parenchyma is lost after tumor removal. Resection of small and deep-seated tumors can be more challenging; in such patients where resection might require removal of a large amount of functional hepatic parenchyma, an ablative alternative or even transplantation might be more suitable.

The effort to preserve as much functional liver as possible may make the resection more technically challenging. For example, multiple limited resections may be performed to avoid performing a formal hemihepatectomy.^{78,79} Some go so far as to reconstruct the right hepatic vein for the purpose of preserving venous outflow in segments V and VI after resection of segments VII and VIII. In cirrhotic patients, hepatectomy is most commonly performed for HCC.⁵ For such patients, as long as the resection margin is microscopically clear of cancer, the exact size of the margin does not correlate with the incidence of recurrent disease.⁸⁰ The acceptance of limited margins, coupled with the acceptance of non-anatomic resections aimed at preserving as much functional parenchyma as possible, has been responsible for significant improvements in the safety of hepatic resection in cirrhotic patients worldwide.

Operative Technique

A number of specific technical challenges are posed by the cirrhotic liver that substantially increase the complexity of hepatic resection. The parenchyma of the cirrhotic liver is very firm, making retraction and transection of the liver difficult. In addition, anatomic landmarks are distorted and difficult to locate as a consequence of hepatic fibrosis and

atrophy-hypertrophy. Finally, portal hypertension and tissue friability contribute to increased blood loss during liver mobilization and parenchymal transection.

Exposure and mobilization Trifurcated incisions and thoracoabdominal incisions should be avoided in cirrhotic patients because of the potential for ascites leak externally or into the chest. The increased firmness of the cirrhotic liver and the consequent difficulty of retraction can lead to significant blood loss from retroperitoneal or phrenic collateral vessels during mobilization. To prevent such bleeding, it may be preferable to use an anterior approach in which the liver parenchyma is split within the principal scissura down to the anterior surface of the vena cava before the right hemiliver is mobilized off the retroperitoneum.⁶⁰ The right hemiliver is then mobilized in a medial-to-lateral direction, and the right hepatic vein is secured during mobilization of the right hemiliver off the vena cava.

Inflow control In the past, the safety of the Pringle maneuver in cirrhotic patients has been questioned. More recently, numerous studies have confirmed that hepatic inflow occlusion may be performed for extended periods in cirrhotic patients without increasing operative morbidity or mortality.^{81–86} Nevertheless, it is advisable to employ the Pringle maneuver sparingly in this population so as to minimize ischemic stress. Our practice is to clamp the portal triad with a vessel loop tourniquet for 10-minute periods with 5-minute breaks between. We have not found additional protective maneuvers (e.g., topical cooling^{87,88}) to be necessary.

Parenchymal transection In patients with normal liver parenchyma, most experienced hepatic surgeons use blunt dissection, with either the clamp-crushing technique or the finger-fracture technique, to transect the liver tissue.⁸⁹ In patients with cirrhosis, however, the firmness of the parenchyma makes the clamp-crushing technique less than ideal; because the parenchyma is often harder than the underlying vasculature and biliary radicles, blunt dissection is likely to tear these vessels. As a result, ultrasonic dissectors that coagulate and seal vessels during dissection are more suitable for parenchymal transection in this population.

Closure and drainage Because of the likelihood of postoperative ascites, the abdominal wall is reapproximated with a heavy continuous absorbable monofilament suture to create a watertight closure. To prevent major fluid and protein losses and ascending infections, abdominal drains are generally avoided.⁵⁰ Studies specifically examining the role of drainage in cirrhotic patients have documented a much lower incidence of postoperative complications and a shorter hospital stay for patients in whom no drains were placed.^{90,91}

Postoperative Care

The focus of postoperative care in cirrhotic patients is on the management of cirrhosis and portal hypertension. In most cirrhotic patients who undergo hepatic resection, transient hepatic insufficiency develops postoperatively, characterized by hyperbilirubinemia, ascites formation, hypoalbuminemia, edema, and worsening of baseline coagulopathy.

In the first 24 hours after the procedure, crystalloid must be administered at a level sufficient to maintain adequate portal perfusion.⁹² If patients are stable after the first 24 hours, they are subjected to water and sodium restriction and receive liberal amounts of salt-poor albumin for volume expansion if needed. Spironolactone is started in all patients as soon as an oral diet is resumed, and furosemide is added as needed. On very rare occasions, a peritoneovenous shunt may be employed to control postoperative ascites,⁹³ but this measure is usually unnecessary if patients are properly selected. The PT or international normalized ratio is checked twice daily during the immediate postoperative period; a PT longer than 17 seconds is corrected by administering fresh frozen plasma.

CHEMOTHERAPY-ASSOCIATED STEATOHEPATITIS

One of the most important advances in the treatment of metastatic colon cancer over the past several years has been the development and approval of a number of newer chemotherapeutic agents such as irinotecan, oxaliplatin, cetuximab, and bevacizumab. These agents target the cancer cell cycle, paracrine growth factors, and angiogenic factors and have led to substantial improvements in survival for patients with hepatic colorectal metastases. They are currently being used not only as effective palliative treatment in cases where resection is not feasible but also to downstage unresectable hepatic tumors to permit effective surgical treatment. Consequently, it is now common for patients to be subjected to intensive chemotherapy prior to partial hepatectomy.⁹⁴ Unfortunately, the recognition of hepatotoxic side effects associated with these newer chemotherapeutics has introduced newer challenges in the operative and postoperative management of these patients.⁹⁵

Determination of operative candidacy must therefore include consideration of a condition known as chemotherapy-associated steatohepatitis (CASH).⁹⁶ This disease is associated with a characteristic clinical triad consisting of (1) hepatic steatosis, (2) splenomegaly, and (3) thrombocytopenia. Fatty infiltration of the liver is likely if hepatic attenuation is lower than splenic attenuation on CT imaging, but the absence of this finding does not exclude the possibility of clinically significant steatosis.⁹⁷ Splenomegaly is a sign of portal hypertension, as is refractory consumptive thrombocytopenia. Because this thrombocytopenia is not related to bone marrow suppression, it is not corrected even after chemotherapy is stopped.

When CASH is documented, patients should be selected for partial hepatectomy according to the same criteria used for patients with early cirrhosis. Consideration should also be given to preoperative portal vein embolization (PVE) (see below) before partial hepatectomy to increase the size of the anticipated hepatic remnant.

PREOPERATIVE PORTAL VEIN EMBOLIZATION

Most liver surgeons would be reluctant to resect more than the equivalent of two segments of functional liver in a patient with documented cirrhosis.⁹⁸ Consequently, many cirrhotic patients with technically resectable tumors are relegated to noncurative ablative therapy out of concern for possible postoperative hepatic failure. These limitations may be relieved with the growing use of preoperative PVE, which may extend

the opportunities to undertake major hepatic resections in patients with cirrhosis.

In PVE, access to the portal vein on the side of the liver to be resected is gained via a percutaneous transhepatic approach. The vein is embolized approximately 1 month before the planned resection so as to produce ipsilateral atrophy along with compensatory hypertrophy of the contralateral future hepatic remnant.⁹⁹ The degree of compensatory hypertrophy can be dramatic [see Figure 17] and may modulate postoperative hepatic dysfunction. PVE is also employed in patients with normal parenchyma in whom extensive resection may result in a very small hepatic remnant. In patients undergoing right trisectionectomy, particularly those with a congenitally small left lateral section, the entire area of the extended right hepatectomy, including the main right portal vein and the segmental branches supplying segment IV, can be embolized.¹⁰⁰

There is substantial evidence that preoperative PVE may be successfully used for patients with cirrhosis or impaired hepatic function; moreover, PVE appears to be generally well tolerated for these patients.^{101–103} One immediate benefit of PVE is that it may act as a kind of stress test for the liver, allowing preoperative determination of the likelihood of liver regeneration. If no compensatory hypertrophy is seen 4 weeks after PVE, the decision to perform a major hepatic resection should be reconsidered.

Repeat Hepatic Resection

Since 1984, when one of the earliest descriptions of repeat hepatic resection was published,¹⁰⁴ a number of reports have demonstrated that repeat resection can be performed safely and with good long-term results, even for patients with recurrent malignancy. When appropriately selected, the morbidity and mortality rates associated with repeat partial hepatectomy for metastatic colorectal cancer^{105–117} and HCC^{118–125} are comparable to those observed after initial hepatectomy. Extended survival has been demonstrated, and in selected cases, survival is at least equivalent to that observed after initial resection.^{106,113,120,126} In this section, we concentrate on the key technical aspects of repeat hepatic resection; discussion of indications, patient selection, and outcome are available in other sources.^{106,113,120,126}

Repeat hepatic resection poses unique technical difficulties that are not typically encountered during initial resection.^{105,127,128} First, adhesions at the previous line of parenchymal transection can make reexposure of the liver difficult. Mobilizing the liver off the vena cava and reexposing the porta hepatis and the hepatic veins can be extremely hazardous if dissection was previously undertaken in these areas. Second, liver regeneration and systemic chemotherapy can induce accumulation of fat within the liver, making it more friable¹⁰⁶; this increased parenchymal friability further potentiates the difficulties of exposure and predisposes to inadvertent tearing of the Glisson capsule.¹²⁷ Third, regeneration alters the normal anatomic configuration of the portal structures [see Figure 18].¹²⁹ For example, after right hepatectomy, the porta hepatis is rotated posteriorly and to the right. The normal anatomic relations among the portal structures are altered, with the bile duct becoming displaced posteriorly and the portal vein becoming displaced anteriorly.

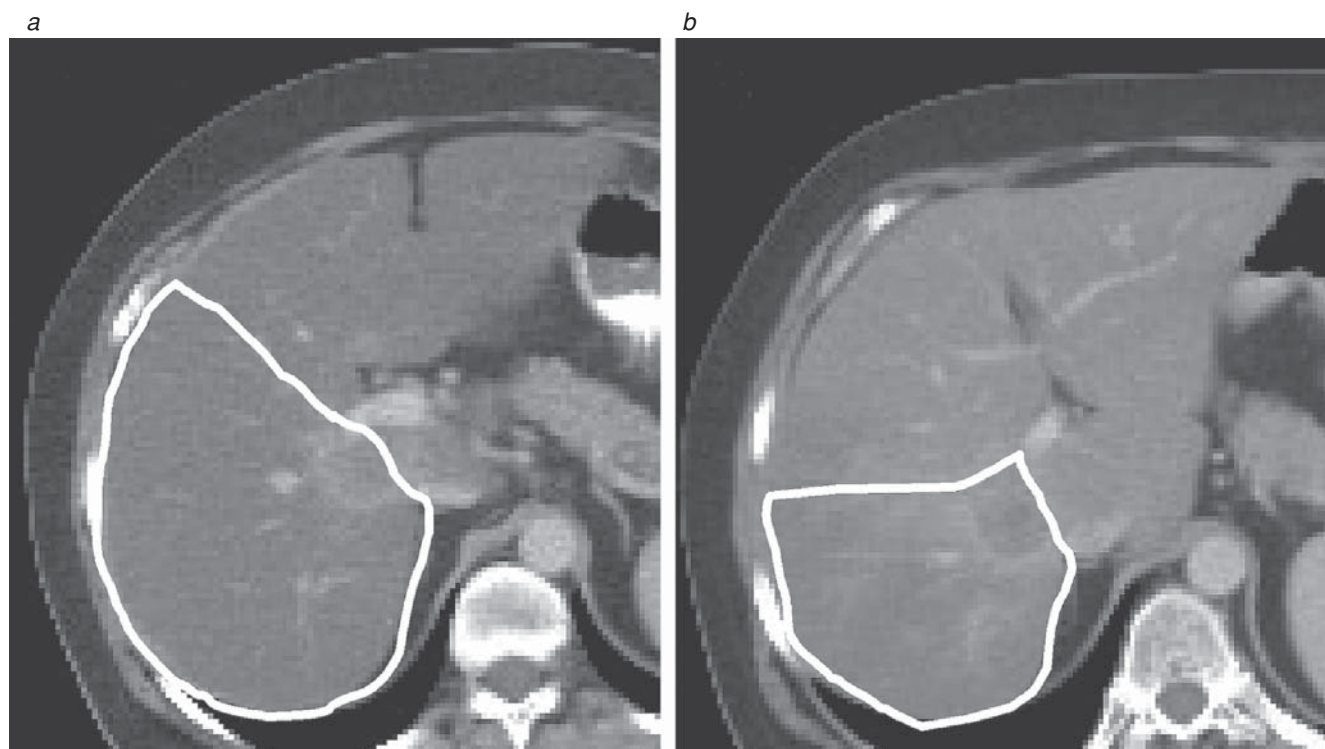


Figure 17 Liver atrophy and hypertrophy occur after right portal vein embolization. Shown are images of the liver (a) at baseline and (b) 6 weeks after portal vein embolization. The right hemiliver is outlined in white.

Preoperative imaging is therefore even more important for repeat resections than for primary resections; another reason for this is that postoperative adhesions will limit full access to the liver for intraoperative assessment via palpation or ultrasonography. Before undertaking a repeat resection, it is

essential to know the exact number and locations of the lesions to be treated within the regenerated parenchyma. Preoperative imaging also facilitates operative planning by accurately delineating the vasculature within the regenerated liver.

During repeat resection after a previous major right hepatectomy, preparations should be in place to convert to a thoracoabdominal incision if necessary. Access through the right chest may be required for mobilization of the liver because of dense adherence of the previous resection margin to the diaphragm; alternatively, it may be required for access to the rotated CBD and portal vasculature at the porta hepatis.

During dissection of the right upper quadrant after a previous right hepatectomy, three landmarks are particularly helpful in defining the anatomic structures within the regenerated left hemiliver. The first landmark is the remnant of the ligamentum teres, which defines the demarcation between the left lateral section (segments II and III) and the left medial section (segment IV); these should be identified early during operative exploration. The ligamentum teres may then be followed to the base of the umbilical fissure to define the location of the left hepatic artery. Regardless of whether this artery arises from the common hepatic artery or from the left gastric artery, it passes into the liver parenchyma at the base of the umbilical fissure. The second landmark is the caudate lobe. The lesser omentum should be opened early on to expose this structure, after which an index finger can then be passed in front of the caudate toward the obliterated foramen of Winslow to define the porta hepatis and the location of the portal vein. The third landmark is the vena cava. Performing

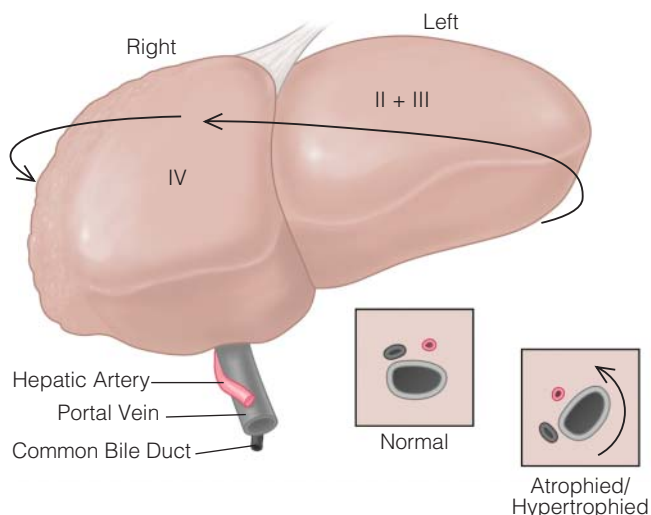


Figure 18 Repeat hepatic resection. Depicted are the changes in the relations of the portal structures that occur as a result of right-liver atrophy or resection and left-sided hypertrophy. The structures in the porta hepatis rotate to the right, with the common bile duct coming to rest laterally rather than anteriorly. The Roman numerals refer to the hepatic segments.

a Kocher maneuver to mobilize the duodenum off the vena cava allows this vessel to be dissected, helping to define the portocaval plane. This will define the proper plane for dissection and mobilization of the liver off the vena cava and allows isolation of the hepatoduodenal ligament for application of the Pringle maneuver and for extrahepatic dissection of the inflow vessels.

In a repeat resection after a previous left hepatectomy, the main concern with regard to mobilization of the liver is the anterior displacement of the portal vasculature after right-sided hypertrophy. It is therefore prudent to mobilize the right hemiliver, perform a Kocher maneuver, and follow the vena cava caudally to identify the portal vein from the right. The stomach and the colon are usually adherent against the edge of the previous resection and must be carefully dissected free to allow access to the liver. If the middle hepatic vein was preserved in the earlier left hepatectomy, it will lie immediately deep to the plane of the stomach or the colon and may therefore become a source of hemorrhage during dissection.

Control of the inflow or outflow vasculature may be compromised by scarring resulting from the previous operation. If extensive extrahepatic dissection was performed for control of inflow vasculature in the earlier procedure, control of these vessels in the repeat resection is more safely accomplished via intrahepatic pedicle ligation [see Operative Technique, Right Hepatectomy, Step 6—Alternative (Intrahepatic Pedicle Ligation): Control of Inflow Vessels, *above*].

Another major concern with repeat partial hepatectomy is that it is often necessary to perform more limited resections than would be indicated during a primary resection. During primary resections, we typically avoid wedge excisions as these nonanatomic resections are associated with greater blood loss and a higher likelihood of positive margins compared with anatomic resections.^{112,130} However, during a repeat partial hepatectomy, the absence of multiple inflow or outflow vessels and other anatomic considerations arising in the regenerated liver may make a wedge resection or ablation the best choice.

With appropriate patient selection and careful operative planning, very favorable perioperative and long-term results can be achieved after repeat hepatic resection. Notably, studies of repeat resection have not documented substantial increases in blood loss, operative duration, or complication rates in comparison with initial resection.^{106–110,131}

Laparoscopic Hepatic Resection

In addition to revolutionizing the treatment of gallstone disease,¹³² laparoscopic techniques have been used increasingly for fenestration of benign cysts of the liver^{133,134} and for staging of hepatobiliary malignancies to prevent unnecessary laparotomies.^{38,135–137} Until relatively recently, laparoscopic resection of liver tumors was described only in case reports or small series.^{133,138–142} One reason for the strong resistance to laparoscopic hepatic resection has been fear of catastrophic bleeding. If inadvertent damage to a major hepatic vein or the vena cava occurs during an open operation, the bleeding can be temporarily controlled with direct manual compression until the vessel is repaired; however, if such damage occurs during a laparoscopic operation, initial control of the

bleeding is considerably more difficult. In addition, damage to a hepatic vein or the vena cava during a laparoscopic procedure may theoretically result in CO₂ embolism. Another concern is that the loss of tactile sensation characteristic of laparoscopic surgery may lead to inadequate tumor clearance. Finally, although there are many liver retractors designed to hold the liver in one position, there is no good retractor for repeatedly moving the liver from side to side, as would be necessary during a laparoscopic hepatectomy. The human hand is still the best tool for this purpose.

Laparoscopic hepatic resection has been greatly facilitated by several recent technologic advances, including the introduction of laparoscopic staplers¹⁴³ and ultrasonic dissectors,¹⁴⁴ which can be used for ligation of the hepatic vasculature and transection of liver parenchyma. Another important instrument is the hand access port, a small port through which one hand can be introduced into the abdomen for a hand-assisted laparoscopic resection [see Figure 19].^{145–147} This approach retains a measure of tactile sensation, permits the employment of the hand for optimal liver retraction, and allows for direct manual compression of any bleeding vessels. Furthermore, the incision made for the hand access port can be used for extraction of the resected specimen.

Appropriate patient selection is essential for safe laparoscopic resection of liver tumors. Resection of any two segments along the lower edge of the liver is easily accomplished laparoscopically. We have laparoscopically resected lesions from all segments.⁴⁷ In the following section, we provide a general overview of laparoscopic hepatic resection; more in-depth discussions of the technical aspects of these procedures and the results reported from various centers are available elsewhere.¹⁴⁸

OPERATIVE TECHNIQUE

The patient is placed on the operating table in a supine position and is securely strapped down to allow for rotation of the table. For a right hepatectomy or resection of segments VII and VIII (bisegmentectomy VII, VIII), the patient may

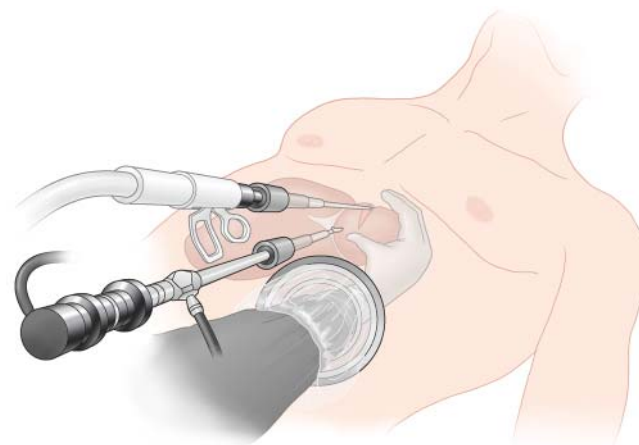


Figure 19 Laparoscopic hepatic resection: hand assisted. Introduction of the hand within the abdomen restores tactile sensation to the surgeon and facilitates resection of the liver. The hand is the best liver retractor available and can be used to dissect the parenchyma. The specimen can be extracted through the hand access port.

be positioned in a left lateral decubitus position, although we have not found this to be universally necessary.

As outlined earlier, a hand access port can be of great utility in laparoscopic liver resection. However, care must be taken in placing the hand port in a location that will not impede access of other trocar sites. For left-sided resection, the hand access port can be placed through a transverse incision in the left upper quadrant [see Figure 19] or through an upper midline incision. For right-sided resection, the port may be placed in the right lower quadrant [see Figure 20b] or through an upper midline incision.

Left-sided resections typically require placement of three to four ports [see Figure 20a]. Pneumoperitoneum is established using an initial port placed at the umbilicus; to prevent gas embolism during liver transection, it is maintained at the lowest pressure possible (typically 10 to 12 mm Hg). A 10 to 12 mm port is placed at the intersection of the subcostal and midclavicular lines to permit dissection of the triangular ligament, hepatic vein, and inferior vena cava. An additional 5 mm port may be placed between the previous two ports to facilitate dissection near the porta hepatic and umbilical fissure. A 10 to 12 mm port is placed in the right midclavicular line to permit the introduction of an endovascular stapler for division of the portal structures and liver parenchyma. We generally use the 45 mm rotating articulated stapler loaded with the white 2.5 mm cartridge.

Right-sided resections generally require placement of four ports. Pneumoperitoneum is again established using a port placed at the umbilicus. If the hand access port is placed in

the right lower quadrant, a 10 to 12 mm port is placed in a subxiphoid position through which an endovascular stapler may be passed for division of the portal structures, liver parenchyma, and hepatic vein. An additional 5 mm port placed in the midepigastrium will facilitate dissection in the porta hepatis, and a 5 mm port placed in a subcostal location along the anterior axillary line will facilitate mobilization of the right hemiliver off the diaphragm and inferior vena cava.

Laparoscopic partial hepatectomy begins with a staging exploration to confirm that the lesion is resectable and, in cases of malignancy, to exclude the presence of distant extrahepatic metastases. IOUS is especially critical in laparoscopic resections for identification of major inflow and outflow vessels, tumor location, and guidance of parenchymal transection. We place a laparotomy sponge into the abdomen to facilitate retraction, absorb blood, and cleanse the laparoscopic camera as needed. A long bulldog clamp may be inserted into the peritoneal cavity in the event that a Pringle maneuver should prove necessary; a long umbilical tape is tied to the bulldog clamp so that the instrument can be easily located throughout the procedure.

Once the liver is mobilized and the tumor is located, the plane of planned transection is marked with the electrocautery. The liver is manually retracted, and parenchymal transection is initiated using ultrasonic dissection. We typically do not attempt to dissect the inflow and outflow vessels extrahepatically. Rather, when parenchymal dissection approaches the major portal pedicles and hepatic veins, we use an endoscopic GIA vascular stapler for transection. After removal of

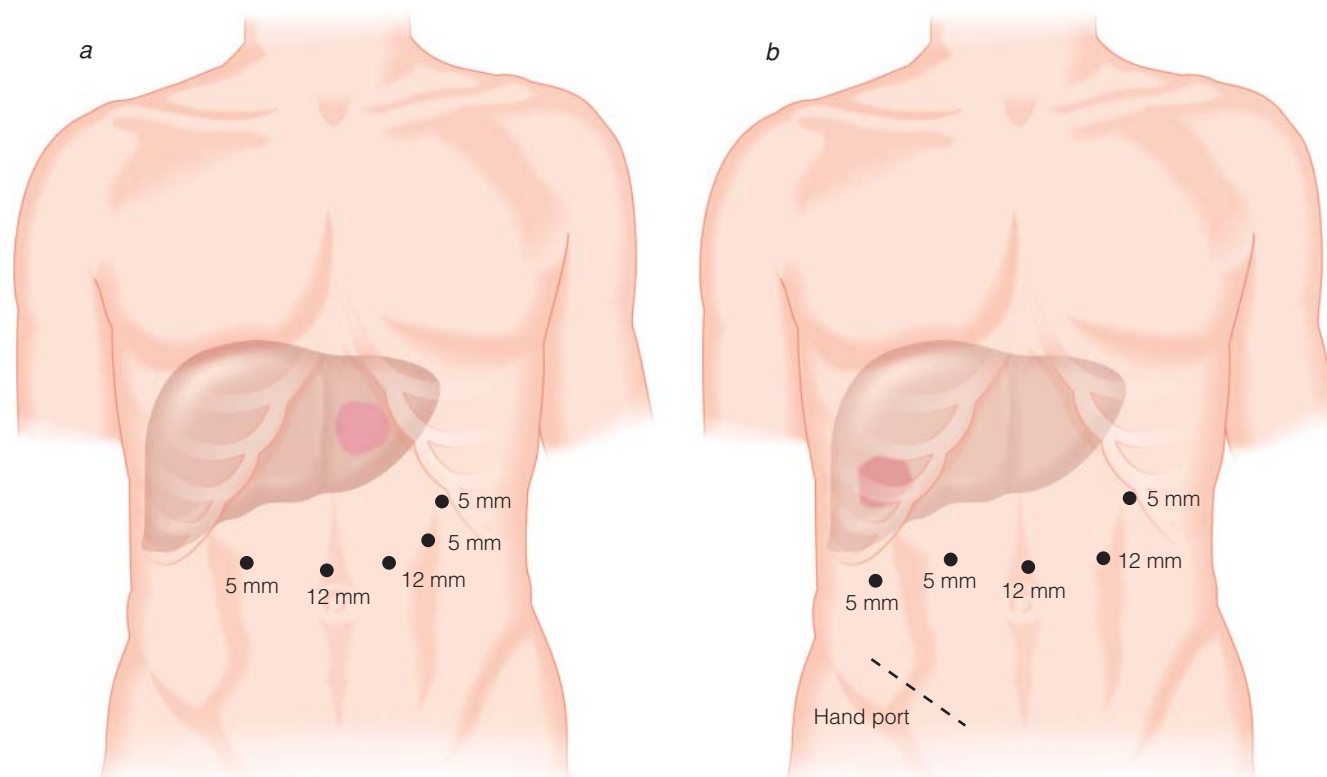


Figure 20 Shown are the recommended port placements for (a) laparoscopic left lateral sectionectomy and (b) hand-assisted laparoscopic right hepatectomy.

the specimen, the laparoscopic argon beam coagulator and topical agents are used to ensure adequate hemostasis.

As experience with laparoscopic partial hepatectomy is increasing, evidence supporting the safety and oncologic efficacy of major laparoscopic hepatic resections is accumu-

lating.^{149–151} Ongoing analysis of laparoscopic hepatic resection with respect to long-term measures of quality of life and survival continues.

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Figures 1, 3 through 15, 18, 19 Tom Moore
Figure 16 Thom Graves, CMI

24 PROCEDURES FOR BENIGN AND MALIGNANT PANCREATIC DISEASE

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Over the past two decades, both the mortality and the morbidity associated with pancreatic surgery have been reduced substantially. In many high-volume centers, the perioperative mortality for pancreatic resection is now less than 3%.¹⁻³ This decline in mortality may be attributed to more careful patient selection, better understanding of surgical anatomy, advances in critical care medicine, and improvements in the management of perioperative complications.

In this chapter, we describe the operative techniques we employ in the management of both benign and malignant pancreatic disease, including pancreaticoduodenectomy (the Whipple procedure), distal pancreatectomy (open and laparoscopic), longitudinal pancreaticojejunostomy (the Puestow procedure), duodenum-preserving pancreatic head resections (Frey and Beger procedures), enteric drainage of pancreatic pseudocysts (open and laparoscopic), and palliative bypass for unresectable periampullary cancer.

Preoperative Evaluation

A number of different imaging options are available to help determine the appropriate surgical approach to management of pancreatic disease. These options include both noninvasive (e.g., transabdominal ultrasonography, computed tomography [CT], and magnetic resonance imaging [MRI]) and invasive modalities (e.g., endoscopic retrograde cholangiopancreatography [ERCP] and endoscopic ultrasonography [EUS]).

Transabdominal ultrasonography can identify changes associated with chronic pancreatitis, biliary and pancreatic duct dilation, and the presence of pseudocysts. In the setting of malignant disease, it may demonstrate dilated intrahepatic and extrahepatic bile ducts, liver metastases, pancreatic masses, ascites, and enlarged peripancreatic lymph nodes. A malignancy of the pancreas typically appears as a hypoechoic mass; ultrasonography reveals a pancreatic mass in 60 to 70% of pancreatic cancer patients.

Helical (spiral) CT is now the preferred noninvasive imaging test for pancreatic disease, having largely supplanted ultrasonography in this context. Helical CT can delineate the anatomy of the pancreas and the surrounding organs in considerable detail. It can also easily define pancreatic calcifications, inflammation, necrosis, and masses. Pancreatic cancer usually appears as an area of pancreatic enlargement with a localized hypodense lesion. A triple-phase intravenous

(IV) contrast study is ideal for the assessment. Thin cuts are obtained through the pancreas and the liver during both the arterial phase and the venous phase after the injection of IV contrast material. Besides determining the primary tumor size, CT can also identify and evaluate invasion into local structures or metastatic disease.

In general, MRI has no significant advantages over CT: its signal-to-noise ratio is low, it is prone to motion artifacts, it does not opacify the bowel, and it has low spatial resolution. Nevertheless, magnetic resonance cholangiopancreatography (MRCP) can be quite useful for defining the anatomy and pathology of the bile ducts and the pancreatic duct noninvasively. It can be especially helpful in cases where the ampulla of Vater is not accessible (as in patients who have previously undergone Roux-en-Y or Billroth II reconstructions).

ERCP allows direct imaging of the pancreatic and bile ducts and is the gold standard for diagnosing chronic pancreatitis. It also allows therapeutic stenting of biliary and pancreatic duct strictures. The sensitivity of ERCP for the diagnosis of pancreatic cancer approaches 90%. The presence of a long, irregular stricture in an otherwise normal pancreatic duct is highly suggestive of a pancreatic malignancy. Often the pancreatic duct is obstructed, with no distal filling.

EUS, although newer than the aforementioned modalities, now plays an important role in the evaluation of pancreatic diseases. It is a semi-invasive test that can be performed with a very low rate of complications (< 0.1%). EUS can diagnose the most common causes of extrahepatic biliary obstruction (e.g., choledocholithiasis and pancreaticobiliary malignancies) with a degree of accuracy equaling or exceeding that of direct cholangiography or ERCP. It is the most sensitive modality for the diagnosis of pancreatic carcinoma. The particular strengths of EUS in the diagnosis of pancreatic cancer include its ability to (1) clarify small (< 2 cm) lesions when CT findings are questionable or negative, (2) detect malignant lymphadenopathy, and (3) guide fine-needle aspiration (FNA) for definitive diagnosis and staging. On average, EUS without FNA is 85% accurate for T stage disease and 70% accurate for N stage disease. The combination of EUS and FNA is 93% sensitive and 100% specific for T stage disease and 88% accurate for N stage disease.⁴

Pylorus-Preserving Pancreaticoduodenectomy (Whipple Procedure)

Surgical resection of a periampullary carcinoma can be accomplished by means of either a pylorus-preserving pancreaticoduodenectomy (PPPD) or the classic Whipple resection (including an antrectomy). Multiple randomized trials have failed to show any significant differences between the two

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procedures in terms of either relative ease of performance or short- or long-term outcome (including survival). The choice between them is usually made on the basis of individual surgeons' preferences (unless there is obvious tumor encroachment on the first portion of the duodenum). In the ensuing technical description, we focus primarily on the pylorus-preserving modification but also refer to certain important components of the classic Whipple resection.

OPERATIVE PLANNING

Operative management of periampullary cancer is carried out in three phases. First, the resectability of the tumor is assessed; then, if the tumor is resectable, a pancreaticoduodenectomy is performed, and, finally, gastrointestinal continuity is restored. Selective use of staging laparoscopy should be considered for patients at high risk for occult metastatic disease, such as patients with large primary tumors; patients with lesions in the neck, body, or tail of the pancreas; patients with equivocal radiographic findings suggestive of occult distant metastatic disease (e.g., low-volume ascites, CT findings indicating possible carcinomatosis, and small hypodense regions in the hepatic parenchyma indicating possible hepatic metastases that are not amenable to percutaneous biopsy); and patients with clinical and laboratory findings suggesting more advanced disease (e.g., marked hypoalbuminemia or weight loss, significant increases in the CA19-9 level, and severe back or abdominal pain).

OPERATIVE TECHNIQUE

The peritoneal cavity is entered through an upper midline or a bilateral subcostal incision. The liver, the omentum, and the peritoneal surfaces are inspected and palpated, and suspicious lesions are biopsied and submitted for frozen-section analysis. Regional lymph nodes are examined for evidence of tumor involvement. The presence of tumor in the periaortic lymph nodes of the celiac axis indicates that the tumor has extended beyond the limits of normal resection; however, the presence of tumor in lymph nodes that normally would be incorporated within the resection specimen does not constitute a contraindication to resection.

Once distant metastases have been excluded, the resectability of the primary tumor is assessed. Various local factors may preclude pancreaticoduodenal resection, including retroperitoneal extension of the tumor to involve the inferior vena cava or the aorta and direct involvement or encasement of the superior mesenteric artery (SMA), the superior mesenteric vein (SMV), or the portal vein. Often the determination of resectability is made on the basis of a careful review of the preoperative imaging (CT plus EUS) in conjunction with operative exploration.

Operative assessment of resectability begins with a Kocher maneuver and mobilization of the duodenum and the head of the pancreas from the underlying inferior vena cava and aorta. When the duodenum and head of the pancreas have been mobilized sufficiently, a hand is placed under the duodenum and the head of the pancreas to palpate the tumor mass and determine its relation to the SMA. Inability to identify a plane of normal tissue between the mass and the arterial pulsation indicates that the tumor directly involves the SMA. In these cases, complete tumor resection is not possible.

The final operative step for determining resectability involves dissection of the SMV and portal vein to rule out tumor invasion. Identification of the portal vein is greatly simplified if the common hepatic duct is divided early in the dissection.⁵ Once the hepatic duct has been divided, the anterior surface of the portal vein is easily and quickly identified [see Figure 1]. The lymph node tissue lateral to the hepatic duct and the portal vein should be dissected off the structures to be included in the surgical specimen. It must be remembered that important variations in the hepatic arterial anatomy, including a replaced right hepatic artery, may be encountered during this dissection. If the appropriate plane is found along the anterior surface of the portal vein, it should be easy to pass the index finger of the left hand on top of the vessel posterior to the first portion of the duodenum and the neck of the pancreas (because there usually are no veins joining the anterior surface of the portal vein). If this maneuver proves difficult, the gastroduodenal artery should be identified where it comes off the common hepatic artery. Once adequate dissection has been carried out, the artery should first be clamped with a nonoccluding vascular clamp and then, if the hepatic artery pulse is preserved, divided and ligated with 2-0 silk ties. (The initial clamping of the gastroduodenal artery with a vascular clamp confirms that the arterial supply to the liver will not be interrupted should either variations in hepatic arterial anatomy or important collateral circulation be present in the face of celiac artery stenosis.) After the artery has been divided and ligated, an additional ligature of 3-0 polypropylene should be placed on the proximal stump. Division of the gastroduodenal artery unroofs part of the tunnel through which the index finger is slipped, thereby greatly facilitating the separation of the portal vein from the posterior aspect of the first portion of the duodenum and the neck of the pancreas.

Once the anterior surface of the portal vein has been dissected posterior to the neck of the pancreas, the next step is to identify the SMV and dissect its anterior surface. This is most easily accomplished by extending the Kocher maneuver past the second portion of the duodenum to include the third and fourth portions. During this extensive Kocherization, the first structure encountered anterior to the third portion of the duodenum is the SMV [see Figure 2]. The anterior surface of the vein can then be cleaned and dissected under direct vision by retracting the neck of the pancreas anteriorly. This dissection is continued until it connects to the portal vein dissection from above. If this maneuver can be completed without evidence of SMV or portal vein involvement, the tumor can generally be considered resectable. It is still possible, however, for an uncinate tumor to involve the right lateral surface and the undersurface of the SMV, and this possibility should be carefully evaluated.

If the neck of the pancreas can be successfully dissected off the anterior and lateral surfaces of the portal vein and SMV, most experienced pancreatic surgeons will proceed with pancreaticoduodenectomy without obtaining a tissue diagnosis. In defining the diagnosis of malignancy, an intraoperative biopsy is less conclusive than the combination of the clinical presentation, the results of preoperative CT scanning and cholangiography, and the operative finding of a palpable mass in the head of the pancreas.

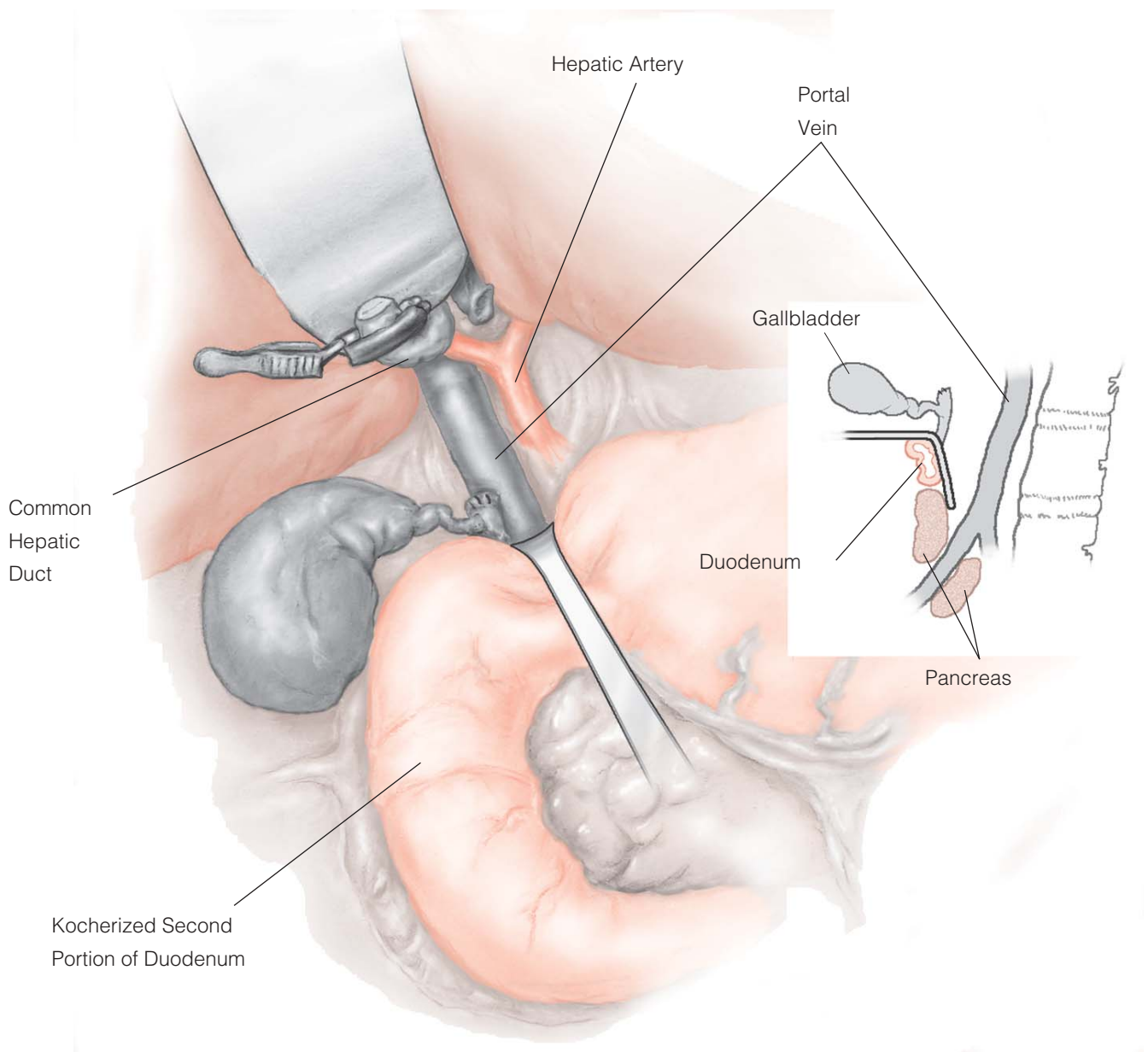


Figure 1 Whipple procedure. The common hepatic duct is divided at an early stage to facilitate identification of the portal vein. This division also untethers the first portion of the duodenum and allows it to be retracted anteriorly.

In a PPPD,⁶ the duodenum is first mobilized and divided approximately 2 cm distal to the pylorus with a gastrointestinal anastomosis (GIA) stapler. The posterior surface of the proximal first portion of the duodenum is dissected until the lesser sac is entered. At this point, the soft tissue attachments from the inferior border of the duodenum to the inferior border of the pancreas are divided. The right gastroepiploic vessels, which can be sizable, are clamped, divided, and ligated. In a similar fashion, the soft tissue areolar attachments found superiorly are divided with the electrocautery. The right gastric artery, which comes off the common hepatic artery, is also ligated.

In a classic Whipple procedure, an antrectomy is performed. The right gastroepiploic arcade and the right gastric vessels are divided to permit mobilization of the antrum.

The stomach is then divided with a GIA stapler, usually at the level of the incisura. At this point, if the gastroduodenal artery was not divided earlier, it is identified, divided, and ligated as described (see above). During this step, particular care must be taken to ensure that the lumen of the common hepatic artery is not encroached on by one of the proximal ties.

The neck of the pancreas is then divided with the electrocautery [see Figure 3], with care taken not to injure the underlying SMV and portal vein. These veins are mobilized away from the uncinate process of the pancreas; the dissection should continue until the SMV, clearly palpable with the index finger of the left hand, is visualized. If a replaced right hepatic artery is present, its origin from the SMA will be encountered at this point and must be preserved. The

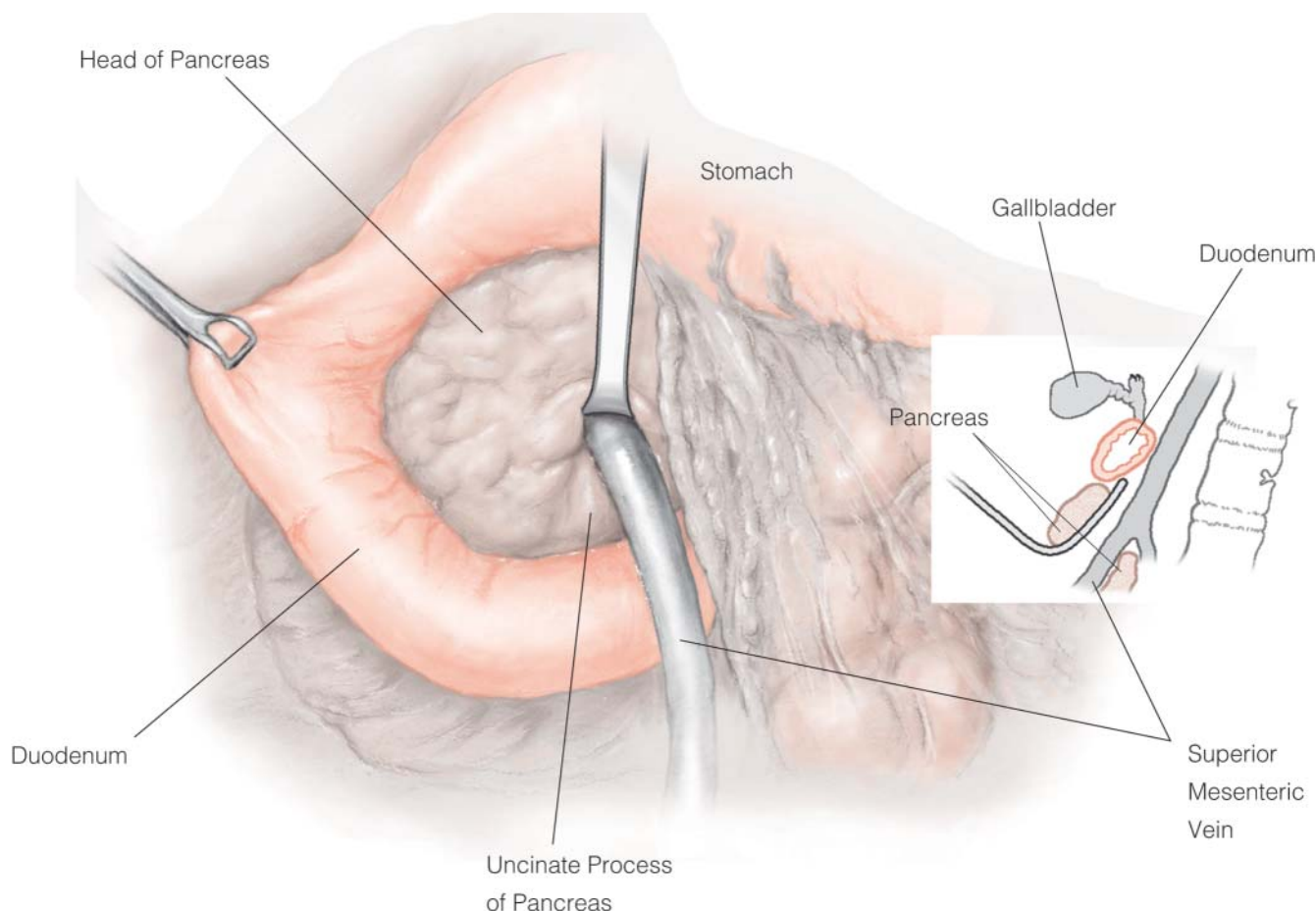


Figure 2 Whipple procedure. Kocherization of the duodenum is continued along the third portion until the superior mesenteric vein is reached. This vein can then be easily cleaned up to its connection with the portal vein.

uncinate process is divided between clamps flush with the SMA [see Figure 4] and then ligated with 2-0 silk ties; alternatively, either a vessel-sealing system (e.g., LigaSure; Valleylab, Boulder, Colorado) or ultrasonic shears may be used. The SMA is completely exposed during this dissection, which proceeds from cephalad to caudad. As a rule, there are two large veins joining the SMV inferiorly that must be dissected free, doubly ligated, and divided.

Once the uncinate process has been completely divided, the specimen is attached only by the third portion of the duodenum. At this point, the upper abdomen is copiously irrigated with an antibiotic solution and packed. The transverse colon, along with the greater omentum, is reflected cephalad. The proximal jejunum and the ligament of Treitz, along with the fourth portion of the duodenum, are dissected free, and the dissection is continued until it meets the right-side upper abdominal dissection. At a convenient point where there is a wide vascular arcade, the proximal jejunum is divided with a GIA stapler approximately 10 to 12 cm distal to the ligament of Treitz. The proximal jejunum is then grasped with a Babcock clamp and retracted cephalad. The mesentery to the proximal jejunum is divided between clamps and ligated with 2-0 silk (or divided with a vessel-sealing energy device).

When division of the mesentery is complete, the specimen is free and can be removed from the operative field. The bile duct, the pancreatic neck, and the uncinate margins should be tagged with sutures for frozen-section analysis. The bed of the tumor should be carefully inspected for hemostasis and its margins may be marked with ligating clips (e.g., LigaClip; Ethicon Endo-Surgery, Inc., Cincinnati, Ohio) to facilitate postoperative radiation therapy.

There are several technical options for restoring GI continuity after a pancreaticoduodenal resection. Our preferred technique is to bring the end of the divided jejunum through the transverse mesocolon to the right of the middle colic vessels in a retrocolic fashion and to perform an end-to-side pancreaticojejunostomy. A row of interrupted 3-0 silk Lembert sutures is placed between the side of the jejunum and the posterior capsule of the end of the pancreas. A small enterotomy, matching the size of the pancreatic duct, is made in the jejunum, and an inner layer of interrupted 5-0 absorbable monofilament sutures is placed to create a duct-to-mucosa anastomosis [see Figure 5]. Meticulous stitch placement is crucial, and many surgeons use some degree of magnification to complete the anastomosis in small ducts. Often a pediatric feeding tube (either externalized or cut short) is placed across the anastomosis to be used as a temporary indwelling stent.

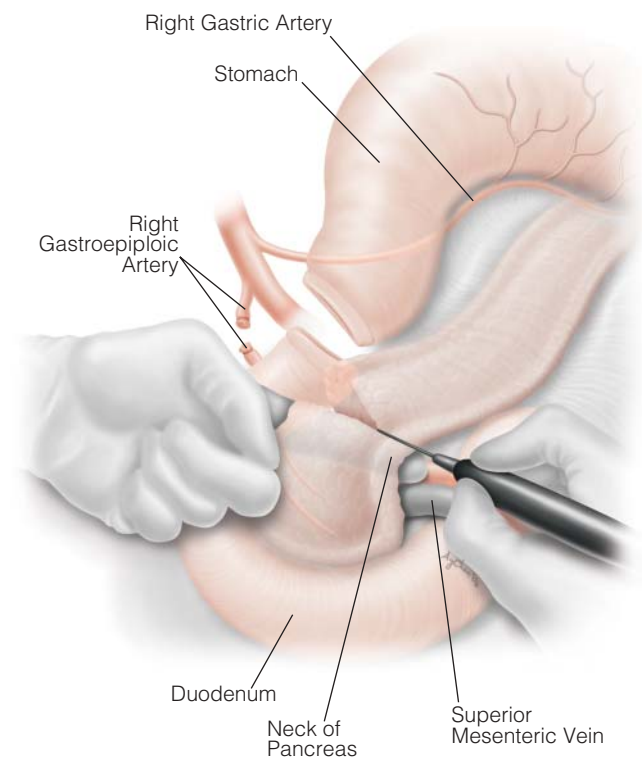


Figure 3 Whipple procedure. Transection of the neck of the pancreas with electrocautery.

The anastomosis is completed with an outer layer of 3-0 silk Lembert sutures placed between the anterior pancreatic capsule and the jejunum. This layer should be completed in a fashion to invaginate the gland into the seromuscular layer of the bowel. A popular alternative to this duct-to-mucosa technique is to create an enterotomy approximately the same size as the pancreatic neck and to place an inner continuous layer of 3-0 absorbable synthetic suture material circumferentially around the entire gland. The neck is then invaginated 1 to 2 cm into the lumen of the bowel, and an outer interrupted layer of 3-0 silk is placed to complete the anastomosis.

The biliary-enteric anastomosis is performed 6 to 10 cm distal to the pancreaticojejunostomy. An end-to-side hepaticojejunostomy is fashioned with a single interrupted layer of 4-0 absorbable synthetic suture material [see Figure 6]. Generally, there is no need for a T tube or a stent.

Approximately 15 cm distal to the biliary-enteric anastomosis, an end-to-side duodenojejunostomy is performed with an inner continuous layer of 3-0 absorbable synthetic suture material and an outer interrupted layer of 3-0 silk [see Figure 7]. Some experienced pancreatic surgeons prefer to perform the duodenojejunostomy further distally in an antecolic position, in the belief that doing so reduces the incidence of early postoperative delayed gastric emptying. If an antrectomy was performed, the medial half of the gastric staple line is reinforced with interrupted 3-0 silk seromuscular Lembert sutures. The gastrojejunal anastomosis is completed to the lateral (greater curvature) aspect of the staple line as a two-layer Hofmeister-style anastomosis.

The abdomen is copiously irrigated with an antibiotic solution. The jejunal loop is tacked to the rent in the transverse

mesocolon with interrupted 3-0 silk sutures. The defect in the retroperitoneum previously occupied by the fourth portion of the duodenum is closed with a continuous 2-0 silk suture. One or two closed-suction Silastic drains are placed in the vicinity of the hepaticojejunostomy and the pancreaticojejunostomy and brought out through a stab wound in the right upper quadrant. The abdomen is closed in a standard fashion.

Distal Pancreatectomy with Splenectomy

Distal pancreatic resection is performed for a variety of conditions, including inflammatory processes, benign tumors and cysts, and pancreatic malignancies. The following discussion focuses on distal pancreatectomy for malignancy, but the basic technical principles remain the same for distal pancreatectomy for benign disease.

OPERATIVE TECHNIQUE

The peritoneal cavity is usually entered through a left subcostal incision that extends to the right of midline. In thin patients, an upper midline incision may be employed. On entry into the abdomen, a careful exploration is performed to confirm the absence of disseminated disease.

The lesser sac is entered by dividing the gastrocolic omentum. Generally, this is best done by separating the greater omentum off the transverse colon and leaving it attached to the greater curvature of the stomach. Once the lesser sac has been entered, the posterior wall of the stomach is separated from the pancreas with sharp and blunt dissection to expose the body and tail of the pancreas. The duodenum is Kocherized, and the head and the uncinate process of the pancreas are palpated and visualized; the entire gland can then be inspected and palpated. Intraoperative ultrasonography may be employed for further delineation of the tumor's relation to the surrounding vascular structures.

Once the pancreas has been exposed, the celiac axis and the superior mesenteric vessels are identified and assessed to determine whether the tumor is resectable. The splenic artery is identified where it originates from the celiac axis, and a vessel loop is placed around it. As a result, the vessel is controlled at an early stage of the procedure and can be promptly ligated if bleeding should occur. A patient with a thrombosed splenic vein may have left-side portal hypertension and multiple collateral vessels leading from the spleen to the stomach via the short gastric vessels. With such a patient, it is usually preferable to ligate and divide the splenic artery early in the procedure.

The spleen is retracted toward the midline with the left hand; it should be compressed medially toward the spine rather than retracted anteriorly. It is then mobilized out of the retroperitoneum with the electrocautery. The retroperitoneum usually consists of loose areolar tissue that is easily mobilized. The omental attachments anterior to the hilum of the spleen are divided between Kelly clamps and ligated with 2-0 silk. The line of division is easily determined if the omentum has previously been completely taken off the transverse colon. As the division extends up toward and then along the greater curvature of the stomach, the vasa brevia are encountered and are doubly clamped, divided, and ligated (alternatively, an energy-sealing device may be used). The splenic

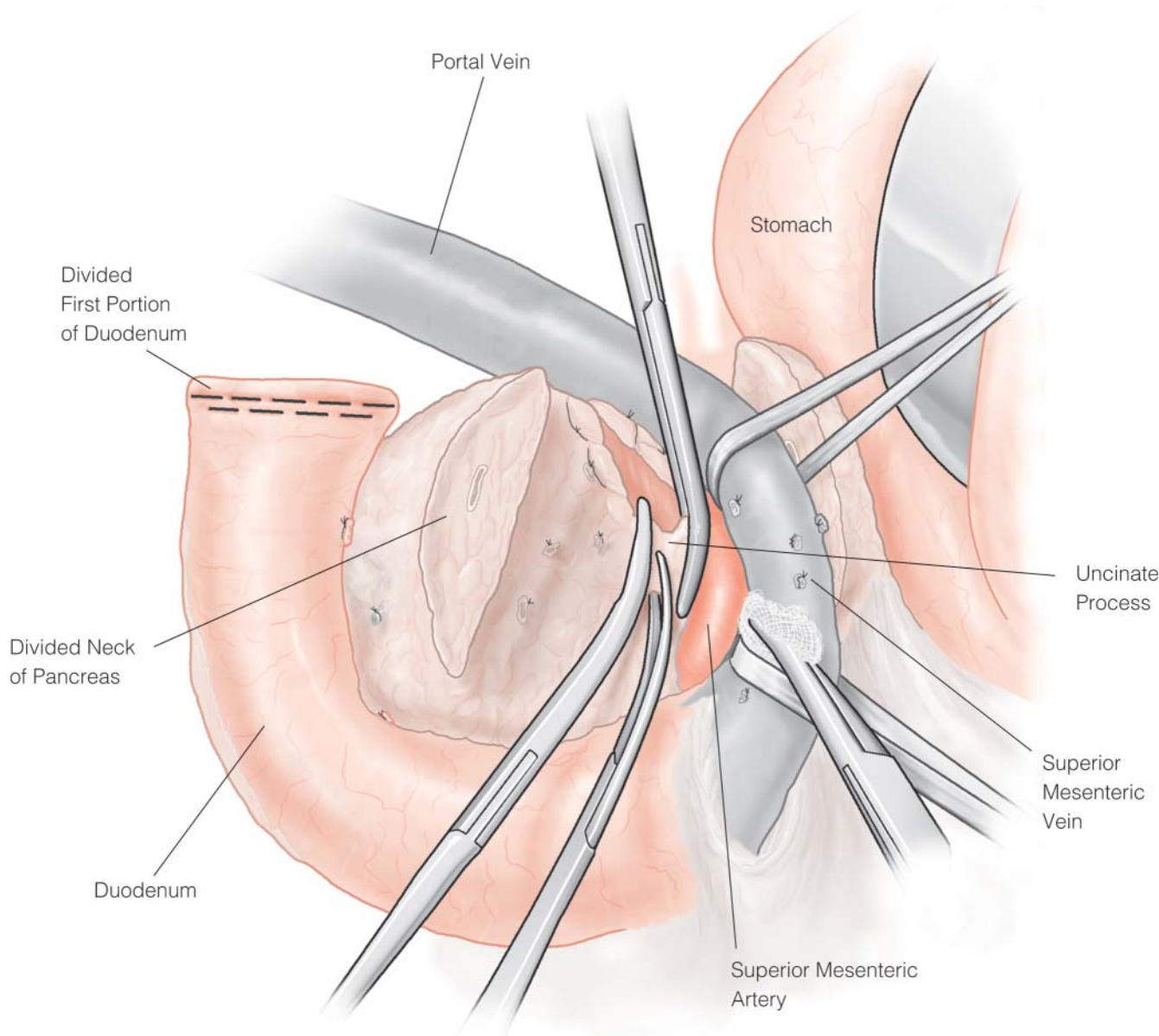


Figure 4 Whipple procedure. The uncinate process is divided flush with the superior mesenteric artery.

flexure of the colon is carefully dissected away from the inferior pole of the spleen, and the peritoneal attachments that make up the splenocolic ligament are divided.

The tail and the body of the pancreas are further mobilized out of the retroperitoneum by retracting the spleen and pancreatic tail medially. In the course of this mobilization, care must be taken not to injure the left adrenal gland, which often occupies a fairly superficial position in the retroperitoneum, anterior and medial to the superior pole of the left kidney; care must also be taken not to carry the dissection too deep and thereby risk injuring the kidney or renal vessels. The splenic vein is easily identified in the middle portion of the posterior aspect of the pancreas. The inferior mesenteric vein, which joins the splenic vein at the middle of the body of the pancreas, is identified in the retroperitoneum just lateral to the ligament of Treitz and can be divided at this point.

Further mobilization of the pancreas to the midline exposes the splenic artery where it originates from the celiac axis. As noted (see above), this artery will already have been isolated with a vessel loop. The splenic artery is triply clamped, divided, and triply ligated with 2-0 silk and a 3-0 polypropylene suture near its point of origin.

The SMV can then be identified. A plane is developed by dissecting between the anterior surface of the SMV and the neck of the pancreas; a Penrose drain may be looped around the neck to facilitate exposure. With larger pancreatic cancers, tumor extension into the retroperitoneum may involve the splenic vein. Dividing the pancreatic neck with the electrocautery at this point may facilitate dissection of the splenic vein–portal vein confluence under direct vision. The splenic vein is clamped, divided (without compromising the portal vein–SMV complex), and ligated with 2-0 silk ties

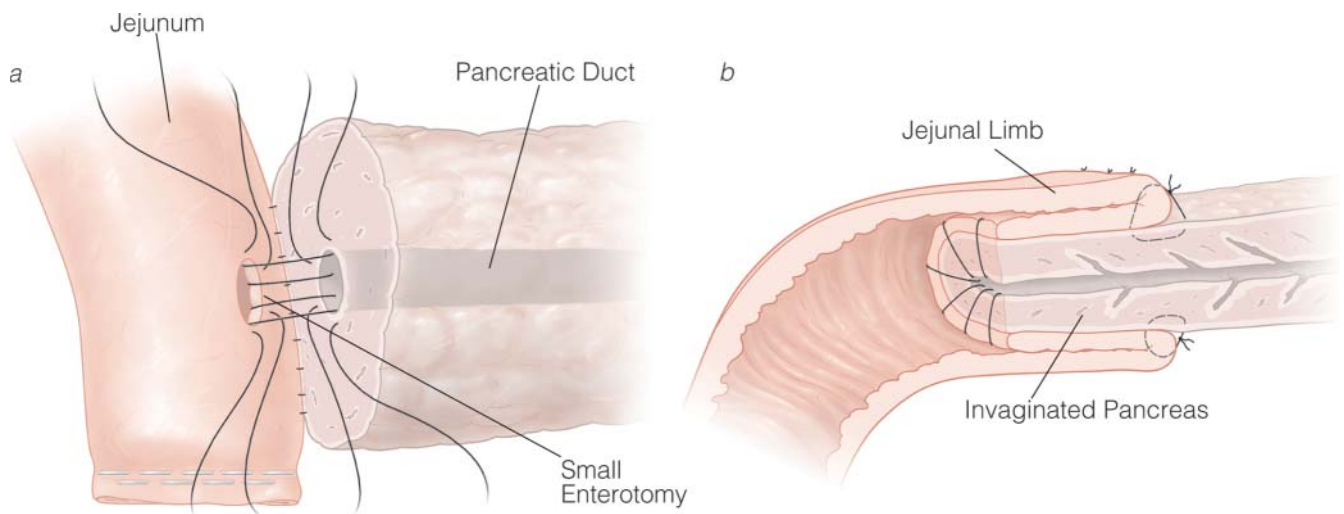


Figure 5 Whipple procedure. (a) An end-to-side mucosa-to-mucosa pancreaticojejunostomy is done in two layers with an outer layer of interrupted 3-0 silk sutures and an inner layer of interrupted 4-0 absorbable synthetic sutures. (b) Alternatively, the end of the pancreas can be invaginated into the end of the jejunum for approximately 2 cm. The anastomosis is done with an outer interrupted layer of 3-0 silk and an inner continuous layer of 3-0 absorbable synthetic suture material.

and a 3-0 polypropylene suture on the proximal stump [see Figure 8]. If there is a pancreatic tumor arising from the proximal body of the gland, the splenic vein may be ligated flush with the SMV. At this location, it is best to oversew the vein with a continuous 4-0 polypropylene suture so as not to compromise the portal vein–SMV complex.

The portal vein and the SMV are carefully dissected away from the undersurface of the neck of the pancreas. Stay sutures of 2-0 silk are placed at the superior and inferior edges of the pancreas proximal to the site of transection, and

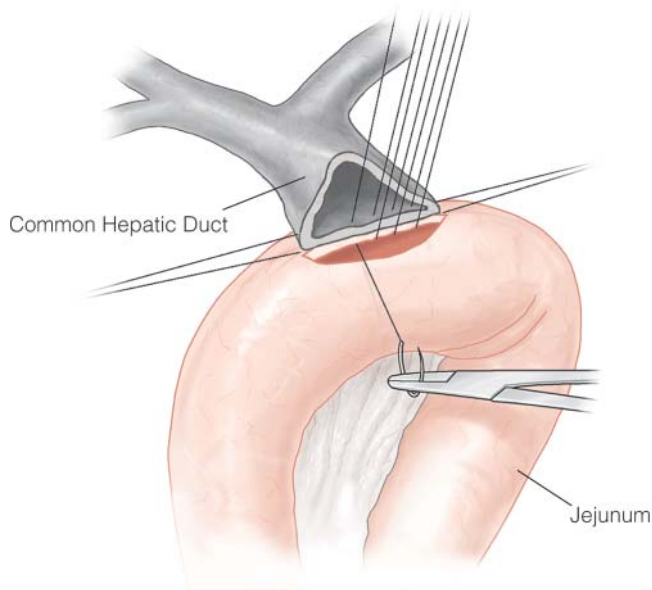


Figure 6 Whipple procedure. The common hepatic duct is anastomosed to the jejunum in an end-to-side fashion with a single layer of 4-0 interrupted absorbable synthetic sutures.

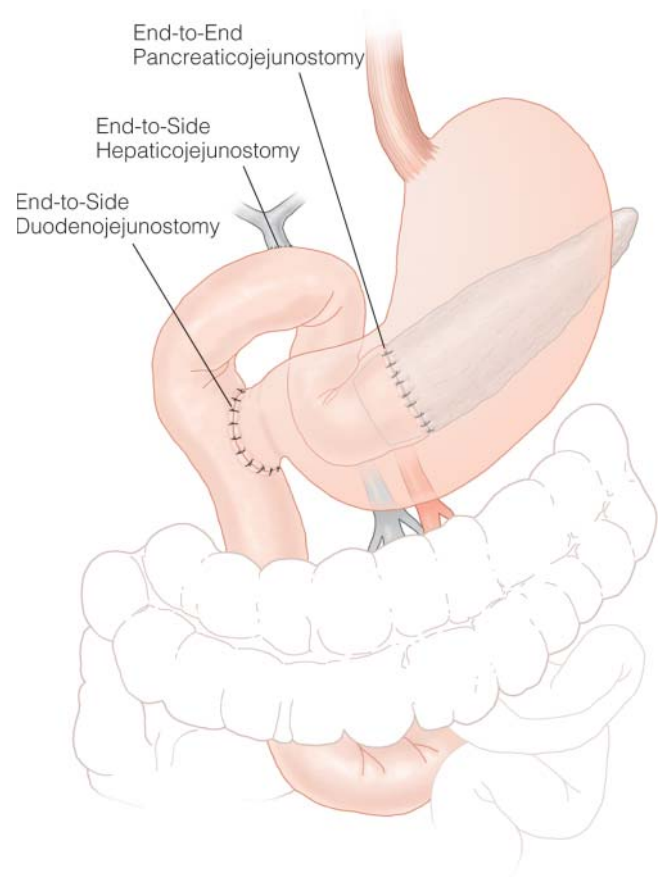


Figure 7 Whipple procedure. After the end-to-end pancreaticojejunostomy and the end-to-side hepaticojejunostomy, the duodenum is anastomosed to the jejunum in an end-to-side fashion with an inner continuous layer of 3-0 absorbable suture material and an outer interrupted layer of 3-0 silk.

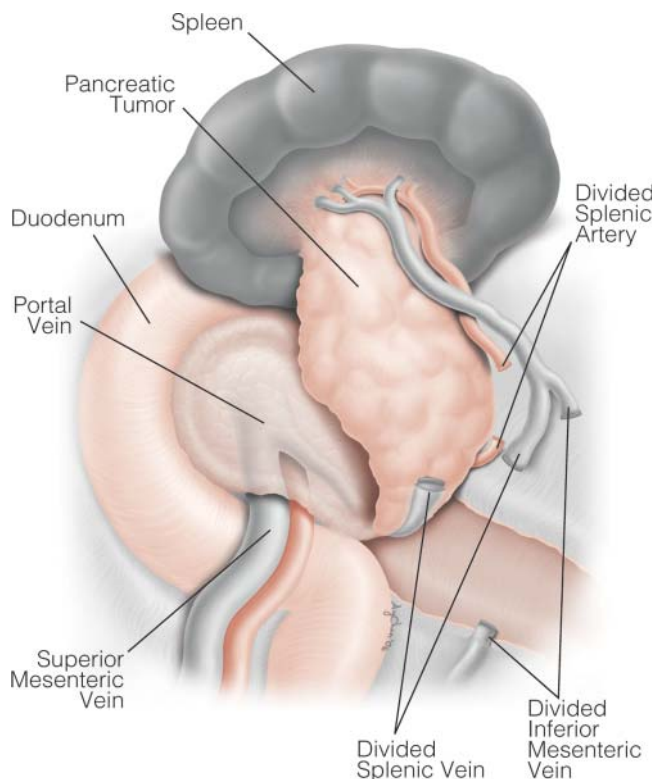


Figure 8 Distal pancreatectomy. The splenic vein is divided just distal to its junction with the inferior mesenteric vein and then dissected away from the posterior surface of the pancreas from the point of division up to the point where it joins the superior mesenteric vein to form the portal vein.

the neck of the pancreas is divided with the electrocautery (or, alternatively, with a transverse anastomosis or GIA stapler or ultrasonic shears). The operative specimen should be sent for frozen-section evaluation to ensure a negative microscopic margin.

A row of figure-eight sutures of 3-0 absorbable synthetic suture material is placed over the end of the pancreas [see Figure 9]. Using large needles that have been straightened makes this task simple even if the head-neck junction through which the needles are passed is thickened. If the pancreatic duct can be identified, it should be separately oversewn with a figure-eight or mattress suture of 5-0 absorbable synthetic suture material. The resection bed can be marked with titanium clips to guide postoperative radiation therapy if necessary.

The abdomen is copiously irrigated with an antibiotic solution. The pancreatic remnant is drained with a closed-suction Silastic drain brought out through a stab wound in the left upper quadrant. There is no need to drain the splenic bed. The abdomen is then closed in a standard fashion.

Laparoscopic Distal Pancreatectomy with or without Splenectomy

Selected patients may benefit from a laparoscopic spleen-preserving distal pancreatectomy (SPDP) or a laparoscopic distal pancreatectomy with splenectomy. Conditions that are

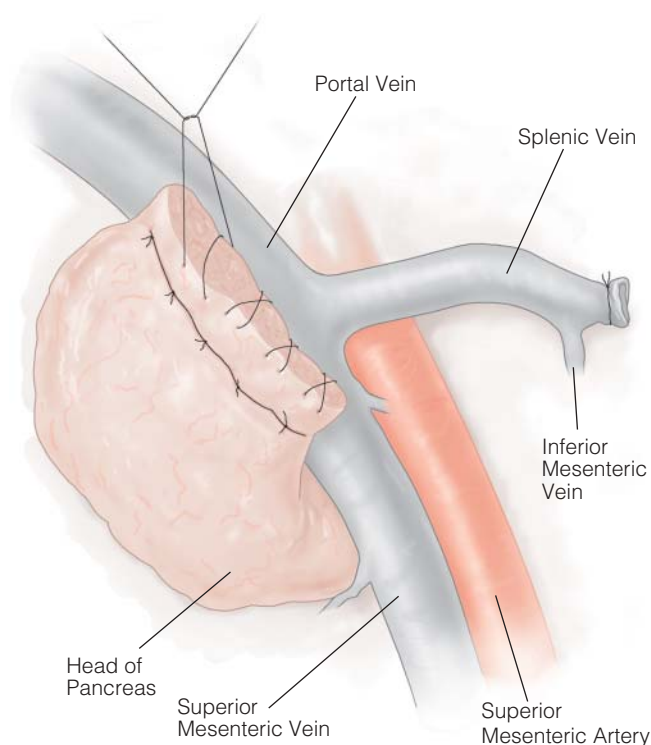


Figure 9 Distal pancreatectomy. A row of overlapping horizontal mattress sutures is placed in the neck of the pancreas just proximal to where it is to be divided, the neck is divided with the electrocautery, and a row of figure-eight sutures of 3-0 absorbable synthetic suture material is placed over the end of the pancreas.

potentially amenable to treatment with a laparoscopic distal pancreatectomy include benign or premalignant cystic neoplasms, islet cell tumors of the pancreas, chronic pancreatitis with symptomatic ductal obstruction, and pancreatic pseudocysts confined to the distal body and tail of the pancreas.

OPERATIVE TECHNIQUE

The patient can be placed either supine in a low lithotomy position or in a semilateral position with the left side up. For lesions in the distal body or tail of the pancreas, we prefer the semilateral position; for lesions closer to the neck of the pancreas, we prefer the low lithotomy position. Four to five ports are placed [see Figure 10], and a 10 mm 30° laparoscope is used. As in all pancreatic procedures, the peritoneal surfaces, the omentum, the mesentery, and the viscera should each be carefully inspected to rule out metastatic disease. Intraoperative ultrasonography may be employed to evaluate the liver and locate the lesion in the pancreas.

The body and tail of the pancreas are exposed by opening the lesser sac. The gastrocolic omentum is divided and widely mobilized with an ultrasonic scalpel (e.g., Harmonic Scalpel; Ethicon Endo-Surgery, Inc., Cincinnati, Ohio), with care taken to stay outside the gastroepiploic vessels. Either a retractor is advanced into the lesser sac through the sub-xiphoid port or suture retraction to the abdominal wall is employed to elevate the stomach anteromedially. The splenocolic ligament is divided, and the splenic flexure of the colon is reflected inferiorly.

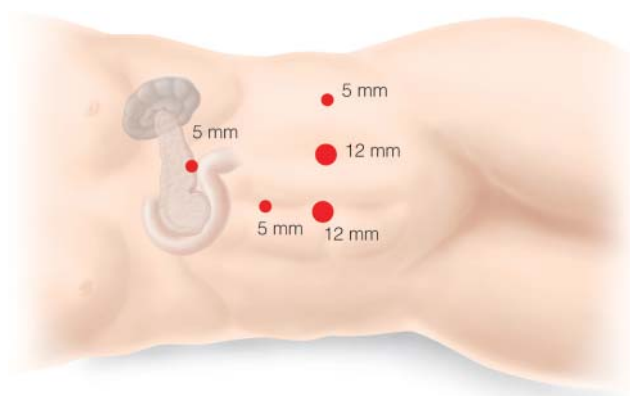


Figure 10 Laparoscopic distal pancreatectomy. Shown is the placement of ports for distal pancreatectomy.

After these maneuvers, the inferior pancreatic margin is exposed. The peritoneum is then incised along the inferior pancreatic border, and the pancreatic body is separated from the retroperitoneum by means of sharp and blunt dissection along its inferior border. Laparoscopic ultrasonography and direct visual inspection, combined with the findings from pre-operative imaging, may be employed to determine the extent of the dissection. Initially, the dissection should be directed so that it is medial to the pancreatic lesion. The pancreatic body is elevated by means of blunt and sharp dissection, after which the splenic vein should be easily identifiable [see Figure 11]. Care must be exercised to prevent inadvertent injury to this vessel. Once the splenic vein has been identified, a careful circumferential dissection around the splenic vein is performed with a right-angle clamp, and a vessel loop is placed around the vein. This dissection helps identify the splenic artery as well, which also is controlled with a vessel loop. These precautionary measures allow quick control of bleeding should a vascular tear occur later in the procedure.

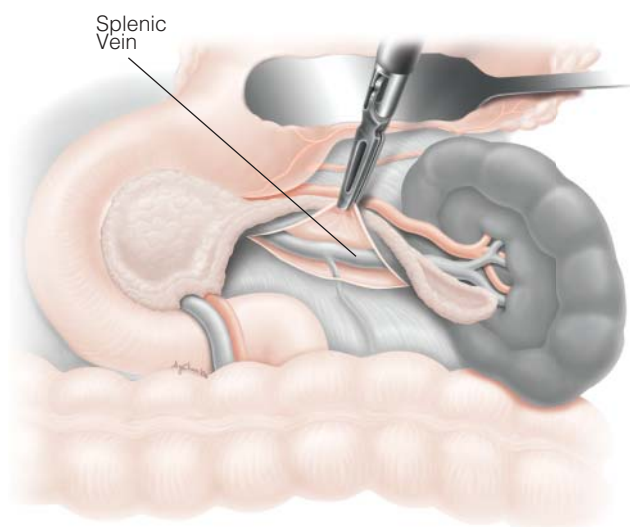


Figure 11 Laparoscopic distal pancreatectomy. Once the pancreatic body has been mobilized from the retroperitoneum, the splenic vein can be identified.

Once the pancreatic body has been adequately mobilized from the splenic vessels, the pancreatic parenchyma is divided. This may be done with an endoscopic stapler, but we prefer using the ultrasonic scalpel. Once the proximal pancreatic tissue is divided, the specimen is grasped and gently retracted anteriorly to allow further dissection of the vessels. The dissection proceeds toward the splenic hilum in a medial-to-lateral direction. The pancreatic branches of the splenic vein are sequentially identified, dissected free with laparoscopic Metzenbaum scissors, and divided with the ultrasonic scalpel [see Figure 12]. The branches of the splenic artery, which runs just superior to the vein, are treated similarly. Special care must be taken as the dissection approaches the hilum of the spleen.

At the completion of an SPDP, the specimen is placed and removed in a standard endoscopic retrieval device (e.g., Endo Catch; United States Surgical, Norwalk, Connecticut). Some surgeons then oversew the pancreatic remnant with a series of interrupted absorbable horizontal mattress sutures. Alternatively, the exposed end of the pancreatic remnant can be sealed with an energy device. A single round Jackson-Pratt drain is placed near the pancreatic transection line and brought out through one of the 5 mm lateral ports.

An alternative approach to SPDP involves dividing the splenic vessels proximally and distally while preserving the short gastric and left gastroepiploic vessels to maintain splenic perfusion [see Figure 13]. The initial steps of this technique are essentially the same as those already described (see above), up to the division of the pancreas. In the alternative approach to SPDP, after pancreatic transection, the splenic artery and vein are divided with an endovascular stapler. The left portion of the pancreas is lifted up and mobilized posteriorly along with the splenic artery and vein, and the vessels are again divided as they emerge from the pancreatic tail to enter

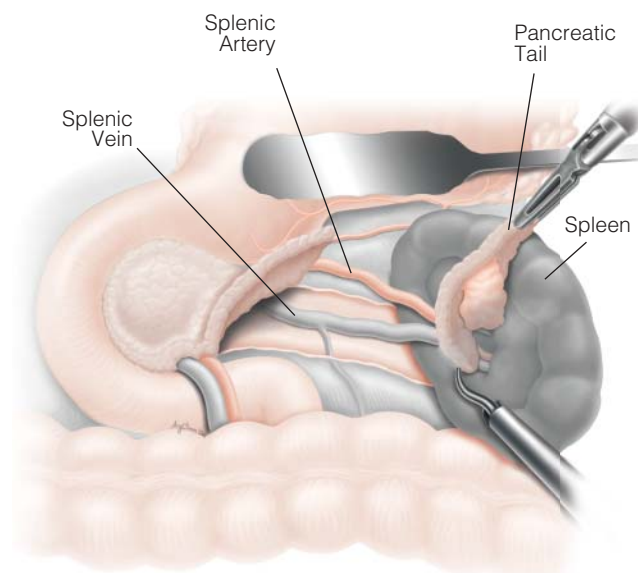


Figure 12 Laparoscopic distal pancreatectomy. After having been transected, the distal portion of the pancreas is dissected away from the splenic vessels in a medial-to-lateral direction. The pancreatic branches of the splenic vessels are divided sequentially as they are encountered.

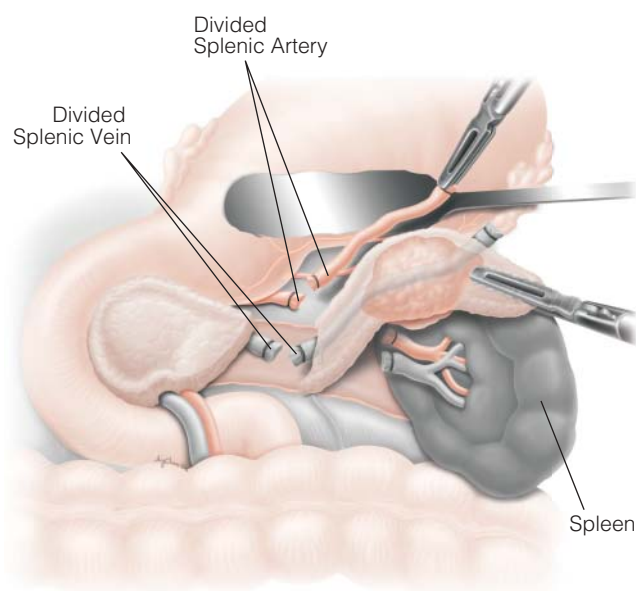


Figure 13 Laparoscopic distal pancreatectomy. In an alternative approach to spleen-preserving distal pancreatectomy, the splenic artery and the splenic vein are divided, and the viability of the spleen is maintained by preserving the short gastric and left gastroepiploic vessels.

the hilum of the spleen. The spleen is then supplied solely by the short gastric vessels and the left gastroepiploic vessels.

If an en bloc distal pancreatectomy with splenectomy is performed, the splenic artery and vein are divided after the pancreas is transected. The distal pancreas is dissected free in a medial-to-lateral direction. The short gastric vessels are divided with an ultrasonic scalpel, with care taken not to injure the stomach wall. The retroperitoneal attachments of the spleen and the tail of the pancreas are also divided with the ultrasonic scalpel. The specimen is then placed in a specimen retrieval bag and extracted from a port site that has been enlarged to a size of 3 to 6 cm. To facilitate extraction of the specimen, the spleen may be morcellated within the bag.

Laparoscopic Pancreatic Enucleation

Recently, laparoscopic techniques have been applied to the enucleation of benign neuroendocrine tumors of the pancreas. This approach is indicated for tumors located in the body and tail of the pancreas that do not appear to involve the pancreatic duct on preoperative imaging. Patient positioning and trocar placement are similar to those for laparoscopic distal pancreatectomy (see above). The body and tail of the pancreas are widely exposed by entering the lesser sac through the gastocolic omentum. Intraoperative ultrasonography is again useful for the identification of the tumor and to further delineate the relationship of the lesion to the splenic vessels and the pancreatic duct. The lesion can then be dissected out of the pancreatic parenchyma using the ultrasonic shears or electrocautery. The specimen is placed in a retrieval bag and removed. The enucleation bed is then inspected for hemostasis and a closed-suction drain is placed to control any potential pancreatic leak.

Longitudinal Pancreaticojejunostomy (Puestow Procedure)

OPERATIVE TECHNIQUE

The abdomen is entered through an upper midline or bilateral subcostal incision. The lesser sac is accessed by removing the greater omentum from the transverse colon along virtually its entire length, thereby exposing the tail, body, neck, and head of the pancreas. The pancreas often appears markedly fibrotic and scarred. The posterior wall of the stomach may be adherent to a portion of the body of the pancreas as a result of multiple episodes of inflammation; if it is adherent, it is easily dissected free. The duodenum is Kocherized, and the head and the uncinate process of the pancreas are palpated from both an anterior and a posterior direction. In many cases, the pancreatic duct is markedly dilated and can actually be palpated through the anterior surface in the middle portion of the body of the pancreas. The rest of the abdomen is explored to check for the presence of other pathologic conditions. To confirm the position of the dilated pancreatic duct, a 20-gauge needle on a 10 mL syringe is used to aspirate the duct. The use of intraoperative ultrasonography can be quite helpful to identify the dilated pancreatic duct. Once pancreatic juice is obtained, the syringe is removed from the needle hub, with the needle left in place.

The pancreatic duct is entered by dividing the pancreatic parenchyma with the electrocautery on either side of the needle. A large right-angle clamp is inserted, and the duct is filleted open with the electrocautery both proximally and distally [see Figure 14]. Small pancreatic ductal concretions are carefully removed. At least 6 cm of the duct must be opened to yield a good chance of long-term success. Ideally, if the

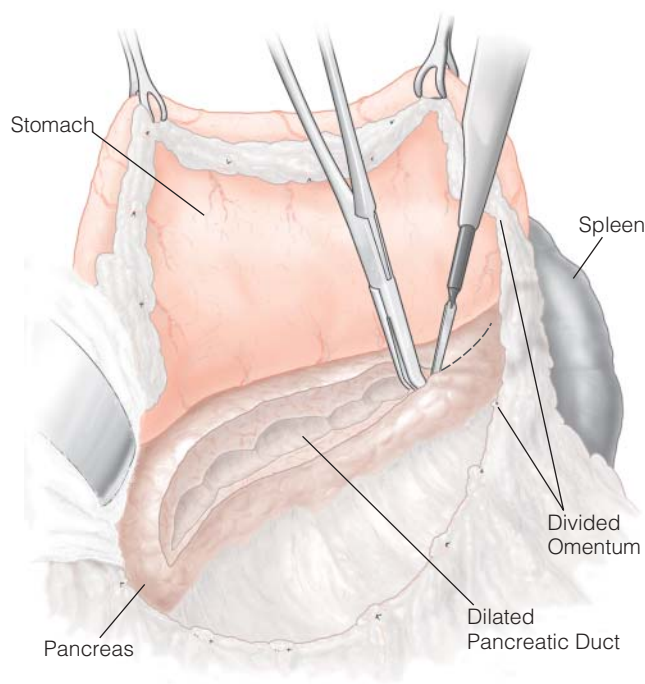


Figure 14 Puestow procedure. The dilated pancreatic duct is filleted open with the electrocautery both proximally and distally. At least 6 cm of the duct should be opened.

duct is dilated all the way out to the tail, it can be filleted open virtually to the tip of the pancreas. In the proximal direction, the duct can easily be opened as far as the neck of the pancreas. Beyond this point, however, the duct passes posteriorly and inferiorly into the head of the pancreas; because the head can be very thick, opening up the duct any further can be difficult.

A Bakes dilator is carefully passed proximally through the open pancreatic duct, down through the pancreatic duct in the unopened head, through the ampulla of Vater, and into the duodenum. If a Bakes dilator cannot be passed into the duodenum, some surgeons elect to open the duodenum and perform a sphincteroplasty, so that by working both from within the duodenum and from within the open pancreatic duct, they can ensure the patency of the entire pancreatic duct.

A Roux-en-Y jejunal loop approximately 50 cm long is constructed. The most proximal loop of jejunum in which there is a good vascular arcade is selected. A 2 cm segment of this loop is cleaned and divided with a GIA stapler. The small bowel mesentery is divided between clamps down through the arcade vessel and is ligated with 3-0 silk. The end of the distal jejunum is oversewn with a layer of 3-0 silk Lembert sutures. Alimentary tract continuity is reestablished by means of an end-to-side jejunojejunostomy, in which the most proximal portion of the divided jejunum is anastomosed to the side of the Roux-en-Y jejunal loop 50 cm distally with an inner continuous layer of 3-0 absorbable synthetic suture material and an outer interrupted layer of 3-0 silk. The defect in the small bowel mesentery is closed with a continuous 4-0 silk suture.

The Roux-en-Y jejunal loop is brought up into the lesser sac in a retrocolic position through a small rent in the transverse mesocolon. A side-to-side pancreaticojejunostomy is performed in two layers. Before the Roux loop is opened, an outer interrupted layer of 3-0 silk is placed between the jejunal loop and the pancreatotomy, passing through the capsule of the pancreas and out through the opened pancreatic parenchyma along the inferior border of the pancreas. When this layer is complete, an enterotomy approximately 2 mm from the jejunal suture line is made along the entire length of this line. Starting at the distal pancreatic tail, an inner continuous layer of 3-0 absorbable synthetic suture material is placed in an over-and-over locking fashion through the entire wall of the jejunum and the entire divided surface of the pancreas and into the duct [see Figure 15]. The inner layer of the superior suture line is placed in an over-and-over fashion without locking, again with a continuous 3-0 absorbable synthetic suture. The outer layer of the superior suture line consists of interrupted 3-0 silk sutures placed in a Lembert fashion.

When the pancreatic duct is dilated to a diameter of 1 cm or greater, a two-layer anastomosis is possible and is, in fact, preferred. When the diameter of the duct is between 5 mm and 1 cm, however, a two-layer anastomosis is generally difficult, and a one-layer anastomosis is preferred. A single layer of interrupted 3-0 silk sutures is placed so that the knots are tied on the outside. This is easily accomplished with the superior suture line. With the inferior suture line, which is placed first, the suture passes from outside inward on the pancreas and then from inside outward on the jejunum. In a single-layer side-to-side pancreaticojejunostomy, the jejunostomy must be performed before any sutures are placed.

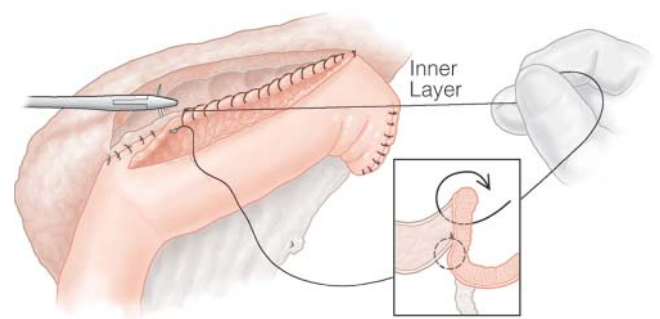


Figure 15 Puestow procedure. When the diameter of the dilated pancreatic duct is 1 cm or wider, a side-to-side pancreaticojejunostomy should be done in two layers. Once an outer layer of interrupted 3-0 silk sutures is placed between the jejunal loop and the pancreatotomy, an enterotomy is made along the entire length of the jejunal suture line, and an inner layer consisting of a continuous 3-0 absorbable synthetic suture is placed.

The procedure is completed by tacking the Roux-en-Y jejunal loop to the rent in the transverse mesocolon with interrupted 3-0 silk sutures. The pancreaticojejunostomy is drained with closed-suction Silastic drains placed on either side of the anastomosis and brought out through separate stab wounds in the left upper quadrant. The abdomen is copiously irrigated with an antibiotic solution and closed in a standard fashion.

Duodenum-Preserving Pancreatic Head Resection (Frey Procedure)

The Frey procedure is indicated in patients with symptomatic chronic pancreatitis and (1) multiple pancreatic duct strictures, (2) an enlarged fibrotic pancreatic head with multiple impacted ductal calculi, and/or (3) a dilated obstructed main pancreatic duct.

OPERATIVE TECHNIQUE

The peritoneal cavity is entered through either a midline or bilateral subcostal incision, and the abdomen is explored. An extensive Kocher maneuver is completed, followed by division of the gastrocolic ligament to obtain exposure to the anterior surface of the pancreas. The pancreatic duct is identified in the body of the gland via inserting a 20-gauge needle on a 10 mL syringe while aspirating. Once the duct is located, it is opened longitudinally along its length using electrocautery (as in a Puestow procedure). Classically, hemostatic absorbable sutures are also placed between the pancreas and the inner layer of the duodenum. A probe inserted into the pancreatic duct toward the ampulla is helpful for identification of the duct trajectory. The head of the pancreas is then cored out using electrocautery. This leaves a pancreatic cuff along the inner duodenum with an intact posterior pancreatic capsule. It should be noted that the surgeon's left hand is placed behind the pancreas to assist in determining the depth of this coring-out process. Care is also taken not to injure the bile duct at this level. The distal pancreatic duct within the remaining head (1.5 to 2.0 cm) is probed to ensure that all calculi have been removed. Once completed, a standard

Roux-en-Y jejunal limb is brought up through a defect in the transverse mesocolon to create a pancreaticojejunostomy. This anastomosis does not have to precisely approximate the pancreatic duct to the jejunal mucosa. It is generally completed in one or two layers using a 3-0 absorbable monofilament suture. The jejunojejunostomy should be constructed in the standard manner to create a 60 cm Roux-en-Y limb. Closed-suction drainage adjacent to the pancreas is optional. The abdomen is closed in a standard fashion.

Duodenum-Preserving Pancreatic Head Resection (Beger Procedure)

The Beger operation begins with the same steps as the Whipple procedure. The peritoneal cavity is entered through either a midline or bilateral subcostal incision, and the abdomen is explored. An extensive Kocher maneuver is completed prior to dividing the gastocolic ligament to obtain exposure to the anterior surface of the pancreas. The superior mesenteric and portal veins, as well as the common hepatic artery and bile duct, are identified. The portal vein is then dissected off the posterior pancreatic capsule in the same manner as during a Whipple procedure. Caution must be employed during this step, given the frequent inflammatory attachments between the pancreas and the portal vein as a result of chronic pancreatitis. The gastroduodenal artery is doubly ligated once it has been test occluded. The neck of the pancreas is then transected using electrocautery with special attention to identifying the main pancreatic duct during transection. The pancreatic head is then rotated 90° into an anterior-posterior position prior to its complete separation from the portal vein. Mobilizing the portal vein typically entails the ligation of two small branches during this step. The subtotal resection of the pancreatic head is synonymous to that performed during the Frey procedure. Again, a probe inserted into the pancreatic duct toward the ampulla is helpful for identification of the duct trajectory. Reconstruction involves two pancreaticojejunostomies after a Roux-en-Y limb of jejunum is passed to the pancreatic head in a retrocolic manner. The first anastomosis is completed between the remaining left pancreas and the jejunum in a side-to-end manner. This two-layer duct to mucosa anastomosis is the same as during a Whipple procedure. The second anastomosis is a one- or two-layer side-to-end pancreaticojejunostomy approximately 8 cm distal to the left pancreatic anastomosis. The jejunal incision approximates 5 cm in length, and the anastomosis is identical to the one described during the Frey procedure. Finally, a distal jejunojejunostomy is created to complete the 60 cm Roux-en-Y limb. It should also be noted that in patients with multiple stenoses of a dilated main pancreatic duct, the duct can also be opened longitudinally toward the tail of the gland. A side-to-side pancreaticojejunostomy, identical to a Puestow procedure, is then completed.

Drainage of Pancreatic Pseudocyst

OPERATIVE TECHNIQUE

Drainage into Roux-en-Y Jejunal Loop

The peritoneal cavity is entered through a midline incision, and the abdomen is explored. Typically, a substantial mass

that is cystic and easily ballotable is palpable posterior to the stomach. The duodenum and the head of the pancreas are Kocherized so that the head may be palpated both anteriorly and posteriorly. The physical characteristics of chronic pancreatitis are usually present. The body and the tail of the pancreas are palpated as well; the pancreas is usually fibrotic, firm, and somewhat enlarged. The rest of the abdomen is explored to check for the presence of other pathologic conditions.

At this point, the size and configuration of the cyst are compared with the findings on the preoperative CT scan. If the CT scan shows a unilocular solitary cyst and if, at the time of laparotomy, there appears to be a mass that coincides exactly with what is observed on the CT scan, there is no need to enter the lesser sac. The lesion can be drained into a Roux-en-Y jejunal loop through the transverse mesocolon, and the lesser sac need not be explored. Most pseudocysts are formed by anterior disruptions of the main pancreatic duct. When pancreatic secretions leak out into the lesser sac, the body walls off the leak through an inflammatory response. The transverse mesocolon becomes adherent to the posterior wall of the stomach, which in turn adheres to other adjacent structures in and around the retroperitoneum. As a result, the leak is sealed off. Thus, the transverse mesocolon is usually the inferior and most dependent portion of the pseudocyst, and this site is the ideal location for drainage [see Figure 16].

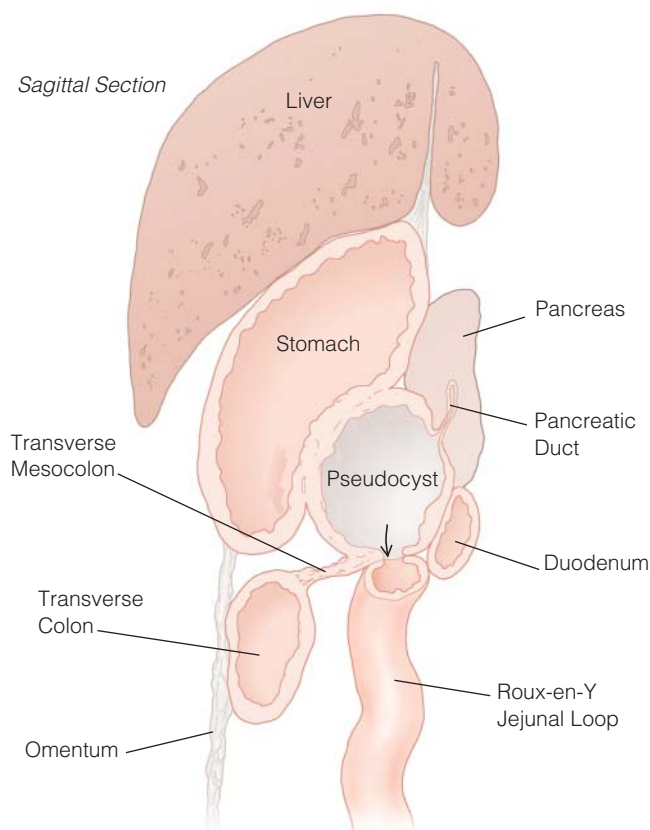


Figure 16 Drainage of pancreatic pseudocyst into Roux-en-Y jejunal loop. The transverse mesocolon is usually the most inferior and dependent part of a pancreatic pseudocyst; thus, drainage through the transverse mesocolon into a Roux loop is usually the ideal approach.

The transverse colon is retracted cephalad, and the cyst is easily visualized and palpated through the transverse mesocolon. The location of the cyst is confirmed by aspirating pancreatic juice through the transverse mesocolon with a 10 mL syringe and a 20-gauge needle. The middle colic vessels must be carefully identified and avoided. A 60 cm long Roux-en-Y jejunal loop is constructed. The proximal jejunum is divided with a GIA stapler at the first convenient arcade. The small bowel mesentery is divided down through the arcade. The distal end of the jejunum is inverted with an interrupted layer of 3-0 silk Lembert sutures.

Alimentary tract continuity is reestablished by means of an end-to-side jejunojejunostomy, in which the proximal jejunum is anastomosed to the side of the Roux-en-Y jejunal loop 60 cm from the inverted end. This anastomosis is performed with an inner continuous layer of 3-0 absorbable synthetic suture material and an outer interrupted layer of 3-0 silk. The rent in the small bowel mesentery is closed with a continuous 3-0 silk suture.

A side-to-side cystojejunostomy is performed with an outer interrupted layer of 3-0 silk and an inner continuous layer of 3-0 absorbable synthetic suture material. The posterior outer layer of the anastomosis consists of a series of 3-0 silk sutures passed through and through the jejunal loop and through and through the transverse mesocolon (which is the inferior wall of the pseudocyst) [see Figure 17]. The suture line should be

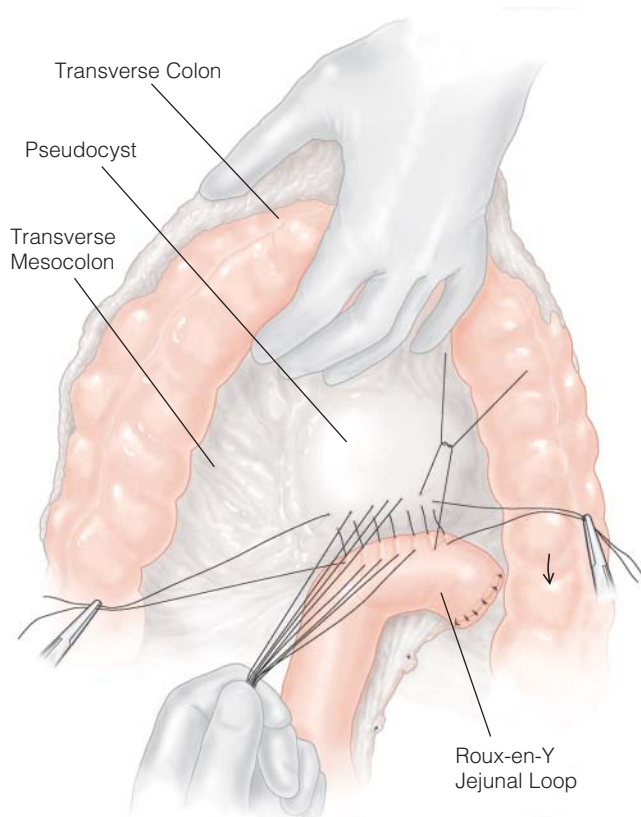


Figure 17 Drainage of pancreatic pseudocyst into Roux-en-Y jejunal loop. The outer posterior layer of the side-to-side cystojejunostomy comprises a series of 3-0 silk sutures placed through and through the jejunal loop and the transverse mesocolon.

approximately 2.5 to 5 cm long. After the posterior layer has been secured, a cystotomy is performed with the electrocautery. An ellipse of cyst wall is removed and sent for frozen-section examination. No matter how clear it seems to be that the lesion is a pseudocyst, a specimen from the cyst wall should always be sent for frozen-section examination. Some of these lesions are cystic neoplasms, which must be resected rather than drained. If no epithelial lining is found on frozen-section examination, it is safe to assume that the lesion is not a cystic neoplasm but a pancreatic pseudocyst and to proceed accordingly.

A parallel enterotomy is made in the jejunum. An inner continuous layer of 3-0 absorbable synthetic suture material is placed inferiorly in a locking fashion and then brought around superiorly in a Connell stitch. An outer interrupted layer of 3-0 silk is placed superiorly. With the cyst decompressed, a sizable lumen should be easily palpable in the anastomosis between the cyst and the jejunal loop.

A closed-suction Silastic drain is left near the anastomosis and brought out through a stab wound in the left upper quadrant. The abdomen is copiously irrigated with an antibiotic solution and closed in a standard fashion.

Drainage into Stomach

The peritoneal cavity is entered through an upper midline incision, and the abdomen is explored. Typically, a pseudocyst that is not amenable to drainage through the transverse mesocolon presents as a mass that is cystic and is palpable through the anterior wall of the stomach and the lesser omentum in the upper abdomen; such a mass is not generally palpable through the root of the transverse mesocolon with the transverse mesocolon reflected cephalad and thus is not easily drained into a Roux-en-Y jejunal loop. The duodenum and the head of the pancreas are Kocherized, and the head of the pancreas is palpated. Signs of chronic pancreatitis are invariably present. The rest of the abdomen is explored to check for the presence of other pathologic conditions.

Stay sutures of 3-0 silk are placed in the anterior wall of the body of the stomach. A transverse gastrotomy is made with the electrocautery. The cyst wall is easily palpable through the posterior wall of the stomach. The location of the cyst is confirmed by aspirating pancreatic juice through the back wall of the stomach with a 10 mL syringe and a 20-gauge needle. The mass palpated at the time of operation is compared with the cyst as it appears on the preoperative CT scan. If the CT scan shows a solitary unilocular cyst that corresponds to the palpable mass identified at the time of laparotomy, it is safe to conclude that the cyst is solitary and can be drained effectively into the stomach.

A transverse incision is made with the electrocautery through the posterior wall of the stomach, through the cyst wall, and into the pseudocyst. It is often desirable to leave the 20-gauge needle in place and to perform the posterior wall gastrotomy on either side of the needle. An ellipse of cyst wall is sent for frozen-section examination. Again, this step is mandatory, no matter how obvious it seems that the lesion is an inflammatory cyst. A continuous locking suture of 3-0 absorbable synthetic material is placed through and through the posterior wall of the stomach and the anterior wall of the cyst [see Figure 18]. This step may or may not actually be important for achieving long-term patency of the opening

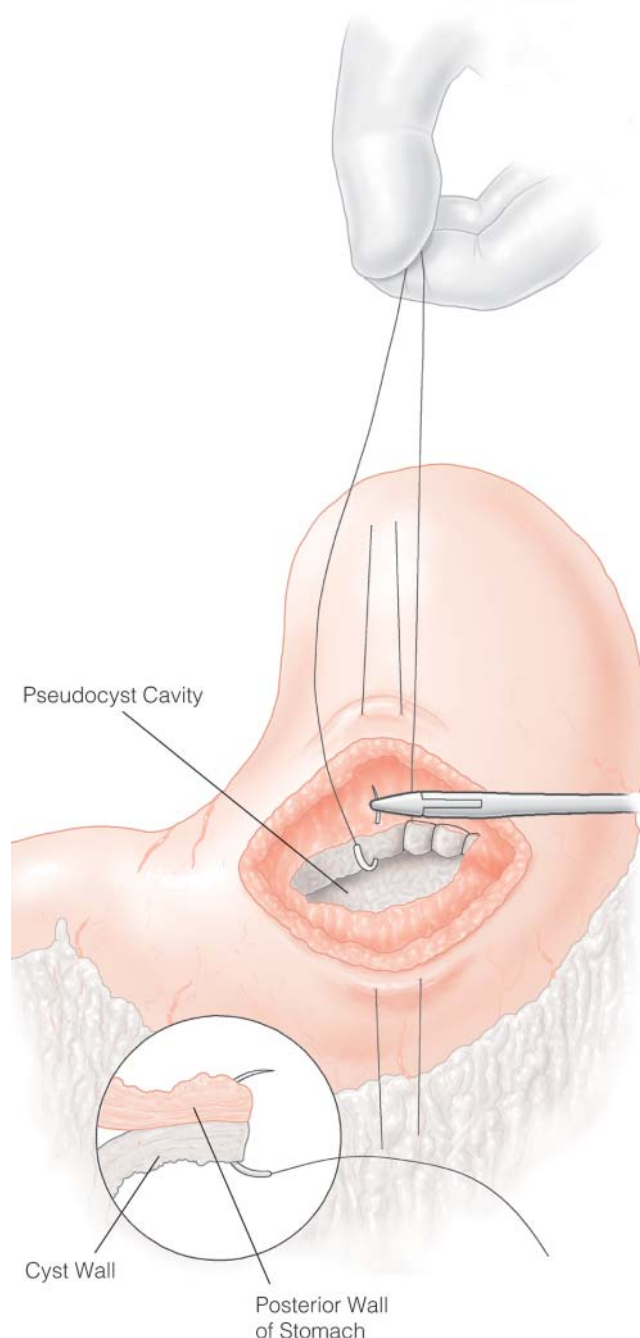


Figure 18 Drainage of pancreatic pseudocyst into stomach. Once an incision has been made through the posterior wall of the stomach, through the cyst wall, and into the pseudocyst, a continuous locking 3-0 absorbable synthetic suture is placed through and through the posterior wall of the stomach and the cyst wall.

between the cyst and the posterior wall of the stomach, but it does ensure good hemostasis. The anterior gastrotomy is closed with an inner continuous layer of 3-0 absorbable synthetic suture material in a Connell stitch and an outer interrupted layer of 3-0 silk. The abdomen is closed in a standard fashion. It should also be noted that drainage may be achieved endoscopically in many cases.

Laparoscopic Drainage of Pancreatic Pseudocysts

Five distinct laparoscopic approaches have been described for the treatment of pancreatic pseudocysts: (1) transgastric cystgastrostomy, (2) intragastric cystgastrostomy, (3) mini-laparoscopic intragastric cystgastrostomy, (4) cystgastrostomy via the lesser sac approach, and (5) Roux-en-Y cystjejunostomy.

The laparoscopic transgastric cystgastrostomy involves making an anterior gastrotomy, followed by using electrocautery to open the cyst wall through the posterior wall of the stomach. A cystgastrostomy can then be created using an endoscopic stapler or via a handsewn anastomosis with intracorporeal suturing. Intragastric cystgastrostomy involves inserting trocars percutaneously through the abdominal wall and directly into the gastric lumen using simultaneous laparoscopic and gastroscopic guidance. Cautery and sharp dissection are used to create the cystgastrostomy. The mini-laparoscopic intraluminal cystgastrostomy is performed in a similar fashion, with the exception that 2 mm intragastric ports are used to minimize invasiveness and trauma to the anterior gastric wall. Laparoscopic cystgastrostomy via the lesser sac approach is becoming the preferred approach when the anatomy is favorable. The advantages of this approach include the avoidance of an anterior gastrotomy, as well as the assurance of a large anastomosis that is not dependent on the adherence of the cyst to the posterior gastric wall. Because the entire anastomosis is either stapled or sutured, the risk of bleeding is minimized. The technique involves creating a window in the gastrocolic omentum through which the lesser sac is entered. The stomach is then elevated, and a cystotomy is made adjacent to a posterior gastric wall gastrotomy. A cystgastrostomy is then created with an endoscopic stapler, followed by a suture closure of the opening.

For large cysts, or those not in direct contact with the posterior wall of the stomach, a laparoscopic Roux-en-Y cyst jejunostomy can be performed. The omentum and transverse colon are retracted cephalad and the pseudocyst can often be visualized through the transverse mesocolon. Laparoscopic ultrasonography can also be used to help identify the location of the cyst. The jejunum is divided approximately 30 cm distal to the ligament of Treitz to create a Roux limb. The pseudocyst is next opened with the Harmonic Scalpel through the transverse mesocolon. A small enterotomy is made in the Roux limb, and a stapled cyst jejunostomy can be performed. The cyst enterostomy is then closed with a running suture. The procedure is completed with the jejunojunction performed at least 30 cm distal to the cyst jejunostomy.

Palliative Bypass for Unresectable Periapillary Cancer

The peritoneal cavity is entered through an upper midline incision, and the abdomen is examined for evidence of liver metastases, serosal spread, carcinomatosis, involvement of regional lymph nodes, and invasion of major vascular structures. Once the tumor has been shown to be unresectable and histologic confirmation of malignancy has been received, a palliative double-bypass procedure is begun, in which the duodenum is bypassed with a retrocolic gastrojejunostomy and the distally obstructed biliary tree is bypassed with a

hepaticojejunostomy. A chemical splanchnicectomy is also performed to reduce pain.

Approximately 4 cm of the most dependent portion of the greater curvature of the stomach is cleaned by doubly clamping, dividing, and ligating attachments of the greater omentum. Once this is accomplished, a small rent is made in the transverse mesocolon, and a proximal loop of jejunum is brought up through this rent and anastomosed in an isoperistaltic fashion to the dependent wall of the stomach. The anastomosis is performed with an outer interrupted layer of 3-0 silk and an inner continuous layer of 3-0 absorbable synthetic suture material.

In the past, palliative duodenal bypasses for pancreatic cancer were frequently performed by carrying out an anterior antecolic gastrojejunostomy. Delayed gastric emptying proved to be a common occurrence with this approach. Fortunately, this complication can be virtually eliminated by performing a posterior gastroenterostomy. Once the posterior gastroenterostomy is complete, the anastomosis is tacked to the rent in the transverse mesocolon on the gastric side with interrupted 3-0 silk sutures to prevent the afferent and efferent jejunal limbs from herniating up through the transverse mesocolon [see Figure 19].

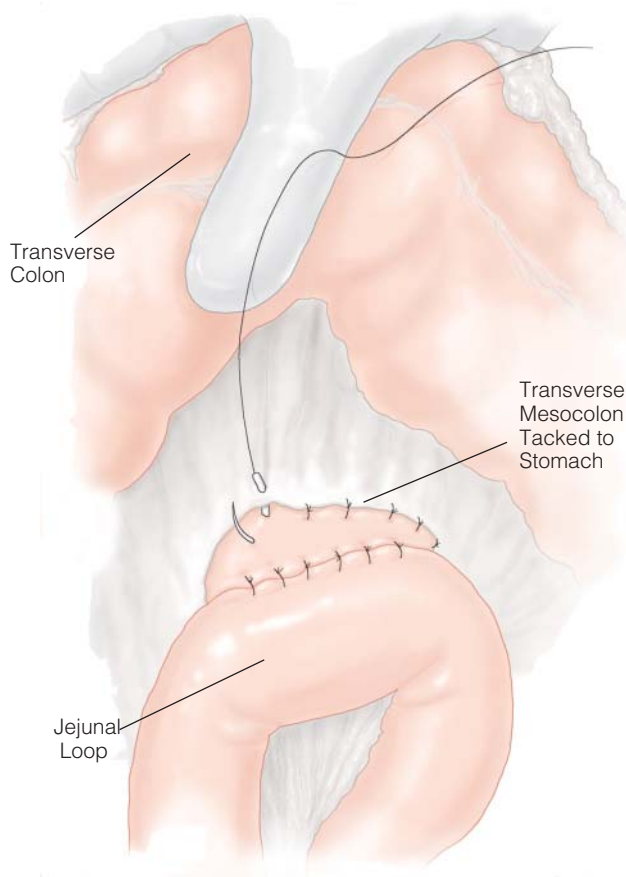


Figure 19 Palliative double bypass for unresectable pancreatic cancer. Once the retrocolic gastrojejunostomy is complete, the anastomosis is tacked to the rent in the transverse mesocolon on the gastric side with interrupted 3-0 silk sutures.

The gallbladder is mobilized out of the liver bed in a retrograde fashion and placed on traction to facilitate identification of the common hepatic duct. Once identified, the common hepatic duct is divided just proximal to the cystic duct. The gallbladder is removed, and the distal biliary segment is oversewn with a continuous 3-0 polypropylene suture. The jejunum is divided approximately 30 cm distal to the gastrojejunostomy, and a Roux-en-Y limb is brought up into the right upper quadrant through a second opening in the transverse mesocolon. An end-to-side hepaticojejunostomy is performed with a single layer of interrupted 4-0 absorbable synthetic sutures [see Figure 20]. An end-to-side jejunojejunostomy is then performed 60 cm downstream to restore enteric continuity and complete the Roux-en-Y. This anastomosis is performed with an inner continuous layer of 3-0 absorbable synthetic suture material and an outer interrupted layer of 3-0 silk. The Roux-en-Y limb is tacked to the opening in the transverse mesocolon to prevent herniation.

The lesser omentum is divided, and a chemical splanchnicectomy is performed by injecting 20 mL of 50% alcohol into the celiac plexus on each side of the aorta at the level of the celiac axis using a 22-gauge needle. The level of the celiac axis is easily determined by palpating the thrill that is invariably present in the common hepatic artery as it comes off the celiac axis.

A closed-suction Silastic drain may be left posterior to the area of the hepaticojejunostomy and brought out through a stab wound in the right upper quadrant. If tissue confirmation of the presence of adenocarcinoma of the head of

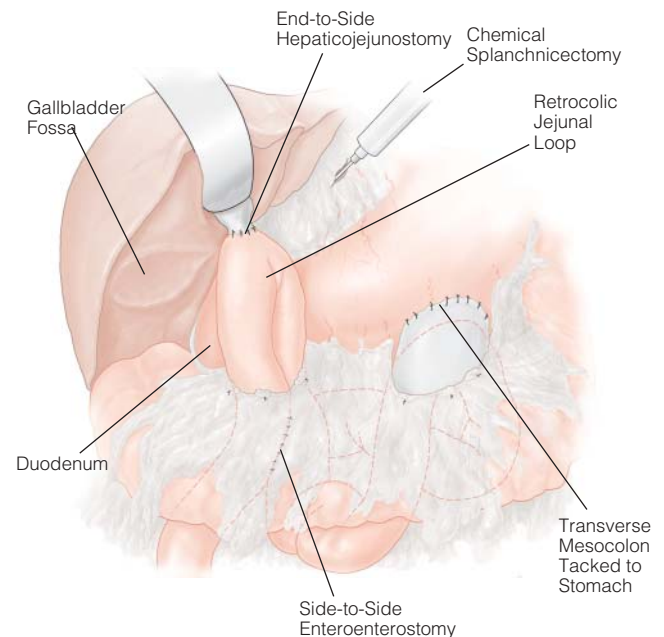


Figure 20 Palliative double bypass for unresectable pancreatic cancer. An end-to-side hepaticojejunostomy is performed, followed by a side-to-side jejunojejunostomy between the afferent loop leading to the biliary anastomosis and the efferent loop leading from it. An opening is made in the lesser omentum, and a chemical splanchnicectomy is performed by injecting alcohol into the celiac plexus.

the pancreas was not obtained preoperatively, it should be obtained during the operation. As a rule, this is most easily accomplished by performing a transduodenal needle biopsy (e.g., with a Tru-Cut needle; Cardinal Health, Dublin, Ohio).

The abdomen is irrigated with an antibiotic solution and closed in a standard fashion.

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Figures 1, 2, and 5 Tom Moore
Figures 3, 8, and 10 through 13 Alice Chen
Figures 4, 6, 7, 9, and 14 through 20 Tom Moore. Adapted from originals by Corinne Sandone.

25 SPLENECTOMY

Eric C. Poulin, MD, MSc, FACS, FRCSC, Christopher M. Schlachta, MDCM, FACS, FRSCS, and Joseph Mamazza, MDCM, FRSC

Medicine is not an exact science, and nowhere is this observation more appropriate than in the operating room when a spleen is being removed.¹

The first reported splenectomy in the Western world was performed by Zacarello in 1549, although the veracity of his operative description has been questioned. Between this initial report and the 1800s, very few cases were recorded. The first reported splenectomy in North America was performed by O'Brien in 1816. The patient was in the act of committing a rape when his victim plunged a large knife into his left side. As in this case, most early splenectomies were done in patients who had undergone penetrating trauma; often the spleen was protruding from the wound, and the surgeon proceeded with en masse ligation. The first elective splenectomy was performed by Quittenbaum in 1826 for sequelae of portal hypertension, and soon afterward, Wells performed one of the first splenectomies using general anesthesia; both patients died. In 1866, Bryant was the first to attempt splenectomy in a patient with leukemia. Over the following 15 years, 14 splenectomies were attempted as therapy for leukemia; none of the patients survived. In a 1908 review of 49 similar cases, Johnston reported a mortality of 87.7%.² These dismal results led to the abandonment of splenectomy for leukemia. In 1916, Kaznelson, of Prague, was the first to report good results from splenectomy in patients with thrombocytopenic purpura.

As the 20th century progressed, splenectomy became more common in direct proportion to the increase in the use of the automobile. The eventual recognition of the syndrome known as overwhelming postsplenectomy infection (OPSI) made splenic conservation an important consideration. Partial splenectomy had initially been described by the French surgeon Péan in the 19th century. This procedure received little further study until almost 100 years later, when the Brazilian surgeon Campos Cristo reevaluated Péan's technique in his report of eight trauma patients treated with partial splenectomy.³ Upadhyaya and Simpson's report on 16 children admitted for splenic trauma to The Hospital for Sick Children in Toronto between 1948 and 1955 was instrumental in establishing the validity of nonoperative treatment of splenic trauma.⁴

In late 1991 and early 1992, four groups working independently—Delaitre in Paris, Carroll in Los Angeles, Cushieri in the United Kingdom, and our group in Canada—published the first reports of laparoscopic splenectomy in patients with hematologic disorders.^{5–7} Since then, the development of operative techniques for partial laparoscopic splenectomy has tested the limits of minimally invasive surgery and encouraged clinical research into methods of simplifying the execution of the operation.^{8–10} The adoption of laparoscopic

splenectomy has led to a gradual decrease in the indications for open splenectomy; however, both procedures are still essential components of spleen surgery.

Anatomic Considerations

Most anatomy texts suggest that the splenic artery is constant in its course and branches; however, as the classic essay by Michels made clear, each spleen has its own peculiar pattern of terminal artery branches.¹¹

SPLENIC ARTERY

The celiac axis is the largest but shortest branch of the abdominal aorta: it is only 15 to 20 mm long. The celiac axis arises above the body of the pancreas and, in 82% of specimens, divides into three primary branches: the left gastric artery, which is the first branch, and the hepatic and splenic arteries, which derive from a common stem. In rare instances, the splenic artery originates directly from the aorta; even less often, a second splenic artery arises from the celiac axis. There are numerous other possible variations, in which the splenic artery may originate from the aorta, the superior mesenteric artery, the middle colic artery, the left gastric artery, the left hepatic artery, or the accessory right hepatic artery. As a rule, however, the splenic artery arises from the celiac axis to the right of the midline, which means that the aorta must be crossed to reach the spleen and that selective angiography is likely to be difficult at times. The splenic artery can take a very tortuous course, particularly in patients who are elderly or who have a longer artery.

In his study of 100 cadaver spleens, Michels divided splenic arterial geography into two types, distributed and magistral (or bundled) [see Figure 1].¹¹ In the distributed type, found in 70% of dissections, the splenic trunk is short, and six to 12 long branches enter the spleen over approximately 75% of its medial surface. The branches originate between 3 and 13 cm from the hilum [see Figure 1a]. In the bundled type, found in the remaining 30% of dissections, there is a long main splenic artery that divides near the hilum into three or four large, short terminal branches that enter the spleen over only 25 to 35% of its medial surface. These short splenic branches originate, on average, 3.5 cm from the spleen, and they reach the center of the organ as a compact bundle [see Figure 1b]. Early identification of the type of splenic blood supply present can help the surgeon estimate how difficult a particular splenectomy is likely to be. Operation on a spleen with a distributed vascular anatomy usually involves dissection of more blood vessels; however, the vessels, being spread over a wider area of the splenic hilum, are relatively easy to deal with. Operation on a spleen with a bundled-type blood supply typically involves dissection of fewer vessels; however, because the

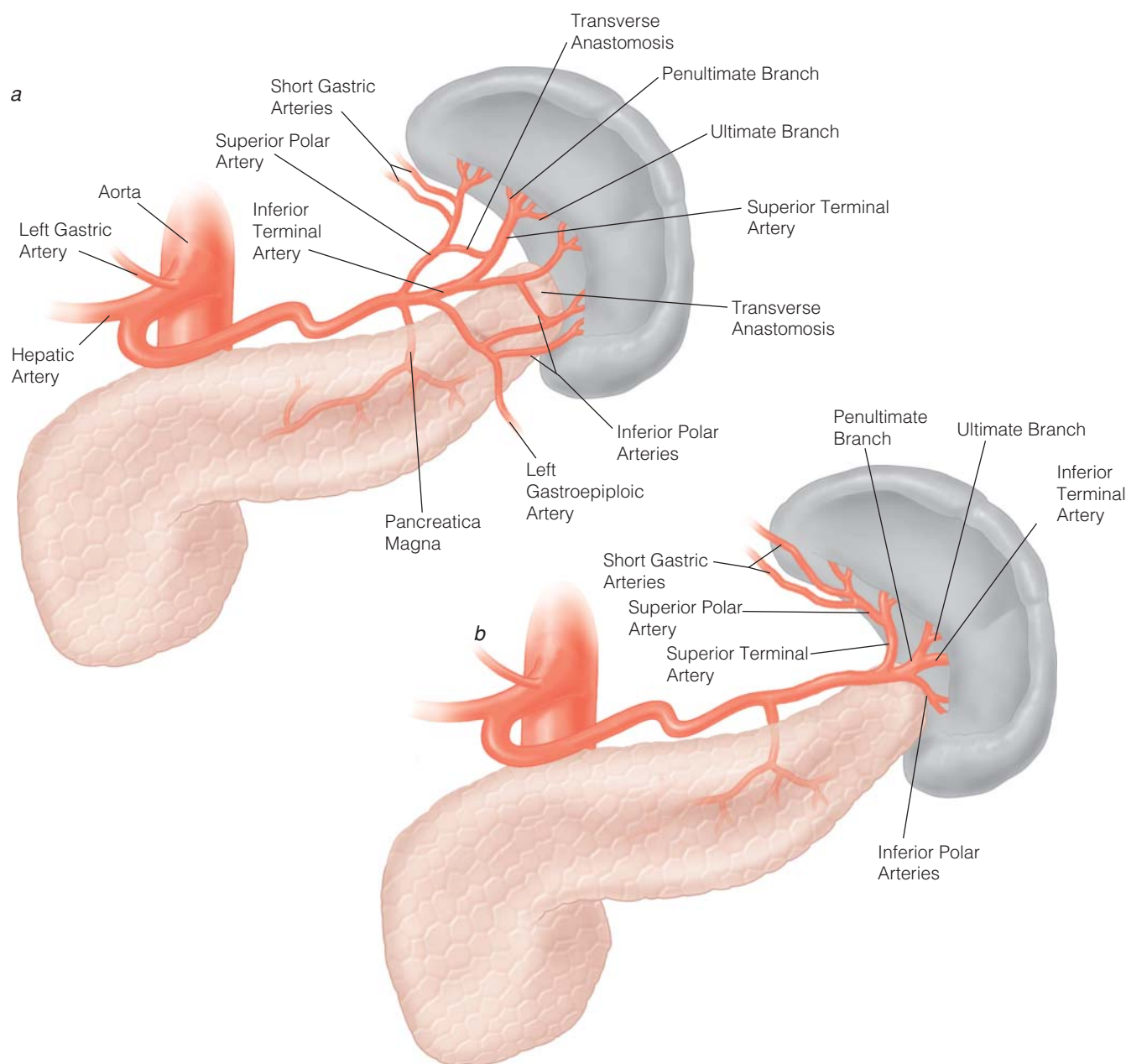


Figure 1 Splenic vascularization. Shown are (a) the distributed type and (b) the magistral (bundled) type of splenic vascularization.

hilum is narrower and more compact, dissection and separation of the vessels are more difficult.

BRANCHES OF SPLENIC ARTERY

The splenic branches vary so markedly in length, size, and origin that no two spleens have the same anatomy. Outside the spleen, the arteries also frequently form transverse anastomoses with each other that, like most collaterals, arise at a 90° angle to the vessels involved [see Figure 1].¹² As a consequence, attempts to occlude a branch of the splenic artery by means of clips or embolization, if carried out proximal to such an anastomosis, may fail to devascularize the corresponding splenic segment. Before the splenic trunk divides, it usually gives off a few slender

branches to the tail of the pancreas. The most important of these is called the pancreatica magna (a vessel familiar to vascular radiologists); occlusion of this branch with embolic material has been reported to result in pancreatitis. Next, the splenic artery divides into two to six first and second terminal branches, and these branches undergo two further levels of division into two to 12 penultimate and ultimate branches. Segmental and subsegmental division can occur either outside or inside the spleen. The number of arteries entering the spleen ranges from six to 36. The size of the spleen does not determine the number of arteries entering it; however, the presence of notches and tubercles usually correlates well with a higher number of entering arteries.

A reasonable general scheme of splenic artery branches might include as many as seven principal branches at various division levels and in various anatomic arrangements: (1) the superior terminal artery, (2) the inferior terminal artery, (3) the medial terminal artery, (4) the short gastric arteries, (5) the left gastroepiploic artery, (6) the inferior polar artery, and (7) the superior polar artery [see Figure 2]. Veins are usually located behind the corresponding arteries, except at the ultimate level of division, where they may be either anterior or posterior.

First Terminal Division Branches

A classic study from 1917 found that 72% of specimens had three terminal branches (superior polar, superior terminal, and inferior terminal) and 28% had two; the medial terminal artery was observed in only 20% of cases.¹³ When the superior terminal artery is excessively large, the inferior terminal is rudimentary, with an added blood supply often coming from the left gastroepiploic and polar vessels.

Second Terminal Division Branches

Superior polar artery The superior polar artery is present in 65% of patients. It usually arises from the main splenic trunk (75% of cases) or the superior terminal artery (20% of cases), but, on occasion, it may originate from the inferior terminal artery or separately from the celiac axis (thus providing the spleen with a double splenic artery). In most instances, the superior polar artery gives rise to one or two short gastric branches; rarely, it gives rise to the left inferior phrenic and pancreatic rami. The presence and size of this artery appear to be correlated with tubercle formation in that it is more

prominent in spleens with large tubercles. The superior polar artery is frequently very long and slender and thus easily torn during splenectomy; accordingly, it was suggested in 1928 that ligation of splenic branches be started from the inferior pole of the spleen.¹⁴

Inferior polar artery The inferior polar artery is present in 82% of cases. As many as five collateral branches may arise from the splenic trunk, the inferior terminal artery, or, as noted, the left gastroepiploic artery. Inferior polar branches may have multiple origins, and they tend to be of smaller caliber than the superior polar artery.

Left gastroepiploic artery The left gastroepiploic artery, the most varied of the splenic branches, courses along the left side of the greater curvature in the anterior layer of the greater omentum. In 72% of cases, it arises from the splenic trunk several centimeters from its primary terminal division, and in 22% of cases, it originates from the inferior terminal artery or its branches; however, it may also originate from the middle of the splenic trunk or from the superior terminal artery. Characteristically, the left gastroepiploic artery gives off inferior polar arteries, which vary in number (ranging from one to five), size, and length. Typically, these branches are addressed first during laparoscopic splenectomy. When they are small, they can usually be controlled with the electrocautery.

Collaterals

As many as six short gastric arteries may arise from the fundus of the stomach, but, as a rule, only the one to three

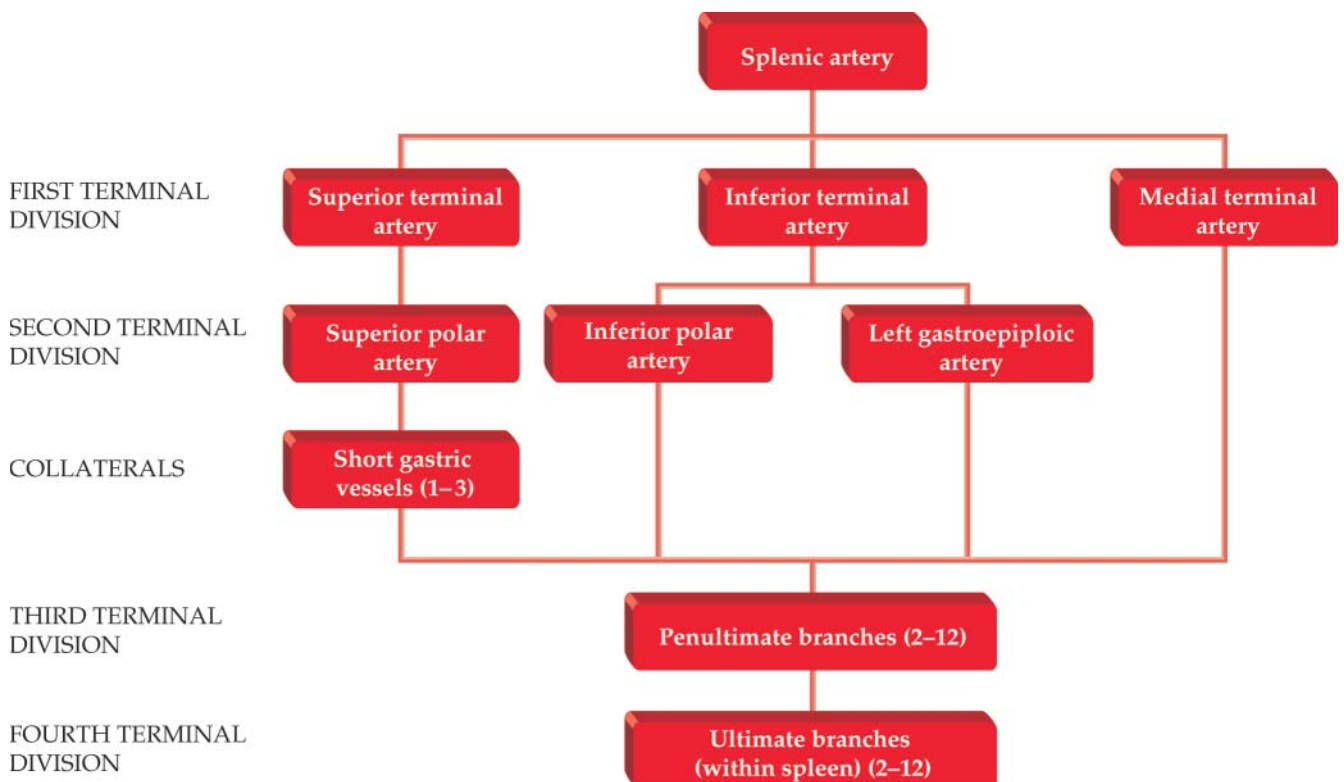


Figure 2 Division of splenic artery branches. Outlined is a general scheme of the levels of division of the splenic artery branches.

that open into the superior polar artery must be ligated during laparoscopic splenectomy [see *Figure 1*].

SUSPENSORY LIGAMENTS OF SPLEEN AND TAIL OF PANCREAS

Duplications of the peritoneum form the many suspensory ligaments of the spleen [see *Figure 3*]. Medially and posteriorly, the splenorenal ligament contains the tail of the pancreas and the splenic vessels. Anteriorly, the gastrosplenic ligament contains the short gastric and gastroepiploic arteries. In the lateral approach to laparoscopic splenectomy [see *Operative Technique, below*], the splenorenal and gastrosplenic ligaments are easily distinguished, and dissection of the anatomic structures they contain is relatively simple. In the anterior approach, these two ligaments lie on top of each other, and to separate them correctly and safely requires considerable experience with splenic anatomy.

The phrenicocolic ligament courses laterally from the diaphragm to the splenic flexure of the colon; its upper portion is called the phrenicosplenic ligament. The attachment of the lower pole on the internal side is called the splenocolic ligament. Between these two structures, a horizontal shelf of areolar tissue, known as the sustentaculum lienis, is formed on which the inferior pole of the spleen rests. The sustentaculum lienis is often molded into a sac that opens cephalad and acts as a support for the lower pole. This structure, often overlooked during open procedures, is readily visible through a laparoscope. The phrenicocolic ligament, the splenocolic

ligament, and the sustentaculum lienis are usually avascular, except in patients who have portal hypertension or myeloid metaplasia.

A 1937 study found that the tail of the pancreas was in direct contact with the spleen in 30% of cadavers.¹⁵ A subsequent report confirmed this finding and added that in 73% of patients, the distance between the two structures was no more than 1 cm.¹⁶ Although a recent anatomic study based on computed tomography (CT) mapping shows slightly different measures, the message is the same.¹⁷ Care must be exercised to avoid pancreas damage with the electrocautery during dissection as well as damage with the linear stapler in the course of en masse ligation of the splenic hilum (a maneuver more easily performed via the lateral approach to laparoscopic splenectomy).

Laparoscopic Splenectomy

PREOPERATIVE EVALUATION

Currently, we consider all patients evaluated for elective splenectomy to be potential candidates for laparoscopic splenectomy. Contraindications to a laparoscopic approach include severe portal hypertension, uncorrectable coagulopathy, severe ascites, and most traumatic injuries to the spleen. Extreme splenomegaly remains a relative contraindication as well. Because most patients scheduled for laparoscopic splenectomy have hematologic disorders, they undergo the same hematologic preparation that patients scheduled for open surgery do—namely, steroids, γ -globulins, fresh frozen plasma, cryoprecipitate, or platelets when required. Ultrasonography is performed to determine the size of the spleen. Spleen size is expressed in terms of the maximum interpole length (i.e., the length of the line joining the two organ poles) and is generally classified into three categories: (1) normal spleen size (< 11 cm), (2) moderate splenomegaly (11 to 20 cm), and (3) severe splenomegaly (> 20 cm).¹⁸ Because extremely large spleens present special technical problems that test the current limits of laparoscopic surgery, we make use of a fourth category for spleens longer than 30 cm or heavier than 3 kg, which we call megaspleens [see *Table 1*]. The ultrasonographer is also asked to try to identify any accessory spleens that may be present. CT is done when there is doubt about the exactness of the ultrasonographic measurement; such measurement is sometimes inaccurate at the upper pole and with spleens longer than 16 cm.

Patients receive thorough counseling about the consequences of the asplenic state. Polyvalent pneumococcal vaccine is administered at least 2 weeks before operation in all cases with boosters every 5 to 10 years as dictated by the levels of antibody titers;

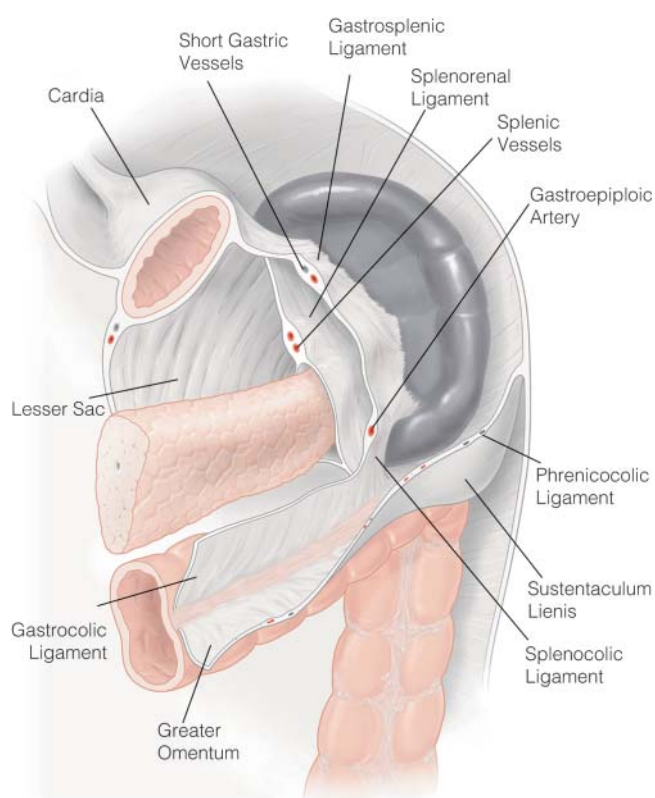


Figure 3 Suspensory ligaments of the spleen. Depicted are the suspensory ligaments of the spleen.

Table 1 Classification of Spleens According to Spleen Length*

Spleen Class	Spleen Length (cm)
Normal-size spleen	7–11
Moderate splenomegaly	12–20
Massive splenomegaly	21–30
Megaspleen	> 30

*Spleen length is defined as interpole length, measured along a straight line connecting the two poles.

preoperative vaccination against *Haemophilus influenzae* type B and meningococcus serogroup C is also given. Annual influenza vaccination should also be suggested. Heparin prophylaxis for thrombophlebitis is administered according to standard guidelines provided that there is no hematologic contraindication. Nonsteroidal antiinflammatory drugs (NSAIDs) are often given orally before operation to minimize postoperative pain; however, on empirical grounds, NSAIDs are not used when heparin prophylaxis is employed. Platelets are rarely, if ever, required when laparoscopic splenectomy is performed for idiopathic (immune) thrombocytopenic purpura (ITP).¹⁹

OPERATIVE PLANNING

Laparoscopic splenectomy presents special problems, such as the necessity of dealing with a fragile and richly vascularized organ that is situated close to the stomach, the colon, and the pancreas and the difficulty of devising an extraction strategy that is compatible with proper histologic confirmation of the pathologic process while maintaining the advantages of minimal access surgery. For successful performance of laparoscopic splenectomy, detailed knowledge of both splenic anatomy and potential complications is essential. The operative strategy is largely determined by the anatomic features, which, as noted [see *Anatomic Considerations, above*], may vary considerably from patient to patient.²⁰

OPERATIVE TECHNIQUE

Lateral Approach

This approach was first described in connection with laparoscopic adrenalectomy and is currently used for most laparoscopic splenectomies.²¹ At present, the only indication for the anterior approach to laparoscopic splenectomy is the presence of massive splenomegaly, a megaspleen, or when a secondary procedure is required, especially in pediatric patients.²² Typically, this alternative approach is taken when a spleen reaches or exceeds 23 cm in length or 3 kg in weight.

Step 1: placement of trocars The patient is placed in the right lateral decubitus position, much as he or she would be for a left-side posterolateral thoracotomy. The operating table is flexed and the kidney bolster raised to increase the distance between the lower rib and the iliac crest. Usually, four 12 mm trocars are used around the costal margin so that the camera, the clip applier, and the linear stapler can be interchanged with maximum flexibility [see *Figure 4*]. The trocars must be far enough apart to permit good working angles. Some advantage may be gained from tilting the patient slightly backward; this step gives the operating team more freedom in moving the instruments placed along the left costal margins, especially during lifting movements, when it is easy for instrument handles to touch the operating table. For the same reason, it is also advisable to place the anterior or abdominal side of the patient closer to the edge of the operating table.

A local anesthetic is infiltrated into the skin at the midpoint of the anterior costal margin, and a 12 mm incision is made. The first trocar is inserted under direct vision, and a symmetrical 15 mm Hg pneumoperitoneum is created. The locations of the remaining trocars are determined by considering the anatomic configuration in relation to the size of the spleen

to be excised. In most cases, the fourth posterior trocar cannot be inserted until the splenic flexure of the colon has been mobilized. Accordingly, the procedure is usually started with three trocars in place. In the end, three trocars are placed anteriorly along the costal margin and one is located in the left flank.

Troubleshooting After years of using the Veress needle, we now prefer the open method of inserting the first trocar. It is true that use of the Veress needle is, for the most part, safe; however, the small number of catastrophic complications that occur with blind methods of first trocar insertion are more and more difficult to justify. Admittedly, these complications are infrequent; thus, it is unlikely that even a large randomized trial would be able to show any significant differences between various methods of first trocar insertion. Nevertheless, even though complications occur with the open method of first trocar insertion as well, they are very uncommon and tend to be limited to trauma to the intestine or the omental blood vessels; they do not have the same serious consequences as the major vessel injury that may arise from blind trocar insertion.

Trocar placements differing from the ones we describe may be considered. More experienced surgeons (or those simply wishing to make the procedure easier) may choose to replace one or two 12 mm trocars with 5 mm trocars [see *Figure 5a*]. The procedure can also be performed with only three trocars. In leaner patients, one of the trocars can be inserted into the umbilicus to gain a cosmetic advantage. The advent of needlescopic techniques has made it possible to replace some of the 5 and 12 mm trocars with 3 mm trocars. The ultimate (i.e., least invasive) technique, usually reserved for lean patients with ITP and normal-size spleens, involves one 12 mm trocar placed in the umbilicus and two 3 mm trocars placed subcostally [see *Figure 5b*]. This approach requires two different camera-laparoscope setups so that a 3 mm laparoscope can be interchanged with a 10 mm laparoscope as necessary to permit application of clips or staplers through the umbilical incision once the dissection is completed. This can also be achieved with a single camera setup using a sterile clip-on camera sleeve with an acrylic window. The specimen is then retrieved through the umbilicus. Because the use of 3 mm laparoscopes is accompanied by a decrease in available intra-abdominal light and focal width, a meticulously bloodless field and sophisticated surgical judgment are critical for successful performance of needlescopic splenectomy.

Step 2: search for and retrieval of accessory spleens

The camera is inserted, and the stomach is retracted medially to expose the spleen. Then a fairly standard sequence is followed. A thorough search is then made for accessory spleens. To maximize retrieval, all known locations of accessory spleens should be carefully explored [see *Figure 6*]. Any accessory spleens found should be removed immediately; they are considerably harder to locate once the spleen is removed and the field is stained with blood.

Troubleshooting It is especially important to retrieve accessory spleens from patients with ITP, in whom the presence of overlooked accessory spleens has been associated with recurrence of the disease. Remedial operation for excision of missed accessory spleens has been reported to bring remission of recurrent disease; such an operation can be performed

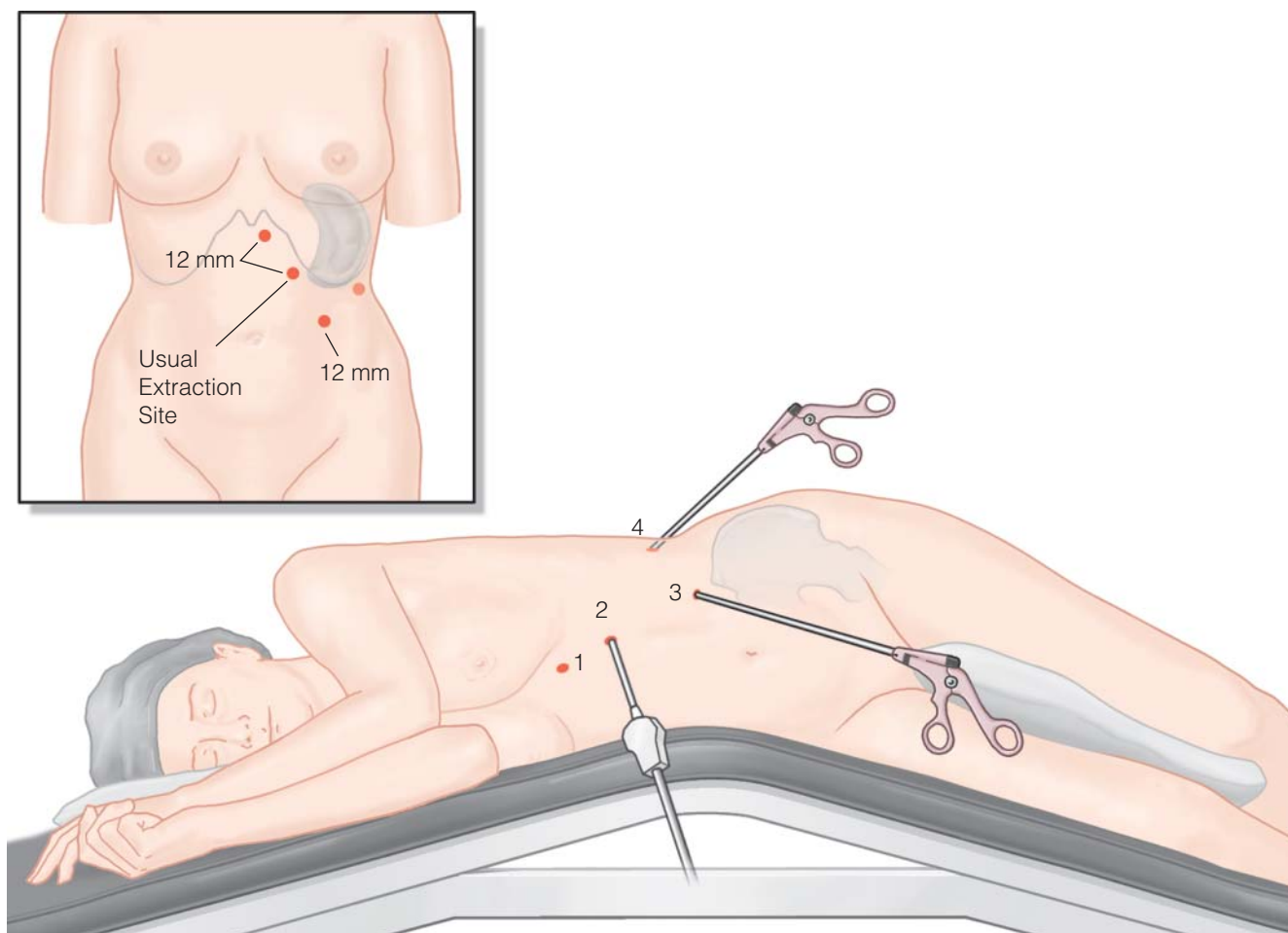


Figure 4 Laparoscopic splenectomy: lateral approach. Shown is standard trocar placement. Four trocars are used. In most cases, the procedure is begun without the posterior trocar in place.

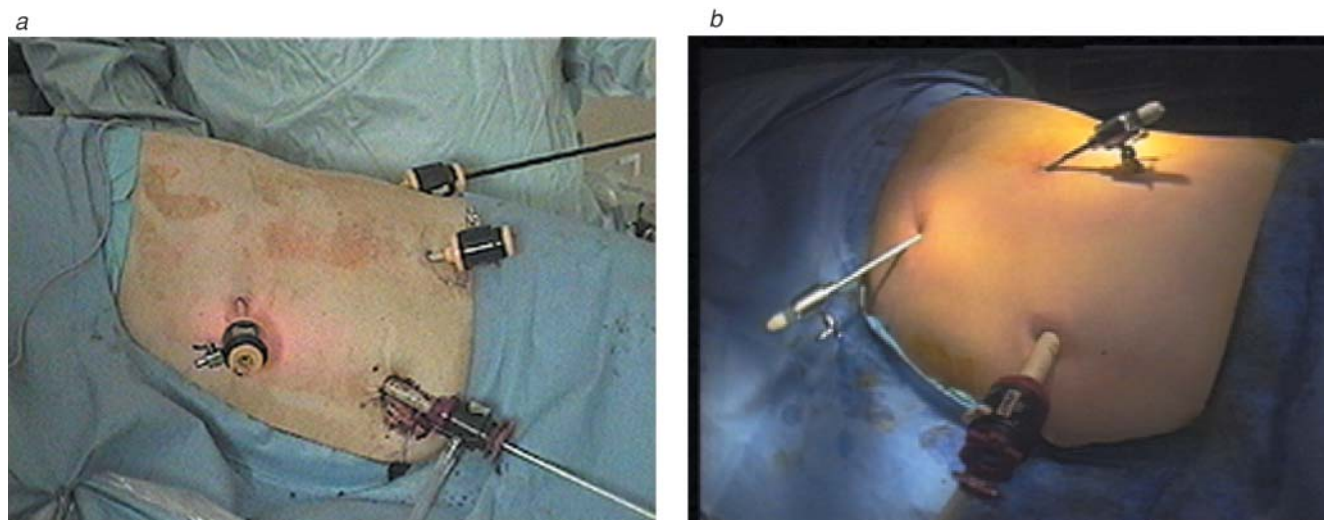


Figure 5 Laparoscopic splenectomy: lateral approach. Shown are alternative trocar placements. (a) In some patients (e.g., thin patients with normal-size spleens), a 12 mm trocar may be placed in the umbilicus to gain a cosmetic advantage, and most of the other trocars may be downsized to 5 mm. (b) In the needlescopic approach, only three trocars are placed: a 12 mm trocar in the umbilicus and two 3 mm subcostal trocars. Two camera-laparoscope setups (3 and 10 mm) are required.

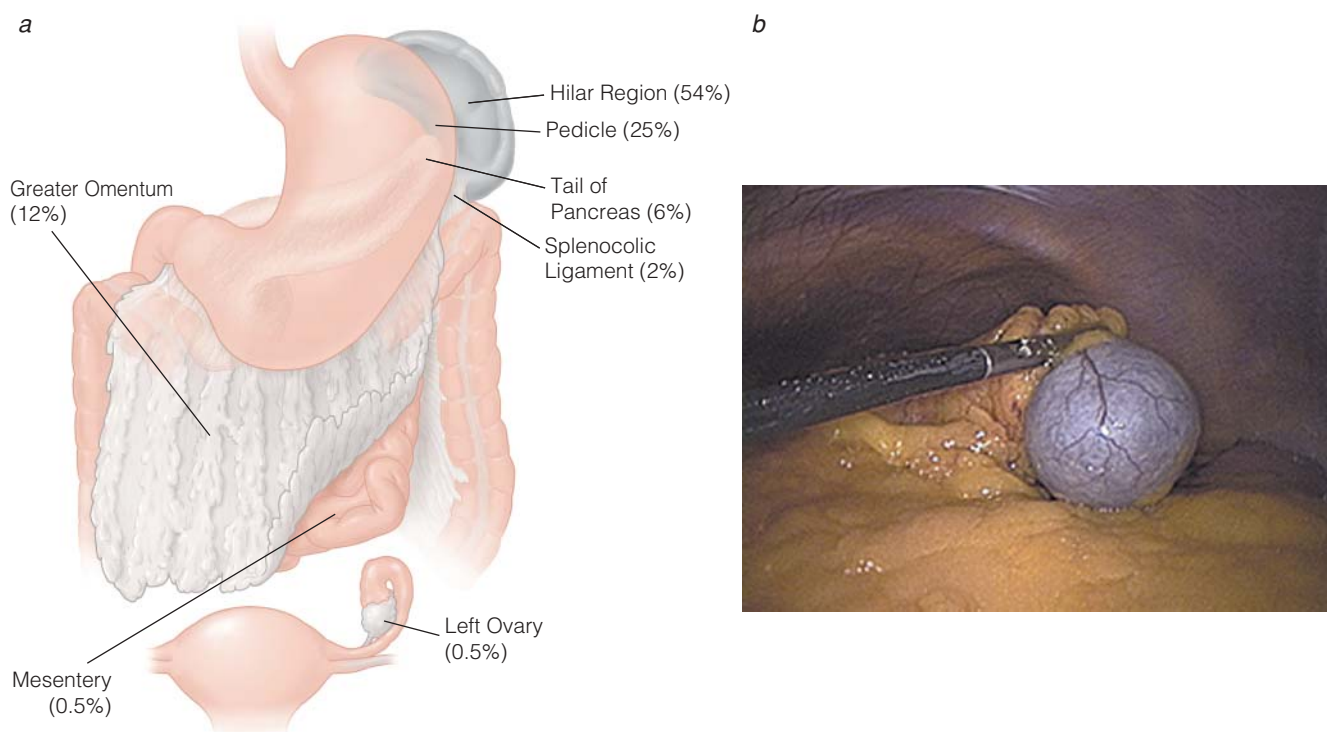


Figure 6 Laparoscopic splenectomy: lateral approach. (a) Accessory spleens are known to occur at specific sites. (b) Shown is an accessory spleen.

laparoscopically, with some authors suggesting the use of a handheld gamma probe and/or CT-guided methylene blue injection for identifying retained accessory spleens.²³ The overall retrieval rate for accessory spleens should fall between 15 and 30%.

Splenic activity has been demonstrated after open and laparoscopic splenectomy for trauma and hematologic disorders^{24,25}; accordingly, it is advisable to wash out and recover all splenic fragments resulting from intraoperative trauma at the end of the procedure. This step is particularly important for patients with ITP, in whom intraoperative trauma to the spleen is thought to contribute to postoperative scan-detectable splenic activity.

Step 3: control of vessels at lower pole, demonstration of “splenic tent,” and incision of phrenicocolic ligament The splenic flexure is partially mobilized by incising the splenocolic ligament, the lower part of the phrenicocolic ligament, and the sustentaculum lienis. The incision is carried slightly into the left side of the gastrocolic ligament. This step affords access to the gastrosplenic ligament, which can then be readily separated from the splenorenal ligament to create what looks like a tent. This maneuver cannot be accomplished in all cases, but when it can be done, it simplifies the procedure considerably. The walls of this so-called splenic tent are made of the gastrosplenic ligament on the left and the splenorenal ligament on the right, and the floor is made up of the stomach. In fact, this maneuver opens the lesser sac in its lateral portion (a point that is better demonstrated with gentle upward retraction of the splenic tip) [see Figure 7].

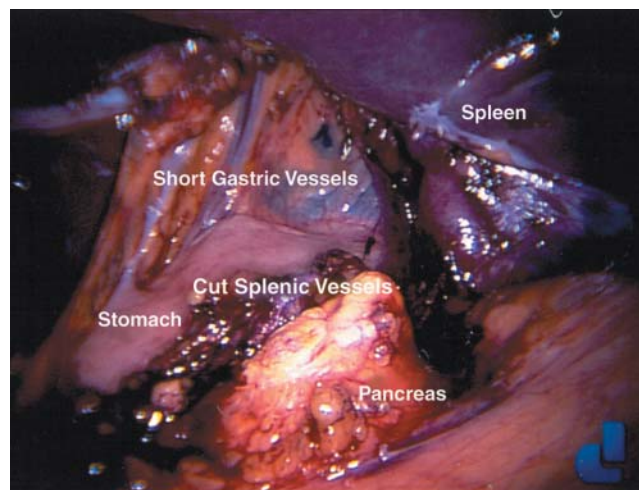


Figure 7 Laparoscopic splenectomy: lateral approach. The so-called splenic tent is formed by the gastrosplenic and splenorenal ligaments laterally and the stomach below.

The branches of the left gastroepiploic artery are controlled with the electrocautery or with clips, depending on the size of the branches. The avascular portion of the gastrosplenic ligament, situated between the gastroepiploic artery (and its branches) and the short gastric vessels, is then incised sufficiently to expose the hilar structures in the splenorenal ligament. To accomplish this, the lower pole is gently elevated; in this position, the spleen almost retracts itself as it naturally

falls toward the left lobe of the liver. At this point, the surgeon can usually assess the geography of the hilum and determine the degree of difficulty of the operation. The fourth trocar, if needed, is then placed posteriorly under direct vision, with care taken to avoid the left kidney. Caution must also be exercised in placing the trocars situated immediately anterior and posterior to the iliac crest. The iliac crest can impede movement and hinder upward mobilization of structures if the trocars are placed over it rather than in front of or behind it [see Figure 8].

Finally, the phrenicocolic ligament is incised all the way to the left crus of the diaphragm, either with a monopolar electrocautery with an L hook or with scissors. A small portion of the ligament is left to keep the spleen suspended and facilitate subsequent bagging. The phrenicocolic ligament is avascular except in patients with portal hypertension or myeloproliferative disorders (e.g., myeloid metaplasia). Leaving 1 to 2 cm of ligament all along the spleen side facilitates retraction and handling of the spleen with instruments.

Troubleshooting Remarkably few instruments are needed for laparoscopic splenectomy: most of the operation is done with three reusable instruments. A dolphin-nose 5 mm atraumatic grasper is used to elevate and hold the spleen. It is also used to separate tissue planes and vessels with blunt dissection because its atraumatic tip is easily insinuated between tissue planes. A gently curved 5 mm fine-tip dissector (Crile or Maryland) and a 10 mm 90° right-angle dissector are the only other tools required for cost-efficient dissection.

When a powered instrument is called for, we use a monopolar electrocautery with an L hook or a gently curved scissors. Alternatively, an ultrasonic dissector or a tissue-welding device may be used, albeit at a much higher cost. We tend to limit the use of these very elegant technologies to cases where some operative difficulty is anticipated.

Step 4: dealing with splenic hilum and tailoring operative strategy to anatomy It is advisable to base one's operative strategy on the specific splenic anatomy. If a

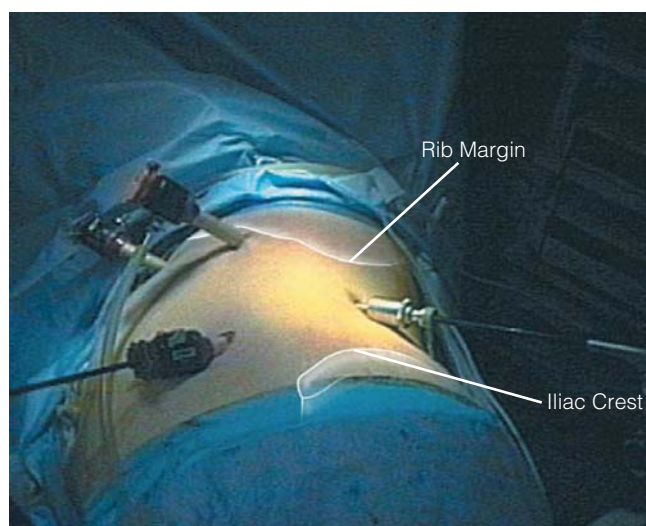


Figure 8 Laparoscopic splenectomy: lateral approach. Shown is the recommended trocar placement around the iliac crest.

distributed anatomy is present, the splenic branches are usually dissected and clipped. This is not only the least costly approach but also the simplest, in that the vessels are spread over a wider area of the splenic hilum and are easier to dissect and separate [see Figure 9].

A bundled anatomy lends itself more to a single use of the linear stapler provided that the tail of the pancreas is identified and dissected away when required. When possible, a window is created above the hilar pedicle in the splenorenal ligament so that all structures can be included within the markings of the linear stapler under direct vision [see Figure 10]. The angles provided by the various trocars make this maneuver much easier via the lateral approach than via the anterior approach. Dissection continues with individual dissection and clipping of the short gastric vessels; occasionally, these vessels can also be taken en masse with the linear stapler. We rarely have had to use intracorporeal sutures in this setting, except occasionally to control a short gastric vessel too short to be clipped safely. This portion of the operation is performed while the spleen is hanging from the upper portion of the phrenicocolic ligament, which has not yet been entirely cut.

Troubleshooting At this point in the procedure, experience in designing the operative strategy pays off in reduced operating time. Because of the many variations in size, shape, vascular patterns, and relations to adjacent organs, spleens are almost as individual as fingerprints. Accordingly, an experienced spleen surgeon learns to keep an open mind with regard to operative strategy and must be able to call on a wide range of skills to facilitate the procedure.

The surgeon should start by looking at the internal surface of the spleen. If the splenic vessels cover more than 75% of the internal surface (as is the case in 70% of patients), a distributed anatomy is present. With a distributed vascular anatomy, the vessels tend to be easier to dissect and isolate and thus can be readily (and cost-effectively) controlled with clips. On the other hand, if the splenic vessels entering the spleen cover only 25 to 35% of the inner surface of the hilum (30% of patients), the pattern is bundled. With a bundled vascular anatomy, the vessels, being fewer and closer together, can usually be controlled with a single application of the vascular stapler across the hilum provided that the tail of the pancreas can be protected.

Experienced surgeons also become very clever in using the position of the operating table to their advantage. The reverse Trendelenburg position (Fowler) allows the spleen to move away from the diaphragm in cases where the dissection of the upper pole is made more difficult by adhesions from previous surgery, large spleens, obesity, or previous infarctions of the spleen. With the patient stabilized by a bean bag, changing the degree of the lateral position is also useful. The surgeon learns to move the spleen back and forth so that it can be observed from an anterior and posterior perspective. The surgeon can then decide whether the approach to the splenic vessels is more appropriate from the front or the back.

Step 5: extraction of spleen A medium-size or large heavy-duty plastic freezer bag, of the sort commercially available in grocery stores, is used to bag the spleen. This bag is sterilized and folded and then introduced into the abdominal cavity through one of the 12 mm trocars [see Figure 11]. The

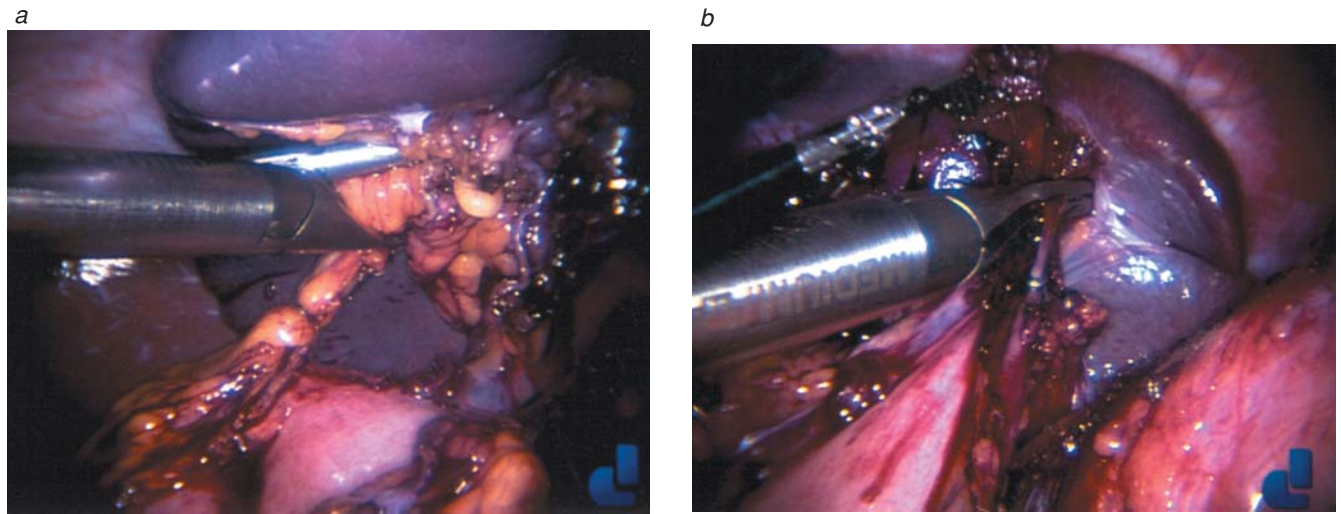


Figure 9 Laparoscopic splenectomy: lateral approach. (a, b) Clipping is well suited to controlling short gastric or gastroepiploic vessels. It is also appropriate for distributed-type splenic vasculatures, in which more splenic vessels are spread over a wider area of the hilum.

bag is unfolded and the spleen slipped inside to prevent splenosis during the subsequent manipulations. Grasping forceps are used to hold the two rigid edges of the bag and to effect partial closure. Bagging is facilitated by preserving the upper portion of the phrenicocolic ligament. After final section of the phrenicocolic ligament and any diaphragmatic adhesions present, extraction is performed through one of the anterior port sites. Extraction through a posterior site is more difficult because of the thickness of the muscle mass; usually, the incision must be opened, and more muscle must be fulgurated than is desirable.

The subcostal or umbilical incision through which extraction is to take place is extended slightly. Grasping forceps are inserted through the extraction incision to hold the edges of the bag inside the abdomen. Gentle traction on the bag from outside brings the spleen close to the peritoneal surface of the umbilical incision and then out of the wound [see Figure 12]. Specimen retrieval bags have been developed that can accommodate a normal-size spleen and thus make bagging much easier, but they are costly.

A biopsy specimen of a size suitable for pathologic identification is obtained by incising the splenic tip. The spleen is then fragmented with finger fracture, and the resulting blood is suctioned. The remaining stromal tissue of the spleen is then extracted through the small incision, hemostasis is again verified, and all trocars are removed. No drains are used. The incisions are closed with absorbable sutures and paper strips.

Troubleshooting The freezer bags can be more easily introduced into the abdomen if they are pulled in rather than pushed in [see Figure 11]. This may be accomplished by bringing out a 5 mm toothed grasper through the introduction trocar from another properly angled trocar, grasping the specimen bag, and pulling the bag back down through the trocar. A laparoscopic hernia mesh introducer may also be used.

Slipping the spleen into a freezer bag is also an acquired skill that takes some time to master. It is an important skill that is useful in many other instances where specimen retrieval

is needed (e.g., in procedures involving the gallbladder, the appendix, the adrenal glands, or the colon). In addition, it is highly cost-effective in that these commercially available bags cost only a few cents each. Admittedly, laparoscopic retrieval bags are easier to use, but their substantially higher cost can become a factor in a busy minimally invasive surgery unit. A suction machine (–70 mm Hg) and a custom-made sharp beveled 10 mm cannula can be used to suction splenic tissue from the plastic retrieval bag. When extraction is done with the use of any type of forceps or graspers, surgeons have noticed that initially the extracted spleen fragments tend to be small and tedious to extract. As the extraction proceeds, the fragments get bigger and easier to extract. Definitely, imagination and patience are required for this part of the procedure.

Anterior Approach

The anterior approach is seldom used nowadays; however, it remains the preferable approach in some patients with massive splenomegaly (21 to 30 cm long) and all patients with megaspleens (> 30 cm or > 3 kg) with the aid of hand-assisted devices [see Special Considerations, Hand-Assisted Laparoscopic Splenectomy, below]. Very large spleens are extremely heavy and difficult to manipulate with laparoscopic instruments, and it is complicated to lift them so as to gain access to the phrenicocolic ligament posteriorly. The anterior approach can also be considered if another procedure (e.g., cholecystectomy) is being contemplated; alternatively, in this situation, the lateral approach can be used, and the patient can be repositioned for the secondary procedure.

Step 1: placement of trocars Under general anesthesia, the patient is placed in a modified lithotomy position to allow the surgeon to operate between the patient's legs and to allow the assistants to stand on each side of the patient. The procedure is performed through five trocars in the upper abdomen [see Figure 13], with the patient in a steep Fowler position with left-side elevation. A 12 mm trocar is introduced through an

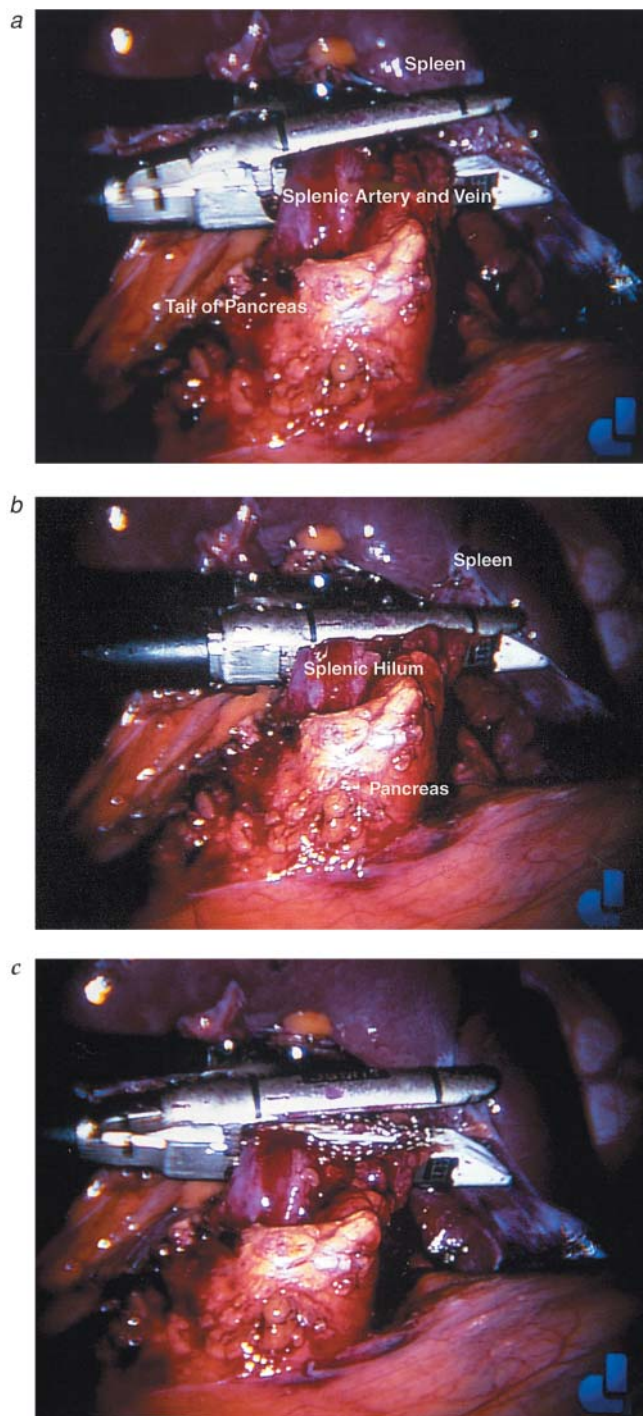


Figure 10 Laparoscopic splenectomy: lateral approach. (a through c) Stapling is particularly well suited to the compact hilum found in the magistral-type distribution of splenic vessels. As shown, all of the vascular structures are within the stapler markers, and the tail of the pancreas is well protected.

umbilical incision, and a 10 mm laparoscope (0° or 30°) is connected to a video system. A 12 mm trocar is placed in each upper quadrant, and two 5 mm trocars are inserted close to the rib margin on the left and right sides of the abdomen.



Figure 11 Laparoscopic splenectomy: lateral approach. Illustrated is the introduction of a sterile freezer bag for specimen extraction via the pull method. A toothed grasper is passed across the abdomen between two trocars and brought out through the 12 mm umbilical trocar site. This grasper is used to pull the extraction bag back into the abdomen.

Alternatively, trocars can be deployed in a semicircle away from the left upper quadrant. Trocar sites are carefully selected to optimize working angles. The 12 mm ports are used to allow introduction of clip appliers, staplers, or the laparoscope from a variety of angles as needed.

Troubleshooting With increasing experience, we find that we prefer to do as many laparoscopic splenectomies as possible via the lateral approach because it is so much easier, even with spleens that are longer than 20 cm and are readily palpable. The decision is arbitrarily made on the basis of estimated available working space. If the spleen comes too close to the iliac crest or the midline, the anterior approach should be taken instead.

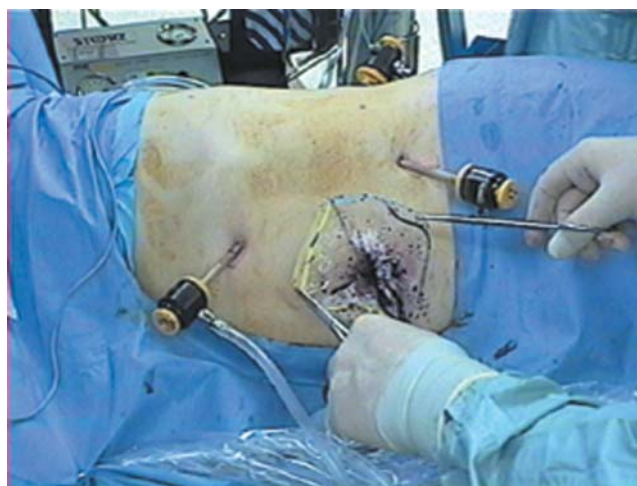


Figure 12 Laparoscopic splenectomy: lateral approach. Shown is the position of the specimen bag before finger fragmentation or pulp suction.

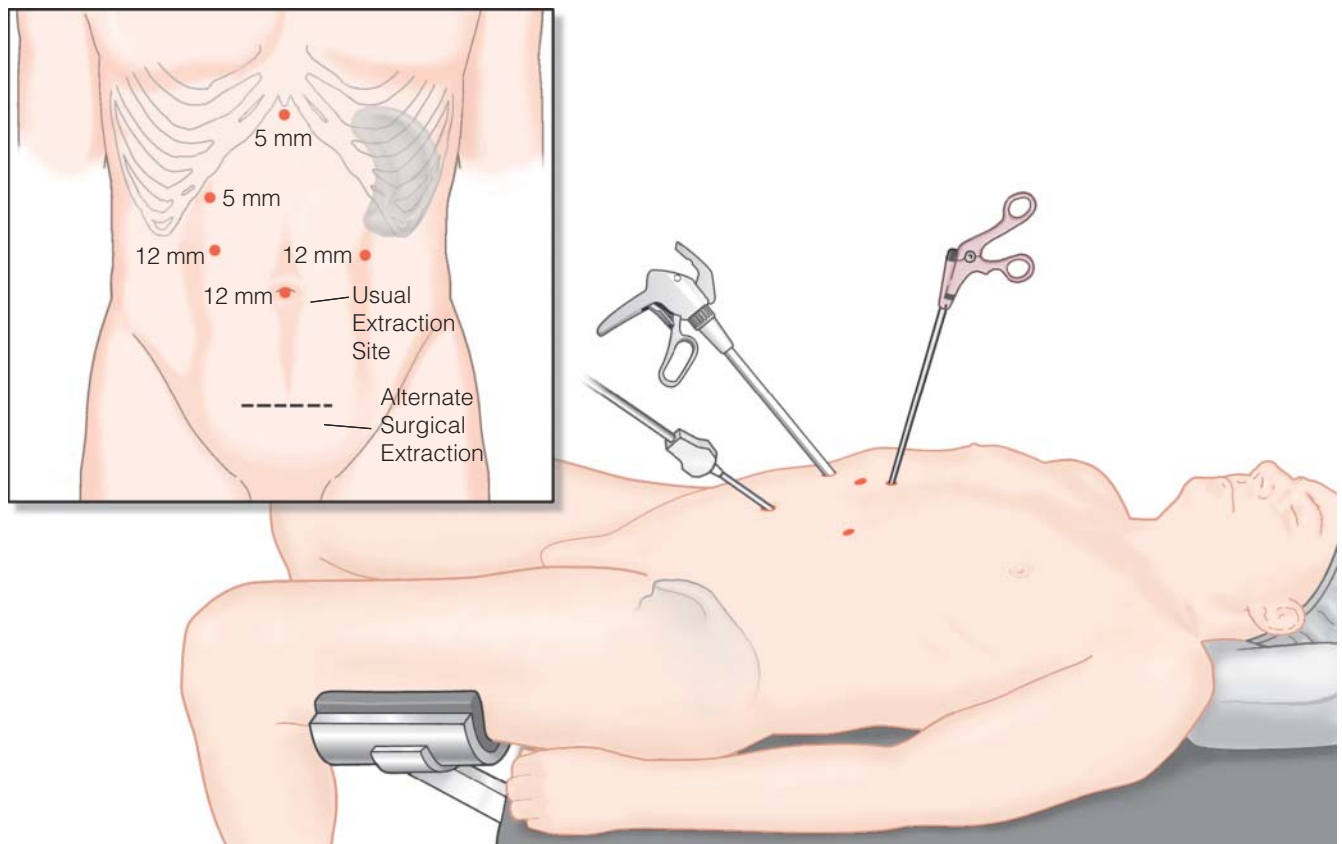


Figure 13 Laparoscopic splenectomy: anterior approach. Shown is standard trocar placement. The umbilical site is used for the camera. The remaining trocars are placed in the left and right upper quadrants, the epigastrium, and the right subcostal region. Depending on the size of the spleen, the trocars can also be disposed in a semicircle away from the left upper quadrant.

Step 2: isolation of lower pole and control of blood supply The left hepatic lobe is retracted, and the stomach is retracted medially to expose the spleen. Accessory spleens are searched for, and the phrenicocolic ligament, the splenocolic ligament, and the sustentaculum lienis are incised near the lower pole with an electrocautery and a hook probe or with scissors. Vascular adhesions—frequently found on the medial side of the spleen—are cauterized. They are also called *criminal folds* for their tendency to be avulsed off the spleen during dissection and cause nuisance bleeding from the capsular injury. The gastrosplenic ligament is carefully dissected close to the spleen, and the left gastroepiploic vessels are ligated one by one with metallic clips or, if small, simply cauterized. The upper and lower poles of the spleen are gently lifted with one or both palpators (placed through the 5 mm ports) to expose the splenic hilum and the tail of the pancreas within the splenorenal ligament, thereby facilitating individual dissection and clipping of all the branches of the splenic artery and vein close to the spleen. The short gastric vessels are then identified and ligated with clips or, occasionally, with staples. No sutures are used. Alternatively, the splenic artery itself can be isolated and clipped within the lesser sac before extensive dissection of the lower pole and suspensory ligaments.

Because of the segmental and terminal distribution of splenic arteries, it is easy to determine the devascularized

portions of the spleen: these segments exhibit a characteristic grayish color, whereas the vascularized segments retain a pinkish hue. When the organ is completely isolated, it is left in its natural cavity, and hemostasis is verified.

Troubleshooting If one elects first to clip the splenic artery within the lesser sac, a few precautions must be taken. First, the clipping must be done distal to the pancreatic magna to prevent pancreatic injury. Second, one must make sure that the splenic artery proper is clipped, not one of its branches (e.g., the superior terminal branch). This is an easy mistake to commit with the distributed type of splenic vasculature [see Figure 1] because the splenic artery itself is short and the branches can take off very early. Third, one must always keep in mind the possibility of an anastomotic branch between the major splenic branches, as described by Testut.¹² Should a major terminal branch be clipped rather than the splenic artery proper, there will be no spleen ischemia if such an anastomosis is present [see Figure 1].

Yet another challenge posed by the anterior approach is that if bleeding occurs, the blood tends to pool in the area of the hilum and obscure vision even more, whereas in the lateral approach, the blood tends to flow away from the operative field. One quickly learns that there is a steep price to pay for cutting corners during the dissection. The dissection must be meticulous, especially behind branches of the splenic vein.

Step 3: extraction of spleen Given that the anterior approach is now used only in cases of massive splenomegaly or megaspleen, bagging can be problematic. The largest commercially available freezer bag we have seen measures 27 by 28 cm, and the largest spleen we have been able to bag in one of them was 24 cm long. Furthermore, an accessory extraction incision is often required; a Pfannenstiel incision gives better cosmetic results, but a left lower quadrant incision can also be used. Hand-assisted devices are used with increasing frequency in laparoscopic removal of large spleens [see Special Considerations, Hand-Assisted Laparoscopic Splenectomy, *below*] and are becoming the preferred method for dealing with massive splenomegaly laparoscopically.

Laparoscopic Partial Splenectomy

Concern regarding the risk of OPSI has encouraged the practice of preserving splenic tissue and function whenever possible. For this reason, partial splenectomy has occasionally been indicated for treatment of benign tumors of the spleen and for excision of cystic lesions.²⁶ Its use has been described in connection with the management of type I Gaucher disease, cholesteryl ester storage disease, chronic myelogenous leukemia, single metastasis, thalassemia major, staging of Hodgkin disease, and spherocytosis.^{27–30} It has also been suggested for some cystic fibrosis patients with hypersplenism. Partial splenectomy is an option in the management of splenic trauma when the patient's condition is stable enough to permit the meticulous dissection required for the operation.^{31,32}

Like standard laparoscopic splenectomy, laparoscopic partial splenectomy is performed with the patient in the right lateral decubitus position. Trocar placement is similar as well. The splenocolic ligament and the lower part of the phrenicocolic ligament are incised to permit mobilization of the lower pole of the spleen. If the lower portion of the spleen is to be excised, branches of the gastropiploic vessels supplying the lower pole are dissected and clipped close to the parenchyma. An appropriate number of penultimate branches of the inferior polar artery are then taken in such a way as to create a clear line of demarcation between normal spleen and devascularized spleen. This process is continued until the desired number of splenic segments are devascularized.

Next, a standard monopolar electrocautery is used to score the splenic capsule circumferentially, with care taken to ensure that a 5 mm rim of devascularized splenic tissue remains in situ; this is the most important technical point for this procedure [see *Figure 14*]. The incision is then carried into the splenic pulp. Atraumatic intestinal graspers are also used to fracture the splenic pulp in a bloodless fashion. The laparoscopic L hook and scissors provide excellent hemostatic control with simple spot coagulation or spray current in the coagulation mode. No drains are used. Alternative methods of hemostasis have also been used, including argon beam coagulators, ultrasonic shears, linear staplers, bipolar tissue welding instruments, and radiofrequency ablation probes.²⁹

Once the spleen has been allowed to demarcate, resection is remarkably bloodless, provided that the 5 mm rim of ischemic tissue is left in place. Complete control of the splenic artery is not required before splenic separation, because division occurs in an ischemic segment of spleen.⁹ The feasibility of leaving portions of ischemic spleen in situ has been demonstrated in a

large prospective, randomized trial involving partial splenic embolization as primary treatment of hematologic disorders.³³

If the superior pole is to be removed, the phrenicocolic ligament must be incised almost entirely so that the spleen can be easily mobilized and the proper exposure achieved. The short gastric branches are taken first, along with the desired number of superior polar artery branches.

Laparoscopic partial splenectomy can be performed either with or without the aid of selective preoperative arterial embolization (see below). Radiologists are capable of cannulating the desired segmental splenic arterial branch and embolizing the segment that is to be resected. This is well documented in the recent trauma literature.³⁴

Preoperative Splenic Artery Embolization

Preoperative splenic artery embolization is used as an adjuvant in a few patients to make laparoscopic splenectomy possible and to reduce blood loss. Although it is now infrequently used, it remains a useful tool in the armamentarium of spleen surgeons.³⁵

Generally speaking, the technique involves embolization of the spleen with coils placed proximally in the splenic artery and absorbable gelatin sponges and small coils placed distally in each splenic arterial branch (the double embolization technique), with care taken to spare vessels supplying the tail of the pancreas [see *Figure 15*].

The procedure is ended when it is estimated radiologically that 80% or more of the splenic tissue has been successfully embolized. In most cases, successful embolization is achieved with both proximal and distal emboli; in a minority of cases, it is achieved with proximal emboli alone or with distal emboli alone.³⁵

Troubleshooting Preoperative splenic artery embolization is safe provided that two main principles are adhered to. First, embolization must be done distal to the pancreatica magna to avoid damaging the pancreas. Second, neither microspheres nor absorbable gelatin powder should be used, because particles of this small size may migrate to unintended target organ capillaries and cause tissue necrosis; only coils and absorbable gelatin sponge fragments should be used.

POSTOPERATIVE CARE

Postoperative care for patients who have undergone laparoscopic splenectomy is usually simple. The nasogastric tube inserted after induction of general anesthesia is removed either in the recovery room, once stomach emptying has been verified, or the next morning, depending on the duration and the degree of technical difficulty of the procedure. The urinary catheter is usually removed before the patient leaves the recovery room. The patient is allowed to drink clear fluids on the morning after the operation; when clear fluids are well tolerated, the patient is allowed to proceed to a diet of his or her choice.

A proper pain control process is started before the procedure. If the patient has no history of ulcer or dyspepsia, celecoxib, a cyclooxygenase-2 NSAID, is started preoperatively because there is little effect on platelet function. Alternatively, 50 mg of ketorolac can be given 30 minutes before the end of the procedure. All trocar sites are infiltrated with local anesthetic at the start of surgery. This is done to prevent the establishment of peripheral and central sensitization (“wind-up”), conditions that

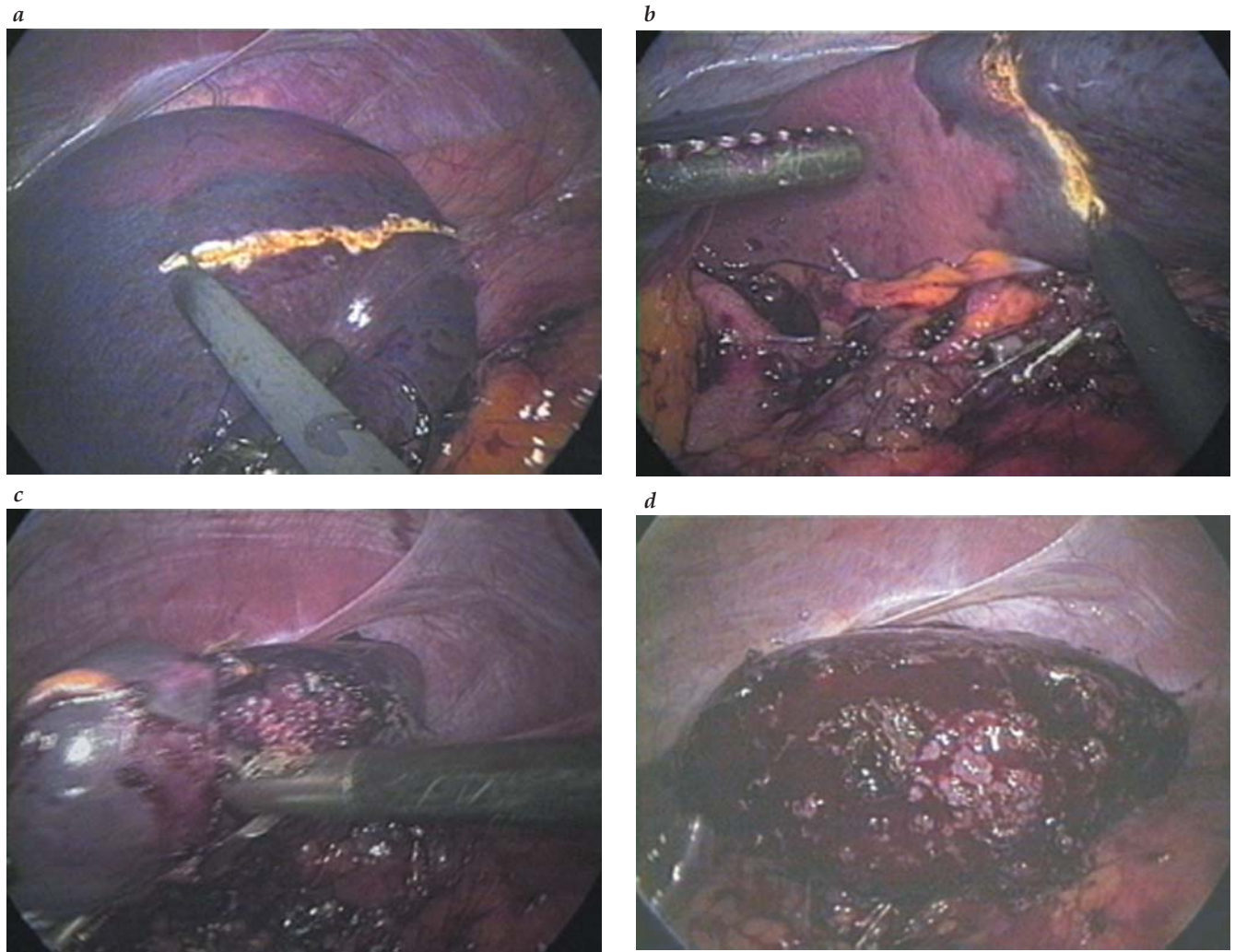


Figure 14 Laparoscopic splenectomy: partial splenectomy. (a, b) The splenic capsule is scored with the monopolar cautery, and a 5 mm margin of devitalized tissue is left. (c) The splenic pulp is fractured with an atraumatic grasper. The electrocautery with the L hook is also used to control parenchymal bleeding. (d) Shown is the cut surface of the spleen after transection. The operative field remains remarkably dry.

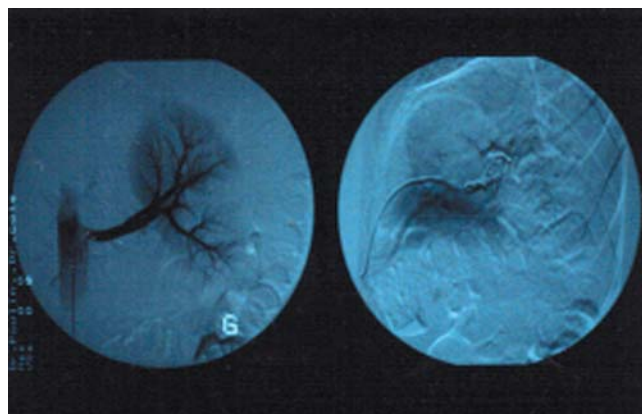


Figure 15 Laparoscopic splenectomy: splenic artery embolization. Shown are splenic angiograms of a patient with thrombotic thrombocytopenic purpura before (left) and after (right) splenic artery embolization with 3, 5, and 7 cm coils and absorbable gelatin sponge fragments.

promote an increased response to pain stimuli. Ketorolac or another NSAID is administered regularly in the postoperative period following the “first in last out” principle of NSAID administration for pain control. NSAIDs have been shown to have a 30 to 50% opioid-sparing effect. Morphine-based patient-controlled analgesia is used the first night after surgery. The following morning, acetaminophen and NSAIDs usually suffice. Oral hydromorphone hydrochloride, 2 to 4 mg, is reserved for breakthrough pain. A prescription for these three oral drugs is given on discharge. Because of its adverse effects of nausea, vomiting, abdominal fullness, and constipation, codeine is avoided. Furthermore, increased reports of codeine intoxication associated with ultrarapid CYP2D6 metabolism make it a poor choice.

Patients receiving intravenous (IV) cortisone are given oral steroids on postoperative day 1 after an overlap IV injection; thereafter, steroids are gradually tapered. Patients are allowed to shower 12 hours after surgery and are advised to keep the paper strips covering the trocar incisions in place for 7 to 10 days. No drains are used. No limitations are imposed on

physical activity, and patients are allowed to tailor their activities to their degree of asthenia or discomfort. An exception is made for patients with partial laparoscopic splenectomy where empirically they are asked to refrain from strenuous activity for a month.

COMPLICATIONS

Postoperative complications directly related to splenectomy include intraoperative and postoperative hemorrhage; left lower lobe atelectasis and pneumonia; left pleural effusion; subphrenic collection; iatrogenic pancreatic, gastric, and colonic injury; venous thrombosis; and overwhelming post-splenectomy sepsis.^{31,36–38}

Successful laparoscopic splenectomy depends to a large extent on proper preparation. Recognition of anatomic elements and their arrangement is paramount. As with other laparoscopic procedures, the keys are avoiding complications and minimizing technical misadventures. Vascular structures should be cleanly isolated and dissected from surrounding fat; they then can usually be controlled with two clips proximally and distally. Staplers should be used with care and should not be applied blindly. The stapler tip should be clearly seen to be free of tissue before it is closed; otherwise, hemorrhage from partial section of a major splenic branch might occur after the instrument is released. Blind application of the stapler may also result in damage to the tail of the pancreas, which often lies in close proximity to the inner surface of the spleen. If both clips and a linear stapler are used, it is vital to prevent interposition of clips in the staple line, which will cause the stapler to misfire and possibly to jam.

Improper use of the electrocautery during the procedure can cause iatrogenic injury to the stomach, the colon, or the pancreas. In a smoke-filled environment, where controlling vessels is difficult and time consuming, blind fulguration of fat in the hilum can lead to bleeding. Structures close to the lower pole in the gastocolic ligament can be approached more aggressively, but not those in the hilum. To prevent arcing and spot necrosis, which may result in delayed perforation and sepsis, the instrument should be activated only in proximity to the target organ.

The assistants also play an important role in preventing complications. All instruments, including those handled by assistants, should be moved under direct vision. Especially in the anterior approach, retraction of the liver and stomach and elevation of the spleen require constant concentration if lacerations and subsequent hemorrhage or perforation are to be avoided.

SPECIAL CONSIDERATIONS

Extraction of Specimens

Spleens removed via the anterior approach are extracted through the umbilical trocar site after finger fragmentation in a plastic bag. It is rarely necessary to enlarge the umbilical incision to more than 2 or 3 cm. When the lateral approach is used, extraction is more easily performed through one of the ports situated anteriorly. This extraction site also requires little or no enlargement. On occasion, for a spleen longer than 20 cm, a 7.5 to 10 cm Pfannenstiel incision is made, and the operator's forearm is introduced into the abdomen to deliver the spleen into the pelvis for extraction in large fragments under direct vision.³⁹ The abdomen is copiously irrigated before closure.

Special mention should be made of extraction of the splenic specimen from patients with malignant disease. If lymphoma or Hodgkin disease is suspected, neither preoperative splenic artery embolization nor finger fragmentation in a plastic bag should be performed, for fear of making the histologic diagnosis difficult. Extraction of intact spleens through a small left subcostal or median incision has also been employed when preservation of tissue architecture is required. Alternatively, a port site may be slightly enlarged, and a knife or Mayo scissors may be used to furnish the pathologist with intact specimen pieces of various sizes. The various techniques of fragmentation and extraction of splenic tissue during laparoscopic splenectomy should be discussed and agreed on with the pathologist ahead of time to ensure that proper pathologic diagnoses are not compromised by either necrotic tissue (in the case of preoperative splenic artery embolization) or altered tissue architecture (in the case of finger fragmentation), especially if malignancy is suspected but not proved. In practice, however, we have found that the diagnosis is made preoperatively in more than 90% of patients with benign and malignant hematologic disease; hence, the issue rarely arises.

Hand-Assisted Laparoscopic Splenectomy

The term *hand-assisted laparoscopic surgery* refers to laparoscopic procedures performed with the aid of a plastic device inserted in a 7.5 to 10 cm wound. This plastic hand port consists of a sealed cuff that enables a hand to be inserted into and withdrawn from the abdomen without loss of pneumoperitoneum during the operation; in this way, the surgeon regains some of the tactile feedback lost in conventional laparoscopic surgery [see Figure 16]. A number of different models have been developed, some of them quite expensive. Most use either an inflatable sleeve clipped to an O-ring,

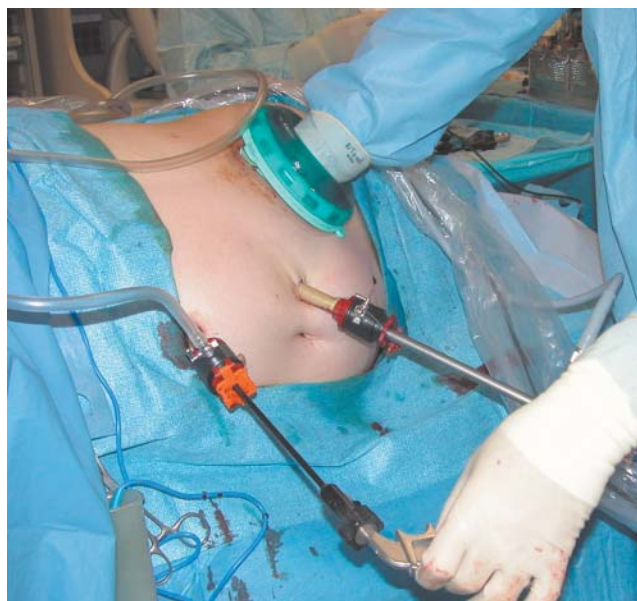


Figure 16 Laparoscopic splenectomy: hand assisted. Shown is the use of a hand port in the left lower quadrant to facilitate laparoscopic splenectomy in a patient with a large spleen.

a spiral inflatable valve, or a flap valve to maintain pneumoperitoneum.

The optimal placement of the incision for a hand-assisted laparoscopic splenectomy remains a subject of debate: recommended locations have included the upper midline, the right upper quadrant, the left iliac fossa, and, for very large spleens, the Pfannenstiel position. Whether the surgeon is left-handed or right-handed plays a role; most surgeons agree that the nondominant hand should be used in the device.

There are obvious advantages and drawbacks to hand-assisted laparoscopic splenectomy. The most apparent disadvantage is the cosmetic cost of a longer abdominal incision (except when a Pfannenstiel incision is employed). More generally, the use of a longer incision would seem to be at odds with the current trend toward developing surgical techniques that reduce surgical trauma as much as possible. Nevertheless, comparative studies of splenectomy in patients with large spleens (> 700 g) seem to indicate that, for the most part, the hand-assisted approach yields outcomes similar to those of conventional laparoscopic splenectomy.⁴⁰

Although the precise role of hand-assisted laparoscopic splenectomy remains to be defined, this technique has an increasing place in the surgical management of patients with large spleens. In addition, the hand-assisted approach may be a valuable aid for surgeons who have not yet completed the learning curve for conventional laparoscopic splenectomy. Finally, this technique may render preoperative splenic embolization unnecessary for most very large spleens.¹⁹

Postoperative Splenic and Portal Vein Thrombosis

An increasing number of reports in the literature seem to indicate that thrombosis of the portal vein and its branches may have been underreported. This complication is important because of its potential lethality. What confuses the issue is the difference in reported incidence between retrospective (0.87 to 13.5%) and prospective (8.3 to 52%) studies in which all patients underwent postoperative imaging. Furthermore, the identification of asymptomatic patients in 25 to 38% of cases complicates management decisions. There also seems to be a difference in the clinical significance between thrombosis of the splenic vein stump, the portal vein, the superior mesenteric vein, and secondary branches of these vessels. One report suggests a higher incidence in the laparoscopic setting. Most authors agree that malignancy, especially of myeloid origin, and spleen size are independent risk factors, although the condition has been reported after splenectomy for any condition.

Although symptoms are often vague (abdominal pain, nausea, fever, ileus, diarrhea, jaundice, anorexia, ascites), the index of suspicion should be high. Once diagnosed, prompt anticoagulation therapy can prove lifesaving. More studies are needed to help determine who needs prospective imaging postoperatively, what thrombosed vessel needs more aggressive therapy, and which of the asymptomatic patients should be treated. Guidance is also needed as to the duration and type of treatment when the complication arises.^{41,42}

Overwhelming Postsplenectomy Infection

Splenectomy results in reduced clearance of extracellular (bacteria) or intracellular (malaria) particulate antigen, impaired phagocytosis, and decreased levels of properdin

and tuftsin, a tetrapeptide produced by enzymatic cleavage of the Fc domain of the heavy chain of immunoglobulin G produced mainly in the spleen. Splenectomized patients are more susceptible to sepsis caused by certain bacteria and, occasionally, protozoa, and these infections can be fulminant. OPSI is one of the few conditions where circulating or intra-leukocytic bacteria can be found in the peripheral blood or buffy coat film.⁴³

Therefore, any clinical suggestion of infection needs to be taken seriously in the splenectomized patients. From a few nonspecific symptoms, patients can rapidly progress quickly to septic shock, disseminated intravascular coagulation, and multiple organ failure.⁴⁴

The most common organism remains *Streptococcus pneumoniae* in 50 to 90% of isolates. Others include *H. influenzae* type B, *Streptococcus* type B, *Staphylococcus aureus*, *Salmonella*, *Escherichia coli*, *Campylobacter jejuni*, and, rarely, *Pseudomonas aeruginosa*.⁴³

Despite the voluminous literature, the true incidence of OPSI, its nature, the risk in various age groups, and the role of underlying conditions leading to splenectomy all remain unsettled. The incidence of infection appears highest in the first 2 years after surgery even if some controversy still exists as to whether the rate of OPSI decreases over time. Cases of fulminating infection have been reported more than 20 years after splenectomy. Reasonable estimates of the incidence of OPSI derived from cohort studies vary from 0.23 to 0.42% per year, with a lifetime risk of 5%. The risk is higher in children; in patients splenectomized for hematologic illnesses, especially malignancy, thalassemia major, and sickle cell disease; and patients with an immunocompromised status. The lowest infection and mortality have been observed in patients splenectomized for trauma, immune thrombocytopenic purpura (ITP), and spherocytosis and incidentally to other operations, such as gastrectomy. Over half of first infections occur in patients under 15 years of age. The mortality from OPSI is high (38 to 69%).^{43,45–47}

Proper vaccination against *Pneumococcus*, *Haemophilus*, and *Meningococcus*, as described in the preoperative preparation section of this text, should be adhered to. Most hospitals now have a vaccination clinic for splenectomized patients offered by infection control departments. Annual influenza vaccination should also be suggested. Other important measures include giving patients a 5-day supply of standby antibiotics to be taken at the first sign of infection even before consulting a physician. Many suggest covering dental procedures. Patients should also wear a medical bracelet or carry a medical alert card. Patients should be aware of the danger of infection from human or animal bites, and those traveling to malaria-endemic countries should avoid mosquito bites and take appropriate antimalarial prophylaxis.

The question of prophylactic antibiotics is more controversial, especially for adult patients, for whom compliance has been an issue, along with the fear of emergence of resistant bacterial strains. However, with the available imperfect data, most would suggest prophylaxis in children until 5 years of age or 2 years after splenectomy with penicillin V potassium, 125 mg twice daily. Other antibiotics are also used, including co-amoxiclav, cefotaxime, ceftriaxone, and ciprofloxacin. In adults, with the fact that pneumonia is the only infectious disease ranking in the 10 most common causes of death in the United States, it would require large numbers to be

recorded after splenectomy before it would be possible to say that these were not chance events. Some authors feel that so few reports in the literature can only be interpreted as indicating that infection in adults undergoing splenectomy for benign disease is uncommon, and they are reluctant to agree that this number of reports constitutes a proven increased susceptibility to infection after splenectomy in adults. These authors point to the fact that 73% of the pneumococcal infections reported after splenectomy were made up of isolated case reports.⁴⁵

Despite the controversies, the risk of OPSI should be reduced by the measures already described even if accurate data from any of these interventions are scant. Yet in a study at The Hospital for Sick Children in Toronto, children who had splenectomy between 1958 and 1970 (6% infection, 3.9% mortality) were compared with children who had splenectomy between 1971 and 1975. In the latter group, all the children received prophylactic antibiotics and more than two thirds of them were given polyvalent pneumococcal vaccine. In the latter group, the infection rate was reduced by 47% and the mortality by 88%. The use of vaccines against encapsulated organism is thought to have led to a drop in the overall incidence of OPSI to less than 1%.^{44,47}

OUTCOME EVALUATION

No randomized, prospective trials comparing open splenectomy with laparoscopic splenectomy have yet been conducted. At present, such trials are unlikely to be held, for a variety of reasons. For one thing, randomization is difficult with procedures that are still in evolution. At one end of the spectrum, laparoscopic splenectomy is done for patients with ITP, who usually are relatively healthy and have normal-size spleens. In many of these patients, needlescopic instruments (< 3 mm) can be used in conjunction with a single 12 mm port site in the umbilicus. This approach permits hospital discharge within 24 hours of operation in a significant number of cases. At the other end of the spectrum, laparoscopic splenectomy is done for patients with myeloid metaplasia and spleens longer than 30 cm. In this setting, a laparoscopic approach poses formidable challenges, and the optimal technique and its justification remain to be determined. The window of opportunity for randomized comparative trials may have been lost.

Large case series and nonrandomized comparative trials, however, have consistently reported better outcomes from laparoscopic splenectomy than from open splenectomy (E.C. Poulin, C.M. Schlachta, J. Mamazza, unpublished data, February 2001).^{48–53} For example, in one set of 528 patients [see Table 2],^{49–51} the rate of postoperative pneumonia was 1.1% (6 of 528), and no subphrenic abscesses occurred as postoperative complications (E.C. Poulin, C.M. Schlachta, J. Mamazza, unpublished data, February 2001). Many surgeons who have completed the learning curve associated with the procedure feel that there is still room for improvement regarding complication rates and length of stay for patients with ITP and other relatively benign conditions necessitating laparoscopic splenectomy. The more serious conditions and the mortality seen in conjunction with the procedure tend to occur in patients with advanced hematologic malignancies or megaspleens. In such cases, most of the adverse results are related to the disease state rather than to the operation, and

it remains to be seen whether laparoscopic splenectomy will have a positive effect on outcome.

One of the great attractions of minimally invasive surgery has been the prospect of significant cost reductions. At this point in the development of laparoscopic splenectomy, however, we are reluctant to place too much trust in premature cost analyses that do not take into account the “work in progress” nature of minimally invasive surgery. Most surgeons can now perform most laparoscopic splenectomies with simplified trays of reusable instruments. Our basic laparoscopic tray contains a few instruments and two sizes of reusable clip appliers with inexpensive clips. As noted [see Operative Technique, *above*], clips are used for distributed-type spleens, and single-use linear staplers are mostly used for magistral-bundled type spleens. To reduce costs, ultrasonic dissectors are rarely used. In addition, the use of commercially available freezer bags instead of laparoscopic retrieval bags further reduces the cost of specimen extraction. Finally, even if intraoperative costs are higher with laparoscopic splenectomy, our experience is that the increase is offset by reductions in postoperative stay.¹⁹

We, like most authorities, believe that as a surgeon gains experience with laparoscopic splenectomy, operating time tends to fall until it approaches that of open splenectomy. We also concur with the numerous authors who have suggested that once laparoscopic splenectomy is mastered, use of blood products tends to decrease substantially.

Open Splenectomy

PREOPERATIVE EVALUATION

With the growing acceptance of laparoscopic splenectomy, the indications for open splenectomy have essentially been reduced to (1) elective removal of megaspleens and (2) treatment of splenic trauma when conservative treatment either is not indicated or has failed. In rare cases, open splenectomy may be done for iatrogenic injuries incurred during left upper quadrant surgical procedures.

Preoperative evaluation for elective open splenectomy is similar to that for laparoscopic splenectomy [see Laparoscopic Splenectomy, Preoperative Evaluation, *above*]. Preoperative evaluation of trauma patients is covered in more detail elsewhere. Essentially, a coagulogram and blood typing and cross-matching are required. A preoperative CT scan will have established the size of the spleen, the grade of the splenic injury, the presence of other injuries (if any), and, in elective cases, the location and configuration of any masses or cysts.

OPERATIVE PLANNING

Most surgeons would agree that the lessons learned from successful performance of minimally invasive procedures have had a positive impact on the refinement of the corresponding open procedures. The principles of careful appreciation of fine anatomic details (as described for laparoscopic splenectomy) and maximal reduction of tissue trauma from retractors or excessive tissue handling should be incorporated into the planning of open splenectomy.

Total versus Partial Splenectomy

As a consequence of the recognition that splenectomy renders patients susceptible to a lifelong risk of OPSI, it is now

Table 2 Clinical Results of Laparoscopic Splenectomy

Study	N	ITP/ Non-ITP	Conversion Rate (%)	OR Time (min)	Morbidity (%)	Mortality (%)	Length of Stay (days)	Accessory Spleen Present (%)
All diagnoses								
Katkhouda et al (1998) ⁵¹	103	67/36	3.9	161	6	0	2.5	16.5
Targarona et al (2000) ⁴⁹	122	54/68	7.4	153	18	0	4.0	12
Park et al (2000) ⁵⁰	203	129/74	3.0	145	9	0.5	2.7	12.3
Poulin et al (2001)	100	50/50	8.0	180	15	4	3.0	25
ITP								
Trias et al (2000) ⁵²	48	—	4.2	142	12	NA	4.0	11
Poulin et al (2001)	51	—	3.9	160	5.9	0	2.0	32
Malignancy								
Schlachta et al (1999) ⁵³	14	—	21	239	18	9	3.0	—
Trias et al (2000) ⁵²	28	—	14*	171	28	NA	5.5	—

ITP = idiopathic thrombocytopenic purpura; NA = not available; OR = operating room.
*71% required accessory incision because of spleen size.

routine practice to attempt splenic conservation. Accordingly, saving normally functioning splenic parenchyma has become the most important goal in the management of splenic injuries. In some 50% of adults (and over 80% of children), this goal can be achieved by means of nonoperative treatment. In approximately 20% of adults, splenorrhaphy and partial splenectomy are possible; splenectomy is indicated in the remainder. Partial splenectomy is also favored on occasion when excision of splenic tissue is required for the treatment of other elective conditions.³¹

For the sake of brevity, we describe the surgical technique for total splenectomy and partial splenectomy concurrently, noting differences only where significant.

OPERATIVE TECHNIQUE

Step 1: Incision

The patient is supine, in a reverse Trendelenburg position with a 15° tilt to the right. For maximal exposure, a midline incision is made, starting on the left side of the xiphoid process [see Figure 17]. The incision is extended below the umbilicus for a variable distance, depending on circumstances such as the size of the patient, the surgical situation (traumatic versus nontraumatic), the possibility of associated injury, and the size of the spleen. Occasionally, a left subcostal incision may be used for nontraumatic indications in patients with normal-size spleens. This incision may be extended onto the right side to form a chevron incision if necessary; however, this may impede the search for accessory spleens. Some surgeons have performed splenectomy via a thoracoabdominal approach, but most have abandoned this approach. Appropriate retraction of the left lobe of the liver and the abdominal wall is achieved with the help of surgical assistants placed on each side of the table or the use of self-retaining retractors.

Troubleshooting In trauma cases, the anesthetist should always be informed when the peritoneum is opened; release

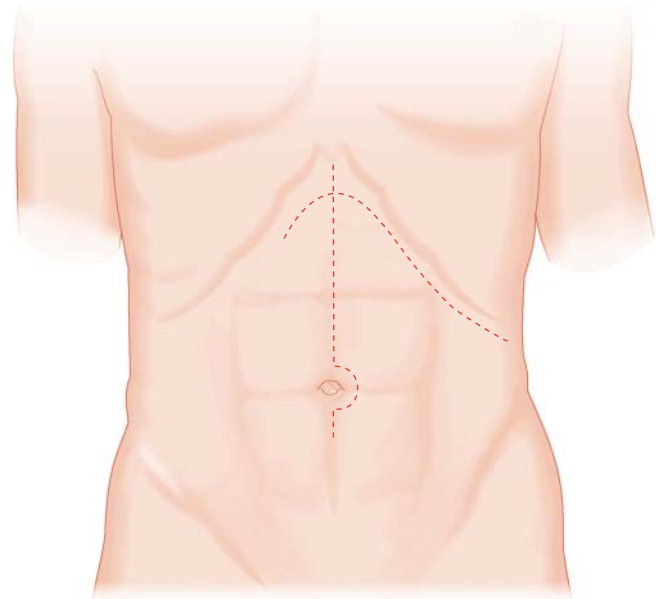


Figure 17 Open splenectomy. Shown are midline and left subcostal incisions.

of a tense hemoperitoneum can precipitate hypotension with the loss of tamponade.

Step 2: Evacuation of Blood and Packing of the Abdomen

In trauma cases, gross blood and clots are evacuated manually with large laparotomy sponges. All quadrants of the abdomen are then packed with laparotomy pads. Standard suction equipment is not very useful for evacuating large quantities of blood from the abdomen.

Step 3: Control of Splenic Artery

Once other major injuries are excluded, the first decision to be made is whether to control the splenic artery first or to

mobilize the spleen to the midline. This decision is dictated by the urgency of the clinical situation, the spleen size, and the presence of underlying disease.

If the decision is made to control the splenic artery first, the main splenic trunk is identified above the pancreas via an approach that leads to the lesser sac either through the gastrocolic ligament or through the avascular plane of the greater omentum above the distal transverse colon. Once dissected, the artery is controlled with a vascular loop. The main artery can also be accessed and dissected posteriorly after the spleen is mobilized [see Figure 18].

Troubleshooting One advantage of dissecting the splenic artery in the lesser sac (as opposed to the hilum) is that the splenic vein is rarely damaged, being located under the pancreas and away from the artery. Good proximal control of the splenic blood supply facilitates the performance of the more complex variations of partial splenectomy or total splenectomy for megaspleens.

Step 4: Mobilization of Spleen

If the decision is made to mobilize the spleen first, as in most trauma cases, mobilization should be carried out in a carefully planned manner; it is all too easy to compound splenic injury with ill-advised maneuvers that obligate the surgeon to perform a total splenectomy.

Gastric decompression is ensured with a properly placed nasogastric tube. The spleen is then retracted anteromedially with the left hand, with care taken to confirm proper retraction of the left abdominal wall. The phrenicocolic ligament is thereby placed on stretch, and the ligament insertion on the lateral abdominal wall serves as countertraction. The phrenicocolic ligament is then incised from the bottom up with either long scissors or the 45°-angle tip of a monopolar cautery [see Figure 19]. Efforts should be made to leave 2 cm of ligament on the spleen side and to avoid capsular injury. If the surgeon cannot put a finger behind the ligament, an

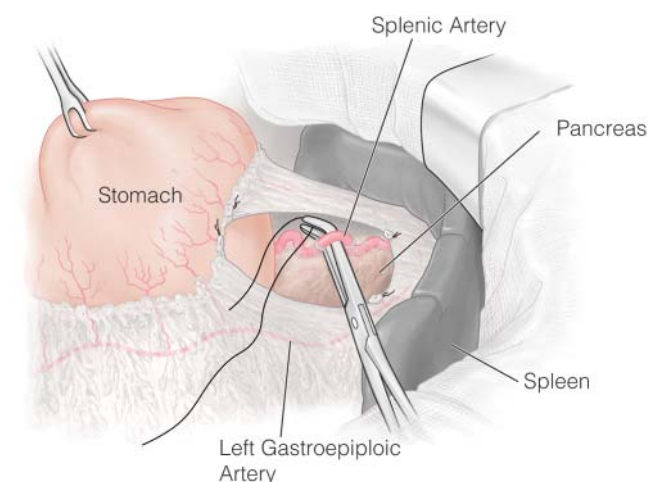


Figure 18 Open splenectomy. The splenic artery is controlled above the pancreas in the lesser sac. The artery must be ligated distal to the pancreatic magna artery.

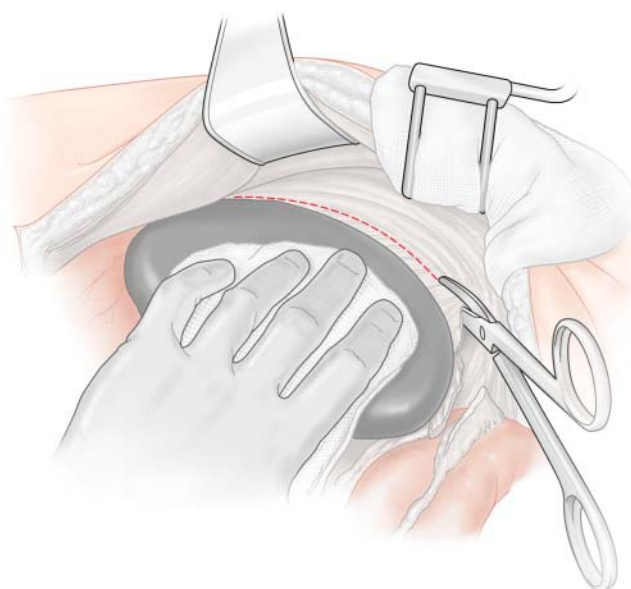


Figure 19 Open splenectomy. With the spleen retracted medially, the phrenicocolic ligament is incised.

assistant should elevate the ligament between the jaws of a right-angle clamp. The incision of the phrenicocolic ligament is then extended to the left crus of the diaphragm. Except in patients with portal hypertension or myeloproliferative disorders, this ligament is avascular. The left lateral portion of the gastrocolic ligament (the greater omentum) is also dissected away from the splenic flexure of the colon to facilitate mobilization of the spleen. At this point, the splenocolic ligament and the sustentaculum lienis are left alone.

After complete division of the phrenicocolic ligament, a plane is developed between the pancreas and the retroperitoneal structures with gentle blunt finger dissection. The spleen can then be delivered to the midline, where the splenectomy can be planned in an unhurried manner [see Figure 20]. Continuing splenic bleeding during this maneuver can be controlled with manual compression of the organ. The splenic pedicle may also be gently compressed between the thumb and the index finger at this stage. Laparotomy sponges are placed in the left subphrenic space.

Troubleshooting When performing elective resections of very large spleens, experienced spleen surgeons use a few tricks to simplify the procedure. In most patients with megaspleens, the suspensory ligaments have been stretched over time, allowing the surgeon much more leeway in mobilizing or turning the spleen. This greater leeway allows the surgeon to rotate the spleen from the lower pole so as to deliver it transversely into the incision. Thus, the presence of a large spleen does not always necessitate the creation of a long xiphopubic incision, because a transversely placed spleen can be extracted into the abdominal wall through a shorter incision.

Step 5a (Total Splenectomy): Planning of Resection

To devise the appropriate operative strategy, the surgeon performing open total splenectomy must address the same

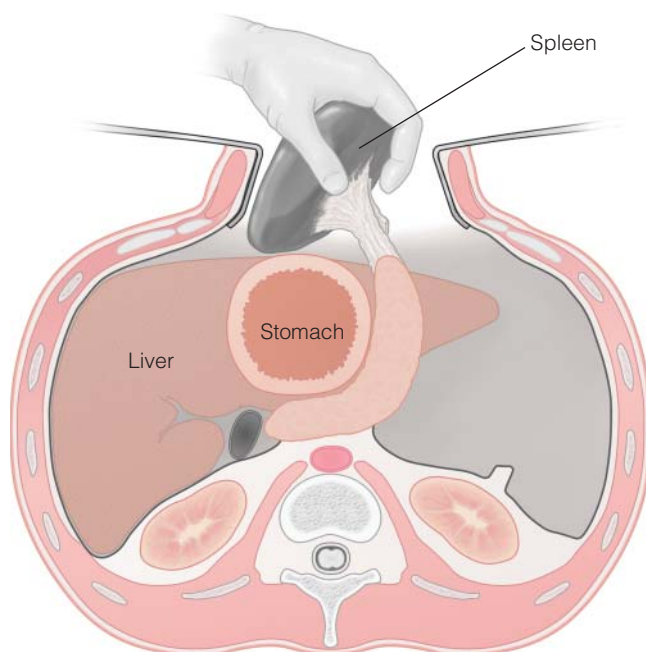


Figure 20 Open splenectomy. The spleen is delivered to the midline by means of blunt and sharp dissection of the areolar plane between the kidney and the pancreas.

anatomic issues that he or she would if performing laparoscopic total splenectomy—for example, the nature of the splenic blood supply (distributed or bundled) and the distance between the tip of the pancreas and the splenic hilum. The anatomy must be appreciated before the operative strategy can be defined.

Once the spleen has been delivered into the abdominal wall, various techniques may be employed to control the blood supply. The classic approach is to serially clamp, ligate, or suture-ligate the vessels between curved clamps, starting from the lower pole. Alternatively, the vessels may be controlled with clips.

Troubleshooting We frequently use laparoscopic clip appliers to achieve vascular control in open splenectomy. The long, slender design of these devices is particularly useful in obese patients, in whom it is often difficult to achieve complete mobilization of the spleen without causing additional splenic trauma. With laparoscopic clip appliers, vessels can be safely controlled inside the abdomen. Locking plastic clips may also be used. Moreover, provided that the same precautions are taken as in laparoscopic splenectomy, a linear stapler with a vascular cartridge may be used to control the hilum in one step once the gastroepiploic branches have been controlled.

Step 5b (Partial Splenectomy): Planning of Resection

Once the spleen is appropriately placed for full evaluation and adequate hemostasis is ensured, planning for partial splenectomy can start. In trauma cases, such planning is guided by the extent of the injury, and in elective cases, it is guided by the nature of the underlying pathologic condition [see Table 3].

Table 3 Indications and Contraindications for Partial Splenectomy

Indications
Selected grade II–IV splenic injuries with the following:
Hemodynamic stability
No evidence of other intra-abdominal organ injury
No associated head injury
No coagulopathy
CT confirmation of isolated splenic injury
Selective elective indications
Resection of nonparasitic cysts
Hamartomas and other benign splenic tumors
Inflammatory pseudotumor of the spleen
Type I Gaucher disease
Cholesteryl ester storage disease
Chronic myelogenous leukemia
Thalassemia major
Spherocytosis
Staging of Hodgkin disease in children
Absolute/relative contraindications in trauma
Inadequate exposure
Inability to mobilize spleen and tail of pancreas to midline
Inability to leave > 25% of splenic mass for complete splenic function

CT = computed tomography.

In most cases, as noted, the spleen can be divided into independent lobes or segments, each with its own terminal blood supply. The superior pole is supplied by the short gastric vessels, and the lower pole is supplied by branches of the gastroepiploic artery, which are known to form anastomoses with the inferior polar artery. In addition, most patients, possible variations notwithstanding, have two or three major vessels entering the hilum. Thus, usually four or five discrete regions or lobes may be removed, individually or in combination, in a partial splenectomy. It should be kept in mind that the vessels supplying the spleen lie in different supportive ligaments. The vessels supplying the superior pole (the short gastrics) and the inferior pole (the gastroepiploic branches) rest in the gastrosplenic ligament, whereas the splenic branches proper lie in the splenorenal ligament along with the tail of the pancreas.

Step 6 (Partial Splenectomy): Exposure of Entire Hilum and Ligation of Appropriate Arteries

The entire hilum of the spleen is then exposed close to the parenchyma. The gastrosplenic ligament and the splenorenal ligament must be separated, with care taken to preserve the blood supply to both poles of the spleen. There is a fairly avascular area of the gastrosplenic ligament, between the short gastric vessels supplying the superior pole and the gastroepiploic branches supplying the lower pole, that must be opened; once this is done, a complete view of the entire splenic blood supply is available. The surgeon can then determine whether partial splenectomy is feasible and how many lobes he or she can resect while still leaving enough spleen tissue behind for adequate splenic function. Any number of segmental resections are possible. If the surgeon is unsure of the extent of the necessary resection, an accurate assessment can be made by temporarily compressing the splenic arterial branches.

Selected arterial branches are then carefully dissected as close to the spleen parenchyma as possible, with the understanding that the veins are situated posteriorly in close

proximity. The vessels may be doubly ligated, transfixed, or clipped. If clips are used, care is taken not to dislodge them with inappropriate manipulations. Once the arterial blood supply is controlled, the affected area of the spleen will rapidly become visibly demarcated. If the devitalized area of the spleen corresponds to the intended resection, a similar technique is applied to the venous side. Access to the venous side can also be achieved from the posterior aspect of the spleen. When this approach is followed, it is helpful to identify the tail of the pancreas if possible to avoid inadvertent damage: the tail of the pancreas touches the hilum of the spleen in 30% of cases and lies within 1 cm of the hilum in 70%.

Step 7 (Partial Splenectomy): Incision of Splenic Capsule and Partial Resection of Spleen

The capsule of the spleen is incised circumferentially with a scalpel or a monopolar cautery, and a 5 mm rim of devitalized tissue is left in situ. The splenic fragments may be transected with a scalpel, scissors, a monopolar cautery, or a combination thereof. Various techniques have been used to control residual bleeding, including use of a monopolar cautery on spray current; use of a cutaneous ultrasonic surgical aspirator; use of an argon beam coagulator; suture compression, with or without Teflon pledgets; and omental pedicle packing. One low-tech way of dealing with residual hemostatic requirements is to employ the hollow part of a Poole suction device to aspirate blood while employing a coagulating monopolar current on the suction tip. In some cases, wrapping the splenic remnant in an absorbable polyglycolic mesh is useful. Our experience suggests that when enough residual devitalized tissue (i.e., at least 5 mm) is left behind circumferentially, good hemostasis is easily achieved,

typically requiring nothing more than simple measures and topical agents. No drains are used unless the tail of the pancreas has been damaged, in which case a closed-suction drain is placed.

POSTOPERATIVE CARE

The principles of postoperative care are essentially the same for open splenectomy as for laparoscopic splenectomy [see Laparoscopic Splenectomy, Postoperative Care, *above*], although most authors agree that the pace of aftercare is slower with the former. It should be kept in mind that acute postoperative gastric distention occurs more frequently in children and may necessitate more prolonged gastric decompression.

COMPLICATIONS

The complications seen after open splenectomy are the same as those seen after its laparoscopic counterpart [see Laparoscopic Splenectomy, Complications, *above*]. Hemorrhagic complications may necessitate transfusion, reoperation, or both.

Although the rate of serious postoperative infection after splenic surgery is generally considered to be 8%, it is thought to be lower in patients undergoing splenorrhaphy or partial splenectomy. The lower rate is probably attributable to the presence of less severe underlying injuries rather than to the preservation of splenic tissue. Infectious complications usually manifest themselves between postoperative days 5 and 10 and are typically diagnosed by means of physical examination, chest x-ray, ultrasonography, and CT.

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Figures 1, 3, 4, 6a, 13, and 17 through 20 Tom Moore

26 ADRENALECTOMY

Steven Hodgett, MD, and L. Michael Brunt, MD

The surgical approach to the adrenals has evolved substantially over the past decade with the development and refinement of techniques for performing laparoscopic adrenalectomy. At present, the majority of adrenal tumors are removed laparoscopically because minimally invasive approaches result in reduced pain, faster recovery, and fewer complications and because the rate of adrenal malignancy is low. Nevertheless, open adrenalectomy still has a role in the management of selected patients with large or malignant tumors. With both open adrenalectomy and laparoscopic adrenalectomy, several different surgical approaches to the adrenals are possible [see *Operative Planning, Choice of Procedure, below*]. Regardless of the particular approach followed, the keys to successful adrenalectomy are the same: proper patient selection for operation, a solid understanding of adrenal pathophysiology, and a thorough knowledge of adrenal anatomy.

Anatomic Considerations

The adrenal glands are retroperitoneal organs that lie along the superomedial aspects of the two kidneys [see *Figure 1*]. Each gland comprises two discrete anatomic and functional units: the adrenal cortex, which is the site for synthesis and secretion of cortisol, aldosterone, and adrenal androgens, and the medulla, which is derived from the neural crest and is the site for synthesis of the catecholamines epinephrine and norepinephrine. A normal adrenal gland typically weighs between 4 and 6 g and measures approximately 4 to 5 cm by 2 to 3 cm by 0.5 to 1 cm. The right adrenal is relatively pyramidal in shape, whereas the left is somewhat flattened and is more closely applied to the kidney. Grossly, the adrenals may be distinguished from the surrounding retroperitoneal fat by their golden-orange color, which is a result of the high intracellular lipid content. The glands have a fibrous capsule but

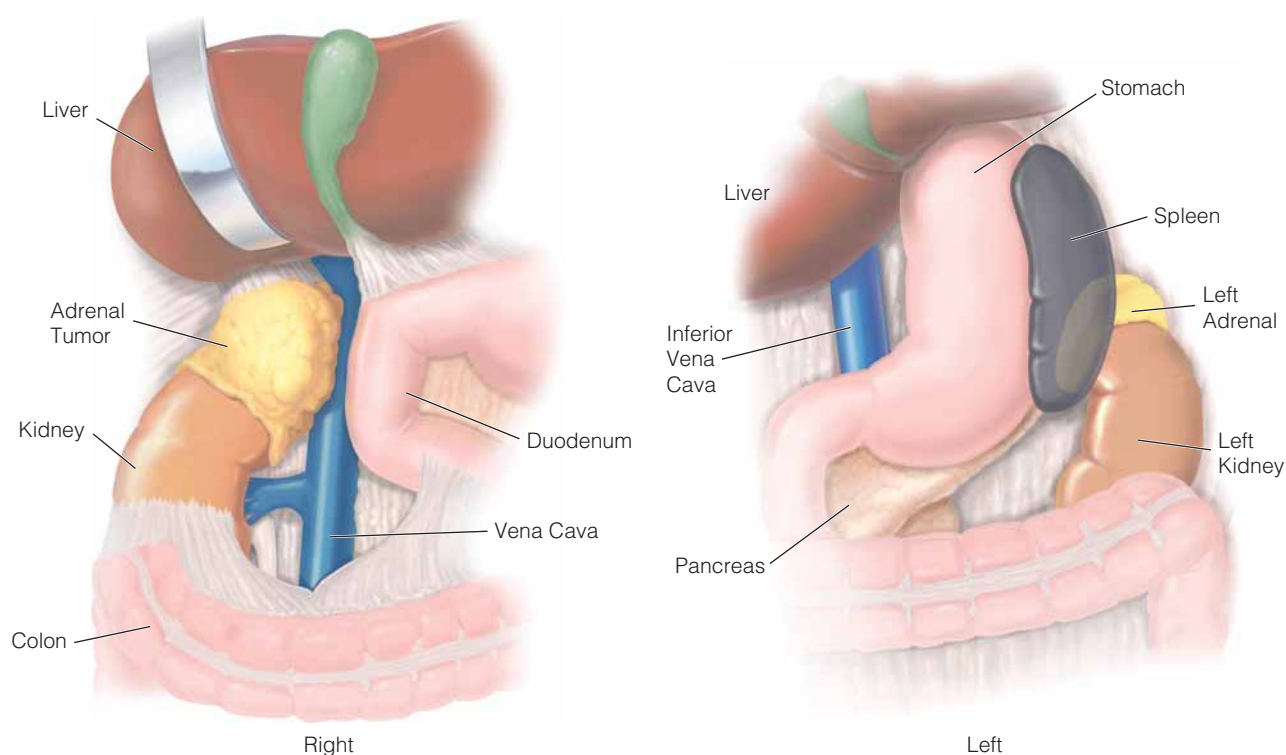


Figure 1 Depicted is the relation of the adrenal glands to adjacent structures.

are relatively fragile and can be easily cracked or fragmented with surgical manipulation.

RIGHT ADRENAL

Anteriorly, the right adrenal is partially covered by the liver and the right triangular ligament. The gland abuts the inferior vena cava (IVC) medially and may, in part, lie posterior to the lateral aspect of the vena cava. Inferiorly, the adrenal sits just above the upper pole of the kidney. The diaphragm forms the posterior and lateral boundaries of the gland.

The blood supply of the right adrenal is derived from branches of the inferior phrenic artery, the right renal artery, and the aorta [see Figure 2]. Typically, multiple small branches enter the gland along its superior, medial, and inferior aspects. Arterial branches from the aorta generally course posterior to the vena cava before entering the adrenal. Each adrenal is drained by a single central vein. On the right, this vein is short (1 to 1.5 cm long), runs transversely, and joins the lateral aspect of the IVC. In some cases, a more superiorly located accessory adrenal vein may enter either the IVC or one of the hepatic veins. Control of the adrenal vein is the most critical aspect of right adrenalectomy in that the short course of this vessel makes it susceptible to tearing or avulsion from the IVC.

LEFT ADRENAL

The spleen and tail of the pancreas overlie the anterior and medial borders of the left adrenal. The inferolateral aspect of the gland lies over the superomedial aspect of the left kidney, to which it is more closely applied than the right adrenal is to the right kidney. The inferior aspect of the adrenal is in close proximity to the renal vessels, especially the renal vein. As on the right side, the posterior aspect of the adrenal rests on the diaphragm.

The arterial blood supply of the left adrenal is similar to that of the right adrenal [see Figure 2]. The left adrenal vein is longer than the right adrenal vein and runs somewhat obliquely from the inferomedial aspect of the gland to enter the left renal vein. The inferior phrenic vein courses in a superior-to-inferior direction just medial to the adrenal and usually joins the left adrenal vein cephalad to its junction with the renal vein.

Preoperative Evaluation

INDICATIONS FOR OPERATION

The main indications for adrenalectomy are well established [see Table 1]. Any adrenal lesion that either is hypersecretory for one of the adrenal hormones or appears to be malignant or

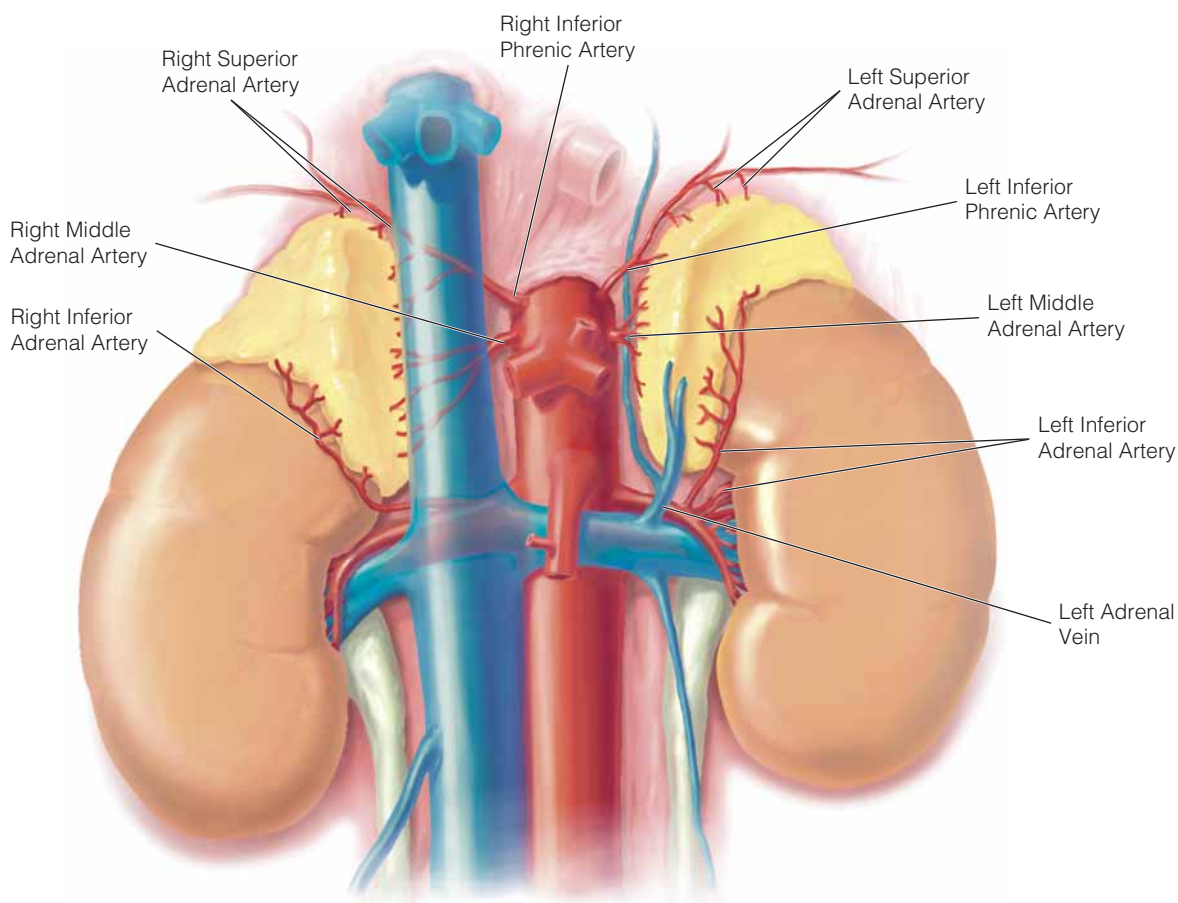


Figure 2 Depicted is the adrenal blood supply. Multiple adrenal arteries are present; a single central adrenal vein drains into the inferior vena cava on the right side and the renal vein on the left side.

Table 1 Indications for Adrenalectomy

Aldosteronoma
Cushing syndrome
Cortisol-producing adenoma
Primary adrenal hyperplasia
Failed treatment of ACTH-dependent Cushing syndrome
Pheochromocytoma
Sporadic or familial
Malignant pheochromocytoma
Nonfunctioning incidental lesion
≥ 4–5 cm or atypical radiologic appearance
Adrenal metastasis
Solitary, unilateral in the absence of extra-adrenal cancer
Adrenal cortical carcinoma
Adrenal sarcoma
Adrenal myelolipomas (only if symptomatic or enlarging)
Miscellaneous other lesions (atypical cysts, ganglioneuromas)

ACTH = adrenocorticotrophic hormone.

possibly malignant should be removed. In selected cases, it may be appropriate to remove adrenal metastases if they are solitary and if there is no evidence of extra-adrenal metastatic disease. Nonfunctioning adrenal lesions that appear to be benign on the basis of their size (< 4 cm) and their appearance on computed tomography (CT) or magnetic resonance imaging (MRI) need not be removed unless they enlarge during follow-up. Adrenal myelolipomas and cysts usually can be diagnosed radiographically and should not be removed unless they cause symptoms or if there is uncertainty in the diagnosis.

Most of the conditions for which adrenalectomy is indicated are amenable to a laparoscopic approach. However, the role of laparoscopy in patients with large adrenal tumors (> 6 to 8 cm) or potentially malignant primary adrenal lesions remains controversial. In the presence of a locally invasive tumor, a laparoscopic approach is contraindicated because of the need to perform en bloc resection of the tumor and any adjacent involved structures.

COMMON ADRENAL TUMORS

A brief review of the pertinent clinical and biochemical features of the various hypersecretory adrenal tumors [see Table 2] will facilitate evaluation of adrenal lesions (including adrenal incidentalomas) and planning for adrenal surgery.

Table 2 Clinical and Diagnostic Features of Common Adrenal Tumors

Adrenal Tumor	Clinical Presentation	Biochemical Testing	Preferred Method of Imaging/Localization
Aldosteronoma	Hypertension ± hypokalemia	Elevated PAC with suppressed PRA (PAC:PRA > 20–30)	Thin-section (3 mm) adrenal CT
		Urine aldosterone > 12 µg/24 hr	Adrenal vein sampling
		Urine potassium > 30 mEq/24 hr	
Cortisol-producing adenoma (Cushing syndrome)	Centripetal obesity, moon facies, hypertension, purple skin striae, osteopenia, plethora, amenorrhea	Elevated 24 hr urinary free cortisol	Abdominal CT
		Nonsuppressed low-dose dexamethasone test	
		Decreased plasma ACTH	
Pheochromocytoma	Severe episodic hypertension or hypertension with spells of tachycardia, headache, anxiety, and diaphoresis	Elevated plasma fractionated metanephrines or urinary catecholamines and metabolites	MRI (T ₂ -weighted sequences showing bright-appearing adrenal lesion)
			¹²³ I-MIBG scan or Octreo-scan if MRI is negative or if malignant or extra-adrenal tumor is suspected
Adrenal cortical carcinoma	Cushing syndrome, virilizing features, local pain or mass	24 hr urinary free cortisol and metabolites	CT of chest/abdomen/pelvis
		Plasma DHEA-sulfate	
Adrenal metastasis	None (often seen on follow-up imaging) or local pain	Plasma fractionated metanephrines and low-dose DM test to exclude functioning lesion	Abdominal CT, PET imaging to evaluate for extra-adrenal metastatic disease
		FNA biopsy only if unresectable	
Myelolipoma	None; occasionally local pain	None if radiographic appearance is unequivocal for myelolipoma	Presence of macroscopic fat on CT or MRI

ACTH = adrenocorticotrophic hormone; CT = computed tomography; DHEA = dehydroepiandrosterone; DM = dexamethasone; FNA = fine-needle aspiration; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; PAC = plasma aldosterone concentration; PET = positron emission tomography; PRA = plasma renin activity.

Aldosteronoma

Primary hyperaldosteronism is the most common form of secondary hypertension, and aldosterone-producing adenoma is the most common hypersecretory adrenal tumor. The prevalence of this diagnosis is much higher than was previously thought,^{1,2} reaching levels as high as 12% of hypertensive individuals in some series.¹ The classic finding in primary hyperaldosteronism is hypertension in conjunction with hypokalemia, but many patients have a normal or low-normal serum potassium level. The hypertension in these patients is often refractory to standard medical therapy. Therefore, any patient who becomes hypertensive at an early age or who has malignant or difficult-to-control hypertension should be screened for this diagnosis. Screening consists of measuring plasma aldosterone concentration (PAC) and plasma renin activity (PRA). A PAC-to-PRA ratio higher than 25 to 30, in conjunction with a plasma aldosterone concentration higher than 15 ng/dL and renin < 0.5 ng/mL/hr, is suggestive of the diagnosis and should be confirmed by suppression measuring 24-hour urine aldosterone, sodium, and potassium levels while the patient is on a high-sodium diet.² A 24-hour urine aldosterone level higher than 12 µg/24 hr in this setting is confirmatory; the urine potassium should be > 30 mEq/24 hr.

Because 25% or more of cases of primary hyperaldosteronism may be idiopathic as a result of bilateral adrenal hyperplasia and should therefore be managed medically and not surgically, the next step should be imaging with thin-section (3 mm cuts) CT or MRI. The finding of a discrete unilateral adenoma larger than 1 cm on CT in conjunction with a normal contralateral adrenal is sufficient localization to allow the surgeon to proceed with adrenalectomy. If CT shows bilateral nodules, bilateral normal adrenals, or a unilateral nodule smaller than 1 cm, then adrenal vein sampling for aldosterone and cortisol should be done to determine whether a unilateral gradient of increased aldosterone production exists.³

Cortisol-Producing Adenoma

Approximately 20% of cases of Cushing syndrome are related to increased production of cortisol by an adrenal cortical tumor. Adrenal Cushing syndrome is most commonly attributable to adenoma but may also result from adrenal cortical carcinoma or primary adrenal hyperplasia. The classic features of full-blown Cushing syndrome are usually obvious and include centripetal obesity, moon facies, hypertension, purple skin striae, proximal muscle weakness, osteopenia, and amenorrhea. Not all patients present with advanced clinical signs, however, and the high prevalence of hypertension and obesity in the general population necessitates liberal use of diagnostic testing.

Suspected Cushing syndrome should be evaluated initially by measuring 24-hour urinary free cortisol levels or by administering a single low-dose dexamethasone test. Plasma cortisol that does not fall to a level below 3 to 5 µg/dL the morning after administration of 1 mg of dexamethasone at 11 pm is indicative of a loss of autonomy of cortisol secretion, and further testing is required. Once the diagnosis of hypercortisolism is established, plasma levels of adrenocorticotropic hormone (ACTH) should be measured to differentiate ACTH-dependent (resulting from increased ACTH production by a pituitary tumor or an ectopic source) from

ACTH-independent (primary adrenal) causative conditions. The plasma ACTH level should be in the low-normal or suppressed range in patients with primary adrenal tumors, whereas it is normal or elevated in patients with ACTH-dependent Cushing syndrome. Imaging should then be carried out with CT (or MRI) to localize the adrenal tumor.

Pheochromocytoma

Pheochromocytoma should be suspected in any patient who experiences either severe episodic hypertension or hypertension that is associated with spells of tachycardia, headache, anxiety, and diaphoresis. Biochemical evaluation consists of measuring urinary concentrations of catecholamines and metabolites (e.g., metanephrine and normetanephrine), plasma concentrations of fractionated metanephrines, or both. MRI is our preferred imaging modality for suspected pheochromocytomas because of the typical bright appearance these tumors exhibit on T₂-weighted imaging sequences. Occasionally, radionuclide imaging with iodine-123–metaiodobenzylguanidine (¹²³I-MIBG) or octreotide scintigraphy is necessary to localize an extra-adrenal pheochromocytoma.

Adrenocortical Carcinoma

Adrenocortical carcinomas are rare, with an incidence of approximately one per 1.5 to 2.0 million in the general population. These tumors are typically large (> 6 to 8 cm) at diagnosis, and most patients have advanced (stage III or IV) disease at presentation. Consequently, patients often have a mass or complain of abdominal or back pain. A significant percentage of patients with adrenocortical carcinoma present with evidence of hormone overproduction in the form of Cushing syndrome or virilizing features. Complete surgical resection offers the only chance for cure; thus, the role of laparoscopic adrenalectomy in the treatment of adrenocortical carcinoma remains controversial [see Troubleshooting, Large Tumors, *below*].

Adrenal Incidentaloma

Adrenal incidentalomas are the adrenal lesions most frequently referred to surgeons and are seen on 1 to 5% of all abdominal CT scans.⁴ Practical recommendations for the evaluation and management of patients with incidentally discovered adrenal lesions are available.^{5,6} The most common adrenal incidentaloma is a nonfunctioning cortical adenoma for which adrenalectomy is not usually required. All patients with adrenal incidentalomas should be screened for hypercortisolism by administering an overnight low-dose dexamethasone test and for pheochromocytoma by measuring plasma concentrations of fractionated metanephrines or urine levels of catecholamines and metanephrines. Patients who are hypertensive or hypokalemic should also undergo testing for hyperaldosteronism with measurement of plasma aldosterone and renin levels. Some patients with adrenal incidentalomas are found to have subclinical Cushing syndrome with evidence of autonomous corticoid steroid production, as demonstrated by lack of suppressibility with a dexamethasone test and by low plasma ACTH levels.⁷ These patients do not exhibit the classic features of Cushing syndrome but do have a high incidence of hypertension, diabetes, and osteoporosis. Adrenalectomy is generally indicated if the operative risk is suitably low. Supplemental corticosteroids should be given before, during, and

after operation because contralateral adrenal function is often suppressed and adrenal insufficiency may ensue.

The nonfunctioning adrenal lesion should also be assessed for malignant potential on the basis of its size and appearance on diagnostic imaging. Cortical adenomas typically have low attenuation values (< 10 Hounsfield units) on unenhanced CT imaging and show loss of signal intensity on MRI chemical shift imaging sequences. Needle biopsy is not useful in differentiating benign from malignant primary adrenal lesions and is rarely indicated. Adrenal biopsy should never be done unless a pheochromocytoma has first been excluded biochemically. Most experts recommend removing any nonfunctioning adrenal lesion larger than 4 to 5 cm unless the radiographic appearance of the lesion is diagnostic of a cyst or myelolipoma. Smaller tumors should be followed with imaging at 4 and 12 months after the initial presentation.

Operative Planning

PREPARATION FOR OPERATION

Preoperative preparation of the patient for adrenalectomy entails control of hypertension and correction of any electrolyte imbalances. Patients with a pheochromocytoma should receive 7 to 10 days of alpha-adrenergic blockade with phenoxybenzamine to minimize any exacerbation of hypertension during the operation. The usual starting dosage is 10 mg twice daily, which is increased by 10 to 20 mg/day until the hypertension and tachycardia are controlled and the patient is mildly orthostatic. Patients with Cushing syndrome or subclinical Cushing syndrome should receive perioperative dosages of stress steroids. Mechanical bowel preparation is not routinely employed.

CHOICE OF PROCEDURE

The retroperitoneal location of the adrenals renders them accessible via either transabdominal or retroperitoneal approaches. The choice of surgical approach in any given patient depends on a number of factors, including the nature of the underlying adrenal pathology, the size of the tumor, the patient's body habitus, and the experience of the operating surgeon. For the vast majority of adrenal lesions, laparoscopic adrenalectomy is preferred. Most centers favor the transabdominal lateral approach to laparoscopic adrenalectomy,⁸ which has the advantages of a large working space, familiar anatomic landmarks, and widespread success. Some centers, however, prefer a retroperitoneal endoscopic approach.^{9,10} The advantages of this technique are that the peritoneal cavity is not entered, there is no need to retract overlying organs, and the incidence of postoperative ileus may be lower. The disadvantages are that the retroperitoneal approach employs a smaller working space, is more difficult to learn with fewer anatomic landmarks for orientation, and may be more difficult with larger tumors.

The only absolute contraindications to laparoscopic adrenalectomy are local tumor invasion and the presence of regional lymphadenopathy. Cases in which the adrenal tumor is large (> 8 to 10 cm), are suspected to be primary adrenal malignancies; a history of previous nephrectomy, splenectomy, or liver resection on the side of the lesion to be removed should be considered relative contraindications to a laparoscopic approach in all but the most experienced hands. Portal

hypertension is also a contraindication to a laparoscopic approach because of the dilated collateral vessels in the retroperitoneum.

Options for open adrenalectomy include transabdominal, flank, posterior retroperitoneal, and thoracoabdominal approaches. The lateral flank approach and the posterior retroperitoneal approach have been replaced by laparoscopic approaches and are now rarely used. Open posterior retroperitoneal adrenalectomy is done through a hockey-stick incision in the back, with subperiosteal resection of the 12th rib. This approach has low morbidity and yields adequate exposure of the adrenal gland, but the visual field is often limited, and there is a high incidence of residual incisional complaints. The current consensus is that open posterior retroperitoneal adrenalectomy is indicated only in patients who require bilateral adrenalectomy but are not candidates for laparoscopic adrenalectomy. Most large or malignant adrenal tumors that necessitate an open approach can be removed via an anterior abdominal incision, usually a unilateral or bilateral subcostal incision (with subxiphoid extension if necessary); a thoracoabdominal incision is rarely needed.

Operative Technique

LAPAROSCOPIC ADRENALECTOMY

Transabdominal Approach

Patient positioning A gel-padded bean-bag mattress is placed on the operating table before the patient enters the room. The patient is placed in the supine position, general anesthesia is induced, and sequential compression stockings are placed. A urinary catheter may be optional for uncomplicated cases but should be used for all pheochromocytomas and larger tumors. The stomach may be decompressed with an orogastric tube. Invasive monitoring is not usually necessary unless the patient has a vasoactive pheochromocytoma, in which case, an arterial line is routinely placed.

Next, the patient is moved into a lateral decubitus position with the affected side up [see Figure 3]. A soft roll is placed



Figure 3 The patient is placed in a lateral decubitus position with the affected side up (here, right lateral decubitus for left adrenalectomy).

underneath the chest wall to protect the axilla. The bean-bag mattress is molded around the patient and the legs are wrapped in a foam pad to protect all pressure points. The patient is secured to the operating table with tape placed across the padded lower extremities and a safety strap across the pelvis. The operating table is then flexed at the waist. The combination of the lateral position, the flexed operating table, and the reverse Trendelenburg position facilitates placement of the laparoscopic ports and provides optimal access to the superior retroperitoneum.

Equipment Our preferred instrumentation for laparoscopic adrenalectomy is as follows [see Table 3]. An angled (30°) laparoscope, preferably 5 mm in diameter, is used to optimize viewing angles. One 10/12 mm port is employed to allow insertion of a clip applier and extraction of the specimen; the other ports can all be 5 mm if a 5 mm laparoscope is employed. The principal instruments needed for dissection and hemostasis are atraumatic graspers, an L-hook electrocautery, and a medium-large clip applier. An ultrasonic coagulator or bipolar coagulation device is optional for right adrenalectomy, but both are very useful for mobilization of the splenic ligaments and dissection of the adrenal from the retroperitoneal fat during a left adrenalectomy. An endovascular stapler should be available for a right adrenalectomy because it will occasionally be needed to divide the right adrenal vein. Other essential items are a suction-irrigation device and an impermeable specimen retrieval bag.

Initial access and placement of trocars Because the patient is in a lateral position, initial access to the peritoneal cavity is usually achieved in a closed fashion with a Veress needle. After insufflation to a pressure of 15 mm Hg, a 5 mm direct-view trocar is placed to afford direct visualization of the peritoneal cavity. An open insertion technique may be used instead, but this approach requires a larger incision and is hindered somewhat by the bulky overlapping muscle layers in the subcostal region. Open insertion at the umbilicus is an option in nonobese patients.

The initial access site is generally at or somewhat medial to the anterior axillary line about two fingerbreadths below the

costal margin [see Figure 4]. Subsequent ports should be placed at least 5 cm apart to allow freedom of movement externally. The most dorsal port should be approximately at the posterior axillary line. It is helpful to outline the anterior and posterior axillary lines with a marker before the patient is prepared to ensure that the ports are positioned properly. Four ports are required for a right adrenalectomy, but a left adrenalectomy can be done with either three or four ports, depending on the surgeon's preference and experience. On the left side, the splenic flexure of the colon usually must be mobilized before the fourth port (the most dorsal one) can be inserted.

Right adrenalectomy *Step 1: exposure of right adrenal gland and vein* The key to exposure of the right adrenal gland is extensive division of the right triangular ligament of the liver. This maneuver should be continued until the liver can be easily elevated and retracted medially and both the right adrenal and the IVC are visible. A retractor is then inserted through the most medial port to hold the right lobe of the liver up and away from the operative site [see Figure 5].

Next, the plane between the medial border of the adrenal and the lateral aspect of the IVC is developed. An L-hook cautery is used for gentle elevation and division of the peritoneum and the small arterial branches here [see Figure 5]. The adrenal is pushed laterally with an atraumatic grasper to apply traction to the dissection site; however, the gland itself should not be grasped because it is fragile, and the capsule and adrenal parenchyma are easily fractured. At all times, it is imperative to know where the lateral border of the vena cava is, both to ensure that the dissection is extra-adrenal and to avoid injuring it. The right adrenal vein should come into view as the medial border is dissected.

Step 2: isolation, clipping, and division of right adrenal vein The right adrenal vein is first exposed by gentle blunt spreading, and a right-angle dissector is then used to isolate enough of the vein to permit clip placement [see Figure 6]. A medium-large clip is usually sufficient for securing the vein, although sometimes it is necessary to use larger clips or even an endovascular

Table 3 Instrumentation for Laparoscopic Adrenalectomy

Veress needle
Angled (30°) laparoscope
5 and 12 mm laparoscopic ports
5 mm retractor for right adrenalectomy
L-hook electrocautery
Atraumatic graspers, blunt dissector
Right-angle dissector
Medium-large clip applier
Ultrasonic coagulator or bipolar coagulating device (essential for left adrenalectomy)
Suction-irrigation cannula
Specimen extraction bag
Laparoscopic ultrasound*
Endovascular stapler*

*Not routinely needed but should be available.



Figure 4 Shown is the recommended port site placement for laparoscopic adrenalectomy (here, left adrenalectomy). Dashed lines indicate the costal margin and the anterior and posterior axillary lines.

stapler. (We use an endovascular stapler primarily in cases in which the tumor is located in the medial area of the adrenal and the vein must be taken along with a portion of the IVC

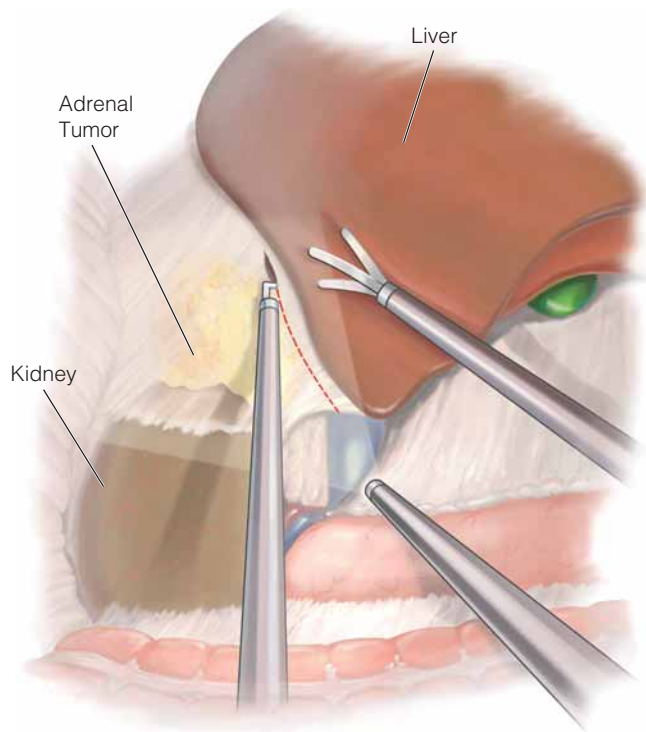
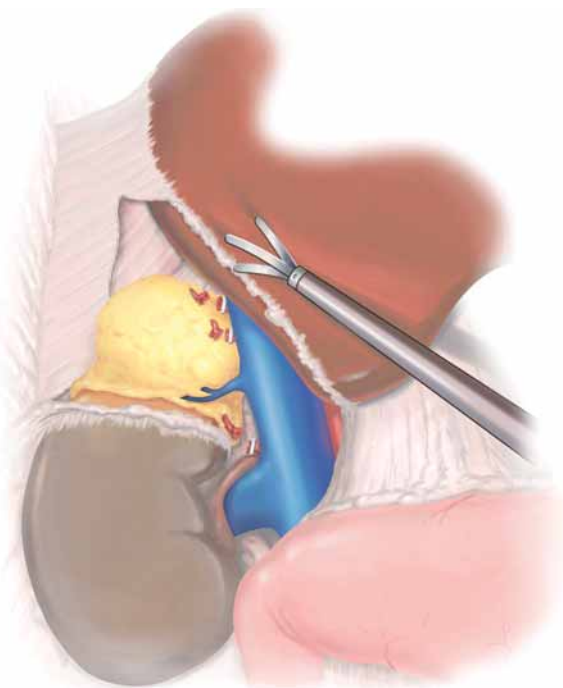


Figure 5 Depicted is the anatomic exposure for right adrenalectomy. The liver is retracted medially, and the right triangular ligament of the liver is divided with an L-hook electrocautery.

a



junction.) Usually, two clips are placed on the IVC side and one or two on the adrenal side, depending on the length of vein available. Meticulous hemostasis throughout the dissection is important: even minimal bleeding will stain the tissue planes and make the dissection more difficult and potentially treacherous.

Step 3: mobilization and detachment of specimen Once the adrenal vein is divided, dissection is continued superiorly and inferiorly with the L-hook cautery. The numerous small arteries that enter the gland at its superior, medial, and inferior margins can be safely cauterized, but larger branches may have to be clipped. Superiorly, as the adrenal is mobilized, the musculature of the posterior diaphragm is exposed and serves as a marker of the proper plane for the posterior dissection. Inferiorly, the dissection should stay close to the margin of the adrenal so as not to injure vessels to the superior pole of the kidney. The inferior dissection then proceeds in a medial-to-lateral direction as the gland is elevated off the superior pole of the right kidney. The remaining attachments to the back muscles and the retroperitoneal fat are relatively avascular and can be divided with the electrocautery or other coagulation device.

Once the specimen has been detached, it is placed in an impermeable bag. The retroperitoneum is then irrigated and inspected for hemostasis and for secure placement of the clips on the IVC.

Step 4: extraction of specimen The fascial opening at the 10/12 mm port site is enlarged somewhat, and the specimen bag is removed through this site. For larger tumors, a remote extraction site (e.g., the umbilicus or the suprapubic region) may be a preferable alternative. Large pheochromocytomas may be morcellated within the entrapment bag and removed piecemeal, but, ideally, cortical tumors and metastatic lesions should be extracted intact to permit full pathologic examination.

b

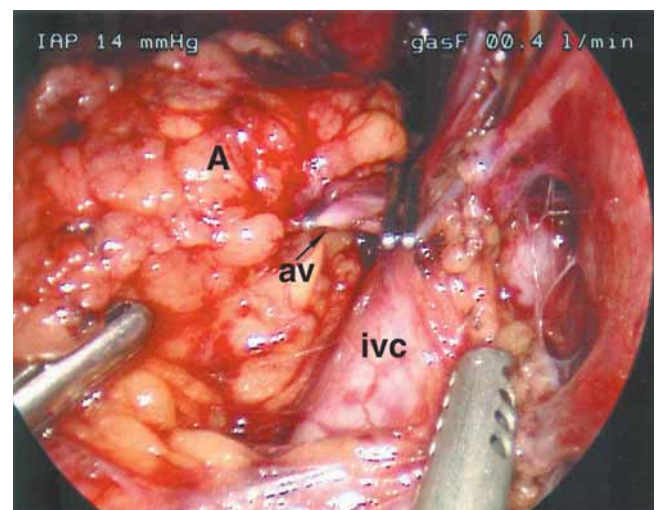


Figure 6 Once the right adrenal and adrenal vein are exposed, the vein is isolated and clipped. Shown are (a) a schematic representation and (b) an intraoperative view showing the right adrenal gland/tumor (A), the right adrenal vein (AV), and the inferior vena cava (IVC).

Left adrenalectomy *Step 1: exposure of left adrenal gland and vein* The splenic flexure of the colon is mobilized. The lateral attachments of the flexure are divided to allow placement of the fourth port, and the colon is then released from the inferior pole of the spleen and away from the left kidney. Next, the splenorenal ligament is incised from the inferior pole of the spleen to the diaphragm to allow full medial rotation of the spleen and provide access to the left retroperitoneum [see Figure 7]. It is important not to dissect lateral to the kidney; doing so will cause the kidney to tilt forward and will interfere with exposure. Once the spleen is completely mobilized, it should fall medially, with minimal or no retraction needed to keep it out of the operative field. Division of the ligaments can be accomplished more quickly and with less bleeding if an ultrasonic coagulator is used.

At this point in the dissection, the tail of the pancreas should be visible, along with the splenic artery and vein. The plane between the pancreas and the left kidney is then developed, and this key maneuver allows the tail of the pancreas along with the spleen to be retracted medially. The adrenal is located on the superomedial aspect of the kidney just cephalad to the tail of the pancreas and should be visible at this point unless there is a great deal of retroperitoneal fat (as is often the case in patients with Cushing syndrome). If the adrenal gland is not readily visible, laparoscopic ultrasonography should be employed to help locate it and to delineate the surrounding anatomy, particularly the upper kidney and the renal hilar vessels. If the dissection starts too low, the renal hilar vessels or the ureter could be injured.

Once the adrenal is visualized, the medial and lateral borders are usually defined by means of dissection with the hook cautery or ultrasonic coagulator and division of areolar attachments and small vessels. The dissection is then continued inferiorly to locate the adrenal vein as it obliquely exits the

inferomedial border of the gland [see Figure 8]. The inferior border of the adrenal often sits adjacent to the left renal vein, from which it can be separated by means of gentle blunt dissection and judicious use of the electrocautery.

Step 2: isolation, clipping, and division of left adrenal vein Once the adrenal vein has been visualized, it is isolated, doubly clipped, and divided. Because the adrenal vein is usually joined by the inferior phrenic vein cephalad to its junction with the renal vein, it is often necessary to clip the inferior phrenic vein again as the dissection proceeds more proximally.

Step 3: mobilization and detachment of specimen Once the left adrenal vein has been securely clipped and divided, the dissection is continued cephalad along both the lateral and the medial borders of the gland. Because of the surrounding retroperitoneal fat, it is advisable to use the ultrasonic coagulator for this part of the left-side dissection. The left adrenal is more flattened out on the superomedial aspect of the left kidney than the right adrenal; therefore, more of the kidney will be exposed during dissection in a left adrenalectomy than on the right, and one must be careful to stay close to the adrenal until the gland is off the upper kidney to avoid injuring a superior pole renal artery. Finally, the posterior and superior attachments to the diaphragm and the retroperitoneal fat are divided.

Step 4: extraction of specimen Once the gland is free, the retroperitoneum is inspected and the specimen extracted as in a right adrenalectomy. If there is any possibility that the pancreatic parenchyma may have been violated, a closed suction drain is left in place.

Retroperitoneal Approach

Retroperitoneal endoscopic adrenalectomy is typically carried out with the patient in a prone position, although it can also be done from a lateral position. In general, this technique

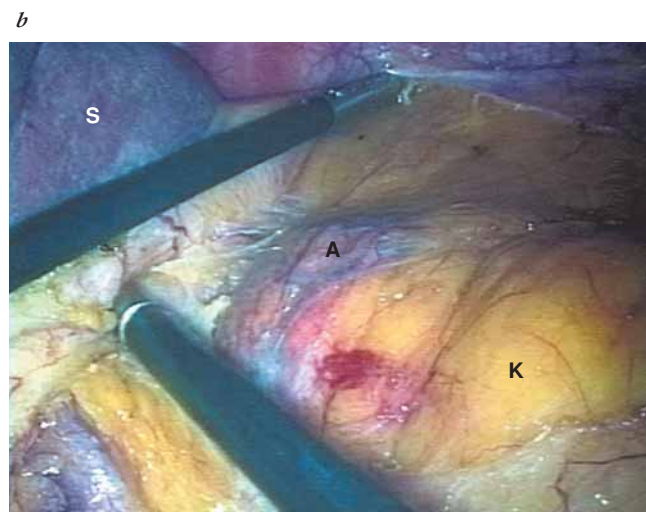
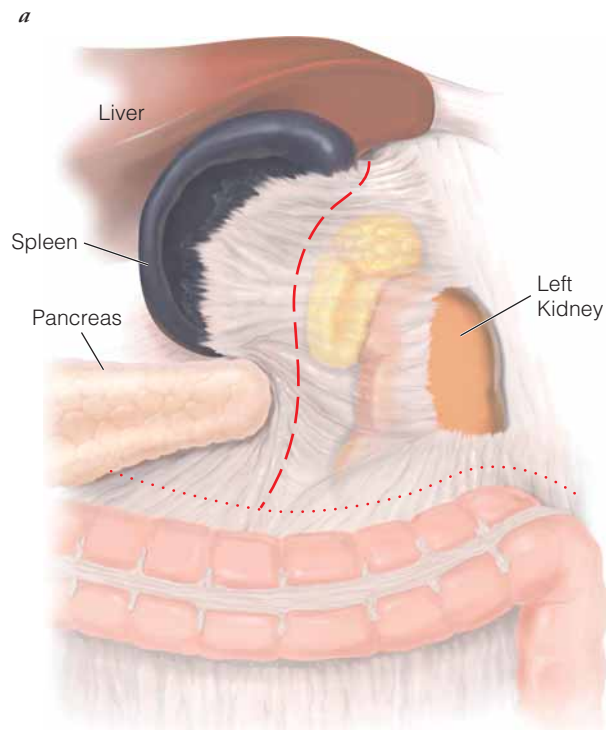


Figure 7 Depicted is the anatomic exposure for left adrenalectomy. (a) The splenic flexure of the colon is divided first (dotted line), and the splenorenal ligament is then divided (dashed line). (b) Shown is an intraoperative view. A = adrenal; K = kidney; S = spleen.

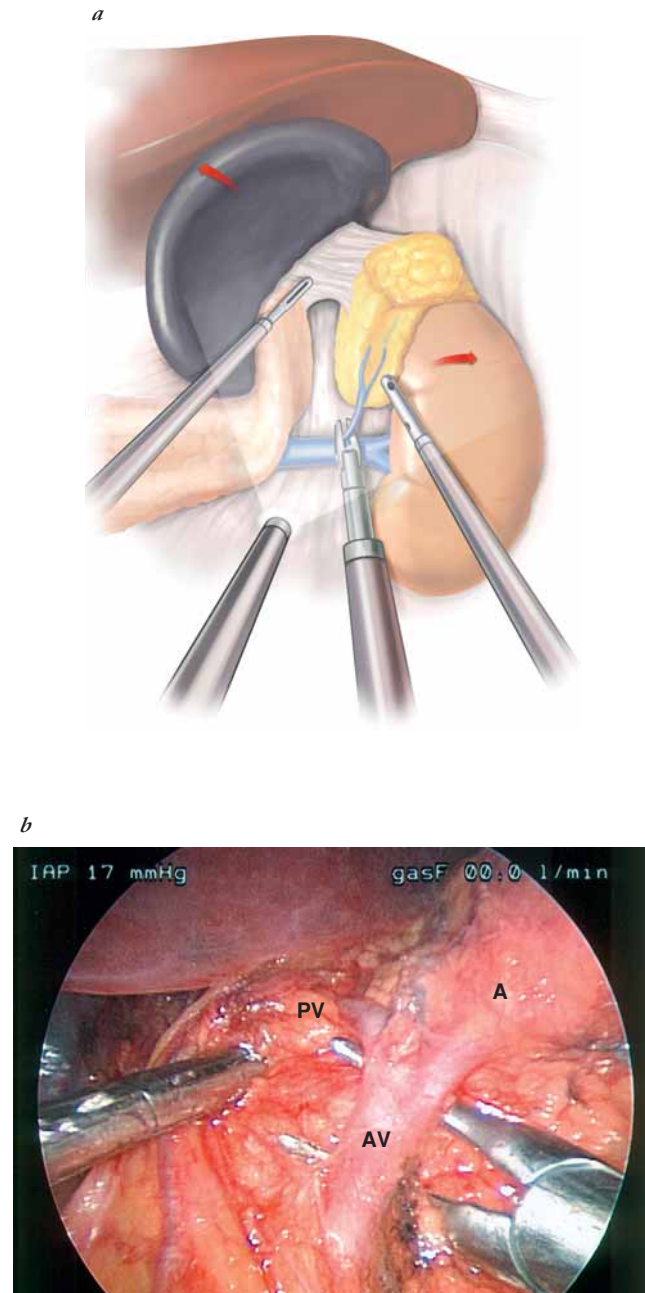


Figure 8 Once the left adrenal and adrenal vein are exposed, the vein is isolated and clipped. Shown are (a) a schematic representation and (b) an intraoperative view showing the left adrenal gland/tumor (A), the left adrenal vein (AV), and the phrenic vein (PV). The phrenic vein joins the left adrenal vein above its junction with the renal vein.

is more challenging to learn than transabdominal adrenalectomy, the working space is smaller, and it is easier for surgeons to become disoriented unless they have experience working in the retroperitoneum. On the other hand, the retroperitoneal approach is the most direct approach to the adrenals, and it allows surgeons to avoid having to reposition patients for bilateral adrenalectomy (if the prone position is used). It may



Figure 9 Shown is the patient position and recommended port site placement. The middle port is placed just below the tip of the 12th rib.

simplify access in patients who have previously undergone extensive upper abdominal procedures.

The technique for performing retroperitoneoscopic adrenalectomy has been well described by Walz and colleagues in over 500 cases.¹¹ The patient is in a prone position and is lying on a rectangular support that allows the abdominal wall to hang freely so that the retroperitoneum may be more easily expanded by the CO₂ gas. The initial access incision is placed just below the tip of the 12th rib, and the retroperitoneum is entered under direct visualization. The cavity is developed digitally, a second trocar is placed 4 to 5 cm laterally beneath the 11th rib, and a third port is placed medially through an incision 3 cm below the 12th rib [see Figure 9]. Alternatively, the retroperitoneal space can be developed using a balloon dissection device. It is helpful to use an adjustable blunt trocar with an inflatable balloon for the initial access site to maintain a good seal.

The retroperitoneal space should be inflated at 20 to 25 mm Hg to aid in both increasing the size of the working space and decreasing the amount of bleeding. The space is then further developed by bluntly pushing down the retroperitoneal fat beneath the diaphragm and exposing the upper pole of the kidney. The dissection then begins laterally and proceeds medially and the adrenal gland should come into view. As for the transabdominal approach, if the adrenal is difficult to locate, laparoscopic ultrasonography may be useful for defining the upper portion of the kidney and the adrenal gland and tumor.

The adrenal should first be mobilized medially, and diaphragmatic and medial arterial branches are divided. On the right side, arterial branches cross posterior to the vena cava and are divided with electrocautery or ultrasonic/bipolar energy. The adrenal vein is found by gently lifting the adrenal and exposing the medial-posterior aspect of the gland. The remaining posterior and lateral attachments are then divided. The steps in exposure of the left adrenal are similar to the right approach, but the adrenal vein is located at the medial/inferior aspect of the gland.

OPEN ADRENALECTOMY

Of the four approaches to open adrenalectomy [see *Operative Planning, Choice of Procedure, above*], the anterior transabdominal approach is the preferred method for tumors that are too large to be removed laparoscopically and for all invasive adrenal malignancies. The incision most commonly used is an extended unilateral or bilateral subcostal incision, although a midline incision is also an option [see *Figure 10*]. The extended subcostal incision yields exposure of both adrenal glands, as well as the rest of the peritoneal cavity. If necessary, it may be extended superiorly in the midline to the xiphoid to provide better upper abdominal exposure for full mobilization of the liver and access to the hepatic veins and the vena cava. The exposure obtained with this incision is sufficient for all but the most extensive adrenal malignancies. If the tumor involves the vena cava, the incision may be extended into a median sternotomy to provide access to the superior vena cava and the heart. The classic thoracoabdominal incision, which extends from the abdomen up through the seventh or eighth intercostal space and through the diaphragm, provides excellent exposure but is associated with increased incision-related morbidity and is rarely used.

Much of the exposure and dissection is the same as in a laparoscopic adrenalectomy; however, because open adrenalectomy is often employed for removal of particularly large tumors, some additional maneuvers may be necessary to achieve adequate exposure and vascular control. For exam-

ple, it may be helpful to elevate the flank with a roll or a bean-bag mattress and then flex the operating table to open up the space between the costal margin and the iliac crest. Once the abdomen is entered, exploration is carried out for the presence of metastatic disease.

Exposure of the adrenal on the right side is achieved by dividing the right triangular ligament of the liver, as in the laparoscopic approach. The hepatic flexure of the colon is also reflected inferiorly. With large tumors, a Kocher maneuver should be performed to afford better exposure of the vena cava and the renal vessels. The remainder of the dissection proceeds in much the same manner as in a laparoscopic right adrenalectomy. For suspected adrenal malignancies, a wide resection should be carried out, with removal of periadrenal fat and lymphatic tissue and any suspicious lymph nodes. For tumors that appear to involve the vena cava, vascular control of both the IVC proximal and distal to the tumor and the renal veins should be achieved before the lesion is removed.

Open left adrenalectomy entails mobilization of the splenic flexure of the colon and division of the splenorenal ligament. The spleen, the tail of the pancreas, and the stomach are reflected medially en bloc to expose the left kidney and the left adrenal. The left adrenal vein is ligated with clips or silk ties near its junction with the renal vein. The remainder of the dissection proceeds as in a laparoscopic left adrenalectomy [See *Left adrenalectomy; Step 3: mobilization and detachment of specimen, above*]. For left-side primary adrenal malignancies, periaortic lymphatic vessels and lymph nodes should be removed along with the specimen. If a large left-side tumor is invading adjacent structures, removal may require en bloc resection of the spleen, the distal pancreas, and the kidney.

Troubleshooting

INABILITY TO LOCATE THE ADRENAL

The adrenal is usually not difficult to find on the right side, where it should be visible once the right hemiliver has been mobilized. Important landmarks on that side are the IVC, which is medial to the adrenal, and the kidney, which is inferior to the adrenal. Once these structures have been identified, the location of the adrenal should be apparent. In contrast, the adrenal can be difficult to find on the left side, especially if the tumor is small or the patient is obese. To locate the left adrenal, the splenorenal ligament should be fully divided, and then the plane between the kidney and the tail of the pancreas should be developed, with the tail of the pancreas rotated medially. As dissection proceeds superiorly, the adrenal can be visually distinguished from the retroperitoneal fat by its golden-orange appearance. If the adrenal is not yet visualized at this point, laparoscopic ultrasonography should be used to verify the locations of the superior pole of the left kidney and the renal vessels. Ultrasonography should also be able to image the adrenal gland and tumor within the retroperitoneal fat [see *Figure 11*].

BLEEDING

The most effective strategy for managing bleeding during adrenalectomy is prevention. Important measures for minimizing bleeding risk include obtaining good exposure of the

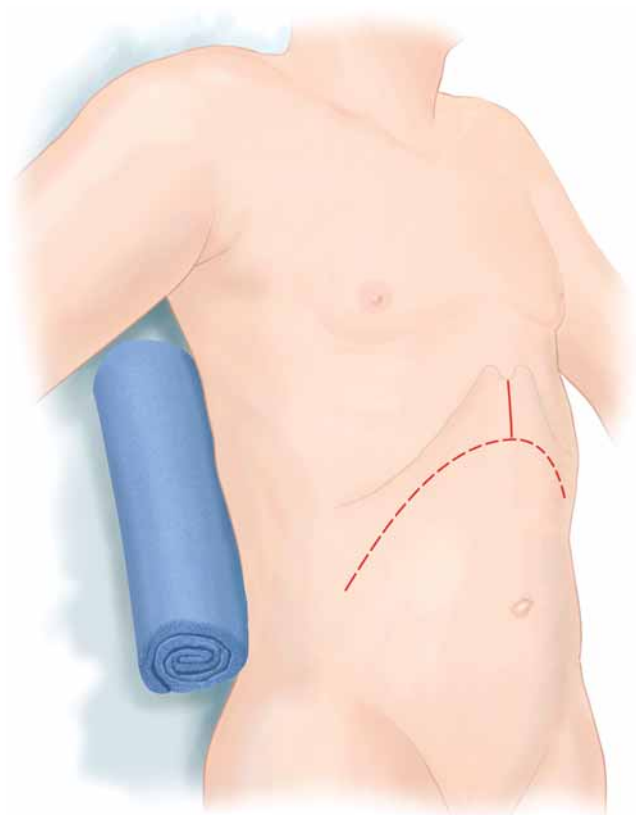


Figure 10 The procedure is generally done through a unilateral or bilateral subcostal incision. For better exposure for large adrenal malignancies, the incision may be extended cephalad in the midline.

operative field and employing meticulous dissection and gentle handling of the adrenal and surrounding structures. When bleeding does occur, it may be from the adrenal veins, the adrenal gland itself, the IVC, the renal veins, the liver, the pancreas, the spleen, or the kidney. For bleeding during laparoscopic adrenalectomy, the first maneuver should be to tamponade the bleeding site with an atraumatic instrument as the bleeding will often stop with pressure. If this maneuver is successful, dissection should be directed away from the bleeding site for a while, until better exposure of the area can be obtained. Major hemorrhage from the IVC, renal veins, or arterial vessels that is not immediately controlled should be managed by prompt conversion to open adrenalectomy [see Conversion to Open Adrenalectomy, below]. Lesser bleeding may also be an indication for conversion to open adrenalectomy if it obscures the tissue planes and thereby increases the risk of inadvertent entry into the adrenal gland or tumor.

CONVERSION TO OPEN ADRENALECTOMY

Conversion to open adrenalectomy may sometimes be necessary because of bleeding, failure to progress with the dissection, or a locally invasive tumor. If the patient is in the lateral decubitus position, conversion may be accomplished by means of a subcostal incision extended into the flank. With the patient on a bean-bag mattress, the operating table can be rotated out of the straight lateral plane so that the patient comes to occupy more of a hemilateral position. If the procedure is a bilateral adrenalectomy, then either a bilateral subcostal incision or a midline incision may be employed after the patient has first been returned to more of a supine position. For this reason, it is important to extend the initial preparation and draping past the midline of the abdomen. Alternatively, if the conversion is not being done on an urgent basis because of bleeding, the port sites may be closed, and

the patient may then be moved into the supine position, repped, and redraped.

An option that may be considered before conversion to an open procedure is the use of a hand access port. A hand-assisted technique may be particularly useful for larger, noninvasive tumors that are harder to manipulate with laparoscopic instruments. The location of the incision for the hand port may vary according to the patient's body habitus; generally, however, an ipsilateral subcostal or midline location medial to the working ports allows adequate hand access while preserving visualization through the more lateral ports.

LARGE TUMORS

As surgeons become more familiar and proficient with laparoscopic adrenalectomy, the indications for removing large tumors laparoscopically have expanded. Large adrenal tumors (> 6 to 8 cm) are more difficult to remove than smaller ones because they are bulkier and more vascular and because they are harder to manipulate and retract. Accordingly, the dissection should stay extra-adrenal, and care must be exercised during manipulation to avoid entering the tumor. Surgeons should keep in mind that the larger an adrenal tumor is, the more likely it may be malignant. Laparoscopic ultrasonography should also be employed to verify that the tumor is well circumscribed and noninvasive. Surgeons who attempt to remove large adrenal tumors laparoscopically should be highly experienced in laparoscopic adrenalectomy techniques.

For large invasive adrenal malignancies, an open approach, involving a generous bilateral subcostal incision, is indicated, and the chest should be prepared in case a thoracoabdominal or median sternotomy extension proves necessary. The important principles are to obtain wide exposure of the operative field and to control all major vessels that may be involved before removing the tumor.

OBESE PATIENTS

Obese patients present a particular challenge during adrenalectomy for several reasons: initial access is more difficult, retraction and exposure are more challenging, and the copious amount of retroperitoneal fat makes it difficult to identify the adrenal and to clearly define the margins of the gland within the retroperitoneum. Our practice is to attempt to gain initial access to the peritoneal cavity by using a closed Veress needle technique. Because resting intra-abdominal pressure may be higher in obese patients, especially if they are in the lateral position, it may be necessary to increase the CO₂ pressure to 20 mm Hg temporarily until the first trocar is inserted. If it proves difficult to establish pneumoperitoneum with the Veress needle technique, the initial trocar should be placed at the umbilicus by means of an open insertion technique. The subcostal and flank ports are then inserted in the usual locations under direct vision.

On the right side, the presence of a bulky, fatty liver should be anticipated, and the locations of the port sites should be adjusted accordingly by placing them somewhat more caudad. It may be beneficial to place obese patients on a restricted-calorie diet (< 1,400 calories/day) for 2 to 3 weeks before surgery to decrease the extent of fat and thereby overall bulk of the liver. Ample time should be taken to mobilize the liver fully so that the adrenal and the IVC can be safely accessed.

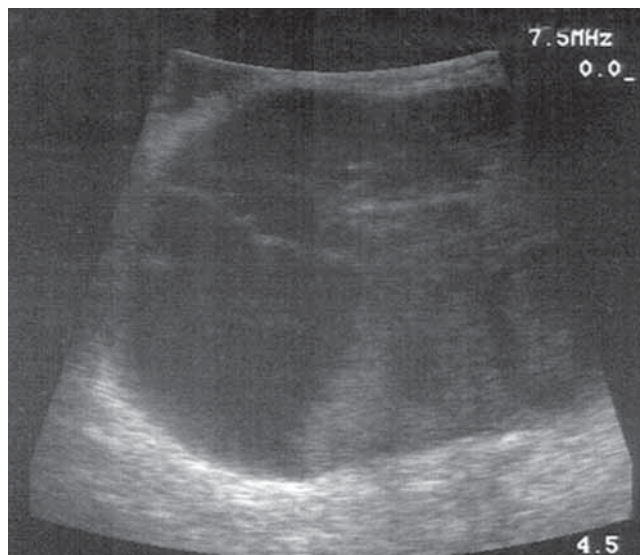


Figure 11 If the left adrenal proves difficult to find, laparoscopic ultrasonography may be employed to locate the gland and the lesion within the retroperitoneal fat. This laparoscopic ultrasonogram shows an enlarged left adrenal gland secondary to metastatic squamous cell carcinoma of the lung.

On the left, the ports may be placed in the standard locations. The splenic flexure should be fully mobilized, as should the spleen and the tail of the pancreas. Laparoscopic ultrasonography is often needed to locate the gland in the retroperitoneal fat. In addition, use of an ultrasonic coagulator may facilitate division of the retroperitoneal fat.

Postoperative Care

After laparoscopic adrenalectomy, most patients are admitted to a regular nursing unit, although some patients with pheochromocytomas will need to undergo a short stay in the intensive care unit for invasive monitoring. Patients are started on clear liquids once they are awake and alert, and the diet is advanced as tolerated. The urinary catheter is usually removed on postoperative day 1. Intravenous analgesia is switched to oral analgesia as soon as the patient can tolerate oral feeding. A complete blood count is obtained on postoperative day 1 in all patients, and electrolyte levels are monitored in patients with aldosteronomas and hypercortisolism. Patients with Cushing syndrome should be given stress doses of steroids perioperatively and should be discharged on a maintenance prednisone dosage of 10 to 15 mg/day in divided doses. These patients should be advised that it may take 6 to 12 months or longer for the contralateral adrenal to recover to the point where prednisone can be discontinued. Patients undergoing bilateral adrenalectomy will need lifelong replacement therapy with a glucocorticoid (e.g., prednisone) and a mineralocorticoid (e.g., fludrocortisone acetate 0.1 mg/day).

Postoperative management of hypertensive medications depends on the pathology of the underlying adrenal lesion. In patients with aldosteronomas, spironolactone is stopped immediately after adrenalectomy, and the other antihypertensive agents are usually continued while blood pressure is monitored closely on an outpatient basis; further medication reductions are made as clinically warranted. In most patients with Cushing syndrome, antihypertensive medications are continued, whereas in most patients with pheochromocytomas, they are not. In both sets of patients, however, close outpatient monitoring of blood pressure should be carried out in the early postoperative period. Adrenalectomy can have a dramatic impact on hypertensive control and can lead to hypotension if medications are not appropriately adjusted.

In most routine cases, patients can be discharged within 24 hours after laparoscopic adrenalectomy, although some patients require longer in-hospital observation for blood pressure monitoring, for adjustment of steroid replacement therapy, or for resumption of a regular diet. After open adrenalectomy, resumption of an oral diet occurs later, and postoperative hospital stays of 4 to 5 days are more typical.

After discharge, patients are seen in the clinic within 2 to 3 weeks for a wound check, blood pressure evaluation, and a review of antihypertensive medications. In patients who underwent adrenalectomy for an aldosteronoma, electrolyte levels and the creatinine concentration should be checked. In patients who underwent adrenalectomy for pheochromocytoma, yearly clinical and biochemical follow-up is indicated, with measurement of either plasma levels of fractionated

metanephrines or urine levels of catecholamines and metanephrines. In selected patients on steroid replacement therapy who are proving difficult to wean from prednisone, an ACTH stimulation test may be necessary to assess the responsiveness of the pituitary-adrenal axis.

Complications

It appears that laparoscopic adrenalectomy has a major advantage over open adrenalectomy in terms of the incidence of postoperative complications. In a meta-analysis of 98 adrenalectomy series reported between 1980 and 2000, the overall complication rate was 10.9% with laparoscopic procedures and 25.2% with open procedures.¹² This difference between the complication rates was primarily attributable to the occurrence of fewer wound, pulmonary, and infectious complications in the laparoscopic series. The most common complication of laparoscopic adrenalectomy is bleeding, which was reported in 4.7% of patients from the series reviewed in the meta-analysis. Bleeding is also the most common reason for conversion to open adrenalectomy; however, major bleeding that leads to transfusion is relatively uncommon. The risk of bleeding can be minimized by obtaining meticulous hemostasis, taking care not to grasp the adrenal gland, and handling tissue gently. If bleeding does occur, the prudent course of action is to maintain pressure on the bleeding source while obtaining better exposure or even starting the dissection in another area rather than to resort to indiscriminate use of clips or electrocautery. The surgeon must be prepared to convert rapidly to an open procedure should major hemorrhage occur.

Other potential complications of adrenalectomy (either laparoscopic or open) include injury to the tail of the pancreas (with resultant pancreatic leakage or pancreatitis), injury to the diaphragm, and pneumothorax. Wound infections are uncommon with laparoscopic adrenalectomy. Trocar site hernias are infrequent as well, provided that the fascia is closed at all port sites that are 10 mm or larger. Deep vein thrombosis occurs in 0.8% of cases, and pulmonary embolism in 0.5%.¹² Pneumatic compression stockings should be used perioperatively to minimize the risk of venous thromboembolism. Renovascular hypertension from injury to the renal artery has also been reported.^{13,14} Recently, severe high-grade complications of adrenalectomy have been described, including porta hepatis and hepatic artery injuries that resulted in liver transplantation and injuries to the renal vessels and to the ureter that resulted in a loss of renal function.¹⁵ The operative mortality associated with laparoscopic adrenalectomy is about 0.3%.

Several cases of local or regional tumor recurrence have been reported after laparoscopic adrenalectomy. In most of these cases, the tumors removed were either suspected or unsuspected adrenal malignancies, and the extensive nature of the recurrences was probably related to aggressive tumor biology rather than to the minimally invasive surgical technique. In some of these cases, however, the pattern of recurrence, characterized by the development of multiple intraperitoneal or port site metastases, suggested that laparoscopic dissection and pneumoperitoneum might have contributed to tumor spread.¹⁶⁻¹⁹ One group treated three patients

for recurrent pheochromocytomatosis that developed after laparoscopic adrenalectomy.²⁰ These patients were found to have multiple small tumor nodules in the adrenalectomy bed during open reoperation after removal of apparently benign pheochromocytomas. Fragmentation of the tumor and excessive tumor manipulation during the laparoscopic dissection were considered the probable mechanisms of tumor recurrence.

These reports highlight the need for caution in approaching large, malignant, or potentially malignant adrenal tumors. Surgeons who attempt a laparoscopic approach in this setting should be highly experienced in laparoscopic adrenalectomy techniques, and the tumor should be well circumscribed and not locally invasive. The use of a hand port may be a valuable adjunct to resection in these cases. Regardless of the specific surgical approach followed, wide excision of the lesion along with the surrounding periadrenal fat is crucial for minimizing recurrence rates in this population.

Outcome Evaluation

The safety and efficacy of laparoscopic adrenalectomy for the removal of small, benign adrenal tumors have been clearly established. Rates of conversion to open adrenalectomy in high-volume centers have ranged from 3 to 13%, and operating times have averaged 2 to 3 hours.^{10,13,21–26} Most patients are now discharged from the hospital within 24 to 48 hours after operation. Although no prospective, randomized trial comparing laparoscopic with open adrenalectomy has been carried out, several retrospective studies have consistently shown that the laparoscopic approach is associated with

decreased pain, a shorter hospital stay, and a faster recovery.^{27–30} Complication rates have also been low, and, overall, complications appear to be less common than with open adrenalectomy.¹²

The results of a laparoscopic approach in patients with large (> 6 cm) adrenal tumors or malignant primary or metastatic adrenal lesions have been reviewed³¹; generally, the conversion rates for large or malignant tumors have been higher than those reported in other laparoscopic adrenalectomy series. Overall, tumor recurrence rates after laparoscopic adrenalectomy have been low.^{32–36} In one series, however, local or regional tumor recurrence developed in three of five patients with adrenocortical carcinomas that were treated laparoscopically.³⁷ Other groups have also published anecdotal reports of local tumor recurrences after resection of unsuspected adrenal carcinomas.^{16–19} In another series from M. D. Anderson Cancer Center of patients with local recurrence after adrenalectomy, peritoneal carcinomatosis developed in five of six patients (83%) after laparoscopic resection compared with only 8% of patients with local recurrences after open adrenalectomy.³⁸ Whether the recurrences in these reported cases were related primarily to the surgical technique employed or to the underlying tumor biology is unclear. It would appear, therefore, that in most cases, primary adrenal malignancies are best approached in an open fashion unless the tumor is small and well circumscribed and the surgeon is highly experienced.

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Figures 1, 2, 5, 6a, 7a, 8a, 9, 10 Tom Moore.

27 REPAIR OF VENTRAL ABDOMINAL WALL HERNIAS

*Karem Harth, MD, MHS, and Michael J. Rosen, MD, FACS**

The repair of noninguinal abdominal wall defects is one of the most common procedures performed by general surgeons. With greater than 200,000 annual operations, there is little agreement or consensus in the literature as to the ideal approach for this difficult problem. In the past, personal recollections and single-center series were the principal data sources that surgeons relied on in choosing the optimum treatment strategy for a patient. In recent years, fortunately, population-based studies have provided better data on the true failure rates associated with the various herniorrhaphies.

In this chapter, we describe different operations for noninguinal abdominal wall hernias. In the repair of abdominal wall defects, the surgeon must consider a multitude of factors to identify the appropriate surgical technique to accomplish the reconstructive goals. Given that a full spectrum of patients develop hernias, it is unlikely that any single technique will be appropriate for all hernias. An individualized approach is needed to find the appropriate procedure. To do this all surgeons must familiarize themselves with important factors such as patient age, comorbidities, physiologic status, defect size, available local tissue and presence of contamination. Likewise, an understanding of the available reconstructive techniques and an honest assessment of the surgeon's ability to perform each of these techniques should guide the surgeon in establishing the most appropriate repair for the patient. A well-known surgical dictum states that when numerous different operations exist to treat the same disease, the perfect procedure does not exist. This dictum does not hold true for abdominal wall herniorrhaphy, however. Because the disease is so heterogeneous, different techniques are needed to address individual patients' needs.

Epidemiology

In the United States, approximately 1,000,000 abdominal wall herniorrhaphies are performed each year, of which 750,000 are for inguinal hernias, 166,000 for umbilical hernias, 97,000 for incisional hernias, 25,000 for femoral hernias, and 76,000 for miscellaneous hernias.¹ The prevalence of abdominal wall hernias is difficult to determine as the wide range of published figures in the literature illustrates. The major reasons for this difficulty are (1) the lack of standardization in how ventral hernias are defined; (2) the

inconsistency of the data sources used (which include self-reporting by patients, audits of routine physical examinations, and insurance company databases, among others); (3) the subjectivity of physical examination, even when performed by trained surgeons; and (4) the lack of long-term follow-up on all patients with prior surgery at risk for developing incisional hernias.

The incidence of the most common type of ventral hernia, incisional hernia, depends on how the condition is defined. The best definition of incisional hernia is any abdominal wall gap, with or without a bulge that is perceptible on clinical examination or diagnostic imaging within 1 year after the index operation. A definition that requires the presence of a visible bulge will lead to underestimation of the true incidence of the condition. The reported incidence of incisional hernia after a midline laparotomy ranges from 3 and 20% and doubles if the index operation was associated with infection. Incisional hernias are most common after midline and transverse incisions but are also well documented after paramedian, subcostal, McBurney (gridiron), and Pfannenstiel incisions.² An analysis of 11 publications dealing with ventral hernia incidence after various types of incisions concluded that the risk was 10.5% for midline incisions, 7.5% for transverse incisions, and 2.5% for paramedian incisions.³ A randomized controlled trial comparing midline versus transverse incisions did not find a difference in analgesia use, pulmonary complications, or hernia recurrence after 1 year but did find increased wound infections in the transverse incision group.⁴ Muscle-splitting incisions probably have a lower incidence of incisional hernias, but such incisions restrict access to the abdominal cavity. Given similar recurrence rates between midline and transverse incisions, the operative visualization required should dictate the choice of incision. Most incisional hernias are detected within 1 year of surgery; the most common cause is believed to be separation of aponeurotic edges in the early postoperative period. The male-to-female incidence ratio is 1:1, even though early evisceration is more common in males.

At present, little information is available on the risk of major complications arising from untreated noninguinal abdominal wall hernias. The main reason for this scarcity of data is that surgeons are taught, first, that all hernias, even asymptomatic ones, should be repaired at diagnosis to prevent potential strangulation or bowel obstruction and, second, that herniorrhaphy becomes more difficult the longer the repair is delayed. As a result, it is difficult to find a whole population in which at least some of the members do not routinely have their hernias repaired regardless of symptoms. In these circumstances, accurate estimates of the natural history of the disease are impossible.

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Table 1 Zollinger Classification System for Ventral Abdominal Wall Hernias

Type	Examples
Congenital	Omphalocele Gastroschisis Umbilical (infant)
Acquired	Midline Diastasis recti Epigastric Umbilical (adult, acquired, paraumbilical) Median Supravesical (anterior, posterior, lateral) Paramedian Spigelian Interparietal
Incisional	Midline Paramedian Transverse Special operative sites
Traumatic	Penetrating, autopenetrating* Blunt Focal, minimal injury Moderate injury Extensive force or shear Destructive

*Penetration from host tissue such as bone.

Classification of Ventral Hernias

A classification system for abdominal wall hernias outside the groin has been proposed by Zollinger [see Table 1].⁵ Ventral incisional hernias are common enough to warrant their own discrete classification system. The scheme most often used for categorizing incisional hernias [see Table 2] was the result of a 1998 consensus conference held in conjunction

Table 2 Classification System for Incisional Hernias

Parameter	Categories
Location	Vertical Midline, above or below umbilicus Midline, including umbilicus Paramedian Transverse Above or below umbilicus Crosses midline Oblique Above or below umbilicus Combined
Size*	< 5 cm 5–10 cm > 10 cm
Recurrence	Primary Multiply recurrent Stratification for type of previous repair
Reducibility	Yes Obstruction No obstruction No Obstruction No obstruction
Symptoms	Asymptomatic Symptomatic

*Difficult to measure consistently.

with the European Hernia Society's annual congress.⁶ This system is important in that it affords investigators a reliable means of comparing results between one procedure and another or between one center and another.

Abdominal Wall Anatomy

The skin of the lower anterior abdominal wall is innervated by anterior and lateral cutaneous branches of the ventral rami of the seventh through 12th intercostal nerves and by the ventral rami of the first and second lumbar nerves. These nerves course between the lateral flat muscles of the abdominal wall and enter the skin through the subcutaneous tissue.

The first layers encountered beneath the skin are the Camper and Scarpa fasciae in the subcutaneous tissue. The only significance of these layers is that when sufficiently developed, they can be reapproximated to provide another layer between a repaired abdominal wall and the outside. The major blood vessels of this superficial fatty layer are the superficial inferior and superior epigastric vessels, the intercostal vessels, and the superficial circumflex iliac vessels (which are branches of the femoral vessels). These vessels run superficial to the Scarpa fascia.

The external oblique muscle is the most superficial of the great flat muscles of the abdominal wall [see Figure 1]. This muscle arises from the posterior aspects of the lower eight ribs and interdigitates with both the serratus anterior and the latissimus dorsi at its origin. The posterior portion of the external oblique muscle is oriented vertically and inserts on the crest of the ilium. The anterior portion of the muscle courses inferiorly and obliquely toward the midline and the pubis. The muscle fibers give way to form its aponeurosis, which occurs well above the inguinal region. The obliquely arranged anterior inferior fibers of the aponeurosis of the external oblique muscle fold back on themselves to form the inguinal ligament, which attaches laterally to the anterior superior iliac spine. In most persons, the medial insertion of the inguinal ligament is dual: one portion of the ligament inserts on the pubic tubercle and the pubic bone, whereas the other portion is fan shaped and spans the distance between the inguinal ligament proper and the pectineal line of the pubis. This fan-shaped portion of the inguinal ligament is called the lacunar ligament. It blends laterally with the Cooper ligament (or, to be anatomically correct, the pectineal ligament). The more medial fibers of the aponeurosis of the external oblique muscle divide into a medial crus and a lateral crus to form the external or superficial inguinal ring, through which the spermatic cord (in females, the round ligament) and branches of the ilioinguinal and genitofemoral nerves pass. The rest of the medial fibers insert into the linea alba after contributing to the anterior portion of the rectus sheath.

Beneath the external oblique muscle is the internal oblique muscle. The fibers of the internal oblique muscle fan out following the shape of the iliac cres so that the superior fibers course obliquely upward toward the distal ends of the lower three or four ribs, whereas the lower fibers orient themselves inferomedially toward the pubis to run parallel to the external oblique aponeurotic fibers. These fibers arch over the round ligament or the spermatic cord, forming the superficial part of the internal (deep) inguinal ring.

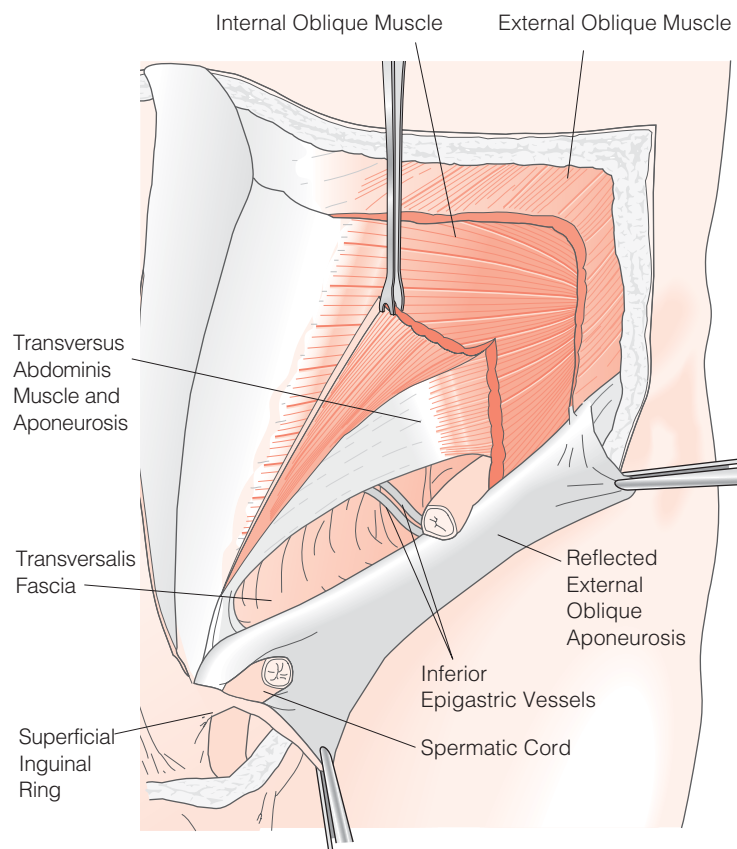


Figure 1 Shown are the great flat muscles of the abdominal wall, depicting the relationship of the great muscles to the groin.

Beneath the internal oblique muscle is the transversus abdominis. This muscle arises from the inguinal ligament, the inner side of the iliac crest, the endoabdominal fascia, and the lower six costal cartilages and ribs, where it interdigitates with the lateral diaphragmatic fibers. The medial aponeurotic fibers of the transversus abdominis contribute to the rectus sheath and insert on the pecten ossis pubis and the crest of the pubis, forming the falx inguinalis. Infrequently, these fibers are joined by a portion of the internal oblique aponeurosis; only when this occurs is a true conjoint tendon formed.⁷

Aponeurotic fibers of the transversus abdominis also form the structure known as the aponeurotic arch. It is theorized that contraction of the transversus abdominis causes the arch to move downward toward the inguinal ligament, thereby constituting a form of shutter mechanism that reinforces the weakest area of the groin when intra-abdominal pressure is raised. The area beneath the arch varies. Many authorities believe that a high arch, resulting in a larger area from which the transversus abdominis is, by definition, absent, is a predisposing factor for a direct inguinal hernia. The transverse aponeurotic arch is also important because the term is used by many authors to describe the medial structure that is sewn to the inguinal ligament in many of the older inguinal hernia repairs.

The rectus abdominis forms the central anchoring muscle mass of the anterior abdomen. It arises from the fifth through seventh costal cartilages and inserts on the pubic symphysis

and the pubic crest. It is innervated by the seventh through 12th intercostal nerves, which laterally pierce the aponeurotic sheath of the muscle. The semilunar line is the slight depression in the aponeurotic fibers coursing toward the muscle. In a minority of persons, the small pyramidalis muscle accompanies the rectus abdominis at its insertion. This muscle arises from the pubic symphysis. It lies within the rectus sheath and tapers to attach to the linea alba, which represents the conjunction of the two rectus sheaths and is the major site of insertion for three aponeuroses from all three lateral muscle layers. The line of Douglas (i.e., the arcuate line of the rectus sheath) is formed at a variable distance between the umbilicus and the inguinal space because the fasciae of the large flat muscles of the abdominal wall contribute their aponeuroses to the anterior surface of the muscle, leaving only transversalis fascia to cover the posterior surface of the rectus abdominis.

The innervation of the anterior wall muscles is multifaceted. The seventh through 12th intercostal nerves and the first and second lumbar nerves provide most of the innervation of the lateral muscles, as well as of the rectus abdominis and the overlying skin. The nerves pass anteriorly in a plane between the internal oblique muscle and the transversus abdominis, eventually piercing the lateral aspect of the rectus sheath to innervate the muscle therein. The external oblique muscle receives branches of the intercostal nerves, which penetrate the internal oblique muscle to reach it. The anterior ends of the nerves form part of the cutaneous innervation of the abdominal wall. The first lumbar nerve divides into the

ilioinguinal nerve and the iliohypogastric nerve [see Figure 2]. These important nerves lie in the space between the internal oblique muscle and the external oblique aponeurosis. They may divide within the psoas major or between the internal oblique muscle and the transversus abdominis. The ilioinguinal nerve may communicate with the iliohypogastric nerve before innervating the internal oblique muscle. The ilioinguinal nerve then passes through the external inguinal ring to run parallel to the spermatic cord, whereas the iliohypogastric nerve pierces the external oblique muscle to innervate the skin above the pubis. The cremaster muscle fibers, which are derived from the internal oblique muscle, are innervated by the genitofemoral nerve. There can be considerable variability and overlap.

The blood supply of the lateral muscles of the anterior wall comes primarily from the lower three or four intercostal arteries, the deep circumflex iliac artery, and the lumbar arteries. The rectus abdominis has a complicated blood supply that derives from the superior epigastric artery (a terminal branch of the internal thoracic [internal mammary] artery), the inferior epigastric artery (a branch of the external iliac artery), and the lower intercostal arteries. The lower intercostal arteries enter the sides of the muscle after traveling between the oblique muscles; the superior and the inferior epigastric arteries enter the rectus sheath and anastomose near the umbilicus. During the creation of skin flaps for component separation, preservation of this region has been described as a way to decrease complications such as skin flap necrosis.⁸

The endoabdominal fascia is the deep fascia covering the internal surface of the transversus abdominis, the iliacus, the

psoas major and minor, the obturator internus, and portions of the periosteum. It is a continuous sheet that extends throughout the extraperitoneal space and is sometimes referred to as the wallpaper of the abdominal cavity. Commonly, the endoabdominal fascia is subclassified according to the muscle being covered (e.g., iliac fascia or obturator fascia).

Between the transversalis fascia and the peritoneum is the preperitoneal space. In the midline behind the pubis, this space is known as the space of Retzius; laterally, it is referred to as the space of Bogros. The preperitoneal space is of particular importance for surgeons because several hernia repairs (see below) are performed in this area. The inferior epigastric vessels, the deep inferior epigastric vein, the iliopubic vein, the rectus vein, the retropubic vein, the communicating rectusioepigastric vein, the internal spermatic vessels, and the vas deferens are all encountered in this space.⁹

Choice of Prosthetic Material

For most abdominal wall hernias, the procedure of choice includes the use of a prosthesis. A multitude of prosthetic grafts are currently available, all with their own unique advantages and disadvantages. Most prosthetic grafts can be categorized as derived from polypropylene, polyester, or polytetrafluoroethylene (PTFE). Uscher is credited with developing polypropylene mesh and introduced it in the early 1960s.¹⁰ Since their introduction, there has been an increase in use. An American population-based study of approximately 11,000 patients reflected an increase in mesh use for hernia repair from 35% in 1987 to 65% by 1999.¹¹ A detailed discussion comparing various prosthetic materials is beyond the scope of this chapter; however, some general statements may be made.

The use of mesh presupposes a situation in which the prosthesis can be isolated from contact with intra-abdominal viscera by one or more layers of human tissue (e.g., peritoneum). In situations where contact with intra-abdominal viscera cannot be avoided, a standard mesh prosthesis should not be used as it causes a significant fibroblastic response and risks subsequent bowel-related complications. Either the prosthesis should be composed of a nonmesh material, such as expanded polytetrafluoroethylene (ePTFE), or a dual-layer prosthesis should be used, with a standard plastic mesh on the side facing the abdominal wall (to encourage an intense fibroplastic response) and an adhesion barrier of some type coating the peritoneal side. Numerous dual-sided prosthetics, incorporating a variety of adhesion barriers, are now available [see Table 3]. It has consistently been shown that when these materials are used, adhesions are not only less common but also less tenacious than when mesh alone is used in an intra-peritoneal position. Often bowel adhesions can be easily wiped from the peritoneal surface of a dual-layer prosthesis with gentle blunt traction, in sharp contrast to the typically tedious and sometimes impossible dissection of bowel loops from an unprotected mesh prosthesis placed directly on the viscera. Although all of the dual-layer prostheses currently on the market are approved for decreasing adhesions to the adhesion barrier side, no manufacturer has sought approval for complete prevention of adhesions. Consequently, the

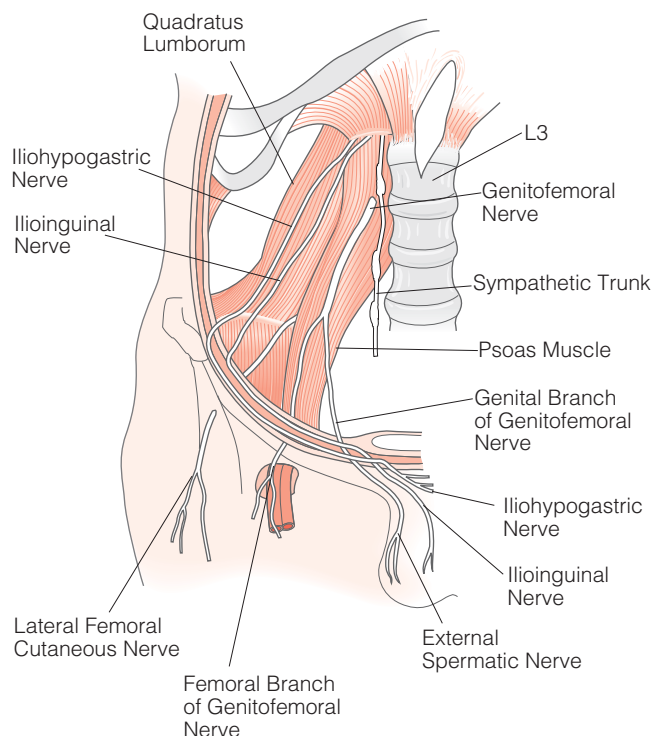


Figure 2 Shown are the important nerves of the lower abdominal wall.

Table 3 Commercially Available Synthetic Prostheses for Abdominal Wall Hernia Repair

Bard Composix E/X Mesh (PPL + ePTFE)
Bard Dulex Mesh (dual-sided) (PPL + ePTFE)
Bard Kugel Hernia Patch (PPL + ePTFE + PPL ring)
Bard Ventralex (PPL + ePTFE + PPL tail)
Bard Sepramesh (PPL + Seprafilm)
Covidien Parietene (PPL + hydrophilic collagen)
Covidien Parietex (POL + hydrophilic collagen)
Ethicon Prolene Soft Mesh (PPL)
Ethicon Proceed (PPL + PDS + ORC)
Ethicon Ultrapro (PPL + poliglecaprone 25)
Ethicon Vicryl Knitted Mesh
Gore Soft Tissue Patch (ePTFE)
Gore DualMesh (ePTFE)
Gore DualMesh Plus (ePTFE + silver + chlorhexidine)
Gore MycroMesh (ePTFE)
Gore Infini mesh (knitted PTFE)
Atrium CQur (PPL + omega-3 fatty acid coating)

ePTFE = expanded polytetrafluoroethylene; ORC = oxidized regenerated cellulose; POL = polyester; PPL = polypropylene.

long-term effects of these less severe (but still present) adhesions are unknown; further study is required to address this issue.

At present, there is some controversy regarding the weight of polypropylene mesh used in abdominal wall hernia repairs, although the controversy almost certainly applies to the other types of mesh prosthesis as well. Data from randomized studies indicate that use of a lightweight polypropylene mesh compared with standard mesh results in similar long-term pain in incisional hernia repair.¹² When used in the setting of inguinal hernia repair, two randomized controlled trials have shown varied results with regard to pain control.^{12–14} In the randomized controlled multicenter trial for incisional hernia repair, no difference in recurrence was found at 24 months in the lightweight (17%) versus the standard (7%) mesh repair (*p* value .052). However, a closer look at their methodology reveals important considerations. After 24 months, there was approximately 20% loss of follow-up for each lightweight and standard mesh group, which may underpower their ability to detect a statistically significant difference. Also, technical variables may have impacted the observed hernia recurrence rates, including poor cephalad mesh tissue coverage and use of absorbable sutures to secure the mesh and close the midline. Having recognized these important issues, newer trials have been designed to control for these factors and are currently in progress.

Lighter-weight mesh also addresses the theoretical concern about the possible carcinogenic effects of polypropylene, as has been suggested by experimental studies in rats, although it should be kept in mind that there has never been a documented case of a sarcoma developing in a human being as a result of an inguinal hernia prosthesis.¹⁵ To illustrate the difference between a lightweight mesh and a normal one, a 7.5 × 15 cm piece of polypropylene mesh (Prolene, Ethicon, Inc., Somerville, NJ) weighs about 80 g/m², whereas a similarly sized piece of a polypropylene–poliglecaprone 25 (Monocryl, Ethicon, Inc.) lightweight mesh (UltraPro, Ethicon, Inc.) weighs less than 30 g/m² after absorption of the poliglecaprone 25 component.

North American surgeons have been slow to accept the use of lightweight mesh for inguinal hernia repair, fearing a higher recurrence rate.^{12,16} Many also have some concerns about possible bias in the data, noting that the research supporting the use of lightweight mesh has been almost exclusively funded by industry. Nevertheless, the randomized trials mentioned earlier cannot be entirely discounted. Most likely, lightweight mesh will have a role in abdominal wall reconstruction in appropriately selected patients. The limits of this mesh are currently being evaluated in several long-term studies.

The potential for mesh infection is also a topic with significant research in hernia surgery, particularly as mesh infection has been diagnosed as late as 39 months following implantation.¹⁷ Inherent mesh characteristics can influence the likelihood of mesh infection and the ability to treat this complication. The hydrophobicity, porosity, and weave characteristics are all important factors that affect the outcomes of mesh sepsis. Although some macroporous mesh (polypropylene, polyester) infections can be treated with local measures, it is very rare to salvage an infected microporous (PTFE) prosthetic. Several nonrandomized studies have evaluated risk factors for surgical site infection as they relate to different mesh morphologies in the setting of laparoscopic or open incisional hernia repair. Although most studies are not designed with infection as the primary end point, some noteworthy trends can be generalized. Studies have found greater potential for infection with ePTFE mesh compared with lower rates with monofilament polypropylene mesh.^{17,18} Polyester-based materials have varied results in the literature, with some studies showing acceptable rates of infection.^{19–21} The continued understanding of how intrinsic mesh characteristics relate to future risk of infection will likely lead to parallel advances in the biomaterial industry.

The quest for the perfect mesh has driven the introduction of a wide variety of synthetic meshes into the market since the 1960s. More recently, one of the fastest growing markets for hernia repair is that for prosthetics derived from animal or human tissue called biologics [see Table 4]. The widespread use of these grafts in abdominal wall reconstruction has resulted in close to 400 million dollars spent on biologic grafts in the United States in 2007. The market value for these biomaterials is predicted to increase to 500 million dollars by 2013 and far exceed the rate of growth for synthetic materials. These expensive materials are reported to be superior to synthetic meshes given their hypothetical ability to resist infection and biodegrade over time, leaving behind only native, regenerated collagen. The evidence behind this reported advantage is lacking, and research regarding their performance is mainly limited to clean cases.

The sources of biologic grafts may be different (human, porcine, bovine), their processing techniques are varied (crosslinked and noncrosslinked), and so are their sterilizing techniques (γ radiation, ethylene oxide gas sterilization, or nonsterilization). Biologic grafts are designed to serve as an extracellular matrix scaffold for neovascularization and new collagen ingrowth, promoting vessel ingrowth and eventual remodeling of tissue to resemble the native type. The incorporation of native tissue and vessels into these bioscaffolds gives them the theoretical advantage of resisting bacterial proliferation as cells such as macrophages and antibiotics are able to reach the bacteria. Much like synthetic mesh, the best

Table 4 Commercially Available Biologic Prostheses Approved for Abdominal Wall Hernia Repair

Biologic Mesh	US Approval	Manufacturer	List Price* (US\$/cm ²)	Source	Crosslinking	Sterilization
Surgisis	1999	Cook	18.00	Porcine SIS	No	EO
Tutopatch	2000	Tutogen Medical/Bard	Unavailable	Bovine pericardium	No	γ irradiation
Permacol	2000	TSL → Covidien	21.00	Porcine dermis	Diisocyanate	γ irradiation
Alloderm	2001	LifeCell	32.00	Human dermis	No	γ irradiation
Periguard	2002	Synovis	Unavailable	Bovine pericardium	Glutaraldehyde	Liquid alcohol
SurgiMend	2002	TEI Biosciences Inc.	22.00	Fetal bovine dermis	No	EO
Veritas	2003	Synovis	20.00	Bovine pericardium	No	E-beam
Xenmatrix	2003	Bard/Davol Inc.	27.36	Porcine dermis	No	E-beam
Allomax	2006	Bard/Davol Inc.	32.50	Human dermis	No	γ irradiation
Collamend	2006	Bard/Davol Inc.	18.00	Porcine dermis	EDAC	EO
Strattice	2007	LifeCell	28.00	Porcine dermis	No	E-beam
FlexHD	2008	MTF — Ethicon	30.00	Human dermis	No	Proprietary

EDAC = 1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride; EO = ethylene oxide; SIS = small intestinal submucosa.

*Prices are as of January 2010. Pricing may vary based on institutional contracts and quantity of annual sales.

practices of biologic graft placement are unknown and highly varied at this time. The use of biologic materials is a relatively new area in hernia surgery, and further animal and clinical studies are needed to answer many important questions. Currently, these grafts appear to tolerate clean contaminated cases, but their long-term durability and role in hernia recurrence are largely unknown. Although biologic prostheses are much more expensive than synthetic prostheses, the long-term cost-effective benefits of using these materials, particularly in contaminated cases, may be beneficial. More recently, newer absorbable synthetics that do not biodegrade for several months (unlike polyglactin 910 [Vicryl, Ethicon, Inc.] mesh) have been introduced into the market and proposed as less costly alternatives to biologic grafts. However, few data exist for these new materials. Further studies are required before their exact place in the armamentarium of the abdominal wall hernia surgeon can be determined.

Incisional Hernia Repair

Incisional hernias occur as a complication of previous surgery. As noted, their incidence depends on how they are defined [see Epidemiology, above]. In the literature, the incidence of incisional hernia ranges from 3 to 12% of all laparotomy incisions and largely depends on several underlying patient characteristics.^{2,22} Postoperative wound infections result in a much higher incidence of incisional hernia formation.

The root cause of incisional hernia is undoubtedly multifactorial. Technical factors such as slippage of knots, suture fractures, excessive tension, or rapidly absorbable sutures can result in incisional hernia formation.²³ However, certain patients with collagen metabolism disorders are also prone to incisional hernia formation. In particular, patients with aortic aneurysms and diverticular disease likely have systemic disorders of collagen metabolism [see Table 5]. Nevertheless, the importance of careful attention to technical detail in the closure of any abdominal incision should not be minimized.

Surgeons' practices in closing laparotomies tend to be far more dependent on tradition and often lack high-quality level I scientific evidence.²⁴ Techniques of continuous versus interrupted closure or use of absorbable versus nonabsorbable suture are approaches without consensus as shown by review of the literature and a recent survey of general surgeons performing hernia repair.²⁵ The authors found that a strong consensus (treatment applied in > 95% of cases) regarding closure of midline wounds was not achieved. A meta-analysis of randomized controlled trials evaluating different midline closure techniques concluded that nonabsorbable suture in a continuous fashion led to lower rates of incisional hernia.²⁴ A follow-up meta-analysis with similar criteria found no difference in hernia recurrence between slowly absorbable suture versus nonabsorbable suture.²⁶ This study, however, found higher rates of suture-related sinus drainage and pain in the nonabsorbable group and found no difference in hernia recurrence when continuous versus interrupted techniques were compared. The most recent randomized controlled trial evaluating interrupted rapidly absorbable suture (polyglactin 910) with continuous slowly absorbing suture (polydioxanone [PDS, Ethicon, Inc. and MonoPlus, B. Braun, Germany]) was unable to detect a difference in hernia recurrence between the groups, although it appeared that polydioxanone had the least overall rates of recurrence.²⁷

Despite the varied literature, some general recommendations can be made on the basis of current data and experience. Although a general consensus precludes identification of a "gold standard" for midline closure, a continuous

Table 5 Causes of Incisional Hernias

Technical
Patient related
Wound related
Genetic
Molecular

polydioxanone suture, with stitches placed 1 cm from the fascial edge and 1 cm apart, does as well in terms of hernia recurrence as a continuous monofilament polypropylene suture. The long-term advantages of polydioxanone are its decreased sinus formation and chronic pain.

Other factors should be considered in the closure of midline wounds. To prevent excessive tension, the length of the suture should be four times the length of the wound.²⁴ Monofilament sutures perform better than braided sutures because bacteria tend to form colonies among the braids of multifilament sutures.^{28–31} Nonabsorbable suture material has the advantage of greater longevity than absorbable suture material but is more likely to result in sinus formation and chronic wound pain.^{3,24} The incidence of wound infection is not affected by the suture material or the closure method.

Various patient-related risk factors for incisional hernia have been identified [see Table 6].^{32,33} Although some controversy remains, the current consensus is that there appears to be an association between these comorbid conditions and the incidence of incisional hernia. The type of wound incurred also plays a role. Incisional herniation appears most common after midline laparotomies, especially upper midline incisions, and less common after transverse or oblique incisions.² An analysis of 11 publications addressing ventral hernia incidence after various types of incisions found the risk to be 10.5% for midline incisions, 7.5% for transverse incisions, and 2.5% for paramedian incisions.³ A recent randomized controlled trial evaluating midline versus transverse incisions with a secondary end point of hernia recurrence found no difference between either approach at the 1-year follow-up.⁴ However, the authors noted that to truly detect a difference in hernia recurrence between these approaches, nearly 2,500 patients would be required in each group. Thus, the authors recommend that surgeons select the incision that ultimately yields the best exposure.

Over longer periods, the incidence of incisional hernia recurrence increases, with the majority developing in the first 4 years after the sentinel operation.³⁴ It is anticipated that as the use of minimally invasive surgical techniques increases, the incidence of incisional hernia will drop. Hernias developing within 10 and 12 mm port sites are well documented; hernias in 5 mm port incisions are rare. At present, long-term

data on the incidence and natural history of port-site hernias are lacking.³⁵

Genetic factors are important as well: familial predisposition to incisional hernia has long been recognized as contributory by surgeons caring for patients with this condition. An increased incidence of incisional herniation in patients with certain connective tissue diseases (e.g., osteogenesis imperfecta, Marfan syndrome, and Ehlers-Danlos syndrome) has been documented. Finally, the molecular details of incisional hernia causation are now beginning to be appreciated. Type 1 to type 3 collagen imbalance, abnormal matrix metalloproteinase (MMP) expression, and growth factor relations are among the molecular-level processes that are currently under intense scrutiny by the scientific community with regard to the etiology of incisional hernia.

Not every patient who presents to a surgeon with an incisional hernia is necessarily a candidate for surgical repair. There are three indications for operation: (1) a hernia that is symptomatic, causing pain, discomfort, or changes in bowel habits; (2) a hernia resulting in an unsightly bulge that affects the patient's quality of life; and (3) a hernia that poses a significant risk of bowel obstruction (e.g., a large hernia with a narrow neck). However, the natural history of slow continued growth of incisional hernias attributable to increased intra-abdominal pressure should be taken into consideration. In young patients with moderate-size hernias, a nonoperative approach can result in a more complex reconstruction in the future if the hernia becomes larger and more symptomatic.

The repair of incisional hernias is often more complicated than inguinal repair for several reasons. By definition, all incisional hernias are reoperative cases, demanding careful adhesiolysis and delineation of the anatomy. Additionally, it is important that the patient and the surgeon have a clear understanding of the goals of the procedure. For all ventral hernias, the surgeon must reduce the hernia contents into the abdominal cavity and prevent future migration and recurrent herniation. This can be performed by simply patching a defect with prosthetic material or can similarly be accomplished by reconstructing a functional dynamic abdominal wall via medialization of the rectus muscles with potential prosthetic reinforcement. Each of these approaches has its own unique merits, and careful consideration should be given to each technique to find the ideal reconstruction for the patient.

Open Ventral Hernia Repair: Operative Technique

NONPROSTHETIC REPAIRS

Historically, primary suture repair was the procedure of choice for most incisional hernias; prosthetic material was reserved for particularly difficult cases as a result of the perceived risks of this material. In the latter part of the 20th century, large population-based studies changed this way of thinking, revealing that primary suture repair was associated with a much higher recurrence rate than most surgeons would have assumed (25 to 55%).⁶ Studies comparing primary suture with prosthetic repair showed that the recurrence rate was dramatically lower with the latter.³⁶ In a randomized controlled study from the Netherlands, even small incisional

Table 6 Comorbid Factors Associated with Incisional Hernia

Male sex
Old age
Morbid obesity
Abdominal distention
Cigarette smoking
Pulmonary disease
Mechanical ventilation
Type 2 diabetes mellitus
Oral anticoagulants
Malnourishment
Hypoalbuminemia
Anemia/transfusion
Malignancy
Jaundice
Corticosteroid therapy
Chemotherapy
Radiation therapy
Renal failure

hernias (< 10 cm²) had a recurrence rate of 67% when primary suture repair was employed.³⁷ Additionally, a recent Cochrane review of available randomized trials with a minimum of 1-year follow-up showed that suture repair had a recurrence risk of 85% greater compared with mesh repair.³⁸

PROSTHETIC REPAIRS

The use of prosthetic material to reduce tension in ventral hernia repair was first described in the 1950s.¹⁰ Since its introduction, inclusion of mesh in ventral hernia repair has unquestionably reduced the recurrence rate. With the addition of synthetic prosthetics to the surgeon's armamentarium, the debate for the ideal surgical approach for placing mesh continues unanswered. Although each approach has its ardent supporters, there are few data carefully evaluating each approach in appropriately designed comparative trials. Given the lack of definitive data, it is difficult to provide a clear, concise recommendation as to the ideal approach. However, certain general guidelines can be stated. Basically, three options exist for mesh placement: as an overlay (onlay), as a bridge secured to the fascial edges (inlay), or as an underlay (sublay) in either a retrorectus, preperitoneal, or intraperitoneal position [see Figure 3].

A mesh overlay (onlay) may be placed on top of any of a variety of simple repairs. Although some series have reported that this approach yields acceptable results in selected patients, most surgeons feel that it offers little advantage over the simple repair that the prosthesis overlies and that it is typically associated with a similarly disappointing recurrence rate of up to 25%.^{6,39} Additional disadvantages of placing prosthetic material in this position are its close proximity to the skin with higher potential for exposure following a wound infection and the wide skin undermining needed to achieve broad coverage.⁴⁰ Wound complications are estimated to be between 4 and 26% using this approach secondary to the creation of skin flaps necessary to secure the mesh.⁶ Proponents of this technique claim an advantage of the mesh not being placed in direct contact with the abdominal viscera. However, if the midline fascial closure breaks down, the bowel will interact with an often unprotected macroporous mesh.

Prosthetic inlay (bridging) repair became popular in the 1990s, in keeping with the tension-free ideal for inguinal herniorrhaphy. The principle underlying this technique is that for a prosthetic repair to be truly tension free, the defect should be bridged. Unfortunately, the abdominal wall likely experiences different forces during activity than the groin. In fact, a true tension-free repair might not be ideal in the anterior abdominal wall. Given that contraction of the rectus and lateral abdominal wall muscles that are not joined at the linea alba results in lateral displacement, a constant force of separation is placed on the prosthetic. Coupled with the incidence of some shrinkage of most prosthetics, this has resulted in a predictably high recurrence rate at the mesh–native tissue interface.^{41,42} Following a systematic review of 119 studies on ventral hernia repair, the inlay technique was found to have the highest reported rate of recurrence, largely attributed to poor mesh fixation and inadequate lateral overlap.⁴² The recurrence rate is especially high in obese patients and greater with increasing hernia size. In a study from the Netherlands,

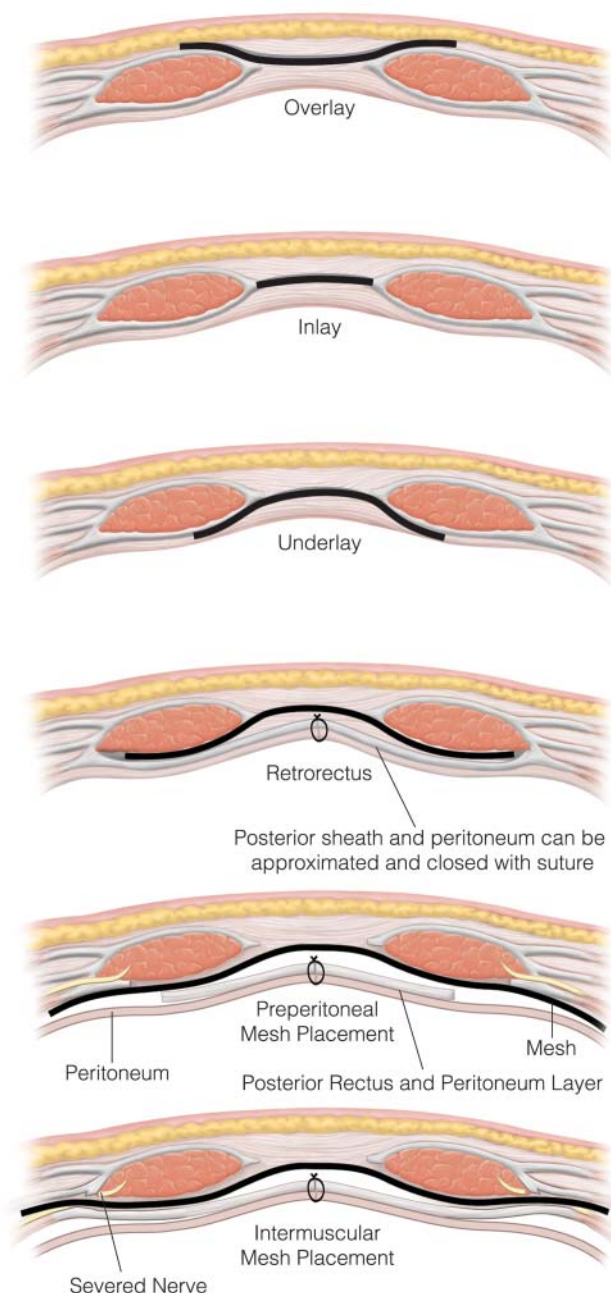


Figure 3 Incisional hernia repair. Depicted are three potential positions for placement of a prosthesis for repair of ventral abdominal wall defects.

the recurrence rate even with mesh repairs (mostly onlay and inlay) was 32% for large defects and 17% for small (< 10 cm²) defects.³⁷

Sublay prosthetic repair is sometimes referred to as the retromuscular approach. A sublay prosthetic repair is characterized by the placement of a large prosthesis in the space between the abdominal muscles and the posterior fascia, the transversalis fascia, or the peritoneum, depending on what part of the abdomen is being repaired (there is no posterior fascia inferior to the arcuate line).⁴³ The technique described

in this chapter is similar to that described by Flament, Vela-menta, Stoppa, and Wantz [see Figure 4].^{44,45} The operation was originally envisioned for treatment of large and multiply recurrent hernias in cases where most of the abdominal wall had to be reconstructed. Because it has proven so successful, it is now being increasingly used to repair smaller defects. Sublay prosthetic repair is currently considered the most effective conventional incisional hernia repair and is therefore the one against which all other procedures are measured.

Placing a mesh underneath the abdominal musculature can be achieved using multiple techniques. Intraperitoneal placement can be performed laparoscopically and is discussed in another chapter. Open approaches can also be used to place mesh intraperitoneally. This can be done using a dual-layer mesh. Unfortunately, this typically requires raising large subcutaneous flaps and substantial transfascial fixation sutures to prevent bowel from slipping around the sides of the mesh and subsequently risking obstruction. The mesh can also be placed in an extraperitoneal position either in the preperitoneal plane or the retrorectus space. This is our preferred method, which relies on the basic principles of the Stoppa approach for inguinal hernias and is described in detail here.

Step 1: Incision

The initial incision is typically midline and should remove all old scar tissue that might compromise subsequent wound healing. In certain patients with a large pannus, a transverse panniculectomy-type incision can be employed. Some authors advocate remaining in the extraperitoneal space throughout the dissection. This provides the distinct advantage of avoiding potential bowel complications; however, it can be a very tedious and difficult dissection plane, especially in large hernia sacs and complicated defects. It is our preference to enter the peritoneal cavity and perform a complete adhesiolysis to identify all defects and mobilize the entire abdominal wall.

Step 2: Entering the Retrorectus Plane

Several options exist for entering the correct plane in the lateral abdominal wall. One technique involves maintaining a preperitoneal dissection. This is similar to the groin dissection, but along the anterior abdominal wall, the peritoneum can be densely invested in the posterior rectus sheath, making this very difficult. Alternatively, the posterior rectus sheath can be entered at the linea alba. Graspers are placed on the linea alba and the posterior rectus sheath is incised just off the midline. This release is completed throughout the length of the incision and at least 5 cm beyond the defect in a cephalad-caudad orientation. The dissection is then carried laterally deep to the rectus muscle above the posterior rectus sheath. Below the arcuate line, this is above the transversalis fascia and peritoneum. The dissection is continued laterally to the linea semilunaris at the edge of the rectus muscle. In routine hernias, the rectus muscle is typically anywhere from 5 to 10 cm in width. This provides ample overlap of the mesh. However, in larger hernias and multiply recurrent hernias, often there is atrophy, or loss of the rectus muscle, and this dissection does not provide adequate mesh overlap. In these circumstances, several options exist. The lateral abdominal compartment can be accessed in either the intermuscular or preperitoneal plane. The intermuscular plane can be reached by incising the lateral border of the posterior rectus sheath. The plane between the transversus abdominis and the

internal oblique can be carried far laterally to obtain substantially more mesh overlap. One of the drawbacks of this approach is that the perforating nerves to the rectus muscle can be damaged, rendering it nonfunctional. In addition, the intercostal vessels travel within this intermuscular plane. Another approach involves entering the preperitoneal plane. This can be achieved by incising the posterior rectus sheath 1 cm medial to the linea semilunaris. Once this plane is entered (the preperitoneal plane or space), the dissection can be continued far lateral, all the way to the psoas muscle if necessary.

Step 3: Reapproximating the Posterior Rectus Sheath

The posterior rectus sheath, peritoneum, and transversalis fascia are reapproximated in the midline. Recreation of this anatomic plane completely excludes the viscera from the mesh. Alternatively, the hernia sac or a piece of absorbable mesh can be used to recreate this space.

Step 4: Mesh Placement

The mesh is placed in the retrorectus position. If necessary, the mesh can be secured to the Cooper ligament along the pelvis and placed under the xiphoid process. Several transfascial fixation sutures are placed through puncture sites in the lateral abdominal wall. These sutures are placed through the full thickness of the abdominal wall, with the knots placed below the skin. These sutures should be placed under moderate tension. By placing these sutures under tension, when they are tied, the rectus muscle is medialized and the forces are distributed to the lateral abdominal wall away from the midline. Securing the mesh to the lateral abdominal wall under tension also allows the rectus muscle to be reapproximated over the mesh without buckling of the prosthetic material.

In certain circumstances, the posterior rectus or preperitoneal plane cannot be created. In these situations, one can place the mesh intraperitoneally. However, a barrier mesh should be used to avoid bowel complications.

Step 5: Closure

After the mesh is secured, every attempt should be made to reapproximate the linea alba in the midline. This serves the functional purpose of restoring the native abdominal wall contour and function. Also, it covers the mesh to avoid potential wound complications and subsequent mesh sepsis.

There are single-center series with evidence of improved outcomes using this technique.⁴⁶ For example, in a Finnish study of 84 consecutive patients treated with a retromuscular polypropylene mesh repair and followed for 3 years, the recurrence rate was 5%. In a separate US study, no recurrences were reported in 102 patients after 28 months of follow-up.⁴⁷ A 2006 study from Sweden confirmed the superiority of this operation, reporting a 7.3% recurrence rate for sublay prosthetic repair, compared with 19.3% for onlay mesh repair and 29.1% for suture repair.⁴⁸ Sublay prosthetic repair has been successfully employed to treat massive hernias with substantial loss of domain.⁴⁹ A retrospective review from the Mayo Clinic evaluated their experience with a modified Rives-Stoppa technique using prosthetic mesh in complex incisional hernia repair over a 13-year period.⁵⁰ With a median follow-up of 59 months and 254 patients, their overall hernia recurrence rate was 5%, with most hernias being detected within 12 months of repair.

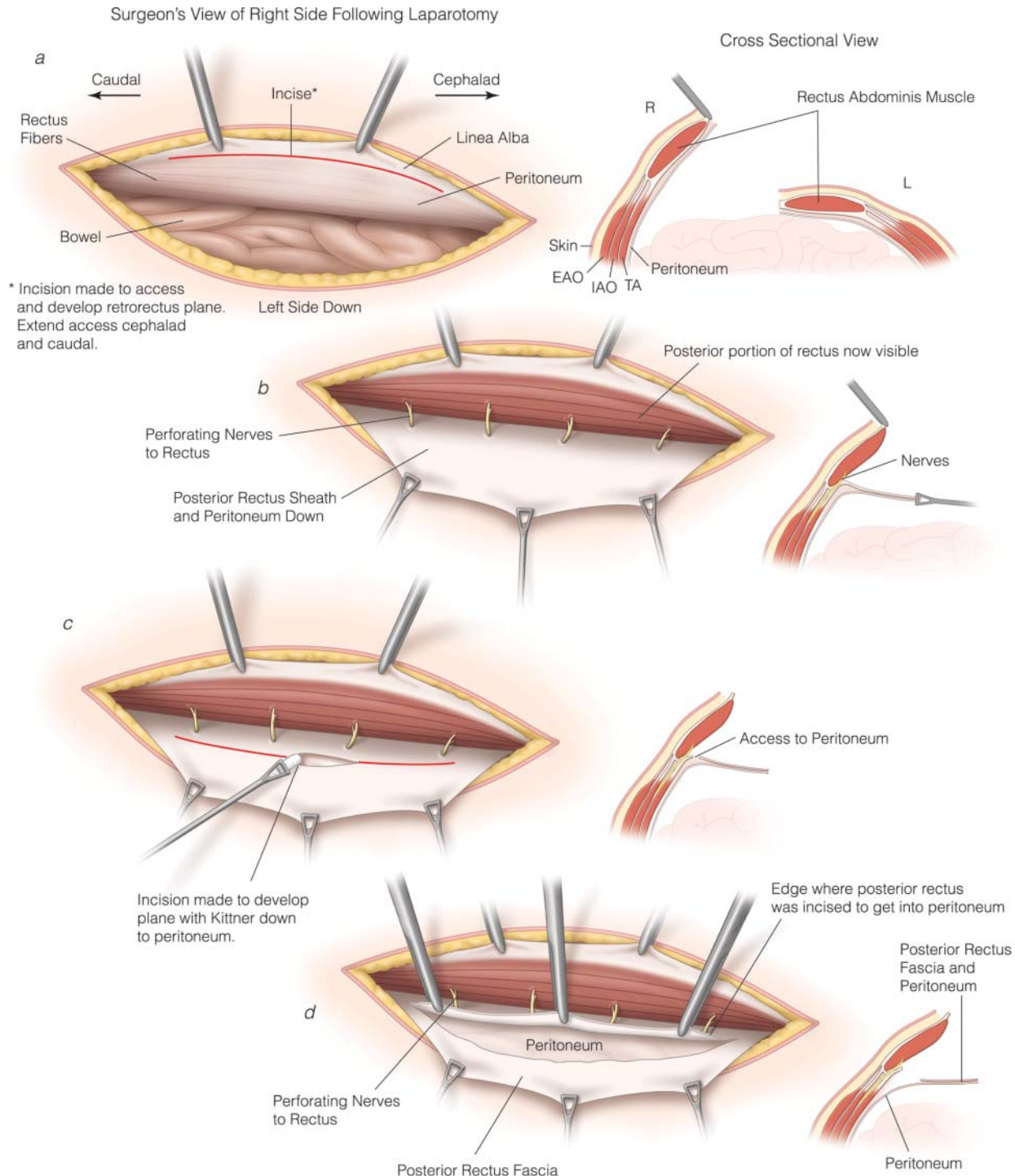


Figure 4 Incisional hernia repair. Illustrated is a retromuscular approach. (a) The anterior rectus sheath has already been incised, rotated medially, and closed in the midline. The space beneath the rectus abdominis is being developed. Dissection should continue to the lateral edge of the posterior rectus sheath, but care should be taken to prevent injury to the neurovascular bundles; denervation or abdominal wall necrosis is possible if these bundles are injured. (b) The prosthesis is prepared with U-shaped sutures. (c) A suture passer is used to push the two tails of each U stitch through separate musculofascial sites. However, the two tails exit through the same skin incision; this eventually allows the prosthesis to be firmly secured deep in the pocket. The sutures are tied above the skin, and the knot is secured down to the fascial level. The suture is cut under tension so that the tails will retract back into the skin incision, which is then closed. If the flaps permit, the sutures can be tied in the subcutaneous tissue and not passed through the skin. The disadvantage of this latter approach is that there are likely to be more problems with seromas because of the more extensive dissection. (d) A penetrating towel clip is used to release the skin dimples created by the gathering of subcutaneous tissue when the full-thickness sutures are tied. This measure prevents a potentially permanent deformity. It is important to inspect the sutures to confirm that they have not been disrupted. EAO = external abdominal oblique; IAO = internal abdominal oblique; TA = transversus abdominus.

Component Separation Repair

The concept of separating the lateral abdominal wall musculature, allowing medialization of the rectus muscle complex, was first described by Ramirez and colleagues in 1990.⁵¹ Based on cadaveric studies, up to 10 cm of unilateral advancement of the abdominal wall can be achieved with release of the external oblique aponeurosis. A distinct advantage of this approach is the ability to achieve midline closure and recreation of the linea alba. Unlike mesh repair in a bridging fashion, a dynamic abdominal wall can be achieved. A hindrance to broader acceptance of this technique is that the large lipocutaneous flaps created to access the lateral abdominal wall are associated with major wound morbidity.

Historically, component separation has been reserved for complicated hernias when synthetic mesh is contraindicated.^{52–54} A recent trial on large midline abdominal wall hernias randomized 39 patients to either component separation or prosthetic repair using antibiotic-impregnated ePTFE.⁵⁵ Hernia recurrence was not different between the component separation technique and prosthetic repair (56% versus 58%, respectively; p value > .05) following a 36-month follow-up period.⁵⁵ Wound-related complications, including infection and skin necrosis, were also not different between the component separation technique and prosthetic repair (53% versus 72% respectively; p value > .05). However, 54% of infections in the ePTFE group required reoperation for removal of infected mesh. On interim analysis, this latter event caused early cessation of the study. Given the morbidity associated with reoperation in the prosthetic repair group compared with the asymptomatic small hernia recurrences observed in the component separation technique group, the authors concluded that the component separation technique was a favorable repair option for giant midline hernias. Typically, after a component separation, there is still tension on the midline closure. For this reason, most authors advocate reinforcement with a prosthetic. Whether the addition of a prosthetic material (either biologic or synthetic) to reinforce the repair after component separation might reduce recurrence rates further has not been adequately evaluated in the literature.

Patients undergoing abdominal wall reconstruction for massive defects each require individualized preparation and consideration prior to surgery. Physiologic changes occur in both the abdominal and the thoracic cavities following definitive closure of these large defects. In addition to the general preoperative screening, each patient should be assessed for pulmonary status and the potential for return to routine daily activities. Additionally, smoking status is critical as patients who smoke are at significantly higher risk for wound complications. Since its original description in 1990, component separation has undergone several adaptations. We describe the traditional open approach and two newer techniques to achieving a more minimally invasive separation of components.

OPEN COMPONENT SEPARATION

Step 1: Incision

A long midline incision or transverse panniculectomy-type incision is made through the scar to expose the hernia. The hernia sac is dissected up to its neck, deep to the fascial edge.

Step 2: Creation of Flaps

The lipocutaneous flap is dissected away from the anterior sheath of the rectus abdominis and the aponeurosis of the external abdominal oblique muscle. A technique that may help decrease skin flap necrosis is to preserve the periumbilical perforators.⁸ There are no exact landmarks to delineate the lateralmost extent of this flap. The surgeon must bimanually assess the rectus muscle belly. Once the lateral edge of the rectus is palpated, the dissection is carried 2 cm lateral to the linea semilunaris.

Step 3: Incising the External Oblique Muscle

The aponeurosis of the external oblique muscle is transected longitudinally about 2 cm lateral to the rectus sheath, with care to avoid cutting into the linea semilunaris [see Figure 5]. Transecting the linea semilunaris will result in a

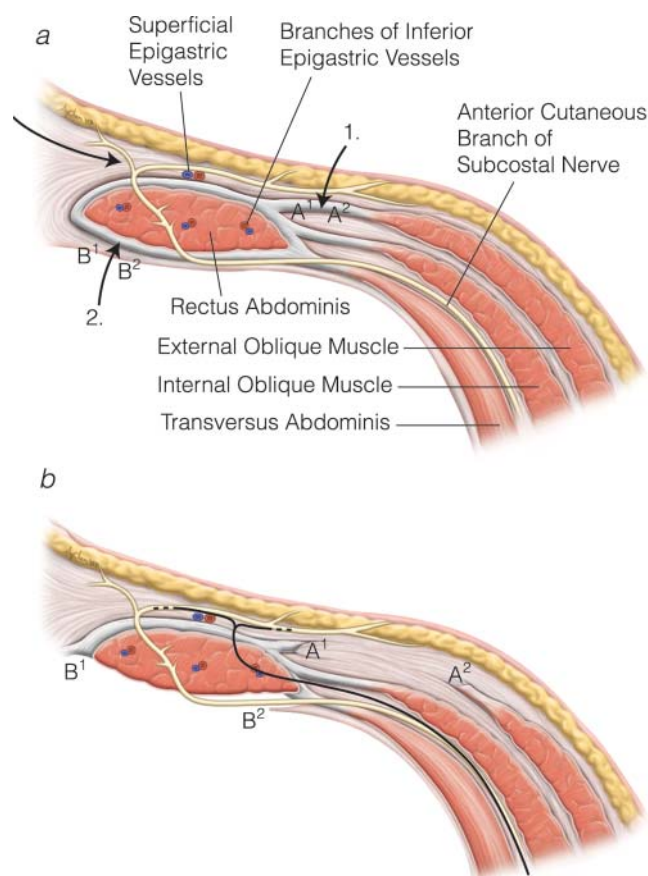


Figure 5 Component separation repair. Depicted is the technique of component separation, as described by Ramirez and colleagues.⁵¹ (a) A longitudinal incision is made in the aponeurosis of the external oblique muscle (1) approximately 2 cm lateral to the rectus sheath, overlapping the hernia defect caudally and extending 5 to 7 cm cranial to the costal margin. Additional length can be gained by incising the posterior rectal sheath (2). (b) The external oblique muscle is separated from the internal oblique muscle as far laterally as possible. Care must be taken not to damage the neurovascular structures that run between the internal oblique muscle and the transversus abdominis to enter the rectus sheath on its posterolateral side (black line). A¹, A² = cut edges of the external oblique aponeurosis; B¹, B² = cut edges of the posterior rectus sheath.

full-thickness defect and a subsequent lateral hernia. If the surgeon inadvertently begins incising the external oblique muscle too medially, he or she runs the risk of potentially transecting the internal oblique fascia too. Transecting the internal oblique muscle will likely result in a lateral abdominal wall bulge. By making the incision lateral on the external oblique muscle, the internal oblique muscle is often muscular and can be clearly delineated from the external oblique. This incision is extended cranially onto the muscular components of the external abdominal oblique to about 5 to 7 cm above the costal margin and caudally to the inguinal ligament. The external oblique muscle is then separated from the internal oblique muscle in the avascular plane to the posterior axillary line.

Step 4: Posterior Rectus Sheath Release

If primary closure is still not possible without undue tension, 2 to 4 cm of additional length can be gained by separating the posterior rectus sheath from the rectus abdominis.

Step 5: Mesh Placement

Depending on the nature of the case (i.e., clean or contaminated), synthetic or biologic mesh, either in the retrorectus or intraperitoneal position, with a minimum 3 to 4 cm of tissue-mesh overlap can be placed. Others have described onlay positioning of the mesh after open component separation.^{39,56} Technically, onlay mesh positioning is easier than underlay placement. However, the mesh is then placed in the subcutaneous position, with a fairly high potential for wound breakdown and mesh exposure. Additionally, the mesh is placed below a devascularized subcutaneous fatty tissue, potentially impeding ingrowth.

Step 6: Skin Closure

Excess skin should be liberally resected. Resecting excess skin provides two distinct advantages: the most devascularized tissue is removed and excess dead space is reduced. Finally, the subcutaneous space should be widely drained with the use of Jackson-Pratt drains.

ENDOSCOPIC COMPONENT SEPARATION

In an effort to avoid the significant tissue trauma and the large open surface areas created following the open component separation technique, endoscopic approaches have been described.^{57–60} This minimizes the lipocutaneous flaps created in the open approach and can be used in conjunction with a planned laparotomy. Adaptations from its original approach have been made over time. This technique maintains the same principles as the open approach, which is to achieve medialization of the abdominal wall through lateral release of the external abdominal oblique fascia.

Step 1: Incision

In the setting of contaminated single-stage abdominal wall reconstruction, a standard laparotomy incision is commenced and the major infectious issues are addressed, including takedown of fistulas or removing an infected prosthetic. The entire anterior abdominal wall is freed of adhesions,

and the defect size is assessed. Those cases that will not close primarily undergo component separation. There is no absolute indication for this as all patients have a different level of compliance to their abdominal wall. A more compliant abdominal wall will come together more easily at the midline than one that is not very compliant. Generally, good surgical judgment, coupled with realistic expectations, should guide the decision-making process.

Step 2: Initial Component Separation Incision

Once a component separation is deemed necessary, a 1 cm incision just inferior to the tip of the 11th rib is made and the external abdominal oblique is identified with blunt dissection and Kocher clamps. The avascular plane between the external abdominal oblique and the internal abdominal oblique is identified by use of retractors. Careful identification of the correct anatomic plane is imperative at this juncture to avoid placing the dissecting balloon in the wrong plane and requiring conversion to an open procedure.

Step 3: Balloon Dissector

A bilateral inguinal hernia balloon dissector is inserted in a caudal direction toward the pubic tubercle. Under direct visualization, the balloon is inflated and the orientation of the muscle fibers is confirmed.⁶⁰ A structural balloon port is placed, and insufflation pressures of 10 to 12 mm Hg are maintained. The camera tip bluntly completes the posterior lateral dissection.

Step 4: External Oblique Release

A 5 mm port is placed in the posterior axillary line. This port needs to be quite lateral to obtain the appropriate angle to incise the external oblique fascia. Much like in the open approach, the linea semilunaris should be carefully identified and avoided to prevent a lateral hernia. Anatomically, the linea semilunaris is identified at the junction of the external and internal oblique. Typically, scissors and cautery are used to release the external oblique fascia to the inguinal ligament.

Step 5: Cephalad Dissection

Another 5 mm port is placed medially through this inferior release to be used for the cephalad release of the external abdominal oblique fascia and muscle. The camera is now positioned in the lateral trocar. Given that the external oblique is typically quite muscular at its cephalad extent, some form of ultrasonic dissection is helpful in maintaining hemostasis. The external oblique is then released for at least 5 to 7 cm above the costal margin. Once this is performed bilaterally, it completes the endoscopic component separation and the surgery.

Reinforcement or bridging of a midline defect for both the open and endoscopic approaches can be performed with mesh in the retrorectus or intra-abdominal position with lateral transfascial fixation sutures. The exact technique regarding mesh placement is still under debate. Biologic mesh may be used in the setting of contamination. Synthetic mesh can be used for elective clean cases. If synthetic mesh needs to be placed in the intraperitoneal position, a synthetic mesh of choice with an antiadhesive side should face the bowel.

COMPLICATIONS

There is overwhelming proof that tension-free prosthetic repairs yield lower recurrence rates than direct suture repairs. In a Medline search for complications of incisional hernia repair, recurrence rates ranged from 31 to 63% for direct suture repairs and from 0 to 32% (mostly less than 10%) for prosthetic repairs.^{61,62} Although the primary adverse outcome of hernia repair is recurrence, the short-term morbidity of open hernia repair must also be assessed. In one meta-analysis, the overall complication rate after open repair was 27%.⁶³ Ileus, postoperative pain, sepsis, fistulization, and necrotizing fasciitis have all been documented. Tissue response, which is variable from person to person, can be so intense that the prosthetic material is deformed by contraction. Erosion can result in intestinal obstruction or fistulization, especially if there is physical contact between the intestine and the prosthesis.^{64,65}

Prosthesis-related infection, although it occurs less with the laparoscopic technique, remains a major problem with open incisional hernia repairs. A pooled analysis of randomized trials comparing primary versus mesh repair of incisional hernias found an overall 10% infection rate.³⁸ Prosthesis-related infection occurs in as many as 25% of repairs in some series, delays healing for prolonged periods, and is one of the most important risk factors for recurrence. Higher rates of prosthesis infection are associated with preexisting infection, ulceration of the skin overlying the hernia, obesity, incarcerated or obstructed bowel within the hernia, and perforation of the bowel during hernia repair. Seromas are common, especially when a large prosthesis is required or there has been extensive flap dissection of the subcutaneous layer from the fascia. Untreated seromas can become infected secondarily. Suction drains can be useful, but there is little guidance in the literature as to appropriate times for removal. Drains can both remove bacteria or function as a two-way street, allowing seeding of the mesh. Strategies for preventing and managing seromas are largely based on empirical evidence and personal opinion; objective data are virtually nonexistent. It is not always necessary to remove the mesh if infection develops. A trial of local wound care after opening the incision and debriding the infected area is warranted. Some authorities believe that ePTFE prostheses are less prone to infection; however, once infection is established, ePTFE prostheses, unlike mesh prostheses, are almost never salvageable.

Laparoscopic Ventral Hernia Repair

Le Blanc and Booth were the first to describe successful laparoscopic ventral hernia repair in 1993.⁶⁶ Several technical benefits are ascribed to a laparoscopic approach, including the opportunity to evaluate the entire abdominal wall for other smaller, Swiss cheese–like defects that may otherwise be missed and allowing for wide underlay mesh placement while avoiding large tissue dissection and the associated wound morbidity. Studies with varied design methodologies have compared a laparoscopic approach with an open approach on several important outcome parameters, including wound morbidity, mesh infections, hernia recurrence, and hospital length of stay.

One of the largest series evaluating the safety and efficacy of laparoscopic ventral hernia repair was reported in 2003.⁶⁷ In this 10-year study, the authors reported a 3.6% conversion

rate from laparoscopic repair to open repair, an average length of stay of 2.3 days (0 to 33 days), and an overall complication rate of 13%, with an overall infection rate of 1.8% (including wounds and mesh infection). Other important complications reported included bowel or bladder injury (1.7%), prolonged ileus (3%), prolonged seroma (2.6%), and prolonged pain (1.6%). Following an average 20-month follow-up (range 0 to 96 months), they reported a 4.7% hernia recurrence rate. Important factors associated with their recurrences included larger hernias, increased operative times, history of prior hernia repairs, and postoperative complications. A more recent prospective randomized study of open versus laparoscopic incisional hernia repair supported this study with similar findings, including improved rates of complications, decreased hospital length of stay, and quicker return to work in the laparoscopic group.⁶⁸ Given similar patient characteristics and an average defect size of approximately 9 to 10 cm, the authors noted a decrease in postoperative complications (16% versus 29%), including decreased wound complications (1.1% versus 8.2%), for the laparoscopic group. Hospital length of stay (2.7 versus 9.9 days), rates of complications (16 versus 29%), and quicker return to work (13 versus 25 days) were significantly decreased in the laparoscopic group. Hernia recurrences were similar at approximately 2% after an average 24-month (range 16 to 15 months) follow-up in each group.

Other studies have also described benefits similar to those of a laparoscopic approach for ventral hernia repair but point toward a need to standardize issues related to patient selection. A recent meta-analysis summarized the results of five randomized controlled trials comparing open versus laparoscopic ventral hernia repair.⁶⁹ This study supported the associated decreased length of stay and decreased rates of complications reported by other studies. However, the authors were unable to find decreases in operative time, pain, and recurrence between the two groups. An important contributor to this lack of difference was attributed to the heterogeneity that existed across the various study methodologies. This resulted from the lack of double-blinded randomized trials, patient selection factors such as the varied hernia sizes included across studies, and the varied open techniques being compared. This subsequently underscores the need to clarify these important variables within the context of a well-defined multicenter trial. Furthermore, there are still areas of significant controversy that require further well-controlled trials, such as the method of securing the mesh in place (sutures, tacks, fibrin glue, or a combination), the best approach to address postoperative pain related to mesh fixation techniques, and the management of seromas.

A laparoscopic approach might have distinct advantages over an open ventral hernia repair for obese patients. As obesity has been identified as a risk factor for wound infections and recurrence in open surgery, studies have investigated the safety and efficacy of laparoscopy for this group of patients.^{70,71} Although comparable decreased rates of complications such as wound and mesh infections are reported in obese patients, it is unclear if the same benefit of decreased recurrence rates applies this population. A multi-institutional case series of 901 laparoscopic ventral hernia repairs compared outcomes for patients with a body mass index (BMI) above 40 versus

those with a BMI less than 40.⁷¹ Although similar improved rates of conversion to open repair ($\approx 2.5\%$) and mesh infections ($\approx 1\%$) were found between the two groups, the rates of recurrence were higher in the obese group (BMI ≥ 40 ; 8.3 versus 2.9%) and had an associated fourfold risk after a 19-month follow-up. Although this rate of 8% at 19 months might be acceptable relative to an open approach, it is important that obese patients understand that their rates of recurrence following laparoscopic repair may differ from those of their less obese counterparts. Several issues further complicate the decision to perform surgery in this select group of patients, such as the timing of gastric bypass surgery in relation to ventral hernia repair and the indications for panniculectomy. Although some small studies have attempted to evaluate this question, there are no high-quality studies available to guide answers to these complex problems.

As the benefits of an open versus a laparoscopic approach for varied groups of patients become more defined, an important criterion for choosing an approach is surgeon comfort. A laparoscopic ventral hernia repair, particularly for more complex patients with multiple prior surgeries, requires a special skill set. Here we describe our technique for laparoscopic ventral hernia repair.

Step 1: Intraoperative Patient Preparation

Following general anesthesia, the patient should be placed in the supine position, arms abducted, with appropriate padding. Gastric and bladder decompression should be performed with the aid of a nasogastric tube and Foley catheter prior to entering the abdominal cavity. A three-way Foley catheter is used for hernias below the umbilicus to aid in identifying and potentially mobilizing the bladder for mesh placement. Appropriate antibiotic and venous antithrombosis prophylaxis should be administered.

Step 2: Gaining Access to the Abdominal Cavity

The initial access port (10 or 12 mm) can be placed in the right or left upper quadrant using an open cut-down technique. A 5 mm 30° laparoscope is preferred to have adequate visualization of the anterior abdominal wall and allow placement through any trocar. Two to three other ports (5 mm) can be placed along the same side of the lateral abdominal wall under direct laparoscopic visualization. As a general rule, these ports should be placed as far laterally as possible to the midline defect to allow sufficient distance to place a large piece of mesh and to allow the surgeon to work in the midline without difficulty.

Step 3: Adhesiolysis and Defect Measurement

To avoid bowel injury, we prefer use of sharp dissection. If bleeding is encountered, liberal use of clips may be applied. If any part of this step becomes too challenging and the repair is compromised, conversion to an open repair should be considered. When working near the bladder, if there is any concern for an inadvertent bladder injury, the three-way Foley catheter can be used to fill the bladder and inspect for any evidence of leak. Following completion of adhesiolysis, the defect can be measured in preparation for mesh placement. Under direct laparoscopic visualization, long spinal needles are placed intra-abdominally along the edge of the

hernia defect. A 15 cm ruler is then placed intra-abdominally and used to measure the hernia defect under standard insufflation pressures and estimate the mesh size required for repair.

Step 4: Mesh Placement

Following defect measurement, the desired mesh can be cut with the goal of achieving an additional 4 to 5 cm of mesh overlap. Given its intra-abdominal position, either a dual-sided antiadhesive mesh or PTFE mesh should be used for this repair. The cephalad and caudal ends of the mesh can be marked to guide intra-abdominal orientation and placement. Nonabsorbable monofilament or PTFE sutures are secured in four quadrants of the mesh, with the knot landing on the ingrowth-promoting side. The mesh can then be rolled and inserted through the 10 mm trocar. Transfascial fixation sutures are additionally placed with suture passers at approximately 5 cm intervals to further secure the mesh in place. All knots are buried in the subcutaneous space. Additionally, helical tacks are placed circumferentially every 5 mm to secure the mesh in place at the edges.

Step 5: Postoperative Management

Most laparoscopic ventral hernia repairs require overnight admission secondary to perioperative pain management. Despite the minimally invasive nature of the procedure, most patients experience significant discomfort and the average length of hospital admission ranges from 2 to 4 days. We place an abdominal binder on all patients for 6 weeks to reduce seroma formation. Patients are restricted from heavy lifting for at least 6 weeks.

COMPLICATIONS

Special consideration should be given to complications associated with laparoscopic ventral hernia repair. An enterotomy is a critical complication of a laparoscopic approach that may occur while achieving abdominal cavity access or during adhesiolysis. It has been reported to occur in 1 to 6% of cases, with greater challenges encountered in the reoperative abdomen.^{67,72–74} Varied methods of accessing the abdominal cavity have been described, with no prospective randomized trial evaluating the true risk associated with the several available approaches. Although there is no standard way to access the abdominal cavity prior to pneumoperitoneum, an open cut-down technique with access under direct visualization may provide a safer route for complex patients. Extensive adhesiolysis, particularly in the patient with multiple prior surgeries and with prior intra-abdominal mesh placement, is another high-risk opportunity to inadvertently cause an enterotomy. Judicious use of cautery and opting for sharp dissection with the use of clips for hemostasis may help decrease cautery-related injury. In situations where there are dense adhesions onto intra-abdominally placed mesh, resecting the involved piece of mesh and bowel off the abdominal wall allows for safer clearance of the abdominal wall in preparation for mesh placement. Whether an enterotomy is encountered or questioned, conversion to an open approach is a safe next step to the management of this complication as diagnosing a delayed enterotomy is associated with increased morbidity and mortality.⁷⁵ The ideal surgical management to an enterotomy is controversial and in some cases may require delaying definitive hernia repair.

Special Circumstances

LOSS OF ABDOMINAL DOMAIN

Loss of abdominal domain is a poorly understood phenomenon that lacks clear definitions in the literature. In its simplest terms, it implies a massive hernia where the herniated contents have resided for so long outside the abdominal cavity that they cannot simply be replaced into the peritoneum. Unfortunately, several circumstances can result in this occurrence, and each poses unique reconstructive challenges. We typically divide loss of domain hernias into those in which there is contamination or no contamination. Next, each group is subcategorized into those patients with a small hernia defect and a large mushroom cloud of hernia contents and those patients with a massive abdominal wall defect and a massive hernia sac. In the former group, the challenges are mainly focused around having the patient accommodate the abdominal contents. In the latter group, not only must the patients be able to accommodate the abdominal contents, but the surgeon must also use various reconstructive methods to rebuild the abdominal wall.

In approaching these patients, the surgeon must give ample preoperative evaluation and clearance. In particular, the patients should be counseled as to the potential morbidity and mortality of these reconstructive efforts. The surgeon and the patient must set reasonable goals as to what can be accomplished. First, the abdominal contents must be returned to the abdominal cavity without causing respiratory embarrassment and hemodynamic compromise. In these circumstances, the use of progressive preoperative pneumoperitoneum and staged mesh excision has been described.^{76,77} After the contents are returned to the abdominal cavity, the reconstructive procedure must begin. Depending on the circumstances, a retrorectus repair, a bridged repair, component separation, and serial mesh excision may all be appropriate.⁷⁸ These procedures are technically demanding, require ample hospital resources, and likely should be attempted only in high-volume centers.

VENTRAL HERNIA REPAIR IN THE SETTING OF CONTAMINATION

A dilemma arises when a patient has a large incisional hernia and the wound is contaminated either by skin infection or by injury to the bowel during the repair at the time of adhesiolysis. In this situation, a nonabsorbable mesh would have a significant chance of becoming infected, and an enterocutaneous fistula could complicate matters further. In the past, the use of absorbable mesh made of polyglycolic acid was recommended to prevent evisceration.^{79,80} This staged approach to repair a contaminated ventral hernia would result in granulation tissue development over the mesh, allowing for subsequent skin grafting. The mesh itself is absorbed in about 3 weeks, leaving no permanent foreign body to serve as a persistent focus of infection. Unfortunately, recurrence of the incisional hernia is nearly inevitable and leads to a multistage approach to a contaminated abdominal wall defect. Single-stage repairs for this complex problem have been reported in the literature, particularly in conjunction with component separation technique.^{59,81} Currently, many surgeons prefer to use one of the newer biologic prostheses in this setting to achieve closure or add repair reinforcement. This has now

become the best indication for these very expensive materials. Long-term data are not yet available.

Periumbilical Hernia Repair

GASTROSCHISIS

This life-threatening condition is seen in the newborn. It may also be found in the fetus during ultrasound examination of a pregnant patient. There is full-thickness deficiency of the abdominal wall, to the right of a normal umbilicus, through which the bowels protrude. There is no hernial sac.

OMPHALOCELE (EXOMPHALOS)

Like gastroschisis, this condition is seen in the fetus in utero and in the newborn. It is a hernia into the umbilical cord; the hernia contents are therefore covered by Wharton jelly and amnion.

UMBILICAL AND PARAUMBILICAL HERNIA

Unlike an omphalocele, an umbilical hernia is covered by skin. If the defect is located to one side of the umbilicus, it is called a paraumbilical hernia (this variant is more common in adults). Umbilical hernias developing during childhood are congenital, whereas those developing during adult life are acquired. Accordingly, in adult patients, it is important to look for an underlying cause of increased intra-abdominal pressure (e.g., ascites or an intra-abdominal tumor). The differential diagnosis of an umbilical hernia includes caput medusae of varices at the umbilicus from portal hypertension, a metastatic tumor deposit (the so-called Sister Mary Joseph node), a granuloma, an omphalomesenteric duct cyst, and a urachal cyst.

Management of umbilical hernia is determined by the age of the patient. The majority of hernias occurring in children younger than 2 years will heal spontaneously; therefore, watchful waiting is the rule, and only symptomatic hernias are operated on. In children older than 2 years and in adults, surgical correction is required, with the type of repair employed depending on the size of the hernia. If the defect is small (< 3 cm), a direct suture repair may be performed. For larger umbilical and paraumbilical hernias, particularly those in adults, a mesh repair is preferred. The sac is dissected away from the undersurface of the rectus and the linea alba circumferentially and then reduced into the abdomen. If the peritoneum remains intact, a mesh prosthesis may be placed in a subfascial position and secured with sutures. If the abdomen is entered, a dual-layer prosthesis with an adhesion barrier on the visceral side is recommended. In a series of 100 adult patients with a median follow-up period of 4.5 years, the recurrence rate was 11.5% for suture repairs and 0% for mesh repairs.⁸²

A patient with an umbilical hernia and cirrhosis with or without ascites presents a challenging scenario to the general surgeon. Over their lifetime, a patient with cirrhosis has a 20% risk of developing an umbilical hernia, and in the presence of ascites, the risk is as high as 40%.^{83,84} Knowing the surgical complications that can occur following operating on a cirrhotic patient creates a tempting scenario for delayed umbilical hernia repair. However, with advancing disease and progression of umbilical hernia come greater risks, including

incarceration, skin ulceration, perforation, leakage of ascitis, bacterial peritonitis, and possibly evisceration. Although there are certainly risks with elective repair in a patient with cirrhosis, the counterpart morbidity and mortality associated with emergent repair are far greater and have prompted many surgeons to consider early repair.

Aggressive control of ascites is necessary before and after surgery to ensure an improved repair. Several studies have shown that when ascites is controlled, hernia repair outcomes are improved.⁸⁵ In addition to medical approaches to controlling ascites, other approaches, such as concomitant peritoneovenous shunting, transjugular intrahepatic portosystemic shunt, or the use of a peritoneal dialysis catheter, have been described but mainly through descriptive studies.⁸⁵ A recent review of 34 patients with a symptomatic umbilical hernia and cirrhosis showed greater morbidity and mortality in patients in the watchful nonoperative group compared with those who underwent elective repair with primary closure.⁸⁶ A comparison of cirrhotic and noncirrhotic patients undergoing repair of a noninguinal hernia had similar morbidity and mortality when repair was performed electively; however, higher morbidity and a nearly sevenfold mortality was observed in the cirrhotic patients when surgery was emergent.^{84,87} Given the challenges of conducting a randomized study on such a small subset of patients, questions that remain unanswered include primary repair versus mesh repair, type of mesh to be used, timing for elective repair, and use of adjunct interventional procedures for ascitic control.

Miscellaneous Ventral Abdominal Wall Hernia Repairs

EPIGASTRIC HERNIA

Epigastric hernias occur through a single defect or multiple defects in the linea alba. In most patients with these hernias, only a single decussation of the fibers of the linea alba is present, as opposed to the triple decussation seen in most persons.⁸⁸ The reported incidence of epigastric hernia ranges from less than 1% to as high as 5%. Hernias are two to three times more common in men than in women, and 20% are multiple. Most defects are smaller than 1 cm and contain only incarcerated preperitoneal fat, with no peritoneal sac. For this reason, they generally cannot be visualized laparoscopically.

The usual complaint is a painful nodule in the upper midline. As a rule, reduction of the preperitoneal fat followed by simple closure of the defect resolves the complaint. Given the relatively high recurrence rate (up to 10%), some surgeons prefer to place a postage stamp-sized piece of prosthetic material in the preperitoneal space to reinforce the repair. Others bridge the defect by suturing the prosthesis circumferentially. Some authorities recommend exposure of the entire linea alba because of the incidence of multicentricity. This practice leads to unnecessary morbidity. Instead, we make a small incision with the patient under local anesthesia and explain to him or her that additional repairs may be required later.

Left untreated, an epigastric hernia can become large enough to develop a peritoneal sac into which intra-abdominal contents can protrude. Usually, however, the sac is wide, and serious complications are infrequent.

DIASTASIS RECTI

In diastasis recti, the two rectus abdominis muscles are separated quite widely, and the linea alba is stretched and protrudes like a fin. Although the protrusion is easily reducible and almost never produces complications, many patients find it unsightly and request treatment. Most patients, when reassured that this is, in fact, not a true hernia, will decline further surgical intervention. The usual therapy involves removing a strip of the weakened linea alba and reapproximating it; however, this could result in tension, which in turn might lead to recurrence. The alternative would be a mesh repair.

PARASTOMAL HERNIA

Parastomal hernia is one of the most common complications of stoma formation. By definition, the creation of a stoma implies some form of an abdominal wall hernia. There is good evidence to suggest that more than 50% of patients will eventually be found to have a paracolostomy hernia if followed for longer than 5 years.⁸⁹ The rate of herniation with small bowel stomas is also discouraging, although less so than that with colostomies. The results of parastomal hernia repair are particularly dismal, with recurrence being the rule rather than the exception.

Some parastomal hernias can be accounted for by poor site selection or technical errors (e.g., making the fascial opening too large or placing a stoma in an incision), but the overall incidence is too high to be explained by these causes alone. Placement of the stoma lateral to the rectus sheath is widely touted as a cause of parastomal hernia, but high-quality scientific evidence to support this claim is not available. Obesity, malnutrition, advanced age, collagen abnormalities, postoperative sepsis, abdominal distention, constipation, obstructive uropathy, steroid use, and chronic lung disease are also contributing factors.^{90,91}

Newer techniques for stoma construction, such as extraperitoneal tunneling, have had little impact on the incidence of parastomal hernia. Fortunately, patients tolerate these hernias well, and life-threatening complications, such as bowel obstruction and strangulation, are rare. Most are asymptomatic. Routine repair, therefore, is not recommended; repair is appropriate only when there is an absolute or relative indication [see Table 7]. If repair is considered, patients must be informed that there is a significant chance that the hernia will recur.

Table 7 Indications for Repair of Parastomal Hernia

Absolute indications
Obstruction
Incarceration with strangulation
Relative indications
Incarceration
Prolapse
Stenosis
Intractable dermatitis
Difficulty with appliance management
Large size
Cosmesis
Pain

Three general types of parastomal hernia repairs are currently performed: (1) fascial repair, (2) stoma relocation, and (3) prosthetic repair. Fascial repair involves local exploration around the stoma site, with primary closure of the defect. This approach should be considered of historical interest only because the results are so poor. We reserve this approach for elderly patients or in emergent situations as a bridge to a future definitive repair. Stoma relocation yields much better results and is considered the procedure of choice by many surgeons. This approach is especially appropriate for patients who have other stoma problems, such as skin excoriation or suboptimal stoma construction. The use of a permanent prosthesis with a stoma relocation is not generally recommended because of the inherent danger of contamination. However, biologic mesh reinforcement has shown some promise in reducing recurrence rates. Stoma relocation is a significantly more invasive procedure and subjects patients to a triple threat of hernia recurrence: (1) at the old stoma site, (2) at the new stoma site, and (3) in the laparotomy incision used to move the stoma. Given these risks, we typically place a large sheet of biologic mesh in the retrorectus position. This mesh is keyholed around the new stoma site and is used to reinforce the old stoma site and the midline closure.

Prosthetic repair can provide a reasonable outcome, but it is necessary to accept the complications inherent in the placement of a foreign body. The stoma exit site must be isolated from the surgical field to lower the risk of prosthesis infection. The prosthesis can be placed extraperitoneally by making a hockey-stick incision around the stoma, with care taken to ensure that the incision is outside the periphery of the stoma appliance. Once the subcutaneous tissue is divided, dissection proceeds along the fascia until the sac is identified and removed. The defect is then closed with an overlying prosthesis buttress sutured in place. Alternatively, the fascial defect is bridged with the prosthesis for a tension-free repair.

The extraperitoneal approach seems logical but can be technically demanding in that it is sometimes difficult to define the entire extent of the hernia defect. Moreover, the considerable undermining involved can lead to seroma formation, eventual infection, or peristomal skin necrosis. As an alternative, an intra-abdominal prosthetic approach has been described that is theoretically attractive because it avoids the local complications of the extraperitoneal operation and incorporates the mechanical advantage gained by placing the prosthesis on the peritoneal side of the abdominal wall.^{92,93} Intra-abdominal pressure then serves to fuse the prosthetic material to the abdominal wall rather than being a factor in recurrence. Either ePTFE, polypropylene, or polyester mesh with an adhesion barrier can be used for the prosthesis. One technique is to slit the prosthesis and create a keyhole in its center and then suture this directly around the peritoneal side of the stoma so that it widely overlaps the hernia defect. Sugarbaker's practice is to mobilize the bowel thoroughly and then lateralize it with the prosthesis, in effect creating a long tunnel in addition to covering the hernia defect.⁹³ The detractors of the intra-abdominal approach argue that the risk of complications (e.g., adhesive bowel obstruction and fistula formation) outweighs the advantages. The intra-abdominal approach is particularly well suited for adaptation to laparoscopic methods.⁹⁴⁻⁹⁶

SPIGELIAN HERNIA

A spigelian hernia, first described 400 years ago by the Flemish anatomist Adriaan van den Spiegel, is a hernia through a defect in the spigelian fascia.⁹⁷ The spigelian fascia is the area between the semilunar line and the lateral border of the rectus abdominis. The majority of spigelian hernias occur just below the arcuate line, where the posterior rectus sheath becomes deficient. This region, known as the spigelian belt, is a band between the iliac crest and a line drawn 6 cm above [see Figure 6].⁹⁸ These rare hernias are being reported with increasing frequency: there are more than 100 cases in the surgical literature.

A spigelian hernia may present as a bulge lateral to the rectus. However, because many of these hernias are interparietal, they may not be clinically apparent; often they are picked up incidentally during laparoscopy. A significant percentage of patients present with an incarcerated or even strangulated hernia. If such a hernia is interparietal, the diagnosis frequently is not made until a laparotomy is done for treatment of the acute process.

The standard treatment is operative repair.⁹⁹ A transverse incision is made over the bulge. The anterior rectus sheath is incised transversely, and the sac is dissected as far as its neck and either excised or inverted. The defect is then repaired with a continuous suture of nonabsorbable material. Alternatively, a mesh may be placed in the defect and sutured to the edges of the defect. Laparoscopic methods are increasingly being employed to repair spigelian hernias.¹⁰⁰

RICHTER HERNIA

In a Richter hernia, part of the bowel wall herniates through the defect. The herniated bowel wall may become ischemic and gangrenous, but intestinal obstruction does not occur. The overlying skin may be discolored. The herniated bowel wall is exposed by opening the sac, and the neck of the sac is enlarged to allow delivery of the bowel into the wound. The gangrenous patch is excised, and the bowel wall is reconstituted. The hernia is then repaired.

SUPRAVESICAL HERNIA

Supravesical hernias develop anterior to the urinary bladder as a consequence of failure of the integrity of the transversus abdominis and the transversalis fascia, both of which insert into the Cooper ligament. The preperitoneal space is continuous with the retropubic space of Retzius, and the hernia sac protrudes into this area. The sac is directed laterally and emerges at the lateral border of the rectus abdominis in the inguinal region, the femoral region, or the obturator region. It may therefore mimic a hernia from any of these areas and sometimes is associated with a hernia from one of these regions. It is important to recognize this hernia during groin exploration for a suspected groin hernia and then to repair the defect appropriately.

A variant of this hernia, known as an internal supravesical hernia, may also arise. These hernias are classified according to whether they cross in front of, extend beside, or pass behind the bladder. Bowel symptoms predominate in patients with these defects, and urinary tract symptoms may develop in as many as 30%. Treatment is surgical and is accomplished

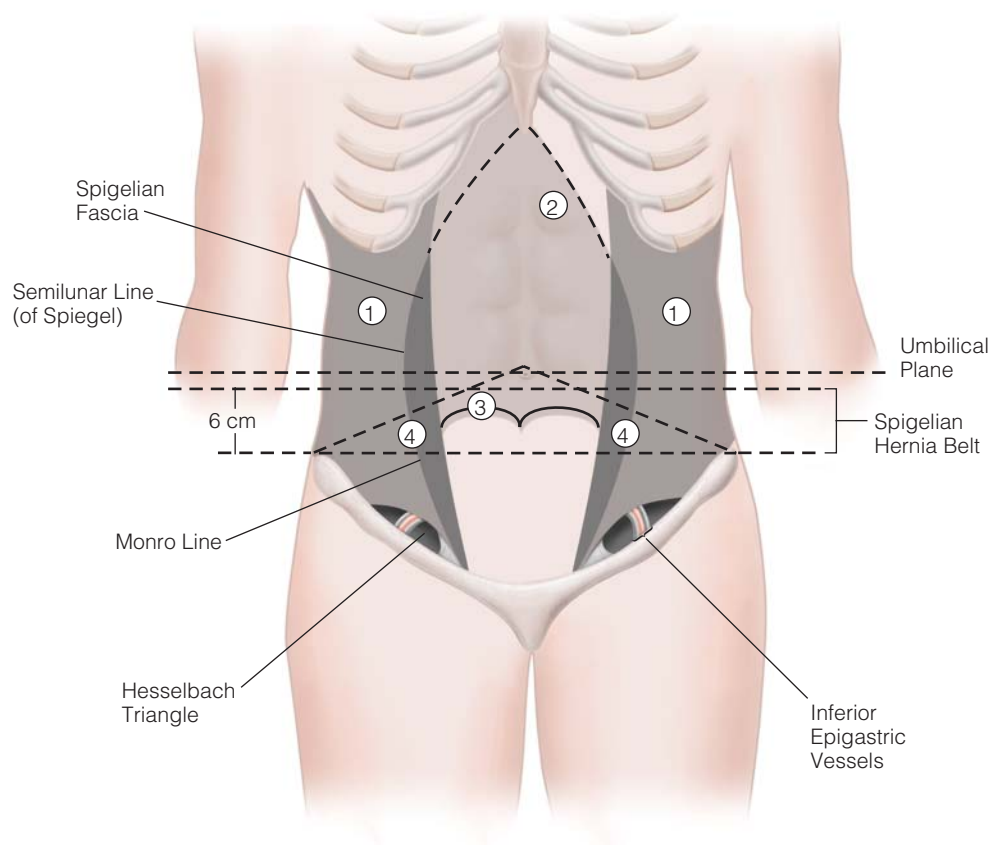


Figure 6 Depicted is the spigelian hernia belt, with a diagrammatic representation of the relevant components of the anterior abdominal wall, including (1) the transversus abdominis, (2) the dorsal lamella of the rectus sheath (the rectus abdominis itself having been cut away), (3) the semicircular line (of Douglas), and (4) the spigelian aponeurosis.

transperitoneally via a low midline incision. The sac can usually be reduced without difficulty, and the neck of the sac should be divided and closed.

LUMBAR HERNIA

The lumbar region is the area bounded inferiorly by the iliac crest, superiorly by the 12th rib, posteriorly by the erector spinae group of muscles, and anteriorly by the posterior border of the external oblique muscle as it extends from the 12th rib to the iliac crest. There are three varieties of lumbar hernia:

1. The superior lumbar hernia of Grynfeltt. In this variety, the defect is in a space between the latissimus dorsi, the serratus posterior inferior, and the posterior border of the internal oblique muscle.
2. The inferior lumbar hernia of Petit. Here the defect is in the space bounded by the latissimus dorsi posteriorly, the iliac crest inferiorly, and the posterior border of the external oblique muscle anteriorly.
3. Secondary lumbar hernia that develops as a result of trauma—mostly surgical (e.g., renal surgery)—or infection.¹⁰¹ In the past, it was encountered relatively frequently as a consequence of spinal tuberculosis with paraspinal

abscesses but is less common today. Surgical repair is discouraged because the natural history is more consistent with that of diastasis recti than that of a true hernia. Denervation appears to play a significant role in the pathogenesis. In other words, this “hernia” reflects a weakness in the abdominal wall more than it does a dangerous hernia defect. Therefore, appropriate repair is commonly followed by gradual eventration, which is perceived by the patient as a recurrence.

Lumbar hernias should be repaired if they are large or symptomatic. A prosthesis or a tissue flap of some kind is usually required for a successful repair. A rotation flap of fascia lata can be used for inferior lumbar hernias. Bony landmarks limit anterior open approaches. We typically perform a preperitoneal Stoppa-type repair. If necessary, the mesh can be fixed to the iliac bone with orthopedic bone fixation devices.¹⁰² Laparoscopic repair of lumbar hernias is now being performed with increasing frequency and is proving successful.¹⁰³

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Acknowledgments

Figures 1, 5, 6 Alice Y. Chen
Figures 2 Tom Moore

28 INGUINAL HERNIA REPAIR

Simon Bergman, MD, MSC, FRCSC, and Liane S. Feldman, MD, FACS, FRCSC

In the United States, approximately 1,000,000 abdominal wall herniorrhaphies are performed each year, of which almost 80% are for inguinal or femoral hernias.¹ Worldwide, some 20 million groin hernias are repaired each year.² The lifetime risk of having to undergo an inguinal hernia repair is 27% for men and 3% for women.³ In male patients, indirect inguinal hernias are the most common type (more often located on the right), occurring approximately twice as frequently as direct inguinal hernias; femoral hernias account for a much smaller percentage. In female patients, indirect inguinal hernias are also the most common type, but femoral hernias are seen more frequently than direct hernias, which are rare in this population. Femoral hernias account for fewer than 10% of all groin hernias; however, 40% present as emergencies (i.e., with incarceration or strangulation), and mortality is higher for emergency repair than for elective repair. A two-peak theory has been described, stating that a new diagnosis of an inguinal hernia is most likely in patients younger than 1 year and in patients older than 55 years, although hernias can be diagnosed across any given age group.⁴

Numerous classification schemes for groin hernias have been devised, and the variety of classifications in current use indicates that the perfect system has yet to be developed.⁵ The main problem in developing a single classification scheme suitable for wide application is that it is impossible to eliminate subjective measurements so as to ensure consistency from observer to observer. The advent of laparoscopic herniorrhaphy has further complicated the issue in that some of the measurements needed cannot be obtained via a laparoscopic approach. At present, the Nyhus system enjoys the greatest degree of acceptance [see Table 1].

In what follows, we discuss open and laparoscopic repairs of inguinal hernias. In addition to describing current operative techniques, we address inguinal surgical anatomy, preoperative planning, and complications. Finally, we review selected trials measuring the results of laparoscopic repair against those of open repair.

Anatomy

MUSCULAR LAYERS OF THE ABDOMINAL WALL

External Oblique

The obliquely arranged anteroinferior fibers of the external oblique aponeurosis fold back on themselves to form the inguinal ligament, which attaches laterally to the anterosuperior iliac spine [see Figure 1]. In most people, its medial insertion is dual: one portion of the ligament inserts on the pubic tubercle and the pubic bone, whereas the other portion,

the lacunar ligament, is fan-shaped and spans the distance between the inguinal ligament proper and the pectineal line of the pubis. It blends laterally with the Cooper ligament. The more medial fibers of the aponeurosis of the external oblique muscle divide into a medial crus and a lateral crus to form the external or superficial inguinal ring, through which the spermatic cord or round ligament passes. The inguinal ligament forms the base of the Hesselbach triangle, whereas the edge of the rectus abdominis and the inferior epigastric vessels forms its medial and superolateral borders, respectively.

Internal Oblique

Located beneath the external oblique muscle, the internal oblique fibers orient themselves inferomedially toward the pubis to run parallel to the external oblique aponeurotic fibers. These fibers arch over the round ligament or the spermatic cord, forming the superficial part of the internal inguinal ring.

Transversus Abdominis

Deep to the internal oblique muscle, the transversus abdominis arises from the inguinal ligament, the inner side of the

Table 1 Nyhus Classification System for Groin Hernias

Type	Description
1	Indirect hernia with normal internal abdominal ring. This type is typically seen in infants, children, and small adults.
2	Indirect hernia in which internal ring is enlarged without impingement on the floor of the inguinal canal. Hernia does not extend to the scrotum.
3A	Direct hernia. Size is not taken into account.
3B	Indirect hernia that has enlarged enough to encroach on the posterior inguinal wall. Indirect sliding or scrotal hernias are usually placed in this category because they are commonly associated with extension to direct space. This type also includes pantaloon hernias.
3C	Femoral hernia.
4	Recurrent hernia. Modifiers A, B, C, and D are sometimes added to type 4, corresponding to indirect, direct, femoral, and mixed, respectively.

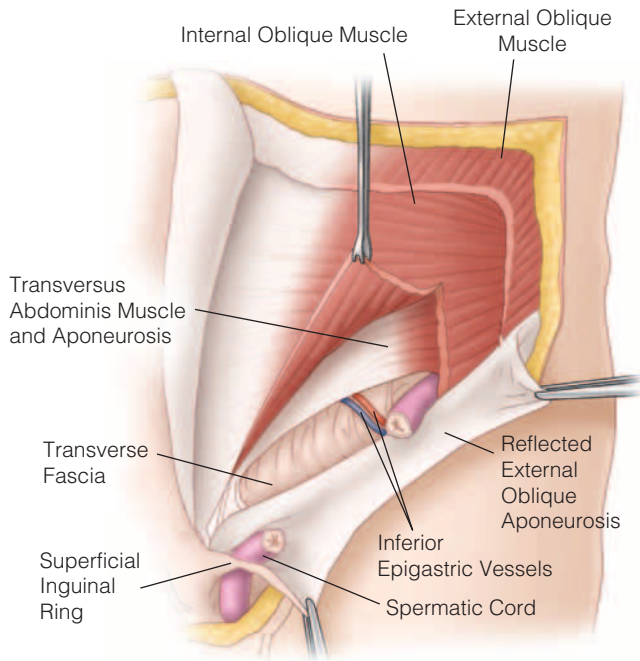
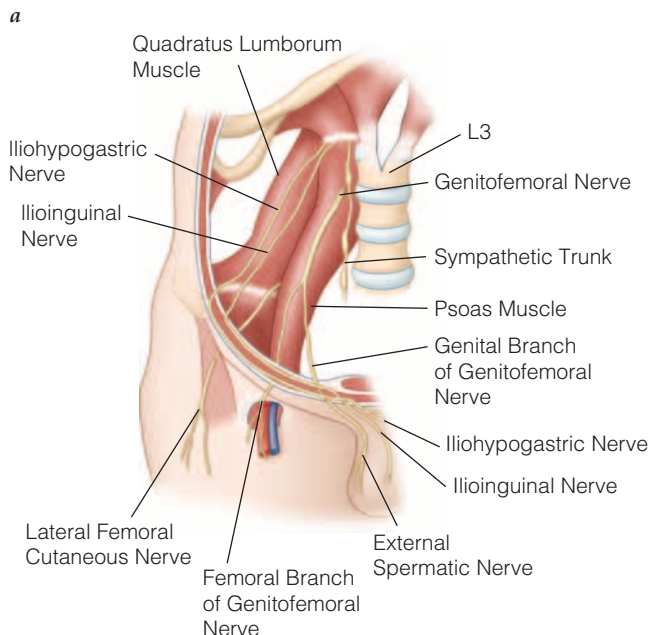


Figure 1 Shown is the relationship of the great muscles to the groin.

iliac crest, the endoabdominal fascia, and the lower six costal cartilages and ribs. The medial aponeurotic fibers of the transversus abdominis contribute to the rectus sheath. Infrequently, these fibers are joined by a portion of the internal oblique aponeurosis to form the conjoint tendon.



Transversalis Fascia

The transversalis fascia lies just superficial to the peritoneum and forms the ilipectineal arch, the iliopubic tract, and the crura of the deep inguinal ring. The latter forms a sling around the deep inguinal ring. This sling has functional significance in that as the crura of the ring are pulled upward and laterally by the contraction of the transversus abdominis, a valvular action is generated that helps preclude indirect hernia formation. The iliopubic tract is the thickened band of the transversalis fascia that courses parallel to the more superficially located inguinal ligament. It is attached to the iliac crest laterally and inserts on the pubic tubercle medially. The insertion curves inferolaterally for 1 to 2 cm along the pectineal line of the pubis to blend with the Cooper ligament, ending at the midportion of the superior pubic ramus.

Rectus Abdominis

The rectus abdominis is the central anchoring mass of the abdominal wall. It arises from the fifth through seventh costal cartilages and inserts on the pubic symphysis and the pubic crest.

Femoral Area

Inferior to the iliopubic tract, midway along the inguinal ligament, is the femoral sheath, containing the femoral artery and branch of the genitofemoral nerve, the femoral vein, and the femoral canal. The latter is a 1 to 2 cm blind pouch that begins at the femoral ring and extends to the level of the fossa ovalis. The femoral ring is bordered by the superior pubic ramus inferiorly, the femoral vein laterally, and the iliopubic tract (with its curved insertion onto the pubic ramus) anteriorly and medially. The femoral canal, which normally contains preperitoneal fat and lymph nodes, is the site of femoral hernias when a peritoneal sac protrudes through its ring.

NERVES

The seventh through 12th intercostal nerves and the first and second lumbar nerves provide most of the innervation for the anterior wall muscles and overlying skin [see Figure 2].

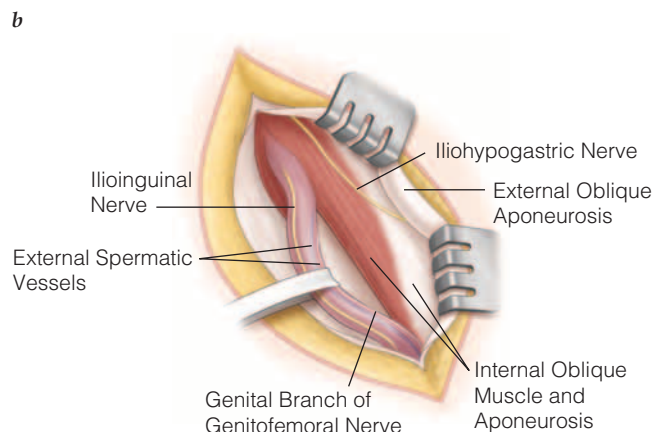


Figure 2 Shown are the (a) important nerves of the lower abdominal wall and (b) anatomy of the nerves in the inguinal region as seen during the open anterior approach.

Genitofemoral Nerve

Arising from the first and second lumbar nerves, the genitofemoral nerve pierces the psoas muscle and fascia at its medial border, descends under the peritoneum on the psoas major, and divides into a medial genital and a lateral femoral branch. The femoral branch descends lateral to the external iliac artery and spermatic cord, passing posteroinferior to the iliopubic tract and into the femoral sheath to supply the skin over the femoral triangle. The genital branch crosses the lower end of the external iliac artery and enters the inguinal canal through the internal inguinal ring with the testicular vessels. This branch supplies the coverings of the spermatic cord down to the skin of the scrotum. The genitofemoral nerve is the most visible of the cutaneous nerves and is sometimes confused with the testicular vessels if the latter are not well appreciated in their more medial position.

Ilioinguinal and Iliohypogastric Nerves

These nerves arise from the 12th thoracic and first lumbar nerve roots, run subperitoneally, and emerge from the lateral psoas border to pierce the transversus abdominis near the iliac crest. They course between the external and internal oblique muscles above the internal inguinal ring. The ilioinguinal nerve runs parallel to the spermatic cord and innervates a small cutaneous area near the external genitals, whereas the iliohypogastric nerve pierces the external oblique muscle to innervate the skin above the pubis.

Lateral Cutaneous Nerve of the Thigh

Arising from the second and third lumbar nerves, the lateral cutaneous nerve descends deep to the peritoneum on the iliac muscle and comes to lie in a superficial position only 3 cm below the anterosuperior iliac spine. It innervates the front and lateral aspects of the thigh.

THE PREPERITONEAL SPACE

Deep to the transversalis fascia and superficial to the peritoneum, the preperitoneal space is known as the space of Retzius in the midline behind the pubis and the space of Bogros, laterally. This is the space that is accessed for laparoscopic repairs [see Figure 3]. The surgical perspective on the pelvic anatomy from the intraperitoneal view has been elegantly described by Skandalakis and colleagues⁶ and Spaw and colleagues,⁷ whose work forms the basis of the descriptions we present in this chapter. Excellent descriptions of the preperitoneal space by Wantz⁸ and Condon⁹ are also worthy of review.

Medial Umbilical Ligament

The medial umbilical ligament is an unfamiliar but sometimes prominent structure that is seen in the transabdominal preperitoneal (TAPP) approach. It courses along the anterior abdominal wall toward the umbilicus, often with an apparent mesentery. It is most prominent in the region of the medial inguinal space. This ligament is most readily identified when the umbilical laparoscope is directed toward the pelvic midline, where the ligament's bilateral structure is best seen as it is oriented toward the umbilicus. Medial retraction of this structure is usually necessary for full exposure of the medial aspect of the inguinal canal.

Spermatic Cord Structures

The testicular artery and vein descend from the retroperitoneum, travel directly over and slightly lateral to the external iliac artery, and enter the internal spermatic ring

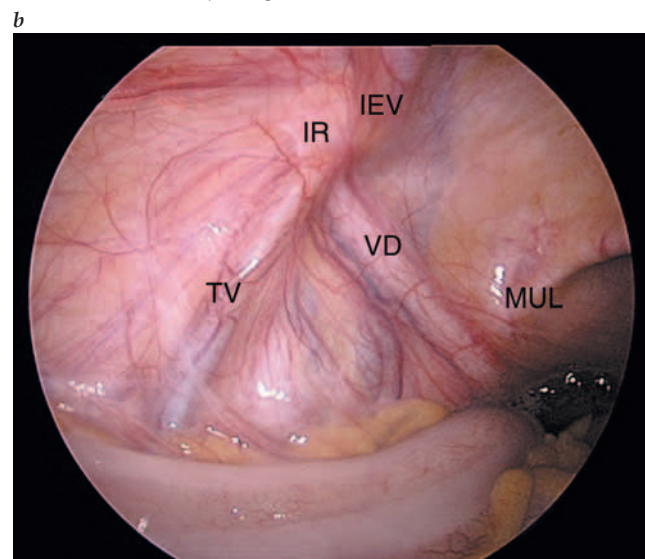
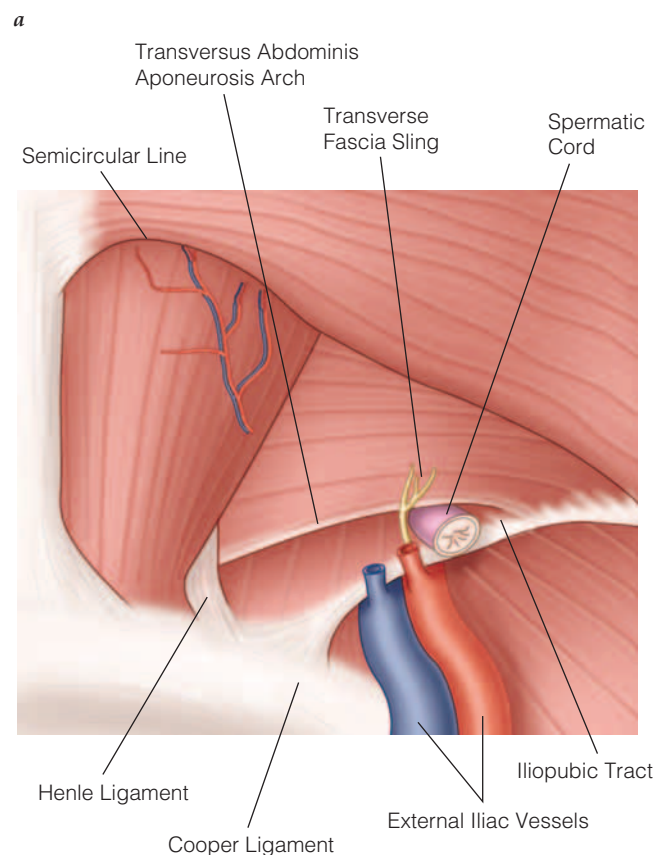


Figure 3 (a) Shown is the anatomy of the right groin from the posterior, or peritoneal, approach. (b) Shown is a laparoscopic view of the anatomy of the left groin with the peritoneum intact in a patient without a hernia. IEV = inferior epigastric vessels; IR = internal ring; MUL = medial umbilical ligament; TV = testicular vessels; VD = vas deferens.

posteriorly. These vessels are covered only by the peritoneum and are usually well visualized as flat structures in the abdominal cavity that assume a cordlike appearance when joined by the vas deferens immediately before entering the internal spermatic ring. The vas deferens is best identified where it joins the spermatic vessels. From there, the vas deferens can be traced back medially as it courses over the pelvic brim and falls into the pelvis and behind the bladder.

Inferior Epigastric Vessels

The inferior epigastric artery and vein lie on the medial aspect of the internal inguinal ring and ascend the deep surface of the rectus abdominis. In the TAPP approach, these vessels may be difficult to visualize, particularly in obese patients. They are best identified by locating the internal inguinal ring at the junction of the vas deferens and the testicular artery and vein. At this location, the vessels exit the medial margin of the internal ring. However, they can quickly fade from view as they travel superiorly and medially along the anterior abdominal wall.

Cooper Ligament

The Cooper ligament is a condensation of the transversalis fascia and the periosteum of the superior pubic ramus lateral to the pubic tubercle. It can be seen only in the preperitoneal space. With the peritoneum intact, it is often easier to palpate the ligament than to see it, but once the ligament has been identified and cleaned, its glistening white fibers are apparent. Care must be taken during dissection to avoid the tiny branches of the obturator vein that often run along the ligament's sur-

face. The iliopubic tract inserts into the superior ramus of the pubis just lateral to the Cooper ligament, blending into it.

Internal Inguinal Ring

The medial border of the internal inguinal ring is formed by the transversalis fascia and the inferior epigastric vessels. The inferior border is formed by the iliopubic tract, and, anteriorly, it is bordered by the transversus abdominis arch, which passes laterally over the internal ring and forms a very well-defined visible edge. The layers of the abdominal wall constituting the lateral border of the internal inguinal ring appear the same as when viewed from the exterior approach. An indirect hernia sac lies anterior and lateral to the spermatic cord at this level as opposed to the familiar medial cord position seen in the classic exterior groin approach to open herniorrhaphy.

Iliopubic Tract

Frequently confused with the inguinal ligament, which is part of the superficial musculoaponeurotic layer and not seen posteriorly, the iliopubic tract is part of the deep layer. All inguinal hernia defects lie above the iliopubic tract, either anterior or superior to it. Conversely, femoral hernias occur below the tract, either posterior or inferior to it. Fibers of the iliopubic tract extend into the Cooper ligament medially, where they become the medial margin of the femoral canal, also called the lacunar ligament.

Triangle of Doom

The lateral spermatic vessels and the medial vas deferens merge at the internal inguinal ring, where they form the apex of the so-called triangle of doom [see *Figure 4*]. Beneath this

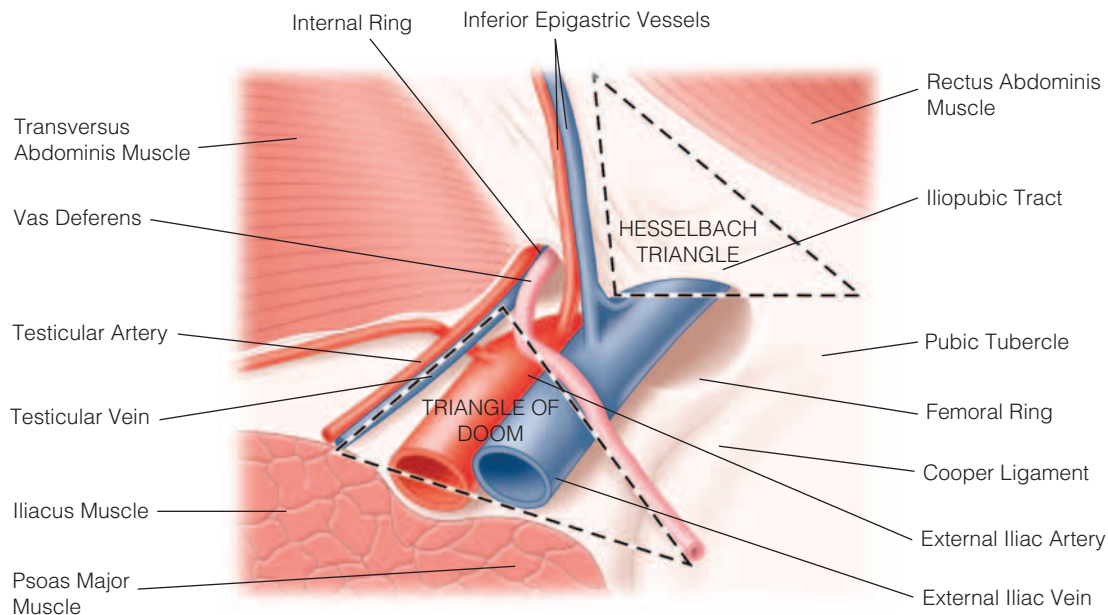


Figure 4 Shown is the left inguinal region with the peritoneum removed, as seen during laparoscopic inguinal hernia repair. The “triangle of doom” contains the external iliac vessels.

triangle lie the external iliac vessels. They are often poorly visualized, and extreme care must be taken not to extend dissection into this area.

Triangle of Pain

Another area worthy of careful attention, the triangle of pain is situated inferior to the iliopubic tract and bordered medially by the spermatic vessels. Using tacks within this triangle risks injury to the genitofemoral, ilioinguinal, iliohypogastric, and lateral cutaneous nerves of the thigh, a cause of postherniorrhaphy neuralgia.

Operative Planning

CHOICE OF ANESTHETIC

The open approach to inguinal hernia repair lends itself well to many different anesthetic techniques. Depending on the setting and on patient and physician preferences, the procedure can be undertaken under general, regional (spinal or epidural), or local anesthesia. The need for pneumoperitoneum and thus for general anesthesia in laparoscopic herniorrhaphy is sometimes considered a major disadvantage. Nausea, dizziness, and headache are more common in the recovery room after TAPP repair than after Lichtenstein repair.¹⁰ It is not necessarily true, however, that local or regional anesthesia is safer than general anesthesia.¹¹ For open repair, local anesthesia or general anesthesia with short-acting agents avoid the higher risk of urinary retention associated with spinal anesthesia while maintaining the benefits of rapid recovery.¹² If general or regional anesthesia is chosen, a local anesthetic is injected in the groin incision.

For open anterior repair, local anesthesia combined with intravenous (IV) infusion of a rapid-acting, short-lasting, amnesic, and anxiolytic agent (e.g., propofol) is a popular anesthetic option that may minimize many of the systemic side effects or complications. In addition to a field block injected in the subcutaneous and deeper tissues in the area of the proposed incision, a nerve block is performed by injecting the anesthetic of choice 1 cm medial and 1 cm inferior to the anterosuperior iliac spine as well as by injecting the areas of the pubic tubercle and the Cooper ligament.

PATIENT POSITIONING

The laparoscopic approach requires patient positioning that is quite different from the more familiar supine position used for the open approach. The patient is placed in the supine position with both arms tucked against the sides. After the laparoscope has been introduced, the patient is placed in a deep Trendelenburg position so that the viscera will fall away from the inguinal areas. Further bowel manipulation is rarely necessary, except to reduce hernial contents. Rotation of the table to elevate the side of the hernia can provide additional exposure, if necessary. A single video monitor is placed at the foot of the bed, directly facing the patient's head. The surgeon stands on the side contralateral to the defect; the assistant surgeon stands opposite the surgeon, and the nurse stands on the ipsilateral side [see Figure 5].

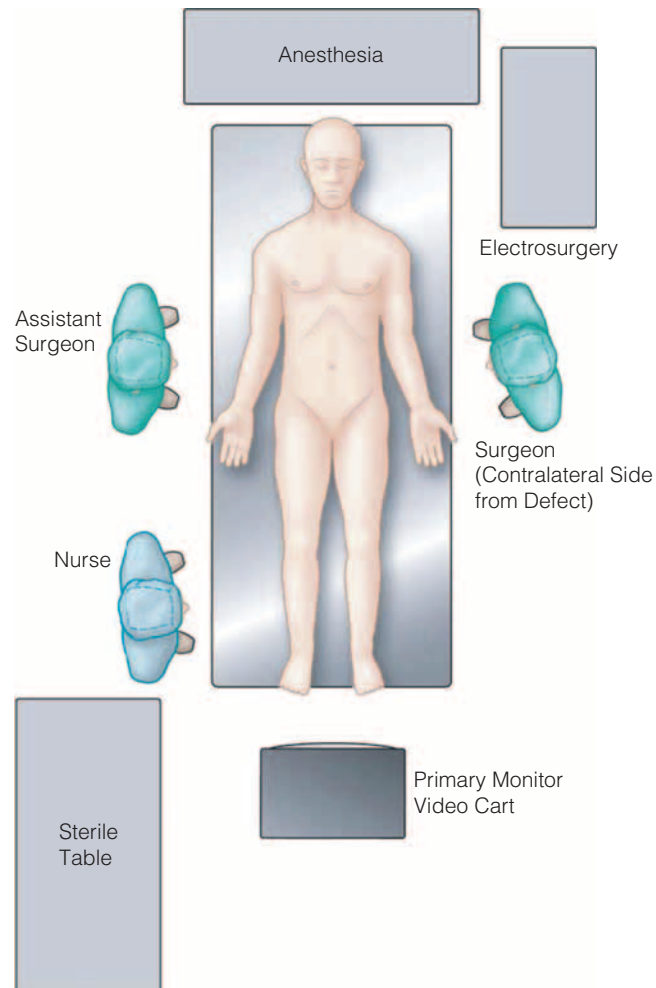


Figure 5 Shown is one of several possible operating room setups. The surgeon stands on the side contralateral to the defect, with a nurse on the ipsilateral side. The assistant surgeon stands opposite the surgeon. This positioning may vary, depending on the surgeon's preference and handedness, the visibility of the defect, and the type of defect present, as well as on the prominence of the medial umbilical ligament and the need for its retraction.

EQUIPMENT

In laparoscopic repairs, because inguinal hernias occur in the anterior abdominal wall, visualization through the umbilicus requires that the laparoscope be angled close to the horizontal plane. For these reasons, we recommend routine use of a 30° or 45° laparoscope. For the TAPP repair, one 10/12 mm and two 5 mm trocars are used. The dissection is performed with a dissector and scissors, to which an electrocautery may be attached. In a totally extraperitoneal (TEP) repair, the initial 10/12 mm trocar is replaced by a balloon-tipped blunt trocar. We usually develop the preperitoneal space with a balloon system, but this can also be done with blunt dissection. The dissection is performed with two blunt-tipped dissectors. For mesh fixation, we usually use tacks, but fibrin glue fixation is another option.

Operative Techniques

There are a great deal of described techniques for inguinal hernia repair, both open and laparoscopic, and a degree of controversy remains regarding the ideal approach to and outcome for inguinal hernia repair. The evidence supports the use of mesh as it is associated with a significant reduction in the risk of recurrence between 50 and 75%.¹⁴ With the evolution of the open anterior approach to tension-free prosthetic mesh repair, determining which patients will benefit significantly from laparoscopic herniorrhaphy has become increasingly important. Patients are well served when a surgeon has several approaches at his or her command that can be applied to and, if necessary, modified for individual circumstances.

Practical considerations do not allow a description of every single named inguinal hernia repair in the literature. The nonprosthetic named repairs alone number more than 70.¹⁵ Rather than address every known variant, we describe the major repairs appropriate for adults on which these variants are based.

ANTERIOR HERNIORRHAPHY

Step 1: Initial Incision

Traditionally, the skin is opened by making an oblique incision between the anterosuperior iliac spine and the pubic tubercle. For cosmetic reasons, however, many surgeons now prefer a more horizontal skin incision placed in the natural skin lines. In either case, the incision is deepened through Scarpa fasciae and the subcutaneous tissue to expose the external oblique aponeurosis. The external oblique aponeurosis is then opened through the external inguinal ring. If a prosthesis is to be used, a space is created beneath the external oblique aponeurosis from the anterior rectus sheath medially toward the anterosuperior iliac spine laterally. The iliohypogastric, ilioinguinal, and genital nerves should be identified and protected. Efforts to mobilize these structures out of the operative field may increase postoperative groin pain.¹⁵ Although identification of the nerves is important, routine division of the iliohypogastric and ilioinguinal nerves does not seem to be consistently associated with postoperative groin pain either way.¹⁶

Step 2: Mobilization of the Cord Structures

The cord structures are bluntly dissected away from the inferior flap of the external oblique aponeurosis to expose the inguinal ligament (shelving edge) and the iliopubic tract. This dissection is continued over the pubic tubercle and onto the anterior rectus sheath. The cord structures are then lifted with the fingers of one hand at the pubic tubercle so that the index finger can be passed underneath to meet the ipsilateral thumb or the fingers of the other hand. Mobilization of the cord structures is completed by means of blunt dissection, and a Penrose drain is placed around them so that they can be retracted during the procedure. The cremasteric muscle is then opened longitudinally, rather than completely divided; this reduces the chances of damage to the cord and prevents testicular descent.

Step 3: Management of the Hernia Sac

The indirect hernia sac, if present, is located anterior and medial to the cord structures. The sac is dissected free of the

cord structures by peeling away or dividing the adhesions between them. The sac can then be ligated and divided but, in adults, is preferably simply reduced into the peritoneal cavity. Proponents of sac inversion believe that this measure results in less pain (because the richly innervated peritoneum is not incised) and may be less likely to cause adhesive complications. Furthermore, sac eversion in lieu of excision protects intra-abdominal viscera in cases of unrecognized incarcerated sac contents or sliding hernia. For large inguinal scrotal hernial sacs, it may be preferential to divide the sac in the middle of the inguinal canal once it is clear that no abdominal contents are present rather than persist at full removal of the sac from the scrotum. The anterior wall of the distal sac is opened as far as possible, and the proximal sac is closed and reduced into the peritoneal cavity.

Direct hernia sacs are separated from the cord and other surrounding structures and reduced into the preperitoneal space. Dividing the superficial layers of the neck of the sac circumferentially—thereby, in effect, opening the inguinal floor—usually facilitates reduction and helps maintain it while the prosthesis is being placed. The opening in the inguinal floor also allows the surgeon to palpate for a femoral hernia. Sutures can be used to maintain reduction of the sac, but they have no real strength in this setting.

Step 4: Repair of the Inguinal Floor

Methods of repairing the inguinal floor differ significantly among the various anterior herniorrhaphies and thus are described separately below.

Step 5: Closure

Closure of the external oblique fascia serves to reconstruct the superficial (external) ring. The external ring must be loose enough to prevent strangulation of the cord structures yet tight enough to ensure that an inexperienced examiner will not confuse a dilated ring with a recurrence. Scarpa fascia and the skin are closed with resorbable sutures.

TISSUE REPAIRS

Bassini Repair

After performing the initial dissection and the reduction or ligation of the sac, the transversalis fascia is opened from the internal inguinal ring to the pubic tubercle, thereby exposing the preperitoneal fat, which is then bluntly dissected away from the undersurface of the superior flap of the transversalis fascia [see *Figure 6a*].

A relaxing incision was not part of Bassini's original description but now is commonly added. The incision is made through the anterior rectus sheath, extending superiorly from the pubic tubercle for a variable distance, as determined by the degree of tension present. A so-called hockey-stick incision oriented laterally at the superior end is a common choice. The posterior rectus sheath is strong enough to prevent future incisional herniation. The relaxing incision works because as the anterior rectus sheath separates, the various components of the abdominal wall are displaced laterally and inferiorly.

The first stitch in Bassini's repair includes the triple layer (comprising the transversalis fascia, the transversus abdominis, and the internal oblique muscle) superiorly and the periosteum of the medial side of the pubic tubercle, along

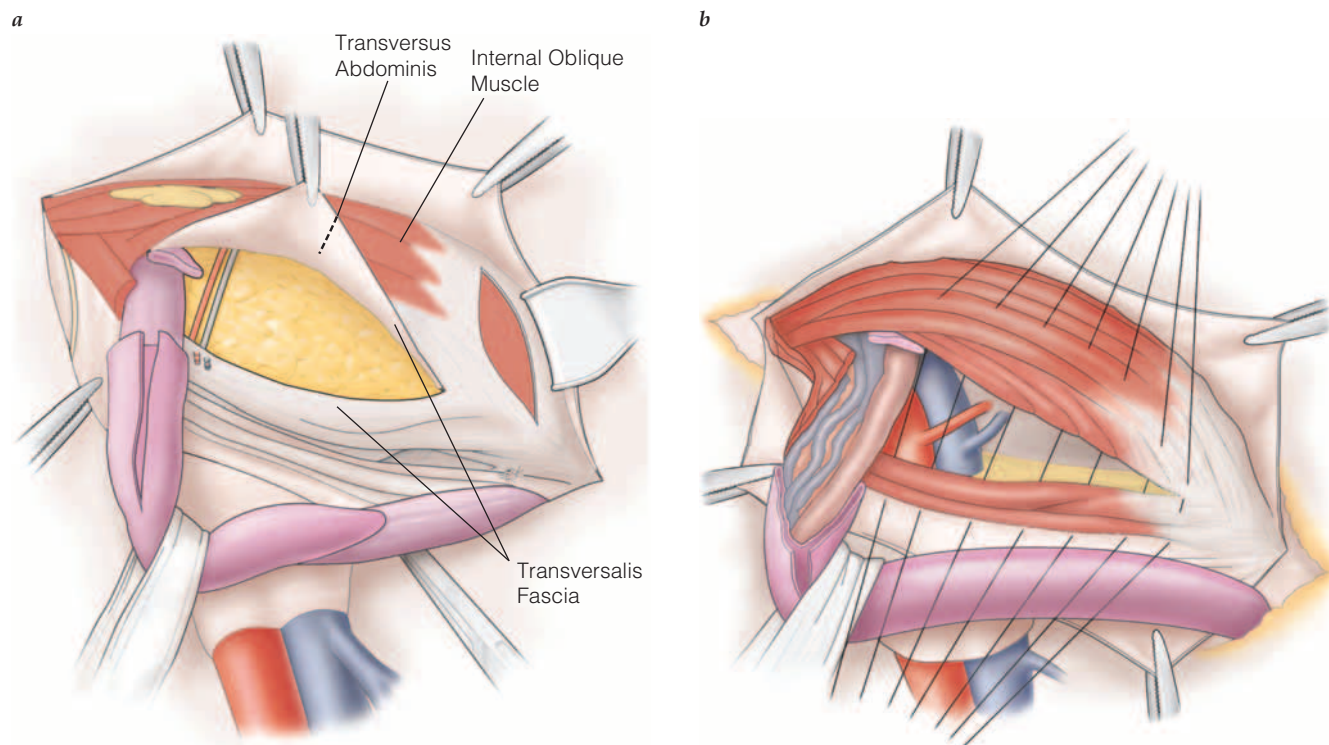


Figure 6 Bassini repair. (a) The transversalis fascia has been opened and the preperitoneal fat stripped away to prepare the deepest structure in Bassini's triple layer (comprising the transversalis fascia, the transversus abdominis, and the internal oblique muscle). (b) The triple layer superiorly is approximated to the inguinal ligament, beginning medially at the pubic tubercle and extending laterally until the deep inguinal ring is sufficiently narrowed.

with the rectus sheath. In current practice, however, most surgeons try to avoid the periosteum of the pubic tubercle so as to decrease the incidence of osteitis pubis. The repair is then continued laterally, and the triple layer is secured to the reflected inguinal ligament (Poupart ligament) with nonabsorbable sutures. The sutures are continued until the internal ring is closed on its medial side [see Figure 6b].

Concerns about injuries to neurovascular structures in the preperitoneal space and to the bladder led many surgeons, especially in North America, to abandon the opening of the transversalis fascia. The unfortunate consequence of this decision is that the proper development of the triple layer is severely compromised. In lieu of opening the floor, a forceps (e.g., an Allis clamp) is used to grasp tissue blindly in the hope of including the transversalis fascia and the transversus abdominis. The layer is then sutured, along with the internal oblique muscle, to the reflected inguinal ligament as in the classic Bassini repair.

Shouldice Repair

The initial steps proceed as per the Bassini repair, including division of the transversalis fascia and relaxing incision. A continuous nonabsorbable suture (traditionally monofilament steel wire) is used for the repair. Eventually, four suture line layers are placed. The repair starts at the pubic tubercle by approximating the iliopubic tract laterally to the undersurface of the lateral edge of the rectus abdominis [see Figure 7a]. The suture is continued laterally, approximating the iliopubic

tract to the medial flap, which is made up of the transversalis fascia, the internal oblique muscle, and the transversus abdominis. The continuous suture is extended to the internal ring, where the lateral stump of the cremaster muscle is picked up to form a new internal ring. Next, the direction of the suture is reversed back toward the pubic tubercle, approximating the medial edges of the internal oblique muscle and the transversus abdominis to the Poupart ligament, and the wire is tied to itself and then the first knot [see Figure 7b]. Thus, two suture lines are formed by the first suture.

A second suture is started near the internal ring, approximating the internal oblique muscle and the transversus abdominis to a band of external oblique aponeurosis superficial and parallel to the Poupart ligament. This third suture line ends at the pubic crest. The suture is then reversed, and a fourth suture line is constructed in a similar manner, superficial to the third line.

Although the Shouldice clinic has outstanding results, a major criticism of this operation is that the results may not be reproducible in general practice because surgeons may find it hard to identify the various layers in the medial flap reliably—a step that is crucial for developing the multiple suture lines.

McVay Cooper Ligament Repair

This operation is similar to the Bassini repair, except that it uses the Cooper ligament instead of the inguinal ligament for the medial portion of the repair. Interrupted sutures are placed from the pubic tubercle laterally along the Cooper

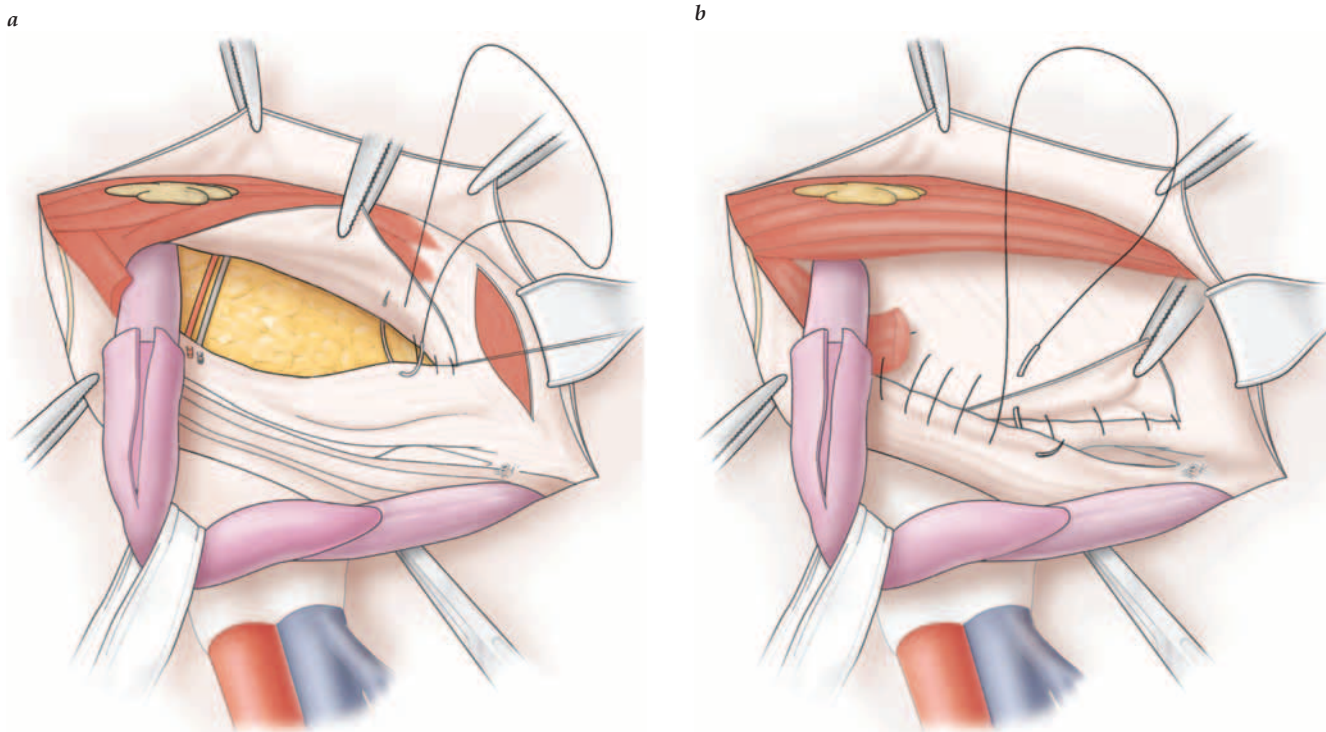


Figure 7 Shouldice repair. (a) The first suture line starts at the pubic tubercle by approximating the iliopubic tract to the undersurface of the lateral edge of the rectus abdominis. The suture is continued laterally, approximating to the medial flap (made up of the transversalis fascia, the internal oblique muscle, and the transversus abdominis). (b) The second suture line begins after the stump of the divided cremaster muscle has been picked up. The direction of the suture is reversed back toward the pubic tubercle, approximating the medial edges of the internal oblique muscle and the transversus abdominis to the Poupart ligament. Two more suture lines will be constructed by approximating the internal oblique muscle and the transversus abdominis to a band of the inferior flap of the external oblique aponeurosis superficial and parallel to the Poupart ligament—in effect, creating a second and a third artificial Poupart ligament.

ligament, progressively narrowing the femoral ring; this constitutes the most common application of the repair—namely, treatment of a femoral hernia [see Figure 8]. The last stitch in Cooper's ligament is known as a transition stitch and includes the inguinal ligament. This stitch has two purposes: (1) to complete the narrowing of the femoral ring by approximating the inguinal ligament to the Cooper ligament, as well as to the medial tissue, and (2) to provide a smooth transition to the inguinal ligament over the femoral vessel so that the repair can be continued laterally (as in a Bassini repair). Given the considerable tension required to bridge such a large distance, a relaxing incision (as described in the Bassini repair) should always be used. In the view of many authorities, this tension results in more pain than is noted with other herniorrhaphies and predisposes to recurrence. For this reason, the McVay repair is rarely chosen today, the main exception being for treatment of a patient with a femoral hernia or a patient with specific contraindications to mesh repair.

TENSION-FREE REPAIRS

Lichtenstein Repair

This operation is the current standard for inguinal herniorrhaphy. The initial preparation of the inguinal floor does not differ substantially from that carried out in a nonprosthetic

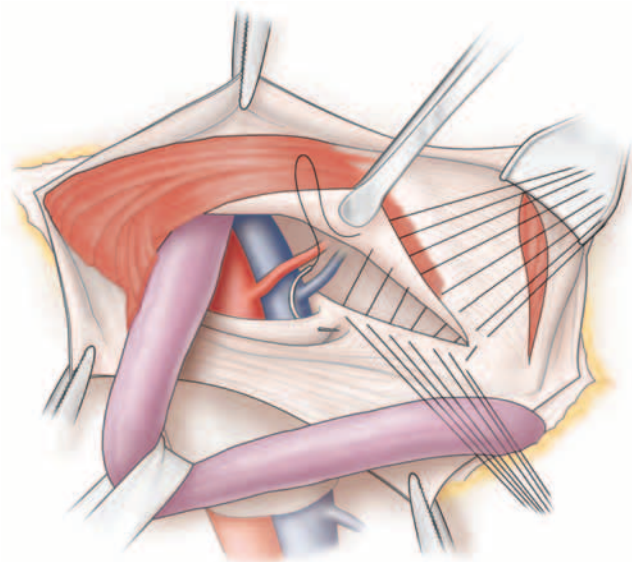


Figure 8 McVay Cooper ligament repair. The lateral stitch is the transition stitch to the femoral sheath and the inguinal ligament.

repair. The transversalis fascia is not opened—a practice that has occasionally been criticized on the grounds that it might cause an occult femoral hernia to be missed. To date, however, an excessive incidence of missed femoral hernias has not been reported in men. The situation may be different in women in that femoral recurrence is much more common than one might assume when the entire myopectineal orifice is not addressed (as is the case with the McVay procedure or any of the preperitoneal operations).¹⁷

The key to the operation is the placement of a large prosthesis (at least 15 × 10 cm for an adult) extending from a point 2 cm medial to the pubic tubercle (to prevent the commonly seen pubic tubercle recurrences) to the anterosuperior iliac spine laterally. The medial end is rounded to correspond to the patient's particular anatomy, and a continuous suture of either nonabsorbable or long-lasting absorbable material is begun between the prosthesis and the anterior rectus sheath 2 cm medial to the pubic tubercle [see Figure 9]. The suture is continued laterally, securing the prosthesis to either side of the pubic tubercle (not into it) and then to the shelving edge of the inguinal ligament. The suture is tied at the internal ring.

A slit is made on the lateral side of the prosthesis to create two tails, a wider one (approximately two thirds of the total height) above and a narrower one below. The tails are positioned around the cord structures and placed beneath the external oblique aponeurosis laterally to about the

anterosuperior iliac spine, with the upper tail placed on top of the lower. A single interrupted suture is placed to secure the lower edge of the superior tail to the lower edge of the inferior tail and the inguinal ligament—thereby, in effect, creating a shutter valve. This step is considered important for preventing indirect recurrences. The maneuver provides a cradling effect as well, preventing direct contact between the cut edges of the prosthesis and the cord structures, which could result in damage when linear approximation is used. The suture also incorporates the shelving edge of the inguinal ligament so as to create a domelike buckling effect over the direct space, thereby ensuring that there is no tension, especially when the patient assumes an upright position.

Two interrupted sutures are placed to attach the superior aspect of the mesh to the internal oblique aponeurosis and rectus fascia. Care is taken to tie these loosely and to avoid placing them laterally so as to minimize the risk of damaging the intramuscular and therefore invisible portions of the important nerves. The prosthesis should be sutured with enough laxity to allow for the difference between the supine and upright positions and, more importantly, to account for contraction of the mesh.

Plug-and-Patch Repair

The mesh plug technique was first developed by Gilbert and subsequently modified by Rutkow and Robbins, Millikan and colleagues, and others [see Figure 10].^{18–20} The groin is entered

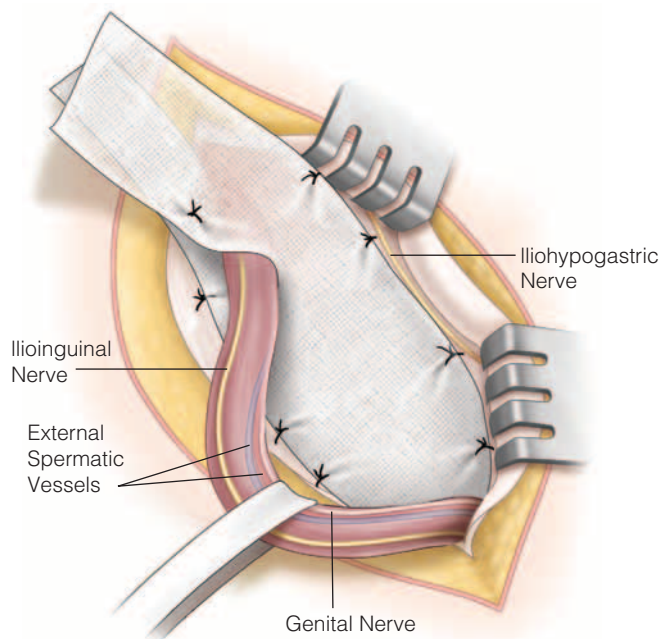


Figure 9 Lichtenstein repair. A mesh prosthesis is positioned over the inguinal floor to extend approximately 2 cm medial to the pubic tubercle. A slit is made in the mesh to accommodate the cord structures, and the two tails are secured to each other and to the shelving edge of the inguinal ligament with a single interrupted suture. The superior and medial aspects of the prosthesis are secured to the internal oblique muscle and the rectus fascia with a few interrupted sutures.

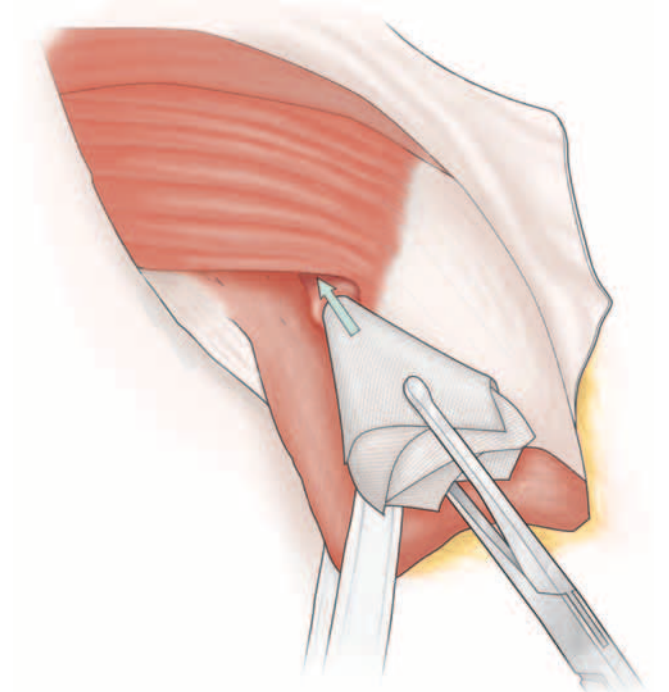


Figure 10 Gilbert plug-and-patch repair. Depicted is the mesh plug technique for repair of an inguinal hernia. A sheet of polypropylene mesh is formed into a cone (as shown here), inserted into the defect, and secured to either the internal ring (arrow) (for an indirect hernia) or the neck of the defect (for a direct hernia) with interrupted sutures. Prefabricated mesh plugs are also available.

via a standard anterior approach. The hernial sac is dissected away from surrounding structures and reduced into the preperitoneal space. A sheet of polypropylene mesh is formed into a cone, tied, inserted in the defect, and secured with interrupted sutures to either the internal ring (for an indirect hernia) or the neck of the defect (for a direct hernia).

A prefabricated prosthesis that has the configuration of a flower is commercially available and is recommended by Rutkow and Robbins.²⁰ This prosthesis is tailored to each patient's particular anatomy by removing some of the "petals" to avoid unnecessary bulk. Many surgeons consider this step important for preventing erosion into surrounding structures (e.g., the bladder); indeed, such complications have been reported, albeit rarely.

Millikan and colleagues further modified the procedure by recommending that the inside petals be sewn to the ring of the defect.¹⁹ For an indirect hernia, the inside pedals are sewn to the internal oblique portion of the internal ring; this forces the outside of the prosthesis underneath the inner side of the defect and makes it act like a preperitoneal underlay. For direct hernias, the inside petals are sewn to the Cooper ligament and the shelving edge of the inguinal ligament, as well as to the conjoint tendon; this, again, forces the outside of the prosthesis to act as an underlay.

The patch portion of the procedure is optional and involves placing a flat piece of polypropylene in the conventional inguinal space so that it widely overlaps the plug, much as in a Lichtenstein repair. The difference with a plug-and-patch repair is that only one or two sutures—or, sometimes, no sutures—are used to secure the flat prosthesis to the underlying inguinal floor. Some surgeons, however, place so many sutures that they have, in effect, performed a Lichtenstein operation on top of the plug.

The plug-and-patch repair, in all of its varieties, is fast and easy to teach, which has made it popular in both private and academic centers. A randomized controlled trial has shown it to be equivalent to the Lichtenstein repair in terms of recurrence and morbidity.²¹ However, case reports in the literature have described removal of plugs for pain, migration, or erosion, and, as a result, the benefits of the plug-and-patch repair compared with those of the Lichtenstein repair have been scrutinized.

Femoral Hernia Repair

Femoral hernias in females can be approached using a groin incision with dissection beneath the inguinal ligament without opening the external oblique fascia. To facilitate reduction of the contents of the hernia, the femoral canal may need to be opened by dividing the inguinal ligament and/or lacunar ligament. The defect can be closed with sutures or with a mesh plug from below the inguinal ligament [see Figure 11]. Larger femoral hernias on females and femoral hernias in males are better repaired using a McVay Cooper ligament repair.

POSTERIOR (PREPERITONEAL) HERNIORRHAPHY

A key technical issue in a preperitoneal hernia repair is how the surgeon chooses to enter the preperitoneal space. In fact, within this general class of repair, the method of entry into this space constitutes the major difference between the

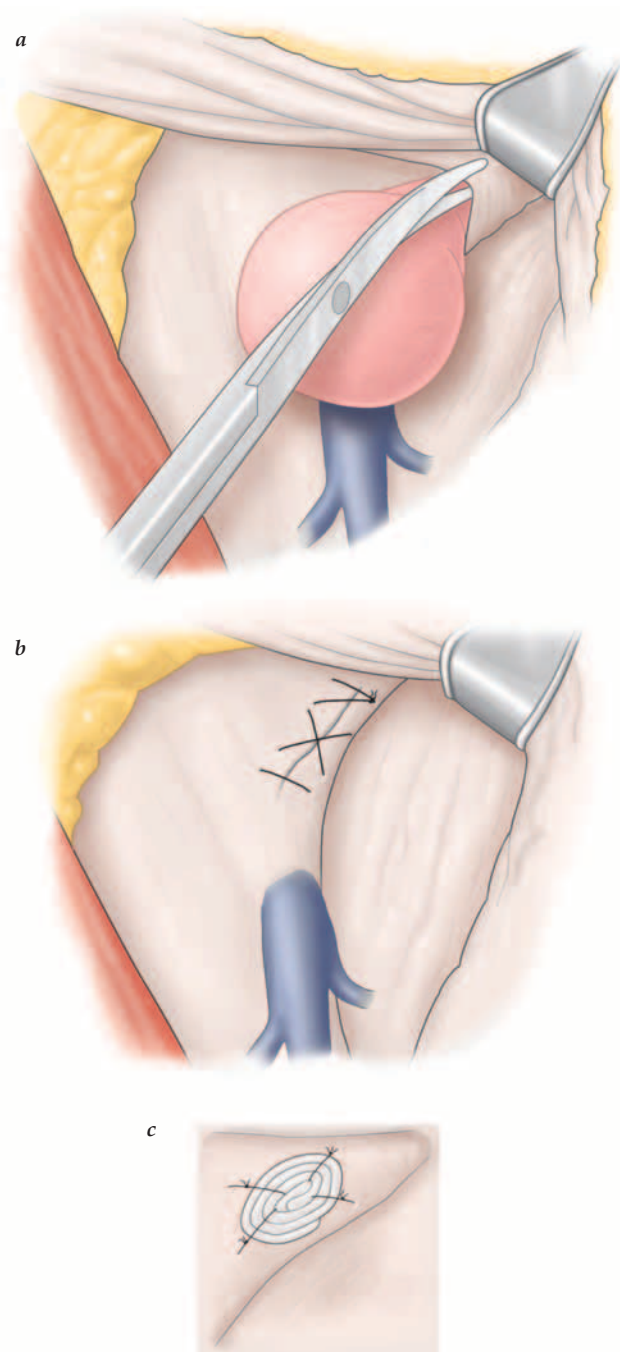


Figure 11 Femoral hernia repair in females. The femoral canal is opened by dividing the inguinal ligament, the lacunar ligament, or both to allow for reduction of the hernia contents (a). The repair is then accomplished with sutures (b) or a mesh plug (c).

various procedures as all the repairs involve placement of a large prosthesis in the preperitoneal space. The theoretical advantage of this measure is that whereas in a conventional repair, abdominal pressure might contribute to recurrence, in a preperitoneal repair, the abdominal pressure would help fix the mesh material against the abdominal wall, thereby adding strength to the repair.

The preperitoneal space may be entered using an open or laparoscopic approach. The two principal laparoscopic techniques are the TAPP and TEP laparoscopic repairs. Although the laparoscopic repairs are the most prevalent posterior repairs at this time, the major open approaches are also described.

TAPP Repair

Step 1: trocar placement Pneumoperitoneum is established through a small infraumbilical incision. We generally prefer an open technique, in which a blunt-tipped 12 mm trocar is inserted into the peritoneal cavity under direct vision. CO₂ is then insufflated into the abdomen to a pressure of 12 to 15 mm Hg. The angled laparoscope is introduced, and both inguinal areas are inspected. Two 5 mm ports are placed, one at the lateral border of each rectus abdominis at the level of the umbilicus.

Step 2: identification of anatomic landmarks Four important landmarks should be seen initially during laparoscopic inspection of the inguinal region: the spermatic vessels, the obliterated umbilical artery (also referred to as the medial umbilical ligament or the bladder ligament), the inferior epigastric vessels (also referred to as the lateral umbilical ligament), and the external iliac vessels [see Figure 3]. In the TAPP approach, an indirect hernia, if present, will be immediately apparent and will have an obvious opening. The internal inguinal ring is then easily identified by the presence of a discrete hole lateral to the junction of the vas deferens, the testicular vessels, and the inferior epigastric vessels. Identification of a direct hernia can be more difficult. Sometimes a direct hernia appears as a complete circle or hole; at other times, it appears as a cleft, medial to the vas deferens-vascular junction; and at still other times, it is completely hidden by preperitoneal fat and the bladder and umbilical ligaments. Visualization can be particularly difficult in obese patients, who may have considerable lipomatous tissue between the peritoneum and the transversalis fascia, or in patients whose hernia consists of a weakness and bulging of the entire inguinal floor rather than a distinct sac.

For adequate definition of this type of hernia and deeper anatomic structures, the peritoneum must be opened, a peritoneal flap developed, and the underlying fatty layer dissected.²² Traction on the ipsilateral testicle can demonstrate the vas deferens when visualization is obscured by overlying fat or pressure from the pneumoperitoneum.

Step 3: creation of peritoneal flap The curved scissors or the hook cautery is used to create a peritoneal flap by making a transverse incision along the peritoneum, beginning several centimeters above the upper border of the internal inguinal ring and extending medially above the pubic tubercle and laterally at least 5 cm beyond the internal inguinal ring or to the level of the ipsilateral trocar [see Figure 12]. Care must be taken to avoid the inferior epigastric vessels. Bleeding from these vessels can usually be controlled by cauterization, but application of hemostatic clips may be necessary on occasion. Another solution is to pass percutaneously placed sutures above and below the bleeding point while applying pressure to the bleeding vessel so as not to obscure the field of vision. Division of the ipsilateral umbilical ligament may be useful in creating an appropriate medial space; however, the surgeon should be aware that the obliterated umbilical artery may still be patent and that use of the electrocautery or clips is prudent.

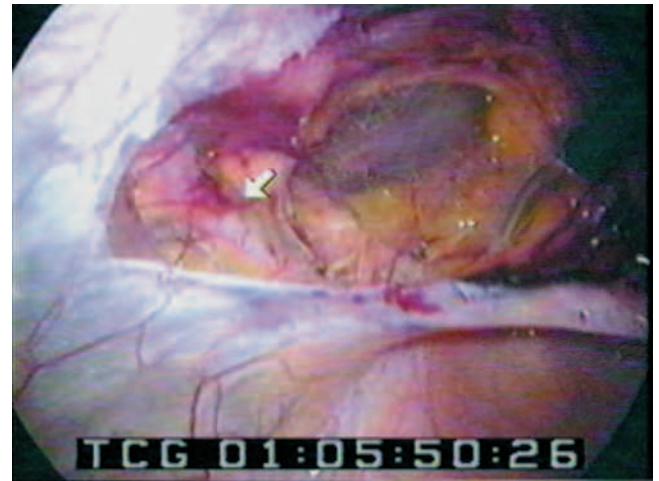


Figure 12 Laparoscopic inguinal hernia repair, TAPP approach, left-sided direct hernia. A flap of peritoneum is dissected downward, revealing a hernial defect and the inferior epigastric vessels (arrow).

The incised peritoneum is grasped along with the attached preperitoneal fat and the peritoneal sac and is dissected cephalad with blunt and sharp instruments to create a lower peritoneal flap. Dissection should stay close to the abdominal wall. A significant amount of preperitoneal fat may be encountered, and this should remain with the peritoneal flap so that the abdominal wall is cleared. When the correct preperitoneal plane is entered, dissection is almost bloodless and is easily carried out.

Step 4: dissection of hernia sac The hernia sac, if present, is removed from the Hesselbach triangle or the spermatic cord and surrounding muscle through inward traction, countertraction, and blunt dissection with progressive inversion of the sac until the musculofascial boundary of the internal inguinal ring and the key deep anatomic structures are identified. In most cases, the hernia sac can be slowly drawn away from the transversalis fascia or the spermatic cord [see Figure 13]. The indirect sac may be visualized more easily if it is grasped and retracted medially; this step facilitates its dissection away from the cord structures.

Spermatic cord lipomas usually lie posterolaterally and are extensions of preperitoneal fat. In the presence of an indirect defect, such lipomas should be dissected off the cord along with the peritoneal flap to lie cephalad to the internal inguinal ring and the subsequent repair so that prolapse through the ring can be prevented. A large indirect hernia sac can be divided at the internal ring if it cannot be readily dissected away from the cord structures. This step may prevent cord injury that can result from extensive dissection.

The pubic tubercle is often more easily felt than seen. The Cooper ligament is initially felt and subsequently seen along the pectineal prominence of the superior pubic ramus as dissection continues medially and fatty tissue is swept off to expose the glistening white structure. Care must be taken to avoid the numerous small veins that often run on the surface of the ligament, as well as to avoid the occasional aberrant obturator artery. The iliopubic tract is initially identified at

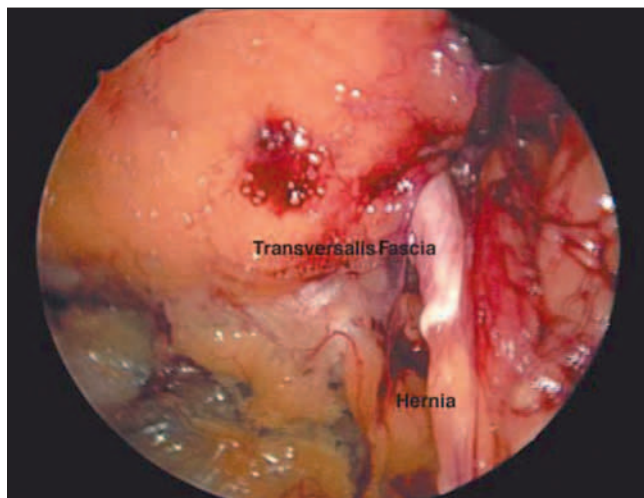


Figure 13 Laparoscopic inguinal hernia repair: transversalis fascia. The transversalis fascia is seen adherent to the hernia sac. The sac must be separated from the fascia and dissected cephalad.

the inferior margin of the internal inguinal ring, with the spermatic cord above, and is then followed in both a medial and a lateral direction. Minimal dissection is carried out inferior to the iliopubic tract so as to avoid neurovascular injuries.

Step 5: mesh placement A 15 × 10 cm sheet of polypropylene or polyester mesh is rolled into a tubular shape and introduced into the abdomen through the 10/12 mm umbilical trocar. The mesh is used to cover the direct, indirect, and femoral spaces (i.e., the entire inguinal floor).

A multifire spiral tacker is used to secure the mesh, beginning medially and proceeding laterally. Medially, tacks are placed in the Cooper ligament. A two-handed technique is recommended for lateral tack placement: one hand is on the tacker, and the other is on the abdominal wall, applying external pressure to place the wall against the tacker. Care must be taken not to force the tacker too deeply into the abdominal wall superolateral to the spermatic cord; doing so might lead to inadvertent entrapment of the sensory nerves. The tacker can be moved from the left to the right port, depending on which position more readily allows placement of the staples perpendicular to the mesh and the abdominal wall. Lateral to the cord structures, all tacks are placed superior to the iliopubic tract to prevent subsequent neuralgias involving the lateral cutaneous nerve of the thigh or the branches of the genitofemoral nerve. If the surgeon can palpate the tacker through the abdominal wall with the non-dominant hand, the tacker is above the iliopubic tract. The mesh should lie flat.

Step 6: closure The peritoneal flap, including the redundant inverted hernia sac, is placed over the mesh, and the peritoneum is reapproximated with the tacker along its superior edge [see Figure 14]. Inferior epigastric vessels must be avoided. Reduction of the intra-abdominal pressure to 8 mm Hg, coupled with external abdominal wall pressure, facilitates a tension-free reapproximation. The peritoneal repair is inspected to ensure that there are no major gaps that might result in exposure of the mesh and subsequent formation of adhesions. The trocars are then removed under direct vision,

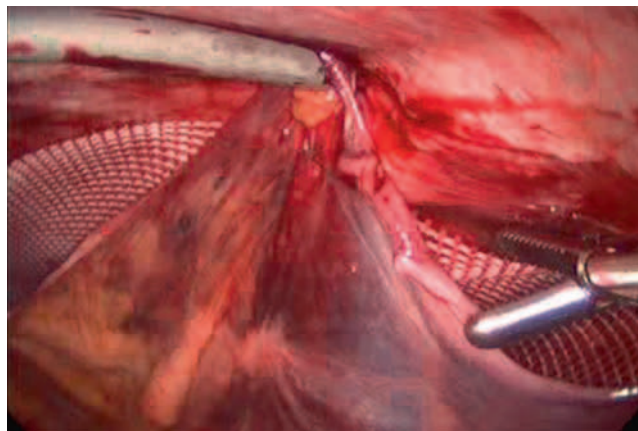


Figure 14 Laparoscopic inguinal hernia repair: peritoneal flap. The peritoneal flap is placed so as to entirely cover the mesh in the preperitoneal space.

and the pneumoperitoneum is released. The fascia at the 10/12 mm port sites is sutured closed, and the skin is closed with 4-0 absorbable subcuticular sutures.

TEP Repair

The extra-abdominal preperitoneal approach to laparoscopic hernia repair, developed by McKernan and Laws,^{23,24} attempts to duplicate the open preperitoneal repair described by Stoppa and colleagues²⁵⁻²⁷ and Wantz.^{8,28} In a TEP repair, the trocars are placed preperitoneally in a space created between the fascia and the peritoneum. Ideally, the dissection remains in the extra-abdominal plane at all times, and the peritoneum is never penetrated.

Step 1: creation of preperitoneal space With the patient in the Trendelenburg position, the anterior rectus fascia is opened through a 1 cm infraumbilical transverse incision placed slightly toward the side of the hernia, which helps prevent inadvertent opening of the peritoneum. The rectus is retracted laterally and a narrow retractor is slid over the posterior rectus sheath. In this plane, a preperitoneal tunnel between the rectus muscles and the peritoneum is created in the midline by inserting a dissecting balloon to the level of the symphysis pubis. The preperitoneal working space is developed by gradual inflation of the balloon to a volume of 1 L or until the creases in the balloon are effaced. This is done under direct vision using a 30° or 45° laparoscope as the transparency of the balloon permits constant laparoscopic visualization throughout the distention process. The balloon is then withdrawn and replaced with a 10/12 mm balloon-tipped trocar. Maximal inflation pressure is 10 to 15 mm Hg to prevent disruption of the peritoneum or development of extensive subcutaneous emphysema. Blunt, gentle dissection with the laparoscope can be employed to develop the space sufficiently to allow placement of additional trocars [see Figure 15].

Step 2: trocar placement After the peritoneum is dissected away from the rectus abdominis, a midline 5 mm trocar is inserted under direct vision three fingerbreadths below the infraumbilical port. A second 5 mm trocar is then

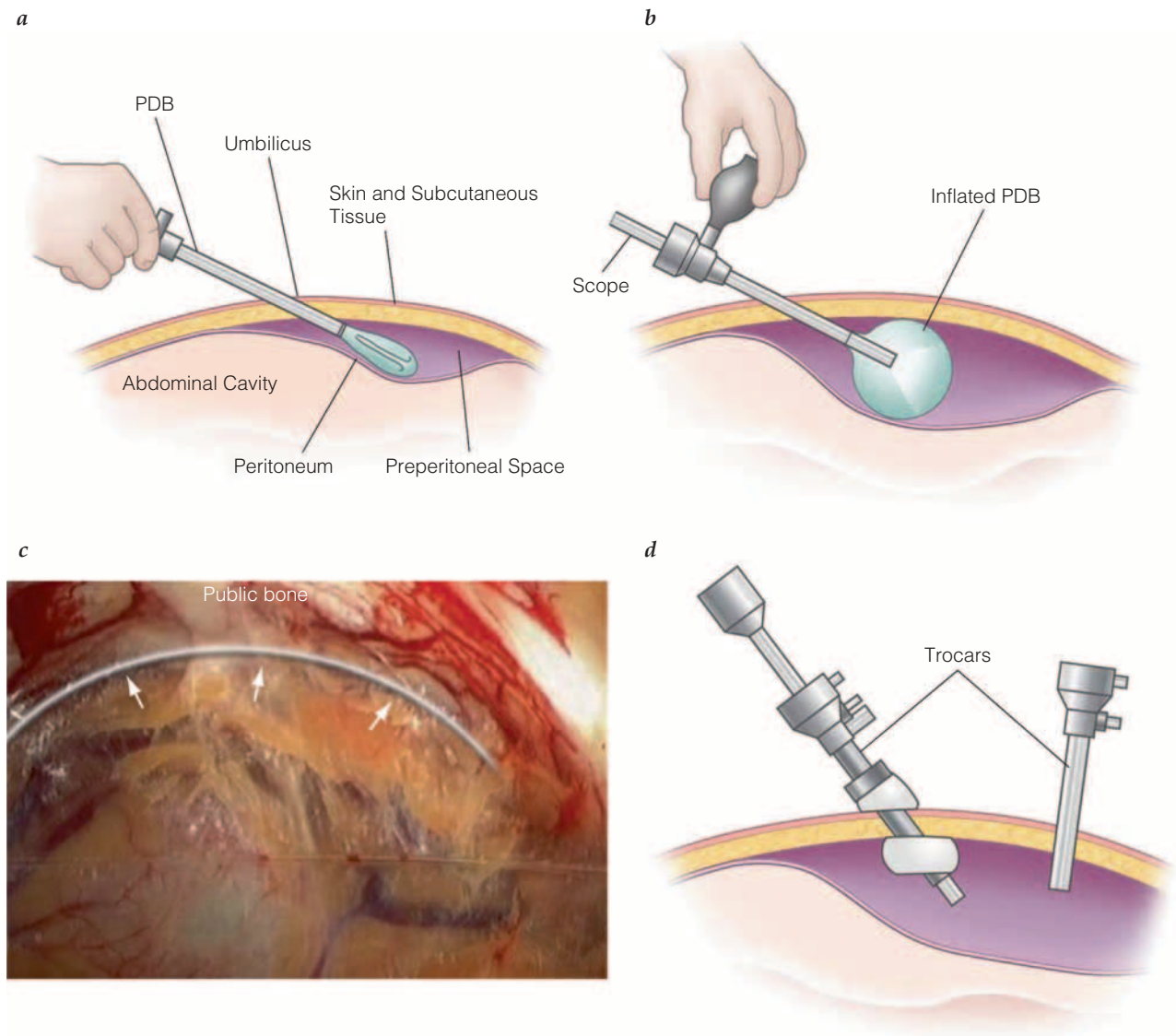


Figure 15 Laparoscopic inguinal hernia repair: TEP approach. Shown is the preperitoneal distention balloon (PDB) system. The balloon is introduced into the preperitoneal space (a). As it is tunneled inferiorly toward the pubis, the balloon is inflated under laparoscopic vision (b). As the balloon is inflated, the pubic bone and peritoneal edge come into view (line and arrows) (c). Once the preperitoneal space is created, the balloon is removed and replaced with a blunt-tipped trocar. The preperitoneal space is insufflated under low pressure, additional trocars are placed, and the repair is begun (d).

inserted another three fingerbreadths below the first 5 mm trocar. Placement of the working trocars away from the pubis facilitates mesh placement in that the bottom port is not covered by the top of the mesh and thereby rendered nonfunctional. Care must be taken not to penetrate the peritoneum during trocar placement. If the peritoneum is penetrated, the resulting pneumoperitoneum can reduce the already limited working space. If the working space is compromised to the point where the repair cannot continue (which is not always the case), the surgeon can either try to repair the rent with a suture or place a Veress needle or angiocath in the upper abdominal peritoneal cavity. If such maneuvers are unsuccessful, the loss of working space may necessitate conversion to a TAPP approach.

Step 3: dissection of hernia sac The inferior epigastric vessels, which help guide lateral dissection and identification of the internal ring, are identified first and are kept up against the abdominal wall during peritoneal dissection. The Cooper ligament is exposed first, during which care must be taken not to injure the obturator branch that crosses it [see Figure 16]. Wide lateral dissection of the preperitoneal space is then undertaken with blunt graspers in a two-handed technique by bluntly dividing the avascular areolar tissue between the peritoneum and the abdominal wall. Proper lateral dissection is crucial to optimal mesh placement.

If a direct hernia is present medial to the inferior epigastric vessels, it will often be reduced by the balloon dissector. If not, the sac and the preperitoneal contents are carefully

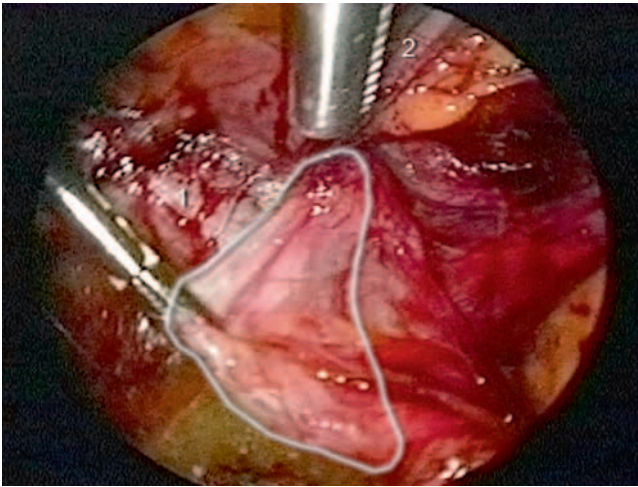


Figure 16 Laparoscopic inguinal hernia repair: TEP approach, right-sided indirect hernia. The principal landmarks are the Cooper ligament (1) and the inferior epigastric vessels (2). The indirect sac (outlined in the image) is adherent to the cord structures entering the internal ring.

dissected away from the fascial defect and swept cephalad as far as possible. Gentle traction is applied to expose and dissect away the attachment of the peritoneum to the transversalis fascia.

The indirect space is then exposed by sweeping off the tissue lateral to the inferior epigastric vessels until the peritoneum is found. If a lipoma of the cord is present, it will be lateral to and covering the peritoneum and should be dissected out of the internal ring in a cephalad direction to prevent it from displacing the mesh.²⁹ If there is no indirect hernia, the peritoneum will be found cephalad to the internal ring. To ensure secure mesh placement, the peritoneum is bluntly dissected off the cord structures and placed as far cephalad as possible. If an indirect hernia is present, the sac will be lateral and anterior to the cord structures. These must be clearly identified and protected during dissection. A small indirect hernial sac is bluntly dissected off the spermatic cord with a hand-over-hand technique and reduced until an area sufficient for mesh placement is created. To prevent early recurrence, all attachments of the peritoneum should be dissected cephalad to where the inferior edge of the mesh will be. If a large indirect sac is not easily reduced from the scrotum, it may be transected in its superolateral edge, dissected off the cord structures, and closed with clips or a ligating loop. The distal sac is then left in place without ligation.

Unlike a TAPP repair, in which any indirect hernia present is readily apparent at first inspection, a TEP repair always requires that the space lateral to the inferior epigastric vessels be dissected to make sure that there is no indirect component. This dissection should be done even if a direct or femoral hernia is identified.

Step 4: mesh placement A number of different prostheses in a variety of contoured or flat configurations are available, including various forms of polypropylene and several types of polyester. Whichever is chosen, it should be large enough (15 × 10 cm) to provide adequate coverage. A marking suture

is placed or a mark is made to identify the inferomedial aspect of the mesh to be placed against the Cooper ligament. The mesh is wrapped around a grasper in a tubular fashion and then inserted through the umbilical trocar into the preperitoneal space. Once in the preperitoneal space, the mesh is manipulated to cover the pubic tubercle, the internal ring, the Cooper ligament, the femoral canal, and the rectus abdominis superiorly. The inferior edge of the mesh must be tucked behind the peritoneal reflection to prevent folding of the mesh [see Figure 17]. Tacks are placed into the Cooper ligament and on the superolateral edge of the mesh on the anterior abdominal wall. To prevent nerve injury, no tacks should be placed inferior to the iliopubic tract lateral to the internal ring.

Step 5: closure The operative site is inspected for hemostasis. The trocars are removed under direct vision. The insufflated CO₂ is slowly released so that the mesh may be visualized as the preperitoneal fat and contents collapse back

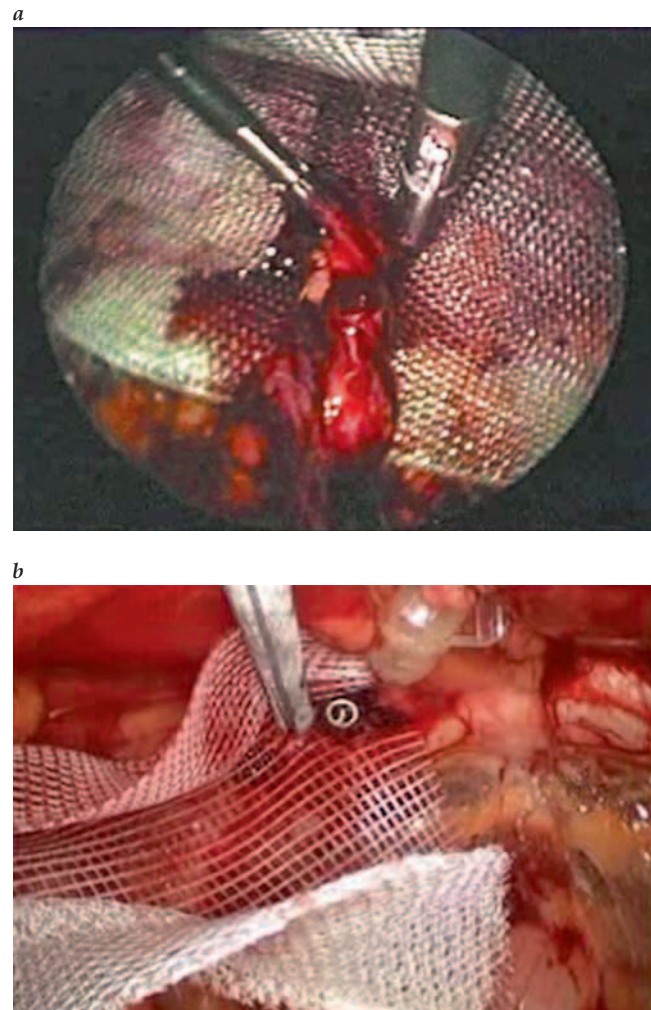


Figure 17 Laparoscopic inguinal hernia repair: TEP approach. (a) The mesh is oriented to cover the direct, indirect, and femoral spaces. The dissected sac is placed over the mesh to reduce the chance that the sac will slide under the mesh and cause a recurrence of the hernia. (b) Tacks are placed into the Cooper ligament to fix the mesh medially.

onto the mesh. The fascia at trocar sites 10 mm or larger is sutured closed, and the skin is closed with subcuticular sutures.

OPEN POSTERIOR PROSTHETIC REPAIRS

For open access, the space can be entered either anteriorly or posteriorly. If an anterior technique is to be used, the initial steps of the operation are similar to those of a conventional anterior herniorrhaphy. If a posterior technique is to be used, any of several incisions (lower midline, paramedian, or Pfannenstiel) will allow an extraperitoneal dissection. The preperitoneal space can also be entered transabdominally. This approach is useful when the patient is undergoing a laparotomy for some other condition and the hernia is to be repaired incidentally.

Read-Rives Repair

The posterior space is accessed directly through the groin; thus, the initial part of a Read-Rives repair, including the opening of the inguinal floor, is much like that of a classic Bassini repair. The inferior epigastric vessels are identified, and the preperitoneal space is completely dissected. The spermatic cord is parietalized by separating the ductus deferens from the spermatic vessels. A 12 × 16 cm piece of mesh is positioned in the preperitoneal space deep to the inferior epigastric vessels and secured with three sutures placed in the pubic tubercle, in the Cooper ligament, and in the psoas muscle laterally. The transversalis fascia is closed over the prosthesis, and the cord structures are replaced.

Stoppa-Rignault-Wantz Repair (Giant Prosthetic Reinforcement of Visceral Sac)

Giant prosthetic reinforcement of the visceral sac (GPRVS) has its roots in the important contribution that Henri Fruchaud, who was Stoppa's mentor, made to herniology. Instead of subdividing hernias into direct, indirect, and femoral and then examining their specific causes, Fruchaud emphasized that the common cause of all inguinal hernias was the failure of the transversalis fascia to retain the peritoneum. This concept led Stoppa to develop GPRVS, which reestablishes the integrity of the peritoneal sac by inserting a large permanent prosthesis that entirely replaces the transversalis fascia over the myopectineal orifice of Fruchaud [see Figure 18] with wide overlapping of surrounding tissue. The technique has not gained routine acceptance in North America, however.

Step 1: skin incision A lower midline, Pfannenstiel, or inguinal incision can be used. The inguinal incision is placed 2 to 3 cm below the level of the anterosuperior iliac spine but above the internal ring; it is begun at the midline and extended laterally for 8 to 9 cm.³⁰

Step 2: preperitoneal dissection The fascia overlying the space of Retzius is opened without violation of the peritoneum. A combination of blunt and sharp dissection is continued laterally posterior to the rectus abdominis and the inferior epigastric vessels. The preperitoneal space is completely dissected to a point lateral to the anterosuperior iliac spine. The symphysis pubis, the Cooper ligament, and the iliopubic tract are identified. Inferiorly, the peritoneum is generously dissected away from the vas deferens and the internal spermatic vessels to create a large pocket, which will

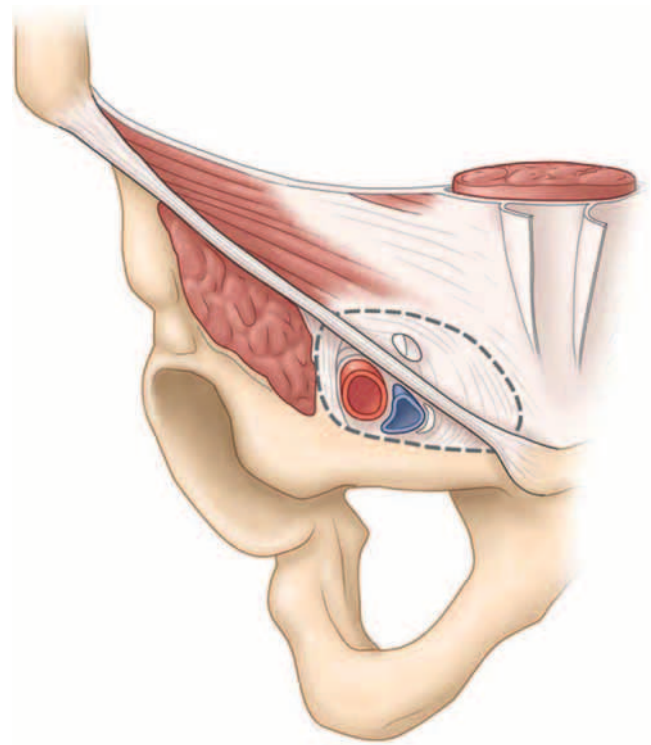


Figure 18 Depicted is the myopectineal orifice of Fruchaud. The area is bounded superiorly by the internal oblique muscle and the transversus abdominis, medially by the rectus abdominis and the rectus sheath, laterally by the iliopsoas muscle, and inferiorly by the Cooper ligament. Critical anatomic landmarks (e.g., the inguinal ligament, the spermatic cord, and the femoral vessels) are contained within this structure.

eventually accommodate a prosthesis. In the inguinal approach, the anterior rectus sheath and the oblique muscles are incised for the length of the skin incision. The lower flaps of these structures are retracted inferiorly toward the pubis. The transversalis fascia is incised along the lateral edge of the rectus abdominis, and the preperitoneal space is entered; dissection then proceeds as previously indicated.

Step 3: management of hernial sac Direct hernial sacs are reduced during the course of the preperitoneal dissection. Care must be taken to stay in the plane between the peritoneum and the transversalis fascia, allowing the latter structure to retract into the hernia defect toward the skin.

Indirect sacs are more difficult to deal with than direct sacs are in that they often adhere to the cord structures. Trauma to the cord must be minimized to prevent damage to the vas deferens or the testicular blood supply. Small sacs should be mobilized from the cord structures and reduced back into the peritoneal cavity. Large sacs may be difficult to mobilize from the cord without undue trauma if an attempt is made to remove the sac in its entirety. Accordingly, large sacs should be divided, with the distal portion left in situ and the proximal portion dissected away from the cord structures. Division of the sac is most easily accomplished by opening the sac on the side opposite the cord structures. A finger is placed in the sac to facilitate its separation from the cord. Downward traction is then placed on the cord structures to reduce any

excessive fatty tissue (so-called lipoma of the cord) back into the preperitoneal space. This step prevents the “pseudorecurrences” that may occur if the abnormality palpated during the preoperative physical examination was not a hernia but a lipoma of the cord.

Step 4: management of abdominal wall defect This step varies most from one author to another. In Nyhus’s approach, the defect is formally repaired, and only then is a tailored mesh prosthesis sutured to the Cooper ligament and the transversalis fascia for reinforcement. Rignault prefers to close the defect loosely to prevent an unsightly early postoperative bulge.³¹ In Stoppa’s and Wantz’s technique,^{26,28} the defect is usually left alone, but the transversalis fascia in the defect is occasionally plicated by suturing it to the Cooper ligament to prevent the bulge caused by a seroma in the undisturbed sac.

Step 5: parietalization of spermatic cord The term *parietalization of the spermatic cord*, popularized by Stoppa,²⁶ refers to a thorough dissection of the cord aimed at providing sufficient length to permit lateral movement of the structure [see Figure 19]. In Stoppa’s view, this step is essential in that it allows a prosthesis to be placed without having to be split laterally to accommodate the cord structures;²⁶ the keyhole defect created when the prosthesis is split has been linked with recurrences. In Rignault’s opinion,³¹ creation of a keyhole defect in the mesh to encircle the spermatic cord is preferable, the rationale being that this gives the prosthesis enough security to allow the surgeon to dispense with fixation sutures

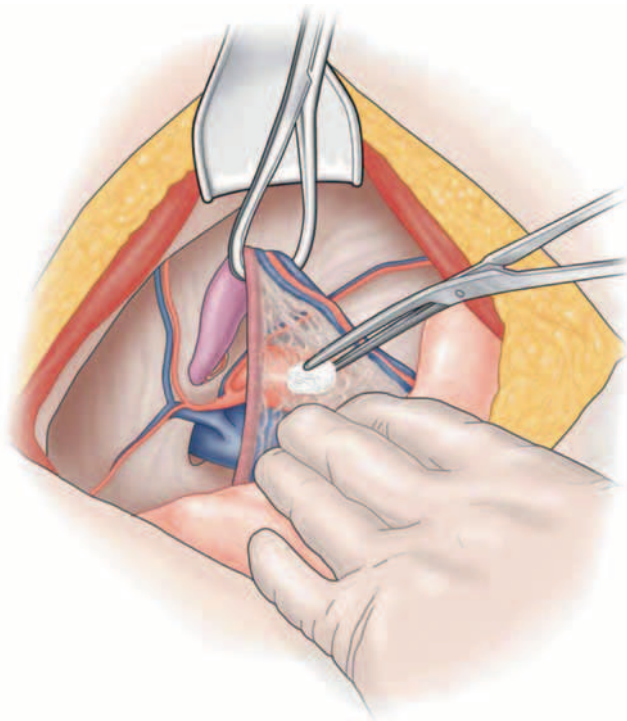


Figure 19 Preperitoneal inguinal prosthetic herniorrhaphy. Illustrated is parietalization of the spermatic cord. The spermatic vessels and the vas deferens are mobilized so that they move laterally. This step is carried out so that the surgeon can place a large prosthesis that widely overlaps the myopectineal orifice without having to slit the prosthesis to accommodate the cord structures.

or tacks. Minimizing fixation in this area is important because of the numerous anatomic elements in the preperitoneal space that can be inadvertently damaged during suture placement.

Step 6: placement of prosthesis Stoppa’s technique is most often associated with a single large prosthesis for bilateral hernias.²⁶ The prosthesis is cut in the shape of a chevron (24 cm in length), and eight clamps are positioned strategically around the prosthesis to facilitate placement into the preperitoneal space.

Unilateral repairs use a prosthesis that is approximately 15 × 12 cm but is cut so that the bottom edge is wider than the top edge and the lateral side is longer than the medial side. In Wantz’s technique,²⁸ three absorbable sutures are used to attach the superior border of the prosthesis to the anterior abdominal wall well above the defect [see Figure 20]. The sutures are placed from medial to lateral near the linea alba, the semilunar line, and the anterosuperior iliac spine. Three long clamps are then placed on each corner and the middle of the prosthesis of the inferior flap and used to direct the mesh deep into the preperitoneal space with the peritoneal sac pushed cephalad.

Step 7: closure of wound The surgical wound is closed anatomically once the surgeon is assured that there has been no displacement or roll-up of the prosthesis.

Kugel and Ugahary Repairs

The Kugel and Ugahary repairs were developed to compete with laparoscopic repairs. They require only a small (2 to 3 cm) skin incision placed 2 to 3 cm above the internal ring.^{32,33} In Kugel’s operation, the incision is oriented obliquely, with one third of the incision lateral to a point halfway between the anterosuperior iliac spine and the pubic tubercle and the remaining two thirds medial to this point. The incision is deepened through the external oblique fascia, and the internal oblique muscle is bluntly spread apart. The transversalis fascia is opened vertically for a distance of about 3 cm, but the internal ring is not violated. The preperitoneal space is entered, and a blunt dissection is performed. The inferior epigastric vessels are identified to confirm that the dissection is being done in the correct plane. These vessels should be left adherent to the overlying transversalis fascia and retracted medially and anteriorly. The iliac vessels, the Cooper ligament, the pubic bone, and the hernia defect are identified by palpation. Most hernial sacs are simply reduced; the exceptions are large indirect sacs, which must sometimes be divided, with the distal sac left in situ and the proximal sac closed. To prevent recurrences, the cord structures are thoroughly parietalized to allow adequate posterior dissection.

The key to Kugel’s procedure is a specially designed 8 × 12 cm prosthesis. The construction of the prosthesis allows it to be deformed so that it can fit through the small incision; once inserted, it springs open to regain its normal shape, providing a wide overlap of the myopectineal orifice. The prosthesis also has a slit on its anterior surface, through which the surgeon places a finger to facilitate positioning.

Ugahary’s operation is similar to Kugel’s, but it does not require a special prosthesis. In what is known as the gridiron technique, the preperitoneal space is prepared through a 3 cm incision, much as in a Kugel repair. The space is held open with a narrow Langenbeck retractor and two ribbon

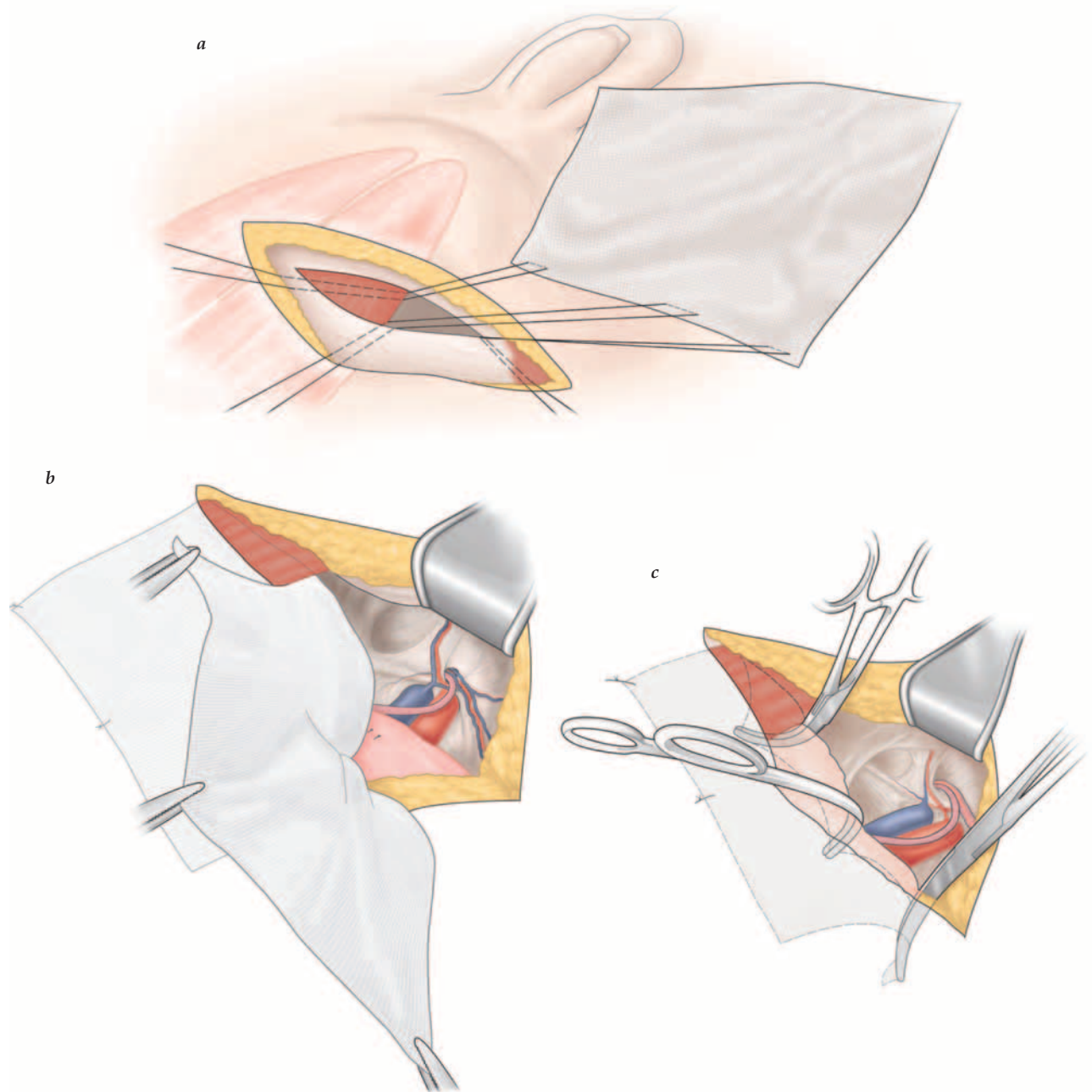


Figure 20 Unilateral giant prosthetic reinforcement of the visceral sac (Wantz technique). (a, b) The prosthesis is cut so that the inferior edge is wider than the superior edge by 2 to 4 cm and the lateral side is longer than the medial side. The width at the superior edge is approximately the distance between the umbilicus and the anterosuperior iliac spine minus 1 cm, and the height is approximately 14 cm. Anteriorly, three sutures are placed—near the linea alba, near the semilunar line, and near the anterosuperior iliac spine—from medial to lateral to fix the superior border. (c) Three long clamps on the inferior edge are used to implant the prosthesis deep into the preperitoneal space with the peritoneal sac retracted cranially.

retractors. A 10 × 15 cm piece of polypropylene mesh is rolled onto a long forceps after the edges have been rounded and sutures placed to correspond to various anatomic landmarks. The forceps with the rolled-up mesh on it is introduced into the preperitoneal space, and the mesh is unrolled with the help of clamps and specific movements of the ribbon retractors.

COMBINED ANTERIOR AND POSTERIOR (PREPERITONEAL) HERNIORRHAPHY

Bilayer Prosthetic Repair

The bilayer prosthetic repair involves the use of a dumbbell-shaped prosthesis consisting of two flat pieces of polypropylene mesh connected by a cylinder of the same material.

The purpose of this design is to allow the surgeon to take advantage of the presumed benefits of both anterior and posterior approaches by placing prosthetic material in both the preperitoneal space and the extraperitoneal space.

The initial steps are identical to those of a Lichtenstein repair. Once the conventional anterior space has been prepared, the preperitoneal space is entered through the hernia defect. Indirect hernias are reduced, and a gauze sponge is used to develop the preperitoneal space through the internal ring. For direct hernias, the transversalis fascia is opened, and the space between this structure and the peritoneum is developed with a gauze sponge. The deep layer of the prosthesis is deployed in the preperitoneal space, overlapping the direct and indirect spaces and the Cooper ligament. The superficial layer of the device occupies the conventional anterior space, much as in a Lichtenstein repair. It is slit laterally or centrally to accommodate the cord structures and then affixed to the area of the pubic tubercle, the middle of the inguinal ligament, and the internal oblique muscle with three or four interrupted sutures.

Complications

RECURRENCE

An analysis of nearly 18,000 herniorrhaphies in Sweden reported that 15% of operations were performed to treat recurrent hernias.³⁴ This figure is remarkably consistent with the data from other large population-based series and is influenced by the type of repair, type of hernia (primary versus recurrent), patient characteristics, and surgeon characteristics (hernia specialist or not). The use of mesh is an important factor, with a Cochrane meta-analysis of open mesh inguinal hernia repair versus open nonmesh repair finding that tension-free mesh repair led to a significant reduction in hernia recurrence of between 50 and 75%.¹⁴ Two randomized trials using the Lichtenstein repair as the control operation documented 2-year recurrence rates between 1 and 4%, setting a benchmark for primary inguinal hernia repair.^{35,36}

Similar low recurrence rates have been demonstrated regardless of the technique of mesh placement, whether laparoscopic or open.^{37,38} On the other hand, a large, randomized, multicenter Veterans Affairs (VA) study found that for primary, unilateral hernias, the laparoscopic approach was associated with a higher overall recurrence rate at 2 years (10%) when compared to open mesh repair (4%).³⁶ Most reported recurrences after laparoscopic herniorrhaphy come at an early stage in the surgeon's experience with these procedures and arise soon after operation.^{36,39} The majority can be attributed to (1) inadequate preperitoneal dissection; (2) use of an inadequately sized patch, which may migrate or fail to support the entire inguinal area, including direct, indirect, and femoral spaces; or (3) staple failure with TAPP repair.

PAIN

Chronic postoperative groin pain is one of the major complications facing patients undergoing inguinal hernia repairs. Although some degree of postoperative groin pain is experienced by as many as 53% of patients,⁴⁰ significant long-term pain is probably seen in 5 to 15% of patients,^{36,37,41} regardless of whether the nerves were divided or preserved.⁴² Persistent

pain and burning sensations in the inguinal region, the upper medial thigh, or the spermatic cord and scrotal skin region occur when the genitofemoral nerve or the ilioinguinal nerve is stimulated, entrapped, or unintentionally injured. When the lateral cutaneous nerve is involved, lateral or central upper medial thigh numbness is experienced and often lasts several months or longer. Unlike patients who undergo open anterior herniorrhaphy, in whom discomfort or numbness is usually localized to the operative area, patients who undergo laparoscopic repair occasionally describe unusual but specific symptoms of deep discomfort that are usually positional and are often of a transient, shooting nature suggestive of nerve irritation. Postoperative chronic pain is more likely to be observed in younger patients and in patients who report preoperative pain attributable to their hernia, but other risk factors have also been identified. In general, patients seem to report less postoperative pain after laparoscopic repair.^{10,33–47}

When confronted with this complication, recurrence must be ruled out. Usually, this can be done by physical examination with or without the use of ultrasonography. A cord lipoma, sometimes left in place following laparoscopic repair, should be distinguished from a recurrence. If pain is felt to be neuropathic in origin, it is best treated initially with reassurance and conservative treatment, such as antiinflammatory medications and local nerve blocks. Reexploration is avoided in the first year after the procedure to allow for the possibility of spontaneous resolution. The only exception to this rule is the patient with severe groin pain in the recovery room, who is best treated with immediate reexploration.⁴⁸ When groin exploration is required, neurectomy and neuroma excision, adhesiolysis, muscle or tendon repair, and foreign body removal are all possibilities, with less than satisfying results.

GENITOURINARY TRACT COMPLICATIONS

Urinary tract infection and hematuria may be seen especially if bladder catheterization was used. Urinary retention still occurs in 1.5 to 3% of patients.³⁶ Spinal anesthesia and the administration of large volumes of IV fluids may also predispose to retention.¹²

Ischemic Orchitis

Wantz believed that the most common cause of postoperative testicular swelling, orchitis, and ischemic atrophy is surgical trauma to the testicular veins (i.e., venous congestion and subsequent thrombosis).⁴⁹ Orchitis is defined as postoperative inflammation of the testicle occurring within the first 2 postoperative days. Testicular pain occurs in about 1% of patients after laparoscopic repair,⁵⁰ an incidence comparable to that seen after open repair.^{36,45} Patients experience painful enlargement and hardening of the testicle, usually associated with a low-grade fever; the pain is severe and may last several weeks but is usually self-limited. Because spermatic cord dissection is minimized with the laparoscopic approach, the risk of groin and testicular complications resulting from injury to cord structures and adjacent nerves may be reduced.³⁶ The vast majority of patients who experience testicular complications go on to recover without atrophy, which probably occurs in less than 0.04% of primary inguinal hernia repairs and less than 0.5% of recurrent hernia repairs.⁴⁵

Vas Deferens Injuries

The risk of injury to the vas deferens appears to be much the same in laparoscopic repair as in open repair.³⁷ If fertility is an issue, the cut ends should be reapproximated if the injury is recognized intraoperatively.

Urinary Tract Injuries

Bladder injuries necessitating repair have been reported in only a handful of cases following laparoscopic herniorrhaphy.^{43,51,52} They are most likely to occur when the space of Retzius has been previously dissected (e.g., in a prostatectomy). In such cases, an in-dwelling catheter may be useful to help identify the bladder and avoid injuring it. Although indwelling catheter drainage may constitute sufficient treatment of a missed retroperitoneal bladder injury, intraperitoneal injuries are best treated by direct repair. Renal and ureteral injuries identified intraoperatively should be repaired immediately. Often, however, these injuries are not apparent until the postoperative period, when they present as lower abdominal pain, renal failure, ascites, dysuria, or hematuria—all of which should be investigated promptly.

VASCULAR INJURIES

Postherniorrhaphy bleeding is usually the result of delayed bleeding from the cremasteric artery, the internal spermatic artery, or branches of the inferior epigastric vessels. This bleeding is usually self-limited but can produce an impressive wound or scrotal hematoma, which usually resolves over time. Injuries to the deep circumflex artery or the external iliac vessels may result in a large retroperitoneal hematoma. During laparoscopic repairs, the most common vascular injuries occurring are those involving the inferior epigastric vessels and the spermatic vessels.³⁷ The external iliac, circumflex iliac, profunda, and obturator vessels are also at risk. A previous lower abdominal operation is a risk factor.⁴⁸ The source of any abnormal bleeding during the procedure must be quickly identified. All vessels in the groin can be ligated except the external iliac vessels, which must be repaired.³⁷ Conversion of a laparoscopic procedure for bleeding is rare and occurs in less than 3% of cases.⁴⁸

MESH COMPLICATIONS

Infection

Mesh infection is rare. In a 2003 Cochrane review of antibiotic prophylaxis for nonmesh hernia repairs, the overall infection rate was 4.69% in the control group and 3.08% in the treatment group.¹³ Thus, to prevent one infection in 30 days, 50 patients would have to be treated, and these patients would then be at risk for antibiotic-associated complications. Laparoscopic repairs were excluded from this review; however, in a meta-analysis comparing postoperative complications after laparoscopic inguinal hernia repair with those after open repair, superficial infection was less frequent in the laparoscopic groups.³⁷ Deep mesh infection was rare in both groups. Mesh infection usually responds to conservative treatment with antibiotics and drainage. On rare occasions, the mesh must be removed; this may be accomplished via an external approach. If, however, a prosthesis composed of a hydrophobic material (e.g., expanded polytetrafluoroethylene) becomes infected, it is very difficult to sterilize and virtually

always must be removed. It is noteworthy that removal of the mesh does not always lead to recurrence of the hernia, a finding that may be attributable to the resulting fibrosis.⁵³

Adhesions and Erosions

Tissue response, which is variable from person to person, can be so intense that the prosthetic material is deformed by contraction. This can lead to migration with subsequent hernia recurrence. In addition, erosion can result in intestinal obstruction or fistulization, especially if there is physical contact between the intestine and the prosthesis, as is sometimes the case when tears in the peritoneum leave the mesh partially uncovered following preperitoneal repairs.^{54,55} Such complications usually become apparent weeks to years after the initial repair, presenting as abscess, fistula, or small bowel obstruction. Erosion into the cord structures and vas deferens obstruction have also been reported.^{56,57}

PERITONEAL ACCESS COMPLICATIONS

Most randomized trials comparing laparoscopic repair with open mesh repair have found the overall complication rate to be comparable between groups.^{36,37} In general, however, the rate of serious perioperative complications, although still low, is increased with the laparoscopic approach.³⁶ This is probably attributable to injuries related to peritoneal or preperitoneal access. Trocar injuries to the bowel, the bladder, and the vascular structures can occur during the creation of the initial pneumoperitoneum or the subsequent insertion of the trocars.^{37,51} Visceral injury rates reported for the laparoscopic approach, although quite low, are still about 10 times those reported for the open approach.³⁷ Another complication related to trocar placement is incisional hernia,¹⁵ which can lead to postoperative bowel obstruction^{36,37,58}; however, this complication can be minimized by using 5 mm trocars and a 5 mm laparoscope instead of the larger 10 or 12 mm instruments.

Outcomes

In addition to the differences in recurrence rates and postoperative pain discussed in the previous section, other important outcomes are worth mentioning when considering the optimal hernia repair option for a particular patient.

COST-EFFECTIVENESS

A study comparing costs at North American teaching hospitals found that TEP repair cost \$852 more than Lichtenstein repair; however, this study could not quantify the cost savings arising from faster recuperation and earlier reentry into the workforce.⁵⁹ On the other hand, some studies have demonstrated economic savings with the use of a laparoscopic approach, in the form of fewer days of work missed and reduced worker's compensation costs.^{44,50} Operating costs can also be reduced by avoiding the use of disposable instruments.³⁸ In addition, operating time has been shown to decrease as the surgeon's experience with the procedure increases.^{36,60,61}

OPERATING TIME

A Cochrane meta-analysis suggested that overall, the average operating time was 15 minutes longer with the laparoscopic approach; however, for bilateral hernias, laparoscopic repair

required no more time than open repair.³⁷ It has been shown that with more experience and greater specialization, the differences in operating time between laparoscopic and open repair tend to decrease and become clinically unimportant.^{60,62}

RECOVERY TIME

The most significant short-term outcome measure after hernia repair is recovery time, defined as the time required for the patient to return to normal activities. One of the most frequently cited benefits of laparoscopic herniorrhaphy is the patient's more rapid return to unrestricted activity, including work. A Cochrane meta-analysis revealed that recovery time was significantly shorter after laparoscopic repair than after open mesh repair.³⁷ In a cost comparison between TEP repair and Lichtenstein repair, recovery time was 15 days after the former compared with 34 days after the latter.⁵⁹ In the 2004 VA study, laparoscopic repair patients returned to their normal activities 1 day earlier.³⁶

QUALITY OF LIFE

The studies that have assessed quality of life immediately after hernia repair have tended to favor the laparoscopic approach, albeit marginally. Using the SF-36 (a widely accepted general health-related quality-of-life questionnaire), one group found that at 1 month, greater improvements from baseline were apparent in the laparoscopic group in every dimension except general health; however, by 3 months, the differences between the two groups were no longer significant.¹⁰ Another group also found no differences in any SF-36 domains at 3 months after operation.⁵¹ Yet another study, however, using the Sickness Impact Profile, found some benefit to the laparoscopic approach.⁶³ In contrast, no postoperative differences in SF-36 domains were found in the VA study.³⁶

Procedure Selection

ASYMPTOMATIC HERNIAS

The natural history of an untreated, minimally symptomatic inguinal hernia was addressed in a randomized controlled trial in which 364 men were assigned to "watchful waiting" (WW) and 356 men underwent routine operation.³⁶ Only two patients in the WW group required emergency operations for strangulation over the follow-up period of 2 to 4.5 years. This result translated into a rate of 1.8 per 1,000 patient-years (0.18%), or about one fifth of 1% for each year that the hernia remains unrepaired. The two patients who required emergency operations recovered uneventfully. The question that remained to be answered was which group fared better overall, the WW group or the group whose hernias were repaired immediately in accordance with conventional teaching? The answer to this question was at variance with conventional assumptions. At the conclusion of the study, functional status, as measured by quality-of-life instruments and pain scales, was identical in the two groups. About one third of the patients in the WW group crossed over to undergo operative treatment, principally because of symptom progression. However, there appeared to be no penalty for delaying surgery. Before this study, most surgeons assumed that a hernia would become harder to repair the longer it remained (because of enlargement and buildup of scar tissue) and that patients

whose operations were delayed would experience more complications. The investigators found, however, that postoperative complication rates were the same in patients who underwent immediate surgery as in those who were assigned to WW but had to cross over to surgical treatment.

PRIMARY UNILATERAL HERNIAS

For unilateral primary hernias, the most important consideration in choosing an inguinal hernia procedure may well be the experience of the surgeon, with excellent results demonstrated after both open and laparoscopic mesh repairs in experienced hands. The next consideration should be to tailor the operation to the patient's particular hernia. In infants and young children with indirect hernias, for whom repair of the posterior canal wall is unnecessary, high ligation of the sac via the anterior approach is a sufficient procedure but is not adequate in most adults, where a mesh is recommended to decrease recurrence. The conventional anterior prosthetic repairs are particularly useful in high-risk patients because they can be readily performed with local anesthesia, a safer approach than laparoscopic surgery, for which the pneumoperitoneum could result in adverse events. Similarly, we do not treat acutely incarcerated hernias laparoscopically. Large indirect scrotal hernias are another category of challenging laparoscopic cases. Previous lower abdominal surgery, although not an absolute contraindication, may make laparoscopic dissection difficult. In particular, with respect to TEP repair, previous lower abdominal wall incisions may make it impossible to safely separate the peritoneum from the abdominal parietes for entry into the extraperitoneal plane, and conversion to a TAPP repair or an open repair may be required. Previous surgery in the retropubic space of Retzius, as in prostatic procedures, is a relative contraindication that is associated with an increased risk of bladder injury⁴⁸ and other complications.⁶⁴ Similarly, previous pelvic irradiation may preclude safe dissection of the peritoneum from the abdominal wall.³⁰ Finally, if local or systemic infection is present, a nonprosthetic repair is usually considered preferable, although the newer biologic prostheses now being evaluated may eventually change this view.

RECURRENT HERNIAS

In patients with recurrent hernias after previous anterior repair, a laparoscopic or other posterior approach allows the surgeon to avoid the scar tissue and distorted anatomy present in the anterior abdominal wall by performing the repair through unviolated tissue, thereby potentially reducing the risk of damage to the vas deferens or the testicular vessels. This is especially true when mesh has previously been placed anteriorly. Similarly, recurrence following a preperitoneal approach may be more favorably treated with an anterior herniorrhaphy.

BILATERAL HERNIAS

Laparoscopy allows simultaneous exploration of the abdominal cavity (TAPP) and diagnosis and treatment of bilateral groin hernias, as well as coexisting femoral hernias (which are often unrecognized preoperatively), potentially without added risk or disability. Bilateral hernias accounted

for 9% of the hernias reviewed in the Cochrane database.³⁷ Operating time was longer in the laparoscopic groups than in the open groups; however, recovery time, the incidence of persistent numbness, and the risk of wound infection were significantly reduced in the former. These results are consistent with those of a prospective, randomized, controlled trial that compared TAPP repair with open mesh repair for bilateral and recurrent hernias.⁶⁵ In this study, TAPP repair not only was less painful and led to an earlier

return to work but also was associated with a shorter operating time.

Liane S. Feldman, MD, FACS, FRCS, has no commercial relationships with manufacturers of products or providers of services discussed in this chapter.

Simon Bergman, MD, MSc, FRCSC, has no commercial relationships with manufacturers of products or providers of services discussed in this chapter.

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29 INTESTINAL ANASTOMOSIS

Neil J. Mortensen, MD, and Shazad Ashraf, MD

The creation of a join between two bowel ends is an operative procedure that is of central importance in the practice of a general surgeon. Despite the potentially disastrous consequences that can arise from leakage of an intestinal anastomosis, joining bowel segments is one of the procedures that junior surgeons often perform in the emergency setting. With proper supervision and appreciation of fundamental concerns, however, there is little difference between the outcomes of anastomoses performed by trainees and those performed by established surgeons.¹

To minimize the risk of potential complications, it is imperative to adhere to several well-established principles [see Table 1]. The main ones relate to the creation of a tension-free join with good apposition of the bowel edges in the presence of an excellent blood supply.² The importance of surgical technique is underscored by the wide variations of anastomotic leakage rates among surgeons.³

The frequency of anastomotic leakage ranges from 1 to 24%.⁴⁻⁶ The rate of leakage is generally considered to be higher for elective rectal anastomoses (12 to 19%) than for colonic anastomoses (11%).⁷⁻⁹ The consequences of postoperative dehiscence are dire and include peritonitis, bloodstream infection, further surgery, creation of a defunctioning stoma and death. A threefold rise in mortality was seen (from 7% to 22%) in the St. Mary's Large Bowel Cancer Project, when anastomotic leakage occurred.⁷ Also other problems encountered include a significant increase in hospital stay, and there is a proportion of patients who do not go on to have their stomas reversed.⁴

This chapter is divided into three broad sections. The first discusses factors that influence intestinal anastomotic healing. The second analyzes different technical options for creating anastomoses. The third and final section concentrates on the operative techniques that are currently used in constructing intestinal anastomoses.

Intestinal Healing

The process of intestinal anastomotic healing mimics that of wound healing elsewhere in the body in that it can be arbitrarily divided into an acute inflammatory (lag) phase, a proliferative phase, and, finally, a remodeling or maturation phase. Collagen is the single most important molecule for determining intestinal wall strength, which makes its metabolism of particular interest for understanding anastomotic healing. During the proliferative stage, fibroblasts become the predominant cell type, playing an important role in laying down collagen in the extracellular space. At the epithelial level, the crypts undergo division to cover the defect on the luminal surface of the bowel. The density of collagen synthesis is in a constant state of dynamic equilibrium, which is dependent on the balance between the rate of synthesis and

that of collagenolysis. After surgery, degradation of mature collagen begins in the first 24 hours and predominates for the first 4 days. This is caused by the upregulation of matrix metalloproteinases (MMPs), which are an important class of enzymes involved in collagen metabolism.¹⁰ This family includes 20 zinc-dependent endopeptidases, among which is collagenase (MMP-1).¹⁰ In vivo use of MMP inhibitors has been found to increase the strength of intestinal anastomoses by up to 48% at postoperative day 3, which suggests that these enzymes may be important in determining the risk of leakage.¹¹ Sepsis is thought to increase the level of transcription and activity of these enzymes, thereby potentially leading to problems in the early postoperative period. In an animal model where bacterial peritonitis was induced, increased MMP levels were seen on postoperative day 3, coinciding with a fall in the bursting pressure.¹⁰ However, no increase in anastomotic dehiscence was found in comparison with the control group. By postoperative day 7, collagen synthesis becomes the dominant force, particularly proximal to the anastomosis. After 5 to 6 weeks, there is no significant increase in the amount of collagen in a healing wound or anastomosis, though turnover and thus synthesis are extensive. The strength of the scar continues to increase for many months after injury.

The cross-linking between collagen fibers and their orientation are the major factors that determine the tensile strength of tissues. Bursting pressure is used as a quantitative measure to grade the strength of an anastomosis in vivo. This pressure has been found to increase rapidly in the early postoperative period, reaching 60% of the strength of the surrounding bowel by 3 to 4 days and 100% by 1 week.^{12,13} The submucosal layer is, in fact, where the tensile strength of the bowel lies, as a consequence of its high content of collagen fibers [see Figure 1]. Therefore, in constructing a hand-sewn intestinal anastomosis, it is imperative that this layer is included when extramucosal bites are taken. Collagen synthetic capacity is relatively uniform throughout the large bowel but less so in the small intestine: synthesis is significantly higher in the proximal and distal small intestine than in the midjejunum. Overall collagen synthetic capacity is somewhat less in the small intestine. Although no significant difference has been found between the strength of ileal anastomoses and that of colonic anastomoses at 4 days, colonic collagen formation is much greater in the first 48 hours.¹⁴ It is noteworthy that the synthetic response is not restricted to the anastomotic site but appears to be generalized to a significant extent.¹⁵ The presence of the visceral peritoneum on the bowel wall also has an influence on the ease with which two bowel ends can be joined. This effect is highlighted by the increased technical difficulty of joining extraperitoneal bowel ends, for example the thoracic esophagus and the rectum.

Table 1 Principles of Successful Intestinal Anastomosis

Well-nourished patient with no systemic illness
No fecal contamination, either within gut or in surrounding peritoneal cavity
Adequate exposure and access
Well-vascularized tissues
Absence of tension at anastomosis
Meticulous technique

SYSTEMIC FACTORS

Dehiscence has been linked adversely with increasing age.^{16,17} This connection may be secondary to a number of factors, including the presence of comorbid conditions, malnutrition, and vitamin deficiency. A study employing an in vivo model of severe protein malnutrition, which can occur in advanced cancer, demonstrated a reduction in tissue collagen, as well as in the bursting pressure of colonic anastomoses.¹⁸ However, the introduction of parenteral nutrition has not been shown to enhance anastomotic healing.¹⁸ Several factors that are known to inhibit collagen synthesis, such as vitamin C deficiency, zinc deficiency, jaundice, and uremia, have a detrimental effect on tissue healing.¹⁶ A

critical stage in collagen formation is the hydroxylation of proline to produce hydroxyproline; this process is believed to be important for maintaining the three-dimensional triple-helix conformation of mature collagen, which gives the molecule its structural strength. The amount of collagen found in a tissue is indirectly determined by measuring the amount of hydroxyproline, though no significant statistical correlation between hydroxyproline content and objective measurements of anastomotic strength has ever been demonstrated.¹⁹ Vitamin C deficiency results in impaired hydroxylation of proline and the accumulation of proline-rich, hydroxyproline-poor molecules in intracellular vacuoles.

In high doses, corticosteroids have been associated with poor healing. One study employing therapeutic doses, however, reported no difference in leakage rates was found between control subjects and those treated with steroids.¹⁷

LOCAL FACTORS

Blood flow is a critical factor in tissue healing. The increased vascularity of the bowel wall is the reason why gastric and small bowel anastomoses heal more rapidly than anastomoses involving the esophagus or the large bowel. In preparing the bowel ends for anastomosis, it is imperative that the mesentery be prepared carefully and not dissected too far

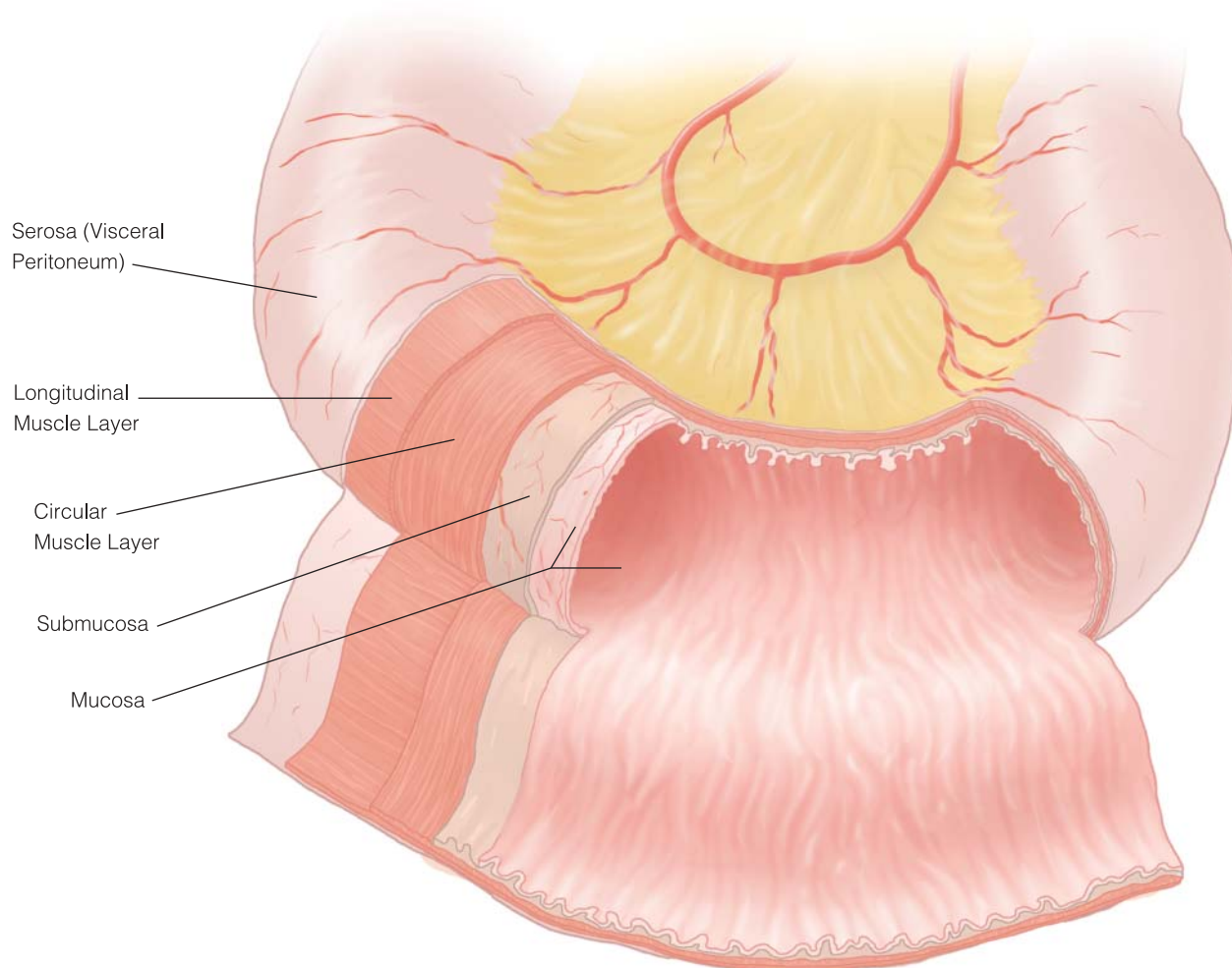


Figure 1 Shown are the tissue layers of the jejunum. Most of the bowel wall's strength is provided by the submucosa.

from the bowel edge. Mesenteric compromise, secondary to overly enthusiastic dissection or inappropriate suturing, may result in a reduction of perianastomotic blood flow. The avoidance of tension at the anastomosis is also critical; this is achieved through the appropriate mobilization of the splenic flexure. Other factors that influence blood flow at the site of anastomoses are hypovolemia and the viscosity of the blood.²⁰ Radiation may damage the microcirculation and thereby predispose to poor healing.¹⁷

Technical Options for Fashioning Anastomoses

Over the past 160 years, numerous different materials have been used to join one bowel end to another, including substances such as catgut and stainless steel. Newer materials include monofilaments and absorbable sutures. In the past 30 years, stapling devices have been embraced enthusiastically by the surgical community. The main attraction of these devices lies in their ability to create a robust anastomosis in a relatively short space of time. Their main drawback, as with any technologically advanced device, is their cost. More important, there continues to be some controversy regarding which of the two methods of creating an anastomosis yields better clinical outcomes.²¹ Accordingly, the following sections review the relative merits of hand-sewn and stapled anastomoses.

SUTURING: TECHNICAL ISSUES

Choice of Suture Material

Apart from inert substances, most foreign materials will evoke an inflammatory reaction in the human body. Surgical sutures are no exception. Studies that have examined the relative abilities of different suture materials to elicit such a reaction have found that silk has a potent ability to cause a cellular infiltrate at the site of the anastomosis that may persist as long as 6 weeks after implantation.²² Substances such as polypropylene (Prolene), catgut, and polyglycolic acid (Dexon) evoked a milder response.^{22,23} There is little difference between absorbable and nonabsorbable sutures with respect to the strength of the anastomosis.

The ideal suture material is one that elicits little or no inflammation while maintaining the strength of the anastomosis during the lag phase of healing. This ideal substance has yet to be discovered, but the newer generation of sutures, which include monofilament sutures and coated braided sutures, represent a substantial advance beyond silk and other multifilament materials.

Continuous versus Interrupted Sutures

Both continuous and interrupted sutures are commonly used in fashioning intestinal anastomoses [see Figure 2]. Retrospective reviews have not shown interrupted sutures to have any advantage over continuous sutures in a single-layer anastomosis.^{24–26} Oxygen tension and blood flow, as discussed previously, are critical factors in anastomotic healing. Animal studies indicated that perianastomotic tissue oxygen tension was significantly lower with continuous sutures than with interrupted sutures.²⁷ This finding was correlated with an increased anastomotic complication rate and impaired collagen synthesis and healing with continuous sutures in a rat model.²⁸ A prospective, randomized trial compared the

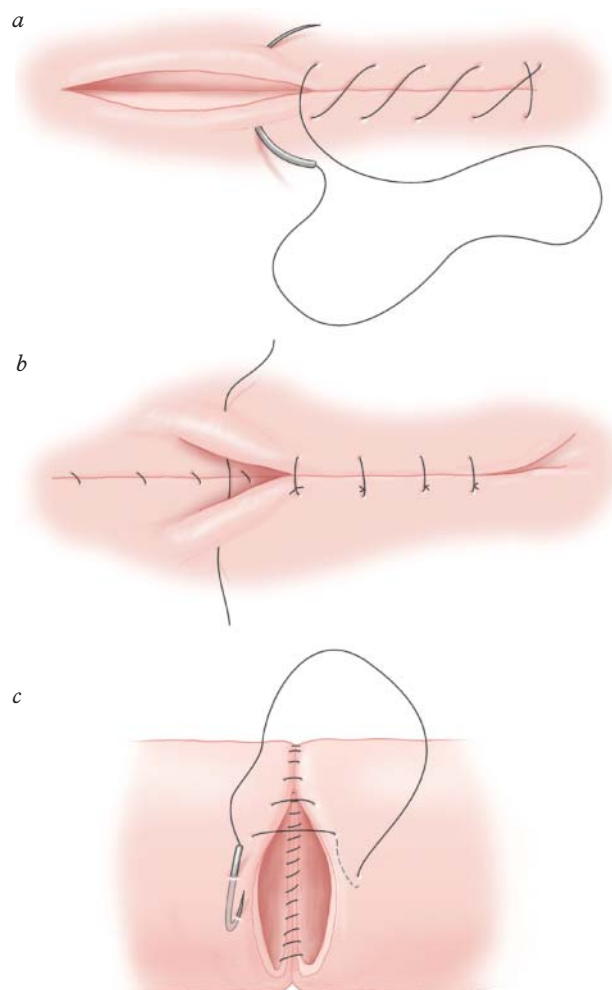


Figure 2 Shown are stitches commonly used in fashioning intestinal anastomoses: (a) the continuous over-and-over suture, (b) the interrupted Lembert suture, and (c) the Connell suture.

continuous single-layer technique for intestinal anastomosis (in the small bowel and colon) with the two-layer interrupted technique. No significant difference was seen in the leakage rate (3.1% for the single-layer technique versus 1.5% for the two-layer). The added advantages of reduced operating times and cost were observed. In a case series review that included 3,027 patients who had single-layer anastomoses done with continuous sutures, fistula rates ranged from 0 to 6.8% (mean fistula rate, 1.7%), which demonstrated that this suture technique could be safely performed.²⁹

Single-Layer versus Double-Layer Anastomoses

The technique of double-layer anastomosis, originating from work done by Travers and Lembert,²⁹ has been used traditionally for more than 100 years. A double-layer anastomosis consists of an inner layer of continuous or interrupted absorbable suture and outer layer of interrupted absorbable or nonabsorbable suture [see Figure 3]. The technique of single-layer anastomosis was championed because of potential advantages such as reduced operating time and lower cost. The main issue to consider, however, is safety. A

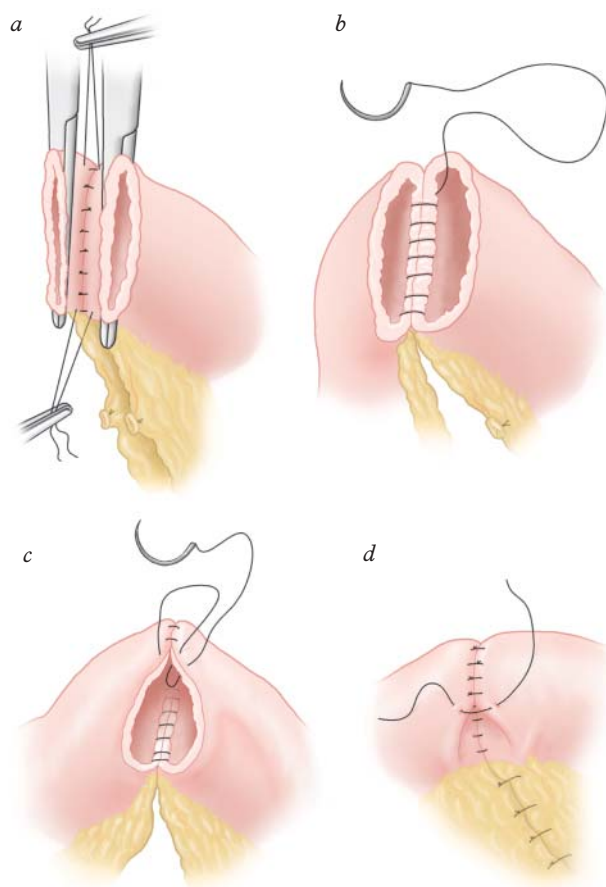


Figure 3 Double-layer end-to-end anastomosis. (a) Interrupted Lembert stitches are used to form the posterior outer layer. (b) A full-thickness continuous over-and-over stitch is used to form the posterior inner layer. (c) A Connell stitch is used to form the anterior inner layer. (d) Interrupted Lembert stitches are used to form the anterior outer layer.

randomized trial comparing the single- and double-layer techniques of anastomosis found no evidence that there was an increased risk of leak with the single-layer approach.²⁹ However, the study groups (65 and 67 patients) were too small for any significant difference to be detected; the authors stated that a multicenter trial comprising at least 1,500 patients would be required to establish whether any such difference existed. Furthermore, a 2006 meta-analysis that addressed this issue by analyzing six trials with data from 670 patients (299 in the single-layer group, 371 in the double-layer group) concluded that there was no evidence that two-layer anastomoses yielded a lower rate of postoperative leakage than single-layer anastomoses.³⁰

STAPLING: TECHNICAL ISSUES

Choice of Stapler

Surgical stapling devices were first introduced by Hülthl in 1908; however, they did not gain popularity at that time and for some time afterward because the early instruments were cumbersome and unreliable. The development of reliable, disposable instruments over the past 30 years has changed

surgical practice dramatically. With modern devices, technical failures are rare, the staple lines are of more consistent quality, and anastomoses in difficult locations are easier to construct.

Three different types of stapler are commonly used for fashioning intestinal anastomoses. The transverse anastomosis (TA) stapler is the simplest of these. This device places two staggered rows of B-shaped staples across the bowel but does not cut it: the bowel must then be divided in a separate step. The gastrointestinal anastomosis (GIA) stapler places two double staggered rows of staples and simultaneously cuts between the double rows. The circular, or end-to-end anastomosis (EEA), stapler places a double row of staples in a circle and then cuts out the tissue within the circle of staples with a built-in cylindrical knife. All of these staplers are available in a range of lengths or diameters. Staplers may be used to create functional or true anatomic end-to-end anastomoses as well as side-to-side anastomoses. The original staplers were all designed for use in open procedures, but there are now a number of instruments (mostly of the GIA type) available for use in laparoscopic procedures. The staples themselves are all made of titanium, which causes little tissue reaction. They are not magnetic and do not cause subsequent difficulties with magnetic resonance imaging (MRI).

In a functional end-to-end anastomosis, two cut ends of bowel (either open or stapled closed) are placed side by side with their blind ends beside each other. If the bowel ends are closed, an enterotomy must be made in each loop of bowel to allow insertion of the stapler. A cutting linear (i.e., GIA) stapler is then used to fuse the two bowel walls into a single septum with two double staggered rows of staples and to create a lumen between the two bowel segments by dividing this septum between the rows. A noncutting linear (i.e., TA) stapler is then used to close the defect at the apex of the anastomosis where the GIA stapler was inserted. An alternative, and cheaper, method of closing the defect is to use a continuous suture. The cut and stapled edges of the bowel should be inspected for adequacy of hemostasis before the apex is closed. Some authors suggest cauterizing these edges to ensure hemostasis³¹; however, given that electrical current may be conducted along the metallic staple line to the rest of the bowel, it is probably easier and safer simply to underpin bleeding vessels with a fine absorbable suture. It is also important to offset the two inverted staple lines before closing the apex.³²

True anatomic end-to-end stapled anastomoses may be fashioned with a linear stapler by triangulating the two cut ends and then firing the stapler three times in intersecting vectors to achieve complete closure [see Figure 4]. The potential drawback of this approach is that the staple lines are all everted. It is often easier to join two cut ends of bowel with an EEA stapler, which creates a directly apposed, inverted, stapled end-to-end anastomosis. However, circular staplers can be more difficult to use at times because of the need to invert a complete circle of full-thickness bowel wall. In addition—at least at locations other than the anus—they typically require closure of an adjacent enterotomy.

Staple Height

TA and GIA staplers are available with a variety of inserts containing several different types of staples. These inserts

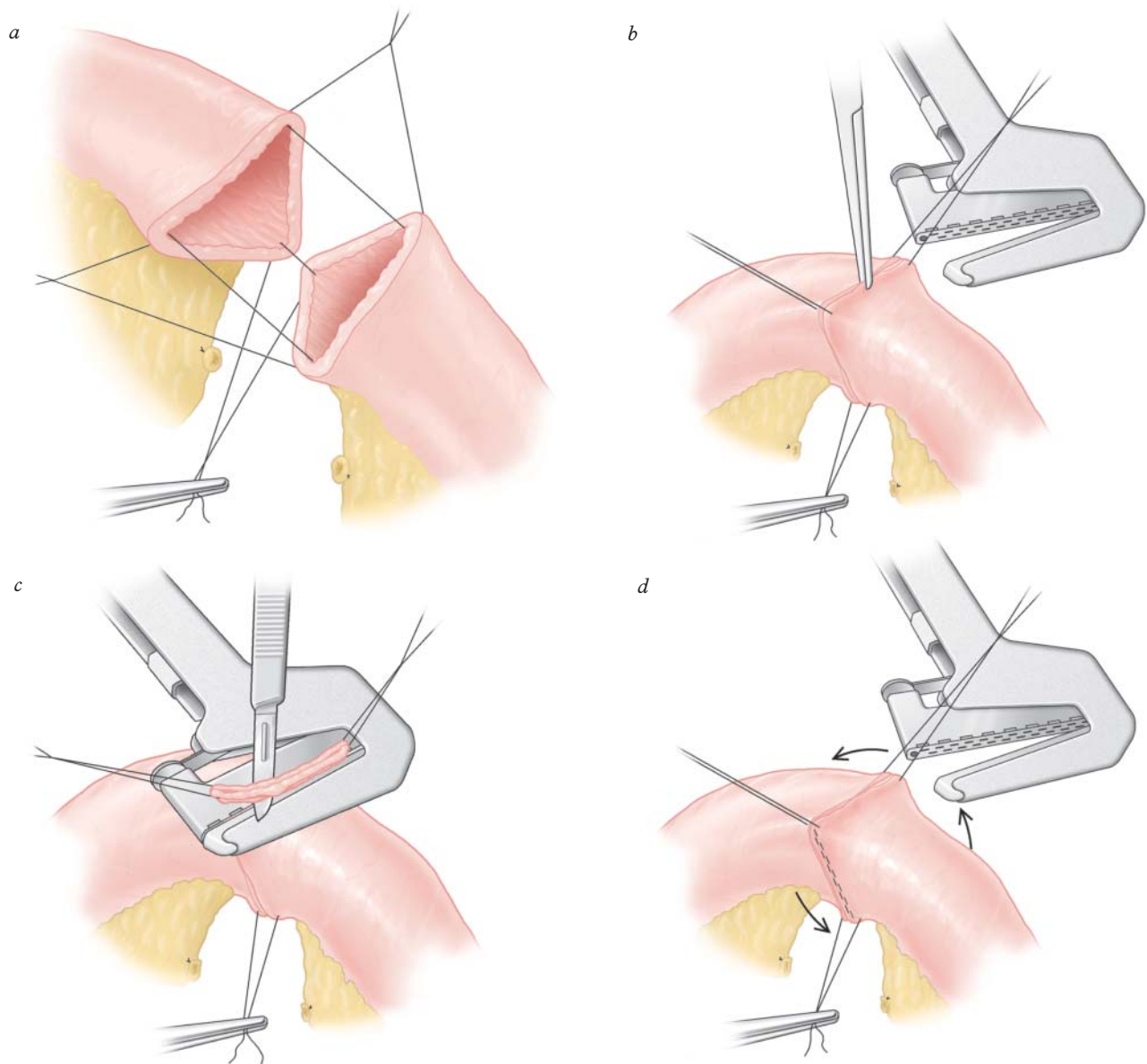


Figure 4 (a) The bowel ends are triangulated with three traction sutures. (b) A noncutting linear stapler (TA) is placed between two of the sutures. (c) The stapler is closed and the excess tissue excised. (d) The bowel is rotated, and steps b and c are repeated twice more to close the remaining two sides of the triangle.

vary with respect to width, the height (or depth) of the closed staple, and the distance between the staples in the rows. They are designed for use in specific tissues, and it is important to choose the correct stapler insert for a given application. In particular, inserts designed for closing blood vessels should not be used on the bowel, and vice versa. With TA and EEA staplers, it is possible to vary the depth of the closed staples by altering the distance between the staples and the anvil as the instrument is closed. The safe range of closure is usually indicated by a colored or shaded area on the shaft of the instrument. Thus, if full closure would cause excessive crushing of the intervening tissues, the stapler need not be closed to its maximum extent. A 1987 comparison of anastomotic techniques that used blood flow to the divided tissues as a measure of outcome found that the best blood flow to the

healing site was provided by stapled anastomoses in which the staple height was adjusted to the thickness of the bowel wall.³³ The next best blood flow was provided by double-layer stapled and sutured anastomoses, followed by double-layer sutured anastomoses and tightly stapled anastomoses, in that order.

Single-Stapled versus Double-Stapled Anastomoses

To accomplish many of these anastomoses, intersecting staple lines are created. Initially, some concern was expressed about the security of these areas and about the ability of the blade in the cutting staplers to divide a double staggered row of staples. Animal studies, however, demonstrated that even though nearly all (> 90%) of the staple lines that were subsequently transected by a second staple line contained

bent or cut staples, the integrity of the anastomosis was not compromised in any way, nor was healing adversely affected.^{34,35}

HAND-SEWN VERSUS STAPLED ANASTOMOSES

Titanium staples are ideal for tissue apposition at anastomotic sites because they provoke only a minimal inflammatory response and provide immediate strength to the cut surfaces during the weakest phase of healing. Initially, tissue eversion at the stapled anastomosis was a major concern, given that everted handsewn anastomoses had previously been shown to be inferior to inverted ones; however, the greater support and improved blood supply to the healing tissues associated with stapling tend to counteract the negative effects of eversion. In fact, one study found that bursting strength for canine colonic end-to-end anastomoses was six times greater when the procedure was performed with an EEA stapler than when it was done with interrupted Dacron sutures.³⁶

In 1993, a randomized multicenter trial studied 440 patients who had either hand-sewn or stapled anastomoses after ileocolic resection for cancer.³⁷ The patients were assessed both clinically and by imaging for the presence of a leak (consisting of a contrast enema at about 10 days after the operation). The overall leakage rate in the hand-sewn group was 8.3%, which compared unfavorably with the 2.8% rate in the stapled group. A possible explanation for the higher rate in the hand-sewn group might have been surgical inexperience with the variety of suture techniques used in the study (end-to-end and end-to-side with either continuous or interrupted sutures). In a study from the West of Scotland and Highland Anastomosis Study Group that included data on 732 patients at 5 centers, the rate of radiologically proven leakage was significantly higher in the sutured group (14.4% versus 5.2%); however, no difference was seen with respect to clinical leaks, morbidity, or postoperative mortality.³⁸ A 1998 meta-analysis comparing the hand-sewn and stapled techniques of intestinal anastomosis addressed 13 trials published from 1980 to 1995.³⁹ For colorectal anastomoses, no significant differences were seen in mortality, total leakage rate, clinical leakage rate, radiologic leakage rate, tumor recurrence rate, or incidence of wound sepsis. Strictures and technical problems, however, were more common in the stapled group. A subsequent meta-analysis that reviewed data from 955 patients with ileocolic anastomoses reported a significant reduction in the overall leakage rate and the clinical leakage rate when stapling was employed.⁴⁰

Even when the anastomosis had to heal under adverse conditions (e.g., carcinomatosis, malnutrition, previous chemotherapy or radiation therapy, bowel obstruction, anemia, or leukopenia), no significant differences have been demonstrated between stapled and hand-sewn anastomoses. Stapling has, however, been shown to shorten operating time, especially for low pelvic anastomoses. Cancer recurrence rates at the site of the anastomosis have been reported to be higher or lower depending on the technique used. Certainly, suture materials engender a more pronounced cellular proliferative response than titanium staples do, particularly with full-thickness sutures as opposed to seromuscular ones, and malignant cells have been shown to adhere to suture materials.^{41,42}

UNUSUAL TECHNIQUES

In 1892, Murphy introduced his button, which consisted of a two-part metal stud that was designed to hold the bowel edges in apposition without suturing until adhesion had occurred.⁴³ Thereafter, the stud was voided via the rectum. Several modifications of this technique have been described since then, primarily focusing on the composition of the rings or stents. In particular, dissolvable polyglycolic acid systems have been developed. These so-called biofragmentable anastomotic rings leave a gap of 1.5, 2.0, or 2.5 mm between the bowel ends to prevent ischemia of the anastomotic line.

The use of adhesive agents such as methyl-2-cyanoacrylate to approximate the divided ends of intestinal segments has been studied as well.⁴⁴ There was only a moderate inflammatory response at the wound, which persisted for 2 to 3 weeks. Leakage rates were high, however, and many technical problems remained (e.g., how to stabilize the bowel edges while they underwent adhesion). Fibrin glues have also been employed in this setting. Although these substances are not strong enough to hold two pieces of bowel in apposition, they have been used to coat a sutured bowel anastomosis in an effort to reduce the risk of anastomotic failure. To date, no controlled clinical trials have confirmed that this approach is worthwhile.

FACTORS CONTRIBUTING TO FAILURE OF ANASTOMOSES

Type and Location of Anastomosis

Since the introduction of stapling, there has been an increase in the number of extremely low anterior resections being performed routinely. The literature seems to suggest that rectal anastomoses are more prone to leakage than more proximal joins are.⁷⁻⁹ A retrospective review of risk factors in patients undergoing rectal resection for cancer found that low anastomoses, defined as being 5 cm or less from the anal verge, were associated with a 6.5-fold increased risk of leakage when compared to anastomoses that were more than 5 cm from the anal verge.⁴⁵ Another study showed that the leakage rate was increased in patients undergoing low colorectal anterior resection in the absence of a proximal stoma (the leakage rate was 17%, which fell to 6% when a stoma was present).⁴⁶ The technique of total mesorectal excision (TME), which is now standard for rectal cancer operations, has reduced the local recurrence rate to 5% at 5 years.⁴⁷ However, the incidence of anastomotic leakage in patients undergoing TME for low anterior resection is higher in the absence of a defunctioning stoma (25% versus 8%).⁴⁸ The Rectal Cancer Trial on Defunctioning Stoma (a randomized multicenter trial) studied the outcomes of 234 patients undergoing low anterior resection with a defunctioning stoma.⁴ The overall leakage rate was 19.2%; however, the rate in the group that had a stoma was only 10.3%, compared with 28.0% in the group that did not. Therefore, it is safe practice to cover a low anterior resection with a defunctioning stoma.

Patient Preparation

Patients who present in the emergency setting are usually compromised in terms of hydration status, typically as a consequence of sepsis, obstruction, or a combination of the two. Preoperative fluid optimization is always necessary and may

require the aid of intensivists. Before an elective procedure, the patient is assessed with regard to systemic diseases (e.g., cardiovascular, respiratory, or diabetes), and anemia is corrected. Adequate preoperative antibiotic prophylaxis has been shown to reduce the risk of postoperative infection in all types of bowel surgery and must be given at the start of the operation [see 1:1 *Prevention of Postoperative Infection*]. Some patients require additional steroids perioperatively [see 8:10 *Endocrine Problems*].

Mechanical bowel preparation (MBP) has been thought to be an essential component of colorectal surgery for more than 100 years.^{49,50} Emptying the bowel before elective operations on the colon was traditional until about 5 years ago, and indeed, this practice was recommended by the Association of Surgeons of Great Britain and Ireland (ASGBI) until relatively recently.^{51,52} The evidence for MBP was derived from observational studies showing that mechanical clearance of feces from the bowel was associated with reduced morbidity and mortality in colonic surgery.⁵³ Proponents of MBP listed several advantages, such as reduction in intraluminal bacterial load, prevention of potential anastomotic disruption by fecal pellets and also easier handling of bowel.⁵⁴ In recent years, however, there has been a shift in practice regarding the use of MBP.

A Swiss randomized clinical trial published in 2005 studied the effect of MBP on patients undergoing left-side colorectal resection with primary anastomosis.⁵⁴ The anastomotic leakage rate proved to be lower in the group that did not receive MBP than in the group that did. Furthermore, the former group spent less time in hospital and exhibited less extra-abdominal morbidity (e.g., pneumonia and cardiac-related problems). These results seemed to agree with the findings of a Cochrane review.⁵² Two large randomized trials published in 2007 compared the outcomes of patients who underwent MBP (with either polyethylene glycol or sodium phosphate) and patients who did not.^{55,56} One recruited 1,431 patients undergoing elective colorectal surgery from 13 centers.⁵⁵ Leakage was defined by the onset of significant symptoms and corroborated by means of imaging. The rate of leakage was 4.8% in the MBP group, which was not significantly different from the 5.4% rate in the non-MBP group. The other trial examined 1,343 patients from 21 centers and found no significant differences in outcomes (such as cardiovascular problems, general infections and surgical site infections) between the MBP group and the non-MBP group.⁵⁶ However, in a subsequent meta-analysis⁵⁷ that examined data from 10 randomized trials conducted over the past 24 years, the rates of both anastomotic leakage and wound infection were significantly higher in the MBP group than in the non-MBP group (5.1 versus 2.6% and 8.2% versus 5.5%, respectively).⁵⁷ Possible explanations of these findings include immune changes in the colonic mucosa that might impede wound repair.⁵⁷ In view of the currently available evidence, some surgical institutions, including our own, have chosen to adopt a policy of employing fluid restriction and enemas rather than MBP before elective colorectal surgery.⁵⁸

Enemas are given to patients undergoing anterior resections to ensure that fecal matter does not impede the use of stapling devices. It is advisable for patients to stop eating solid food 24 hours before the operation. Many trials have confirmed the benefits of giving IV antibiotics over the perioperative period.⁵⁹ However, there is some evidence to

suggest that there is an increased risk of *Clostridium difficile*-associated diarrhea with the use of cephalosporin, penicillin, and clindamycin.^{60–62} Prophylaxis of thromboembolism [see 6:6 *Venous Thromboembolism*] is mandatory in all patients scheduled to undergo intestinal anastomosis. There is very little evidence in the literature to indicate that thromboembolism has any direct effect on anastomotic leakage rates. However, mesenteric venous thrombosis (MVT) accounts for one-tenth of acute mesenteric ischemic events.⁶³ The extent of thromboses is variable, with the worst outcome being mesenteric infarction necessitating urgent repeat laparotomy. Inadequate prophylaxis may increase the risk that MVT will occur postoperatively, especially in patients with other risk factors (e.g., a hypercoagulable state, previous thrombosis, or a history of smoking).

Associated Diseases and Systemic Factors

Anemia, diabetes mellitus, previous irradiation or chemotherapy, malnutrition with hypoalbuminemia, and vitamin deficiencies are all associated with poor anastomotic healing. Some of these factors can be corrected preoperatively. Malnourished patients benefit from nutritional support delivered enterally or parenterally before and after operation [see 8:22 *Nutritional Support*]. Well-nourished patients appear not to derive similar benefits from such support.⁶⁴

Resections for Crohn disease appear to carry a significant risk of anastomotic dehiscence (12% in one prospective study) even when macroscopically normal margins are obtained.⁶⁵ With the lifetime risk of repeated resections, strictureplasty has therefore become an attractive alternative to resectional management of Crohn disease even in the presence of moderately long strictures, diseased tissue, or sites of previous anastomoses. This approach allows preservation of more of the length of the small intestine.

The glucocorticoid response to injury may attenuate physiologic responses to other mediators whose combined effects could be deleterious to the organism.⁶⁶ In animal experiments, wound healing, as measured by the bursting pressure of an ileal anastomosis 1 week after operation, was optimal at a plasma corticosterone level that maintained maximal nitrogen balance and corresponded to the mean corticosterone level of normal animals.⁶⁷ Both supranormal and subnormal cortisol levels resulted in significantly impaired wound healing, probably through different mechanisms. It is believed that slow protein turnover is responsible for delayed anastomotic healing in adrenalectomized animals, whereas negative nitrogen metabolic balance is responsible for increased protein breakdown and delayed healing in animals with excess glucocorticoid activity.^{67,68}

Lifestyle factors have also been associated with an increased risk of leakage. A Danish prospective study of 333 consecutive patients undergoing colorectal resection collected lifestyle information by means of a questionnaire.⁶⁹ The overall leakage rate was 15.9% (53 out of 333). Smoking was found to be associated with an increased risk of anastomotic leakage (relative risk 3.18), as was alcohol consumption exceeding 35 units a week (relative risk 7.18).

CONTROVERSIAL ISSUES IN INTESTINAL ANASTOMOSIS

Inversion versus Eversion

The question of the importance of inversion (as described by Lembert in the early 1800s) versus eversion of the

anastomotic line has long been a controversial one. It has been argued that the traditional inverting methods ignore the basic principle of accurately opposing clean-cut tissues. In the late 19th century, Halsted proposed an interrupted extramucosal technique, which has since been assessed in retrospective³ and prospective⁶⁵ reviews and found to have a low leakage rate (1.3% to 6.0%) in a wide variety of circumstances. A 1969 study reported greater anastomotic strength, less luminal narrowing, and less edema and inflammation with everted small intestinal anastomoses in dogs.⁷⁰ Subsequent laboratory and clinical studies have not confirmed these findings and, in fact, have often yielded quite the opposite results: lower bursting pressure, slower healing, and more severe inflammation have all been associated with an everted suture line.^{71–73} A 1970 trial, however, conclusively demonstrated the importance of inverting the cut edges of bowel in colorectal surgery. In this study, the rate of fecal fistula formation was far higher in the group that had everted suture anastomoses (43%) than in the group with inverted suture anastomoses (8%).⁷⁴

Nasogastric Decompression

Routine nasogastric decompression in patients undergoing a procedure involving an intestinal anastomosis remains controversial. In retrospective⁷⁵ and prospective,⁷⁶ randomized, controlled trials, routine use of a nasogastric tube conferred no significant advantage in terms of reducing the risk of anastomotic leakage. In fact, there was a trend toward an increased incidence of respiratory tract infections after routine gastric decompression.⁷⁷ Nonetheless, one study found that nearly 20% of patients required insertion of a gastric tube in the early postoperative period.⁷⁶ If the choice is made not to place a nasogastric tube routinely, it is important to remain alert to the potential for gastric dilatation, which can develop suddenly and without warning.

Abdominal Drains

Fecal contamination from bowel surgery is a dreaded complication. Peritoneal drainage is of the subject of considerable controversy, with two basic schools of thought dominating.⁷⁸ The first school accepts the possibility that drains may help with diagnosis by serving as an early warning system for either anastomotic leakage or bleeding and makes the point that evacuating blood and serous fluid will reduce the risk of abscesses. The other school is skeptical about the benefits, arguing that drains may irritate the peritoneum, thus increasing the production of serous fluid, and may provide a route whereby microbes can enter the peritoneal cavity. In addition, there is a potential risk that the drain may physically impede the movement of the omentum and adjacent organs and consequently may hinder the body's innate ability to wall off any possible infection. Finally, it is thought that drains are at high risk for blockage.

Even before World War I, the old dictum “when in doubt, drain” was called into question by Yates, who wrote that the peritoneal cavity could not be effectively drained because of adhesions and rapid sealing of the drain tract.⁷⁹ Six decades later, one study showed a dramatic increase in the incidence of anastomotic dehiscence (from 15% to 55%) after the placement of perianastomotic drains in dogs.⁸⁰ This increase was associated with a significant increase in mortality. A 1999

study of pelvic drainage after a rectal or anal anastomosis showed that prophylactic drainage did not improve outcome or reduce complications.⁸¹ Yet another study reported the severe inflammatory reaction caused by drains at anastomoses.⁸²

Despite these findings, many surgeons elect to place an intra-abdominal drain in the pelvis after an anterior resection or a coloanal anastomosis because of the higher than usual risk that a fluid collection will develop. Drainage is rarely helpful, or indeed easy, after a gastric or small bowel anastomosis. Drains are indicated, however, after emergency operations for peritonitis or trauma in which it was necessary to close or anastomose damaged or inflamed bowel.

Operative Techniques for Selected Anastomoses

The following section covers the essential preliminary steps before a bowel anastomosis and then describes three generic operations involving the small and large bowel. These procedures illustrate many of the general principles previously discussed (see above).

PATIENT POSITIONING AND INCISION

Patients must be positioned on the operating table in a manner that is appropriate for the planned operation. Most abdominal operations are performed through a midline incision of adequate length with the patient supine. For pelvic procedures, the patient is placed in the lithotomy position to allow access to the abdomen and the anus; care must be taken to position the legs and feet in the stirrups correctly, without excessive flexion or abduction and with sufficient padding to prevent pressure ulceration, thrombosis, and neurapraxia. For esophageal procedures, the patient is positioned lying on the appropriate side, and the incision of choice is a lateral thoracotomy [see 4:7 *Open Esophageal Procedures*]. Occasionally, the patient must be shifted to a different position during the course of an operation. Gravity can be useful for moving structures out of the way. Accordingly, it is often helpful to alter the axis of the operating table. For example, a 30° head-down or Trendelenburg position facilitates pelvic operations.

EXPOSURE, MOBILIZATION, AND DISSECTION

Access is a critical determinant of the ease with which an operative procedure can be carried out. Accordingly, the incision must be made in such a way as to allow adequate exposure of the operating field. The lateral aspects of the field can be controlled by using a suitable retractor, which can be attached to the operating table. This measure allows more efficient use of operating assistants and space. Often, the colorectal surgeon is faced with operating in confined spaces, such as the pelvis. Therefore, it is important to be able to compartmentalize the abdomen. This can be achieved in a number of ways. The small bowel can be extremely difficult to handle and therefore is commonly packed away by placing wet gauze. The next stage involves bringing the bowel to the surface. In the absence of adhesions or tethering caused by disease, the small bowel is usually sufficiently mobile to allow the relevant segment to be brought out of the abdomen. Doing so makes the operation easier and allows the remainder of the bowel to be kept warm and tension free

inside the abdominal cavity. Sometimes, the transverse colon and the sigmoid colon are mobile enough to be brought to the surface. More commonly, however, as with the other sections of the large bowel, the peritoneum must be divided along the lateral border of the colon and the retroperitoneal structures reflected posteriorly. Tension is rarely a problem with small bowel anastomoses, but with colonic or esophageal anastomoses, it is absolutely vital that the two ends of bowel to be joined lie together easily. For a large bowel anastomosis, this means that the splenic flexure or the hepatic flexure—or, sometimes, both—must be adequately mobilized.

Classically, the tissues around the bowel are divided with a scissors, whereas the mesentery is divided between clamps and tied with a suitable thread. Recognized tissue planes are separated by means of blunt dissection with either the fingers or a swab. Minor bleeding points are occluded with a coagulating electrocautery, though this approach is often relatively ineffective on mesenteric or omental vessels. The disadvantages of this dissection technique are that oozing from raw surfaces can be a nuisance and that the tissues beyond a tie are often bulky and leave dead tissue within the body that may act as a focus for infection and adhesions. Newer methods of dissection that make use of the ultrasonic scalpel or the bloodless bipolar electrocautery prevent these problems by coagulating a small section of tissue between the jaws of the instrument and simultaneously occluding all blood vessels up to a certain size within the tissues. Consequently, bleeding is reduced, fewer (or no) ties are needed, and only a small quantity of dead tissue results at each point. Becoming skilled in the use of these instruments often takes a little time, but the time is well spent, in that it is now possible to perform an intestinal resection without resort to a single tie.

BOWEL RESECTION

The precise techniques involved in resecting specific bowel segments will not be discussed in great detail here. (Colonic resection, for example, is described elsewhere [see 5:34 *Segmental Colon Resection*].) The following discussion outlines only the general principles.

Preparation

The segment of bowel to be removed must be isolated with an adequate resection margin. To this end, all surrounding adhesions are divided. Next, the mesentery is divided. The key consideration in this step is to preserve the blood supply to the two remaining ends of bowel while still achieving adequate excision of the diseased bowel. This is more easily accomplished in the small bowel than in the large bowel, thanks to the ample blood supply of the former; even so, transillumination of the mesentery and careful division of the vascular arcade are vital. In the colon, the surrounding fat and the appendices epiploicae should be cleared from the remaining bowel ends so that subsequent suture placement is straightforward.

Care should be taken to avoid two common problems. First, ties placed close to the bowel can bunch tissues excessively and thereby cause angulation or distortion of the free edge of the intestine, which can make the anastomosis difficult and threaten the blood supply. Second, because mesenteric vessels are usually tied very close to their ends, the arteries sometimes slip back beyond the ties. Such slippage

results in a hematoma within the leaves of the mesentery, which can itself threaten the viability of the bowel. Generally, the bleeding vessel can be secured with a fine stitch; sometimes, however, a limited further bowel resection is the only safe course of action. Both of these problems can be avoided by using the ultrasonic scalpel or the bipolar coagulating electrocautery.

Division of Bowel

If staplers are not available, the bowel segment to be removed is isolated between noncrushing clamps placed across the intestinal lumen some distance away from the resection margin so as to limit the amount of bowel contents that can escape into the wound. Crushing clamps are then placed on the specimen side of the diseased segment at the point of the resection, and the bowel is divided with a knife just proximal and distal to the clamps. Thus, the lumen of the diseased segment is never open within the abdominal wound. Even so, the contents of the bowel between the open ends and the non-crushing clamps can leak into the wound. To minimize this problem, it is usual to isolate the working area with abdominal packs, which are sometimes soaked in an antiseptic (e.g., povidone-iodine).

One advantage of using staplers for an anastomosis is that in most instances, division of the bowel can be accomplished without opening the lumen. A linear cutting stapler (e.g., GIA) transects the bowel and seals the two cut ends simultaneously. Unfortunately, in the pelvis, it is usually necessary to employ an angulated noncutting linear stapler (e.g., TA) so as to obtain as much length as possible distal to the lesion. The proximal rectum is then clamped with a crushing bowel clamp, and a long knife is used to transect the rectum above the staple line. Even so, there remains the potential for leakage of a small amount of fecal material, which must then be suctioned away.

SIMPLE BOWEL CLOSURE

There are occasions where the bowel damage requires simple repair rather than a formal resection, as in the case of a perforated duodenal ulcer or an iatrogenic injury sustained during adhesiolysis. Such holes may be closed in a number of ways. Most surgeons would use a double layer of absorbable sutures. Special mention should be made of the technique of strictureplasty, which is employed for a number of benign small bowel strictures (especially those resulting from Crohn disease) as a means of avoiding small bowel resection and anastomoses. In this procedure, the bowel is opened longitudinally and closed transversely with a single layer of 2-0 polyglycolic acid sutures in a Connell stitch. Excellent functional results have been achieved with this technique despite its reputation for fistula formation, which is associated with Crohn disease.

SINGLE-LAYER SUTURED EXTRAMUCOSAL SIDE-TO-SIDE ENTEROENTEROSTOMY

A side-to-side anastomosis [see Figure 5] may be performed when no resection is done, as a bypass procedure (e.g., a gastroenterostomy); after a small bowel resection; when there is a discrepancy in the diameter of the two ends to be anastomosed (e.g., an ileocolic anastomosis after a right hemicolectomy); or when the anatomy is such that the most

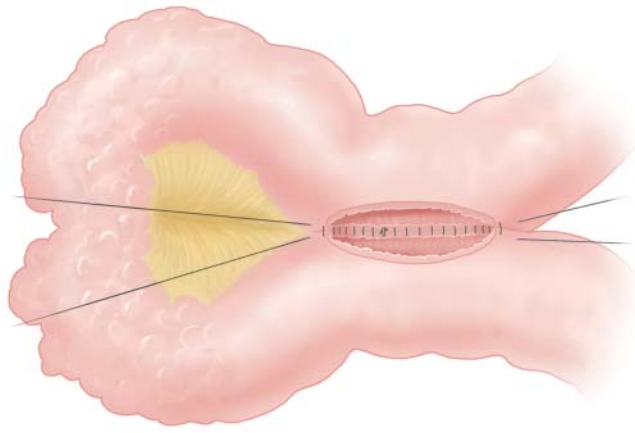


Figure 5 Single-layer sutured extramucosal side-to-side enteroenterostomy. A full-length suture is started in the back wall and run through the seromuscular and submucosal layers in the direction of the surgeon; the corners of the enterotomy are approximated with a baseball stitch, and a single Connell stitch is used to invert the anterior layer. A second suture is started at the same spot on the posterior wall and run in the opposite direction, again through all layers except the mucosa; the corners of the enterotomies are approximated with a baseball stitch, and the suture is continued in either the Connell stitch or the over-and-over stitch to complete the anterior wall of the anastomosis.

tension-free position for the anastomosis is with the two bowel segments parallel (as in a Finney strictureplasty).

Two stay sutures of 3-0 polyglycolic acid are placed approximately 8 cm apart on the inner aspect of the antimesenteric border. A 5 cm enterotomy is made on each loop with an electrocautery or a blade on the inner aspect of the antimesenteric border. If an electrocautery is used, care must be taken not to injure the mucosa of the posterior wall during this maneuver; placement of a hemostat into the enterotomy to lift the anterior wall usually prevents this problem. Hemostasis of the cut edges is ensured, and the remaining enteric contents are gently suctioned out. A swab soaked in povidone-iodine may be used at this point to cleanse the lumen of the bowel in the perianastomotic region.

A full-length seromuscular and submucosal stitch of 4-0 polyglycolic acid is placed and tied on the inside approximately 5 to 10 mm from the far end of the enterotomies. The stitch is not passed through the mucosa: to do so would add no strength to the anastomosis and would hinder epithelialization by rendering the tissue ischemic. A hemostat is placed on the short end of the tied suture, and the assistant applies continuous gentle tension to the long end of the suture. An over-and-over stitch is started in the direction of the surgeon; small bites are taken, and proper inversion of the suture line is ensured with each pass through tissue. When the proximal ends of the enterotomies are reached, this so-called baseball stitch is continued almost completely around to the anterior wall of the anastomosis. A single Connell stitch may be used to invert this anterior layer.

Another full-length seromuscular and submucosal suture of 4-0 polyglycolic acid is then inserted and tied at the same location in the posterior wall as the first. If the two sutures are placed close enough together, the short ends need not be

tied together and may simply be cut off. The remainder of the posterior wall is sewn away from the surgeon in the same manner as the portion already sewn, and the corners are approximated with the baseball stitch. The anterior wall is then completed with this second suture, either with the Connell stitch or with an over-and-over stitch with the assistant inverting the edges before applying tension to the previous stitch.

When the defect is completely closed, the two sutures are tied across the anastomotic line. The stay sutures are removed, and the anastomosis is carefully inspected. Often, there is no mesenteric defect to close in a side-to-side anastomosis, but if there is one, it should be approximated at this point with continuous or interrupted absorbable sutures, with care taken not to injure the vascular supply to the anastomosis.

DOUBLE-LAYER SUTURED END-TO-SIDE ENTEROCOLOSTOMY

In this procedure, the end of the ileum is joined to the side of the transverse colon [see Figure 6]. The distal colon is divided with a cutting stapler so that a blind end is left. Some surgeons underpin or bury this staple line, though this practice is probably unnecessary. The proximal cut end of the intestine is similarly closed either with staples after division with a cutting linear stapler or with a crushing bowel clamp. This proximal end is brought into apposition with the side of the distal bowel segment at a point no farther than 2.5 to 5 cm from the blind end of the distal segment; this proximity to the cut end is important for prevention of the blind loop syndrome.

Stay sutures of 3-0 polyglycolic acid are placed between the serosa of the proximal limb, about 10 to 15 mm from the clamp, and the serosa of the distal limb. Interrupted seromuscular sutures of 3-0 polyglycolic acid are then placed between these stay sutures, spaced about three to six to the centimeter. These stitches may be tied sequentially or snapped and tied once they are all in place. It is crucial not to apply excessive tension, which could cut the seromuscular layer or render it ischemic. Suction is then readied. The staple line or crushed tissue on the proximal limb is cut off with a coagulating electrocautery or a knife; this maneuver opens the lumen of the proximal limb. All residual intestinal content is gently suctioned.

An enterotomy or colotomy is created on the distal limb opposite the open lumen of the proximal bowel. A full-thickness suture of 3-0 polyglycolic acid is inserted in the posterior wall at a point close to the far end of the enterotomy and run in an over-and-over stitch back toward the surgeon. The corner is rounded with the baseball stitch, and when the anterior wall is reached, the Connell stitch is used. A second full-length 3-0 suture is started at the same point on the posterior wall as the first, and the short ends of the two sutures are tied together and cut. This second suture is then run away from the surgeon to complete the posterior wall, and the anterior wall is completed with the Connell stitch. The two sutures are then tied across the anastomotic line.

A second series of interrupted seromuscular stitches is then placed anteriorly in the same fashion as the seromuscular stitches placed in the posterior wall. It is important not to narrow either lumen excessively by imbricating too much of the bowel wall into this second layer. The lumen of the

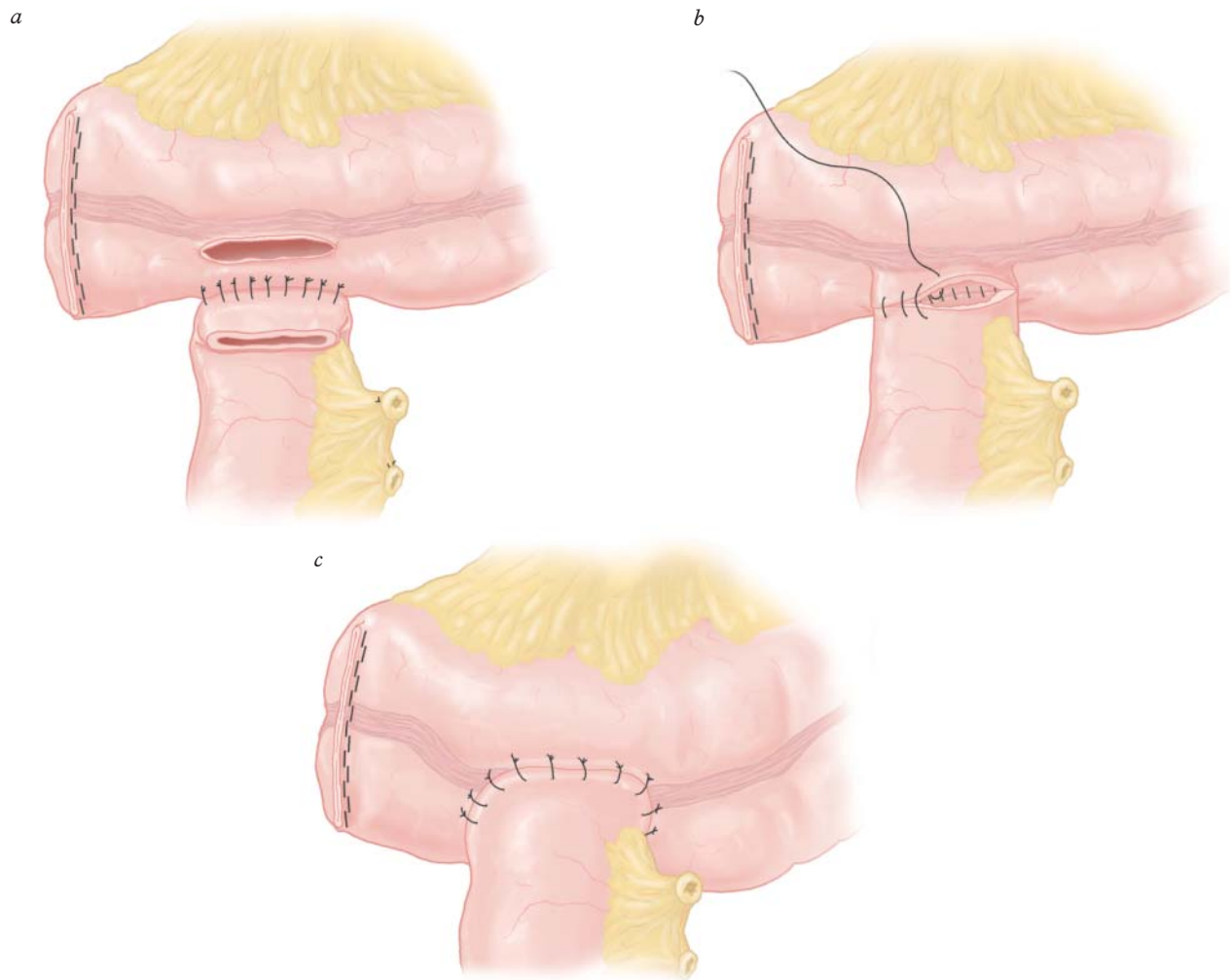


Figure 6 Double-layer sutured end-to-side enterocolostomy. (a) The proximal bowel end is stapled, interrupted Lembert stitches are used to form the posterior outer layer, and a colotomy is made. (b) Two continuous sutures are used to form the inner layer of the anastomosis; the posterior portion is done with the over-and-over stitch, the anterior with the Connell stitch. (c) Interrupted Lembert stitches are used to form the anterior outer layer.

anastomosis is palpated to confirm patency, and the mesenteric defect is closed if possible with either continuous or interrupted absorbable sutures. The integrity of the join can be tested by injecting 20 mL of saline into the lumen of the bowel, which is then placed under gentle pressure by simultaneously finger-clamping the bowel a couple of centimeters distal to the anastomosis and a couple of centimeters proximally.

DOUBLE-STAPLED END-TO-END COLOANAL ANASTOMOSIS

Resection of the distal sigmoid colon and the rectum is a common procedure. In the past, it often resulted in a permanent colostomy because of the technical difficulties associated with a hand-sewn anastomosis deep in the pelvis. The development of circular staplers reduced the technical difficulty of the operation and made possible anastomoses as far down as the anus [see Figure 7].

Proper preparation of the patient and the bowel is essential before resection of the rectum. The patient is placed in the

lithotomy position with the head tilted down, and the small bowel is packed away in the upper abdomen. This positioning gives the surgeon the best access to the pelvis. The splenic flexure and all of the distal large bowel are fully mobilized along with the rectum. The proximal resection margin is determined and cleared of serosal fat, and the bowel is divided either with a GIA stapler or between crushing bowel clamps. An angled TA stapler is fired across the distal rectal resection margin, and another bowel clamp is placed proximal to it. The rectum is divided with a long-handled knife, with care taken to avoid plunging the blade into the pelvic sidewall, which could cause significant neurovascular damage. The specimen is removed and the stapler withdrawn. Adequate pelvic hemostasis is ensured.

Once the surgeon is satisfied that the bowel is sufficiently mobilized, a noncrushing bowel clamp is placed on the colon 10 to 15 cm proximal to the margin, and the crushing clamp is removed. At this stage, it is usual to create an 8 to 10 cm colonic J pouch; this measure typically yields a substantially

improved functional outcome, especially in the early postoperative period in older patients.⁸³ A whip-stitch (or purse-string suture) of 2-0 polypropylene is placed around the colotomy, and the anvil from the appropriately sized curved EEA stapler is inserted into the open end and secured in place by tying the suture [see Figure 7]. The proximal bowel clamp is removed. The assistant—who may also, if desired, gently wash out the rectal stump with a dilute povidone-iodine solution—performs a digital rectal examination.

The stapler, with its trocar attachment in place, is then inserted into the anus under the careful guidance of the surgeon. The pointed shaft is brought out through or adjacent to the linear staple line, and the sharp point is removed. The peg from the anvil in the proximal colon is snapped into the protruding shaft of the stapler, and the two edges are slowly brought together. The colonic mesentery must not be twisted, and the ends must come together without any tension whatsoever. The stapler is fired. In some types of stapling guns, a

crunching sound is heard. The anvil is then loosened the appropriate amount, and the entire mechanism is withdrawn through the anus. Finally, the proximal and distal rings of tissue, which remain on the stapler, are carefully inspected to confirm circumferential closure of the staple line.

The pelvis is then filled with body-temperature saline, and a Toomey or bladder syringe is used to insufflate the neorectum with air. The surgeon watches for bubbling in the pelvis as a sign of leakage from the anastomosis. If there is a leak, additional soluble sutures must be placed to close the defect and another air test performed. A rectal tube may then be inserted by the assistant or may be placed at the end of the procedure. When the anastomosis is very low or there is some concern about healing, a drain may be placed in the pelvis behind the staple line; however, as noted [see Controversial Issues in Intestinal Anastomosis, *above*], this practice has not been shown to be beneficial and may in fact impair healing.

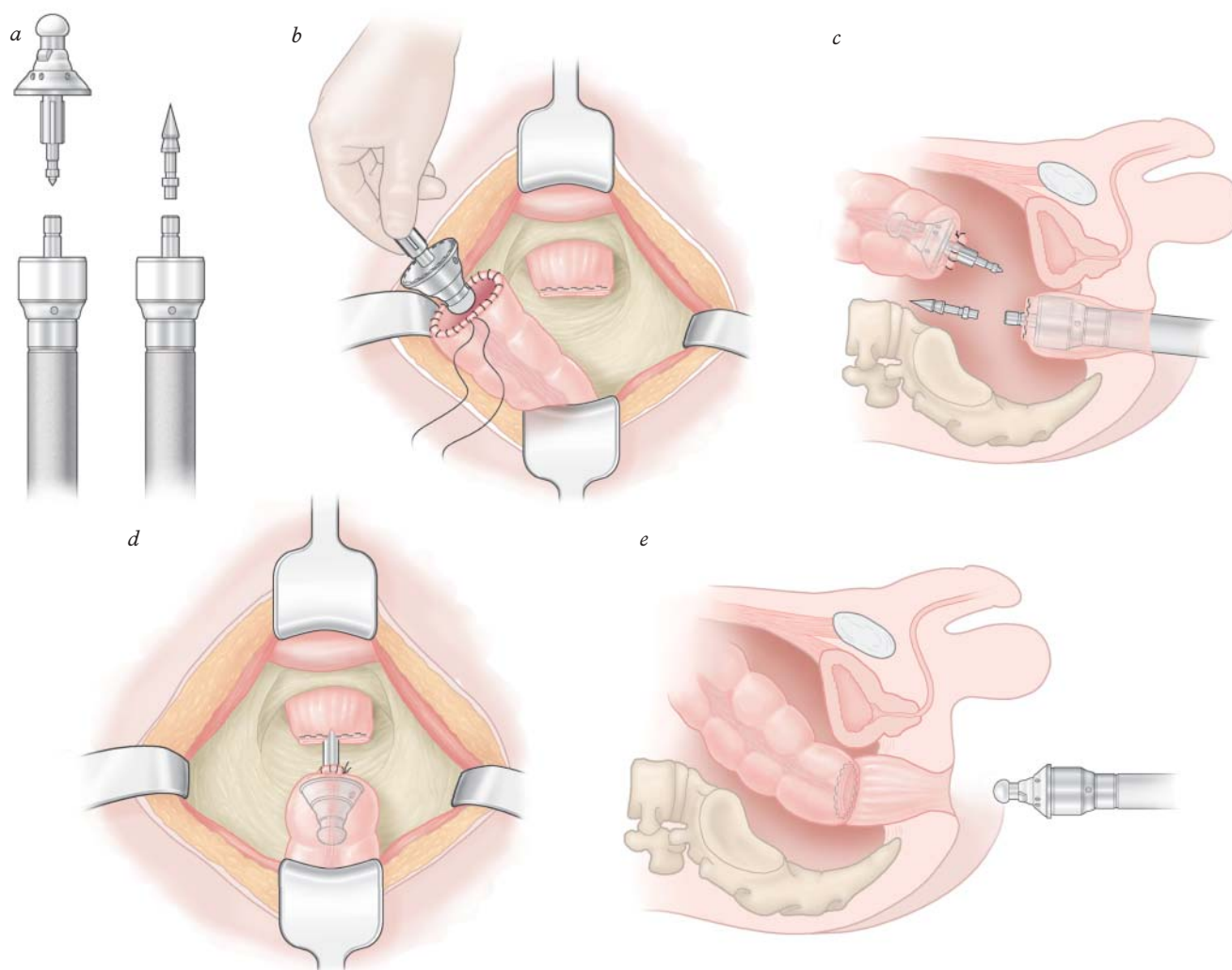


Figure 7 Double-stapled end-to-end coloanal anastomosis. (a) The C-EEA stapler comes with both a standard anvil (left) and a trocar attachment (right). A more recent version of these staplers comes with a trocar in the body rather than in the head of the device. (b) The rectal stump is closed with an angled linear noncutting stapler. A purse-string suture is placed around the colotomy, and the anvil of the stapler is placed in the open end and secured. (c) The stapler, with the sharp trocar attachment in place, is inserted into the anus, and the trocar is made to pierce the rectal stump at or near the staple line, after which the trocar is removed. (d) The anvil in the proximal colon is joined with the stapler in the rectal stump, and the two edges are slowly brought together. (e) The stapler is fired and then gently withdrawn.

As noted (see above), a 1998 meta-analysis by Macrae demonstrated an association between stapled anastomoses and an increased incidence of colorectal anastomotic strictures, in comparison with hand-sewn anastomoses.³⁹ The cause of this association remains uncertain. Most of these patients were asymptomatic and in those who required treatment, simple dilatation was sufficient to rectify the problem. A 2007 Cochrane review did not find the risk of anastomotic stricture to be increased in patients undergoing ileocolic resection with a linear cutting stapler.⁴⁰

Conclusion

Any anastomosis, no matter how technically sound on creation, may fail. The limiting factor may be the tissue or the resulting inflammatory sequelae that follow closure of the abdominal wall. Therefore, as for ultralow anterior resections, it is important to recognize any potential risk

factors and take the measures necessary to prevent any harm that may ensue if leakage results. This may mean giving the patient a temporary stoma. Even if fecal diversion has been carried out, it is important to keep watching closely for any signs of failure and to take prompt action if such signs appear.

Anastomotic failure rates have improved over the past two centuries, and postoperative morbidity and mortality have decreased accordingly. These beneficial developments can be attributed to a combination of factors, such as better appreciation of the principles of healing, improved anesthesia, appropriate antibiotic prophylaxis, and enhanced postoperative monitoring. Currently, with the emergence of laparoscopic colorectal surgery, it is essential that the surgeon continues to practice the same principles of creating a join—good apposition of the edges, without tension and with an optimal blood supply—just as for open colorectal surgery.

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30 INTESTINAL STOMAS

J. Graham Williams, MCh, FRCS

Formation of an intestinal stoma is frequently a component of surgical intervention for diseases of the small bowel and the colon. The most common intestinal stomas are the ileostomies (end and loop) and the colostomies (end and loop); the less common stomas, such as cecostomy and appendicostomy, have limited applications and thus are not considered further in this chapter.

For optimal results, it is essential that stoma creation be considered an integral part of the surgical procedure, not merely an irritating and time-consuming addendum at the end of a long operation. Accordingly, the potential requirement for a stoma should be appropriately addressed in the planning of an intestinal procedure. A great effort should be made to counsel the patient before operation as to whether a stoma is likely to be needed, what stoma creation would involve, where the stoma would be situated, and whether the stoma is likely to be permanent or temporary.

Operative Planning

PREOPERATIVE COUNSELING

Ideally, as soon as surgical intervention that may involve a stoma is contemplated, the enterostomal nursing service should become involved, although this may not be possible in an emergency setting. Patients often have misconceptions about the effects a stoma will have on their quality of life and consequently may experience considerable anxiety. Adequate preoperative counseling helps correct these misconceptions and reduce the attendant anxiety. Enough time should be set aside to allow the counselor to explore the patient's knowledge of the disease and understanding of why a stoma may be required. This process involves reviewing the planned operation, describing what the stoma will look like, and explaining how the stoma will function. Visual aids (e.g., videos, CD-ROMs, and booklets) can be very useful in this regard and should be freely available to patients and their families. As simple a measure as showing the patient a stoma appliance and attaching it to the abdominal wall before the procedure can be helpful in preparing the patient for a stoma. Many patients facing the prospect of stoma surgery also derive great benefit from meeting patients of similar age and background who have a stoma.

CHOICE OF PROCEDURE

A number of common indications for stoma formation have been identified [see Table 1]. These indications are usually associated with particular types of stoma, but the

association is not always a simple or automatic one. In many situations, more than one option exists, and it can be difficult to select the best available option for a particular patient.

Loop Ileostomy versus Loop Colostomy

Defunctioning of a distal anastomosis after rectal excision and anastomosis may be achieved with either a loop ileostomy or a loop transverse colostomy. A number of nonrandomized studies¹⁻³ and randomized control trials⁴⁻⁷ have been performed in an effort to determine which of these two approaches is superior. Both types of stoma effectively defunction the distal bowel; however, loop ileostomy appears to be associated with a lower incidence of complications related to stoma formation and closure, although it may also carry a higher risk of postoperative intestinal obstruction.⁶ The two types of stoma are comparable with respect to patient quality of life, and the degree of subsequent social restriction is influenced more by the number and type of complications than by the type of stoma formed.⁸

SELECTION OF STOMA SITE

A poorly sited stoma will cause considerable morbidity and adversely affect quality of life. For this reason, great emphasis should be placed on selecting the best site for the stoma on the abdominal wall. In many instances [see Table 1], it may not be possible to decide beforehand whether a colostomy or an ileostomy is to be performed. An example would be the case of a patient with a tumor in the lower rectum in which the surgeon's intention is to perform a restorative resection covered by a loop ileostomy. In such a case, the surgeon sometimes finds that restorative resection is not technically possible and elects to perform an abdominoperineal resection or a low Hartmann resection with an end colostomy instead.

A stoma should be brought out through a separate opening in the abdominal wall, not through the main incision: there is a high incidence of wound infection and incisional hernia formation if the main incision is used as a stoma site. In general, ileostomies are sited in the right iliac fossa, sigmoid colostomies (loop or end) in the left iliac fossa, and transverse loop colostomies in either the right or the left upper quadrant. These positions are preferred because they are conveniently close to the particular bowel segments to be used for creating the various stomas. At need, however—as when finding a suitable site proves difficult because of previous scars or deformity—both the ileum and the colon can be mobilized to provide sufficient length to reach most sites on the abdominal wall.

Table 1 Indications for Different Types of Intestinal Stomas

Disease	Presentation	Indication	Stoma Type	Intention
Colorectal cancer	Perforation	Defunctioning of bowel	Loop or end colostomy	Temporary, often permanent
	Obstruction	Relief of obstruction	Loop or end colostomy	Temporary
	Rectal cancer	Low tumor (abdominoperineal resection)	End colostomy	Permanent
		Defunctioning of low anastomosis	Loop ileostomy or colostomy	Temporary
Diverticular disease	Perforation	Resolution of sepsis; defunctioning of bowel	Colostomy	Temporary, sometimes permanent
	Obstruction	Relief of obstruction	Loop or end colostomy	Temporary, sometimes permanent
	Elective resection for fistula	Protection of anastomosis	Loop ileostomy or colostomy	Temporary
Ulcerative colitis	Acute colitis	Defunctioning of bowel	End ileostomy (after subtotal colectomy)	Temporary or permanent
	Chronic colitis	Eradication of disease	End ileostomy (after panproctocolectomy)	Permanent
		Ileoanal pouch procedure	Loop ileostomy	Temporary
Crohn disease	Crohn colitis	Defunctioning of bowel	Loop or split ileostomy	Temporary, sometimes permanent
		Defunctioning of bowel after excision	End ileostomy or colostomy	Temporary, often permanent
	Small bowel disease	Defunctioning of bowel	Loop, end, or split ileostomy	Temporary, sometimes permanent
	Perianal disease	Defunctioning of bowel	Loop or split ileostomy	Temporary, often permanent
		Excision of disease	Ileostomy (after panproctocolectomy) Colostomy (after rectal excision)	Permanent
	Elective resection for septic complications	Defunctioning of bowel	Loop or divided loop ileostomy	Temporary
Trauma	Colon injury	Defunctioning of bowel	Colostomy or loop ileostomy	Temporary, sometimes permanent
	Rectal injury	Defunctioning of bowel	Colostomy	Temporary, sometimes permanent
Functional disorders	Fecal incontinence	Defunctioning of anus	End colostomy	Permanent
	Sphincter repair	Defunctioning of bowel	Loop ileostomy or colostomy	Temporary

In selecting and marking a stoma site, the following key considerations should be taken into account:

1. A flat area of skin is required for adequate adhesion of the appliance.
2. The patient should be able to see the stoma.
3. Skin creases, folds, previous scars, and bony prominences should be avoided.
4. The stoma site should not be located at the beltline.
5. The site should be identified with the patient lying, sitting, and standing.
6. Preexisting disabilities should be taken into account.

According to received wisdom, the stoma should be brought out of the abdomen through the rectus abdominis so that the emerging stoma will be supported and the incidence of parastomal hernia reduced. Several studies, however, have shown that

this approach is not always ideal and that the optimum site for a stoma should be selected without regard to its position in relation to the rectus abdominis.⁹⁻¹¹ Once selected, the site is marked with an indelible pen or tattooed with India ink and a fine needle.

Operative Technique

GENERAL PRINCIPLES

Most abdominal stomas are formed at the end of an open operation performed to resect bowel, drain an infectious focus, or relieve obstruction. In this setting, a midline incision is generally the most appropriate choice for gaining access to the abdominal cavity because it leaves the areas to either side of the midline available for stoma placement. Other incisions may be used as well, but more careful operative planning will be required.

A defunctioning stoma can be created without opening the abdomen by making a trephine hole and using retractors and forceps to identify the relevant bowel loop from which the stoma will be formed. I generally avoid this approach, for two reasons. First, the trephine hole invariably ends up larger than is ideal, and the greater size leads to an increased risk of parastomal hernia. Second, it is often difficult to be sure that the correct bowel loop has been identified and the correct end opened as a stoma. These disadvantages can be overcome by taking a laparoscopic approach, now favored by many surgeons when a simple defunctioning stoma is indicated in isolation. One port is placed through the previously marked site. A tissue forceps is passed down this port and used to grasp and orient the relevant bowel segment. If necessary, the bowel can be mobilized by means of laparoscopic dissection. If colon is being used to form an end colostomy, it is then divided with a linear stapler, and the proximal end is brought out through a small trephine hole made at the port site. For a loop colostomy or loop ileostomy, the bowel is simply brought through the trephine with correct orientation of the emerging loop of intestine.

The fundamental concept in stoma formation is that a stoma is simply an anastomosis between a piece of bowel and the skin of the abdominal wall. For this reason, the same basic principles that apply to intestinal anastomosis also apply to stoma formation—namely, maintaining an adequate blood supply to both sides of the anastomosis, ensuring that the anastomosis is performed without tension, and avoiding any preexisting infection. In accordance with these principles, the bowel segment used should have as much of its blood supply as possible preserved during mobilization, and mobilization should be sufficient to allow the bowel to be brought through the abdominal wall without tension and without occlusion of the blood supply at the fascial level by a too small hole in the abdominal wall. If these criteria are not met, then either the bowel should be mobilized further or a new bowel segment should be selected. It is important to make the best possible technical choices at the time of initial stoma formation. If the correct principles are not followed at the beginning of the procedure, it is generally futile to hope that the situation will improve thereafter; the usual result is a poor stoma that requires surgical revision.

Creation of Stoma Aperture

It is wise to leave formation of the hole for the stoma until the end of the procedure because unforeseen events during the operation may necessitate a change in the type or the site of the stoma. A circular incision 2.5 cm in diameter is made at the marked site, and the skin is excised. The subcutaneous fat is parted with scissors and small retractors until the fascia of the abdominal wall is reached. The fat need not be excised: it supports the emerging stoma, and its absence would leave a potential dead space. A cruciate incision is made in the rectus sheath, initially no more than 2 cm in each direction. The muscle fibers of the underlying rectus abdominis are split in the direction of their fibers with an arterial clamp or the tips of heavy scissors. The small retractors are inserted deeper to keep the muscle fibers apart, and a small cruciate incision is made in the posterior rectus sheath with an electrocautery. A swab held against the peritoneum at the stoma site will protect the intra-abdominal organs and the assistant's fingers from being injured by the electrocautery point. A recent clinical trial, with long-term follow-up, has shown that bringing the emerging

bowel through a lightweight semiabsorbable mesh placed in the preperitoneal plane significantly reduces the incidence of parastomal hernia after formation of a permanent colostomy.^{12,13}

On occasion, the epigastric vessels, which lie between the rectus abdominis and the posterior sheath, are injured. Should this occur, the simplest way of dealing with the problem is to open the posterior sheath from inside the abdominal cavity and suture-ligate the bleeding point.

COLOSTOMY

End

The typical site for an end colostomy is the left iliac fossa, and either the sigmoid or the descending colon is used for the stoma. If the rectum has been excised, the inferior mesenteric vessels will have been divided, and the blood supply to the distal colon will come from the middle colic vessels via the marginal artery. It is not usually necessary to take down the splenic flexure to mobilize the colon adequately; however, if there is any concern regarding tension on the stoma, full splenic flexure mobilization should be performed. For a simple defunctioning end colostomy, only a few small vessels in the mesentery will have to be divided.

The colon is divided at the relevant site with either crushing clamps or a linear intestinal stapler. The adequacy of the vascular supply is checked by inspection. A nontraumatic bowel clamp or a Babcock tissue forceps is passed through the hole in the abdominal wall and used to grasp the closed-off end of the colon. Care is taken when drawing the colon through the abdominal wall to keep from twisting the colon and damaging the small vessels in the supporting mesentery. The end of the colon should sit 2 cm above the skin surface. To prevent wound contamination, the colostomy is constructed only after the skin incision has been fully closed and dressed. The closed-off end of the colon is excised with a sharp knife, and the colostomy is constructed with a small spout by everting the bowel wall. The spout helps the patient position the stoma appliance but should not protrude more than 0.5 to 1 cm above the surface of the skin. The anastomosis is performed with interrupted absorbable sutures that take bites of the full thickness of the end of the colon and the subcuticular layer of the skin. Small bites are also taken of the seromuscular layer of the emerging colon at the level of the skin [see *Figure 1*].

This technique is sometimes modified by closing the lateral space between the abdominal wall and the colon with absorbable sutures in an effort to prevent internal herniation of the small bowel. An alternative approach is to tunnel the colostomy to the hole in the abdominal wall via an extraperitoneal route. This approach may prevent herniation and colostomy prolapse,⁹ but the stoma may be slow to function and difficult to mobilize if a reversal or revision operation is performed.

Loop

A loop colostomy is usually performed as a quick and temporary method of relieving acute colonic obstruction or to cover an anastomosis in the distal colon or rectum. Whenever possible, I avoid using loop colostomies, for the following reasons:

1. Because of the need to accommodate two pieces of bowel, a loop colostomy requires a larger hole in the abdominal wall than an end colostomy does. This is a particular concern in emergency situations, in which the colon may be greatly dilated.

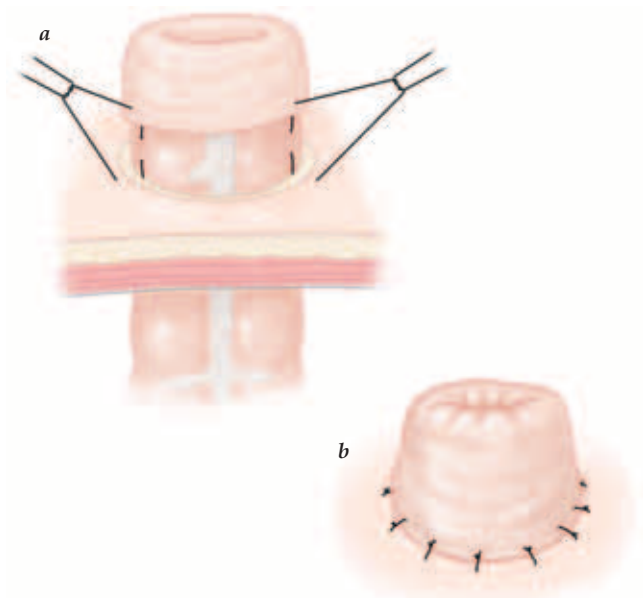


Figure 1 End colostomy. (a) The end of the colon sits 1 to 2 cm above skin level. Four absorbable sutures are placed, one in each quadrant of the stoma. Each suture takes a full-thickness bite of the end of the colon, a seromuscular bite of the emerging colon at skin level, and a subcutaneous bite of the edge of the skin opening. (b) The stoma is completed by filling in the gaps between the four quadrant sutures with interrupted sutures that take full-thickness bites of the end of the colon and subepidermal bites of the skin edge. The stoma should have a small (0.5 to 1 cm) lip, which facilitates accurate positioning of the colostomy bag.

2. The larger hole predisposes to formation of a parastomal hernia, which can be a problem if the stoma is not reversed.
3. Loop colostomies are more prone to prolapse than end colostomies are, possibly as a consequence of parastomal hernia formation.
4. The effluent from the transverse colon can be very liquid, and the absence of a spout with loop colostomy may lead to difficulties with appliance leakage.
5. When a loop colostomy is used to defunction a distal anastomosis, there is a theoretical risk of damage to the marginal artery, which may be the only vessel supplying the distal side of the anastomosis.

The usual site for a loop colostomy is either the right upper quadrant (using the proximal transverse colon) or the left iliac fossa (using the left colon). The colon segment that will be used to form the stoma is identified, and peritoneal attachments are divided to provide sufficient length to reach the desired site on the abdominal wall without tension. If the transverse colon is to be used, the omentum is removed. Care is taken not to damage the marginal artery, which, if occluded, may compromise vascular supply to the distal bowel.

A trephine hole is made at the marked site as described [see Operative Technique, General Principles, *above*]. The hole is usually larger than it would be in an end colostomy; the bowel loop to be brought out is often bulky, especially when the colon is obstructed. A small window is made in the mesentery

immediately adjacent to the colon wall, and a Jacques catheter is passed through this aperture. The Jacques catheter is used as a handle by which the colon loop is drawn through the trephine hole in the abdominal wall, with care taken to maintain the orientation of the colon and avoid twisting [see Figure 2a]. The catheter is then replaced by a plastic or glass stoma rod, which supports the loop at the level of the skin.

The main incision is closed, and the stoma is matured. A transverse incision is made in the apex of the bowel loop [see Figure 2b], and the two edges are peeled back and sutured to the skin edge of the trephine hole to produce a double opening [see Figure 2, c and d]. The bridge remains in place for 5 days, by which time the stoma is usually beginning to function properly. The rod can then be removed because by this point, the stoma is fixed in place and unable to retract into the abdominal cavity.

Double-Barrel

At one time, there was a vogue for creating a double-barrel colostomy to defunction the colon. Although the height of the trend has passed, this type of stoma still has a place in the management of colorectal trauma. After resection of a damaged segment of the colon, the proximal and distal ends of the colon are tacked together along the antimesenteric surfaces with interrupted absorbable sutures. The resulting double end is then brought out through a trephine incision at the relevant site. The double-barrel configuration makes the colostomy easier to close: closure can be performed after mobilization by resection and a sutured anastomosis or via a double-stapled technique.

ILEOSTOMY

End

End ileostomy is most frequently performed after colectomy for inflammatory bowel disease. The most distal segment of the ileum is used (i.e., that immediately proximal to the ileocecal valve), the reason being that it is important to preserve intestinal length, both for nutritional reasons and to allow for the possibility that an ileoanal pouch may have to be fashioned in the future. In certain instances, it is necessary to create an end ileostomy from a more proximal segment of the ileum.

The terminal ileum is mobilized, a large avascular window is opened between the ileocolic vessels and the ileal branches of the superior mesenteric vessels, and the ileocolic vessels are divided where they branch from the superior mesenteric vessels. The terminal ileum is usually supplied by two arcades of vessels, which join the ileocolic vessels adjacent to the cecum. These arcades must be divided as close to the ileocolic vessels as possible to preserve the blood supply to the terminal ileum [see Figure 3]. The ileocecal fold (Treves fold) is dissected away from the terminal ileum, which can then be divided flush with the ileocecal valve, either with a linear stapler or with a knife between bowel clamps.

The trephine incision is created at the previously marked site, and a Babcock tissue forceps is passed into the abdominal cavity and used to grasp the divided end of the ileum. The terminal ileum and the supporting mesentery are gently eased through the aperture, with the mesenteric surface oriented superiorly, until 5 cm of ileum protrudes above the abdominal skin. The risk of parastomal hernia formation may be reduced by bringing the emerging ileum through a piece of light-weight

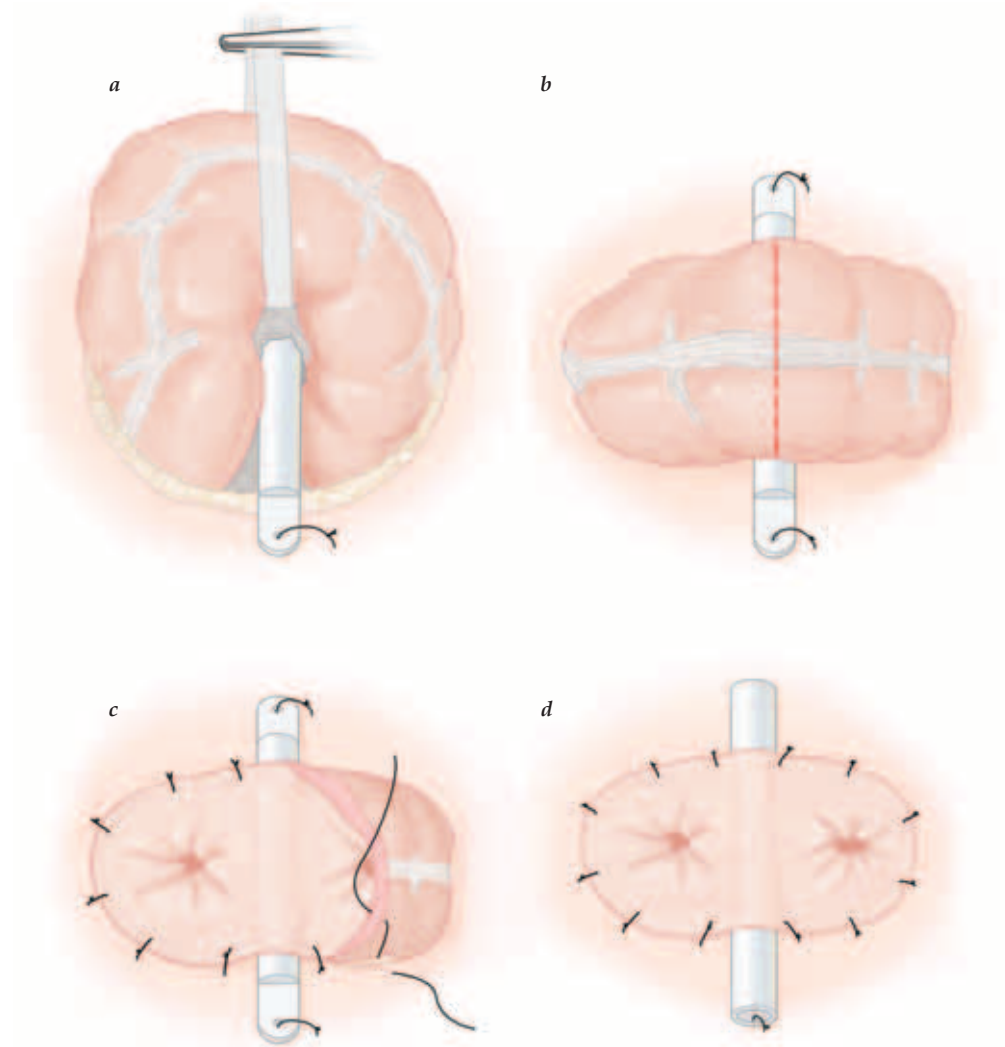


Figure 2 Loop colostomy. (a) A soft catheter or a length of nylon tape is passed through a small window made in the mesentery of the colon, and the prepared loop of colon is eased through the hole in the abdominal wall with the aid of the catheter. The catheter or tube is replaced by a supporting colostomy rod. (b) A transverse incision is made across the apex of the colon loop. (c) The cut edges of the colon are everted and sutured to the skin edge of the stoma hole with interrupted absorbable sutures that take full-thickness bites of the colon and subepidermal bites of the skin. (d) The rod is left in place for 5 days to support the loop stoma during the early phase of healing.

semiabsorbable mesh, placed in the preperitoneal plane. However, the trial supporting this approach only included end colostomy formation.¹³ The cut edge of the ileal mesentery is secured to the peritoneum of the back of the anterior abdominal wall, along the line of the lateral border of the rectus abdominis, with an absorbable suture. This measure helps stabilize the stoma and is thought to prevent stoma prolapse, volvulus, and internal herniation around the stoma.

The stapled end of the ileum is excised to produce a fresh bleeding end. The emerging ileum is then everted to yield a spout about 2.5 cm long. This is accomplished by placing a suture on either side of the mesentery and a third suture on the antimesenteric side, which lies inferiorly. The superior sutures take bites of the serosa of the emerging ileum, 5 cm

from the cut end of the bowel, and the inferior suture includes a serosal bite 4 cm from the cut edge [see Figure 4]. When the sutures are tied, an everted spout is created that points downward into the ileostomy appliance.¹⁴ The mucocutaneous anastomosis is then completed with a series of interrupted absorbable sutures.

Loop

A loop ileostomy is employed to rest the distal bowel or to protect an anastomosis. The ileal loop used should be as distal as possible while still maintaining adequate mobility; if there is any tension, a more proximal loop may be required. The technique of loop ileostomy formation is similar to that of loop colostomy formation. A Jacques catheter is used to

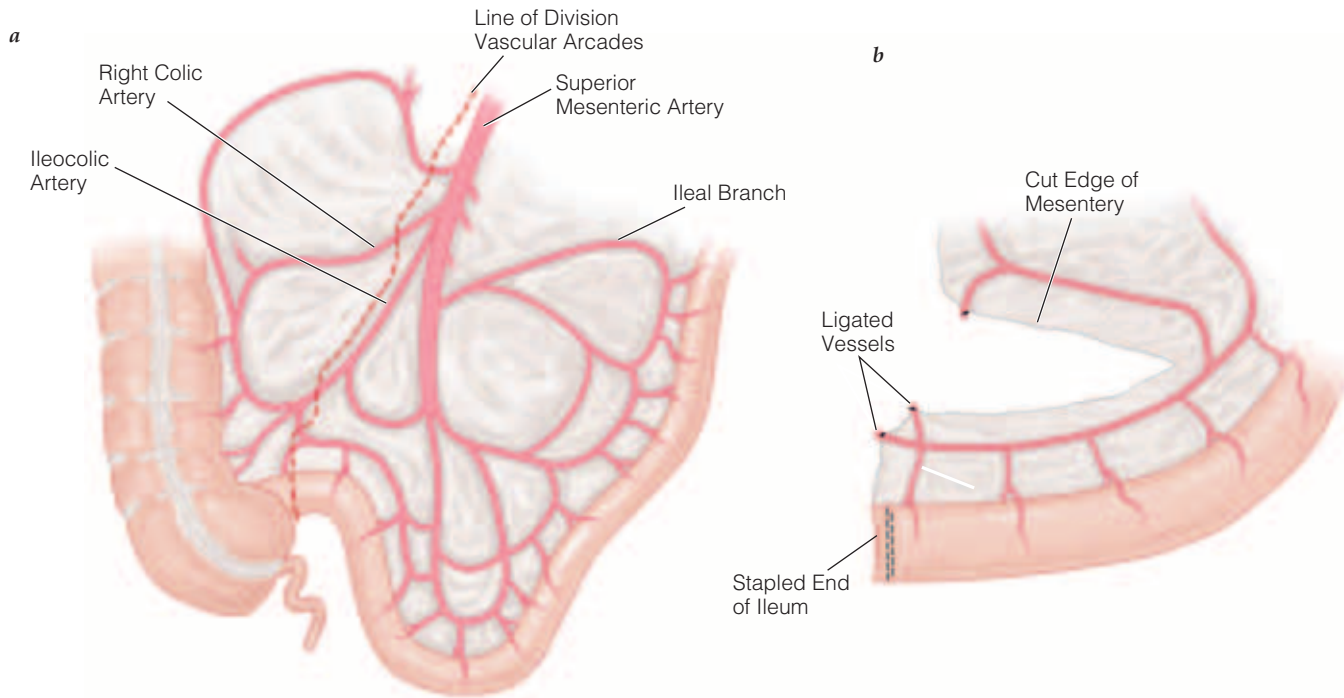


Figure 3 End ileostomy. Shown is preparation of the terminal ileum. (a) Care is taken when dividing the blood supply of the right colon to preserve the arcades supplying the terminal ileum. The line of division of the vessels and the mesentery is shown (dashed line). (b) The mesentery of the terminal ileum is divided to preserve the vascular arcade adjacent to the ileum. A segment of well-perfused ileum at least 10 cm long is created, which can be brought through the abdominal wall opening to provide sufficient ileum for creation of a spout.

draw the loop through the abdominal wall trephine hole, ideally with the proximal limb in the lower position [see Figure 5a]. Care is taken to distinguish the proximal and distal limbs of the loop and to keep from rotating the loop during its passage through the abdominal wall. A marking suture is useful for identifying the proximal side of the loop. A supporting rod may be used, but it is not necessary and can hinder the fitting of the stoma appliance.

The ileostomy is created by making a circumferential incision around 80% of the distal limb at the level of the skin, with the mesenteric side preserved [see Figure 5b]. The cut edge of the proximal limb is then everted to create a spout for the ileostomy [see Figure 5c]. A Babcock tissue forceps is sometimes used to apply gentle traction to the mucosal side of the proximal limb. The cut edge of the ileum is anastomosed to the skin with a series of interrupted subcuticular absorbable sutures. The distal limb is sutured flush with the skin. On the proximal side, several sutures take bites of the serosa of the emerging ileum at skin level. The corners of the incision in the ileum are drawn around the proximal limb of the ileostomy to accentuate the spout effect and create a thin, semilunar distal limb opening [see Figure 5d].

An alternative approach is to create a divided loop ileostomy, which some consider superior to a conventional loop stoma.¹⁵ The construction technique for this stoma is similar to that of its conventional counterpart. The distal limb of the ileostomy is divided with a linear cutting stapler after the loop is brought through the abdominal wall. The closed distal end is tacked to the side of the emerging spout of the proximal

end below skin level, and the proximal end is fashioned into an everted spout as in a conventional end ileostomy. A divided loop ileostomy is slightly more difficult and expensive to construct than a conventional loop ileostomy, but it has the advantage of achieving complete defunctioning of the distal bowel (because there is no chance that the ileostomy contents will spill over).

Loop-End

A loop-end ileostomy can be useful in cases in which the ileum and its supporting mesentery are grossly thickened and the surgeon is encountering difficulty in preparing a sufficient length of well-vascularized ileum for a conventional end ileostomy. In a loop-end ileostomy, the ileum is prepared as in a conventional end ileostomy, but the vascular arcades are left undisturbed. A small window is made in the mesentery 5 to 10 cm proximal to the closed end of the ileum, and a nylon tape or a Jacques catheter is used to draw this distal ileal loop through the abdominal wall. The stapled closed end of the ileum lies just within the abdominal cavity. The ileostomy is then constructed in essentially the same manner as a conventional loop ileostomy.

Split

A split ileostomy is created by bringing out the two cut bowel ends at different sites. The proximal end is usually terminal ileum, but the distal end may be either ileum or colon, depending on the indication for stoma formation. This procedure forms a mucous fistula, and only a small stoma

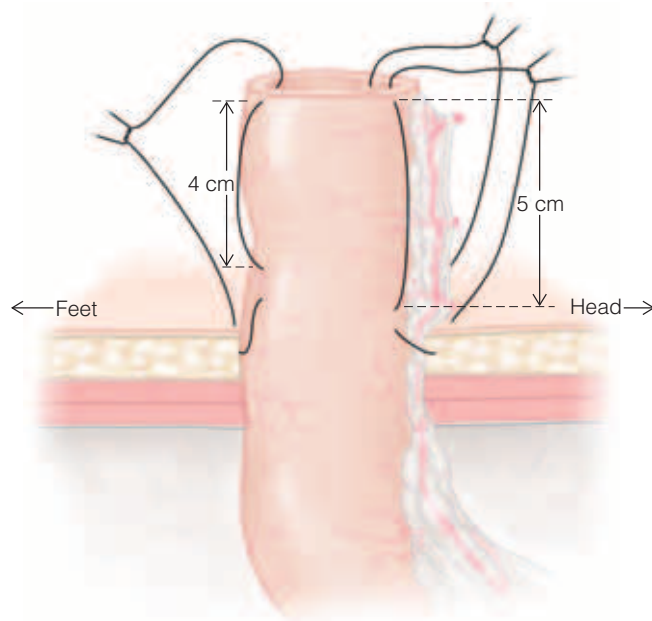


Figure 4 End ileostomy. The ileum having been brought through the abdominal wall, the ileostomy is created by everting the end of the ileum. Three sutures are placed: one on the antimesenteric side and one to each side of the mesentery. Each suture takes a full-thickness bite of the cut edge of the ileum, a seromuscular bite of the emerging ileum at skin level, and a subepidermal bite of the skin edge. The spout is created when these sutures are tied. A nontoothed forceps or a Babcock tissue forceps is sometimes helpful for everting the ileum. Gaps between the three sutures are filled in with further absorbable sutures, which include only the end of the ileum and the skin edge.

appliance is usually required. The distal end can be either included in the closure of the abdominal wound or brought out through a separate trephine hole on the opposite side of the abdomen from the ileostomy. The advantage of a split ileostomy is that it completely defunctions the bowel without the risk of intra-abdominal leakage from a closed distal stump. The disadvantage is that it is more difficult to close; closure usually necessitates reopening of the main incision.

Continent

A continent ileostomy involves formation of a reservoir and placement of a nonreturn nipple valve, which is emptied regularly via a catheter, so that the patient need wear only a small cap appliance. The surgical technique is demanding and beyond the scope of this chapter; it is described more fully elsewhere.¹⁶

STOMA CLOSURE

Loop Ileostomy

Closure of a loop ileostomy is usually a simple local procedure that does not require the main incision to be opened. The operation is easier to perform if a period of at least 12 weeks is allowed to elapse between formation of the stoma and closure so that there is time for edema and inflammatory adhesions to settle. Dissection is facilitated by injecting

epinephrine (1:100,000 solution) into the subcutaneous plane around the stoma.

An incision is made in the peristomal skin 2 mm from the mucocutaneous junction [see Figure 6a]. The incision is deepened into the subcutaneous fat until the serosa of the emerging bowel appears. Sharp dissection is continued circumferentially in this plane, dividing the fine adhesions between the bowel and its mesentery and the subcutaneous fat [see Figure 6b]. Blunt dissection should be avoided because it can easily lead to serosal tears. Some difficulty may be encountered at the fascial level, and care must be taken with the dissection if adhesions are particularly dense. Eventually, the peritoneal cavity is entered, and the remaining adhesions are identified with a finger and divided.

The emerging ileal loop is withdrawn from the abdominal cavity, and the mucocutaneous junction and the rim of skin are excised. The everted proximal end of the stoma is unfolded [see Figure 6c]; some sharp dissection is usually required to accomplish this. The freshened edges of the enterotomy are then approximated with interrupted seromuscular absorbable sutures [see Figure 6d]. Sometimes, a limited ileal resection is required if the stoma site is in poor condition, and a conventional end-to-end anastomosis is performed to restore intestinal continuity. It is possible to close a loop ileostomy with a double-stapled technique; however, there does not appear to be much advantage in doing so. Two randomized trials and a nonrandomized study comparing suture closure with stapled closure yielded conflicting results with respect to complication rates,¹⁷⁻¹⁹ but both randomized trials reported that extra costs were incurred when staples were used. Once the enterotomy is closed, the loop of ileum is returned to the abdominal cavity, and the stoma site is closed with interrupted nonabsorbable sutures.

A divided loop ileostomy is closed in the same manner as described above. Care should be taken to identify the closed distal end and to fully mobilize both limbs of the ileum from the abdomen. The closed distal end is separated from the proximal limb, and the staple line is excised to yield a fresh end. The proximal end is unfolded, and a simple end-to-end anastomosis is performed with interrupted sutures. There may be a significant size discrepancy between the two limbs. Again, a double-stapled technique may be employed as an alternative closure method.

Loop Colostomy

A loop colostomy is closed in much the same manner as a loop ileostomy after the emerging colon is mobilized away from the subcutaneous fat and the abdominal wall by means of sharp dissection. Transverse closure is achieved with interrupted absorbable sutures.

Postoperative Care

A clear stoma appliance is cut to the proper size and placed on the stoma before the patient leaves the operating room. A degree of edema is to be expected in the first week. In addition, the stoma may appear somewhat dusky; this is a sign that the aperture in the abdominal wall is the correct size. It often happens that the patient becomes alarmed at the initial appearance of the stoma and requires reassurance that the stoma will look better as time passes.

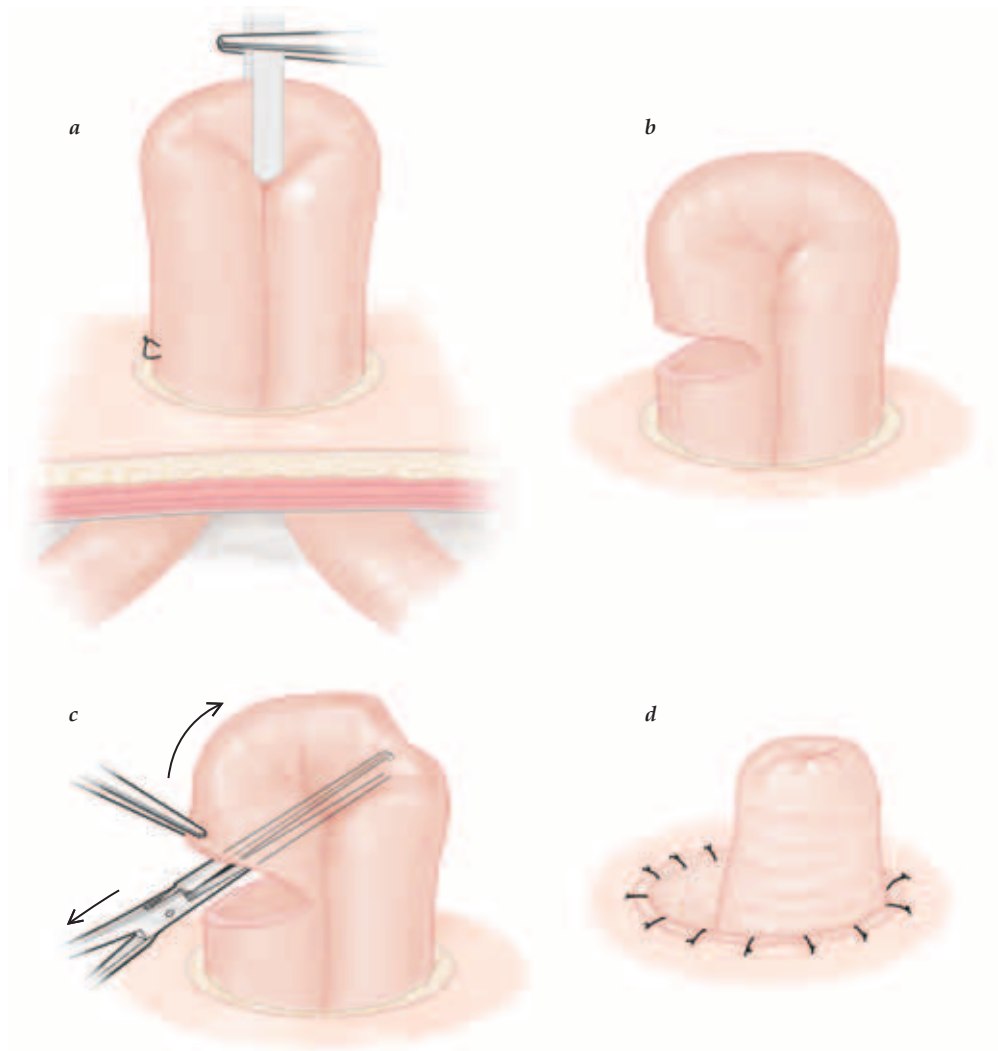


Figure 5 Loop ileostomy. (a) A soft catheter or a length of nylon tape is passed through a small window made in the mesentery of the ileum, and the ileal loop to be used for the stoma is eased through the hole in the abdominal wall and left protruding a few centimeters above skin level. A suture is placed to mark the distal limb. (b) A semilunar incision is made in the mesenteric border of the distal limb at skin level, extending around most of the circumference of the ileum. (c) A Babcock tissue forceps is inserted into the loop and used to grasp the wall of the proximal limb. The cut edge of the ileum is peeled back to evert the bowel wall and create a spout from the proximal limb of the loop. (d) The stoma is completed by placing interrupted absorbable sutures between the cut edge of the ileum and the subepidermal layer of the skin. A few of these sutures also take a seromuscular bite of the emerging ileum at skin level.

When the stoma starts to function, the clear appliance is changed for the chosen appliance, and the patient is instructed in how and when to empty the pouch. When confident with this aspect of stoma management, the patient is instructed in how to cut the plate to the correct size and how to change the stoma bag or flange (if he or she is using a two-piece appliance). An ileostomy works throughout the day, often showing an increase in activity after meals. The appliance will therefore require regular emptying, a task that some patients find inconvenient. A loop transverse colostomy may be as unpredictable as an ileostomy in this regard; however, a sigmoid colostomy may have a more predictable activity, similar to the frequency of normal bowel movements. Some patients find

that quality of life is improved by irrigating the colostomy with water instilled via a special appliance. This procedure induces a full colonic clear-out and allows the patient to wear a less obtrusive cap appliance for 24 to 48 hours, until irrigation is repeated.

Detailed discussion of stoma care is beyond the scope of this chapter. A key role is played by the enterostomal therapist, who is an important point of contact for the patient, providing advice, instruction, and emotional support in the postoperative period. Skin complications are common, and most can be managed by the enterostomal therapist. Many such complications result from contact between the peristomal skin and digestive enzymes; common causes include poor

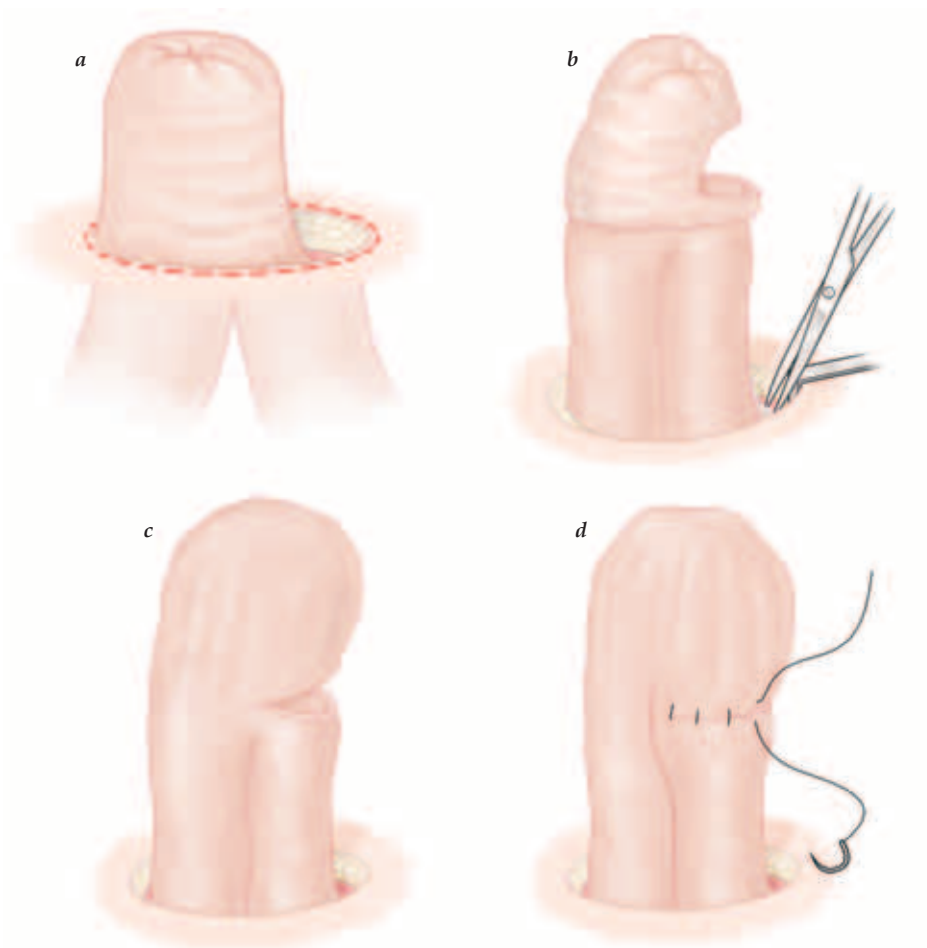


Figure 6 Stoma closure: loop ileostomy. (a) Epinephrine is infiltrated into the subcutaneous tissues around the ileostomy, and an incision is made through the full thickness of the skin 2 mm from the mucocutaneous junction. (b) The emerging ileum is mobilized by dividing adhesions between the bowel and the subcutaneous fat and the abdominal wall until the bowel is completely free. (c) The everted segment of ileum is reduced by a combination of sharp and blunt dissection, and the edge of the opening in the ileum is excised to leave fresh supple ileum for anastomosis. (d) The opening in the ileum is closed with a single layer of interrupted absorbable sutures that take bites of the seromuscular layers only. The ileal loop is then returned to the abdominal cavity, and the defect in the abdominal wall is closed with interrupted nonabsorbable sutures.

appliance fit and stoma retraction. Skin problems can usually be resolved by means of simple measures such as switching to a different appliance, using a convex flange, applying barrier cream, or filling dips in the peristomal skin with stoma paste. Given that surgical complications such as fistula formation and parastomal hernia may present as skin problems, it is important that the surgeon and the enterostomal therapist work closely together in addressing these problems.

Troubleshooting

Wound infection after stoma closure is common. Drainage of the incision with a small corrugated drain can help reduce the incidence of such infection. Some surgeons leave the stoma site open and allow it to heal by second intention.

Incisional hernia can develop in the stoma site, and its incidence is increased by wound infection in the postoperative period. Because the defect is relatively narrow, the hernia can lead to significant symptoms. Repair is usually necessary.

Breakdown of the anastomosis lying beneath the incision will lead to a fecal fistula, with discharge from the stoma site. If the fistula is simple and there is no distal obstruction, it is likely to heal spontaneously. Expert nursing is required to manage the fistula effluent while healing occurs to prevent damage to the surrounding skin.

If there is a complex inflammatory mass at the closure site, spontaneous healing is less likely. Laparotomy may be required, with resection of the stoma site and reanastomosis or further stoma formation, depending on the patient's condition.

Complications

Complications after stoma formation are frequent and varied [see Table 2] and can adversely affect quality of life. The complication rate has been reported to be about 25% after colostomy formation and as high as 57% after end ileostomy²⁰ and 75% after a loop ileostomy.²¹ Cumulative complication rates at 20 years have reached 76% in patients undergoing ileostomy for ulcerative colitis and 56% in those undergoing ileostomy for Crohn disease.²² As noted [see Postoperative Care, *above*], many complications can be successfully managed with enterostomal care.²⁰ This is fortunate because the results of surgical correction are often unsatisfactory, with many patients requiring further surgical revision of their stomas.²³

Careful assessment is warranted when a patient presents with stomal complications. Such complications may be interrelated or may have a different cause from what initial examination suggests. For example, skin damage may be a result of a poorly fitting appliance, but the poor fit may itself be caused by a parastomal hernia or a flush ileostomy. Furthermore, stomal complications may arise from renewed activity of the underlying disease (e.g., recrudescence of Crohn disease^{23–25} or recurrence of cancer).

ISCHEMIA

Mild ischemia of the stoma is common in the early postoperative period but usually resolves within a few days. More profound ischemia can result in necrosis of all or part of the circumference of the bowel end used to form the stoma. Satisfactory healing of the stoma depends on an adequate blood supply. Problems with the blood supply are more common with end stomas than with loop stomas; likely causes include excessive division of mesenteric blood vessels, tension on the stoma from inadequate mobilization, and a too narrow aperture through the abdominal wall that constricts the vessels at the fascial level. It is a good idea to prepare the relevant bowel segment for use in a stoma some time before the end of the operation so that any problems with the blood supply will be evident before the stoma is fashioned. An obviously ischemic stoma should be revised at the time of operation. Such

revision may include mobilization of a more proximal bowel segment.

Patchy necrosis that is confined to the mucosa can be managed expectantly and usually heals by second intention. Complete necrosis of an ileostomy is an indication for urgent revision. Necrosis of a colostomy may not necessitate revision if the segment is short. However, a fistula may form at the fascial level, or stenosis may develop as the necrotic segment heals.

STENOSIS

Stenosis of the stoma is a consequence of postoperative ischemia. Mild stenosis can be managed with simple dilatation and may not cause many symptoms, particularly if the effluent is liquid. Substantial stenosis of a colostomy can lead to subacute obstruction that must be managed with surgical revision. Sometimes revision can be accomplished as a local procedure. A disk of skin that includes the stenosed stoma site is excised. The distal colon is mobilized and sutured to the new skin opening. In most instances, however, it is not possible to mobilize sufficient length with this approach, and laparotomy is required for adequate mobilization.

PROLAPSE

Prolapse may occur with any type of stoma but is most common with loop colostomy. Patients with loop colostomies usually have a degree of parastomal hernia, which allows adequate space for prolapse of the emerging bowel. Appearances are often alarming, and symptoms are usually related to difficulties with fitting an appliance or to leakage. The best treatment option is to close the stoma (if appropriate). Another option is to divide the loop stoma, thus creating an end colostomy, and then to return the closed distal end to the abdomen. Amputation of the prolapsed stoma corrects the problem in the short term, but the prolapse often recurs quickly. Repairing a coexisting parastomal hernia can lower the risk of recurrence, but it involves a more extensive operation [see Parastomal Hernia, *below*]. Neither ensuring that the emerging stoma is brought through the rectus abdominis nor fixing the mesentery to the abdominal wall appears to prevent stoma prolapse.²²

Table 2 Incidence of Common Complications of the Intestinal Stomas

Complication	Ileostomy Patients ¹⁸ (N = 150)	Colostomy Patients ⁴⁶ (N = 126)	Colostomy Patients ⁹ (N = 203)
	n (%) [*]	n (%) [†]	n (%) [‡]
Skin problems	44 (34)	17 (14)	24 (17.4)
Obstruction	27 (23)	9 (7)	11 (13.7)
Retraction	19 (17)	—	3 (1.5)
Hernia	16 (16)	14 (11)	43 (36.7)
Prolapse	12 (11)	4 (3)	11 (11.8)
Fistula	11 (12)	3 (2)	2 (1.0)
Stenosis	6 (5)	11 (9)	10 (7.3)
Necrosis	1 (1)	—	—

^{*}All complications recorded at clinic review. Complication rate expressed as cumulative probability from life-table analysis.

[†]Retrospective review of all patients who underwent end colostomy formation.

[‡]All complications recorded at clinic review. Complication rate expressed as cumulative probability from life-table analysis.

RETRACTION

Stoma retraction is more of a concern with an ileostomy than with a colostomy because of the possibility of leakage from the appliance. Retraction generally results from poor adhesion between the serosal surfaces of the everted stoma but may also reflect the presence of a parastomal hernia. If the retracted ileostomy is fixed in position, laparotomy will probably be required to correct the problem, although it is worthwhile to attempt local mobilization of the stoma after incising the mucocutaneous junction. If the retracted ileostomy is mobile, the problem can be corrected by inserting a series of interrupted absorbable sutures through the full thickness of the everted stoma to fix the walls together. A similar effect can be obtained by pulling the retracted stoma upward with tissue forceps and then fixing the walls together with several firings of a noncutting linear stapler inserted into the ileostomy, with care taken to avoid the mesentery [see Figure 7].²⁶

PARASTOMAL HERNIA

Formation of an abdominal stoma necessarily involves creating a defect in the abdominal wall to accommodate the emerging bowel. Such defects may become enlarged as a result of tangential force applied to the edge of the opening, and this enlargement may lead to hernia formation. The

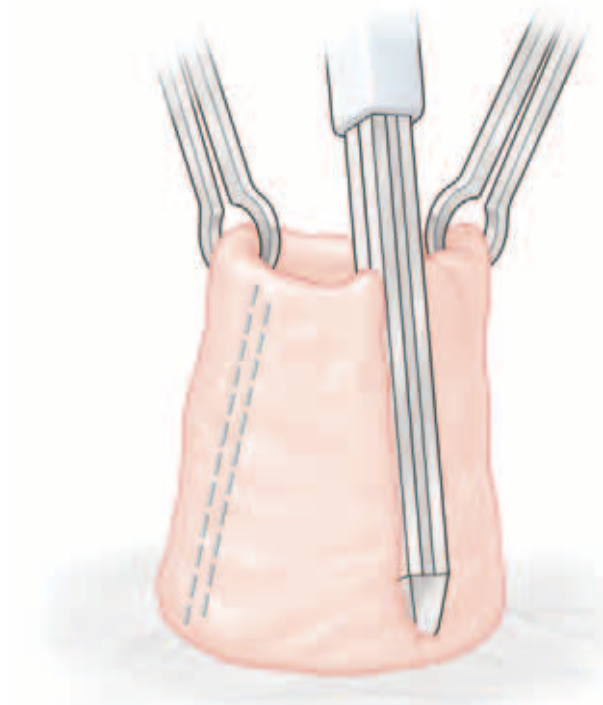


Figure 7 Illustrated is an alternative method of stabilizing a retracted ileostomy. The ileostomy is everted to its full extent with a Babcock tissue forceps. The site of the mesentery is identified. A noncutting linear stapler is inserted with the anvil in the stoma, with care taken to avoid the mesentery. The stapler is fired several times to fix the two walls of the ileum together.

tangential force is related to the radial force and the radius of the opening; in turn, the radial force is related to the intra-abdominal pressure and the radius of the abdominal cavity.²⁷ Consequently, tangential forces are greater in larger openings in obese patients, who are thus at greater risk for parastomal hernia. A recent study demonstrated an incidence of parastomal hernia of 75% in patients with a waist circumference greater than 100 cm compared with an incidence of 46% for the whole group of patients included in this study.²⁸ Patients undergoing emergency procedures, in which dilated bowel is used to form a stoma, are also likely to be at increased risk for hernia formation. Care must be taken to make an opening that is just large enough for the emerging bowel. An incision that admits only two fingers is appropriate for most elective indications.

Several authors have addressed the problem of enlargement of the stoma opening by reinforcing the opening with a prosthetic ring or a sheet of Marlex mesh.^{27,29} One randomized trial compared the incidence of parastomal hernia in patients undergoing conventional end colostomy with the incidence in patients undergoing colostomy with insertion of a partially absorbable lightweight mesh between the posterior rectus sheath and the rectus abdominis.¹² At 12 months, eight of the 18 patients with a conventional colostomy showed evidence of parastomal hernia formation, compared with none of the 16 patients with a mesh-reinforced colostomy.¹² The results remain impressive after a full, 5-year follow-up: 17 of the surviving 21 patients who underwent conventional colostomy formation had developed a paracolostomy hernia compared with only two of 15 surviving patients who had mesh inserted at the time of colostomy formation.¹³ Some controversy remains over the issue of where the stoma site should be located in relation to the rectus abdominis. Some authors claim that hernia formation is less frequent when the stoma emerges through the rectus abdominis^{30–32}; however, other authors dispute this claim,^{9–11} and a clinical and radiologic study of paraileostomy hernia found no differences in incidence between stomas brought out through the rectus abdominis and stomas brought out more laterally.³³

The incidence of parastomal hernia formation varies widely among published studies [see Table 3].^{9,10,24,28,32–50} This wide variation reflects both differences in the length of follow-up and differences in the methods used to identify parastomal hernias. Given that many hernias are small and asymptomatic, the true incidence of hernia formation may well be higher than the reported figures. It is generally accepted, however, that paracolostomy hernias are more common than paraileostomy hernias. It is unclear why this is so, but the reason is likely to involve the size of the opening in the abdominal wall.

Parastomal hernias are often asymptomatic, and in obese patients, they may not be apparent on clinical examination. Patients usually present with an unsightly bulge at the stoma site, but they may also have other symptoms, such as leakage around the stoma appliance, skin problems, or difficulty in irrigating a colostomy. Rarer presenting symptoms include intestinal obstruction and strangulation of the bowel loop within the hernia. Clinical examination usually suffices for making the diagnosis, particularly when performed with the

Table 3 Incidence of Parastomal Hernia Formation

Study	Date	Stoma Type	Duration of Follow-Up (yr)	Total No. of Patients	Patients with Hernia, n (%)
Watts et al ³⁵	1966	Ileostomy	3.4 (mean)	119	3 (2.5)
Burns ³⁶	1970	Colostomy*	1–21	307	16 (5.2)
Saha et al ³⁷	1973	Colostomy*	1–6	200	2 (1.0)
Kronberg et al ³⁸	1974	Colostomy†	1–10	362	42 (11.6)
Harshaw et al ³⁹	1974	Colostomy‡	1–7	99	9 (9.1)
Marks and Ritchie ⁴⁰	1975	Colostomy‡	1–6	227	23 (32.6 [§])
Burgess et al ⁴¹	1984	Colostomy†	1–10	124	6 (4.8)
von Smitten et al ⁴²	1986	Colostomy	8	54	26 (48)
Carlstedt et al ⁴³	1987	Ileostomy	1–26	203	3 (1.5)
Weaver et al ²⁴	1988	Ileostomy	NA	111	9 (8.1)
Sjödahl et al ³²	1988	All stomas [¶]	1–36	130	9 (6.9)
Porter et al ³⁴	1989	Colostomy‡	<8	130	14 (10.8)
Williams et al ³³	1990	Ileostomy [#]	1–16	46	13 (28.2)
Hoffman et al ⁴⁴	1992	Colostomy‡	<10	111	5 (4.5)
Leong et al ¹⁰	1994	Ileostomy†	<20	150	16 (16.0 [§])
Martin and Foster ⁴⁵	1994	All stomas [¶]	NA	242	15 (6.2)
Londono-Schimmer et al ⁹	1994	Colostomy‡	10	203	43 (36.7 [§])
Carlsen and Bergan ⁴⁶	1995	Ileostomy	2.6 (mean)	224	4 (1.8)
Mäkelä et al ⁴⁷	1997	Colostomy	8	80	9 (11.3)
Cheung et al ⁴⁸	2001	Colostomy	7	322	126 (39.1)
Cingi et al ⁴⁹	2006	All stomas [#]	1.3 (median)	23	18 (78)
De Raet et al ²⁸	2008	Colostomy	1–8	41	19 (46)
Moreno-Matias et al ⁵⁰	2008	Colostomy [#]	1–9	73	35 (44)

NA = not available.

*Details of method of follow-up not provided.

†Prospective follow-up of patients undergoing stoma construction.

‡Retrospective study of patients undergoing stoma construction.

§Figure represents cumulative rate, based on life-table analysis.

|| Incidence based on reoperation rate.

¶Patients presenting to a specialist stoma clinic.

#Patients specifically reviewed for hernia formation, clinical examination combined with computed tomographic scan of stoma site.

patient standing. Small hernias in obese patients can be a challenge to diagnose; in this setting, computed tomographic scanning limited to the stoma area can be helpful.^{33,49,50}

Surgical repair of a parastomal hernia often yields disappointing results and should be considered only if the patient's symptoms are troublesome. Many patients manage reasonably well by wearing a suitably adapted appliance and a support belt. When surgical repair is indicated, it follows one of three possible approaches:

1. *Local repair.* This approach to hernia repair is the simplest of the three but also the least successful.^{51–53} The stoma is mobilized, and the sac is identified and removed. The defect in the fascia of the abdominal wall is narrowed around the emerging bowel with a series of interrupted nonabsorbable sutures. The repair is completed by recreating the mucocutaneous anastomosis.
2. *Stoma relocation.* The stoma can be moved to a fresh site on the abdominal wall without reopening the main incision. The stoma is fully mobilized, and a new hole is made

in the abdominal wall. A plane is developed between the peritoneum and the abdominal contents by means of blunt finger dissection between the existing stoma site and the new one. The mobilized stoma is then passed through the new hole.⁵⁴ If difficulties are encountered, a laparotomy will be required. An alternative approach is to reroute the stoma through a new fascial defect while maintaining the existing skin aperture. The original fascial defect is repaired with mesh.⁵⁵

3. *Repair with prosthetic mesh.* Mesh repairs have become increasingly popular as different meshes have become available and as surgeons have become aware of the advantages of these materials in hernia surgery. The mesh can be inserted intra-abdominally,^{56–63} in the preperitoneal plane [see Figure 8],^{51,64,65} or in the subcutaneous plane.^{66,67} Regardless of where the mesh is inserted, the basic principle is the same—namely, to achieve and maintain a narrowing of the stoma site by surrounding the emerging bowel with a sheet of mesh in which a hole is cut to accommodate the stoma. An alternative approach is to cover the

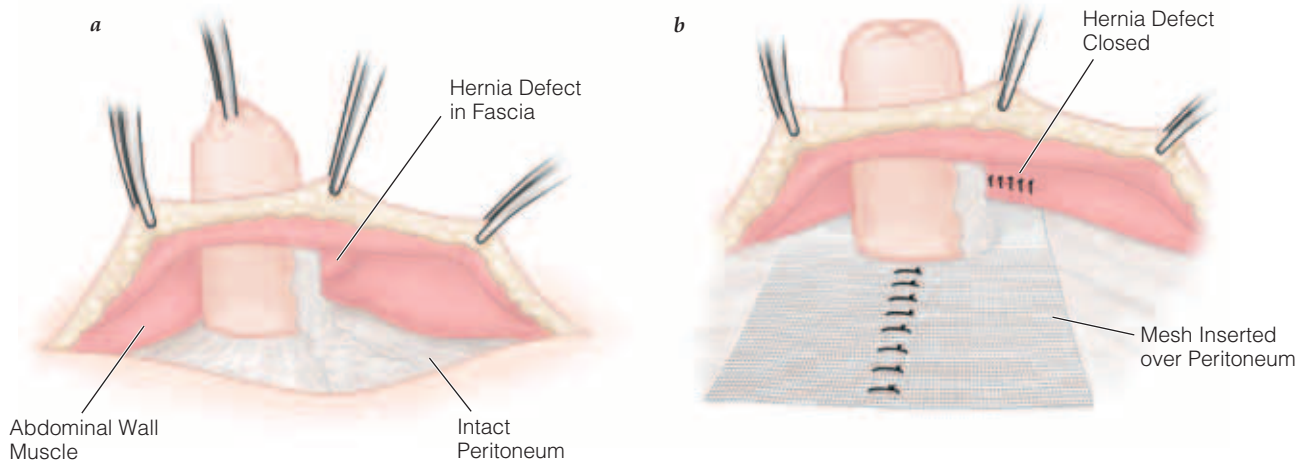


Figure 8 Depicted is preperitoneal mesh repair of parastomal hernia. (a) The midline incision is reopened without disturbing the stoma. The space between the peritoneum and the muscles of the abdominal wall is opened widely, with care taken not to damage the bowel as it emerges from the abdominal cavity. The contents of the hernia are returned to the abdominal cavity, and the defect in the peritoneum is repaired with absorbable sutures. (b) A piece of nonabsorbable mesh is cut to shape to cover the defect in the abdominal wall and to just accommodate the emerging bowel. The mesh swatch is placed round the bowel on the intact peritoneum, and the two tails of the swatch are sutured together to encircle the bowel. The defect in the muscle layer is closed with a few interrupted nonabsorbable sutures.

internal defect of the parastomal hernia with a sheet of mesh, without creating a defect in the mesh for the emerging bowel. The mesh is draped over the inside of the anterior abdominal wall with the emerging bowel passing under the lateral edge of the mesh.⁵⁹ Repair of parastomal hernia lends itself to a laparoscopic approach [see Figure 9], with a growing number of studies describing this approach, with impressive early results and recurrence rates in single figures.^{59–63}

The best method of repair has not been established.⁶⁸ Most published studies have included relatively few patients who were followed for a relatively short time. With longer follow-up, recurrence rates as high as 76% have been reported. Local repair is associated with the highest recurrence rate,⁶⁹ and stoma relocation carries an increased morbidity (from incisional hernia at the original stoma site).⁷⁰ Nor is mesh repair free of problems: intra-abdominal placement of mesh is associated with a significant risk of adhesions to the mesh and

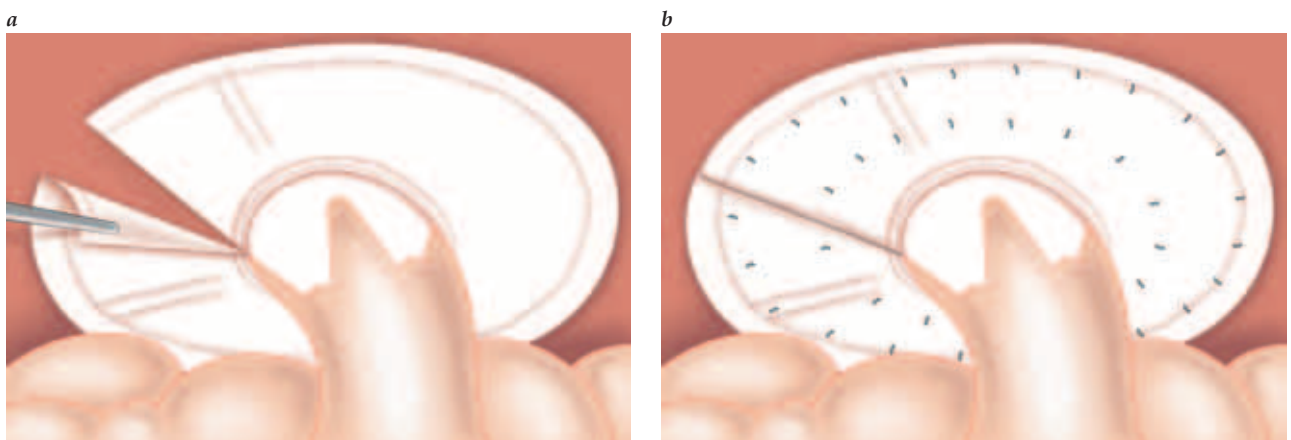


Figure 9 Depicted is laparoscopic intra-abdominal placement of polytetrafluoroethylene coated mesh. (a) The edges of the hernia defect have been defined and the contents of the hernia have been returned to the abdominal cavity. The mesh is passed into the abdominal cavity, rolled up down one of the ports. The mesh is then unrolled and passed round the emerging stoma with the tails of the slit overlapped. (b) The two tails of the mesh are sutured or tacked together to encircle the bowel. Mesh is fixed to the peritoneum of the abdominal wall, either by sutures or a laparoscopic mesh tacking device. Multiple anchoring points are required.

Table 4 Additional Complications Arising after Stoma Formation

Complication	Cause	Differential Diagnosis	Treatment
Bleeding	Trauma	Portal hypertension	Review of stoma appliance and technique
	Inflammatory polyps	Recurrent disease	
Perforation	Traumatic (irrigation)	Stercoral (constipation)	Laparotomy and revision of stoma
	Recurrent disease		
Skin ulceration	Contact dermatitis	Pyoderma gangrenosum	Review of stoma appliance and technique
Cancer formation	Recurrence at stoma site	Inflammatory polyps	Resection
	De novo cancer formation		

of small bowel obstruction.⁷¹ However, series have been reported in which polypropylene mesh has been inserted intra-abdominally without any apparent problems.⁶⁰ More recent developments have seen the use of polytetrafluoroethylene (PTFE) coated mesh, which carries much less risk of adhesion formation between the mesh and the abdominal contents^{58,59,62,63} and biological meshes made from porcine collagen.⁷² The risk of mesh infection is highest when the mesh is placed in a superficial position through a parastomal incision.

At present, the best approach is to tailor repair to the individual patient's condition and situation. Mesh repair is emerging as the procedure of choice, based on short-term follow-up data. Laparoscopic repair using PTFE coated mesh appears to have a number of advantages over open mesh placement, and associated incisional hernia can be repaired during the same operation. This area of surgery has seen rapid developments in the last 5 years, which are likely to continue, with lighter and stronger meshes emerging. There is good evidence in favor of inserting prosthetic mesh at the time of stoma formation in a effort to reduce the incidence of this complication.

OBSTRUCTION

Conditions that may cause intestinal obstruction after stoma formation include stenosis of the stoma, parastomal

hernia, postoperative adhesions, and recurrent disease (e.g., Crohn disease in the proximal ileum or recurrent cancer). Management depends on the cause of the obstruction. Retrograde contrast studies are useful for identifying the site and determining the likely cause of obstruction.

FISTULA

A fistula may form adjacent to a stoma as a consequence of inadvertent full-thickness placement of a suture through both walls of the stoma during formation, pressure necrosis at skin level from a tightly fitting stoma appliance, or recurrent disease, especially Crohn disease in the ileum proximal to the stoma. Surgical treatment usually involves laparotomy and reformation of the stoma at a new site.

OTHER COMPLICATIONS

Other, less common complications arising after stoma formation include bleeding, perforation, skin ulceration, and the development of cancer [see Table 4].

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Figures 1 through 8 Tom Moore.
Figure 9 Monique Guilderson.

31 APPENDECTOMY

Hung S. Ho, MD, FACS

First depicted in anatomic drawings in 1492 by Leonardo da Vinci, the vermiform appendix was described as an anatomic structure in 1521 by Jacopo Berengari da Carpi, a professor of human anatomy at Bologna. Appendicitis became recognized as a surgical disease when the Harvard University pathologist Reginald Heber Fitz read his analysis of 257 cases of perforating inflammation of the appendix and 209 cases of typhlitis or perityphlitis at the 1886 meeting of the Association of American Physicians. In this landmark report, Fitz correctly pointed out that the frequent abscesses in the right iliac fossa were often attributable to perforation of the vermiform appendix, and he referred to the condition as appendicitis.¹ Among his classic observations of the disease was the emphasis on the “vital importance of early recognition” and its “eventual treatment by laparotomy.” It was not until 1894 that Charles McBurney first described the surgical incision that bears his name and the surgical technique that was to become the gold standard for appendectomy.²

Although appendectomy has traditionally been done—and largely continues to be done—as an open procedure, there has been increasing interest in laparoscopic appendectomy in the last two decades. At present, however, the only patients for whom laparoscopic appendectomy appears to offer significant advantages are women of childbearing age, obese patients, and patients with an unclear diagnosis [see Figure 1]. Accordingly, the gold standard for surgical treatment of acute appendicitis remains open appendectomy as described by McBurney, although the occasional patient with chronic appendicitis can be electively treated with the laparoscopic approach.

Operative Technique

OPEN APPENDECTOMY

With the patient under general anesthesia and in the supine position, the abdomen is prepared and draped in a sterile fashion so as to expose the right lower quadrant. The skin incision is made in an oblique direction, crossing a line drawn between the anterior superior iliac spine and the umbilicus at nearly a right angle at a point about 2 to 3 cm from the iliac spine. This point, the McBurney point, is approximately one third of the way from the iliac spine to the umbilicus [see Figure 2]. The subcutaneous fat and fascia are incised to expose the external oblique aponeurosis. A slightly shorter incision is made in this aponeurosis; first, a scalpel is used, and then the incision is extended with scissors in the direction of the fibers of the muscle and its tendon in such a way that the fibers are separated but not cut.

The fibers of the internal oblique muscle and the transversus abdominis are separated with a blunt instrument at nearly a right angle to the incision on the external oblique aponeurosis. The parietal peritoneum is lifted up, with care

taken not to include the underlying viscera, and is opened in a transverse fashion with a scalpel. This incision is then enlarged transversely with scissors. When greater exposure is required, the lateral edge of the rectus sheath is incised and the rectus abdominis is retracted medially without being divided [see Figure 3].

A foul smell or the presence of pus on entry into the peritoneum is an indication of advanced or perforating appendicitis. The free peritoneal fluid is collected for bacteriologic analysis. The ascending colon or cecum is located, and the appendix is found by following the cecal taeniae distally. The inflamed appendix typically feels firm and turgid. The appendix, together with the cecum, is delivered into the surgical incision and held with a Babcock tissue forceps. If this step proves difficult, the appendix can sometimes be swept into the field with the surgeon's right index finger as gentle traction is maintained on the cecum with a small, moist gauze pad held in the left hand [see Figure 4]. Care should be taken at this point not to avulse the friable and possibly necrotic appendix. To deliver a retrocecal appendix, it may be necessary to mobilize the ascending colon partially by sharply dividing the peritoneum on its lateral side, starting from the terminal ileum and proceeding toward the hepatic flexure.

The mesoappendix, containing the appendicular artery, is divided between clamps and ligated with 3-0 absorbable sutures [see Figure 5]. The appendix is held up with a Babcock tissue forceps, and its base is gently crushed with a straight mosquito arterial forceps. The mosquito forceps is then opened, moved up the appendix, and closed again. The base of the appendix is doubly ligated with 2-0 absorbable sutures at the point where it was crushed, so that a cuff of about 3 mm is left between the forceps and the tie.

The appendix is divided by running a scalpel along the underside of the forceps. The mucosa of the appendiceal stump is fulgurated with the electrocautery. The stump is not routinely invaginated into the cecum. In those rare cases in which the viability of the appendiceal base is in question, a 2-0 absorbable purse-string suture is placed in the cecum, and the stump is invaginated as the suture is tied. Alternatively, a partial cecectomy is performed using a gastrointestinal anastomosis (GIA) stapler loaded with an intestinal cartridge. If either maneuver is done, palpation for a patent ileocecal valve is indicated. The operative field is then checked for hemostasis, and the ascending colon is returned back to the abdomen. In cases of perforating appendicitis, the right paracolic gutter and pelvis are irrigated and thoroughly aspirated to ensure that any collected pus or particulate material is removed.

The peritoneum is then closed with a continuous 3-0 absorbable suture. The fibers of the transversus abdominis and the internal oblique muscle fall together readily, and their

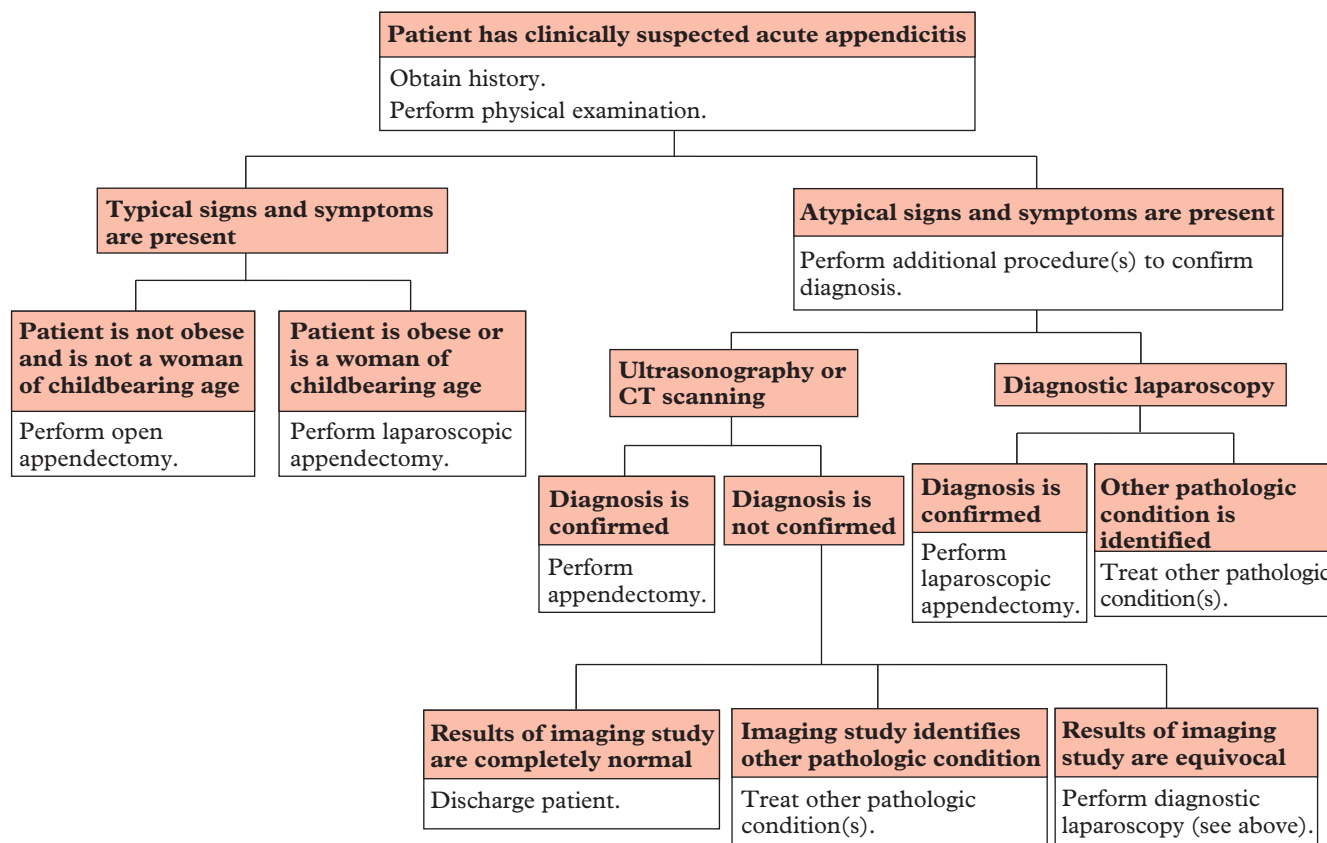


Figure 1 Shown is an algorithm for choosing between treatment options for patients with suspected acute appendicitis. CT = computed tomographic.

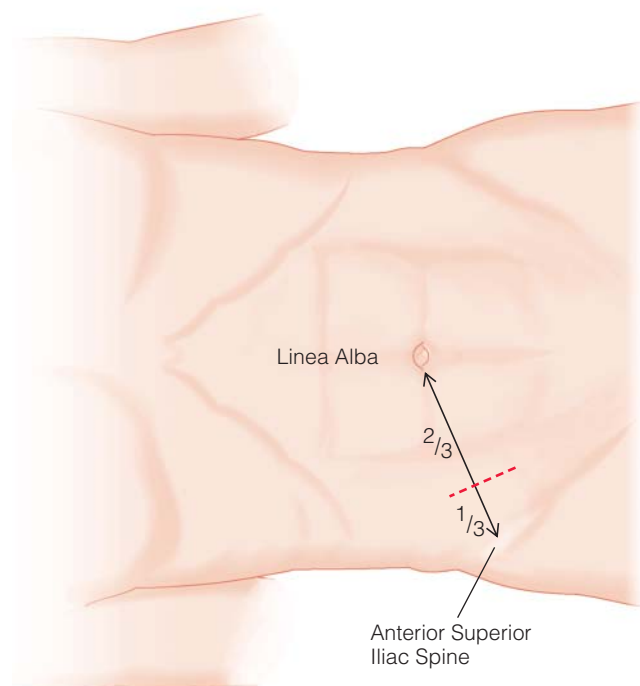


Figure 2 Open appendectomy. Shown are the McBurney point and the McBurney incision.

closure can be completed with two interrupted 3-0 absorbable ligatures. The external oblique aponeurosis is closed from end to end with a continuous 2-0 absorbable suture. The Scarpa fascia is approximated with interrupted 3-0 absorbable sutures, and the skin is closed with a continuous subcuticular 4-0 absorbable suture and reinforcing tapes (Steri-Strips, 3M, St. Paul, MN).

If the wound has been grossly contaminated, the fascia and muscles are closed as described, but the skin is loosely approximated with Steri-Strips, which can easily be removed postoperatively if surgical site infection develops. An alternative approach is to leave the skin and the subcutaneous tissue open but dressed with sterile nonadherent material and then to perform delayed primary closure with Steri-Strips on postoperative day 4 or 5. A meta-analysis of 27 studies involving 2,532 patients with gangrenous or perforating appendicitis concluded that the risk of surgical site infection was no higher with primary closure than with delayed primary closure.³

LAPAROSCOPIC APPENDECTOMY

The patient is under general anesthesia and in the supine position, with both arms tucked along the sides. Decompression with an orogastric tube should be routine, as should placement of a urinary Foley catheter and use of lower extremity sequential compression devices. The abdomen is prepared and draped in a sterile fashion so as to expose the entire abdomen.



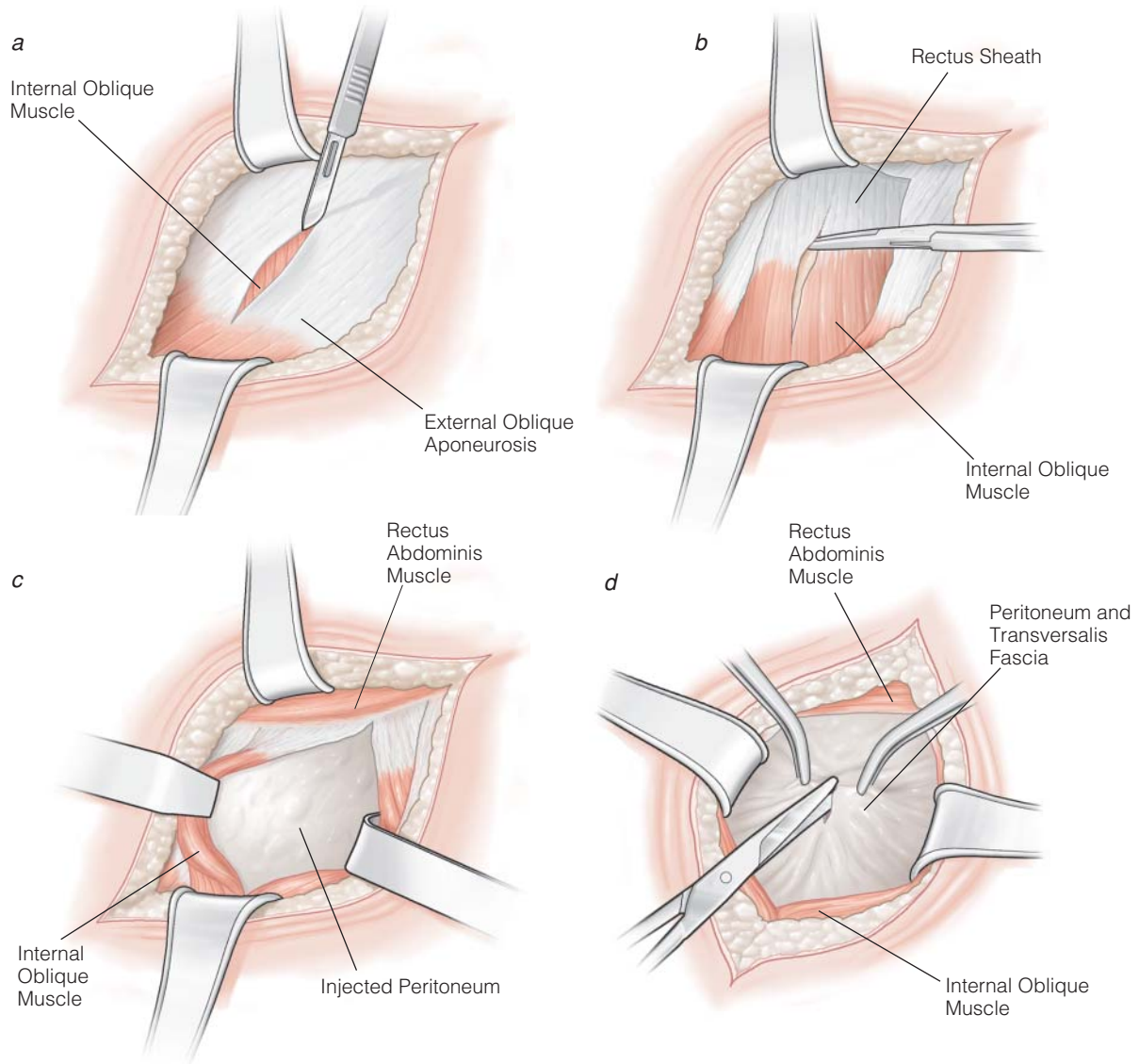


Figure 3 Open appendectomy. Depicted is exposure of the abdominal cavity. The external oblique aponeurosis is opened (a). The fibers of the internal oblique muscle are separated bluntly (b). The parietal peritoneum is exposed (c) and opened transversely (d).

The surgeon should stand on the patient's left side, with the assistant (who operates the camera) near the patient's left shoulder [see Figure 6]. The monitors are placed on the opposite side of the operating table so that both the surgeon and the assistant can view the procedure at all times.

A three-port approach is routinely used [see Figure 6]. All skin incisions along the midline are made vertically to allow a more cosmetically acceptable conversion to laparotomy should this become necessary. The midline suprapubic port must be large enough to accommodate the laparoscopic stapler or specimen retrieval bag (usually 12 mm); the other two ports can be smaller (e.g., 5 or 10 mm). The left lower quadrant port is placed as far away from the operative field as possible to permit the application of a two-handed

dissection technique. The use of a 30° angled scope facilitates operative viewing and dissection.

With the patient pharmacologically relaxed and in the Trendelenburg position, a Veress needle is inserted into the peritoneal cavity at the base of the umbilical ligament. Aspiration and the saline-drop test are performed to ensure that the tip of the needle is correctly positioned. Pneumoperitoneum is established by insufflating CO₂ to an intra-abdominal pressure of 14 mm Hg. The first port is placed at the infra-umbilical skin incision, the laparoscope is inserted, and a complete diagnostic laparoscopy is performed. Once the diagnosis of acute appendicitis is confirmed by inspection, the two remaining ports are placed under direct vision. In many cases, however, the diagnosis cannot be confirmed without

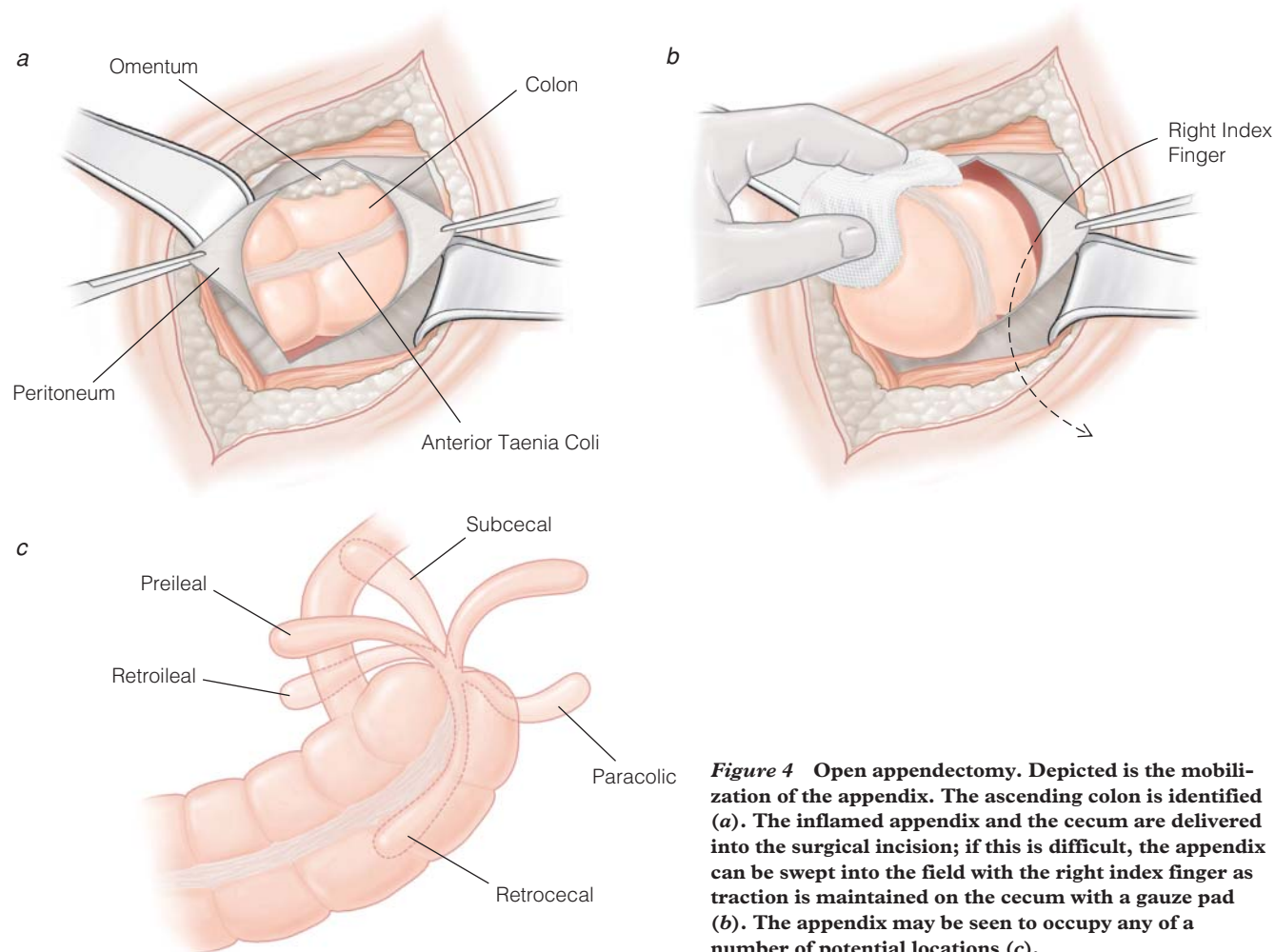


Figure 4 Open appendectomy. Depicted is the mobilization of the appendix. The ascending colon is identified (a). The inflamed appendix and the cecum are delivered into the surgical incision; if this is difficult, the appendix can be swept into the field with the right index finger as traction is maintained on the cecum with a gauze pad (b). The appendix may be seen to occupy any of a number of potential locations (c).

first placing the second and third ports and exposing the appendix. If purulent fluid is encountered, it should be carefully aspirated dry without irrigation to ensure that the infected fluid is not disseminated throughout the abdominal cavity.

The patient is tilted toward the left, and the appendix is exposed and traced to its base on the cecum by using an atraumatic retracting forceps. In cases of retrocecal appendix or severe appendiceal inflammation, it is best first to mobilize the cecum medially by taking down the lateral reflection of the peritoneum around the terminal ileum and up the ascending colon with either endoscopic scissors or an ultrasonic scalpel (e.g., the Harmonic Scalpel, Ethicon Endo-Surgery, Inc., Cincinnati, OH). Surrounding structures, such as the iliac and gonadal vessels and the ureter, should be clearly identified to minimize the risk of injury. Dissection of the appendix can then begin.

The tip of the appendix is grasped and retracted anteriorly toward the anterior abdominal wall and slightly toward the pelvis; the mesoappendix is thus exposed in a triangular fashion. A window between the base of the appendix and the blood supply is created with a curved dissecting forceps. The mesoappendix is divided either with hemostatic clips

and scissors or with a laparoscopic GIA stapler loaded with a vascular cartridge [see Figure 7]. If a window on the mesoappendix cannot be safely created because of intense inflammation, antegrade dissection of the blood supply is necessary. The ultrasonic scalpel is a handy (albeit expensive) instrument for this purpose. Endoscopic hemostatic clips usually suffice to control the small branches of the appendicular artery during the course of this dissection.

The base of the appendix is then cleared circumferentially of any adipose or connective tissue and is divided with a laparoscopic GIA stapler loaded with an intestinal cartridge [see Figure 8]. To ensure an adequate closure away from the inflamed appendiceal base, a small portion of the cecum may have to be included within the stapler. To ensure proper placement of the stapler and to prevent injury to the right ureter or the adjacent small bowel, the tips of the stapler must be clearly visualized before the instrument is closed. The use of an angled scope and an articulated rotating laparoscopic GIA stapler (e.g., Roticulator, AutoSuture, Norwalk, CT) will facilitate this maneuver. Once closed, the stapler should be rotated to inspect the back side before firing. A noninflamed or minimally inflamed appendix can be ligated with sutures, as described earlier [see Open Appendectomy, above].

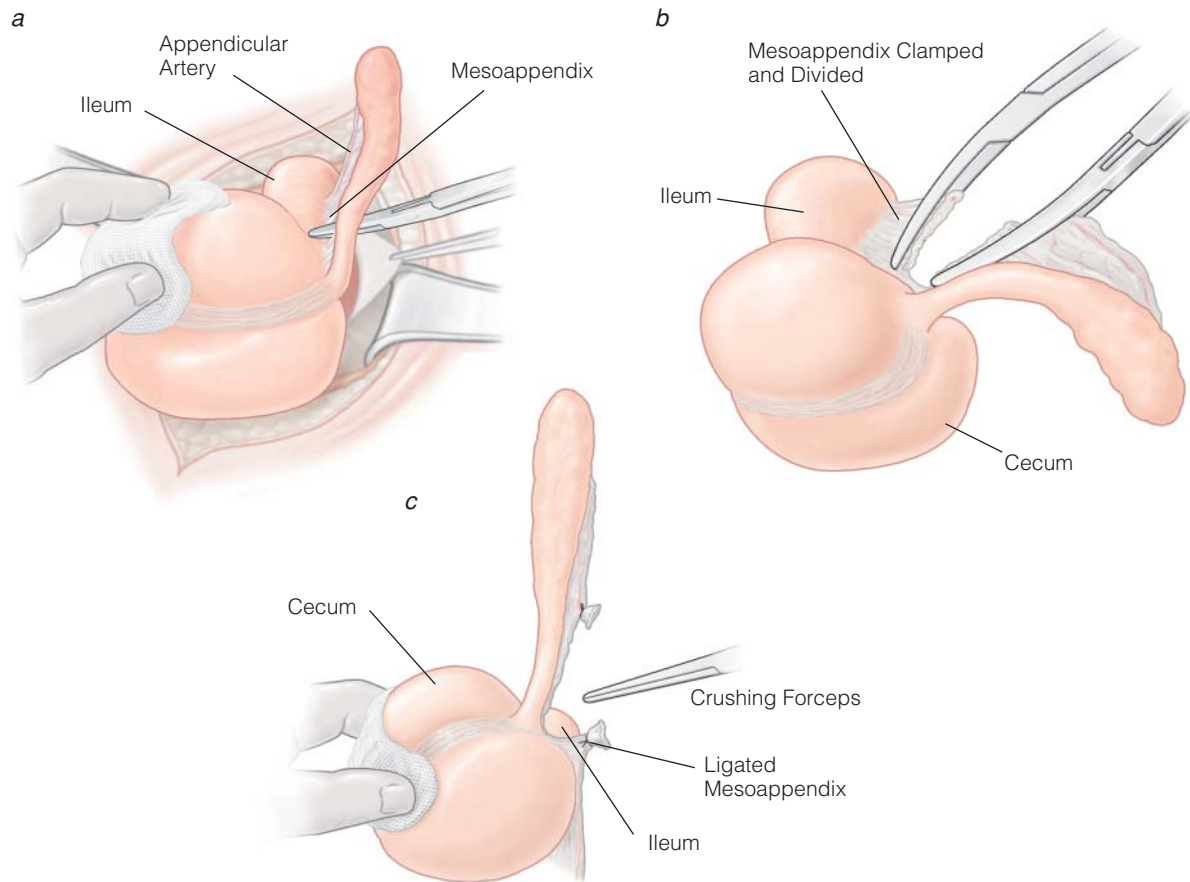


Figure 5 Open appendectomy. The appendicular artery is isolated and controlled (a). The mesoappendix is divided and ligated (b). The appendix is held up in preparation for its ligation and division (c).

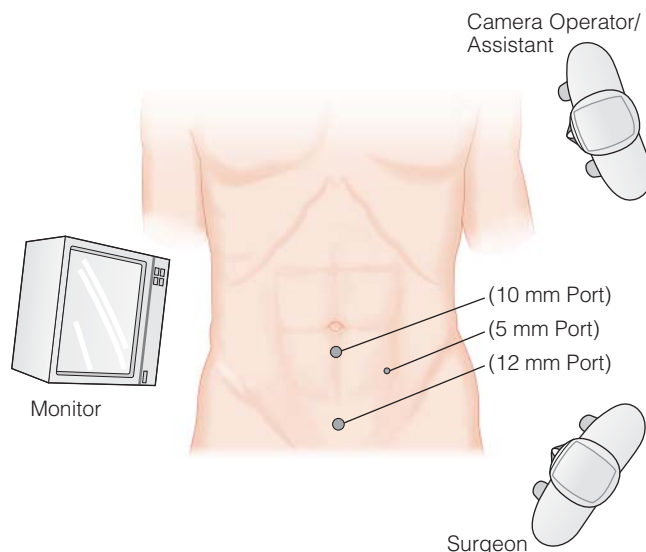


Figure 6 Laparoscopic appendectomy. Shown are the positioning and placement of the operative ports, as well as the recommended positions for the surgeon, the camera operator, and the video monitor.

The appendix is removed from the abdominal cavity, with care taken to avoid direct contact with the abdominal wall. A mildly inflamed appendix can be delivered through one of the larger ports; a severely inflamed appendix is often too big and hence should be delivered in a specimen retrieval bag to avoid contamination [see Figure 9].

Hemostasis is confirmed, and the cecum is inspected to ensure proper closure of the appendiceal stump. The operative field is irrigated and aspirated dry. The ports are removed under direct vision, the absence of back-bleeding from the port sites is confirmed, and the abdomen is completely decompressed. All fascial defects larger than 5 mm are closed with 0 absorbable sutures. The skin incisions are reapproximated with a subcuticular 4-0 absorbable suture and reinforcing tapes (Steri-Strips).

Special Considerations

THE HISTOLOGICALLY NORMAL APPENDIX

Acute appendicitis is the most common cause of an acute surgical abdomen in the United States and remains one of the most challenging diagnoses to make in the emergency

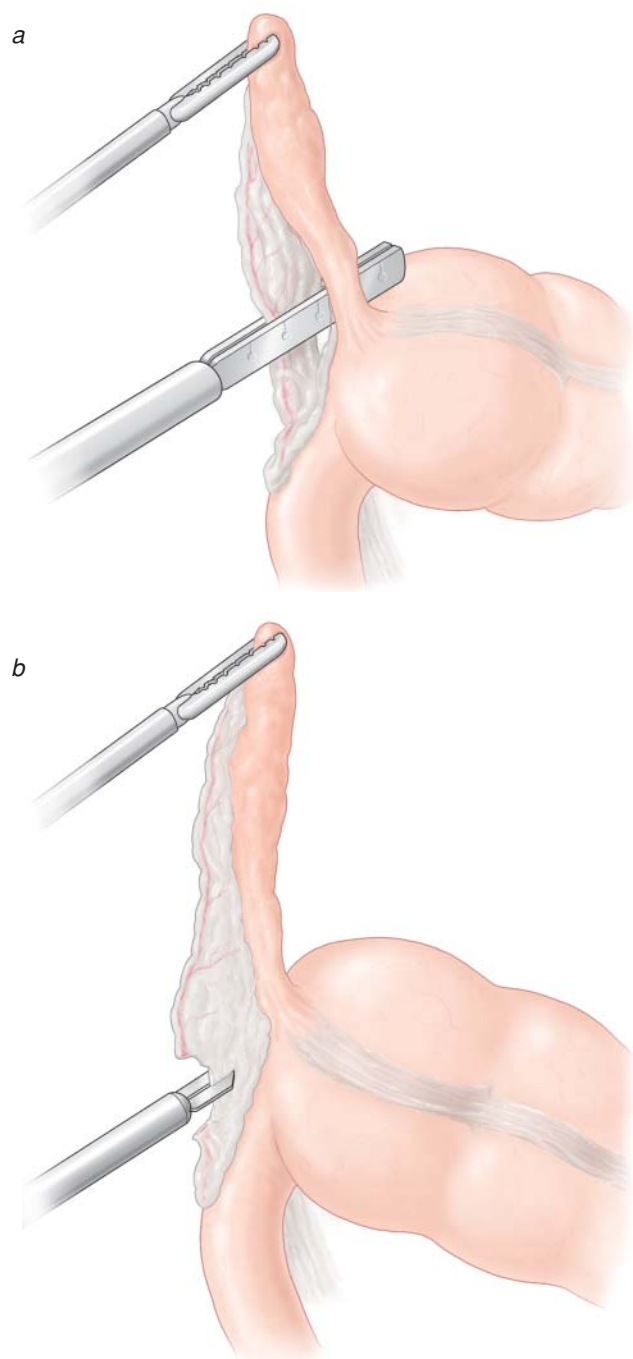


Figure 7 Laparoscopic appendectomy. The mesoappendix is divided either with a laparoscopic gastrointestinal anastomosis stapler (a) or with hemostatic clips and scissors (b).

department. Although the use of advanced diagnostic imaging modalities (e.g., ultrasonography and computed tomography) has led to more accurate diagnosis of acute appendicitis in research settings, it has not been shown to reduce the rate of misdiagnosis of acute appendicitis in the general population.⁴

The incidence of histologically normal appendix in patients with clinical signs and symptoms of acute appendicitis ranges

from 8 to 41%.^{5–14} Nonetheless, appendectomy relieves symptoms in the vast majority of these patients. When extensive sectioning is done on histologically normal specimens, often a focus of inflammation is found in only a few serial sections. This condition is known as focal appendicitis—so called because the polymorphonuclear infiltration is confined to a single focus, whereas the remaining appendix is devoid of any polymorphonuclear cells.¹⁵ It is not clear that all cases of acute appendicitis arise from this focal inflammation; however, such inflammatory foci may be the earliest recognizable manifestations of appendicitis in some so-called negative appendectomies. Furthermore, a substantial proportion of histologically normal appendices removed from patients with clinical signs and symptoms of acute appendicitis exhibit significantly increased expression of tumor necrosis factor- α and interleukin-2 messenger RNA (a sensitive marker of inflammation in appendicitis) in germinal centers, the submucosa, and the lamina propria.¹⁶ Therefore, when a patient with clinically suspected acute appendicitis is explored and the appendix does not appear to be inflamed and no other pathology is encountered, appendectomy is still recommended.¹⁷

Laparoscopic appendectomy has not been shown to reduce the incidence of negative exploration in patients with clinically suspected acute appendicitis [see Complications and Outcome Evaluation, Open versus Laparoscopic Appendectomy, *below*].

APPENDICEAL NEOPLASM

Neoplastic lesions of the appendix are found in as many as 5% of specimens obtained with routine appendectomy for acute appendicitis.^{18–21} Most are benign. Preoperative detection of such conditions is rare, and intraoperative diagnosis is made in fewer than 50% of cases. Appendectomy alone may be curative for appendiceal mucocoele, localized pseudomyxoma peritonei, most appendiceal carcinoids, and other benign tumors. Definitive management of an appendiceal mass unexpectedly encountered during exploration for clinically suspected acute appendicitis depends on whether the tumor is carcinoid, its size and location, the presence or absence of metastatic disease, and histologic and immunohistochemical findings [see Figure 10].

Benign neoplasms of the appendix include mucosal hyperplasia or metaplasia, leiomyomas, neuromas, lipomas, angiomas, and other rare lesions. Appendiceal adenomas tend to be diffuse and to have a predominant villous character. Mucus-producing cystadenomas predispose to appendiceal mucocoele, sometimes accompanied by localized pseudomyxoma peritonei. These lesions are rarely symptomatic and are often encountered incidentally during operation; however, they may also be clinically manifested as acute appendicitis, torsion, intussusception, ureteral obstruction, or another acute condition. If the base of the appendix is free of disease, appendectomy alone is sufficient treatment.

Malignant tumors of the appendix primarily consist of carcinoids and adenocarcinomas; all together, they account for 0.5% of all gastrointestinal malignancies.²² The incidence of malignancy in the appendix is 1.35%.¹⁸ Metastasis to the appendix is rare. Carcinoids are substantially more common than adenocarcinomas in the appendix: as many as 80% of

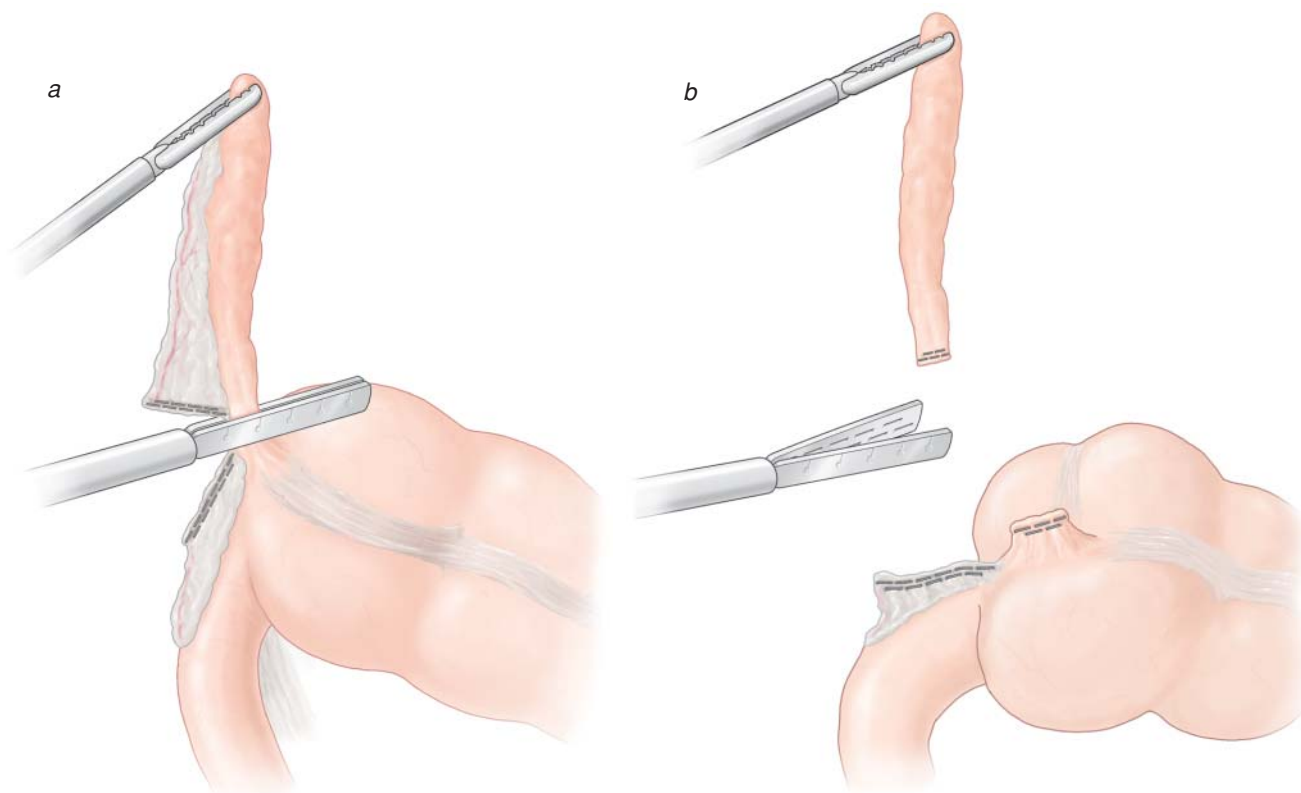


Figure 8 Laparoscopic appendectomy. The mesoappendix having been divided (a), the base of the appendix is cleared circumferentially and divided with a gastrointestinal anastomosis stapler (b).

all appendiceal masses are carcinoid tumors. Overall, carcinoid tumors are found in 0.5% of all appendiceal specimens, and appendiceal carcinoid tumors account for 18.9% of all carcinoid lesions.²³ These tumors are predominantly of neural cellular origin and have a better prognosis than all other intestinal carcinoid tumors, which typically are of mucosal cellular origin. If the tumor is less than 2 cm in diameter, is located within the body or the tip of the appendix, and has not metastasized, appendectomy is the treatment of choice. If the lesion is at the base of the appendix, is larger than 2 cm in diameter, or has metastasized, right hemicolectomy is indicated. In addition, secondary right hemicolectomy is indicated if the tumor is invasive, if mucin production is noted, or if the tumor is found to be of mucosal cellular origin at the final pathologic examination.^{24,25} Patients with metastatic appendiceal carcinoid tumors appear to have a far better prognosis than those with other types of metastatic cancers.²⁴ Therefore, hepatic debulking for symptomatic control is indicated and justified in cases of liver metastasis.

Primary adenocarcinoma of the appendix is rare, and as yet there is no firm consensus regarding prognosis, treatment of choice, and outcome.²⁶ Currently, the recommended treatment is right hemicolectomy: a 1993 study found that this approach resulted in an overall 5-year survival rate of 68% compared with a rate of 20% when appendectomy alone was performed.²⁵ The prognosis is determined by the degree of tumor differentiation and by the histologic stage. As many as one third of these patients have a second primary neoplasm,

which will be located within the gastrointestinal tract about half the time.

Finally, nonepithelial appendiceal tumors, although extremely rare, occur as well. Such lesions include malignant and Burkitt lymphomas, smooth muscle tumors, granular cell tumors, ganglioneuromas, and Kaposi sarcoma.

INFLAMMATORY BOWEL DISEASE

The appendix is frequently involved in Crohn disease and ulcerative colitis (25 and 50% of cases, respectively), but isolated Crohn disease of the appendix is rare.^{27–30} When a histologically normal appendix is encountered in a patient with active Crohn disease, appendectomy should be performed because of the high risk of recurrent right lower quadrant pain, fever, and tenderness. Although isolated Crohn disease of the appendix may present as acute appendicitis, it is not clear that this condition will necessarily develop into a more extensive form of Crohn disease. Appendectomy is safe in such cases because fistulas almost never develop after appendectomy in patients with isolated involvement of the appendix.

GYNECOLOGIC CONDITIONS

It is clear that the presentation of right lower quadrant pain in a woman remains a challenge to the treating physician. Frequently, the causes can be identified by means of proper blood work or ultrasonography, but often they can be revealed only through surgical exploration. In such cases, diagnostic

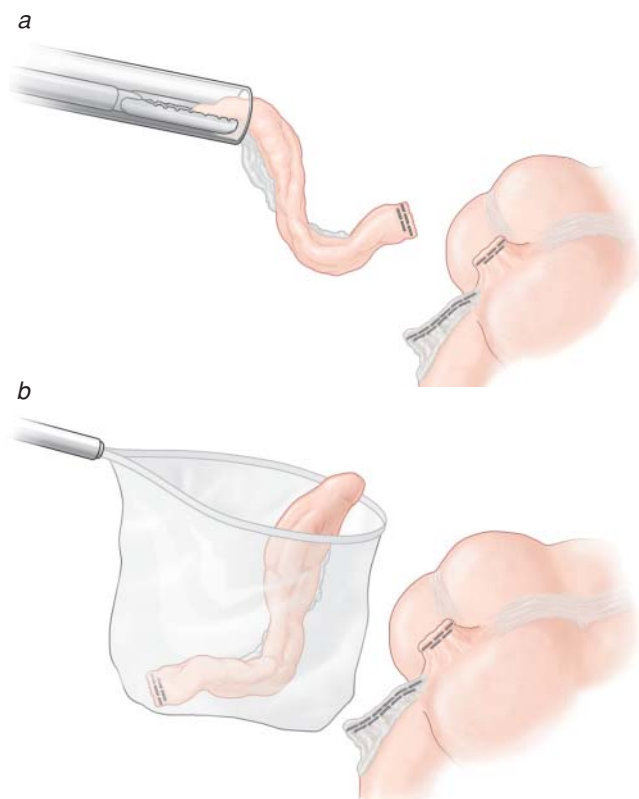


Figure 9 Laparoscopic appendectomy. The specimen is delivered either through one of the larger ports (a) or in a specimen retrieval bag (b).

laparoscopy provides an excellent view of the pelvic organs and offers the potential for easy continuation on to laparoscopic treatment. Ovarian cysts found in premenopausal women include unilocular clear fluid cysts (e.g., follicular cysts and corpus luteum cysts), dermoid cysts, and endometrial cysts. They can be removed by making an incision on the ovary and separating the cyst from the ovarian cortex. Dermoid cysts should be removed in toto to prevent chemical peritonitis. Endometrial cysts are best evaporated with the laser: complete removal is very difficult and sometimes impossible. Torsion of the fallopian tube or the ovary can be reversed by gentle detorsion of the organ with atraumatic forceps. If there is no evidence of ischemia, no further therapy is indicated. If there is gangrene with no indication of recovery, resection is indicated. If the organ shows partial recovery within 10 minutes after the pedicle is untwisted, a second-look laparoscopy is indicated in 24 hours. Pelvic inflammatory disease should be treated on an individualized basis in accordance with the degree of inflammation, the patient's age and desire to have children, and the microbiologic findings.

Complications and Outcome Evaluation

OPEN VERSUS LAPAROSCOPIC APPENDECTOMY

To date, 31 randomized, controlled trials comparing laparoscopic appendectomy with open appendectomy have been

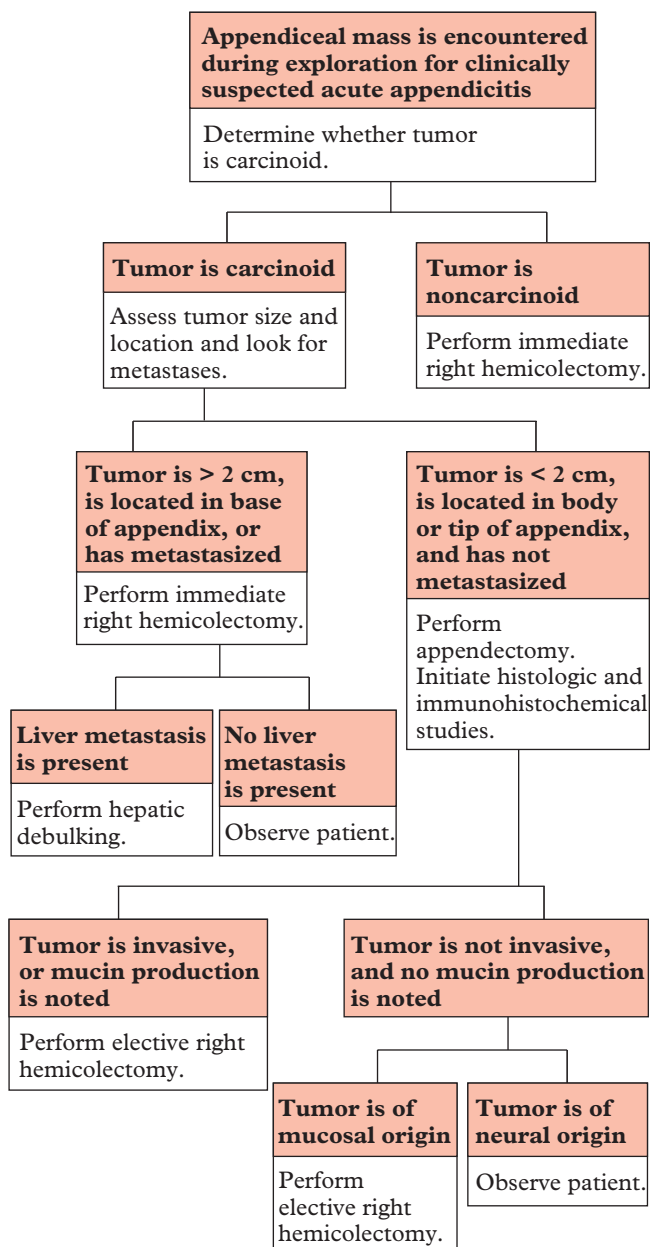


Figure 10 Shown is an algorithm for the management of an appendiceal mass encountered during exploration for clinically suspected acute appendicitis.

published as full articles in English [see Table 1].^{31–61} These reports involved a total of 4,352 patients, of whom 2,194 underwent laparoscopic appendectomy and 2,158 underwent open appendectomy. The incidence of histologically normal appendix (negative appendectomy rate) was similar in the two groups (14.3% with laparoscopic appendectomy versus 14.8% with open appendectomy). The conversion rate from laparoscopic appendectomy to open appendectomy was 10% (range 0 to 23%). Laparoscopic appendectomy was associated with a lower incidence of postoperative wound infection than open appendectomy was (3.5% versus 6.7%), but it was also associated with a higher incidence of postoperative

Table 1 Results of 31 Prospective, Randomized Trials Comparing Laparoscopic Appendectomy with Open Appendectomy^{31–61}

Variable	Laparoscopic Appendectomy (n = 2,194)		Open Appendectomy (n = 2,158)	
	n (%)	Range	n (%)	Range
Negative appendix	314 (14.3)	7.7–36.0%	319 (14.8)	0–35.5%
Conversion to open procedure	223 (10.2)	0–23.9%	NA	NA
Surgical site infection	77 (3.5)	0–18.3%	144 (6.7)	0–17.3%
Intra-abdominal abscess	55 (2.5)	0–7.4%	24 (1.1)	0–4.6%
Days in hospital	2.7	1–4.9	3.2	1.2–5.3

NA = not applicable.

intra-abdominal abscess (2.5% versus 1.1%). The length of stay was slightly shorter after laparoscopic appendectomy (1 to 4.9 days; average 2.7 days) than after open appendectomy (1.2 to 5.3 days; average 3.2 days). There has been no further randomized, controlled trial published since 2005. The inclusion of non-English literature, both in full articles and in abstract reports, by the Cochrane Collaboration⁶² has not led to any significant changes in the general statistical picture. In the 2008 update, the authors concluded that laparoscopic appendectomy seems to have various advantages over open appendectomy, but they are small and of limited clinical relevance.

In men and children with suspected acute appendicitis, laparoscopic appendectomy has no major advantage over open appendectomy.³⁷ In women of childbearing age and in equivocal cases, laparoscopy may be valuable as a diagnostic tool, but the practice of not removing a normal-looking appendix during exploration for right lower quadrant pain remains controversial.^{63,64} Laparoscopic appendectomy appears to offer the potential benefit of less postoperative adhesion formation, but the evidence is inconclusive in light of the short follow-up times reported in these trials, and the higher incidence of intra-abdominal abscess formation remains cause for concern. To date, unfortunately, there have been no studies designed specifically to address reduced adhesion formation as a primary end point.

Although laparoscopic appendectomy is being performed with increased frequency, it continues to be used selectively. Laparoscopic appendectomy is at least as safe as the corresponding open procedure, but it is undeniably more time-consuming and more costly. Moreover, it remains questionable whether the benefits of laparoscopic appendectomy—reduced postoperative pain, earlier resumption of oral feeding, shortened hospital stay, quicker return to normal preoperative activities, and lower incidence of surgical site infection—outweigh the higher incidence of postoperative intra-abdominal abscess formation. **In clinical settings when the patient is either a woman of childbearing age, is obese, or has an unclear diagnosis and where surgical expertise is available and equipment is affordable, a laparoscopic approach may offer significant advantages over an open procedure.** Further randomized clinical studies focusing on the efficacy of laparoscopic appendectomy as a diagnostic tool and on the incidence of postoperative intra-abdominal abscess and adhesion formation are needed, as are additional cost analyses.

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Acknowledgments

Figures 1 and 10 Marcia Kammerer
Figures 2 through 9 Tom Moore

32 PROCEDURES FOR DIVERTICULAR DISEASE

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Preoperative Evaluation

The extent of the preoperative evaluation received by patients undergoing surgical treatment of diverticular disease is dictated predominantly by the urgency of the situation. Whereas patients with recurrent symptoms will undergo repeated assessments with myriad diagnostic tests before the decision is made to proceed with surgical intervention, patients with perforated diverticulitis may have only a chest x-ray documenting free air before they are taken to the operating room. Given the varied complications of diverticular disease and the numerous options for surgical treatment, we believe it is most convenient to divide the relevant operations into emergency procedures and elective procedures. Such a division facilitates discussion of technical issues, preoperative evaluation, and management of complications.

As noted, in the emergency setting, a demonstration of pneumoperitoneum may be the only workup performed. In fact, in most patients with perforated diverticulitis, pneumoperitoneum is the initial presentation.^{1,2} In patients who present with massive lower gastrointestinal hemorrhage, angiographic demonstration of the bleeding site is known to reduce operative mortality, even if therapeutic superselective embolization is unsuccessful in controlling the bleeding.^{3,4} The other complication of diverticular disease that may necessitate an emergency operation is colonic obstruction. A careful history may reveal progressive obstructive symptoms, but if the patient presents with complete obstruction and cecal dilatation, urgent decompression is required. In this setting, retrograde administration of a water-soluble enema may be very helpful—at least for delineating the level of the obstruction, if not the specific cause.^{1,5} Communication with the radiologist should be maintained to prevent both overly forceful instillation of the contrast material and the use of barium, which may cause problems if the agent cannot be evacuated.

When surgical treatment of diverticular disease is to be performed in the elective setting, a detailed preoperative evaluation is imperative. The key point here is that objective evidence of diverticulitis must be obtained at some point in the care of the patient. Too often, symptoms of irritable bowel syndrome are confused with those of diverticulitis, with the result that the patient carries an incorrect diagnosis.^{6–9} In the most common scenario, computed tomographic (CT) scanning is performed when a patient is experiencing left-side pain, possibly associated with fever, nausea, anorexia, or abdominal distention. A finding of pericolic inflammation

in an area of diverticulosis is the definitive radiographic presentation.^{10,11} Preoperative endoscopic evaluation of the colon, whenever feasible, is extremely valuable not only for confirming the presence of diverticulosis but also for ruling out inflammatory bowel disease or even a neoplastic lesion.

It is possible to expend a great deal of effort on trying to demonstrate a diverticular fistula. In many circumstances, however, this task proves difficult to accomplish. In our view, demonstration of a diverticular fistula should not be considered a mandatory precondition for operative treatment. A strong history of either a colovaginal or a colovesical fistula with suggestive findings on CT scans (e.g., air in the bladder or pericolic inflammation contiguous with either the bladder or the vagina) constitutes a sufficient indication for surgical resection.^{12,13}

Operative Planning

In planning the operative approach to a patient with diverticular disease, the major decision is whether to perform a one-stage or a two-stage procedure. Traditionally, an emergency operation for perforation, obstruction, or massive bleeding includes a temporary stoma procedure to eliminate the risk of anastomotic leakage.^{14,15} The operation most commonly performed in this setting is the Hartmann procedure [*see* Emergency Procedures, Hartmann Procedure, *below*], named after Henri Hartmann, who first described the use of this operation to treat colon cancer in 1923.¹⁶ The obvious advantage of the Hartmann procedure is that it removes the inflammatory focus without putting the compromised patient at risk for anastomotic leakage. Unfortunately, to restore intestinal continuity after this procedure, it is necessary to perform a potentially difficult second operation; as many as one third of patients never undergo reversal of their colostomy.^{17,18}

Another therapeutic option is to perform a primary anastomosis with a diverting loop ileostomy instead of a colostomy. In this situation, the risk of anastomotic leakage with possible fecal peritonitis is still avoided, but only a relatively minor second procedure is necessary to reverse the ileostomy.¹⁹ Primary anastomosis with a defunctioning stoma may be the optimal strategy for selected patients with diverticular peritonitis (Hinchey III or IV); it may represent a good compromise between postoperative adverse events, long-term quality of life, and risk of a permanent stoma.²⁰ Occasionally, it may be appropriate to perform on-table colonic lavage with a primary anastomosis. This approach is most useful in the setting of

colonic obstruction secondary to a diverticular stricture in a patient who is otherwise hemodynamically stable but has a large fecal load proximal to the intended anastomosis.^{21,22}

Laparoscopic intestinal surgery has shown tremendous development of late, benefited both by significant technological improvements and by growing surgical experience with advanced laparoscopic procedures.^{23,24} Newer approaches (e.g., hand-assisted techniques) have markedly reduced the learning curve and shortened the operating time.^{25,26} Minimum-access techniques have been shown to reduce the risk of postoperative wound infection and hernia formation.²⁷ Recent literature suggests that fistulizing diverticular disease can be resected safely via a laparoscopic approach with good clinical outcome.^{28,29} Moreover, a recent prospective series has described laparoscopic peritoneal lavage with drain placement for complicated perforated sigmoid diverticulitis as a bridge to interval elective laparoscopic resection with primary anastomosis.³⁰ The newest frontier in elective diverticular resection is single access/port surgery with an operating laparoscope.³¹ Consequently, minimal-access surgery is rapidly becoming the approach of choice in the management of nearly all elective diverticular resections.^{32–35}

Emergency Procedures

Patient setup and positioning are similar for all emergency operations. The patient is placed in a modified lithotomy position to facilitate access to the rectum. Urinary drainage with a Foley catheter and temporary gastric decompression with a nasogastric tube is performed. When feasible, the stoma is marked by an enterostomal therapist before operation.

HARTMANN PROCEDURE

Step 1: Incision and Initial Exploration

A lower midline incision is made and extended above the umbilicus as necessary. The abdomen is thoroughly explored to confirm the diagnosis of diverticular disease and to wash out any gross fecal spillage. A self-retaining retractor (e.g., a Bookwalter retractor) is placed, with care taken to pad the abdominal wall.

Step 2: Mobilization and Division of Sigmoid Colon

The patient is placed in the Trendelenburg position, with the small bowel carefully retracted into the upper abdomen. The sigmoid colon is mobilized away from the lateral peritoneal attachments. Mobilization is continued into the pelvis lateral to the upper portion of the rectum.

Troubleshooting If a severe phlegmon is stuck to the pelvic sidewall, it may be helpful at some point in the mobilization to dissect cephalad from below the mass so as to isolate the area from above and below.

Step 3: Identification of Ureter

As the sigmoid colon is retracted medially, the ureter can usually be identified where it crosses over the bifurcation of the iliac vessels. The gonadal vessels are usually identified first; the ureter lies slightly medial and deep to them [see Figure 1].

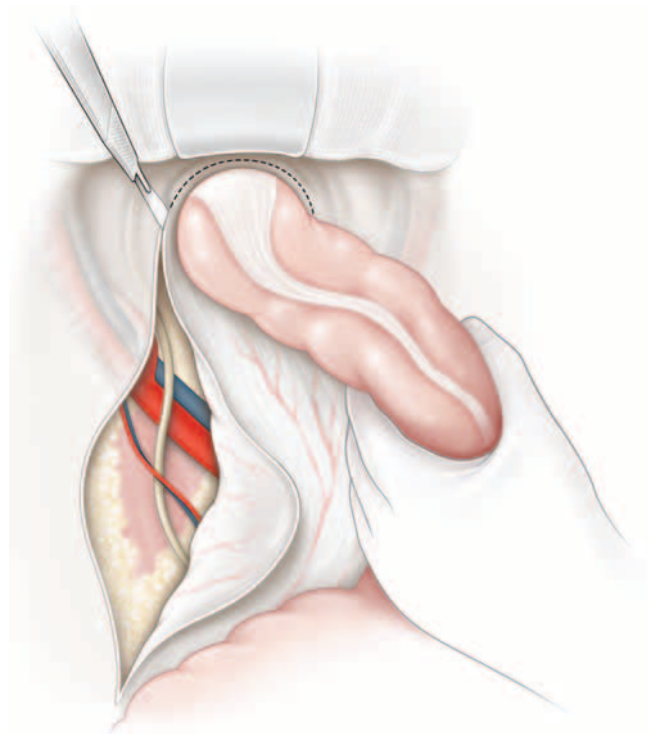


Figure 1 Hartmann procedure. Illustrated is the relation of the ureter to other structures in the left lower quadrant.

Step 4: Division of Sigmoid Colon

The proximal sigmoid colon is divided through noninflamed tissue with a linear cutting stapler [see Figure 2a]. The sigmoid vessels are sequentially divided (with attention paid to their relation to the left ureter) up to the rectosigmoid junction, which is identified by the loss of the taenia coli. The rectum is then transected through noninflamed tissue with a linear cutting stapler [see Figure 2b].

Troubleshooting The top of the rectal stump can be marked with a nonabsorbable suture to facilitate subsequent identification.

Step 5: Construction of Colostomy

The proximal colon is delivered through the previously marked stoma site in the left lower quadrant with a muscle-splitting incision in the rectus abdominis (with care taken not to twist it on its mesentery), and a colostomy is created.

Step 5—Alternative (Primary Anastomosis with Diverting Ileostomy): Creation of Colorectal Anastomosis

As an alternative to a colostomy, the surgeon may elect to perform a primary colorectal anastomosis with a diverting ileostomy. The anvil of a circular stapler is positioned in the proximal colon, and a purse-string suture is placed around it. If there is any gaping of the tissue around the shaft of the anvil, a second suture may be added for reinforcement.

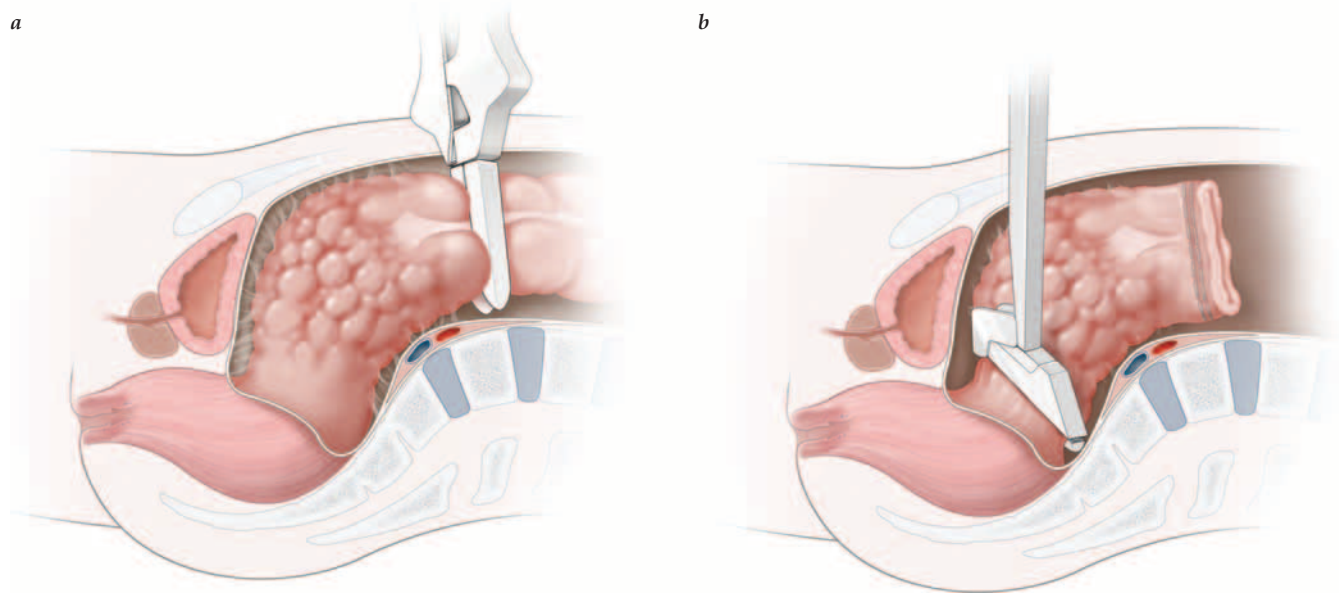


Figure 2 Hartmann procedure. (a) The colon is divided above the level of the inflammatory mass. (b) The rectum is divided below the inflammatory mass; division must be through normal tissue.

The stapler is inserted through the anus, with the shaft being brought out either through the anterior wall of the rectum or through the top of the rectal stump, adjacent to the staple line. The stapler is then engaged, with care taken to ensure that no extraneous tissue is caught between the body of the stapler and the anvil and that the proximal bowel is not twisted on its mesentery. The stapler is fired to create the anastomosis, and the integrity of the anastomosis is tested by occluding the proximal bowel and placing the anastomotic area under water while air is insufflated into the rectum via a rigid proctoscope.

Troubleshooting It is helpful to divide the mesentery where it is draped over the anvil. This measure diminishes the risk of bleeding from the circular staple line while also providing a greater length of colon for the anastomosis. If there is any question regarding possible tension on the anastomosis, the splenic flexure should be fully mobilized.

Step 6—Alternative (Primary Anastomosis with Diverting Ileostomy): Construction of Loop Ileostomy

A loop ileostomy is created in the right lower quadrant using a muscle-splitting incision in the rectus abdominis. Loop ileostomies can usually be designed to be diverting; however, stapling the distal end and leaving it at skin level will ensure complete diversion.

Troubleshooting If there is a column of stool between the ileostomy and the anastomosis, it should be washed out before the ileostomy is completed.

ON-TABLE COLONIC LAVAGE

Steps 1 through 4

Steps 1, 2, 3, and 4 of on-table colonic lavage are the same as the first four steps of the Hartmann procedure.

Step 5: Mobilization of Flexures

After the sigmoid resection, the hepatic flexure and the splenic flexure are carefully mobilized to facilitate the wash-out process.

Step 6: Placement of Tubing

Corrugated anesthesia tubing is placed in the colon proximal to the resected segment and secured in place with umbilical tape. The distal end of the tubing is passed off the operating table and is connected to a device that collects the effluent [see Figure 3].



Figure 3 On-table colonic lavage. Shown is full mobilization of the colon, with corrugated anesthesia tubing secured in the colon and connected to a collection system. A Foley catheter is inserted through an appendicostomy into the base of the cecum.

Step 7: Construction of Appendicostomy

An appendicostomy is performed, a Foley catheter is placed, and a purse-string suture is tied around the tube with the balloon inflated. If the patient has previously undergone appendectomy, the terminal ileum is used instead.

Step 8: Irrigation of Colon

The colon is washed with an irrigant until the effluent is relatively clear. It may be necessary to manipulate the colon so as to initiate flushing of formed stool.

Step 9: Excision of Appendix and Creation of Colorectal Anastomosis

A formal appendectomy is performed. The corrugated anesthesia tubing is removed from the colon, and a colorectal anastomosis is performed, usually with a circular stapler.

Elective Procedures

OPEN RESECTION

Open resection in the elective setting consists of steps 1 through 4 of the Hartmann procedure, followed by creation of a primary colorectal anastomosis and a diverting loop ileostomy (alternative steps 5 and 6) [see Emergency Procedures, Hartmann Procedure, *above*].

LAPAROSCOPIC RESECTION

The patient is placed in a low lithotomy position with minimal hip flexion. The right arm is well padded and tucked at the side because both surgeons will be operating from the right side of the table. Video monitors are placed on both sides of the table. It is beneficial to place the patient on a bean bag because a significant portion of the operation will be performed with the patient in extremes of positioning.

Step 1: Placement of Trocars

The first port is placed at a periumbilical location by means of an open Hasson approach, and a 30° laparoscope is inserted. After pneumoperitoneum is achieved, the other ports are placed under direct vision: 5 and 12 mm ports are placed in the right lower quadrant, and an optional 5 mm port may be placed in the midepigastrium [see Figure 4]. The midepigastRIC port facilitates mobilization of the left colon and is essential for mobilization of the splenic flexure.

Step 2: Mobilization of Sigmoid Colon

After the abdomen has been explored, the patient is placed in a steep Trendelenburg position, with the right side tilted down. This position allows gravity to retract the small bowel into the upper abdomen. The sigmoid colon is mobilized from its lateral peritoneal attachments, and the colon is thereby converted to a midline structure. Mobilization is extended superiorly along the descending colon and inferiorly to the pelvic cul-de-sac. The left ureter is then identified and swept laterally away from the base of the mesentery.

Division of colovaginal or colovesical fistula In most patients, the fistula can be pinched off with no visible defect in either the bladder or vagina or a very small defect. Management

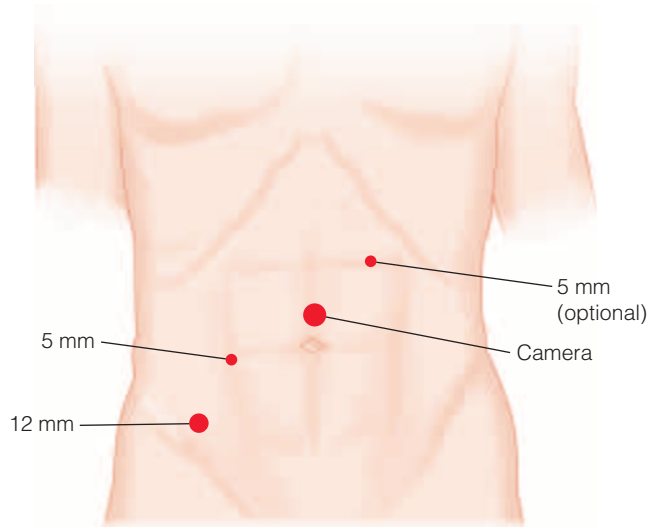


Figure 4 Laparoscopic sigmoid resection. Shown is recommended port placement. The midepigastRIC 5 mm port is essential for mobilization of the splenic flexure.

options include leaving a Foley catheter for 7 to 10 days or placing a few absorbable sutures over the defect and leaving a closed suction drain behind the bladder or vagina.

Alternative approach to colonic mobilization and division In place of the conventional approach (see above), a medial-to-lateral approach can be undertaken. In this approach, the initial dissection proceeds from the right side of the colon, mobilizing the superior rectal vessels from the sacral promontory. The left ureter is then visualized through the window thus created before the sigmoid mesentery is divided. Division of the sigmoid mesentery is performed in a proximal-to-distal direction, with the inferior mesenteric vessels generally divided first. Once the sigmoid mesentery has been completely divided, the bowel is transected with staplers at the rectosigmoid junction.

The advantage of the traditional approach is that surgeons are more familiar with it from corresponding open procedures. In our view, given the difficulty of mastering laparoscopic colon surgery, the medial-to-lateral approach to colonic mobilization only increases the steepness of the learning curve without affording any significant benefit.

Step 3: Division of Rectum and Sigmoid Mesentery

An incision is made in the peritoneum along the right side of the rectosigmoid mesentery and extended inferiorly to the pelvic cul-de-sac. A window is created between the upper rectum and its mesentery and enlarged to allow insertion of an endoscopic gastrointestinal anastomosis (GIA) stapler [see Figure 5]. The stapler is then fired once or twice to divide the rectosigmoid bowel. The mesentery of the sigmoid colon is sequentially divided with staplers, clips, an ultrasonic scalpel, or the LigaSure system (Valleylab, Boulder, Colorado).

Step 4: Exteriorization of Sigmoid Colon

Once the colon is mobilized and the blood supply divided, either the Hasson incision is enlarged or a Pfannenstiel incision is made to exteriorize the bowel, which is then divided

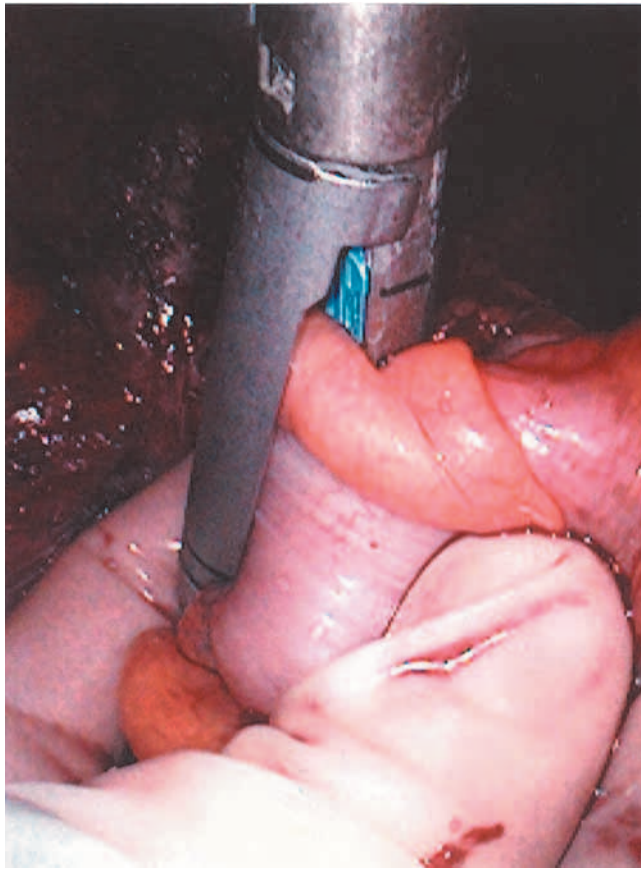


Figure 5 Laparoscopic sigmoid resection. Shown is division of the rectum with the endoscopic stapler.

proximally. The anvil of a circular stapler is inserted in the proximal colon and secured with a purse-string suture. The bowel is then replaced into the abdomen, and the incision is closed.

Step 5: Creation of Colorectal Anastomosis

After pneumoperitoneum is recreated, the circular stapler is inserted transanally. The shaft is brought out either through the top of the rectal stump or through the anterior wall of the rectum [see Figure 6]; the former is preferred if bowel length is an issue. After the stapler is engaged but before it is fired, the proximal colon is inspected to confirm that it is not twisted. The stapler is then fired, and the anastomosis is then tested under water to confirm the absence of an air leak. Intraoperative colonoscopy may also be performed to ensure the integrity of the anastomosis. If a leak is detected, laparoscopic sutures can be placed across the anastomosis and tied either intracorporeally or extracorporeally. This process is more challenging for leaks detected in the posterior aspect of the staple line. Underwater testing is then repeated.

HAND-ASSISTED LAPAROSCOPIC RESECTION

Steps 1 and 2

The first two steps of a hand-assisted laparoscopic resection are identical to steps 1 and 2 of a full laparoscopic resection.

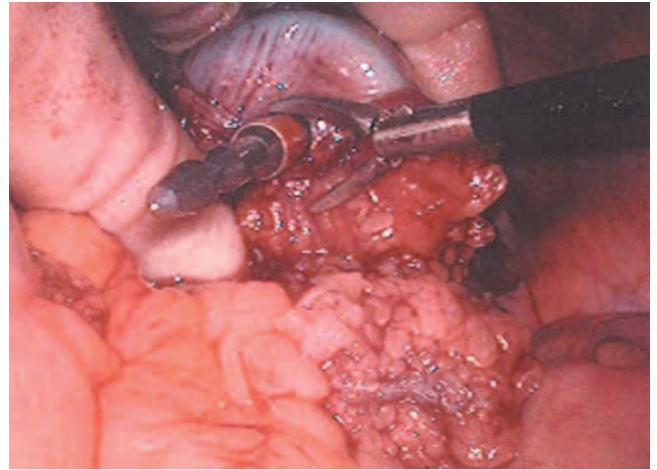


Figure 6 Laparoscopic sigmoid resection. The shaft of the circular stapler is guided through the top of the rectal stump by applying countertraction with a laparoscopic instrument.



Figure 7 Hand-assisted laparoscopic resection. Shown is the placement of one of the hand devices through which the surgeon's hand is advanced into the pelvis.

Step 3: Placement of Hand Device

A 6 to 8 cm muscle-splitting incision is made in the left lower quadrant, and the hand device is placed [see Figure 7]. The surgeon's left hand is placed through this device into the abdomen.

Step 4: Division of Rectum and Sigmoid Mesentery

The surgeon's left hand is used to facilitate creation of a window between the rectum and the underlying mesentery. An endoscopic GIA stapler is safely guided through this window, and the bowel is divided [see Figure 8a]. The hand is then used to isolate segments of the mesentery for division [see Figure 8b], as well as to help control vessels that continue to bleed despite having been divided.

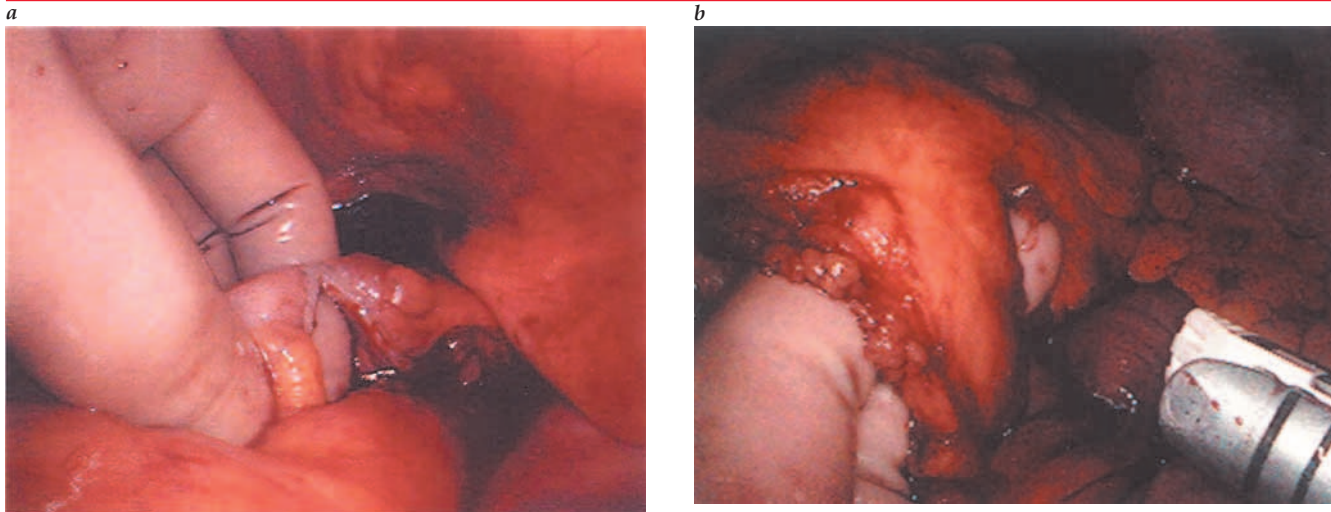


Figure 8 Hand-assisted laparoscopic resection. (a) Placement of the surgeon's hand intracorporeally facilitates division of the rectum. (b) The surgeon's hand isolates mesenteric vessels for subsequent division.

Steps 5 and 6

Steps 5 and 6 are identical to steps 4 and 5 of a full laparoscopic resection.

Troubleshooting Having the surgeon's hand in the pelvis greatly facilitates engagement of the circular stapler and makes its closure safer by protecting the surrounding structures [see Figure 9]. Furthermore, the presence of the hand in the pelvis not only assists in testing the anastomosis but also helps the surgeon better assess the degree of tension (if any) on the anastomosis. Given that the size of the hand port is similar to that of the extraction site in a full laparoscopic resection, we recommend that a hand-assisted approach be used in difficult or complex cases.

LAPAROSCOPIC HARTMANN CLOSURE

Step 1: Placement of Trocars

A port is placed by means of the Hasson technique at an upper midline location, cephalad to the previous incision if possible. A 30° laparoscope is inserted through this port. After pneumoperitoneum is achieved, two 5 mm ports are placed in the right lower quadrant to facilitate dissection of pelvic and midline adhesions as necessary.

Step 2: Mobilization of Colostomy and Rectal Stump

All adhesions and attachments should be cleared away from the intra-abdominal portions of the colostomy [see Figure 10]. In addition, the top of the Hartmann pouch should be cleared of all adherent small bowel or adjacent structures. Occasionally, other ports may have to be placed to facilitate takedown of adhesions, especially those from the original midline incision. The colostomy is detached from the skin circumferentially. The anvil of a circular stapler is then placed in the proximal bowel after the exposed portion of the colostomy has been resected.

Step 3: Placement of Hand and Completion of Anastomosis (for Hand-Assisted Approach)

The colostomy site is enlarged slightly so that the surgeon's left hand can be placed in the abdomen. The stapler is

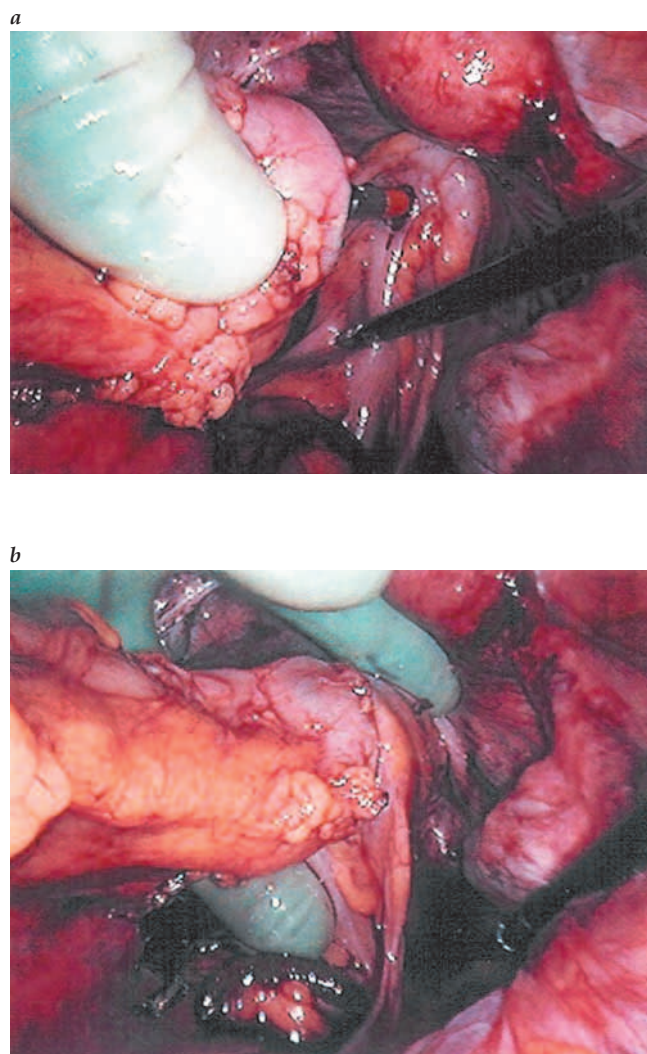


Figure 9 Hand-assisted laparoscopic resection. The surgeon's hand guides engagement of the circular stapler, protecting surrounding pelvic structures.

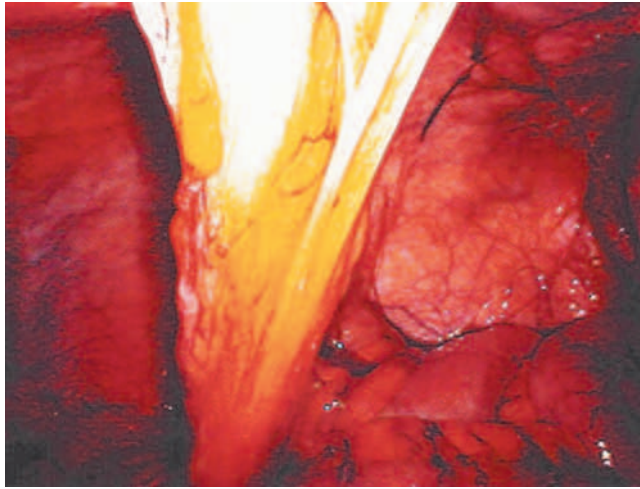


Figure 10 Laparoscopic Hartmann closure. Shown is a laparoscopic view of the colostomy after intra-abdominal adhesions have been divided.

engaged and fired while the surgeon's hand keeps any extraneous tissue away from the anastomotic area. The anastomosis is then tested by placing it under water and insufflating air via a proctoscope.

Troubleshooting It is often easier to bring out the shaft of the stapler through the anterior wall of the rectum, especially if there has been a significant inflammatory response around the area of the Hartmann pouch. Occasionally, the end of the Hartmann pouch cannot be reached with the stapler secondary to rectal tortuosity and a lengthy stump. The operator can guide the stapler with his or her hand, attempt further mobilization and resection of the stump, and/or bring the spike through at a more distal location and leave a blind segment of rectum, as long as the distal sigmoid colon is resected.

Complications

Operative management of diverticular disease poses distinct challenges, the level of which is proportional to the degree of inflammation present and to the urgency of the procedure. Whereas many of the complications encountered are not specific to this setting but are common to all abdominal procedures, there are several that warrant particular attention in the context of surgical treatment of diverticular disease.

ANASTOMOTIC LEAKAGE

The most serious and potentially life-threatening complication of procedures for diverticular disease is the development of an anastomotic leak. Many factors contribute to the maintenance of anastomotic integrity, ranging from the surgeon's technical ability to the patient's comorbidities. Of these factors, however, the single most important one is probably the setting in which the operation is carried out. Patients undergoing emergency procedures are at four times higher risk for anastomotic leakage than those undergoing elective procedures.^{36,37} Furthermore, mortality is 13% in patients presenting with purulent peritonitis and 43% in those presenting with feculent peritonitis; these figures suggest that performing an anastomosis in these settings is unwise.^{14,15,38,39}

As with any anastomosis, the long-established basic technical principles—using healthy, uninflamed tissue; ensuring an adequate blood supply; and avoiding tension on the anastomosis—should be strictly adhered to. If any of these principles cannot be followed, then either the patient should undergo proximal diversion or (preferably) the problem with the anastomosis should be corrected. For instance, in a situation where the sigmoid inflammatory process extends into the rectal mesentery, attempts should be made to resect below the level of the inflammation, even if the process is reaching well into the rectum itself. Another technical point worth mentioning involves preserving the superior rectal vessels, although no randomized, prospective study has yet been performed to determine whether this measure has any significant positive effect.

RECURRENT DISEASE

It is unusual for a recurrent diverticular fistula to develop after takedown with resection of the involved colon. Much more likely than the persistence of a diverticular fistula is the development of a recurrent colovesical or colovaginal fistula secondary to an anastomotic leak with drainage through the point of least resistance (i.e., the anastomosis).

There is some question as to whether a recurrence of diverticulitis after sigmoid resection is actually a complication of the procedure. Although it has been shown that resection of all diverticulum-bearing colon is not required for successful treatment of the disease process, it does appear that the location of any remaining diverticulosis influences the recurrence of the disease. Studies have demonstrated that if a sigmoid resection with a colorectal anastomosis is performed, the recurrence rate is 5%, whereas if the anastomosis is performed to the distal sigmoid colon, the recurrence rate rises to 12%.^{40,41} When recurrent diverticulitis develops, it is important to reexamine the histologic findings from the original operation to rule out the possibility that the patient was misdiagnosed. Occasionally, diverticulosis and Crohn disease coexist; recurrence of Crohn disease is much more common than recurrence of diverticulosis and, given a long enough follow-up period, is actually to be expected.

URETERAL INJURY

Ureteral injuries occur in as many as 1% of patients undergoing diverticular resection.⁴² Because of the inflammatory process associated with severe diverticular disease, it may be difficult to identify the ureter as it crosses the bifurcation of the iliac vessels; however, it is always possible to identify the ureter more proximally and then follow it down to the inflamed area. If a difficult dissection is anticipated or if technical difficulties are encountered intraoperatively, ureteral stents may be placed. These stents do not prevent injuries from occurring, but they can facilitate early identification of developing problems. Ureteral injuries should always be repaired at the time of operation, in consultation with the urologist.

ANASTOMOTIC STRICTURE

Occasionally, patients may experience feelings of incomplete evacuation, tenesmus, or abdominal bloating. These symptoms may be indicative of an anastomotic stricture. Confirmation may be obtained using a Gastrografin enema or

flexible endoscopy. The incidence of symptomatic anastomotic stenosis after elective laparoscopic sigmoidectomy is reported to be as high as 17.6%.⁴³ Although no single risk factor could be identified, adherence to good surgical principles of a tension-free anastomosis with adequate blood supply is essential. It is our opinion that less than an intraluminal stapler (Ethicon) 29 mm or end-to-end anastomosis 31 mm stapler should never be used to perform the

anastomosis. The treatment of fibrotic strictures ranges from dilatation or division with electrocautery to resection of the stricture with performance of a new anastomosis.

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Acknowledgments

Figures 1 and 2 Dragonfly Media Group.
Figure 4 Tom Moore.

33 THE SURGICAL MANAGEMENT OF ULCERATIVE COLITIS

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Inflammatory bowel disease is divided into two broad categories: Crohn disease and chronic ulcerative colitis (CUC). The role of medical therapy in CUC is directed at symptom control or at the underlying inflammatory process. Medications are not curative for either the intestinal or the extraintestinal manifestation of CUC. Unlike Crohn disease, the intestinal manifestations of CUC and the associated risk of malignancy can be effectively cured by surgical intervention, which involves removal of the entire large intestine. CUC is an inflammatory condition limited to the mucosa of the rectum and colon. It is characterized by contiguous inflammation beginning in the rectum and progressing for variable distances proximally. The etiology of the disease is unknown. This chronic inflammatory state is characterized by intermittent exacerbation of the disease notable for bloody diarrhea associated with urgency and tenesmus. In a minority of patients, the first episode of the disease can be a fulminant presentation that might be fatal without prompt surgical intervention. The indications for surgery and the surgical options are quite varied.

Surgery for CUC is indicated in a variety of situations. The easiest classification scheme divides the indications for surgery into two categories: emergency and elective surgery. Emergency surgery is performed in those patients who present with fulminant disease that cannot be treated medically, toxic megacolon, or massive hemorrhage. In these situations, the primary surgical strategy is to remove the bulk of the diseased colon to allow the patient's medical condition to improve. An important secondary consideration is to perform an operation that will not preclude a future restorative procedure such as ileal pouch-anal anastomosis (IPAA). Elective surgery encompasses a number of diverse indications. Given the chronic nature of CUC, the indications for surgery may occur early in a patient's disease or may arise after years of relatively mild disease. The indications for elective surgery in CUC include (1) failure of medical management to control symptoms; (2) complications associated with side effects of medications; (3) stricture formation; (4) mucosal dysplasia, dysplasia-associated lesion or mass (DALM), or malignancy; (5) extraintestinal manifestations of CUC; and (6) growth retardation in children.

Currently, there are two widely accepted surgical options for the treatment of CUC: a total proctocolectomy with an end (Brooke) ileostomy and total proctocolectomy with IPAA.

A third option, total abdominal colectomy with an ileorectal anastomosis, may be considered in a highly select group of patients: those who have relatively mild disease and who have a contraindication to an ostomy, such as portal hypertension or ascites, or those in whom an ileal pouch procedure would be technically impossible, and the patient refuses to have an ileostomy. Previously, a fourth option was employed, proctocolectomy with construction of a continent ileostomy or Kock pouch. However, there was such a high rate of pouch dysfunction that often required surgical correction in the majority of patients that this operation is no longer routinely offered or performed. Also, given the outstanding functional results of the IPAA procedure, the continent ileostomy is only of historical interest and is not discussed further.

Overall, the choice of surgical procedure needs to be individualized to the patient, based on the underlying physical and medical condition as well as the social and psychological situation. Today, in the majority of patients, the preferred operation is the proctocolectomy with IPAA because it removes the diseased colon while preserving fecal continence and nearly normal defecation through the anus. In almost all series of patients who have had an IPAA, the majority of patients report good functional results and a high degree of satisfaction with quality of life, which is stable over time. Adaptation of newer technologies such as laparoscopic surgery to this procedure might further increase patient satisfaction and decrease morbidity.

Indications for Surgery in Ulcerative Colitis

EMERGENCY SURGERY

Fulminant Colitis

Although CUC commonly is a chronic disease that allows deliberate and coordinated care, occasionally, patients present with severe disease. This is the initial presentation in approximately 10% of patients.¹ Fulminant disease is characterized by the sudden onset of severe frequent bloody bowel movements (more than 10 per day), abdominal pain, dehydration, and anemia [see 5:13 *Fulminant Ulcerative Colitis*]. Criteria for fulminant colitis, as originally described by True-love and Witts in 1955, include the above signs and symptoms and at least two of the following conditions: tachycardia, body temperature higher than 38.6°C, leukocytosis (more than

10,500 cells per decaliter), and hypoalbuminemia.² These patients are extremely ill and require rapid aggressive medical therapy. Medical therapy consists of fluid resuscitation and correction of electrolyte abnormalities. Blood transfusions may be necessary. The patient should be given nothing by mouth. Nasogastric tube decompression may be required if colonic distention is a component of the presentation. If the patient is known to have CUC, then high-dosage intravenous steroids should be initiated. Stool cultures should be obtained. If no previous diagnosis of CUC has been made, the patient should undergo expeditious endoscopic evaluation of the colon. Urgent endoscopy is meant not to evaluate the entire colon but only to visualize the rectal and distal colonic mucosa. If the examination is obviously consistent with CUC, then the endoscope can be withdrawn without evaluating the remainder of the entire colon. If the patient is clinically stable, there is no indication for antibiotic therapy. However, if the patient is very ill or has a high fever or leukocytosis, appropriate broad-spectrum antibiotics should be initiated after cultures are obtained. The patient should be observed closely for 24 to 48 hours while on maximal medical therapy. If there is no improvement or if the patient's condition deteriorates, then surgery is advised. If there is evidence of peritonitis, hemodynamic instability, or perforation, the patient should be operated on immediately.

Toxic Megacolon

Another surgical emergency is toxic megacolon [see 5:13 *Fulminant Ulcerative Colitis*]. This process may be the initial presentation of ulcerative colitis or may represent a flare in a patient with long-standing disease. The entire colon or an isolated segment of the colon (usually transverse or the left colon) is involved. Although there is a radiographic definition of toxic megacolon being dilatation of the transverse colon greater than 5.5 cm on a supine abdominal film, toxic megacolon is truly a clinical diagnosis. The medical treatment of toxic megacolon is similar to that used for patients with fulminant colitis, namely, nothing given by mouth, nasogastric tube decompression, correction of fluid deficits and electrolyte abnormalities, high-dosage steroids, and antibiotics if there is fever or an elevated leukocyte count. Emergency surgery is indicated if the patient's clinical or radiographic status worsens, if there is evidence of perforation, or if there is no improvement 24 to 36 hours after beginning aggressive medical therapy. Delaying surgery increases the risk of perforation, which raises the mortality from less than 5% to nearly 30%.¹ Fortunately, fewer patients are seen with the severe complications of CUC today because of improved medical therapies and earlier surgical intervention in patients with CUC.

Other Surgical Emergencies

Other surgical emergencies in CUC patients are perforation and severe hemorrhage. A patient presenting with a perforation without megacolon should raise concern that the actual diagnosis could be Crohn disease or that there is another cause for the perforation, such as a gastric or duodenal ulcer related to steroid use. Whatever the cause, there is no role for conservative therapy, and the patient should immediately undergo exploration.

Hemorrhage resulting in hemodynamic instability is an unusual complication. Decisions regarding intervention are made after consultation with the treating gastroenterologist. Initial treatment should be aggressive fluid and blood-product resuscitation. Correction of any electrolyte or clotting deficiencies should be undertaken. Identification of another possible source of bleeding should be sought by upper endoscopy to exclude a possible gastric or duodenal ulcer. The timing of operation is determined by the clinical situation. If the patient is hemodynamically unstable even after effective resuscitation, then operation is indicated because medical therapy takes too long to decrease the mucosal inflammation responsible for the bleeding. If there is slow but continuing hemorrhage that does not cause hemodynamic instability or symptoms, then a trial of high-dose steroids may be instituted for 48 to 72 hours prior to consideration of surgery.

ELECTIVE SURGERY

Elective surgical intervention in CUC is performed to address the intractability of symptoms or complications of prolonged medical treatment, for dysplasia, or for suspected or known malignancies. Intractability is a clinical definition occurring in both the acute and chronic states of CUC. During an acute flare, intractability refers to the inability to control a patient's symptoms on maximal medical therapy, whereas in the chronic state, it refers to either the inability to taper steroids to a reasonable maintenance dose or the development of severe drug-related side effects. The most common medical management of an acute CUC flare is with intravenous steroid therapy for 5 to 10 days. If there is no clinical improvement, then elective surgery is recommended. Some centers recommend the initiation of intravenous or oral cyclosporine for patients suffering from an acute flare of CUC not responding to intravenous steroid therapy.³ However, a recent report with a larger number of patients and longer follow-up showed that nearly 50% of all patients subsequently required colectomy within 1 year.⁴ It is important during this treatment period for acute disease that the patient receives adequate nutritional support, often through the use of total parenteral nutrition. A significant decline in the nutritional status of the patient may result in the need for a three-stage surgical procedure to improve the surgical outcomes.⁵

Elective surgery is also appropriate if there is a finding of dysplasia or a malignancy in the colon. The development of malignancy in the setting of CUC has been well described. The estimated risk of colon cancer in a patient with CUC has been estimated to be anywhere from 2% at 20 years after onset of CUC to 43% at 35 years.⁶ A patient's individual risk for colon cancer is likely increased if there is evidence of high-grade dysplasia on random colon biopsies or if there is a DALM. The presence of low-grade dysplasia on random biopsy is a more difficult clinical situation; most clinicians recommend increasing the frequency of surveillance colonoscopies and not surgery. However, some preliminary reports indicate that the presence of any degree of dysplasia not associated with a mass lesion should be viewed with a very high degree of suspicion, and surgery should be recommended.⁷ Also, any colonic stricture, even if it is benign appearing on endoscopy or is significant enough to cause obstructive symptoms, should be considered to harbor a malignancy, and the

patient should proceed to surgery. If there is a suspected or known colonic or rectal malignancy, oncologic principles should drive the surgical options. In most patients, except for patients with low rectal cancers or metastatic disease, total colectomy with IPAA is an acceptable surgical treatment modality. In the setting of a rectal cancer, there is a particular concern about performing an IPAA as any required radiation may severely compromise pouch function. In general, CUC patients with malignancies have a stage-for-stage prognosis similar to that of patients without CUC. Those patients who have undergone surgery, particularly with an IPAA, tolerate the chemotherapy as well as cohorts of patients without CUC.⁸⁻¹⁰ In general, if oncologic principles are not compromised, then an IPAA can be performed without a deleterious impact on oncologic outcomes or long-term IPAA function.

Surgical Procedures for Ulcerative Colitis

The choice of operation depends on a number of factors that must be individualized to the patient's clinical condition. Currently, there are three major operative approaches used in the treatment of ulcerative colitis: (1) proctocolectomy with an end ileostomy, (2) total colectomy with IPAA, and (3) total abdominal colectomy with ileorectal anastomosis. In general, the operative approach used is dictated by the presentation of the disease either requiring emergency or elective operation.

For those patients who require emergency surgery, are in a poor medical condition because of their underlying disease, or are significantly immunosuppressed, a three-stage procedure is performed. Stage I is total abdominal colectomy with a Hartmann closure and an end ileostomy. This allows the majority of diseased colon to be removed, thus improving the patient's clinical condition while being tapered off of any immunosuppressive medications. Once recovered and clinically ready for another operation, again depending on the patient's condition, stage II entails either a completion proctectomy with end ileostomy or an IPAA with diverting loop ileostomy. In the latter situation, the patient will have to undergo a third stage to reverse the ileostomy. The reason behind not performing a proctectomy in an emergency is that, by leaving the rectum in place, a restorative operation can be performed in the future without having disturbed the dissection planes in the pelvis. In addition, an emergency proctectomy is associated with a higher risk of bleeding and injury to the nerves of the pelvic floor, bladder, and genitalia. Usually, the small amount of diseased tissue left behind does not present a clinical problem. In the nonemergency setting, the procedure of choice in the appropriate patient is the IPAA with a diverting loop ileostomy. However, in some practices, placement of a diverting loop ileostomy is selectively omitted.

ILEAL POUCH-ANAL ANASTOMOSIS

IPAA is considered the standard elective surgical therapy for the treatment of CUC. Parks and Nichols first described the procedure in 1978.^{11,12} The decision to proceed with operations other than IPAA is based on individual patient circumstances or preexisting medical or physiologic conditions that are contraindications for this type of restorative procedure. IPAA is the ideal operation for the treatment of

CUC because it removes the entire diseased organ while simultaneously preserving the normal anatomic route for defecation. Construction of the ileal pouch is the key to the success of this operation as it provides an adequate fecal reservoir to allow voluntary defecation, albeit at a higher but manageable daily frequency than for patients with an intact rectum.

Since the introduction of IPAA in the early 1980s, the procedure continues to evolve, especially with the application of new technologies such as laparoscopic surgery.¹³⁻¹⁵ The operation basically involves four phases: (1) removal of the intra-abdominal colon; (2) dissection and removal of the rectum, sparing the pelvic nerves and the anal sphincter mechanism; (3) construction of an ileal reservoir; and (4) anastomosis of the ileal reservoir to the anal canal.

The general techniques, both open and laparoscopic, used at the Mayo Clinic are described below. Depending on surgeon preference, the patient may receive a bowel preparation the evening before surgery. Oral antibiotics are not used. The patient receives appropriate intravenous antibiotic in the operating room within 1 hour of incision. Once induced into anesthesia, the patient is positioned in the modified lithotomy position, which allows easy access to both the abdomen and the perineum.

For the traditional open technique, the abdomen is entered through a midline vertical incision starting at the pubis and extended as far cephalad as required to remove the colon. The abdomen is thoroughly explored to determine if there are any technical or pathologic contraindications to proceeding with the total colectomy and IPAA. The entire colon is mobilized from its retroperitoneal attachments. The transverse colon is freed from the greater omentum, which is preserved if it is of good quality and quantity. Once the intra-abdominal colon has been mobilized, the terminal ileum is divided from the right colon adjacent to the ileocecal junction using a linear stapling device. The mesentery is divided as close to the right colon as possible to avoid injuring the ileocolic vessels supplying the terminal ileum. Once the right colon has been mobilized, the remainder of the colon is divided from its mesentery in a routine fashion. When the intra-abdominal colon has been fully mobilized and the mesentery has been divided, the patient is placed in a steep Trendelenburg position to facilitate the pelvic dissection of the rectum. The rectum is freed down to the pelvic floor. Great care is taken to avoid the pelvic nerves that lie in the interface between the mesorectum and the presacral fascia. The rectum is divided at the pelvic floor with a stapling device [see Figure 1]. The entire colon and rectum is then sent for pathologic evaluation.

After the colon has been removed, the ileal pouch is constructed. The small bowel mesentery is completely mobilized from the retroperitoneum up to the inferior border of the pancreas. It is important to perform this mobilization completely to ensure adequate length for the ileal pouch to reach the pelvic floor. Also, to increase the length, the visceral peritoneum is scored at intervals along the course of the vessels supplying the distal small bowel. Once the mesentery has been mobilized, the pouch is fashioned. It has become our practice to use the J-shaped reservoir constructed from the last 30 to 35 cm of the terminal ileum. The J-shaped reservoir is simpler to construct, uses less intestine length, and is associated with fewer complications related to pouch-emptying

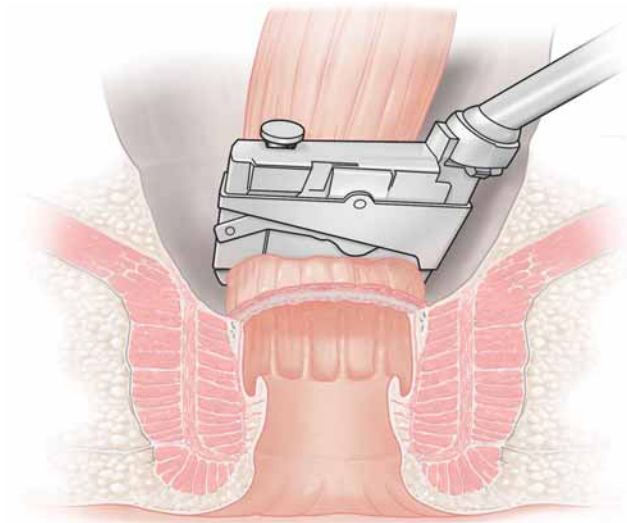


Figure 1 Once the rectum has been dissected down to the level of the pelvic floor, it is divided with a stapler. The stapler is positioned 1 to 2 cm above the dentate line and fired. This positioning ensures that the final pouch-anal anastomosis is within the anal canal and not in the rectum.

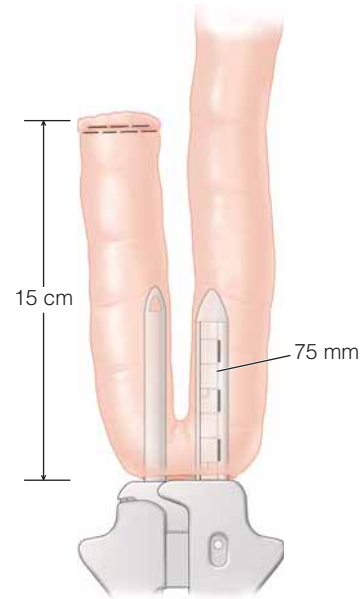


Figure 2 The ileal pouch is constructed by dividing the common wall of the afferent and efferent limbs of the distal ileum by means of multiple firings of a linear cutting stapler.

problems than other described - or -type reservoirs. To ultimately achieve a pouch with a reservoir capacity of approximately 400 cc, the pouch is constructed by folding the terminal ileum into a J shape. The hook of the “J” should be approximately 15 cm in length. This efferent limb of the J is then loosely secured to the afferent limb of the small bowel.

Prior to forming the reservoir, an adequate length of small bowel has to be determined. To ensure that the pouch will reach the pelvic floor and the region of the anastomosis without tension, the apex of the pouch should be able to be pulled 3 to 5 cm below the upper aspect of the pubic symphysis. If after full mesenteric mobilization and scoring of the visceral peritoneum the pouch does not easily reach the pelvic floor, it may be necessary to divide either the ileocolic vessel or one of the proximal branches of the superior mesenteric vessels. When there is a concern that the J-shaped reservoir will not reach the pelvic floor satisfactorily, one may alternatively construct an - or -shaped pouch. If the J pouch will reach the pelvic floor, the reservoir is constructed by two firings of the 75 mm linear cutting stapling device from the apex of the pouch dividing the common wall between the two limbs of the J pouch [see Figure 2]. Prior to bringing the pouch down to the anus, it is important to verify that the small intestine from the ligament of Treitz to the ileal pouch is not twisted. At this point in the operation, one of two options is available to perform the anastomosis. The pouch may be secured to the anal canal by performing a double-stapled technique in which the head of the end-to-end anastomosis (EEA) stapling device is secured in the apex of the pouch with a purse-string suture [see Figure 3]. The stapling device is then placed into the anus, and the attachment pin is placed through the staple line where the rectum was divided at the level of the pelvic floor. The pouch is then brought down into the pelvis, maintaining the proper orientation, and the stapled anastomosis is performed [see Figure 4].

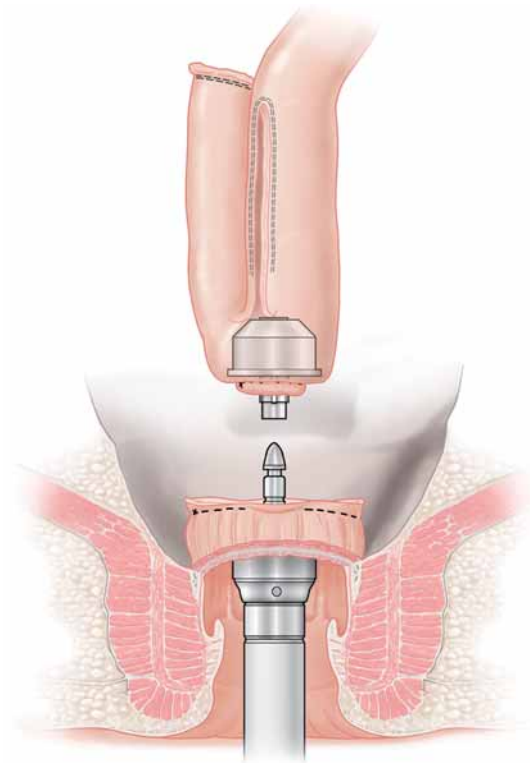


Figure 3 After the pouch is constructed, the head of an end-to-end anastomosis stapler is secured in the apex of the pouch and connected to the pin of the stapler, which is placed upward through the anus.

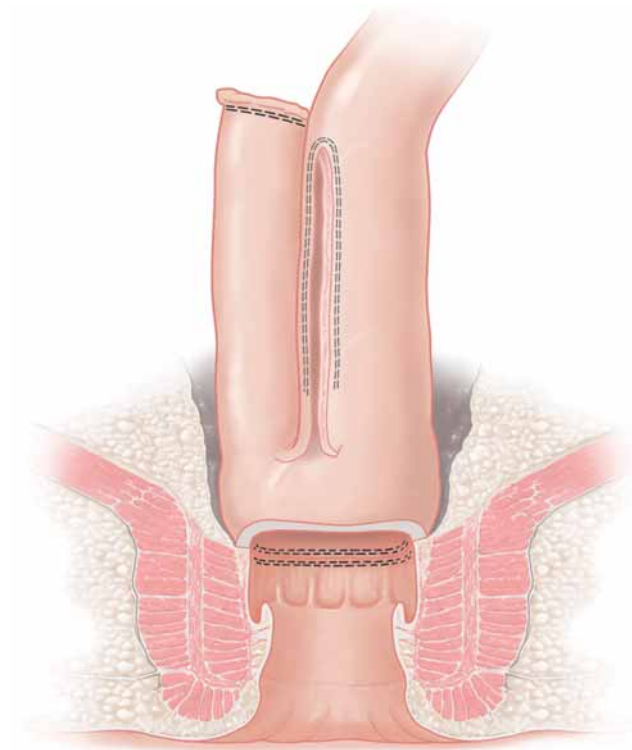


Figure 4 Shown is the completed ileal J pouch with the circular stapled anastomosis within the anal canal, just above the dentate line.

The other anastomotic option is to perform a mucosectomy of the anal canal and lower rectal remnant. To perform the mucosectomy, the dentate line area is exposed using a Lone Star retractor. A dilute solution of epinephrine is injected into the submucosa to facilitate circumferential excision of the anal canal mucus, leaving the muscularis propria intact. The excision is carried proximal to the level of the stapled rectum. Once the staple line is reached, the full thickness of the rectal wall is divided, allowing removal of the intact lower rectal remnant and the anal canal mucus. A long Babcock clamp is placed into the pelvis through the anal opening, and the pouch apex is brought down to the level of the dentate line. A side-to-end handsewn anastomosis between the apex of the pouch and the dentate line is performed with absorbable suture. Once the anastomosis is completed, one or two closed suction drains are placed behind the pouch and brought out of separate left abdominal stab wounds. In the majority of patients, we construct a loop ileostomy in the right lower abdomen.

Two to 3 months after the original operation, the patient has a Hypaque study through the anus. If the reservoir and the anastomosis have healed without evidence of a leak, then the loop ileostomy can be reversed during a second operation. Often the ileostomy can be closed by mobilizing the ileostomy through a small transverse biconvex incision around the stoma. The loop of the ileum is then fully mobilized and an end-to-end handsewn anastomosis or a stapled side-to-side functional end-to-end anastomosis is performed to close the ileostomy site.

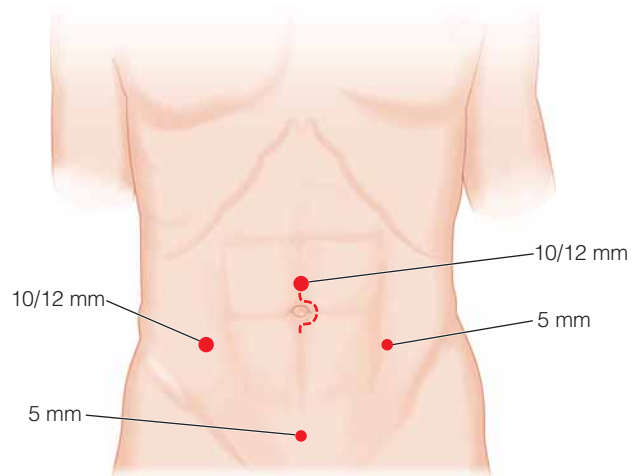


Figure 5 Four trocars are placed in a diamond-shaped pattern: a 12 mm trocar is placed supraumbilically for the camera, another 12 mm trocar is placed in the right lower quadrant, a 5 mm trocar is placed in the left lower quadrant, and another 5 mm trocar is placed above the pubis. A disk of skin and fat is excised for the ileostomy.

LAPAROSCOPIC IPAA

Laparoscopic approaches for IPAA were developed to reduce the impact of this procedure on patients who are already physiologically stressed, decrease the length of hospital stay, reduce morbidity, and improve cosmesis. The initial reports of laparoscopic IPAA were discouraging because of very long operative times and no real beneficial impact on postoperative recovery.^{16–19}

Subsequent reports, from our institution and others, have clearly demonstrated the benefits of a minimally invasive approach in regard to postoperative decreased length of stay, narcotic use, and decreased overall morbidity.^{20,21} The technical demands of laparoscopic IPAA have been addressed by developing a simplified technique, building on lessons learned from segmental procedures. Our laparoscopic approach to the IPAA has been described in detail elsewhere.²² In brief, a four-port technique is used [see Figure 5], a lateral-to-medial dissection of both the right and the left colon is performed, and intracorporeal division of the mesentery is performed followed by an intracorporeal mobilization of the rectum. A 4 to 5 cm periumbilical incision is made for specimen extraction, and the right lower quadrant (RLQ) port site is used for the ileostomy.

Operating Room Set-Up, Positioning, and Personnel

As work proceeds in different quadrants of the abdomen and pelvis, the monitors are moved between the patient's shoulders and ankles, in line with the surgeon's field of view. An instrument stand is placed above the head, and a larger instrument table is placed behind the scrub nurse. Both arms are tucked adjacent to the body, and the thighs are level with the abdomen to prevent interference with instruments used in the lower ports. The patient is carefully secured (e.g., with padded straps or bean bag) as steep position changes are used.

The bladder is decompressed with a urinary catheter as well as the stomach with an orogastric tube, which is removed at the end of the case. In general, the first assistant stands opposite the surgeon and the camera holder stands next to the surgeon.

Laparoscopic Proctocolectomy and Ileal J Pouch-Anal Anastomosis

The simplified procedure contains five steps. Step 1 involves trocar placement and abdominal exploration. In step 2, the intra-abdominal colon is mobilized laparoscopically in a manner similar to the open procedure. Laparoscopic pelvic dissection with full mobilization of the rectum and transection at the pelvic floor is performed in step 3. In step 4, exteriorization, resection, and pouch creation are performed via a 4 to 5 cm periumbilical incision. Step 5 is construction of the laparoscopic IPAA.

Step 1: trocar placement and exploration A 12 mm blunt port placed above the umbilicus via a cut-down technique is used for a 30° laparoscope. After exploration, three additional trocars are placed in a diamond shape [see Figure 5]. Two 5 mm trocars are inserted, in the left lower quadrant and suprapubic midline. If a loop ileostomy is planned, the site is marked prior to operation and is used for the 12 mm RLQ trocar, which allows passage of the stapler and does not require closure as it becomes the stoma site. A disk of skin and subcutaneous fat is excised from the planned stoma site before the trocar is placed directly through the fascia.

Step 2: Mobilization of the intra-abdominal colon
A. Left colon The operating table is placed in the Trendelenburg position with the left side tilted up. Gravity moves omentum and small bowel away from the operative site. With the laparoscope in the supraumbilical port, the surgeon faces the left colon, using the suprapubic and LLQ ports [see Figure 1]. The first assistant provides retraction via the RLQ port. The left ureter is identified after opening the left lateral peritoneal reflection, and the descending and sigmoid colon are mobilized medially [see Figure 6].

B. Mobilization of splenic flexure With the operating room table in the reverse Trendelenburg position and the left side tilted up, the surgeon stands between the legs. Mobilization of the splenic flexure requires a combination of lateral dissection off the retroperitoneum and dissection of the omentum off the distal transverse colon [see Figure 7]. The first assistant elevates the omentum, which is dissected off the medial aspect of the splenic flexure sufficiently to allow the flexure to reach below the level of the umbilicus, to facilitate later exteriorization.

C. Right colon In the Trendelenburg position, with the right side tilted up, the right ureter is identified prior to opening the peritoneum in a slim patient. In heavier patients, identification of the ureter occurs after the peritoneum has been opened. The correct retroperitoneal plane is entered by scoring the peritoneum around the base of the cecum and terminal ileum. The ascending colon is mobilized medially after opening the right lateral peritoneal reflection [see Figure 8]. Medially, the peritoneal attachments of the terminal ileum are divided up to the inferior border of the duodenum to produce sufficient mobilization of the terminal ileum.

D. Hepatic flexure With the right side inclined up and in the reverse Trendelenburg position, the attachments of the hepatic

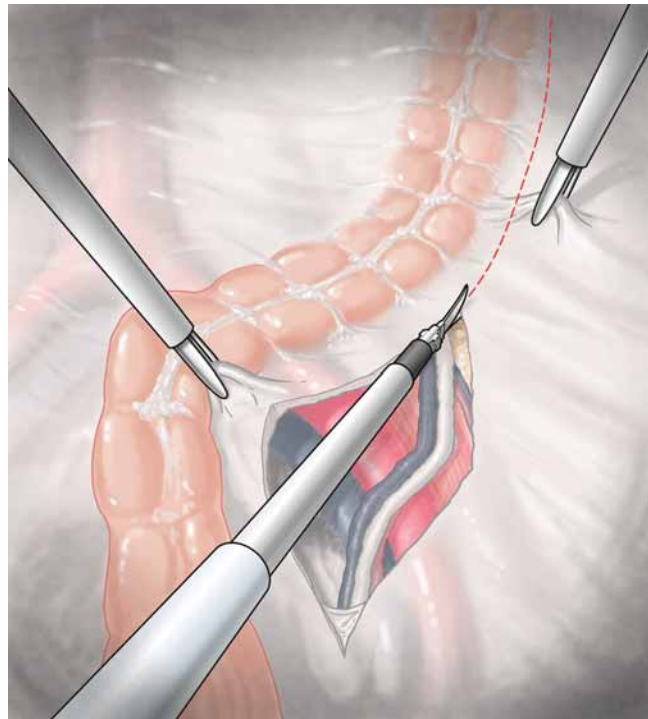


Figure 6 Illustrated is mobilization of the left colon. With the patient in the Trendelenburg position and the left side tilted up, the left lateral peritoneal reflection is opened and the left ureter identified. The descending colon and the sigmoid colon are mobilized medially.

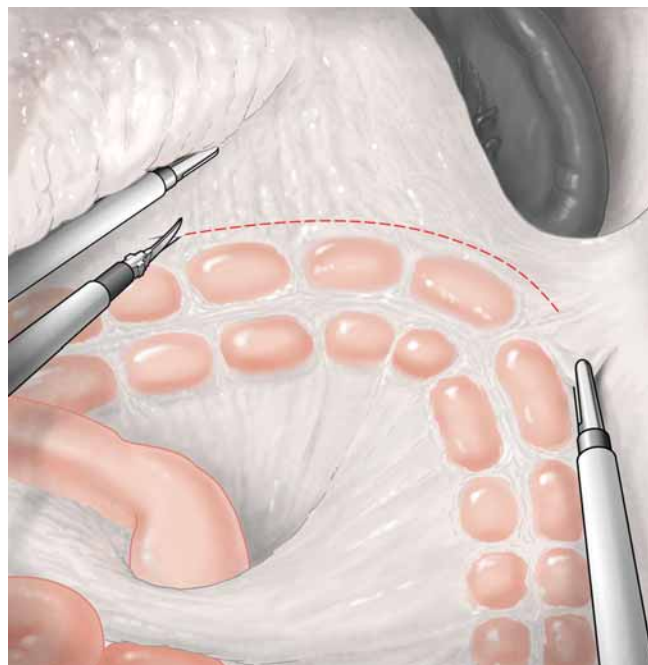


Figure 7 Illustrated is mobilization of the splenic flexure. With the patient in the reverse Trendelenburg position and the left side tilted up, the splenic flexure is mobilized off the retroperitoneum, and the omentum is dissected off the distal transverse colon.

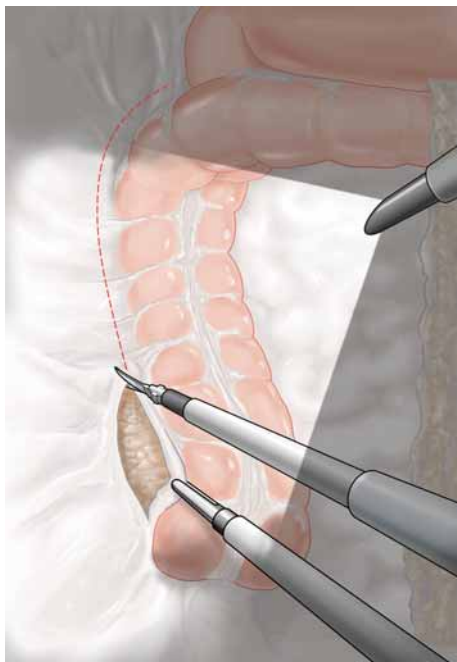


Figure 8 Illustrated is mobilization of the right colon. With the patient in the Trendelenburg position and the right side tilted up, the peritoneum around the cecum and the terminal ileum is scored to enter the correct retroperitoneal plane.

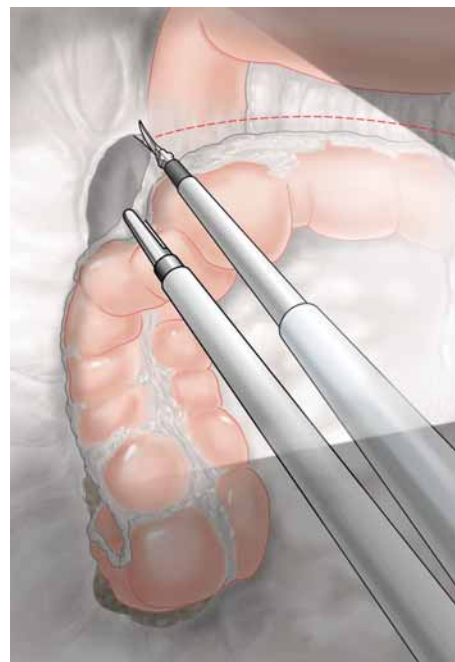


Figure 9 Illustrated is mobilization of the hepatic flexure. With the patient in the reverse Trendelenburg position and the right side tilted up, the gastrocolic ligament is elevated.

flexure are exposed. Starting where the prior dissection ended, the gastrocolic ligament is grasped immediately cephalad to the transverse colon and elevated. The duodenum is identified and protected as dissection proceeds medially [see Figure 9]. When the hepatic flexure can be brought down to the level of the umbilicus, it is mobilized sufficiently.¹⁹

Step 3: Pelvic dissection The operating table is moved into the Trendelenburg position and placed level in the horizontal axis. The surgeon may stand on either the right or left, performing the dissection for that side of the pelvis and exposing the planes for the assistant during dissection of the other side. The presacral space is entered by scoring the left pararectal peritoneum, and the plane is developed posteriorly and laterally. The right pararectal peritoneum is similarly scored, entering the presacral space and joining the previous dissection. Anteriorly, care is taken in male patients to identify the seminal vesicles and prostate. To obtain anterior exposure in female patients, the uterus is suspended with two sutures passed through the abdominal wall or a fan retractor (which requires an additional port). The rectum is circumferentially dissected down to the pelvic floor, where digital rectal examination confirms the level of the dissection [see Figure 10]. The rectum is transected at the pelvic floor with a laparoscopic articulated linear stapler introduced through the 12 mm RLQ port. If indicated, mucosectomy is performed at this point.

Step 4: exteriorization, resection, and pouch creation The supraumbilical trocar incision is enlarged around the umbilicus to 4 to 5 cm. The colon and rectum are exteriorized from the terminal ileum to the transected distal rectum. The



Figure 10 Illustrated is mobilization of the rectum. With the patient in the Trendelenburg position and the table tilted neither to the left nor to the right, the left pararectal peritoneum is scored and the presacral space is entered.

omentum may be preserved or removed with the specimen. The mesentery is divided and ligated, preserving the ileocolic pedicle if desired. In lean patients (body mass index [BMI] < 25), the mesenteric vessels are divided at their origin, but increasing BMI requires division closer to the colon. In benign disease, this is not a critical consideration. Alternatively, the mesentery can be divided intracorporeally, but the method described here is faster, safer (bleeding is readily controlled), and cheaper as multiple clips or stapler applications are unnecessary. The terminal ileum is divided with a linear stapler. The small bowel is exteriorized to inspect for Crohn disease. The small bowel is returned into the abdomen, maintaining correct orientation of the cut edge of the small bowel mesentery. A standard 15 cm J pouch is constructed, and the head of a circular stapler is secured in the apex of the pouch. The pouch is returned to the abdomen, which is irrigated, and the midline incision is closed with interrupted sutures, two of which are used to secure the blunt port in the incision, and the pneumoperitoneum is reestablished.

Step 5: IPAA The circular stapler is inserted into the anus, and the spike is brought out adjacent to the staple line. The pouch mesentery is traced from the pouch to the duodenum to confirm correct orientation. The pouch and anvil are then docked onto the stapler handle, which is approximated and fired. A drain is left adjacent to the pouch and brought out through the suprapubic port site. To create an ileostomy, an appropriate point on the ileum is identified and brought up through the trocar site in the RLQ after incising the anterior and posterior rectus fascia in cruciate fashion. The ileostomy is drawn through the site under direct visualization to ensure correct orientation. The remaining trocars are removed, the sites are inspected for hemostasis, the skin incisions are closed, and the stoma is matured.

Hand-Assisted Laparoscopic IPAA

Performing a laparoscopically assisted IPAA is a technically demanding operation that requires a surgeon highly experienced in complex laparoscopy. Furthermore, some patients, either because of their body habitus or because of previous abdominal surgery, may not be considered ideal laparoscopic candidates. The development of laparoscopic hand access devices allows the surgeon to overcome these limitations as well as reduce the technical demands of the operation. The hand access device allows the surgeon to have a hand inside the abdomen to facilitate retraction, dissection, and vascular control all under laparoscopic visualization. For an IPAA, the hand access device replaces the suprapubic trocar [see Figure 11]. It is placed in a lower midline or Pfannenstiel incision. The surgeon performs the operation standing between the patient's legs. The rectal dissection can be performed either laparoscopically or in an open fashion through the abdominal incision. At the Mayo Clinic, Rochester, this has become our preferred approach to a minimally invasive IPAA because of shorter operative times and outcomes similar to those of the laparoscopically assisted approach.²¹

Postoperative Care

On postoperative day (POD) 1, a limited (800 cc/24 hr) full-liquid diet is started. The next day, a low-fiber diet is instituted and the urinary catheter is removed. Communication



Figure 11 A hand access device permits the surgeon to place a hand in the abdomen and still use laparoscopic visualization and instrumentation through standard trocars. The typical incision is 7 to 7.5 cm in length.

with the enterostomal therapist is important as these patients are often sufficiently comfortable on POD 1 to start teaching, and some patients are ready for discharge by POD 3.

Results of Laparoscopic IPAA

Indications for operative intervention are not changed by the laparoscopic approach. In a case-matched series of 40 patients undergoing laparoscopic IPAA, each matched to two open controls, controlling for disease, age, gender, BMI, and date of operation, the laparoscopic group exhibited significant benefits in time to clear liquids (1 versus 3 days, $p < .001$), a regular diet (3 versus 4 days, $p < .001$), and bowel function (2 versus 3 days, $p < .001$).²³ The duration of narcotic use was shorter in the laparoscopic group ($p < .001$), and length of stay was reduced (4 versus 7 days, $p < .001$). Laparoscopic patients had greater operative time (270 versus 192 minutes, $p < .001$), but operative time decreased with experience and is now 3 to 3.5 hours on average.

SURGICAL CONTROVERSIES

The two main surgical “controversies” regarding the technical aspects of the IPAA involve the choice of anastomotic technique and the need for a diverting ileostomy. Ultimately, the choice of anastomotic technique depends on the clinical situation and surgeon preference. Currently, most authors believe that the double-stapled technique is easier to perform and results in superior functional outcomes as it relates to episodes of incontinence or soiling.^{24,25} Those surgeons who advocate a double-stapled pouch-anal anastomosis at the level of the pelvic floor believe that the remaining 1.5 to 2.0 cm of anal mucosa proximal to the dentate line improves the functional result by improving anal canal sensation. Not all authors have found this to be the case. In a randomized prospective trial performed at the Mayo Clinic in 41 patients with CUC, there was no significant difference in functional outcomes as measured by stool frequency or episodes of fecal incontinence at 6 months after ileostomy closure.²⁶ However, there was a higher resting sphincter pressure as measured by manometry and a trend toward less nocturnal incontinence in those patients who had a double-stapled anastomosis.

Proponents of performing a mucosectomy and handsewn anastomosis believe that all of the diseased at-risk anal canal mucosa is removed. However, the fate of the anal canal mucosa after mucosectomy has been evaluated, and even after mucosectomy, there are islands of residual rectal mucosa.^{27,28} It would seem that all of the available evidence suggests that the double-stapled technique for the anastomosis might provide a slightly better functional result compared with the handsewn anastomosis.

The need for the temporary ileostomy has also been questioned by a number of authors. The majority of large series of IPAA patients have included a temporary ileostomy to divert the fecal stream from the pouch while the pouch staple line and anastomosis heal.^{29–31} It is thought that the diversion will decrease the rate of pelvic sepsis, which is known to result in worse long-term functional results. On the other hand, supporters of a one-stage procedure believe that an IPAA can be performed without an increased risk of pelvic sepsis.^{32,33} Also, a one-stage procedure avoids an ileostomy and a second hospitalization and operation, lowers the total cost, and results in a shorter hospital stay and perhaps a decreased incidence of small bowel obstruction. In the large single-institution study reported by Sugerman and colleagues, there were no differences in the complication rates and functional outcomes of patients who had not been diverted compared with those who had been diverted; there was also no relationship to steroid use.³² Although there might be no significant difference in the rate of complications without a diverting ileostomy, some studies have suggested that the severity of complications was greater in those patients without a protecting ileostomy.^{34,35} In properly selected patients, who have uncomplicated procedures performed by experienced surgeons, a one-stage IPAA might be appropriate. However, the surgeon and patient care team must be vigilant to the early signs of pelvic sepsis and aggressively investigate the possibility of a pouch or an anastomotic leak and intervene as needed.

FUNCTIONAL RESULTS AND QUALITY OF LIFE AFTER IPAA

Given the complexity of the IPAA procedure and the often-debilitated condition of the patients, the functional results from many different surgeons and institutions are quite similar.^{25,30,32} Most patients when surveyed report good to excellent pouch function. The most commonly used marker of pouch function is the number of bowel movements per day and night, episodes of soiling, episodes of incontinence, and use of medications to control bowel activity. In the Mayo Clinic series of patients who underwent an open IPAA, the average number of daytime bowel movements at the time of discharge after closure of the ileostomy was six and the average number of nocturnal bowel movements was one.²⁹ Nearly 80% of patients reported complete daytime continence, whereas 19% had occasional incontinence and 2% had frequent episodes of incontinence. Occasional nocturnal incontinence occurred in 49% of patients. Nearly 50% of patients were discharged home on some type of medication to slow their bowels or to provide dietary bulk. The functional results of IPAA are quite stable over time. In a study of patients with up to 20-year follow-up, 92% of patients had a functioning

pouch and the numbers of bowel movements per day had increased by approximately one per day, with a reported mean frequency of 6.4 per 24 hours. However, there was a reported 24% increase in episodes of minor incontinence at night.^{36,37} Many groups have reported similar stable functional results.^{38,39}

As previously discussed, most patients report a high degree of satisfaction with the functional result after an IPAA. Recently, there have been a number of studies investigating a patient's quality of life after having surgical treatment for CUC. Fazio and colleagues showed that the quality of life after IPAA is comparable to the norms for the general healthy US population.⁴⁰ Other authors have reported that quality of life measures after an IPAA are better than after an end or continent ileostomy.^{41–43} However, does this mean that the IPAA is the treatment of choice for all patients with CUC and that those patients who either request an end ileostomy or are unable to have an IPAA are consigned to a poorer quality of life?⁴⁴ Reports have shown that quality of life most likely improves no matter what procedure is performed and is probably attributable to eradication of the underlying disease.^{45–49} Therefore, the choice of operation needs to be individualized to each patient, considering a number of health and personal factors.

COMPLICATIONS AFTER IPAA

Total proctocolectomy with IPAA is a technically demanding operation. The patient commonly has to endure two and sometimes three operations. A number of centers have reported on the incidence and impact of postoperative complications.^{48–54} The most commonly encountered complications are small bowel obstruction, pouch leak, pelvic abscesses, anastomotic stricture formation, pouch fistulas, and pouchitis.

The most common short-term and long-term complication after IPAA is small bowel obstruction. The incidence of perioperative small bowel obstruction in the Mayo Clinic series of 1,310 patients who underwent an open IPAA was 15%.³⁹ In this series, 24% of patients required early reoperation for the bowel obstruction. The long-term rate of small bowel obstruction is also relatively high. Maclean and colleagues' review of the literature on the incidence of late small bowel obstruction after IPAA revealed a reported incidence of 18% at 1 year, 27% at 5 years, and 31% at 10 years.⁴⁹ The majority of patients responded to conservative management, but the rate of operative treatment increased from 2.7% at 1 year to 7.5% at 10 years. Operative findings in those patients who required exploration for relief of the small bowel obstruction were most commonly pelvic adhesions (32%) followed by adhesions to the ileostomy closure site (20%).

Pouch leak and the associated pelvic sepsis are potentially devastating complications after IPAA. The incidence of such complications has been reported to range from 5 to 14%.^{39,41,44} In our experience, sepsis occurred in 74 of 1,310 (6%) patients, of whom 73 patients had pelvic sepsis as the result of the pouch procedure.^{30,39,50,51} The majority of these patients (63%) required operative intervention, whereas the remaining patients were treated with either antibiotics or a combination of antibiotics and computed tomography-guided drainage. In our series and in other series that have been

reported, the rate of pouch leaks and episodes of pelvic sepsis declined as experience with the procedure increased.

Another fairly common complication related to IPAA is formation of an anastomotic stricture. In the Mayo Clinic experience, of the 114 patients who required reoperative treatment for pouch-related complications, 42 (37%) had symptomatic anastomotic strictures.⁵² There is no clear correlation with stricture formation and the type of anastomotic technique. These strictures can often be treated with intermittent dilatation, which can often be performed by the patient after an initial operative dilatation.

Fistulas after IPAA are extremely difficult postoperative complications to treat. Pouch-vaginal fistulas and, rarely, pouch-perineal fistulas can occur in either the perioperative period or years later. Early pouch fistulas are most likely the result of a technical error or the complication of a pouch leak or pelvic abscess. The occurrence of late fistulas is worrisome for Crohn disease. Most fistulas are low and originate at the level of the anastomosis. They have been reported with equal frequency in both handsewn and double-stapled anastomoses. The reported incidence of pouch-vaginal fistulas ranges from 4 to 12%.^{53–57} Prior to any surgical treatment of a fistula, an examination under anesthesia and biopsies should be performed to rule out the presence of Crohn disease. Principles of management include local control of any septic process and repair of the fistula by the interposition of healthy tissue between the pouch and the vagina or perineal opening. Repairs have been reported via transanal, transvaginal, transperineal, and transabdominal approaches to pouch-vaginal fistulas, with rates of successful closure ranging from 10 to 78%.^{53–57} However, simple interventions, such as the use of seton fistulotomy, can be used to successfully manage pouch-perineal or pouch-vaginal fistulas. The most important considerations in managing a postpouch fistula are to rule out Crohn disease and to be conservative in the surgical management. Furthermore, if the diagnosis of Crohn disease is established, a comprehensive combined surgical and medical therapy regimen needs to be initiated in the hope of saving the pouch. Severely symptomatic patients may eventually require pouch diversion or complete pouch excision.

Pouchitis is a late complication of IPAA for which there is no clear etiology. It is an acute inflammatory process of the pouch. In a minority of patients, less than 10%, it can become a chronic problem.³⁶ Chronic pouchitis may eventually lead to pouch failure requiring pouch excision, which, fortunately, is quite rare. It occurs more frequently in patients with extraintestinal manifestation than those without them.⁵⁸ Measuring the exact incidence of pouchitis is difficult because of varying presentations and different diagnostic criteria. Most series report an incidence of pouchitis between 12 and 50%.^{30,36,51} Pouchitis should be suspected in any patient who experiences abdominal cramps, increased stool frequency, watery or bloody diarrhea, and flulike symptoms. Although many patients are treated on clinical grounds alone, accurate diagnosis requires endoscopic visualization of the pouch and histologic evaluation. Although the exact cause of pouchitis is unclear, the successful use of antibiotics, particularly metronidazole, in the treatment of acute and chronic pouchitis lends support to a theory that an interaction between pouch bacteria levels and the mucosal immune system is important. Chronic pouchitis is an unrelenting

inflammatory process involving the pouch that may require addition of immunosuppression agents to achieve control of the symptoms. Less than 8% of patients who have an IPAA will go on to develop chronic pouchitis, and about half will require pouch excision.^{36,37}

SPECIAL CONSIDERATIONS RELATED TO THE IPAA PROCEDURE

Age

The majority of patients suffering from CUC are younger, and unless there are unusual circumstances, they should be offered proctocolectomy and IPAA. However, CUC is known to have a bimodal age distribution, and older patients are being referred for surgical evaluation. Although many institutions have reported their long-term results with IPAA, few have regularly performed IPAA in elderly patients. In the Mayo Clinic survey of 1,386 patients who underwent IPAA, the median age at the time of operation was 32 years, with a range from 5 to 65 years.³¹ Only 16% were older than 45 years of age, and none were older than 65 years. The functional outcomes as noted by nocturnal stool frequency, daytime and nocturnal incontinence, and the need for constipating medications were all significantly higher in those patients who were older than 45 years at the time of the IPAA. Results such as these have often led gastroenterologists and surgeons not to recommend the IPAA procedure in elderly patients. However, Tan and colleagues evaluated their experience with IPAA patients from the age of 50 years to more than 70 years.⁵⁹ Twenty-eight of 227 patients were older than 50 years when the IPAA was performed; of that 28, 10 were between 60 and 70 years old, and five were between the ages of 70 and 80 years. When the elderly patients were compared with younger patients with CUC, there were no significant differences between the groups for the major complications of pelvic sepsis, pouch-related fistula, or anastomotic leak. Pouch-anal stenosis was, however, significantly more common in the older patient group. In regard to functional outcome, including frequency of daytime and nighttime bowel movements, use of pads, and incontinence episodes, there were no significant differences. Overall, advanced age is not an absolute contraindication to IPAA. In healthy older patients with good sphincter tone, the data would suggest that these patients might have functional results similar to those of younger patients.

Fertility and Fecundity

Given that most patients diagnosed with CUC are in their childbearing years, the impact of surgery on fertility is an important consideration when discussing surgery with a young woman. A number of studies have evaluated fertility and the course of a subsequent pregnancy after surgery.^{60,61} Patients who have had a proctocolectomy and end ileostomy or Kock pouch can expect to have a normal pregnancy and delivery. Although these women may have uneventful pregnancies and deliveries, they often may have temporary stoma or Kock pouch dysfunction.⁶² A similar type of dysfunction is seen in IPAA patients, in whom a slight increase in stool frequency, incontinence, and pad use during the pregnancy is reported.^{60,61} However, all patients returned to their baseline pouch function after the delivery. There was a higher rate of

cesarean sections in post-IPAA patients compared with other studies that reported on modes of fetal delivery in patients with Kock pouches and end ostomies. Overall, there appears to be no contraindication to vaginal delivery, and the decision to proceed to a cesarean section should be based on obstetric considerations.

Although older studies have looked at the course of pregnancies and complications that arose after IPAA, the specific issue of fecundicity, or the ability to become pregnant after IPAA, has not been thoroughly investigated. In a recent analysis of the rate of pregnancy after IPAA, a significant reduction in postoperative fertility was shown.⁶³ In a large population-based study in Sweden, the rate of pregnancy in women who had undergone an IPAA was significantly reduced.⁶³ More important, of the post-IPAA patients who became pregnant, 29% of the pregnancies occurred only after in vitro fertilization compared with the expected 1% of all births in Sweden during the study period. The basis of this decreased fertility is unknown, but the authors believe that anatomic changes in the pelvis may be a contributor to the problem. A recent study using a case-control design compared women with IPAA versus control women who had previous abdominal surgery and found that women who had an IPAA had significantly more infertility evaluations and need for infertility treatments.⁶⁴ Furthermore, an analysis of the required treatments for the women with pouches revealed that they suffered a reduction in the probability of conception rather than complete infertility. Women who have undergone ileorectal anastomosis for familial adenomatous polyposis do not have this reduction in fecundity compared with women who received a pouch, which supports postoperative adhesions or altered pelvic anatomy contributing to this problem.⁶⁵ Given the growing evidence that IPAA reduces a young woman's ability to conceive, they need to be counseled regarding this prospect during the informed consent process. Consideration of a subtotal colectomy and ileostomy to control the disease and allow future pregnancy may be offered with a planned restorative surgery after completion of childbearing.

Biologic Medical Therapy

As medical therapy for CUC has evolved to include biologic agents, such as infliximab (IFX), the impact on surgical outcomes in pouch patients has received increasing attention. In a study by Selvasekar and colleagues, 47 CUC patients received preoperative IPAA IFX therapy, and 254 did not.⁶⁶ Those patients who received IFX were more likely to have infectious complications and pelvic abscesses. After multivariate adjustment for both disease severity and other medication use, IFX remained independently associated with an

increased risk of ileal pouch-related and infectious complications. Another recent study of 85 patients with CUC who received IFX preoperatively found that they were at increased risk of postoperative septic complications as well as late complications, compared with patients who did not receive IFX.⁶⁷ Furthermore, the authors noted that patients who received IFX were more likely to have undergone a three-stage IPAA likely as a result of surgeon reluctance to perform an anastomosis in the setting of preoperative IFX administration. The limitations of these studies are the retrospective nature of the analysis and possible bias in patient selection. Furthermore, there can be no causal relationship drawn between IFX use and postoperative complications. Most likely, those patients who require IFX for treatment of their CUC represent a sicker and thus higher-risk group of patients at the time of surgery. Further studies need to be performed to clarify this important issue. In the meantime, consideration of a three-stage approach in patients who have received preoperative IFX could be considered.

Conclusions

Ulcerative colitis is an inflammatory disease of unknown etiology that is limited to the colonic mucosa. The intestinal manifestations of the disease can be cured by removal of the entire colon. The indications for surgical intervention in CUC occur in both the emergency and the elective setting. Emergency surgery is directed at treating severe complications of the disease. The goal is to remove the majority of the diseased colon in such a manner that a future restorative procedure can be performed. Elective surgery is directed at dealing with disease that is refractory to medical therapy or when there is a concern for increased malignant transformation in the colon. Two commonly used definitive surgical procedures for CUC are total proctocolectomy with end ileostomy and proctocolectomy with IPAA. Patient characteristics and overall medical condition determine the choice of procedure. IPAA has become the procedure of choice in the majority of patients requiring colectomy because it avoids a permanent abdominal wall stoma while maintaining the normal route of defecation. IPAA is a technically demanding operation that has a relatively high rate of morbidity even in experienced hands. However, the majority of patients report a high degree of satisfaction with the functional results of IPAA. Application of newer techniques such as laparoscopic surgery might further improve patient satisfaction and decrease morbidity.

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34 SEGMENTAL COLON RESECTION

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Segmental colectomy is one of the most commonly performed procedures in the United States. Based on nationally representative figures, over 200,000 colectomies were performed in 2005.¹ More recent data from the Hospital Care Utilization Project estimated that approximately 282,000 colon resections were performed in 2007.²

Colorectal resections—of which segmental colectomies comprise the vast majority—are a growing focus of national attention because of the considerable rates of morbidity and mortality generated by these procedures.³ Overall morbidity rates are 24%, with major morbidity occurring in 11% and mortality in 3%.⁴ In this chapter, we review the indications, preoperative planning, technical considerations, and postoperative care involved in performing this important and commonly performed procedure.

Indications

Segmental colectomy may be performed for a variety of reasons. Of the 282,000 colectomies performed in 2007, resections for cancer and diverticular disease comprised the vast majority [see Figure 1].²

COLON CANCER

Invasive colon cancer is the most common indication for colectomy. Although a small subset of patients may not be candidates for surgical resection due to medical comorbidity, resection is the mainstay of therapy for all patients with nonmetastatic disease. Decision making regarding the appropriateness of resecting a primary tumor in a patient with metastatic disease is complex and needs to encompass factors related to the symptomatology of the tumor, the fitness of the patient, and the burden of systemic disease. Although those with resectable metastases are candidates for resection of the primary tumor, the majority of patients with metastatic disease will not require surgical treatment.⁵

Invasive adenocarcinoma may also be present within a polyp, which is predominantly benign. In general, such a polyp should be considered an indication for surgery unless very clear criteria are met. The cancer should not demonstrate any adverse histopathologic features (poorly differentiated, perineural or lymphovascular invasion, no ulceration or extensive budding). A margin of at least 2 mm should be obtained via polypectomy, and the tumor should be limited to the superficial submucosal layer.^{6,7} Piecemeal polypectomy with any question of a positive margin also implies residual disease.

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POLYPS

Benign polyps that are not amenable to endoscopic resection due to size or sessile nature are another indication for colectomy. The rationale for an aggressive surgical approach is twofold.

First, a residual polyp may harbor a malignancy. The likelihood of carcinoma in an adenomatous polyp depends heavily on the size and histologic characteristics of the polyp. In the largest review of its kind, Nusko and colleagues found a 64% likelihood of malignancy in polyps greater than 34 mm and a 79% likelihood in polyps greater than 42 mm.⁸ Polyps with tubulovillous or villous histology were also much more likely to harbor cancer than tubular adenomas (30% versus 4%). It is also impossible to definitively declare a polyp as “benign.” Studies examining the ability of endoscopic biopsy to diagnose malignancy find that the technique is only 81 to 84% sensitive.^{9,10} Because of the distinct possibility of malignancy, a surgical resection for an unresectable polyp should be performed with the same respect for margins and mesenteric harvest as for a cancer. The second reason for an aggressive surgical approach to colonic polyps is the documented propensity of polyps to grow and undergo malignant degeneration.¹¹

The clinical decision to perform a colectomy for a colonic polyp should be made on a case-by-case basis. Factors to consider should include the histologic characteristics of the polyp and the patient’s operative risk and preferences. In addition, more widespread adoption of newer techniques such as endoscopic mucosal resection and endoscopic submucosal dissection may obviate the need for surgery in a subset of patients with large polyps and no evidence of invasive cancer.

DIVERTICULAR DISEASE

Diverticular disease is another common indication for colectomy due to the presence or history of diverticulitis or bleeding. Although diverticulitis afflicts the sigmoid colon in 95% of cases, it can affect other regions of the colon. Historically, colectomy has been offered on the basis of complications of diverticulitis (abscess, perforation, obstruction, fistula), medically refractory disease, or serial episodes of acute diverticulitis, which resolve with medical management.¹² These indications have evolved over time, however, and are now in a state of significant flux. Patients who have an episode of acute diverticulitis with an associated abscess typically undergo percutaneous drainage; such patients are apparently at no greater risk for recurrence than are patients who have acute diverticulitis and no need for percutaneous drainage.¹³ The threshold to operate on patients with serial episodes of diverticulitis has shifted over time. Although no randomized trial data are available to support one strategy over another, current practice guidelines advocate that a colectomy should be recommended based on specific patient factors but usually after at least two episodes.¹⁴ Others advocate waiting until at least four such episodes.¹⁵ Patients who fail to resolve their symptoms of diverticulitis promptly

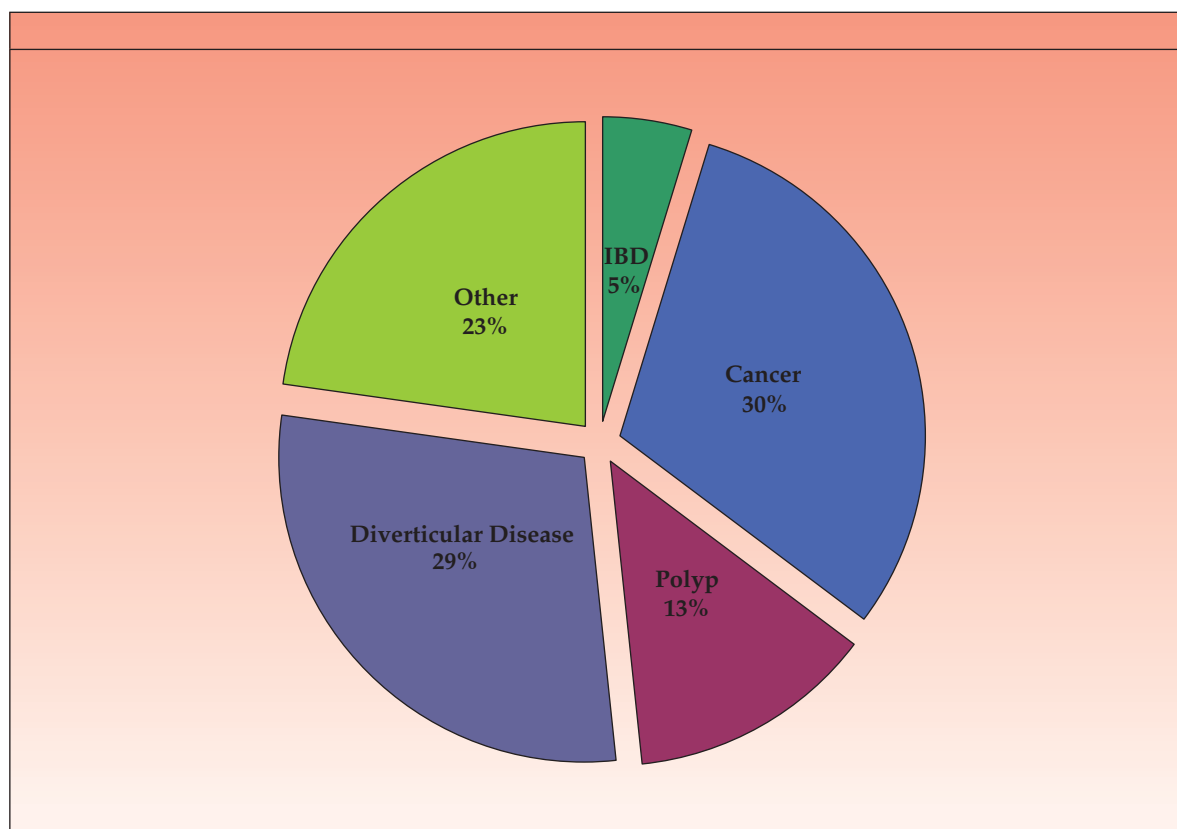


Figure 1 Indications for colectomy in the United States, 2007. IBD = inflammatory bowel disease.

with an appropriate regimen of antibiotics and bowel rest represent a strong indication for colectomy.

Surgical treatment is much more commonly required for the treatment of diverticulitis than for diverticular bleeding. However, approximately 33% of lower gastrointestinal bleeding is the result of diverticulosis, and resection is indicated when hemorrhage is ongoing or in the case of multiple episodes documented from the same location.¹⁶

In evaluating patients with suspected acute diverticulitis, it is critical that surgeons be vigilant for the possibility that the diagnosis is incorrect. Computed tomographic (CT) scan findings of colon wall thickening and micro- or macroperforation are also often found in association with colon cancer. An unequivocal diagnosis can be made in only 49% of cases based on radiologic studies with significant overlap in the appearance of colon cancers and diverticulitis on a CT scan.¹⁷ In addition, 4% of definite CT diagnoses of cancer are actually diverticulitis on subsequent colonoscopy or surgery, and 4% of diagnoses of diverticulitis are in fact cancer discovered on following colonoscopy or surgery.¹⁷ Colonoscopy is therefore an important part of the evaluation for patients who are hospitalized for acute diverticulitis. Conventional wisdom dictates that an endoscopic examination in a patient with an inflamed, microperforated colon is contraindicated, but recent research in small series of patients has challenged this wisdom.^{18,19} Until the safety of early colonoscopy can be proven in a broader population, patients who are hospitalized with acute diverticulitis should undergo colonoscopy 6 to 8 weeks after resolution of symptoms.

INFLAMMATORY BOWEL DISEASE

Patients with ulcerative colitis may be candidates for total colectomy or proctocolectomy with or without reconstruction for the following indications: refractory to medical therapy, findings of cancer or dysplasia, complications of medications, patient preference, and, in children, growth retardation. In the setting of a patient with fulminant disease or significant debility, a three-stage procedure beginning with total abdominal colectomy with end-ileostomy is usually performed. For patients with ulcerative colitis that is more chronic and who are not debilitated, a total proctocolectomy with ileoanal pouch construction is the procedure of choice. Rarely, in the context of relative rectal sparing, a patient with chronic disease may be a candidate for total abdominal colectomy and ileorectal anastomosis, although this finding should prompt consideration of Crohn disease. Segmental colectomy has no role in the treatment of ulcerative colitis as the colon should be considered a single organ; any manifestation of disease sufficient to warrant a colectomy therefore warrants removal of the entire organ.

Patients with Crohn disease may present with a confined segment of disease, at which time it may be reasonable to resect only the affected portion. Indications for resection most commonly include stricture, fistula, and dysplasia, with other indications including failure of medical therapy, abscess, obstruction, and, rarely, perforation. Up to 80% of patients with Crohn disease will require surgery at some point.²⁰ Of those requiring resection, approximately 20% undergo isolated segmental colectomy.²¹

OTHER

Other disease processes appropriate for segmental colectomy include ischemia, volvulus, localized bleeding source, and infectious colitides. Neoplasms in the colon other than colon cancer, such as lipoma, leiomyoma, gastrointestinal stromal tumors, lymphomas, and carcinoid, may also require segmental resection. The diagnosis, evaluation, and treatment algorithms for these relatively infrequent indications for colectomy are beyond the scope of this chapter.

Preoperative Planning

The specific elements of preoperative planning that might be considered appropriate vary widely and are determined by the patient's disease process. Most importantly, pathology and location of disease should be confirmed prior to proceeding with surgery. The informed consent process should involve a discussion of the possibility of anastomotic leak and temporary ostomy (either at the time of surgery or as a result of postoperative complication).

COLONOSCOPY

For a patient with colonic pathology, an endoscopic examination should be considered a natural extension of the physical examination for two main reasons. First, the possibility of previously unsuspected pathology is significant. In one study of patients with obstructing colonic cancers, 58% had adenomas outside the field of resection and 6% had synchronous cancers.²² Second, it is incumbent upon the operating surgeon to ensure concordance between the suspected and actual location of pathology. Permanent tattooing should be performed routinely except in rare situations where localization is straightforward. Unless clinical circumstances contraindicate such an investigation, any patient for whom a colectomy is planned should undergo a complete colonoscopy. Importantly, mechanical bowel preparation (taken orally) should be considered contraindicated in patients with a significant colonic obstruction.

An adjunct in the management of distal colonic obstruction is endoluminal stenting. Although it is not without significant complications, it can be an excellent bridge to resection in the patient with obstruction secondary to malignancy or benign stricture or as palliation in the patient with advanced disease.²³ In patients for whom resection is planned, decompression of the proximal bowel may facilitate primary anastomosis by minimizing size mismatch and bowel compromise. In addition, this allows for time to correct electrolyte abnormalities and give a bowel preparation if considered necessary. Patients who are candidates for stenting do not need two surgical procedures, with a reported average of 7 days from stenting to operative resection. Approximately 70% of patients with malignant colon obstructions will be successfully managed with a stent and subsequent definitive resection.^{24,25} Stenting as a bridge to resection is generally not useful in patients with right-sided colonic obstructions as an ileocolic anastomosis is safe in all but the most advanced cases of obstruction.

COMPUTED TOMOGRAPHY

CT scanning of the abdomen/pelvis is almost universally performed prior to colectomy. In cases of malignancy, CT is an invaluable element of the staging evaluation. Patients with a significant burden of hepatic metastases with replacement of more than 50% of the hepatic parenchyma may be a prohibitive risk for surgery.²⁶ The direct extension of the tumor into adjacent structures may alter the surgical plan, possibly necessitating the involvement of other surgical disciplines. CT combined with positron emission tomography (PET) is more sensitive for extrahepatic metastases and recurrences and should be strongly considered in preoperative staging.²⁷ In the setting of diverticular disease, CT is necessary for confirmation of diagnosis and is generally performed prior to surgical evaluation. A close examination of the locations and severity of prior episodes of acute diverticulitis is important to determine the extent of colon resection.

BOWEL PREPARATION

The importance of preoperative mechanical bowel preparation in patients undergoing colectomy is a topic of ongoing debate. Historically, the justification for the exercise has been concern over the risks of surgical site infections and anastomotic leakage. This concern appears to be at least somewhat overstated. The risk of overall complications is similar between patients who had versus those who did not have a mechanical bowel preparation. In the largest randomized trials, however, there is a significantly lower rate of abdominal abscess among patients who underwent preparation, although there is a significantly higher rate of wound infections.²⁸ These same studies failed to show a significant difference in anastomotic leakage. Notably, fast-track protocols specifically have omitted mechanical bowel preparation as it is thought that this may minimize fluid shifts and the consequences of aggressive fluid resuscitation.²⁹

There may be situations in which bowel preparation has particular utility, above and beyond the outcomes mentioned above. When the preoperative localization of a colonic lesion is questionable, an intraoperative endoscopic examination is facilitated by a preoperative mechanical bowel preparation. Laparoscopic manipulation of a colon that is loaded with solid stool can be challenging, and the decompressed colon is easier to exteriorize through a small fascial defect. Colorectal anastomotic techniques using a circular stapler can also be compromised if the distal colorectum is filled with solid stool, thereby impeding the passage of the stapler and the formation of the anastomosis.

The debate regarding bowel preparation goes well beyond what can be covered in this chapter. Given the equivocal evidence regarding the impact of bowel preparation on patient outcomes, the decision should be made on a case-by-case basis by the surgeon based on interpretation of the data and the utility of preparation.

STOMA MARKING

In patients with a high likelihood or certainty of stoma, preoperative marking can assist in planning an appropriate site. Patients who have preoperative education are less likely

to have anxiety about caring for a stoma at home. In addition, there are significantly fewer stoma-related complications in patients who have been marked prior to being placed on the operating table.³⁰

DEEP VEIN THROMBOSIS PROPHYLAXIS

Patients undergoing colorectal surgery have an increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE), and without prophylaxis, the rate of DVT is 30%.³¹ In addition to routine postoperative therapy, preoperative heparin administration has been shown to decrease venous thromboembolism; heparin three times daily or other chemical DVT prophylaxis should be administered postoperatively, as well as mechanical devices.³² These regimens have not been associated with any significantly increased risk of bleeding.³³

PREOPERATIVE ANTIBIOTICS

Preoperative antibiotics with both aerobic and anaerobic coverage should also be given. Current guidelines under the Surgical Care Improvement Project include an appropriate antibiotic (e.g., ertapenem or metronidazole plus a fluoroquinolone, first-generation cephalosporin, or aminoglycoside) started within 1 hour of incision, with hair clipped rather than shaved, urinary catheters removed by postoperative day 2, and normothermia maintained perioperatively. Wound infection rates are decreased by as much as 75% when antibiotics are given preoperatively; the postoperative duration of antibiotic therapy does not impact outcomes, and recommendations are for a single preoperative dose or a total of 24 hours of therapy.³⁴

PREOPERATIVE URETERAL STENTING

An in-depth knowledge of colon anatomy and its surrounding relations can prevent inadvertent injuries during the procedure, but the intimate association of both ureters with the colon must be given preoperative consideration. In the setting of bulky tumors or expected severe inflammation in the sigmoid or cecum, ureteral stents may be useful. Ureteral stents offer a means for both visualization and palpation of the ureters to protect them from harm. It is also commonly acknowledged that ureteral stents assist in identifying injury at the time it is caused more so than actually preventing injury³⁴; this fact reasserts that there is no substitute for cautious dissection and constant vigilance for the presence of the ureter or other structures, particularly when cautery or transection of tissue occurs.

Technical Considerations

LAPAROSCOPIC VERSUS OPEN SURGERY

Laparoscopic surgical treatment of colon disease is now widely accepted as the standard of care for most colectomies. A growing number of reports have described the short-term benefits of laparoscopy in treating benign conditions of the colon (e.g., diverticulitis, Crohn disease, and ulcerative colitis).³⁵ Controlled studies performed by experienced surgeons have found laparoscopy to have advantages over open resection in terms of resolution of ileus, duration of hospitalization, level of postoperative pain and narcotic use, recovery of pulmonary function, complication rates,

and quality of life in the initial postoperative period.^{36–42} Cost analyses also favor laparoscopic colectomy over conventional surgery, finding that the higher costs of the surgical instruments and the potentially longer operating times are outweighed by the shorter duration of hospitalization.^{41–44} There also appears to be a lower incidence of surgical site complications after laparoscopy than after open surgery, as well as a lower incidence of postoperative complications.^{45,46} Overall complications over time are significantly diminished.³⁵ There have also been studies suggesting that cosmetic outcome and body image are improved by laparoscopic surgery, although quality of life is generally similar.⁴⁷

Although there was initial concern that pneumoperitoneum and multiple areas of entry might lead to intra-abdominal spread or port site recurrences, wound recurrences are now recognized to be no more common in laparoscopy than in open surgery.^{48–50} In addition, the multicenter, randomized, prospective trial carried out by the Clinical Outcomes of Surgical Therapy Study Group showed that survival, recurrence, and complications were not significantly different between laparoscopic and open approaches over long-term follow-up (median 4.4 years).^{36,42}

ONCOLOGIC CONSIDERATIONS

When colectomy is performed for an oncologic indication, special deliberation must be given to specific elements of the planned operation. First and foremost, the operation should provide adequate extirpation of the patient's tumor burden and an appropriate mesenteric resection. In general, a proximal and distal margin of at least 5 cm is considered appropriate, although this is further determined by the vascular supply to the colon segment. Usually, the linear margins are easily obtained when an adequate mesenteric resection is executed. When a colon cancer has invaded locally into surrounding structures, an en bloc resection should be planned, with the engagement of other surgical disciplines as required.

In evaluating the appropriateness of a resection for cancer, a significant amount of attention has been paid to the correlation between the number of lymph nodes analyzed and the patient's oncologic outcomes. Greater numbers of lymph nodes analyzed are associated with better survival in stage II and stage III colon cancer, and these findings have led to a belief that an adequate lymph node analysis is a measure of quality of care.⁴³ The relation between the extent of surgical resection (lymph node harvest), number of nodes analyzed (pathologic examination), and long-term oncologic outcomes is at best speculative at this point.^{51,52} Patient quality of care is best served by surgeons and pathologists who are focused on appropriate techniques rather than on achieving a specific lymph node "count."

The extent of resection should encompass one blood vessel proximal and one below the tumor [see Figure 2]. Tumors in the cecum or ascending colon require 5 to 10 cm of terminal ileum with ligation of the ileocolic pedicle and right branch of the middle colic vessels, with transection at the level of the proximal to midtransverse colon. A tumor at the hepatic flexure or proximal transverse colon mandates an extended right hemicolectomy, with ligation of the ileocolic, right colic, and middle colic at its origin, with transection at the distal transverse or descending colon. Lesions

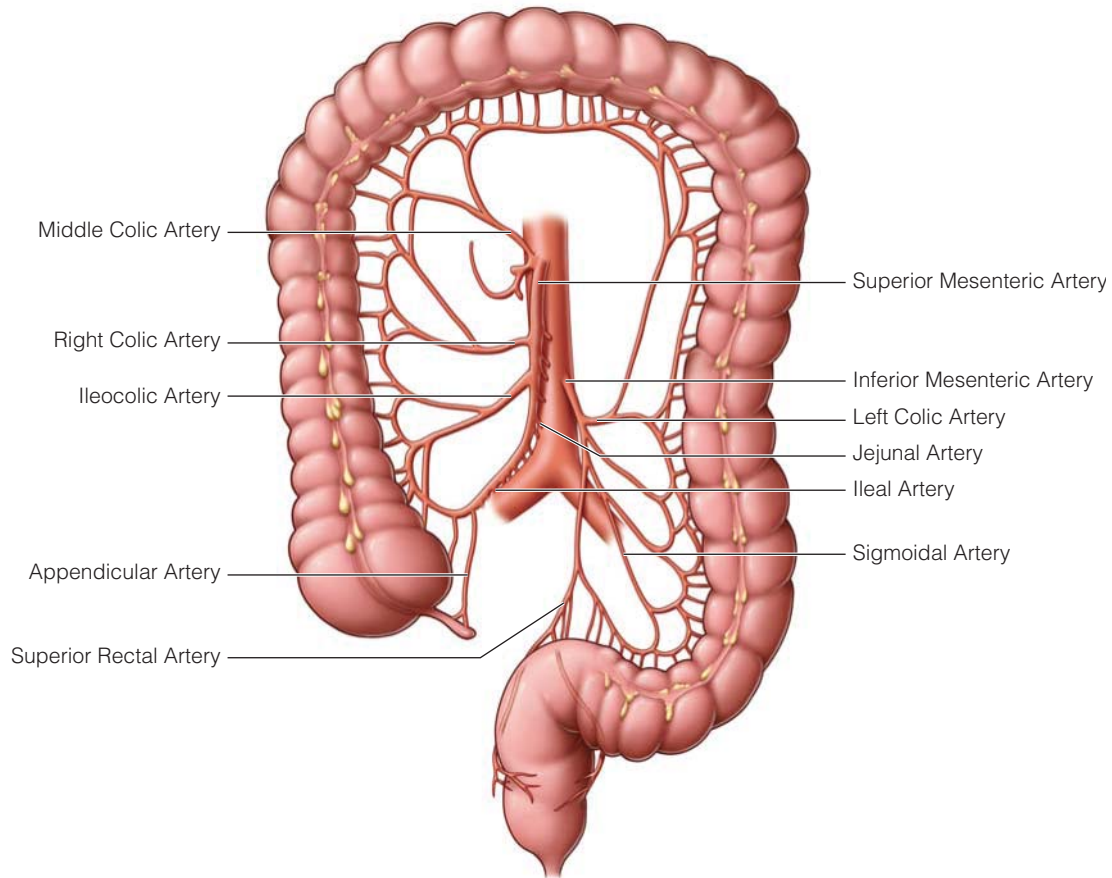


Figure 2 Vascular anatomy of the colon.

in the midtransverse colon are usually treated with an extended right hemicolectomy. Tumors in the distal transverse or splenic flexure can be treated with either a subtotal colectomy or a left colectomy with ligation of the left branches of the middle colic vessels and one or both branches of the left colic vessels. A lesion in the sigmoid colon requires division of the inferior mesenteric vessels distal to the left colic arterial origin, with resection of the sigmoid colon, as more extensive resection does not positively affect outcomes.^{44–46} The surgical approach to cancers in the descending colon is difficult to standardize but should involve ligation of the left colic vessels at their roots, depending on the location of the tumor, and ligation of the arcade vessels or left branch of the middle colic at the proximal point of transection. A lesion at the junction of the descending and sigmoid colon between the left colic and superior hemorrhoidal vessels should prompt consideration of transection of the inferior mesenteric artery at its root.

Once the specimen is completely removed, it is critical that the resected colon be opened and examined promptly to ensure that the pathology is adequately removed.

CONSIDERATIONS IN OPEN SURGERY

Open colon surgery may be selected over a laparoscopic approach in many instances. Bulky or locally invading

tumors are more easily handled in the open setting. Frequently, although surgery may be feasibly performed laparoscopically, the length of the extraction site for a bulky tumor may be such that any laparoscopic benefit is negated. In cases of severe inflammation, such as in persistent or acute diverticulitis, laparoscopic instrumentation is often unable to provide sufficient retraction and tactile feedback.

Incision choices are made based on the most distant or difficult point of dissection. In the case of a right colectomy, the incision is largely above the umbilicus as the cecum is generally easily mobilized out of the right lower quadrant, whereas the more difficult extent of dissection is in the right upper quadrant at the level of the hepatic flexure. Similarly, in the case of a sigmoid resection, the dissection is primarily infraumbilical, although some superior extension of the incision may be needed for careful release of the splenic flexure.

A variety of self-retaining retractors may be used to assist in open surgery. These range from simple choices such as the Alexis wound protector (Applied Medical, Rancho Santa Margarita, CA) and the Balfour to the Bookwalter and Omni (Integra, St. Paul, MN). The Bookwalter is a common choice, allowing both tilting and repositioning of the ring for combined lateral and anterior retraction.

CONSIDERATIONS IN LAPAROSCOPIC SURGERY

Planning a laparoscopic procedure involves a set of considerations that are not inherently a part of open surgery. Patient positioning is critical in laparoscopic colectomy. For all laparoscopic colectomies other than a right hemicolectomy, the patient is placed in the low lithotomy position to allow for a surgeon or assistant to stand between the legs. Both arms should be carefully padded at all pressure points and tucked at the sides, with the hands well protected from the moving parts of the lower extremity stirrups. Specific attention should be given to securing the patient to the bed to avoid slipping during surgery. Once the patient is secured, this should be confirmed by tilting the table in all extremes to ensure that the patient will not slide once draped. This careful positioning will allow the patient to be placed safely in deep Trendelenburg, reverse Trendelenburg, and lateral rotation, thereby allowing gravity to function as a retractor.

Laparoscopic port placement for colectomy is largely a matter of personal preference. In most instances, an extraction site of approximately 3 to 4 cm in length will be required; this can be made around the umbilicus, in the lower midline, above the pubis as a mini Pfannenstiel, or at a planned ostomy site. In any of these cases, this incision should start as a port site incision at the level of the fascia, although the complete skin incision may be made at the beginning of the case. One preferred configuration that can be used for most colon mobilizations is a diamond configuration, with a periumbilical Hasson trochar placement, and three additional ports, one each in the right lower quadrant, left lower quadrant, and suprapubic area. With this configuration, the majority of colon mobilization can be completed. Additional ports in the right or left upper quadrant may be needed for improved retraction or access.

As with open surgery, ureteral stent placement may be a necessary part of the procedure if there is significant inflammation or suspicion for retroperitoneal adherence. The utility of ureteral stents is slightly diminished in the context of laparoscopic surgery as the tactile sense is less; lighted stents are available that work very well in laparoscopic procedures.

ENERGY DELIVERY DEVICES

An additional component that is important to performing safe and efficient colon resection is the use of electrosurgical instruments. In open surgery, a colectomy can be performed effectively without the use of special energy delivery devices, but they are very helpful for most laparoscopic colectomies.

Several instruments are available, including ultrasonic shears and a host of bipolar sealing devices. The Harmonic Scalpel (Ethicon Endosurgery, Somerville, NJ) works by converting electrical to mechanical energy, thereby creating a very high-frequency vibration that can be adjusted to both cut and coagulate tissue. LigaSure products (Valleylab, Boulder, CO) are pulsatile, bipolar instruments that recognize the changing impedance of tissue and continually alter the current and voltage. After tissue is sealed, a cutting blade is fired. Gyrus products (Gyrus ACMI, Maplegrove,

MN) function as a bipolar device by generating a radiofrequency waveform to cut or coagulate tissue. The EnSeal (SurgRx, Redwood City, CA) delivers current to tissue via a temperature-sensitive electrode in combination with a cutting blade, which can be used simultaneously with coagulation or after coagulation is completed.⁴⁷

Although the LigaSure products and the EnSeal are superior in terms of burst pressure that is similar to that of surgical titanium clips, the lengths of time to achieve vessel sealing grossly are greater for the EnSeal on large vessels and for the LigaSure on medium vessels, with the EnSeal, Gyrus, and LigaSure products effective for sealing vessels of up to 7 mm in diameter, and the Harmonic Scalpel approved for sealing vessels up to 5 mm.^{53,54} Failure rates after sealing were 0 in the LigaSure and EnSeal products but were 41% in the Gyrus products and 8 to 22% for the Harmonic based on vessel size, suggesting that feedback-controlled bipolar sealing devices are superior to the ultrasonic shears, and both are superior to standard electrocautery.⁴⁷ Thermal spread does extend for 2 to 3 mm beyond the transected portion of vessels for both the ultrasonic and bipolar devices, although the bipolar devices exhibit increased coagulation necrosis and bonding of nucleated cells beyond the tips of the instrument.^{47,48}

In comparing the use of ultrasonic shears versus bipolar impedance-controlled sealing devices, Campagnacci and colleagues found that although there were trends toward shorter operative times and lengths of stay with the bipolar device used in laparoscopic colorectal surgery, the blood loss was significantly less in the bipolar group.⁴⁹ These data would suggest that one of many bipolar devices or the ultrasonic shears may be used for mesenteric transection, although the bipolar devices demonstrate improved coagulation for larger vessels. However, as with any sharp or cauterizing device, care must be exercised when using these close to the colon or the retroperitoneum.

COLONIC DISSECTION

There is no single correct way to perform a colectomy, and expert surgeons advocate widely varying techniques. Most early instruction in laparoscopic colon surgery described a medial to lateral dissection, a technique that is not commonly employed for standard open resections. This technique advocates vascular isolation first, followed by dissection into the retromesenteric plane, with lateral attachments left intact until the end of the dissection.

Many surgeons find that a lateral to medial approach, performed similarly in both open and laparoscopic cases, is more straightforward. Other variations may also be useful, depending on the preferences of the operating team. One example is an inferior to superior approach to mobilizing the right colon, with dissection of the terminal ileum. Regardless of the technique advocated, it is wise to be familiar with anatomy and various choices for dissection whether operating open or laparoscopically in case of unexpected pathology or other anatomic obstacles. In this chapter, we discuss the technical aspects of colectomy in terms of approaches to mobilizing different portions of the colon. These component elements can be combined to form a variety of operations for both benign and malignant disease.

OPEN RIGHT COLON MOBILIZATION

The cecum is retracted anteriorly and medially, and the peritoneal attachments of the inferolateral portions of the cecum and the terminal ileum are divided with electrocautery. With appropriate retraction on the cecum, sharp dissection is used to release the mesentery from the retroperitoneum. In this maneuver, the lateral peritoneal attachment (i.e., the white line of Toldt) is clearly defined using sharp dissection and gentle sweeping motions.

The right ureter can usually be seen laterally, crossing the iliac artery at its point of bifurcation [see Figure 3]. If the retroperitoneum is left intact, the ureter should be posterior to the field of dissection. The lateral dissection continues cephalad with medial traction on the ascending colon. As the colon is swept medially, the duodenum will enter the operative field at the posteromedial border of the right colon mesentery. During this dissection, Gerota fascia overlying the right kidney should be appreciated, and caution should

be used to avoid dissecting posterior to the kidney or into Gerota fascia. In obese individuals, the appropriate plane may be difficult to appreciate and is evident only as a thin line of glistening areolar tissue between two masses of adipose tissue. The mesentery of the right colon should be sharply mobilized from the anterolateral portion of the lateral duodenum, with caution to prevent injury to the duodenal serosa.

Once the right colon is mobilized off the retroperitoneum, the hepatic flexure must be released. In conducting this maneuver, a decision should be made regarding whether an omentectomy will be performed. It is generally accepted that partial omentectomy should be performed in the case of malignancies near or distal to the hepatic flexure. The lesser sac can be entered in one of several ways. First, it can be approached from the right side of the hepatic flexure, staying close to the cephalad border of the colon. Second, it can be entered by lifting the omentum anteriorly and incising

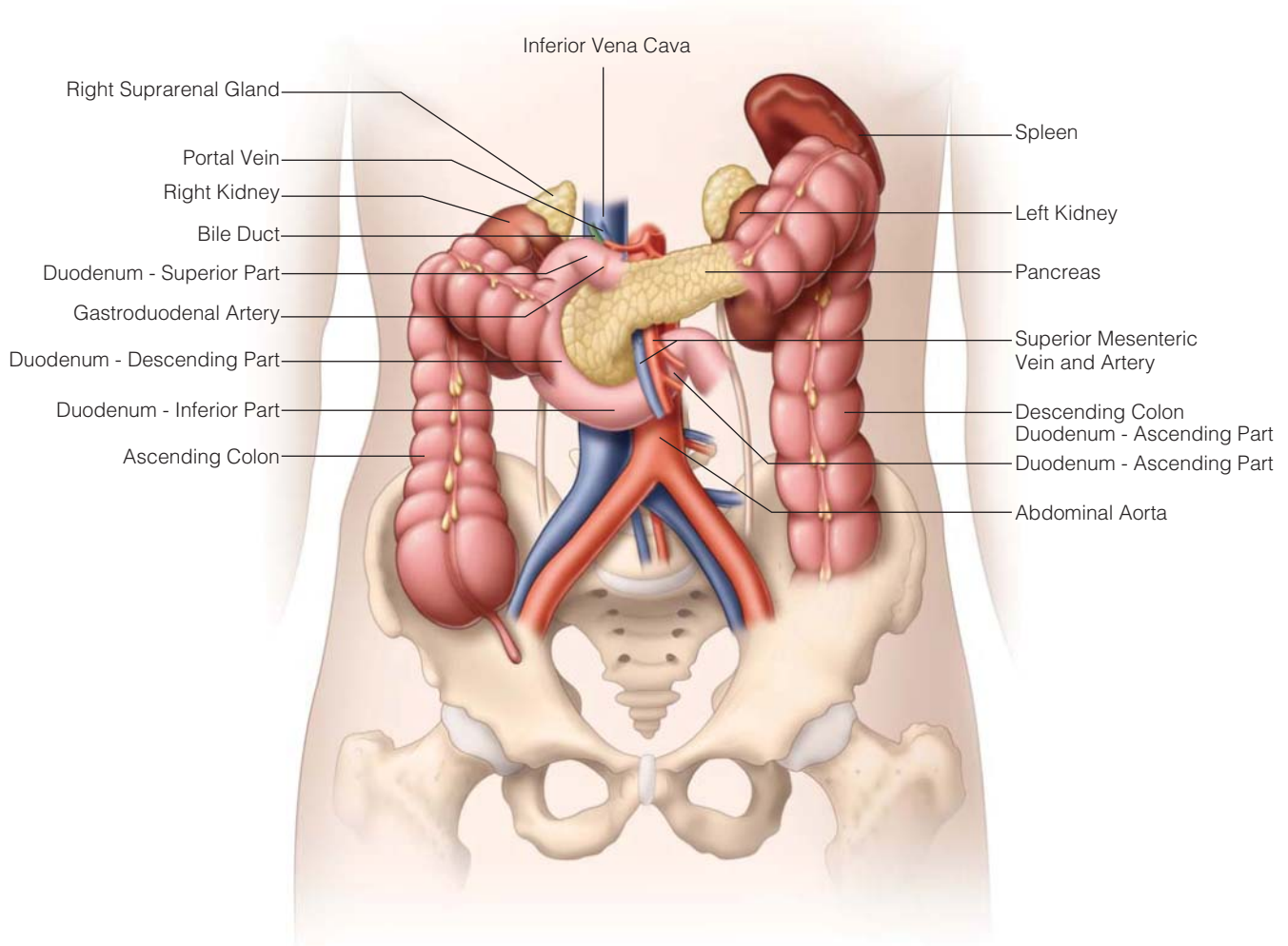


Figure 3 Anatomic relations between the colon and the retroperitoneal organs.

the avascular attachment of the posterior leaflet of the omentum to the anterior surface of the colon. Third, if the omentum is planned to be mobilized en bloc with the transverse colon, dissection can proceed through the omentum itself, leaving a small portion of omentum attached to the stomach and gastroepiploic vessels. Regardless of which technique is employed to enter the lesser sac, dissection proceeds within this plane to mobilize the proximal transverse colon. Care should be taken during this dissection as aggressive medial traction on the hepatic flexure or deep dissection may injure the superior mesenteric vessels, branches of the pancreatoduodenal vessels, the right gastroepiploic vein, particularly as it converges with the right colic vein, or the head of the pancreas.

From within the lesser sac, the duodenum is again encountered from above. The middle colic vessels will be found arising from the superior mesenteric vessels. The proximal and distal margins in a right hemicolectomy for malignant disease are standard. Proximally, resection should occur at the terminal ileum within 5 to 10 cm of the ileocecal valve. Distally, there is a distinction between a right hemicolectomy and an extended right hemicolectomy. A traditional right hemicolectomy removes the right branch of the middle colic artery down to its origin at the middle colic artery, along with any associated nodal tissue. This extent of resection is generally considered adequate for malignancies proximal to the hepatic flexure. Disease at or distal to the hepatic flexure is an indication for an extended right hemicolectomy, which encompasses resection of the right plus left branches of the middle colic vessels, along with the accompanying mesentery.

Two aspects of an extended right hemicolectomy make the resection considerably more complicated. First, an extended right hemicolectomy may require that the splenic flexure be mobilized to allow adequate exposure through a midline incision. Second, with removal of the entire middle colic perfusion, the distal transverse colon is therefore perfused via marginal arterial circulation arising from the left colic arteries. Although this is usually sufficient, there may be patients in whom the distal transverse colon or splenic flexure is poorly perfused after resection of the middle colic vessels. Prior to completing an anastomosis after an extended right hemicolectomy, the surgeon should be satisfied that the blood flow in this portion of the colon is adequate, relying on the presence of pulsatile vessels in the mesocolon or vigorous arterial bleeding from the cut edge of the colon. If these findings are not present, the resection should proceed distally, with an anastomosis in the descending colon.

Once the proximal and distal points of transection have been selected based on the location of the tumor, the ileocolic pedicle and the appropriate branch(es) of the middle colic vessels should be isolated, transected, and ligated securely. The mesentery may then be divided, thereby releasing the specimen. Once the mesentery is transected, anastomosis may be performed. A variety of techniques may be performed; the selection of technique should depend on the experience and preferences of the operating surgeon. In a recent meta-analysis, stapled ileocolic anastomoses demonstrated a lower leak rate (odds ratio of 0.34), although the rates of reoperation and other anastomotic complications

were not significantly different.⁵⁰ Several key technical points should be observed when performing the anastomosis, regardless of the chosen method. The anastomosis should be performed on the antimesenteric border of the small bowel and colon, in an area with no adherent serosal fat deposits. Great care must be taken not to allow the small bowel to twist proximal to the anastomosis, especially in laparoscopic resections, where the anastomosis is performed via a mini-laparotomy.

LAPAROSCOPIC RIGHT COLON MOBILIZATION

With the lateral to medial dissection, the steps are very similar to those described above. The patient is placed in the steep Trendelenburg position with the right side elevated. The small bowel is swept out of the pelvis and to the left, and the omentum is also swept into the left upper quadrant. The cecum is grasped, typically by the mesentery or the appendix, and retracted anteriorly and medially. The surrounding peritoneal attachments are incised with laparoscopic scissors with a cautery attachment.

As the hepatic flexure is approached, the patient should be repositioned in the reverse Trendelenburg position, still with the right side up, allowing the weight of the transverse colon to provide caudad retraction. With the attachments of the hepatic flexure on tension, an energy delivery device can be used to divide this tissue. In some patients with a fatty omentum, it may be easier to leave the omentum on the colon and enter the lesser sac from above, or this may be mandated by a tumor near the hepatic flexure or the proximal transverse colon. Otherwise, the omentum can be pushed up over the liver, and the lesser sac can be entered by incising the posterior leaflet of the omentum where it attaches to the transverse colon.

Once the transverse colonic dissection is past the midline, the colon is replaced in its anatomic position. With adequate medial mobilization, the right colon can be extracted without dividing the ileocolic vascular pedicle laparoscopically. In cases of malignancy, however, proximal transection of the ileocolic pedicle may be easier using laparoscopic techniques. By lifting anteriorly and laterally on the cecum, the ileocolic pedicle is visualized as a ridge of tension from the base of the mesentery to the ileocecal junction. A mesenteric window is created cephalad and caudad to the ileocolic vessels, and the pedicle is then divided at the level of the lateral border of the duodenum according to the surgeon's preferred technique. Great care must be taken to adequately mobilize this pedicle away from the duodenum.

Once these steps are completed, the cecum is grasped with a locking grasper through one of the lateral ports. After releasing the insufflation and allowing the abdomen to decompress, an incision is made to allow for the specimen to be removed and for construction of the ileocolic anastomosis. A wound protector (for malignant or potentially malignant disease) is placed, and the colon is fed through the midline incision. The specimen is laid out on the abdomen in the anatomic position, and the remainder of the case proceeds similar to open right colectomy. Specific attention is paid to the orientation of the bowel to ensure that there are no twists in the small bowel leading into the anastomosis. Once the anastomosis is performed, the bowel is replaced in the abdomen, and the abdomen is irrigated. If there is

concern for bleeding, the abdomen can be reinsufflated, and the areas of dissection can be inspected.

LEFT COLON MOBILIZATION

Typically, any resection of the descending or sigmoid colon includes mobilization of the sigmoid colon, and this is our chosen starting point for any left colon resection. The sigmoid colon provides a well-defined starting point for both more proximal and more distal dissection. In starting this dissection, the sigmoid colon is grasped and retracted medially. There are frequently adhesions between the sigmoid colon, its mesentery, and the lateral abdominal wall, secondary to inflammatory conditions. Blunt dissection with occasional careful cautery or sharp transection of tissue is used to free these attachments. In cases of diverticulitis, particularly medically refractory diverticulitis, or fistulizing diverticular disease, finger fracturing may be necessary to tease the sigmoid and its mesentery from the abdominal side wall.

After the sigmoid is freed of any inflammatory adhesions, the white line of Toldt is visualized by gentle medial retraction on the sigmoid colon. Cautery is used along this line medially to free the mesentery from the retroperitoneum. This may be assisted by placing a right-angled clamp or a finger in the plane of dissection and lifting the tissue anteriorly, ensuring that the underlying retroperitoneum is protected. Maintaining the retroperitoneal covering and a dry field should aid in visualization of the left ureter as it crosses the iliacs and descends into the pelvis. If chronic or acute inflammation has obscured the planes, extra care must be invoked as the ureter and iliac vessels are intimately associated with the posterolateral aspect of the sigmoid mesentery. The peritoneal reflection is swept away from the colon laterally, and sharp dissection is used to continue this mobilization proximally to the level of the splenic flexure.

LAPAROSCOPIC LEFT COLON MOBILIZATION

Compared with the open approach, the laparoscopic approach to sigmoid and descending colon mobilization is very similar. The patient is placed in the Trendelenburg position with the left side rotated anteriorly, and the sigmoid is grasped and retracted medially. In cases of medically refractory diverticulitis or fistulizing diverticular disease, the adhesions between the lateral abdominal wall and the sigmoid may be so dense as to preclude safe laparoscopic dissection. If laparoscopy is to be abandoned, the proximal descending and splenic flexure mobilization can be completed laparoscopically prior to opening as this can significantly decrease the size of the open incision.

Presuming that laparoscopic dissection can proceed, the lateral adhesions are taken down bluntly and with cautery as necessary. Continuous medial traction placed on the peritonealized surfaces provides visualization while preventing bleeding from the fragile mesentery. Gentle sweeping of the peritoneal reflection laterally with judicious cautery will reveal the underlying ureter and iliac vessels underneath the peritoneal covering. This dissection proceeds distally to the pelvic brim and proximally to the splenic flexure. As in right colon mobilization, the plane is often more medial than expected; too lateral a plane of dissection will penetrate the retroperitoneum and potentially lead to dissection behind

the kidney if not recognized. As the reach of the instruments becomes limited at the upper extent of the descending colon, the patient is shifted into the reverse Trendelenburg position, and splenic flexure mobilization proceeds.

SPLENIC FLEXURE MOBILIZATION

Splenic flexure mobilization is a critical technical element that allows the surgeon to mobilize the transverse and left colon out of the left upper quadrant, facilitating a tension-free anastomosis in left-sided colectomies and proctectomies. The mobilization can be challenging, primarily due to issues regarding exposure and the risk of injuring the splenic capsule, vessels within the splenicocolic ligament, or the colon mesentery.

The incision used generally needs to extend above the umbilicus, although there are patients in whom the splenic flexure is unusually mobile or low. In exposing the splenic flexure, a self-retaining retractor is used, elevating the ring or fixed bar so that retractors pull the abdominal wall anteriorly as well as radially. The flexure can be approached in one of two directions: clockwise or counterclockwise. Usually, both directions need to be undertaken to perform a complete mobilization [see Figure 4].

The counterclockwise dissection is a natural continuation of the sigmoid and left colon mobilization. From either between the legs or on the patient's right side, the operating surgeon places the right hand behind the proximal descending colon, using sweeping motions to dissect the areolar attachments between the colon and the retroperitoneum. The surgeon's left hand is responsible for sweeping bowel and omentum off the area of dissection into the right side of the abdomen. The sometimes bulky tissue attaching the apex of the flexure to the spleen usually requires ligation or division using an energy delivery device. A note of caution here: traction on the apex of the flexure places tension on the splenicocolic ligament; therefore, attention must be kept on the amount of tension on the spleen to avoid avulsing the capsule. To minimize this risk, the surgeon should expose these attachments and allow them to be divided *in situ* instead of attempting to retract them anteriorly. As the apex of the flexure is released, dissection proceeds medially. The pancreas and duodenum are directly posterior and medial to the splenic flexure and are subject to injury. Again, the lesser sac can be entered through the gastrocolic omentum, leaving the omentum on the transverse colon, or the omentum can be manipulated superiorly and the lesser sac entered from beneath the omentum along the border of the transverse colon, leaving the omentum attached to the stomach.

The splenic flexure can also be exposed from within the lesser sac, with dissection advancing in a clockwise direction. As the lesser sac is opened, moving from right to left, the splenic flexure is released. The medial extent of transverse colonic dissection depends on the intended anastomosis; it may be simply released to allow an ileocolic anastomosis after extended right colectomy, or it may need to reach to the pelvis for a colorectal anastomosis.

LAPAROSCOPIC SPLENIC FLEXURE MOBILIZATION

Laparoscopic mobilization of the splenic flexure is similar to that described above. With the counterclockwise dissection, adequate tension must be maintained medially as the

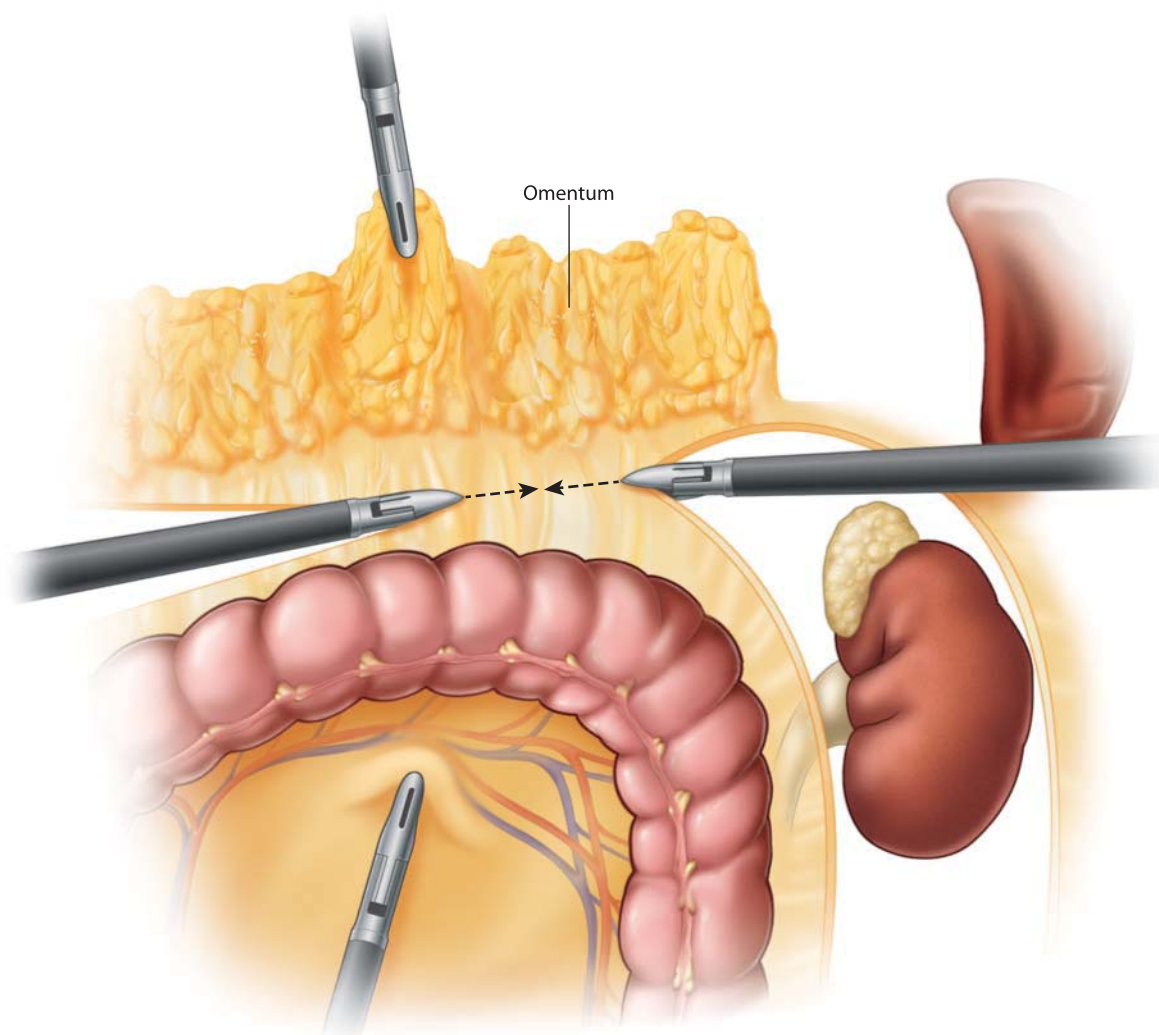


Figure 4 Dissection of the splenic flexure can be approached in one of two directions: clockwise or counterclockwise. Usually, both directions need to be undertaken to perform a complete mobilization.

splenic flexure is approached to avoid wandering into or behind the kidney. As the apex of the flexure is mobilized, the underlying pancreas and neighboring duodenum should be identified to prevent injury. The splenocolic ligament and other attachments between the transverse colon mesentery and the retroperitoneum are best divided using some form of energy delivery device.

LEFT COLON RESECTION

As discussed earlier, the left colon resection is the most poorly defined of all colectomies. Proximal margins are alternatively defined as the distal transverse colon or some site in the descending colon. The distal margin has been described as the rectosigmoid junction or the sigmoid colon. The actual operation that is undertaken should respect basic oncologic principles, with the resection of one blood vessel proximal and one distal to the tumor. If nodal disease is obvious and extends outside this scope of resection, then a broader mesenteric resection should be undertaken for locoregional control.

Some technical principles also should govern the extent of resection. A tension-free anastomosis with good blood supply is critical. The sigmoid arteries arise entirely from the inferior mesenteric artery (IMA) in the majority of patients, but there can be branches that arise from the descending branch of the left colic artery.⁵⁵ If a resection is planned that incorporates the sigmoid colon as the distal portion of the anastomosis, then it is important to carefully preserve the sigmoid arteries arising from the IMA. The portion of colon that comprises the proximal portion of the anastomosis—whichever portion this may be—should be mobilized sufficiently to allow a tension-free anastomosis. This may require the mobilization of both the hepatic and the splenic flexures.

When the splenic flexure and descending and sigmoid colon are mobilized, the points of transection are selected, and the associated mesentery is scored lightly with cautery and then taken by serially clamping, dividing, and ligating the intervening vascular tissue. After the specimen is completely freed and resected, an anastomosis is performed.

A stapled side-to-side anastomosis should be avoided in the left colon as these anastomoses create a reservoir in the middle of a colonic segment, which is prone to stagnation, and anecdotally have a higher leak rate. A handsewn anastomosis is preferred in these circumstances. Colorectal anastomoses can be handsewn or stapled using an end-end-anastomosis (EEA) stapling device.

If the sigmoid colon is resected, an EEA stapler can be used to perform an end-to-end anastomosis into the upper rectum. The largest stapler that will fit is selected; this may be ascertained by placing sizers in the rectum and colon to ensure fit. Prior to suturing the EEA anvil into the colon, the ability of the EEA stapler to reach the top of the rectal stump should be confirmed. When an appropriate size of the EEA is selected, a purse-string or baseball stitch is placed around the cut edge of the colon, and the anvil is tied in place. The stapler is placed through the anus into the rectum and guided such that the spike of the stapler can be protracted adjacent to the staple line rather than through it, which runs the risk of separating the staple line. After docking the anvil to the stapler, the stapler is fired, released, and removed. The donuts are removed from the stapler and examined for completeness; these may be sent for microscopic assessment of margins if warranted. The pelvis is then filled with irrigant, and a rigid proctoscope is inserted. With the colon clamped proximal to the anastomosis, the rectum is insufflated to ascertain if there is any air leak. In cases where an air leak is appreciated, the anastomosis should either be reinforced and reevaluated or completely resected and reconstructed.

LAPAROSCOPIC LEFT COLON RESECTION

After mobilization is completed for a left colectomy, an extraction incision is made and the colon is extracted. The resection and anastomosis are then performed in the same manner employed for the open procedure.

The mobilization and control of vascular pedicles involved in a laparoscopic left colectomy vary depending on factors related to tumor location and patient anatomy. As with an open left colectomy, the goal is to fashion a technically sound anastomosis between two portions of colorectum, which are well vascularized and joined without tension, while at the same time respecting oncologic principles (when the operation is performed for cancer). Achieving these goals may require resection of all or part of the rectum, sigmoid colon, descending colon, and transverse colon.

For resections that include the sigmoid colon and/or upper rectum, dissection should proceed distally into the pelvis to mobilize the upper rectum. The mesentery and other fatty tissue are then cleared up to the posterior wall of the rectum/rectosigmoid junction, allowing for division of the bowel in a region that has minimal adherent fat or mesentery. An endoscopic stapling device with a 3.5 mm staple height is placed across this area and fired.

The proximal margin for a laparoscopic resection needs to be planned carefully. Usually, the proximal margin of bowel is divided extracorporeally, but in so doing, the surgeon must ensure that there is enough proximal bowel to fashion a tension-free anastomosis. The marginal arterial circulation from the middle colic vessels is almost always adequate to perfuse the descending colon in cases where the IMA and/or left colic artery are resected.

If a colorectal anastomosis is planned, an EEA anvil is introduced into the proximal colon as previously discussed. Prior to suturing the anvil in place, the surgeon should be confident that the planned EEA stapler will reach the top of the rectal stump. Once this is done, the colon is then returned to the abdomen and the abdominal incision is closed. The EEA stapler is placed transanally and guided to the apex of the rectal stump, where the spike is ejected just above or below the staple line. The anvil is then docked onto the spike, the cut edge of the mesentery is assessed for twisting, and the stapler is closed and fired. After releasing and removing the stapler, the pelvis is filled with irrigant, and the rectum is insufflated to check for air leaks.

Most colocolonic anastomoses cannot be performed with an EEA. In these situations, the sites of proximal and distal transaction should be mobilized sufficiently to allow an extracorporeal handsewn anastomosis. The extraction site should be placed strategically to facilitate construction of the anastomosis.

POSTOPERATIVE CARE

Care after colectomy is primarily a function of three main goals: (1) adequate pain control, (2) awaiting the return of bowel function, and (3) vigilance for complications of surgery. Patient-controlled analgesia is widely accepted as effective management of postoperative pain, although many protocols call for the use of epidural catheters when appropriate. The routine use of nasogastric tubes after colectomy is no longer considered acceptable. Similarly, a course of antibiotics longer than 24 hours postoperatively is also not recommended. Early enteral feeding has been proven to be safe. Once patients are tolerating a low-residue diet, which decreases the local inflammatory response at the anastomosis, and passing flatus or stool, they can be discharged home, with follow-up after 2 weeks.⁵¹

Fast-track protocols have been developed and studied in multiple institutions in the hope of creating uniformity of care and decreasing postoperative stay. Common characteristics of these protocols are fluid minimization both in the operating room and postoperatively, epidural use, and early enteral feeding.⁵² Further components of fast tracking include Foley catheter removal on postoperative day 1, no oral bowel preparation, scheduled nonnarcotic analgesia (e.g., intravenous ketorolac or oral acetaminophen), and early ambulation.^{29,56} These strategies have commonly been shown to decrease length of stay by 4 to 6 days without increasing readmissions and potentially decrease complications by nearly 50% in open colorectal surgery.^{52,57} The efficacy of fast-track protocols has been demonstrated in laparoscopic surgery as well, with fast-track patients having shorter times to enteral feeding (decreased by 1 day) and first bowel movement (decreased by 1 day), shorter lengths of stay (3 versus 4 to 5 days), and fewer complications (15 to 29% versus 25 to 56%).^{29,56}

COMPLICATIONS

As with any major operation, colectomies are associated with a distinct risk of complications. These include those common to any abdominal surgery requiring general anesthesia, such as anesthetic complications, DVT and PE, myocardial infarction, stroke, pneumonia, wound infection,

and urinary tract infection. The rates of these complications may be minimized by following national guidelines for prevention and treatment.

Complications specific to colorectal surgery include nerve injury or even compartment syndrome in the extremities secondary to positioning, injury to the spleen mandating splenectomy (approximately 1% of cases), and problems related to the anastomosis. Anastomotic leaks occur on the order of 1 to 5% depending on where in the colon the anastomosis is made; in general, the more distal the anastomosis, the higher the rate of leakage. Significant anastomotic bleeding occurs approximately 1% of the time, and abscesses (1% of cases) and strictures (up to 10% long term) also can occur, which may be related to anastomotic compromise secondary to ischemia, tension, or inflammation.^{53,58} Although assessment of blood flow, tension, and bowel appearance makes anastomotic complications less likely, these will still occur. Finally, mortality may occur in 1% or more of cases, although this risk depends heavily on patient preoperative risk factors, emergent indications for surgery, and the complexity of the surgery itself.⁵⁸

One notable theme that has emerged in the recent literature investigating the quality of surgical care is the concept of “rescue.” In examining hospitals with widely varying death rates, it has been demonstrated that the underlying rate of serious complications is similar across these hospitals.⁵⁴ What is markedly different is the ability of hospitals to respond quickly and adequately to prevent worsened morbidity or mortality from a complication of surgery. This ability to “rescue” patients is an emergent property of various aspects of each hospital, including nursing care, ancillary staff, and culture. It is incumbent on each surgeon who performs colectomies to be part of a system that is focused not only on preventing complications but also on recognizing them and treating them quickly and appropriately.

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Acknowledgement

Figures 2 through 4 Christine Kenney

35 PROCEDURES FOR RECTAL CANCER

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Rectal cancer is a common and lethal malignancy diagnosed in over 40,000 Americans each year.¹ Treatment may be undertaken with curative or palliative intent. Cure is almost never achieved without a surgical resection that achieves microscopically clear margins (R0 resection). Other surgical goals are to maintain or restore bowel continuity with normal or near-normal anal continence, preserve sexual and bladder function, and minimize other treatment-associated morbidity and mortality. Low anterior resection (LAR) and abdominoperineal resection (APR) are the most common operations for rectal cancer. Ricciardi and colleagues reported that of 41,631 patients undergoing radical extirpative surgery for rectal cancer in the United States between 1988 and 2003, 60% had sphincter-sacrificing procedures and 40% had sphincter-sparing procedures.² Sphincter-sparing operations increased from 27% in 1988 to 48% in 2003. Today, a wide variety of treatment regimens are available to treat rectal cancer spanning the spectrum from simple polypectomy to prolonged and potentially morbid multimodality regimens of neoadjuvant chemoradiation therapy, radical extirpative multivisceral and extended resections, adjuvant chemotherapy, and biologic agents.

Choosing the optimal therapy for rectal cancer is a complex process. Although physicians from different disciplines are increasingly involved, it is the colorectal surgeon who generally directs the initial evaluation of patients with rectal cancer and leads the discussion with a multidisciplinary team and the patient to select a treatment protocol. In this chapter, we examine the surgeon's unique and critical role in the pretreatment evaluation and decisions leading to choice of therapy, review alternative operative approaches, address key technical aspects of the operations performed to treat rectal cancer, and discuss postoperative therapy and follow-up.

Pretreatment Evaluation

The pretreatment evaluation of the patient with a rectal cancer is the basis for rational decision making regarding choice of therapy. Evaluation includes assessment of the patient and the primary cancer as well as a search for metastases and synchronous colonic abnormalities.

PATIENT ASSESSMENT

A complete clinical assessment is done to identify pre-existing comorbidities, define operative risk, and explore the patient's psychosocial state and ability to manage the stresses accompanying the diagnosis and treatment of rectal cancer.

Comorbidities

A history and physical examination with standard preoperative blood and urine tests, electrocardiogram, and serum

carcinoembryonic antigen (CEA) are obtained. Important general medical issues that the surgeon must review include current medications and allergies; smoking status; use of alcohol or other drugs; major organ dysfunction (cardiopulmonary, renal, and hepatic); hypertension; obesity; anemia; malnutrition; diabetes; deep vein thrombosis; and pulmonary embolism. Knowledge of prior operations (especially those involving the digestive or genitourinary organs), prior infections following surgical procedures, prior pelvic irradiation, baseline bowel and anal sphincter function, a personal history of colorectal polyps or cancers, and a family history suggestive of a hereditary cancer syndrome are vital for the colorectal surgeon. During the physical examination, the surgeon should be especially alert for the presence of liver enlargement, abdominal tenderness or masses, lymphadenopathy, muscle wasting or ascites, and abdominal scars or ventral hernias that may complicate planned surgery. The integrity and function of the anal sphincter are carefully assessed by means of digital rectal examination and, if necessary, by additional physiologic testing and endoanal ultrasonography.

Operative Risk

The risk of postoperative adverse events is important for surgical shared decision making and obtaining informed consent from the patient. In modern series, 30-day postoperative mortality after resection of the rectum ranges from 1.6 to 4.8% and morbidity remains high.³ Numerous perioperative scoring systems have been developed either to predict the likelihood of postoperative morbidity and mortality or to allow risk-stratified comparison of outcomes between institutions and surgeons.⁴ Although none of these scoring systems are specific for the rectal cancer patient, a morbidity and mortality risk calculator for colorectal surgery was recently developed by the American College of Surgeons National Surgery Quality Improvement Program.⁵ This tool predicts mortality, overall morbidity, and serious morbidity and provides assessment of hospital effects on adverse outcomes for patients undergoing colorectal surgery.

The influence of age on operative mortality is complex. Although the elderly may tolerate a complex procedure quite well, they often cannot tolerate complications. Thus, prediction of potential morbidity is particularly important in decision making for the elderly patient with rectal cancer. We recently assessed the association between older age (≥ 75 years) and short-term outcomes after major oncologic resections in 8,781 patients, including 485 who underwent proctectomy for rectal cancer with or without total abdominal colectomy.⁶ Older patients had increased preoperative comorbidities, higher operative mortality (4.83% if > 75 years versus

1.09% if aged 40 to 55 years), higher rates of major complications, and longer hospital stays. Older age is independently associated with worse short-term outcomes after major oncologic resections, but the effect of older age is comparable to other preoperative risks.

Psychosocial Evaluation

The surgeon must understand the patient's desires, knowledge base, expectations, lifestyle, and social support resources. The goal is to obtain information that may impact the treatment plan and identify preexisting conditions that can be addressed and optimized before an elective operation. The needs of a homeless individual or a down-and-out drug addict with no resources, no access to reliable transportation, and no family available for support are quite different from those of a well-educated, upper middle class individual with financial resources and a supportive network of family and friends. Similarly, in some cultures and for some people, a colostomy is worse than death. Each patient deserves optimal care, and the surgeon must recognize and adjust the approach to meet the individual patient's needs. Some patients will require significantly more social resources to help them through the treatment process, whereas others will require more counseling time and direct support from the surgeon or other caregivers.

RECTAL CANCER ASSESSMENT

The gross morphology and histology, precise location, and local extent of the primary rectal cancer are assessed by biopsy, clinical assessment, proctosigmoidoscopy, and imaging studies. The American Joint Committee on Cancer's TNM classification system is clinically useful and accepted worldwide [see Table 1 and Table 2].

Gross and Histopathology

The gross morphology is noted. Ulcerated lesions are generally more invasive and aggressive than exophytic lesions. Biopsy (or review of prior biopsies) is an essential first step to confirm the diagnosis of adenocarcinoma and to ascertain the presence of unfavorable histologic features (e.g., mucin production, lymphovascular invasion, or signet cell histology) that may influence choice of therapy.

Location

The precise level and the quadrants and percentage of rectal circumference involved by a rectal cancer are determined by digital rectal examination (DRE) and proctosigmoidoscopy. The surgeon should not rely on the level as determined by another physician as it is often estimated quite inaccurately. Although the level is traditionally measured as centimeters proximal to the anal verge, most experienced rectal cancer surgeons find it more useful to assess the level of a rectal cancer relative to the anal sphincter muscles and anorectal ring and to measure the distance of normal rectum distal to the lower border of the cancer to the dentate line. Such anatomic information is useful to predict whether sphincter-sparing or sphincter-sacrificing resection is likely and whether a temporary diverting ileostomy is likely to be constructed if a low anastomosis is done.

Local Disease

The extent of local spread of rectal cancer includes assessment of four factors: (1) the depth of invasion of the primary

lesion (T stage); (2) the presence of local perirectal nodal metastases (N stage); (3) the presence of a threatened or involved mesorectal circumferential resection margin (CRM); and (4) direct intrapelvic spread from the primary.

T staging is generally done by endorectal ultrasonography (ERUS) or magnetic resonance imaging (MRI). Computed tomography (CT) is not able to visualize the layers of the rectal wall and, not surprisingly, is not very useful in determining the T stage of early lesions. In contrast, ERUS is especially useful for assessment of early T-stage tumors.⁷ It was found to be 95% accurate in distinguishing cancers confined to the bowel wall (T1 and T2) from those invading through the wall into the perirectal fat ($\geq T3$).⁸ Kim and colleagues reported an overall accuracy in T staging of 81.1% by ERUS, 65.2% by CT, and 81% by endorectal coil MRI.⁹

N staging remains a major challenge despite the many advances in imaging technologies. Overall accuracy for staging lymph node metastases was 63.5% for ERUS, 56.5% for CT, and 63% for MRI.⁹ ERUS accuracy for N staging is highly dependent on the operator but has been reported as high as 80 to 85%.¹⁰ MRI accuracy is also variable, but when border contour and signal intensity characteristics of lymph nodes are used to identify lymph node metastases instead of size criteria, the accuracy is significantly improved with a sensitivity of 95% and a specificity of 95%.¹¹

CRM clearance by properly performing total mesorectal excision (TME) within the endopelvic fascial plane is critical.^{12,13} A positive CRM is highly correlated with high local recurrence rates and worse survival rates. The surgeon has anatomic bony constraints within the pelvis that may make it impossible to get widely around mesorectal nodal or soft tissue spread from a rectal cancer. One of the strategies currently employed to manage the patient with a threatened or involved CRM is to subject such patients to neoadjuvant chemoradiation. Thus, accurate imaging of the mesorectum is essential to select patients who would potentially benefit from this approach. Modern thin-section MRI is extremely accurate in assessing the depth of invasion of a rectal cancer into the mesorectum and can accurately predict an involved margin.¹⁴ The other imaging techniques are not as accurate.

Extrarectal pelvic spread from the primary rectal cancer directly to adjacent structures including the anal sphincters, pelvic sidewall, prostate, seminal vesicles, vagina, bladder, and sacrum may be suspected when tethering or fixation is noted during a DRE. The precise extent of such local invasion is accurately assessed by MRI and pelvic CT. Presacral stranding, obliteration of normal landmarks lateral to the rectum, direct invasion into the bladder or sacrum, and evidence of hydronephrosis are all signs of extensive pelvic disease. Although ERUS may be useful in assessing involvement of the vagina or prostate or seminal vesicles, it is not very effective in assessing other areas of extrarectal spread.¹⁵

High-spatial resolution surface coil thin-slice MRI has improved in recent years and has essentially replaced the use of endorectal coil MRI for staging rectal cancer. It not only accurately assesses T stage but also has the advantages of being less operator dependent and more useful in stenotic tumors. It is the best method to assess the extent of rectal cancer spread within the mesorectum and can identify tumors with other poor prognostic features, including extramural

Table 1 American Joint Committee on Cancer TNM Clinical Classification of Colorectal Cancer¹⁰⁰

Stage	Description	
Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ; intraepithelial or invasion of lamina propria*
	T1	Tumor invades submucosa
	T2	Tumor invades muscularis propria
	T3	Tumor invades through the muscularis propria into the subserosa or into nonperitonealized pericolic or perirectal tissues
	T4	Tumor directly invades other organs or structures and/or perforates visceral peritoneum†‡
Regional lymph nodes (N) [§]	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in 1 to 3 regional lymph nodes
	N2	Metastasis in 4 or more regional lymph nodes
Distant metastasis (M)	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis

*Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

†Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa, for example, invasion of the sigmoid colon by a carcinoma of the cecum.

‡Tumor that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumor is present in the adhesion, microscopically, the classification should be pT3. The V and L substaging should be used to identify the presence or absence of vascular or lymphatic invasion.

§A tumor nodule in the pericorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the T category and coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident) because there is a strong likelihood that it represents venous invasion.

spread > 5 mm, extramural venous invasion, nodal involvement, and peritoneal infiltration. Importantly, it provides surgeons with anatomic images that define the tumor's location in relation to the anal sphincters, the obturator foramen, and other structures in the pelvis. The MERCURY Research Project demonstrated that high-quality MRI can be performed in routine practice after appropriate training of diagnostic radiologists.¹⁶ Because this information is critical to planning radical resection of the rectum, MRI has increasingly become the diagnostic imaging study of choice for rectal cancer.¹⁷

Distant Metastases

The presence of distant metastases may completely change the approach to a rectal cancer. The vast majority of distant

metastases from a rectal cancer are to the liver and lungs and are generally asymptomatic. Thus, both organ sites should be routinely surveyed by imaging. All patients with rectal cancer are evaluated either with a chest x-ray or CT of the chest to exclude pulmonary metastases. Liver metastases are excluded either by CT or MRI in the United States; abdominal ultrasonography is used in other parts of the world for the same purpose.

If symptoms or findings on physical examination raise suspicion of other sites of spread, appropriate testing is done. The role of positron emission tomography (PET) is not well delineated at this time and remains controversial. It is highly (96%) sensitive in detecting a primary cancer, of limited value in detecting local pelvic lymph node metastases, and possibly of value in detecting distant metastases.¹⁸ Its major current uses are to (1) clarify equivocal findings on other scans and (2) minimize the risk of missing a distant metastasis to an unusual site in a patient being considered for a highly morbid resection of an extensive primary or recurrent rectal cancer. Combined PET-CT has advantages over using either test alone or both tests separately and may be indicated when multivisceral and extended resections are being contemplated to increase the assurance that such a radical procedure can be done with curative intent. Serum CEA may be useful as a baseline study. A CEA that is elevated and drops to normal levels after resection is reassuring. Persistence of an elevated CEA after treatment or a rising CEA should alert the surgeon to the possible presence of a metastasis or incomplete resection of the primary. Prompt additional evaluation is indicated.

Table 2 American Joint Committee on Cancer Staging System for Colorectal Cancer¹⁰⁰

Stage	T	N	M
0	Tis	N0	M0
I	T1–T2	N0	M0
IIA	T3	N0	M0
IIB	T4	N0	M0
IIIA	T1–T2	N1	M0
IIIB	T3–T4	N1	M0
IIIC	Any T	N2	M0

SYNCHRONOUS COLORECTAL NEOPLASMS AND COLONIC DISEASE

Patients with rectal cancer should undergo colonoscopy not only to assess and biopsy the rectal cancer but also to identify and remove synchronous polyps (13 to 62% of cases) or to localize and biopsy synchronous cancers (2 to 8% of cases).^{19,20} The location and nature of a synchronous cancer usually alter the treatment plan for the rectal cancer. Colonoscopy is especially useful to plan the extent of colectomy if the rectal cancer developed in the setting of familial adenomatous polyposis, inflammatory bowel disease, diverticular disease, or other colonic pathologic conditions. If colonoscopy is incomplete, a double-contrast barium enema or virtual colonoscopy with CT colography is a suitable alternative.²⁰ If preoperative surveillance of the proximal colon is not possible, intraoperative or postoperative colonoscopy should be done.

Choosing a Therapy Protocol

Advances in surgery and anesthesia, medical and radiation oncology, imaging, and staging, as well as improved understanding of the biology of rectal cancer, have all influenced the way we treat the patient with rectal cancer. Ideally, a multidisciplinary team of surgeons, medical oncologists, radiation oncologists, diagnostic radiologists, pathologists, and other caregivers with specific expertise in rectal cancer jointly review the results of the pretreatment evaluation to recommend a specific treatment protocol based on its therapeutic value, that is, the ratio of the relative benefit and the relative harm likely to follow a specific therapy protocol for a specific rectal cancer in a specific patient. Whereas most proximal rectal cancers are treated with LAR regardless of stage, mid- and distal cancers are treated variably, often with multimodality protocols, depending on cancer stage and other factors delineated during the preoperative assessment. Because treatment is so highly individualized, it is difficult to be dogmatic about what constitutes optimal therapy for rectal cancer. Nonetheless, there are certain generally accepted treatment guidelines based on intent of therapy and the perceived role and effectiveness of the components of multimodality therapy including surgical options.^{21,22} A frank and honest discussion with the patient is essential for shared decision making and obtaining informed consent.

TREATMENT INTENT

Treatment may be done with curative or palliative intent. On occasion, curative intent therapy may be deliberately compromised either because the patient's comorbidities are so severe that standard resection cannot be safely performed or because the patient refuses to accept a recommended standard curative intent therapy protocol. Curative intent treatment of rectal cancer requires resection and/or ablation of all neoplastic tissue, generally accomplished by an R0 resection usually in the form of a radical resection such as LAR or APR. In the past, stage IV rectal cancer was thought to preclude curative intent therapy, but that dogma was questioned when it was shown that isolated liver or lung metastasis could be safely resected either synchronously with the primary tumor or in sequential operations, with resultant

5-year survival in 25 to 40% of patients.²³ Today, what was once a clear case for palliative care only is now often considered for aggressive, multimodality therapy with the hope of improving the disease state to the point that curative intent surgery can be employed. A multimodality regimen of neoadjuvant chemoradiation plus extended radical resection and intraoperative radiotherapy followed by adjuvant chemotherapy was used for management of 146 patients who presented with unresectable primary colon ($n=40$) or rectal ($n=106$) cancers.²⁴ This regimen resulted in good local disease control and a 5-year disease-free and overall survival of 43% and 52%, respectively. Similarly, patients who present with advanced or symptomatic distant metastases but have a minimally symptomatic primary rectal cancer are often first treated by aggressive chemotherapy plus biologics. If restaging shows resolution or good local control of the distant metastases, resection of the primary and metastases may then be done. A recent retrospective study reported the outcome of 233 patients who presented with synchronous stage IV colorectal cancer judged not amenable to curative intent therapy but treated instead with modern combination chemotherapy with or without bevacizumab as their initial treatment (unresected primary cancer).²⁵ In 47 patients (20%), the response was so marked that curative intent resection of the primary cancer and the metastatic disease was possible.

MULTIMODALITY THERAPY OPTIONS

Although surgery remains the dominant form of therapy for rectal cancer, the roles of radiation, chemotherapy, and new biologic agents are expanding.

Surgical Options

The decision to use a standard radical resection, a local or an extended operation, or palliative surgery is primarily based on the pretreatment assessment. Mature judgment is required, and the surgeon's role to select the optimal approach is critical as it is a primary determinant of outcome for patients with rectal cancer. As the multidisciplinary team reviews the workup, the experienced surgeon can identify potential technical challenges and reasonably estimate the likelihood of doing a primary anastomosis with or without temporary proximal diversion versus a permanent colostomy. Most often, a standard radical resection (LAR or APR) is needed, but local approaches are sometimes indicated. Information obtained during the preoperative assessment can alert the surgeon to alter standard approaches to fit the specific features of a rectal cancer. For instance, signet ring histology will increase the standard distal mural margin requirement and synchronous colonic pathology may require an extended colectomy. Multivisceral resections may be indicated based on extent of local spread. Depending on their magnitude, the colorectal surgeon may enlist the expertise of a hepatic, thoracic, plastic, urologic, gynecologic, neurosurgical, or orthopedic surgical colleague. Anticipated impact of contemplated surgery on fecal continence and urinary and sexual function should be considered and discussed honestly with the patient. A patient with preexisting fecal incontinence or sphincter injury may be better served by an APR and colostomy than by a well-intentioned but ill-conceived heroic effort to save the anal sphincter with an extended LAR.

Controversies

Today, the main controversies surrounding the use of multimodality therapy for rectal cancer are (1) the tumor selection criteria (i.e., when will multimodality therapy increase the likelihood of achieving an R0 resection or improve the oncologic, functional, or quality of life outcomes for the patient?); (2) the timing of therapy (i.e., should it be preoperative, postoperative, or both?); (3) the dosing and course of radiation therapy; (4) the choice of chemotherapy and biologic agents; (5) the use of chemoradiation in conjunction with local surgical therapy; (6) whether the surgical distal margin should be based on pretreatment assessment of the level of the cancer or on the post-neoadjuvant chemoradiation assessment; and (7) whether a complete clinical response to neoadjuvant chemoradiation therapy is sufficient to follow the patient without radical surgery being performed. Detailed discussion of these issues is beyond the scope of this chapter, which is focused on surgical approaches, technique, and outcomes. Nonetheless, it is useful to briefly review the evolution and current indications for neoadjuvant therapy and to acknowledge the controversies regarding use of long-course radiation versus short-course therapy.

Neoadjuvant Chemoradiation

In the past, most rectal cancers were treated by radical surgery alone. Patients surviving their operation often died of distant metastases or of locally recurrent cancer in the pelvis. Chemotherapy (primarily 5-fluorouracil) and pelvic radiotherapy (using what is now considered suboptimal doses and less than ideal delivery techniques) were generally ineffective. By the 1980s, local recurrence in the pelvis was reported in up to 40% of patients following “curative intent” rectal cancer excision in some series.²⁶ In the United States, clinicians and researchers renewed their efforts to improve radiation therapy techniques and to make it a more effective modality by adding “sensitizing” chemotherapy. New and more effective chemotherapy agents for postoperative adjuvant use were developed. This trend to using multimodality therapy gained significant momentum in the United States when a 1990 National Institutes of Health consensus conference endorsed postoperative chemoradiation treatment of all stage II and III rectal cancers generally initiated 4 to 8 weeks following LAR or APR.²⁷ The consensus statement based on clinical trials suggested that a combination of what is now called “long-course” radiation therapy delivering 50.4 Gy over 6 to 8 weeks to the pelvis coupled with 5-fluorouracil-based chemotherapy would reduce local recurrence rates and prolong survival in patients with stage II and III rectal cancer.

Reports of morbidity from postoperative chemoradiation pushed investigators to propose neoadjuvant (preoperative) chemoradiation as a viable alternative to treat advanced-stage rectal cancers.²⁸ The same dose was delivered over the same time period, but because preoperative irradiation treats undisturbed, well-oxygenated rectal cancers, it was argued that it would be more effective than postoperative irradiation, resulting in improved local control and better survival. In addition, neoadjuvant therapy should theoretically increase the rate of curative resection and the rate of sphincter preservation by decreasing the size of bulky rectal cancers. It was also thought that a neoadjuvant approach would diminish the incidence of

radiation injury seen after postoperative irradiation when small bowel is adherent to the pelvic operative site. Presently, there is considerable evidence that neoadjuvant therapy decreases local recurrence rates for rectal cancer and that it may improve survival and possibly decrease the need for a permanent colostomy. The German Rectal Cancer Study randomly assigned patients with locally advanced rectal cancer to either preoperative or postoperative chemoradiation.²⁹ Following TME, local recurrence was significantly lower in the preoperative chemoradiotherapy group. In addition, the neoadjuvant therapy group was characterized by significant tumor downstaging. Despite equivalent 5-year disease-free survival and overall survival rates, the decreased local recurrence rate led the National Comprehensive Cancer Network to recommend consideration for preoperative chemoradiation (long course) for all patients with T3 or T4 rectal cancers.²² New chemotherapy regimens are now being used with high-dose radiation.³⁰

Short-Course Radiation

To prevent radiation-related complications and to avoid delaying the timing of surgery for months, many European centers, especially in Scandinavia, developed preoperative “short-course,” high-dose, hypofractionation irradiation, which usually delivered 25 Gy over a period of 5 days. This delivers the biologically equivalent dose of that delivered by the long-course chemoradiation protocols (50.4 Gy) typically used in the United States.³¹ Radical resection is performed 3 to 4 days after completion of the radiation. Short-course irradiation does not downsize tumors and is not advocated if the CRM is threatened or involved but does appear to be highly effective in many advanced cancers and seems well tolerated.³² In 2007, Peeters and colleagues published the long-term results of the Dutch study that showed that reduced rates of local recurrence (5.6% after short course versus 10.9% after TME surgery alone, $p=.001$) are maintained after 6 years of follow-up.³³ Unfortunately, no survival benefit was found after short-course radiotherapy. American radiation therapists have been resistant to its use, but that view is now being questioned.³⁴

INFORMED CONSENT

After determining whether treatment is offered with curative, compromised, or palliative intent, decisions are made to include or exclude neoadjuvant therapy and to use standard radical resection, local or extended operations, or palliative surgery. Once selected, the treatment protocol must be explained to the patient and consent obtained. The surgeon usually leads this discussion by reviewing the clinical staging information in the context of anticipated operative technical challenges, the likely functional results, operative risk, comorbidities, previous treatments, and specific needs of the patient. Fear of treatment-related morbidity and poor functional outcomes or a misunderstanding of what is to be done and what alternatives are available often underlies the patient’s refusal to accept a recommended treatment protocol. This is especially true when the patient is told that a permanent colostomy is needed to achieve optimal control of the rectal cancer. Specific education provided by an ostomy nurse and an honest discussion to ascertain patient preferences and discuss trade-offs between oncologic outcomes, functional outcomes,

treatment morbidity, postoperative rehabilitation, and time investment for any particular treatment plan often mitigate the initial refusal. A compromise treatment plan may still be needed even if that choice negatively impacts the oncologic outcome. No matter what treatment protocol is ultimately selected, the experienced surgeon is probably best suited to counsel the patient about therapeutic options, realistic expectations regarding function, and prognosis.

Surgical Approaches and Outcomes

The surgeon's options include local procedures, standard radical resections, extended multivisceral resections, and other less used techniques. The rationale and role for each approach as well as the specific outcomes are detailed below.

LOCAL PROCEDURES

Role of Local Therapy

Today, controversy surrounds the use of local procedures for rectal cancer especially if done with curative intent. Their benefits include minimal morbidity and negligible mortality, rapid postoperative recovery, and preservation of genitourinary and anal sphincter function. In some cases, local therapy is the only alternative to permanent colostomy. Although there is considerable controversy about the role of local therapy for curative intent, almost all surgeons agree that local therapy has a role in compromise situations, that is, for patients who might not tolerate a radical procedure or who refuse a recommended radical resection (usually because of the potential for a permanent colostomy). Local therapy may also be used in select cases for palliation of symptomatic but incurable rectal cancers.

Proponents of curative-intent local therapy argue that in properly selected cases, long-term cancer-free survival is achieved.³⁵ It is known that the incidence of lymph node metastases correlates most closely with the depth of rectal wall invasion and is especially high if the cancer extends through the wall.³⁶ Proponents of curative intent local therapy argue that preoperative staging with ERUS or MRI can differentiate intramural (T1 to T2) cancers from transmural (T3) cancers with a high degree of accuracy and can distinguish most of the T1 and T2 cancers in which lymph node metastases are present. In addition, they note that poorly differentiated tumors recur three times more often than well-differentiated to moderately differentiated tumors and that lymph node metastases are more common if preoperative biopsy reveals poor differentiation, lymphovascular invasion, mucin production, or signet cell histology. Proponents of local therapy use these selection criteria to restrict local therapy to the most favorable T1 to T2,N0,M0 rectal cancers.

Critics of local therapy argue that local therapy inevitably compromises oncologic outcomes by not including lymphadenectomy, thus resulting in higher local recurrence rates and decreased survival compared to radical resection.^{37,38} They note that occult node-positive disease was found in final pathology specimens in 12% of patients with T1 cancers and 22% of those with T2 cancers who underwent radical resection of lesions that fit the selection criteria for local therapy.³⁹ Had local therapy been done, such node-positive disease

would not have been identified or treated. They conclude that the imaging inaccuracy in detecting lymph nodes prior to instituting treatment inevitably results in worse oncologic outcomes.

Local Therapy Options

Local procedures to treat rectal cancer include surgical excision or ablative techniques of fulguration and endocavitary radiation. Polypectomy is not advised as a planned procedure to treat a known cancer, but as noted below, an unsuspected cancer arising in a polyp can sometimes be cured by polypectomy alone. Excision has the advantage of providing a biopsy specimen that can be examined to determine the depth of tumor invasion and thereby confirm or change the preoperative T stage. If microscopic examination of the specimen shows involvement of the circumferential or deep margins or if the pathologic T stage is more advanced than the preoperative clinical or imaging T stage, radical surgery or chemoradiation may be employed to improve local control. It is not clear whether this approach—excisional biopsy with subsequent additional therapy depending on the final pathologic examination of the specimen—compromises survival in comparison with a more aggressive initial approach. Obviously, this approach is not feasible if local ablative techniques are employed as the primary lesion is destroyed and thus unavailable for pathologic study.

Polypectomy Not infrequently, after snare polypectomy of what was thought to be a benign polyp, the clinician is informed that microscopy reveals the presence of an unsuspected cancer. The first response is to tattoo the polypectomy site if not done initially and the second is to review the pathology. Polypectomy alone is adequate for treating cancer arising in a rectal polyp if the lesion is noninvasive (i.e., confined to the mucosa) or if an invasive cancer is confined to the head, neck, or stalk of a pedunculated polyp and the margins are clear. If tumor is present within 1 to 2 mm of the margin or if the cancer extends into the submucosa of a pedunculated or sessile polyp, additional therapy should be considered. Decision making is based on comparing the risk of local recurrence and of lymph node or distant metastasis with the risk of surgical or other treatment.⁴⁰ In general, no further treatment is recommended if the following criteria are fulfilled: (1) the polyp is completely excised and submitted in total for pathologic examination; (2) it is possible to accurately determine the depth of invasion, grade of differentiation, and completeness of excision of the carcinoma; (3) the cancer is not poorly differentiated; (4) there is no vascular or lymphatic involvement; and (5) the margin of excision is not involved. If these criteria are not met, then the patient may be a better candidate for one of the local or radical procedures described below. Professional gastroenterology and surgical societies offer frequently updated guidelines accessible through Web sites to assist decision making in this complex and somewhat controversial area.

Local excision The goal of local excision procedures is to perform a full-thickness resection of the primary lesion with a 1.0 cm margin.⁴¹ Local excision is most often accomplished via a transanal approach under direct vision or by means of transanal endoscopic microsurgery (TEM). The

transanal approach is appropriate for tumors up to 7 to 10 cm from the anal verge, whereas TEM can be performed with tumors as high as 20 cm from the anal verge. Visibility with TEM techniques is superior to traditional transanal techniques, but TEM equipment makes it difficult to use for distal tumors close to or overlying the sphincter mechanism. Posterior approaches (transsacral or transsphincteric) have been described for local excision but are rarely used today because of significant associated morbidity (wound infections, bowel fistulas, and impaired continence) and because effective, less morbid transanal techniques are available. Rarely, it is helpful to expose the anorectum via a parasacral incision so as to facilitate local excision of a rectal cancer that is otherwise difficult to access.

Transanal local excision: results Many surgeons predicted that excellent oncologic outcomes could be achieved by restricting curative intent local excision to lesions that are histologically favorable, accessible, small enough to be totally removed, and confined to the bowel wall without sphincter invasion or nodal metastases. Unfortunately, this hope has not been realized. Clinical studies showed that the risk of local recurrence after local excision of selected, presumably favorable lesions is 18% for T1 cancers and 37 to 47% for T2 cancers.^{37–39} Although these retrospective studies with relatively short-term follow-up have not demonstrated any impact on cancer-free survival for T1 cancers, some have shown decreased survival in T2 cancers treated by local excision as the only therapy. In addition, a recent study showed that survival is compromised in the setting of rectal cancers with poor histologic markers treated by local excision alone.⁴²

Proponents of curative intent local therapy had theorized that close follow-up would detect local recurrence after local therapy at a stage where salvage surgery could be done. However, it appears that although salvage surgery is often possible, the long-term outcome in patients undergoing radical resection after local excision is less than expected, especially considering the early stage of their initial disease. In addition, pelvic recurrence following transanal excision often requires an extended pelvic dissection with en bloc resection of adjacent pelvic organs.

TEM: results A review of TEM in combination with radiotherapy for 137 patients showed this to be a safe technique with 8% minor morbidity, 2% major morbidity, and no mortality. The authors reported a combined 5% recurrence rate for T1 to T3 tumors, but the follow-up was only 6 months.⁴³ A recently reported Danish multicenter study of 143 consecutive patients with rectal adenocarcinoma treated by TEM showed a cancer-specific survival for T1 tumors to be 94%.⁴⁴ In a recent, slightly larger study, 200 patients underwent TEM and the overall and disease-free 5-year survival rates for patients with carcinomas were 76% and 65%, respectively.⁴⁵ Further data are needed to draw definitive conclusions regarding the use of TEM for these presumably low-risk tumors.

New approaches to optimize local excision Three approaches have been proposed to overcome the poor outcomes reported after local excision of selected favorable T1 and T2 cancers of the rectum. One approach is to be even more selective by limiting the use of curative intent local therapy to only those

T1 lesions that extend into the superficial third or the middle third of the submucosa^{46,47} and by using modern MRI to identify lymph node metastases by the criteria of border contour and signal intensity characteristics instead of size criteria.^{11,17} Such restricted criteria may prove to be an effective strategy to select the most favorable and least invasive cancers, but further studies are needed.

A second approach is to lower local recurrence rates after local excision by adding adjuvant or neoadjuvant radiation therapy, with or without chemotherapy. Estimated local recurrence rates after local excision followed by adjuvant therapy range from 0 to 9% for T1 tumors and from 0 to 24% for T2 tumors.^{35,48} The 5-year survival rate for T2/T3 patients who underwent neoadjuvant therapy prior to local excision was 84%.⁴⁹ Local excision may be particularly useful in patients who seem to have evidence of complete pathologic response after neoadjuvant therapy; however, the data supporting this approach are sparse.

A third and recently described approach uses dorsoposterior extraperitoneal pelviscopy to overcome the failure of local excision to remove any of the mesorectal lymph nodes.⁵⁰ This hybrid procedure combines local surgery with minimally invasive methods to dissect the mesorectum. The goal is to lower morbidity compared to traditional anterior resection while achieving locoregional control comparable to that of radical surgery. Recently published results reveal that the median number of lymph nodes removed is lower compared to traditional anterior resection. In addition, only two of 25 patients had documented evidence of positive lymph nodes and none of the patients developed locoregional recurrence after a short follow-up period.⁵¹ This technique is still under investigation and requires more supporting data before it can be recommended as a safe option for rectal cancer.

Local ablation techniques

Fulguration (electrocoagulation) In the past, fulguration has been used as curative intent treatment, with reported 5-year survival rates reaching 58%, but it is now used primarily for palliative purposes. The main advantage of fulguration is that it controls bleeding from incurable, bulky rectal cancers with minimal morbidity and is well tolerated by patients who are too ill to undergo radical resection. The disadvantages of this procedure include postoperative fever, the lack of a surgical specimen for staging, the requirement for repeated procedures, and the need to convert to more radical procedures in a large number of patients.

Endocavitary radiation (Papillon technique) This ablative technique has the distinct advantage of being performed in the outpatient setting with local anesthesia and sedation. However, because it requires special equipment and expertise and is dependent on placing the delivery device directly on a small superficial cancer, it is not widely available and used infrequently. Occasionally, it is used in conjunction with local excision. The reported 5-year survival rate is 76%, with a local recurrence rate of 8.3% and a mortality of 7.7%.

RADICAL PROCEDURES

The majority of patients with nonmetastatic rectal cancer require a radical resection, usually an LAR or APR. The

primary goal of curative intent radical resection is to perform a resection of the rectal cancer, the rectosigmoid mesentery, and the mesorectum with clear proximal, radial, and distal margins. Radical resections are classified on the basis of the final pathologic assessment as R0 if all margins are clear, R1 if microscopic tumor is present at the margin, and R2 if gross disease is present.

Evolution and Oncologic Outcomes of Radical Surgery

For the first half of the 20th century, APR with permanent end descending colostomy was accepted as the treatment of choice for most rectal cancers including those at the rectosigmoid junction. This highly morbid and not infrequently fatal radical resection was designed to resect the extensive local spread and lymphatic metastases identified at autopsy of patients who had died of advanced-stage rectal cancer. By midcentury, improvements in perioperative care, anesthesia, and surgical technique reduced operative mortality and made laparotomy with colonic anastomosis safer. Studies then revealed that the primary lymphatic spread of most rectal cancers is upward along the inferior mesenteric artery and that distal and lateral spread from all but very distal lesions occurs only after the proximal lymphatics are choked with tumor. This information provided the rationale to pursue LAR and anastomosis whenever technically feasible.

Local recurrence The technical difficulties inherent in hand suturing reliable low colorectal anastomoses and the traditional insistence on achieving a 5.0 cm distal margin were major impediments to routinely doing sphincter-sparing proctectomies for any but the most proximal rectal cancers. The introduction of reliable circular stapling devices in the late 1970s, coupled with knowledge that a distal resection margin of as little as 1.0 to 2.0 cm was oncologically sufficient for most rectal cancers, overcame these impediments.^{52,53} Although investigators cautioned that intramural distal margins less than 1.0 cm were associated with increased local recurrence rates and decreased survival, surgeons aggressively pursued lower and lower anastomoses after curative intent proctectomy.⁵⁴ By the 1980s, reports appeared noting that local recurrence after “curative intent” proctectomy for rectal cancer was highly variable, ranging from 2 to 40%.²⁶ It was observed that local recurrence after radical resection correlated not just with the stage of the disease but also with the surgeon performing the operation.

Total mesorectal excision Based on pathology assessment of the mesorectum after proctectomy, Heald and colleagues suggested that local recurrence might be attributable to inadequate resection of nodal or other tumor deposits within the mesorectum.^{55,56} After completing studies of the embryology and anatomy of the mesorectum, they popularized a technique now termed TME to decrease local recurrence and optimize outcomes. Sharp dissection in the endopelvic fascial plane, which is virtually bloodless, provided a reliable method to keep the cancer-bearing rectum and its mesorectum intact. Heald and others who adopted TME reported local recurrence rates under 10% following anterior resection without neoadjuvant or adjuvant therapy.⁵⁴

Circumferential resection margin Heald initially believed that optimized proctectomy with TME would

obviate the need for chemoradiation as an adjunct to surgery. However, careful analyses showed that local recurrence was still a problem despite optimized technique if the lesion was transmural and in the distal half of the rectum and if the cancer involved or was within 1 to 2 mm of the mesorectal endopelvic fascia. This led to the understanding that the CRM, a pathology variable that had never been properly assessed and reported prior to this time, was critically linked to oncologic outcome. A positive CRM correlates with high local recurrence and shortened survival.^{12,13,57} In a recent study, local recurrence occurred in 22% of patients if CRM was positive versus 5% if the CRM was negative for cancer.⁵⁸ Such results explain why TME has become the standard method used for radical resection of rectal cancer. Workshops have been held in a variety of European nations for surgeons to acquire the skills needed to perform TME and for pathologists to learn how to properly assess the rectal cancer specimen, including the mesorectum, as described by Quirke and colleagues.^{59,60} Marked improvement in oncologic outcomes has resulted.^{61,62}

Quality of life and functional outcomes of radical surgery Quality of life is an important factor in the treatment of rectal cancer. Unlike colon cancer treatment, which generally does not have a major impact on bowel function, rectal cancer surgery introduces the real possibility of either a temporary or a permanent stoma. Furthermore, even if a restorative resection is achieved, bowel function can be poor, especially after a very low anastomosis. In addition to bowel dysfunction, pelvic dissection is associated with a risk of sexual or urinary dysfunction because of autonomic nerve injury. Indeed, the combined risk of a stoma, poor functional outcome, and genitourinary function motivates otherwise fit candidates for radical resection to consider local treatment options, despite their higher recurrence risks.

Anastomosis alternatives and bowel function A straight end-to-end colorectal anastomosis is the traditional choice after radical proctectomy for cancers of the proximal half of the rectum. A side-to-end (Baker technique) colorectal anastomosis was an occasionally used alternative. Either anastomosis can be handsewn, but today most surgeons prefer to use a circular stapler. Functional results after such anastomoses are generally good. However, as surgeons developed better means of performing lower colorectal and coloanal anastomoses, two new problems arose: increased anastomotic leaks and anterior resection syndrome.

Anastomotic complications and temporary fecal diversion The incidence of anastomotic complications, including stricture and leakage, is correlated with the level of the anastomosis. In general, the lower the anastomosis, the higher the complication rate is. Other factors, including previous radiation therapy, immunosuppression, underlying vascular insufficiency or diabetes, and technical problems such as tension that cannot be resolved by additional mobilization may also increase the risk of anastomotic complications. The consequences of a leaking anastomosis remain a major source of morbidity and death after surgical resection of rectal cancer. To overcome the problem of leaks, some surgeons advocated for increased use of the side-to-end Baker anastomosis,

suggesting that it offered a more reliable blood supply than the traditional end-to-end anastomosis. Many surgeons routinely perform temporary proximal fecal diversion for patients undergoing low anastomoses, especially for those subjected to preoperative irradiation, to mitigate the consequences of a leak.⁶³ Loop ileostomy is the most commonly performed temporary diversion, although some surgeons prefer proximal loop colostomy. Proximal fecal diversion does not protect against anastomotic leakage or prevent anastomotic complications, but it does diminish the morbidity resulting from leakage and reduce the likelihood of an emergency reoperation.⁶³ Our practice is to consider diversion for all patients with a low (< 5 cm) colorectal or coloanal anastomosis especially if they have undergone preoperative radiation therapy.

Anterior resection syndrome This syndrome encompasses a variety of bowel functional problems, including frequency, fecal urgency, stool fragmentation (multiple incomplete evacuations), varying degrees of incontinence, or a combination of all of these symptoms. Lange and colleagues reported fecal incontinence in 38.8% of nonirradiated and 61.5% of irradiated patients in the Dutch TME trial.⁶⁴ To remedy the problem of anterior resection syndrome, surgeons devised techniques to increase neorectal capacity with a colonic pouch or a colooplasty.^{65–67} Initial data indicated that the functional advantages were most discernible early on after operation.^{68,69} More recently, however, a randomized, controlled trial comparing functional outcomes of colooplasty, colonic J pouch, or a straight anastomosis revealed significant and lasting benefits for the colonic J pouch compared to the straight anastomosis or colooplasty reconstruction.⁷⁰

A colonic J pouch is considered only for low anastomoses and should be small.⁶⁶ If the procedure is performed more proximally than 8 cm from the anal verge, it offers no functional advantages over a straight colorectal anastomosis.⁶⁵ In fact, the greatest functional improvements are observed in patients with a colonic J pouch anastomosis 4 cm or less from the anal verge.^{70–72} The colooplasty was developed to overcome the difficulty of doing a colonic pouch in a patient with a narrow pelvis and thick mesentery, but a recent trial showed that colooplasty did not improve bowel function over patients with a straight anastomosis,⁷⁰ and other data from Singapore reveal an increased incidence of anastomotic leak after colooplasty reconstruction compared to colonic J pouch reconstruction.⁶⁹ An end-to-side anastomosis may be optimal as the functional and surgical results are similar to those seen with other colonic pouch anastomoses.⁷¹

Colostomy Although many assume that avoidance of a stoma is inevitably associated with an improved quality of life, data are conflicting. A Cochrane review of the subject identified studies that both supported and refuted this notion, and its authors concluded that firm conclusions could not be drawn based on currently available data.⁷³ Patients with the most distal anastomoses tend to have the most functional difficulties postoperatively. Surgeon and patient alike must consider the likely functional outcomes before pursuing a policy of sphincter preservation at any cost. Debilitated patients and individuals with baseline sphincter dysfunction are often best served by creation of a well-constructed stoma

rather than an ultralow anastomosis, especially if they have received radiotherapy.

Genitourinary dysfunction In addition to bowel dysfunction, pelvic dissection is associated with a risk of urinary or sexual dysfunction attributable to autonomic nerve injury. Surgical injury to pelvic autonomic nerves is usually the proximate cause of postoperative dysfunction, and this is best avoided by careful anatomic dissection as described below [see TME and Preservation of Autonomic Nerves, below]. However, other factors play important roles: baseline sexual function, psychological issues (most often related to the presence of a stoma), associated medical disorders (atherosclerotic peripheral vascular disease, diabetes mellitus, hypertension), medications (especially antihypertensives and beta blockers), alcohol use, and pelvic radiation therapy.^{64,74}

Widely variable figures for the risk of sexual dysfunction can be cited from the literature. Often these numbers are more a reflection of the stringency of follow-up than the actual incidence of sexual dysfunction, so they must be interpreted with caution. In the 1940s, sexual dysfunction was reported in 95% of male patients after APR.⁷⁵ In contrast, Havenga and colleagues reported that 86% of male patients younger than 60 years retain sexual function if TME is done carefully to preserve autonomic nerve function.⁷⁶ Conversely, recent data from the Dutch TME trial suggest that approximately 75% of men and 60% of women suffer from sexual dysfunction following TME surgery.⁷⁴

Urinary dysfunction is another common complication of rectal cancer therapy. In the Dutch TME trial, 38.1% of patients complained of urinary incontinence and 30.6% complained of impaired bladder emptying.⁷⁷ In contrast to sexual dysfunction, preoperative radiotherapy was not a risk factor for urinary dysfunction.

OTHER OPERATIVE APPROACHES

Extended resection is needed for locally advanced rectal cancer that invades adjacent organs or the sacrum. The prognosis is primarily dependent on achieving an R0 resection. Stoma construction without resection may be needed to control local symptoms caused by obstruction, incontinence, or fistulas to the bladder, the vagina, or other sites. Such an approach may be palliative or part of a staged approach ultimately leading to curative intent therapy.

Local Procedures: Operative Techniques

POLYPECTOMY

Most benign-appearing pedunculated polyps and most small, sessile polyps of the rectum are removed by snare polypectomy or endoscopic excisional biopsy or ablation performed during colonoscopic examination. Polyps larger than 1.0 cm, especially if sessile, villous lesions, and polyps with firm ulcerated edges are those most likely to harbor invasive cancer. If these characteristics are noted, snare polypectomy is not advised. Instead, diagnostic biopsies are done, and if positive, definitive workup and surgery are planned. If biopsies are negative or equivocal, the lesion must be completely removed in one piece to provide the pathologist with an intact specimen that can be properly oriented

for histologic examination. This is essential to accurately determine the depth of tumor invasion, which, in turn, directs subsequent therapy. Most often this requires local full-thickness excision, but snare polypectomy may be considered as a definitive biopsy providing that the lesion can be removed safely in one piece. A full-thickness excision avoids the difficulties in achieving accurate staging that arise when an unsuspected invasive cancer is identified microscopically following partial or piecemeal excision. The polyp removal site is tattooed to facilitate accurate localization should additional therapy be needed. Rarely, a giant villous adenoma may require more radical surgical excision.

LOCAL EXCISION TECHNIQUES

Transanal Local Excision

Because of its relative simplicity and safety, transanal excision is the most commonly performed local procedure [see Figure 1]. Full mechanical bowel preparation is recommended to reduce the possibility of postoperative impaction and to maintain optimal visualization. The procedure can be performed with the patient in lithotomy, lateral decubitus, or the prone jackknife position. The prone position has the advantages of providing easier access for an assistant surgeon and of being suitable for rectal cancers in any quadrant, whereas the lithotomy position is most suitable for distal posterior tumors. We prefer to use a headlight or lighted retractors for adequate visualization. A Lone Star self-retaining retractor or Gelpi retractors may be used to efface the anus, and a handheld Pratt bivalve retractor, a Ferguson-Hill retractor, or a Parks anoscope may be used to provide exposure of the lesion. Deep retractors (e.g., narrow Deaver retractors) and laparoscopic instruments are often helpful for exposing and excising more proximal cancers. In addition, we have used the operating transanal endoscopic microscope to assist with retraction to facilitate simple transanal excision of more proximal rectal lesions.

Injecting saline or a local anesthetic with epinephrine solution into the rectal wall near the lesion facilitates the dissection. It is sometimes helpful to place a traction suture 2 cm distal to the lesion to facilitate prolapse of the rectal wall

before dissection is begun. Electrocautery with a needle tip is generally employed to perform a full-thickness excision of the cancer with a 1.0 cm margin, but surgeons are increasingly using laparoscopic and TEM instruments to facilitate the excision. It is critical to maintain hemostasis and proper orientation throughout the procedure. Some surgeons close the defect in the rectal wall as the dissection progresses. Each suture can be used for traction to keep the lesion in view. Other techniques using laparoscopic or conventional staplers have also been developed and have yielded reasonable results for polypoid lesions.

Once the specimen has been resected, it should be inspected to confirm that adequate margins have been obtained and then marked for orientation and pinned out for fixation before histologic examination. At times and based on the size of the defect, additional tissue at the margin is taken from the excision site to confirm adequate clearance of the lesion. The operative site is then irrigated with sterile water or other tumoricidal agents to minimize the risk that viable tumor cells will be left in the rectal wall. In the case of an extraperitoneal rectal wall defect, the excision site may be left open to heal by secondary intention; however, many surgeons prefer to close all rectal wounds primarily. If the defect is intraperitoneal, a watertight closure is essential and is usually performed with a durable absorbable suture. Care must be taken to prevent stricture formation, especially with large or circumferential lesions. In such cases, a sleeve closure with a hand-sewn anastomosis after advancement of the proximal rectal wall to the more distal rectum is often the best choice. Once the defect is closed, the surgeon should perform proctoscopy to ensure that the rectal lumen has not been compromised.

Transanal Endoscopic Microsurgery

TEM is a novel technique that has found a niche in local treatment of sessile polyps and of favorable T1 cancers in the middle to upper rectum. It may be used in combination with chemoradiation to treat more advanced cancers of the middle and upper rectum, especially in high-risk patients who cannot tolerate an anterior resection. Following setup, TEM begins with insufflation of CO₂ into the rectum via a 4 cm operating rectoscope. Most units allow simultaneous CO₂ insufflation

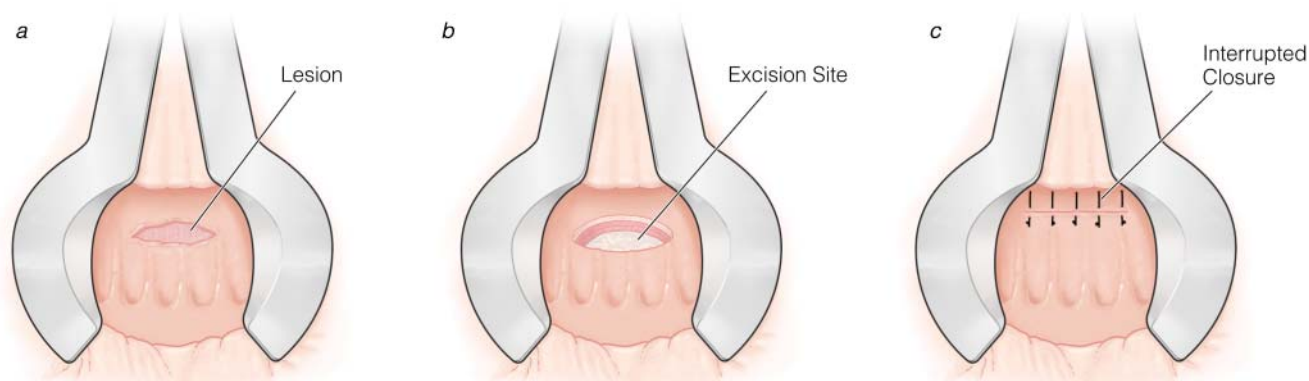


Figure 1 Local excision. (a) The rectal lesion is exposed with a bivalve retractor. (b) Full-thickness excision of the lesion is performed. (c) The defect is closed with interrupted sutures.

with continuous assessment of pressure within the rectum. The entire apparatus is held in place by a “Martin Arm,” a unique, “multielbowed” holder attached to the operating table permitting stable visualization throughout the procedure.⁷⁸ Endoscopic instruments with a diameter of 5 mm and downward deflecting tips are then inserted and used under magnification to perform the local resection. The principles of resection are the same as for transanal excision (see above).

Posterior Approaches to Local Excision

Local excision of rectal cancers can be performed via either a transsacral or a transsphincteric approach with the patient in the prone jackknife position. The Kraske procedure uses a transsacral approach. An incision is made in the midline of the sacrum to expose the posterior rectum by excising the coccyx and the last two sacral vertebrae. Either a short segmental resection of the rectum with primary anastomosis or a proctotomy to expose and locally excise an intraluminal lesion is performed. In closing the rectal wall defect, care is taken not to compromise the lumen and thus creating a stricture.

The York-Mason procedure takes a transsphincteric approach to expose the posterior rectum without resection of the sacrum. Instead, the pelvic floor muscles are divided in the posterior plane, and the resection then proceeds as in the Kraske procedure. The sphincter muscles must be carefully reconstructed to reduce the difficulties with postoperative incontinence.

Endoscopic Posterior Mesorectal Excision after Local Excision

This rectum-sparing endoscopic posterior mesorectal resection begins with local excision as described above. Posterior mesorectal excision is subsequently performed 4 to 6 weeks after the local procedure barring any postoperative complications. The posterior mesorectal excision is performed with a laparoscopic camera placed through a perineal incision between the anus and the tip of the coccyx. A distention balloon system is then inserted under digital transanal control to establish a sufficiently large operating space.^{50,51} CO₂ pneumoperitoneum is established followed by placement of two 10 mm dilation trocars on either side of the coccyx. Ultrasound scissors are then used to perform the dissection en bloc up to the level of the sacral promontory taking the superior rectal artery.

ABLATION TECHNIQUES

Fulguration (Electrocoagulation)

The technique of fulguration or electrocoagulation involves destroying a cancer with an electrode inserted into the wall of the lesion. As coagulum builds up, it is débrided to allow additional coagulation until the lesion and a circumferential rim of normal tissue have been ablated.

Endocavitary Radiation (Papillon Technique)

Endocavitary radiation involves high-dose contact (superficial) radiotherapy delivered via a specially designed proctoscope. A total radiation dose of 9 to 15 Gy is delivered in several sessions, usually over a period of 60 days. This modality is appropriate for small noncircumferential lesions located within 10 cm of the anal verge.

Radical Procedures: Operative Techniques

LAPAROSCOPIC AND ROBOTIC PROCEDURES

Laparoscopic and robotic approaches to rectal cancer have been described with more regularity in the literature. Small, nonrandomized studies indicate that the procedure is technically demanding but able to reproduce the oncologic results of open surgery at least in the short term.^{79,80} Theoretically, laparoscopy-assisted anterior resection and APR should demonstrate improved short-term outcomes such as fewer cases of prolonged ileus, decreased pain, and shorter hospital stay. One multicenter, randomized clinical trial of 794 patients with colorectal cancer revealed a higher rate of positive circumferential margins in laparoscopy-assisted anterior resections of the rectum.⁸¹ Although follow-up data revealed no significant difference in short-term oncologic outcomes,⁸² the technical difficulty in performing laparoscopic TME has made many surgeons wary of extrapolating the oncologic results from laparoscopic colectomy to laparoscopic proctectomy. The MRC CLASICC trial revealed that 29% of patients underwent conversion from laparoscopic to open surgery.⁸¹ Further prospective, randomized trials focusing on laparoscopic resection of rectal cancer need to be concluded before definitive recommendations can be made concerning the safety and oncologic efficacy of laparoscopic procedures.

Robotic assisted procedures have become increasingly used for prostatectomy and some gynecologic procedures. However, at the first Pelvic Surgery Meeting, the participants found that robotic proctectomy remains far less widely accepted.⁸³ The participants felt that the loss of haptic feedback, increased operative times, and increased cost overshadowed the theoretical small benefits provided by robotic methods. Proponents suggest that the advantages of robotic methods in closed spaces such as a narrow pelvis will ultimately prove to be of value and that robotic proctectomy will prove useful.

OPERATIVE PRELIMINARIES

Radical treatment of locally advanced rectal cancer should include appropriate mesorectal excision, preservation of the autonomic nerves, the possibility of sphincter preservation, and maintenance of gastrointestinal and genitourinary function. The possibility of a permanent or temporary stoma should prompt a consultation with an enterostomal therapy nurse to counsel the patient and mark the abdominal wall at the appropriate location for a colostomy or temporary ileostomy. Generally, bowel preparation is performed on an outpatient basis the day before operation as per the surgeon's usual protocol. In recent years, some surgeons have stopped using a bowel preparation for most colorectal surgery, but most still use at least a modified preparation such as enemas prior to radical surgery for rectal cancer. An antibiotic is administered intravenously just before induction of anesthesia.

General anesthesia is employed, and an epidural catheter can be considered to provide postoperative analgesia. If there is a large, bulky upper rectal tumor or an associated inflammatory mass, ureteral stents may be placed to facilitate intraoperative identification and protection of the ureters. A bladder catheter is inserted, and the patient is placed in a modified lithotomy position with the legs in padded stirrups.

Some surgeons prefer split leg support devices when laparoscopic proctectomy is being done. Pneumatic compression devices and stockings are used routinely, with or without heparin for deep vein thromboembolism prophylaxis. DRE and rigid proctoscopy are performed to empty the rectum and reassess the rectal cancer. The degree of involvement of the anal sphincter or other organs, the level of the distal edge of the tumor, and the response of the tumor to chemoradiation are noted.

The conduct of radical extirpative procedures is easier if appropriate instruments are available. Headlights and lighted retractors allow visualization deep in the pelvis. Self-retaining retractors (e.g., Balfour, Bookwalter, or Omni-track retractors) are usually necessary. The St. Mark pelvic retractors and the Wylie renal vein retractors facilitate deep pelvic dissection. Long instruments are essential, and a variety of staplers should be available. The assistance of an experienced second surgeon or a highly trained technician is invaluable.

INTRAOPERATIVE DECISION MAKING

After the midline incision is made, a thorough abdominal exploration is performed to exclude metastases or other unforeseen problems. The preoperative plan is altered as necessary to accommodate the findings. Most often, the choice between a sphincter-sparing approach and a sphincter-sacrificing approach has been made before operation, but for distal rectal cancer, it is not always possible to determine whether a restorative anastomosis is feasible until the rectum has been fully mobilized. Additionally, neoadjuvant therapy can reduce the size of a tumor so that it is amenable to sphincter-sparing techniques instead of APR.^{29,84} In such cases, the choice between sphincter-sparing and sphincter-sacrificing proctectomy must be based on assessment of the adequacy of the distal margin [see Anterior Resection Technique, Step 4, *below*].

For these lower tumors, the surgeon assesses the possibility of obtaining clear radial and distal margins after TME and decides to proceed with either resection and anastomosis or APR and colostomy. It is important to acknowledge that the desire to perform an anastomosis must not compromise oncologic outcomes, and, in particular, one should avoid the “waist” observed in APR specimens [see APR Technique, *below*].⁸⁵ Occasionally, circumstances arise in which the cancer is larger than anticipated or is extending into tissues outside the bounds of the usual TME dissection plane. In such cases, a more extensive operation than was originally planned is appropriate if curative resection can be achieved. Alternatively, the surgeon may be forced to perform a palliative operation.

ANTERIOR RESECTION TECHNIQUE

All curative intent radical resections for rectal cancer use the same technique for mobilizing the rectum and achieving proximal, lateral, and radial margin clearance. Anterior resections are classified as high, low, or ultralow depending on the extent of rectal mobilization and resection and on the level of the restorative anastomosis. The open technique is described below. This is modified if a laparoscopic or robotic approach is used. A prospective trial is now being done by the American College of Surgeons Oncology Group to determine

if the laparoscopic technique for rectal cancer resection is a safe and effective alternative to the open technique.

Step 1: Mobilization of Colon

After abdominal exploration, the small bowel is packed into the upper abdomen and the patient is placed in a slight Trendelenburg position. The rectosigmoid is retracted to the right, and the peritoneal attachments to the left of the sigmoid colon are incised along the avascular plane. The left ureter and gonadal vessels are identified and preserved by using sharp and gentle blunt dissection to separate the retroperitoneal tissues from the sigmoid mesentery. The peritoneum is incised along the left side of the descending colon as far as the splenic flexure. Adhesions to the spleen are divided, and the splenic flexure is taken down. The colon mobilization extends proximally to the left transverse colon.

Step 2: Ligation of Inferior Mesenteric Artery

The mobilized rectosigmoid is retracted anteriorly and to the left to expose the inferior mesenteric artery (IMA). Transillumination of the mesentery facilitates identification of an avascular space adjacent to the IMA at the base of the mesentery. The peritoneum overlying this space is incised on either side of the IMA. Some surgeons prefer a high ligation of the IMA where it branches from the aorta, suggesting that this measure provides a more complete lymph node harvest. Others prefer a low ligation of the IMA just distal to the left colic artery, suggesting that this approach ensures better blood supply to the proximal colon and prevents nerve injury at the base of the IMA [see *Figure 2*]. At present, there is not enough evidence to permit recommendation of one approach over the other. For anastomosis to the mid- or distal anorectum, it is our practice to divide and ligate the left colic artery and the inferior mesenteric vein to ensure adequate mobility of the descending colon. After ligation of the proximal vascular pedicle, it is convenient to divide and ligate the mesentery to the colon at the descending-sigmoid junction and divide the colon with a linear stapler.

Step 3: TME and Preservation of Autonomic Nerves

TME is the standard technique for low to midrectal cancers in which the dissection proceeds along the areolar plane between the visceral fascia of the mesorectum and the parietal fascia of the pelvic walls. When performed properly, the intact mesorectum with all of the lymph nodes and the rectum are included as one specimen. For proximal rectal cancers, a partial mesorectal excision with distal clearance of at least 5 cm of mesorectum is acceptable.

The rectosigmoid is retracted anteriorly and inferiorly toward the pubis to expose the avascular plane posterior to the rectum. Sharp incision of this avascular plane while traction is placed on the rectosigmoid typically allows air to enter the areolar tissue posterior and lateral to the rectum. The surgeon follows the air, sharply dividing the loose areolar tissue posteriorly and laterally [see *Figure 3*]. Traction with the nonoperating hand and appropriate repositioning of handheld retractors is essential to keep the plane of the mesorectal dissection in view and accessible to sharp division with scissors or cautery. During the retrorectal portion of the mesorectal dissection, the hypogastric nerves are identified at the sacral promontory. These nerves descend in the presacral

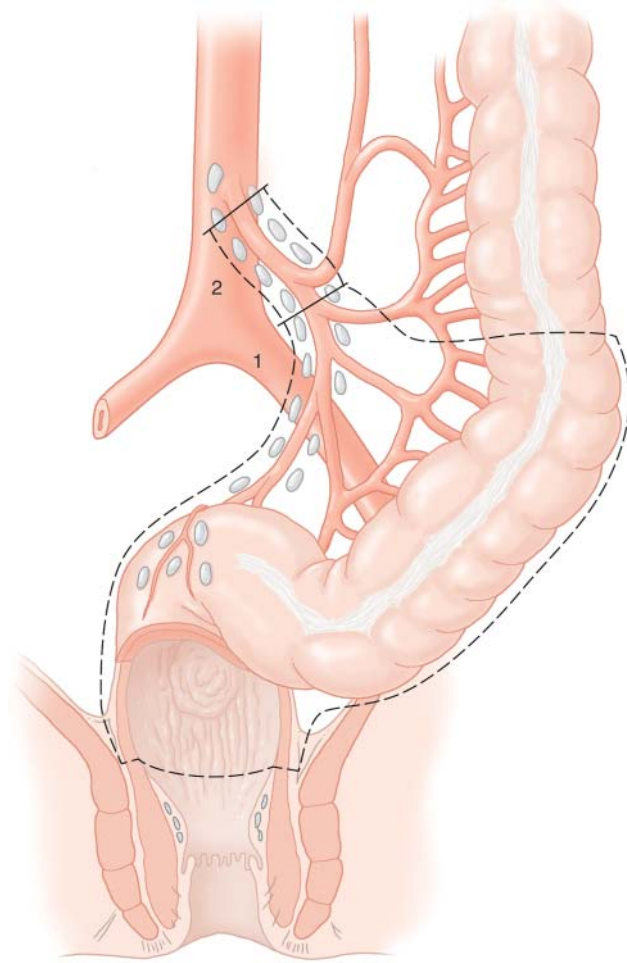


Figure 2 Anterior resection. Illustrated is the tissue excised during anterior resection. The surgeon may perform either a low ligation of the inferior mesenteric artery (IMA) (1), with preservation of the ascending branch, or a high ligation (2), where the IMA branches from the aorta.

space in a wishbone shape and must be preserved to maintain postoperative sexual and urinary function. As the dissection proceeds posteriorly, the rectosacral (Waldeyer) fascia is divided under direct vision, and the dissection proceeds distally to the level of the coccyx. The rectum is mobilized posterolaterally dissecting in a posterior-to-lateral direction, with care taken to maintain the integrity of the endopelvic fascial envelope encasing the bilobed mesorectum. The nervi erigentes are identified and preserved on the lateral pelvic sidewalls.

To complete the anterolateral dissection, the cul-de-sac is opened and attachments are divided anterolaterally. Exposure for the anterior dissection is facilitated by reducing the angle of the Trendelenburg position or even shifting the patient to a reverse Trendelenburg position. Deep pelvic retractors are used to protect the seminal vesicles and prostate in males or the vagina in females as the dissection continues anteriorly and distally. Denonvilliers fascia is incised in the midline anteriorly. In Heald's classic description of TME, Denonvilliers fascia is considered the most

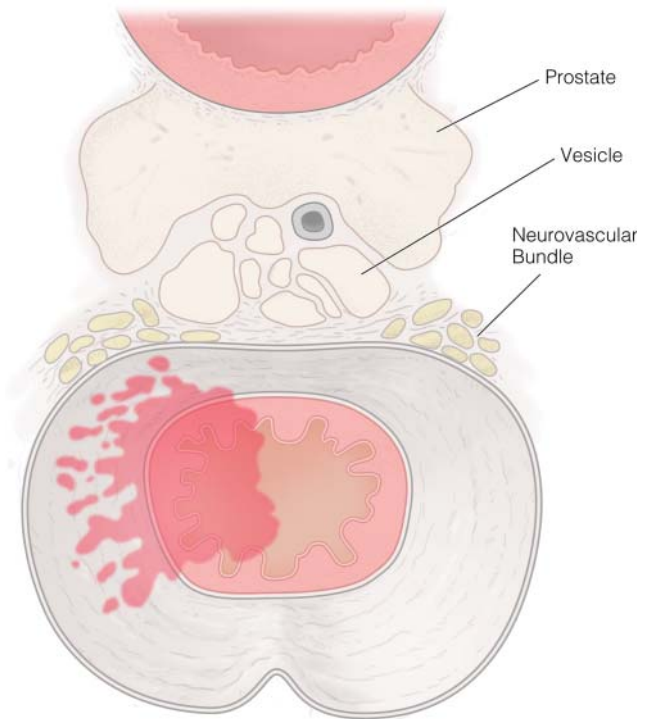


Figure 3 Anterior resection. Shown is a schematic depiction of total mesorectal excision, highlighting the endopelvic fascial dissection plane.

anterior limit of the mesorectum and is thus removed with the specimen.^{54–56} We similarly excise Denonvilliers fascia for circumferential and anterior rectal tumors to obtain a negative circumferential margin. For posterior tumors, we follow the visceral fascia propria of the rectum and spare the parietal Denonvilliers fascia to minimize the risk of injury to the nearby periprostatic pelvic nerves. Most often the middle rectal artery is not present as a distinct vessel, and the antero-lateral dissection at the level of the levators is done with electrocautery with minimal bleeding. Occasionally, however, the middle rectal artery is large enough that ligation is necessary.

Step 4: Assessment of Distal Margin

At this point in the operation, the rectum has been fully mobilized via the abdominal approach, and the surgeon must decide whether a sphincter-preserving anastomosis is possible or whether a sphincter-sacrificing resection with construction of a permanent colostomy is necessary. Because all radical resections for rectal cancer use the same proximal, lateral, and radial dissection technique, the decision to perform an anastomosis is based on the ability to obtain a clear distal margin and a tension-free, well-vascularized anastomosis, patient preferences, and assumptions about postoperative bowel function.

If distal clearance (both intramural and mesorectal) is adequate and if anal sphincter function justifies proceeding with an anastomosis, a right-angle clamp is placed distal to the tumor. Irrigation of the rectum is done to eliminate debris and any viable tumor cells. If an open purse-string suture is

to be placed in the distal rectal cuff, a second right-angle clamp is then placed distally on the irrigated anorectum, and the rectum is divided between the two clamps. Alternatively, if a double-stapled reconstruction is planned instead, a transverse anastomosis (TA) stapler is placed distal to the right-angle clamp. The stapler is fired and the rectum divided, leaving a closed rectal cuff for subsequent anastomosis. The surgeon should then examine the resected specimen to assess the radial and distal margins and evaluate the integrity of the mesorectal and rectal dissection. If the margins are inadequate, the mesorectum has been violated, or perforation of the rectum occurred, local recurrence is a major concern. The treatment plan may have to be altered to reduce the risk of recurrence.

Step 5: Creation of Anastomosis

A straight end-to-end colorectal anastomosis is the traditional choice after radical proctectomy for cancers of the proximal half of the rectum. A side-to-end (Baker technique) colorectal anastomosis was an occasionally used alternative. Either anastomosis can be handsewn, but today most surgeons prefer to use a circular stapler. Functional results after such anastomoses are generally good following proctectomy for more proximal lesions. A variety of alternative techniques have been devised to improve reliability and function after more distal anastomoses.

Handsewn end-to-end anastomosis This anastomosis may be performed in one or two layers with either interrupted or continuous sutures. Handsewn colorectal anastomoses are typically performed from the abdominal side of the operation usually for more proximally based rectal cancers. It is often easiest to place all of the sutures first and then “parachute” the proximal bowel down to the rectal cuff as the sutures are tied. Mucosal inversion is achieved by using Lembert sutures or by tying the knots on the inside of the lumen. Occasionally, for low anastomoses, a handsewn coloanal anastomosis may be performed transanally if the distal cuff cannot be visualized from the abdominal field. This procedure is generally more easily accomplished with the patient in the prone jackknife position and can be done with or without a mucosectomy.

Double purse-string end-to-end anastomosis Reliable circular staplers using a double purse-string technique were introduced in the late 1970s as an alternative to the handsewn colorectal anastomosis. A continuous purse-string monofilament suture is placed in the proximal end of the open rectal cuff, and a second purse-string suture is placed in the descending colon [see Figure 4]. The circular stapler is placed through the anus, and the anastomosis is fashioned and checked for leaks as described below in the double-stapled technique.

Double-stapled end-to-end anastomosis The double-stapled technique was devised to eliminate the need for a purse-string suture on the rectal cuff and to prevent fecal contamination. A purse-string suture is placed in the cut edge of the distal descending colon [see Figure 5a]. The anvil of a circular stapler is inserted into the descending colon, and the purse-string is tied. A TA stapler is used to divide the anorectum distal to the cancer. The integrity of the stapled

distal rectal stump is checked by insufflating air into the rectum via a proctoscope while the rectal stump is covered with saline. If no air leak is noted, the circular stapler, without the anvil but with the cartridge and trocar attachment, is inserted through the anus and advanced proximally to the apex of the closed stump. The stapler is opened to drive the trocar through the apex of the rectal stump adjacent to the staple line [see Figure 5b]. The trocar attachment is removed, and the mobilized descending colon, with the anvil in place, is mated to the stapler [see Figure 5c]. The stapler is closed and fired, resulting in an end-to-end anastomosis [see Figure 5d]. The integrity of the anastomosis is assessed by insufflating air into the rectum with a proctoscope while the anastomosis is under water [see Figure 6].

Side-to-end anastomosis Although the side-to-end colorectal (Baker) anastomosis is not a new technique, it is gaining popularity as an alternative to the more complex colonic J pouch or coloplasty procedures. After the rectal resection, the anvil of the stapler is inserted through the divided distal end of the descending colon. The trocar end of the anvil is brought out through the antimesenteric side of the colon approximately 4 to 5 cm proximal to the distal end of the descending colon. The open end of the descending colon is then closed. A circular stapler is then used to anastomose the side of the colon to the end of the rectum or the anal canal [see Figure 7].

Colonic J pouch To create a colonic J pouch, the descending colon must be totally mobilized by taking down the splenic flexure and dividing the left colic artery and the inferior mesenteric vein. The well-vascularized distal descending colon is then folded into a J configuration [see Figure 8a]. It is essential that the efferent limb of the J be no longer than 5 to 6 cm because longer limb lengths are associated with difficulty in evacuation.⁶⁶ A linear cutting stapler is inserted through a colotomy on the antimesenteric surface of the apex of the J pouch and then closed and fired. Once the linear staple line has been checked for bleeding, the anvil of a circular stapler is placed in the colotomy of the J pouch and secured in place with a 2-0 nonabsorbable suture. The J pouch–anal anastomosis is then performed with the circular stapler [see Figure 8b].

Coloplasty Approximately 25% of patients are not suitable candidates for a colonic J pouch because of a narrow pelvis or obesity with a thick colonic mesentery.⁶⁷ For these patients, coloplasty, a procedure that is similar to pyloroplasty, has been suggested as an alternative. Coloplasty is performed with an 8 to 10 cm long antimesenteric colotomy at a point 5 to 6 cm from the cut end of the descending colon [see Figure 9a]. The anvil of a circular stapler is placed in the colon and brought out the end of the colon before closure of the coloplasty. The colotomy is closed in a transverse direction, perpendicular to the antimesenteric border, with either absorbable sutures or a linear stapler [see Figure 9, b and c]. An end-to-end anastomosis is then performed with the circular stapler [see Figure 9d].

Intersphincteric resection and ultralow anastomosis This technique has been promoted as a sphincter-preserving alternative to APR for cancers within 5 cm of the anal verge.

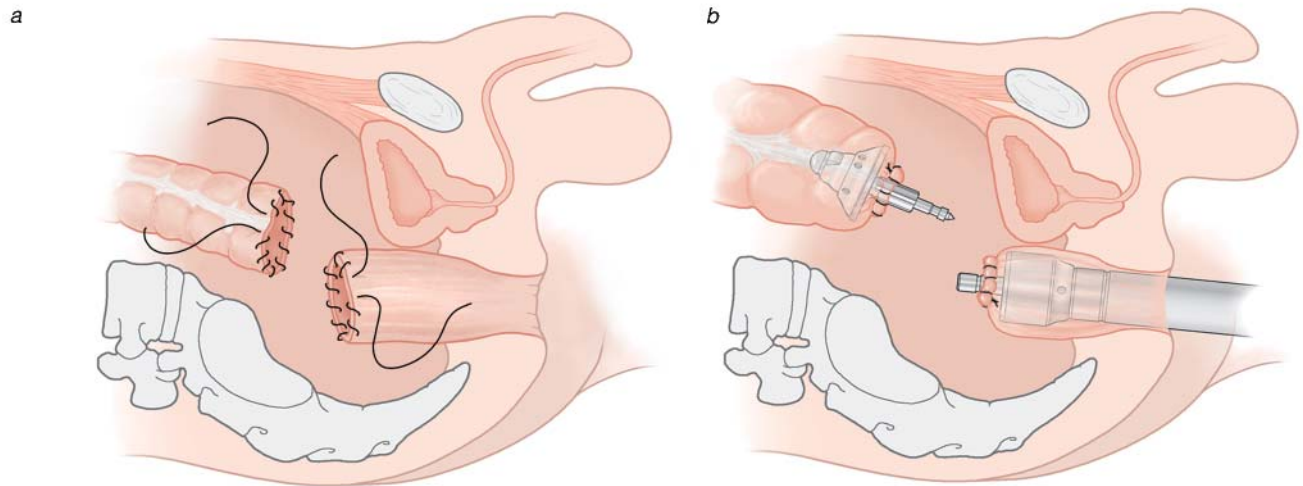


Figure 4 Anterior resection. Shown is a purse-string end-to-end anastomosis. (a) Purse-string sutures are placed on the rectum and on the proximal bowel. (b) The anvil of a circular stapler is placed in the proximal bowel, and the stapler is placed through the anus. The anvil is joined with the body of the stapler, and the stapler is fired to complete the anastomosis.

Schiessel and colleagues recently updated their experience combining TME and autonomic nerve preservation with a total or partial intersphincteric resection at the intersphincteric groove followed by handsewn coloanal anastomosis.⁸⁶ Invasion into the external sphincter or levator ani muscle is generally a contraindication for its use, although some authors now are advocating partial external sphincter excision as well. Long-term functional and oncologic results need to be assessed.

APR TECHNIQUE

APR involves en bloc resection of the rectosigmoid, the rectum, and the anus along with the surrounding mesentery, mesorectum, and perianal soft tissues [see Figure 10]. Current efforts to perform more restorative anastomoses after radical resection of rectal cancer are based on data suggesting that APR offers no survival advantage over sphincter-sparing procedures except for those distal lesions invading the sphincters.⁸⁷ Nevertheless, APR is still performed in the United States in an estimated 30 to 60% of rectal cancer patients.^{2,88} Reasons for this persistently high APR rate are unclear.

Special Considerations

Curative intent APR is associated with higher rates of perforation, positive margins, and local recurrence than observed after anterior resection, and these differences are independent of tumor stage or size.^{85,89,90} The poor outcomes after APR have been ascribed primarily to the biology of distal rectal cancers.^{91,92} Hojo and Koyama reported that 25% of transmural cancers in the distal half of the rectum had lateral pelvic lymph node metastases beyond the dissection plane followed by TME.⁹¹ Today, there is increasing awareness that the poor results may be attributed in large part to anatomic and technical considerations not previously considered. Specifically, it has been suggested that the poor outcomes after APR are a result of the close proximity of the cancer to the circumferential resection margin at the level of the

anorectum distal to the levator muscle sling.⁹³ As opposed to a more proximal rectal cancer with its surrounding mesorectum enveloped within the endopelvic fascial plane, the distal anorectum has no comparable tissue surrounding it. Nagtegaal and colleagues assessed cancers less than 5 cm from the anal verge and found that there was little or no levator and sphincter muscle surrounding the specimen at the level of the cancer.⁸⁵ This has now been termed the “waist” in an APR specimen. Salerno and colleagues assessed the sites of waisting in 12 patients and found that the site between 35 and 42 mm proximal to the anal verge was the most common site of such a waist and that site correlated with the puborectalis.⁹³

Synchronous Two-Team Technique

APR, as the name suggests, may be thought of as comprising two phases: an abdominal phase and a perineal phase. The perineal phase of the operation may be done synchronously with the abdominal phase, with the patient maintained in a modified lithotomy position. Proper positioning and exposure are critical. The buttocks should be elevated with a pad extending over the edge of the operating table and should be taped laterally to provide good exposure of the perineum. The synchronous approach may reduce operating time and is useful if the surgeon anticipates difficulty in removing the rectum because of lateral fixation. While working from both above and below, the area of fixation can be slowly dissected free from surrounding structures and the dissection safely completed en bloc. Clearly, this approach demands the collaboration of two experienced surgeons as performing the perineal phase with the patient in the lithotomy position can be very demanding technically.

Sequential APR

Alternatively, the perineal phase may be performed with the patient in the prone jackknife position after completion of the abdominal phase or in lithotomy with the legs elevated.

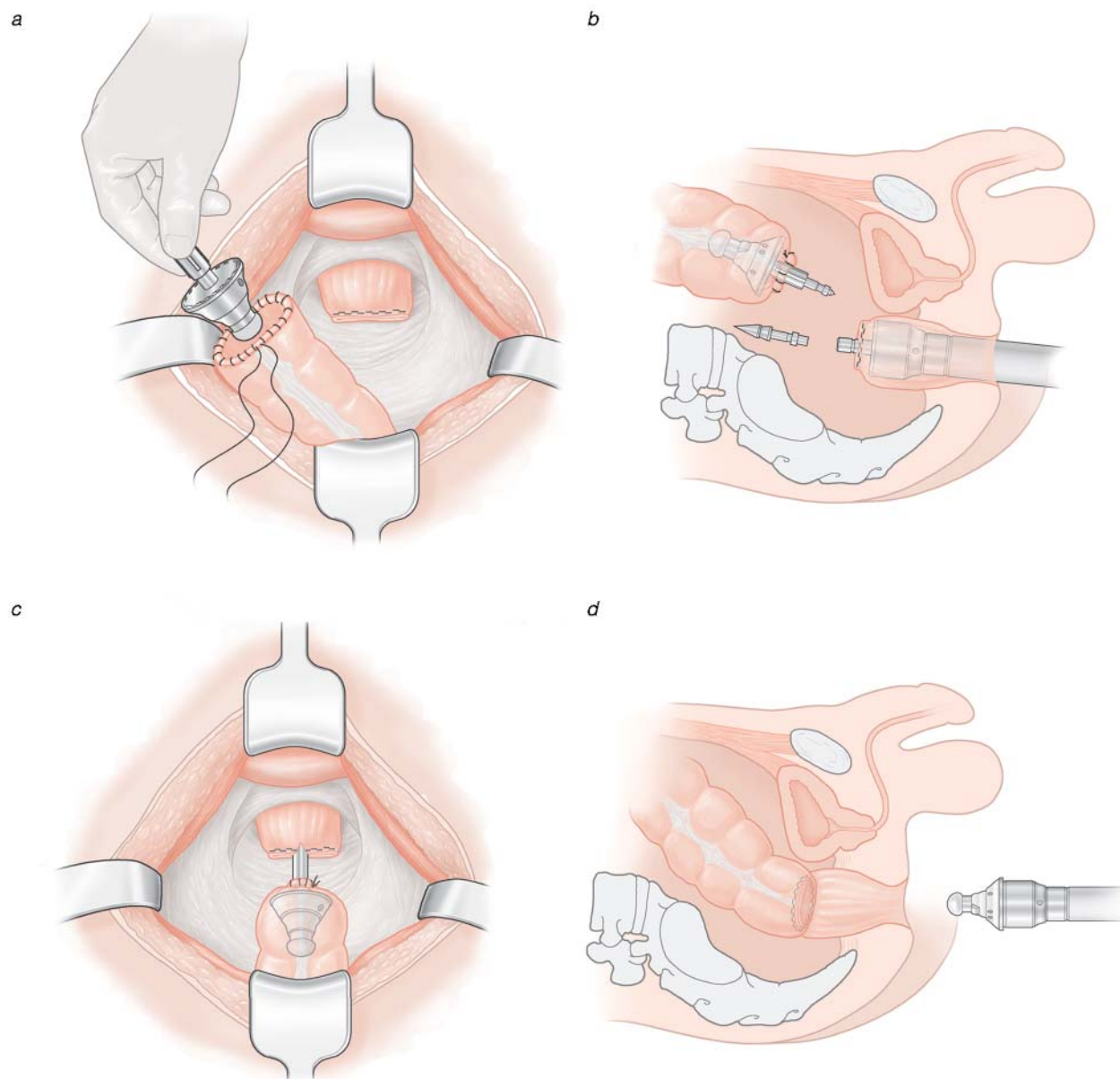


Figure 5 Anterior resection. Shown is a double-stapled end-to-end anastomosis. (a) The rectal stump is closed with a linear noncutting stapler. A purse-string suture is placed around the colotomy, and the anvil of the circular stapler is placed in the open end and secured. (b) The stapler, with the sharp trocar attachment in place, is inserted into the anus, and the trocar is made to pierce the rectal stump at or near the staple line, after which the trocar is removed. (c) The anvil in the proximal colon is joined with the stapler in the rectal stump, and the two edges are slowly brought together. (d) The stapler is fired and then gently withdrawn.

Unless there are strong reasons to pursue a synchronous APR as noted above, we prefer the prone jackknife position and a sequential APR. It provides excellent visualization for the perineal dissection and is especially useful if the tumor is fixed anteriorly. In addition, it has the advantage of providing more room for an assistant.

Operative Technique

Steps 1 through 4 The abdominal phase of APR, including TME and nerve preservation, is identical to steps 1

through 4 of an anterior resection [see Anterior Resection Technique, *above*]. The focus on the waist of the APR surgical specimen has led several authors to recommend a change in APR technique to overcome the poor results following radical APR.^{85,93,94} They note that a well-intentioned surgeon focused on performing a low anastomosis after TME for a distal rectal cancer may unintentionally follow the mesorectum distally to the point where it thins and blends with the intersphincteric plane, leaving almost no surrounding tissue on the anorectum where it is excised, that is, at the

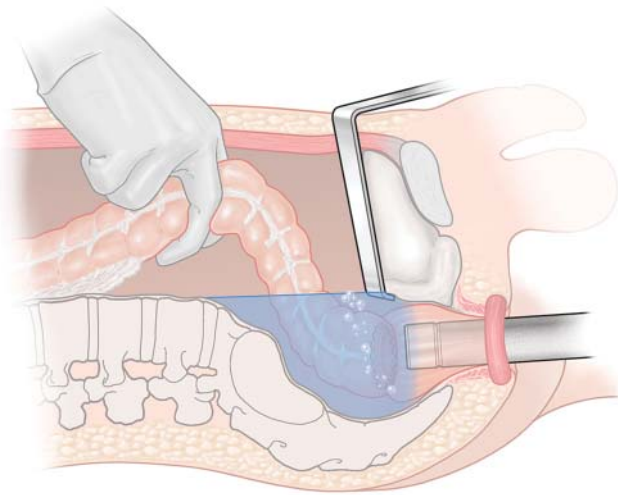


Figure 6 Anterior resection. The integrity of the anastomosis is assessed by holding it under water and insufflating air via a proctoscope while the bowel is clamped.

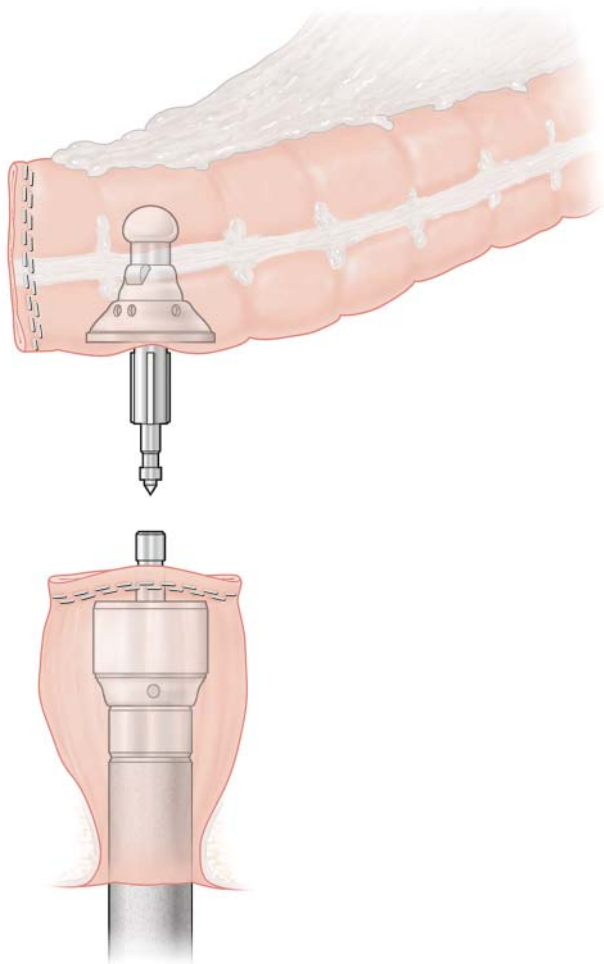


Figure 7 Anterior resection. Depicted is a double-stapled end-to-side colorectal anastomosis.

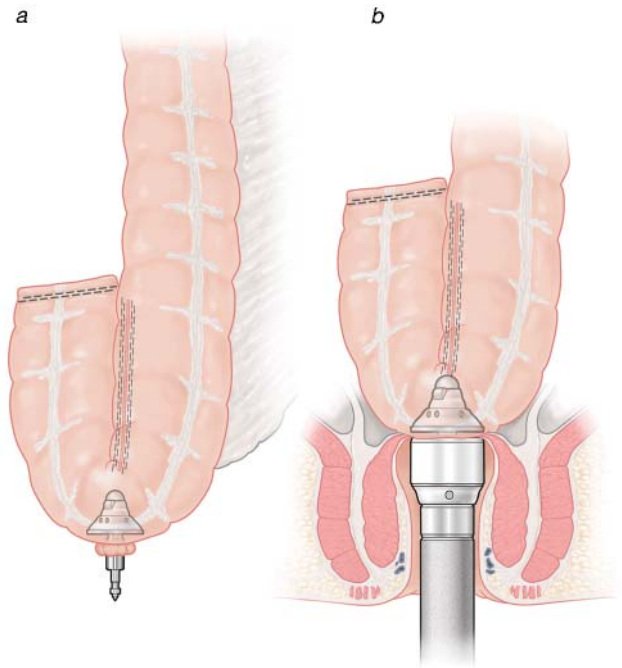


Figure 8 Anterior resection. Shown is the creation of a coloanal anastomosis with a colonic J pouch. (a) The proximal bowel is stapled closed and folded into a J shape, with the hook of the J being about 5 to 6 cm long. A colotomy is made in the base of the J, and a J pouch is formed by inserting and firing a linear stapler. The anvil of a circular stapler is placed in the base of the pouch. (b) The J pouch is brought down to the anus, and the circular stapler is used to create the coloanal anastomosis.

waist. This results in high local recurrence rates. The technique can be modified by stopping the abdominal dissection at the proximal level of the levator muscle and then performing a more radical perineal excision of the levators and puborectalis as described below.

Step 5: perineal resection The perineal phase of APR is performed with the patient in either the lithotomy or the prone jackknife position, depending on whether the synchronous or the sequential approach is followed. We agree with Holm and colleagues that the perineal proctectomy is facilitated by placing the patient in the prone jackknife position.⁹⁴ The perineum is exposed with the aid of self-retaining retractors [see Figure 11]. After irrigating and emptying the rectum, the anus is closed with a heavy purse-string suture to minimize the risk of spillage of feces or tumor. An alternative means of accomplishing this goal is to make the initial elliptical incision around the anus and then approximate the perianal skin edges with sutures or Kocher clamps. The elliptical incision should extend from the perineal body anteriorly to the level of the coccyx posteriorly. Laterally, the incision should overlie the ischial tuberosities. The surgeon can consciously avoid the waist problem described above by directing the dissection in the ischioanal fossa bilaterally with electrocautery toward the ischial tuberosities to ensure adequate lateral clearance. The posterior dissection is directed to the

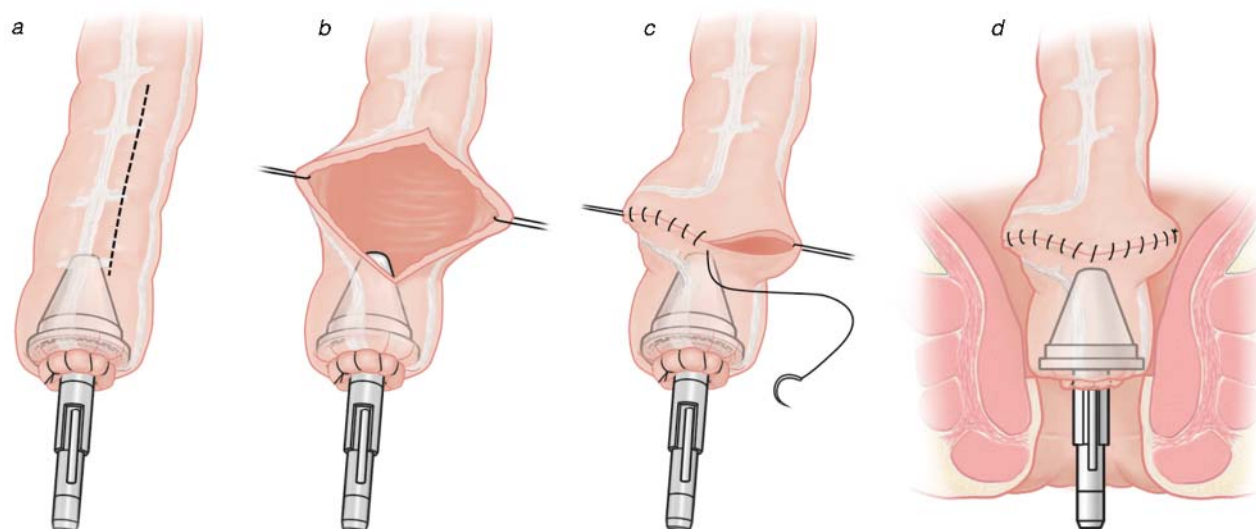


Figure 9 Anterior resection. Illustrated is the coloplasty technique. (a) A longitudinal colotomy is made in the antimesenteric side of the colon. (b) Sutures are placed on either side of the incision and used to apply traction transversely. (c) The colotomy is closed in a transverse direction. (d) An end-to-end anastomosis to the anus is performed.

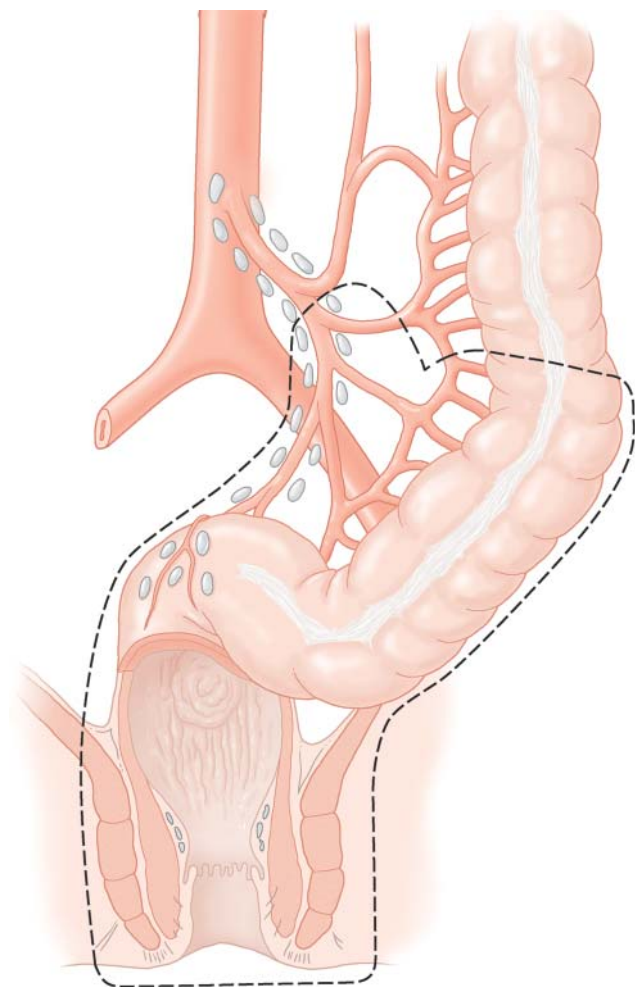


Figure 10 Abdominoperineal resection (APR). Illustrated is the tissue excised during APR.

coccyx. The anococcygeal ligament is divided posteriorly and the pubococcygeus and puborectalis are divided without narrowing the dissection plane. In this way, a more radical clearance is achieved as the perineal dissection meets the previously performed abdominal presacral dissection. The perineal surgeon can then insert an index finger into the pelvis to guide division of posterolateral soft tissues with aid of the electrocautery or the LigaSure device. An appendectomy retractor, self-retaining springs, or deep Gelpi retractors may be used to improve visualization during deeper dissection into the perineum laterally and anterolaterally.

At this point, the anterior perineal incision is deepened using the posterior border of the superficial transverse perineal muscle as the guide to the rectoprostatic or rectovaginal space. It is often useful at this point to pass the proximal end of the divided and stapled colon through the aperture created by the posterolateral dissection between the coccyx and the anus. Traction is applied to the everted specimen to help the surgeon develop the anterior dissection plane. In a female patient, an anterior lesion may necessitate a posterior wall vaginectomy to ensure adequate margins. If not, the rectovaginal septum is dissected proximally, often with a guiding digit in the vagina to avoid inadvertent vaginal perforation. In a male patient, anterior dissection is facilitated by palpating the Foley catheter to help avoid injury to the urethra and the prostate. As the dissection is completed anteriorly, the specimen is resected, inspected for completeness and any sign of perforation, and then sent for pathologic examination. The pelvis is irrigated and hemostasis is ensured. Some surgeons prefer to place a mobilized pedicle of omentum or a myocutaneous flap such as the vertical rectus abdominis flap or a gluteal rotation flap into the pelvis to facilitate healing and reduce the risk of small bowel adhesions in the depths of the pelvis.⁹⁴ The use of such flaps is beyond the scope of this chapter. The perineal incision is closed in several layers

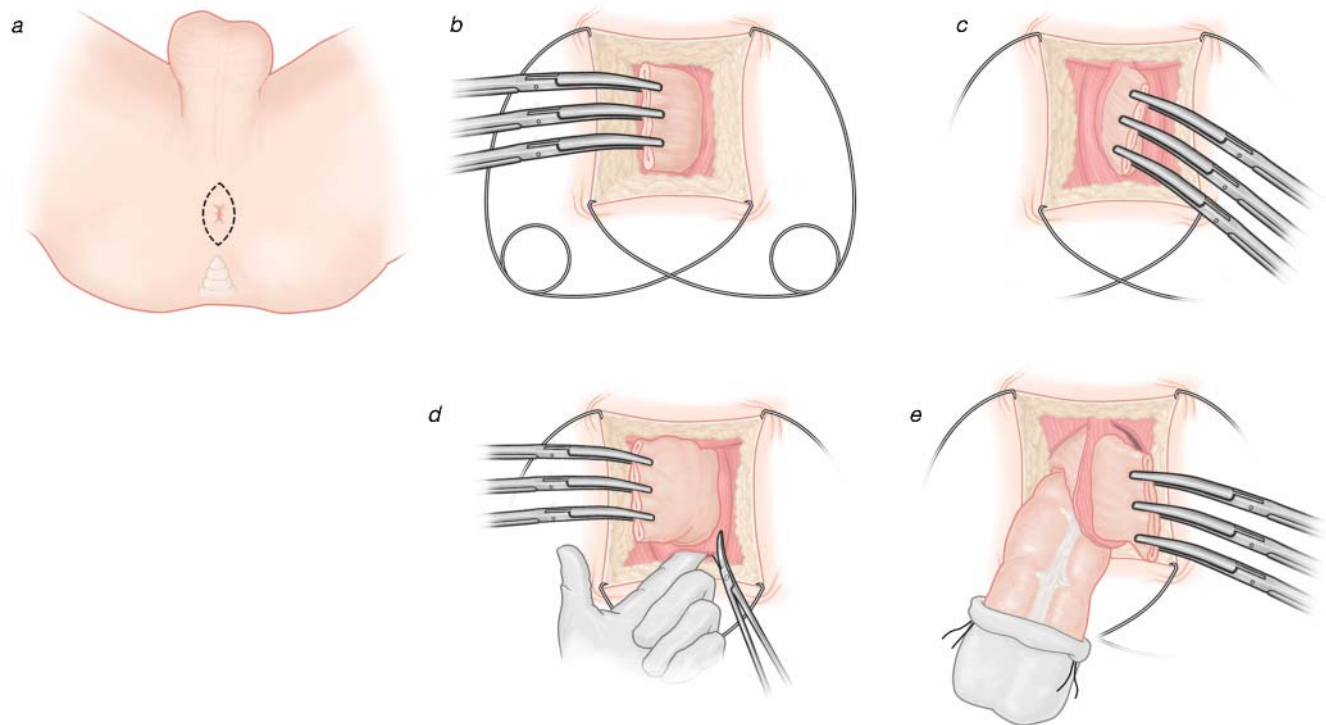


Figure 11 Abdominoperineal resection (APR). Shown is the perineal phase of APR. (a) An elliptical incision is made around the anus. (b) Springs or retractors are used to provide exposure. (c) Mobilization continues up to the transversus perinei superficialis. (d) The levator muscles are divided posteriorly. (e) The specimen is delivered through the wound posteriorly, and the anterior dissection is complete.

with absorbable sutures. A transabdominal rather than transperineal drain is placed in the pelvis.

Step 6: creation of colostomy An end colostomy is created before the perineal dissection is begun if performing a sequential prone APR, but the colostomy may be created simultaneously with the perineal resection if a two-team synchronous APR is performed. A 2 cm circular incision is made in the skin and subcutaneous tissues overlying the premarked stoma site, which is usually in the left lower quadrant of the abdomen. A cruciate incision is made in the anterior fascia, the rectus abdominis is split, and a second cruciate incision is made in the posterior fascia. The mobilized colon is passed through this site and fixed to the skin with 3-0 or 4-0 absorbable sutures. Because many enterostomal therapists and patients find it easier to pouch an elevated left-side colostomy, an eversion technique is used to mature the stoma.

OTHER RADICAL PROCEDURES

Hartmann Procedure

The Hartmann procedure is a seldom-used option that plays only a limited role in the treatment of rectal cancer. It may be a good choice if the likelihood of local recurrence is high (as with a perforated cancer) or if the patient with a rectal cancer normally suited for anterior resection and restorative anastomosis has preexisting sphincter dysfunction.

In these situations, perineal dissection subjects the patient to unnecessary morbidity. The distal rectum or anal canal is stapled closed and left in situ in the pelvis. Because the incidence of “blowout” of the short Hartmann pouch seems high, we often oversew the staple line closure, place a large fluted drain in the pelvis to evacuate blood and serum in the early postoperative period, and leave a soft drain in the anal canal to vent the Hartmann pouch. The end colostomy is performed as in APR.

Pelvic Exenteration, Sacrectomy, and Multivisceral Resections

A full discussion of pelvic exenteration, sacrectomy, and multivisceral resections for patients with advanced-stage rectal cancer is beyond the scope of this chapter. The indications for pelvic exenteration are limited by the relatively high morbidity and mortality associated with the procedure. Yet pelvic exenteration for locally advanced or recurrent rectal cancer has been shown to have oncologic and palliative benefits. Reported 5-year survival rates after pelvic exenteration for locally recurrent rectal cancer range from 20 to 30%.⁹⁵ As opposed to recurrent rectal cancer, primary advanced rectal cancer is less often amenable to pelvic exenteration.

Pelvic exenteration may involve resection of the anus, the rectum, and sometimes the bladder, ureters, and pelvic reproductive organs. Sacrectomy is also often necessary if the rectal cancer is invading posteriorly.⁹⁶ Reconstruction after these procedures involves both fecal and urinary diversion; consequently, a multidisciplinary team is usually needed,

including a urologist, the rectal cancer surgeon, and a plastic surgeon.

Detailed preoperative and intraoperative examination is essential to verify the presence of localized resectable disease before proceeding with exenteration. If there is evidence of carcinomatosis, liver metastases, pelvic sidewall invasion, bilateral ureteral obstruction, or aortic node metastases, then curative exenteration generally cannot be performed. Invasion of the upper sacral vertebra is a contraindication to sacrectomy as in this setting, the procedure would result in an unacceptably high morbidity and debilitating functional sequelae. In the setting of advanced disease, the surgeon should consider comfort care or additional adjuvant therapy before performing palliative exenteration. Other treatment modalities (e.g., intraoperative radiotherapy, brachytherapy, and further chemoradiation) may be useful in this population of patients.

Postoperative Therapy

As noted above, it is now accepted that preoperative (neoadjuvant) chemoradiation is preferable to postoperative chemoradiation therapy when adjuvant therapy is a consideration.²⁹ One disadvantage of this approach is that clinically overstaged tumors receive chemoradiation when it is not indicated. Conversely, some patients with clinical early-stage rectal cancer prove to have more advanced disease than expected on pathologic examination. Such patients may benefit from the addition of postoperative chemotherapy, radiotherapy, or both.

There are clear data that support the use of adjuvant chemotherapy for node-positive colon cancer. Fewer data are available that address the issue of chemotherapy alone for rectal cancer, but most authorities agree that, by analogy, adjuvant chemotherapy is indicated for node-positive rectal cancer. Unfortunately, this issue is not always clear-cut following preoperative chemoradiation. For example, many clinically node-positive rectal cancer patients are downstaged by their chemoradiation, and suspected pathologic nodes disappear. In this circumstance, we recommend completing the full course of chemotherapy postoperatively based on the preoperative clinical stage.

A second important issue is the role of postoperative chemoradiation for understaged T3 or node-positive tumors that did not receive neoadjuvant therapy. Many surgeons agree that preoperative chemotherapy is indicated for either T3 or node-positive tumors, but there is less agreement as to the proper role of postoperative chemoradiation when an R0 resection has been achieved. In this case, an individual decision must be made regarding the relative risk of local recurrence versus the known morbidity and functional consequences of postoperative adjuvant chemoradiation. Although many North American medical and radiation oncologists advise postoperative chemoradiation under these circumstances, elsewhere in the world postoperative chemoradiation is not recommended following R0 rectal resections of T0 to T3, N1 to N2 lesions.

A third important issue is the role of adjuvant therapy for R1 and R2 rectal cancer resections. There is little argument that a positive circumferential resection margin is a highly significant risk factor for local recurrence. Because of this, postoperative chemoradiation is generally recommended

following R1 and R2 resections, although its efficacy in this setting has not been clearly documented.

Follow-up Regimens

The primary purpose of surveillance after treatment of rectal cancer is to detect early recurrence so that salvage therapy can be instituted. A secondary purpose is to prevent development of a metachronous cancer by identifying and removing new polyps. Symptoms of pain, pressure, weight loss, or bowel dysfunction should be investigated. In addition to the physical examination, various laboratory studies, endoscopic procedures, and imaging modalities are used to detect or exclude recurrences.

Most follow-up regimens include a routine history and physical examination, CEA testing, CT, and routine colonoscopic evaluation. MRI and PET-CT scans are generally reserved to evaluate suspected recurrence. Our practice is to follow good-risk rectal cancer patients who have undergone curative intent therapy with sphincter preservation every 4 months with ERUS and proctoscopy for the first 3 years and then every 6 months for 2 more years. However, the efficacy and cost-effectiveness of this approach have not been proven.

MANAGEMENT OF RECURRENCE

Local Recurrence

Avoidance of local recurrence is a central goal of rectal cancer surgery. Although the problem of local recurrence has substantially decreased with the advent of TME surgery and neoadjuvant therapy, local recurrence remains a significant and challenging problem. Untreated or untreatable locally recurrent rectal cancer can cause myriad symptoms, including bleeding, obstruction, vaginal or urinary fistulas, malodorous discharge, and intractable pain. The severity of these symptoms cannot be underestimated when “compromise” therapy is being considered. Friel reviewed our experience with radical salvage surgery following tumor recurrence after local excision.⁹⁷ Ninety-three percent of the recurrent tumors were more advanced than at the time of initial presentation. “Curative” surgery was possible in 79% of patients. However, at a mean follow-up of 39 months, only 59% of patients remained disease free.

Recurrence after initial radical resection is generally more extensive than after failed local therapy. As noted above, treatment of locally recurrent rectal cancer often involves complex multivisceral resections with involvement of a multidisciplinary surgical team. Preoperative planning requires exclusion of metastatic disease by PET-CT and careful assessment of local disease by MRI. Surgery should be undertaken only when there is a reasonable expectation that an R0 resection can be achieved. Patients who have not previously received chemoradiation should undergo it before resection is attempted.

Surgery for recurrent rectal cancer is a major undertaking with substantial associated risks. Multivisceral resections may require 12 to 16 hours to complete, and the risk of major complications ranges from 25 to 50% in even the most skilled hands. Most series report 5-year survival rates in the 25% range.⁹⁸ Because of the complexity of this surgery and the magnitude of its associated risks, major resections of recurrent rectal cancers are best managed at tertiary care

centers with experienced multidisciplinary surgical teams and adequate institutional resources.⁹⁹

Distant Recurrence

Detailed management of metastatic rectal cancer is beyond the scope of this chapter. However, it is worth noting that hepatic and pulmonary metastases that are resectable for

cure ought to be resected. Most series report 5-year survival rates of 25 to 30% in this group of patients.²³ Patients with more widely disseminated disease are treated with a combination of chemo- and biologic (bevacizumab, cetuximab) therapies.

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36 PROCEDURES FOR RECTAL PROLAPSE

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Rectal prolapse is an intussusception of the rectum, which may be categorized as occult (internal), mucosal, or complete. Occult rectal prolapse does not extend beyond the anal canal and often is not associated with any symptoms; it may be a precursor to complete prolapse. Mucosal prolapse involves protrusion of the mucosa only, with the muscular layers of the rectum remaining in place. Complete rectal prolapse, or rectal procidentia, involves full-thickness protrusion of the rectum through the anus [see Figure 1].

Whereas the exact pathophysiology of rectal prolapse remains unclear, several factors have been associated with its development, including constipation, female gender, postmenopausal status, and previous anorectal surgical procedures. The constipation frequently arises from conditions such as colonic inertia, neurologic disease, psychiatric illness, and obstructed defecation. Obstructed defecation is also referred to as anismus, spastic pelvic floor, and paradoxical or nonrelaxing puborectalis syndrome. Patients with this condition experience significant pain and have difficulty passing stool; digital compression or any of a variety of perineal maneuvers may be necessary to relieve the functional obstruction.

Chronic constipation and straining are thought to lead to herniation of the rectum through the muscular aperture of the pelvic floor, much as occurs with a hiatal or ventral hernia.

As herniation progresses, the mesorectum lengthens and the lateral and rectosigmoid attachments stretch. Weakened pelvic floor muscles (from aging and the postmenopausal state) contribute to the herniation process, as do sphincter defects and pudendal neuropathy from previous anorectal operations or obstetric injuries.

Initially, prolapse occurs only with straining; later in the course of the disease, it occurs with any increase in intra-abdominal pressure or may develop into a chronic condition. Chronic prolapse results in the development of a patulous anus and incontinence. The incontinence may derive from direct sphincteric stretching, from traction injury of the pudendal nerves caused by straining, or from continuous stimulation of the rectoinhibitory reflex by the intussusception, which results in chronic reflexive relaxation of the internal anal sphincter and inappropriate leakage of stool and mucus.

The anatomic abnormalities resulting from rectal prolapse include a deep cul-de-sac, a redundant rectosigmoid, an elongated mesorectum, diastasis of the levator ani, perineal descent, a patulous anus, and loss of support of the uterus and the bladder [see Table 1]. Rectal prolapse also is frequently associated with other anatomic defects of the pelvic floor, such as rectoceles, enteroceles, cystoceles, and uterine and vaginal prolapse. Recognition of how the functional

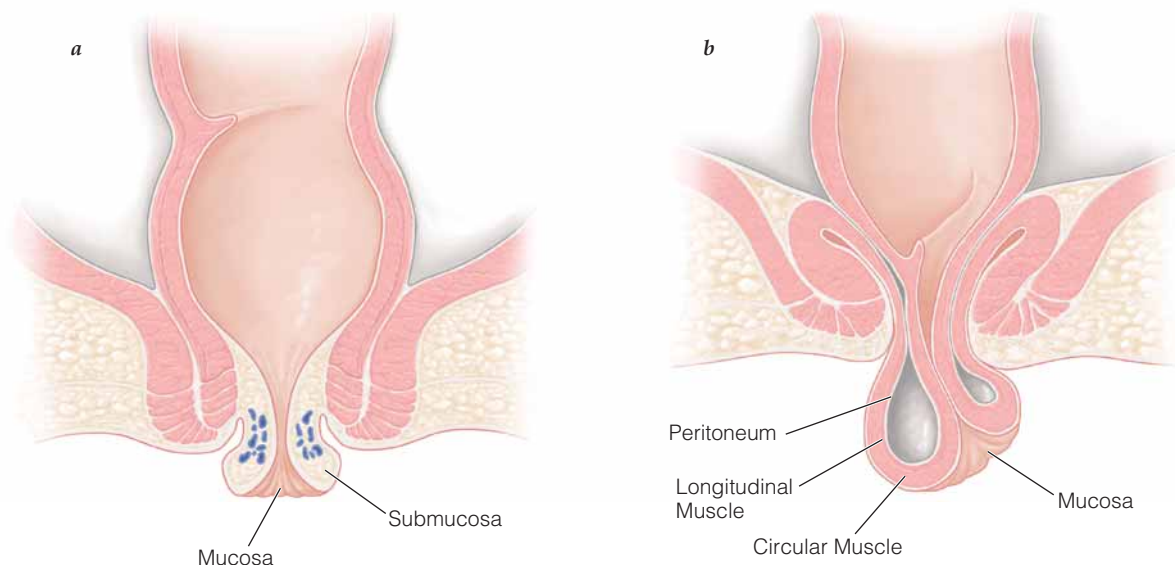


Figure 1 In mucosal prolapse (a), only the mucosa protrudes, whereas in complete rectal prolapse (b), the full thickness of the rectal wall protrudes.

Table 1 Anatomic Abnormalities Associated with Rectal Prolapse
Deep cul-de-sac
Redundant rectosigmoid colon
Elongated mesorectum
Diastasis of levator ani
Perineal descent
Herniation of pelvic organs through pelvic funnel
Patulous anus
Loss of support of uterus and bladder

pathology of the pelvic floor results in the anatomic abnormalities seen with rectal prolapse is essential to understanding the various operative approaches and determining appropriate long-term management. Patients with rectal prolapse, like most patients with pelvic floor dysfunction, frequently require postoperative bowel retraining with fiber therapy, laxatives, or biofeedback to address the functional component of this disease and thereby prevent recurrence once the prolapse has been surgically corrected.

More than 120 operations for treating rectal prolapse have been described. A detailed description of all available options is clearly beyond the scope of this chapter. Instead, we focus on a few key procedures that currently are frequently employed and enjoy widespread acceptance. For present purposes, we have excluded a number of procedures that, although popular in certain regions of the world, are not universally accepted.

Preoperative Evaluation

Because of the protrusion of tissue through the anus and the frequent bloody discharge, most patients initially mistake rectal prolapse for hemorrhoids [see Table 2]. Such patients often present with a complaint of “persistent hemorrhoids” after a recent hemorrhoid operation. Similarly, many patients mistake incarcerated rectal prolapse for thrombosed hemorrhoids. Consequently, a high level of suspicion and careful physical examination are required to differentiate hemorrhoids from rectal procidentia [see Table 3].

The diagnosis is most easily made with the patient straining while seated on the toilet. If the prolapse cannot be reproduced in the office setting, administration of a phosphate enema may reveal it. The appearance of circumferential, concentric folds of rectal mucosa serves to differentiate rectal prolapse from hemorrhoids, in which the folds (sulci) occur in a radial pattern, yielding three discrete anatomic bundles [see Figure 2]. In addition, close inspection of a full-thickness rectal prolapse reveals a circumferential sulcus between the

Table 2 Symptoms of Rectal Prolapse
Sensation of protrusion of tissue through anus
“Persistent hemorrhoids”
Mucoid or bloody discharge
Constipation
Straining
Incontinence
Incomplete evacuation
Perineal pressure
Excoriation of perianal skin

anus and the rectum, and palpation reveals a double rectal wall. The prolapse should be easily reducible unless incarcerated.

Chronic prolapse leads to inflammation, edema, and ulceration of the rectal mucosa. Biopsy of these areas should be undertaken to determine whether a neoplastic lesion is acting as the source of the intussusception. In addition, complete colonoscopy is performed to search for lesions elsewhere in the colon, which may affect the surgical approach to the prolapse. Occasionally, a solitary rectal ulcer in the anterior rectum is seen in a patient with obstructed defecation caused by ischemia of the rectal wall from chronic straining. Barium enemas may induce strangulation and thus should be avoided; however, water-soluble contrast enemas may be of some use in identifying pathologic conditions in the remainder of the colon. Defecography is useful when occult intussusception or mucosal prolapse is suspected or when the patient has a history of prolapse but is unable to reproduce the prolapse in the office. If the prolapse is associated with conditions arising from pelvic floor defects (e.g., urinary incontinence, rectocele, enterocele, cystocele, and uterine and vaginal prolapse), consultation with a gynecology team for combined surgical intervention is warranted.^{1,2}

About 50% of patients with prolapse have a history of constipation.^{1,3} Possible causes of the underlying constipation—such as electrolyte (calcium) imbalance, hormonal (thyroid) dysfunction, obstructed defecation, and colonic inertia—should be investigated. Surface electromyography may be used to diagnose paradoxical contraction of the puborectalis muscle. In patients with severe constipation, a colonic transit study using ingested radiopaque markers aids in diagnosing colonic inertia, which may necessitate inclusion of subtotal colectomy as part of surgical management.

Fecal incontinence is a presenting symptom in 30 to 80% of patients with rectal prolapse.^{3,4} For these patients, anal ultrasonography, manometry, electromyography, and pudendal nerve terminal motor latency testing are indicated to help guide the choice of surgical procedure to treat the prolapse.

Table 3 Differences between Rectal Prolapse and Hemorrhoids		
Finding on Evaluation	Rectal Prolapse	Hemorrhoids
Tissue folds	Circumferential	Radial
Sulcus between prolapse and rectum	Circumferential	None
Abnormality on palpation	Double rectal wall	Hemorrhoidal plexus
Resting and squeeze pressure	Decreased	Normal

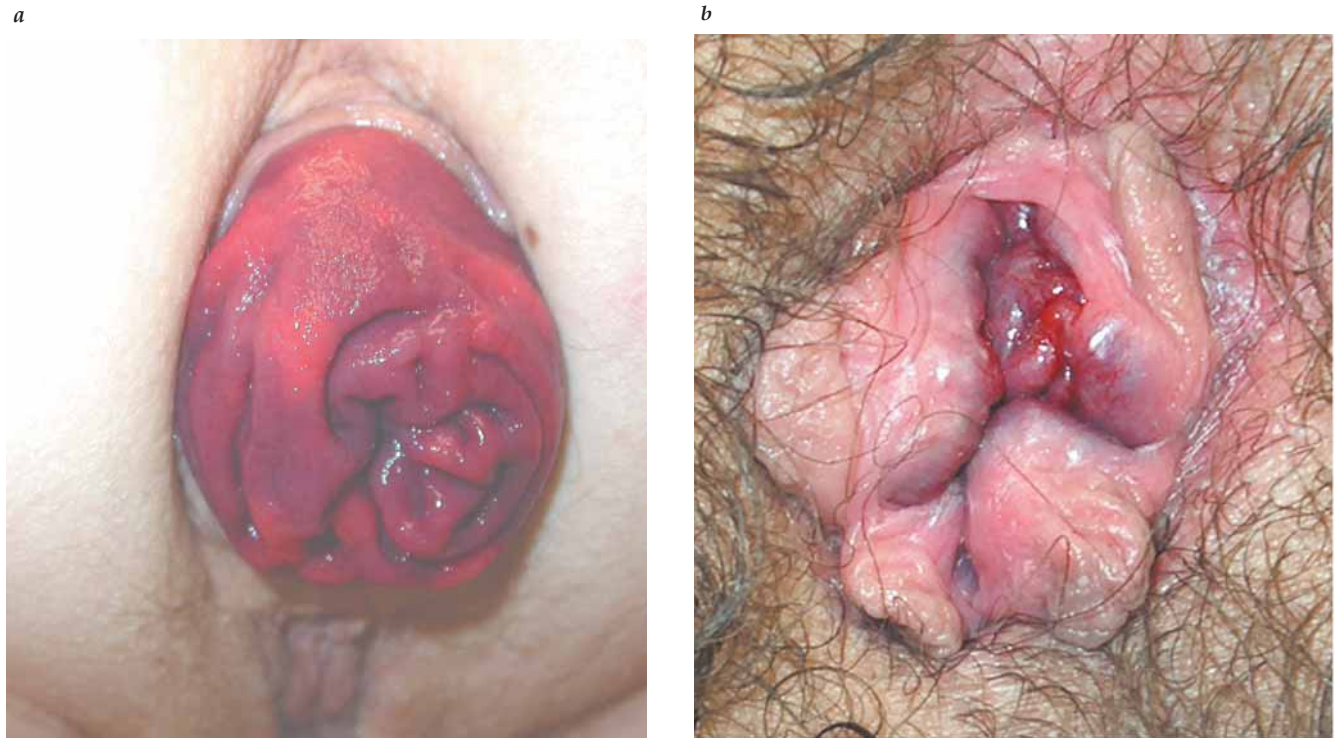


Figure 2 Rectal prolapse can be differentiated from hemorrhoids on the basis of physical appearance. (a) Rectal prolapse is distinguished by concentric mucosal folds. (b) Hemorrhoids are distinguished by radial sulci and discrete hemorrhoidal bundles.

Operative Planning

CHOICE OF PROCEDURE

Because the etiology and pathophysiology of rectal prolapse are not well understood and appear to vary, it has not proved possible to identify any individual procedure as the optimal surgical approach to this condition. The current focus in the literature is on developing criteria by which specific patients can be matched to the specific operations that are most appropriate for them. The choice of operation is determined by the patient's age, sex, level of operative risk, associated pelvic floor defects, degree of incontinence, and history of constipation, as well as by the surgeon's experience. The goal is to correct the greatest number of anatomic problems (including the prolapse and any associated functional disorders) safely and efficiently while minimizing both perioperative morbidity and postoperative recurrence.

The procedures performed for repair of rectal prolapse may be divided into two broad categories: perineal and abdominal [see Table 4]. The perineal operations include anal encirclement (the Thiersch wire procedure), mucosal sleeve resection (the Delorme procedure), and perineal rectosigmoidectomy (the Altemeier procedure). In the original description of the Thiersch wire procedure, silver wire was placed in the subcutaneous tissues surrounding the anus through two small incisions and then tied around the assistant's finger to narrow the anal aperture.⁵ It was believed that this operation controlled the prolapse by reinforcing the anal sphincter and fixing the rectum to surrounding structures through induction of tissue reaction to the foreign material. The simplicity of the operation

was offset by many problems, including breakage of the wire, sloughing of the overlying skin, perineal sepsis, and fecal impaction. Various other, more compliant materials

Table 4 Operations Performed to Treat Rectal Prolapse

Perineal procedures	Anal encirclement (Thiersch wire procedure)
	Mucosal sleeve resection (Delorme procedure)
	Perineal rectosigmoidectomy (Altemeier procedure)
Transabdominal procedures	Rectopexy
	Suture
	Anterior sling (Ripstein procedure)
	Ivalon sponge (posterior rectopexy)
	Posterior sling (modified Ripstein procedure)
	Resection
	Suture rectopexy with resection (Frykman-Goldberg procedure)
	Laparoscopic repairs
	Resection rectopexy
	Suture rectopexy
	Rectopexy with mesh

(e.g., Marlex mesh and Silastic rods) have since been used in place of the silver wire, but none of these modifications have proved universally successful. In addition, better anesthetic techniques and improved perioperative medical management have made it possible to employ other perineal or abdominal procedures safely in most patients. Consequently, anal encirclement remains an option only for those patients who would be at unacceptably high risk with other types of procedures.

Mucosal sleeve resection, as described by Delorme in 1900, involves stripping the mucosa from the redundant rectum and plicating the denuded rectal wall with sutures to create bulk and thus prevent future prolapse.⁶ Perineal rectosigmoidectomy, originally described by Mikulicz⁷ and subsequently modified by Altemeier and colleagues,⁸ involves transanal amputation of the prolapsed rectum coupled with a coloanal anastomosis.

The various abdominal operations may be performed as either open or laparoscopic procedures, and they differ with respect to how far rectal mobilization extends, whether the lateral ligaments are divided, whether the rectum is fixed anteriorly or posteriorly, what fixation material is used (sutures, mesh, or sponge), and whether sigmoid resection is included. At present, the operation most commonly performed to treat rectal prolapse in the United States is suture rectopexy, with sigmoid resection added (the Frykman-Goldberg procedure) if constipation is a significant presenting complaint. The various posterior rectopexies with sutures or mesh are more popular than the procedures involving anterior fixation with mesh or posterior placement of a polyvinyl alcohol (Ivalon) sponge. Anterior fixation of the rectum using a sling was proposed by Ripstein and Lantern as a way of restoring the natural contour of the rectum and preventing intussusception.⁹ Originally, fascia lata was used for the sling; subsequently, various artificial materials (e.g., Teflon, Marlex, and Gore-Tex mesh) came to be used instead. The Ivalon (polyvinyl alcohol) sponge operation (the Wells procedure) entails placement of the sponge posterior to the rectum to create an inflammatory reaction and a consequent rectopexy.¹⁰ Because of the risks imposed by the foreign materials (including infection, erosion, and stenosis), few surgeons now perform either anterior fixation or foreign body placement.

Laparoscopic resection rectopexy involves a laparoscopically assisted approach with intracorporeal mobilization of the sigmoid colon and the rectum, division of the mesenteric vessels, and distal transection of the bowel. The bowel is then exteriorized through a small incision (often a Pfannenstiel incision), and the proximal transection is performed. The rectopexy sutures are placed by means of an open technique, and the anastomosis is created with a transanally placed circular stapler. Laparoscopic suture rectopexy without resection is performed entirely laparoscopically, with intracorporeal mobilization and suture placement.

MATCHING THE PATIENT TO THE OPERATION

The best way to think of prolapse operations is to divide them into broad categories of abdominal and perineal. The balance that must be discussed with the patient is the balance between immediate safety and long-term results. The abdominal approaches, including rectopexy, resection rectopexy, and other choices, whether by laparotomy or laparoscopy, tend to have lower recurrence rates and better functional

outcomes than do the perineal methods. Conversely, the perineal approaches tend to have less intraoperative and postoperative morbidity and mortality but have higher rates of recurrence and inferior functional outcomes compared with the abdominal approaches. Therefore, major considerations to selection of the operation are the age and overall physical condition of the patient. In general, young, healthy patients are far better served by an abdominal procedure as they can better tolerate any potential intraoperative or postoperative morbidity and have a longer life expectancy. Therefore, the best possible function over the longest possible period of time is of paramount importance. The preferred operation then is a laparoscopically assisted resection rectopexy to optimize function, decrease recurrence potential, and minimize incisional length.

Elderly, frail patients may best be served by a perineal approach to limit intra-abdominal trauma. The perineal procedure preferred is the perineal rectosigmoidectomy with, when possible, several adjuncts. First, if the levator muscles are identifiable, then a levatorplasty is added, with the hope of helping improve continence. Second, if sufficient redundancy exists, then we try to create a transperineal colonic J pouch with coloanal anastomosis to confer the same advantages to this operation as given to the patients with rectal carcinoma who undergo a transabdominal restorative proctectomy with a colonic J pouch compared with a straight transabdominal coloanal anastomosis. In these instances, we create a 6 cm × 6 cm to 8 cm × 8 cm colonic J pouch and then affect either a handsewn or a circular stapled coloanal anastomosis.

If only a minor amount of prolapse can be delivered, then a Delorme procedure is performed. In our experience, the Delorme procedure has a higher recurrence rate and far less improvement in continence than does the perineal rectosigmoidectomy. Therefore, the Delorme procedure is infrequently undertaken.

Patients with recurrent rectal prolapse need to be assessed and managed in part according to the original operation. Paramount importance must be paid to the blood supply to the rectum and to any previous interruptions in that blood supply. Specifically, if a perineal rectosigmoidectomy was performed, then a resection rectopexy might not be possible, whereas if a resection rectopexy was the index operation, then a perineal rectosigmoidectomy could be undertaken. In reoperative situations, both rectopexy without resection and Delorme procedure can be offered without fear of significant vascular compromise.

Perineal Procedures

MUCOSAL SLEEVE RESECTION (DELORME PROCEDURE)

Both mucosal sleeve resection and perineal rectosigmoidectomy may be performed with the patient under either general or spinal anesthesia. Preoperatively, the patient undergoes mechanical and antibiotic bowel preparation. Such preparation consists of oral administration of 45 mL of sodium phosphate solution, followed by three 8 oz glasses of water at 4 pm and 9 pm and administration of 1 g of neomycin with 500 mg of metronidazole at 7 pm and 11 pm. Before

the procedure, the patient receives prophylactic antibiotics, and subcutaneous heparin is used in conjunction with sequential compression devices to prevent venous thromboembolism.

After induction of anesthesia or administration of intravenous sedation, a bladder catheter is inserted, and the patient is placed in the prone jackknife position with a Kraske roll beneath the hips and the buttocks abducted with tape. A self-retaining retractor may be used to evert the anus. The muscular stripping can be undertaken with the prolapse either everted or reduced. Our preference is to evert the prolapse, and the following technical description embodies that preference.

Operative Technique

Step 1: eversion of the rectum The rectal prolapse is everted by placing gentle traction on the rectal wall with Babcock tissue forceps passed through the anus. As the prolapsed

tissue emerges, the Babcock forceps are repositioned more proximally on the rectal wall to provide a better grasp and facilitate delivery of the prolapse through the anus and into the operative field.

Step 2: submucosal injection of anesthetic Once the rectum has been everted, a local anesthetic solution containing 0.25% bupivacaine, 0.5% lidocaine, and epinephrine (in a 1:400,000 dilution) is circumferentially injected 1 to 1.5 cm above the dentate line to minimize bleeding.

Step 3: circumferential incision of mucosa The rectal mucosa is incised at this level with a conventional diathermy, and four clamps are placed on the proximal mucosal edge for traction [see Figure 3].

Step 4: dissection of mucosa from muscle Gentle traction is placed on the clamps, and the mucosa is dissected away from the muscle with the electrocautery. A finger is placed inside the muscular tube to facilitate traction and help prevent full-thickness injury. Resection of the mucosal sleeve

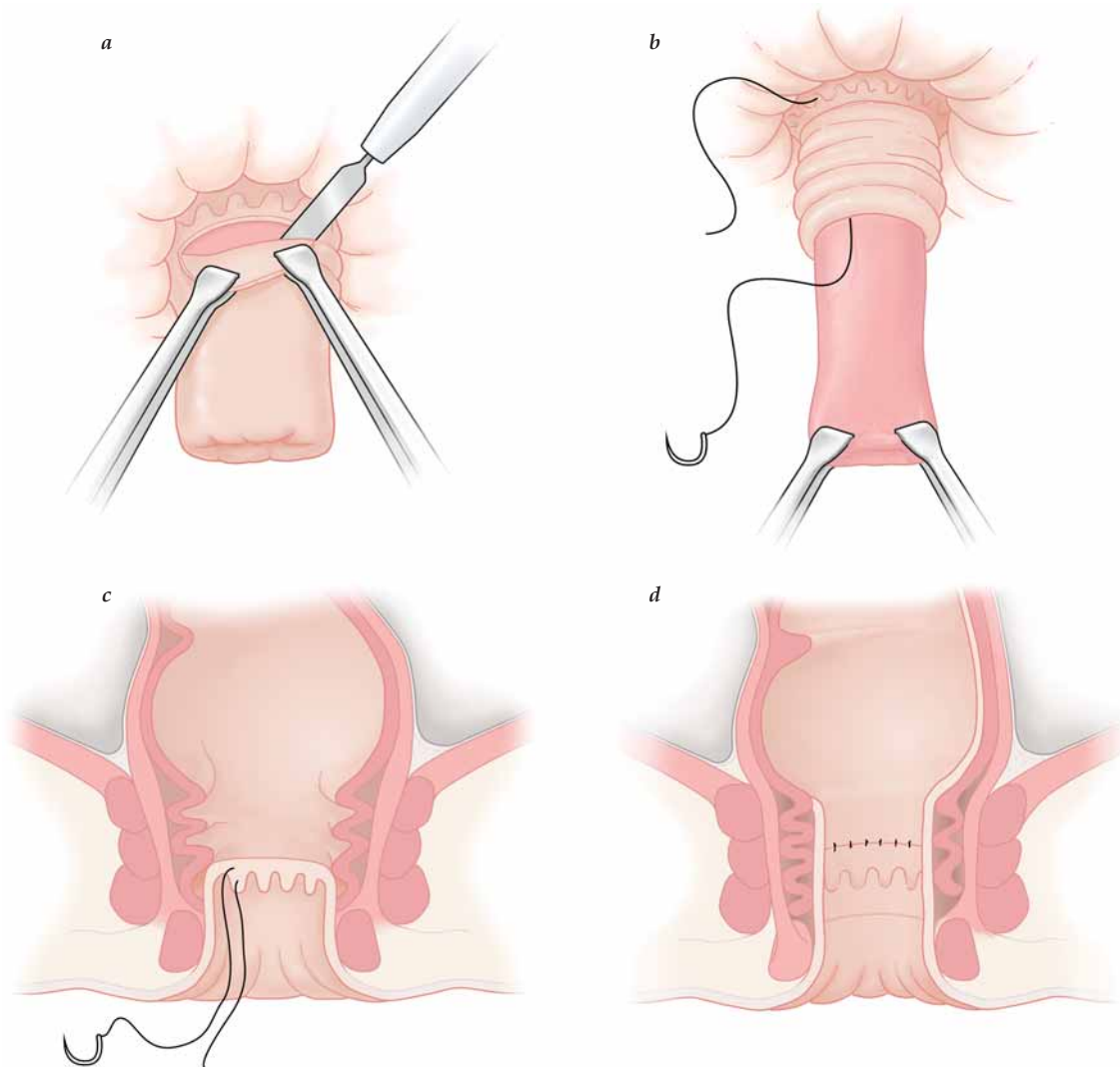


Figure 3 Mucosal sleeve resection. (a) With the rectum everted, the mucosa is incised and dissected away from the muscular tube. (b) The muscular tube is plicated with sutures to form a muscular pessary. (c) A mucosa-to-mucosa anastomosis is fashioned. (d) The anastomosis spontaneously reduces into its anatomic position.

is continued until resistance prevents further dissection. A tube of redundant muscular tissue then remains.

Step 5: plication of rectal muscle The muscular tube is plicated by placing eight reefing sutures circumferentially in the wall.

Step 6: resection of mucosa and anastomosis The excess mucosa is transected in a superior-to-inferior direction, and the two cut edges of mucosa are approximated with sutures. Transection is continued on one side for a quarter of the circumference, at which point, a second suture is placed. With traction applied to these two sutures, two additional sutures are placed at 90° intervals to establish four quadrants. Transection and anastomosis are serially performed in each of the four quadrants until the mucosa is completely excised and the anastomosis has been completed. With the removal of the retractor, the anastomosis should spontaneously reduce into its anatomic position.

Postoperative care Because the patients are often elderly, 1 to 3 days of observation may be indicated. The bladder catheter is removed on the following morning, and the patient is advanced to a regular diet as soon as he or she can tolerate it. The patient is sent home on a regimen of fiber supplementation and sitz baths as soon as medical stability is ensured and appropriate social circumstances are arranged.

Troubleshooting

The Delorme procedure prevents rectal intussusception by resecting redundant mucosa and by removing laxity in the rectal wall through plication of the muscular redundancy. The key to success is to continue the sleeve resection until some resistance is met and the dissection cannot proceed further. Sometimes, the anterior wall is longer than the posterior wall or vice versa, but such discrepancies should not affect the repair. The anastomosis is performed one quadrant at a time to prevent retraction of the transected mucosa into the proximal bowel.

PERINEAL RECTOSIGMOIDECTOMY

Operative Technique

Anesthesia and positioning are the same for perineal rectosigmoidectomy as for mucosal sleeve resection.

Steps 1 and 2 Steps 1 and 2 of this procedure are the same as steps 1 and 2 of mucosal sleeve resection (see above).

Step 3: circumferential incision through the rectal wall With the rectum everted, the prolapse consists of two tubes of rectal wall, with the inner tube consisting of rectum attached to the sigmoid and the outer tube consisting of rectum attached to the dentate line. The mucosa is circumferentially scored with a standard diathermy 1 to 1.5 cm cephalad to the dentate line [see Figure 4]. The incision should be made at the top of the anal columns to preserve the entire transition zone, which is important for nocturnal continence. The incision is deepened through all layers of the outer rectal tube until perirectal fat is encountered and the mesorectum is identified on the superior aspect of the prolapse with the patient prone.

Step 4: mobilization of the rectum and division of the mesentery Rectal mobilization is accomplished by clamping, ligating, and dividing the vessels of the mesorectum. As the mesorectum is divided, tension on the rectum delivers

more of the prolapse into the operative field. Division of the mesorectum is continued close to the bowel wall until no more bowel can be delivered. During this phase, the sliding hernia of peritoneum (cul-de-sac) anterior to the rectum (on the inferior aspect of the prolapse with the patient prone) may be opened to allow palpation of the intraperitoneal contents and determination of whether the colon is straight in the pelvis.

A finger may be inserted into the pelvis alongside the rectum to facilitate assessment of the redundancy of or the tension on the remaining rectum and sigmoid. If redundancy is still encountered, more mesorectum is divided to allow further mobilization of the bowel through the anus. Careful control of the mesentery with ligatures is advised to prevent retraction of bleeding vessels into the pelvis. One of the newer energy sources (bipolar or ultrasonic) may facilitate the dissection.

Step 5: ligation of the hernia sac Once the redundant rectum and sigmoid have been adequately mobilized, the hernia sac of peritoneum is sutured closed. Care is taken to resect any redundant hernia sac to prevent future anterior intussusception; this step is similar to the high ligation performed for other types of hernias.

Step 6: levatorplasty Levatorplasty is then performed to restore the appropriate angles of the pelvic floor muscles, to aid in treatment of incontinence, and to narrow the aperture through which herniation occurs and thereby prevent recurrence. It can be performed anterior to the rectum, posterior to the rectum, or both. A narrow retractor is employed to expose the outer tube of rectum and uncover the levator muscles. Interrupted 2-0 nonabsorbable sutures are placed through the levator muscles on each side and secured loosely enough to allow a finger to be inserted alongside the rectum.

Step 7: proximal transection of the rectum and anastomosis The point at which the redundant rectum is to be transected is identified at the level at which the mesorectum is divided. The bowel wall is circumferentially cleared of appendages in preparation for transection and anastomosis. Transection is begun by dividing a small area of the bowel wall superiorly and placing a suture through the edge of the outer tube of rectum and the newly transected proximal edge of the bowel. Transection is continued inferiorly on one side for a quarter of the circumference, and a second suture is placed. With traction on these two sutures, two additional sutures are placed around the remaining circumference to mark four quadrants. Transection and anastomosis are serially performed in each of the four quadrants until the rectum is completely transected. When the anastomosis is complete, it retracts into the pelvis, where it may be inspected with a bivalve retractor. When possible a transperineal colonic J pouch can be created. In these instances, a sufficient length of well-vascularized redundant colon is left to fold back on itself. An 8 cm × 8 cm colonic J pouch is created with a linear cutting stapler. The afferent limb is sutured to the efferent limb with 3-0 absorbable sutures. The anastomosis, whether straight coloanal or pouch anal, can be affected by a circular stapler if the luminal diameters are relatively similar. However, if significant discrepancy exists, then a handsewn anastomosis is preferable.

Postoperative care Patients are often observed in the hospital for 1 to 3 days. Their diet is advanced as tolerated, and the bladder catheter is removed on postoperative day 1. Patients are sent home on a regimen of fiber supplementation and sitz baths.

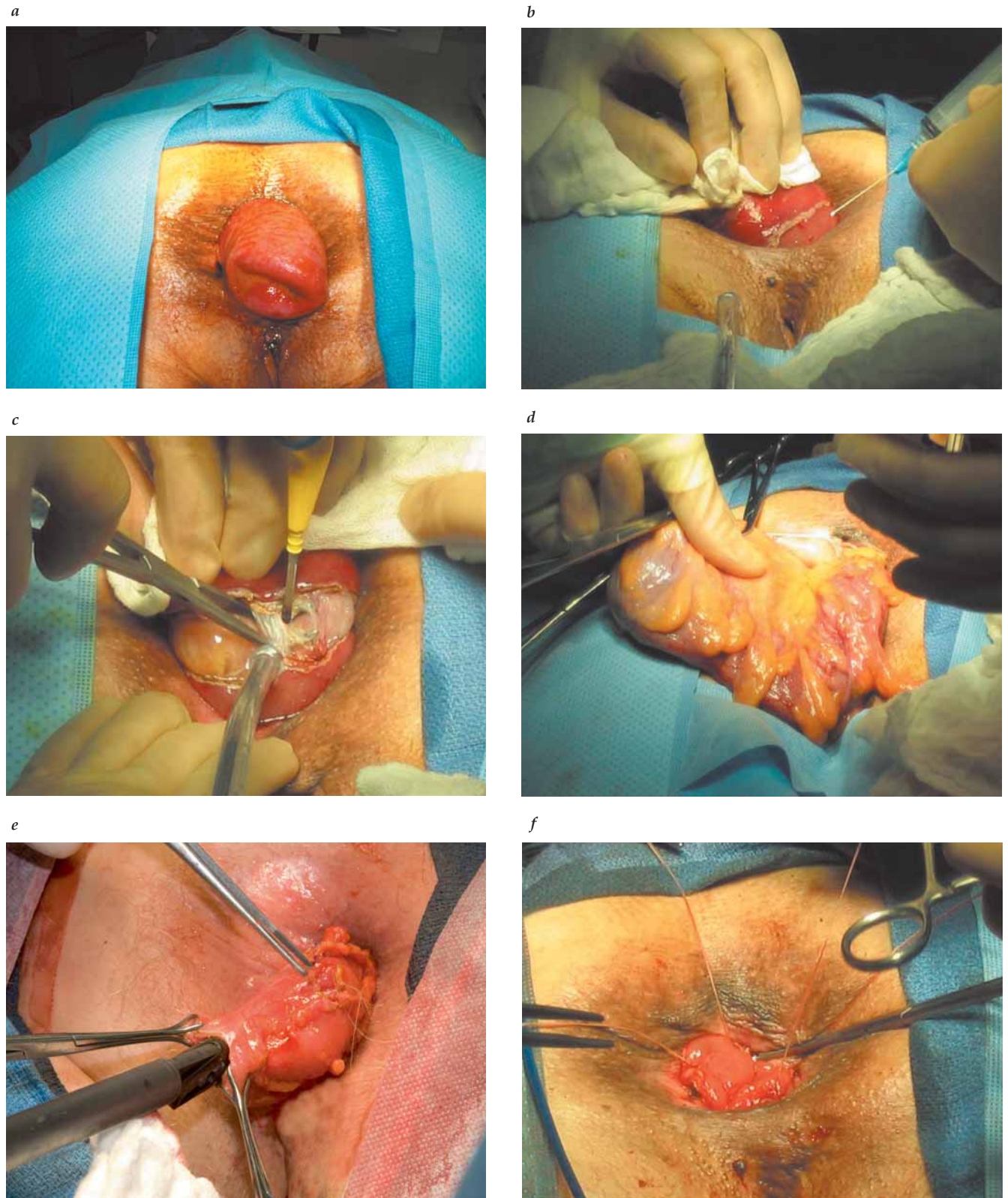


Figure 4 Perineal rectosigmoidectomy. (a) The rectum is everted. (b) The anesthetic is injected submucosally. (c) A circumferential incision is made and deepened through the outer rectal tube until perirectal fat is encountered. (d) The rectum and the sigmoid are mobilized with division of the mesentery; levatorplasty is then done. (e) A colonic J-pouch is created. (f) The remaining sutures are placed.

Troubleshooting

Perineal rectosigmoidectomy involves a combination of repairs of anatomic abnormalities associated with rectal prolapse. Rectal mobilization yields a rectopexy from scarring; resection removes redundant bowel; ligation of the enterocele obliterates the hernia sac; and levatorplasty provides reconstruction of the pelvic floor. Each step requires that attention be paid to appropriate planes of dissection and that meticulous hemostasis be maintained. For example, transection of the outer rectal wall may lead to inadvertent division of the mesentery before vascular control is obtained; if this occurs, traction should be placed on the inner wall to expose the proximal mesentery and allow the surgeon to regain vascular control. In addition, transection of the outer rectal wall may lead to inadvertent simultaneous transection of both walls; if this occurs, clamps should be placed on the inner wall to prevent retraction into the pelvis and to facilitate rectal mobilization and division of the mesorectum [see Step 4: mobilization of the rectum and division of the mesentery, *above*].

To help prevent recurrence, all redundant bowel should be resected once mobilization of the rectum and division of the mesentery are complete. If, at the start of the procedure, only a short segment of prolapse is produced or the patient is found to have only a mucosal prolapse, a Delorme operation may be performed instead.

COMPLICATIONS

Partial separation of the mucosal anastomosis after mucosal sleeve resection is not uncommon and usually does not warrant intervention. After perineal rectosigmoid resection, anastomotic separation may lead to leakage and pelvic sepsis, which must be treated with bowel rest and antibiotics or, in extreme cases, with débridement, repair, and stoma formation.

Early postoperative bleeding from the mucosal edges or, in the case of perineal rectosigmoidectomy, from the presacral space may be observed. Late postoperative bleeding may result from tearing of the sutures through the mucosa or from separation of the anastomosis. All significant bleeding should be evaluated and controlled in the operating room (OR), with the source of the bleeding dictating the type of repair required.

Anastomotic strictures may occur after either mucosal sleeve resection or perineal rectosigmoidectomy. They are treated with serial dilations either at home or in the OR.

OUTCOME EVALUATION

The advantages of the perineal procedures include (1) the option to use spinal anesthesia, (2) avoidance of peritoneal adhesions, (3) short hospital stays (1 to 4 days), (4) a lower risk of injury to the pelvic nerves, (5) reduced pain, and (6) the opportunity for concomitant repair of other anorectal problems (e.g., sphincter defects, hemorrhoids, rectoceles, cystoceles, and vaginal prolapse). The disadvantages include (1) a higher recurrence rate and (2) reduced improvement of any fecal incontinence.

Reported recurrence rates for the perineal approaches range from 5 to 21%^{11–13} and are higher than those for the abdominal approaches; however, the perineal repairs can be performed multiple times in the same patient as necessary.¹⁴ Because they are less invasive, perineal procedures generally carry a lower morbidity than abdominal procedures do, with the majority of the complications being medical in nature.^{11,12}

Whereas constipation is neither exacerbated nor alleviated by the perineal procedures, continence is significantly improved, although not as much as it is improved by the abdominal procedures.^{15,16} The improvement in continence seen after both abdominal and perineal procedures for rectal prolapse is related to cessation of rectoanal inhibition and recovery of sphincter function with reduction of the prolapse. The lesser improvement reported after perineal procedures may be related to sphincter stretching or, in the case of perineal rectosigmoidectomy, to loss of the rectal reservoir. A comparison of various perineal procedures—including the Delorme procedure, perineal rectosigmoidectomy, and rectosigmoidectomy with levatorplasty—found that the addition of a levatorplasty yielded the greatest improvement in continence, the least morbidity, and the lowest recurrence rate.¹⁶

As already mentioned in this chapter, we also add a transperineal colonic J-pouch whenever feasible. Because the incidence of rectal prolapse peaks in the sixth and seventh decades of life, patients undergoing these procedures frequently are elderly and have significant comorbid conditions.¹⁷ The perineal procedures are economically and physiologically advantageous in the short term and are therefore ideal for elderly patients or for any patients with multiple comorbid conditions, as well as for those who are at high operative risk or who need combined intervention from various pelvic surgical specialists. In these patients, who generally have limited life expectancies, the high risk of recurrence associated with the perineal procedures may be irrelevant. Perineal operations may also be indicated for patients who have undergone multiple previous abdominal operations and are likely to have dense adhesions, as well as for young men who do not wish to risk impairment of sexual function.

Abdominal Procedures

OPEN RECTOPEXY

Resection Rectopexy (Frykman-Goldberg Procedure)

Just as with perineal procedures, patients undergo mechanical and antibiotic bowel preparation on the day before surgery. Before operation, parenteral antibiotics and subcutaneous heparin are administered, and sequential compression devices are placed on the legs.

After induction of general anesthesia, the patient is placed in the modified lithotomy position with the legs in padded stirrups. If there is a history of one or more previous pelvic operations, bilateral ureteral stents are placed by a urologist, and a urinary catheter is inserted. The rectum is irrigated with saline through a transanally placed mushroom catheter until the effluent is clear, after which point, additional irrigation is undertaken with a povidone-iodine solution. The catheter is left in place for the initial portion of the procedure, and the extra effluent is allowed to drain into a plastic bag secured to the catheter. The surgeon stands on the patient's left side.

Operative technique *Step 1: initial incision and exploration* A low midline or Pfannenstiel incision is made, the pelvis is explored, a Balfour or Buchwalter retractor is placed, and the small bowel is packed into the upper abdomen.

Step 2: mobilization of the sigmoid colon The sigmoid colon is mobilized away from the left lateral wall by incising the lateral

peritoneal reflection [see Figure 5a]. Because the sigmoid colon is redundant in patients with rectal prolapse, minimal mobilization is performed, since acquiring length to perform a tension-free anastomosis is easily accomplished. For the same reasons, the splenic flexure is not mobilized. The gonadal vessels and the ureter are identified and swept posteriorly. The peritoneal incision is continued to the left of the rectum, curving anteriorly in the rectouterine or rectovesical sulcus. The peritoneum at the base of the sigmoid mesentery on the right is also incised, and this incision is continued to the right of the rectum to unite with the previous incision at the anterior rectum.

Step 3: proximal transection of the sigmoid colon and placement of a stapler anvil The proximal point of transection is chosen by finding an area of colon that easily falls into the

pelvis and is proximal to the redundant sigmoid colon. This level of the colon, the sigmoid-descending portion, is circumferentially cleaned of surrounding tissue. A straight clamp is placed proximally and an adjacent bowel clamp distally. The bowel is divided with a knife along the straight clamp. The straight clamp is released, and three Babcock forceps are placed to hold open the lumen. A purse-string suture of 2-0 Prolene is placed, and the head of a 33 mm circular stapler is secured in the lumen. Alternatively, a purse-string clamp may be used.

Step 4: division of the sigmoid mesentery The mesentery of the sigmoid colon is clamped, ligated, and divided close to the colon [see Figure 5b]. The superior rectal vessels are carefully preserved.

Step 5: mobilization of the rectum and division of the lateral ligaments A Babcock clamp is placed on the rectal stump and lifted upward. The avascular plane of areolar tissue between the mesorectum and the presacral fascia is identified and divided with the electrocautery. A St. Marks' retractor is placed behind the rectum to provide traction and then advanced with dissection distally along the rectum to the level of the coccyx. Again the superior rectal artery is preserved to avoid necrosis of the rectum.

Dissection of the right side of the rectum is performed with the surgeon standing to the patient's left. The left hand places traction on the rectum while the right hand uses the electrocautery to divide the entire lateral stalk in a posterior-to-anterior direction down to the level of the levators. The St. Marks' retractor is used to retract the tissues of the side-wall away from the rectum.

Dissection of the left side of the rectum is performed with the surgeon on the patient's right. Again, the left hand places traction on the rectum while the right hand performs the dissection in a posterior-to-anterior direction.

Dissection anterior to the rectum is performed by using the retractor to place traction on either the uterus (in women) or the bladder (in men) and then proceeding anterior to the rectum down to the level of the lower third of the vagina (in women) or below the seminal vesicles (in men).

Step 6: placement of sutures for rectopexy With upward traction applied to the rectal stump, horizontal mattress sutures of 2-0 Prolene with a large heavy needle (i.e., CT-1) are placed to perform the rectopexy. Starting on one side, a suture is placed through the peritoneum and the endopelvic fascia adjacent to the rectum, with care taken not to penetrate the rectal wall. The suture is guided through the presacral fascia and the periosteum to the side of the midline and approximately 1 cm below the level of the sacral promontory. A significant amount of force is usually needed to penetrate the bone of the sacrum to ensure stability of the sutures placed. It is then completed by passing it back through the peritoneum and the endopelvic fascia. One or two sutures are placed on each side; they are left untied and are tagged with hemostats.

Step 7: transection of bowel at the upper rectum The rectosigmoid junction is identified on the basis of the splaying of the taeniae coli, the absence of appendices epiploicae, and the proximity to the sacral promontory. This junction marks the site of distal transection. Proctoscopic examination is helpful for determining the appropriate location. Transection may be performed with a stapler, a purse-string suture clamp, or a knife followed by a handsewn purse-string suture.

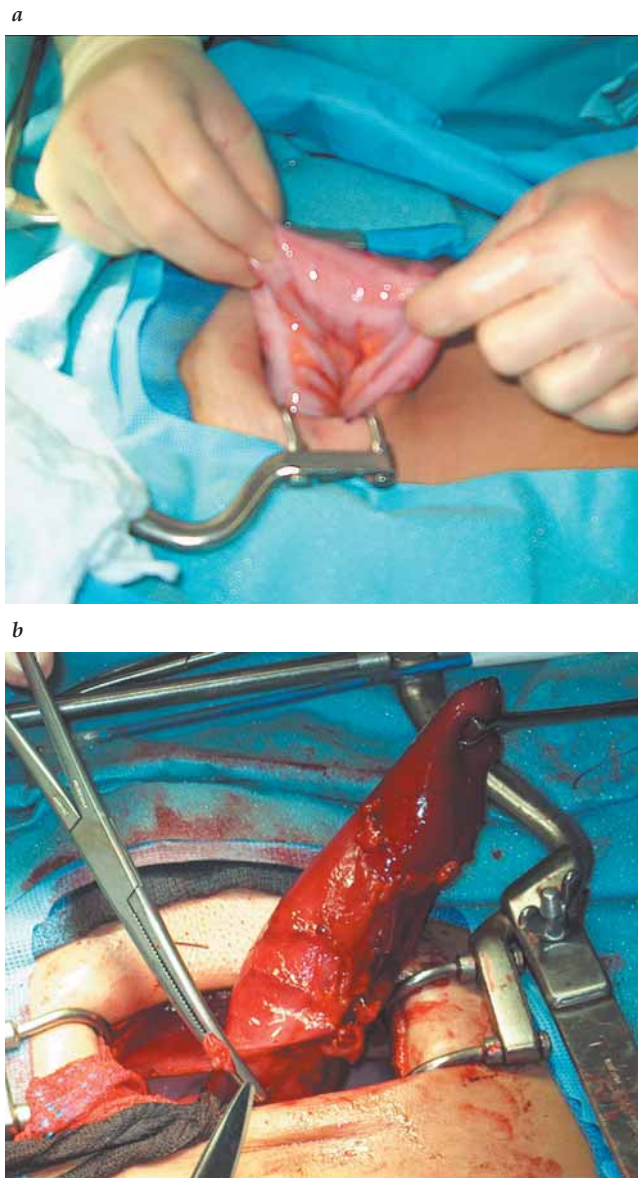


Figure 5 Open resection rectopexy. (a) The redundant sigmoid is mobilized through the abdominal wound. (b) The proximal sigmoid is transected, and the sigmoid mesentery is clamped, ligated, and divided.

Step 8: completion of colorectal anastomosis The circular stapler is advanced through the anus to the rectal stump. Under the manual and visual guidance of the abdominal and perineal operating surgeons, the trocar is advanced and the anvil engaged. The circular stapler is closed and fired. The stapler is then gently removed, and the “doughnuts” are checked for integrity. The anastomosis is tested for leaks by filling the pelvis with irrigant, clamping the colon proximal to the anastomosis, and insufflating air into the rectum. Air bubbles from the anastomosis indicate a leak that requires suture reinforcement or anastomosis reconstruction. The rectopexy sutures are secured snugly to complete the procedure, after which flexible sigmoidoscopy is performed to exclude narrowing of the rectum from the rectopexy sutures. If any narrowing is noted one or more can be removed and replaced as needed so as to prevent narrowing. Ultimately the abdomen is irrigated and closed in the usual fashion.

An alternative approach to this step is to perform endoscopic visualization of the anastomosis while simultaneously insufflating air through either the rigid proctoscope or the flexible sigmoidoscope. This method allows reliable confirmation of mucosal viability and anastomotic integrity. Moreover, if any supplemental anastomotic reinforcement sutures are needed, they can be placed much more easily at this time than after the rectopexy sutures have been secured. Sheets of sodium hyaluronate–based bioresorbable membrane are placed before closure of the fascia to help minimize postoperative adhesion formation; at our institution, these sheets are routinely used during most laparotomies.¹⁸ The abdominal incision is closed in the usual fashion.

Postoperative care After operation, the patient is started on a clear liquid diet and then advanced to a regular diet when bowel function returns. The bladder catheter is removed on postoperative day 1, when ambulation also begins.

Troubleshooting Either suture rectopexy or sigmoid resection can be performed alone by following some of the steps just outlined (see above). Circumferential mobilization of the rectum to the level of the coccyx posteriorly and the upper third of the vagina anteriorly, with division of the lateral ligaments, is advocated to minimize recurrence. Division of the lateral ligaments increases the risk of postoperative constipation; however, inadequate distal mobilization or posterior mobilization performed without lateral ligament division results in laxity of the rectum and the attachments below the level of sacral fixation, which increases the risk of early recurrence. During the sigmoid resection, it is important to remove all redundant bowel; however, it is equally important to ensure that the anastomosis is tension free and well vascularized. During both rectal mobilization and sigmoid resection, careful attention should be paid to preserving the superior rectal artery and the sacral nerves.

Complications Presacral bleeding may result from placement of sutures in the presacral fascia and consequent injury to the presacral veins. It may be controlled by tying down the sutures and applying direct manual pressure. For persistent bleeding, thumbtacks may be required.

Injury to the pelvic nerves and consequent impotence are possibilities with any procedure in which the rectum is mobilized. Performing the dissection close to the bowel wall minimizes the chances that these complications will occur.

Suturing the rectum too close to the sacrum may compress the lumen. This problem may be corrected by removing and

replacing the sutures. Any uncertainty about rectal compression can be resolved by means of intraoperative proctoscopy.

The incidence of abdominal sepsis from an anastomotic leak can be minimized by ensuring a well-vascularized and tension-free anastomosis.

LAPAROSCOPIC RECTOPEXY

Laparoscopic Resection Rectopexy

Laparoscopic resection rectopexy is not commonly performed. This procedure necessitates an extraction site in the form of a Pfannenstiel, or lower midline, incision. An entire procedure of open resection rectopexy can also be performed though similarly small incisions making laparoscopic approach unnecessary. In addition, when resection is performed, the rectopexy should be performed with sutures and not mesh to avoid septic complications. Placement of sutures requires significant force to penetrate the sacral bone which cannot usually be accomplished laparoscopically. However, since this procedure is described in the literature, the steps will not be outlined here.

Preoperative management includes full mechanical bowel preparation. In addition, cefotetan, 2 g intravenously, is administered along with heparin, 5,000 units subcutaneously, at the start of the operation.

After the induction of general anesthesia, the patient is placed in the modified lithotomy position with the legs in pneumatic compression stockings and padded stirrups. The arms are tucked at the sides, and extra care is taken to secure the patient to the bed because of the rotation and tilting required during surgery. Two or more monitors are placed on opposite sides of the operating table. The rectum is irrigated with saline through a transanally placed mushroom catheter until the effluent is clear, at which point, additional irrigation is initiated with a povidone-iodine solution. The catheter is left in place for the initial portion of the procedure, and the extra effluent is allowed to drain into a plastic bag secured to the catheter. If requested, bilateral ureteral stents are placed by a urologist, and a urinary catheter and an orogastric tube are inserted. The abdomen is shaved, prepared with povidone-iodine solution, and appropriately draped.

Operative technique *Step 1: placement of ports* A 10 mm trocar is placed infraumbilically or supraumbilically (depending on patient size) by means of the open Hasson technique; this port will be used for the camera. Pneumoperitoneum is established, and two additional 10 mm trocars are placed along the lateral edge of the rectus abdominis in the right midabdomen and the right iliac fossa [see Figure 6]. If necessary, one or two additional trocars may be placed laterally on the left of the abdomen to assist with sigmoid retraction.

Step 2: mobilization of the sigmoid colon and rectum The operating table is tilted to the patient's right to facilitate medial retraction of the left colon, which is gently grasped with a Babcock forceps. An ultrasonic scalpel is placed through the right lower port and used to mobilize the sigmoid colon and the descending colon away from the left lateral side wall. Early identification of retroperitoneal structures, including the left ureter and the gonadal and iliac vessels, is achieved. The extent of mobilization is limited because the goal is to resect only the redundant portion of the colon. Laparoscopic resection rectopexy is the only type of left-side resection in

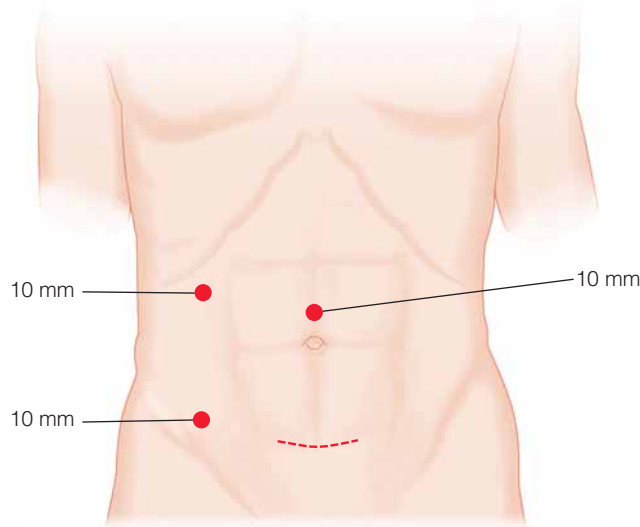


Figure 6 Laparoscopic resection rectopexy. Shown is the recommended port placement. A 10 mm trocar is placed in the periumbilical region by means of an open technique. Two 10 mm trocars are then placed in the right abdomen.

which the splenic flexure is deliberately not mobilized to prevent redundancy and therefore recurrence of the prolapse. Dissection is extended into the pelvis, and the upper lateral rectal attachments are divided. With cephalad traction applied to the rectum, the mesorectum is circumferentially divided to the level of the coccyx.

Step 3: division of the mesenteric vessels The peritoneum of the left mesocolon is scored to permit identification and preparation of the vessels for transection. After both creters are visualized, a 10 mm bipolar cutting instrument is inserted through the right iliac fossa port, and the vessels are individually transected. We try to preserve the inferior mesenteric and superior rectal vessels in these operations.

Step 4: intracorporeal transection of the rectum at the rectosigmoid junction At the point where the taenia coli coalesce, the rectosigmoid junction is divided with a laparoscopic linear stapler passed through the right lower quadrant port.

Step 5: extracorporeal transection of the proximal bowel A small (4 to 5 cm) Pfannenstiel incision is made, a wound protector drape is inserted, and the sigmoid is delivered through the wound. Transection of the proximal bowel is performed in an area of the colon that easily reaches the sacral promontory without redundancy. A purse-string suture is placed in the edge of the proximal bowel, and the anvil of a 33 mm circular stapler is inserted and secured. The bowel is then placed back into the abdomen.

Step 6: placement of rectopexy sutures Via the Pfannenstiel incision, mattress sutures of nonabsorbable material are passed through the peritoneum and fascia on the lateral rectum, through the presacral fascia just off the midline and 1 cm below the sacral promontory, and back through the lateral tissue. One or two sutures are placed on each side but are not secured until the anastomosis has been created.

Step 7: creation of anastomosis The circular stapler is inserted transanally to the level of the rectal stump, and the trocar is carefully advanced. The anvil is engaged on the trocar, the surgeon confirms that there is no inclusion

of extraneous tissue and no rotation of the bowel or its mesentery, and the stapler is closed. The locations of the ureters and the vagina are reconfirmed to ensure that these structures are not incorporated into the staple line. The stapler is fired, and the tissue doughnuts are inspected to verify circumferential integrity. The anastomosis should be tension free and well vascularized. Its integrity is tested by insufflating air into the rectum with the anastomosis submerged in fluid, and any leaks identified are reinforced with sutures. As with open rectopexy, endoscopic visualization can be a useful alternative; this is, in fact, our preferred approach for all circular stapled anastomoses. Insufflation of air during visualization completes the assessment.

Finally, the rectopexy sutures are tied and the abdominal and port site incisions are closed.

Postoperative care Patients are immediately started on a clear liquid diet and advanced to a solid diet when bowel function returns. The bladder catheter is removed on postoperative day 1.

Laparoscopic Suture or Mesh Rectopexy

Patient preparation, positioning, and placement of ureteral stents are the same for laparoscopic suture or mesh rectopexy as for laparoscopic resection rectopexy.

Operative technique **Step 1: placement of ports** An infraumbilical or supraumbilical port is placed, followed by two additional ports in the lower abdomen (one in each quadrant), positioned so that the camera and the needle holders can be exchanged to afford access to both sides of the rectum [see Figure 7]. The surgeon stands to the patient's left.

Step 2: mobilization of the rectum Two bowel graspers are used to retract the rectosigmoid junction and the midrectum upward. An ultrasonic scalpel is employed to perform the presacral dissection and to divide the entire lateral ligaments.

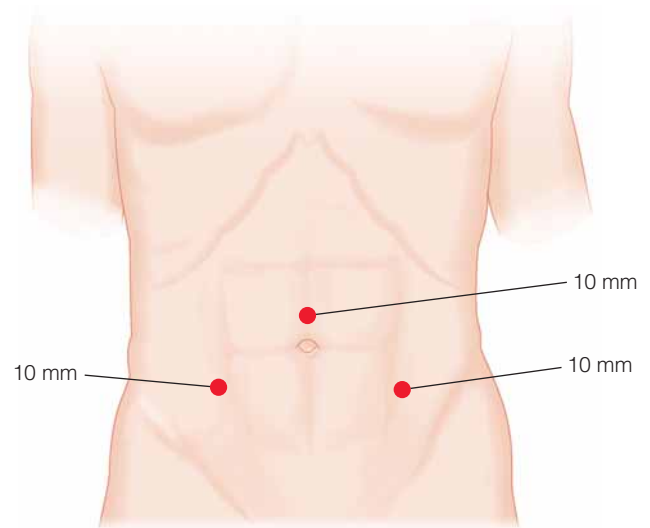


Figure 7 Laparoscopic suture or mesh rectopexy. A 10 mm trocar is placed in the periumbilical region. Two additional 10 mm trocars are then placed, one in each lower quadrant.

Step 3: intracorporeal placement of mesh A piece of mesh is rolled up and inserted through a port. The mesh is tacked to the sacrum with a laparoscopic stapler, and the lateral edges of wrapped mesh are secured to the rectal wall with sutures [see Figure 8]. This type of posterior mesh sling procedure is also known as the modified Ripstein procedure.

Postoperative care The patient is started on a clear liquid diet and advanced to a regular diet on the morning of postoperative day 1. The bladder catheter is also removed at this time.

Troubleshooting

Laparoscopic repair of rectal prolapse follows the same basic principles as open repair. There are multiple variant forms of laparoscopic rectopexy, differing not only with respect to technical details (e.g., resection versus no resection and suture versus mesh) but also with respect to whether the procedure contains an open component or is fully laparoscopic. The essential steps, however, are the same in all of the variants and include adequate mobilization of the rectum, careful placement of sutures, and appropriate resection with healthy anastomosis of the segments. For example, in the approach to laparoscopic resection rectopexy we describe (see above), most of the mobilization is performed laparoscopically, with resection, anastomosis, and suture placement performed in an open fashion, whereas in laparoscopic rectopexy performed without resection, the mesh is secured intracorporeally. The modified Ripstein procedure (see

above) can be performed in a totally laparoscopic fashion if desired.

Complications

Intraoperative complications of laparoscopic rectopexy include inadvertent enterotomy or colotomy, ureteral injury, and organ injury from trocar placement. Most of these injuries are associated with the presence of adhesions and can usually be prevented by careful intra-abdominal dissection in appropriate planes. The incidence of ureteral injury can be minimized by early identification of these structures, which may be facilitated by the use of ureteral catheters.

Vascular injury can occur at several different points of the operation. Injury to the epigastric vessels during port placement is usually avoided by transilluminating the abdominal wall with the camera to identify the vessels. The iliac and gonadal vessels are retroperitoneal structures, which, like the ureter, can be avoided with careful dissection and identification. The mesenteric vessels must be properly identified and controlled with graspers before the mesocolon is transected. The use of endoscopic clips as the sole means of vascular control before transection is discouraged; the calcified vessels commonly encountered in this mainly elderly population lead to clip slippage and incomplete hemostasis.

The incidence of anastomotic leakage can be minimized by ensuring a tension-free, nonrotated, airtight connection with a good blood supply and by making sure not to incorporate diverticula into the suture line.

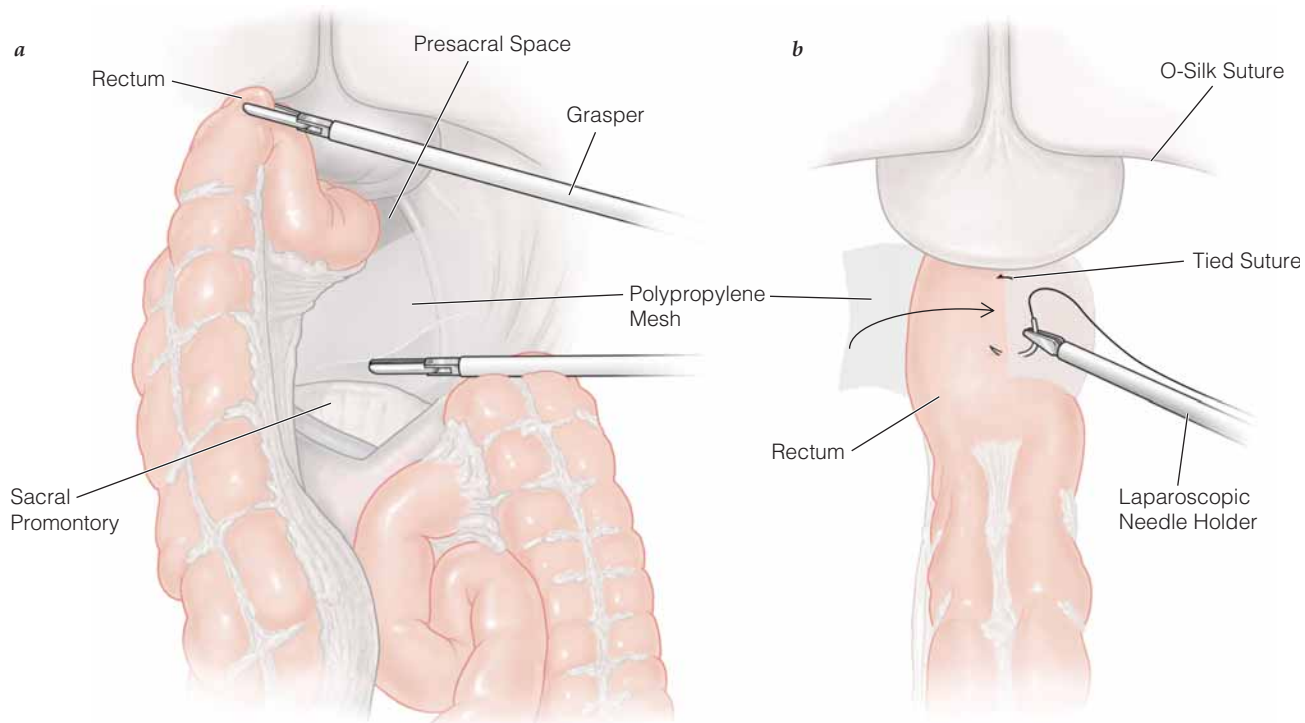


Figure 8 Laparoscopic mesh rectopexy. (a) A piece of mesh is inserted into the abdomen through a port and then stapled to the sacrum. (b) The lateral edges of the mesh are wrapped around three quarters of the rectal circumference and sutured to the rectal wall.

Surgical site infections are a common complication of all colorectal resections. Their incidence can be minimized by performing appropriate bowel preparation, providing intravenous antibiotic prophylaxis before surgery, and, possibly, employing a plastic wound protector at the site of colon extraction. Copious wound irrigation before closure at the end of the procedure is also helpful.

MESH AND SPONGE REPAIRS

Ripstein Procedure

Preoperative care and patient positioning are the same for the Ripstein procedure as for open resection rectopexy.

Operative technique *Step 1: initial incision and exploration* Step 1 in the Ripstein procedure is identical to step 1 in resection rectopexy.

Step 2: mobilization of the rectum The lateral peritoneal folds of the rectum in the pelvis are incised from the rectosigmoid junction to the anterior midline on each side. With the St. Marks' retractor used to supply traction, the rectum is dissected away from the sacrum with the electrocautery down to the level of the coccyx. Anterior dissection separates the rectum from the vagina or the seminal vesicles. The upper one third to two thirds of the lateral stalks are divided to facilitate mesh placement.

Step 3: placement of mesh A 5 cm rectangle of mesh is placed around the anterior rectum at the level of the peritoneal reflection and firmly sutured to the presacral fascia on one side, 5 cm below the promontory [see Figure 9a]. The rectum is pulled taut with upward traction, partial-thickness nonabsorbable sutures are placed in rows along the anterior rectum to hold the mesh in place, and the mesh is sutured to the presacral fascia on the other side [see Figure 9b]. The sling is left loose enough to allow two fingers to pass between the bowel and the sac.

Because of the high risk of constipation and even obstipation after anterior mesh encirclement, a modified version of the Ripstein procedure was developed that involved posterior fixation of mesh to the sacrum, leaving the anterior rectal wall free of any potential constriction. In this modified approach,

the mesh is first tacked to the sacrum. The lateral edges of the mesh are then wrapped around three quarters of the circumference of the rectum and sutured anterolaterally to the rectal wall. Intraoperative rigid proctoscopy may be helpful for ensuring that the positioning of the mesh does not result in obstruction.

Step 4: closure of the peritoneum The peritoneal reflection is closed so that the mesh is excluded from the peritoneal cavity and the small bowel is prevented from migrating into the pelvis on top of the mesh. The abdomen is irrigated and closed in the usual fashion.

Postoperative care The patient is started on a clear liquid diet and advanced to a solid diet with resumption of bowel function. The bladder catheter is removed 2 days after operation.

Ivalon (Polyvinyl Alcohol) Sponge Repair (Wells Procedure)

Preoperative care and positioning are the same for the Wells procedure as for open resection rectopexy.

Operative technique *Steps 1 and 2* Steps 1 and 2 are the same as in the Ripstein procedure.

Step 3: placement of the sponge A rectangular piece of sterilized and moistened Ivalon (polyvinyl alcohol) sponge is secured in place with mattress sutures passed through the sponge, through the presacral fascia, and back through the sponge. Careful hemostasis is ensured to prevent purulent collections in the area of the sponge. The rectum is retracted cephalad, and the lateral edges of the sponge are folded around it for approximately three quarters of its circumference. The edges are secured to the anterior portion of the rectum with seromuscular sutures [see Figure 10].

Step 4: closure of the peritoneum The pelvic peritoneum is closed to exclude the small bowel from the pelvis and thus prevent it from coming in contact with the sponge.

Postoperative care Postoperative care is the same for the Wells procedure as for the Ripstein procedure.

Complications

Fecal impaction may result from making the sling too tight or from severe constipation caused by leaving a redundant rectosigmoid colon above the level of the repair.

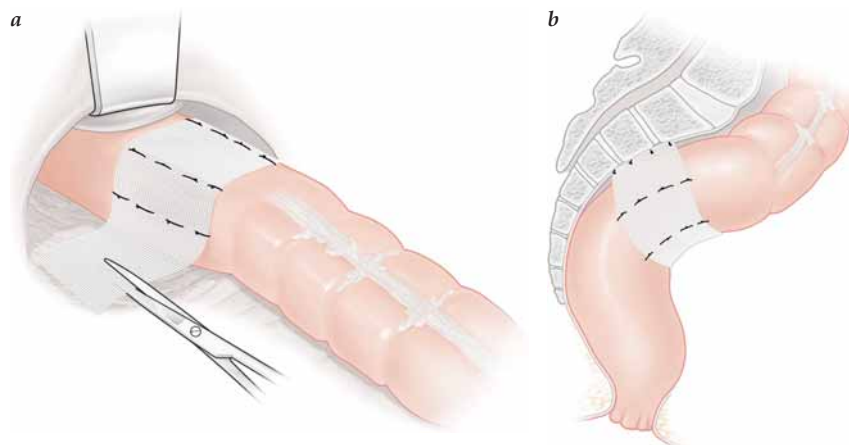


Figure 9 Ripstein procedure. (a) With the rectum under tension, a piece of mesh is sutured to the presacral fascia on one side and then sutured to the muscularis of the anterior rectum. (b) The rectum is then secured to the presacral fascia on the other side to form a sling.

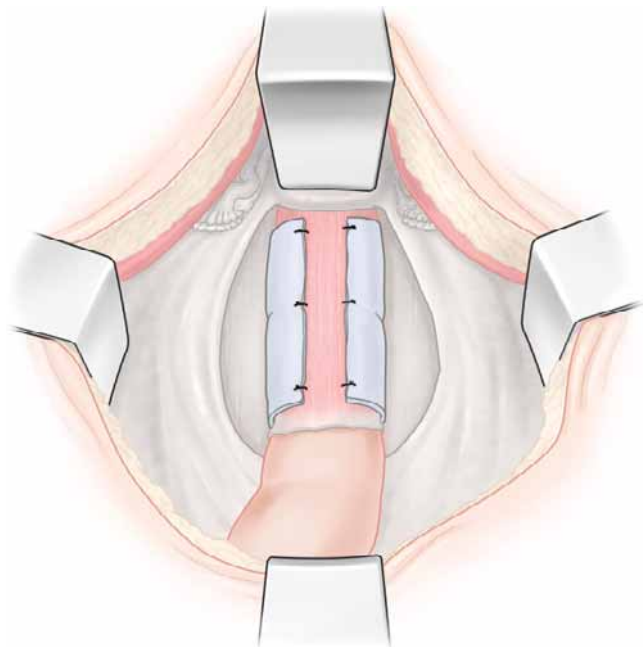


Figure 10 Ivalon (polyvinyl alcohol) sponge repair (Wells procedure). The sponge is anchored to the sacrum. With the rectum under tension, the edges of the sponge are brought around three quarters of the rectal circumference and sutured to the muscularis of the anterior rectum.

Presacral bleeding may result from placement of sutures in the presacral fascia and consequent injury to the veins. If bleeding occurs, the sutures should be immediately secured and manual pressure applied. If these measures fail, thumb-tacks may be required.

Strictures may result at the site of the sling and may be diagnosed by means of barium enema or sigmoidoscopy. If the mesh is wrapped anteriorly, revision may involve laterally transecting the mesh where it is not fused to the rectum, removing the mesh, or resecting the portion of the rectum where stricture occurs. To minimize the risk of this complication, either the mesh should be placed posteriorly (see above) without a circumferential wrap or, if an anteriorly based sling is employed, care should be taken not to encircle the rectum too tightly.

Sepsis may result when placement of full-thickness sutures or erosion into the bowel wall leads to mesh or sponge infection. Pelvic abscesses and fistulas are treated by removing the mesh or sponge and, in some circumstances, by performing a diverting colostomy. Preventive measures include giving perioperative antibiotics, placing seromuscular sutures, and ensuring that the synthetic material is not too tightly wrapped.

Adhesions to the mesh may be associated with small bowel obstruction. This complication can be prevented by reperitonealizing the pelvis to prevent migration of the small bowel onto the foreign substances. Placement of Seprafilm beneath the fascial closure helps reduce adhesions.

OUTCOME EVALUATION

Overall, abdominal operations yield better results than perineal operations with respect to recurrence rates (which

range from 0 to 8%) and functional outcome.¹⁹ The abdominal approach allows the rectum to be maximally mobilized and fixed to the sacrum. In addition, transabdominal procedures can be tailored to the presence or absence of functional disorders (e.g., constipation or incontinence) through the addition or omission of sigmoid resection. Morbidity, however, is greater with abdominal procedures than with perineal procedures. In planning surgical treatment of rectal prolapse, therefore, it is essential to consider risk factors for complications in addition to likelihood of cure.

For many surgeons, posterior rectopexy is the procedure of choice because of its low morbidity and recurrence rates.^{13,20,21} Some 50 to 88% of patients show improved continence,^{22–24} but as many as 53% experience either new-onset constipation or exacerbation of preexisting constipation.²² The constipation is thought to be attributable to rectal denervation resulting from division of the lateral ligaments; however, preservation of these ligaments is associated with a significantly higher (> 50%) recurrence rate.^{25,26} Resection does not decrease recurrence rate but counterbalances preexisting constipation or constipation resulting from lateral ligament division. Resection may also be necessary in those with severely redundant colon despite fecal incontinence to avoid the possibility of future sigmoid volvulus. The type of material used to perform the rectopexy has no effect on recurrence: recurrence rates are the same for suture repairs as for mesh repairs.²⁷ Suture repairs, however, carry a lower risk of associated pelvic sepsis and luminal constriction, especially when compared with repairs involving mesh wrapped around the anterior rectum. Our practice is to perform open resection rectopexy through a small Pfannenstiel incision with minimal mobilization of the sigmoid and complete mobilization of the rectum down to the level of the levators posteriorly and laterally. Complete anterior dissection is not always necessary since these patients already have a deep pouch of Douglas. The superior rectal artery is preserved and the rectopexy is completed with sutures. Since this procedure can be performed with thoracic epidural, it is still a good option in the elderly patient. Our practice, therefore, is to resect the upper one third to one half of each lateral stalk in an attempt to balance functional outcome against cure of the prolapse.

The constipation produced by rectopexy and lateral ligament division may be overcome by adding sigmoid resection to the procedure. Several prospective randomized trials revealed a reduction in postoperative constipation when resection was added to rectopexy in patients with preoperative constipation.^{28,29} Recurrence rates after resection rectopexy were comparable to those after rectopexy alone, and although the resection imposed additional risks (i.e., anastomotic leakage and wound infection), morbidity rates were comparable as well. Continence rates are improved with resection rectopexy because the rectal reservoir is maintained (by limiting resection to the portion of the large bowel above the peritoneal reflection). Because of the risk of pelvic sepsis, resection is combined only with suture rectopexy, not with Ivalon sponge or mesh repairs.

Isolated resection of the sigmoid colon is an effective method of preventing recurrence permanently; limiting the length of the bowel definitively inhibits the mobility of the rectum.³⁰ Recurrence rates are the same for this procedure as for other abdominal procedures, and morbidity is determined

by the level of the anastomosis. Patients with constipation secondary to colonic inertia associated with rectal procidentia may require an extended resection that includes subtotal colectomy with ileorectal anastomosis.³¹

Disadvantages of the open abdominal procedures for rectal prolapse include a significant incidence of peritoneal adhesions, the need for general anesthesia, a longer hospital stay, greater morbidity, and possible compromise of sexual function. Certain disadvantages (e.g., more extensive intra-abdominal invasion, scarring, and longer recovery time) are reduced when the laparoscopic approach is employed. Controlled studies of laparoscopic rectopexy revealed recurrence rates and morbidity comparable to those of open approaches.^{32,33} A subsequent study comparing laparoscopic resection rectopexy with the corresponding open approach found that with the former, although longer operating times were noted, less time was required for return of bowel function, toleration of a regular diet, and hospital stay.³⁴ Another study found that continence improved to a significant extent after laparoscopic rectopexy without significant changes in postoperative constipation.³⁵

Special Situations

INCARCERATION, STRANGULATION, AND GANGRENE

On rare occasions, a rectal prolapse becomes incarcerated. If the bowel is viable, sedation and gentle manual reduction in the emergency department usually suffice. Sprinkling table sugar on the prolapse helps reduce edema.³⁶ If such measures are unsuccessful, paralyzing the perianal muscles with an anal block or general anesthesia in the OR may help resolve the problem. If the incarceration is irreducible or the viability of the bowel is questionable, emergency perineal rectosigmoidectomy should be performed, with or without fecal diversion.³⁷

RUPTURED PROLAPSE

Rupture of the prolapse usually involves opening of the hernia sac and exposure of the small bowel to the perineum. Emergency transabdominal repair is indicated, with closure of the peritoneal hernia sac and suture rectopexy constituting the safest and most efficient repair.

PROLAPSE IN MALE PATIENTS

Prolapse in male patients, although relatively rare, may occur at any age. Rectal mobilization should be modified so as to preserve the presacral nerves, keep from damaging Denonvilliers fascia, and avoid division of one of the lateral ligaments.³⁸ Lateral pararectal tissues carry parasympathetic fibers and are important in normal ejaculatory function.

RECURRENT PROLAPSE

Currently, there is no standardized strategy for primary or recurrent rectal prolapse. Publications regarding recurrent rectal prolapse do not describe a treatment algorithm or rationale for decision-making with regard to choice of the second operation. However, most agree the approach should be tailored to the patient using the same factors as the choice of the initial operation keeping in mind the blood supply to the remaining rectum. The “best” operation should be minimally invasive, include low morbidity and mortality, provide optimal functional results, and minimal risk of recurrence. Some authorities advocate an abdominal procedure for the second operation, regardless of what the initial operation was, because of the superior rates of success with such procedures³⁹; however, care must be taken in performing repeat resectional procedures (e.g., anterior resection after perineal rectosigmoidectomy, or vice versa) because of the risk of bowel ischemia between the two anastomoses if the superior rectal artery is not preserved. In our view, unless the previous anastomosis can be resected in the second procedure, repeat resectional procedures should be avoided.^{39,40} Perineal rectosigmoidectomies are an exception to this broad rule: they can be safely repeated because the recurrent prolapse contains the previous anastomosis.⁴¹ Recurrence rates and morbidity after operative treatment of recurrent rectal prolapse are essentially the same as those after operative treatment of primary rectal prolapse.⁴² Early recurrence (within the first 2 years) is thought to be related to technical factors such as inadequate mobilization of the rectum or inadequate placement of the suture or mesh at the time of the original operation.³⁹ All types of second repairs are feasible, but because of the paucity of published studies, a defined standard of care in strategy is lacking. Extensive investigation should be undertaken before repeat repair to elucidate factors that might predispose to recurrence, such as slow-transit constipation and anismus.

RECTAL PROLAPSE WITH SOLITARY RECTAL ULCER SYNDROME

As many as 80% of patients with solitary rectal ulcer syndrome (SRUS) have an associated rectal prolapse,^{43,44} a finding that indicates a close relationship between these two entities. In cases of symptomatic SRUS associated with asymptomatic prolapse, a trial of medical therapy is warranted⁴⁵; if such therapy fails, surgical intervention with procedures used for rectal prolapse should be considered.⁴⁶ In cases of symptomatic prolapse associated with asymptomatic SRUS, healing of the ulcer can be demonstrated in one third of patients undergoing operation for the prolapse.⁴⁶

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Figures 1, 3, and 6 through 10 Tom Moore.

37 ANAL PROCEDURES FOR BENIGN DISEASE

Ira J. Kodner, MD, FACS, FASCRS

Operative Management of Hemorrhoids

The frequency of hemorrhoid surgery continues to diminish. More patients seem to be achieving adequate symptomatic relief by means of bowel control medications and improved diet (e.g., increased intake of fiber, fruit, vegetables, and grain) [see 5:17 *Benign and Malignant Rectal, Anal, and Perineal Problems*]. It is probable that both for these reasons and because more and better patient information is available, fewer patients today have hemorrhoids that progress to a stage advanced enough to necessitate operative treatment for relief of symptoms.

OPERATIVE PLANNING

It is important to distinguish between internal and external hemorrhoids [see Figure 1]. Internal hemorrhoids are treated to relieve specific symptoms, including prolapse and bleeding,

not simply because hemorrhoidal tissue was seen on routine examinations. Prolapsing tissue occasionally results in maceration of the perianal skin that may not be clearly evident at the time of examination, especially if the patient is in the prone position. External hemorrhoids are treated because they thrombose and cause pain. No other symptoms of the anorectum should be attributed to the presence of hemorrhoids [see Table 1]; in particular, difficulties with bowel movements (e.g., straining, the need for digital evacuation of the rectum, and cramping abdominal pain) must not be ascribed to hemorrhoids.

Accordingly, the ability to recognize and diagnose the spectrum of pelvic floor abnormalities (of which rectal prolapse is the most florid manifestation), especially obstructed defecation, is critical to the decision whether to correct hemorrhoids

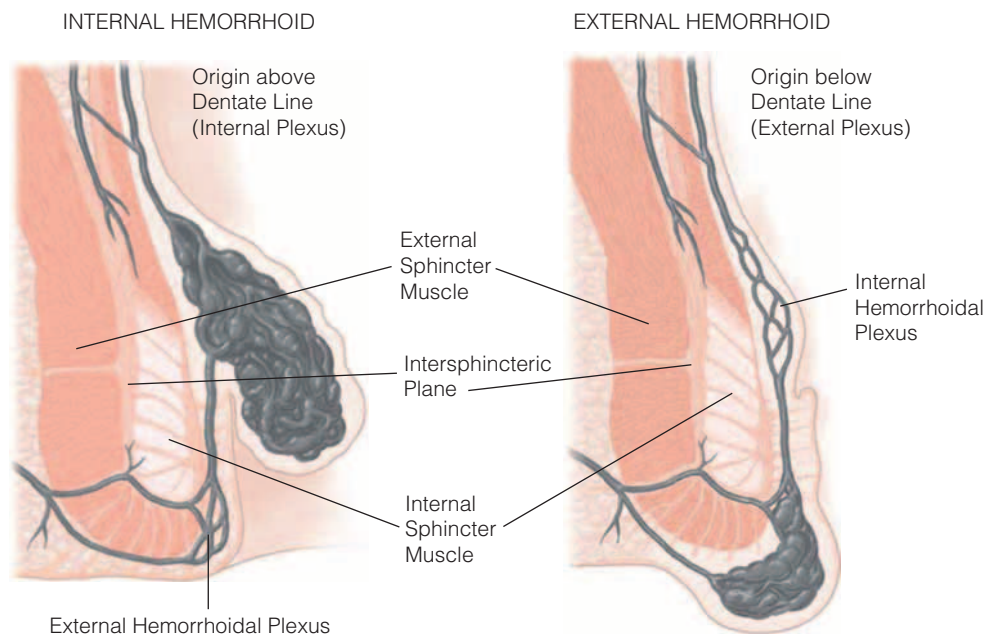


Figure 1 Operative management of hemorrhoids. A key issue is the differentiation of internal hemorrhoids from external hemorrhoids. Internal hemorrhoids (*left*) originate from the internal hemorrhoidal plexus, above the dentate line. External hemorrhoids (*right*) originate from the external hemorrhoidal plexus, below the dentate line.

Table 1 Anal Symptoms Mistakenly Attributed to Hemorrhoids

Symptoms	Cause
Pain and bleeding after bowel movement	Ulcer/fissure disease
Forceful straining to have bowel movement	Pelvic floor abnormality (paradoxical contraction of anal sphincter)
Blood mixed with stool	Neoplasm
Drainage of pus during or after bowel movement	Abscess/fistula, inflammatory bowel disease
Constant moisture	Condyloma acuminatum
Mucous drainage and incontinence	Rectal prolapse
Anal pain with no physical findings	Caution: possible psychiatric disorder

surgically. Attempting to alleviate nonhemorrhoidal symptoms by means of hemorrhoid surgery is likely to yield unsatisfactory results for both the patient and the surgeon. It is not uncommon for anal fissure/ulcer disease to coexist with hemorrhoids, in which case, the chances of a good operative result can be increased by performing a posterior lateral internal sphincterotomy at the time of hemorrhoid surgery.

Before embarking on the surgical treatment of hemorrhoids, one must always rule out neoplastic disease, compromise of the immune system, and defective clotting mechanisms. Patients with a personal or family history of colorectal cancer and those 50 years of age or older should undergo colonoscopy to eliminate the possibility of polyps or cancer before surgical treatment of hemorrhoids is initiated. The patient's general health status and ability to tolerate pain and an operative procedure should also be taken into account. The postoperative response to anorectal surgery varies enormously among patients. For example, young men tend to strain to have bowel movements after anorectal procedures, and this tendency can lead to bleeding and disruption of postoperative healing. These patients often benefit from the administration of parenteral pain medication for the first 12 to 24 hours after operation, which usually requires hospitalization. Elderly patients, on the other hand, prefer not to be in the hospital. For these patients, single elastic ligation of individual clusters of internal hemorrhoids is performed in the outpatient office.

The next step is to determine the appropriate procedure for the patient. The options include (1) elastic ligation of internal hemorrhoids, (2) excision of thrombosed external hemorrhoids, (3) complete excisional hemorrhoidectomy, and (4) elastic ligation of internal hemorrhoids combined with excision of external hemorrhoids. One should always consider whether complete sigmoidoscopy, rigid or flexible, will be necessary at the time of the procedure and whether anal sphincterotomy will be indicated, especially in young men with a history of straining. This second consideration is important because many patients are treated for hemorrhoids when, in fact, their primary disease is anal ulcer/fissure disease, the symptoms of which are pain and some bleeding at defecation. These are not symptoms that can be attributed to hemorrhoids. If a patient undergoes hemorrhoid surgery when the primary disease is anal fissure, proper healing will be impeded.

Finally, one should explain the procedure and its attendant risks to the patient in the outpatient office because in most cases, given the restrictions imposed by health care insurers and managed care administrators, one will not see the patient again until arriving at the day of operation. Specific complications to be discussed preoperatively include urinary retention, bleeding, and infection. In the event that several symptomatic hemorrhoids are present, surgeon and patient should jointly decide between multiple small procedures done in the office and a single larger procedure done in the operating room (OR). Individual economic concerns, as well as employment and lifestyle, should be considered.

Special Situations

Acute thrombosed external hemorrhoids This condition is signaled by acute pain and a swelling blood clot within the skin-covered external hemorrhoid. Often the clot is eroding through the skin, causing bleeding that may be frightening to the patient but is typically insignificant. If I encounter this problem days after its onset, I generally treat it with bowel control and topical medications as the process resolves. If the hemorrhoid is acutely painful or the clot is eroding, the best therapy is surgical excision of the external hemorrhoid, with the anoderm left intact; this is best done with the patient under adequate local anesthesia. Mere evacuation of the clot is rarely appropriate.

Postpartum hemorrhoids The postpartum rosette of acute thrombosed external (and, often, prolapsed internal) hemorrhoidal tissue is appropriately treated with hemorrhoidectomy (see below), carried out as soon after delivery as is convenient. The risk of infection is minimal, and I know of no good reason to send a new mother home with hemorrhoids in addition to a new baby and a healing episiotomy.

OPERATIVE TECHNIQUE

Step 1: Positioning

Operative treatment of hemorrhoids, like the vast majority of anorectal procedures, should be done with the patient in the prone-flexed position [see Figure 2]. The transporting stretcher should be kept in the room. The patient will be

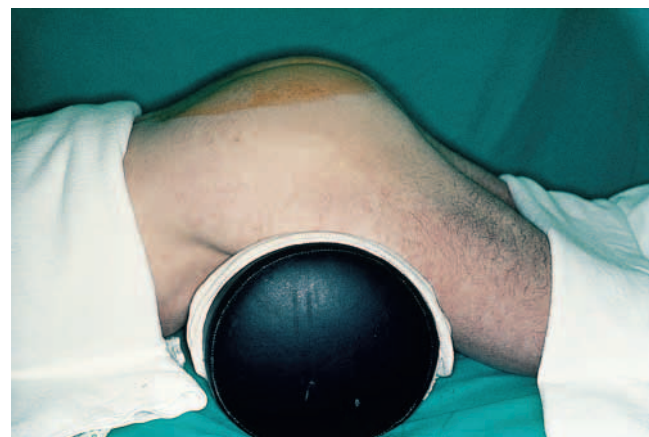


Figure 2 Operative management of hemorrhoids. The patient is positioned on the operating table in the prone-flexed position, with a soft roll under the hips.

given intravenous (IV) narcotics to allow painless injection of local anesthetics, and if any respiratory compromise results because of the prone-flexed position, the patient can quickly be returned to the supine position on the stretcher until respiration resumes without difficulty.

Step 2: Intravenous Sedation and Local Anesthesia

Before administering a local anesthetic, I usually give the following drugs for sedation: midazolam, 2 to 5 mg, given in the holding area for sedation and amnesia; alfentanil, 0.5 to 1 mg, or fentanyl, 50 to 100 mg, for analgesia to help alleviate the discomfort of the local anesthetic injection; and propofol, 20 to 50 mg, or methohexital, 20 to 50 mg, to achieve patient cooperation with the injection. Sedation is followed by the injection into perianal tissue of 40 mL of bupivacaine (0.5%) along with a buffer that is added immediately before injection (0.5 mL of 8.4% sodium bicarbonate [1 mEq/mL] added to 50 mL of local anesthetic). If resection is anticipated, epinephrine (1:200,000) is usually included with the local anesthetic. To achieve adequate local anesthesia, 5 mL of bupivacaine is injected into the subcutaneous tissue in each quadrant of the tissue immediately surrounding the anus [see Figure 3a]. Next, 10 mL of local anesthetic is injected deep into the sphincter mechanism on each side of the anal canal [see Figure 3b].

Step 3: Anoscopy or Sigmoidoscopy

Anoscopy, sigmoidoscopy, or both should be performed at this point if neither procedure was done before the operation.

Step 4: Sphincterotomy

As noted, sphincterotomy should always be considered, especially if a hypertrophic band of the lower third of the internal sphincter muscle persists after the local anesthetic has been injected and an anoscope has been inserted. It is always best to obtain permission to do this beforehand on the operative consent form.

Step 5: Treatment of Hemorrhoids

Elastic ligation of internal hemorrhoids This is a very safe operation because by the nature of the banding procedure [see Figure 4], bridges of normal mucosa are maintained between treated clusters of hemorrhoids. Any clusters of tissue with squamous metaplasia and obviously friable internal hemorrhoids can be treated in this manner. I find that these tissue clusters are not always confined to the three classic positions identified for hemorrhoids and that, in many cases, it is necessary to band three or four clusters. If the bands do not stay on, then the tissue probably need not be treated and no further action need be taken.

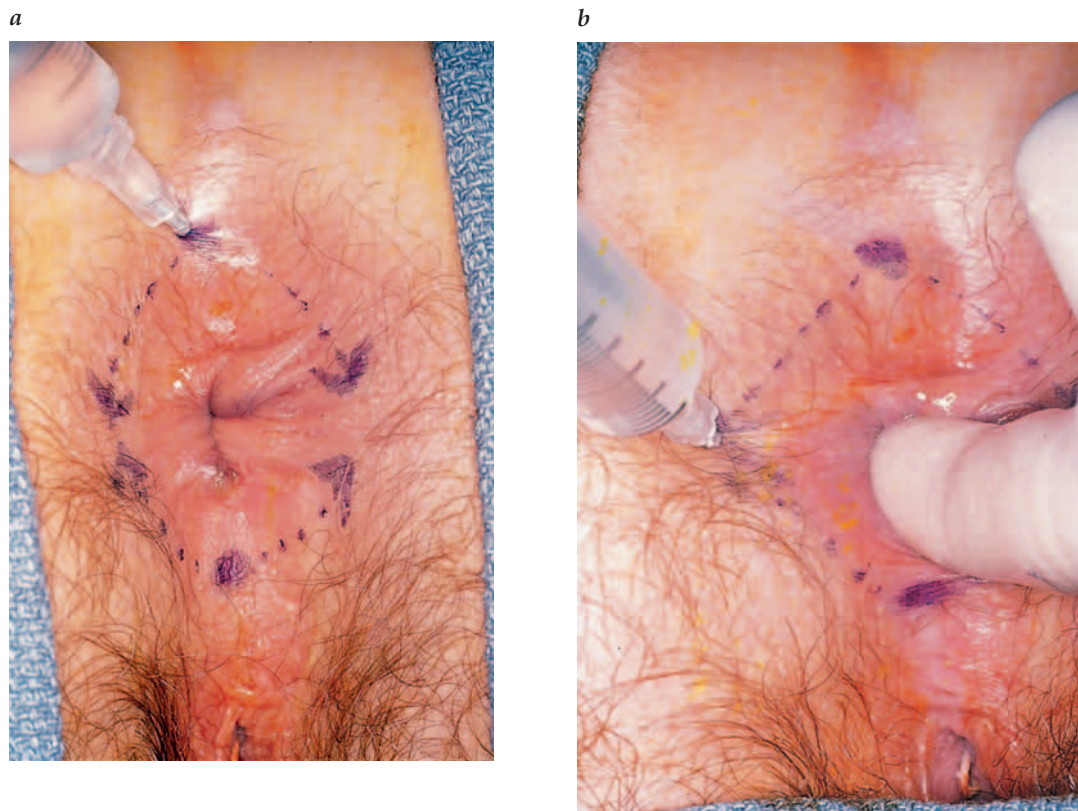


Figure 3 Operative management of hemorrhoids. (a) Five milliliters of bupivacaine is injected into subcutaneous tissue. (b) Ten milliliters of local anesthetic is injected deep into the sphincter muscle on each side of the anal canal.

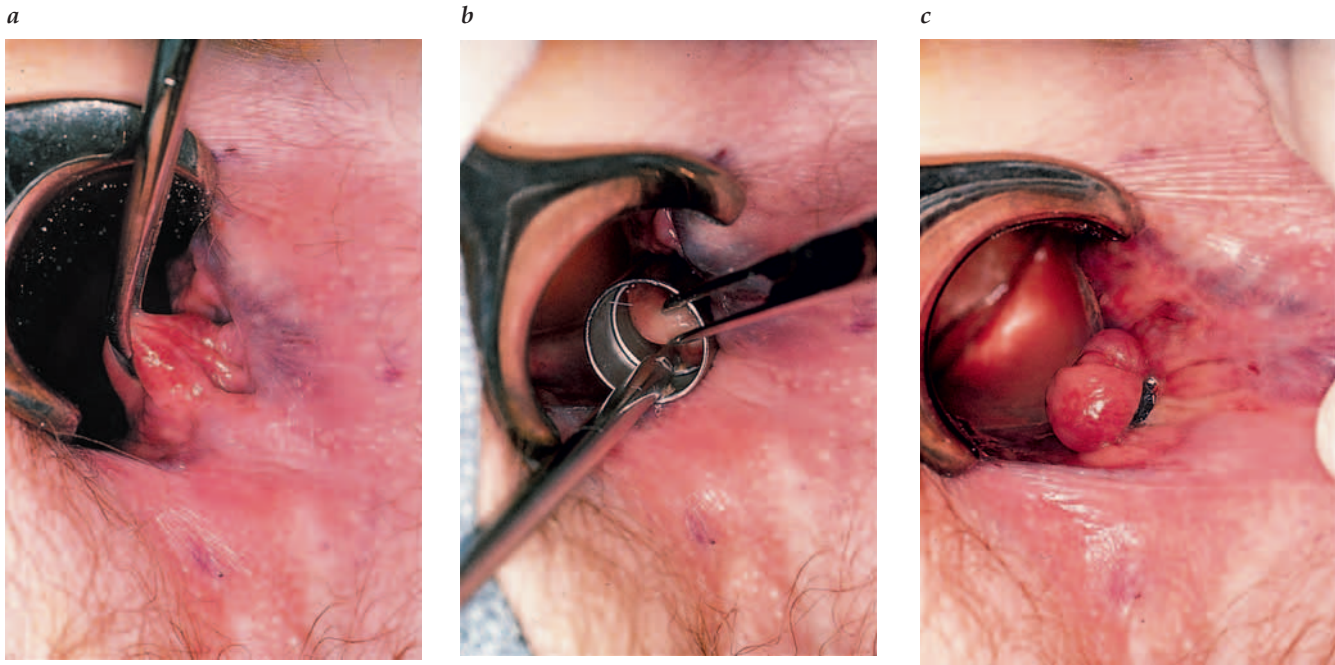


Figure 4 Operative management of hemorrhoids. Shown is the elastic ligation technique for internal hemorrhoids. (a) The hemorrhoidal tissue is identified. (b) The hemorrhoid is grasped and pulled through the drum. (c) The elastic band is applied to the base of the hemorrhoid.

I use two rubber bands on each cluster. If one of them breaks, bleeding is unlikely to occur, because the tissue rapidly becomes edematous and necrotic. It is important that the placement of the rubber band be proximal to the mucocutaneous junction; if it is not, the procedure will be too painful, given the extensive innervation of the skin. On the other hand, the band should not be placed so proximally as to incorporate the full thickness of the rectal wall; to do so can be risky for patients in whom difficulties with bowel movements indicate the presence of intussusception or some other pelvic floor abnormality. Occasionally, the friable tissue gives rise to a suspicion of cancer. If this is the case, rubber bands may be placed at the base, and the tip may be excised for biopsy.

Excision of residual external hemorrhoids Residual external hemorrhoids are rarely treated as a primary problem: true symptoms are few, and the main indication for treatment is maintenance of hygiene. In addition, I find that much of the external tissue is pulled in when the internal hemorrhoids are ligated. Accordingly, I do the internal ligation first and then excise any residual symptomatic external tissue. An elliptical incision is made in the perianal skin, with care taken to protect the underlying sphincter muscle and avoid the previously placed elastic band [see Figure 5a]. Although the perianal skin is very forgiving, it is essential to protect the anoderm; this is achieved through careful placement of the rubber band. The elliptical defect is then closed with a continuous absorbable suture in a three-point placement to obliterate the underlying dead space [see Figure 5b and 5c]. The suture is tied loosely to allow for swelling. There is no need for separate ligation or coagulation of the small bleeding vessels; this problem is obviated by the continuous suture. It is important not to use slowly absorbable suture material because it may give rise to infection in this highly

susceptible tissue. I prefer to use 3-0 chromic catgut on an exaggeratedly curved needle.

Complete excisional hemorrhoidectomy This procedure is indicated in patients who have large combined internal and external hemorrhoids, patients who are receiving anticoagulants, and patients who have massive edema and thrombosis, as seen in the postpartum rosette of tissue [see Figure 6]. I find that even massive edema generally resolves after the local anesthetic is injected and the muscle is allowed to relax. Resolution of edema then permits identification of the specific clusters of hemorrhoids, which can be isolated with a forceps and excised via an elliptical incision. Care must be taken to preserve the underlying muscle, especially in the anterior region in women. I use 3-0 chromic catgut with a deep stitch at the apex and a continuous three-point suture that is extended on the perianal skin [see Figure 5b]. It is important to preserve a bridge of anoderm between the areas of excision. I know of no indications for a radical circumferential procedure (the so-called Whitehead procedure); in fact, I see numerous patients who are seeking a remedy for the stenosis and ectropion that frequently occur after this radical operation [see Figure 7].

A newer technique, in which a circumferential band of anorectal mucosa is excised with a special circular stapler, is currently under investigation. This technique is intended for patients who have profound prolapsing internal hemorrhoids without much of an external component. Its proponents claim that it results in minimum postoperative discomfort; however, special training with the instrument is required. European centers have reported excellent success rates, and trials have now been completed in the United States. There appears to be some advantage to this procedure in that patients tend to experience less immediate postoperative pain; however, the

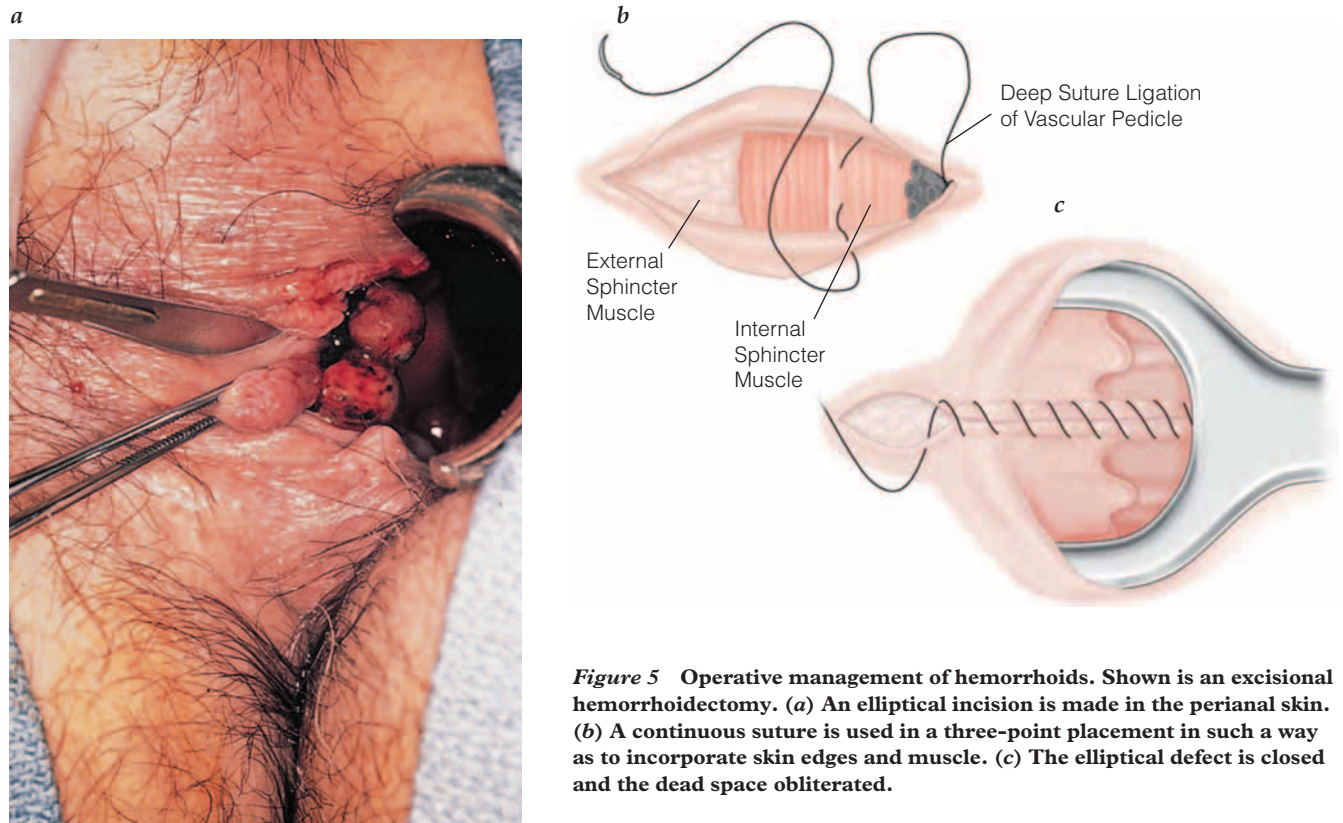


Figure 5 Operative management of hemorrhoids. Shown is an excisional hemorrhoidectomy. (a) An elliptical incision is made in the perianal skin. (b) A continuous suture is used in a three-point placement in such a way as to incorporate skin edges and muscle. (c) The elliptical defect is closed and the dead space obliterated.

long-term results seem no better than those achieved with more conventional approaches, and the rate of recurrent tissue prolapse may, in fact, be higher than that noted after standard excisional hemorrhoidectomy.¹ In addition, the circumferential stapling procedure has not yet been compared with rubber band ligation, which is now used almost routinely. Perhaps the greatest disadvantage of the new procedure is the finding that there is a significant incidence of serious postoperative complications. At present, given the results available to date, it is difficult to advocate routine use of this modality.

There also exist various forms of nonsurgical treatment for grade 1 and early grade 2 internal hemorrhoids. These entail some form of local tissue destruction (e.g., with infrared coagulation or injection of a sclerosing agent). I do not use these modalities myself, because I find that the symptoms they are used to treat can be managed just as easily, and more safely, by means of dietary changes, bulk-forming agents, and stool softeners.

Step 6: Postoperative Care

Immediately after the procedure—in fact, after any anorectal procedure—antibiotic ointment and a gauze pad are applied. Pressure dressings are unnecessary. Only a very small amount of adhesive tape should be used so as to prevent traction avulsion of the perianal skin, an event for which we surgeons too often avoid responsibility by ascribing it to a “tape allergy” on the part of the patient.

TROUBLESHOOTING

The most fundamental way of preventing problems is to make an accurate diagnosis. Surgical treatment of hemorrhoids in a patient whose main disease process is Crohn disease, a pelvic floor abnormality, or ulcer/fissure disease inevitably yields inferior results. It is especially important to recognize the anal pain and spasm of ulcer/fissure disease because in patients with this condition, excision of hemorrhoidal tissue without sphincterotomy leads to increased postoperative pain and poor wound healing.

I prefer to operate with the patient in the prone-flexed position, using local anesthesia supplemented by IV medication. I have found over the years that with this approach, patients retain no unpleasant memories of the OR experience, and good pain control is achieved in the immediate postoperative period.

In the postoperative period, efforts must be made to minimize straining on the part of the patient. To accomplish this, pain must be kept at a low level. I prefer to give only parenteral pain medication, in relatively high doses, on the first night. The patient and the nursing staff must be cautioned that the first sensation of pain, especially after elastic ligation of hemorrhoids, is the urge to defecate. This urge is an indication that pain medication should be given. The patient must not sit on the toilet and strain; to do so is likely to result in extrusion of the recently ligated tissue.

At least 20% of patients experience some degree of urinary retention. If this occurs, an indwelling catheter should be placed. In-and-out straight catheterization is contraindicated.

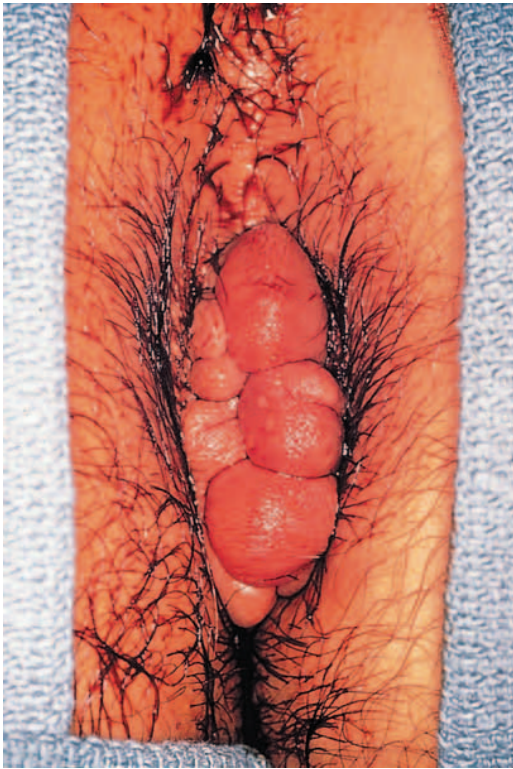


Figure 6 Operative management of hemorrhoids. Massive edema and thrombosis, as seen in the postpartum rosette of tissue, can be reduced after a local anesthetic is injected and the muscle is allowed to relax.

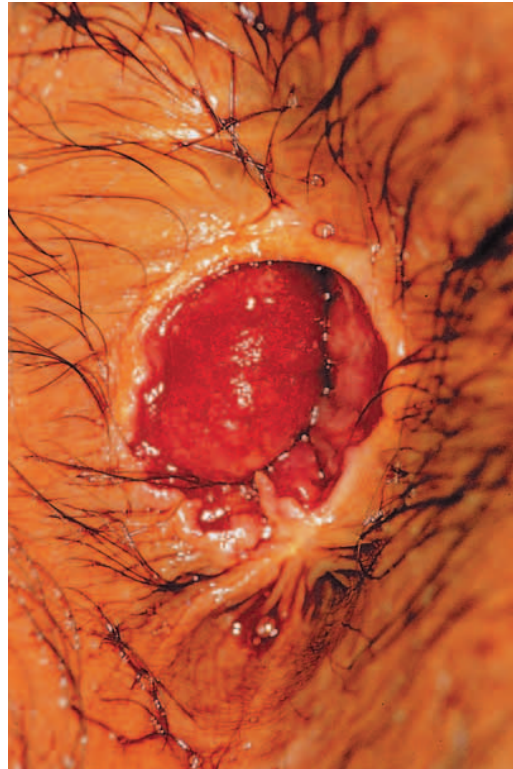


Figure 7 Operative management of hemorrhoids. Stenosis and ectropion often result from radical circumferential (Whitehead) procedures.

No bladder stimulants should be given: such agents encourage straining and increase the risk of complications.

Bulk-forming agents and stool softeners are started in the immediate postoperative period. I encourage patients to take warm soaks, either in a bathtub or in a shower, rather than try to squeeze into the disposable sitz bath mechanisms provided by the hospitals, which are often too small. I also encourage patients to sit on soft cushions rather than the rubber rings marketed for postoperative care; the rings seem to cause more dependent edema and pain.

COMPLICATIONS

Bleeding

Either immediate or delayed bleeding may occur after hemorrhoid surgery. Bleeding within the first 12 to 24 hours after the operation represents a technical error. The only management is to return the patient to the OR, with good anesthesia and adequate visualization, so that the bleeding site can be suture ligated. Frequently, spinal or epidural anesthesia is necessary because the patient is too uncomfortable, and the tissue perhaps too edematous, to allow local anesthesia. Bleeding within 5 to 10 days after the operation usually results from sloughing of the eschar created by suturing or elastic ligation. This delayed bleeding is usually minimal, and the patient is encouraged to rest and to take stool softeners. If the bleeding is significant, examination with adequate anesthesia is indicated to allow cauterization or suture ligation of the bleeding site.

It is important to discourage patients from taking aspirin-containing compounds in the postoperative period, and it is especially important to follow patients taking systemic anticoagulants closely. I prefer to treat these patients with excisional hemorrhoidectomy so that sutures can be placed; in this way, I avoid the risk that the elastic-ligated tissue will slough after 5 to 10 days.

Infection

Infection is unusual after hemorrhoidectomy because perianal tissue is normally well vascularized and extremely resistant to infection despite constant bombardment by bacteria. When it does occur, it is most likely to be in an immunocompromised patient—that is, one who has a blood dyscrasia, diabetes, or AIDS or has recently undergone chemotherapy. In my view, it is imperative to obtain at least a complete blood count and a chemistry profile before embarking on anorectal procedures; if the results are abnormal, elective hemorrhoid surgery is contraindicated.

Any local focus of infection noted in the postoperative period must be drained. I have seen this complication only when slowly absorbable suture material was used, which is the reason why I have returned to using 3-0 chromic catgut. Postoperative perianal infection can be severe and life-threatening; therefore, it is critically important to be familiar with its symptoms and to treat it intensively. Frequently, such infection is initially manifested by pain that is greater than anticipated, urinary retention, and fever. These symptoms have occasionally been

reported after elastic ligation of hemorrhoids. In this event, it is critical that the patient be seen on an emergency basis, the elastic bands removed, the patient hospitalized, and parenteral administration of antibiotics begun. In retrospect, I find that all such patients whom I have seen had preoperative symptoms of a pelvic floor abnormality with difficulty in defecation—not clear symptoms of hemorrhoids.

Urinary Retention

Urinary retention is apparently caused by reflex spasm of the pelvic musculature, which may not become evident until the local anesthesia wears off. Often a patient still under the influence of local anesthesia seems to be doing exceedingly well for the first few hours after operation, only to go into urinary retention later that night. It may be helpful to reduce the fluid load in the perioperative period. When a patient has trouble urinating, an indwelling urinary catheter should be placed and left in place for at least 12 hours. This, in my view, is one of the major reasons for in-hospital observation after treatment of more than one cluster of hemorrhoids. Placement of the indwelling catheter is of particular importance for the patient's well-being, even if it is not looked on with favor by managed care administrators. Urinary retention is a frightening experience for the patient to undergo at home. What is more, if placement of an indwelling catheter is postponed for 12 to 24 hours, recovery may be delayed. Again, it is important to remember that urinary retention may be an early sign of pelvic infection.

Stricture

Stricture, with or without ectropion, results from circumferential excision of hemorrhoids. I mention this point only to discourage the performance of this procedure.

OUTCOME EVALUATION

Because hemorrhoids are treated only when symptoms—bleeding, prolapse, pain, and difficulty with hygiene—are present, success is determined simply by the extent to which the symptoms are alleviated. If other symptoms were present before operation and persist after the procedure, the primary diagnosis should be called into question. Many elderly patients with a single prolapsing hemorrhoid that causes bleeding or maceration of the perianal skin are well served by outpatient ligation; occasionally, there is a second cluster that requires treatment some months later.

The basic point is that any patient treated surgically for hemorrhoids should experience symptomatic relief. With newer surgical techniques and improved methods of postoperative management, there is no reason for the patient to experience the severe pain described by those who have undergone extensive excisional procedures.

Operative Management of Abscess and Fistula

The conditions that cause suppurative processes in the anoperineum are cryptoglandular abscess and fistula, Crohn disease, and hidradenitis suppurativa [see 5:17 *Benign and Malignant Rectal, Anal, and Perineal Problems*]. Accurate diagnosis is essential for proper surgical management. Although these conditions may appear similar at times, each one is managed somewhat differently.

OPERATIVE PLANNING

The most important initial step is to determine the activity and severity of the disease process and the immune status of the patient. For example, a large, fluctuant abscess surrounded by erythema, induration, and superficial necrosis of the skin in an insulin-dependent diabetic is a surgical emergency. On the other hand, a chronic abscess or fistula that drains periodically over a matter of months is not nearly as urgent a problem. Multiple fistula tracts to the perineum in a patient with Crohn disease require that one perform an adequate study of the intestinal tract and the sphincter mechanism before attempting definitive surgical treatment. It is important to determine the etiology of the process whenever possible. Unfortunately, the determination cannot always be made without examination under anesthesia, during which treatment and diagnosis could be accomplished, and this complicates the obtaining of informed consent and the choice of anesthesia.

It is also important to gain as accurate a picture as possible of the complexity of the disease process; this facilitates the planning of the procedure, the choice of anesthesia, and the selection of the information given to the patient and the family before treatment. For example, in the absence of other significant health problems, a small, well-localized, low intersphincteric abscess often can be easily drained with the patient under local anesthesia if an internal opening can be seen preoperatively on anoscopy, although, on occasion, even this procedure calls for spinal or epidural anesthesia. (It should be remembered that use of the prone-flexed position [see Figure 2], which is my preference, makes general anesthesia more difficult.) Multiple infected tracts associated with undrained infectious foci in a case of rectal Crohn disease necessitate examination with the patient under spinal or epidural anesthesia. The treating surgeon should perform careful anoscopy and sigmoidoscopy and conservative temporary drainage procedures until consultation with a specialist can be arranged. Severe destruction and suspected deep tissue necrosis, especially in immunocompromised patients, may necessitate extensive resection of tissue and perhaps a completely diverting colostomy.

Bowel preparation should include mechanical cleansing and antibiotics but may not be possible when the situation is urgent (as is most often the case). Appropriate antibiotic coverage (i.e., agents effective against gram-negative organisms and anaerobes) is indicated for all but the simplest cases, with special consideration given to patients who require prophylaxis because of cardiac disease or the presence of prosthetic material.² Usually, a urinary catheter should be inserted before operation, especially if the infectious process is located in the anterior region in a man, where the urethra is at risk for injury.

OPERATIVE TECHNIQUE

Many technical elements are common to all operations for conditions that cause suppurative processes in the perineum. The patient should be in the prone-flexed position, with the buttocks taped apart. Conduction anesthesia (spinal, caudal, or epidural) is usually required. The perineum should be examined carefully with an eye to areas of abscess or external drainage sites. Endoscopic examination of the anus, the rectum, and the vagina should be undertaken to search for primary inflammatory bowel disease, internal openings of the fistula, or vaginal openings of the fistula.

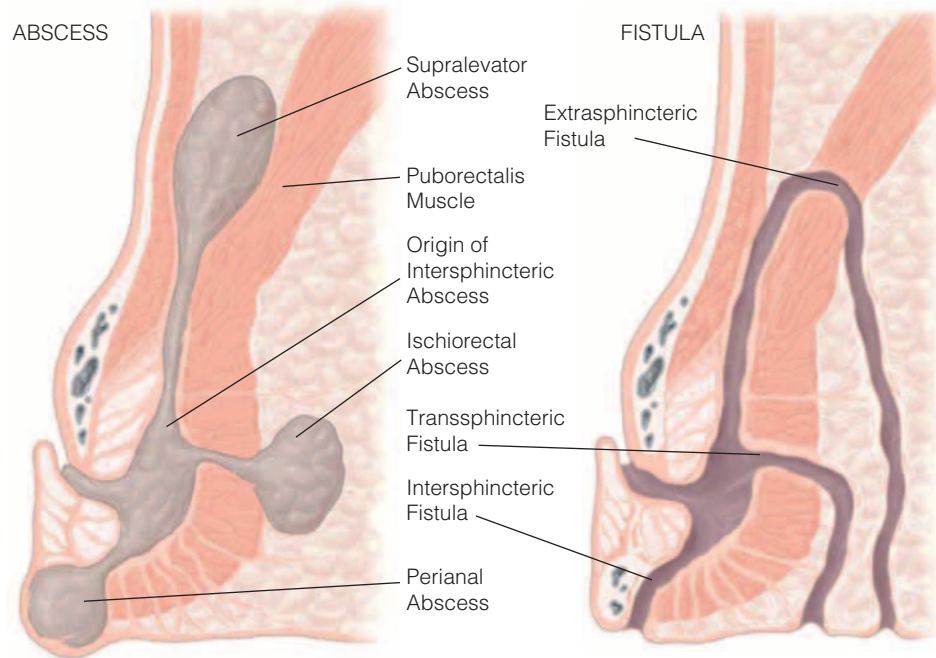


Figure 8 Operative management of abscess and fistula. Abscess and fistula are, respectively, the acute aspect and the chronic aspect of a single disease process. Acute inflammation can lead to different types of abscesses (left), depending on the direction in which the inflammation extends. Chronic inflammation leads to communication of the abscess sites with the surface—that is, fistula tracts (right).

Cryptoglandular Abscess and Fistula

The abscess must be located and characterized because drainage will depend on the location of the abscess, the course of the fistula tract, and any related infectious processes [see Figure 8].³ It is important not to create a fistula through the levator plate of the pelvic floor. This means that an abscess with a low origin must be drained low, with care taken to avoid iatrogenic perforation of the rectum, and an abscess with a high origin (e.g., a high intersphincteric abscess) must be drained high by incising the mucosa and the longitudinal (internal sphincter) muscle of the rectal wall (not a procedure for the occasional rectal surgeon). The internal opening—that is, the crypt where the abscess originated—must be sought; this is best done by means of anoscopy, very careful probing, and sigmoidoscopy to rule out a high source (e.g., Crohn disease). If the internal opening is found, the abscess can be drained or a fistulotomy can be performed [see Figure 9]. With a fistulotomy, determination of safety is a paramount concern. Careful consideration must be given to which muscle—and how much of the muscle—is to be cut. The anterior location in a woman is especially precarious. If the fistula involves a significant amount of muscle, or any muscle in the anterior region in a woman, either a seton should be placed or a drain should be placed without disruption of the muscle, in preparation for advancement flap closure of the internal opening.

If the internal opening is not found, one should not make one by probing. The abscess should be drained with a mushroom-tipped catheter [see Figure 10]; in my experience, this is preferable to unroofing and eliminates painful packing. The catheter can be left in place for an extended period, and

it permits subsequent injection of dye or contrast material. Once the mushroom catheter is in place in the OR, the surgeon can inject diluted methylene blue to search again for internal openings, which, if found, allow one to consider fistulotomy. The drain is usually sutured in place. The patient should be seen a few days after the operation to confirm that the abscess is adequately drained.

After 2 weeks, the patient is seen in the office, and povidone-iodine is injected through the drain while the inside of the anal canal is inspected via an anoscope. If an internal opening is seen, then fistulotomy is planned. If no internal opening is seen (as is the case in about 50% of patients), the drain should be removed 1 week later. This allows any irritant effect of the povidone-iodine to resolve and prevents the abscess from recurring.

If the fistula tract is known to have an external opening and fistulotomy is planned, the following approach should be considered. First, fistulectomy is never indicated. Fistulotomy is performed rarely and with great caution in the face of Crohn disease. To perform the fistulotomy, one must first find the internal opening. In this regard, the Goodsall rule is often helpful: external fistula openings anterior to the midanal line are usually connected to internal openings via short, straight tracts, whereas external openings posterior to this line usually follow a curved course to internal openings in the posterior midline. Dilute methylene blue is injected through the external opening, often via a plastic IV catheter.

Careful probing, perhaps with a lacrimal duct probe, is then carried out. If the internal opening still cannot be found, a drain is placed so that the surgeon can return at another

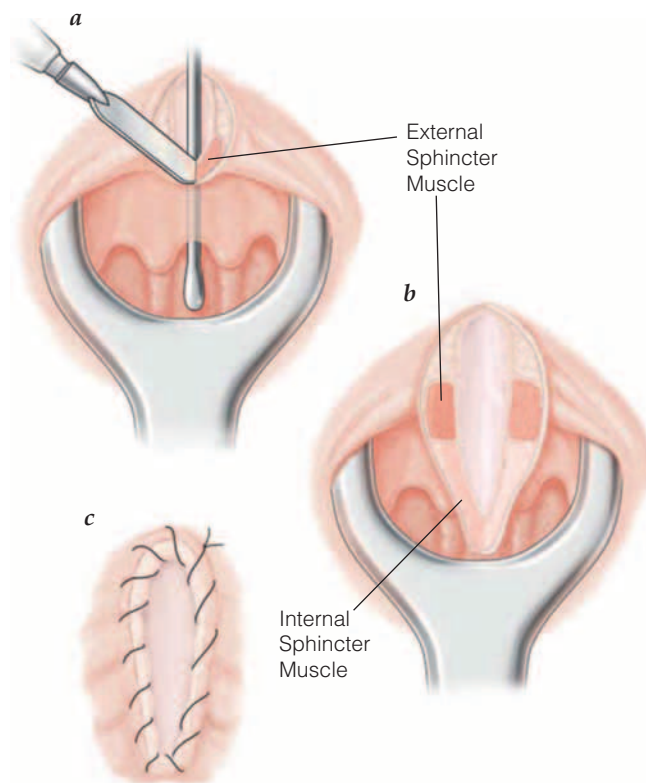


Figure 9 Operative management of abscess and fistula. Shown is a fistulotomy in a patient with cryptoglandular abscess/fistula. (a) The fistula tract is carefully probed, a decision is made about which muscle and how much muscle to cut, and the tract is incised. (b) Once the tract is open, the involved crypt is excised. (c) The defect is marsupialized by sewing skin to the tract.

time to search for the internal opening. If the internal opening is found, a probe is passed and an effort is made to determine how much muscle and which muscle must be transected to accomplish the fistulotomy and how much muscle will remain to maintain continence [see Figure 11].

If the surgeon is not sure of the extent of muscle involvement or of how safe a fistulotomy would be, the infectious process should be drained, and either the patient should be referred to a specialist or plans should be made for an advancement flap procedure to close the internal opening. If a fistulotomy is done, a biopsy specimen should be obtained from the infected tract, and the tract should be marsupialized to prevent premature healing of the superficial aspect.

It is important to keep in mind that the sphincter mechanism is innervated by a branch of the pudendal nerve that enters the sphincter from the posterolateral aspect. Accordingly, extreme caution must be exercised when a deep fistulotomy is required in the posterolateral perianal quadrants.

A growing body of evidence suggests that injection of commercially available fibrin glue is effective for treatment of fistulas in perianal tissue. Longer tracts appear to respond better to this modality than shorter tracts do. The long-term efficacy of this approach remains to be proved.

Special problems A cryptoglandular abscess that extends into the posterior anal and posterior rectal spaces is

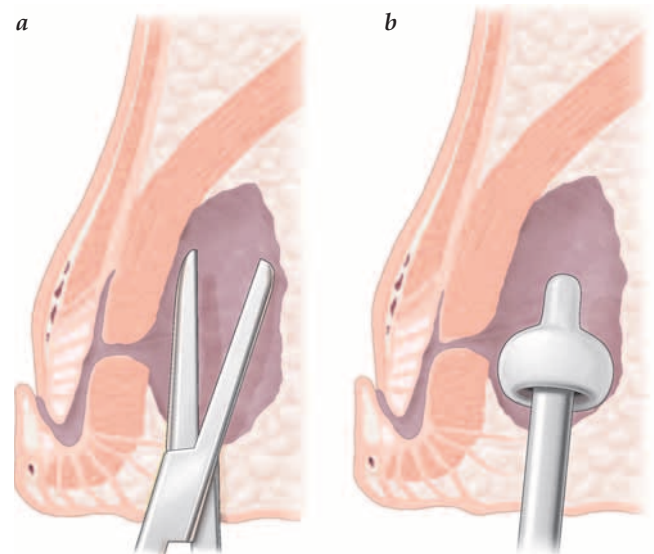


Figure 10 Operative management of abscess and fistula. Shown is drainage of an ischioanal abscess. Such abscesses may be palpated above the anorectal ring, even though their location is more inferior. (a) The abscess is incised. (b) A mushroom-tipped catheter is placed.

often missed as a source of infection. Diagnosis of such abscesses typically involves bidigital examination, often with the patient under anesthesia; needle aspiration may be required as well. Fistulotomy in this area often necessitates opening large amounts of tissue, including partial transection of the sphincter muscle; the tract may also have to be marsupialized. If one is unsure of the anatomy or has never done the procedure before, the abscess should be drained as simply as possible and the patient referred to a specialist.

The so-called horseshoe abscess [see Figure 12] results from an undiagnosed posterior space abscess that has dissected laterally and may have been drained several times through the lateral extension into one or both ischioanal fossae. This condition is cured by opening the posterior space and placing a long-term lateral drain, after which healing proceeds by secondary intention (the so-called Hanley procedure). The drain should not be removed until there is solid healing in the posterior midline; this may take weeks or even months.

Abscess and Fistula Associated with Crohn Disease

The goals of treatment are to drain and control the focus of infection, to preserve sphincter function, to plan and implement a staged approach to preservation of anorectal function, and to make the correct diagnosis. To these ends, careful identification of the location and course of the abscess and any associated fistulas is essential; this is accomplished via endoscopic dye injection, probing, and vaginoscopy.

The safest approach, in my view, is to place mushroom catheters in abscesses and complicated fistula tracts or, in some cases, to use setons to allow drainage of the fistulas (not to cut through the tissue, which is often the intended result of seton placement) [see Figure 13]. For optimal resolution of inflammation at the site of the internal opening in anticipation

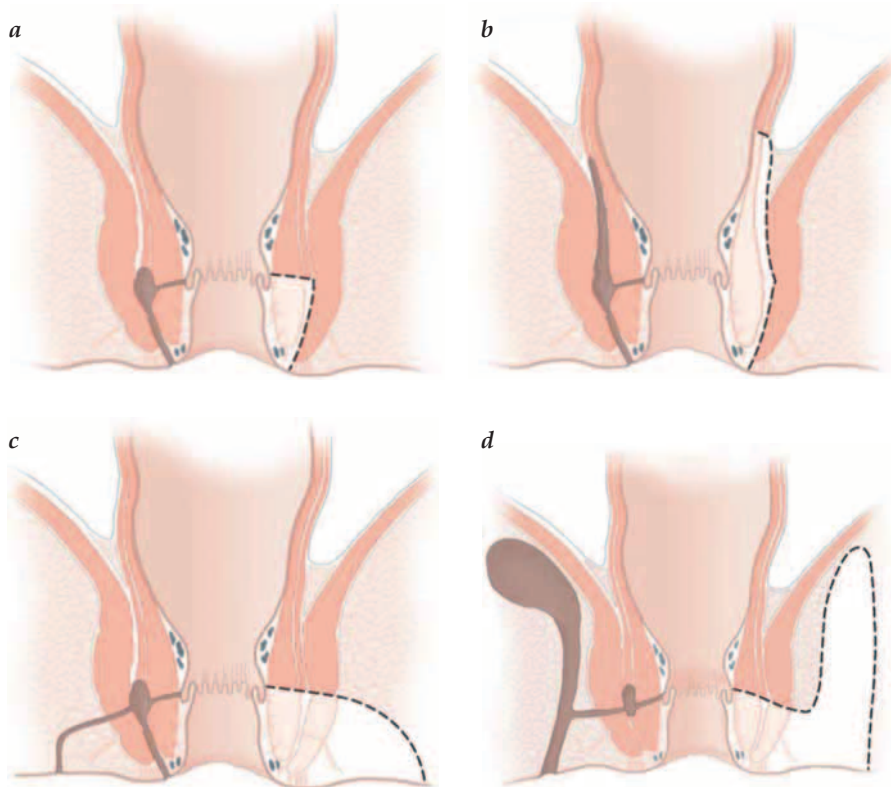


Figure 11 Operative management of abscess and fistula. Shown are examples of the different types of fistulotomies indicated for some of the many types of fistulas: intersphincteric fistula with a simple low tract (a), intersphincteric fistula with a high blind tract (b), uncomplicated transsphincteric fistula (c), and transsphincteric fistula with a high blind tract (d). In each image, the left half of the drawing shows the disease process, and the right half illustrates the recommended operation.

of a possible advancement flap procedure, perirectal mushroom catheters are preferable to setons placed through the internal opening. Superficial fistula tracts may occasionally be managed with fistulotomy if the Crohn disease is otherwise inactive. Sphincterotomy is never indicated in a patient with Crohn disease if severe infection is present or the disease is active. When a patient is known or believed to have Crohn disease, biopsy of the edematous external skin tags that are often present can be a good way of finding granulomatous tissue to confirm the diagnosis.

The newer forms of medical treatment of Crohn disease, in which a monoclonal antibody to tumor necrosis factor (infliximab) is given either by itself or in combination with immunosuppressive agents, seem to display some of their most beneficial results in patients with complicated anoperineal fistulas. In my view, a good way of managing abscess and fistula associated with Crohn disease is for the surgeon to drain and control the suppurative process and for the gastroenterologist then to employ the latest medical regimen to force the disease into remission.

Hidradenitis Suppurativa

Patients with infected fistula tracts or abscesses secondary to hidradenitis suppurativa must be positioned in such a way

as to allow visualization of and access to all tracts. This is crucial because some of the tracts may extend into the scrotum, the labia, the inguinal areas, or the suprapubic area. Conduction anesthesia is important in that it covers broad areas of the perineum; adequate local anesthesia is impossible unless one is dealing with very small, isolated tracts.

The definitive therapeutic surgical procedure is incision (rather than excision) of these often extensive inflammatory tracts [see Figure 14]. The surgeon should do as much as possible at one time, with the understanding that it is not unusual to leave a few tracts undrained or to return later to address new areas of dissection. Because the primary disease process does not involve the sphincter, intestinal diversion is rarely indicated. Biopsy is indicated because on rare occasions, these long, infected tracts exhibit malignant changes or result from an anal malignancy. The perineal skin can tolerate the extensive incisions necessary to cure the process. Special precautions must be taken not only to preserve the sphincter itself but also to avoid damaging the neurovascular bundle that enters the anus from the posterolateral aspect. In male patients, efforts must be made to avoid the urethra during incision in the anterior midline; to this end, a Foley catheter should always be placed before the surgical procedure is begun. Because so many incised skin edges remain after treatment of extensive hidradenitis, it is

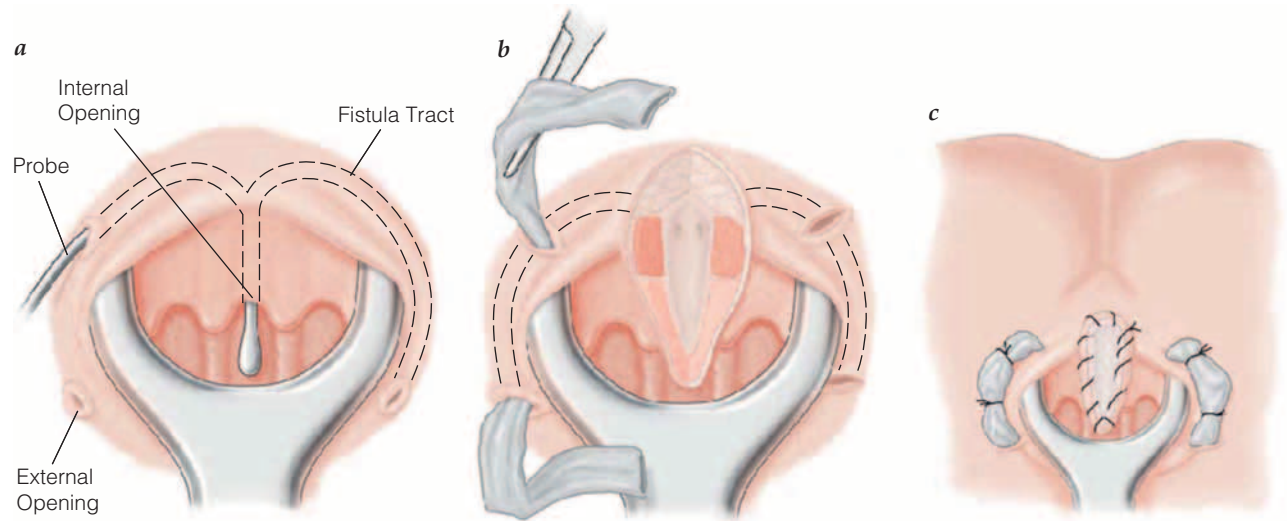


Figure 12 Operative management of abscess and fistula. Shown is the surgical treatment of a horseshoe fistula. (a) The main posterior tract of the fistula is identified by probing. (b) The posterior tract is opened, and drains are placed laterally. (c) The posterior tract is marsupialized.

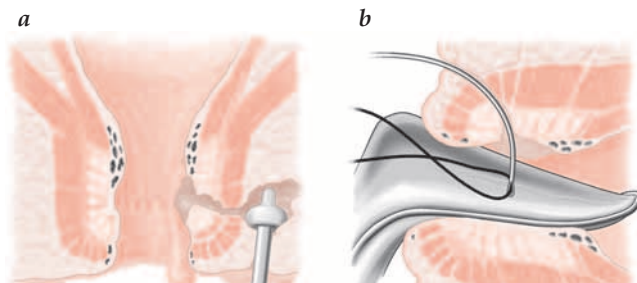


Figure 13 Operative management of abscess and fistula. Shown are alternatives for treating abscess or fistula associated with Crohn disease. In Crohn disease, multiple perianal and perineal fistulas and abscesses may be seen, often in atypical locations. (a) Abscesses may be drained by placing a small mushroom-tipped catheter as close to the anus as possible. A Malecot catheter should not be used. (b) In some settings, it is appropriate to place a seton between internal and external openings. This seton may then be left in situ for a time for drainage and for prevention of further disease progression.

imperative to achieve adequate hemostasis. The disposable suction cautery units currently available can be especially helpful for this purpose. The wounds may be either left open or loosely packed until good granulation tissue forms.

Bathing the perineum, especially after a bowel movement, is helpful. Often showers are better for this purpose than the portable minuscule sitz baths commonly used. For patients who have undergone extensive procedures, twice-daily trips to a whirlpool bath (often located in the physical therapy department) are helpful. Despite the multiple lengthy incisions, there is usually little pain, and most of the postoperative care can be done at home. Adequate follow-up is necessary to treat residual or new areas of disease before the dissection becomes extensive again. Care must be taken, especially in the OR, to search for the infected tracts, which may contain little pus and may be apparent only as indurated cords within the perineal skin.

TROUBLESHOOTING

Most of the important steps for avoiding problems have already been described in the course of addressing preoperative planning and operative technique (see above). The goals in the treatment of all of the processes associated with anorectal abscess and fistula in ano are to preserve sphincter function, to control acute infection, and to eliminate the source of the infection. If it is likely that sphincter function will be compromised at all, a baseline level of sphincter function (including the status of muscles and nerves) must be determined before any surgical procedure is initiated. One should never hesitate to perform an examination with the patient under anesthesia and to inject dilute methylene blue to delineate the extent and location of the infectious process.

Anyone embarking on surgical management of such processes must keep in mind the option of performing an advancement flap procedure to close the internal opening, especially in the anterior region and most particularly in women. If such a procedure is planned, initial drainage should be done external to the rectum with a mushroom catheter rather than through the internal opening with a seton. Simple 3-0 chromic catgut should be used to marsupialize fistula tracts because employing the newer, less quickly absorbable materials may lead to a chronic nidus that gives rise to ongoing infection. Patients should be watched closely in the immediate postoperative period to ensure that all infection is controlled. Not uncommonly, a superficial collection is drained, but a deeper abscess remains that must be sought more aggressively.

One should always take into account the risk of anoperineal infection in immunocompromised patients. Given that the anatomy of the anal tissue planes is complex and can be rendered even more so by multiple surgical procedures, one should not venture beyond one's level of expertise. One should never hesitate to drain an infectious focus with a simple mushroom-tipped catheter and, if appropriate, refer the patient to a colon

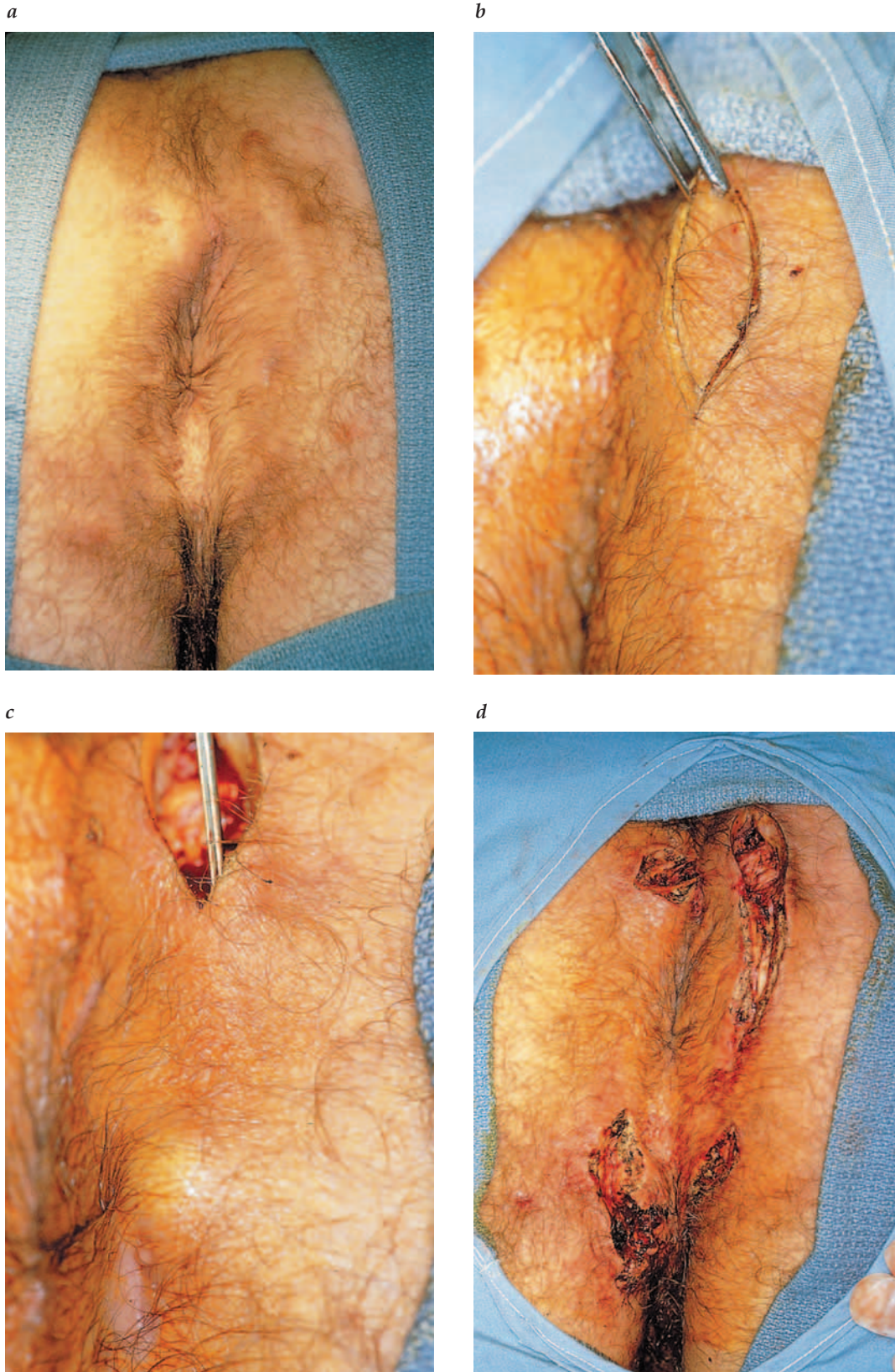


Figure 14 Operative management of abscess and fistula. In this patient, the causative condition is hidradenitis suppurativa. (a) Multiple openings of sinus tracts can be seen and extensive indurated tracts palpated. (b) Abscesses are unroofed. (c) Indurated tracts are probed. (d) All tracts are identified and incised.

and rectal surgical specialist who is trained to manage complex anoperineal suppurative processes safely and definitively.

COMPLICATIONS

Complications occur if one or more of the goals just mentioned (see above) have not been achieved. Persistent or recurrent infection is seen with some frequency. In patients with cryptoglandular abscess or fistula, infection usually results from failure to locate the internal opening or to discover a deep posterior midline abscess; such failure is often seen in patients with a horseshoe abscess, in whom repeated lateral drainage procedures may have been undertaken without the primary cavity in the posterior anal or posterior rectal space being discovered and dealt with.

In patients with Crohn disease, infection can persist if a deeper pocket or extension has gone undiscovered or if the disease has recurred, leading to further penetration and infection in the anoperineum or the perirectal tissue. Extensive examination with the patient under anesthesia, including transrectal ultrasonography or computed tomography (CT), may be required to determine the source and extent of the infection. It is always possible that the infection derives from a superlevator abscess secondary to intestinal disease; consequently, a detailed evaluation of the intestinal tract is indicated in patients with Crohn disease.

In patients with hidradenitis suppurativa, the most common problems are residual undrained tracts and recurrent disease. Again, examination with the patient under anesthesia and repeated drainage are called for. Because this disease process does not originate in the rectum, care must be taken not to enter the rectum or to cut any of the nerves entering the anus from the posterolateral aspect. It has been reported anecdotally that very chronic or persistent fistula tracts may eventually exhibit malignant changes (squamous cell carcinoma); for this reason, such tracts should be biopsied.

OUTCOME EVALUATION

No sophisticated surveillance is necessary: if drainage persists or some degree of incontinence develops, the patient usually will volunteer the information freely. Either of these complaints could be an indication for a detailed examination, including a sophisticated evaluation of sphincter function.

Operative Management of Ulcer/Fissure Disease

Ulcer and fissure are two aspects of a single anorectal disease process with an unclearly defined pathophysiology [see Figure 15]. Accurate diagnosis is crucial [see 5:17 *Benign and Malignant Rectal, Anal, and Perineal Problems*]. Not uncommonly, patients are treated for hemorrhoids when the true primary condition is ulcer/fissure disease.

OPERATIVE PLANNING

Fundamental concerns in planning the operation—besides confirming the diagnosis—are to verify that no other conditions could threaten complete healing of an incision in the anal tissue and to make sure that there is no significant incontinence before the sphincterotomy.

For example, a history of diarrhea compatible with the presence of inflammatory bowel disease indicates the need for

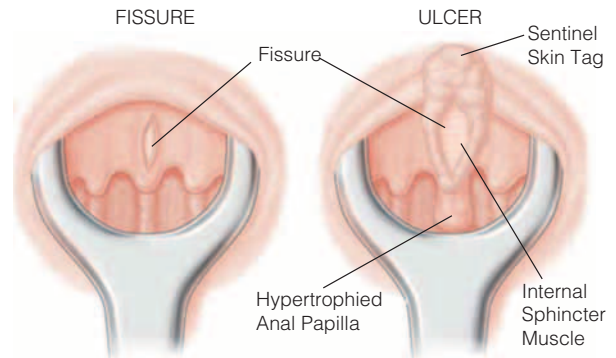


Figure 15 Operative management of ulcer/fissure disease. Anal fissure (*left*) and anal ulcer (*right*) are, respectively, the acute aspect and the chronic aspect of a single disease process.

further evaluation to eliminate the possibility of Crohn disease; if Crohn disease is present, the risk of poor healing is greater, and it will be necessary to preserve all of the available sphincter function of the anus for a long period. As another example, a woman who has borne children by vaginal delivery and has any degree of incontinence should undergo manometry, ultrasonography, and perhaps electromyography to confirm that the sphincter is not compromised by a mechanical or neurologic deficiency. Yet another example is a patient with irritable bowel syndrome or a pelvic floor abnormality who experiences a multitude of difficulties with bowel movements. It is important to recognize such conditions and to advise the patient of the need for special attention to maintain adequate bowel function in the postoperative period.

It is essential to clearly explain the nature of the operative procedure (i.e., the incision of a portion of the internal sphincter mechanism) to the patient and to warn him or her that minor incontinence or flatus may persist for as long as a few months postoperatively. To be fair, significant incontinence is highly unusual; in fact, most patients experience very rapid relief of their often distressing symptoms. One should also advise the patient that any other anal procedures that may be indicated (e.g., elastic ligation of internal hemorrhoids or excision of symptomatic external hemorrhoids) can and should be accomplished at the time of sphincterotomy, with or without excision of the anal ulcer, and that he or she should take 3 to 5 days off from work. The risk of urinary retention, pain, and bleeding must also be discussed. In planning the operative procedure and immediate postoperative care, one must take into account the patient's specific needs, idiosyncrasies, and home environment. Some patients are comfortable undergoing the procedure completely on an outpatient basis, whereas others clearly need to be admitted for short-term observation and parenteral administration of pain medication.

When possible, I keep patients on a liquid diet for 24 hours before operation and use small, self-administered enemas to empty the rectum immediately before the procedure. I advise patients to discontinue any aspirin-containing products and any other anticoagulants, if possible, at least 10 days beforehand.

OPERATIVE TECHNIQUE

Operative treatment of ulcer/fissure disease consists of a posterior lateral internal anal sphincterotomy, in which the

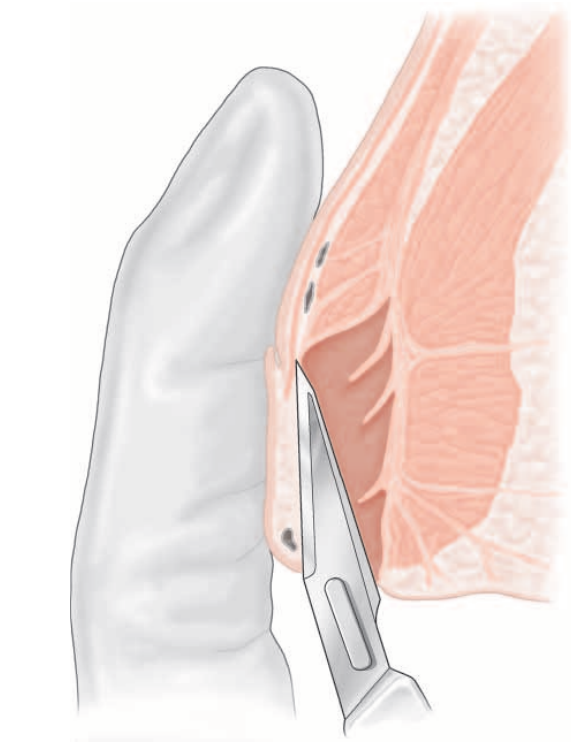


Figure 16 Operative management of ulcer/fissure disease. Shown is the closed approach to posterior lateral internal sphincterotomy. A No. 11 blade is inserted in the intersphincteric groove and moved upward to the level of the dentate line. Medial movement of the blade divides a portion of the internal sphincter muscle. The anoderm and the other anal muscles are not divided.

internal sphincter is divided but the external sphincter, the anoderm, and the longitudinal muscle remain intact. I generally prefer to place the patient in the prone-flexed position with the buttocks taped apart and adequate local anesthesia in place. The operation can then be performed in one of three ways: (1) as a closed procedure involving the use of a No. 11 blade and digital palpation of the muscle [see Figure 16], (2) as an open procedure without direct visualization of the muscle, or (3) as an open procedure with clear identification of the muscle before its transection. The third option is the one I prefer.

An open procedure with visualization of the muscle is done as follows [see Figure 17]. The first step is anoscopy, preferably with a medium Hill-Ferguson instrument. The hypertrophied band of the lower third of the internal sphincter muscle is clearly identified. If this band is not a distinctly identifiable entity, sphincterotomy should not be performed. The ulcer or fissure itself need not be present, because the disease may be in a relatively inactive state at the time of surgery.

Rigid or flexible sigmoidoscopy should then be performed if it was not done in the immediate preoperative period. The primary purpose of this step is to make sure that no features of Crohn disease are visible in the rectum. When the endoscopic examination is complete, I usually repeat the preparation of the anal opening.

A 1 cm incision is made in the posterior lateral aspect of the perianal skin, hemostasis is obtained, and a delicate dissection is done with a curved hemostat in the intersphincteric plane. The posterior midline is avoided because healing in this position may result in scar tissue that interferes with perfect continence (the so-called keyhole deformity). The white hypertrophied band of muscle is then elevated into the wound with a curved hemostat. If a rent is made in the anal mucosa, it must be repaired with 3-0 chromic catgut. The band of muscle is then incised with the electrocautery, and pressure is maintained for a few minutes to ensure hemostasis. Digital examination confirms adequate transection of the band. The skin is left open.

Attention is then directed to the ulcer, which may be excised sharply in an elliptical fashion so as to incorporate the entire triad of the ulcer (i.e., the ulcer itself, the sentinel hemorrhoidal tag, and the hypertrophied anal papilla) while avoiding additional transection of the underlying muscle. If I excise the ulcer complex, I usually close the wound with a continuous three-point suture of 3-0 chromic catgut to obliterate any dead space and thus to lower the risk of postoperative infection.

Any additional anal surgery required is then completed, the surgical site is covered with antibiotic ointment, and a very light gauze bandage is applied with a minimum of tape and traction on the perianal skin.

TROUBLESHOOTING

To perform this simple procedure well, one must have a clear understanding of the surgical anatomy of the anal canal and must be able to clearly identify the internal sphincter, the intersphincteric groove, and the external sphincter muscle. The hypertrophied band of muscle must be accurately identified and cleanly transected. No attempt should be made to extend or amplify the procedure by stretching the anal canal and thus bursting the muscle. Although the procedure and anatomy are simple, the best way of learning the operation is to watch an experienced surgeon perform it. I do not believe this procedure can be learned through reading alone.

COMPLICATIONS

Because the internal sphincter muscle is responsible for resting, involuntary continence, injury to this structure can lead to nocturnal incontinence. Again, special caution is advised with respect to the anterior aspect of the anoperineum in women. On the other hand, incising the posterior midline can also lead to the keyhole deformity, which may cause prolonged anal seepage because of the configuration of the scar tissue; a good analogy is a bent rim on a tubeless tire. It is tempting to close the tiny skin incision at the site of sphincterotomy, but I think it should be left open to reduce the already low risk of infection.

There should be very little postoperative pain. If the patient does complain of significant pain, especially in the presence of fever or urinary hesitancy, one must assume that infection is present in the anoperineum, a structure that is normally highly resistant to microbial invasion. Urgent evaluation, removal of sutures, antibiotic therapy, bowel rest, placement of a urinary catheter, and very close observation in the hospital are indicated.

The major causes of complications are incorrect diagnosis of the disease process (especially overlooking the presence of

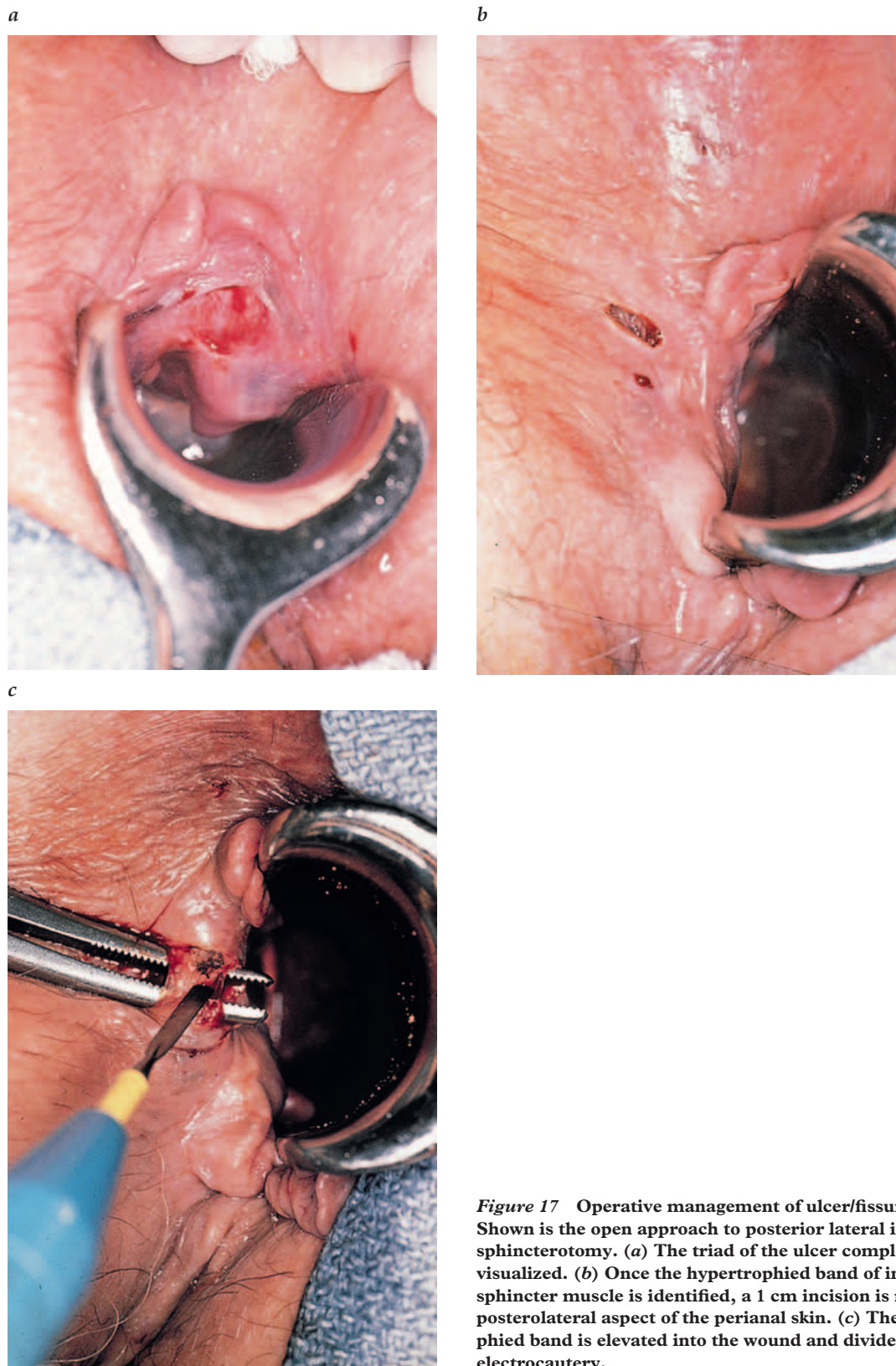


Figure 17 Operative management of ulcer/fissure disease. Shown is the open approach to posterior lateral internal sphincterotomy. (a) The triad of the ulcer complex is visualized. (b) Once the hypertrophied band of internal sphincter muscle is identified, a 1 cm incision is made in the posterolateral aspect of the perianal skin. (c) The hypertrophied band is elevated into the wound and divided with the electrocautery.

Crohn disease) and failure to fully understand the anatomy of the continence mechanism of the anal canal. If too much of the internal sphincter muscle is cut, if this muscle is already compromised, or if the external sphincter muscle is

transected by mistake, the patient will be rendered incontinent. On the other hand, if not enough of the internal muscle is transected, the ulcer will not heal and the symptoms will persist.

Overall, the single most common cause of complications that I have observed is the failure even to suspect, much less diagnose, ulcer/fissure disease as the source of a patient's symptoms. I frequently see patients who seem to have failed to heal months after a hemorrhoidectomy. When their symptoms are reviewed and a thorough examination is performed, it becomes apparent that the underlying disease process was always ulcer/fissure disease rather than hemorrhoids and that the hemorrhoidectomy only intensified the anal pain and bleeding. These patients are finally cured when an adequate sphincterotomy is performed.

In very rare instances, drainage continues at the site of the sphincterotomy. If drainage persists for weeks, the patient should be examined under appropriate anesthesia, and the focus of infection should be opened. This is essentially equivalent to a very superficial fistulotomy.

OUTCOME EVALUATION

Again, no sophisticated surveillance is necessary: when the patient returns 2 weeks after the procedure, free of pain and bleeding and able to have bowel movements without difficulty, one may be sure that an acceptable outcome has been achieved. Digital rectal examination should confirm good healing and normal sphincter tone (both while resting and while contracting). For additional confirmation, I have patients continue to take bulk-forming agents and stool softeners and then examine them 1 month later to verify that healing is complete.

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Tom Moore. Adapted from original illustrations by John Craig.

38 DISORDERS OF THE ADRENAL GLANDS

L. Michael Brunt, MD, FACS

The adrenal glands may be affected by a variety of different pathologic conditions. Although not among the most common disorders encountered by surgeons, functioning adrenal tumors that produce excessive amounts of adrenal hormones are remarkable for the range of clinical syndromes they give rise to. In this chapter, the clinical presentation, diagnostic evaluation, and management of the various adrenal tumors are reviewed, and the workup of incidentally discovered adrenal masses (adrenal incidentalomas) is outlined.

Disorders of the Adrenal Cortex

PRIMARY HYPERALDOSTERONISM

Clinical Evaluation

Primary hyperaldosteronism (Conn syndrome) is now known to be a much more common cause of hypertension than was previously thought, occurring in as many as 8 to 12% of hypertensive patients.¹ The diagnosis of primary hyperaldosteronism should be considered in any patient who has hypertension of early onset, hypertension that is difficult to control, or hypertension with hypokalemia [see Figure 1]. Although the classic presentation is that of hypertension with hypokalemia, many patients with primary hyperaldosteronism have a normal or low-normal serum potassium level; indeed, current data suggest that as many as 60% of patients diagnosed with this condition—and perhaps more—were normokalemic at the time of diagnosis.² The hypertension that results from primary hyperaldosteronism is moderate to severe and may be refractory to standard antihypertensive medications. Symptoms are nonspecific and may include headache caused by the hypertension. Most of the other symptoms observed are attributable to hypokalemia; these include muscle weakness, cramps, fatigue, and, if the hypokalemia is severe, polydipsia, polyuria, nocturia, and even paralysis.

The pathophysiology of primary hyperaldosteronism primarily consists of increased aldosterone secretion by the adrenal gland, which leads to increased sodium retention, expansion of intravascular fluid volume, and suppression of renin secretion by the kidney. Aldosterone also promotes the exchange of sodium for potassium and hydrogen ion in the distal tubule, which leads to potassium depletion and alkalosis. The alkalosis may be aggravated by the movement of hydrogen ion into the cells to replace intracellular potassium. Significant potassium depletion may also be accompanied by mild glucose intolerance.

Investigative Studies

The initial biochemical evaluation for suspected primary hyperaldosteronism should consist of measurement of the

plasma aldosterone concentration (PAC) and assessment of plasma renin activity (PRA). A PAC-to-PRA ratio greater than 25 to 30, in conjunction with suppressed PRA (< 0.2 to 0.5 ng/mL/hr) and a PAC higher than 15 ng/dL, is consistent with primary hyperaldosteronism.³ The diagnosis may be confirmed by means of suppression testing with either oral salt loading or intravenous (IV) administration of saline. With oral salt loading, hypokalemia is corrected and the patient is placed on a high-salt diet for 3 days. On day 3, a 24-hour urine collection is obtained for measurement of sodium, potassium, creatinine, and aldosterone concentrations. Patients with primary hyperaldosteronism should have a 24-hour urine aldosterone value higher than 12 μ g/24 hr.¹ Plasma aldosterone levels should be higher than 10 ng/dL after IV salt loading.

Once the diagnosis of primary hyperaldosteronism has been confirmed biochemically, the next step is to identify the cause or determine the subtype [see Table 1]. Historically, aldosterone-secreting adenomas (aldosteronomas) have accounted for approximately 60% of cases, and idiopathic hyperaldosteronism from bilateral cortical hyperplasia has accounted for the bulk of the remaining cases. In the past few years, however, this picture has begun to change: several series in which hypertensive patients were screened on the basis of aldosterone-to-renin ratios found that only 30 to 50% of patients with primary hyperaldosteronism had aldosteronomas, whereas 50 to 70% had bilateral adrenal hyperplasia.² It is important to distinguish between these two conditions because aldosteronomas are treated surgically and idiopathic hyperaldosteronism is treated medically. Aldosterone-producing carcinomas are rare and account for fewer than 1% of cases of primary hyperaldosteronism.

Glucocorticoid-remediable hyperaldosteronism (also known as familial hyperaldosteronism type 1) is a rare type of hyperaldosteronism that is inherited in an autosomal dominant pattern. This condition is due to a chimeric gene that results from fusion of two components: (1) the promoter region for the enzyme 11α -hydroxylase (CYP11B1), which catalyzes the conversion of deoxycortisol to cortisol, and (2) the gene that codes for aldosterone synthesis (CYP11B2). As a result, aldosterone synthesis is primarily dependent on activation by adrenocorticotrophic hormone (ACTH) and is suppressed by exogenous glucocorticoid administration.³ Its extreme rarity notwithstanding, familial hyperaldosteronism type 1 has been associated with a significant increased risk of hemorrhagic stroke. Familial hyperaldosteronism type 2 is associated with the development of both aldosteronomas and idiopathic hyperaldosteronism.

The initial step in subtype determination should be to perform cross-sectional imaging to look for an adrenal adenoma. Aldosteronomas are generally small, typically measuring no

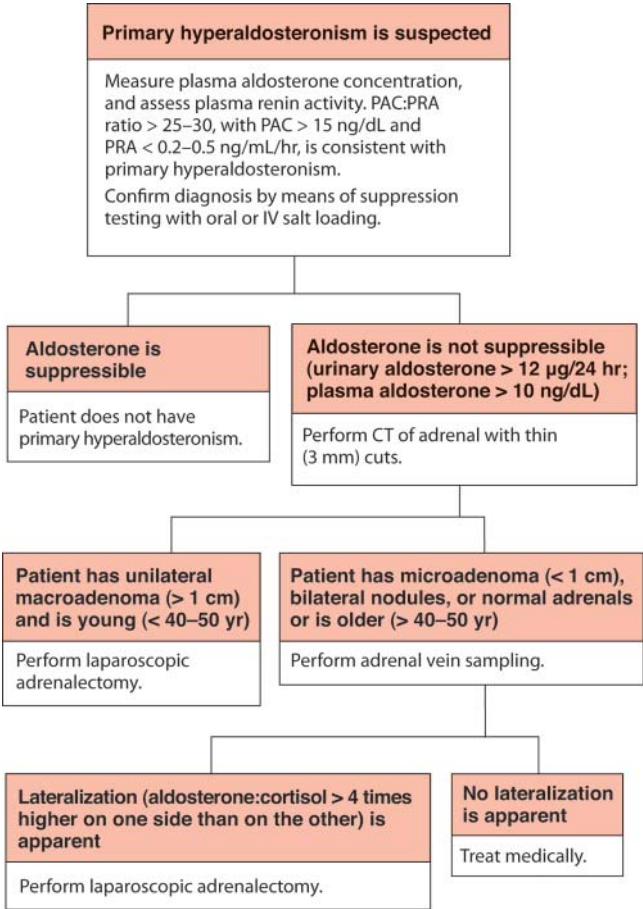


Figure 1 Algorithm illustrating diagnostic evaluation of the patient with suspected primary hyperaldosteronism. CT = computed tomography; PAC = plasma aldosterone concentration; PRA = plasma renin activity.

more than 1 to 2 cm in diameter. Thin-section imaging with computed tomography (CT) possesses excellent spatial resolution for small adrenal nodules and is therefore the preferred imaging modality for this purpose [see Figure 2]. Magnetic resonance imaging (MRI) may also be used but is more costly, and the images can be harder for clinicians to interpret. Findings on CT or MRI may include a unilateral macroadenoma (> 1 cm) or microadenoma (< 1 cm) with a normal contralateral adrenal gland, bilateral adrenal nodules or bilateral adrenal thickening, and bilateral normal glands. Patients with a unilateral macroadenoma and a normal contralateral adrenal gland may be considered for adrenalectomy, without any need for further testing. For all other patients, adrenal vein sampling is recommended to



Figure 2 Computed tomography scan showing a right adrenal aldosteronoma (arrow).

differentiate aldosteronoma from idiopathic hyperaldosteronism. In this procedure, aldosterone and cortisol levels are measured from both adrenal veins and from the inferior vena cava. ACTH is usually infused during the procedure to minimize stress-related fluctuations in cortisol and aldosterone levels. An aldosterone-to-cortisol ratio that is at least four to five times greater on one side than on the other is considered diagnostic of a unilateral source of increased aldosterone production (i.e., an aldosteronoma) and constitutes an indication for adrenalectomy [see Table 2].

Adrenal vein sampling is a technically demanding procedure that should be carried out only by radiologists who have considerable experience with it. The value of this procedure was demonstrated in a 2004 study of 194 patients with hyperaldosteronism at the Mayo Clinic.⁴ In this study, adrenal vein sampling identified a unilateral source of increased aldosterone production in 87 of 176 patients with the following CT findings: a normal CT scan (24 of 58), a unilateral micronodule (24 of 47), a unilateral macronodule (21 of 32), bilateral micronodules (16 of 33), and bilateral macronodules (2 of 6). If the treating physicians had relied on CT scan findings alone, 42 patients (21.7%) would have been inappropriately excluded from consideration for adrenalectomy, and an additional 48 patients (24.7%) who showed no lateralization on adrenal vein sampling might have been subjected to an unnecessary operation. In a more recent study, a lateralizing source of increased aldosterone production was found in only one of 22 patients (5%) with bilaterally normal adrenals on CT, three of nine (33%) with bilateral nodules or thickening, and 27 of 39 (69%) with a unilateral nodule. However, all five patients under age 40 who had a solitary > 1 cm unilateral nodule and normal contralateral adrenal had aldosteronomas proven on vein sampling.⁵ These results argue for liberal use of adrenal vein sampling in older patients with primary hyperaldosteronism.

Table 1 Subtypes of Primary Hyperaldosteronism
Aldosterone-producing adenoma
Idiopathic hyperaldosteronism
Aldosterone-producing adrenal carcinoma
Familial hyperaldosteronism
Type I (glucocorticoid remediable)
Type II (aldosteronoma or carcinoma idiopathic)

Table 2 Adrenal Vein Sampling Results in a Patient with Primary Hyperaldosteronism

Sampling Site	Aldosterone Level (ng/dL)	Cortisol Level (μg/dL)	Aldosterone-to-Cortisol Ratio	Aldosterone Ratio*
Right adrenal vein	480	346.7	1.38	16.9
Left adrenal vein	33,765	1,448	23.3	
Inferior vena cava	67.0	24.1	2.78	

*Defined as the aldosterone-to-cortisol ratio in the left adrenal vein divided by the aldosterone-to-cortisol ratio in the right adrenal vein. The results show a lateralizing source of increased aldosterone production from the left adrenal gland.

Management

For patients with an aldosteronoma, the treatment of choice is laparoscopic adrenalectomy. Before the operation, hypertension should be brought under control and hypokalemia corrected. The aldosterone antagonist spironolactone may be useful for preoperative control of blood pressure. Adrenalectomy cures hypertension in as many as 30 to 80% of patients and improves blood pressure control in the remainder.⁶⁻⁹ The reasons for failure to cure hypertension in some patients may be related to the effects of long-standing hypertension from the hyperaldosteronism, more advanced age, or coexisting essential hypertension. In one follow-up study, a positive family history of hypertension and the use of more than two antihypertensive medications preoperatively were independent predictors of residual hypertension after adrenalectomy.⁶ Hypokalemia should be corrected in virtually 100% of patients.

For patients with idiopathic hyperaldosteronism, treatment is medical, consisting of dietary sodium restriction and potassium supplementation. As in patients with aldosteronomas, spironolactone is effective in controlling hypertension and hypokalemia. However, it also blocks testosterone synthesis and peripheral androgen action and thus may have undesirable side effects—namely, impotence, decreased libido, and gynecomastia. Eplerenone is a newer aldosterone-receptor antagonist that exhibits little binding to androgen receptors and therefore may not have the same side effects as spironolactone.¹⁰

SECONDARY HYPERALDOSTERONISM

In secondary hyperaldosteronism, an elevation of plasma aldosterone occurs in response to increased renin production by the kidney. It may be caused by a variety of conditions, including renovascular hypertension, reduced intravascular volume (from congestive heart failure, nephrosis, or cirrhosis), Bartter syndrome, and normal pregnancy. Adrenal function is normal in such cases, and treatment should be directed at the underlying disorder.

CUSHING SYNDROME

Cushing syndrome is an uncommon condition, with an annual incidence of one to 10 cases per million.¹¹ It may be caused by ACTH-secreting pituitary tumors, by ectopic ACTH-secreting tumors, or by cortisol-producing adrenal tumors. Of these conditions, ACTH-secreting tumors of the pituitary are the most common cause of Cushing syndrome, accounting for approximately 65 to 70% of cases. Ectopic production of ACTH accounts for between 10 and 15% of cases; small cell lung carcinomas are the most common

ectopic ACTH-secreting tumors (50% of ectopic cases), but thymic tumors, carcinoid tumors, and medullary thyroid carcinomas may also give rise to this syndrome. Adrenal tumors account for about 20% of cases of Cushing syndrome. Cortisol-producing adenomas are the most common cause of adrenal Cushing syndrome, followed by adrenocortical carcinomas (ACCAs). Primary nodular adrenal hyperplasia is a rare cause of adrenal Cushing syndrome.

Clinical Evaluation

A number of characteristic clinical symptoms and signs are associated with Cushing syndrome [see Table 3]. Obesity is the most consistent feature and is typically distributed in a central pattern around the face, the trunk, the neck, and the abdomen. Patients may have especially prominent supraclavicular fat pads and fat over the upper back (so-called buffalo hump). Skin changes are common and include easy bruising, increased fragility, and skin striae (often pigmented). Facial plethora is also frequently present. Generalized skin hyperpigmentation is seen more often in patients with ectopic ACTH production. Hirsutism from increased secretion of adrenal androgens may be present in women, but virilizing features are more often associated with ACCA. Increased production of adrenal androgens also causes gonadal dysfunction, manifested by amenorrhea and infertility. In men, increased cortisol secretion may result in reduced libido, decreased body hair, and testicular atrophy.

The initial goal in the evaluation of a person who may have Cushing syndrome is to determine whether a state of increased

Table 3 Symptoms and Signs of Cushing Syndrome

Symptoms
Weight gain
Florid complexion
Oligomenorrhea or amenorrhea
Decreased libido
Spontaneous bruising
Muscle weakness and fatigue
Mood swings, depression
Insomnia
Signs
Obesity (central distribution)
Facial fullness (moon facies)
Buffalo hump
Prominent supraclavicular fat pads
Telangiectasias
Skin striae (violaceous)
Osteopenia and osteoporosis
Hirsutism*

*May be associated with adrenocortical carcinoma.

cortisol production exists. If it does, subsequent testing should be undertaken (1) to determine whether the cause is ACTH dependent (a pituitary or ectopic ACTH-producing tumor) or ACTH independent (a primary adrenal lesion) and (2) to locate the source [see Figure 3].

Investigative Studies

Detection of Cushing syndrome When Cushing syndrome is suspected on clinical grounds, the initial diagnostic tests should be measurement of urinary free cortisol and an overnight dexamethasone suppression test. Urinary free cortisol levels are elevated in more than 90% of patients with Cushing syndrome.¹² False positive elevations can, however, occur as a result of use of medications (e.g., barbiturates or phenytoin), obesity, serious illnesses, or depression. Furthermore, mild degrees of hypercortisolism may be missed in a single 24-hour collection because of variation in cortisol secretion rates.

Dexamethasone is a potent glucocorticoid that suppresses adrenal production of corticosteroids in normal persons but not in persons with Cushing syndrome. To screen for this syndrome, the low-dose dexamethasone suppression test is usually employed. A single 1 to 3 mg dose of dexamethasone is administered orally at 11:00 pm, and the plasma cortisol level is measured at 8:00 am. In normal persons, the 8:00 am plasma cortisol levels are typically lower than 1.8 µg/dL, whereas in patients with Cushing syndrome, the cortisol levels are usually higher than 10 µg/dL. If both the dexamethasone test and the urinary free cortisol measurement yield normal results, the patient does not have Cushing syndrome. A notable feature of Cushing syndrome is the loss of the normal diurnal variation in cortisol; however, because of variation in levels, random cortisol determinations cannot be relied on in making the diagnosis. Late-night (11:00 pm) salivary cortisol levels have now been found to be highly

sensitive and specific in screening for Cushing syndrome and, as a result, may see increasing use in the future.^{13,14}

Levels of 17-hydroxycorticosteroid and 17-ketosteroid (urinary metabolites of cortisol) may be measured, but these levels are less useful in the diagnosis of Cushing syndrome than urinary free cortisol levels are. If the patient exhibits virilizing features, a plasma testosterone level should be obtained.

Differentiation of ACTH-dependent causes from independent causes Once the diagnosis of Cushing syndrome is established, a plasma ACTH level should be obtained to differentiate ACTH-dependent causes of the syndrome (i.e., pituitary and ectopic ACTH-secreting tumors) from ACTH-independent causes (i.e., adrenal lesions). In patients with pituitary Cushing syndrome, ACTH levels are typically normal or only moderately elevated (> 20 pg/mL). In patients with ectopic ACTH-secreting tumors, ACTH levels are usually higher, although there is some overlap with the levels measured in patients with Cushing disease. In patients with Cushing syndrome caused by an adrenocortical tumor, plasma ACTH levels are suppressed (< 5 pg/mL).

If it appears that the syndrome has an ACTH-dependent cause, the next step is to determine whether the cause is of pituitary or ectopic origin. Historically, the high-dose dexamethasone suppression test has generally been employed for this purpose. The rationale for this test is that high doses of glucocorticoids will suppress ACTH secretion from most ACTH-secreting pituitary adenomas but not from ectopic ACTH-secreting tumors. Dexamethasone is administered either in eight doses over 2 days (2 mg every 6 hours) or in a single oral 8 mg dose. Cortisol levels (in plasma for the single-dose version, in urine for the 2-day version) are measured before, during, and after administration of dexamethasone. With either version of the test, if the patient has pituitary Cushing syndrome, the plasma or urinary cortisol levels should be markedly suppressed (< 50% of the basal level), whereas if the patient has an ectopic ACTH-producing tumor, the cortisol levels should generally be unchanged. However, between 20 and 30% of patients with mildly increased ACTH secretion and pituitary Cushing syndrome do not show suppression of steroid production to a level below 50% of baseline, and some patients with ACTH-secreting tumors do show this degree of suppression of plasma or urinary steroids. Therefore, the overall diagnostic accuracy of high-dose dexamethasone suppression testing is only 70 to 80%.¹⁵ Other tests, such as the corticotropin-releasing hormone (CRH) stimulation test, are available for differentiating among the possible causes of ACTH-dependent Cushing syndrome, but at present, they are less commonly employed.

Localization Once biochemical evaluation is complete, the next step is radiographic localization of the source of the Cushing syndrome. If adrenal Cushing syndrome is suspected, abdominal cross-sectional imaging with CT is recommended. If a pituitary source is suspected, MRI of the pituitary should be the initial imaging test. Pituitary MRI with gadolinium enhancement will identify an adenoma in more than 60% of patients with pituitary Cushing syndrome. However, as much as 10% of the general population may

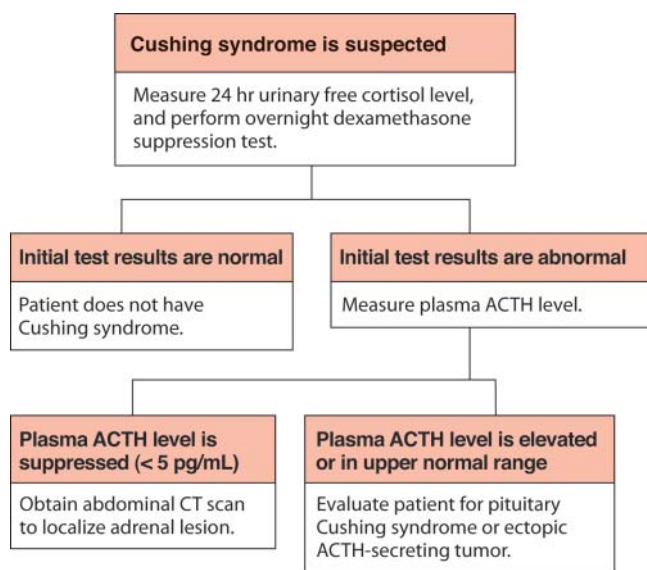


Figure 3 Algorithm illustrating diagnostic evaluation of the patient with suspected Cushing syndrome. ACTH = adrenocorticotrophic hormone; CT = computed tomographic.

have a pituitary incidentaloma, although these lesions are typically small (< 5 mm in diameter). If MRI is not conclusive, measurement of inferior petrosal sinus ACTH levels is recommended as the most direct method of differentiating pituitary from nonpituitary causes of ACTH-dependent Cushing syndrome. In this test, ACTH levels are simultaneously measured peripherally and in the two inferior petrosal sinuses both before and after IV administration of CRH (100 µg). An inferior petrosal sinus-to-periphery ACTH ratio that is higher than 3.0 is diagnostic of pituitary Cushing syndrome; a ratio that is lower than 1.8 is indicative of an ectopic ACTH-secreting tumor.¹⁶ In experienced hands, this procedure has a sensitivity and specificity of 80 to 90%.^{12,16} Ectopic ACTH-producing tumors are most often detected by means of CT scanning or radionuclide imaging with indium-111-labeled octreotide analogues, which detect tumors that express somatostatin receptors.

Subclinical Cushing Syndrome

Subclinical Cushing syndrome (SCS) is characterized by abnormalities in cortisol secretion in the absence of overt signs of classic Cushing syndrome. Such findings have been observed in up to 20% of adrenal incidentalomas.^{17,18} The array of biochemical abnormalities that define subclinical hypercortisolism include nonsuppressibility of cortisol secretion with dexamethasone, loss of the diurnal variation in cortisol secretion, low or suppressed plasma ACTH levels, and blunted response of ACTH to CRH. Twenty-four-hour urine free cortisol levels are elevated in only about 50% of patients with SCS, and the degree of elevation is usually mild.

The natural history of SCS has not been carefully studied, but these patients do have a higher incidence of hypertension, obesity, and diabetes than controls. In one series, the progression to overt Cushing syndrome at 1 year was 12.5%.¹⁹ Recently, outcomes were compared in 45 patients with SCS randomized to undergo adrenalectomy or conservative management.²⁰ Assessment was carried out yearly, with a mean follow-up of 7.7 years. In the surgical group, diabetes normalized or improved in 62.5% of patients, hypertension in 67%, hyperlipidemia in 37.5%, and obesity in 50%. In contrast, some worsening of diabetes, hypertension, and hyperlipidemia was observed in the conservatively managed group. No changes in osteoporosis parameters were seen in either group. These results suggest that adrenalectomy results in improved outcomes over conservative management in patients with SCS.

Most patients with SCS are detected during workup of an adrenal incidentaloma, usually by screening with an overnight dexamethasone test. Failure to suppress with dexamethasone should be evaluated further as outlined above for Cushing syndrome. Patients with SCS are at increased risk for adrenal insufficiency (AI) after adrenalectomy; therefore, they should be given perioperative glucocorticoids intravenously until they can take oral replacement. Replacement therapy may be necessary for up to 6 to 12 months until the pituitary–adrenal axis recovers.

DISORDERS OF EXCESS ADRENAL ANDROGEN PRODUCTION

Excess androgen production may be either acquired (as in Cushing syndrome or ACCA) or congenital (as in congenital

adrenal hyperplasia). Congenital adrenal hyperplasia comprises a group of autosomal recessive disorders characterized by defective synthesis of cortisol. This defect in cortisol synthesis results in increased ACTH production, which, in turn, leads to adrenal hyperplasia and increased production of adrenal androgens and androgen precursors. The most common variant of congenital adrenal hyperplasia is 21 α -hydroxylase deficiency, which accounts for about 95% of cases. 21 α -Hydroxylase deficiency may be divided into three main subtypes: classic salt wasting, classic non-salt wasting, and nonclassic. The two classic subtypes generally are more severe and typically present early in life (i.e., in infancy or early childhood) with virilizing features and AI. The non-classic subtype tends to be milder: the androgen excess is less pronounced, and there is no cortisol deficiency. As many as 80% of patients with the classic salt-wasting subtype experience severe electrolyte and fluid losses as a result of an associated defect in aldosterone production.

Excess adrenal androgen production from an androgen-secreting tumor can lead to testicular atrophy (in men) or to hirsutism, acne, and irregular or absent menses (in women). Women may also experience other virilizing features, such as male pattern baldness, clitoral enlargement, increased facial hair, and deepening of the voice. Biochemically, the diagnosis is established by measuring plasma levels of androgens, including dehydroepiandrosterone (DHEA), DHEA sulfate, testosterone, and dihydrotestosterone. Other causes of hirsutism and virilism that must be considered in women include the polycystic ovary syndrome and androgen-secreting ovarian tumors.

ADRENOCORTICAL CARCINOMA

ACCA is a rare tumor: the estimated annual incidence ranges from 0.5 to 2 per one million adults. The age distribution is bimodal, with peak occurrences noted in childhood and in the fourth and fifth decades of life.²¹

Clinical Evaluation and Investigative Studies

ACCAs are typically large (> 6 to 8 cm) at presentation, and most patients present with advanced (i.e., stage III or IV) disease [see Table 4]. In two large series, the mean tumor size at diagnosis was 12 and 15 cm.^{22,23} The increased use of imaging in clinical practice in recent years has not led to detection of ACCA at an earlier stage or impacted patient survival.^{24,25} The clinical presentation may be related to the large size of the tumor (e.g., abdominal or back pain or other mass effects) or to increased secretion of one or more steroid

Table 4 Staging of Adrenocortical Carcinoma*

Stage	Description
I	T1 (< 5 cm) N0 M0
II	T2 (> 5 cm) N0 M0
III	T3 (locally invasive), or T1–2 N1 M0
IV	T4 (invasion of adjacent organs), or any T with distant metastases (M1)

*Based on the staging system of the Union Internationale Centre le Cancer (UICC).⁵⁸

hormones. Approximately 60% of ACCAs are hyperfunctioning²⁶; about 30% secrete cortisol and give rise to Cushing syndrome, and 20% secrete androgen and have virilizing effects. A mixed hormone secretion pattern is frequently present. Adrenal cancers that secrete estrogen or aldosterone exist but are much less common.

Biochemical evaluation of ACCA patients should consist of testing for hypercortisolism [see Cushing Syndrome, *above*] and measurement of adrenal androgens (i.e., DHEA sulfate and testosterone).

Management

ACCA is an aggressive tumor that may spread locally to regional lymph nodes, adjacent organs, and distant sites (including the liver, the lungs, and bones). Complete surgical resection offers the only chance for a cure and is the best predictor of clinical outcome.²¹ Overall 5-year actuarial survival rates after complete resection range from 32 to 48%.²¹ Patients whose tumors are incompletely resected (i.e., who have residual local or distant gross disease) have a median survival of less than 1 year. The presence of tumor thrombus in the renal vein or inferior vena cava is not a contraindication for surgical resection provided that the tumor can be completely excised.^{21,26}

Treatment options for patients with unresectable or recurrent ACCA are limited. Locally recurrent tumors may be resected surgically. Radiation therapy is generally ineffective, although a few investigators have reported tumor response rates as high as 42%.²⁶ Mitotane is toxic for adrenocortical cells and is the most specific chemotherapeutic agent available for the treatment of ACCA. Objective tumor response rates as high as 25% have been reported, but complete responses to mitotane are rare,²⁶ and treatment is often limited by gastrointestinal and central nervous system side effects. In addition, because of mitotane's toxic effects on normal adrenal cortical function, patients being treated for ACCA with this agent require glucocorticoid replacement. Mitotane has occasionally been used as adjuvant therapy after resection of ACCA, but the data are inconclusive. The results of conventional cytotoxic chemotherapy in ACCA patients have been disappointing. The poor response rates to chemotherapy may be related to high expression of the multiple drug resistance gene *MDR1*; this results in high levels of P-glycoprotein, which acts as a drug efflux pump.^{26,27}

ADRENAL INSUFFICIENCY

AI may be either primary or secondary. In industrialized countries, the primary cause of spontaneous AI is autoimmune adrenal disease; in the developing world, it is tuberculosis.²⁸ Other causes of primary AI include bilateral adrenal hemorrhage, adrenal metastases, adrenal leukodystrophy, and certain viral or fungal infections. The primary cause of secondary AI is suppression of ACTH secretion and normal adrenal cortical function as a result of long-term steroid administration. Several weeks of exogenous administration of glucocorticoids are required before AI develops on steroid withdrawal.²⁸

Clinical Evaluation

Chronic AI (Addison disease) is characterized by weakness, chronic fatigue, anorexia, loss of appetite, abdominal pain,

nausea, and diarrhea. Hyperpigmentation of the skin from chronic hypersecretion of melatonin (a product of the ACTH precursor pro-opiomelanocortin) may be apparent as well. Many patients with primary AI also have an associated mineralocorticoid deficiency, the symptoms and signs of which include salt craving, postural hypotension, and electrolyte abnormalities. Because many of the symptoms of AI are non-specific, patients may go undiagnosed for a long time. The symptoms of primary AI are usually more severe than those of secondary AI.

In patients with inadequate adrenal reserve, an acute adrenal crisis may be precipitated by the stress imposed by surgery, trauma, infection, or dehydration and may result in vascular collapse with hypotension, shock, and, if untreated, death. Consequently, patients with unexplained cardiovascular collapse in whom this diagnosis is suspected should be treated empirically with replacement corticosteroids.

Investigative Studies

Laboratory abnormalities associated with AI include hyponatremia, hyperkalemia (in primary AI), hypoglycemia, and azotemia, with increased blood urea nitrogen and creatinine concentrations. The diagnosis is confirmed by measurement of plasma cortisol and ACTH levels. In primary AI, 8:00 am plasma cortisol levels are typically low (< 3 µg/dL),²⁹ and plasma ACTH levels are high (> 100 pg/mL). Plasma ACTH levels are usually low or inappropriately normal if pituitary failure or hypothalamus pathology is the cause.²⁸ The ACTH stimulation test may be necessary to establish the diagnosis in patients with partial AI or to assess recovery of the pituitary-adrenal function after treatment of Cushing syndrome. For this test, 250 µg of synthetic ACTH is administered intravenously, and plasma cortisol levels are measured at 0, 30, and 60 minutes. A serum cortisol level higher than 18 µg/dL at either 30 or 60 minutes is considered a normal response.

Management

AI is treated with exogenously administered glucocorticoids [see Table 5]. If the patient is in an acute adrenal crisis, hydrocortisone should be given in a dosage of 100 mg IV every 8 hours. If the patient requires oral replacement therapy for chronic AI, hydrocortisone should be given in a dosage of 10 to 12.5 mg/m²/day.²⁸ Hydrocortisone (20 to 30 mg/day) is often preferred to other steroids because its short half-life (8 to 12 hours) more closely mimics the normal circadian rhythm of cortisol secretion; however, it must be administered twice or three times daily, whereas prednisone (equivalent dose,

Table 5 Equivalent Dosages for Commonly Used Glucocorticoids^{21,22}

Glucocorticoid	Relative Potency	Dose Equivalent (mg/day)	t _{1/2} (hr)
Hydrocortisone	1	20	8–12
Prednisone	4	5	18–36
Methylprednisolone	5	4	18–36
Dexamethasone	25–50	0.5	36–54

t_{1/2} = half-life.

5 mg/day) may be administered once or twice daily. For patients who are on long-term steroid therapy, outcomes after surgery appear to be essentially the same whether they received their normal replacement doses orally or whether they received stress doses intravenously.³⁰ Patients who have primary AI or have undergone bilateral adrenalectomy should also receive mineralocorticoid therapy (fludrocortisone 0.05 to 0.2 mg/day).

Disorders of the Adrenal Medulla

PHEOCHROMOCYTOMA

Pheochromocytomas are catecholamine-producing tumors that arise from chromaffin tissue.³¹ The majority (85 to 90%) develop in the adrenal gland, but some occur at extra-adrenal sites. These tumors have their peak incidence during the fourth and fifth decades of life, and they affect males and females with equal frequency. The prevalence of pheochromocytoma in hypertensive patients is approximately 0.1 to 0.5%. Clinically silent pheochromocytomas may be present in as many as 10% of patients who present with an adrenal incidentaloma.³² Several features of pheochromocytomas have been characterized by a 10% frequency of distribution: 10% are extra-adrenal, 10% are bilateral, 10% occur in children, 10% are familial, and 10% are malignant. Some more recent series, however, have reported lower percentages of malignant pheochromocytomas.^{33,34} Because extra-adrenal pheochromocytomas (also referred to as paragangliomas) lack the enzyme phenylethanolamine-*N*-methyltransferase (PNMT), they can secrete norepinephrine but not epinephrine.

Clinical Evaluation

The clinical features of pheochromocytoma are related to the effects of increased secretion of norepinephrine and epinephrine.³¹ Hypertension is the most consistent feature and may be either paroxysmal or sustained. Paroxysmal hypertension can be severe and may be associated with “spells” consisting of pounding in the chest, tachycardia, headache, anxiety, and pallor; these spells are related to catecholamine surges. Other symptoms that may be noted include temperature elevation, flushing, and sweating, and some patients experience a feeling of marked anxiety and an impending sense of doom. Most attacks are short and last less than 15 minutes. The paroxysms may occur spontaneously, or they may be precipitated by postural changes, vigorous exercise, sexual intercourse, alcohol, and the use of certain drugs (e.g., histamine, tricyclic antidepressants, and metoclopramide) or anesthetic agents.

Some patients with pheochromocytoma present with an extreme hypertensive crisis that may result in severe headaches, diaphoresis, visual changes, acute myocardial infarction, cardiac dysrhythmias, congestive heart failure, pulmonary edema, or even stroke. Sudden death has been reported in patients with unsuspected pheochromocytomas who have undergone percutaneous biopsy of the tumor^{35,36} or surgical procedures for other indications. Hypertensive emergencies are treated with IV esmolol, phentolamine (or sodium nitroprusside), or both.

Pheochromocytoma should be suspected in any patient with severe hypertension, any patient with hypertension that

is episodic or associated with spells, any hypertensive pediatric patient, any patient with a family history of pheochromocytoma or multiple endocrine neoplasia (MEN) type IIA or MEN IIB, and any hypertensive patient with medullary thyroid carcinoma.

Investigative Studies

Laboratory tests The diagnosis of pheochromocytoma is established by demonstrating elevated levels either of catecholamines and metabolites (metanephrines) in urine or of fractionated metanephrines in plasma.^{37,38} The urinary vanillylmandelic acid (VMA) concentration is the least specific test because of the frequency of false positive results caused by ingestion of related foods (e.g., coffee, tea, and raw fruits) or drugs (e.g., alpha-methyldopa). Because the plasma fractionated metanephrine concentration is both sensitive for pheochromocytoma and considerably simpler than a 24-hour urine collection, it is the preferred initial screening test in many institutions; however, some investigators have found that measurement of 24-hour urinary catecholamine and metanephrine levels yields fewer false positive results.³⁷ In most cases, abnormal plasma metanephrine and norepinephrine levels should be confirmed by measurement of urinary catecholamine and metanephrine concentrations. In cases where diagnosis is particularly difficult, direct measurement of plasma catecholamine levels during a hypertensive episode may be useful.

Certain agents may interfere with biochemical testing for pheochromocytoma, including iodine-containing contrast media, labetalol, tricyclic antidepressants, and levodopa.³⁹ Major stress (e.g., from a recent stroke, a major operation, obstructive sleep apnea, or renal failure) may also affect catecholamine and metabolite levels. Because of the sensitivity of current tests and the risk of blood pressure alterations, provocative testing with agents such as glucagon or histamine and suppression testing with clonidine are no longer commonly used for diagnosis of pheochromocytoma.

Imaging Given that only 2 to 3% of pheochromocytomas are found outside the abdomen, localization of suspected tumors should begin with abdominal CT or MRI.³⁸ The uniquely bright appearance pheochromocytomas typically exhibit on T₂-weighted MRI sequences [see Figure 4] makes MRI the preferred imaging modality in many institutions. Another option is scintigraphy with iodine-labeled metaiodobenzylguanidine (I-MIBG). MIBG labeled with ¹³¹I or ¹²³I selectively accumulates in chromaffin tissues but does so more rapidly in pheochromocytomas than in normal adrenal medullary tissue. Multi-institutional experience with ¹³¹I-MIBG imaging for pheochromocytomas has found this modality to have an overall sensitivity of 77 to 90% and a specificity of 96 to 100%.⁴⁰ ¹²³I-MIBG is now available for use and appears to have greater sensitivity than does I-MIBG scintigraphy. Indium-labeled octreotide scintigraphy has also been used to localize pheochromocytomas but has much less sensitivity for benign pheochromocytomas than does MIBG and should be reserved for cases in which all other imaging studies are inconclusive.⁴¹ I-MIBG scintigraphy is most useful for localizing extra-adrenal tumors that are not visualized by conventional imaging modalities and for following patients with malignant pheochromocytomas. Its main disadvantages



Figure 4 Magnetic resonance image showing a left adrenal pheochromocytoma (arrows). Pheochromocytomas typically appear bright on T₂-weighted images.

are its greater complexity and cost (in comparison with other imaging techniques), the need to block thyroid uptake with oral iodine, and the fact that some medications interfere with pharmacologic uptake of the tracer. I-MIBG is not warranted in patients with uncomplicated pheochromocytomas that are localized on CT or MRI as it is expensive and rarely alters treatment in this setting.^{42,43}

Pharmacologic Preparation for Operation

Once the diagnosis of pheochromocytoma has been established biochemically and radiographically, the next step is to prepare the patient for adrenalectomy pharmacologically so as to prevent an intraoperative hypertensive crisis. Preoperative alpha blockade with phenoxybenzamine is initiated, usually starting at a dosage of 10 mg twice daily, which is then gradually increased to a total of 60 to 90 mg/day in divided doses until hypertension is controlled and the patient is mildly orthostatic. As alpha blockade progresses, fluids should be administered liberally to fill the expanded intravascular space. If the patient has marked tachycardia or dysrhythmia, beta blockade with atenolol or metoprolol may also be required. Beta blockade should never be initiated until alpha blockade has first been achieved, because unopposed alpha-receptor stimulation can induce a hypertensive crisis.

Associated Inherited Syndromes

Pheochromocytomas may occur in the setting of a number of different inherited endocrine tumor syndromes [see Table 6]. Of these, the ones most commonly associated with pheochromocytoma are von Hippel-Lindau (VHL) syndrome and the MEN II syndromes. In addition to pheochromocytoma, VHL syndrome is characterized by bilateral renal tumors and cysts, cerebellar and spinal hemangioblastomas, retinal angiomas, pancreatic cysts and tumors, epididymal cystadenomas, and inner ear canal tumors.⁴⁴ MEN IIA and IIB are associated with medullary thyroid carcinoma in 100% of cases. The incidence of pheochromocytomas in MEN IIA and IIB

patients ranges from 30 to 50%. MEN II arises from mutations in the *ret* proto-oncogene on chromosome 10. Specific *ret* mutations associated with pheochromocytoma occur predominantly on codons 618 and 634.⁴⁵ In addition, familial paragangliomas of the neck are now known to be associated with mutations in the succinate dehydrogenase subunit B (*SDHB*) and succinate dehydrogenase subunit D (*SDHD*) genes,^{46,47} which encode mitochondrial enzymes involved in oxidative phosphorylation.⁴⁸

Familial pheochromocytoma may be more common than was previously thought. A 2002 study found mutations in 24% of patients who presented without a known familial pheochromocytoma association: 30 had mutations of the *VHL* gene, 13 of *ret*, 11 of the *SDHD* gene, and 12 of the *SDHB* gene.⁴⁹ These findings suggest the need for careful screening for a familial disorder in this setting.

Management

Patients undergoing adrenalectomy for pheochromocytoma should be monitored intraoperatively via an arterial line. Although pheochromocytomas are highly vascular, and the larger ones can be quite challenging to remove, a laparoscopic approach is feasible in most cases. Any intraoperative exacerbation of hypertension may be managed with esmolol or nitroglycerine.

After resection, patients who have significant cardiac disease or who exhibited significant hemodynamic changes during the operation should be observed in the intensive care unit overnight. Glucose levels should be monitored because catecholamine-induced suppression of insulin secretion may lead to rebound hyperinsulinemia and thence to hypoglycemia. Most patients can be discharged within 24 to 48 hours after adrenalectomy. Periodic follow-up biochemical testing is indicated because of the potential for recurrence after resection of even benign-appearing tumors.

Adrenal Incidentaloma

Today, the incidentally discovered adrenal mass is by far the most commonly encountered adrenal lesion, primarily because of the frequency with which patients currently undergo cross-sectional imaging.⁵⁰ Various series have reported finding adrenal incidentalomas in 1 to 5% of patients who undergo CT scanning for other reasons.⁵¹

CLINICAL EVALUATION

Most adrenal incidentalomas are clinically silent, do not secrete excess adrenal hormones, and do not cause pain. The differential diagnosis of an adrenal incidentaloma includes all of the functioning adrenal tumors, primary or metastatic adrenal malignancy, and various nonfunctioning lesions.⁵² Nonfunctioning cortical adenoma is the most common adrenal incidentaloma, accounting for approximately 60% of cases.⁵² Other miscellaneous adrenal lesions that are sometimes seen in this setting are myelolipomas and cysts. Of the hyperfunctioning tumors, cortisol-producing adenomas (most of which are subclinical in behavior) and pheochromocytomas are the most frequently identified. Some adrenal incidentalomas are bilateral; in such cases, the differential diagnosis includes adrenal cortical hyperplasia, bilateral pheochromocytomas, metastases, lymphoma, myelolipomas, and infection (tuberculosis).

Table 6 Inherited Pheochromocytoma Syndromes

Syndrome	Mutation	Chromosome	Frequency (%)*
MEN IIA and IIB	<i>ret</i> (proto-oncogene)	10q11	30–50
von Hippel-Lindau syndrome	<i>VHL</i> (tumor suppressor gene)	3p25	15–20
Neurofibromatosis	<i>NF1</i>	17q11	1–5
Familial paraganglioma and extra-adrenal pheochromocytoma	<i>SDHD</i> [†]	11q23	—
	<i>SDHB</i> [†]	1p35-36	—
	<i>SDHC</i> [†]	1q21	—

MEN = multiple endocrine neoplasia.

*Clinical incidence of tumors within persons affected by the mutation.

[†]*SDHD*, *SDHB*, and *SDHC* designate specific mutations within the succinate dehydrogenase gene (*SDH*). Patients with *SDHD* mutations are more likely to have head and neck paragangliomas, whereas *SDHB* mutations are more likely to be associated with extra-adrenal pheochromocytomas and malignant tumors.

INVESTIGATIVE STUDIES

Evaluation of the patient with an adrenal incidentaloma should be directed toward determining whether the lesion is hypersecretory and assessing the likelihood of malignancy [see Figure 5].

Laboratory Tests

For all patients with adrenal incidentalomas, biochemical screening should include, at a minimum, an overnight dexamethasone test to exclude hypercortisolism and measurement of the concentrations of either plasma metanephrines or urinary catecholamines and metabolites to test for pheochromocytoma. Although aldosteronomas, being relatively small, do not often present as incidentalomas, measurement of

plasma aldosterone and renin levels is nonetheless indicated for hypertensive or hypokalemic patients with an incidentally discovered adrenal mass. Approximately 8% of patients with adrenal incidentalomas have SCS, as discussed above.¹⁷ Adrenalectomy is appropriate in these patients if the operative risk is acceptable.

Imaging

The second component of the evaluation of an adrenal incidentaloma is assessment of the imaging features. Size is the variable that should be addressed first; a lesion smaller than 4 cm in a patient without a known malignancy is very unlikely to be malignant. The shape and visual texture of the lesion should then be considered. Benign lesions tend to be smooth and homogeneous, whereas malignant lesions often have irregular contours and areas of inhomogeneity. Cortical adenomas are further characterized by the presence of intracellular lipid, which on noncontrast CT scanning gives the mass an appearance that is homogeneous and low in attenuation (< 10 Hounsfield units, which is less than the liver or the kidney but higher than retroperitoneal fat) [see Figure 6].

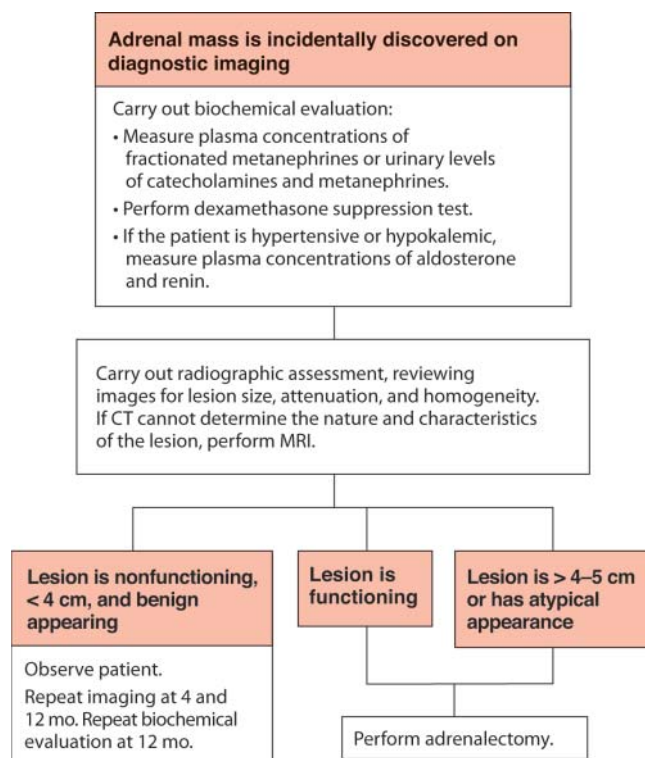


Figure 5 Algorithm illustrating diagnostic evaluation of the patient with an incidentally discovered adrenal mass. CT = computed tomography; MRI = magnetic resonance imaging.

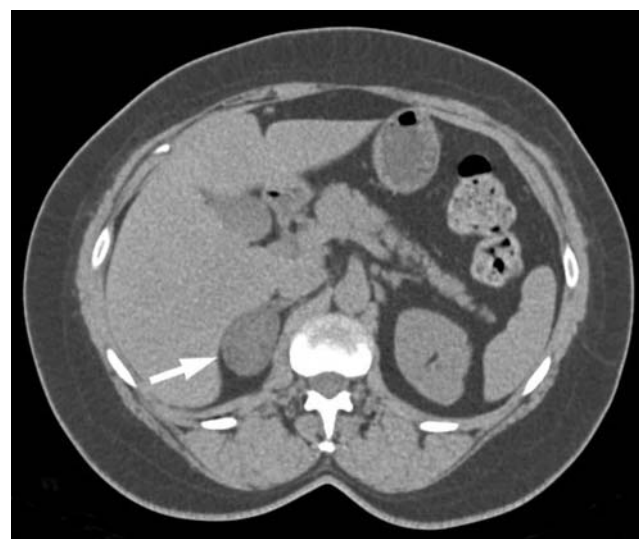


Figure 6 Computed tomographic scan showing a nonfunctioning cortical adenoma (arrow).

ACCAs and metastases are higher in water content and therefore have higher attenuation values (usually > 18 Hounsfield units). There may, however, be some overlap in attenuation values between adenomas and malignancies, and, in any case, many patients with incidentalomas initially underwent CT scanning with IV contrast, which makes subsequent assessment of attenuation values problematic. Pheochromocytomas, because of their vascularity, show prominent enhancement on IV contrast studies and may have areas of cystic degeneration. On unenhanced scans, their density is similar to that of the liver.

In cases where the nature of the lesion cannot be determined on the basis of CT scanning, MRI can provide additional characterization of the lesion that may help direct management. For example, on T₂-weighted sequences, adenomas typically exhibit low signal activity, whereas pheochromocytomas and metastases appear bright. Magnetic resonance (MR) chemical-shift imaging may also have significant diagnostic value. This modality is based on the different resonance frequencies of the protons in water and those in fat. Depending on the imaging parameters, the water and lipid magnetic dipoles will be either in phase or out of phase. If an adrenal lesion with a high lipid content (e.g., an adrenal adenoma) is imaged with MR chemical-shift imaging, the mass will lose signal intensity on opposed-phase images (because the water signal and the fat signal will tend to cancel each other out). In contrast, if an adrenal lesion with a low lipid content (e.g., an adrenal malignancy or a pheochromocytoma) is imaged with this technique, the mass will not show a significant loss of signal intensity on opposed-phase images (because there will not be sufficient fat protons to cancel out the water signal). Some reports have found the loss of signal on MR chemical-shift imaging to be highly predictive of an adenoma.⁵³

Although positron emission tomography (PET) is increasingly employed for evaluation of adrenal incidentalomas, its role in this setting remains to be determined. The main value of PET with respect to adrenal disease is to identify extra-adrenal tumor sites in patients with a known cancer.

Biopsy

Needle biopsy of adrenal masses is rarely indicated. It does not often yield diagnostic information, it cannot differentiate benign from malignant adrenal cortical tumors, and it is associated with a not insignificant risk of complications.⁵⁴ Moreover, if the lesion is an undiagnosed pheochromocytoma, needle biopsy may lead to hypertensive crisis and sudden death. Despite these known drawbacks, in three series from the past few years, a number of patients with undiagnosed pheochromocytomas presenting as incidentalomas underwent adrenal biopsy before any biochemical testing.^{33,34,54}

MANAGEMENT

Most adrenal surgeons recommend removing nonfunctioning adrenal masses larger than 5 cm and observing masses smaller than 3 cm unless they are obvious myelolipomas or cysts [see Miscellaneous Adrenal Lesions, *below*]. Management of masses 4 to 5 cm in size should be individualized, with adrenalectomy favored if the patient is young or if the imaging features are at all atypical for an adenoma. Patients

for whom resection is not appropriate should be followed with repeat imaging at 4 to 6 months and with both repeat imaging and biochemical testing at 1 year. If the lesion is nonfunctioning and stable in size throughout the follow-up period, no further monitoring is required.

Adrenal Metastases

Adrenal metastases occur most commonly in the setting of more widespread metastatic disease. Renal cell cancer, lung cancer, and melanoma are the malignancies that most frequently metastasize to the adrenal gland, but various other tumors (e.g., breast cancers, colon and other gastrointestinal cancers, and lymphomas) may also involve the adrenal. Occasionally, the adrenal gland is the site of an apparent solitary metastasis for which resection is indicated. Imaging characteristics associated with adrenal metastases include larger size (> 3 cm), higher attenuation on CT, and no signal loss on MR chemical-shift imaging. PET is often indicated to exclude extra-adrenal metastatic disease that would preclude resection [see *Figure 7*]. Biopsy of a suspected adrenal metastasis should be carried out only if a tissue diagnosis is needed to direct therapy—that is, if the patient is not a surgical candidate either for medical reasons or because of metastases at other sites. Biopsy is not indicated before resection of a solitary resectable lesion, because it could lead to tumor seeding or other complications. Reported 5-year actuarial survival rates after resection of an isolated adrenal metastasis range from 24 to 29%.⁵⁵

Miscellaneous Adrenal Lesions

The adrenal disorders previously described (see above) are the ones most frequently seen and managed by surgeons; however, there are a number of other adrenal lesions that surgeons may also encounter, such as myelolipomas, ganglioneuromas, cysts, and hemorrhage.

Myelolipomas are benign lesions that are composed of fat and bone marrow elements and are usually identified as incidentalomas. In most instances, they can be diagnosed radiographically on the basis of macroscopic fat that is present within the mass [see *Figure 8*]. Myelolipomas may become quite large (> 6 cm), but regardless of their size, they should not be removed unless they are causing symptoms. Ganglioneuromas are benign tumors that may arise either within the adrenal medulla or at an extra-adrenal site. Most adrenal cysts are lymphangiomatous cysts, but pseudocysts from previous hemorrhage may also develop.

Hemorrhage in the adrenal gland is most often the consequence either of trauma or of an underlying adrenal tumor. Accordingly, follow-up imaging should be performed to search for an adrenal mass that may be obscured by the bleeding.

Indications for Adrenalectomy

Any adrenal lesion that is hyperfunctioning or that is suspected of being malignant or possibly malignant on the basis of size or other imaging criteria should be removed. Adrenal metastases should be resected only if they are solitary

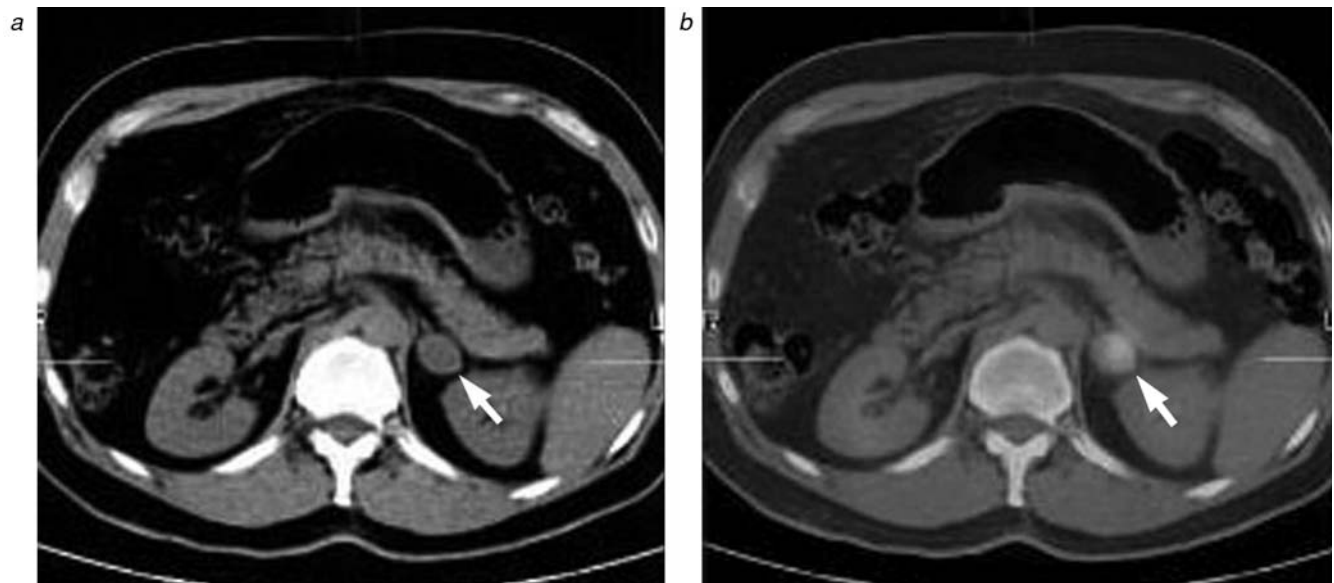


Figure 7 Shown are (a) computed tomography and (b) positron emission tomography images of a metastasis to the left adrenal gland (arrows).



and appear in the absence of extra-adrenal metastatic disease. Most of the adrenal disorders discussed in this chapter are amenable to laparoscopic resection. At present, the only absolute contraindication to laparoscopic adrenalectomy is a tumor with local or regional extension. Some controversy remains surrounding laparoscopic removal of large (> 6 to 8 cm) or potentially malignant primary adrenal lesions; this issue is beyond the scope of the present discussion but has been reviewed in greater detail elsewhere.⁵⁶ Surgeons who attempt laparoscopic adrenalectomy in this setting should be highly experienced with the procedure. Preparation for adrenalectomy consists of control of hypertension, correction of underlying electrolyte abnormalities, and management of comorbid conditions (to the extent possible).

Figure 8 Shown is a myelolipoma of the right adrenal gland. The areas of macroscopic fat (arrows) are typical for this lesion.

Discussion

Adrenal Physiology

The ensuing discussion focuses on adrenal physiology—specifically, on the secretion of steroid hormones and catecholamines.

The adrenal cortex is the site where cortisol, aldosterone, and androgens are synthesized. These steroid hormones are all derived from cholesterol, which is converted to pregnenolone under the influence of ACTH. There are three histologic zones within the adrenal cortex: the zona glomerulosa, the zona fasciculata, and the zona reticularis. The zona glomerulosa lacks the enzyme 17α -hydroxylase, which is necessary for synthesis of cortisol and androgens; consequently, it is the exclusive site for the synthesis of aldosterone. Cortisol

secretion is regulated by the hypothalamus, which secretes CRH, and the pituitary, which secretes ACTH. ACTH stimulates cortisol synthesis and secretion from the adrenal gland, and high circulating cortisol levels inhibit pituitary and hypothalamic secretion of ACTH and CRH. Cortisol exerts its effects on intermediary metabolism via a wide range of cells and tissues. These effects include stimulation of hepatic gluconeogenesis and glycogen synthesis, inhibition of protein synthesis, increased protein catabolism, and lipolysis of fat. Cortisol also inhibits peripheral uptake of glucose in most tissues (except in the liver, the brain, and red blood cells), and this inhibitory effect may cause hyperglycemia and increased insulin secretion, especially in states of chronic

cortisol excess.⁵⁷ Other effects of glucocorticoids include promotion of collagen loss and impairment of wound healing by inhibition of fibroblast activity, inhibition of bone formation and acceleration of the development of osteoporosis, and numerous antiinflammatory actions. Glucocorticoids are also critical for cardiovascular stability, which helps explain why some patients with acute AI experience cardiovascular collapse.

Adrenal androgens are synthesized predominantly in the zona reticularis. The primary androgen produced by the adrenal is DHEA, although DHEA sulfate and androstenedione also play important roles. Peripherally, the adrenal androgens undergo conversion to testosterone and dihydrotestosterone. A number of different conditions may result in increased adrenal androgen production, including Cushing syndrome, adrenal carcinoma, and congenital adrenal hyperplasia. In normal males, adrenal androgens account for less than 5% of total testosterone production, but in normal females, they are the major source of androgens.

The principal action of aldosterone is regulation of extracellular fluid volume and sodium and potassium balance. Aldosterone is secreted in response to increased renin production via the renin-angiotensin-aldosterone pathway. Decreased pressure in the renal afferent arterioles (as a consequence of hypotension or other conditions causing reduced intravascular volume) and decreased plasma sodium levels stimulate increased renin secretion from the juxtaglomerular

cells. Renin then stimulates conversion of angiotensinogen into angiotensin I, which is in turn cleaved by angiotensin-converting enzyme (ACE) in the lung to form angiotensin II. Angiotensin II, in addition to its direct vasoconstrictive effects, acts on the zona glomerulosa to stimulate aldosterone secretion. Aldosterone then stimulates renal tubular retention of sodium, which is reabsorbed in exchange for potassium and hydrogen ion. The ultimate effect of these actions is to expand intravascular volume. In pathologic states such as primary hyperaldosteronism, the cumulative effect is chronic volume expansion and sodium retention, leading to hypertension and hypokalemia.

The adrenal medulla is derived embryologically from the neural crest and is the principal site for synthesis of the catecholamines epinephrine and norepinephrine. Only the adrenal medulla has the enzyme PNMT, which is necessary for conversion of norepinephrine to epinephrine; however, norepinephrine itself may be synthesized in other chromaffin tissues. Catecholamines are secreted in response to a variety of stimuli, including bleeding, trauma, exercise, hypoglycemia, angina, myocardial infarction, hypoxia, and fright. The effects of increased catecholamine secretion include vasoconstriction (alpha receptor) and increased heart rate and myocardial contractility (beta₁ receptor). The effects of epinephrine include vasodilatation and bronchial dilatation, which are mediated via beta₂ receptors.

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39 ACUTE AND CHRONIC PANCREATITIS

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Clinical evaluation and surgical decision making in patients with acute and chronic pancreatitis are arguably the most complex that a general surgeon faces. These patients require an accurate and precise history of present illness, a detailed past medical history, and a complete physical examination. Laboratory testing confirms the diagnosis and, in the case of acute pancreatitis (AP), helps in the stratification of disease severity. Radiographic imaging is essential as an “anatomic roadmap,” delineating pancreatic ductal anatomy and gland morphology to allow the proper selection of a specific operation from a wide range of possibilities. Disease-specific outcomes in patients with necrotizing pancreatitis are optimal in centers that use a multidisciplinary approach to treatment. These institutions can care for critically ill patients with organ failure, have the ability to intervene using a wide range of approaches (percutaneously, endoscopically, laparoscopically, or operatively), and can provide longitudinal care in both the inpatient and outpatient settings throughout a 3- to 6-month course of illness. Acute and chronic pancreatitis, although occasionally present in the same patient (acute on chronic pancreatitis), are two separate disease entities with unique laboratory and radiographic investigations, operations, and postoperative care. For these reasons, this chapter is divided into two independent but sequential sections.

Acute Pancreatitis

INITIAL CLINICAL EVALUATION

History

AP is a common disease affecting approximately 79.8 in 100,000 patients per year in the United States, and the surgeon is usually contacted to see them in the emergency department or as surgical consultations on the medical ward.¹ A careful history is the first step in establishing a correct diagnosis [see *Figure 1*]. The pain of AP is characteristically abrupt in onset (occasionally waking the patient from sleep), severe in intensity, boring and constant in character, and upper abdominal (supraumbilical) in location. The pain is frequently described as radiating to the back, chest, flanks, or upper quadrant and commonly conveyed as the worst pain the patient has ever experienced. Nausea and vomiting are prominent associated features related to the accompanying paralytic ileus. Fever is a ubiquitous finding that reflects

the inflammatory nature of the underlying disease state. Although pain is a common finding, it should be emphasized that AP can also occur without abdominal pain in patients who present with shock of unknown origin or in patients early in the postoperative period, when analgesics often mask their abdominal symptoms.

The patient's past medical history should be carefully assessed for previous bouts of pancreatitis, hyperlipidemia, parathyroid disease, abdominal trauma, or past endoscopic manipulations (i.e., endoscopic retrograde cholangiopancreatography [ERCP], sphincterotomy) to identify a possible etiology. The patient's use of alcohol and tobacco should be elicited, noting the type of alcohol, volume consumed, and patterns of consumption (daily, weekend, binge drinker). The pack-year smoking history should also be recorded. The presence of prior biliary symptoms, for example, episodic colicky right upper quadrant abdominal pain associated with fatty food intake, or a prior history of gallstones or cholecystectomy should be sought. Careful review of the patient's home medications should be done, focusing carefully on those carrying a close association with the development of pancreatitis.²

Physical Examination

After obtaining a history, a careful physical examination should be performed. Inspection of the patient often finds the patient lying in bed in moderate distress. Their mucous membranes are dry, and their eyes are sunken. Note the presence or absence of scleral icterus. The abdomen is usually mild to moderately distended and symmetrical. Bluish discoloration around the umbilicus (Cullen sign) and a blue-gray discoloration of the abdominal flanks (Grey-Turner sign), although renowned in surgical lore, are rare findings. Auscultation reveals decreased breath sounds at the lung bases (reflective of sympathetic pleural effusions), commonly left greater than right, and hypoactive bowel sounds. Palpation allows an estimated quantification of the degree of volume deficit based on a patient's loss of skin turgor and dryness of the mucous membranes. Abdominal examination demonstrates a diffusely tender abdomen with rigidity and involuntary guarding. Occasionally, patients will present in writhing abdominal pain, a rigid abdomen, and accompanying peritoneal signs mimicking an intra-abdominal catastrophe. Late in a patient's clinical course (2 to 6 weeks postpancreatitis),

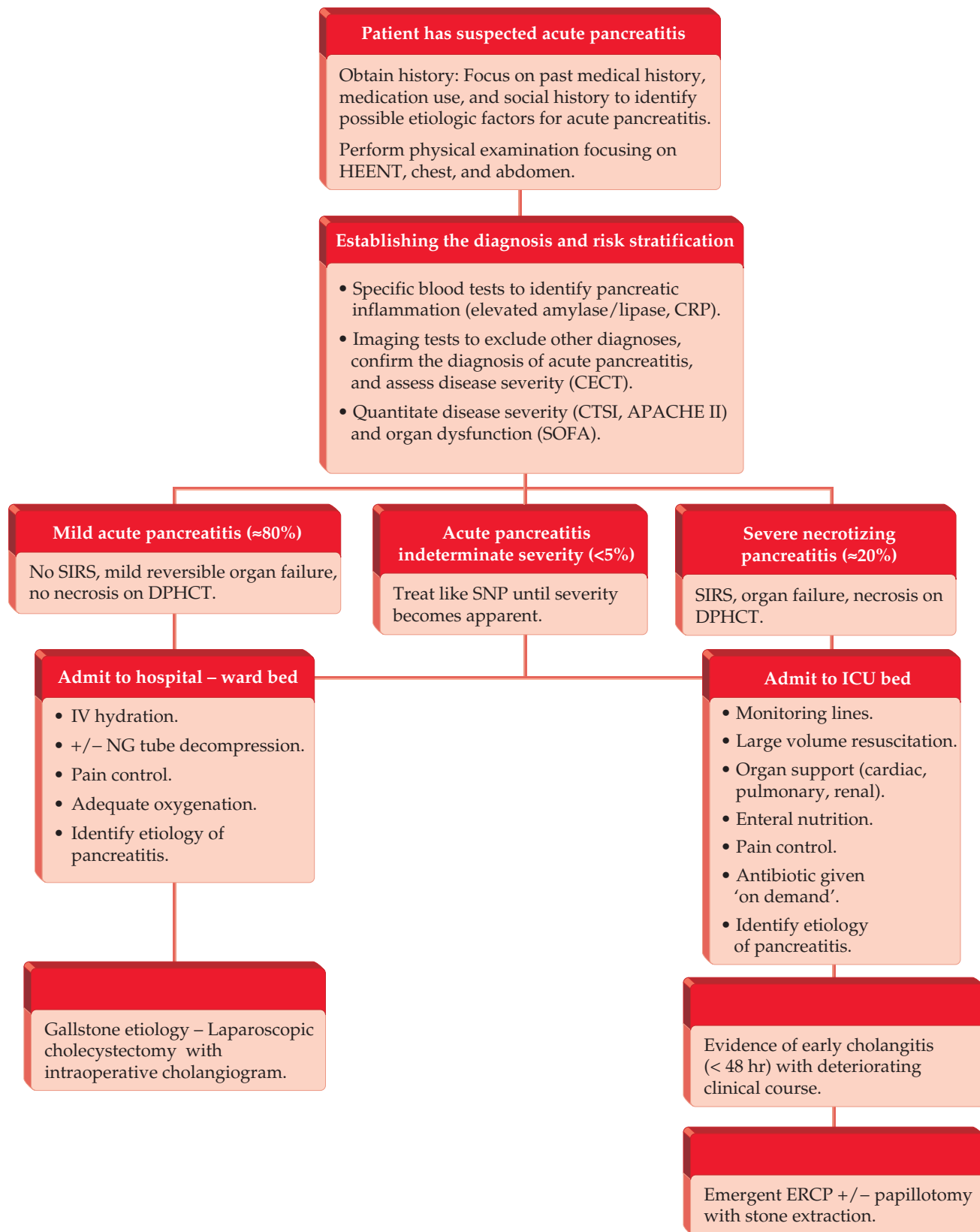


Figure 1 Diagnosis and initial treatment of acute pancreatitis. APACHE II = Acute Physiology and Chronic Health Evaluation II; CECT = contrast-enhanced computed tomography; CRP = C-reactive protein; CTSI = Computed Tomography Severity Index; DPHCT = dual-phase helical computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; HEENT = head, ears, eyes, nose, and throat; ICU = intensive care unit; IV = intravenous; NG = nasogastric; SIRS = systemic inflammatory response syndrome; SNP = severe necrotizing pancreatitis; SOFA = sequential organ failure assessment.

poorly defined upper abdominal masses reflect peripancreatic lesser sac fluid collections or pancreatic pseudocysts.

ESTABLISHING THE DIAGNOSIS

Laboratory Tests

Up until this point, the patient's clinical history, signs, and symptoms are suspicious but not diagnostic of AP and, in fact, are consistent with those of many other common surgical illnesses, such as perforated duodenal ulcer, mechanical small bowel obstruction, volvulus, or acute mesenteric ischemia. The diagnosis of AP requires two of the following three features: (1) abdominal pain suspicious for pancreatic origin, (2) serum amylase and/or lipase activity usually at least three times greater than the upper limit of normal, or (3) characteristic findings on contrast-enhanced computed tomography (CECT). Laboratory and/or radiologic investigations are not only essential for diagnosis but also provide important information to allow for risk stratification of disease severity.

Serum pancreatic enzyme measurements are the gold standard for identifying AP. Amylase, lipase, elastase, and trypsin are released into the bloodstream simultaneously at the onset of the disease but are then cleared from the blood at different rates. Amylase is cleared most rapidly (< 48 hours), whereas lipase and elastase remain elevated for over 96 hours. It is because of this differential clearance that the magnitude of elevation for any specific enzyme is dependent on the timing of the blood draw in relation to the onset of disease. In AP, disease onset is defined as the time that the patient's abdominal pain began, not when the patient is first evaluated by medical personnel. Many patients have been home with severe abdominal pain for 24 to 48 hours prior to their presentation in the emergency room, placing them well into the course of their disease process. Amylase traditionally has been the serum test of choice for diagnosis, although its overall sensitivity (83%) is limited by extrapancreatic causes of hyperamylasemia, a short serum half-life, and its unreliability in patients with chronic acinar cell damage (chronic pancreatitis). Currently, serum lipase levels greater than three times normal are the most accurate single test (sensitivity 92%) for diagnosing AP.³

A complete blood count (CBC) with differential and platelet count, comprehensive metabolic panel, arterial blood gas, and serum lactate are appropriate laboratory tests to review. The purpose of these is to assess both the degree of systemic inflammatory response and corresponding organ dysfunction in patients with AP. Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase, alkaline phosphatase, bilirubin) are used primarily to distinguish biliary pancreatitis from other causes of AP and to identify those patients who may have an impacted stone at the ampulla of Vater causing persistent pancreatic and biliary ductal obstruction. A recent meta-analysis showed that a threefold or greater elevation of ALT has a 95% positive predictive value for a gallstone etiology of AP. As a corollary to this statement, only half of all patients with known gallstone pancreatitis have significant elevations of their serum ALT. Therefore, although reasonably specific, an ALT less than three times normal is not particularly sensitive. C-reactive protein levels over 150 mg/L after 72 hours are closely related to necrotizing AP,

and these values can be used to follow the clinical disease course over time.

Imaging Studies

CECT is the most accurate single imaging test for establishing the diagnosis, quantifying the inflammatory process, and staging the severity of the disease.⁴ Precision in terms is essential in describing the morphology of disease states in AP, and this chapter uses definitions and terminology developed at the Atlanta symposium in 1992 [see Table 1].⁵ A good-quality chest x-ray is useful to have early in the clinical course to identify a pleural effusion (poor prognostic factor) and to gauge the degree of interstitial pulmonary infiltration. In patients with known or suspected biliary pancreatitis, a right upper quadrant sonogram is useful in both identifying cholelithiasis and providing supportive evidence for choledocholithiasis based on the findings of intra- and/or extrahepatic biliary dilatation.^{6,7} Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) have been used extensively in Europe but less so in the United States. The benefits of MRI over computed tomography (CT) are the lack of ionizing radiation, better definition of solid versus liquid components of necrosis, and delineation of ductal structures. The drawbacks are limited image resolution in critically ill patients who cannot follow commands. Endoscopic ultrasonography (EUS) is the most sensitive imaging modality for detecting cholelithiasis and

Table 1 Definitions from the Atlanta Classification of Acute Pancreatitis⁵

Term	Definition
Acute pancreatitis	Acute inflammation of the pancreas
Mild acute pancreatitis	Minimal organ dysfunction response to fluid administration
Severe acute pancreatitis	One of the following: Local complications (pancreatic necrosis, pancreatic pseudocyst, pancreatic abscess) Organ failure ≥ 3 Ranson criteria ≥ 8 APACHE II points
Acute fluid collections	Fluid collection in or near the pancreas, occurring early in clinical course, lacking a defined wall
Pancreatic necrosis	Nonviable pancreatic tissue diagnosed by intravenous contrast-enhanced computed tomographic scan
Acute pseudocyst	Fluid collection containing pancreatic secretions and a defined wall
Pancreatic abscess	Collection of pus, usually near the pancreas

choledocholithiasis and is not limited like transabdominal ultrasonography by intestinal gas or body wall edema.⁸

Risk Stratification

The severity of an episode of AP, as well as the disease-related morbidity and mortality, can be prognosticated based on the etiology [see Table 2] and a number of measured clinical and laboratory data points that can be calculated by established scoring systems (APACHE II [Acute Physiology and Chronic Health Evaluation II], Glasgow score, Ranson criteria). Recent observations that obesity is associated with a more severe course of AP have led to the addition of obesity to most scoring systems. Body mass index (BMI) in this application is categorized as normal (score 0), overweight (BMI 26 to 30, score 1), or obese (BMI > 30, score 2). Predicting severity is important for two reasons: (1) it allows patient triage to an appropriate level of hospital care (surgical ward versus intensive care unit [ICU]), and (2) it allows objective quantification of disease severity for both clinical trial recruitment and to compare patient outcomes between different clinical series.

Both the Glasgow and Ranson scoring systems are hampered by requiring 48 hours worth of data collection prior to calculation and are limited to prognosticating at this one point in time. Both scores have a low positive predictive value (below 50%) for disease severity. The APACHE II scoring has sensitivity and specificity similar to those of the Glasgow and Ranson systems but a greater than 90% negative predictive value for disease severity in patients with scores less than or equal to 7. Unfortunately, APACHE II scoring has a low positive predictive value (50%) for disease severity in patients with scores above 7. Although APACHE II can be calculated at any time in the clinical course and sequential scores can

reveal trends in the disease state over time, the complexity of its scoring hinders its general clinical applicability.

Although of interest, almost all of these scoring systems have fallen out of favor because of the simplicity and directness of measuring the systemic inflammatory response syndrome (SIRS) and/or organ failure. The most accurate and earliest markers of severity in AP are measuring the SIRS or the inflammatory mediators contributing to the systemic effects that are witnessed, such as granulocyte (polymorphonuclear neutrophil) elastase, tumor necrosis factor, interleukin-6, interleukin-8, and C-reactive protein (CRP). The most useful serum test currently available in clinical practice is CRP, with severe pancreatitis defined by a value greater than 150 mg/L within 72 hours after the onset of disease. SIRS is defined by two or more of the following clinical criteria: pulse greater than 90 beats/min; rectal temperature less than 36°C (96.8°F) or greater than 38°C (100.4°F); white blood count less than 4,000 or > 12,000/ μ L; and respirations greater than 20 breaths/min or carbon dioxide tension less than 32 mm Hg.

Organ failure is most easily and reproducibly defined using the Marshall or Sequential Organ Failure Assessment (SOFA) scoring system [see Table 3]. Up to one half of the patients who eventually die of AP do so within the first 7 days of illness from unrelenting multiorgan dysfunction syndrome.⁹ The morphologic severity of AP can be defined by the Computed Tomography Severity Index (CTSI) developed by Balthazar and colleagues [see Table 4].⁴ This system assigns a numeric score to the quantity and location of necrosis to establish disease-related morbidity and mortality [see Table 4].

Mild AP Most attacks of AP (80%) are of the mild, edematous variety, consisting of an inflammatory disease state in the pancreatic parenchyma that is self-limited, runs its course over a 5- to 7-day period, and results in complete resolution and full constitutional recovery to the structure and function of the pancreas. The clinician's role in treatment is to provide intravenous fluid hydration, correct electrolyte or blood glucose abnormalities, and provide adequate organ support. Intravascular and interstitial hypovolemia may require 3 to 4 L of a balanced electrolyte solution (9% saline or lactated Ringer solution) over the first 24 hours or correction of deficits. Targeted response to volume resuscitation should include a lowering of the pulse rate, improvement of the blood pressure, and urine output of at least 30 mL/hr. Blood glucose levels tend to rise in AP and may be difficult to control in the initial phases of the disease. Close monitoring and control of blood sugar are essential during the first 24 to 36 hours of a patient's hospitalization, and close control has been found to improve both morbidity and mortality in hospitalized patients. This monitoring can be discontinued in nondiabetic patients as their pancreatitis resolves and they clinically improve. Oxygen saturation should be measured continuously and supplemental oxygen given to maintain an arterial saturation greater than 95%. Any evidence of respiratory insufficiency requires a chest x-ray to assess for pulmonary edema or acute respiratory distress syndrome. Narcotic analgesics are essential in patients with AP, and parenteral administration ensures adequate delivery in patients during their acute illness and period of unreliable gastrointestinal absorption. Patient-controlled analgesia is a safe and effective

Table 2 Etiologic Factors for Acute Pancreatitis

Common
Gallstone (including microlithiasis)
Alcohol
Hyperlipidemia
Hypercalcemia
Drugs and toxins
Traumatic
Postoperative
Sphincter of Oddi dysfunction
Post-endoscopic retrograde cholangiopancreatography
Uncommon
Pancreatic cancer
Periampullary diverticulum
Pancreas divisum
Vasculitis
Rare
Infection: mumps, coxsackievirus, HIV, parasitic (ascariasis)
Autoimmune: systemic lupus erythromatosus, Sjögren syndrome, autoimmune pancreatitis
α_1 -Antitrypsin deficiency

Table 3 Marshall and SOFA Organ Failure Scoring Systems Used in Acute Pancreatitis

Organ System	Parameter	0	1	2	3	4
Marshall score Respiratory	PO ₂ /F _I O ₂	> 400	301–400	201–300	101–200	≤ 101
Renal	Creatinine, μ mol/L	≤ 134	134–169	170–310	311–439	> 439
Cardiovascular	SBP, mm Hg	> 90	< 90	< 90	< 90	< 90
			Fluid responsive	Fluid unresponsive	p.H. < 7.3	p.H. < 7.2
SOFA score Respiratory	PO ₂ /F _I O ₂	> 400	≤ 400	≤ 300	≤ 200 (RS)	≤ 100 (RS)
Hematologic	Platelet count × 10 ³ mm	> 150	± 150	≤ 100	≤ 50	≤ 20
Cardiovascular	BP, mm Hg	Normal	MAP < 70	Dopamine < 5 Dobutamine (any dose)	Dopamine > 5 Epinephrine ≤ 0.1 Nor- epinephrine ≤ 0.1	Dopamine > 15 Epinephrine > 0.1 Nor- epinephrine > 0.1
Neurologic	GCS	15	13–14	10–12	6–9	< 6
Renal	Creatinine mg/dL	< 1.2	1.2–1.9	2.0–3.4	3.5–4.9	> 5.0
	Urine output mL/d				< 500	< 200

BP = blood pressure; F_IO₂ = fraction of inspired oxygen; GCS = Glasgow Coma Scale; MAP = mean arterial pressure; RS = respiratory support; SBP = systolic blood pressure; SOFA = sequential organ failure assessment.

Table 4 Computed Tomography Severity Index (CTSI) Grading System⁴

	Definition	Score
CT grade		
A	Normal pancreas	0
B	Focal, diffuse pancreatic enlargement, mild heterogeneity	1
C	Intrinsic and extrinsic pancreatic inflammatory changes	2
D	Prominent peripancreatic inflammatory changes	3
E	Multiple extrapancreatic fluid collections or abscesses	4
Necrosis score		
None	Necrosis is defined as a focal or diffuse area of diminished parenchymal contrast enhancement (< 50 Hounsfield units)	0
33%		2
50%		4
> 50%		6
Total score	CT grading score + necrosis score	0–10

method to deliver morphine, dilaudid, or rarely fentanyl. A nasogastric tube can often be helpful not only in relieving nausea and vomiting but also in helping to improve abdominal pain in patients with gastric ileus. A patient's pain should be under control within the first 3 hours of admission using both a loading dose and periodic bolus dosages. Adequate tissue oxygenation is ensured by the provision of supplemental oxygen, and chemoprophylaxis for deep vein thrombosis is mandatory in all patients.

Patients with mild edematous AP improve quickly over a course of 24 to 36 hours and can then be weaned off their intravenous narcotic medication and placed on either oral narcotic analgesics or nonsteroidal antiinflammatory medication. Their diet can be advanced even if their amylase level remains elevated as long as the patient feels like eating. Identification and treatment of the underlying etiology become the focus of treatment. Patients with hypertriglyceridemia or hypercalcemia require a full metabolic evaluation. Relatively

few drugs have been rigorously implicated as a cause of AP.³ Specific genetic testing or evaluation of the ampulla (sphincter of Oddi dysfunction) would require more than at least two separate documented episodes of AP. The presence of gallstones is confirmed by either transabdominal or endoscopic ultrasonography. Patients with mild biliary pancreatitis benefit from elective laparoscopic cholecystectomy and intraoperative cholangiography after their acute pancreatic inflammation has subsided (roughly 3 to 5 days after onset) but prior to their hospital discharge (roughly 5 to 7 days after disease onset).¹⁰ Patients can safely undergo laparoscopic cholecystectomy in this setting without waiting for complete normalization of their laboratory values or complete resolution of their symptoms. Despite these observations, careful judgment should be exercised in those patients with persistent clinical symptoms or evidence of continued pancreatic inflammation.

Severe necrotizing pancreatitis Severe necrotizing pancreatitis accounts for the remaining 20% of all episodes of AP and is characterized by glandular destruction, tissue necrosis, leaking pancreatic enzymes, and a SIRS that can lead to organ failure (renal, pulmonary, hepatic, cardiovascular), local and systemic complications, and a significant mortality rate [see Table 5]. New concepts concerning the clinical course of patients with severe necrotizing pancreatitis emphasize that it occurs in two rather distinct phases [see Figure 2]. The first phase of illness (approximately days 0 to 14) is dominated by the host's systemic inflammatory response to tissue injury. Infection attributable to the pancreas (infected pancreatic necrosis) manifest as systemic sepsis (hypotension) is usually during this early phase of illness.¹¹ More common is the systemic manifestation of associated intra-abdominal processes such as abdominal compartment syndrome, gangrenous cholecystitis, or intestinal ischemia (colonic). Aggressive critical care medicine maximizing organ support is the key treatment during this early phase of the disease process. A second disease phase occurs after the initial systemic inflammatory response has subsided and lasts for approximately an additional 2 weeks (characteristically days 15 to 45). During this later period, the disease can progress along several different paths: resolution, stagnation, or complication. Morphologic abnormalities of the gland (both parenchyma and ductal system) and peripancreatic tissues predominate during this phase of the disease.

Clinical course Some patients progress quickly after their initial presentation to organ failure requiring endotracheal intubation, mechanical ventilation, and vascular and renal support. The complexity of the renal response to severe AP involves decreased renal perfusion (prerenal) and altered renal mechanics with poor tubular function (renal and post-renal), making urine output a poor surrogate for adequate intravascular volume and resuscitation. Oliguria progressing to acute renal failure during this critical time period is often due to underresuscitation rather than intrinsic renal dysfunction. Large volumes of intravenous fluid (5 to 10 L) are sometimes needed early in the course of patients with severe disease for whom the administration is often facilitated by central venous access combined with the capability of measuring right heart pressures. Neurologic manifestations of delirium and confusion, particularly in the elderly, are the predominant clinical findings related to hypoxemia, metabolic

disturbances, hypotension, or toxemia. Vascular pressor support is occasionally needed to maintain adequate organ perfusion. The degree of temperature elevations early in the clinical course can often be a gauge as to the severity of the systemic inflammatory response.

Within the first 48 hours of illness, all patients with severe AP should be evaluated for the possibility of gallstone impaction at the ampulla of Vater as an explanation for their deteriorating clinical course. Most investigators agree that biliary pancreatitis occurs from a transient obstruction of the ampulla of Vater by a migrating gallstone. In certain circumstances, stone impaction at the ampulla negatively influences the clinical course of patients with severe AP. Despite a number of prospective, randomized clinical trials addressing early ERCP in patients with AP, methodological differences have hampered a general consensus for treatment.¹² Despite this lack of consensus, two points are salient: (1) ERCP with or without endoscopic sphincterotomy (ES) for stone extraction should be carried out in patients with severe AP and evidence of cholangitis (jaundice, fever, leukocytosis, and evidence of biliary obstruction, i.e., dilated common bile duct) and (2) if indicated, ERCP $\pm$ ES should be done early in the clinical course (< 48 hours after onset) following the onset of AP. Admittedly, the devil is in the details of making this diagnosis. Often in the ICU considerable uncertainty surrounds the diagnosis of cholangitis, especially in critically ill patients with necrotizing pancreatitis. Nevertheless, careful consideration of this possibility and sound clinical judgment should be used, particularly in those patients who deteriorate following an adequate initial resuscitation.

In patients with severe AP, metabolic expenditure rates are extremely high and nutritional depletion occurs rapidly unless some form of nutrition support is delivered. Nutrition has been provided through both parenteral and enteral mechanisms in these critically ill patients. Parenteral nutrition (PN) has been advocated in the past on the belief that patients with a significant ileus from AP did not tolerate enteral nutrients and enteral feeds would stimulate pancreatic secretion and exacerbate trypsin-induced fat and parenchymal digestion, worsening the pancreatitis. These concerns have not been proven in clinical trials, and the use of PN puts patients at high risk for developing catheter-associated line infections. Furthermore, microcirculatory disruptions of the insuloacinar axis make patients relatively intolerant to the high glucose and fat concentrations delivered in PN. In contrast, the benefits of enteral nutrition (EN) are substantial: it is less expensive than PN, maintains gut mucosal integrity, initiates housekeeping functions of the intestine and liver, sets the tone for systemic immunity, and attenuates oxidative stress and the systemic inflammatory response. In the clinical trials done to date in patients with severe AP, EN reduces infections, the need for surgical intervention, and the length of hospital stay more than PN.¹³ Controversy remains over whether EN should be delivered past the ligament of Treitz ($\approx$ 40 cm) into the jejunum (nasojejunal) or can be instilled directly into the stomach (nasogastric). Until further data are known, distal nasojejunal feeding is the safest method, although nasogastric feeding may prove to be simpler, cheaper, and more easy to use in patients with severe AP.¹⁴

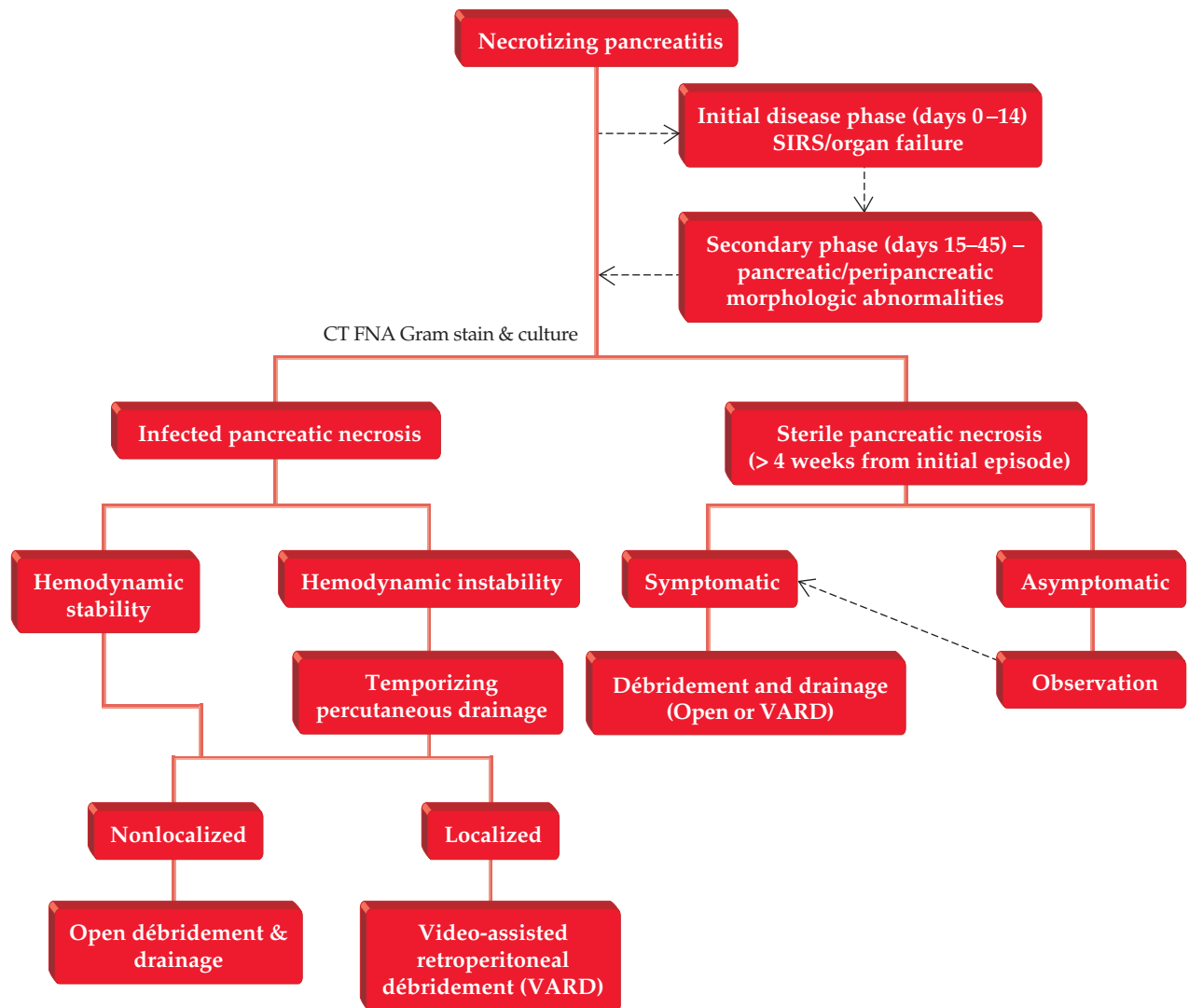


Figure 2 Intervention in necrotizing pancreatitis. CT = computed tomography; FNA = fine-needle aspiration; SIRS = systemic inflammatory response syndrome.

Significant controversy surrounds the use of prophylactic antibiotics in patients with severe AP. Despite early, small, uncontrolled trials and a meta-analysis showing a benefit to patients with severe AP treated by prophylactic antibiotics, recent large, prospective, multi-institutional, placebo-controlled, double-blind, randomized trials have failed to show any benefit for antibiotic prophylaxis in preventing infection in pancreatic necrosis. Based on the equivalence in outcome between treatment and control groups in the two recent clinical trials, the notion that antibiotics be given “on demand” to critically ill patients in the ICU for specific indications may be just as effective as prophylactic antibiotics in patients with severe AP.^{15,16} Based on the current data, there is no evidence to support the routine use of prophylactic antibiotics in severe AP.

Following the initial systemic inflammatory response and its associated organ failure (initial phase 1 to 14 days), most patients’ clinical course stabilizes. Their pulmonary and renal dysfunction will often improve, allowing extubation and withdrawal from renal support. Although the initial systemic

inflammatory response was that of an acute febrile illness, during this phase of the disease process, a patient’s temperature elevations generally diminish or subside. It is critical at this juncture that the patient is provided with adequate EN, pulmonary toilet, and aggressive physical and occupational therapy to improve range of motion and assist with ambulation training. All intravenous lines that are not essential should be removed. Those patients who eventually go on to resolve their necrotizing pancreatitis without intervention characteristically have a low volume of necrosis; it is localized to the retroperitoneum, and the necrosis is confluent (no disconnected segments) from the tail toward the head (i.e., central cavitory necrosis).¹⁷ In this situation, the necrotizing process is able to be walled off and isolated by the host. As a result, these patients are asymptomatic (no pain, fever, normal white blood cell count) and able to eat without difficulty, and the necrosis slowly resolves over time. Unlike patients with acute edematous pancreatitis, in whom complete structural and functional restitution occurs, these patients have

parenchymal loss with persistent structural and/or functional (endocrine or exocrine insufficiency) abnormalities in the gland.

Fever spikes or clinical toxicity (tachycardia, hypotension, and leukocytosis) during the second stage of illness (weeks 2 to 4 from initial onset) represents either line infection, urinary tract infection, pulmonary infection, acute cholecystitis, ischemic colitis, or infected pancreatic necrosis. All episodes should be carefully investigated with routine blood cultures, urine cultures, chest x-ray, and intravenous line evaluation. If this surveillance fails to identify the source of infection, CT-directed fine-needle aspiration (FNA) with Gram stain and culture of the pancreatic necrosis should be pursued.¹⁸ It is critically important at this juncture to ensure that the patient's clinical decompensation is due to infected pancreatic necrosis rather than a simple line infection as the earlier in the clinical course that one is required to débride, the greater the post-operative morbidity and mortality and the more likely it is that multiple interventions will be necessary for complete resolution of the disease process.¹⁹ A positive Gram stain or culture on FNA indicates infected pancreatic necrosis that mandates treatment with parenteral antibiotics combined with either percutaneous, operative, laparoscopic, or endoscopic débridement or drainage.^{11,20} Open necrosectomy and external drainage remain the current standard of care for infected pancreatic necrosis.²⁰ In patients with localized (lesser sac) infected necrosis and a surgeon with advanced laparoendoscopic skills, minimally invasive approaches, including laparoscopic, endoscopic, or video-assisted retroperitoneal débridement, can be used.²¹ In those patients felt to be too unstable to undergo an operation, broad-spectrum antibiotics combined with percutaneous drainage can be a useful temporizing measure to allow stabilization of a patient's physiologic status prior to definitive débridement. At the time of débridement, cultures should always be taken for aerobic, anaerobic, and fungal organisms and antibiotics modified based on these results. Cholecystectomy should be considered in all patients at the time of initial débridement provided that the hepatoduodenal ligament dissection is judged to be safe by the operating surgeon. Patients with a presumed biliary etiology for their pancreatitis should also have intraoperative cholangiography to visualize the extrahepatic biliary system and ensure that no stones are retained in the common bile duct. If this is unable to be completed because of inflammation or anatomic distortion in the hepatoduodenal ligament, MRCP should be done. An enteric feeding tube, either a jejunal tube or a gastrojejun tube, should routinely be inserted at the time of operation to facilitate direct access to the gastrointestinal tract for postoperative alimentation.

Fluid collections in patients with pancreatic necrosis are common. A recent document circulated by the Acute Pancreatitis Classification Working Group that proposes revisions to the original Atlanta Classification nomenclature suggests that this fluid collection be categorized as either acute peripancreatic fluid collections (APFCs) or acute post-necrotic collections (APNCs). APFCs are collections of fluid without associated necrosis and with no definable wall and are commonly located in the lesser sac or peripancreatic region. These were previously termed acute fluid collections using the Atlanta Classification terminology [see Table 1]. In

contrast, APNCs are collections of fluid with necrosis of the pancreatic parenchyma, peripancreatic tissues, or both. APFCs are common during the early clinical course (2 to 4 weeks) of patients following necrotizing pancreatitis and can be classified as either sterile or infected based on FNA for Gram stain and culture. The vast majorities of these early acute fluid collections are sterile and, as such, are capable of resolution by the body over time. Only when these fluid collections are suspected to be the source of ongoing clinical deterioration or sepsis should they be aspirated for Gram stain with culture, and if they are found to be infected, they should be drained. If the acute fluid collections remain asymptomatic, it is important to follow these collections for resolution over time, withholding elective operations such as cholecystectomy until the clinical course of the fluid collections is known.²² In patients with clinical deterioration and infected acute fluid collections, percutaneous drainage can often be an important temporizing measure to facilitate sepsis control and organ failure stabilization prior to proceeding with formal pancreatic débridement.²³

In some patients, after 4 weeks of recovery from the acute systemic illness associated with pancreatic necrosis, their clinical progress becomes stagnant and plateaulike. Typically, these patients have a moderately large volume of sterile necrosis, which, although localized and walled off, continues to exert subtle physiologic and constitutional derangements such as low-grade fever, mild leukocytosis, inability to eat, and nausea. These clinical symptoms have been termed "persistent unwellness," a pathologic state in which the volume of retroperitoneal necrosis prevents patients from returning to their pre-morbid functional status. In these patients, débridement of noninfected necrosis has a role in removing this nidus of devitalized tissue and allowing the body an opportunity to resolve the persistent inflammatory state that this necrotic debris incites. Although intervention in patients with noninfected necrosis remains controversial, after 4 weeks of medical treatment, the necrosis is "mature," which implies a decrease in the inflammatory vascularity, localization of the necrotic process, and the ability of the operating surgeon to discriminate between live and dead tissue. At this time in the patient's clinical course, débridement seems warranted as further medical management beyond this point does not result in symptom resolution.²⁴

Reoperation is not infrequent in the clinical course of this complex disease process and is indicated following initial pancreatic débridement for drainage of recurrent fluid collections and/or residual necrosis that is either too extensive, thick, or numerous for simple image-guided percutaneous drainage.²⁵ These collections often represent areas of continued leakage from the pancreatic duct, a consequence of parenchymal necrosis.

It is gratifying to know that despite the high rate of morbidity and mortality associated with patients who have acute necrotizing pancreatitis and the large amount of both surgical and medical resources required to care for them, their long-term quality of life as assessed by the Short Form-36 Health Survey, once they have recovered fully, is similar to that of patients who undergo medical management of chronic pancreatitis or patients who have elective pancreatic surgery for ductal abnormalities.²⁶

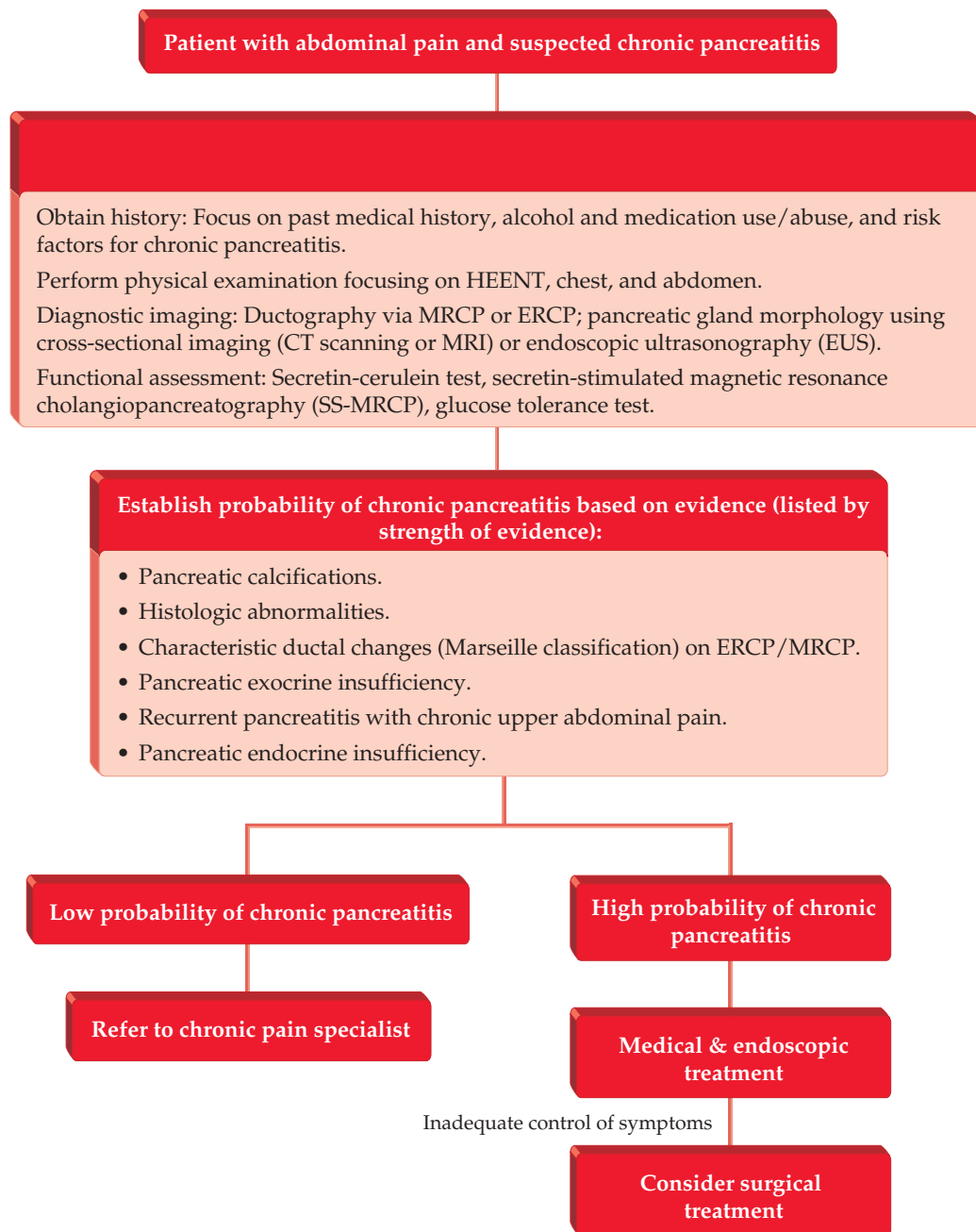


Figure 3 Diagnosis and treatment of patients with chronic pancreatitis. CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; HEENT = heads, ears, eyes, nose, and throat; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging.

Chronic Pancreatitis

Chronic pancreatitis is an inflammatory disorder of the pancreas characterized by glandular fibrosis resulting in permanent structural and functional changes in the organ and leading ultimately to pancreatic endocrine and exocrine failure. Clinical manifestations of this disease are erratic and can range from an asymptomatic state, to circumscribed recurrent bouts of AP (elevated pancreatic enzymes, glandular inflammation), to continuously disabling pain [see Figure 3]. Contiguous organ

involvement can lead to obstruction of the duodenum (gastric outlet obstruction), distal common bile duct (secondary biliary cirrhosis), or splenic vein (sinistral [left-sided] portal hypertension with isolated gastric varices and hypersplenism). A precise diagnosis can be made only by direct pancreatic biopsy showing fibrosis and a chronic inflammatory cell infiltration. Because of the technical difficulties and potential morbidity associated with this procedure, provisional diagnoses are made using indirect evidence such as pancreatic duct morphology (Cambridge classifications), decreased pancreatic exocrine

Table 5 Summary of the Official International Association of Pancreatology Guidelines for the Surgical Management of Acute Pancreatitis²⁴

1. Mild acute pancreatitis is not an indication for pancreatic surgery.
2. The use of prophylactic broad-spectrum antibiotics reduces infection rates in CT-proven necrotizing pancreatitis but may not improve survival.
3. Fine-needle aspiration biopsy (FNAB) should be performed to differentiate between sterile and infected pancreatic necrosis in patients with sepsis syndrome.
4. Infected pancreatic necrosis in patients with clinical signs and symptoms of sepsis is an indication for intervention, including surgery and radiologic drainage.
5. Patients with sterile pancreatic necrosis (FNAB negative) should be managed conservatively, and only selected cases should undergo intervention.
6. Early surgery within 14 days after onset of the disease is not recommended in patients with necrotizing pancreatitis unless there are specific indications.
7. Surgical and other forms of interventional management should favor an organ-preserving approach, which involves débridement or necrosectomy combined with a postoperative management concept that maximizes postoperative evacuation of retroperitoneal debris and exudate.
8. Cholecystectomy should be performed to avoid recurrence of gallstone-associated acute pancreatitis.
9. In mild gallstone-associated acute pancreatitis, cholecystectomy should be performed as soon as the patient has recovered and ideally during the same hospital admission.
10. In severe gallstone-associated acute pancreatitis, cholecystectomy should be delayed until there is sufficient resolution of the inflammatory response and clinical recovery.
11. Endoscopic sphincterotomy is an alternative to cholecystectomy in those who are not fit to undergo surgery to lower the risk of recurrence of gallstone-associated acute pancreatitis. There is, however, a theoretical risk of introducing infection into sterile pancreatic necrosis.

CT = computed tomography.

function (low pancreatic juice HCO_3^- level), or clinical criteria (right upper quadrant abdominal pain with radiation to the back). Recently, advances in imaging (EUS) and molecular genetic techniques have permitted the identification of patients who have subtle, early-stage disease or those patients with a genetic predisposition to eventually develop the disease. Overconsumption of alcohol is the primary etiology for chronic pancreatitis in the developed world with other etiologies, including hereditary pancreatitis, autoimmune pancreatitis, traumatic pancreatitis, post-ERCP pancreatitis, obstructive pancreatitis, or systemic conditions such as hypertriglyceridemia or hypercalcemia contributing to the total population of patients. Chronic pancreatitis is a disease treated primarily by medical therapy, with the surgeon's role limited to the treatment of specific disease complications [see Table 6].

INITIAL CLINICAL EVALUATION

History

Abdominal pain is by far the most common complication of chronic pancreatitis for which a patient is referred to a

surgeon. Unfortunately, because of the subjective quality of this symptom and our inability to accurately establish causation between a particular patient's pancreas and abdominal complaints, correctly identifying patients in whom an operation will be beneficial is currently more art than science. Classic abdominal pain syndromes (midepigastric radiating to the back) combined with morphologic abnormality of the pancreas (i.e., inflammatory mass in the pancreatic head, pseudocyst, obstructing stone in the pancreatic duct) are more reassuring than patients with atypical pain syndromes and minimal change in the morphology of their pancreas, but these associations still suffer from our inexact understanding of the mechanism of pain in this disease process. Theories as to the pathogenesis of pancreatic pain include high pancreatic tissue or pancreatic duct pressure (compartment syndrome), alteration of sensory nerves with increased transmission as a result of the loss of their myelin sheath, molecular changes within nerve cells surrounding the pancreas, or a relative increase in the size and number of peripancreatic nerves. Despite these theories of pain pathogenesis, current surgical treatment of chronic pancreatitis relies on empirical results from applying a specific type of operation, either resection or drainage procedure, to the dominant anatomic abnormality found in a patient's pancreas.

All patients with chronic pancreatitis should have a complete medical history and physical examination. The history of present illness should focus on the qualities of their pain: type, location, radiation, chronicity, quality (intermittent or constant), temporal relation to food, and aggregating or alleviating factors. This information is important because when congruent, these clues often lend supporting evidence that the identified anatomic abnormality is related to the patient's pain. For instance, patients with pancreatic head disease should have midepigastric to right upper quadrant pain

Table 6 Surgically Remedial Complications of Chronic Pancreatitis

Pain
Relapsing pancreatitis (inflammatory mass in the head, pancreatic duct strictures)
Complicated pancreatic pseudocyst
Biliary obstruction
Duodenal obstruction
Bleeding pseudoaneurysm
Sinistral portal hypertension

syndromes, whereas those with obstructive pancreatitis classically have left upper quadrant pain syndromes that radiate to their back. In those patients with pancreatic duct strictures, clinical improvement in their pain with successful pancreatic duct stenting (adequate ductal decompression) is generally viewed as presumptive evidence for pancreatic duct stricture pathophysiologic significance. The number of episodes of AP, their severity, whether or not a hospital admission was required, and the frequency of their recurrence should be carefully documented. All patients with chronic pancreatitis should fill out a validated quality of life instrument to objectively document their baseline preoperative status, and these metrics should be periodically readministered (every 6 to 12 months) to objectively quantify the effectiveness of treatment.

In the past medical history, special attention should be made to previous abdominal operations, particularly those involving the upper gastrointestinal tract (liver, bile duct, gallbladder, or pancreas). Careful questioning should be carried out on the patient's use of alcohol, prescription drugs (narcotic analgesics), and tobacco. Alcohol abuse, as mentioned previously, is the leading cause of chronic pancreatitis in the Western world. Patients with chronic pancreatitis and chronic abdominal pain often have personality disorders in which substance abuse (alcohol, tobacco, narcotics, and street drugs) is common. Careful documentation of the type, quantity, and frequency of pain medication use should be done. It is critically important that all patients with chronic pancreatitis be abstinent of alcohol at the time of operation as operative outcomes are notoriously low in the setting of recidivism. Tobacco use is an underrecognized pancreatic toxin in patients with chronic pancreatitis despite the fact that it has been shown to influence both the clinical course and the severity of the disease. Family history is important to consider as genetic factors that either increase proteolytic activity (the cationic trypsinogen [*PRSSI*] gene) or decreased protease inhibition (the pancreatic secretory trypsin inhibitor [*PSTI*] gene) can influence the course of recurrent pancreatic inflammation. Genetically transmitted impairment of pancreatic duct function (cystic fibrosis transmembrane conductance regulator [*CFTR*] gene) has also been implicated in the pathogenesis of the disease.

Physical Examination

A detailed physical examination should be done with particular focus on the abdomen. Inspection of patients should start with a general assessment of their affect, particularly with regard to depression. Note should be made of their level of family support, as well as identification of abnormal codependency relationships between family members, which might enable addictive or maladaptive behaviors. Look carefully for sclera icterus, a sign of distal common bile duct obstruction or advanced liver disease from alcohol abuse. Supraclavicular (deltoid, suprascapular, sternocleidomastoid, bitemporal) muscle wasting is a sign of significant weight loss attributable to poor oral intake, poorly controlled exocrine or endocrine insufficiency, or a combination of factors. Spider angiomas on the anterior chest wall are a sign of active liver disease. The abdominal examination also often gives clues to the extent of disease. Note the presence or absence of ascites, an enlarged or shrunken liver, or abdominal wall signs of portal venous hypertension (caput medusa) as all suggest

underlying advanced liver disease. Some patients with chronic abdominal pain syndromes will have hyperpigmented discoloration of their abdomen, termed "water bottle stomach," from the repeated applications of warm objects (heating pad, water bottle) to their stomachs to soothe their abdominal pain. Occasionally, an upper abdominal mass may be the physical manifestation of an inflammatory mass or pancreatic pseudocyst. Diffuse abdominal tenderness and mild involuntary guarding during palpation are common, nonspecific physical findings in most patients with chronic pancreatitis.

Laboratory Tests

Whereas patients with AP are identified by hyperamylasemia, patients with chronic pancreatitis rarely have evidence of active pancreatic inflammation unless they are evaluated during an acute episode of pancreatitis (acute on chronic pancreatitis) or they have an associated pancreatic pseudocyst. CBC with differential and platelet count, comprehensive metabolic panel, prealbumin, hemoglobin A_{1C}, and fecal elastase are appropriate laboratory tests to review. The purpose of these is to gauge both the overall functional (renal, hepatic) and nutritional status of the patient.^{27–29} Assessment of both the endocrine (hemoglobin A_{1C}) and exocrine (fecal elastase) function of the pancreas is important at baseline and over the course of the illness. Occasionally, metabolic abnormalities such as hypercalcemia or hypertriglyceridemia are identified as the etiology of recurrent pancreatic inflammation in patients with chronic pancreatitis. Genetic testing to identify patients with a predisposition to pancreatitis and their ultimate role in evaluation and treatment of patients with chronic pancreatitis are currently being elucidated.³⁰ The most direct evidence that genetic abnormalities influence pancreatic disease comes from the observation that mutations in codons 29 (exon 2) and 122 (exon 3) of the cationic trypsinogen gene are responsible for the autosomal dominant forms of hereditary pancreatitis.³¹ Other mutations, such as the *CFTR* gene and the pancreatic secretory trypsin inhibitor (*SPINK1*) genes, although common in the general population, have been identified with increasing frequency in patients with idiopathic chronic pancreatitis. Although significant progress in the implication of genetic influences on pancreatic diseases has been made, genetic testing should be limited to clinicians who understand the implications of genetic testing, use the obtained information for clinical decision making, are prepared to provide pretest and posttest counseling to patients (or refer to a genetic counselor), and ensure that testing is done with full informed consent.

Imaging Studies

The role of diagnostic imaging in patients with chronic pancreatitis who are being evaluated for surgical intervention is to both confirm the diagnosis and provide anatomic information to assist in the application of a specific operative procedure to the variant anatomy that gives the highest likelihood of success in relieving the patient's symptoms [see Figure 4]. Because both ductal (main and side branch anatomy) and parenchymal (gland structure) information is required to accurately classify patients, imaging of both the pancreatic duct (e.g., MRCP, ERCP) and gland morphology (e.g., CT, MRI) are required for complete evaluation. ERCP shows the structural changes to the main pancreatic duct and

its side branches. Abnormal findings can be quantified using the Cambridge Classification system, which is considered a reference standard for both establishing the diagnosis of chronic pancreatitis and grading its severity. Limitations to this grading system arise in those patients who are early in the clinical course of their disease where ductal abnormalities may not be evident, and it should be noted that structural changes found by ERCP do not correlate well with the level of gland functioning. Parenchymal abnormalities (gland morphology) identified by the cross-sectional imaging of CT or MRI include pancreatic head enlargement or hypertrophy, gland atrophy, ductal dilatation, presence of calcifications, or evidence of inflammation. MRI and MRCP with intravenous secretin is a relatively new technique that in one study provided a global assessment of the pancreas, providing

information on gland morphology, ductal anatomy, and functional secretory status (pancreatic exocrine function).³² Secretin is a polypeptide hormone that increases the volume of bicarbonate-rich pancreatic secretion with concomitant contraction of the sphincter of Oddi. Using this dual physiologic mechanism during imaging theoretically improves distention of the pancreatic ducts, particularly the small side branch ducts, allowing better visualization during sequence acquisition to allow for the radiographic identification of subtle side branch changes in patients with chronic pancreatitis.³² EUS has become the most sensitive imaging test available to detect small abnormalities of the pancreas. It is useful in identifying both ductal and parenchymal abnormalities that may not be evident on other imaging modalities, but its drawbacks are the lack of anatomic detail it provides for surgical planning.

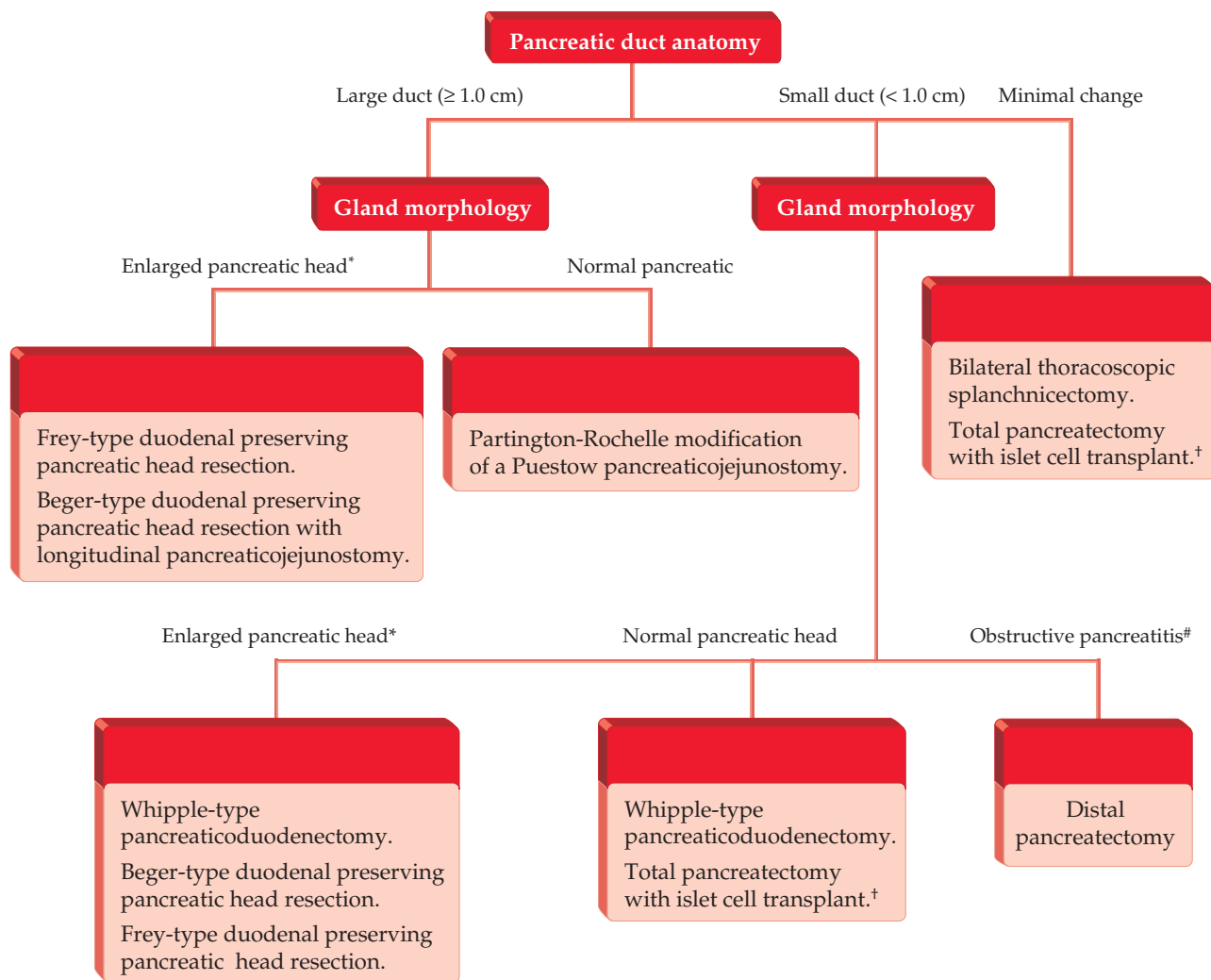


Figure 4 Surgical treatment options based on pancreatic duct anatomy and gland morphology.

* Enlarged pancreatic head is defined as > 3 cm in cross-sectional diameter on imaging;

† Total pancreatectomy with islet cell transplantation should currently be done only under an approved investigational protocol;

Obstructive pancreatitis = a high-grade pancreatic duct stricture in the body or tail of the pancreas with upstream (toward the spleen) side branch changes and evidence of pancreatic inflammation.

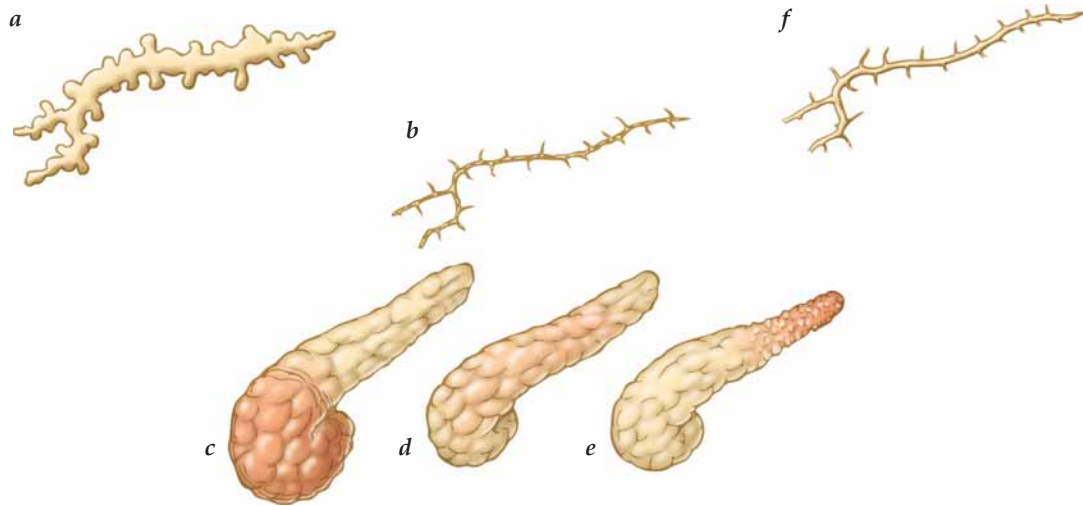


Figure 5 (a) Large duct pancreatitis—Puestow or Frey procedures are recommended. (b) Small pancreatic duct—the Whipple, Beger, or Frey procedures are recommended for small ducts with an enlarged pancreatic head, such as (c); the Whipple procedure and/or a total pancreatectomy with islet cell transplantation is recommended for small ducts with no pancreatic head enlargement, such as (d); and distal pancreatectomy is recommended for obstructive pancreatitis in the tail, such as (e). (f) Duct with minimal change—denervation via thoracoscopic splanchnicectomy is recommended.

Because of its high level of sensitivity in detecting subtle parenchymal or ductal abnormalities, most investigators set a minimum of at least three distinct parenchymal or ductal abnormalities as criteria for making the diagnosis of chronic pancreatitis using this modality.

ANATOMIC AND MORPHOLOGIC SUBTYPES OF CHRONIC PANCREATITIS

Operations directed at patients with chronic pancreatitis can be divided into four basic types: resection, drainage, combined resection and drainage, and denervation. Dominant anatomic abnormalities found in patients with chronic pancreatitis can be broken down into three groups: large duct, small duct, or minimal change variants based on the anatomic configuration of their main pancreatic duct [see Figure 5]. Large duct variants have a cross-sectional diameter of their main pancreatic duct of 1.0 cm, whereas small duct variants have a smaller main pancreatic duct diameter. Patients with minimal change pancreatitis have symptoms of the disease but few or no anatomic changes in their gland or duct to confirm this. In the small duct variant of chronic pancreatitis, there are three specific subgroups: a large pancreatic head, a small pancreatic head, and obstructive pancreatitis. The precise measurements of a large, hypertrophic pancreatic head have not been specifically defined, but enlargement is generally considered to be above 3 cm when measured in anteroposterior diameter on cross-sectional imaging. Obstructive pancreatitis occurs in the setting of a physiologically significant stricture of the main pancreatic duct with upstream (toward the spleen) changes in pancreatic duct dilatation, blunted side branches, and parenchymal inflammation.

Surgical Treatment Options

Choosing the correct operation in patients with chronic pancreatitis comes from interpreting the results of published clinical experience when applied to different anatomic and morphologic patient subsets. For instance, the Partington-Rochelle modification of the Puestow procedure has the best results when applied to patients with large (> 1.0 cm) dilated pancreatic ducts and is much less successful when used in patients with small (< 6 mm) pancreatic ducts. Similarly, using a pancreatic head resection in a patient with obstructive pancreatitis would remove the unaffected portion of the gland upstream from the ductal obstruction. For some anatomic subsets, several different operations can be successfully applied, such as patients with small duct, enlarged head chronic pancreatitis for which either pancreaticoduodenectomy or the Beger- or Frey-type duodenum-preserving pancreatic head resection (DPPHR) can be successfully used depending on the specific patient and surgeon preferences. Below is a brief description of the operations currently available to treat patients with chronic pancreatitis.

Resection operations Pancreaticoduodenectomy, either the classic or the pylorus-preserving variant, is the traditional resection operation used in patients with chronic pancreatitis. Pancreaticoduodenectomy removes the head of the pancreas, duodenum, and distal common bile duct, a region of the pancreas that has been called by William P. Longmire the “pace-maker” of the disease.³³ This operation is generally applied to small duct variants and has the flexibility to be used in both large and small head subtypes [see Figure 6].

The Beger operation, termed one of the DPPHR procedures, involves transecting the pancreatic neck followed by a subtotal resection of the pancreatic head and removes diseased tissue in the head and uncinate process while preserving the

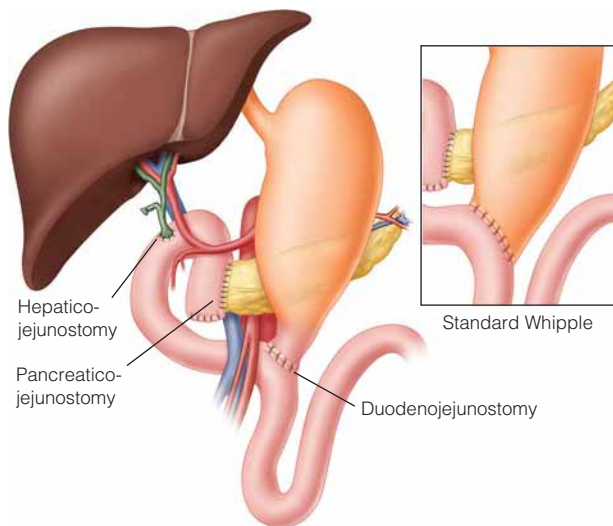


Figure 6 Whipple diagram. Pancreaticoduodenectomy: pylorus-preserving variant and standard pancreaticoduodenectomy with hemigastrectomy.

normal relationship and function of the duodenum and distal common bile duct. This operation is applied to patients with small duct chronic pancreatitis and a large, hypertrophic pancreatic head. It has also been selectively used with good overall results in patients with small duct chronic pancreatitis and normal pancreatic heads (pancreas divisum).

Distal pancreatectomy removes pancreatic parenchyma to the left of the confluence of the splenic vein with the portal vein (body and tail of the pancreas). This operation is used very selectively in patients with obstructive chronic pancreatitis. A high-grade pancreatic duct stricture in the body or tail of the pancreas with upstream (toward the spleen) side branch changes and evidence of pancreatic inflammation is the key to diagnosis. Care should be taken to evaluate these strictures for the possibility of pancreatic cancer.

Total pancreatectomy removes the entire pancreas and is extremely limited in its applicability to patients with chronic pancreatitis outside of clinical trials using salvage procedures for the pancreatic islets with isolation and reinfusion as an islet cell transplant or as a last result in patients who have exhausted all other therapeutic options. It is used predominantly in patients with small duct or minimal change chronic pancreatitis who have not undergone previous resection of drainage procedures.

Drainage operation The Partington-Rochelle modification of the Puestow procedure, a longitudinal pancreaticojejunostomy, is the classic operation used to treat patients with large duct pancreatitis by decompressing the entire length of the pancreatic duct (head to tail) into a defunctionalized (Roux-en-Y) limb of jejunum [see Figure 7].

Combined resection and drainage The Frey operation is the other procedure termed a DPPHR, but in contrast to the Beger operation, the pancreatic neck is not transected. The surgeon identifies the pancreatic duct in the neck of the pancreas and then opens the duct longitudinally by following it down into the pancreatic head and out to the tail. In the pancreatic head, the surgeon then cores out pancreatic tissue from the pancreatic duct outward until just a thin rim of

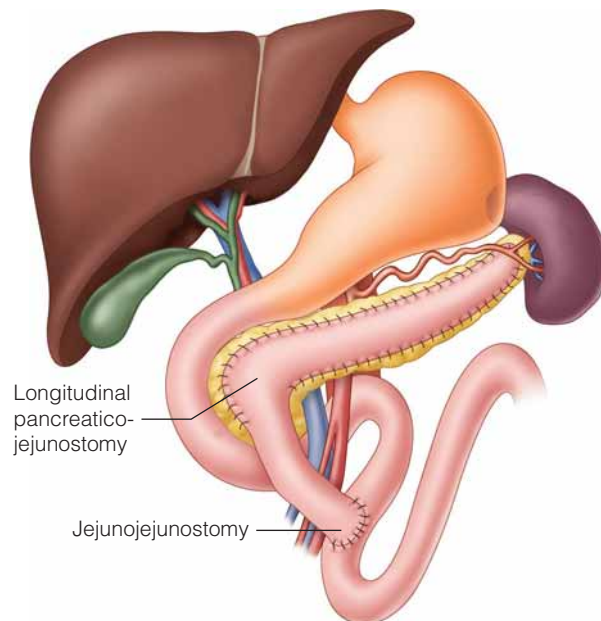


Figure 7 Puestow diagram. Longitudinal pancreaticojejunostomy.

tissue remains around the head of the pancreas contiguous with the duodenum. A defunctionalized limb of jejunum (Roux-en-Y) is then anastomosed side to side to the pancreatic duct in the body and tail and to the remaining rim of pancreatic tissue in the head to effect complete drainage of the entire gland. This operation is perhaps the most versatile as it can be applied to patients with either small or large duct chronic pancreatitis as well as patients with either a large or a normal pancreatic head size [see Figure 8].

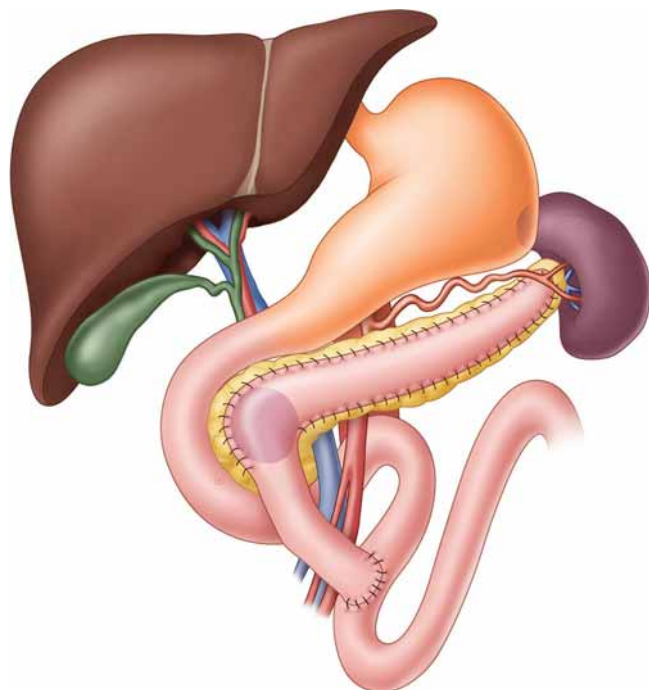


Figure 8 Duodenum-preserving pancreatic head resection (DPPHR)—Frey operation.

Denervation operations Bilateral thoracoscopic splanchnicectomy is a minimally invasive approach to splanchnic denervation used to treat pain in patients with chronic pancreatitis. Candidates are generally patients with no other surgical targets (i.e., minimal change pancreatitis) who have been shown to have a splanchnic-mediated pain pathway based on their response to a differential epidural anesthetic.

Clinical results In measuring the results of surgery in patients with chronic pancreatitis, long-term success is typically defined by a thorough clinical follow-up of at least 5 years' duration. When restricting data to long-term outcome measures, the results for pancreatic head resections are as shown in Table 7. DPPHRs in a recent meta-analysis were shown to be equivalent in outcome to pancreaticoduodenectomy in the outcome variables of pain relief, overall morbidity, and incidence of postoperative endocrine insufficiency.³⁴ In this same analysis, DPPHRs were judged to be superior to pancreaticoduodenectomy in terms of operative time, postoperative hospital stay, and overall quality of life measures. When one compares the two most common DPPHRs, the Beger operation and the Frey operation, there are no significant differences in a randomized controlled clinical trial when patients were followed for over 8 years [see Table 7].³⁵ Outcomes of patients with chronic pancreatitis treated by longitudinal or lateral pancreaticojejunostomy (drainage operation) are shown in Table 8. After a mean follow-up of 79 months, 72% of patients experienced either complete or partial pain relief following operation, with a mean perioperative mortality in this group of patients of only 1%. A surgical denervation procedure as exemplified by bilateral thoracoscopic splanchnicectomy is a minimally invasive treatment of chronic pancreatitis with low perioperative morbidity and mortality. Based on currently available data, complete or partial pain relief is achieved in only 50% of patients during long-term clinical follow-up [see Table 9].

Table 7 Clinical Effectiveness of Pancreatic Head Resection in Patients with Chronic Pancreatitis: Comparison of DPPHR versus PD³⁴ and Frey Operation versus Beger Operation³⁵

Measured Variable	DPPHR	PD
Pain relief	=	=
Overall morbidity	=	=
Endocrine insufficiency	=	=
Operative time	+++	—
Hospital stay	+	—
Quality of life	++	—
Measured Variable	Frey Operation (N = 36)	Beger Operation (N = 38)
Quality of life	58.35 (0–100)	66.7 (0–100)
Pain score	11.25 (0–99.75)	11.25 (0–75)
Exocrine insufficiency	78%	88%
Endocrine insufficiency	60%	56%
Late mortality	32% (8/25)	31% (8/26)

DPPHR = duodenum-preserving pancreatic head resection; PD = pancreaticoduodenectomy; = = equal; + = positive; — = negative.

*Median follow-up 102 months.

Table 8 Outcomes of Longitudinal/Lateral Pancreaticojejunostomy in Patients with Chronic Pancreatitis

Study	No. of Patients	Complete or Partial Pain Relief (%)	Mortality (%)	Mean Follow-up (mo)
Greenlee et al ³⁶	86	80	3	95
Adloff et al ³⁷	105	93	2	65
Adams et al ³⁸	85	55	0	76
Sieleznoff et al ³⁹	57	84	0	65
Sakorafas et al ⁴⁰	120	81	0	96
Mean results	453	72	1	79

Table 9 Outcome of Bilateral Thoracoscopic Splanchnicectomy in Patients with Chronic Pancreatitis

Study	No. of Patients	Mean Follow-up (mo)	Complete or Partial Pain Relief (%)
Moodley et al ⁴¹	17	12	94
Ihse et al ⁴²	21	43	50
Buscher et al ⁴³	44	36	46
Howard ⁴⁴	55	32	35
Hammond ⁴⁵	20	15	60
Mean results	157	30	50

Pancreatic pseudocysts Complicated pseudocysts frequently occur in patients with chronic pancreatitis in association with an underlying pancreatic duct abnormality, and their surgical treatment should take this into account. Patients with pseudocysts and chronic pancreatitis should not be treated by cyst drainage solely, as is often the case in patients with a pseudocyst following a bout of AP. Patients with chronic pancreatitis frequently require some form of pancreatic duct drainage done and at times a parenchymal resection to treat the underlying anatomic abnormality that contributed to the formation of the pancreatic pseudocyst. Less common complications occur as a consequence of fibrotic stricturing of adjacent organs, including the biliary tract (elevated alkaline phosphatase, transaminases, and a dilated common bile duct) or duodenum (early satiety, weight loss, inability to eat); the majority of these complications can be addressed by the judicious application of one of the aforementioned operative procedures. Pseudoaneurysms occur as a consequence of severe inflammation and are commonly related to a pseudocyst. Angiographic embolization for control is generally the treatment of choice. Following control of hemorrhage, formal resection of the involved pancreas can be carried out.

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40 NEUROENDOCRINE TUMORS OF THE PANCREAS

Dina Elaraj, MD, and Cord Sturgeon, MD

The endocrine pancreas is composed of four main cell types, glucagon, insulin, somatostatin, and pancreatic polypeptide (PP) cells, residing within the islets of Langerhans. Neoplasms of these endocrine cell types are a heterogeneous group of benign and malignant tumors that can elaborate hormones of the endocrine pancreas and hormones that are not normally found in the adult pancreas, such as gastrin, growth hormone–releasing factor, adrenocorticotrophic hormone (ACTH), and vasoactive intestinal peptide (VIP).

The annual incidence of pancreatic neuroendocrine tumors (PNETs) is approximately 4 to 12 cases per million.¹ Approximately 60% of PNETs secrete a bioactive hormone that leads to a clinical syndrome. For those tumors that produce bioactive hormones, the clinical presentation of disease is usually characteristic of the hormone elaborated by the tumor. The diagnosis is made based on clinical features and through biochemical demonstration of inappropriately elevated hormone levels. Confirmation of disease is usually followed by imaging studies, including cross-sectional imaging, endoscopic ultrasonography (EUS), scintigraphy, and perhaps more invasive testing as detailed below. Treatment is largely surgical, but multimodal therapy is often used, especially to modulate the hormonal effects.

Although rare, the possibility of a syndromic association with multiple endocrine neoplasia type I (MEN I), von Hippel-Lindau (VHL) disease, neurofibromatosis type I (NF-1), or tuberous sclerosis should be considered when evaluating patients with PNETs. Patients with MEN I frequently have multiple PNETs, which may or may not be functional.² PNETs in patients with VHL disease are usually nonfunctional.¹

Consensus guidelines for the diagnosis and management of patients with PNETs were published by the National Comprehensive Cancer Network (NCCN) in 2008,³ the European Neuroendocrine Tumor Society (ENETS) in 2004,¹ and a MEN I international consensus workshop in 2001.² The following recommendations are based largely on these consensus guidelines.

General Principles

PRESENTATION

Neuroendocrine tumors can be found incidentally or discovered when searching for the cause of an endocrinopathy or the source of compressive or obstructive symptoms. Likewise, neuroendocrine tumors may be clinically silent or symptomatic as a result of the production of hormones or local mass effect. When an asymptomatic PNET is found incidentally, the main clinical concern is whether it represents benign or malignant disease.

LOCALIZATION PROCEDURES

Imaging studies should be done not only to localize the primary tumor but also to evaluate for metastatic disease. Because malignancy is not accurately predicted from histopathology alone, it is important to evaluate the tumor for clinical, pathologic, or radiographic evidence of invasion into adjacent organs; involvement of regional lymph nodes; or distant metastases. Multiple imaging modalities have been used, including computed tomography (CT), magnetic resonance imaging (MRI), somatostatin receptor scintigraphy (SRS), transabdominal ultrasonography, EUS, visceral angiography, selective arterial injection with hepatic venous sampling, and transhepatic portal venous sampling. Positron emission tomography (PET) with 5-hydroxytryptophan or levodopa has also been used.

Initial imaging of the pancreas is usually done with a high-resolution cross-sectional modality such as helical CT or MRI. EUS is usually the next imaging study employed and can give precise information about the relationship between the tumor and the pancreatic duct. EUS can also be used to guide fine-needle aspiration biopsy of these tumors, if necessary. EUS has a sensitivity of 82 to 93% and a specificity of 95% for the localization of PNETs.^{4,5} SRS is highly sensitive for most PNETs other than insulinoma but yields very little anatomic detail. Selective visceral arteriography takes advantage of the hypervascular nature of neuroendocrine tumors but has low sensitivity for small tumors. Selective intra-arterial injection with calcium and measurement of the target hormone from the hepatic veins can be done at the same time as the pancreatic arteriography and has been demonstrated to have higher sensitivity. Portal venous sampling for the target hormone is more invasive and involves transhepatic puncture of the portal vein and selective catheterization of the veins draining the pancreas. These tests can only regionalize the location of the tumor to the head and uncinate region, the neck and body region, and the tail of the pancreas.

PREOPERATIVE MANAGEMENT CONSIDERATIONS

Initial management of a patient with a hormone-producing PNET should focus on pharmacologic control of the effects of hormonal hypersecretion and, in some cases, hydration with correction of electrolyte abnormalities. If an operation is planned that may involve a splenectomy, patients should receive a trivalent vaccine to pneumococcus, *Haemophilus influenzae* b, and meningococcus group C.³

Patients should be evaluated for the possibility of an underlying genetic syndrome. MEN I is the most common genetic syndrome associated with PNETs, and additional testing should be done to evaluate for MEN I–associated conditions

such as other functional or nonfunctional PNETs, hyperparathyroidism, and pituitary tumors.³ Genetic counseling should be offered to patients and their first-degree relatives.

SURGICAL RESECTION

Sporadic PNETs with low malignant potential, such as insulinoma, can be treated with enucleation when anatomically feasible based on tumor location and unifocality. Formal pancreatic resection is appropriate for other neuroendocrine tumors because of their higher malignant potential and should also be performed for insulinoma when the anatomic location precludes safe enucleation. Specific surgical techniques for each functional tumor are discussed in greater detail below. It is important to keep in mind that for the malignant islet cell tumors, patients who undergo R0 resection have a better survival than those who undergo R1 or R2 resection.⁶

Surgical management of MEN I-associated PNETs is controversial because these patients usually have multiple synchronous functional and nonfunctional pancreatic or duodenal tumors and are rarely cured by surgery. The ENETS advocates surgery for all PNETs greater than 2 cm to avoid the development of malignancy and recommends distal pancreatectomy combined with intraoperative ultrasonography, bidigital palpation, and enucleation of tumors from the head of the pancreas to remove the bulk of PNETs that are present.¹ Duodenotomy with enucleation of tumors from the duodenal submucosa should be done in patients with concomitant elevated secretin-stimulated gastrin levels.^{1,2} Pancreaticoduodenectomy should be considered if the main tumor burden is located in the head of the pancreas.² Patients should also undergo dissection of lymph nodes along the celiac trunk and hepatic ligament.² The NCCN advocates a similar approach but does not give a specific tumor size criterion.³ The MEN I international consensus workshop, in contrast, advocates surgery for insulinomas and for most other PNETs except gastrinomas.² The management of MEN I-associated gastrinoma is detailed in the gastrinoma section of this chapter.

MANAGEMENT OF METASTATIC DISEASE

PNETs metastasize most commonly to the regional lymph nodes and liver. Regional lymph node metastases should be resected en bloc with the primary tumor. Because neuroendocrine tumors are slow-growing, a reduction in tumor volume can lead to significant palliation of symptoms. Therefore, consideration should be given to a debulking procedure even if the metastases are not completely resectable. Liver metastases can be treated with resection or ablation (radiofrequency ablation or cryotherapy) depending on tumor burden and resectability.^{1,3} Cholecystectomy is frequently done prophylactically to eliminate potential gallstone-related complications associated with possible future octreotide therapy. Liver transplantation has been offered as a palliative measure to young patients whose primary tumor is resected but who have developed metastatic disease limited to the liver and debilitating symptoms of hormonal excess.⁷ Other treatment options for unresectable liver metastases include hepatic arterial embolization, chemoembolization, and systemic therapy.^{1,3}

Systemic treatments for unresectable metastatic disease include octreotide, interferon, chemotherapy, and other investigational agents. Long-acting somatostatin analogues such as octreotide are tumorostatic as a result of an unknown mechanism and take advantage of the expression or overexpression of somatostatin receptors that most neuroendocrine tumors have been shown to have.⁸ Octreotide is recommended for patients with positive SRS who have symptomatic or progressing distant metastases or those with large tumor burdens.³ Interferon therapy has also been shown to stabilize tumor growth, but the mechanism is not well understood.⁹

Other treatment options for patients with distant metastases include systemic chemotherapy³ or entry onto a clinical trial. The chemotherapeutic agents most commonly used are streptozocin, 5-fluorouracil, and doxorubicin for well- to moderately differentiated tumors and cisplatin or carboplatin and etoposide for poorly differentiated tumors.¹ Although not approved outside of clinical trials, the effects of peptide receptor radionuclide therapy (PRRT) have been reported in several studies.^{10–15} PRRT involves administering radiolabeled somatostatin analogues in an attempt to deliver a cytotoxic level of radiation to the neuroendocrine tumor. Although responses have been noted, there have been no reports of improved survival in controlled trials.⁹ Inhibitors of vascular endothelial growth factor (VEGF) and multiple tyrosine kinases are currently under investigation. External beam radiotherapy has been effective in the palliation of bony and brain metastases.¹⁶

STAGING

The World Health Organization (WHO) classifies neuroendocrine tumors as either well-differentiated neuroendocrine tumors, well-differentiated carcinomas, or poorly differentiated carcinomas based on features such as site, size, angioinvasion, proliferative index, and evidence of metastasis.¹⁷ The ENETS has proposed a tumor-node-metastasis (TNM) classification for PNETs.¹⁸ Both of these systems have been found to be reliable and are highly correlated.¹⁹

LONG-TERM FOLLOW-UP

The malignant potential of an islet cell tumor is not always predictable based on the histopathology. Disease progression can occur late, and surveillance must be lifelong.

For patients with sporadic islet cell tumors, initial surveillance should consist of a history; physical examination; CT of the chest, abdomen, and pelvis; and measurement of tumor markers 3 to 6 months after tumor resection. For patients with gastrinoma, biochemical testing should consist of both a fasting serum gastrin level and a secretin stimulation test.²⁰ Surveillance by history, physical examination, and measurement of tumor markers should then be done every 6 to 12 months for the first 3 years³ and annually thereafter. Imaging studies should be ordered as clinically indicated (if the patient is symptomatic or tumor markers are elevated).

Patients with MEN I should have the above tests and serum calcium checked 3 months postresection, followed by clinical and biochemical surveillance every 6 months for the first 3 years and annually thereafter.³ Imaging studies should be ordered as clinically indicated.

Nonfunctional Pancreatic Neuroendocrine Tumors

EPIDEMIOLOGY

Nonfunctional PNETs represent 30 to 40% of islet cell tumors and have an annual incidence of 1 to 2 per million.²¹ Most cases are sporadic, whereas about 20% are associated with MEN I.²¹ About 20% of patients with MEN I will develop a nonfunctional PNET by the age of 40.² The majority (60 to 90%) of nonfunctional PNETs are malignant.⁹

BIOLOGY OF DISEASE

Nonfunctional PNETs may not secrete anything or may secrete peptides or hormones that fail to result in an overt clinical syndrome. These tumors may elaborate PP, neurotensin, chromogranin A, neuron-specific enolase, or human chorionic gonadotropin subunits.

Most nonfunctional PNETs are malignant, with metastases present in greater than 50% of patients at the time of diagnosis, most commonly to the liver.

CLINICAL FEATURES

Because nonfunctional PNETs do not have a syndrome of hormonal excess, most of these tumors are identified either incidentally or late in the disease course, when they become symptomatic because of a mass effect or metastatic disease. Symptoms and signs can include weight loss, obstructive jaundice, a palpable abdominal mass, hepatomegaly, and bowel obstruction [see Table 1].

LOCATION OF PRIMARY TUMOR(S)

Most nonfunctional PNETs are usually larger than 2 cm in size, with the tumors typically measuring between 6.5 and 10 cm in size.²² Most reside in the head of the pancreas.²²

LOCALIZATION PROCEDURES

Initial identification is usually by a cross-sectional imaging study such as CT or MRI because of the signs or symptoms

with which nonfunctional PNETs present. SRS should be done as clinically warranted, that is, to evaluate for additional tumors in a patient with MEN I or to evaluate for the extent of metastatic disease.³

SURGICAL MANAGEMENT OF PRIMARY TUMOR

Patients with locoregional disease should undergo resection. Because of the high malignant potential of nonfunctional PNETs, enucleation should not be done. The NCCN recommends consideration of laparoscopy for staging, followed by resection of the primary tumor with peripancreatic lymph node dissection.³ Because nonfunctional PNETs are most commonly located in the head of the pancreas, surgical resection usually consists of pancreaticoduodenectomy.

The management of patients with MEN I-associated nonfunctional PNETs is similar to that of patients with sporadic disease but also must take into account the presence of other functional and nonfunctional PNETs that may be present. Consensus guidelines for the treatment of nonfunctional and other PNETs in this context are detailed in the General Principles section of this chapter.¹⁻³

PROGNOSIS/OUTCOMES

Despite the predominantly malignant nature of nonfunctional PNETs, they are slow-growing tumors, and long-term survival is possible. Mean survival of patients with nonmetastatic and metastatic nonfunctional PNETs has been reported as 7 years and 5 years, respectively.²³

Insulinoma

EPIDEMIOLOGY

Insulinomas are rare PNETs with an annual incidence of 1 to 2 per million.²¹ They are the most common functional PNETs. Most cases of insulinoma are sporadic, whereas about 5% are associated with MEN I.²¹ About 10% of patients with MEN I will develop an insulinoma by the age of 40.² Insulinomas are malignant in 5 to 15% of cases.^{9,21}

Table 1 Summary of Features of Nonfunctional and Functional Pancreatic Neuroendocrine Tumors

PNET	% Malignant	% Associated with MEN I	Symptoms and Signs	Location	Initial Imaging Studies
Nonfunctional	60–90	20	None or symptoms of local invasion or metastasis	Most in head of pancreas	CT or MRI
Insulinoma	5–15	5	Whipple triad*	Equal distribution throughout pancreas	CT or MRI, EUS
Gastrinoma	60–90	25–40	Triad of abdominal pain, diarrhea, and weight loss in the presence of PUD	Two thirds in gastrinoma triangle	CT or MRI, SRS
Glucagonoma	50–80	10	4 “D’s”†	Most in tail of pancreas	CT or MRI, SRS
Somatostatinoma	70–80	45	Cholelithiasis, mild diabetes, malabsorption	Half in duodenum; most pancreatic somatostatinomas in head	CT or MRI, SRS
VIPoma	40–70	5	WDHA syndrome	Three quarters in pancreas, most in body or tail	CT or MRI, SRS

CT = computed tomography; EUS = endoscopic ultrasonography; MEN I = multiple endocrine neoplasia type I; MRI = magnetic resonance imaging; PNET = pancreatic neuroendocrine tumor; PUD = peptic ulcer disease; SRS = somatostatin receptor scintigraphy; WDHA = watery diarrhea, hypokalemia, achlorhydria.

*Whipple triad: fasting hypoglycemia, accompanied by neuroglycopenic symptoms, which are resolved by the administration of glucose.

†4 “D’s”: dermatitis (necrolytic migratory erythema), diabetes, depression, deep vein thrombosis.

BIOLOGY OF DISEASE

Insulinomas arise from the insulin-secreting beta islet cells located in the pancreas. Beta cells produce proinsulin, which consists of two peptide chains connected by an otherwise inactive C-peptide bridge. Proinsulin is cleaved prior to release from the cell, resulting ultimately in the secretion of equivalent amounts of C-peptide and active insulin. Insulin facilitates the entry of glucose into muscle, adipose, and other tissues and stimulates glycogen and fatty acid synthesis in the liver and glycerol synthesis in adipocytes. Given that insulinomas elaborate excessive amounts of active insulin and C-peptide, both substances are found to be elevated during hypoglycemic episodes. The finding of hyperinsulinism without elevated C-peptide levels indicates an exogenous (factitious) insulin source.

Sporadic insulinomas are usually unifocal and benign. In contrast, insulinomas associated with MEN I are commonly found in the context of other functional and nonfunctional PNETs, making it difficult to diagnose whether one or multiple insulinomas are present.²

CLINICAL FEATURES

Insulinoma has been described as causing a classic “Whipple triad” of symptoms (fasting hypoglycemia accompanied by neuroglycopenic symptoms that are then resolved with the administration of glucose) [see Table 1].²⁴ The fasting hypoglycemia is attributed to the release of excessive and unregulated amounts of insulin. The symptoms from profoundly low serum glucose levels may include confusion, combativeness, seizures, visual changes, and loss of consciousness and are collectively described as neuroglycopenic symptoms.

DIAGNOSTIC TESTS AND CONFIRMATION OF DIAGNOSIS

The diagnosis of insulinoma is suspected when the clinical features of hypoglycemia are present. In addition to insulinoma, however, other conditions can cause hypoglycemia, including medications (insulin, oral hypoglycemic, others), alcohol, sepsis or other critical illness, cortisol deficiency, functional beta cell disorders (nesidioblastosis), and insulin autoimmune hypoglycemia (antibodies to insulin or the insulin receptor).²⁵

The gold standard diagnostic test for the diagnosis of insulinoma is the 72-hour observed fast,^{3,25} although the vast majority of patients will become hypoglycemic within the first 48 hours.²⁶ Blood is usually drawn for glucose, insulin, C-peptide, proinsulin, and β -hydroxybutyrate every 6 hours or when neuroglycopenic signs and/or symptoms occur. Insulin antibodies should also be measured. A urine sample should be collected and analyzed for oral hypoglycemic agents. Glucose is administered, and the symptomatic response is recorded. Multiple measurements are prudent for confirmation of the biochemical diagnosis. Criteria for the diagnosis of endogenous hyperinsulinism published in a Clinical Practice Guideline from the Endocrine Society in 2009²⁵ are as follows:

- Signs and/or symptoms of hypoglycemia with a plasma glucose concentration of less than 55 mg/dL (3.0 mmol/L)
- Insulin 3.0 uU/mL (18 pmol/L) or greater

- C-peptide 0.6 ng/mL (0.2 nmol/L) or greater
- Proinsulin 5.0 pmol/L or greater
- β -Hydroxybutyrate 2.7 mmol/L or less
- An increase in plasma glucose of at least 25 mg/dL (1.4 mmol/L) after the intravenous administration of 1.0 mg glucagon

Patients who meet the above criteria who have a negative screening for oral hypoglycemic agents and no circulating insulin antibodies should undergo localization procedures for an insulinoma.

LOCATION OF PRIMARY TUMOR(S)

Approximately 80% of sporadic insulinomas are unifocal. The vast majority of insulinomas are smaller than 2 cm in size. The tumor distribution is equal in frequency between the pancreatic head, body, and tail.

LOCALIZATION PROCEDURES

Initial testing should consist of a cross-sectional imaging study such as triphasic CT or MRI in conjunction with transgastric EUS.³ Figure 1 shows a 1.2 cm insulinoma in the uncinate process of a 47-year-old man that was seen on EUS but not seen on CT. SRS, although useful for most PNETs, has a lower sensitivity for insulinoma. It does have a role, however, in the workup of a patient with MEN I-associated insulinoma because of the other functional and nonfunctional PNETs that are invariably present.

If the above tests are unable to localize the insulinoma, more invasive testing such as visceral arteriography, selective intra-arterial calcium injection with hepatic venous sampling for insulin, or selective portal venous sampling for insulin can be done. Visceral arteriography has a sensitivity of only 35% as a result of the small nature of insulinomas.²⁷ Selective intra-arterial calcium injection with hepatic venous sampling for insulin can be used to regionalize the insulinoma to either



Figure 1 Endoscopic sonogram demonstrating a 1.2 cm insulinoma in the uncinate process of a 47-year-old man who had negative or equivocal cross-sectional imaging. Because of the location of the tumor, the patient required pancreaticoduodenectomy. PD = pancreatic duct; SMA = superior mesenteric artery; SMV/PV CONF = superior mesenteric vein-portal vein confluence.

the head, uncinate, or body or tail of the pancreas with a sensitivity of 88%,²⁷ and portal venous sampling for insulin has a sensitivity of 77 to 81%^{28,29} for the regionalization of insulinomas. In addition, intraoperative ultrasonography is very helpful for identifying the tumor location and characterizing the relationship between the tumor and the pancreatic duct and adjacent vessels.

PREOPERATIVE MANAGEMENT CONSIDERATIONS

Initial management of a patient with insulinoma should focus on stabilizing blood glucose levels. This is usually done with diet alone, but in some cases, octreotide and/or diazoxide (an antihypertensive agent that also inhibits insulin release and promotes hyperglycemia by enhancing glycogenolysis) may be necessary.^{3,30}

SURGICAL MANAGEMENT

The surgical approach is dictated by the tumor location within the pancreas, clinical suspicion of malignancy, multifocality, and whether it arises sporadically or in association with MEN I.³ Because sporadic insulinomas are typically solitary and benign, they can usually be treated safely by enucleation, either as an open procedure or laparoscopically. If enucleation results in a disruption of the pancreatic duct, then pancreatic resection may be required. Insulinomas in the tail of the pancreas can be treated with distal pancreatectomy, with splenic preservation, if possible. If the tumor arises in the head or uncinate process and cannot be safely enucleated, pancreaticoduodenectomy may be required. If a malignant insulinoma is suspected, formal resection with peripancreatic lymphadenectomy is required.

The treatment of MEN I-associated insulinomas must take into account the presence of other functional and nonfunctional PNETs that may be present. Consensus guidelines for the treatment of insulinomas and other PNETs in this context are detailed in the General Principles section of this chapter.¹⁻³

PROGNOSIS

Benign unifocal insulinoma has an excellent prognosis following surgical resection. Transient mild hyperglycemia is usually observed for several days. There should be no recurrence of neuroglycopenic symptoms in the postoperative setting. If hypoglycemia recurs, there should be suspicion of tumor recurrence at the enucleation site, metastasis from malignant insulinoma, or MEN I. Benign insulinomas that are completely resected should have a 100% long-term recurrence-free survival.^{31,32} When elevated preoperatively, neuroendocrine tumor markers such as chromogranin A and neuron-specific enolase may be useful as postoperative markers for tumor recurrence.⁹

Gastrinoma

EPIDEMIOLOGY

Gastrinomas (causing Zollinger-Ellison syndrome) are a rare cause of gastric acid hypersecretion and peptic ulcer disease with an annual incidence of 1 to 2 per million.^{21,33} This disease is most commonly diagnosed in the fifth decade of life, with 90% of cases diagnosed between the ages of 20

and 60.³³ Most cases of gastrinomas are sporadic, whereas 25 to 40% are associated with MEN I.^{2,21} About 40% of patients with MEN I will develop Zollinger-Ellison syndrome by the age of 40.² Gastrinomas have also been reported in association with neurofibromatosis (von Recklinghausen disease).³⁴ Gastrinomas are malignant in 60 to 90% of cases.^{3,35,36}

BIOLOGY OF DISEASE

Gastrinomas predominantly arise from gastrin-secreting G cells located in the duodenal mucosa and pancreas, although most G cells are located in the gastric antrum. Gastrin stimulates acid secretion from parietal cells in the stomach and aids in gastric motility. Hypergastrinemia causes gastric acid hypersecretion, parietal cell hyperplasia, and pancreatic hypersecretion as a result of an increased acid load in the duodenum and the direct trophic effects of gastrin on pancreatic acinar cells.

Gastrinomas are different in sporadic versus MEN I-associated cases; sporadic gastrinomas are monoclonal in etiology, whereas those associated with MEN I have been found to be polyclonal.³³ This may be attributable to a progression from islet cell hyperplasia to microadenosis to neoplasia in MEN I, a hypothesis favored by many authorities.³⁷ Sporadic and MEN I-associated gastrinomas also differ in the extent of disease at the initial presentation. Sporadic gastrinomas have lymph node metastases in 30 to 50% of cases and have liver metastases at initial presentation in 7 to 22% of cases, whereas MEN I-associated gastrinomas more commonly have lymph node metastases (61 to 80% of cases) but have liver metastases at initial presentation in only 5 to 14% of cases.^{35,38,39} Liver metastases correlate with the size of the primary tumor and occur more often with pancreatic versus duodenal primary tumors.^{38,40}

CLINICAL FEATURES

Gastrinoma has been described as causing a classic triad of symptoms (abdominal pain, diarrhea, and weight loss) in the presence of peptic ulcer disease [see Table 1].³³ There is a mean delay of 5 to 8 years between the onset of symptoms and diagnosis.^{39,41} Abdominal pain and diarrhea (as a result of small bowel mucosal injury and increased gastric and pancreatic secretions that may overwhelm the absorptive capacity of the intestine) are the most common symptoms, occurring in 70% of patients, with other symptoms occurring less frequently (heartburn 44%, nausea 33%, vomiting 25%, weight loss 17%).⁴¹ The location or extent of disease does not seem to affect symptom severity.⁴¹ In the current era, complications from peptic ulcer disease such as bleeding or perforation are uncommon. Upper endoscopy usually demonstrates prominent gastric rugal folds, which are attributable to the trophic effects of gastrin on the gastric mucosa.³⁵

DIAGNOSTIC TESTS AND CONFIRMATION OF DIAGNOSIS

The diagnosis of gastrinoma is suspected when the clinical features of gastric acid hypersecretion are accompanied by an elevated fasting serum gastrin level. In addition to gastrinoma, however, other conditions can cause hypergastrinemia [see Table 2]. The use of proton pump inhibitors or H₂ receptor blockers is associated with elevated gastrin secondary to high gastric pH. To establish a diagnosis of gastrinoma,

Table 2 Differential Diagnosis of Hypergastrinemia

Gastrinoma
Antral G cell hyperplasia
Conditions associated with achlorhydria or reduced gastric acid secretion
Pernicious anemia
Chronic atrophic gastritis
Proton pump inhibitor therapy
Conditions associated with gastric acid hypersecretion
<i>Helicobacter pylori</i> infection
Gastric outlet obstruction
Truncal vagotomy
Retained gastric antrum (in patients who have undergone prior antrectomy)
Short bowel syndrome
Renal failure

however, the hypergastrinemia must accompany low gastric pH or high basal acid output.

A fasting serum gastrin level of more than 1,000 pg/mL (10 times the upper limit of normal) is diagnostic of gastrinoma; however, only one third of patients have gastrin levels this high. The remaining two thirds of patients have fasting serum gastrin levels of 500 to 1,000 pg/mL, values that overlap with the more common conditions associated with hypergastrinemia [see Table 2].⁴² Gastrinoma can be distinguished from these other conditions by virtue of its paradoxical effect on serum gastrin levels in response to a secretin infusion (secretin stimulation test)^{43,44} [see Table 3]. Patients who have a strong clinical suspicion of gastrinoma with gastric acid hypersecretion but a negative secretin stimulation test should undergo a calcium infusion test⁴⁴ [see Table 3]. Criteria for the diagnosis of gastrinoma in patients with a fasting serum gastrin level of less than 1,000 pg/mL include

Table 3 Secretin and Calcium Provocative Testing for Gastrinoma

Withdraw patient from PPIs for at least 3 days, possibly up to 7 days
Withdraw patient from H ₂ blocker for at least 30 hours
Overnight fast
Secretin stimulation test
Administer 2 U/kg secretin IV bolus
Measure serum gastrin levels at 0, 2, 5, 10, 20, 30 min
An increase in serum gastrin by more than 200 pg/mL over baseline levels is diagnostic of gastrinoma ⁴⁴ ; new criterion using 120 pg/mL has been found to have increased sensitivity and specificity (sensitivity 94%, specificity 100%) ⁷⁵
Calcium infusion test
Administer 54 mg/kg/hr of 10% calcium gluconate (5 mg/kg/hr of calcium) by continuous IV infusion for 3 hours
Measure serum calcium and serum gastrin levels every 30 min for 3 hours
An increase in serum gastrin level by more than 395 pg/mL over baseline levels is diagnostic of gastrinoma ⁴⁴

IV = intravenous; PPI = proton pump inhibitor.

a fasting serum gastrin level of more than 200 pg/mL with a basal acid output of greater than 15 mEq/hr (> 5 mEq/hr in a patient who has had an acid-reducing surgical procedure) and a positive secretin or calcium stimulation test.⁴⁵

Although hypercalcemia increases gastrin secretion from gastrinomas, studies differ with respect to gastrin levels in patients with sporadic versus MEN I-associated gastrinomas. Some studies have shown that patients with MEN I-associated gastrinomas do not have higher serum gastrin levels or higher increases in serum gastrin levels with secretin than those with sporadic gastrinomas,^{35,42} whereas others have shown higher fasting serum gastrin levels in patients with MEN I.³⁹

LOCATION OF PRIMARY TUMOR(S)

Two thirds of gastrinomas are located in the gastrinoma triangle, a triangle bordered by the junction of the cystic and common bile ducts superiorly, the junction of the second and third portions of the duodenum inferiorly, and the junction of the neck and body of the pancreas medially.⁴⁶ Large series also report lymph node-only primary gastrinomas in 4 to 13% of patients,^{39,47} although these cases may represent lymph node metastases from an occult primary tumor.⁴⁸ Other primary sites for gastrinomas have been reported in up to 11% of patients and include the liver, common bile duct, pylorus, jejunum, omentum, heart, and ovary.³⁹

Sporadic and MEN I-associated gastrinomas differ with respect to the most common location of the primary tumor; sporadic gastrinomas are located in the duodenum and pancreas with almost equal frequency, whereas MEN I-associated gastrinomas are more commonly located in the duodenum (80%).³⁵ Furthermore, sporadic gastrinomas tend to be solitary, whereas MEN I-associated gastrinomas are usually multicentric and small (< 0.5 cm).^{49,50}

LOCALIZATION STUDIES

Initial testing should consist of a cross-sectional imaging study such as triphasic CT or MRI in conjunction with SRS.³ The sensitivity of these imaging modalities is related to tumor size. Sensitivity of CT and MRI for the detection of a primary gastrinoma varies from 22 to 90%, with increased sensitivity for the detection of liver metastases (54 to 90%).²¹ SRS has a sensitivity of 53 to 72% for the detection of a primary gastrinoma and a sensitivity of 92 to 97% for the detection of liver metastases.^{21,36,40}

If these tests are unable to localize the gastrinoma, more invasive testing, such as EUS, selective visceral arteriography, selective intra-arterial secretin or calcium injection with hepatic venous sampling for gastrin, or pancreatic venous sampling for gastrin, can be done. EUS has a sensitivity of 67 to 100%^{21,40} for the detection of a primary gastrinoma. Similar to insulinoma, selective visceral arteriography has low sensitivity for the detection of a primary gastrinoma (13 to 28%)^{36,51}; therefore, other techniques have been developed. Selective intra-arterial injection of secretin or calcium with hepatic venous sampling for gastrin has a sensitivity of 77 to 93% for the regionalization of a primary gastrinoma,^{21,27} whereas pancreatic venous sampling has a similar sensitivity of 94%.⁵¹

PREOPERATIVE MANAGEMENT CONSIDERATIONS

Initial management of a patient with gastrinoma should focus on pharmacologic control of gastric acid hypersecretion. In the current era, this is most commonly done with proton pump inhibitors.⁵² In addition to the known effect of hypercalcemia on serum gastrin levels, hypercalcemia also decreases the effectiveness of the antisecretory drugs by an unknown mechanism.³⁵ Thus, patients with MEN I–associated gastrinomas should undergo parathyroidectomy both for treatment of their hyperparathyroidism and to allow better pharmacologic control of gastric acid hypersecretion.^{53,54}

SURGICAL MANAGEMENT OF PRIMARY TUMOR

Historically, surgery for patients with gastrinoma focused on acid-reducing procedures, including total gastrectomy. With the development of excellent pharmacologic therapy for the control of gastric acid hypersecretion, surgery for gastrinoma has shifted toward tumor localization and resection.

The surgical treatment of the primary tumor can vary depending on if the patient has sporadic versus MEN I–associated gastrinoma. Consensus guidelines recommend surgical resection of sporadic gastrinomas.^{1,3} Specific recommendations by the NCCN are as follows.³ Operative exploration is recommended even if the gastrinoma has not been localized preoperatively; however, observation is an acceptable alternative for these patients with a category 2B recommendation (based on lower-level evidence, including clinical experience and nonuniform consensus, but no major disagreement).³ Intraoperative maneuvers that should be done to localize the tumor include intraoperative ultrasonography, transduodenal palpation, intraoperative upper endoscopy with transduodenal illumination, and duodenotomy with palpation.^{55,56} If the tumor is found in the duodenal mucosa, it should undergo enucleation with periduodenal lymph node dissection.³ Noninvasive tumors 5 cm or smaller that are located in the head of the pancreas should also undergo enucleation and periduodenal lymph node dissection; however, tumors larger than 5 cm or those that are invasive should undergo pancreaticoduodenectomy.³ Tumors located in the body or tail of the pancreas should undergo enucleation or distal pancreatectomy (spleen preserving, if possible).³

There is no consensus as to the best approach to the treatment of MEN I–associated gastrinoma, especially in light of the additional PNETs that are frequently present.³⁵ Some experts advocate observation with pharmacologic control of gastric hypersecretion, some advocate routine exploration and resection, and others advocate operative exploration based on pancreatic tumor size.²

Proponents of observation argue that excellent control of gastric acid hypersecretion can be obtained with medical therapy, identification of the primary gastrinoma(s) may not be possible, and there is a lack of data to support the effectiveness of surgery in altering the natural history of disease in these patients. Most MEN I patients have duodenal gastrinomas, and the pancreatic tumors seen on imaging are usually not the gastrinomas.⁴⁹ Furthermore, in MEN I patients who develop liver metastases, it is unclear if these metastases are from the gastrinoma or from the other PNETs, calling into question the utility of resecting primary gastrinomas to prevent metastasis. Finally, studies have shown that very

few MEN I patients (< 1 to 16%) are biochemically cured immediately postoperatively,^{39,57} and other studies have shown conflicting results with respect to the impact of primary gastrinoma resection on overall survival.

Proponents of surgical resection of MEN I–associated gastrinomas argue that surgery is the only modality that can cure gastrinoma and prevent the later development of malignancy^{1,57} and that surgery for curative intent is most effective when tumors are small. Liver metastases, which are the most important predictor of survival, are associated with the increasing size of the primary tumor.⁴⁰ Despite these arguments, however, there is no clear consensus as to the timing of surgery for patients with MEN I. The NCCN recommends a similar approach to MEN I–associated gastrinomas as sporadic gastrinomas with the addition of consideration of a distal pancreatectomy (category 2B recommendation) to duodenotomy and enucleation of the primary tumor(s) from the duodenum and/or head of the pancreas to remove the bulk of PNETs that are present.³ Surgery is likewise advocated by the ENETS and is recommended before tumors become larger than 2 cm.¹ The 2001 MEN I international consensus workshop was unable to come to a consensus with respect to the primacy of surgical versus nonsurgical management in patients with MEN I–associated gastrinomas.²

PROGNOSIS/OUTCOMES

The prognosis of patients with gastrinoma depends on the size and location of the primary tumor, the presence of liver metastases, and sporadic versus MEN I–associated disease. The presence of liver metastases is the most important determinant of survival.⁴⁰ Other predictors of an aggressive or malignant course include short duration from onset of symptoms to diagnosis, very high gastrin levels, and large primary tumors that are pancreatic in location.³⁸ Interestingly, lymph node metastases do not appear to be associated with decreased survival,³⁸ and long-term survival is possible even with lymph node metastases at the initial presentation.

Biochemical cure rates are better for sporadic gastrinoma versus MEN I–associated gastrinoma. Without pancreaticoduodenectomy, 51 to 60% of patients with sporadic gastrinoma are disease-free immediately postoperatively and 30 to 49% are disease-free at 5 years.^{39,57} This is in contrast to less than 1 to 16% of patients with MEN I–associated gastrinoma who are disease-free immediately postoperatively and less than 1 to 6% who are disease-free at 5 years.^{39,57} Long-term survival is possible, however, even without biochemical cure. Eventually, about one third of patients with both sporadic and MEN I–associated gastrinoma will die of their malignancy.²

Glucagonoma

EPIDEMIOLOGY

Glucagonomas are rare PNETs with an annual incidence of 0.1 per million.²¹ This disease is most commonly diagnosed in the fourth or fifth decade of life.⁵⁸ Most cases of glucagonomas are sporadic, whereas about 10% are associated with MEN I.²¹ About 2% of patients with MEN I will develop a glucagonoma by the age of 40.² Glucagonomas are malignant in up to 90% of cases.^{3,21}

BIOLOGY OF DISEASE

Glucagonomas arise from glucagon-secreting alpha islet cells of the pancreas. In addition to pancreatic alpha cells, glucagon is also produced by some enterochromaffin cells of the gastrointestinal tract and salivary glands. Glucagon is a catabolic hormone that maintains blood glucose levels during periods of hypoglycemia by acting predominantly on hepatocytes and adipocytes to increase gluconeogenesis and glycogenolysis. Glucagon also stimulates insulin release. Normal glucagon release is stimulated by hypoglycemia and vagal nerve stimulation and is inhibited by somatostatin.

Most glucagonomas are malignant. Metastases are present at initial presentation in 78 to 90% of patients,^{59,60} most commonly to the liver but also to peripancreatic lymph nodes, bone, adrenal glands, kidney, and lung.⁶¹

CLINICAL FEATURES

Glucagonomas have been described as causing the 4 “D’s”: dermatitis, diabetes, depression, and deep vein thrombosis [see Table 1]. Patients often also experience hypoproteinemia, malnutrition, and weight loss because the hyperglycemia is a result of the breakdown of protein stores. Anemia is also frequently present and is related to glucagon’s effect on suppression of erythropoiesis in the bone marrow.⁶¹ There is a mean delay of 2 years between the onset of symptoms and diagnosis.⁵⁸

Weight loss and a characteristic skin rash (necrolytic migratory erythema) are the most common presenting features, occurring in about 70% of patients, with other symptoms occurring less frequently at initial presentation (diabetes 38%, stomatitis 29%, diarrhea 29%).⁶¹ Necrolytic migratory erythema, which is an intensely pruritic rash that usually presents on the lower abdomen, perineum, perioral area, or lower extremities, may present before any other signs or symptoms and is pathognomonic for glucagonoma. The diabetes is usually mild and eventually develops in 76 to 93% of patients.⁵⁸ Neuropsychiatric manifestations occur in about 20% of patients at some point during the course of their illness and can include depression, anxiety, dementia, and psychoses.⁵⁸ Thromboembolic events distinguish glucagonomas from other neuroendocrine tumors and occur in up to 30% of patients.⁵⁸ The hypercoagulable state is thought to be related to a factor X-like antigen that is secreted by the tumor.⁶²

Glucagonomas sometimes secrete secondary hormones and are associated with Zollinger-Ellison syndrome in about 10% of cases.^{60,61} Other, less common, secondary hormones secreted by glucagonomas include VIP, pancreatic polypeptide, somatostatin, and ACTH.⁵⁸

DIAGNOSTIC TESTS AND CONFIRMING THE DIAGNOSIS

The diagnosis of glucagonoma is suspected when the fasting serum glucagon level is elevated. In addition to glucagonoma, however, other conditions can cause hyperglucagonemia [see Table 4] and are, in fact, more common reasons for an elevated serum glucagon level.

Most glucagonoma patients have glucose intolerance and fasting serum glucagon levels between 1,000 and 5,000 pg/mL (normal < 150 pg/mL).^{61,63} Because of the association of glucagonoma with other functional neuroendocrine

Table 4 Differential Diagnosis of Hyperglucagonemia⁵⁸

Glucagonoma
Prolonged fasting/starvation
Diabetic ketoacidosis/hyperosmotic nonketotic state
Other endocrine causes
Familial hyperglucagonemia
Cushing syndrome
Liver disease associated with decreased degradation of glucagon
Hepatitis
Cirrhosis
Hemachromatosis
Conditions associated with a malabsorptive state
Pancreatic disease
Celiac disease
Inflammatory bowel disease
Renal failure
Danazol therapy
Trauma/burns/sepsis

tumors, fasting levels of other hormones should be measured.⁵⁸ Other laboratory abnormalities seen in patients with glucagonomas include hyperglycemia, anemia, and hypoaminoacidemia. Because glucagon stimulates insulin release, patients also often have elevated basal insulin levels.

LOCATION OF PRIMARY TUMOR

Most glucagonomas (50 to 75%) are located in the tail of the pancreas, with the remainder distributed throughout the gland.⁵⁸ Up to 5% of cases may occur in an extrapancreatic location such as the duodenal wall, accessory pancreatic tissue, or kidney.⁶⁴

LOCALIZATION STUDIES

Initial testing should consist of a cross-sectional imaging study such as triphasic CT or MRI in conjunction with SRS.³ In the majority of cases, the tumor burden is such that the location of the primary tumor can be identified by noninvasive imaging.

If noninvasive tests are unable to localize the glucagonoma, more invasive testing such as EUS, selective visceral arteriography, or pancreatic venous sampling for glucagon can be done.^{63,65}

PREOPERATIVE MANAGEMENT CONSIDERATIONS

Once the biochemical diagnosis is made, the initial management of a patient with glucagonoma should focus on blocking and treating the metabolic effects of glucagon hypersecretion and preventing or treating venous thromboembolism. Octreotide and intravenous fluids should be administered.³ Octreotide is administered subcutaneously at a dose of 50 µg two to three times daily and titrated to a maximum dose of 500 µg four times daily.⁶⁰ Nutrition should be optimized, with total parenteral nutrition, if necessary. Octreotide and total parenteral nutrition have been reported to ameliorate necrolytic migratory erythema. Zinc should

be administered orally in the form of zinc sulfate.³ Hyperglycemia should be controlled. Severe anemia may require transfusion. Because of the hypercoagulable state and predisposition to thromboembolic events, patients should be fully anticoagulated at the time of diagnosis, and an inferior vena cava filter should be considered perioperatively.³

SURGICAL MANAGEMENT OF PRIMARY TUMOR

Patients with locoregional disease should undergo resection. Because of the high malignant potential of glucagonoma, enucleation should not be done. The NCCN recommends consideration of laparoscopy for staging, followed by resection of the primary tumor with peripancreatic lymph node dissection.³ Because glucagonomas are most commonly located in the tail of the pancreas, surgical resection usually consists of distal pancreatectomy with splenectomy. Cholecystectomy should be performed prophylactically to eliminate the potential gallstone-related complications associated with possible future octreotide therapy.³ The ENETS also recommends radical surgery as the only treatment for cure of glucagonoma.¹

The management of patients with MEN I-associated glucagonoma is similar to that of patients with sporadic disease but also must take into account the presence of other functional and nonfunctional PNETs that may be present. Consensus guidelines for the treatment of glucagonomas and other PNETs in this context are detailed in the General Principles section of this chapter.¹⁻³

PROGNOSIS/OUTCOMES

Glucagonoma is a rare tumor, and there is a paucity of outcomes data. The development of liver metastases is a poor prognostic sign. MEN I patients with glucagonoma, somatostatinoma, and VIPoma were found to have an approximately 54% 10-year survival in a study from the Groupe des Tumeurs Endocrines registry.⁶⁶ Glucagonoma is relatively chemoresistant.

Somatostatinoma

EPIDEMIOLOGY

Somatostatinomas are rare neuroendocrine tumors of the pancreas or duodenum with an annual incidence of less than 0.1 per million.²¹ Somatostatinomas are most commonly diagnosed in the fifth decade of life, with an equal male to female ratio.⁶⁷ Most cases of somatostatinomas are sporadic, whereas about 45% are associated with MEN I.²¹ About 2% of patients with MEN I will develop somatostatinomas by the age of 40.² Somatostatinomas have also been reported in association with neurofibromatosis (von Recklinghausen disease),⁶⁸ and somatostatin expression has also been found in gangliocytic paragangliomas.⁶⁹ Somatostatinomas are malignant in 70 to 80% of cases.^{3,21}

BIOLOGY OF DISEASE

Somatostatinomas arise from somatostatin-secreting delta islet cells located in the duodenal mucosa and pancreas. Somatostatin has a broad spectrum of inhibitory activity in the gastrointestinal tract, including inhibiting the release of gastric acid, pepsin, pancreatic exocrine secretions, and

multiple hormones (insulin, glucagon, gastrin, secretin, VIP, PP, and cholecystokinin). It also inhibits gastrointestinal blood flow and motility.

Most somatostatinomas are malignant. Metastases, most commonly to regional lymph nodes and the liver, are more common in patients with sporadic or neurofibromatosis-associated somatostatinomas and uncommon in MEN I-associated somatostatinoma or gangliocytic paraganglioma.⁷⁰

CLINICAL FEATURES

Pancreatic somatostatinoma has been described as causing a syndrome of cholelithiasis, mild diabetes, malabsorption and steatorrhea [see Table 1].⁷¹ Other manifestations of the syndrome include weight loss, anemia, hypochlorhydria.⁶⁷ Patients most commonly present with abdominal pain (39%), and cholelithiasis (33%), jaundice (28%), and anemia (28%), with other symptoms occurring less commonly (gastrointestinal bleeding 22%, nausea/vomiting 6%).⁷⁰ Duodenal somatostatinomas only rarely lead to a clinically recognized syndrome.

DIAGNOSIS

The diagnosis of somatostatinoma is made on the basis of a pancreatic or duodenal mass and an elevated fasting plasma somatostatin level. There are no provocative tests for somatostatinoma.

LOCATION OF PRIMARY TUMOR

Approximately half of the cases of somatostatinoma arise in the duodenum.²¹ Most pancreatic somatostatinomas are located in the head of the gland. Other locations described for primary somatostatinomas include the bile ducts and ovaries.⁷⁰ Most somatostatinomas are solitary, whereas those associated with MEN I are usually multiple, very small, and incidental findings in patients undergoing operation for gastrinoma.⁷⁰

LOCALIZATION STUDIES

Initial testing should consist of a cross-sectional imaging study such as triphasic CT or MRI in conjunction with SRS.^{1,3}

SURGICAL MANAGEMENT OF PRIMARY TUMOR

Patients with locoregional disease should undergo operation. Similar to glucagonoma, because of the high malignant potential of somatostatinoma, enucleation should not be done. The NCCN recommends consideration of laparoscopy for staging, followed by resection of the primary tumor with peripancreatic lymph node dissection.³ Because somatostatinomas are most commonly located in the duodenum or head of the pancreas, surgical resection usually consists of pancreaticoduodenectomy. Also similar to glucagonoma, cholecystectomy should be performed prophylactically to eliminate potential gallstone-related complications.³ The ENETS also recommends radical surgery as the only treatment for cure of somatostatinoma.¹

The management of patients with MEN I-associated somatostatinoma is similar to that of patients with sporadic disease but also must take into account the presence of other functional and nonfunctional PNETs that may be present. Consensus guidelines for the treatment of somatostatinomas

and other PNETs in this context are detailed in the General Principles section of this chapter.¹⁻³

PROGNOSIS/OUTCOMES

The 5-year survival for completely resected somatostatinoma without metastasis is 100%. The 5-year survival is approximately 30 to 60% for patients with metastatic disease.^{66,72}

VIPoma

EPIDEMIOLOGY

VIPomas (causing Verner-Morrison syndrome, also known as WDHA [watery diarrhea, hypokalemia, and achlorhydria] or pancreatic cholera) are rare neuroendocrine tumors with an annual incidence of 0.1 per million.²¹ VIPoma is most commonly diagnosed in the fifth decade of life, with an equal male to female ratio.⁷³ Patients with VIP-producing neurogenic tumors (ganglioneuromas, ganglioneuroblastomas, neuroblastomas, neurofibromatosis) are usually diagnosed in the first decade of life, although some cases of VIP-producing adrenal neurogenic tumors have been diagnosed in adulthood.⁷³ Most cases of VIPomas are sporadic, whereas about 5% are associated with MEN I.²¹ About 2% of patients with MEN I will develop VIPomas by the age of 40.² VIPomas are malignant in 40 to 70% of cases.^{3,21}

BIOLOGY OF DISEASE

VIPomas arise from cholinergic nerves that terminate in the pancreatic islets. VIP is a neuropeptide that stimulates the secretion of fluids and electrolytes into the intestinal lumen, causing losses of sodium, chloride, water, and potassium. It also inhibits gastric acid secretion, causing hypo/achlorhydria.

Most VIPomas are malignant, with metastases most commonly to the liver. Metastatic disease occurs more often with pancreatic primary tumors.⁷³ Pancreatic VIPomas have lymph node metastases in 16% of cases and have liver metastases at the initial presentation in 49% of cases.⁷³ VIP-producing neurogenic tumors have lymph node metastases as commonly as pancreatic VIPomas but have a lower rate of liver metastases (4%).⁷³ There is no difference with respect to malignancy rates in sporadic versus MEN I-associated VIPomas.⁷³

CLINICAL FEATURES

VIPomas present with a syndrome of profuse watery diarrhea (> 5 L of watery, tea-colored stool/day) with severe hypokalemia and hypo/achlorhydria [see Table 1]. The diarrhea is a secretory diarrhea that persists despite fasting and may be intermittent. Diarrhea and hypokalemia (as a result of potassium losses in the stool) are the most common presenting features, occurring in 98% and 89% of patients, respectively, with other signs and symptoms occurring less frequently (hypo/achlorhydria 43%, weight loss 33%, nausea/vomiting 16%, flushing 14%, abdominal pain 10%, anemia 10%).⁷³ Severe muscle weakness attributable to hypokalemia is also common.

DIAGNOSTIC TESTS

The diagnosis of VIPoma is made on the basis of an elevated fasting serum VIP level when diarrhea is present.

VIP secretion may be episodic, and several measurements may be necessary to make the diagnosis. Because the severe diarrhea can cause severe electrolyte derangements, serum electrolytes should be measured.

LOCATION OF PRIMARY TUMOR(S)

Three fourths of VIPomas are located within the pancreas, with the remainder of cases consisting of VIP-producing neurogenic tumors (20%) located in the adrenal gland, retroperitoneum, or mediastinum or nonneurogenic extrapancreatic tumors (5%) located in the small intestine, lung, liver, kidney, or colon.⁷³ Of the intrapancreatic VIPomas, about 70% are located in the body or tail of the pancreas, with about 30% located in the head.⁷³ The great majority of VIPomas are solitary, with 4% of cases attributable to multiple tumors.⁷³

LOCALIZATION

Initial testing should consist of a cross-sectional imaging study such as triphasic CT or MRI in conjunction with SRS.³ If noninvasive tests are unable to localize the VIPoma, more invasive testing such as EUS or selective visceral arteriography should be done.⁷⁴

PREOPERATIVE MANAGEMENT CONSIDERATIONS

Initial management of a patient with a VIPoma should focus on blocking and treating the metabolic effects of VIP hypersecretion. Octreotide and intravenous fluids should be administered.³ Electrolyte imbalances (particularly potassium, magnesium, and bicarbonate) should be corrected.³

SURGICAL MANAGEMENT OF PRIMARY TUMOR

Patients with locoregional disease should undergo operation. Similar to glucagonoma and somatostatinoma, enucleation of a VIPoma should not be done. The NCCN recommends consideration of laparoscopy for staging, followed by resection of the primary tumor with peripancreatic lymph node dissection.³ Depending on the location of the primary tumor, this may consist of distal pancreatectomy with splenectomy or pancreaticoduodenectomy. Also similar to glucagonoma and somatostatinoma, cholecystectomy should be performed prophylactically to eliminate potential gallstone-related complications associated with possible future octreotide therapy.³ The ENETS also recommends radical surgery as the only treatment for cure of VIPoma.¹

The management of patients with MEN I-associated VIPoma is similar to that of patients with sporadic disease but also must take into account the presence of other functional and nonfunctional PNETs that may be present. Consensus guidelines for the treatment of somatostatinomas and other PNETs in this context are detailed in the General Principles section of this chapter.¹⁻³

PROGNOSIS/OUTCOMES

Five-year survival rates after resection of pancreatic VIPomas are approximately 68%, with better survival for patients without metastatic disease at the initial presentation (94% versus 60%).⁷³

Conclusions

PNETs comprise approximately 1 to 2% of all pancreatic tumors. The possibility of a syndromic association with MEN I, VHL disease, NF-1, or tuberous sclerosis should be considered when evaluating patients with PNETs. PNETs are frequently nonfunctional, but a number of bioactive peptides, including insulin, gastrin, glucagon, VIP, somatostatin, parathyroid hormone-related peptide, growth hormone-releasing factor, and others, may be elaborated. For functional tumors, the clinical presentation of disease is usually characteristic of the hormone elaborated by the tumor. The diagnosis is made based on clinical features and

biochemical demonstration of inappropriately elevated hormone levels. Confirmation of disease is followed by localizing studies, which may include cross-sectional imaging, EUS, scintigraphy, arteriography, and selective venous sampling. Complete surgical resection offers the only possibility of cure. Treatment, therefore, centers mainly on surgical resection, but multimodal therapy, including biotherapy with somatostatin analogues, is often used in advanced disease, especially for the modulation of debilitating hormonal excess. Adjuvant therapies via PPRT and novel inhibitors of VEGF and tyrosine kinases are being explored.

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1 STROKE AND TRANSIENT ISCHEMIC ATTACK

Billy J. Kim, MD, and Thomas S. Maldonado, MD

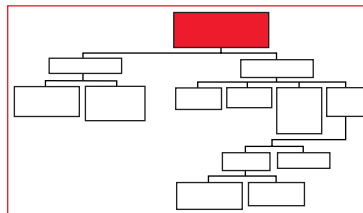
Stroke is defined as any damage to the central nervous system (CNS) caused by an interruption in blood supply. Ischemic strokes result from the failure of oxygen and nutrients to reach the affected brain. Transient ischemic attacks (TIAs) are defined as transient neurologic deficits lasting no longer than 24 hours; longer-lasting deficits are considered to be indicative of a cerebral infarction (“brain attack”).

Infarction from ischemia is typically confined to a vascular territory, at whose center can be found the injured or obstructed artery supplying that parenchyma. The full extent of a stroke may not become apparent until days or weeks later, when the tenuous peripheral watershed zone, or penumbra, either survives or succumbs to cell death. Smaller infarcts, adequate collateral circulation, and prompt intervention and resuscitation are associated with improved outcome.

Hemorrhagic stroke damages the brain by cutting off connecting pathways and causing localized or generalized pressure injury. Brain edema and hydrocephalus after hemorrhagic stroke may also be deleterious. In some cases, hemorrhagic stroke can lead to ischemia as a consequence of vasospasm, as seen in the setting of subarachnoid hemorrhage (SAH). Likewise, some ischemic strokes can undergo hemorrhagic transformation.

Incidence and Risk Factors

Stroke is the third leading cause of death in the United States with about 137,265 stroke-related deaths each year.¹ Annually, there are greater than 750,000 incident strokes in the United States. In addition, stroke is the leading cause of serious long-term disability in the United States and poses a substantial economic burden. For 2009, US expenditures on stroke-related medical costs and disability amount to roughly \$68.9 billion. Although a sharp decline in stroke incidence and mortality was noted throughout most of the 20th century, the decline leveled off in the early 1990s, and stroke incidence and mortality are now rising for the first time since 1915.^{2–4}



Numerous population studies and stroke registries have been designed to examine stroke incidence, risk factors, and natural history of stroke.^{5–11} Some of the independent risk factors that have been identified—such as age (> 55 years), sex (male), race (African American and American Indian/Alaskan Native), and genetic predisposition—cannot be modified and therefore carry a fixed level of stroke risk. The Rochester (Minnesota) population study demonstrated a marked progressive incidence of cerebral infarction with advancing age, as well as a nearly 1.5 times greater risk of stroke in males.⁵ The Lausanne Stroke Registry data confirmed the overall higher incidence of stroke in males, although it also demonstrated a female preponderance in very young (< 30 years) and very old (> 80 years) patients. These latter findings may be attributable to the high frequency of oral contraceptive use in young women in that study, as well as to the lower life expectancy of men, especially those with vascular risk factors.¹⁰ Race and genetic predisposition are also considered independent risk factors, with African Americans having a threefold higher multivariate-adjusted risk ratio of a lacunar stroke than whites.^{11,12} The underlying mechanism of stroke appears to vary with race as well: intracranial occlusive disease tends to occur more frequently in African Americans and Asian Americans than in whites or in males as a whole.^{13,14} The importance of hereditary risk for stroke has long been recognized. In the Framingham Study, both paternal and maternal histories of stroke were associated with an increased risk of stroke.^{11,15}

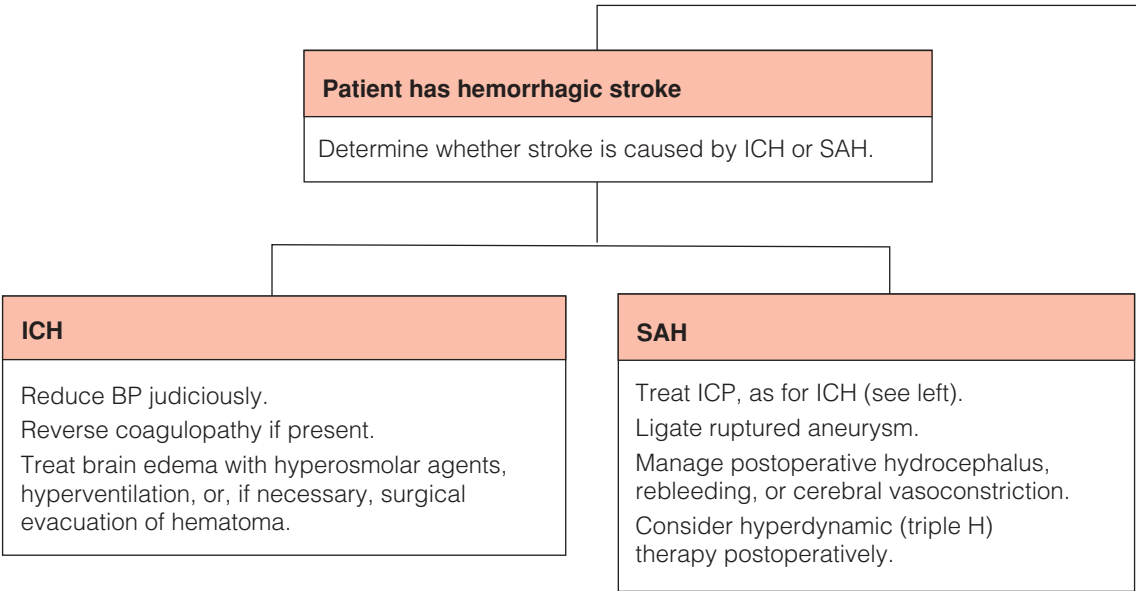
There are, however, certain risk factors for stroke that are clearly modifiable, including hypertension, smoking, hyperlipidemia, asymptomatic high-grade carotid stenosis, and atrial fibrillation (AF).^{16–18} Other purported modifiable risk factors for stroke (e.g., obesity, diabetes, oral contraceptive use, and alcohol intake) are more controversial.^{19–22} Hypertension (systolic as well as diastolic) is perhaps the most prominent modifiable risk factor for stroke and is associated with substantial risk of atherothrombotic, lacunar, or subarachnoid hemorrhage. The Systolic Hypertension in the Elderly Program (SHEP) study demonstrated that treating systolic hypertension in patients 60 years of age or older can reduce the incidence of stroke by as much as 36%.²³ Prompt diagnosis and intervention for stroke may be critical, but many authorities feel that primary prevention is the true cornerstone of therapy for this lethal disease.

Clinical Evaluation

When assessing a patient who presents with a neurologic deficit, clinicians must immediately ask themselves the following two questions: (1) what is the mechanism of the

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Algorithm for the Assessment and Management of Stroke and TIA



Patient presentation

Rule out nonvascular causes of stroke, such as trauma, and evaluate for systemic disease.
Perform thorough physical examination.
Perform imaging studies.
Order laboratory tests.
Distinguish between ischemic and hemorrhagic stroke.

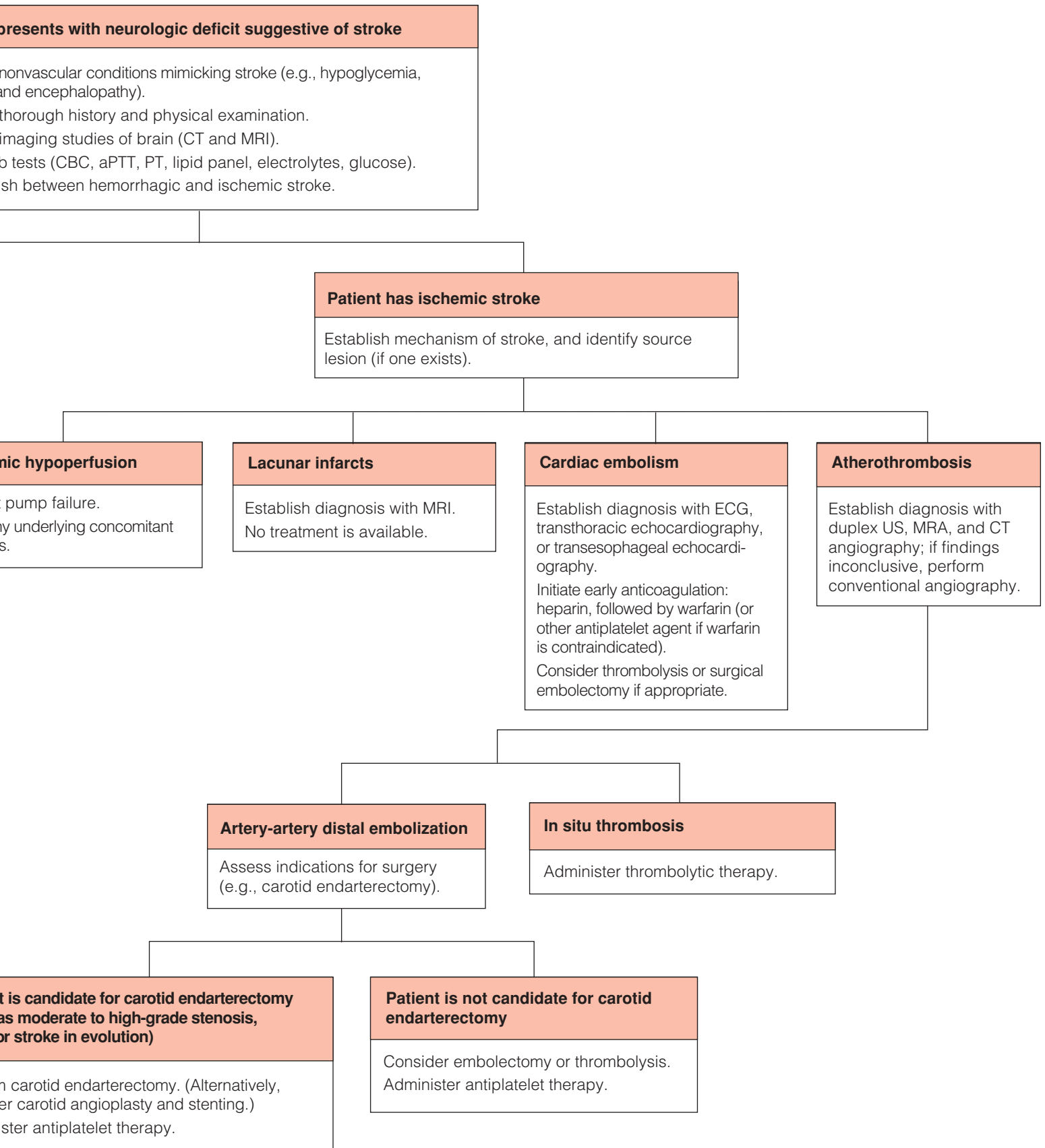
Systemic hypertension

Correct pump failure.
Treat any underlying stenosis.

Patient is comatose (i.e., has multiple TIAs, or stroke)

Perform cardiac monitoring.
Consider cardiac catheterization.
Administer aspirin.

ICH = intracerebral hemorrhage; SAH = subarachnoid hemorrhage; BP = blood pressure; ICP = intracranial pressure; TIAs = transient ischemic attacks; CT = computed tomography; MRI = magnetic resonance imaging; CBC = complete blood count; aPTT = activated partial thromboplastin time; PT = prothrombin time; ECG = electrocardiogram; US = ultrasound; MRA = magnetic resonance angiography.



deficit (i.e., ischemic or hemorrhagic) and (2) where is the lesion (e.g., cerebral lacunae, the territory around a large vessel, or a watershed region)? A thorough history and physical examination, in conjunction with brain imaging studies, usually suffice to guide initial management. Nonvascular conditions that can mimic stroke (e.g., hypoglycemia, migraine, postictal state, encephalopathy, trauma, and brain tumors or abscesses) must be excluded. Although these syndromes can all cause focal findings, they usually lack the abrupt onset of symptoms consistently seen with stroke.

Ischemic and hemorrhagic stroke must be differentiated early on in the course of acute stroke because a number of therapeutic interventions that are beneficial for some subtypes of stroke are potentially catastrophic for others. Approximately 71% of all strokes are ischemic and 26% are hemorrhagic; the remaining 3% are of unknown origin²⁴ [see Table 1]. Hemorrhagic strokes result from subarachnoid or intracerebral bleeding, whereas ischemic strokes result from systemic hypoperfusion, cardioembolism, or atherothrombosis. Although various different laboratory and radiographic tests are available and should be performed, the diagnosis of stroke is primarily a clinical one.

HISTORY

A patient who has suffered a stroke typically presents with a history of sudden onset of a focal brain deficit and a clinical syndrome on neurologic examination. A medical history should elicit any number of risk factors associated with either ischemic or hemorrhagic stroke. For example, hypertension is often associated with deep infarcts and hemorrhages, whereas cigarette smoking and hyperlipidemia are more commonly associated with ischemic infarcts resulting from atherosclerosis.¹⁰ (Hypertension can, however, be associated with infarcts caused by hypertensive arteriopathy.) The presence of AF, a recent myocardial infarction (MI) (< 6 weeks old), or a prosthetic heart valve suggests a possible cardioembolic mechanism.

The onset and course of neurologic deficit may also be telling. A steady onset is suggestive of hemorrhage, whereas

symptoms that progress in stepwise fashion are more likely derived from ischemia. Likewise, accompanying signs are frequently useful in differentiating stroke mechanism subtypes. Headache, vomiting, and loss of consciousness constitute the classic picture of hemorrhagic stroke, whereas a focal deficit preceded by TIAs is more suggestive of ischemic strokes.²⁵ Although the clinical manifestations are generally helpful in differentiating stroke subtypes, sometimes large infarcts mimic the classic picture of hemorrhage or lobar or small deep hemorrhages resemble infarction resulting from atherosclerosis. Analysis of 1,000 consecutive patients from the Lausanne Stroke Registry who experienced their first stroke confirmed that the classic hemorrhagic picture (headaches, progressive neurologic deficits, and decreased level of consciousness) was indeed more common in patients with hemorrhage but found that only one third of patients with hemorrhagic strokes had this clinical triad.¹⁰

PHYSICAL AND NEUROLOGIC EXAMINATION

A general physical and neurologic examination should detect vascular and cardiac abnormalities and localize the process within the CNS. Heart size and sounds, irregular rhythms or discrepant pulse examinations, and carotid bruits should all be noted. Careful examination of the extremities is essential in that peripheral vascular disease is highly correlated with the presence of atherosclerosis of the carotid and vertebral arteries.^{7,26} An ophthalmologic examination should detect subhyaloid hemorrhages, as well as cholesterol emboli (Hollenhorst plaques).

Besides localizing the lesion anatomically, the neurologic examination should be able to identify a probable cause. The absence of major focal neurologic signs is often consistent with SAH; focal deficits localized to the superficial cortex are often attributable to thromboembolism or ischemia. A number of well-described lacunar syndromes also exist; these typically suggest small-vessel disease.

Investigative Studies

IMAGING

Imaging is a mandatory and integral part of evaluation for acute stroke and should be performed expeditiously. Computed tomography (CT) is the initial test of choice; it is readily available in most hospitals and is well tolerated by critically ill patients.²⁷ CT can promptly identify nonvascular causative conditions (e.g., masses) and can readily diagnose intracerebral hemorrhage (ICH) [see Figure 1]. Diagnosis of SAH without intravenous (IV) contrast can be more difficult, especially if bleeding is minor or occurred more than 1 day before; the accuracy of CT in detecting SAH decreases after 24 hours.²⁸ SAH should appear as an increased density in the cerebrospinal fluid (CSF). If SAH is clinically suspected, lumbar puncture may be necessary for definitive diagnosis.

In cases of acute ischemic stroke, diagnosis of infarction by means of CT can be more difficult. IV contrast CT is of limited value in this setting. Signs of infarction can be absent or subtle in the first few hours after the stroke. A lesion may appear as a slight hypodensity within the infarcted zone or as a loss of definition between gray and white matter.²⁹ Newer

Table 1 Causes of Stroke as Recorded in the NINCDS Data Bank²⁴

Cause	%
Cerebral ischemia	71
Atherosclerosis	10
Larger-artery stenosis	6
Tandem arterial lesions	4
Lacunae	19
Cardioembolism	14
Infarct of undetermined cause	27
Cerebral hemorrhage	26
Parenchymatous	13
Subarachnoid	13
Other	3

NINCDS = National Institute of Neurological and Communicative Disorders and Stroke.

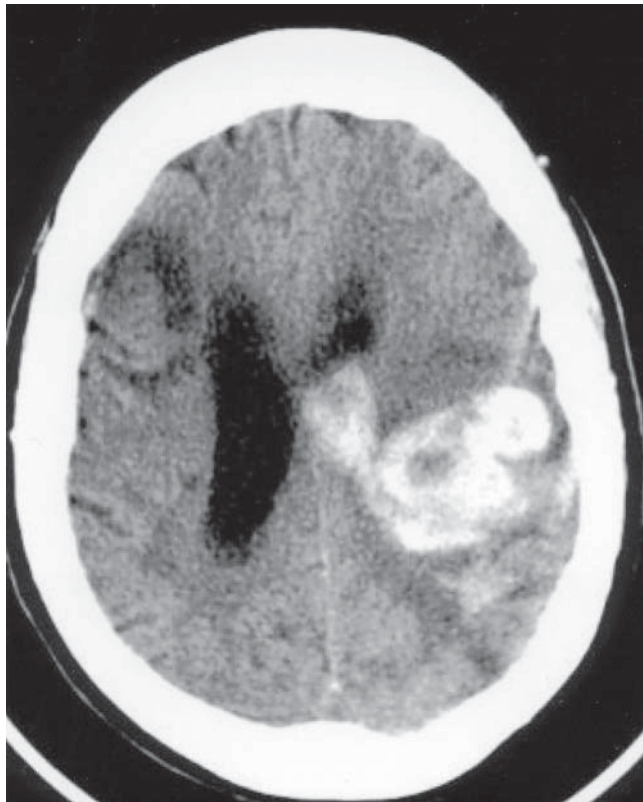


Figure 1 Shown is a computed tomography image of an acute hemorrhagic infarct, with intracerebral bleeding apparent.

CT scanners may be better at delineating these nuances.^{30,31} In the days following an ischemic stroke, an infarct may first appear round or oval and then as a hypodense, dark, or wedge-shaped lesion on CT.

Magnetic resonance imaging (MRI) is more expensive and time-consuming than CT and is less well tolerated by critically ill patients. Nonetheless, MRI is more sensitive than CT in detecting early ischemic changes after a stroke. The speed of MRI acquisition and reconstruction has decreased markedly, the quality of the images has improved, and the diversity of the pulsing sequences has increased significantly. It can be used to distinguish an old stroke from a new one and to assess the size and location of a lesion, especially when the lesion is adjacent to bony structures [see Figure 2].³² The size of the infarct as determined by MRI may be of great importance for prognosis. Although lesion size may not correlate with the severity of the clinical presentation, larger infarcts in the same vascular territory are associated with more severe deficits than smaller infarcts in a similar anatomic location area.

MRI is especially useful for diagnosing lacunar infarcts. In a review of 227 patients with lacunar infarcts, 44% were demonstrated by CT and 78% by MRI.³³ Infarction appears as dark, hypodense areas on T₁-weighted sequences and as bright areas on T₂-weighted sequences. Edema usually develops around the infarct within the first few days and is readily apparent on MRI as a low-density area surrounding the lesion with mass effect. Sometimes the infarct is small but is still associated with substantial edema. Such edema may be insignificant in an older patient with an atrophied brain whose

cranium is able to accommodate a mass effect but may be life-threatening in a younger patient with little intracranial room to spare.

The high sensitivity of MRI in detecting infarction has been demonstrated in studies evaluating patients experiencing TIAs. When patients without signs or symptoms of infarction underwent brain imaging after a TIA, 27% were found to have evidence of so-called silent infarcts on CT and 73% on MRI.³⁴

Diagnosis of ICH can be a more delicate task with MRI than with CT. Careful scrutiny by an experienced observer using different acquisition techniques is required. The appearance of a cerebral hematoma on T₁- and T₂-weighted sequences varies as the lesion matures and edema resolves. Acute hematomas are black on T₁-weighted images, and chronic hematomas are white on T₁- and T₂-weighted images.

Normal neuroimaging findings are not uncommon in patients presenting with neurologic deficits suggestive of acute stroke. A patient with a neurologic deficit and a negative CT scan should undergo further cerebral imaging with MRI. The absence of ischemic infarction and hemorrhage on both CT and MRI may suggest transient ischemia or persistent ischemia without infarction. In such cases, one may have to rely on signs and symptoms to localize the ischemic lesion responsible for the stroke. Alternatively, electroencephalography (EEG), positron emission tomography (PET), single-photon emission computed tomography (SPECT), or xenon-enhanced computed tomography (XeCT) may be employed to help localize ischemic foci.^{35,36}

LABORATORY TESTS

Blood should be sent to the laboratory as part of the initial assessment of a patient with an acute stroke. Measurement of serum electrolyte and glucose levels is essential to rule out nonvascular conditions mimicking stroke (e.g., hypoglycemia and dehydration). A complete blood count (CBC), an activated partial thromboplastin time (aPTT), a prothrombin time (PT), and a lipid panel are likewise essential components of the initial assessment. Severe anemia has the potential to exacerbate or precipitate cerebral ischemia in stroke; although this is an uncommon occurrence, it should be considered and, if present, corrected.³⁷ Additional laboratory blood tests (e.g., cardiac injury panel to rule out MI or an erythrocyte sedimentation rate to assess the possibility of vasculitis) may be helpful.

Screening should be performed for hematologic disorders that result in hypercoagulable states, including homocystinuria,³⁸ antiphospholipid antibody syndrome, protein C and S deficiency, antithrombin deficiency, and activated protein C resistance from factor V Leiden mutation.^{39,40} Hemoglobinopathies (e.g., sickle cell disease and thalassemia) can also lead to altered blood flow, hypercoagulability, and stroke.⁴¹ Finally, hyperviscosity syndromes (e.g., polycythemia vera, thrombocytosis, myeloproliferative disorders) should be included in the differential diagnosis. If a hyperviscosity syndrome is recognized in the setting of acute stroke, hemodilution therapy may be warranted. Experimental and clinical trials have shown hemodilution to increase blood flow in the ischemic brain; however, other studies have failed to show improvement in neurologic status.^{42,43} Hemodilution remains indicated in stroke patients who have a high hematocrit or are

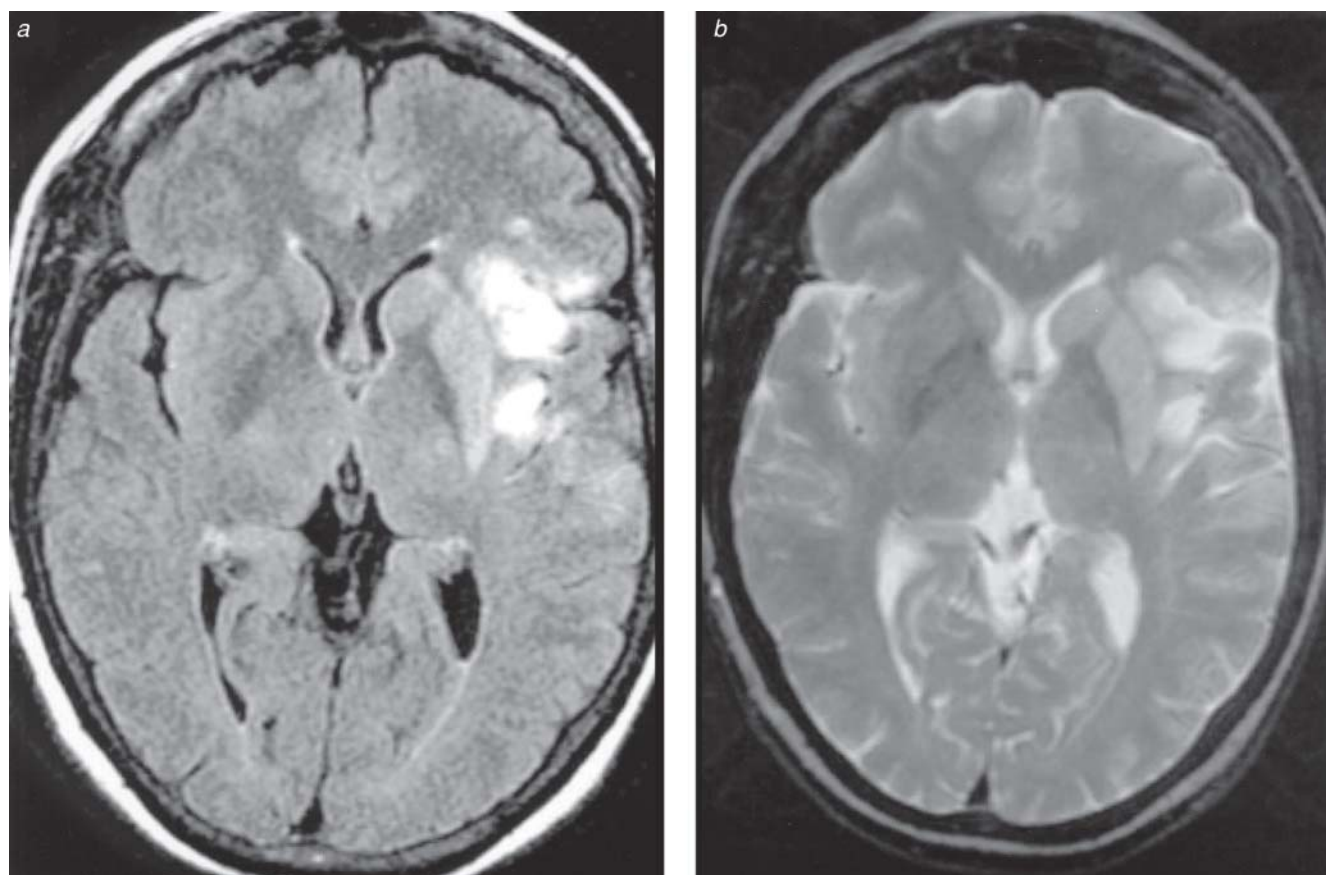


Figure 2 Shown are (a) a fluid-attenuated inversion-recovery (FLAIR) magnetic resonance image (MRI) and (b) a T₂-weighted MRI of an acute ischemic infarct in the left middle cerebral artery distribution.

in a hyperviscosity state; however, close monitoring is required in patients with heart disease or cerebral edema.

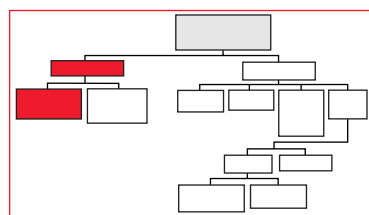
Recognition and Management of Specific Stroke Subtypes

HEMORRHAGIC STROKE

Hemorrhagic stroke can result from ICH or SAH. The consequences of cerebral bleeding can progress rapidly from neurologic deficit to coma to death in a significant number of patients.

Intracerebral Hemorrhage

ICH accounts for approximately 10 to 15% of all strokes in the United States and Europe.^{24,44,45} Potential causative mechanisms include hypertension, trauma, arteriovenous malformations, cerebral amyloid angiopathy, brain tumors, blood dyscrasias, and medications (e.g., anticoagulants and thrombolytics). Of these, hypertensive arteriopathy is most commonly responsible for nontraumatic ICH.^{24,46,47} Hypertensive brain hemorrhages are usually deep and are typically located in the lateral ganglionic region, subcortex, thalamus, caudate nucleus, pons, or cerebellum. As early as the 1870s, Charcot and Bouchard correctly postulated that



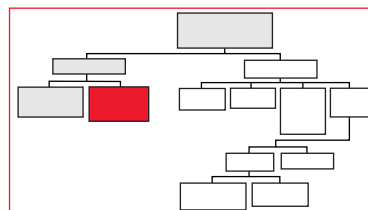
such events were the result of microaneurysmal disease of arteries and arterioles penetrating deep in the brain of hypertensive patients.^{48,49} These discrete hemorrhages go on to compress neighboring capillary networks, causing them to burst and bringing about a rapid enlargement of the intracerebral hematoma. Indeed, such enlargement is not uncommon: one prospective study found that 38% of patients with ICH had a hematoma that was enlarged at 3 hours in comparison with its size on baseline CT after the initial bleed event.⁵⁰ Most hematoma enlargement occurs within 3 hours, although enlargement can occur up to 12 hours after onset.⁵¹ Early large edema volume relative to hematoma volume makes the greatest determination to outcomes.⁵² Edema that is initially small can increase in volume in the first 24 hours after hemorrhage.⁵³

Patients presenting with sizable ICH often rely on a marked compensatory elevation of blood pressure to maintain a pressure gradient in the setting of acute increases in intracranial pressure (ICP). It is vital to resist the impulse to lower blood pressure aggressively in these patients: a rapid drop in blood pressure may induce brain ischemia. Short-acting antihypertensives should be administered only when the systolic blood pressure is persistently higher than 180 to 200 mm Hg or when there is evidence of active bleeding or enlarging hematoma. Other medical treatment of hemorrhagic stroke from ICH includes reversal of coagulopathies with transfusions of fresh frozen plasma and platelets when appropriate.

Mortality from ICH has plummeted from 90% before the 1970s to less than 50% in the first decade of the 21st century.^{2,24,54,55} This precipitous decline probably reflects a decreased prevalence of hypertension, as well as aggressive medical management (e.g., antihypertensive medication) and specialist care in intensive care neurology units.^{56,57} Death from ICH most commonly occurs from mass effects resulting from hematomas, edematous tissue surrounding hematomas, and obstructive hydrocephalus with subsequent herniation.^{54,58} Monitoring of ICP might identify the risk of neurologic deterioration in patients with impaired consciousness.^{59,60} Aggressive care to maintain cerebral perfusion pressure of 50 to 70 mm Hg might improve outcomes.⁶⁰ Airway support, blood pressure control, ICP treatment, and anticoagulation reversal are the early steps in management of ICH patients. One of the initial steps in the management of ICH is dealing with brain edema. Corticosteroids, although indicated for reducing cerebral edema in patients with tumors or abscesses, are contraindicated in patients with ICH because they are not beneficial and may, in fact, be injurious, predisposing patients to infection and worsening diabetes.⁶¹ Hyperosmolar agents (e.g., mannitol or glycerol solutions) may be useful for reducing cerebral edema rapidly, yet two randomized trials showed no benefit on regional cerebral blood flow, neurologic improvement, mortality, and functional outcomes from regular use of IV mannitol boluses.^{62–64} Only short-term use of mannitol in patients with ICH and special circumstances (e.g., transtentorial herniation or acute neurologic deterioration with high ICP or mass effect) should be considered. Hyperventilation may also reduce ICP through diffuse vasoconstriction in the brain. Likewise, any physiologic perturbation that might increase cerebral blood volume (e.g., hypercarbia, hypoxia, or vasodilation) or reduce cerebral perfusion (e.g., hypotension) should be avoided. The European Stroke Initiative (EUSI) guidelines recommend monitoring ICP for patients who need mechanical ventilation and recommend treatment in patients who have neurologic deterioration or elevated ICPs.⁶⁵ Selective use of mannitol, hypertonic saline, and short-term hyperventilation to maintain cerebral perfusion pressure greater than 70 mm Hg is also recommended.⁶⁵ Surgical evacuation may prevent expansion, decrease mass effects, block the release of neuropathic products from hematomas, and prevent initiation of pathologic processes. The American Heart Association (AHA)/American Stroke Association Stroke Council and EUSI guidelines do not recommend routine evacuation of supratentorial hemorrhage by standard craniotomy within 96 hours of ictus.^{65,66} Both guidelines recommend surgery for patients with good neurologic status deteriorating clinically and presenting with lobar hemorrhage within 1 cm of the surface. However, very early craniotomy might be associated with an increased risk of recurrent bleeding.⁶⁷

Subarachnoid Hemorrhage

Rupture of saccular or berry aneurysms with subsequent SAH carries significant morbidity and mortality, depending largely on



the patient's age, the extent of the hemorrhage, and the presence and severity of rebleeding, cerebral vasospasm, and surgical complications.⁶⁸ SAH accounts for approximately 5% of all strokes, yet outcomes for patients are poor, with population-based mortality rates as high as 45% and significant morbidity among survivors.⁶⁹ The reported incidence of incidental aneurysms discovered in autopsy studies ranges from 0.8 to 18% and has not changed dramatically over the past four decades.^{69–72} The incidence of SAH increases with age and tends to occur in patients aged 40 to 60 years of age and in women more often than men (12.3% versus 7.9%).^{73–75} The pathogenesis of saccular aneurysms has not been fully explicated, but the risk factors are well described and include a family history of SAH,⁷⁶ hypertension, pregnancy,⁷⁷ and black race.⁷⁸

Clinical manifestation of SAH is one of the most distinctive in medicine, by the classic presenting complaint. Awake patients will complain of “the worst headache of my life,” described by approximately 80% of patients who can give a history, but warning signs are also described by approximately 20% of patients.⁷⁹ Such warning signs include a so-called sentinel headache, oculomotor symptoms, nausea and vomiting, and loss of consciousness.⁷⁹ Most intracranial aneurysms remain asymptomatic until they rupture, which can be frequently induced during physical exertion or stress. Nevertheless, SAH can occur at any time.⁸⁰ The rupture itself is accompanied by sudden severe headache, nuchal rigidity, back pain, nausea and/or vomiting, photophobia, lethargy, loss of consciousness, and seizure.^{77,81} The cornerstone of SAH diagnosis is the noncontrast cranial CT scan.⁸² The diagnostic sensitivity of CT scanning is not 100%; therefore, a diagnostic lumbar puncture should be performed if the initial CT scan is negative to evaluate the CSF. A normal CT scan and CSF examination exclude a warning leak in most cases and predict a more favorable prognosis in the setting of a severe and sudden headache.^{83,84}

Medical management of SAH is designed to prevent rebleeding. Bedrest with head elevation to 30° alone is not enough to prevent rebleeding after SAH but is an important component of a broader treatment strategy.⁸⁵ Blood pressure should be closely monitored and controlled to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressures.⁶⁹ Broader treatment management also includes stool softeners, antiemetics, and analgesics, as well as deep vein thrombosis (DVT) prophylaxis using pneumatic compression boots. Management of ICP in SAH patients is similar to that in ICH patients (see above). Furthermore, one must be vigilant for signs of hypothalamic dysfunction manifesting as cardiac dysrhythmias or the syndrome of inappropriate antidiuretic hormone (SIADH).

Surgical or endovascular treatment of ruptured aneurysms in SAH patients includes microsurgical clipping or endovascular coiling, which prevents rebleeding. Aneurysms that are incompletely clipped or coiled have an increased risk of rehemorrhage compared with those that are completely occluded.⁶⁹ The International Cooperative Study showed no overall differences in outcome between early surgery (0 to 3 days after SAH) and delayed surgery (11 to 14 days after SAH). Early treatment did reduce the risk of rebleeding after SAH.^{69,86} In addition, patients who were alert preoperatively

did better with early surgery and demonstrated significantly better rates of good recovery.⁸⁶

Three major neurologic complications affect outcome after surgery for SAH: hydrocephalus, rebleeding, and cerebral vasoconstriction. Hydrocephalus may develop acutely because of obstruction of CSF outflow. Temporary or permanent CSF diversion (e.g., ventriculostomy) can result in immediate decompression of intracerebral pressure and improvement in neurologic symptoms.⁸⁷ The risk of rebleeding peaks on postoperative day 1; it is as high as 20% in the first 2 weeks and rises to 50% within 6 months if the aneurysm is not treated.⁶⁸ Unlike rebleeding, vasospasm is the delayed narrowing of larger capacitance arteries at the base of the brain after SAH. The typical onset is 3 to 5 days after hemorrhage, maximal narrowing at 5 to 14 days, and a gradual resolution over 2 to 4 weeks.⁶⁹ Contemporary series demonstrate 15 to 20% stroke rate or death despite maximal therapy.^{86,88} The development of a new focal deficit, unexplained by hydrocephalus or rebleeding, is the first objective sign of symptomatic vasospasm. The diagnosis is initially made with angiography and monitored using transcranial Doppler sonography.^{89,90}

Hyperdynamic, or triple H, therapy consists of keeping patients hyperdynamic (to increase cardiac output), hypervolemic-hypertensive (to augment cerebral perfusion pressure), and hemodiluted (to improve cerebral microcirculation by decreasing viscosity). Because of the risk that the aneurysm will rerupture before operation, triple H therapy is reserved for postoperative patients.^{91,92} Calcium channel blockers (e.g., nimodipine) may also reduce the incidence of symptoms secondary to vasospasm by cerebral protection, although they most likely have little effect on spasm *per se*.^{93,94}

Ischemic Stroke

If hemorrhagic stroke is ruled out and ischemic stroke is diagnosed, the next step is to establish the mechanism of the stroke and identify the source lesion responsible (if one exists). Systemic hypoperfusion, cardiac embolism, large-artery atherosclerosis, and small-vessel disease should be systematically examined as potential causes.

SYSTEMIC HYPOPERFUSION

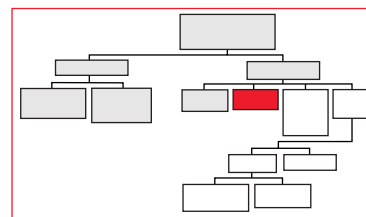
Only a small fraction of all ischemic strokes are attributable to systemic hypoperfusion. A quick assessment of vital signs and symptoms may provide the first clues that a patient is suffering from cerebral ischemia secondary to systemic hypoperfusion. Patients are characteristically either unconscious on arrival in the emergency department or awake but exhibiting neurologic symptoms resembling near-syncope.⁹⁵ Generally, they are pale, diaphoretic, and hypotensive. Neurologic signs and symptoms are varied and are explained by ischemia in the border zone (or watershed) between two or three adjacent arterial territories. Difficulty in reading or identifying visual stimuli (or even frank blindness) may be observed;

this may be attributed to ischemia between the middle and posterior cerebral arteries. Bilateral arm weakness or cognitive difficulty may suggest ischemia between the middle and anterior cerebral arteries. Global symptoms usually arise from bilateral border-zone infarcts, which can develop in association with prolonged cardiogenic shock, dysrhythmias, or cardiac arrest.^{96,97} Alternatively, symptoms may be asymmetrical if they derive from inadequate perfusion distal to a site of severe stenosis or occlusion of major feeding cerebral vessels.

Treatment should focus primarily on correcting the pump failure. Certain patients with concomitant underlying stenosis proximal to border-zone ischemic territories may benefit from treatment of the flow-limiting lesions to eliminate the hemodynamic impairment and thus may do better than patients with systemic hypoperfusion.⁹⁸

Lacunar Infarcts

Neurologic examination of a patient believed to have experienced an acute ischemic stroke should be attentive to the possibility of lacunar infarcts, manifested

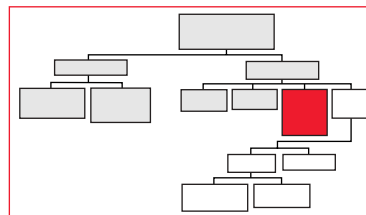


by pure motor hemiparesis, pure sensory syndrome, sensorimotor syndrome, ataxic hemiparesis, and dysarthria-clumsy hand syndrome.^{99,100} Lacunae are small (1 to 2 cm) subcortical lesions that result from small-vessel disease deep in the brain. They can either occur alone or in groups and may be present in as many as 23% of persons over the age of 65. Lacunar infarcts, unlike other forms of stroke, do not present with headache and are associated with hypertension and diabetes.¹⁰¹ Although they are asymptomatic (silent) in as many as 89% of patients, their benignity is currently in some doubt; there is evidence to suggest that they may increase the risk for dementia and cognitive decline.^{102,103} Lacunar syndromes are characteristic and highly predictive of the presence of lacunae, but they may be less reliable for excluding other mechanisms of stroke. A review of the Northern Manhattan Stroke Study experience demonstrated that as many as 25% of patients presenting with radiographically confirmed lacunar infarcts were ultimately found to have other mechanisms of ischemic stroke.¹⁰⁴ Thus, MRI should be used to confirm or exclude the presence of lacunar infarct and to screen for nonlacunar mechanisms of stroke.

At present, there is no optimal treatment for lacunar infarcts, but the prognosis is quite good. The survival rate is high, the recurrence rate is low (mean annual stroke rate, 4 to 7%), and the patients generally achieve a relatively good functional recovery, with as many as 74% experiencing mild or no disability at 1 year.^{105–108}

Cardiac Embolism

Embolism of cardiac origin accounts for approximately 20% of ischemic strokes [see Table 1]. Given that many infarcts of undetermined cause are



probably of cardioembolic origin, this figure may, in fact, be an underestimate.²⁴ Whereas clinical suspicion for cardioembolism may be high in the setting of acute stroke, confirming the diagnosis can be more difficult. In most instances, cardioembolic stroke can be diagnosed on the basis of the history, the physical examination, and electrocardiography (ECG). A number of conditions are known to predispose to cardioembolism, including AF or atrial flutter, recent MI (< 6 weeks old), placement of a prosthetic valve, disease of the aortic or mitral valves, and paradoxical emboli (usually from DVT).⁴ Key clinical manifestations include sudden onset with rapid progression to maximal deficit, infarcts in multiple cerebral vascular territories, a predilection for branch occlusion not necessarily associated with in situ cerebral atherosclerosis, rapid regression of symptoms, decreased consciousness at onset, and the presence of a documented cardiogenic source of embolism.^{109–112} Factors not supportive of cardioembolic stroke include hemiparesis without cortical or sensory and pure sensorimotor strokes. Headaches and seizure activity are also not specific for cardioembolic strokes. The rapid regression of symptoms—also known as the spectacular shrinking deficit—is thought to result from rapid recanalization or fragmentation and migration of cardioembolus downstream.¹¹³ Ironically, the very mechanism purported to result in rapid regression of symptoms may trigger the hemorrhagic transformation seen in as many as 70% of cardioembolic strokes.^{114,115} The vast majority of hemorrhagic transformations are caused by cardioembolism. A 2001 study found that delayed recanalization occurring less than 6 hours after acute cardioembolic stroke developed in 52.8% of patients and was an independent risk factor for hemorrhagic transformation.¹¹⁵ Other risk factors for such transformation are severe strokes, decreased alertness, and absence of collateral flow.¹¹⁶

The prevalence of AF is roughly 1% at age 60, 5% for patients aged 70 to 75 years, and up to 10% for patients older than 80 years of age.¹¹⁷ However, lone AF in patients younger than 60 years of age is associated with a low risk of stroke.¹¹⁸ The presence of valvular heart disease other than mitral valve prolapse is associated with a roughly 17-fold increased risk of stroke.¹¹⁹ AF may or may not be detected on ECG, especially if it is paroxysmal; it remains an elusive but increasingly important risk factor for cardioembolic strokes in older patients.¹²⁰ Holter monitoring and electrophysiologic testing may be especially useful for diagnosing paroxysmal AF.¹²¹ Likewise, transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are useful for detecting mural thrombus caused by AF or another cardiomyopathy, as well as for detecting valvular diseases, vegetations, tumors, or patent foramina ovalia.

In the presence of nonrheumatic AF, the overall incidence of stroke is nearly five times higher, rising from 1.5% in persons 50 to 59 years of age to 23.5% in those 80 to 89 years of age.¹²² Moreover, data from the International Stroke Trial indicated that mortality is twice as high in patients with AF as in those without AF (17% versus 7.5% at 2 weeks).¹²³ It is noteworthy that noncardioembolic strokes are estimated to account for about one third of the strokes that occur in AF patients. A 1997 autopsy study in 82 consecutive patients with symptomatic stroke and nonrheumatic AF demonstrated that 29 (35%) of the infarctions in patients

with nonrheumatic AF were, in fact, of noncardioembolic origin.¹²⁰

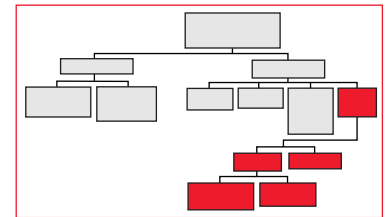
As a rule, acute ischemic stroke of cardioembolic origin is best treated with early anticoagulation to prevent recurrent brain embolism. Numerous studies have shown that recurrent embolism to the brain occurs within 2 weeks in 6 to 12% of patients after an initial ischemic infarct from a cardioembolic source.^{124–126} A 1999 meta-analysis of 16 AF trials indicated that the overall risk of stroke could be reduced by an average of 62% with anticoagulation.¹²⁷ Thus, once a hemorrhagic stroke has been ruled out, heparinization and treatment with warfarin are indicated. Patients with ischemic stroke attributed to cardioembolism who are at increased risk for hemorrhage or who have contraindications to warfarin may be treated with aspirin or another antiplatelet agents; however, such agents are less effective than warfarin in secondary prevention of cardioembolic ischemic stroke.^{128,129} Finally, despite the clear benefits of early anticoagulation in stroke patients with cardioembolism, such therapy has not been shown to be advantageous in the general stroke population.

For patients who suffer ischemic strokes of noncardioembolic origin, warfarin appears to offer no additional benefit over aspirin in preventing stroke recurrence.¹³⁰ Furthermore, most authorities would agree that patients with acute ischemic stroke who present within 48 hours of the onset of symptoms should be given aspirin, 160 to 325 mg/day, to reduce mortality and morbidity from stroke.^{131,132}

Atherothrombosis

Approximately 20% of all new, acute ischemic strokes are believed to occur secondary to large-vessel atherosclerosis, thrombosis, or artery-to-artery distal embolization.²⁴

Smoking and age are the most important contributors to the development and progression of carotid atheroma.¹³³ Unlike cardioembolism, carotid atheroemboli and thrombosis are more likely to present with TIAs. Moreover, TIAs of carotid artery origin tend to occur in the same vascular territory, whereas TIAs of cardioembolic origin are more haphazard in location.^{109,111} Once the history, the physical examination, and brain imaging studies are complete, duplex ultrasonography should be performed to search for extracranial atherosclerosis of the carotid arteries. Duplex ultrasonography identifies significant luminal narrowing based on increased velocity of blood flow across a stenotic lesion. Duplex examination of the carotid arteries may also identify ulceration and assess plaque echolucency, both of which may increase the level of risk.^{134,135} In regard to the sensitivity and specificity of ultrasound studies, one meta-analysis found that in most reports, all of the ultrasound studies had sensitivities greater than 80% and specificities greater than 90%.¹³⁶ Other important diagnostic modalities commonly used to assess extracranial sources for atherothrombotic-embolic mechanisms of stroke are magnetic resonance angiography (MRA) and CT angiography. We routinely use these modalities to corroborate the findings of duplex ultrasonography because it only covers a small region of the carotid



and vertebral arteries in the neck. In patients with carotid arterial stenosis, conventional angiography is usually limited to cases in which duplex ultrasonography disagrees with MRA or CT angiography; in patients with vertebral artery stenosis, angiography is mandatory before any attempt is made at reconstruction.

Diagnosis of symptomatic carotid artery lesions in the setting of acute ischemic stroke is critical because this subtype of stroke patient stands to benefit significantly from surgical intervention. The results of three prospective randomized trials from the early 1990s comparing medical to surgical treatment of symptomatic carotid artery stenosis demonstrated that carotid endarterectomy (CEA) had a significant advantage over medical treatment (aspirin).^{137–139} Perhaps the most convincing of the three studies was the North American Symptomatic Carotid Endarterectomy Trial (NASCET), which was terminated prematurely because of the clear superiority of the results in the surgical arm.¹³⁷ In the NASCET, the cumulative risk of ipsilateral stroke was 9% with surgical treatment and 26% with medical treatment at the 2-year follow-up, for an absolute risk reduction of 17% and a relative risk reduction of 65.4%. Patients with carotid artery stenosis less than 50% did not benefit from CEA. Conversely, studies have shown that patients who have a completely occluded carotid artery in the setting of an acute stroke should not undergo CEA either. Emergency CEA in an acutely occluded artery can result in conversion of an ischemic infarct to a hemorrhagic cerebral infarct, with potentially catastrophic results.¹⁴⁰

Indications for and the Timing of Therapy

SURGICAL THERAPY

Carotid Endarterectomy

Based on the major landmark CEA trials mentioned earlier, the American Heart Association recommended that symptomatic patients with more than 50 to 99% stenosis are best treated by CEA if the risk of the perioperative stroke or death rate is less than 6%. The greatest benefit was seen in those with severe stenosis (> 70 to 99%).^{137,141–143} When a symptomatic patient with moderate or high-grade stenosis presents with TIAs or a mild stroke, the decision to perform a CEA is relatively straightforward. There is a great deal of complexity about risk assessment in those patients with only a moderate degree of stenosis. Patients who have suffered devastating infarcts, however, usually are not appropriate surgical candidates. Generally speaking, the extent to which neurologic function is spared, the presence and severity of medical comorbidities, and the patient's life expectancy should all be assessed before the decision is made to embark on CEA. Medical management has also changed considerably since the early CEA trials, perhaps indicating that the stroke risk reduction benefit from operative therapy may be overstated. The early CEA trials also had exclusion criteria (e.g., > 80 years old; failure of the kidney, liver, or lung; cancer with survival within 5 years; cardiac valvular or rhythm disorder; uncontrolled hypertension or diabetes mellitus; unstable angina; MI within the previous 6 months; and recent major surgery), which raises a valid concern that the general population of patients with carotid stenosis has significantly

different demographics than those patients who met strict eligibility criteria in the randomized trials.¹³⁷ Therefore, the general population with carotid stenosis may be more likely older and less healthy compared with the CEA trials, with a higher perioperative morbidity and mortality.¹⁴⁴

The timing of CEA after an acute stroke continues to be a subject of controversy. According to some authorities, the risk that an ischemic infarct will undergo hemorrhagic transformation after urgent CEA is a contraindication to early surgery.^{145,146} ICH after endarterectomy is most likely the result of postoperative hyperperfusion. The combination of hypertension (which is common after stroke) and diminished vasomotor regulation in the penumbra may predispose small vessels in this region to hemorrhage. Other authorities, however, argue that delaying surgery exposes the patient to a substantial risk of recurrent stroke or carotid occlusion and that early intervention is therefore warranted.¹⁴⁷ Although most authorities would agree that waiting an obligatory 30 days prior to surgery is prudent, an abundance of small series in the literature suggest that early CEA following acute ischemic stroke is indeed safe and may be indicated.^{148,149} Pooled analysis of the randomized controlled trials (RCTs) suggests that the benefit from CEA was maximal in patients who had the operation within 2 weeks of a qualifying event. In symptomatic stenosis of 70 to 99%, the absolute risk reduction decreased from 23% to 16% and then to 8% when patients were treated within 2 weeks, between 2 and 4 weeks, and after 4 weeks, respectively.¹⁵⁰ Nevertheless, the location and size of the infarct may help stratify those strokes at increased risk for hemorrhagic transformation following CEA.¹⁴⁹ There is a difference seen in men and women and the timing of CEA. There is a decreasing benefit of CEA with increasing time from the qualifying ischemic event, particularly in women.¹⁵¹ In fact, the benefit of treatment was lost in women when treatment was delayed more than 2 weeks.¹⁵¹ Despite the reluctance of surgeons to operate within 1 month of a qualifying TIA or a minor stroke because of a perceived higher risk of periprocedural complications, subgroup analysis of RCTs showed that the perioperative risks of stroke and death were not increased in patients who underwent an operation within 2 weeks of the qualifying events. Recent guidelines for secondary stroke prevention recommend that CEA be performed within 2 weeks for patients presenting with a TIA or a minor stroke.¹⁵²

Stroke in evolution A patient with neurologic deficits that worsen progressively in a stuttering fashion is considered to have a stroke in evolution. This state is associated with the highest level of risk, whether it is treated medically or surgically.¹⁵³ A patient with a stroke in evolution should promptly undergo CT to rule out hemorrhagic stroke, followed immediately by systemic anticoagulation with heparin and urgent operation. In a 1981 study of patients with stroke in evolution or crescendo TIAs that compared medical treatment ($n = 31$) with urgent CEA ($n = 24$), nonoperative management of stroke in evolution yielded a significantly higher mortality than surgical management (15% versus 6%).¹⁵⁴ Furthermore, 70% of the patients who underwent CEA achieved complete or near-complete recovery, compared with 19% of those managed medically.

Carotid Angioplasty and Stenting

In keeping with the continuing growth of minimally invasive surgery, carotid angioplasty and stenting (CAS) has come to play an emerging role in the management of both symptomatic and asymptomatic carotid stenosis. CAS might avoid the risks associated with CEA, including cranial nerve palsy, MIs, or pulmonary embolism, thus making it especially appealing in patients at high surgical risk. Over the past 10 years, many researchers have tried to add to the wealth of case series, registries, and RCTs to discern the safety and value of CAS compared with CEA. The advent of neuroprotection techniques using distal balloon occlusion and aspiration of debris, filter wires placed distal to the lesion, or reversal-of-flow technology has allowed interventionalists to perform CAS more safely, with complication rates approximating those of CEA.^{155,156} Despite the fact that embolic protection device (EPDs) provide additional cerebral protection, there is still a risk of stroke associated with CAS secondary to particle embolization from the aortic arch. In addition, the EPDs have their own inherent risks and complications, such as the inability to cross the target lesion, failure to capture emboli through the filter pores, and vasospasm or injury to the vessel wall.¹⁵⁷ However, EPD use has become standardized and is currently mandated by the Centers for Medicare and Medicaid Services. Even with the routine use of EPDs, the precise role of CAS in the treatment or prevention of stroke has not been completely defined. The two primary questions that remain unresolved are (1) which patients benefit most from CAS as opposed to open surgery and (2) are the immediate and long-term results of CAS as good as those of CEA? Determination of the part CAS will eventually play in the management of cerebrovascular disease awaits the results of ongoing clinical trials comparing CAS with CEA.

Selection of patients Initially, CAS was considered a procedure that would be most beneficial for high-risk patients, for example, patients who were poor surgical candidates because of substantial medical comorbidities and patients with so-called hostile anatomy (such as an extremely high or low bifurcation or a neck that had previously been irradiated or operated on). Indeed, one clear benefit of CAS over CEA is that the risk of nerve injury for patients undergoing the former procedure is 0%. A precise definition of a high-risk patient, however, has proven elusive. One study reviewed CEAs that were performed in 228 patients who, because of their increased level of risk, would not have met the NASCET inclusion criteria.¹⁵⁸ This study was unable to demonstrate that these supposedly high-risk patients actually had inferior outcomes with CEA. A subsequent study that included more than 13,000 CEAs found that cardiopulmonary comorbid conditions did not increase the risk of perioperative stroke, death, or cardiac events.¹⁵⁹ Finally, although many investigators have considered patients over the age of 80 (who were ineligible for NASCET and the Asymptomatic Carotid Atherosclerosis Study [ACAS]) to be at increased risk with open surgery, the interim results from the lead-in phase of the Carotid Revascularization Endarterectomy versus Stent Trial (CREST), which is currently in progress, indicated that the risk of 30-day stroke and death from patients undergoing CAS, surprisingly, was substantially higher (12.1%) in the 99

patients who were over the age of 80 compared with 3.2% among nonoctogenarians.¹⁶⁰ The reason for this increasing risk in older patients is not clear; the CREST results were not affected by adjustment for potential confounding factors such as symptomatic status, the use of EPDs, gender, the degree of carotid stenosis, or the presence of distal arterial tortuosity. Similarly, other studies indicated that CAS in octogenarians was associated with a statistically significant higher rate of adverse events at 30 days and at the 1-year follow-up, which indicates that CAS should be cautiously considered in the elderly population.¹⁶¹ The etiology of increased adverse event risk for CAS in the elderly remains incompletely understood. Suggestions of adverse vascular anatomy (e.g., aortic arch calcification, common carotid and innominate artery stenosis, and the tortuosity of the common and internal carotid arteries) and lesion characteristics (e.g., severe lesion stenosis greater than 85% and plaque ulceration) that have the potential to increase the technical complexity of CAS may account for this finding.^{162–164} However, it is important to note that these anatomic and lesion characteristics (e.g., abnormal arch anatomy, vessel tortuosity, long stenotic lesions greater than 15 mm, involvement of the internal carotid ostium, and plaque echolucency) are thought to be more common in the elderly population; younger patients may also have similar unfavorable risk factors.^{165–168} Therefore, the presence of certain anatomic factors that preclude safe passage or proper positioning of EPDs and stents must be considered high risk at any age and thus may not be appropriate candidates for CAS.

The goal of reliably predicting which patients may be at high risk with either stenting or open surgery has impelled some investigators to develop risk stratification scales for CAS. A 2006 prospective study of 606 consecutive patients who underwent CAS identified the following independent risk factors: diabetes mellitus with inadequate glycemic control (hemoglobin A_{1c} level > 7%), advanced age (80 years), ulceration of the carotid artery stenosis, and a significant contralateral stenosis (50%). Patients with two or more of these risk factors had an 11% risk of a periprocedural complication, whereas patients with none or only one had a 2% risk.¹⁶⁹

Assessment of results The results of various clinical trials comparing CAS with CEA, some already completed and some still under way, will help determine whether there is a clinical equipoise between the two procedures.^{160,170–174} The results of early RCTs were mixed. The first RCT comparing endovascular and surgical treatments for carotid artery stenosis, Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), was designed to compare balloon angioplasty alone without an EPD with CEA in symptomatic patients.¹⁷² The trial randomly assigned 504 patients to the two treatment arms, and the incidence of major stroke or death at 30 days (10.0% for endovascular versus 9.9% CEA) or at 3 years (14.3% endovascular versus 14.2% CEA).¹⁷² This study was, however, criticized for a number of reasons: lack of embolic protection; 26% stent use, which is in contrast to current standard practice; and a substantially higher stroke rate of 9.9% in the CEA arm. The Wallstent trial was the first multicenter RCT designed to compare CAS and CEA equivalence but was stopped early after interim analysis

showed worse outcomes in the CAS arm with a combined risk of stroke or death at 30 days of 12.1% versus 4.5% in the CEA group.¹⁷⁵ Once again, EPDs were not used in this trial, which may have contributed in part to the high risk associated with CAS. Single-center RCTs were conducted by Brooks and colleagues, which had encouraging results.^{176,177} The trials looked at both symptomatic and asymptomatic patients with extremely low complication rates in both arms, and the results suggested equivalence of CAS to CEA, but these results were criticized because of the small, single-institution studies carried out by a highly select experienced team. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was the first randomized trial to use mandatory distal embolic protection and was designed to demonstrate noninferiority of CAS to CEA in 334 patients with coexisting conditions that potentially increased the risk associated with endarterectomy.¹⁷¹ The 30-day and 1-year outcomes (including death, stroke, and MI) found that CAS was not inferior to CEA.¹⁷¹ However, the overall risk levels were disturbingly high in both arms of this trial: 12.2% for CAS patients and 20.1% for CEA patients. In addition, the differences in event rates between CAS and CEA were from the greater association of CEA with non-Q wave MI, which is notably a nontraditional surgical end point. Excluding MI, no significant difference was found between CAS (5.5%) and CEA (8.4%) patients. Also, the high event rates in both groups cast serious doubt as to the appropriateness or durability of any intervention in the high-risk, asymptomatic patient population. The Carotid Revascularization using Endarterectomy or Stenting Systems (CaRESS) trial was a multicenter prospective study that compared the two techniques in 397 patients on a nonrandom basis.¹⁷³ The results indicated that both the 30-day risk and the 1-year risk of death, stroke, or MI were essentially the same in CAS patients as in CEA patients. Two multicenter, randomized European trials, Stent-Protected Angioplasty Versus Carotid Endarterectomy (SPACE) and Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S), sought to establish noninferiority in standard-risk, symptomatic patients.^{174,178} The SPACE trial randomly assigned 1,183 patients with symptomatic carotid artery stenosis to either CAS or CEA.¹⁷⁴ At 30 days, the incidence of stroke or death was 6.9% in the CAS group and 6.3% in the CEA group. The difference between the CAS and CEA group was 0.51%, yet the upper 90% confidence limit of this difference between the two groups was 2.9%. This was greater than the predefined equivalence threshold of 2.5%; thus, the one-sided *p* value for noninferiority is .09 (9% chance of erroneously concluding that CAS is not inferior to CEA). The investigators concluded (1) that the results failed to prove the noninferiority of CAS compared with CEA and (2) that CEA should remain the preferred treatment for patients with symptomatic stenosis. The EVA-3S trial also failed to demonstrate the noninferiority of CAS in symptomatic patients.¹⁷⁸ The study randomized 527 patients and was subsequently ended prematurely for safety reasons after interim results revealed a significantly higher 30-day adverse event rate in the CAS group (9.6%) compared with the CEA group (3.9%). Several criticisms of this trial include the significantly high 30-day stroke rate in the CAS group, lack of initial EPD

use, and lack of comparison of physicians with equal experience performing CEA and CAS. The conclusion from the EVA-3S authors essentially supported the notion that CEA remains an excellent option for symptomatic patients with low complication rates that are currently not matched or bested by CAS.

The challenge of interpreting the collective results from the RCTs is attributable to the different conclusions reached by each about the safety and efficacy of CAS versus CEA. Nevertheless, the questions of whether CAS offers an advantage or is equivalent to CEA and which subgroup of patients would most benefit from CAS still remain. While we await the conclusion of the larger RCTs, CAS should be considered for patients with an indication for carotid revascularization and high surgical risk. Currently, the Centers for Medicare and Medicaid Services reimburses the cost of CAS only for patients with symptomatic carotid artery stenosis of a severity of at least 70% who are considered high-risk patients for open surgery. In all other patient categories, the procedure is reimbursed only in the setting of one of the numerous ongoing postmarketing registries or clinical trials.

THROMBOLYTICS

Any patient who presents with an acute ischemic stroke, regardless of subtype, is potentially a candidate for thrombolytic therapy. However, ICH documented on the initial head CT is a clear, absolute contraindication to IV thrombolysis. Other considerations affecting the decision whether to administer thrombolytic agents include a history of gastrointestinal or urologic hemorrhage, recent major surgery, and rapidly improving neurologic signs, any of which may constitute a clinical contraindications to medical treatment. Vigilant monitoring of the aPTT, PT (or the international normalized ratio [INR]), platelet count, and fibrinogen level is essential throughout the course of thrombolytic treatment.

It has been suggested that maximal benefit is derived from IV thrombolytic therapy for acute ischemic stroke when it is delivered within a “golden 3-hour window” starting from the onset of symptoms. The National Institute for Neurological Disorders and Stroke (NINDS) trial (parts 1 and 2) randomly assigned 624 patients to receive either recombinant tissue plasminogen activator (rt-PA), 0.9 mg/kg IV to a maximum of 90 mg/kg, or placebo.¹⁷⁹ Patients with all types of ischemic stroke were eligible provided that they could be treated within 3 hours of the onset of symptoms. Outcome at 3 months was better with rt-PA than with placebo on each of the four outcome measures studied. The odds ratio for a favorable outcome in the rt-PA group was 1.7. The overall rate of symptomatic hemorrhage was 6.4% in the rt-PA group and 0.6% in the placebo group. The beneficial effects of rt-PA were similar for all stroke subtypes and persisted for up to 12 months after the stroke.¹⁸⁰ Patients treated with rt-PA were at least 30% more likely to have minimal or no disability at 12 months than patients treated with placebo were. Mortality at 1 year was comparable in the two groups.

Other randomized, double-blind, placebo-controlled trials of rt-PA for treatment of acute ischemic stroke have examined the effect of thrombolytic therapy given within the first 6 hours after the onset of symptoms. The European Cooperative Acute Stroke Study (ECASS) found no significant

differences in functional outcome measures at 90 days between placebo and rt-PA in an intention-to-treat analysis.¹⁸¹ Similarly, the Alteplase ThromboLysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) trial reported no benefit in patients treated with rt-PA within 3 to 5 hours of onset of symptoms.^{182,183} However, patients treated within the golden 3-hour window were more likely to have a favorable outcome at 90 days than patients treated with placebo (60.9% versus 26.3%).

Unfortunately, most patients are ineligible for IV rt-PA because of delays in obtaining treatment. Indeed, studies show that only 1 to 2% of ischemic stroke patients receive IV rt-PA.^{184,185} The recently published ECASS-3 study results are the first data from a randomized placebo-controlled trial that demonstrated the efficacy of IV rt-PA beyond the established 3-hour time window.¹⁸⁶ This trial randomly assigned 821 stroke patients between placebo and rt-PA in the 3- to 4.5-hour time window. Compared with placebo patients, rt-PA-treated patients experienced a 7.2% absolute increase in the rate of excellent recovery at the 90-day follow-up. A recent meta-analysis was undertaken to determine the efficacy of rt-PA in the 3- to 4.5-hour time window.¹⁸⁷ This meta-analysis evaluated patients in the ECASS-1, ECASS-2, ECASS-3, and ATLANTIS trials, and the rt-PA treatment in the 3- to 4.5-hour window was associated with an increased chance of favorable outcome (odds ratio 1.31) and no significant difference in mortality (odds ratio 1.04) compared to placebo.

Compared to IV thrombolysis, intra-arterial thrombolytic therapy ought, in theory, to be able to deliver a higher local

concentration of agent where it is needed while minimizing the systemic concentration. Proponents of intra-arterial thrombolysis hope that it may lengthen the 3-hour treatment window. The PROACT II trial provided the best evidence to date that intra-arterial thrombolysis can improve patient outcomes.¹⁸⁸ This randomized, open-label, multicenter study with blinded follow-up randomly assigned 180 patients with stroke less than 6 hours' duration to receive either heparin with recombinant prourokinase (r-proUK), 9 mg intra-arterially, or heparin alone. Intra-arterial thrombolysis resulted in significantly better recanalization rates than heparin alone did (66% versus 18%). In addition, more of the r-proUK group had no neurologic deficit or only a slight deficit at 90 days (40% versus 25%). However, intra-arterial thrombolysis did result in significantly increased rates of ICH (35% versus 13%). Symptomatic ICH with neurologic deterioration within 24 hours occurred in 10% of r-proUK patients and 2% of control patients. Patients who experienced ICH after r-proUK therapy had a high mortality (83%).¹⁸⁹ It is noteworthy that only 2% (180 of 12,333) of the screened patients in the PROACT II trial were randomized according to inclusion criteria, which suggests that intra-arterial thrombolysis may be of limited applicability. Finally, intra-arterial thrombolysis requires an experienced staff capable of performing cerebral angiography and navigating a microcatheter to the clot. At present, IV thrombolysis is certainly more practical than intra-arterial thrombolysis; more importantly, it can be done earlier in the course of the stroke.

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2 ASYMPTOMATIC CAROTID BRUIT/CAROTID ARTERY STENOSIS

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Stroke is the third leading cause of death in the United States, behind coronary artery disease and cancer. It is also the leading cause of disability. Nearly 80% of strokes are ischemic, and approximately 20% are hemorrhagic.¹ Unfortunately, only 15% of stroke patients have warning transient ischemic attacks (TIAs) prior to stroke, and waiting until symptoms occur is not ideal.² Ideally, patients who are at high risk for stroke could be identified and treated prior to permanent neurologic deficit.

The management of patients with asymptomatic carotid stenosis has been controversial over the past few decades because most of the landmark studies comparing best medical therapy with best medical therapy with carotid endarterectomy (CEA) used only aspirin as the antiplatelet agent and occurred prior to the widespread use of statin therapy. In this chapter, we provide a stepwise approach to the evaluation and management of patients with asymptomatic carotid bruit/extracranial carotid artery stenosis.

Clinical Evaluation

It is imperative in evaluating a patient with carotid artery stenosis to determine if the patient is classified as symptomatic or asymptomatic. This requires a careful history and review of the patient's medical records and a detailed neurovascular examination. Most TIAs involve the distribution of the internal carotid arteries, although some may affect the vertebrobasilar system. Typical carotid TIA symptoms include contralateral weakness of the face, arm, and/or leg; contralateral sensory deficit or paresthesia of the face, arm, and/or leg; or transient ipsilateral blindness (amaurosis fugax). If the right cerebral hemisphere is affected, other manifestations may be noted, for example, agnosognosia, asomatognosia, neglect, and sensory or visual extinction. In contrast, if the left hemisphere is affected, patients may show manifestation of alexia, aphasias, agraphesthesia, and anomia. Patients with vertebrobasilar TIAs may have a combination of symptoms, including vertigo, diplopia, ataxia, dysarthria, nausea, vomiting, visual disturbances, decreased consciousness, and weakness, which may include quadriparesis.

Occasionally, patients will present with headache and vague neurologic symptoms and have cerebral imaging, that is, magnetic resonance imaging (MRI) or computed tomographic (CT) scans that show recent cerebral infarcts, which may be the result of carotid pathology. Overall, if these infarcts are old, the patients would be considered asymptomatic. However, Kakkos and colleagues reported a higher stroke rate in patients with more than 60 to 79% asymptomatic stenosis with an annual TIA/stroke rate of 1.3% if

there was no silent infarct versus 4.4 if a silent infarct was present.³

Physical examination may show signs of stroke: facial/eyelid drooping, sensory or motor deficits, and speech disturbances. Ocular examinations can occasionally identify Hollenhorst plaques, but this generally requires examination by an optometrist or ophthalmologist. Palpation of the carotid artery provides limited data unless there is asymmetry in the pulsation between the two carotids. Neck auscultation may elicit carotid bruit.

CAROTID BRUITS

Carotid bruits may be helpful in detecting asymptomatic carotid artery stenosis. Carotid bruits must be differentiated from venous hums, which are found in one quarter of young adults or in individuals with cardiac murmurs.⁴ In contrast to a carotid bruit, the venous hum typically increases in quality with the neck turned away from the auscultated side. Also, the venous hum often disappears with Valsalva maneuver and when the patient lies down. There is no definitive way to differentiate a radiated cardiac murmur or bruit originating from intrathoracic vessels from a carotid bruit, but cardiac murmurs are more frequently bilateral and more audible in the chest and lower neck than in the mid- to upper neck.^{5,6} Patients on dialysis can also have bruits that radiate into the neck secondary to arteriovenous fistula placement.⁷

Once a neck bruit is determined to be carotid in origin, the next stage is to determine whether this bruit is asymptomatic or symptomatic. This can be determined by the presence or absence of TIA symptoms or stroke, as indicated earlier. It should be noted that symptoms referable to the contralateral carotid artery, even in the absence of bruit on that side, should prompt evaluation of the patient for stenosis on the contralateral side. Carotid bruit may be absent in patients with severe carotid stenosis in 20 to 35% of patients.⁸ In a subset analysis of the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the presence of carotid bruits was compared with angiographic imaging of the carotid system. The presence of focal ipsilateral carotid bruits had a sensitivity of 63% and a specificity of 61% for high-grade carotid stenosis (70 to 99%), and the absence of a bruit did not significantly change the probability of significant stenosis in this group of patients (pretest 52%, posttest 40%).⁹

Several studies have analyzed the significance of carotid bruits. Ratchford and colleagues found in a diverse group of patients that the sensitivity of bruit auscultation to detect a stenosis was low at 56%, but specificity was high at 98%, with positive and negative predictive values of 25% and 99%, respectively.¹⁰ Several conclusions were made from their

study, including that the prevalence of carotid bruits is low in the general population. Also, if bruit is heard in an asymptomatic patient, 25% will have a greater than 60% stenosis; however, the ability to predict plaque by ultrasonography was 89%. Asymptomatic carotid bruits have also been associated with an increased risk of ischemic stroke compared with age-matched patients without carotid bruits.¹¹ Carotid bruits have also been shown in a meta-analysis to be a prognostic indicator of myocardial infarction (MI) and death.¹² MI and death occurred twice as often in patients with versus patients without carotid bruits.¹²

In another prospective clinicopathophysiologic follow-up study of asymptomatic neck bruits, we followed 300 asymptomatic patients with carotid bruits using serial clinical examinations and duplex ultrasonography with Gee/ocular plethysmography (OPG) for a period ranging from 1 to 72 months (mean 32 months). All patients underwent baseline duplex/OPG, which was repeated every 6 months until the end point, TIA or stroke. One hundred seven had arteriograms. Five classes were identified: class I (normal): 96 of 300 (32%) patients, 79 of whom were followed and one had TIA (1 of 79, 1.3%); class II (< 50% stenosis): 118 of 300 (39%) patients, 105 of whom were followed, with three having TIA, and one having stroke (4 of 105, 3.8%); class III (50 to 60% stenosis): 25 of 300 (8%), 21 of whom were followed, with one having TIA (1 of 21, 4.7%); class IV (> 60% stenosis with negative OPG): 39 of 300 (13%), 34 of whom were followed, with three having TIA and one having stroke (4 of 34, 11.7%); and class V (> 60% stenosis with positive OPG): 22 of 300 (7%), 18 of whom were followed, with three having TIA, and one having stroke (4 of 18, 22.2%). From these data, we concluded that in asymptomatic patients with carotid bruits, 32% had no carotid stenosis and 39% had minimal disease with minimal risk of TIA or stroke. Patients with the most severe stenoses (classes IV and V) had a statistically significantly higher likelihood of TIA or stroke occurring during the follow-up period. This last group (class V) would be ideal for prophylactic CEA.¹³

Vascular Risk Evaluation

Vascular risk factors are common in patients with asymptomatic carotid bruits. These patients should be evaluated for the presence of controllable risk factors, including hypertension, diabetes mellitus, hyperlipidemia, and smoking. Hypertension is generally twice as common in these patients than in the general population; similarly, smoking, ischemic heart disease, and peripheral disease are more prevalent.¹⁴⁻¹⁷

The absolute risk of stroke is generally increased in the presence of carotid bruit. In population-based studies, the annual risk of stroke was 2.1% (95% confidence interval [CI] 0.6 to 8.5) for persons who had a carotid bruit versus 0.86% (95% CI 0.8 to 0.9) for those who did not.¹⁸⁻²⁰ This represents an absolute risk increase for stroke of 1.24% a year and a relative risk for stroke of 2.4. The presence of a carotid bruit remained an independently significant variable, with a relative risk of 2.0, even after adjustment for various risk factors, including hypertension, age, and sex.¹⁸

With these facts in mind, and given the low absolute risk of stroke in patients with asymptomatic carotid bruits [see

Table 1] and the low prevalence of surgically relevant significant carotid stenosis in these patients [see Table 2] with a relatively small absolute benefit of CEA, most clinicians pursue further investigations only in patients who carry a high risk of carotid stenosis and stroke and who also carry a low operative risk for CEA.^{21,22} Further evaluation in these patients should be done only if the patients prefer to undergo carotid intervention, whether CEA or stenting; otherwise, no further evaluation is indicated.

For any therapy to receive widespread support, the risk attended to this therapy must be significantly less than the actual risk if the disease is not treated. Therefore, carotid intervention must have a significantly lower perioperative complication rate than the natural history of asymptomatic carotid stenosis. This is a particular issue in patients undergoing evaluation for stroke prevention: these patients tend to be elderly, harbor general atherosclerosis, and have concomitant coronary artery disease, hypertension, diabetes mellitus, chronic lung disease, and renal insufficiency. All of these comorbidities may impact the perioperative outcome after CEA or carotid stenting.

A number of caveats must be considered when examining the evidence that carotid artery interventions reduce the risk of stroke and death in patients with carotid disease. First, a significant number of patients were excluded from both the NASCET²³ and the Asymptomatic Carotid Atherosclerosis

Table 1 Annual Risk of Stroke

Patient Population	Annual Risk of Stroke, % (95% CI)
Population without bruits, age > 60 yr ¹⁶⁻¹⁸	0.86 (0.8-0.9)
Population with bruits, age > 60 yr ^{16,17,59}	2.1 (0.6-8.5)
Male population without bruits, age > 60 yr ^{14,16}	0.9 (0.1-3.0)
Male population with bruits, age > 60 yr ¹⁶	8.0 (0.2-38.0)
Female population without bruits, age > 60 yr ¹⁴	2.0 (0.8-4.2)
Female population with bruits, age > 60 yr ¹⁶	2.4 (0.7-5.5)

Table 2 Prevalence of Carotid Stenosis in Patients with Bruits and in Healthy Volunteers

Patient Population	Prevalence of Carotid Stenosis, % (95% CI)
Overall population with cervical bruits	
> 35% stenosis ^{13,59-62}	58 (55-60)
> 60-75% stenosis ^{13,60,61}	21 (18-24)
Healthy volunteers*	
Age > 70 yr ⁶³	5.1 (2.6-9.0)
Age ≤ 70 yr ⁶³	1.5 (0.2-5.3)

*In healthy volunteers, the incidence of asymptomatic carotid stenosis is significantly correlated with age ($p < .01$) and with the presence of hypertension ($p < .005$).

Study (ACAS)²⁴ because of coexisting medical conditions that could produce significant mortality and/or morbidity. During 6 years of enrolment in the ACAS, 42,000 patients were screened to randomize 1,662 patients. Strict nonneurologic exclusion criteria for ACAS and NASCET included age younger than 40 years or older than 79 years, a less than 5-year life expectancy, or diseases that would seriously complicate surgery, for example, unstable angina, atrial fibrillation, severe diabetes, uncontrolled hypertension, and chronic renal insufficiency. A second caveat is that new lines of medical therapy, such as statins, beta blockers, and modern antiplatelet therapies, were not available at the time of the original ACAS and NASCET. These agents represent current “best medical therapy” and may impact the results comparing interventions with medical therapy alone. Studies such as the Transatlantic Asymptomatic Carotid Intervention Trial (TACIT) may help in determining the outcome of these patients. This ongoing multicenter, prospective, randomized trial involves 100 sites enrolling over 2,000 patients. High- and low-risk individuals with greater than 70% asymptomatic carotid stenosis are randomized into one of three arms: (1) CEA and best medical therapy, (2) carotid artery stenting and best medical therapy, and (3) best medical therapy with antiplatelet, statin, and antihypertensive agents only.²⁵ Until the trial results are known, our belief is that if these patients have a good likelihood of significant carotid stenosis as evidenced by the presence of other vascular risk factors, have a reasonable life expectancy, and are at low risk for carotid intervention, they should be thoroughly investigated because they will benefit from prophylactic CEA.

Imaging Modalities

Several imaging modalities have been proposed, including carotid duplex ultrasonography, carotid MRI, and CT.

CAROTID DUPLEX ULTRASONOGRAPHY

The initial evaluation of patients with carotid bruit or cerebrovascular symptoms should begin with duplex imaging of the extracranial carotid arteries. Duplex ultrasonography is an accurate and reliable noninvasive tool to determine the degree of carotid stenosis and plaque morphology in most patients. It is important that images be reviewed by the vascular surgeon/vascular interventionalist to understand the quality of the testing. Often duplex ultrasonography performed at nonaccredited facilities provides results that are not acceptable for proceeding with intervention. We continue to use previously validated criteria from our institution to make treatment decisions without secondary imaging prior to carotid intervention [see Table 3].²⁶

Table 3 Duplex Velocity Criteria for Carotid Stenosis

Stenosis (%)	PSV (cm/s)	EDV (cm/s)
< 30	< 120	< 65
30–50	120–139	< 65
50–60	> 140	< 65
60–70	> 150	> 65
70–99	> 150	> 90

EDV = end diastolic velocity; PSV = peak systolic velocity.

Duplex ultrasonography has been shown to be highly accurate in estimating the degree of carotid stenosis. A meta-analysis conducted in 1995 concluded that for detecting greater than 50% stenosis (determined by arteriography), duplex ultrasonography had a sensitivity of 91% and a specificity of 93%.²⁷ Given a disease prevalence of about 41% in patients referred for duplex ultrasonography, these findings translated into a positive predictive value of 90% and an overall accuracy of 92%.

In addition to estimating severity of stenosis, duplex ultrasonography can also be used to assess plaque morphology, an important tool that may help predict a patient’s future risk of neurologic events. Reilly and colleagues have characterized plaques as homogeneous or heterogeneous.²⁸ Homogeneous plaques consist of uniform medium- to high-level echoes, whereas heterogeneous plaques consist of a mixture of high-, medium-, and low-level echoes. Homogeneous plaques on duplex ultrasonography have been correlated with fibrous lesions intraplaque hemorrhage on pathologic examination. Pathologic evidence of ulceration and loose stroma-containing lipids and proteinaceous deposits are characteristic of heterogeneous lesions.²⁸ Heterogeneous plaques [see Figure 1] have been shown to increase the risk of neurologic symptoms (TIA/stroke), as previously reported by our group. Heterogeneous plaques were also associated with an incidence of TIA/stroke that was higher than that in homogeneous plaques for all grades of stenosis.²⁹ Plaque morphology has been shown to be an important predictor of neurologic events using other imaging techniques. Nicolaides used computerized image analysis to assess plaque morphology by quantifying the grayscale median (GSM) of the plaque.³⁰ The incidence of cerebral infarction in those with GSM of greater than 50 was 9% versus 40% in those with GSM less than 50. Recently, investigators have suggested the importance of normalization of the B-mode value to allow interscan comparison. The Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) study obtained longitudinal images of the plaque and vessel wall, transferred the images to a workstation, and used commercially available software to normalize the data.³¹ They adjusted the GSM of the blood pool to 0 to 5 and the adventitia of the wall to 185 to 195. The region of interest, therefore, was selected and its GSM value was calculated. The investigators of this study demonstrated that GSM values of 25 or less were associated with a stroke risk of 7.1% and GSM values exceeding 25 had a stroke risk of 1.5% during carotid stenting procedures. However, Reiter and colleagues, in a later study, failed to demonstrate the correlation between plaque echogenicity and an increased risk of stroke during carotid stenting.³²

Recently, intravascular ultrasonography has been used to characterize arterial lesions before intervention, particularly in the evaluation of coronary artery disease. A similar system has also been used for evaluating carotid plaques where tissue characterization algorithms, creating images of “virtual histology” of the arterial wall, are made. These need further validation before having a clinical implication.³³

Duplex imaging of the carotid artery has a few major limitations. These include quality dependence on the technician’s examination and limitations of visualization of the proximal carotid artery and intracranial portions. Although the intracranial cerebral arteries can be assessed with transcranial

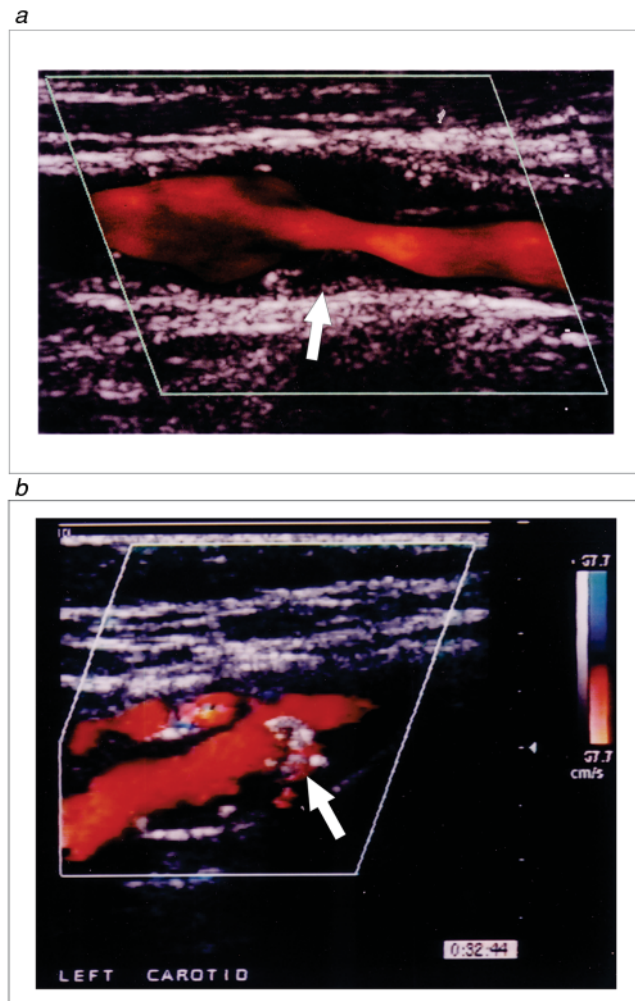


Figure 1 (a) Color duplex ultrasound image of the carotid bifurcation showing a complex heterogeneous plaque at the origin of the internal carotid artery (arrow). (b) Color duplex ultrasound image of the carotid artery showing a smooth heterogeneous plaque (arrow). The dark center of the plaque may represent intraplaque hemorrhage. Reproduced with permission from Duplex scanning of the carotid arteries. In: AbuRahma AF, Bergan JJ, editors. *Noninvasive Vascular Diagnosis: a Practical Guide to Therapy*. London: Springer; 2007. p. 70.

Doppler imaging, this technique is not as widely available at most institutions as other imaging modalities. It may also overestimate stenosis contralateral to carotid occlusion due to increased compensatory flow; however, most of the recent studies take this into consideration and adjust velocity thresholds accordingly.²⁶

CONTRAST-BASED IMAGING

Magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) are additional tests that can assess the carotid circulation to aid the physician in planning intervention. Compared with catheter-based arteriography, the sensitivity and specificity of MRA in detecting carotid stenosis of 70 to 99% has been 84 to 100% and 75 to 93%, respectively, by using two- and three-dimensional time of

flight techniques.^{34,35} Proximal lesions (below the clavicle) and intracranial lesions can be assessed when clinically suspected or in cases in which duplex imaging is suggestive. Proximal lesions lead to lower velocities distally with dampened Doppler waveforms. Our group has relied more on CTA when duplex examinations are inconclusive. Rapid acquisition of spiral CT images can allow for excellent timing with contrast administration and provide quality images that can be viewed in multiple plains. Plaque morphology can also be assessed, similar to that of ultrasound-based techniques. The limitations of this technique include cost, contrast exposure, and the added concern of radiation exposure. Additionally, a large calcium burden can limit the ability to distinguish contrast from calcium during postprocessing imaging.

Conventional angiography, once considered the gold standard for carotid imaging, is now reserved for patients with conflicting studies or patients being considered for carotid stenting. Conventional contrast angiography poses a stroke risk of approximately 1% and therefore has a limited role in place of modern MRA and CTA, except in cases of planned carotid stenting. Importantly, in the ACAS study, 1.2% of patients developed a neurologic event following carotid angiography, accounting for 40% of the strokes in the intervention arm.²⁴ In addition to the neurologic events, access-related complications can occur, increasing the overall morbidity of this invasive diagnostic method.

Natural History of Asymptomatic Carotid Artery Disease

Asymptomatic carotid artery stenosis has been evaluated by multiple investigators over the past several decades. The degree of stenosis, plaque morphology, and development of disease progression have also been correlated to future neurologic event rates. In a group of 121 patients with greater than 75% stenosis determined by duplex ultrasonography, 60% developed a neurologic event during a 5-year follow-up, whereas only 12% of those with less than 75% stenosis developed an event. The plaque morphology was also assessed to determine the effect, if any, on the future risk of stroke. Soft plaques were more frequently associated with events than those with dense calcifications.³⁶ Roederer and colleagues found a 46% incidence of ischemic symptoms or carotid occlusion 12 months after progression to more than 80% stenosis.³⁷ This is in comparison with less than 2% of those plaques that did not show progression over a similar period.³⁷

The natural history of asymptomatic carotid disease may be altered by the addition of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. This medication has been shown to reduce neurologic events, even with normal serum cholesterol levels.³⁸ There has been increasing interest in using statins to slow the progression of carotid disease. In the Asymptomatic Carotid Artery Plaque Study (ACAPS), lovastatin was compared in a double-blinded study to evaluate the effect on intimal medial thickness and cardiovascular events. In men and women with moderately elevated low-density lipoprotein (LDL) levels, the progression of intimal medial thickness in the carotid arteries was reduced compared with placebo, and lovastatin was also associated with reduced cardiovascular events and mortality.³⁹

NATURAL HISTORY OF 60% OR GREATER STENOSIS CONTRALATERAL TO CAROTID OCCLUSION

In a study of the natural history of $\geq 60\%$ asymptomatic carotid stenosis in patients with contralateral carotid occlusion, AbuRahma and colleagues reported that during a 10-year period, patients with 60 to less than 70% asymptomatic carotid stenosis with contralateral carotid occlusion were entered into a protocol of clinical examination and duplex surveillance every 6 months. All patients underwent maximum medical therapy: antiplatelet therapy, primarily an aspirin regimen; risk factor modification, for example, control of high blood pressure, and diabetes mellitus; some had cholesterol-lowering medications. Late CEAs were considered if lesions became symptomatic or progressed to 70% or greater stenosis. Eighty-two patients were enrolled with a mean follow-up of 59.5 months (range 7 to 141 months). Late strokes were noted in 27 of the 82 patients (33%); 19 (23%) were ipsilateral and eight (10%) were contralateral (side of contralateral carotid occlusion). Late TIAs were noted in 22 of 82 (27%, seven ipsilateral and 15 contralateral). The combined neurologic event (TIA/stroke) rate was 60% (49 of 82, 32% ipsilateral and 28% contralateral). Kaplan-Meier life table analysis showed that the rates of freedom from ipsilateral strokes, all strokes, and progression to 70% or greater stenosis at 1, 2, 3, 4, and 5 years were 94%, 90%, 85%, 80%, 73%; 94%, 89%, 84%, 77%, and 67% and 99%, 96%, 92%, 86%, and 82%, respectively. The ipsilateral stroke-free survival rates at 1, 2, 3, 4, and 5 years were 94%, 88%, 78%, 70%, and 63%. Twenty-one late CEAs were performed with no perioperative stroke/deaths (five for ipsilateral TIAs, nine for ipsilateral strokes, and seven for 70% or greater asymptomatic carotid stenosis). Overall, 20 (24%, 11 with symptoms and 9 asymptomatic) progressed to 70% or greater stenosis. We concluded that even with maximal medical therapy, patients with 60 to less than 70% asymptomatic carotid stenosis and contralateral carotid occlusion carry a higher incidence of ipsilateral strokes and all strokes than what was reported by the ACAS; therefore, prophylactic CEA may be justified in these patients.⁴⁰

NATURAL HISTORY OF CAROTID STENOSIS CONTRALATERAL TO CEA

A few nonrandomized studies have reported the natural history of an asymptomatic carotid artery stenosis contralateral to CEA. AbuRahma and colleagues followed the contralateral carotid arteries of 534 patients after CEA.⁴¹ These patients were from two previously reported randomized trials that compared CEA with primary closure versus patching. All patients were followed up clinically and with duplex ultrasound scanning at 1 month and then every 6 months. Progression was defined as progress to a higher category of stenosis. Of 534 patients, 61 had initial contralateral CEA and 53 had contralateral occlusion, leaving 420 patients available for analysis. At baseline, 162 patients had normal carotid arteries, 157 had less than 50% stenosis, and 95 had 50 to 79% stenoses. Six other patients had 80 to 99% or greater stenosis but refused further treatment or follow-up (too sick to undergo intervention). Overall, carotid artery stenosis progressed in 109 of the 420 patients (26%) at a mean follow-up of 41 months. Progression of carotid artery stenosis was noted in five of 162 patients (3%) with baseline normal carotid

arteries. Carotid artery stenosis progressed in 56 of 157 patients (36%) with less than 50% stenosis versus 45 of 95 patients (47%) with 50 to 79% stenosis ($p = .003$). The median time to progression was 24 months for less than 50% carotid artery stenosis and 12 months for 50 to 79% carotid artery stenosis ($p = .035$). At 1, 2, 3, 4, and 5 years, freedom from disease progression in patients with baseline carotid artery stenosis less than 50% was 95%, 78%, 69%, 61%, and 48%, respectively, and in patients with 50 to 79% carotid artery stenosis was 75%, 61%, 51%, 43%, and 33%, respectively ($p = .003$). Freedom from progression in patients with baseline normal carotid arteries at 1 through 5 years was 99%, 98%, 96%, 96%, and 94%, respectively. Late neurologic events referable to the contralateral carotid artery were infrequent (28 of 420 [6.7%] in the entire series; 28 of 258 [which included 157 patients with $< 50\%$ stenosis, 95 with ≥ 50 to 79% stenosis, and six with ≥ 80 to 99% stenosis; 10.9%] patients with a contralateral carotid artery stenosis at baseline) and included 10 strokes (3.9% of patients with baseline contralateral stenosis, 2.4% of the whole series) and 18 TIAs (7% in patients with baseline contralateral stenosis; 4.3% for the whole series). However, late contralateral CEA was performed in 62 patients (62 of 420 [15%] in the entire series; 24% [62 of 258] patients with initial contralateral carotid artery stenosis). Survival rates were 96%, 92%, 90%, 87%, and 82%, respectively, at 1 through 5 years. Based on these data, the authors concluded that progression of contralateral carotid artery stenosis was noted in a significant number of patients with baseline contralateral carotid artery stenosis after CEA. Serial clinical studies and duplex ultrasound scanning every 6 to 12 months in patients with 50 to 79% carotid artery stenosis and every 12 to 24 months in patients with 50% or less carotid artery stenosis was adequate to detect disease progression in these patients.

Recommendations for Carotid Intervention/Medical Therapy

Patients with carotid plaque and asymptomatic lesions of less than 60% should be managed with medical treatment only. In asymptomatic patients with greater than 60% carotid stenosis, medical treatment and CEA are currently recommended in good surgical risk patients, particularly those who are at high risk for stroke [see Table 4 and Table 5], as long as the risk of stroke in the perioperative period is low.⁴² Low is defined by the American Heart Association (AHA) as a less than 3% risk of major perioperative morbidity and mortality.⁴³

Table 4 lists the primary and secondary risk factors for stroke, and Table 5 ranks the relative increased risk. The following is a brief summary of these risk factors.

Clinical trials confirmed the reduced risk of stroke and coronary artery disease in hypertensive patients who are treated with both diuretics and beta blockers, but not with angiotensin-converting enzymes (ACE) inhibitors or calcium channel blocking agents. A meta-analysis of several trials of blood pressure reduction showed that a 5.8 mm Hg drop in diastolic blood pressure produced a 42% reduction in the incidence of all stroke over a 2- to 3-year period.⁴⁴ Paradoxically, it should be noted that aggressive lowering of hypertension in elderly patients may cause an increase in stroke.

Table 4 Risk Factors for Stroke

Primary
Increasing age
Male sex
Family history
African-American and Asian race
Smoking*
Hypertension*
Cholesterol*
Diabetes*
Secondary
Past TIA or stroke
Carotid artery stenosis
Previous angina/MI
Cardiac arrhythmias
Peripheral vascular disease
Left ventricular hypertrophy

MI = myocardial infarction; TIA = transient ischemic stroke.
*Can be modified.

Table 5 Ranking of Modifiable Stroke Risk Factors

Factor	Median Risk
Past TIA or stroke	10.0 times
Hypertension	6.0 times
Atrial fibrillation	5.6 times
Carotid bruits	3.0 times
Coronary artery disease	2.2 times
Left ventricular hypertrophy	2.2 times
Hypercholesterolemia	2 times
Smoking	2 times
Diabetes	1.7 times
Congestive heart failure	1.7 times

TIA = transient ischemic attack.

Isolated systolic hypertension, as defined by a systolic blood pressure of greater than 170 mm Hg, should also be treated because an 11 mm Hg decrease in the systolic pressure was associated with a 36% reduction in the stroke risk.⁴⁴

Diabetes mellitus increases the risk of stroke by 2.5 to 3.5 times compared with controls. Insulin resistance is also associated with increased atherosclerosis of the carotid arteries independent of the glucose level, insulin levels, and other major cardiovascular risk factors. However, the ability of oral hypoglycemic medication and insulin to reduce the risk of stroke has yet to be proven in prospective trials.⁴⁵

Cigarette smoking increases the risk of stroke by two times because of accelerated atherosclerosis of the carotid artery, which may be independent of other factors. The risk of stroke decreases rapidly with the cessation of cigarette smoking, regardless of age, compared with a 50% reduction of risk of coronary events in 1 year.⁴⁵

Several studies correlated the relation between cholesterol and stroke risk with variable results. It is generally believed that elevated total cholesterol and LDL are independent risk factors for ischemic events. A pooled meta-analysis of four pravastatin trials documented a 46% reduction in the risk

of stroke,⁴⁶ and the ACAPS documented fewer strokes in the lovastatin group than in the placebo group (five versus zero).⁴⁷

The AHA guidelines for risk factor modification include the following recommendations concerning tobacco use, hypertension, cholesterol management, and blood glucose goals.⁴³ Blood pressure should be aggressively lowered to less than 120/80 mm Hg. ACEs and angiotension receptor blockers should be first-line therapy in patients who are diabetic, in addition to lifestyle changes that include diet and exercise. Target levels for the hemoglobin A_{1c} should be less than 7% to reduce the risk of both micro- and macrovascular sequelae of hyperglycemia. Statin agents are recommended to manage hypercholesterolemia with target goals of LDL cholesterol < 100 mg/dL and in patients with multiple risk factors to be lowered to less than 70 mg/dL. In addition to the benefit of stroke reduction, many other benefits of statins have been demonstrated in vascular patients, including reduction of cardiovascular events and overall mortality; this was irrespective of age, gender, or cholesterol level, raising the question of a possible pleiotrophic effect by these agents.⁴⁸

Other studies have continued to accumulate in the literature that have shown a favorable decrease in neurologic event rates of both carotid surgery and stenting with the perioperative administration of statin agents. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial enrolled patients with recent TIA or stroke, and the 5-year risk of stroke was reduced by 16% with statin therapy compared with placebo.⁴⁹

ANTIPLATELET THERAPY IN THE PREVENTION OF STROKE

The current consensus is that patients who have an ischemic cerebral event secondary to atherosclerosis should receive antiplatelet therapy. Several clinical trials have reviewed the efficacy of these medications. The Ticlopidine Aspirin Stroke Study (TASS) was a blinded trial at 56 medical centers that compared the effects of ticlopidine with aspirin.⁵⁰ At 3 years, 3,069 patients were evaluated and the rates of fatal and nonfatal stroke were 10% for the ticlopidine and 13% for aspirin, a 21% risk reduction. It should be noted that severe, but reversible, neutropenia developed in less than 1% of patients taking ticlopidine. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study randomized 19,185 patients over a 3-year period.⁵¹ Patients treated with clopidogrel experienced a 5.32% annual risk of ischemic stroke, MI, or vascular death versus 5.83% with aspirin, with a relative risk reduction of 8.7% in favor of clopidogrel. Finally, the European Stroke Prevention Study 2 (ESPS-2) was a multicenter, blinded, randomized, placebo-controlled study with four treatment arms consisting of aspirin, dipyridamole, aspirin with dipyridamole, and placebo. This study showed that the combination of extended-release dipyridamole plus aspirin was additive and produced highly sufficient benefits, with a 37% risk reduction for stroke prevention.⁵² There is no level 1 evidence to support the use of clopidogrel over aspirin in asymptomatic patients. However, our recommendation is to use one aspirin daily (81 or 325 mg). Clopidogrel (75 mg daily) is used only if aspirin therapy is contraindicated.

LEVEL I EVIDENCE SUPPORTING CEA IN ASYMPTOMATIC PATIENTS

Two large prospective randomized trials [see Table 6] have shown the superiority of CEA plus medical treatment versus medical treatment alone.^{24,53}

The ACAS was the largest randomized trial to examine the management of asymptomatic carotid stenosis. Patients with 60% or greater asymptomatic carotid artery stenosis ($n = 1,662$) were randomized to best medical treatment or CEA. After a median follow-up of 2.7 years, the 5-year risk of ipsilateral stroke by Kaplan-Meier projection was 5.1% for CEA and 11% for medically treated patients ($p = .004$). This showed a relative risk reduction of 53% and an absolute risk reduction of 5.9%. The estimated 5-year event rate was more favorable with surgery for men than women: 4.1% versus 12.1% in men, compared with 7.3% versus 8.7% in women. Part of this was attributed to higher perioperative events in women: 3.6% versus 1.7% in men.

The second largest trial is the UK Medical Research Council Asymptomatic Carotid Surgery Trial (ACST). This was a prospective randomized trial of CEA in asymptomatic patients in which more than 3,000 patients were randomly assigned either to undergo immediate CEA or to be placed on indefinite deferral. For patients who were referred for immediate CEA, half underwent surgery within 1 month of referral: 88% underwent surgery within 1 year. Combining the rate of perioperative events and the nonperioperative strokes, the 5-year results indicate a stroke rate of 6.4% in the group undergoing immediate surgery compared with 11.8% in the deferred group. These findings were similar to the ACAS findings; however, the ACST found a similar benefit for men and women. In addition, no difference was found in the degree of stenosis and the benefit of surgery. Presently, the second ACST-2 is being conducted comparing CEA versus carotid artery stenting for asymptomatic carotid stenosis.

The medical community has questioned the current accuracy of these studies, considering the current improvements in best medical treatment. These two prospective randomized trials were performed prior to widespread use of agents (statins) that have been shown to reduce the risk of stroke. In addition, these studies required surgeons preselected with excellent surgical results and may not be extrapolated to all surgeons performing CEA. As stated earlier, for the patient to derive benefit from prophylactic intervention, the patient's risk of medical therapy alone with the projected natural history for that patient must exceed that of the specific surgeon's

intervention. Several patient factors should be considered prior to offering intervention.

Duplex criteria were used for enrolment in the medical treatment arm for the ACAS study and arteriographic confirmation prior to CEA. However, some centers were allowed to do CEA based on duplex ultrasonography if their duplex ultrasonographic findings were validated against angiography. This requirement was associated with a 1.2% combined event rate with angiography, which, if eliminated by imaging today, that is, duplex ultrasonography or noninvasive testing, would have increased the interventional benefit compared with medical therapy at that time.

Decision Making for Medical Therapy Alone versus Intervention

ANATOMIC FACTORS

Asymptomatic lesions that are either higher or lower than can easily be accessed by the surgeon pose specific limitations. High lesions are defined as those at or above the second cervical vertebrae often requiring additional surgical maneuvers to safely remove the lesion. These include but are not limited to dividing external carotid branches, the ansa cervicalis, and the digastric muscle and, rarely, excessive traction and even mandibular manipulation. Associated cranial nerve morbidity can be substantial; even if the patient does not have an intraoperative neurologic event, the long-term morbidity may exceed the risk of medical treatment. Similarly for lesions below the clavicle, the natural history has not been well defined, and surgical treatment often requires extra-anatomic bypass or sternotomy. Our group has used retrograde stenting techniques for these proximal lesions as other groups have described, but no prospective studies have shown the best way to treat these combined lesions.

The status of the contralateral carotid artery has also been associated with increased risk of carotid intervention. Contralateral occlusion has been shown to be associated with increased risk of perioperative events with CEA.²³ However, we have not found this to be true in our experience: our perioperative, late stroke, and survival rates of CEA were comparable in patients with and without contralateral occlusion.⁵⁴

An increasing degree of stenosis may also be associated with higher chances of stroke in asymptomatic patients; however, in the ACAS study, there were too few strokes to permit a subgroup analysis of the effect of the degree of stenosis on the ability to benefit from CEA.²⁴ However, in both the NASCET and the European Carotid Surgery Trialist (ECST) study, a higher degree of stenosis in symptomatic patients was consistently observed to be associated with a higher stroke risk, as well as a greater benefit from surgical therapy. The ECST study, using angiographic data from the asymptomatic carotid arteries from 2,295 patients, reported that the Kaplan-Meier estimate of stroke risk at 3 years was only 2% and remained low, below 2%, in patients with less than 70% stenosis, in contrast to a stroke rate of 9.8% for patients with 70 to 79% stenosis and 14.4% for those with 80 to 99% stenosis.⁵⁵

Table 6 Asymptomatic Randomized Trials Comparing Medical to Medical and Surgical Treatment (Stenosis > 60%)

Trial	n	Perioperative Stroke Rate (%)	5 yr Stroke (Surgery/Medical %)	NNT
ACAS	1,662	2.3	5.1/11	17
ACST	3,120	2.8	6.4/11.8	19

ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; NNT = number needed to treat to prevent one stroke.

Recurrent stenosis following CEA has been an exclusion criterion in large prospective randomized trials. The national trend has been to consider carotid stenting (for $\geq 80\%$ asymptomatic recurrent stenosis or $\geq 50\%$ symptomatic recurrent stenosis) in this group secondary to increased risk of perioperative neurologic deficits compared with the initial procedure. Cranial nerve injury also occurs more frequently in the setting of redo surgery and has also been avoided by transcatheter intervention.⁵⁶

The presence of asymptomatic cerebral infarct ipsilateral to the asymptomatic carotid stenosis on a CT scan or MRI may identify patients who would benefit from surgery.⁵⁷ In asymptomatic carotid stenosis patients, the incidence of silent strokes demonstrated by CT has been reported to be 10% in patients with 35 to 50% stenosis on duplex ultrasonography, 17% in those with 50 to 75% stenosis, and 50% in those with greater than 75% stenosis. The incidence of silent cerebral infarct demonstrated by MRI in the same type of population has also been reported to be 42%, increasing to 75% for greater than 50% stenosis.⁵⁷

PATIENT FACTORS

As noted, octogenarians were excluded in the ACAS. Increasing age has been associated with overall increased risk of events following surgery. Therefore, prophylactic CEA for asymptomatic stenosis in the elderly should be performed with caution unless the overall medical status is good.

The derived benefit from CEA for women compared with men has also been less in several studies.²⁴ For uncertain reasons, CEA in women has been associated with increased stroke rates compared with men. Interestingly, women with asymptomatic carotid disease treated medically may do better than their male counterparts. In a subgroup analysis, the ACAS showed that the absolute reduction in the risk of perioperative stroke or death or ipsilateral stroke at 2.7 years was 3.6% (95% CI 1.1 to 9.9) for men and 0.5% (95% CI 0.01 to 2.7) for women. With this combination, a more conservative approach may apply for women, particularly with 60 to 80% asymptomatic stenosis.

The presence of atherosclerosis in other locations appears to carry additional risk. In particular, concomitant severe coronary disease and asymptomatic carotid stenosis has been extensively studied. Perioperative stroke and death have been seen with combined coronary artery bypass grafting (CABG) and CEA, as reported by Naylor and colleagues.⁵⁸

SURGEON FACTORS

Surgeons should use and quote their own perioperative events; not infrequently, surgeons report the risk with major landmark studies and not their personal results. These studies typically have rigorous standards that are required for enrollment. It has been shown in multiple surgical procedures that higher volume surgeons generally have better perioperative results than lower volume surgeons. The American College of Surgeons has stressed personal evaluation of surgical results and has included this in the continued competency guidelines. The AHA currently recommends regular review of independent results and performing combined carotid surgery only when the surgeon's event rate is less than 5%.⁴³

Figure 2 summarizes a practical approach for managing patients with asymptomatic carotid bruit/asymptomatic carotid artery stenosis, as follows:

- Step 1.* This step distinguishes a carotid bruit from a non-carotid bruit, for example, venous hum, cardiac murmur, or intrathoracic vascular structures.
- Step 2.* This step determines if the carotid bruit is symptomatic or asymptomatic.
- Step 3.* A carotid duplex sonogram is obtained to determine the severity of the carotid artery stenosis if the patient is felt to have a carotid bruit secondary to carotid stenosis.
- Step 4.* For patients with less than 60% stenosis, medical therapy, as indicated earlier, with carotid surveillance is recommended.
- Step 5.* The frequency of surveillance will depend on the severity of the carotid stenosis; that is, patients with less than 50% can be screened every 1 to 2 years, and patients with greater than 50% stenosis can be screened every 6 to 12 months.
- Step 6.* If the stenosis was 60 to less than 80%, a determination needs to be made whether it was progressive stenosis (stenosis that was $< 60\%$ and progressed to $< 80\%$).
- Step 7.* If not, the patient should be evaluated for stroke risk factors.
- Step 8.* If the stroke risk is low, medical treatment and surveillance are adequate.
- Step 9.* If risk factors are present, the patient should be evaluated for his or her life expectancy.
- Step 10.* If the life expectancy is poor, medical treatment is adequate.
- Steps 11 and 12.* If the life expectancy is good, the patient should be evaluated for his or her operative risk.
- Steps 13 and 14.* If the patient is a good surgical candidate, carotid duplex ultrasonography is technically adequate.
- Step 15.* A CEA may be considered.
- Step 16.* If carotid duplex ultrasonography is inadequate, other imaging is necessary; however, for patients with poor surgical risk, medical therapy is recommended.
- Step 17.* Meanwhile, if the stenosis was progressive, and if after evaluation of life expectancy, the patient is felt to be in good condition and a good operative risk, CEA would be recommended; otherwise, medical therapy is adequate.
- Step 18.* For patients who are poor operative risks, medical therapy is recommended.
- Step 19.* Patients with 80 to 99% stenosis should be evaluated for their life expectancy, and if it is felt to be good, operative evaluation will follow, and if satisfactory with good quality duplex ultrasonography, they will undergo CEA.
- Step 20.* In poor surgical risk patients with adequate life expectancy, carotid artery stenting can be an alternative therapy.

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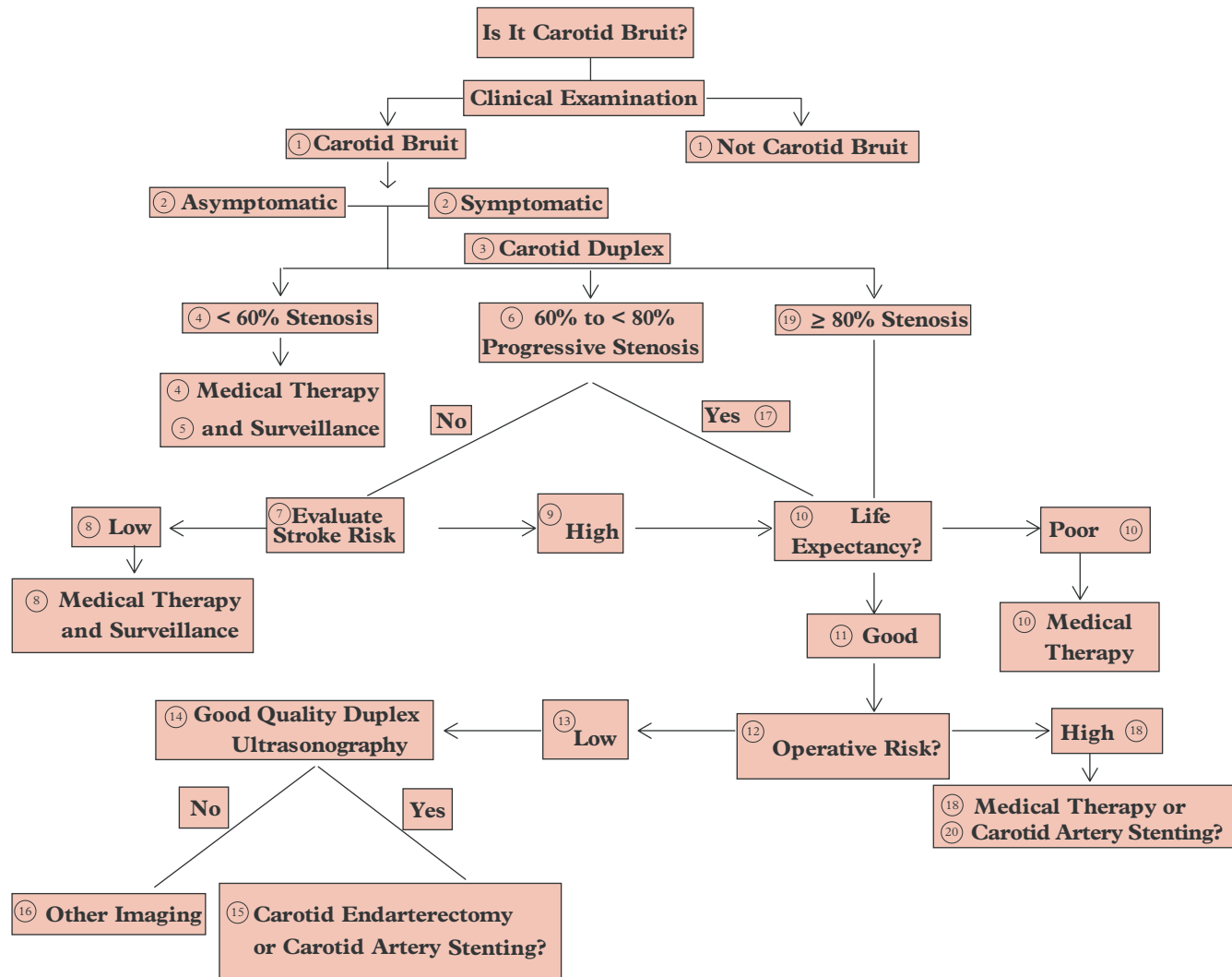


Figure 2 Protocol of management of asymptomatic carotid bruit/carotid artery stenosis.

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3 PULSATILE ABDOMINAL MASS

*Guillermo A. Escobar, MD, and Gilbert R. Upchurch Jr, MD**

Assessment of a Pulsatile Abdominal Mass

When a pulsatile abdominal mass is found on physical examination, the location of the mass and the symptoms associated with it become essential clinical clues. The underlying condition may range in severity from benign to life threatening. Pulsatile masses in the abdomen are either attributable to a large blood vessel or from another mass (e.g., lymph node, tumor, abscess) that is simply in close proximity to a blood vessel and the pulsations are transmitted to the skin. Thus, further evaluation is imperative because in certain clinical settings, immediate transport to the operating room will be necessary. Consequentially, inappropriate treatment can be catastrophic, so it is important to base one's approach to assessment and management of a pulsatile abdominal mass as firmly as possible on the available evidence. In what follows, a clinical approach based on relevant evidence is outlined.

Clinical Evaluation

The most feared cause of a pulsatile abdominal mass is an abdominal aortic aneurysm (AAA). In the United States, AAAs are present in 3 to 9% of the population, resulting in approximately 15,000 fatalities each year.¹ The incidence and penetrance of aneurysms are variable according to age and race. As an example, in 2002, AAAs were one of the 10 most common causes of death in Asian or Pacific Islander males 20 to 24 years of age as well as those 65 to 84 years of age!² Although the number of total aneurysms repaired has remained stable in the last 5 years, the number of deaths from AAA and their rupture has significantly declined over the years.^{3,4} On the other hand, with the overall aging of the US population, this disease remains a major threat to public health and should be immediately considered as the diagnosis if the patient is in a high-risk category for AAA.

PRESENTATION

Asymptomatic AAAs are considerably more common than symptomatic AAAs and are often discovered on abdominal or pelvic scans done for other indications (e.g., back pain or renal cysts) rather than on physical examination.^{5,6} Plain films of the lumbar region, routinely obtained in patients with back pain, may show a calcified shell of the aorta [see Figure 1]. In one review of 31 patients with surgically proven ruptured AAAs,

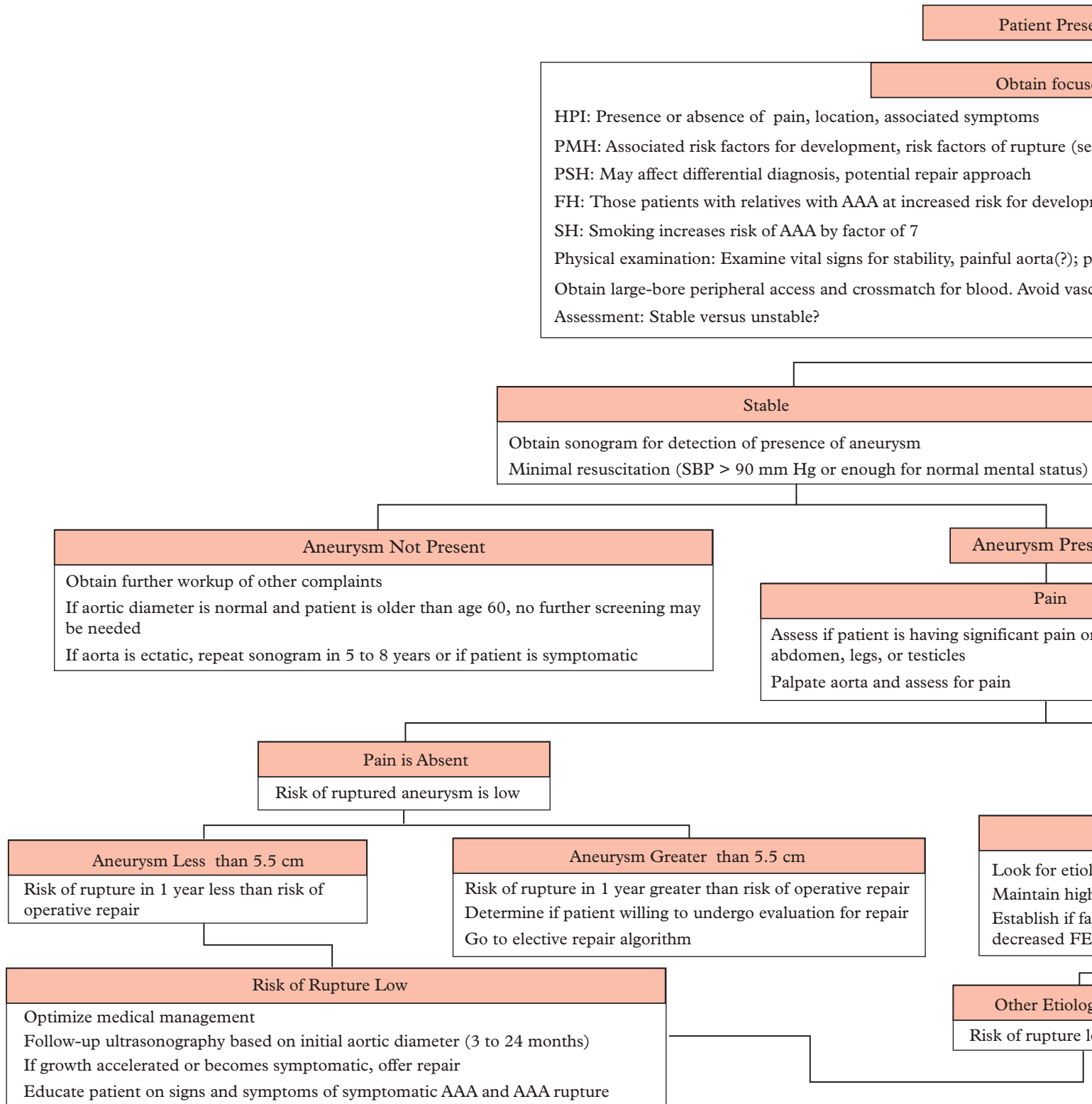


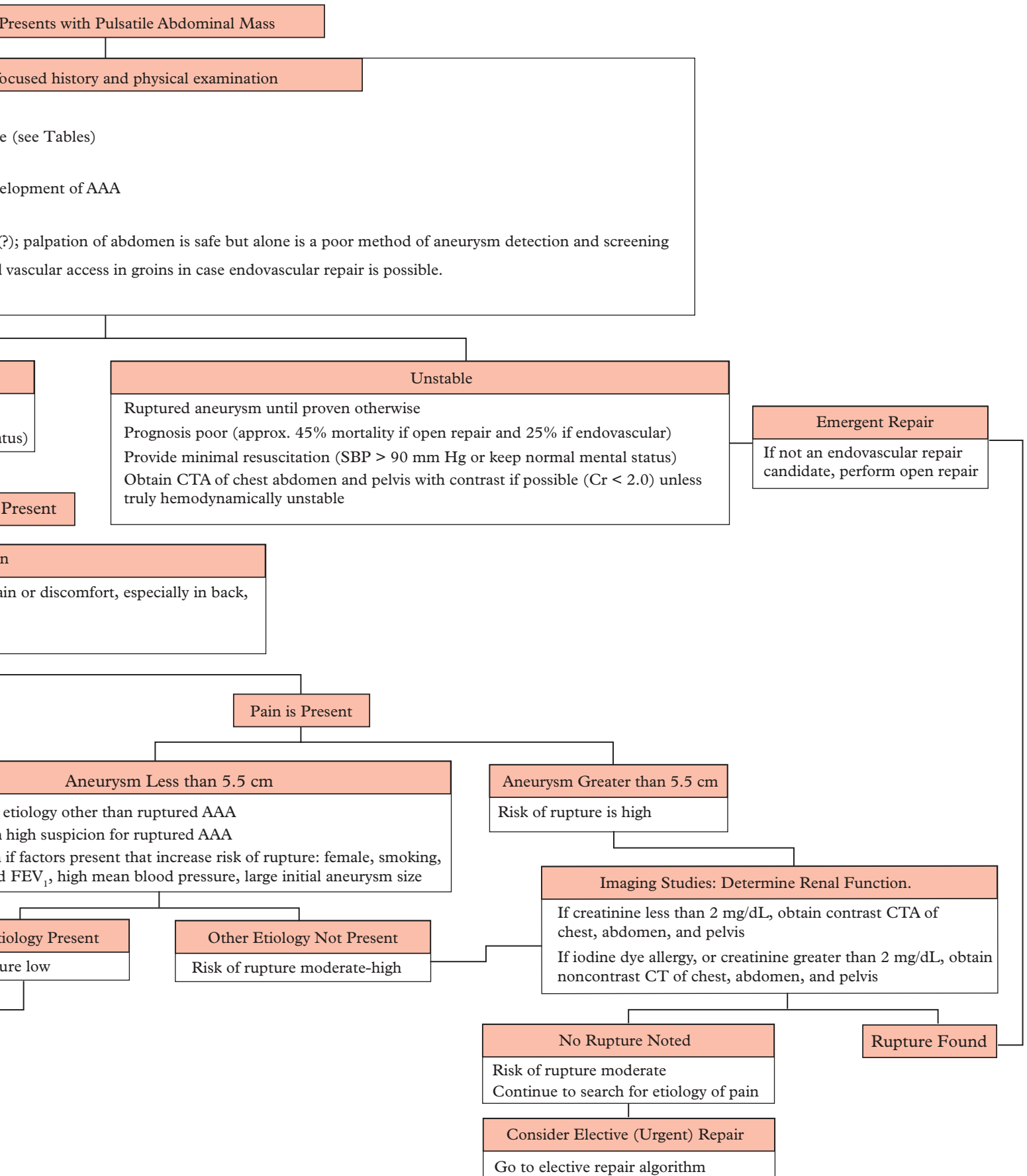
65% had calcification of the aneurysm that was visible on a plain abdominal radiograph.⁷ In addition, ultrasonography (US) and computed tomography (CT) are nearly 100% sensitive in detecting AAAs.⁸ In elderly patients, evaluation of the aorta should be routinely included in abdominal US; scanning of the aorta adds, on average, only 43 seconds to the study.⁹ If an AAA is unexpectedly found, either the patient is followed or the aneurysm is repaired, depending on the clinical situation and the size of the aneurysm (see below).

Ruptured AAAs, on the other hand, give rise to pronounced symptoms, and the patient's condition may range from hemodynamic stability to class IV shock. When the patient is unstable, further workup is unnecessary and emergency repair is indicated. The situation is less clear when the patient is stable, albeit without normal vital signs. The traditional presentation of a ruptured AAA is a triad comprising hypotension, back or abdominal pain, and a pulsatile abdominal mass. Unfortunately, this traditional presentation occurs less than half of the time. In a study of 116 patients with ruptured AAAs, 45% were hypotensive, 72% had pain, and 83% had a pulsatile abdominal mass.¹⁰ Accordingly, it is essential not to be lulled into a false sense of security when evaluating a hemodynamically stable patient with a pulsatile abdominal mass. Although a ruptured AAA is an uncommon event in a patient with a stable blood pressure and no abdominal pain, the absence of these symptoms does not rule out the possibility. Another misleading scenario occurs when a patient arrives at the hospital several days after the rupture complaining of unrelenting back or abdominal pain and this is disregarded for a musculoskeletal etiology. Bruising may be seen around the pubis, which represents blood in the retroperitoneum that has been there long enough to diffuse to the skin.

Symptomatic or ruptured aneurysms can mimic many other acute medical conditions and therefore are part of multiple differential diagnoses. The following conditions all may be confused with ruptured aneurysms: (1) perforated viscus, (2) mesenteric ischemia, (3) strangulated hernia, (4) ruptured visceral artery aneurysm, (5) acute cholecystitis, (6) acute pancreatitis, (7) acute appendicitis, (8) ruptured necrotic hepatobiliary cancer, (9) lymphoma, and (10) abscess. One must remember that patients with risk factors for AAA are at high risk for other cardiovascular diseases [see History, below]. A potentially lethal mistake is to rush to operate on a patient who has an AAA that presents with chest pain and hemodynamic instability without considering that the pain and instability may all be attributable to an acute myocardial infarction (MI) or pulmonary embolus rather than a nonruptured AAA. Therefore, care must be taken to thoughtfully and expeditiously evaluate patients with this constellation of signs and symptoms. Fortunately, misdiagnosis of a ruptured AAA is rare, and most patients who make it to the emergency department will allow enough time to undergo proper imaging prior to having to undergo resection.^{11,12} One

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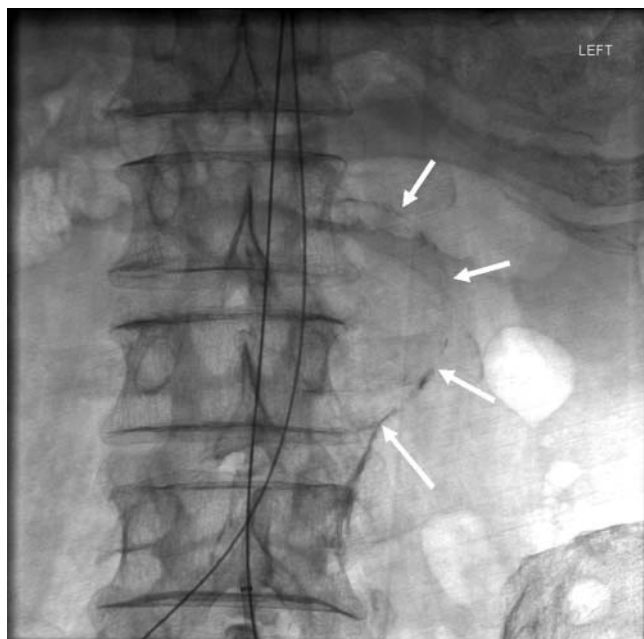


Figure 1 Plain abdominal x-ray for the diagnosis of aneurysms. Noncontrast x-ray film of the abdomen demonstrating the calcified outline (arrows) of an abdominal aortic aneurysm.

should be exceptionally skeptical of an aneurysm being the cause for instability if the aneurysm is small (< 5 cm). Most patients who do undergo an operation for a misdiagnosis either benefit from or at least are not harmed by the operation as most abdominal catastrophes may benefit from surgical exploration. This alleviates some potential concerns about taking an aggressive approach to a suspected ruptured AAA.¹³ Conversely, AAAs can mimic other disease processes. In one study, nearly one in five patients with symptomatic AAAs in an emergency department were originally diagnosed as having nephroureterolithiasis.¹⁴ Patients who have urologic symptoms, but whose urinalysis is normal, may benefit from an AAA workup; radiologic evidence of ureteral involvement is present in as many as 71% of AAAs.¹⁵

HISTORY

The patient's medical history may be helpful in determining the patient's level of risk for an AAA. Even in the absence of clinical symptoms, knowledge of the risk factors may facilitate earlier diagnosis. The Aneurysm Detection and Management Veterans Affairs Cooperative Study Group trial (commonly referred to as the ADAM trial) found a number of factors to be associated with increased risk for AAA: advanced age, greater height, coronary artery disease (CAD), atherosclerosis, high cholesterol levels, hypertension, and, in particular, smoking.¹⁶ The risk was lower in women, African Americans, and diabetic patients.

AAAs occur almost exclusively in elderly males and are rarely seen in patients younger than 50 years of age. In a 2001 study, the mean age of patients undergoing repair for AAAs in the United States was 72 years.⁵ Male patients outnumber female patients by a factor of 4:1 to 6:1 depending on the study cited.^{5,17–20} The family members of patients with an

AAA are also at significant risk: 12 to 19% of persons undergoing AAA repair have a first-degree relative with an AAA.^{21–23} Accordingly, screening is recommended in all men and women older than 50 years who have a family history of AAA.²⁴ AAAs are over seven times more likely to develop in smokers than in nonsmokers, with the duration of smoking, rather than total number of cigarettes smoked, being the key variable [see Table 1].²⁵

Of particular importance is identification of risk factors for rupture. The United Kingdom Small Aneurysm (UKSA) trial reported 103 AAA ruptures in 2,257 patients over a period of 7 years, with an annual rupture rate of 2.2%. The factors found to be significantly and independently associated with an increased risk of rupture were female sex, a larger initial AAA diameter, a lower forced expiratory volume in 1 second (FEV₁), a current smoking habit, and a higher mean blood pressure.^{25,26} Women are two to four times more likely to experience rupture of an AAA than men are.²⁷ In a small cohort of 18 patients with aneurysmal aortas greater than 3.5 cm who underwent cardiac and abdominal organ transplantations, seven (41%) of the untreated aortas ruptured and the average growth rate was 1 cm per year. The smallest diameter of a ruptured aorta was 5.1 cm and the mortality of a rupture was 71%. As all eight patients who underwent elective repair survived, aggressive treatment of AAA in patients with or considered for transplantation may be warranted.²⁸

The patient's surgical history is also crucial, particularly in that it can shorten the differential diagnosis at presentation by ruling out disease processes (e.g., appendicitis and cholecystitis). In addition, the nature and extent of any previous abdominal procedures may influence the surgeon's operative approach to the AAA repair. When a pulsatile abdominal mass is discovered in a patient who previously underwent open repair of an AAA, it is important to remember that anastomotic pseudoaneurysms²⁹ or synchronous lesions (e.g., iliac artery aneurysms³⁰) can occur at sites remote from the previous repair.

Patients who have undergone endovascular AAA repair may also present with symptoms in the presence or absence of an endoleak. In a 2002 review, most ruptures after endovascular AAA repair occurred with type I endoleaks (lack of a seal with the proximal or distal seal zone of the graft).³¹ This clinical scenario is well described and can present as a new pulsatile abdominal mass if the endograft migrates into the aneurysm sac and no longer excludes blood flow from it [see Figure 2].^{31–33} When this occurs in the proximal seal zone

Table 1 Risk Factors Associated with AAA Development

Factors positively associated with development of AAA

- Increased age
- Increased height
- Coronary artery disease
- Any atherosclerosis
- High cholesterol levels
- Hypertension
- Smoking
- Male sex
- Family history (first-degree relative)

Factors negatively associated with development of AAA

- Female sex
- Black race
- Presence of diabetes

AAA = abdominal aortic aneurysm.

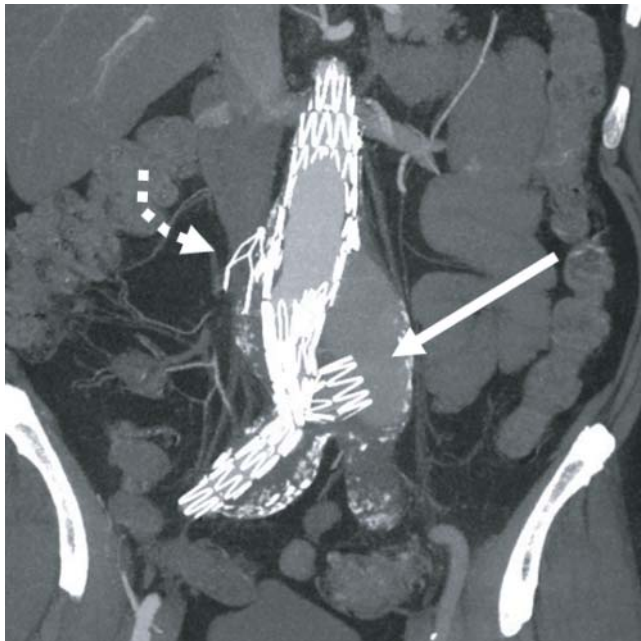


Figure 2 Type Ib endoleak. A patient who was not followed after placement of an aortic endograft presented with reappearance of a palpable, pulsatile mass. This was secondary to the left limb of the graft migrating into the aneurysm sac (solid arrow) and returned blood pressure into the aneurysm. Broken arrow indicates an unassociated inferior vena cava filter.

(type Ia endoleak), then blood flows into the sac and has limited outflow, so the risk of rupture may be significant. Type Ib endoleaks occur when the distal fixation site is not sealed and blood flows back into the sac from the graft and may occur from migration of the limb into the aneurysm after deployment. The operative mortality in patients with previous endografts who subsequently rupture is 41% (just like a rupture de novo).²⁹ Overall, however, the risk of rupture after endovascular repair is small,³¹ and over time, survival is no different from that of open repair, although patients will likely undergo several reinterventions during their lifetime.³⁴

PHYSICAL EXAMINATION

Before the advent of modern radiologic tests, the abdominal examination was the key to detecting an AAA. The abdominal aorta begins at the level of the diaphragm and the 12th thoracic vertebra and runs in the retroperitoneal space just anterior to and slightly to the left of the spine. At approximately the level of the umbilicus and the fourth lumbar vertebra, it bifurcates into the right and left common iliac arteries. In young, thin individuals, the abdominal aorta runs close to the surface of the abdomen and thus can often be palpated during a normal physical examination. Conversely, in thin patients with AAAs, the aneurysm can also be seen pulsating and deforming the contour of the abdomen [see Figure 3]. Palpation of an AAA is safe and has not been reported to precipitate rupture. A 1997 report found, however, that only 31% of the AAAs studied at a major teaching institution were initially detected by physical examination.³⁵ Nonaneurysmal common iliac arteries also are often difficult to palpate, even in thin individuals. Placing a stethoscope on

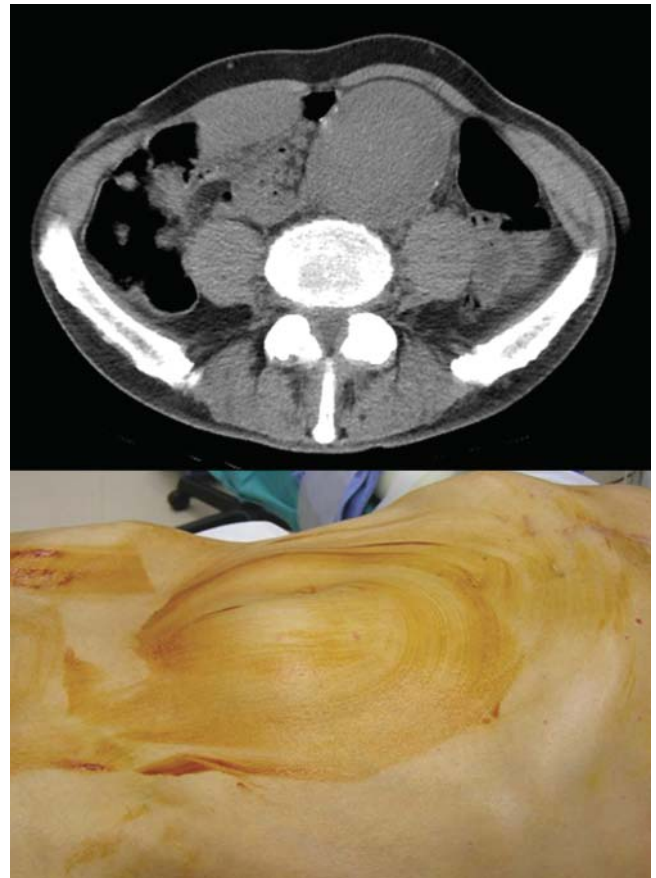


Figure 3 Visible, palpable abdominal mass. *Top:* Axial computed tomographic scan of the abdomen demonstrating how an abdominal aortic aneurysm can deform the abdominal wall in a thin patient. *Bottom:* Photograph of the same patient demonstrating the visible deformity of the anterior abdominal wall.

the abdomen may also detect bruits (manifestations of turbulent blood flow) that may be due to either an aneurysm or from stenosis of visceral arteries—both of which may require some intervention even though it may not be emergent.

There are several methods of conducting a proper physical examination of the abdominal aorta. Our preferred approach resembles that of Lederle and Simel³⁶:

1. Have the patient lie supine with the knees raised. Encourage the patient to relax the abdomen. A relaxed abdomen is often obtainable with passive exhalation after a deep inhalation.
2. Beginning a few centimeters cephalad to the umbilicus and just to the left of the midline, palpate deeply for the pulsation of the aorta.
3. To confirm that the aorta is being palpated, place both hands on the abdomen with the palms down in such a way that the pulsation is between the tips of the index fingers. The index fingers should move apart with each heartbeat.
4. Once it is certain that the index fingers are bracketing the aorta, estimate the diameter of the aorta by measuring the distance between the fingertips, taking into account the thickness of the overlying tissue. When evaluating a patient for a possible symptomatic (painful) aneurysm, holding the aorta will be painful and may further strengthen the

diagnosis even before any adjuvant imaging. Although this is not specific for a symptomatic AAA, if compressing the aorta itself is not painful, then the etiology is likely elsewhere.

Unfortunately, physical examination is not very accurate in detecting AAAs: in one study, approximately 62% of known AAAs were missed.³⁷ Whether an AAA is detectable on physical examination alone depends primarily on the size of the aneurysm. AAAs more than 5 cm in diameter are detectable on physical examination in 76% of the population, whereas those 3 to 3.9 cm in diameter are detectable in only 29%. Palpation of an AAA 3.0 cm in diameter or larger has a positive predictive value of only 43%.³⁶ In addition, detection of AAAs is significantly limited by truncal obesity.^{38,39} Thus, physical examination is clearly insufficient for ruling out or screening for AAAs, but performing a complete abdominal examination will assist in discovering any other sources of pain.^{36,39}

In the past, it was considered important to measure the abdominal aorta accurately by means of physical examination. Several studies have been published comparing US, the currently preferred screening method, with physical examination.^{38,40} One such study found that abdominal palpation had a poor (14.7%) positive predictive value for detecting AAAs greater than 3.5 cm in diameter.⁴⁰ At present, with the wide availability of ultrasound screening, physical examination is playing a smaller role in AAA detection.

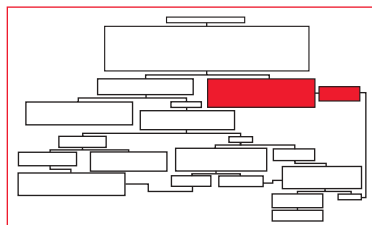
Although most AAAs appear supraumbilically, not all pulsatile abdominal masses appear there. In some patients, the abdominal aorta becomes more tortuous and elongated with age. As a result, an AAA may appear infraumbilically or to one side of the abdomen or the other. The abdominal portion that is palpable may also be part of a thoracoabdominal aneurysm for which full imaging of the chest and abdomen is necessary to evaluate the aorta in its entirety. The iliac arteries may become aneurysmal and become palpable in the lower quadrants of the abdomen independently or simultaneously of an aortic aneurysm [see Figure 4].⁴¹

Another indication that an AAA may exist is the presence of a femoral or popliteal artery aneurysm on physical examination. A patient with a femoral artery aneurysm has an 85% chance of having a concomitant AAA, and a patient with a popliteal artery aneurysm has a 62% chance.^{42,43} Conversely, in a study evaluating 251 patients with documented AAAs, 14% had either a femoral or a popliteal artery aneurysm.⁴⁴ There is a significant male predominance, for unknown reasons.^{20,44,45} If a patient has a history of a AAA that was repaired with an endovascular graft and subsequently has a palpable abdominal mass, then you must suspect that the graft may have failed and repressurized the aneurysm and therefore needs emergent repair.

Indications for Emergency Repair versus Further Workup

PATIENT IS UNSTABLE

If a patient presents with a painful, pulsatile abdominal mass and is truly unstable, no further study or workup is necessary provided that there



is no suspicion of acute MI as the cause: the diagnosis, until proved otherwise, is a ruptured AAA, and the patient should be taken to an operating room with angiographic capabilities. Patients who have stable (but not necessarily normal) vital signs may undergo a computed tomographic angiography (CTA) scan of the abdomen, which will greatly assist not only the diagnosis but also operative planning. The only cure for a ruptured AAA is some sort of emergency repair. Indeed, before the endovascular era, when all patients experiencing a ruptured AAA are taken into account, including both those who arrive at the hospital alive and those who do not, overall mortality is still between 77 and 94%, with over 50% of patients expiring before reaching the hospital.^{46,47} Most ruptured AAAs leak into the left retroperitoneum, which may tamponade the bleeding and is referred to as a “contained” rupture.⁴⁵ AAAs that rupture freely into the abdominal cavity usually result in death, either at home or en route to the hospital as the volume of blood that can flow into the peritoneum before tamponading is usually lethal. For all patients who have an open repair for a ruptured AAA, the expected mortality exceeds 50% for open repair⁴⁸ (although values as low as 15% and as high as 90% have been noted⁴⁹). Mortality after a ruptured AAA has declined since the middle of the 20th century by approximately 3.5% per decade; however, most modern series will report a mortality close to 41% for open repair of ruptured AAA.⁵⁰ Although some suggest that patients with predictably high morbidity and mortality from a ruptured AAA may not benefit from open repair,⁴⁹ most would still maintain that even in this population, this presentation necessitates operative intervention unless the patient or family feels strongly against it.⁵¹ The high cost of repair and the substantial operative mortality notwithstanding, surgical repair of ruptured AAAs appears to be cost-effective in comparison with no intervention.⁵² Thus, cost should not be considered in the management of patients with AAAs, and endovascular repair of ruptured aneurysms may change this paradigm.

Endovascular repair is rapidly becoming the standard of care for ruptured AAAs since the first report by Yusuf and colleagues in 1994.⁵³ This technique is rapidly becoming standard of care in all patients because the mortality is approaching half of that of open repair, with a dramatically shorter hospital stay. A 2003 study described endovascular repair of 29 ruptured AAAs and reported one of the lowest mortalities (only 11%).⁵⁴ As centers have begun to establish protocols for management and experience is much better, the average mortality of endovascular repair likely approaches 25 to 30%.⁵⁵⁻⁵⁷ The main benefit is that patients can quickly be stabilized and even treated with local anesthesia. This is accomplished by positioning aortic occlusion balloons above the aneurysm percutaneously, thus allowing the patient to be stable much faster than by using conventional, open techniques and, ultimately, be discharged home sooner.⁵⁶

PATIENT IS STABLE

If a patient with a pulsatile abdominal mass is medically stable, further workup is always indicated. As noted, ultrasound imaging is significantly more accurate in detect-



ing an AAA than physical examination alone.⁴⁰ Duplex US is used extensively as a primary screening tool for evaluating the size of an abdominal aorta because of certain advantages it possesses over other, more extensive modalities, such as CT,

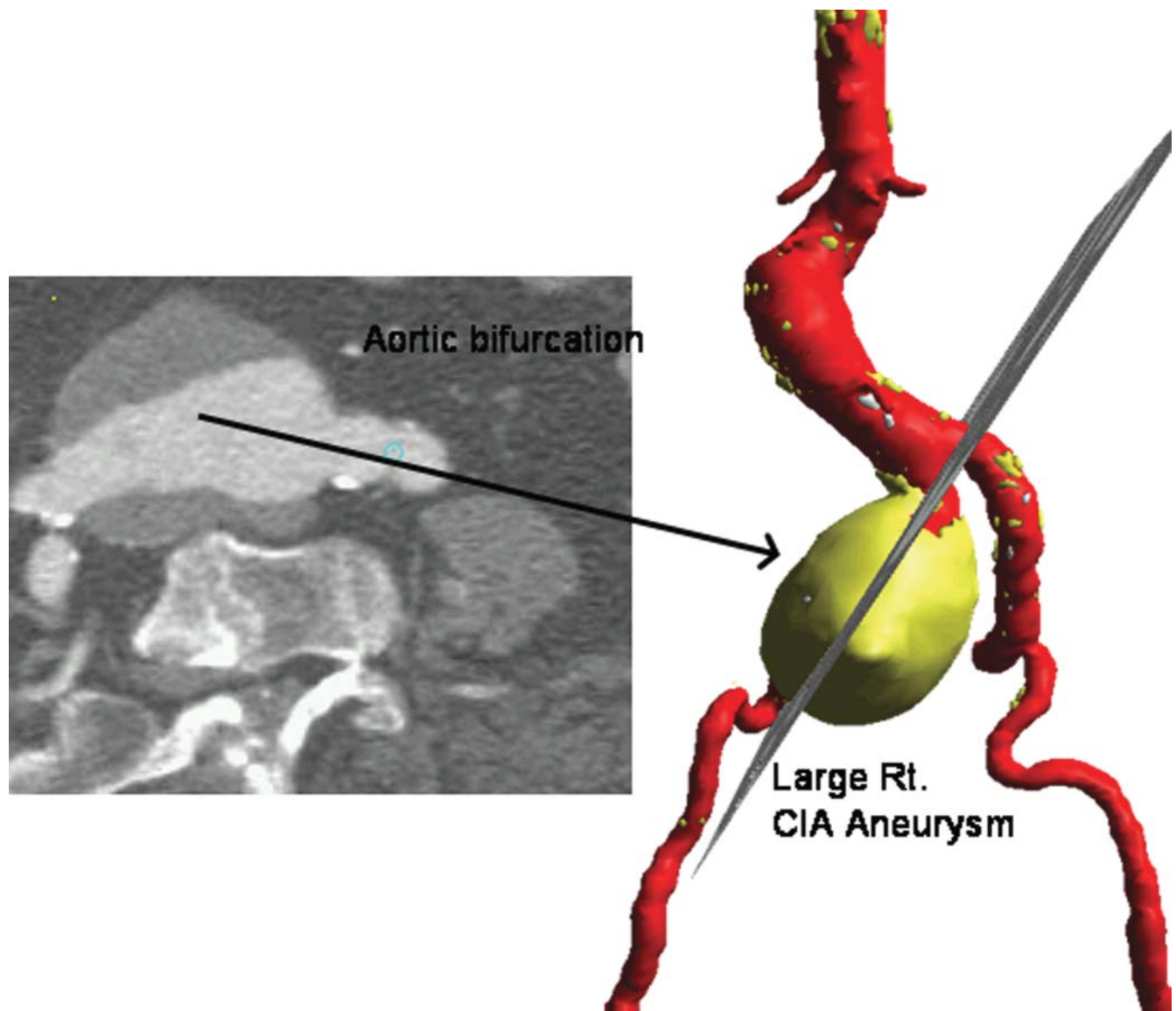


Figure 4 Right common iliac artery aneurysm. Axial and three-dimensional reconstructions of a computed tomographic angiogram of a right common iliac artery (CIA) aneurysm.

magnetic resonance angiography (MRA), and conventional angiography. Its main advantages are as follows: (1) it is noninvasive, (2) it is relatively inexpensive, (3) it does not require exposure to radiation, (4) it is portable, and (5) it is as reliable as the other modalities in determining aortic anterior-posterior (AP) diameter. Ultrasound-derived measurements are reproducible to within 3 to 5 mm,⁵⁸ and the interobserver variability is less than 5 mm in 84% of AP measurements.⁵⁹ On the other hand, in about 75% of cases, US underestimates the size of the aorta. A comparison study found that AAA diameter measurements were consistently and significantly larger with CT than with US (5.69 ± 0.89 cm versus 4.74 ± 0.91 cm).⁶⁰ It appears that when radiologists take more care with their measurements (e.g., by using magnifying glasses and calipers), the results correlate better.⁶¹

Ultrasound measurement of the infrarenal aorta and the common iliac arteries has been evaluated in patients with no

known vascular disease. In one study of patients older than 50 years (the age group in which abdominal aortic and iliac artery aneurysms are most common), the aorta measured 1.68 ± 0.29 cm in men and 1.46 ± 0.19 cm in women ($p < .001$).⁶² The common iliac arteries measured 1.01 ± 0.20 cm in men and 0.92 ± 0.13 cm in women. An aneurysm is commonly defined as a permanent localized or focal expansion of an artery to 1.5 times its expected diameter.⁴⁵ Thus, an infrarenal AAA would generally be considered to be approximately 3 cm in diameter if the average aortic diameter is 2 cm. It must be remembered, however, that infrarenal aortic diameter is affected by height, age, race, body surface area, and sex.⁶³⁻⁶⁵ An aneurysm should be differentiated from arteriomegaly and from arterial or aortic ectasia. Arteriomegaly is a diffuse enlargement of an artery by an amount that is at least 50% of the normal diameter; ectasia is an enlargement of an artery by an amount that is less than 50% of the normal diameter.⁶⁶

The main limitations of US are as follows: (1) the results are highly technician dependent and (2) resolution is dependent on body habitus and intestinal gas.⁴⁵ Another limitation is that it is unreliable in detecting rupture [see Figure 5]. Because US does not provide an accurate picture of the aorta proximal to the renal arteries and because it is subject to the limitations already mentioned, it cannot be routinely used to differentiate a ruptured AAA from a symptomatic intact AAA. If US is inconclusive in the evaluation of a palpable abdominal mass, then either CT or MRA (see below) is the next step [see Table 2].

Once a patient has either undergone screening US or if the patient is deemed to have a pathology that can be differentiated better by a CT scan, then fine-cut CTA will be the best imaging modality. In a patient with a pulsatile abdominal mass and back pain, CTA of the chest, abdomen, and pelvis will greatly assist in differentiating from most abdominal catastrophes that require surgery. Including the chest not only will assist in determining the proximal limit of the aneurysm (which may not be seen if only an abdominal CT scan is obtained and the patient has a thoracoabdominal aneurysm) but will also allow the surgeon to evaluate the aneurysm for possible endovascular repair. Knowing the complete extent of the aneurysm is also critical to appropriately choose the incision (thoracoabdominal, retroperitoneal, or midline laparotomy) if open repair is chosen. If the pelvis is not completely imaged, then potential issues with the iliac and femoral arteries could be missed. The major drawback of CTA is that it requires iodinated contrast, which may precipitate or worsen renal failure. This can be circumvented by even obtaining a noncontrast CTA of the chest, abdomen, and pelvis as this will again help differentiate some diagnoses (e.g., renal stones, free air, bowel obstruction) and also approximate the extent of the aneurysm and degree of calcification.

Management

STABLE PATIENT WITHOUT ANEURYSM

If imaging indicates that a patient with a pulsatile abdominal mass does not have an

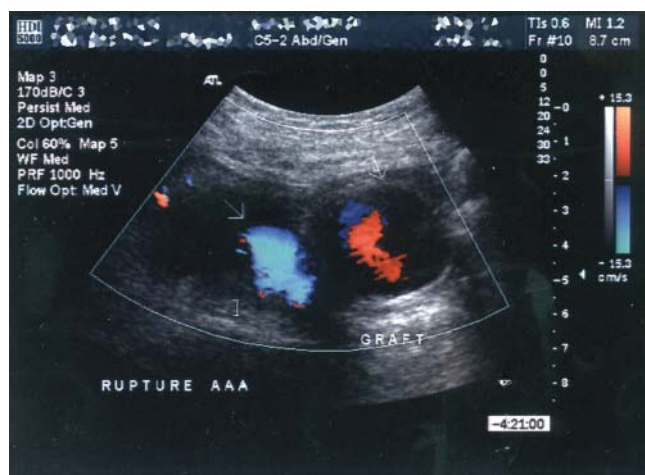
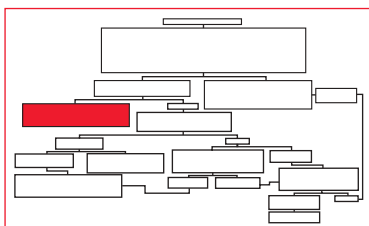


Figure 5 Ultrasound evaluation of ruptured aneurysms. Color duplex sonogram demonstrating turbulent flow outside an aortic graft wall consistent with extravasation from a ruptured iliac artery aneurysm.

aneurysm, the risk of aortic or common iliac artery rupture is very low. Consequently, if symptoms (e.g., abdominal pain) persist, another causative condition must be considered.

If arteriomegaly is found to be the cause of the pulsatile abdominal mass and there are no symptoms of occlusion, then no specific treatment is required. Routine ultrasonographic follow-up is indicated because the risk of rupture still applies as the aorta continues to expand. In one study, an aneurysm was present in 1.6% of aortas with arteriomegaly.⁶⁷ If aortic ectasia (large aorta less than 1.5 times the normal size—usually 2.5 to 3 cm) is found, follow-up US in 5 to 8 years is recommended.^{66,68} It has been suggested that for a 65-year-old man with a normal aortic diameter (defined as less than 2.2 cm), the risk that a significantly dilated aneurysm will develop during the remainder of his life is essentially zero.⁶⁹ The distinction between a normal and an ectatic aorta remains something of a gray area, and the preferred follow-up period remains controversial. In general, ectatic infrarenal aortas expand slowly and are not associated with rupture.⁶⁶

In the ADAM trial, independent and significant predictors of a new aneurysm on follow-up US included (1) current smoking (odds ratio 3.09), (2) coexisting CAD (1.81), and, in a separate model with composite variables, (3) any atherosclerosis (1.97).⁶⁸ Accordingly, when a patient has any of these risk factors, a lower threshold for follow-up US and a shorter period between examinations may be practical. When patients have a pulsatile mass without a dilated blood vessel, then malignancies or retroperitoneal lymph nodes that envelop surrounding blood vessels may transmit pulsations and explain this physical finding.

STABLE PATIENT WITH ANEURYSM

Once the diagnosis of an aneurysm is made in a stable patient, the subsequent course of action is determined by the clinical presentation and the size of the pulsatile abdominal mass. It must be emphasized that if the patient becomes hemodynamically unstable at any point during evaluation, operative intervention is necessary—unless the patient has a terminal condition or has indicated that nothing further should be done to prolong life.

If the patient is experiencing no discomfort and is otherwise stable, the risk of active rupture can be considered extremely low. On the other hand, if the patient is experiencing significant abdominal or back pain and discomfort, AAA rupture should remain a strong diagnostic possibility. Patients with AAA are also at risk for other cardiovascular diseases, so careful evaluation of the patient's signs and symptoms must be done to determine if the patient's presentation is attributable to the AAA or to something else.

Pain Is Absent

A patient with a pulsatile abdominal mass

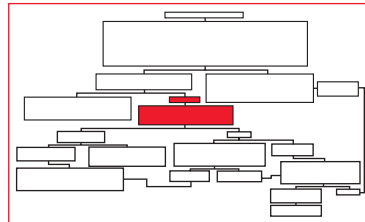


Table 2 Advantages and Disadvantages of Aortic Imaging Techniques

Imaging Modality	Advantages	Disadvantages
Ultrasonography	1. Noninvasive 2. Relatively inexpensive 3. Does not require radiation exposure 4. Portable 5. Comparable in reliability to other modalities in determining aortic diameter	1. Highly dependent on the skill of the operator 2. Resolution dependent on body habitus and amount of intestinal gas 3. Unreliable in the detection of AAA rupture 4. Poor visualization of the aorta proximal to renal arteries and distal to the iliac arteries 5. Cannot use it to plan operation
Computed tomography (CT)	1. Fast and easy to obtain 2. Highly precise measurements 3. Defines proximal and distal extent of AAAs precisely 4. Delineates the anatomy of the iliac arteries 5. Evaluates AAA wall integrity (notes location and amount of calcification and thrombus) 6. Effective at discovering venous anomalies, retroperitoneal blood, aortic dissection, inflammatory aneurysms, and other intra-abdominal pathology and anomalies 7. Can be done quickly and without contrast to plan for emergent endovascular repair of ruptured AAA	1. Radiation exposure 2. Generally requires iodinated contrast 3. More expensive than ultrasonography
Magnetic resonance angiography	1. Comparable to CT in preoperative evaluation 2. Can be obtained without contrast 3. Highly sensitive and specific in detecting stenoses of the splanchnic, renal, and iliac arteries	1. Not widely available 2. The most expensive 3. Potential claustrophobia in select patients 4. Longer scan time 5. Contraindicated in patients with certain metal foreign bodies (even some endografts)
Angiography	1. Superior in evaluating • Intraluminal characteristics of the aorta • Determining visceral branch involvement • Delineating variations in vascular anatomy 2. Can be done during aortic endograft placement	1. More expensive than CT (3–4 times) 2. Multiple risks, including • Arterial injury • Distal embolization • Local arterial dissection • Risk of renal failure secondary to contrast 3. Only shows luminal characteristics and not mural thrombus or aortic wall diameter

AAA = abdominal aortic aneurysm.

who has a known AAA and who is hemodynamically stable without complaints of pain should be further categorized on the basis of the size of the aneurysm. This categorization is traditionally based on the physics of an expanding aneurysm and on the association between increased risk of rupture and increased aneurysm size. The key considerations in these patients are (1) whether the risk associated with AAA repair exceeds the risk of rupture in a given period and (2) what other factors are present that may affect this decision.

Indications for operative intervention The physics of aneurysm expansion and rupture are probably best understood via the law of Laplace,⁹ according to which the tangential stress (t) placed on a cylinder filled with fluid (e.g., a blood vessel) is determined by the equation

$$t = Pr/d$$

where P is the pressure (dynes/cm²) exerted by the fluid, r is the internal radius (cm) of the cylinder, and d is the thickness (cm) of the cylinder wall. When the aorta expands, its radius increases, whereas its wall thickness decreases; thus, there is a geometric increase in tangential stress. As an aneurysm grows from 2 to 4 cm in diameter, tangential pressure increases not twofold but fourfold. When the increased tangential stress exceeds the elastic capacity of the wall, rupture occurs. Elastic tissue in the

abdominal aorta becomes attenuated as a result of age and of certain acquired and genetic factors; thus, a modest degree of expansion over time is not uncommon. An abnormal rate of expansion is usually considered to be greater than 5 mm/yr. Documentation of an accelerated aneurysm growth rate should cause the surgeon to give serious consideration to operative intervention.⁴⁵

The decision on when to operate on patients with AAA began with autopsy studies of individuals with aneurysms who did not have surgery.⁷⁰ These autopsy studies also paved the way to try to confirm if it is true that the larger the aneurysm, the higher the risk of rupture and that patients with ruptured aneurysms may live hours to weeks prior to having surgery.¹¹ This conclusion has been challenged by studies using three-dimensional CT to evaluate wall stress via a mathematical technique called finite element analysis.^{71–73} In these studies, maximal wall stress was a better predictor of rupture than maximal AP diameter was. For example, one patient with a ruptured 4.8 cm aneurysm had a wall stress equivalent to that of a patient with an electively repaired 6.3 cm AAA.⁷² Future management of AAAs may be based on actual wall stress in addition to maximum AP diameter.

In a 2001 study addressing open operative repair of intact AAAs, increased mortality was associated with increased patient age, female sex, cerebrovascular occlusive disease, preoperative

renal insufficiency, and the presence of more than three comorbid conditions before operation.⁵ In the UK Small Aneurysm Trial, the 30-day mortality in patients undergoing elective open AAA repair was 5.8%.⁷⁴ The point at which the risk of elective repair became acceptable in relation to the risk of rupture with medical management and serial ultrasonographic follow-up was an aneurysm diameter of 5.5 cm. The investigators suggested that in patients with AAAs less than 5.5 cm in diameter, medical management is the best course of action. The operative mortality reported in this study is considered high in that many single-center series have documented mortalities of 1 to 3% after open repair of intact AAAs.⁷⁵⁻⁷⁷ The ADAM investigators also found that survival was not improved when AAAs smaller than 5.5 cm were repaired electively, even if a low operative mortality was associated with the procedure.⁷⁷

Hospital volume may have a significant effect on patient outcome after elective AAA repair. A 2002 study found that mortality after this procedure was 56% higher at low-volume hospitals than at high-volume hospitals.⁷⁸ Moreover, mortality after repair of an intact AAA exhibited a ninefold variation that could be attributed to hospital volume, sex, and age alone. Thus, when a patient is being evaluated for AAA repair, it is important to take into account not only the size of the aneurysm but also age, sex, comorbidities, and hospital volume. In turn, more than half of the effect of hospital volume on operative mortality in elective AAA repair appears to be mediated by surgeon volume.⁷⁹ Surgeon specialty also appears to affect operative mortality after elective AAA repair.⁸⁰ Outcomes of endovascular repair of ruptured AAAs compared to open repair in the United States using the National Inpatient Sample database documented that the mortality is more than double if the procedure is done at smaller-volume and nonteaching hospitals (55% versus 21%). The outcomes of endovascular repair in teaching hospitals for ruptured aneurysms were even better than those of elective endovascular repair in nonteaching hospitals, all of which strongly support regionalization of AAA repair.⁸¹⁻⁸³

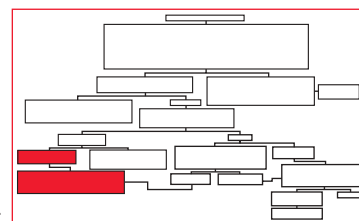
Given the various possible complicating factors, it is clear that no single aortic diameter can serve as a definitive indication for operative intervention in every patient. It is well known that ruptures can occur unpredictably at aneurysm diameters smaller than 5.5 cm.⁸⁴ Therefore, the timing of AAA repair must be individualized, with the 5.5 cm figure serving as a general guideline in the counseling of patients.

Age has been shown to increase the risk of operative mortality in patients undergoing open repair. The overall operative mortality after elective, open repair of AAA is reported by most series to be less than 5%. However, in the Nationwide Inpatient Sample, if the patients were less than 60 years old, it was 2.2%, whereas it was 9.2% in patients over 80 years old.⁸² With regard to endovascular repair, mortality in Medicare patients (all over 65 years old) demonstrated an early mortality benefit in endovascular repair that was consistently better than open repair regardless of the age of the patient, even in those over 85 years of age.³⁴ Regardless of the technique used, advanced age, terminal conditions, and various end-of-life issues may deter patients from wishing to proceed with operative intervention. In addition, severe coexisting diseases significantly affect the morbidity and mortality associated with AAA repair.^{48,85} Accordingly, older patients with multiple comorbidities may be preferentially offered endovascular AAA approach in place of open repair.³² The surgeon must, however, consider the possibility that any operative intervention will be too risky in this population or

that other interventions must be carried out before AAA repair can be attempted. These issues should be addressed via appropriate preoperative evaluation [see Figure 6].

Small AAAs (< 5 cm): medical management and follow-up

When a patient with stable vital signs and no abdominal pain is diagnosed as having a small AAA, serial US and optimization of



medical management are indicated.^{86,87} Small AAAs usually do not rupture.^{26,77,86-88} Most small AAAs continue to grow, however, typically by 0.2 to 0.4 cm in diameter per year.⁷⁸⁻⁸⁰ Small AAAs can also expand rapidly with unpredictable frequency. A rapidly expanding AAA is at high risk for rupture, regardless of how small it may be.^{74,77,88,89}

Many risk factors have been identified that may affect the risk of small aneurysm expansion and rupture. For example, one study suggested that diastolic hypertension and chronic

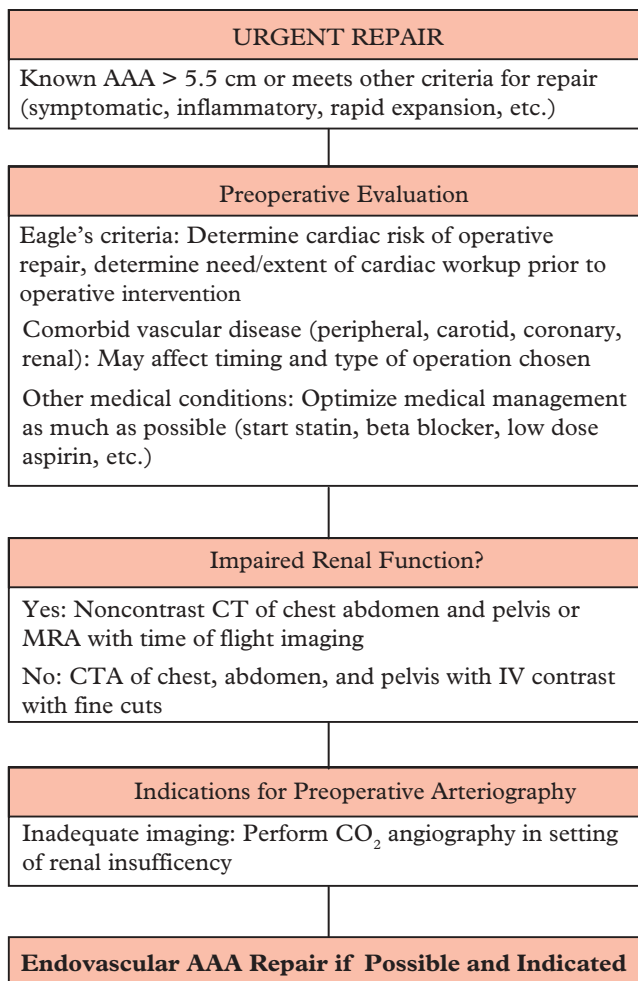


Figure 6 Algorithm for urgent repair of abdominal aortic aneurysm (AAA). CT = computed tomography; CTA = computed tomographic angiography; MRA = magnetic resonance angiography; IV = intravenous.

obstructive pulmonary disease (COPD) increased the risk that a small AAA would rupture,⁸⁴ whereas another found advanced age, severe cardiac disease, previous stroke, and a history of cigarette smoking to be risk factors for rapid expansion.⁸⁸ AAAs smaller than 5.5 cm may rupture more frequently in women than in men. A 2002 study found that in almost one quarter of women with ruptured AAAs, the diameter of the aneurysm was less than 5.5 cm at the time of rupture.⁴⁷ Currently, the safest and easiest method of following small AAAs is serial US.^{14,90} When the diameter of an AAA approaches 5.5 cm, a more detailed study (e.g., CT or MRA) is indicated if repair is being considered.⁴⁵

Over the past several decades, the number of AAAs (especially smaller ones) detected has increased.⁹¹ This increase has been attributed to two causes: (1) increased serendipitous detection in the course of scans done for other indications and (2) the progressive aging of the population.^{45,91} There is growing evidence worldwide^{92,93} that early screening is cost-effective.^{24,94} The U.S. Preventive Services Task Force recommends screening all males 65 to 75 of years who smoked more than 100 cigarettes. This is supported by both Medicare and the Veterans' Administration (among others). Other groups who perhaps will benefit from screening are individuals who have a family history of AAAs.

Basic science studies have helped elucidate the etiology of AAAs in greater detail. In particular, current research is focusing on (1) evaluating the role various proteolytic enzymes, such as matrix metalloproteinases (MMPs), play in processes involving the structural elements in the aortic wall; (2) investigating the importance of the immune system, specifically the macrophage, in the development of AAAs; (3) determining how hemodynamic and biomechanical stress affects aortic wall remodeling; and (4) identifying molecular genetic variables that contribute to AAA development.⁹⁵

Proteolytic enzymes are currently being evaluated as potential predictors of the course of AAA growth.⁹⁶ Doxycycline, which decreases MMPs in animal aneurysm models independently of its antibiotic properties, was evaluated in a prospective, randomized phase II trial published in 2002.⁹⁷ Although it did not exert a significant effect on aneurysm growth over the short study period (6 months), doxycycline significantly reduced serum levels of MMP9, a gelatinase that plays a central role in degrading elastin and collagen in the abdominal aortic wall. Few side effects were noted, and most of them were easily reversible. These findings, although not conclusive, suggest that the use of doxycycline may one day prove to be a viable medical means of slowing AAA growth.

Control of hypertension would seem to be an obvious approach to medical control of aneurysms as hypertension is a significant risk factor for both development and rupture of AAAs.^{20,27,84,87} To this end, various antihypertensive agents, including beta blockers, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors, have been evaluated in patients with AAAs.²⁵ The results have been somewhat equivocal and continue to be evaluated.

Beta blockers have been shown to reduce the expansion rate of large AAAs (> 5 cm) but not that of smaller AAAs.^{98,99} Some of them (e.g., propranolol) may be poorly tolerated at high doses.^{98,99} In addition, beta blockers may be contraindicated in patients with severe COPD, although as many as

11% of COPD patients have AAAs.²⁶ A 1999 study suggested that receiving a calcium channel blocker was an independent risk factor for the presence of an AAA (odds ratio 2.6).²⁵ The same study also noted, however, that patients receiving calcium channel blockers had stiffer aortic walls. ACE inhibitors, in contrast, were associated with decreased aortic wall stiffness and increased collagen turnover, whereas diuretics and beta blockers had no effect on aortic wall stiffness. None of the medications examined were found to affect the growth rate of AAAs. Aortic stiffness appears to be an important variable: increased aortic wall distensibility is associated with an increased risk of AAA rupture and is almost as powerful a predictor of rupture as actual AAA diameter.¹⁰⁰

A link between COPD and AAAs is suggested by the presence of a common development pathway: both conditions are associated with elastin breakdown and smoking. A 1999 study argued, however, that the strong association between AAAs and COPD was most likely attributable to coexisting cardiovascular disease and medications.²⁶ In this study, the average annual aortic diameter expansion rate was 4.7 mm in patients who used oral steroids but only 2.6 mm in those who did not. The use of beta-adrenergic agonists was also a positive predictor of aneurysm expansion. Thus, oral steroids and beta agonists must be used cautiously in COPD patients who have AAAs. If an AAA patient must use one of these medications, close follow-up is indicated to monitor the expansion rate of the aneurysm.

Atherosclerosis is associated with AAAs but is currently believed to be a secondary phenomenon, with inflammation and matrix-degrading enzymes being the primary factors in AAA development.¹⁰¹ Lipoprotein (a) has been found to be an independent risk factor for atherosclerosis and is elevated in patients with AAAs independently of the patients' cardiovascular risk factors or the extent of atherosclerosis.¹⁰² It seems reasonable that lowering lipid levels would decrease the development of atherosclerosis of the abdominal aorta. This is a potentially important effect because patients with small atherosclerotic AAAs often experience thrombotic complications involving the lower extremities.¹⁰³ Levels of apolipoprotein A-I and high-density lipoproteins have also been found to be significantly lower in patients with AAAs.¹⁰⁴ Overall, however, lipids appear to play only a minor role in AAA progression.¹⁰⁵ An animal study suggested that regression of plaque by lowering serum lipid levels after atherosclerotic aneurysm formation may result in increased aneurysm dilation in the abdominal aorta.¹⁰⁶ A subsequent study, however, demonstrated that statins reduce the production of MMPs in the wall of AAAs.¹⁰⁷ The role of lipid-lowering medications in the treatment of AAAs remains to be clarified. Elevated levels of homocysteine in the blood are a recognized independent risk factor for atherosclerosis, and a study of AAA patients has found significantly higher levels of plasma homocysteine, along with lower levels of vitamin B₁₂.¹⁰⁸ Given this finding, and the possible role of vitamin B₁₂ in homocysteine regulation, use of supplemental vitamins may theoretically modify AAA progression.¹⁰⁸

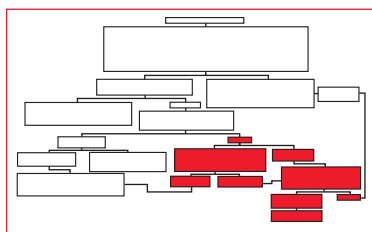
Smoking is an independent risk factor for AAA development,^{20,68} expansion,^{88,105} and rupture.²⁷ Current smokers are 7.6 times more likely to have an AAA than nonsmokers are, and ex-smokers are three times more likely to have an AAA.²⁵ The duration of smoking is the key variable^{16,20,25}; the relative

risk of AAA development is increased by 4% for each year of smoking.²⁵ The ADAM trial noted that a longer interval since the cessation of smoking was significantly associated with a decreased risk of AAA formation¹⁶; however, the decline in risk appears to be slow.²⁵ The UKSA trial showed that former smokers were at lower risk for death from AAA repair than current smokers were.⁷⁴ A 2002 study found that there was an independent association between smoking and high-grade tissue inflammation in AAAs,¹⁰⁹ lending support to the idea that smoking is an initiating event in AAA formation.

At present, intriguing possibilities notwithstanding, few definitive recommendations can be made regarding the use of medical therapy to reduce AAA growth. The indications for perioperative beta blockade are primarily cardioprotective. Administration of antihypertensives may be beneficial from a practical perspective, but current level I data supporting this practice are lacking. If an antihypertensive is given, the choice of agent should be based on associated clinical data (e.g., the presence of coexisting medical conditions, such as angina or renal insufficiency, whose management must be optimized). The administration of lipid-lowering drugs to patients with AAAs also requires further study, although the utility of such agents in the presence of CAD, which is found in almost 50% of AAA patients,¹¹⁰ is well documented, and long-term statin use after successful AAA surgery has been associated with reduced mortality (both all-cause and cardiovascular).¹¹¹ Finally, smoking cessation is clearly mandatory.

Pain Is Present

When a patient presenting with a pulsatile abdominal mass is hemodynamically stable but complains of pain in the abdomen, the back, the testicles, or the femoral



region, the index of suspicion must be high for a symptomatic or ruptured AAA. Other possible causes should be considered as well. As previously noted above, many abdominal processes may mimic an AAA; however, it is important that recognition of an AAA not be delayed unduly, because the length of the interval between the onset of symptoms and subsequent diagnosis and operation may have a direct bearing on overall survival. The size of the aneurysm is helpful for identifying patients at highest risk for rupture.

In stable patients with AAAs larger than 5.5 cm who are experiencing pain, either CT (faster and more available) or MRA (slower but without contrast nor radiation) may be used to detect AAA rupture; the choice typically depends on the patient's medical history and degree of stability [see Figure 6].

After ultrasound evaluation, if an aneurysm smaller than 5.5 cm was found and no associated risk factors for rupture were identified, a search for other possible causes of the pain is reasonable, provided that it is performed expeditiously.

If no other cause for the pain can be found, inflammatory aneurysms or rupture should remain prime considerations, and the next step in evaluation—namely, spiral CTA or MRA—should be implemented. Missing or delaying the diagnosis of a ruptured AAA can be disastrous. If retroperitoneal blood is noted [see Figure 7], then the patient should be taken to an operating suite with fluoroscopic capabilities. If the aneurysm is not

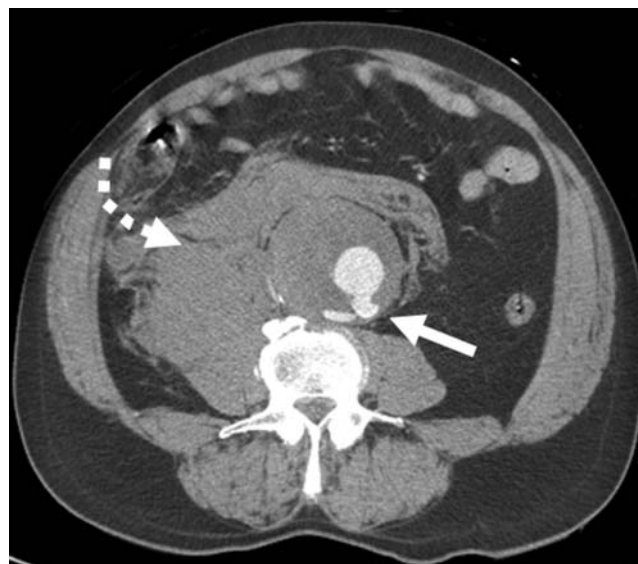


Figure 7 Ruptured abdominal aortic aneurysm. Computed tomographic angiography of the abdominal aorta demonstrating a large right-sided retroperitoneal hematoma (broken arrow) and a 7.9 cm abdominal aortic aneurysm (solid arrow).

ruptured, repair should be undertaken with the patient's medical condition optimized to the best extent possible. Precipitous repairs of nonruptured symptomatic AAAs have an operative mortality five times that of elective repairs,¹¹² for reasons yet unknown. Conversely, if no other source of abdominal pain is found, then treating the aneurysm may resolve the pain, even if done via endovascular repair (and leaving the aneurysm behind) for reasons unknown.

Preoperative Evaluation of Nonemergency AAA Repair Candidates

Evaluation of a patient before elective AAA repair begins with assessment of the expected benefit of repair in relation to the estimated risk. If the decision is made to operate, the history and the physical examination should be completed as described earlier [see Clinical Evaluation, above]. The clinical findings, in conjunction with electrocardiographic (ECG) and routine laboratory test results, provide most of the information that is needed for evaluating a patient's candidacy for AAA repair.

COMORBID CONDITIONS

CAD is common in patients with AAAs and is the leading cause of early and late mortality after AAA repair.¹¹³ Renal insufficiency, COPD, and diabetes mellitus also may influence morbidity and mortality after AAA repair. Accordingly, when any of these disease entities is present, further evaluation before repair may be beneficial. Optimization of perioperative medications is also important for maximizing risk reduction. Finally, adequate preoperative imaging is essential. The decision regarding which type of repair is most appropriate in an AAA patient should be based on the preoperative evaluation.

Coronary Artery Disease

Before elective AAA repair, it is important to identify patients who are at high risk for a perioperative cardiac event and may benefit from preoperative cardiac intervention. It is also important to identify patients who are at low risk so that they are not subjected to unneeded testing. The most recent report from the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines is from 2007.¹¹⁴ It provided useful guidelines for preoperative cardiac evaluation in patients undergoing non-cardiac vascular surgery [see Table 3], with the express goal of limiting the use of perioperative cardiac procedures in patients at moderate and high risk for complications.^{114,115} Use of these guidelines and permutations thereof has proved both safe and effective at reducing resource use and overall costs.^{116–118}

According to the ACC/AHA guidelines, patients needing elective AAA repair are stratified first by whether the patient has active cardiac conditions or high-risk factors. If so, and symptoms have not recurred, the patient is cleared for operation. If the patient never underwent coronary revascularization, underwent revascularization more than 5 years before, or is experiencing recurrent symptoms or signs of cardiac ischemia, further evaluation of clinical predictors is necessary.

Clinical predictors of major perioperative cardiovascular risk—defined as MI, congestive heart failure, or death—may be divided into three categories¹¹⁵: major, intermediate, and minor. The presence of a major predictor requires that the symptom or disease be managed appropriately before nonemergency surgery. The presence of an intermediate predictor is associated with an

increased risk of perioperative cardiac complications and requires that current status be fully investigated. The presence of a minor predictor is indicative of cardiovascular disease but has not been shown to independently increase the risk of perioperative cardiovascular complications.

Once the clinical predictors have been evaluated, additional predictive factors, involving the patient's ability to perform various activities (ranging from minor activities of daily living to strenuous sports), are assessed. The energy required to perform an activity is quantified in terms of metabolic equivalents (METs). The number of METs of which a patient is capable directly correlates with the ability to perform specific tasks [see Table 4]. Patients who are unable to attain 4 METs are considered to be at high risk for perioperative cardiac events and long-term complications. Finally, the inherent risk of the procedure to be performed is evaluated. AAA repair is considered high risk.

To date, there have only been two large, controlled, randomized trials including AAA repair to evaluate if preoperative coronary intervention (either coronary artery bypass grafting [CABG] or percutaneous transluminal coronary angioplasty [PTCA]) improved mortality in elective, major vascular surgery. Thirty percent of the 510 patients in the Coronary Artery Revascularization Prophylaxis [CARP] trial were undergoing open AAA repair (70% had peripheral artery disease), and all had at least one significant coronary artery stenosis. They were randomized to either preoperative revascularization or no revascularization procedure. Overall, there was no difference with respect to perioperative (30 days) MI in either group (12% versus 14%. $p = .37$). At 2.7 years after randomization, there was no difference in

Table 3 Risk Stratification Criteria to Determine the Need for Preoperative Cardiac Evaluation for Nonvascular Surgery Patients (Only Indicated for Moderate or High Risk Patients)¹¹⁴

1. Major clinical predictor of risk present?	Major clinical predictors include • Unstable coronary syndromes • Decompensated CHF • Significant arrhythmias • Severe valvular disease The presence of these predictors cancels or delays elective intervention until they are ameliorated and/or studied via coronary angiography.
2. Intermediate clinical predictor of risk present?	Intermediate clinical predictors include • Mild angina pectoris • Prior MI • Compensated or prior CHF • Diabetes mellitus • Renal insufficiency, carotid surgery, or aortic endograft Noninvasive testing is unlikely to change management in this risk group; therefore, continue with operation if low risk. If risk is high (several risk factors), then consider stress testing or angiography and go to 4.
3. Minor or no clinical predictors present?	Minor clinical predictors include • Advanced age • Abnormal ECG • Nonsinus rhythm • Low functional capacity • Previous stroke • Uncontrolled systemic hypertension If minor or no clinical predictors are present and the patient can attain 4 METs or more, proceed with surgery. Consider testing when < 4 METs are attained, especially in the presence of multiple minor clinical predictors; then go to 4.
4. Risk after noninvasive testing?	Low risk: Proceed with operation. High risk: Consider coronary angiography.

CHF = congestive heart failure; ECG = electrocardiogram; MET = metabolic equivalent; MI = myocardial infarction.

Table 4 Estimated Energy Required for Various Activities^{116,156}

Activity Level	METs*	Sample Activities
Mild	1–3	Eating; playing a musical instrument; walking at 2 mph; getting dressed; golfing (with cart)
Moderate	3–5	Calisthenics without weights; climbing a flight of stairs; housework; golfing (without cart); running a short distance
Vigorous	4–12+	Chopping wood; strenuous sports such as football, basketball, singles tennis, karate, or jogging (10 min mile or faster)

*1 MET = 3.5 mL·kg⁻¹·min⁻¹ oxygen uptake.

mortality between the groups (23% versus 22%, $p = .92$) and the number of perioperative MIs was also the same (24.2 versus 28.6%; $p = .32$), albeit a predictor of mortality.¹¹⁹ These data demonstrate that there is no need of preoperative coronary revascularization in patients with stable CAD. Therefore, in stable patients without evidence of heart failure, there may be no role for preoperative intervention as long as aggressive (beta blocker, statin, and aspirin) medical therapy can be initiated (not possible on emergent cases).¹¹⁹ Of note, this is only one trial, mostly in men, and it should be validated prior to taking these data as absolute recommendations. The DECREASE-V pilot study sought to find if high-risk patients needing vascular surgery would benefit from revascularization or just best medical therapy (beta blockers to a heart rate of 60 to 65 beats/min and aspirin) prior to surgery.¹²⁰ The 101 patients who had extensive stress-induced ischemia (≥ 5 segments or ≥ 3 walls) were randomized. The results demonstrated no difference in mortality, and one patient in the revascularization-first group died from a ruptured aneurysm. Although ultimately the sample size was small, the results were similar in the two trials; thus, there may not be a benefit to revascularization in the era of modern medical therapy.

Small observational studies have indicated a low cardiac mortality when preoperative PTCA is performed in this setting; complications after PTCA are not infrequent and include the need for emergency CABG. One retrospective review found that patients who underwent prophylactic PTCA before noncardiac surgery were twice as likely to have an adverse cardiac outcome as healthy patients were.¹²¹ This study did not control for CAD severity, medical management, or comorbidities. A later study concluded that both CABG and PTCA offered only modest protection against adverse cardiac events after major arterial surgery (CABG, < 5 years; PTCA, < 2 years).¹²² General indications for PTCA use are outlined in the 2001 revision of the 1993 ACC/AHA guidelines for percutaneous coronary intervention.¹²³ It is recommended that patients wait at least 2 weeks—preferably, 4 to 6 weeks—after PTCA before undergoing AAA repair; this delay allows the plaque to stabilize after stenting and permits full treatment with all antiplatelet agents.

The original ACC/AHA recommendations for supplemental preoperative testing were updated in a 2007 statement.¹¹⁴ Currently, it is generally agreed that preoperative testing should be limited to patients in whom the results have the potential to alter the current course of management. The following noninvasive tests may be considered in high-risk vascular patients:

1. **12-lead ECG.** This test is recommended. Certain ECG abnormalities are clinical predictors of perioperative and

Table 5 ECG Findings as Clinical Predictors of Increased Perioperative Cardiovascular Risk¹⁵⁵

Major predictors
High-grade atrioventricular block
Symptomatic ventricular arrhythmias in the presence of underlying heart disease
Supraventricular arrhythmias with uncontrolled ventricular rate
Intermediate predictor
Pathologic Q wave indicating previous myocardial infarction
Minor predictors
Left ventricular hypertrophy
Left bundle branch block
ST-T abnormalities
Rhythm other than sinus (e.g., atrial fibrillation)

ECG = electrocardiogram.

long-term cardiac risks in patients undergoing high-risk operative procedures [see Table 5].

2. **Transthoracic echocardiography to evaluate resting left ventricular function.** This test is indicated in the presence of heart failure. If it was previously done and demonstrated severe left ventricular dysfunction, repeat evaluation is unnecessary. It may be of benefit in patients with prior heart failure and those with dyspnea of unknown etiology. Routine use is not beneficial in the absence of heart failure.
3. **Exercise or pharmacologic stress testing.** Such testing is useful for diagnosing CAD in patients with an intermediate pretest probability of CAD, but its value is less well established in those with a high or low pretest probability. It is a good prognosticator for patients with suspected or proven CAD who are undergoing initial evaluation, for patients whose clinical disposition has changed significantly, and for those who have experienced an acute coronary syndrome.¹²⁴ Stress testing is also recommended for demonstrating the presence of myocardial ischemia before coronary revascularization and for evaluating the efficacy of medical therapy. It may be useful in patients whose subjective assessment of exercise tolerance is unreliable and in whom evaluation in terms of METs is therefore impossible. Less clear are the following indications for stress testing: (1) diagnosis of CAD in patients who have resting ST depression of less than 1 mm, are on digitalis, or show evidence of left ventricular hypertrophy on ECG and (2) detection of restenosis in high-risk patients who have recently (i.e., within the past few months) undergone PTCA. Exercise stress testing should not be done (1) to diagnose patients with ECG findings that would prevent adequate assessment, (2) in patients with severe comorbidities that would preclude coronary revascularization,

(3) for routine screening of asymptomatic patients, or (4) to evaluate young patients with isolated ectopic beats on ECG.

If indicated in the very high risk patients, coronary angiography may be performed next. Current indications in patients scheduled to undergo elective AAA repair include (1) a previous history of high-risk status after noninvasive testing, (2) continued angina despite adequate medical therapy, (3) unstable angina, and (4) an equivocal result on noninvasive testing in high-risk patients. Coronary angiography may be beneficial in patients with multiple intermediate clinical risk factors. If noninvasive testing reveals moderate-size to large areas of ischemia in a patient without high-risk criteria and a lower left ventricular ejection fraction, or if testing is nondiagnostic in a patient at intermediate clinical risk, coronary angiography may also be indicated. The indication for coronary angiography is more controversial in patients who have experienced a perioperative MI. Coronary angiography is not indicated in patients who are asymptomatic after coronary revascularization and who are capable of at least 7 METs.

Both CABG and PTCA have been employed to treat CAD before AAA repair. CABG is usually done in this setting only if it has been decided that the patient needs the intervention regardless of the current status of the abdominal aorta. Such patients have a high-risk coronary anatomy and have a long-term prognosis that is generally thought to improve if coronary revascularization is performed. The combination of AAA repair and CABG has been evaluated, and there are some data to support its use in carefully selected patients, but the perioperative mortality may be more than 10%. Although this may be more significant in the era when the AAA repair was exclusively done via a laparotomy and not endovascularly, the mortality is higher when the two procedures are staged (CABG first and then AAA repair), and aneurysms have been reported to rupture in the hospital while recovering from the CABG.^{125–127} Surgery should be delayed 2 to 4 weeks after an angioplasty to balance the risk of operating too soon on an unhealed plaque versus too late on a restenosed vessel. Coronary arteries that have bare metal stents should be allowed to heal for 6 to 8 weeks but less than 12 weeks for the same reasons as above. Finally, drug-eluting stents have a very high occlusion rate if the antiplatelet agents are stopped; thus, the current recommendations are to not suspend these for ideally 1 year after placement or at least 1 month without stopping aspirin if absolutely necessary to do the procedure.^{114,128}

Pulmonary Disease

Between 7 and 11% of patients with COPD have an AAA.²⁶ Traditionally, when such patients are to undergo AAA repair, room air arterial blood gas values are determined and pulmonary function tests performed to assess the extent of COPD. If COPD is severe, formal pulmonary consultation may be necessary for prediction of short- and long-term prognoses and optimization of treatment. Several studies have reported that COPD is an independent predictor of operative mortality.^{5,76,129} A 2001 study of Veterans Affairs (VA) patients, however, found no significant correlation between the presence of COPD and increased operative mortality (although morbidity was notably higher).¹³⁰ A 2003 study evaluating

morbidity and mortality after AAA repair in patients with COPD showed that the preoperative factors significantly associated with a poor outcome included (1) suboptimal COPD management, as evidenced by fewer inhalers used, (2) a lower preoperative hematocrit, (3) preoperative renal insufficiency, and (4) the presence of CAD.¹³¹ It is noteworthy that abnormal preoperative pulmonary function tests and arterial blood gas values were not predictive of a poor outcome. Thus, COPD by itself is not a contraindication to AAA repair.

Renal Failure

Preoperative renal insufficiency is known to be a risk factor for a poor outcome after AAA repair^{5,76,130,131} and thus should be evaluated and corrected if possible. In certain patients with AAAs, renal artery stenosis may be contributing to impaired renal function; if so, it may be corrected either noninvasively, before AAA repair, or in the course of the repair.⁴⁵

Diabetes Mellitus

Whether diabetes mellitus is truly an independent risk factor for morbidity or mortality after aortic surgery is controversial. Several studies have shown that the risk of death is not increased in diabetic patients, but the risk of perioperative complications may be.^{132–134} Most of these studies had small study groups and thus lacked the statistical power needed to demonstrate that diabetes had a significant influence. A 2002 study of patients at VA medical centers who underwent major vascular procedures found that diabetic patients were indeed at higher risk for death and cardiovascular complications. When examined separately, however, patients undergoing AAA repair did not have higher rates of cardiovascular complications or death than patients undergoing other procedures.

PERIOPERATIVE MEDICATIONS

Multiple studies have addressed optimization of medical management in patients with AAAs. Beta blockers, alpha₂-adrenergic agonists, nitrates, calcium channel blockers, and insulin infusions have all been evaluated in this setting. Other agents used in the treatment of cardiovascular disease (e.g., aspirin) have not been specifically evaluated in regard to reduction of perioperative cardiac complications in patients undergoing aortic surgery.^{114,135}

A review of the literature supporting perioperative beta blockade was published in 2002.¹³⁶ Five randomized, controlled trials were evaluated, and the results suggested that this measure had a beneficial effect on perioperative cardiac morbidity. The number needed to treat to prevent one MI was 2.5 to 6.7 patients; the number needed to treat to produce a significant effect on cardiac or all-cause mortality was 3.2 to 8.3 patients. All but one of the studies reported a significant reduction in postoperative MIs after beta blocker use, with the effect being most obvious in high-risk patients. Thus, it appeared that perioperative beta blockade is most likely beneficial for patients at high risk for cardiac events who are to undergo AAA repair, unless it is otherwise contraindicated (e.g., by severe bradycardia or COPD) or if they have only one risk factor (low-risk patients). These data seemed to suggest that a goal should be to attain a

resting heart rate of 60 beats/min or lower before operation.^{114,135} Since then, a large randomized trial with over 8,000 patients studied the effect of perioperative long-acting metoprolol. The PeriOperative ISchemic Evaluation (POISE) trial found that once again there was a statistical decrease in the rate of perioperative MIs, yet there was an increase in mortality and strokes.¹³⁷ This evolving controversy may be substantiated as a recent, large meta-analysis of randomized trials that included perioperative beta blockers in 12,306 patients found again a decrease in MIs but no difference in mortality and a statistically higher risk of strokes.¹³⁸ Thus, it is likely that there is a group of high-risk patients with AAA who will benefit, but care must be taken to select the ideal patient to receive perioperative beta blockers, even though their use is listed in the 2007 ACC guidelines.¹³⁹

Alpha₂-adrenergic agonists (e.g., clonidine) have not been shown to reduce MI rates or mortality from cardiac causes. In one study, mivazerol did not exert a significant overall effect in patients undergoing major vascular or orthopedic procedures but was associated with a significant reduction in MI rates and mortality from cardiac causes in patients with known CAD.¹⁴⁰ Therefore, when perioperative beta blockade is contraindicated, administration of alpha₂-adrenergic agonists may be of benefit in high-risk patients with known CAD undergoing AAA repair.¹¹⁴

To date, studies evaluating the perioperative use of nitroglycerin and diltiazem to lower the risk of cardiac events have not found this practice to be beneficial in this regard. It may be best to reserve these agents for patients who need them for angina or ischemic symptoms and for those who have myocardial ischemia after operation.¹³⁵

In the last decade, there has been increasing interest in the role of tight insulin control in critically ill patients and during major surgery. A randomized, controlled trial in 236 patients undergoing vascular surgery (bypass, AAA repair, or amputations) compared continuous insulin infusion versus intermittent dosing in the perioperative period and found that intensive, continuous insulin infusions decreased the all-cause mortality, heart attack, and heart failure rate by a factor of 4.¹⁴¹

It is widely accepted that aspirin is beneficial in reducing the risks associated with CAD.¹⁴² Its continued use throughout the perioperative period is controversial in some groups, however, because of the potential complications associated with decreased platelet function.¹⁴³ Currently, low doses of aspirin are continued throughout all vascular cases, including aortic surgery. However, clopidogrel should be avoided for at least 10 days prior to aortic surgery attributable to a high risk of bleeding. If an emergent need for surgery arrives, then platelet transfusions should be done prophylactically on the day of surgery.

Statins are an emerging group of medications that seem to dramatically lower all causes of cardiovascular mortality. Their use specifically in aortic surgery should be continued throughout the perioperative period.¹¹⁴

FURTHER IMAGING

The methods used to evaluate the aortic anatomy before AAA repair are US, CT, MRA, and aortography. Which method is employed in a given situation depends largely on the clinical presentation, the history, the comorbid conditions present, and the availability of equipment and expertise. Each has its advantages and disadvantages [see Table 2].

Ultrasonography

Once the decision has been made to repair a documented AAA, further preoperative ultrasonographic evaluation is no longer needed [see Patient Is Stable, above].

Computed Tomographic Angiography

The current standard for preoperative imaging of AAAs is contrast-enhanced CTA scanning. This modality is more accurate than aortography at measuring the true AAA diameter and diagnosing ruptures.⁵⁸ With CTA, it is possible to obtain a three-dimensional view of the abdominal aorta. CT scanning is highly accurate, with measurements reproducible to less than 1 mm. Historically, measurement variations as great as 5 mm were sometimes seen in older scanners occurring 9 to 17% of the time; however, with the current enhancements in resolution and number of slices, this is no longer the case.^{59,60} Such variations may be reduced by standardizing measurements, reducing the number of radiologists reading the images, and using calipers and magnification for greater accuracy.^{56,60}

The advantages of CT over US include (1) more precise definition of the proximal and distal extent of AAAs; (2) better delineation of the iliac arterial anatomy; (3) the ability to evaluate AAA wall integrity, noting the location and amount of calcification within vessel walls; and (4) the ability to identify venous anomalies, retroperitoneal blood, aortic dissection, inflammatory aneurysms, and other intra-abdominal pathologic conditions and anomalies (e.g., horseshoe kidney). Therefore, CT is the study of choice for excluding AAA rupture in stable but symptomatic patients.^{58,144,145} Thin-cut helical/spiral CTA with multiplanar reconstruction is a recommended study for evaluating patients before endovascular AAA repair; CT arteriography is also preferred for determining whether an endoleak has occurred after endovascular AAA repair.¹⁴⁶ In the near future, US may supplant CT for these applications.

The main drawbacks associated with CT scanning are (1) radiation exposure (which can be substantial as patients undergo multiple in their lifetime)¹⁴⁷ and (2) the requirement for iodinated contrast material, which cannot be used in patients with dye allergies or renal insufficiency. In addition, spiral CTA with three-dimensional reconstruction is relatively expensive. Allergic reactions to the contrast agent can usually be prevented by giving a standard steroid-diphenhydramine preparation. If the patient has renal insufficiency, MRA may be more appropriate, assuming that the patient is stable enough, does not have metal implants that preclude it, and MRA is actually available. Alternatively, CT scanning may be done without contrast to determine whether there is a large retroperitoneal hematoma, which not only is sufficient to diagnose a ruptured AAA but also is useful to determine if the patient can undergo an endovascular repair. For this reason, in patients with renal failure, nonintra-venous contrast CT of the chest, abdomen, and pelvis is the preferred test when ruptured aneurysm is high on the list of differential diagnoses.

Magnetic Resonance Angiography

In patients with renal insufficiency who are scheduled for AAA repair, MRA with gadolinium and the breath-hold technique used to be the preoperative study of choice as it was comparable to CT scanning in evaluating elective AAA repair candidates.^{96,148} Since then, growing concern for the

incidence of nephrogenic fibrosing dermopathy in patients with renal failure exposed to gadolinium has now excluded this patient population from being studied with this contrast agent. In patients who do not have renal failure and are studied with MRA, the main advantages include the following: (1) it does not always require the use of nephrotoxic agents or radiation and (2) it is highly sensitive and specific in detecting stenoses of the splanchnic, renal, and iliac arteries.⁹⁵ Its main drawbacks are as follows: (1) it is not widely available, (2) it is expensive, (3) it may cause claustrophobia, and (4) it takes longer to perform than CT. MRA is contraindicated in patients with pacemakers, metallic foreign bodies in the eye, cochlear implants, pulmonary artery catheters, and certain intracranial aneurysm clips, among others.

Aortography

Preoperative digital subtraction angiography of the aorta (aortography) is not routinely used for preoperative diagnosis. In the present era, where CTA and MRA is so often used, rarely is angiography the imaging technique to first discover a AAA. The most common use of aortography in the treatment of AAAs is during the endovascular repair of a known aneurysm. The aortogram is obtained to mark the level of the renal arteries and iliac bifurcation to confirm the appropriate length and positioning of the endograft.

Being an invasive test, aortography carries an added risk over other imaging modalities. Aortography is currently indicated in the preoperative evaluation of an AAA when (1) the extent of the aneurysm may include the juxtarenal or suprarenal aorta; (2) the clinical history is indicative of lower extremity arterial occlusive disease (i.e., claudication or rest pain); (3) renovascular disease may be present, as evidenced by uncontrolled hypertension or azotemia; or (4) the patient has previously undergone arterial reconstruction.^{20,90} Aortography is superior at evaluating the intraluminal characteristics of the aorta, determining visceral branch involvement, and delineating variations in the vascular anatomy.¹⁴

Aortography has a number of important limitations in comparison with CT or MRA starting with the need to gain arterial access with needles and catheters. In particular, it is associated with particular risks not found in CT or MRA, such as infection, arterial thrombosis necessitating emergent thrombectomy and repair, distal embolization, groin hematoma, and local arterial dissection.¹⁴⁹ There is also a 10% risk of renal failure in patients with elevated creatinine levels (≥ 2.5 mg/dL)¹⁴⁹; this can often be prevented with adequate hydration before the study or by using carbon dioxide gas as the contrast agent to evaluate the infradiaphragmatic blood vessels. The limitation of carbon dioxide angiography is that the resolution is directly proportional to the quality of the

image intensifier and operator, although it is inversely proportional to the surrounding bowel gas and thickness of the patient.¹⁵⁰ Finally, the cost of aortography is three to four times that of spiral CT, which gives health care providers an incentive to replace aortography with spiral CT whenever possible.¹⁵¹

Complications of AAAs

Rupture of an AAA is obviously life threatening, but erosion of an aneurysm into adjacent structures may be catastrophic as well. In certain instances, ruptured AAAs may form a continuous luminal connection with a surrounding structure. High-output cardiac failure may result from an arteriovenous shunt between the aorta and the inferior vena cava (aortocaval fistula), which occurs in as many as 2 to 4% of patients with ruptured AAAs.^{152,153} AAA patients with intermittent gastrointestinal bleeding may present with so-called herald bleeding from a primary aortoenteric fistula. Most such fistulas occur in the third or fourth part of the duodenum after a repaired aorta, and the graft material can be seen in the duodenum during upper endoscopy.¹⁵⁴ Aorta–inferior vena cava shunts and aortoenteric fistulas are medical emergencies that demand urgent operative attention.

AAAs may also give rise to distal lower extremity atheroemboli. Small AAAs appear to be the most common sources: infrarenal AAAs with mean diameters of 3.5 cm have been linked to lower extremity atheroemboli.¹⁵⁵ Thrombosis of an AAA also occurs; if it develops acutely, severe ischemia of the entire lower torso may result, manifested by a bilateral lack of femoral pulses, a drop in skin temperature beginning at the level of the upper thigh, and a change in skin color beginning at the level of the knees.¹⁵⁴ This can also be seen after direct abdominal trauma or after a motor vehicle crash where the seatbelt dislodges aortic thrombus from the AAA to the lower extremities. Recognizing these symptoms as potential complications of AAAs can facilitate diagnosis.

Rare Causes of Pulsatile Abdominal Mass

Finally, when a patient presents with a pulsatile abdominal mass that is suggestive of aneurysmal disease, the most likely diagnosis is an infrarenal AAA as 80 to 90% of aortic aneurysms are found in this location. It is important to keep in mind, however, that various, less common types of aneurysms may also present as a pulsatile abdominal mass, including (but not limited to) iliac artery aneurysms [see Figure 4], traumatic pseudoaneurysms, and visceral artery aneurysms.¹

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4 ACUTE MESENTERIC ISCHEMIA

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Diagnosis and Management of Acute Bowel Ischemia

Acute mesenteric ischemia is an uncommon life-threatening clinical entity that ultimately leads to death unless it is diagnosed and treated appropriately. Despite diagnostic and therapeutic advances and an improved understanding of the pathophysiology, the morbidity and mortality associated with acute mesenteric ischemia remain high, having changed relatively little over the past several decades. Accordingly, the index of suspicion for this disease should be high whenever a patient presents with acute-onset severe abdominal pain that is out of proportion to the physical findings. Once the diagnosis is made, prompt intervention is required to minimize morbidity and mortality.

Acute mesenteric ischemia can result from any of four distinct processes: (1) embolic occlusion of the mesenteric circulation (usually the superior mesenteric artery [SMA]); (2) acute thrombosis of the mesenteric circulation; (3) intense splanchnic vasoconstriction—so-called nonocclusive mesenteric ischemia (NOMI)—which is usually associated with a low-flow state or profound hypovolemia; or (4) mesenteric venous thrombosis (MVT).

Clinical Evaluation

The classic presentation for patients with embolic disease of the mesenteric vessels is sudden-onset midabdominal pain that is described as being out of proportion to the physical findings and is associated with immediate bowel evacuation.

In fact, only about one third of patients present with the triad of abdominal pain, fever, and heme-positive stools. A study that considered all causes of acute mesenteric ischemia found that 95% of patients presented with abdominal pain, 44% with nausea, 35% with vomiting, and 35% with diarrhea¹; only 16% presented with blood per rectum.

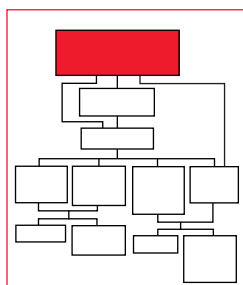
Patients with thrombotic mesenteric occlusion also present with sudden-onset severe midabdominal pain that is out of proportion to the physical findings, but unlike patients with acute embolic occlusion, they typically have a history of chronic postprandial abdominal pain and significant weight loss.

Patients with NOMI present somewhat differently. The pain reported is usually not as sudden as that noted with embolic or thrombotic occlusion: it is generally more diffuse and tends to wax and wane, unlike the pain associated with embolic or thrombotic disease, which tends to get progressively worse.

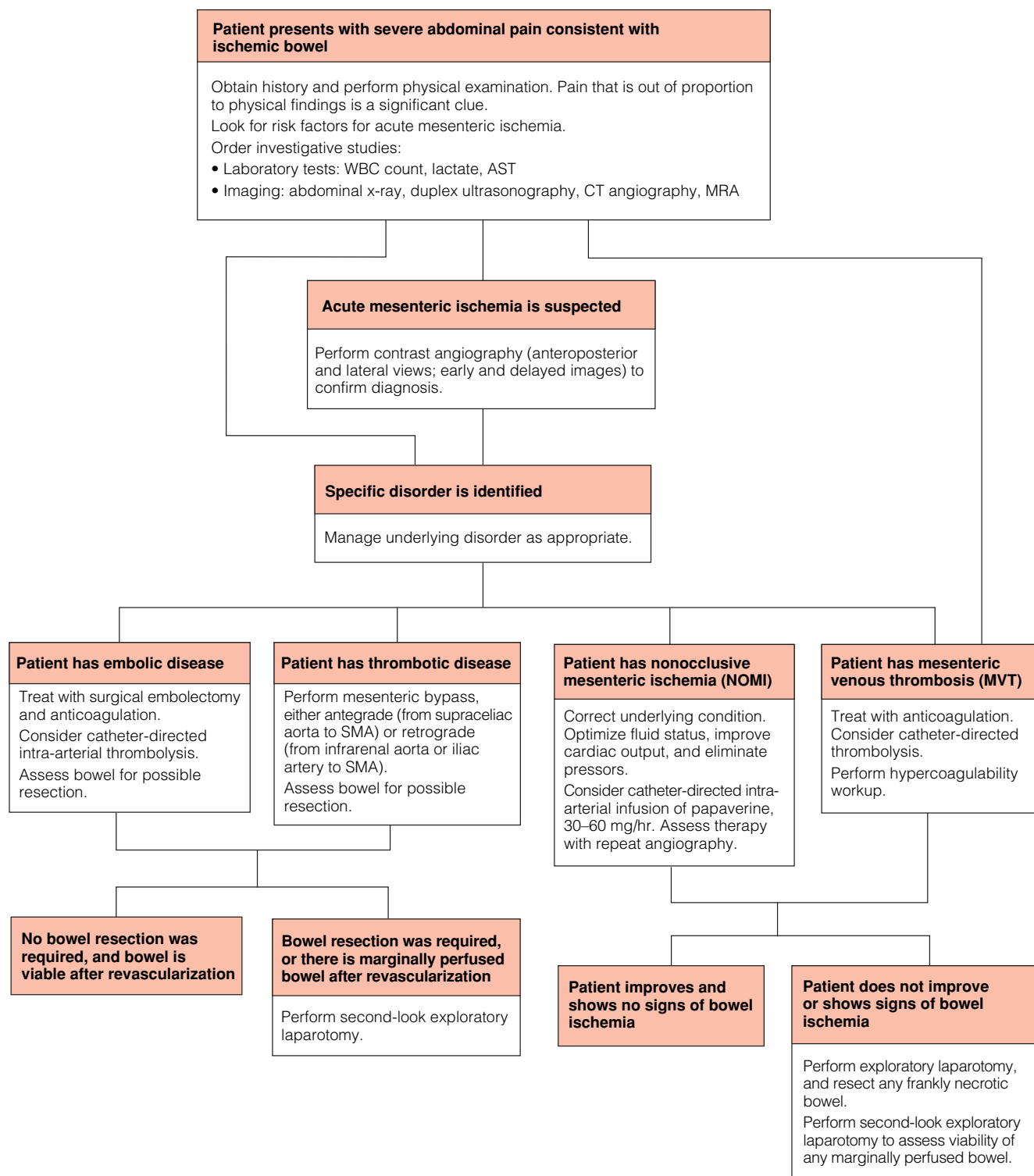
Patients with MVT often present with various nonspecific abdominal complaints; accordingly, this diagnosis may be especially challenging. Common complaints include nausea, vomiting, diarrhea, abdominal cramping, and nonlocalized abdominal pain. As a rule, these symptoms are not acute. A study of MVT patients found that 84% presented with abdominal pain.² Of those 84%, only 16% presented with peritoneal signs, whereas 68% presented with vague abdominal pain. Other presenting symptoms included diarrhea (42%), nausea and vomiting (32%), malaise (16%), and upper gastrointestinal bleeding (10%).²

In addition to the clinical presentation, risk factors provide essential clues for correct identification of these disease processes. Certain general risk factors for acute mesenteric ischemia have been identified. In one study, 78% of the patients presented with a history of hypertension, 71% with a history of tobacco use, 62% with a history of peripheral vascular disease, and 50% with a history of coronary artery disease (CAD).¹ Acosta-Merida and colleagues found that the presence of cardiac illness, elevated plasma urea levels, and both small and large bowel involvement independently predicted perioperative mortality.³

There are also more specific risk factors for individual causes of acute mesenteric ischemia. Patients with embolic occlusion of the mesenteric circulation typically have a history of recent cardiac events (e.g., myocardial infarction, atrial fibrillation, mural thrombus, mitral valve disease, or left ventricular aneurysm) or previous embolic disease. In the study just cited, 50% of the patients who presented with embolic occlusive disease had atrial fibrillation.¹ Patients with acute mesenteric ischemia secondary to thrombotic occlusive disease typically have other manifestations of diffuse atherosclerotic disease (e.g., CAD, peripheral artery disease, and carotid stenosis). The risk factors for NOMI are slightly different. This condition usually occurs during severe low-flow states and represents extreme mesenteric vasoconstriction. It is much more common among severely ill patients in an intensive care unit (ICU) who require vasopressors and among patients undergoing dialysis with excessive fluid removal. The risk factors for MVT include a history of previous venous thrombosis or pulmonary embolism, a known or suspected hypercoagulable state, oral contraception, and estrogen supplementation. In a study of 31 patients who presented with MVT at Northwestern University, 13 (42%) were diagnosed with a hypercoagulable state, six (19%) had a history of previous thrombotic episodes, and four (13%) had a history of cancer.²



Diagnosis and Management of Acute Bowel Ischemia



Lastly, the importance of prompt surgical evaluation and diagnosis cannot be overemphasized. Given the often nonspecific presentation of patients with acute mesenteric ischemia, the diagnosis is delayed in many patients. Eltarawy and colleagues found that a delay in surgical consultation of more than 24 hours after the onset of symptoms resulted in a statistically significant increase in mortality, with an odds ratio of 9.4.⁴ Furthermore, a delay in operation of more than 6 hours following surgical consultation was also associated with an increase in mortality, with an odds ratio of 4.9. Interestingly, the authors found that patients who presented with abdominal distention, elevated lactate, acute renal failure, vasopressor administration, and a lack of abdominal pain were more likely to have a delay in surgical consultation. Thus, having a heightened awareness of acute mesenteric ischemia may lead to more prompt surgical consultation, diagnosis, and treatment and may improve patient outcomes.

Investigative Studies

Although there are no basic laboratory or radiographic studies that are diagnostic for acute mesenteric ischemia, such studies can help confirm the diagnosis when it is suspected on the basis of the history and the physical examination.

LABORATORY TESTS

In most cases, the white blood cell count is elevated. In a study from the Mayo Clinic, 98% of patients who presented with acute mesenteric ischemia were found to have an elevation of the leukocyte count, and 50% were found to have counts higher than 20,000/ μ L.¹ Lactate is another nonspecific indicator of mesenteric bowel ischemia. In the same Mayo Clinic study, approximately 91% of patients had elevated lactate levels, with 61% having levels higher than 3 mmol/L. In addition, 71% of patients presented with an elevated aspartate aminotransferase, whereas 52% presented with an abnormal base deficit.¹ D-dimer is another test that has been suggested to aid in the diagnosis of acute mesenteric ischemia.⁵ However, recently Akyildiz and colleagues demonstrated that whereas the sensitivity of D-dimer testing for the diagnosis of acute mesenteric ischemia was 94.7%, the specificity was only 78.6% as many other pathologies may result in a rise in D-dimer levels.⁶ Thus, this test should be used with caution.

IMAGING

Abdominal X-rays

Although abdominal radiographic films can neither establish nor exclude the diagnosis of acute mesenteric ischemia, they may reveal signs that are consistent with bowel ischemia. If obtained early, abdominal plain films should show no abnormalities. If obtained late in the presentation, however, they may reveal edematous bowel with thumbprinting. In severe cases, abdominal plain films may reveal gas in the bowel wall and the portal vein. More commonly, however, they reveal a pattern consistent with ileus or are completely unremarkable. In a study of patients operated on for acute mesenteric ischemia, mortality was 29% in patients with normal plain radiographic films, compared to 78% in those

with abnormal films.⁷ Nevertheless, it must be emphasized that the primary role of abdominal plain radiographic films in this setting is to exclude other identifiable causes of abdominal pain (e.g., obstruction and perforation with free air).

Duplex Ultrasonography

Although duplex ultrasonography does have a definite and well-defined role in the diagnosis of chronic mesenteric ischemia, it plays only a limited role in the management of acute mesenteric ischemia. This is not surprising given the acute nature of the presentation, the accompanying ileus with excessive bowel gas and bowel edema (which hinders visualization of the mesenteric vessels), and the reduced access to the vascular laboratory during off-hours. Furthermore, duplex ultrasonography, although capable of imaging stenotic and occlusive lesions at the origin of a mesenteric vessel, is of little value in detecting emboli beyond the proximal portion of the vessel. Similarly, it has a limited role in the diagnosis of NOMI.

Computed Tomographic Angiography

Computed tomographic (CT) angiography and magnetic resonance angiography (MRA) are more commonly used to confirm the diagnosis of acute mesenteric ischemia than duplex ultrasonography is. Both CT and MRA have undergone significant advances over the past decade. Traditional CT scanning can evaluate arterial patency and anatomy and detect calcifications and aneurysms. In addition, it can evaluate the status of the bowel and help identify other causes of abdominal pain (e.g., pancreatitis, bowel perforation, and bowel obstruction). However, it was not until the advent of helical (spiral) CT scanning—and, subsequently, of multislice, multiarray helical CT scan technology with maximum-intensity projection—that the visceral arterial anatomy could be visualized with three-dimensional spatial resolution [see Figure 1]. This technology allows much more rapid acquisition of data and thereby improves the quality of vascular imaging tremendously. A study comparing spiral CT angiography with conventional contrast angiography found that the former had a sensitivity of 75% and a specificity of 100% for the detection of greater than 75% stenosis of the celiac artery.⁸ Furthermore, spiral CT angiography had a sensitivity of 100% and a specificity of 91% for the detection of SMA stenosis. More recent studies with multidetector 16-row CT angiography have revealed a sensitivity and specificity of 96.4% and 97.9%, respectively, in diagnosing acute mesenteric ischemia and an overall accuracy of 95.6%.^{9,10} Thus, multidetector CT angiography is a useful tool for fast and accurate diagnosis of acute mesenteric ischemia.

Although CT technology has become much more sophisticated and the image clarity and definition have improved greatly, there are still limits that warrant discussion to what can be determined by means of CT in the setting of acute embolic or thrombotic disease. The origins of the celiac artery and the SMA are well visualized with CT, but secondary, tertiary, and smaller branches are less well defined; for visualizing these branches, contrast angiography remains the gold standard [see Contrast Angiography, below]. Another limitation of current CT scanning technology is the need to administer intravenous (IV) contrast agents, which can be nephrotoxic or, in some patients, trigger contrast allergies.

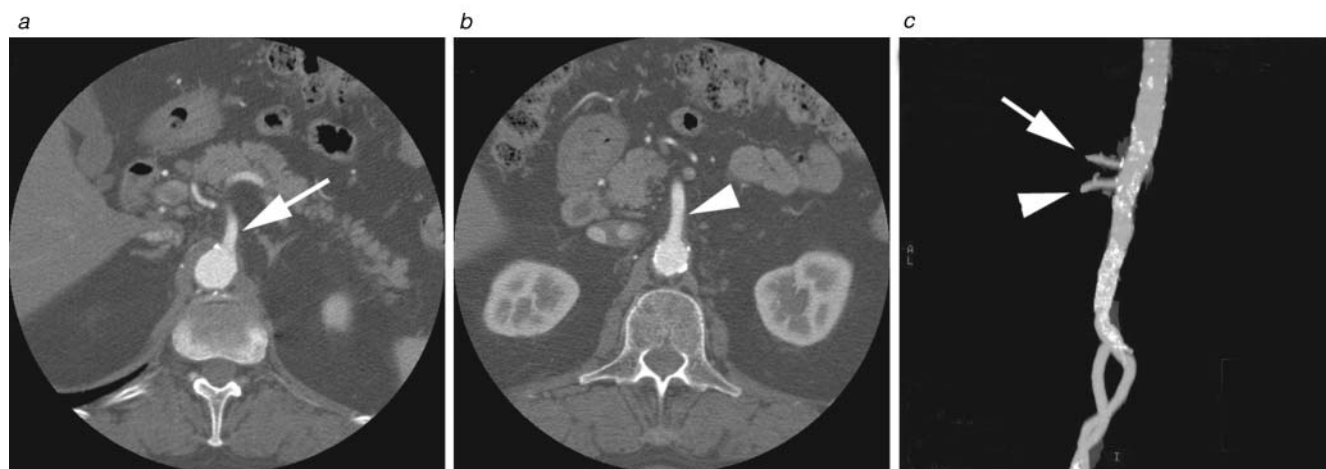


Figure 1 Shown are computed tomography scans of mesenteric vessels: (a) transaxial image of celiac artery (arrow); (b) transaxial image of the superior mesenteric artery (SMA) (arrowhead); and (c) three-dimensional reconstruction of aorta and origins of celiac artery (arrow) and SMA (arrowhead).

CT angiography also tends to overestimate the degree of critical stenosis when compared with conventional angiography; however, this limitation appears to be less of an issue with the advent of multiarray or multidetector technology, which is more sensitive in detecting arterial stenosis. Finally, significant calcification at the origin of the vessel can make it difficult to determine the true degree of stenosis with CT scanning.

In contrast to its relatively limited role in the diagnosis of acute mesenteric ischemia of embolic or thrombotic origin, CT plays a valuable role in diagnosing MVT and is the preferred diagnostic imaging modality in patients presenting with abdominal pain who have a history of deep vein

thrombosis or a known hypercoagulable disorder.¹¹ CT scanning can readily reveal thrombosis of the superior mesenteric vein (SMV), with or without associated bowel abnormalities [see Figure 2]. In fact, CT scans of SMV thrombosis in asymptomatic patients have provided useful information on the pathophysiology of MVT and broadened our understanding of the wide spectrum of this disease entity. In a study from the Mayo Clinic, CT scanning correctly identified 100% of patients who presented with acute MVT and 93% of those who presented with chronic venous thrombosis.¹² In a subsequent study from our institution (Northwestern University), CT scanning identified 100% of MVT patients who presented with vague abdominal pain or diarrhea and 90%

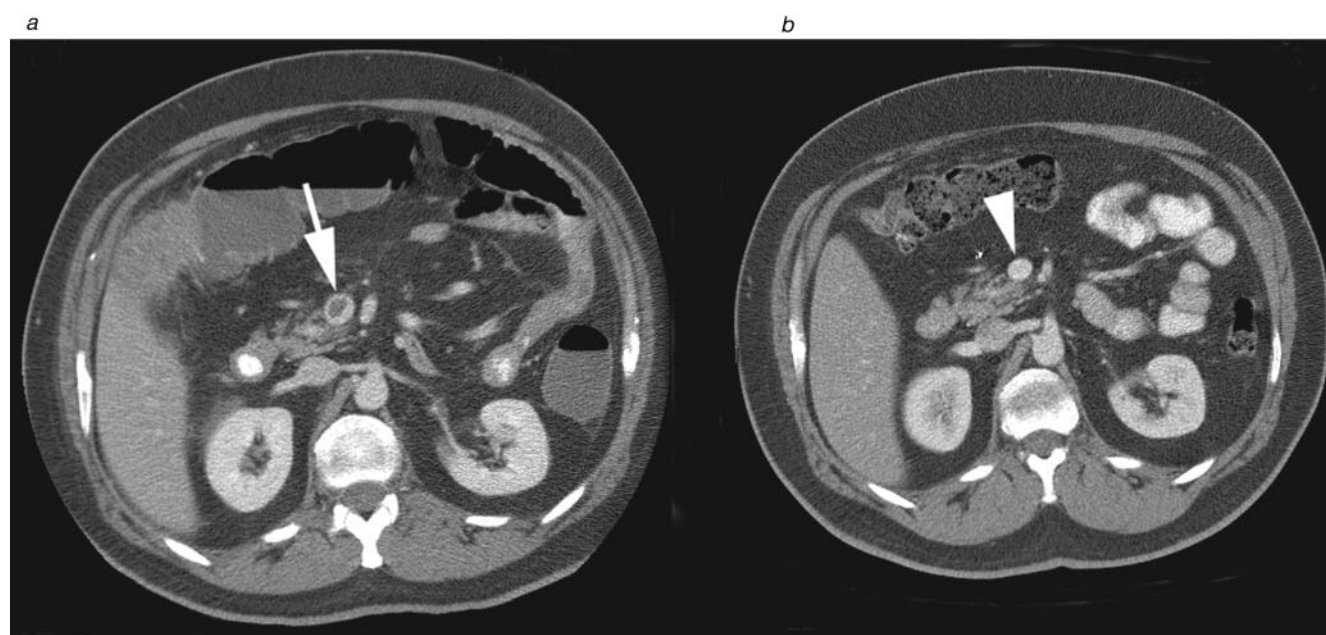


Figure 2 (a) Computed tomography (CT) scan shows partially occluding thrombus in the superior mesenteric vein (SMV) (arrow). (b) CT scan obtained 4 months later reveals complete resolution of thrombus (arrowhead).

of MVT patients who underwent a CT scan.² In contrast, conventional angiography correctly diagnosed MVT in only five of nine patients.²

Magnetic Resonance Angiography

Advances in magnetic resonance technology—in particular, the development of contrast-enhanced three-dimensional MRA—have made MRA imaging of visceral vessels much more practical than was once the case. Fast imaging techniques using IV administration of gadolinium over a single breath-hold can provide high-quality three-dimensional images [see Figure 3] in axial, sagittal, or oblique planes. An advantage MRA has over CT angiography is that gadolinium is significantly less nephrotoxic than the contrast agents used for CT scans. Like CT angiography, however, MRA does not adequately assess the distal branches of the mesenteric vessels. One study compared contrast-enhanced breath-hold MRA with conventional digital subtraction angiography in 33 patients.¹³ There was excellent agreement between the two studies for the celiac artery and the SMA; however, there was poor agreement for the distal branches of the SMA, as well as for the intrahepatic branches of the hepatic artery.

Given the current state of imaging technology, it is possible to confirm the diagnosis of acute mesenteric ischemia with either CT angiography or MRA. If the cause of the ischemia is confirmed—and, in the case of SMA thrombosis, if distal targets are identified for revascularization—it is conceivable that the patient could be explored in the operating room (OR) without undergoing conventional angiography. Many institutions, however, do not have ready access to all of the latest imaging technology. In such situations, contrast angiography remains the best imaging modality for evaluation of the mesenteric vasculature.

Contrast Angiography

Contrast angiography has long been considered the gold standard for imaging the visceral vessels. This modality can visualize the aorta and the main trunks of the mesenteric vessels and can adequately assess several orders of distal branches. The images obtained with contrast angiography are superior to those obtained with CT angiography or MRA. The procedure is performed in a transfemoral manner by means of the Seldinger technique, with infusion of approximately 60 to 100 mL of contrast material. Arteriography should include both anteroposterior and lateral views of the celiac artery, the SMA, and the inferior mesenteric artery (IMA). The origins of the celiac artery and the SMA are best seen on the lateral view, whereas the middle and distal SMA and the IMA are best seen on the anteroposterior view. Delayed views are useful in evaluating a patient for NOMI.

There are classic angiographic patterns that serve to distinguish mesenteric ischemia of embolic origin from that of thrombotic origin [see Figure 4]. Of the three mesenteric vessels, the SMA is most likely to be the site of embolic lodgment because it takes off from the main axis of the aorta at a less sharp angle than the celiac artery and the IMA, which arise from the aorta more perpendicularly. When

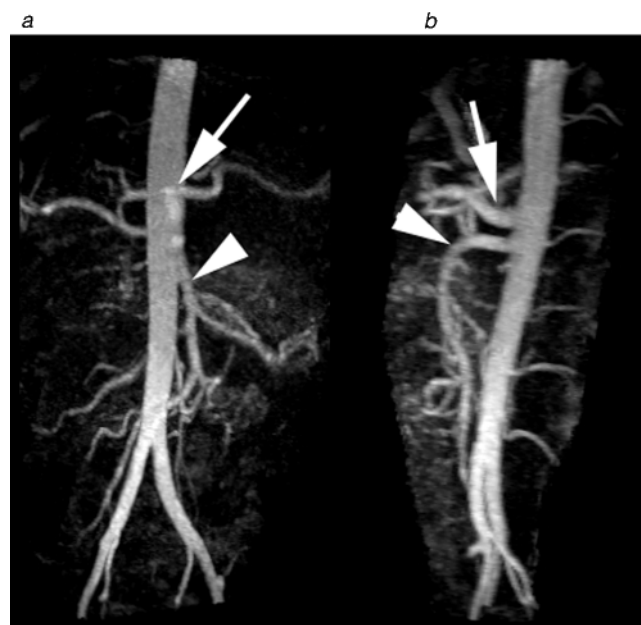


Figure 3 Shown are contrast-enhanced three-dimensional magnetic resonance angiography images of aorta and mesenteric vessels. (a) Anterior projection shows celiac artery (arrow) and the superior mesenteric artery (SMA) (arrowhead). (b) Lateral projection shows celiac artery (arrow) and SMA (arrowhead).

emboli lodge in the SMA, they usually lodge distal to the middle colic branch and the jejunal branch [see Figure 5]. In thrombotic disease, the thrombus usually forms at the atherosclerotic plaque, which, for most patients, is usually at the origin of the mesenteric vessel. Consequently, the angiogram typically demonstrates complete absence of flow in the mesenteric vessel, which often makes it difficult to ascertain the location of the vessel's origin [see Figure 6].

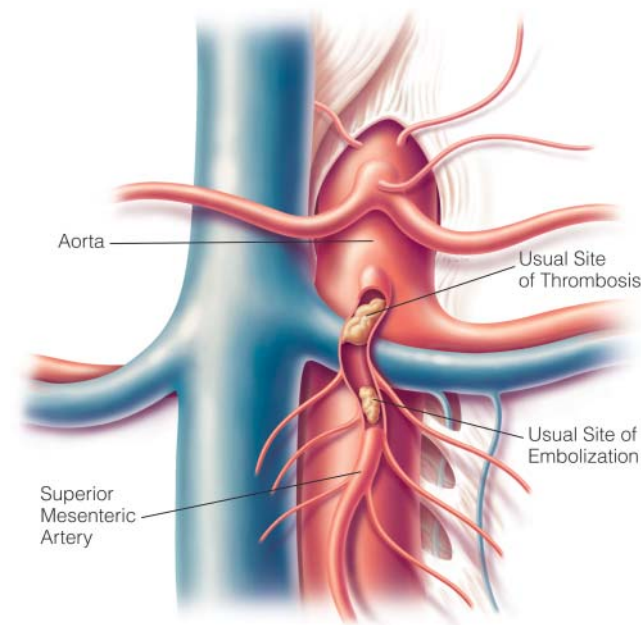


Figure 4 Schematic drawing demonstrates usual site for superior mesenteric artery (SMA) thrombosis versus that for SMA embolus.



Figure 5 Selective angiogram of the superior mesenteric artery in anterior projection demonstrates embolus within vessel (arrow) at typical location.

Patients with NOMI typically exhibit angiographic evidence of SMA vasospasm. A small SMA trunk is visualized, with very few branching vessels visible, and the branches that are visualized show a characteristic tapering of the vessel to the point of occlusion [see Figure 7a]. These patterns are best seen on the anteroposterior projection.

Angiography is less useful for the diagnosis of MVT. Typically, MVT is diagnosed on the venous phase of the selective arterial contrast injection; however, as noted above [see Computed Tomographic Angiography], conventional angiography is less sensitive and specific for MVT than the diagnostic imaging modality of choice—namely, CT.

Besides providing superior image quality, contrast angiography enables the surgeon to perform selective injection of any of the mesenteric vessels and to perform therapeutic intervention. In patients with NOMI, for example, the SMA may be selectively catheterized and papaverine infused directly into the vessel [see Figure 7b]. In a stable patient with acute mesenteric ischemia from a partially occluding embolus but no peritoneal signs, selective catheterization of the SMA allows the institution of catheter-directed intra-arterial thrombolytic therapy [see Figure 8]. Thus, contrast angiography not



Figure 6 Lateral contrast angiogram of aorta demonstrates complete occlusion of both celiac artery (arrow) and superior mesenteric artery (arrowhead) at their origins, consistent with in situ thrombosis. Lack of collaterals suggests an acute process.

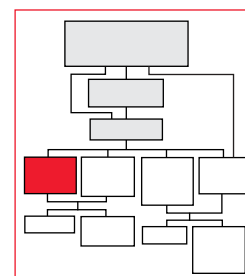
only represents the gold standard for diagnostic imaging but also provides important therapeutic options.

Management

TREATMENT OF SPECIFIC DISORDERS

Embolic Occlusion of Mesenteric Vessels

The goals in the surgical treatment of acute mesenteric ischemia are (1) to restore normal pulsatile flow to the SMA and (2) to resect any nonviable intestine. In general, revascularization precedes resection. The therapeutic approach varies, depending on the specific underlying cause. For embolic disease of the SMA, the standard treatment is surgical embolectomy.



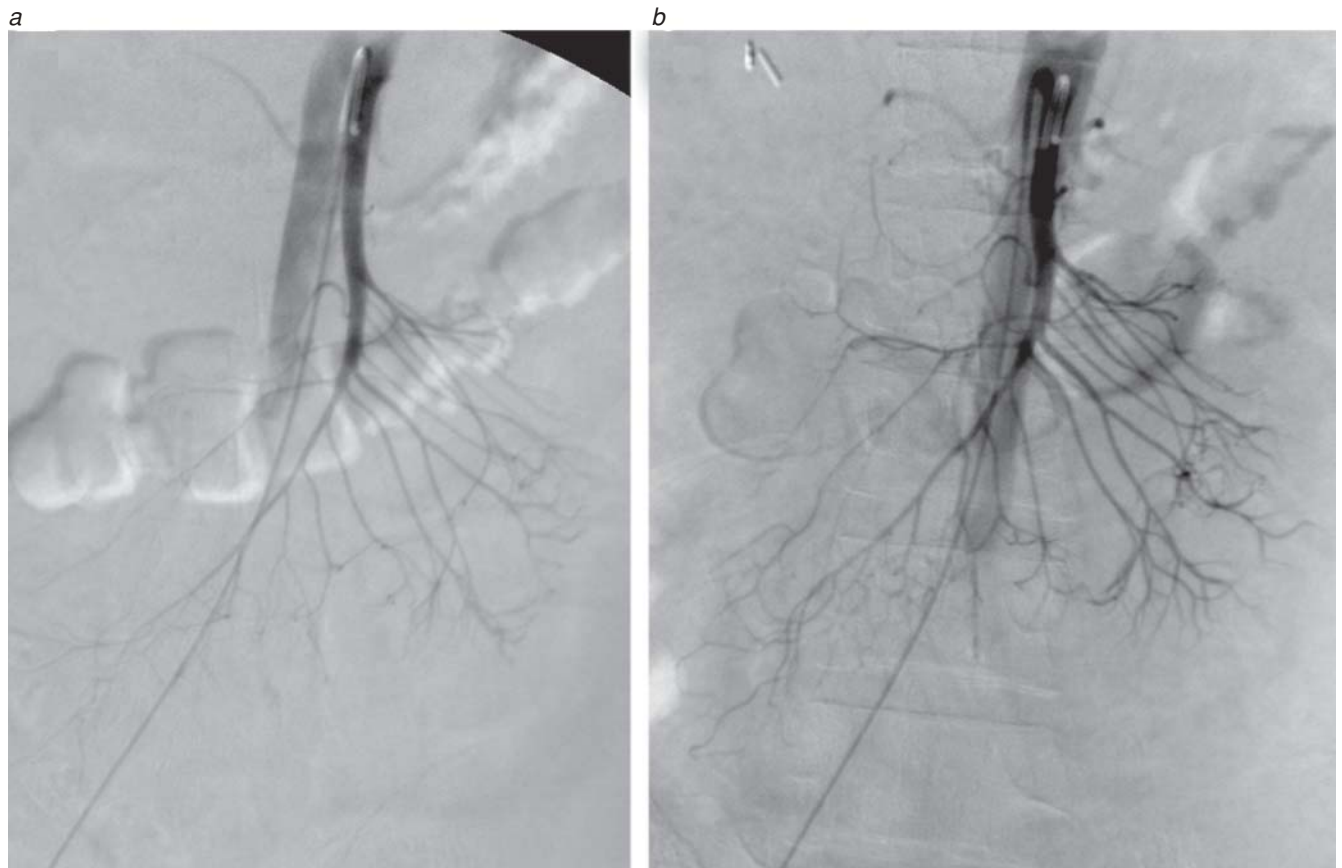


Figure 7 Shown are contrast angiograms of aorta and mesenteric vessels in a patient with nonocclusive mesenteric ischemia. (a) Selective angiogram (anterior projection) of the superior mesenteric artery (SMA) demonstrates distal spasm of SMA. (b) Selective angiogram (anterior projection) of SMA after intra-arterial papaverine infusion demonstrates improved filling of distal branches of SMA.

Percutaneous interventional treatment of acute SMA occlusion has also been described in the literature. At present, however, the applicability of this approach is limited in that most patients present with symptoms that warrant an exploratory laparotomy for evaluation of intestinal viability. In

patients who present with abdominal pain, have no peritoneal signs that would necessitate an immediate exploratory laparotomy, and are found to have a partially occluding embolus in the SMA, catheter-directed intra-arterial thrombolytic therapy is worth considering. Demirpolat and colleagues reported performing mechanical thrombus fragmentation in three such patients with good success.¹⁴ We have treated a few patients with partially occlusive emboli and no peritoneal signs on presentation at our institution using endovascular approaches. This route should be used cautiously, however, and if intra-arterial thrombolytic therapy is instituted, the patient should be closely monitored in the ICU with serial abdominal examinations. Even if thrombolytic therapy does restore blood flow to the ischemic intestine, the patient may still experience pain sufficient to necessitate exploration. For these reasons, our use of thrombolytic therapy is highly selective.

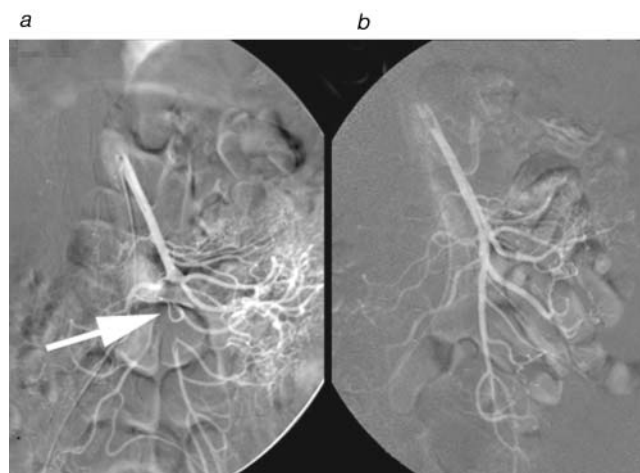
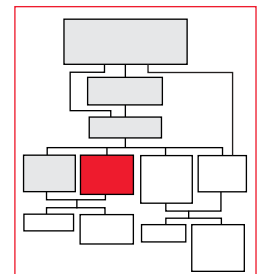


Figure 8 (a) Selective angiogram of the superior mesenteric artery demonstrates partially occluding embolus in distal vessel (arrow). (b) Selective angiogram after catheter-directed intra-arterial thrombolytic therapy shows resolution of embolus.

Thrombotic Occlusion of Mesenteric Vessels

Acute mesenteric ischemia secondary to thrombotic disease occurs in patients with long-standing atherosclerotic disease of the mesenteric vessels. In this situation, the entire midgut is usually involved.



Surgical treatment consists of a bypass procedure, which may be done in either an antegrade or a retrograde manner. The conduit of choice is a reversed autologous great saphenous vein graft. If possible, synthetic graft material should be avoided in the setting of acute bowel ischemia given the high risk of transmural bowel infarction and perforation.

There are several different inflow options for revascularizing the SMA that must be considered carefully. The main choices for inflow are the supraceliac aorta, the infrarenal aorta, and the iliac artery. In cases of acute mesenteric ischemia where time is of the essence and prompt revascularization of the bowel is required, it is often easier to perform a retrograde bypass from the infrarenal aorta or iliac artery in that the exposure is relatively simple and readily familiar to all vascular surgeons. Furthermore, a retrograde bypass yields less hemodynamic compromise because it avoids supraceliac clamping and the associated mesenteric and renal ischemia. Accordingly, retrograde bypass is the preferred approach in our institution. In cases of acute mesenteric ischemia where the suprarenal aorta is easily approachable and not calcified, however, an antegrade vein graft from the suprarenal aorta to the SMA will lie better because it is less susceptible to kinking than a retrograde graft once the bowel is restored to its correct anatomic position.

More recently, a technique that successfully combined an open and endovascular approach for the treatment of thrombotic occlusion of an atherosclerotic SMA lesion has been described.^{15,16} In this approach, the infracolic SMA was exposed as usual, and following thrombectomy and patch angioplasty, a sheath was placed in the infracolic SMA through the distal end of the patch for retrograde cannulation and stenting of the culprit lesion. This hybrid technique is an attractive alternative to the traditional surgical approach because it combines open laparotomy and bowel assessment with a rapid approach to revascularization that limits ischemic time.

Nonocclusive Mesenteric Ischemia

Management of NOMI is largely nonoperative. Once the diagnosis has been established with angiography [see Figure 7], treatment of the underlying precipitating cause is the key therapeutic intervention. Optimization of fluid resuscitation, improvement of cardiac output, and elimination of vaso-pressors are the measures that have the greatest impact on outcome. Selective catheterization of the SMA with direct intra-arterial infusion of papaverine (30 to 60 mg/hr) may be employed as adjunctive therapy. The infusion is continued for at least 24 hours, with repeat angiography performed at regular intervals to determine the effectiveness of this therapy. Alternatively, Sommer and Radeleff described using direct intra-arterial administration of tolazoline and glycerol trinitrate as local vasodilators in patients with NOMI with good clinical success.¹⁷

If the patient presents with peritoneal signs on physical examination, an exploratory laparotomy will be required for resection of frankly necrotic or gangrenous bowel. If an intra-arterial infusion of papaverine has been initiated, it should be continued throughout the exploratory laparotomy. Given the known propensity of this disease process for waxing

and waning, a second-look laparotomy is also imperative [see Second-Look Laparotomy, below].

Mesenteric Venous Thrombosis

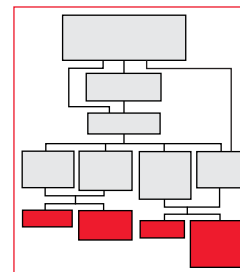
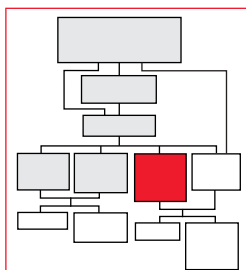
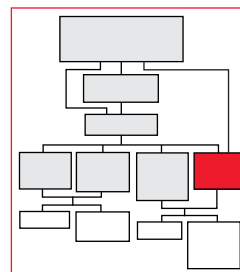
Once MVT is diagnosed, the mainstay of therapy is anticoagulation. If the patient's condition does not improve or worsens after anticoagulation or if signs or symptoms of bowel ischemia (e.g., peritonitis) develop, abdominal exploration is warranted. Typically, the bowel is dusky and edematous. All frankly necrotic bowel should be resected. Within 24 to 48 hours, a second-look laparotomy should be performed to evaluate the viability of any marginally perfused bowel [see Second-Look Laparotomy, below]. In a study of 31 MVT patients from our institution, the majority were successfully treated with anticoagulation alone and experienced complete resolution of their symptoms; however, 32% did require small bowel resection.² Perioperative mortality was 23%. Among those who survived operation, the long-term survival rate was 88%; all of these survivors were symptom free at last follow-up.

Thrombolytic therapy has also been employed to treat MVT. The catheter may be directed into the SMA for lysis of portal vein thrombus.² Alternatively, it may be directed into the SMV or the portal vein intraoperatively.¹⁸

Once the diagnosis of MVT has been established, a hypercoagulability workup should be performed in an effort to identify the underlying cause. If the cause is found to be a hematologic hypercoagulable state, lifelong anticoagulation is recommended. If the cause is reversible, anticoagulation may be discontinued after 3 to 6 months.

SECOND-LOOK LAPAROTOMY

Second-look laparotomy is an essential part of the management of acute mesenteric ischemia. No matter which adjunctive method is used intraoperatively to assess bowel perfusion and viability, second-look laparotomy is the most reliable means of determining the viability of marginally perfused bowel after revascularization. A second-look laparotomy should be preceded by adequate fluid resuscitation and correction of the acid-base imbalance. Furthermore, the decision to perform a second-look laparotomy should be made during the first operation and adhered to no matter what the patient's condition is 24 to 48 hours later. Yanar and colleagues proposed to perform a second-look laparotomy when patients present with a low-flow state, when small bowel is resected and anastomosed during the initial operation, or when a mesenteric thromboembolism is performed during the first operation.¹⁹ Occasionally, even though the patient is in better physical condition 24 to 48 hours later—largely because of aggressive fluid resuscitation and correction of the acid-base imbalance—there is still some necrotic bowel that must be resected. Accordingly, we adhere to a strict policy of planned reexploration for acute mesenteric ischemia patients who require bowel resection during the initial operation or who have areas of marginally viable bowel after revascularization.



Intraoperative Consultation

Vascular surgeons are frequently consulted intraoperatively to evaluate a patient for acute mesenteric ischemia. Often the patient has been taken to the OR on an emergency basis for acute abdominal pain with peritoneal signs or hemodynamic instability [see Figure 9]. In the OR, acute mesenteric ischemia typically presents as diffuse bowel ischemia. The first decision point in the evaluation is the determination of whether the bowel is salvageable.

Determination of Bowel Viability

If diffuse bowel necrosis exists and the bowel is not salvageable, it is best to close the abdomen without attempting

further therapy. Approximately 50 cm of viable bowel is required to sustain life if the ileocecal valve is present, and 100 cm is preferable.²⁰ Therefore, if it is obvious that no bowel can be preserved, further intervention is pointless. If the bowel is salvageable, blood flow to the bowel is evaluated by assessing the pulses and/or Doppler signals in the SMA. If no pulse can be detected in the SMA, revascularization should be undertaken before bowel resection.

INTRAOPERATIVE EVALUATION OF SMA

SMA pulses are assessed by palpating the root of the mesentery. The transverse colon is reflected superiorly, and the small bowel is reflected to the patient's right. The SMA is then palpated by placing four fingers of the hand behind

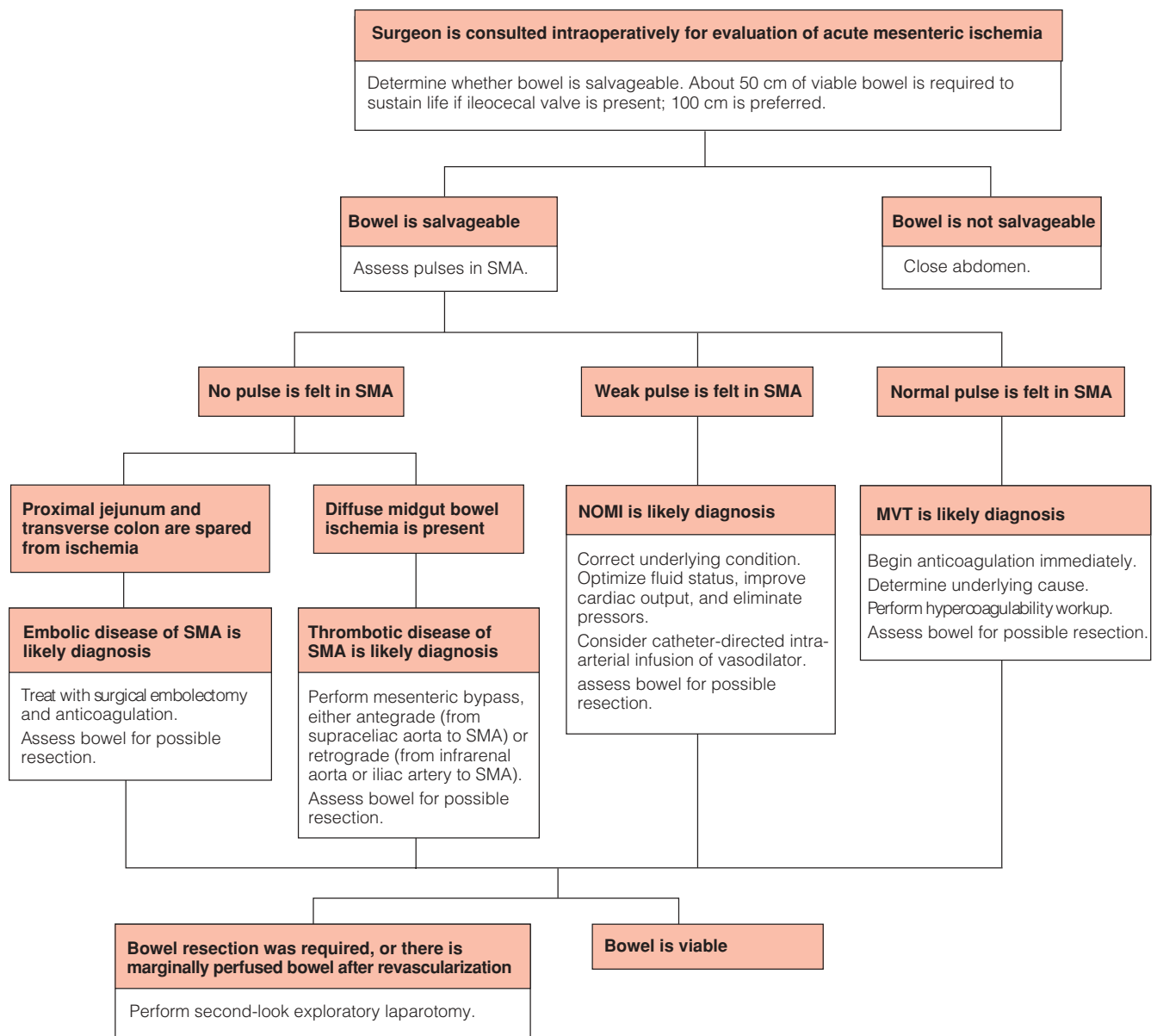


Figure 9 Algorithm illustrates intraoperative determination of bowel salvageability, evaluation of the superior mesenteric artery (SMA) pulses, and assessment of bowel viability after revascularization. MVT = mesenteric venous thrombosis; NOMI = nonocclusive mesenteric ischemia.

the root of the mesentery, with the thumb opposite and anterior to the root. The SMA can also be identified by following the middle colic artery proximally until it enters the SMA. Alternatively, a handheld Doppler device may be employed to listen to the quality and character of the arterial signal at the root of the mesentery. It is important to palpate the SMA pulse distally as well as proximally to ensure that the patient does not have an embolus to the distal SMA. Intraoperative angiography may also be used for evaluation, but it is often difficult to perform in the OR if there has not been adequate preparation and setup ahead of time, and it may not be feasible in some institutions.

If a strong pulse is appreciated throughout the length of the SMA, MVT is the probable cause of the diffuse bowel ischemia. Once MVT is suspected, IV administration of heparin should immediately follow. If the SMA pulse is present but weak, the diagnosis of NOMI should be entertained. However, if there is no SMA pulse at the root of the mesentery, the most likely diagnosis is in situ thrombosis from chronic mesenteric arterial disease [see Figure 4]. If the SMA pulse is palpable proximally but not several centimeters distally, the likely diagnosis is an embolus to the SMA [see Figure 4]. Distinguishing between these two conditions is important because their surgical treatments differ significantly. To make this distinction correctly, the surgeon should be aware of how the patient presented, whether the patient experienced postprandial abdominal pain for an extended period before the acute presentation, and whether the patient has other risk factors of arterial occlusive disease [see Clinical Evaluation, *above*]. In addition, the surgeon should be aware of the specific pattern of bowel ischemia present.

DIFFERENTIATION OF PATTERNS OF BOWEL ISCHEMIA

The different causes of acute mesenteric ischemia are associated with different classic patterns of bowel ischemia, which must be distinguished from one another. The basic distinction between arterial and venous pathologic conditions is relatively simple. In mesenteric ischemia resulting from venous disease, the bowel typically is diffusely edematous, congested, and dilated. In mesenteric ischemia resulting from arterial disease, the small bowel is typically contracted during the early phase of presentation, although it may be dilated and edematous when the patient presents late with frank bowel necrosis.

Within the category of arterial causes of acute mesenteric ischemia, the various underlying conditions are also associated with distinct patterns of bowel ischemia. Typically, in embolic disease, the small bowel and the proximal colon are affected, and the proximal jejunal segment and the transverse colon are spared [see Figure 10]; the reason is that the embolus usually lodges just past the middle colic artery and the jejunal branches of the SMA. If the entire small bowel is diffusely affected, as well as the ascending and transverse colon, the origin of the SMA is probably occluded; this disease pattern is consistent with thrombotic occlusion of the vessel

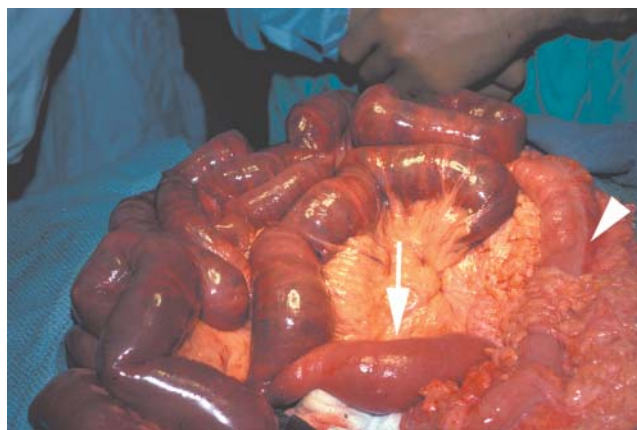


Figure 10 Intraoperative photograph of patient who presented with acute mesenteric ischemia secondary to embolus of the superior mesenteric artery shows diffuse bowel ischemia with classic sparing of proximal jejunum (arrow) and transverse colon (arrowhead).

by underlying atherosclerotic lesions. In NOMI, the entire small bowel may be affected, but the pattern of ischemia tends to be patchy, with segmental areas of involvement.

INTRAOPERATIVE ASSESSMENT OF BOWEL VIABILITY AFTER REVASCULARIZATION

Approximately 10 to 20 minutes after revascularization, the viability of the intestine should be assessed. Waiting until after revascularization to assess the extent of irreversible bowel ischemia or necrosis requiring resection makes it possible to preserve more bowel length. After restoration of flow, the bowel may contain frankly necrotic areas, normal areas, and marginally perfused areas. Obviously, clearly necrotic or nonviable bowel must be resected at the time of the operation. Determination of the viability of marginally perfused bowel is more difficult.

Intraoperatively, the color, motility, and integrity of the bowel should be evaluated. The characteristic appearance of ischemic bowel includes loss of the normal sheen, dull-gray discoloration, and lack of peristalsis. Determination of the character and quality of the pulses in the antimesenteric border and the mesenteric arcades may help determine which areas of the bowel will remain viable once revascularization has been performed. Intraoperative Doppler assessment of bowel perfusion may be performed with a sterilized continuous-wave Doppler ultrasound flow detector. The probe is placed on the antimesenteric border of the intestine to detect pulsatile Doppler signals. Even in the best of hands, however, this technique remains unreliable in predicting subsequent bowel viability.

Other diagnostic options include IV administration of fluorescein, transcutaneous oxygen measurement, and second-look exploratory laparotomy. All of these measures are relatively simple to perform, but each has limitations.

Discussion

Mesenteric Ischemia and Reperfusion

Although acute mesenteric ischemia is initially managed surgically, significant morbidity and mortality remain after treatment, largely resulting from local and systemic inflammation and the subsequent development of multiple organ dysfunction syndrome (MODS). Mesenteric ischemia-reperfusion promotes local synthesis and release of various inflammatory mediators that exacerbate gut injury and prime circulating neutrophils for enhanced superoxide anion production and subsequent remote (i.e., pulmonary and hepatic) injury.²¹ At the cellular level, mesenteric ischemia-reperfusion activates a cascade of oxidative stress-sensitive protein kinases that converge on specific transcriptional factors to regulate expression of proinflammatory genes. These gene products include enzymes (e.g., inducible nitric oxide synthase [iNOS], cyclooxygenase, and phospholipase A₂), cytokines (e.g., tumor necrosis factor- α [TNF- α] and interleukin-1 [IL-1]), chemokines (e.g., IL-8), and adhesion molecules (e.g., intercellular adhesion molecule-1 [ICAM-1]).^{22–28} Excessive gene activation leads to a maladaptive systemic inflammatory response syndrome that can trigger early MODS. Alternatively, this hyperinflammatory state can cause local gut dysfunction, characterized by histologic evidence of mucosal injury, increased intestinal epithelial and microvascular permeability, and impaired motility; patients become more susceptible to bacteremia and endotoxemia and, eventually, to late MODS.²⁹

Experimental work suggests that mesenteric ischemia-reperfusion triggers protein phosphorylation cascades that converge on specific transcription factors to regulate the pattern, timing, and magnitude of expression of not only proinflammatory but also anti-inflammatory gene products.²⁹ Presumably, this process is mediated by alterations in the cellular redox state induced by the conversion of xanthine dehydrogenase to xanthine oxidase during ischemia, with subsequent production of reactive oxygen metabolites and hydrogen peroxide during reperfusion.³⁰ Alterations in the cellular redox state activate families of stress-sensitive protein kinases, such as the nonreceptor tyrosine kinases c-Src and Syk, PI3-kinase/Akt, and the mitogen-activated protein kinases. These parallel kinase cascades phosphorylate nascent transcription factors (e.g., nuclear factor- κ B [NF- κ B] and activator protein-1 [AP-1]), which target genes that encode proteins involved in mediator synthesis.^{29,31}

Therapies directed at attenuating these pathways have been successful in laboratory models of mesenteric ischemia-reperfusion and may eventually be able to affect outcome in patients presenting with acute intestinal ischemia.^{32–36} However, clinical trials investigating the efficacy of pharmacologic blockade of individual mediators (e.g., TNF- α , IL-1, and iNOS) have found this approach to be largely unsuccessful and sometimes even deleterious in treating patients with sepsis and MODS.³² The reasons for the failure of these trials are probably multifactorial, but it appears that both the redundancy and breadth of the inflammatory cascade and the poor timing of therapy (i.e., the inability to target early

inflammatory events) are major contributing factors. The application of more broad-based therapeutic modalities such as regional controlled hypothermia for organ protection during ischemia may alleviate these aforementioned limitations and prove yet to be efficacious in the clinical setting.^{37,38} Nonetheless, it is likely that to achieve any meaningful improvements in our ability to treat patients with acute mesenteric ischemia, we will have to expand our knowledge of the early molecular pathways involved in the activation and proliferation of both local and systemic inflammation.

Outcome after Surgical Treatment

Most studies that include a large number of patients with acute mesenteric ischemia report perioperative mortalities ranging from 32 to 69% and 5-year survival rates ranging from 18 to 50%.^{1,39,40} A 2003 study reviewed the institutional experience at Wake Forest University between 1990 and 2000.³⁷ Seventy-six patients were treated for acute mesenteric ischemia, of whom 42% had embolic disease and 58% had thrombotic disease. Various surgical treatment options were employed, including exploration alone, bowel resection alone, and revascularization with or without bowel resection. Overall perioperative mortality was 62%. When mortality was examined in relation to the cause of ischemia, however, patients with embolic disease tended to fare better: overall perioperative mortality was 62 to 70% for patients with thrombotic disease and 50% for those with embolic disease. None of the patients who underwent exploration alone survived; 33% of those who underwent intestinal resection alone survived. In contrast to perioperative mortality, morbidity was higher in the embolic disease group than in the thrombotic disease group (69% versus 46%). The 5-year survival rates were dismal in both groups (18%). Peritonitis and bowel necrosis at presentation were found to be independent predictors of death or survival dependent on total parenteral nutrition.

In a 10-year institutional review from the Mayo Clinic, 58 patients were treated for acute mesenteric ischemia.¹ Overall 30-day mortality was 32%; however, when the data were further analyzed according to the cause of ischemia, it was found that mortality from embolic disease was 31%, mortality from thrombotic disease was 32%, and mortality from NOMI was 80%. Multiple organ failure was the most frequent cause of death. The 1-year and 3-year cumulative survival rates were 43% and 32%, respectively. Independent predictors of survival included age less than 60 years, bowel resection, and the absence of a recent major cardiovascular procedure.

Schoots and colleagues performed a systematic review of survival after acute mesenteric ischemia according to underlying cause by evaluating available data from the period between 1966 and 2002.⁴¹ The investigators examined 45 observational studies, which included 3,692 patients with acute mesenteric ischemia. They reported that mortality varied substantially according to the cause of the acute mesenteric episode. Overall survival was better for patients with ischemia of venous origin (i.e., MVT) than with ischemia of arterial origin. Within the category of arterial causes, mortality was 54.1% after treatment

of arterial embolic disease, 77.4% after treatment of arterial thrombotic disease, and 72.7% after treatment of NOMI. The difference in mortality between embolic and thrombotic disease may be accounted for by the tendency of thrombosis to occur more proximally and thus to be associated with a greater degree of bowel infarction than that of embolic disease, and that patients with thrombotic disease have a greater burden of underlying cardiovascular comorbidity. A recent article highlighted the increasing trend in the United States toward the use of endovascular revascularization for acute mesenteric ischemia and its potential impact on improved outcomes.⁴² This study investigated the outcomes of 1,857 patients who underwent

SMA percutaneous transluminal angioplasty with or without stenting (PTA/S) versus 3,380 patients who underwent surgical revascularization from the Nationwide Inpatient Sample from 1988 to 2006. In-hospital mortality was significantly less for patients treated with PTA/S (15.6%) versus surgical revascularization (38.6%). Although this large retrospective study certainly has inherent limitations with regard to a comparative effectiveness analysis, novel, less invasive therapies may prove to be effective in reducing the tremendous morbidity and mortality associated with this disease.

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Figure 4. Alice Y. Chen.

5 PULSELESS EXTREMITY AND ATHEROEMBOLISM

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Approach to the Acutely Ischemic Limb

Pulseless Extremity (Acute Limb Ischemia)

Limb ischemia occurs when blood flow to an extremity is inadequate. It is commonly the result of stenosis or occlusion of a native vessel or bypass graft, and the symptoms are directly related to the duration and severity of the hypoperfusion. Acute limb ischemia (ALI) is a sudden reduction in limb perfusion that threatens the viability of an extremity [see Discussion, Pathophysiology of ALI, below]. The incidence of ALI in the general population is approximately 1.7/10,000 per year.¹ The clinical presentation ranges from subtle to dramatic and is often complicated by various comorbid conditions typically seen in patients with vascular diseases [see Table 1]. The goals of management include limb salvage, minimization of morbidity, and prevention of death. However, given that no objective markers of limb viability are currently available, the initial determination of whether a limb is likely to be viable must be made on clinical grounds.

A study from the 1970s that comprised more than 3,000 patients with ALI from 35 centers documented a mortality of 26% and an amputation rate of 37%.² Since then, substantial progress in surgical management has been made and major technological advances have occurred, but morbidity and mortality remain high, with death rates approximating 15% and amputation rates ranging from 10% to 30%.³

Given the general frailty of ALI patients and the multiplicity of available therapeutic options, it is prudent to take a methodical approach to the management of ALI. Making use of algorithms,

decision trees, or clinical pathways can help the clinician visualize and evaluate multiple potential options that then serve as the basis for selecting the path likely to yield the best outcome.

CLINICAL EVALUATION

History

Because ALI is a clinical diagnosis, a complete history is essential (unless it is unobtainable for some reason). Generally, the dominant symptoms are related to pain (usually the first manifestation) or to loss of function. The onset and duration of symptoms should be determined, and the location and the intensity of any changes should be established. The pain of ALI is often not well localized and is unaffected by gravity. An effort should be made to determine whether the likely cause is embolic or thrombotic: pain of sudden onset suggests an embolic cause, whereas long-standing pain before the acute event suggests a thrombotic cause [see Discussion, Etiology of ALI, below].

It is imperative to ask whether the patient experienced pain before the current ischemic episode and whether the current episode is the first. It is also important to ask about previous surgical revascularization, as well as previous or current cardiac disease (e.g., myocardial infarction [MI], atrial fibrillation, or valvular disease), aneurysmal disease, or vasculitis. Finally, inquiries

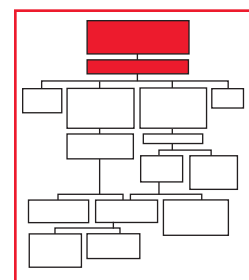


Table 1 Incidence of Medical Comorbidities in Patients Presenting with ALI⁹⁷

Comorbidity	Incidence (%)			
	Rochester Trial (N = 114)	TOPAS-1 Trial (N = 213)	TOPAS-2 Trial (N = 544)	Total (N = 871)
Cerebrovascular disease	NR	15.4	11.5	11.6
Congestive heart failure	NR	15.5	12.5	13.3
Coronary artery disease	56.1	47.1	42.5	45.4
Diabetes mellitus	28.1	36.7	29.0	30.8
Hypercholesterolemia	31.6	29.6	23.5	26.0
Hypertension	63.2	60.9	69.6	60.3
Malignancy	NR	11.9	11.5	11.6
Tobacco history	51.8	79.3	77.5	74.6

NR—not reported TOPAS—Thrombolysis Or Peripheral Arterial Surgery

Approach to the Acutely Ischemic Limb

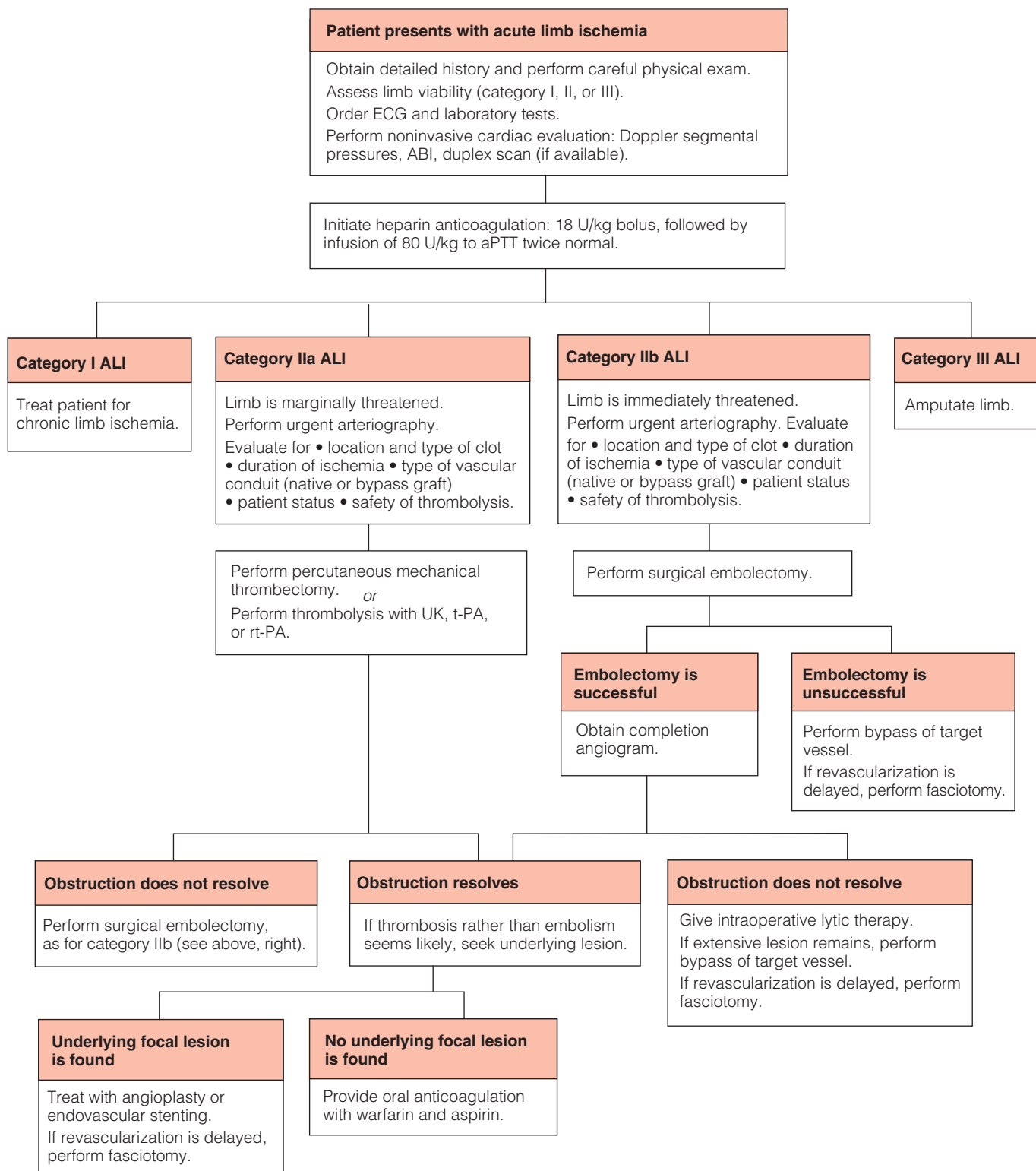


Table 2 Localization of Arterial Obstruction through Palpation of Peripheral Pulses⁹⁷

Palpable Pulses			Location of Obstruction	Possible Causes
Femoral	Popliteal	Pedal		
–	–	–	Aortoiliac segment	Aortoiliac atherosclerosis; embolus to common iliac bifurcation
+	–	–	Femoral segment	Thrombosis, femoral atherosclerosis; common femoral embolus
+	++	–	Distal popliteal ± tibials	Popliteal aneurysm with embolization
+	+	–	Distal popliteal ± tibials	Popliteal embolus; popliteal/tibial atherosclerosis, diabetes

should be made about previous atherosclerotic disease, current risk factors for atherosclerosis (e.g., hypertension, smoking, diabetes, tobacco abuse, hyperlipidemia, and stroke), and previous clotting episodes.

The characteristic signs of ALI may be summarized as the six Ps: Pulselessness, Pain, Pallor, Poikilothermia, Paresthesia, and Paralysis.

1. Pulses should be palpated and documented. Any previous documentation should be noted and used for comparison. Careful evaluation of pulses will help localize the area of arterial obstruction. When clot is fresh, its soft, semiliquid consistency allows the pulse to be translated at the level of obstruction. Only when the thrombus becomes organized and densely compacted is the pulse lost at the site of occlusion. As an example, in a patient with obstruction at the popliteal artery, popliteal pulses remain palpable in the earlier stages of the process, but distal pulses are lost [see Table 2].
2. Pain should be documented with regard to severity, area, and progression.
3. Pallor may be seen in the early stages, followed by cyanosis.
4. Poikilothermia may propagate the ischemic cascade through its vasoconstrictive effects. The level of coolness and pallor is typically one level below the point of occlusion on the arterial tree, and it should correlate with the pulses or signals found. As always, baseline documentation should be done so that the progression or resolution of the process can be tracked.
5. Paresthesia is an essential finding. The earliest sign of tissue loss is the loss of light touch, two-point discrimination, vibratory perception, and proprioception, especially in the first dorsal web space of the foot.
6. Paralysis, if present, is an indication of advanced limb-

threatening ischemia. The extent of paralysis must be determined. The intrinsic muscles of the foot are affected by ischemia of the vessels around the ankle. Dorsiflexion and plantar flexion of the foot are functions of muscles that rely on blood supplied by the popliteal and superficial femoral arteries. Loss of dorsiflexion and plantar flexion indicates that blood flow is cut off at a higher level and signals that more tissue may be at risk.

Staging of Limb Ischemia

The primary goal of the clinical evaluation is to determine the severity of the disease process so that appropriate management can be rapidly instituted. To this end, the key question that must be answered is whether the limb is viable. In 1997, the Joint Council of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery developed reporting standards for ALI and stratified it into three distinct categories on the basis of the severity of the disease process [see Table 3].⁴

In category I ALI, patients present with acute occlusion of an artery that is chronically narrowed. Therefore, abundant collaterals can be found, and the limb is viable. In category II ALI, the ischemic limb is threatened but may be salvaged without the need for an amputation if adequate revascularization can be achieved. This category is further subdivided into categories IIa and IIb. Category IIa includes patients with mild forefoot numbness or any lesion for which prompt revascularization of the limb achieves a good result. Category IIb includes patients with diminished sensation of the entire foot and weakness of calf muscles whose limb is still salvageable but who require immediate revascularization. In category III, ischemia is irreversible and amputation is required. Clinical features include permanent tissue loss, anesthesia, and paralysis of the limb.

Table 3 Clinical Categorization of ALI⁴

Category	Findings			Doppler Signals	
	Description/Prognosis	Sensory Loss	Muscle Weakness	Arterial	Venous
I. Viable	Not immediately threatened	None	None	Audible	Audible
IIa. Marginally threatened	Salvageable if promptly treated	Minimal (toes) or none	None	(Often) inaudible	Audible
IIb. Immediately threatened	Salvageable with immediate revascularization	More than toes, associated with rest pain	Mild, moderate	(Usually) inaudible	Audible
III. Irreversible*	Major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

*When presenting early, category IIb and category III may be difficult to differentiate.

INVESTIGATIVE STUDIES

Additional diagnostic tests should be performed to support the clinical evaluation. An electrocardiogram should be obtained, and if a cardiac source is suspected, a transesophageal echocardiogram should be obtained as well. A full set of laboratory tests, including a complete blood count and a platelet count, blood chemistries, and coagulation profiles, should be ordered. In addition, chest and abdominal x-rays should be done to look for obvious calcifications. If it appears that a hypercoagulable state may be causing thrombosis, a hypercoagulability profile should be ordered. If, however, a limb is acutely ischemic and exhibits clear motor or sensory deficits, diagnostic tests—other than an ECG and basic hematologic and blood chemistry studies—should not be allowed to delay treatment.

Evaluation of Arterial Tree

An objective evaluation of the arterial tree should be performed when feasible. If ischemia is particularly severe and long-lasting, a full angiographic evaluation may not be possible; however, noninvasive duplex studies and, if time permits, angiography should be considered strongly in this setting.

Doppler segmental pressures and ankle-brachial index

Evaluation of Doppler segmental pressures should begin at the level of the ankle and should include assessment of arterial signals and venous hums. When arterial signals are found, the ankle-brachial index (ABI) should be measured.

The ABI is derived from the ankle systolic pressure and the brachial systolic pressure and is determined as follows. The systolic pressure is measured in each arm, and the higher of the two measurements is taken to be the brachial systolic pressure. A cuff is then placed on each calf, and the examiner listens to signals in the dorsalis pedis and posterior tibial arteries. The cuff is inflated until the signal is no longer heard. At this point, the cuff is slowly released, and the systolic pressure is recorded at the point where the signal is once again audible. Again, the higher of the two systolic measurements is taken to be the ankle systolic pressure. The systolic ankle pressure is then divided by the brachial systolic pressure to yield the ABI. An ABI in the range of 0.9 to 1.0 is normal; however, the ABI can be falsely elevated if the distal arteries are not compressible. When the ABI falls below 0.6, there is a significant difference in blood pressure between the proximal arterial tree and the distal extremity, which usually denotes an occlusive process. Next, segmental pressures are obtained by placing cuffs at the ankle, below the knee, above the knee, and on the thigh. Systolic blood pressures are measured at each location, and any pressure drop greater than 15 mm Hg is considered significant.

When the venous Doppler signal or hum is lost in addition to the arterial Doppler signal, the ischemia is severe. However, the absence of signals does not always signify an irreversibly threatened limb.

Duplex ultrasonography Duplex scanning can be valuable for localizing the site of occlusion, especially in bypass grafts. Unfortunately, it is not always a practical option in acute circumstances, both because the machine is often unavailable in the emergency setting and because the results of scanning are highly operator dependent. However, in specialized centers where a duplex ultrasound machine is readily available and personnel are experienced in its use, a quick look at the suspected site may yield helpful information.⁵ In stenotic regions, the velocities measured across the lesion are greatly increased.^{6,7} In addition, duplex ultrasonography can be used to assess plaque morphology, stenoses,

dissections, and thrombi. In some centers, duplex ultrasound technology has obviated the need for lengthy arteriograms and has benefited patients by reducing ischemia time.

Arteriography Arteriography remains the gold standard for diagnosis of ALI and may even be a primary tool in its management. It should not, however, be performed if doing so would keep a critically ischemic leg from receiving prompt surgical therapy. Arteriography should be reserved for patients with viable limbs who can tolerate the additional delay before revascularization.

Arteriography should be performed from a site remote from the point of concern. Thus, if lytic therapy is to be administered, entry-site bleeding will be minimized. A complete angiogram that includes the runoff vessels in the foot should be performed to establish the baseline degree of arterial disease and delineate the anatomy of the inflow and outflow vessels. This information facilitates subsequent planning for revascularization, should this step prove necessary. Digital subtraction angiography is preferred in that it allows a reduced contrast load and lowers the incidence of contrast-associated renal injury.^{8,9} If the patient is allergic to the contrast agent or has renal insufficiency, CO₂- or gadolinium-based angiography may be performed instead. These two modalities have the advantage of minimizing nephrotoxicity, but they yield poorer suprainguinal arterial visualization than standard contrast angiography does.^{10,11}

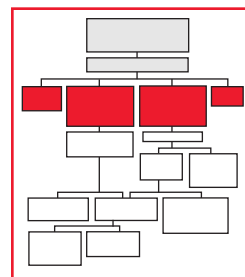
The arteriogram can provide useful clues for differentiating emboli from thrombi. In a patient with arterial embolism, there is often an identifiable source, there is rarely a history of claudication, contralateral and proximal pulses are normal, cutoff is sharp, atherosclerosis is minimal, a few collateral vessels are present, and a discrete clot is clearly visible on contrast studies. In a patient with arterial thrombosis, the thrombus has no identifiable source, there is a history of claudication with evidence of peripheral vascular disease, diffuse atherosclerotic vessel wall disease is present, cutoff is tapered and irregular, and there is ample collateral circulation.

Other modalities Depending on availability within a given institution and the level of quality achievable within the institution, either computed tomographic angiography (CTA) or magnetic resonance angiography (MRA) may be employed as alternative means of evaluating the vasculature of the limb. These two modalities are less invasive than conventional angiography, but depending on the particular information being sought, they may yield images of lower resolution than a standard angiogram, and they may be less diagnostically accurate. Nevertheless, as scanning technology continues to advance, the role of CTA and MRA in the evaluation of limb ischemia will continue to evolve.

MANAGEMENT

Until the middle of the 20th century, when revascularization techniques were developed, amputation was the only treatment for acute lower-extremity ischemia. Today, however, the vascular surgeon possesses an immense armamentarium for the treatment of this condition, ranging from emergency bypass to embolectomy or thrombectomy to thrombolytic therapy [see 6:17 *Infrainguinal Arterial Procedures* and 6:19 *Endovascular Procedures for Lower-Extremity Disease*].

ALI constitutes a clinical emergency. Rapid restoration of flow to the extremity substantially reduces morbidity and mortality. Accordingly, the clinician must be thoroughly familiar with the



therapeutic modalities available and capable of making an appropriate choice among them without undue delay. Whichever therapeutic modality is chosen for a given patient, several primary measures should be undertaken to protect and optimize the status of the extremity. Full, systemic anticoagulation (usually with heparin unless contraindicated) should not be delayed. The extremity should be placed in a dependent position, with care taken to avoid extrinsic pressure on the limb. Temperature fluxes should be minimized: cold induces vasoconstriction, and heat increases tissue demand and metabolic and circulatory demands. Finally, tissue oxygenation should be maximized via transfusion, improvement of cardiac function, and restoration of intravascular volume.

Proper and timely preoperative preparation is crucial for preventing rapid deterioration of the patient's condition. Laboratory tests and radiologic studies are necessary, and a cardiology evaluation is often helpful. The ABI should be documented. Abnormalities in blood counts, electrolyte concentrations, and coagulation profiles should be corrected. The duration of ischemia should be noted and any comorbid conditions identified so that the examiner can determine the appropriate degree of monitoring required (e.g., arterial line or pulmonary arterial catheter).

Anticoagulation

Heparin administration should be started as soon as the diagnosis of ALI is entertained. Numerous studies have shown that this measure decreases the morbidity and mortality associated with ALI and increases the limb salvage rate. Heparin impedes the propagation of clots and, in the instance of embolism, may help prevent additional events.

Heparin acts at multiple sites in the normal coagulation system, inhibiting reactions that lead to the clotting of blood and the formation of fibrin clots both in vitro and in vivo. Small amounts of heparin, in combination with antithrombin (heparin cofactor), can inhibit thrombosis by inactivating activated factor X and inhibiting the conversion of prothrombin to thrombin.¹² Once active thrombosis has developed, larger amounts of heparin can inhibit further coagulation by inactivating thrombin and preventing the conversion of fibrinogen to fibrin. Heparin also prevents the formation of a stable fibrin clot by inhibiting the activation of fibrin-stabilizing factor.¹²⁻¹⁴

Heparin does not have fibrinolytic activity and therefore does not lyse existing clots. Heparin therapy can be complicated by thrombocytopenia, which has a reported incidence of 0% to 30%.¹⁵ If the thrombocyte count falls below 100,000/mm³ or if recurrent thrombosis develops, heparin should be discontinued.^{16,17} Patients receiving heparin may experience new thrombus formation, either early or late, in association with this thrombocytopenic phenomenon as a consequence of irreversible heparin-induced platelet aggregation (the so-called white clot syndrome). This process may lead to severe thromboembolic complications, including skin necrosis, gangrene of the extremities, MI, pulmonary embolism, stroke, and, possibly, death.^{16,18,19} Accordingly, if new thrombosis develops in association with thrombocytopenia, heparin should be promptly discontinued and a suitable alternative (e.g., a direct thrombin inhibitor) used instead.

Periodic platelet counts, hematocrits, and tests for fecal occult blood are recommended during the entire course of heparin therapy, regardless of the route of administration. Bleeding time is usually unaffected by heparin. Clotting time is prolonged by full therapeutic doses of heparin, but in most cases, it is not measurably affected by low doses.

Thrombolytic Therapy

The use of thrombolytic agents to treat chronic and acute arterial insufficiency dates back to the 1970s, when it was popularized by Dotter.²⁰ Systemic fibrinolytic therapy has not proved effective and consequently has been supplanted by intra-arterial (catheter-directed) thrombolysis, which yields significantly better results. Still, the role of thrombolytic therapy for ALI is somewhat controversial. In addition, such therapy requires a skilled team with considerable clinical expertise, typically including a vascular surgeon, an interventional radiologist, and a well-trained ancillary staff. The benefits of pharmacologic clot lysis must always be weighed against those of surgical intervention and the risk of bleeding associated with fibrinolysis.

Despite the use of fibrin-specific agents and catheter-directed infusion, thrombolytic agents still exert systemic effects, most of which are dose related. About 10% of patients receiving thrombolytic therapy experience significant bleeding, including bleeding from both puncture and remote sites. Absolute contraindications to the use of lytic agents include recent surgery, recent stroke or brain tumor, pregnancy, a bleeding diathesis, recent trauma, and active bleeding [see Table 4].

Thrombolysis versus surgical treatment Three prospective, randomized trials—the University of Rochester trial, the Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) trial, and the Thrombolysis Or Peripheral Arterial Surgery (TOPAS) trial—addressed the differences between thrombolytic therapy and traditional surgery.²¹⁻²⁴

Rochester trial. This randomized, controlled single-center trial compared urokinase (UK) with surgery in patients with ischemia of less than 7 days' duration.²¹ At the end of 1 year, overall mortality was lower in the thrombolysis group (25%) than in the

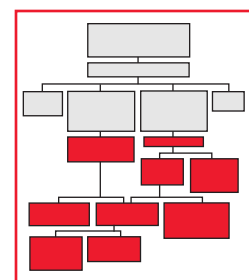


Table 4 Contraindications to Thrombolytic Therapy⁹⁸

Absolute contraindications

- Established cerebrovascular event (including TIAs) within past 2 mo
- Active bleeding diathesis
- GI bleeding within past 10 days
- Neurosurgery (intracranial, spinal) within past 3 mo
- Intracranial trauma within past 3 mo

Major relative contraindications

- Cardiopulmonary resuscitation within past 10 days
- Major nonvascular surgery or trauma within past 10 days
- Uncontrolled hypertension: systolic BP > 180 mm Hg, diastolic BP > 110 mm Hg
- Puncture of noncompressible vessel
- Intracranial tumor
- Recent eye surgery

Minor relative contraindications

- Hepatic failure, particularly in patients with coagulopathy
- Bacterial endocarditis
- Pregnancy
- Diabetic hemorrhagic retinopathy

TIA—transient ischemic attack

surgery group (48%). The amputation rates were similar in the two groups. Total hospital charges were comparable as well, which suggests that at initial treatment, thrombolytic therapy is as costly as surgery. Major bleeding was encountered in 11% of patients.

STILE trial. This randomized, controlled multicenter trial compared surgery with recombinant tissue plasminogen activator (rt-PA) and with UK.²² It was stopped early because of an increase in the number of patients with ongoing ischemia in the thrombolysis groups. An ad hoc committee later determined that the reason for this increase was the inclusion of chronically symptomatic patients in the study. In any case, the study clearly demonstrated that patients with less than 14 days of ischemia had a lower amputation rate when treated with thrombolysis (11% versus 30%) but that patients with more than 14 days of ischemia had a lower amputation rate when treated with surgery.

TOPAS trial. This randomized, controlled multicenter trial compared surgery with recombinant urokinase (r-UK) thrombolysis in patients with ischemic symptoms of less than 14 days' duration.^{23,24} At the end of 1 year, the amputation rates in the two groups were similar. Bleeding complications were seen only in patients undergoing thrombolysis, four of whom had intracranial hemorrhage. When additional end points were considered, the thrombolysis group was found to require significantly fewer major interventions at the time of discharge and at 12 months.

Recombinant tissue plasminogen activator versus urokinase. A prospective, randomized multicenter trial evaluated local thrombolysis with either rt-PA or UK in 234 patients with thrombotic occlusions (223 native femoral or popliteal arteries, 11 bypass grafts).²⁵ Complete reperfusion occurred in 62% of the patients treated with rt-PA and in 50% of the patients treated with UK. However, bleeding was observed in 12.8% of rt-PA-treated patients (including one instance of cerebral hemorrhage) and in 9.1% of UK-treated patients (none of whom experienced cerebral bleeding).

Current recommendations. Current data suggest, but do not prove, that thrombolytic therapy is effective as initial therapy for patients with acute arterial and graft occlusions and no sensorimotor deficits. Such an approach, however, is not suitable for patients with common femoral artery emboli, which should be treated surgically, and there are certain patients with sensorimotor deficits (e.g., those without any runoff) for whom the potential benefits of thrombolysis outweigh the risks of delay.

At present, acute thrombotic arterial occlusion in an occluded bypass graft is the area where intra-arterial fibrinolysis may be most useful, permitting better planning of the subsequent operation and resulting in a less extensive procedure. Such therapy, however, does not necessarily yield improvements in major long-term end points. It is important to remember that thrombosis of femoral-popliteal or similar bypasses is related to early or late surgical stenosis and atherosclerosis and that restoring flow usually does not suffice to ensure continued patency.

Logistics of thrombolysis In patients with mild or no sensory deficits, angiography is performed first. Depending on the location of the obstruction, the type of clot present, and the level of patient risk, the patient may be offered thrombolysis as initial therapy.

In our practice, the patient is taken from the emergency department to the angiography suite. Informed consent is obtained for

diagnostic and therapeutic angiography (including the use of stents, balloon angioplasty, stent grafts, and thrombolysis) and finally for the performance of an emergency surgical procedure. A discussion is undertaken with the patient to outline the course of treatment and to explain that indwelling catheters may have to be placed and that a stay in the ICU may be required.

Access to the arterial system is gained via a single-wall puncture technique [see 6:8 *Fundamentals of Endovascular Surgery*]; the risk of posterior-wall bleeding associated with a double-wall technique is thereby avoided. Access should be obtained from a site as remote from the intervention site as possible. Generally, this is accomplished by starting from the contralateral counterpart of the target artery and going up and over the aortic bifurcation, then back to the ipsilateral artery. By removing the puncture site from the site of catheter-directed thrombolysis, the incidence of bleeding and formation of hematomas or pseudoaneurysms is reduced.

After completion of the angiogram and delineation of the pathology, a guide wire is passed into the occluded area. We use a 0.035 in. hydrophilic guide wire, which has a slippery, wet coating that enables it to cross nonhydrophilic lesions. Once in place, the wire is guided through the clot. A multiple-sidehole catheter is placed through the clot, and a hand-injection angiogram is performed to confirm that the catheter tip is in the true lumen. The guide wire is then left within the catheter to occlude the tip, so that the lytic agent is infused through the sideholes preferentially. This graded "coaxial" infusion technique allows the agent to reach the greatest possible surface area, maximizes the length of infusion, and enables the surgeon to treat some of the longest bypass grafts. If the guide wire-catheter system cannot be advanced into the clot, it is highly unlikely that thrombolysis will be successful.

In many cases, mechanical thrombus removal, with or without pulse spray, is employed initially, followed by continuous infusion of a thrombolytic agent. In addition to lytic therapy, administration of heparin is started (200 to 400 units I.V. or via sheath) to prevent pericatheter thrombosis. Serial laboratory evaluation is carried out to verify that the patient is not bleeding and that the fibrinogen level is higher than 100 mg/dl. Serial follow-up arteriograms are obtained to monitor progress. It is critically important that successful thrombolysis be followed by treatment, whether endovascular or open, of any lesions uncovered during thrombolysis; if it is not, reocclusion is inevitable. At the conclusion of thrombolysis and before intervention, the patient must be kept on a heparin drip (or on another anticoagulant) to prevent the formation of a new thrombus. The rate of successful reperfusion is approximately 90% to 95% in most studies.

An important advantage of this selective approach is that it allows simultaneous angiographic definition of the nature of the occlusion (i.e., embolic or thrombotic) and of any vessel wall abnormalities that would lead to rethrombosis if not corrected by means of surgery or balloon angioplasty. A major drawback to this approach is that arterial catheterization is required for prolonged periods (20 hours, on average), leading to major bleeding and thromboembolic complications in 6% to 20% of patients. Therefore, the end points of thrombolytic therapy are (1) resolution and reconstitution of flow through the obstruction, (2) absence of change in the occlusion of the vessel on angiography, and (3) bleeding complications. If it is determined that thrombolysis is not progressing, it should be abandoned and surgical intervention undertaken.

Thrombectomy

Percutaneous aspiration thrombectomy This technique uses a large, thin-walled catheter and a large syringe to remove an

embolus or thrombus from a vascular conduit, whether native vessel or graft. The catheter is placed as previously described [see Logistics of Thrombolysis, *above*] and is parked immediately by the clot. Aspiration of the clot with the syringe is then attempted. If the clot is new, success is likely, but an old clot that is organized will not be as amenable to removal. Percutaneous aspiration thrombectomy is most effective as an adjunct to catheter-directed thrombolysis.^{26,27}

Percutaneous mechanical thrombectomy Percutaneous mechanical thrombectomy (PMT) functions on the basis of a hydrodynamic circulation. The basic concept is that a hydrodynamic vortex is created around the tip of the PMT catheter. Thrombectomy is accomplished with the introduction of a pressurized saline jet stream through the directed orifices in the distal tip of the catheter. The jets generate a localized low-pressure zone via the Bernoulli effect, which entrains and macerates thrombus. The saline and the fragmented thrombus are then sucked back into the exhaust lumen of the catheter and out of the body for disposal.

This technique has proved beneficial when used in appropriate settings and properly selected patients. Its efficacy depends on the age of the clot. Fresh thrombus is readily treated with PMT, but older clots are much less amenable to this technique and may have to be treated with an adjunctive catheter-based modality (e.g., angioplasty, intra-arterial thrombolysis, or atherectomy).²⁸⁻³¹

Surgical Embolectomy and Revascularization

When a patient has significant sensory and motor deficits related to a profoundly ischemic limb, immediate surgical revascularization is indicated. The decision whether to accomplish this percutaneously or surgically should be made expeditiously. Operating room availability should be determined, the method of anesthesia should be chosen, and the technical details of the procedure should be planned. Heparin administration should be started before the patient enters the OR. General anesthesia is the preferred method of anesthesia.

For lower-extremity emboli, access to the femoral vessels should be obtained rapidly. The common, deep, and superficial femoral arteries are controlled proximally and distally with vessel loops, and the common femoral artery is opened transversely. Catheter embolectomy of the superficial femoral, deep femoral, common femoral, and external iliac arteries is then performed. Differently sized embolectomy catheters are used, depending on the size of each artery. In our experience, a No. 3 catheter is usually suitable for the deep femoral artery, a No. 4 for the superficial femoral artery, and a No. 5 for the common femoral and external iliac arteries. The extracted clot is sent for pathologic evaluation. When the clot is believed to be in the distal vessels of the lower extremity, control of the popliteal artery and its trifurcation is obtained via a popliteal incision. A No. 3 catheter should be adequate at this site.

For upper-extremity emboli, a curvilinear incision is made that starts on the medial aspect of the upper arm, extends transversely across the antecubital fossa, and ends halfway down the middle of the lower arm [see 6:15 *Upper-Extremity Revascularization Procedures*]. This incision allows control of the brachial, radial, and ulnar arteries. A No. 3 embolectomy catheter is typically used here.

Several passes are done in each vessel until no more clot can be seen and there is brisk back-bleeding from the vessel. When no further clot can be retrieved, a completion angiogram is obtained to visualize the distal vessels and elucidate any anatomic pathology in the native vessels. If distal clot is still present after the completion angiogram, intraoperative thrombolysis can be employed for a brief

period to soften the clot. The multiple-sidehole catheter is advanced distally to the location of the clot, the guide wire is passed through the lesion, and the catheter is passed over the wire into the substance of the clot. Infusion of the lytic agent is then started.

Repeat angiograms indicate whether the clot has dissolved or is still present. If the clot is still apparent, repeat embolectomy is attempted. If thrombosis rather than embolism is suspected, an underlying lesion must be sought. In performing the embolectomy, attention should be paid to the tactile sensations felt as the balloon is withdrawn. Such sensations give the operator a sense of the disease process. When several deflations are needed and the withdrawal path of the balloon feels rough, a long-standing process (e.g., an atherosclerotic calcified vessel with anatomic discrepancies) is likely.

If there appears to be no residual clot after embolectomy, then a completion angiogram is sufficient and the artery can be closed primarily. Heparin is continued, and the patient is eventually switched to warfarin, which is continued for at least 6 months postoperatively. Finally, the location from which the embolus originated is sought and appropriately treated. When an underlying lesion is identified, a decision must be made as to whether it can be treated with angioplasty or stenting or whether a formal bypass is required to correct the problem and salvage the limb.

Key to the final management of these patients is assessment of the lower extremities, especially the calves, for compartment syndrome. To minimize the chances that an otherwise successful surgical operation may fail as a consequence of this syndrome, we typically perform intraoperative fasciotomies on the extremity if profound ischemia has been present for several hours.

Cost Considerations

A retrospective study published in 1995 compared thrombolysis with surgical thrombectomy as first-line therapy for ALI.³² Only the costs of the initial admission were documented. The average charge for the two treatments ranged from \$20,000 to \$26,000. Economic analysis confirmed that the total economic impact of thrombolysis approximated that of initial operative therapy. The conclusion of the study was that there was no difference between an endovascular approach and an operative approach with respect to cost. Thus, when acute treatment of ALI is being considered, cost should not be factored into the decision-making process.^{32,33}

Atheroembolism

Atheroembolism is a condition in which microscopic cholesterol-laden debris travels from proximal arteries until it reaches the most distal arterial segments, typically in the skin of the lower extremities and in the end-organs.³⁴⁻³⁷ This debris usually originates from unstable plaque found at inflection points in the arterial tree, especially in the aorta.^{38,39} It may also originate from aneurysmal sacs either in the aorta or in the peripheral arteries.

CLINICAL EVALUATION

Patients with atheroembolism usually present with focal toe ischemia—the so-called blue toe syndrome—in conjunction with palpable pulses in the distal extremity [see *Figure 1*]. Acute pain of sudden onset is typically noted in the affected area. This pain can often establish the exact timing of embolization. Cyanosis is present either on the toe or over a more extensive area if the atheroemboli were circulated throughout the extremity.^{40,41} When both lower extremities are involved, an aortic source of the microemboli is commonly found.

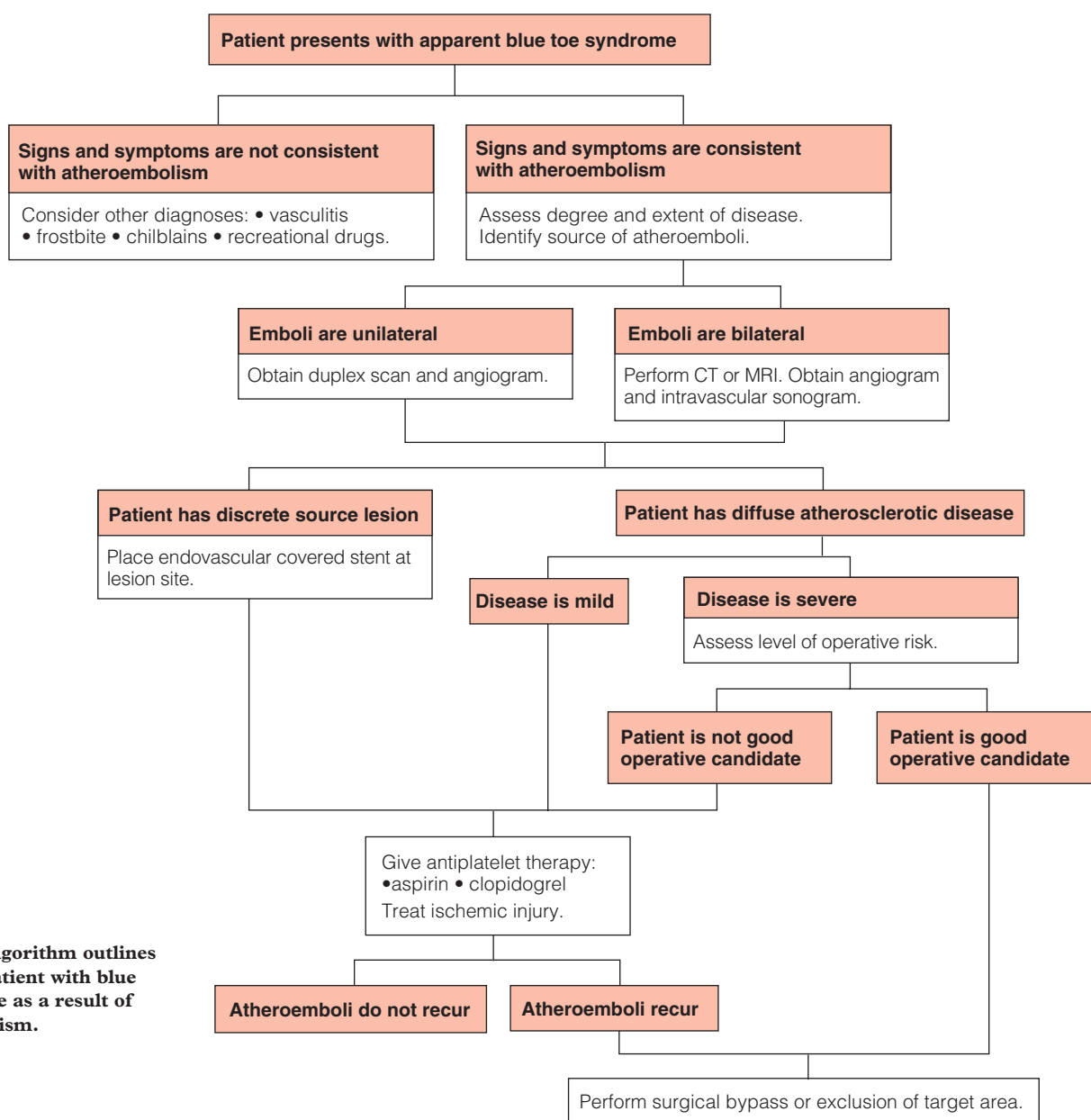


Figure 1 Algorithm outlines workup of patient with blue toe syndrome as a result of atheroembolism.

A complete vascular examination should be performed and pulses documented. Although a patent arterial tree is the rule, emboli that are sufficiently small may travel through collateral channels. Palpation should be done to detect any aneurysmal disease. A massive proximal atheroembolic event may affect the entire abdominal wall and both extremities, giving the appearance of livedo reticularis. As the source of the atheroemboli ascends in the arterial tree, more vital organs (e.g., the kidneys and the GI tract) may be damaged.

Manipulation of an intra-arterial catheter or clamping or surgical manipulation of the arterial tree can also result in plaque disruption. In these cases, the adverse effects are usually apparent immediately after the procedure.

INVESTIGATIVE STUDIES

Doppler examination may visualize unstable ulcerated plaques or aneurysmal disease. Doppler segmental pressures may be used to identify the responsible lesion by localizing a significant drop in pressure and determining where the plaque is. Duplex imaging

with noncolor flow can also provide clues to the morphology of a plaque. This is only true, however, in the extremity arteries. When the aorta is the suspected source of the emboli, computed tomography, magnetic resonance imaging, or MRA is performed; these modalities provide better visualization of intraluminal disease. Arteriography also plays a useful role in identifying intraluminal pathology along the entire vascular tree. In addition, intravascular ultrasonography may be performed with the guide wire in place and may help delineate the extent of the underlying disease.

MANAGEMENT

If the atheroembolic events are minor and solitary, conservative medical management is recommended. If, however, the emboli are recurrent or massive, a thorough evaluation should be initiated, followed by urgent treatment.

Medical management of atheroembolism consists primarily of antiplatelet therapy and statin therapy. Given that most patients with atheroemboli are already receiving aspirin, addition of clopidogrel or ticlopidine is appropriate. The optimal agents for pre-

venting recurrence of atheroembolism may prove to be lipid-lowering drugs, particularly statins. Furthermore, given the goal of preventing recurrence, all patients who continue to smoke should be counseled to attempt cessation, which is beneficial in curbing atherosclerosis. Aggressive treatment of diabetes is also warranted.

The role of warfarin therapy in treating atheroembolic disease has not been established with certainty. Such therapy may even aggravate the disease process by causing intraplaque hemorrhage and increased embolization. The Warfarin Aspirin Recurrent Stroke Study (WARSS), a randomized multicenter study that included 2,206 patients who had recently experienced an ischemic stroke, found no evidence that warfarin is superior to aspirin for preventing recurrent ischemic stroke or death within 2 years.⁴² The WARSS also found that there was a significant difference in bleeding risk between warfarin-treated patients and aspirin-treated patients.

For patients with diffuse atherosclerotic disease, the mainstay of therapy is an antiplatelet regimen. Traditionally, an atheroembolic source has been treated by surgical excision or by exclusion of the disease process with a bypass graft, either of which provides a good degree of safety from further embolization.⁴³ With the advent of endovascular surgery, however, the use of covered stents, placed securely and precisely at the site of the offending lesion, appears to be an increasingly effective and popular option [see Table 5].^{44,45}

Our current approach to treating atheroembolism may be summarized as follows. The source lesion is first identified by means of the modalities already discussed. If embolization is minor, aspirin and clopidogrel are started. If embolization is recurrent or

Table 5 Surgical Management of Atheroembolism

Source of Emboli	Treatment
Upper extremity	Bypass of subclavian or axillary artery First rib or cervical rib resection
Aorta	Focal disease: covered aortic stent Diffuse disease: aortobifemoral bypass
Iliac artery	Covered iliac stent
Popliteal artery	Ligation and bypass of popliteal artery

massive, an endovascular approach is attempted, involving the placement of a covered stent over the lesion. This approach is indicated for segments of the arterial tree where there are no collaterals, so that vital blood flow to organs is not hindered. If aneurysmal disease is present, either conventional or endovascular therapeutic approaches may be applied to exclude any source of emboli. In the case of thoracic aortic disease, covered stents may be placed to push the plaque against the wall and prevent further embolization. If suprarenal plaque cannot be treated with a stented graft, aortic ligation with an axillobifemoral bypass [see 6:12 *Aortoiliac Reconstruction*] may be performed. Such treatment does not, however, protect the renal and visceral vessels, and these patients require lifelong strict antiplatelet therapy.

Discussion

Pathophysiology of ALI

ALI begins when arterial embolization, local thrombosis, or arterial trauma results in occlusion of a peripheral artery or bypass graft. The ischemic process may then develop slowly, over an extended period, or quickly, over a few hours. A protracted course leading to thrombosis allows collateral vessels to form, resulting in the gradual onset of symptoms. When occlusion is acute, however, as in trauma, embolization, or acute thrombosis of a vessel or a bypass graft, signs and symptoms of acute ischemia may become rapidly apparent, including excruciating pain, mottling, cyanosis, and, commonly, sensory and motor changes. The magnitude of the ischemic injury is directly proportional to the duration of ischemia and the amount of tissue affected.

The pathophysiology of limb ischemia is related to the progression of tissue infarction and irreversible cell death. Compared with other organs and tissues (e.g., the brain and the heart), the extremities are relatively resistant to ischemia. However, the various tissue types of which an extremity is composed have different metabolic rates. The extent to which each cell type can tolerate ischemia depends on its metabolic rate. Bone and skin are the most resistant to ischemia, nervous tissue is the least resistant, and muscle is somewhere in between. Although nerve tissue is the type that is most sensitive to ischemia, it is skeletal muscle, the major structural component of an extremity, that plays the largest pathophysiologic role in the local and systemic effects of ALI. For muscle tissue, 6 hours is the approximate upper limit of ischemic tolerance; nervous tissue is affected well before this point.⁴⁶

Knowledge of the varying degrees of ischemic tolerance helps in determining the viability of the limb.

HYPOPERFUSION-REPERFUSION STATE

Regardless of the cause, hypoperfusion leads to ischemic infarcts via various mechanisms. During the hypoperfusion state, three major physiologic events occur. First, movement of blood through the vessels is slowed. As a result, the thrombus is able to grow and propagate, occluding collateral vessels and further decreasing blood flow. Second, ischemic cells swell and accumulate water. The resulting increase in pressure within a fixed space between fascial structures creates an elevation of pressure within the compartment that further decreases flow and exacerbates the injury. Third, the precapillary arteriolar cells swell, narrowing the lumina of distal arterioles, capillaries, and venules and again reducing blood flow. As a result, toxic metabolites accumulate within the ischemic tissues.

The reperfusion state that results when flow is restored can be as detrimental to the ischemic extremity as the hypoperfusion state was. During reperfusion, highly active oxygen metabolites are produced by neutrophils.⁴⁷ These free radicals destroy cells by attacking the unsaturated bonds of fatty acids within the phospholipid membrane, thereby disrupting the cell membrane, allowing water to enter the cell, and eventually causing cell lysis. Free radical scavengers (e.g., mannitol and superoxide dismutase) have a slight protective effect against reperfusion injury when given before large-scale release of these radicals.^{48,49} In addition, myoglobin from injured muscle cells is released into the circulation and is

cleared via the renal system. Myoglobin may cause renal failure through its direct toxic effect on the renal tubules and through the accumulation of casts in the tubules.

Creatinine phosphokinase levels may also increase to dramatic levels once perfusion is reestablished. High concentrations of lactic acid, potassium, thromboxane, and cellular enzymes are secreted as a consequence of the rhabdomyolysis; these substances accumulate in the ischemic limb and are released into the systemic circulation upon reperfusion.⁵⁰ In one study that measured the venous effluent from a series of patients with limb ischemia, the pH was 7.07 and the mean potassium level 5.7 mEq/L 5 minutes after surgical embolectomy.⁵¹

Detrimental physiologic changes are seen when toxic oxygen metabolites are released systemically. Depression of myocardial function, an increase in cardiac dysrhythmias, and loss of vascular tone may induce shock and even death.⁵²

Etiology of ALI

The etiology of ALI can be divided into two distinct categories: thrombosis and embolism. A thorough evaluation must be performed to elucidate the precise cause of ischemia in each individual patient. The two categories are each associated with specific symptoms and signs [see Table 6]. Knowledge of these associations helps direct the clinician toward the most appropriate means of accomplishing limb salvage in a given situation.

Thrombosis of a native vessel or bypass graft almost always develops in conjunction with an underlying lesion in the vessel or graft. The lesion usually has been present for some time, and the thrombosis occurs as a result of it. In contrast, embolic events occur in smaller-caliber vessels that are not diseased, with emboli commonly resting at or immediately distal to branch points.

THROMBOSIS

Native Artery Thrombosis

Native artery thrombosis is usually the end stage of a long-standing disease process of atheromatous plaque formation at specific sites in the arterial tree. Atherosclerotic plaque begins with the slow deposition of lipids in the intima of the vessel and continues with the deposition of calcium, resulting in an atherosclerotic core.⁵³ This core is a highly thrombogenic surface that encourages platelet aggregation, which results in disturbances of blood flow.⁵⁴ The flow disturbances create a zone of separation, stagnation, turbulence, and distorted velocity vectors. These factors cause low shear rates at inflection points in the arterial tree,

and endothelial damage ensues. The endothelial damage activates a repair process that results in intimal hyperplasia, which causes further attraction of platelets and eventual thrombus formation. The process by which occlusion develops from an atheromatous plaque may be more important than the degree of stenosis within the lumen. This would explain why acute occlusion occurs in vessels with minimal (< 50%) stenosis: the contact between the atherosclerotic core and the bloodstream leads to platelet aggregation and hence to eventual thrombosis.

Occasionally, thrombosis of a native artery occurs without any obvious underlying pathologic condition. In such cases, a thorough investigation should be initiated into other causes of thrombosis (e.g., hypovolemia, malignancy, hypercoagulable states, and blood dyscrasias).

Bypass Graft Thrombosis

Aggressive management of patients with peripheral arterial disease has led to an increase in bypass graft procedures. As a result, graft thrombosis has become the leading cause of acute lower-extremity ischemia. In patients with native conduits, intimal hyperplasia and valvular hyperplasia are the two leading causes of graft failure.⁵⁵ The situation is different in the prosthetic graft population, where the inherent thrombogenicity of the graft material and kinking of the graft from crossing joints are believed to be the leading causes. These patients often have graft occlusions without any definable underlying lesion. Anastomotic irregularities can also contribute to graft thrombosis.⁵⁵

EMBOLISM

Peripheral arterial embolization results in the sudden onset of extreme ischemia as the absence of collateral vessels compounds the reduction in flow to the extremity. The heart is by far the most important source of spontaneous arterial emboli. The incidence of embolic phenomena increases as the population ages, with a corresponding increase in the number of patients with significant cardiac disease. Over the past 25 years, the incidence of embolization has doubled, from 23 to 51 per 100,000 admissions. Atherosclerotic heart disease currently accounts for as many as 60% to 70% of all cases of arterial embolism.^{56,57} Atrial fibrillation and rheumatic valvular disease account for the remaining 30% to 40%.^{56,58}

With respect to peripheral emboli in particular, atrial fibrillation is currently associated with two thirds to three quarters of cases. Transthoracic echocardiography is insensitive in visualizing atrial clots, especially in the left atrial appendage, which is the most common cardiac source of emboli.^{59,60} Transesophageal echocardiography, however, offers significantly better imaging of all four chambers and thus is considered the superior diagnostic test for suspected cardiac embolic sources.⁶¹⁻⁶⁴

MI is the next most important cause of peripheral emboli. One study from 1986 evaluated 400 patients and found that MI was a causative factor in 20%.⁵⁸ After an MI, a left ventricular wall thrombus is often seen, with or without a left ventricular wall aneurysm; however, only 5% of such thrombi embolize and result in ischemia.⁶⁵⁻⁶⁸ Other studies suggest that day 3 to day 28 is the period during which the risk of embolization is highest for an intracardiac thrombus.⁶⁹

The ring portions of prosthetic cardiac valves are major intracardiac embolic sources before anticoagulation, as are biologic xenovalves, which do not require anticoagulation.^{70,71} Finally, tumors (e.g., atrial myxomas) are occasional sources of peripheral emboli.⁶⁹ Cardiac vegetations from bacterial or fungal endocarditis should be considered as possible sources of peripheral emboli when I.V. drug abuse is suspected in a patient with no previous

Table 6 Differentiation of Embolism from Thrombosis

Variable	Embolism	Thrombosis
Identifiable source	Frequently detected	None
Claudication	Rare	Frequent
Physical findings	Proximal and contralateral pulses normal	Evidence of ipsilateral and contralateral peripheral vascular disease
Angiographic findings	Minimal atherosclerosis; sharp cutoff; few collaterals; multiple occlusions	Diffuse atherosclerotic disease; tapered and irregular cutoff; well-developed collateral circulation

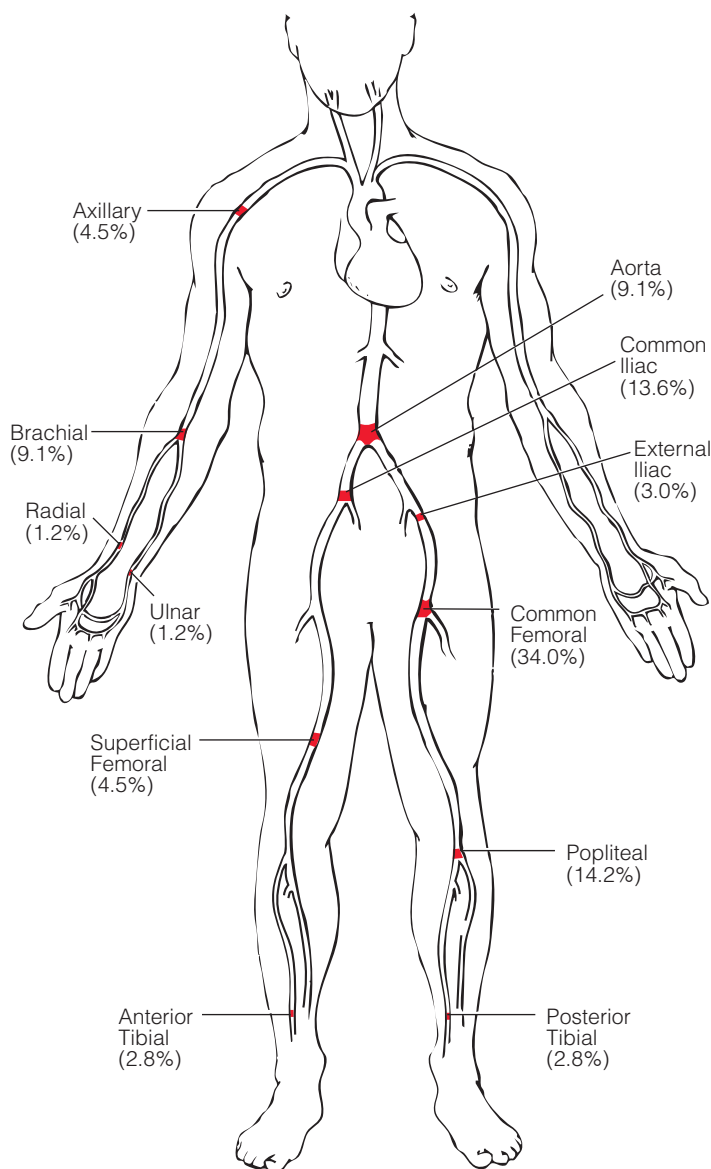


Figure 2 Depicted are the most common sites of arterial embolic occlusions.

history of cardiac disease.^{72,73}

Noncardiac sources account for 5% to 10% of peripheral emboli. The majority of these involve downstream atherosclerotic arterial disease (e.g., aneurysms or unstable plaques).⁷⁴⁻⁷⁷ Foreign objects (e.g., missiles) and tumors (e.g., melanoma) can also embolize if they gain access to the arterial tree.⁷⁸⁻⁸¹ Paradoxical embolization occurs when a venous thrombus crosses from right to left via an atrial or ventricular route, gains access to the arterial

side, and becomes an arterial embolus.⁸²⁻⁸⁴ About 5% to 10% of emboli remain unidentified despite a thorough diagnostic evaluation^{85,86}; some of these are now being attributed to hypercoagulable states.⁸⁷

Incidence

The increase in the number of endovascular interventions being performed has affected the overall incidence patterns for arterial embolism, with a greater number of embolic episodes now arising from endovascular procedures. A 1996 study found that 45% of all atheroemboli were iatrogenic and that the majority of these originated during manipulation of the abdominal aorta, the iliac artery, or the femoropopliteal artery, with the remainder originating during surgery.⁸⁸ Emboli usually lodge at arterial bifurcations and thus cause hypoperfusion of more than one vessel. Axial limb vessels account for 60% to 80% of clinically significant embolic events, with the remainder divided between cerebral vessels (20%) and upper-extremity vessels (10% to 20%).^{58,69,89} The most common site for embolic lodgment is the common femoral bifurcation [see Figure 2]. The aortoiliac region is the next most common site, followed closely by the popliteal artery.^{52,57,58,69,90,91}

The presence of normal pulses in the contralateral leg in a patient with an ischemic leg should elicit an aggressive workup to rule out a cardiac embolic source and may be a clue that the occlusive event is embolic rather than thrombotic.

Upper-Extremity Emboli

Acute ischemia of the upper extremity is usually caused by embolism, usually from an intracardiac source. Subclavian aneurysms, arteriovenous fistulae, upper-extremity arterial bypasses, and iatrogenic manipulation of the arteries are rare causes.⁹² As noted (see above), emboli lodge at bifurcations within the arterial tree. In the upper extremity, the bifurcation of the brachial artery into the radial and ulnar arteries is the most common lodgment site, followed by the takeoff of the deep brachial artery. Adequate exposure of all three arteries can be obtained via an elongated S-shaped incision that runs medially to laterally across the elbow joint.

Other Causes

Sepsis and cardiogenic shock result in a low-flow state that places patients at high risk for thrombosis. Certain vasoconstrictors and recreational drugs are also associated with lower-extremity thrombosis.^{93,94} Patients with these conditions usually present with bilateral extremity ischemia. Vasculitides (e.g., Takayasu) may also cause extremity ischemia.⁹⁵

The hypercoagulable states (e.g., antithrombin deficiency, antiphospholipid syndrome, protein C and S deficiencies, activated protein C resistance, and hyperprothrombinemia) are the most common disorders associated with acute arterial thrombosis.⁹⁶ The contribution of these states to ALI, with usually devastating consequences, is increasingly being recognized.

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6 VENOUS THROMBOEMBOLISM

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Assessment of a Venous Thromboembolic Event

Deep vein thrombosis (DVT) and pulmonary embolism (PE) comprise venous thromboembolism (VTE). Together, they comprise a serious health problem as there are over 600,000 new cases of VTE in the United States, resulting in a prevalence of one to two per 1,000 individuals, with some studies suggesting that the incidence may even be double that.^{1,2} The European Union reports an incidence of VTE of over 760,000 cases a year, with more than 370,000 VTE-related deaths, and one third were sudden deaths.³ It is estimated that about 10 to 25% of patients with acute PE die from sudden death prior to diagnosis and, thus, do not receive therapy, resulting in approximately 60,000 Americans dying each year from complications associated with VTE⁴⁻⁶ Post-mortem studies have identified that sudden death from PE is misdiagnosed in almost 80% of cases,⁷ exemplifying the poor ability we have to identify and prevent it. Of the more than 500,000 patients who survive at least 1 hour to have the opportunity to be diagnosed and treated, only 29% actually receive treatment and 92% of them survive, whereas the untreated 71% have a mortality of 30%.⁸ These numbers are staggering when compared with the death rates of other common diseases. Altogether, death from VTE is five times more common than deaths from breast cancer, AIDS, and motor vehicle crashes combined.

 The long-term complications of nonfatal DVT are morbid, including one third suffering postthrombotic syndrome (PTS) and another 30% having a recurrent VTE within 10 years of the first.^{2,9} Finally, in patients with cancer, VTE-related complications are the second leading cause of death; they increase the mortality associated with increased bleeding complications and the use of health care resources.¹⁰⁻¹²

Patients with PTS may suffer poor quality of life as a result of chronic limb symptoms.^{13,14} PTS occurs in up to 30% of patients with DVT at 8-year follow-up, varying in severity from edema to venous claudication and ulcers.^{15,16} Risks for PTS include recurrent DVT, a proximal (iliofemoral) DVT, older age, a high body mass index, and female gender.¹⁵ Preventing recurrent DVT is a primary means to decrease PTS. Most of the time, therapy for PTS is palliative, but at times, patients with PTS require (or request) lower extremity amputations because of chronic, unrelenting pain and ulceration. A 12-year review of a Nationwide Inpatient Sample database sampling all hospitalized patients with chronic venous disease found that 1.2% of patients underwent an amputation.¹³ This number may be higher at tertiary referral centers, which have a large number of complex venous patients.

Considering that PE and PTS are often preceded by DVT, there is an impetus for prevention, early detection, and

aggressive treatment of DVT prior to the presentation of these complications, all while providing appropriate acute management and evaluating the response to treatment. This all begins with a careful history and physical examination.

Clinical Evaluation

The importance of obtaining a good history of present illness and review of systems in patients is critical in the decision tree for the diagnosis and management of patients with acute VTE as subtle clinical findings may dramatically change the treatment plan and are not driven by imaging or laboratory tests alone. For example, a patient with only shortness of breath or tachycardia as a symptom or sign of PE may require a D-dimer prior to receiving any further treatment or imaging, whereas one with tachycardia and leg swelling may benefit from anticoagulation prior to imaging (without needing a D-dimer) because of a higher likelihood of PE.¹⁷

If a patient presents with a VTE, one must distinguish between those patients who have a temporary risk factor (such as surgery or bed rest) and those who have a lifelong secondary condition, inherited disease, or undefined state that predisposes to thrombosis and may benefit from prolonged anticoagulation after the VTE [see Table 1]. This distinction helps determine the long-term treatment and risk of future VTE.

In addition to advancing age, acquired VTE risk factors that are considered lifelong to the patient include a history of previous VTE, active cancer (may be reversible in some cases), extremity paresis or paralysis, medical disorders causing prolonged bed rest, and congenital or autoimmune thrombophilia. Temporary or provoked VTE risk factors include pregnancy, oral contraceptive or hormone therapy, surgery and trauma, central venous catheters, and bed rest or other states of prolonged immobility.

Table 1 Clinical Scenarios Possibly Benefiting from Prolonged Anticoagulation after VTE¹⁴⁵

Antiphospholipid antibody and systemic lupus
Homozygous factor V Leiden mutation
Prothrombin gene mutation (G20210A)
Elevated factor VIII
Protein C or S deficiency
Hyperhomocysteinemia
Cancer (while cancer is active)
Otherwise unexplained, repeated deep vein thrombosis or pulmonary embolus

VTE = venous thromboembolism.

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Medical History

THROMBOPHILIC RISK FACTORS

Rudolf Virchow first stated in 1859 that clots in the pulmonary artery originated from the venous circulation and coined the term “embolus.” He also described the three components of hypercoagulability that are now referred to as a triad that bears his name: hypercoagulability, stasis, and injury to the vessel wall.¹⁸ These factors are still relevant today.

“Thrombophilia” is defined by the World Health Organization (WHO) as “a tendency towards thrombosis.”¹⁹ Thrombophilia, whether acquired or inherited, plays a direct role in about 50% of all VTEs. Most commonly, surgeons evaluate patients for these risks preoperatively. Aggressive screening for VTE risk to provide appropriate prophylaxis or treatment can best be obtained by interviewing the patient. These risks can be determined via group consensus guidelines such as those of the American College of Chest Physicians (ACCP)²⁰ or via the use of an individualized risk assessment scoring such as the modified Caprini score.²¹ The ACCP guidelines account for most risk scenarios by taking into account patient cohorts (e.g., all medical patients, those undergoing hip replacement, patients with cancer, etc.). However, individual patients may overlap into several simultaneous categories. Alternatively, individual risk assessment can be performed by directed intake sheet [see Figure 1]. This allows risk factor summation and suggests appropriate prophylaxis choices. The questionnaire collects information from the patient’s personal (age) and medical history (e.g., family history of VTE, personal history of DVT) and takes into consideration what type of procedure is to be done and the intended mobility status. This system has recently been retrospectively validated.²¹

IRREVERSIBLE RISK FACTORS FOR VTE

Age

Age alone confers an acquired thrombophilic state. Older patients tend to accumulate risk factors such as infections, surgery, and cancer, each of which increases the likelihood of having thrombotic complications. Patients over 50 years of age also have higher concentrations of antiphospholipid antibodies of unknown significance.²² The older the patient is who suffers a VTE, the lower the likelihood that the VTE was attributable to an inherited etiology and, conversely, the greater the likelihood that it was attributable to an acquired condition.²³ Older patients also have a higher risk of developing limb complications such as PTS¹⁵ as well as PE. Experimental animal data also suggest that age may lead to a higher concentration of P-selectin and impaired fibrinolysis, which may contribute to age-related thrombophilia.²⁴

Malignancy

The clinical constellation of asymptomatic cancer and lower extremity deep vein thrombosis (LEDVT) was first described in 1865 by Armand Trousseau,²⁵ and this syndrome bears his name. The 19th century was also marked by the suggestion by Theodor Billroth that cancer used clot as a mechanism to spread.²⁶

Since then, a search for the etiologic factor involved in cancer-related thrombophilia has only been partially fruitful.

A “cancer procoagulant” factor was found in 1985 exclusively in amniochorial tissue and associated with multiple malignancies.²⁷ It is a cysteine protease that specifically activates coagulation factor X. However, even after more than 25 years since this discovery, it has been purified only from several malignant tissue cultures, and no gene has been identified.²⁸

Of all types of malignancies, mucin-producing tumors such as adenocarcinomas, small cell lung cancers, gastrointestinal cancer (such as the gastric cancer that led to Trousseau’s own DVT),²⁹ and ovarian cancer are most likely associated with VTE.³⁰ This notwithstanding, any malignancy increases the risk of VTE. Additional risk factors linked to patients with malignancies are those related to therapy, such as central venous catheters, chemotherapy, and surgical procedures, all of which are independent risk factors for VTE.³¹ An additional risk factor found in some cancer patients is an elevated (greater than 75th percentile) soluble P-selectin concentration. It increases the cumulative DVT probability from 3.7 to 11.9% in multiple types of cancer.³² Whether mucin-producing cancers have increased P-selectin as the mechanism of thrombosis is under investigation.³³

Inherited Thrombophilia

The WHO defines an inherited thrombophilia as “the presence of an inherited factor that by itself predisposes towards thrombosis but due to the episodic nature of thrombosis, requires interaction with other components. . . before onset of the clinical disorder.”¹⁹ To evaluate patients with suspected primary thrombophilia, an international consensus was formed to standardize who needs advanced testing. Indications for laboratory investigation of secondary thrombophilia are listed in Table 2, and venous thromboembolic risk according to hypercoagulable state are listed in Table 3.^{34,35}

In 1994, the Leiden Institute discovered the point mutation in factor V that explains the most common inheritable thrombophilia. This “factor V Leiden mutation” accounts for up to 25% of secondary thrombophilias.³⁶ It occurs in 6 to 9% of whites and in up to 50% of families with a history of DVT.^{23,37} The G20210A mutation of the prothrombin (coagulation factor II) gene is another common etiology of thrombophilia that is associated with DVT.³⁶ Impaired fibrinolysis is a hypercoagulable state associated with 4G/5G polymorphisms of the plasminogen activator inhibitor-1 (*PAI-1*) gene. These patients have a threefold increased risk of DVT higher than the general population.³⁸ As many as one third of non-catheter-related upper extremity deep vein thrombosis (UEDVT) may be due to the above-mentioned inheritable disorders.³⁹

Other notable inheritable syndromes include deficiencies of the natural anticoagulants, including antithrombin III and proteins C and S.^{40,41} These tend to be more aggressive thrombophilias, with presentation in younger patients. Obtaining a positive screen for these entities directs the long-term anticoagulation strategy for and future risk of VTE.

ANTIBODY-MEDIATED AND RHEUMATOLOGIC RISK FACTORS

The majority of these factors are encountered in rheumatologic disorders. The disease most commonly associated with both arterial and VTE is antiphospholipid syndrome. For decades, clinicians noted that patients with systemic lupus erythematosus (SLE) would present with spontaneous

Figure 1 Modified Caprini score questionnaire used at the University of Michigan to determine individual risk for venous thromboembolism and the indicated prophylaxis regimen.

Table 2 Indications for Laboratory Investigation of Secondary Thrombophilia^{34,35}

Any first, spontaneous VTE without known risk factors
VTE in patients < 50 years, even with a transient predisposing factor
Patients whose only risk factor is estrogen therapy or pregnancy
Recurrent VTE regardless of risk factors (even superficial phlebitis if not associated with cancer or varicosities)
VTE in patients < 50 years in uncommon sites (e.g., intra-abdominal, intracranial, retinal)
Warfarin-induced skin necrosis and purpura fulminans (when not associated with sepsis)
Two consecutive abortions, three nonconsecutive abortions, or one fetal death after 20 wk gestation
Asymptomatic first-degree relatives of a patient with proven thrombophilia
VTE with severe preeclampsia
Children with VTE

VTE = venous thromboembolism.

Table 3 Venous Thromboembolic Risk Accorded to Hypercoagulable States

Hypercoagulable Risk Factor	VTE Risk Compared with Unaffected Population
Factor V Leiden mutation	80× in homozygous (5–8× in heterozygous)
Antithrombin III, protein C and S deficiencies	10×
Elevated factor VIII	6×
Prothrombin gene mutation	2.8×
Hyperhomocysteinemia	2.5–4×
Antiphospholipid antibody	Lifetime risk 10% of positive patients

VTE = venous thromboembolism.

clotting yet paradoxically have prolonged activated partial thromboplastin times (aPTTs).⁴² This is now known to be attributable to antibodies against the negatively charged phospholipids that interfere with the aPTT assay itself. These antibodies are not specific to lupus as they may be independent (true antiphospholipid antibody syndrome [APS]) or associated with other rheumatologic diseases, such as rheumatoid arthritis, systemic sclerosis, Sjögren syndrome, and systemic vasculitis, among others. The most common antibodies identified are antiphosphatidylserine (lupus anticoagulant), anticardiolipin, anti- β_2 -GPI, and sometimes antiprothrombin.^{43,44} There is a high IgM anticardiolipin antibody level in females when compared with males⁴⁵ and an increased incidence of PE among APS patients. The exact mechanism for thrombophilia in APS is unknown,⁴⁶ but it is not simply attributable to antibody- or complement-mediated activation of platelets.⁴⁷ This is highlighted by the fact that clinically silent antiphospholipid antibodies may be found in as much as 2% of the population (age related) and that although 30 to 40% of patients with SLE have antiphospholipid antibodies, only 10% will manifest with thrombosis.⁴⁸

Another rheumatologic disorder that confers an increased risk of arterial and venous thrombosis (particularly in the cerebral sinus and lower extremities) is Behçet syndrome. This presents most commonly in patients from the “old silk road” (between China and the Mediterranean Sea) and has yet to have a clear mechanism elucidated.^{49,50}

ACQUIRED RISK FACTORS FOR VTE

Immobilization

Stasis is often considered a risk factor for VTE because of sluggish venous flow seen in a spectrum of scenarios ranging from being seated on a transoceanic flight to a paralyzed trauma patient. Although this alone is an inconsistent risk for VTE, even sitting in a chair for 6 to 8 hours may be what unmasks other, more prevalent VTE risk factors by increasing the regional procoagulant factors in the region of stasis.⁵¹ A meta-analysis of medical patients suggests that the risk of VTE in immobilized patients is about twice that of ambulatory patients.⁵²

The risk of VTE in those individuals with low or moderate risk after a flight lasting more than 4 hours has been studied and is thought to be 1% or less and 4 to 6% in those who are high risk, presumably from prolonged immobilization.^{53,54} Although uncommon, the association of VTE with air travel has been linked to the distance traveled. The lowest risk occurs after flights less than 3,000 miles (0.01 cases per million), and the highest occurs after flights greater than 6,000 miles (4.6 cases per million).⁵⁵ Given that these numbers are very small and that there are no control groups, consensus guidelines only recommend frequent ambulation and compression stockings during long flights and reserve pharmacologic prophylaxis for patients with other major risk factors for VTE.⁵⁶ Most studies evaluating compression stockings to improve edema after long flights show a benefit, but their role in preventing significant (DVT and PE) VTE depends more on the patient’s risk factors than on the length of the flight. It has not been shown that stockings diminish the risk of DVT after prolonged air travel in patients who are low risk, regardless of the length of the flight. Conversely, compression stockings likely reduce the risk of DVT after flights that last more than 8 hours in all patients who are otherwise at high risk for VTE.^{54–59} Patients who are at moderate risk for DVT and travel more than 11 hours also may benefit from stockings with compression gradients of 20 to 30 mm Hg, whereas no DVT has been demonstrated in this patient population after flights that last less than this.

Surgery and Trauma

All patients undergoing surgical procedures have an increased risk of thrombosis, with an incidence ranging from 15 to 40% and an odds ratio of more than 10 compared with controls.⁶⁰ This may be attributable to accelerated production of procoagulant and inflammatory cytokines that activate platelets, inflammatory cells, and endothelial cells in addition to postoperative inactivity, which increases blood stasis. Although controversial, the incidence may also be attributable to reduced capacity for fibrinolysis during the perioperative period, associated with increased PAI-1 activity.^{61,62} Procedures that require prolonged immobility in the postoperative period (such as hip replacements and spine procedures) have the highest risk of DVT (historical prevalence

40 to 60%). Interestingly, decreased concentrations of fibrinolytic enzymes have been documented in patients undergoing orthopedic procedures (compared with general surgical patients) and may partially explain the greater thrombosis risk in these patients.⁶³

Although preoperative and operative risk factors are important to predict VTE, the interventions and medical complications associated with the patient's postoperative course also impact the incidence of symptomatic VTE. A cohort study involving over 76,000 patients having surgery in the Veterans Affairs system over a 5-year period found that the strongest predictors of postoperative VTE were myocardial infarction, blood transfusion (> 4 units), pneumonia, and urinary tract infections.⁶⁴ This suggests that postoperative systemic inflammatory conditions may substantially contribute to the thrombophilic state. However, the exact mechanism(s) are unknown.

Major trauma patients are also known to be at high risk for VTE (historical prevalence of 40 to 80%),²⁰ and DVT may occur in up to one third of patients (mostly in the calf of the leg) with a moderate to severe brain injury, especially when associated with extremity injuries.^{65,66} For these reasons, prophylaxis with sequential compression devices (SCDs) and eventually heparin or low-molecular-weight heparin (LMWH) when the bleeding risk is deemed safe are strongly encouraged (see below).

Intravenous Catheters

Macroscopically, vessel trauma and foreign bodies placed within veins damage the endothelium and will locally accumulate platelet and coagulation factors. These conditions alone will usually not lead to vessel thrombosis, but when combined with other prothrombotic factors, such as tissue factor, von Willebrand factor, and fibronectin, the likelihood of DVT increases.⁶⁷ The conversion from local clot to occlusive thrombus is likely dependent on the time of exposure to the etiologic factor. As such, central venous catheters (including peripherally inserted catheters) have a relatively high rate of thrombosis. Central venous catheters account for two thirds to three quarters of UEDVT and are the strongest independent predictor of UEDVT (7.3-fold increase).^{68,69}

Clinical Presentation of VTE

The most common presentation of DVT is limb swelling, calf pain, and discrepant circumference. However, the manifestations of DVT or PE may be subtle and subclinical in many cases. It has been found that over 50% of patients with a DVT may have an unrecognized PE (based on imaging testing)⁷⁰ and that over 70% of patients with PE have an undiagnosed LEDVT.¹⁸

To aid in the appropriate management of PE, Wells and colleagues published clinical criteria that accurately stratify a patient as low, moderate, or high risk and determine who needs further imaging to evaluate for PE.⁷¹ Their 2001 criteria for PE include hemoptysis, malignancy (patients with cancer who are receiving treatment or for whom treatment has been stopped in the previous 6 months or those receiving palliative care), a history of DVT or PE, tachycardia, and no other likely diagnosis. Additional criteria include immobilization for more than 3 consecutive days or surgery less than 30 days from presentation and clinical signs and symptoms

of DVT (objectively measured calf swelling and pain with palpation in the deep venous system). Wells and colleagues determined that in cases of low or moderate risk with a normal D-dimer (a serum marker of fibrinolysis), no further imaging was necessary. However, if the D-dimer was positive, then a ventilation-perfusion (V/Q) scan or angiogram was used to confirm the clinical suspicion. In patients with chest symptoms suspicious for PE, the patient should be evaluated for these criteria to determine the need to pursue further imaging or laboratory studies. Patients found to be at intermediate risk or high risk for PE should also be heparinized prior to obtaining imaging.⁷²

The first Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study found that of the more than 250 patients with angiographically demonstrated PE, only 11% had physical examinations consistent with DVT.⁷³ Hemoptysis and pleuritic pain may be present in only about 40% of all patients with PE.⁷⁴ Like DVT, patients with clinical manifestations of PE will likely only have nonspecific clinical findings. The most common findings include dyspnea (84%), pleuritic pain (74%), apprehension (63%), and cough (50%). Of these clinically positive patients with PE, dyspnea or tachypnea occurred in 96%, whereas 99% of them demonstrated dyspnea, tachypnea, or DVT.⁷⁵ As in other diseases that are shared by the young and old, PIOPED II revealed that dyspnea or tachypnea was less commonly reported in elderly patients.⁷⁴

Rarely, massive iliofemoral DVT may cause phlegmasia alba dolens (swollen white/milk leg), a clinical scenario when arterial inflow becomes obstructed as a result of extreme venous hypertension.²⁵ Phlegmasia cerulea dolens (swollen blue leg) occurs from severe venous hypertension that occludes the capillaries and may result in venous gangrene. The legs become red or purpuric, and the toes may become cyanotic and often is accompanied by blistering of the skin [see Figure 2]. Venous gangrene is always preceded by phlegmasia cerulea dolens, and is often associated with an underlying malignancy.



Figure 2 Phlegmasia cerulea dolens secondary to acute left iliofemoral deep vein thrombosis after thigh trauma. The condition was completely resolved after thrombolysis and stenting of his left common and external iliac veins, followed by anticoagulation and compression stockings.

Physical Examination



The most common physical findings associated with LEDVT are edema, calf swelling, and tenderness, but these are not specific to DVT. Homan sign (calf pain at dorsiflexion of the foot) and pain on manual compression of the calf muscle against the tibia (Olow sign) are uncommon signs but are suggestive of calf DVT. The extremity may also be warm and ruborous with brisk capillary refill, and care must be taken not to misdiagnose LEDVT for cellulitis. Although the lower leg is the most common site for DVT, thigh pain and arm pain may also be noted in cases of iliofemoral and UEDVT, respectively.

Although physical examination alone is accurate in less than one third of cases,⁷⁶ it is critical to determine the next step in the clinical investigation or treatment, particularly in the case of PE,⁷⁷ and limb threat, which may mandate urgent therapies (see below). One must remember that unless there is vena cava thrombosis, the clinical findings of DVT are rarely bilateral. This diagnostic rule assists in eliminating other systemic causes of lower extremity edema, such as renal failure or congestive heart failure, which may manifest with edema. Other illnesses that may mimic unilateral leg DVT include popliteal (Baker) cysts, trauma, cellulitis, popliteal aneurysm thrombosis, lymphedema, and muscle strain.

Patients with phlegmasia syndromes will have dramatic swelling associated with tight, plethoric extremities that may be ruborous or pale. A careful evaluation of the motor function of the extremity is necessary to determine which patient has immediate limb threat and requires urgent intervention to resolve the venous hypertension or open the compartment [see in Indications for Immediate Intervention (Limb or Life Threat), below].

Superficial venous thrombosis may often manifest in the setting of a vessel cannulation. Superficial thrombophlebitis is most often accompanied by pain, an inflamed palpable cord, or both along the axis of the affected vein. Sometimes this may also be accompanied by extremity edema and, if infected, may have purulent discharge at the catheter site.⁷⁸

Laboratory Evaluation



D-dimer is most useful for ruling out a VTE in a low-risk patient. If negative, there is almost no risk for VTE, and no further testing is required. This clinical strategy has been adopted by both the American and European consensus groups as the appropriate workup for a VTE.^{56,60} However, D-dimer is not useful for those patients with a high pretest probability of a VTE. We now know that in patients with a high clinical suspicion of VTE, almost 10% may have a false negative D-dimer assay with a VTE, although in those with a low suspicion, it will be accurate nearly 100% of the time. Thus, in a high-risk patient, a D-dimer will not safely rule out a VTE; thus, there is no reason to obtain such a level in a high-risk or even a moderate-risk patient.⁷⁹ Furthermore, patients who have undergone surgery or trauma may have an elevated D-dimer from postoperative blood that is being lysed, and this finding may be elevated for over 2 weeks.⁸⁰ Thus, D-dimer has less utility in the postoperative period, and reliance on imaging such as computed tomographic angiography (CTA) for PE is important.

Whenever possible, blood screening for patients suspected of thrombophilia should use samples obtained prior to anticoagulation to obtain a baseline partial thromboplastin time, prothrombin time, platelet count, antithrombin, and proteins C and S levels, although with significant thrombosis, these coagulation proteins may be consumed into the thrombus, leading to falsely low levels. Anticoagulation will also change the above-mentioned values. However, accurate results can help predict the etiology of the hypercoagulable state. For example, a prolonged aPTT may be attributable to antiphospholipid antibody syndrome, whereas a low protein C may be attributable to genetic protein C deficiency. The remaining genetic or antibody tests obtained during a thrombophilia evaluation, such as factor V Leiden mutation, factor II G20210A mutation, anticardiolipin, anti- β_2 -GPI, and fasting homocysteine, will not be altered by anticoagulation and can be obtained at any time in the patient's course.

Imaging

When used in symptomatic patients, compression duplex ultrasonography (CDU) alone has a sensitivity to detect proximal DVT and calf DVT of 96% and 80%, respectively. In asymptomatic patients, the sensitivity is significantly lower (76% for proximal calf DVT and 11% for isolated calf vein thrombosis).⁸¹ Thus, CDU is the initial screening and diagnostic test of choice in patients with a moderate to high suspicion for DVT or is the second test to be done if a positive D-dimer assay is found when evaluating a low-risk patient for a DVT.

The diagnosis of PE may be further studied with a radionuclide V/Q scan, pulmonary CTA, or pulmonary arteriography. Vena cava or extremity venography is rarely indicated except when combined with a planned catheter-directed fibrinolysis procedure (e.g., May-Thurner or Paget-Schroetter syndrome).

Although V/Q scans do not require radiation or use nephrotoxic contrast agents, they provide a definitive diagnosis in less than half of cases, with a sensitivity of only 41%.⁷³ Anywhere from 30 to 70% of V/Q scans are interpreted (often erroneously) as “indeterminate,” and the management of these patients is unclear, especially as 30 to 40% of these patients may have a PE and are not treated appropriately.⁸² This modality has fallen out of favor except where a CTA cannot be obtained and the pulmonary function portion of the test is predicted to be normal. When a patient has other pathologies that alter the ventilatory (such as chronic obstructive pulmonary disease or pneumonia) or perfusion portions (previous infarcts, previous lung resections, or old infarcts) of the test, V/Q imaging is not useful for detecting acute PE.

A prospective multicenter trial evaluating multidetector CTA alone versus CTA combined with venous phase computed tomography (CT) of the pelvic and thigh veins for the diagnosis of acute PE was conducted in the PIOPED II study.^{74,83} It revealed that combining pulmonary CTA with CT venography (in the same scan) was more useful in managing suspected PE and DVT than by pulmonary CTA alone. The combination of pulmonary CTA and CT venography for PE yielded a sensitivity and specificity of 90% and 95%, respectively. If the clinical findings correlated with the CT findings, then the positive predictive value is over 92% in all

scenarios. Another benefit of the use of CT, even though it requires the infusion of intravenous contrast dye and radiation,⁸⁴ is that although it is positive in less than one third of patients who undergo CTA for PE, an alternative diagnosis may be found in more than 70% of those patients.

Of the available imaging modalities, pulmonary arteriography is the most invasive and exposes the patient to potentially nephrotoxic contrast dye. Although historically this was considered the diagnostic test of choice, the use of high-resolution CTA is now the standard for the aforementioned reasons. Angiography is more commonly used when catheter-directed thrombus removal is being contemplated (see below).

Prophylaxis against Perioperative VTE



Without prophylaxis, surgical procedures may have a VTE prevalence of up to 80%.²⁰ Historically, trials comparing no perioperative VTE prophylaxis with prophylaxis methods ranging from stockings and SCDs or any form of anticoagulation showed that each prophylactic modality could decrease the risk of VTE at least two- to threefold.^{85–87} For this reason, every patient undergoing surgery should have some form of prophylaxis unless it is a minor or ambulatory procedure and the patient has no other VTE risk factor other than the procedure (see below).⁵⁶ There is no evidence to support the use of inferior vena cava (IVC) filters for perioperative or peritrauma PE prophylaxis without the diagnosis of DVT [see Vena Cava Filters, *below*].

As previously stated, one way to determine prophylaxis recommendations is the ACCP consensus guidelines.²⁰ Whether based on a category or risk score, most at-risk patients who undergo major surgical procedures or suffer significant trauma should receive prophylaxis with an anticoagulant unless they have a high bleeding risk; in these cases, SCDs are recommended until the bleeding risk subsides. In high-risk VTE cases such as in spine injury or hip replacement, stronger pharmacologic agents (LMWH, pentasaccharides, or warfarin) are recommended for prophylaxis, whereas unfractionated heparin (UFH), SCDs, and aspirin alone are not effective prophylaxis [see *Table 4*]. In surgical procedures where the bleeding risk outweighs the benefit of an anticoagulant, such as certain neurologic and vascular procedures, mechanical prophylaxis usually suffices. These include graduated compression stockings and SCDs, which are comparable to low-dose heparin in patients without other risk factors.⁸⁸ The caveat is that these devices need to be on the patient's limbs and working, requiring surveillance for compliance.

Indications for Immediate Intervention (Limb or Life Threat)

PULMONARY EMBOLUS



Barring a medical contraindication, full-dose anticoagulation should be started in cases of high clinical suspicion for PE until it is refuted as the cause.⁵⁶ If PE is diagnosed, then anticoagulation should be continued with either continuous UFH titrated to an aPTT of 60 to 80 seconds, weight-based, full-dose LMWH, or fondaparinux according to both the American (ACCP) and European (European Society of Cardiology) guidelines.^{56,60}

Table 4 Recommended VTE Prophylaxis Stratified by Surgical Procedure and Associated VTE Risk Factors According to the 8th ACCP Consensus Statement²⁰

Surgical Procedure	Prophylaxis
Minor general surgery without other risk factors	Early ambulation alone
Major general surgery	LMWH, LDUH, or Fx
High-risk general surgery	LMWH, LDUH, or Fx with SCD or GCS
Major urologic or gynecologic surgery	LMWH, LDUH, Fx, or SCD
Elective hip or knee arthroplasty	LMWH, Fx, or VKA
Hip fracture surgery	Fx, VKA, or LDUH for 10–35 days
Spine surgery without other risk factors	Early ambulation alone
Major trauma and spinal cord injury	LMWH, LDUH, Fx, or SCD
Major vascular surgery without other risk factors	Early ambulation alone
Cancer patient undergoing surgical procedure	Same as above: “high risk”

ACCP = American College of Chest Physicians; Fx = fondaparinux; GCS = graduated compression stocking; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; SCD = sequential compression device; VKA = vitamin K antagonist to international normalized ratio 2.0 to 3.0; VTE = venous thromboembolism.

The management of PE is then determined by the clinical severity, highlighting the importance of a good medical history and physical examination.⁷⁷ Massive, unstable PE consists of shock and/or hypotension (systolic blood pressure < 90 mm Hg or drop of 40 mm Hg for > 15 minutes without other cause), usually associated with severe shortness of breath or respiratory insufficiency. Nonmassive PE should be evaluated for echocardiographic signs of right ventricular hypokinesis (“submassive” PE), which may still require thromboreduction of some sort, whereas lack of right heart strain allows for systemic anticoagulation alone. In addition to emergent echocardiography, serum brain natriuretic peptide levels and serum troponins may aid in stratifying the severity of PE.

In the case of clinically unstable PE or submassive PE with significant right heart strain, thrombolytics are the treatment of choice (barring contraindication to them). They can be administered systemically if the patient is too unstable for transfer or if the technical requirements are not available for catheter-directed administration. Systemically, tissue plasminogen activator 10 mg bolus followed by a continued infusion of the remaining 90 mg over 2 hours is administered. This may acutely avoid cardiogenic shock and death or, later, the development of chronic thromboembolic pulmonary hypertension.⁸⁹

An evolving treatment option for hemodynamically significant PE is endovascular catheter-directed infusion of lytics into the affected pulmonary vessel or mechanical thrombus reduction. A combination of transjugular, catheter-directed pulmonary embolectomy and thrombofragmentation with

fibrinolytics is performed. This technique has been successful in three quarters of cases, with a mortality of 25%.⁹⁰ The technology involved in these techniques is still being developed. As a result of the scarcity of both patients with this form of PE and physicians experienced in catheter-directed treatments for PE, the ideal technique is still unclear.⁹¹ In patients with cardiopulmonary instability who either cannot wait for pharmacologic thrombolysis to work or have a contraindication to thrombolytics, open thrombectomy is the only other option. The mortality is high, but in centers with experience, the outcomes are improved over no treatment.

After parenteral anticoagulation has been established, anticoagulation is continued with a vitamin K antagonist (VKA) for 3 to 6 months if the PE was attributable to an isolated or acquired etiology or continued for life if the PE was attributable to a permanent or recurrent etiology.⁵⁶

PHLEGMASIA CERULEA DOLENS AND PHLEGMASIA ALBA DOLENS

As described above, phlegmasia cerulea dolens and phlegmasia alba dolens of the limbs have amputation rates of 20 to 50% (prior to the advent of fibrinolytic therapies) and PE rates of 12 to 40%. Phlegmasia syndromes have a high mortality rate that in addition to the acute, extensive DVT is also likely attributable to the comorbidities that tend to accompany them, such as advanced malignancy and trauma.⁹² Phlegmasia syndromes that are associated with acute iliofemoral vein thrombosis have been successfully treated by catheter-directed fibrinolysis. There is no specific endovascular technique shown to be superior to others, but in small series, endovascular techniques show great promise for limb salvage and is the preferred management strategy if the patient still has good motor function and no contraindication to lytics.^{93,94} If the patient is not a candidate for fibrinolysis, then open surgical venous thrombectomy and creation of an arteriovenous fistula are necessary to obtain rapid venous decompression and decreased risk of PTS.^{95,96}

If the phlegmasia syndrome appears secondary to extensive, microvascular venous thrombosis (and not iliofemoral vein thrombosis), then it is unlikely to benefit from thrombolytic procedures; limb salvage may thus be possible only with fasciotomies. Another scenario potentially requiring fasciotomies for limb salvage occurs if there is evidence of advanced compartment syndrome (motor impairment), although the morbidity of this in the setting of an acutely swollen leg is quite high.

Indications for Urgent Intervention

PRIMARY AXILLARY-SUBCLAVIAN VEIN DVT (EFFORT THROMBOSIS OR PAGET-SCHROETTER SYNDROME)

Primary thrombosis of the axillary-subclavian veins is usually found in young athletes who perform sports with repetitive motion (e.g., baseball, volleyball, swimming) and is known as effort thrombosis or Paget-Schroetter syndrome. It is attributable to hypertrophy and/or a lateral insertion of the subclavius muscle, which compresses the subclavian vein and promotes thrombosis. This syndrome was historically treated with anticoagulation alone with a high rate of pain and swelling, but in the last decade, the treatment has evolved, and patients do better with multimodality treatment.⁹⁷

Current treatment includes early anticoagulation and endovascular thrombolysis and recanalization of the axillary-subclavian vein with balloon venoplasty of the narrowed segment. To return patency to the subclavian vein, thrombolysis may require a several-day infusion of plasminogen activators and/or the use of endovascular devices to fragment clots and aid thrombolysis. If the subclavian vein can be recannulated, then this treatment is followed by removal of the ipsilateral first rib to decompress the thoracic outlet to avoid rethrombosis. The timing for surgical removal of the rib varies by practitioners; some perform it during the same hospitalization, whereas others remove it a few weeks later. Attempts with angioplasty or stenting without prior surgical decompression will invariably fail. Neither can overcome the extrinsic pressure created by the musculoskeletal compression of the vein, and the constant motion of the subclavian vessels at this site will lead to stent fracture.^{98,99} If the vein cannot be opened, then the patient can only be anticoagulated and must rely on venous collaterals.

ILIOFEMORAL DVT AND MAY-THURNER SYNDROME

Iliac vein compression syndrome and secondary thrombosis (May-Thurner syndrome) occur when there is an obstruction or thrombosis of the lower left extremity venous outflow as a result of compression by the overlying right iliac artery. They most commonly present spontaneously in the left iliac vein and in young females who may or may not have additional risk factors for DVT, such as factor V Leiden or the use of oral contraceptives.^{100,101} They rarely affect the right iliac vein and vena cava but can occur in cases with a high iliac artery bifurcation or left-sided IVC.¹⁰² They can be successfully treated with endovascular venoplasty and stenting [see Figure 3] because unlike Paget-Schroetter syndrome, the extrinsic compression to the vein is not attributable to a firm, muscular structure.

Historically, iliofemoral DVT was treated exclusively with anticoagulation or open thrombectomy with subsequent anticoagulation.⁹⁶ However, many small series using catheter-directed thrombolysis and mechanical thrombolysis to treat iliofemoral DVT are rapidly demonstrating less PTS than with anticoagulation alone.^{103,104} There is a growing consensus that in addition to anticoagulation, primary iliofemoral thrombosis and May-Thurner syndrome should be treated with catheter-directed thrombolysis and placement of a closed-cell stent in the compressed vein (or residual thrombus) to diminish PTS and maintain patency.^{56,105} The placement of stents and evaluation of residual stenosis is often guided by the use of intravascular ultrasound probes in addition to venograms to ensure that the confluence of the vena cava is not compromised.¹⁰⁶ The randomized, multicenter Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis (ATTRACT) trial (ClinicalTrials.gov identifier: NCT00790335)¹⁰⁷ and the European Catheter-directed Venous Thrombolysis in acute iliofemoral vein thrombosis (CaVenT) trial (ClinicalTrials.gov identifier: NCT00251771)¹⁰⁸ are both enrolling patients to evaluate the outcomes of anticoagulation alone versus the use of pharmacomechanical means for thrombus removal in the iliofemoral segment.

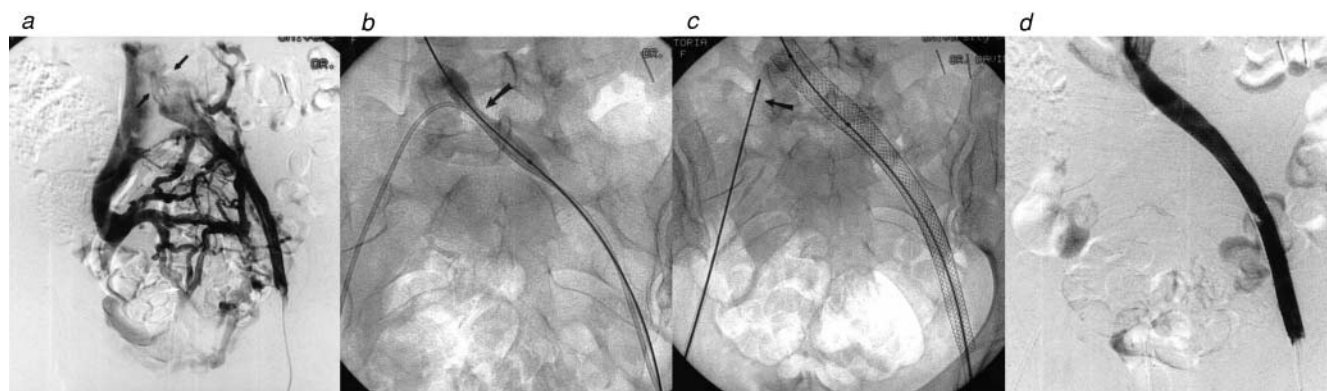


Figure 3 This panel depicts a lower extremity venogram of a patient with May-Thurner syndrome and its subsequent endovascular treatment. (a) Descending venogram demonstrating minimal reflux into the left iliac system and extensive, secondary pelvic collaterals. Arrows indicate the area of stenosis of the left common iliac vein. (b) Balloon venoplasty of the left common iliac vein. The arrow identifies the area of compression on the balloon within the vein. (c) Placement of a stent from the common iliac vein to the external iliac vein. The arrow demonstrates an intravascular ultrasound probe in the right iliac vein. (d) Retrograde venogram after venoplasty and stenting of the left iliac vein demonstrating a patent iliac venous system and resolution of the left-sided pelvic collaterals. Reproduced with permission from Hurst DR et al.¹⁰⁶

In addition to the use of plasminogen activator infusions into the thrombus, there are many different types of endovascular devices designed to accelerate the resolution of vessel thrombosis. They range from physically breaking up the clot with a spinning cage to catheters that spray fluid (saline, heparin, or tissue plasminogen activator) from multiple holes at a high pressure to fragment and aspirate the thrombus. None have been compared in a head-to-head randomized study and collectively have variable published effects on the reduction of thrombolysis infusion and final vessel patency. However, small studies seem to show that pharmacomechanical lysis may minimize the amount of thrombolytic administered and the total treatment time required to complete thrombolysis.^{109–111}

If the thrombus extends below the inguinal ligament, then open thrombectomy and an arteriovenous fistula may be required to improve the venous inflow and potentially decrease recurrent thrombosis, as well as the sequelae of PTS.¹¹² All cases are subsequently managed by anticoagulation with a VKA.⁵⁶

Management of Nonemergent VTE

SCORE **UNCOMPLICATED LOWER AND UPPER EXTREMITY VTE AND FOLLOW-UP**

Avoiding the progression and recurrence of DVT is paramount to decrease both the incidence of PE and the occurrence of PTS. The risk of the latter is dramatically increased in the setting of recurrent DVT (hazard ratio 6.4).¹⁶ To avoid this progression, all treatment guidelines recommend that patients with uncomplicated DVT be initially anticoagulated using a parenteral drug (UFH, LMWH, fondaparinux, or hirudin derivative) followed by an oral VKA lasting at least 3 months.^{56,60} The VKA is titrated to achieve a target international normalized ratio (INR) between 2.0 and 3.0, and, subsequently, the parenteral drug is ceased.

Almost 90% of patients anticoagulated for only 3 months for VTE will not have a recurrence within 5 years, but because

of the morbidity associated with recurrences, much effort has been made to identify patients at risk for recurrences. It has been found that those with an elevated D-dimer or continued scar tissue (from unresolved thrombosis) visualized on CDU seen at the 3-month evaluation should continue their anticoagulation to lower their risk of recurrence.^{113,114} For example, if CDU reveals significant residual scar tissue, there is a hazard ratio of 2.4 for recurrent DVT; therefore, these patients may benefit from continued anticoagulation until the risks associated with prolonged anticoagulation are deemed by the clinician to be greater than the risks of recurrent DVT.^{113,115}

In patients with DVT and cancer, continued treatment with LMWH is recommended as long as the cancer is active or for at least 3 months of therapy (whichever is longer). This is because the risk of DVT recurrence in these patients is up to 14%, and there is a higher risk of prolonged thrombus resolution (only 23% at 1 year) even with long-term anticoagulation.^{16,30,116}

Compression stockings should be worn immediately on starting therapy to decrease the risk of PTS and continued as long as the patient has swelling, usually for at least 2 years.⁵⁶ This measure is often forgotten and can significantly reduce the long-term risk of PTS.

Patients with certain inherited or antibody-mediated hypercoagulable states are at high risk for recurrence, and risk assessment needs to be obtained to determine if they require lifelong anticoagulation.¹¹⁷ There is no indication for anticoagulation with a VKA to an INR over 3, regardless of the risk factor, even in cases of antiphospholipid syndrome that have the highest risk of arterial and venous thrombotic syndromes, as found by both randomized controlled trials and the ACCP guideline statement.^{56,118}

General consensus for the management of UEDVT associated with catheter placement is to use anticoagulation, but some controversy exists regarding whether to remove the offending catheter. The 8th ACCP guidelines state that if the catheter is functional, then there is no need to remove it, and anticoagulation therapy is initiated alone as for LEDVT.⁵⁶

SCORE

A recent study found that when specifically looking at complete thrombus resolution in UEDVT, only removing the catheter had a significant impact on complete thrombus resolution (52% versus 25%, odds ratio 3.25), whereas anticoagulation alone did not have an impact on resolution (36% with anticoagulation versus 56% without any anticoagulation; $p = .10$).¹¹⁹ Of note, patients who had a catheter replaced had an increased risk of a new clot, thus highlighting the thrombophilic state of patients with catheter-related DVT.

SUPERFICIAL VEIN THROMBOSIS AND SUPPURATIVE THROMBOPHLEBITIS



Generally, uncomplicated superficial vein thrombosis (particularly when associated with intravenous catheters) can be treated with local warmth and oral or topical antiinflammatory agents to control symptoms.¹²⁰ However, there has been growing concern over the rate of underappreciated extension into the deep venous system resulting in PE. The incidence of PE and DVT has been reported as high as 25% with lower extremity superficial vein thrombosis.¹²¹ Thus, duplex ultrasonography is now recommended for cases of superficial vein thrombosis, and if propagation or encroachment into the deep system is seen, then systemic anticoagulation for 3 months is recommended.⁵⁶ Surgical excision of superficial vein thrombosis may be indicated if the patient has prolonged or incapacitating pain, if there is no resolution of the acute clot after 3 months of treatment, or as an alternative to anticoagulation if propagation into the deep system is identified.^{78,120}

With the advent of great saphenous vein ablations using catheter-delivered energy (laser or radiofrequency thermal energy) for chronic venous insufficiency, an increased number of thrombi have been identified at the saphenofemoral junction. Although there is no consensus for the management of this problem, if clot propagation into the femoral vein is identified during the initial procedure (thrombus “tail”), then we immediately start LMWH and treat for 1 week, although the evidence for the need for this treatment is evolving. Most clots resolve in this short interval of time. However, if a clot continues to be seen near or extending into the deep venous system, then standard DVT treatment guidelines may be followed or surgical thrombus removal and ligation of the saphenous vein can be performed as an alternative (particularly if there is a contraindication to anticoagulation).

Local intravenous catheter-site infections may occur in up to 8% of venous accesses and 18% of arterial catheterizations. Although most do not result in systemic infections, bacteremia can be detected in about one of every 400 intravenous catheterizations and 4% of arterial ones.¹²² Localized catheter-site infections may progress to superficial suppurative thrombophlebitis. In these cases, excision or open phlebectomy is indicated to drain all pus, remove the infected hematoma, and control the spread of the thrombosis and infection, removing the entire involved vein. Prevention is best obtained by changing all intravenous sites every 48 to 72 hours.

VENA CAVA FILTERS



IVC filters lower the risk of fatal PE in patients with a DVT who are unable to be anticoagulated or in those who have a recurrence during therapeutic anticoagulation. However, IVC filters are placed in many patients because of the relative

ease of the procedure, but often with unfounded indications. A prospective study of over 5,400 patients with DVT in an American registry found that 14% (781) of them had an IVC filter implanted. The indication in one third of these was only “prophylaxis” and not treatment failure.¹²³ There is evidence that DVT prophylaxis is used in less than half of surgical patients, with a concomitant increase in the placement of IVC filters that may not be indicated.¹²⁴

IVC filters should be placed only in cases where there is a contraindication to anticoagulation or when there is VTE recurrence in the setting of therapeutic anticoagulation. In most instances, IVC filters should not be used in patients without a DVT or PE as a prophylactic measure alone, regardless of the DVT risk factors, including trauma, surgery, and even cancer.¹²⁵ Although an example of an indication for a temporary IVC filter may be a trauma patient at high risk for bleeding (contraindication for anticoagulation) with a concomitant DVT or PE, filters are commonly placed as a prophylactic measure (patients without a DVT or PE) in patients undergoing bariatric surgery, after trauma, or with spinal cord injuries even though studies and consensus statements recommend against it.^{20,56,60,126}

Patients undergoing bariatric surgery have been undergoing a dramatic increase in the placement of prophylactic IVC filters (from 7 to 55% of patients over the last 10 years).¹²⁷ Using only pneumatic compression devices and early ambulation, the risk of DVT in laparoscopic Roux-en-Y gastric bypass is only 0.3%.¹²⁸ Studies using IVC filters for primary prophylaxis in bariatric surgery have demonstrated a 2% incidence of PE, in the setting of a 2.5% incidence of IVC filter complications, which include hemopericardium and pneumothorax.¹²⁹ The lack of methodologically sound studies and an overall low incidence of VTE (in patients who can usually ambulate and receive all other forms of mechanical and pharmacologic prophylaxis) have led to an overall consensus by the ACCP and others that filters not be used for primary VTE prophylaxis in this or any other surgical procedure.¹³⁰

Deployment of a vena cava filter may be done via the common femoral or the internal jugular veins. Although femoral access is generally used, preplacement imaging of the venous system is imperative to determine if the access route is without thrombus. If clot is identified, then the filter should not be placed through this route to minimize embolization. If there is thrombus in the IVC, then the filter must be placed above it via the internal jugular access. Venography is also done to ensure that the patient has normal venous anatomy (he or she may require two filters if a duplicated vena cava is found), to identify the location of both renal veins to choose the site for deployment, and to measure the diameter of the IVC (it must be less than 30 cm for most filters to minimize their migration). Filters are generally positioned in the IVC with their fixation prongs caudal to the renal veins.

There are two broad types of vena cava filters: permanent and removable. The longest follow-up for a single IVC filter is the permanent, over-the-wire Greenfield filter, which, after more than 20 years, has a very low incidence of IVC thrombosis (< 4%) and migration (only non-clinically significant in 8%)¹³¹ and has not increased the incidence of DVT.¹³² The randomized PREPIC trial compared the long-term outcomes of patients with DVT treated with four different permanent filters and anticoagulation with the outcomes of patients

treated with anticoagulation alone for 3 months. The authors found that although at 8 years there was a significantly lower incidence of PE (6.2% versus 15.1%, $p = .008$) in those with IVC filters, no difference in mortality or PTS was found. However, an increased risk of DVT (35.7% versus 27.5%, $p = .04$) was observed in the group receiving a permanent filter. Of note, almost half of the patients with filters registered to have had a DVT also had filter thrombosis.^{133,134} Permanent filters are covered with endothelium and affix into the IVC wall after 2 to 3 weeks, so the risk of attempting to completely remove them in the operating room may be very high.¹³⁵ In general, we have found that if IVC filter prongs protruding from the vein wall cause symptoms or bleeding, then the metal that is visible outside the IVC should only be trimmed flush with the vein (in addition to any other repair needed), and the remaining filter should be left in place.

To treat patients with filters only during their acute thrombophilia, optional retrievable filters have become more popular than permanent ones. The theoretical advantage of using retrievable filters for patients with temporary prothrombotic states is often mitigated by poor long-term follow-up, and

over 75% are never removed, even in the military experience,^{136,137} or may require extreme surgical techniques to remove them when complications arise.¹³⁸ These include migration, IVC thrombosis (2 to 14%, especially in biconcave retrievable or bird nest filters),¹³⁹ renal vein thrombosis, and erosion into bowel¹⁴⁰ or aorta.¹⁴¹

There is no large randomized trial assessing the use of superior vena cava (SVC) filters for UEDVT. Almost two thirds of patients with SVC filters will die of their underlying diseases, and not of PE, within 2 months of placement.¹⁴² SVC perforations from filters with migration may result in a high mortality secondary to tamponade.¹⁴³ Once they are in place, it is imperative to adequately warn all practitioners that the SVC filter is there to avoid blind central line placement with standard J wires that may dislodge the filter or entangle themselves in it.¹⁴⁴ Therefore, the benefit of SVC filters is still unclear for patients with UEDVT, and they should be judiciously used for patients whose mortality is high from other causes.

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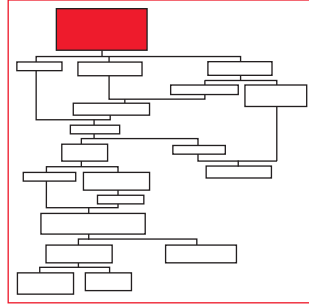
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7 DIABETIC FOOT

Richard C. Hsu, MD, PhD, and Allen D. Hamdan, MD, FACS

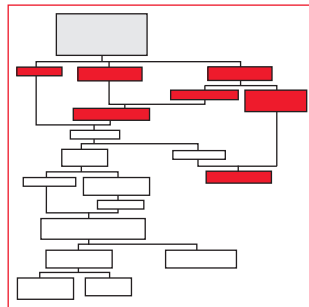
Evaluation and Management of the Diabetic Foot

Surgeons caring for diabetic patients are faced with a diverse spectrum of foot disease.^{1,2} The clinical presentation may range from the asymptomatic patient who requires nothing more than preventive foot care to the unstable and critically ill patient in whom both loss of limb and death are imminent threats. This wide range of disease severity contributes to the clinical confusion that often leads to delays in diagnosis and treatment and, ultimately, to limb loss. The annual rate of amputation is as high as 5% in patients with type 2 diabetes, which is roughly 15 times the rate that is seen in the nondiabetic population.³ It is important, therefore, that surgeons caring for diabetic patients develop a simple but comprehensive and orderly approach to diabetic foot problems that (1) can be implemented for any such problem; (2) recognizes the pathogenic roles of neuropathy, ischemia, and infection; and (3) emphasizes the initial clinical assessment at the bedside.⁴



Clinical Evaluation

Evaluation of any diabetic foot problem begins with a complete history and a careful physical examination. Broadly speaking, such evaluation should address the healing potential of the foot, the details of the foot problem (e.g., ulcer, gangrene, infection, or osteomyelitis), the systemic consequences of diabetes, and any immediate threats to life or limb. With this information in hand, the surgeon can usually make an accurate diagnosis and start a comprehensive treatment plan.



HISTORY

The history of the foot problem can yield valuable insights into the potential for healing, the presence of coexisting infection or arterial occlusive disease, and the need for further treatment. Whenever a patient presents with a foot ulceration or gangrene, possible underlying arterial insufficiency should immediately be suspected, even if neuropathy

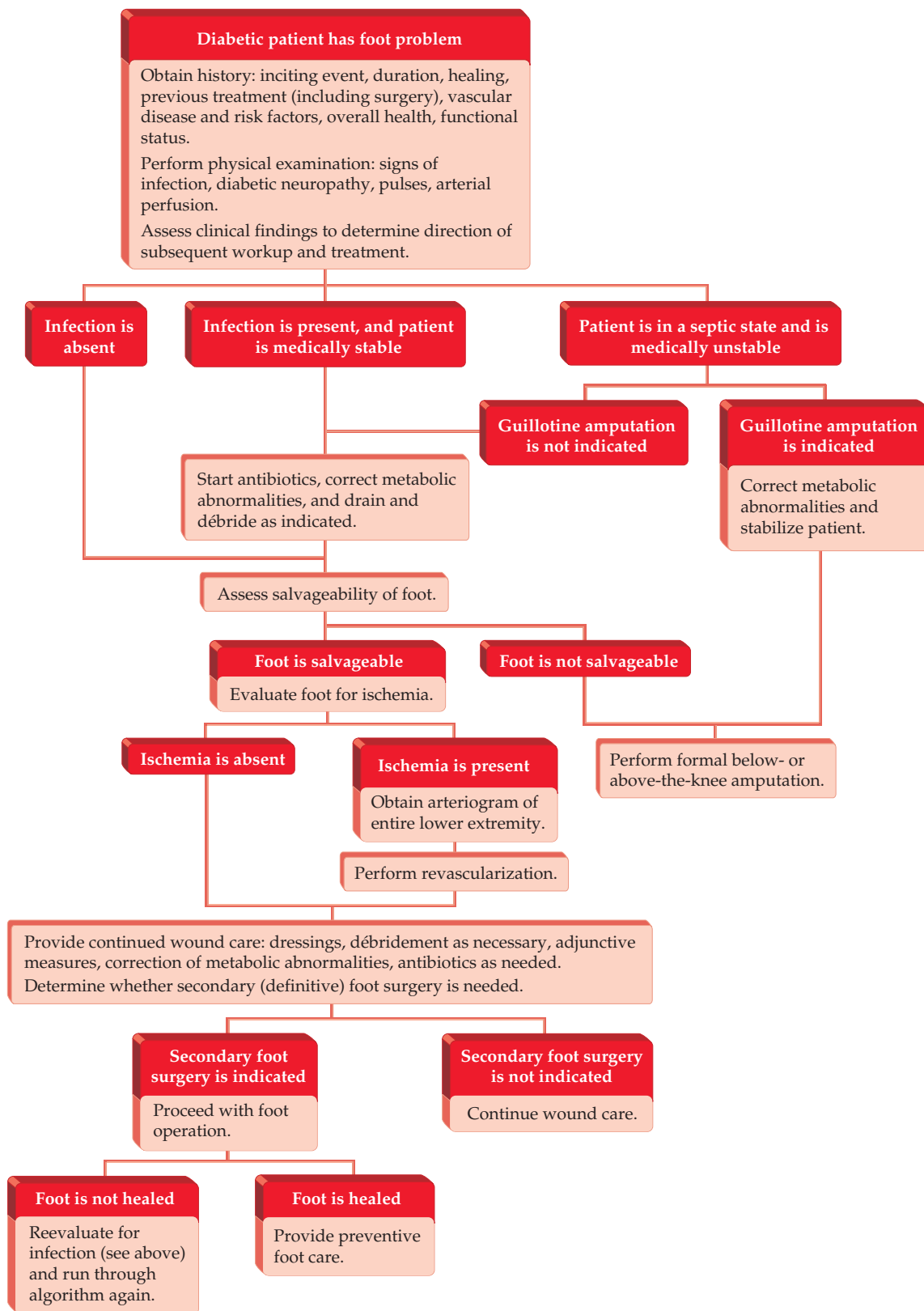
or infection is present. It is helpful to be aware of the event that incited the foot problem. In a patient with diabetes and arterial insufficiency, the inciting event for a foot ulcer may be a seemingly benign action, such as cutting a toenail, soaking the foot in a warm bath, or applying a heating pad. Unfortunately, because of the broad microvascular and macrovascular abnormalities associated with diabetes, these relatively innocuous actions can progress to a nonhealing ulcer and gangrene. Similarly, failure to heal after any podiatric procedure is strongly suggestive of underlying unrecognized arterial insufficiency.

The duration of the ulcer also provides important clues, in that a long-standing, nonhealing ulcer is strongly suggestive of ischemia. Certainly, an ulcer or gangrenous area that has been present for several months is unlikely to heal without some further treatment, whether it be offloading of weight-bearing areas, treatment of infection, or, most commonly, correction of arterial insufficiency. A history of intermittent healing followed by relapse raises the possibility of underlying untreated infection (e.g., recurrent osteomyelitis) or an uncorrected architectural abnormality (e.g., a bony pressure point or a varus deformity).

In view of the many vague and unsupported therapies advocated for the diabetic foot, it is helpful to know the type and duration of any treatments the patient has already undergone for the current problem. For example, a patient with an ischemic ulceration may have completed several different courses of antibiotics without success. Thus, if antibiotic therapy is contemplated for a current infection, possible antibiotic resistance must be taken into account in choosing the appropriate agent. It is also helpful to know which treatments were not previously offered to the patient and to look critically at why they were not offered. For example, many diabetic patients with correctable foot ulceration and limb ischemia are told that their only option is limb amputation, usually because of the physician's inherited pessimism or his or her inadequate knowledge of the advances made in limb and foot salvage. No patient should be denied an opportunity for limb salvage on the basis of a previous medical or surgical opinion without a new comprehensive evaluation being performed.

Inquiries should be made about any previous foot and limb problems—for instance, whether the patient had other ulcers on the same foot that healed spontaneously, how long such healing took, and whether foot surgery was ever performed on that side. A history of recent ipsilateral ulceration or foot surgery that healed in a timely and uncomplicated manner suggests, but does not prove, that the arterial supply is adequate. Problems and procedures more remote in time,

Evaluation and Management of the Diabetic Foot



however, are less useful indicators. A history of previous leg revascularization (including percutaneous therapies) is also an important clue to possible underlying arterial insufficiency. Because of the predilection for mirror image-type atherosclerotic occlusive disease, the contralateral leg must be considered as well: previous revascularization in the opposite leg is often associated with arterial insufficiency on the affected side. Other cardiovascular risk factors, such as cigarette smoking and hyperlipidemia, must also be taken into account: their presence increases the likelihood that ischemia is contributing to the current foot problem.

Although claudication and rest pain have traditionally been associated with vascular disease, they may be obscured by diabetic neuropathy; hence, their absence in the diabetic patient certainly does not rule out ischemia. Because even moderate ischemia precludes healing in the diabetic foot, the absence of rest pain is not a reliable indicator of an adequate arterial blood supply; moreover, many patients may not be walking long enough distances for vasculogenic claudication to develop. Conversely, some patients with true ischemic rest pain are dismissed for years as having “painful neuropathy.”

Both the systemic effects of the foot problem and the systemic consequences of diabetes itself should be assessed. Because unrecognized infection in the diabetic patient may rapidly progress to a life-threatening condition, attention should be directed toward detecting the subtle manifestations of an infected foot ulcer. The patient should be asked about worsening hyperglycemia, recent erratic blood glucose control, and higher insulin requirements. As a consequence of the microvascular and neuropathic abnormalities in the diabetic foot, classic symptoms of infection (e.g., chills and pain) are often absent, and hyperglycemia is often the sole presenting symptom of undrained infection. Faced with ongoing infection and hyperglycemia, the surgeon should strongly suspect impending ketoacidosis or nonketotic hyperglycemic hyperosmolar coma, with the attendant symptoms of weakness, confusion, and altered mental status.

Because a patient with a diabetic foot problem often needs some type of operative intervention, the history should also include a comprehensive assessment of overall health status to help stratify perioperative risk [see *ECP:6 Risk Stratification, Preoperative Testing, and Operative Planning*]. For example, knowledge of previous cardiac events (e.g., myocardial infarction or revascularization) and current cardiac status (e.g., New York Heart Association [NYHA] class or anginal severity) can help determine whether perioperative cardiac monitoring or preoperative cardiac testing is indicated and what form such monitoring or testing should take. Similarly, in a patient with suspected infection and ischemia, a history of worsening renal function or impending need for hemodialysis can help determine the choice and dosage of antibiotics and may alter plans for standard contrast arteriography. The essential point is that diabetes may affect virtually every organ system, often in an indolent pattern; thus, in the evaluation of any diabetic patient with foot disease, attention must be paid to all of these systems.

Functional status also becomes an important consideration at this point, and the history should carefully determine the patient’s ambulatory and rehabilitative potential. Many different methods of quantifying functional status have been suggested. One simple approach is to classify functional status

as a point on a continuum. One end of the continuum might be a fully ambulatory patient; almost all surgeons would recognize that such a patient should be offered every attempt at limb salvage. The other end might be a completely bedridden patient with multiple comorbid conditions; most surgeons would adopt a far less aggressive approach to such a patient. In practice, many patients fall somewhere between these two extremes, in which case, a more thorough evaluation of functional and social status becomes imperative before any firm decisions can be made regarding limb salvage.

PHYSICAL EXAMINATION

Fever and tachycardia are strongly suggestive of deep or undrained infection, with hypotension being a late manifestation of ongoing sepsis. It is important to remember, however, that these signs may be absent in diabetic patients with impending or progressive infection. A focused cardiopulmonary examination helps confirm the presence or absence of congestive heart failure, valvular abnormalities, or rhythm disturbances, which must be recognized in diabetic patients with poor underlying medical reserve.

Evaluation of the diabetic foot ulcer should include a strong suspicion of infection and a thorough search for it. In a patient with cellulitis, the entire foot, including the web spaces and the nail beds, should be examined for any potential portals of entry, such as a puncture wound or an interdigital (“kissing”) ulcer. Encrusted and heavily calloused areas over the ulceration should be unroofed and the wound thoroughly inspected to determine the extent of involvement. A benign-appearing, dry, gangrenous eschar often hides an undrained infectious collection [see *Figure 1*]. Cultures should be taken from the base of the ulcer; superficial swabs may yield only colonizing organisms.

Findings consistent with infection include purulent drainage, crepitus, tenderness, mild erythema, and sinus formation [see *Figure 2*], although these findings may be entirely absent in the neuropathic foot. With more advanced and deep infection, edema may be present as a result of elevated pressures within one or more of the plantar compartments [see *Figure 3*]. If left untreated, this process may spread proximally along tendon sheaths to involve the ankle or even the calf. Close inspection of the ulcer and the use of a sterile probe may also confirm the presence of osteomyelitis, which occurs commonly even in conjunction with benign-appearing ulcers. If bone is detected with gentle probing, osteomyelitis is presumed present.

Because of its prevalence and its causative role in diabetic foot ulceration and limb loss, neuropathy should be assessed in every diabetic patient, and appropriate preventive measures should be taken to guard against foot ulceration in the high-risk neuropathic foot. Protective sensation may be evaluated by pressing a Semmes-Weinstein 5.07 monofilament against the skin; inability to feel the monofilament correlates well with an increased risk of foot ulceration. Advanced sensorimotor neuropathy will lead to the presence of a so-called

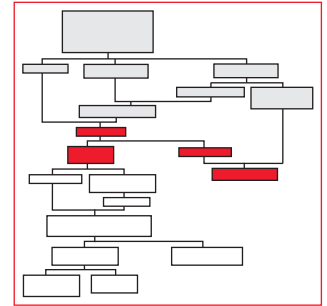




Figure 1 Shown is a benign-appearing gangrenous eschar (a) on the foot of a diabetic patient. Plain x-ray (b) reveals extensive subcutaneous air in soft tissue, consistent with severe necrotizing fasciitis.



Figure 2 Purulent drainage is seen from a submetatarsal ulcer on the plantar surface of the foot of a diabetic patient.

claw foot (from gradual atrophy of the intrinsic muscles) or to Charcot degeneration with bone and joint destruction at the midfoot. Both of these conditions give rise to abnormal pressure points on the plantar prominences and the potential for foot ulceration.

Assessment of the arterial perfusion in the diabetic foot is a fundamental consideration in that the diabetic foot needs maximal perfusion to heal. In the presence of ischemia, all efforts at limb salvage will fail. Therefore, the physical examination must include a systematic approach to the assessment of arterial insufficiency. Simple inspection of the leg and foot, including the ulcer, often provides suggestive clues. For example, distal ulceration (on the tip of a digit), ulceration unassociated with an exostosis or a weight-bearing area, and gangrene are all strongly consistent with underlying ischemia [see Figure 4]. The presence of multiple ulcerations or gangrenous areas on the foot, the absence of granulation tissue, and the lack of bleeding with débridement of the ulcer should immediately be taken as signals of possible underlying arterial insufficiency. Other signs suggestive of ischemia are pallor with elevation, fissures (particularly at the heel), and the absence of hair growth. Poor skin condition and hyperkeratosis, although not always good indicators of arterial disease, should be noted because they may help confirm initial clinical impressions.



Figure 3 Shown is wet gangrene with edema and undrained severe infection in the foot of a diabetic patient presenting with hyperglycemia and ketoacidosis.



Figure 4 Shown is dry gangrene of several toes in a diabetic patient with femoropopliteal and tibial arterial occlusive disease.



Figure 5 Illustrated is the correct technique for palpation of the dorsalis pedis pulse.

The pulse examination, including the status of the foot pulses, is the single most important component of the physical examination. In the absence of a palpable pulse, ischemia is always presumed to be present. Although an accurate pulse examination of the lower extremities is not difficult, it is an acquired skill, and time should be devoted to practicing and perfecting the technique.

The femoral pulse is palpated midway between the superior iliac spine and the pubic tubercle, just below the inguinal

ligament. The popliteal pulse is palpated with both hands and with the knee flexed no more than 15°. Palpation of the foot pulses is somewhat more demanding, requiring close attention and a good knowledge of the usual locations of the native arteries. The dorsalis pedis is located between the first and second metatarsal bones, just lateral to the extensor hallucis longus tendon, and its pulse is palpated with the pads of the fingers as the hand is partially wrapped around the foot [see Figure 5]. If the pulse cannot be palpated, the fingers may be moved a few millimeters in each direction; the dorsalis pedis occasionally follows a slightly aberrant course. A common mistake is to place a single finger at one location on the dorsum of the foot. The posterior tibial artery is typically located in the hollow curve just behind the medial malleolus, approximately halfway between the malleolus and the Achilles tendon. The examiner's hand should be contralateral to the examined foot (i.e., the right hand should be used to palpate the left foot, and vice versa), so that the curvature of the hand naturally follows the contours of the ankle [see Figure 6].

Assessment of Clinical Findings

Once the clinical evaluation is complete, the next step is to assess the findings from the history and the physical examination so as to determine the course and urgency of the subsequent workup and treatment. This assessment is made at the bedside, focusing on three main concerns: (1) the presence and severity of infection, (2) the salvageability of the limb, and (3) the presence of ischemia.

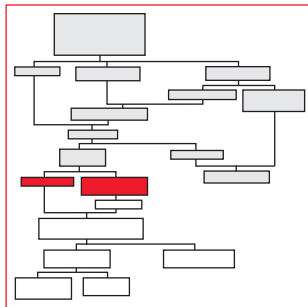


Figure 6 Illustrated is the correct technique for finding the posterior tibial pulse.

PRESENCE OF INFECTION

Evaluation for and treatment of infection are the first priority in the management of any diabetic foot problem.^{5,6} Although radiographic tests may confirm initial clinical suspicions, the determination of the severity of infection is almost always made on the basis of clinical findings. Infection in the diabetic foot may range from a minimal superficial infection to fulminant sepsis with extensive necrosis and destruction of foot tissue. Accordingly, the treatment plan should address the choice of antibiotic (which requires knowledge of the microbiology), the need for drainage, the option of local or even guillotine amputation, and the patient's overall medical condition.

The microbiology of the diabetic foot varies according to the depth and severity of the infection and the nature of the patient's environment (e.g., hospitalized or outpatient). Certain general assumptions can be made about likely causative organisms. Mild localized and superficial ulcerations, particularly in outpatients, are usually caused by aerobic gram-positive cocci (e.g., *Staphylococcus aureus* and streptococci). In contrast, deeper ulcers and generalized limb-threatening infections are usually polymicrobial. In addition to gram-positive cocci, potential causative organisms include gram-negative bacilli (e.g., *Escherichia coli*, *Klebsiella*, *Enterobacter aerogenes*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*) and anaerobes (e.g., *Bacteroides fragilis* and peptostreptococci). Enterococci may also be isolated from the wound, notably in hospitalized patients; in the absence of other cultured virulent organisms, they should probably be considered pathogenic.



Currently, it is clear that resistant organisms, particularly methicillin-resistant *S. aureus* (MRSA), are playing a growing role in the development of skin and soft tissue infections. Traditionally arising in patients who had previously been hospitalized and those who had previously received antibiotic therapy, MRSA-associated infections are now frequently encountered in outpatient settings. Indeed, in many US cities, these so-called community-acquired MRSA infections are the most common skin and soft tissue infections seen in patients presenting to the emergency department.⁷ Accordingly, in both outpatient and inpatient settings, it is advisable to assume that MRSA is present in a patient with a diabetic foot infection until the culture data suggest otherwise. Awareness of the increasing prevalence of resistant organisms is critical for current management of diabetic foot infections, especially with respect to the initiation of antibiotic coverage.

Initially, the choice of antibiotics is made empirically on the basis of these general assumptions. When the results of the initial cultures become available, antibiotic coverage may be broadened or narrowed as appropriate. In a compliant patient with a small ulcer and no evidence of deep space involvement or systemic infection, treatment may be delivered on an outpatient basis. A dual-antibiotic regimen (pending culture results) is instituted, typically consisting of a cephalosporin or a β -lactam antibiotic (for activity against staphylococci and streptococci) and trimethoprim-sulfamethoxazole or a tetracycline (for activity against MRSA). A dual regimen consisting of fluoroquinolone and linezolid is an acceptable alternative that also provides adequate coverage. In addition, the patient is instructed to offload weight from the involved extremity and is taught appropriate methods for changing wound dressings. Frequent follow-up is vital, and guidelines should be imparted by which improvement or worsening of the lesion can be determined.

A more common presentation, unfortunately, is a patient with ulceration or gangrene who has a deep infection affecting tendon or bone and possible systemic involvement. For such patients, immediate hospitalization is indicated, including bed rest with elevation of the infected foot, correction of any systemic abnormalities, and broad-spectrum intravenous (IV) antibiotic therapy (which may be focused more tightly once culture results are complete). Because the clinical findings of impending sepsis may be subtle, these patients should undergo a complete laboratory workup aimed at detecting and correcting electrolyte and acid-base imbalances.

The choice of antibiotic agent and the duration of therapy are dependent on the extent of the infection. For patients with deep or chronic recurrent ulcers, which are typically polymicrobial, or those with limb-threatening or life-threatening infections, appropriate empirical antibiotic options include (1) vancomycin plus a β -lactam antibiotic with a β -lactamase inhibitor (e.g., piperacillin-tazobactam) and (2) vancomycin plus metronidazole plus a quinolone (in cases of penicillin allergy). Subsequent culture results then dictate further antibiotic coverage, if any. In the absence of osteomyelitis, antibiotics should be continued until the wound appears clean and all surrounding cellulitis has resolved (typically, 10 to 14 days). If osteomyelitis is present, treatment should include both surgical débridement and a prolonged (4- to 6-week) course of antibiotic therapy (although the course may be abbreviated if the entire infected bone has

been removed, as with digital or transmetatarsal amputation). Heel lesions often present with some degree of calcaneal destruction, and determination of osteomyelitis may be made by clinical examination either alone or in conjunction with other radiographic tests (e.g., magnetic resonance imaging [MRI]) [see Figure 7].

In the presence of an abscess or deep space infection, immediate incision and drainage of all infected tissue planes are mandatory. Incisions should be chosen with an eye to the normal anatomy of the foot (including the various compartments) and the need for subsequent secondary (foot salvage)

procedures [see Figure 8]. Drainage should be complete, with incisions placed to allow for dependent drainage, and all necrotic tissue must be débrided. Repeat cultures (including both aerobes and anaerobes) should be obtained from the deep tissues. Drainage incisions on the dorsum of the foot should be avoided. Abscesses in the medial, central, or lateral compartment should be drained via longitudinal incisions made in the direction of the neurovascular bundle and extending the entire length of the abscess. The medial and central compartments are drained through a medial incision, and the lateral compartment is drained through a lateral incision; both of

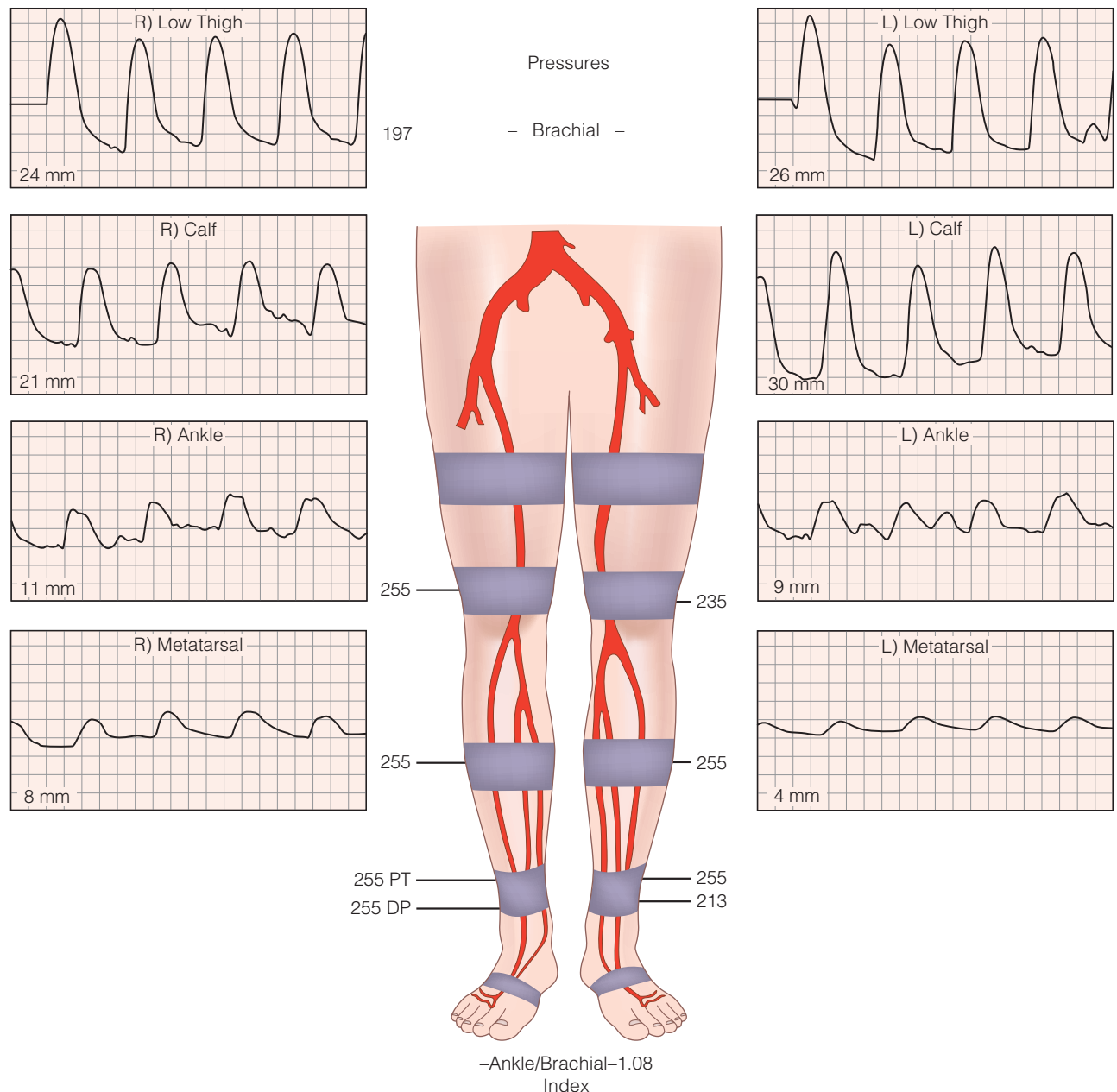


Figure 7 Pulse volume recording (PVR) taken from a diabetic patient. Note the “dampening” of the waveforms on both extremities beginning at the level of the ankle. This suggests that an occlusive vascular lesion exists between the level of the calf and ankle.

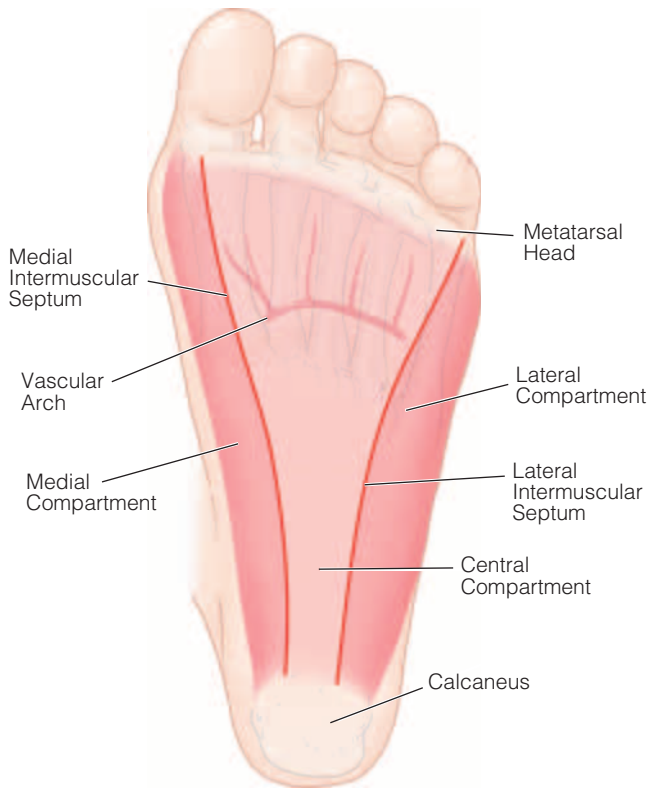


Figure 8 The foot has three plantar compartments: medial, central, and lateral. The intrinsic muscles of the great toe are in the medial compartment, and those of the fifth toe are in the lateral compartment. The central compartment contains the intrinsic muscles of the second through fourth toes, the extensor flexor tendons of the toes, the plantar nerves, and the plantar vascular structures. The floor of each compartment is the rigid plantar fascia; the roof is composed of the metatarsal bones and interosseous fascia. The medial and central compartments are separated by the medial intermuscular septum, which extends from the medial calcaneal tuberosity to the head of the first metatarsal. The lateral and central compartments are separated by the lateral intermuscular septum, which extends from the calcaneus to the head of the fifth metatarsal.

these incisions are made just above the plantar surface of the forefoot [see Figure 9]. Web space infections may be drained similarly through the plantar aspect of the foot. In some instances, open amputation of the foot (e.g., an open toe or transmetatarsal amputation) may be necessary to allow complete drainage and resection of necrotic tissue. Strict adherence to textbook amputations may lead to unnecessary soft tissue removal and possibly to a higher amputation during future closure; therefore, all viable tissue should be conserved.

A patient with an ongoing undrained infection may present with an unsalvageable foot and fulminant sepsis, manifested by hemodynamic instability, bacteremia, and severe acid-base and electrolyte abnormalities. Such patients should undergo prompt open (guillotine) below-the-knee amputation [see 6:20 *Lower-Extremity Amputation for Ischemia*]. This type of amputation is usually performed at the ankle level, with the aim of removing the septic source while allowing for revision and closure at a later date. Administration of IV antibiotics, correction of dehydration and electrolyte abnormalities, and



Figure 9 Shown is an infection in the central compartment of the foot from a submetatarsal ulcer that has extended proximally to include the medial compartment (a). A plantar incision through the ulcer and both compartments (including the septum) allows complete dependent drainage (b).

continuous cardiac monitoring are absolutely essential throughout treatment.

Once the infection has been drained and tissues débrided, continued wound inspection and management are essential. Ongoing necrosis should raise the possibility of undrained infection or untreated ischemia, in which case further débridement and treatment may be necessary. Avoidance of weight bearing should be continued. Neither whirlpool therapy nor soaks are beneficial.

Medical Stabilization

Concomitant with the measures outlined above to control infection, medical stabilization of the diabetic patient must be carried out, and the surgeon must be directly involved in this process. Hyperglycemia is almost always seen when infection is present; it should be gradually corrected. More advanced

hyperglycemia leads to ketotic or nonketotic hyperosmolar states, which carry a 10 to 25% mortality. Serum concentrations of electrolytes, magnesium, and creatinine should be obtained and osmolality determined at frequent intervals; any abnormalities should be corrected [see 8:24 *Disorders of Water and Sodium Balance* and 8:8 *Acid-Base Disorders*]. Dehydration is common in hyperglycemic patients and should be corrected. A urinary catheter is mandatory to help guide the response to fluid therapy; in unstable patients, a central venous pressure catheter or a pulmonary arterial catheter may be needed. Continuous cardiac monitoring is essential in patients with the hyperglycemic hyperosmolar syndrome or ketoacidosis.

SALVAGEABILITY OF LIMB

While the infection is being treated and controlled, the surgeon should determine whether limb salvage is feasible. This determination is based largely on the patient's functional status and the degree of foot destruction. For example, primary limb amputation may be considered in a nonambulatory, bedridden patient or in a patient with severe Charcot destruction and degeneration, for whom no further reconstructive foot surgery is possible. Poor medical condition, by itself, is not necessarily an indication for primary limb amputation, given the high perioperative morbidity associated with amputation. Moreover, it is often possible to improve the patient's overall medical status while he or she is being treated for infection and evaluated for ischemia.

Assessment of limb salvageability should be carried out simultaneously with treatment of infection because appropriate drainage and antibiotics can dramatically change the appearance and viability of the foot. If limb salvage is not deemed possible, the patient should undergo formal below-the-knee or above-the-knee amputation [see 6:20 *Lower-Extremity Amputation for Ischemia*].

PRESENCE OF ISCHEMIA

Evaluation of the diabetic foot for ischemia begins with the history and the physical examination. By the conclusion of the clinical evaluation, the surgeon can usually make an accurate assessment of the adequacy of the arterial circulation to the foot. As noted [see *Clinical Evaluation, Physical Examination, above*], the absence of a palpable foot pulse strongly suggests ischemia unless proved otherwise. In a patient with a severe foot infection requiring open resection/débridement or in a setting with multiple toe gangrene, just the lack of a foot pulse is enough to proceed to angiography. In more subtle cases, including those with absent foot pulses who have a superficial ulcer with evidence of healing or a previous history of a healed foot ulcer and those without any foot lesions who are scheduled to undergo elective foot surgery, various noninvasive modalities are available to the clinician. The noninvasive arterial study is a first-line test to establish the pattern and severity of arterial ischemia. This examination involves determining segmental pressure measurements, ankle-brachial indices (ABIs), arterial waveforms, and pulse volume recordings (PVRs). Segmental pressures are systolic blood pressure measurements using cuffs at standard locations from thigh to ankle (thigh-high and -low, below the knee, and at the ankle). In individuals with normal arterial perfusion, the thigh-high value is 30 mm higher, the ankle

value is slightly higher, and toe pressures are 80% of brachial. There should not be more than a 20 mm pressure drop between segments. Equally important is a comparison of values between the two legs. The ABI is calculated as part of this study, defined by dividing the leg pressure by the brachial artery pressure. An ABI greater than 0.90 indicates normal perfusion, and values less than 0.40 are associated with rest pain and gangrene. In patients with long-standing diabetes mellitus, medial calcific stenosis occurs and will render the vessels incompressible. Therefore, in diabetic patients, very low ABIs may be presumed to be accurate, whereas normal or high values need validation, such as the presence of a palpable pulse. However, vessels in the diabetic foot are generally spared from the atherosclerotic changes in the more proximal vessels. Vincent and colleagues showed that toe pressure is an "accurate hemodynamic indicator of total peripheral arterial obstructive disease" in diabetics.⁸ Toe pressures less than 40 mm Hg predict healing difficulties.

Arterial waveforms are graphic representations of the Doppler shift as erythrocytes flow through the artery being evaluated. High-resistance vessels, such as those found in the lower extremity, should produce a triphasic signal. Forward flow in systole produces a sharp upstroke, followed by reversal of flow in early diastole as reactive vessels recoil from distention. Calcified vessels will lose this small, short notch below the baseline. Then in late diastole, forward flow recurs as vessels contract and propel blood forward, producing a small notch above the baseline. These three phases produce the triphasic pattern. Worsening stenoses results in loss of flow reversal and spectral broadening, eventually resulting in a monophasic waveform indicating severe disease.

PVRs are generated by sensing devices calibrated with air (pneumoplethysmograph). With each cardiac cycle, the leg subtly increases in volume and then returns to baseline. A normal PVR shows a sharp systolic peak with a dicrotic notch. With worsening arterial disease, the systolic peak flattens, the dicrotic wave obliterates, and the amplitude decreases. Because the PVR is influenced by factors such as cardiac output, limb size, and vasomotor tone, the test is not useful as a quantitative tool. However, because the test is not influenced by arterial wall calcification, PVRs can be very helpful in a patient with diabetes mellitus and an ulcer who have a falsely elevated or nonrecordable ABI. In general, a PVR greater than 15 mm of deflection at the metatarsal level is considered normal, and a PVR less than 5 mm indicates very severe disease [see *Figure 7*].

Once ischemia is suspected in a diabetic patient with tissue loss, arteriography of the entire lower extremity should be performed. The decision to perform arteriography and vascular reconstruction should be made as soon as infection has started to resolve and signs of systemic toxicity have disappeared; prolonged delays in making this decision may result in further tissue loss and make salvage impossible. Digital subtraction angiography remains the gold standard in the assessment of occlusive disease. The technology enhances the images of conventional angiography by using subtraction of the bone and soft tissue components to provide better visualization of the contrast column. Post-image processing can further enhance the information provided. In patients with diabetes mellitus, where tibial occlusive disease is prevalent, visualization of pedal vessels becomes exceedingly important.

Two views of the foot (anteroposterior and lateral) should be obtained, and care should be taken to avoid plantar flexion during the examination as this may impede flow to the dorsalis pedis artery.

Concern over possible contrast-induced renal failure should not be considered a contraindication to high-quality angiography of the entire lower extremity. The incidence of contrast nephropathy is not higher in diabetic patients without preexisting renal disease, even when ionic contrast agents are employed. The most important factor in the prevention of renal failure in patients with preexisting renal insufficiency has been the use of IV hydration prior to obtaining the angiogram.⁹ Both sodium bicarbonate solution and normal saline have been shown to be efficacious in preventing contrast-induced nephropathy,¹⁰ and neither one has been definitely shown to be superior to the other. In conjunction with hydration, prophylactic oral administration of the antioxidant *N*-acetylcysteine, 600 mg twice daily started on the day before the arteriogram and continued for 48 hours, has been shown to prevent reduction in renal function in at-risk patients.^{11,12} Other strategies for renal protection include the use of non-ionic contrast agents, use of carbon dioxide as the contrast agent, and judicious use of contrast media. Selective catheterization of the distal superficial femoral artery (SFA) or popliteal artery in the absence of proximal disease allows for focused visualization of the distal vessels with limited contrast delivery. When renal failure does occur, it is almost always reversible,¹³ but it may delay arterial reconstructive surgery while renal function returns to baseline.

Magnetic resonance angiography (MRA) and spiral computed tomographic angiography (CTA) have been proposed as alternatives to invasive angiography in the evaluation of vascular occlusive disease. MRA has acceptable resolution of tibial vessels but is not sufficiently capable of evaluating pedal vasculature.¹⁴ The accuracy of CTA depends on the timing of image acquisition to contrast delivery. Imaging of the pedal vessels is hindered by opacification of veins and calcification of vessel walls and would require a tremendous contrast load. In practice, a combination of these tests may be required to achieve the best balance of information acquisition and risk exposure.

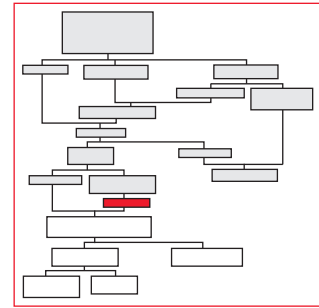
Management

MEDICAL THERAPY

Management of the diabetic patient with foot ulcer requires management of the whole patient. Diabetes affects every organ system in the body, and the same processes leading to lower extremity ischemia also contribute to coronary ischemia. A comprehensive discussion of diabetes care is beyond the scope of this chapter, but some key points are worth mentioning. Unless specifically contraindicated, all patients should be placed on aspirin and/or clopidogrel, beta blockade with perioperative goal heart rates of less than 70 bpm, angiotensin blockade, intensive glucose control, and statins. Statins appear to stabilize coronary plaques, reducing perioperative cardiac events, improve dyslipidemia, and improve the patency of infrainguinal reconstructions.^{14–18} Careful attention to perioperative care contributes to improved outcomes in this high-risk population.

REVASCARIZATION

The goals of arterial reconstruction are to restore maximal perfusion to the foot and, ideally, to restore a palpable foot pulse. Possible approaches include endovascular techniques (angioplasty and stenting), bypass grafting (with autogenous or prosthetic grafts), and some combination of the two.



Ultimately, the choice of procedure in any given case is based on the individual patient's anatomy, the comorbid conditions present, and the results of the preoperative assessment, with the aim being to provide the most durable procedure with the least risk. For example, in rare patients with isolated iliac artery stenoses, angioplasty may be effective by itself, but in patients with multilevel disease, it may have to be combined with an infrainguinal bypass [see 6:17 *Infrainguinal Arterial Procedures*].

Arterial bypass grafting provides the most durable results for restoration of distal perfusion.¹⁹ Three aspects to consider in planning any arterial bypass reconstruction are the quality of the inflow and outflow vessels and the choice of conduit. A bypass graft with poor quality inflow is likely doomed for failure. However, the choice of inflow vessel is often determined by the length of good-quality conduit; as such, the distalmost inflow vessel available can be used. In patients with diabetes, the SFA is often spared, with the occlusive disease limited to the infragenicular arteries. In this situation, the SFA or popliteal artery can be used for inflow. Two advantages of this approach are the shorter length of conduit required and the avoidance of a groin incision, which can be a major source of morbidity, especially in obese individuals. Adequacy of inflow vessels can be assessed by the presence of a palpable pulse or through angiography. Proximal bypass to either the popliteal artery or the tibial and peroneal arteries may restore foot pulses, and preference should be given to these vessels if they are in continuity with the foot. Often, however, because of the presence of more distal obstructive disease, bypass grafting to the popliteal or even the tibial artery will not restore the foot pulse. In such cases, restoration of pulsatile flow to the foot may be accomplished with autogenous vein bypass grafts to the paramalleolar or infra-malleolar arteries (e.g., the dorsalis pedis). Limb salvage rates of 78% at 5 years and 58% at 10 years can be achieved with bypasses to the dorsalis pedis artery,²⁰ whereas bypasses to the tarsal or plantar arteries are associated with a limb salvage rate of 69% at 5 years.²¹ The great saphenous vein outperforms all other grafts with respect to patency and is the preferred conduit when performing distal bypass surgery. The vein graft can be prepared as an in situ graft, a reversed graft, or a nonreversed graft, without any significant difference in outcome; the choice of approach should be based on the patient's particular vascular anatomy. But the absence of an ipsilateral great saphenous vein is not a contraindication to pedal bypass: satisfactory results may be obtained by using arm vein or small saphenous vein grafts. Prosthetic material should never be used for dorsalis pedis or other extreme distal

(inframalleolar) bypass grafts. Active infection in the foot is not a contraindication to pedal bypass, provided that the proximal dorsum of the foot is free of infection and that incisions can be placed in clean tissue planes. The foot should be free of cellulitis, lymphangitis, and edema before any inframalleolar bypass.

Current advances in endovascular therapy are allowing this approach to be used more frequently and successfully in the peripheral vasculature. The goal of endovascular intervention should be the same as that of bypass grafting: to restore the foot pulse and maximal blood flow to the foot. In patients who are deemed to be high surgical risk candidates, lack suitable autogenous conduit, or have limited mobility or life expectancy, endovascular therapy provides a viable alternative to peripheral bypass. Lesions determined to be favorable on the basis of arteriography may be treated with angioplasty and/or stenting. The success for these procedures depends on the location and morphology of the lesion being treated.²² Generally, iliac artery lesions are best suited for endovascular therapy, with 5-year patency rates greater than 70% with angioplasty and stent. Long-term results of tibial endovascular interventions are not yet available, but a 1-year limb salvage rate of 92% in patients with critical limb ischemia was achieved in one study.²³ However, tibial angioplasty carries a risk of the potential loss of a bypass target via dissection or thrombosis. Judicial use of endovascular interventions in peripheral occlusive disease provides another option in lower extremity revascularization, and every effort must be made to preserve bypass options.

CONTINUED WOUND CARE

Once the foot is fully revascularized—or once it is clear that the foot was adequately perfused to begin with—care of the foot wound should be continued. Revascularization of a severely ischemic foot ulcer may result in an immediate paradoxical worsening of the infection, and frequent inspection is mandatory postoperatively. New-onset cellulitis, hyperglycemia, or fever should prompt concern regarding potential worsening of the foot infection. Frequent débridement to healthy, bleeding tissue is required more often than not.

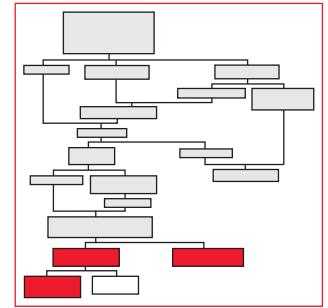
Wounds should be kept moist, with wet-to-dry dressings avoided in favor of normal saline wet-to-wet dressings. Various adjunctive wound treatments are available, including chemical enzymatic débriding agents, growth factors, and hyperbaric oxygen therapy. Some of these may offer a slight additional benefit in terms of improved healing, but they are expensive; blanket use of these costly modalities is therefore discouraged. Failure of wound healing in the diabetic foot is usually attributable to unrecognized ischemia, ongoing infection, or poor conventional wound care—not, as a rule, to the absence of more sophisticated wound therapy.

Hyperglycemia and malnutrition are common in hospitalized diabetic patients with foot ulceration, and both adversely affect wound healing. Correction of these abnormalities

should begin early and continue throughout the wound-healing period. Attention should also be directed toward preventing new foot lesions (e.g., decubitus ulcers on the heel from prolonged bed rest). Heel splints, air mattresses, and leg pillows are all valuable in this regard.

SECONDARY FOOT PROCEDURES

After successful revascularization, secondary procedures on the foot may be performed for maximal foot salvage, with the aim of addressing both the acute problem and the underlying cause. The basic goals of such procedures are (1) to remove infected bone (if present), (2) to restore functional stability, and (3) to reduce the risk of subsequent ulceration.

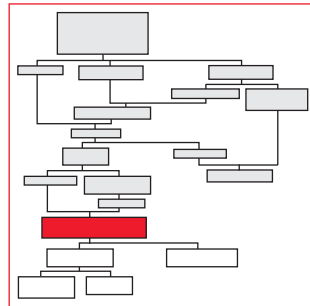


In the forefoot, digital, single metatarsal (ray), or transmetatarsal amputation [see 6:20 *Lower-Extremity Amputation for Ischemia*] may be performed, depending on the location of the ulcer. Tissue should be handled gently, forceps should not be used, and incisions should be carefully placed. Care must be taken to prevent dead spaces along tendon sheaths, bone splintering, and areas of residual necrosis, all of which can lead to failure of the procedure. If there is persistent infection or an abscess, the wound should be left open. Every effort, however, should be made to perform a closed amputation so as to avoid the time and cost associated with open wound care. This is a particularly important consideration in the occasional diabetic patient with unreconstructable foot ischemia because open amputations rarely heal in the presence of ischemia.

Underlying bony structural abnormalities in the diabetic foot are often the cause of ulceration. Such abnormalities may be corrected with hallux arthroplasty, metatarsal head resection, metatarsal osteotomy, or sesamoidectomy; if ulceration is present, these procedures may be combined with ulcer excision. Similarly, ulceration on a previous transmetatarsal amputation may be the result of an equinovarus deformity (from disrupted tendons and a decrease in calcaneal inclination). This problem should be treated with revision of the transmetatarsal amputation (perhaps in conjunction with ulcer excision) and biomechanical correction (e.g., Achilles tendon lengthening or, in more severe cases, posterior tibial tendon release).

Heel lesions are particularly formidable, and there is considerable confusion regarding how best to manage them. Generally, dry eschars with no evidence of deep infection or abscess may be treated with offloading alone so as to allow healing beneath the eschar in the fully revascularized foot. In patients with chronic ulceration or osteomyelitis, partial calcanectomy may be considered. The presence of calcaneal osteomyelitis may be determined by means of probing or adjunctive studies such as MRI [see Figure 10]. Primary closure is occasionally possible, but given the relatively fixed nature of the heel, either secondary healing or some type of flap coverage is usually indicated. Both local and free flaps may be used in the fully revascularized foot.

After any type of surgery of the diabetic foot, frequent postoperative observation of the wound is mandatory. Delays in



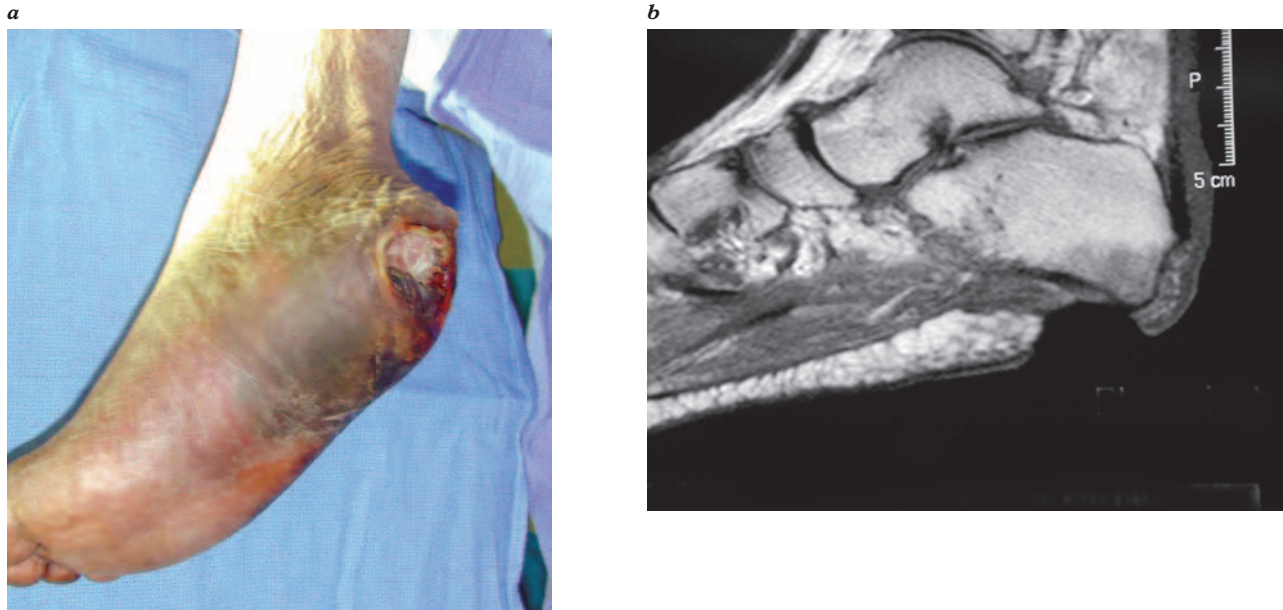
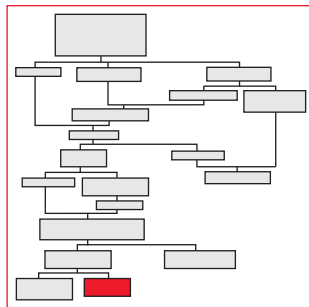


Figure 10 Shown is heel ulceration with eschar (a) in a diabetic patient. MRI findings (b) are consistent with calcaneal osteomyelitis.

healing or wound breakdown should immediately raise the possibility of infection or unrecognized ischemia and should trigger the appropriate workup.

PREVENTIVE FOOT CARE

Once the foot has healed, preventive measures should be initiated to prevent future ulceration. Foremost among these measures is patient education, focusing on general hygiene (e.g., daily washing and moisturizer use) and daily inspection of the feet. Walking barefoot, employing heat pads, wearing thong sandals, and using caustic over-the-counter foot medications should all be strongly discouraged.



Neuropathy continues to be the most common cause of diabetic foot ulceration, and its presence is a strong predictor of the likelihood of future ulceration. As noted (see above), inability to feel a Semmes-Weinstein 5.07 monofilament when it is pressed to the skin correlates well with an increased risk of foot ulceration. In addition, abnormal pressure points (secondary to mechanical deformity of the foot and motor neuropathy) can be identified by means of pedobarography, a procedure in which plantar pressure is measured on specialized contour plots as the patient walks on a pressure-sensitive platform. Identification of any high-pressure areas can facilitate the construction of specific, custom-molded orthotics and insoles to help in offloading.

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Figure 8 Tom Moore.

8 FUNDAMENTALS OF ENDOVASCULAR SURGERY

Jon S. Matsumura, MD, FACS, and Brian G. Peterson, MD, FACS

Endovascular techniques are an important part of vascular surgery. Ongoing technological advances have made it possible to treat the majority of vascular diseases by less invasive means. To perform these new therapeutic techniques, it is necessary to possess certain basic endovascular skills. In this chapter, we describe some of the fundamental techniques that a skilled vascular interventionalist must master and discuss more advanced options to address difficult access when large sheaths are used in aortic interventions.

Choice of Vascular Access Site

The initial step in endovascular surgery is selection of the vascular access site. Several choices are available. The ideal access vessel is large, close to the treatment site, relatively free of disease, and only minimally tortuous. Such a vessel is less likely to be associated with complications.¹ For most endovascular interventions, the femoral artery is the preferred choice, although the axillary, brachial, subclavian, common carotid, and iliac arteries may also be used. Although most vascular surgeons are capable of performing the retroperitoneal approach for iliac artery access, this approach can add significant morbidity to the procedure. Occasionally, the aorta is accessed via direct puncture, laparotomy, or thoracotomy.

Before puncture, the vessel undergoes evaluation, including palpation to assess the strength of the pulse in comparison with the opposite side. A weak pulse suggests disease at or proximal to the area, and the vessel should therefore be used with caution. Preoperative assessment may include non-invasive imaging (e.g., duplex ultrasonography, computed tomography, or magnetic resonance angiography) to visualize significant lesions. Finally, with any endovascular procedure, it is helpful to assess and document the peripheral pulses and the ankle-brachial index (ABI) beforehand to provide reference points against which to measure the adequacy of the intervention and to assess for procedure-related complications.

Puncture of Artery

GENERAL TECHNICAL PRINCIPLES

Once the skin site has been prepared and draped, 1% lidocaine is infiltrated into the skin and the perivascular tissue. Besides providing anesthesia to the area, lidocaine helps prevent vasospasm.² The pain and discomfort from intradermal injection of lidocaine are caused by the low pH of commercially available preparations and can be reduced by adding sodium bicarbonate (1 mL of a 1 mEq/mL NaHCO₃ solution

in 10 mL of 1% lidocaine).³ A small nick should be made in the skin about 1 to 2 cm (largely determined by the patient's body habitus and vessel depth, i.e., 2 cm in deeper vessels) beyond the intended site of arterial entry, and the subcutaneous tissue should be gently dissected with a clamp; this measure allows smoother entry of the needle, the guide wire, the sheath, and the catheter. Access needles are available in different sizes, of which the two most common are the 18-gauge thin-walled needle, which accepts a 0.035-inch guide wire, and the 21-gauge needle, which accepts an 0.018-inch guide wire. The latter is used for micropuncture techniques and is favored for axillary and brachial approaches, for antegrade common femoral artery (CFA) punctures, and in conjunction with ultrasound when faced with heavily diseased vessels requiring an extremely precise puncture. Micropuncture needles with a radiopaque tip are available and can be used with ultrasound, further enhancing the precision of the arterial puncture. Longer needles are used for translumbar puncture.

There are two main methods of cannulating the artery with the needle [see Figure 1]: double-wall entry and single-wall entry. Certain principles apply to both methods. The needle is advanced at an angle of 45° to 60°. When it is within the subcutaneous tissue, it should proceed in a straight line: the needle tip is sharp, and side-to-side movement may cause inadvertent laceration of a neurovascular structure. When a needle must be repositioned, it should be withdrawn into the subcutaneous tissue superficial to the intended target, back to the level of the dermis, and redirected along another course. If the needle becomes dulled as a result of contact with bone or other hard surfaces, it should be discarded and a new one used.

The double-wall entry method involves a through-and-through puncture of both the anterior wall and the posterior wall of the vessel. A multipart needle with an inner trocar may be helpful. After the needle is advanced through both walls of the artery, the inner trocar is removed. The needle is then slowly withdrawn until arterial pulsation is noted. The needle is stabilized, and a guide wire is advanced through it into the artery. Once the guide wire is in place, the needle is removed.

In the single-wall entry method, the needle is slowly moved toward the anterior wall of the vessel. The arterial pulsation can be felt through the shaft of the needle. Gentle pressure is applied, and the needle is advanced through the anterior wall only. It may be helpful to think of the arterial pulse wave as pushing the anterior arterial wall onto the needle. The appearance of pulsatile flow confirms entry into the arterial lumen. The needle may be rotated or deflected slightly to optimize

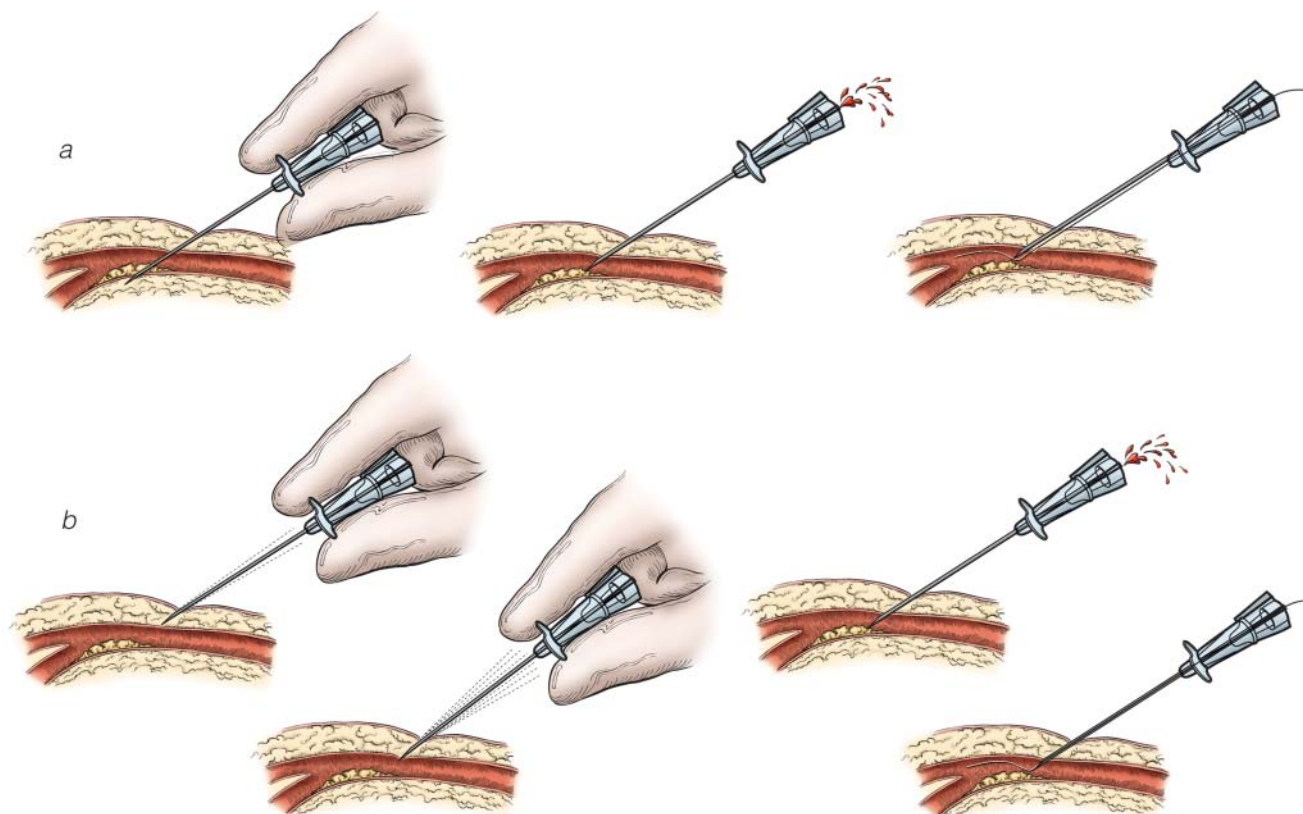


Figure 1 Shown are the two methods of entry into an artery: (a) through-and-through puncture of both walls and (b) puncture of the anterior wall only.

pulsatile back-bleeding. A guide wire is then passed into the needle, and the needle is removed. Immediately after needle removal and prior to catheter or sheath placement, manual compression is held over the puncture site until a catheter or sheath is placed into the access site obtaining hemostasis. This is to prevent periarterial hematomas, which may interfere with vessel closure on completion of the procedure.

Pulsations should be transmitted through the needle shaft in an anterior-to-posterior manner. If the needle is either medial or lateral to the artery, the pulsations may deflect the needle from side to side.² Once the needle is in the vessel, the flow pattern should be observed. A barely pulsatile flow may signal occlusive disease, a subintimal location of the needle, or a venous puncture.² If the guide wire cannot be passed with minimal resistance after access is obtained, the needle tip may be against the wall or against plaque, or (if the needle tip has already entered the wall) a dissection may have been started. Often the situation can be remedied by making a small change in the needle's insertion angle or by withdrawing the needle slightly.

FEMORAL ARTERY PUNCTURE

As noted, the CFA is the vessel most commonly used for arterial access. It is generally well suited to this purpose, being readily accessible, fairly large, and easily compressible. CFA puncture facilitates study and treatment of a number of key structures, including the lower extremity arteries, the

abdominal aorta and its branches, the thoracic aorta, the brachiocephalic vessels, the coronary arteries, and the left ventricle. In addition, CFA puncture is associated with a lower complication rate than puncture of other arteries.¹ The CFA should, however, be avoided when the patient is known to have severe iliofemoral occlusive disease, a local infection, a thrombus-lined femoral artery aneurysm, or marked tortuosity of the iliac arteries that would preclude catheter placement or manipulation.

The CFA runs lateral to the common femoral vein (CFV) and beneath the inguinal ligament. It may be localized by palpation just proximal to its bifurcation into the superficial femoral artery (SFA) and the profunda femoris (PF). The inguinal ligament, which runs from the anterior superior iliac spine to the pubic tubercle, is a convenient landmark for localization of the CFA, but these bony landmarks provide only a rough approximation of the location of the inguinal ligament. The CFA typically lies about two fingerbreadths lateral to the pubic tubercle along the line of the inguinal ligament. The artery should be punctured over the middle of the medial third of the femoral head in the posterior-anterior projection [see Figure 2]. The window available for safe CFA puncture is small—only 3 to 5 cm.

Several methods can be used to localize the CFA in patients with difficult anatomy (e.g., those who have previously undergone groin surgery, those who are obese, and those who have a pulseless artery). The bony landmarks are even less

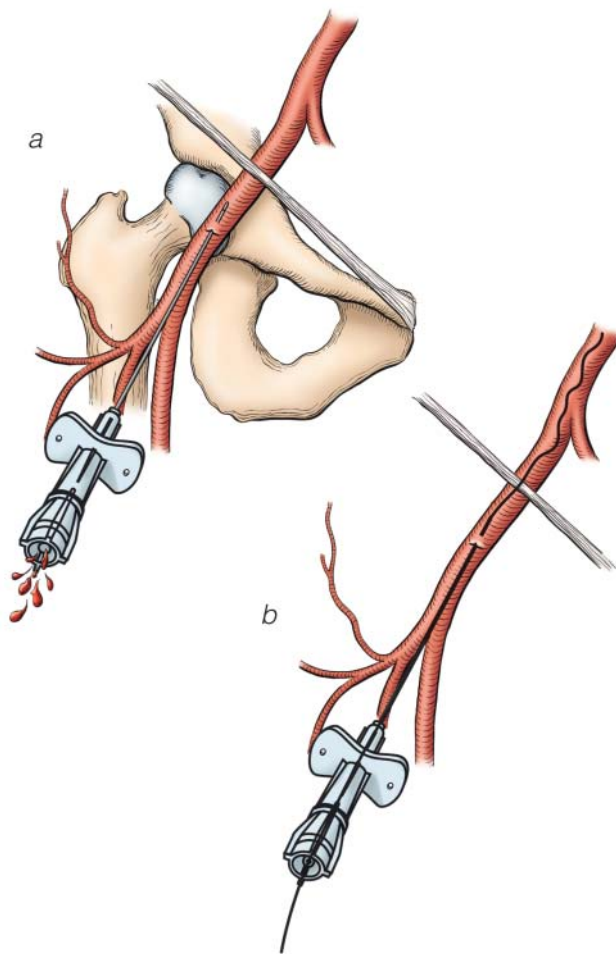


Figure 2 Shown is a puncture of the common femoral artery. (a) The needle enters the common femoral artery. (b) The guide wire is passed through the needle.

reliable guides to the location of the inguinal ligament in these patients. According to a 1993 anatomic study, in the majority of cases, the position of the inguinal ligament is about 1 to 2 cm below where palpation would suggest it to be, and the average position of the ligament is approximately 1.5 cm superior to the midfemoral head.⁴

Fluoroscopy may help localize the CFA over the medial third of the femoral head. The chances of hitting the artery are maximized by aiming for the middle (craniocaudal) portion of the medial third of the femoral head. To minimize parallax errors, the femoral head should be centered in the image intensifier. The anatomic relations of the arteries in this area vary little with body habitus, gender, or age. A 1999 anatomic study showed that the CFA bifurcates into the SFA and the PF approximately 2 cm below the femoral head.⁵ Occasionally, calcifications in the arteries may serve as landmarks for locating the CFA.

Another localization approach involves palpation of anatomic landmarks; this approach may be especially useful when the artery is pulseless.⁶ With a finger placed immediately lateral to the pubic tubercle and inferior to the inguinal

ligament, palpation is carried out to locate the point allowing the greatest degree of posterior depression. Anatomically, this point of maximal depression lies between the iliopsoas muscle laterally and the pectineus muscle medially. The CFV lies in the floor of this depression, and the CFA lies 1.5 cm lateral to the depression.⁶

Ultrasonography has proved useful for finding the CFA. The projection of choice with real-time ultrasonography is the transverse plane. The nonpalpable CFA is identified lateral to the compressible CFV. Occasionally, the artery can be identified on the basis of sonographic shadowing from calcified atheromatous plaques.⁷ A second ultrasonographic technique involves the use of a so-called smart needle, which has an ultrasound probe at its tip. The needle emits a signal as it approaches the artery, thereby giving notice of proximity to the vessel. Alternatively, as mentioned above, use of a micropuncture needle with an echogenic tip in conjunction with handheld, B-mode ultrasonography provides added precision.

Another method of localizing and puncturing a pulseless CFA involves performing a contralateral femoral artery puncture, obtaining a diagnostic angiogram, and roadmapping. A similar method that is useful in patients who may be moving or who cannot receive additional contrast material is to pass a guide wire over the aortic bifurcation and then antegrade through the iliac artery into the target femoral artery.⁸ Under fluoroscopy, the guide wire becomes a visible target for introduction of the needle into the CFA.

Troubleshooting

The CFA is typically described as lateral to the CFV; however, one study showed that attempts to puncture the CFA frequently result in puncture of the CFV, signaled by the appearance of dark, nonpulsatile venous blood. If this occurs, one should note the position of the original puncture, move the needle 1 to 1.5 cm laterally, and reinsert the needle. It should be noted that when using a micropuncture needle as opposed to a standard entry needle (21-gauge versus 18-gauge, respectively), often, even with arterial puncture, pulsatile back-bleeding is not encountered because of the micropuncture needle's smaller-caliber lumen. At times, especially in emergency procedures, arterial blood may be dark and may resemble venous blood. If it is unclear whether the blood is coming from an artery or a vein, a small amount of a contrast agent should be gently injected into the needle by hand; the source of the blood should then be easily identifiable. When contrast is injected in the femoral sheath outside the artery, the resulting tubular "filling defect" can be used to identify the femoral artery.

If the puncture is done too high (in the external iliac artery), the inguinal ligament and the deeper location of the external iliac artery may make adequate compression of the vessel impossible. Many closure systems will not work in the external iliac artery. High puncture is associated with retroperitoneal bleeding, which should be suspected in any patient with an unexplained drop in the hematocrit, hypotension, or flank pain. Retroperitoneal bleeding is often exacerbated by the use of intra- or periprocedural anticoagulation and antiplatelet agents leading to uncontrollable hemorrhage with devastating outcomes if not recognized early. To minimize this problem, the artery should be entered caudal to the inguinal ligament

at a site where it can be compressed against the femoral head.⁹

If the puncture is done too low (in the SFA or the PF), there is a greater incidence of hematoma, pseudoaneurysm, arteriovenous fistula, and catheter-related thrombosis.^{4,10} The reason for this increased incidence may be that it is harder to compress the SFA and the PF adequately than it is to compress the CFA, which lies over bone for most of its length. The CFA is larger in diameter than either the SFA or the PF and thus is better suited for the passage of large catheters and sheaths.

Experience is critical for achieving easy and complication-free femoral artery access. Although standard learning points are helpful in the accumulation of this experience, veteran interventionalists typically develop their own individual procedural algorithms, based on what is most familiar and works best for them. Routine use of femoral arteriography and ultrasonography can shorten the learning period by visually demonstrating the nuances of the anatomy in tandem with the tactile learning. Thoughtful study of failed access and access-related complications, including observing the vascular anatomy when surgical repair becomes necessary, can also help develop experience more rapidly. In such cases, exploration often reveals altered femoral anatomy, side-wall punctures, low and high punctures, and posterior wall dissection. For even the most masterful interventionalist, femoral puncture complications are an ever-present risk, despite his or her best efforts.

BRACHIAL ARTERY PUNCTURE

The brachial artery is typically the second choice for arterial access after the femoral artery. This vessel is located in the lower third of the upper arm, anteromedial to the humerus. The median nerve lies just medial to the brachial artery at this level, and the radial nerve lies posterior to the artery. Even though the brachial artery is best palpated in the lower middle third of the arm, some clinicians prefer to puncture it in the high brachial position because complications may be less frequent with this approach.

The patient's arm is extended and supinated. The upper portion of the brachial artery is entered several fingerbreadths distal to the axillary crease, over the proximal humeral shaft. The middle portion of the brachial artery is entered just above the antecubital fossa. Because this vessel is very mobile, it may be advisable to fix it between the surgeon's middle and index fingers before puncture.

Troubleshooting

The brachial artery is typically smaller than the CFA and more prone to thrombosis. Accordingly, the needles, guide wires, catheters, and sheaths used for brachial artery puncture must be smaller as well. Occasionally, the median nerve or the radial nerve may be damaged by the puncture. Any distal neurologic symptoms (e.g., median nerve distribution paresthesias or pain or weakness of the opponens muscle) that arise are evaluated on an urgent basis; on occasion, emergency exploration proves necessary. Frequently, there is no palpable hematoma, and the symptoms are attributable to a very small hematoma adjacent to the nerve. Not uncommonly, the brachial artery goes into spasm after puncture.

Intra-arterial injection of papaverine, nitroglycerin, or other vasodilators may reduce the risk of spasm.

AXILLARY ARTERY PUNCTURE

The axillary artery is divided into three parts on the basis of its relation to the overlying pectoralis minor. The third portion of the artery lies lateral to the pectoralis minor, and its most distal portion extends beyond the pectoralis major, at which location it is very superficial.² The axillary artery is typically used for vascular access when neither the femoral nor the brachial artery is available. The use of this approach may be restricted in patients who have subclavian artery occlusive disease or aneurysmal disease. A physical examination should be performed before the procedure to look for a blood pressure differential between the two arms, as well as to auscultate for the presence of a supraclavicular bruit. A blood pressure differential greater than 20 mm Hg suggests the presence of hemodynamically significant arterial stenosis in the arm with the lower pressure.

Axillary artery puncture is useful in patients with a steeply downward-coursing (caudal) mesenteric or renal artery, patients with infrarenal aortic or bilateral iliac occlusion, and patients with a history of embolization from infrarenal aortic catheterization.³ However, access at this site poses an added risk, in that the artery is located near the brachial plexus, which may be damaged by direct trauma or compression from a hematoma. In addition, access via the axillary artery is relatively uncomfortable for both patient and physician. Generally, for access to the descending thoracic aorta, the abdominal aorta, and the lower extremity vessels, the left axillary artery may be preferred, whereas for access to the ascending aorta and the coronary vessels, the right axillary artery may be preferred.

The arm can be placed in either of two positions: (1) abducted 90° or (2) maximally abducted with the patient's hand placed under the head. The second position stretches the artery and fixes it in place. The artery is palpated along the lateral axillary fold over the proximal humerus at the neck so that the underlying bone provides support during compression.¹¹ The vessel is then entered over the proximal humeral shaft just distal to the axillary fold. Like the brachial artery, the axillary artery is relatively mobile. It may be compressed along its length between the index and middle fingers to fix it in place for subsequent puncture.

Troubleshooting

Thrombosis and pseudoaneurysm formation are more common with the axillary artery approach.³ In addition, the median and ulnar nerves run along with the axillary and proximal brachial arteries in a fascial sheath, so that a small hematoma can cause nerve compression. If a sensory or motor deficit develops, surgical decompression may be required. Cerebral embolization may occur with axillary artery puncture.³ When performing distal interventions via a left brachial or axillary artery approach, it is important to maintain a long guide catheter or sheath across the origin of the left subclavian artery into the aorta. This access reduces the risk of wire shear and potential vessel damage created at the angle of the left subclavian artery and the descending thoracic aorta during exchanges over the wire.

TRANSLUMBAR PUNCTURE

Translumbar puncture of the aorta is indicated when femoral, axillary, and brachial methods are all relatively unsuitable. It is frequently used in patients who have endoleaks and aneurysm sac expansion following endovascular aortic aneurysm repair.

An upper translumbar approach is indicated if visualization of the visceral and renal arteries is required. The patient is placed in a prone position. The 12th thoracic vertebra is located either by palpating the 12th rib or, more accurately, by means of fluoroscopy. The skin is entered 1 to 2 cm below the level of the 12th rib and 8 to 10 cm to the left, lateral to the posterior spinous process of the 12th vertebra. The needle is aimed ventrally and cephalad toward the level of the middle to lower portion of the body of T12 until the needle strikes the vertebra. Care must be taken to keep the needle below the diaphragm so that it does not hit the lung and the pleura. Particular care must also be taken to avoid the renal arteries inferiorly. After striking T12, the needle is withdrawn several centimeters and aimed laterally and ventrally until the pulsations of the aorta are felt. When the needle hits the aorta, slight resistance will be felt, followed by release of tension and a very slight give or “pop” when the needle enters the aorta. Only the proximal wall should be punctured. The needle is then advanced about 3 to 5 mm to the middle of the lumen [see Figure 3].

A lower translumbar approach may be used to access an aortic aneurysm sac after endovascular repair. The puncture

site is located via fluoroscopy of radiopaque markers on the device already in place. With the patient in the prone position, the needle is introduced 8 to 10 cm lateral to the spinous process of L2 and directed anterior to the lumbar spine. Often careful review of the CT images suggests a specific target and tract. As with an upper translumbar puncture, a “pop” can be felt when the needle enters the aneurysm sac; alternatively, the needle can be visualized entering a calcified wall.

Troubleshooting

The high translumbar technique is limited by its inability to deliver the contrast material at the bifurcation of the aorta or to perform selective catheterization of vessels. Too high a puncture (e.g., at T11) can lead to inadvertent puncture of the lung and cause a hemothorax or a pneumothorax. If the needle moves with the respiratory diaphragmatic movements of the patient, it may be in the thoracic cavity. If the initial needle stick is too medial, only the lateral wall of the aorta is reached. If the needle stick is too lateral, the needle passes between the vertebral body and the aorta. If the needle is advanced at too shallow an angle, it may enter the spinal canal.² If resistance is felt when the guide wire is placed, the wire may have entered the renal, celiac, or superior mesenteric artery. Small retroperitoneal hematomas develop in most patients who undergo translumbar puncture, but the incidence of major complications is only 3%.

Placement of Guide Wires

Once vascular access has been obtained through arterial puncture, it is maintained through placement of a guide wire. Most guide wires consist of a soft tip and a stiffer main body. The flexibility of the soft tip allows the surgeon to manipulate the guide wire past stenoses while minimizing the risk of perforation or dissection. For best results, the guide wire must be suitable for the intended procedure in terms of (1) tip configuration, (2) diameter, and (3) length. Sometimes multiple wires are used at different stages of the procedure.

Guide wires come in several different tip configurations, including straight, angled, and J-shaped. Straight-tipped wires are used in vessels that are relatively straight and free of disease. For crossing a severe stenosis or selective catheterization of a branch, an angled or shapeable tip may be preferred. J-tipped guide wires are sometimes preferred for atherosclerotic vessels because the shape of the tip reduces the likelihood that the wire will pass subintimally and cause unintentional dissection. Many specialty wires are available for specific uses (e.g., crossing chronic total occlusions).

Guide wires also come in a variety of diameters, typically ranging from 0.014 to 0.052 inches. The diameters most commonly used for endovascular procedures are 0.035, 0.018, and 0.014 inches. Larger guide wires are typically stiffer, which makes it easier to deliver sheaths and catheters over them. Smaller wires are typically used for endovascular work involving the carotid, renal, or infragenicular vessels. In choosing the diameter of the initial wire, the interventionalist must keep in mind the gauge of the needle that was used to access the vessel. As the procedure progresses, alternative guide wires are often indicated, and new guidewires may be exchanged with a catheter. After selective catheterization has

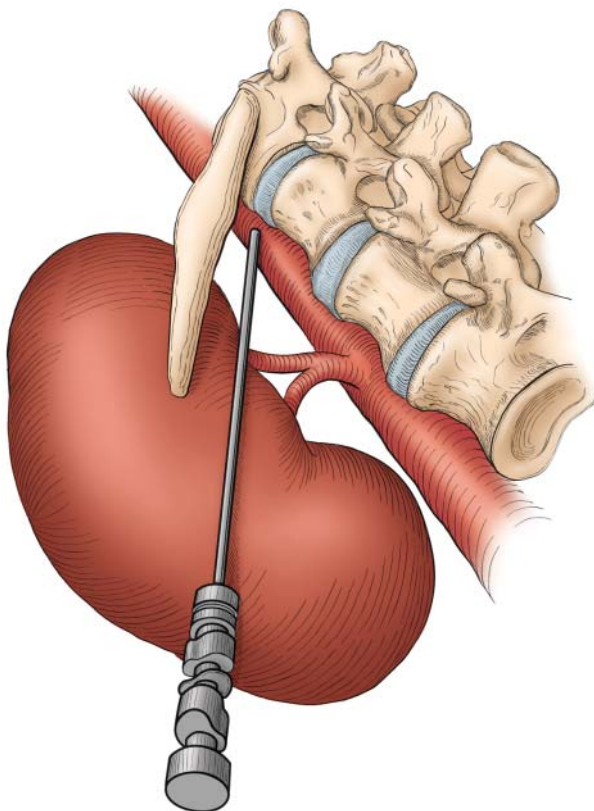


Figure 3 Shown is a translumbar puncture of the aorta. The vessel is approached at the level of T12.

been obtained, specifically designed stiff guide wires are often needed for delivery of bulky interventional devices.

The length of the guide wire is an important concern because choosing an appropriate length facilitates exchange of catheters or interventional devices without loss of access across a remote lesion. A general rule for determining optimal guide wire length is as follows¹²:

Optimal guide wire length = length from outer edge of sheath or insertion site to lesion + length of longest catheter or interventional device + at least 10 cm

In an average adult, the wire used for selective angiography is typically about 145 to 180 cm long. Longer wires (260 to 300 cm) are used for exchanging long over-the-wire vascular devices, especially during infrainguinal interventions performed up-and-over the aortic bifurcation from contralateral femoral artery access. Occasionally, a 450 cm long wire is needed for combined brachial-femoral access—the so-called “body floss.”

Once arterial access is obtained, several safety measures should be undertaken. The needle should have its bevel facing upward to optimize conditions for wire advancement; a downward-facing bevel may cause the sharp edge of the needle to damage or even sever the wire. The floppy end of the wire should be used for initial introduction into the needle and the vessel; the stiff end may damage the vessel. Caution should be exercised in introducing the guide wire if there is unexpected poor flow from the needle as this may lead to advancing the guide wire in a subintimal plane.

After entry into the lumen, the guide wire is advanced about 15 to 20 cm. The needle is then removed, and a catheter or an introducer sheath is placed over the wire. Further advancement of the wire is done under fluoroscopic guidance. Once placed, the guide wire should be carefully monitored and kept in place (pinned) whenever any other devices are manipulated. As a general rule, the guide wire is not removed until the very end of the procedure. After removal, guide wires are rinsed and loosely coiled in one-foot loops for storage (in case they are needed later).

TROUBLESHOOTING

The guide wire should never be forcefully introduced into the vessel. If significant resistance is encountered, the end of the needle may be against the vessel wall or partially within the wall. In this situation, the needle should be repositioned slightly and another attempt made to pass the wire. Occasionally, the guide wire may pass easily for several centimeters before encountering resistance to further advancement. Such resistance may be secondary to stenosis or tortuosity of the vessel. Placement of a different wire with a different tip configuration or insertion of a guide catheter may be necessary to advance the wire further.

Wiping the guide wire with heparinized saline minimizes thrombus formation on the wire. If thrombus is allowed to build up, friction will increase during catheter exchange, making the exchange more difficult. Some hydrophilic-coated guide wires require constant wetting to maintain their characteristics. Other guide wire coatings swell after prolonged wetting and thus may inhibit catheter exchanges. Hydrophilic wires should not be used for initial cannulation through the access needle because they may be sheared off by the needle

tip when withdrawn. Damaged or kinked guide wires should be exchanged for new, undamaged wires when this can be done safely.

Placement of Sheaths

Once guide wire access is achieved, a sheath or guide is typically placed over the guide wire to maintain a stable pathway for catheter exchange or for placement of a device. Before the sheath is placed, dilators are first passed over the guide wire to create a smooth tract through the soft tissue into the vessel. Whereas sheaths are measured according to their inner circumference (1 mm circumference = 1 French), guides are measured according to their outer circumference; thus, a 6 French guide fits inside a 6 French sheath. Dilators are also measured according to their outer circumference. Therefore, when a 5 French sheath is to be placed in scarred fibrous tissue, a 6 French dilator must be placed to create a similarly sized tract. Most commonly, there is a smooth transition between the dilator and the tip of the sheath so that the dilator and sheath of the same size are pinned and placed together.

Most introducer sheaths have hemostatic valves and side ports. Guide catheters can be effectively converted to sheaths by adding a Touhy-Borst valve apparatus. These valves seal around a smaller catheter and reduce back-bleeding. The side port can be used for continuous infusion of heparinized saline to reduce the risk of thrombus formation. The sheath can also be used to straighten tortuous arteries (e.g., the iliac arteries). For example, when a guide wire has been passed through the iliac artery and into the abdominal aorta, the sheath can be advanced over a wire into the abdominal aorta after passing a catheter over the access guide wire and exchanging the guide wire for a stiffer wire. Stiffer wires help straighten out tortuous iliac arteries, and passage of a sheath through the tortuous iliac vessel facilitates subsequent passage of catheters and devices.

Once properly placed, sheaths should be secured in position (i.e., pinned or sutured) so that they are not inadvertently advanced without the introducer or accidentally withdrawn.

Insertion of Catheters

There are many differentiating characteristics by which various types of catheters can be distinguished from one another, including size, shape, stiffness, coating, radiopacity, and side-hole configuration. As a rule, catheters are sized according to their outer diameter (French) and their length (cm). “French” can be converted into “millimeters” by dividing the French size by 3.14. Numerous tip shapes are available [see Figure 4] (e.g., straight, cobra, headhunter, angled, shepherd’s crook, reverse curve, pigtail, and racquet). The initial catheter shape is selected on the basis of the specific requirements of the procedure and the individual patient anatomy. Generally, within the abdominal aorta, the angle of the primary curve of the catheter tip should be similar to that of the vessel takeoff. Several complex shapes of catheters are specifically designed for arch vessel catheterization. In some cases, multiple catheters may be needed, used either in sequence or coaxially to perform superselective

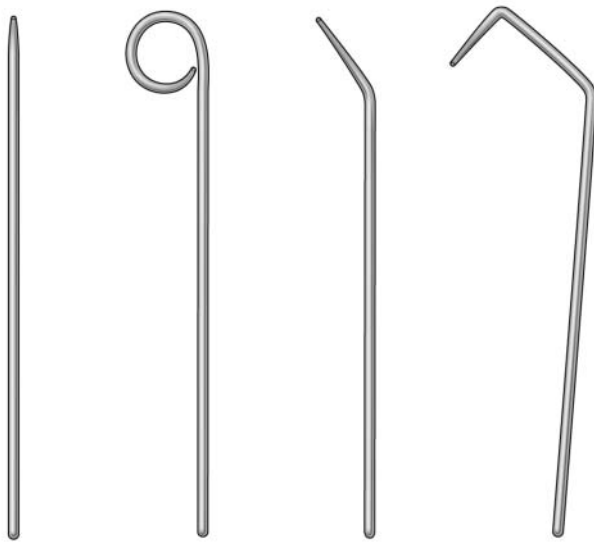


Figure 4 Catheters come with various tip configurations. Shown are straight, pigtail, angled, and double-angled tips (left to right).

catheterizations. A variety of complex catheter shapes may be used to select vessels that have steep angles of origin. The use of coatings (e.g., hydrophilic surfaces and Teflon) can facilitate advancement of the catheter in tortuous vessels. Specialty catheters may come with radiopaque tips or with multiple radiopaque markers placed at 1 cm intervals for reference during vessel sizing. Multi-side-hole catheters have a spiraling set of holes that allow more even distribution of a large volume of contrast or other infusate; they are typically used to opacify large vessels with high flows. Generally, opacification of smaller vessels requires a smaller dose of contrast material administered at a slower rate; for this purpose, an end-hole catheter suffices.

Before contrast is injected, the catheter should be aspirated to remove any air bubbles and to verify intraluminal location by means of free-flowing back-bleeding. A small test injection is useful for checking the catheter's position. Depending on the clinical circumstances, the patient may undergo anticoagulation to reduce the risk of thrombus formation on the outside of the catheter. Periodically, the catheter may be flushed with heparinized saline to prevent thrombus formation within it. When a stiffer catheter is advanced forward, it is usually advanced over a guide wire; however, a softer catheter can be used in the same way as a guide wire. Some complex curved catheters may have to be removed over a wire to reduce the risk that the catheter will scrape the vessel wall.

TROUBLESHOOTING

There are several areas in the handling of catheters where attention to detail and good technique can help optimize results. Two common errors of selective catheterization are (1) looking for a specific artery in the wrong location (e.g., as a consequence of misidentification of bone landmarks) and (2) failing to recognize when the appropriate vessel has been entered (particularly in patients with anomalous vessels or

postoperative changes).¹³ These errors can be prevented by first performing roadmapping with nonselective catheterization and angiography; in the past, repeated roadmapping in multiple projections could be required. Modern flat detector systems allow three-dimensional rotational angiography and roadmapping, which minimizes the need for repeated contrast injections. Another potential problem is accidental loss of guide wire access, which may be more common with inexperienced operators who are not pinning the guide wire in place while a catheter is being pulled out—the so-called “pin-pull” technique. There are many advanced techniques for handling catheters and guide wires, but these are outside the scope of this discussion.

Use of Balloon Catheters

The purpose of a balloon catheter is to exert a radial force on the luminal surface of a blood vessel to dilate a stenotic lesion. As the balloon inflates, the media and adventitia of the artery stretch, causing a longitudinal fracture of the plaque. Minor arterial dissection is expected with this technique. Thus, the compression of the plaque is not the principal means of increasing the cross-sectional area of the vessel.

Several features are considered in selecting a balloon catheter for a specific intervention, including wire and sheath compatibility, balloon diameter and length, catheter size and length, trackability, balloon type (e.g., compliant, noncompliant, cutting, scoring, cryoplasty, drug eluting, or trilobed), and catheter profile [see Figure 5]. Typically, balloons range from 1.5 to 40 mm in diameter and from 1.5 to 20 cm in length. In many applications, the vessel should be slightly overdilated when the balloon is inflated. Thus, measuring the diameter of the normal vessel distal to the lesion will help determine an appropriate balloon diameter. If the operator is unsure of the proper balloon diameter, it is best to choose a smaller-diameter balloon and then move to a larger balloon if necessary. The shortest balloon length that spans the entire lesion with a slight extension into the normal artery should be chosen so that the shoulder of the balloon dilates as little as possible of the normal portion of the vessel. This reduces the risk of creating a dissection in a relatively normal portion of the vessel and increasing the length of the lesion being treated. If the balloon is too short and is not centered, it may be squeezed away from the stenosis during inflation—the so-called “watermelon seed” effect. Balloon catheters typically range from 70 to 150 cm in length. The shortest catheter length that reaches the lesion from the access site is preferred because a shorter catheter is easier to manipulate. The diameter (or profile) of the catheter depends on the type and size of the balloon and typically ranges from 3 to 14 French. Sometimes a smaller-profile balloon may be used if a smaller-diameter guide wire provides enough support for treatment of the lesion. If the balloon catheter is smaller than the sheath, contrast injection is possible when the balloon is in position; this allows the balloon's position to be fine-tuned immediately before inflation.

The balloon catheter is advanced over the guide wire through the sheath to the lesion, and the balloon is centered over the lesion. The balloon is inflated with a dilute contrast solution so that its expansion can be monitored fluoroscopically. Guidelines for inflation and deflation techniques vary

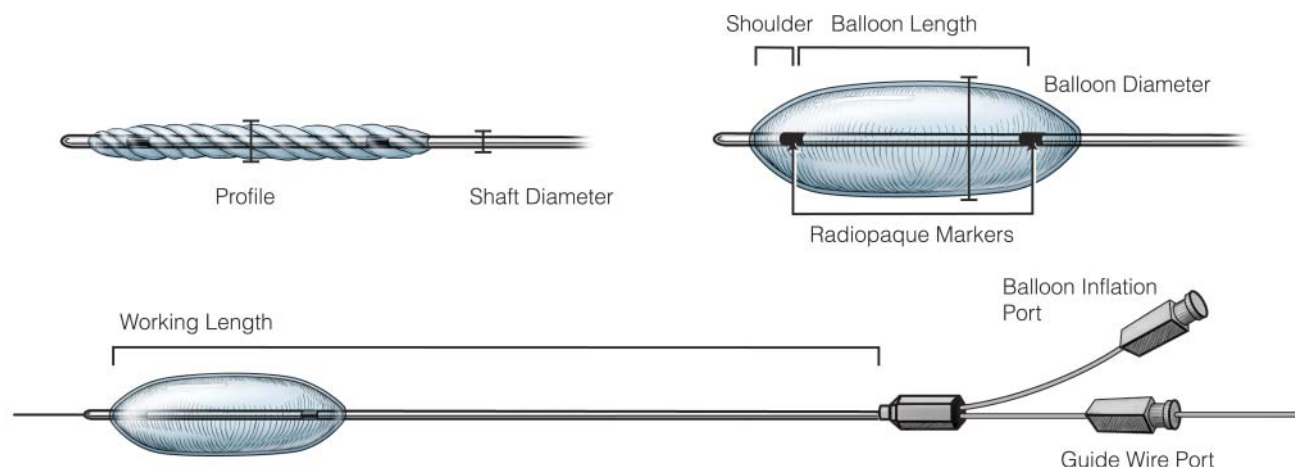


Figure 5 Shown is a balloon angioplasty catheter.

with respect to speed and duration of inflation, number of dilatations, and balloon pressure. Typically, the balloon is inflated to a pressure that results in a smooth parallel profile of the balloon walls, held for 20 to 60 seconds (sometimes even prolonged inflation of up to 2 to 3 minutes during tibial artery angioplasty), and then deflated. Short inflations are used for carotid artery stenting to reduce activation of baroreceptors. In most clinical circumstances, the inflation pressure should not exceed rated burst pressures. After dilatation, the balloon catheter is removed, with the guide wire left in place across the lesion (in case stenting proves necessary). Completion angiography is performed for evaluation of the results, including assessment of distal vascular beds.

Dilatation may be considered successful if (1) flow-limiting dissection is absent, (2) residual luminal diameter stenosis is less than 30%, and (3) the systolic pressure gradient is less than 5 to 10 mm Hg. Vasodilators can unmask a significant gradient.

TROUBLESHOOTING

Complications associated with the use of balloon catheters include thrombosis, vessel rupture, embolization, and dissection. The incidence of these complications is influenced by patient selection and by the nature of the lesion being treated. For example, complications may be more likely with treatment of stenoses adjacent to aneurysms, long segments of occlusion, tandem lesions, lesions near major branches, and calcified, eccentric plaques. Even though some degree of dissection is expected after balloon angioplasty, larger flow-limiting dissections may call for further management. This problem can often be solved by placing a stent over the dissection.

Most patients feel discomfort and mild pain during balloon inflation. If a patient experiences severe pain that persists after deflation of the balloon, the possibility of vessel rupture must be considered. If the vessel ruptures, the balloon may be reinflated over the injury to tamponade it. Prolonged balloon inflation often closes the leak, but at the risk of causing thrombosis. If the vessel continues to leak, a covered stent may be placed over the injury, or open vascular repair may be necessary.

If inflation of the balloon fails to dilate the vessel completely, it may be helpful to use a larger-diameter balloon, a less compliant balloon, or a higher inflation pressure. Higher inflation pressures may be cautiously attempted, but the vessel may simply recoil after dilatation.¹⁴ A stent is often useful in this scenario.

If the balloon crosses the lesions only partially, it should not be inflated. The position of the guide wire should be checked: the wire may be in a subintimal location. If the stenosis is very tight, the lesion may be predilated with a smaller-profile balloon catheter.

Placement of Vascular Stents

Intravascular stents are commonly used in endovascular surgery, particularly after failed percutaneous transluminal angioplasty. Placement of an iliac artery stent is indicated when there is significant residual stenosis, flow-limiting dissection, or a persistent pressure gradient. Although angioplasty is often successful, it may fail when there is elastic recoil of the arterial wall or when the lesion is resistant to dilatation because of heavy calcification. Stenting can often remedy these situations by providing physical support to keep the vessel open. Many physicians now regard primary stenting (i.e., routine use of stents) as a preferred approach for many vascular lesions. As mentioned above, the lesion may need to be predilated with a small-profile, small-diameter balloon first to facilitate delivery of the stent across the lesion.

CHOICE OF STENT TYPE

Stents are divided into two categories: balloon-expandable stents and self-expanding stents. They may also be described as being covered (with a graft material), coated (with a therapeutic compound), or absorbable. Stent types differ with respect to hoop strength (for resisting arterial recoil), cell size (open or closed cell), cell structure, shape (e.g., tapered or nontapered), radiopacity, longitudinal flexibility (for crossing tortuous vessels), radial elasticity (for resisting repeated external compression), and profile. Stents come in many different lengths and expanded diameters on a wide variety of deployment catheters.

Balloon-Expandable Stents

Balloon-expandable stents come either premounted on balloon catheters or unmounted; unmounted stents must be manually crimped onto a balloon to be delivered. With unmounted stents, a smaller inventory can be maintained, and a wider range of stent-balloon combinations is available. Premounted stents, however, tend to be more solidly mounted and less likely to be dislodged during delivery. Once the stent is at the desired lesion, the balloon is inflated and the stent expanded.

The main advantage balloon-expandable stents have over self-expanding stents is that they have greater hoop strength, which means that they can better resist the recoil of the vessel after full expansion of the stent. An example of this would be in the treatment of a heavily calcified vessel or in a chronic total iliac occlusion. In addition, many interventionalists feel that balloon-expandable stents can be more precisely placed than self-expanding stents and thus are preferable when accuracy is of high clinical importance. An example of this would be in the treatment of an ostial, visceral vessel lesion where preservation of branches is important. However, older balloon-expandable stents are less flexible than current models, and navigating such older devices in a tortuous vessel can be difficult.

Self-Expanding Stents

Self-expanding stents are placed within a delivery catheter and rely on a self-expansion mechanism for full deployment. A common deployment mechanism involves the use of an outer jacket and a plunger: the jacket is withdrawn while the stent is held in position by the plunger, and the stent then expands to its predetermined diameter. Commonly, a balloon is employed to ensure that the stent is fully expanded and impacted into the plaque.

An advantage self-expanding stents have over balloon-expandable stents is that they offer a greater degree of longitudinal flexibility and thus are more easily tracked into position. Self-expanding stents come in lengths of up to 20 cm, which means that fewer overlap zones and fewer stents are required in the treatment of long lesions. In addition, they may be delivered by catheters with smaller profiles, which may reduce arterial access complications. Self-expanding stents may also be placed in regions of the body where they are subject to crushing forces (e.g., the carotid artery) because they are capable of recovering from the deformation and maintaining the arterial lumen.¹⁵ As noted, however, self-expanding stents have less hoop strength than the balloon-expandable stents.

Covered Stents

Stents may be covered with polyester, polytetrafluoroethylene (with or without a heparin coating), or other materials. Currently, covered stents are being used frequently for treating occlusive lesions, but they are more commonly employed for treating aneurysms, arterial rupture, and arteriovenous fistulas.^{15,16}

GENERAL TECHNICAL PRINCIPLES

Conceptually, stent placement is very similar to balloon angioplasty [see Figure 6]. Preoperatively, the patient is often given an antiplatelet agent, which may be continued for

4 weeks or longer postoperatively to reduce the risk of thrombosis. In general, the diameter of the fully deployed stent should slightly exceed that of the vessel, although many interventionalists do not fully dilate stents in the aorta and the carotid bifurcation.¹¹ If occlusion makes the exact diameter of the artery difficult to measure, the vessel's contralateral counterpart can be used as a guide.¹⁶ The stent should also be slightly longer than the lesion to ensure that the entire lesion is covered. In this way, good wall apposition can be achieved and stent migration prevented.

The classic approach is to advance a guide (or a long sheath) across the stenosis over the previously placed guide wire; the vascular stent is then passed through the guide and positioned at the lesion, the guide is withdrawn, and the stent is deployed. With newer stent delivery systems, the leading tip often allows the stent to be delivered without precrossing the lesion with a guide or sheath. Multiple stents are sometimes required to complete the procedure.

TROUBLESHOOTING

It is often helpful to place the leading end of a self-expanding stent slightly beyond the lesion and then draw it back. This measure removes loaded tension from the system; it also allows the stent to be pulled back slightly after the initiation of deployment, at which point various forces sometimes cause the stent to move forward. However, the partially deployed struts of the stent can injure the vessel wall if moved too much or advanced forward. It is also important to keep in mind the potential for foreshortening of the stent during deployment. Failure to cover the entire lesion with the stent results in residual disease after the procedure, which can cause subsequent thrombosis and necessitate the placement of an additional stent. To prevent restenosis, multiple stents should generally be placed so as to overlap one another, but doing so may increase the risk of fatigue fractures. Clearly, the nuances of stent deployment vary according to the system being used; frequent use of a particular system will enhance the surgeon's familiarity with the behavior of the device and improve the subsequent clinical results.

Postprocedural Management of Arterial Access Site

After any endovascular procedure, the arterial access site must be addressed. Manual compression is one of the most common methods of hemostasis and is effective in most instances. The artery often must be compressed for longer than 20 minutes to prevent bleeding complications. If the patient is receiving anticoagulant therapy, it may be necessary to wait until the coagulation parameters have normalized before pulling out the sheath. This can be done when the patient is out of the operating room or the interventional suite and in the recovery room or when the patient has been moved onto the hospital floor. It is important that the person applying manual compression knows to maintain pressure over the actual puncture site in the artery as opposed to the skin incision site. This may be above or below the skin incision site depending on whether an antegrade or retrograde approach is used during the intervention. Failure to do so may lead to bleeding and pseudoaneurysm formation. After hemostasis has been achieved at the access site, the patient should refrain from walking for about 6 hours, after which the

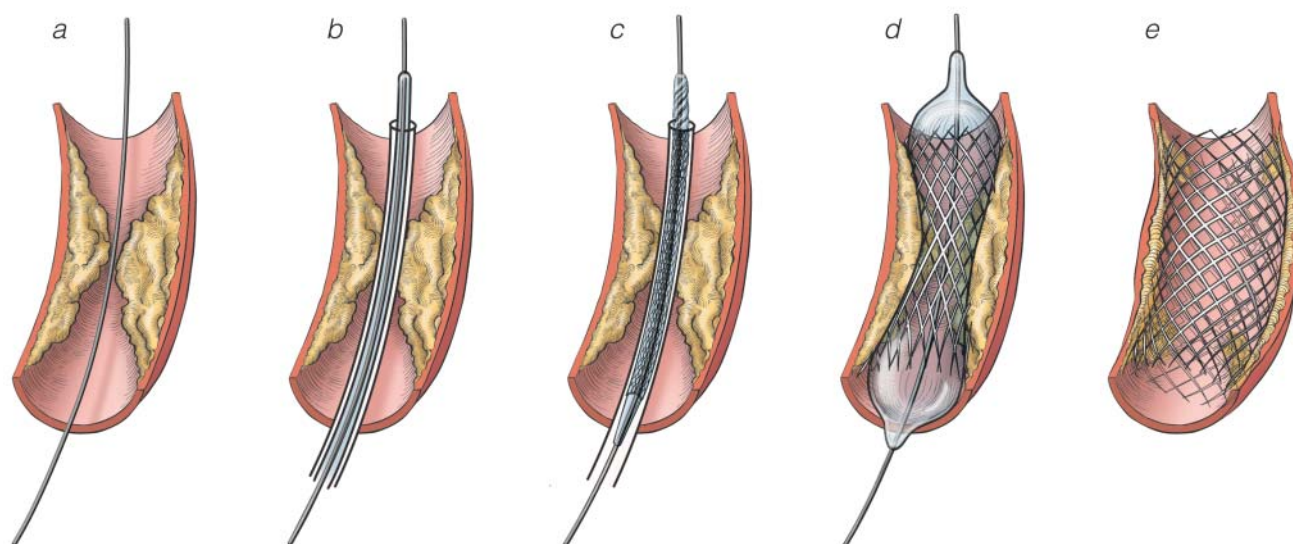


Figure 6 Shown is the deployment of a balloon-expandable stent. (a) The guide wire is passed across the lesion. (b) The sheath-dilator combination is passed over the guide wire across the lesion. (c) The dilator is removed, and the balloon-expandable stent is advanced. (d) The sheath is retracted and the balloon inflated. (e) The balloon is deflated and withdrawn, leaving the stent fully deployed.

puncture site generally is sufficiently stable. After therapeutic procedures involving relatively large devices, use of an arterial closure device may be advantageous. Several such closure devices are now commercially available. These devices are improving in quality and are certain to be used more frequently in the future.

Large Sheath Access during Aortic Interventions

As opposed to most peripheral interventions using 5, 6, or 7 French sheaths, aortic interventions for the treatment of aneurysms or dissections use large sheaths ranging from 12 to 24 French. Often occlusive disease in the iliac arteries makes remote arterial access from a femoral approach much more problematic [see Figure 7]. In fact, the EUROSTAR registry reported access-related complications in 13% of patients undergoing endovascular abdominal aortic aneurysm repair.¹⁷ Similarly, large industry-sponsored trials using devices designed to treat thoracic aortic aneurysms have reported that the use of surgically created conduits because of small-caliber or diseased iliac vessels ranges from 9.4 to 21%.^{18–20}

Several methods have been developed to overcome unfavorable iliac artery anatomy and to still allow aortic interventions to be performed through remote femoral access. Each of these has its own advantages and disadvantages, and detailed descriptions of their use can be found elsewhere.²¹ A creative method has been developed to safely perform aortic interventions requiring large sheaths from a femoral approach using an endoconduit.

The concept behind the endoconduit is to deploy a covered stent across the diseased segment of iliac artery, aggressively balloon within the stent graft, and create a controlled rupture of the iliac artery to allow for passage of the large delivery sheath through the diseased vessel lined by the covered stent [see Figure 8]. The rupture occurs in the midportion of the



Figure 7 Aortoiliac angiogram demonstrating a heavily diseased, small-caliber, right external iliac artery. Note that the 18 French sheath in the right external iliac artery is unable to be passed into the aorta.

external iliac artery and is controlled because adequate proximal and distal seals are created between the stent graft and a relatively disease-free portion of the common iliac artery and the CFA, respectively. Depending on the size of the delivery sheath needed to accommodate the device or the size of the device itself, the stent graft is ballooned with a 10 or 12 mm noncompliant balloon.

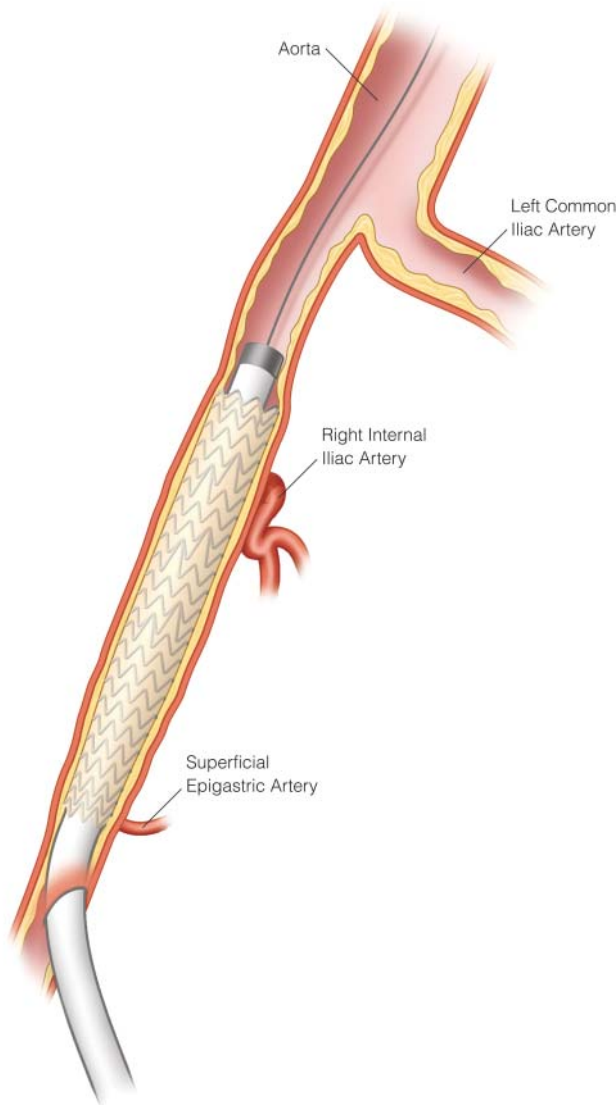


Figure 8 Shown is a graphic representation of the endoconduit used in the patient whose angiogram is presented in Figure 7: deployment of a covered stent from the right common iliac artery into the common femoral artery and passage of a large delivery sheath through the stent graft after ballooning inside it to create a controlled rupture of a heavily diseased external iliac artery. Note the extension of the endoconduit into the common femoral artery distally.

TROUBLESHOOTING

This technique has been used safely and effectively without encountering the theoretical complications of hemorrhage from rupture occurring adjacent to a patent internal iliac artery or of paraplegia and buttock ischemia from decrease pelvic perfusion. It is important that the covered stent extend into the CFA to avoid disruption of the vessel between the sheath entry point into the vessel and the end of the stent graft. If vessel rupture does occur in this intervening segment, a short interposition prosthetic graft between the end of the stent graft and the CFA access site is required. This complication shows that emergent surgical repair may still be

necessary even with adjunctive access techniques such as the endoconduit. In the future, lower-profile devices may allow less hazardous aortic interventions.

Summary: Basic Steps in Endovascular Procedures

1. Before operation, assess the patient with respect to renal function, medications, allergies, active infections, anticoagulant management, and skin condition (in cases of planned access). Consider prescribing antiplatelet agents.
2. Monitor and sedate the patient as necessary.
3. Prepare and drape the selected arterial access site or sites.
4. Infiltrate a local anesthetic at the selected site.
5. Use a scalpel to nick the skin at the planned needle entry site, a few centimeters remote of the intended arterial puncture site.
6. Cannulate the artery with the entry needle.
7. Pass the guide wire into the needle for at least 20 to 25 cm under direct fluoroscopic guidance. Take care that the wire passes without resistance.
8. Remove the needle while pinning the guide wire in place.
9. Apply manual compression during exchanges to prevent hematoma formation around the artery.
10. Use dilators to create an appropriate tract while pinning the guide wire.
11. Pass a sheath over the pinned guide wire. Often with small sheaths and minimal scarring, the dilator and the sheath are placed simultaneously. Remove the dilator.
12. Administer anticoagulation as indicated.
13. Manipulate the guide wire to the appropriate position past the lesion (in cases of nonselective catheterization).
14. Pass the catheter over the guide wire and through the sheath. Manipulate the catheter to select the branches for guide wire cannulation.
15. Perform angiography through the catheter or the sheath to clarify the anatomy.
16. Remove the catheter while pinning the guide wire.
17. Pass the balloon catheter over the guide wire. Advance the balloon across and center it over the lesion. If indicated, primary stenting may be performed.
18. Inflate the balloon.
19. Deflate the balloon.
20. Remove the balloon catheter while pinning the guide wire.
21. Perform angiography.
22. If necessary, pass the vascular stent over the guide wire and advance it across the lesion.
23. Deploy the stent.
24. Perform completion angiography.
25. If the angiogram is satisfactory, remove the guide wire, the catheter, and the sheath.
26. Apply manual compression to the access site, or use a closure device.

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Figures 1 through 6 Alice Y. Chen.
Figure 8 Tony Stubblefield.

9 SURGICAL TREATMENT OF CAROTID ARTERY DISEASE

Wesley S. Moore, M.D., F.A.C.S.

The rationale for operating on patients with carotid artery disease is to prevent stroke. It has been estimated that in 50% to 80% of patients who experience an ischemic stroke, the underlying cause is a lesion in the distribution of the carotid artery, usually in the vicinity of the carotid bifurcation. It would follow, then, that appropriate identification and intervention could significantly reduce the incidence of ischemic stroke.

Carotid endarterectomy (CEA) for both symptomatic and asymptomatic carotid artery stenosis has been extensively evaluated in prospective, randomized trials. Symptomatic patients have been studied in the North American Symptomatic Carotid Endarterectomy Trial (NASCET),¹ the European Carotid Stenosis Trial (ECST),² and the symptomatic carotid stenosis trial from the Veterans Affairs (VA) Cooperative Studies Program.³ The results of all three trials conclusively demonstrate that symptomatic patients with greater than 50% stenosis on arteriography are at substantially lower risk for stroke after CEA than control subjects receiving medical management alone. Asymptomatic patients with hemodynamically significant stenosis also benefit from surgical treatment: the Asymptomatic Carotid Atherosclerosis Study (ACAS)⁴ and the asymptomatic carotid stenosis trial from the VA Cooperative Studies Program⁵ show that the risk of both transient ischemic attacks (TIAs) and stroke is markedly lower in patients treated with CEA and best medical management than in control subjects treated with best medical management alone. The Medical Research Council study of the Asymptomatic Carotid Stenosis Trial (ACST) confirmed the findings of these two studies, citing results virtually identical to those originally reported by ACAS.⁶

Surgical reconstruction of the carotid artery yields the greatest benefits when done by surgeons who can keep complication rates to an absolute minimum. The majority of complications associated with carotid arterial procedures are either technical or judgmental; accordingly, in what follows, I emphasize the procedural details that I consider particularly important for deriving the best short- and long-term results from surgical intervention.

Preoperative Evaluation

PATIENT SELECTION

Indications for carotid artery surgery can be divided into two major categories: (1) asymptomatic critical stenosis and (2) symptomatic hemodynamically significant stenosis.⁷

Asymptomatic Critical Stenosis

The VA asymptomatic carotid stenosis study, ACAS, and ACST all found that in patients with diameter-reducing stenosis of 60% or greater on angiography, CEA resulted in fewer fatal and nonfatal strokes over a 5-year period than nonoperative treatment with best medical management alone. It is important to keep in mind that there are several different ways of measuring stenosis [see 6:2 *Asymptomatic Carotid Bruit*]. The 60% figure cited by ACAS and the VA study was determined according to the North American

method rather than the European method. Moreover, it was determined by means of contrast angiography rather than duplex ultrasonography (DUS) or magnetic resonance imaging. If the decision for CEA is to be based on DUS, some conversion of values is required. A patient who has an 80% to 99% stenosis on DUS can generally be assumed to have a diameter-reducing stenosis of at least 60% on angiography; a stenosis that is less than 80% on DUS may fall short of a 60% diameter-reducing stenosis on angiography.

Symptomatic Hemodynamically Significant Carotid Stenosis

Both NASCET and ECST found that symptomatic patients with hemodynamically significant stenoses experienced fewer fatal and nonfatal strokes after CEA combined with best medical management than after best medical management alone, provided that the perioperative morbidity and mortality from stroke was 6.0% or less. Thus, patients with monocular or hemispheric TIAs are good candidates for CEA. Global ischemic attacks have also been used as an indication for CEA. This practice has not been evaluated in clinical trials; it is usually justified on the basis of the ACAS data alone.

Patients who have previously experienced a hemispheric stroke but who are not disabled and have made a reasonable recovery are also good candidates for CEA if they have a hemodynamically significant stenosis.

IMAGING

Identification of a carotid lesion that can be treated with endarterectomy usually begins with a carotid duplex scan. Indications for carotid duplex scanning fall into three main categories: symptoms, signs, and risk factors. Symptoms include classic TIAs and strokes that give rise to clinical suspicion of carotid bifurcation disease. The primary sign is the presence of a carotid bruit on auscultation. Risk factors include cigarette smoking, hypertension, diabetes mellitus, hypercholesterolemia, peripheral vascular disease, and coronary artery disease. As the number of risk factors present increases, the likelihood of associated carotid bifurcation disease increases exponentially.

Patients who present with focal ischemic symptoms are likely to have associated carotid bifurcation disease; however, other pathologic conditions (e.g., emboli of cardiac origin, aortic arch disease, intracranial vascular disease, coagulopathy, and brain tumors) can also be responsible for focal symptoms. Accordingly, a complete workup of a symptomatic patient should include cardiac evaluation as well as intracranial imaging.

The accuracy of carotid duplex scanning is highly dependent on the technician performing it and on the laboratory where it is done. A carefully performed carotid duplex scan is often the most accurate indicator of carotid bifurcation disease; however, a hastily or carelessly performed scan can result in overestimation of the extent of the carotid bifurcation disease. For this reason, additional imaging studies (e.g., magnetic resonance angiography, computed tomographic angiography, and, when there is serious doubt, contrast angiography) may be indicated.

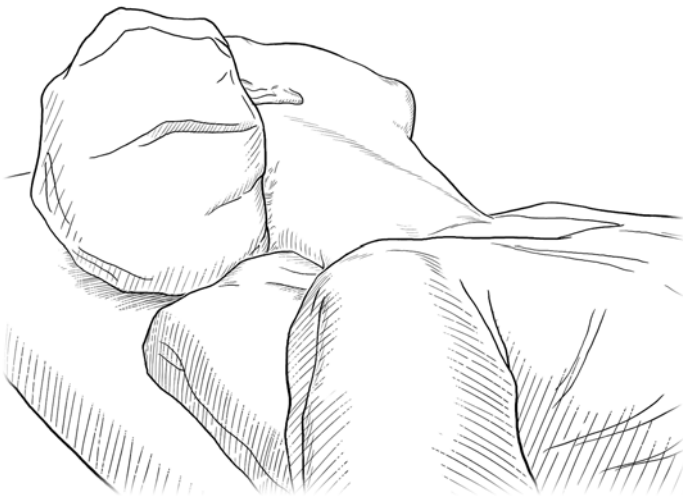


Figure 1 Carotid arterial procedures. Shown is the recommended patient positioning.

Operative Planning

Before operation is scheduled, the general health of the patient must be assessed, with particular attention paid to cardiac and pulmonary status. Given that many patients with carotid artery disease are hypertensive or diabetic, good preoperative control of diabetes mellitus and blood pressure is mandatory. In addition, to reduce the risk of thromboembolic complications, patients should receive antiplatelet drugs (e.g., aspirin) up to and on the day of operation. Finally, it is well documented that the risk of perioperative cardiac complications can be materially reduced by placing patients on a combination regimen that includes a statin and a beta blocker.

ANESTHESIA

Surgery on the cervical portion of the carotid artery may be performed with the patient under either general or cervical block anesthesia. Both techniques have their advocates, their advantages, and their disadvantages.

The advantages of general anesthesia include a quiet operative field, maximal patient comfort, and good airway control. In addition, general anesthesia may lead to improved cerebral blood flow and give better protection against reduced blood flow during carotid clamping. The disadvantages of general anesthesia include blood pressure swings during induction and the inability to monitor the patient's conscious response to carotid clamping. Some reports also suggest that the incidence of cardiac complications is higher during general anesthesia than during cervical block anesthesia.

The main advantage of cervical block anesthesia is the ability to monitor cerebral function during carotid clamping: an awake patient can be engaged in conversation and can be asked to carry out motor activities of the extremities. The disadvantages of cervical block anesthesia include possible patient discomfort, restlessness, and intolerance of the longer operations that are sometimes necessary for technical reasons. Another disadvantage is that on occasion, a patient cannot tolerate carotid clamping and demonstrates an immediate neurologic deficit with clamp application. Such an occurrence heightens the anxiety level of the surgical team, thereby increasing the risk that they will commit technical errors in the rush to place an internal shunt.

Besides considering the inherent advantages and disadvantages of these two anesthetic techniques with respect to the patient, it is important to consider their advantages and disadvantages with respect to individual surgical practice. A given

surgeon may well work better and achieve better results with one technique or the other.

Whichever anesthetic approach is used, all patients should have a radial arterial line in place to allow continuous blood pressure monitoring and to provide access for determining blood gas levels. As a rule, there is no need to place a central venous line or a right heart catheter, except in patients with marginal cardiac function.

PATIENT POSITIONING

Proper positioning of the patient is necessary to provide optimal exposure of the neck from the clavicle up to the mastoid process on the side of the proposed operation [see *Figure 1*]. The patient is placed in the supine position with a folded sheet under the shoulders to induce a mild degree of neck extension. Excessive neck extension should be avoided, however, because it places tension on the artery and actually hinders rather than facilitates exposure. This potential problem can be addressed by placing one or more towels under the head to adjust the neck to the optimal degree of extension. The patient's head is then turned away from the side of the operation to improve cervical exposure further. Finally, the table top may be rotated slightly away from the side of the operation so as to provide a flat surgical field. The head of the table may be elevated slightly if the patient's blood pressure is adequate; this step helps lower venous pressure and reduce venous bleeding during the operation [see *Figure 1*].

Operative Technique

STEP 1: INITIAL INCISION

Either of two incisions may be used for exposure of the cervical carotid artery. The more common choice is a vertical incision placed along an imaginary line that extends from the sternoclavicular junction to the mastoid process, paralleling the anterior margin of the sternocleidomastoid muscle as well as the course of the carotid artery and the contents of the carotid sheath [see *Figure 2*]. The incision is centered over the presumed location of the carotid bifurcation. The advantage of this incision is that it pro-

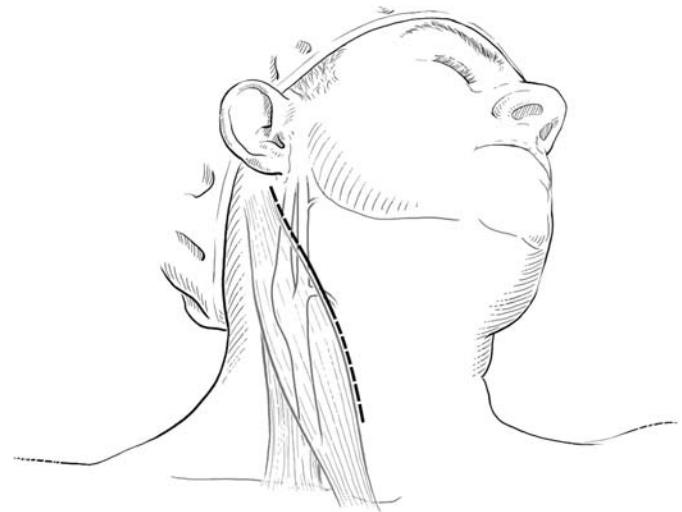


Figure 2 Carotid arterial procedures. The incision most commonly used to expose the cervical carotid artery is a vertical one placed along the anterior margin of the sternocleidomastoid muscle and centered over the presumed location of the carotid bifurcation. It may be extended proximally or distally, depending on where the carotid bifurcation turns out to be.

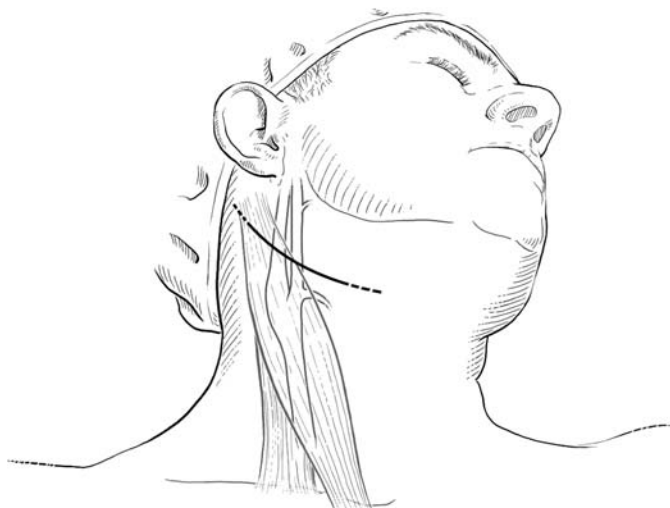


Figure 3 Carotid arterial procedures. An alternative incision to the vertical incision is a transverse incision along a skin crease in the vicinity of the carotid bifurcation.

vides optimal exposure of the cervical carotid artery and can readily be extended either proximally or distally along the aforementioned imaginary line to give additional exposure when needed (e.g., when the carotid bifurcation is unusually high). The disadvantage of this incision is that it runs against Langer's lines; thus, if a keloid occurs, it is likely to be in an unsightly position. In most patients, the incision heals to a fine line, and it usually is not noticeable once healing is complete.

The alternative to the vertical incision is a transverse incision that is placed in a skin crease on the anterior portion of the neck and then curved toward the mastoid process posteriorly [see Figure 3].

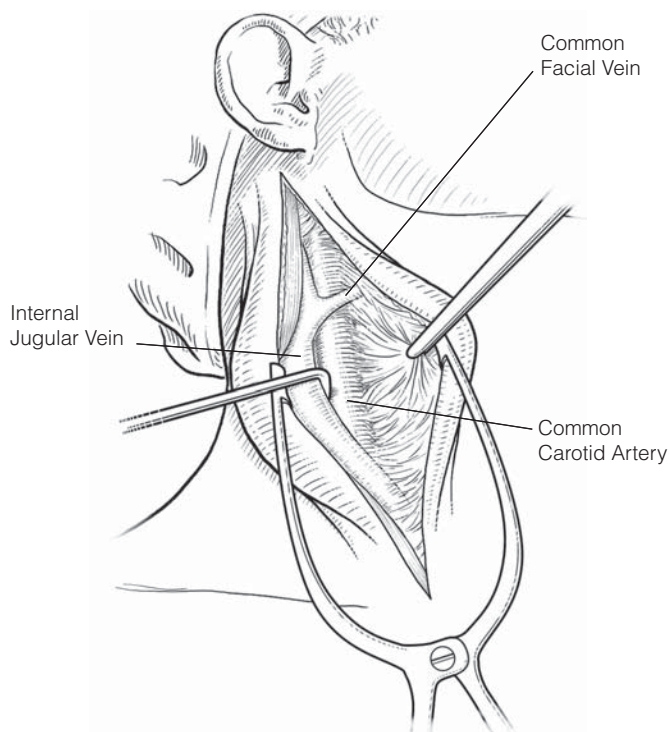


Figure 4 Carotid arterial procedures. After the sternocleidomastoid muscle is mobilized off the carotid sheath, the jugular vein is identified. The perivascular plane along the jugular vein is opened until the common facial vein is exposed.

Skin flaps are raised in a subplatysmal layer, and the incision is deepened along the anterior border of the sternocleidomastoid muscle. The advantage of this alternative incision is that it may be more cosmetically acceptable; however, its inferior portion frequently crosses the neck anteriorly, which may make it more visible than an incision confined to the line of the sternocleidomastoid muscle would be. The disadvantage of this incision is that it requires the raising of skin flaps, which takes additional time and may limit the extent of any proximal exposure that may be required.

STEP 2: EXPOSURE OF CAROTID ARTERY

Once the incision through the platysmal layer has been completed, an avascular areolar plane is developed along the anterior border of the sternocleidomastoid muscle for the full length of the incision so as to expose the carotid sheath. The internal jugular vein is usually the most visible vessel, and the carotid sheath is opened along this vessel's anterior border. The common facial vein, which drains into the internal jugular vein, is a relatively constant landmark. Because the common facial vein is the venous analogue of the external carotid artery, it can generally be used as a guide to the position of the carotid bifurcation [see Figure 4]. On occasion, a patient has several accessory facial veins instead of a single common facial vein. The common facial vein or the accessory facial veins are then divided between ligatures so that the jugular vein can be retracted laterally. The common carotid artery and the carotid bifurcation lie immediately beneath the divided facial veins.

At this point, care must be taken to look for the vagus nerve. This nerve is usually located posterior to the common carotid artery, but it is sometimes rotated into a more superficial position. Another important neurologic structure in this area is the ansa cervicalis, which is formed by the junction of fibers from the hypoglossal (12th cranial) nerve and fibers from the first cervical nerve and which continues inferiorly as a single trunk, providing innervation to the strap muscles. This nerve should be spared if possible, but it can be divided without significant sequelae if it interferes with optimal exposure of the carotid bifurcation. One convenient method of separating the nerve from the artery is to divide the fibers running from the first cervical nerve to the ansa cervicalis; when this is done, the nerve is readily mobilized and retracted anteriorly away from the carotid artery.

The perivascular plane of the common carotid artery is then entered, and the common carotid artery is circumferentially mobilized. The common carotid artery is palpated against a right-angle clamp to determine the proximal extent of the atherosclerotic plaque. If possible, the common carotid artery should be mobilized proximal to the plaque until a circumferentially soft portion of that vessel is reached. During mobilization, the vagus nerve should be identified in its usual location posterior to the vessel and carefully protected; this nerve sometimes spirals anterior to the carotid artery as the vessel is dissected distally.

Dissection is then extended distally toward the carotid bifurcation and continued along both the internal and external carotid arteries. Excessive manipulation of the area around the carotid bifurcation must be avoided. In particular, it is important to be careful around the bulb of the internal carotid artery: this is where the majority of the plaque will be located, and manipulation can easily dislodge plaque or thromboembolic material. With exposure of the carotid bifurcation, the hypoglossal nerve may come into view. Care should be taken not to injure this nerve, though it may have to be mobilized to permit sufficient distal exposure of the internal carotid artery.

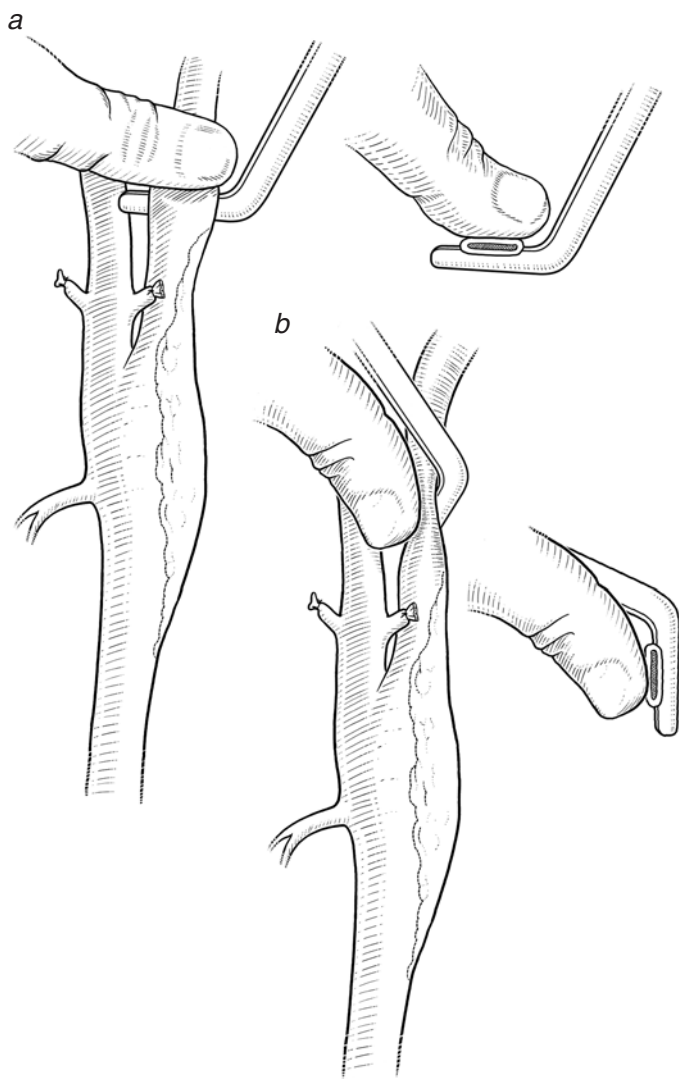


Figure 5 Carotid arterial procedures. After the common carotid artery and the internal and external carotid arteries have been mobilized, the internal carotid artery is palpated against a right-angle clamp in at least two planes (*a*, *b*) to confirm that the artery has been freed beyond the end point of the plaque.

Next, dissection is continued distally beyond the bulb of the internal carotid artery to a point where the internal carotid artery is normal. At this point, the relevant portion of the vessel is circumferentially mobilized and palpated against a right-angle clamp in at least two planes to confirm that the atheromatous plaque does not reach up to the level of the proposed clamping [see Figure 5]. Once this is accomplished, the external carotid artery is mobilized beyond the end point of plaque extension in a similar manner.

If the patient has a high carotid bifurcation or if the plaque in the internal carotid artery extends further distally than usual, a more extensive exposure of the carotid bifurcation, the internal carotid artery, or both is required. To provide such exposure, the skin incision is extended all the way to the mastoid process. The sternocleidomastoid muscle is fully mobilized up to the mastoid process, with care taken to look for the spinal portion of the accessory (11th cranial) nerve as it enters the sternocleidomastoid muscle on the medial surface. With the sternocleidomastoid muscle fully mobilized and retractors in place, the internal carotid artery can then be further exposed.

The jugular vein is mobilized up toward the base of the skull, with care taken to look for additional accessory facial branches, which must be divided between ligatures so that the jugular vein can be fully mobilized and moved posteriorly. The perivascular plane of the internal carotid artery is carefully defined, and the artery is gently mobilized; the more distal portion of the internal carotid artery can then be mobilized downward. If the vessel is still insufficiently mobile, then the nerve to the carotid body and the ascending pharyngeal artery within the crotch between the internal and external carotid arteries are mobilized and divided between ligatures. These two structures often serve as a de facto suspensory ligament for the carotid bulb; dividing them allows the carotid bifurcation to drop down and permits further downward traction of the internal carotid artery as the vessel is gently mobilized distally [see Figure 6].

Once the internal carotid artery is further exposed distally and the hypoglossal nerve is mobilized along its vertical portion and moved anteriorly, the posterior belly of the digastric muscle is encountered. An areolar plane is developed posteriorly and superiorly along the inferior margin of the posterior belly of the digastric muscle, allowing the muscle to be mobilized anteriorly to yield additional exposure of the internal carotid artery. If the

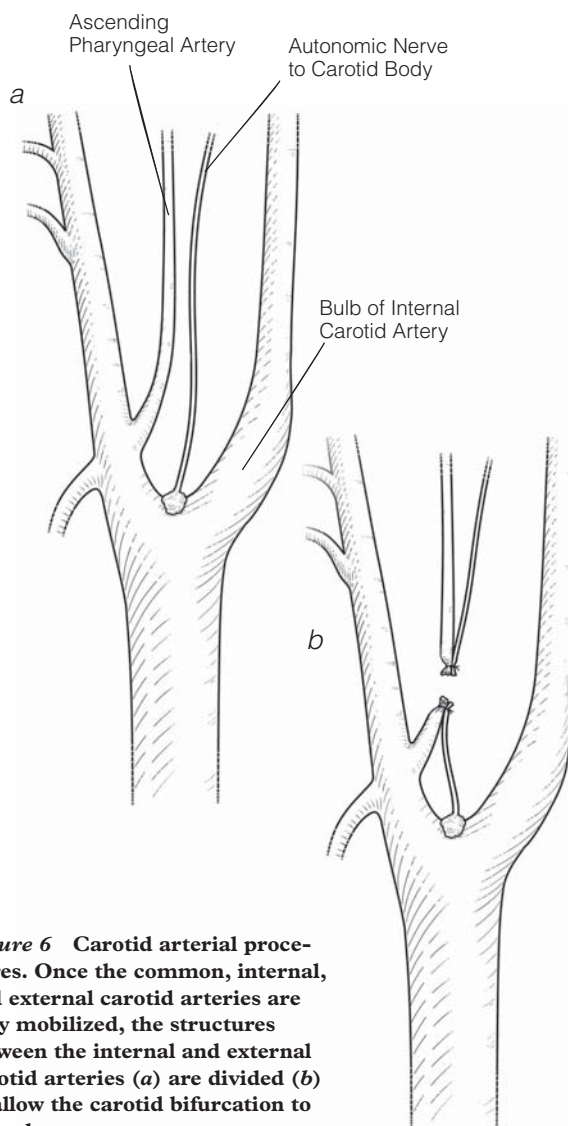


Figure 6 Carotid arterial procedures. Once the common, internal, and external carotid arteries are fully mobilized, the structures between the internal and external carotid arteries (*a*) are divided (*b*) to allow the carotid bifurcation to drop down.

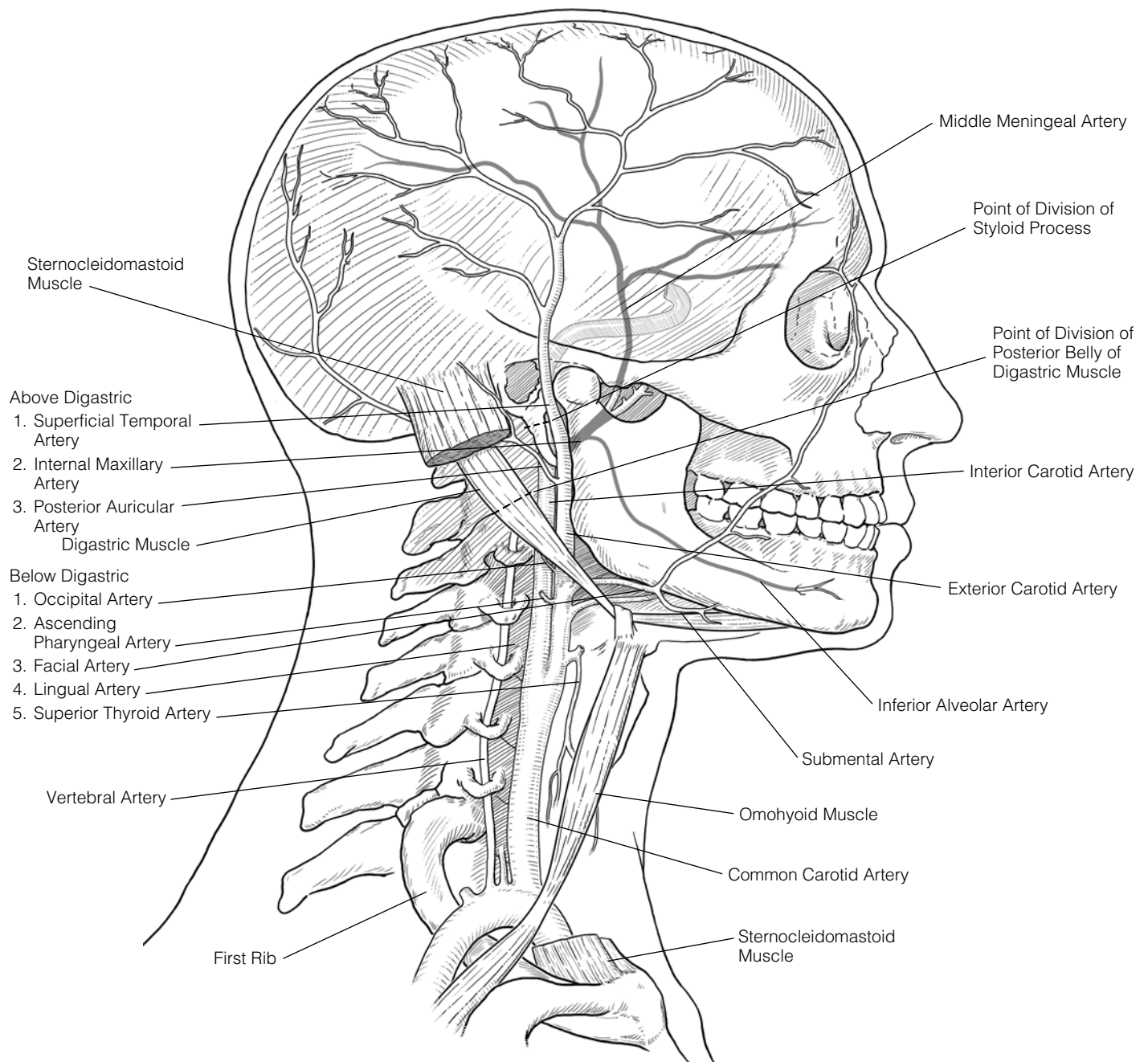


Figure 7 Carotid arterial procedures. Division of the posterior belly of the digastric muscle yields additional exposure of the internal carotid artery. If the internal carotid artery must be mobilized all the way to the base of the skull, further distal exposure is obtained by separating the attachments of the ligaments to the styloid process and dividing the styloid process.

resulting exposure is not sufficient, the muscle may be carefully encircled with a right-angle clamp and divided [see Figure 7]. In those relatively uncommon cases in which even further distal exposure is required, the styloid process is palpated and the muscular and ligamentous attachments to the styloid process divided, so that the styloid process can be exposed with a periosteal elevator. Once the styloid process has been completely freed of its muscular and ligamentous attachments and the cranial nerves in the vicinity have been identified and carefully protected, the styloid process is cut close to the base of the skull [see Figure 7]. This step yields optimal exposure of the internal carotid artery all the way to the base of the skull.

Additional adjunctive measures for more extensive exposure of the internal carotid artery have been described. These include subluxation or dislocation of the mandible,⁸ wiring of the mandible into a subluxed position, and division of the ramus of the mandible with rotation of the mandible away from the base of the skull. In my view, these measures are unnecessary, provided that the sternocleidomastoid muscle and the jugular vein have been adequately mobilized, the plane around the internal carotid artery has been developed, and the carotid bifurcation has been released.

A significant risk associated with extended exposure of the internal carotid artery is possible injury to the vagus nerve, the accessory nerve, or the hypoglossal nerve. Retraction of the vagus

nerve may produce either temporary or permanent vocal cord palsy, and extensive retraction of or injury to the hypoglossal nerve causes denervation of the ipsilateral side of the tongue, manifested by tongue deviation to the ipsilateral side on protrusion or difficulty with mastication or swallowing. In addition, posterior exposure of a high carotid bifurcation may result in injury to branches of the glossopharyngeal (ninth cranial) nerve.

A common error in carotid artery mobilization is failure to recognize that the plaque in the internal carotid artery extends beyond the upper limit of the arterial exposure. It is far better to anticipate this problem before clamping and opening the artery than to discover it afterward and be forced to mobilize the vessel after it has been clamped. Once the common carotid and internal carotid arteries have been mobilized sufficiently, they are encircled with umbilical tapes; Rumel tourniquets are used if an internal shunt is required or desired.

STEP 3: CEREBRAL CIRCULATORY SUPPORT

Clamping of the carotid artery necessarily results in interruption of blood flow through the vessel. Patients who have good collateral circulation via the contralateral carotid artery or the vertebral arteries generally (though not always) tolerate the temporary interruption of flow through the clamped artery well.⁹ Patients who have inadequate collateral blood flow require cerebral circulatory support, usually in the form of placement of an internal shunt. There are three basic approaches to shunt use: (1) routine use of an internal shunt, (2) selective use of an internal shunt, and (3) routine avoidance of shunting in an attempt to minimize clamp time.

Shunting Options

Routine shunting In approximately 10% of patients undergoing carotid artery surgery, collateral blood flow is inadequate and temporary use of an indwelling shunt is necessary to prevent brain damage. In the remaining 90%, collateral blood flow is adequate and clamping generally well tolerated, and shunting is therefore unnecessary. Clearly, routine use of an internal shunt takes care of the 10% of patients who require shunts. Its disadvantage is that it is an additional procedure that carries its own complications, to which not only the 10% of patients who require shunting but also the 90% who do not are subjected. The potential complications associated with placement of a shunt include intimal injury (including the raising of an intimal flap), atheroma embolization (if atheromatous material is scooped up during shunt placement), and air embolization (if air bubbles are trapped within the shunt and not recognized).

Selective shunting Selective placement of a shunt has an advantage over routine placement in that the procedure and its potential complications are limited to the 10% of patients who actually require a shunt. Its main disadvantage is that the methods used to identify patients who require shunting may not be entirely reliable.

Selective identification of patients who require shunting can be accomplished in several ways. The most direct—and perhaps safest—method is to employ local or cervical block anesthesia so that the effect of temporary carotid clamping can be assessed in a conscious patient; if clamping leads to a neurologic deficit, then the patient clearly requires an internal shunt. Other methods of identifying patients who require a shunt make use of techniques such as continuous electroencephalographic monitoring, measurement of somatosensory evoked potential, and monitoring of middle cerebral blood flow with transcranial Doppler ultrasonography.

A useful method of determining the adequacy of collateral cere-

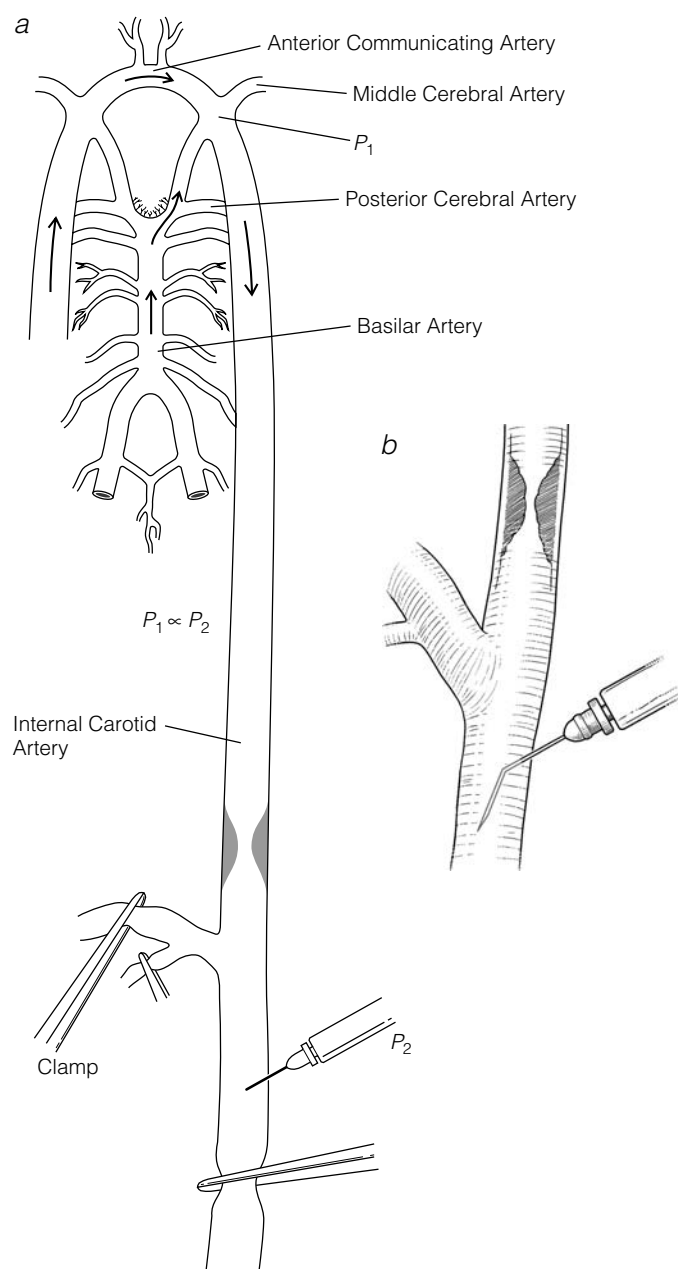


Figure 8 Carotid arterial procedures. (a) Shown is a graphic representation of the measurement of internal carotid artery back-pressure. (b) The needle is bent at a 45° angle before being inserted into the common carotid artery.

bral blood flow is measurement of back-pressure in the internal carotid artery.¹⁰ Back-pressure has been shown to be a good index of the adequacy of collateral blood flow, and it correlates well with the safety of temporary clamping and thus with the necessity of placing an internal shunt. Back-pressure is measured by placing into the common carotid artery a needle that is connected to pressure tubing and a pressure transducer. The tip of the needle is bent at a 45° angle. Systemic blood pressure is measured, and clamps are placed on the common carotid artery proximal to the needle and on the external carotid artery. The residual pressure in the common carotid artery, which is in continuity with the internal carotid artery, is then allowed to equilibrate; the resulting pressure reading represents internal carotid artery back-pressure [see Figure 8]. It has been determined that patients with back-pressures high-

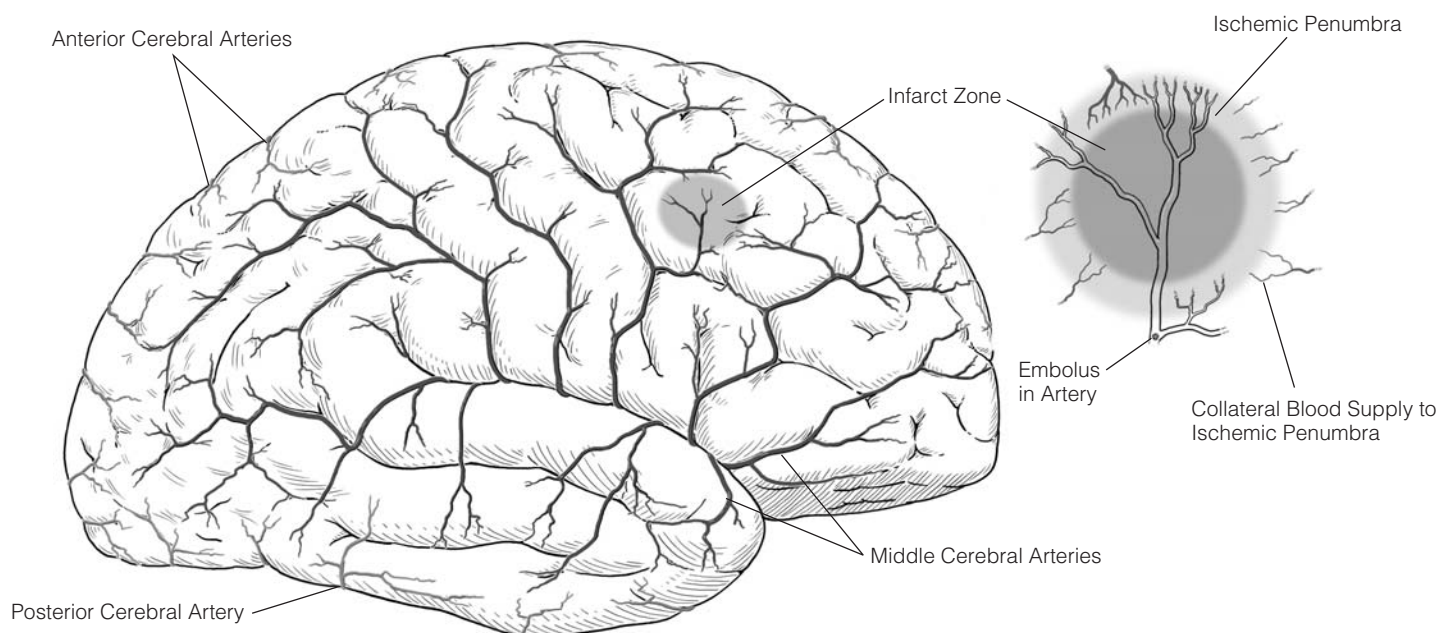


Figure 9 Carotid arterial procedures. When a thromboembolic fragment occludes a cortical arterial branch, a central infarct zone develops, surrounded by an ischemic zone that derives some residual blood supply from collateral vessels. In this zone, known as the ischemic penumbra, the residual blood supply is sufficient to maintain viability.

er than 25 mm Hg can tolerate temporary clamping without incurring brain damage.

The utility of selective shunting in appropriate settings notwithstanding, routine shunting is recommended for patients who have previously had a stroke, regardless of the degree of neurologic recovery. In these patients, a central area of cerebral infarction is surrounded by a zone of relatively ischemic tissue—the so-called ischemic penumbra. The ischemic penumbra is made up of live and potentially functional brain tissue, but its viability is highly dependent on maximization of cerebral perfusion pressure through collateral channels. Accordingly, any interruption of carotid circulation, regardless of the degree of collateral circulation present, may threaten the ischemic penumbra and extend the infarct [see Figure 9]. In my opinion, all CEA patients with prior strokes should receive shunts on a routine basis.

Routine avoidance of shunting The advantage of routinely avoiding the use of shunts is that the technical issues and potential complications associated with the additional procedure are avoided entirely. The disadvantage is that unshunted patients with poor collateral blood flow may sustain ischemic brain damage, particularly if the clamp time turns out to be longer than was anticipated.

Technique of Shunt Placement

Internal shunts must be placed with great care if shunt-associated complications are to be avoided. Of the various shunts currently available, I prefer the Javid shunt, which is tapered, has smooth leading edges, and possesses external bulbous circumferential extensions that permit it to be held in place with a circumferential Rumel tourniquet, thereby minimizing the chances of inadvertent dislodgment. Optimal placement of an internal shunt may be achieved by means of the following steps [see Figure 10].

After the patient has been adequately heparinized and the artery clamped and opened, the distal portion of the internal shunt is placed into the internal carotid artery. A clamp is placed

on the shunt and briefly opened to allow back-bleeding; good back-bleeding confirms that the shunt is lying free in the lumen of the internal carotid artery. The shunt is then secured by tightening a Rumel tourniquet, and the bulbous portion of the shunt is engaged to prevent dislodgment.

Next, the proximal portion of the shunt is placed into the common carotid artery. As this is done, the clamp is removed from the shunt so that backflow from the shunt will dislodge any loose material and air within the common carotid artery. The shunt is then reclamped, and the clamp is removed from the common carotid artery as the proximal portion of the shunt is passed into that vessel.

When the proximal portion of the shunt is in the proper position in the common carotid artery, it is secured by tightening a Rumel tourniquet on the vessel. The clamp on the shunt is then slowly opened so that the surgeon can observe flow through the translucent device and thus verify that no solid particles or air bubbles are passing through it. Because the shunt is relatively long, the surgeon has a reasonable amount of time in which to observe flow. If any particles or air bubbles are identified, the shunt can be quickly clamped, removed from the common carotid artery, and back-bled, and the procedure can then be repeated.

Once the shunt is secured in place and open, its length and redundancy allow it to be easily manipulated medially and laterally; endarterectomy can then be performed without the encumbrance of an inlying shunt.

STEP 4: RECONSTRUCTION OPTIONS

There are four principal reconstructions involving the common carotid artery and the carotid bifurcation: (1) conventional open CEA with either patch angioplasty or primary closure, (2) eversion endarterectomy, (3) reconstruction for proximal lesions of the common carotid artery, and (4) reconstruction for recurrent stenosis with resection of the carotid bifurcation and grafting.

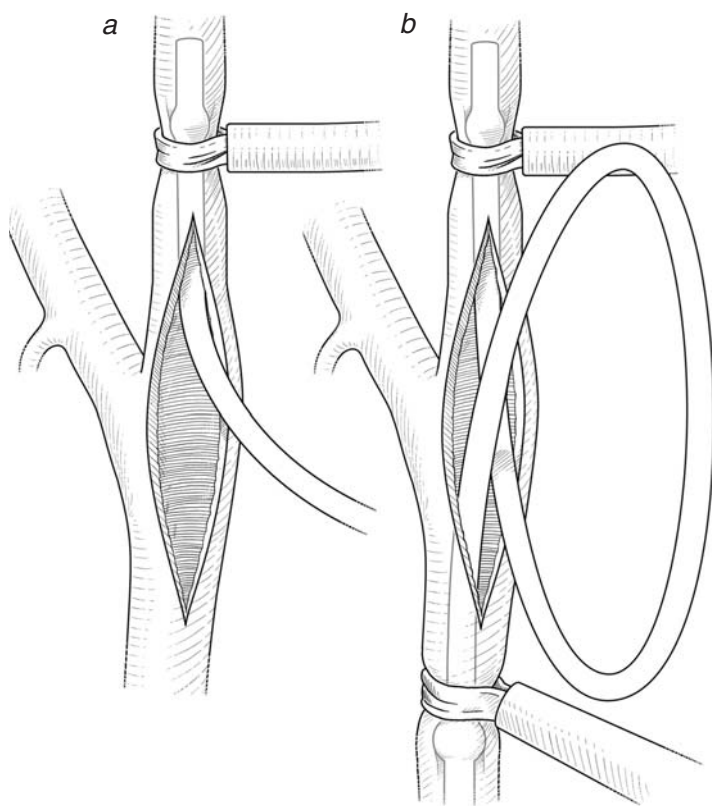


Figure 10 Carotid arterial procedures. Shown is the technique of shunt placement, first distally (a) and then proximally (b).

Open Carotid Endarterectomy

Once the carotid bifurcation has been fully mobilized both proximal and distal to the lesion, systemic anticoagulation with heparin is initiated. I generally give 5,000 units, an amount that is sufficient to produce adequate anticoagulation for the duration of carotid clamping but is not large enough to necessitate heparin reversal on completion of the operation. If the patient has been receiving clopidogrel—particularly if clopidogrel was given in combination with aspirin—the heparin dose must be reduced to allow adequate hemostasis to be achieved after reconstruction. In these cases, I usually limit the heparin dose to 3,000 units. If internal carotid artery back-pressure is to be used to determine whether the patient requires an internal shunt, then it is measured at this time. If cerebral electrical activity is to be the determinant, then the internal, external, and common carotid arteries are clamped and electrical activity is monitored (e.g., via EEG) with the clamps in place. If electrical changes are noted with clamping, an internal shunt is required.

Arteriotomy The common carotid artery and the carotid bifurcation are rotated so as to be positioned for an arteriotomy that begins on the common carotid artery and extends through the bulb of the internal carotid artery to a point 180° opposite the flow divider [see Figure 11]. This incision effectively bivalves the carotid bulb, thus making possible a more accurate primary or patch closure. The arteriotomy continues through the plaque and extends well up into the internal carotid artery, beyond the visible end point of the atherosclerotic plaque.

Plaque removal A dissection plane separating the atherosclerotic intima from the media and the adventitia is then developed with a sharp-bladed dissector. As a rule, it is easiest to begin

the endarterectomy at the point where the plaque is bulkiest. At this point, the medial fibers are usually gone, but as the dissection continues both proximally and distally, more normal medial tissue may be seen. It is important to develop the dissection plane between the intima and the media if possible because doing so permits the creation of a feathered end point distally as dissection proceeds into a relatively normal portion of the internal carotid artery [see Figure 12]. If the dissection plane is between the media and the adventitia, a feathered end point is much harder to achieve. Failure to achieve a feathered end point often results in a sharp shelf at the internal carotid artery level, which increases the risk of subsequent intimal dissection when blood flow is restored.

Once the dissection plane is complete on one side of the arteriotomy at the level of the common carotid artery, a right-angle clamp is gently inserted into the plane and advanced through it to the opposite side of the arteriotomy, thereby separating the plaque from the arterial wall around the entire circumference of the vessel. The clamp is then gently spread and brought downward to complete the circumferential dissection of the plaque proximally. The proximal end point of plaque dissection is obtained by cutting the intima with a No. 15 blade.

With the same depth of dissection now existing on both sides of the open common carotid artery, dissection then continues distally up to the carotid bifurcation. At this point, the plaque within the external carotid artery is carefully separated in a circumferential fashion. This is usually done by using a sharp mosquito clamp until all of the plaque has been separated from the vessel wall and dissection has reached normal intima. The freed plaque is gently grasped with the opened mosquito clamp, traction is applied, and

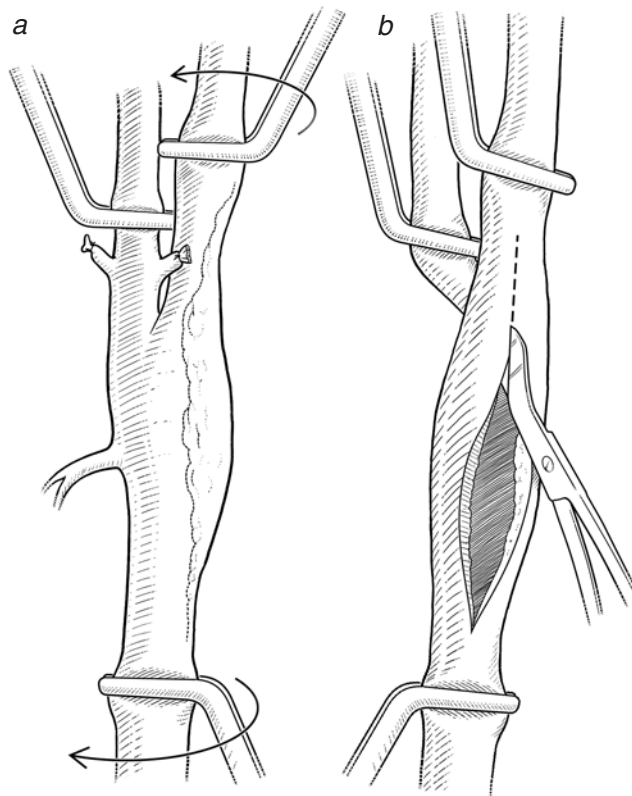


Figure 11 Carotid arterial procedures: open endarterectomy. Clamps are applied to the common, internal, and external carotid arteries, and the structures are rotated (a) so that an arteriotomy can be made in the common carotid artery 180° opposite the flow divider (b).

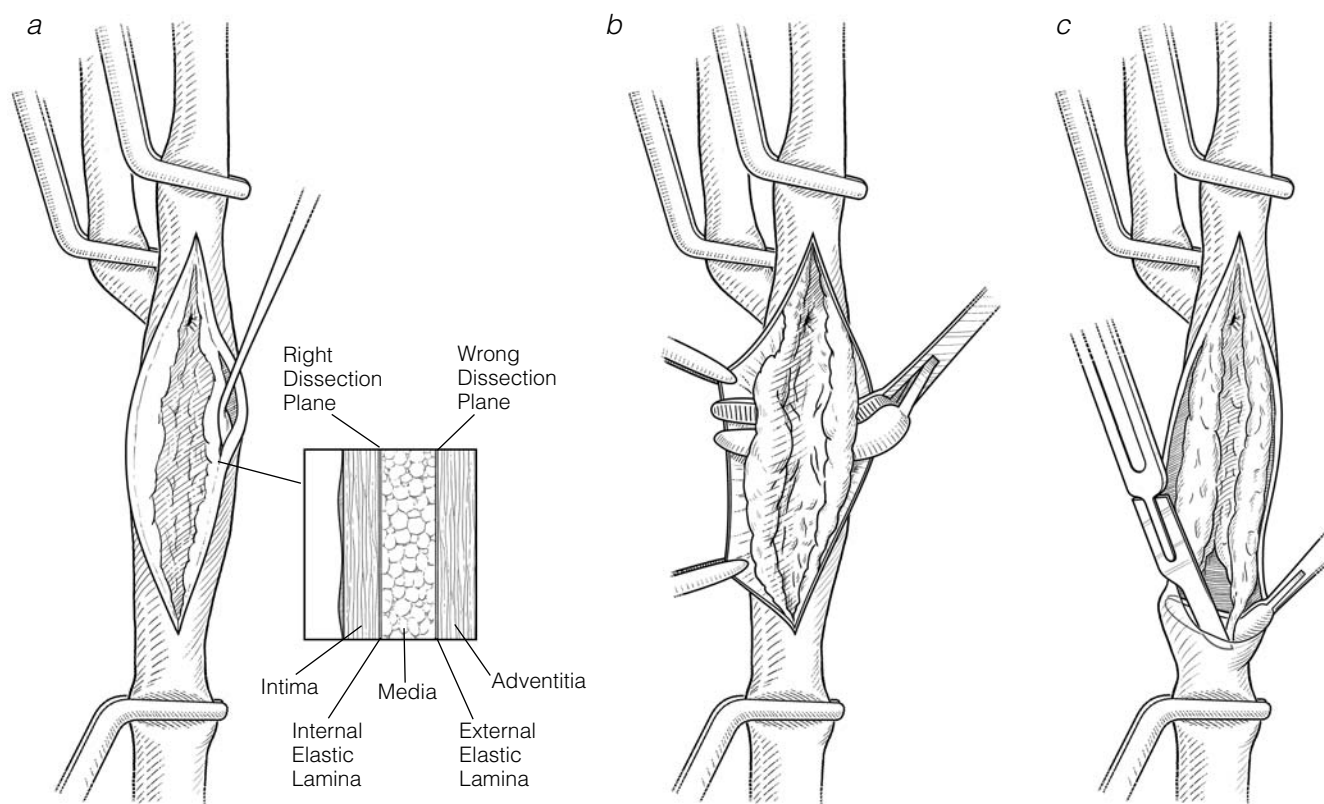


Figure 12 Carotid arterial procedures: open endarterectomy. (a) Dissection is started where plaque is thickest. Often, medial fibers are completely gone here. Dissection proceeds both proximally and distally along one side, and more normal medial tissue may be found. Development of a plane between intima and media, if possible, is valuable for creating a feathered end point distally. (b) Once dissection is complete on one side, the same plane is established on the opposite side. (c) The end point of proximal dissection is established by sharp division of plaque against the clamp.

the distal end point of plaque dissection in the external carotid artery is obtained.

Dissection then continues up the internal carotid artery, with care taken to leave normal intima behind. Often, the plaque becomes a relatively narrow tongue of atheroma on the posterior wall of the internal carotid artery. If the edge of the atheromatous plaque is followed to its end, a tapered, feathered end point can be achieved.

Irrigation and clearing of debris After removal of the specimen, the intimestomized surface is vigorously irrigated with heparinized saline. Any medial debris present is carefully removed. The distal end point is irrigated to determine whether there is a residual flap that might lead to subsequent intimal dissection; if there is a flap, it is carefully removed. If there is a sharp shelf at the distal end point, it is usually an indication that the endarterectomy has not been carried far enough distally. When this is the case, the arteriotomy should be lengthened so that the endarterectomy can be extended to a point where the intima is completely normal. If the patient has a very high carotid bifurcation, very distal plaque, or both and further dissection is impeded by the base of the skull, it may be necessary to secure the distal end point with tacking sutures. Tacking sutures should be used only in exceptional circumstances because their use may lead to healing abnormalities or to the presence of platelet aggregate material that can cause thromboembolic or occlusive complications.

Once the intimestomized surface is completely clear of debris, the lumen of the external carotid artery should be visually inspect-

ed to confirm that all overlying dissected intima has been cleared. Any residual dissected intima can be gently teased out with a mosquito clamp. Once the vessel is completely clear, preparation is made for closure of the arteriotomy.

Closure of arteriotomy If the arteriotomy is relatively short and extends only up to the central portion of the bulb of the internal carotid artery, it can usually be closed primarily with a continuous 6-0 polypropylene suture. Placing very small stitches close together in the internal carotid artery should minimize the risk of vessel narrowing.

If the vessel is relatively small or the arteriotomy was extended well up on the internal carotid artery to ensure a complete endarterectomy, the arteriotomy should be closed with a patch angioplasty. Of the several patch options available, the basic choice is between a prosthetic patch and an autogenous patch composed of a segment of saphenous vein obtained from an extremity. The relative merits of autogenous and prosthetic patches have been extensively debated in the literature, but no definitive conclusions have been reached. One of the disadvantages of an autogenous patch is that surgeons tend to use the entire open portion of the saphenous vein, which then dilates further under arterial pressure, leading to an artery of aneurysmal proportions. Another disadvantage is the potential for patch blowout, which, though rare, has been reported in several series. The main disadvantage of a prosthetic patch is the risk of infection, but this is extremely low.

At present, it would appear that a prosthetic patch is at least as acceptable as an autogenous patch, and the prosthetic patch has

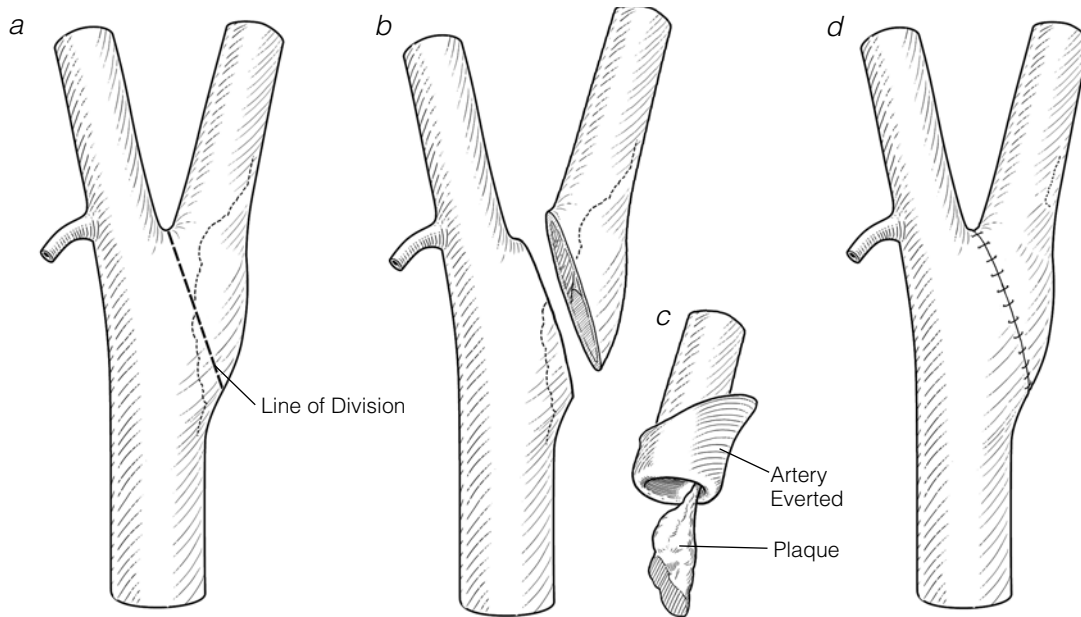


Figure 13 Carotid arterial procedures: eversion endarterectomy. (a, b) The internal carotid artery is divided from the common carotid artery in an oblique line. (c) The divided internal carotid artery is everted on itself so that it can be separated from the underlying plaque. Eversion proceeds distally until the plaque end point is encountered, and the plaque is removed from the internal carotid artery. Proximal endarterectomy of the common carotid artery and endarterectomy of the external carotid artery are then carried out. (d) Once all of the plaque has been removed, the internal carotid artery is reverted and an end-to-side anastomosis is fashioned between the common carotid artery opening and the internal carotid artery.

an additional advantage in that there is no need to remove a normal saphenous vein segment from an extremity. Prosthetic patches can be composed of either fabric or polytetrafluoroethylene (PTFE). Fabric patches now come impregnated with either collagen or gelatin to make them leakproof; PTFE patches do not leak on the surface, but they are prone to leakage at suture needle puncture sites.

Patch size is a crucial consideration: it is important that the patch be neither too wide nor too narrow. If the patch is too narrow, it will not provide the additional material needed to restore the carotid bifurcation to a normal diameter. If the patch is too wide, it will provide too much additional material and create what virtually amounts to a carotid aneurysm; this would represent a significant disadvantage to the patient in terms of flow dynamics and the risk of producing laminated thrombus in the most dilated portion of the carotid bulb. My preference is to use a 6.0 mm wide collagen-impregnated fabric patch for patch angioplasty.

Whichever patch is selected is cut to length, beveled at each end, and sewn in place with a continuous 6-0 polypropylene suture.

Before completion of the closure, the internal carotid artery and the external carotid artery are back-bled and the common carotid artery flushed. The arteriotomy is then completely closed. Removing the clamp on the internal carotid artery allows blood flow to fill the carotid bulb and permits one last internal flush. The origin of the internal carotid artery is then occluded with a vascular forceps, and the clamps are removed first from the external carotid artery and then from the common carotid artery to allow resumption of blood flow. After several heartbeats, the forceps on the origin of the internal carotid artery is removed, and blood flow through the internal carotid artery is restored. There may be some leakage of blood along the suture line, which can usually be controlled with the placement of thrombin-soaked absorbable gelatin

sponge. If any obvious defect is noted between sutures, an additional stitch should be placed.

Eversion Endarterectomy

Eversion endarterectomy was designed and developed to eliminate the need for a suture line on the internal carotid artery, in the hope that doing so would reduce the incidence of myointimal hyperplasia and consequent restenosis. There is evidence to suggest that the use of eversion endarterectomy has led to some reduction in the incidence of myointimal hyperplasia, but the data are controversial and certainly are not conclusive. Nonetheless, the technique may well have merit, and it should be a part of the vascular surgeon's armamentarium.

Besides the avoidance of a suture line on the internal carotid artery, the advantages of eversion endarterectomy include the simple end-to-side anastomotic closure and the possibility of managing a redundant internal carotid artery by moving it down the common carotid artery. One disadvantage is the potential difficulty of achieving an end point in cases in which the bifurcation is high or plaque extends well up the internal carotid artery toward the base of the skull. Another disadvantage arises with patients who require an internal shunt, in that it is not possible to keep an internal shunt in place for the entire duration of an eversion endarterectomy. Yet another disadvantage is that the distal end point cannot be viewed as clearly as it can in open endarterectomy. A fourth disadvantage is that eversion endarterectomy is poorly suited to cases in which the internal carotid artery is relatively small and contracted and thus better treated with patch angioplasty.

Eversion and plaque dissection After the carotid bifurcation is fully mobilized, the internal, external, and common carotid arteries are clamped. A circumferential incision is placed in an

oblique fashion at the junction of the common carotid artery and the bulb of the internal carotid artery to permit division of the bulbous portion of the internal carotid artery from the common carotid [see Figure 13]. The edges of the adventitia of the bulb of the internal carotid artery are grasped, and the outer layers of the vessel wall are gradually everted away from the plaque within the artery. Eversion continues cephalad until it reaches the distal end point of the atherosclerotic lesion, which is marked by the presence of a thin, filmy intima that clearly separates with the specimen, leaving normal vessel behind. The plaque in the common carotid artery and the external carotid artery is then removed in the traditional manner; the opening in the common carotid artery may be extended proximally to facilitate this portion of the endarterectomy.

Reversion and reanastomosis The internal carotid artery is then reverted to its normal anatomic position, and an anastomosis between the end of the divided bulb of the internal carotid artery and the common carotid artery is fashioned with a continuous 6-0 polypropylene suture. If the internal carotid artery is redundant [see Special Considerations, below], the arteriotomy on the common carotid artery is extended proximally and the arteriotomy on the medial aspect of the bulb of the internal carotid artery is extended distally so that the carotid bifurcation may be advanced between the internal and common carotid arteries to eliminate the redundancy.

Reconstruction for Proximal Lesions of Common Carotid Artery

Lesions at the origin of the common carotid artery, either at the level of the aortic arch (in the case of the left common carotid artery) or at the innominate bifurcation (in the case of the right common carotid artery), are relatively rare but do occur. Such lesions may arise either in isolation or in combination with carotid bifurcation disease. They can be managed by dividing the common carotid artery and transposing it to the adjacent subclavian artery, provided that there is no occlusive disease in the ipsilateral subclavian artery.

Exposure and mobilization If the lesion at the origin of the common carotid artery is the only one being treated, both the common carotid artery and the subclavian artery should be exposed through a supraclavicular incision that parallels the clavicle. If a carotid bifurcation lesion is present in conjunction with the lesion at the origin of the common carotid artery, the supraclavicular incision is supplemented with a vertical incision along the sternocleidomastoid muscle to permit exposure of the carotid bifurcation. Exposure of the bifurcation has already been addressed (see above); accordingly, I focus here on exposure of the subclavian artery and the proximal common carotid artery.

A supraclavicular incision is placed approximately 1.5 fingerbreadths above the clavicle and centered over the lateral head of the sternocleidomastoid muscle. The lateral head of the sternocleidomastoid muscle is divided, and the scalene triangle is defined. The scalene fat pad is mobilized off the anterior scalene muscle. The phrenic nerve is identified, mobilized off the scalene muscle, and gently retracted. A plane is developed with gentle dissection between the posterior portion of the anterior scalene muscle and the underlying subclavian artery, and the anterior scalene muscle is divided. Division of the muscle exposes the underlying subclavian artery, a sufficient length of which can then be mobilized in the perivascular plane to permit an anastomosis.

The jugular vein is identified at the medial aspect of the incision and mobilized anteriorly and medially to expose the common

carotid artery. The vagus nerve is identified and carefully protected. The common carotid artery is then mobilized both proximally and distally; proximal mobilization should extend as far behind the sternoclavicular junction as the surgeon can comfortably manage.

Transection and anastomosis The common carotid artery is clamped proximally and distally, then divided; the proximal portion of the vessel is oversewn. The transected common carotid artery is brought posterior to the jugular vein in the vicinity of the subclavian artery. The subclavian artery is clamped proximally and distally, a longitudinal arteriotomy is made, and a small ellipse of subclavian arterial tissue is removed. The end of the common carotid artery is then sewn to the side of the subclavian artery with a continuous 6-0 polypropylene suture.

Before completion, the vessels are back-bled and flushed. Once the anastomosis is complete, blood flow is restored, first to the distal subclavian artery and then to the common carotid artery.

Reconstruction for Recurrent Carotid Stenosis

For an initial recurrence of carotid stenosis that primarily results from myointimal hyperplasia, conversion to a patch angioplasty is generally the best treatment. For second or third recurrences or for recurrences that develop in spite of patch angioplasty, resection of the carotid bifurcation with interposition grafting between the common carotid artery and the normal distal internal carotid artery is the best treatment.

Exposure and mobilization Exposure of a carotid bifurcation for treatment of recurrent carotid stenosis can be challenging. The initial skin incision is reopened, and dissection is carried down through the scar tissue to the common carotid artery. The common carotid artery is sharply dissected from the surrounding scar tissue, with the dissection plane kept close to the adventitia to minimize the risk of injury to the vagus nerve and the hypoglossal nerve. Once the common carotid artery has been adequately mobilized, dissection is carried distally to include the carotid bifurcation and the internal carotid artery. In the course of distal dissection, care must be taken to watch for the hypoglossal nerve, which may be incorporated into the scar tissue; this structure must be carefully dissected away from the artery and protected.

Distal dissection continues beyond the end point of the previous closure of the internal carotid artery. Beyond this end point, it is usually possible to enter a previously undissected plane of the internal carotid artery; from here onward, the artery typically is soft around its circumference and is not involved in the recurrent stenosis. The external carotid artery is then mobilized sufficiently to allow the surgeon to control back-bleeding.

Conversion to patch angioplasty If the artery was originally closed primarily, an arteriotomy is made through the old suture line and carried distally through the area of stenosis and onto a relatively normal area of the internal carotid artery. Exploration of the luminal surface usually reveals a smooth, glistening neointima, and observation of the cut section of the artery reveals an area where a whitish, firm thickening of the intimal wall has occurred as a result of myointimal hyperplasia. No attempt should be made to reendarterectomize the stenotic area, because the intimal lesion is not, in fact, plaque but scar tissue. If the intima is removed, the cascade of events that led to the myointimal hyperplasia will simply be reinitiated. Accordingly, the healed intimal surface should be carefully protected. A patch angioplasty across the stenotic area, extending from the common carotid

artery proximally to a relatively normal portion of the internal carotid artery distally, is usually sufficient to treat the lesion.

Resection of carotid bifurcation with interposition grafting If the stenosis is recurring for the second or third time or the artery was originally closed with a patch, the surgeon should proceed with resection and interposition grafting. In most cases, it is necessary to sacrifice the external carotid artery and oversew its origin. The internal carotid artery is divided distal to the intimal hyperplastic lesion, the common carotid artery is divided proximally, and the diseased specimen is removed.

I prefer to use 6.0 mm thin-walled PTFE for the interposition graft. The internal carotid artery distally and the common carotid artery proximally are spatulated by making vertical incisions approximately 6.0 mm in length. The PTFE graft is appropriately beveled both proximally and distally, and beveled or spatulated end-to-end anastomoses are performed, first to the internal carotid artery and then to the common carotid artery.

Before completion, the vessels are back-bled and flushed; once the anastomoses are complete, blood flow is reestablished.

Some surgeons may be tempted to use autogenous saphenous vein for the interposition graft. To use such grafts would appear, on the face of it, to be a good idea; in fact, it is a mistake. For reasons not clearly understood, the use of autogenous saphenous vein in the neck has an extremely poor track record, yielding unacceptably high rates of recurrent stenosis and occlusion in comparison with the use of prosthetic grafts.

Special Considerations

Fibromuscular dysplasia of internal carotid artery

Fibromuscular dysplasia of the internal carotid artery is a congenital or acquired lesion that has been subdivided into four pathologic varieties, of which the most common is medial fibroplasia. On contrast angiography, medial fibroplasia has a characteristic appearance, resembling a string of beads in the extracranial portion of the internal carotid artery [see Figure 14]. A common initial manifestation is a relatively loud bruit in the neck of a young woman. Fibromuscular dysplasia can cause symptoms of monocular or hemispheric TIAs, or it may go on to cause a stroke, usually as a consequence of a dissection resulting in thrombotic occlusion. If symptoms develop, they can generally be controlled by means of antiplatelet drugs. Currently, the only indication for surgical intervention is the persistence of symptoms despite antiplatelet therapy.

Treatment of fibromuscular dysplasia has evolved over the years. The first attempts at surgical repair involved a total resection of the internal carotid artery coupled with interposition of a graft (usually composed of saphenous vein). This technique has largely been abandoned because of the extensive surgical dissection required and the substantial risk of cranial nerve injury; its only remaining application is in cases where there is associated aneurysmal dilatation in the dysplastic segment that calls for resection and graft interposition. At present, the two most popular modes of therapy both involve intraluminal dilatation with disruption of the small septa within the artery. One mode achieves intraluminal dilatation via an open approach, and the other achieves the same end via a percutaneous approach that includes balloon angioplasty. Dilatation and fracturing of the intraluminal septa often result in the release of particles of septal tissue, which in turn can lead to cerebral embolization and infarction. Consequently, an open approach, which enables the surgeon to flush out the disrupted segments, or balloon angioplasty with cerebral embolic protection is usually favored.



Figure 14 Carotid arterial procedures: repair of fibromuscular dysplasia. Depicted is the so-called string of beads deformity of the cervical portion of the internal carotid artery, which is characteristic of medial fibroplasia.

In symptomatic patients with fibromuscular dysplasia, the carotid bifurcation may be exposed in the usual manner. If there is significant redundancy of the internal carotid artery, as documented by preoperative imaging, the artery should be mobilized relatively extensively so that it can be straightened by downward traction before intraluminal dilatation is begun. If, on the other hand, the artery is relatively straight, only minimal mobilization is required. It should be kept in mind that approximately 25% of patients with fibromuscular dysplasia have associated atherosclerotic disease of the carotid bifurcation that must be dealt with at the time of operation. In addition, about the same number of

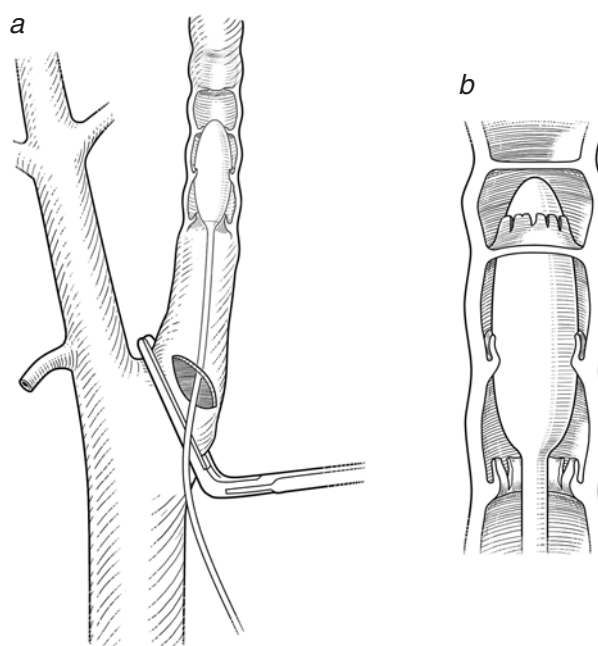


Figure 15 Carotid arterial procedures: repair of fibromuscular dysplasia. (a) The proximal portion of the internal carotid bulb is clamped, a transverse arteriotomy is made, and a coronary dilator is passed into the internal carotid artery and advanced up the vessel to the base of the skull. (b) The small septa in the internal carotid artery are disrupted by the advancing probe.

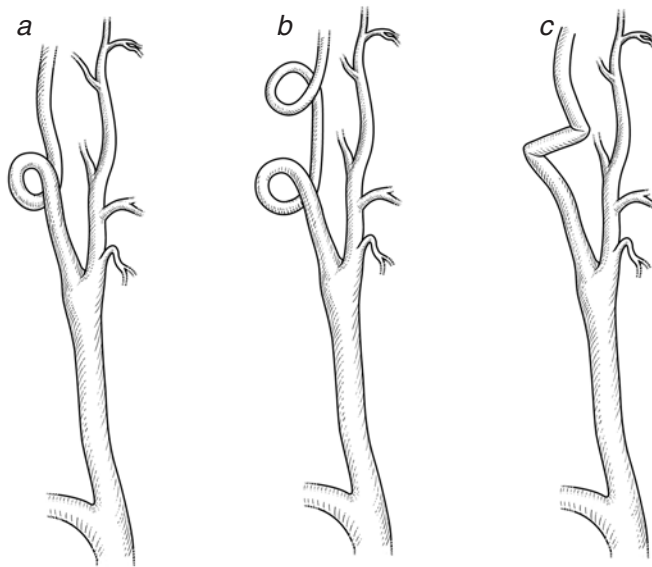


Figure 16 Carotid arterial procedures: repair of coiling or kinking of the internal carotid artery. (a, b) Redundancy of the internal carotid artery can result in one or more 360° coils in the vessel. (c) Degenerative atheromatous changes of the internal carotid artery can cause elongation with associated kinking or buckling.

patients have associated intracranial aneurysms that should be checked for by means of intracranial imaging studies.

Once the carotid bifurcation has been suitably mobilized and it has been established that no associated atheromatous plaque is present, a small transverse incision is made on the bulb of the internal carotid artery, with flow being maintained between the common and external carotid arteries. Serial intraluminal dilations are then performed with coronary artery dilators of progressively increasing diameter [see Figure 15]. The first dilator (usually 2.5 mm in diameter) is passed up the carotid artery to the base of the skull under digital control. The dilator is then withdrawn, and the artery is back-bled to flush out any fractured segments. The next larger dilator (3.0 mm in diameter) is passed in a similar fashion. Dilatation is repeated with progressively larger dilators (3.5, 4.0, and possibly 4.5 mm in diameter) to complete the procedure.

The transverse arteriotomy is closed with 6-0 polypropylene suture material and flow is reestablished. A completion angiogram verifies that the dysplastic segment is fully restored.

Coiling or kinking of internal carotid artery Redundancy of the internal carotid artery, often resulting in a 360° coil of the high cervical portion of the internal carotid artery, is usually thought to be developmental in origin [see Figure 16a]. Elongation of the internal carotid artery, which often results in kinking of the vessel, is believed to be related to the degenerative changes that occur with aging and atherosclerosis [see Figure 16b]. Both of these phenomena, in and of themselves, are usually asymptomatic; exceptions occur when an atheromatous plaque develops at the apex of the coil or when kinking of the internal carotid artery is accentuated with changes in head position in a patient who depends on relatively normal blood flow through that vessel. Redundancy of the internal carotid artery often becomes a technical consideration during standard surgical treatment of a carotid bifurcation atheroma. When redundancy occurs, it must be appropriately dealt with to prevent postoperative complications.

Anticipated redundancy of the internal carotid artery at the time of carotid bifurcation endarterectomy can usually be managed with

a patch angioplasty. Provided that the arteriotomy extends beyond the apex of the kink, the patch should smooth out the curvature of the redundant vessel and eliminate the kink. If it appears that internal carotid artery redundancy is greater than can be corrected by an elongated patch, then detachment of the internal carotid artery followed by eversion endarterectomy and reimplantation is indicated.

If the arteriotomy has already been closed when it becomes apparent that a kink is present, the problem may be dealt with by mobilizing the external carotid artery sufficiently and then resecting a segment of the common carotid artery and pulling down on the carotid bifurcation with a new end-to-end anastomosis to straighten the redundant internal carotid artery [see Figure 17]. Segmental resection of the internal carotid artery itself combined with end-to-end repair has also been described; this approach is less desirable, being more technically demanding and hence more subject to technical error.

Patients with coiling of the internal carotid artery may present a more difficult problem. If the atheromatous plaque involves only the first portion of the internal carotid artery and the vessel beyond that first portion is relatively normal up to the point where coiling begins, the surgeon can simply avoid the problem by leaving the smooth coil in place and not carrying out an extensive distal dissection. If, on the other hand, it appears that there may be plaque in the coil, then the entire coil must be dissected free, and the patient is left with a very redundant internal carotid artery that must be dealt with. Once again, the best method of managing the problem is to resect the redundant segment of the internal carotid artery, with or without eversion endarterectomy, and to reimplant the internal carotid artery onto the distal common carotid artery at the point of transection.

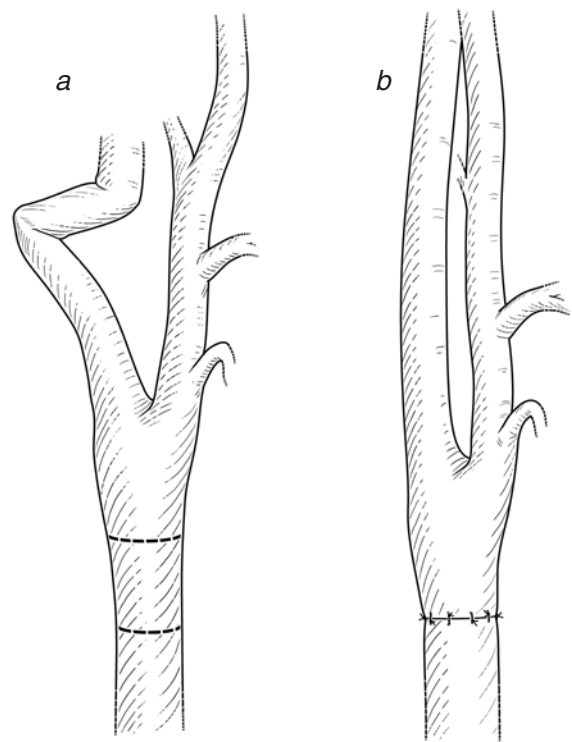


Figure 17 Carotid arterial procedures: repair of coiling or kinking of the internal carotid artery. Kinking or redundancy of the internal carotid artery can be managed by mobilizing the external carotid artery, then resecting a segment of the common carotid artery (a). The surgeon can then draw down the carotid bifurcation for a new primary anastomosis (b).

Upon completion of the reconstruction, a completion angiogram should be obtained to verify that the coiling or kinking has been adequately treated.

STEP 5: COMPLETION IMAGING

Given that the majority of neurologic complications after carotid artery surgery are attributable to technical error, it is imperative that the technical accuracy of the reconstruction be confirmed before the incision is closed and the patient is sent to the recovery room. There are two principal methods of determining the technical quality of the reconstruction: on-table angiography and direct-contact duplex scanning of the carotid artery. To perform either of these techniques routinely in all patients adds relatively little time to the surgical procedure and offers significant advantages to both the patient and the surgeon.^{11,12}

My preferred method of confirming the quality of the reconstruction is completion angiography using a C-arm with digital imaging. For this reason, the operation is done on a table that has angiographic capability, and the radiology technician and the equipment are called for at the beginning of the arteriotomy closure. A 10 ml syringe is connected to flexible tubing, and a 20-gauge needle is attached to the end of the tubing and bent at a 45° angle. Air bubbles are carefully evacuated from the tubing and the needle. Placing the needle into the artery or, in the case of a patched artery, into the midportion of the patch in a retrograde fashion will provide good stability for the needle, which lies in the lumen of the artery in an axial position. Once the C-arm is in place and the fluoroscopy unit turned on, the contrast material is injected by hand. The resulting image of the carotid bifurcation can be continuously replayed until maximal radiographic opacity of the carotid bifurcation and the intracranial circulation has been attained. The image is then carefully inspected for defects at the end points in the internal and external carotid arteries.

Intimal defects in the internal carotid artery are unusual, though not rare. Defects in the external carotid artery are more common because the endarterectomy is essentially done in a blind or closed manner. Defects in the external carotid artery are matters of concern because they may lead to thrombus formation in this vessel; if the thrombus propagates proximally, it may embolize up the internal carotid artery and cause a stroke.¹³ For this reason, if a defect is found in the external carotid artery, it is repaired at the time of the operation. To accomplish the repair, clamps are placed on the external carotid artery proximally at its origin and distally beyond the intimal flap. A transverse arteriotomy is made in the external carotid artery to permit identification and removal of the intimal flap. Once the flap has been carefully removed, the transverse arteriotomy is closed with two or three interrupted 6-0 polypropylene sutures and flow is restored.

Completion angiography also has the advantage of permitting the surgeon to image the intracranial circulation. Now that many operations are being performed on the basis of preoperative carotid duplex scanning, intracranial imaging is typically unavailable beforehand, which means that the status of the intracranial circulation with respect to atherosclerotic lesions in the area of the siphon or the middle cerebral artery or with respect to intracranial aneurysms is usually unknown at the start of the procedure. A completion angiogram gives the surgeon the opportunity to rule out these lesions by looking not only at the area around the reconstruction but also at the intracranial circulation.

An alternative to completion angiography is intraoperative DUS. DUS can be a highly satisfactory way of examining the area of reconstruction, provided that the operating room has duplex scanning capability and that a technologist is available to operate

the equipment. Standard B-mode imaging, in conjunction with Doppler ultrasonography, can accurately identify patent or compromised internal and external carotid arteries.

Once the surgeon has confirmed that a good technical reconstruction has been achieved, preparations can be made for closure.

STEP 6: CLOSURE

The dissected area around the reconstructed carotid artery is carefully irrigated with an antibiotic solution, and the wound is meticulously inspected for hemostasis. Even when good hemostasis has been achieved, it is my practice to place a drain overnight—specifically, a 7.0 mm Jackson-Pratt drain brought out through a small separate stab wound. The platysmal layer is closed with a continuous 3-0 absorbable suture, and the skin is closed with a continuous 4-0 subcuticular absorbable suture. A clear adhesive plastic dressing is applied to the skin, and the patient is sent to the recovery room.

Postoperative Care

The main patient variables to be evaluated in the postoperative period are neurologic status, blood pressure, and wound stability.

On awakening from anesthesia, the patient is carefully observed with a view to determining gross cerebral function on the basis of response to commands and movement of extremities. When the patient is fully awake, vagus nerve and hypoglossal nerve function can be tested.

Blood pressure monitoring is of critical importance after CEA. It is essential first to decide on an acceptable blood pressure range for the patient and then to ensure that this pressure is maintained: neither hypertension nor hypotension is acceptable. Patients with severe carotid bifurcation disease who have undergone CEA temporarily lose autoregulation on the side of the operation; therefore, hypertension can result in reperfusion injury to that side of the brain, ranging all the way from simple headache to fatal intracerebral hemorrhage.

The surgical site should be carefully observed for possible wound expansion resulting from hematoma formation. Even when good hemostasis is achieved and a drain is in place, there is still the possibility of delayed bleeding leading to hematoma and airway compromise. If an expanding hematoma is noted, the safest response is to return the patient to the OR so that the hematoma can be evacuated and a bleeding site sought. The earlier this is done, the better.

If the patient is neurologically intact, blood pressure is well controlled, and there is no evidence of an expanding hematoma, then the remaining postoperative care can be provided in a regular hospital room. It is seldom necessary to observe the patient in the intensive care unit, as was once standard practice.

Follow-up

Periodic follow-up examination is essential. There are two major areas of concern: (1) the possibility of recurrent stenosis on the side that was operated on and (2) the possibility of disease developing or progressing in the contralateral carotid artery. It is my practice to see the patient approximately 3 weeks after CEA. In that visit, the patient is examined for quality of wound healing and the presence or absence of a carotid bruit on both the operated side and the contralateral side, and a carotid duplex scan is performed. If at this time there are no grounds for concern about the contralateral side, scanning is done only on the side of the operation. The scan serves to establish the new baseline and confirms that the carotid reconstruc-

tion is satisfactory. The new baseline is then used as the basis for assessing patient status during subsequent follow-up.

The next patient visit takes place 6 months after operation, at which time a bilateral carotid duplex scan is performed. If the operated side continues to be normal and there are no major problems on the contralateral side, the patient is seen again at the 1-year anniversary of the procedure. If examinations yield satisfactory results at this time, the patient may thereafter be seen at 1-year intervals, with bilateral carotid duplex scanning done at each visit.

Alternatives to Direct Carotid Reconstruction

Carotid angioplasty with stenting (CAS) has been investigated as a therapeutic alternative to CEA for carotid artery stenosis [see 6:10 *Carotid Angioplasty and Stenting*]. In the Wallstent trial (an industry-supported prospective, randomized study), patients with stenosis of 60% to 99%, which was angiographically confirmed according to the North American method of measurement, were randomly assigned to undergo either CAS or CEA.¹⁴ Initially, it was proposed that the study would include 700 patients with symptomatic lesions; however, the trial was stopped by the safety-monitoring committee after 219 patients were randomized. The results were reported at the 26th International Stroke Conference in February 2001.

Of the 219 patients, 107 were entered into the CAS arm and 112 into the CEA arm. Patients were well matched with respect to age, gender, symptoms, degree of stenosis, and median follow-up. The primary end point was ipsilateral stroke, procedure-related death, or vascular death within 1 year. At approximately 1 year, the primary end-point rate was 12.1% in the CAS group and 3.6% in the CEA group. The 30-day stroke morbidity and mortality was 12.1% in the CAS group and 4.5% in the CEA group. Upon cessation of the study, the investigators concluded that CAS was not equivalent to CEA for treatment of symptomatic carotid stenosis.

In the SAPHIRE (Stenting and Angioplasty with Protection in Patients at High-Risk for Endarterectomy) trial, which was also an industry-sponsored study, CAS with the use of a cerebral antiembolism device was compared with CEA.¹⁵ Nonrandomized patients were entered into either a stent registry or a surgical reg-

istry, but the important part of the study was a randomized, multicenter trial involving 307 patients at 29 investigational sites. Of these 307 patients, 156 were entered into the CAS–cerebral protection arm and 151 into the CEA arm. The primary end points were (1) death, any stroke, or nonfatal myocardial infarction (MI) within 30 days after the procedure and (2) 30-day major morbidity plus death and ipsilateral stroke between 31 days and 12 months after the procedure. Secondary end points included (1) patency (defined by restenosis < 50%), (2) disabling stroke between 30 days and 6 months, and (3) a composite of major adverse clinical events at 6 months, 1 year, 2 years, and 3 years.

At 30 days, there were no statistically significant differences between the two study arms when the individual parameters—death, stroke, and nonfatal MI—were considered separately. When these events were viewed in the aggregate, their composite incidence was 5.8% in the CAS–cerebral protection group and 12.6% in the CEA group. When death and stroke were considered together, however, the incidence was 4.5% in the CAS–cerebral protection group and 6.6% in the CEA group. Thus, it is apparent that the major benefit of CAS over CEA lies in reducing the incidence of nonfatal MI.

In November 2006, the results of a large French trial that compared CAS with CEA in good-risk symptomatic patients were published.¹⁶ The study design called for the prospective randomization of 872 patients so as to yield a statistical power of 80%, the aim being to determine whether CAS was not inferior to CEA. After the inclusion of 527 patients, the trial was stopped prematurely for reasons of unsafety and futility. The 30-day incidence of any stroke or death was 3.9% after CEA and 9.6% after CAS. At 6 months, the incidence of stroke or death was 6.1% after CEA and 11.7% after CAS.¹⁶

On the basis of the evidence accumulated to date, the Medicare guidelines are still appropriate. CAS is indicated only for (1) symptomatic patients in whom CEA, in the opinion of a vascular surgeon, poses unacceptable risks or (2) patients who are willing to participate in an approved clinical trial (e.g., CREST [Carotid Revascularization Endarterectomy versus Stenting Trial]). CEA remains the treatment of choice for patients with suitable lesions of the carotid bifurcation.

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Figures 1 through 17 Tom Moore.

10 CAROTID ANGIOPLASTY AND STENTING

Mark K. Eskandari, MD, FACS

Choice between Carotid Endarterectomy and Carotid Angioplasty and Stenting

OPERATIVE RISK AND PATIENT SELECTION

For most patients with high-grade carotid lesions, whether symptomatic or asymptomatic, surgical endarterectomy [see 6:9 *Surgical Treatment of Carotid Artery Disease*], rather than best medical therapy (i.e., risk factor reduction and antiplatelet agents), is the treatment of choice for stroke prophylaxis, as the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the Asymptomatic Carotid Atherosclerosis Study (ACAS) have shown.¹⁻³ In NASCET, the risk of disabling stroke or death after carotid endarterectomy (CEA) was 1.9%, and the risk of minor stroke was 3.9%. In ACAS, the risk of major stroke or death was 0.6% when the 1.2% risk of stroke caused by diagnostic arteriography was excluded. These findings have led to the performance of CEA in increasing numbers of patients.

In the past few years, however, despite the proven efficacy of CEA in preventing ischemic stroke, great interest has been generated in carotid angioplasty and stenting (CAS) as an alternative to surgical therapy, and CEA has again come under attack.⁴ Proponents of CAS have suggested that the results of NASCET and ACAS are not achievable in general practice outside selected centers of excellence. Both ACAS and NASCET included patients who were determined to be good operative risks on the basis of reasonable life expectancy (so that they would be available for follow-up) and the absence of other potential causes of stroke (e.g., atrial fibrillation) [see Table 1].

A number of investigators have examined the results of CEA in high-risk subsets, albeit using several different ways of defining high risk [see Table 2 and Table 3].⁵⁻⁸ In one study, involving 776 consecutive CEAs performed at the Mayo Clinic in Rochester, Minnesota, procedures were categorized as high risk according to the patient inclusion and exclusion criteria employed by the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial of CAS with cerebral embolic protection.⁷ Of the 776 CEAs, 323 (42%) were considered high risk. The clinical presentation was similar in the high-risk and low-risk groups. The overall postoperative stroke rate was 1.4% (symptomatic, 2.9%; asymptomatic, 0.9%), and there was no statistical difference in stroke rate between the high-risk group and the low-risk group. Patients at significantly increased stroke risk were those who underwent cervical radiation therapy, those who had class III or IV angina, those who were symptomatic

at presentation, and those who were 60 years of age or younger. Overall mortality was 0.3% (symptomatic, 0.5%; asymptomatic, 0.2%), and there was no significant difference between the high-risk group (0.6%) and the low-risk group (0.0%). Myocardial infarction (MI) was more frequent in the high-risk group (3.1%) than in the low-risk group (0.9%); notably, all of the MIs reported in this series were nontransmural (non-Q). A composite cluster of adverse clinical events (death, stroke, and MI) was more frequent in the symptomatic high-risk group (9.3% versus 1.6%) but not in the asymptomatic cohort. There was a trend toward a higher incidence of major cranial nerve injuries in patients with local risk factors (e.g., high carotid bifurcation, reoperation, and cervical radiation therapy) (4.6% versus 1.7%). The authors concluded that SAPPHIRE-eligible high-risk patients could undergo CEA with stroke and death rates that were well within accepted standards and that patients with local risk factors were at higher risk for cranial nerve injuries but not necessarily for stroke. These conclusions call into question the application of CAS as an alternative to CEA, even in high-risk patients.

Although these studies do not support the premise that operative risk is higher in patients who would be excluded by NASCET and ACAS criteria, there may, in fact, be categories of patients for whom CEA is not optimal therapy. A 2001 study from the Cleveland Clinic attempted to identify a subgroup of patients who, on retrospective analysis, were at increased risk for CEA and therefore might be better served by CAS.⁸ A total of 3,061 CEAs were examined from a prospective database covering a 10-year period. A high-risk cohort was identified on the basis of the presence of severe coronary artery disease, a history of congestive heart failure (CHF), the presence of severe chronic obstructive pulmonary disease (COPD), or the development of renal insufficiency [see Table 2]. For the composite end point of stroke, death, and MI, the rate was 3.8% in the group as a whole (stroke, 2.1%; MI, 1.2%; death, 1.1%); however, the rate was 7.4% in high-risk patients, compared with only 2.9% in low-risk patients. High-risk patients were further subdivided into those who underwent CEA alone and those who underwent CEA combined with coronary artery bypass grafting (CABG). Not surprisingly, the incidence of the composite end point was greater in the latter subgroup than in the former. Among patients who underwent CEA alone, the risk of death was significantly greater in the high-risk group. Notably, although the risk of the combined end point was greater in the high-risk group, the difference was not statistically significant. In addition, the rates of the individual end points of MI and

Table 1 High-Risk Carotid Endarterectomy as Defined by Major Exclusion Criteria for NASCET and ACAS

Study	Exclusion Criteria						
	Age	History	Comorbidities				Anatomic Criteria
			Cardiac	Pulmonary	Renal	Other	
NASCET ¹	> 79 yr	Contralateral CEA < 4 mo Major surgical procedure < 1 mo Stroke in evolution	Unstable angina Atrial fibrillation Valvular heart disease Symptomatic CHF MI < 6 mo	Pulmonary failure	Renal failure	Uncontrolled hypertension Uncontrolled diabetes mellitus Hepatic failure Cancer with < 50% chance of 5 yr survival	Previous ipsilateral CEA Tandem lesion > target stenosis
ACAS ²	> 79 yr	Major surgical procedure < 1 mo Stroke in evolution	Unstable angina Atrial fibrillation Valvular heart disease Symptomatic CHF	Pulmonary failure with impact on 5 yr survival	SCr > 3 mg/dL	> 180 mm Hg systolic BP, > 115 mm Hg diastolic BP Fasting glucose > 400 mg/dL Hepatic failure Cancer with < 50% chance of 5 yr survival Active ulcer disease Warfarin anticoagulation	Previous ipsilateral CEA Tandem lesion > target stenosis Cervical radiation treatment

ACAS = Asymptomatic Carotid Atherosclerosis Study; BP = blood pressure; CEA = carotid endarterectomy; CHF = chronic heart failure; MI = myocardial infarction; NASCET = North American Symptomatic Carotid Endarterectomy Trial; SCr = serum creatinine concentration.

stroke did not differ statistically between the high-risk group and the low-risk group.

These data appear to support the notion that the patients enrolled in the multicenter trials of CEA (i.e., NASCET and ACAS) were probably similar to the Cleveland Clinic's low-risk group and that the patients in the clinic's high-risk group might not have had such stellar outcomes if they had been included in those multicenter endarterectomy trials. Subsequent clinical investigations have therefore focused on medically compromised, high-risk patients who may benefit from alternatives to CEA (e.g., CAS).

INDICATIONS FOR CAS

The exact role of CAS remains in flux until the results from prospective randomized controlled trials such as the Carotid Revascularization Endarterectomy versus Stent Trial (CREST), Carotid and Vertebral Artery Transluminal Angioplasty Trial (CAVATAS-II), and Asymptomatic Carotid Stent Trial (ACT I) become available. Nevertheless, the basic indications for CAS are essentially the same as those for standard open CEA:

1. Asymptomatic lesions that fall within the high-grade stenosis (typically, 80 to 99%) range on duplex ultrasonography, which correlates with a stenosis of at least 60% on angiography [see 6:2 *Asymptomatic Carotid Bruit*]. Most clinical

trials of CAS in asymptomatic patients require an angiographic stenosis of at least 80% for study inclusion.

2. Symptomatic lesions (e.g., hemispheric transient ischemic attack, amaurosis fugax, or stroke with minimal residua) with a stenosis of at least 70% on angiography [see 6:1 *Stroke and Transient Ischemic Attack*]. Symptomatic patients who have greater than 50% stenoses with ulceration may benefit from endarterectomy; however, this finding has not yet been extrapolated to carotid intervention.

Additionally, use of an embolic protection device (EPD) in conjunction with the procedure is strongly advocated. Reasonable criteria for patients at increased risk for CEA have been developed, and these criteria may serve as a general guide for those embarking on a program of carotid stenting [see Table 3]. Relative contraindications to CAS have also been determined [see Table 4]. CAS should be performed by physicians with a thorough knowledge of the pathophysiology and natural history of carotid disease and by those with current expertise in peripheral, cardiac, or neurointerventional procedures. If a physician is unable to participate in Food and Drug Administration (FDA)-approved trials, the procedure should be performed as part of a local Institutional Review Board-approved protocol with dispassionate oversight, independent preprocedural and postprocedural neurologic examinations, and prospective case review. In addition,

Table 2 High-Risk Carotid Endarterectomy as Defined by Major Inclusion Criteria for Selected Studies

Study	Inclusion Criteria						Anatomic Criteria
	Age	History	Comorbidities				
			Cardiac	Pulmonary	Renal	Other	
Ouriel (2001) ⁸			PTCA or CABG < 6 mo History of CHF	Severe COPD	SCr > 3 mg/dL		
Jordan et al (2002) ⁶		Major vascular procedure < 1 mo	Coronary procedure < 1 mo CABG < 6 wk Angina NYHA class III or IV EF < 30% MI < 4 wk	FEV ₁ < 1 L Home oxygen			Previous ipsilateral CEA Cervical radiation treatment Contralateral carotid occlusion High cervical lesion Lesion below clavicle
Gasparis (2003) ⁵	80 yr		NYHA functional class III or IV Heart failure Canadian class III or IV CABG < 6 mo	Steroid dependence Oxygen dependence	SCr > 3 mg/dL		Previous ipsilateral CEA Cervical radiation treatment Contralateral carotid occlusion High cervical lesion
SAPPHIRE ⁷	> 80 yr		Open heart surgery < 6 wk MI < 4 wk Angina CCS class III or IV CHF class III or IV EF < 30% Abnormal cardiac stress test result				Previous ipsilateral CEA Severe tandem lesion Cervical radiation treatment Contralateral carotid occlusion High cervical lesion (at least C2) Lesion below clavicle Contralateral laryngeal palsy

CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; CEA = carotid endarterectomy; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; FEV₁ = forced expiratory volume in 1 second; MI = myocardial infarction; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty; SAPPHIRE = Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SCr = serum creatinine concentration.

development of a carotid stenting program may facilitate cooperation among the various specialists who may desire to participate in this high-profile arena. A team of experienced personnel should be assembled (including one or two physicians and a technician) to ensure patient safety, maximize exposure within a small cadre of operators, and avoid duplication of effort. All patients considered for CAS should have provided informed consent, should receive counseling regarding the risks and benefits vis-à-vis CEA and best medical therapy, and should possess a clear understanding of the

investigational nature of the procedure. In addition, patients must agree to regular and careful follow-up examinations.

Anatomic Considerations

A solid grasp of the anatomy of the cerebral circulation is crucial for the planning of CAS. Several anatomic considerations are particularly germane. The first important anatomic issue to address is the configuration of the aortic arch. With advancing age, the apex of the arch tends to become displaced

Table 3 Indications for Carotid Angioplasty and Stenting in High-Risk Patients

Severe cardiac disease
Requirement for PTCA or CABG
History of CHF
Severe chronic obstructive pulmonary disease
Requirement for home oxygen
FEV ₁ < 20% of predicted
Severe chronic renal insufficiency
Serum creatinine concentration > 3.0 mg/dL
Patient currently on dialysis
Previous CEA (restenosis)
Contralateral vocal cord paralysis
Surgically inaccessible lesions
Lesion at or above C2
Lesion inferior to clavicle
Radiation-induced carotid stenosis
Previous ipsilateral radical neck dissection

CABG = coronary artery bypass graft; CEA = carotid endarterectomy; CHF = congestive heart failure; FEV₁ = forced expiratory volume in 1 second; PTCA = percutaneous transluminal coronary angioplasty.

Table 4 Limitations of and Contraindications to Carotid Angioplasty and Stenting

Inability to obtain femoral artery access
Unfavorable aortic arch anatomy
Severe tortuosity of CCA or ICA
Severely calcified or undilatable stenoses
Lesions containing fresh thrombus
Large amount of laminated thrombus at site of patch angioplasty (previous CEA) on duplex ultrasonography
Extensive stenoses (> 2 cm)
Critical (99%) stenoses
Lesions adjacent to carotid artery aneurysms
Contrast-related issues
Chronic renal insufficiency
Previous life-threatening contrast reaction
Preload-dependent states (e.g., severe aortic valvular stenosis)

CCA = common carotid artery; CEA = carotid endarterectomy; ICA = internal carotid artery.

further distally. This displacement makes selective catheterization of the brachiocephalic vessels more challenging and influences the choice of a catheter. The interventionalist should become familiar with a variety of selective catheters, both simple curved (i.e., vertebral, Davis, headhunter) and complex curved (i.e., Simmons, Vitek). As the level of the vessel's origin becomes farther from the dome of the arch, the task of obtaining guide-wire and sheath access becomes more difficult. Cannulation of a left common carotid artery (CCA) arising from a common brachiocephalic trunk (bovine arch) may be particularly difficult to accomplish [see Figure 1].



Figure 1 Arch aortogram in a left anterior oblique projection demonstrating a bovine arch configuration with the left common carotid artery arising as a branch from the innominate artery.

Problematic arch configurations should be identified on preprocedural contrast studies or magnetic resonance angiography (MRA) of the aorta. Especially at the beginning of an operator's experience with these interventions, a complete study that includes the aortic arch and the origins of the brachiocephalic trunks is essential.

Another important issue is the presence of any tandem lesions along the course of the cerebral circulation. If a proximal CCA lesion is present, intervention may be required before revascularization of the internal carotid artery (ICA) to provide safe access to the ICA. A third concern is the tortuosity of the ICA. Fortunately, most ICAs are relatively straight; however, some patients do have extremely tortuous ICAs, which may preclude safe passage of a guide wire or EPD and thus render safe intervention impossible. The anatomic configuration of the external carotid artery (ECA) typically is not an important consideration in carotid intervention, even when this vessel is affected by stenosis of iatrogenic origin or is covered with a bare stent.

Finally, the collateral circulation (or lack thereof) through the circle of Willis is an important consideration that may profoundly influence procedural strategy. The status of the contralateral ICA, the vertebrobasilar system, and the intracranial

collaterals may affect the type of embolic protection to be used. Anatomic variations in the circle of Willis are actually the rule rather than the exception: a complete circle is present in fewer than 50% of all cases. Common variations include a hypoplastic (10%) or absent A1 segment of the anterior cerebral artery and a plexiform (10 to 33%) or duplicated (18%) anterior communicating artery. Anomalies of the posterior portion of the circle of Willis, including a hypoplastic (33%) or absent posterior communicating artery, occur in about 50% of all cases. During preprocedural angiography or intracranial MRA, careful attention should be paid to the anterior and posterior communicating arteries. Patients with limited collateral circulation may exhibit reversible neurologic symptoms during inflation of a protective balloon or angioplasty of the target lesion.⁹ They may also be at higher risk for permanent neurologic deficits because their limited collateral blood supply is less likely to be able to compensate for any iatrogenic arterial occlusions that may complicate the procedure.

CEREBRAL PROTECTION

Ischemic stroke remains the most devastating complication of procedures directed at the extracranial carotid artery, whether open or endovascular. A number of different causes of stroke have been described, but the majority of strokes are attributable to cerebral embolization of atheromatous debris or thrombus. Even when cerebral emboli do not produce a major stroke, they may cause substantial cognitive impairment. A prospective study of 100 patients monitored with transcranial Doppler ultrasonography (TCD) during CEA found that microemboli were detected during 92% of procedures.¹⁰ Although most of the emboli were air emboli (and were not associated with adverse clinical events), there were more than 10 particulate emboli whose presence was correlated with significant deterioration of postoperative cognitive function.

A subsequent study evaluated 70 patients who underwent cardiac surgery with cardiopulmonary bypass, measuring cognitive function at 1 week, 2 months, and 6 months after operation; elderly patients who underwent urologic surgery served as the control group.¹¹ TCD detected more than 200 emboli in 40 patients, principally during aortic clamping and release, when bypass was initiated, and during defibrillation. Emboli were associated with significant memory loss. In addition, cognitive function deteriorated more in the study group than in the control group, although it recovered by 2 months after operation.

A study using a rat model examined the effect of atheroemboli of varying sizes on neuronal cell death.¹² The animals exposed to particles less than 200 μm in diameter showed no evidence of brain injury at 1 and 3 days, whereas those exposed to particles between 200 and 500 μm showed a scattered pattern of neuronal cell death at necropsy. At 7 days after embolization, however, both groups showed evidence of cell death. These findings suggest that whereas the brain may have a substantial tolerance for small emboli in the acute setting, even particles smaller than 200 μm may cause neuronal ischemia at a later point.

Angioplasty and Carotid Embolization

Various studies have assessed the embolic potential of carotid plaques in ex vivo models. One such study, which used specimens of human atherosclerotic plaque in a flow

chamber to model CAS, found that substantial numbers of particles were released from the lesions during angioplasty and that most of these particles were captured by an experimental filter device.¹³ The filter device itself produced very few particles, thanks to its low crossing profile.

A subsequent study also addressed the embolic potential of human carotid plaques during experimental angioplasty.¹⁴ An average of 133 emboli per angioplasty were measured, and there was a positive correlation between lesion severity and the maximum size of the embolic particles. A notable finding was that patients who had been placed on statin therapy more than 4 weeks before operation had significantly fewer and smaller emboli.

A clinical study that employed a distal balloon occlusion system during CAS found that the median number of particles, their maximum diameter, and their maximum area were all significantly higher in patients with periprocedural neurologic complications.¹⁵ Three procedural steps are associated with an increased risk of embolization: predilation, stent deployment, and postdilation [see Operative Technique, Steps 7, 8, and 9, *below*].¹⁶

Devices for Cerebral Embolic Protection

The use of embolic protection in large numbers of patients has been described with respect to the coronary vascular bed, where interventional procedures performed on diseased aorto-coronary saphenous vein grafts carry a 20% risk of periprocedural complications, largely related to distal embolization of atheromatous debris. The Saphenous vein graft Angioplasty Free of Emboli Randomized (SAFER) trial was the first multicenter randomized study to evaluate the use of distal embolic protection during saphenous vein graft interventions.¹⁷ Of the 801 eligible patients, 406 were randomly assigned to angioplasty and stenting with distal balloon protection and 395 to angioplasty and stenting over a conventional guide wire. The composite primary end point (death, MI, emergency coronary bypass, target lesion revascularization) was reached in 16.5% of the control group and 9.6% of the study group; the differences between the two groups were largely driven by decreases in MI and distal embolization. These dramatic results suggest that patients with lesions of high embolic potential (e.g., those at the carotid bifurcation) may benefit from some type of embolic protection. A 2000 study using an ex vivo model of angioplasty confirmed the findings of other investigators that emboli occur at several stages of carotid intervention and stressed that cerebral protection techniques should be effective from the earliest stages of the procedure.¹⁸

Three types of EPD have been developed: (1) distal balloon occlusion, (2) distal filter protection, and (3) proximal balloon occlusion with or without flow reversal.¹⁹ Currently, only the distal filtration devices have FDA approval for use in conjunction with CAS, whereas the other categories are available only for use in CAS as part of an FDA-approved clinical trial or as an “off-label” application of a device approved for noncarotid use. A 1987 study was the first to report on the use of an angioplasty technique involving temporary occlusion of the ICA during manipulation of ulcerated plaques.²⁰ The same investigators subsequently reported on the use of a triple-coaxial catheter system for angioplasty with cerebral protection in 13 patients²¹; cholesterol crystals ranging in size from 600 to 1,200 μm were aspirated at the time

of intervention. The PercuSurge GuardWire (Medtronic AVE, Santa Rosa, California), which is approved for aorto-coronary saphenous vein graft intervention, has been used in the MAVERIC trial of carotid intervention and has been employed extensively for off-label carotid intervention outside FDA-approved clinical trials [see Figure 2]. The advantages of this device include its low profile (which allows it to cross the target lesion easily), its procedural simplicity, and its ability to aspirate large debris particles after intervention. The disadvantages include the potential for incomplete occlusion of the ICA in patients with particularly large arteries (because the device can be inflated only from 3 to 6 mm in diameter) and the device's inability to aspirate exceptionally large particles into the suction catheter after intervention.¹⁵ In addition, as flow is diverted into the ECA, emboli may travel by this route and into the ipsilateral middle cerebral artery via periorbital and ophthalmic artery collaterals.²² Finally, a small percentage of patients with an incomplete circle of Willis and an isolated cerebral hemisphere may be intolerant of even temporary ICA occlusion.⁹ A 2002 study that evaluated the PercuSurge device in 75 CAS procedures found that four patients (5%) experienced transient neurologic symptoms during balloon occlusion that resolved with deflation and restoration of internal carotid flow.²³ Embolic material was aspirated from the ICA in all patients; no patients had suffered major or minor stroke at 30 days after the intervention.

Filter protection devices have been the object of a great deal of interest in the past few years. Such devices are designed to be able to trap large particulate debris while maintaining flow in the ICA, thereby not only providing continued cerebral perfusion during intervention but also allowing angiography of the target vessel during various phases of the procedure. All of the currently available filters have pores larger than 100 μ m, which means that they allow passage of smaller particles that may not cause clinically significant neurologic events but may nonetheless cause silent neuronal injury. These filters also have higher physical profiles than balloon occlusion devices and thus may be difficult to pass across particularly severe stenoses. Filters that are not completely apposed to the vessel wall may allow emboli to pass around the device and into the distal cerebral circulation. A 2001 study described CAS performed in 86 lesions with three different filter devices.²⁴ In three cases, the filter could not be advanced across the lesion. However, more than half of the successfully deployed filters contained macroscopic embolic material, and only one patient (1.2%) experienced a neurologic complication (a minor stroke).

Finally, a device has been developed that induces reversal of flow in the ICA through balloon occlusion of the CCA and the ECA and creation of a temporary arteriovenous shunt between the ICA and the femoral vein.²⁵ This device, although potentially more cumbersome than other protection devices, may produce virtually complete protection by preventing any emboli from traveling to the intracranial circulation.

The evidence accumulated to date suggests that most, if not all, CAS procedures should be performed with a cerebral EPD. In time, more such devices will be approved by the FDA and will be available outside the setting of clinical trials.

Preoperative Evaluation

For those with limited experience in carotid intervention, diagnostic angiography of the arch, the carotid arteries, and the cerebral arteries (done well in advance of the proposed intervention) is suggested; high-quality MRA or computed tomographic angiography (CTA) that includes the aortic arch is an acceptable substitute. This measure allows the interventionalist to make a careful, unhurried evaluation of the aortic arch and the brachiocephalic origins, which is essential for determining the ease or difficulty of sheath or guide access to the CCAs—an issue that has a direct bearing on the success of the procedure. If the brachiocephalic trunk (i.e., the innominate artery) or the left CCA originates in a location more than two CCA diameters (approximately 2 cm) below the dome of the aortic arch, some difficulty with access should be anticipated. In addition, the length of the lesion, the maximum degree of stenosis, and the diameters of the CCA and the ICA can be determined by placing a radiopaque marker of known diameter in the field of view; ball bearings of progressively increasing diameter (2 through 7 mm) are ideal for this purpose. These measurements facilitate preprocedural selection of appropriately sized balloons and stents and make performance of the procedure smoother and more efficient, thereby serving the main goals of therapy—patient safety and exemplary results.

In all cases, a thorough history should be taken and a careful physical examination performed, with close attention paid to comorbid medical conditions and femoral pulses. A complete neurologic examination should be performed. In addition to preprocedural arteriography, CTA, MRA, or duplex ultrasonography should be performed in an accredited vascular laboratory—ideally, the same laboratory where the follow-up examinations will be performed. Patients typically receive aspirin, 325 mg daily for at least 1 week before the procedure, and clopidogrel, 75 mg daily for at least 3 days beforehand. All patients receive antibiotics (typically cefazolin, 1 g IV) immediately before the procedure.

Operative Planning

Regardless of the exact physical location at which the procedure is performed, access to high-quality imaging equipment is mandatory; portable C-arms are less than ideal for this purpose. Standard monitoring includes continuous electrocardiography, blood pressure, and pulse oximetry readings. Patients are placed in a supine position, and both groins are prepared. The head is placed in a cradle and gently secured to minimize patient motion during critical portions of the procedure. The procedure is generally performed with the patient awake, although minimal sedation is acceptable if the patient is particularly anxious.

Operative Technique

The technique of CAS has evolved over time. In its current iteration, the procedure is performed in the following steps, with few exceptions. Although it is, of course, essential to be able to adjust the technical approach to deal with unanticipated situations, it is nonetheless desirable to standardize the procedure as much as possible.

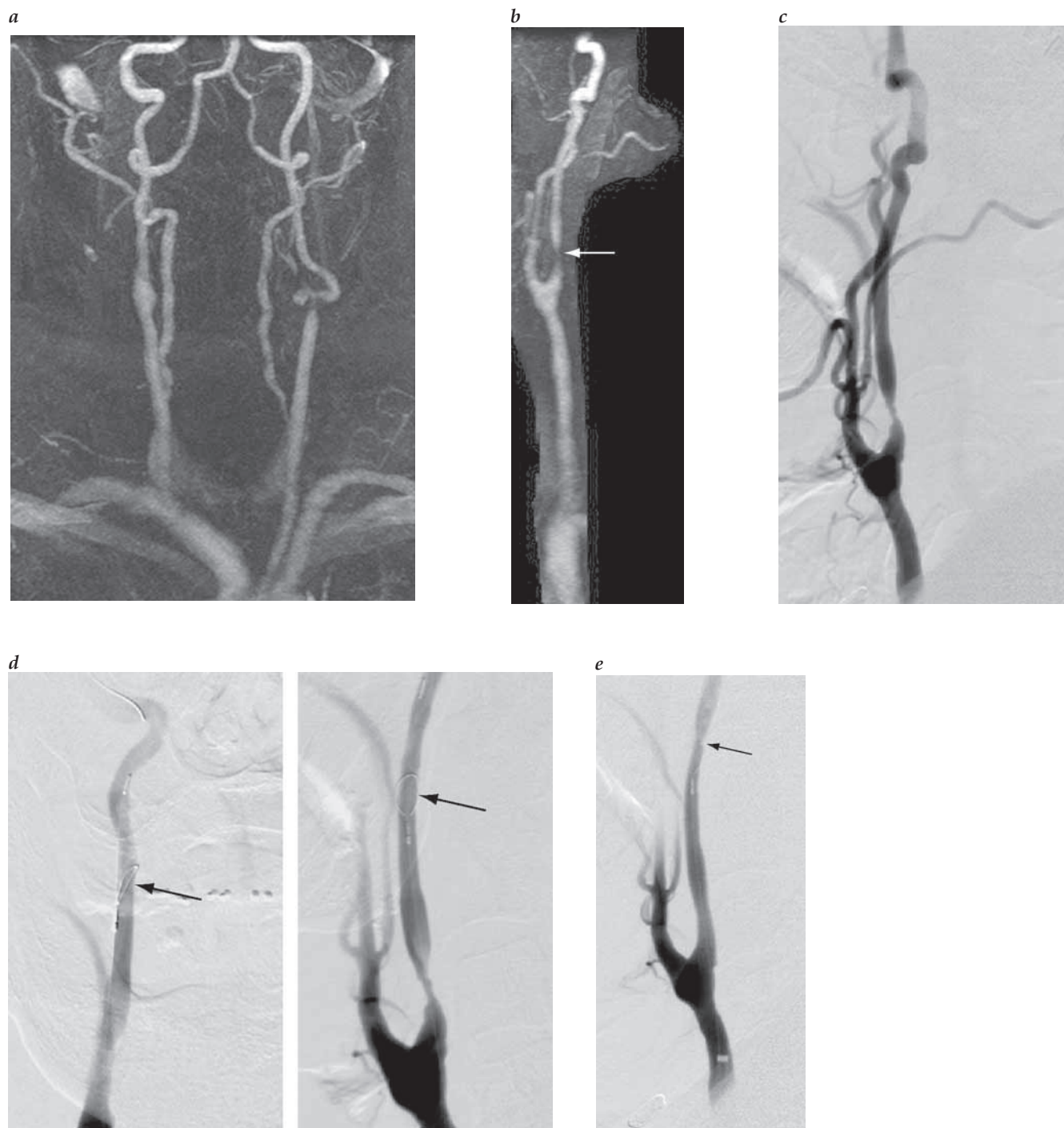


Figure 2 Carotid angioplasty and stenting. In this example, a filter device is used for cerebral protection. (a) Magnetic resonance angiography (MRA) shows aortic arch and cervical carotid and vertebral arteries. (b) MRA shows recurrent (postendarterectomy) high-grade stenosis of the right internal carotid artery (ICA). (c) Selective angiogram shows right carotid bifurcation. (d) FilterWire EX (Boston Scientific, Natick, Massachusetts) is deployed within the ICA; angiographic assessment is performed in two planes (left, right) to confirm adequate apposition of the filter to the vessel wall (arrows). (e) Shown is vessel after angioplasty and placement of a self-expanding nitinol stent. The sheath is properly positioned in the distal common carotid artery (star). Spasm may be seen at the site of the filter (arrow).

Basic principles of endovascular surgery are discussed more fully elsewhere [see 6:8 *Fundamentals of Endovascular Surgery*]; the following steps focus primarily on the procedural elements specific to CAS.

STEP 1: SECURING OF ARTERIAL ACCESS

Retrograde femoral access is obtained, and a 5 French sheath is inserted. Full heparin anticoagulation (typically 100 mg/kg body mass) is instituted after arterial access is secured and before manipulation of catheters in the aortic arch and the brachiocephalic vessels.

STEP 2: SELECTIVE CAROTID CATHETERIZATION AND ARTERIOGRAPHY

Selective catheterization of the aortic arch vessels is best performed after an arch aortogram in a left anterior oblique projection of 30 to 40 degrees. Although this will usually suffice, when cannulating the right CCA, sometimes it is helpful to image the innominate artery in a right anterior oblique projection. This will allow for a clear delineation of the innominate bifurcation [see Figure 3]. After selective catheterization of the midportion of the ipsilateral CCA (typically starting with a simple curved catheter), a selective arteriogram of the carotid bifurcation is obtained, with care taken to choose a view that yields minimal overlapping of the ICA and the ECA and maximal visualization of the target lesion. A cerebral arteriogram with at least anterior-posterior and lateral views, if not previously obtained, is obtained at this point to serve as a baseline and to identify any intracranial pathologic conditions (e.g., aneurysms and arteriovenous communications) that may be present.



Figure 3 Right anterior oblique angle angiogram of the right subclavian and common carotid arteries. Note stenosis in the proximal right common carotid artery and the ability to visualize the origins of the two vessels in this projection.

STEP 3: ADVANCEMENT OF SHEATH AND DILATOR INTO CCA

Two techniques have been employed to advance a sheath into the CCA. The first technique, which is most commonly employed, is to place an exchange-length 0.035-inch guide wire into the terminal branches of the ECA. The diagnostic catheter and the 5 French sheath are removed. Care should be taken to pay close attention to the tip of the stiff wire to ensure that it does not perforate or otherwise traumatize a branch of the ECA. Hematoma formation and airway compromise can be a devastating complication. Sometimes for an angulated CCA, a stiff wire will not successfully pass into the ECA. In these circumstances, the use of a 0.035-inch angled glide wire or stiff angled glide wire will facilitate passage of the diagnostic catheter into the ECA, which will then allow for introduction of stiff wire into the ECA. A long (70 to 90 cm length, depending on patient body habitus) 6 French sheath is then advanced, along with its dilator, into the CCA. Care must be taken to identify the tip of the dilator (which is not radiopaque) because it may extend a significant distance from the end of the sheath, depending on the brand of sheath used. Obviously, inadvertently advancing the dilator into the carotid bulb may have disastrous consequences. In patients with short CCAs or low bifurcations, the sheath can be advanced over the dilator once the sheath edge (a radiopaque marker) is past the origin of the CCA. Generally, the tip of the sheath should be positioned to within 2 cm of the target lesion.

The second technique, often referred to as the “telescoping technique,” is to advance the long sheath into the transverse arch over a guide wire. The dilator is removed, and an appropriate selective diagnostic catheter is advanced into the CCA. This catheter must be substantially longer than the sheath, typically more than 100 cm long. A stiff guide wire is then advanced into the ECA. Both the wire and the catheter are pinned at the groin to provide support, and the sheath (without the dilator) is advanced into the CCA. This technique may be advantageous in so-called hostile arches, in that the catheter and the wire provide more support than a wire alone would; however, without the protection of the sheath dilator, there is a risk of “snowplowing” the edge of the sheath at the junction of the aortic arch and the innominate artery or the left CCA, which can cause dissection or distal embolization. The Shuttle Select system by Cook Incorporated has a unified system to accommodate this approach.

The importance of gaining and maintaining sheath access to the distal CCA should not be underestimated: once the 0.035-inch guide wire is removed (and, eventually, exchanged for a 0.014-inch wire), support for angioplasty and stent placement is provided solely by the sheath. If the sheath backs up into the aortic arch during the interventional procedure, it is virtually impossible to advance it into the CCA over a 0.014-inch guide wire or protection device. Appropriate patient selection and accurate recognition of which arches to avoid are essential for success. In particularly difficult arches, deep inspiration or expiration may facilitate sheath advancement by subtly changing the configuration of the brachiocephalic origins once guide-wire access has been obtained. Alternatively, when a sheath cannot be advanced into the CCA, a preshaped guide catheter can be seated in the proximal CCA. Although this maneuver may facilitate an otherwise

impossible intervention, it should be kept in mind that guide catheters require a larger arterial puncture and provide a less stable support platform than sheaths do and should be used only if there is no other reasonable alternative [see Figure 4].

Troubleshooting

In patients with an occluded ECA, sheath access to the CCA may be difficult to obtain. Two techniques may be employed to overcome this difficulty. The first is to place a stiff 0.035-inch wire with a preshaped J into the distal CCA, taking care to avoid the bulb and the bifurcation. The J configuration keeps the guide wire from crossing the lesion. A stiff wire with a shapeable tip can be used to the same end.

The second technique is to use a variable-diameter wire (0.018 inches at the tip, enlarging to 0.035 inches more proximally) to cross the internal carotid lesion, providing additional guide-wire support to facilitate sheath advancement. This approach is a reasonable option, but it ultimately necessitates crossing the target lesion twice.

STEP 4: REMOVAL OF GUIDE WIRE AND DILATOR AND SELECTIVE ARTERIOGRAPHY OF CAROTID BIFURCATION

Once the sheath is in place, the guide wire and the dilator are removed. The sheath sidearm may be attached to a slow, continuous infusion of heparin-saline solution to keep blood



Figure 4 Selective left common carotid angiogram showing severe angulation (two 90° bends) of the proximal artery and a high-grade stenosis of the external carotid artery.

from stagnating in the sheath. Selective angiography of the carotid bifurcation is then performed through the sheath, again demonstrating the area of maximal stenosis, the extent of the lesion, and the normal ICA and CCA above and below the lesion. Roadmapping, if available, is helpful in crossing the lesion with an EPD or guide wire [see Step 6, below]. The overwhelming majority of procedures are performed with an EPD, typically a distal filter device [see Figure 5].

STEP 5: MEASUREMENT OF ACTIVATED CLOTTING TIME

It is advisable to measure the activated clotting time (ACT) before crossing the lesion and performing CAS. An ACT of 250 to 300 seconds is generally advised for most instances. The interventional team should discuss, in detail, all of the subsequent steps to be performed. Balloons are flushed and prepared, and special care should be taken to remove all air from the system as a protective measure against the unlikely event of balloon rupture [see Figure 6]. The self-expanding stent is opened and placed on the table, and the crossing guide wire or EPD is prepared.

STEP 6: DELIVERY OF EPD ACROSS TARGET LESION

After the target lesion has been clearly identified, the next step is to deliver the constrained filter element across the stenotic target lesion and into the distal normal ICA. If the constrained filter element does not pass because of the severity of stenosis, it may be best to abort the CAS procedure rather than dilate the lesion with a small balloon without distal protection to facilitate passage of the device. If the EPD does not advance beyond the lesion because of angulation of the vessel, the use of a “buddy wire” to straighten the vessel may be employed using a stiffer 0.014-inch wire [see Figure 7].

Troubleshooting

Rare complications of filter EPDs have been reported, including filter detachment, filter entanglement with the stent, and iatrogenic ICA dissection, but the more common occurrences are ICA spasm, filter thrombosis, and inability to retrieve the filter. One of the primary problems with distal EPDs when working over long distances—the femoral approach to the carotid artery—is minimizing movement of the filter during the CAS procedure [see Figure 8]. Newer filter delivery systems have addressed this to a certain degree by having the filter “free-floating” on a specific wire in the ICA, such as the Emboshield system (Abbott Vascular). Nevertheless, motion of the filter in the distal ICA can induce varying degrees of vasospasm, which may be severe enough to halt flow through the collapsed filter element. Fortunately, this can be easily remedied with an intra-arterial administration of nitroglycerin (100 µg) [see Figure 9]. In rare circumstances, vasospasm can be relieved only by removing the filter, but it is important to differentiate spasm from thrombosis of the filter.

Determining the causation for flow arrest at the level of the filter element can be challenging and anxiety provoking. Generally, it is either attributable to intense vasospasm or filter thrombosis. Whereas the former typically improves with nitroglycerin, the latter may require additional maneuvers. A first step is to redose systemic anticoagulation—heparin or angiomas—and recheck the ACT to ensure that it is greater

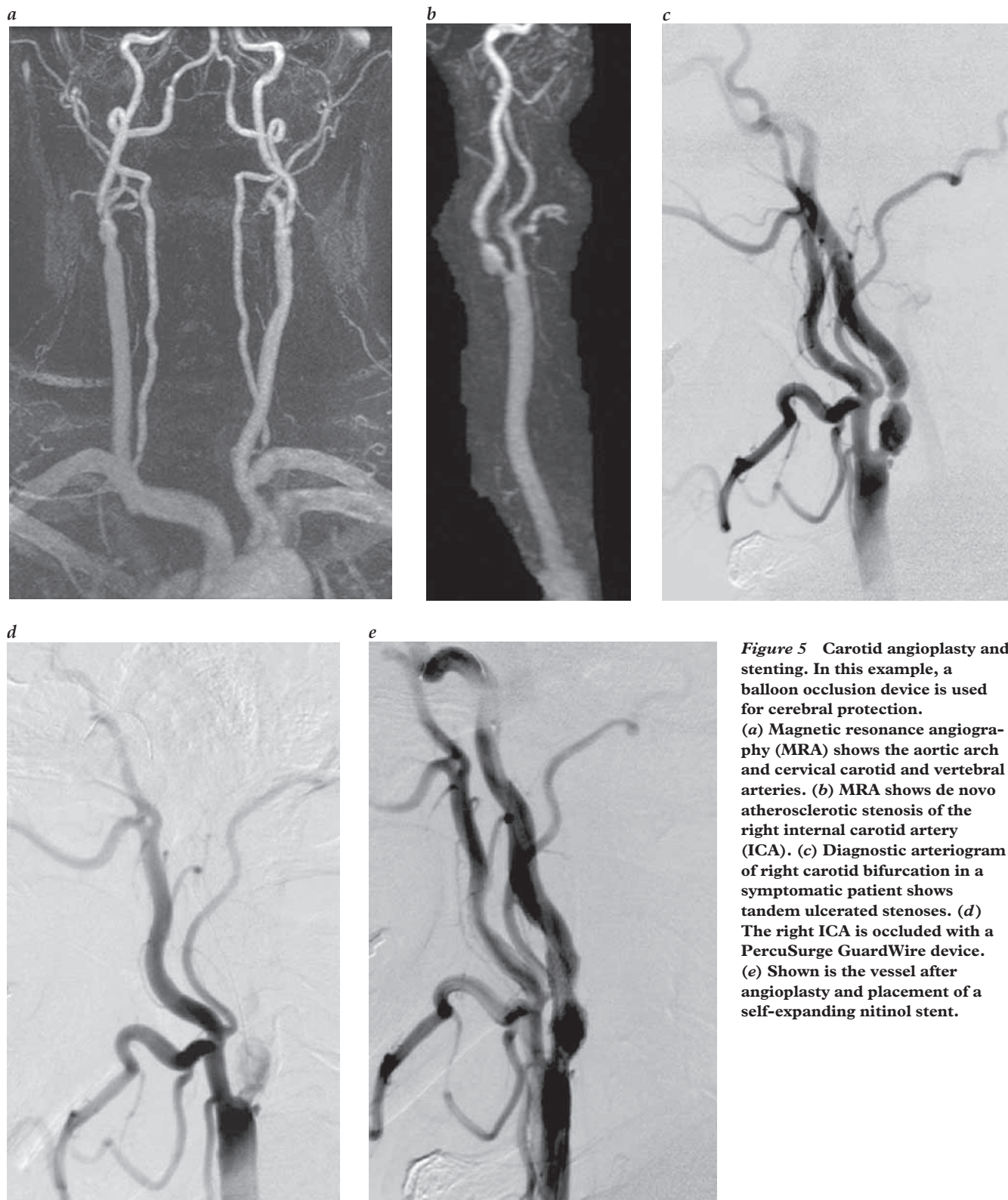


Figure 5 Carotid angioplasty and stenting. In this example, a balloon occlusion device is used for cerebral protection.

(a) Magnetic resonance angiography (MRA) shows the aortic arch and cervical carotid and vertebral arteries. (b) MRA shows de novo atherosclerotic stenosis of the right internal carotid artery (ICA). (c) Diagnostic arteriogram of right carotid bifurcation in a symptomatic patient shows tandem ulcerated stenoses. (d) The right ICA is occluded with a PercuSurge GuardWire device. (e) Shown is the vessel after angioplasty and placement of a self-expanding nitinol stent.

than 250 seconds. Next, try intra-arterial nitroglycerin. If these simple steps do not improve the flow, an attempt to aspirate captured debris from inside the filter basket should be made. Available devices to achieve this are the Pronto system (Vascular Solutions) and the Export catheter (Medtronic). After aspirating from the filter down into the

CCA with several passes and removal of at least 50 cc of blood, flow should be reassessed. If there is still no improvement, intra-arterial tissue plasminogen activator can be given. Once adequate flow is restored or if all else fails, the filter should then be removed. Luckily, this is an infrequent phenomenon.

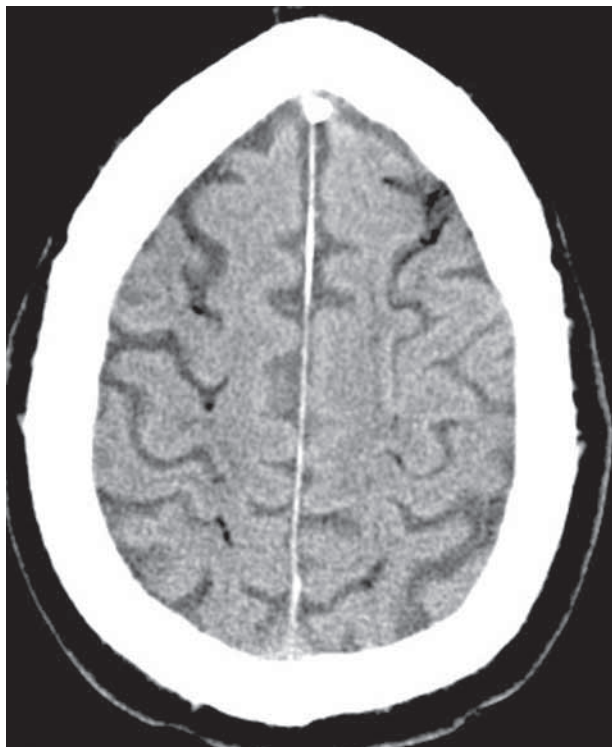


Figure 6 Noncontrast computed tomographic scan of the brain showing bihemispheric intracerebral air.

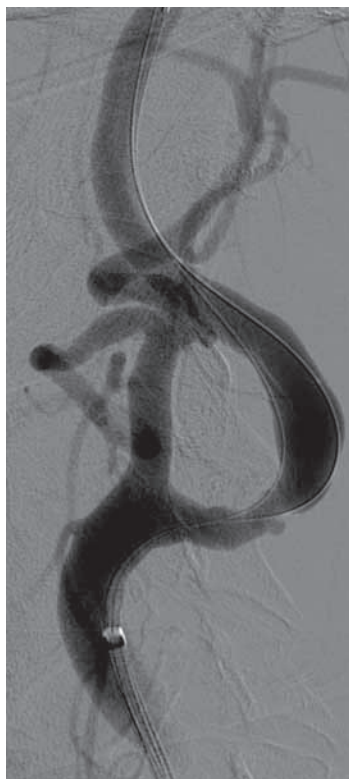


Figure 7 Use of the “buddy wire” technique to straighten out the carotid bifurcation and allow for delivery of the embolic protection device. Note the two 0.014-inch wires crossing the internal carotid artery lesion.



Figure 8 Deployed distal filter embolic protection device inadvertently pulled down across the target lesion.

STEP 7: PREDILATION OF LESION

After the EPD has been appropriately deployed in the distal ICA and flow through the filter element is confirmed, the offending lesion is predilated with a 3.5 to 4.0 × 20 mm angioplasty balloon, typically on a monorail or rapid-exchange platform. In most cases, the desired balloon profile can be achieved with relatively low inflation pressures (4 to 6 mm Hg). This balloon angioplasty to the target lesion is performed to allow for easy passage of the stent delivery system across the atherosclerotic plaque. Some data have shown that systemic administration of atropine (0.4 to 1.0 mg) given intravenously prior to balloon angioplasty of the carotid will minimize the effects on the baroreceptors and the clinic manifestation of profound bradycardia or asystole in de novo lesions.²⁶ After the predilation balloon is removed, another bifurcation angiogram is performed through the sheath to visualize the lesion and confirm continued unimpeded antegrade flow through the filter element.

STEP 8: DEPLOYMENT OF STENT

Once correct positioning has been confirmed, a self-expanding stent is deployed. The diameter of the stent is determined by the diameter of the largest portion of the vessel, which is typically the distal CCA (not the ICA). It is important that there be no unapposed stent in the CCA: any part of the stent that is not apposed to the vessel wall may become a nidus



Figure 9 (a) Carotid angiogram after initial angioplasty of the internal carotid artery lesion, showing flow arrest at the level of the embolic protection device (EPD). (b) Angiogram after the intra-arterial administration of nitroglycerin to alleviate the severe vasospasm induced by the indwelling EPD. Adequate antegrade flow has been restored through the EPD and the distal internal carotid artery.

for thrombus formation. The diameter of the unconstrained stent should be at least 10% (approximately 1 to 2 mm) larger than the maximum diameter of the CCA. On occasion, the lesion is limited to the ICA well above the carotid bifurcation; in such cases, a shorter stent confined to the ICA may be used. Current approved self-expanding stents for the carotid artery are either open or closed cell designs. The cell design confers scaffolding and flexibility to the stent such that a closed cell stent is generally more rigid than an open cell stent, but because the stent struts are all interconnected, “fish scaling”—or stent strut protrusion into the lumen—does not occur. Stents also are designed in tapered and nontapered configurations, with the goal of the former being better accommodation to the natural carotid bifurcation. Whether specific stent design systems confer an impact on clinical outcomes remains controversial today, but some speculate that closed cell stents may be associated with a lower periprocedural stroke risk in symptomatic patients treated with CAS.²⁷

There are other important points in regard to stent deployment for CAS: (1) a residual stenosis of 10 to 20% is not significant and is best left alone rather than overdilating the vessel; (2) remember that the lesion is longer than what is seen angiographically, so use a longer stent—30 or 40 mm lengths are most commonly used; (3) stenting across the origin of the ECA is very common and will not alter flow into the ECA in the vast majority of cases²⁸; and (4) when using a nontapered stent, size the stent according to the CCA so that the stent is not undersized and free-floating in the CCA.

STEP 9: POSTDILATION OF LESION

Generally, the stented lesion is then postdilated with a 5.0 to 5.5 mm × 20 mm balloon; larger balloons are rarely necessary. A residual stenosis of 10 to 20% or so is completely acceptable; the goal of the intervention is protection from embolic stroke, not necessarily a perfect angiographic result.

STEP 10: EPD RETRIEVAL

At the conclusion of the procedure, the filter element needs to be reconstrained and removed. Each manufacturer has a dedicated retrieval device to collapse the filter element and captured debris, which then can be pulled through the stented lesion and removed from the circulation. On occasion, inability to retrieve the filter element can occur because of vessel tortuosity or “fish scaling” of an open cell stent. Some manufacturers provide a catheter with a shapeable tip, whereas others use a tapered tip to allow easy passage through the stented segment. It is important to watch the tip as it passes through the stent to ensure that it does not catch a stent strut and deform the stent or pull down the filter basket. If the catheter does not pass unimpeded, torquing the catheter to alter the tip angle, having the patient turn the head, or advancing the sheath within the stented segment will usually allow the catheter to negotiate through angulated anatomy [see Figure 10].

STEP 11: COMPLETION ARTERIOGRAPHY

A completion angiogram of the carotid bulb and bifurcation and the distal extracranial ICA is obtained to verify that no dissection or occlusion has occurred. Severe vasospasm may be encountered (sometimes mimicking dissection); watchful waiting, coupled on occasion with administration of vasodilators through the sheath (e.g., nitroglycerin in 100 µg aliquots), usually resolves this problem. Completion angiography of the carotid bifurcation and intracranial circulation is performed in two views (anterior-posterior and lateral).

STEP 12: ACCESS-SITE HEMOSTASIS

Heparin anticoagulation typically is not reversed. Access-site hemostasis is achieved with a percutaneous closure device or manual compression.

Postoperative Care

After the procedure, the patient is monitored in the recovery area for approximately 30 minutes and then transferred to a monitored floor; admission to an intensive care unit generally is not necessary. In 2 to 3 hours, patients are allowed to ambulate if a closure device was used and are allowed to resume a regular diet. Some patients experience prolonged hypotension from carotid sinus stimulation; this problem can be managed with judicious fluid administration, pharmacologic treatment of bradycardia, and, occasionally, IV infusion of a vasopressor (e.g., dopamine). Rarely, a patient experiences prolonged hypotension that must be treated with an oral agent (e.g., phenylephrine or midodrine).

A duplex ultrasonogram is obtained within the first month of the procedure as a baseline study. Subsequent ultrasound examinations are performed at 6 month and then annually thereafter. Neurologic evaluation is performed according to the same schedule as the duplex

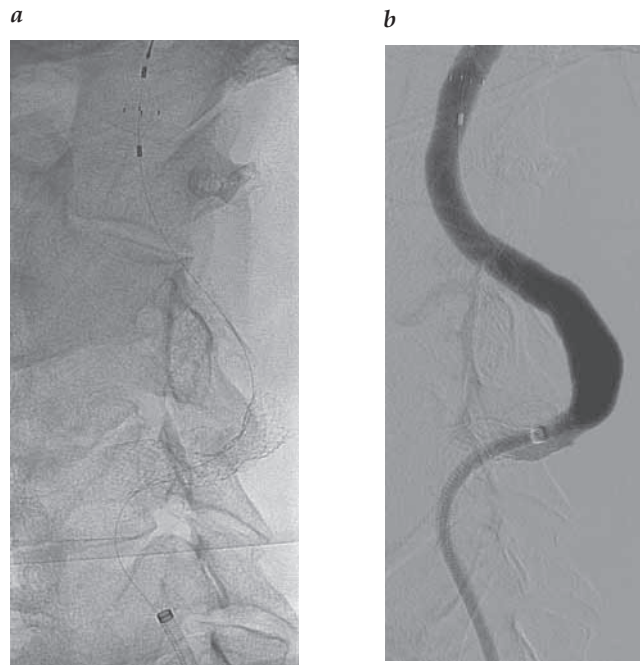


Figure 10 Severe angulation of the carotid bifurcation. (a) X-ray image showing the position of the stent and the distal filter element. (b) Advancement of the sheath over the wire and retrieval catheter were necessary to allow for the capture of the embolic protection device.

studies. Patients are treated with aspirin for life and with clopidogrel for 4 to 6 weeks.

As with CEA, proper patient selection, procedural standardization, and meticulous attention to detail are mandatory for a successful procedure, regardless of the exact technique used for CAS.

Outcome Evaluation

The short-term results of CAS depend largely on the presence or absence of cerebral embolization. It is therefore not surprising that the addition of cerebral protection to CAS appears to have reduced the stroke risk associated with the procedure. Admittedly, however, ongoing technological developments have created something of a moving target, making evaluation of the results of CAS difficult at best.

In a study from the University of Alabama at Birmingham and Lenox Hill Hospital in New York, 604 arteries were treated in 528 consecutive patients over a 5-year period.²⁹ CAS was performed both with balloon-expandable stents and with self-expanding stents and both with and without cerebral protection devices. The overall 30-day combined stroke-death rate was 8.1% (minor stroke, 5.5%; major stroke, 1.6%; nonneurologic death, 1%). On a year-by-year basis, the risk of stroke and death reached its maximum (12.5%) in the period ending in September 1997 and fell to its minimum (3.2%) the following year. This rather dramatic change in results from one year to the next probably is attributable to technical advances (e.g., in protection devices, stents, and guide wires), as well as to improvements in the investigators' ability to select appropriate patients for intervention.

A subsequent report describes the authors' experience with CAS in a vascular surgery practice.³⁰ During a 40-month period from 1997 to 2001, 135 procedures were performed in 132 patients, most (60%) of whom were asymptomatic. The rate of complications was acceptable (2%), and only one patient had a significant restenosis at follow-up (mean follow-up interval, 16 months). Perhaps more important, these 132 patients represented 41% of all patients being treated for carotid disease in this practice. This percentage seems extraordinarily high, but it may simply be a bellwether of things to come in the practice of vascular surgery, and it underscores the importance of multispecialty involvement in this new technology.

The results of the SAPHIRE trial of CAS in high-risk patients were published in 2004.³¹ To date, this trial, which included 334 patients randomly assigned to either CAS ($n = 167$) or CEA ($n = 167$), is the only industry-sponsored, FDA-approved trial that was actually randomized. A separate registry of nonrandomized patients was compiled that included those who were felt to be at unacceptably high risk for CEA and therefore underwent CAS ($n = 406$), as well as those who were not suitable candidates for CAS and therefore underwent CEA ($n = 7$). The goal of the SAPHIRE trial was to evaluate the combined end point of major adverse events (stroke, death, and MI). Patients were independently evaluated by a certified neurologist before and after the procedure. The majority of the randomized patients were asymptomatic: in the CAS group, only 30% were symptomatic, and in the CEA group, only 28% were symptomatic. A key point to keep in mind is that this trial was designed to test the idea that CAS was not inferior to CEA, not to establish that CAS was superior to CEA or CEA to CAS. At 30 days, the risk of stroke was not significantly different in the two groups (CAS, 3.6%; CEA 3.1%). Two patients in the CAS group (1.2%) and four patients in the CEA group (2.5%) died within 30 days; this difference did not reach statistical significance ($p = .39$). More patients experienced periprocedural MI in the CEA group (6.1%) than in the CAS group (2.4%), a difference that did not reach statistical significance on the basis of intent to treat. Notably, most of the MIs were non-Q MIs, identified by routine postprocedural laboratory studies. The incidence of the combined end point (stroke-death-MI) was higher in the CEA group (9.8%) than in the CAS group (4.8%), but this difference was statistically insignificant as well. These results have been used to support FDA approval of the stent and filter protection device used in this important study.

Detracting from the growing successful reported outcomes of CAS are two recent prospective randomized European studies evaluating the 30-day death and stroke rates among symptomatic patients treated with either CAS or CEA.^{32,33} The first one, Endarterectomy versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S), randomized 527 patients with symptomatic 60% or greater carotid stenosis. The investigators reported a 30-day combined stroke and death rate of 3.9% after CEA compared with 9.6% after CAS. Unfortunately, the conclusions of this study have been heavily criticized because of several flaws: (1) insufficient interventionalist training and experience, (2) lack of mandated periprocedural dual antiplatelet use for CAS, and (3) skewed institutional enrollment. Published in the same year were the results from the Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy

(SPACE) trial, which randomized 1,183 symptomatic patients with 50% or greater carotid stenosis. The reported 30-day ipsilateral stroke and death outcomes were 6.34% following CEA and 6.84% after CAS. Although this study is admirable because of the large number of patients enrolled and the rigorous oversight of both surgeons and interventionalists, two critical design flaws weaken the conclusions: (1) nearly 70% of CAS procedures were performed without the use of an EPD and (2) the category of carotid stenosis ($\geq 50\%$) was rather broad.

As it stands today, CAS with EPD is a useful option for the treatment of symptomatic carotid artery disease in a subset of

patients (i.e., recurrent carotid stenosis, prior external beam neck irradiation, class III or IV CHF, or difficult anatomic circumstances). What remains to be determined is the role of CAS in asymptomatic patients, standard-risk patients, and our growing elderly population.

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11 REPAIR OF INFRARENAL ABDOMINAL AORTIC ANEURYSMS

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An arterial aneurysm is defined as a permanent localized enlargement of an artery to a diameter more than 1.5 times its expected diameter. Aneurysms are classified according to morphology, etiology, and anatomic site. The most common morphology is a fusiform, symmetrical, circumferential enlargement that involves all layers of the arterial wall. A saccular morphology is also seen, in which aneurysmal degeneration affects only part of the arterial circumference.

The most common cause of an arterial aneurysm is atherosclerotic degeneration of the arterial wall. The pathogenesis is a multifactorial process involving genetic predisposition, aging, atherosclerosis, inflammation, and localized activation of proteolytic enzymes. Most aneurysms occur in elderly persons, and the prevalence rises with increasing age. Aneurysms also occur in genetically susceptible individuals with Ehlers-Danlos syndrome or Marfan syndrome. Other causes include tertiary syphilis and localized infection resulting in a mycotic aneurysm.

Aneurysms of the infrarenal aorta are by far the most common arterial aneurysms encountered in clinical practice today: they are three to seven times more common than thoracic aneurysms and affect four times as many men as women.¹ Abdominal aortic aneurysms (AAAs) have a tendency to enlarge and rupture, causing death. In the United States, AAAs result in approximately 15,000 deaths each year and are thus the 13th leading cause of death.^{2,3} The only way to reduce the death rate is to identify and treat aortic aneurysms before they rupture [see 6:3 *Pulsatile Abdominal Mass*].

The relationship between aneurysm size and risk of rupture is well known. The annual risk of rupture is 1% to 2% for aneurysms less than 5 cm in diameter, 10% for aneurysms 5 to 6 cm in diameter, and 25% or higher for aneurysms larger than 6 cm.⁴ Although large aneurysms are much more likely to rupture than small aneurysms, small aneurysms can and do rupture on occasion.

The exact size at which an asymptomatic small AAA should be treated remains unsettled. This issue was the subject of two prospective, randomized clinical trials: the United Kingdom Small Aneurysm Trial⁵ and the Aneurysm Detection And Management (ADAM) Veterans Affairs (VA) Cooperative Study.⁶ Both trials randomly assigned low-risk patients with small (4.0 to 5.4 cm) AAAs to either open surgical repair or ultrasound surveillance. Patients in the surveillance groups were closely monitored with serial ultrasound examinations and underwent open surgical repair if the aneurysm enlarged, became tender to palpation, or became symptomatic. With respect to the primary end point—overall survival—the two trials came to similar conclusions: there was no difference in overall survival between the surgery group and the surveillance group.^{5,6} There was, however, a late survival benefit in the surgery group in the U.K. Small Aneurysm Trial.⁷

Aneurysm rupture rates were low (1%) in both trials, leading many clinicians to conclude that aneurysms smaller than 5.5 cm need not be treated, because the risk of rupture is so low. Closer examination of the data, however, reveals that more than 60% of the patients in the surveillance groups underwent open surgical

repair during the two trials: 81% of patients with 5.0 to 5.4 cm aneurysms in the ADAM trial underwent surgery, and almost all patients in the U.K. trial ultimately required surgical management. Thus, it is likely that the reason for the low rupture risk in these trials was that surgical treatment of the aneurysm was provided when clinically indicated. This conclusion is supported by data from a prospective study of patients from the VA hospitals involved in the ADAM trial who were not eligible for randomization and did not undergo operative repair. In these patients, the 1-year risk of rupture for slightly larger (5.5 to 5.9 cm) aneurysms was 9.4%.⁸ Furthermore, very close surveillance with ultrasound examinations every 3 to 6 months did not prevent aneurysm rupture in 1% of patients. Thus, the decision whether to treat an aneurysm is based on assessment of the risk of aneurysm rupture relative to the risk associated with treatment rather than on an absolute size criterion or a surveillance protocol.

Open Repair

PREOPERATIVE EVALUATION

Identification of Risk Factors

For successful surgical reconstruction of AAAs, any significant comorbidities that would increase the risk of operative repair must be identified and managed at an early stage. Patients undergoing the procedure usually are elderly and often have coexisting cardiac, pulmonary, cerebrovascular, renal, or peripheral vascular disease. The major anesthetic risk factors for elective resection of AAAs are similar to those for other major intra-abdominal operations; in particular, they include inadequate cardiopulmonary and renal function. Patients with unstable angina or angina at rest, a cardiac ejection fraction of less than 25%, a serum creatinine concentration higher than 3 mg/dl, or pulmonary disease (manifested by arterial oxygen tension < 50 mm Hg, elevated arterial carbon dioxide tension, or both on room air) are considered to be at high risk.^{9,10}

Myocardial ischemia is the most common cause of perioperative morbidity and mortality after arterial reconstruction of the aorta. Optimization of preoperative medical management, perioperative invasive monitoring, and long-term risk-factor modification are all facilitated by an accurate preoperative cardiac evaluation. Such evaluation may include transthoracic echocardiography, exercise stress testing, myocardial scintigraphy, stress echocardiography, and coronary angiography; each test has its own merits and limitations with regard to clinical risk assessment.

There has been considerable controversy over the potential benefit of preoperative coronary revascularization in this setting. This issue was addressed by a clinical trial in which patients requiring AAA or peripheral vascular surgery who had high-risk cardiac disease were randomly assigned to undergo either vascular surgery without preoperative coronary revascularization or coronary revascularization followed by vascular surgery.¹¹ There was no differ-

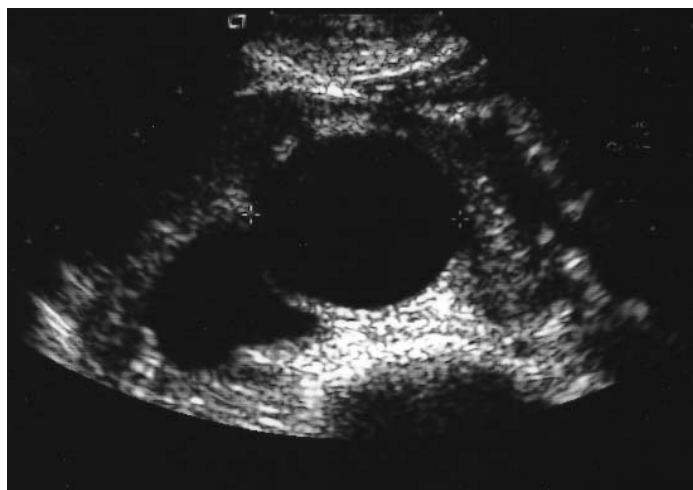


Figure 1 Duplex ultrasonography may be used as a screening test and to determine the actual size of the aneurysm.

ence between the two groups with respect to the incidence of postoperative MI or overall mortality. The investigators concluded that patients with stable coronary disease do not benefit from preoperative coronary revascularization. Patients with unstable severe coronary disease may benefit from invasive cardiac evaluation and preliminary coronary intervention.

To reduce the mortality associated with resection of AAAs, it is necessary not only to identify high-risk groups but also to institute appropriate preoperative, intraoperative, and postoperative alterations in patient care. With intensive perioperative monitoring and support in place, resection of AAAs has been successfully performed even in high-risk patients, with operative mortalities of less than 6%.¹²⁻¹⁴

Confirmation of Diagnosis and Determination of Aneurysm Size

Physical examination suffices for detection of most large aneurysms. To determine the exact size of the aneurysm and to identify smaller aneurysms, however, more objective methods are available and should be used. Determination of the size of the aneurysm is extremely important because size is the most important determinant of the likelihood of rupture and plays a crucial role in subsequent management decisions. Imaging modalities commonly employed to diagnose and measure aneurysms include duplex ultrasonography (DUS), aortography, computed tomography, and magnetic resonance imaging.

The main advantages of DUS are its ready availability in both inpatient and outpatient settings, its low cost, its safety, and its good performance; many studies have documented the ability of DUS to establish the diagnosis and accurately determine the size of AAAs [see Figure 1].¹⁵⁻¹⁷ The primary limitations of DUS are that imaging of the thoracic and suprarenal aorta is poor, that the quality of the images is considerably lower in the presence of obesity or large amounts of intestinal gas, and that it must be performed by a skilled imaging technician.

Aortography yields excellent images of the contours of the aortic lumen, but it is not a reliable method for determining the diameter of an aneurysm or even for establishing its presence, because the mural thrombus within the aneurysm tends to reduce the lumen to near-normal size. Nonetheless, aortography can be helpful in determining the extent of an aneurysm (especially when there is iliac or suprarenal involvement), defining associated arterial lesions involving the renal and visceral arteries, and detecting

lower-extremity occlusive disease. There are risks associated with aortography that place some restrictions on its use. Among these risks are the potential renal toxicity resulting from the use of contrast agents. In addition, manipulation of catheters through the laminated mural thrombus increases the risk of distal embolization. Finally, local arterial complications may arise at the arterial puncture site.

CT provides reliable information about the size of the entire aorta, thereby allowing accurate determination of both the size and the extent of the AAA [see Figure 2]. Spiral CT scanning permits identification of the visceral and renal arteries and their relationship to the aneurysm. The administration of I.V. contrast material allows assessment of the aortic lumen, the amount and location of mural thrombus, and the presence or absence of retroperitoneal hematoma [see Figure 3]. Overall, spiral CT is currently the most useful imaging method for evaluation of the abdominal aorta.

MRI is also useful in the preoperative evaluation of aortic aneurysms.^{18,19} It employs radiofrequency energy and a magnetic field to produce images in longitudinal, transverse, and coronal planes. The advantages of MRI over CT are that no ionizing radiation is administered, multiplane images can be obtained, and no nephrotoxic contrast agents are used.

Classification of Patients for Elective or Urgent Repair

Patients may usefully be classified into three categories according to how they present for repair: (1) elective patients, (2) symptomatic patients, and (3) patients with ruptured aneurysms.



Figure 2 Shown is a CT angiogram providing a three-dimensional reconstruction of an infrarenal AAA after endovascular repair. Of particular interest is the relation of the graft to the renal arteries and the hypogastric arteries distally.

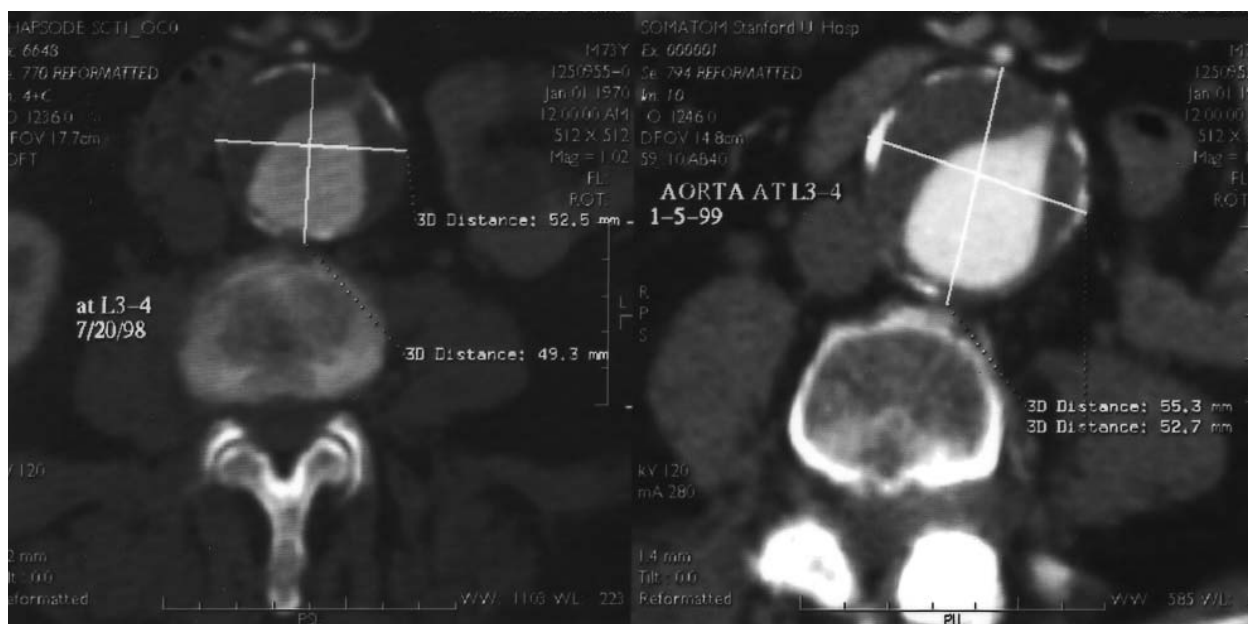


Figure 3 CT scanning assesses the size of the aneurysm, the amount of mural thrombus present, and the relation of other intra-abdominal structures to the aneurysm.

Elective aneurysm repair is recommended for asymptomatic patients who have aneurysms 5.0 cm in diameter or larger, who have an acceptable level of operative risk, and who have a life expectancy of 1 year or more. Furthermore, elective operation should be considered for patients with aneurysms smaller than 5.0 cm who are not at high operative risk if they are hypertensive or live in a remote area where proper medical care is not readily available. Repair is also appropriate for aneurysms that are between 4.0 and 5.0 cm in diameter and have shown growth of more than 0.5 cm on serial images in less than 6 to 12 months. Peripheral embolization originating from the aneurysm is an indication for repair, regardless of the size of the aneurysm.

Urgent operation is indicated for patients with symptomatic aneurysms, regardless of the size of the aneurysm. Such patients typically present with abdominal or back pain. Sometimes, the back pain radiates to the groin, much as in ureteral colic; this pain may be elicited by palpating the aneurysm. In most cases, DUS, CT, and MRI will reliably detect the presence of periaortic blood; however, the absence of this finding should not delay operation, because actual rupture of the aneurysm can occur at any time.

Emergency operation is indicated for almost all patients with known or suspected rupture of an aneurysm.

OPERATIVE PLANNING

Preoperative planning is essential for a successful outcome after repair of an infrarenal AAA. Like the choice between elective and urgent or emergency repair, operative planning is governed by the presentation of the patient. In patients with ruptured aneurysms, diagnosis is immediately followed by operative repair. In patients with symptomatic aneurysms, the amount of preoperative imaging done is balanced against the risk of impending rupture. In patients presenting for elective repair, it is generally possible to perform extensive imaging to determine whether the repair is best done via an endovascular approach [see Endovascular Repair, below] or a standard open approach. Current preoperative imaging methods utilizing CT angiography (CTA) obviate several common pitfalls. The availability of endovascular techniques for excluding an aneurysm should not alter the patient selection criteria for

aneurysm repair. Consideration of endovascular aneurysm repair (EVAR) does introduce certain morphologic criteria into the process of patient selection, in that stent grafting is appropriate only for patients in whom the infrarenal neck and the iliac arteries are suitable.

Given that the long-term outcome of endovascular grafting is currently unknown, younger patients who are at low operative risk and are expected to survive into the long term are typically better served with open surgical repair. In addition, patients who require additional abdominal or pelvic revascularization procedures, who have small or diseased access vessels, or who have short (< 10 mm) or tortuous infrarenal necks are not candidates for endovascular grafting and should undergo open surgical repair instead.

Preoperative preparation to optimize cardiopulmonary function, administration of preoperative antibiotics, and intraoperative hemodynamic monitoring with appropriate fluid management can significantly reduce the risks associated with AAA repair. Before aortic cross-clamping, appropriate volume loading, combined with vasodilatation, is carried out to help prevent declamping hypotension.

OPERATIVE TECHNIQUE

Step 1: Initial Incision and Choice of Approach

Open surgical repair of infrarenal AAAs is performed through a transperitoneal or retroperitoneal exposure of the aorta with the patient under general endotracheal anesthesia. The aneurysm may be exposed through either a long midline incision (for the transperitoneal approach) or an oblique flank incision (for the retroperitoneal approach) [see Figure 4a]. An upper abdominal transverse incision may also be used for either retroperitoneal or transperitoneal exposure. The results with the two exposures are equivalent. The transperitoneal approach is preferred when exposure of the right renal artery is required and when access to the distal right iliac system or to intra-abdominal organs is necessary. The retroperitoneal exposure offers advantages when extensive peritoneal adhesions, an intestinal stoma, or severe pulmonary disease is present and when there is a need for suprarenal exposure. Use of the retroperitoneal approach has been associated with a shorter

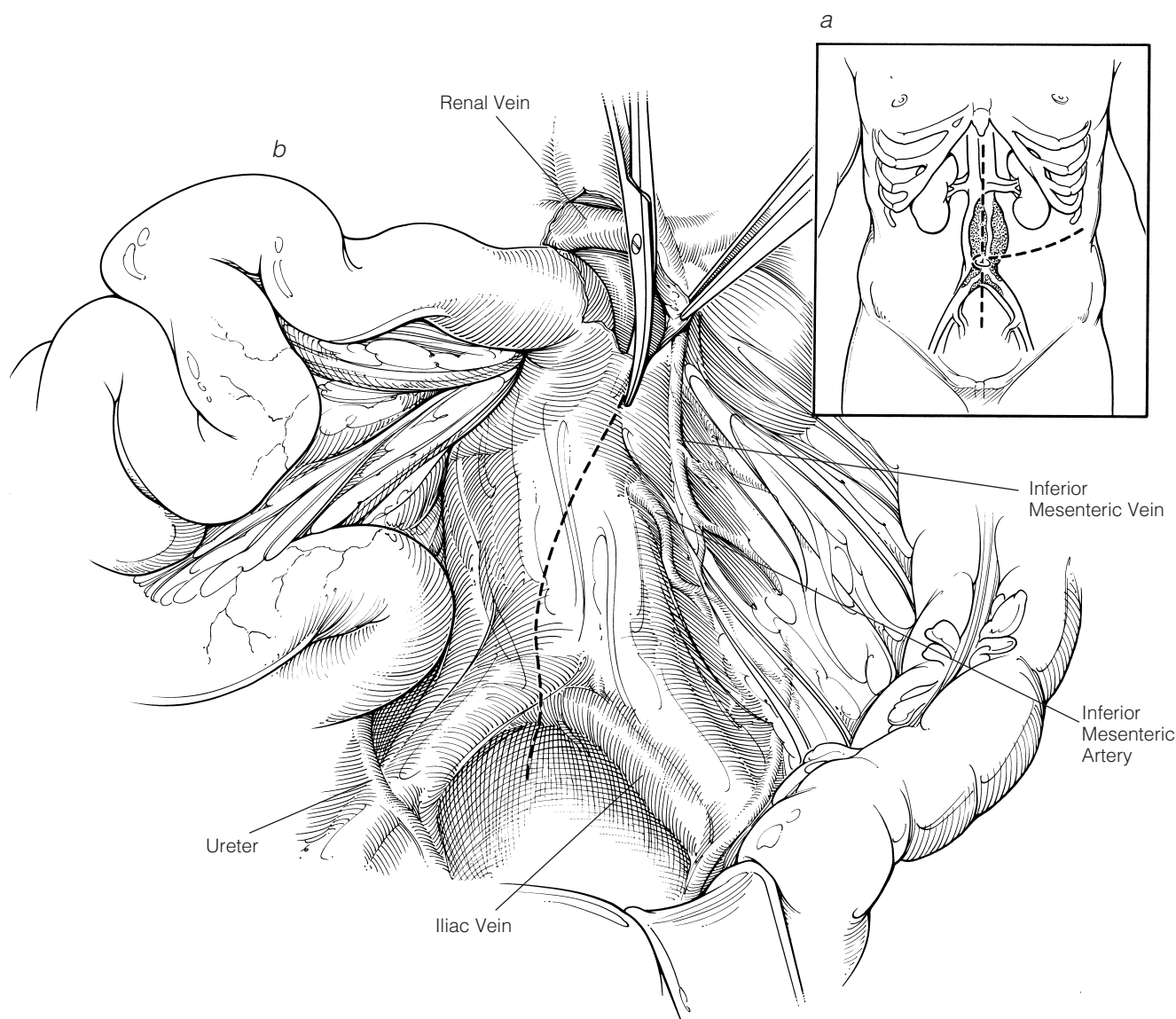


Figure 4 Open repair of infrarenal AAAs. (a) For the transabdominal approach to the abdominal aorta, a midline or transverse incision is appropriate. For the retroperitoneal approach, an oblique flank incision may be used. (b) The small intestine (including the duodenum) is retracted laterally after the ligament of Treitz is mobilized, and the retroperitoneum is incised in the midline. The left renal vein is the landmark for the infrarenal neck.

duration of postoperative ileus, a lower incidence of pulmonary complications, and a reduction in length of stay in the ICU.

Step 2 (Transperitoneal Approach): Exposure and Control of Aorta and Iliac Arteries

When the transperitoneal approach is taken, the small bowel (including the duodenum) is retracted to the right, and the retroperitoneum overlying the aneurysm is divided to the left of the midline [see Figure 4b]. The duodenum is completely mobilized, and the left renal vein is identified and exposed. The normal infrarenal neck, which is just below the left renal vein, is then exposed and encircled for proximal control. Both common iliac arteries are mobilized and controlled, with care taken to avoid the underlying iliac veins and ureters that cross over at the iliac bifurcation [see Figure 5]. If the common iliac arteries are aneurysmal, then both the internal and the external iliac arteries are controlled. The inferior mesenteric artery is then dissected out and controlled for possible reimplantation into the graft after the aneurysm has been repaired.

Step 2 (Retroperitoneal Approach): Exposure and Control of Aorta and Iliac Arteries

When the retroperitoneal approach is taken, a transverse left abdominal or flank incision is made, and the peritoneum is reflected anteriorly. The left kidney usually is left in place but may be mobilized anteriorly to expose the posterolateral aorta. Exposure of the right iliac system can be achieved by dividing the inferior mesenteric artery early in the course of dissection. The aorta and the iliac arteries are controlled in essentially the same fashion regardless of the type of incision used.

Step 3: Opening of Aneurysm and Creation of Proximal Anastomosis

Systemic anticoagulation with I.V. heparin is then performed. After sufficient time (3 to 5 minutes) has elapsed to permit adequate circulation, the infrarenal neck and the iliac arteries are clamped. To prevent distal embolization, the distal clamps should be applied before the proximal aortic clamp. The aneurysm is then

opened longitudinally, the mural thrombus is removed, and back-bleeding lumbar arteries are oversewn. Depending on its degree of backflow and on the patency of the hypogastric arteries, the inferior mesenteric artery may be either ligated or clamped and left with a rim of aortic wall for subsequent reimplantation [see Troubleshooting, *below*].

The aortic neck is then partially or completely transected, and an appropriately sized tubular or bifurcated graft is sutured to the aorta with a continuous nonabsorbable monofilament suture [see Figure 6]. When the proximal aortic neck is very short, suprarenal aortic

clamping may be required for performance of the proximal anastomosis. If suprarenal clamping is necessary, the security of the proximal anastomosis should be verified, and the clamp should then be moved onto the graft below the renal arteries as soon as possible to minimize renal ischemia. If the aorta is especially weak or friable, the anastomosis may be supported with Teflon-felt pledgets.

Step 4: Creation of Distal Anastomosis

When the aneurysm is confined to the aorta, the distal anastomosis is performed by suturing a straight tube graft to the aortic

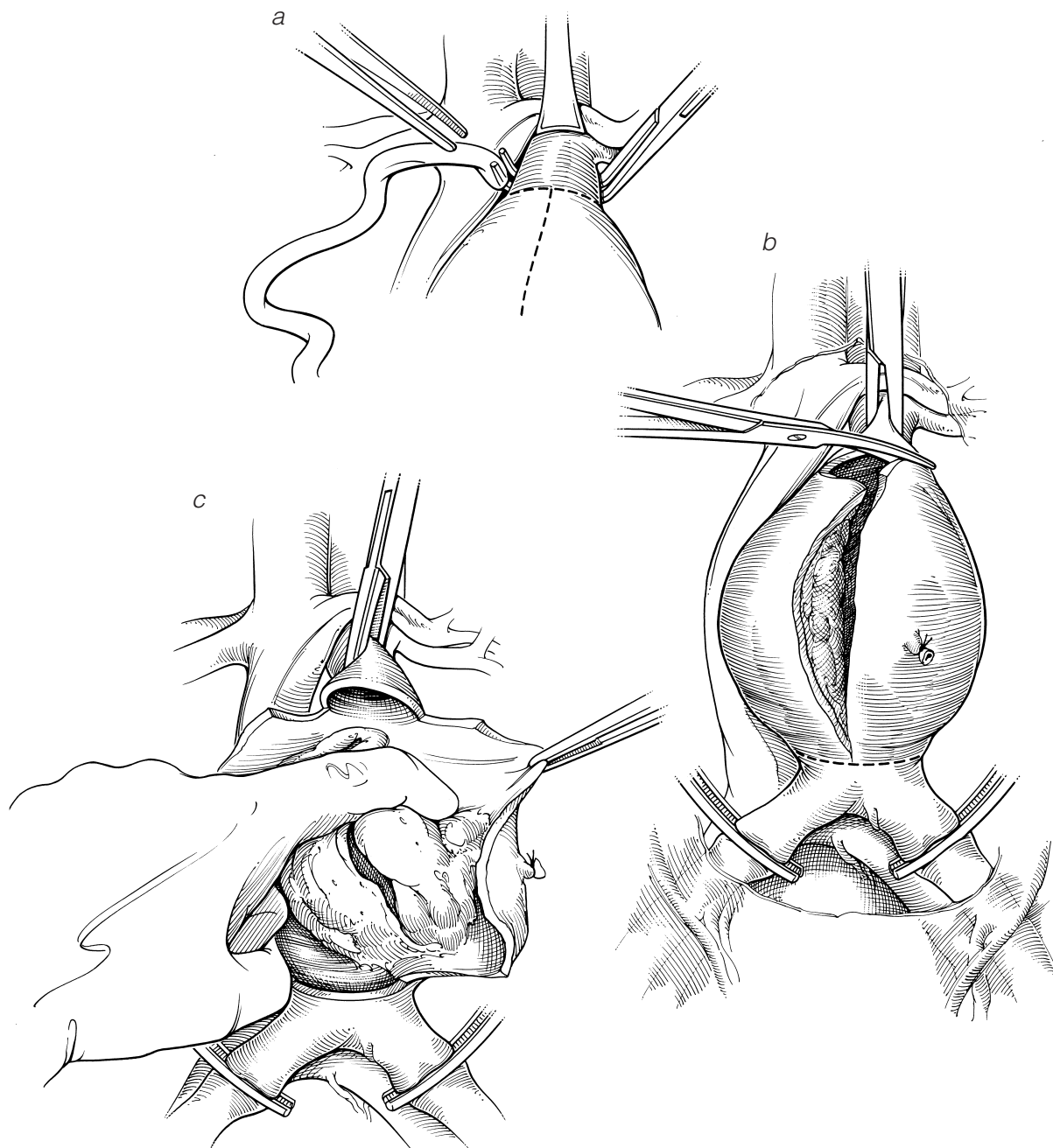


Figure 5 Open repair of infrarenal AAAs. (a) Once the aneurysm is exposed, proximal control is obtained by encircling the proximal neck with an umbilical tape or heavy Silastic. The inferior mesenteric artery is identified and then either clamped or ligated for possible reimplantation at the end of the procedure. (b) The iliac arteries are dissected free, systemic heparin anticoagulation is instituted, and distal control is obtained, followed by proximal control to prevent distal embolization. The aneurysm sac is then opened longitudinally. (c) All mural thrombus is removed, and the proximal and distal necks of the aorta are incised.

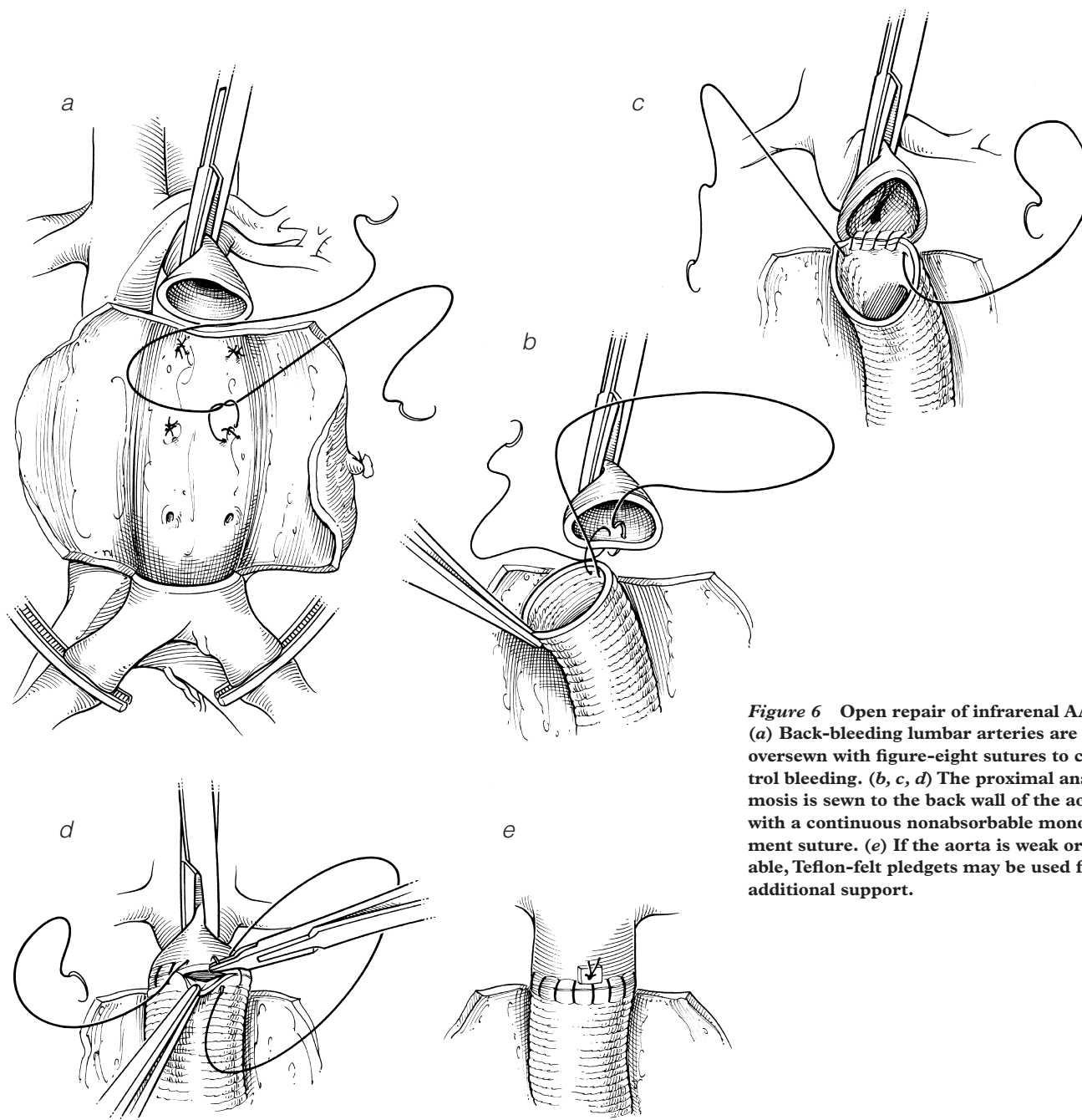


Figure 6 Open repair of infrarenal AAAs. (a) Back-bleeding lumbar arteries are oversewn with figure-eight sutures to control bleeding. (b, c, d) The proximal anastomosis is sewn to the back wall of the aorta with a continuous nonabsorbable monofilament suture. (e) If the aorta is weak or friable, Teflon-felt pledgets may be used for additional support.

bifurcation [see Figure 7]; straight tube graft reconstructions are used about 30% of the time. Distally, the dissection should avoid the fibroareolar tissue overlying the left common iliac artery because this tissue contains branches of the inferior mesenteric artery and the autonomic nerves that control sexual function in men.

When the aneurysm extends into the common iliac arteries, the distal anastomosis is accomplished by suturing a bifurcated graft to the distal common iliac arteries or, in the case of significant occlusive disease, to the common femoral arteries. In these situations, control of the iliac arteries is best achieved by mobilizing the external and internal arteries and clamping them individually [see Figure 8]. It is sometimes easier to control iliac artery back-bleeding by using intraluminal balloon catheters and oversewing the common iliac arteries from within the opened aortic or iliac aneurysms. Care must be taken not to injure the accompanying venous structures or the ureters, which cross anterior to the iliac bifurcation.

Every effort should be made to ensure perfusion of at least one hypogastric artery to help minimize the risk of postoperative left colon ischemia.

Declamping hypotension may occur after reperfusion of the lower extremities. It is essential to maintain communication with the anesthesiologist so that blood and fluid replacement can be adjusted in anticipation of lower-extremity reperfusion. Even though the graft and vessels are flushed and back-bled before distal flow is reestablished, it is preferable first to establish flow into one of the hypogastric arteries so as to minimize the chances of distal embolization to the legs.

Before the abdomen is closed, adequate perfusion of the lower extremities and the left colon should be ensured via either direct inspection or noninvasive monitoring. The open aneurysm sac is then sutured closed over the aortic graft to separate the graft from the duodenum and the viscera [see Figure 9]. This step reduces the risk of aortoenteric fistula.

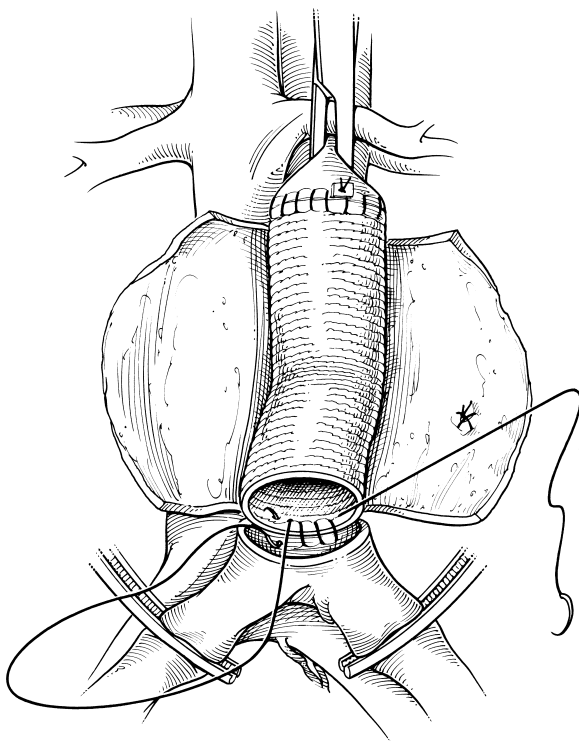


Figure 7 Open repair of infrarenal AAAs. When the aneurysm does not extend into the iliac arteries, a straight tube graft is used. The distal anastomosis is completed with a continuous suture. Before completion of the anastomosis, the graft is flushed by back-bleeding the iliac arteries and flushing the proximal anastomosis.

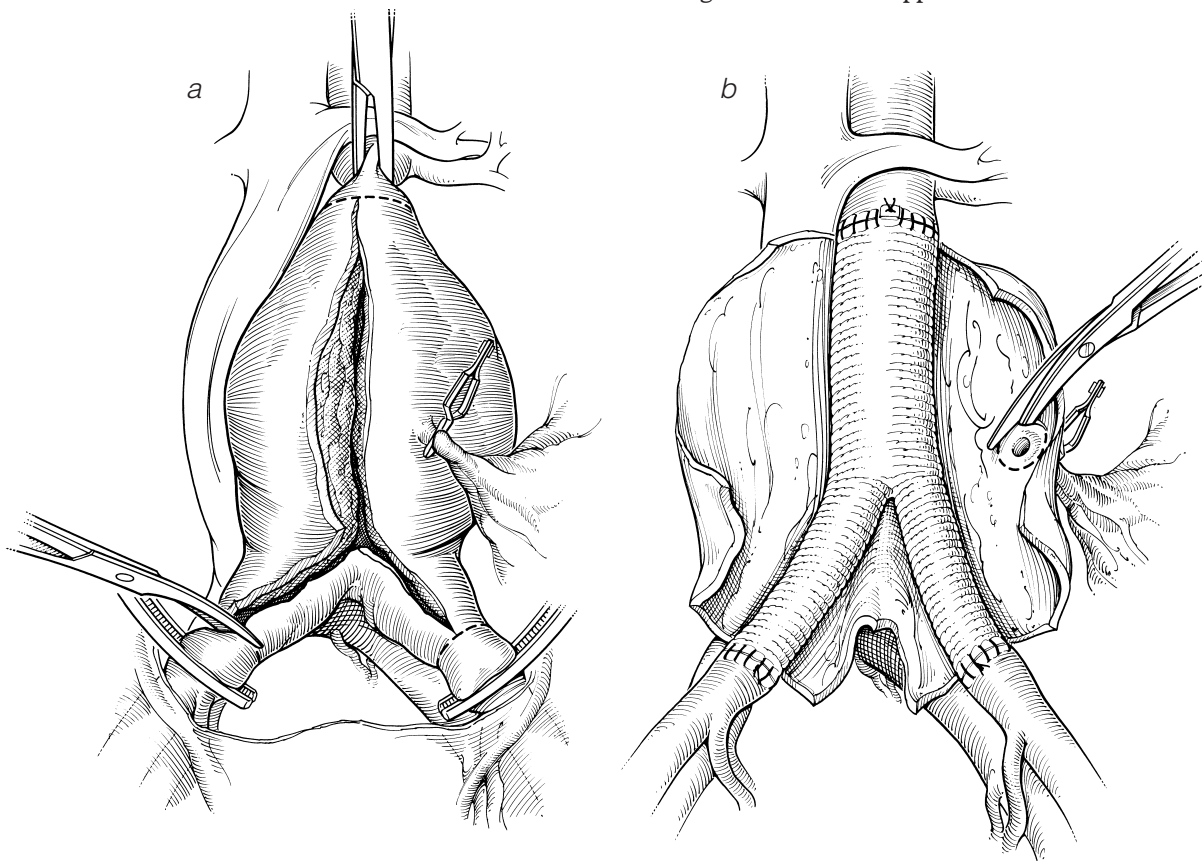


Figure 8 Open repair of infrarenal AAAs. When the common iliac arteries are aneurysmal, both the internal and the external iliac arteries must be clamped individually (a), and a bifurcated graft is sewn to the iliac arteries bilaterally (b).

Troubleshooting

If the inferior mesenteric artery is small and back-bleeding is adequate, it may be ligated [see Figure 10a]; however, if the vessel is large or back-bleeding is meager, it should be reimplanted. Reimplantation of the inferior mesenteric artery can be accomplished with relative ease by using the Carrel patch technique. After the graft has been completely sewn to the aorta, a partial occluding clamp is placed on the main body of the graft or on one of the limbs. An opening in the graft is then created, and an end-to-side anastomosis [see Figure 10b]—with an interposition graft added if necessary [see Figure 10c]—is used to reconstruct the inferior mesenteric artery. This anastomosis is created with a continuous monofilament suture.

SPECIAL CONSIDERATIONS

Concurrent Disease Processes

At times, a concurrent disease process complicates repair of an AAA. The most common problems encountered are hepatobiliary, pancreatic, gastrointestinal, gynecologic, and genitourinary disorders. Careful evaluation of the situation is necessary to determine whether to treat the two disease entities concurrently. As a rule, the more life-threatening disorder is treated first.

There are three key points that should be remembered in the management of patients with AAAs and concurrent diseases. First, a careful preoperative diagnostic workup usually detects any concomitant disease processes. Second, in emergency situations such as ruptured or symptomatic aneurysms, the aneurysm always takes priority unless the other condition is life-threatening and the aneurysm clearly is not the cause of the critical symptoms. Finally, many concomitant intra-abdominal problems can be avoided by taking an endovascular approach.

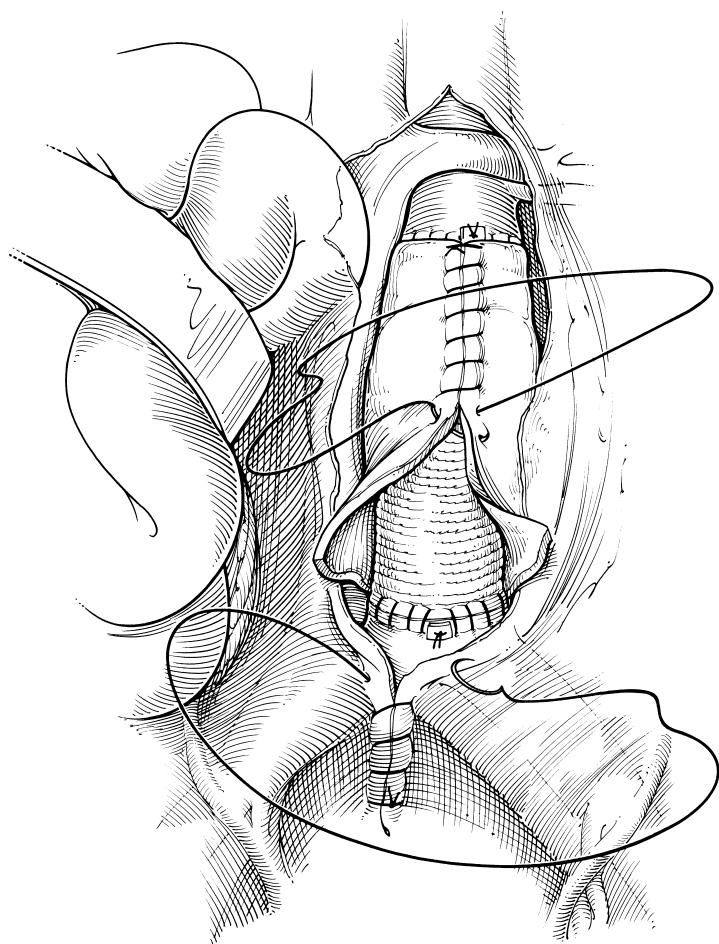


Figure 9 Open repair of infrarenal AAAs. Once the anastomoses have been completed and adequate flow to the lower extremities and the left colon has been confirmed, the open aneurysm sac is sutured closed over the aortic graft.

Anatomic Variants

Several anatomic variants may be encountered during repair of AAAs, including horseshoe kidney, accessory renal arteries, and venous anomalies.

Horseshoe kidney The incidence of horseshoe kidney in the general population is less than 3%. Most patients with horseshoe kidneys have between three and five renal arteries.²⁰ To preserve renal function, renal arteries arising from the aneurysm should be reimplanted. In patients with horseshoe kidneys who have more than five renal arteries, there often are multiple small accessory arteries, some of which originate from the aneurysm, the iliac arteries, or both.

The presence of a horseshoe kidney may complicate—but does not preclude—an anterior approach to repair of an infrarenal AAA.²¹ In such cases, the left retroperitoneal approach provides excellent exposure of the infrarenal aorta. This approach requires that the surgeon dissect the space between the aneurysm and the left portion and isthmus of the kidney; the kidney can then be reflected to the right and the aneurysm fully exposed. The left ureter crosses the iliac arteries from the right in this position, and duplication of ureters may be noted.

Venous anomalies A number of different venous anomalies may be observed in the course of AAA repair; however, the overall

incidence is quite low. Left renal vein variants, such as retroaortic left renal veins and circumaortic venous rings, are the most commonly seen venous anomalies.²² Azygous continuation of the inferior vena cava and bilateral inferior vena cava have also been noted. Unnecessary bleeding can be prevented by means of careful dissection and meticulous technique.

Inflammatory Aneurysm

Approximately 5% of infrarenal AAAs are inflammatory.²³ These AAAs have a dense fibroinflammatory rind that typically adheres to the fourth portion of the duodenum; they may also involve the inferior vena cava, the left renal vein, or the ureters. Patients with inflammatory AAAs typically experience abdominal or flank pain and may present with weight loss. The erythrocyte sedimentation rate is usually elevated as well. Inflammatory aneurysms rarely rupture, because most are symptomatic and consequently are treated before rupture can occur. Repair of inflammatory aneurysms poses technical problems because of the involvement of adjacent structures. A retroperitoneal approach is usually advocated for these aneurysms.

Ruptured Aneurysm

Infrarenal AAAs can rupture freely into the peritoneal cavity or into the retroperitoneum. Free rupture into the peritoneal cavity is usually anterior and is typically accompanied by immediate hemodynamic collapse and a very high mortality. Retroperitoneal ruptures are usually posterior and may be contained by the psoas muscle and adjacent periaortic and perivertebral tissue. This type of rupture may occur without significant blood loss initially, and the patient may be hemodynamically stable.

When an aortic aneurysm ruptures, immediate surgical repair is indicated. If the patient is unstable and either an abdominal aortic aneurysm was previously diagnosed or a palpable abdominal mass is present, no further evaluation is necessary and the patient should be taken directly to the OR. If the patient is stable and the diagnosis is questionable, CT scanning may be performed to confirm the presence of an aneurysm and determine its extent, the site of the rupture, and the degree of iliac involvement. Bedside ultrasonography may also be used for quick confirmation of the presence of an AAA.

Surgical repair of ruptured aneurysms is performed via a transperitoneal approach. In cases of contained rupture, supraceliac control should be achieved before infrarenal dissection; once the neck of the aneurysm has been dissected free, the aortic clamp may be moved to the infrarenal level. In cases of free rupture, efforts to obtain vascular control may include compression of the aorta at the hiatus and infrarenal control with a clamp or an intraluminal balloon. Once proximal and distal control have been achieved, the operation is conducted in much the same way as an elective repair.

OUTCOME EVALUATION

The mortality associated with repair of AAAs has been greatly reduced by improvements in preoperative evaluation and perioperative care: leading centers currently report death rates ranging from 0% to 5%.²⁴ Mortality after repair of inflammatory aneurysms and after emergency repair of symptomatic nonruptured aneurysms continues to be somewhat higher (5% to 10%), primarily as a consequence of less thorough preoperative evaluation.

Overall morbidity after elective aneurysm repair ranges from 10% to 30%. The most common complication is myocardial ischemia, and MI is the most common cause of postoperative death. Mild renal insufficiency is the second most frequent com-

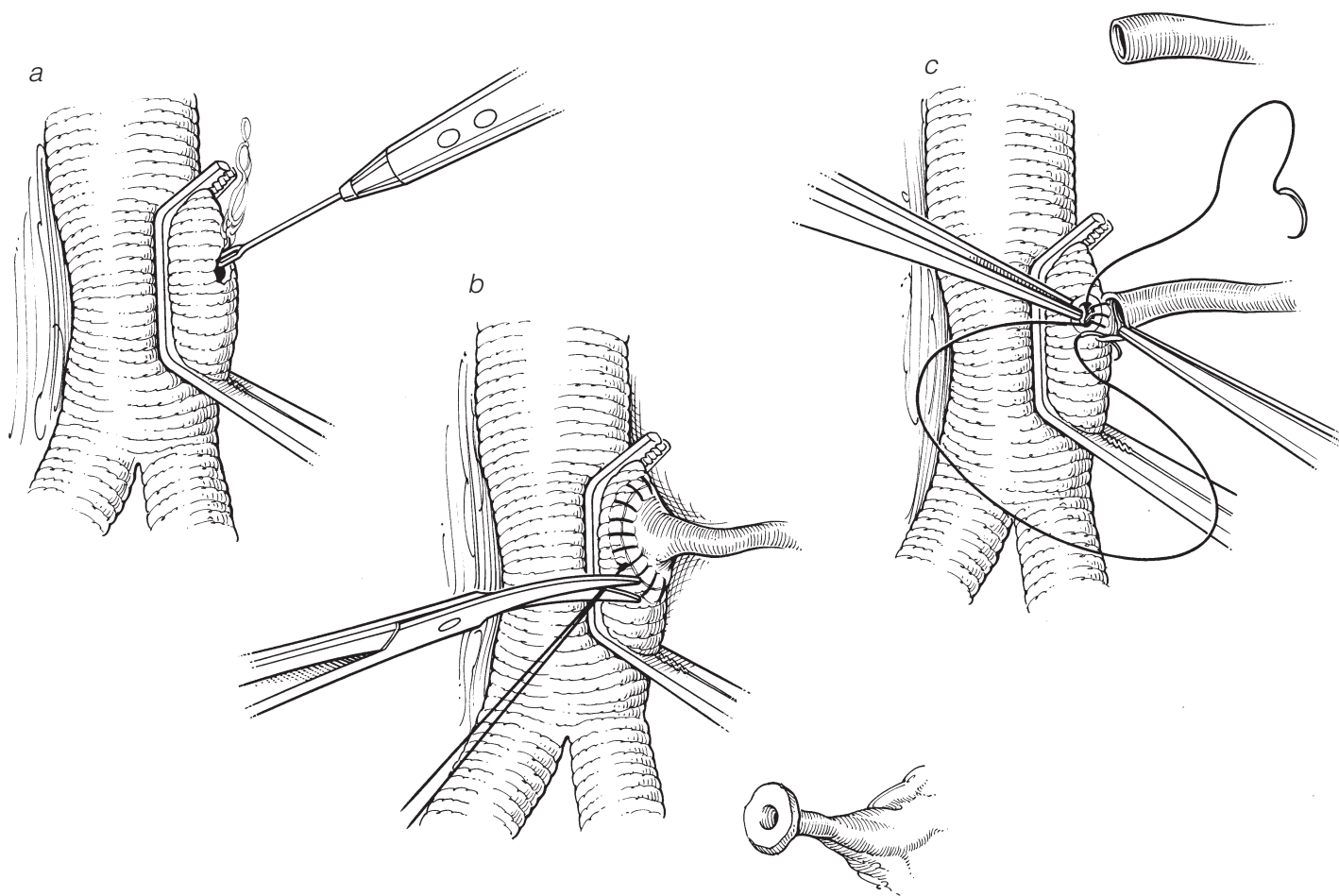


Figure 10 Open repair of infrarenal AAAs. (a) A small, adequately back-bleeding inferior mesenteric artery may be ligated. (b) A large or meagerly back-bleeding inferior mesenteric artery should be reimplanted. A side-biting clamp is applied to the graft, and an end-to-side anastomosis is created with a fine monofilament suture. (c) If the inferior mesenteric artery is not long enough for a direct anastomosis, an interposition graft—either a segment of a vein or a prosthetic graft—may be used for added length.

plication, occurring after 6% of elective aneurysm repairs; however, severe renal failure necessitating dialysis is rare in this setting. The third most common complication is pulmonary disease; the incidence of postoperative pneumonia is approximately 5%.

Postoperative bleeding may occur as well. Common sources of such bleeding include the anastomotic suture lines, inadequately recognized venous injuries, and coagulopathies resulting from intraoperative hypothermia or excessive blood loss. Any evidence of ongoing bleeding is an indication for early exploration.

Lower-extremity ischemia may occur as a result of either emboli or thrombosis of the graft and may necessitate reoperation and thrombectomy. So-called trash foot may also develop when diffuse microemboli are carried into the distal circulation.

Colon ischemia develops after 1% of elective aneurysm repairs. Patients usually present with bloody diarrhea, abdominal pain, a distended abdomen, and leukocytosis. The diagnosis is confirmed by sigmoidoscopy, which reveals mucosal sloughing. In cases of transmural colonic necrosis, colon resection and exteriorization of stomas are warranted.

Paraplegia is rare after repair of infrarenal AAAs: the incidence is only 0.2%. Most instances of paraplegia occur after repair of a ruptured aneurysm or when the pelvis has been devascularized. The majority of patients recover at least some degree of neurologic function.

Late complications (e.g., pseudoaneurysms at the suture lines,

graft or graft limb thrombosis, and graft infection) may occur but are extremely rare. Graft infection may be associated with graft-enteric fistula and is notoriously difficult to diagnose and treat.

Long-term survival in patients who have undergone successful AAA repair is reduced in comparison with that in the general population. The 5-year survival rate after AAA repair is 67% (range, 49% to 84%), compared with 80% to 85% in age-matched control subjects, and the mean duration of survival after AAA repair is 7.4 years. Part of the difference in survival can be attributed to associated coronary disease in patients with aneurysms. Late deaths result primarily from cardiac causes.

Endovascular Repair

Endovascular repair was introduced during the 1990s as a less invasive approach to treating infrarenal AAAs. In this approach, a stent-graft is placed endoluminally via bilateral groin incisions; thus, there is no need for a major abdominal incision and aortic clamping. The results to date have been promising: blood loss is decreased, hospital stay is shortened, and earlier return to function is achieved. Not all patients are candidates for endovascular repair, however. In September 1999, the Food and Drug Administration approved two stent-graft devices for use in surgical management of AAAs: the Ancure device (Guidant, Indianapolis, Indiana), which is a balloon-expandable one-piece bifurcated stent-graft, and the

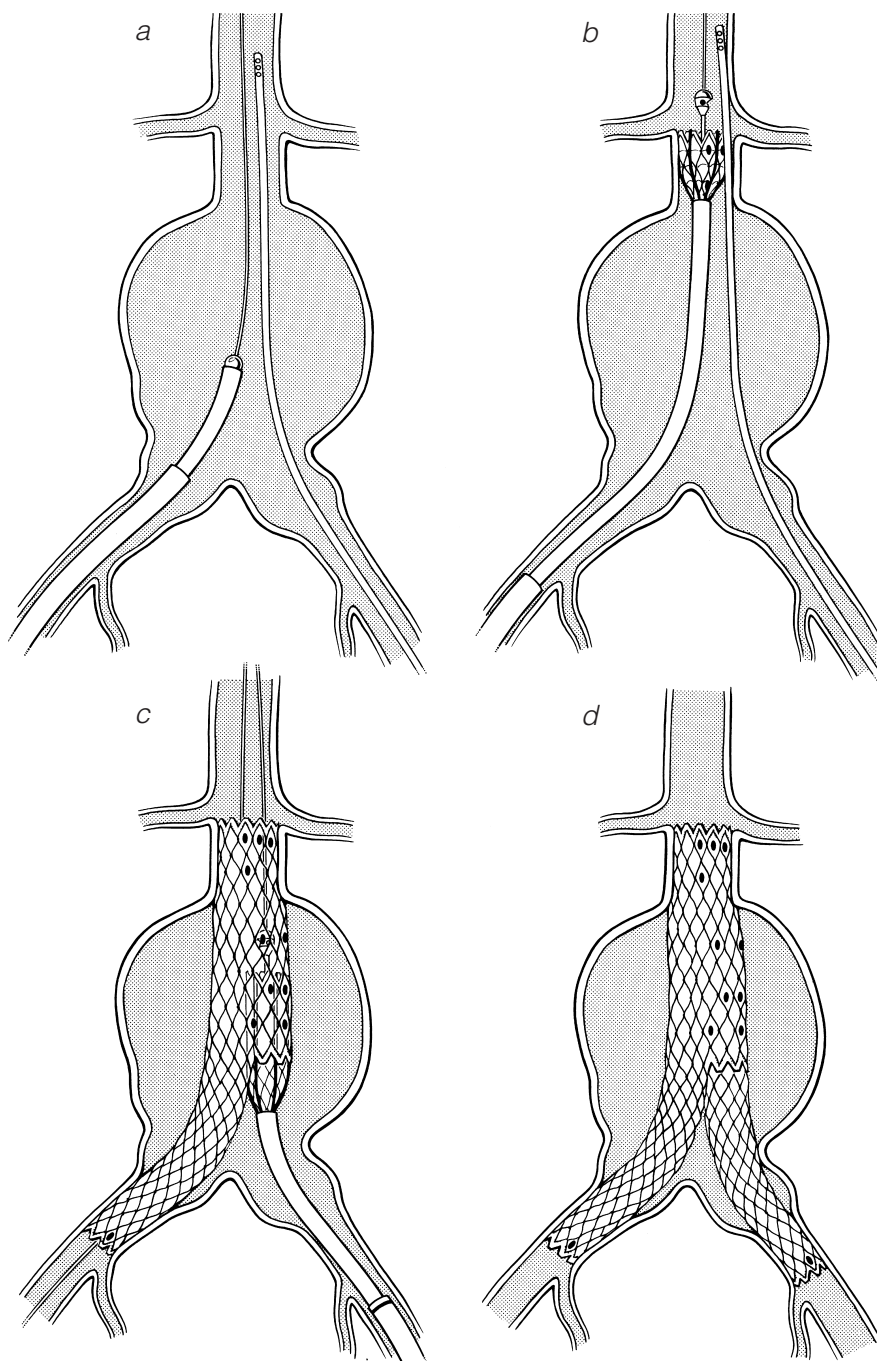


Figure 11 Endovascular repair of infrarenal AAAs. (a) The main bifurcated stent-graft is advanced through the aortoiliac system under fluoroscopic guidance. (b) The sheath over the stent-graft is retracted under fluoroscopic guidance. Controlled deployment allows the graft to be gradually positioned directly below the renal arteries. (c) With the main body of the stent-graft deployed, the contralateral limb is cannulated. Once this is done, the contralateral limb is positioned within the junction gate and the common iliac artery. (d) Shown is proper deployment of the stent-graft within the aortoiliac system, with good proximal and distal fixation of the stent to the arterial wall.

AneuRx device (Medtronic AVE, Santa Rosa, California), which is a self-expanding bifurcated modular device that is fully supported externally by a nitinol stent. Subsequently, the FDA approved three more devices for endovascular repair of AAAs: the Excluder Bifurcated Endoprosthesis (W. L. Gore and Associates, Flagstaff, Arizona), in November 2002, the Zenith AAA Endovascular Graft (Cook Incorporated, Bloomington, Indiana), in May 2003, and

the Endologix Powerlink System (Endologix Incorporated, Irvine, California), in November 2004. The Ancure device is no longer available.

PREOPERATIVE PREPARATION

Precise preoperative evaluation that yields accurate measurements will result in proper planning and effective prevention of

problems. Both CTA and contrast biplane angiography are used for this purpose. Of the two, spiral CTA is currently preferred. This imaging modality is capable of obtaining high-quality images of the vascular anatomy and reconfiguring them into detailed three-dimensional images. For optimal evaluation, images should be obtained at 1.5 to 3 mm intervals from the celiac artery to the femoral arteries. Spiral CTA accurately defines the proximal and distal characteristics of the AAA, as well as detects any significant renal, visceral, or iliac occlusive disease. It is particularly helpful in defining the infrarenal neck between the renal arteries and the proximal portion of the aneurysm.

Angiography is employed as a complement to spiral CTA in this setting. An arteriogram is useful in that it helps define renal, mesenteric, and distal arterial anatomy; helps characterize tortuosity, calcification, and stenoses in access arteries; and helps determine the angles between the aorta, the proximal neck, and the aneurysm.

Intravascular ultrasonography (IVUS) is a useful intraoperative imaging adjunct in the process of sizing and selecting endograft components. It can be used to measure vessel diameters and landing zone lengths, as well as to determine the amount of mural thrombus in the aneurysm neck. In patients with severe renal insufficiency, IVUS is used primarily to identify the renal and hypogastric arteries, allowing the endograft to be deployed with minimal or no resort to angiography.

Proper patient selection is mandatory for successful outcome. The common femoral arteries must be large enough to accept a delivery system larger than 21 French. The proximal infrarenal aortic neck must be suitable for device implantation—that is, its diameter must be between 16 and 28 mm, and its length should be at least 15 mm. The common iliac artery implantation should be carried out as close to the iliac bifurcation as possible to increase the columnar strength of the implanted device. The iliac artery diameter must be between 8 and 20 mm. In patients with iliac artery aneurysms, it is possible to land the end of the stent in the external iliac artery and thereby exclude one internal iliac artery. Exclusion of both internal iliac arteries should be avoided so as to prevent ischemic sequelae (e.g., buttock claudication, colon ischemia, and erectile dysfunction). Coil embolization may be performed in conjunction with EVAR to treat internal iliac aneurysms. However, a waiting period of several weeks between coil embolization of a hypogastric artery on one side and the same procedure on the other side should be considered to allow recruitment of collateral vessels and reduce the incidence of pelvic ischemia.

TECHNIQUE

The methods and technical principles we briefly describe here derive from the personal experience of two surgeons (F.R.A and C.K.Z) with more than 1,000 modular implants. The ensuing technical description is not intended to be exhaustive, nor is it meant as a substitute for the instructions provided by any of the manufacturers.

The patient is placed under epidural or general anesthesia. Bilateral femoral artery cutdowns are performed through transverse groin incisions to allow exposure of the common femoral artery from the inguinal ligament to the femoral bifurcation. Proximal control of the femoral arteries is obtained with umbilical tapes. Systemic anticoagulation with I.V. heparin is instituted to prolong the activated clotting time (ACT) to greater than 250 seconds. The ACT is monitored and maintained at this level throughout the procedure, and additional heparin is given as needed.

The femoral arteries are cannulated with an 18-gauge needle,

and 0.035-in. guide wires are placed bilaterally under fluoroscopic guidance; 10 French sheaths are then placed over the two guide wires and advanced into the aneurysm under fluoroscopic guidance. A superstiff 0.035-in. guide wire 260 cm in length is inserted into the thoracic aorta, usually from the right limb. In the contralateral iliac artery, a pigtail catheter is placed just above the level of the renal arteries, and an initial roadmapping aortogram is obtained. The 10 French sheath in the right femoral artery is then exchanged for the device, which is placed over the superstiff guide wire and carefully advanced into the proximal infrarenal aorta under fluoroscopic guidance, then into the perirenal aorta [see Figure 11a]. A second aortogram is performed to verify the position of the renal arteries. Under fluoroscopic guidance, the stent-graft is then gradually deployed by retracting the outer sheath and allowing the graft to expand, and it is positioned directly below the level of the renal arteries [see Figure 11b].

Once the main bifurcation module has been deployed, the 10 French sheath in the contralateral iliac artery is pulled back, and a 0.035-in. angled hydrophilic wire and a guide catheter are inserted into the contralateral limb of the bifurcation module. The hydrophilic wire is then exchanged for a superstiff guide wire, over which the contralateral limb is then advanced through the sheath into the contralateral vessel and deployed [see Figure 11c]. A final aortogram is then performed to confirm that a satisfactory technical result has been achieved [see Figure 11d]. Proximal and distal extender cuffs may be placed if necessary. The femoral arteriotomies are repaired, and lower-extremity perfusion is reestablished.

OUTCOME EVALUATION

EVAR is significantly less invasive than open surgical repair and consequently is associated with a significant reduction in major procedure-related morbidity. Prospective clinical trials comparing open AAA repair with EVAR have consistently found that patients undergoing the latter experience less intraoperative blood loss, need less postoperative ICU care, have shorter lengths of stay, and regain normal function earlier.^{25,26} Procedure-related mortality after EVAR is 1% to 2%, which is essentially equivalent to that reported after open repair in prospective clinical trials but lower than the 5% mortality reported after open repair in most multicenter studies.^{27,28}

In the past few years, two randomized, controlled trials comparing EVAR with open AAA repair have been published. The Dutch Randomized Endovascular Aneurysm Management (DREAM) trial found EVAR to have a significant advantage in the first 30 days, with reduced mortality and a lower incidence of severe complications.²⁹ This survival advantage was not sustained, however, and at 1 year, there was no difference between EVAR and open AAA repair. The EVAR 1 trial, carried out in the United Kingdom, found EVAR to yield a similar reduction in 30-day mortality.³⁰ Again, this survival advantage was not sustained, and at 4 years, there was no difference between EVAR and open repair in terms of overall mortality or health-related quality of life. EVAR did, however, have a significant advantage over open AAA repair with regard to 4-year aneurysm-related mortality. The impact of this advantage will continue to be assessed as this trial's follow-up period lengthens.

On occasion, EVAR fails to exclude blood flow from the aneurysm sac completely. This condition, known as endoleak, may arise from an incomplete seal at the site where the endograft is affixed to the aortic neck or the iliac arteries (type I endoleak), from retrograde flow into the aneurysm from the inferior mesenteric artery or the lumbar arteries (type II endoleak), or from the graft or modular junction site (type III endoleak). Type I and type

III endoleaks call for secondary treatment to prevent possible aneurysm rupture. The significance of type II endoleaks is less certain. There is no clear evidence that type II endoleaks lead to aneurysm rupture; however, most such endoleaks are treated if they are associated with aneurysm enlargement.

Although numerous studies have shown that endovascular AAA repair results in less morbidity and perioperative mortality than open repair,³¹⁻³⁴ reports describing endograft migration over time, aneurysm enlargement, and occasional aneurysm rupture have raised questions about the long-term durability of the procedure.^{35,36} These adverse events, though uncommon, serve as reminders that EVAR is still a new technology, one whose long-term outcome is unknown. Accordingly, close patient monitoring and follow-up surveillance are warranted, and secondary treatments may be required (e.g., additional endovascular procedures

or, possibly, open surgical repair). New endovascular devices are currently being designed and evaluated in clinical trials, and endovascular treatment strategies continue to evolve and improve.

Clinical follow-up of patients treated during the initial prospective clinical trials now extends to more than 7 years, and EVAR continues to show favorable results. The largest multicenter endovascular clinical trial to date, involving 1,193 patients who were followed for as long as 6 years, found that prevention of aneurysm rupture (the primary objective) was achieved in 99% of patients, whereas procedure-, aneurysm-, or graft-related death was avoided in 97%.^{37,38} These results are consistent with the favorable overall outcomes reported from a European registry of EVAR using a variety of endovascular devices.³⁹ Thus, the midterm results of EVAR are favorable and support the consideration of this approach for most patients who are candidates for the procedure.

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Figures 4 through 11 Susan Brust, C.M.I.

12 AORTOILIAC RECONSTRUCTION

Mark K. Eskandari, MD, FACS

Symptomatic aortoiliac occlusive disease is the consequence of a diffuse atherosclerotic process that is exacerbated by smoking, hypertension, hypercholesterolemia, and diabetes.¹⁻⁴ The resultant narrowing of the aorta and the iliac vessels impairs circulation into the pelvis and the lower extremities, thereby causing myriad patient complaints. Manifestations range from impotence, claudication (in the buttock, the thigh, or the calf), and rest pain (in the forefoot) to ulceration or gangrene.

Hemodynamically significant obstruction of blood flow arising from aortoiliac occlusion may be either segmental or diffuse. Fortunately, a number of different vascular reconstructions can be performed to reestablish sufficient flow to the lower body. The choice of a surgical revascularization approach is based on two factors: (1) anatomic constraints and (2) comorbid conditions. Regardless of which technique is selected, the preoperative workup and planning are essentially the same.

Preoperative Evaluation

Once it has been established that a patient's symptoms (e.g., claudication, rest pain, or a nonhealing wound) are attributable to hemodynamically significant aortoiliac occlusive disease, a thorough preoperative evaluation is initiated. Such evaluation typically includes obtaining objective physiologic documentation of the extent of occlusive disease by measuring lower extremity blood flow with arterial waveforms and ankle-brachial indices. An imaging study is also required to guide revascularization. Percutaneous diagnostic angiography is widely used for this purpose; however, technological advancements may allow magnetic resonance angiography to supplant traditional contrast arteriography.⁵⁻⁷ If an extra-anatomic bypass is anticipated, ancillary tests, including bilateral arm blood pressure measurements and computed tomography scans of the chest, abdomen, or pelvis, may be necessary. A standard cardiac risk assessment is mandatory before any form of revascularization, and the extent of testing is tailored to the level of cardiac risk.

Operative Technique

AORTOILIAC ENDARTERECTOMY

Although localized aortoiliac endarterectomy is less commonly performed today than it once was, it remains useful for a subgroup of patients with focal aortic bifurcation disease. The classic candidate for this procedure has minimal disease of the infrarenal abdominal aorta and the external iliac arteries but a severely diseased and narrowed aortic bifurcation.

Step 1: Incision and Approach

A standard lower midline transperitoneal incision allows rapid, direct access. Usually, the incision can be made below the umbilicus and extended to the pubis.

Step 2: Exposure and Control of the Aorta and Iliac Arteries

Upon entry into the abdominal cavity, exposure of the aortic bifurcation is achieved by retracting the small bowel cephalad. A self-retaining retractor, such as an Omni (Omni-Tract Surgical, Minneapolis, MN) or a Bookwalter (Cardinal Health, V. Mueller, McGaw Park, IL), is often helpful. The retroperitoneum overlying the aortic bifurcation is then incised in the midline, and the aorta is exposed to the level of the inferior mesenteric artery [see 6:11 *Repair of Infrarenal Abdominal Aortic Aneurysms*]. Both common iliac arteries are exposed, with care taken not to damage the underlying iliac veins and the overlying ureters, which normally cross at the iliac bifurcation.

Given that this procedure is best suited for treatment of localized disease, exposure beyond the iliac bifurcation is rarely necessary. If it appears that the disease process extends into the external iliac arteries or more proximally in the infrarenal aorta, another form of treatment, such as aortofemoral bypass (see below), may be indicated.

Step 3: Aortoiliac Endarterectomy

Once the aorta and the iliac vessels are exposed, IV heparin is given for systemic anticoagulation. The vessels are then controlled with vascular clamps. As a rule, the iliac vessels should be clamped first to reduce the risk of distal embolization during placement of the aortic cross-clamp. These vessels should be clamped only enough to prevent retrograde bleeding. They must not be repeatedly clamped and unclamped because they are prone to the development of flow-limiting intimal flaps or fractured atherosclerotic plaques.

Next, the aorta is incised longitudinally from a point just above the bifurcation (where the aorta is soft) and down into the common iliac artery, in which the disease process extends further. Sometimes the middle sacral or lower lumbar arteries must be oversewn to control back-bleeding. A dissection plane is developed between the media and the adventitia, and a standard endarterectomy of the infrarenal aorta and the more diseased iliac artery is performed. The endarterectomy of the contralateral iliac artery is performed by means of eversion through the aortotomy [see Figure 1]. If the distal termination points in the iliac vessels are irregular or have a significant step-off, the plaque should be tacked down with two or three 6-0 polypropylene sutures, with the knots tied on the outside of the vessel wall.

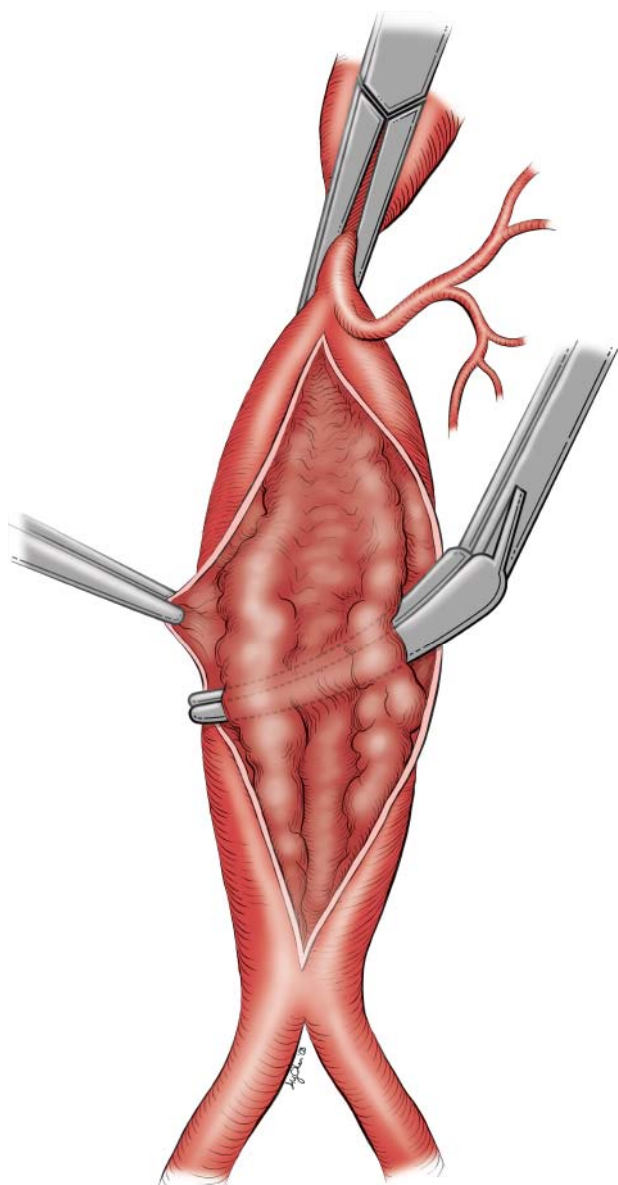


Figure 1 Aortoiliac endarterectomy. Plaque is removed through a longitudinal aortotomy.

Occasionally, endarterectomy results in a very thin residual wall, or the distal termination points are too steep to fix with tacking sutures alone. In such cases, the best recourse is to replace this section of the aorta and the common iliac vessels with a short standard bifurcated prosthetic interposition graft. Proximally, the graft is sewn to the infrarenal aorta in an end-to-end fashion. Distally, the two limbs are sewn to the two common iliac arteries in the same manner.

Step 4: Repair of Arteriotomy

The arteriotomy can be closed either primarily or with a patch, depending on the size of the aorta and the iliac vessels. Primary closure is preferred, but if it appears that such closure will significantly narrow the aorta or the iliac artery, a patch (either prosthetic or autogenous) should be used

instead. Before closure is completed, the vessels should be flushed and back-bled to diminish the risk of distal embolization to the legs upon reestablishment of inline flow. The adequacy of the repair is confirmed primarily by the palpation of normal femoral pulses in the groins.

Step 5: Closure of the Retroperitoneum

Before abdominal closure, the retroperitoneum is closed with an absorbable suture so as to isolate the repair from the gastrointestinal tract. This step reduces the risk of an aortoenteric fistula.

ILIOFEMORAL BYPASS

Iliofemoral bypass, already an uncommon procedure, has now largely been supplanted by advances in percutaneous endoluminal techniques. Nevertheless, it is still used on occasion and thus is worth knowing. One limitation on the application of iliofemoral bypass is that aortoiliac occlusive disease typically causes diffuse aortic and bilateral iliac artery narrowing. For this operation to be successful, there must be a relatively disease-free common iliac artery that can provide unimpeded inflow. Accordingly, iliofemoral bypass is most suitable for those rare patients who have isolated unilateral external iliac artery disease.

Step 1: Incision and Approach

The patient is placed in the supine position, and two incisions are made [see Figure 2]. The common iliac artery is approached through a lower-quadrant retroperitoneal incision positioned medial to the lateral border of the rectus muscle. The femoral artery is approached through a standard vertical groin incision.

Step 2: Exposure of the Iliac and Femoral Arteries

Once the retroperitoneum is entered, the visceral contents and the ureter are bluntly dissected away from the psoas muscle medially. This dissection, which takes place through a mostly bloodless field, yields full exposure of the targeted common iliac artery and its bifurcation into the external and internal iliac arteries. It should proceed far enough to allow control of the arteries with vascular clamps. Care must be taken not to damage the underlying iliac veins. In particular, no attempt should be made to isolate these vessels circumferentially, which can lead to troublesome bleeding.

The vertical incision in the groin permits full exposure of the common femoral artery and its bifurcation into the superficial femoral artery and the profunda femoris. Unlike the iliac arteries, the femoral artery and its branches may be circumferentially dissected.

Step 3: Tunneling of the Bypass Graft

Once the inflow and outflow vessels are adequately exposed, the bypass graft is tunneled from the retroperitoneum to the groin, passing beneath the ureter and the inguinal ligament. During tunneling, care must be taken not to avulse the bridging epigastric vein found just cephalad and posterior to the inguinal ligament. Typically, a prosthetic graft 8 to 10 mm in diameter is used; however, autogenous material (e.g., a segment of the greater saphenous vein) may be used if desired.

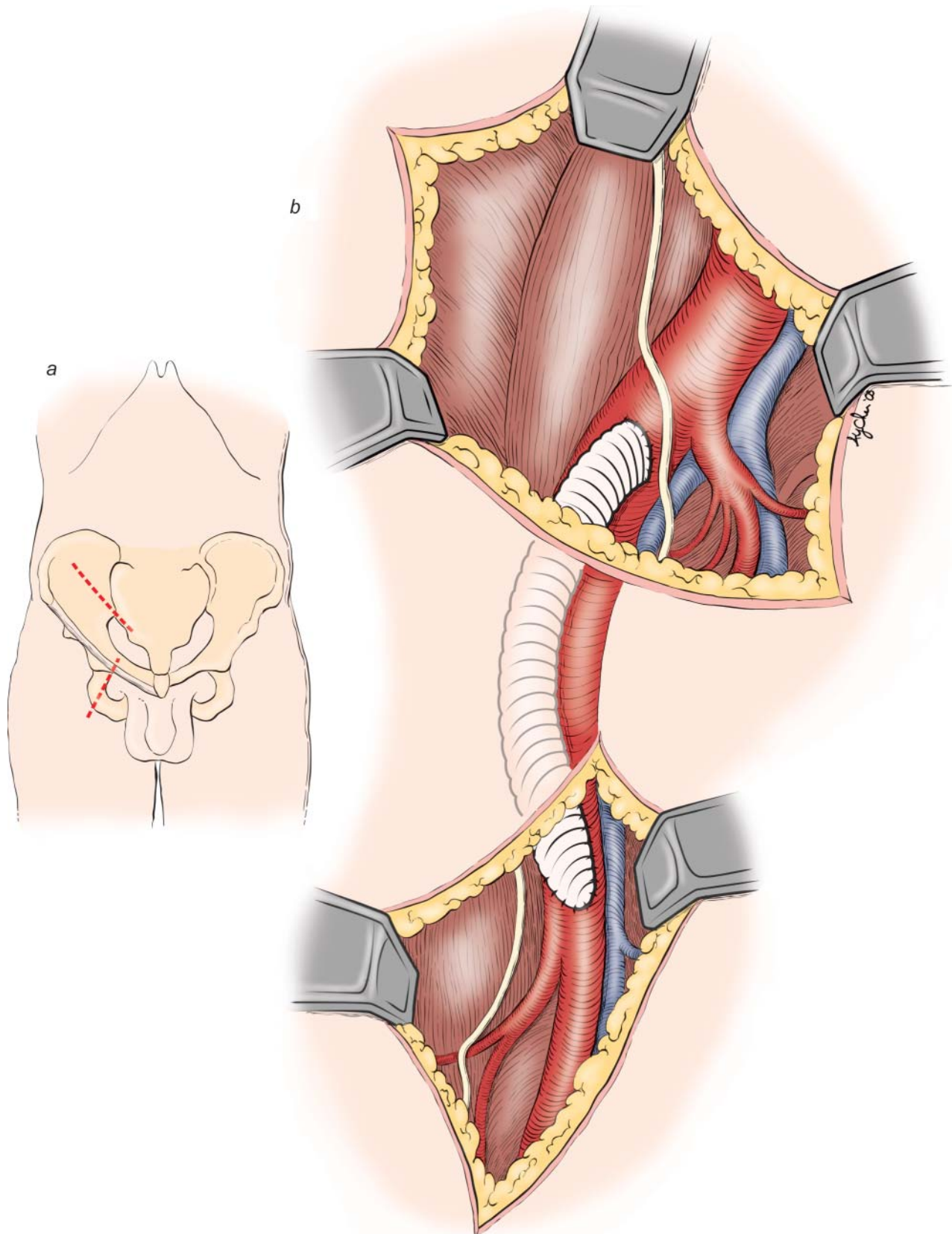


Figure 2 Iliofemoral bypass. (a) A low retroperitoneal incision and an ipsilateral groin incision are made for exposure of the inflow and outflow bypass vessels. Dashed lines denote skin incision. (b) The graft is tunneled beneath the ureter and the inguinal ligament.

Step 4: Proximal Anastomosis to the Iliac Artery

With the bypass graft in position, the patient undergoes systemic anticoagulation with IV heparin. The common, external, and internal iliac arteries are controlled with vascular clamps. The proximal anastomosis is then performed to the selected common iliac artery. If practicable, the anastomosis should be an end-to-side one so as to preserve antegrade flow into the internal iliac artery.

Troubleshooting Occasionally, the common iliac artery is too diseased to clamp or to use as an inflow source. In such cases, the infrarenal aorta may be clamped instead or used as the site of the proximal anastomosis.

Step 5: Distal Anastomosis to the Femoral Artery

Vascular clamps are placed on the common femoral artery and its branches, and the distal anastomosis is performed in an end-to-side manner. The configuration of the longitudinal arteriotomy depends on the presence and extent of disease in the femoral arteries. If both the superficial femoral artery and the profunda femoris are relatively free of disease, the arteriotomy should extend from the common femoral artery into the superficial femoral artery. If, however, the superficial femoral artery is occluded or heavily diseased, the arteriotomy should extend down into the profunda femoris [see Figure 3]. In either case, an end-to-side anastomosis is fashioned. Before completion of the bypass, the inflow vessel is flushed and the outflow vessel back-bled to reduce the risk of distal embolization to the legs.

AORTOFEMORAL BYPASS

Before the application of percutaneous balloon angioplasty and stenting, aortofemoral bypass grafting was the revascularization operation of choice for patients with diffuse aortoiliac

occlusive disease. This operation is still favored by many, and it yields excellent long-term patency.

Step 1: Incision and Approach

Typically, the patient is placed in the supine position, and the operation is performed through a midline laparotomy and two longitudinal groin incisions. A self-retaining retractor is recommended to facilitate exposure of the infrarenal aorta.

Alternatively, the infrarenal aorta may be exposed via a left retroperitoneal incision extending obliquely from the lateral border of the rectus muscle, at the level of the umbilicus, to the tip of the 11th rib. For this approach, the patient is placed in a right semilateral decubitus position with the assistance of an inflatable beanbag. The hips are rotated so that they are flat on the bed, providing easy access to the groins.

Step 2: Exposure of the Aorta

Upon entry into the abdominal cavity, the fourth portion of the duodenum is dissected free of its retroperitoneal attachments, and the small bowel is retracted to the right of the aorta. The self-retaining retractor may then be placed to facilitate exposure. Next, the retroperitoneum overlying the infrarenal aorta is incised in the midline to expose the vessel, ideally in a location that is not heavily diseased or calcified. Unlike the dissection required in a localized endarterectomy [see Aortoiliac Endarterectomy, above], this dissection is primarily between the renal arteries and the inferior mesenteric artery. In most cases, the dissection need not be extended downward below the aortic bifurcation into the iliac arteries.

When this operation is performed through a left retroperitoneal incision, the external and internal oblique muscles and the transversus abdominis are divided, and

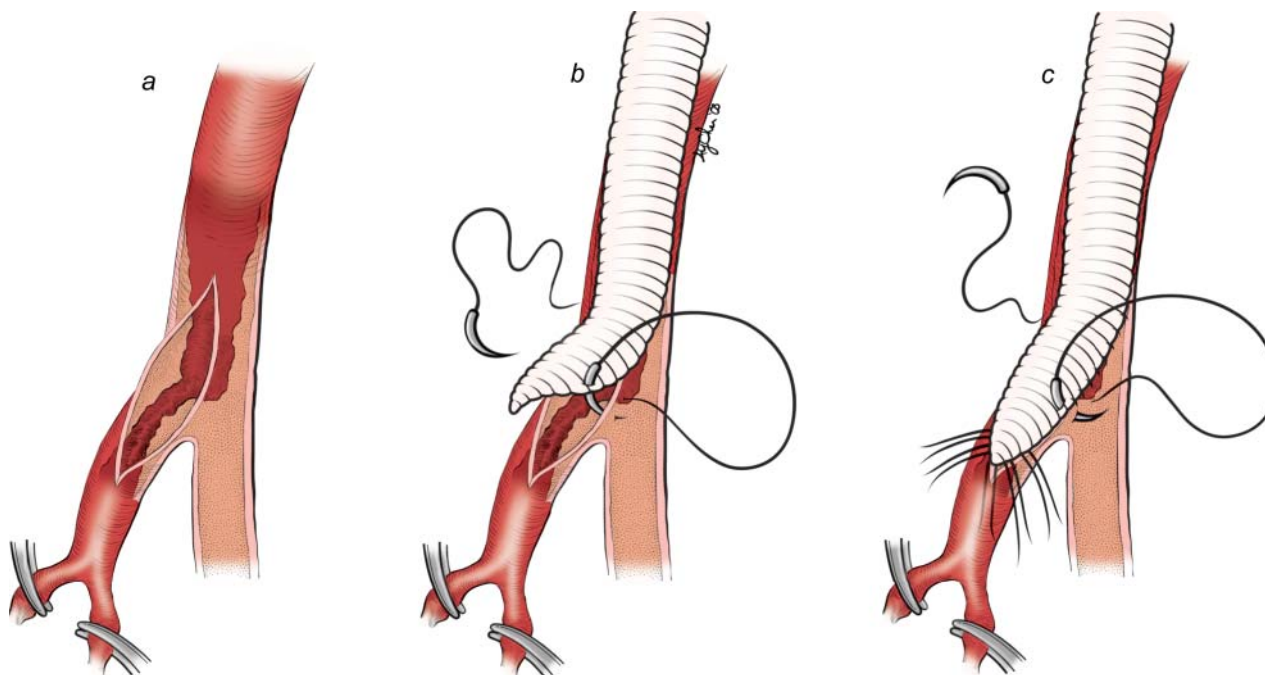


Figure 3 Iliofemoral bypass. (a) When concomitant superficial femoral artery disease is present, the distal anastomosis is performed to a longitudinal arteriotomy that extends onto the proximal profunda femoris. (b) The heel of the hood of the graft is anastomosed to the common femoral artery. (c) The tip of the graft is extended down the profunda femoris.

the retroperitoneum is entered. Complete exposure of the infrarenal aorta is obtained by mobilizing the abdominal contents, the left kidney, and the left ureter medially after blunt dissection along the anterior border of the psoas muscle.

Troubleshooting In those cases in which aortofemoral bypass is being done for a patient with complete infrarenal aortic occlusion, the operative approach is modified to allow placement of a vascular clamp above the renal arteries. The dissection is carried cephalad by retracting the small bowel mesentery and the superior mesenteric artery to the right. The left renal vein is found anterior to the aorta at the level of the renal arteries. Generally, this vein need not be divided to expose the suprarenal aorta. Rather, it should be thoroughly dissected and encircled with a vessel loop so that it can be retracted cephalad and caudad. Sometimes an adrenal or gonadal vein draining into the left renal vein must be ligated and divided to give the renal vein added mobility. With the left renal vein retracted caudad, the suprarenal aorta is dissected.

Step 3: Exposure of the Femoral Artery

A vertical groin incision provides full exposure of the common femoral artery and its bifurcation into the superficial femoral artery and the profunda femoris. The femoral artery and its branches should be circumferentially dissected to give the surgeon an unobstructed view for placement of the vascular clamps.

Step 4: Tunneling of the Bypass Graft

Once the inflow and outflow vessels are adequately exposed, the bypass graft—typically, a bifurcated prosthetic graft measuring 14×7 mm or 16×8 mm—is tunneled from the abdomen to the groins. Its course should pass beneath the ureter and the inguinal ligament. To create the tunnel, one index finger, oriented so that its dorsum faces the vessel wall, is inserted in the midline incision and advanced caudad down to the groin. Simultaneously, the other index finger, oriented so that its volar aspect faces the common femoral artery, is inserted into a groin incision and advanced cephalad until the two fingers meet. As with an iliofemoral bypass graft, care must be taken not to avulse the bridging epigastric vein found just cephalad and posterior to the inguinal ligament. With one of the two fingers held in place, a Silastic tube or vessel loop is passed through the tunnel. The limbs of the graft are attached to the tube or loop and passed through the tunnel down to the groins.

Step 5: Proximal Anastomosis to the Aorta

The proximal aortic anastomosis can be done in either an end-to-end or an end-to-side configuration. An end-to-side beveled anastomosis is preferable for (1) patients with a small (< 1.5 cm) infrarenal aorta and (2) patients with severe occlusive disease of both external iliac arteries in whom it is desirable to preserve flow into the pelvic circulation via the internal iliac arteries. An end-to-end anastomosis is preferable for (1) patients with occlusive iliac disease and a concomitant aortic aneurysm and (2) patients undergoing revascularization for chronic total aortic occlusion. The latter configuration is also less bulky and easier to cover and isolate from the gastrointestinal (GI) tract at the conclusion of the operation.

Once a configuration for the anastomosis has been chosen, IV heparin is given for systemic anticoagulation. The graft is trimmed so that its bifurcation lies close to the proximal anastomosis. The infrarenal aorta is controlled, most commonly with vascular clamps above and below the site of the intended anastomosis. Control of the aorta with a partially occluding vascular clamp may be attempted, but the size of the vessel and the coexistence of aortic disease typically make this difficult or impossible to accomplish.

If an end-to-side anastomosis is to be performed, a longitudinal aortotomy is made and the graft is sewn in place in a spatulated fashion. The toe of the graft is oriented cephalad [see Figure 4]. The anastomosis should be spatulated steeply so that it is not too bulky in the retroperitoneum and can be covered at the end of the procedure. Before

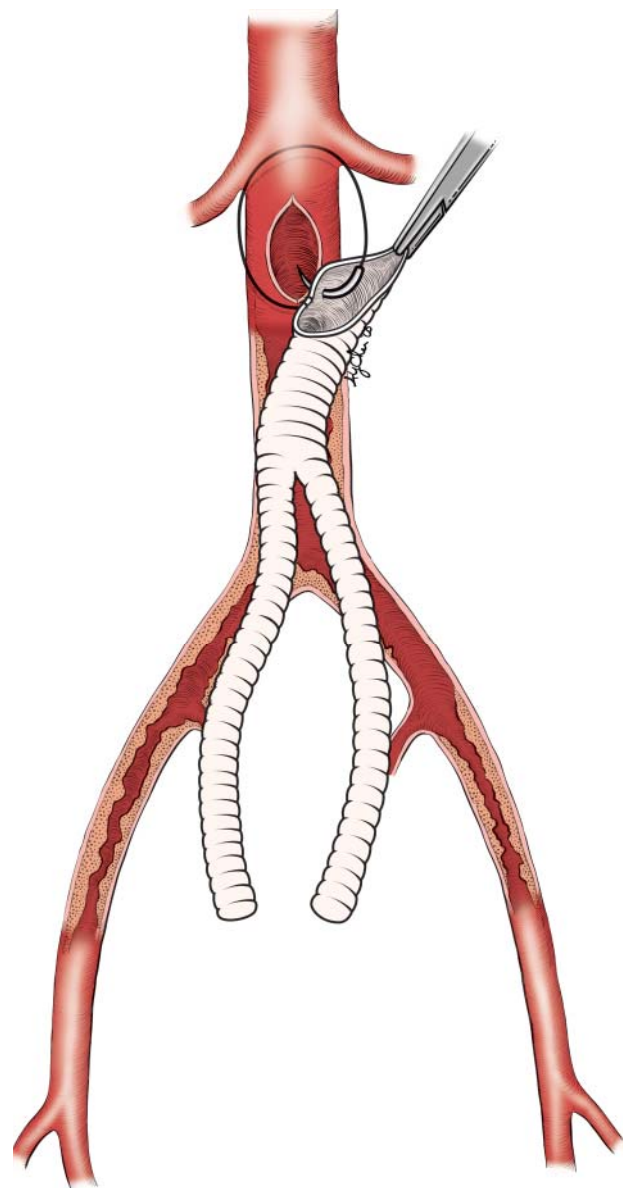


Figure 4 Aortofemoral bypass. Shown is an end-to-side proximal anastomosis.

completion of the anastomosis, the graft is flushed and back-bled.

If an end-to-end anastomosis is to be performed, a small portion of the aorta is resected to allow the graft to fit neatly into the retroperitoneum. In some cases, back-bleeding lumbar arteries in the region of the resected aorta must be oversewn. The distal stump is oversewn with 2-0 or 3-0 polypropylene in two rows; the first row is done with a continuous suture in a horizontal mattress stitch and the second with a continuous suture in a baseball stitch [see Figure 5].

Troubleshooting Vascular control of the aorta is achieved differently when chronic infrarenal aortic occlusion is present. In this setting, placement of a vascular clamp just below the renal arteries may squeeze atherosclerotic debris up into the renal arteries. To prevent this, the vascular clamp should be placed between the superior mesenteric artery and the renal arteries. Once the distal clamp is in place, the aorta is opened below the renal arteries and the atherosclerotic plug is removed. The suprarenal clamp can then be moved to just below the renal arteries, and the proximal anastomosis can be fashioned as already described (see above).

A heavily calcified infrarenal aorta encountered at the time of operation presents a difficult problem. In most cases, the infrarenal aorta can still be used, but the proximal anastomosis should be performed in an end-to-end configuration. Even in the most calcified aortas, the region 1 to 2 cm below the renal arteries is often soft enough to allow an anastomosis to be fashioned. If this is not the case, there are two alternatives: (1) suprarenal aortic control and endarterectomy of the infrarenal aorta just below the renal ostia before the proximal anastomosis and (2) conversion to a thoracofemoral bypass graft [see Thoracofemoral Bypass, below].

Step 6: Distal Anastomosis to the Femoral Artery

Vascular clamps are placed on the common femoral artery and its branches, and the distal anastomosis is performed. As with an iliofemoral bypass, the configuration of the longitudinal arteriotomy depends on the existence of disease in the femoral arteries. If both the superficial femoral artery and the profunda femoris are relatively free of disease, the arteriotomy should extend from the common femoral artery into the superficial femoral artery. If, however, the superficial femoral artery is occluded or heavily diseased, the arteriotomy should

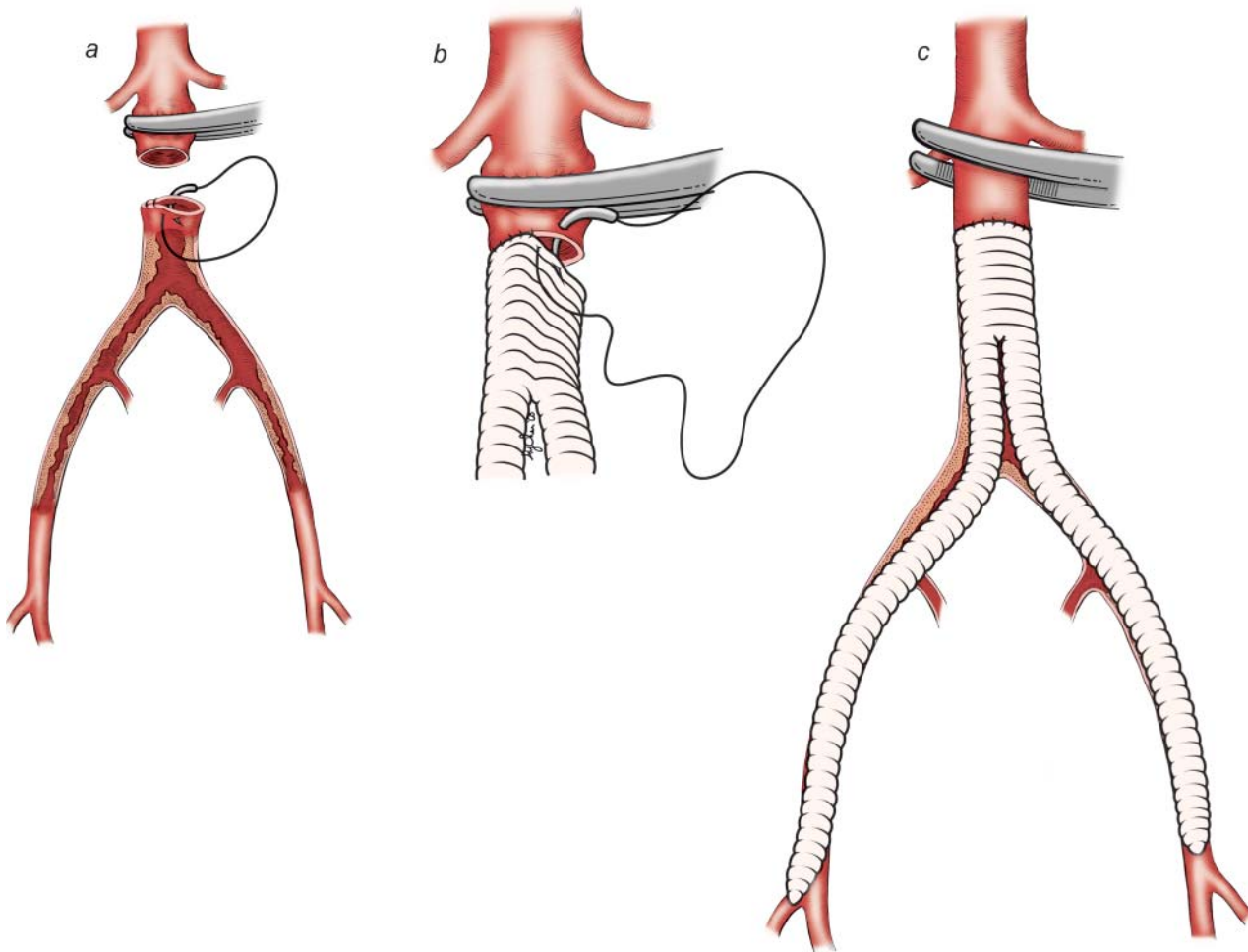


Figure 5 Aortofemoral bypass. Shown is an end-to-end proximal anastomosis. (a) A segment of diseased aorta is resected, and the distal aortic stump is oversewn. (b) The proximal end of the graft is sutured to the open infrarenal aorta. (c) The distal anastomoses are completed in an end-to-side fashion.

extend downward into the profunda femoris. In either case, an end-to-side anastomosis is indicated. Before completion of the bypass, the inflow vessel is flushed and the outflow vessel back-bled to diminish the risk of distal embolization to the legs.

Step 7: Closure of the Retroperitoneum

Before abdominal closure, the retroperitoneum is closed with an absorbable suture to isolate the repair from the GI tract and reduce the risk of an aortoenteric fistula. The ureters should be visualized and preserved. Careless closure of the retroperitoneum can lead to laceration or entrapment of the ureter, particularly the right ureter. Every attempt should be made to cover the graft. If the retroperitoneum is too thin or the graft too bulky, an omental pedicle flap may be used.

THORACOFEMORAL BYPASS

A thoracofemoral bypass is ideal for a small subgroup of patients, comprising (1) those with an occluded old aortofemoral bypass graft, (2) those with a so-called lead-pipe calcified infrarenal aorta that is unusable as an inflow source, and (3) those with a so-called hostile abdomen (i.e., those with an ileal conduit, an ileostomy or colostomy, or a previous aortic graft infection). Candidates for this procedure must have adequate pulmonary reserve and be able to tolerate a thoracotomy. They must also be informed of and accept the low but real risk of paralysis.

The patient is placed in a right semilateral decubitus position so that the hips are nearly flat on the table and the torso is slightly rotated to the patient's right [see Figure 6]. An axillary roll and an inflatable beanbag will help maintain this

position. Because single-lung ventilation will be necessary when the proximal anastomosis is done, either a double-lumen endotracheal tube or a bronchial blocker must be used. Placement of an orogastric tube to decompress the stomach helps keep the diaphragm down during exposure of the descending thoracic aorta.

Step 1: Incision and Exposure of the Descending Thoracic Aorta

The descending thoracic aorta is approached through a left posterior lateral thoracotomy at the level of the seventh or eighth interspace. Additional exposure can be gained by resecting part of the rib and using a self-retaining table-mounted retractor. With the left lung decompressed, the parietal pleura overlying the descending thoracic aorta is incised. The aorta is cleanly dissected, with care taken not to damage the esophagus, which lies medially. Having an orogastric tube in place is advantageous in this regard: the esophagus can easily be located by palpating the tube. Any intercostal vessels in the region of the anticipated aortotomy can be preserved and controlled at the time of the anastomosis.

Step 2: Exposure of the Femoral Artery

Full exposure of the common femoral artery and its bifurcation into the superficial femoral artery and the profunda femoris is obtained via a standard groin incision.

Step 3: Tunneling of the Bypass Graft

The tunnel for the prosthetic graft has two components: (1) a left retroperitoneal tunnel and (2) a subcutaneous tunnel over the pubis. Usually, a tube prosthetic graft is sutured to

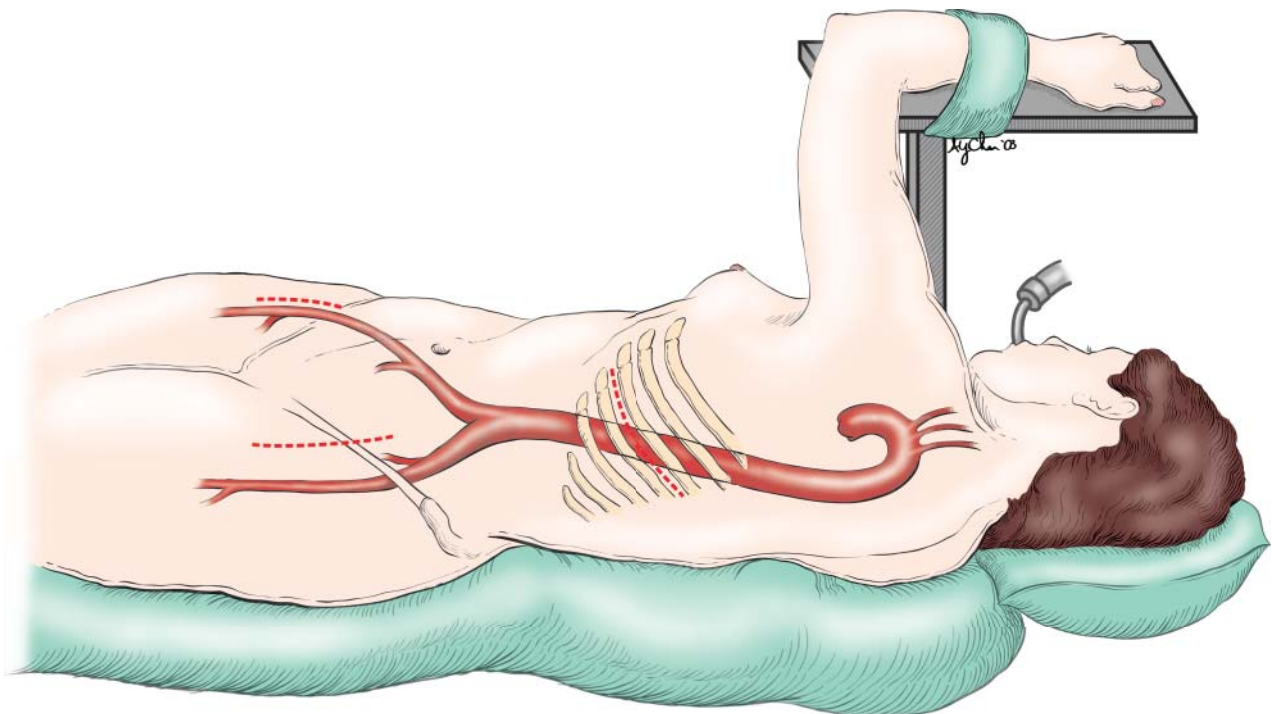


Figure 6 Thoracofemoral bypass. The patient is positioned so that the hips are flat, but the torso is slightly rotated to the patient's right. Three incisions are made: a left posterolateral thoracotomy and two groin incisions. Dashed lines denote skin incision.

a bifurcated graft before being tunneled through the retroperitoneum. The retroperitoneal tunnel is started in the chest by making a 1 cm hole in the posterior lateral aspect of the left diaphragm. An index finger is inserted through this hole and advanced caudad into the retroperitoneum as far as it can go. The other index finger is inserted through the left groin incision, oriented directly over the external iliac artery, and advanced cephalad into the retroperitoneum [see Figure 7]. Care is taken not to avulse the bridging epigastric vein found posterior and inferior to the inguinal ligament. In most cases, the left retroperitoneal tunnel must then be completed by using a long, hollow metal tunneling device such as the Gore Tunneler (W. L. Gore & Associates, Inc., Tempe, AZ). Once this tunnel is completed, the graft is passed through it in such a way that the bifurcated limbs are brought caudad down into the left groin wound.

Next, the subcutaneous tunnel from the left groin to the right groin is bluntly fashioned anterior to the pubis. It should not be oriented superior to the pubis because of the risk of injury to an overdistended bladder. To minimize this risk, an indwelling urinary catheter is advocated. The subcutaneous tunnel is used to pass the right limb of the graft over to the right groin. It is not uncommon for the bifurcation of the prosthetic graft to lie just cephalad to the left groin wound.

Step 4: Proximal Anastomosis to the Descending Thoracic Aorta

Once the graft has been tunneled, the patient undergoes systemic anticoagulation with IV heparin. The descending thoracic aorta is controlled either with a side-biting clamp or with two completely occluding aortic clamps placed in close proximity to each other. In the latter case, one or two intercostal arteries may have to be temporarily controlled as well. A longitudinal aortotomy is then made along the left lateral aspect of the thoracic aorta, and a beveled end-to-side

anastomosis is fashioned. Exposure can be enhanced by ventilating the right lung and attaching the orogastric tube to suction to decompress the stomach. Before completion of the anastomosis, the aorta is flushed and back-bled.

Troubleshooting Partial aortic control with a side-biting vascular clamp is successful in most cases, but it is not recommended when the descending thoracic aorta is heavily diseased and calcified or when preoperative imaging studies show thrombus in this location. If an intercostal artery cannot be temporarily controlled with clamps, it can be oversewn from the inside of the aorta to prevent nuisance back-bleeding.

Step 5: Distal Anastomosis to the Femoral Artery

Vascular clamps are placed on the common femoral artery and its branches, and an end-to-side anastomosis is fashioned distally. Again, the configuration of the longitudinal arteriotomy depends on the existence of disease in the femoral arteries. If both the superficial femoral artery and the profunda femoris are relatively free of disease, the arteriotomy should extend from the common femoral artery into the superficial femoral artery. If, however, the superficial femoral artery is occluded or heavily diseased, the arteriotomy should extend downward into the profunda femoris. Before completion of the bypass, the inflow vessel is flushed and the outflow vessel is back-bled.

Step 6: Closure of the Chest

Once the proximal anastomosis is complete, the left lung is reinflated. At the conclusion of the operation, the chest is closed in a standard fashion over two chest tubes. The proximal anastomosis should be covered with either a prosthetic patch or bovine pericardium to diminish the risk of an aorto-pulmonary fistula.

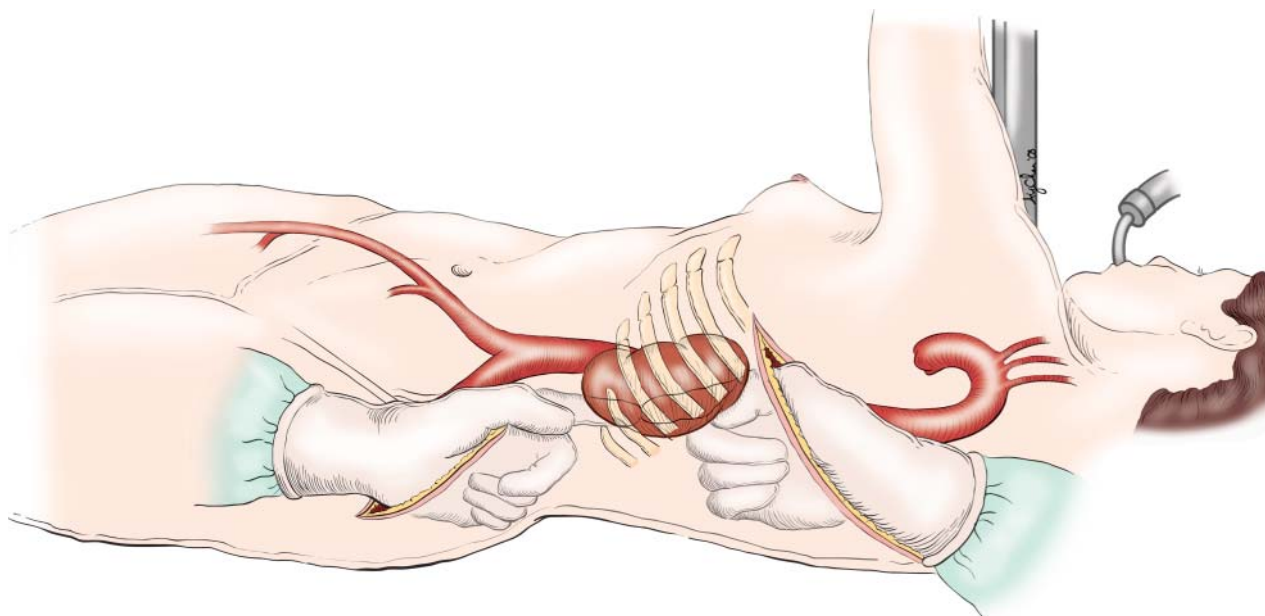


Figure 7 Thoracofemoral bypass. A left retroperitoneal tunnel is fashioned for passage of the prosthetic graft downward to the groin. (The right arm of the graft is subsequently passed to the right groin via a subcutaneous tunnel anterior to the pubis.)

AXILLOFEMORAL BYPASS

Axillofemoral bypass is ideally suited to elderly patients who cannot tolerate an aortic operation. The hemodynamic changes occurring during the operation are minimal, and recovery from the three small incisions used is substantially quicker than that from a laparotomy or a thoracotomy.

Because hemodynamically significant occlusive disease is less common in the right innominate artery than in the left subclavian artery, the right axillary is more often used as the inflow vessel than the left axillary artery. Such occlusion can easily be identified preoperatively by measuring blood pressure in both arms. The sterile field includes both groins, the appropriate side of the chest (usually the right) up to the neck, and the appropriate flank (again, usually the right). It need not include the entire inflow arm; however, the arm should be abducted 90° and positioned on an arm board.

Step 1: Incision and Exposure of the Axillary Artery

The patient is placed in the supine position. The axillary artery is approached through a horizontal 6 cm infraclavicular incision placed approximately 2 cm below the inferior border of the clavicle. Dissection is carried through the subcutaneous tissue, the fascia overlying the pectoralis major is incised, and the muscle is bluntly dissected along the length of its fibers. The dissection plane should remain medial to the pectoralis minor.

Next, the axillary vein is encountered and retracted caudad, and the underlying axillary artery is visualized. The axillary artery is cleanly dissected, with care taken not to retract or damage the brachial plexus lying deep and superior to the artery. For full exposure of the axillary artery, the thoracoacromial artery may have to be ligated at its origin. For easier retraction, the axillary artery may be encircled with vessel loops.

Step 2: Exposure of the Femoral Artery

The femoral artery and its bifurcation into the superficial femoral and profunda femoris arteries are approached through a standard groin incision.

Step 3: Tunneling of the Bypass Graft

Once the inflow and outflow vessels are adequately exposed, a prosthetic graft 80 to 100 cm long and 8 or 10 mm in diameter is tunneled from the axillary incision, anterior to the pectoralis minor, and down to the flank. The use of a long, hollow metal tunneler is recommended at this point. To facilitate tunneling, a single counterincision is made in the midaxillary line over the sixth or seventh intercostal space. From this counterincision, the graft is tunneled along the flank, over the iliac crest, anterior to the anterior superior iliac process, and into the ipsilateral groin wound. Except for the portions in the axilla and the groin, the entire graft should lie in a subcutaneous plane.

Next, a subcutaneous tunnel from the ipsilateral groin to the contralateral groin is bluntly fashioned anterior to the pubis to allow passage of a second prosthetic graft (a short crossover graft 8 mm in diameter). This tunnel should not be oriented superior to the pubis because of the risk of injury to an overdistended bladder.

Step 4: Proximal Anastomosis to the Axillary Artery

With the long graft in place, IV heparin is given for systemic anticoagulation. The pectoralis minor may be retracted laterally to provide additional exposure. The axillary artery is controlled with vascular clamps, with care taken not to include any part of the brachial plexus lying nearby. A longitudinal arteriotomy is made along the length of the axillary artery. The proximal anastomosis is then fashioned in an end-to-side configuration. The anastomosis must lie medial to the medial border of the pectoralis minor. This is critical for preventing avulsion of the graft from the axillary artery when the patient fully abducts the arm postoperatively. Before the anastomosis is completed, it is flushed and back-bled. Once blood flow to the arm is reestablished, the graft should be positioned so that it lies parallel to the axillary artery for a length of 2 to 3 cm before diving deep and caudad.

Step 5: Distal Anastomosis to the Femoral Artery

The distal anastomosis to the femoral arteries is performed as described earlier [see Thoracofemoral Bypass, above]. Some controversy remains over the formation of the short crossover graft from the axillary bypass graft to the contralateral femoral artery. My practice is to place the proximal anastomosis of the crossover femorofemoral anastomosis on the hood (or distal anastomosis) of the axillofemoral bypass graft [see Figure 8]. Others prefer to use a commercially available bifurcated axillofemoral prosthetic graft or to place the crossover graft more proximally along the length of the axillofemoral graft.

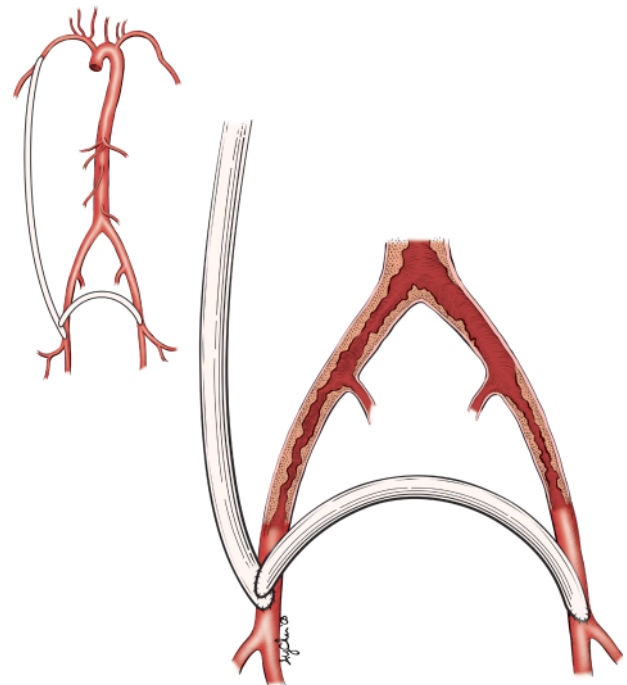


Figure 8 Axillofemoral bypass. Shown is the recommended configuration for the short femorofemoral crossover graft originating from the long axillofemoral graft. The femoro-femoral graft originated from the hood of the axillofemoral graft.

FEMOROFEMORAL BYPASS

A femorofemoral crossover bypass is well suited to patients who have unilateral complete occlusion or a diffusely diseased iliac system but have a relatively normal contralateral iliac system. It is performed with the patient supine and is conducted in essentially the same fashion as an axillofemoral bypass, but without the axillary anastomosis.

ENDOVASCULAR THERAPY

The use of percutaneous balloon angioplasty and stenting for the treatment of peripheral vascular disease has grown exponentially since its introduction in the 1990s. With regard to short-term results, patients clearly experience less pain, recover more quickly, and regain function earlier. Initially, there was some question about the durability of stenting; however, data from longer follow-up periods indicate that this approach is an acceptable alternative for patients with focal aortoiliac occlusive disease.^{8–10}

Complications

Certain complications are associated with all of the revascularization procedures discussed, such as bleeding, distal embolization, graft thrombosis, and graft infection. Late graft infection, recurrent disease, and pseudoaneurysm formation are known long-term complications as well. In addition, the following complications are unique to one or more of the procedures but do not arise with the others:

1. Injury to the ureters, resulting from their position overlying the iliac vessels (aortoiliac endarterectomy, iliofemoral bypass, axillofemoral bypass)
2. Impotence, resulting from damage to the autonomic nerve fibers around the origin of the left common iliac artery (aortoiliac endarterectomy, iliofemoral bypass, axillofemoral bypass)
3. Bleeding or deep vein thrombosis, related to trauma to the underlying iliac venous structures (all)
4. Paraplegia, resulting from the sacrifice of intercostal vessels supplying the anterior spinal artery (thoracofemoral bypass)
5. Colonic ischemia or infarction, resulting from hindered primary flow via the inferior mesenteric artery or collateral vessels from the hypogastric arteries (all)

6. Buttock claudication, resulting from disruption of inline flow to the pelvic circulation (all)
7. Aortoduodenal fistula, resulting from incomplete coverage of an aortic graft (aortofemoral and iliofemoral bypass)
8. Renal failure, resulting from acute tubular necrosis or embolization when a suprarenal aortic clamp is used (thoracofemoral bypass and aortobifemoral bypass)
9. Arm paralysis, resulting from injury to the deep and superiorly oriented brachial plexus (axillofemoral bypass)
10. Respiratory failure resulting from effusion or hemothorax after a left thoracotomy or from inadvertent pneumothorax during exposure of the axillary artery (thoracofemoral bypass, axillofemoral bypass)

Outcome Evaluation

Regardless of which operation is performed to treat aortoiliac occlusive disease, the subsequent outcome should be immediate relief of presenting symptoms—for example, reduced claudication, resolution of rest pain, or improved distal wound healing. Unfortunately, overall long-term survival in patients with symptomatic aortoiliac occlusive disease is not improved by operative management and is typically 10 to 15 years less than that in a normal age-matched group. Not surprisingly, by far the most significant long-term cause of death in these patients is atherosclerotic cardiac disease, which underscores the importance of a thorough preoperative cardiac evaluation.

In general, direct aortoiliac reconstructions (i.e., endarterectomy, aortofemoral bypass, and thoracofemoral bypass) have an expected patency rate of 85 to 90% at 5 years and 70 to 75% at 10 years.^{11–13} When these operations are performed at experienced centers on patients who are considered to be good risk candidates, mortality is typically less than 3%.^{14,15} Femorofemoral bypass and axillobifemoral bypass have expected 5-year patency rates of 70 to 75% and 60 to 85%, respectively.^{16–19} Coexistent superficial femoral artery disease in the recipient vessels has a detrimental effect on the long-term patency of these bypasses.²⁰ Long-term anticoagulation with warfarin may improve the patency for an axillobifemoral bypass graft.

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Figures 1 through 8 Alice Y. Chen.

13 SURGICAL TREATMENT OF THE INFECTED AORTIC GRAFT

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In dealing with an infected aortic graft, the primary goal of treatment is to save life and limb. This goal is best accomplished by eradicating all infected graft material and maintaining adequate circulation with appropriate vascular reconstruction. Secondary goals are to minimize morbidity, restore normal function and maintain long-term function without the need for repeated intervention or amputation. Despite advances in perioperative critical care and antimicrobial therapy, the morbidity and mortality associated with aortic graft infections remain high.

Before definitive reconstruction, all infected graft material must be débrided, along with any grossly infected vascular tissue and surrounding soft tissue. Once débridement is complete, there are several options for reconstruction, including (1) extra-anatomic bypass, (2) use of an arterial allograft, (3) placement of vascular prostheses treated with or soaked in antibiotic solutions, and (4) in situ replacement with a femoropopliteal vein (FPV) graft. The choice among these options is made on the basis of the specific clinical situation present. The primary focus of the technical description in this chapter, however, is on the fourth option [*see Operative Technique, below*].

Choice of Procedure

EXTRA-ANATOMIC BYPASS

Extra-anatomic bypass, usually performed as an axillofemoral bypass [*see Figure 1*], is a good option for treatment of an infected aortic graft when groin infection is absent and lower extremity runoff is good. The primary advantages of extra-anatomic bypass are that it minimizes lower extremity ischemic time and that it is less of a physiologic insult than an aorta-based bypass procedure (mainly because it is typically done in a staged fashion). The primary disadvantages are that long-term patency is poor and that there is a significant risk of reinfection. In addition, if groin infection is present, the bypass is compromised even further by the need to use vessels such as the profunda femoris artery or the popliteal artery for distal targets. Bilateral axillofemoral bypasses are often required in this situation. Because of these factors, the durability of an extra-anatomic bypass may be limited despite aggressive antithrombotic treatment.

Extra-anatomic bypasses are plagued by sudden thrombotic occlusion, and amputation rates are high. In one large series, one third of patients required a major amputation

during long-term follow-up.¹ Reinfection also is a major concern when prosthetic grafts are employed in patients with ongoing infection: it occurs in 10 to 20% of such patients and often proves lethal. A final major concern in patients who undergo excision of an infected aortic graft and extra-anatomic bypass is the possibility of blowout of the aortic stump. This is an infrequent occurrence (incidence < 10%) but one that is almost always fatal.

AORTIC ALLOGRAFT

Several modern reports have confirmed the efficacy of cryopreserved allografts in the treatment of aortic prosthetic graft infection.²⁻⁵ A recent systemic review and meta-analysis suggested that although cryopreserved allografts are not as resistant to infection as an autogenous FPV, the incidence of reinfection after in situ reconstruction with a cryopreserved allograft is still fairly low.⁶ Graft-related complications such as aneurysmal degeneration and rupture have been reported.⁶ Some authors report that the main advantages of cryopreserved vein to replace an infected aortic graft are improved patency rates compared with extra-anatomic bypass and avoidance of the prolonged operating time associated with in situ replacement with FPVs.⁷⁻⁹ However, because aortic allografts are available in the United States only on a limited basis, this technique is not a useful option in emergency situations.

ANTIBIOTIC-TREATED PROSTHETIC GRAFT

Use of antibiotic-treated prosthetic graft material for reconstruction has the advantage of permitting an expeditious reconstruction that leaves no aortic stump.^{7,10-14} However, the reinfection rate is unpredictable, and patients must undergo lifelong antibiotic therapy. Typically, the new prosthetic graft is soaked in rifampin, 60 mg/mL, for 15 minutes before implantation.^{12,13}

IN SITU AUTOGENOUS RECONSTRUCTION

Dissatisfaction with the long-term patency of extra-anatomic bypass led to the development of in situ autogenous venous reconstruction.¹⁵⁻¹⁷ Early reconstructive attempts that made use of great saphenous vein grafts proved unsuccessful because the small caliber of the venous conduit resulted in low patency rates. Subsequent attempts that made use of larger-caliber FPV grafts, however, proved highly successful.

FPV grafts have excellent long-term patency and are resistant to reinfection. In addition, they are ideal conduits for patients with extensive multilevel occlusive disease, in whom venous grafts theoretically would have better patency than prosthetic grafts. An analogy would be the superior durability of venous grafts for femoropopliteal bypass in comparison

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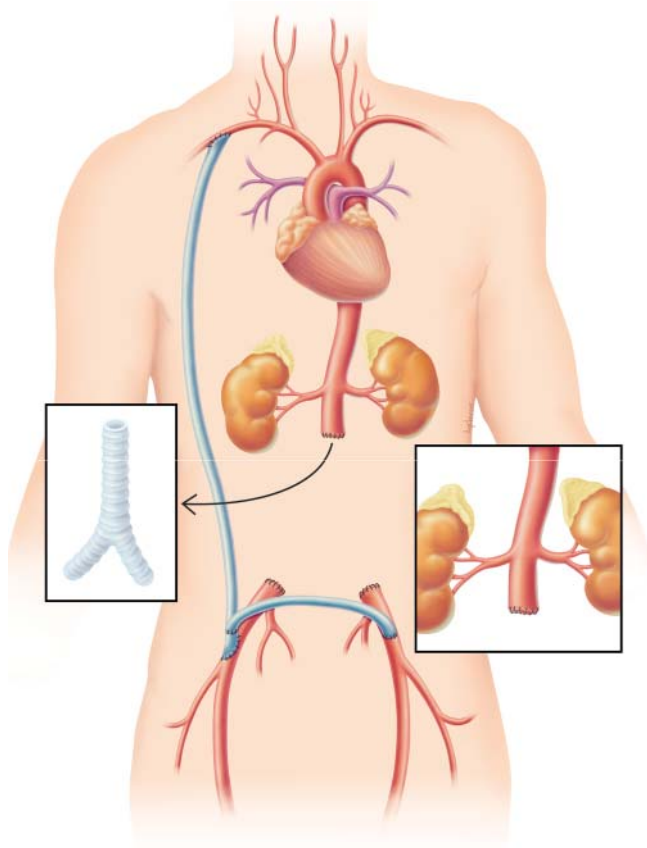


Figure 1 Standard treatment of aortic graft infection involves axillobifemoral bypass, removal of the infected prosthesis, and oversewing of the aortic stump. This procedure can be performed in either one or two stages. It is most useful in patients who do not have infection extending into the femoral area.

with prosthetic grafts. The primary disadvantage of reconstruction with FPV grafts is that the procedure is time consuming and technically demanding. In our experience, the mean operating time is about 8 hours. The lower extremity ischemic time is longer than that in patients undergoing extra-anatomic bypass but can be minimized by sequencing the operation so as to shorten the cross-clamp time and by using a two-team approach. Alternatively, FPV harvest can be staged as a separate operation from graft excision and in situ reconstruction.¹⁸ An additional disadvantage of using FPV grafts is the associated short-term venous morbidity. Approximately 12% of patients who undergo FPV harvesting will require fasciotomy, typically performed at the time of vein harvest. The fasciotomy rate is highest in patients who undergo concurrent great saphenous vein harvesting and in those who have severe, preexisting lower extremity ischemia (ankle-brachial index [ABI] < 0.4).¹⁹ Long-term venous morbidity appears to be low, with rare cases of venous ulceration or venous claudication reported in late follow-up.¹⁸ Mild to moderate chronic edema develops in approximately 15% of patients but has been easily controlled with compression stockings. Aneurysmal degeneration of the vein grafts is a theoretical risk but, in practice, is rare. Vein graft stenosis is

uncommon but is often amenable to balloon angioplasty to preserve graft patency.²⁰

Preoperative Evaluation

The preoperative workup should assess the extent of infection, look for concomitant occlusive disease (indicating a possible need for infrainguinal, visceral, or renal reconstruction), and determine whether there are other associated infectious complications that must be treated surgically (e.g., a psoas abscess, an entrapped ureter with hydronephrosis, or duodenal erosion necessitating duodenal repair). In patients who have previously undergone prosthetic aortofemoral bypass, infection may be limited to one limb of the graft and may be treatable by replacing only that limb. In patients who have previously undergone prosthetic infrainguinal bypass, the prosthetic graft may have to be removed and replaced with an autogenous graft.

Traditionally, the mainstay of the preoperative workup was arteriography complemented by computed tomography (CT), but, currently, the workup is with CT angiography alone. CT angiography is often capable of evaluating the extent of infection, visualizing the sites of previous prosthetic anastomoses, and delineating the arterial anatomy. Magnetic resonance angiography has been a satisfactory alternative, particularly in patients with renal insufficiency. Graft duplex imaging may be useful to diagnose graft infection: the finding of a hypoechoic rim around the graft is indicative of a graft infection. In our experience, tagged white blood cell scanning has rarely been necessary to make the diagnosis of a graft infection and is associated with significant rates of both false positive and false negative results.

When autogenous reconstruction with deep vein grafts is being considered, preoperative assessment of the adequacy of the vein segments must also be performed. This is accomplished by means of venous duplex ultrasonography. Duplex examination of the lower-extremity venous system establishes the diameter and the available length of the deep veins. In addition, the duplex scan can evaluate acute or chronic thrombosis of the deep veins, changes indicative of recanalization, congenital absence or duplication of venous segments, and unusually small deep veins. When the FPV is small (< 6 mm), absent, or incomplete, a dominant profunda femoris vein is usually present. This vein courses posteriorly through the thigh to connect with the popliteal vein and can also be used as a venous autograft. A vein less than 6 mm or a chronically occluded vein is not routinely used. Duplex vein mapping of the great saphenous system is also routinely performed and may provide useful information in the event that concomitant infrainguinal reconstruction is planned or may have to be performed unexpectedly.

Operative Planning

Removal of an infected aortic graft and autogenous reconstruction require prolonged exposure of large portions of the body surface. Significant drops in core body temperature, combined with blood and other fluid losses, may lead to metabolic acidosis, coagulopathy, cardiac dysrhythmia, and immune compromise. Accordingly, core body temperature should be kept above 36°C by applying heated-air warming

blankets to the upper body, using warmed fluid for resuscitation, and maintaining a warm ambient temperature in the operating room. Ongoing fluid losses should be anticipated, and aggressive resuscitation should be based on maintaining a normal urine output and/or central venous pressures.

To minimize ischemic time with cross-clamping, the major tasks involved in excision of an infected aortic graft and in situ autogenous reconstruction should be sequenced as follows: (1) dissection of FPVs, which are left in situ until needed; (2) isolation and control of the femoral vessels; (3) entry into the abdomen and control of the aorta; (4) removal of the infected prosthesis; and (5) reconstruction with the deep vein grafts.²¹ The entire operation has been termed the creation of a neoaortoiliac system (NAIS).

Operative Technique

STEP 1: THIGH INCISION AND EXPOSURE OF FEMORAL VESSELS

The patient is placed in the supine position with the legs “froglegged” and supported under the thighs. An incision is made on the thigh along the lateral border of the sartorius muscle. This lateral incision not only facilitates vein harvesting but also allows the surgeon to expose the femoral vessels while avoiding the infected femoral incision medially in the groins.

The sartorius is reflected medially so as to preserve the medial segmental blood supply. The subsartorial canal is entered, and the femoral vessels are exposed. The femoral vein is usually located posterior to and slightly lateral to the artery at this level. The entire venous system is then exposed from the distal common femoral vein downward, including the proximal profunda femoris vein through the Hunter canal to the midpopliteal level [see Figure 2]. The saphenous nerve

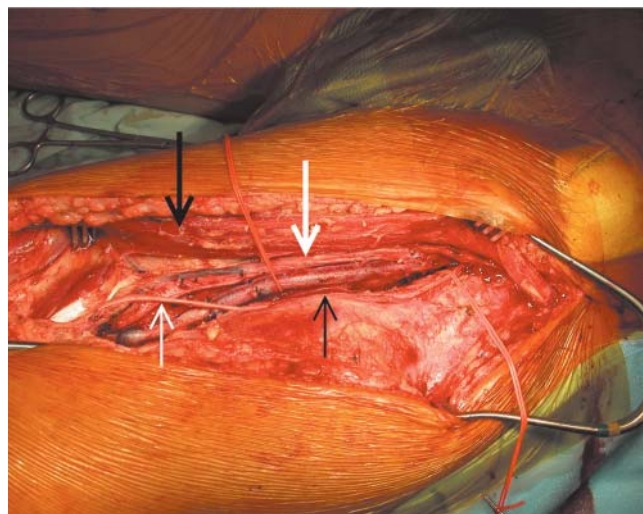


Figure 2 The femoropopliteal vein (*thin black arrow*), the superficial femoral artery (*thick white arrow*), and the saphenous nerve (*thin white arrow*) lie deep to the sartorius (*thick black arrow*) in the subsartorial canal. The sartorius is reflected medially to expose these structures. The adductor magnus tendon is divided to expose these structures as they traverse the Hunter canal.

is located in this canal and is intimately associated with the femoral vessels. Care must be taken not to injure this nerve either directly or through excessive traction; such an injury will cause irritating postoperative saphenous neuralgia.

Care must also be taken to preserve major branches of the superficial femoral artery when this vessel is occluded or severely diseased. Interruption of these branches, which may supply collateral circulation to distal beds, may result in unexpected critical ischemia of the lower extremity after completion of the proximal reconstruction, and further infrainguinal arterial reconstruction may be necessary.

STEP 2: DISSECTION OF FPV

The FPV has many large and small side branches. Careful, meticulous, and unhurried ligation of these branches is critical. Most are doubly ligated, with suture ligation reserved for the larger branches. Failure to ligate a branch adequately will result in exsanguinating hemorrhage if a tie loosens and pops off when exposed to aortic pressure. The large diameter of the FPVs, in comparison with the saphenous veins, results in an increase in wall tension that can predispose to a “popped tie.” Although, as a rule, the FPV is larger and sturdier than the typical great saphenous vein, it is thin walled in some areas where branches are present. If a branch is avulsed during dissection, suture repair with 6-0 or 7-0 polypropylene is necessary. Branch ligation during FPV harvesting differs from the typical branch ligation during saphenous vein harvesting. The branches of the FPV are ligated close to their bases because this is where the vein wall tends to be thin; the larger caliber of the FPV makes this technique possible. In contrast, the branches of the great saphenous vein, which is of smaller caliber, are ligated slightly away from the vessel wall to ensure that the lumen of the vein is not encroached on.

The extent of the harvest depends on the length of venous conduit required for reconstruction. Proximal dissection extends to the level of the junction of the femoral and profunda femoris veins. These veins join to form the common femoral vein, which is also exposed in the dissection. The profunda femoris vein is easily recognizable as a large, posteriorly penetrating vein in the proximal thigh. Distally, dissection is carried through the adductor hiatus by dividing the tendon of the adductor magnus; this measure allows easy access to the proximal portion of the popliteal vein. The popliteal segment of the vein has multiple large branches, which must be carefully ligated. The dissection can easily be taken down to the level of the knee joint. The veins are left in situ until the required length of conduit can be determined.

STEP 3: DISSECTION AND CONTROL OF FEMORAL VESSELS

The femoral vessels can usually be dissected by extending the vein harvest incision cephalad along the lateral border of the sartorius to the level of the anterior superior iliac spine. Through this incision, control of the superficial femoral, profunda femoris, and common femoral vessels is gained. In addition, the distal limbs of the existing aortofemoral graft can be controlled. Occasionally, control is difficult to obtain from a position lateral to the sartorius, in which case, the medial aspect of the muscle may be dissected from the subcutaneous tissue to afford improved exposure. Only rarely is a more medial incision required. As noted [see Step 1: Thigh

Incision and Exposure of Femoral Vessels, *above*], the lateral approach allows the surgeon to avoid entering the previous incision, where there may be a draining sinus or cellulitis.

STEP 4: ABDOMINAL INCISION AND DISSECTION OF AORTA

The abdomen is then entered either through a midline abdominal incision or via a retroperitoneal approach; the latter is particularly helpful in avoiding tedious abdominal adhesions. Dissection for control of the aorta above the aortic anastomosis is performed. The anastomosis may be near the level of the renal arteries, in which case, suprarenal or supraceliac aortic control may be required.

STEP 5: REMOVAL AND PREPARATION OF VENOUS GRAFTS

Before cross-clamping, the vein grafts are removed and prepared. The required lengths of each graft are determined by measuring from the aortic anastomosis to the femoral anastomoses on both sides. The femoral vein is divided flush with the profunda femoris vein and oversewn with a 5-0 polypropylene suture. This creates a smooth transition point from the profunda femoris vein to the common femoral vein and leaves no stump in which blood can stagnate and create thrombus. The grafts are then distended in a 4°C solution containing lactated Ringer solution (1 L), heparin (5,000 U), albumin (25 g), and papaverine (60 mg). Any leaks are repaired either with additional silk ties or with figure-eight fine polypropylene sutures. Any adventitial bands that distort the lumen are lysed.

Next, the valves in the grafts must be lysed. This is a critical step because the grafts are placed in a nonreversed fashion to optimize size matching with the aorta for the proximal anastomosis. Valvulotomes have been used for valve lysis in these large-caliber veins, but the results have been unsatisfactory: lysis is often incomplete, and the remnants of the valves may become sites of graft stenosis. Our current practice is to evert the venous grafts completely and to excise all valves under direct vision [see *Figure 3*].

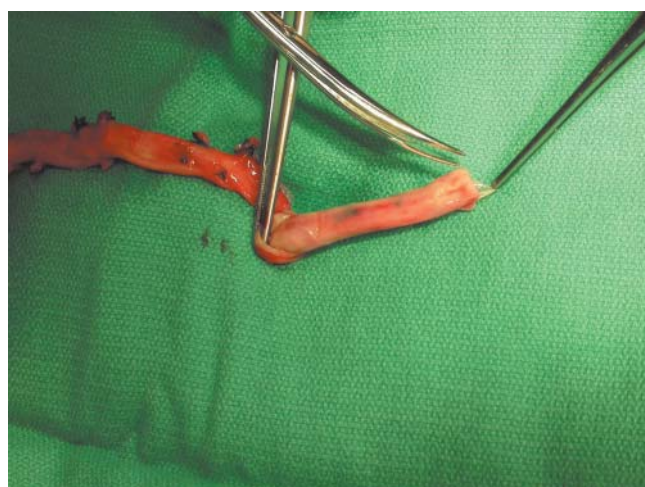


Figure 3 Use of a valvulotome typically results in incomplete valve lysis. It is preferable to evert the entire venous graft and excise the valves (which usually number three or four) completely with scissors.

STEP 6: REMOVAL OF BODY OF PREVIOUS GRAFT AND PROXIMAL ANASTOMOSIS OF NEW GRAFT TO AORTA

The patient is systemically heparinized, and the aorta above the anastomosis and both limbs of the graft are cross-clamped. The body of the graft is then excised, with the limbs left in place. All prosthetic material, including sutures, is removed. The previous aortic anastomosis may have been done in either an end-to-end or an end-to-side fashion. If it was an end-to-side anastomosis, the distal end of the aorta will have to be oversewn with a large suture (e.g., 0 or 1-0 polypropylene). Balloon occlusion of the distal lumen is a helpful adjunctive measure before ligation. Regardless of how the previous aortic anastomosis was done, the new anastomosis is typically constructed in an end-to-end fashion. The distal limbs of the existing graft are left in place while the aortic anastomosis is performed so as to decrease the blood loss that typically occurs when the limbs are removed from their tunnels.

Multiple configurations have been successfully employed to reconstruct the distal aortic and iliac-femoral vasculature [see *Figure 4*]. The proximal anastomosis is performed with a continuous 4-0 polypropylene suture. The diameter of the proximal FPV graft is typically about 1.5 cm or a little greater, and the mismatch in diameter between the graft and the aorta is dealt with by taking slightly more advancement (i.e., placing sutures slightly farther apart) on the aortic wall than on the graft wall [see *Figure 5a*]. If the caliber discrepancy between the two structures is too large, other techniques must be employed, such as plication of the aorta, joining of the venous grafts in a pantaloony configuration, or placement of a triangular patch at the proximal aspect of the graft [see *Figure 5, b through d*].

After the proximal anastomosis is complete, the venous graft is distended under aortic pressure, and the side branches are carefully examined to confirm that all ligatures are securely placed. Any questionable areas are repaired. Anastomotic leakage is also repaired with the aorta clamped to ensure that the venous graft is not torn during repair.

STEP 7: REMOVAL OF LIMBS OF PREVIOUS GRAFT AND DISTAL ANASTOMOSES OF NEW GRAFTS TO FEMORAL ARTERIES

The femoral limbs of the prosthetic aortobifemoral grafts are then removed by pulling them through the groin incisions. When the FPV grafts are tunneled to the groins, care must be taken to ensure that ligated side branches are not torn or dislodged. To reduce this risk, we have found it helpful to bring the grafts through the tunnels in the nondistended state. Because it may be difficult to create new tunnels through the scarred retroperitoneum, the vein grafts may be tunneled through the existing tunnels. In many cases, the existing tunnels are smaller in caliber than the new vein grafts, and careful finger dilation of the tunnels is required.

The femoral anastomoses are fashioned in a standard manner. Once again, all prosthetic material and all surrounding infected tissue must be debrided. On occasion, profunda-plasty or reimplantation of the profunda femoris may be required. If possible, the femoral anastomoses should be performed in an end-to-side manner to preserve retrograde pelvic perfusion.

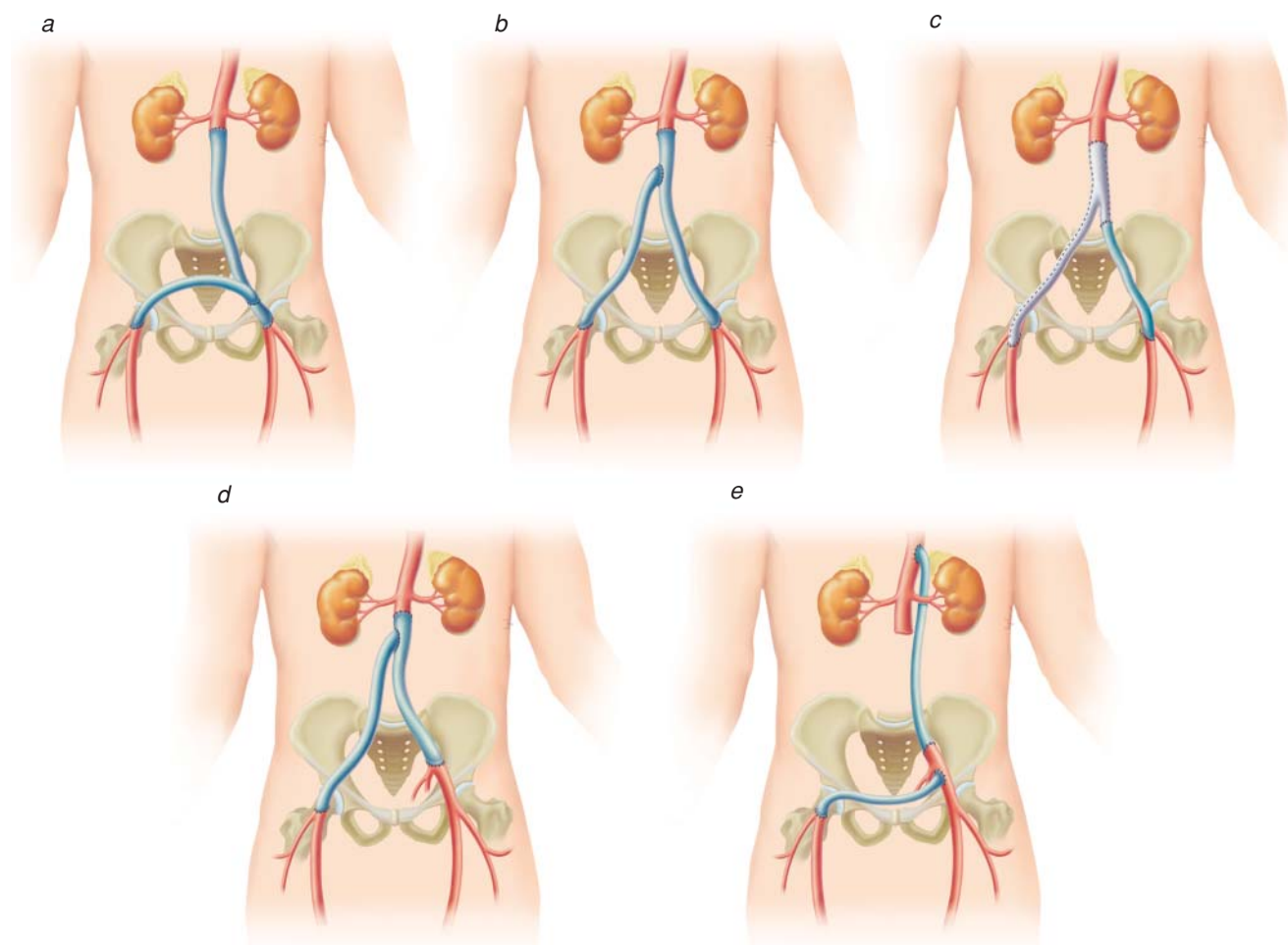


Figure 4 Multiple anatomic reconstructions have been used to recreate the aorto-iliac-femoral anatomy. (a) Shown is an aortounifemoral bypass with a femorofemoral crossover. (b) Instead of a femorofemoral bypass, the second limb may be brought off the midportion of the first limb in an end-to-side manner. (c) If infection is limited to one limb of an aortofemoral bypass, a femoropopliteal vein graft may be used to replace only the infected portion. (d) One segment of vein may be used to replace both segments of an aortoiliac or aortofemoral graft. (e) In some instances, it may be easier to approach the paraceliac aorta via a retroperitoneal approach for the proximal anastomosis.

Perfusion of the extremities must be assessed before the leg wounds are closed. If Doppler arterial signals are absent at the level of the ankle, a femoropopliteal or distal bypass may be necessary. Because the popliteal artery is exposed during FPV harvesting, adjunctive femoropopliteal bypass is easily accomplished in this setting.

STEP 8: CLOSURE

After reversal of heparinization, the thigh wounds are copiously irrigated and closed over closed-suction drains. Placement of drains prevents postoperative seromas and subsequent wound complications. Even though these wounds are contaminated as a consequence of the proximity of the infected graft in the groin wound, infection is rare. Often there are draining sinuses medial to the vein harvest incisions, which are débrided and left open.

Postoperative Care

Parenteral antibiotics are continued for 7 to 10 days, and antibiotic coverage is modified on the basis of intraoperative

cultures of the graft material and wound swabs. A longer antibiotic course for up to 6 weeks may be required after incomplete graft removal (because the entire graft was not involved). Patients with associated aortoenteric fistulas (AEFs) are started on antifungal agents in the immediate postoperative period.

Intermittent pneumatic compression and low-dose subcutaneous heparin (5,000 U every 8 to 12 hours) are employed for prevention of deep vein thrombosis. Thrombosis of the residual popliteal vein is common, and aggressive prophylaxis may prevent extension of the thrombus into the calf veins. With the FPV absent, the risk of pulmonary embolism is low. Most of our patients are started on low-dose aspirin as a part of general medical treatment for cardiovascular disease; however, very few require anticoagulation with a vitamin K antagonist.

Outcomes

In our experience, long-term primary patency after NAIS is 81% at 6 years, with secondary patency of 91%.¹⁸ Limb

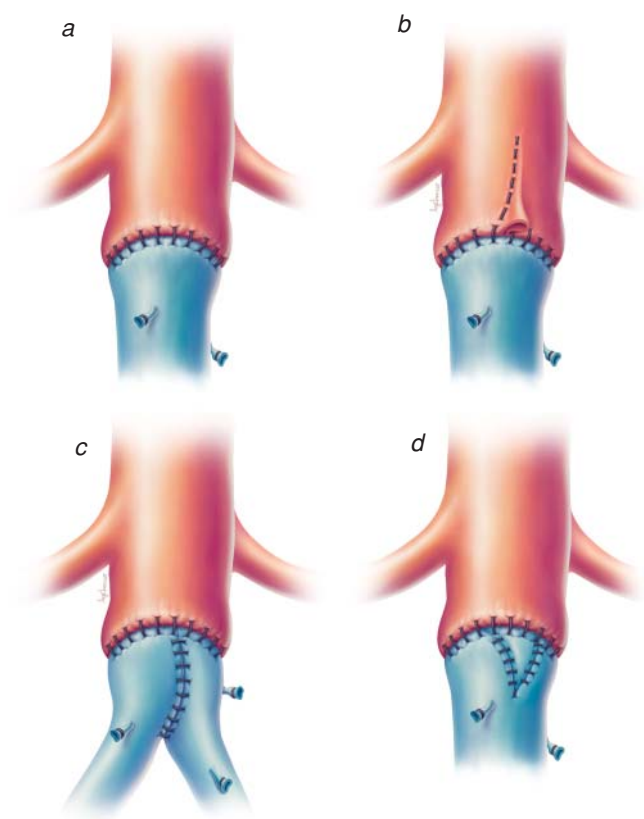


Figure 5 (a) An end-to-end proximal anastomosis is usually possible if the diameter of the femoropopliteal vein (FPV) graft is large enough and the aorta is of normal size. (b) If the end of the aorta is significantly larger in diameter than the venous graft, plication of the aorta can be performed. (c) A pantaloon technique may also be used to deal with a size mismatch between the aorta and the FPV graft. This technique effectively doubles the circumference of the vein. (d) The proximal anastomosis can also be facilitated by incorporating a wedge-shaped portion of vein into the proximal end of the graft.

salvage and long-term survival have been reported as 89% and 52%, respectively. Most patients die of cardiovascular causes; those who present with aortoduodenal fistula have worse outcomes.¹⁸

The incidence of graft disruption is about 5%, and most occur within 2 weeks of the initial operation. It is thought that this is secondary to reinfection of the vein graft, usually attributable to virulent organisms or to poor host defenses. This complication has a particularly poor outcome with a high mortality rate.

Complications

The incidence of chronic venous morbidity after FPV harvesting is low, with fewer than 15% of patients demonstrating manifestations of chronic venous insufficiency on long-term follow-up. Very few patients require long-term compression therapy for venous insufficiency. As noted above, the fasciotomy rate is approximately 12% in recent studies. In our practice, the decision to perform a fasciotomy is based

primarily on clinical examination of the legs. We specifically assess progressive compartment swelling and firmness on serial examination after reperfusion of the lower extremities. We also consider risk factors in making this decision. Two specific risk factors for fasciotomy are (1) a low preoperative ABI (< 0.4) and (2) concurrent great saphenous vein harvesting.^{18,19} Other factors may also help determine the need for fasciotomy, including the indication for operation, the length of vein harvested, the duration of arterial cross-clamping, and the amount of fluid administered intraoperatively.

Special Consideration: Aortoenteric Fistulas

AEF may be classified as primary or secondary, depending on the presence of a previously placed aortic graft. A primary AEF occurs between the native aorta and diseased bowel lumen, whereas a secondary AEF represents a communication between bowel and a previously placed aortic graft. The secondary AEF usually occurs at the third or fourth portion of the duodenum, and the associated graft is considered to be infected. The secondary AEF presents an especially difficult therapeutic challenge because the infected prosthesis must be removed, the distal perfusion preserved, and the gastrointestinal tract repaired. Although AEF may be associated with acute gastrointestinal hemorrhage that requires emergency control, reports suggest that those who present with gastrointestinal bleeding do not have a worse outcome compared with patients who present without bleeding (aortoenteric erosion).^{22,23} AEF and aortoenteric erosions have equally high morbidity and mortality rates.²²

When AEF is suspected, broad-spectrum antibiotics should be initiated immediately. In our experience, a significant percentage of involved grafts have had positive fungal cultures; therefore, we routinely include antifungal agents along with antibiotic therapy. At our institution, the type of repair for secondary AEF is dictated by the presence or absence of active hemorrhage, the hemodynamic stability of the patient, and the degree of retroperitoneal contamination. We prefer in situ replacement with femoropopliteal veins (NAIS) in hemodynamically stable patients without active bleeding. Rifampin-soaked Dacron graft may be an option if there is minimal contamination, particularly in a frail patient. In unstable patients with active bleeding, we perform aortic ligation with extra-anatomic bypass.

The modern era of endovascular therapy has garnered enthusiasm for endovascular aortic repair (EVAR) to treat secondary AEF. Scattered reports suggest early success to control hemorrhage.^{24,25} However, reinfection has been reported in several case series, with morbid consequences.²³⁻²⁵ Use of EVAR to treat AEF violates fundamental principles, especially control of the infectious source and repair of the bowel. In general, EVAR should be considered a temporizing, lifesaving alternative in patients who are hemodynamically unstable from bleeding. EVAR should not be considered a permanent treatment in these circumstances, and more definitive intervention will be necessary as soon as the patient is medically able to tolerate it.

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Figures 1, 4, and 5 Alice Y. Chen

14 MESENTERIC REVASCULARIZATION PROCEDURES

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Mesenteric ischemia is encountered infrequently. To date, there have been no randomized, controlled trials comparing treatment modalities for either acute or chronic mesenteric ischemia. Consequently, decisions on how to treat this condition must be based on a few large case series in which a variety of procedures were used.

Overall evaluation and management of acute mesenteric ischemia are addressed more fully elsewhere. In what follows, we focus specifically on the operative techniques used to treat mesenteric ischemia (whether chronic or acute) and discuss the available literature supporting their use. The appropriate technique for a particular patient varies according to the individual anatomy and intraoperative findings. The relevant surgical procedures may be conveniently divided into those employed for chronic mesenteric ischemia and those employed for acute ischemia.

Procedures for Chronic Intestinal Ischemia

PREOPERATIVE EVALUATION

In 1936, J. E. Dunphy was the first to suggest that timely diagnosis and intervention for mesenteric artery occlusive disease may prevent intestinal infarction.¹ It is now clear that optimal treatment of mesenteric ischemia depends on prompt diagnosis and that a high index of suspicion is vital.

Patients with chronic intestinal ischemia generally, but not always, report experiencing colicky, dull, or aching abdominal pain, primarily located in the epigastrium but occasionally radiating to the back. Symptoms typically begin 15 to 30 minutes after eating and may last as long as 3 to 4 hours. Peritonitis is not a characteristic of reversible intestinal ischemia; rather, it is indicative of intestinal infarction. Chronic postprandial abdominal symptoms result in markedly reduced food intake (so-called food fear),² which generally leads to weight loss.

Physical examination often yields no significant abdominal findings. Abdominal bruits may be audible but are a non-specific finding. Patients often, but not always, show evidence of atherosclerotic disease in other vascular territories. Bowel habits vary, ranging from normal elimination to diarrhea or constipation.

Mesenteric ischemia is a clinical diagnosis. Imaging studies are therefore used to confirm mesenteric artery stenosis or occlusion, supportive of a diagnosis of mesenteric ischemia. Useful imaging modalities include duplex ultrasonography, contrast angiography, multi-detector computed tomographic (CT) angiography, and magnetic resonance angiography. Duplex scanning is effective in detecting visceral artery stenosis [see Figure 1] and may allow earlier detection of visceral

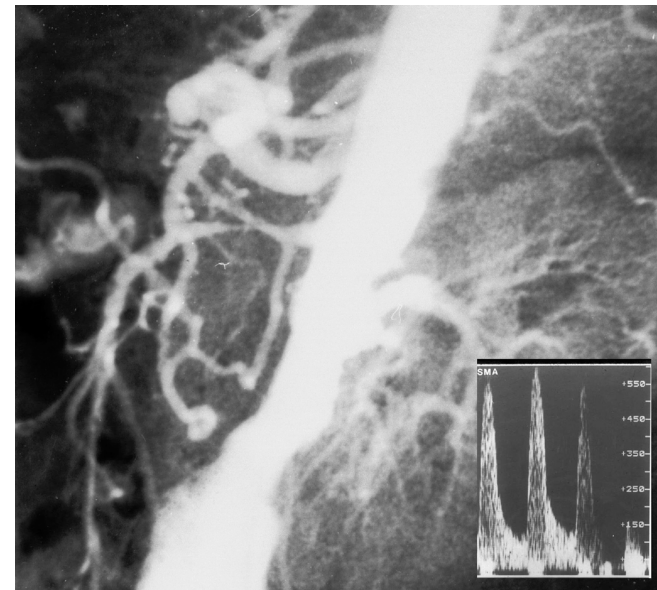


Figure 1 Example of a duplex spectral waveform with comparative arteriography in a patient with superior mesenteric artery (SMA) stenosis. The peak systolic velocity (> 550 cm/s) is dramatically increased over normal (< 275 cm/s).

artery stenosis associated with chronic mesenteric ischemia.^{3,4} Although it is a technically difficult examination to perform, in experienced hands, the sensitivity of duplex scanning for detecting lesions in the superior mesenteric artery (SMA) and celiac artery is 92% and 87%, respectively. When compared with catheter-based angiography, the overall accuracy for detection of a 70% lesion in the SMA and celiac artery was 96% and 82%, respectively.⁵ By itself, however, duplex scanning is not sufficient for planning a mesenteric revascularization procedure.

Multidetector CT angiography is the most frequently used technique for the diagnosis of mesenteric artery stenosis or occlusions consistent with mesenteric ischemia. Multidetector CT angiography has in many cases replaced other modalities as the imaging study of choice for evaluation of chronic mesenteric ischemia [see Figure 2]. It can accurately identify significant stenosis in the celiac artery and SMA, identify significant visceral collaterals, and exclude other potential intra-abdominal processes.^{6,7} CT angiography has higher spatial resolution and allows for assessment of visceral branches, including the inferior mesenteric artery, with greater accuracy than contrast-enhanced magnetic resonance angiography.^{8,9}



Figure 2 Computed tomographic angiography is being used more frequently to demonstrate mesenteric artery lesions. With three-dimensional reconstruction, segmental stenosis or occlusions can be demonstrated in mesenteric arteries. Above is an example of proximal occlusion (arrow) of the superior mesenteric artery with distal reconstitution via collaterals.

Together with noncontrast images, CT, in many cases, offers enough anatomic details to plan open procedures. Limitations include contrast-related nephropathy, hypersensitivity reactions, and inaccurate timing of contrast infusion that may lead to an indeterminate study and delayed diagnosis.

Arteriography is the traditional imaging technique employed in planning mesenteric revascularization for chronic intestinal ischemia [see *Figure 3* and *Figure 4*]. Lateral and anteroposterior views of the aorta are required for full evaluation of the severity of visceral stenosis or occlusion and the extent of collateral development. In most cases, a transfemoral Seldinger technique is suitable, although in the setting of iliofemoral occlusive disease, a transaxillary approach is occasionally required. Between 60 and 100 mL of contrast material is required for appropriate lateral and anteroposterior views of the abdominal aorta. Visceral artery lesions are usually ostial but may extend beyond the orifice of the vessel as a posterior plaque, especially in the SMA. Selective catheterization of the main intestinal arteries is rarely necessary and may be

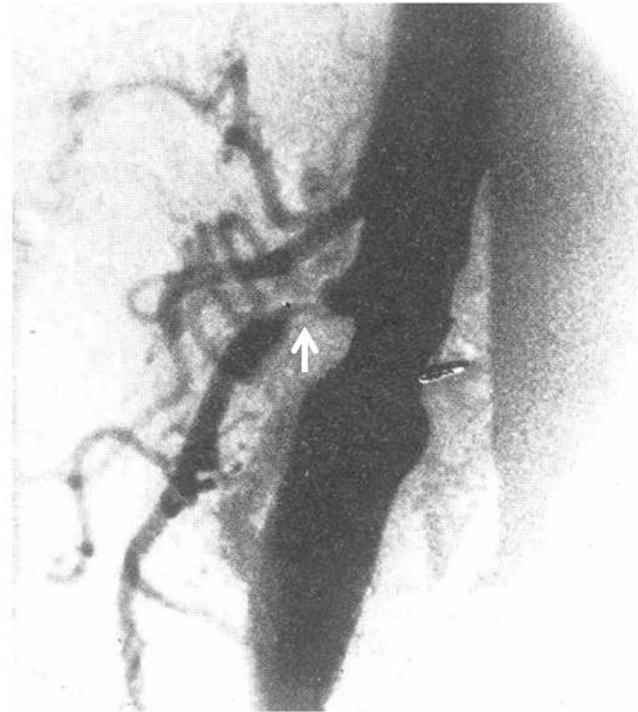


Figure 3 A lateral aortogram clearly shows severe stenosis of the superior mesenteric artery (arrow) in a patient with intestinal ischemia.

dangerous. Appropriate magnification views generally allow characterization of the proximal SMA beyond its origin, even without selective catheterization of the SMA. Intra-arterial digital subtraction techniques are usually adequate for lateral views and require less contrast material than other techniques. Arteriography also demonstrates coexisting lesions of the aorta and of the renal and iliac arteries that may be important in planning revascularization.

OPERATIVE PLANNING

Essentially all patients with peripheral artery disease have some degree of concomitant coronary artery disease (CAD). Although no symptoms of CAD may be evident, care must still be taken to provide perioperative cardiac protection. Perioperative beta blockade, antiplatelet therapy, and statin medications should be routinely employed whenever possible in patients undergoing elective arterial reconstructive procedures.

If the patient is undergoing a bypass procedure, the choice of graft material should be addressed. In general, prosthetic grafts work well for mesenteric artery bypasses. However, the entire abdomen and both legs should still be included in the operative field in case autologous vein proves necessary for the bypass conduit. Autologous vein is often required in cases involving bowel resection and may also be preferable for bypasses to smaller visceral vessels. If an autologous vein bypass procedure is planned, preoperative duplex scanning of the greater saphenous and femoral veins is recommended to facilitate selection of the best available vein for the conduit.



Figure 4 Lateral aortogram showing so-called coral reef atheroma involving the visceral aorta with occlusion of the origin of the superior mesenteric artery. A patient with mesenteric ischemia and this angiogram may be best treated with transaortic endarterectomy.

OPERATIVE TECHNIQUE

Visceral Endarterectomy

Visceral endarterectomy for treatment of mesenteric ischemia was first described in 1958 by Shaw and Maynard,¹⁰ who performed endarterectomy of the SMA in a blind, retrograde fashion through a distal arteriotomy. At present, retrograde endarterectomy cannot be recommended.

The SMA can be approached directly once control of the supraceliac aorta has been obtained.¹¹ A longitudinal incision is made across the origin of the SMA, and an endarterectomy is performed. In most patients, the exposure is limited. This direct approach may be considered when the SMA is widely separated from the renal arteries and the visceral aorta is relatively free of disease; however, this scenario is uncommon.

A more versatile endarterectomy technique is transaortic endarterectomy.¹² This procedure involves a posterolateral approach to the aorta, in which the aorta is exposed transperitoneally with medial visceral rotation. Alternatively, a completely retroperitoneal approach may be taken. The main disadvantage of the retroperitoneal approach is that it restricts

the surgeon's ability to assess the bowel at the completion of revascularization.

Transaortic endarterectomy *Step 1: incision and initial approach* A midline incision is recommended. A complete medial visceral rotation is performed, with the left kidney left in its bed.

Step 2: exposure The lateral aorta is exposed, and the celiac artery and the SMA may be identified anteriorly; the left renal artery lies posteriorly.

Step 3: endarterectomy A trapdoor incision is made in the aortic wall in such a way as to encompass the orifices of the SMA and the celiac artery. Partial occlusion of the aorta with a clamp is sometimes possible, but in most cases, complete aortic occlusion is required. If necessary, the aortotomy can be extended distally and posteriorly to include the renal artery orifices as well.

Among the advantages of this operation are that it permits simultaneous endarterectomy of the aorta and all visceral vessel orifices and that it does not require the use of prosthetic material [see Figure 4]. The disadvantages include the potential risks associated with suprarenal clamping (e.g., cardiac overload, renal and lower extremity embolization, and ischemia). Because of these risks, the need for more extensive dissection, and the unfamiliarity of most surgeons with this procedure, arterial bypass procedures are generally preferred for treatment of chronic mesenteric ischemia.

Mesenteric Arterial Bypass

Technical considerations *Single-vessel versus multiple-vessel revascularization* There are two schools of thought on the extent of revascularization for chronic mesenteric ischemia. Proponents of so-called complete revascularization advocate revascularization of both the celiac artery and the SMA and suggest that this approach makes recurrent ischemia less likely should one graft or graft limb undergo thrombosis.¹³ In a 1992 study, overall graft patency and survival were better in patients who underwent multiple-vessel bypass than in those who underwent single-vessel bypass. The investigators concluded that multiple-vessel bypass patients were likely to remain asymptomatic because of the presence of additional grafts or graft limbs that remained patent.¹³

Others maintain that the critical vessel involved in chronic mesenteric ischemia is the SMA and argue that bypass to the SMA alone is a relatively simple procedure that relieves symptoms of mesenteric ischemia. In a 2000 study evaluating 49 patients who underwent bypass to the SMA alone, the 9-year primary assisted graft patency rate was 79% and the 5-year survival rate was 61%¹⁴—results equivalent to those noted in contemporary studies of multiple-vessel revascularization for chronic intestinal ischemia.¹⁵

Antegrade versus retrograde bypass Mesenteric bypass grafts may originate either above or below the renal arteries. Bypass grafts are considered antegrade if they originate on the anterior surface of the abdominal aorta cephalad to the celiac artery and retrograde if they originate from the infrarenal aorta or a common iliac artery. The distal thoracic aorta can also serve as an inflow site for antegrade mesenteric bypass. Antegrade bypass from the supraceliac aorta, using either

prosthetic material or autologous vein, has certain advantages, including a straight graft configuration that minimizes turbulence and graft kinking. Typically, there is also reduced atherosclerotic calcification in the supraceliac aorta.¹⁶ The disadvantages of antegrade bypass are similar to those of visceral endarterectomy and derive from the need to clamp the supraceliac aorta for the proximal anastomosis. As with visceral endarterectomy, partial occlusion clamping is theoretically possible but not always practical. Clamping of the supraceliac aorta may increase the risk of cardiac events, visceral or renal emboli, and ischemia. One prerequisite for use of the supraceliac aorta in an antegrade bypass is that the vessel must be angiographically normal to ensure that it can safely be clamped. It should also be kept in mind that reoperation on the supraceliac aorta is difficult: once this site has been used, reexposure generally is not safe.

Antegrade bypass *Step 1: incision and initial approach* Supraceliac aorta–visceral artery bypass is performed through an upper midline incision. Self-retaining retractors are very helpful.

Step 2: exposure The dissection begins with division of the gastrohepatic ligament and retraction of the left lobe of the liver to the right, followed by incision of the diaphragmatic crus and exposure of the anterior aspect of the aorta.

Step 3: choice of graft In clean cases with no intestinal necrosis or perforation, we use woven Dacron grafts. If a single-vessel bypass is to be performed, a single limb is cut from the bifurcated graft, incorporating a flange of the main body of the bifurcated graft for the proximal anastomosis. Autologous vein grafts are usually reserved for contaminated cases. The femoral vein is an excellent autogenous conduit for mesenteric arterial bypass.

Step 4: anastomosis of graft to supraceliac aorta and visceral artery If the celiac artery alone is to be revascularized, the usual procedure is to perform an end-to-side proximal anastomosis to the aorta, followed by an end-to-side distal anastomosis to the common hepatic artery. If the SMA alone is to be revascularized, it is generally necessary to tunnel the graft beneath the pancreas to the inferior border of the pancreas and then perform an end-to-side anastomosis to the SMA at that level [see Figure 5a]. Extreme care must be exercised in developing the retropancreatic tunnel. If this area appears too narrow or is scarred as a result of previous pancreatic inflammation, the graft should be tunneled anterior to the pancreas to ensure that it is not compressed and to avoid causing bleeding from disrupted pancreatic veins.¹⁷ If a prepancreatic tunnel is required, an autogenous conduit should be considered because the graft will be lying adjacent to the posterior wall of the stomach. If both the celiac artery and the SMA are to be revascularized from the supraceliac aorta, a bifurcated prosthetic graft is attached to the supraceliac aorta proximally, with one distal limb anastomosed to the hepatic artery and the other to the SMA [see Figure 5b].

Retrograde bypass In a retrograde bypass, the infrarenal aorta or, more commonly, common iliac artery is used as the inflow vessel. One clear advantage of this procedure is that the approach to the infrarenal aorta is more familiar to most surgeons. Another is that dissection and clamping of the infrarenal aorta are less risky than dissection and clamping of the

supraceliac aorta. Yet another is that the surgeon can work within a single operative field. Once the self-retaining retractor is placed, the operation on the infrarenal aorta and the SMA can be performed without further adjustment of the retractor. The main disadvantage is the potential for graft kinking.

Step 1: incision and initial approach Here, too, a midline incision and a transperitoneal approach are preferred. The transverse mesocolon is retracted upward, and the ligament of Treitz is divided.

Step 2: exposure After division of the ligament of Treitz, the duodenum and the small bowel are retracted to the right. The SMA may then be identified arising from beneath the inferior border of the pancreas. The retroperitoneum is divided distally along the aorta to a point just beyond the level of the aortic bifurcation. The distal aorta and both common iliac arteries are assessed to allow determination of the optimal location for the proximal anastomosis.

Step 3: choice of graft As a rule, grafts made of Dacron or of ringed, reinforced expanded polytetrafluoroethylene (ePTFE) are preferred. Problems may arise when retrograde bypasses are performed with autologous vein grafts, in that such grafts are prone to kinking when the viscera are replaced. When a retrograde vein bypass is performed, the graft may be brought straight up from the right iliac artery so that it lies between the aorta and the duodenum and then anastomosed to the posteromedial wall of the SMA.

Step 4: anastomosis to infrarenal aorta or common iliac artery and SMA Our preference is to use the area near the junction of the aorta with the right common iliac artery for the proximal anastomosis. (Short grafts originating from the midportion of the infrarenal aorta, although commonly described, are prone to kinking when the viscera are returned to their normal position.) The graft to the SMA is passed cephalad, turned anteriorly and inferiorly 180°, and anastomosed to the anterior wall of the SMA just beyond the inferior border of the pancreas.¹⁷ In this manner, a gentle C loop is formed that, if placed correctly, keeps the graft from kinking when the viscera are restored to their anatomic position after retractor removal [see Figure 6]. The ligament of Treitz and the parietal and mesenteric peritoneum are closed over the graft to exclude it from the peritoneal cavity.

Endovascular Techniques

Endovascular techniques, usually a combination of angioplasty and stent placement, are being used with greater frequency for chronic mesenteric ischemia [see Figure 7]. By 2002, endovascular procedures (angioplasty/stent) surpassed all surgical procedures performed for chronic mesenteric ischemia, with decreased 30-day mortality compared with open procedures (4 versus 13%).¹⁸ Early reports describing the use of percutaneous transluminal angioplasty (PTA) to treat visceral atherosclerotic lesions indicated that initial technical success rates were as high as 80% but that recurrence rates ranged from 20 to 40%.^{17,19} Recent reports of endovascular therapy for chronic mesenteric ischemia showed no difference in in-hospital morbidity or mortality or 2-year survival. Also, there was no difference in symptomatic (23 versus 22%) or radiographic (32 versus 37%) recurrence. However, radiographic primary patency (58 versus 90%) and primary assisted patency (65 versus 96%) were significantly lower

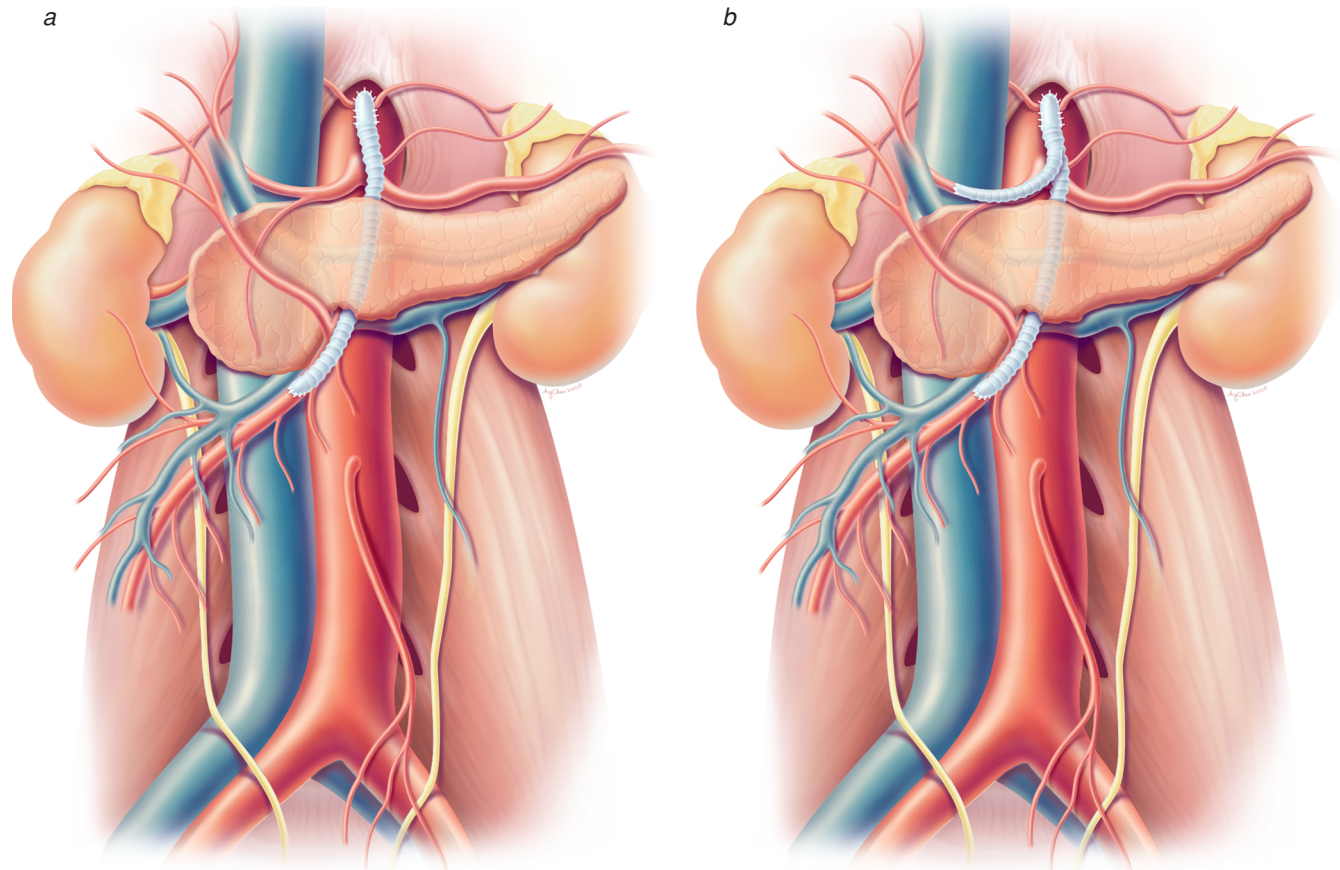


Figure 5 Arterial bypass: antegrade. Shown is bypass from the supraceliac aorta to the superior mesenteric artery (SMA) alone (a) or to the hepatic artery and the SMA (b).³⁹

in the patients who received endovascular treatment.²⁰ Another study with longer follow-up showed 3-year actuarial patency of 63%. About 30% of patients required reintervention for recurrent symptoms. The median time to reintervention for symptom recurrence was 15 months. Because of this high rate of restenosis and symptom recurrence, close follow-up is mandatory in all patients treated with mesenteric artery stents. Most importantly, initial endovascular treatment did not preclude any future surgical bypass options.²¹ These early results indicate that an endovascular approach to chronic mesenteric ischemia is a viable option in carefully selected patients.

COMPLICATIONS

Technical

The main technical complication of mesenteric bypass is acute graft thrombosis. This event is rare, but when it occurs, prompt recognition is essential to prevent intestinal infarction. Kinking and compression of the graft are the most common causes of this condition. If the retrograde graft is too long, the redundancy makes it more susceptible to kinking. Similarly, if the graft is not positioned so as to form a gentle C loop, it is at risk for kinking when the viscera are returned to their normal position. An antegrade graft that is too long is equally at risk for kinking and occlusion. When an antegrade bypass is tunneled behind the pancreas, an adequate

amount of space must be present to ensure that the graft is not compressed. In general, prosthetic grafts are more resistant to kinking and compression than vein grafts are.

Identification of perioperative graft occlusion is hindered by postoperative incisional pain, fluid shifts, fever, and leukocytosis, all of which are common in the postoperative period and may mask signs of intestinal ischemia. Patients with chronic mesenteric ischemia often have symptoms only when eating and thus may be asymptomatic in the postoperative period until they resume oral feeding. For these reasons, we advocate evaluating the graft early in the postoperative period with either conventional contrast angiography or CT angiography [see Outcome Evaluation, below].

Additional technical complications may occur as a result of clamp placement. Clamping of the supraceliac aorta can lead to renal atheroemboli or ischemia. These problems can be minimized by using a supraceliac clamp only on an angiographically normal aorta.

Systemic

Myocardial infarction is the most common cause of mortality in patients treated for mesenteric ischemia. Pulmonary compromise is also a common systemic complication of mesenteric revascularization. Renal failure after mesenteric revascularization is more common in patients with preoperative renal insufficiency.²² Mortality is markedly increased when renal failure occurs postoperatively.²² Postoperative renal

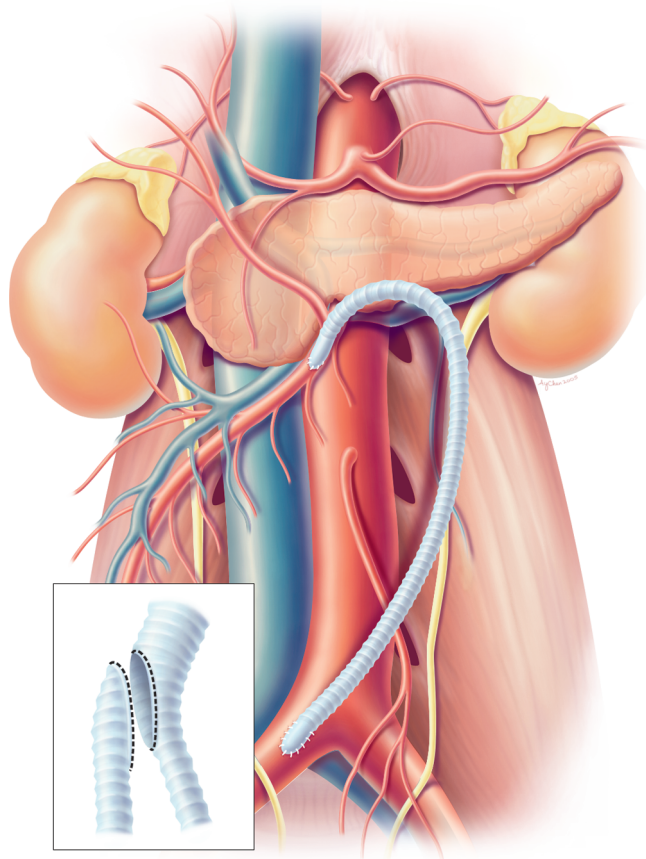


Figure 6 Arterial bypass: retrograde. Shown is bypass from the right common iliac artery to the superior mesenteric artery.³⁹ The inset shows a method of graft preparation using the main body of a bifurcated graft to provide a flange for the proximal anastomosis.

insufficiency can be minimized by administering mannitol, furosemide, and, possibly, vasodilators intraoperatively.

Patients who undergo mesenteric revascularization occasionally experience a profound reperfusion syndrome manifested by acidosis, pulmonary compromise, and coagulopathy. We recommend administering sodium bicarbonate (to minimize the effects of metabolic acidosis) and mannitol (for its free radical-scavenging properties) before restoring intestinal perfusion.

OUTCOME EVALUATION

Restoration of pulsatile flow to the small bowel usually results in immediate active peristalsis and intestinal edema. The technical success of surgical revascularization is assessed intraoperatively through visual examination of the intestine and continuous-wave Doppler examination of the distal mesenteric vasculature and the bowel wall. Doppler signals should be detected along the antimesenteric border, and pulses should be palpable in the mesentery. Intraoperative duplex scanning may also be used to visualize anastomotic sites directly.²³

Electromagnetic flow measurements can be helpful in evaluating the adequacy of mesenteric revascularization. Such measurements must be made after all packs and retractors have been removed. In most cases, the flow rate through the

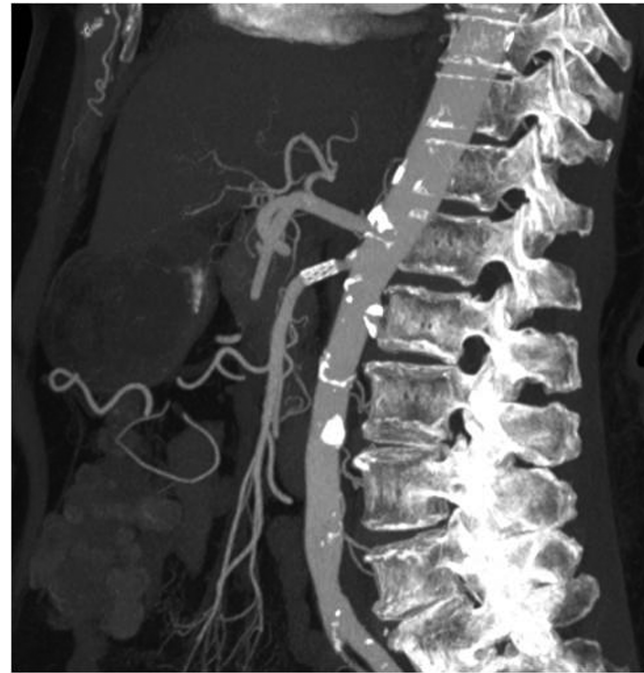


Figure 7 Computed tomographic angiogram showing a stent in a superior mesenteric artery. Mesenteric artery stents are being used with increasing frequency as an alternative to bypass for treatment for chronic visceral ischemia in higher-risk patients.

graft should be between 500 and 800 mL/min, but flow rates as high as 1,000 mL/min may be recorded.¹⁷

To confirm technical success after mesenteric revascularization, we advocate routine postoperative imaging of the graft. Ideally, this is done early in the postoperative period. Catheter-based contrast angiography is optimal for evaluating the bypass graft and the distal vasculature, allowing identification of anastomotic stenoses, kinking [see Figure 8a], or, in the case of autologous grafts, narrowing caused by valves. If a technical defect is discovered, reoperation and correction are required to ensure prolonged patency. In the past few years, we have started evaluating selected patients perioperatively with CT angiography. This modality is less invasive than traditional contrast angiography but still requires administration of contrast material and exposure to radiation [see Figure 8b].

Duplex ultrasonography has been used for postoperative graft surveillance after mesenteric revascularization.²⁴ Although it can be difficult in the early postoperative period because of incisional tenderness and postoperative ileus, it has proven to be a valuable tool to follow bypass grafts. A retrospective study at our institution has defined normal duplex ultrasonography-derived velocity characteristics of mesenteric artery bypass grafts. The anastomotic and mid-graft peak systolic velocities are not affected by the orientation of the graft. Mean peak systemic velocity for most grafts is between 140 and 200 cm/s and remains relatively stable on repeat examinations. Serial duplex examinations can be used to assess the patency of bypass grafts to mesenteric arteries.²⁵ We routinely use postoperative duplex scanning to establish

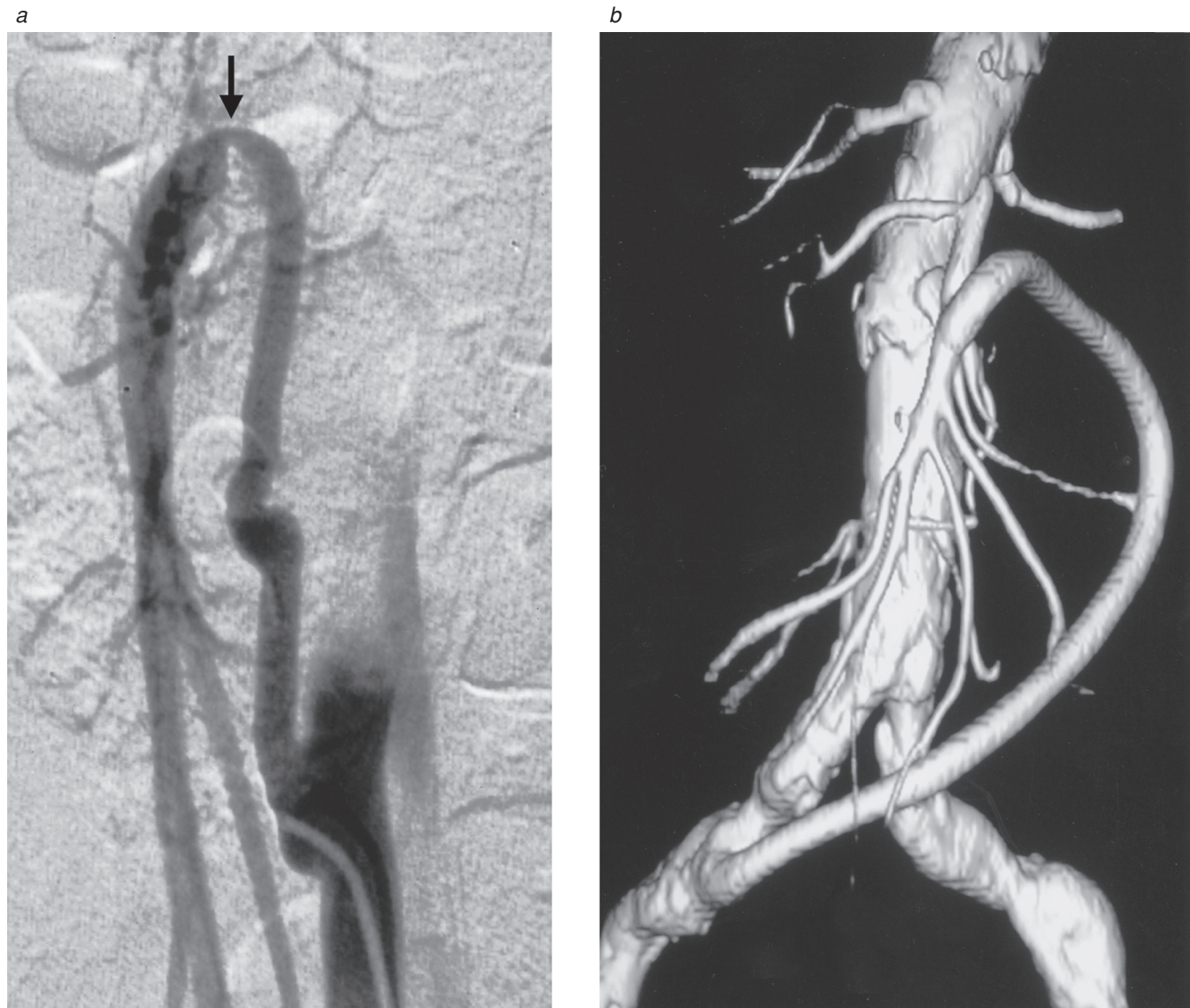


Figure 8 Routine postoperative imaging is performed to confirm technical success after revascularization. (a) A postoperative arteriogram shows a iliac artery–superior mesenteric artery (SMA) saphenous vein graft with a kink (arrow). This problem was asymptomatic and was corrected by reoperation on postoperative day 5. (b) A postoperative computed tomographic arteriogram shows a retrograde iliac artery–SMA prosthetic graft. C (hook) configuration of distal anastomosis provides antegrade flow into the SMA.

baseline values and to permit comparisons for follow-up evaluation of graft patency. If markedly elevated focal peak systolic velocities (> 300 cm/s) are recorded, especially if they increase on serial examinations, secondary imaging (CT or conventional angiography) should be obtained to confirm graft stenosis and to possibly plan intervention.

Procedures for Acute Intestinal Ischemia

PREOPERATIVE EVALUATION

As in the evaluation of patients with chronic mesenteric ischemia, a high index of suspicion is of primary importance in the evaluation of patients with possible acute mesenteric ischemia. Most cases of acute intestinal ischemia result either

from thrombosis of a preexisting stenotic lesion or from embolization (most frequently to the SMA).²⁶ Cardiac emboli are the most common variety, although tumor emboli²⁷ and atheroemboli are seen as well. Atheroemboli generally result from iatrogenically induced cholesterol embolization caused by aortic catheterization. The prognosis for acute intestinal ischemia of embolic origin is more favorable than that for acute ischemia of thrombotic origin. Emboli typically lodge distally in the SMA distribution; therefore, the proximal intestine is still partially perfused.²⁶ In contrast, thrombotic occlusion occurs at the origin of the vessel, resulting in complete interruption of midgut perfusion.

Acute, severe abdominal pain that is out of proportion to the physical findings is the classic manifestation and is strongly suggestive of intestinal ischemia. The duration of symptoms

does not appear to correlate with the degree of intestinal infarction.²⁸ Peritonitis is initially absent, but vomiting and diarrhea may be present, and occult gastric or rectal bleeding may be identified in as many as 25% of patients.²⁸

There are no reliable serum markers for acute intestinal ischemia. Leukocytosis, hyperamylasemia, or elevated lactate levels may be present, but these findings are insensitive and inconsistent. Abdominal radiographs may reveal dilated bowel loops and, occasionally, thickened bowel wall, but these findings are similarly inconsistent. In theory, duplex ultrasonography may be helpful, but in practice, its applicability is often limited by the gaseous visceral distention frequently associated with acute intestinal ischemia.

Acute intestinal ischemia is a true surgical emergency. Any evidence of acute abdomen should result in prompt operative intervention. In stable patients suspected of having acute mesenteric ischemia, the paradigm for diagnostic workup has been slowly shifting toward the use of multidetector CT angiography. Multidetector CT angiography uses thinner collimation and overlapping data acquisition, which reduces the amount of volume averaging and creates higher quality volume sets for three-dimensional reconstruction. There are several advantages to CT angiography, including near-universal 24-hour access to a high-resolution scanner. With three-dimensional reconstruction, mesenteric vessels can be evaluated for embolus or thrombotic occlusion with accuracy. Also, bowel can be evaluated concomitantly to support or refute the diagnosis, and other intra-abdominal pathology can be evaluated. A prospective study compared preoperative radiographic findings with operative findings in 62 patients suspected of acute myocardial infarction. Initial radiologist interpretation had a sensitivity of 100% and a specificity of 89%.²⁹ A subsequent study using CT angiography had similar results in terms of accuracy.³⁰ Significant limitations include the need for proper timing of the contrast to evaluate the vasculature and that the modality does not offer any therapeutic options.

The use of preoperative arteriography to diagnose acute ischemia is controversial. Delaying treatment to perform arteriography could result in further intestinal infarction. Angiography may be considered in patients who have abdominal pain without any other signs or symptoms of systemic illness [see Figure 9]. In patients who have rebound tenderness, rigidity, or evidence of toxicity or shock, emergency exploration is indicated.

OPERATIVE PLANNING

Patients with acute intestinal ischemia who present with evidence of toxicity must be resuscitated expeditiously to ensure that surgical intervention is not delayed. Once it is determined that surgery is indicated, no further delay is justified. The patient is placed supine on the operating table, and the entire abdomen and both legs are prepared. As in operative treatment of chronic intestinal ischemia, the possibility that autologous vein will be needed for bypass grafting must be anticipated.

OPERATIVE TECHNIQUE

Intraoperative Considerations

Mesenteric revascularization and bowel resection

The goals of surgical therapy are to restore normal pulsatile

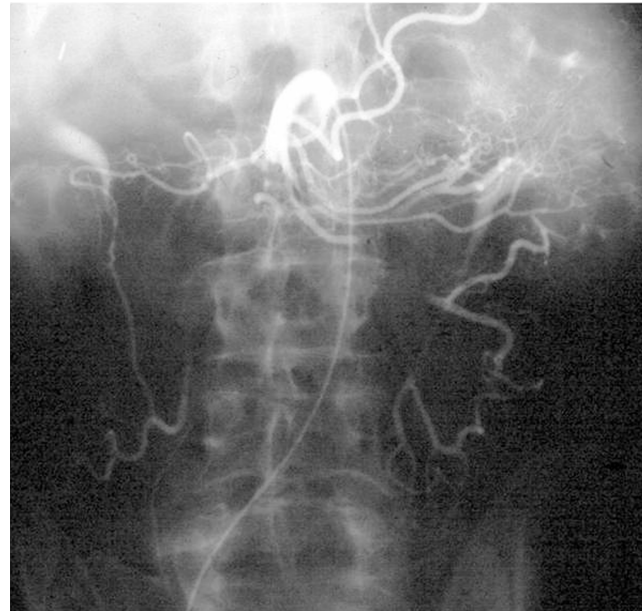


Figure 9 Preoperative arteriogram shows embolic occlusion of the superior mesenteric artery distal to its origin.

inflow, to ensure that questionably viable bowel is adequately perfused, and to resect any clearly nonviable bowel. During abdominal exploration, the viability of the intestine and the status of the blood flow to the SMA are assessed with an eye to determining the appropriate treatment. The surgeon should be prepared to perform both intestinal revascularization and intestinal resection. Segments of clearly viable bowel are often interspersed with segments of marginally viable bowel and segments of necrotic bowel. Acutely ischemic bowel that is not yet necrotic may appear deceptively normal. Mildly to moderately ischemic bowel may exhibit loss of normal sheen, absence of peristalsis, and dull-gray discoloration. Other objective signs of ischemia are the absence of a palpable pulse in the SMA or in its distal branches, the absence of visible pulsations in the mesentery, and the absence of flow on continuous-wave Doppler examination of the vessels of the bowel wall. The small bowel may be deeply cyanotic yet still viable. In most cases, bowel resection should not be performed until after revascularization.

The distribution of ischemic changes provides valuable information about the cause of the ischemia. SMA thrombosis often results in ischemia to the entire small bowel, with the stomach, the duodenum, and the distal colon spared; in severe cases, however, the entire foregut may be ischemic. In contrast, ischemia secondary to SMA embolism generally spares the stomach, the duodenum, and the proximal jejunum because the emboli tend to lodge at the level of the middle colic artery rather than at the origin of the SMA. The choice of operation for revascularizing the bowel depends on the underlying causative condition. Embolectomy is indicated for arterial embolism, whereas bypass is indicated for thrombotic occlusion.

Revascularization of the acutely ischemic intestine

Patients with very advanced intestinal ischemia may have

obvious widespread bowel necrosis. This situation almost invariably proves fatal; thus, revascularization is not likely indicated. In many patients, however, substantial portions of the bowel are ischemic but not frankly necrotic. Whether such bowel segments can be restored to viability cannot be accurately predicted. In most instances, therefore, revascularization should precede resection.

Restoration of normal flow to the SMA can produce remarkable changes in an ischemic bowel. Because these changes do not always occur immediately, it is often necessary to preserve questionably viable portions of the bowel initially and then perform a second-look laparotomy within 12 to 36 hours. If the questionably viable bowel is not in significantly better condition at the time of the second-look operation, it should be resected. Occasionally, however, even a third look is prudent. Revascularized intestine that was profoundly ischemic may swell dramatically. Temporary abdominal closure with mesh or leaving the abdomen open with a temporary closure device may permit tension-free abdominal “closure,” prevent abdominal compartment syndrome, and perhaps even improve intestinal perfusion by reducing intra-abdominal pressure.

Superior Mesenteric Artery Embolectomy

Step 1: incision and initial approach A midline incision and transperitoneal approach is used.

Step 2: exposure of SMA at root of mesentery The SMA is exposed after division of the ligament of Treitz at the base of the transverse colon mesentery. The duodenum and the small bowel are retracted to the right [see Figure 10]. The visceral peritoneum is incised above the ligament of Treitz, just cephalad to the third portion of the duodenum. The SMA should be readily palpable in this location as it crosses over the third portion of the duodenum. The dissection is continued to obtain sufficient proximal and distal control of the vessel. Heparin is administered, and the vessel is clamped proximally and distally.

Step 3: arteriotomy An arteriotomy is then made in the SMA. The incision may be either transverse or longitudinal. We prefer to perform a longitudinal arteriotomy if there is any possibility that a bypass graft may be needed. The arteriotomy should be made approximately 2 to 3 cm distal to the origin of the SMA, although alternative placements may be appropriate on occasion, depending on the anatomy and the estimated location of the occlusion [see Figure 11, a and b].

Step 4: embolectomy Proximal embolectomy should be performed first to ensure adequate inflow. A 3 or 4 French balloon catheter is sufficient in most cases. If very good pulsatile inflow is not achieved after embolectomy, then thrombosis of a stenotic lesion is likely to be the underlying cause of the acute intestinal ischemia, and a bypass graft should be placed. Even when inflow is apparently adequate, a bypass should be strongly considered if the proximal SMA is palpably abnormal.

The narrowness and fragility of the distal SMA and its branches can make distal embolectomy particularly challenging. It is best to use a 2 French embolectomy catheter for this procedure. The catheter must be passed gently, without undue force.

Step 5: closure Once all possible thrombus has been removed, the arteriotomy is closed. A transverse arteriotomy may be closed primarily with interrupted monofilament sutures [see Figure 11c]; however, a longitudinal arteriotomy frequently must be closed with an autologous vein patch. If adequate flow is not restored after the clamps are removed, the arteriotomy is used as the distal anastomotic site of a bypass graft.

Superior Mesenteric Artery Bypass

Patients with SMA thrombosis who are seen early enough and who have no intestinal necrosis may undergo SMA bypass grafting with a prosthetic conduit. At exploration, many of these patients have fluid within the peritoneal cavity. This finding is not, in itself, a contraindication to the use of a prosthetic graft. However, if the patient has necrotic bowel that must be resected or if perforation has occurred, a prosthetic graft should not be used. In these situations, an autologous vein graft is preferred. A good-quality vein is mandatory; if the saphenous vein is inadequate, the femoral vein may be used instead.

The techniques of mesenteric bypass for acute intestinal ischemia are identical to those for chronic intestinal ischemia. Because these patients are often acutely ill, it is vital to perform the operation rapidly and efficiently. In the acute setting, bypass to the SMA alone is strongly preferred [see Figure 12]. As a rule, a retrograde approach, using the infrarenal aorta or a common iliac artery for inflow, is best; the supraceliac aorta is used for inflow only if the infrarenal vessels are unsuitable for this purpose. Even highly calcified iliac arteries can be used for inflow provided that there is no significant pressure gradient and that the surgeon is familiar with intraluminal balloon occlusion techniques for proximal and distal control.

Hybrid Technique: Retrograde Open Mesenteric Stenting

Recently, a hybrid technique has been described that combines the attributes of both endovascular and open procedures. It allows for both endovascular treatment of mesenteric vessels and thorough assessment of bowel viability. Initial results show a 100% initial success and a lower in-hospital mortality rate of 17% compared with surgical bypass or endovascular treatment.^{31,32}

Step 1: Incision and exposure A patient suspected of acute myocardial infarction is brought directly to the operating room with ongoing resuscitation. The left arm is abducted and prepared along with standard preparation for potential brachial access. Once the diagnosis is confirmed, initial midline exploration and control of the infracolic SMA is obtained as described for an SMA embolectomy procedure.

Step 2: Patch angioplasty and cannulation of infracolic SMA Once exposure and control of infracolic SMA are obtained, the patient is fully heparinized to activated clotting time of more than 300 seconds. The artery is incised longitudinally, and a local thromboendarterectomy with patch angioplasty is performed. Either bovine pericardium or saphenous vein can be used for the patch. A purse-string suture is placed in the patch, through which a 6 French sheath is placed into the SMA in retrograde fashion through the distal end of

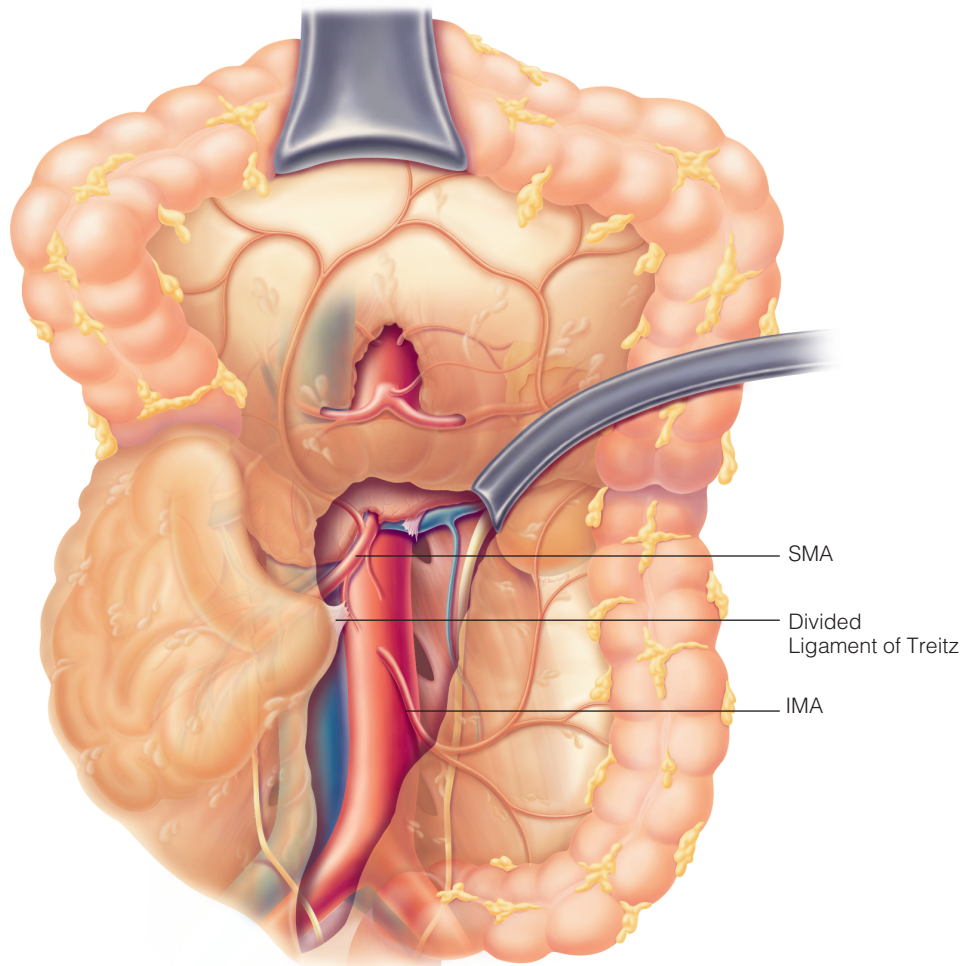


Figure 10 Superior mesenteric artery (SMA) embolectomy. Exposure of the infrarenal aorta, proximal right common iliac artery, and proximal SMA is achieved by intestinal retraction and division of the posterior peritoneum, ligament of Treitz, and base of small bowel mesentery.⁴⁰ IMA = inferior mesenteric artery.

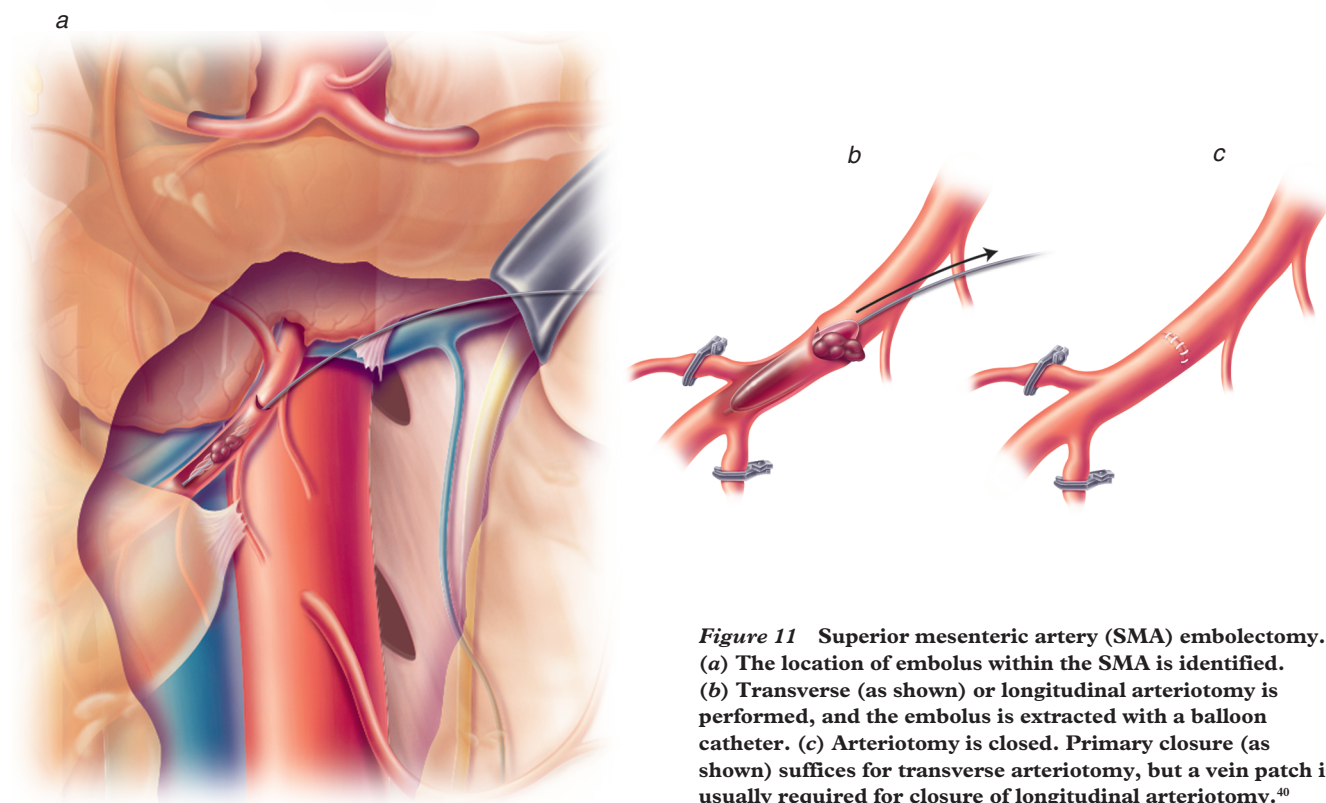


Figure 11 Superior mesenteric artery (SMA) embolectomy. (a) The location of embolus within the SMA is identified. (b) Transverse (as shown) or longitudinal arteriotomy is performed, and the embolus is extracted with a balloon catheter. (c) Arteriotomy is closed. Primary closure (as shown) suffices for transverse arteriotomy, but a vein patch is usually required for closure of longitudinal arteriotomy.⁴⁰

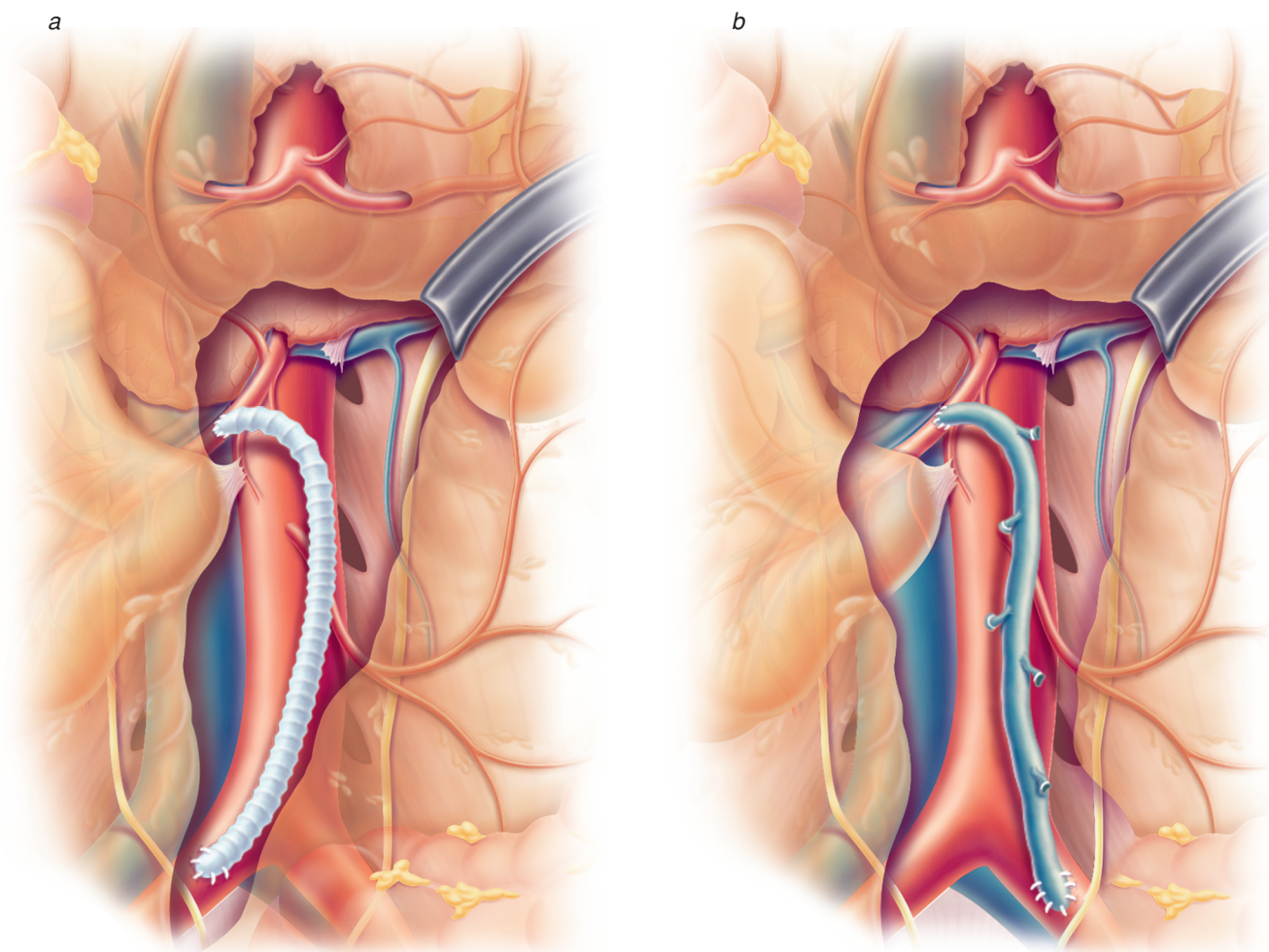


Figure 12 Superior mesenteric artery (SMA) bypass. (a) Iliac artery–SMA bypass with a prosthetic graft is suitable for cases in which SMA thrombosis produces ischemic but salvageable bowel. (b) Iliac artery–SMA bypass with a saphenous vein is suitable for cases in which some segments of necrotic or perforated bowel must be resected.⁴⁰

the patch. This allows for placement and removal of the sheath without clamping of the vessel. Once the sheath is in place, all metal retractors are removed. The sheath should be long enough to allow the surgeon to work out of the wound and away from the image intensifier.

Step 3: Crossing the lesion with a guidewire Initially, hand-injected, retrograde, lateral angiography is performed to delineate the lesion. This angiogram is used as a road map to cross the lesion with a 0.035-inch guidewire. This is then catheter exchanged for a lower profile 0.018- or 0.014-inch platform.

Step 4: Predilatation and stent deployment The lesion is then predilated with a 2 or 3 mm angioplasty balloon. A 5 to 7 mm low-profile balloon-expandable stent is deployed in a retrograde fashion. The proximal-most stent is allowed to protrude 1 to 2 mm into the aortic lumen. More than one stent may be required to cross the entire length of the lesion. Completion angiography in the anteroposterior and lateral projections and pressure measurements are performed across the lesion.

Step 5: Sheath removal and assessment of bowel viability After completion angiography is performed, the sheath is removed and the puncture site in the patch is repaired. The entire bowel is thoroughly examined, and any grossly necrotic bowel is expeditiously resected. Final assessment and reanastomosis are usually delayed for 24 to 48 hours.

Endovascular Techniques

Purely endovascular techniques have a limited role in the treatment of acute mesenteric ischemia as they do not offer assessment of ischemic bowel. General surgical principles of thorough abdominal exploration, along with sepsis control and routine second-look operations, must be honored in all patients with acute mesenteric ischemia to optimize favorable outcomes. It would seem reasonable that endovascular therapies might come to play a role in the treatment of acute intestinal ischemia, given that preoperative angiography is usually feasible in stable patients. Several groups have reported treating acute arterial embolism with intra-arterial thrombolysis^{33,34}; others have reported treating acute embolism, as well as thrombotic occlusion, with PTA.^{35,36} Although a degree

of anecdotal success with these techniques has been achieved in selected cases, it should be kept in mind that reliance on endovascular therapy alone for presumed acute intestinal ischemia runs the risk of missing bowel necrosis. After endovascular therapy, frequent clinical reevaluation is necessary to identify patients with persistent intestinal ischemia. Abdominal exploration should be very strongly considered in most cases, even if the angiographic result of the endovascular procedure is good.

TROUBLESHOOTING

Occasionally, patients present with emboli that have lodged in the small arterial branches of the SMA. These vessels are often too small to allow the passage of embolectomy catheters, and bypass beyond the point of obstruction frequently is not possible. In these situations, resection of marginally viable bowel is the best option.

As noted (see above), avoidance of graft kinking is crucial for preventing early graft failure. Graft failure can have an even greater adverse effect on bowel viability in the setting of acute ischemia than in the setting of chronic intestinal ischemia.

Recovery after revascularization is often prolonged. Early and prolonged parenteral nutrition may be necessary in patients with extensive bowel infarction. Only rarely, however, is lifelong parenteral nutrition required.

OUTCOME EVALUATION

The techniques employed to evaluate the success of mesenteric revascularization for acute ischemia include clinical inspection, continuous-wave Doppler ultrasonography,

and intravenous (IV) administration of fluorescein. Clinical inspection entails visual assessment of pulsatile flow in the mesenteric arcades, peristalsis, bleeding from cut surfaces, and, of course, color. In one study, clinical parameters were found to be 82% sensitive and 91% specific for bowel viability.³⁷

We routinely use a sterile continuous-wave Doppler ultrasonography to evaluate pulsatile flow on the bowel surface. Grossly discolored bowel with no Doppler signal after a period of observation should be resected; marginal bowel with no Doppler signal is an indication for second-look laparotomy.

With the fluorescein fluorescence method, 10 to 15 mg/kg of fluorescein is injected intravenously, and the intestine is inspected with a Wood lamp. A complete absence of fluorescence is diagnostic of nonviability; rapid, confluent, bright fluorescence indicates viability. There is, however, a large gray area between these two extremes in which interpretation is subjective. In one study, the IV fluorescein method was found to be 100% sensitive and specific for detecting nonviable bowel.³⁸ The disadvantages of this technique are that it requires special equipment and that it exposes the critically ill patient to the risk of an adverse reaction to the dye. Other assessment methods (e.g., surface oximetry, infrared photoplethysmography, and laser Doppler velocimetry) are available, but at present, they are mostly experimental and are not in general use for evaluation of bowel viability in a clinical setting.

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Figures 5, 6, 10, 11, and 12 Alice Y. Chen

15 UPPER-EXTREMITY REVASCULARIZATION PROCEDURES

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Vascular surgeons are commonly called on to treat patients with acute arm ischemia. Elective arm revascularization is an infrequently performed procedure, one that usually prompts surgeons to resort to reference texts. Even in busier centers, elective arm reconstructions currently account for only 3.2% of elective limb revascularizations. Balloon angioplasty has largely replaced surgical bypass in the treatment of subclavian occlusions; however, the very growth of endoluminal approaches to arm revascularization has led to a paradoxical increase in the need for so-called prophylactic carotid-subclavian bypass in patients with thoracic aneurysms. In addition, the rising incidence of diabetes and the longer survival times reported in patients with renal impairment have led to increased use of distal bypass procedures in the arm (analogous to pedal bypass procedures in the leg [see 6:17 *Infrainguinal Arterial Procedures*]). Finally, the growing number of dialysis access procedures performed has led to an increased incidence of arm ischemia resulting from these operations.

In this chapter, we describe the technical aspects of the procedures employed for emergency and elective arm revascularization. We also touch on pharmacologic alternatives to elective revascularization and briefly consider the potential role of minimally invasive techniques (e.g., thoroscopic sympathectomy).

Procedures for Acute Arm Ischemia

Acute arm ischemia accounts for one fifth of all episodes of acute limb ischemia. It occurs twice as often in females as in males. Brachial embolectomy is the most common treatment. After successful brachial embolectomy, 95% of patients are symptom free¹; however, the operative mortality may be as high as 12%.² Most reports that address acute arm ischemia include only those patients who are treated surgically. In fact, between 9% and 30% of patients who present to vascular surgeons with acute arm ischemia are managed conservatively, either because they are unfit for surgery or because they have minimal symptoms. These conservatively managed patients are probably underrepresented in the literature. In the few reported series, assessment of symptoms and disability has been largely inconsistent. However, in a 1964 series that included 95 patients, 32% of those who were managed conservatively were left with abnormal function in the arm after treatment.³ In a 1977 report, 75% of the conservatively managed patients had poor functional outcomes.⁴ In a 1985 study, 50% of the conservatively managed patients had persistent forearm claudication.⁵ The conclusion to be drawn is that although conservative management is appropriate for some patients with acute arm ischemia, every effort should be made to restore blood flow in patients who have a reasonable life expectancy.

BRACHIAL EMBOLECTOMY

Preoperative Evaluation

Patients with acute arm ischemia tend to be slightly older at presentation than patients with leg ischemia (74 years versus 70

years).⁶ Usually, there is an underlying embolic source (e.g., cardiac dysrhythmia). Most arm emboli (75%) are of cardiac origin. The brachial artery is the most common site of emboli (60% of cases), followed by the axillary artery (26%). In situ thrombosis accounts for 5% of episodes of arm ischemia.⁷

Selection of patients All patients with acute-onset arm ischemia are candidates for embolectomy. Conservative management should be considered only for patients who are terminally ill or unfit for surgical intervention.

Alternative therapy Some authors have achieved good results by using thrombolysis to treat acute occlusion of the axillary artery or the brachial artery.⁸ However, in a 2001 series that included 38 patients with 40 occlusions treated with thrombolysis, the success rate of this approach was only 55%, and eight patients had to undergo surgical thrombectomy after thrombolysis failed.⁹ Excellent outcomes have also been reported for the treatment of acute arm ischemia with rotational thrombectomy devices (e.g., Rotarex; Straub Medical, Wangs, Switzerland). To date, however, no large published studies have evaluated these devices, and clinical experience with them is currently limited to case reports.¹⁰

Operative Planning

In most patients with acute arm ischemia, diagnosis is straightforward and surgical treatment relatively easy. Some instances of acute arm ischemia, however, are caused by an inflow lesion in the subclavian artery (SA) (e.g., from ulcerated plaques, a thrombosed SA aneurysm, or an arterial thoracic outlet syndrome). In such situations, even a technically perfect embolectomy will fail to restore normal hand perfusion.

The majority of brachial embolectomies are performed with local anesthesia, with or without monitored conscious sedation.

Operative Technique

The origins of the ulnar and radial arteries are exposed by means of a so-called lazy S incision [see *Figure 1a*], which prevents the elbow contracture that can occur with a vertical incision. The skin and the subcutaneous tissues are divided. Care is taken to preserve the superficial veins, especially the median antecubital vein, which may be needed to patch the brachial artery. The bicipital fascia is incised, and the brachial artery is found between the tendon of the biceps laterally and the median nerve medially [see *Figure 1b*]. Dissection is continued distally until the ulnar and radial arteries are encountered. The radial artery is a continuation of the brachial artery; the ulnar artery comes off the brachial artery medially and, within 2 to 3 cm of its origin, dives beneath the pronator and epitrochlear muscles. It is important to expose the origins of both forearm arteries because the embolectomy catheter must be passed down each vessel. If the catheter is blindly passed down the brachial artery, it will probably travel down the radial artery.

An arteriotomy (usually vertical) is made in the brachial artery. Clot may be encountered at the bifurcation; if so, it is readily

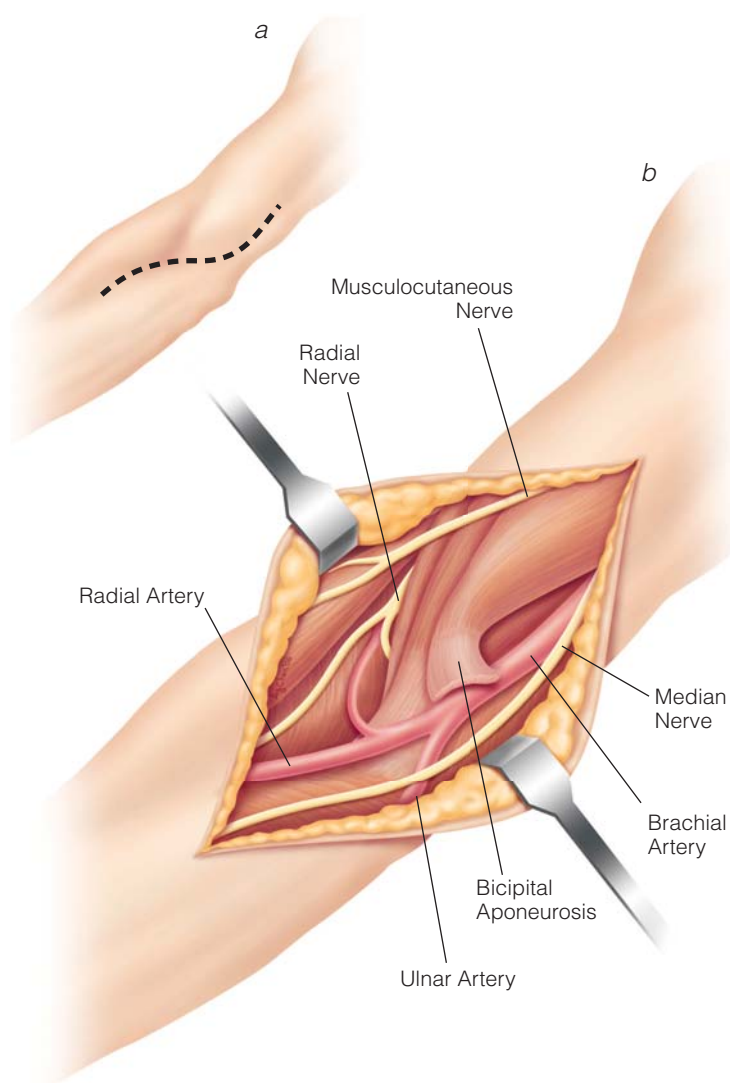


Figure 1 Brachial embolectomy. Shown are (a) a lazy S skin incision and (b) the main nerves and vessels exposed.

removed. In some cases, the brachial artery is pulseless, which indicates that the embolus is lodged more proximally. Once inflow is established, a size 2 or 3 embolectomy catheter is passed distally down each forearm artery. The arteriotomy is then closed either primarily or with a vein patch. A segment of vein may be harvested from the antecubital fossa. Adequate flow in the radial and ulnar arteries is confirmed by means of an intraoperative Doppler probe.

Occasionally, the hand continues to appear ischemic even after an adequate embolectomy. This persistent ischemia is caused either by an unrecognized inflow lesion or by embolization to the digital arteries that has been occurring over an extended period. In these patients, an arch aortogram with selective views of the affected arm should be performed immediately after operation. Any lesion in the SA or the innominate artery can be treated with angioplasty and stenting.

Postoperative Care

The mainstay of postoperative management is adequate anticoagulation. Embolization recurs after successful embolectomy in one third of patients if systemic anticoagulation is not instituted. It may recur even in the face of oral anticoagulation: in a 1989 study, 11% of patients given warfarin after embolectomy sus-

tained a further embolic episode, and all had ongoing atrial fibrillation.⁶ Patients are routinely followed up by means of noninvasive studies 4 to 6 weeks after operation.

FOREARM FASCIOTOMY

Unlike calf fasciotomies, which are commonly necessary for leg ischemia, forearm fasciotomies are rarely required for acute arm ischemia. They are more commonly required for traumatic injuries to the arm (e.g., crush injuries or supracondylar fractures of the humerus) or for iatrogenic injuries (e.g., inadvertent infusion of fluid into the muscle compartments of the forearm). Forearm fasciotomies are immediately effective when they are performed, and the incisions, though extensive, usually heal quickly.

Preoperative Evaluation

The forearm muscles are typically tense and tender, though the diagnosis can be difficult to make. One option for assessment is to test compartment pressures with a needle and a transducer; if the intracompartmental pressure is higher than 30 mm Hg, fasciotomy may be indicated. Another option is insonation of the radial and ulnar arteries; if the signal is absent or severely obstructed, fasciotomy may be indicated. Neither of these techniques, however, is reliable. As with lower-extremity ischemia, even the finding of a pulse does not eliminate the need for fasciotomy. The decision whether to perform the procedure is made on clinical grounds.¹¹ The relevant dictum is "If one is thinking about a fasciotomy, it is probably indicated."

Selection of patients Awareness of the diagnosis is crucial. Any patient with the traumatic or iatrogenic conditions previously mentioned (see above) should be considered to be at risk for compartment syndrome.

Alternative therapy There is no alternative to fasciotomy. Failure to recognize the problem or undue delay in performing adequate fasciotomies will lead to forearm muscle ischemia and a Volkmann's ischemia contracture, resulting in a useless hand.

Operative Planning

Because this procedure is rarely performed, the surgeon may find it useful to mark the incisions on the skin with an indelible pen before operation. The operation is generally performed with general anesthesia, but if the patient is profoundly ill, it may be performed with local anesthesia instead.

Operative Technique

Both a volar and a dorsal incision are required [see Figure 2]; there is no single-incision option, as there is for leg fasciotomy. On the volar aspect of the arm, a curvilinear incision is made to allow decompression of the flexor compartment. Because this compartment is supplied by a single vessel (the interosseous artery) and lacks any collateral circulation, it is particularly susceptible to ischemia. On the dorsal aspect, a vertical incision is made to release the dorsal compartment. Because of its deep location in the forearm, the median nerve is especially susceptible to compartment syndrome. At the level of the elbow, the bicipital aponeurosis is divided so that it can be decompressed. At the wrist, the flexor retinaculum is divided in much the same way as in a carpal tunnel decompression. In severe cases, the deep intramuscular fascia enveloping the flexor digitorum superficialis, the flexor digitorum profundus, and the flexor pollicis longus may be opened as well. As a rule, the skin incisions are loosely approximated to facilitate later closure. In any case, the incisions usually heal very well.

Postoperative Care

Regular dressings are applied to the area. Often, delayed primary closure of the fasciotomy sites may be performed once the muscle edema has resolved. Further pressure measurements may be performed to confirm that all muscle compartments have been released.

Procedures for Chronic Arm Ischemia

The etiology of chronic arm ischemia is diverse. Although atherosclerosis is still the major cause, other potential causes (including thoracic outlet syndrome and iatrogenic injury, as well as rarer causes such as Takayasu arteritis, giant cell arthritis, and radiation-induced injury) must also be considered. Initial assessment is carried out by means of noninvasive studies (e.g., pulse-volume recordings [PVRs] and duplex ultrasonography), followed by magnetic resonance angiography (MRA) or computed tomographic angiography (CTA). Confirmation of the findings obtained from these studies may be obtained by means of arch and arm angiography. As a rule, any occlusive lesions found will be in the innominate, subclavian, axillary, or forearm arteries. Each location calls for a different treatment stratagem.

AORTOSUBCLAVIAN BYPASS AND EXTRATHORACIC OPTIONS FOR INNOMINATE ARTERY OCCLUSION

Innominate artery reconstruction is a major surgical procedure. In one major series, the reported operative mortality was 5.4%.¹² Currently, innominate artery bypass is rarely performed, having been largely supplanted by balloon angioplasty and stenting. Nevertheless, there are still some patients who, for technical

reasons, may not be candidates for endovascular procedures (e.g., those with an occluded stent and those in whom the anatomy is unsuitable). In patients for whom it is indicated, innominate artery bypass has durable beneficial effects and thus is an option worth considering, despite its potential for significant morbidity.

Preoperative Evaluation

Arm ischemia is the typical presentation for patients with innominate artery occlusion. Cerebrovascular symptoms related to the vertebral or carotid arteries are the second most common presentation.

In many patients, noninvasive imaging yields the first indication of innominate artery stenosis. It is difficult, however, to distinguish between an occlusion in the proximal SA and one in the innominate artery on a duplex ultrasonogram. Contrast angiography is the gold standard for making this distinction. As with all major vascular procedures, standard cardiac investigations and clearance are mandatory.

Selection of patients Innominate artery bypass is the operative standard for selected patients with upper-extremity ischemia. In patients who are at particularly high risk, however, extrathoracic options (e.g., carotid-carotid bypass or, rarely, axilloaxillary crossover grafting) should be considered. We prefer carotid-carotid crossover for higher-risk patients. Cerebrovascular considerations (e.g., asymptomatic high-grade lesions [i.e., > 70% occlusion] or ulcerated plaques with greater than 50% luminal narrowing) may also warrant intervention.

Alternative therapy Indirect or extra-anatomic approaches to innominate artery reconstruction include axilloaxillary crossover grafting, carotid-carotid crossover, and femoroaxillary bypass. In general, these approaches are reserved for higher-risk patients in whom endovascular therapy is not an option.

Operative Planning

Operative planning must take into account relevant anatomic details. It is important to keep in mind that the anatomy of the aortic arch is not invariable: in 30% of patients, there are variations in the arch anatomy that may make innominate artery bypass more difficult. The most common variation is an innominate artery that branches into a right common carotid artery (CCA) and a right SA, with the right CCA and the right SA coming directly off the arch. In 16% of patients, however, the innominate artery and the right CCA may have a common ostium. In 8% of patients, the left CCA comes off the innominate artery, leaving the left SA as the only other artery coming off the arch. In 6% of patients, the left vertebral artery comes off the arch between the left CCA and the left SA. In fewer than 1% of patients, the right SA comes off the descending aorta as the last arch branch, then travels behind the esophagus (as the retroesophageal right SA) to reach the right supraclavicular fossa.¹³

Operative Technique

The innominate artery is approached via a median sternotomy.¹⁴ A sternal retractor is placed and opened. The thymus is divided along its midline with the electrocautery, and the inferior thymic vein is ligated and divided. The brachiocephalic vein is identified as it crosses the innominate artery, then mobilized and placed in a vessel sling. The pericardium is opened from the ventricular surface to a point just below the origin of the innominate artery. It is held away from the operative field with stay sutures.

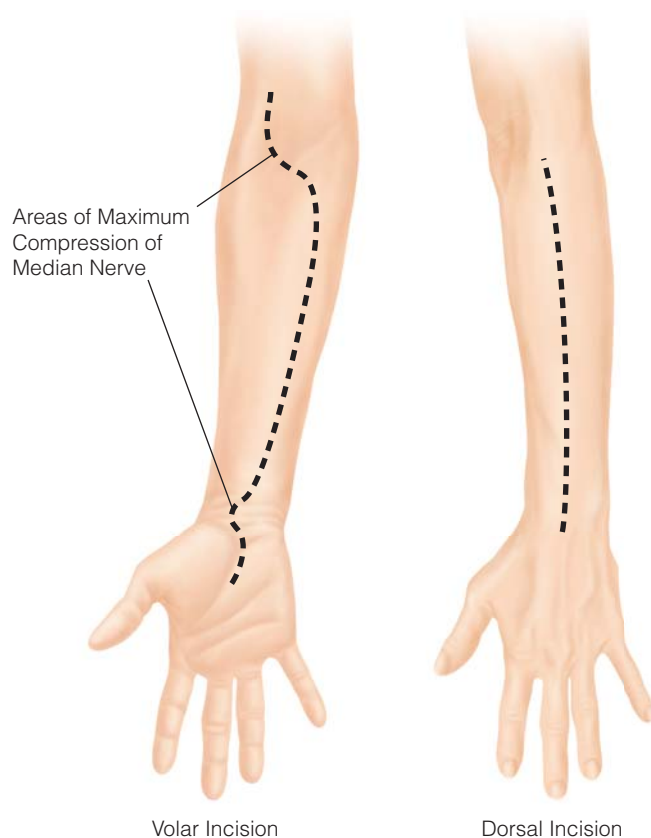


Figure 2 Forearm fasciotomy. Shown are (a) a volar incision and (b) a dorsal incision in the forearm.

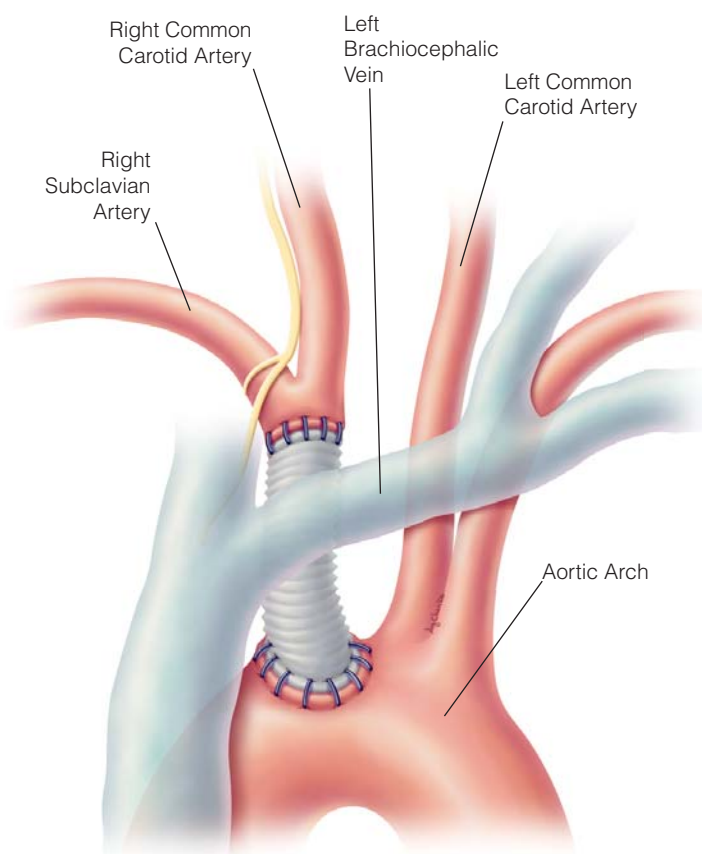


Figure 3 Innominate artery bypass. One end of the graft is sewn to the aorta in an end-to-side fashion, and the other is sewn to the common ostium of the right SA and the right CCA in an end-to-end fashion.

The ascending aorta is then exposed. Fat and visceral pericardium are cleared from the anterior and lateral walls of the aorta to allow placement of a partial exclusion clamp.

The brachiocephalic vein is retracted downwards, and dissection is continued distally along the innominate artery toward the origins of the right SA and the right CCA. Care must be taken to keep from injuring any major nerves, particularly the right recurrent laryngeal nerve.

Some authors have employed a partial median sternotomy approach to the innominate artery, which is useful when access to the distal half of the innominate artery is required and access to the ascending aorta is not required. The advantage of this approach is that it preserves the lower sternum, thereby enhancing the stability of the chest and reducing postoperative pain. The incision extends only to the fourth intercostal space.

After heparinization, a partial exclusion clamp is placed on the ascending aorta, and an arteriotomy is made. An 8 mm graft is sutured to the aorta in an end-to-side fashion with 3-0 or 4-0 polypropylene. If the innominate artery is occluded, the right CCA and the right SA are clamped, and the innominate artery is divided and oversewn. The graft is then sewn to the common ostium of the SA and the CCA in an end-to-end fashion [see Figure 3]. Flow is confirmed with a Doppler probe, as with all the reconstructions we describe in this chapter.

Postoperative Care

After the operation, patients are observed in the intensive care unit. In general, anticoagulation is not indicated. After

recovery, patients are followed by means of noninvasive graft surveillance.

CAROTID-SUBCLAVIAN BYPASS OR TRANSPOSITION

Most patients with SA stenosis or occlusion require no treatment. In many cases, overt symptoms are absent, and the diagnosis is made serendipitously when a reduced pulse pressure is encountered in one arm. For patients with symptomatic lesions, balloon angioplasty with stent insertion is currently the treatment of choice, having been shown to be a durable and effective therapy.^{15,16} Elective bypass is typically reserved for lesions that are not amenable to balloon angioplasty. As stenting of thoracic aortic aneurysms becomes more common, however, stents are increasingly being applied across the origin of the left SA to facilitate proximal fixation, which means that a carotid-subclavian transposition or bypass is required to maintain flow. Thus, the growth of endovascular surgical treatment of thoracic aortic aneurysms has, paradoxically, created a growing population of patients who require a carotid-subclavian bypass. It is important, therefore, that this procedure remain part of the armamentarium of all vascular surgeons.

Preoperative Evaluation

A healthy CCA is an excellent inflow source for an SA bypass procedure. Before operation, the CCA should be evaluated with duplex ultrasonography, supplemented by arteriography. Aortic arch anomalies (e.g., the presence of a bovine aortic arch) should be identified. In patients with contrast allergies or renal impairment, MRA may be employed. In the future, CTA may prove to be the modality of choice.

Selection of patients It is important to confirm that arm symptoms are in fact caused by subclavian disease. In young patients, the possibility of thoracic outlet syndrome should be considered. In older patients, the differential may include cervical disc problems or osteoarthritis. In patients with thoracic aortic aneurysms, our threshold for treatment is a diameter of 5 cm. Given the complexity of the anatomy and the potential for nerve injury, some surgeons are reluctant to perform carotid-subclavian bypass or transposition, instead favoring axilloaxillary crossover grafting. However, axilloaxillary crossover has a lower patency rate than carotid-subclavian bypass or transposition, and its subcutaneous placement and prominence make it less acceptable to most patients. In addition, instances of erosion through the skin have been reported.

Alternative therapy Subclavian artery balloon angioplasty is less invasive than surgical bypass and is a durably effective procedure that is well tolerated by most patients.¹⁷ However, patients who have recurrent stenosis or whose lesions are too close to the vertebral arteries may not be candidates for angioplasty. For such patients, prosthetic bypass or reimplantation of the subclavian artery is an ideal option. The temptation to perform a lesser procedure (e.g., axilloaxillary bypass) should be resisted.

Operative Planning

The two key considerations in the planning of the operation are (1) whether to perform a bypass or a transposition and (2), if a bypass is chosen, whether to use autologous vein or synthetic material as the conduit. For a bypass, prosthetic grafts, being short and of large caliber, are generally considered preferable to autologous vein grafts^{18,19}; they are less likely to become kinked or give rise to intrinsic disease, and the long-term patency of prosthetic reconstructions is excellent.

Transposition of the SA is an excellent alternative to carotid-subclavian bypass, with long-term patency rates approaching 100%.²⁰ Preoperative consent should include acknowledgment of the potential for injury to the phrenic nerve or the brachial plexus.

Operative Technique

The patient is placed in the supine position, with a towel roll placed between the scapulae. The neck is tilted toward the contralateral shoulder. A transverse incision is made 1 cm superior to the clavicle. The underlying platysma and the lateral portion of the sternocleidomastoid muscle are divided in the line of the incision. The underlying omohyoid muscle and the external jugular veins are divided, and the scalene fat pad is mobilized and retracted laterally and cephalad. Minor lymphatic vessels are identified and ligated. The internal jugular vein is visible medially in the carotid sheath, and the carotid artery is usually situated posteriorly. Every effort should be made to keep from injuring the vagus nerve and the thoracic duct on the left; the risk of thoracic duct injury may be minimized by not dividing the lymphatic tissue lying between the phrenic nerve and the lateral border of the internal jugular vein. The anterior scalene muscle is divided as far caudad as possible to reveal the SA; care must be taken to avoid the overlying phrenic nerve, which courses diagonally in a lateral-to-medial direction along the anterior surface of the muscle.

A bypass from the CCA to the SA is then performed in an end-to-side fashion with a 6 mm or 8 mm prosthetic graft [see Figure 4]. The graft is usually tunneled under the internal jugular vein. Often, the graft-SA anastomosis is constructed first. A clamp is placed on the proximal graft, and the anastomosis to the CCA is

constructed. The CCA is mobilized so that once two straight vascular clamps are placed and rotated anteriorly, the graft-CCA anastomosis may be performed more easily. Once the bypass has been completed, flow is restored—first to the arm, then to the proximal SA, and finally to the distal CCA, so as to minimize the carriage of embolic debris to the brain. Flow should then be assessed with a pencil Doppler probe.

After completion of the bypass, the scalene fat pad is tacked to its former medial and inferior attachments; failure to do so may leave a visible defect in this area. The wound is drained with a closed suction apparatus. An upright chest x-ray is obtained to rule out pneumothorax or hemidiaphragmatic elevation secondary to phrenic nerve injury. Postoperative evaluation of bypass patency is accomplished by physical examination with palpation of pulses at the wrist. Further objective documentation of patency is obtained by means of PVRs, duplex ultrasonography, or both.

Postoperative Care

The major postoperative complication is phrenic nerve injury and resulting paralysis of the hemidiaphragm [see 4:6 *Paralyzed Diaphragm*]. Another significant complication is lymphatic leakage, which may occur as a result of either minor or major duct injury. Adequate wound drainage and prompt recognition of the lymphatic leak are the keys to management. Minor leaks usually seal with adequate drainage. If drainage is excessive, the patient will have to be maintained on parenteral nutrition with a formula that includes medium-chain triglycerides. On occasion, thoracic duct ligation via thoracotomy or thoracoscopy may be necessary. Other complications include pneumothorax, brachial plexus injury, and stroke.

Patients are followed with serial PVRs of the arm and duplex ultrasonography of the grafts.

AXILLOBRACHIAL BYPASS

Axillobrachial bypass may be performed to treat severe occlusive disease in the axillary or proximal brachial arteries. It is infrequently performed for chronic ischemia and more frequently performed for shoulder trauma. In the latter setting, it is often associated with brachial plexus injuries.

Preoperative Evaluation

Axillobrachial bypass is not commonly performed on an elective basis. The axillary and proximal brachial arteries seem to be remarkably impervious to the effects of systemic atherosclerosis. In those rare cases in which this procedure is indicated, preoperative evaluation of the affected arm with selective angiography is appropriate. Vein mapping should be performed. It is important to confirm that the patient's symptoms derive from arm ischemia and not from other conditions (e.g., neuropathy).

Alternative therapy If arm ischemia is truly symptomatic at this level, sympathectomy may be considered [see *Alternative Therapies for Chronic Arm Ischemia, below*]. Angioplasty may be an option for axillary artery lesions, but it is infrequently performed in this setting, and data on its effectiveness and durability are relatively sparse.

Operative Planning

Autogenous vein is the conduit of choice for axillobrachial bypass. Prosthetic bypasses have lower patency rates than venous bypasses in this setting and should therefore be avoided. The greater saphenous vein is the preferred source of the venous conduit, though the use of the cephalic vein in situ has also been described.

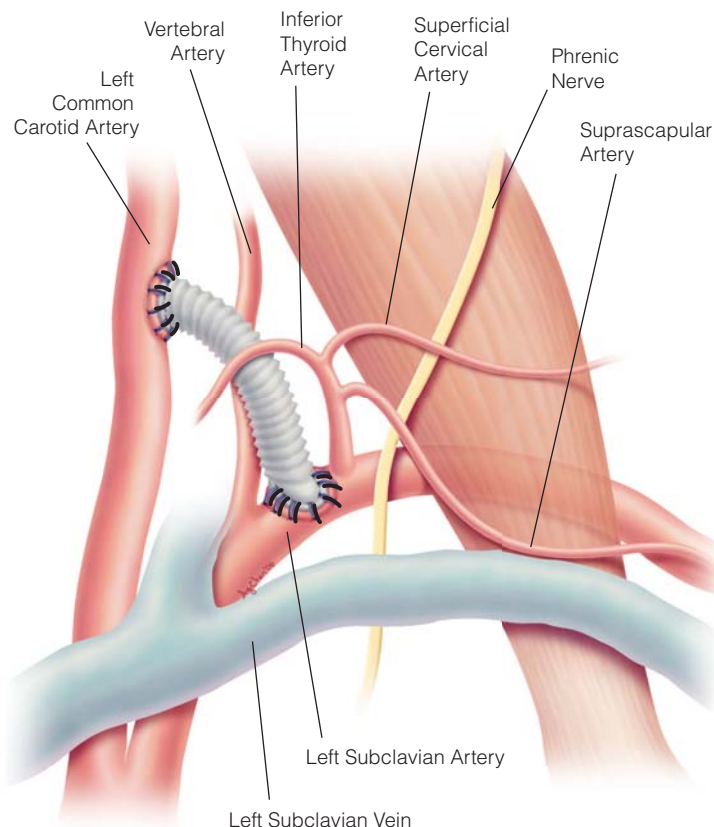
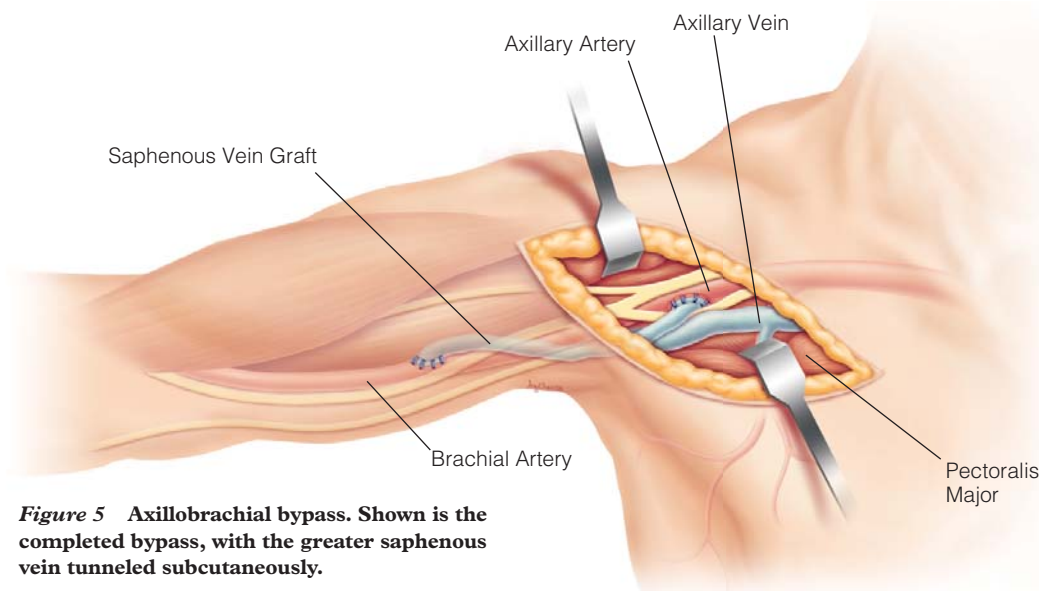


Figure 4 Carotid-subclavian bypass. One end of the graft is sewn to the left SA in an end-to-side fashion, and the other is sewn to the left CCA in an end-to-side fashion.



Operative Technique

The patient is placed in the supine position, and the arm is draped circumferentially. A previously mapped leg is draped in preparation for vein harvesting. The axillary artery is approached via a transverse incision placed 2 cm below the middle third of the clavicle. The underlying pectoralis major is divided in the line of the decussation between its sternocostal and clavicular portions. Despite the assurances of most operative texts, the decussation is not always readily apparent. Division of the pectoralis major exposes the clavipectoral fascia, which is then divided. The axillary artery is identified cephalad to the axillary vein and is carefully dissected, with care taken not to injure the surrounding branches of the brachial plexus. The second part of the axillary artery is exposed by dividing the pectoralis minor.

If necessary, the distal third of the axillary artery may be exposed. An oblique incision is made along the lateral margin of the pectoralis major with the arm abducted 90° relative to the thorax. Once the subcutaneous tissue is divided, the axillary sheath is located near the posteroinferior border of the coracobrachialis. Care should be taken to keep from injuring the medial and lateral cords of the brachial plexus medially and the median and ulnar nerves laterally.

By preference, bypasses originating from the axillary artery are tunneled anatomically along the axis of the axillary and brachial arteries. Alternatively, they may be positioned subcutaneously; however, subcutaneous bypasses are more susceptible to distraction injuries caused by forcible abduction of the shoulder. Accordingly, some degree of redundancy should be built into a subcutaneous bypass.

The middle or the distal portion of the brachial artery is exposed as necessary. The proximal or the middle third of the vessel is exposed by making a medial incision over the bicipital groove, with care taken to keep from injuring the basilic vein and the cutaneous nerves located within the subcutaneous tissue. Traction on or transection of the median antebrachial cutaneous nerve may lead to hyperesthesia or anesthesia along the medial dorsal surface of the forearm; these problems occasionally occur after dialysis access procedures (e.g., basilic vein transposition) and can be highly debilitating, sometimes even rendering the fistula unusable. The brachial sheath is then incised longitudinally. The median nerve is the most superficial structure encountered

within the sheath. It is gently mobilized and retracted to afford access to the brachial artery. Any venous branches that cross the artery should be divided carefully, and every effort should be made to keep from injuring the posteriorly located ulnar nerve.

In contrast, the distal third of the brachial artery and its bifurcation are exposed in the antecubital fossa. A lazy S or sigmoid incision [see Figure 1a] is made to expose the brachial artery while avoiding wound contracture. The bicipital aponeurosis is then incised to expose the brachial artery, which is sandwiched between the biceps tendon laterally and the median nerve medially. Further dissection exposes the origins of the ulnar and radial arteries.

After systemic heparinization, the venous conduit is harvested, and its side branches are ligated with fine polypropylene suture ligatures or silk ties. The vein is distended with a solution containing dextrose 70 (500 ml I.V.), heparin (1,000 U), and papaverine (120 mg). The excised conduit may be employed in either a reversed or an orthograde (nonreversed) orientation, depending on the taper of the conduit. If the orthograde orientation is used, the proximal anastomosis is performed, the conduit is distended, and the valves are lysed with a retrograde Mills valvulotome. In either case, the conduit is tunneled anatomically wherever possible; in this way, it will be less prone to movement, distraction, or distortion. After tunneling, the distal anastomosis is constructed [see Figure 5]. Immediately upon completion of the bypass, patency and augmentation of flow are assessed with a pencil Doppler probe.

Major potential complications include injuries to the brachial plexus, the median nerve, or the ulnar nerve. Such injuries usually are caused by traction and may be minimized by careful dissection during operative exposure. The median and ulnar nerves and the brachial plexus are also vulnerable to direct thermal injury; accordingly, dissection with the electrocautery should be avoided.

Postoperative Care

Postoperatively, the patency of the bypass is documented by surveillance with noninvasive studies. In general, duplex ultrasonography is valuable for determining the patency of the reconstruction and for detecting any early flow abnormalities in the venous conduit. Graft infection should be watched for and appropriately treated if found.

DISTAL REVASCULARIZATION–INTERVAL LIGATION AND REVISION USING DISTAL INFLOW

The rising incidence of diabetes in the United States has led to a corresponding rise in the number of patients in whom vascular access is required for hemodialysis.^{21,22} As reconstructions become more complex, these patients are increasingly coming under the care of vascular surgeons. An unfortunate consequence of the growing number of upper-arm fistulas is that the incidence of dialysis-associated steal syndrome (DASS) is increasing as well. DASS is rare after Cimino or radiocephalic fistula procedures,²³ but it occurs in 6% to 8% of patients who undergo upper-arm brachial artery–based fistula or graft procedures.^{24,25} DASS may present in either an acute form (characterized by severe rest pain and obvious ischemia developing within 24 to 48 hours after operation) or a chronic form (characterized by symptoms and signs developing several weeks or even months after the original operation), each of which is managed in its own distinct fashion.

In cases of acute ischemia that develops within 24 to 48 hours after an upper-arm fistula procedure, the fistula should be ligated to restore flow down the native arteries. In cases of chronic ischemia, however, the aim is to preserve the fistula and avoid ligation. To this end, there are two main surgical options that should be considered. The first option is distal revascularization–interval ligation (DRIL), which involves the creation of a venous bypass from the proximal portion of the brachial artery to the distal portion of the vessel [see Figure 6]. The brachial artery distal to the origin of the fistula is ligated, flow to the distal arm is restored, and the fistula is preserved.²⁶ The second option is revision using distal inflow (RUDI), which involves ligation of the fistula at its origin, followed by reestablishment of the fistula by means of a venous bypass from the radial or the ulnar artery.²⁷ By using a

smaller distal artery as the inflow source, RUDI lengthens the fistula and preserves antegrade flow in the brachial artery.

Of the two options, DRIL is better established and more widely used at present. It is our preferred option and thus is the primary focus of the ensuing description. Nevertheless, there are aspects of the DRIL procedure that many vascular surgeons find counterintuitive—namely, the ligation of a healthy artery and the bypassing of a normal arterial segment with a venous conduit. There does seem to be a good argument in favor of RUDI. Long-term evaluation of this procedure is awaited.

Preoperative Evaluation

Preoperative evaluation for DRIL should follow the same pattern as that for any elective procedure performed to treat arm or leg ischemia. Preoperative angiography is performed with vein mapping to identify an adequate source of a venous conduit. Cardiac clearance is obtained.

Selection of patients DRIL is generally reserved for patients with chronic arm ischemia in whom a fistula has been established that must be preserved. If the option of creating a new fistula in the other arm is available, DRIL is probably a less appropriate choice than simply ligating the original fistula.

Alternative therapy Besides simple ligation of the offending fistula, which is an option that should always at least be considered in these patients, there are two techniques that deserve mention as alternatives to DRIL. The first technique is aimed at preventing steal from an upper-arm fistula (always a laudable aim). In this technique, the fistula is formed by extending the cephalic vein or the basilic vein down the arm and anastomosing it to the proximal ulnar artery or the radial artery just below the brachial bifurcation so as to preserve part of the blood supply to the hand. The median cubital vein may also be used.²⁸

The second technique is RUDI [see Figure 7]. This procedure differs from DRIL in that it is the fistula, not the native arterial supply, that is placed at risk by the surgical revision, so that in the event of graft failure, the fistula is lost but the arm is not endangered.

Operative Planning

We do not use prosthetic grafts for this procedure; we prefer to use autogenous vein for the graft, usually a segment of the greater saphenous vein from the leg. As a rule, the operation is performed with the patient under general anesthesia.

Operative Technique

A vertical incision is made in the upper arm at the level of the proximal brachial artery. The skin and the subcutaneous fat are divided, and the proximal brachial artery is sharply dissected free. The portion of the brachial artery distal to the origin of the fistula is also dissected free. An adequately long segment of vein is obtained and prepared. Anticoagulation is initiated, and a proximal end-to-side anastomosis is fashioned with 6-0 polypropylene. The vein graft is tunneled subcutaneously, and a distal end-to-end anastomosis to the distal brachial artery is created. Some surgeons prefer an end-to-side distal anastomosis with ligation of the brachial artery proximal to the anastomosis. Adequate flow is confirmed by means of intraoperative Doppler ultrasonography.

Postoperative Care

Postoperative anticoagulation is generally not warranted; however, a postoperative graft surveillance protocol is initiated. If the

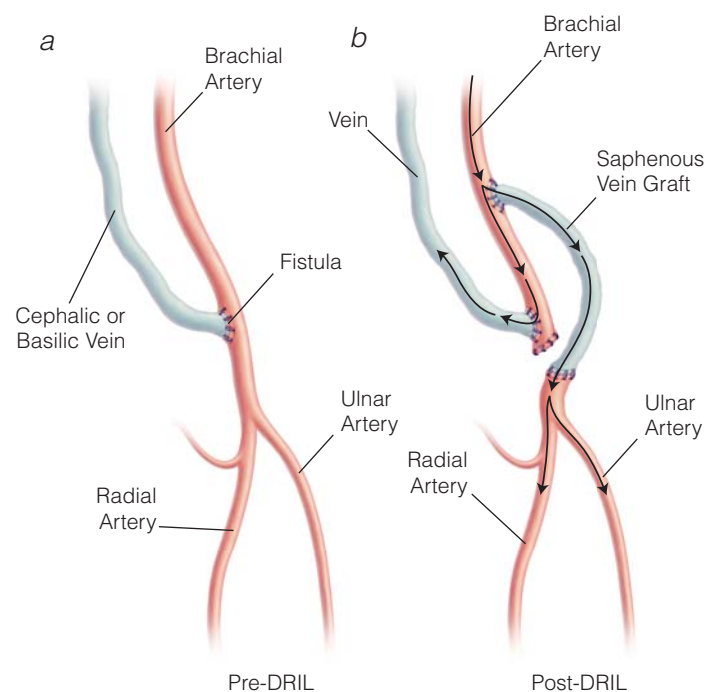


Figure 6 Distal revascularization–interval ligation (DRIL). In patients with a brachial artery–based fistula (a), chronic ischemia may develop weeks or months after the procedure. The best established surgical treatment option is DRIL (b), which preserves the fistula by creating a venous bypass between the proximal brachial artery (above the origin of the fistula) and the distal brachial artery.

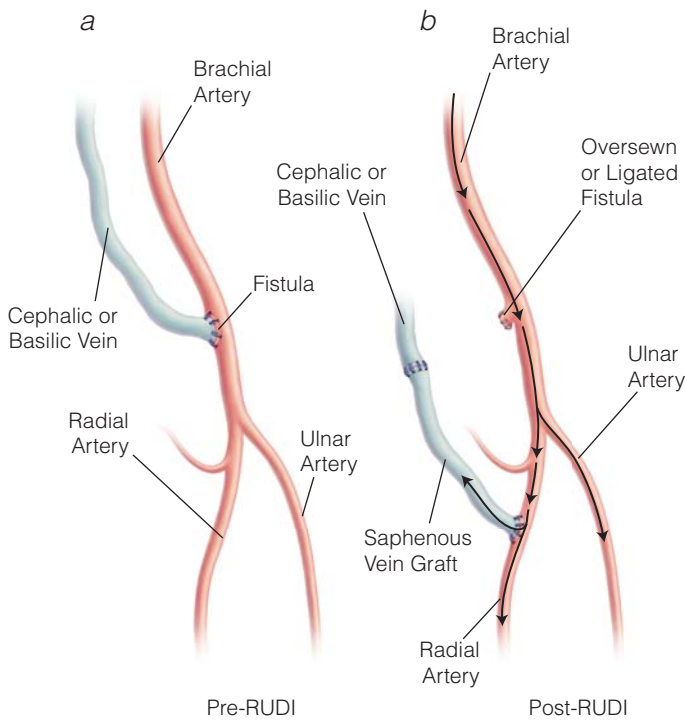


Figure 7 Revision using distal inflow (RUDI). Another option for patients with a brachial artery–based fistula (a) is RUDI (b), which involves ligating the fistula at its origin, lengthening the original venous graft with an additional vein segment, and reestablishing the fistula by anastomosing the lengthened graft to the radial artery (as shown) or the ulnar artery.

venous graft becomes occluded, the fistula is ligated. This step frequently leads to resolution of the symptoms of arm ischemia.

HAND REVASCULARIZATION

Patients with rest pain in the hands and digital ulcers often have significant comorbid conditions (e.g., collagen vascular or rheumatologic disorders, end-stage renal disease, or hypercoagulable states). In addition, patients who have received organ transplants and are taking immunosuppressive medications may experience severe occlusion of forearm or palmar arteries. Younger patients with hand ischemia are often manual laborers who have hypothenar hammer syndrome. Patients with established signs and symptoms of hand ischemia have little to lose by undergoing revascularization: there are few viable therapeutic alternatives.

Aggressive treatment of hand ischemia is worthwhile, in that it achieves rapid relief of symptoms and offers the opportunity for hand and limb salvage. The techniques resemble those employed for distal bypass in the leg [see 6:17 *Infrapopliteal Arterial Procedures*]. Early results from several centers indicate that hand bypass procedures can be performed with low morbidity and good long-term patency.^{29,30} Postoperative life expectancy, however, is often limited by the comorbid conditions present.

Preoperative Evaluation

Preoperative evaluation for hand bypass should follow the same protocol as that for any elective revascularization: preoperative angiography to delineate anatomy with vein mapping to identify a venous conduit.

Many patients with hand ischemia have intractable pain from ulcerative lesions, gangrene, or both. Their main requirement is adequate relief of pain; improved hand function is a secondary

consideration. Vascular reconstruction offers a chance to gain both. The alternative to attempted arm salvage is amputation.

Selection of patients At our institution (Albany Medical Center), all patients with rest pain, digital necrosis, or nonhealing ulcers are evaluated for possible palmar artery reconstruction, provided that they are surgical candidates. Reconstruction is feasible in approximately half of the patients who have renal disease or diabetes.

Alternative therapy Sympathectomy, in various incarnations, has been employed in the treatment of hand ischemia. Isolated reports of success notwithstanding, the experience of most vascular surgeons with sympathectomy in this setting has not been favorable.

Operative Planning

Fortunately, exposure of the palmar vessels beyond the wrist is not as difficult as might be imagined [see *Operative Technique, below*]. Nevertheless, because hand bypass procedures are relatively new territory for many vascular surgeons, operative planning may benefit from a brief review of the normal anatomy. The hand is supplied with blood by the superficial and deep palmar arches. The superficial palmar arch is supplied by a branch of the radial artery and by the ulnar artery. The deep palmar arch is supplied by the radial artery itself and by a deep branch of the ulnar artery.

Venous grafts are preferred to prosthetic grafts for hand bypasses. All venous grafts are tunneled anatomically. In a radial artery reconstruction, the graft is tunneled over the anatomic snuff box onto the dorsum of the hand, between the thumb and the index finger, to join the deep palmar arch. In an ulnar artery reconstruction, the venous graft takes a less circuitous course, passing superficial to the flexor retinaculum at the wrist to join the superficial palmar arch.

Operative Technique

The donor limb that will provide the venous graft is prepared. The brachial artery is exposed as described previously [see *Procedures for Acute Arm Ischemia, Brachial Embolectomy, Operative Technique, above*].

The course of the radial artery in the forearm follows an oblique line from the brachial artery pulse medial to the biceps tendon to the styloid process of the radius. In the midforearm, the radial artery is medial to the brachioradialis and lateral to the flexor carpi radialis. A lateral longitudinal incision is made, and the muscles are separated to reveal the radial artery. At the wrist, the radial artery is exposed by making a longitudinal incision between the tendon of the flexor carpi radialis and the tendon of the brachioradialis. This is the site of the radial artery pulse in normal persons. Here, the artery is superficial, and exposure is relatively straightforward. Care must, however, be taken not to injure the superficial branch of the radial nerve, which is often located near the lateral aspect of the artery. Injury to this nerve branch can result in troublesome paresthesia along the lateral aspect of the thumb.

The course of the ulnar artery runs from the medial epicondyle of the humerus to the pisiform bone. In the midforearm, the ulnar artery lies beneath the deep fascia between the belly of the flexor digitorum laterally and the belly of the flexor carpi ulnaris medially. The ulnar nerve joins the artery on its lateral aspect for the distal two thirds of the vessel's length; this nerve may be injured if not carefully identified and preserved. At the wrist, the ulnar artery is lateral to the tendon of the flexor carpi ulnaris. It is exposed by locating this tendon (which is the most medial tendon palpable at

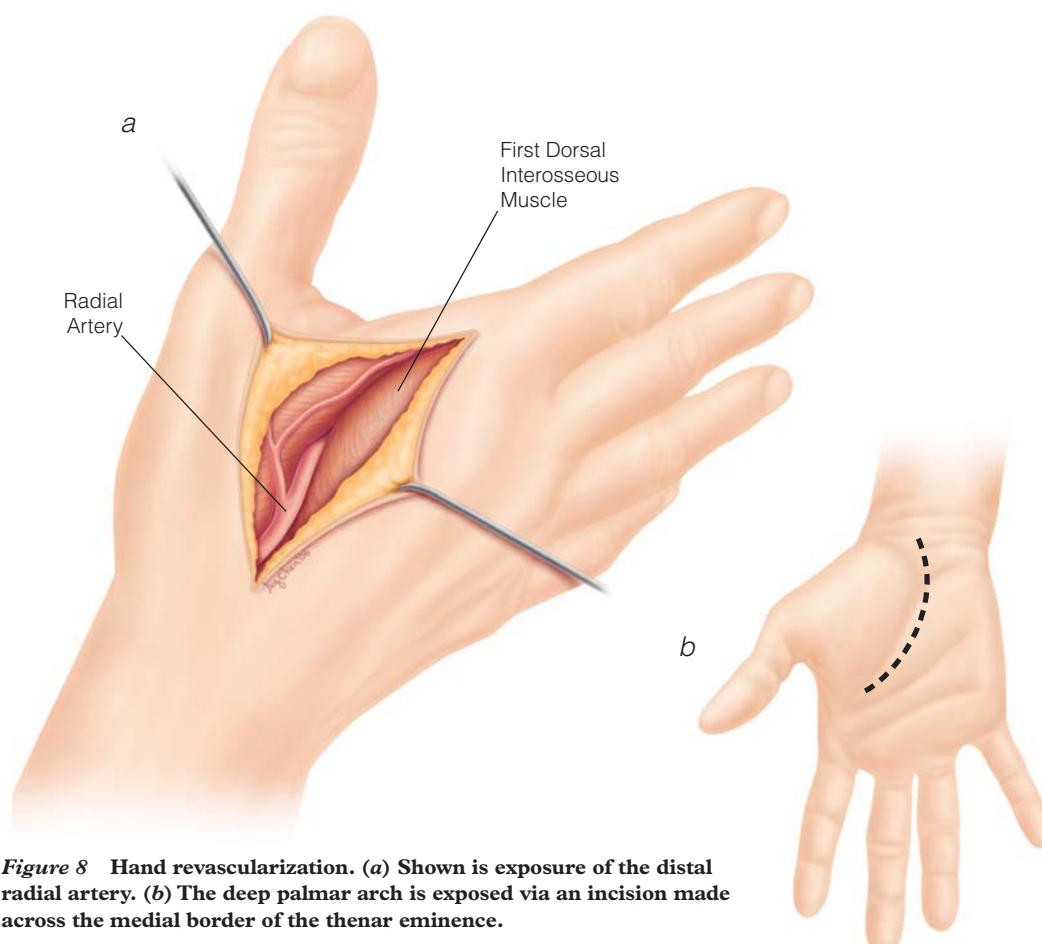


Figure 8 Hand revascularization. (a) Shown is exposure of the distal radial artery. (b) The deep palmar arch is exposed via an incision made across the medial border of the thenar eminence.

the wrist) and making a vertical skin incision lateral to it. Although the ulnar artery lies deeper than the radial artery at the wrist, it is just as easily exposed. Superficial to the ulnar artery, palmar cutaneous branches of the ulnar nerve may be identified; these should also be preserved.

Grafts originating from the brachial artery are tunneled in the subcutaneous plane. Subcutaneous tunneling facilitates physical examination to determine the patency of the bypass, as well as surveillance of the bypass with duplex ultrasonography. Alternatively, if good-quality basilic or cephalic veins are present, an in situ bypass may be performed.

Exposure of radial artery and deep palmar arch Exposure of the radial artery is relatively straightforward. Generally, it may be accomplished as previously described (see above). Alternatively, it may be accomplished by making a vertical incision over the anatomic snuff box (which lies between the extensor pollicis longus tendon posteriorly and the tendons of the extensor pollicis brevis and the abductor pollicis longus anteriorly). This incision is then deepened through the subcutaneous tissues to expose the radial artery in the floor of the snuff box [see Figure 8a]. This area contains no significant nerves and thus is often chosen as a site for hemodialysis access.

The deep palmar arch is much less accessible than the radial artery. Consequently, exposure of this vascular structure is considerably more difficult than exposure of the radial artery. The deep palmar arch extends across the palm, level with the proximal border of the outstretched thumb. To expose it, an incision is made along the medial border of the thenar eminence [see Figure 8b]. Extensive dissection of the superficial and deep flexor tendons of

the hand and division of the oblique head of the adductor pollicis are then required to provide access to the origin of the deep palmar arch.

Exposure of ulnar artery and superficial palmar arch

Like exposure of the radial artery, exposure of the ulnar artery and the superficial palmar arch is fairly straightforward. In reality, these vessels are no smaller than the tibial and pedal vessels in the leg. A curved incision is made along the lateral border of the hypothenar eminence [see Figure 9a]. The aponeurotic layer is divided, and the artery is exposed in the upper part of the palm at the origin of the superficial palmar arch. There are no major nerves in the vicinity, and it usually is not difficult to expose a reasonable length of artery for an arterial anastomosis [see Figure 9b]. Alternatively, the superficial palmar arch may be exposed in the palm by making an incision along one of the larger vertical or oblique skin creases.

Postoperative Care

As with all venous grafts, postoperative graft surveillance is essential. Routine postoperative anticoagulation generally is not warranted.

Alternative Therapies for Chronic Arm Ischemia

THORACOSCOPIC SYMPATHECTOMY AND DIGITAL SYMPATHECTOMY

Our experience with sympathectomy in the treatment of patients with critical hand ischemia or digital ulceration has been, frankly, disappointing. When we do perform sympathectomy, we

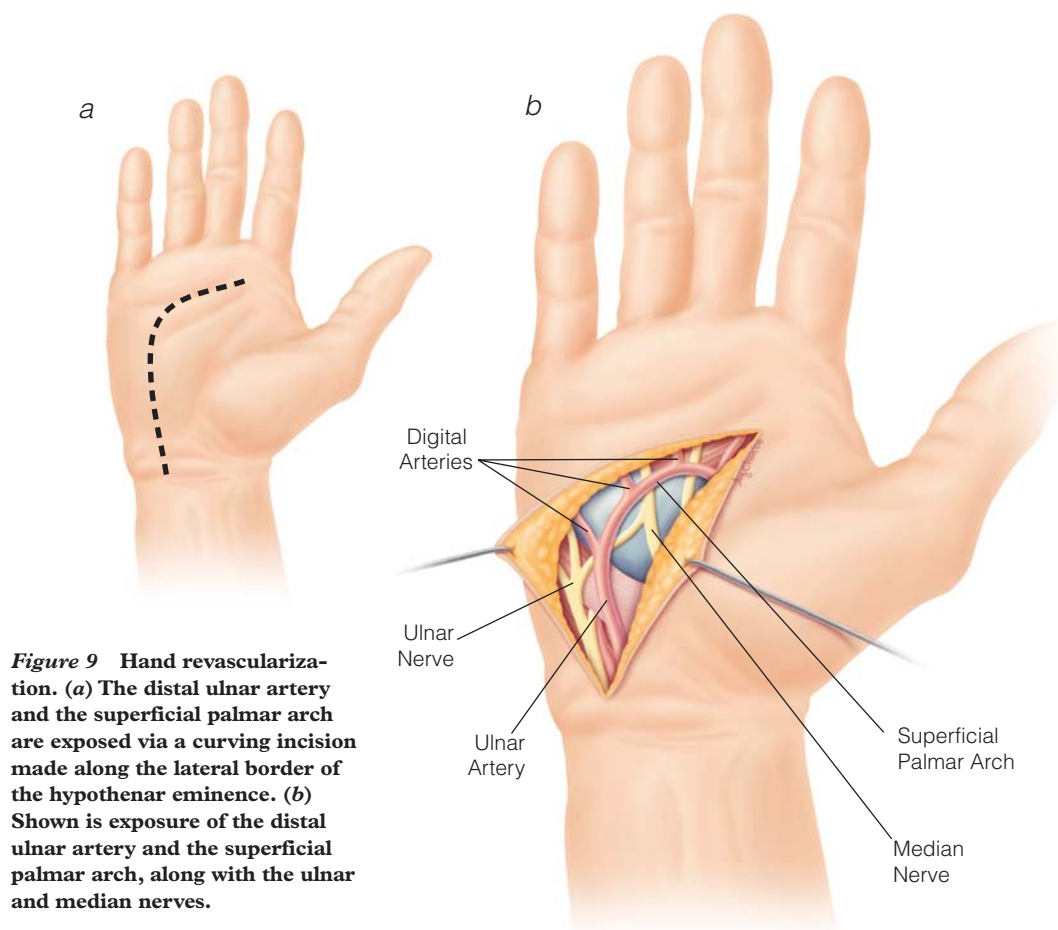


Figure 9 Hand revascularization. (a) The distal ulnar artery and the superficial palmar arch are exposed via a curving incision made along the lateral border of the hypothenar eminence. (b) Shown is exposure of the distal ulnar artery and the superficial palmar arch, along with the ulnar and median nerves.

prefer the thoracoscopic approach to the traditional cervical route. Either way, however, the results have been discouraging; any improvements noted prove to be only temporary. Sympathectomy may help alleviate pain in these patients, but even in this regard, the results are, at best, unpredictable. A review of the literature seems to support this conclusion. Admittedly, the available data on thoracoscopic sympathectomy for digital ischemia are sparse: to date, only three reports encompassing 21 patients have been published.³¹⁻³³ In contrast, there is a wealth of data on thoracoscopic sympathectomy for hyperhidrosis.

An alternative technique has been devised in which a very distal sympathectomy is performed at the level of the origin of the proper digital arteries. The sympathectomy site is exposed via a palmar approach, and a 3 to 4 mm length of the adventitia is removed from the proper digital arteries distal to the junction of the distal perforating artery with the common digital artery. This procedure appears to be well tolerated, and data from small series attest to its value in selected patients with digital ulcers.³⁴

PROSTACYCLINS

The prostacyclin analogue iloprost has been used in Europe to treat patients with hand ischemia. Although iloprost therapy appears to be reasonably effective in patients with vasospastic disorders, such as Raynaud syndrome [see 6:24 Raynaud

Phenomenon],³⁵ the results in patients with peripheral ischemia are less encouraging. At present, iloprost is mainly used to treat patients with digital ulcers caused by systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease, or cutaneous polyarteritis nodosa. There are no good data on its use to treat patients with digital ulcers caused by diabetes mellitus, atherosclerosis, or renal impairment; however, a study of iloprost therapy for arterial leg ulcers found that the success rate was lower than 50%.³⁶

GUANETHIDINE BLOCKS

Transvenous regional guanethidine blocks have also been employed to treat critical digital ischemia. Patients receive a single block, with 5 mg of guanethidine in 60 ml of normal saline injected into a superficial vein of the affected hand under 30 minutes of arterial arrest. In successful cases, hyperemia is induced in the treated upper limb, and blood flow to the fingers improves. The effects of these blocks are said to persist for up to 1 month. Patients who have finger ulcers, however, appear to be less responsive than those whose only symptom is pain. The advantages of this treatment approach are that it is free of side effects and that it can be repeated for as long as necessary³⁷; the disadvantage is that it *must* be repeated at monthly intervals for as long as necessary.

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Figures 1 through 9 Alice Y. Chen.

16 REPAIR OF FEMORAL AND POPLITEAL ARTERY ANEURYSMS

Patrick J. O'Hara, MD, FACS*

Femoral and popliteal artery aneurysms constitute the majority of peripheral aneurysms. Recognition of these aneurysms is increasing, perhaps because of better surveillance of the aging population, as well as improvements in and more widespread use of vascular imaging modalities.¹ Femoral and popliteal aneurysms rarely rupture but have a significant potential for limb-threatening complications such as embolization and thrombosis. Large aneurysms can also exert a mass effect and thereby cause compression of veins or nerves.

In general, with both femoral and popliteal aneurysms, elective repair and reconstruction tend to be associated with significantly better postoperative outcomes than is emergency repair undertaken after a limb-threatening complication. Specific treatment decisions may be influenced by the presence or absence of symptoms of aneurysmal disease. There is little disagreement regarding optimal management of symptomatic femoral or popliteal aneurysms, but there is some controversy regarding optimal management of aneurysms that are asymptomatic when detected, especially if they are small. The extent of aneurysmal disease may also influence management choices. For example, a more extensive and complex reconstruction is required for treatment of diffuse arteriomegaly than is necessary for treatment of a focal femoral or popliteal aneurysm.

Lower extremity aneurysms may be either true aneurysms, in which the degenerative process involves all three layers of the arterial wall, or pseudoaneurysms, which result from trauma, anastomotic disruption, or infection. The pathogenesis of true (i.e., degenerative) lower extremity aneurysmal disease has not been definitively established, but it is known that the disease is much more common in men than in women; in fact, men with true femoral or popliteal aneurysms may outnumber women with such lesions by more than 30 to 1.^{2,3} One of the factors proposed as a possible contributor to aneurysm formation is turbulent flow beyond a relative stenosis. At the groin, the inguinal ligament may act as a constricting band, and at the popliteal level, the tendinous hiatus, the heads of the gastrocnemius, and the popliteal ligament may compress the artery in certain susceptible individuals. In addition, there is evidence for the existence of a genetic predisposition to true aneurysm formation in the femoral and popliteal arteries, in view of the demonstrated association of femoral and popliteal aneurysms with abdominal aortic aneurysms.^{4,5} Accordingly, all patients presenting with femoral or popliteal aneurysms

should be carefully evaluated for other aneurysms, especially in the aortoiliac segment and the contralateral limb.

Regardless of the underlying cause of disease, repair of peripheral artery aneurysms follows the same basic principles applicable to repair of aneurysms in other locations. Specifically, the objectives of treatment are to (1) eliminate the embolic source, (2) minimize the risk of rupture, (3) eliminate the mass effect produced by the aneurysm (if present), (4) restore adequate distal limb perfusion, and (5) accomplish all of the preceding objectives in a durable fashion. In this chapter, key components of the management of femoral and popliteal artery aneurysms are described, with specific attention to preoperative planning and intraoperative exposure and technique.

Femoral Artery Aneurysms

True (degenerative) aneurysms of the femoral artery are relatively unusual. They are generally confined to the common femoral artery, but in approximately 50% of cases, they extend to the femoral artery bifurcation. According to a classification scheme proposed by Cutler and Darling in 1973, femoral artery aneurysms are classified as type I if they are confined to the common femoral artery and as type II if they involve the orifice of the profunda femoris artery.⁶ This classification scheme is convenient for the discussion of operative repair in that type II aneurysms frequently necessitate more extensive surgical reconstruction than do type I aneurysms.

Like peripheral aneurysms elsewhere, true femoral artery aneurysms are frequently associated with abdominal aortic aneurysms, as well as with aneurysms in other locations. In a large series of patients with multiple aneurysms, 95% of patients with a femoral artery aneurysm had a second aneurysm, 92% had an aortoiliac aneurysm, and 62% had an aneurysm in the contralateral femoral artery.⁷ Conversely, 14% of men presenting with abdominal aortic aneurysms were also found to have associated femoral or popliteal aneurysms.⁵ The natural history of these lesions is not fully understood; it may be relatively benign unless they are symptomatic or large at presentation.

Femoral pseudoaneurysms, on the other hand, are increasingly encountered after trauma (e.g., iatrogenic catheter injury) or after arterial reconstruction. These lesions, especially those arising from disrupted anastomoses, are thought to have a more ominous course if untreated. Aneurysms confined to the superficial femoral artery or the profunda femoris artery alone are distinctly unusual and are often of mycotic or traumatic origin.

PREOPERATIVE EVALUATION

Asymptomatic patients may present with a smooth, fusiform, nontender, pulsatile mass discovered either during a physical examination or incidentally on imaging studies done for other reasons. Symptoms may result from local

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compression of the femoral nerve, which causes pain in the groin or the anterior thigh, or compression of the femoral vein, which may be associated with lower extremity edema and skin changes suggestive of venous stasis. Arterial symptoms (e.g., claudication or lower extremity ischemia) may be present in as many as 40% of patients with femoral artery aneurysms. Atheroemboli originating from the aneurysm can cause painful ischemic lesions; however, such lesions may also be partly a result of concomitant atherosclerotic occlusive disease rather than a direct result of the aneurysm itself.⁷

Complications of femoral artery aneurysms include thrombosis, embolization, and rupture. In one series of 45 patients with 63 aneurysms, nearly one half (47%) of the patients had experienced a complication by the time of initial presentation.⁴ Acute thrombosis, because it involves compromise of both the profunda femoris artery and the superficial femoral artery, may result in a critically threatened limb that initially exhibits sensory or motor deficits and eventually manifests frank gangrene. Acute thrombosis secondary to a femoral artery aneurysm is associated with substantial morbidity: limb loss is reported to occur in more than 28% of cases.⁷ Patients with gradual or chronic thrombosis, who have had time to develop collateral circulation, may present with claudication.

Embolization from a femoral artery aneurysm may be clinically silent or, if extensive, may present as the so-called blue toe syndrome. Embolic debris originating in the aneurysm may lodge in the digital arteries or obstruct the microcirculation, leading to characteristic painful distal ischemic lesions, despite the presence of palpable distal pulses [see Figure 1]. In more severe cases, obstruction of the



Figure 1 An example of extensive atheroembolization to the foot. The source of the atheromatous debris may be a proximal aneurysm or an ulcerating atherosclerotic lesion.

outflow bed may compromise blood flow to the entire limb, resulting in limb-threatening ischemia. Rupture of a femoral pseudoaneurysm is not unusual, especially if the lesion is enlarging. Rupture of a true femoral artery aneurysm, however, is a relatively uncommon event, with reported rupture rates ranging from 1 to 12%, and is accompanied by severe groin pain, ecchymosis, and swelling.^{3,7}

Femoral artery aneurysms can usually be diagnosed by means of physical examination alone. Ultrasonography is a useful adjunctive measure for delineating the aneurysm, as well as for screening patients for associated popliteal or aortoiliac aneurysms [see Figure 2a]. Computed tomography (CT) and magnetic resonance imaging (MRI) can be helpful in delineating the extent and morphology of the aneurysm, as well as the status of the adjacent arteries, especially in obese patients [see Figures 2b and 2c]. Once the diagnosis has been made, CT or catheter angiography should be performed to establish the extent of aneurysmal and associated occlusive or embolic disease by providing detailed information about the inflow and outflow vessels [see Figure 3, a and b]. In selected circumstances (e.g., the presence of recent thrombosis of the outflow bed), catheter arteriography may provide the opportunity for a trial of preoperative thrombolytic therapy to improve available outflow. Good judgment must be exercised, however, in that there may not be enough time for adequate thrombolysis if the limb is severely ischemic.

Finally, preoperative evaluation should include careful assessment and optimization of comorbid medical conditions often present in patients with femoral artery aneurysms. Because cardiac complications are a major source of early postoperative and late morbidity in this population, special emphasis should be placed on evaluating patients for associated coronary artery disease by means of cardiac stress testing or coronary angiography and on following evaluation with appropriate treatment when indicated. Similarly, imaging of the contralateral limb and the aortoiliac vessels is prudent to detect associated aneurysms and establish treatment priorities.

OPERATIVE PLANNING

Repair is clearly indicated for all symptomatic femoral aneurysms, irrespective of cause. Patients who present with limb-threatening complications require expeditious intervention. Asymptomatic femoral pseudoaneurysms should also be repaired once the diagnosis is established because they are often associated with complications. Currently, however, there is no firm consensus on the indications for treatment of asymptomatic true femoral aneurysms, because the natural history of these lesions is not known with certainty and is thought to be relatively benign. Furthermore, no specific aneurysm size has been identified at which the incidence of complications increases dramatically, although it appears that symptomatic lesions tend to be larger than asymptomatic ones. Most surgeons, however, would probably agree that true femoral artery aneurysms larger than 2.5 cm in diameter should be repaired in good-risk patients, especially if the aneurysm is known to have enlarged.^{7,8} Smaller asymptomatic true femoral artery aneurysms, particularly in high-risk patients, should be followed, with intervention reserved for cases in which symptoms develop or the lesion enlarges significantly. On occasion, it

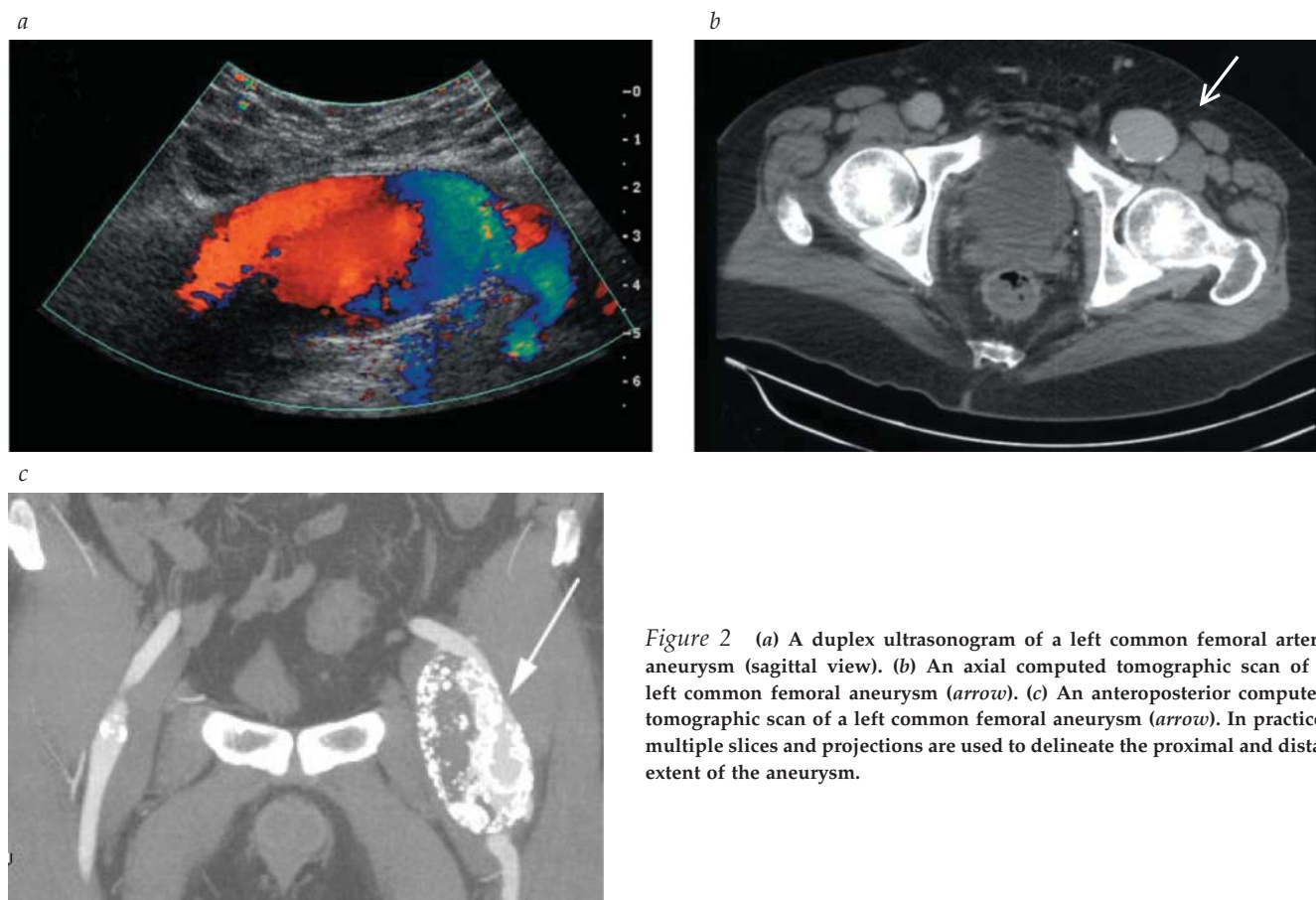


Figure 2 (a) A duplex ultrasonogram of a left common femoral artery aneurysm (sagittal view). (b) An axial computed tomographic scan of a left common femoral aneurysm (arrow). (c) An anteroposterior computed tomographic scan of a left common femoral aneurysm (arrow). In practice, multiple slices and projections are used to delineate the proximal and distal extent of the aneurysm.

may also be necessary to repair a small asymptomatic true femoral aneurysm in conjunction with an aortofemoral or femoropopliteal bypass graft procedure to avoid performing an anastomosis to a diseased artery.

OPERATIVE TECHNIQUE

Endovascular Repair

At present, endovascular approaches to definitive treatment of femoral artery aneurysms are limited because the femoral artery crosses the groin crease and is subject to repeated flexion and extension stresses in this location.^{8,9} Current endoprotheses are likely to fail at this site because of kinking, migration, or metal fatigue. Furthermore, the femoral incision required for standard surgical repair is not extensive and is usually well tolerated by most patients. Consequently, the potential advantages of an endovascular approach are less apparent with respect to the repair of femoral artery aneurysms than they are with respect to the repair of abdominal or thoracic aneurysms.

Ultrasound-Guided Compression

Small femoral pseudoaneurysms arising after catheter diagnostic or interventional procedures may resolve over time or sometimes may be managed with ultrasound-guided compression or thrombin injection at the time of diagnostic imaging.⁸ Patient selection is important, however, because compression or thrombin injection for the treatment

of femoral pseudoaneurysms with short or wide necks may be more likely to be associated with embolic complications. Surgical repair is usually reserved for pseudoaneurysms that enlarge, become symptomatic, or do not resolve spontaneously and for anastomotic pseudoaneurysms [see Figure 4]. A potential advantage of open repair of large pseudoaneurysms is the capacity for decompression of large hematomas, which may be especially important if continued anticoagulation is likely to be required.

Open Surgical Repair

The common femoral artery may be approached through either a longitudinal or an oblique incision over the femoral artery. The usual preference, however, is a longitudinal incision angled approximately 20 degrees medially, which permits exposure of the distal profunda femoris artery without the creation of a skin flap. Both the distal extent of the femoral aneurysm and the degree of associated occlusive disease may influence the configuration of open surgical repair [see Figure 5]. Type I aneurysms, which spare the origins of the profunda femoris and superficial femoral arteries, are usually managed by constructing a short interposition graft with the proximal anastomosis at the level of the distal external iliac artery or the proximal common femoral artery [see Figure 6]. Occasionally, if proximal control of the retroperitoneal iliac artery is required, a flank incision may be needed. When it is necessary to repair

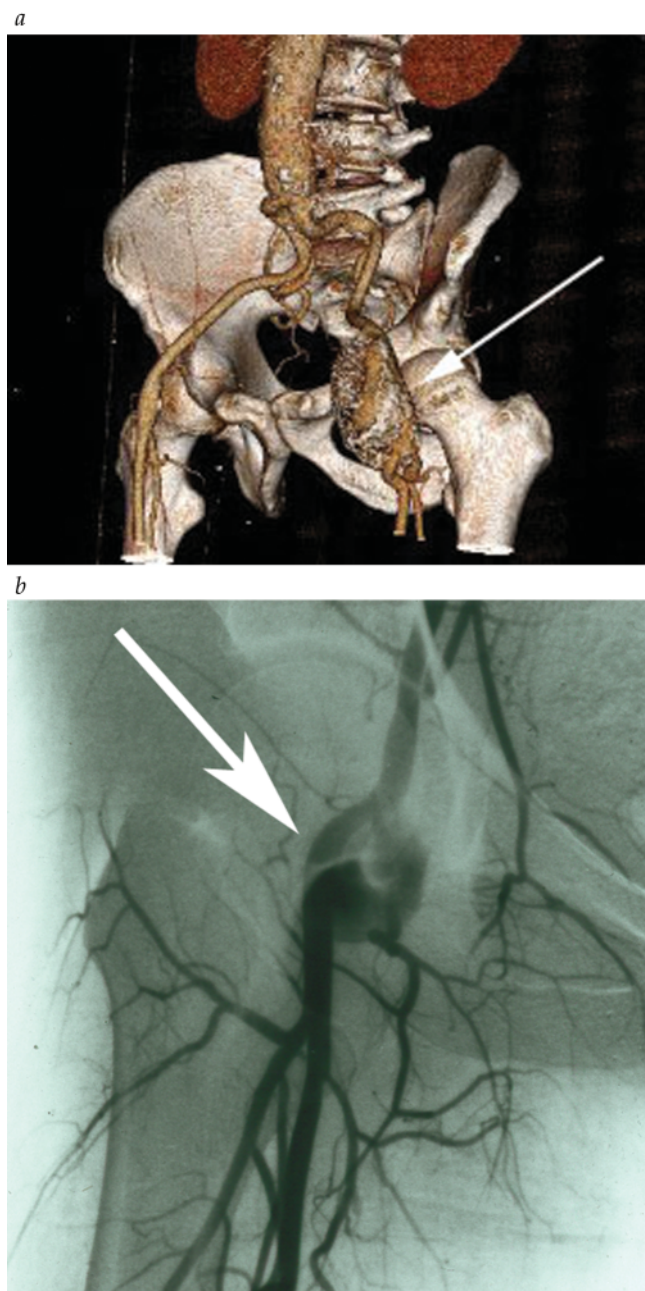


Figure 3 (a) Three-dimensional reconstruction of a computed tomographic scan of a large left common femoral artery aneurysm (arrow). (b) Anteroposterior arteriogram demonstrates a localized common femoral artery aneurysm (arrow).

additional proximal or distal aneurysms, the short femoral interposition graft may also act as the recipient of an aorto-femoral or iliofemoral graft or as the origin of a femorodistal bypass graft.

If the femoral aneurysm is more extensive, a bypass from the common femoral artery to the profunda femoris artery with a jump graft to the superficial femoral artery is usually preferred [see Figure 5d and Figure 7]. This approach allows the surgeon to work sequentially from the deep tissue planes to the more superficial ones.

Alternatively, some surgeons favor implantation of the distal profunda femoris artery into an interposition graft placed between the common femoral artery and the superficial femoral artery [see Figure 5b]. Others have described joining the superficial and deep femoral arteries at their bifurcation to form a common outflow tract that serves as the distal anastomotic end point for the interposition graft, a technique sometimes referred to as syndactylization [see Figure 5e]. Application of these two methods may be hampered by the presence of associated occlusive disease, which is frequently present. Nevertheless, the surgeon should be familiar with all of the available options for reconstruction and should be prepared to adapt his or her choice of reconstruction method to the details of the local anatomy.

For treatment of noninfected femoral aneurysms, especially anastomotic pseudoaneurysms, synthetic grafts have been used with good results; they usually offer a better size match with the native femoral arteries [see Figure 4d]. If local infection is present or the potential for wound complications is high, autogenous grafts are preferred.

OUTCOME EVALUATION

The results of operative repair of femoral artery aneurysms are generally excellent. In published series, the perioperative mortality ranges from none (for isolated asymptomatic femoral aneurysm repair) to approximately 4% (if aneurysm repair is combined with more extensive aortic procedures).^{6,7,10} The reported 5-year patency rate for saphenous vein and Dacron interposition grafts used for repair of isolated femoral artery aneurysms is 80 to 83%.^{6,10} In general, patients who are operated on before they show evidence of impaired limb perfusion fare better than those presenting with lower extremity complications.⁷

Popliteal Artery Aneurysms

Aneurysms of the popliteal artery are the most commonly encountered peripheral aneurysms. Unlike femoral aneurysms, popliteal aneurysms are more likely to be true (i.e., degenerative) aneurysms than pseudoaneurysms. True popliteal aneurysms typically occur in men in their fifth and sixth decades. Their clinical importance lies in their propensity to cause limb-threatening complications. When true popliteal aneurysms are left untreated, the future incidence of thromboembolic events in initially asymptomatic patients is high. In one series of patients who were managed conservatively, only 32% had no complications at the 5-year follow-up.¹¹ Multiple aneurysms are common in this population, and it has been reported that nearly 50% of patients presenting with a popliteal aneurysm have associated abdominal aortic aneurysms and that 40% may also have coexisting femoral artery aneurysms.^{4,11,12} In the largest reported series, 70% of these patients had a popliteal artery aneurysm in the contralateral extremity.¹³ The clear link between the presence of popliteal aneurysms and the presence of other associated aneurysms underscores the importance of careful investigation of all patients who present with a newly diagnosed popliteal artery aneurysm. In approximately 50% of cases, popliteal artery aneurysms are confined to the popliteal artery itself; in the remaining cases,

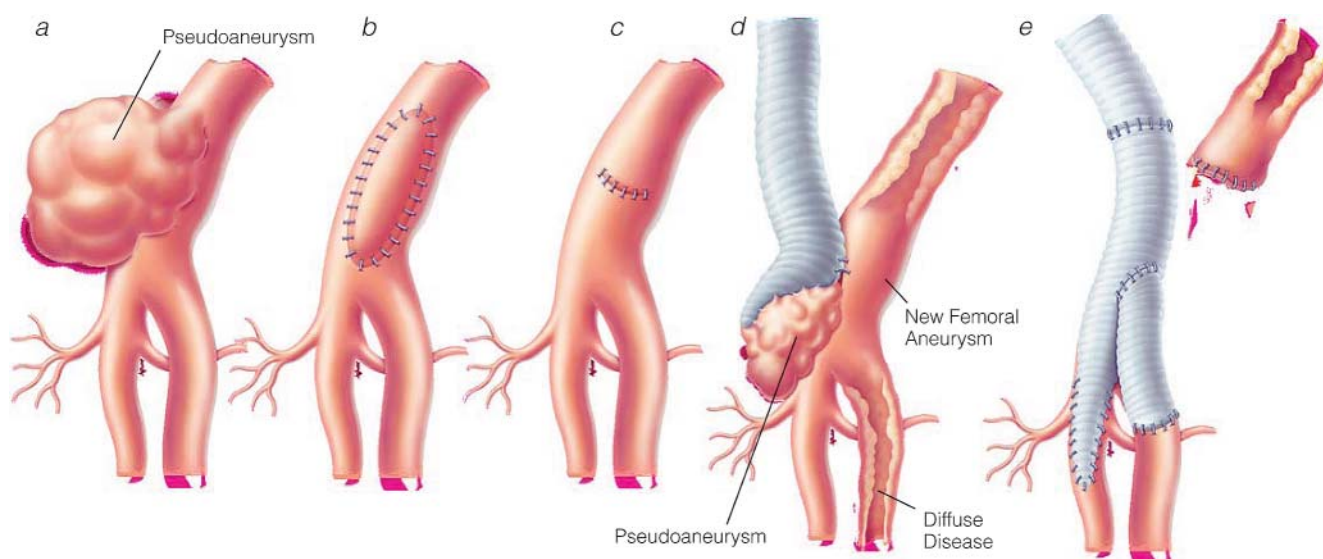


Figure 4 Repair of femoral artery aneurysms (pseudoaneurysms) (a). Depicted are commonly employed options for repair of femoral artery pseudoaneurysms: (b) patch angioplasty with either autogenous or synthetic patch material and (c) primary closure. Also depicted is repair of anastomotic femoral pseudoaneurysms (d). An interposition graft is placed to the profunda femoris, and a jump graft is placed to the superficial femoral artery (e).

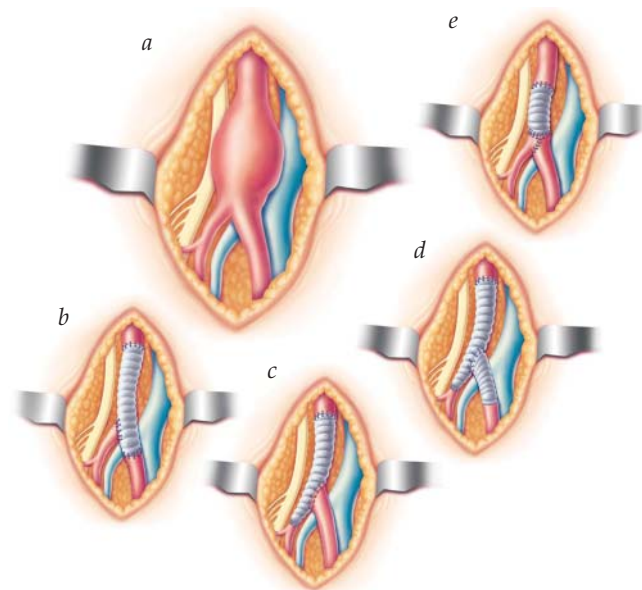


Figure 5 Repair of femoral artery aneurysms (type II true aneurysms) (a). Depicted are commonly employed options for repair of true femoral artery aneurysms involving the origins of the profunda femoris and superficial femoral arteries (type II femoral aneurysms). (b) The profunda femoris artery may be implanted into an interposition graft placed to the superficial femoral artery. (c) The superficial femoral artery may be implanted into an interposition graft placed to the profunda femoris artery. (d) An interposition graft may be placed to the profunda femoris artery, with a jump graft to the superficial femoral artery. Alternatively, the superficial femoral artery may be reimplanted into the interposition graft if there is sufficient length to allow the reconstruction to be performed without tension. (e) Syndactylization of the profunda femoris and superficial femoral arteries may be done to form a common outflow channel for a synthetic interposition graft originating from the common femoral artery or the distal external iliac artery.

aneurysmal degeneration may extend proximally to involve the superficial femoral artery or distally down to the level of the tibioperoneal trunk.¹²

PREOPERATIVE EVALUATION

Popliteal artery aneurysms may be asymptomatic on initial presentation. The diagnosis is usually suspected on the basis of the detection of a prominent pulsatile mass behind the knee during physical examination. The mass is often best felt with the knee in a slightly flexed position. Small aneurysms may be more difficult to detect during physical examination, especially if thrombosis has already occurred. A high index of suspicion, usually based on recognition of an aneurysm in another location, is helpful in identifying these lesions.

The most frequent initial presentation of a symptomatic popliteal aneurysm is the development of acute limb-threatening ischemia as a consequence of arterial occlusion from thrombosis of the aneurysm or distal embolization.^{12,14} Early manifestations (i.e., those occurring before complete occlusion of the popliteal artery itself) may be limited to painful petechial hemorrhages or localized gangrenous changes in the digital arteries that result from microembolization [see Figure 1]. In some series, claudication has been a presenting symptom in 40 to 75% of patients with popliteal aneurysms.¹² Rupture is a distinctly unusual event: fewer than 5% of patients present with this complication.¹² In rare instances, patients with very large popliteal aneurysms may present with symptoms resulting from compression of adjacent structures, such as paresthesias or neuropraxia involving the lower leg (from direct popliteal nerve compression) or deep vein thrombosis, superficial varicosity formation, and phlebitis (from popliteal vein compression).

Plain radiographs of the knee may demonstrate calcium in the aneurysm wall; however, once the diagnosis is suspected, it is best confirmed by means of ultrasonography

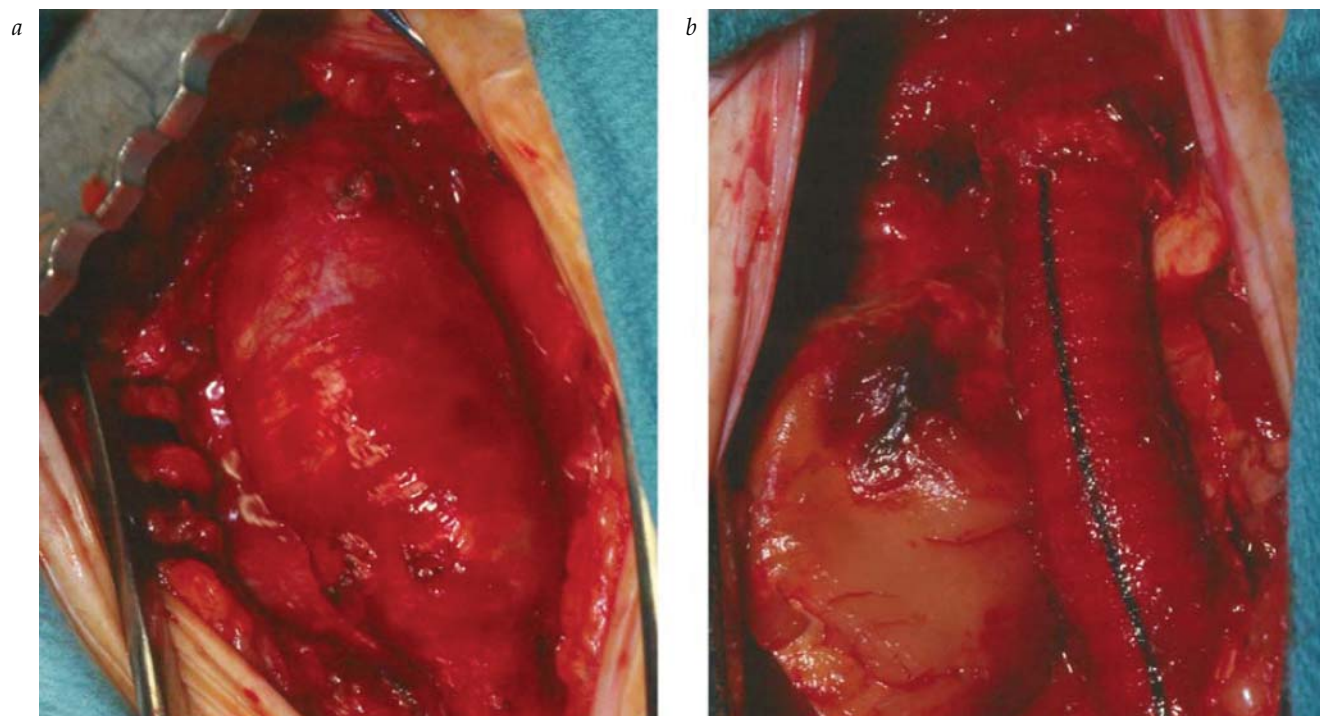


Figure 6 Repair of femoral artery aneurysms (type I true aneurysms). Shown is a type I true aneurysm of the common femoral artery (*a*) before and (*b*) after reconstruction with a Dacron interposition graft.

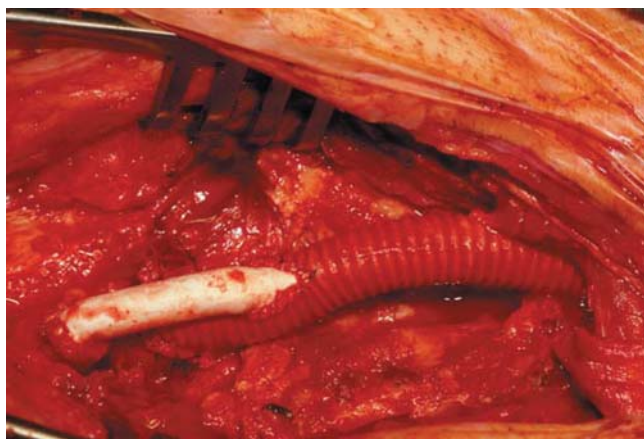


Figure 7 Repair of femoral artery aneurysms (type II true aneurysms). Shown is the repair of a type II femoral artery aneurysm with a Dacron interposition graft to the profunda femoris artery and a polytetrafluoroethylene jump graft to the superficial femoral artery.

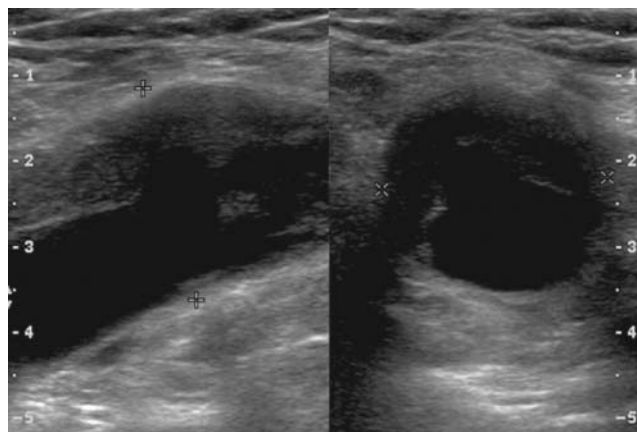


Figure 8 Repair of popliteal artery aneurysms. Ultrasonographic examination of the right popliteal artery demonstrates a 2.6 cm right popliteal artery aneurysm, shown in both sagittal (*left*) and transverse (*right*) views.

[see Figure 8], CT, or MRI. These imaging modalities are particularly helpful in distinguishing popliteal aneurysms from other space-occupying lesions of the popliteal fossa (e.g., Baker cyst). CT angiography can provide useful images of the available arterial outflow and offers three-dimensional image reconstruction capability.

Traditional catheter angiography is less useful for the diagnosis of popliteal artery aneurysms: it demonstrates only the flow channel of the vessel, and any intramural thrombus that is present may obscure the presence of the

popliteal aneurysm. Nevertheless, angiography can play a valuable role in the planning of operative reconstruction because it can delineate the extent of aneurysmal involvement of the popliteal and adjacent arteries and detect the presence of associated occlusive disease [see Figure 9]. Catheter angiography can also provide the opportunity to deliver preoperative thrombolytic therapy when this is required.

It is also important to remember that among patients with popliteal artery aneurysms, as in those with femoral



Figure 9 Repair of popliteal artery aneurysms. Preoperative arteriograms illustrate two common varieties of popliteal artery aneurysm. The extent of disease influences the choice of reconstruction. (a) The aneurysm is localized to the popliteal artery. (b) Arteriomegaly extends proximally to involve the superficial femoral artery.

artery aneurysms, there is a high incidence of associated atherosclerotic disorders: nearly 50% have some degree of myocardial dysfunction, and nearly two thirds are hypertensive.¹⁵ Consequently, preoperative evaluation of patients under consideration for popliteal aneurysm repair should include careful optimization of associated coexisting medical conditions, especially associated coronary artery disease.

OPERATIVE PLANNING

Indications for Repair

There is a consensus that all patients with symptomatic popliteal aneurysms should undergo expeditious operative repair; conservative management in these cases is associated with a substantial risk of limb loss, especially in the presence of limb-threatening ischemia. There is also general agreement that asymptomatic popliteal aneurysms should be repaired on diagnosis; such lesions are associated with the development of limb-threatening complications in a substantial number of patients. In a series of 94 patients with asymptomatic popliteal artery aneurysms who were followed for nearly 7 years, 18% of the limbs with aneurysms eventually became symptomatic (25% acutely and 75% chronically), and 4% had to be amputated.¹⁶ In this cohort, aneurysm size greater than 2 cm, the presence of mural thrombus, and poor distal lower extremity runoff were significant predictors of the development of symptoms. In a meta-analysis of the published literature that encompassed nearly 2,500 popliteal artery aneurysms, nearly 35% of the patients who were treated conservatively eventually experienced ischemic complications, and 25% of the patients who required surgical treatment for an ischemic complication eventually required amputation.¹⁷ Given these results, most surgeons would agree that surgical repair of

asymptomatic popliteal artery aneurysms is indicated for all but extremely high-risk patients.

Although the likelihood that popliteal aneurysms will give rise to complications does not appear to be related to the size of the aneurysms, optimal management of small asymptomatic popliteal aneurysms remains controversial—in part because of problems with their definition, especially in the presence of generalized arteriomegaly. Factors believed to be associated with the eventual development of ischemic complications include size greater than 2 cm, deformation of the artery itself, and the existence of intraluminal thrombus.^{18–20} The presence of these factors, especially if the popliteal aneurysm is localized, makes a case for operative repair, especially if the patient is a good surgical risk.

Preoperative Arterial Thrombolysis

In addition to providing anatomic information (see above), preoperative catheter angiography may facilitate the use of adjunctive thrombolytic therapy, which may be particularly beneficial if the outflow bed has been severely compromised by distal thrombosis or embolization.^{21,22} The goal of thrombolysis of occluded outflow vessels is to uncover a suitable target vessel that can be used to provide outflow for a surgical bypass. If time permits, thrombolysis may be particularly useful in this setting of poor outflow because intraoperative balloon thromboembolectomy sometimes cannot clear sufficient thrombus from small vessels to maintain long-term graft patency. In one study of selected patients with poor outflow, thrombolytic therapy followed by surgical repair yielded results that compared favorably with those of isolated surgical repair, and the combined approach was associated with lower amputation rates.²³ It should be kept in mind, however, that thrombolytic therapy is more rapid and effective if the thrombosis is recent and the volume of thrombus is not large. If limb ischemia is severe, the length of time required to establish reperfusion may be prohibitive, and it may be best to proceed with direct surgical intervention before irreversible tissue loss occurs.

OPERATIVE TECHNIQUE

The primary therapeutic objectives of popliteal artery aneurysm repair are to (1) eliminate the aneurysm as a source of emboli or thrombosis and (2) maintain distal perfusion in a durable fashion. Other objectives are to prevent hemorrhage resulting from rupture, eliminate the mass effect exerted by large aneurysms, and prevent recurrence.

Open Surgical Repair of Popliteal Aneurysms

The two most important factors influencing the surgical approach to popliteal aneurysm repair and the configuration of the reconstruction used are (1) the extent of the aneurysmal disease and (2) the size of the aneurysm. In most settings, the medial approach with the patient in the supine position is preferred by the author. This approach allows exposure of the entire popliteal artery, if necessary, through division of the semimembranosus, semitendinosus, and gastrocnemius tendons, which can be repaired at the time of closure. In addition, it offers the most flexibility for expanding the reconstruction proximally or distally if the aneurysm is large, extensive, or multilobed [see Figure 10].

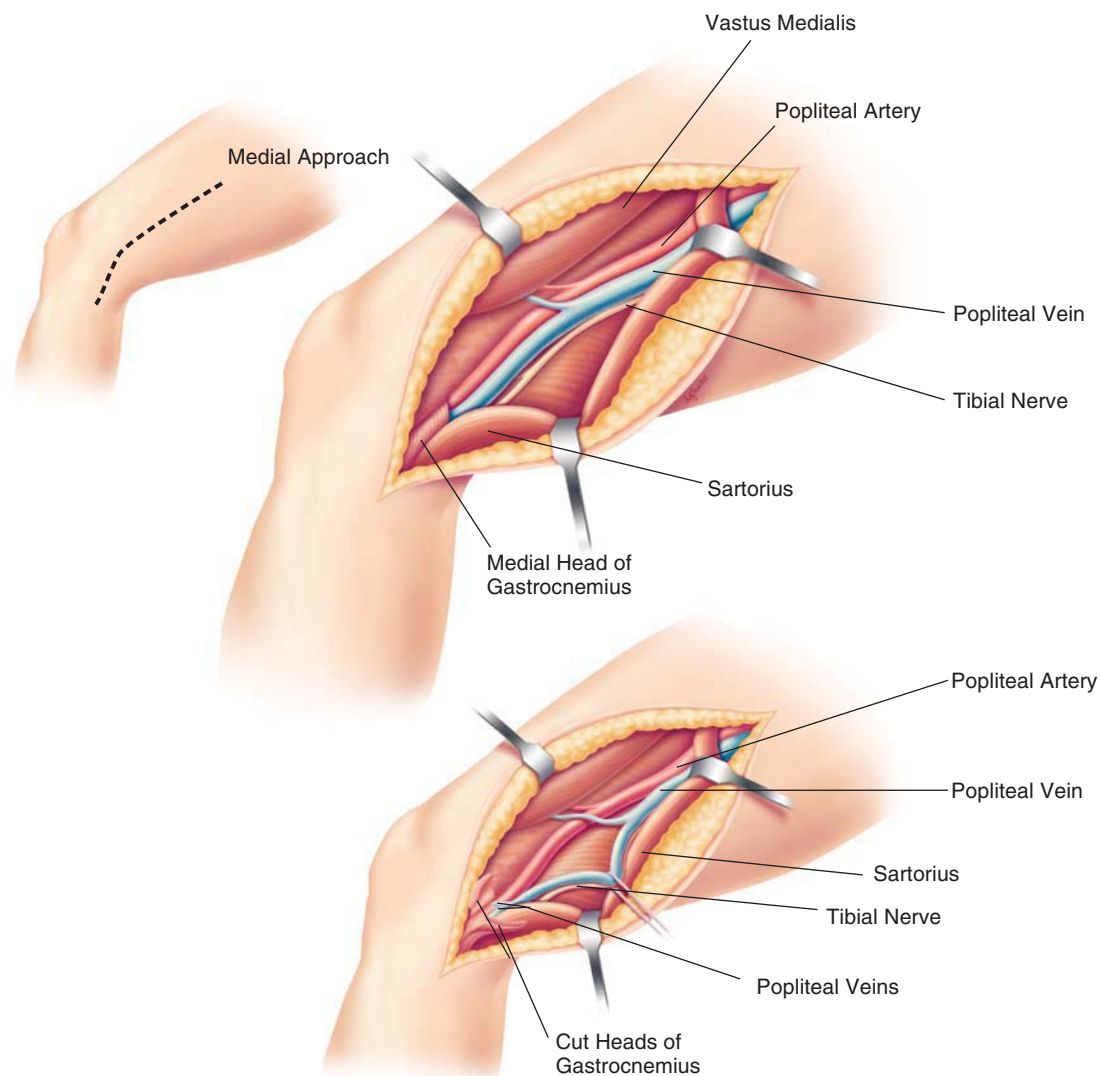


Figure 10 Repair of popliteal artery aneurysms. Depicted is the medial approach to the popliteal artery, which can afford complete exposure of the vessel.

The posterior approach to the popliteal artery, which is favored by some surgeons, can also provide adequate exposure of localized popliteal aneurysms but requires that the patient be prone [see Figure 11].²⁴ Although it is well tolerated, the posterior approach precludes exposure of the common and superficial femoral arteries or the great saphenous vein and offers less flexibility for proximal or distal extension. Familiarity with both approaches permits the vascular surgeon to choose the one that best suits the given clinical situation.²⁵

A small, localized popliteal artery aneurysm with few side branches may be treated with simple proximal and distal ligation of the aneurysm sac, accompanied by construction of a bypass graft with a short segment of autologous saphenous vein. The venous graft may be tunneled in the anatomic position, deep to the medial head of the gastrocnemius muscle. The proximal and distal anastomoses are fashioned in either an end-to-end or an end-to-side configuration, depending on the compatibility of the graft's

diameter with that of the artery [see Figure 12]. In the past few years, instances of continued expansion of the popliteal aneurysm sac despite ligation and bypass have been reported.^{26,27} This phenomenon may result from inadequate ligation of the aneurysm sac but also from retrograde perfusion of the sac via patent geniculate collateral vessels. Consequently, it seems advisable to ligate all large collateral vessels feeding the aneurysm sac at the time of the initial aneurysm repair.

In the case of a large aneurysm for which evacuation of mural thrombus is required to relieve mass effect symptoms, it may be feasible to construct a short interposition graft [see Figure 13]. Opening the sac also allows ligation of the feeding geniculate branches, which may help minimize the risk of late enlargement of the aneurysm sac associated with recurrence of mass effect symptoms.^{26,27}

If the superficial femoral artery is severely involved with occlusive or aneurysmal disease, it may be necessary to construct a long saphenous vein bypass graft originating

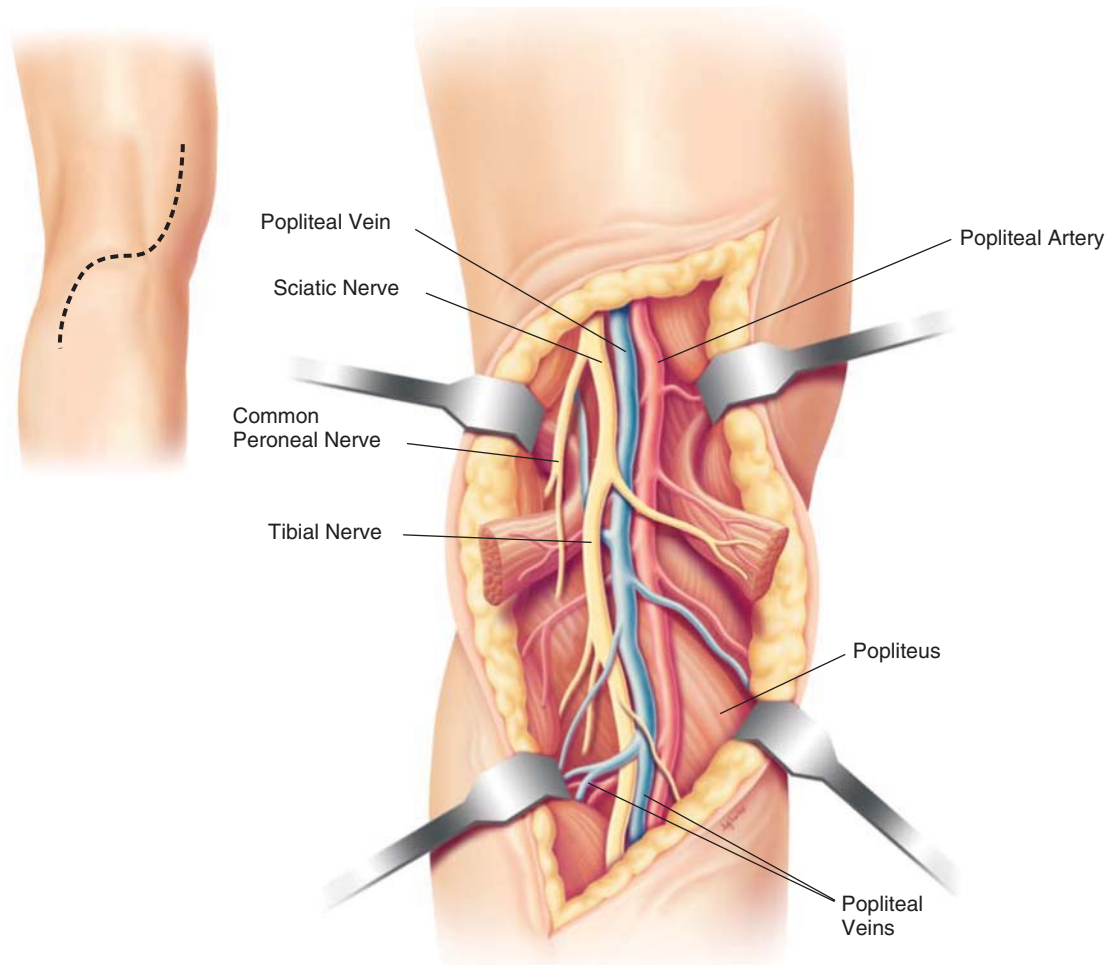


Figure 11 Repair of popliteal artery aneurysms. Depicted is the posterior approach to the popliteal fossa.

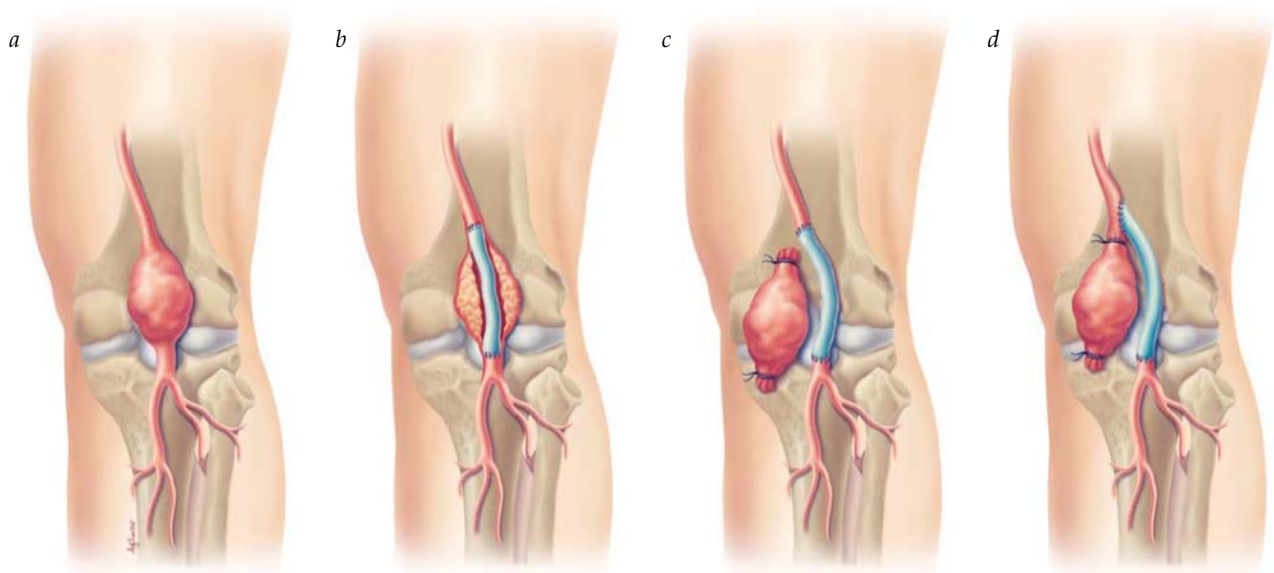


Figure 12 Repair of popliteal artery aneurysms (a). Depicted are various bypass configurations that can be employed for repair of popliteal aneurysms. (b) An interposition graft may be placed within a large aneurysm. (c) If the graft and the artery are sufficiently well matched in terms of size, ligation and bypass of the aneurysm with end-to-end proximal and distal anastomoses may be employed. (d) If there is a significant size mismatch between the graft and the artery, ligation and bypass of the aneurysm with an end-to-side proximal anastomosis may be employed.

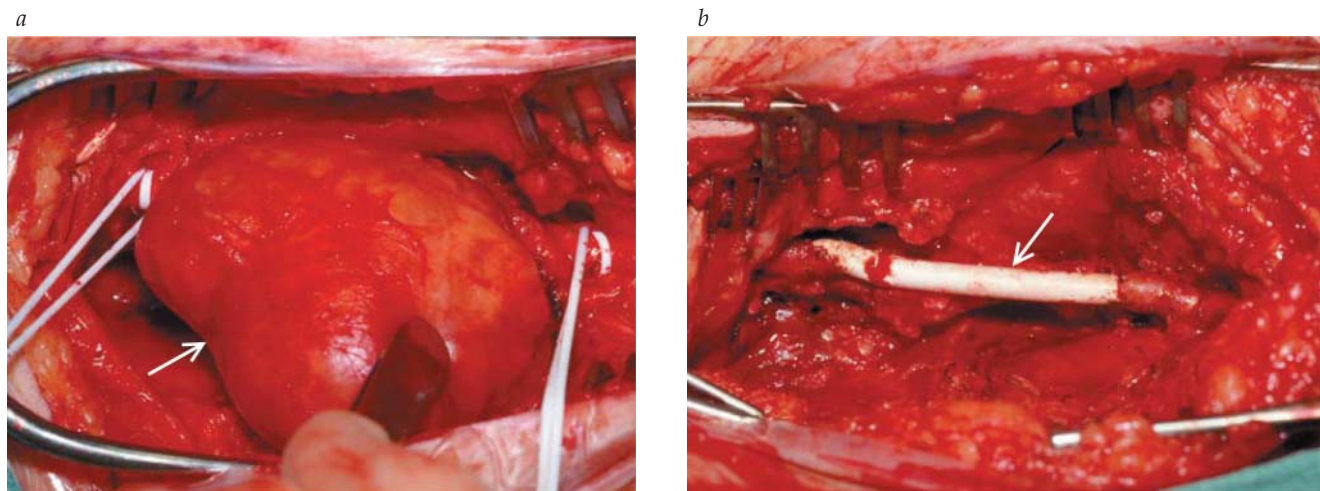


Figure 13 Repair of popliteal artery aneurysms. (a) Operative photograph shows a large popliteal aneurysm (arrow) exposed via the medial approach. (b) A polytetrafluoroethylene interposition graft (arrow) is placed within the aneurysm sac, which has been decompressed. Saphenous vein is the preferred graft material, but a synthetic conduit may be required if the autogenous conduit is unavailable or inadequate. Collateral inflow into the sac has been interrupted.

from the common femoral artery, in either an in situ or a reversed configuration [see Figure 14]. The distal anastomotic site is determined on the basis of the preoperative angiographic findings, in conjunction with intraoperative assessment.

As a rule, grafts constructed from autogenous vein are preferred, but synthetic grafts may be required if the autogenous vein is unavailable or inadequate. Another innovative option in the absence of suitable autogenous vein is popliteal reconstruction using a superficial femoral artery autograft and replacing the superficial femoral artery segment with a synthetic interposition graft.²⁸ An effort should be made to keep graft length to the minimum necessary to treat the aneurysmal disease. Intraoperative completion angiography is recommended to allow detection and correction of technical problems with the reconstruction before closure [see Figure 15].

Endovascular Repair of Popliteal Aneurysms

Several reports have evaluated the feasibility of endovascular treatment of popliteal aneurysms with covered stents delivered under fluoroscopic guidance.^{29–31} It appears that, in selected patients, with suitable (localized) anatomy, endovascular repair can be safe and may provide a quicker early recovery than conventional open repair. Disadvantages include the need for aggressive postoperative antiplatelet therapy to maintain graft patency, the potential for aneurysm enlargement from retrograde perfusion by geniculate branches, and unresolved issues regarding endograft durability. Stent fractures after endovascular popliteal artery aneurysm repair may be underreported, although their effect on long-term graft patency is not known with certainty.^{32–34} Endovascular repair also seems less suitable in the presence of arteriomegaly. At present, endovascular treatment of popliteal aneurysms probably should be confined to those patients with suitable anatomy who are elderly and are considered to be at unacceptable risk with standard surgical therapy. If endovascular therapy is

employed, close late follow-up is necessary to detect fracture, migration, or thrombosis of the stent graft, as well as expansion of the aneurysm.

OUTCOME EVALUATION

Surgical Repair

In a study from the Cleveland Clinic that described the surgical management of 110 popliteal aneurysms, there were eight (7.3%) early postoperative deaths.¹² Six (75%) of the eight early postoperative deaths were attributable to cardiac complications—an observation that highlights the need for careful cardiac evaluation, when feasible, before the treatment of popliteal artery aneurysms. A contemporary large series of 583 open popliteal aneurysm repairs yielded a 30-day postoperative mortality rate of 1.4% and 2-year limb salvage and survival rates of 96% and 86%, respectively, even in high-risk patients.³⁵

The presence of symptoms, the adequacy of the outflow bed on presentation, and the choice of autogenous graft material for reconstruction are the main factors that influence limb salvage and graft patency rates after repair of popliteal artery aneurysms. In one study, the 5-year patency rate for saphenous vein grafts was 92% for patients who had asymptomatic popliteal aneurysms and in whom good outflow vessels were identified compared with 66% for a matched cohort with known occlusive disease.³⁶ In other studies that included similar patients, the 10-year patency rate was in excess of 80% and the limb salvage rate was approximately 95%.^{12,37}

Patients who undergo urgent surgical treatment of popliteal aneurysms that were symptomatic on presentation may have less favorable outcomes.³⁸ In one study, when thrombosis of the popliteal aneurysm was apparent on presentation or distal outflow was poor, the 5-year patency rate was approximately 50%, and the limb salvage rate was only 60%.³⁹ In contrast, a retrospective study of 37 elective repairs compared with 14 emergent procedures yielded



Figure 14 Repair of popliteal artery aneurysms. When femoral and popliteal aneurysms are accompanied by diffuse arteriomegaly or associated arterial occlusive disease, more extensive reconstructions are required. For example, as shown, a femoral interposition graft may provide the inflow for an infrapopliteal bypass.

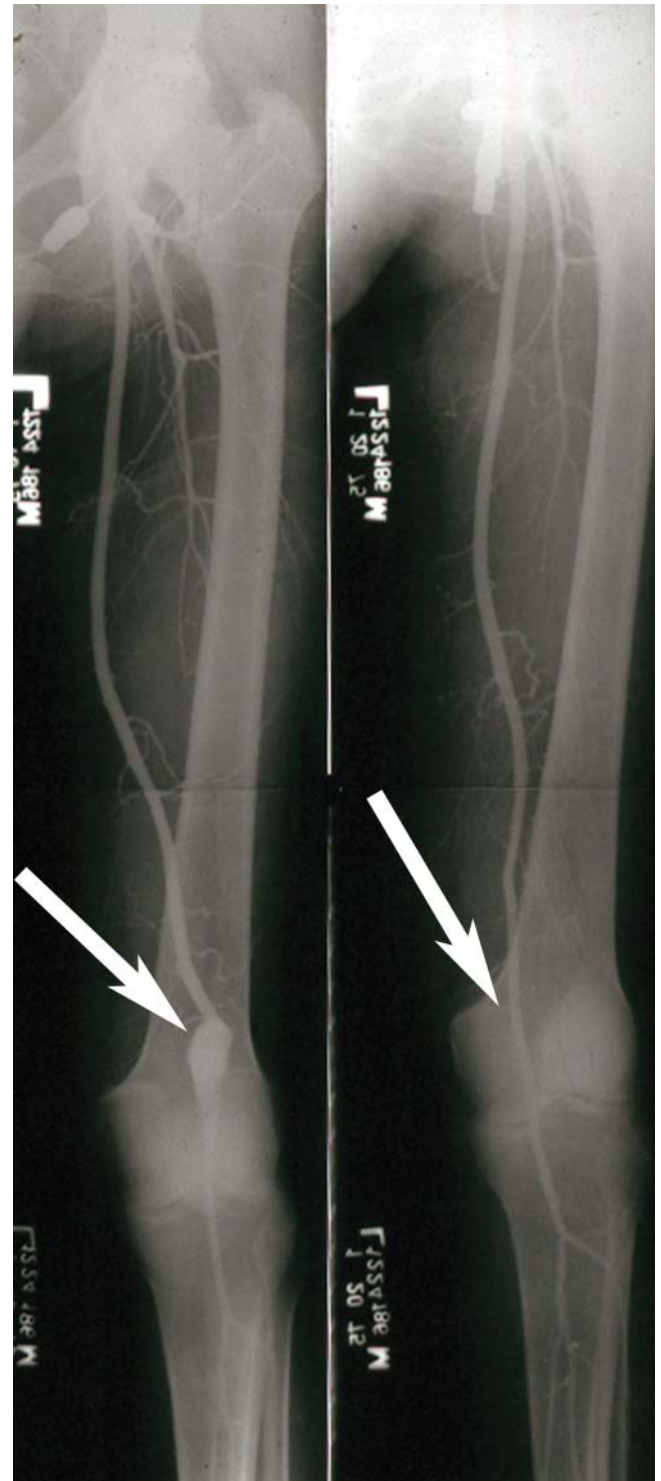


Figure 15 Repair of popliteal artery aneurysms. Preoperative and postoperative arteriograms show a localized popliteal artery aneurysm (arrow, left) and its subsequent repair with a saphenous vein interposition graft (arrow, right).

similar results for patency, limb salvage, and survival.⁴⁰ This apparent discrepancy may be related to patient selection, small sample size, or other factors. Several studies documented the influence of the choice of conduit graft material on bypass durability; each demonstrated that patency rates

were nearly four times higher with saphenous vein grafts than with nonvenous alternative grafts.^{11,16,41} Limb salvage rates were also higher with autogenous saphenous vein grafts. For example, in one report, 23% (7 of 31) of the popliteal artery bypasses performed with a prosthetic conduit resulted in limb loss, whereas only 2% (1 of 42) performed with a saphenous vein graft resulted in amputation.¹⁶

Endovascular Repair

In properly selected patients with suitable anatomy, endovascular popliteal aneurysm repair has yielded encouraging early and midterm results. A prospective, randomized study of 48 asymptomatic, localized popliteal aneurysms treated with surgery (27) or endovascular repair (21) revealed no difference in early or late patency rates, although 14% of the endovascular patients were converted to open repair because of endograft occlusion.⁴² A retrospective study of 15 localized popliteal aneurysm repairs performed with a covered stent graft reported 85% patency at the 54-month follow-up, but two limbs developed endoleaks requiring further treatment and one patient was lost to follow-up.⁴³

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Figures 4, 5, 10, 11, 12, and 14 Alice Y. Chen

17 INFRAINGUINAL ARTERIAL PROCEDURES

William D. Suggs, M.D., F.A.C.S., and Frank J. Veith, M.D., F.A.C.S.

Since the early 1980s, there have been enormous advances in the treatment of lower-extremity ischemia secondary to infrainguinal arteriosclerosis. Effective interventional management strategies have been developed for virtually all patterns of arteriosclerosis underlying limb-threatening ischemia.^{1,2} Bypasses to the infrainguinal arteries using segments of autologous vein have become routine for limb salvage. As this technique has evolved, the distal limits of revascularization have been extended. Bypasses to arteries near the ankle or in the foot can now be offered to patients who have no patent arteries suitable for more proximal bypasses. In addition, bypasses to distal tibial or tarsal vessels may be performed in some patients whose popliteal arteries are patent but who have three-vessel distal occlusive disease and forefoot gangrene.^{3,4} Frequently, patients who require very distal bypasses have already undergone vascular reconstruction; these patients may be candidates for alternative approaches, such as a popliteal-distal bypass or a tibiotibial bypass.⁵⁻⁷

Patients with limbs threatened by distal tibial occlusive disease present an ongoing challenge to the vascular surgeon. Provided that careful attention is paid to obtaining high-quality preoperative angiograms and that the surgeon is willing to consider alternative approaches, it is generally possible to achieve good results from limb salvage procedures.

It should be kept in mind that only patients with threatened limbs—manifested by rest pain, frank gangrene, or nonhealing ulcers—should be considered candidates for infrainguinal bypass. Patients who have gangrene that extends into the deeper tarsal region of the foot, who have a severe organic mental syndrome, or who are nonambulatory are not candidates for limb salvage surgery and should be treated with primary amputation instead.^{1,2}

Preoperative Evaluation

HISTORY AND PHYSICAL EXAMINATION

A careful history and a thorough physical examination are crucial for accurate assessment of the extent of the patient's atherosclerotic disease. In the course of the history, the examiner should pay particular attention to distinguishing true rest pain from other causes of pain (e.g., arthritis and neuritis). Significant ischemic pain is usually associated not only with decreased pulses but also with other manifestations of ischemia (e.g., atrophy, decreased skin temperature, marked rubor, and pain that is relieved when the foot is dangled). In the course of the physical examination, the examiner should look for and assess the extent of any underlying infection and should closely examine any surgical scars for clues to the nature and extent of any previous vascular operations involving the use of the saphenous vein. In addition, a careful pulse examination should be performed to assess the patient's baseline arterial status; these baseline measurements provide a basis for comparison if the disease subsequently progresses and may help determine the approach to be used to salvage the threatened limb.

NONINVASIVE TESTING

Noninvasive tests are helpful in that they provide semiquantitative assessment of the circulation and help confirm the diagnosis made on the basis of the history and the physical examination. Such test measurements include the ankle-brachial index (ABI) and pulse volume recordings (PVRs).

The ABI is determined by dividing the ankle pressure in each lower limb by the higher of the two brachial pressures. Normal circulation typically yields an ABI of 1.0 to 1.2; claudication, an ABI of 0.40 to 0.95; and limb-threatening ischemia, an ABI of 0 to 0.5. It is vital to remember, however, that lower-extremity pressure measurements are less reliable in patients with heavily calcified vessels (e.g., diabetics and patients with end-stage renal disease). In these patients, ABIs are falsely elevated as a result of the higher cuff pressures required to occlude calcified vessels, which in some cases are not occluded even with pressures higher than 300 mm Hg.

PVRs are obtained by means of calibrated air-cuff plethysmography. Standard blood pressure cuffs are placed at different levels of the lower extremity, and the increases in pressure within the cuffs resulting from the volume increase during systole are recorded as pulse waves. Tracings exhibiting a brisk rise during systole and a dicrotic notch are characterized as normal, those exhibiting loss of the notch and a more prolonged downslope are characterized as moderately abnormal, and those exhibiting a flattened wave are characterized as severely abnormal. Absolute amplitudes on PVRs are not directly comparable between patients; however, serial PVRs from a single patient are highly reproducible and thus are quite useful for following the course of severe peripheral vascular disease in individual cases.⁴ One disadvantage of PVRs is that they cannot differentiate proximal femoral disease from iliac occlusive disease.⁸

IMAGING

Duplex Scanning

Duplex scanning is a useful noninvasive method of assessing the aortoiliac and infrainguinal arterial systems. Several studies have evaluated the ability of duplex scanning to predict iliac artery stenosis. A 1987 trial found that duplex scanning was highly sensitive (89%) and specific (90%) in predicting iliac stenosis of 50% or greater.⁹ Three subsequent trials corroborated these findings, reporting sensitivities ranging from 81% to 89% and specificities ranging from 88% to 99%.¹⁰⁻¹² This noninvasive modality may be especially useful for improving evaluation of diabetic patients before invasive procedures (e.g., angiography and angioplasty).¹⁰

Duplex scanning has been increasingly employed in performing infrainguinal bypasses to both popliteal and tibial vessels without preoperative angiography. In one study, a limb salvage rate of 86% was achieved with this approach, and completion arteriography matched the runoff status predicted by duplex scanning in 96% of cases.¹³ In a study from our own institution, we were able to perform femoropopliteal bypasses without preoperative arteriography

and were able to perform distal bypasses with confirmatory arteriograms at the time of operation.¹⁴

Magnetic Resonance Angiography

Magnetic resonance angiography (MRA), a noninvasive modality that does not require contrast agents, often yields good arterial images and may, in fact, be more sensitive than angiography in imaging distal lower-extremity runoff vessels.^{15,16} Developments such as gadolinium enhancement, multistation examination, and the floating table technique have further improved the resolution of MRA,¹⁷⁻¹⁹ to the point where many institutions that use current forms of MRA no longer routinely obtain preoperative angiograms. The development of time-resolved imaging of contrast kinetics (TRICKS) MRA has further improved the accuracy of MRA for assessing the distal vasculature in preparation for a bypass.²⁰ MRA, in conjunction with arterial duplex scanning, has the potential to replace contrast arteriography in the evaluation of patients with distal arterial occlusive disease.

Computed Tomographic Angiography

Computed tomographic angiography (CTA) has become a viable alternative to both MRA and conventional digital subtraction angiography for imaging the aortoiliac region and the lower-extremity arteries. Current variants of this modality (e.g., 16-detector row CTA) have been shown to be as accurate as conventional angiography for imaging distal vessels. As a consequence, operative planning can be done without the need for an invasive angiographic procedure. CTA has also shown promise in the evaluation of graft-related complications, including graft stenosis, aneurysmal changes, and arteriovenous fistulas.²¹⁻²³

Arteriography

Contrast angiography remains the gold standard for the evaluation of patients with distal arterial occlusive disease. A complete evaluation of the existing arterial disease from the aorta to the pedal vessels is necessary for diabetic patients, who frequently have multilevel occlusive disease. Obtaining intra-arterial pressure measurements at the time of angiography significantly improves detection of clinically significant stenosis. The systolic pressure gradient across the lesion should also be measured: gradients greater than 15 mm Hg are considered hemodynamically significant.²⁴

In the general population, arteriography has a complication rate of only 1.7% to 3.3%.²⁵ Elderly patients with severe aortoiliac or infrainguinal disease must be carefully evaluated before the procedure because they are more likely to experience local and systemic complications than patients in the general population are. For the majority of patients, the transfemoral approach is the safest; how-

ever, for patients with weak or nonpalpable femoral pulses, other approaches (e.g., translumbar, transbrachial, or transaxillary) may be preferable. These alternative approaches are associated with higher rates of local complications, including hematomas, pseudoaneurysms, dissections, thrombosis, and embolization.

Renal insufficiency is an important complication of angiography: 6.5% to 8.2% of patients who undergo arteriography experience some degree of impairment associated with contrast agents.^{26,27} Patients who have preexisting azotemia and whose baseline creatinine concentrations exceed 2.0 mg/dl are at highest risk for renal complications after angiography. Elderly patients typically have lower creatinine clearances for a given serum creatinine level and thus should always be considered at higher risk for nephrotoxicity. All possible precautions should be taken to limit the renal insult. There is some evidence to suggest that the use of low-osmolar contrast agents can decrease the incidence of renal impairment,^{28,29} but the data are not unanimous on this point.³⁰ Adequate hydration with oral administration of acetylcysteine before arteriography is highly effective in diminishing the risk of contrast nephropathy. Administration of mannitol, which has an osmotic diuretic effect, helps prevent contrast toxicity as well. These measures, coupled with judicious use of contrast agents, should minimize renal impairment associated with arteriography.

Femoropopliteal Bypass

Patients whose limbs are clearly threatened and who have undergone arteriographic examination should undergo femoropopliteal bypass when the superficial femoral artery or the popliteal artery is occluded and when arteriography indicates that a patent popliteal artery segment distal to the occlusion has luminal continuity with any of its three terminal branches (even if one or more of these branches ends in an occlusion anywhere in the leg). Even if the popliteal artery segment into which the graft is to be inserted is occluded distally, femoropopliteal bypass to this segment can be considered.^{31,32} If the isolated popliteal segment is shorter than 7 cm or if there is extensive gangrene or infection in the foot, a femorodistal artery bypass or a sequential bypass is sometimes performed in one or two stages.

OPERATIVE TECHNIQUE

Femoropopliteal bypass may be carried out either above or below the knee.

Above-the-Knee Bypass

For above-the-knee bypass, the patient is placed in the supine position with the thigh externally rotated and the knee flexed

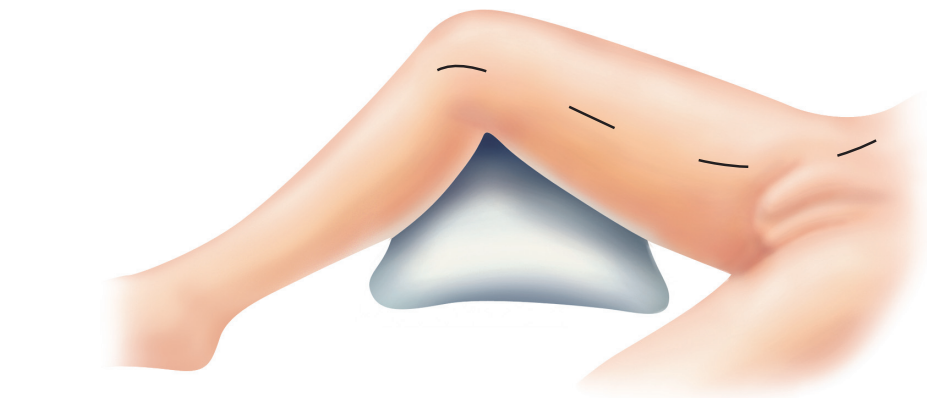


Figure 1 Femoropopliteal bypass: above knee. Shown is the appropriate position of the leg. Interrupted skin incisions are made in the thigh and upper leg to permit harvesting of the great saphenous vein.

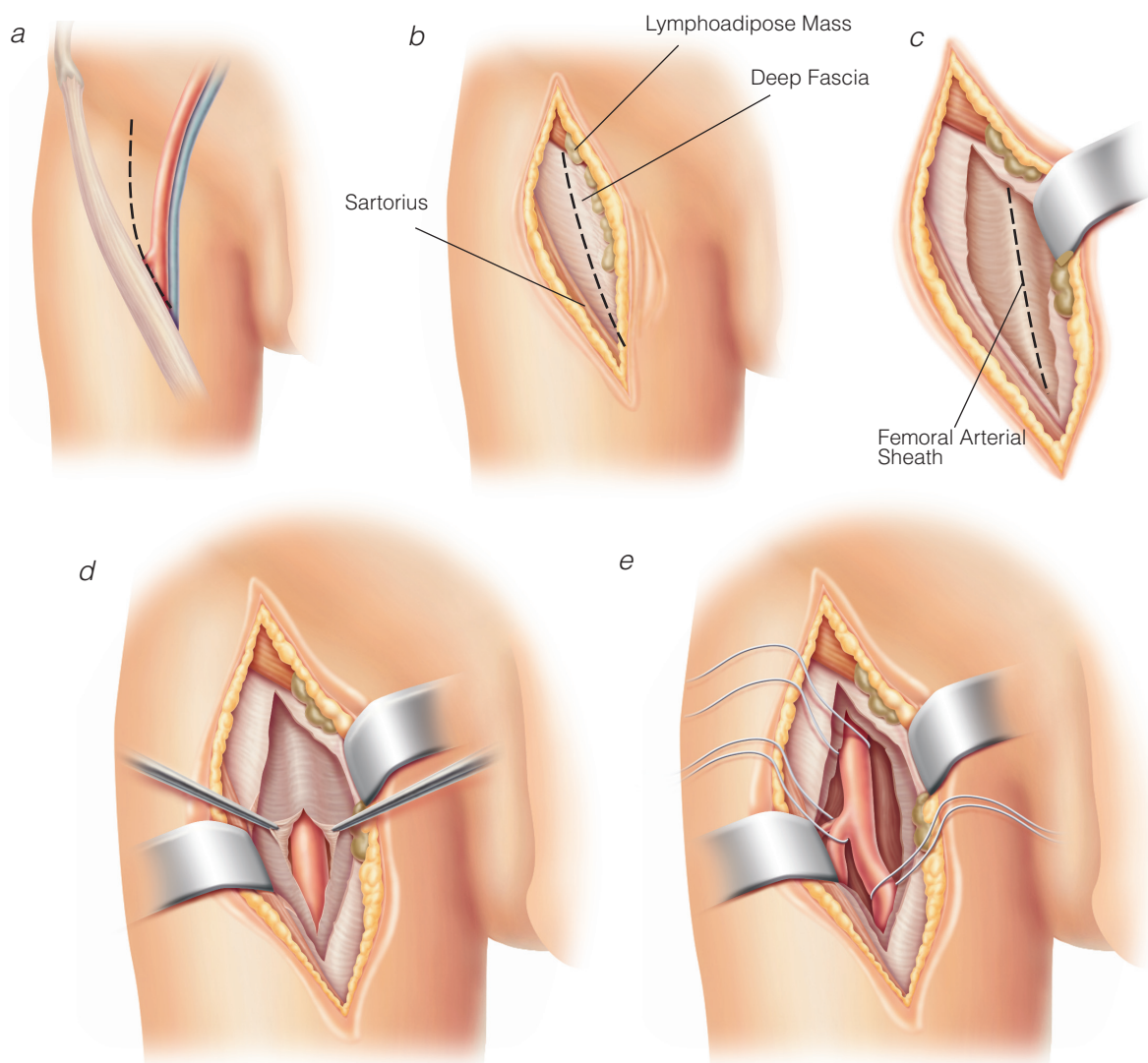


Figure 2 Femoropopliteal bypass: above knee. Depicted is exposure of the femoral artery. (a) A curved 10 to 12.5 cm skin incision is made slightly lateral to the pulsation of the femoral artery. (b) Lymphoadipose tissue is retracted to expose the deep fascia overlying the course of the femoral artery. (c) The deep fascia is incised, exposing the femoral arterial sheath, which is then opened along its axis (d). (e) The common and superficial femoral arteries are mobilized and encircled with Silastic vessel loops.

approximately 30°. This position affords easy exposure of the femoral and popliteal arteries, as well as of the great saphenous vein (GSV).

Harvesting of great saphenous vein The GSV is harvested through intermittent skip incisions starting in the groin and proceeding distally toward the knee [see Figure 1]. Multiple short skin incisions heal better than a single long one and are less likely to result in skin necrosis.

Dissection of the GSV begins at the groin. This proximal incision is also used for exposure of the femoral artery. The saphenofemoral junction is carefully mobilized, and the tributaries are ligated with fine silk close to where they enter the main trunk, with care taken not to impinge on the wall of the trunk. As dissection continues distally, the main trunk of the GSV is progressively elevated, and all tributaries are identified and ligated. The vein is then removed from its bed and immediately placed into a basin containing heparinized saline (or heparinized whole blood) at a temperature of 4° C or cold Hanks solution. A small cannula is passed

through the distal end of the divided vein, and the vessel is irrigated with cold Hanks solution to expel any liquid blood or clot and to locate any leaks. If a leak is found, it is repaired with 6-0 polypropylene.

Step 1: exposure of femoral artery A slightly curved skin incision, with the concavity facing the medial aspect, is made starting at a point slightly above the inguinal crease and extending distally for 10 to 12.5 cm [see Figure 2a]. The incision should be slightly lateral to the pulsation of the femoral artery so as to avoid the lymphatics as much as possible. Any minor bleeding or divided lymphatic vessels should be controlled with electrocoagulation or fine ligatures. Self-retaining retractors are placed both proximally and distally in the wound, and the lymphoadipose tissue is gently retracted medially [see Figure 2b].

The deep fascia is opened along the femoral artery [see Figure 2c], and the sheath of the artery is opened along its axis [see Figure 2d]. The common and superficial femoral arteries are mobilized, and Silastic loops are placed around them [see Figure 2e]. These

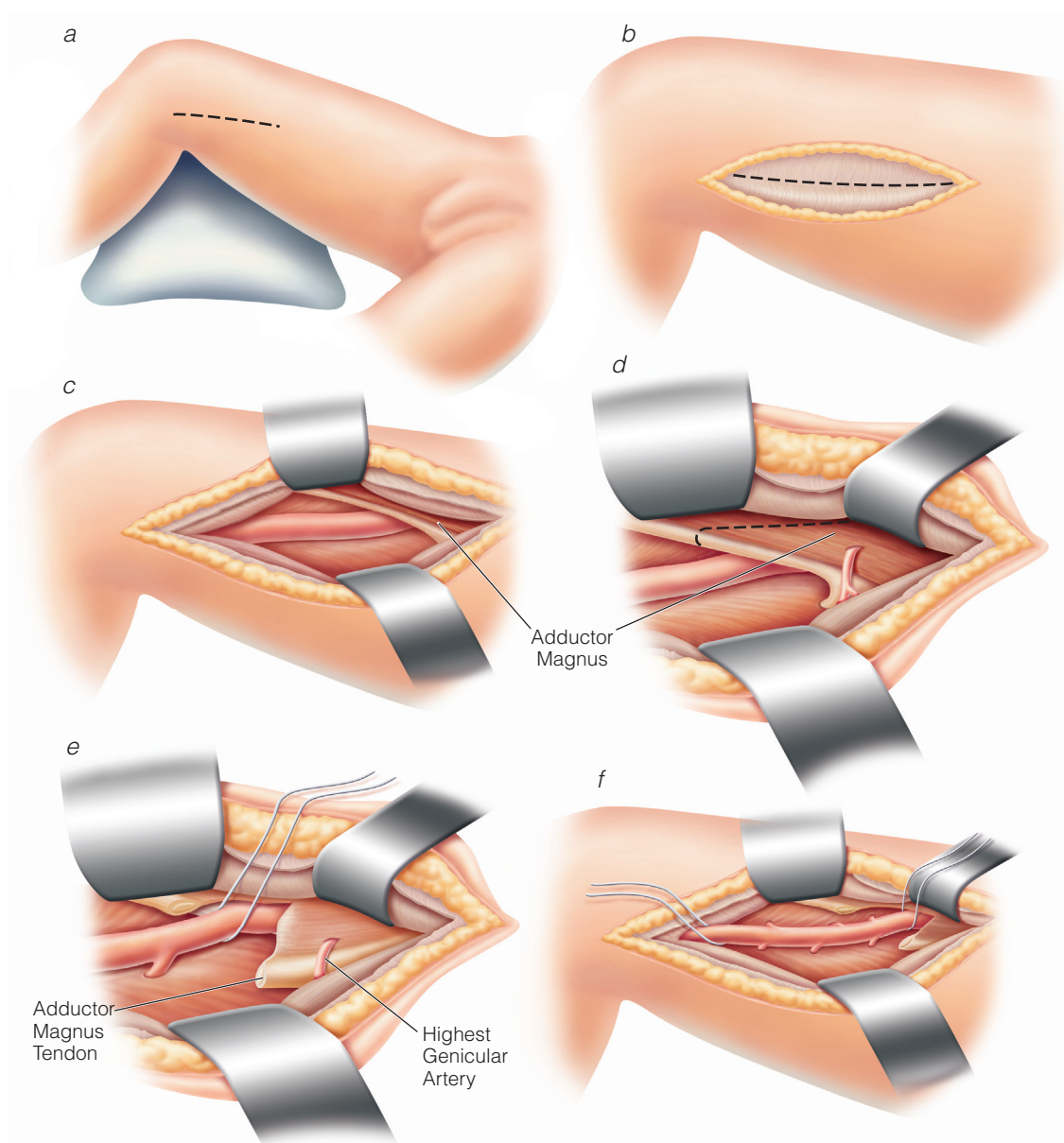


Figure 3 Femoropopliteal bypass: above knee. Depicted is medial exposure of the proximal popliteal artery. (a) An incision is made in the lower third of the thigh, anterior to the sartorius. (b) The deep fascia is incised, and the sartorius is retracted posteriorly, allowing the popliteal artery to be readily palpated. (c) The popliteal arterial sheath is opened, exposing the vessel and its surrounding venules. The adductor magnus tendon may be seen covering the proximal end of the artery (d), and it may have to be divided (e) to provide better exposure of the artery. (f) The popliteal artery, freed of the venous plexus, is mobilized between two vessel loops.

vessels are then elevated slightly, and the origin of the deep femoral artery comes into view lateral and posterior to the common femoral artery and just proximal to the superficial femoral artery. Dissection of the origin of the deep femoral artery must be done carefully so as not to injure the collateral vessels coming off the artery at that level and the one or two branches of the satellite veins that cross the anterior portion of its initial segment. If mobilization of the deep femoral artery proves difficult, the satellite vein branches can be divided and ligated.

Step 2: exposure of proximal popliteal artery For the approach to the popliteal artery, the surgeon moves to the opposite side of the table. An incision is made in the lower third of the thigh anterior to the sartorius and is extended close to the medial aspect

of the knee [see Figure 3a]. The deep fascia anterior to the sartorius is opened, and the sartorius is detached from the vastus medialis and retracted posteriorly. The popliteal artery is identified by palpation; it is the most superficial structure palpable through this exposure [see Figure 3b]. The overlying fascia is incised, and the adipose tissue usually present at this level is dissected until the vascular bundle is reached.

The sheath of the artery is opened [see Figure 3c]. At this level, there is almost always a network of venules surrounding the artery, which must be carefully dissected away from the arterial wall. Division of the adductor magnus tendon may be required to yield adequate exposure of the proximal portion of the popliteal artery [see Figures 3d and 3e]. The venous network is separated from the arterial adventitia, and the various branches are divided and ligat-

Next, the sheath of the popliteal artery is opened farther distally, and the tributaries of the veins surrounding the artery are further dissected away from it. Dissection of the middle portion of the popliteal artery may be facilitated by flexing the knee; this measure relaxes the artery, thereby allowing it to be readily drawn closer to the superficial level of the exposure.

a tunneler or an aortic clamp with a red rubber catheter attached to it to mark the tunnel.

The GSV segment is then brought into the field. It is reversed so that its proximal end becomes the distal end for the anastomosis. This distal end is then enlarged with a longitudinal incision in its posterior wall, and the right-angle tips of the two sides of the divided posterior wall are cut away. Double-armed sutures are placed through the proximal angle (or heel) of the graft, with the needles going from the outside of the arteriotomy to the inside and then from the inside to the outside. Next, a similar double-armed suture is passed through the distal angle (or toe) of the graft from the outside to the inside and then from the inside to the outside through the end of the arteriotomy.

The edge of the vein is then approximated to that of the arteriotomy with a continuous suture starting at the toe of the graft and proceeding toward the heel [see Figure 4]. When half of the anastomosis has been completed, the edge of the vein graft is separated from the edge of the opposite side of the arteriotomy to permit inspection of the arterial lumen and the completed suture. The other half of the anastomosis is then completed by placing a second continuous suture, starting at the heel and proceeding toward the toe. Finally, the two sutures are tied together midway between the heel and the toe to complete the popliteal anastomosis.

Step 5: placement of graft in tunnel The graft is distended by injecting heparinized saline solution into it to test for leaks either from the vein segment itself or from the anastomotic site. The graft is then marked to ensure that it does not become twisted when brought through the tunnel. The graft is brought through the tunnel either by using an aortic clamp or by attaching it to the previously placed red rubber catheter.

Step 6: construction of proximal anastomosis to femoral artery Before the proximal anastomosis is begun, the proper length of the graft should be determined to ensure that there is no redundancy. The proximal end of the graft is split and enlarged in the same fashion as the distal end, and the resulting right-angle corners are similarly trimmed. The graft is then anastomosed to the arteriotomy made in the femoral artery (which, like the popliteal arteriotomy, should be at least twice as long as the vessel is wide). The graft is attached by double-armed needles at its proximal angle and then in a similar fashion at its distal angle. The anastomosis is then completed from each end toward the center, just as the popliteal anastomosis was.

Below-the-Knee Bypass

When occlusion or marked stenosis renders the proximal and middle portions of the popliteal artery unsuitable for graft implantation, the lower portion of the vessel, which is often relatively free of atherosclerosis, may be used for the distal anastomosis instead.

Step 1: exposure of popliteal artery With the knee moderately flexed and supported by a rolled sheet placed under it, a ver-

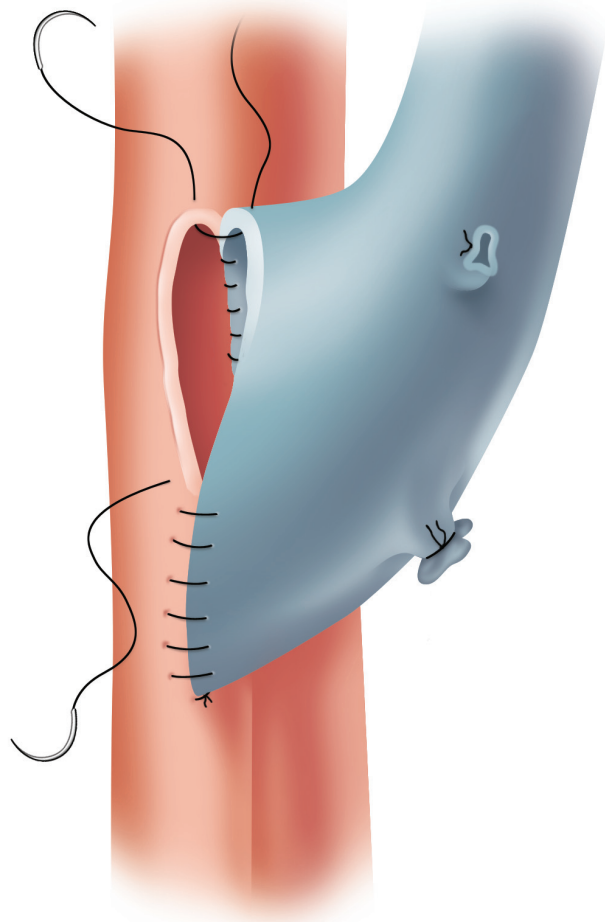


Figure 4 Femoropopliteal bypass: above knee. Shown are details of the anastomotic suturing, which is begun at the distal end and continued to the middle portion of each side of the anastomosis of the artery and the GSV graft. Equal bites of all layers of each vessel are included in each stitch, all of which are placed under direct vision.

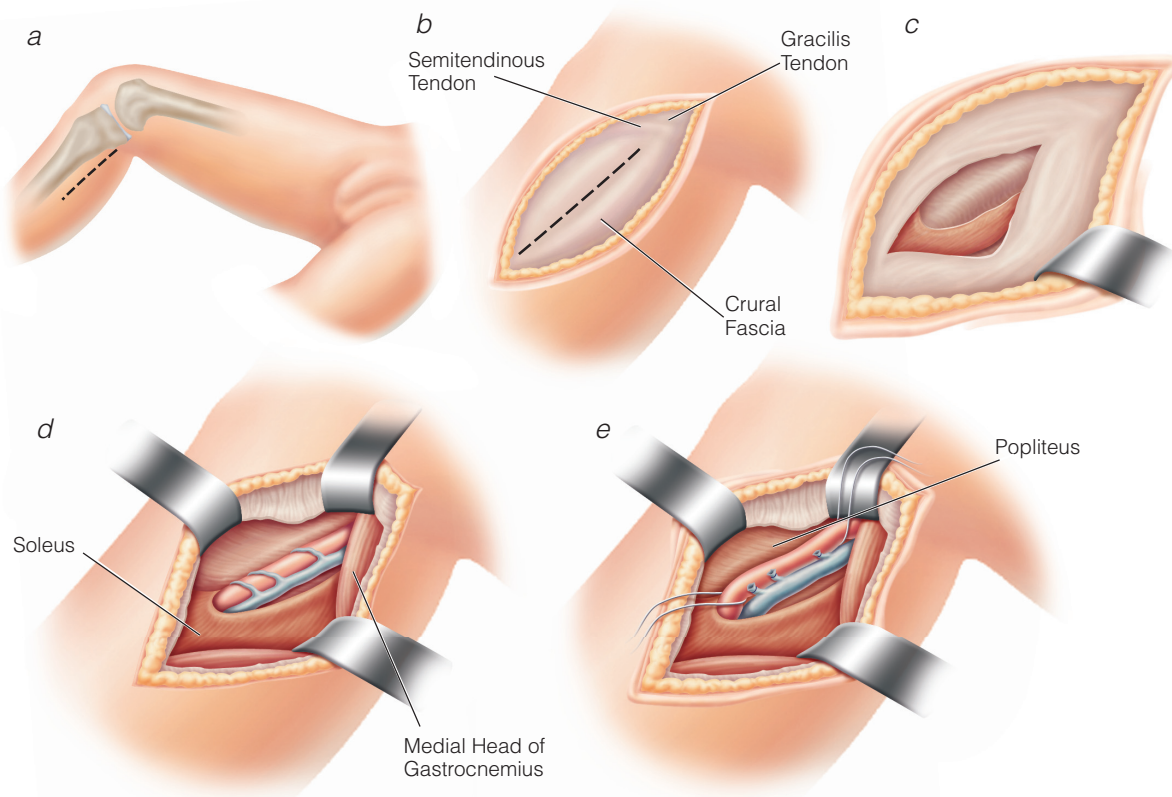


Figure 5 Femoropopliteal bypass: below knee. Depicted is medial exposure of the distal popliteal artery. (a) An incision is made just behind the posteromedial surface of the tibia. (b) The crural fascia is exposed. (c) The fascia is incised, exposing the vascular bundle. (d) The medial head of the gastrocnemius is retracted posteriorly, exposing the distal popliteal vessels and the arcade of the soleus. (e) The distal popliteal artery is freed and mobilized between vessel loops.

tical skin incision is made just behind the posteromedial surface of the tibia [see Figure 5a], exposing the crural fascia [see Figure 5b]. Care must be taken to avoid injury to the GSV during the skin incision. When a GSV graft is to be used, the same incision can serve both for harvesting of the vein and for exposure of the artery.

The crural fascia is opened along its fibers [see Figure 5c], its distal attachments are separated from the semitendinosus and gracilis tendons, and the two tendons are mobilized proximally and, if necessary, divided. The medial head of the gastrocnemius is retracted posteriorly [see Figure 5d] to expose the popliteal artery and vein and the posterior tibial nerve as these structures cross the popliteus posteriorly [see Figure 5e].

It should be noted that (1) the distal popliteal artery has few branches below the inferior geniculate arteries, (2) atheromatous plaques are rarely present at this level, and (3) the arterial wall is often more suitable for graft implantation in this portion of the popliteal wall than it is above the knee.

Step 2: exposure of femoral artery This exposure is accomplished in essentially the same way as it would be in an above-the-knee bypass.

Step 3: creation of tunnel Tunneling for a below-the-knee femoropopliteal bypass is carried out through Hunter's canal, through the upper popliteal space, and finally through the region behind the popliteus.

Steps 4 through 6 Steps 4, 5, and 6 of a below-the-knee

femoropopliteal bypass—the distal anastomosis of the vein graft to the distal popliteal artery, the placement of the graft in the tunnel, and the proximal anastomosis to the femoral artery—are carried out in much the same way as the corresponding steps in an above-the-knee bypass. A completion angiogram should be obtained to confirm the adequacy of the distal anastomosis and verify the position of the graft in the tunnel [see Figure 6].

OUTCOME EVALUATION

Femoropopliteal bypasses performed with segments of the GSV are associated with 4-year primary patency rates ranging from 68% to 80% and limb salvage rates ranging from 75% to 80%.³³ Femoropopliteal bypasses performed with polytetrafluoroethylene (PTFE) grafts yield comparable patency and limb salvage rates above the knee but are significantly less successful below the knee.³⁴

Newer vein harvesting techniques may help improve outcome further. The use of endoscopic vein harvesting methods has been shown to reduce the incidence of wound complications associated with femoropopliteal bypass.³⁵ This approach allows above-the-knee bypasses to be performed through two incisions.

Infrapopliteal Bypass

Bypasses to the small arteries beyond the popliteal artery are performed only when femoropopliteal bypass is contraindicated according to accepted criteria [see Femoropopliteal Bypass, above]. Infrapopliteal bypasses are performed to the posterior tibial artery,

the anterior tibial artery, or the peroneal artery, in that order of preference. As a rule, a tibial artery is used only if its lumen runs without obstruction into the foot, though bypasses to isolated tibial artery segments and other disadvantaged outflow tracts have been performed and have remained patent for more than 4 years.^{2,3} Generally, the peroneal artery is used only if it is continuous with one or two of its terminal branches, which communicate with foot arteries [see Figure 7]. Neither the absence of a plantar arch nor vascular calcification is considered a contraindication to a reconstruction.^{2,7} With both femoropopliteal and infrapopliteal bypasses, stenosis of less than 50% of the diameter of the vessel is acceptable at or distal to the site chosen for the distal anastomosis.

OPERATIVE TECHNIQUE

Bypasses to tibial arteries should be performed with autogenous vein grafts, and either the reversed technique (as previously described [see Femoropopliteal Bypass, *above*]) or the in situ technique [see In Situ Bypass, *below*] may be used. Placement of a tourniquet above the knee allows the distal anastomosis to be performed without extensive dissection of the tibial vessels or the application of clamps.³⁶ Exposure of the inflow vessel (i.e., the femoral artery or the popliteal artery) is achieved in the same way as in femoropopliteal bypass. Accordingly, bypasses to tibial and peroneal arteries are best described in terms of the approaches required for exposure of these vessels and the tunnels required for routing the bypass conduits.

Exposure of Posterior Tibial Artery

The very proximal portion of the posterior tibial artery is approached via a below-the-knee popliteal incision. The deep fascia



Figure 6 Femoropopliteal bypass: below knee. A completion arteriogram from a patient who underwent below-the-knee femoropopliteal bypass for a nonhealing toe amputation site shows runoff through all three tibial vessels.



Figure 7 Infrapopliteal bypass. An arteriogram from a 65-year-old female with rest pain in the right foot who underwent in situ bypass to the middle portion of the peroneal artery shows communication of the peroneal artery with foot arteries and reconstitution of the dorsalis pedis artery.

is incised, and the popliteal space is entered. The gastrocnemius is retracted posteriorly, and the soleus is separated from the posterior surface of the tibia. The distal portion of the posterior tibial artery is approached via a medial incision along the posterior edge of the tibia [see Figure 8]; deepening this incision along the posterior tibialis muscle and the posterior surface of the tibia allows exposure of the posterior tibial artery. The tunnel from the popliteal fossa to the distal posterior tibial artery is made just below the muscle fascia, ideally with a long, gently curved clamp.

Exposure of Anterior Tibial Artery

To expose the proximal portion of the anterior tibial artery, an anterolateral incision is made in the leg midway between the tibia and the fibula over the appropriate segment of patent artery [see Figure 9a]. Additional small medial incisions are also required for tunneling. The anterior incision is carried through the deep fascia, and the fibers of the anterior tibial muscle and the extensor digitorum longus are separated to reveal the neurovascular bundle. The accompanying veins are mobilized and their branches divided to allow visualization of the anterior tibial artery, which can then be carefully mobilized [see Figure 9b]. With the artery mobilized, further posterior dissection can be performed, and the interosseous

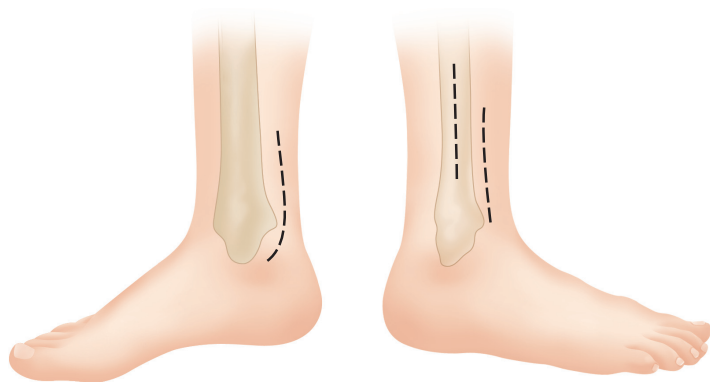


Figure 8 Infrapopliteal bypass: posterior tibial artery. Shown are incisions for bypasses to the distal regions of the leg.

membrane can then be visualized and incised in a cruciate fashion.

Careful blunt finger dissection via the anterior incision and from the popliteal fossa via the medial incision facilitates creation of a tunnel without injury to the numerous veins in the area [see Figure 9c]. Alternatively, the tunnel for the bypass may be placed lateral to the knee in a subcutaneous plane.

The distal anterior tibial artery is approached via an anterior incision placed midway between the tibia and the fibula [see Figure 8]. A tunnel is made from the distal popliteal fossa across the interosseous membrane (like the tunnel to the peroneal artery) and beneath the deep fascia to a point 5 to 7 cm above the lateral malleolus. Once the distal anastomosis is complete and the graft has been drawn through the tunnel, any tendons that may be distorting or compressing the graft in its course around the tibia are divided; this measure proves necessary in most low anterior tibial bypasses.

Exposure of Peroneal Artery

The peroneal artery is usually approached via the same incision as the posterior tibial artery [see Exposure of Posterior Tibial Artery, above]. The artery is located and isolated just medial to the medial edge of the fibula. In its distal third, however, and in patients with stout calves and ankles, the peroneal artery should be approached via a lateral incision [see Figure 8], followed by excision of the fibula.

For lateral exposure of the peroneal artery, a long segment of fibula is freed from its muscle attachments with a combination of blunt and sharp dissection; particular care should be taken in dissecting along the medial edge of the bone because the peroneal vessels run just below this edge and are easily injured by instruments. Next, a finger is passed around the fibula [see Figure 10a]; once this is done, the free edge of bone is further developed by forcefully pushing a right-angle clamp inferiorly and superiorly [see Figure 10b]. A right-angle retractor is passed behind the bone, and the fibula is divided with a power saw. The peroneal artery can then be dissected free from surrounding veins and used in the construction of the distal anastomosis. Gentle blunt finger dissection is required to develop a tunnel from this lateral wound to the distal popliteal fossa, and great care should be taken to avoid injury to the numerous veins in the area. Because the peroneal artery is the least accessible of the three leg arteries used for infrapopliteal bypasses and normally has the poorest connections with the arteries of the foot, we recommend that it be used as a distal implantation site only when the anterior and posterior tibial arteries are not suitable.

Exposure of Dorsalis Pedis Artery

When no more proximal procedure is possible, a bypass to the ankle region or the foot may be performed. The dorsalis pedis

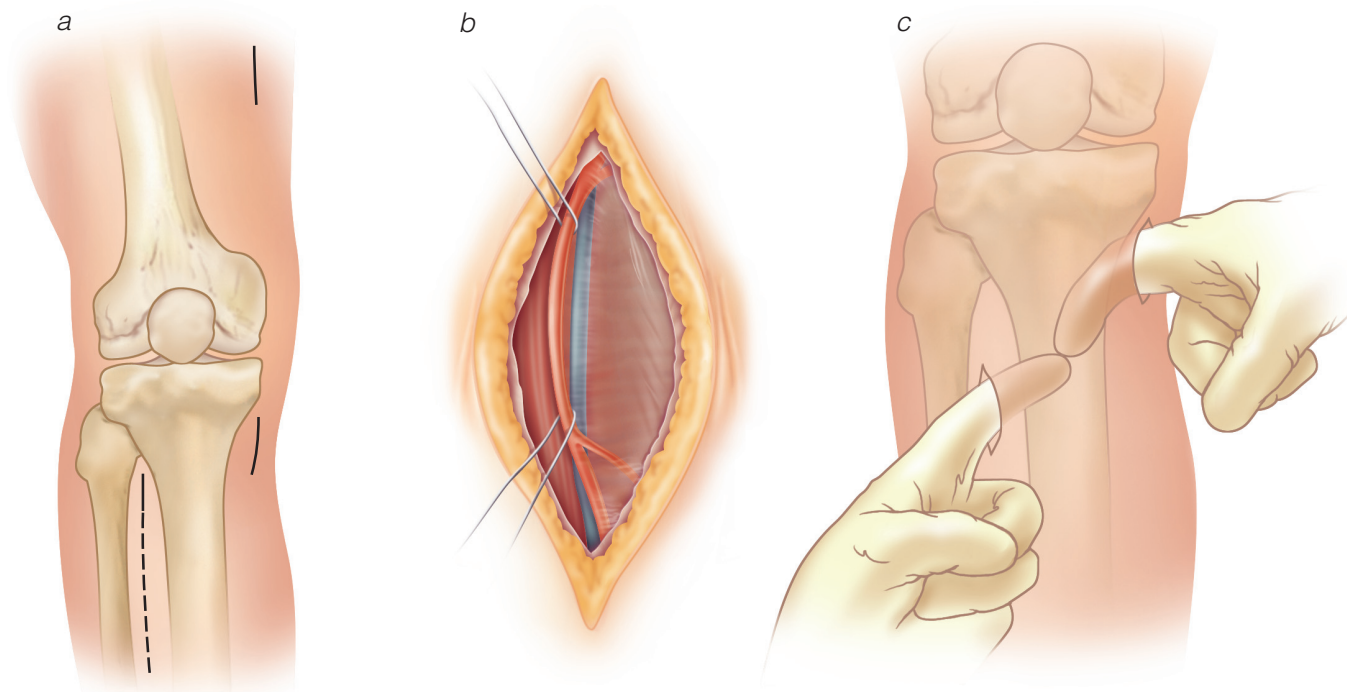


Figure 9 Infrapopliteal bypass: anterior tibial artery. (a) An anterolateral incision is made midway between the tibia and the fibula over the artery; small medial incisions are also made for tunneling. (b) The anterior incision is carried through the deep fascia, the anterior tibial muscle and the extensor digitorum longus are separated, the accompanying veins are mobilized and divided, and the anterior tibial artery is mobilized. (c) A tunnel is created with careful blunt finger dissection.

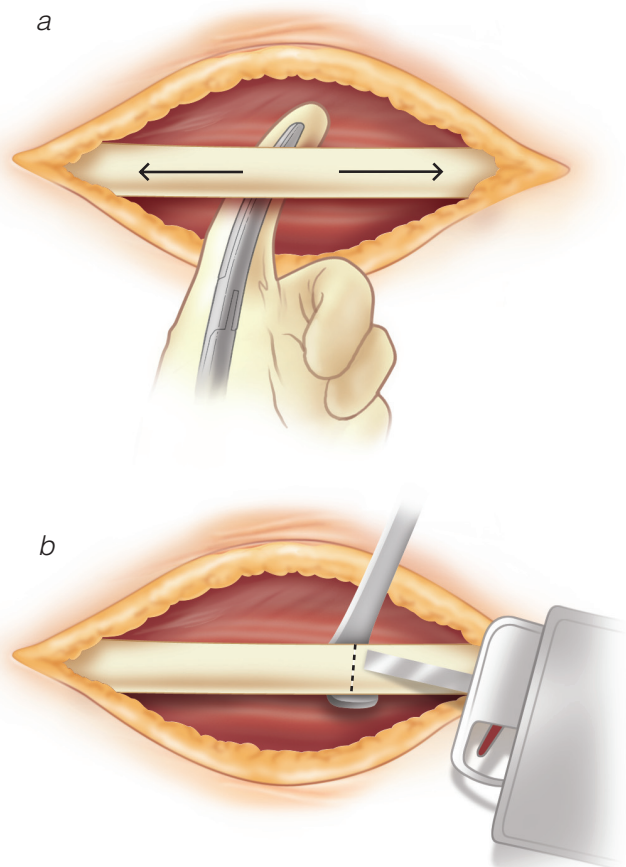


Figure 10 Infrapopliteal bypass: lateral exposure of peroneal artery. Lateral exposure of the peroneal artery typically requires excision of part of the fibula; this is done by (a) passing a finger behind the fibula, developing the free bone edge further with a right-angle clamp, (b) passing a right-angle retractor behind the fibula, and dividing the bone with a power saw.

artery is easily approached via a lateral incision on the dorsum of the foot [see Figure 11a]. The incision is curved slightly and a flap raised so that the incision will not be directly over the anastomosis [see Figure 11b]. If the artery must be approached at the ankle, the extensor retinaculum must be divided. Otherwise, the operation is performed in much the same fashion as a distal anterior tibial bypass [see Figure 12]. The posterior tibial artery can be approached down to a point several centimeters below the medial malleolus.

In Situ Bypass

In situ bypass is an acceptable alternative to reversed vein bypass. In situ procedures were traditionally done through long skin incisions to access the GSV and its side branches. Subsequently, minimally invasive techniques were developed to reduce the wound complications encountered when an in situ bypass is performed via long skin incisions.

Side-branch occlusion involves the use of an endoscopic vein harvesting system. Three skin incisions are made: two incisions for arterial access and one 2 cm incision above the knee for insertion of an endoscopic device to locate and clip the side branches of the saphenous vein. Once the proximal anastomosis is complete, the valves are lysed with a flexible valvulotome passed through the distal end of the vein. Completion cineangiography is then performed to confirm side-branch occlusion and to assess the entire reconstruction.³⁷

OUTCOME EVALUATION

Infrapopliteal bypasses should have 5-year primary patency rates ranging from 60% to 67% and limb salvage rates ranging from 70% to 75% whether they are done with the reversed-vein technique or with the in situ technique.^{38,39} For all such grafts, close patient follow-up and graft surveillance improve secondary patency rates. Reduced complications and decreased length of stay have been reported for patients undergoing distal in situ bypasses using the endoscopic side-branch occlusion approach.⁴⁰

Plantar Bypass

Extension of the standard approaches to limb salvage has led to the performance of bypasses to vessels below the ankle joint [see Figures 13 and 14]. Such bypasses are indicated when the more proximal tibial vessels are occluded, which frequently occurs secondary to failure of a more proximal bypass. The technique required for performing bypasses to secondary branches in the foot is essentially the same as that required for performing bypasses to major infrapopliteal vessels.

Optimal illumination by means of head lamps is important for achieving technical success with plantar bypass, and loupe magnification is helpful when the vessel is less than 1.5 mm in diameter. In addition, visualization of perimalleolar and inframalleolar arteries requires excellent preoperative imaging studies.

These very distal bypasses offer a viable alternative to a major amputation. Like infrapopliteal bypasses, they are best described in terms of the anatomic approaches to the distal branch vessels. In what follows, we outline exposure of the plantar and tarsal arteries; exposure of the dorsalis pedis artery is outlined elsewhere [see Infrapopliteal Bypass, above].

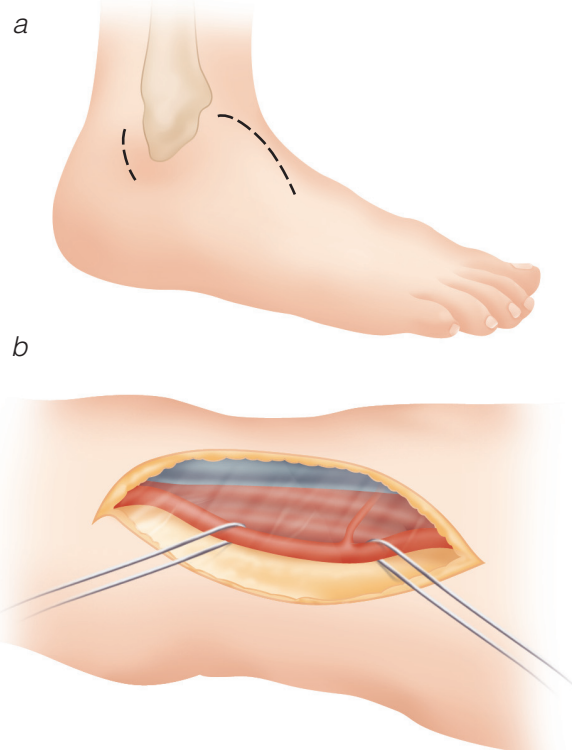


Figure 11 Infrapopliteal bypass: dorsalis pedis artery. (a) The dorsalis pedis artery is approached via an incision on the dorsum of the foot. (b) The incision is curved and a flap raised so that the incision is not directly over the anastomosis.



Figure 12 Infrapopliteal bypass: dorsalis pedis artery. Shown is an arteriogram from a 72-year-old diabetic patient who underwent a popliteal artery–dorsalis pedis artery bypass with a reversed GSV graft for a nonhealing great toe amputation.

OPERATIVE TECHNIQUE

Exposure of Lateral and Medial Plantar Arteries

The lateral and medial plantar branches are the continuation of the posterior tibial artery in the foot [see Figure 15]. The lateral plantar artery forms the deep plantar arch and is larger than the medial plantar artery. If the lateral branch is occluded, the medial branch may enlarge and feed the plantar arch through collateral vessels.

The initial incision is made over the termination of the posterior tibial artery below the malleolus. The artery is isolated, and the incision is extended inferiorly and laterally onto the sole. A direct approach to the individual branches is difficult, for several reasons. First, because the skin of the sole is not easily retracted, adequate exposure of the lateral and medial plantar arteries is hard to obtain if the incision does not follow their course exactly. Second, because these arteries are small in diameter and lie deep within the foot, they can be quite difficult to locate. Third, it is sometimes hard to distinguish the lateral plantar artery from the medial plantar artery. Dissection of the termination of the posterior tibial artery can help the surgeon make this distinction. The lateral branch is usually located inferiorly when the foot is externally rotated on the operating table.

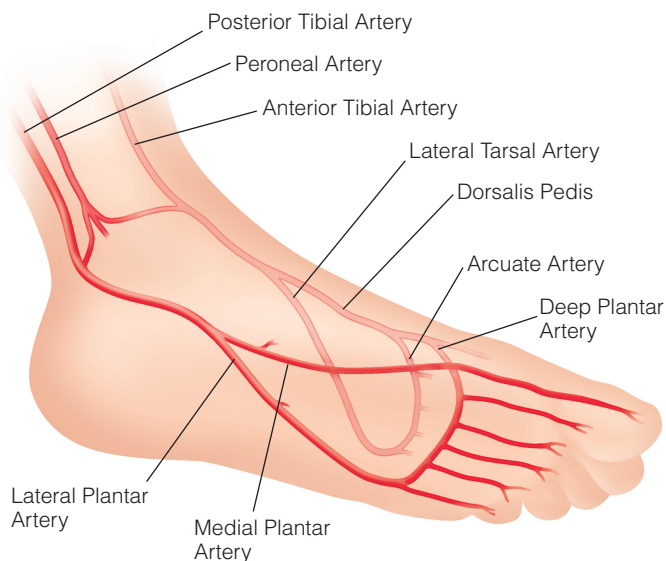


Figure 13 Plantar bypass. Shown are the major arteries of the foot, including the two major branches of the posterior tibial artery.³ The lateral plantar artery is usually the larger and ends in the deep plantar arch.

Exposure of the proximal 2 to 3 cm of the plantar branches is accomplished by incising the flexor retinaculum and the adductor muscle of the great toe. More distal exposure of these branches can be obtained by dividing the medial border of the plantar aponeurosis and the extensor digitorum brevis.

Exposure of Deep Plantar Artery and Lateral Tarsal Artery

The deep plantar artery and the lateral tarsal artery are branches of the dorsalis pedis artery. The deep plantar artery originates at the metatarsal level, where it descends into a foramen bounded proximally by the dorsal metatarsal ligament, distally by the dorsal interosseous muscle ring, and medially and



Figure 14 Plantar bypass. A completion arteriogram from a 62-year-old diabetic with nonhealing toe ulcers who underwent a popliteal artery–medial plantar artery bypass with a reversed GSV graft shows the distal anastomosis, with flow visible through a small but patent medial plantar artery.

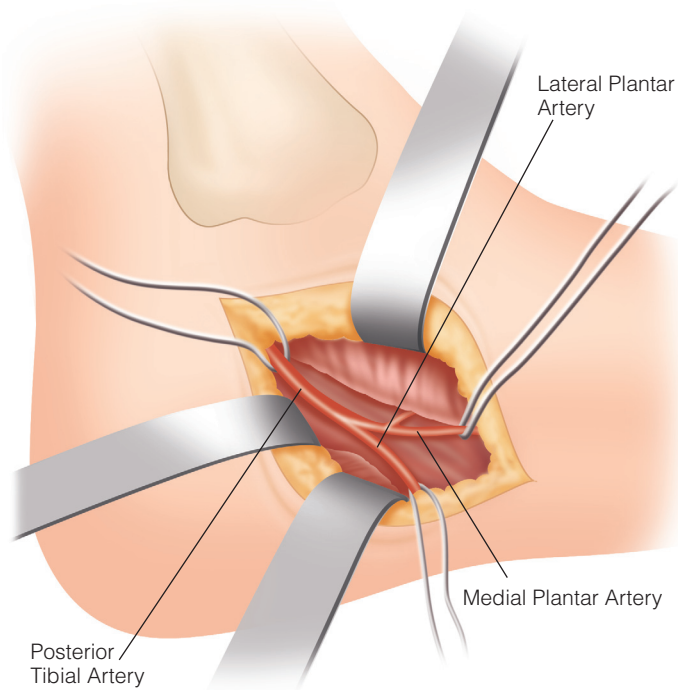


Figure 15 Plantar bypass. Depicted is exposure of the distal portion of the posterior tibial artery. The lateral and medial plantar arteries branch from this vessel and lie beneath the flexor retinaculum and the abductor hallucis, which can be incised.

laterally by the bases of the first and second metatarsal bones. As the deep plantar artery exits from this tunnel, it connects with the lateral plantar artery to form the deep plantar arch [see Figure 16].

A slightly curved longitudinal 3 to 4 cm incision is made over the dorsum of the middle portion of the foot, and the dorsalis pedis artery is dissected distally down to its bifurcation into the deep plantar and first dorsal metatarsal branches. The extensor

hallucis brevis is retracted laterally—or, if necessary, transected—and the dorsal interosseous muscle ring is split to allow better exposure of the proximal portion of the deep plantar artery. The periosteum of the proximal portion of the second metatarsal bone is then incised and elevated. A fine-tipped rongeur is used to excise enough of the metatarsal shaft to permit ample exposure of the deep plantar artery.

OUTCOME EVALUATION

Bypasses to the dorsalis pedis artery and its branches have yielded results comparable to those of bypasses to more proximal tibial vessels, with 3-year primary patency rates ranging from 58% to 60% and limb salvage rates ranging from 75% to 95%.⁴¹⁻⁴³ In one review, patency rates were higher in patients who had an intact plantar arch than in those who did not; however, failure to visualize the plantar arch on preoperative arteriograms does not preclude the performance of these bypasses for limb salvage. With careful follow-up, the assisted primary patency rates for these grafts have been substantially improved.⁴⁴ The available reports emphasize the need to repair failing grafts because their secondary patency was much better than that of failed grafts. In one study, patients who required shorter bypasses or had lower preoperative C-reactive protein levels experienced significantly better outcomes.⁴⁵ In some patients, occlusion of the distal tibial vessel necessitates performance of a tibiotibial bypass to achieve wound healing.⁷

Bypasses to plantar or tarsal vessels performed with vein grafts yield 2-year patency rates ranging from 65% to 75% and limb salvage rates higher than 80%.^{4,5} In one report, the primary patency rate for these grafts was 74% at 1 year and 67% at 2 years, and the limb salvage rate was 78% at 2 years.³

Alternative Bypasses Using More Distal Inflow Vessels

Traditionally, the femoral artery has been the inflow site of choice for infrainguinal bypasses. Since the early 1980s, the superficial femoral, deep femoral, popliteal, and tibial arteries have all

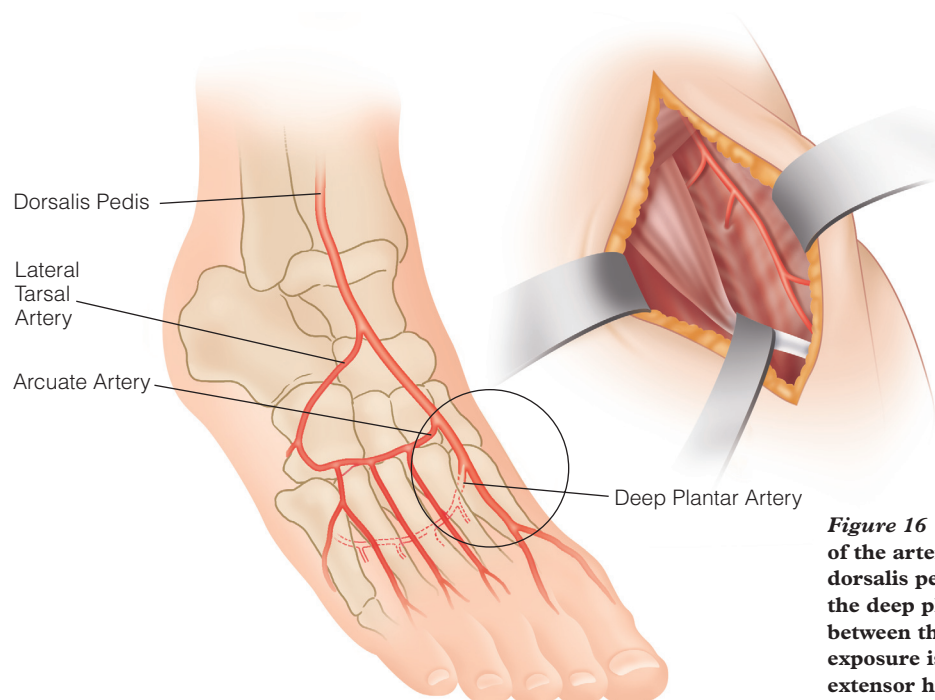


Figure 16 Plantar bypass. Shown is a dorsal view of the arteries of the foot. Exposure of the distal dorsalis pedis artery (insert) highlights the origin of the deep plantar artery and its downward course between the first and second metatarsal bones. This exposure is facilitated by lateral retraction of the extensor hallucis brevis.

been used as inflow sources when these vessels were relatively disease free or when the amount of autologous vein available was limited. Currently, the superficial femoral artery and the popliteal artery are preferentially used for primary bypasses when they are free of disease.

The strategy of utilizing more distal inflow sources is particularly applicable to inframalleolar bypasses, in which very long vein segments would be required to reach the dorsalis pedis or other pedal arteries from the usual more proximal inflow sites. Two studies from the latter half of the 1980s reported that the patency rates in bypasses originating from the superficial femoral and popliteal arteries were comparable to those in bypasses originating from the common femoral artery.^{46,47} In a review of our own experience with popliteal-distal vein graft bypasses,⁵ we reported a patency rate of 65% at 4 years—a figure comparable to rates reported for femorodistal bypasses with reversed or in situ vein grafts (67% and 69%, respectively).³⁸ Given these results, surgeons should not hesitate to employ either the popliteal artery or the superficial femoral artery as an inflow source. Use of these more distal inflow sites results in shorter grafts and allows por-

tions of the GSV to be preserved for other purposes.

An increasing number of limb salvage procedures are secondary interventions. These secondary procedures are generally more difficult to perform because the access routes to the arteries have been previously dissected and because there frequently is little good autologous vein left. In some cases, patients present with gangrene developing below a functioning bypass or after a previous failed bypass. Some of these patients need nothing more than a short distal extension of their functioning bypass; others have only enough vein left to make up a short graft. For such patients, a tibiotibial bypass may be an effective alternative revascularization approach.

In 1994, our group reported our 11-year experience with tibiotibial bypasses, comprising 42 procedures in 41 patients.⁷ Ten of these bypasses were performed because previous bypasses failed; the remainder were performed because the amount of autologous vein available was limited. Approximately 50% of the bypasses were to pedal or tarsal vessels. At 5 years, the patency rate for these grafts was 65%, and the limb salvage rate was 73%.⁷ A subsequent study reported comparable results.^{48,49}

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18 VARICOSE VEIN SURGERY

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Varicose veins are a common problem, accounting for approximately 85% of the venous conditions treated. Over the past decade, management options for varicose veins and venous insufficiency of the lower extremity have become more diverse. Operative vein stripping is rapidly being replaced with a variety of endovenous techniques, ranging from laser vein obliteration to radiofrequency (RF) closure to foam sclerotherapy. Conventional surgical stripping has a poor image with the public, being associated with large unsightly incisions, severe postoperative pain, and a significant risk of recurrence. Current evidence indicates that patients experience less pain and return to work more quickly after endovenous treatment of varicosities than after surgical vein stripping.¹ In addition, the elimination of the word stripping from the technical description has facilitated the public's growing preference for endovenous therapy over conventional surgical therapy (even though the basic therapeutic principles are essentially similar for the two approaches).

As a consequence of the minimally invasive nature of endovenous therapy, treatment of vein disease is moving from the hospital to the office. This shift has allowed a diverse group of physicians (e.g., dermatologists, gynecologists, and cardiologists) to enter a field that previously had been left to surgeons. Accordingly, to remain up to date with respect to the treatment of vein disease, it is essential for surgeons to acquire the knowledge and skills required to use the new endovenous techniques. In this chapter, we review the procedures, results, and complications associated with endovenous therapy, as well as traditional surgical techniques.

Terminology

All physicians treating lower-extremity venous disease should be familiar with the current names for the veins of the thigh and leg, as specified in the 2001 revision of the official *terminologia anatomica* by the International Interdisciplinary Consensus Committee on Venous Anatomical Terminology.² Failure to employ current standardized terminology can hinder data exchange in translated research studies. In addition, retention of the traditional nomenclature can result in potentially dangerous clinical scenarios. For instance, ultrasonographically diagnosed thrombosis of the superficial femoral vein might, because of the term used for the vein, be erroneously interpreted as superficial thrombophlebitis instead of true deep vein thrombosis (DVT). To prevent these and other errors, a more accurate delineation of the branches of the common femoral vein is required. Thus, the terms femoral vein (instead of superficial femoral vein) and deep femoral vein (instead of profunda femoris) are now employed.

Of particular significance for the purposes of this chapter is that the greater (long) saphenous vein is now referred to as the great saphenous vein (GSV), and the lesser (short) saphenous vein is now referred to as the small saphenous vein (SSV). In addition, the terms saphenofemoral junction and saphenopopliteal junction have been accepted into the official nomenclature—a change that is especially relevant to endovenous treatment of varicose veins. Various other changes in the names of lower-extremity and pelvic veins were also

recommended in the Committee's consensus statement; however, these changes have little bearing on the current discussion and thus are not addressed further here.

Indications for Varicose Vein Surgery

The indications for surgical treatment of varicose veins are well established [see *Table 1*]. Although many physicians believe that varicose veins are nothing more than a cosmetic nuisance, this is in fact true only for some men. Women, for the most part, have specific symptoms (e.g., aching, burning pain, and heaviness) that are related to their varicose veins and are exacerbated by the presence of progesterone. Such symptoms develop with prolonged standing or sitting and reach maximal levels on the first day of the menstrual period, when progesterone levels are at their peak. Men, lacking progesterone, have few such symptoms until the varicose veins progress with aging to the point where they press on somatic nerves. In general, the severity of the symptoms bears no relation to the size of the vessels being treated. Telangiectasias can produce symptoms identical to those of varicose veins, and such symptoms can be relieved by simple sclerotherapy [see 6:25 *Sclerotherapy*].

Longitudinal studies have shown that large varicose veins can produce venous ulcerations within 15 years. Given that the incidence of venous ulceration is 20% in patients who are first seen with large varicose veins, large varicosities constitute an indication for surgery. Various skin changes characteristic of chronic venous insufficiency precede the development of venous ulceration.

Varicose thrombophlebitis is followed by recurrent varicose thrombophlebitis in nearly every case, at intervals ranging from a few weeks to many months. Nevertheless, superficial thrombophlebitis, which can be quite disabling, can be prevented by removing varicose vein clusters.

It is true that for many women, the undesirable appearance of varicose veins is a major reason for seeking surgical treatment. When questioned, however, such patients often admit to having symptoms such as pain, heaviness, and fatigue. Typically, they do not relate these symptoms to the varices themselves but instead attribute them to prolonged standing during daily work.

Table 1 Indications for Varicose Vein Surgery

Pain: leg aching, leg heaviness
Patchy burning (venous neuropathy)
Swelling: foot, ankle, leg
Dermatitis: focal, extensive
Lipodermatosclerosis
Ulceration: present or healed
Superficial thrombophlebitis
External hemorrhage
Appearance

Preoperative Evaluation

DUPLEX MAPPING

Over the years, surgical treatises have devoted a great deal of space to clinical examination of the patient with varicose veins. Numerous clinical tests have been described, many of which carry the names of famous persons interested in venous pathophysiology. This august history notwithstanding, the Trendelenburg test, the Schwartz test, the Perthes test, and the Mahorner and Ochsner modifications of the Trendelenburg test are, for the most part, useless in preoperative evaluation of patients today.³ There is no doubt that clinical evaluation can be improved by using handheld Doppler devices. In our view, however, preoperative evaluation is best performed by combining duplex scanning with physical examination.⁴ Duplex mapping defines individual patient anatomy with considerable precision and provides valuable information that supplements the physician's clinical impression. This information allows the physician to develop a strategy that will treat abnormal refluxing veins while leaving normal portions of the venous system in place, thereby minimizing operative trauma and reducing long-term recurrence.

A protocol for duplex mapping of incompetent superficial veins has been published.⁴ In essence, the examination consists of interrogating specific points of reflux with the patient standing [see Table 2]. Forward flow is produced with muscular compression, and reverse flow is then assessed in the crucial areas that are important to subsequent procedural planning.

The patient is placed in an upright position so that the leg veins are maximally dilated. No clothing is worn on the lower extremities from the waist down, except for nonconstricting underwear. The patient is instructed to inform the sonographer of any sensation of light-headedness, faintness, dizziness, or nausea. These symptoms seem to be associated with the overall atmosphere of the room and the presence of Doppler velocity signals; they appear to be less likely to occur when the examination itself is performed silently. If a tendency to fainting because of vagovagal reflux is encountered, the examination may have to be modified so that the patient is in a semiupright position instead.

Examination should include both lower extremities, though post-treatment examinations may target a single extremity or a single area of an extremity. The full length of the axial venous system from ankle to groin is examined. The probe is aligned transversely so that specific named veins can be identified and their relations to other limb structures determined. The veins are scanned by moving the probe up and down along their courses. Double segments, sites of tributary confluence, and large perforating veins (along with their deep venous connections) are identified. (Perforating veins are those that course from the subcutaneous tissue through deep fascia to anastomose with one of the named deep venous structures; communicating veins are those that anastomose with one another within a single anatomic plane.) Varicose veins are often arranged in multiple parallel channels. It is unnecessary to follow reflux into all of the varicose clusters, because these are obvious to the treating physician. Augmentation of flow (distal compression) is done sharply, quickly, and aggressively, and pressure is applied to the calf to activate the gastrocnemius-soleus pump. When a color or pulsed-wave Doppler device is used, the probe is angled to provide an insonation angle of 60° or less.

For the anterior examination, the patient faces the sonographer with his or her weight borne on the lower extremity that is not being examined. The non-weight-bearing extremity is then evaluated. The common femoral vein and the saphenofemoral junction are assessed with the Valsalva maneuver and with distal compression and release. If reflux is present, the diameter of the refluxing GSV is not-

Table 2 Interrogation Points in the Venous Reflux Examination

Common femoral vein
Femoral vein
 Upper third
 Distal third
Popliteal vein
Sural veins
Saphenofemoral junction*
Saphenous vein, above the knee
Saphenous vein, below the knee
Saphenopopliteal junction†
Mode of termination, lesser saphenous vein

*Record diameter of refluxing long saphenous vein.

†Record distance from floor.

ed for subsequent use in selecting the proper endovenous catheter during saphenous ablation.

The GSV is identified on the basis of its relation to the deep and superficial fascia that ensheathes it to form the saphenous compartment. High-resolution B-mode ultrasonographic imaging of the superficial fascia in the transverse plane has shown that this structure reflects ultrasound strongly, yielding a characteristic image of the GSV known as the saphenous eye [see Figure 1]. The saphenous eye is a constant marker that is clearly demonstrable in transverse sections of the medial aspect of the thigh and that readily differentiates the GSV from varicose tributaries and other superficial veins. Casual examination of the thigh often reveals an elongated, dilated vein that is incorrectly assumed to be the GSV. This mistaken assumption can be corrected by means of ultrasound scanning with the saphenous eye as an anatomic marker.

Venous reflux can be elicited manually by calf muscle compression and release, by the Valsalva maneuver, or by pneumatic tourniquet release. In terms of efficacy, there is no difference between pneumatic tourniquet release and manual compression and release. However, pneumatic tourniquet release is cumbersome and requires two vascular sonographers, which makes the manual compression and release method very attractive by comparison. If saphenofemoral reflux lasting longer than 0.5 second is present, the diameter of the GSV is recorded 2.5 cm distal to the saphenofemoral junction.

The examination continues distally along the GSV, with distal augmentation of flow performed at intervals to check for reflux. Reflux frequently ends in the region of the knee. The point at which reflux stops is recorded in terms of distance from the floor in centimeters. The femoral vein (i.e., the vessel formerly termed the superficial femoral vein) is checked at midthigh for reflux and vein wall irregularities.

The posterior examination is also done on the non-weight-bearing lower extremity, with attention paid to reflux in the popliteal vein, the saphenopopliteal junction, and the SSV. The Valsalva maneuver may be used to stimulate reflux, as may distal augmentation and release. Valsalva-induced reflux is halted by competent proximal valves. The SSV is followed from its retromalleolar position on the lateral aspect of the ankle proximally to the saphenopopliteal junction, and augmentation maneuvers are performed every few centimeters.

The termination of the SSV is noted. If the vein terminates proximally in the vein of Giacomini, the femoropopliteal vein, or another vein, a specific check is made for a connection to the popliteal

vein. If the SSV shows reflux, the distance from the saphenopopliteal junction to the floor is measured and recorded.

A search for incompetent perforating veins is necessary only in limbs with chronic venous insufficiency (CVI) manifested by hyperpigmentation, atrophie blanche, woody edema, scars from healed ulceration, or actual open ulcers. Incompetent perforating veins in limbs without CVI are associated with varicose veins and can be controlled with varicose phlebectomy. Identification of perforating veins in the lower extremity can be difficult even for the experienced sonographer.

Procedural Planning

For varicose vein treatment to be successful, two goals must be met: (1) reflux must be ablated from the deep veins to the superficial veins, and (2) all branch varicosities must be removed. Reflux must be eliminated from all major problem areas, including the saphenofemoral junction, the saphenopopliteal junction, and the mid thigh Hunterian perforator vein. To identify these problem areas, careful preoperative duplex mapping of major superficial venous reflux is essential. All varicose vein clusters are meticulously marked before operation; they may be difficult to identify during the procedure, when the patient is supine.

At present, three techniques are approved for the elimination of axial reflux in the GSV and the SSV: (1) traditional surgical stripping, (2) laser vein ablation (i.e., endovenous laser therapy [EVL]), and (3) radiofrequency (RF) ablation. Regardless of which technique is employed, the principal goals of treatment (see above) are the same. In addition, the procedure must be done in a manner that optimizes cosmetic results and minimizes complications.

Endovenous Procedures

Current endovenous techniques for treating varicose veins are based on three major developments: (1) the availability of laser and RF probes that deliver heat endovenously, (2) the introduction of tumescent anesthesia, and (3) the evolution of duplex ultrasonography. Tumescent anesthesia allows physicians to use large volumes (500 ml) of dilute (0.1%) lidocaine in a single session while achieving anesthesia levels equivalent to those achieved with 1% lidocaine. In this way, the entire thigh portion of the GSV can be safely anes-

thetized (and consequently obliterated) at one time. Epinephrine can be added to the solution to improve postoperative hemostasis, increase venous contraction around the heat-generating catheter, and lengthen the duration of postprocedural analgesia. A common formula for the tumescent anesthesia solution is 450 ml of normal saline mixed with 50 ml of 1% lidocaine with epinephrine (1:100,000 dilution) and 10 ml of sodium bicarbonate to buffer the acidity of the lidocaine.

Duplex ultrasonography has revolutionized treatment of varicose veins. It dramatically enhances physicians' ability to evaluate the cause of varicosities and to tailor treatment so that only the diseased vein segments are ablated while the normal segments are preserved. It also serves to guide placement of sheaths and heat-generating catheter tips, allowing these devices to be situated very precisely within the vein.

TECHNIQUE

Laser Vein Ablation

Laser vein ablation [see Figure 2] may be performed either in the office or in the hospital. Reimbursement issues make in-office treatment advantageous for most physicians. Neither conscious sedation nor noninvasive monitoring is required. On occasion, a nervous patient may benefit from administration of an oral anxiolytic agent 1 to 2 hours before the procedure.

Standard surgical preparation and draping are indicated, including the use of sterile gowns, masks, drapes and aseptic technique. Depending on the results of the preoperative physical examination and duplex ultrasonography, the GSV, the SSV, the anterior accessory saphenous vein, or the posterior accessory saphenous vein may be treated, either alone or in combination with other vessels as necessary. The GSV is usually treated from the upper third of the calf to the saphenofemoral junction. If the calf portion of the GSV is to be treated, tumescent anesthesia should be liberally employed to reduce the risk of saphenous nerve injury. The SSV is treated from the distal third of the calf to the point where it angles toward the popliteal vein in the popliteal fossa. The relation of the sural nerve to the distal third of the SSV precludes safe treatment of this portion of the vein, and the proximity of the popliteal nerve to the SSV in the popliteal fossa precludes safe treatment of the most proximal portion of the vein. The procedure does not allow flush ligation of the saphenofemoral junction, but current evidence suggests that this measure may not be indicated: flush ligation eliminates normal venous drainage from the saphenofemoral junction and may increase the risk of neovascularization of the saphenofemoral junction and recurrence of varicosities.

The saphenous vein being treated is accessed with a micropuncture system after a small amount of lidocaine (sufficient to raise a small skin wheal) is injected into the dermis. The position of the 0.015-in. wire in the saphenous vein is confirmed by means of ultrasonography. A 4 French catheter is then passed over the wire, allowing the placement of a 0.035-in. wire for access to the proximal portion of the saphenous vein. Next, the 0.035-in. wire is positioned at the appropriate saphenous junction, and a 5 French vascular sheath is advanced over the wire to the junction. The sheath is positioned either just below the superior epigastric vein or 1 to 2 cm distal to the junction of the GSV; if the SSV is being treated, the tip is positioned 2 to 3 cm below the junction at the point where the vein makes its transition from an oblique course to a parallel path under the fascia of the leg. The 600 μ m laser fiber is then passed to the tip of the sheath, which is pinned and pulled to expose the tip of the laser fiber. The rigidity and sharpness of the laser fiber makes advancing its tip dangerous. Most laser systems allow the fiber to be locked to the sheath, so that the

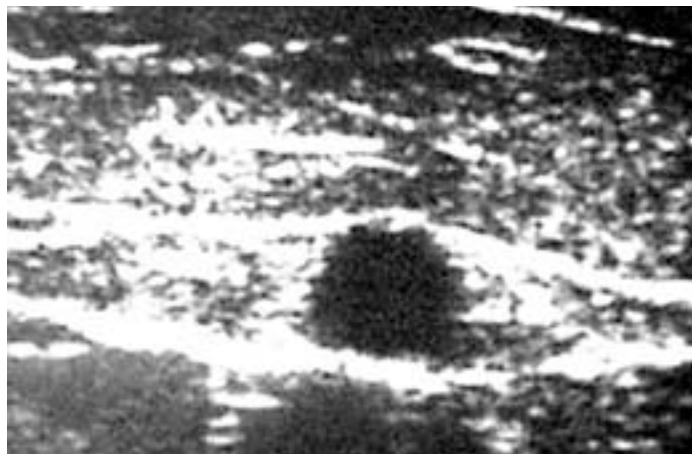


Figure 1 Shown is an ultrasonographic image of the so-called saphenous eye. Correct identification of this marker is crucial to correct performance of the preoperative ultrasonographic reflux examination.

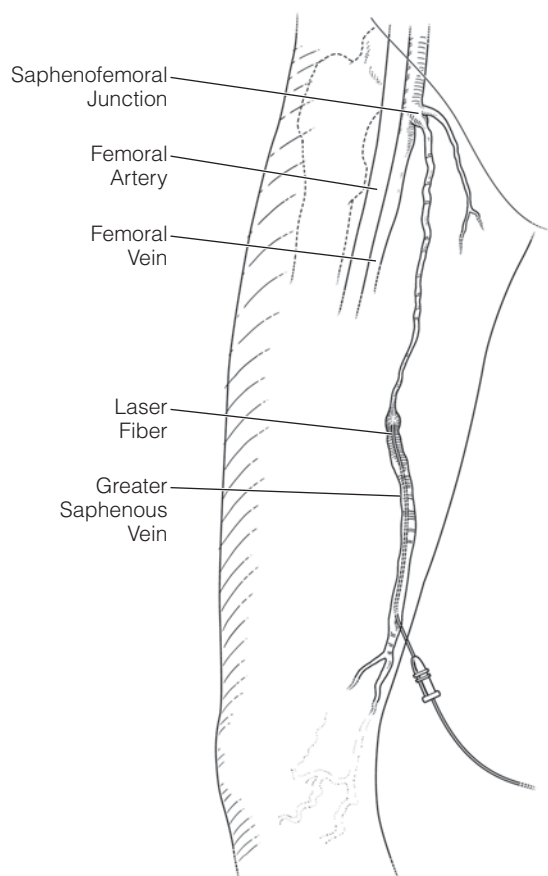
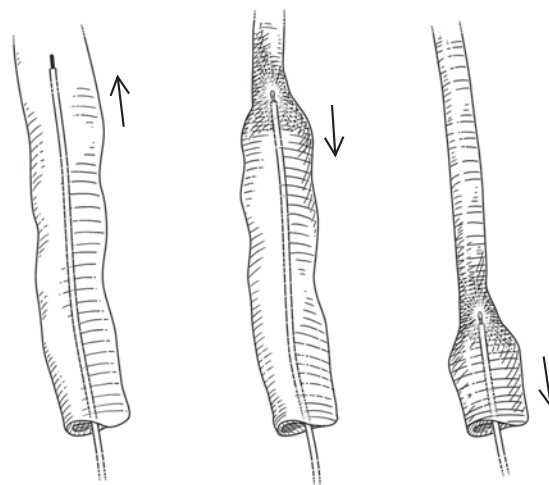


Figure 2 Ablation of great saphenous vein. Shown is percutaneous placement of a quartz fiber for laser ablation of the GSV. In practice, the catheter used for RF ablation is placed in a similar fashion. Both laser ablation and RF ablation deliver electromagnetic energy to the vein wall to destroy the vessel and remove it from the circulation.



two devices can be advanced and positioned as a single unit.

To this point in the procedure, no anesthesia other than the initial dermal injection has been employed. The next step, accordingly, is to initiate tumescent anesthesia, with or without epinephrine, along the saphenous compartment. The addition of epinephrine to the anesthetic solution results in improved constriction of the vein around the laser sheath, particularly when a saphenous vein larger than 12 mm in diameter is being treated; it also prolongs the analgesic effect of lidocaine, providing pain relief for as long as 6 to 8 hours after the procedure. A particular benefit of tumescent anesthesia is that the large volume of the injectate constitutes a heat sink that absorbs the heat created by the laser, thereby eliminating injury to surrounding soft tissue structures (e.g., nerves, fat, and skin). Further protection against injury is provided by rapid pullback of the laser fiber. As a result, the reported incidence of thermal skin or nerve injuries with laser vein ablation is almost zero.

Administration of the tumescent anesthesia solution starts at the sheath entry site and continues proximally until the entire vein segment to be treated exhibits a circumferential zone of echolucence. The vein is generally treated in the saphenous compartment between the superficial and deep fasciae of the leg. The anesthetic is administered via a 22-gauge needle with a 20 ml syringe or, alternatively, via a 10 ml autofill syringe or a Klein pump (both of which have the advantage of allowing more rapid administration with less risk of needle-stick injury to the staff). The needle is kept in a static position during administration, and the fluid is allowed to dissect up and down the fascial compartment.

Besides providing pain relief, tumescent anesthesia serves to move the saphenous vein being treated away from any structure that might be injured by the heat produced by the laser (e.g., the skin and the femoral vein). A 1 cm distance between the skin and the laser fiber is optimal. More liberal amounts of tumescent anesthesia

solution are administered when the vein being treated lies in close proximity to one or more nerves (e.g., the SSV and the calf portion of the GSV). As a rule, we prefer not to treat the subdermal portions of the GSV with laser ablation; the presence of an inflamed and tender vein just beneath the dermis is likely to lead to increased postoperative pain and noticeable skin discoloration. The superficial segments of the GSV are best treated with phlebectomy at the time of laser ablation.

When administration of the tumescent anesthesia solution is complete, the position of the laser fiber's tip is again confirmed. As the vein constricts, it also shortens, and this process may advance the tip of the laser fiber into the saphenofemoral or saphenopopliteal junction. If the tip is found to have moved in this manner, it is withdrawn until it is again 1 to 2 cm below the junction. A quick scan down the vein is done to confirm that the entire vein is surrounded by the anesthetic solution and is at least 1 cm from the skin.

At this point, the laser may be safely activated. The laser is always used in the continuous mode. The power setting may range from 10 to 12 W, depending on the physician's personal preference. We typically employ a 10 W setting for veins smaller than 10 mm and a 12 W setting for veins larger than 10 mm. The essential point is that between 50 and 100 J must be delivered to each centimeter of vein treated; according to one study, 70 J/cm is the ideal amount for reliable long-term vein obliteration.⁵ Energy delivery can easily be determined as the laser fiber is withdrawn. Most laser sheaths have markings 1 cm apart, and the laser machines have digital readouts that indicate the total amount of energy (J) delivered in real time. A simple calculation after 10 cm of the catheter has been withdrawn provides instant feedback on the energy delivered per centimeter of vein. On the 12 W power setting, delivery of the recommended amount of energy generally necessitates a pullback rate of 1 cm every 4 to 5 seconds (2.0 to 2.5 mm/sec). One group has advocated

delivery of 140 J/cm proximally (pullback rate of 1 mm/sec) and roughly 70 J/cm distally (pullback rate of 3 mm/sec), theorizing that for long-term success, more energy is required proximally.⁶ At the completion of the procedure, the laser is deactivated before the fiber is withdrawn from the skin. Ultrasonography is then performed to confirm that the common femoral vein and the superficial epigastric vein are patent and that the GSV is occluded.

An adhesive strip (e.g., Steri-Strip; 3M, St. Paul, Minnesota) covered by a transparent surgical adhesive dressing is applied over the entry site. The patient is then placed in a prescription compression stocking, which is worn for 1 to 2 weeks after the procedure. Whereas most physicians use a class 2 (30 to 40 mm Hg) compression stocking, we have switched to using a class 1 (20 to 30 mm Hg) stocking without observing any changes in complications (e.g., postoperative pain and swelling) or results. This switch has enhanced patient satisfaction, in that a class 1 stocking is easier to don and more comfortable to wear.

A 2003 study that followed 499 limbs over 2 years demonstrated a varicosity recurrence rate of less than 7% after ablation of the GSV with an 810 nm diode laser.⁷ This rate is comparable to or lower than those reported after traditional surgical stripping, RF ablation, and ultrasound-guided sclerotherapy. Several smaller studies documented similar outcomes, making it evident that laser vein ablation is both effective and safe when compared to other means of treating varicose veins [see Table 3].^{1,6,8-11}

At present, the question of how to manage residual varicosities after laser ablation remains controversial. The two main options are (1) to perform phlebectomy simultaneously with laser vein ablation and (2) to perform laser ablation alone, then observe the patient for spontaneous regression of varicosities. When the residual varicosities are left untreated, 10% to 20% of patients show sufficient regression to render further intervention unnecessary; however, 5% to 10% of patients experience superficial thrombophlebitis in the residual varicosities as a consequence of stasis from altered venous drainage. If delayed treatment of residual varicosities proves necessary, it may be accomplished with either phlebectomy or sclerotherapy, depending on the physician's preference. Our treatment of choice is laser vein ablation with concurrent phlebectomy. This approach adds only 10 to 20 minutes to the length of the procedure while offering the patient a more rapid and complete resolution of visible varicose veins and greatly reducing the risk of secondary thrombophlebitis.

Radiofrequency Ablation

In an attempt to minimize postoperative discomfort while main-

taining the benefits of saphenous vein ablation, RF alternating current has been employed to effect rapid thermic electrocoagulation of the vein wall and its valves. This approach is exemplified by the Closure procedure (VNUS Medical Technologies, Inc., San Jose, California). Prolonged exposure to the high-frequency energy results in total loss of vessel wall architecture, disintegration, and carbonization.¹² Ultrasonographic follow-up shows that treated saphenous veins disappear after the 2-year point. Clinical observations suggest that patients are much more comfortable after RF ablation than after surgical stripping.¹³

The technique of RF ablation is somewhat similar to that of laser ablation [see Figure 2] but differs in several important respects [see Laser Vein Ablation, above]. After percutaneous access is obtained, either a 6 or an 8 French RF radiofrequency catheter is placed 1 to 2 cm from the saphenofemoral junction, and tumescent anesthesia is instituted. The probe is connected to the RF generator box, the tines of the probe are exposed, and the unit is activated. The catheter is pulled back slowly (1 cm every 30 seconds) while its temperature and impedance are monitored. In the procedure as originally performed, the catheter was heated to 85° C, but current approaches often involve heating the catheter to 90° or 95° C with the aim of shortening the pullback time (to compete with the shorter pullback times characteristic of laser ablation). In general, however, pullback times are still somewhat longer with RF ablation than with laser ablation, allowing more dissemination of heat to surrounding tissue; postprocedural paresthesia continues to be reported in about 12% of cases.¹⁴ The technical results of RF ablation are excellent: with the Closure procedure, the closure rate at 4 years is 89%.¹⁴ However, the continued occurrence of paresthesias and the slower pullback times associated with RF ablation still appear to make laser vein ablation a safer and more rapid procedure.

The issue of recurrent varicosities after obliteration of the GSV without disconnection of the saphenofemoral junction tributaries is unsettled at present. It does appear, however, that endovenous RF ablation of the GSV (e.g., with the Closure procedure) prevents subsequent neovascularization in the groin. Many centers have reported that neovascularization does not occur in the absence of a groin incision.

The specific goal of endoluminal treatment of venous reflux is obliteration of the saphenous vein. Follow-up to 4 years shows that RF ablation with the Closure procedure accomplishes this goal.¹⁴

OUTCOMES AND COMPLICATIONS

Both EVLT and RF ablation have proved to be effective and safe

Table 3 Complications of Laser Vein Ablation and Radiofrequency (RF) Ablation in Selected Studies¹⁵

Ablation Method	Study	Limbs Treated (N)	Skin Burn (%)	Paresthesia (%)	Phlebitis (%)	DVT (%)	Recanalization (%)
Laser	Navarro ⁴³	40	0	0	0	0	0
	Proebstle ⁴⁴	109	0	0	10	0	10
	Min ⁷	504	0	0	5	0	2
	Perkowski ⁴⁵	154	0	0	0	0	3
RF	Weiss ⁴⁶	140	0	4	0	0	10
	Merchant ⁴⁷	318	4	15	2	1	15
	Hingorani ⁴⁸	73	0	0	0.3	16	4
	Merchant ¹⁴	1,078	2	12	3	0.5	11

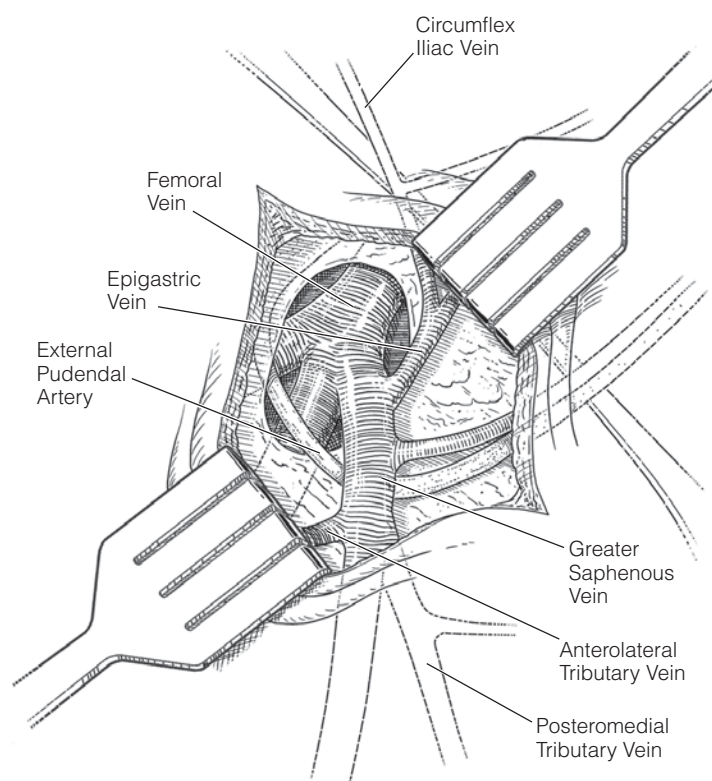


Figure 3 Shown are a typical saphenofemoral junction and the most important tributary vessels. The classic surgical approach dictates total disconnection of all tributaries at this junction.

for the treatment of venous reflux disease. Several studies that followed treated limbs for 2 years or longer have shown that with respect to efficacy, these modalities are equivalent or superior to standard surgical techniques.^{7,11,15,16} It is noteworthy that neovascularization seems to be almost nonexistent with endovenous procedures; this result appears to be related exclusively to standard ligation surgery.

Multiple studies have reported similar end-point results for EVLT and RF ablation: long-term occlusion of the GSV is consistently achieved at rates approaching or exceeding 90%. In general, EVLT has somewhat better long-term success rates, ranging from 92% to 95%; RF ablation generally yields success rates between 85% and 91%. The incidence of DVT (which is more accurately described as extension of thrombus from the treated vein into the deep venous system) is low with both procedures but is slightly higher with RF ablation. No cases of life-threatening pulmonary embolism have been reported with either EVLT or RF ablation, and both are associated with only negligible rates of superficial thrombophlebitis, cellulitis, (excessive) pain, and transient paresthesias.

A 2006 study stressed the importance of treating the posterior thigh circumflex vein so as to lower the incidence of recanalization.¹⁵ A large posterior thigh circumflex vein can drain cool blood into the segment being ablated, thus inhibiting proper heating of the refluxing segment and making adequate closure more difficult. Accordingly, the authors recommended ablating any posterior thigh circumflex veins larger 4 mm in tandem with the primary procedure.

Surgical Vein Stripping

Ligation of the GSV at the saphenofemoral junction [see Figure 3] has been widely practiced in the belief that it would control gravitational reflux while preserving the vein for subsequent arterial bypass.

It is true that the GSV is largely preserved after proximal ligation¹⁷; however, reflux continues, and hydrostatic forces are not controlled.¹⁸ Recurrent varicose veins are more frequent after saphenous ligation than after stripping.¹⁹ Varicosities also recur more frequently after ligation and sclerotherapy than after stripping and sclerotherapy.²⁰ A prospective, randomized trial that compared proximal GSV ligation and stab avulsion of varices with stripping of the thigh portion of the GSV and stab avulsion of varices showed the latter approach to be superior.^{21,22} Routine GSV stripping reduces the rate of recurrent varicosities and the need for reoperation for recurrent saphenofemoral incompetence.

Although it can be argued that the GSV should be retained for possible use in arterial bypass grafting, the relatively high (> 20%) reoperation rate makes this strategy undesirable. Almost three quarters of limbs that undergo GSV ligation alone have an incompetent GSV on follow-up duplex imaging. Until studies show a clear advantage to retaining the GSV in defined patient populations, surgical stripping should remain a routine part of primary GSV surgery. In several studies, preservation of the patency of the GSV and continuing reflux in this vein were found to be the factors most frequently associated with recurrence of varicosities.²³⁻²⁵ In one study of patients who underwent reoperation for relief of recurrent variceal symptoms, two thirds of the patients required removal of the GSV as part of the procedure.²³

Over the past 100 years, ankle-to-groin stripping of the GSV has been the dominant approach to treatment of varicose veins.²⁶⁻²⁸ It has been argued, however, that routine stripping of the leg (i.e., ankle-to-knee) portion of the GSV is inadvisable. One argument against this practice is that there is a significant risk of concomitant saphenous nerve injury [see Figure 4].¹⁹ Another argument is that whereas the objective of GSV removal is detachment of perforating veins emanating from the GSV in the thigh, the perforating veins in the leg are actually part of the posterior arch vein system rather than of the saphenous vein system. This latter argument notwithstanding, preoperative ultrasonography often demonstrates that the leg portion of the GSV is in fact directly connected to perforating veins. It is clear, however, that elimination of the refluxing thigh portion of the GSV frequently eliminates reflux in the calf portion of the vein, even when the calf portion is left behind. Therefore, removal of the GSV from ankle to knee generally is not necessary. If reflux subsequently becomes a problem in this portion of the vein, it can usually be controlled with sclerotherapy.

OPERATIVE TECHNIQUE

The surgical approach to vein stripping must be tailored to the individual patient and the individual limb being treated. As a rule, general or spinal anesthesia is required, though the procedure can also be performed with tumescent anesthesia. Groin-to-knee stripping of the GSV should be considered in every patient requiring surgical intervention.²⁹ In nearly all patients, this measure is supplemented by removal of the varicose vein clusters via stab avulsion or some form of sclerotherapy [see Table 4].

Step 1: Placement of Incisions

Preoperative marking, if correctly performed, will have documented the extent of varicose vein clusters and identified the clinical points where control of varices is required. Incisions can then be planned. As a rule, incisions in the groin and at the ankle should be transverse and should be placed within skin lines. In the groin, an oblique variation of the transverse incision may be appropriate. This incision should be placed high enough to permit identification of the saphenofemoral junction [see Figure 3]. The use of a portable ultrasound unit in the operating room facilitates placement of the inci-

sion directly over the saphenofemoral junction. Generally, throughout the leg and the thigh, the best cosmetic results are obtained with vertical incisions. Transverse incisions are used in the region of the knee, and oblique incisions are appropriate over the patella when the incisions are placed in skin lines.

A major cause of discomfort and occasional permanent skin pigmentation is subcutaneous extravasation of blood during and after saphenous vein stripping. Such extravasation can be minimized by using tumescent anesthesia around the vein to be stripped.

The practice of identifying and carefully dividing each of the tributaries to the saphenofemoral junction has been dominant over the past 50 years. The rationale for this practice is to avoid leaving behind a network of interanastomosing inguinal tributaries. Accordingly, special efforts have been made to draw each of the saphenous tributaries into the groin incision so that when they are placed on traction, their primary and even secondary tributaries can be controlled. The importance of these efforts has been underscored by de-

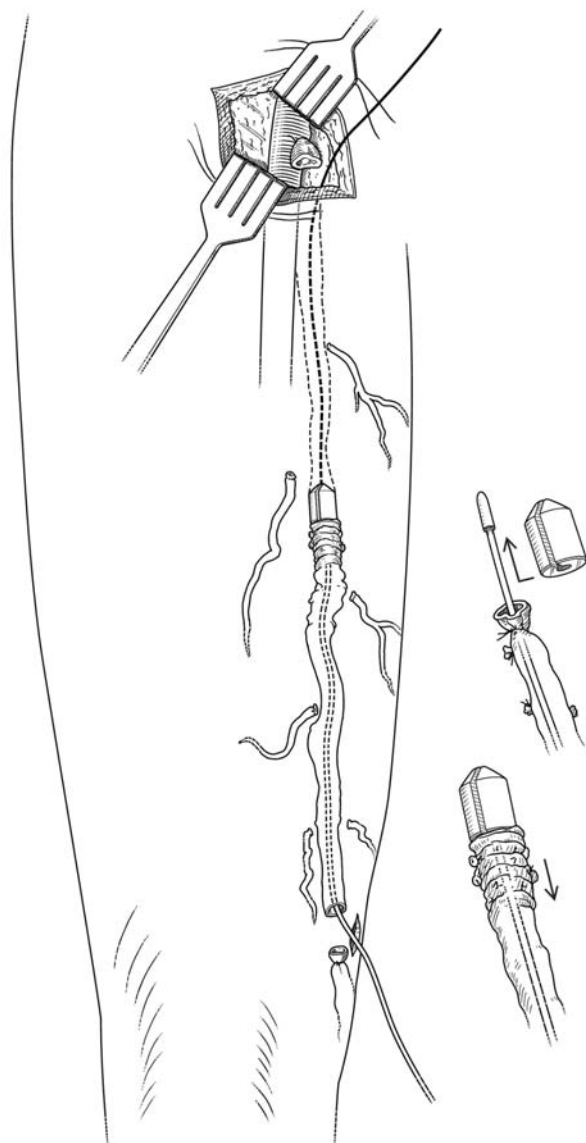


Figure 4 Surgical stripping of great saphenous vein. Illustrated is an early attempt to minimize distal incisions and prevent saphenous nerve injury at the knee. The stripper and its obturator are pulled to knee level, then retrieved through the groin incision. (Note division of perforating and communicating veins.)

Table 4 Methods of Variceal Ablation

Formal ligation, division, and excision
Stab avulsion
Sclerotherapy
With liquid sclerosant
With foamed sclerosant
Sclerotherapy aided by transillumination
Sclerotherapy aided by ultrasound guidance

scriptions of residual inguinal networks as an important cause of varicose vein recurrence.²³ Currently, however, this central principle of varicose vein surgery is under challenge, on the grounds that groin dissection can lead to neovascularization and hence to recurrence of varicosities [see Outcome Evaluation, below].

Step 2: Introduction of Stripping Device

Preoperative duplex studies having already demonstrated incompetent valves in the saphenous system, a disposable plastic Codman stripper can be introduced from above downward; alternatively, an Oesch stripper can be employed.³⁰ Both of these devices can be used to strip the GSV from groin to knee via the inversion technique [see Figure 5]. This approach has been shown to reduce soft tissue trauma in the thigh.³¹

In the groin, the stripper is inserted proximally into the upper end of the divided internal saphenous vein and passed down the main channel through incompetent valves until it can be felt lying distally approximately 1 cm medial to the medial border of the tibia at a point approximately 4 to 6 cm distal to the level of the tibial tubercle. The GSV is anatomically constant in this location, just as it is in the groin and ankle. If the GSV is removed from the groin to this level, both the midthigh perforating vein, which usually enters the GSV, and the most distal incompetent perforating veins, which are in the distal third of the thigh, will be treated.

A small incision is made over the palpable distal end of the stripper. The GSV will subsequently be divided through this incision, and the stripper and the inverted vein will be delivered through it. In exposing the GSV at knee level, the superficial fascia must be incised because the vein lies between this structure and the deep fascia of the thigh.

If the stripper passes unimpeded to the ankle, it can be exposed there with an exceedingly small skin incision placed in a carefully chosen skin line. Passage of the stripper from above downward to the ankle serves to confirm the absence of functioning valves, and stripping of the vein from above downward is unlikely to cause nerve damage. At the ankle, the vein should be carefully and cleanly dissected to free it from surrounding nerve fibers. If this is not done, saphenous nerve injury will result, and the patient will experience numbness of the foot below the ankle.

Step 3: Removal of Saphenous Vein

The previously placed stripper is pulled distally to remove the GSV. Although plastic disposable vein strippers and their metallic equivalents were designed to be used with various-sized olives to remove the GSV, in fact, a more efficient technique is simply to tie the vein to the stripper below its tip so that the vessel can then be inverted into itself and removed distally, usually at knee level.

Phlebectomy for Management of Residual Varicosities

Management of residual varicose veins after vein stripping traditionally has been done at the same time as the surgical procedure.

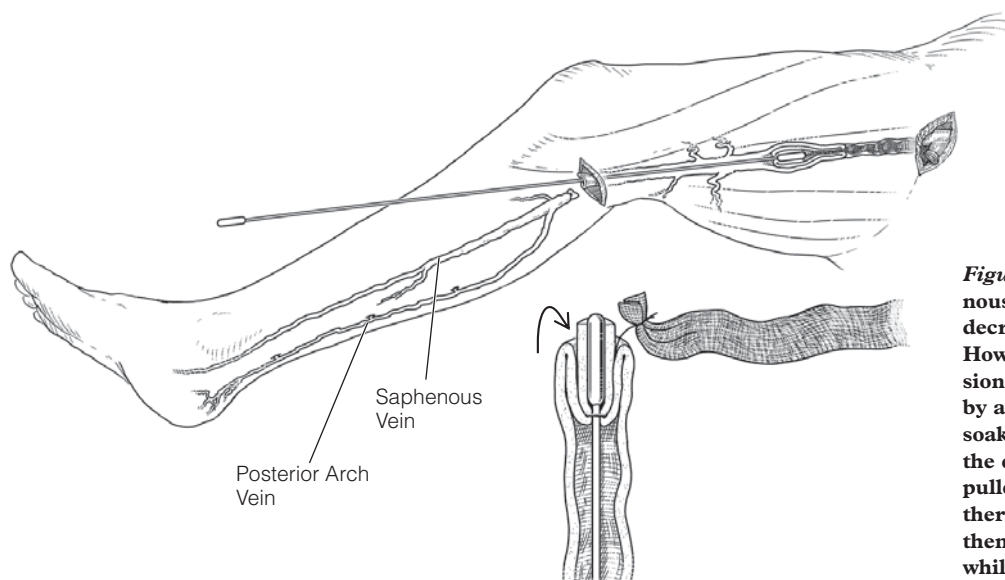


Figure 5 Surgical stripping of great saphenous vein. Inversion stripping of the GSV decreases soft tissue trauma in the thigh. However, tearing of the vein occurs on occasion. This problem may be largely prevented by attaching a corner of a 2 in. gauze roll soaked in lidocaine-epinephrine solution to the end of the stripper. As the stripper is pulled, the gauze is drawn into the vein, thereby assisting hemostasis. The gauze can then be left in place for 10 to 20 minutes while the stab wounds from the avulsion part of the procedure are being closed.

Management of residual varicose veins after vein ablation is more controversial. Currently, many physicians who treat vein disease are not familiar with the surgical technique of phlebectomy and therefore elect to wait for varicosities to regress after vein ablation. In 10% to 20% of cases, enough regression of varicose veins occurs after ablation that no further treatment is required. If delayed treatment proves necessary, it may be accomplished by means of either phlebectomy or sclerotherapy, depending on the physician's preference.

The technique of phlebectomy is easy to learn. A tumescent anesthesia solution is infused between the skin and the superficial fascia of the leg in the area of the previously marked varicosities. The infusion of the anesthetic tends to dissect the GSV away from the surrounding tissue and causes vasoconstriction. Vertical incisions 1 to 3 mm in length are made where appropriate. In the anterior knee and ankle regions, where skin lines are obviously horizontal, incisions are hidden in the lines [see Figure 6]. Varicosities are exteriorized by means of hooks or forceps; particularly useful for this purpose are specially designed vein hooks such as the Varady dissector, the Muller hook, and the Oesch hook [see Figures 7 and 8].³² Nothing should penetrate the skin other than the small end of the hook. Usually, the vein is easily distinguished from the surrounding fat by its taut rubber band feel. The vessel is brought out of the skin, then removed proximally and distally by using a hand-over-hand technique with mosquito clamps. Eventually, the vein tears in each direction, but because of the epinephrine in the tumescent anesthesia solution, very little bleeding occurs. The procedure is continued in a proximal-to-distal direction until all varicose clusters have been removed; generally, between 10 and 15 incisions are required for removal of all clusters. Veins of any size can be removed by means of this technique, even in the office setting. In patients who have had superficial phlebitis or have previously undergone sclerotherapy, the veins typically are fibrotic and adherent to the surrounding tissue and cannot be easily removed. If treatment of such veins proves necessary at some point in the future, sclerotherapy is generally the method of choice.

When all phlebectomies have been completed, small elastic strips are used to close the skin incisions. A compressive dressing is applied for 24 hours to minimize bleeding, bruising, and swelling. When the procedure is done properly, the incisions are invisible by 6 to 8 weeks and the patients are very happy with the results. Experienced workers in Europe have achieved marked refinements of phlebectomy techniques for varicose clusters.³³

COMPLICATIONS

Surgical removal of the GSV on an outpatient basis still requires two incisions, one in the groin and the other near the knee. Postoper-

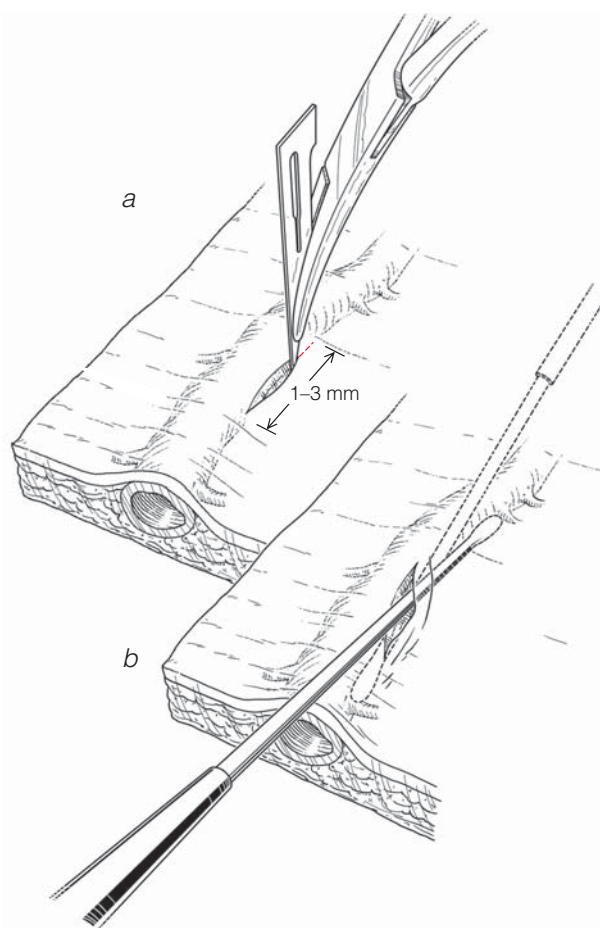


Figure 6 Surgical stripping of great saphenous vein: phlebectomy for residual varicosities. (a) Skin incisions for stab avulsion of varicosities are limited with respect to both length and depth. (b) The dissector blade facilitates mobilization of the vein before removal.

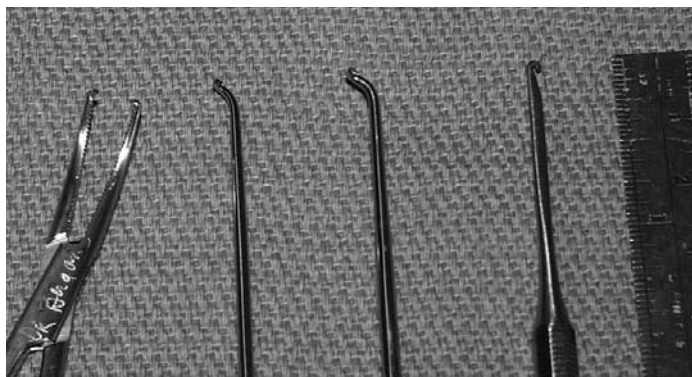


Figure 7 Surgical stripping of great saphenous vein: phlebectomy for residual varicosities. Shown are tools used for exteriorizing varicosities: a Hartman clamp with its single tooth placed distally, two Muller clamps, and a Varady hook and dissector (left to right).

ative compression bandaging is standard, and most patients experience little downtime. Some, however, do experience hematoma, pain, and extensive bruising. These three complications are linked; thus, every effort should be made to prevent oozing. The most feared complication of varicose vein surgery is venous thromboembolism, but the incidence of this complication is quite low (probably about 1%). In countries where postoperative immobilization, hospitalization, and delayed ambulation are employed for patients with varicosities, prophylaxis against venous thromboembolism is common. In the United States, however, this measure is generally considered unnecessary in these patients. The most common complication of varicose vein surgery is recurrence of varicosities, which is experienced by 15% to 30% of patients treated.²⁴

To speak of permanent removal of varicosities implies that all potential causes of recurrence have been considered and that surgical management has been planned so as to address them. There are four principal causes of recurrence of varicose veins, three of which can be dealt with at the time of the primary operation.

One cause of recurrent varicosities is failure to perform the primary operation correctly. Common errors include missing a duplicated saphenous vein and mistaking an anterolateral or accessory saphenous vein for the GSV. Careful and thorough anatomic identification will help minimize such errors. It has long been held that a second cause of recurrent varicose veins is failure to do a proper groin dissection; however, it is now known that such dissection causes neovascularization in the groin, leading to recurrence of varicose veins [see Outcome Evaluation, below]. A third cause is failure to remove the GSV from the circulation. A reason often cited for this failure is the desire to preserve the GSV for subsequent use as an arterial bypass, but it is clear that the preserved GSV continues to reflux and continues to elongate and dilate its tributaries, thereby producing more varicosities even after primary operative treatment has removed the varicose veins present at the time. A fourth cause of recurrent varicosities is persistence of venous hypertension through nonsaphenous sources—chiefly perforating veins with incompetent valves. Muscular contraction generates enormous pressures that are directed against valves in perforating veins. Venous hypertension induces a leukocyte endothelial reaction, which, in turn, incites an inflammatory response that ultimately destroys the venous valves and weakens the venous wall.³⁴ The perforating veins most commonly associated with recurrent varicosities are the midthigh perforating vein, the distal thigh perforating vein, the proximal anteromedial calf perforating vein, and the lateral thigh perforating vein, which connects the deep femoral vein to surface varicosities.

In addition to the four principal causes of recurrent varicosities, there is a fifth cause, which is beyond the operating surgeon's control—namely, the genetic tendency to form varicosities. This tendency results in the development of localized or generalized venous wall weakness, localized blowouts of venous walls, or stretched, elongated, and floppy venous valves.^{35,36}

OUTCOME EVALUATION

As a rule, when undesirable outcomes occur after surgical saphenous vein stripping, they become evident quite early.²¹ As noted (see above), it has long been accepted practice to dissect tributary vessels at the saphenofemoral junction very carefully, taking each of the vessels back beyond the primary and even the secondary tributaries if possible.³¹ In practice, however, such dissection appears to cause neovascularization in the groin³⁷; surveillance with duplex ultrasonography supports this finding.³⁸ It has now been amply confirmed that neovascularization causes recurrent varicose veins. Clearly, this is a significant disadvantage of standard surgical treatment of varicosities. This disadvantage has been a major impetus for the development of less invasive alternatives to surgical saphenous vein stripping [see Endovenous Procedures, above, and Foam Sclerotherapy, below]. These alternatives are proving to be effective and may be superior to surgical stripping, if only because they are not followed by groin neovascularization.

Foam Sclerotherapy

The prospect of a rapid, minimally invasive, and durable treatment of varicose veins is an attractive one. Current evidence suggests that these objectives may be achieved without operative intervention by using sclerosant microfoam [see Figure 9]. In 1944 and 1950, E. J. Orbach introduced the concept of a macrobubble air-block technique to enhance the properties of sclerosants in performing macrosclerotherapy.^{39,40} At the time, few clinicians evinced much interest in the subject, and the technique languished.

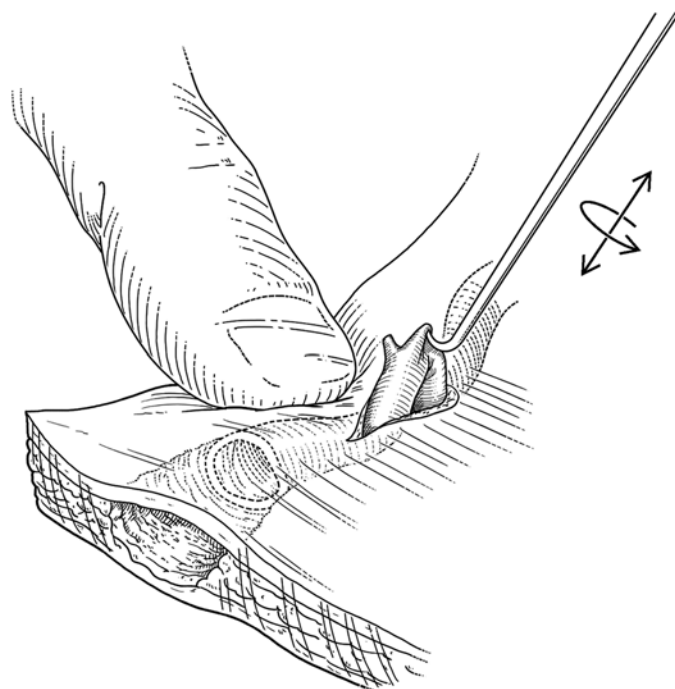


Figure 8 Surgical stripping of great saphenous vein: phlebectomy for residual varicosities. The varix is exteriorized with a hook, then divided to permit proximal and distal avulsion.

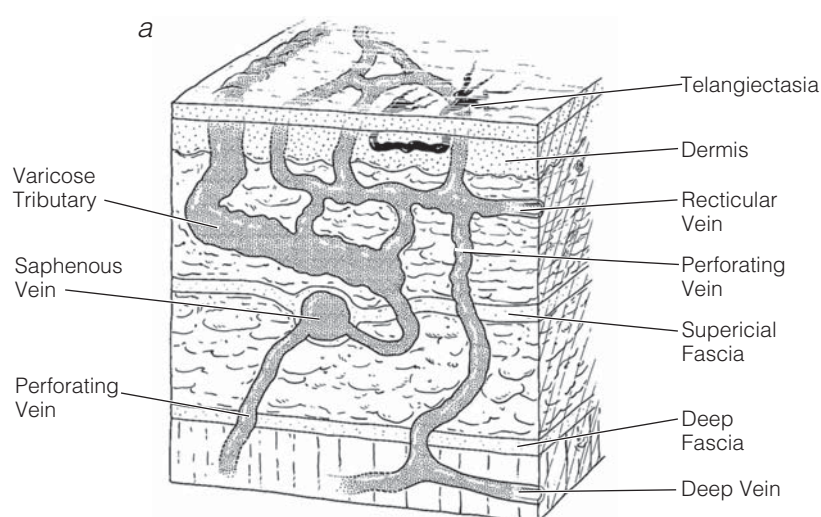


Figure 9 Microfoam sclerotherapy. (a) The relationships among the venous structures in a lower extremity with varicosities explain why microfoam sclerotherapy can succeed. Injections into varices, reticular veins, or perforating veins can place the foam into varicose structures and even into telangiectatic blemishes. (b) Sclerosant foam is made by mixing room air with 0.5% sodium tetradecyl sulfate (STS) in a 2:1 ratio via a three-way stopcock. The syringes are emptied 35 times to create a foam that lasts about 5 minutes. (c) A halogen light (vein light), as used here during a foam injection, is helpful for treating persistent or recurrent varices along with the GSV in situations where surgery is undesirable.

Half a century later, the work of Juan Cabrera and colleagues in Granada attracted the attention of some phlebologists and reawakened interest in using foam technology for the treatment of venous insufficiency.⁴¹ These investigators showed that foam sclerotherapy was technically simple and worked well in small to moderate-sized varicose veins, and they demonstrated that the limitations of liquid sclerotherapy could be erased by using microfoam. Their 5-year report represents the longest observation period to date for microfoam sclerotherapy for varicose veins. In most of the cases, a single injection sufficed to treat saphenous veins and varicose tributaries. Extensive vasospasm was seen immediately, but compression was applied after treatment. Complete fibrosis of the saphenous vein was achieved in 81% of cases, and patency with reflux persisted in only 14%. Tributary varicosities disappeared in 96% of cases. Vessels that remained open and were refluxing were successfully closed with retreatment.

A subsequent study demonstrated that even severely affected

limbs could be safely and effectively treated by means of foam sclerotherapy combined with compression.⁴² In this study, limbs affected by lipodermatosclerosis, atrophie blanche, or even open venous ulcers showed statistically significant improvement after the injection of a foamed sclerosant followed by compression with a medical-grade stocking or an Unna boot. The study results also underscored the importance of applying compression immediately after the injection of the sclerosant. Limbs that underwent foam sclerotherapy and compression healed better and more quickly than limbs that were treated by sclerotherapy alone.

If subsequent work continues to confirm these favorable results, it may be that microfoam sclerotherapy will eventually replace all other methods of varicose vein treatment. As of December 2006, however, foam sclerotherapy had not been approved by the United States Food and Drug Administration, because of concerns about potential air embolization after the injection of the sclerosant.

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Figures 2 through 6, 8, and 9a Tom Moore.

19 ENDOVASCULAR PROCEDURES FOR LOWER-EXTREMITY DISEASE

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Endovascular procedures are increasingly being applied to the treatment of lower-extremity vascular disease: for many common vascular conditions, minimally invasive approaches have become important supplements to (or even supplanted) conventional open surgical approaches.¹ The evolution of these endovascular techniques is likely to result in a corresponding evolution in the therapeutic decision-making process for patients with lower-extremity vascular disease. Research into the long-term outcomes of lower-extremity endovascular procedures will be necessary for a better understanding of the indications for treatment and of the risks and benefits for patients.

Arterial Procedures

Arterial conditions of the lower extremity that may be treated with endoluminal therapy include chronic ischemia, acute ischemia, and aneurysmal disease. The fundamental skill set and the basic techniques employed are the same for all of these conditions. Accordingly, the ensuing discussion first reviews the basics of endovascular therapy and then focuses on specific areas of chronic, acute, and aneurysmal arterial disease of the lower extremity that are amenable to endoluminal intervention.

BASIC ENDOVASCULAR PROCEDURES

Preprocedural Evaluation

Clinical evaluation The first step in the intervention consists of a thorough history and a careful physical examination. Patients should be specifically asked about chronic renal insufficiency, current or past anticoagulant therapy, and previous vascular and endovascular interventions. Lower-extremity pulses should be assessed, and the degree of ischemia present should be determined [see Table 1]. Basic serum biochemical and hematologic data should be obtained and reviewed. The results of any previous imaging studies should also be obtained and reviewed. Patients with serum creatinine concentrations higher than 1.5 mg/dl should be considered for a renal protection protocol [see Table 2], and at the time of the procedure, the use of an alternative contrast

agent to decrease total nephrotoxic dye volumes (see below) may be considered. Patients taking oral hypoglycemic agents are asked to stop doing so on the day of the procedure and not to resume for 48 hours after the procedure. In general, to prevent bleeding complications, it is preferred that the international normalized ratio (INR) be lower than 1.6 and the platelet count higher than 50,000/mm³ at the time of intervention.

If a therapeutic intervention is planned, the patient should be given aspirin, 81 mg/day, and clopidogrel, 75 mg/day, for at least 3 days beforehand. If there is not enough time to do this, the patient may be given clopidogrel, 150 to 300 mg, within the 2 hours preceding the procedure.

Investigative studies Imaging is required before any intervention. Noninvasive vascular ultrasonographic studies document the initial status of the arterial blood supply and allow localization of the culprit lesions. The ankle-brachial index (ABI) (or, in diabetics and patients with incompressible ankle vessels, the toe-brachial index), pulse-volume recordings (PVRs), and segmental pressures quantify arterial perfusion and define areas of stenosis or occlusion within each leg. Duplex ultrasonography is an alternative to PVRs and segmental pressures and provides further diagnostic information that allows the interventionalist to identify involved vessel segments and lesions amenable to percutaneous therapy. These objective measurements serve as a baseline against which postinterventional results may be assessed.

Generally, noninvasive studies provide sufficient information to allow one to proceed with diagnostic angiography and possible endoluminal intervention. In many cases, however, additional studies are required to refine the interventional plan and to reduce the time and resources required. Computed tomographic angiography (CTA) provides two-dimensional images of the arterial system, which are then postprocessed to generate three-dimensional reconstructions. It is particularly effective for imaging tibial vessels. The main drawbacks of CTA are the time necessary to reconstruct the images, the possibility of interference from metal implants, and the contrast load involved. Magnetic resonance angiography (MRA) also provides potentially helpful preprocedural

Table 1 Classification of Critical Ischemia

Grade	Limb Status	Prognosis for Limb	Capillary Refill	Motor Changes	Sensory Loss	Arterial Doppler US	Venous Doppler US
I	Viable	Not threatened	Intact	None	None	+	+
IIa	Threatened	Salvageable	Slow	None	Partial	—	+
IIb	Threatened	Salvageable with emergency intervention	Slow or absent	Diminished function	Partial	—	+
III	Irreversible	Nonsalvageable	Absent	No function	Complete	—	—

US—ultrasonography

Table 2 Renal Protection Strategies

Oral Therapy	Other Strategies
<i>N</i> -acetylcysteine, 600 mg p.o., b.i.d., for total of four doses; first dose given 12 hr before procedure Theophylline, 200 mg I.V., given 30 min before procedure, or 200 mg p.o., b.i.d., starting 24 hr before procedure and continued for 48 hr after procedure	Hydration with normal saline, starting 1 hr before procedure and continued for 3 hr after procedure Sodium bicarbonate drip, 154 mEq/L, starting 1 hr before procedure and continued for 6 hr after procedure Use of alternative contrast agent

information and has the advantage of using gadolinium, which is a relatively low risk contrast agent for patients with renal insufficiency. The main drawbacks of MRA are relatively poor patient tolerance of the machine, the tendency to overestimate lesion severity, the long image acquisition time, and the variability in image quality as one proceeds distally in the leg. Patients with limited arterial access will benefit from a cross-sectional imaging algorithm: such an approach allows one to perform a focused angiogram and to make more efficient use of resources during a therapeutic intervention.

Preprocedural Planning

Choice of arterial access site The common femoral artery (CFA) contralateral to the affected side is the arterial access site most commonly employed. If the patient has an occluded CFA or a “hostile groin,” a radial, high brachial, or axillary artery approach may be chosen instead; however, access at these sites is associated with a relatively higher incidence of complications. Ideally, to facilitate manual compression, the access site should lie over a flat bony prominence. An antegrade ipsilateral CFA approach is a useful alternative to contralateral access if there is a contraindication to working from the contralateral side (e.g., significant contralateral iliac disease, a heavily scarred groin, recent application of a vascular closure device, or a bifurcated aortic graft) and if preoperative imaging has demonstrated that there is an adequate working distance (generally, at least 15 to 20 cm) between the CFA access point and the target lesion. If an antegrade approach fails, a retrograde approach may be employed to target ipsilateral iliac arterial disease from the CFA or superficial femoral artery (SFA) disease from the popliteal artery.

Selective Lower-Extremity Angiography

Technique Standard methods of obtaining vascular access for angiography are described in more detail elsewhere [see 6:8 *Fundamentals of Endovascular Surgery*]. For selective angiography of the lower extremity, a 4 or 5 French diagnostic sheath is initially placed in the CFA contralateral to the affected extremity. A 4 or

5 French multi-side-hole diagnostic catheter (in a straight, curved, or pigtail configuration) is then placed over a wire into the juxtarenal aorta. After the initial aortic films are obtained in the anteroposterior (AP) projection, the diagnostic catheter is moved down to a point 2 to 3 cm above the aortic bifurcation, and a series of pelvic images are taken in the AP and lateral projections.

The aortic bifurcation is generally traversed with a curved catheter; the curve of the tip should be similar to the angle of the bifurcation. A wire is maneuvered into the iliac system and positioned in the external iliac artery or the CFA, and the curved diagnostic catheter is advanced to the point where its tip lies within the distal external iliac artery and its holes are beyond the ostium of the internal iliac artery.

Once the catheter has been correctly positioned, further contrast injections are performed. Complete lower-extremity images, which should include tibial and pedal vessels (in AP and magnified lateral foot views), are taken before the intervention so that preprocedural status can be compared with postprocedural status and any distal complications can be recognized. Contrast doses commonly employed for digital subtraction arteriography (DSA) depend on the specific arterial segment being addressed [see Table 3].

Alternative contrast agents. Standard angiography is performed with an iodinated nonionic contrast agent. In patients with creatinine concentrations higher than 1.5 mg/dl, an alternative contrast agent may be preferable. Carbon dioxide may be used to image the abdominal aorta, the iliac arteries, and, occasionally, the proximal leg arteries. As the vessels become smaller, however, CO₂ images become less clear. Elevating the legs may help in obtaining adequate imaging to the level of the knees. For CO₂ imaging, a 60 ml syringe is connected to a three-way stopcock, and CO₂ from a tank is loaded into the syringe through the stopcock assembly while the stopcock is submerged in normal saline and manually kept under pressure. The submerged system is flushed with CO₂ several times to purge any residual air. The CO₂-containing syringe is connected to an indwelling catheter, and the CO₂ is then injected forcefully by hand while the fluoroscopy unit is activated. The resulting images must undergo postprocessing to be viewed correctly. CO₂ imaging should not be used above the diaphragm or in the visceral artery segment of the aorta.

Gadolinium may also be used to image the pelvic vessels and the proximal leg arteries. Like CO₂ images, gadolinium images become less clear as the lower-extremity arteries become smaller and more distal. Gadolinium is loaded into the power injector or injected by hand, like standard contrast agents. Doses higher than 0.3 mmol/kg may be nephrotoxic.²

Troubleshooting If crossing the aortic bifurcation proves difficult, changing to a hydrophilic wire (e.g., a 0.035-in. soft or

Table 3 DSA Imaging Techniques with Power Injector

Arterial Segment Imaged	View	Contrast Dosage	Delay
Infrarenal aorta	AP	10–20 ml/sec for 2 sec	No
Iliac arteries	AP/oblique	3–10 ml/sec for 2–3 sec	No
CFA and SFA	AP	3–10 ml/sec for 2–3 sec	Flow dependent
Tibial arteries	AP	3–5 ml/sec for 3–4 sec	Yes
Pedal artery	AP/lateral foot	3–6 ml/sec for 3–4 sec	Yes

AP—anteroposterior CFA—common femoral artery SFA—superficial femoral artery

stiff glide wire) may help. Occasionally, if one has trouble advancing the 5 French catheter, using a 4 French hydrophilic catheter may mitigate the problem. Attempts at passing the bifurcation should not be abandoned until several different angled catheters have been tried. If all such attempts fail and contralateral access is imperative, ipsilateral puncture with introduction of a snare to grasp the contralateral wire in the abdominal aorta should be considered. Alternatively, DSA may be performed from the aortic bifurcation; however, the contrast loads will be significantly higher in this situation.

Crossing of Lesion

The diagnostic imaging studies and the preliminary angiogram should suffice to identify a lesion that is amenable to endovascular therapy. Once such a lesion is identified, wire access across the target lesion is required to establish a platform for subsequent intervention.

Technique Iliac lesions may be approached either in a retrograde fashion from the ipsilateral CFA or in an antegrade fashion from the contralateral CFA if there is adequate working distance between the bifurcation and the iliac lesion. For more distal lesions, when a contralateral CFA approach is used, a guide sheath is required to stabilize catheters and wires. A wire is placed in the external iliac artery on the affected side (see above), and the diagnostic catheter placed across the bifurcation is replaced with a stiff sheath, such as a 6 French Balkin sheath (Cook Incorporated, Bloomington, Indiana), which has a curve that naturally rests over the bifurcation. Occasionally, it is difficult to get the sheath to cross the bifurcation. In such a situation, the initial wire may be exchanged for a stiffer wire, such as a 0.035-in. Amplatz wire (Cook Urological, Spencer, Indiana), and the sheath may be placed over this wire. The use of a reinforced or stiff guide sheath eliminates the mechanical disadvantage of a wire that moves away from the limb with all manipulations, and it solidifies unilateral limb access for subsequent angiography during the therapeutic portion of the procedure.

Once the sheath is in place, a long, angled end-hole catheter and a glide wire are directed toward the specific vessel segment being treated and carefully manipulated so as to cross the target lesion. Road mapping, fluoroscopy fade, or intermittent puffing of contrast material through the guide catheter can delineate the contours of the vessel, identify the correct path to take, and help keep the wire within the true lumen. In general, a stenosis can be crossed by a curved or J-tip wire, a 0.035-in. hydrophilic glide wire, or a Wholey wire (a 0.035-in. wire with a floppy tip; Mallinckrodt, St. Louis, Missouri). The hydrophilic coating on the glide wire makes it more prone to dissection than the other wires are. With angled catheters, it is essential to use torque devices to direct the tip of the wire in the appropriate direction. In some cases, using a TAD II wire with a 0.018-in. distal tip and a 0.035-in. main body (Mallinckrodt, St. Louis, Missouri) makes access through a tight lesion easier to obtain; in addition, it provides a transition to a larger, more robust wire, which can be a very effective platform. For tibial stenoses, a 0.014-in. or 0.018-in. system is generally employed to cross tighter lesions. To stabilize the 0.014-in. wire, a 3 or 4 French catheter may be used as a guide catheter, placed just proximal to the lesion.

Occlusions can be difficult to cross, particularly when significant calcification is apparent on the plain films obtained before angiography. The techniques employed are the same as those used to cross a stenosis. The goal is to traverse the occlusion and gain access to the true lumen distally; accordingly, a J-tip or Wholey

wire may be preferred, in that hydrophilic wires tend to create dissection planes. Often, the occlusion cannot be crossed, and a subintimal plane must be developed. A glide wire is used to gain access near the proximal portion of the lesion at a branch point and allowed to deform in such a way as to form a loop; the wire is then pushed forward, supported by a 4 or 5 French catheter. Often, the true lumen is accessed without any difficulty, and the location of the wire within the lumen is confirmed by contrast injections. Occasionally, however, reentry into the true lumen proves difficult. Various manipulations and techniques may be employed to help with this technical issue. In addition, two systems have been developed with this potential problem in mind. The CrossPoint IVUS catheter (Medtronic, Minneapolis, Minnesota) combines an intravascular ultrasound probe with a puncture needle and allows one to visualize the true lumen, enter it with a hollow needle, and pass a wire to maintain access. The Outback catheter (LuMend, Redwood City, California) has a special tip that microdissects the plaque to facilitate reentry into the true lumen. If these options fail, retrograde puncture and retrograde passage of a wire, with interval snaring to “floss” the occlusion, may be considered.

Troubleshooting In crossing occlusions, the following three points must be emphasized.

1. Care must be taken to ensure that the operator is in the true lumen.
2. To preserve subsequent bypass targets, the next segment of the vessel must not be compromised by an overly aggressive attempt to regain access from a subintimal dissection plane.
3. Wire access across the lesion must be maintained at all times.

A low-dose intravenous bolus of heparin (2,000 to 5,000 IU) must be given before any intervention to help prevent the thrombosis that may result from manipulation and transient occlusion of the lesion.

Angioplasty and Stenting

Technique *Angioplasty.* Angioplasty is the initial treatment for most lower-extremity lesions. It may be the only therapeutic intervention required, or it may be employed as a prelude to stent deployment as a means of ensuring that the arterial lumen is wide enough to allow free passage of a platform. Angioplasty balloons exist in several varieties, which are reviewed in more detail elsewhere [see 6:8 *Fundamentals of Endovascular Surgery*]. In general, a noncompliant balloon is chosen that is 1 to 2 mm smaller than the normal or anticipated final vessel diameter for the area of the vasculature being addressed. The normal vessel diameter may be estimated on the basis of operator experience, measured with a radiopaque ruler placed alongside the vessel, or quantitated with the calibration software available on most imaging systems.

Once the balloon has been successfully maneuvered into position across the lesion, it is inflated with a manual inflation device to allow controlled delivery of a defined pressure load. Inflation is continued until the waist of the balloon disappears or maximal balloon inflation pressure (8 to 15 atm on most standard balloons) is reached. If an optimally sized balloon or stent will not cross a highly stenotic lesion, preangioplasty dilatation with a lower-profile, smaller-diameter balloon is required.

If the lesion is in close proximity to or involves a bifurcation (e.g., the aortic bifurcation, the femoral bifurcation, or the tibioperoneal trunk), care must be taken to prevent occlusion of the other branching vessel during dilatation of the target lesion. To this end, most interventionalists advocate use of the so-called kissing balloon technique, which involves simultaneous dilatation or

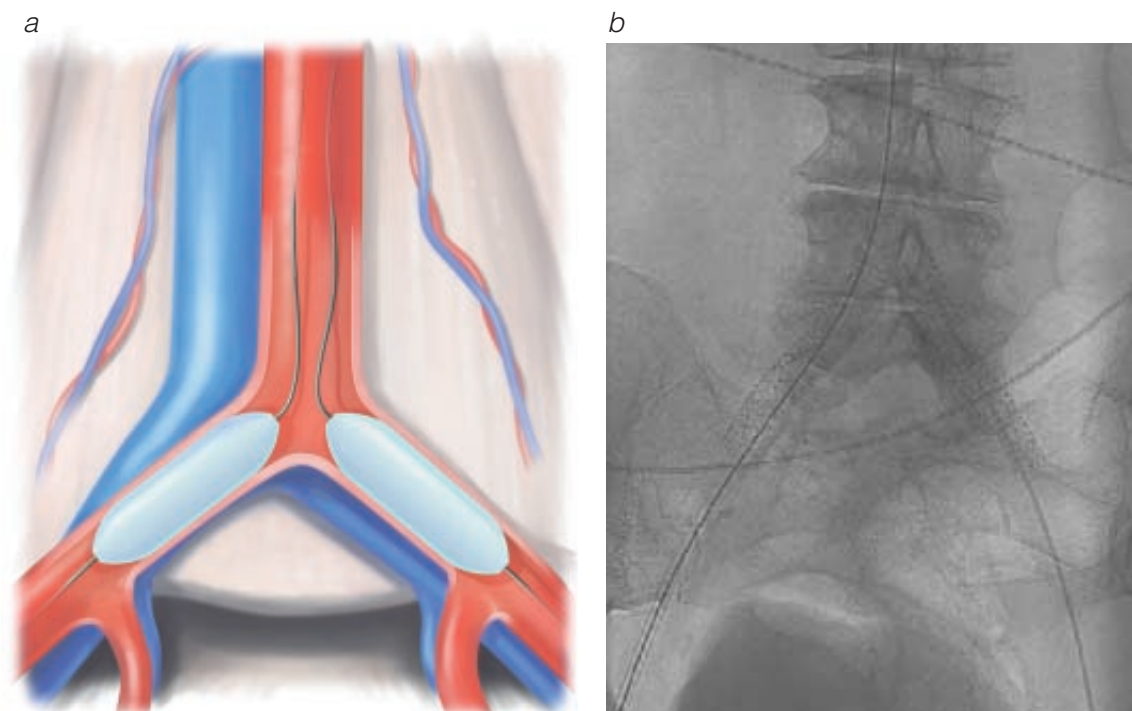


Figure 1 Basic endovascular techniques: angioplasty and stenting. Shown is the so-called kissing balloon technique. The patient presented with bilateral claudication, a decreased ABI on exercise treadmill testing, and a duplex ultrasonogram that suggested iliac occlusive disease. (a) Illustration shows two balloons “kissing” in the common iliac arteries. (b) Radiograph shows two stents “kissing” in the iliac arteries.

stenting of both branching vessels of the bifurcation to preserve both lumina. This technique is most commonly employed for proximal common iliac artery lesions [see Figure 1]. Alternatively, one may place a guard wire in the unaffected vessel and use this wire as a safety measure if there is a danger of luminal compromise, or one may deploy a balloon in the unaffected ostium while the affected ostium is treated.

Stenting. Basic stent choices are discussed more fully elsewhere [see 6:8 *Fundamentals of Endovascular Surgery*]. Stents may be placed either primarily or as a secondary procedure when initial angioplasty yields inadequate results (generally defined as either greater than 30% residual stenosis or the occurrence of an angioplasty-related complication, such as arterial wall perforation or flow-limiting dissection). Stents are generally sized according to the normal diameter of the adjacent vessel; 10% to 15% oversizing is acceptable. If the stent will be crossing two vessel segments with mismatched diameters (e.g., the common iliac artery and the external iliac artery), it is preferable to use a self-expanding stent, which is better able to adjust to such mismatching. Treatment of specific arteries is discussed more fully in connection with management of chronic lower-extremity ischemia [see Procedures for Chronic Lower-Extremity Ischemia, below].

Adjuncts to angioplasty and stenting. Over the past few years, several innovative devices have been developed that expand on the basic concepts of angioplasty and stenting in the lower extremities. One such device is the PolarCath cryoplasty balloon (Boston Scientific, Natick, Massachusetts) [see Figure 2a]. This device delivers cold thermal energy to the vessel wall in the form of nitrous oxide (-10°C) and is inflated to a pressure of 8 atm. It is presumed that the freezing of the vessel allows a more controlled vessel wall injury

and concomitantly promotes apoptosis and reduces the restenosis response. To date, the PolarCath has been employed mainly in the SFA; it is currently being tested for use in the tibial vessels. In initial reports, anatomic patency rates in the femoropopliteal arteries have exceeded 80% at 1 year for TransAtlantic Inter-Society Consensus (TASC) grade A, B, and C lesions.³

Another such device is the Peripheral Cutting Balloon (Boston Scientific, Natick, Massachusetts) [see Figure 2b], which is increasingly being used on lower-extremity vascular lesions, particularly those that proved resistant to balloon angioplasty. This device consists of a noncompliant balloon that has four thin blades placed longitudinally around it; it is available in sizes ranging from 2 mm to 8 mm, and it operates over a 0.018-in. platform. The theoretical rationale for its use is that fracturing or cutting the lesion in a controlled pattern may reduce the severity of the vessel injury while achieving a satisfactory luminal response and mitigating the restenosis response. Initial results in stenotic vein grafts have been encouraging, with 95% patency reported at 11 months' follow-up in one small study.⁴

Directional atherectomy devices are being used to treat chronic atherosclerotic leg ischemia in the belief that debulking the lesion will allow greater increases in luminal diameter than the conventional methods of angioplasty and stenting, which merely displace plaque. Multiple different systems are available, all of which appear to be yielding roughly equivalent results. One of the more widely used directional atherectomy devices is the SilverHawk Plaque Excision System (FoxHollow Technologies, Redwood City, California), which consists of a catheter that is compatible with a 0.014-in. wire and that has a rotating blade at the tip. As the blade shaves plaque off the vessel wall, the shavings are stored in the tip of the catheter. When the storage unit in the tip becomes full, the catheter is removed and cleaned, then reinserted. Initial intermediate-term results have been satisfactory; however, wider

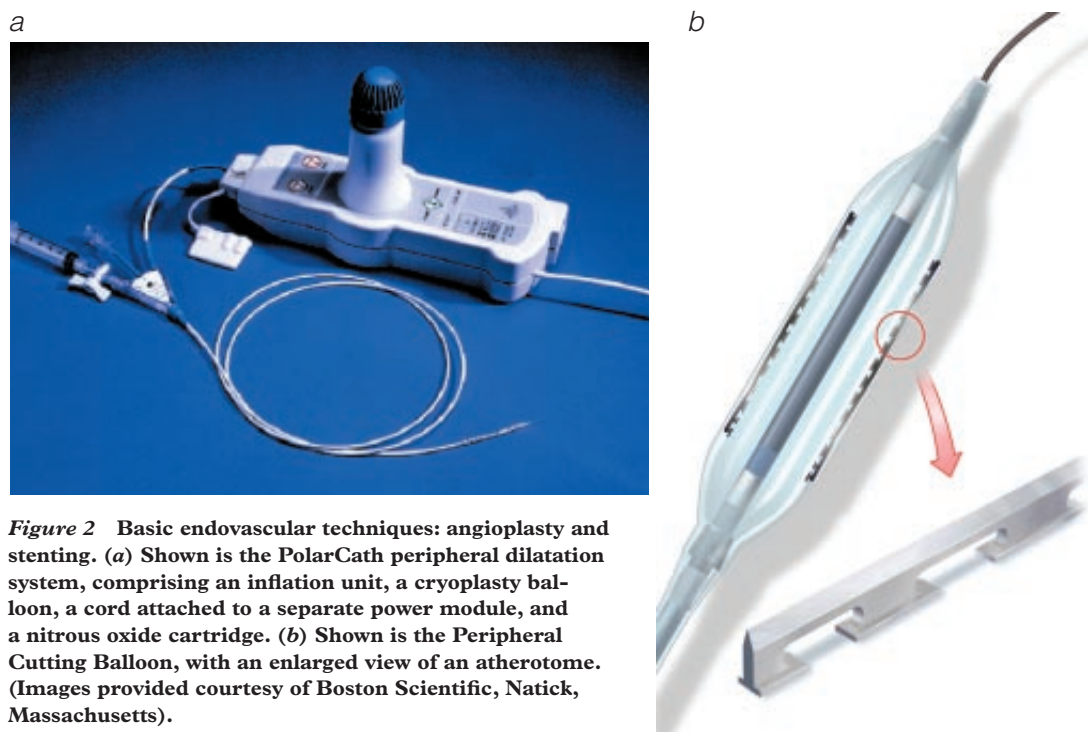


Figure 2 Basic endovascular techniques: angioplasty and stenting. (a) Shown is the PolarCath peripheral dilatation system, comprising an inflation unit, a cryoplasty balloon, a cord attached to a separate power module, and a nitrous oxide cartridge. (b) Shown is the Peripheral Cutting Balloon, with an enlarged view of an atherotome. (Images provided courtesy of Boston Scientific, Natick, Massachusetts).

use of this device will depend on the results of the multicenter TALON registry.⁵

Drug-eluting stents have become popular for use within the coronary circulation, but at present, they are only in the initial stages of investigation for treatment of lower-extremity arterial disease. Initial trials with the sirolimus-coated S.M.A.R.T. stent (Cordis, Miami Lakes, Florida) showed a nonsignificant trend toward decreased restenosis rates.⁶

Troubleshooting Angioplasty can result in either non-flow-limiting or flow-limiting dissections. If dissection occurs, reinflation of the balloon over the dissection for 5 to 10 minutes may anneal the flap to the wall. If balloon reinflation fails and flow is still disrupted, a stent should be placed.

In situ thrombosis of the vessel occasionally occurs after angioplasty or stent placement. If it develops in a patient who underwent angioplasty alone, the thrombosed vessel may be stented open. If this measure fails or if the in situ thrombosis develops after stent placement, a thrombolysis catheter is placed across the lesion and a single bolus of a thrombolytic agent administered. If this approach yields suboptimal results, an indwelling catheter is placed for a 12- to 24-hour infusion [see Procedures for Acute Lower-Extremity Ischemia, *below*]. Alternatively, mechanical thrombectomy with a rheolytic catheter may be considered. Finally, restenting with an open or covered stent is an option, but it may result in distal embolization.

Perforation of the vessel can occur during angioplasty or recanalization. Perforations that are small or that occurred during a failed recanalization need not be treated. Perforations associated with persistent extravasation of contrast may be managed primarily with balloon tamponade (20 minutes of inflation, with intermittent deflations to allow distal circulation and reversal of anticoagulation) and secondarily with placement of a covered stent.

Endoluminal intervention to treat plaque can result in distal embolization of cholesterol or plaque or distal dislodgment of thrombi. Mechanical or pharmacologic thrombolysis remains the mainstay option in such cases. If, however, one is concerned about

a possible nonthrombotic embolic event, aspiration or open embolectomy may be required to achieve satisfactory reconstitution of flow.

When a vessel is heavily calcified, a self-expanding stent may be unable to deploy and may be effectively “jailed” in the lesion. In this situation, wire access must be maintained, and a low-profile balloon should be used to enlarge the operating lumen so that a high-pressure balloon can then be introduced. The introduction of a series of balloons with successively larger diameters will eventually allow the stent to be deployed. Balloon perforation often occurs in these cases, and care should be taken to extract the perforated balloon intact.

Unplanned stent dislodgment is rare but not unknown. If it occurs, the errant stent may be fixed in place by placing an additional overlapping stent. Alternatively, a balloon may be inflated distal to the tip of the dislodged stent and used to move the stent to another vessel, where it may be safely deployed.

Complications The most common complications of angioplasty and stenting in the lower extremities are access-related issues, including hematoma, arteriovenous fistula formation, and pseudoaneurysm. The incidence of hematoma can be minimized by using the smallest sheath possible, waiting for normalization of the activated clotting time before pulling the sheath, and holding manual pressure for 30 minutes after the procedure. Devices designed for vessel closure after percutaneous intervention are available but have not been proved to reduce the incidence of access-related complications.⁷ With several of these closure devices, it is recommended that access of the groin not be attempted for up to 90 days after insertion.

PROCEDURES FOR CHRONIC LOWER-EXTREMITY ISCHEMIA

Preprocedural Evaluation

Patients presenting with chronic lower-limb ischemia are evaluated as previously outlined [see Basic Endovascular Procedures, Preprocedural Evaluation, *above*]. Patients with claudication are

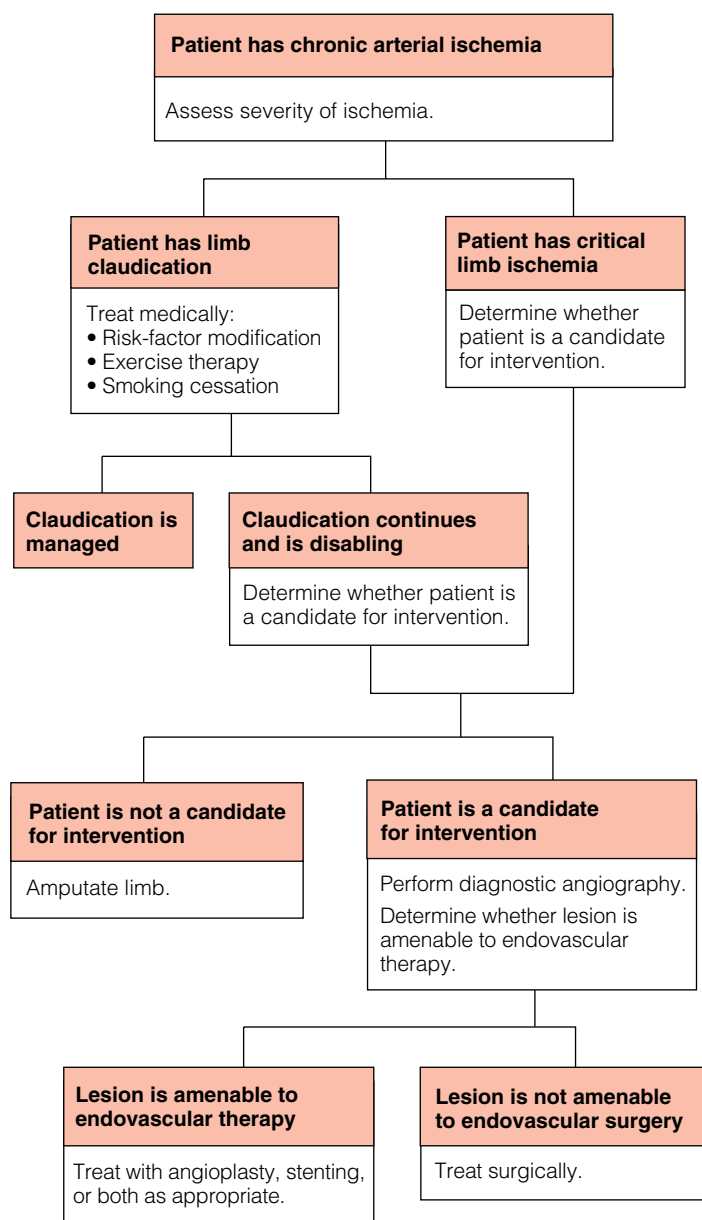


Figure 3 Algorithm illustrates workup of patients with chronic lower-extremity ischemia.

managed medically by controlling risk factors, instituting exercise therapy, and providing advice on smoking cessation.⁸ In patients with disabling claudication, rest pain, or tissue loss, diagnostic imaging studies are performed with the intent of identifying and subsequently treating any lesion that is amenable to endovascular therapy [see Figure 3]. If an intervention is indicated, patients are pretreated with antiplatelet agents as appropriate.

Technique

Techniques and protocols for diagnostic angiography and accessing the target lesion have been outlined [see Basic Endovascular Procedures, *above*]. If it is unclear whether a vessel has a hemodynamically significant stenosis, arterial pressures can be measured across the lesion by connecting an end-hole catheter to a pressure transducer. A drop of more than 10 mm Hg in systolic blood pressure or more than 5 mm Hg in mean arterial pressure across the lesion is considered significant. The area in question

should also be subjected to a chemical challenge. Local intra-arterial delivery of a vasodilator (e.g., papaverine, 30 mg; prazosin, 25 mg; or nitroglycerin, 200 µg) will create distal vasodilatation, accentuate the translesional gradient, and, in many cases, unmask a significant lesion that might otherwise be missed.

Iliac lesions may be treated either by means of primary angioplasty, with stenting reserved for cases in which angioplasty yields unsatisfactory results, or by means of primary stenting. Either balloon-expandable or self-expanding stents may be used in the iliac vessels. Highly calcified lesions and lesions in smaller iliac vessels (< 7 mm) generally are best treated with self-expanding stents. Lesions in the external iliac artery or the femoral artery (including the CFA, the profunda femoris [PF], and the SFA) are best treated with angioplasty alone. In these vessels, stents usually are placed only when angioplasty has been unsuccessful or dissection or vessel rupture has occurred. As a rule, stenting for SFA lesions is best done with self-expanding stents, though very focal lesions may be treated with balloon-expandable stents. Stenting is relatively contraindicated in the popliteal artery; the extended range of motion across the nearby joint often leads to stent fracture. At present, stents are not used as primary therapy in infrapopliteal vessels. If stenting is required at infrapopliteal sites, coronary balloon-mounted platforms are the only available choices.

Postprocedural Care

After the procedure, patients require at least 2 to 12 hours of bed rest. Hydration with I.V. infusion of normal saline should be initiated, and appropriate dosages of renal-protective agents should be given. Aspirin, 81 mg/day, should be given on a long-term basis, and clopidogrel, 75 mg/day, should be administered for 30 days.

Outcome Evaluation

In most series, rates of technical success (defined as less than 30% residual stenosis) have exceeded 90%. Secondary patency rates for iliac interventions at 10 years have exceeded 50%.⁹ Angioplasty and stenting in the SFA have been studied, for the most part, in a retrospective fashion. Intermediate-term data have suggested patency rates of 70%, 60% and 50% at 1, 3, and 5 years, respectively. The reported clinical benefit has generally exceeded the anatomic patency rates.¹⁰⁻¹² None of the randomized studies published to date have found primary stenting to have any advantage over primary angioplasty in the femoral vessels.¹³⁻¹⁶ Factors indicative of a poor prognosis include intervention for more advanced limb ischemia, diabetes, complete occlusion (as opposed to stenosis), lesions longer than 10 cm, and poor distal runoff.⁸ The use of TASC criteria to stratify lesions anatomically helps predict which patients are likely to benefit most from endovascular therapy in the SFA.¹⁷ In one study that included almost 400 SFA interventions, patients who had TASC A and B lesions experienced significantly better outcomes than those who had TASC C and D lesions, with an overall 6-year patency rate of 52%.¹⁰ Currently, angioplasty is being evaluated for use in infrapopliteal disease. Some initial success has been reported, though it still appears that this approach is best reserved for patients in whom open surgical management is relatively contraindicated.¹⁸

PROCEDURES FOR ACUTE LOWER-EXTREMITY ISCHEMIA

Preprocedural Evaluation

The initial decision in managing acute lower-extremity ischemia limb should be whether to proceed directly to surgery or to obtain a diagnostic angiogram and consider endovascular therapy. The Working Party on Thrombolysis developed a consensus

Table 4 Contraindications to Thrombolysis

Relative Contraindications	Absolute Contraindications
Recent surgery (within 2 wk)	Active internal bleeding
Recent trauma (within 1 mo)	Recent stroke (within 2 mo)
History of coagulopathy	Intracranial pathology
Pregnancy or recent delivery	

on how to approach patients with acute arterial ischemia. The main message of this consensus was that classifying patients according to their grade of ischemia is essential to forming treatment plans [see 6:5 *Pulseless Extremity and Atheroembolism*].¹⁹ Grade IIa and early grade IIb ischemia may be amenable to endoluminal therapy, including thrombolysis. Established grade IIb ischemia is best treated by means of surgical embolectomy or thrombectomy, with intraoperative angiography, intraoperative thrombolysis, and over-the-wire embolectomy as options. Grade III ischemia is nonsalvageable and generally necessitates amputation [see 6:20 *Lower-Extremity Amputation for Ischemia*].

Arterial Thrombolysis

Thrombolysis, either pharmacologic or mechanical, is the mainstay of endovascular therapy for acute arterial ischemia.²⁰ Relative and absolute contraindications to thrombolytic therapy have been established [see Table 4].

Technique An initial diagnostic angiogram of the affected limb is obtained, with care taken to gain arterial access in such a way that thrombolytic therapy is not prevented. The standard approach is from the contralateral groin (see above). To reduce the chances of access site hematoma during administration of a thrombolytic agent, access should be gained at a substantial distance from the occlusion. Crossing the lesion involves identifying the origin of the occlusion. In cases of native vessel occlusion, this is generally a straightforward process. If a bypass graft is occluded, one may be able to visualize a stump of the graft, which will aid in direct management [see Figure 4]. The standard methods of crossing a stenosis or an occlusion [see Basic Endovascular Procedures, Crossing of Lesion, above] should be employed.

Once the lesion has been crossed securely with a wire, an infusion catheter (e.g., a 3 French multi-side-hole catheter) is advanced over the wire and situated in the occlusion. An infusion wire may also be inserted through the infusion catheter in a coaxial fashion and placed distally to increase the area of direct lysis, to protect the outflow vessel, or to address two separate lesions [see Figure 5]. The position of the catheter and the wire are then documented by means of fluoroscopy. With the infusion catheter left securely in place, the thrombolytic infusion is begun. Often, it helps to insert a guide sheath into the contralateral iliac system to prevent dislodgment and facilitate subsequent access.

Pharmacologic agents. The use of thrombolytic drugs has been refined over the past decade. In the United States, urokinase and tissue plasminogen activator (t-PA) have been the most widely used agents. Urokinase was popular in the 1980s and 1990s, but its temporary withdrawal from the market in 1998 because of manufacturing problems allowed physicians to become more comfortable working with t-PA. At present, recombinant t-PA (rt-PA) (e.g., alteplase) is the lytic agent most commonly used in the United States. Reteplase is a newer recombinant agent that is similar to rt-PA but has a longer half-life and a less specific affinity for

fibrin.^{21,22} To prevent buildup of clot around the sheath, all patients undergoing pharmacologic thrombolysis also receive heparin in a continuously administered low dosage (200 to 500 U/hr); higher dosages are associated with a substantially increased risk of hemorrhagic complications.

Mechanical adjuncts to thrombolysis. Several mechanical adjuncts are available to reduce thrombolytic time or enhance the completeness of clot dissolution. These adjuncts can also be beneficial when thrombolytic therapy is contraindicated.

Various mechanical thrombectomy systems are commercially available. One such system is the AngioJet system (Possis Medical, Minneapolis, Minnesota). The AngioJet consists of a pump drive unit and a 4 to 6 French catheter, which is passed over a 0.035-in. wire to the target area. The catheter has two lumens: one is used to pulse heparinized normal saline at a pressure of 10,000 psi, and the other contains the wire and serves as the route by which clot debris

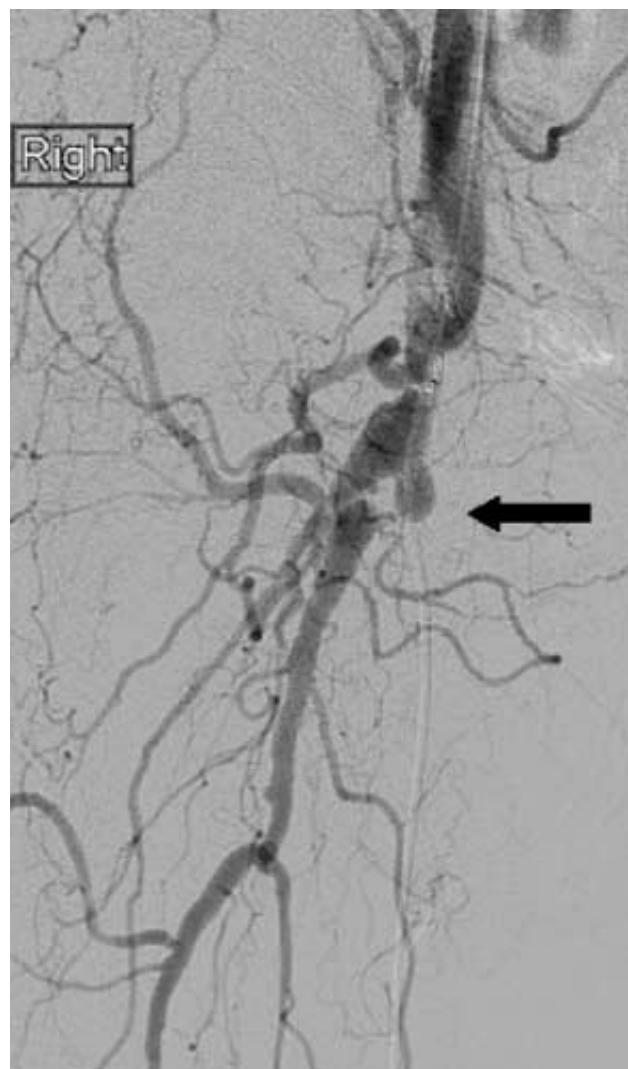


Figure 4 Arterial thrombolysis. Patient presented with grade IIa ischemia, and duplex ultrasonography showed evidence of an occluded femoropopliteal reverse saphenous vein bypass graft. Angiogram taken from the ipsilateral external iliac artery demonstrating a patent but diseased CFA and a patent PF. The SFA is occluded. The stump of the occluded arterial bypass graft is visible (arrow).



Figure 5 Arterial thrombolysis. Follow-up imaging of the patient in Figure 4 illustrates the use of a thrombolytic infusion catheter. (a) Shown is the proximal end of the occluded CFA–popliteal artery bypass graft. (b) The infusion catheter (black arrow) is placed. (c) The infusion wire rests in the distal bypass graft (hollow arrow), increasing the infusion length for the thrombolytic agent.

is removed. The power pulse spray technique, with rt-PA added to the saline (10 mg in 100 ml) and delivered by the rheolytic catheter directly into the clot, may also be employed to help dissolve clot. In this technique, the system is modified so that the outflow circuit is closed and the unit pulses the saline–rt-PA mixture into the clot, allowing simultaneous lysis and maceration. Once the thrombus has been treated and an additional 15-minute interval has elapsed, conventional catheter therapy is employed to remove the clot and the residual rt-PA. The advantage of this approach is that it permits high-dose lysis while imposing only a low systemic load.²³ If more than 750 ml of saline is used with the AngioJet catheter during a single session, there is a significant risk of acute renal impairment secondary to hemolytic debris.

Also used for mechanical thrombectomy are wall-contact instruments such as the Arrow-Trerotola device (Arrow International, Reading, Pennsylvania). Such devices result in significant endothelial damage and distal clot embolization and thus are better suited for hemodialysis grafts. Another option is the Helix Clot Buster (ev3, Plymouth, Minnesota), which creates a vortex at the catheter tip that macerates the clot into microscopic fragments; it differs from the AngioJet in that it lacks an aspirating port. The Oasis thrombectomy catheter (Boston Scientific, Natick, Massachusetts) also fragments thrombus into small particles. The use of these devices in the setting of acute arterial occlusion was addressed in a comprehensive review published in 2001.²⁴ All of these devices may be used either in place of or in addition to pharmacologic thrombolysis.

At present, the evidence supporting the use of mechanical thrombectomy devices in the setting of acute limb ischemia is modest. One retrospective study demonstrated successful recanalization in approximately 60% of patients.²⁵ At our own institution, we have found these devices to be useful in decreasing the clot burden on the second or third t-PA check (24 to 36 hours after commencement of the infusion), after the clot has been softened by the initial pharmacologic lysis. It remains to be seen whether this approach reduces the overall time needed for thrombolytic therapy.

Over-the-wire embolectomy is another mechanical means of removing clot. Newer designs of the standard Fogarty embolectomy catheter have been developed that include an inner lumen, so that the catheter can be passed over a 0.035-in. wire. Use of these devices facilitates fluoroscopically guided embolectomy and ensures that the catheter can be passed to all target vessels. Over-the-wire embolectomy provides an efficient percutaneous method of removing clot without any need for the constant monitoring that pharmacologic thrombolysis requires.

This embolectomy technique may be supplemented by intraoperative catheter-directed thrombolytic therapy when postoperative imaging reveals residual clot or inadequate perfusion. Under fluoroscopic guidance, an end-hole catheter or a multi-side-hole infusion catheter is guided over a wire into the target vessel or vessels, and a thrombolytic agent (e.g., rt-PA, 0.5 mg/kg over 30 minutes) is directly infused with inflow occlusion. Imaging is recommended both before and after thrombolysis. Adjunctive use of an embolectomy catheter may also be beneficial. If, however, there is still no perfusion after adequate thrombolytic therapy and embolectomy, the situation generally is not retrievable, and alternative therapies should be explored. In the clinical trials of perioperative thrombolytic therapy published to date, success rates ranged from 64% to 100%. Bleeding was the most common complication.

Postprocedural care After the intervention, the patient is observed in a monitored unit by personnel trained in the management of thrombolytic therapy. Lower-extremity neurovascular examinations are carried out frequently (every 1 to 2 hours). The patient's clinical status is also monitored for evidence of bleeding, including access-site hematoma, neurologic changes, and hypotension. Repeat angiograms are performed at 12-hour intervals (or sooner if clinical examination reveals significant deterioration) to assess the progress of lytic therapy and to allow changes in catheter positioning. Some physicians recommend following fibrinogen levels and discontinuing the lytic agent if levels fall below 150 mg/dl. Other end points for the thrombolytic therapy are failure to

progress, complete lysis of the target thrombus, or significant bleeding complications necessitating discontinuance of lysis.

Once lysis is discontinued, the heparin dosage should be increased to achieve therapeutic levels of anticoagulation. Any lesions unmasked by thrombolytic therapy should be treated, either by endovascular means or with an open procedure. Whether long-term anticoagulation is indicated depends on the patient's circumstances and the specific cause of the thrombosis.

Troubleshooting Many of the issues raised in connection with basic arterial access techniques arise during attempts at thrombolysis. Occasionally, the interventionalist experiences significant difficulty in accessing an occluded bypass graft. Thrombolysis of these occluded grafts can often be facilitated by employing a double-puncture technique, in which both a retrograde and an antegrade puncture of a bypass graft are performed under ultrasonographic guidance, allowing the infusion catheters to be placed so as to cover the entire length of the graft [see Figure 6].²⁶ With this approach, there is no need for CFA puncture, which is often made difficult by the presence of scar tissue, and the problem of finding access to the graft takeoff is eliminated. If a lesion cannot be

crossed, the thrombolytic agent may be delivered just proximal to the lesion for 2 to 4 hours after initiation of therapy, but the chances of a good outcome with this approach are diminished.

Whereas it is common for clinical findings to worsen slightly (as a result of distal microembolization) before improving—the so-called storm before the calm phenomenon—dramatic worsening of the physical findings calls for urgent angiography. Possible reasons for ischemic progression include propagation of clot (treatable by performing open embolectomy or thrombectomy), displacement of the lysis catheter (treatable by repositioning the catheter), or distal embolization of clot resulting in obstruction of the principal runoff vessels (treatable by advancing the infusion catheter or wire more distally, employing a rheolytic catheter, or performing open embolectomy or thrombectomy).

Complications General access-site complications—including hematoma, pseudoaneurysm formation, ischemia to the contralateral leg from an occlusive sheath, nerve damage (which is more common with axillary or brachial puncture secondary to an axillary sheath hematoma), arterial dissection of the access vessel, and distal embolization of the clot—are also seen with thrombolyt-

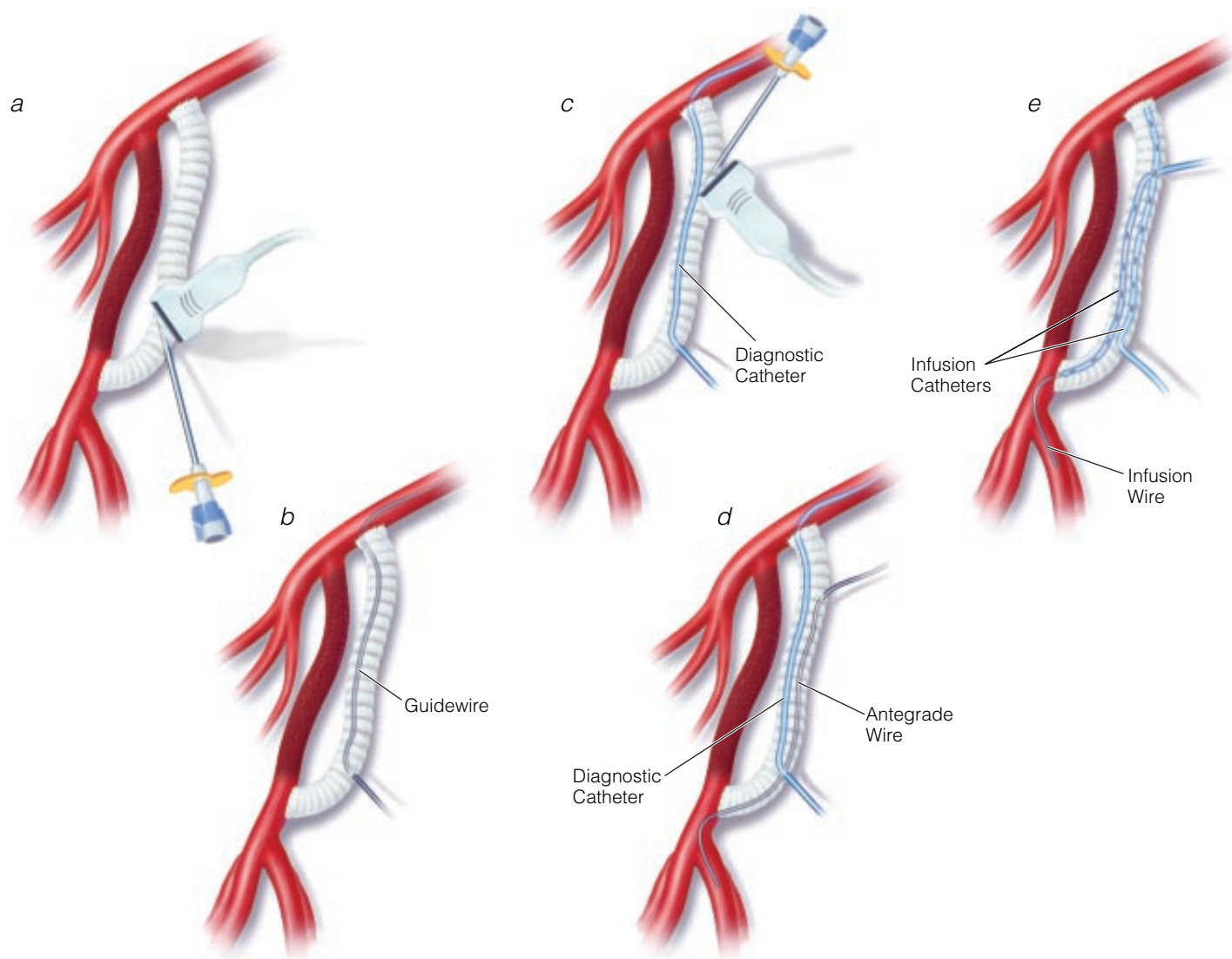


Figure 6 Arterial thrombolysis. Illustrated is ultrasound-guided double puncture of an arterial bypass graft for thrombolysis.²⁶

Table 5 Prospective, Randomized, Controlled Trials of Arterial Thrombolytic Therapy

Trial (Date)	N	Lytic Agent	Limb Salvage Rate at 1 Yr (Surgery vs. Lytic Therapy)	30-Day Mortality (Surgery vs. Lytic Therapy)	Bleeding Complication Rate with Lytic Therapy
Rochester (1994) ⁴¹	114	Urokinase	82% vs. 82% (NS)	18% vs. 12% (NS)	11%
STILE (1994) ²⁷	393	Urokinase/rt-PA	100% vs. 90%	No difference	5.6%
TOPAS (1996) ⁴²	213	Urokinase	65% vs. 75% (NS)	5% vs. 3% (NS)	10%

NS—not significant STILE—Surgery versus Thrombolysis for Ischemia of the Lower Extremity TOPAS—Thrombolysis Or Peripheral Arterial Surgery

ic therapy. Bleeding complications have presented a significant hurdle for thrombolytic therapy. Early studies that used therapeutic doses of heparin and higher doses of thrombolytics reported unacceptable rates of intracranial hemorrhage and other bleeding complications. Currently, most physicians employ rt-PA doses in the range of 0.25 to 0.50 mg/hr without compromising results. Overall, rates of bleeding complications with urokinase and rt-PA range from 5% to 10%, and the incidence of intracranial hemorrhage is less than 2%.²² As with open surgical therapy, compartment syndrome can complicate reperfusion of the ischemic limb; this complication should be checked for on serial clinical examinations.

Outcome evaluation The use of thrombolysis to treat acute lower-extremity arterial occlusion has been extensively studied. The results of the major prospective, randomized trials [see Table 5] showed thrombolytic therapy to be equivalent to surgery with respect to limb salvage and mortality and superior with respect to the need for complex surgical intervention. Most of these major trials were performed with urokinase and t-PA. The information gained from them has helped surgeons determine which patients are good candidates for thrombolytic therapy. Factors predictive of successful thrombolysis include symptoms of less than 14 days' duration, prosthetic graft occlusion, and high medical risk for open operation. Factors predictive of a poor outcome include chronic occlusion, native artery occlusion, and a lesion that cannot be crossed with a wire.²⁷

PROCEDURES FOR LOWER-EXTREMITY ARTERIAL ANEURYSMS

Ultrasound-Guided Thrombin Injection

Pseudoaneurysms of the CFA are a complication of femoral access for therapeutic procedures and are often amenable to percutaneous therapy. The pseudoaneurysm is visualized with a 7.5-MHz duplex ultrasound probe. Contraindications to injection of the sac are the presence of a wide mouth and no discernible neck, the development of an arteriovenous fistula, compression of adjacent structures by the pseudoaneurysm, and skin changes overlying the pseudoaneurysm. If infection is a possibility, the procedure should not be attempted. The ABI should be determined and duplex ultrasonography of the groin performed before injection.

Once it is certain that the pseudoaneurysm meets the criteria for thrombin injection, the sac is injected in the fundus area, away from the native artery, under direct ultrasonographic visualization and after infiltration of a local anesthetic. Usually, 1,000 units of thrombin is injected, and injection may be repeated one or more times. With multilobar aneurysms, serial injections into each fundus may be required to achieve complete resolution.

Factors associated with successful treatment are a long, narrow pseudoaneurysm neck and a sac diameter smaller than 8 cm.

Overall success rates may exceed 95%. Complications include distal native artery thrombosis and distal embolization, which generally can be treated with I.V. heparin.²⁸

Placement of Covered Stent

Treatment of lower-extremity aneurysms with covered stents is currently being studied. Isolated iliac artery and SFA lesions, though rare, lend themselves to endovascular repair [see Figure 7]. Initial data suggest that repair of popliteal aneurysms with covered stents is also feasible in high-risk patients.²⁹ Newer stents are being developed that are better able to withstand the stresses imposed by the repetitive motion of the knee joint.

Venous Procedures

As endovascular therapy for arterial disease continues to evolve, techniques learned in the arterial tree are increasingly being applied to the venous system. At present, the main venous disease processes being treated with endovascular techniques are iliofemoral deep vein thrombosis (DVT) and superficial reflux of the greater saphenous system causing symptomatic varicose veins.

VENOUS THROMBOLYSIS

Lower-extremity DVT can have a significant impact on patients' quality of life. Multiple studies indicate that approximately 50% of patients experience postthrombotic syndrome (PTS) and that the majority of patients with PTS report that physical and emotional well-being are negatively affected.³⁰ The goals of venous lysis are to relieve obstruction and to preserve valve function.

Preprocedural Evaluation

If DVT is less than 1 month old, a trial of lytic therapy is appropriate. The ideal candidate for such therapy has a symptomatic clot with lower-extremity swelling, is young and mobile, is not in a hypercoagulable state, and has no contraindications to lysis. Currently, lytic therapy is more commonly employed in active patients, whose quality of life is more likely to be negatively affected by PTS. In cases of unprovoked DVT or recurrent DVT, a hypercoagulability workup is indicated.³¹ Venous thrombosis is discussed more fully elsewhere [see 6:6 *Venous Thromboembolism*].

Technique

The initial diagnostic venogram can be obtained via almost any venous access site. Our preference is to perform an ipsilateral popliteal vein stick with the patient in the prone position; the posterior tibial vein or the contralateral femoral vein can also be used. The popliteal vein is accessed with a micropuncture needle under ultrasonographic guidance by means of a Seldinger technique.

The micropuncture sheath is then replaced with a 5 French sheath over a 0.035-in. wire. The diagnostic venogram is performed through the sheath or with a straight multi-side-hole diagnostic catheter.

As in arterial thrombolysis [see Arterial Procedures, Procedures for Acute Lower-Extremity Ischemia, Arterial Thrombolysis, *above*], a 3 French infusion catheter is advanced over the wire and positioned within the clot. Longer lesions can be managed with a coaxial infusion catheter–wire system. The lytic infusion is started, and a low-dose intravenous heparin infusion is initiated through the sheath. Mechanical thrombectomy and power pulse spray thrombectomy can efficiently debulk thrombus and may be beneficial in patients with phlegmasia caerulea dolens.³² The patient is kept in a monitored floor bed, and repeat venograms are performed every 12 to 24 hours.

In some patients, May-Thurner syndrome (compression of the iliac vein by the overlying iliac artery) develops; it is treated by placing a venous stent in the iliac vein to help reduce the effect of external compression and presumably treat the initiating factor. Venous stents are larger than corresponding arterial stents in a given vascular bed. Because of the increased compliance of the venous wall, self-expanding stents are preferred for use in veins.

Once lysis either is complete or has been continued for 72 hours, the lytic infusion is stopped, and the heparin infusion is increased to therapeutic levels. The patient is placed on warfarin therapy and should be treated in accordance with current algorithms for DVT [see 6:6 Venous Thromboembolism].

Complications

Reported rates of bleeding complications after venous lysis are higher than those after arterial lysis, typically ranging from 10% to 15%.³³ Pulmonary embolism, though rare in this setting, is known to occur, presumably as a result of partially lysed clot breaking off. To prevent this complication, some authors advocate prophylactic placement of an inferior vena cava (IVC) filter.³⁴ Ongoing development and wider use of retrievable IVC filters may accelerate the application of this adjunctive technique.

Outcome Evaluation

In a large retrospective study of 312 cases of iliofemoral and femoropopliteal DVT treated with urokinase infusion, greater

than 50% lysis was achieved in 83% of the patients; 11% experienced complications, and 1% had pulmonary emboli.³³ Small prospective, randomized trials found that thrombolysis yielded increased patency and decreased venous reflux in comparison with standard anticoagulation therapy.³⁵ Retrospective studies indicated that this improved venous patency and valve function might translate into better quality of life than would be achieved with anticoagulation alone.³⁶

TREATMENT OF SAPHENOFEMORAL VENOUS REFLUX

The application of endovascular techniques to saphenofemoral venous reflux has significantly changed the treatment of this condition.³⁷ Over the past decade, two minimally invasive approaches have been developed to replace standard high ligation and stripping of the greater saphenous vein (GSV): radiofrequency ablation (RFA) and endolaser obliteration.

Preprocedural Evaluation

Initially, symptomatic varicose veins are treated conservatively, with compression stockings. If conservative methods fail to provide relief, a varicose vein–related complication develops, and there is evidence of significant superficial reflux on duplex ultrasonography, the patient may be considered for endovenous treatment of GSV reflux.

Preprocedural Planning

GSV ablation procedures may be performed either in an office or in an operating or procedure room. If an office setting is chosen, the patient must be able to tolerate a small amount of discomfort with light sedation. The interventionalist must be certified to deliver conscious sedation and must be laser qualified if providing laser therapy. The procedure room, whether in an office or a medical facility, should be equipped with a procedure table capable of a steep Trendelenburg position, a high-resolution duplex ultrasonography device, and the appropriate ablation equipment. For more symptomatic side-branch varicosities, stab avulsions may be needed; as a rule, these are best done in the OR.

Technique

RFA of GSV The development of the Closure system (VNUS Medical Technologies, Sunnyvale, California) has allowed

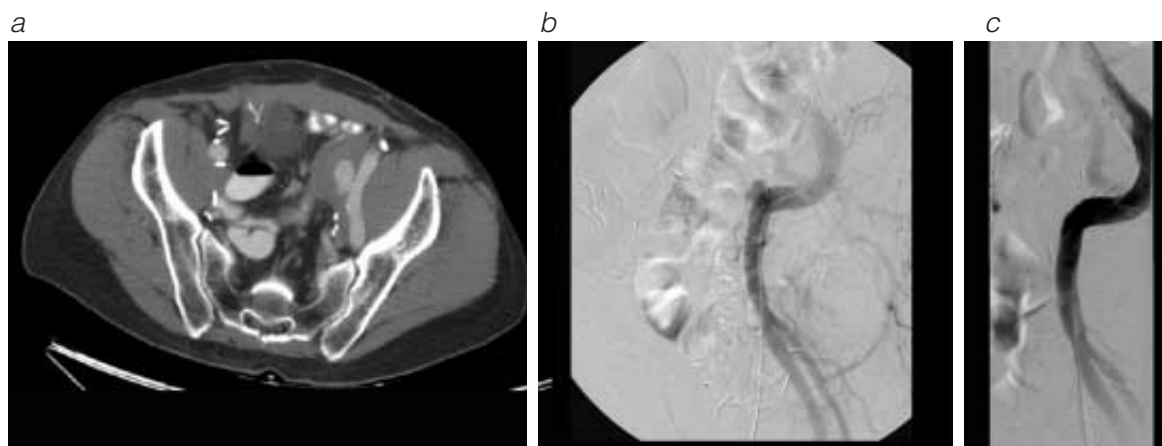


Figure 7 Placement of covered stent. Shown is endovascular repair of an external iliac artery aneurysm. The patient presented with left groin pain several months after undergoing urologic surgery. (a) CT scan demonstrates a left external iliac artery pseudoaneurysm. (b) Angiogram demonstrates the same pseudoaneurysm. (c) Shown is the left external iliac artery after covered stent placement successfully excluded the pseudoaneurysm.

the application of RFA to GSV reflux therapy. Before the procedure, the GSV is mapped by means of ultrasonography. The patient is placed in the Trendelenburg position with a tourniquet around the upper thigh. Access to the GSV is obtained at the knee with an introducer needle and a wire threaded into the vein, and the needle is then replaced with a proprietary sheath. The Closure catheter is threaded through the sheath, and the tip is placed under ultrasonographic guidance just proximal to the takeoff of the superficial epigastric vein at the saphenofemoral junction (SFJ). A mixture of normal saline (500 ml), 1% lidocaine with epinephrine (50 ml), and sodium bicarbonate (5 mg) is injected under ultrasonographic guidance through the sheath and into the area surrounding the GSV to provide anesthesia, improve impedance, and protect the overlying tissues from exposure to the heat (so-called tumescent anesthesia).

The Closure device is then connected to the RFA delivery system, deployed, and pulled back at a controlled rate (initially, 1 cm every 30 seconds), with both impedance and temperature checked periodically. Manual compression, particularly in the upper thigh, may help in obtaining optimal numeric values on the RFA unit, as well as increase the efficiency of ablation. After the catheter has been withdrawn into the sheath, it is removed, and ultrasonography is performed to confirm that the GSV has been obliterated.

Endovenous laser treatment of GSV Access to the GSV is obtained as in RFA (see above), and a wire is advanced under ultrasonographic guidance to a point above the SFJ. A 600 μ m laser fiber is placed over the wire and positioned just distal to the SFJ in the GSV. A tumescent anesthetic solution is injected. Laser energy is delivered (e.g., with an 810 nm diode laser) as the laser fiber is pulled back. One advantage endolaser obliteration has over

RFA is that the laser wire can be pulled back relatively quickly (up to 18 mm/min).

Complications

The most serious complication associated with any of these endovenous techniques is DVT. There have been several reports of DVT resulting from RFA of the GSV, with incidences as high as 16%.³⁸ As of September 2005, four instances of pulmonary embolism from these clots had been reported in the United States Food and Drug Administration's Manufacturer and User Facility Device Experience (MAUDE) database (<http://www.fda.gov/cdrh/maude.html>), with at least one patient dying of a pulmonary embolism after the procedure.

Lower-extremity DVT has also been reported after endovenous laser therapy. Other problems include saphenous nerve paresthesias along the course of the GSV, bruising, skin burns, and superficial phlebitis. If endovenous laser therapy fails to obliterate the GSV, the problem can be remedied by prompt high ligation at the time of ablation. Clot in the common femoral vein can be treated with standard anticoagulation. Clot abutting the common femoral vein can be treated with clopidogrel, 75 mg/day orally for 1 month; serial ultrasonograms should be obtained to confirm that the clot is not propagating.

Outcome Evaluation

Overall, good results are obtained with endovenous treatment of GSV reflux. In one study of patients who underwent RFA of the GSV, 85% of patients had complete occlusion of the GSV at 2 years, and 90% of all patients were free of GSV reflux at that time.³⁹ In a study of patients who underwent endolaser obliteration, similar results were obtained: ultrasonographic surveillance documented a 93% rate of complete GSV closure at 2 years.⁴⁰

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Figures 1a, 2b, and 6 Tom Moore.

20 LOWER-EXTREMITY AMPUTATION FOR ISCHEMIA

William C. Pevec, MD, FACS

Patients with infected, painful, or necrotic lower extremities can be restored to a better functional level by means of a properly selected and performed amputation. This procedure should be considered reconstructive and restorative. In what follows, I address amputations across the toe, the forefoot, the leg, and the thigh. Because Symes amputations and hip disarticulations are seldom appropriate on ischemic limbs, I omit discussion of these procedures.

General Operative Planning

Selecting the appropriate level of amputation is of primary importance for healing and preservation of function. For an ambulatory patient who has either a palpable pulse over the dorsal pedal or posterior tibial artery or a functioning infrapopliteal arterial bypass graft, amputation on the foot (either toe amputation or transmetatarsal amputation) is appropriate. For an ambulatory patient who has a palpable femoral pulse and a patent deep femoral (profunda femoris) artery, whose skin is warm at least to the level of the ankle, and who has no skin lesions on the proposed amputation flaps, amputation below the knee is appropriate. For a nonambulatory patient who has ischemic rest pain, ulceration, or gangrene, amputation above the knee is appropriate. Arterial reconstruction is not indicated if the extremity is nonfunctional. Below-the-knee amputation does not offer nonambulatory patients any functional advantage; moreover, it is less likely to heal and often results in a flexion contracture at the knee that leads to pressure ulceration of the stump. Above-the-knee amputation depends on pulsatile flow into the ipsilateral internal iliac artery for successful healing. Above-the-knee amputation is also necessary for a patient whose skin is cool at or above the midcalf or who has skin lesions at or proximal to the midcalf.

Several adjunctive measurements (e.g., transcutaneous oxygen tension and segmental arterial pressure) have been used to select the level of amputation but have not proved particularly helpful. Generally, these adjuncts can reliably determine a level of amputation at which healing is virtually ensured, but they cannot reliably determine the level at which an amputation will not heal. Consequently, reliance on such measures to select the level of amputation will result in an unnecessarily high percentage of more proximal amputations.

In most cases, definitive amputation can be accomplished in a single stage. Local cellulitis can usually be controlled beforehand with bed rest and systemic administration of antibiotics. Undrained pus or recalcitrant cellulitis, however, must be treated with débridement and drainage in advance of

definitive amputation. This can be accomplished with local soft tissue débridement, single-toe open amputation, or guillotine amputation across the ankle.

Careful preoperative medical assessment is essential. Lower-extremity amputation for ischemia is associated with a mortality of 4.5 to 18%,¹⁻⁹ owing to the poor overall condition of the patient population. Accordingly, optimization of cardiac and pulmonary function and control of systemic infection are mandatory.

Finally, the timing of elective amputation is crucial. Because the loss of a limb is a difficult and frightening thing for a patient to accept, there is a natural tendency to delay amputation for as long as possible. This tendency is understandable but must be weighed against the potential problems associated with delay, such as poor preoperative pain control, which leads to an increased incidence of postamputation phantom limb pain, and extended preoperative immobility, which leads to physical deconditioning and makes prosthetic limb rehabilitation more difficult. A preoperative consultation with a physiatrist can allay some of the patient's anxiety by addressing the expected postoperative course of rehabilitation and thereby removing some of the fear of the unknown.

Toe Amputation

Amputation of the toe can be done either across a phalanx or across a metatarsal bone; the latter procedure is commonly referred to as a ray amputation. Many of the perioperative issues are essentially similar for the two approaches; however, indications and operative details differ somewhat and thus will be described separately.

OPERATIVE PLANNING

As noted (see above), for a toe amputation to heal properly, there must be either a palpable pulse over the dorsal pedal or posterior tibial artery or a functioning bypass graft to an infrapopliteal artery. If tissue necrosis or infection is confined to the distal or middle phalanx, transphalangeal amputation is appropriate; if tissue loss or necrosis involves the proximal phalanx, ray amputation is indicated. If tissue necrosis or infection extends over the metatarsophalangeal joint, either transmetatarsal amputation of the entire forefoot or below-the-knee amputation is usually necessary (see below).

Multiple transphalangeal amputations are functionally well tolerated. If, however, ray amputation of the great toe or of more than one smaller toe is called for, it may be preferable to perform a transmetatarsal amputation of the forefoot. Adequate skin coverage may be difficult to achieve with a

great-toe or multiple-toe ray amputation. In addition, ray amputation of more than one of the middle toes often causes central deviation of the remaining outside toes, which can lead to ulcerations secondary to abnormal pressure points. Finally, loss of the first metatarsal head or of several of the other metatarsal heads results in abnormal weight bearing on the remaining metatarsal heads, which may give rise to late ulceration.

OPERATIVE TECHNIQUE

Transphalangeal Amputation

Digital block anesthesia is ideal for transphalangeal amputation. A 25-gauge needle is inserted into the skin over the medial aspect of the dorsum of the proximal phalanx and advanced until the bone is encountered. The needle is then withdrawn slightly, and a small amount of fluid is aspirated to confirm that the tip of the needle is not in a blood vessel. Next, 0.5 to 1.0 ml of lidocaine, 0.5% or 1.0% without epinephrine, is slowly injected. The needle is then carefully advanced medial to the bone until the tip can be felt pressing against (but not puncturing) the plantar skin. Again, the needle is withdrawn slightly, fluid is aspirated, and 0.5 to 1.0 ml of lidocaine is injected. The same technique is repeated on the lateral aspect of the proximal phalanx. In this way, all four digital nerve branches are blocked. If multiple toe amputations are required, an ankle block, epidural anesthesia, spinal anesthesia, or general anesthesia may be used.

An incision is made to create dorsal and plantar skin flaps. Typically, these flaps are equal in length; however, depending on the location of the skin lesion, either the dorsal flap or the plantar flap can be left longer [see Figure 1]. Care must be

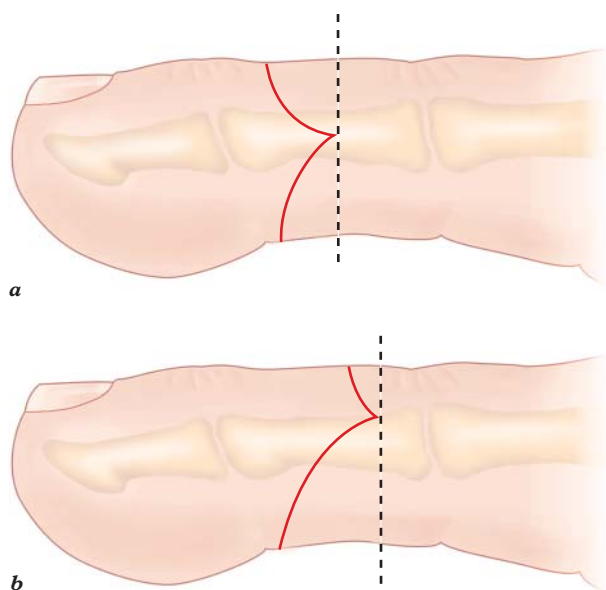


Figure 1 Toe amputation: transphalangeal amputation. Transphalangeal amputation can be performed either with dorsal and plantar flaps of equal length (a) or with a plantar flap that is longer than the dorsal flap (b). The phalanx is transected at the level of the apex of the skin flaps (dashed line). The bone is transected through the shaft of the phalanx, never across the joint.

taken not to create excessively long flaps, which may lack sufficient perfusion for healing, or to create undermined bevels with the scalpel [see Figure 2], which will lead to epidermolysis of the suture line.

The incision is extended down to the phalanx, and the soft tissues are gently separated from the bone with a small periosteal elevator. All tendons and tendon sheaths are débrided because the poor vascularity of these tissues may compromise the healing of the toe. The phalanx is transected at the level of the apices of the skin incisions [see Figure 1]. Care must be taken not to leave the remaining bone segment too long: this places undue tension on the skin flaps and is a primary cause of poor healing. The best way of transecting the phalanx is to use a pneumatic oscillating saw. Manual bone cutters can splinter the bone, and manual saws can cause extensive damage to the soft tissues. The bone is always transected across the shaft; because of the poor vascularity of the articular cartilage, disarticulation across a joint typically leads to poor healing.

Hemostasis is achieved with absorbable sutures and limited use of the electrocautery. Excessive tissue manipulation and electrocauterization should be avoided. The skin edges are carefully approximated with simple interrupted nonabsorbable monofilament sutures; perfect apposition is necessary to maximize the potential for primary healing. The sutures must not be placed too close to the skin edges, because the heavily keratinized skin of the foot is easily lacerated. The final step is the application of a soft dressing.

Ray Amputation

For ray amputation [see Figure 3], spinal, epidural, or general anesthesia may be employed. A so-called tennis-racket incision is made—that is, a straight incision along the dorsal surface of the affected metatarsal bone coupled with a circumferential incision around the base of the toe. The goal is to save all available viable skin on the toe; this skin is used to ensure a tension-free closure, and any excess skin can be débrided later, at the time of closure. Again, undermined bevels are avoided. The incision is taken down to the bone, and the soft tissues are separated from the distal metatarsal bone with a periosteal elevator. Dissection must be kept close to the affected metatarsal head to prevent injury to the adjacent metatarsophalangeal joint, which can lead to necrosis of the adjacent toe. The metatarsal bone is transected across the shaft with a pneumatic oscillating saw. The tendons and the tendon sheaths are débrided.

Meticulous hemostasis is achieved with absorbable sutures and limited use of the electrocautery. The skin is approximated with simple interrupted nonabsorbable monofilament sutures [see Figure 4]. If sufficient viable skin was preserved, a flap of plantar skin is rotated dorsally, and the incision is closed in the shape of a Y. Alternatively, the medial and lateral edges are shifted (one proximally and the other distally), the corners are trimmed, and the incision is closed in a linear fashion. A soft supportive dressing is applied.

COMPLICATIONS

Complications of toe amputation include bleeding, infection, and failure to heal. Because even a small amount of bleeding under the skin flaps can prevent proper healing, meticulous hemostasis is mandatory. In most cases, infection

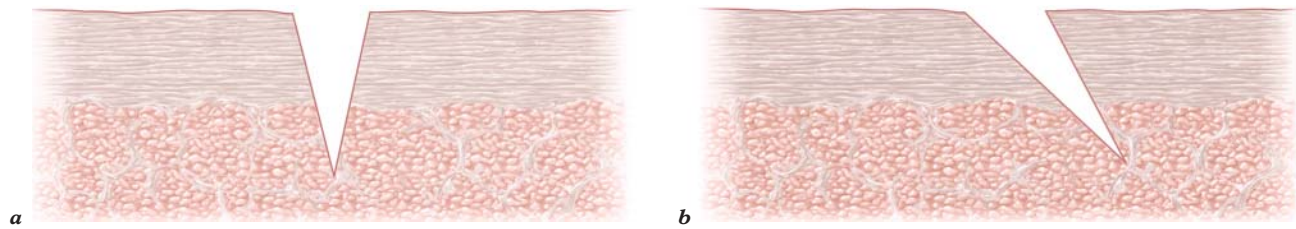


Figure 2 In a lower-extremity amputation, the skin is always incised perpendicular to its surface (a). Given the varying contours encountered during extremity amputation, it can be difficult to maintain the perpendicular orientation of the scalpel; however, an incision that undermines the proximal skin flap (b) will devascularize the epidermis and lead to necrosis of the suture line.

and failure to heal are attributable to poor patient selection and poor surgical technique; the usual result is a more proximal amputation.

OUTCOME

For optimal healing, there must be an extended period (2 to 3 weeks) during which no weight is borne by the foot that underwent toe amputation. Once healing is complete, the patient should be able to walk normally, with no need for orthotic or assist devices. Beginning ambulation too early can disrupt healing flaps and necessitate more proximal amputation, which lengthens the hospital stay and increases long-term disability. For these reasons, toe amputation in patients with arterial occlusive disease is not an outpatient procedure. Patients are kept on bed rest and instructed in techniques (e.g., use of a wheelchair, a walker, or crutches) that allow

them to function without stepping on the foot that was operated on. Hospital discharge is delayed until such techniques are mastered.

Transmetatarsal Amputation

OPERATIVE PLANNING

As noted (see above), transmetatarsal amputation is indicated if there is tissue loss in the forefoot involving the first metatarsal head, two or more of the other metatarsal heads, or the dorsal forefoot. It is contraindicated if there is extensive skin loss on the plantar surface of the foot or on the dorsum proximal to the midshaft of the metatarsal bones. The peroneus longus and the peroneus brevis insert on the proximal portions of the fourth and fifth metatarsal bones; if

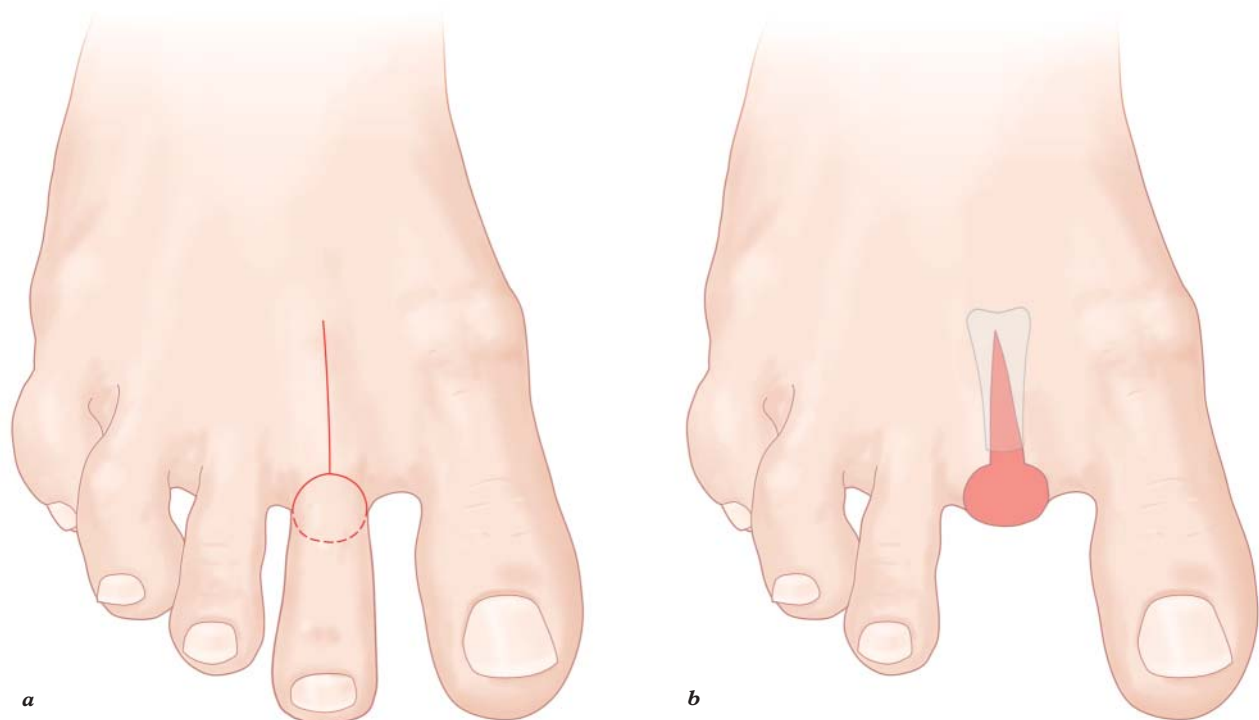


Figure 3 Toe amputation: ray amputation. (a) A longitudinal incision is made along the dorsum of the shaft of the metatarsal bone of the affected toe. A circumferential incision is then made around the phalanx. The circumferential incision should be placed as distal on the toe as there is viable skin so that as much skin as possible is retained for closure of the wound. (b) The metatarsal bone is transected across its shaft, proximal to the metatarsal head; the joint is never disarticulated.

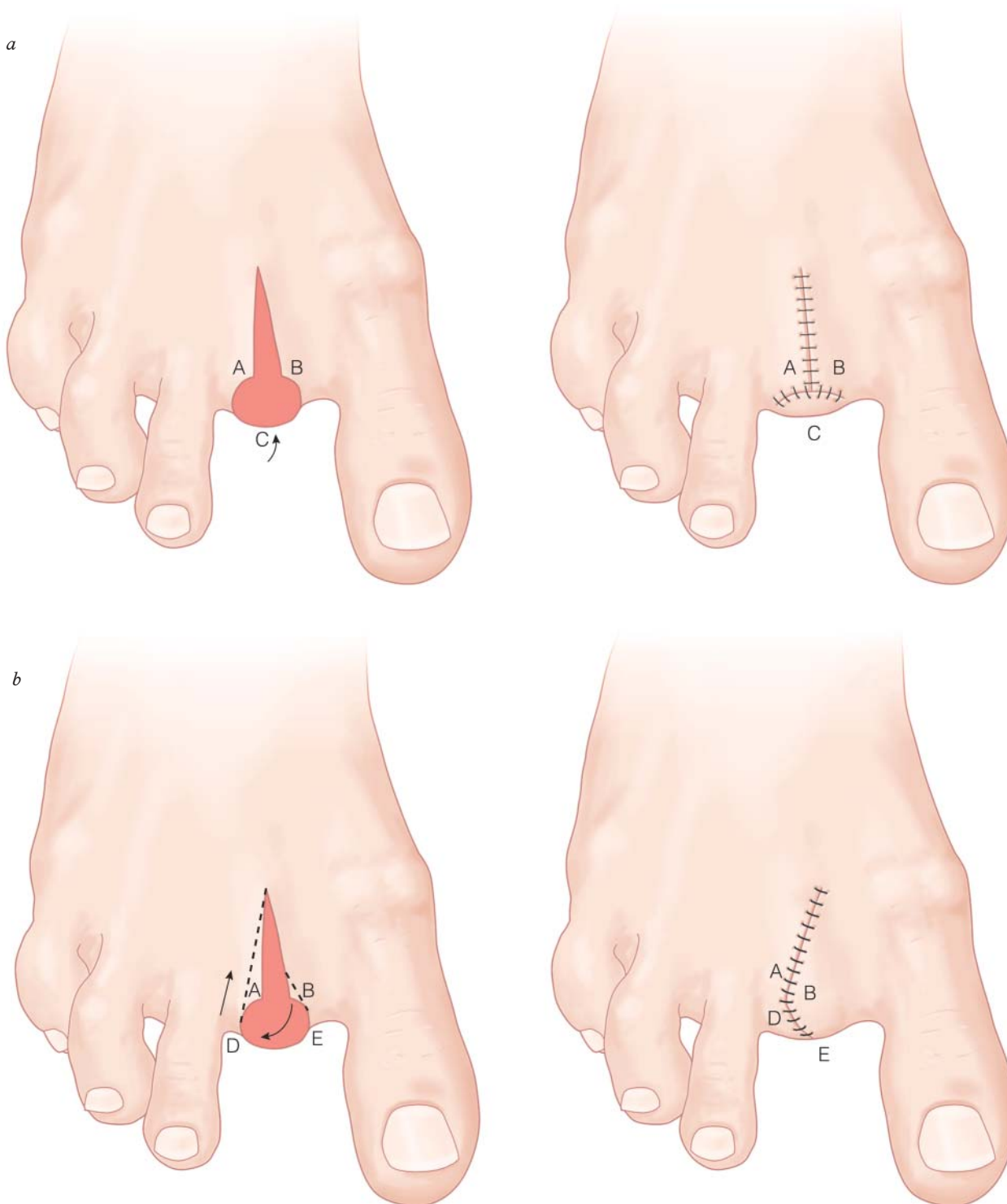


Figure 4 Toe amputation: ray amputation. (a) If adequate skin is available, a plantar flap can be rotated dorsally and the skin closed in a Y configuration. This closure is technically easy to perform; however, there is a risk of skin necrosis at corners A and B. (b) Alternatively, the skin can be closed in a linear fashion. Corners A and B are gently trimmed. Corner B is shifted distally toward point D as corner A is shifted proximally. A slight dog-ear will result at point E; however, it will diminish with time.

these insertions are sacrificed, inversion of the foot results, eventually leading to chronic skin breakdown from the side of the foot repeatedly striking the ground during ambulation. Transmetatarsal amputation is also contraindicated if there is a preexisting footdrop (peroneal palsy).

OPERATIVE TECHNIQUE

Spinal, epidural, or general anesthesia may be employed for transmetatarsal amputation. Placement of a tourniquet on the calf is a useful adjunctive measure. This step greatly reduces intraoperative blood loss. More important, the blood-

less operative field that results allows more accurate assessment of tissue viability and hence more precise selection of the level of amputation; in a field stained with extravasated blood, it is easy to leave behind nonviable tissue that will doom the amputation. Use of a tourniquet is, however, contraindicated in patients who have a functioning infrapopliteal artery bypass graft.

After sterile preparation and draping, the leg is elevated to help drain the venous blood, and a sterile pneumatic tourniquet is placed around the calf, with care taken to pad the skin under the tourniquet and to position the tourniquet over the calf muscles, where it will not apply pressure over the fibular head (and the common peroneal nerve) or other osseous prominences. The tourniquet is then inflated to a pressure higher than the systolic blood pressure. In patients who do not have diabetes mellitus, a tourniquet inflation pressure of 250 mm Hg is typically employed; in patients who have diabetes mellitus and calcified arteries, a pressure of 350 to 400 mm Hg is preferred.

An incision is made across the dorsum of the foot at the level of the middle of the shafts of the metatarsal bones, extending medially and laterally to the level of the center of the first and fifth metatarsal bones, respectively [see Figure 5]. The dorsal incision is curved proximally at the medial and lateral edges to ensure that no dog-ears remain at the time of closure. The dorsal incision is continued perpendicularly through the soft tissues on the dorsum down to the metatarsal bones. The plantar incision is extended distally to a point just proximal to the toe crease. Care is taken not to bevel the skin incisions.

A plantar flap is created by making an incision with the scalpel adjacent to the metatarsophalangeal joints; the incision is then carried more deeply to the level of the midshafts of the metatarsal bones on their plantar surfaces. The periosteum of the first metatarsal bone is scored circumferentially

with the scalpel, and the soft tissue is dissected away from the first metatarsal bone with a periosteal elevator to a point about 1 cm proximal to the dorsal skin incision. The first metatarsal bone is then transected perpendicular to its shaft at the level of the dorsal skin incision with a pneumatic oscillating saw. This process is repeated for each individual metatarsal bone, with care taken to follow the normal contour of the forefoot by cutting the lateral metatarsal bones at a level slightly proximal to the level at which the more medial bones are transected. All visible digital arteries are clamped and tied with absorbable ligatures. If a tourniquet was used, it is deflated at this time. All tendons and tendon sheaths are débrided from the wound.

Meticulous hemostasis is achieved with absorbable sutures and limited use of the electrocautery. Any sharp edges on the metatarsal bones are smoothed with a rongeur or a rasp. The wound is irrigated to flush out devitalized tissue and thrombus. The plantar flap is trimmed as needed. The dermis is approximated with simple interrupted absorbable sutures, and the knots are buried. Because the edge of the plantar flap is generally longer than the edge of the dorsal flap, the sutures must be placed slightly farther apart on the plantar flap than on the dorsal flap if perfect alignment is to be obtained. It is imperative to achieve the correct skin alignment with the dermal suture layer. Once this is accomplished, the skin edges are gently and perfectly apposed with interrupted vertical mattress sutures of nonabsorbable monofilament material. Finally, a soft supportive dressing with good padding of the heel is applied; casts and splints are avoided because of the risk of ulceration of the heel or over the malleoli.

COMPLICATIONS

If a tourniquet is not used, intraoperative blood loss can be substantial; the blood pools in the sponges and drapes, often out of the anesthesiologist's field of view. Consequently, good

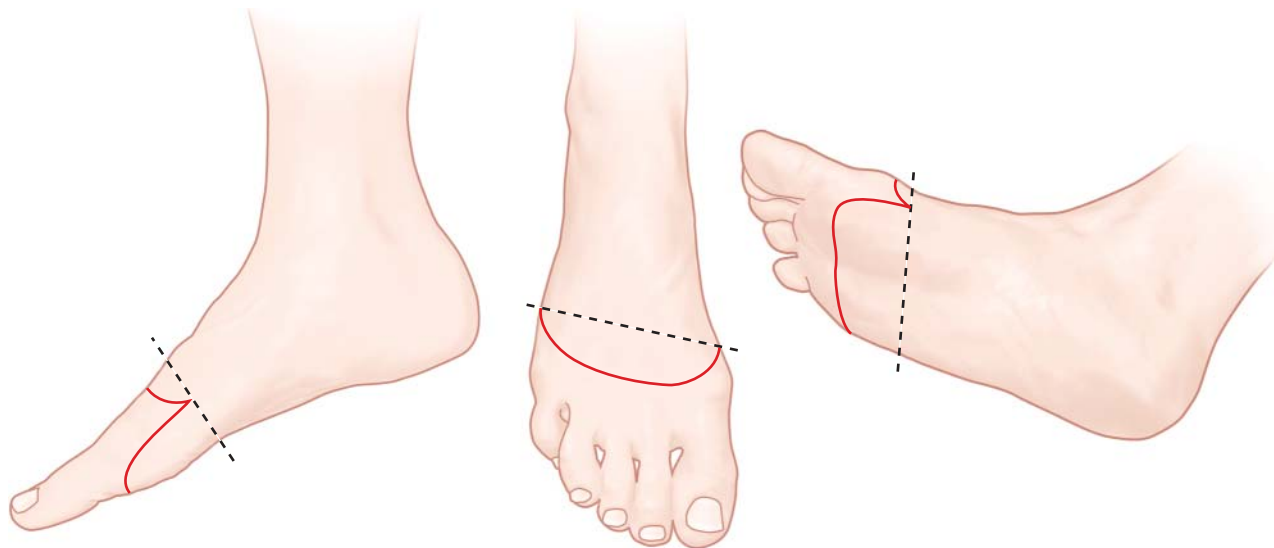


Figure 5 Transmetatarsal amputation. The skin incisions are shown from various angles. The metatarsal shafts are divided in their midportions (dashed line). The metatarsal bone transection is at the level of the apices of the skin incision, and the lateral metatarsal bones are cut slightly more proximally than the medial metatarsal bones, in a pattern reflecting the normal contour of the forefoot.

communication between the surgeon and the anesthesiologist is crucial for preventing ischemic complications secondary to hemorrhage.

Postoperative complications include bleeding, infection, and failure to heal, all of which are likely to result in more proximal amputation. They can best be prevented by means of careful patient selection and meticulous surgical technique.

OUTCOME

For proper healing, postoperative edema must be avoided and the plantar flap protected against shear forces. To prevent swelling, the patient is kept on bed rest with the foot elevated for the first 3 to 5 days. This step is particularly important if the transmetatarsal amputation was performed simultaneously with arterial reconstruction, which carries a high risk of reperfusion edema of the foot. After 3 to 5 days, the patient is instructed in techniques for moving in and out of the wheelchair without stepping on the foot. The foot that was operated on should not bear any weight at all for at least 3 weeks; early weight bearing may disrupt the healing of the plantar flap and necessitate more proximal amputation.

Once healed, patients should be able to walk independently with standard shoes. There is, however, a risk that they may trip over the unsupported toe of the shoe. In addition, the pushoff normally provided by the toes is lost after transmetatarsal amputation, and this change results in a halting, flat-footed gait. These problems can be obviated by using an orthotic shoe with a steel shank (to keep the toe of the shoe from bending and causing tripping) and a rocker bottom (to provide a smooth heel-to-toe motion).

Guillotine Ankle Amputation

OPERATIVE PLANNING

Guillotine amputation across the ankle is indicated when a patient presents with extensive wet gangrene that precludes salvage of a functional foot (e.g., wet gangrene that destroys the heel, the plantar skin of the forefoot, or the dorsal skin of the proximal foot). In such patients, initial guillotine amputation through the ankle is safer than extensive débridement: the operation is shorter, less blood is lost, the risk of bacteremia is reduced, and better control of infection is possible. Guillotine amputation is also indicated in patients with foot infections who have cellulitis extending into the leg. Transection at the ankle, perpendicular to the muscle compartments, tendon sheaths, and lymphatic vessels, allows effective drainage and usually brings about rapid resolution of the cellulitis of the leg, thus permitting salvage of the knee in many cases in which the knee might otherwise be unsalvageable.

OPERATIVE TECHNIQUE

General anesthesia is preferred for guillotine ankle amputation; regional anesthesia is relatively contraindicated for critically ill patients who are in a septic state. Anesthesia is required for no more than 15 to 20 minutes.

A circumferential incision is made at the narrowest part of the ankle (i.e., at the proximal malleoli) regardless of the level of the cellulitis [see Figure 6]. This placement takes the line of incision across the tendons, thereby preventing bleeding from transected muscle bellies. The incision is then carried through

the skin and soft tissues to the bone. If the arteries are patent, the assistant applies circumferential pressure to the distal calf. The distal tibia and fibula are then divided with a Gigli saw. Hemostasis is achieved with suture ligation and electrocauterization. A moist dressing is applied.

OUTCOME

After the procedure, the patient is kept on bed rest and given systemic antibiotics. Formal below-the-knee amputation can be performed when the cellulitis resolves, usually within 3 to 5 days. Routine dressing changes are unnecessary—first, because they are painful, and second, because the decision to proceed with formal below-the-knee amputation is based on the extent of the cellulitis in the calf, not on the appearance of the transected ankle.

Below-the-Knee Amputation

OPERATIVE PLANNING

Below-the-knee amputation is indicated when the lower extremity is functional but the foot cannot be salvaged by arterial reconstruction or by amputation of one or more of the toes or the forefoot. Healing can be expected if there is a palpable femoral pulse with at least a patent deep femoral artery, provided that the skin is warm and free of lesions at the distal calf. Before formal below-the-knee amputation, infection should be controlled with antibiotic therapy, débridement, and, if indicated, guillotine amputation. It is advisable to obtain consent to possible above-the-knee amputation beforehand in case unexpected muscle necrosis is encountered below the knee.

As with any amputation, the surgeon's preoperative interaction with the patient should be as positive as possible.

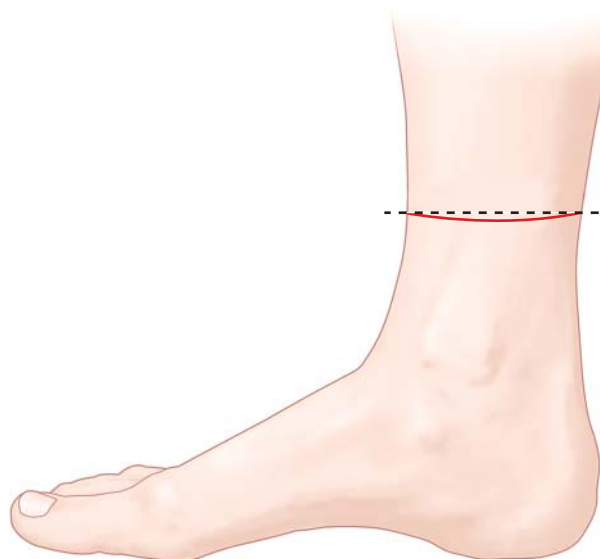


Figure 6 Guillotine ankle amputation. The skin incision is made circumferentially at the narrowest portion of the ankle. The bones are then transected at the same level (dashed line).

A constructive perspective to convey is that the amputation, though regrettably necessary, is in fact the first step toward rehabilitation. A well-motivated patient whose cardiopulmonary status is not too greatly compromised can generally be expected to walk again, albeit at an increased energy cost. In this regard, a preoperative discussion with a physiatrist can be very helpful, as can a meeting with an amputee who is doing well with a prosthesis. By inculcating a positive attitude in the patient before the procedure, the surgeon can greatly improve the patient's chances of achieving full rehabilitation, as well as decrease the time needed for rehabilitation.

OPERATIVE TECHNIQUE

Epidural, spinal, or general anesthesia is appropriate for below-the-knee amputation. The lines of incision should be marked on the skin. The primary level of amputation is determined by measuring a distance of 10 cm from the tibial tuberosity [see Figure 7]. The circumference of the leg at this level is then measured by passing a heavy ligature around the leg and cutting the ligature to a length equal to the circumference. The ligature is folded into thirds and cut once more at one of the folds, so that two segments of unequal length remain. The longer segment of the ligature, which is equal in length to two-thirds of the leg's circumference 10 cm below the tibial tuberosity, is used to measure the anterior transverse incision; this incision is centered not on the tibial crest but on the gastrocnemius-soleus muscle complex. The shorter segment, which is one-third of the leg's circumference at this level, is used to measure the posterior flap; the line of the posterior incision runs parallel with the gastrocnemius-soleus complex. To prevent dog-ears, the medial and lateral ends of the anterior transverse incision are curved cephalad before meeting the posterior incision, and the distal corners of the posterior incision are curved as well.

Blood loss can be reduced by using a sterile pneumatic tourniquet. A gauze roll is passed around the distal thigh. The leg is elevated to drain the venous blood, and the tourniquet is applied over the gauze roll. The tourniquet is inflated to a pressure of 250 mm Hg (350 to 400 mm Hg if the patient has heavily calcified arteries). The assistant elevates the leg, and the incision on the posterior flap is made first, followed by the anterior transverse incision; this sequence helps prevent blood from obscuring the field while the incisions are being made. The incisions are carried fully through the dermis, and the skin edges are allowed to separate and expose the subcutaneous fat. Care is taken to keep the scalpel perpendicular to the skin so as not to bevel the incision, which can lead to necrosis of the epidermal edges [see Figure 2].

The anterior muscles are transected with the scalpel in a direction parallel to the transverse skin incision. The tibia is scored circumferentially, and a periosteal elevator is used to dissect the soft tissues away from the tibia for a distance of approximately 3 to 4 cm. The tibia is then transected just proximal to the transverse skin incision. Dividing the tibia more than 1 cm proximal to the anterior skin incision will cause the thin skin of the anterior leg to be pulled taut over the cut end of the tibia by the weight of the posterior flap, thereby leading to skin ulceration. The tibia is transected perpendicularly, with a cephalad bevel of the anterior 1 cm

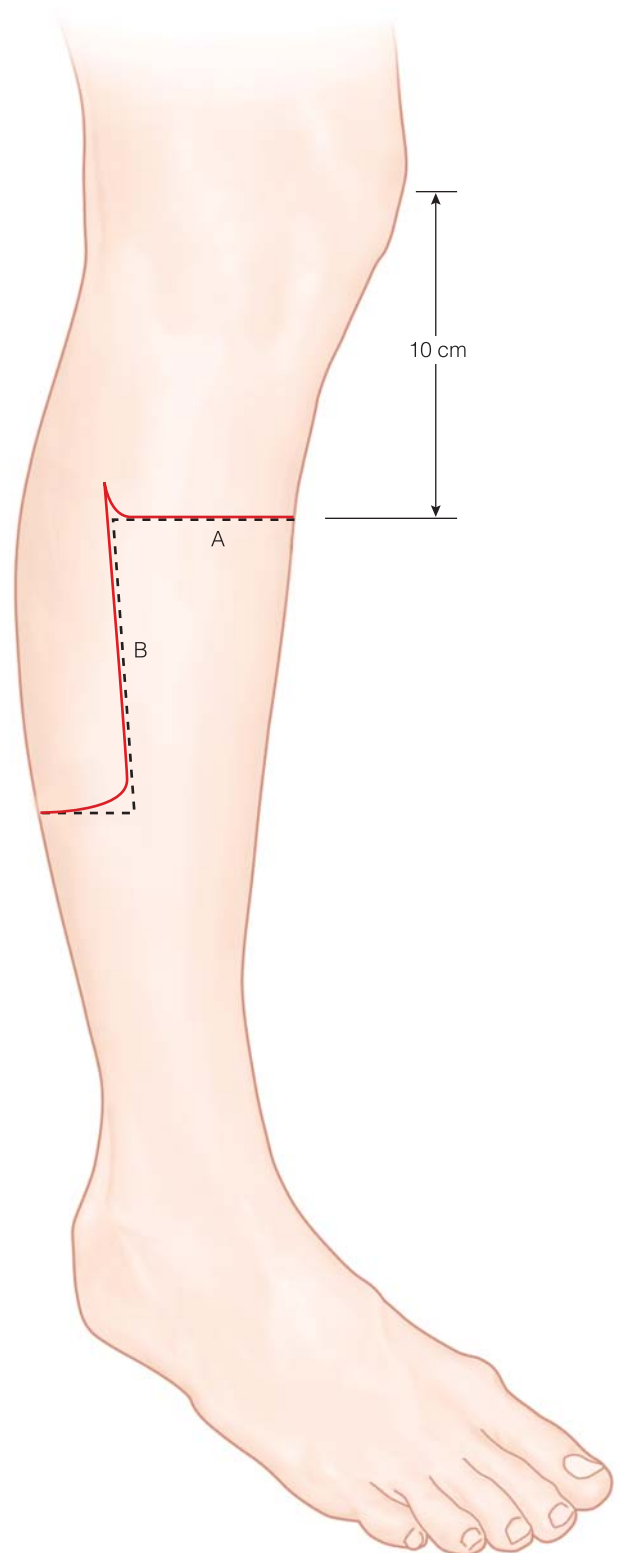


Figure 7 Below-the-knee amputation. The transverse incision (A) is made 10 cm distal to the tibial tuberosity. Its length is equal to two thirds of the circumference of the leg at that level. The posterior incision (B) is made parallel with the gastrocnemius-soleus muscle complex. The length of the posterior flap is equal to one third of the measured circumference of the leg. The corners of the incisions are curved to avoid dog-ears.

to keep from creating a sharp point at the tibial crest [see Figure 8]. The tibia can be transected with either a Gigli saw or an oscillating saw; because of the unpleasant sound of the power saw, the Gigli saw is preferred if the patient is under regional anesthesia. Sedation should be augmented in awake patients before division of the tibia. Benzodiazepines provide good sedation and amnesia.

The lateral muscles are divided, and the fibula is scored circumferentially. A periosteal elevator is used to dissect the soft tissues away from the fibula to a point 2 to 3 cm cephalad to the level at which the tibia was transected. The fibula is then transected with a bone cutter at least 1 cm cephalad

to the tibial transection level. The distal end of the tibia is lifted with a bone hook, and division of the posterior muscles is completed with an amputation knife. The specimen is then handed off the field.

The anterior tibial, posterior tibial, and peroneal arteries and veins are clamped, and the tourniquet is released. Clamps are placed on all other bleeding vessels. The posterior tibial and sural nerves are placed on gentle traction and clamped proximally. The nerves are transected and ligated, and the proximal nerves are allowed to retract into the soft tissues so as to prevent painful neuromas at the end of the stump. All clamped structures are then ligated with absorbable ligatures. The nerves are ligated because their nutrient vessels can bleed significantly. The distal anterior tip of the tibia is smoothed with a rasp to decrease the risk of skin ulceration over this osseous prominence. The stump is gently irrigated to remove all thrombus and devitalized tissue and to reveal any bleeding sites that may have been missed. Electrocauterization is rarely necessary.

The deep muscle fascia—not the Achilles tendon—is approximated with simple interrupted absorbable sutures, with care taken to align the posterior flap with the anterior incision. The skin is approximated by placing simple interrupted absorbable sutures, with buried knots, at the dermal-epidermal junction (interrupted subcuticular sutures). A carefully padded posterior splint is applied to prevent flexion contracture.

COMPLICATIONS

The most common complications after below-the-knee amputation are bleeding, infection, and failure to heal, all of which are likely to result in a more proximal amputation, frequently accompanied by loss of the knee. Prevention of these complications depends on careful patient selection, preoperative control of infection, and meticulous surgical technique.

To walk with a prosthetic leg, the patient must be capable of fully extending and locking the knee; thus, flexion contracture at the knee is a major complication. Such contractures are usually attributable either to poor pain control or to non-compliance with knee extension exercises. Good perioperative analgesia is of vital importance because knee flexion is the position of comfort and the patient will be unwilling to extend the knee if doing so proves too painful. To maintain knee extension, the patient should be placed in a splint in the early postoperative period. Once postoperative pain has abated, the splint can be removed. At this point, the patient must be taught extension exercises, in which the quadriceps muscles are contracted to maintain the length of the hamstring muscles. If a patient spends all of his or her time in a sitting position with the knee flexed, a flexion contracture will quickly develop. Once this happens, the patient may find it very difficult to regain full knee extension, and without full knee extension, prosthetic limb rehabilitation is impossible.

Phantom sensation is a common complication after below-the-knee amputation but is rarely of any consequence. Phantom pain, on the other hand, can be devastating. Sometimes, phantom pain develops as a consequence of unintentional suggestions made to the patient by medical personnel

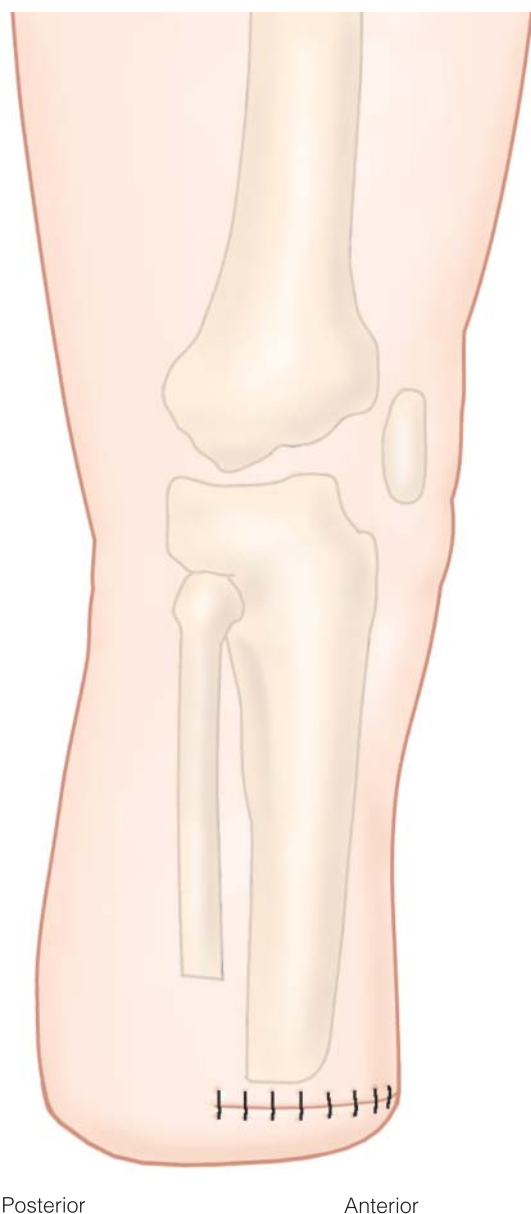


Figure 8 Below-the-knee amputation. In this lateral view of the right leg, the tibia is beveled anteriorly, and the anterior portion is smoothed with a rasp. The fibula is transected at least 1 cm proximal to the level of transection of the tibia.

who fail to distinguish between the two entities. For example, a patient remarks to a medical attendant that he or she can still feel the amputated foot and toes, and the attendant suggests in response that the patient has phantom pain; the patient then focuses on the sensation and exaggerates the severity of the foot and toe discomfort, setting up a cycle of ever-worsening pain. This scenario is even more likely if the patient had prolonged ischemic rest pain before the amputation. Phantom pain can be prevented by (1) encouraging early amputation in a patient with a hopelessly ischemic foot (while taking into account the patient's need to come to grips with the prospect of amputation), (2) providing good pain control in the early postoperative period, and (3) assuring the patient that phantom sensation after a below-the-knee amputation is common and that any discomfort in the foot immediately after the operation period will vanish once he or she begins walking again with a prosthetic leg.

Ulceration of the skin over the transected anterior portion of the tibia is another serious complication that may preclude successful prosthetic limb fitting. This complication is also best managed through prevention, which depends on meticulous surgical technique. As noted (see above), the anterior tibial crest must be carefully beveled and smoothed at the level of transection, and the tibia must not be transected more than 1 cm proximal to the anterior skin incision.

With a standard below-the-knee prosthetic leg, weight is borne on the femoral condyles, the patella, and the tibial tuberosity. Breakdown of the stump can occur if weight is borne on the distal portion of the stump. Several decades ago, Jan Ertl described a tibiofibular synostosis designed to allow distal weight bearing; however, this technique has not been widely adopted.¹⁰

OUTCOME

Shortly after the amputation, the patient should be encouraged to start working on strengthening the upper body; upper-body strength is critical for making transfers and for using parallel bars, crutches, or a walker. In patients who have preoperative intractable ischemic rest pain, postoperative administration of epidural analgesia can break the cycle of pain. Once postoperative pain is adequately controlled, patients are taught to transfer in and out of a wheelchair. A compression garment is used on the stump once the sutures have been removed and the stump is fully healed.

Prosthetic rehabilitation begins when the stump achieves a conical shape. Unfortunately, a number of patients who have undergone amputation for ischemia are unable to walk with a prosthetic limb because of comorbid medical conditions and general debility. In many cases, however, even if full ambulation is impossible, patients can maintain relative independence if the knee is salvaged by using a combination of a prosthetic leg and a walker for transfers and movement around the house.⁶

Above-the-Knee Amputation

OPERATIVE PLANNING

Above-the-knee amputation is indicated if the lower extremity is unsalvageable and there is no femoral pulse.

The presence of pulsatile flow into a well-developed ipsilateral internal iliac artery usually ensures healing, but even when there is more severe arterial occlusive disease in the pelvis, healing can sometimes be achieved. Above-the-knee amputation is also indicated if there is tissue necrosis or uncontrollable infection extending cephalad to the midleg. Above-the-knee amputation is the procedure of choice in the case of gangrene or ulceration of a completely nonfunctional lower extremity.

OPERATIVE TECHNIQUE

Epidural, spinal, or general anesthesia may be used for above-the-knee amputation. For the best functional results, it is desirable to keep the femur as long as possible. A longer stump improves the prognosis for prosthetic limb rehabilitation and provides better balance for sitting and transfers. Healing potential, however, is lower with a longer stump; therefore, if the pelvic circulation is severely compromised, a shorter stump should be fashioned.

Anterior and posterior flaps of equal length are marked on the skin. The flaps should be wide and long [see *Figure 9*], and their apices should be centered on the line dividing the

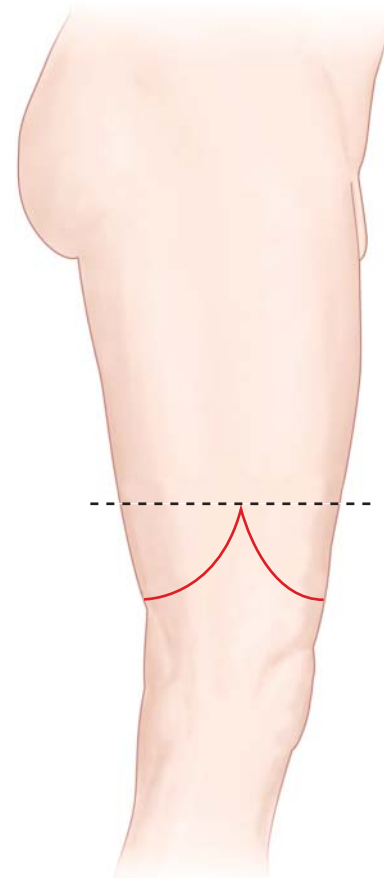


Figure 9 Above-the-knee amputation. Broadly based anterior and posterior flaps are created. The femur is transected along the dashed line, at the apices of the skin flaps. The skin flaps and the level of transection of the femur can be placed more proximally if clinically indicated.

anterior and posterior muscle compartments. The posterior incision is made first to minimize the presence of blood in the operative field. The anterior incision is made second and carried through the anterior muscles in a plane parallel to the skin incision. The skin incisions are carried through the dermis, and the skin edges are allowed to separate and expose the subcutaneous fat; as in other amputations, they should be perpendicular to the skin surface so as not to undermine the skin.

If the superficial femoral artery is patent, the artery and vein are isolated and clamped after the sartorius is divided but before the remainder of the anterior muscles are divided. The femur is scored circumferentially. The soft tissues are dissected away from the femur to the level of the apices of the flaps, and the femur is divided with an oscillating saw at this level. If the end of the resected femur extends beyond the apices of the flaps, the wound cannot be closed without

tension. The posterior flap is completed with an amputation knife, and the specimen is handed off the field.

All bleeding points are clamped and tied with absorbable sutures. The sciatic nerve is placed on gentle traction, clamped, divided, and ligated, and the transected nerve is allowed to retract into the muscles. The deep fascia is approximated with interrupted absorbable sutures, with adjustments made for any discrepancy in length between the two flaps. The skin is approximated by placing interrupted absorbable sutures, with buried knots, at the dermal-epidermal junction (interrupted subcuticular sutures).

A nonadherent dressing is placed on the suture line and covered with dry, fluffed gauze bandages. An aerosol tincture of benzoin is sprayed on the thigh, the hip, and the lower abdomen. When the benzoin is dry, a cloth stockinette with a diameter of 4 in. is stretched over the stump [see Figure 10]. The cuff of the stockinette is cut medially at the groin, and

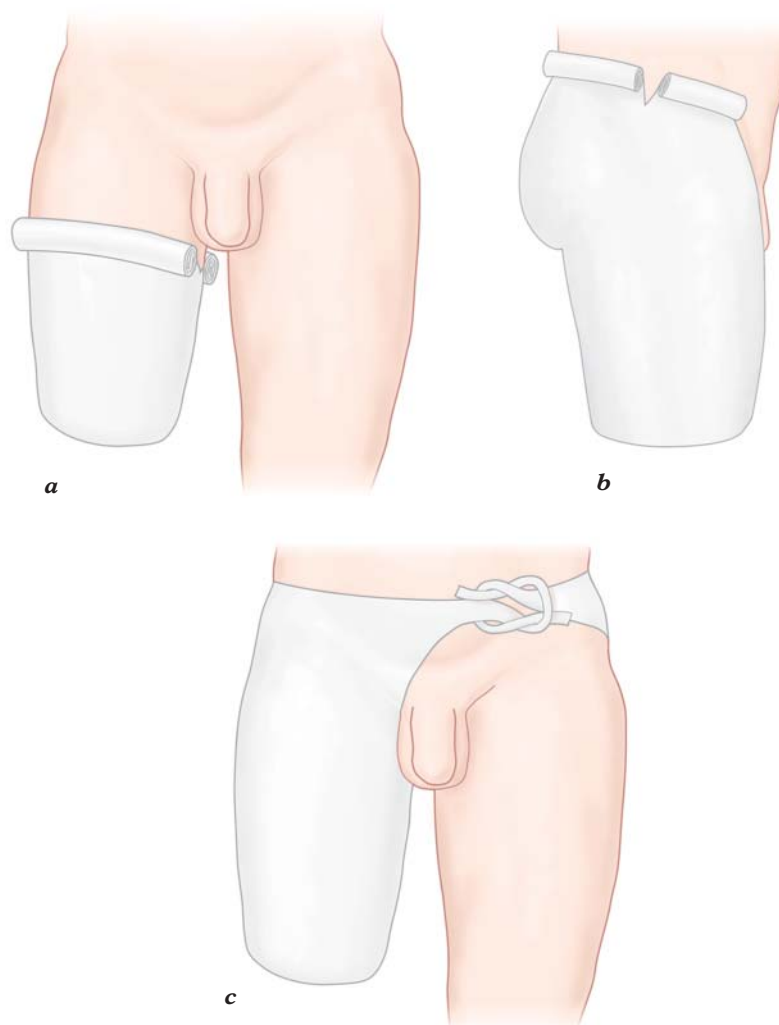


Figure 10 Above-the-knee amputation. (a) After an aerosol tincture of benzoin is applied to the thigh, the hip, and the lower abdomen, a 4 in. wide stockinette is rolled over the amputation stump. The cuff of the stockinette is cut medially at the groin. (b) The remainder of the stockinette is then rolled laterally up over the hip, and the cuff is cut on the lateral midline. (c) The two resulting strips of cloth are passed around the waist, one anteriorly and one posteriorly, and these strips are tied on the anterior midline to complete the dressing.

the stockinette is rolled laterally above the hip, where the cuff is then cut on the midaxillary line. This process yields two strips of cloth, one anterior and one posterior, which are passed around the patient's waist and tied on the anterior midline.

If the patient is a candidate for prosthetic limb rehabilitation, a traction rope is passed through a hole cut in the distal end of the stockinette and tied. The rope is hung over the end of the bed and tied to a 5 lb weight; this step helps prevent flexion contracture at the hip.

The stockinette need not be removed for the wound to be inspected. A window is cut in the distal end of the stockinette, and the gauze is removed. Once the incision has been inspected, fresh gauze is applied, and the window in the stockinette is closed with safety pins.

COMPLICATIONS

Postoperative complications include bleeding, infection, and failure to heal, all of which are likely to result in the need for surgical revision of the amputation stump. Control of preoperative infection and meticulous surgical technique and hemostasis are necessary to prevent these complications.

Flexion contracture of the hip is a major complication of above-the-knee amputation. Such contractures preclude

successful prosthetic limb rehabilitation. In dealing with this complication, prevention is far more effective than treatment: once a flexion contracture at the hip becomes fixed, it is very difficult to reverse. If a patient is a candidate for prosthetic limb rehabilitation, the traction weight mentioned earlier (see above) can be very helpful. As soon as postoperative pain is controlled, the patient should be taught to spend three periods daily in a prone position to help extend the hip. He or she should then be taught exercises for maintaining range of motion in the hip before prosthetic limb rehabilitation is initiated. Flexion contracture of the hip is less of a problem in nonambulatory patients; however, it can still lead to wound breakdown and chronic skin ulceration.

Gottschalk noted that loss of the adductor magnus leads to abnormal abduction of the femur. Accordingly, he proposed preservation of the adductor magnus and myodesis of the transected muscles to the femur to improve the biomechanics after above-the-knee amputation.^{11,12}

OUTCOME

Once postoperative pain has abated, patients are mobilized to wheelchair transfers. The prognosis for successful prosthetic limb ambulation in patients undergoing above-the-knee amputation for ischemia is very poor.

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Figures 1 through 10 Tom Moore.

21 RENOVASCULAR HYPERTENSION AND STENOSIS

Michael T. Watkins, M.D., F.A.C.S., and Marvin D. Atkins, M.D.

Approach to Suspected Renovascular Disease

Vascular disease that affects the renal arteries is an increasingly common clinical scenario encountered by general and vascular surgeons. As a result of heightened clinical awareness and advances in vascular imaging, more patients than ever before are being identified as having some degree of atherosclerotic or fibromuscular renovascular disease. The vast majority of these lesions cause no symptoms, are hemodynamically insignificant, or both. Some, however, are severe enough to alter renal perfusion pressure, leading to changes in blood pressure regulation and renal function. Symptomatic renovascular disease can have a variety of manifestations, ranging from mild renovascular hypertension to congestive heart failure and ischemic nephropathy.

Our purpose in this chapter is to outline an approach to the diagnosis and management of renovascular disease that is based on an understanding of the relevant pathophysiology [see Discussion, Pathophysiology of Renovascular Hypertension, *below*]. The procedures employed for surgical and endovascular treatment of renovascular disease are described in greater depth in other chapters [see 6:22 *Open Procedures for Renovascular Disease* and 6:23 *Endovascular Procedures for Renovascular Disease*].

Incidence and Risk Factors

In the United States, hypertension affects approximately 24% of the entire population and 50% of persons over the age of 60 years.¹ It is an independent risk factor for increased cardiovascular morbidity and mortality: cardiovascular risk doubles for every 20/10 mm Hg increase in blood pressure.² In fact, it is the number-one modifiable risk factor associated with increased cardiovascular morbidity and mortality. Data from the National Health and Nutrition Examination Survey (NHANES) revealed that 30% of hypertensive persons in the United States were unaware that they had hypertension, that more than 40% of hypertensive persons were not being treated for their condition, and that in two thirds of hypertensive patients who were being treated, blood pressure was not maintained below the recommended target level of 140/90 mm Hg.

An estimated 90% to 95% of cases of hypertension are classified as essential or idiopathic, with the remaining 5% to 10% considered to be secondary to another cause. Secondary hypertension is sometimes refractory to usual medical treatment, the reason being that the underlying pathophysiologic state must be identified and treated in addition to the hypertension itself. There are many possible causes of secondary hypertension [see Table 1], and it can be difficult to determine which one is operative in a given clinical situation. As a result of the increasing use of diagnostic

imaging, renal artery stenosis (RAS) is frequently diagnosed in hypertensive patients. However, the precise contribution RAS makes to hypertension and renal dysfunction is not always clear, and therefore, the patient's response to treatment may not be readily predictable.

The natural history of RAS consists of continued narrowing of the renal artery. Studies in which duplex ultrasonography (DUS) was employed to follow untreated patients with greater than 60% renal artery stenosis documented a 20% progression of disease per year, with 11% of patients progressing to renal occlusion within 2 years.³ RAS is associated with loss of renal mass, which is a surrogate marker for renal function. Occlusion of a renal artery is associated with substantial loss of renal size and function. Historical studies of the clinical course of RAS suggested that chronic renal failure developed within 6 years in as many as 27% of patients with RAS.⁴

The two main conditions associated with RAS are atherosclerosis and fibromuscular dysplasia. The former accounts for the vast majority of renovascular lesions. Atherosclerotic RAS is typically located at the aortic orifice or the proximal renal artery and probably represents spillover of aortic atherosclerotic disease [see Figure 1]. It is most commonly found in patients older than 50 years who have signs of atherosclerosis in other vascular beds. RAS associat-

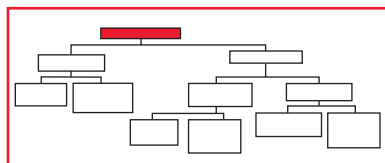
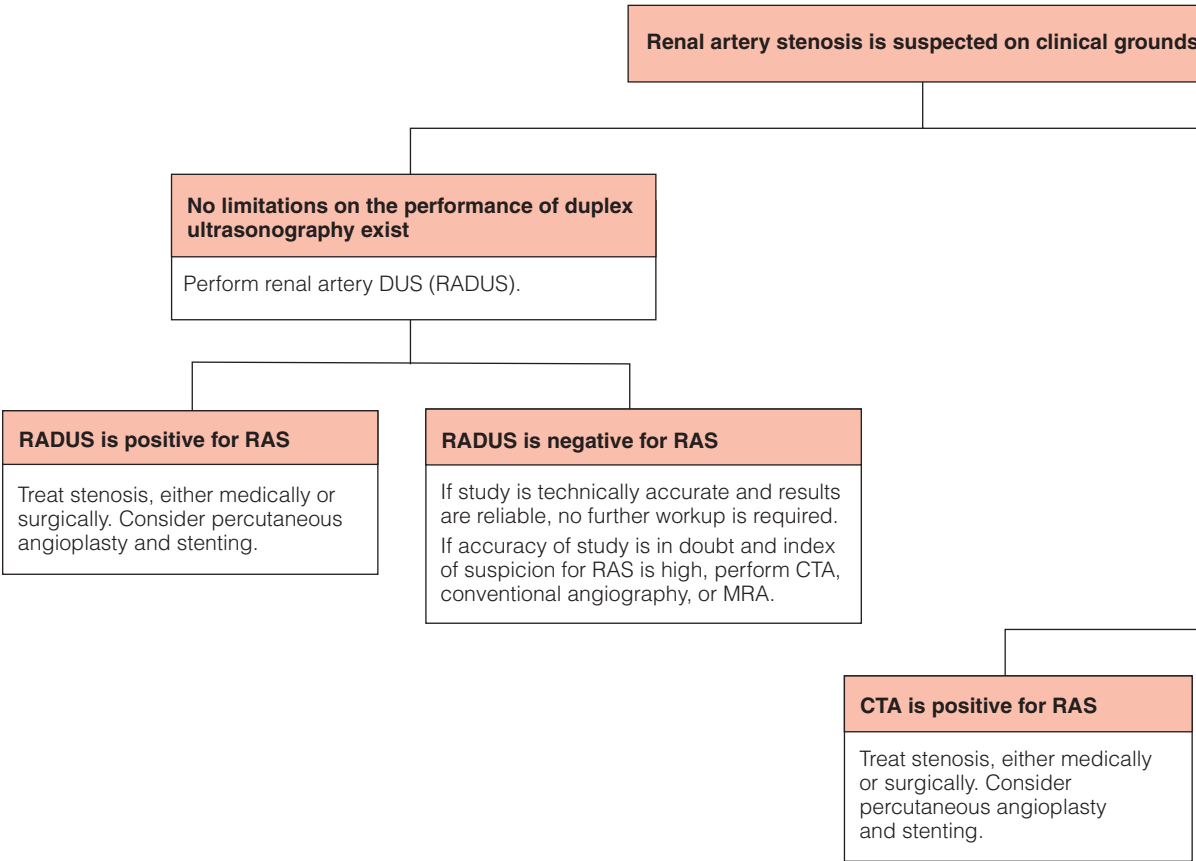


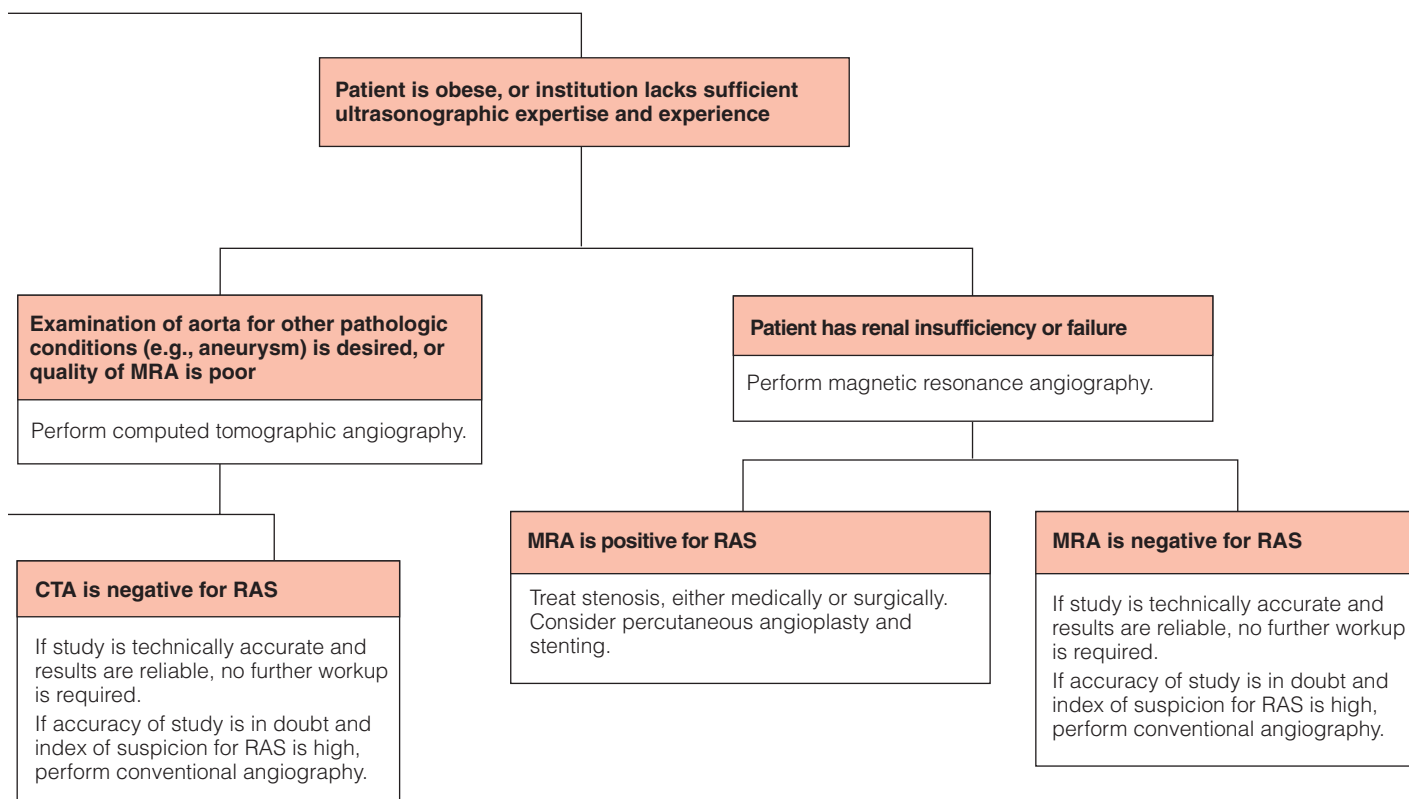
Table 1 Screening Tests for Secondary Causes of Hypertension

Diagnosis	Diagnostic Study
Chronic renal disease and salt retention	Serum creatinine, GFR
Renal artery stenosis	DUS, MRA, CTA
Primary hyperaldosteronism	24-hr urinary aldosterone
Pheochromocytoma	24-hr urinary metanephrine, normetanephrine
Cushing syndrome or chronic steroid use	History, cortisol, dexamethasone suppression test
Thyroid or parathyroid disease	TSH, calcium, serum PTH
Coarctation of aorta	CTA
Sleep apnea	Sleep study with oxygen saturation
Effect of medication	History, drug screen

CTA—computed tomographic angiography DUS—duplex ultrasonography GFR—glomerular filtration rate MRA—magnetic resonance angiography PTH—parathyroid hormone TSH—thyroid-stimulating hormone



Approach to Suspected Renovascular Disease



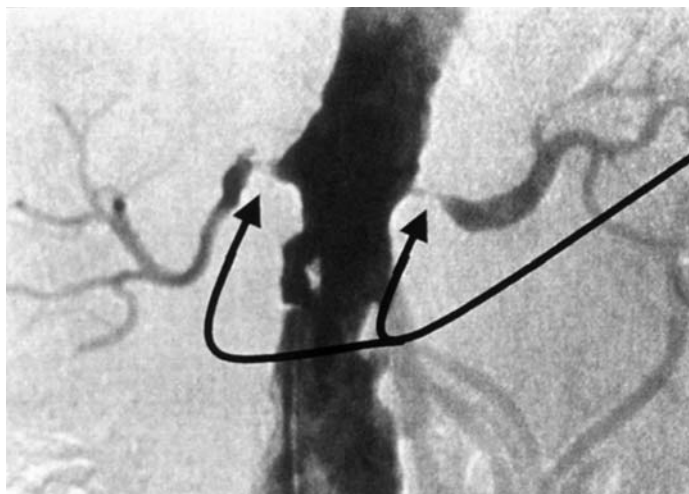


Figure 1 Shown is severe bilateral RAS with poststenotic dilation in a severely diseased aorta.

ed with fibromuscular dysplasia is usually seen in patients younger than 40 years and usually affects the middle and distal segments of the renal artery. These lesions have a characteristic “string of beads” appearance.

Population-based studies indicate that hemodynamically significant atherosclerotic RAS is present in approximately 6% of persons older than 65 years, with a somewhat higher incidence in men (9.1%) than in women (5.5%). Incidental RAS is seen in approximately 20% of patients undergoing coronary angiography and in 35% to 50% of patients undergoing peripheral vascular angiography for occlusive disease of the aorta and the lower extremity. The prevalence of renovascular disease corresponds to the overall atherosclerotic burden. In the vast majority of patients, no direct causal relation between significant RAS and hypertension or ischemic nephropathy can be identified. Efforts to define such a relation are confounded by the fact that the same population in which renovascular disease is prevalent is also at risk for essential hypertension, diabetes, and baseline renal insufficiency. Other risk factors associated with renovascular disease include smoking, increased age, and hyperlipidemia.

RAS is believed to be the cause of hypertension in only 3% to 5% of the 90 million hypertensive persons in the United States. In those with mild hypertension (the vast majority), it plays only a negligible role; however, it plays a significantly larger role in those with severe systemic hypertension. (The severity of a case of hypertension is related to the patient’s blood pressure without medication, not necessarily to the difficulty or ease with which blood pressure can be controlled medically.) At the extremes of age (i.e., in the very young and the elderly), severe hypertension is substantially more likely to be renovascular than essential in origin [see Table 2].

Patients with RAS are at higher risk for cardiovascular morbidity and mortality than similar patients without RAS are. One series, in which patients underwent renal angiography after coronary angiography, found that 4-year survival was significantly decreased in patients with incidentally discovered RAS.⁵ Several series have suggested that the risk of adverse cardiovascular events is high in this population and exceeds the risk that might have been expected on the basis of the severity of hypertension.^{6,7} Blood pressure control—measured by the number of antihypertensive medications used, as well as by systolic and diastolic pressures—is the most commonly used end point in series examining treatment

of RAS. These studies make the points that cardiovascular risk is high in RAS patients and that blood pressure control may be a poor surrogate for clinical outcome. At present, it is not known whether the higher cardiovascular morbidity and mortality associated with RAS are attributable to the effects of renal ischemia or to the systemic effects of activation of the renin-angiotensin-aldosterone system (RAAS) [see Discussion, Pathophysiology of Renovascular Hypertension, below] or whether RAS is simply a marker of more advanced atherosclerotic disease.

Ischemic nephropathy may be defined as a progressive decline in renal function secondary to global renal ischemia. It is estimated that for 5% to 15% of the patients in whom end-stage renal disease necessitating dialysis develops each year, ischemic nephropathy is the underlying cause of the decline in renal function.^{8,9}

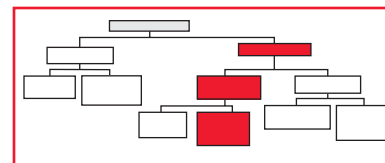
Investigative Screening Studies

Screening for suspected RAS is performed to identify those patients who are most likely to benefit from renal artery interventions aimed at managing hypertension or renal insufficiency. The decision regarding which screening test or tests to perform is not, however, a simple and obvious one. All of the noninvasive studies currently in use have their strengths and weaknesses, many of which are institution dependent. Constant improvements in technology and institutional variations in reporting standards, techniques, and published results have further complicated the process of determining the optimal first-line screening method. A variety of physiologic tests have been employed to screen for RAS and assess the contribution of RAS to hypertension or ischemic nephropathy. Peripheral plasma renin assays, rapid-sequence intravenous pyelography (for indirect assessment of differences in renal filtration), and isotope renography have all proved insufficiently sensitive to be useful for screening purposes. Catheter-based angiography has been widely used to screen for RAS, but technical improvements in DUS, computed tomographic angiography (CTA), and magnetic resonance angiography (MRA) have caused many physicians to prefer one or another of these imaging modalities for this purpose. A thorough understanding of the strengths and limitations of all of the screening tests, as well as an informed awareness of specific institutional limitations, is required to define the place of each test in one’s preferred diagnostic approach.

IMAGING

Contrast Arteriography

Of the several noninvasive or functional studies that are used to diagnose RAS and renovascular hypertension, none has displaced catheter-based contrast arteriography from its role as the diagnostic gold standard. In many institutions, however, CTA is now considered preferable to formal catheter-based arteriography as an easily reproducible screening test for RAS. The obvious drawback of CTA, as compared with the other imaging modalities, is the necessity of administering iodinated contrast material and the consequent risk of contrast-induced nephropathy (CIN). We frequently use CTA for the diagnosis of RAS in cases where concomitant aortoiliac aneurysmal or occlusive disease is suspected [see Figure 2].



“Drive-by” renal arteriography In a 1992 study of screening renal angiography (the largest such study published to date), 1,235 consecutive patients underwent renal arteriography at

Table 2 Clinical Clues to Diagnosis of Renal Artery Stenosis

Onset of hypertension at extremes of age (< 30 or > 60 yr)
Severe hypertension at > 55 yr
Accelerated, resistant, or malignant hypertension
Unexplained renal insufficiency or failure
Renal dysfunction associated with initiation of ACE inhibitor or ARB therapy
Unexplained congestive failure, pulmonary edema, or both
Unexplained atrophic kidney or size discrepancy between kidneys
Abdominal bruit

the conclusion of coronary angiography.¹⁰ Approximately 30% of these patients were found to have evidence of RAS, and 15% had greater than 50% stenosis. A 2001 study confirmed that RAS is associated with an increased risk of myocardial infarction, stroke, and death and that its presence in patients with coronary disease doubles the risk of mortality even when coronary revascularization is performed.⁵ This same study found that the severity of RAS was also predictive of mortality: 4-year survival was significantly lower (47%) in patients with bilateral RAS than in those with unilateral RAS (59%). The addition of nonselective renal arteriography in cases where the patient's serum creatinine concentration was lower than 2.0 mg/dl was associated with minimal additional cost and no clinically significant deterioration in renal function.

In 2006, on the basis of the findings from these studies, the American Heart Association (AHA) published a science advisory that made recommendations concerning routine renal arteriography in patients undergoing coronary angiography.¹¹ The AHA concluded that screening renal arteriography can reasonably be performed at the time of cardiac catheterization in patients at increased risk for RAS who are candidates for revascularization; however, it made no recommendation regarding concomitant treatment of RAS discovered during cardiac catheterization. In most cases, such a combined intervention is not feasible, whether because of the lack of preprocedural informed consent about renal artery endovascular intervention, the risk of CIN, or both.

Duplex Ultrasonography

In many institutions, including our own, renal artery duplex ultrasonography (RADUS) is currently used as the first-line screening test for RAS. Compared with other imaging modalities, RADUS has several unique advantages. In B mode, it provides direct images of the renal arteries, as well as a clear picture of contralateral kidney size (see below). It allows ongoing surveillance of lesions and interventions. It also achieves excellent imaging through renal stents, which on MRA appear only as flow voids. Finally, unlike CTA or even gadolinium-enhanced MRA, RADUS carries no risk of CIN.

Before RADUS is performed, the patient should fast overnight, should be given simethicone (to minimize interference on the images caused by bowel gas), or both. The study is done from both the anterior approach and the oblique flank approach; the latter is particularly helpful in obese patients, whose body habitus may severely limit the accuracy of the study. The renal arteries are imaged at their aortic origin and in their middle and distal segments. The peak systolic and end-diastolic arterial velocities are measured in

B mode with a Doppler angle of less than 60°. The ratios between the velocities in the renal artery and those in the aorta are determined, and the Doppler spectral waveform is recorded [see Figure 3]. The normal Doppler spectral waveform of the low-resistance renal vascular bed shows continuous diastolic flow.



Figure 2 CTA in a woman with a 7 cm infrarenal abdominal aortic aneurysm and chronic renal insufficiency shows severe bilateral stenosis of the renal artery origins and small, atrophic kidneys.

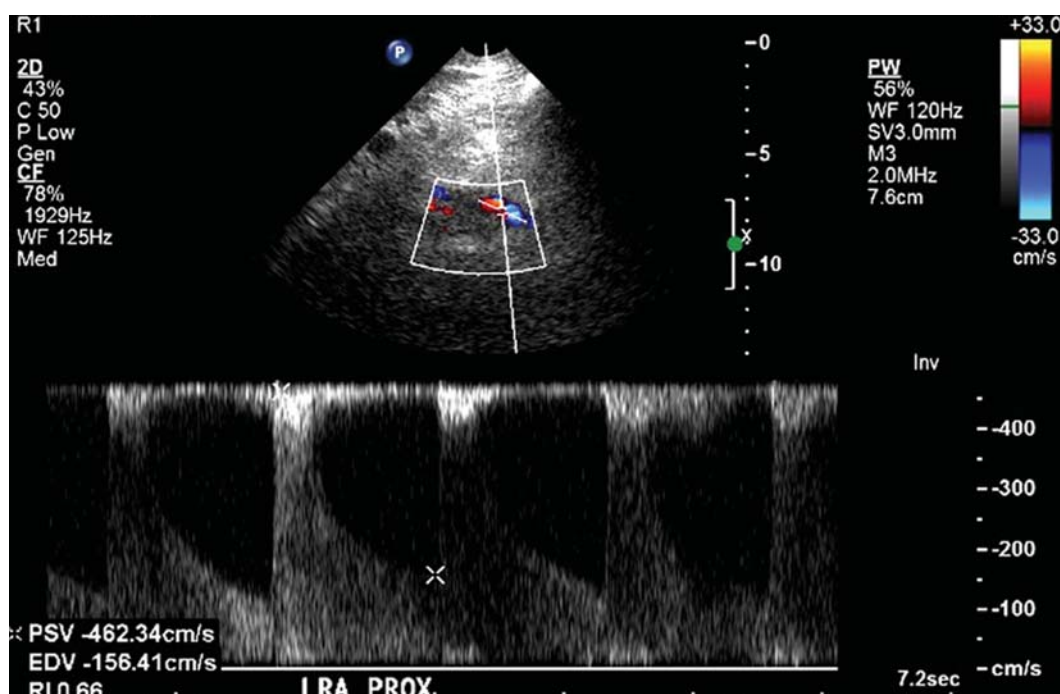


Figure 3 DUS focused on the proximal left renal artery reveals severe stenosis with markedly elevated peak systolic velocity (PSV) and end-diastolic velocity (EDV).

The size of the contralateral kidney is a useful surrogate marker for kidney function. A significant discrepancy in size and mass between the two kidneys should prompt the ultrasonographer to search for significant RAS or an occluded renal artery.

Doppler examination of the renal parenchyma is also employed as a means of indirectly evaluating RAS. This technique, performed via a flank approach, is very useful with obese patients and with cases in which examination is hindered by the presence of bowel gas. The acceleration time (the interval from the onset of the upstroke of the arterial waveform to the systolic peak), the acceleration index (the slope of the acceleration curve), and the resistive index (a measure of the resistance within the renal circulation) are determined. There is evidence to suggest that a normal resistive index (< 80) before renal revascularization (whether endovascular or surgical) predicts improvement with respect to blood pressure, renal function, and freedom from dialysis.¹² The resistive index itself, however, is not useful in predicting the degree of stenosis, because it may already be elevated in elderly patients and those with renal parenchymal disease.

One disadvantage of RADUS is that the diagnostic value of the images can be limited by the patient's body habitus or the presence of overlying bowel gas. In addition, RADUS can be time consuming to perform (requiring 30 to 60 minutes), and its accuracy is highly dependent on the experience of the ultrasonographer. Finally, polar or accessory renal arteries can easily be missed on RADUS, potentially leading to a false negative study result.

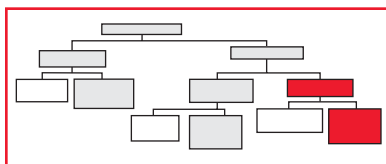
enhanced MRA is the technique of choice, in that the presumably less nephrotoxic gadolinium enhances visualization of the renal arteries. Multiplanar reconstruction (MPR) and maximum-intensity projection (MIP) techniques provide three-dimensional anatomic detail that is superior to what can be obtained with contrast arteriography [see Figure 4]. On a two-dimensional arteriogram, vessel overlap can cause the examiner to miss a severe stenosis; this problem rarely arises with three-dimensional images. We find renal MRA to be especially helpful in evaluating patients with RAS and ischemic nephropathy necessitating endovascular intervention.

Before the intervention is carried out, we review the axial MRA images of the aorta and the origins of the renal vessels. Working from these images, we rotate the image intensifier camera so as to obtain a perpendicular view of the renal orifice [see Figure 5]. This step allows us to use smaller quantities of contrast material and cannulate the renal orifice more quickly during endovascular intervention. It must be kept in mind that MPR and MIP postprocessing techniques are well known to exaggerate or even create the appearance of a stenosis and that the original source axial images must therefore be evaluated. The three-dimensional data set is digitally subtracted from the precontrast source images to create the contrast MRA images. Other signs of significant RAS include poststenotic dilation, loss of cortical medullary differentiation, and delayed renal enhancement or asymmetric filling of the collecting system during contrast injection.

The utility of MRA can be limited by several factors that are capable of degrading the acquired data. The presence of nearby metal (e.g., clips or stents) and air-tissue interfaces can lead to focal signal drop-out and simulate stenosis or obstruction. Movement by the patient during the scan (or even bowel peristalsis) can result in degraded, blurred images. The timing of the contrast bolus must be right to ensure adequate visualization of the arterial vessels. A contrast bolus that is delivered too late will not opacify the vessels and will appear as a stenosis, whereas a bolus that is

Magnetic Resonance Angiography

Many practitioners prefer MRA as the initial screening test for RAS. One advantage of renal MRA in this setting is that the quality of the results is less dependent on operator technique than is the case with RADUS. Gadolinium-



delivered too early will opacify the veins, resulting in so-called venous contamination of the images. We have found that the image quality attained with MRA is highly dependent on the institution where it is performed.

MRA is contraindicated in patients with pacemakers, automatic implantable cardioverter defibrillators (AICDs), brain aneurysm clips, cochlear implants, or metal fragments in the eyes. It is not contraindicated in patients with vascular stents, coils, or inferior vena cava filters, nor is it contraindicated in those with metal orthopedic devices, heart valves, or dental devices and materials.

Captopril Renal Scintigraphy

Radionuclide imaging is a noninvasive and safe means of evaluating renal blood flow and excretory function. The addition of an angiotensin-converting enzyme (ACE) inhibitor, such as captopril, to isotope renography improves the sensitivity and specificity of the test. In the presence of unilateral RAS, administration of captopril is associated with a 30% reduction of the glomerular filtration rate (GFR) in the affected kidney. The contralateral kidney shows a rise in the GFR, an increase in urine flow, and enhanced salt excretion, leading to marked retention of the isotope in the cortex of the affected kidney. The presence of significant renal dys-

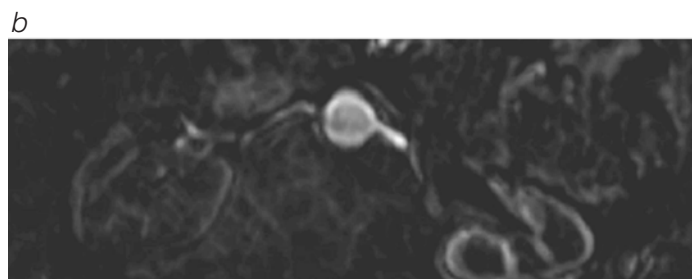
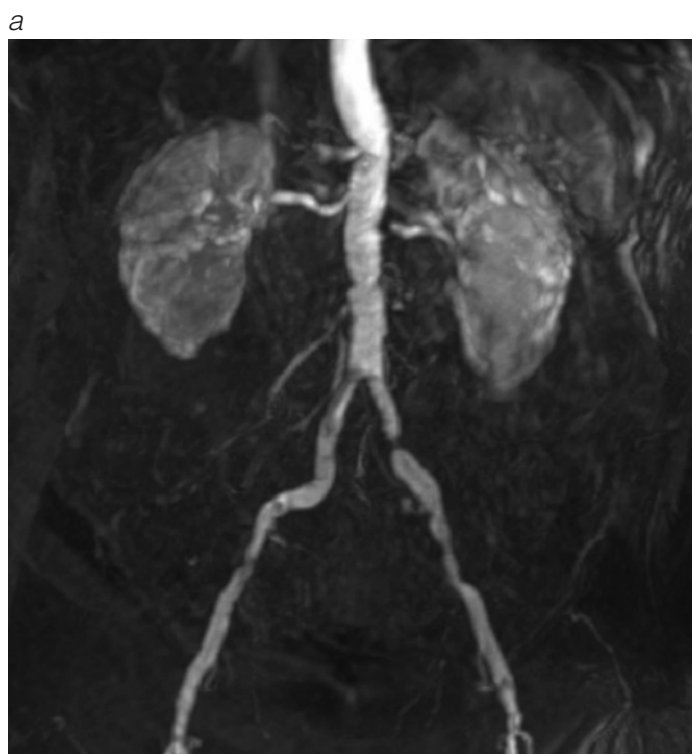


Figure 4 (a) Gadolinium-enhanced MRA reveals signal dropout (flow void) at the origin of the left renal artery, signifying severe stenosis. (b) Axial MRA image reveals severe right renal artery stenosis.

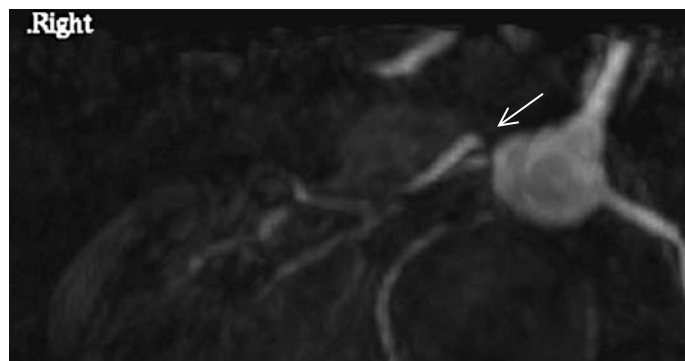


Figure 5 For optimal viewing of the right renal artery during endovascular intervention, the C arm should be set to a 30° left anterior oblique position. Evaluation of axial MRA images before the procedure is begun facilitates cannulation and limits the amount of contrast material used.

function at baseline (serum creatinine concentration greater than 2.0 mg/dl), bilateral RAS, or both adversely affects the sensitivity and specificity of captopril renal scintigraphy, thereby limiting its utility as a screening test. In addition, the necessity of discontinuing ACE inhibitors and angiotensin-receptor blockers (ARBs) before the study may preclude the use of this test in patients with severe hypertension. Improvements in DUS, CTA, and MRA have now relegated captopril renal scintigraphy to secondary status as a screening modality.

Contrast-Induced Nephrotoxicity

The increasing use of diagnostic imaging studies (e.g., CTA and MRA) and catheter-based interventions in patients with significant RAS has made treatment and prevention of CIN important issues in this patient population. Current strategies for preventing CIN have generally involved one of three approaches: (1) providing hydration, (2) using low-osmolar or iso-osmolar iodinated contrast agents, and (3) administering the free radical scavenger N-acetylcysteine.

Intravascular volume depletion is an important risk factor for the development of CIN. Although to date, no randomized, controlled trials comparing hydration with placebo have been published, it has been standard practice for some time to institute hydration (usually intravenous) before administering a contrast agent. A small randomized, controlled trial from 2003 that compared I.V. hydration (0.9% saline, 1 ml/kg, starting 12 hours before infusion of contrast material) with unlimited oral fluid intake found I.V. hydration to be far superior for preventing CIN.¹³ In a subsequent study, 119 patients at a single center were randomly assigned to receive a 154 mEq/L infusion of either sodium chloride or sodium bicarbonate both before and after administration of contrast material (starting with a 3 ml/kg bolus 1 hour before contrast administration and continued at a rate of 1 ml/kg/hr for 6 hours afterward).¹⁴ Sodium bicarbonate hydration was found to reduce the incidence of CIN from 13.6% to 1.7%. Although this study is probably underpowered from a statistical perspective, the findings are suggestive. Sodium bicarbonate hydration is inexpensive and well tolerated and has become standard practice at most institutions.

The optimal choice of contrast media for preventing CIN has also been a subject of debate. There is evidence that the use of iso-osmolar nonionic contrast agents (e.g., iodixanol [Visipaque; GE Healthcare, Princeton, New Jersey]) yields significantly lower rates of CIN than the use of low-osmolar contrast agents (e.g., iohexol [Omnipaque; GE Healthcare, Princeton, New Jersey]) in

patients with diabetes or baseline renal insufficiency who undergo cardiac or vascular angiography.¹⁵

N-acetylcysteine, a thiol-containing antioxidant, is believed to act as a free-radical scavenger to prevent toxic effects on the renal tubular epithelium. Multiple clinical studies have examined the question of whether administration of *N*-acetylcysteine is beneficial in preventing CIN, but the results have been mixed. Although pooled meta-analyses have recommended giving *N*-acetylcysteine to patients who are at high risk, the overall effect of this measure is small in comparison with that of simple hydration. Nevertheless, *N*-acetylcysteine is inexpensive and generally well tolerated, and its use in those at high risk for CIN may reasonably be recommended.

On the basis of the existing evidence regarding prevention of CIN, we routinely preadmit patients with baseline serum creatinine concentrations higher than 2.5 mg/dl for overnight hydration, usually with saline; we then switch to sodium bicarbonate hydration (see above) before administering the contrast agent. We also use *N*-acetylcysteine (600 orally twice daily on the day before, the day of, and the 2 days after contrast administration) in this high-risk patient subset. Patients with serum creatinine concentrations between 1.5 and 2.5 mg/dl receive sodium bicarbonate hydration on the day of the procedure. We try to limit the amount of contrast material given during the procedure, and we currently favor iodixanol over iohexol in patients with baseline serum creatinine concentrations higher than 1.5 mg/dl or other risk factors for CIN (e.g., diabetes or a solitary kidney). Because of its substantial cost, we do not routinely use iodixanol in all patients. Well-hydrated persons with normal renal function receive I.V. saline before and after the procedure. In such patients, we routinely use iohexol, without other adjuncts.

LABORATORY TESTS

Renal-Vein Renin Assay

When hemodynamically significant RAS is found, functional studies may be indicated to determine the physiologic significance of the lesion. One such study involves measuring the renin concentration in blood samples from the two renal veins to determine whether unilateral renin hypersecretion is occurring. If the ratio of the renin concentration in the affected side to that in the unaffected side is greater than 1.5, the assay is considered to have yielded a positive result. The sensitivity and specificity of this test are diminished by the presence of bilateral RAS or RAS of a solitary kidney. Other factors that may reduce the reliability of the results include the inherent limitations of the renin assay itself and the potential for sampling errors. Because of the invasive nature of the selective renin assay and the concerns about its accuracy, we do not routinely use this test in RAS patients.

Management

MEDICAL THERAPY

Given the known association between RAS and systemic cardiovascular disease, medical treatment aimed at preventing or retarding further progression of systemic atherosclerosis is clearly a paramount concern in the management of RAS patients. Measures for modifying cardiovascular risk factors include effective blood pressure control, weight reduction, smoking cessation, lipid-lowering therapy, and antiplatelet therapy. It is the responsibility of the surgeon evaluating a patient with RAS to use this opportunity to ensure

that appropriate cardiovascular risk factor modification measures are being undertaken. After consultation with the patient's primary care provider, we routinely provide prescriptions for a cholesterol-lowering medication (e.g., a 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase inhibitor) and an antiplatelet drug (e.g., acetylsalicylic acid [ASA]) if the patient has not already been taking these agents.

It is worth remembering that although medical treatment may lead to significant reductions in cardiovascular morbidity and mortality, no medical therapy has yet been shown to prevent the progression of ischemic nephropathy and renal failure. For patients with these latter conditions, renal revascularization is likely to be preferable to medical therapy.

Antihypertensive Agents

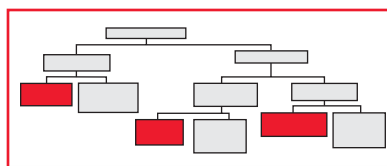
Both ACE inhibitors and ARBs have proved to be safe and effective for the treatment of hypertension in the setting of renovascular disease. In addition to their effects on the RAAS, these agents have been shown to reduce proteinuria and glomerular scarring in patients with a variety of renal diseases. Close clinical supervision is necessary when ACE inhibitors or ARBs are given to patients with renal insufficiency or failure. In this population, serum creatinine and potassium levels should be obtained weekly for 2 to 3 weeks after antihypertensive therapy with an ACE inhibitor or an ARB is started. These patients are at increased risk for acute renal failure (ARF); if ARF develops, the medications should be promptly discontinued. Patients with significant RAS who take ACE inhibitors or ARBs are also at risk for ARF when severely dehydrated; accordingly, they should be instructed to refrain from taking these agents when affected by severe vomiting, diarrhea, or dehydration. As a rule, ARF that occurs in this latter setting responds rapidly to fluid rehydration and temporary suspension of the ACE inhibitor or ARB. Once renal function has returned to baseline, the medications can usually be safely restarted.

It is important to be aware that some antihypertensive drugs may be associated with lack of energy (e.g., beta blockers and calcium channel blockers) or chronic cough (ACE inhibitors), either of which may have substantial effects on patient compliance. Several studies have shown that as many as 50% of such medications are changed or discontinued within 6 months. Proponents of renovascular revascularization have cited such studies as evidence favoring aggressive use of open or endovascular treatment of RAS over reliance on medical therapy alone.

Lipid-Lowering Agents

Lipid-lowering therapy with HMG-CoA reductase inhibitors (also referred to as statins) effectively reduces total and low-density lipoprotein (LDL) cholesterol levels while increasing high-density lipoprotein (HDL) cholesterol levels. There is compelling level 1 evidence that this reduction of total and LDL cholesterol levels markedly lowers the incidence of secondary cardiovascular events and mortality. There is, however, no direct evidence that lipid control has an effect on the progression of renal artery disease, though one might reasonably suspect that it would.

Statins generally are well tolerated, but on occasion, they may be associated with hepatic toxicity (0.5% to 3% of cases) or myositis. Accordingly, liver function tests should be performed at baseline and again 3 months after the start of therapy. If a threefold or greater increase in aminotransferase levels is noted, the statin should be discontinued, and alternative therapy with another lipid-lowering medication (e.g., a fibrate, a bile acid sequestrant, a cholesterol absorption inhibitor, or nicotinic acid) should be started in conjunction with diet modification.



Muscle injury is uncommon with statin therapy alone: myalgias occur in 2% to 11% of patients, myositis in 0.5%, and rhabdomyolysis in fewer than 0.1%. Myositis associated with statin therapy is treated by switching to another HMG-CoA reductase inhibitor. Routine measurement of serum creatine kinase levels is not recommended, but patients taking statins should be warned about the risk of myositis and weakness and instructed to stop statin therapy if such side effects occur.

Antiplatelet Agents

Antiplatelet therapy has been shown to reduce the risk of secondary events in patients with coronary artery disease and carotid stenosis. The data currently available do not conclusively demonstrate that antiplatelet therapy has a beneficial effect on RAS, but given that RAS is a manifestation of systemic atherosclerosis, antiplatelet therapy appears warranted on the same grounds that statin therapy would be. After endovascular intervention to treat RAS, we typically place patients on ASA, 81 mg/day, and clopidogrel, 75 mg/day, for 4 to 6 weeks while the stent is undergoing endothelialization. After this period, patients are switched to ASA, 325 mg/day. Admittedly, there is no direct evidence supporting this practice in patients with RAS who undergo endovascular intervention; however, data extracted from the coronary stenting literature suggest that such an approach may be reasonable.

ENDOASCULAR AND OPEN SURGICAL THERAPY

Despite the relatively high prevalence of RAS, especially in persons who have atherosclerosis in other vascular beds, there is currently no consensus on diagnosis, therapy, or follow-up. In the absence of well-designed, evidence-based studies, many practitioners have adopted a “find it and fix it” approach to managing RAS. The endovascular and surgical interventions employed to treat RAS are described more fully elsewhere [see 6:22 *Open Procedures for Renovascular Disease* and 6:23 *Endovascular Procedures for Renovascular Disease*]. We ourselves generally take an aggressive stance toward the application of renal artery stenting, especially in patients with evidence of ischemic nephropathy (who presumably would be the patients most likely to benefit from renal revascularization).

It must be admitted, however, that the current evidence for renal artery percutaneous intervention is circumstantial at best. Clearly, there are three possible outcomes associated with renal revascularization. Some patients derive tremendous benefit from the procedure, showing substantial improvements in blood pressure and renal function. Others (a very small subset) experience a rapid decline in renal function, probably resulting from either atheroembolization or CIN associated with the procedure itself. Still others exhibit no changes in renal function, number of antihypertensive medications used, or blood pressure control. Unfortunately, there are, at present, no good methods of reliably predicting which patients will benefit from renal revascularization.

Several uncontrolled reports suggested that hypertension and renal function may improve after successful renal artery stenting. However, three small trials evaluating angioplasty alone (i.e., without stenting)

were unable to demonstrate any beneficial effect on blood pressure.¹⁶⁻¹⁸ Proponents of renal artery intervention have argued that these three trials were flawed by their failure to include stenting and by the fact that blood pressure control may be a poor surrogate clinical end point. These studies were plagued by several other weaknesses as well, including high rates of crossover to angioplasty and marked variations in the medical therapy provided. The inclusion of stenting as a component of endovascular treatment of RAS is now considered the standard of care by many, in that it significantly improves technical success rates and lowers the incidence of restenosis.

Revascularization of RAS with stenting treats the root cause of the neurohormonal activation that leads to end-organ heart and kidney damage; best medical therapy, when adequately carried out, yields substantial reductions in cardiovascular morbidity and mortality in and of itself. Consequently, it is difficult to detect significant differences between best medical therapy alone and best medical therapy plus renal artery stenting. Until sufficient evidence (from adequately powered, well-designed, and unbiased trials) has been accumulated to confirm or rule out such differences, the debate regarding the benefits of percutaneous renal artery revascularization will continue.

To date, no trials comparing best medical therapy with best medical therapy plus angioplasty and stenting have been completed. Currently, however, patients are being recruited into a clinical trial sponsored by the National Heart, Lung, and Blood Institute, which is likely to answer several important questions about the management of RAS that have not been answered by previous studies. This study, known as the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial, is expected to yield important information about which groups of RAS patients benefit from endovascular intervention. A total of 1,080 patients will be enrolled in the trial and will be randomly assigned to receive either best medical therapy or best medical therapy with angioplasty and stenting. The primary outcome evaluated will be adverse cardiovascular and renal events. Best medical therapy will be provided on the basis of current evidence-based guidelines, which include tight control of blood pressure (< 140/90 mm Hg; < 130/80 mm Hg in patients with diabetes or proteinuria), treatment of hypercholesterolemia (LDL concentration < 100 mg/dl) and diabetes (glycosylated hemoglobin [HbA_{1c}] level < 7 mg/dl), smoking cessation, and antiplatelet therapy (with ASA, clopidogrel, or ticlopidine). All patients will receive an ARB as the first-line antihypertensive agent, and a specific stepwise algorithm will be implemented for patients requiring combination antihypertensive therapy. All patients will undergo diagnostic angiography to assess the severity of their lesions. Patients will be followed for as long as 5 years with an eye to both primary end points (e.g., death, stroke, myocardial infarction, ARF, and dialysis) and secondary end points (e.g., hypertension, medication use, quality of life, and cost). It is expected that enrollment in the CORAL trial will conclude in 2009, though interim data will probably be reported earlier. This important study should make a major contribution to determining the appropriate role of endovascular stenting in the management of RAS.

Discussion

Pathophysiology of Renovascular Hypertension

The seminal studies performed by Goldblatt and associates in the 1930s demonstrated that reduction of renal perfusion can result in sustained elevation of arterial pressures.¹⁹ Later work revealed that the renin-angiotensin-aldosterone system plays an intricate and crit-

ical role in this process. The RAAS maintains vascular tone, water and salt balance, and cardiac function. It works through the sympathetic nervous system and the actions of several hormones to maintain hemodynamic stability. The RAAS is activated through several mechanisms, including hypotension and decreased intravascular

volume. These mechanisms cause decreased renal perfusion and the secretion of renin from the juxtaglomerular apparatus within the kidneys. Renin cleaves angiotensinogen in the liver to form angiotensin I; ACE then transforms angiotensin I into angiotensin II in the lung. Angiotensin II is a potent vasoconstrictor (considerably more potent than epinephrine) and is implicated in end-organ damage to the heart and the kidney.^{20,21} Angiotensin II promotes the release of aldosterone from the adrenal cortex, and this release of aldosterone leads to the reabsorption of sodium in the distal convoluted tubules of the kidney, resulting in increased intravascular volume.

In patients who have unilateral RAS with a normal contralateral kidney, the elevation of blood pressure is renin dependent and is characterized by increased peripheral vascular resistance. Such patients are considered to have volume-independent hypertension, in that the normal contralateral kidney compensates for the unilateral RAS by increasing its excretion of fluid. In patients who have bilateral RAS or unilateral RAS with no contralateral kidney, intravascular volume increases and renin secretion decreases over time. Such patients are considered to have volume-dependent or Goldblatt hypertension.

Ischemic injury to the affected kidney, hypertensive nephrosclerosis of the contralateral kidney, and smooth muscle hypertrophy in the peripheral blood vessels may all contribute to sustained hypertension independently of RAAS activity. In addition, both the sympathetic nervous system and the central nervous system contribute to hypertension associated with RAS.²² Several neuroendocrine systems activated by RAS have also been shown to have deleterious cardiovascular effects. Besides increasing peripheral resistance, angiotensin II is thought to cause smooth muscle hypertrophy (both in peripheral arteries and in cardiac myocytes), plaque rupture, endothelial dysfunction, and inhibition of fibrinolysis.²³⁻²⁵ An elevated angiotensin II level is believed to cause left ventricular hypertrophy (LVH) on occasion, even in cases where blood pressure is well controlled.²⁶ Angiotensin II also interacts with tumor growth factor- β , platelet-derived growth factor, and endothelin, each of which has been implicated in the development of vascular muscle hypertrophy, cardiac myocyte hypertrophy, and renal parenchymal damage. Clearly, RAS and activation of the RAAS have systemic effects that go beyond simply causing hypertension.

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22 OPEN PROCEDURES FOR RENOVASCULAR DISEASE

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With the introduction of potent new antihypertensive agents and percutaneous endovascular methods of management, the indication and methods for renovascular intervention have changed. Currently, open surgical repair is commonly reserved for (1) patients who have severe hypertension despite optimal medical therapy, (2) patients in whom percutaneous transluminal renal artery angioplasty (PTRA) fails or who have disease patterns that are not amenable to PTRA, and (3) patients who have renovascular disease associated with excretory renal insufficiency (i.e., ischemic nephropathy).¹

The experience of our center (Wake Forest University School of Medicine) in the management of more than 1,000 patients over a 20-year period indicates that atherosclerotic renovascular disease frequently exists in combination with diffuse extrarenal atherosclerosis and renal insufficiency. In one study, bilateral atherosclerotic renal artery lesions were present in two thirds of patients, and complete renal artery occlusion was present in more than one third.² Although practitioners frequently cite selected data to support a particular management scheme in this setting, the question of what constitutes optimal management of atherosclerotic renovascular disease responsible for either hypertension or renal insufficiency is still unanswerable. To date, no prospective, randomized trials have compared the best medical management with PTRA and with open surgical repair.

Preoperative Evaluation

Evaluation and diagnosis of renovascular hypertension and renovascular renal insufficiency (i.e., ischemic nephropathy) are discussed in more detail elsewhere, as are general issues related to the question of medical versus surgical therapy.^{2,3}

The progressive nature of the atherosclerotic renovascular lesions seen in combination with severe hypertension and the deterioration of renal function seen in selected patients who are managed medically lends support to the idea that renal artery intervention is indicated when either renovascular hypertension or ischemic nephropathy is present. In our view, renal artery intervention is appropriate in patients with severe hypertension and, specifically, in all patients who have severe hypertension in combination with excretory renal insufficiency (i.e., ischemic nephropathy). Open operative management is preferred for children and young adults and for patients with bilateral renovascular disease, especially if renal artery occlusion is present.²

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Financial disclosure information is located at the end of this chapter before the references.

PTRA is liberally used as an alternative to open renal artery revascularization, but the data currently available suggest that it should be employed selectively. The best results with PTRA alone have been achieved with nonostial atherosclerotic renal artery lesions and medial fibroplasia of the main renal artery. Suboptimal results have been achieved with hypoplastic (i.e., developmental) lesions, fibrodysplasia of the intimal and perimedial variety, ostial atherosclerotic renal artery lesions, and renal artery occlusions. For ostial renal artery atherosclerosis, some surgeons have advocated PTRA with primary endoluminal stenting in an effort to improve results; however, the recovery of renal function after PTRA and primary stenting in this setting have been inferior to those of open operative repair. Consequently, in the majority of cases of bilateral ostial atherosclerosis in combination with renal insufficiency, we advise operative intervention for good-risk patients.

These recommendations are not absolute. Decisions regarding therapy for renovascular disease must be individualized. Factors contributing to the choice of treatment include the expected morbidity and mortality of operative repair and the presence of predictors of death and dialysis dependence at follow-up. In this regard, severe left ventricular systolic and diastolic dysfunction with clinical congestive heart failure, diabetes mellitus, and uncorrectable azotemia have all been shown to be significant and independent predictors of reduced dialysis-free survival.^{2,3}

Operative Planning

Our use of open surgical methods to treat atherosclerotic renovascular disease is based on several guiding principles [see Table 1]. We consider severe hypertension a prerequisite for open operative management and do not perform prophylactic renal artery repair in patients who are not hypertensive. Although we employ renal vein renin assays

Table 1 Recommended Principles for Contemporary Surgical Management of Renovascular Disease¹⁰

Renal artery repair is done on an empirical, but not prophylactic, basis
Complete renal artery repair is done in one operation when feasible; bilateral ex vivo reconstruction may be staged
Direct aortorenal methods of reconstruction are preferred
Nephrectomy is reserved for nonreconstructable disease in a nonfunctioning kidney
Combined aortic reconstruction is limited to clinically significant disease
Intraoperative duplex sonography is performed to assess technical success

to guide management of unilateral lesions in many cases, we typically perform empirical renal artery repair without functional studies when the hypertension is severe or uncontrolled and when renal artery disease is bilateral or involves a solitary kidney. We attempt to correct all hemodynamically significant renovascular disease in a single operation; we perform staged repair only in cases in which the disease necessitates bilateral ex vivo reconstruction. Because the lower limit of renal function retrieval is not known but improved renal function is known to be the strongest predictor of dialysis-free survival, we reserve nephrectomy for patients who have an unreconstructable lesion in a renal artery supplying a nonfunctioning kidney (i.e., a kidney providing less than 10% glomerular filtration on renography).⁴ In the majority of open operative repairs, we employ direct aortorenal reconstruction methods; we seldom use indirect (splanchnorenal) methods because celiac axis stenosis is present in 30 to 40% of patients and bilateral repair is required in more than 50%.² Regardless of the method of reconstruction employed, we perform intraoperative renal duplex sonography as a completion study to look for any technical errors in the repair that might lead to restenosis or occlusion. Failed renal artery repair has been associated with a significant and independent risk of eventual dependence on dialysis.⁵

Operative Technique

Various open surgical techniques are used to correct atherosclerotic renovascular disease; however, no single repair technique is optimal for all renovascular lesions. The best approach to renal artery reconstruction in any given case depends on patient characteristics, the pattern of renal artery disease, and the presence or absence of associated aortic lesions that may have to be corrected simultaneously. The open procedures most commonly performed to treat renovascular disease are (1) aortorenal bypass, (2) renal artery thromboendarterectomy, and (3) renal artery reimplantation. In general, aortorenal bypass is the most versatile of these procedures. Transaortic thromboendarterectomy may be especially useful when ostial atherosclerosis ends within 1 cm of the origin of the renal artery and involves multiple renal arteries. Renal artery reimplantation is often particularly appropriate for the correction of renovascular disease in children and adolescents in that concerns regarding graft material are eliminated.

With all of these reconstruction techniques, multiple small doses of mannitol are administered intravenously during perirenal aortic and renal artery dissection. Mannitol is given both before and after periods of warm renal ischemia up to a total dose of 1 g/kg. During cross-clamping of the aorta and the renal artery, the patient is given heparin, 100 units/kg, to establish systemic anticoagulation. When a purely autogenous reconstruction is performed, antibiotics are unnecessary; however, when a prosthetic graft is employed, administration of a first-generation cephalosporin is begun 2 hours before operation and continued for 24 hours.

AORTORENAL BYPASS

Aortorenal bypass [see Figure 1] may be performed with either an autogenous conduit or a prosthetic graft. If an entirely autogenous repair is possible, we prefer to use a

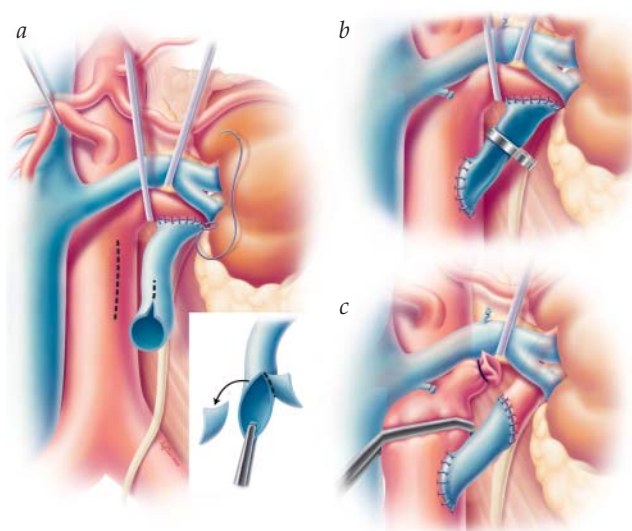


Figure 1 Aortorenal bypass.⁸ Technique for end-to-side (a, b) and end-to-end (c) aortorenal bypass grafting. The length of arteriotomy is at least three times the diameter of the artery to prevent recurrent anastomotic stenosis. For the anastomosis, 6-0 or 7-0 monofilament polypropylene sutures are used in continuous fashion, under loupe magnification. If the apex sutures are placed too deeply or with excess advancement, stenosis can be created, posing a risk of late graft thrombosis. The dotted lines demonstrate aortotomy and spatulation of the vein. Inset demonstrates final step in spatulation of the vein.

reversed segment of the great saphenous vein as the conduit. If the saphenous vein is inadequate in size (i.e., < 4 mm in diameter) or of inadequate quality, a 6 mm thin-walled polytetrafluoroethylene (PTFE) graft is used instead. In either case, the infrarenal aorta is dissected and clamped proximally and distally, and a longitudinal elliptical opening is created anterolaterally in the aortic wall (e.g., with two or three applications of a 4.0 mm aortic punch). If required, a local endarterectomy at the site of the anastomosis may be performed through this aortotomy.

The proximal and distal anastomoses are then created. Although end-to-side distal renal artery anastomoses were commonly performed at one time, current aortorenal bypass techniques typically employ end-to-end distal renal artery anastomoses. For both the proximal and the distal anastomosis, the length of the arteriotomy should be at least three times the diameter of the smallest conduit, and the ends of the conduit should be widely spatulated to guard against late suture line stenosis. The proximal anastomosis is usually made with a continuous 6-0 monofilament polypropylene suture, and the distal anastomosis is created with a continuous 7-0 monofilament polypropylene suture.

THROMBOENDARTERECTOMY

Thromboendarterectomy of the renal arteries and the perirenal aorta may be performed via either a transrenal or a transaortic approach. When the renal artery atheroma extends 1 cm or less from the ostium and involves both or multiple renal arteries, the transaortic technique [see Figure 2] is especially useful. With both endarterectomy techniques, extensive aortic exposure is required. The aorta proximal to the origin of the superior mesenteric artery (SMA) is exposed and controlled. This exposure is facilitated by partially

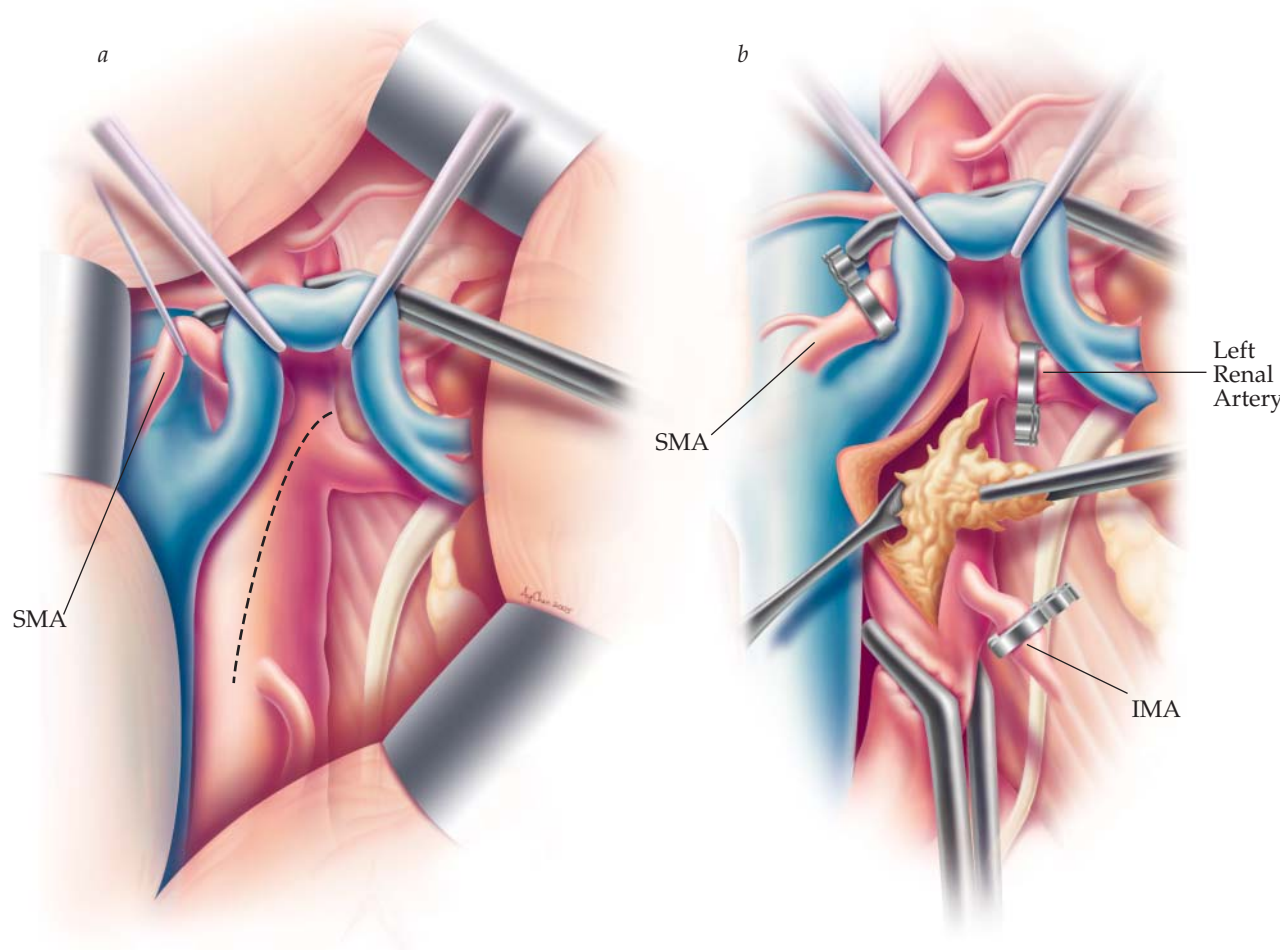


Figure 2 Thromboendarterectomy.⁸ Exposure for a longitudinal transaortic endarterectomy is obtained via the standard transperitoneal approach. The duodenum is mobilized from the aorta laterally in the standard fashion; alternatively, for more complete exposure, the ascending colon and the small bowel are mobilized. (a) The dotted line shows the location of the aortotomy. (b) The plaque is transected proximally and distally, the renal arteries are everted, and the atherosclerotic plaque is removed from each renal ostium. The aortotomy is typically closed with a continuous 4-0 or 5-0 polypropylene suture. IMA = inferior mesenteric artery; SMA = superior mesenteric artery.

dividing the aortic crura and controlling the SMA with a Silastic loop.

Currently, the majority of aortorenal endarterectomies are performed through a longitudinal aortotomy extending from a point 2 to 3 cm below the renal arteries to the base of the SMA. A sleeve of aortic atheroma is created and then divided sharply at the base of the SMA proximally and well below the most inferior renal artery distally. After the aortic endarterectomy is completed, an eversion-type endarterectomy is performed for each renal artery. The surgical assistant retracts the anterior lip of the aortic wall and inverts the renal artery into the aorta, and the operating surgeon retracts the renal artery atheroma while gently pushing the remaining renal artery away with a dissector. In this manner, the end point of the endarterectomy can easily be visualized to confirm that the endarterectomy is complete. The endarterectomy site is then irrigated with heparinized saline, and the longitudinal aortotomy is closed with a continuous 4-0 or 5-0 monofilament polypropylene suture.

Both transrenal and transaortic thromboendarterectomy are contraindicated if aneurysmal degeneration of the perirenal aorta is present or if there is transmural calcification at the site of endarterectomy.

RENAL ARTERY REIMPLANTATION

In the course of renal artery exposure, the vessel is dissected from its aortic origin to its primary bifurcation. On occasion, after complete dissection, the vessel is found to have sufficient redundancy to allow tension-free reimplantation into the infrarenal aorta [see Figure 3]. As in a renal artery bypass [see Aortorenal Bypass, above], an elliptical section of the aortic wall is resected, and a widely spatulated aortorenal anastomosis is fashioned.

Although this technique has only limited applicability to the treatment of atherosclerotic renovascular disease in adults, it may be particularly useful in children and young adolescents, who often have congenital or developmental lesions that involve the renal artery orifice. The main advantage of

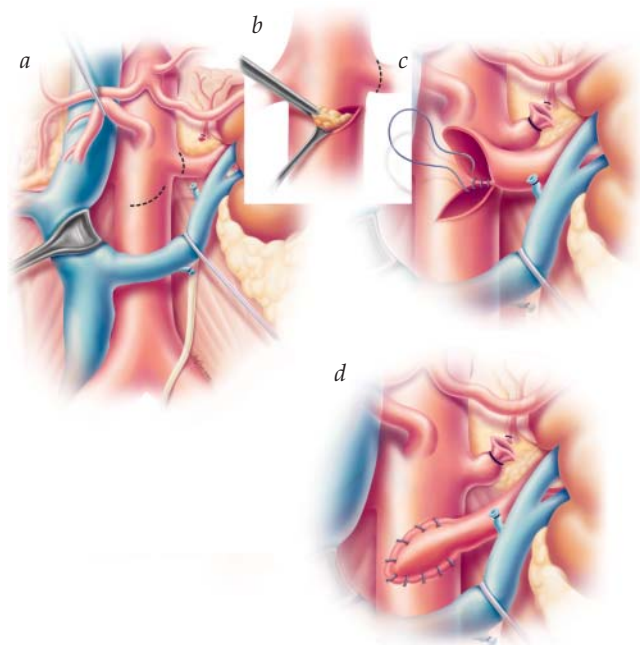


Figure 3 Renal artery reimplantation.⁹ (a) When the renal artery is redundant and the disease involves the orifice of the renal artery, it is usually possible to reimplant the vessel at a lower level. The dotted lines indicate the location of the aortotomy and the point where the renal artery is divided. (b) An elliptical opening is created in the aortic wall, and a local endarterectomy is done as required. (c) A monofilament suture is placed in the aortic wall. (d) The native renal artery is ligated, proximally spatulated, and reimplanted.

reimplantation is that it obviates concerns regarding the durability of the renal artery conduit.

EX VIVO RENAL ARTERY RECONSTRUCTION

Due to the widespread use of percutaneous techniques for main renal artery pathologies, a significant proportion of open renal artery reconstructions require branch exposure and branch reconstruction. These procedures may require a complex repair, culminating in prolonged renal ischemia. Available data suggest that when more than 40 minutes of warm renal ischemia is required for renal revascularization, measures to protect renal function should be instituted.

Several pharmacologic therapies have been promoted to provide protection during renal ischemia; however, no therapy to date has surpassed hypothermia for protection when renal ischemia exceeds 1 hour. Surface cooling and hypothermic perfusion have been proposed; however, the advantages of each are not well defined. Renal tolerance to ischemia is, in part, related to the duration of ischemia, to the adequacy of collateral circulation, and to the method of vascular control. Unprotected warm renal ischemia is best tolerated when only the renal artery is controlled. Control of both renal artery and vein is associated with greater dysfunction than isolated arterial control, as is intermittent control with repeated renal perfusion.

Numerous methods for renal cooling and hypothermia during branch renal artery repair have been described; however, our preference has been intermittent hypothermic perfusion with topical ice slush. Otherwise, several steps

are common to each branch renal artery reconstruction. To promote renal cortical perfusion, small doses of intravenous mannitol are administered throughout renal artery exposure and reperfusion. Before the division of the renal artery, intravenous heparin (100 units/kg) is administered and monitored as described earlier.

Hypothermia appears to be more important than the composition of perfusate; however, our preference is a perfusate with an intracellular composition of electrolytes. This composition theoretically limits ion exchange and intracellular volume shifts that contribute to organelle dysfunction associated with decreased activity of membrane-bound sodium potassium adenosine triphosphatase. Regardless of whether there is division and reattachment of the renal vein, branch renal artery repairs using cold perfusion preservation are made in an orthotopic fashion, with the kidney returned to the renal fossa rather than autotransplanted into the pelvis.

Several exposures for hypothermic branch renal artery reconstructions are available. When isolated branch renal repair is performed with orthotopic replacement, an extended flank incision is made from the lower rib margin and carried to the posterior axillary line as described earlier. This latter method is our preferred approach for ex vivo reconstruction. The ureter is mobilized to the pelvic brim with a large amount of periureteric soft tissue. An elastic sling is placed around the ureter to control ureteric collaterals and prevent subsequent renal rewarming.⁶

The Gerota fascia is opened with a cruciate incision, the kidney is completely mobilized, and the renal vessels are divided. The kidney is placed in a plastic sling and perfused with a chilled renal preservation solution. Continuous perfusion during the period of total renal ischemia is possible with perfusion pump systems and may be superior for prolonged renal preservation. However, simple intermittent flushing with a chilled preservation solution provides equal protection during the shorter periods (2 to 3 hours) required for ex vivo dissection and branch renal artery reconstructions.⁶ For this technique, we refrigerate the preservative overnight, add additional components immediately before use to make up a liter of solution and hang the chilled (5 to 10°C) solution at a height of at least 2 m. Three to 500 milliliters of solution are flushed through the kidney immediately after its removal from the renal fossa until the venous effluent is clear and all segments of the kidney have blanched. As each anastomosis is completed, the kidney is perfused with an additional 100 to 200 mL of chilled solution. In addition to maintaining satisfactory hypothermia, periodic perfusion demonstrates suture line leaks that are repaired prior to reimplantation. With this technique, renal core temperatures are maintained at 10°C or below throughout the period of reconstruction.

Even though it is an accepted method after ex vivo reconstruction, autotransplantation to the iliac fossa is unnecessary for most ex vivo reconstructions. This technique was adopted from renal transplantation. Reduction in the magnitude of the operative exposure, manual palpation of the transplanted kidney, and ease of removal when treatment of rejection fails are all practical reasons for placing the transplanted kidney into the recipient's iliac fossa. However, none of these advantages apply to the patient requiring autogenous ex vivo reconstruction. Because many ex vivo procedures are performed in relatively young patients, the durability of the operation must be measured in terms of

decades. For this reason, attachment of the kidney to the iliac arterial system within or below sites that are susceptible to subsequent atherosclerosis subjects the repaired vessels to disease that may threaten their long-term patency. Moreover, subsequent management of peripheral vascular disease may be complicated by the presence of the autotransplanted kidney. Finally, if the kidney is replaced in the renal fossa and the renal artery graft is properly attached to the aorta at a proximal infrarenal site, the result should equal that of the standard aortorenal bypass and thus carry a high probability of technical success and long-term durability.

SPLANCHNORENAL BYPASS

Indirect, or splanchnorenal, bypass [see Figure 4 and Figure 5] is an uncommon procedure at our center. In large part, its relative rarity reflects the frequent presence of simultaneous disease of the celiac axis and the frequent need for bilateral renal artery reconstruction in combination with aortic repair. In addition, this approach does not yield long-term patency equivalent to that provided by direct aortorenal reconstruction. Consequently, these indirect bypass techniques are reserved for a selected subgroup of high-risk patients.

Hepatorenal bypass is most frequently performed through a right subcostal incision and splenorenal bypass through a left subcostal incision. In either procedure, the patient is positioned with a roll beneath the ipsilateral flank, with the operating table flexed and the ipsilateral arm padded and tucked to the side. The incision may be extended to the contralateral semilunar line and into the ipsilateral flank as necessary for exposure. In a hepatorenal bypass, a great saphenous vein graft is usually employed, originating from the common hepatic artery and coursing posterior to the portal triad and anterior to the vena cava before the end-to-end renal artery anastomosis [see Figure 4]. A splenorenal bypass may be created either in a similar fashion (i.e., with a great saphenous vein graft) or by anastomosing the transected splenic artery directly to the left renal artery [see Figure 5]. If the latter approach is taken, the collateral circulation to the spleen is sufficient to maintain splenic viability in most cases.

NEPHRECTOMY

In patients with renovascular renal insufficiency or ischemic nephropathy, an incremental increase in excretory

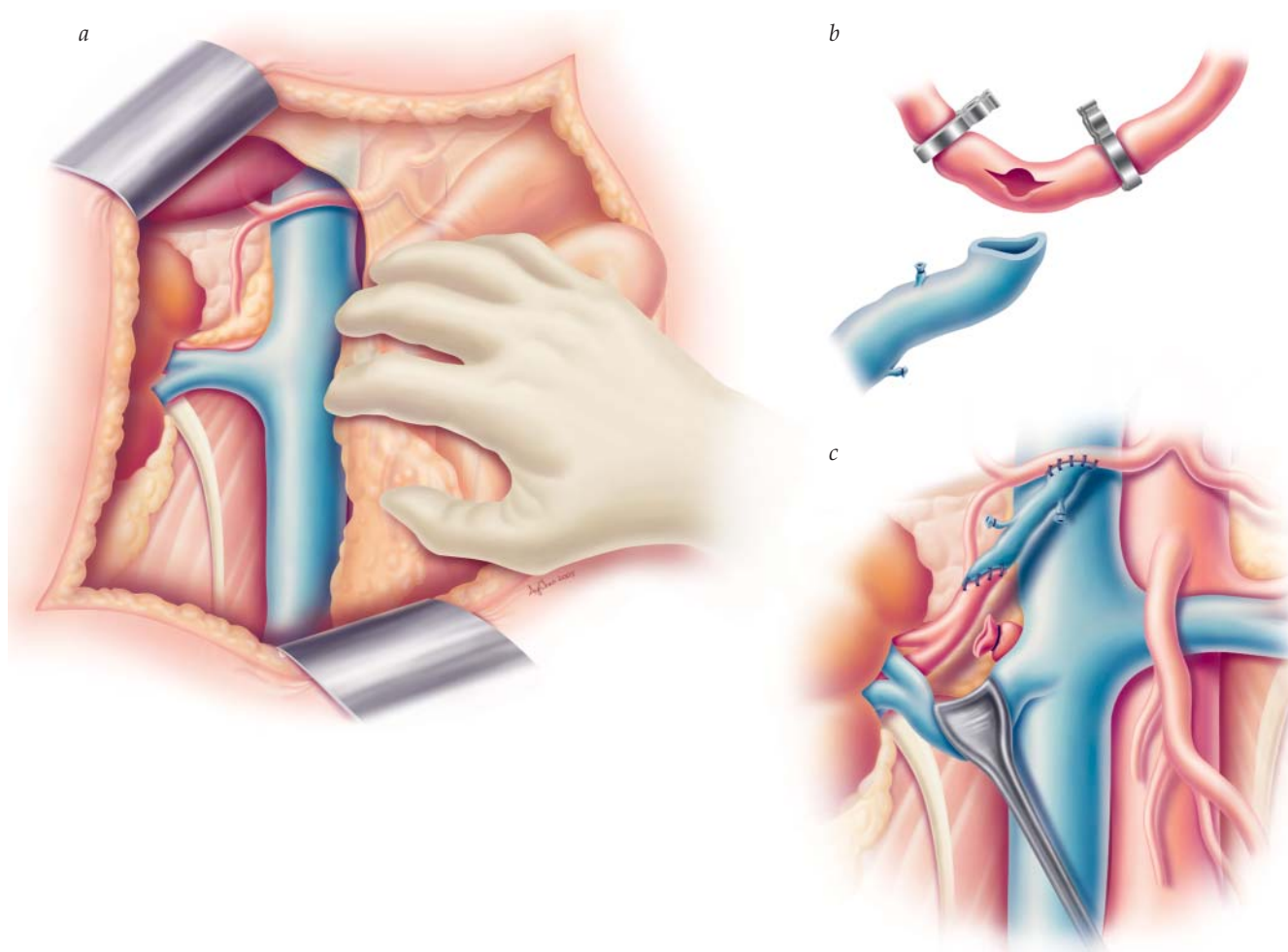


Figure 4 Hepatorenal bypass.⁹ (a) Exposure of the common hepatic artery and the proximal gastroduodenal artery in the hepatoduodenal ligament in preparation for hepatorenal bypass (typically through a right subcostal skin incision). (b, c) The reconstruction is completed by placing a greater saphenous vein interposition graft between the side of the hepatic artery and the distal end of the transected right renal artery.

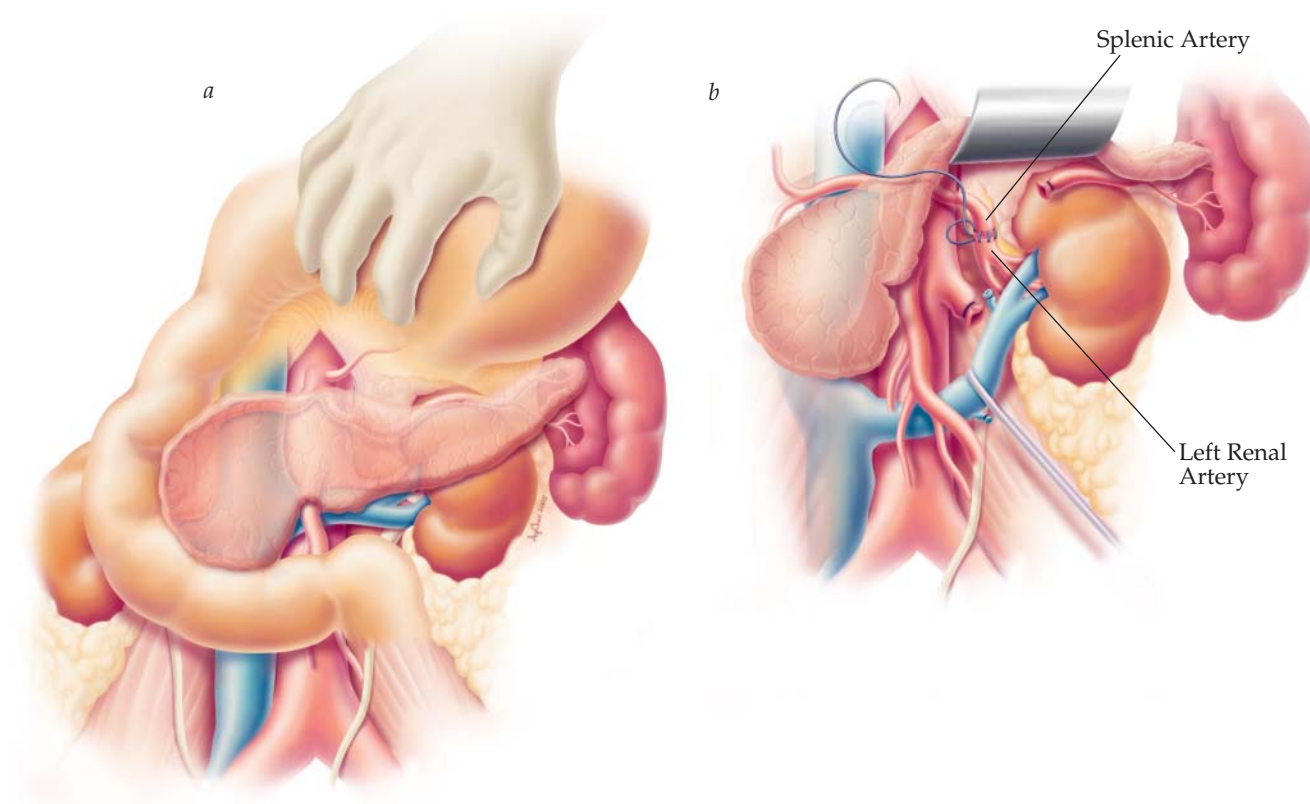


Figure 5 Splenorenal bypass.⁹ (a) Exposure of the left renal hilum in preparation for splenorenal bypass (typically obtained through a left subcostal incision). The pancreas has been mobilized along its inferior margin and retracted superiorly. (b) The transected splenic artery is anastomosed to the transected left renal artery in an end-to-end manner. A splenectomy is not routinely performed.

renal function after operation is the dominant determinant of dialysis-free survival. As noted [see Operative Planning, above], we reserve nephrectomy for patients in whom an unreconstructable renal artery is supplying a nonfunctioning kidney. When the renal artery is occluded, reconstruction is performed if the distal renal artery is normal at the time of surgical exploration. Past recommendations regarding the management of renal artery occlusion have emphasized kidney length, distal renal artery reconstitution, and the appearance of a nephrogram during angiography as criteria for determining whether reconstruction is indicated. Our practice, however, has been to perform renal artery reconstruction whenever a normal distal renal artery is demonstrated. In a study employing this strategy, we reported retrieval of renal function in 60% of occluded renal arteries that underwent operative repair.⁴

INTRAOPERATIVE RENAL DUPLEX ULTRASONOGRAPHY

The surgeon's technique plays a dominant role in determining patency after renal artery reconstruction. To look for technical errors at the time of operation, we employ intraoperative renal duplex ultrasonography. A 10.0/5.0 mHz compact linear array probe with Doppler color-flow capability is placed within a sterile sheath that has a latex tip containing sterile gel. The operative field is flooded with warm saline solution, and B-scan images are obtained from the sites of aortic control and of renal artery repair. All defects noted on

the B-scan images are then examined in both longitudinal and transverse projections. Doppler samples are obtained proximal and distal to the lesions to determine their hemodynamic significance.⁷ In 249 consecutive renal artery repairs with anatomic follow-up, 10% had a focal increase in peak systolic velocities consistent with residual stenosis.² Each defect was revised immediately, and in each case, a significant defect was found. At 12 months after operation, primary patency of the renal reconstruction was observed in 97% of repairs. This product-limit estimate of patency is stable up to 10 years after operation.

Outcome Evaluation

Surgical repair of atherosclerotic renovascular disease can be accomplished with a high rate of success and sustained long-term patency. With proper patient selection, the majority of patients demonstrate beneficial blood pressure response and renal function response, albeit with perioperative mortality and morbidity that vary according to the complexity of the procedure.

In a 2002 report, we reviewed our center's experience with 500 consecutive patients who underwent open surgical repair for treatment of atherosclerotic renovascular disease between January 1987 and December 1999.² These patients included 254 women and 246 men, with a mean age of 65 ± 9 years. Each patient had severe hypertension. The mean

preoperative blood pressure for the group was $200 \pm 35/104 \pm 21$ mm Hg. Most of the patients had diffuse extrarenal atherosclerosis. Eighty-one percent had at least one manifestation of cardiac disease, 34% had a history of significant cerebrovascular disease, and 78% were considered to have at least mild renal insufficiency, as evidenced by a serum creatinine concentration of 1.3 mg/dL or greater. Ischemic nephropathy was seen in 244 patients (49%), including 40 patients who were dependent on dialysis before operation.

Angiographic evaluation demonstrated the presence of bilateral renal artery disease in 60% of these atherosclerotic patients. The renal artery lesion was considered ostial in 97% of cases, and 16% of renal arteries were completely occluded. A total of 720 renal artery reconstructions were performed [see Table 2]. Aortorenal bypass was performed in two thirds of the repairs, and two thirds of these bypasses were done with venous grafts. Thromboendarterectomy was performed in almost one third of the cases. Renal artery reimplantation was performed in 56 instances and splanchnorenal bypass in only 13 instances. Although there were 124 renal artery occlusions, only 56 of these were treated by means of nephrectomy.

Twenty-three patients (4.6%) died in the hospital or within 30 days of renal reconstruction. Mortality varied significantly with the magnitude of procedure. Mortality after isolated renal artery repair was substantially lower than mortality after combined aortic and bilateral renal artery repair (0.8% versus 6.9%). Moreover, perioperative mortality demonstrated significant and independent associations with advanced age and clinical congestive heart failure. The estimated primary patency rate for all 720 renal artery reconstructions was 97% at the 8-year follow-up.

HYPERTENSION RESPONSE

Early blood pressure response was estimated on the basis of ambulatory blood pressure values and medication requirements determined at least 1 month after operative repair. Among surgical survivors, 12% were considered cured, 73% were considered improved, and 15% were considered failed [see Table 3].

RENAL FUNCTION RESPONSE

A significant change in excretory renal function was defined as a change of at least 20% in the estimated glomerular filtration rate (EGFR), measured at least 3 weeks

Table 3 Results of Operative Treatment of Atherosclerotic Renovascular Disease among 477 Surgical Survivors²

Result	Rate (%)
Perioperative mortality	4.6
Hypertension response	
Cured	12
Improved	73
Failed	15
Renal function response*	
Improved	58
Unchanged	35
Worsened	7

*For 225 patients with preoperative serum creatinine concentrations ≥ 1.8 mg/dL; a significant change is defined as a $\geq 20\%$ change in the estimated glomerular filtration rate.

after repair. Of patients with preoperative ischemic nephropathy, 58% showed improvements in renal function, including 30 patients removed from dialysis dependence [see Table 3]. In contrast to previous reports that suggested the existence of a lower limit of renal dysfunction beyond which recovery could not be observed, the percentage of patients who showed improvement rose with increasing preoperative serum creatinine concentration. Overall, 75% of dialysis-dependent patients were permanently removed from dialysis after renal artery repair. In addition, the site of disease and the extent of repair were found to influence increases in the EGFR. Although each subgroup of patients who underwent operation demonstrated some improvement in renal function, the greatest incremental increase in the EGFR was observed in those who underwent bilateral renal reconstruction for significant bilateral disease.^{3,6}

RELATIONSHIP OF HYPERTENSION RESPONSE AND RENAL FUNCTION RESPONSE TO DIALYSIS-FREE SURVIVAL

At a mean follow-up of 56 months, 171 patient deaths had occurred. When outcomes were considered in terms of the blood pressure response to operative intervention, only hypertension cured was found to be significantly and independently associated with survival or dialysis dependence: patients whose hypertension was cured experienced improved dialysis-free survival [see Figure 6]. In contrast, all outcome categories for the renal function response influenced both survival and eventual dialysis dependence. Patients with improved renal function experienced a significant increase in dialysis-free survival [see Figure 7].² For patients whose renal function remained unchanged after operation, however, the risk of eventual dialysis dependence and death was equivalent to that of patients whose renal function worsened after surgery. Although renal function that is unchanged after intervention is frequently described as “stabilized” or “preserved,” our experience suggests that patients with ischemic nephropathy and atherosclerotic renovascular disease whose renal function is unchanged postoperatively remain at increased risk for eventual dialysis dependence and death. Whether similar associations exist for patients treated by means of catheter-based

Table 2 Summary of Operative Management of Atherosclerotic Renovascular Disease²

	<i>n</i>
Total renal reconstructions	720
Aortorenal bypass	384
Venous graft	204
PTFE graft	159
Dacron graft	21
Reimplantation	56
Thromboendarterectomy	267
Splanchnorenal bypass	13
Total nephrectomies	56
Total kidneys operated on	776

PTFE = polytetrafluoroethylene.

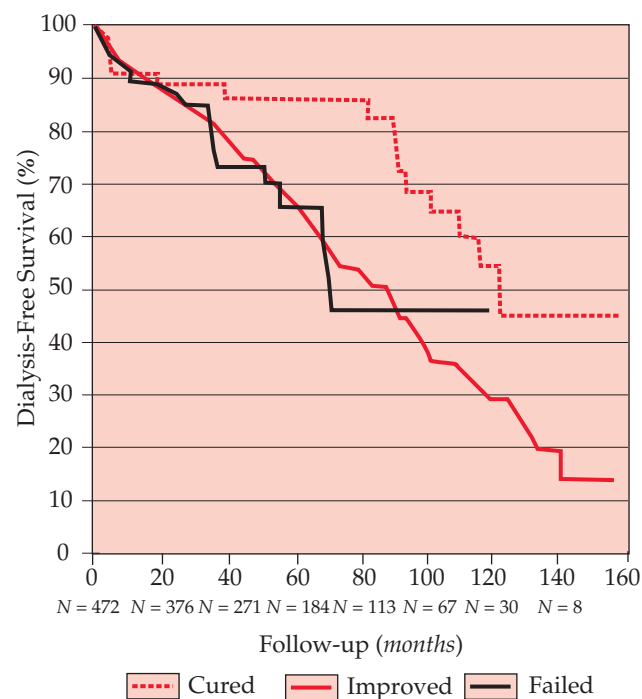


Figure 6 Product-limit estimates of time to death or dialysis, stratified according to blood pressure response to operation for atherosclerotic renovascular disease.²

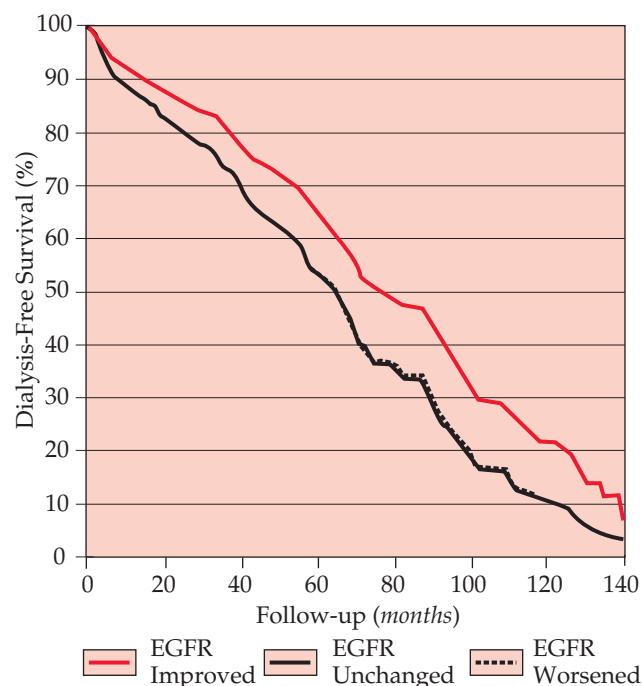


Figure 7 Product-limit estimates of time to death or dialysis, stratified according to postoperative renal function response for patients with a preoperative estimated glomerular filtration rate (EGFR) of 25 mL/min/m². The interaction between preoperative EGFR and renal function response for dialysis-free survival was significant and independent.²

methods is unknown, but the question certainly merits future study.

Financial Disclosures: None Reported

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Figures 1 through 5 Alice Y. Chen

23 ENDOVASCULAR PROCEDURES FOR RENOVASCULAR DISEASE

Matthew S. Edwards, MD, FACS, William B. Newton III, MD, and Kimberley J. Hansen, MD, FACS

The treatment of renovascular disease is currently in a state of evolution. Open surgical revascularization remains the gold standard, having demonstrated its durability and efficacy in treating renovascular hypertension and ischemic nephropathy; however, it is associated with substantial morbidity and mortality, even when performed at centers with extensive experience.¹⁻⁴ As a result, endovascular techniques for renal revascularization, including percutaneous transluminal angioplasty with or without endoluminal stent placement (PTAS), have emerged as the preferred option for revascularization of occlusive renal artery lesions. Compared with conventional open surgical revascularization, these endovascular techniques offer a number of potential benefits (e.g., decreased morbidity, lower mortality, shorter recovery times, and reduced hospital resource use); however, they also possess certain potential drawbacks (e.g., reduced effectiveness and decreased durability).

Predictably, controversy persists regarding the appropriate application of surgical and endovascular therapies to the treatment of renovascular disease, with proponents of each modality citing selected literature to support their position. In what follows, we review key technical aspects of endovascular renal revascularization and summarize the current data on technical results, clinical outcomes, and associated complications.

Preoperative Evaluation

The general principles of preoperative evaluation and patient selection for persons being considered for renal revascularization, whether open or endovascular, are addressed in more detail elsewhere. As a rule, our group reserves renal artery PTAS for patients with renal artery stenosis in combination with severe hypertension with or without renal insufficiency.

CONTRAST ARTERIOGRAPHY

Despite advances in diagnostic imaging that allows noninvasive identification of patients with renovascular disease,⁵⁻⁹ the formulation of an endovascular therapeutic plan depends on visualization of the renal artery anatomy by means of angiography. Accordingly, contrast angiography of the renal arteries should be considered an integral component of the therapeutic armamentarium for clinically significant renal artery lesions.

CONTRAST-INDUCED NEPHROPATHY

Patients with renovascular disease have a high prevalence of associated medical comorbidities (e.g., diabetes mellitus,

congestive heart failure, chronic renal insufficiency, and diuretic-induced intravascular volume depletion). These conditions may necessitate alterations in the usual routines for patient preparation and use of iodinated contrast agents. Such agents are known to be capable of impairing excretory renal function,¹⁰ sometimes permanently. The risk of this complication is highest in persons with preexisting dehydration,¹¹ renal insufficiency,¹²⁻¹⁴ or diabetes mellitus,¹⁵⁻¹⁷ especially the juvenile variety. Administration of large volumes of iodinated contrast material^{18,19} and use of high-osmolality agents¹⁵⁻¹⁷ may also increase the risk of renal function impairment. Several reports, however, have suggested that periprocedural administration of acetylcysteine,^{20,21} sodium bicarbonate hydration,²² and vitamin C can lower the risk of renal function impairment after angiography.

In light of available evidence, our current policy is to prepare all patients for aortorenal arteriography with saline hydration (limited in patients with significant heart failure) and periprocedural administration of acetylcysteine, along with limited use of sodium bicarbonate in patients who have preexisting renal insufficiency. Furthermore, we routinely select low-osmolality iodinated contrast agents in these patients and limit the volumes infused. In patients with moderate to severe preexisting renal insufficiency, carbon dioxide^{23,24} may also be employed as an intra-arterial contrast agent to reduce or eliminate the use of iodinated contrast material. Our practice with such patients is to use carbon dioxide for initial localization [see Figure 1a] and selective cannulation [see Figure 1b] of the renal artery and then to employ an iodinated contrast agent in small volumes for definitive planning and performance of the required intervention.

TECHNICAL CONSIDERATIONS

Femoral artery access is the most versatile and lowest risk option. For nonselective renal arteriography, either femoral artery provides adequate access. For selective renal cannulation, however, it is generally better to use the femoral artery contralateral to the renal artery for intervention; this approach takes advantage of the tendency of the catheter to track preferentially toward the contralateral aortic wall and facilitates cannulation of the renal ostia.

If the patient has downsloping renal arteries or if femoral access is not advisable, brachial artery access is a useful alternative. It is preferable to access the left brachial artery so as not to cross the origin of the right common carotid artery. Access may be established by means of either percutaneous or open techniques. The risk of complications is higher with percutaneous brachial artery access, and the maximum permissible sheath and catheter sizes are smaller.²⁵ Accordingly, we generally use an open approach for brachial artery access, with puncture, cannulation, and suture closure carried out under direct vision.

Financial disclosure information is located at the end of this chapter before the references.

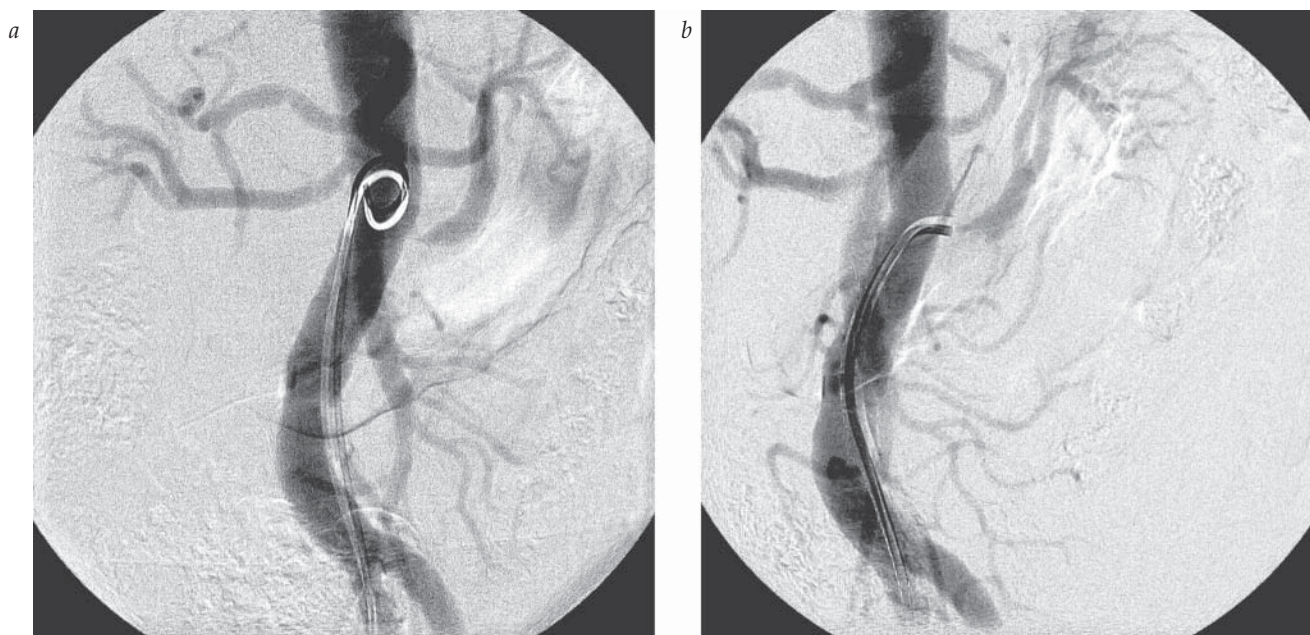


Figure 1 (a) Bilateral high-grade renal artery stenosis visualized by using carbon dioxide angiography to localize the renal ostia. (b) Selective right renal artery cannulation with placement of a 6 French left internal mammary artery guide catheter and selective renal arteriography using hand-injected half-strength iso-osmolar contrast material.

PROJECTIONS

Aortography and selective renal angiography with multiple projections are necessary for full radiographic evaluation of the renal arteries and the juxtarenal aorta. Initial anteroposterior (AP) images of the visceral aorta are obtained by delivering power contrast injections through a flush catheter with multiple side holes positioned at the L1-L2 interspace. These initial AP views provide an overview of the renal artery and the perivisceral aortic anatomy [see Figure 2]. Additional nonselective images of the renal arteries should be obtained by moving the catheter to a location below the origin of the superior mesenteric artery to prevent contrast opacification of the visceral vessels, which could obscure the anatomic details of the renal arteries.

The renal arteries usually arise from the anterolateral right or the posterolateral left aspect of the aorta. As a result, lesions within the renal ostia often are not seen or appear insignificant on AP aortograms. Oblique aortography and oblique selective renal arteriography project these portions of the vessel in profile and thus are often better at identifying any renal ostial lesions present. As a rule, the single most useful projection for visualizing the renal ostia is a 15° to 20° left anterior oblique view, although other oblique views may also be necessary.^{26,27} Axial images of the renal origins (i.e., computed tomographic scans) may allow estimation of the necessary degree of obliquity and permit the use of smaller amounts of iodinated contrast material and lower doses of ionizing radiation [see Figure 3].

For full delineation of lesions within the body of the renal artery, selective arteriographic views may be required. Selective cannulation is usually performed with a configured



Figure 2 An anteroposterior aortogram is obtained by delivering a power injection of iso-osmolar iodinated contrast material through a 5 French pigtail catheter positioned at the L1-L2 interspace.



Figure 3 Axial computed tomographic scan of the renal artery origins allows estimation of the degree of obliquity required for optimal imaging of the renal ostia.

catheter (e.g., a cobra catheter, a Sos catheter, or a renal double-curve catheter). The varying configurations of available catheters offer specific advantages in particular anatomic situations. Before selective renal artery cannulation, we administer heparin intravenously. Once the guide wire has been gently advanced into the renal artery ostia, contrast material is injected by hand to confirm intraluminal placement. Selective images are then obtained with low-volume power injection or hand injection (our preference) of contrast material [see Figure 4]. The proximal third of the left

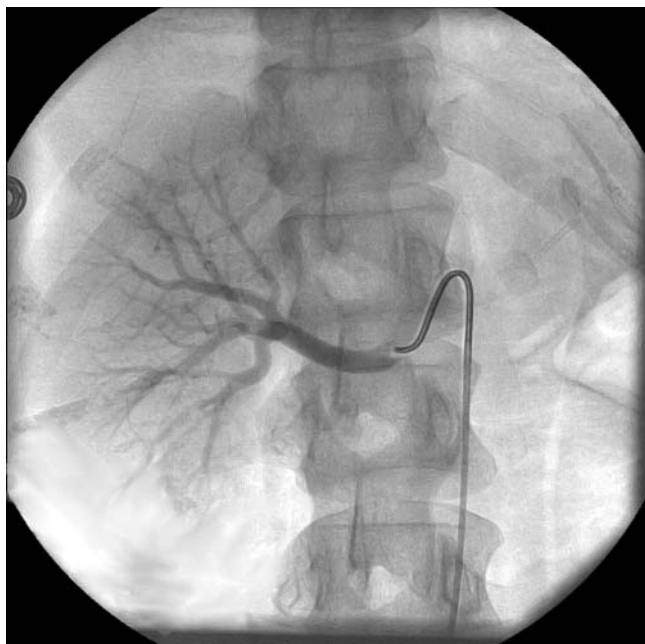


Figure 4 Selective arteriography of the right renal artery using hand-injected iso-osmolar contrast material through a complexly curved Simmons catheter.

renal artery usually courses anteriorly, the middle third transversely, and the distal third posteriorly; the right renal artery generally pursues a more consistent posterior course. For full delineation of lesions in the various segments, oblique and cranial-caudal projections may be necessary.

ADJUNCTIVE MEASURES

Renal artery angiography affords the surgeon the opportunity to employ other measures to characterize a renal artery lesion. For example, the hemodynamic effects of an angiographic stenosis or interaction can be assessed by making direct pressure measurements proximal and distal to the lesion. In general, we consider any pressure gradient greater than 12 mm Hg to be indicative of hemodynamically significant renovascular disease. Additional anatomic information can be obtained by means of intravascular ultrasonography of the renal artery, which can provide detailed information on plaque morphology, vessel size, and potential dissection flaps to complement the data obtained through arteriography.^{28,29}

ANGIOGRAPHIC CHARACTERISTICS

Atherosclerotic renovascular disease

Atherosclerosis of the renal artery accounts for approximately 85% of all renovascular lesions. Elderly persons with multiple comorbid medical conditions and manifestations of atherosclerosis are most frequently affected.^{30–33} Atherosclerotic renal lesions represent a continuation of a process that begins in the aorta and spills over into the origin of the renal vessels [see Figure 5]. These lesions are characterized by an eccentric, irregular narrowing of the ostium and the proximal portion of the renal artery [see Figure 6]. In the majority of cases, the lesions are limited to the ostia and the proximal renal artery.³⁴ The aortic origin of the lesion has important implications for treatment. Placement of an endovascular stent into the proximal renal artery, without covering the aortic origin of the plaque, may result in residual or recurrent disease. Occlusions of the renal artery are also common in patients with clinically significant disease [see Figure 7] and frequently occur in the setting of contralateral renal artery stenosis.^{2,3}

Fibromuscular dysplasia

Fibromuscular dysplasia (FMD) is a term used to describe a group of histologically distinct pathologic conditions of

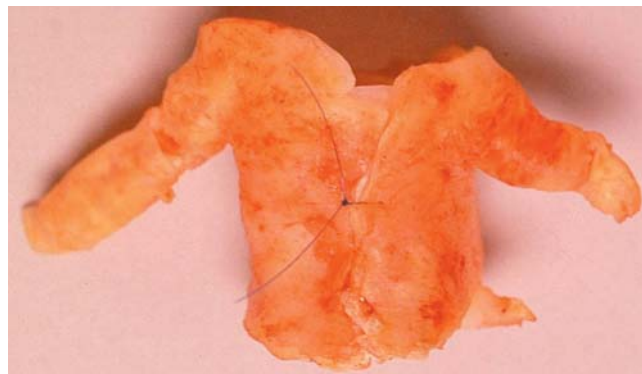


Figure 5 An aortic endarterectomy specimen demonstrates the pathologic basis of atherosclerotic renovascular disease.



Figure 6 A magnified preintervention aortogram demonstrates ostial right renal artery atherosclerotic stenosis.

the arterial wall that most commonly affect the main renal artery and its branches. FMD of the renal artery, with resultant renal artery stenosis, is responsible for approximately 10 to 15% of treated cases of renovascular hypertension.³⁵ The lesions are categorized according to the layer of the



Figure 7 An aortogram demonstrates right renal artery stenosis and left renal artery occlusion with distal renal artery reconstitution.

arterial wall involved—hence the terms medial fibroplasia, perimedial dysplasia, and intimal fibroplasia. Medial fibroplasia is the most common variant, representing 85% of recognized cases. It is encountered almost exclusively in women, most commonly in the third or fourth decade of life.^{35,36} The arteriographic pattern most frequently associated with medial fibroplasia resembles a string of beads [see Figure 8], an appearance created by weblike stenotic areas with intervening areas of poststenotic dilatation. These lesions are frequently bilateral and can be associated with renal artery aneurysm or dissection.³⁷ Medial fibroplasia of the main renal artery is among the lesions most amenable to endovascular treatment. In our view, however, the presence of branch vessel disease or aneurysms precludes safe treatment.

Perimedial dysplasia accounts for approximately 15% of cases of FMD and is most commonly manifested by the appearance of multiple irregular stenoses without microaneurysms.³⁶ Intimal fibroplasia is the least common variant of FMD, representing fewer than 5% of recognized cases, and the typical lesions are smooth concentric stenoses.^{35,36} In general, perimedial dysplasia and intimal fibroplasia tend to respond less well to endovascular treatment than the medial fibroplasia variety.

Procedural Planning

PATIENT PREPARATION

Recently, the use of statins has been associated with a significant and independent decrease in restenosis. Corriere and colleagues reported that patients not receiving statin therapy have a threefold increase in estimated restenosis over time.³⁸ Consequently, statin therapy is initiated prior to intervention. Patient preparation for renal artery PTAS is similar to that routinely carried out for diagnostic arteriography. Oral intake of food and liquid is stopped at midnight the evening before the procedure. Warfarin is discontinued at least 4 days beforehand; aspirin and clopidogrel are continued. Intravenous fluids and acetylcysteine



Figure 8 A selective right renal arteriogram demonstrates findings indicative of medial fibroplasia.

are administered the evening before the procedure, with care taken to avoid fluid overload in patients with impaired cardiac function. Routine medications, with the exception of angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists, are taken on the morning of the procedure with a sip of water. A first-generation cephalosporin is administered intravenously 30 minutes before the procedure unless the patient is allergic.

After the intervention, the patient is observed in the hospital overnight to check for access-site problems and severe alterations in blood pressure. Acetylcysteine is continued throughout the hospital stay, and oral administration of clopidogrel is initiated the evening after the procedure. The patient continues to take clopidogrel for at least 30 days after revascularization and remains on aspirin therapy indefinitely.

CORRELATION OF DIAGNOSTIC IMAGES WITH CLINICAL FINDINGS

Once the diagnostic portion of the procedure is completed, the images obtained are closely examined and correlated with the patient's clinical presentation. Intra-arterial pressure measurements are occasionally misleading in renal vessels. Because most renal arteries are approximately 5 to 6 mm in diameter, a stenotic lesion that causes a greater than 60% reduction in the luminal diameter leaves only 2.0 to 2.5 mm of patent lumen. A 4 or 5 French diagnostic catheter may completely occlude this narrowed lumen, thus resulting in an inaccurately low pressure measurement distal to the stenosis. Accordingly, it is our practice to assess the anatomic arteriographic information in light of the functional significance of the lesion as determined by either renal vein renin assays or duplex ultrasonography.

MATERIALS AND INSTRUMENTS

The materials commonly used for renal artery PTAS at our center include various guide wires, catheters, sheaths, balloons, and stents [see Table 1]. The basic principles underlying the use of these devices are outlined more fully elsewhere [search ACS Surgery for further information on endovascular surgery].

Procedural Technique

STEP 1: SECURE RENAL ARTERY ACCESS FOR THERAPEUTIC INTERVENTION

Once the decision for endovascular intervention is made, the patient is systemically heparinized, and the 5 French diagnostic catheter and the introducer sheath are exchanged over a 0.035 in. guide wire so that an access platform can be established that will provide secure renal artery access for the therapeutic intervention.

Most angioplasty and stenting devices in current use will pass through a 6 French lumen. Access options include guide sheaths and guide catheters. Common to both of these options is the provision of a long mechanical support segment for guide-wire placement that affords direct access to the renal artery for easy passage of therapeutic devices to the target lesion [see Figure 9]. Such systems vary in shape and diameter and come in multiple configurations to facilitate renal artery access in different situations.

After the tip of the guide catheter is positioned at or within the renal artery orifice, guide-wire access across the lesion is obtained. For all subsequent manipulations, the sheath or the guide catheter should not be advanced beyond the orifice, because the nontapered tip may injure the vessel. Depending on the type, severity, and location of the lesion, a 0.35, 0.18, or 0.14 in. guide wire with a floppy radiopaque tip is chosen. The smaller guide-wire systems appear to have inherent advantages, in terms of ability to cross tighter stenoses, limitation of renal artery trauma, and liberation of emboli, but whether these apparent advantages are real remains to be proved. Once the guide wire is in place, the access platform is secured and remains in place until the intervention and any postintervention imaging are complete.

STEP 2: TRANSLUMINAL ANGIOPLASTY

With the guide wire secured distal to the lesion, therapeutic intervention may proceed. Both coaxial systems (in which the entire catheter is exchanged over the wire, so that an assistant is required to control the wire during intervention and catheter exchange) and monorail or rapid-exchange systems (in which only the distal portion of the catheter is over the wire, so that a single operator can control the wire during intervention and catheter exchange) are available for renal artery intervention.

Regardless of the system chosen, the principles of intervention remain the same. Transluminal angioplasty of the renal artery may be performed either as the sole therapy for a renal artery lesion or as a means of predilating a lesion so that an endoluminal stent can be placed. Angioplasty may also be employed to treat recurrent renal artery stenoses after surgical or endovascular therapy. Angioplasty is an effective stand-alone therapy in most cases of main renal artery disease (FMD and nonostial atherosclerosis) but is frequently ineffective for atherosclerotic ostial and proximal renal artery disease.

The angioplasty balloon size is chosen on the basis of quantitative angiographic images. Direct cut-film images with ball-bearing or marker-catheter reference points may be used, as may the quantitative software packages available on most contemporary digital angiographic systems. In general, the angioplasty balloon should be slightly larger than the adjacent normal artery for primary treatment and somewhat smaller for predilation of a stenotic lesion. For predilation before endoluminal stent placement, we usually employ a 3 × 20 mm low-profile angioplasty balloon. This choice tends to make the stent passage less traumatic and helps in estimating the stent diameter and length required.

During inflation of the angioplasty balloon, the aortic origin of most ostial plaques is indicated by the appearance of a visible "waist," and the image can be centered over a bony landmark to facilitate subsequent stent placement. It is not unusual for the patient to experience some discomfort during balloon inflation. This discomfort should resolve quickly when the balloon is deflated; if it does not, renal artery trauma should be suspected. It is our practice to inflate the balloon slowly to its fully inflated profile at the rated nominal pressure and then maintain inflation for 30 to 45 seconds before deflation.

Table 1 Standard Equipment for Renal PTAS

Device Category	Type	Proprietary Name	Length	Diameter
Guide wires	Initial	Starter 3 mm J	180 cm	0.035 in.
	Selective	Magic Torque	180 cm	0.035 in.
		Platinum Plus, V-18 Transend, GuardWire	145–180 cm 165–200 cm	0.018 in. 0.014 in.
Catheters	Flush angiography	Pigtail	70 cm	5 Fr
	Selective: diagnostic	Cobra C1 or C2	65 cm	5 Fr
		Contra 2	65 cm	5 Fr
		VS-1 or Sos	65 cm	5 Fr
		Simmons	65 cm	5 Fr
	Selective: guide	Renal Double Curve	55 cm	6 Fr
		LIMA	55 cm	6 Fr
		JR 4	55 cm	6 Fr
		Hockey Stick	55 cm	6 Fr
	Pressure measuring	Straight Glide, Export	90 cm	4 Fr
Sheaths	Initial access		10 cm	4–5 Fr
	Therapeutic access		10 cm	6 Fr
	Selective: guide	Pinnacle Destination	45 cm	6 Fr
		Flexor Check Flow ANL2	45 cm	6 Fr
Angioplasty balloons	Predilation	Savoy, Gazelle, Aviator, Symmetry	1.5–2.0 cm balloon 75–90 cm shaft	3 mm balloon 5 Fr sheath
	Therapeutic	Savoy, Gazelle, Aviator, Symmetry	1.5–2.0 cm balloon 75–90 cm shaft	4–7 mm balloon 5 Fr sheath
Stents*	Balloon-expandable	Genesis, Express	12–29 mm stent	5–7 mm stent
			75–90 cm shaft	6 Fr sheath

PTAS = percutaneous transluminal angioplasty with or without endoluminal stent placement.

*None of these stents are approved by the Food and Drug Administration for use in renal arteries.

Once the balloon has been completely deflated, it is removed, and selective angiography is repeated to assess the response of the lesion to angioplasty and check for complications. Guide-wire access must be maintained until the end of the procedure so that complications or unsatisfactory results (e.g., dissection or residual stenosis) can be addressed.

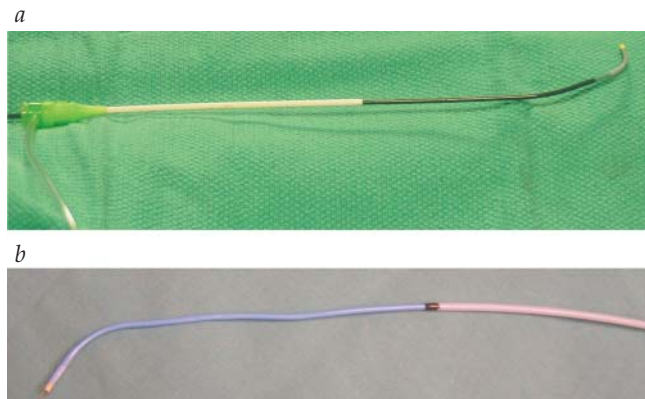


Figure 9 (a) A guide catheter inserted through a short 6 French arterial sheath. (b) A diagnostic catheter inserted through a guide sheath.

STEP 3: ENDOLUMINAL STENTING

Endovascular stent placement may be performed either as a primary procedure or as a secondary procedure in response to suboptimal results from angioplasty. Most FMD lesions and nonostial atherosclerotic lesions respond well to angioplasty alone. Secondary stent placement should, however, be considered for nonostial lesions that do not respond appropriately to angioplasty. Secondary stent placement is typically performed to address elastic recoil, residual stenosis (> 30%), pressure gradients (> 10 mm Hg), and myointimal flaps or dissections. Either balloon-expandable or, less commonly, self-expanding stents may be employed in the renal artery. Typically, balloon-expandable stents have greater radial strength and can be placed more precisely, whereas self-expanding stents are more flexible and conform more readily to the shape of the lumen. We employ balloon-expandable stents primarily in the treatment of ostial atherosclerotic lesions, where their advantages are particularly useful.

In general, the technical aspects of stent placement parallel those of transluminal angioplasty. Frequent hand injections of small amounts of contrast material through the guide sheath or catheter are employed to guide the stent into position across the lesion before deployment [see Figure 10]. After the stent has been deployed, completion angiography is performed while guide-wire access to the renal artery is

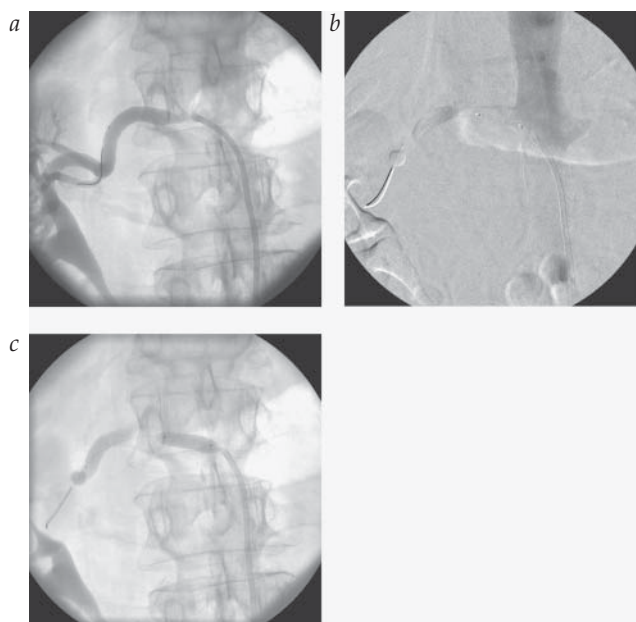


Figure 10 (a) The orifice of a right renal artery with high-grade ostial stenosis is selected with a 5 French cobra catheter, and the lesion is crossed with a 0.014 in. guide wire. (b) A balloon-mounted stent is positioned across the renal artery stenosis with the help of intermittent contrast injections and bony landmarks. (c) A fully expanded stent is positioned in the renal artery.

maintained. This is accomplished by hand injection of contrast through the guide sheath or catheter. For the treatment of ostial or proximal renal artery lesions, it is preferable to position the stent with 1 to 2 mm extension into the aorta. Frequent hand injection of contrast material through the guide sheath allows precise placement of the stent and helps prevent misdeployment. If the stent is placed too far into the artery, the true renal orifice is not supported, and there is a greater chance of residual or recurrent disease.^{39–43} Such recurrent disease often does not respond to further endovascular attempts; accordingly, it is advisable to use the shortest possible stent that will adequately support the lesion. In addition, a stent that extends well out into the distal renal artery can make later surgical options more difficult⁴⁴ and typically carries a higher failure rate.

A balloon-expandable stent is deployed by inflating the angioplasty balloon on which it is mounted. In the past, these stents had to be crimped and hand-mounted on the angioplasty balloon, which made their delivery somewhat insecure. Currently available stents, however, come securely premounted on low-profile delivery systems capable of passing across most lesions with minimal or no predilation. We deploy these stents with 1 to 2 mm extension into the aorta, guided by anatomic information provided by previous positioning over bony landmarks. Self-expanding stents, although not commonly applied to the treatment of renovascular disease, can also be employed in this setting. These devices are deployed by retracting an outer membrane of the delivery device to expose the stent. Care must be taken

during deployment to ensure that foreshortening of the stent does not compromise coverage of the lesion.

After a stent is deployed, there may be residual narrow areas within the stent that necessitate balloon dilatation. These areas may be visible on fluoroscopic evaluation of the stent or detected during postdeployment selective renal angiography.

After all therapeutic measures have been completed, the technical result is assessed and undetected defects are sought by means of repeat pressure-gradient measurements, intravascular ultrasonography, or both. When a satisfactory result is obtained, the guide wire and the sheath are removed and hemostasis is secured. Although it is possible to perform bilateral renal interventions in a single procedure, we prefer, when possible, to stage these interventions so as to minimize contrast loads.

Postprocedural Care

Longitudinal follow-up of all patients undergoing renal revascularization is mandatory to check for recurrent disease, contralateral disease, and deterioration of clinical benefit, as well as other preventable cardiovascular and peripheral vascular conditions. Our current approach to follow-up entails clinical visits at 1, 3, 6, 9, 12, 18, and 24 months after renal artery PTAS, with renal duplex ultrasonography, blood pressure measurement, and serum creatinine measurement at each visit. After 24 months, this intensive early follow-up is relaxed to a yearly visit schedule if no conditions necessitating shorter visit intervals have been identified.

Recurrent disease after renal stenting is a significant concern, and disease that recurs within the stent itself can be a particularly challenging problem [see Figure 11a]. Because most such recurrences are related to intimal hyperplasia, repeat balloon angioplasty generally does little to improve the situation. Initial dilatation with a Cutting Balloon (Boston Scientific, Natick, MA) is extremely useful for releasing the fibrous scar tissue of the restenotic lesion and allowing subsequent dilatation to a larger diameter with a conventional angioplasty balloon. The Cutting Balloon consists of a noncompliant balloon with three or four atherotomes (microsurgical blades) mounted longitudinally on its outer surface [see Figure 11b]. When the device is inflated, the atherotomes score the intimal hyperplasia within the stent; the balloon is then rotated and reinflated to score the lesion in multiple planes. To date, this technique has been used primarily in coronary arteries, but it has also been applied to the treatment of renal artery in-stent restenosis.⁴⁵ After the lesion has been scored, a larger balloon is inserted and inflated to redilate the lesion [see Figure 11c].

Complications

Potential complications include access-site complications (e.g., hematoma, pseudoaneurysm, retroperitoneal hemorrhage, arteriovenous fistula, and closure-device infection), contrast-mediated allergic reactions or nephrotoxicity, atheroembolism, and direct renovascular trauma. In a meta-analysis published in 2000, the reported complication rate after renal PTAS ranged from 0 to 40% (mean rate 11%).³⁴

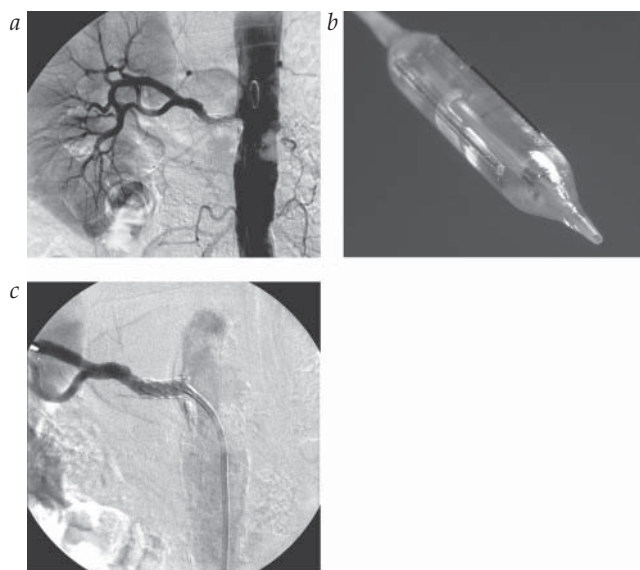


Figure 11 (a) High-grade recurrent in-stent restenosis of the right renal artery. (b) The Cutting Balloon is useful in dealing with such lesions. (c) Dilation with a 4 × 15 mm Cutting Balloon is followed by dilation with a standard 6 × 20 mm angioplasty balloon, and a completion angiogram is obtained.

The most frequently reported complications were hematomas at arterial access sites. Severe complications occurred in 9% of patients and included renal failure, segmental renal infarction, perinephric hematoma, and renal artery thrombosis. The mean mortality was 1%.

A large single-center retrospective review of complications after endovascular treatment with renal artery stenting reported similar results.⁴⁶ Major complications occurred after 15 of 179 procedures (8.4%) and included renal infarction, permanently increased serum creatinine concentration, dialysis dependence, blood transfusion, surgical intervention, and deep vein thrombosis. There was no apparent association between pretreatment patient characteristics and the subsequent incidence of major complications. Two patients (1.1%) died within 30 days after the procedure.

Outcome Evaluation

To be considered successful, renal artery revascularization should (1) improve quality of life, (2) reduce the incidence of adverse cardiovascular disease events, (3) slow or halt the progression of chronic renal insufficiency, (4) lower the incidence of dialysis-dependent renal failure, or (5) improve overall survival. Unfortunately, few studies have addressed these clinical outcome measures. Consequently, the outcome of renal revascularization is currently assessed on the basis of (1) the extent to which the procedure is anatomically or technically successful and (2) the degree to which the procedure alleviates or cures associated hypertension and ischemic nephropathy. Technical success and the response of hypertension or renal dysfunction to therapy are assumed to be the mechanisms by which the five important clinical outcomes listed are achieved.

Interpretation of the results of renal artery PTAS as reported in the current literature is challenging. Despite the publication of hundreds of reports on this procedure, it remains unclear how renal artery PTAS compares with surgical renal revascularization and whether renal artery PTAS conveys any meaningful benefit to patients beyond what can be achieved with medical therapy alone. These shortcomings in our understanding of renal artery PTAS (and of surgical renal revascularization, for that matter) stem largely from the lack of well-designed clinical trials investigating these questions. Such trials will ultimately be necessary to establish the utility and safety of renal artery PTAS in the treatment of renovascular disease. Until such trials are performed, interpretation of the existing literature is a valuable guide for prudent application of renal artery PTAS.

HYPERTENSION RESPONSE

Three pre-2000 randomized, controlled studies have compared endovascular therapy with medical treatment of renovascular hypertension [see Table 2]. These studies provide the best available data on the efficacy of endovascular therapy for managing hypertension but are limited in their contemporary utility in that they all investigated the use of renal artery angioplasty without primary stent placement and use of antiquated medical management. The first study involved 49 patients with unilateral renal artery stenosis who were randomly assigned to either angioplasty or best medical hypertension treatment.⁴⁷ The angioplasty group demonstrated no statistically significant decrease in blood pressure; however, it did demonstrate improvement in hypertension control, as evidenced by a significant reduction in the amount of antihypertensive medications required. The second study, reported by the Scottish and Newcastle Renal Artery Stenosis Collaborative Group, involved 55 patients who were randomly assigned to either angioplasty or best medical antihypertensive therapy.⁴⁸ Patients with both unilateral and bilateral renal artery stenosis were included in this study. There was a modest improvement in blood pressure control in the angioplasty group, but this benefit was confined to those patients who had bilateral disease. None of the patients were cured of their hypertension. The third study was performed by the Dutch Renal Artery Stenosis Intervention Cooperative Study Group.⁴⁹ A total of 106 patients were randomly assigned to either renal artery angioplasty or best medical therapy for renovascular hypertension. At 12 months, there was no significant reduction in either systolic or diastolic blood pressure, although multiple treatment crossovers occurred that might have skewed the results toward the best medical therapy arm. The authors concluded that angioplasty had little advantage over antihypertensive therapy in the treatment of renovascular hypertension.

Table 3 summarizes the hypertensive response in 1,377 patients from various published reports treated with renal artery angioplasty and stenting since 2000. The overall hypertension cure rate was 4%, with a range of 0 to 8%. Fifty-four percent of the patients had improved blood pressure control, with a range of 0 to 91%. However, it is also important to note that the periprocedural morbidity was 6.6% and the periprocedural mortality was 1% for these patients.

Table 2 Summary of Trials Included in Meta-Analysis

<i>Trial</i>	<i>Patients (n)</i>	<i>Unilateral or Bilateral Disease</i>	<i>Randomized Treatment</i>	<i>Duration of Follow-up</i>	<i>Main Endpoints</i>
Webster et al. ⁴⁸	55	Unilateral and bilateral, but two groups analysed separately	Angioplasty vs medical management	Patients reviewed at end of 4-week run-in period (baseline) then at 1, 3 and 6 months, then at 6-monthly intervals	Primary: BP and SCr at 6 months and the change in these from baseline Secondary: major events
Plouin et al. ⁴⁷	49	Unilateral only	Angioplasty (with or without stent insertion) vs medical management	Patients reviewed at end of 2–6 week run-in period (baseline) then at 6 months	Primary: BP at termination* and the change from baseline Secondary: treatment score and incidence of complications
van Jaarsveld et al. ⁴⁹	106	Unilateral and bilateral	Angioplasty vs medical management	Patients reviewed every 1–3 months, and always at 3 and 12 months	Primary: BP at 3 and 12 months Secondary: treatment score, SCr, SCr clearance, patency, and incidence of complications

BP = blood pressure; SCr = serum creatinine concentration.

* Termination defined as 6 months after randomization or earlier in cases of refractory hypertension (diastolic BP > 14 mmHg despite maximal tolerated antihypertensive regimen). In such cases, BP, treatment score and SCr were determined prior to renal arteriograph.

To date, only one prospective, randomized, controlled study has compared endovascular treatment with surgical revascularization for the treatment of renovascular hypertension.⁵⁰ In this report, 58 patients with renovascular hypertension were randomly assigned to either surgical revascularization or angioplasty. In both groups, hypertension was cured or improved in approximately 90% of patients. However, more than half of the patients in whom angioplasty failed were switched to the surgical arm for revascularization. On the basis of these results, the authors recommended angioplasty as the treatment of choice for selected renovascular lesions contributing to renovascular hypertension, with aggressive follow-up and repeat intervention (endovascular and surgical) carried out as needed. Investigators have reported that the beneficial blood pressure response seen after open surgical repair for failed angioplasty may be less than that seen in patients who undergo primary surgical repair without previous endovascular treatment.⁴⁴ Moreover, a previous endovascular procedure may make open surgical repair technically more demanding, especially if an endoluminal stent is present.

Two large contemporary clinical trials of renal artery stent placement and best medical therapy versus best medical therapy alone have also been recently completed. The Angioplasty and Stenting for Renal Artery Lesions (ASTRAL) trial commenced patient recruitment in September 2000.⁵¹ The trial randomized patients with significant anatomic atherosclerotic renovascular disease to either percutaneous transluminal renal angioplasty with stenting (PTRAS) with best medical management (e.g., statins, antiplatelet, antihypertensive therapy) or optimal medical management alone. The primary end point was the rate of change in renal function over time. Secondary end points included blood pressure control, adverse heart and vascular events, and mortality.

The first published report of the ASTRAL trial results is available.⁵¹ A total of 806 patients (403 randomized to each group) were enrolled. The trial included a mean follow-up of 33.6 months, with all surviving patients having completed a minimum of 12 months of follow-up. At baseline, trial group demographics were virtually identical for the two groups. The average degree of stenosis for the most severe renal artery lesion was 76%. Sixty percent of patients had renal artery stenosis exceeding 70%. Mean blood pressures were reported as 149/46 and 152/76 mm Hg in the PTRAS and medically managed groups, respectively. Patients averaged 2.8 antihypertensive medications in both groups.

The ASTRAL trial demonstrated no difference in blood pressure, renal function, adverse renal events, vascular events, or mortality between the two groups. In the PTRAS group, 6.8% of subjects suffered significant complications, including renal artery perforation, thrombosis, embolization, and significant renal insufficiency. Ignoring complications requiring admission, another 20% of PTRAS patients experienced less serious complications, consisting primarily of groin hematoma and mild renal insufficiency. Although the ASTRAL trial represents the largest published prospective, randomized clinical trial to date to examine the role of PTRAS, the trial has received substantial criticism. Patients were excluded from randomization if their physician felt it likely that they would benefit from PTRAS. As a consequence, it may be argued that those patients who would likely benefit from PTRAS were systematically omitted. In addition, of 403 patients randomized to PTRAS, 40% had stenosis between 50 and 70%. Moreover, pressure gradients across the stenosis were not measured before or after therapy. Finally, only 359 of 403 patients randomized to PTRAS underwent the procedure, whereas 24 of 403 patients assigned to medical management underwent intervention.

Table 3 Renal Artery Revascularization with Angioplasty and Stenting*

Reference	Year	Patients	Bilateral Treatment (%)	Preprocedural Renal Dysfunction (%)	Renal Function Response (%)			Hypertension Response (%)			Periprecedural Mortality (%)	Periprecedural Morbidity (%)
					Improved	Unchanged	Worsened	Cured	Improved	Failed		
Burket et al ⁶⁶	2000	126	NR	29	43	24	56	8	NR	NR	2	4
Lederman et al ⁶⁷	2001	265	41	37	7.5	78	14	NR	70	30	< 1	2
Bush et al ⁶⁸	2001	73	16	68	23	51	26	6	89	5	1.4	9
Rocha-Singh et al ⁴⁰	2002	51	55	100	77	18	5	NR	91	9	0	14
Gill and Fowler ⁴¹	2003	100	26	75	31	38	31	4	79	17	2	18
Zeller et al ⁶⁹	2004	456	NR	52	34	39	27	NR	46	54	< 1	NR
Nolan et al ⁷⁰	2005	82	NR	59	23	53	24	0	81	0	0	7
Kayshap et al ⁷¹	2007	125	36	100	42	23	25	0	0	0	1.6	6
Corriere et al ⁵³	2008	99	11	75	28	65	7	1	21	78	0	5.5
Mean% [†]			31	55	28	38	31	4	54	29	1	6.6

NR = not reported.

* Series selected based on publication in 2000 or later, use of angioplasty and stenting, and inclusion of more than 50 patients, and categorical reporting of renal function and/or hypertension responses.

[†] Weighted mean based on number of patients with reported data categorized according to column; references where data was not reported or categorical response categories were combined were not included in calculation.

However, when the trial results are examined on a “per protocol” basis, there was no apparent benefit for PTRAS.

Data from the other outstanding large prospective randomized clinical trial, the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial are eagerly awaited as that trial does not have many of the previously mentioned limitations.

RENAL FUNCTION RESPONSE

Several factors hinder accurate assessment of the effect of renal artery PTAS on renal function. To date, no prospective, controlled studies have compared renal function responses after medical, surgical, and endovascular treatment of renal artery stenosis. Most observational series report results from a diverse group of patients whose baseline renal function and subsequent responses to treatment vary widely. Interpretation of the existing renal function response data is further complicated by the limitation of serum creatinine measurement (the most commonly employed indicator of renal function in these studies) to detect changes in renal function, especially in patients with serum creatinine levels lower than 1.2 mg/dL.

These limitations notwithstanding, a number of reports published between 2000 and 2008 provided useful data on renal function response after renal artery PTAS, expressed in terms of a change (or lack of change) in serum creatinine concentration [see Table 3]. With improvement defined as a 20% or greater decrease in serum creatinine concentration, response rates ranging from 7.5 to 77% were observed (mean 28%). These results are very similar to those reported in the 2000 meta-analysis (range 0 to 50%; mean response rate

30%).³⁴ A number of authorities also make use of the concept of “stabilized” renal function, defined as a less than 20% change in serum creatinine concentration. By this definition, renal function was stabilized in the majority of patients included in the studies published between 2000 and 2008 (range 18 to 78%; mean response rate 38%) [see Table 3]. Again, these results are very similar to those reported in a meta-analysis from 2000 (range 0 to 64%; mean response rate 38%).³⁴ A significant percentage of treated patients (range 5 to 56%; mean 31%) also experienced post-PTAS worsening of renal function.

Although all investigators agree that worsened post-PTAS renal function represents a treatment failure, it is less clear whether an unchanged serum creatinine concentration should be considered beneficial to the patient. In one study, 88% of patients treated for renal dysfunction exhibited improved or stabilized serum creatinine levels after angioplasty, stenting, or both.⁵² Only 25% of patients, however, showed sustained responses over a 5-year follow-up period; the remainder demonstrated continuing deterioration of renal function. These results contrast sharply with those of reports addressing open surgical treatment of renal dysfunction, which documented durable improvement or stabilization rates of 85 to 93% and 5-year dialysis-free survival rates of 50 to 55%.²⁻⁴ Furthermore, patients with ischemic nephropathy whose renal function did not change after open surgical revascularization had increased rates of death and dialysis dependence during follow-up that were similar to those noted in patients with decreased renal function after revascularization.^{2,3} These findings suggest that improved postprocedural renal function may be the most important

surrogate outcome marker for predicting improved survival and dialysis independence; however, function unchanged is not consistent with “preserved” or “stable” renal function.

LONG-TERM COMPLICATIONS

Complications may also develop in a delayed manner. The principal long-term complications include restenosis of the renal artery and inadequate durability of clinical benefit. Restenosis is a common occurrence with all catheter-based methods of revascularization. According to the meta-analysis cited earlier,³⁴ restenosis complicates 11 to 42% (mean 26%) of renal artery angioplasties and 12 to 23% (mean 17%) of renal artery stent procedures including a restenosis rate in excess of 50% at 2 years in our experience. Restenosis may or may not be clinically significant.⁵³ The decision whether to treat restenotic lesions should be made on the basis of the specific physiologic or clinical response to the primary procedure.

The beneficial clinical responses noted after renal artery PTAS frequently are not durable. In two studies that reported on 222 individuals undergoing renal artery PTAS, the investigators found that the clinical response, especially the renal function response, was transient.^{52,54} Overall, at 5 years, 50 to 70% of patients exhibiting a positive hypertension response and fewer than 50% of those exhibiting a positive renal function response (defined as improvement or stabilization) retained any benefit. This deterioration of clinical benefit occurred even though a patent renal artery was maintained in all cases. Such results stand in stark contrast to the documented durability of the clinical response after surgical revascularization and underscore the need for close lifelong follow-up of all patients undergoing renal revascularization.¹⁻⁴

OUTCOMES AFTER RENAL ARTERY PTAS FOR FMD

Patients with FMD respond to renal artery PTAS much differently from those with renal artery atherosclerosis. FMD is most commonly manifested as medial fibroplasia in a young woman. In general, balloon angioplasty appears to be an acceptable treatment for adult patients with such lesions, and this approach yields excellent technical success rates, good clinical benefit, and low morbidity. In a study addressing 85 renal artery stenoses in 66 FMD patients, hypertension was cured or improved in 98% of patients after renal angioplasty, and all patients with elevated creatinine levels exhibited improved or stabilized renal function.⁵⁵ Another study, involving a series of older FMD patients (mean age 59 years) with long-standing hypertension (mean duration 13 years), a similar blood pressure response was noted.⁵⁶ At follow-up more than 3 years later, hypertension was cured in 14% of patients and improved in 74%.

Both studies supported the general consensus that medial fibroplasia of the main renal artery can be adequately treated by means of primary angioplasty, with stent placement reserved for technical complications. Furthermore, it appeared that a beneficial clinical response was seen after endovascular intervention and that this response was more pronounced in younger patients with a shorter duration of hypertension. There is reason to believe that improvements in our ability to select patients most likely to benefit from treatment,^{48,57-61} as well as the emergence of technical

developments aimed at preventing procedure-related embolization⁶²⁻⁶⁴ and long-term restenosis,⁶⁵ may be within reach. Such advances, if realized, may further narrow the gap between the clinical results of surgical renal revascularization and those of its endovascular counterpart and may improve the marginal benefit and safety of renal artery PTAS.

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24 RAYNAUD PHENOMENON

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Raynaud phenomenon is an episodic, exaggerated vascular response to cold or emotional stimuli, typically involving the fingers. The classic triphasic color change, first described by Maurice Raynaud in 1862, consists of initial pallor (secondary to vasospasm), followed first by cyanosis (from deoxygenation of the static blood) and then by rubor (as blood flow to the digits is restored and reactive hyperemia ensues).¹ This classic manifestation of Raynaud phenomenon occurs in as many as two thirds of affected patients; however, less common variants of the phenomenon (e.g., pallor followed by cyanosis alone and pallor followed by rubor alone) also exist.

Raynaud phenomenon occurs throughout the world. Overall, it tends to be more common in colder climates. In warmer areas of the United States and Spain, the prevalence ranges from 3 to 5%, whereas in cooler areas, the prevalence ranges from 15 to 20%.²⁻⁴ In a study of the African-American population, the prevalence was 3%.⁵

Classification

Raynaud phenomenon is generally classified as either primary or secondary. Primary Raynaud phenomenon occurs as an isolated finding in an otherwise healthy individual; secondary Raynaud phenomenon is caused by an associated disease (in most cases, an autoimmune disease) or by identifiable environmental or chemical exposure [see Table 1].⁶ The two types are distinguished from each other on the basis of clinical criteria, and the distinction has significant prognostic implications.

With primary Raynaud phenomenon, the typical age at onset is 15 to 30 years, symptoms are generally symmetrical and less severe, patients are more likely to be female, and multiple family members may be affected.⁷ With secondary Raynaud phenomenon, the typical age at onset is older, symptoms are usually more severe, and a systemic inflammatory disorder is commonly involved. In fact, Raynaud phenomenon is a prominent component of many autoimmune disorders, occurring in 90% of patients with scleroderma, 10 to 45% of patients with systemic lupus erythematosus (SLE), one third of patients with Sjögren syndrome, 20% of patients with dermatomyositis or polymyositis, and 10 to 20% of patients with rheumatoid arthritis.⁸ In 0 to 13% of patients who present with primary Raynaud phenomenon, an identifiable connective tissue disorder develops within a few years after presentation.^{9,10} The best predictors of transition to such a disorder are (1) serologic findings that are positive for auto-antibody and (2) suggestive physical findings (e.g., abnormal nailfold capillary patterns, cutaneous telangiectasias, puffy fingers, and sclerodactyly).^{6,10}

Table 1 Conditions Associated with Raynaud Phenomenon²¹

Rheumatologic diseases
Systemic sclerosis syndrome (scleroderma)
Systemic lupus erythematosus
Dermatomyositis or polymyositis
Rheumatoid arthritis
Takayasu arteritis
Giant cell arteritis
Thromboangiitis obliterans
Primary biliary cirrhosis
Mechanical injury
Vibration (hand/arm vibration syndrome)
Frostbite
Recurrent trauma or injury to large vessels
Crutch pressure
Thoracic outlet syndrome
Arterial diseases
Brachiocephalic atherosclerosis
Vasospastic disorders
Migraine or vascular headache
Prinzmetal angina
Endocrine disorders
Carcinoid syndrome
Pheochromocytoma
Hypothyroidism
Malignant diseases
Ovarian cancer
Angiocentric lymphoma
Abnormal blood elements
Cryoglobulins
Cold agglutinins
Paraproteinemia
Polycythemia
Infections
Parvovirus B19
<i>Helicobacter pylori</i>
Chemicals or drugs
Bleomycin, vinblastine
Polyvinyl chloride
Beta blockers
Ergots (e.g., methysergide)
Interferon alfa, beta
Tegafur

Clinical Evaluation and Investigative Studies

CHARACTERISTIC FINDINGS

Exacerbation of Raynaud phenomenon typically occurs after direct exposure of an extremity to cold temperatures [see *Sidebar Pathophysiology of Raynaud Phenomenon*], but an attack may also be elicited by generalized cooling of the entire body. In addition, attacks may be precipitated by any

Pathophysiology of Raynaud Phenomenon

Blood flow to the skin is regulated by a complex interaction between the endothelium, vascular smooth muscle, circulating hormones, and neural plexus. Patients with Raynaud phenomenon demonstrate an exaggerated vasomotor response to otherwise benign stimuli, notably cold exposure. Normally, on exposure to cold, blood flow to the skin is reduced in an effort to preserve core temperature. This natural response is mediated primarily by the sympathetic nervous system via the neurotransmitter norepinephrine, which causes contraction of vascular smooth muscle in the cutaneous arterial beds. This cold-induced vasoconstriction of cutaneous vascular smooth muscle appears to be mediated specifically by the α_2 receptor.⁴⁵

It has been suggested that the cold-induced vasoconstriction seen in primary Raynaud phenomenon is the result of exaggerated activity of the α_2 receptors. This suggestion was supported by the results of experiments that blocked the cold-induced vasoconstriction in primary Raynaud phenomenon by delivering α_2 receptor antagonists locally.⁴⁶ The mechanism of this Raynaud-specific hyperactive response has not been fully elucidated, although there is evidence to indicate that the response may, in part, be attributable to increased activity in the protein tyrosine kinase signal transduction pathway.⁴⁷ Endothelial derangements may also contribute to the pathogenesis of primary Raynaud phenomenon through increased plasma concentrations of endothelin and decreased levels of nitric oxide.^{48,49}

In secondary Raynaud phenomenon, it is generally accepted that vascular damage from the underlying disease (especially in the case of scleroderma) is responsible for the disruption of normal vasomotor homeostasis. Activated or damaged endothelial cells exacerbate vasospasm and further damage perfusion by mediating the proliferation and contraction of smooth muscle cells; enhancement of procoagulant activity and reduction of fibrinolysis promote the formation of intravascular microthrombi, and the release of chemotactic and adhesion factors activates local inflammatory processes.²¹

stimulation of the sympathetic nervous system, especially at times of emotional stress.

As a rule, Raynaud phenomenon is more likely to affect the hands than the feet. It is characterized by the sudden occurrence of cold digits in association with sharply demarcated pale skin—the so-called ischemic phase. Eventually, the skin may become cyanotic. Subsequently, rapid restoration of blood flow to the digits results in reactive hyperemia—the reperfusion phase. Attacks typically start in a single digit and spread symmetrically to other digits, eventually involving both hands. Other sites may be involved as well—notably, the ears, the nose, the nipples, the face, and the knees. Ischemic attacks may be accompanied by mottling of the skin on the arms and legs. During the ischemic phase, patients may complain of paresthesias and clumsiness in the involved extremities. In the most severe cases of secondary Raynaud phenomenon, critical ischemia may cause painful digital ulceration.

Raynaud phenomenon should be differentiated from simple “cold hands” (a more common and benign condition). In patients with Raynaud phenomenon, cold hands occur in conjunction with clearly distinguished skin-color changes. Moreover, recovery takes longer than it does in patients who merely have cold hands. The guidelines for diagnosing Raynaud phenomenon are based on a history of color change on exposure to cold or other stimuli. A history of repeated episodes of biphasic skin-color change on exposure to cold is indicative of Raynaud phenomenon. A history of uniphasic skin-color change with paresthesias on exposure to cold is suggestive. In the absence of any skin-color change, Raynaud phenomenon is ruled out.¹¹ Generally, additional diagnostic tests are unnecessary; however, both evaluation of digital pressure response to cooling and laser Doppler assessment of skin perfusion pressure have been employed in this setting. The Nielsen technique¹² is performed with a blood pressure cuff at the proximal phalanx and inflated above the patient’s systolic blood pressure. An arterial opening pressure is determined on deflation of the blood pressure cuff. Temperature differences to the finger can be induced with a second cuff of water around the proximal finger, lowering the temperature as needed, precipitating a Raynaud attack. This is detected by Doppler flow meter or a zero systolic digital pressure

as determined by a transducer. The temperature at which the Raynaud attack is precipitated is known as the arterial closing temperature. Laser Doppler assessment of skin perfusion pressure may be capable of distinguishing between normal control subjects, persons with primary Raynaud phenomenon, and persons with secondary Raynaud phenomenon.^{13–15}

Raynaud phenomenon should also be differentiated from carpal tunnel syndrome and other neuropathies, which may cause cold sensitivity but do not induce the skin-color changes characteristic of Raynaud phenomenon. Patients who have asymmetrical, persistent, or positional symptoms should undergo a full evaluation for possible large vessel occlusive disease, embolism, or thoracic outlet compression, any of which might lead to hand-color changes. Raynaud phenomenon may also be a reflection of a more generalized vasospastic disorder (e.g., migraine headache or Prinzmetal angina).^{16,17}

HISTORY AND PHYSICAL EXAMINATION

Once a diagnosis of Raynaud phenomenon has been established—or, at least, strongly suspected—a thorough history and physical examination can help distinguish between primary and secondary forms of the condition. The presence of specific symptoms of connective tissue disease (particularly arthralgia, myalgia, and dry mucous membranes), extended exposure to vibrating machinery, or antecedent use of certain medications is suggestive of secondary Raynaud phenomenon. The earliest specific diagnostic criteria for primary Raynaud phenomenon were described by Allen and Brown in 1932.¹⁸ More current criteria take advantage of modern diagnostic tools and serologic testing. Primary Raynaud phenomenon is suspected when attacks are symmetrical and episodic, when the history and the physical examination reveal no evidence of tissue gangrene or a possible underlying causative condition, when antinuclear antibody titers and erythrocyte sedimentation rates are normal, and when nailfold capillary examination yields unremarkable results.¹⁹

TESTING FOR SUSPECTED SECONDARY RAYNAUD PHENOMENON

If secondary Raynaud phenomenon is suspected on the basis of the history and the physical examination, more

specific testing is appropriate. A particularly helpful test is nailfold capillaroscopy. The bases of the fingernails of the fourth and fifth digits are examined with a handheld ophthalmoscope set to 10 to 40 diopters after a drop of immersion oil is placed on each nailfold. The normal vascular pattern, seen in healthy control subjects and patients with primary Raynaud phenomenon, consists of delicate “hairpin” capillary loops. However, the pattern seen in patients with Raynaud phenomenon secondary to an underlying cause (e.g., scleroderma, dermatomyositis, or undifferentiated connective tissue disease) often includes enlarged capillary loops, with evidence of angiogenesis, architectural derangements, and areas of decreased vascularity.²⁰ Serologic markers provide additional support for the diagnosis of secondary Raynaud phenomenon: the anti-Smith antibody is specific for SLE, and the antitopoisomerase and anti-RNA polymerase antibodies are highly specific for scleroderma-spectrum disorders. Among experts, there is little doubt that patients with Raynaud phenomenon who test positive for autoantibodies are at higher risk for the eventual development of a connective tissue disease.²¹

Koenig and colleagues prospectively studied 586 patients with Raynaud phenomenon without known connective tissue disease.²² In patients with one or more antibodies (antitopoisomerase, anti-RNA polymerase) noted on serologic testing or with abnormal nailfold capillaroscopy, the incidence of diffuse systemic sclerosis was 47%. Those patients with both an antibody and abnormal capillaroscopy had an incidence of systemic sclerosis of about 80%. The combination of both serology and nailfold capillaroscopy offers more information on the risk of systemic sclerosis than either test alone.

Management

Management of Raynaud phenomenon generally consists of lifestyle modification and medical treatment, with surgical options limited to severe or refractory cases. Nonpharmacologic treatment generally suffices for primary Raynaud phenomenon but is often inadequate for management of secondary Raynaud phenomenon, which is usually more severe. Mild forms of Raynaud phenomenon are managed with lifestyle modification, including maintenance of total body warmth (as well as warmth of hands and fingers), avoidance of cold and emotional stress, cessation of smoking, discontinuance of the use of vibrating tools, and avoidance of vasoconstricting substances (e.g., caffeine, cocaine, beta blockers, and decongestants). Biofeedback training has also been shown to be of some utility in reducing symptoms of Raynaud phenomenon, although several studies have questioned its value, especially in comparison to that of medical management.^{23,24}

Calcium channel blockers are the vasodilators most commonly used to treat Raynaud phenomenon and are the first choice for medical treatment after failure of nonmedical treatment. Nifedipine, diltiazem, felodipine, and amlodipine are all effective, although they tend to be more effective in patients with the primary form of the condition than in those with the secondary form. One meta-analysis found short-acting nifedipine, 10 to 20 mg three or four times a day, to be moderately effective at reducing symptoms in patients with Raynaud phenomenon and scleroderma.²⁵ A large clinical study found sustained-release nifedipine to be useful as well.²³

Another recent meta-analysis of trials involving patients with primary Raynaud phenomenon found that calcium channel blockers reduced the severity of attacks by 33% and the frequency of attacks was reduced by 2.8 to 5.0 times per week.²⁶

Other vasodilators have also been shown to be effective. In one study, losartan, an angiotensin receptor blocker, proved to be more effective than nifedipine in reducing the frequency and severity of episodes of both primary and secondary Raynaud phenomenon.²⁷ Topical nitrates provide a degree of benefit as well.²¹ Because serotonin may be partially involved in the pathogenesis of Raynaud phenomenon, a number of studies have focused on the use of serotonin reuptake inhibitors and serotonin receptor antagonists.²⁸ In a small open-label trial that included both patients with primary Raynaud phenomenon and patients with the secondary form of the condition, fluoxetine was more effective than nifedipine in reducing the severity and frequency of attacks over a 6-week period; the effect was most pronounced in female patients and in patients with primary Raynaud phenomenon.²⁹ In another study, ketanserin, a selective serotonin receptor antagonist that is no longer available in the United States, significantly reduced the number of attacks over a 3-month period.³⁰ Intravenous prostaglandins have also been used with success. In one report, iloprost, given as a 5-day infusion, was beneficial in severe cases of Raynaud phenomenon, mitigating symptoms and enhancing the healing of ischemic ulcers³¹; unfortunately, iloprost is also unavailable in the United States. Of the intravenous prostaglandins currently available in the United States, alprostadil (prostaglandin E₁ [PGE₁]) and epoprostenol (PGI₂) have achieved, at best, mixed results,^{32,33} whereas prazosin has been employed with some success against primary and secondary Raynaud phenomenon (although its effectiveness seems to be limited in patients with scleroderma).³⁴

There has been growing interest in the role that phosphodiesterase inhibitors play in the management of Raynaud phenomenon. The most studied to date has been sildenafil. In a study by Fries and colleagues of 20 randomly assigned patients with Raynaud phenomenon, 50 mg of twice-daily sildenafil or a placebo was given, with significant improvement in the attack rate, duration, and objective measures of nailfold capillary blood flow in the sildenafil group.³⁵ A confounding factor in their study, however, is the fact that patients were able to clearly distinguish sildenafil from the placebo based on the pill's physical characteristics. Zamiri and colleagues, however, found no difference in the number of attacks or nailfold capillary blood flow in their randomized, double-blind, placebo-controlled study of 20 patients in sildenafil and placebo groups.³⁶ The data on sildenafil in Raynaud phenomenon are far from conclusive, and further study to delineate its role is required prior to recommending its use in treatment.

Some authors have advocated low-dose aspirin therapy for Raynaud phenomenon, but, to date, trials of antiplatelet therapy have yielded disappointing results.³¹ In a placebo-controlled, randomized trial published in 2003, cilostazol increased blood vessel diameter in patients with primary and secondary Raynaud phenomenon but did not bring about any improvement in symptoms.³⁷ In smaller studies, some success

was achieved with tissue plasminogen activator and with low-molecular-weight heparin; however, these agents were found to carry significant bleeding risks and thus have not been widely accepted for treatment of Raynaud phenomenon.^{31,38}

For refractory, severe Raynaud phenomenon, surgical management, most often involving some form of sympathectomy, is recommended. Both central and distal sympathectomy have been employed for this purpose; initial success rates are good, but there is a high incidence of recurrent symptoms.

For many years, open cervicothoracic sympathectomy was commonly performed for symptomatic treatment of Raynaud phenomenon (which was thought to result from an overactive sympathetic response), but the results were mixed.^{39,40} The open form of the procedure was associated with substantial morbidity and frequent recurrence of symptoms, and, as a result, it has now been largely abandoned. Some surgeons have advocated performing thoroscopic sympathectomy to treat severe Raynaud phenomenon that is refractory to medical management, but the benefits and durability of this approach have not been established. In this procedure, the ipsilateral pleural space is approached thoroscopically, with the patient under general anesthesia. The sympathetic chain is identified as it courses down the ribs near the costovertebral junction, and the second through fourth thoracic sympathetic ganglia lying between the ribs are cauterized. Bilateral sympathectomy may be performed in a sequential fashion during the same operation. Approximately 90% of

patients experience immediate relief of symptoms after thoroscopic sympathectomy, but the majority also experience recurrence of symptoms.^{41,42} Proponents of this procedure argue that these recurrent symptoms are not as severe as the original preoperative symptoms and that patients who undergo the operation for the treatment of ulceration exhibit continued long-term healing. Nonetheless, in our view, it is advisable to reserve thoroscopic sympathectomy for selected cases of Raynaud phenomenon that are refractory to medical management.

At present, localized digital sympathectomy using microsurgical techniques is generally preferred to proximal sympathectomy for treatment of nonhealing ulcerations in patients with severe, refractory Raynaud phenomenon.⁴³ This procedure involves stripping the adventitia, along with digital sympathetic fibers, from the involved digital arteries, with the patient under either regional or general anesthesia. In one small study of seven patients, it was suggested that this digital sympathectomy could be extended to include the palmar arch, the radial and ulnar arteries proximal to the wrist, and the nerve of Henle, which is responsible for the sympathetic innervation of the distal ulnar artery.⁴⁴ The investigators found that by 1.5 years after adventitial stripping of the proximal radial and ulnar arteries with resection of the nerve of Henle, all ischemic ulcerations had resolved.

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25 SCLEROTHERAPY

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Sclerotherapy involves the injection of a caustic solution (a sclerosant) into an abnormal vein so as to cause localized destruction of the venous intima and obliteration of the vessel. It is not a new technique, having been practiced since the early 20th century, but it has evolved significantly over the past 50 years.¹ Improvements in the technology used (e.g., hypodermic syringes, fine needles, sclerosants, compression technique, and duplex ultrasonography) have greatly enhanced the results achievable with sclerotherapy. To ensure optimal results, it is essential to have a thorough knowledge not only of the technique but also of the indications, expected outcomes, and possible complications associated with the procedure.

Sclerotherapy is primarily used to treat small varicose veins, reticular veins, and spider veins. The prevalence of varicose and spider veins is well documented: they affect millions of people in the United States alone.¹ The incidence is two to three times higher in women than in men and increases with age. The precise etiology of varicose veins and spider veins is unknown. Heredity, pregnancy, female sex, obesity, an occupation that requires long periods of standing, and a low-fiber diet have been implicated as causative factors. The choice of treatment method for varicose veins and spider veins must be individualized for each patient. Although sclerotherapy is only one of a number of techniques available for treatment, it is an important therapeutic tool and a key component of a vascular surgeon's armamentarium.

Preoperative Evaluation

Proper evaluation of the patient before sclerotherapy is the most important step in achieving successful results. Such an evaluation should include a thorough clinical arterial and venous examination. Close attention should be paid to the size, location, and distribution of vessels; these variables are critical for determining the appropriate treatment. Sclerotherapy failures are often attributable to improper patient selection. Any patient who is believed to have axial reflux or whose clinical complaints far exceed the findings from physical examination should undergo venous duplex ultrasonography.

Venous duplex ultrasonography has revolutionized the treatment of varicose and spider veins. It is reproducible and noninvasive and can objectively identify areas of reflux in the great and small saphenous systems, as well as detect pathologic conditions in the deep venous system and incompetent perforating vessels.

Patients with axial reflux or reflux from the great or small saphenous junction documented by venous duplex ultrasonography are best managed by means of surgical correction of the reflux rather than primary treatment with sclerotherapy. In a 1993 randomized study, ligation and stripping were compared with compression sclerotherapy in 164 patients who had symptomatic primary varicose veins.² After 5 years, 74% of the patients treated with sclerotherapy were considered to have had treatment failures, compared with only 10% of the patients treated surgically. In a 1991 trial, real-time color duplex ultrasonography was used to evaluate 89 limbs in 55 patients who had previously undergone sclerotherapy of the great saphenous vein.³ Obliteration of the great saphenous vein was noted in only 20% of the injected limbs and in only 6% of the limbs below a refluxing junction. These poor results from sclerotherapy were confirmed in a subsequent study.⁴ The superiority of surgical treatment was also demonstrated in a randomized 10-year study comparing surgery with sclerotherapy alone.⁵

Ultrasound-guided sclerotherapy has also been advocated. The advantages of this approach are that it allows much higher concentrations of the sclerosant solution and permits direct visualization of the injections. Reported recurrence rates, although better than with liquid sclerotherapy, are still quite high: 22.8% at 1 year and 27.2% at 2 years.^{6,7} A number of authors have advocated ultrasound-guided foam sclerotherapy for patients with axial reflux.^{8,9} Myers and colleagues reported just over 50% primary success rate with ultrasound-guided foam sclerotherapy of the saphenous vein at 3 years.¹⁰ The unknown longevity of the results achieved with this technique is still in question, and further studies (including randomized trials) are needed for validation. In addition, the number of early failures compared with surgery and ablation make it difficult to recommend this as the treatment of choice. A 2008 article by Gonzalez-Zeh and colleagues comparing endovenous laser ablation to echocardiography-guide foam sclerotherapy showed at 1 year a 93.4% occlusion of the great saphenous vein versus 77.4% with foam.¹¹

Given the available data, my preferred approach is to treat the axial reflux in the great and/or small saphenous veins as indicated by duplex ultrasonography before sclerotherapy. The choice of endovenous ablation versus open surgery depends on the size of the vessels and the presence of large tortuous branches of the saphenofemoral junction. Large tertiary varicosities are best treated with hook phlebectomy at the time of the primary ablative procedure. Patients who do not have axial reflux and whose vessels are less than 6 mm in diameter can

be treated successfully with sclerotherapy alone. Varicose veins more than 6 mm in diameter without axial reflux are best treated surgically by means of phlebectomy by ambulatory hook phlebectomy. The cosmetic results are far better and the recovery time is much shorter with the surgical option.

Operative Planning

PATIENT PREPARATION

Before undergoing sclerotherapy, the patient should receive a thorough explanation of the procedure, including the possible risks and complications [see Table 1]. He or she should be informed about the expected outcomes and the length of time needed for healing. In particular, it should be emphasized that multiple treatments are usually necessary to eliminate varicosities. Most patients can expect to undergo four or five treatments in a 6-month period. Time and patience are essential for achieving an optimal outcome.

Because sclerotherapy without axial reflux is primarily cosmetic and therefore rarely reimbursable, it is important to have a clear understanding regarding costs. A good-faith estimate of the cost per procedure should be provided to the patient before treatment is initiated. It is advisable to have the patient sign a copy of this estimate so that there is no subsequent misunderstanding about the costs to be incurred during the course of therapy.

To reduce bruising, aspirin and antiplatelet agents should be avoided for 10 days before treatment. On the day of the procedure, the patient should be asked to refrain from applying lotion to the legs so that the tape applied after treatment will adhere better to the skin [see Table 2]. The patient should

sign and date an informed consent form. Once informed consent is obtained, photographs of the areas to be treated should be taken. The digital photography should be standardized as much as possible with respect to lighting and background. The problem areas are photographed again after treatment, and additional pictures are obtained during subsequent treatments to document progress. The aim is to give patients a reliable means of objectively comparing the legs' appearance before and after sclerotherapy [see Figure 1, Figure 2, and Figure 3]. Such photographs often reassure patients that significant cosmetic improvement has been achieved and encourage them to continue treatments.

MATERIALS

Sclerosants cause thrombosis and subsequent fibrosis when injected into a blood vessel. An ideal sclerosant would exert this effect reliably while also being inexpensive, widely available, approved by the Food and Drug Administration (FDA), and nontoxic. In addition, it would be painless on injection and would not cause hyperpigmentation or ulceration with extravasation. Unfortunately, this ideal sclerosant does not exist. All of the solutions currently available have disadvantages.

Sclerosants may be classified into two main categories: osmotic agents and detergents. Hypertonic saline (HS) and chromated glycerin (CG) are the most widely used osmotic agents. HS, approved by the FDA as an abortifacient, is commonly employed to treat superficial telangiectasias. HS in a 23.4% concentration damages the endothelial cells of the vessel walls through hyperosmolarity-induced dehydration. Such damage leads to thrombosis and fibrin deposition.

Table 1 Complications of Sclerotherapy

Complication	Comment
Common	
Itching	Usually mild; lasts for 1–2 days
Hyperpigmentation	Occurs in about 20–30% of patients treated; usually fades in a couple of weeks but may take several months to a year to resolve totally; lasts longer than 1 yr in 1% of cases
Telangiectatic matting	Occurs in approximately 10% of patients treated; usually resolves in 3–12 mo if left untreated but in rare cases can be permanent
Pain	Lasts 1 to, at most, 7 days
Bruising	May be minimized by avoiding aspirin and ibuprofen for 10 days before and after each treatment session
Minor allergic reaction	Typically resolves within about 1 hr
Rare	
Ulceration at injection site	Can take 4 to 6 wk to heal completely; small scar may result
Anaphylaxis	Incidence is extremely low
PE or DVT	Incidence is extremely low

DVT = deep vein thrombosis; PE = pulmonary embolism.

Table 2 Sample Instructions to Patients after Sclerotherapy

NEXT APPOINTMENT _____ TIME _____

Be sure to keep your follow-up appointment so the physician can monitor your progress.

Please be considerate and give our office at least 72 hours' notice if you are unable to keep an appointment. This will allow us time to call patients who are on the waiting list for an appointment.

Please walk for a few minutes before driving home.

Wear your support hose for 48 continuous hours.

After 48 hours, remove the hose, cotton balls, and tape before getting your legs wet.

After 48 hours, wear your support hose for a minimum of 7 days during the waking hours. Note: you may continue to wear them longer if you prefer.

Do not run, do high-impact aerobics, lift weights with your legs, or do sit-ups for 2 weeks. These activities can increase the venous pressure in your legs.

For 2 weeks, do not take hot baths or showers or sit in a hot tub. The heat can cause vein dilatation. You may take a warm shower or bath after 48 hours.

Avoid aspirin and ibuprofen products for 10 days before and after each treatment. These products may increase the amount of bruising that may develop from the treatment. Acetaminophen is permitted.

For further information regarding sclerotherapy, please refer to the handout "Sclerotherapy Informed Consent and Before and After Treatment Instructions."

Preparation for Your Next Treatment

Bring your support hose.

Do not apply creams, lotions, or powders to your legs the evening before or the morning of your treatment.

Bring a pair of loose shorts to wear during your treatment.

Avoid aspirin and ibuprofen products for 10 days before and after each treatment. These products may increase the amount of bruising that may develop from the treatment. Acetaminophen is permitted.

CG, also an osmotic dehydrating agent, is not approved by the FDA and achieves sclerosis by a similar mechanism. Sodium tetradecyl sulfate (STS) and polidocanol (POL) are the most widely used detergent agents in the United States. These agents form aggregates on endothelial cell surfaces and cause endofibrosis by disrupting the integrity of the cells.

In the United States, HS has been used to treat spider and varicose veins for more than 50 years. Because it is a naturally occurring bodily substance, it does not cause allergic reactions; however, it causes patients much more pain and discomfort than either STS or POL.¹² Adding lidocaine to HS reduces the pain associated with the injections without significantly decreasing the effectiveness of treatment or increasing the incidence of complications.¹³ Even with the addition of lidocaine, injection of HS is associated with some degree of patient discomfort. Moreover, HS is more viscous than the detergent agents and thus more difficult to administer. Extravasation of HS is also associated with a higher risk of skin necrosis. CG is used primarily in Europe. It also causes localized pain at the injection sites. Kern and colleagues demonstrated in a randomized study of 150 patients comparing

CG with POL that the patients treated with CG had better clearing of the vessels.¹⁴

Of the detergent sclerosants, both STS and POL are widely used in the United States, but only STS is FDA approved. FDA approval of POL has been pending for years, and it is unclear why it has not yet been granted. POL appears to be a very good sclerosant, comparable to STS: it is safe, relatively painless, and highly effective in all vein types.^{15,16} In a 2002 randomized study comparing STS with POL, both agents were found to be safe and effective, yielding a 70% clinical improvement, and there were no significant differences in adverse effects, aside from a small decrease in ulcerations with POL.¹⁷ Nevertheless, until POL is approved by the FDA, we recommend that it not be used. Two other FDA-approved detergent sclerosants are available: sodium morrhuate (SM) and ethanolamine oleate (EO). However, both SM and EO are associated with an unacceptably high risk of complications, including but not limited to ulceration and anaphylactic reactions, and hence are rarely used. For these reasons, my practice is to use STS for sclerotherapy, and the ensuing technical discussion focuses solely on this agent.



Figure 1 A 63-year-old woman (a) before and (b) after two treatments with 0.2% sodium tetradecyl sulfate.

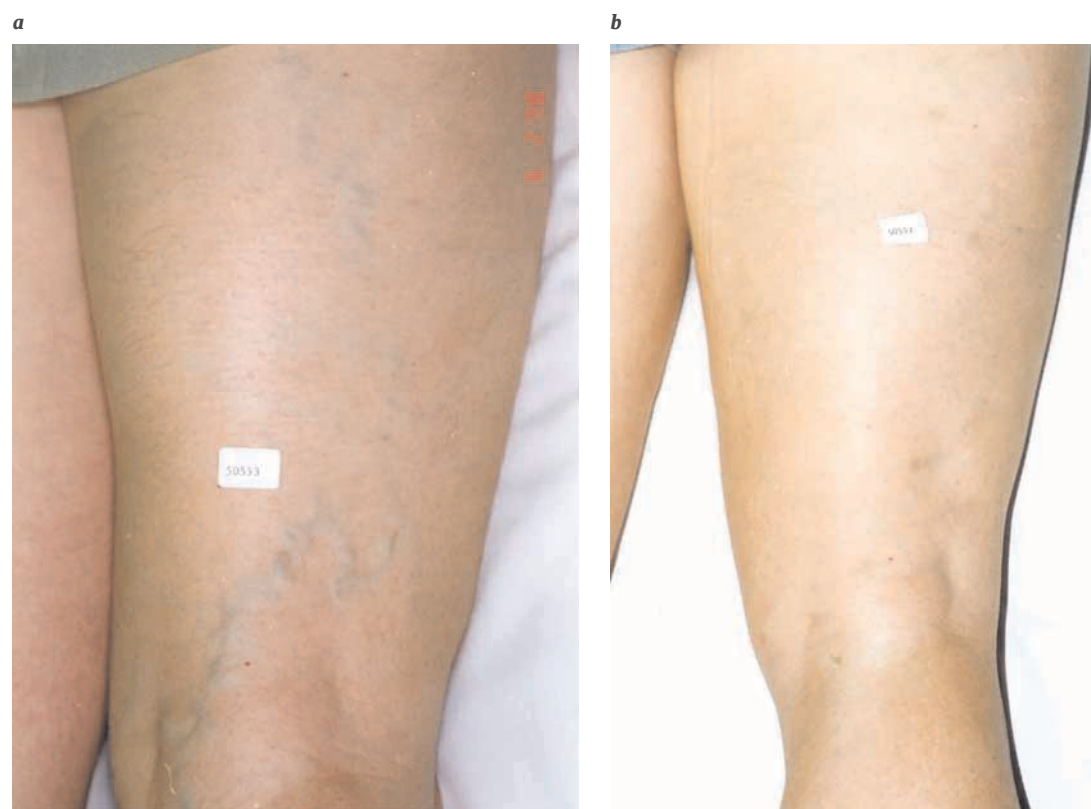


Figure 2 A 52-year-old woman (a) before and (b) after two treatments with 0.5% sodium tetradecyl sulfate.

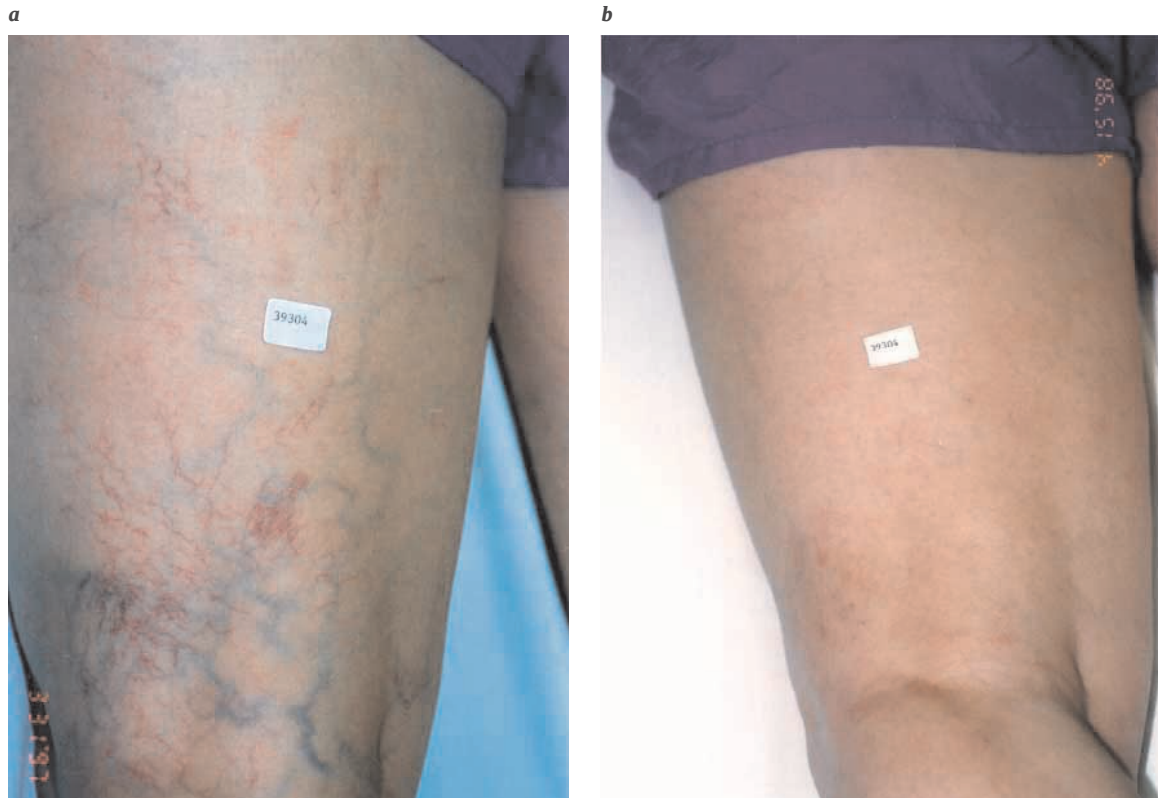


Figure 3 A 36-year-old woman (a) before and (b) after four treatments with a combination of 0.5% and 0.2% sodium tetradecyl sulfate. Mild hyperpigmentation may be seen on the lateral thigh.

Sclerotherapy is an outpatient procedure performed in the physician's office. Aside from the sclerosant, few special materials are needed [see Table 3]. Because there is a risk of significant allergic reactions (albeit an extremely small risk), a fully stocked resuscitation cart including intubation equipment should be available and checked regularly to confirm that all equipment is up to date and ready for immediate use.

Technique

A variety of sclerotherapy techniques have been developed. Typically, each individual practitioner develops his or her own variation of the procedure.

STEP 1: POSITIONING AND SKIN PREPARATION

Sclerotherapy is best performed with the patient supine. On rare occasions, it may be necessary to puncture a vein with the patient standing. However, the sclerosant is not

injected until the patient has been returned to the supine position, thus allowing the vein to empty.

The skin is wiped with alcohol swabs to increase the visibility of the vessels. The sclerosant is then placed in plastic 3 mL syringes. These syringes fit more easily in the hand than tuberculin syringes and are less cumbersome to use. In addition, because injection pressure is inversely proportional to the squared radius of the plunger, a 3 mL syringe generates less pressure than a 1 mL syringe does. The endothelial cells in these small vessels are quite fragile, and using a syringe that generates less pressure substantially reduces the risk of vessel disruption.

STEP 2: CHOICE OF SCLEROSANT CONCENTRATION

The solution concentration selected depends on the size of the vessel. I use 0.2% STS for vessels less than 2 mm in diameter and 0.5% for larger vessels. The volume per injection site is generally less than 0.5 mL, but larger volumes may be preferable for reticular or small varicose veins.

At present, there is enthusiasm in the literature for the use of foam sclerotherapy, a technique in which air is repetitively injected into STS to create a foam.¹⁸ This technique is ultimately based on the work of Orbach, who in 1944 advocated expelling blood from the vein by injecting small boluses of air before injecting the sclerosant.¹⁹ The rationale for foam sclerotherapy is that the foam displaces blood in the vessel, resulting in less dilution of the solution. The sclerosant then has more contact with the surface area of the venous endothelium and thus can sclerose the endothelial cells more efficiently at lower concentrations. Of the various methods of

Table 3 Materials Needed for Sclerotherapy

Alcohol swabs	Cotton balls and tape
Protective gloves	18-gauge needles
3 mL syringes	4 × 4 in. gauze pads
30-gauge needles	Adhesive bandages

creating a foam sclerosant solution,²⁰ the method described by Tessari and colleagues appears to be the easiest.²¹ In this approach, air is injected into the solution via a three-way stopcock and two syringes. Foam sclerotherapy may be used safely in the treatment of varicose, reticular, and spider veins, with excellent results.²²

STEP 3: INJECTION OF SCLEROSANT

I use 30-gauge needles for all sclerotherapy treatments; some physicians prefer 27-gauge needles for larger reticular and small varicose veins. The needle is bent at a 45° angle, with the bevel up. Countertraction is applied with the nondominant hand, and the needle is inserted parallel to the vessel and the skin surface [see Figure 4]. As the vessel is entered, the sclerosant is gently injected. The slight reduction of pressure that occurs when the vessel is entered becomes increasingly easy to appreciate as the physician accumulates experience with sclerotherapy. Blanching of the vein is another signal of entry into the vessel. If the solution is injected outside the vein, a small superficial wheal will appear, in which case, the injection should be discontinued and a new site selected for injection. Such wheals are unlikely to be a problem with STS concentrations lower than 0.25%. When more concentrated solutions are used in larger veins, aspiration of blood ensures correct placement of the needle within the vein before injection.

STEP 4: COVERAGE AND COMPRESSION OF INJECTION AREAS

After injection, cotton balls or foam or gauze pads are secured with tape and applied to the injection areas. Compression hose (20 to 30 or 30 to 40 mm Hg) are then applied. Studies have shown that using some type of bandage or pad in addition to support hose is beneficial. The degree of compression achieved with this approach can be as much as 50% greater than that achieved with support hose alone.²³ Gauze pads or cotton balls are more cost-effective than foam pads while providing comparable compressive effects.²⁴

Compression approximates the endothelial surfaces of the vein walls after sclerotherapy, thereby reducing thrombus

formation and promoting sclerosis of the vessel. It also enhances the calf muscle pump function to help clear any solution that has progressed into the deep venous system. Reduction of thrombus formation after sclerotherapy is important for minimizing hyperpigmentation. In a multicenter randomized trial that evaluated patients who underwent bilateral sclerotherapy but who received compression to only one leg, hyperpigmentation and edema were significantly greater in the uncompressed leg.²⁵ In addition, in a recent article, Kern and colleagues found that wearing compression hose enhanced the efficacy of sclerotherapy in treating patients with telangiectasias and reticular veins.²⁶

Varying recommendations have been made as to how long compression hose should be worn after sclerotherapy. A controlled comparative trial of the effects of compression in patients with reticular and telangiectatic veins found that patients who wore hose for 3 weeks exhibited greater improvement (e.g., less hyperpigmentation) than those who did not wear hose.²⁷ However, the improvement in patients wearing hose for 3 weeks was not appreciably greater than that in patients wearing hose for 1 week. I find that it is difficult to get patients to wear compression hose for several weeks. Therefore, I have adopted the standard practice of instructing the patient first to wear the hose for 48 hours without removing them and then to wear them during waking hours only for the next 7 days.

Once the compression hose are in place, the patient is asked to walk for 15 minutes before leaving the office. This further assists in clearing any solution that may have progressed into the deep venous system.

STEP 5: SCHEDULING OF RETREATMENT

As noted (see above), multiple treatments are usually required for optimal outcome. Therefore, all patients are instructed to return in 4 to 6 weeks for assessment and possible repeat treatment. Intraluminal thrombus excision may be performed at this time. This reduces the discoloration associated with sclerotherapy. After this interval, vessels requiring further treatment are apparent, and additional injections can be performed. The average patient undergoes four to six treatments.

Complications

Although sclerotherapy is generally quite safe, complications do occur. Physicians must therefore be cognizant of the potential risks and prepared to treat any adverse events that arise. The most significant complications of sclerotherapy are allergic reactions (either minor or major), skin necrosis, hyperpigmentation, deep venous thrombosis (DVT), and telangiectatic matting. Cramping, pain, edema, and blistering from tape or compression may be observed as well. With the increased use of foam sclerotherapy for axial reflux, there have been reports of visual scotoma associated with air in the injections. These usually resolve very quickly and cause no long-term harm. There has been, however, a recent report of an air embolism causing a severe stroke secondary to a patent foramen ovale.²⁸

Minor allergic reactions are quite common. For example, localized urticaria and edema may occur secondary to histamine release. In the vast majority of cases, such reactions are



Figure 4 The standard hand position for sclerotherapy. Countertraction is applied with the nondominant hand.

self-limited, typically resolving in less than 1 hour. Itching often accompanies this response but usually resolves by the time the patient leaves the office. Should reactions persist, oral antihistamines or, on rare occasions, steroids may be required.

With the sclerosants used today, anaphylactic reactions are extraordinarily rare but can be life-threatening. The incidence of anaphylaxis with STS is not known with precision but is certainly very low. The reaction is usually mediated by immunoglobulin E and occurs within minutes of exposure. Appropriate emergency measures must be undertaken immediately, including subcutaneous administration of epinephrine, delivery of supplemental oxygen, and securing of the airway. The patient should then be given antihistamines and transferred to an emergency department for continued evaluation and treatment. As noted (see above), a properly stocked emergency response cart, including endotracheal intubation supplies and medications, is essential in any office where sclerotherapy is performed. Periodic review of procedures with staff and maintenance of the emergency medications and supplies is imperative.

Skin necrosis occurs with 0.2 to 1.2% of sclerotherapy injections.²⁹ It is a complication that produces scarring and is often unpreventable. Depending on the extent of necrosis, healing may take months. The main causes of necrosis are extravasation of the sclerosant into subcutaneous tissue, inadvertent injection into an arteriole, and vasospasm. Extravasation of the sclerosant can destroy tissue, with the degree of damage determined by the type, concentration, and amount of sclerosant used [see Figure 5]. Necrosis is rare when small amounts of dilute (< 0.25%) STS are given, but extensive skin and soft tissue necrosis has been observed when higher concentrations of STS (3%) are administered to treat varicose veins.³⁰ Inadvertent injections into the arteriole feeding the telangiectasia are impossible to prevent and probably occur frequently. In a 2001 study, pulsatile Doppler sounds could be detected above spider vein complexes in 72% of cases.²⁹ Backwash of the solution through arteriovenous shunts may cause occlusion of the arteriole and skin necrosis. Blanching of the skin often occurs with intra-arteriolar injections. Skin massage or, if spasm persists, application of nitroglycerin ointment to the skin may increase microcirculation. Why ulcerations develop in some patients but not others is unknown. The question of whether it is related to injection pressure or injectate volume also remains unanswered.

Hyperpigmentation [see Figure 6] is quite common, occurring in a significant percentage of patients, and may be caused by any of the sclerosants in current use. It is more common in persons with dark complexions and in those with dark-purple vessels. Fortunately, hyperpigmentation usually resolves with time, but the process can take months to years. Postsclerotherapy compression lowers the incidence of hyperpigmentation, and microthrombectomy of any intraluminal thrombi remaining after sclerotherapy reduces the degree of hyperpigmentation present. In a multicenter study, Scultetus and colleagues demonstrated that microthrombectomy reduces postsclerotherapy pigmentation in veins less than 1 mm in size.³¹ The latter is accomplished by puncturing the skin with an 18-gauge needle and manually expressing the thrombus. Postsclerotherapy follow-up is essential to help reduce



Figure 5 Skin necrosis on the left posterior calf of a 48-year-old woman after ultrasound-guided sclerotherapy.

hyperpigmentation. There is no firm consensus on how hyperpigmentation should be treated once it develops. Some authorities recommend the use of fade creams, whereas others advocate laser treatments to lighten the pigmentation. A 2001 study found that 80% depigmentation could be achieved with weekly subcutaneous injections of the chelating agent deferoxamine mesylate.³² That various different treatments continue to be recommended suggests that none of them are clearly superior at eliminating hyperpigmentation. The passage of time appears to be the most reliable therapy.

The precise incidence of DVT after sclerotherapy is unknown but appears to be extremely low overall. The risk is somewhat higher when more concentrated solutions are used or larger volumes administered; however, it may be minimized by performing sclerotherapy only for established indications. Treating axial reflux and larger vessels surgically, with sclerotherapy limited to an adjunctive role, will reduce the volume and concentration of solution needed. Ambulation in the physician's office after treatment will help wash away any solution that has progressed into the deep venous system.

The development of tiny new red vessels at an area of previous injection is called telangiectatic matting [see Figure 7]. Like ulceration, it is unpredictable. Excessive pressure during injections is thought to play a causative role, but the exact etiology is unknown. Telangiectatic matting is very difficult

a



b



Figure 6 A 56-year-old woman (a) before treatment and (b) with residual hyperpigmentation after treatment with 0.2% sodium tetradecyl sulfate.



Figure 7 Telangiectatic matting in a 43-year-old woman after treatment with 0.2% sodium tetradecyl sulfate.

to treat once it has developed. Occasionally, it resolves spontaneously, but more often, it must be addressed by means of either repeat sclerotherapy with treatment of the feeding reticular vein or laser therapy. Treatment of telangiectatic matting may, in fact, be the one potential efficacious use for laser-type devices in treating diseased leg veins.

Cost Considerations

I strongly believe that all sclerotherapy, with the exception of that performed for spontaneous hemorrhage, is cosmetic. Accordingly, in the practice to which I belong, patients seeking sclerotherapy for reasons other than hemorrhage are informed well in advance that the procedure is cosmetic and not reimbursable, and they receive a good-faith estimate of expected costs in writing. As noted (see above), venous ablation, either open or catheter directed, is the treatment of choice for symptomatic axial reflux and large varicose veins; therefore, sclerotherapy for these conditions is considered medically unnecessary.

Obtaining reimbursement from insurance carriers for sclerotherapy performed to treat small varicose veins or hemorrhage is frustrating at best. Both physicians and patients have contributed to the problem in the past by filing inappropriate claims for reimbursement of cosmetic procedures. This past misuse of insurance coverage has made it difficult to obtain reimbursement even for the one solid medical indication for sclerotherapy, hemorrhage.

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26 MEDICAL MANAGEMENT OF VASCULAR DISEASE

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Vascular surgery has evolved dramatically with the explosion of noninvasive diagnostic tools and endovascular techniques for the treatment of vascular conditions. Surgeons are now actively involved in all of these technical aspects of care, although many of us still relegate the medical management of the vascular patient to our physician colleagues. Unfortunately, we are also rarely involved in preventive measures. As a result, although we may be able to bypass or open blocked arteries and replace aneurysms with minimally invasive surgery, our patients continue to die from the other cardiovascular consequences of these diseases. The assumption that the family physician, internist, or cardiologist will take care of these issues is not necessarily correct. A number of reports have shown that atherosclerotic risk factors in patients with peripheral arterial disease (PAD) are less intensively treated than in patients with coronary artery disease.^{1,2} In a review of 195 PAD patients discharged from a tertiary care hospital in Canada, Anand and colleagues reported that fewer than half were sent home with antiplatelet medication.² Only 20% were on beta blockers, and, surprisingly, only 16% were on cholesterol-lowering medications. Clearly, this represents a failure of our responsibility to the patient.

Many factors may explain why surgeons are unwilling to be involved in the nonoperative management of their patients. These include insufficient knowledge, lack of time outside the operating room or endovascular suite, or the surgeon's fear that he or she may alienate a referring medical colleague by becoming involved in that physician's management of the atherosclerotic process. Some of the above-mentioned impediments may be valid in a given surgeon's practice, but surgeons at least should know what appropriate care is for their patients' underlying disease, if only to ensure that it is being appropriately treated. This chapter outlines the medical management of atherosclerosis and its relationship to diabetes and the dysmetabolic syndrome. Medications and lifestyle changes that can improve circulation are also described, as well as therapies to counter the negative effects of platelet activation. Treatment options for hypertension and medications for specific aspects of PAD are also discussed.

Medical Management of Atherosclerosis

Fundamental to all treatment approaches for arterial pathology is an understanding of the role of lipids in atherosclerosis. It is now well known that there is more to cholesterol than good and bad varieties and that medical treatment must be

targeted at each abnormality differently. Further, although statins are clearly the dominant medications, not all statins are equal, and other drugs may prove valuable. The beneficial effects of these drugs may go well beyond changes in lipid content. Furthermore, there are patients with asymptomatic PAD who can potentially benefit from these medications even if they have "normal" lipid levels when first screened (especially those with insulin resistance, a family history of atherosclerosis and its complications, truncal obesity, and low high-density lipoprotein [HDL] or high triglycerides). The vascular surgeon, who wishes to be more than a technician and appropriately treat PAD beyond simply intervening for extremity ischemic complications, needs to be aware of such nuances, as well as other key considerations in managing the underlying atherosclerosis process. This includes the value of exercise, good nutrition, and smoking cessation.

There are four major risk factors for the development of atherosclerosis: diabetes, smoking, hypertension, and lipid abnormalities.³ The management of diabetes and hypertension and techniques for smoking prevention are beyond the scope of this chapter but are briefly outlined.

DIABETES

The development of claudication is five times more frequent in males and three times more frequent in females who suffer from diabetes.⁴ Typically, diabetes affects the more distal infrapopliteal arteries, and given that these vessels have the poorest results with revascularization, it is not surprising that diabetics have an increased risk of amputation. Although the degree of glycemic control has never been shown to reliably predict the severity of disease, good control is clearly an important goal of therapy and should be strongly encouraged, although too aggressive control, especially in the elderly, can lead to increased complications.⁵

SMOKING

Cigarette smoking is a major risk factor for the development of PAD. Further, the greater the smoking history, the more likely will be the development and severity of atherosclerotic involvement and subsequent morbidity and mortality. Accordingly, every effort should be made to encourage the patient to quit. Numerous over-the-counter remedies such as nicotine patches have been proposed, as well as some prescription medications, such as the antidepressant bupropion HCl (Wellbutrin, Brentford, Middlesex, England) and the smoking-specific agent varenicline (Chantix, Pfizer, Mission, Kansas).⁶

However, perhaps the single most important treatment that can be offered is simply encouragement by the physician. This should be an integral part of every interaction with the patient. The excess vascular mortality of smoking decreases within 20 years to the level of the never-smoker.⁷

HYPERTENSION

Although hypertension can increase the risk of PAD two- to threefold, it is not as important a risk factor as the others listed above. However, clearly, it will be important to control, if only to prevent the associated cardiac and cerebrovascular morbidity of PAD.^{8–10} In clinical trials, antihypertensive therapy has been associated with a 35 to 40% mean reduction in stroke incidence, a 20 to 25% reduction in myocardial infarction, and a more than 50% reduction in heart failure.¹¹ It is estimated that in patients with stage 1 hypertension and additional risk factors, lowering systolic blood pressure 12 mm Hg for 10 years will prevent one death for every 11 patients treated. If cardiovascular disease or PAD is present or target end-organ damage has occurred, only nine patients would require this treatment to prevent one death.¹²

In our practice treating patients with diagnosed PAD, we have found that only 32% of patients are normotensive during their office visits or vascular laboratory evaluations.^{13,14} This may be because patients are anxious and exhibit so-called “white coat” hypertension. To overcome this limitation in pressure measurements, it has been suggested that the blood pressure be taken at the end of the visit, when the patient has had time to relax. The pressure should also be taken in a standard manner with the patient seated comfortably and with the arm resting at heart level. The medical diagnostic workup in patients with hypertension is not germane to this chapter. However, the surgeon should be aware that sudden onset of hypertension or significant exacerbation may be an indication that the patient is suffering from a correctable cause such as renal artery stenosis. If suspected because of the presence of an abdominal bruit, an aneurysm, or aortic atherosclerosis, Doppler ultrasonography will usually be the first-line test. Magnetic resonance angiography or spiral computed tomographic angiography may also obviate the need for arteriography.

Initial blood pressure control will include lifestyle and dietary changes. These should include restriction of sodium, alcohol, and unsaturated fats, as well as increasing daily exercise and intake of fruits and vegetables.¹⁵ There are now a large number of medications to choose from if drug therapy is required, and these fall into the following main groups: diuretics, alpha and beta blockers, direct vasodilators, central agents, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers. Many are now generic, and different pharmaceutical companies manufacture many very similar drugs. This has led to a great deal of confusion, with multiple studies producing conflicting results. Accordingly, many physicians will follow the guidelines published by the Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure.¹⁶ Current recommendations suggest the use of diuretics as the first line of drug therapy. Initial therapy with two drugs should be considered when the blood pressure is 20/10 mm Hg above goal. In patients with diabetes or chronic renal failure, antihypertensive

medications should be considered if the blood pressure is greater than 130/80 mm Hg, although a benefit may not be seen in patients excreting more than 1 to 2 g of protein/day. In these patients, three drugs may often be necessary.¹⁶

In patients with PAD, there has been a historical concern that the use of beta-adrenergic blockers would potentially worsen the symptoms of claudication. However, several studies have shown that this class of drugs is safe in claudicants and is an acceptable choice for lowering blood pressure.¹⁷ However, large reductions of systolic pressure and leg perfusion by any class of antihypertensive agent may result in modest worsening of claudication symptoms.¹⁸ The role of beta blockers in the prevention of perioperative events is discussed later in this chapter.

The ACE inhibitor drugs have also shown benefit beyond blood pressure lowering in high-risk groups. Specifically, in the Heart Outcomes Prevention Evaluation (HOPE) study, results from the study of 4,046 patients with PAD formed a subgroup in which there was a 22% risk reduction in patients randomized to ramipril compared with placebo.¹⁹ This was independent of lowering of blood pressure. Further, it appears from the same HOPE study that these medications may slow or prevent the onset of diabetes.²⁰ Based on this finding, the Food and Drug Administration (FDA) has now approved ramipril for its cardioprotective benefits in patients at high risk, including those with PAD. Thus, in terms of a drug class, the ACE inhibitors would certainly be recommended in these patients. However, in general, the goals of treating hypertension in patients with PAD should be similar to those of patient populations with other cardiovascular diseases.

HYPERLIPIDEMIA

The term *hyperlipidemia* has the unfortunate connotation that atherosclerosis is a result only of elevated levels of lipid, especially low-density lipoprotein (LDL). However, it is abundantly clear that other abnormalities of plasma lipids, such as triglycerides, can also be deleterious to the arterial wall.^{21,22} Further, deficiencies of some of these substances, for example, HDLs, are equally important in the development of atherosclerosis. The simplistic view that LDL is the root cause of atherosclerosis has also undergone reevaluation as research has uncovered moieties of LDL and HDL that may have differing effects on arterial pathology. It is now apparent that there are different fractions of LDL based on particle size, with the smaller particles being more atherogenic. Similarly, some fractions of HDL may be more protective. In PAD, several lipid fractions are critically important in determining the presence and progression of peripheral atherosclerosis. Independent risk factors for PAD include elevations of total cholesterol, LDL cholesterol, triglycerides, and lipoprotein(a).²³ Protective against PAD are increases in HDL cholesterol and apolipoprotein(a-1).²³ For every 10 mg/dL increase in total cholesterol concentration, the risk of PAD increases approximately 10%.²⁴ Elevations in lipoprotein(a) are also an independent risk factor for PAD, particularly in men.^{25,26}

Hyperlipidemia also implies a simplistic etiology to the manifestations of atherosclerosis, that is, that lipids enter the arterial wall and by virtue of the lipid content result in stenosis. However, the actual pathologic process is significantly more complicated, with vascular inflammation playing a critical role. Within

several days of a high-cholesterol diet, monocytes adhere to the endothelium, particularly at intercellular junctions.²⁷ The aberrations of endothelial function represent an oxidative stress to the cells and occur within minutes to hours of exposure to the noxious stimuli. Oxidative stress perturbs the cell membrane and increases endothelial permeability. Monocytes then migrate into the subendothelium, where they begin to accumulate lipid and become foam cells. These activated monocytes (macrophages) release mitogens and chemoattractants that recruit additional macrophages and vascular smooth muscle cells into the lesion. In addition, they generate reactive oxygen species that increase oxidative stress within the vessel wall and that accelerate oxidation of LDL cholesterol trapped in the subintimal space. The oxidation of LDL particles in the subintimal space promotes more foam cell formation.^{27,28} This is because the oxidized LDL is taken up via the scavenger receptor. Unlike the receptor for native LDL, intracellular levels of cholesterol do not downregulate the scavenger receptor. Accordingly, oxidized LDL continues to be taken up by the macrophage via the scavenger receptor, with the result that the macrophage becomes swollen with lipid. As foam cells accumulate in the subendothelial space, they distort the overlying endothelium and eventually may even rupture through the endothelial surface.²⁸ In these areas of endothelial ulceration, platelets adhere to the vessel wall, releasing epidermal growth factor, platelet-derived growth factor, and other mitogens and cytokines that contribute to smooth muscle migration and proliferation. These factors induce smooth muscle cells in the vessel wall to proliferate and migrate into the area of the lesion. These vascular smooth muscle cells undergo a change in phenotype from a “contractile” cell to a “secretory” cell. These secretory vascular smooth muscle cells elaborate extracellular matrix (e.g., elastin), which transforms the lesion into a fibrous plaque. In addition to elaborating extracellular matrix, the smooth muscle cells may also become engorged with lipid to form more foam cells. The lesion grows with the recruitment of more cells, the elaboration of extracellular matrix, and the accumulation of lipid until it is transformed from a fibrous plaque to a complex plaque.

The complex plaque typically is characterized by a fibrous cap that overlies a necrotic core that is composed of cell debris and cholesterol and contains a high concentration of the thrombogenic tissue factor, secreted by macrophages. In later-stage lesions, calcification may occur. Ultimately, the fibrous cap can rupture, leading to distal embolization or the accumulation of platelets on the plaque and subsequent acute arterial occlusion.

As mentioned, inflammation has been associated with the development of atherosclerosis and the risk of cardiovascular events. In particular, C-reactive protein (CRP) is independently associated with PAD,²⁹ even in patients with normal lipid levels.^{30,31} In the Physician’s Health Study, an elevated CRP was a risk factor for the development of symptomatic PAD and for peripheral revascularization.³² In patients with established PAD, an elevated CRP is an independent predictor of future cardiovascular events.³³ The measurement of CRP may also guide lipid therapy in that statin drugs lower CRP levels and the reduction in CRP levels may contribute to the benefits of statin drugs.³⁴ The JUPITER study (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) suggested that patients who exhibited elevated

levels of CRP despite so-called “normal” cholesterol levels still benefited from statin use.³⁵ This is important because as many as half of all patients with PAD may present with “normal” lipid levels. However, CRP itself is probably a marker for atherosclerosis rather than a cause. This is evidenced by a study on polymorphisms in the CRP gene, which are associated with marked increases in CRP levels and thus with a theoretically predicted increase in the risk of ischemic vascular disease.³⁶ However, these polymorphisms were not in themselves associated with an increased risk of ischemic vascular disease.

Treatment of Hyperlipidemia

Based on the knowledge that the effect of lipids on atherosclerosis is more complex than simply a detrimental effect of hypercholesterolemia, treatment programs are now directed at multiple pathways within the development of plaque. However, the dominant treatment remains reducing cholesterol. This is based on a number of large studies conducted on patients with underlying cardiovascular disease or those at risk for developing these conditions. Some of these included patients with so-called “normal” levels of cholesterol. The major studies include the Helsinki Heart Study,³⁷ the Scandinavian Simvastatin Survival Study (the “4S”),³⁸ The Cholesterol and Recurring Events (CARE) Trial,³⁹ the Program on the Surgical Control of Hyperlipidemias (POSCH),⁴⁰ the Heart Protection Study (HPS),⁴¹ and, more recently, the JUPITER study.³⁵

Diet and exercise There are several methods to alter cholesterol levels, some directed at overall levels, with others more targeted at reducing LDL or triglycerides or elevating HDL. Diet modification has always been a first-line method.⁴² Reducing cholesterol and saturated fat intake and weight loss can modestly reduce LDL and can lead to a significant reduction in triglyceride levels. Dietary fiber can assist in these beneficial results. Exercise can also result in a mild reduction in LDL and an increase in HDL.

Lipid-lowering agents Although lifestyle modification by exercise and diet has been shown to be beneficial in altering lipid metabolism, medications are often mandatory additions for the PAD patient. Unfortunately, it is also important to realize that despite the beneficial effects of a lipid-altering diet and medications, many patients are noncompliant, with discontinuance rates as high as 46% being reported.⁴³

There are now numerous alternative methods for altering lipid levels. Many of these are nonprescription “remedies,” which are, nonetheless, widely used. This chapter deals only with the dominant pharmaceutical agents, the so-called lipid-lowering drugs: statins, fibrates, niacin, ezetimibe, and bile-acid sequestrants.

Statins The statins are the most commonly used medications in the treatment of hypercholesterolemia.⁴⁴ They are also the most powerful drugs for lowering LDL cholesterol, with reductions in the range of 20 to 60%.^{45,46} Currently available statins include rosuvastatin (Crestor, Astra Zeneca, Wilmington, Delaware), atorvastatin (Lipitor, Pfizer, New York, New York), fluvastatin (Lescol, Novartis Pharmaceuticals Corp., East Hanover, New Jersey), lovastatin (Mevacor, Merck, Whitehouse Station, New Jersey), pravastatin (Pravachol, Bristol-Myers Squibb, New York, New York), and simvastatin (Zocor, Merck, Whitehouse Station, New Jersey). Fluvastatin

is somewhat less potent, decreasing LDL levels by 20 to 25% at the maximum recommended dose, whereas rosuvastatin is the most potent, reducing LDL levels by up to 52% and increasing HDL up to 14%. Statins are most effective when taken at night because this is the time when cholesterol production is maximal.

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting step in cholesterol biosynthesis.⁴⁷ A reduction in intrahepatic cholesterol leads to an increase in LDL receptor turnover that results from an enhanced rate of hepatic LDL receptor cycling.⁴⁸ An additional benefit is a reduction in the concentration of small, dense LDL, shifting the LDL subfractions to more buoyant, less atherogenic LDL.⁴⁹ Interestingly, it is not the baseline LDL level that is the most important factor in predicting the beneficial outcome of statin use. Rather, it is the percentage reduction that seems to be critical. Most of the statins have modest HDL-raising properties (about 5%). Triglyceride concentrations fall by an average of 20% because of a decrease in very low density lipoprotein (VLDL) synthesis and to clearance of VLDL remnant particles by apolipoprotein B/E (LDL) receptors.

Although rosuvastatin would seem to be more efficacious and therefore the statin of choice, subtle differences between the statins and price considerations will impact the decision as to which statin should be used. Claims have been made that water-soluble statins such as rosuvastatin, pravastatin, and fluvastatin are less likely to cause side effects and are, as a result, better tolerated by the patient. They may also have beneficial effects on plaque stability and plasminogen activator inhibitor-1 (PAI-1) that are not seen with the lipid-soluble statins, such as atorvastatin. Also, the metabolism of pravastatin is dual (liver and kidney) and compensatory for the degree of renal insufficiency.⁵⁰ This property differs from the other agents in this class; as a result, pravastatin may be safer in patients with renal failure. However, rosuvastatin, atorvastatin, and fluvastatin do not require dose adjustment in renal failure and so may be suitable alternatives.

Side effects Adverse reactions occur less frequently with statins than with the other classes of lipid-lowering agents.

Hepatic dysfunction Although hepatic dysfunction can rarely occur, clinical consequences are exceedingly rare (0.5 to 3% occurrence of persistent elevations in aminotransferases). This primarily occurs during the first 3 months of therapy and is dose dependent. However, two randomized trials have reported no significant difference in the incidence of persistently elevated aminotransferases between statin and placebo therapy.^{38,51} The FDA labeling information includes liver function testing before and at 12 weeks following the initiation of statins, at any elevation of dose, and periodically thereafter.⁵²

Muscle injury Development of muscle toxicity remains an important concern with the use of the statins.⁵³ Myopathic syndromes associated with statins span a spectrum of complaints ranging from myalgias (2%), to myositis (0.5%), to overt rhabdomyolysis, which may be associated with acute renal failure (< 0.1%).⁵⁴ Enhanced susceptibility to statin-associated myopathy occurs in patients with chronic renal failure, obstructive liver diseases, and untreated hypothyroidism and in patients receiving concurrent therapy with a

number of drugs, particularly fibrates and those that inhibit cytochrome CYP3A4. These include cyclosporine, gemfibrozil, nicotinic acid, macrolide antibiotics (e.g., erythromycin), antifungals such as ketoconazole (Nizoral, McNeil-PPC, Fort Washington, Pennsylvania), and HIV protease inhibitors. Unlike other statins, rosuvastatin, pravastatin, and fluvastatin are not extensively metabolized by the CYP3A4 system; as a result, they have few interactions with other drugs. Despite the increased risk of myopathy associated with statin therapy, routine monitoring of serum creatine kinase (CK) levels is not recommended.⁵² Patients and clinicians should, however, remain alert for the symptoms of myopathy. In a small number of patients, coenzyme Q₁₀ may improve symptoms, but in a systematic review of the literature, there was no level I support for this treatment.⁵⁵

Although several animal studies have suggested that statin therapy is associated with an increased risk of cancer,⁵⁶ a meta-analysis of five randomized clinical trials involving 30,817 patients found no association between statin use over a 4- to 6-year period and the risk of fatal or nonfatal cancer.⁵⁷ Unusual and as yet unsubstantiated side effects include alopecia and memory disorders.

Although statins are used primarily for the treatment of hypercholesterolemia, there is growing evidence that they increase bone formation, volume, and density and reduce the risk of osteoporotic fractures, particularly in older patients.⁵⁸ There is also some evidence that statins may lower blood pressure,⁵⁹ prevent Alzheimer disease,⁶⁰ and decrease the risk of certain cancers.

Laboratory monitoring of statin therapy Once initiated, a follow-up lipid profile should be performed at 12 weeks and dose adjusted according to the desired reduction. If this cannot be achieved with the original statin, a more powerful dose or drug should be used. In general, although side effects are rare, they do appear to be dose dependent. If necessary, addition of a nonstatin lipid-lowering drug can be considered. At present, the alternative drug of choice would appear to be ezetimibe. Other agents, such as the fibrates and resins, can also be considered.

At the original follow-up, laboratory evaluation of hepatic transaminases can also be evaluated. Subsequent evaluation of hepatic function is unnecessary except if drug interactions are suspected or if transaminases are elevated by more than three times normal. Monitoring should also be considered for patients with preexisting liver disease. There is no benefit to evaluating CK levels unless the patient is symptomatic.^{61,62} Further, patients may have symptomatic myalgia but have normal CK levels. If a CK level greater than 10 times normal is encountered, the statin should be discontinued even if the patient is asymptomatic. However, it is also important to realize that CK can be elevated by other conditions, such as hypothyroidism and recent heavy exercise.

Fibrates Fibrates are effective for the treatment of hypertriglyceridemia and combined hyperlipidemia. Four fibrates are currently available in the United States: gemfibrozil, fenofibrate, clofibrate, and fenofibric acid. Clofibrate, however, is now rarely prescribed because it has been associated with cholangiocarcinoma and other gastrointestinal cancers.⁶³ Other fibrates that are available worldwide include bezafibrate and ciprofibrate.

The major effects of the fibrates are to lower serum triglycerides (by 35 to 50%) and raise HDL (by 15 to 25%). These effects are mediated at least in part by activation of peroxisome proliferator-activated receptors. This results in complex downregulation or stimulation of apolipoprotein gene expression and concomitant decreased production and increased clearance of VLDL and increased HDL-mediated reversed cholesterol transfer.⁶⁴⁻⁶⁷

The fibrates have a variable effect on serum lipoprotein(a). In one study, for example, bezafibrate reduced serum lipoprotein(a) by approximately 26% overall and by 39% in patients with values above 30 mg/dL. However, the effect of gemfibrozil on lipoprotein(a) may vary with the lipid disorder.⁶⁸ Fibrates also have a variable effect on plasma fibrinogen, with gemfibrozil having no effect and fenofibrate lowering fibrinogen. However, gemfibrozil may have a beneficial effect by reducing PAI-1.⁶⁹ An additional difference among the fibric acid derivatives is the effect on serum homocysteine. They increase with fenofibrate and bezafibrate, a potentially undesirable effect (because elevated homocysteine may be associated with the development or worsening of atherosclerosis and neointimal hyperplasia) but are unchanged with gemfibrozil.^{70,71}

Gemfibrozil Gemfibrozil, at a dose of 600 mg twice daily 30 minutes before the morning and evening meal, increases HDL cholesterol levels by an average of 11%. However, the Helsinki Heart Study showed a more prominent elevation in HDL cholesterol in the lower range of plasma HDL levels (i.e., in those at greatest cardiovascular risk).⁷² Subgroup analysis found that gemfibrozil was particularly effective in preventing heart disease in patients with high serum triglyceride concentrations (> 202 mg/dL) plus either low HDL cholesterol (< 42 mg/dL) or a high LDL to HDL cholesterol ratio (> 5.0).

Fenofibrate and fenofibric acid Fenofibrate has less risk of side effects than gemfibrozil. Dose reduction is warranted in patients with renal disease. An important drug interaction is that fenofibrate increases the clearance of cyclosporine.

Fibrates have been associated with muscle toxicity,⁷³ an effect that is more pronounced in patients also treated with a statin.⁷⁴ This effect may be mediated by competitive inhibition of CYP3A4, leading to a reduction in statin metabolism. Given that pravastatin and fluvastatin are not extensively metabolized by the CYP3A4, they may be safer when combination therapy is required with a fibrate.⁷⁵ Given that fibrates also interfere with the metabolism of warfarin,⁷⁶ the warfarin dose should be reduced by 30% in patients treated with this drug.

Niacin (Nicotinic Acid) Niacin is a well-established antilipemic agent. It comes in several formulations that include immediate-release (crystalline) and sustained-release formulations such as Niaspan (Kos Pharmaceuticals, Miami, Florida). Niacin has a variety of beneficial effects on lipid metabolism. Its major effect is to raise HDL by as much as 30 to 35%, both by reducing lipid transfer of cholesterol from HDL to VLDL and by delaying HDL clearance.^{77,78} It also inhibits the formation of VLDL and its metabolite LDL.⁷⁷ At higher doses, nicotinic acid can also lower lipoprotein(a) levels by as much as 35%.⁷⁸ Niacin may also lower fibrinogen levels.⁷⁹

Niacin is effective in patients with hypercholesterolemia and in combined hyperlipidemia associated with normal and

low levels of HDL cholesterol (hypoalphalipoproteinemia). The HDL-raising properties of nicotinic acid occur with dosages as low as 1 to 1.5 g/day.⁸⁰ In contrast, the VLDL- and LDL-lowering effects are typically seen with higher doses (3 g/day).^{77,78} In one study, nicotinic acid in a dose of 500 mg t.i.d. raised HDL cholesterol by 20% but reduced LDL cholesterol by only 5%. In comparison, a higher dose of 1.5 g t.i.d. produced more prominent changes of 33% (HDL elevation) and 23% (LDL reduction).⁷⁸

Niacin is especially helpful in combination with fibrates or statins. In a study of 269 patients, the reduction in total and LDL cholesterol with sustained-release niacin was 11% and 18%, respectively, compared with 23% and 32%, respectively, in those taking a combination of niacin and a statin.⁸¹ However, the use of nicotinic acid is often limited by symptomatic side effects. At standard doses (1.5 to 4.5 g/day), flushing occurs in 80% of cases and pruritus, paresthesias, and nausea each occur in about 20%.⁷⁸ In addition, elevations in hepatocellular enzymes are common and may lead to severe hepatotoxicity, jaundice, and fulminant hepatitis. The onset of hepatocellular injury is not predictable; therefore, regular monitoring of biochemical studies is mandatory. Crystalline niacin is preferred to most sustained-release preparations because the former is associated with a greater hyperlipidemic effect and seemingly less hepatotoxicity.⁸² However, flushing is more common with crystalline niacin. Combining niacin with a complex carbohydrate, inositol, can reduce flushing, and now many such preparations are available over the counter, usually marketed as no-flush niacin.

Therapy with nicotinic acid is initiated at 100 mg three times daily and gradually increased to the targeted dosage as tolerated.⁸⁰ Pretreatment with aspirin 30 minutes prior to dosing can minimize flushing and the other prostaglandin-mediated side effects noted below. This adverse reaction often diminishes in 7 to 10 days. Nicotinic acid is better tolerated when ingested with food, which minimizes gastrointestinal side effects. Alcohol may make the flushing more aggressive.

Some important medical consequences of niacin must be borne in mind. Most importantly, nicotinic acid causes insulin resistance. As a result, hyperglycemia may develop in susceptible patients and the glycemic state may be worsened in those already being treated for overt diabetes mellitus.⁸³ Nicotinic acid can also induce hyperuricemia and precipitate acute gouty arthritis; it should therefore be avoided in any patient with a history of gout. Hypotension can occur when used in conjunction with vasodilators, and this can aggravate angina.⁸⁴ Nicotinic acid causes a dose-dependent elevation in plasma homocysteine levels that may negate its favorable effects⁸⁵ on the lipid profile in certain subsets of patients.⁸⁶ Thus, after nicotinic acid is titrated to a stable maintenance dose, homocysteine levels should be measured.

Niaspan is a controlled-release formulation of nicotinic acid that has improved patient tolerability compared with an immediate-release preparation. In one study of 269 patients receiving a median dose of 2,000 mg/day for 48 weeks, only 4.8% discontinued the drug because of flushing.⁸⁶ However, we still find that this preparation requires a very slow increase in dosage to improve patient tolerance of the flushing. Niaspan is initiated at a dose of 500 mg nightly for 1 month, and the dosage is titrated to 1,000 mg. The standard dosage of

Niaspan is 1 to 2 g nightly. It is advised that the medication be given with a nighttime snack. The manufacturer does not recommend doses greater than 2,000 mg daily. Women may respond at lower Niaspan doses than men.

Bile acid sequestrants Bile acid sequestrants bind with bile acids in the intestines and are then eliminated in the stool. This results in interruption of the reabsorption of bile acids, which is usually 90% efficient. The ensuing reduction in the cholesterol pool lowers intrahepatic cholesterol, which promotes the synthesis of apolipoprotein B/E (LDL) receptors. The apolipoprotein B/E (LDL) receptors bind LDL from the plasma, causing a further reduction in blood cholesterol. The bile acid sequestrants also induce a minimal elevation in HDL cholesterol via intestinal formation of nascent HDL.⁸⁷

These medications are effective in patients with mild to moderate elevations of LDL cholesterol. Low doses taken before meals (8 g/day of cholestyramine or 10 g/day of colestipol or three 325 mg tablets of colesvalam b.i.d.) can reduce LDL cholesterol by 10 to 15%. A more pronounced reduction (about 24%) can be achieved at maximal recommended doses (24 and 30 g/day, respectively).^{88,89}

Bile acid sequestrants are most effective when used in combination with a statin or nicotinic acid in patients with markedly elevated plasma levels of LDL cholesterol. As an example, bile acid sequestrants and statins have synergistic actions to lower LDL cholesterol (about 50%) and raise HDL cholesterol (11 to 18%).⁹⁰

The use of a bile acid sequestrant is often limited by side effects that include constipation, bloating, nausea, and gas. They can be limited by taking large amounts of liquids. Colestipol (2.5 g) has also been given in combination with psyllium mucilloid (2.5 g), three times daily with meals; this regimen produces equivalent LDL lowering and a more favorable change in the ratio of total cholesterol to HDL cholesterol than full-dose colestipol (5 g t.i.d. with meals).⁹¹

Bile acid sequestrants may also interfere with the absorption of other medications, such as digoxin, warfarin, fat-soluble vitamins, and folic acid, so these medications should be taken at least 1 hour before or 4 to 6 hours after the sequestrant.⁹² Patients on resins may need folic acid supplementation, especially if homocysteine levels are elevated, and patients on some of these previously mentioned drugs might need dosage adjustments or close monitoring of effectiveness.

Ezetimibe This medication interferes with the absorption of cholesterol from the intestines. It can be used as a stand-alone drug (Zetia, Merck, Whitehouse Station, NJ) or in combination (Vytorin, Merck, Whitehouse Station, NJ) with the statin simvastatin.⁹²⁻⁹⁴ Like the statins, this medication can result in myopathy or hepatotoxicity, although this is less frequent. Myopathy is usually seen with drug interactions with itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, or nefazodone or large quantities of grapefruit juice (> 1 quart daily). The concomitant use of Vytorin and fibrates (especially gemfibrozil) should be avoided. The combined use of Vytorin at doses higher than 10 or 20 mg daily with amiodarone or verapamil should be avoided unless the clinical benefit is likely to outweigh the increased risk of myopathy. Because of the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic impairment, ezetimibe is not recommended in these patients.

Although ezetimibe certainly reduces LDL levels, improved morbidity or mortality awaits clinical confirmation. In fact, in a recent highly controversial report, carotid intimal thickening may actually have increased with Vytorin,^{95,96} although an FDA review of that data suggests that intimal thickening was unchanged.

Antiplatelet Agents

This group of medications warrants special mention because they do not specifically affect hyperlipidemia but rather its consequences of plaque inflammation and subsequent platelet adherence and acute arterial occlusion or distal embolization.⁹⁷ In patients with PAD, a meta-analysis of all antiplatelet trials (including studies of aspirin, clopidogrel, ticlopidine, and dipyridamole) demonstrated a 23% odds reduction in ischemic events.⁹⁸

ASPIRIN

Aspirin is the most inexpensive antiplatelet drug with the most evidence supporting its use. The Antithrombotic Trialists' Collaboration meta-analysis concluded that when patients with cardiovascular disease were given aspirin, there was a consistent 25% odds reduction in subsequent cardiovascular events.⁹⁹ The study also clearly demonstrated that low-dose aspirin (75 to 160 mg) was protective and probably safer in terms of gastrointestinal bleeding than higher doses of aspirin. Unfortunately, as many as one in 20 patients may be resistant to the clinical effects of aspirin. Although this can be tested by blood or urine tests, these are seldom performed.¹⁰⁰

CLOPIDOGREL

Clopidogrel is an antiplatelet agent that has been shown to be more potent than aspirin in reducing secondary events in patients with atherosclerotic disease. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, clopidogrel was associated with an overall reduction in primary end points, that is, stroke, myocardial infarction, or death from other vascular causes.¹⁰¹ Although the overall percentage reduction was 8.7%, the absolute change was only 0.5% (5.32% versus 5.83%). However, those with PAD had a higher rate of protection from secondary events compared with those who enrolled because of myocardial infarction or cerebrovascular disease. Patients taking clopidogrel had a higher incidence of diarrhea, rash, and pruritus than those on aspirin but had a lower incidence of other gastrointestinal disturbances and upper gastrointestinal bleeding. Further, given that the current data lack clinical trial evidence on the benefits of aspirin in patients with PAD, clopidogrel would be the preferred antiplatelet agent in this patient population.⁹⁷ However, recent data suggest that approximately 30% of patients concurrently taking proton pump inhibitors may be resistant to clopidogrel.¹⁰² The addition of aspirin to clopidogrel appears to offer no added benefit.¹⁰³

Medical Management of Specific Vascular Conditions

Although the preceding discussion covers the general principles of medical management of patients with PAD, components of this overall disease process warrant specific consideration.

CLAUDICATION

Although claudication is a manifestation of advanced PAD, it seldom leads to amputation, with the majority of patients staying stable over many years. Accordingly, treatment is usually directed at quality of life. Primarily, treatment should be aimed at lifestyle modification and most importantly at the implementation of a routine walking exercise program to allow improvement in walking distance. Unfortunately, compliance is poor with these methods of management usually because the patient is limited by pain or because of cardiac or respiratory conditions.

Treatment of claudication with medicines may improve both pain-free walking distance (PFWD) and maximal walking distance (MWD), but this should be viewed as supplementary. Currently, FDA approval for the treatment of intermittent claudication is limited to pentoxifylline and cilostazol, with the latter appearing to be more effective in increasing PFWD and MWD. Although many patients will demonstrate an improvement, only half will report subjective improvement in their quality of life following treatment with cilostazol. Further, many patients may simply exhibit a placebo effect.

A number of other medications that are used in Europe, Latin America, and Asia have shown promising results, but further clinical evaluation is necessary. New treatment regimens are under evaluation, and they should be accepted only after they have been proven beneficial and appropriately conducted as scientifically based clinical trials.

Pentoxifylline

Pentoxifylline is a methylxanthine derivative that is now widely available as a generic pharmaceutical. Its primary effect is thought to be an improvement in red blood cell deformability. Other effects include a decrease in blood viscosity, platelet aggregation inhibition, and a reduction in fibrinogen levels.

Although there have been numerous reports of good results concerning pentoxifylline's effects in the treatment of intermittent claudication, two major randomized, double-blind studies have provided conflicting results.^{104,105} The first of these two trials compared pentoxifylline with placebo over a 24-week period.¹⁰⁴ The pentoxifylline-treated group had an improvement in PFWD (45% versus a 23% improvement in those given placebo [$p = .02$]) and MWD (32% improvement versus 20% of those treated with placebo [$p = .04$]). In common with other claudication studies is the fact that placebo improved PFWD by 23%. Further, despite significant improvements in PFWD and MWD, subjective assessment was not improved in the pentoxifylline group. The second study randomized 150 patients to 1,200 mg a day of pentoxifylline ($n = 76$) or placebo ($n = 74$).¹⁰⁵ Differing from the findings of the previous study, these investigators found no improvement in PFWD and only a trend that suggested an improvement in MWD in patients given pentoxifylline ($p = .09$). However, certain subpopulations of patients showed significant improvement in both PFWD and MWD when compared with placebo. Patients with moderate versus mild disease tended toward significant improvement, and those with chronic duration of the disease (greater than 1 year) also tended toward significance. Unfortunately, the beneficial effects of pentoxifylline may wear off with long-term administration. In a study by Ernst and colleagues, MWD at certain

time intervals during the study period did demonstrate significant improvement; however, no significant benefit in PFWD or MWD was observed after 12 weeks of pentoxifylline therapy.¹⁰⁶

It appears, then, that pentoxifylline may offer a modest improvement in walking distance in some patients, but this may be too small to offer any improvement in quality of life. However, given that this medication is relatively free of side effects and inexpensive, it is frequently used as a first-line medication. The dosage may need to be adjusted if used with other methylxanthine derivatives (e.g., aminophylline or theophylline).

Cilostazol

Cilostazol is a phosphodiesterase type III inhibitor prescribed at a dose of 100 mg twice a day and is now the most widely prescribed medication for improvement in walking distance. It is also available in a generic form and is thought to exert its mechanism of action by inhibiting cyclic adenosine monophosphate (cAMP) phosphodiesterase. By increasing the levels of cAMP in platelets and blood vessels, there is a resultant inhibition of platelet aggregation and a promotion of smooth muscle cell relaxation. Other additional pharmacologic properties include a modest positive lipid effect, mildly increasing HDL cholesterol, and decreasing triglycerides.¹⁰⁷ In vitro studies have shown that there may be a reduction in smooth muscle cell proliferation.¹⁰⁸ As with pentoxifylline, it does not reduce or prevent worsening plaque burden.

Multiple studies have compared cilostazol with placebo with an average improvement in MWD of 140 meters, with 51% of study participants perceiving this improvement versus 30% for those on placebo. Given that this distance may or may not improve quality of life, it is important for the prescribing physician to inform the patient that pain-free walking will be unlikely, and although improved MWD may occur, this may still not be satisfactory.

Given that cilostazol is associated with nausea, diarrhea, palpitations, and headache, it is important that a trial dose of the medicine be prescribed prior to initiating long-term therapy because many patients will not be able to tolerate the medication. In some patients, starting with half the dose and gradually increasing the dose can allow them to take the medication. Cilostazol is contraindicated in patients with congestive heart failure of any severity because other phosphodiesterase inhibitors, but not cilostazol specifically, have been shown to decrease survival rate compared with placebo in patients with class 3 to class 4 (New York Heart Association) congestive heart failure.¹⁰⁹ Further, cilostazol is partially metabolized in the liver by the CYP3A4 or the CYP2C19 enzymes. Because of this, other drugs that rely on these specific hepatic enzymes may increase cilostazol levels. Examples include antifungals, erythromycin, some selective serotonin reuptake inhibitors, and omeprazole. Although the concurrent use of these medications is not discouraged, one may want to consider reducing the daily dose of cilostazol to 50 mg twice a day.

Statins

As mentioned already, all patients with PAD should be considered for a statin irrespective of their underlying cholesterol levels because of the protective effect of statins on

cardiovascular morbidity and mortality. However, statins have also been shown to improve walking distance. Mohler and colleagues performed a randomized, double-blind, parallel-design study that included 354 persons with claudication attributable to PAD.¹¹⁰ Patients were treated with placebo, atorvastatin 10 mg per day, or atorvastatin 80 mg per day for 12 months. The outcome measures included a change in treadmill exercise time and patient-reported measures of physical activity and quality of life based on questionnaires. Maximal walking time after 12 months of treatment with atorvastatin did not change significantly. However, there was improvement in pain-free walking time after 12 months of treatment for the 80 mg ($p = .025$) group compared with the placebo group. A physical activity questionnaire demonstrated improvement in ambulatory ability for the 10 and 80 mg groups ($p = .011$), whereas two quality of life instruments, the Walking Impairment Questionnaire and Short Form 36 Questionnaire, did not show significant change.

Mondillo and colleagues studied 86 patients with PAD, intermittent claudication, and total cholesterol levels greater than 220 mg/dL.¹¹¹ Patients were enrolled in a randomized, placebo-controlled, double-blind study. Forty-three patients were assigned to simvastatin (40 mg/day); the remaining 43 patients were assigned to placebo treatment. All patients underwent an exercise test and clinical examination and completed a self-assessment questionnaire at 0, 3, and 6 months. Pain-free and total walking distance, resting and postexercise ankle-brachial indexes, and questionnaire scores were determined at each follow-up. At 6 months, the mean PFWD had increased 90 meters (95% confidence interval [CI] 64 to 116 meters; $p < .005$) more in the simvastatin group than in the placebo group. Similar results were seen for the total walking distance (mean between-group difference in the change, 126 meters; 95% CI 101 to 151 meters; $p < .001$). There was also a greater improvement in claudication symptoms among patients treated with simvastatin. The effects on walking performance and questionnaire scores were also significant at 3 months.

McDermott and colleagues attempted to evaluate whether such improvement was related to achieved cholesterol levels in patients with and without PAD.¹¹² They found that statin use was associated with superior leg functioning compared with no statin use, independent of cholesterol levels and other potential confounders, such as aspirin, ACE inhibitors, vasodilators, or beta blockers. Their data suggest that the non-cholesterol-lowering properties of statins may favorably influence functioning in persons with and without PAD.

Aspirin

Aspirin has not been demonstrated to improve walking distance or symptoms in patients with intermittent claudication. Further, specific studies in the PAD population using aspirin have not shown a statistically significant reduction in cardiovascular events.⁹⁹ Thus, although antiplatelet drugs are clearly indicated in the overall management of PAD, aspirin does not have specific FDA approval for use in this patient population.¹¹³

Clopidogrel

There is no evidence to suggest that the symptoms of claudication are reduced by long-term treatment with clopidogrel.

STROKE

There is clear evidence that medical management can significantly reduce the occurrence of stroke. Accordingly, it would seem almost mandatory that patients with carotid artery plaque should be treated with a statin and an antiplatelet agent such as aspirin, aspirin and dipyridamole combination, or clopidogrel, although which medication is superior is still a matter of conjecture.^{114,115} Current data would suggest that combination therapy of aspirin and dipyridamole may be superior to aspirin alone,¹¹⁴ but there are no compelling data to suggest that this combination is superior to clopidogrel. Also, warfarin adds no advantage to aspirin in the prevention of recurrent ischemic stroke.¹¹⁶

In the HOPE study, the addition of the ACE inhibitor ramipril added stroke protection irrespective of its effects on blood pressure.¹⁹ However, hypertension should be actively and aggressively controlled,¹¹⁷ except in the very elderly, for whom more moderate control may be safer.

Also, the use of statins perioperatively may reduce the incidence of perioperative stroke.¹¹⁸ In a nonrandomized retrospective analysis, Kennedy and colleagues found a protective effect of statin therapy in symptomatic patients pretreated at the time of carotid endarterectomy (CEA).¹¹⁸ This was not seen in asymptomatic patients. The latter finding may be because the plaque of asymptomatic patients is not in a state of inflammation that would be ameliorated by statins. This hypothesis is supported by histologic studies performed by Molloy and colleagues.¹¹⁹ They performed an observational study on 137 patients undergoing CEA. Patients on statins were less likely to have had symptoms in the 4 weeks before CEA ($p = .0049$) and were less likely to have spontaneous cerebral embolization detected by transcranial Doppler ultrasonography ($p = .0459$).

Beneficial results following CEA were also demonstrated by McGirt and colleagues.¹²⁰ Adjusting for all demographics and comorbidities in multivariate analysis, statin use independently reduced the odds of stroke threefold (odds ratio [OR] [95% CI], 0.35 [0.15 to 0.85]; $p < .05$) and death fivefold (OR [95% CI], 0.20 [0.04 to 0.99]; $p < .05$).

There are also data that show that initiating statins after an ischemic stroke can improve recovery.^{121–123} Statin use prior to ischemic stroke is also associated with reduced mortality and better recovery.¹²⁴ Unfortunately, despite these benefits, statin use remains low (40%) following CEA.¹²⁵ The relationship between serum lipid levels and recurrent carotid stenosis has been postulated for many years^{126–128} and reconfirmed in recent literature by LaMuraglia and colleagues.¹²⁹ These same authors also showed that concurrent administration of a lipid-lowering drug had a profound effect on early recurrent carotid stenosis and that these drugs might have other relevant properties that might promote the anatomic durability of the CEA reconstruction. Such effects may include the decrease in the inflammatory response in the vessel wall, the increase in circulating endothelial progenitor cells, and the promotion of smooth muscle cell apoptosis, all of which have been described with the use of statins and are known to have a role in the restenotic process.^{130,131}

Although perioperative clopidogrel may also help reduce postendarterectomy neurologic events, increased bleeding has prompted us to discontinue this medication a week prior to endarterectomy except in patients who are having ongoing

symptoms. However, antiplatelet agents such as clopidogrel should be started at least 3 days prior to carotid stenting and continued for at least 3 months thereafter.

Perioperative Medications

Based on evidence that statins may have benefit in reducing early ischemic events following acute coronary syndromes and coronary revascularization,¹³² investigators began to evaluate whether similar reductions in cardiac morbidity could be achieved with statins in the vascular patient.^{133,134} However, unless LDL levels are driven very low, regression of atherosclerosis occurs only in a minority of patients, if at all, yet clinical benefits of statins are seen often within 6 months of initiating therapy. This suggests that factors other than cholesterol lowering or plaque regression are also important in improving outcome.

The Statins for Risk Reduction in Surgery (StaRRS) study is a retrospective study that recorded patient characteristics, past medical history, and admission medications on all patients undergoing CEA, aortic surgery, or lower extremity revascularization over a 2-year period (January 1999 to December 2000) at a tertiary referral center.¹³⁵ Complications occurred in 157 of 1,163 eligible hospitalizations and were significantly fewer in patients receiving statins (9.9%) than in those not receiving statins (16.5%, $p = .001$). The difference was mostly accounted for by reductions in myocardial ischemia and congestive heart failure. After adjusting for other significant predictors of perioperative complications (age, gender, type of surgery, emergent surgery, left ventricular dysfunction, and diabetes mellitus), statins still conferred a highly significant protective effect (OR 0.52, $p = .001$).

Kertai and colleagues studied 570 patients (mean age 69 $\pm$ 9 years, 486 males) who underwent abdominal aortic aneurysm (AAA) surgery between 1991 and 2001.¹³⁶ The main outcome was a composite of perioperative mortality and myocardial infarction within 30 days of surgery. Perioperative mortality or myocardial infarction occurred in 51 (8.9%) patients. The incidence of the composite end point was significantly lower in statin users compared with nonusers (3.7% versus 11.0%; crude OR 0.31, 95% CI 0.13 to 0.74; $p = .01$). Beta blocker use was also associated with a significant reduction in the composite end point (OR 0.24, 95% CI 0.11 to 0.54). Patients using a combination of statins and beta blockers appeared to be at lower risk for the composite end point across multiple cardiac risk strata; in particular, patients with three or more risk factors experienced significantly lower perioperative events.

Durazzo and colleagues randomly assigned 50 patients to receive atorvastatin and 50 patients to placebo once a day for 45 days, irrespective of their serum cholesterol concentration.¹³⁷ Vascular surgery was performed on average 30 days after randomization, and patients were prospectively followed up over 6 months. The incidence of cardiac events was more than three times higher with placebo (26.0%) compared with atorvastatin (8.0%; $p = .031$).

Clearly, the effect of statins on outcome noted in these studies showed that a beneficial effect occurred more rapidly than can be explained by a simple reduction in low-density cholesterol levels. This appears to support the concept that statins have an antiinflammatory effect on coronary vasculature, thus

reducing sudden coronary thrombosis.^{138,139} It should be noted, however, that not all evaluations prove a beneficial effect of statins on cardiovascular surgery outcomes.¹⁴⁰

Although commonly used for their cardioprotective effect, perioperative beta blocker use has recently been questioned because of an apparent slight increase in stroke. However, this has not been our experience, and we continue to prescribe these medications prior to and during major intra-abdominal arterial surgery. Antiplatelet agents are routinely avoided for at least a week to 10 days before such procedures, especially if spinal or epidural anesthesia is anticipated.

GRAFT PATENCY

Two articles suggest that statin therapy may also play a role in graft patency,^{141,142} and we are currently evaluating the data in the PREVENT III study to see if these data can be confirmed in this large study of infrainguinal vein bypasses.¹⁴³

Henke and colleagues evaluated 293 patients who underwent 338 infrainguinal bypass procedures with autologous veins ($n = 218$), prosthetic grafts ($n = 88$), or composite prosthetic vein grafts ($n = 32$).¹⁴¹ Statin drugs were taken by 56% of patients, ACE inhibitors by 54% of patients, and antiplatelet agents or warfarin sodium by 93% of patients. Statins were associated with increased graft patency (OR 3.7; 95% CI 2.1 to 6.4) and a lower rate of amputation. Abbruzzese and colleagues performed a retrospective analysis of consecutive 172 patients who underwent 189 primary autogenous infrainguinal reconstructions with a single segment of great saphenous vein.¹⁴² Patients were categorized according to concurrent use of a statin (94 in the statin group, 95 in the control group). Although there was no difference in primary patency, patients on statins had higher primary-revised (94% $\pm$ 2% versus 83% $\pm$ 5%; $p < .02$) and secondary (97% $\pm$ 2% versus 87% $\pm$ 4%; $p < .02$) graft patency rates at 2 years. The risk of graft failure was 3.2-fold higher for the control group. Perioperative cholesterol levels (available in 47% of patients) were not statistically different between groups.

AORTIC ANEURYSMS

Given that AAA formation may be a result of inflammation and extracellular matrix remodeling mediated by matrix metalloproteinases (MMPs) and that statins have an antiinflammatory effect, it is not surprising that a possible beneficial effect of statins on decreasing aneurysm development has been investigated. Kalyanasundaram and colleagues studied this in rats and found that AAAs in rats given statins were smaller than in those fed a placebo.¹⁴⁴ MMP-9 and nuclear factor- κ B protein levels were also decreased in the aortas of simvastatin-treated animals. Similar findings were also noted by Steinmetz and colleagues, who found that the mechanisms of this effect were independent of lipid lowering and included preservation of medial elastin and smooth muscle cells, as well as altered aortic wall expression of MMPs and their inhibitors.¹⁴⁵ Nagashima and colleagues evaluated the aortic wall in patients, some of whom had been on cerivastatin.¹⁴⁶ Cerivastatin significantly reduced the tissue levels of both total and active MMP-9 in a concentration-dependent manner ($p < .001$) by inhibiting the activation of neutrophils and macrophages. However, cerivastatin has been withdrawn from the US market.

There are also experimental suggestions that doxycycline, a generic tetracycline, may reduce aneurysm growth.^{147,148} Given that the side effects of this drug are very rare, except for increased photosensitivity, I routinely use 100 mg daily in the management of small AAAs.

NONATHEROSCLEROTIC VASCULAR DISEASE

The vascular specialist may be confronted with patients suffering from a multitude of nonatherosclerotic conditions affecting the arterial system. These usually will manifest with Raynaud syndrome and, in advanced cases, with digit ischemia and gangrene. In such patients, an attempt should be made to differentiate the underlying etiology and to alleviate the symptoms. In most patients, avoidance of cold and digit injury is all that is required. However, in advanced cases in which ulceration or gangrene is evidenced, medications may be helpful. These will include vasodilators such as calcium channel blockers. Antiplatelet agents as well as pentoxifylline and clopidogrel have been used, but there is no level I evidence supporting their use.

Miscellaneous Medications: Over-the-Counter Medications, Vitamins, and Herbs

Atherosclerosis is a multifactorial process related to interaction between a multitude of genetic processes and environmental pressures. Not surprisingly, many medications, herbs, and vitamins have been suggested to have beneficial effects.¹⁴⁹ For example, homocysteine-lowering vitamin B₁₂ compounds and folic acid have been touted as effective. However, although elevated levels of homocysteine are associated with premature development of atherosclerosis and coronary neointimal hyperplasia following stents, lowering homo-

cysteine has not been proven to effect clinical outcome.^{85,150} Similarly, antioxidants such as vitamin E have also not been effective.¹⁵¹ Despite a large amount of literature, very few articles have enough scientific merit to warrant serious consideration, and many offer conflicting results. This accounts for the confusion and suspicion that surround many of these treatments.

Currently, none of the treatment modalities except diet and fish oils¹⁵² can be strongly suggested as beneficial for most patients. However, individual patients may benefit from some of these miscellaneous compounds. Examples would be patients on dialysis or those who are nutritionally deficient, such as the very elderly.

Summary

The ravages of atherosclerosis and other rarer conditions affecting the vascular system continue to account for most deaths in the developed world. Increasingly, vascular surgeons are finding themselves at the forefront of the fight against this scourge. Although advances in the technical method of treatment, such as angioplasty, stents, endografts, atherectomy, and lytic therapy, are all achieving some success in reducing morbidity and mortality, it is anticipated that optimal medical management will have an even more pronounced salutary effect. As such, the modern vascular surgeon must be able not only to operate and dilate but also to medicate.

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27 LOWER-EXTREMITY ULCERS

Robert D. Galiano, M.D.

A lower-extremity ulcer presents a unique window into a patient's health. The term ulcer implies a nonhealing wound, meaning that an ulcer is most likely to be present in a patient with an underlying pathophysiologic derangement. Accordingly, the surgeon treating a leg wound is obliged to address any impediments to healing that exist, whether local or systemic, with a well-designed therapeutic plan. Although there are literally scores of different types of lower-extremity ulcer [see Table 1], it is neither practical nor necessary for the surgeon to learn a specific treatment for every single type. In most cases, it is better to develop a logical framework that emphasizes the common features shared by most leg ulcers (rather than the differences). Such a focus on the shared causal factors of lower-extremity ulcers, coupled with a knowledge of modern wound care and an appreciation of the unique anatomy of the leg and foot, will facilitate patient understanding, enhance communication between consultants and primary care physicians, and, most important, enable efficacious patient care.

The following characteristics are common to most lower-extremity ulcers.^{1,2}

1. Ischemia. Several factors, including peripheral arterial disease and edema, contribute to the prevalence of tissue ischemia in the lower extremity. Ischemia may be local or regional, or it may be dependent, associated with episodic ischemia-reperfusion injury. Cells require oxygen to carry out basic metabolic functions, fight infections, and heal wounds.³⁻⁵ Edema contributes to tissue hypoxia by increasing the distance between a cell and the nearest capillary.⁶
2. Age. Most leg ulcers occur in elderly persons. Many comorbid conditions (e.g., diabetes, venous stasis, and peripheral arterial disease) are age dependent, and aged cells lose much of their ability to respond to sublethal ischemia.⁷⁻⁹ Consequently, a given degree of ischemia typically has a greater impact on an elderly person than on a young one.
3. The presence of bacteria. Most chronic ulcers are colonized by bacteria in the form of a biofilm, which is difficult to treat and perpetuates the inflammatory response within a wound.¹⁰ Although the adverse effects of bacteria on wound healing have long been noted, those of biofilm, which does not always give rise to an overt phenotype or infectious picture, have been underappreciated. Indeed, a stalled, nonhealing wound is one of the more common presentations of biofilm. Many of the current advances in wound care practice and dressing use focus on management of the bioburden borne by the wound.

Acknowledging and addressing each of these common factors will allow the surgeon to heal the vast majority of leg ulcers, either surgically or nonsurgically; ignorance of these factors will result in a haphazard approach to leg ulcer care that will inevitably be associated with inferior outcomes.

Wound care practitioners may come from any of several medical specialties. In my view, however, lower-extremity ulcers are best treated when the expertise and know-how of an interested surgeon are closely integrated into patient care. Given that the majority of problem leg wounds occur in patients with significant comorbid

conditions, the involvement of a lower-extremity surgeon is crucial for ensuring that a patient is offered a comprehensive set of management options. One potential obstacle to such involvement, however, is that most surgeons complete their surgical residencies and fellowships without a thorough grounding in wound care. Many, in fact, are still unaware of any dressings other than wet-to-dry dressings. Today, routine management of leg wounds is often left to nurses, physical therapists, and other nonsurgical specialists. Although these practitioners are certainly capable of treating patients with uncomplicated lower-extremity ulcers, it is important to recall that an understanding of how the body heals in response to injury lies at the heart of all surgical care. It is time that surgeons reengaged themselves in the management of wounds, particularly lower-extremity wounds: surgery is the discipline that is best suited, by both training and inclination, to assume the care of these complex, challenging, and often frustrating problems. There is much room for improvement in this rapidly evolving field, and the intellectual and professional rewards to be gained from increased integration of surgeons into the care of patients with leg wounds are enormous.

The goal of modern leg wound care should be expeditious closure and long-term durable coverage, followed by carefully tailored preventive measures. Unfortunately, prevention is relatively neglected in this discipline. For example, a patient with a diabetic foot ulcer may require an Achilles tendon-lengthening procedure to deal with the ankle equinus and the resulting tendinous derangements that shift the weightbearing pressures to the area under the metatarsal heads. A program of offloading and local wound care may heal the ulcer, but recurrence is predictable, often even with the best orthotics, unless the stiff, foreshortened tendon is lengthened and gait biomechanics are restored. The high risk of recurrence—and the easiness of the operation that prevents it—will not be appreciated by a clinician who is not familiar with lower-extremity surgery. Many wounds can be healed by means of offloading and dressing changes, but it is probable that in the future, best-practice management of these lesions will include interventions aimed at minimizing ulcer recidivism, often by addressing any anatomic derangements that may have given rise to the ulcer in the first place.

Before surgical measures or advanced dressings are even considered, much can be done to enhance the healing potential of a lower-extremity ulcer.^{2,11-13} The main goal of any intervention should be to ensure that oxygen and nutrients are reaching the cells within the wound. For most wounds, the most important steps toward this goal are offloading and control of edema. With good wound care, appropriate antibiotic therapy (when indicated), and complete bed rest, even a large ulcer may heal without further treatment. Indeed, it is the dependent position of the lower extremity and the absolute requirement of most patients to ambulate that indirectly accounts for failed ulcer healing in many cases. If the dependent position can be changed and the patient can elevate the leg, the edema will be diminished and local tissue perfusion will be improved. Another step that is often neglected is ensuring adequate hydration, particularly in patients who are hospitalized or

Table 1 Types and Causes of Lower-Extremity Ulcers

Vascular	Venous
	Arterial
	Mixed
	Vascular malformations
	Lymphatic
	Primary lymphedema
Vasculitic	Secondary lymphedema
	Pyoderma gangrenosum
	Systemic lupus erythematosus
	Rheumatoid arthritis
	Wegener granulomatosis
	Scleroderma
Neuropathic	Polyarteritis nodosa
	Diabetic neuropathic ulcer
Traumatic	Peripheral neuropathy, with or without ischemia
	Frostbite
	Burns
	Factitious
Radiation-induced	Injury
	Acute
Hematologic/dyscrasias	Chronic
	Sickle cell ulcers
	Polycythemia vera
	Thalassemia
	Thrombocythemia
Malignancies	Basal cell carcinoma
	Squamous cell carcinoma (Marjolin ulcer)
	Malignant melanoma
Tropical ulcers	Cutaneous tuberculosis
	Syphilis
	Parasitic infections
	Fungal infections
Sarcoidosis	

have recently undergone surgery. Hydration enhances preload and ensures that arteriovenous shunting does not occur to divert blood away from the cutaneous tissues. Control of pain is also important to minimize sympathetic-induced vasoconstriction. Smoking cessation is beneficial: smoking impairs vascular flow, reduces vasodilatation, and accelerates the formation of atherosclerotic disease in vessels. Counseling should therefore be offered to all patients who use tobacco. The extremity should be kept warm so as to open up capillary beds and enhance tissue perfusion. Supplemental oxygen may be helpful for patients with a regional or systemic malperfusion state.

Chronic Wounds and Problem Wounds

As discussed elsewhere [see 1:7 *Acute Wound Care*], wounds normally progress through several temporally overlapping phases of healing. A chronic wound, however, does not progress through all of these phases but is arrested in one of them, usually the inflammatory phase. For practical purposes, a chronic wound can be defined—and, until comparatively recently, generally has been defined—in strictly temporal terms, as a wound that has not healed after 3 months. This once-standard definition is now being reconsidered, on the grounds that it may subject patients to need-

lessly prolonged courses of therapy, it may be used to deny advanced treatments to patients, and it fails to take into account the dynamic nature of wound healing, whereby wounds may improve, stall, and then improve again.

A better definition of a chronic wound is one that has fallen off the trajectory of expected healing.¹⁴ This newer definition has implications for clinical practice, in that it emphasizes the importance of measuring the wound periodically. The wound should be measurably smaller during each office visit: typically, an actively healing wound should show a reduction in area or volume of approximately 10% per week.¹⁵ If the wound is healing at a lesser rate or is scarcely healing at all, an immediate effort should be made to investigate the reason for the delay. There is no time for complacency (e.g., “Let’s see how it’s doing next month”), because the stalled wound is symptomatic of a significant underlying problem. It is imperative for the surgeon to consider possible causes—for example, infection or bacterial colonization. Often, an office debridement is necessary at this stage to reduce the accumulation of tenacious biofilm. If the wound shows no evidence of healing despite vigilant wound care, a biopsy should be considered, particularly if the wound has been present for more than 3 months. Other potential diagnoses besides malignancy should be considered as well, including vasculitis, pyoderma gangrenosum, and fungal or mycobacterial infection.

A number of clinical trials have shown that the rate of healing in the first 30 days after the initiation of good wound care is strongly predictive of an ulcer’s ultimate fate, especially in the case of diabetic and venous stasis ulcers: the lesions that eventually heal are the ones that show the highest initial healing rates.¹⁶⁻²⁰ This observation, though perhaps intuitively obvious, is not always appreciated, nor are its lessons always correctly applied. Part of the problem is that many ulcers are not evaluated frequently enough in the outpatient setting. Weekly measurement is essential for evaluation of healing potential. In fact, it is likely that in the future, the benchmark measured by patients, peers, and insurance companies to evaluate a wound care practitioner’s success will be time to ulcer healing. If an ulcer eventually heals after 9 months, this is still a success in some ways, but one may reasonably wonder whether the time away from work, the cost of dressings, and the multiple office visits might have been substantially reduced if the wound care practitioner had more frequently evaluated the rate of healing, had aggressively and preemptively rethought his or her approach, and perhaps had resorted to different therapeutic measures.

Instead of thinking in terms of acute wounds versus chronic wounds, as has been traditional, it may be more useful to think in terms of uncomplicated wounds versus problem wounds.² The

Table 2 Conditions That Interfere with Healing

- Immunosuppressive medications
 - Transplant patients
 - Arthritic patients
 - Autoimmune diseases
 - Steroid use, including inhalers
- Recent major surgery
- Smoking
- Malnutrition (particularly acute malnourishment or a recent catabolic state)
- Infection
- Age
- Diminished tissue perfusion
- Radiation

category of problem wounds encompasses not only chronic wounds but also wounds occurring in persons whose comorbid conditions will almost certainly result in a protracted course of healing. Such persons include most elderly and hospitalized patients, but there are numerous other conditions besides advanced age and hospitalization that can impair healing [see Table 2]. For example, a week-old Wagner stage 2 ulcer in a diabetic patient is a problem wound and should be treated promptly and comprehensively with offloading, moist wound care, and frequent inspections. A dehiscence at a saphenous vein harvest site in a patient who underwent a cardiac bypass is also a problem wound, both because of the swelling typically present and because of the likelihood of bacterial colonization in the relatively hypovascular subcutaneous tissue of the thigh. The mode of injury also plays a role in determining whether a wound is a problem wound; for example, a heavily devitalized wound in an 18-year-old patient will heal as poorly as a chronic wound if it is not adequately debrided and wound perfusion is not ensured. By preemptively addressing potential impediments to healing, the surgeon can minimize complications, shorten the time to healing, and help the patient return to work in an expeditious fashion.

Incidence and Epidemiology

It is estimated that at any point, the incidence of lower-extremity ulcers in the United States may be as high as 1%.²¹ The actual number of afflicted patients will rise as a consequence of the extension of the expected average lifespan, the proportional increase in atherosclerotic vascular disease, and the growing epidemic of obesity and associated diabetes mellitus.

The transition of baby boomers from middle age to the ranks of the elderly (over the age of 65) is already occurring, and it is estimated that by 2030, the elderly will constitute 20% of the U.S. population.²² Persons older than 85 years constitute the most rapidly growing segment of the population. As noted (see above), by far the greatest number of ulcers occur in the elderly, both because of the increased incidence of atherosclerosis and because of the parallel increase in venous stasis disease.

In parallel with the increase in the elderly population, there is also a substantial increase in the diabetic population. The United States is witnessing (and leading) the dual global epidemics of diabetes and obesity. There are nearly 21 million people with diabetes in the United States, 6 million of whom are unaware that they have the disease.²³ Approximately 15% of these 21 million are at significant risk for the development of a foot ulcer. Indeed, 60% of lower-extremity amputations unrelated to trauma are performed in diabetic patients.²³ Most of these amputations are preventable. The continuing increases in the incidence of atherosclerotic disease, diabetes, and venous stasis disease make it essential for surgeons to improve their awareness of and competence in the management of wounds in the lower extremity.

Anatomic Considerations

Several unique anatomic and functional factors predispose the lower extremity to ulceration. These factors include the relentless effects of gravity and the repetitive trauma of ambulation. Another factor is the formidable challenges involved in transporting blood from the heart to the foot and back. The vascular tree of the foot is a terminal capillary bed, like that in many other organs, but it is exposed to an enormous pressure gradient that is not present in other parts of the body. In humans, the lower extremities evolved differently from the upper extremities (to enable a bipedal gait),

and the limitations and compromises attendant on this evolution are evident in the predisposition of the legs and feet to ulcerate.

The characteristics of the skin of the lower extremity play a role in ulceration. The skin in this area is taut, with minimal intrinsic laxity, and this tautness has implications for flap design.²⁴ Foot skin is extremely thick, and calluses form readily in response to pressure. Unfortunately, excess callus formation can exacerbate pressure in the sole of a diabetic person's foot. Obesity and lymphedema can alter the barrier function of the skin, as well as diminish cellular perfusion²⁵; lymphedema is particularly damaging, in that the accumulation of fluid in the interstitial space causes a relative hypoxia coupled to altered macrophage function in conjunction with the induction of a chronic inflammatory state and tissue fibrosis.²⁶ Contact sensitivities are common and may influence compliance with the wearing of dressings and compression garments. Lipodermatosclerosis may develop as the result of chronic extravasation of red blood cells into the skin and deposition of hemosiderin within macrophages. Either hypo- or hyperpigmentation may occur, along with the characteristic "woody" firmness of subcutaneous fibrosis.²⁷⁻²⁹ Venous eczema is common in patients with venous ulcers; it is probably an inflammatory process and can generally be distinguished from cellulitis on the basis of its chronicity, its poorly demarcated borders, and its pruritic, scaly nature.

The tendons also play a significant role in the etiology of diabetic forefoot ulcers, and their functional relations must be addressed when an amputation is to be performed. Dysregulation of the tendons is a frequent finding in limb ulcer patients. Chronic hyperglycemia leads to glycosylation of collagen, with subsequent loss of elasticity in connective tissues, including muscle, tendons, and skin; an example is glycosylation of the Achilles tendon, which destroys its flexibility and prevents adequate dorsiflexion during normal gait. The forefoot then bears the brunt of the person's weight during walking, and the accumulated stress, particularly in the setting of underlying neuropathy, culminates in a stereotypical diabetic forefoot ulcer (the so-called *mal perforans* ulcer). Correction of underlying biomechanical abnormalities and treatment of underlying medical conditions are as important to the overall treatment plan as debridement and wound care are.

The cutaneous innervation of the leg skin must also be taken into account. The nerves to the lower extremity include the common peroneal nerve, the superficial peroneal nerve, the deep peroneal nerve, the sural nerve, the saphenous nerve, and the tibial nerve. The branches in the foot are the medial plantar nerve, the lateral plantar nerve, and the calcaneal branch. The foot is predisposed to neuropathy for unknown reasons, one of which is almost certainly local-regional ischemia. This predisposition is particularly relevant to the pathogenesis of diabetic neuropathic foot ulcers; chronic tissue hyperglycosylation and fibrosis probably play roles as well. The medial and lateral plantar nerves travel through the tarsal tunnel, a tight anatomic space just under the flexor retinaculum. Division and release of the retinaculum serves a purpose analogous to that served by carpal tunnel release in the hand. In diabetic patients with forefoot ulcers, this procedure can reduce ulceration. Although tarsal tunnel release evolved as a means of treating neuropathic foot pain, it has been shown, in properly selected patients, to prevent foot ulceration by restoring foot sensibility.³⁰

A solid grasp of the structural anatomy of the lower-extremity vasculature is, of course, essential for surgeons treating patients with leg ulcers. Perhaps even more important, however, is an understanding of precisely how the various blood vessels are related to one another, as well as to the specific structures and areas that they supply. Such an understanding may be facilitated by

Table 3 Angiosomes (Vascular Territories) of Foot

Artery	Vascular Territory Supplied
Anterior tibial artery	Anterior aspect of lower leg, anterior ankle
Dorsalis pedis artery	Dorsum of foot
Peroneal artery Anterior perforating branch Calcaneal branch	Posterolateral aspect of lower leg Upper portion of lateral ankle Lateral plantar heel
Posterior tibial artery Calcaneal branch	Posteromedial aspect of lower leg Medial heel
Lateral plantar artery	Lateral aspect of plantar foot, plantar forefoot (usually extends to hallux)
Medial plantar artery	Medial instep region between heel and forefoot

viewing the blood supply to the foot and lower leg through the concept of angiosomes—that is, the specific vascular beds supplied by major named arteries. Angiosomes have been well described by Taylor,³¹ and their application to the foot has been advanced by Attinger and associates.^{32,33} The significance of the angiosome concept (which is frequently employed by plastic surgeons but is less familiar to other surgeons) lies in its ability to relate the major nutritive blood vessels to the surface anatomy, to the physical examination, and to the planning of operations. The lower extremity has several angiosomes [see Table 3]. Most of them reach watershed status in the ankle and foot, which explains why most ischemic ulcers occur below the midcalf area.

Although the major leg arteries supply distinct angiosomes of the foot and ankle in a consistent manner [see Figures 1 through 5], they are not immutably segregated from each other and in fact are linked by anatomically reliable connections. The links are the so-called choke vessels, which represent anastomotic connections between adjacent angiosomes. The significance of these choke vessels is twofold: first, they serve as an alternate route of blood flow from one angiosome to another in situations of low or impaired flow (e.g., stenosis), and second, they can be used by the surgeon in designing flaps and predicting healing status. It is important to be aware of these connections when treating a wound that may be burdened by local ischemia. As an example, the heel is supplied by two distinct angiosomes, the calcaneal branch of the posterior tibial artery and that of the peroneal artery, and native anastomoses exist between these two areas. If there is a necrotic wound in the plantar heel, it follows that both vascular trees must be diseased, because if only one were diseased, the native anastomoses between the two angiosomes would prevent the ulcer from forming.³³ As another example, connections normally exist between the anterior perforating branch of the peroneal artery and the anterior tibial artery at the lateral ankle. The astute surgeon can exploit this knowledge to map blood flow to distinct areas of the foot for the purposes of diagnosis and subsequent reconstructive flap design.^{32,33} By alternately compressing flow above and below the arteries, the surgeon can determine whether retrograde blood flow to an adjacent angiosome is occurring (through choke vessels). If it is not, that area should not be used for a distally based flap.

Clinical Evaluation and Investigative Studies

When confronted with a lower-extremity ulcer, the surgeon should proceed with the physical examination in a systematic, goal-directed manner. It is important to recognize those presentations

that call for emergency triage in the operating room. One such surgical emergency is a leg or foot wound that is also acutely ischemic. The priority in this situation is prompt revascularization of the leg. Another emergency is a gangrenous leg or foot wound that has overcome host resistance and is associated with ascending sepsis (often, necrotizing fasciitis). The priority in this situation is urgent debridement of the devitalized and infected tissues; in some cases, emergency guillotine amputation may be required. All other wounds are not emergencies and may be evaluated in a more systematic fashion. Each patient encounter should commence with a vascular examination. Diligent evaluation of the blood supply to the lower

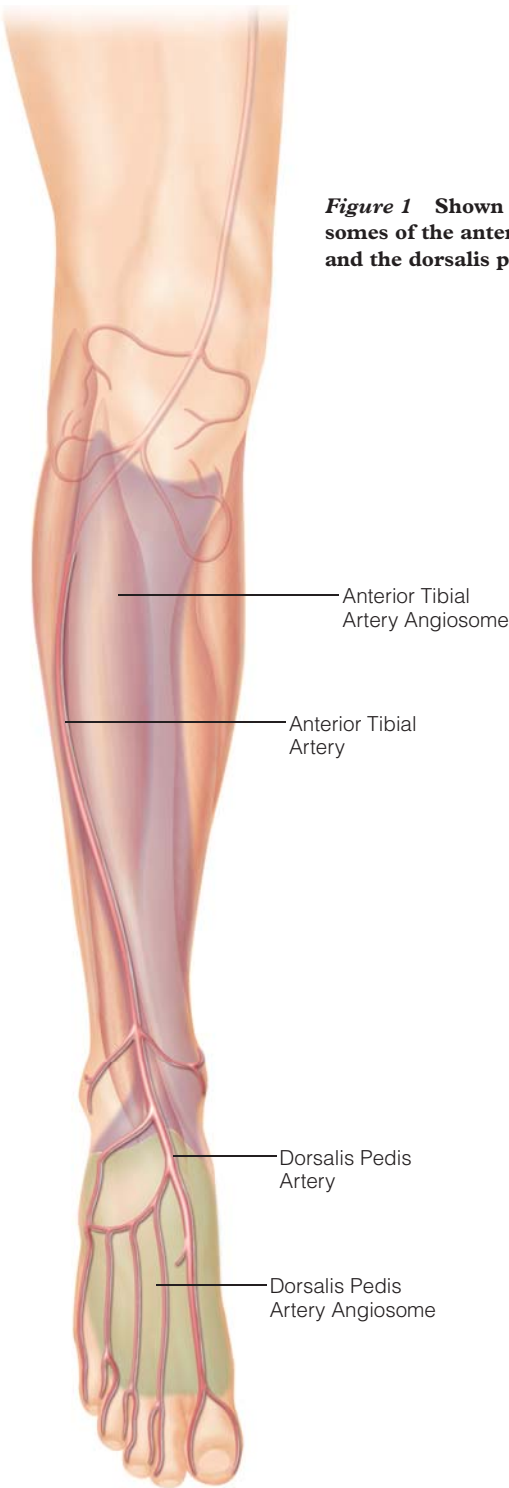


Figure 1 Shown are the angiosomes of the anterior tibial artery and the dorsalis pedis artery.

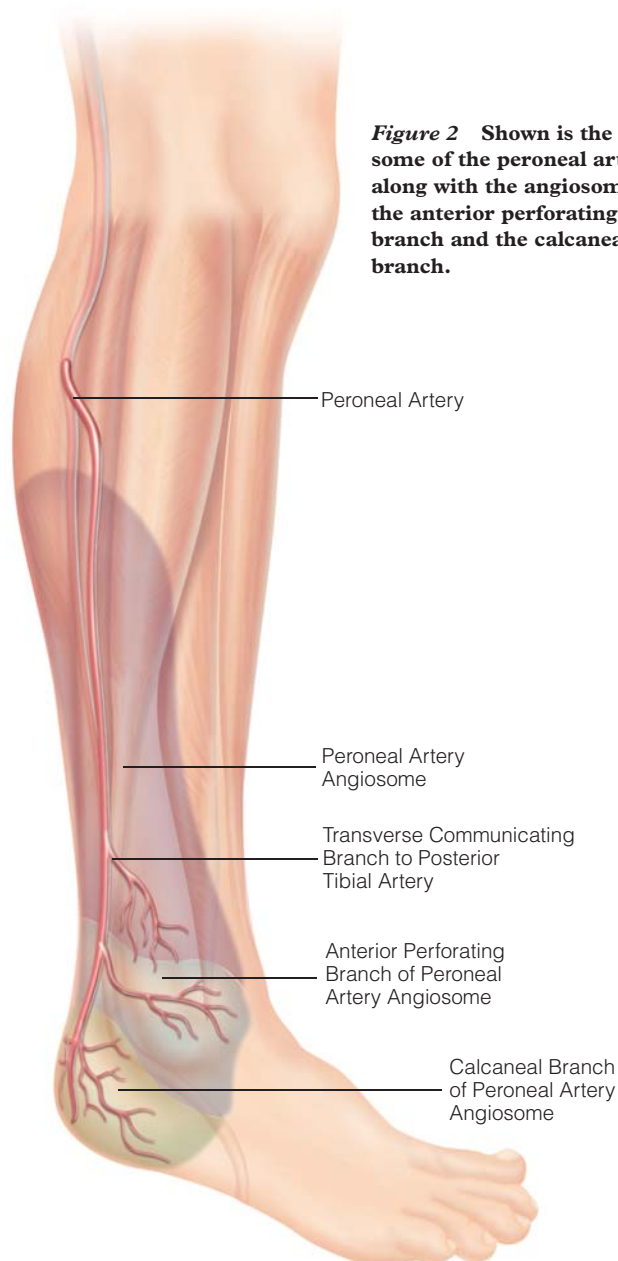


Figure 2 Shown is the angiosome of the peroneal artery, along with the angiosomes of the anterior perforating branch and the calcaneal branch.

blood pressure cuff. As many as 30% to 40% of diabetic leg ulcer patients have falsely elevated ABIs that may mask an ischemic foot. In nondiabetic patients, an ABI lower than 0.5 mandates further imaging to search for possible stenosis or occlusion. In diabetic patients, measurement of the toe-brachial index (TBI) may be more useful.^{36,37} Because toe vessels are less frequently affected by atherosclerotic disease (pedal sparing), toe pressures are a more reliable diagnostic tool in this setting. A value lower than 30 mm Hg is indicative of ischemia.

In addition, measurement of the transcutaneous oxygen tension (P_{tcO_2}) is extremely helpful, particularly for patients with distal foot ulcers that may be prone to impaired oxygenation from local microangiopathy. P_{tcO_2} levels are also useful for evaluating the response to therapy and may help predict healing.^{13,38} Ischemia is present if the P_{tcO_2} is lower than 30 mm Hg.

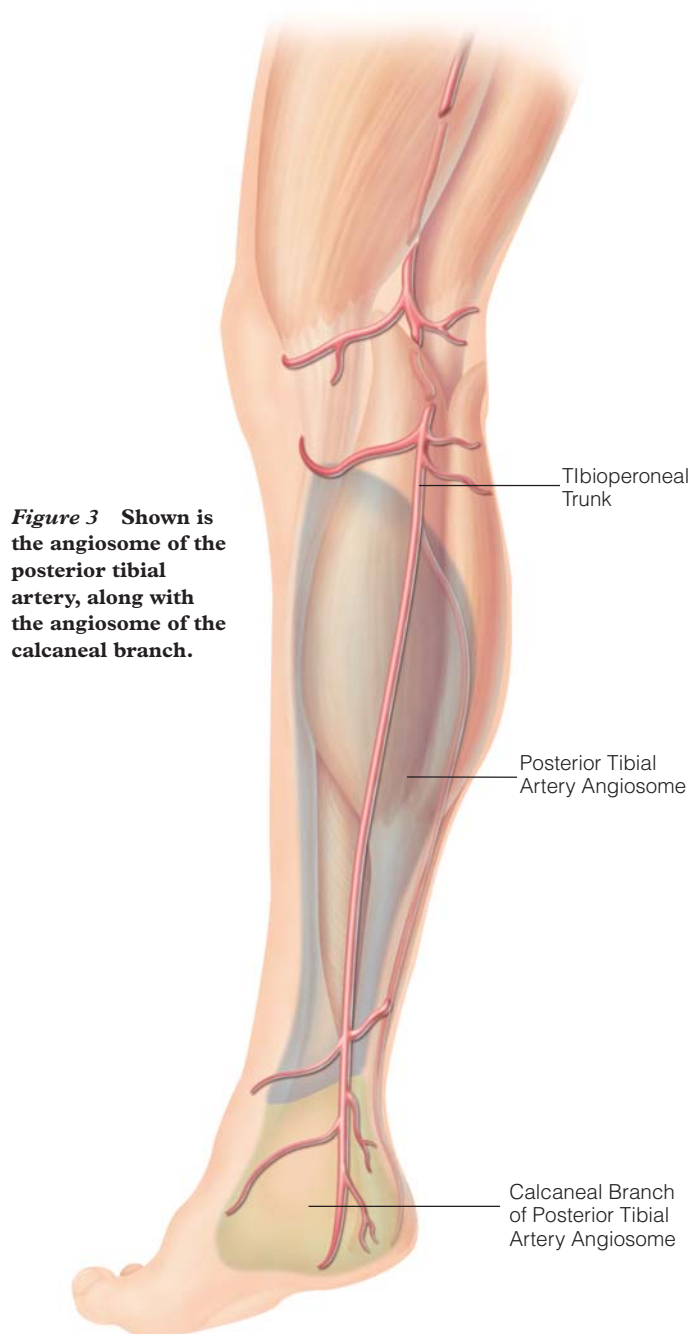


Figure 3 Shown is the angiosome of the posterior tibial artery, along with the angiosome of the calcaneal branch.

extremity is essential in all patients with problem wounds. Comparison to the contralateral leg (if present) can be very useful. The first step is to assess the appearance of the leg, evaluating such data as color, skin texture, swelling, and temperature. Pulses are then palpated, as is capillary refill. If impaired tissue perfusion seems to be a possibility, these examinations should be supplemented with more objective diagnostic studies. As a practical matter, pulses in the foot are notoriously difficult to evaluate: different examiners not infrequently report different findings. Among other variables, the skin in the area may be edematous or fibrotic, hindering assessment. A pulse may appear diminished to one examiner but normal to another. Finally, blood flow may be impaired distal to the ankle, where pulses are typically evaluated. Various modalities are available for diagnosis in this setting; the following are among the more commonly employed and useful ones.^{34,35}

Determination of the ankle-brachial index (ABI) is generally helpful, except in diabetic patients. The reason for the exception is that diabetes is associated with increased calcification of the arterial wall in the calf, which renders the vessel incompressible by the

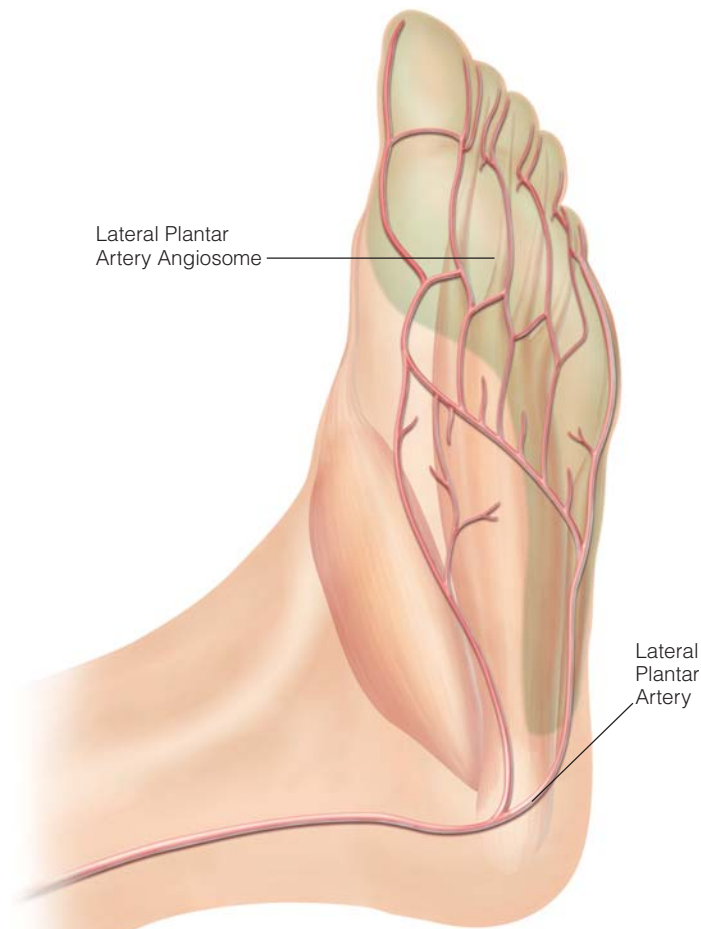


Figure 4 Shown is the angiosome of the lateral plantar artery.

If the quality of the flow is questionable, either a formal noninvasive Doppler evaluation or angiography should be performed. If arterial inflow is found to be inadequate, the patient should be referred to a vascular surgeon—ideally, one who is trained in endovascular techniques and distal revascularizations.

A careful neurologic examination should be done to evaluate sensation and motor function. This is a particularly crucial in the management of a compartment syndrome (whether traumatic or resulting from a vascular accident). In diabetic patients and those with neurologic disorders, the neurologic examination can determine whether neuropathy contributed to the development of the wound. Lack of protective sensation is diagnosed by tonometry: if the patient is unable to feel 10 g of pressure applied by a Semmes-Steinstein 5.07 monofilament, significant sensory loss has occurred. This sensory loss prevents patients from registering skin damage that occurs as a result of excessive local pressure from a prolonged decubitus position; tight shoes, clothes, or dressings; biomechanical abnormalities; or the presence of foreign bodies. In neuropathic patients with biomechanical abnormalities, the repetitive trauma inherent in normal ambulation leads to ulceration as a consequence of the high focal plantar pressures generated during walking.

Management: General Principles

Current surgical education includes little formal training in the proper management of wounds. Accordingly, it is worthwhile to address some of the basic elements of wound care.

PREPARATION OF WOUND FOR HEALING OR RECONSTRUCTION

The first step in wound management is to establish a clean and healthy base. This can be accomplished in a variety of ways. A wound with a heavy eschar and grossly contaminated tissue requires surgical debridement in the OR [see Surgical Treatment, Surgical Debridement, *below*]. A wound with a mild amount of slough may be effectively debrided with an enzymatic dressing or even a water jet device (e.g., Waterpik; Water Pik, Inc., Fort Collins, Colorado). All wounds (except arterial and, usually, vasculitic ulcers) should be debrided down to healthy tissue. This measure resets the clock, so to speak, by effectively converting a chronic wound into an acute one. Because debridement is such a basic step, it tends to be underappreciated, even by surgeons.

There are three components of a leg ulcer that must be removed by means of debridement: (1) biofilm and bacteria, (2) callus, and (3) nonviable tissue.³⁹⁻⁴¹ Whereas the role of bacteria in wound infections has long been recognized, it is only comparatively recently that the contributions of biofilm to wound chronicity have come to be appreciated.^{10,42} Biofilm consists of a sessile community of multiple bacteria species encased by a protective carbohydrate-rich polymeric matrix that is resistant to antimicrobial and immune cell penetration.⁴³ Most wounds are in fact colonized by bacteria that set up residence in a biofilm. Unfortunately, biofilm is exceedingly tenacious and readily reaccumulates after debridement. Thus, proper dressing care consists of dressings that both treat the wound and minimize biofilm accumulation.

Bacteria, whether free-floating or (more commonly) incorporated within a biofilm, are extremely detrimental to wound healing,

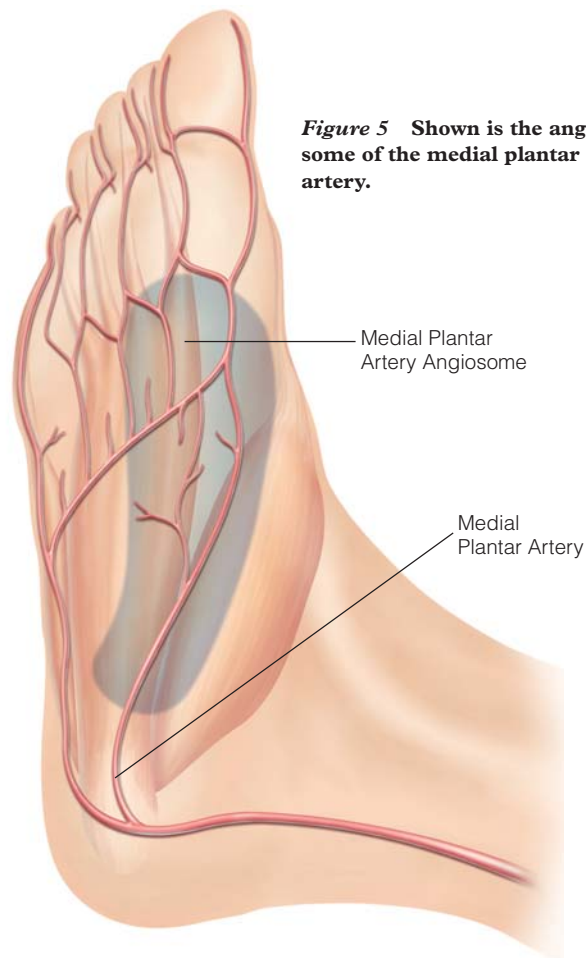
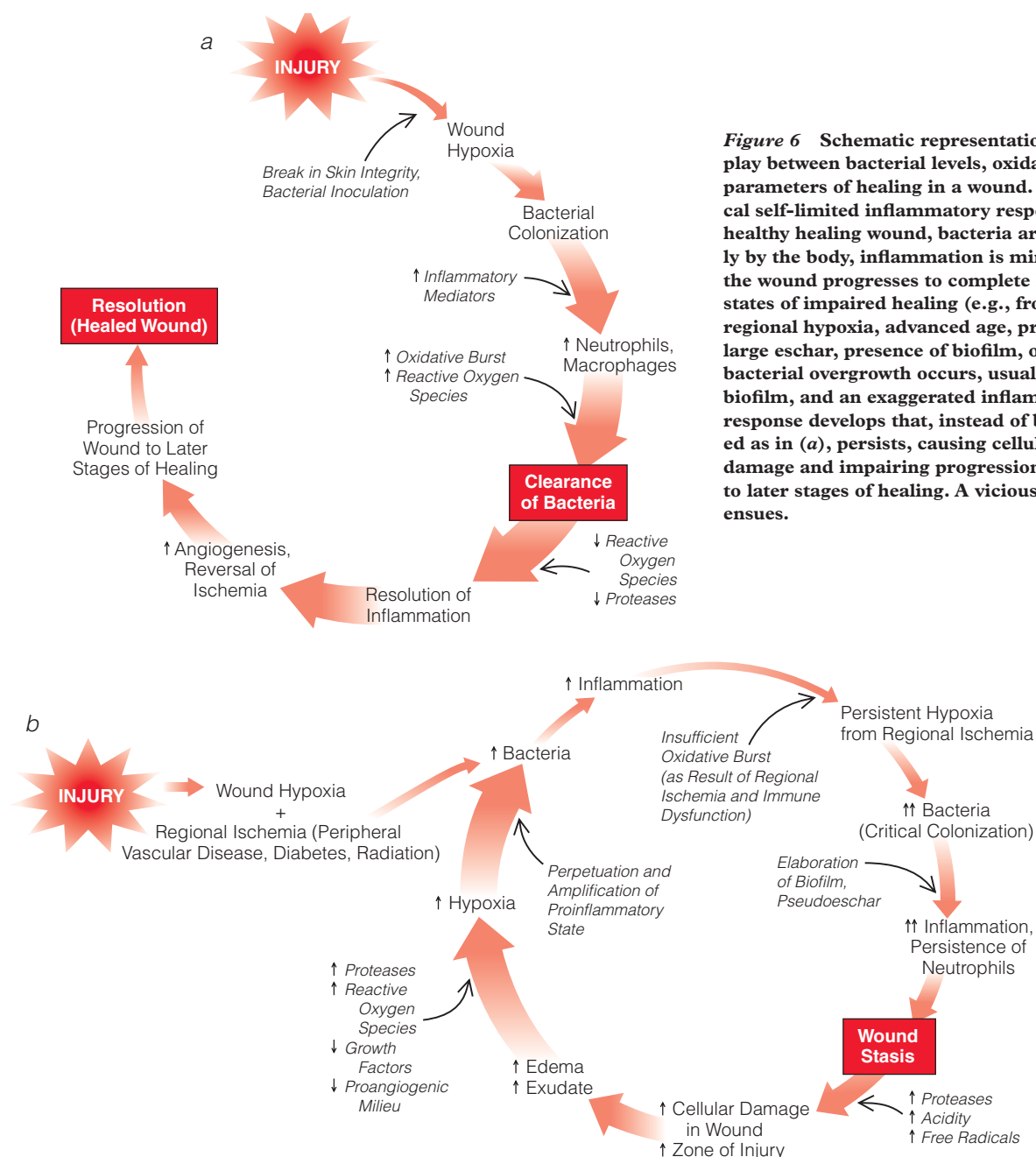


Figure 5 Shown is the angiosome of the medial plantar artery.



particularly when they reach the level of critical colonization.⁴⁴ Wounds may be classified as contaminated, colonized, critically colonized, or infected.⁴⁵ These classifications are useful in that they detail the relation between the bacteria and the patient (or host) and define the level of bioburden (i.e., the cost exacted by bacteria from the resources of the wound and the patient). All wounds are contaminated to some degree, either by skin flora or by environmental pathogens. It is likely that this level of bacterial contamination stimulates wound repair mechanisms by upregulating the inflammatory response. When the contaminating bacteria begin to proliferate, the wound is said to be colonized; however, there is still no overt reaction by the host at this point. When the proliferating bacteria begin to overcome host responses, the wound is said to be critically colonized. Finally, when the wound provokes an inflammatory reaction by the host to the proliferating bacteria, the wound is said to be infected. It is important to keep in mind that the host's inflammatory reaction can contribute as much to a wound's failure to heal as the bacteria themselves do [see Figure 6].^{2,46} Judicious

use of antibiotics, adequate debridement, and proper dressing choices can decrease bacterial numbers and reduce the competition for nutrients and resources occurring in wounds contaminated by bacteria.⁴⁴ As noted (see above), because most leg wounds are found in ischemic, aged tissue beds, reduction of the bioburden can enable healing by restoring the balance between bacterial numbers and the nutrients available to healing cells.

Callus is formed in response to repetitive high pressure, usually over bony prominences on the foot. Once formed, it can further concentrate and propagate this excessive pressure on the underlying tissues. In addition, the grossly hyperkeratotic skin can act as a functional barrier to dressings and to migrating healthy keratinocytes. Therefore, callus should be removed whenever present. This can be done with a sharp, heavy scissors or a No. 10 blade; anesthesia is not required.

Nonviable tissue plays no necessary role in ulcer healing. The old paradigm of allowing wounds to heal under an eschar is obsolete, and the importance of moist healing is now appreciated.

AMOUNT OF EXUDATE	TYPE OF DRESSING
None or Minimal	Film, Hydrogel
Mild	Hydrocolloid
Moderate	Alginate
Large	Foam, Other
Copious	NPWT

Figure 7 The type of dressing used for a wound is influenced by the amount of exudate present.

Eschars are nature’s biologic dressings, but in the settings of ischemia, diabetes, and certain other diseases, they can give rise to an excessively proinflammatory state characterized by high levels of free radicals and proteases.^{47,48} This proinflammatory state is hostile to healing, propagates cellular damage, and competes with host cells for scarce resources. Therefore, all eschar and nonviable tissues should be removed.

DRESSINGS AND ADJUNCTS TO HEALING

There are literally thousands of dressings on the market. The vast majority of these products have not yet been proved superior to gauze by well-designed, randomized, prospective, controlled clinical trials. This is not to say that they are useless; rather, it is to remind practitioners that there are intense commercial and clinical needs driving the marketing of wound dressings and that claims of efficacy should therefore be taken with a grain of salt. Most wounds will heal, even if the dressing does not have the efficacy claimed. The main goal of a dressing should be maintenance of a moisture level optimized to facilitate wound healing and encourage autolytic debridement.⁴⁹ Other goals include coverage of the wound (to prevent soilage) and delivery of antimicrobial agents (e.g., silver ions and cadexomer iodine). It is important to use the proper dressing for a given wound [see Figure 7]: if the wound dries out, the healing cells may die, and if it is too moist, bacterial overgrowth and skin maceration may result.

Autolytic debridement consists of facilitating the body’s removal of dead tissue and cells by providing an optimal (usually moist) wound environment. If a proinflammatory eschar is prevented from forming (by preventing biofilm accumulation and minimizing slough buildup and desiccation), the body’s own phagocytic mechanisms will gradually remove the impediments to healing. Wound healing will then follow a normal trajectory. Film dressings, hydrogels, and other moist products may be used to accomplish autolytic debridement.

A particularly effective debridement method that is enjoying a resurgence in popularity is the use of maggots.^{50,51} Because of the strong propensity of these organisms for ingesting dead tissue, this form of debridement is extremely selective. The maggots are placed on the wound and contained within the wound’s confines with net gauze; every 2 to 3 days, they are changed. Although maggots cause considerable social discomfort among caregivers, they are actually a very good option for wound bed preparation in patients with severe comorbid conditions, and in most cases, they are remarkably well tolerated. Candidates for maggot debridement include patients with severe limb ischemia who are not candidates

for surgery or anesthesia or whose wounds might be exacerbated by surgical trauma (e.g., patients with infected wounds and critical limb ischemia).

Enzymatic debridement employs proteolytic agents to break up the proteinaceous debris that accumulates within the wound. These agents are efficacious in breaking up limited amounts of necrotic tissue but do not penetrate eschar very well. Some tenderness is associated with their use.

The role of ultrasonography in wound debridement is being actively investigated. Currently, the MIST Therapy System (Celleration, Inc., Eden Prairie, Minnesota) is approved and reimbursed as a noninvasive debridement device.^{52,53} Although the mechanism of action is still not fully known, it is likely that the device works by breaking up biofilm; it may also have other cellular effects, such as stimulation of blood flow and direct cell stimulation.

Negative-pressure wound therapy (NPWT) is an important addition to the surgeon’s armamentarium. It acts to encourage granulation tissue ingrowth through multiple mechanisms—in particular, edema reduction, mechanotransduction, and removal of proteases.^{54,55} NPWT must be employed properly: it should ideally be applied to relatively clean wounds, should be applied very cautiously to ischemic wounds, and should not be applied at all to wounds with known malignancies. It is useful in converting emergency wounds for which flap coverage is required into wounds that can be treated more simply. Care must be taken not to overuse or misuse NPWT. For example, it should rarely be used before the wound is completely closed. At some point, the wound will be small enough that it either can heal with simpler, less expensive dressing changes or can be closed primarily or with a simple skin graft.

Hyperbaric oxygen (HBO) is a useful, albeit often maligned, wound care modality. The lingering suspicion surrounding its use today results not from lack of utility but from inappropriate use in the past. The benefits of HBO include improved cellular oxygen delivery, maintenance of cellular metabolism through preservation of cellular adenosine triphosphate (ATP) levels, increased angiogenesis, reduced oxidative stress from persistent ischemia, increased perfusion, increased collagen synthesis and fibroblast function, and reduced infection.⁵⁶ It is likely to be of particular value in patients with irradiated ulcers or diabetic feet. Broadly speaking, HBO will be useful if an increase in tissue P_{iO_2} can be demonstrated when the patient is given supplemental oxygen^{57–59}; typically, an increase of 10 mm Hg suggests that HBO may be worth trying. HBO does require a facility with dedicated staff, and there are risks associated with its use, some of them life-threatening.

Another option is a tissue-engineered dressing, such as Apligraf (Organogenesis Inc., Canton, Massachusetts), which is a cultured bilayered dressing of human foreskin-derived fibroblasts and keratinocytes grown on a bovine collagen matrix.⁶⁰ Because the cells are not autologous, they are not ultimately incorporated into the wound but may persist within it for several weeks. Like the cells in a skin graft, the cells in Apligraf appear to produce a panoply of growth factors, which accounts for the efficacy of this dressing in ulcer care. In addition, Apligraf is easy to apply. Apligraf is approved for use in both diabetic foot ulcers and venous stasis ulcers, and it is widely used off label in other types of wounds.^{61,62} Another useful tissue-engineered dressing is Integra Bilayer Matrix Wound Dressing (Integra, Plainsboro, New Jersey), an acellular scaffold of glycosaminoglycans and collagen. Integra serves as a three-dimensional matrix within which cellular ingrowth takes place, and it eventually becomes completely incorporated within a wound or defect; once incorporated, it is covered with a thin auto-

logous skin graft. Integra may be used to resurface exposed bone, tendon, and orthopedic hardware, and in some case, it may render a flap procedure unnecessary.⁶³ One caveat to the use of tissue-engineered dressings is that they must be applied only to wounds that are free of infection or significant bacterial colonization. Another drawback is that they are expensive and thus must be used strategically.

SURGICAL TREATMENT

Surgical Debridement

Debridement is not always a surgical procedure. In fact, the majority of leg ulcers can be effectively managed with nonsurgical debridement, typically in the form of dressing changes or wound ointments that encourage the body to heal (see above).

Often, however, surgical debridement is the best option. It is extremely effective, but it is also the most invasive type of debridement, the most likely to cause bleeding, and the most painful (except when done in an insensate foot, such as that of a diabetic patient). Whether performed in the OR or in the clinic, the goal of debridement is to remove all nonviable, infected tissue and reach bleeding tissue or viable fat, tendon, or fascia. The benefits of a well-performed debridement are tremendous, including excision of callus (which augments pressure during ambulation), removal of biofilm and necrotic tissue (which amplifies the inflammatory host response and competes with the healing tissue for oxygen and nutrients),⁴⁴ conversion of a chronic wound to an “acute” wound, stimulation of cell proliferation (by injuring healthy cells and releasing growth factors into the wound environment), and ridding the wound bed of senescent cells and chronic wound fluid (which has been demonstrated to contain growth factor–neutralizing proteases).^{64,65}

A novel form of surgical debridement is hydrosurgery (VersaJet; Smith & Nephew, Hull, United Kingdom), which involves using a “water knife” for selective removal of infected or devitalized tissue.⁶⁶ It is expensive, but its benefits are formidable, and it is likely to see expanded use in the future.

Reconstruction with Grafts or Flaps

The optimal closure technique for a given wound depends as much on the wound type as on the patient. In evaluating different reconstructive options, plastic surgeons often rely on the concept of a reconstructive ladder (or elevator). In general, the simpler or less invasive techniques are considered first (representing the lowest rungs on the ladder). If simpler techniques prove unsuitable or inadequate, decision-making proceeds to consider increasingly complex and morbid options (successively higher rungs), culminating in microvascular free flaps or transfers (the top rung). As may be apparent, this schema is simplistic and does not always apply to the lower extremity, where often the first choice (or the only real choice) is a complex free flap. The concept of the reconstructive elevator is more useful in the leg, where the surgeon can directly choose the option best suited for a particular wound or defect.⁶⁷

Skin grafts are often used to close shallow wounds or wounds in the non–pressure-bearing instep of the foot. If a decision is made to close a foot or leg wound surgically, several principles should be kept in mind. The main one is that the simplest solution is usually, but not always, the best. It is important to leave room for creativity in the use of flaps. There are numerous different local flaps that are extremely useful (see below). Most wounds do not require microsurgical flaps, but occasional ones do benefit from microsurgery. There are also important issues related to orthopedic

management of foot wounds, particularly in diabetic patients, that must be taken into account.

Three main types of flaps are employed in the lower extremity: local random-pattern flaps, local pedicled flaps, and free tissue transfers [see 3:3 *Open Wound Requiring Reconstruction* and 3:7 *Surface Reconstruction Procedures*].

Local random-pattern flaps Local random-pattern flaps include such flaps as Z-plasties, advancement flaps (e.g., V-Y), rotation flaps, and transposition flaps.²⁴ These are extremely useful for closing small defects of the foot. One limitation to their use is the tautness of the skin in this area, which limits flap mobility. With imaginative design and careful execution, local random-pattern flaps can be employed for any small foot wound.

Local pedicled flaps Local pedicled flaps are employed for coverage in both the leg and the foot, especially for closure of larger foot wounds and deeper wounds that expose bone, capsule, or hardware. They are reliably based on axial vessels, typically branches of angiosomes. The following are among the more commonly used local pedicled flaps.^{68,69}

1. **Gastrocnemius flap.** This flap is used to cover proximal defects in the knee and the proximal third of the leg. As a rule, half the muscle is used. The medial gastrocnemius is generally preferred unless the wound or defect is laterally based.
2. **Soleus flap.** This flap (preferably from the medial portion of the muscle) is used for coverage of deep wounds in the middle third of the leg.
3. **Reverse sural fasciocutaneous flap.** This flap is an option for defects of the lower leg and ankle.⁷⁰ A delayed procedure is prudent in patients with impaired or uncertain vascular status or comorbid conditions (e.g., diabetes or renal failure).⁷¹ Some surgeons will not use a reverse sural flap, because the donor site in the proximal calf must be covered with a skin graft, which could hinder the wearing of a prosthesis if a below-the-knee amputation proves necessary. This limitation can, however, be addressed by using an anteriorly based skin flap for the amputation to cover the calf muscles. The reverse sural flap is an extremely versatile one that usually covers heel defects well, particularly in patients with tenuous vascular inflow, without requiring microsurgical skills or facilities.
4. **Other flaps for the leg.** Other options in the leg include wide-based adipofascial flaps that can be rotated to cover a defect and skin grafted to achieve cutaneous coverage.^{72,73} These do not have a reliable axial blood supply, particularly in patients with vascular disease⁷⁴; they mostly have a random pattern of blood flow.
5. **Medial plantar flap.**⁷⁵ This flap is particularly well suited to coverage of calcaneal defects. It brings thick, glabrous skin that will resist breakdown and the shearing forces affecting the heel. If the medial plantar nerve is incorporated, the flap will be sensate. The medial plantar flap can also be advanced distally into the forefoot if necessary, typically in the form of a V-Y advancement flap.
6. **Abductor digiti minimi flap.**⁶⁹ This flap is best used for small defects of the lateral ankle and heel, particularly wound dehiscences after orthopedic procedures. It is dissected in a distal-to-proximal direction and transposed to cover proximal defects. The donor site is closed primarily and requires a skin graft for coverage.
7. **Abductor hallucis brevis flap.** With this flap, as with the abductor digiti minimi flap, the dominant arterial pedicle is situated

rather proximally, allowing the distal abductor hallucis brevis to be dissected completely free and rotated to cover defects of the medial heel and ankle. Again, a skin graft is required for coverage of the donor site.

8. Extensor digitorum brevis flap. This flap is a multipennate flap consisting of several slips of muscle that inserts via tendons on the second through fifth toes. It is used for coverage of dorsal foot and ankle defects.

Other useful muscle flaps include the flexor digitorum brevis flap (for heel defects) and the flexor digiti minimi musculocutaneous flap.

Free tissue transfers The rich variety of flaps available for coverage of leg and foot wounds has led to a decline in the use of microsurgical free flaps in the lower extremity. The development of NPWT has also contributed to the declining need for free flaps, in that many wounds are currently being downstaged with NPWT to enable eventual closure with a technique farther down the reconstructive ladder. Nevertheless, there remain certain wounds in all areas of the leg and foot for which free flaps may still be useful or even preferable, such as large defects and wounds characterized by significant exposure of bone or hardware. Flow-through free flaps are also commonly used to achieve revascularization and wound coverage simultaneously. Occasionally, free flaps are used for wounds with venous insufficiency or lymphedema in an attempt to improve these conditions by restoring lymphatic channels or competent venous drainage. The free flaps used in the lower extremity may be either fasciocutaneous or muscle flaps. Most studies have not found either type of flap to be superior to the other for treatment of areas of infection. In general, however, fasciocutaneous flaps are preferred for wounds on the sole of the foot, which are exposed to pressure and shearing forces, whereas muscle flaps are preferred for deep wounds.

Amputation

On occasion, amputation proves necessary [see 6:20 *Lower-Extremity Amputation for Ischemia*].⁷⁶ Factors such as advanced age, uncontrolled diabetes, sepsis and gangrene, unreconstructable blood vessels, and renal failure are all associated with a higher risk of amputation. Nevertheless, a focused, multidisciplinary approach to wound care should be able to reduce amputation levels substantially and achieve limb salvage rates higher than 90%. Overall, the most frequently performed amputations are toetip amputations. Of these procedures, the most common is amputation of the tip of the great toe. This operation is done to treat the claw-type deformity seen in diabetic patients with an intrinsic-minus foot, whereby the toe becomes permanently flexed as a result of the pull of the flexor hallucis longus tendon. The tip amputation may have to be closed with a fishmouth-type incision or a V-Y advancement flap from the plantar surface. In addition, it may be necessary to advance the flexor hallucis longus tendon and perform a volar capsular release to minimize recurrence.

Amputations of the toe rays are frequently performed, most commonly in diabetic patients but also in patients with osteomyelitis of the metatarsal heads. Rebalancing the pull of the extrinsic tendons is crucial for preventing redistribution of the maladaptive forces to adjacent rays and subsequent propagation of serial ulcers in these areas. Therefore, the peroneus brevis and tibialis anterior insertions should be reattached to the cuboid or the cuneiform for proximal fifth and first ray amputations, respectively.²⁴

Most amputations of the foot are performed at the transmetatarsal level. Transmetatarsal amputation is a very useful pro-

cedure that preserves as much of the foot's length as possible while also maintaining a well-balanced walking surface with thick plantar skin. Fundamentally, it is a reconstructive procedure: the vascular supply to both the plantar and the dorsal flap must be ensured prior to closure, and the balance of the foot tendons must be addressed.⁷⁶ The plantar metatarsal arteries, which supply the plantar flap, must be kept intact by avoiding excessive undermining or indiscriminate use of the electrocautery. If the flap appears compromised after closure, the flap sutures should be released, and completion of the flap procedure should be delayed for several days to encourage increased neovascularization. NPWT may be used as a temporizing measure to bridge the wound before formal closure. After a transmetatarsal amputation, the triceps surae may be lengthened to compensate for the loss of ankle dorsiflexion that results from removal of the attachment points to the toe extensor tendons.²⁴

Management of Specific Types of Lower-Extremity Ulcer

In the early stages of management, it is important to focus on the patient's overall health status, with a particular emphasis on the presence or absence of sepsis. It is also vital to determine whether adequate vascularity is present to enable healing. Most wounds benefit from debridement, whether biologic (i.e., dressings and wound care) or surgical. At the same time, normalization of systemic derangements is undertaken. A decision is made whether to treat the wound surgically. In most instances, this does not have to be done right away. Surgical wound closure, when feasible, is best done after a period of optimization.

In addition to these considerations, which are common to all leg ulcers, there are aspects of care that are specific for different ulcer types. Accordingly, in what follows, I focus on specific care of the most prevalent types of leg ulcer—namely, those resulting from arterial insufficiency, those associated with diabetic neuropathy, those resulting from venous stasis, and those of inflammatory origin.

ULCERS RESULTING FROM ARTERIAL INSUFFICIENCY

Most arterial leg ulcers occur in the elderly. A nonhealing ulcer is one of the most common presentations of peripheral vascular disease, the incidence of which is highest in men older than 45 years and women older than 55 years. Modifiable risk factors for peripheral vascular disease include smoking, hyperlipidemia, hypertension, diabetes, and obesity.

In most instances, the diagnosis is suggested by the physical examination. Arterial leg ulcers generally occur in a stereotypical distribution that is well explained by the angiosome concept mentioned earlier [see *Anatomic Considerations, above*], most commonly developing over the toes, heels, and bony prominences of the foot. It is worth noting that a heel ulcer typically results if there is disease in the distributions of both the peroneal artery and the posterior tibial artery, as a consequence of the dual blood supply to the posterior heel from these vascular territories.³³ Ulcers in the toes result from the diminished distribution of blood to these terminal vascular beds. An ulcer in the setting of arterial insufficiency is a symptom of the decreased blood flow and may be associated with rest pain or claudication. The metabolic demands of intact skin are less than those of an open wound, but even so, the impaired blood flow renders the skin thin, atrophic, hairless, and dry in the affected extremity. Patients usually experience significant pain, which is relieved by dangling the leg over the bed at night. The ulcer has a sharply demarcated appearance, with a paucity of granulation tissue. The wound bed is pale or pink and typically

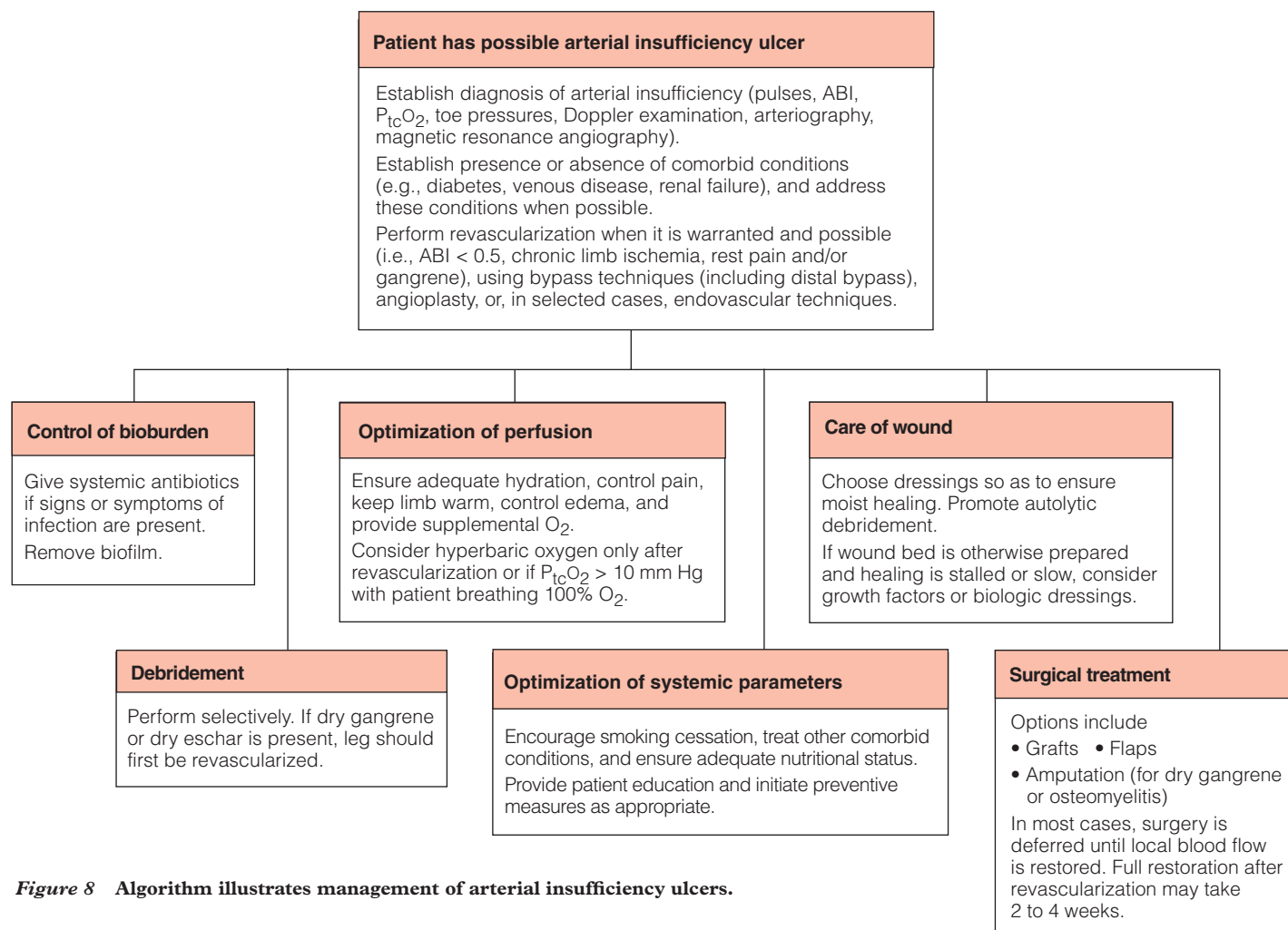


Figure 8 Algorithm illustrates management of arterial insufficiency ulcers.

lacks the red color associated with a hypervascular healing bed. Pulses are usually diminished. Any patient with decreased pulses at the ankle (signaling insufficiency of the dorsalis pedis, the posterior tibial artery, or both) should be referred for vascular studies. In practice, given the wide interindividual variation in the ability to palpate a pulse accurately, it is advisable to set a fairly low threshold for obtaining studies such as an ABI or a TBI. In general, arterial leg ulcer patients with an ABI lower than 0.9 or higher than 1.2 or with a P_{tc}O₂ lower than 30 mm Hg should be referred to a vascular surgeon.

Quite often, the etiology of an arterial leg ulcer is not purely ischemic but includes contributions from other conditions, such as diabetes, venous insufficiency, neuropathy, and renal failure. These ulcers of mixed etiology are particularly challenging to treat, and it is all too common to find a supposedly chronic wound whose chronicity actually resulted from an earlier failure to establish the leg's vascular status.

At the cellular level, the cause of an arterial ulcer goes beyond the simple lack of sufficient oxygen supply to a cell. For example, it is known that sublethal ischemia is much more detrimental to aged cells and diabetic cells than to young cells.^{77,78} Lack of ATP and inadequate clearance of metabolites result in poor healing and aberrant inflammation. Because healing is an anabolic process, much more energy is needed for healing than for tissue maintenance and homeostasis. The persistence of noxious metabolic byproducts that are not cleared by the circulation may be a cause of the pain commonly associated with these wounds.⁷⁹

At the tissue level, chronic regional ischemia results in atrophic changes to the skin and soft tissues. The terminal nature of the vascular tree in the foot, with the distal foot and toes being less well perfused than the calf and thigh, along with the effects of gravity and the rigors of ambulation, means that these downstream areas bear the brunt of the effects of upstream atherosclerosis. In the setting of a minor injury, the atrophic skin is more liable to progress to a full-thickness injury in the distal foot and toes than in more proximal locations and, indeed, is more likely to tear in the first place. As mentioned (see above), synthesis of new tissues and deposition of matrices and collagen, along with collagen crosslinking, are necessary for ulcer healing. These are all rate-dependent processes, with oxygen being the necessary variable. Unfortunately, the impaired tissue perfusion means that the ulcer bed will not receive an adequate supply of oxygen and nutrients to support tissue growth. In addition, because oxygen is necessary for the neutrophil burst, arterial ulcers are especially predisposed to infection.¹¹

These considerations help explain the typical appearance of ulcers resulting from arterial insufficiency: the sharply demarcated boundaries (attributable to the "on/off" borders between the defect and unwounded skin, with a minimal healing interface); the dry wound beds, with minimal transudate and exudate; the pale granulation tissue, indicative of a hypovascular state; the changes in the appearance of the surrounding skin (see above); and the reduced capillary refill time.

In the treatment of a wound with an arterial component [see Figure 8], the *sine qua non* is revascularization: a wound typically

will not heal if the leg’s blood supply is not improved.¹¹ Therefore, the urgent decision to be made at this point is whether revascularization is feasible. It should be kept in mind that the decision as to whether an extremity is a candidate for revascularization should be made only by a vascular specialist who is comfortable with or has access to newer modalities and procedures (e.g., distal bypasses and endovascular techniques). Noninvasive means of revascularization are useful in high-risk patients.

After revascularization, there is a lag phase before the ischemia is reversed in the distal leg and foot. Typically, a rise in P_{iO_2} is seen 1 to 2 weeks after surgical revascularization and is delayed after angioplasty.¹⁵ In patients with foot ulcers, foot pulses must be restored if the ulcers are to heal. The wound must be managed during the weeks after revascularization, and indeed for months to years afterward. It should be noted that techniques associated with lower long-term patency rates can nevertheless be useful if they enable healing of an open wound or amputation site. Once the ulcer is healed, the likelihood that a new wound will develop in the area diminishes (because of the lower energy requirements of healed skin in comparison with those of a healing wound).

Any significant comorbid conditions, such as diabetes or venous stasis disease (see below), should be addressed. Steps must also be taken to prevent or control infection, which can cause rapid deterioration in an arterial ulcer. If signs of local or systemic infection are noted, treatment with systemic antibiotics should be initiated promptly. Unless grossly infected tissue (e.g., wet gangrene) is present, it is best to defer debridement until the vascularity of the area is ensured: debridement while the blood flow to the area is still impaired may promote further ischemia and lead to the formation of a larger ulcer.¹¹ Dressings applied to ischemic ulcers typically must have moisture added in the form of hydrogels as the hypovascular wound bed desiccates. An enzymatic dressing can also be useful for gentle debridement of nonviable tissue. Systemic factors (e.g., global hypoxia, enhancement of cardiac output, pain control, and warmth) are important as well. In patients who respond to an oxygen challenge, HBO should be considered and offered if available; however, it should not be employed in place of surgical revascularization if the latter is an option.

Final surgical treatment, in the form of flaps or skin grafts, is deferred until blood flow is ensured. Occasionally, it is possible to perform what is termed extended limb salvage, wherein a bypass graft to the leg is performed at the same time that a microvascular free flap is used to cover a large defect.^{80–82} With advances in wound care products and the introduction of NPWT, however, most procedures can be staged. Flap procedures are typically undertaken after a period of days to weeks, once the oxygen supply is restored.

These patients are nevertheless at high risk for amputation, typically as a consequence of progressive atherosclerotic disease. Patients with unreconstructable peripheral vascular disease (particularly common in the setting of renal failure) or extensive tissue loss or gangrene usually require a major amputation. Even after the amputation, attention must be paid to the vascular status of the amputation site. If the blood flow to the skin has not been ensured, the amputation incision will be prone to breakdown and necrosis. In fact, as many as 25% of patients who undergo surgical revascularization experience a postoperative wound complication in the surgical incision. This finding underscores the points that a revascularized limb usually is still ischemic and that the surgical procedure must be done meticulously and with careful handling of soft tissue. Application of the angiosome concept can be extremely useful for determining the optimal amputation level and assessing the potential for healing.³²

DIABETIC ULCERS

There is a growing tendency to misapply the term diabetic foot ulcer. Many practitioners use this term to describe any wound that occurs in the leg of a diabetic patient, but strictly speaking, it refers only to a neuropathic plantar ulcer that originally results from pressure necrosis. Diabetic patients also have ischemic wounds and venous insufficiency ulcers, but these lesions are not true diabetic foot ulcers. It is important to keep in mind that diabetic foot ulcers may have several different presentations. For example, some are due solely to neuropathy, whereas others are due to ischemia in conjunction with neuropathy. Diagnosing a diabetic foot ulcer is straightforward; however, evaluating the vascular supply to the foot and determining how much neuropathy and functional microangiopathy contribute to the wound’s failure to heal are not always so straightforward. Evaluation of the diabetic foot is addressed in greater detail elsewhere [see 6:7 *Diabetic Foot*].

Currently, two diabetic foot ulcer classification systems are widely used, the Wagner system and the University of Texas (UT) system [see Table 4].^{83–85} At present, the UT system appears to be a better predictor of ultimate wound and foot outcome⁸⁶ and is more widely used in wound centers. A major shortcoming of the Wagner system is that the presence of ischemia is not a part of early-stage ulcers.

The pathology of diabetic foot ulceration is multifactorial. Chronic hyperglycemia leads to advanced glycosylation end products and crosslinking of proteins, eventually resulting in foreshortening of tendons. Relative ischemia (particularly in the vasa vasorum), coupled with the glycosylated protein buildup, leads to sensory and autonomic neuropathy. The autonomic neuropathy leads to anhidrosis and ultimately to fissuring, which affords bacteria a means of entry through the skin. In addition, it leads to hyperkeratosis, which increases the pressure over pressure points and

Table 4 Staging Systems for Diabetic Foot Ulcer

Wagner classification system	Grade 0: impending skin lesion, presence of predisposing bony deformity, or healed ulcer
	Grade 1: superficial skin ulcer that does not involve subcutis
	Grade 2: full-thickness ulcer that exposes bone, tendon, ligaments, or joint capsule
	Grade 3: full-thickness ulcer with presence of osteitis, osteomyelitis, or abscess
	Grade 4: gangrenous digit
	Grade 5: gangrene severe enough to necessitate foot amputation
University of Texas diabetic foot wound classification system	Grade I-A: noninfected, nonischemic superficial ulceration
	Grade I-B: infected, nonischemic superficial ulceration
	Grade I-C: ischemic, noninfected superficial ulceration
	Grade I-D: ischemic and infected superficial ulceration
	Grade II-A: noninfected, nonischemic ulcer that penetrates to capsule or bone
	Grade II-B: infected, nonischemic ulcer that penetrates to capsule or bone
	Grade II-C: ischemic, noninfected ulcer that penetrates to capsule or bone
	Grade II-D: ischemic and infected ulcer that penetrates to capsule or bone
	Grade III-A: noninfected, nonischemic ulcer that penetrates to bone or deep abscess
	Grade III-B: infected, nonischemic ulcer that penetrates to bone or deep abscess
	Grade III-C: ischemic, noninfected ulcer that penetrates to bone or deep abscess
	Grade III-D: ischemic and infected ulcer that penetrates to bone or deep abscess

reduces sensation in a foot already afflicted by sensory compromise. The tibial nerves may also be compressed.

The immune response is altered in diabetic patients. In particular, granulocyte function is impaired, and surgical debridements and advanced dressings are often required to minimize the effects of this deficiency. Moreover, signs and symptoms of infection are notoriously inaccurate and masked in this setting.

Blood flow is typically impaired in diabetic patients. The impairment usually develops at the macrovascular level as the result of accelerated atherosclerosis in the infrapopliteal area (in contrast to the peripheral vascular disease seen in nondiabetic patients, which mostly affects vessels in the thigh). This process underlies the phenomenon of pedal sparing, whereby the vessels in the foot and the ankle may be free of disease even though the more proximal vessels are not. Pedal sparing makes pedal bypasses and lower-leg bypasses possible, and therefore, revascularization is a mainstay of therapy for an ischemic diabetic foot. For years, many practitioners adhered to the concept of diabetic microvascular disease,⁸⁷ which suggested that performing revascularizations in diabetic patients was futile. This concept was based on anatomic studies that were later shown to be inaccurate.⁸⁸ It would be a mistake, however, to maintain that there is no microangiopathy in diabetic patients. In poorly controlled diabetic patients, a functional microangiopathy probably does exist, particularly in regard to ischemia-mediated angiogenesis.^{2,88,89} Indeed, numerous preclinical studies have demonstrated decreased growth factor expression in diabetic healing models. Accordingly, administration of growth factors (e.g., becaplermin) may be useful, provided that the other components of diabetic foot disease are being adequately addressed.⁹⁰

The so-called Charcot foot is the stereotypical end result of the decreased extensibility of the foot tendons (see above). The reduction in extensibility gives rise to a claw-type foot deformity, which causes the normal gait pattern and frequency to change in such a way as to redistribute the forces affecting the foot, usually leading to increased pressure over the metatarsal heads.⁹¹⁻⁹³ Given that the average ambulatory person takes about 10,000 steps each day, any alteration in the finely balanced gait pattern can have substantial deleterious consequences, including a diabetic foot ulcer.

Evaluation for vascular disease is mandatory in all patients with lower-extremity ulcers. It is of particular importance in diabetic patients, for several reasons. First, the incidence of peripheral arterial disease is much higher in diabetics than in the general population. Second, diabetics are more likely to have disease in the infrapopliteal distribution, and the frequency of arterial calcification in this area accounts for the unreliability of the ABI in these patients. Third, diabetics, unlike other patients with peripheral arterial disease, may not manifest claudication or rest pain, because of their polyneuropathy. In other words, just as diabetic patients may suffer from silent myocardial infarction, they may also suffer from critical ischemia that is not unmasked until after a surgical debridement or infectious episode.

Once the vascular status of the foot has been ensured or restored, the wound must be addressed [see Figure 9].¹³ The wound will heal, and remain healed, only if a diligent effort is made to address the variables that led to the development of the wound in the first place. These variables are present to differing degrees in different patients and thus make differing contributions to the formation of wounds. Consequently, there is no standard protocol that encompasses the care of all diabetic foot ulcers. Treatment of such wounds must be individualized, which is why it is best undertaken in a multidisciplinary fashion. The following are the general steps that should be taken to address the major causative variables,

though, as noted, their relative importance will vary from patient to patient.

First, pressure should be relieved (offloaded). Insensibility resulting from neuropathy plays a large role in pathogenesis, but so do altered biomechanics. For example, most forefoot ulcers occurring under the metatarsal heads result from an imbalance between the long and powerful extrinsic tendons and the smaller and functionally deinnervated intrinsic tendons, which causes the clawed posturing mentioned earlier (see above). There may also be loss or shifting of the plantar fat pad.⁹⁴ Pressure offloading can be achieved with orthotics or a total contact cast (the gold standard for pressure relief),⁹⁵⁻⁹⁷ but if the degree of deformity is severe enough, only an orthopedic or podiatric procedure will relieve the chronic pressure, permit healing, and minimize recurrences.

Second, the bioburden should be controlled. A diabetic patient is more likely to have a severe infection that necessitates antibiotic therapy. Because diabetic foot ulcers are pressure sores, there may be sufficient tissue loss to result in exposure of bone, infection, or, in some cases, osteomyelitis. For these reasons, wounds should be probed to determine whether they reach bone or joint capsules⁹⁸; deep space cultures are particularly useful for guiding antimicrobial regimens.⁹⁹

Third, neuropathy should be addressed if possible. Glycemic control or revascularization may result in some improvement. It may be possible to improve tibial nerve sensation by performing a tarsal tunnel release. Although the indications for tarsal tunnel release are still being investigated, the procedure clearly shows potential in selected patients.^{30,100,101} Offloading addresses the sensory deficit by other means. Patient awareness and diligent foot care and examination also play essential roles.

Fourth, the biomechanical derangements present should be addressed by other means besides simple offloading. Lengthening of the Achilles tendon can help take some pressure off the metatarsal heads.^{102,103} Whether this procedure is indicated can be determined by simply evaluating the degree of flexion possible at the ankle joint. Bony prominences and sesamoids may also be excised to achieve pressure relief.

Fifth, dressings should be tailored to the characteristics of the wound. Moist healing is the key. NPWT is extremely useful in the management of these wounds.

VENOUS STASIS ULCERS AND LYMPHEDEMA

Venous leg ulcers are the most common type of leg ulcer both in the United States and worldwide. Valvular incompetence is present in up to 10% of the population, with venous ulceration developing in 0.2%.¹⁰⁴ These leg ulcers arise as a result of sustained venous hypertension caused by longstanding venous insufficiency. More than 95% of them occur in the so-called gaiter region—especially around the medial malleolus, which is the region that sustains the greatest pressure increase from incompetent veins. Ulceration may be either discrete or circumferential. Ulcers occurring above the midcalf or on the foot are likely to have other causes.

The main risk factor for venous leg ulceration is advanced age, probably as a result of a lifetime of bipedal ambulation: as many as 4% of persons older than 65 years have a venous stasis ulcer. Another risk factor is a history of deep vein thrombosis (DVT); often, previous DVT has gone unrecognized. In about half of all cases, however, the deep venous system is normal, and the ulcers result from superficial venous insufficiency or from incompetence of the perforating veins connecting the superficial venous system to the deep venous system.¹⁰⁴ Incompetence of the valvular system within the perforating veins permits reflux into the superficial sys-

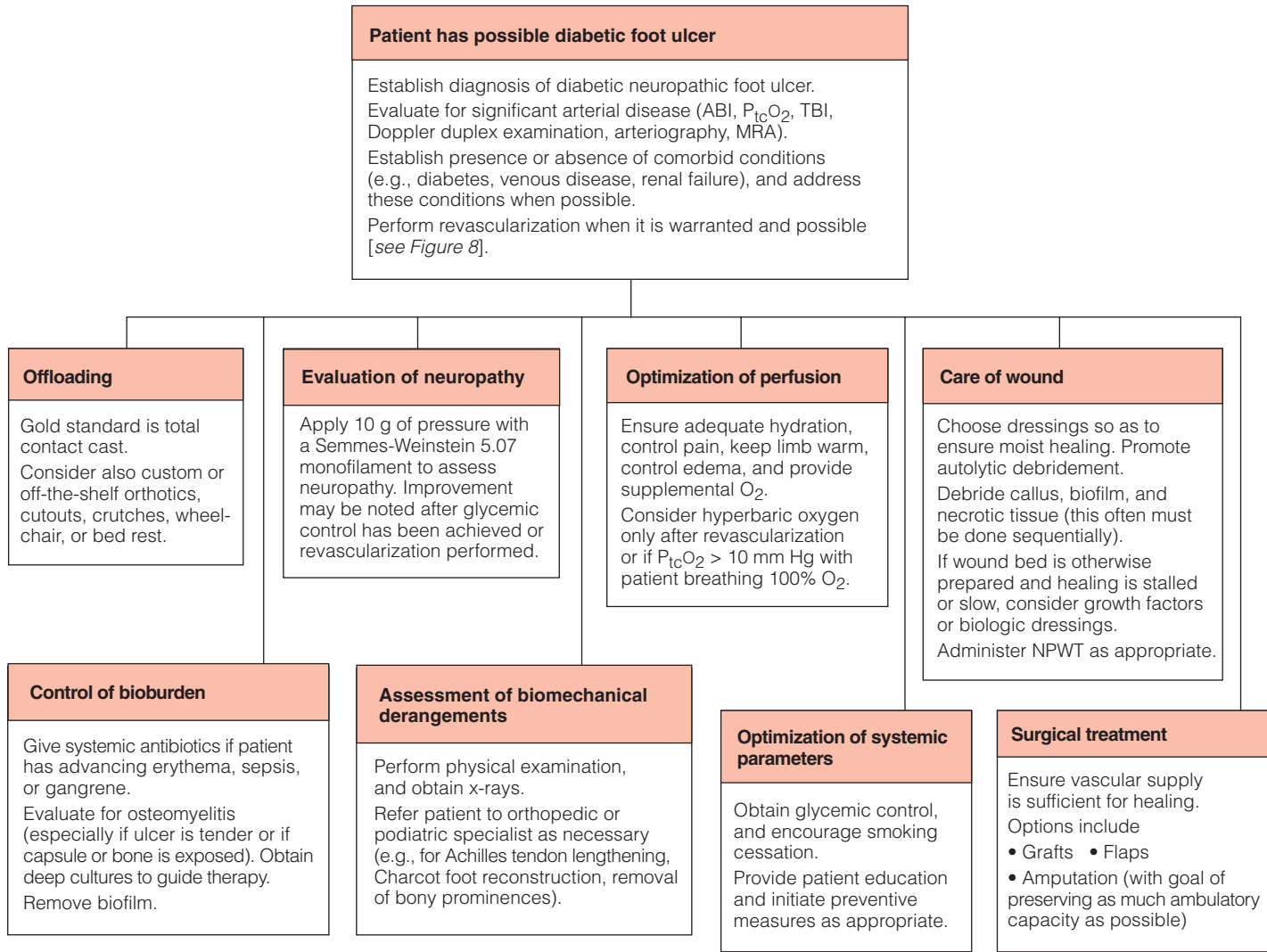


Figure 9 Algorithm illustrates management of diabetic foot ulcers.

tem.¹⁰⁵ Consequently, superficial venous pressure does not decrease during ambulation as the calf muscle pump propels blood to the heart but, rather, remains persistently high because of the reflux. Besides advanced age and a history of DVT, risk factors for venous leg ulcers include any condition leading to prolonged immobility, particularly wheelchair use, varicose veins, obesity, and fractures. For this reason, patients with thrombotic disorders (e.g., deficiencies of antithrombin III, protein C, or protein S) are also predisposed to venous stasis ulcers.

The pathogenesis is complex, and derangements are present at both the microcirculatory level and the macrocirculatory level.¹⁰⁵ Inflammation appears to play a significant role in ulcer propagation.¹⁰⁶⁻¹⁰⁸

Prompt and accurate diagnosis of a lower-extremity venous stasis ulcer is critical for subsequent treatment and wound outcome [see Figure 10].¹² The first and most important step is to rule out a contribution from arterial disease. As noted (see above), compression therapy is contraindicated when the ABI is lower than 0.7. In a diabetic or elderly patient—either of whom may have calcified arteries and an artificially elevated ABI (typically higher than 1.2)—a P_{tcO_2} higher than 30 mm Hg may rule out true ischemia. A TBI may also be useful in this setting; typically, it should be higher than 0.6.

An extremely useful modality for diagnosing venous stasis dis-

ease is color duplex ultrasonography, usually performed with external compression applied proximal to the leg. Duplex imaging is most useful for patients with complicated varicosities, varicose veins that have recurred after previous interventions, suspected deep venous disease, or small saphenous vein incompetence.

Compression dressings are the mainstay of care.¹⁰⁹ There are several types, including the Unna (Duke) boot, multilayer (i.e., three- or four-layer) compression systems, and intermittent pneumatic pressure systems. Compression stockings are categorized as class 1 (14 to 17 mm Hg pressure at the ankle, used for early varicose veins), class 2 (18 to 24 mm Hg pressure, used for mild edema and for patients with thin legs), or class 3 (25 to 35 mm Hg, used for chronic venous insufficiency and in larger legs and more involved edema). A class 3 compression system is required for proper treatment of a venous stasis ulcer.¹¹⁰

Graduated compression, in which the applied pressure is highest (about 40 mm Hg) at the ankle and tapers off to lower levels (about 20 mm Hg) below the knee, increases the hydrostatic pressure in the limb and concomitantly reduces the superficial venous pressure. This approach has been shown by several trials to be more strongly associated with healing than uniform compression is. Perhaps not surprisingly, high-compression bandaging systems and four-layer dressings have also been associated with faster healing of venous stasis ulcers.¹¹⁰ The key to using this modality is that com-

pression must be both sustained and graduated. The exact type of compression system best suited for each particular type of ulcer remains to be determined. In many instances, factors such as patient compliance, cost, and availability are the actual determinants of the type of compression employed in a given case.

The bioburden must also be addressed. Without proper and diligent care, venous stasis ulcers are almost invariably colonized by bacteria, most frequently by biofilm. Bacterial infection is common, with the main isolates being *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and β -hemolytic streptococci. The exact role that biofilm and bacteria play in the pathogenesis of a venous stasis ulcer is still unclear, but it is likely to be a significant one: therapeutic measures that address the bacterial biofilm layer (e.g., low-frequency ultrasound and debridement) have been shown to yield substantial reductions in ulcer size when performed in combination with proper compression therapy. Topical antibiotics should be used judiciously in the treatment of venous leg ulcer infections; systemic antibiotics are indicated if there is evidence of cellulitis or progressive infection. If an area of cellulitis does not resolve with antibiotic therapy but there are no signs of progressive infection, the diagnosis of venous eczema should be entertained. Venous eczema is treated with topical steroids and emollients.

Systemic parameters should be optimized. Many patients are also obese, and leg ulcers in such patients are typically the most difficult to treat and the most likely to recur. It is difficult to achieve compression in these patients, and the presence of a dedi-

cated therapist may be helpful. Severe venous stasis associated with significant lymphedema may have to be treated with intermittent pneumatic compression.¹¹¹ Oral pentoxifylline and micronized purified flavonoid fractions may be given: these agents appear to reduce tissue inflammation and fibrosis in patients with venous stasis disease and hence may prevent ulcers from forming and help active ulcers to heal.^{112,113}

Debridement of the biofilm is frequently necessary. If the ulcer is small and relatively clean, debridement may be performed in the office with a local anesthetic and a curette. If the ulcer is larger or more contaminated, debridement should be carried out promptly in the OR, with deep cultures taken to guide antibiotic therapy if infection is also present.¹² After debridement, compression therapy should be initiated. These ulcers often exhibit copious amounts of fluid and exudate; dressings should be chosen according to the amount of exudate present [see Figure 7]. Foam and alginate dressings are often required. Because of the high propensity of these wounds for accumulation of bacteria and biofilm, silver ion-impregnated dressings are also frequently employed.

Although most venous stasis ulcers eventually heal without surgical intervention, certain indications for operative management do exist. Because a venous stasis ulcer is the most extreme manifestation of the underlying disease (i.e., venous insufficiency), it is best treated by first addressing that disease, whether medically or surgically. Many nonambulatory patients may benefit from anti-DVT therapy. Surgery of the superficial venous system is general-

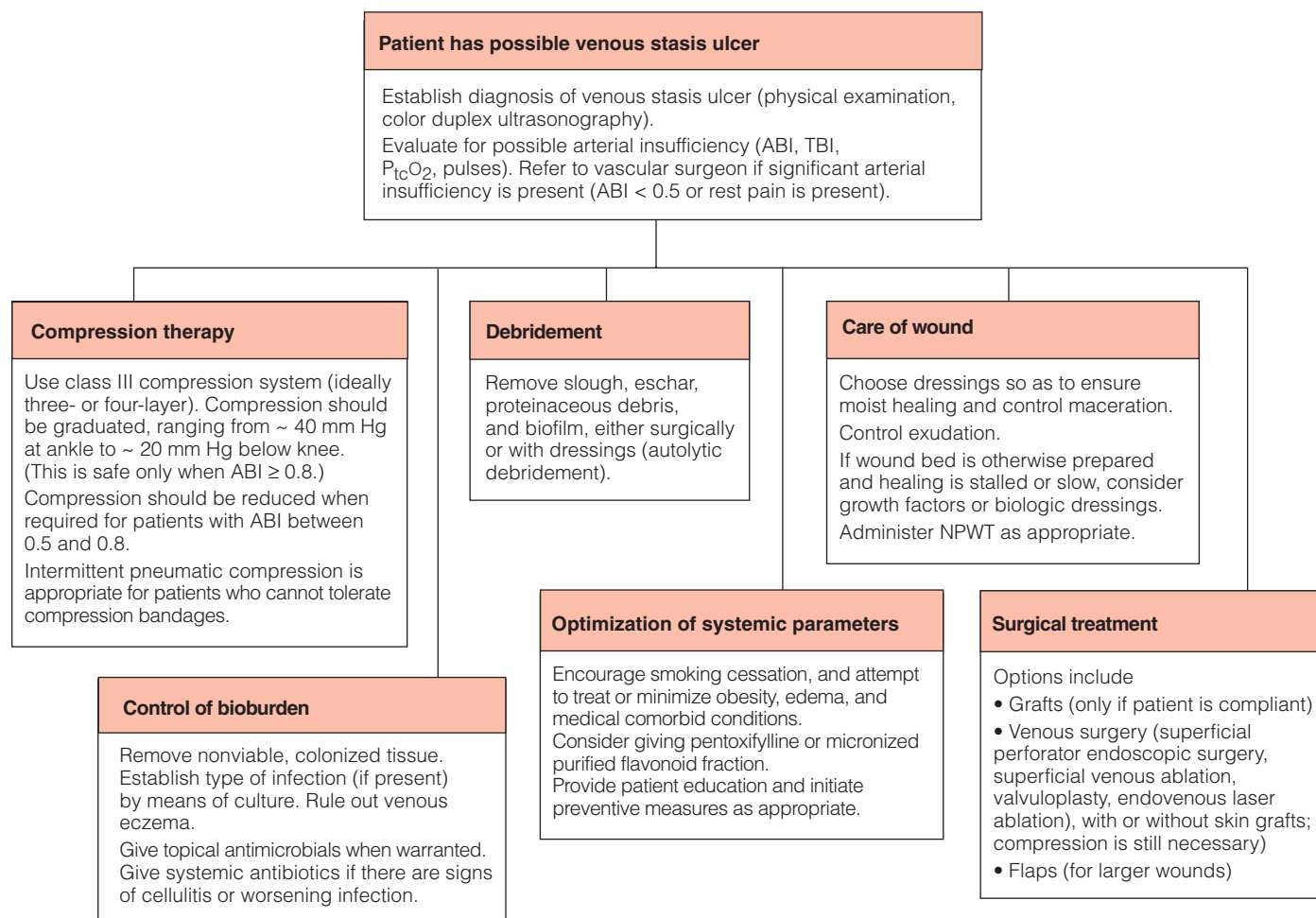


Figure 10 Algorithm illustrates management of venous stasis ulcers.

ly restricted to those patients in whom superficial venous disease is predominant, who show no deep system involvement (i.e., no deep system reflux on duplex imaging), and who are able to ambulate postoperatively (so as to activate the calf muscle pump).^{114,115} In properly selected patients who meet these criteria, surgical management yields faster healing and lower recurrence rates than compression alone does. Certain patients with limited involvement of the deep system may also be candidates for superficial venous surgery, but they will benefit only if vigorous compression is also employed.

Surgical closure is beneficial if the wound is large or causes the patient significant pain. However, it should be undertaken only in compliant patients whose wounds and swelling have been controlled preoperatively with excellent wound care and compression therapy. For these patients, skin grafts can substantially enhance the quality of life. Free flaps are used only to a limited extent in this setting, but there are occasional patients who may benefit from them, including patients with large, deep wounds. Sometimes, flaps can restore a degree of venous drainage to a leg if the anastomosis is performed in the deep venous system or proximally. Some patients benefit from the use of biologic dressings (e.g., Apligraf), particularly when a wound shows signs of stalling after adequate ulcer care.⁶¹ Unfortunately, the recurrence rate after closure of a venous ulcer is high, whether closure is accomplished surgically or not.¹⁰⁴ Patients should be placed on lifelong compression therapy and skin care regimens. Venous stasis disease is controllable but rarely curable.

INFLAMMATORY-VASCULITIC AND OTHER ULCERS

Of the multitude of lower-extremity ulcer subtypes that exist [see *Table 1*], inflammatory ulcers deserve special mention. These lesions, caused by an aberrant inflammatory cascade, are painful, granulated ulcers that resist conventional therapies. As noted (see above), any ulcer that appears not to be healing with proper wound care should undergo biopsy. Proper execution of the biopsy is of critical importance in this setting. Whenever an ulcer is being subjected to biopsy to exclude malignancies or inflammatory processes, specimens should be obtained in several discrete areas. A specimen from the center of the ulcer may not be diagnostic, particularly if necrosis is present. With an inflammatory ulcer, the leading edge of the wound is the area that is likely to have the best diagnostic yield.¹¹⁶ Regardless of the biopsy findings, a careful medical history will generally alert the surgeon to the possibility of an inflammatory ulcer. On examination, such an ulcer shows a characteristic livedo reticularis appearance on the adjacent skin, and the edges often have a dusky hue. The appearance of an ulcer outside the stereotypical distribution pattern may also alert the clinician to an ulcer of unusual origin.

Treatment of a vasculitic ulcer is conducted according to the principles described earlier (see above). Moist healing should be

ensured, and measures should be taken to prevent infection and biofilm accumulation. Debridement usually is not necessary (except for autolytic, nonsurgical debridement), but pain relief and proper dressing selection are. The use of immune modulators (e.g., anti-tumor necrosis factor- α medications) can greatly assist in healing; the use of topical immunosuppressants (e.g., tacrolimus) shows some promise in the care of these ulcers.^{15,116-118} Attempting to close these wounds surgically usually results in failure of the graft or flap unless the inflammatory derangements are first controlled.

Radiation causes not only acute wounds (e.g., radiation dermatitis with acute tissue breakdown) but also delayed wounds, often decades after the initial exposure.¹¹⁹ It must be kept in mind that the effects of radiation on cells and tissues is chronic and ongoing. Local tissue fibrosis and cellular senescence may be present yet may become apparent only when an injury is incurred. Biopsy should be performed to exclude malignancy (in particular, local recurrence of a previously treated neoplasm). Once malignancy is excluded, conservative wound care may suffice for slow healing of the wound. In my experience, however, adjunctive therapies, ranging from HBO¹²⁰ to surgical flaps (especially microsurgical free tissue transfers), are required for most of these wounds. Living biologic tissue-engineered dressings may be useful for shallow wounds.

Sickle cell ulcers develop in the legs of as many as 75% of patients with sickle cell disease, and their incidence increases with advancing age. These lesions are extremely painful, and thus, care depends to a large extent on achievement of proper analgesia, which directly influences compliance with dressings and wound care. Most sickle cell ulcers heal with proper wound care; skin grafts may also be used to achieve expeditious closure when the wound bed is properly prepared.

Tropical ulcers are now being seen more frequently in industrialized nations.¹²¹ Although still rather rare in the United States, they are quite common in the developing world. Accordingly, any patient with a leg ulcer who is a native of a developing or underdeveloped country, particularly if he or she is young, should be worked up for a possible infectious cause. Treatment generally consists of debridement and antimicrobial therapy. After treatment, skin grafting is sometimes undertaken, particularly if the ulcer is large.

Finally, one must always be mindful of the potential for malignancy in a nonhealing wound.¹²² As Dvorak has observed, a tumor may be thought of as a “wound that does not heal.”¹²³ A healthy index of suspicion and biopsy of wounds that do not heal after an appropriate period of therapy are mandatory for ruling out cancer. Malignancies are particularly likely to develop in chronic, inflamed wounds, especially those that have been neglected. Although the prototypical definition of a Marjolin ulcer is that found in a burn wound, squamous cell carcinomas may develop in any chronically open wound.

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28 STRATEGIES OF HEMODIALYSIS ACCESS

Robyn A. Macsata, MD, FACS, and Anton N. Sidawy, MD, MPH, FACS

As the population ages and the incidence of diabetes rises, chronic kidney disease (CKD) and end-stage renal disease (ESRD) are becoming increasingly common diagnoses in the United States. In 2005, data from the United States Renal Data System (USRDS) showed that more than 106,000 new patients began therapy for ESRD, whereas the prevalent dialysis population reached 341,000 and the prevalent transplant population reached 143,693¹ [see Figure 1]. Total Medicare costs for CKD patients neared \$42 billion and for ESRD patients neared \$20 billion; this accounts for 13% and 6%, respectively, of the total Medicare spending in 2005[see Figure 2]. Not surprisingly, most of these costs come between the transition from CKD to ESRD and are related to hemodialysis access.² With these ever-increasing numbers and cost of care of renal disease patients, placement of successful long-term arteriovenous (AV) access has become imperative.

As a response to this need, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) clinical practice guidelines were published, originally in 1997, in an effort to increase the placement of autogenous AV access and to prolong the use of created access by detection of dysfunction prior to thrombosis.³ These guidelines stress early identification of patients with progressive kidney disease, the identification and protection of potential native access construction sites by members of the health care team and patients, and the development of a multifaceted quality assurance program to detect at-risk vascular access,

track complication rates, and implement procedures that maximize access longevity. The guidelines recommend that autogenous AV accesses should be constructed in at least 50% of all new renal failure patients electing to receive hemodialysis as their initial form of renal replacement therapy and that, ultimately, 40% of prevalent patients should have an autogenous AV access.

In 2003, in an effort to reach the goals set forth by the NKF KDOQI guidelines, the Centers for Medicare and Medicaid Services (CMS), the ESRD Network, the Institute for Healthcare Improvement (IHI), and other key provider representatives formed the Fistula First Breakthrough Initiative (FFBI). The work group identified clinical and organizational changes that could be adapted and applied locally by nephrologists, dialysis personnel, access surgeons, and patients to increase the production and use of autogenous AV access. They also identified national system changes such as reimbursement for preoperative vein mapping and reimbursement of autogenous AV access at a higher rate than prosthetic AV access. As a result of the FFBI, the national rate of autogenous access reached 40% prevalence by August 2005; most recent data from December 2009 show a 54.5% prevalence of autogenous access.⁴

In a continuing effort to improve access outcomes, the Society for Vascular Surgery (SVS) recently sponsored a multispecialty expert panel consisting of nephrologists and access surgeons to provide a scientific study of the available evidence



Figure 1 Adjusted incident rates and annual percent changes of US end-stage renal disease (ESRD) patients. Reproduced with permission from United States Renal Data System.¹



Figure 2 Annual Medicare costs for chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients. Reproduced with permission from United States Renal Data System.² ESA = erythropoiesis stimulating agents.

in three main areas of AV access: timing of referral to the access surgeon, type of access placed, and effectiveness of access surveillance. Based on this study of the evidence and consensus of the expert panel, the group developed clinical practice guidelines for the surgical placement and maintenance of AV hemodialysis access. These guidelines were published in the *Journal of Vascular Surgery* in November 2008; this chapter is based on that summary document.⁵

Temporary Hemodialysis Access

SHORT-TERM DIALYSIS CATHETERS

Short-term dialysis catheters are double-lumen, noncuffed, nontunneled catheters that can be placed at the bedside without fluoroscopic guidance. These catheters should be placed in patients needing acute dialysis access and should be used for less than 3 weeks' duration. If dialysis is required longer than this time frame, the catheter should be converted to a long-term dialysis catheter. Short-term dialysis catheters may be placed in the internal jugular, subclavian, or femoral veins. With upper extremity catheters, to achieve best flow rates, the distal tip should be placed in the superior vena cava just above the atrial caval junction. The subclavian vein should be avoided if at all possible to prevent central venous stenosis, which may have an impact on future placement of ipsilateral AV access. When femoral access is used, long catheters (24 to 31 cm) should be placed so that the tip can reach the inferior vena cava for the best flow rates.³

LONG-TERM DIALYSIS CATHETERS

Long-term dialysis catheters are double-lumen, cuffed, tunneled catheters that are placed with fluoroscopic guidance

and are intended to be used over weeks to months. As a result of higher blood flow and lower complication rates, access through the right internal jugular vein with the distal catheter tip in the right atrium is preferred^{6,7}; however, left internal jugular and femoral approaches are also suitable. To decrease the risk of central venous stenosis and subsequent venous hypertension, dialysis catheters should be placed contralateral to the side of any maturing or planned permanent AV access and the subclavian vein approach should be avoided if at all possible.^{3,8}

COMPLICATIONS OF TEMPORARY DIALYSIS CATHETERS

The most common indication and main benefit of short- and long-term dialysis catheters is the need for immediate use for dialysis. Other advantages include their universal applicability, their ability to be placed in multiple access sites without hemodynamic compromise, and no need for repeated skin punctures with dialysis sessions. Also, long-term dialysis catheters may be used for months while waiting for permanent AV access to mature. However, less than half of dialysis catheters are removed electively after successful placement of permanent AV access; the remainder are removed as a result of complications. Catheter thrombosis, because of the development of an intraluminal fibrin sheath, leads to removal in up to 31% of patients. Catheter infections are another frequent cause for removal, occurring in up to 20% of patients; this is most commonly seen with short-term dialysis catheters placed in the femoral position.⁹ Catheter malfunction, including cracked catheters, is cause for removal in 1% of patients.¹⁰ Other disadvantages include the discomfort of an external device and lower blood flow rates, leading to longer dialysis times or less effective dialysis.³ A frequently seen long-term complication of dialysis catheters is subclavian stenosis, which occurs in up to 50% of patients with a subclavian catheter in place for as few as 6 weeks and leads to difficulty with permanent AV access.^{8,11,12}

Catheter thrombosis is seen in up to 31% of patients being dialyzed through a long-term dialysis catheter.¹⁰ This is attributable to the development of an intraluminal fibrin sheath with subsequent thrombus formation leading to decreased catheter blood flows and eventually thrombosis. Treatment options include urokinase infusion or fibrin sheath stripping. Both treatment options were shown to have excellent initial success (97% urokinase, 89% stripping) by Gray and colleagues; however, primary patency at 45 days showed a significant reduction (48% urokinase, 35% stripping).¹³ This study demonstrates the continuing need for new catheter placements in patients who do not receive permanent AV access.

Infection rates are higher with short-term catheters (15.6 to 18.9 per 1,000 catheters) compared with long-term catheters (2.9 to 13.6 per 1,000 catheters). Infection rates as high as 20.0 per 1,000 catheters are seen with femoral placement of short-term catheters.^{9,14,15} Sepsis is associated with catheter infection in 0.3 to 1.3 per 1,000 catheters.^{14,16} Organisms most commonly associated with infection include *Staphylococcus aureus*, coagulase-negative *Staphylococcus*, *Enterococcus*, and *Pseudomonas*; often these infections are polymicrobial.^{9,10} Definitive treatment requires removal of the catheter and broad-spectrum intravenous antibiotics. However, catheter salvage may be attempted with broad-spectrum intravenous

antibiotics alone or in combination with guide-wire exchange of the catheter in nonseptic patients.⁹

Permanent Hemodialysis Accesses

TIMING OF REFERRAL

The NKF KDOQI and the SVS clinical practice guidelines both recommend that patients should be referred to a vascular access surgeon for permanent dialysis access when their creatinine clearance is less than 25 mL/min.^{3,5} Once preoperative evaluation is completed, if the patient is felt to be an adequate candidate for autogenous AV access, the access should be constructed as soon as possible to give adequate time to mature; ideally, this should be greater than 6 months before the anticipated need for dialysis. However, given that prosthetic access patency is limited by the time of access placement and not by access use, if a patient is felt to require a prosthetic access, the access placement should be delayed until 3 to 6 weeks prior to the initiation of dialysis.^{3,5}

PREOPERATIVE EVALUATION

History and Physical Examination

A thorough patient history should be taken documenting the patient's dominant extremity, recent history of peripheral intravenous lines, site of indwelling or previous central lines including pacemakers and defibrillators, all previous access procedures, any history of trauma or previous nonaccess surgery to the extremity, and all comorbid conditions, such as diabetes and peripheral arterial disease. On physical examination, the brachial, radial, and ulnar arteries should be evaluated for compressibility and equality bilaterally. An Allen test should be performed to evaluate palmar arch patency. The superficial venous system should be evaluated with and without a pressure tourniquet in place, examining for distensibility and interruptions. The arm should be examined for prominent venous collaterals and edema, which are signs of central venous stenosis. Lastly, a thorough neurologic examination, including sensory and motor functions of the hands, should be performed.³

Arterial Assessment

If any abnormality is noted on the clinical arterial examination, the patient should be further evaluated with segmental pressures and duplex ultrasonography and/or pulse volume recordings. For optimal outcome, there should be no pressure gradient noted between the bilateral upper extremities, the arterial diameter should be equal to or greater than 2.0 mm throughout the extremity, and a patent palmar arch should be present.¹⁷ Any abnormality noted on noninvasive testing should prompt alternate site selection or be further evaluated with an arteriogram, which gives the surgeon the ability to both identify and possibly treat an arterial inflow stenosis. In patients nearing dialysis, the risk of contrast arteriography should be weighed against the need for access to mature before beginning dialysis. Renal protective agents should be used prearteriography; these include intravenous fluids, N-acetylcysteine, and sodium bicarbonate.^{18,19}

Venous Assessment

If superficial veins cannot be visualized with a pressure tourniquet in place or any abnormality is noted on the

superficial venous examination, the patient should be further evaluated with superficial venous duplex ultrasonography. Using venous duplex imaging, superficial veins should be examined for diameter, distensibility, and continuity. Superficial veins should be of a diameter of 2.5 mm or greater to be used for autogenous AV access.¹⁷ Central venous stenosis should be suspected if there are any prominent venous collaterals or edema, a differential in extremity diameter, any history of previous central venous catheter placement, or multiple previous accesses in the planned extremity to be used for access. If any of these abnormalities are identified, the patient should be examined first with deep venous duplex ultrasonography.³ Venography should be performed in patients with either nondiagnostic or abnormal duplex ultrasound imaging for further evaluation and possible treatment.²⁰ As with arteriography, in predialysis patients, the risk of contrast venography needs to be weighed against the need for access to mature in time for dialysis. Patients should be treated pre-venography with intravenous fluids, N-acetylcysteine, and/or sodium bicarbonate.^{18,19}

ACCESS LOCATION SELECTION

Table 1 lists the various types of autogenous and prosthetic AV access available in the upper and lower extremities and body wall. When planning AV access, a few general principles apply:

1. Given their superior patency rates and lower complication rates, autogenous AV accesses should always be attempted before prosthetic AV accesses.
2. As a result of easier accessibility and lower complication rates, upper extremity access sites are used first, with the nondominant arm given preference over the dominant arm.
3. To preserve proximal sites for future accesses, AV accesses are placed as far distally in the extremity as possible.
4. Autogenous AV access configurations, in order of preference, are direct AV anastomosis, venous transpositions, and venous translocations.
5. Lower extremity and body wall access sites are used only after all upper extremity access sites have been exhausted.

Forearm Accesses

Autogenous forearm accesses *Cephalic vein* For autogenous forearm access, use of the cephalic vein is preferred to the basilic vein because of its lateral location and the need for only minimal dissection. Possible sites of arterial inflow include the posterior branch of the radial artery, the trunk of the radial artery, the ulnar artery, and the brachial artery. The ulnar artery is usually not the first arterial option because of its distance from the cephalic vein. The access is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation to preserve more proximal sites of inflow for future accesses. Therefore, in patients with an adequate posterior branch of the radial artery, an autogenous posterior radial branch-cephalic wrist direct access (snuff-box fistula) [see Figure 3] is performed. In patients with an inadequate posterior branch of the radial artery but an adequate radial artery, an autogenous radial-cephalic wrist direct access (Brescia-Cimino-Appel fistula) [see Figure 4] is performed. In either of these cases, if the

Table 1 Arteriovenous Access Configuration

Upper extremity

Forearm

1. Autogenous
 - a. Autogenous posterior radial branch-cephalic wrist direct access (snuff-box fistula)
 - b. Autogenous radial-cephalic wrist direct access (Brescia-Cimino-Appel fistula)
 - c. Autogenous radial-cephalic forearm transposition
 - d. Autogenous brachial (or proximal radial)-cephalic forearm looped transposition
 - e. Autogenous radial-basilic forearm transposition
 - f. Autogenous ulnar-basilic forearm transposition
 - g. Autogenous brachial (or proximal radial)-basilic forearm looped transposition
 - h. Autogenous radial-antecubital forearm indirect saphenous vein translocation
 - i. Autogenous brachial (or proximal radial)-antecubital forearm indirect looped saphenous vein translocation
 - j. Autogenous radial-antecubital forearm indirect femoral vein translocation
 - k. Autogenous brachial (or proximal radial)-antecubital forearm indirect looped femoral vein translocation
2. Prosthetic
 - a. Prosthetic radial-antecubital forearm straight access
 - b. Prosthetic brachial (or proximal radial)-antecubital forearm looped access

Upper arm

1. Autogenous
 - a. Autogenous brachial (or proximal radial)-cephalic upper arm direct access
 - b. Autogenous brachial (or proximal radial)-cephalic upper arm transposition
 - c. Autogenous brachial (or proximal radial)-basilic upper arm transposition
 - d. Autogenous brachial (or proximal radial)-brachial (vein) upper arm transposition
 - e. Autogenous brachial (or proximal radial)-axillary (or brachial) upper arm indirect saphenous vein translocation
 - f. Autogenous brachial (or proximal radial)-axillary (or brachial) upper arm indirect femoral vein translocation
2. Prosthetic
 - a. Prosthetic brachial (or proximal radial)-axillary (or brachial) upper arm straight access

Lower extremity

1. Autogenous
 - a. Autogenous femoral-saphenous lower extremity (straight or looped) transposition
 - b. Autogenous tibial (anterior or posterior)-saphenous lower extremity direct access
 - c. Autogenous femoral-femoral (vein) lower extremity (straight or looped) transposition
2. Prosthetic
 - a. Prosthetic femoral-femoral (vein) lower extremity (straight or looped) access

Body wall

1. Prosthetic
 - a. Prosthetic axillary-axillary (vein) chest (straight or looped) access
 - b. Prosthetic axillary-internal jugular chest looped access
 - c. Prosthetic axillary-femoral (vein) body wall access

Adapted from Sidawy AN, Gray R, Besarab A, et al. Recommended standards for reports dealing with arteriovenous hemodialysis accesses. *J Vasc Surg* 2002;35:603–10.

cephalic vein is felt to be too deep, as seen in obese patients, or is not located in close proximity to the radial artery in the wrist, an autogenous radial-cephalic forearm transposition is performed. If the radial artery is inadequate, the ulnar artery

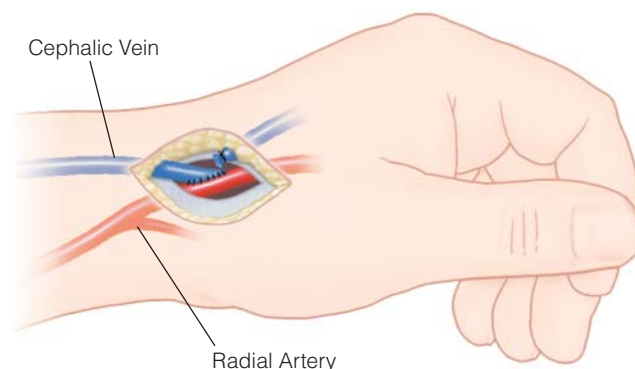


Figure 3 Autogenous posterior radial branch-cephalic wrist direct access (snuff-box fistula).

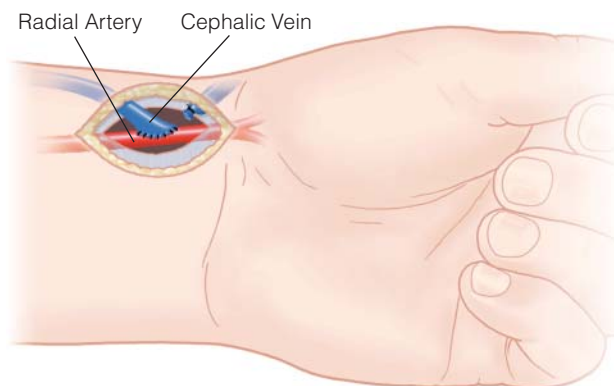


Figure 4 Autogenous radial-cephalic wrist direct access (Brescia-Cimino-Appel fistula).

may provide an alternative distal inflow site; alternatively, the entire trunk of either the radial or the ulnar artery may provide an arterial source. If the radial and ulnar arteries are inadequate but the brachial or proximal radial arteries are adequate, an autogenous brachial (or proximal radial)-cephalic forearm looped transposition can be performed.

Basilic vein When the cephalic vein is not felt to be adequate for an autogenous AV access, the basilic vein is the preferred alternative. Secondary to its medial location in the forearm, a transposition is always required. Possible sites of arterial inflow include the distal radial artery, the ulnar artery, the proximal radial artery, and the brachial artery. Use of the posterior branch of the radial artery is usually not possible secondary to the distance from the basilic vein. Similar to the cephalic vein, the AV access is placed as distally in the arm as possible where an adequate artery is identified by pre-operative evaluation to preserve more proximal sites of inflow for future accesses. Therefore, when the radial artery is adequate, an autogenous radial-basilic forearm transposition [see Figure 5] is performed. If the radial artery is inadequate but the ulnar artery is adequate, an autogenous ulnar-basilic forearm transposition is performed. If the distal radial and ulnar arteries are inadequate, the proximal radial or brachial artery may be used to perform an autogenous brachial (or proximal radial)-basilic forearm looped transposition.

Alternative vein If no lower arm vein is available, autogenous access may still be performed with the use of

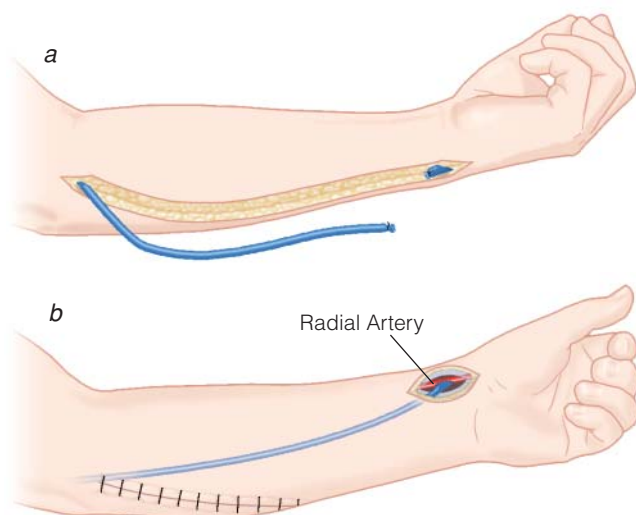


Figure 5 Autogenous radial-basilic forearm transposition.
(a) Forearm basilic vein is mobilized to the antecubital fossa.
(b) Forearm basilic vein is superficially transposed and anastomosed to the radial artery.

translocated lower extremity veins, including the saphenous or femoral (previously named superficial femoral) vein. Sources of arterial inflow include the distal or proximal radial and brachial arteries. Similar to the cephalic and basilic veins, to preserve more proximal arteries for future accesses, the translocated AV access is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation. Therefore, when the distal radial artery is adequate, an autogenous radial-antecubital forearm indirect saphenous vein translocation is performed. If the radial artery is inadequate but the brachial or proximal radial artery is adequate, an autogenous brachial (or proximal radial)-antecubital forearm indirect looped saphenous vein translocation is performed. Alternatively, the femoral vein may be used to perform either an autogenous radial-antecubital forearm indirect femoral vein translocation or an autogenous brachial (or proximal radial)-antecubital forearm indirect looped femoral vein translocation.

Prosthetic forearm accesses If no vein is available, a prosthetic AV forearm access is performed. Sources of arterial inflow include the distal or proximal radial and brachial arteries. Similar to autogenous access, to preserve more proximal arteries for future accesses, the prosthetic AV access is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation. Therefore, when the distal radial artery is adequate, a prosthetic radial-antecubital forearm straight access [see Figure 6] is performed. If the radial artery is inadequate but the brachial or proximal radial artery is adequate, a prosthetic brachial (or proximal radial)-antecubital forearm looped access [see Figure 7] is performed.

One of the interesting debates in this area is whether, after exhausting the forearm autogenous options, the surgeon should recommend a forearm autogenous translocated or prosthetic access before proceeding to an upper arm access. The SVS clinical practice guidelines recommend that the surgeon discuss these alternatives and their advantages and

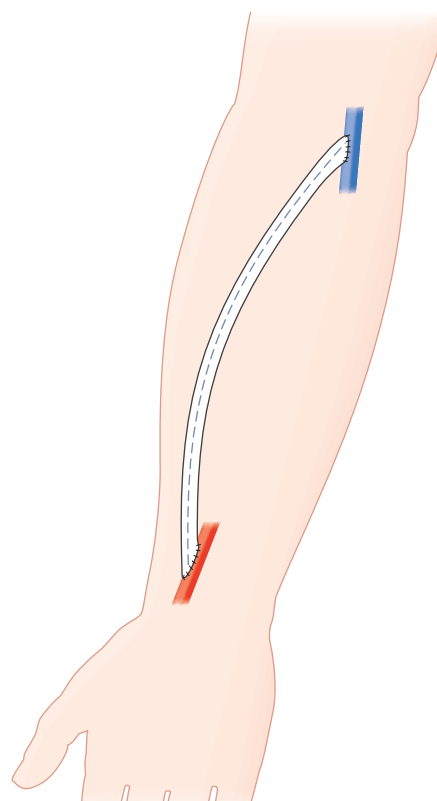


Figure 6 Prosthetic radial-antecubital forearm straight access.

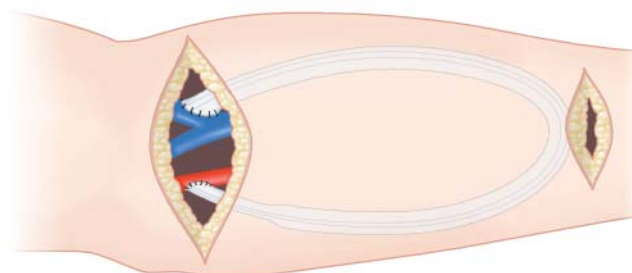


Figure 7 Prosthetic brachial (or proximal radial)-antecubital forearm looped access.

disadvantages with the patient for an informed decision.⁵ If a forearm prosthetic access is chosen, the patient should be told that this access is a “bridge” to an upper arm autogenous access; the patient’s nephrologist should be informed to minimize the number of attempts to salvage the access with endovascular means to avoid damaging the venous outflow so it can still be used for an upper arm autogenous access.⁵

Upper Arm Access

Autogenous upper arm accesses *Cephalic vein* When use of the forearm has been exhausted, efforts at access are directed to the upper arm. Similar to the forearm, use of the upper arm cephalic vein is preferred to use of the basilic vein secondary to its lateral location and need for only minimal dissection. For upper arm access, possible sites of arterial

inflow include the proximal radial and brachial arteries; the AV access is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation to preserve more proximal arteries for future access. Therefore, in patients with an adequate cephalic vein, an autogenous brachial (or proximal radial)-cephalic upper arm direct access [see Figure 8] is performed. If the cephalic vein is felt to be too deep or is located far from the artery, an autogenous brachial (or proximal radial)-cephalic upper arm transposition is performed.

Basilic vein When the cephalic vein is felt to be inadequate for an autogenous AV access, the upper arm basilic vein is the preferred alternative. Secondary to its medial and deep location, a transposition is always required. Similar to the upper arm cephalic vein, possible sites of arterial inflow include the proximal radial and brachial arteries; the AV access is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation to preserve more proximal arteries for future access. Therefore, in patients with an adequate basilic vein, an autogenous brachial (or proximal radial)-basilic upper arm transposition [see Figure 9] is performed.

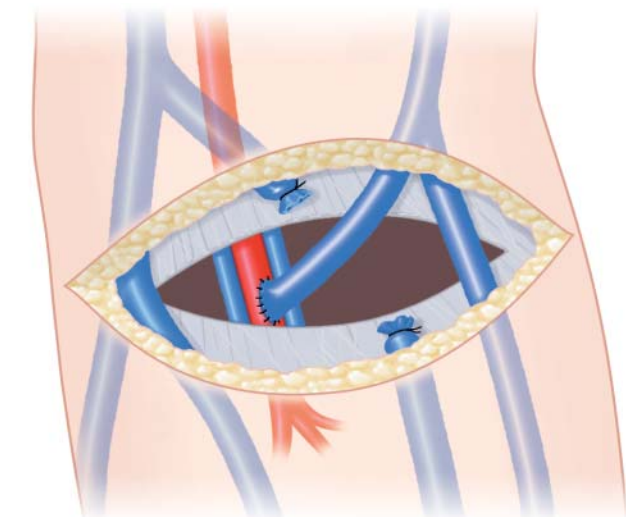


Figure 8 Autogenous brachial (or proximal radial)-cephalic upper arm direct access.

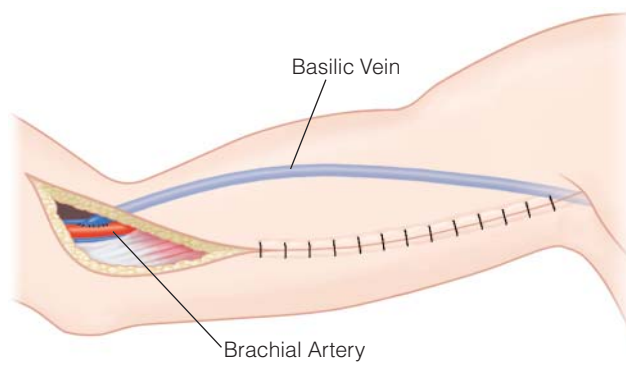


Figure 9 Autogenous brachial (or proximal radial)-basilic upper arm transposition.

Alternative vein If no superficial upper arm vein is available, autogenous access may still be performed with the use of transposed brachial or translocated lower extremity veins, including the saphenous and femoral veins. Sources of arterial inflow include the proximal radial and brachial arteries; the AV access is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation to preserve more proximal arteries for future access. Therefore, alternative options for autogenous access include autogenous brachial (or proximal radial)-brachial (vein) upper arm transposition, autogenous brachial (or proximal radial)-axillary (or brachial) upper arm indirect saphenous vein translocation, and autogenous brachial (or proximal radial)-axillary (or brachial) upper arm indirect femoral vein translocation. Similar to the lower arm, surgeons should discuss the risks and benefits of the use of an alternative vein for autogenous access in the upper arm for an informed decision before turning to prosthetic access.

Prosthetic upper arm accesses If no vein is available, an upper arm prosthetic AV access is performed. Similar to upper arm autogenous AV accesses, possible sites of arterial inflow include the proximal radial and brachial arteries; the AV access is placed as distally in the arm as possible where an adequate artery is identified by preoperative evaluation to preserve more proximal arteries for future access. Therefore, in patients with no adequate vein, a prosthetic brachial (or proximal radial)-axillary (or brachial) upper arm straight access [see Figure 10] is performed.

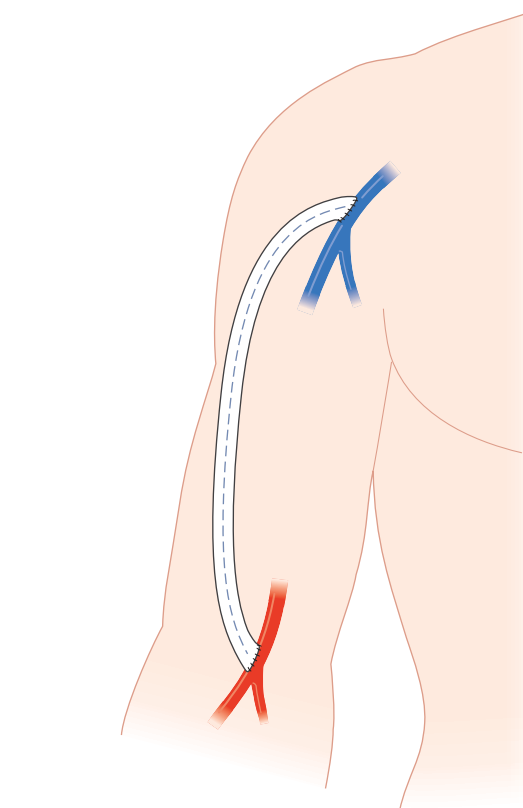


Figure 10 Prosthetic brachial (or proximal radial)-axillary (or brachial) upper arm straight access.

Lower Extremity Access

When use of the bilateral upper extremities has been exhausted, efforts are directed to the lower extremity; as a result of the high risk of complications associated with both autogenous and prosthetic lower extremity AV access, a fair amount of debate still exists over the ideal access. Autogenous AV access may be constructed using the saphenous or femoral vein as a conduit. Similar to the upper extremity, patency rates are superior to prosthetic access; however, they are associated with an increased incidence of complications, including wound infections from large vein harvest sites, arterial steal, compartment syndrome, and venous hypertension.^{21,22} Prosthetic AV access has a lower incidence of these complications but continues to have inferior patency rates and a high rate of graft infections. Furthermore, when patients reach the need for lower extremity AV access, they are usually quite advanced in their ESRD and have an overall high mortality rate.^{23,24} Therefore, the SVS practice guidelines recommend that the surgeon discuss these alternatives and their advantages and disadvantages with the patient for an informed decision.⁵

Autogenous lower extremity accesses *Saphenous vein* When use of the bilateral upper extremities has been exhausted, autogenous lower extremity AV access may be performed with the saphenous vein; secondary to its medial and deep location, transpositions are always required. The femoral artery (preferably the superficial or profunda) is used for inflow. Therefore, in patients with an adequate saphenous vein and femoral artery, an autogenous femoral-saphenous lower extremity transposition is performed, either in a loop or straight configuration. Alternatively, in patients with a palpable posterior or anterior tibial artery pulse, either tibial artery may be used as inflow to create an autogenous tibial-saphenous lower extremity direct access.

Femoral vein As an alternative to the saphenous vein, the femoral vein may be used for autogenous lower extremity AV access; because of its medial and deep location, transpositions are always required. The femoral artery (preferably the superficial or profunda) remains the source of inflow. Therefore, in patients with an adequate femoral vein and artery, an autogenous femoral-femoral (vein) lower extremity transposition is performed, either in a straight or loop configuration.

Of note, a high incidence of arterial steal has been related to use of the femoral vein for a conduit in lower extremity access; this is likely attributable to its large diameter allowing for a relatively low-resistance AV access. To avoid this complication, patients should be evaluated for lower extremity peripheral vascular disease; similar to the upper extremity, any inflow lesions should be treated with either endovascular or open surgical techniques before AV access placement or an alternative access site should be chosen. Options to reduce the incidence of arterial steal related to a large diameter femoral vein include femoral vein banding, femoral vein tapering, or constructing a composite femoral vein graft with the saphenous vein.^{21,22}

Prosthetic lower extremity accesses If no lower extremity vein is available or the patient is felt to be too high risk for complications, a lower extremity prosthetic access

may be performed. The femoral artery (preferably the superficial or profunda) remains the source of inflow. Therefore, in a patient with no adequate lower extremity vein and an adequate femoral artery, a prosthetic femoral-femoral (vein) lower extremity straight or looped access [see Figure 11] is performed.

Body Wall Access

After use of both upper and lower extremities has been exhausted, body wall access can be used as a last alternative access site. Body wall access usually requires a prosthetic graft. The main source of arterial inflow is the axillary artery. Sources of venous outflow include the axillary, internal jugular, and common femoral veins. Appropriate options include a prosthetic axillary-axillary (vein) chest (straight or looped) access, a prosthetic axillary-internal jugular chest looped access, and a prosthetic axillary-femoral (vein) body wall access [see Figure 12].

SURGICAL TECHNIQUE

Despite the multiple anatomic options for both autogenous and prosthetic AV accesses, the principles of surgical techniques remain similar in all AV access procedures.

Autogenous AV Access

The following techniques are common to all autogenous vein accesses:

1. After identification of the vein, the distal end is transected and flushed with heparinized saline. This allows for evaluation of the caliber and extent of the vein and identification of any side branches.
2. With transposition accesses, the vein is completely dissected and mobilized, ligating all side branches, to its origin.
3. After controlling the artery, an arteriotomy of a maximum length of 4 to 6 mm is made. The length of the arteriotomy is limited to decrease the incidence of arterial steal.
4. The artery is flushed proximally and distally with heparinized saline to avoid thrombosis during the anastomosis.

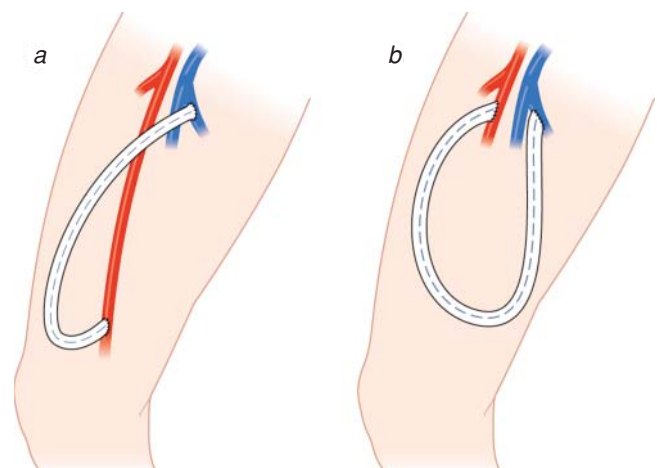


Figure 11 (a) Prosthetic superficial femoral-femoral (vein) lower extremity straight access. (b) Prosthetic superficial femoral-femoral (vein) lower extremity looped access.

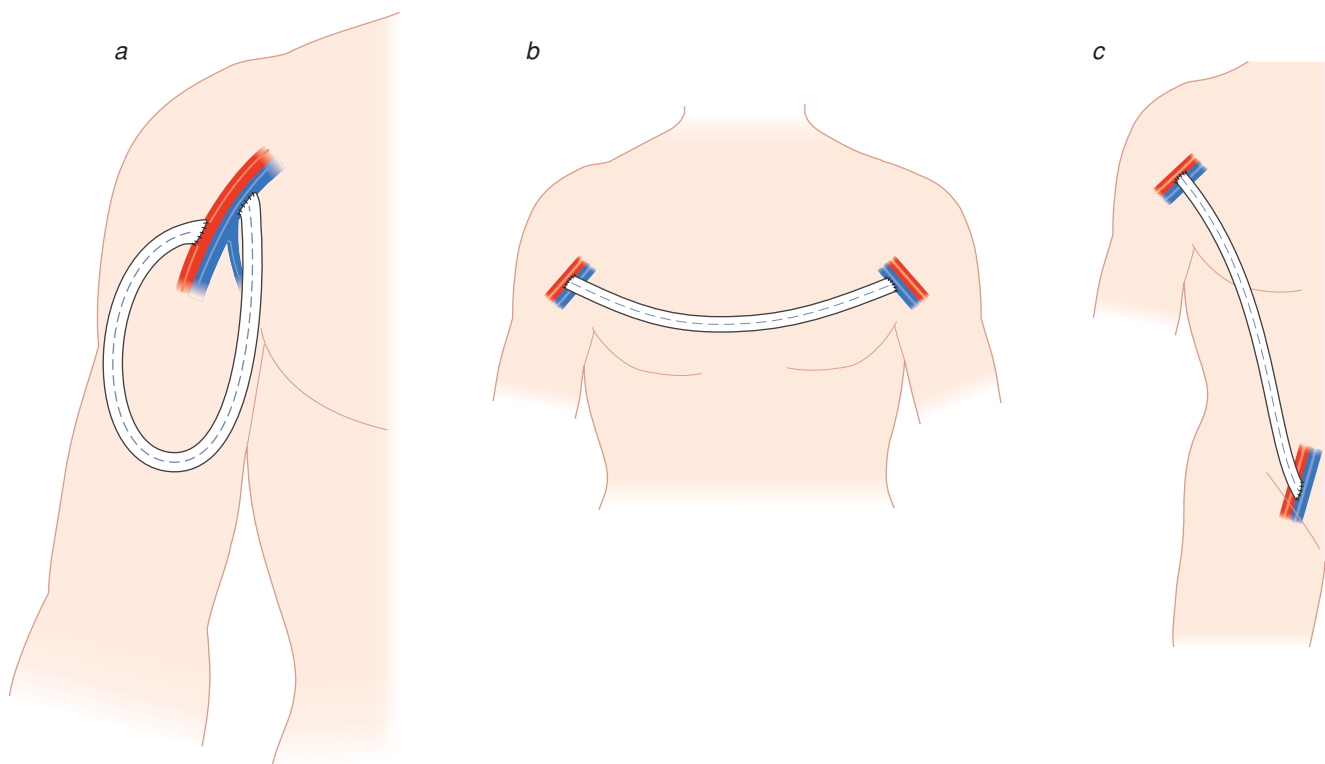


Figure 12 (a) Prosthetic axillary-axillary (vein) chest looped access. (b) Prosthetic axillary-axillary (vein) chest straight access. (c) Prosthetic axillary-femoral (vein) body wall straight access.

5. The AV anastomosis is performed between the side of the artery and the end of the vein; this configuration decreases the subsequent risk of venous hypertension.
6. The AV anastomosis is performed using a 6-0 or 7-0 monofilament nonabsorbable continuous suture to avoid subsequent anastomotic dilatation.
7. With nontransposed access, after completion of the anastomosis, large venous branches can be ligated through stab incisions. This encourages flow in the main venous segment, which may promote earlier maturation.
8. The patient is asked to perform hand exercises 24 to 48 hours postoperatively to increase blood flow through the vein and encourage early maturation of the access.

Prosthetic AV Access

A standard 6 mm expanded polytetrafluoroethylene (ePTFE) is our choice for graft material for prosthetic AV accesses. Variations in the standard ePTFE graft include thin-walled, extended stretch, external rings, various tapered configurations, and heparin coating, which are all meant to ease handling, provide external support, and improve patency rates. To date, there is only minimal evidence that any of these variations improve long-term results; therefore, use of any of these variations remains a matter of surgeon preference.^{25,26}

The following techniques are common to all prosthetic access:

1. The venous outflow is dissected, examined for appropriate quality and caliber, and controlled with vessel loops.
2. The arterial inflow is dissected and controlled with vessel loops.

3. The subcutaneous tunnel for the prosthetic graft is made with a Kelly-Wick tunneler; the tunnel is made as superficial as possible to allow easy detection by dialysis personnel and as long as possible for a large surface area to prevent repetitive trauma to the same area of the graft and subsequent pseudoaneurysm (PSA) formation.
4. If the venous outflow and arterial inflow are located away from each other, a straight prosthetic AV access configuration is performed. If the venous outflow and arterial inflow are located close to each other, a loop prosthetic AV access configuration is performed; this requires a counterincision at the apex of the loop.
5. The length of the arteriotomy and the venotomy does not need to be limited to 4 to 6 mm. The diameter of the graft will limit the incidence of arterial steal.
6. The artery is flushed proximally and distally with heparinized saline to avoid thrombosis during the anastomosis.
7. The anastomoses are performed using a 6-0 or 7-0 monofilament nonabsorbable suture in a continuous manner.
8. Careful attention to sterile technique is paramount to avoid graft infections.

POSTOPERATIVE FOLLOW-UP

From the time of the access placement, autogenous AV access should be mature and ready for cannulation by 12 weeks postoperatively and prosthetic AV access should be mature and ready for cannulation by as early as 2 weeks postoperatively. Determination of maturity may be done by physical examination alone; the access should have a soft pulse that is easily compressible, a continuous low-pitched bruit, and a thrill near the anastomosis and extending along

the outflow vein and should collapse with arm elevation. If the clinical examination remains equivocal after 6 to 8 weeks, the access should be further evaluated with duplex ultrasonography; the outflow vein should have a vein diameter greater than 4 mm and blood flow greater than 500 mL/min. If the access appears to be failing to mature by duplex evaluation, it should be further evaluated with fistulography or venography to identify any underlying problems preventing maturity. Secondary procedures, such as vein patches, interposition vein grafts, vein transposition to proximal arteries, branch ligations, vein superficialization, or endovascular angioplasties, should then be used to salvage the access.⁵

LONG-TERM FOLLOW-UP

After initial maturation, the AV access should be monitored routinely while the patient is on dialysis. The preferred method of monitoring is monthly determinations of access flow by ultrasound dilution, conductance dilution, thermal dilution, or Doppler technique. Access flow less than 600 mL/min or access flow less than 1,000 mL/min that has decreased by 25% over 4 months should be further evaluated with duplex ultrasonography followed by fistulography if further information is needed. Another method of access monitoring that is more useful with prosthetic access is measurement of static venous dialysis pressures; a graft-to-artery ratio of more than 0.75, a graft-to-vein ratio of less than 0.5, or a progressive increase in the venous or arterial segment of more than 0.25 should be further evaluated with duplex ultrasonography followed by fistulography if further information is necessary. Measurements of dynamic venous pressures have been found to be a relatively poor marker of autogenous or prosthetic access function. Other acceptable methods of access surveillance include measurement of prepump arterial dialysis pressure, measurement of access recirculation using urea concentrations or dilution techniques, evaluation of physical findings such as arm edema, altered characteristics of access thrill, and notation of prolonged bleeding after needle removal. Similar to early access failure to mature, after identification, any underlying abnormalities should be treated with secondary procedures to prevent access thrombosis.³

COMPLICATIONS OF AV ACCESS

AV Access Failure

Upper extremity autogenous AV access [see Table 2] has consistently been shown to have excellent primary and secondary patency rates when compared with prosthetic AV access. One-year primary patency rates of autogenous AV access range from 43 to 85%,^{27–34} and 2-year primary patency rates range from 40 to 69%.^{28,32,35,36} In comparison, 1-year primary patency rates of prosthetic AV access range from 40

to 54%,^{27,28,33,34} and 2-year primary patency rates range from 18 to 30%.^{28,35,36} Similarly, secondary patency rates are superior in autogenous access and range from 46 to 90%^{27,28,31–33} at 1 year and from 62 to 75%^{28,35–37} at 2 years compared with prosthetic access, which ranges from 59 to 65%^{27,28,31} at 1 year and from 40 to 60% at 2 years.^{28,35,36} Also of note, to maintain these secondary patency rates, prosthetic AV access requires a higher number of interventions than autogenous AV access. These superior patency rates of autogenous access include basilic vein transpositions, which have demonstrated 1-year primary patency rates from 35 to 76%^{27,30,32,38,39} and secondary patency rates from 47 to 90%.^{27,32,38}

Similar to upper extremity AV access, lower extremity autogenous AV access [see Table 3] has consistently been shown to have superior primary and secondary patency rates to prosthetic AV access. One-year primary patency rates of autogenous access average 73% and 2-year primary patency rates average 86%.^{21,22} In comparison, 1-year primary patency rates of prosthetic access average 54% and 2-year primary patency rates range from 18 to 47%.^{23,24} Similarly, secondary patency rates of autogenous access at 1 year, which average 86%, and at 2 years, which range from 87 to 94%,^{21,22} remain superior to secondary patency rates of prosthetic access at 1 year, which average 64%, and at 2 years, which average 18%.^{23,24} Also, similar to the upper extremity, to maintain these secondary patency rates, prosthetic AV access requires more revisions.^{23,24}

Early AV access thrombosis Early access thrombosis occurs within 30 days of surgery and is attributable to a technical failure. It is most commonly associated with inadequate venous outflow, which may be secondary to inadequate caliber of the outflow vein or central venous stenosis. Other, less common causes include poor arterial inflow and anastomotic stenosis.

Thrombectomies and thrombolysis are rarely successful treatments for autogenous accesses; this situation usually requires complete revision. If early thrombosis is secondary to the small caliber of the outflow vein, the autogenous AV access is redone using a different vein, that is, conversion of an autogenous radial-cephalic direct wrist access to an autogenous radial-basilic forearm transposition or, if no vein is available, a prosthetic AV access. Central venous stenosis is treated with angioplasty and/or stenting or venous bypass, that is, subclavian vein to internal jugular vein bypass [see Venous Hypertension, below], followed by a new AV access. An arterial inflow stenosis is treated with angioplasty and/or stenting or proximal arterial bypass to restore adequate arterial inflow followed by a new AV access; an alternative approach is to move the AV access either proximally or to another extremity where arterial inflow is adequate. Anastomotic stenosis is a primary technical failure and is redone with close attention to surgical technique.

Table 2 Autogenous Arteriovenous Access Patency Rates

Access Location	Primary Patency (%)		Secondary Patency (%)	
	1 yr	2 yr	1 yr	2 yr
Upper extremity	43–85	40–69	46–90	62–75
Basilic vein transposition	35–76	68	47–90	69–75
Lower extremity	73	68	86	87–94

Table 3 Prosthetic Arteriovenous Access Patency Rates

Access Location	Primary Patency (%)		Secondary Patency (%)	
	1 yr	2 yr	1 yr	2 yr
Upper extremity	40–54	18–30	59–65	40–60
Lower extremity	54	18–47	64	18

Prosthetic AV accesses may be successfully salvaged using thrombectomies or thrombolysis; however, as with autogenous access, the surgeon must evaluate the etiology of the acute thrombosis and revise the access appropriately to prevent recurrent thrombosis.⁵



Late AV access thrombosis Late access thrombosis usually occurs 1 to 2 years after access placement and most commonly is attributable to intimal hyperplasia. In an autogenous access, this occurs just distal to the AV anastomosis but may be seen anywhere in the outflow tract; in a prosthetic access, this occurs at the graft-venous anastomosis. Central venous stenosis is a second common cause of late AV access failure and is attributable to intimal hyperplasia of the central venous system, which is commonly associated with central line placements.

Similar to early access thrombosis, thrombectomies and thrombolysis are rarely successful in autogenous accesses; this situation usually requires complete revision. If late thrombosis is attributable to intimal hyperplasia in the outflow vein, the autogenous AV access is redone using a different outflow vein, that is, converting an autogenous radial-cephalic direct wrist access to an autogenous radial-basilic forearm transposition, or using a proximal site of access, that is, converting an autogenous radial-cephalic direct wrist access to an autogenous brachial-cephalic upper arm direct access. Central venous stenosis is treated with angioplasty and/or stent placement or venous bypass, that is, subclavian to internal jugular bypass [see Venous Hypertension, *below*], followed by placement of a new AV access.

Prosthetic AV access may be successfully salvaged using thrombectomies or thrombolysis if treated within 14 days of access thrombosis and therefore is attempted before abandoning the access for a new site. Given that the inciting lesion is most often located in the graft-venous anastomosis, surgical thrombectomy is performed by exposing this anastomosis, followed by a patch angioplasty to alleviate the outflow stenosis and prevent recurrent thrombosis. Alternatively, a bypass may be performed around the distal anastomosis. Thrombolysis and percutaneous mechanical thrombectomy are alternative methods to reopen the access; however, both techniques must be followed by a contrast study and repair of the inciting stenosis with angioplasty and/or stent placement to prevent recurrent thrombosis of the access.⁵



Failing AV access If an AV access is noted to be failing during routine surveillance while on dialysis, it should be further assessed with duplex ultrasonography and/or fistulography and treated appropriately to prevent access thrombosis. As seen in thrombosed accesses, the inciting lesion is usually intimal hyperplasia located in the outflow tract, and treatment options are similar.⁵



Failure of AV access to mature A common tradeoff for the higher long-term patency rates associated with autogenous AV access is failure of maturation of the outflow vein, leading to inadequate venous dilation and either inability to successfully use the AV access for dialysis or early AV access failure. Initial success rates leading to a functional AV access range from 55 to 97%.^{27,28,31,40,41} These poor maturation rates appear to correspond to the increasing use of small and

suboptimal veins in an effort to perform a higher number of autogenous AV accesses. Other technical issues that may lead to failure of maturation include venous side branches, deep location of the outflow tract, poor arterial inflow, and either arterial or venous anastomotic stenosis.⁵

If any access is noted to be failing to mature, it should be further examined with duplex ultrasonography and/or fistulography. If the AV access appears to be failing because of the small caliber of the outflow vein, treatment options include vein patches, interposition vein grafts, and venous transpositions to proximal arteries. If identified, large side branches of the outflow vein should be ligated; if the outflow vein appears too deep, it should be translocated superficially. Endovascular procedures such as arterial or venous angioplasty and/or stent placements are other options for repair.⁵ Using these secondary procedures, McLafferty and colleagues were able to identify treatable problems with 69% of failing autogenous accesses and successfully salvage the access to functional maturation in 83%.⁴⁰ Similarly, Berman and Gentile demonstrated an overall 10% improvement in achieving a successful autogenous AV access using secondary procedures.⁴¹

Arterial Steal

Arterial steal occurs secondary to low access tract resistance, creating a reversal of blood flow in the arterial outflow tract toward the access and away from the hand; it may be associated with arterial stenosis proximal to the AV access. A subtype of arterial steal, ischemic monomelic neuropathy (IMN), occurs secondary to arterial steal leading to ischemia of the nerves only, producing neurologic deficits of the median, radial, and ulnar nerves, but is not sufficient to cause muscle or skin necrosis.

Using Doppler augmentation or pressure studies, reversal of flow in the arterial outflow tract is demonstrated in 73% of autogenous radial-cephalic direct wrist accesses and 91% of autogenous brachial-cephalic direct upper arm accesses; however, patients are only clinically symptomatic in 0.25% to 1.8% of wrist accesses and 4% to 9% of upper arm accesses.⁴² Clinical symptoms vary and range from mild ischemia presenting as coolness and paresthesias, which occur only on dialysis, to severe ischemia presenting as constant rest pain, numbness, paralysis, finger contractures, and gangrene. Patients with IMN present with acute pain, paresthesias, and weakness or paralysis despite a warm hand and palpable radial and ulnar pulses.

Patients with clinically symptomatic arterial steal should be evaluated with an arteriogram to identify any proximal arterial stenosis; treatment of the proximal artery alone with either endovascular or open surgical techniques may resolve symptoms without the need for ligation or revision of the AV access. In patients without proximal arterial stenosis or who do not resolve their symptoms with treatment of the inflow stenosis, there are multiple options for treatment of the access. Ligation of the access will instantly resolve the symptoms but leaves the patient without a dialysis access. Banding of the access tract [see Figure 13] creates a stenosis that increases the resistance to the blood flow in the access and reverses arterial flow in the distal artery; however, it is difficult to judge the degree of stenosis required to alleviate the steal without causing thrombosis of the access. In patients with a forearm access and a patent palmar arch, the distal



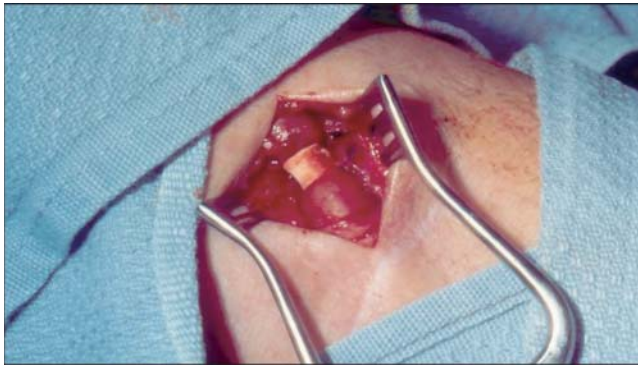


Figure 13 Banding of the outflow access tract. Reproduced with permission from Macsata RA, Sidawy AN. Arteriovenous hemodialysis access. In: Evans SRT, editor. *Surgical pitfalls: prevention and management*. Philadelphia: Elsevier Saunders; 2009. p. 638.

outflow artery may be ligated; however, this approach does not restore possible required inflow to the hand. Distal revascularization with interval ligation [see Figure 14] entails ligation of the arterial outflow tract just distal to the takeoff of the access followed by placement of a bypass from the artery

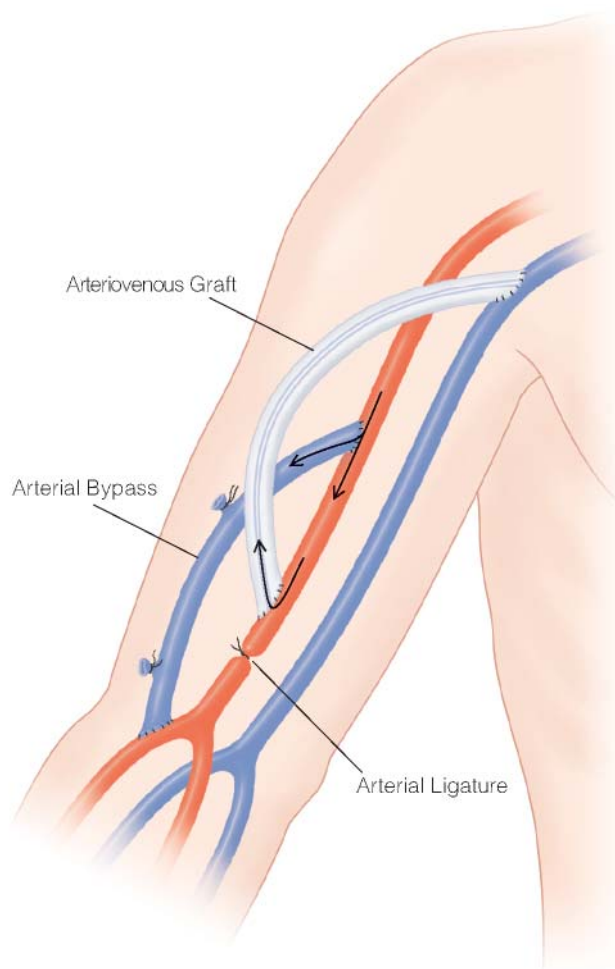


Figure 14 Distal revascularization with interval ligation.

proximal to the takeoff of the access to the artery distal to the area of ligation. This procedure eliminates reversal of flow in the distal outflow artery while keeping the access patent and perfusion pressures to the hand constant. Complete relief of symptoms has been reported in more than 90% of patients; primary 1-year patency rates range from 86 to 100% for the arterial bypass and from 69 to 86% for the AV access.^{43–45}

High-Output Congestive Heart Failure

High-output congestive heart failure (CHF) is seen only with autogenous AV access. It occurs secondary to decreased total peripheral resistance associated with an AV access that is compensated for by an increase in total cardiac output; the cardiac index should be greater than 2.3 L/min/m². However, in patients with poor cardiac function, as commonly seen in the dialysis population, the cardiac index may still be low as a result of an inability to increase cardiac output to compensate for the AV access flow.

Clinical symptoms are similar to those for low-output CHF and include dyspnea on exertion and at rest, orthopnea, peripheral edema, pulmonary edema, and tachycardia. The diagnosis is difficult; physical examination may be helpful by noting a decrease in the pulse rate with compression of the AV access, the Nicoladoni-Branham sign. Techniques to measure AV access flow rates include the indicator dilution and serial ultrasound dilution measurements; AV access flow greater than 3 L/min or an AV access flow that is greater than 30% of the cardiac output is consistent with the diagnosis.⁴²

Treatment options are limited; ligation of the AV access will resolve symptoms but leaves the patient without dialysis access. Banding of the AV access tract is an alternative approach; however, similar to arterial steal, it is difficult to judge the amount of stenosis required to reduce the cardiac output without thrombosis of the access.

Venous Hypertension

Venous hypertension is seen in both autogenous and prosthetic AV access; it occurs secondary to venous outflow stenosis with or without venous valvular incompetence. The outflow obstruction is commonly located in the subclavian vein as a result of intimal hyperplasia associated with central venous catheters but may also be located anywhere in the venous outflow tract.

Clinical presentation ranges from asymptomatic, with only increased dialysis venous pressures, to symptomatic, including prolonged puncture-site bleeding, extremity edema [see Figure 15a], varicosities [Figure 15b], pigmentation, dermatosclerosis, and venous ulceration.

Patients with clinically symptomatic venous hypertension should be evaluated with duplex ultrasonography and/or fistulography. Central venous stenosis is preferably treated with angioplasty; because of the minimal evidence that stenting increases long-term patency, stents are reserved for unsuccessful angioplasties, occlusions, or recurrent lesions. Open surgical repair is a major undertaking and therefore reserved for percutaneous failures; options include subclavian to internal jugular bypass [see Figure 16] or subclavian vein turn-down. Similar to central venous stenosis, peripheral venous stenosis is preferably treated with endovascular techniques such as angioplasty with or without stenting; open surgery is reserved for percutaneous failures, and options include venous

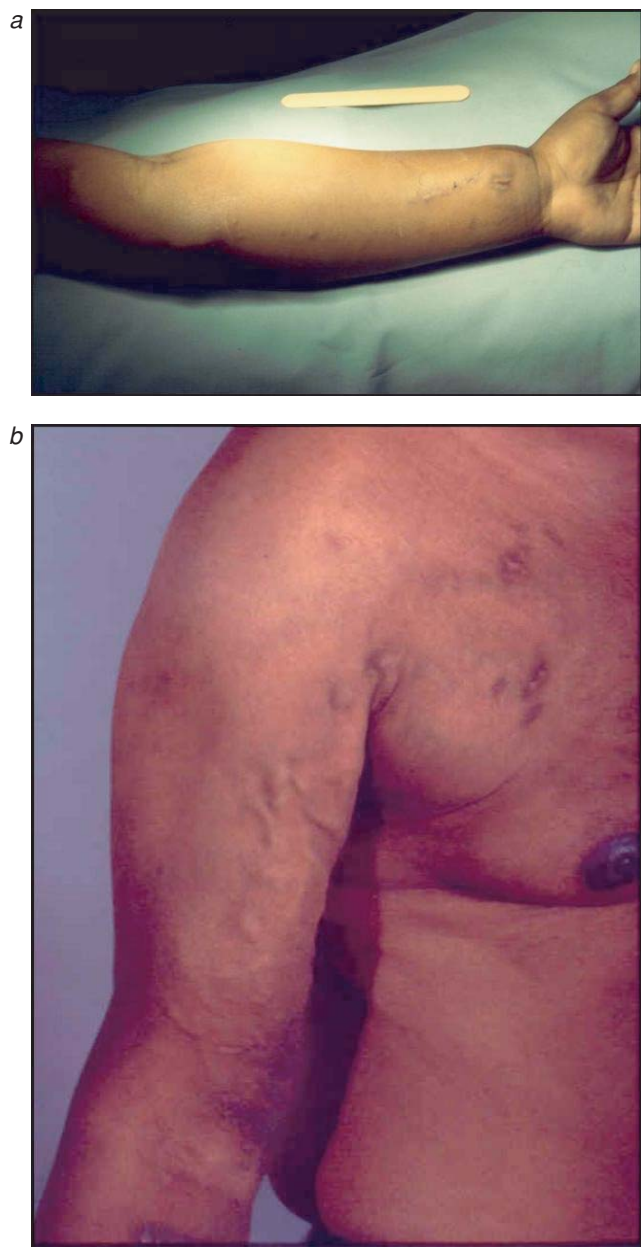


Figure 15 (a) Upper extremity edema associated with venous hypertension. (b) Upper extremity varicosities associated with venous hypertension. Reproduced with permission from Macsata RA, Sidawy AN. Arteriovenous hemodialysis access. In: Evans SRT, editor. *Surgical pitfalls: prevention and management*. Philadelphia: Elsevier Saunders; 2009. p. 634.

patches, interposition vein grafts, or venous transpositions onto more proximal arteries. Valvular incompetence is treated with ligation of all veins distal to the outflow anastomosis noted to have reflux. If the central or peripheral venous stenosis is not amenable to treatment, patients require ligation of their AV access, leaving them with no dialysis access.^{46,47}

Infection

Infections are more commonly seen in prosthetic (4 to 20% per year) than autogenous (0.56 to 5% per year) AV accesses.

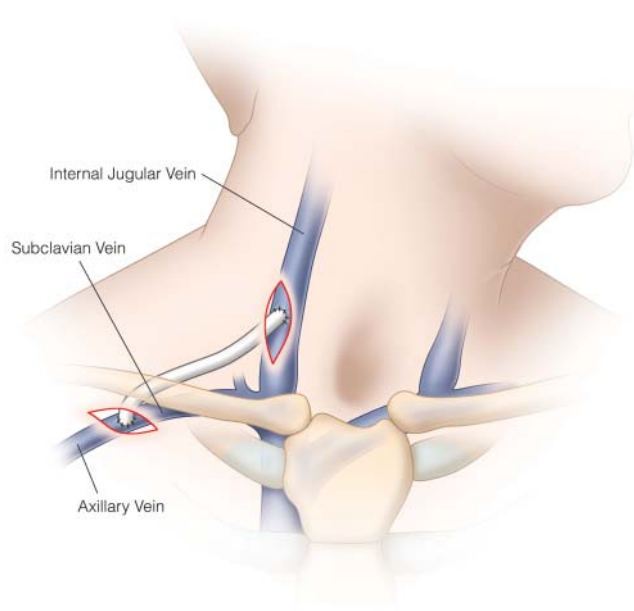


Figure 16 Internal jugular to subclavian venous bypass. Reproduced with permission from Macsata RA, Sidawy AN. Arteriovenous hemodialysis access. In: Evans SRT, editor. *Surgical pitfalls: prevention and management*. Philadelphia: Elsevier Saunders; 2009. p. 635.

Infectious organisms appear to be independent of type of access; there is usually a predominance of gram-positive organisms, most commonly *S. aureus*; however, up to 25% of infections may involve gram-negative organisms or be polymicrobial.⁴²

Clinical presentation may range from diffuse cellulitis or focal abscess overlying the access; patients may or may not be bacteremic. Diagnosis is usually by clinical examination but may be helped with duplex ultrasonography demonstrating fluid surrounding the AV access.

Autogenous AV access infection usually responds to 2 to 4 weeks of broad-spectrum antibiotics; any associated abscess is drained with preservation of the access. A trial of broad-spectrum antibiotics may be attempted in prosthetic accesses presenting with only a mild cellulitis. However, most prosthetic infections require abscess drainage with removal of the infected portion of the graft; if either anastomosis is involved, the entire graft is removed to prevent anastomotic disruption.

Pseudoaneurysm

PSAs are more commonly seen in prosthetic than in autogenous AV accesses, occurring in 2 to 10% of all prosthetic accesses during the functional life of a graft.⁴² They may be seen anywhere along the length of the prosthetic access [see Figure 17] and occur as a result of continuous puncturing of the AV access in the same location by dialysis personnel. When located at either the arterial or the venous anastomosis, they are attributable to graft infection and are treated as such.

Most puncture-site PSAs may be safely monitored without intervention; dialysis personnel should be instructed to use



Figure 17 Puncture site pseudoaneurysms of an arteriovenous access. Reproduced with permission from Macsata RA, Sidawy AN. Arteriovenous hemodialysis access. In: Evans SRT, editor. *Surgical pitfalls: prevention and management*. Philadelphia: Elsevier Saunders; 2009. p. 640.

alternative sections of the access for cannulation. While monitoring, if a PSA appears to be significantly expanding or becomes ulcerated, intervention is indicated. Traditional open surgical treatment is to excise the involved portion of the AV access and replace it with either a transposed vein or a prosthetic graft; in most cases, dialysis is continued by accessing the uninvolved portion of the access. An alternative approach is endovascular treatment with covered stent grafts; current studies show initial success rates up to 100% and primary patency rates at 6 months that range from 29 to 70%.^{48–50}

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Seroma

Seromas affect only prosthetic AV accesses. They usually occur within 1 month of placement and most often surround the arterial anastomosis. The exact etiology is unknown, but seroma is presumed to occur from transudation of serous fluid from porous grafts. Clinically, patients present with a slowly increasing fluid collection, which may be further identified by duplex ultrasonography.⁵¹

Multiple surgical treatments have been reported, including serial aspiration, incision and drainage, cyst removal, and graft replacement. Graft replacement has been shown to be the most successful, with a 92% cure rate.⁵²

Hematoma

Dialysis patients most commonly have hemorrhagic complications attributable to uremia-associated platelet dysfunction, which may present as diffuse intraoperative hemorrhage, postoperative hematoma, prolonged puncture-site bleeding, or needle punctures leading to access-site hematomas.

Platelet dysfunction may be medically managed with desmopressin acetate (DDAVP)^{53–55}; other options include cryoprecipitate⁵⁴ and activated factor VII.⁵⁵ With medical therapy, most hemorrhages will stop, and the resulting hematoma will reabsorb without the need for surgical intervention. Expanding hematomas nonresponsive to medical therapy should be explored with the source of bleeding, usually a puncture site, primarily repaired; rarely does this require access ligation.

Financial Disclosures: None Reported

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29 PERITONEAL DIALYSIS ACCESS

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The population of the United States is experiencing a rapid increase in the prevalence of end-stage renal disease (ESRD) requiring renal replacement therapy (RRT). There were over 548,000 ESRD patients in 2008, consuming 7% of the Medicare budget and \$39.5 billion in total costs. With an annual growth of 6%, the ESRD population is projected to grow to more than 775,000 dialysis patients by 2020.¹ RRT options include hemodialysis (HD), peritoneal dialysis (PD), and renal transplantation. Although renal transplantation remains the RRT of choice, the proportion of ESRD patients receiving a renal transplant has not changed in the past decade. With increasing numbers of ESRD patients requiring dialysis, one would expect a proportionate growth of all dialysis modalities. On the contrary, whereas use of HD has progressively increased, there has been a steady decline in PD use.

When compared with HD, PD is associated with patient survival advantages within the first 2 years of dialysis.²⁻⁹ Unlike the sawtooth pattern of treatment with HD, PD delivers a more steady-state treatment by avoiding fluctuations in plasma volume and solutes and is generally better tolerated by the patients with cardiovascular compromise. PD also provides a flexible schedule, allowing patients to work, travel, and participate in daytime activities. As PD does not involve needle sticks, patient anxiety is mitigated, arteriovenous access sites for future HD are preserved, and the risk of acquiring blood-borne infections such as hepatitis C and HIV is minimized. Additionally, residual renal function is better preserved on PD than on HD⁷⁻¹³ and is beneficial to patients who receive a kidney transplant. There is a significantly lower incidence of delayed graft function and better long-term transplantation outcomes for patients on PD pretransplantation.^{7,14-16} Despite these advantages, the number of patients on PD in the United States remains low^{17,18}: PD is used for 8.8% of the total US dialysis population compared with elsewhere in the world, such as the United Kingdom, New Zealand, and Mexico, where PD is used in up to 80% of ESRD patients.

Overview of Peritoneal Dialysis

PD is achieved by instilling a dialysis solution into the peritoneal cavity via a percutaneous abdominal catheter. The peritoneum acts as a dialyzing membrane, across which water and solutes are exchanged between the capillary blood and the intraperitoneal dialysate.⁷ PD can be done manually (continuous ambulatory peritoneal dialysis [CAPD]) or with automated devices (cyclers). Instillation of dialysate can be either continuous (fluid in the abdominal cavity 24 hours a day, i.e., continuous cycler-assisted peritoneal dialysis

[CCPD]) or intermittent, typically at night, with an empty abdominal cavity during the day (nocturnal intermittent peritoneal dialysis [NIPD]).

Table 1 lists the primary indications for PD as defined by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.¹⁸

There are very few absolute contraindications to PD. Inadequate peritoneal membrane surface area or quality, extensive adhesions, and/or other anatomic abnormalities that preclude filtration are the primary contraindications to PD [see Table 2]. Prior abdominal operations are not necessarily a contraindication for attempting PD placement, although intraperitoneal adhesions may make the technique more prone to failure.

Preoperative Evaluation

Preoperative evaluation begins with a thorough history and physical examination. Adequate vision and manual dexterity are required to perform PD because most PD is performed at home by the patient. Patients with physical or mental handicaps can perform PD if adequate assistance is available. The extent and nature of previous abdominal operations, past episodes of peritonitis, recurrent diverticulitis, or pelvic inflammatory disease are associated with increased risk of failure to place the catheter and should be documented but do not represent absolute contraindications to PD. A history of prior open abdominal operations for noninflammatory conditions does not preclude PD placement.^{19,20} In cases where the surgeon suspects that intra-abdominal adhesions will preclude PD catheter placement, it is prudent to plan for HD access placement in the same operating setting. Although PD is the dialysis mode of first choice, the patient should be offered a native vein arteriovenous fistula (AVF) at the same operation, assuming suitable vascular anatomy. This AVF will then have time to mature and serve as a backup for dialysis should PD be temporarily stopped or fail.

Ideally, the PD catheter should be placed 3 to 4 weeks prior to the anticipated initiation of dialysis to avoid complications related to temporary HD catheters. Ideal candidates for PD include working professionals as PD can be performed with less lifestyle disruption compared with in-center HD.

Operative Planning

LOCATION OF THE CATHETER AND MARKING OF THE SKIN

Preoperative planning is essential as 21% of technique failures within the first year are due to catheter-related mechanical problems.²¹ Noninfectious PD catheter-related complications are strongly associated with catheter failure.^{19,22} Ideally, the curled portion of the PD catheter is located in the true pelvis, allowing for proper dialysate instillation and removal or exchanges. The exit site must be easily accessible,

Financial disclosure information is located at the end of this chapter before the references.

Table 1 Indications for Peritoneal Dialysis

Patient prefers peritoneal dialysis
Patient will not do hemodialysis
Patient cannot tolerate hemodialysis
Patient prefers home dialysis but has no assistance for hemodialysis

visible for the patient, and away from the beltline, skin folds, and scars. The subcutaneous tunnel should be fashioned to avoid catheter stresses and kinks. Preoperative planning should also take into consideration the location of the superior border of the pubic symphysis, the umbilicus, the level of the anterior superior iliac spines, and skin folds.²⁰ To decrease the risk of contamination, an alternate presternal extension exit site is preferred in individuals with colostomy or urinary stoma, those who are morbidly obese, and those who desire to take tub baths.²³

With the patient in the upright and supine positions, the incision, intended subcutaneous tract, and exit site of the catheter are marked [see Figure 1]. This is especially important in obese patients as a pannus will change position on standing. In a virgin abdomen, the left side is chosen because the right iliac fossa is the preferred site for a first kidney transplant [see Figure 1]. Also, as opposed to the right side, the downward intestinal peristalsis of the left colon is thought to maintain proper catheter orientation in the pelvis.

As noted in Table 2, obesity is considered a relative contraindication to PD. This is an important consideration because an estimated 70% of the US population is overweight. In recent years, we have been placing an increasing number of catheters in overweight individuals. PD catheters in obese patients work surprisingly well but require special considerations. As noted above, choosing the exit site in the upper abdomen or on the upper chest using a presternal



Figure 1 Skin markings for the placement of a peritoneal dialysis catheter in the open technique. Note the locations of the planned incision, subcutaneous tunnel, and exit site.

Table 2 Contraindications for Peritoneal Dialysis

Absolute
Documented loss of peritoneal function or extensive abdominal adhesions that limit dialysate volume or flow
In the absence of a suitable assistant, the patient is physically or mentally unable to perform PD
Uncorrectable mechanical defects that prevent effective PD or increase the risk of infection (e.g., surgically irreparable hernia, omphalocele, gastroschisis, diaphragmatic hernia, and bladder extrophy)
Relative
Fresh intra-abdominal foreign bodies (e.g., VP shunts or vascular prosthesis)
Peritoneal leaks
Body size limitations
Intolerance to volume exchanges needed for adequate PD dose
Inflammatory or ischemic bowel disease
Frequent episodes of diverticulitis
Abdominal wall or skin infection
Morbid obesity
Severe malnutrition

PD = peritoneal dialysis; VP = ventriculoperitoneal.

extension segment is the preferred option in these patients.^{23,24}

CHOICE OF CATHETER

PD catheters come in a variety of configurations and with one or two Dacron cuffs [see Figure 2]. With single-cuff configurations, the Dacron cuff is placed at the posterior rectus fascia; with double-cuff configurations, the second or outer cuff is placed in the subcutaneous space 1.5 to 2.0 cm from the skin exit site. Although this is not borne out in randomized, controlled trials,²⁵ the double-cuff configuration is thought to provide an additional barrier from bacterial migration along the catheter and may have lower rates of tunnel tract infections and associated peritonitis. Retrospective reviews suggest that double-cuff configurations have a longer catheter survival time, a delayed first episode of peritonitis,^{24,26} and a trend toward decreased episodes of peritonitis.²⁷

The intraperitoneal and extraperitoneal PD catheter designs vary greatly [see Figure 2]. The intraperitoneal

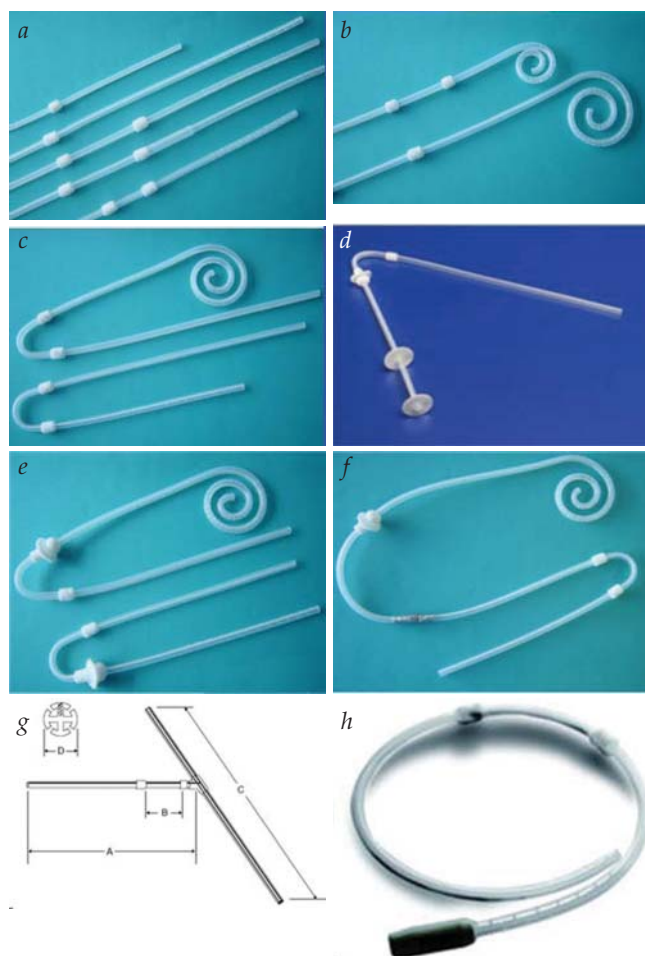


Figure 2 The different commercially available types of peritoneal dialysis catheters. (a) Straight Tenckhoff peritoneal dialysis catheters, in single- and double-cuff configurations. (b) Coiled Tenckhoff peritoneal dialysis catheters, in single- and double-cuff configurations. (c) Swan neck peritoneal dialysis catheters, with straight and coiled intraperitoneal segments. (d) Swan neck Toronto Western Hospital peritoneal dialysis catheter. (e) Swan neck Missouri peritoneal dialysis catheter with a straight intraperitoneal segment. (f) Swan neck presternal peritoneal dialysis catheter with a coiled intraperitoneal segment. (g) T-fluted Ash Advantage peritoneal dialysis catheter. A is the transabdominal tube length, B is the distance between cuffs, C is the overall intraperitoneal length, and D is the flute diameter. (h) The “self-locating” Di Paolo peritoneal dialysis catheter. Note the weighted tip at the end of the intraperitoneal segment.

segments can be straight, coiled, or weighted (so-called self-locating tips²⁸). Catheters with a coiled intraperitoneal segment provide greater surface area and more side holes for fluid passage and therefore increased likelihood of success.²⁶ The coiled segments may be better tolerated than the straight intraperitoneal configurations because the straight tips are thought to produce more pain with instillation of fluid secondary to a “jet” effect.²³

The extraperitoneal segments can be straight or curved. Because the catheter material has inherent “shape memory,” forcing a curve into a straight catheter is thought to increase mechanical complications and infectious complications and cuff extrusion through the skin.²⁶ We use the double-cuff

curled (pigtail) Tenckhoff catheter with straight external configuration.

Surgical Technique/Approach

The choice of surgical approach depends on the experience of the operating surgeon. PD catheters are typically inserted using an open approach or laparoscopic technique. Other methods of placement include the blind Seldinger technique, placement under fluoroscopic guidance, and placement under peritoneoscopic visualization²⁹; these methods are strongly discouraged because of the risk of inadvertent bowel injury. The open and laparoscopic techniques of PD catheter placement are discussed here.

Advantages and disadvantages exist for both methods. The open approach is associated with a shorter operating time and can be performed under spinal or local anesthesia, although general anesthesia is preferred. The open approach is also more cost-effective as only basic equipment is required for the procedure.³⁰ Laparoscopic placement, with the insufflation of carbon dioxide into the peritoneal cavity, requires general anesthesia, which may be precluded in some patients. Laparoscopic placement also requires longer operating times, a finding that has been consistently reported in multiple studies.^{30–37} The main advantage of the laparoscopic approach is that it allows for direct visualization and placement of the tip of the catheter, as well as the ability to secure the tip of the dialysis catheter in the pelvis.^{35,37} The laparoscopic approach also allows for additional procedures, such as repair of umbilical hernias, lysis of adhesions, or omentopexy.^{38,39}

Laparoscopy is the best technique to rescue problem catheters.^{38,40} Studies comparing the rates of complications with open versus laparoscopic PD placement have been mixed,^{36,37} and one method of placement cannot be recommended over another. The PD catheter surgical approach is greatly influenced by the patient’s medical risk, the operating surgeon’s training, and institutional resources.

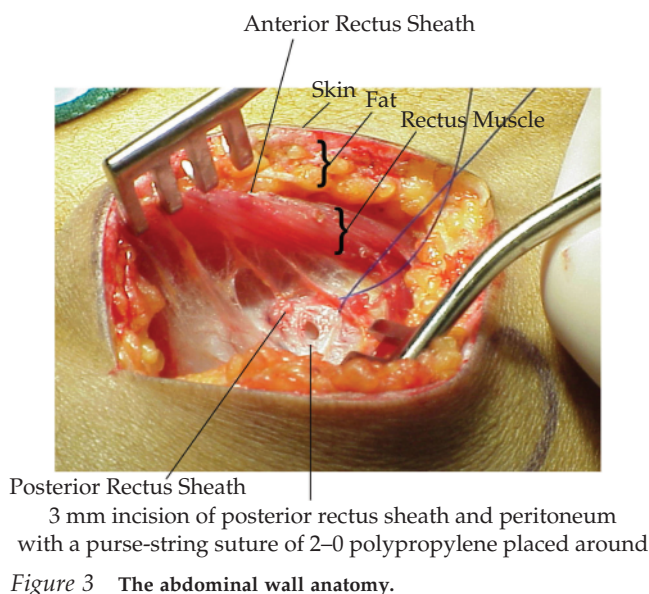
OPERATIVE TECHNIQUE

Open Paramedian Approach

Although open PD catheter placement can be performed under local anesthesia, for patient comfort, general anesthesia is preferred. Preoperative antibiotics, such as first-generation cephalosporin (e.g., cefazolin), are administered prior to skin incision. Patients with penicillin or cephalosporin allergies should receive either clindamycin or vancomycin as alternatives.

The skin incision is placed 2 to 3 cm on either side of the umbilicus, with the left being the preferred side [see Figure 1]. The abdominal wall anatomy is shown in Figure 3. The anterior rectus muscle fascia is divided longitudinally. Muscle-sparing technique is used to expose the posterior rectus fascia. Using fine scissors, the posterior rectus fascia and peritoneum are opened for a length of 3 mm. Caution is advised to avoid inadvertent small bowel injury during entry.

A 2-0 polypropylene purse-string suture is placed around the fascial-peritoneal defect [see Figure 4]. The suture is placed so that the tie will be located cephalad to the cuff; this



suture will also be used to secure the inner Dacron cuff to the posterior rectus fascia. This purse-string suture allows for a watertight seal around the catheter.

The intra-abdominal catheter placement is facilitated by the use of a stiffening stylet [see Figure 5]. The catheter must

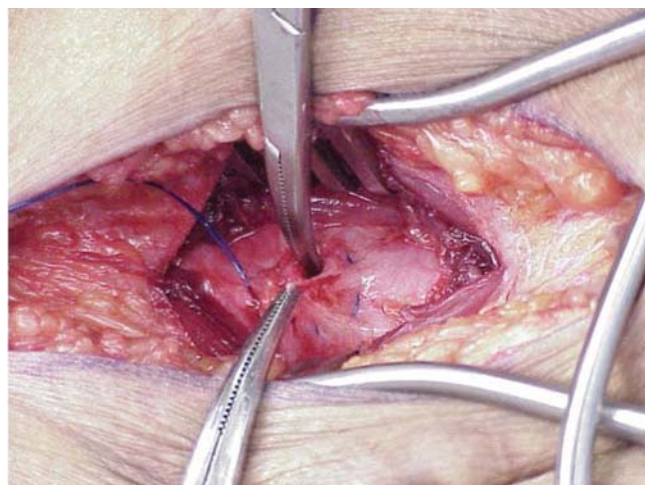


Figure 4 Several bites (6–8) of suture are placed 5 mm from the edge of the small peritoneal opening circumferentially to form a purse-string closure.



Figure 5 Catheter and stylet.

first be flushed with saline for the stylet to slide freely onto the catheter. The tip of the stylet must not pass outside the tip of the catheter, to minimize the risk of visceral injuries during insertion [see Figure 6]. Once inside the abdomen, the stylet is retracted to release the curled end, and the catheter is directed downward along the anterior abdominal wall. Force must not be used. If resistance occurs, redirection of the catheter is attempted until the pelvis is reached. At this point, the stylet is removed with one hand securing the PD catheter at the exit site. Once the catheter is fully inserted, the purse-string suture is tied snugly. The inner Dacron cuff is then secured to the posterior aspect of the posterior rectus fascia with suture [see Figure 7]. A second purse-string suture is not required. Next, the catheter is tunneled through the rectus muscle [see Figure 8] and pulled through the anterior rectus fascia [see Figure 9]. This step secures the cranio-caudad direction of the catheter, making malpositioning unlikely.

The sharp, curved subcutaneous Faller tunneler is used to create a smooth, curved subcutaneous tract as the catheter exits through the skin [see Figure 10 and Figure 11]. The tunneler is the same diameter as the catheter tubing, making the skin exit site snug [see Figure 12]. A snug exit site minimizes irritation from catheter sliding and the risk of infection. The external Dacron cuff is placed 1.5 to 2.0 cm from the exit site.

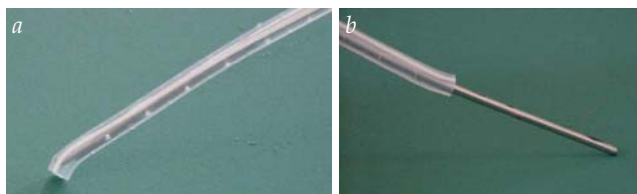


Figure 6 (a) This is the ideal position of the stylet as it is inserted through the small peritoneal incision, minimizing the risk of injuries to visceral structures. (b) The catheter with the stylet protruding is dangerous and leads to injuries.

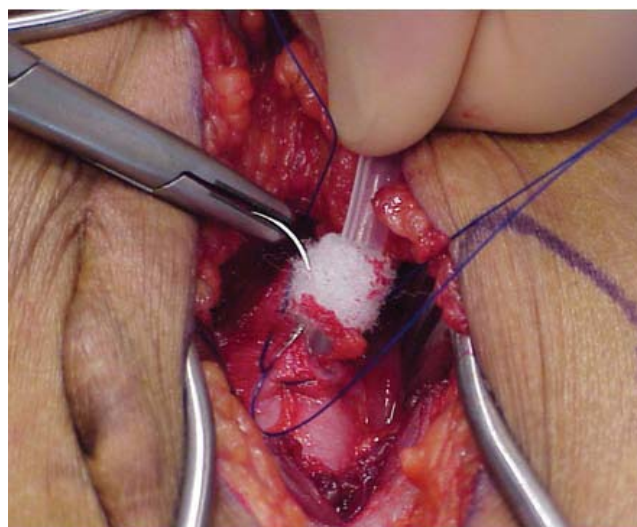


Figure 7 This image details the placement of suture to secure the inner Dacron cuff. Care should be taken not to inadvertently penetrate the catheter.

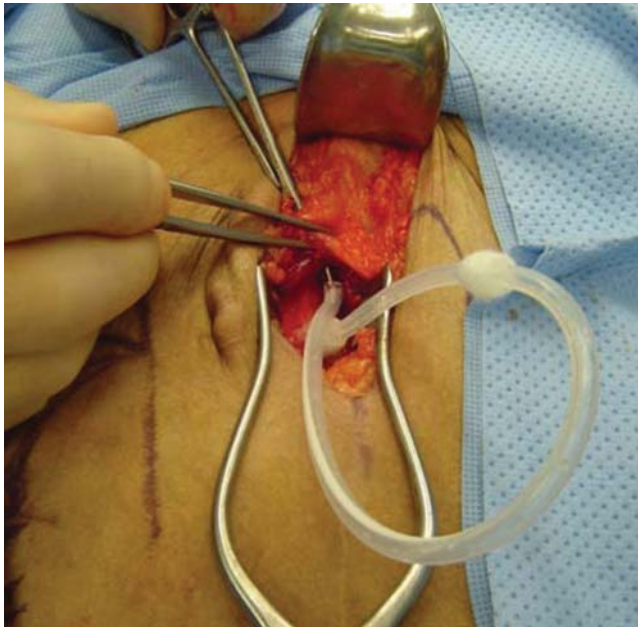


Figure 8 The catheter is tunneled through the rectus muscle and pulled through the anterior rectus fascia.

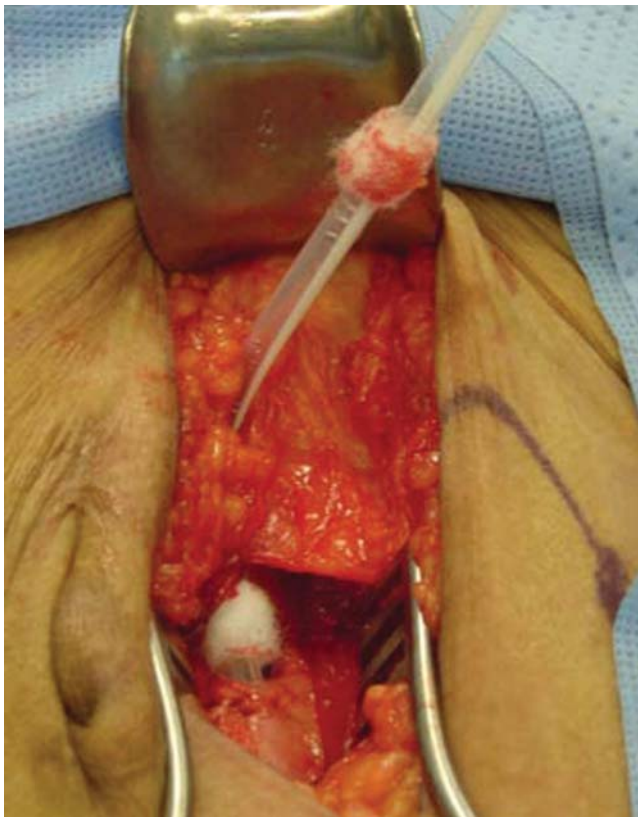


Figure 9 The inner Dacron cuff rests sutured to the posterior rectus muscle fascia. The catheter is aligned in a craniocaudal direction, keeping the coiled portion of the catheter straight down toward the pelvis.

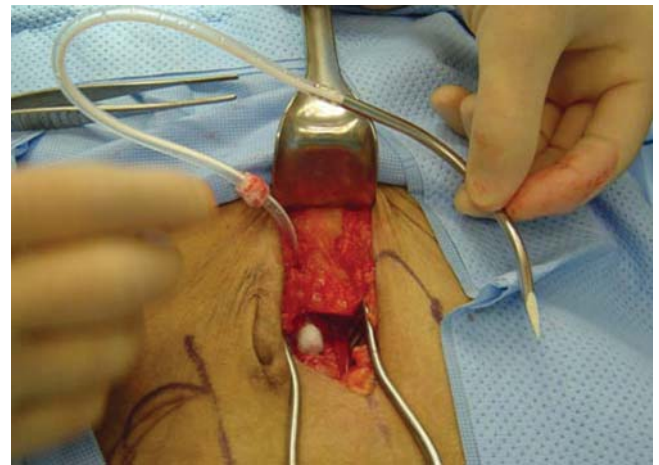


Figure 10 The inner cuff is aligned in a craniocaudal direction. The subcutaneous sharp (Faller) tunneler has now been attached to the catheter.

The tunneler should exit the skin at a 30 to 45° angle to optimize catheter alignment to the skin and comfort for the patient. We strongly advise against the technique of using a skin incision at the exit site and retrograde insertion of a hemostat to catch the PD catheter and pulling through the skin. This technique induces bleeding, is traumatic to the skin, and is prone to complications (mainly infection). The larger skin exit defects (and bleeding) with this technique may require stitching at the skin exit site, which further increases the infection risks and external Dacron cuff migration. Stitches must not be placed at the exit site; sutures here cause trauma and tension and promote infection at the exit site. The anterior fascia is closed in a running fashion with a 2-0 polypropylene suture. The skin is closed with an inverted 4-0 polydioxane or polygalactin subcuticular

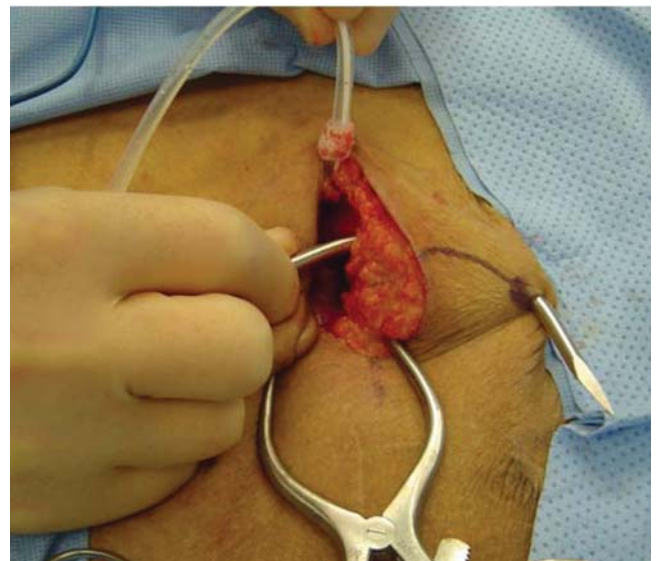


Figure 11 The sharp Faller tunneler has penetrated the skin at the predetermined and marked site. The external cuff ideally will be located 2.0 to 2.5 cm from the skin surface.



Figure 12 This close-up image of the catheter skin exit site shows the importance of using the correctly sized and fitted tunneling device.

suture and covered with half-inch SteriStrips and a sterile dressing.

Laparoscopic Placement

Although laparoscopic placement of the PD catheter can be performed under local anesthesia and sedation, general anesthesia with endotracheal intubation is safer and preferred for patient comfort. Prophylactic antibiotics are given in the operating room before skin incision, as in the open procedure.

For first-time catheters in a patient with no previous abdominal surgeries, a single camera port and the peel-away catheter sheath are needed. Incidental minor surgical procedures such as small umbilical hernia repairs and omentopexy can also be accomplished with a single port. More complicated and extensive repairs will require additional ports.

The site for Veress needle insufflation should be 1 to 2 inches below the costal margin in the midclavicular line on the ipsilateral side as catheter placement [see Figure 13]. Once pneumoperitoneum is established, the Veress needle is exchanged for the camera port. A 5 mm port is placed into the abdomen under direct vision with the camera inside the device. If the patient has had prior abdominal operations or there are concerns for significant adhesions, open Hasson placement in the supraumbilical midline may be used to establish pneumoperitoneum and gain access to the abdominal cavity.

After surveying the abdomen for injury and incidental pathology, the 0° camera is changed to the 30° lens for improved visualization during the PD catheter insertion steps. The desired level of catheter insertion is determined as a location away from the epigastric vessels, or about 3 cm lateral to the midline and 1 to 2 cm above the level of the umbilicus [see Figure 13]. A 5 to 7 mm transverse incision is made at the selected catheter insertion site. A slightly larger skin incision is helpful when pulling the catheter with the external cuff to the skin exit site. An 18-gauge needle is inserted through the incision site directed at 45° caudad. As the needle is advanced along and between the peritoneum

and the posterior rectus fascia for about 3 to 4 cm, local anesthetic (e.g., bupivacaine 0.25%) is injected along the tract and between the peritoneum and the fascia to create a subperitoneal tunnel and to achieve postoperative pain control. The needle is then used to penetrate the peritoneum about 4 to 5 cm below the level of umbilicus and about 3 cm lateral to the midline in a downward direction.

The syringe is removed and a 0.35-inch internal diameter 50 cm guide wire is inserted. With adequate wire length inside the peritoneal cavity, the needle is also removed, leaving only the guide wire in place. The catheter tract is created using only the stiff dilator inserted over the guide wire with the peel-away sheath off. This facilitates the second pass with the complete peel-away set. While keeping the wire in place, the dilator is removed and inserted into the 22 French peel-away sheath.

The complete set (dilator and peel-away sheath) is now reinserted over the guide wire into the abdomen under direct laparoscopic visualization. When the peel-away sheath is visualized in the abdominal cavity, the inner dilator is removed. The PD catheter is prepared on the back table by inserting the stylet into the PD catheter. The double-cuffed 62 cm long PD catheter with stylet is now inserted into the peel-away sheath, and under direct vision, the PD catheter is advanced until the tip of the guide wire is seen exiting the sheath inside the abdomen.

At this point, the guide is retracted as the catheter is advanced, and the catheter will regain its “pigtail” configuration, which is to be located in the deep pelvis. The catheter is advanced until the inner Dacron cuff is seen. The guide is now completely removed, as is the peel-away sheath. The inner Dacron cuff is pulled back to sit at the posterior rectus muscle fascia or in the rectus muscle. The degree of pull-back is determined based on the length needed to place the external cuff at 1.5 to 2.0 cm from the skin exit site. Next, the curved sharp tunneler is attached to the catheter and penetrated first in an upward and then in a downward curvilinear fashion, out through the skin. This subcutaneous tract step is identical to that in the open procedure. The superficial cuff is placed 1.5 to 2.0 cm from the skin.

Before the camera is removed, the proper position of the curled portion of the catheter in the pelvis is confirmed. Should there be some blood in the abdomen, irrigation through the PD catheter under direct camera vision is performed. After the camera is removed, pneumoperitoneum is released prior to removal of the 5 mm cannula. Port sites are closed with one or two inverted sutures.

Closure and Postoperative Care

With either approach, it is recommended that 40 to 60 mL of saline be left in the abdomen. The newly placed catheter is flushed and aspirated gently with saline or, better, allowed to drain by gravity, ruling out catheter obstruction. Three milliliters of heparin (concentration 1,000 U/mL) is injected into the catheter to avoid catheter obstruction from small blood clots or fibrin. The catheter exit site is covered with 2 × 2-inch gauze wrapped around the catheter to keep the site dry. Dressing changes should be performed in sterile fashion until wound healing is complete. If immediate PD use is required, low-volume exchanges can be initiated within 24 to 48 hours, but it is generally recommended that

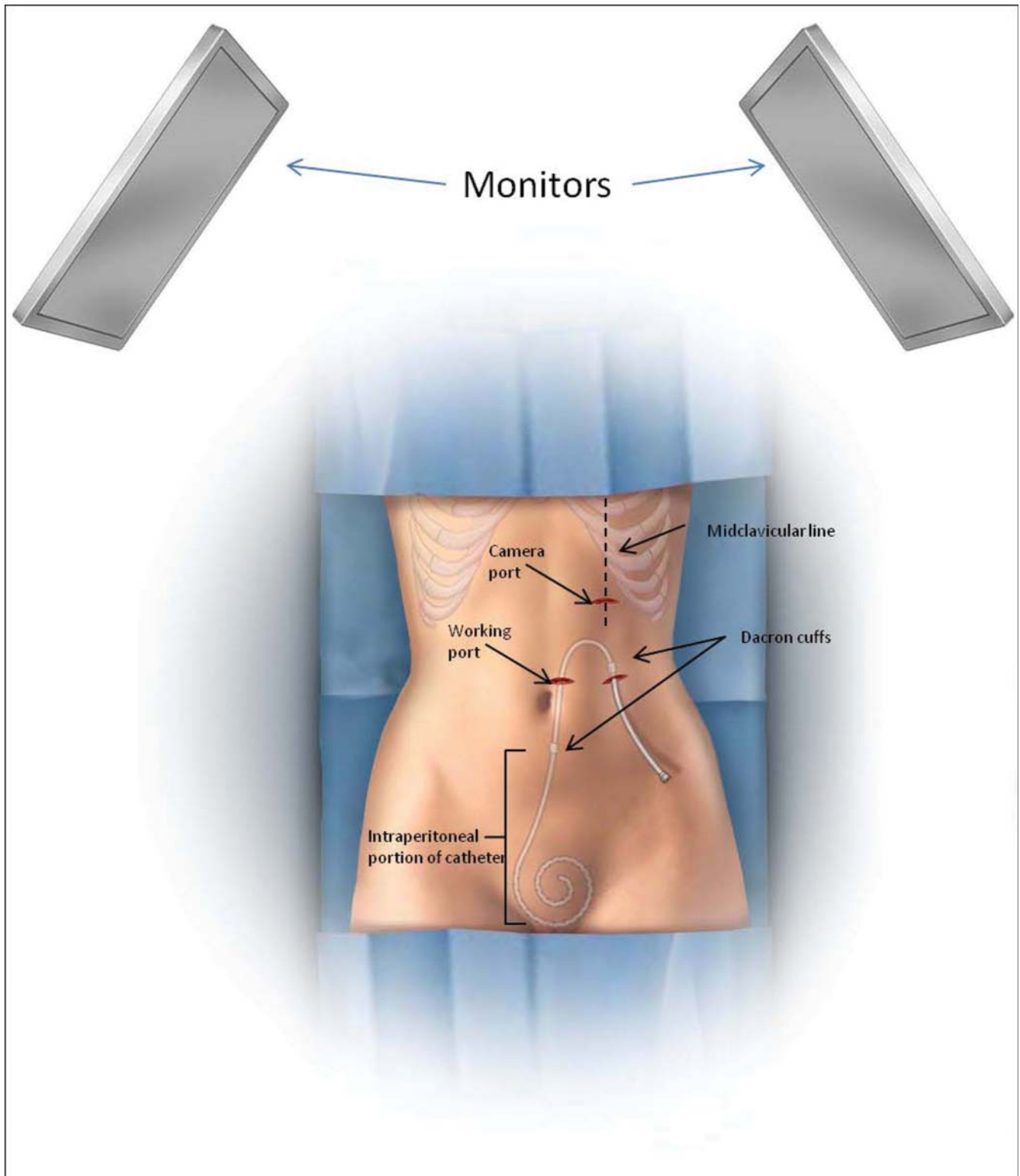


Figure 13 Port locations and final position of the peritoneal dialysis catheter after laparoscopic placement.

dialysis be delayed for approximately 2 to 4 weeks, depending on urgency and the postoperative course.

Catheter Removal

PD catheters may require removal for various reasons, such as after a successful renal transplantation or after

technical malfunctions. During preparation, the catheter should first be clamped next to the skin with a hemostat while the external catheter with the transfer set is removed. The catheter is exposed through the previous incision used for open placement, dissected circumferentially, and then sharply divided. The catheter is then followed down to the

rectus muscle and its posterior fascia. The deep cuff is exposed by dividing the rectus muscle and fascia, and the peritoneal defect becomes visible. Placing a 2-0 polypropylene suture at the edge of the defect, before the cuff is completely free, will prevent losing the deep defect. The defect is closed after the catheter is pulled out. This suture is also hemostatic as bleeding can occur into the abdomen. The surgeon should be careful not to splash infected peritoneal fluid during removal of the intraperitoneal segment of the catheter. Cultures are sent as indicated. Depending on location, the external cuff is excised from inside and sharply divided distal to the cuff, which frees the external portion of the catheter. The skin exit site may require skin excision or débridement and one inverted suture to close.

Complications

Catheter-related complications (leaks, peritonitis, obstruction, or hernias) may occur in up to 70% of patients over the lifetime of the PD catheter.²³ The following summarizes the most common problems related to PD catheters.

HERNIAS

Hernias are the most common noninfectious complication related to long-term PD use. The incidence is less than 5% in patients who undergo open catheter placement in the paramedian position but as high as 10 to 15% with a midline incision.²² Patients present with a painless bulge; pain suggests an incarcerated or strangulated loop of bowel. A small umbilical or inguinal hernia can be repaired at the time of PD placement. Symptomatic hernias occurring after initiation of PD should also be repaired. PD can often be resumed postoperatively with a temporarily modified fluid exchange regimen, including more frequent exchanges of smaller volumes and bed rest during exchanges.

LEAKAGE

Leaks can occur at any time, at the catheter exit site or through the wound. An early leak represents poor surgical technique, most commonly imprecise closure of rectus fascia. Watertight closures are not associated with leaks and allow for early catheter use. Resting the catheter for a short period of time (2 to 3 weeks) may allow small peritoneal defects to seal. Most PD dialysis centers wait 3 to 4 weeks before starting fluid exchanges, while cuff incorporation takes place.

Large leaks weeks after placement are unlikely to close with conservative management alone. Repair of a large defect may be difficult and tends to lead to other complications, such as infection. Relocating the catheter to a new site may be the most appropriate option. A large leak in the presence of infection requires catheter removal. Older catheters that have been in place for an extended period of time can also present with a large leak due to mechanical failure (i.e., fracture) of the catheter itself. Depending on the distance from the skin exit site catheter, fractures can be repaired with prepackaged patch kits. Clinical judgment will guide the clinicians as to the best action to follow based on the patient's medical risk, time after catheter placement, and other dialysis options available. The center's team experience also needs to be taken into consideration.

MECHANICAL DYSFUNCTION OR MALFUNCTION

The most common cause of catheter malfunction (usually impaired or slow draining) is constipation, leading to external catheter obstruction.²³ A plain radiograph may identify abdominal pathology and indicate malpositioning of the catheter.

Obstruction is often caused by dislodgment from the pelvis and omental wrapping of the catheter. Temporary relief is sometimes obtained through the forceful injection of saline, thereby displacing surrounding omental tissue. Permanent corrective intervention requires a mini-laparotomy or laparoscopy to remove tissue from the catheter, redirect the catheter into the pelvis, and suture the catheter in place.^{33,38,40} Dislocation is usually detected by concomitant obstruction; the catheter can usually be returned to the pelvis, either by a small infraumbilical midline incision or through a laparoscopic procedure. During the initial catheter placement, correct alignment of the catheter in the rectus as it exits the abdomen prevents later dislodgment. Attempts at fluoroscopic repositioning with a guide wire usually have limited success.

INFECTIONS

Infections involving PD catheters can be classified into three categories, depending on the segment of the catheter involved: exit site infections, tunnel infections, and peritonitis. The treatment varies with the location of infection and the etiology.

Exit Site Infections

Exit site infections present with erythema and purulent drainage from the skin exit site and are most often due to skin flora. Untreated, these infections often progress to tunnel infections and, eventually, peritonitis. Simple infections without drainage are treated with antibiotics and improved local hygiene.^{41,42} Exit site infections involving the superficial cuff can be treated with simple drainage of the site and externalization of the superficial cuff. Externalization of the superficial cuff of a double-cuff catheter converts the catheter to a single-cuff catheter. We generally "shave" the infected cuff at the time of externalization to decrease bacterial burden on the catheter. Drainage and cuff externalization cannot be performed with single-cuff catheters.

Tunnel Infections

Tunnel infections typically present in conjunction with exit site infections but can occur alone. Patients may have tenderness or erythema overlying the catheter tract. Tunnel infections are treated in a fashion similar to that of exit site infections.

Peritonitis

Peritonitis represents the most common cause of technical failure in PD and the most common reason for conversion to HD. Gram-positive organisms are the etiology in a majority of all episodes of peritonitis (44%), with coagulase-negative staphylococcus being the most frequent gram-positive organism of all.⁴³ Twenty-five percent of peritonitis episodes are due to gram-negative organisms, whereas 20% of cases are culture negative. Overall, a center's peritonitis rate

should not exceed one episode per 18 months as recommended by the International Society for Peritoneal Dialysis (ISPD).⁴⁴ Higher rates should result in a review of techniques and reeducation of both patients and staff to ensure that breaks in technique are not contributing to high rates of peritonitis. The routes of peritoneal infection include transluminal contamination (35 to 50%), periluminal contamination at the exit site or along the tunnel (15 to 25%), and intra-abdominal sources (20%). Translocation through intact bowel may be the etiology in the setting of colonoscopy, colitis or diarrhea, or even constipation. A perforated viscus can also cause peritonitis and should be strongly considered in the appropriate clinical setting.

The most common presentation of peritonitis in the PD patient is abdominal pain with a cloudy effluent. A clear effluent does not rule out peritonitis, and a cloudy effluent alone does not always indicate that the patient has peritonitis. Cloudy effluents are also associated with malignancies, chemical peritonitis, or a sample from a “dry” abdomen. If peritonitis is suspected, empirical antibiotics should be started after sending a sample of peritoneal fluid. Antibiotic selection should cover both gram-positive and gram-negative organisms; intraperitoneal administration is superior to intravenous dosing.⁴² In diagnosing peritonitis, an effluent with a white blood cell count of more than 100/μL with at least 50% polymorphonuclear cells is highly suggestive. Even if the cell count does not reach 100/μL, as in the instance of a “dry” abdomen, a proportion greater than 50% polymorphonuclear cells is a strong indicator of peritonitis. Once culture results are available, antibiotic therapy should be tailored to treat identified organisms. An episode of uncomplicated peritonitis is not an indication for catheter removal, but refractory peritonitis (failure to improve after 5 days of appropriate antibiotics) and relapsing peritonitis (recurrence after 4 weeks of treatment) often require catheter removal. Coagulase-negative staphylococcal infections can lead to the formation of a biofilm that results in recurrent peritonitis; catheters infected by these organisms should also be removed. Fungal and polymicrobial peritonitis are indications for immediate catheter removal.

Summary

PD remains an underused modality for renal replacement, despite ample evidence of improved survival and quality of life when compared with HD. Careful patient selection and planning by the surgeon as part of a multidisciplinary team caring for the ESRD patient can lead to long-term success with PD. One-year actuarial catheter survival of 80% should be expected by ISPD standards.^{25,35,44} Catheter survival rates as high as 91% at 3 years can be accomplished with proper patient management.¹⁹

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30 DESCENDING THORACIC AND THORACOABDOMINAL AORTIC ANEURYSMS: OPEN AND ENDOVASCULAR REPAIR

Nathanial Fernandez, MD, and Robert Y. Rhee, MD

Background

Descending thoracic aneurysms (DTAs) are less prevalent than their abdominal counterparts, with rates reported in the range of 10 cases per 100,000 person-years.¹ Isolated involvement of the descending thoracic aorta occurs in 30 to 40% of all thoracic aneurysm cases.¹⁻³ In one population-based study of thoracic aortic aneurysms, the ascending aorta and aortic arch involvement occurred in 40%, isolated DTA in 31%, and the entire arch and descending thoracic aorta in 29%.¹

Thoracoabdominal aortic aneurysms (TAAAs), like DTAs, are less common than abdominal aortic aneurysms (AAAs).⁴ Similar to AAA disease, there appears to be some degree of genetic predisposition. It has been reported that as many as 20% of patients with TAAA will have a first-degree relative with a thoracic or thoracoabdominal aneurysm.⁵ In addition to the familial link, TAAA has been associated with multiple genetic syndromes. Marfan syndrome (involving a mutation in the fibrillin-1 protein found on chromosome 15) is the most common genetic syndrome associated with TAAAs. These patients tend to develop aneurysms at an earlier age (late third to fourth decade) than other TAAA patients (from atherosclerotic disease) who commonly present with aneurysms when they are older than 60 years. Other genetic syndromes that have been associated with the development of a TAAA are Turner syndrome, Ehlers-Danlos syndrome, and polycystic kidney disease.⁶

TAAAs are also associated with a previous or chronic type B aortic dissection. To that end, as many as 25% of patients with a known TAAA will have had a chronic type B dissection.⁷ Historically, it is estimated that between 20 and 40% of the aortas involved with type B dissections will degenerate into a TAAA over the first 2 to 5 years following diagnosis. A less prevalent percentage of patients with a TAAA will be mycotic (infected) in nature. In mycotic TAAA, cultures will commonly identify *Staphylococcus* species, *Salmonella* species, and *Streptococcus* species, with less commonly identified microbes including *Enterococcus* species, *Escherichia coli*, *Bacteroides* species, and fungal infections.^{8,9}

The main goal of treatment of descending thoracic and thoracoabdominal aneurysms is the prevention of rupture and

death. The natural history of DTAs is poorly defined. In patients with a DTA followed without intervention, it has been estimated that 32 to 43% of these aneurysms will eventually rupture^{5,10} and that more than 90% of these ruptures will be fatal if not treated, whereas survival for patients operated on for rupture has been reported as between 56 and 76% depending on the patient's condition at the time of operation.^{2,11} The reported risk of rupture is varied, but Clouse and colleagues reported the cumulative risk based on size over a 5-year period to be 0% for aneurysms less than 4 cm in diameter, 16% for aneurysms with a diameter between 4 and 5.9 cm, and 31% for an aneurysm larger than 6 cm.¹ In patients with DTA and TAAA, it has been found that hypertension, chronic obstructive pulmonary disease (COPD), and renal failure are risk factors for rupture, with the size of the aneurysm being the most important predictor of rupture.¹² Notably, an aneurysm with a diameter of 6 cm or more has been associated with a fivefold increase in the chance of rupture.¹³ Based on longitudinal data; the thoracic aorta will have an average annual growth rate of approximately 0.1 cm per year. The descending thoracic aorta seems to grow faster than the ascending, 0.19 cm per year versus 0.07cm, and the rate of growth tends to accelerate as the aneurysm gets larger.⁵

For thoracoabdominal aneurysms, like thoracic aneurysms, size is felt to be the single most important risk factor for rupture. Increased rates of growth are also felt to be predictive of an increased chance for rupture. At our institution, growth greater than 1 cm in a year is used as an indication for repair if the patient is a relatively good risk for an intervention. Other factors associated with an increased risk of rupture include advanced age, the presence of coronary artery disease, the presence of COPD, and renal insufficiency.¹¹ Growth rates for TAAA are also variable, with rates ranging between 0.1 and 0.45 cm per year, with faster rates of growth for larger aneurysms. Cambria and colleagues reported an annual growth rate of 0.2 cm per year.¹⁰ In that study, the expansion rate was not influenced by the size at diagnosis, presence of hypertension, tobacco use, or renal failure.¹⁰ They did, however, note an association with increased rates of expansion and COPD, which has also been noted in other studies. Overall rupture rates were 12% at 2 years and 18% for those aneurysms larger than 5 cm.

Survival for patients with DTAs and TAAAs is generally poor compared with that for the general population. The 5-year mortality for DTAs exceeding 6 cm varies from 38 to 64%.¹² One population-based study looking at survival and prognosis for patients with degenerative thoracic aneurysms showed a 5-year survival of only 56%. Rupture was the leading cause of death in this cohort and accounted for 30% of all deaths. Other associated mortality etiologies include cardiac events (25%), pulmonary causes (15%), cancer (10%), and stroke (4%).¹ For thoracoabdominal aneurysms treated nonoperatively, Cambria and colleagues showed an overall survival of 69% at 2 years and 39% at 5 years.¹⁰ A retrospective study looking at the outcomes of 170 aortic aneurysms treated nonoperatively showed 5-year survival of only 39% for thoracic aortic aneurysm (TAA) and 23% for TAAA.¹³ Multivariate analysis revealed that aneurysm diameter, the presence of renal failure, and hypertension were significant risk factors impairing survival. Additionally, the presence of renal failure and aneurysm diameter (greater than 6 cm) were predictive of a fivefold increased risk of rupture.¹³

Evaluation

PRESENTATION

The majority of DTAs are asymptomatic at the time of presentation and are found most commonly as an incidental finding during workup and imaging done for evaluation of another disorder. TAAAs, on the other hand, are asymptomatic at the time of discovery in approximately 43% of patients, 49% will present with symptoms other than rupture, and 9% will present with a leak or frank rupture.¹⁴

The most common presenting complaint for those symptomatic aneurysms that are not ruptured is ill-defined chronic back pain. Often back pain that is musculoskeletal in origin is difficult to differentiate from pain related to the aneurysm. Both types of aneurysms may cause symptoms owing to a local mass and pressure effects as well. These may include hoarseness, which can result from vocal cord paralysis secondary to compression of the left recurrent laryngeal or vagus nerves. This is most commonly seen in patients with large aneurysms of the proximal descending thoracic aorta. Patients also may experience respiratory difficulty or dyspnea related to compression of the tracheobronchial tree. Dysphagia can also occur as a result of extrinsic compression of the esophagus by a large aneurysm. A large TAAA with an extended paravisceral segment can induce pressure against the duodenum and cause weight loss related to early satiety or obstruction or a vague sensation of “fullness,” which may prevent the patient from eating adequately. Rarely, direct erosion of the aneurysm into the adjacent tracheobronchial tree, esophagus, or both can cause exsanguination, presenting as massive hemoptysis or hematemesis, or, less frequently, slow intermittent blood loss [see Table 1].

IMAGING

Given that the majority of patients with DTAs or TAAAs are asymptomatic, most patients are diagnosed incidentally on routine imaging studies done to evaluate another disorder.

For the evaluation of thoracic and thoracoabdominal aortic aneurysms, the primary imaging modality and the most definitive is contrast-enhanced computed tomography (CT) or

Table 1 Symptoms Attributable to Thoracic and Thoracoabdominal Aortic Aneurysms

Back pain
Chronic
Acute change may be sign of impending rupture
Hoarseness
Dyspnea/respiratory difficulty
Dysphagia
Weight loss/early satiety (large TAAA)
Erosion into adjacent structure with bleeding

TAAA = thoracoabdominal aortic aneurysm.

computed tomographic angiography (CTA) of the chest, abdomen, and pelvis. CTA is extremely accurate in its ability to define the aortic anatomy and the extent of the aneurysm. CTA can also precisely define the aortic lumen and outer diameter, (including the distinction between the true and false lumen in acute aortic dissection) and show the presence or absence of mural thrombus and inflammatory changes in the aortic wall. In addition to providing good spatial resolution and accurately evaluating the aorta, it allows you to assess other intrathoracic, intra-abdominal, or intrapelvic solid organs. Evaluation of the aorta for follow-up studies or in patients with renal impairment can be done without contrast if one is interested only in evaluating size progression. CTA is currently the imaging modality of choice for the evaluation of the extent of and the operative planning for DTA and TAAA.

Magnetic resonance angiography (MRA) is another noninvasive imaging modality that is widely available and can be used to evaluate the aorta and its branches. It has the benefit over CTA of not requiring iodinated contrast and can be used in patients with impaired renal function. Previously, gadolinium-enhanced MRA was used over CTA in patients with renal dysfunction, but recognition of the association between nephrogenic systemic fibrosis and the use of gadolinium in this patient population has limited the utility of gadolinium and at least this theoretical benefit of MRA over CTA.¹⁵ Non-contrast-enhanced MRA can still be done with good results, but the spatial resolution on an MRA has been shown to be not as precise as with CTA. Additionally, MRA does not show calcifications or mural thrombus as well as CT.

Transesophageal echocardiography is an invasive imaging modality and is more operator dependent than CTA or MRA. It is a useful tool for evaluation and diagnosis of aortic dissections, especially involving the ascending aorta. It can provide excellent images of the thoracic aorta but does not allow for evaluation of the whole aorta. It can be useful in the operating room too for showing aortic wall disease and assessing cardiac function. Standard duplex scanning (because of the constraints of the chest cavity) cannot image the descending and ascending aorta adequately to be useful as a standard diagnostic tool.

CLASSIFICATION

Aneurysmal disease can involve all segments of the ascending aorta, aortic arch, and the descending thoracic aorta or any combination of these. DTAs are classified as type A if they extend from the left subclavian artery (LSA) to the levels

of the sixth thoracic vertebrae, type B if they extend from T6 to the levels of the diaphragm, and type C if they go from the LSA to the diaphragm [see Figure 1].

A different classification scheme exists for aneurysms involving the thoracic aorta and visceral segment of the abdominal aorta or TAAA. The full extent of the aneurysmal involvement is defined by proper imaging, most commonly CTA. TAAAs are normally classified according to the extent of the aneurysmal involvement of the aorta. Type I classically involves the descending thoracic aorta distal to the LSA and ends above the renal arteries. Like type I, type II involves the thoracic aorta distal to the LSA but extends down to below the renal arteries. Type III extends from the sixth intercostal space or mid-descending thoracic aorta to below the renal arteries. Type IV TAAAs generally involve most if not all of the abdominal aorta, from the 12th intercostal space to the iliac bifurcation [see Figure 2].

PREOPERATIVE EVALUATION

Prior to proceeding with repair of a DTA or a TAAA, patients must be thoroughly evaluated medically to determine if they are physiologically fit enough for repair as this will influence decision making regarding the course of treatment. In addition to a thorough history and physical examination, screening tests to include basic metabolic profile, complete blood cell count, coagulation laboratory tests, chest x-ray, and an electrocardiogram should be obtained.

Generally, patients with thoracic aneurysm disease have multiple comorbidities. Therefore, extensive organ-specific evaluation of the patient's pulmonary status, cardiac status,

and renal function should be obtained prior to treatment. Conditions such as COPD can severely hamper the ability of the patient to recover from a significant, direct operation involving the chest cavity. COPD is defined by a clinically documented history of COPD or pulmonary function tests showing a forced expiratory volume in 1 second (FEV₁) of less than 70% of predicted. The incidence of COPD has been reported in 30 to 40% of patients with TAAA and is associated with increased risk for operative morbidity and mortality, particularly with open repair.^{16,17} It is important to get an accurate and thorough workup of the patient's pulmonary status if he or she is being considered for open repair of a DTA or TAAA. All candidates for open repair should therefore undergo complete pulmonary function testing. Every attempt should be made to improve lung function preoperatively, if possible. This may include immediate cessation of tobacco smoking, initiation of chest physical therapy, administration of bronchodilators, and antibiotics when indicated. Patients with severe pulmonary disease and prohibitive risk for open repair of TAAA should be considered for other, less invasive modes of treatment, such as hybrid endovascular repair.¹⁸

Coronary artery disease, like COPD, is also common in this patient population. All patients undergoing evaluation for repair of a thoracic or thoracoabdominal aortic aneurysm require a thorough cardiac evaluation. This includes a stress test with evaluation of left ventricular function. In the majority of patients, this involves a chemical stress test, which can define ventricular function and screen for reversible cardiac ischemia. Patients with a positive stress test should undergo cardiac catheterization and any indicated coronary artery revascularization

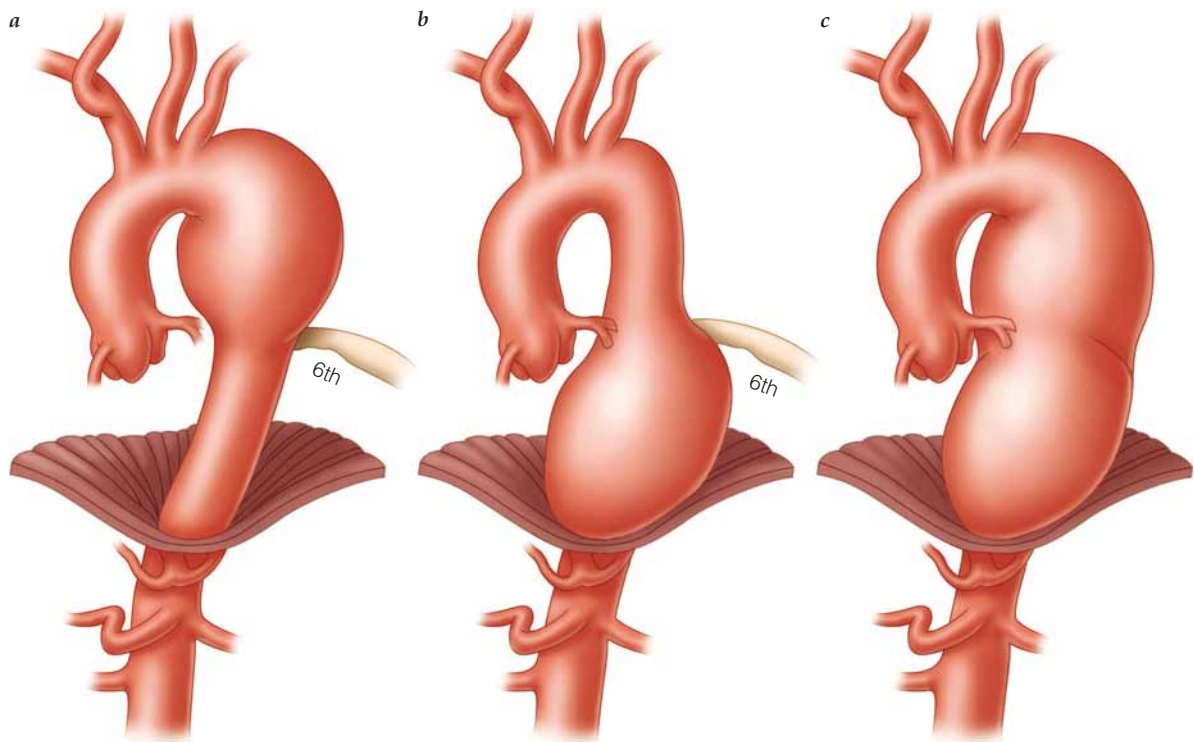


Figure 1 Classification of descending thoracic aortic aneurysms: (a) type A, left subclavian artery to T6; (b) type B, T6 to the diaphragm; or (c) type C, left subclavian artery to the diaphragm. Adapted from Estrera AL et al.¹⁶

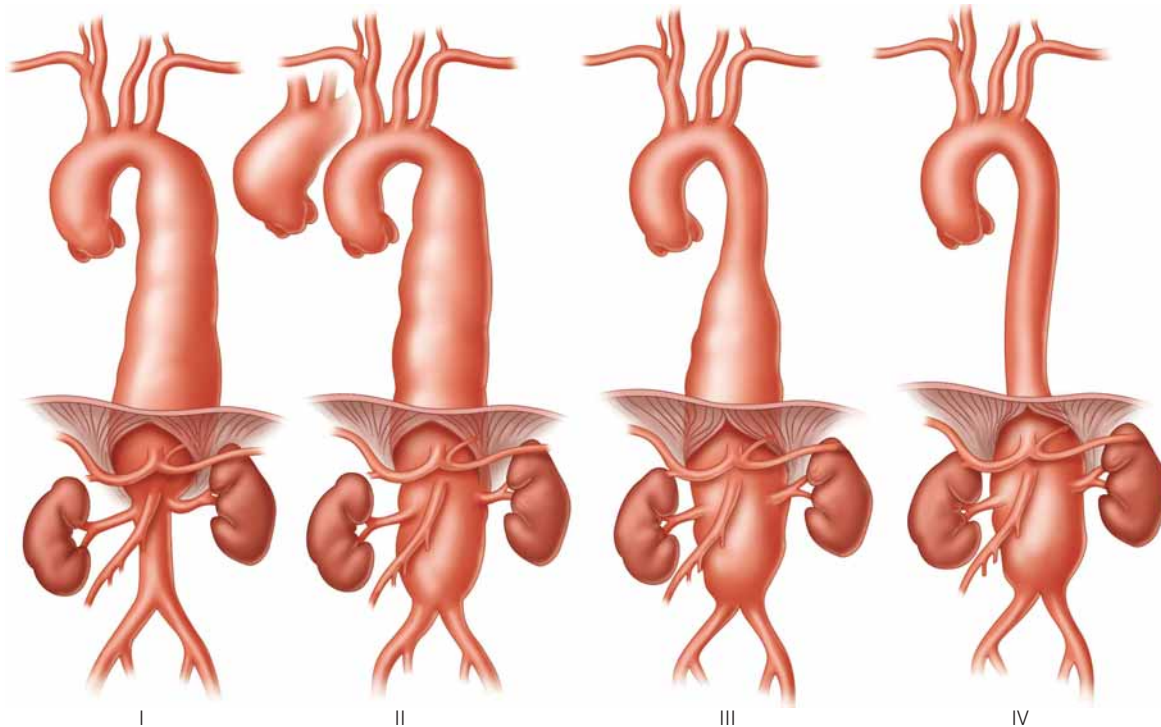


Figure 2 Crawford classification: type I extends from the proximal descending thoracic aorta to the upper abdominal aorta; type II from the proximal descending thoracic aorta to below the renal arteries; and type III from the distal half of the descending thoracic aorta to below the renal arteries; type IV involves most of or the entire abdominal aorta.

prior to open repair of a DTA or a TAAA. In patients who undergo percutaneous coronary artery angioplasty and stenting and who require clopidogrel, repair should be delayed long enough so that the clopidogrel can be stopped safely without increased risk of stent thrombosis. The clopidogrel is generally held for 7 days prior to open repair of a DTA or TAAA. In patients who are candidates for thoracic endovascular aortic repair (TEVAR), the clopidogrel does not need to be discontinued. In patients who undergo coronary artery bypass before repair, saphenous vein grafts are preferable to using the left internal mammary. This reduces the risk for cardiac ischemia if cross-clamping proximal to the LSA is required during open repair or if coverage of the LSA is necessary during TEVAR. Additionally, the internal mammary artery may provide important collateral blood supply to the spinal cord.

Finally, preoperative evaluation of a patient's renal function is mandatory as preoperative renal insufficiency (creatinine greater than 2.0 mg/dL) is a known significant risk factor for poor outcome and mortality.¹⁴ Preoperatively, nephrotoxic medications should be held and exposure to iodinated contrast should be minimized as much as possible. Renal function should be optimized with brisk preoperative hydration when necessary.

Management

THORACIC ANEURYSMS

Indications for Repair

The evaluation and decision-making process for the treatment of DTA are based on prevention of rupture and

minimizing the morbidity and mortality associated with repair. Any symptomatic or ruptured aneurysm mandates urgent repair regardless of the patient's risk factors. Obviously, given that the risk of operative intervention is relatively high, the patient and the family must be made fully aware of all of the possible associated morbidities and consequences of an unsuccessful repair attempt. For asymptomatic patients with nonruptured aneurysms, the decision-making process is a little more complex. Given that the size of the DTA is the number one predictor of the risk of rupture, findings on imaging revealing the diameter to be 6 cm or greater are generally considered an indication for repair at our institution provided that the patient is able to medically tolerate such an operation. Additionally, evidence that the aneurysm has grown at a rate of greater than 1 cm per year is a relative indication for repair. In patients with DTA of less than 6 cm, observation for a period of 6 months with rigorous follow-up imaging is indicated. Follow-up imaging may be performed with repeat CTA or noncontrast CT for a patient with renal insufficiency. If, at any point, the size increases to greater than 6 cm, there is evidence of rapid growth (> 1 cm/year), or the patient has developed any symptoms directly attributable to the aneurysm, we would initiate the process for workup for possible repair [see Figure 3]. Clearly, patients should be instructed that if at any point during the observation period they develop new symptoms attributable to the aneurysm, they should seek medical treatment immediately. If the aneurysm is stable on two consecutive studies, then the aneurysm surveillance can be extended to every 12 months.

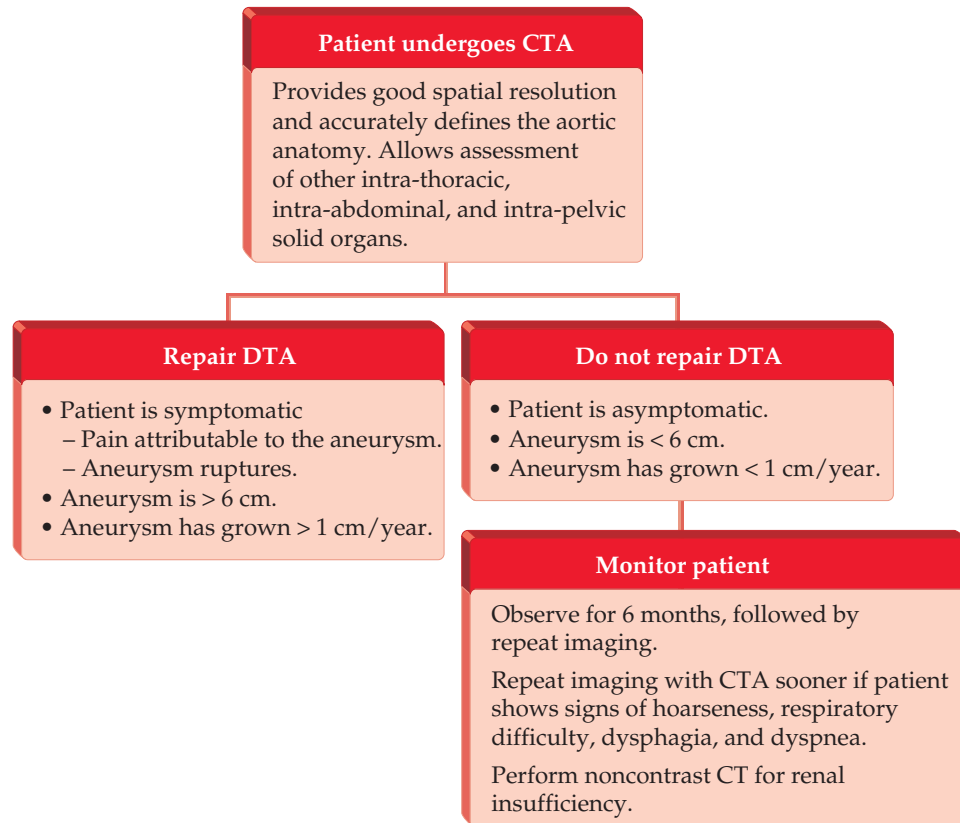


Figure 3 Evaluation of a patient with a thoracic aortic aneurysm. CT = computed tomography; CTA = computed tomographic angiography; DTA = descending thoracic aortic aneurysm.

Repair of DTAs

Open repair of DTA has traditionally been a procedure associated with high morbidity and mortality and has been offered primarily to good surgical candidates. Perioperative death rates exceeding 10%, a paraplegia risk of 4 to 5%, and the physiologic stress of recovery from a thoracotomy make this a difficult option for most patients.^{19,20} Despite advances in surgical technique and perioperative care, open repair of a DTA remains a difficult, often morbid undertaking for patients. Reported complications of open repair include bleeding requiring reoperation (2%), paraplegia (7.5 to 14%), myocardial infarction and all cardiac events (20%), pulmonary insufficiency or pulmonary complications (20 to 50%), and renal failure (13 to 20%).^{21–23}

TEVAR offers the benefits of aneurysm exclusion without the physiologic insult of prolonged proximal aortic cross-clamping and direct surgical exposure, which may improve early morbidity.²¹ This technique was first introduced by Dake and colleagues in 1994 and has become a mainstay of treatment for isolated DTA with favorable anatomy.²⁴ Currently, three endografts are approved by the Food and Drug Administration (FDA) for use in treatment of thoracic aortic pathology and are intended for the endovascular repair of fusiform and saccular aneurysms as well as penetrating ulcers of the descending thoracic aorta in patients with appropriate anatomy. The GORE Excluder (TAG) device was the first thoracic endograft to gain FDA approval. It is designed to

treat aortic neck diameters no smaller than 23 mm and no larger than 37 mm. The Medtronic Talent Thoracic stent graft gained FDA approval in 2008 and is intended to treat aortas with a nonaneurysmal aortic diameter in the range of 18 to 42 mm. It is made of inlaid stents and polyester fabric, and the largest size available is 46 mm. The Cook Zenith TX2 is the third approved endograft and is approved to treat aortas with a proximal neck and distal landing zone with diameters from 24 to 38 mm. It is a two-piece device with both proximal fixation hooks and distal fixation spines [see Figure 4].

There are, however, significant anatomic restrictions for TEVAR. To maximize fixation and obtain an adequate seal, the proximal and distal segments of the aorta must be relatively disease free, small enough in size, and an adequate length (greater than 2 cm) for the currently available endografts [see Figure 5]. To increase the indication for proximal aortic treatment, one may need to cover the origin of the LSA, which is generally well tolerated. In one retrospective review of 171 patients who underwent thoracic endograft for repair of DTA, 22 (12.9%) patients had a distance from the LSA to the beginning of aneurysm, or the primary entry site of a dissection was < 1.5 cm and required coverage of the origin of LSA. None had acute symptoms of malperfusion, and at the 2-year follow-up, 68% were asymptomatic, with 32% having mild symptoms and none requiring revascularization.²⁵ One exception is in a patient with previous coronary artery bypass in which the

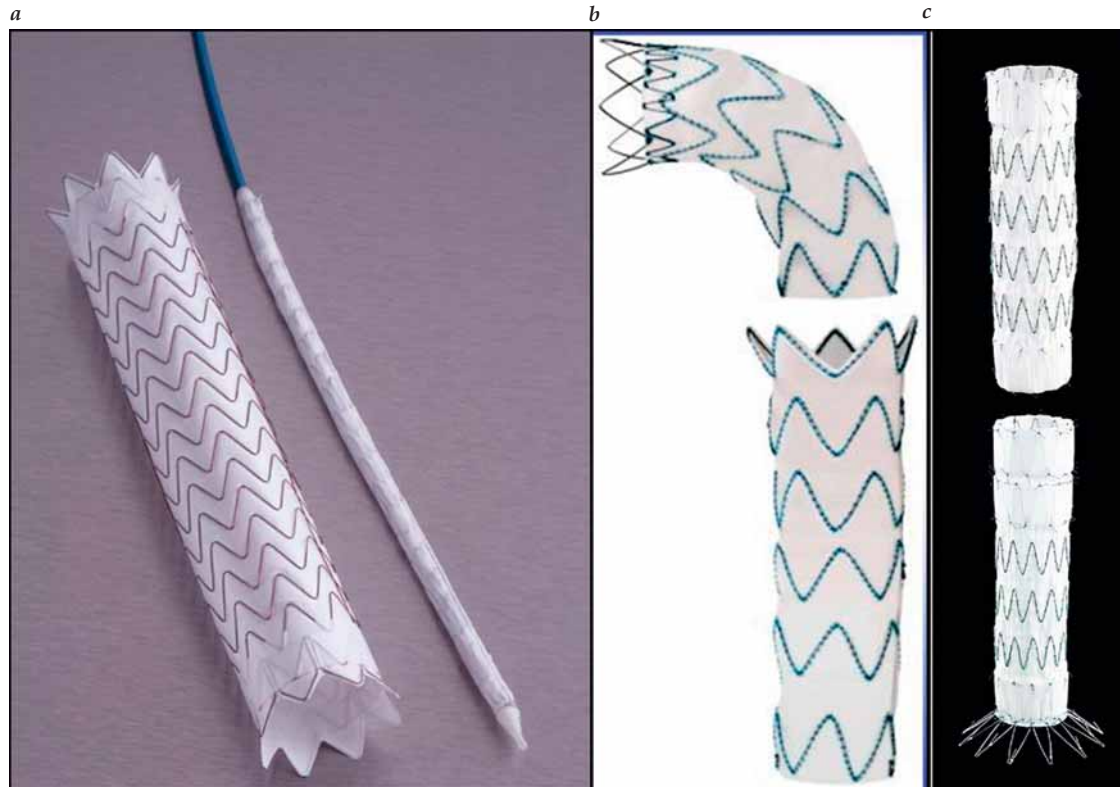


Figure 4 Available thoracic endografts. (a) Gore-Excluder (TAG); (b) Medtronic Talent; and (c) Cook TX2.

left internal mammary artery has been used as a graft to revascularize the heart. In this setting, it is recommended that an LSA transposition or carotid subclavian bypass be performed prior to covering the LSA. Another indication for revascularization of the LSA would be the development of significant upper extremity ischemic symptoms.

Outcomes of Repair for DTA

The theoretical benefit of endovascular repair over open repair is based on the concept that TEVAR is associated with less morbidity and mortality. Even at centers of excellence, morbidity from elective open surgical repair is significant with paraplegia rates of 5 to 21% and 30-day mortality between 5 and 20%.²⁶

The risk of paraplegia with TEVAR for DTAs appears to be less than with open repair, with various studies reporting perioperative paraplegia rates of 0 to 4%.^{26–30} Factors thought to be associated with an increased risk for paraplegia in TEVAR include coverage of the LSA, extensive coverage of the distal thoracic aorta, previous AAA repair, and compromised internal iliac artery circulation.^{27,30} When any of these factors are present, the use of spinal drainage is recommended, as well as maintenance of mean arterial pressures > 90 mm Hg during the procedure and early postoperative period.³⁰

TEVAR results have had encouraging short-, intermediate-, and now longer-term survival outcomes. In the perioperative period, multiple studies have shown very low 30-day mortality rates of 1.5 to 6.9%.^{26–30} Additionally, the reported survival rates have been encouraging, with 1-year overall survival rates of 83% and aneurysm-related survival of 86%. At 2 years, the

reported survival rates are 75 to 77%, and the 5-year survival is 64%.^{27,29,30} These results compare favorably with the overall 5-year survival with open repair of approximately 56% in a recent population-based study.¹

A problem unique to endovascular repair is the presence or development of endoleaks. These occur because (unlike in an open repair, where the graft is sewn to the vessel wall) exclusion of the aneurysm relies on radial force and in some cases fixation barbs to obtain a good seal and hold the stent graft in one place, preventing migration. Perioperative endoleak rates have recently been reported to range from 2.2 to 9.4% of patients, with late endoleaks accounting for another 2.2 to 9%.^{21,27–30} These endoleaks most often can be managed with a repeat endovascular intervention. Many are fortunately not clinically significant and can be observed.^{21,27–30}

However, no prospective studies have compared open surgical repair and TEVAR for the treatment of a DTA, but many of the results from TEVAR have been compared with the historical results reported for open repair. One study looking at and comparing the results of the endovascular stent grafting for the treatment of DTA with those of an open surgical cohort control group involved 140 patients treated as part of the Gore TAG trial.²¹ Comparing operative mortality between the two groups revealed a perioperative mortality of 2.1% in the endograft group versus 11.7% with open repair. Similarly, the rates of spinal cord ischemia (SCI) favored the endograft group, with the total incidence of SCI being 2.9% versus 13.8% in the open surgical control group. Kaplan-Meier analysis revealed similar survival, with an estimated 2-year survival of 78% and 76% in the endograft group and

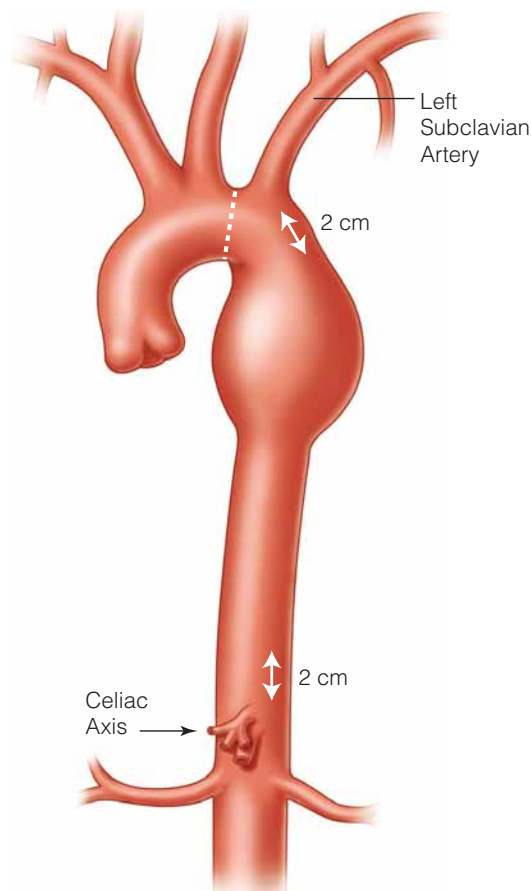


Figure 5 Anatomic restrictions for thoracic endovascular aortic repair (TEVAR).

the open cohort, respectively. Finally, there were no cases of aneurysm rupture in either cohort.

Another study compared the results of endovascular and open repair for the treatment of DTAs and TAAAs. A total of 724 patients underwent repair, 352 in the endograft group and 372 in the surgical group. The patients in the endograft group were, on average, 9 years older and had a higher incidence of coronary artery disease and COPD as well as a lower glomerular filtration rate. Despite the relative increased age and comorbidities, there was a trend toward better survival at 30 days, with a perioperative mortality of 5.7% in the endograft group versus 8.3% in the surgical group. Additionally, there was no difference in survival at 12 months, and there was a borderline difference in the incidence of SCI favoring the endograft group: 4.3% for the endovascular group and 7.5% for the open repair group.²²

Based on these promising results, TEVAR has become the primary mode of treatment of DTAs at our institution and in most hospitals that treat such diseases.

THORACOABDOMINAL AORTIC ANEURYSM

Indications for Repair

The initial evaluation of a patient with a TAAA is similar to that done for a thoracic aortic aneurysm and again centers on the goal of preventing rupture and minimizing the

morbidity and mortality. Evaluation of a patient with a TAAA should include a CT angiogram of the chest abdomen and pelvis to define the anatomy and extent of the aneurysm as well as rule out rupture or signs of impending rupture. Any symptomatic aneurysm or aneurysm with evidence of rupture mandates emergent repair. As with all aneurysms of the aorta, size is the number one predictor of the risk of rupture.

After the initial evaluation and CT angiography are done, the next step in the decision-making process is based on the size of the aneurysm. If the aneurysm is less than 6 cm, then the patient should be observed and seen again in 6 months with a repeat CT scan. If the aneurysm size is stable, without signs of rapid growth (greater than 1 cm per year), and less than 6 cm in diameter, then the plan of observation should be continued. If the TAAA is stable after two consecutive evaluations at 6-month intervals, then this can again be extended to once a year. If there is continued slow growth of the aneurysm, serial evaluation is undertaken every 6 months until the aneurysm reaches the size of 6 cm, at which point, the patient would undergo further evaluation or workup to evaluate fitness for possible repair [see Figure 6].

If the aneurysm is 6 cm in diameter or greater, or if on follow-up it increases in size to 6 cm, then workup of the patient's physiologic status should be done to determine the patient's tolerance for open, direct repair. TAAA repair has significantly higher morbidity and mortality than even open DTA repair. Basic metabolic laboratory tests should be obtained, as well as a chest radiograph, pulmonary function tests (similar requirements for patients with a DTA), and an electrocardiogram. Preoperative renal dysfunction is a significant predictor of postprocedure renal failure. Postoperative renal failure is, in turn, associated with increased mortality.^{14,17} The patient's pulmonary status and cardiac status are the two most important physiologic factors that guide the patient's course of care [see Figure 6].

The options for care of these patients include direct open repair, debranching procedure with subsequent endograft repair, branched or fenestrated endograft repair, or continued observation. Care of the patient should be individualized to the patient based on the anatomy of their aneurysm and overall functional status, especially related to the patient's pulmonary function and cardiac risk factors.

If a patient with a TAAA 6 cm or greater has adequate pulmonary reserve ($FEV_1 > 70\%$ predicted) and low cardiac risk, an open surgical repair is the definitive primary treatment option. However, if a patient were determined to be at low risk from a pulmonary standpoint but felt to be at high risk from a cardiac perspective, then continued observation is usually recommended. If the patient exhibits continued growth of the aneurysm or has direct aneurysm-related symptoms, appropriate cardiac revascularization is indicated prior to any type of direct surgical intervention for the TAAA [see Figure 6].

In patients with poor pulmonary function ($FEV_1 < 70\%$ predicted) on pulmonary function testing and relatively low cardiac risk, then an option that is possible is a debranching procedure followed by endograft repair.³¹⁻³³ Additional options include continued observation and a branched or fenestrated endograft. The latter treatment is available only in select centers, with very ill-defined results.^{34,35} Finally, in patients with poor pulmonary function who are determined

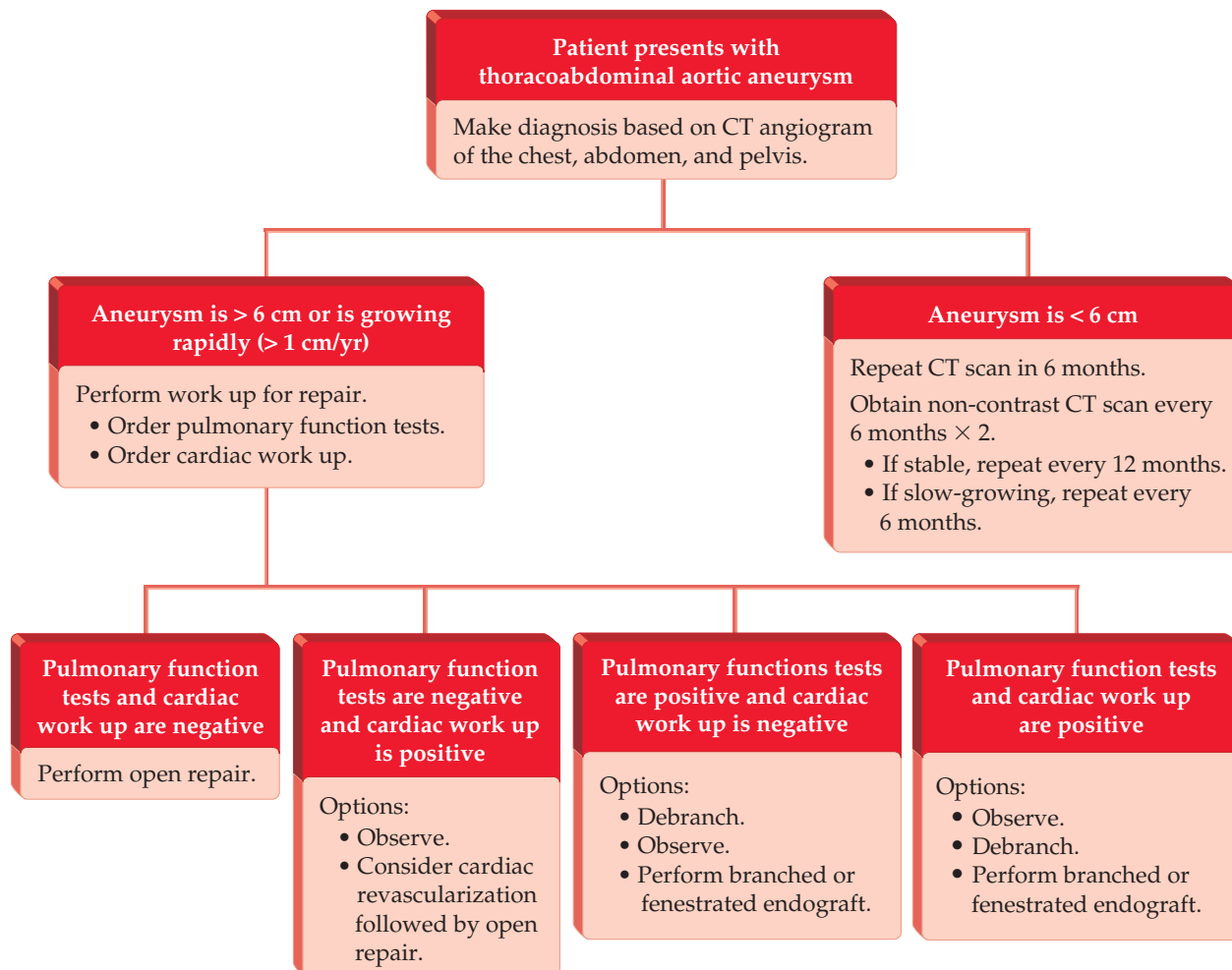


Figure 6 Evaluation of a patient with a thoracoabdominal aneurysm. CT = computed tomographic.

to be at high risk from a cardiac standpoint, the only option is observation [see Figure 6].

Open Repair

Despite improvements in surgical technique, surgical adjuncts, and perioperative care, open surgical repair of a thoracoabdominal aneurysm remains a morbid procedure involving entering two major body cavities and can be a daunting endeavor for both the surgeon and the patient. Successful repair of TAAAs was first reported in the 1950s, and in 1993, Svensson and colleagues' benchmark series describing their experience with 1,509 patients undergoing TAAA repair was published.¹⁷ In this cohort, there was an 18% incidence of postoperative renal failure (9% requiring hemodialysis) and a 16% rate of paraplegia or paraparesis. Factors associated with increased rates of SCI, paraplegia, or paraparesis were extensive replacement of the aorta, increased age of the patient, preoperative rupture, presence of a proximal aortic aneurysm, presence of preoperative renal dysfunction, and increased aortic cross-clamping time. In this study, the mean total aortic cross-clamping time, defined as the time to reestablishment of flow to the lower limbs, was 43 minutes. When the aorta was clamped for less than 30 minutes, paraplegia was rare,

but when the duration of cross-clamping was longer than 60 minutes, the risk of SCI was substantially higher. Additionally, in this study, it was demonstrated that morbidity and mortality of TAAA repair increased in relation to the extent of the aorta replaced, with repair of type II TAAA having the highest rate of mortality (9.7%), followed by SCI (31.5%), bleeding requiring reoperation (9.5%), and renal failure requiring hemodialysis (10.4%).

Over the last several decades, results of thoracoabdominal aortic operations have improved considerably because of improved surgical technique, anesthesia care, and postoperative or intensive care unit (ICU) care. Additionally, specific adjuncts directed at the major complications associated with TAAA repair have been used to decrease the morbidity (in particular, SCI and renal failure) and mortality associated with this procedure.³⁶⁻³⁸

Adjuncts directed at decreasing the rates of SCI have included cerebrospinal fluid (CSF) drainage, reimplantation of key intercostal vessels, regional hypothermia and epidural cooling, pharmacologic interventions, and distal aortic perfusion. CSF drainage, intraoperatively and postoperatively, is used to decrease the risk of SCI and delayed neurologic deficits by helping to maintain the perfusion pressure seen

by the spinal cord. Spinal cord perfusion pressure is defined as the difference in the mean arterial pressure and the CSF pressure. It is conceptually the same as cerebral perfusion pressure, with the idea of maintaining adequate spinal cord perfusion through a combination of keeping the CSF pressure low, through CSF drainage, and maintaining an adequate mean arterial pressure, through the use of vasopressors if needed. Spinal cord swelling has been implicated as a cause of delayed neurologic deficits³⁹ and provides support to the practice of continuing CSF drainage for 48 to 72 hours postoperatively. Additionally, a randomized clinical trial by Coselli and colleagues evaluating the use of CSF drainage showed significantly reduced rates of paraplegia with CSF drainage intraoperatively and for 48 hours postoperatively.⁴⁰ In this study, 145 patients with type I or type II thoracoabdominal aneurysms underwent open repair after randomization to intraoperative and postoperative CSF drainage or no CSF drainage. The patients were then all treated with a consistent approach of heparinization, permissive mild hypothermia, distal aortic perfusion, and reimplantation of critical intercostal arteries. In the patients randomized to CSF drainage, it was started in the operating room and continued for 48 hours postoperatively with a target CSF pressure of 10 mm Hg or less. In the control group, 13% of patients had paraplegia or paraparesis, whereas only 2.6% of the patients in the CSF drainage group did, representing an 80% reduction in the relative risk of postoperative deficits.

When replacing the descending thoracic aorta, the blood supply to the spinal cord is disrupted and the risk of SCI is increased when key intercostal vessels at the levels of T9 to L1 are not reimplanted. Cambria and colleagues showed a

10-fold increased risk of SCI in the repair of type I or II TAAA when the intercostal vessels at the levels of T9 to L2 were not preserved.⁴¹ Similarly, multiple other studies have documented the increased risk of SCI with the sacrifice of intercostal vessels in the critical T9 to L1 levels.^{42–44} A general approach to management of patent intercostal vessels, particularly in the repair of type I and II TAAA, aimed at minimizing the risk of SCI is to ligate vessels at the levels of T8 and above while aggressively reimplanting those at the T9 to L1 levels, thereby minimizing the risk of ischemia in this important watershed distribution.

Regional hypothermia with epidural cooling has been advocated by many others as a principal adjunct to prevent SCI. The target area of the spinal cord cooling is the T9 to L1 levels, in particular where the spinal cord blood flow may be marginal. To achieve regional hypothermia, particularly during aortic cross-clamping, when it is at greatest risk for SCI, an epidural catheter is inserted at the T10 to T12 levels and advanced cephalad a short distance. A second single-lumen intrathecal catheter for the measurement of CSF temperature and pressure is then placed at the L3 to L4 levels. Epidural spinal cord cooling is achieved with the infusion of iced saline (4°C) into the epidural space to allow continuous cooling of the adjacent tissue, thereby lowering the metabolic demands of the nervous tissue and risk for ischemic injury [see Figure 7]. Epidural cooling is used primarily for the repair of type I and II TAAA and has been shown to significantly reduce the risk of SCI in this high-risk group of patients,^{36,37} as well as reduce the number of days in the ICU, with a trend toward improved survival.³⁶

Pharmacologic agents aimed at limiting excitatory mechanisms that can contribute to ischemic injury have been investigated

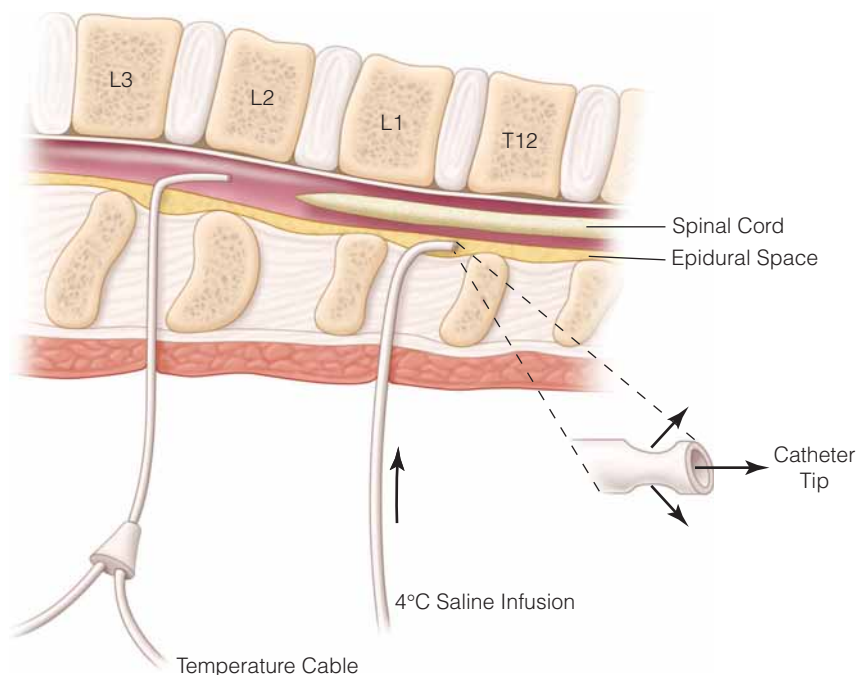


Figure 7 Regional spinal cord hypothermic protection is achieved via epidural cooling. A 4°C epidural saline infusion (arrow) is begun in anticipation of cross-clamping. Cerebrospinal fluid temperature and pressure are simultaneously monitored with a separate intrathecal catheter.

extensively. The use of naloxone, a pharmacologic inhibitor of excitatory neurotransmission, has been evaluated in clinical trials and has been shown to decrease spinal cord metabolism and, in combination with CSF drainage, decrease the incidence of SCI,⁴⁵ leading some centers to use these modalities in combination during the perioperative period.

Early in the experience with the repair of TAAA, the effect of prolonged aortic cross-clamping time on SCI and the need to minimize cross-clamping time were emphasized by Svensson and colleagues.¹⁷ The importance of cross-clamping duration becomes less clear and perhaps less important in centers where distal aortic perfusion methods are used routinely^{46,47} as this maintains perfusion to the spinal cord through important routes of collateral circulation. Coselli and colleagues compared the rates of SCI in patients operated on for TAAA with left heart bypass (LHB) and distal aortic perfusion [see Figure 8] with those in patients undergoing TAAA repair without LHB and found a significant difference in the two groups.⁴⁶ Lower rates of SCI despite longer cross-clamping times were observed in the LHB group.⁴⁶ When distal aortic perfusion is combined with CSF drainage, the incidence of neurologic deficits for all aneurysm types is reduced to 3.3% from 8.4% when these adjuncts are not used. This is particularly evident with the higher-risk type II TAAAs, in which the incidence of neurologic deficit was 7.8% with these adjuncts and 30.6% without.⁴⁸ Theoretical benefits of distal aortic perfusion include maintenance of spinal cord perfusion through collateral circulation, reduction of proximal hypertension, reduced cardiac ischemia, and decreased cardiac afterload.

In addition to preventing SCI, retrograde perfusion of the celiac axis, superior mesenteric arteries, and both renal arteries with cold blood (celiac, superior mesenteric, and right renal arteries) or cold lactated Ringer solution (left renal artery) can reduce end-organ dysfunction and decrease the risk of postoperative renal failure.

At our institution, a patient with a TAAA greater than 6 cm has good pulmonary function and limited cardiac risk and is offered open repair after careful and deliberate consultation, explaining all of the possible outcome morbidities. Prior to the actual operation, after insertion of appropriate lines and a lumbar drain, the patient is positioned in the right lateral decubitus position (with sandbag support) with the hips slightly turned to allow access to both groins. The extent of the incision is tailored to fit the extent of the aneurysmal disease. The full thoracoabdominal incision begins posteriorly between the tip of the scapula and the spinous process. It curves along the sixth intercostal space to the costal cartilage, then obliquely to the umbilicus, and finally in the midline to above the symphysis pubis. After division of the latissimus dorsi and serratus anterior muscles, the left chest is entered following deflation of the left lung. Resection of the sixth rib (or a trapdoor rib flap) is commonly done for TAAA repair as it facilitates exposure, although this is not usually necessary for repair of a type IV aneurysm. Sometimes, depending on the proximal involvement, a type IV aneurysm can be approached through a retroperitoneal incision with division of the diaphragmatic crus and avoidance of a full thoracoabdominal incision. Likewise, a modified thoracoabdominal incision ending at the costal cartilage or above the umbilicus can be used, which provides excellent exposure for surgery involving a type I TAAA if the aneurysm ends above the superior mesenteric artery.

All open repairs of TAAA are performed with the aid of cardiac anesthesiology and dual-lumen endotracheal tube intubation to facilitate entrance into the left thoracic cavity. All patients receive CSF drainage intraoperatively and postoperatively for 48 to 72 hours. In the ICU, the drain is opened to air and placed at a levels of 10 cm above the lumbar spine to maintain a CSF pressure less than or equal to 10 mm Hg. Naloxone is administered as a continuous infusion at 1 µg/kg/hr started before induction and continued for 48 hours after surgery.

In addition to these adjuncts, for all types of TAAA, the repair is performed with distal aortic perfusion using a left atriofemoral bypass and a Biomedicus centrifugal roller pump [see Figure 8]. The clamp and sew technique is used at our institution only if it is not possible to clamp the distal aorta at any levels.

Debranching and TEVAR

An alternative to open surgical repair of TAAA is a hybrid approach involving open visceral arterial bypass, or visceral vessel debranching, followed by endovascular repair of the thoracoabdominal aorta [see Figure 9]. Because the thoracic cavity is not entered, nor is the aorta cross-clamped, the theoretical advantages are apparent. It is thought that this would lead to fewer pulmonary complications and be less stressful physiologically on patients, allowing many patients to undergo repair that previously would have been unfit for open repair, particularly from a pulmonary standpoint. The patient population with thoracoabdominal aneurysms overall is a group with multiple comorbidities: rates of moderate to severe COPD of 29 to 48%, coronary artery disease in the range of 31 to 53%, and preoperative renal insufficiency between 12 and 14%^{17,37,44} have been reported. The earliest reports of small series and case reports had promising results, with perioperative mortality between 0 and 13% and no reported paraplegia.^{31–33} This procedure has generally been done in patients felt to be at too high of a risk for open repair, with the idea that this two-staged approach would be less invasive and more easily tolerated. Subsequent reports have shown perioperative mortality in the range of 14 to 23%, with paraplegia rates as high as 11 to 15%,^{18,49} whereas others have reported mortality as high as 25% for the visceral bypass or first stage of the operation, exclusive of the endografting.⁵⁰ These latter results suggest that the staged or hybrid approach to repair of thoracoabdominal aneurysms may not be the truly less invasive approach that was anticipated.

At our institution, we use the option for visceral artery debranching followed by endografting of the TAAA as the first treatment option for patients with inadequate pulmonary function (FEV₁ less than 70% of predicted) to undergo open repair but who are at relatively low cardiac risk. The patients are taken to the operating room for the visceral vessel revascularization, given a period of 1 to 2 days to recover physiologically from this operation, and then taken back for the TEVAR procedure. This approach is generally reserved for patients felt to be too sick to undergo open repair, and although the morbidity and mortality overall have been similar to those for open repair, these early results are somewhat encouraging in this higher-risk population. Larger studies and longer follow-up are still needed to determine what the long term efficacy of this approach will be.

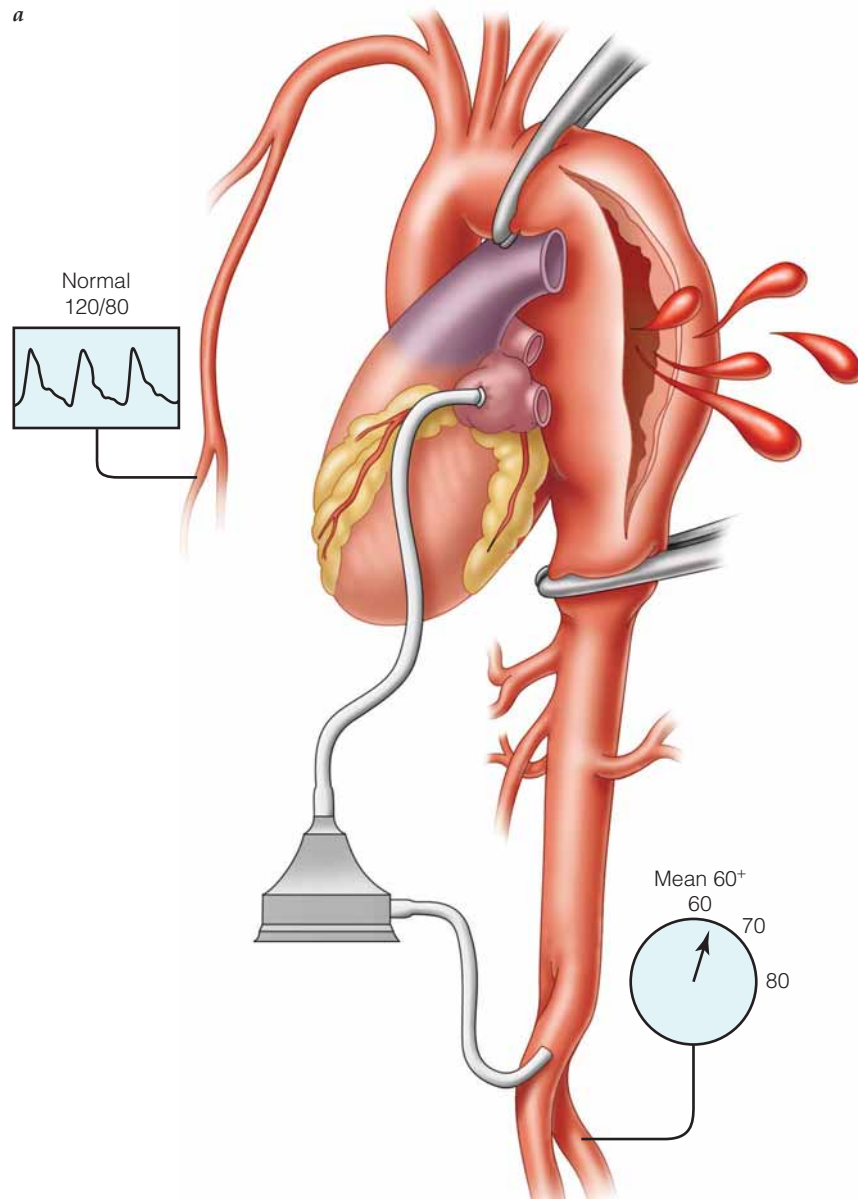


Figure 8 Distal aortic perfusion using a left atriofemoral bypass with a Biomedicus pump.

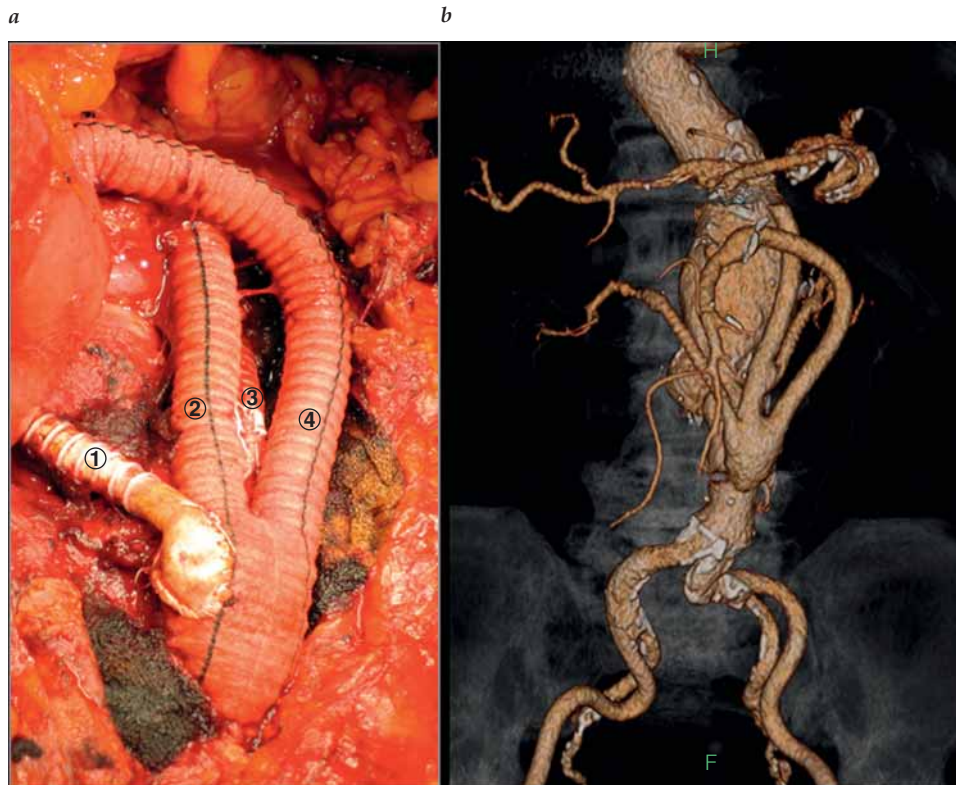


Figure 9 (a) Visceral artery bypass to 1, right renal artery; 2, celiac axis; 3, left renal artery; and 4, superior mesenteric artery. (b) Computed tomographic scan showing visceral bypass debranching prior to placement of an endograft.

Complete Endovascular Repair of TAAA

In an attempt to ameliorate the risks of conventional TAAA repair and expand the range of patients who are amenable to treatment of TAAA, another approach is an entirely endovascular approach. This has been described with two different types of devices. The first type uses fenestrations, preplaced holes in the fabric that are positioned in alignment with the orifices of the visceral arteries. They are then adjoined to the respective visceral arteries with a balloon-expandable stent graft. The second involves aortic endografts to which fabric branches are attached. The branches are then fixed to the visceral vessels with self-expanding stent grafts [see Figure 10].

Fenestrated grafts used to treat TAAA have a nitinol ring sutured around the orifice of each fenestration. This creates a rigid location to which a balloon-expandable stent graft can be attached, allowing one to treat aneurysms involving the visceral arteries. The mating stent graft is advanced into the target vessel an adequate length and deployed, forming a bridge between the aortic stent graft and visceral vessel. The aortic component of the mating stent graft is then dilated with a larger balloon to create an hourglass-type seal against the nitinol ring. Using this technique to treat TAAA was initially described by Anderson and Adam in 2005.⁵¹

Attaching a branch to the endograft provides a segment of overlap that can be used to attain a better sealing zone and fixation [see Figure 10]. Additionally, it allows the use of self-expanding stent grafts, which may allow for the ability to accommodate tortuosity and diameter discrepancy. In this setup, the aortic device is deployed above the target vessel; the branches are then cannulated with a wire from a

brachial approach. The wire is then used to cannulate the target visceral artery, and mating self-expandable stents grafts are deployed to join the target vessel and aortic graft. Advantages of branched grafts over reinforced fenestrations include improved mating stent graft joint integrity. One disadvantage of branched endografts relates to the need to achieve an aortic seal well above the branch origin, which may require coverage of nondiseased aorta and increase the risk of paraplegia.⁵²

Use of this modality to treat TAAA in the United States has been isolated to several highly specialized centers. A report out of the Cleveland Clinic in 2007 documented their experience over 21 months in which 73 patients underwent endovascular repair for TAAA.³⁴ The majority of repairs, 45 patients, were done for type IV TAAA, whereas the other 28 patients were treated for type I, II, or III TAAA. The aneurysms were successfully excluded in 93% of the patients, with no conversions to open surgery and no ruptures. Thirty-day mortality was 5.5%, and the paraplegia rate was 2.7%. They did, however, have an overall incidence of endoleaks of 11% noted prior to discharge, but the majority were treated successfully with secondary endovascular intervention. The authors noted no ruptures or cases of aneurysmal sac enlargement at 12 months of follow-up and concluded that endovascular repair of aortic aneurysms involving the visceral segment in nonsurgical candidates is feasible, with relatively low morbidity and mortality in the high-risk patient population studied. Another recent report out of the University of California-San Francisco documented their experience in treating 22 patients with TAAA with branched endografts.³⁵ Each endograft was manufactured

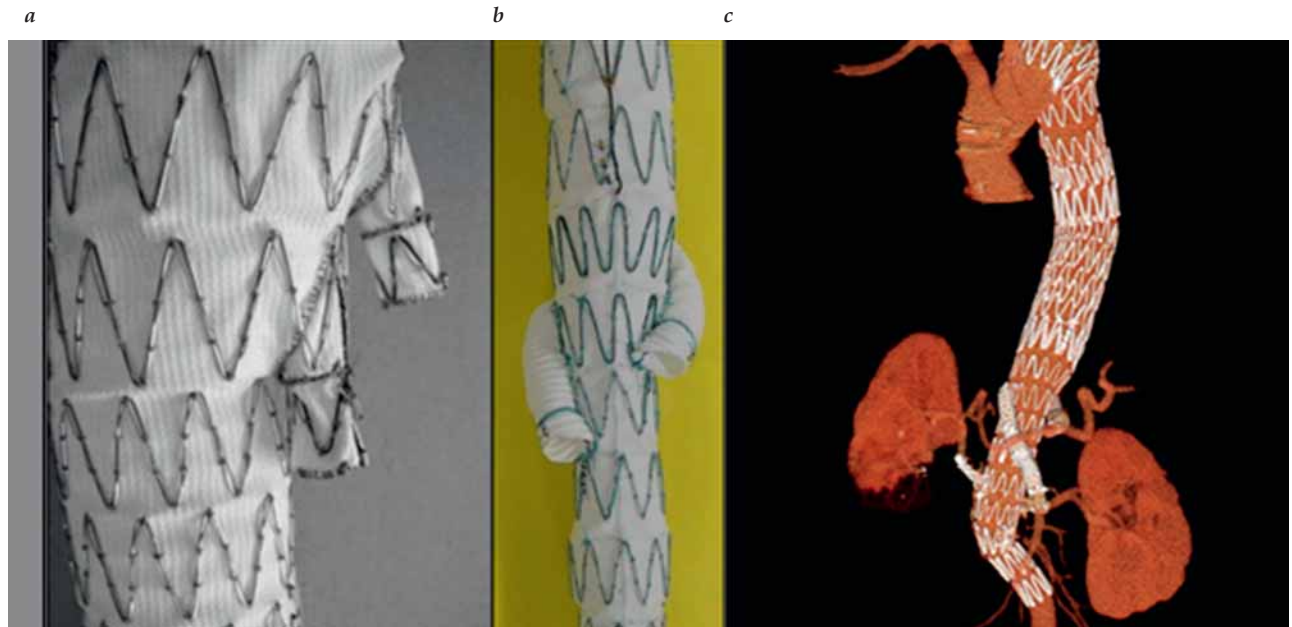


Figure 10 (a and b) Examples of a branched endograft. (c) Reconstruction of a postoperative computed tomographic scan following totally endovascular repair of a type II thoracoabdominal aortic aneurysm.

for the patient, with the caudally directed cuffs positioned to correspond to the location of the arterial branch on the native aortic aneurysm based on dimensional analysis of fine-cut contrast-enhanced CT scans. CSF drainage was used during the procedure and in the early postoperative period. The patients had a perioperative mortality of 9.1%, and the authors noted that renal failure, myocardial infarction, stroke, and paraplegia did not occur in any of the surviving patients. They concluded that their experience suggests that multibranched stent graft implantation is safe, feasible, effective, and applicable in a high proportion of cases and that it supports an expanded role in the treatment of TAAA.

Although the early results are promising, the endovascular repair of TAAA remains a technically demanding modality that at the current time is feasible at a few centers across the country. Longer-term follow-up is needed to determine the durability of this repair and how widely applicable it will become in the future.

Summary

Endovascular treatment of descending thoracic aneurysms is safe and technically feasible. Early, mid-, and longer-term outcomes compare favorably with those of open surgical repair, with the morbidity and mortality attributable to cardiac complications, pulmonary complications, and paraplegia

clearly less common with endovascular repair. At our institution, endovascular repair of isolated DTAs has become the treatment modality of choice.

Treatment of TAAA continues to be a difficult and morbid endeavor. Open repair of TAAA in patients who are physiologically fit enough to undergo repair remains the best option. In patients undergoing open repair, adjuncts such as distal aortic perfusion, CSF drainage, epidural cooling, reimplantation of key intercostal vessels, and intraoperative perfusion of visceral vessels are used to minimize the morbidity and mortality of the operation. Debranching procedures followed by endografting are an option in patients whose pulmonary function makes standard open repair a prohibitive risk. Initially, the hybrid procedures were felt to be a less morbid approach in this high-risk patient population; however, recent reports suggest that the results with this approach may be more morbid than previously thought. Totally endovascular repair of TAAA is a developing technology currently isolated to a few highly specialized centers. This technology will continue to grow and expand, and the longer-term results that will come will determine the degree of applicability.

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31 COMPARTMENT SYNDROME

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Disease Definition

Management of compartment syndromes is a vital tool to have in the surgeon's armamentarium. Understanding of the etiologic mechanisms, along with a thorough knowledge of the pertinent pathophysiology and anatomy, will result in timely recognition and treatment. Decreased morbidity and improved patient function are the desired outcomes. Failure to address a compartment syndrome can lead to permanent neurologic damage, loss of function, amputation, and even severe metabolic derangements, leading to permanent renal failure and cardiorespiratory compromise.

Compartment syndrome is defined as an elevation of the interstitial pressure in a closed fascial compartment that results in microvascular compromise. Compartment syndromes can develop anywhere skeletal muscle or abdominal organs are enveloped by a rigid, unyielding fascial layer. Compartments with relatively noncompliant fascial boundaries are most commonly involved, especially the anterior and deep posterior compartments of the leg and the volar compartment of the forearm. Other sites include the buttock, thigh, foot, arm, hand, paraspinal muscles,¹ and abdomen. Increased pressure within these musculoskeletal compartments can result in relative ischemia with neurologic and soft tissue compromise. Once a given increased pressure threshold is reached, arterial perfusion of the soft tissues is diminished, resulting in ischemic damage to the vulnerable nerves and muscles. This can lead to neurologic injury, muscle necrosis, scarring, and contractures. In addition to the local tissue damage, release of abnormal metabolic products can cause significant cardiorespiratory and renal compromise.

Timely diagnosis of a developing or existent compartment syndrome can be a challenging problem. Although such recognition is often straightforward in the awake, alert patient, it can be most difficult in the patient with altered mental or neurologic status, such as a patient already under general or regional anesthesia, a comatose or obtunded patient, a patient with a peripheral nerve injury, a spinal cord injury patient, or a patient under the influence of drugs.

Epidemiology

Compartment syndromes are classified as acute or chronic depending on the etiology of the insult. Acute compartment syndromes typically result from orthopedic or vascular trauma. They may also occur during or following acute ischemic events such as acute arterial thromboembolism, popliteal artery aneurysm thrombosis, or reperfusion following correction of profound limb ischemia. Chronic compartment syndromes are not the result of acute injury or ischemia. They tend to occur in healthy active individuals, resulting

from increased compartment pressures during repetitive vigorous exertion. Usually occurring in athletes, this chronic syndrome typically involves the leg or the forearm.^{2,3} Chronic exertional compartment syndromes (CECSs) are discussed in more detail below.

There are three basic mechanisms leading to an acute compartment syndrome: increased tissue pressure within the enclosed space, extrinsic compression on the compartment, and decreased volume of the involved compartment. The presence of an existing or a developing acute compartment syndrome is the typical indication for a fasciotomy procedure. Another indication is a clinical situation in which the incipient development of a significant compartment syndrome is very likely, such as prolonged extremity ischemia or combined extremity arterial and venous injuries (especially the popliteal vessels and ligation of the popliteal vein). Other clinical situations that may result in an acute compartment syndrome include severe burns and prolonged limb compression following loss of consciousness from a drug overdose or a stroke. Delayed development of an acute compartment syndrome is common and may be very difficult to document, especially in the patient with altered mental status or the trauma patient with multiple injuries. Development of a compartment syndrome may occur beyond 48 hours after the initial injury.

The most common cause of the development of an acute compartment syndrome is a bony fracture, especially the tibia; the resultant hemorrhage, soft tissue injury, and edema can lead to increased compartmental pressures. Consequently, these are managed by the orthopedic surgeons in most institutions. Arterial bleeding into rigid, fixed compartments, reperfusion following prolonged extremity ischemia attributable to arterial injury (traumatic or iatrogenic), embolic disease, popliteal aneurysm thrombosis, and failure of an existing bypass often result in compartment syndromes. Not surprisingly, compartment syndrome following penetrating trauma is often attributable to direct vascular injury with resultant ischemia and reperfusion injury; associated soft tissue injury compounds the problem. Blunt trauma typically results in compartment syndrome as a result of musculoskeletal injury or direct tissue damage. Development of a clinically relevant compartment syndrome following elective extremity revascularization for chronic extremity ischemia may occur but is distinctly uncommon.

Another common cause of an acute compartment syndrome is reperfusion of an ischemic limb following an acute thromboembolic event or repair of a vascular injury, especially if the ischemia is profound and exceeds 6 hours. The combination of arterial and venous injuries significantly increases the risk of developing this disorder. Iatrogenic extravasation of intravenous fluids into a compartment can result in increased compartmental pressures, especially if the

infused agent is caustic to the local tissues. Increased edema and compartment pressures can also result from electrical or thermal injuries, especially if associated with rigid, circumferential eschars. Venous outflow obstruction from advanced deep vein thrombosis can result in phlegmasia cerulea dolens, increased compartmental pressures, and venous gangrene; this is usually associated with a malignant process or other hypercoagulable state.

Extrinsic compression of muscle compartments can also result in significant compartment syndromes. First recognized during the bombing of Britain during World War II, crush injuries from being trapped in the rubble led to muscle compromise from the unyielding weight of collapsed building materials; those lucky enough to survive the initial insult often died from renal failure resulting from myoglobinemia as a consequence of the muscle ischemia. Although still occurring in combat and earthquake casualties, this extrinsic compression mechanism is more often seen in the comatose drug overdose victim who collapsed on a hard floor surface for many hours before discovery and rescue. Unfortunately, this mechanism can also affect the elderly person with prolonged immobility on the floor after a fall or stroke. A preventable iatrogenic cause of compartment syndrome from extrinsic pressure is inadequate padding of vulnerable pressure points during a prolonged surgical procedure under general or regional anesthesia. Finally, compartment syndromes can result from extrinsic compression from burn eschars, tight casts, or constricting bandaging.

Pathophysiology

The pathophysiology of compartment syndrome involves an insult to normal local tissue homeostasis that results in increased tissue pressure, decreased capillary blood flow, and local tissue necrosis because of a lack of adequate oxygen delivery.³ Local tissue blood flow (LBF) is equal to the arteriovenous pressure gradient (Pa-Pv) divided by the local vascular resistance (R): $LBF = (Pa-Pv)/R$. In the usual setting, tissue ischemia results in vasodilation with decreased vascular resistance, leading to recruitment of increased blood flow. Elevated compartmental pressures can effectively shut down capillary flow, even in the patient with no intrinsic peripheral vascular disease. This can result in significant muscle necrosis if the intracompartmental pressure exceeds 30 mm Hg for more than 8 hours.³ Certainly, significant neuromuscular injury can be expected to occur in a shorter time frame in the settings of even higher compartment pressures, preexisting chronic ischemia from peripheral vascular disease, hypovolemic shock from trauma, cardiogenic shock, or severe soft tissue damage from a crush injury.

Compartment syndrome results from inadequate perfusion of the soft tissues; this process begins when the pressure within the compartment meets or exceeds the perfusion pressure within the capillary beds of the nerves and muscles. Normal compartment tissue pressures range from 0 to 10 mm Hg. Arteriolar and capillary blood flows are very sensitive to changes in compartment pressures. Critical closing pressures have been shown to be 21 mm Hg in the leg and 33 mm Hg in the arm.⁴ When the compartment pressure exceeds these values, arterial perfusion is reduced, resulting in ischemic changes. In the patient with systemic hypotension, compartmental pressures as low as 20 to 40 mm Hg can

result in diminished tissue perfusion and tissue injury. At this point, microcapillary flow ceases and the onset of anaerobic metabolism begins, resulting in lactic acidosis. Inflammatory mediators are activated, and free radicals are released. Cellular damage ensues. Neutrophils are recruited and adhere to vascular endothelium, stimulating the release of more free radicals and proteases. The inflammatory mediators cause cell wall lipid peroxidation, which, in turn, increases basement membrane permeability. Leakage from capillaries further increases tissue edema and, therefore, tissue pressure. This sets in play a vicious cycle of progressive muscle edema, actual closure of the capillary beds, increased capillary permeability, and further soft tissue swelling. Eventually, the pressure becomes great enough to reduce arterial inflow and mechanically compress veins and nerves, resulting in nerve injury and myonecrosis; rarely does the compartment pressure increase sufficiently to compress major arteries. Hence, the patient's pulses will usually remain intact during the development of compartment syndrome.

Diagnosis

The diagnosis of a compartment syndrome is based on clinical suspicion, the mechanism and location of injury, physical examination findings, and objective compartment pressure measurements [see Figure 1]. It cannot be overemphasized that a high level of suspicion must be held for compartment syndrome, especially in trauma victims and patients with vascular disease undergoing revascularization. The clinical presentation may be subtle in the early stage of compartment syndrome, but early diagnosis is critical so that therapy can be initiated prior to the onset of irreversible tissue ischemia.

The most important initial symptom is pain out of proportion to that expected from the injury. Severe tenderness and pain on passive stretching of the musculature are also suggestive of an existing compartment syndrome. Possible neurologic findings are hypesthesia, paresthesia, or decreased motor function (e.g., peroneal nerve involvement and decreased foot dorsiflexion). Diminished sensation in the distribution of relevant nerves within the compartment in question may be an early finding attributable to ischemia of the nerves [see Table 1 and Table 2]; sensory loss usually precedes any compromise of motor function. The neurologic sensory examination should include testing with pinprick, light touch, and two-point discrimination. These diminished sensory findings are often the first abnormality noted with a developing compartment syndrome. Muscle weakness with eventual paralysis follows if the compartment is not promptly released.

These findings are often straightforward and readily evident in the awake and alert patient. The diagnosis of compartment syndrome is straightforward and is based on physical findings and the mechanism of injury. Diagnosis is much more challenging in the patient with an altered mental state or neurologic deficit, as may be seen with alcohol or drug influence, general or regional anesthesia, spinal cord injury, peripheral nerve injury, or unconsciousness. In these instances, compartment pressure measurements are invaluable in the decision-making process. Diagnosis may

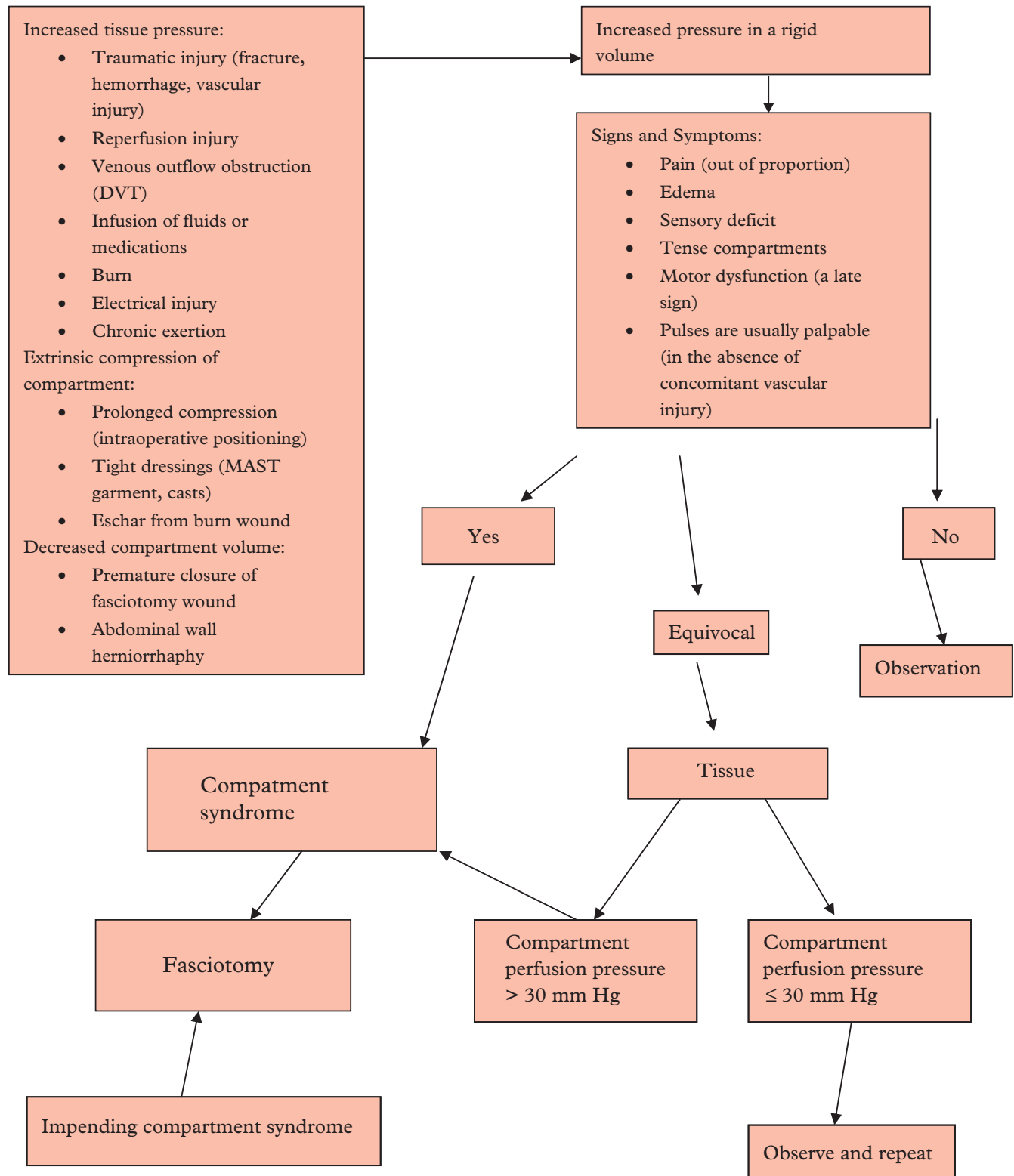


Figure 1 The algorithmic approach to management of compartment syndrome. MAST = military anti-shock trousers; DVT = deep vein thrombosis.

also be quite difficult in the young child as a result of agitation, fear, communication challenges, and lack of cooperation. Appropriate pressure analysis can prevent unnecessary procedures and, at the same time, allow appropriate timely action when a compartment syndrome is documented.

Physical examination findings suggestive of an advanced acute compartment syndrome typically include rigidity and tenderness of muscles in the involved compartment, pallor or mottling of the skin, or neurologic motor deficits. Loss of arterial pulses may be a late sign but is more likely

Table 1 Contents and Function of the Compartments of the Leg

Lower Leg Compartment	Muscles	Arteries	Nerves	Motor Function	Sensory Innervation
Anterior	Tibialis anterior Extensor hallucis longus Extensor digitorum longus Peroneus tertius	Anterior tibial artery	Deep peroneal nerve	Toe extension Foot inversion and dorsiflexion	Webpace between great and second toes
Lateral	Peroneus brevis Peroneus longus	—	Superficial peroneal nerve	Foot dorsiflexion Foot eversion	Dorsal foot
Superficial posterior	Gastrocnemius soleus plantaris	—	Sural nerve	Foot plantar flexion Knee flexion	Lateral foot
Deep posterior	Popliteus Flexor digitorum longus Flexor hallucis longus Tibialis posterior	Posterior tibial artery Peroneal artery	Posterior tibial nerve	Toe flexion Foot plantar flexion Foot eversion	Sole of foot

attributable to a concomitant arterial injury rather than a compartment syndrome. An elevated serum creatine phosphokinase is an ominous finding signifying late diagnosis and established myonecrosis. Myoglobinuria and resultant renal failure add to the morbidity and mortality of this disorder.

Unfortunately, these findings are all nonspecific, and none are diagnostic for an established, significant compartment syndrome. If a compartment syndrome is suspected and the physical findings are not reliable, one should proceed directly with measurement of the intracompartmental pressures. The original technique described by Whitesides in 1975⁵ using intravenous tubing, a three-way stopcock, and a mercury manometer was a significant advance but is cumbersome and not as reliable as more current techniques. Continuous monitoring of compartment pressures can now be accomplished using wick catheter monitors or slit catheters.³ These have the advantage of providing continuous real-time pressure values

but monitor only one compartment per catheter. This approach is particularly useful in the setting of ongoing serial examinations such as might be seen in the burn patient with progressive tissue injury and significant constricting eschar formation. In the acute setting, our preference is to proceed with direct pressure measurements of the involved compartments using the Stryker intracompartmental pressure monitoring system (Stryker Surgical, Kalamazoo, MI). This direct approach allows serial measurements at multiple sites and has been very easy, quick, reasonably reliable, and reproducible. Noninvasive assays exist to assist in the determination of an acute compartment syndrome but are still in the development stage and not widely used; these tend to have a high specificity but a low sensitivity for reliable diagnosis. A surgical philosophy that blends a high index of clinical suspicion, serial examinations, and measurement of compartment pressures will yield excellent clinical outcomes.

Table 2 Contents and Function of the Compartments of the Forearm

Forearm Compartment	Muscles	Arteries	Nerves	Motor Function	Sensory Innervation
Volar	Pronator teres Flexor carpi radialis Palmaris longus Flexor carpi ulnaris Flexor digitorum superficialis Flexor digitorum profundus (pronator quadratus)	Radial artery Ulnar artery	Median nerve Ulnar nerve	Forearm flexion Forearm pronation Wrist flexion Digit flexion	Palm of hand
Mobile wad	Extensor carpi radialis brevis Extensor carpi radialis longus Brachioradialis	—	Superficial branch of the radial nerve	Wrist extension Supination	—
Dorsal	Extensor digitorum Extensor digiti minimi Extensor carpi ulnaris Supinator Abductor pollicis longus Extensor pollicis longus Extensor pollicis brevis Extensor indicis	Posterior interosseous artery Muscular branch of radial artery	Radial nerve	Wrist extension Digit Extension	Dorsum of hand



Measurement of compartment pressures is relatively easy now with the above devices. However, interpretation of the pressure measurements merits further discussion. Three different values are available to define the significance of the pressures and guide the decision-making process: (1) the absolute compartment pressure value, (2) the delta pressure, and (3) the compartmental perfusion pressure.

Normal compartment tissue pressures range from 0 to 10 mm Hg. Measurement of the absolute pressure in the compartment is easy, is reproducible, and can be obtained serially and in various locations within the given compartment. An absolute pressure measurement over 30 mm Hg is considered abnormal but is not necessarily a fail-safe value to mandate fasciotomy. It still remains, however, a common threshold to recommend fasciotomy. Concern for a compartment syndrome and the consideration of a fasciotomy intervention occur when the absolute compartmental pressure reaches 30 mm Hg or greater, especially if the patient has signs and symptoms or if the patient cannot be reliably examined. Some authorities have shown that, with close serial observation, the fasciotomy procedure may be reserved for absolute pressures exceeding 45 mm Hg in the alert patient with no worrisome signs or symptoms. Unfortunately, there is no specific threshold pressure above which compartment syndrome always occurs. Other factors may come into play, such as the duration of compartmental hypertension, preexisting peripheral arterial disease, systemic hypotension, shock, and coexisting tissue injury. These parameters may lower the threshold for action.

To address this shortcoming, two other values have been defined and are outlined below. A dynamic compartmental pressure threshold relative to the diastolic blood pressure or the mean arterial blood pressure is probably a more appropriate and reliable index for proceeding with fasciotomy.⁶ The degree of tissue perfusion has been shown to correlate with the diastolic blood pressure; when the pressure within a compartment exceeds the diastolic blood pressure, arterial perfusion ceases. Compartmental pressures capable of compromising tissue perfusion appear to occur when they rise to within 20 mm Hg of the diastolic blood pressure or to within 30 mm Hg of the mean arterial pressure.

Consequently, some clinicians rely on the comparison of the compartment pressure to the diastolic blood pressure. Delta pressure is defined as the diastolic blood pressure minus the measured compartment pressure. This approach is supported by the observation that relative hypertension may be protective against the development of a compartment syndrome. Therefore, some clinicians advocate the use of the delta pressure to guide timing of a fasciotomy. When the compartment pressure rises to within 30 mm Hg of the diastolic blood pressure, capillary blood flow is compromised and serious consideration should be given to performing a prompt fasciotomy. A delta pressure value between 10 and 30 mm Hg has been recommended as the threshold for surgical intervention.⁴

Finally, the concept of compartmental perfusion pressure (also known as the delta mean arterial pressure) probably yields the most accurate assessment of the impact of increased compartmental pressures on actual tissue perfusion. This value is defined as the mean arterial pressure minus the measured compartment pressure. Capillary blood flow ceases

when the compartmental perfusion pressure is 25 mm Hg or less.⁴ Therefore, a value less than 40 mm Hg is the recognized threshold to proceed to fasciotomy. This approach takes into account variances in perfusion related to systemic hypotension and is particularly helpful in the trauma patient. This is probably the most reliable pressure measurement assessment currently available and the one recommended in most busy clinical practices.

If a fasciotomy is not performed right away, serial pressure measurements are essential as the development of a compartment syndrome may be progressive and insidious. Delayed development of a compartment syndrome is common and may be very difficult to document, especially in the patient with altered mental or neurologic status or in the trauma patient with multiple injuries. Although uncommon, the onset of a compartment syndrome may occur as late as 48 hours after the initial injury.

Pressure within a given compartment is not always uniformly distributed and tends to be higher in the region of injury. Consequently, special attention is given to pressure measurements in the immediate vicinity of a known injury or an area of clinical concern. Measurement of the compartment pressures should be obtained with the limb gently supported as pressure on the limb from an underlying hard surface (e.g., operating room table) may lead to falsely elevated pressure measurements. Pressure measurements can be inaccurate in up to 27% of acute limb trauma patients, so compartment pressure measurements should be used as an adjunct to physical examination and clinical suspicion, not as the sole determinant of the need for fasciotomy.³ Unfortunately, there is no specific absolute pressure threshold for a compartment syndrome. Consequently, the final decision to proceed with a fasciotomy rests on clinical judgment and experience.

Management

Once a compartment syndrome has been diagnosed, immediate decompression is essential. While preparing the patient for the surgical procedure, several supportive measures should be implemented. Removal of all external compression, such as dressings, casts, or splints, is advised. The involved limb should be placed at the level of the heart, not elevated. Supplemental oxygen can also be helpful, along with appropriate volume loading with intravenous fluids to increase or maintain a high-normal blood pressure. If myonecrosis is suspected or already present, renal protection with sodium bicarbonate and stimulation of a brisk diuresis with fluids and mannitol may minimize damage to the kidneys. Finally, hyperkalemia must be addressed with loop diuretics and glucose or insulin challenge to achieve prompt serum potassium reduction. Life-threatening hyperkalemia may even require emergent hemodialysis.

A properly timed, expertly performed fasciotomy procedure is an invaluable tool to have in the surgeon's armamentarium. Knowledge of the appropriate indications, as well as the anatomy involved, will lead to decreased patient morbidity and enhanced functional outcomes. Fasciotomy is performed to treat existing or developing compartment syndromes; the most common anatomic sites for fasciotomy are the leg and forearm. This is because of the well-defined, rigid fascial boundaries of these locations and the frequency

of injury to the distal extremities. Other less common sites for fasciotomy include the arm and the thigh.⁷ Compartment syndromes involving the hand,⁸ foot,^{9–11} shoulder, lumbar paraspinal muscles, and spinal cord also exist but are not addressed herein.

There are four essential components to the optimal functional outcome following a fasciotomy procedure. First, the overlying skin must be completely incised as it can function as a constricting envelope to contribute to persistently elevated compartment pressures, even with an adequate fascial release. Second, the fascia along the entire length of the incision must be incised to allow full decompression. Third, local wound care of the open incisions will hasten prompt healing and help minimize morbidity. Daily inspection and local débridement of nonviable tissues as needed are crucial. Reestablishment of healthy skin coverage with local wound measures, partial-thickness skin grafts, or the use of negative pressure therapy completes the wound healing process. Finally, timely aggressive physical therapy will help rehabilitate the patient and facilitate return to optimal function levels.

Intraoperative assessment of the completeness of fasciotomy is largely visual. The surgeon must be certain that all involved compartments are completely decompressed and that all muscle compression has been released. Muscle bellies should appear viable with normal coloration. Discolored, obviously necrotic tissues should be débrided. Questionably viable muscle should probably be left intact and reexamined in the operating room 24 to 48 hours later at the time of a dressing change. If distal pulses were not present preoperatively, they should be reexamined following fasciotomy. Return of normal pulses documents successful compartmental decompression. However, the lack of pulses may be attributable to concomitant peripheral arterial occlusive disease, especially in the older patient; in this setting, failure to have palpable pulses after fasciotomy does not imply inadequate decompression. The most important parameter to document complete fasciotomy is the neurologic status of the limb. Return of motor and sensory deficits following fasciotomy proves complete decompression and portends an excellent functional outcome. Prolonged, profound ischemia may lead to a delay in return of neurologic function. Unfortunately, this assessment cannot be performed until the patient is awake and alert. Also, this is not possible to assess in the patient with a spinal cord or peripheral nerve injury.

Local complications following fasciotomy are frequent, even with timely intervention. **Complications that may arise from a fasciotomy procedure include wound and soft tissue infection, iatrogenic nerve injury, prolonged hospitalization, and malfunction of the leg venous pump mechanism.^{12,13} As outlined by Modrall, major amputations can occur in 5 to 21%, neurologic deficits in 7 to 36%, and wound complications in 4 to 38% of all patients treated appropriately.⁶ These complication rates are higher if the fasciotomy procedure is delayed more than 6 hours. Exposed orthopedic hardware must be covered with viable tissues at the time of fasciotomy; similarly, vascular bypass grafts must be placed beneath healthy muscle. These factors must be taken into account when planning the incisions used for the fasciotomy procedure.**

There may be some concern regarding wound healing problems and prolonged wound care issues following fasciotomy; this can lead to delay in proceeding with the fasciotomy procedure in the patient with equivocal findings. Although unquestionably some morbidity results from the fasciotomy procedure itself, the consequences and morbidity of a missed compartment syndrome and failure to perform a timely fasciotomy can be disastrous.¹⁴ We subscribe to the notion that if one contemplates performing a fasciotomy, it should be done. This is similar to the philosophy in the modern military trauma surgery setting.¹⁵ If a fasciotomy procedure is performed and a compartment syndrome is not present, the limb musculature is usually not swollen and the possibility of a delayed presentation has been averted. Delayed primary closure a few days later is usually possible without the need for skin grafts. This approach helps minimize both hospital stay and cosmetic issues.

Overall complication rates increase dramatically if the fasciotomy procedure is delayed more than 12 hours. Almost half of patients with delayed fasciotomy required major amputation and 92% had significant neuropathy.⁶ Unfortunately, if amputation is required, it often must be performed at a higher level because of a lack of healthy muscle for bone coverage and stump healing. Loss of the musculature within one or two compartments of the leg usually results in the ability to ambulate following rehabilitation efforts with intensive physical therapy and orthotics. Loss of the muscles with three or more leg compartments almost always results in a functionless limb; in this setting, an early amputation at a level sure to heal followed by aggressive prosthetic rehabilitation may yield independent ambulation.¹⁶ Long-term problems following fasciotomy may include exposed bone or tendon, numbness, dysesthesias, muscle herniation, malfunction of the calf muscle pump, and cosmetic issues.

Anatomy and Surgical Techniques

THE LEG

The leg has four compartments: the anterior, lateral, superficial posterior, and deep posterior. Each compartment has a significant nerve coursing through it: the deep peroneal nerve (anterior compartment), the superficial peroneal nerve (lateral compartment), the sural nerve (posterior compartment), and the posterior tibial nerve (deep posterior compartment) [see Figure 2]. Although the anterior compartment is most commonly involved, more significant damage and morbidity tend to result from involvement of the deep posterior compartment.

Certain types of clinical situations may predispose to the development of a leg compartment syndrome. Injuries to the proximal half of the below-knee arterial segment are the most common cause of the development of compartment syndrome from penetrating trauma of the lower extremity.^{17–21} Shock also predisposes to compartment syndrome.¹⁹

Three distinct surgical techniques are available for complete decompression of all four leg compartments. The most commonly employed is the dual-incision technique, which involves separate medial and lateral leg incisions. Two other approaches permit decompression through a single lateral incision. One involves actual resection of the fibula and is

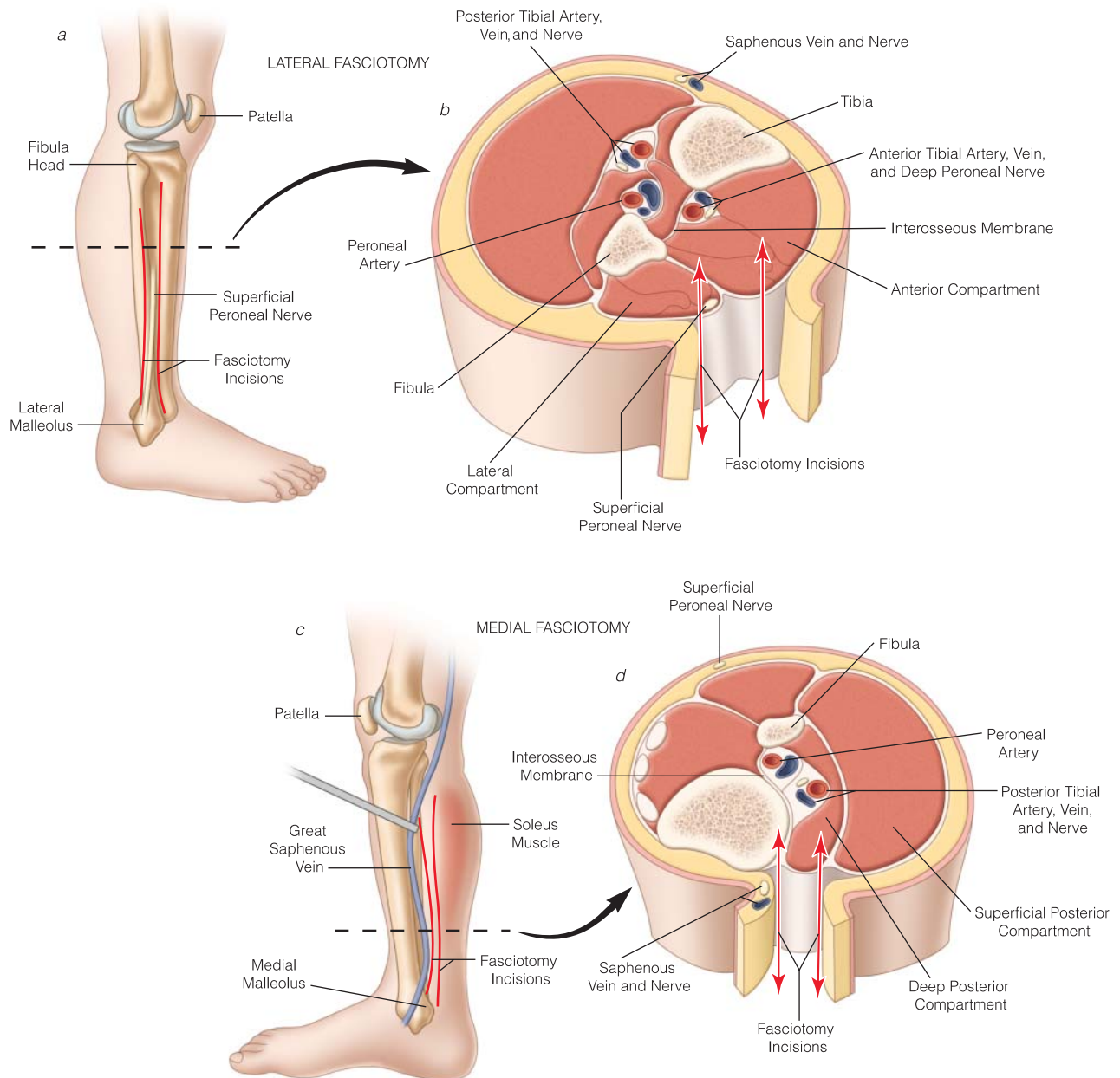


Figure 2 Four-compartment fasciotomy of the leg—dual-incision technique. (a) Lateral leg incision. (b) Cross-sectional view of the decompression of the anterior and lateral compartments through the lateral leg incision. (c) Medial leg incision. (d) Cross-sectional view of the decompression of the superficial and deep posterior compartments through the medial leg incision.

probably of historical interest only. The other is a perifibular technique. These single lateral incision approaches may have some utility if preservation of the integrity of the skin of the medial leg is essential, such as the presence of a comminuted tibia fracture. A medial leg incision in this setting could convert a closed fracture to an open fracture, with attendant risk of infection. However, in most vascular surgery settings, the dual-incision approach is safer, faster, and more effective than the single-incision methods.

The single lateral incision four compartment leg fasciotomy is accomplished through a long incision in line with the fibula that extends from just distal to the head of the fibula down to several centimeters proximal to the lateral malleolus. If performed too far posteriorly, the anterior compartment may not be identified properly and not decompressed adequately. The skin and subcutaneous tissues are undermined anteriorly with care not to injure the superficial peroneal nerve in the proximal aspect of the incision. The intermuscular septum

is identified, and a longitudinal fasciotomy of each of the anterior and lateral compartments is performed for the entire length of the incision. The skin and subcutaneous tissues are then undermined posteriorly to gain access to the superficial posterior compartment, which is released. Then the interval between the lateral and superficial posterior compartments is defined and separated. This exposes the flexor hallucis longus muscle, which is dissected off the fibula and retracted posteromedially, along with the peroneal vessels. Finally, the fascial attachment of the posterior tibial muscle to the fibula is cut longitudinally to allow decompression of the deep posterior compartment.

 The dual-incision technique is accomplished through two vertical skin incisions that are separated by a bridge of skin at least 8 cm wide [see Figure 2]. The first incision is along the lateral aspect of the leg centered over the interval between the anterior and lateral compartments, extending from the head of the fibula down to just above the lateral malleolus. The incision should be halfway between the crest of the tibia and the fibula. The intermuscular septum is identified. The fascia overlying the anterior compartment is divided 1 cm in front of the intermuscular septum along the entire length of the incision with care not to injure the superficial peroneal nerve in the proximal portion of the incision. The fascia of the lateral compartment is then divided 1 cm behind the intermuscular septum distally to include the extensor retinaculum at the lateral malleolus and proximally up to the origin of the muscles. The extensor tendons should not be exposed. The second incision is along the medial aspect of the leg approximately 2 cm posterior to the edge of the tibia. The incision is tailored to avoid injury to the saphenous vein and accompanying saphenous nerve. The fascia overlying the gastrocnemius and soleus muscles is divided, thereby opening the superficial posterior compartment. Using electrocautery, the deep posterior compartment is decompressed by detaching the insertion of the soleus muscle from the tibia, with care to protect the posterior tibial neurovascular bundle. This maneuver exposes the fascia overlying the flexor digitorum longus, which is divided along the length of the muscle, completing full release of this vital compartment. Once the posterior aspect of the tibia is visualized directly, one knows that the deep posterior compartment has been fully decompressed.

THE THIGH AND BUTTOCKS

The thigh has three compartments: the anterior, medial, and posterior. Most thigh compartment syndromes involve the anterior and posterior compartments, each of which has a major nerve coursing through it. Relevant structures within the anterior compartment include the femoral vessels, the femoral nerve, and the lateral cutaneous nerve. The posterior compartment contains the sciatic nerve. The medial compartment has no major neurologic structure within it and does not usually require decompression. Most thigh compartment syndromes are the result of femur fractures or arterial injuries.^{22,23} The gluteal muscle group of the buttocks is enclosed by the fascia lata, defining another compartment vulnerable to increased pressures and involvement of the sciatic nerve, as well as the muscles themselves.²⁴

Decompression of the anterior and posterior thigh compartments is readily accomplished using a full-length lateral

thigh incision extending from the intertrochanteric line down to the lateral femoral epicondyle [see Figure 3]. The anterior compartment is opened by incising the underlying fascia lata. The posterior compartment is decompressed by retracting the vastus lateralis muscle medially to expose the lateral intermuscular septum, which is then opened the length of the incision. Following decompression of the anterior and posterior compartments, a pressure measurement of the medial compartment may be obtained. If necessary, the medial compartment is decompressed with the same medial incision used to expose the superficial femoral artery beneath the sartorius muscle; subcutaneous extension of this approach across the anterior surface of the thigh will also allow decompression of the anterior compartment.²² Decompression of the gluteal musculature of the buttocks is performed using longitudinal incisions through the skin with individual epimysial envelope incisions as needed.⁴

THE FOREARM

The forearm is wrapped in a firm layer of deep fascia that is continuous with the deep fascia of the arm. In addition, there are septa running from the deep fascia to the radius and ulna. Finally, a dense interosseous membrane connects the radius and ulna. This compartmentalization results in three forearm compartments: the volar, dorsal, and mobile wad. Although some authorities further subdivide the volar compartment into a superficial volar and a deep compartment, most reports and technique descriptions focus on the notion of three forearm compartments.²⁵ The two major compartments, volar and dorsal, are divided by the thick interosseous membrane that connects the radius and ulna. The third compartment, the mobile wad compartment, runs along the lateral (radial) aspect of the forearm.

The volar compartment contains the flexor musculature, along with the median and ulnar nerves, which innervate the flexors. The median nerve is most frequently involved in a compartment syndrome of the forearm because it pursues a deeper, more vulnerable course than the ulnar nerve. The radial and ulnar arteries also course through the volar compartment. The dorsal compartment contains the extensor musculature, along with the deep branch of the radial nerve (the posterior interosseous nerve), but no major arteries.²⁶ The mobile wad compartment contains the brachioradialis, extensor carpi radialis brevis, and extensor carpi radialis longus muscles; these muscles are anatomically transitional between the volar and dorsal muscle groups but are properly associated with the extensor group because of their innervation by the superficial branch of the radial nerve. The forearm muscles that are at increased risk for ischemic injury are in the volar compartment, especially the flexor pollicis longus and the flexor digitorum longus, which run deep and lie directly anterior to the unyielding interosseous membrane that connects the radius and ulna; thus, the upper extremity compartment most often requiring decompression is the volar compartment of the forearm.

A wide variety of both blunt and penetrating traumatic mechanisms can lead to the development of a compartment syndrome in the upper extremity.²⁷ The diagnosis should be suspected in children following supracondylar fracture of the humerus, the mechanism of injury leading to the original description of ischemic contracture of the forearm by

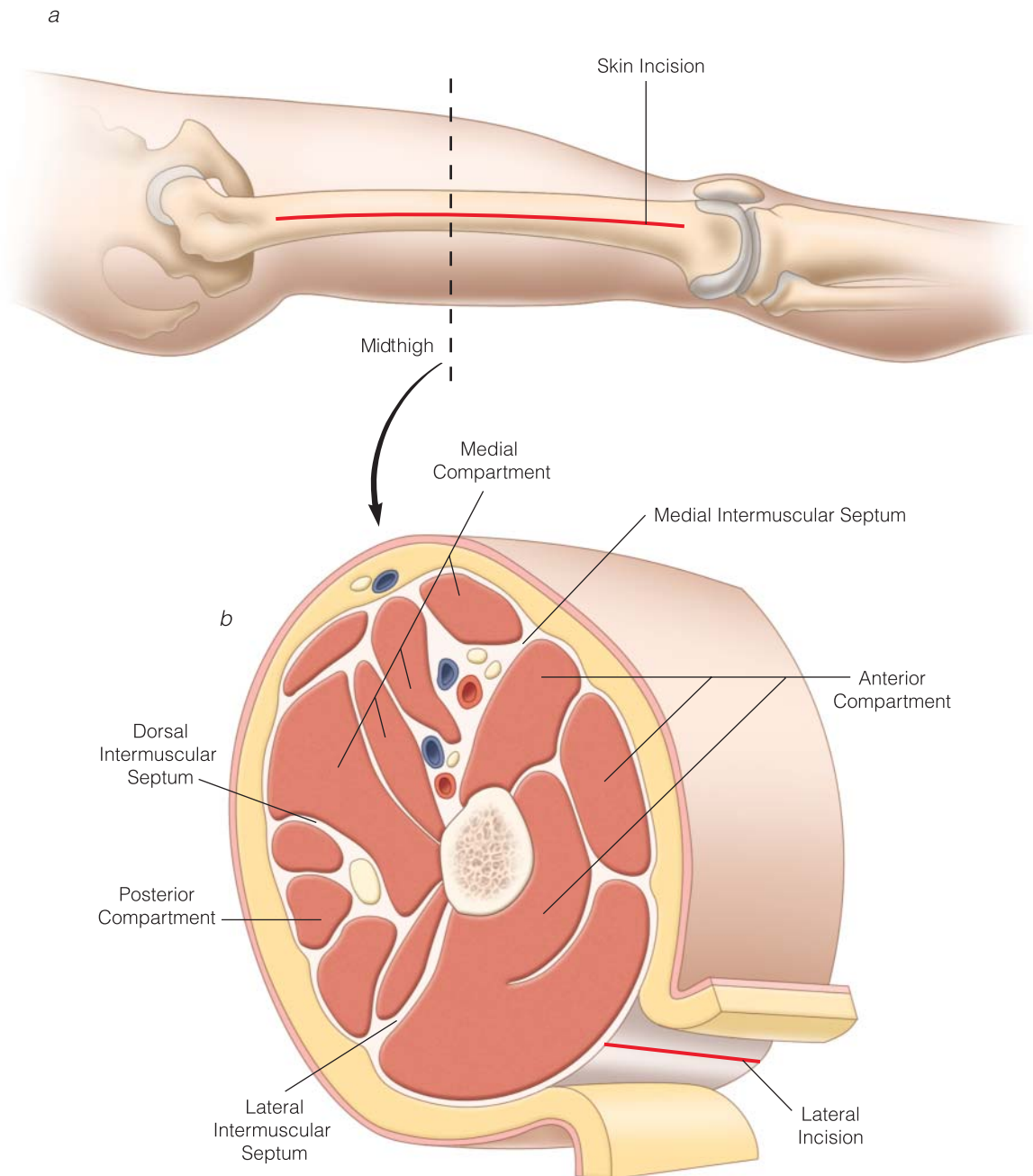


Figure 3 Fasciotomy of the thigh. (a) Skin incision for thigh fasciotomy at the lateral aspect of the leg, along the femur, which allows decompression of the lateral and posterior compartments. (b) Midthigh cross-sectional view of the decompression of the lateral, medial, and posterior compartments of the thigh through two incisions.

Volkmann in 1881.¹ Other clinical situations possibly leading to a forearm compartment syndrome include high-energy injuries with fractures of the forearm, iatrogenic or traumatic arterial injury, subfascial intravenous fluid infiltration, crush injury, and reimplantation of the hand or forearm.^{4,25}

Timely surgical intervention with fasciotomy is the mainstay of treatment. Complete fasciotomy of the forearm is performed using volar and dorsal incisions. However, most forearm compartment syndromes are successfully decompressed with a volar incision only. Two incisions are available

to decompress the volar compartments; one courses along the lateral (radial) aspect of the forearm and the other along the medial (ulnar) side. Each works quite well, and the choice may be based on the pattern of injury and the need for possible soft tissue coverage of an associated orthopedic or vascular repair.

The first approach employs a laterally based (radial) incision for fasciotomy of the volar compartment [see Figure 4a]. This allows exposure of the brachial artery and ready decompression of the mobile wad compartment if needed;

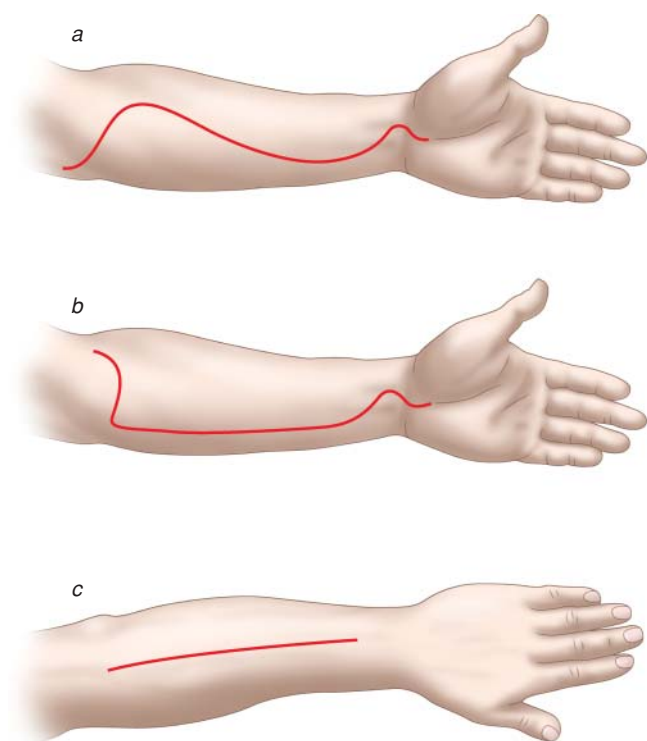


Figure 4 Fasciotomy of the forearm. (a) The preferred volar incision, through which the volar and mobile wad compartments may be decompressed. (b) A variant of the volar incision that may be used in the setting of radial artery reconstruction or radius external fixator placement. This incision allows decompression of the mobile wad and volar compartments. (c) Dorsal incision for decompression of the dorsal forearm compartment.

consequently, release of any pressure on the radial nerve is accomplished through this approach. This volar incision should extend from the distal arm down to the carpal tunnel. The incision is begun medially just proximal to the antecubital crease and has an S-shaped configuration that begins medial to the biceps tendon and extends across the antecubital fossa down the lateral (radial) aspect of the forearm. It continues distally along the medial border of the brachioradialis muscle, continuing across the palm along the thenar crease. The fascia overlying the superficial flexor compartment is released, beginning 1 to 2 cm proximal to the elbow and extending distally across the carpal tunnel onto the palm. The incision may be extended across the wrist out onto the hand to divide the transcarpal ligament to decompress the carpal tunnel as needed. This maneuver decompresses the median, ulnar, and radial nerves, as well as the flexor/pronator musculature and the extrinsic muscles of the fingers and thumb. Proximally at the antecubital fossa, the lacertus fibrosus should be divided to release pressure on the median nerve. The resultant skin flap is designed to maintain soft tissue coverage of the median nerve and the flexor tendons. If possible, the skin overlying the carpal tunnel may be loosely approximated to prevent exposure and desiccation of the flexor tendons. Intraoperative measurement of the deep muscle compartment pressure will guide this decision.

An alternative approach uses a curvilinear medially based (ulnar) volar incision, which allows release of the flexor muscle compartment [see Figure 4b]. The course of the incision may be tailored to accommodate preexisting traumatic wounds and tissue loss.⁴ In severe cases, the deep intramuscular fascia enveloping the flexor digitorum superficialis, the flexor digitorum profundus, and the flexor pollicis longus may also require decompression.⁴

The need for the additional dorsal fasciotomy incision may be determined by intraoperative pressure measurements of the dorsal compartment following release of the volar compartment. A longitudinal incision along the posterior aspect of the forearm releases the dorsal compartment and its extensor musculature. This linear incision extends from the lateral epicondyle down to the midline of the wrist. The interval between the extensor carpi ulnaris and the extensor digitorum communis is identified; the fascia between these two muscle groups is then divided [see Figure 4c]. Postoperatively, the open incisions are loosely dressed with moist saline gauze and the limb is maintained in a functional position.

THE ARM

The arm has two compartments: anterior and posterior. The anterior compartment contains the brachial vessels along with the median, ulnar, and musculocutaneous nerves. The radial nerve runs through the posterior compartment. The fascia encompassing the compartments of the arm is not as rigid and unyielding as that of the leg. As a result, compartment syndromes of the arm are not common and may be difficult to recognize. They most often occur in conjunction with injuries causing a compartment syndrome of the forearm.²⁸ Both compartments of the arm may be decompressed through a single incision along the lateral border of the biceps muscle. This incision releases the anterior compartment. If the posterior compartment requires decompression, it is opened by dividing the intermuscular septum of the arm deep to the biceps muscle. For more extensive injuries with severe swelling, fasciotomy of the arm may be performed using the two incisions depicted in Figure 5.

Postoperative Care and Wound Closure

Discussion regarding fasciotomy is usually focused on its appropriate indications and proper technique. Although less exciting and dramatic than the urgent fasciotomy procedure, its aftermath is equally important. The postoperative care and closure of the wound should not be overlooked. The patient may require support for rhabdomyolysis, myoglobinuria, and renal failure in the acute postoperative phase. Once the patient is clinically stabilized and the acute illness or injury has been overcome, the challenge of closing a large soft tissue defect must be addressed [see Figure 6].

The most commonly described technique of delayed primary closure is the shoelace technique. Sterile rubber bands, or vessel loops, can be placed at the time of fasciotomy in a criss-crossing, shoelace pattern using skin staples for anchors. The vessel loops are stapled to the wound edges of the fasciotomy. The bands are gradually tightened daily as the swelling decreases [see Figure 7]. It is essential to note that the closure process should not be initiated until the acute compartment syndrome has resolved. This method usually results

SCORE

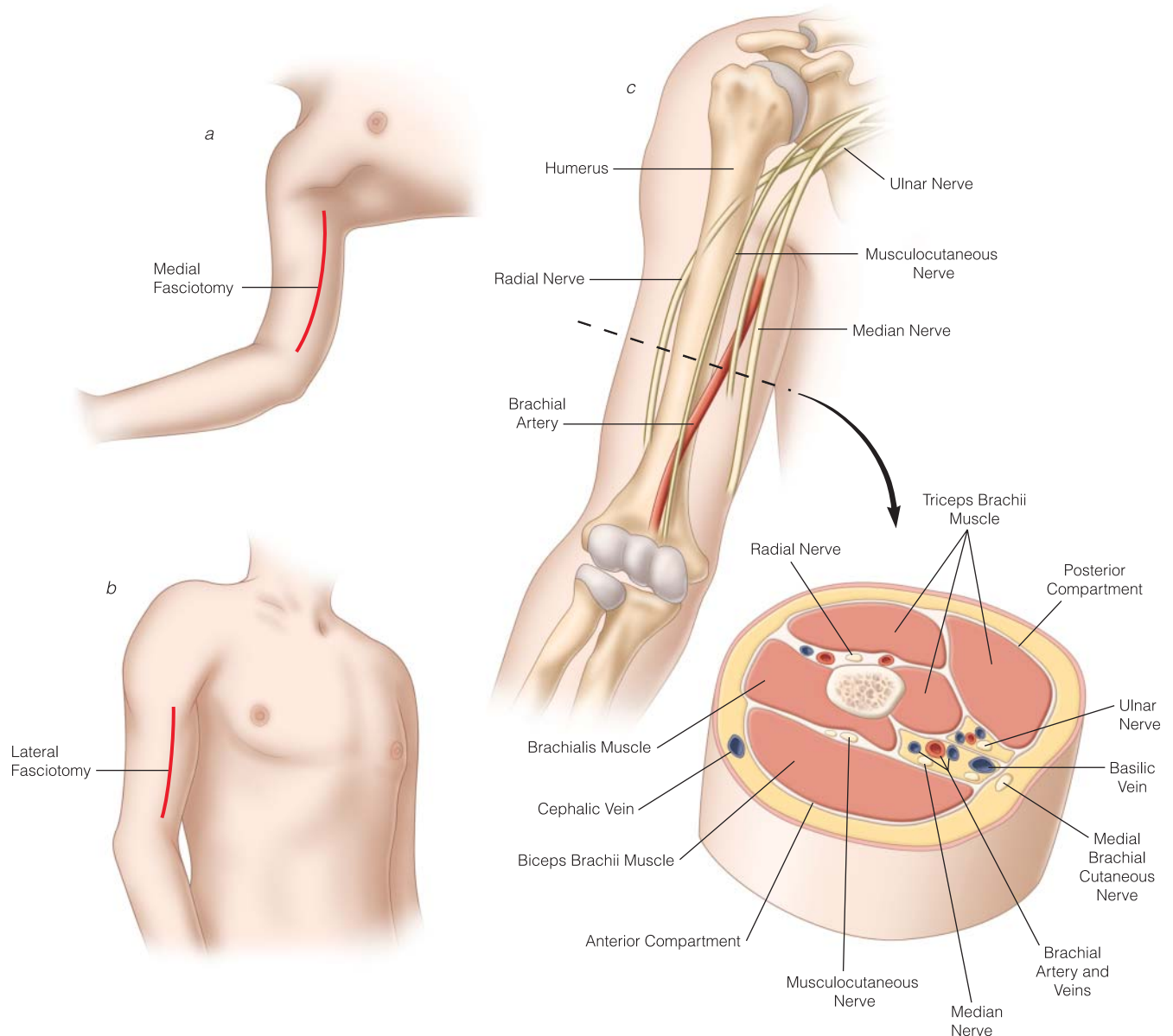


Figure 5 Fasciotomy of the arm. (a) Medial incision for decompression of the anterior compartment. (b) Lateral incision for decompression of the posterior compartment. (c) Three-dimensional view of the contents of the compartments of the arm.

in delayed primary wound closure with very acceptable cosmetic and functional outcomes.

Traditionally, wounds have been managed with moist dressings until they are eventually covered with skin grafts or closed primarily. A newer wound management strategy is the Wound Vac device, which employs negative pressure wound therapy (V.A.C. System, KCI Medical, San Antonio, TX); this method is used in place of standard moist gauze dressings, with reports of a higher rate of primary closure²⁹ [see Figure 8]. For final closure of the wound, several techniques of delayed primary closure have been described for improvement of cosmetic outcome and ease of closure [see Figure 9].

Other innovations have been developed to achieve the same goal of delayed primary closure. The concept of dermatotraction uses the elastic properties of skin to maximize primary closure of a fasciotomy wound. Recently, a new device using stainless steel skin anchors and a nylon line provides an elegant means of applying a defined, calibrated degree of traction to reapproximate the wound margins; an integral clutch mechanism provides a continuous controlled dynamic pulling force (Dermaclose, Wound Care Technologies, Inc., Chanhassen, MN).

The rubber band/vessel loop shoelace technique is probably the most simple and effective method for closure of most fasciotomy wound skin defects. However, the method



Figure 6 Photograph of the large skin defects of the medial leg and thigh fasciotomy wounds following a gunshot wound with superficial femoral arterial and venous injury, second postoperative day.

of closure must be individualized based on patient compliance, equipment availability, cost, and wound factors such as tension and amount of myonecrosis. It is important that the surgeon be familiar with the various closure techniques so that the particular method used optimizes the functional outcome of the fasciotomy procedure for that individual patient.

Chronic Exertional Compartment Syndrome

CECS is a well-recognized entity that tends to occur in relatively young athletes. CECSs arise from repetitive exertion and exercise. Vigorous exercise can increase muscle volume by 20%, causing an increase in pressure within the fixed compartment. Chronically recurring increased pressure within the closed space can cause debilitating symptoms in the athlete; this is most often seen in long-distance runners



Figure 8 Photograph of vacuum dressing for a fasciotomy wound.

and military recruits and usually involves the anterior or deep posterior compartment of the leg.² Weight lifters may also develop this chronic disorder, especially in the forearm.³

Potential causes of CECS include hypertrophy from aggressive training, altered fascial compliance, and myofascial scarring associated with repetitive impact stress and inflammation.² Involvement of the leg is more common, typically affecting runners and soccer players. CECS of the forearm is less common and is seen in competitive motorcyclists,³⁰ weight lifters, and manual laborers. Previous orthopedic trauma is common for both locations. In both sites, diagnosis is based on symptoms and measurement of compartment pressures.

THE FOREARM

Typical symptoms suggestive of CECS of the forearm include forearm pain with exertion that disappears with rest.



Figure 7 Photograph of leg fasciotomy wound approximation using the shoelace technique.



Figure 9 Photograph of delayed primary closure of fasciotomy wounds after vacuum dressing therapy.

Paresthesias are often felt in the fingers. Transient hand dysfunction or cramping has also been described. Examination at the time of symptoms usually reveals a firm, stiff compartment. Diagnosis is confirmed by direct dynamic measurement of compartment pressures using the Stryker STIC device. Measurements are obtained with the patient at rest, during exertion, and following the exercise stress. A finding of a compartment pressure greater than 30 mm Hg in any compartment is abnormal. No further studies are required.³⁰ Treatment requires complete release of involved compartments. Release of the forearm compartments may be performed as an outpatient procedure using a tourniquet under general anesthesia. Release of the compartments is performed using either two volar incisions or two dorsal incisions depending on the compartments involved. Details of the surgical technique are outlined in Croutzet and colleagues' study.³⁰ Sutures are removed at 2 weeks, with initiation of normal daily activities and an exercise program. Full exertional activity is typically reached at 6 weeks following operation.³⁰

THE LEG

CECS involving the leg typically results in atypical claudication symptoms characterized by isolated muscle cramping or swelling with occasional paresthesias localized to the dorsal or plantar surface of the foot. The onset of symptoms is fixed and reproducible but usually occurs at a very long exercise distance, often measured in miles rather than city blocks. Although symptoms may abate with rest, they quickly return with resumption of exertion. These symptoms rarely respond to nonsteroidal antiinflammatory drugs (NSAIDs) or physical therapy. A consistent pattern of failed medical management is characteristic.

Initially noted to be more common in men, the gender profile has shifted dramatically over the past 20 years. Women now comprise more than 70% of patients in Turnipseed's comprehensive analysis of 28 years of experience.² Initially more common in runners, the most common sport associated with CECS of the leg is now soccer. The average age of patients is 32 years. Symptoms are unilateral in 44% of patients.

The most commonly affected lower extremity muscle groups are in the anterolateral (72%), deep posterior (16%), and superficial posterior (12%) compartments. Plantar foot paresthesia is most commonly associated with the deep posterior compartment; dorsal foot paresthesia results from involvement of the anterolateral compartments. Diagnosis is confirmed by measurement of compartment pressures at rest and following exercise. Normal resting pressure within the leg compartments is less than 15 mm Hg. Resting pressures ranging from 16 to 24 mm Hg are suggestive of CECS, whereas pressures greater than 25 mm Hg are considered diagnostic. Those patients with borderline resting compartment pressures (16 to 24 mm Hg) are retested following exercise stress. Postexercise compartment pressure usually returns to baseline within 3 minutes. If the compartment pressure remains elevated (> 25 mm Hg) for more than 10 minutes after exercise, this is considered a positive provocative stress test result.²

Initial treatment of CECS of the leg may include rest, along with modification of the intensity and duration of

workouts; however, most high-level athletes are not willing or are unable to adjust their training schedules as a permanent means of controlling symptoms. Failure to respond to nonsurgical treatment or the inability to pursue a non-invasive treatment regimen leads to the need for surgical intervention.

The surgical approach to CECS involves either a fasciotomy or fasciectomy procedure. Whereas fasciotomy is probably a more common procedure, fasciectomy with open technique seems to yield more durable positive results with fewer complications. As described by Turnipseed, the open procedure is performed through a 2.5 to 3.0 cm incision, an ellipse of the fascia encasing the involved compartments is excised, and then, under direct vision, the fascia can be released from the level of the tibial plateau down to about 2 cm above the ankle level.² The small incisions (< 3 cm) required for this approach yield acceptable cosmetic outcomes with fewer postoperative complications than semi-closed methods with limited incisions and exposure. Either method can be performed in the ambulatory setting using local anesthesia with intravenous sedation. Structured rehabilitation programs allow a graduated return to full activity over 3 months.

Abdominal Compartment Syndrome

The physiology of abdominal compartment syndrome is consistent with that of extremity compartment syndrome in that increased pressure in a rigid volume causes tissue ischemia. Abdominal compartment syndrome can occur postoperatively after abdominal operations (e.g., tight closure after abdominal wall herniorrhaphy, aortic cross-clamping), and secondary abdominal compartment syndrome can result from massive fluid resuscitation. The signs and symptoms of abdominal compartment syndrome differ from those of extremity compartment syndrome because of the contents of the abdominal compartment. Compression of the inferior vena cava results in diminished preload and decreased cardiac output, which may cause hypotension. Decreased venous return of intra-abdominal organs contributes further to organ ischemia, resulting in bowel necrosis and hepatic ischemia. The compliance of the thoracic cavity is decreased, resulting in hypoventilation as a result of the inability to expand the thoracic cavity and elevation in airway pressure. Intra-abdominal hypertension also results in compression of kidneys, resulting in oliguria attributable to mechanisms not yet defined.

In contrast to extremity compartment syndrome, abdominal compartment syndrome is very difficult to diagnose by physical examination. Manometry for the diagnosis of abdominal compartment syndrome should be performed and can be accomplished by the measurement of bladder pressure. Twenty-five milliliters of normal saline solution is instilled in the bladder via a Foley catheter. The catheter is connected to a transducer device, which should be positioned at the level of the midaxillary line. The pressure is measured at end-expiration. For accuracy, multiple measurements are taken. Normal intra-abdominal pressure (IAP) is 5 to 7 mm Hg. Intra-abdominal hypertension is defined as IAP greater than 11 mm Hg.³¹ Abdominal perfusion pressure can also be measured by subtracting the IAP from the systemic mean arterial

pressure. However, the diagnostic value of this has not been confirmed by prospective studies. Therefore, the current standard of diagnosis is the IAP. The grading system instated by the World Congress on Abdominal Compartment Syndrome is as follows: grade I, IAP 12 to 15 mm Hg; grade II, IAP 16 to 20 mm Hg; grade III, IAP 21 to 25 mm Hg; and grade IV, IAP > 25 mm Hg. Those patients in grades I and II can be managed medically with gastric decompression, sedation, diuresis or ultrafiltration. Patients falling within grade III should be clinically evaluated for signs of end-organ failure. If those signs are present, decompressive laparotomy is indicated. For grade III patients without evidence of organ failure, close monitoring is essential. Neuromuscular blockade for relaxation of the abdominal wall musculature may

decrease IAP. For those patients in grade IV, decompressive laparotomy is usually necessary. Failure of medical therapy and signs of end-organ ischemia mandate decompression. For those patients with intra-abdominal fluid, blood, or abscess causing compartment syndrome, catheter drainage is acceptable.³²

After laparotomy for decompression, temporary abdominal closure can be achieved with either a Bogota bag sutured to the skin or a vacuum-assisted device for closure. Primary closure is usually possible within 5 to 7 days of decompression. After closure, the patient must be monitored for recurrent abdominal compartment syndrome.

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Acknowledgments

Figures 2 through 5 Christine Kenney

32 CURRENT MODALITIES FOR IMAGING THE VASCULAR SYSTEM

Aoife N. Keeling, FFRRCSI, and Peter A. Naughton, MD

Over the last two decades, there has been a paradigm shift for both the diagnosis and the treatment of many vascular pathologies. Noninvasive imaging using duplex ultrasonography (US), computed tomography (CT), and magnetic resonance angiography (MRA) is now often preferred to digital subtraction angiography (DSA) for diagnosis, and endovascular intervention has emerged as an attractive alternative to open surgery for the treatment of many vascular conditions. This chapter focuses on the noninvasive imaging modalities currently used in the investigation and diagnosis of both arterial and venous disorders, covering both technical factors and clinical applications with a number of case-based examples.

Plain Film

Previously, prior to the widespread use of computed tomographic angiography (CTA) and MRA, plain film could be used to assist in the diagnosis of certain vascular pathologies, including aneurysmal disease, atherosclerosis, trauma, and postoperative follow-up. Now with the many other imaging modalities available, the emphasis has moved away from plain film radiography. However, vascular specialists should be aware of their current role in vascular diagnosis, often incidentally, and in postprocedural follow-up.

Aneurysms, particularly abdominal aortic aneurysms (AAAs), can be diagnosed incidentally on an abdominal radiograph manifested by the presence of retroperitoneal linear calcification representing the calcified atherosclerotic aortic wall. Similarly, mesenteric arterial aneurysms can also be identified as concentric or curvilinear calcification within the right or left upper quadrant. This finding should prompt further investigation with US or CTA. Thoracic aortic aneurysms and pseudoaneurysms may also be incidentally diagnosed on chest radiographs, usually manifesting as a widened mediastinum. Ascending thoracic aortic aneurysms/pseudoaneurysms can produce a right sided mediastinal mass on CXR, with descending thoracic aortic aneurysms/pseudoaneurysms causing a left sided mediastinal mass. Linear calcification along the aneurysmal aortic wall or within the rim of a pseudoaneurysm can be identified on CXR. CXR may also reveal mass effect from the aneurysms/pseudoaneurysms, manifested by downward displacement of the left mainstem bronchus. Similarly, unrecognized thoracic aortic coarctations can present incidentally on a chest x-ray in teenagers or young adults with the classical rib notching and small mediastinum [see *Figure 1*].

Prior to the widespread use and availability of CTA in the emergency setting, a small study demonstrated that the diagnosis of an AAA contained rupture could be made in a

large proportion (90%) of patients on the basis of plain abdominal radiograph findings.¹ Plain film findings including the presence of aortic rim calcification (65%), soft tissue mass (67%), loss of psoas muscle (75%) or renal (78%) outlines, renal displacement (25%), and properitoneal flank stripe changes (19%) were all associated with an AAA rupture in the correct clinical context.¹ Acute thoracic aortic injury including transection has a number of classical findings on plain chest radiograph, including signs of mediastinal hematoma—widened mediastinum, deviation of the trachea to the right of the T4 spinous process, deviation of a nasogastric tube to the right of the T4 spinous process, obscuration of the margin of the aortic arch, left apical cap, depression of the left mainstem bronchus, and loss of the aortopulmonary window—and associated signs, including fractured first and/or second rib, left pleural effusion from hemothorax, and left pneumothorax or hemopneumothorax. However, these plain film findings are not specific; thus, CTA is required for definitive diagnosis and preprocedural planning.²

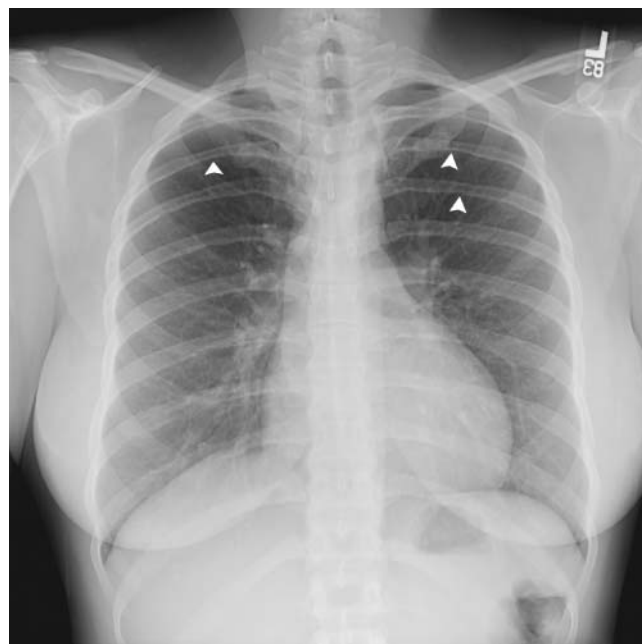


Figure 1 A 21-year-old female with a cough and fever underwent a chest radiograph to evaluate for pneumonia. Incidental note was made of bilateral rib notching (arrows). This was confirmed at time-resolved magnetic resonance angiography to be an aortic coarctation with multiple arterial collaterals resulting in the bilateral rib notching.

Plain film acquisition has been advocated in the annual follow-up of endovascular aneurysm repair (EVAR) of both thoracic and abdominal aortic aneurysms to detect late stent graft-related complications.³ Type III endoleaks can occur from a device-related complication attributable to migration and separation of the iliac extension limbs from the stent graft main body. Plain film can identify limb separation and may be an adequate sole imaging modality to detect this potential complication.⁴ Also, stent grafts, mainly the unsupported devices, can kink, fracture, and infold, all of which can be detected on plain radiographs. Kinking and infolding may lead to stent graft occlusion. Infolding is reported with the earlier Gore TAG thoracic stent graft devices (W.L. Gore & Associates, Flagstaff, AZ) in cases of acute thoracic aortic transection in young patients with normal-size aortas. This infolding is most likely attributable to oversizing of the device.⁵ Plain films can accurately demonstrate this stent graft infolding, as Leung and colleagues have illustrated.⁵

Another endovascular procedure that some authors advocate for imaging follow-up is that of vena caval filter insertion. At present, two filter classes are available on the market, optional or retrievable and permanent, both serving to prevent large pulmonary emboli but for differing clinical scenarios. Optional or retrievable caval filters allow for removal of the caval filter when the risk of pulmonary embolus is removed or when appropriate anticoagulation therapy can be commenced. However, permanent caval filters remain within the cava for the remainder of the patient's life, and some authors advocate imaging follow-up to detect any device-related complications, including fracture, migration, embolization, or caval thrombosis. Greenfield and Rutherford asserted that following filter insertion, a plain abdominal x-ray should be acquired the next day, then every 6 months for 2 years, and then yearly to ensure adequate filter position⁶ [see Figure 2]. Doppler US of the cava was also recommended at 3 months, then every 6 months for 2 years, and then yearly to ensure patency.

Ultrasonography

Duplex US, combining real-time B-mode information and flow characteristics from pulsed-wave Doppler US, has been the first-line investigation for vascular imaging for many years. The main benefits of duplex US are that it is cheap; it provides important hemodynamic, physiologic and anatomic information; it has no ionizing radiation; it is a portable, reproducible, real-time technique; and it can guide arterial and venous interventions. The limitations are that it is operator dependent, patient dependent (it performs poorly in obese patients), and anatomic location dependent (it performs poorly in deep locations such as the pelvis or thorax); it is inhibited by overlying bowel gas, bone, or lung and by arterial wall calcification; and it is time consuming to image the entire peripheral arterial tree.

PERIPHERAL ARTERIAL DISEASE

Various measurements are attained in the vascular laboratory to assess and evaluate for critical arterial stenosis. Measurement of pressure and flow is the cornerstone of assessing for peripheral arterial disease (PAD). Frequently performed pressure assessments include the ankle-brachial index (ABI)

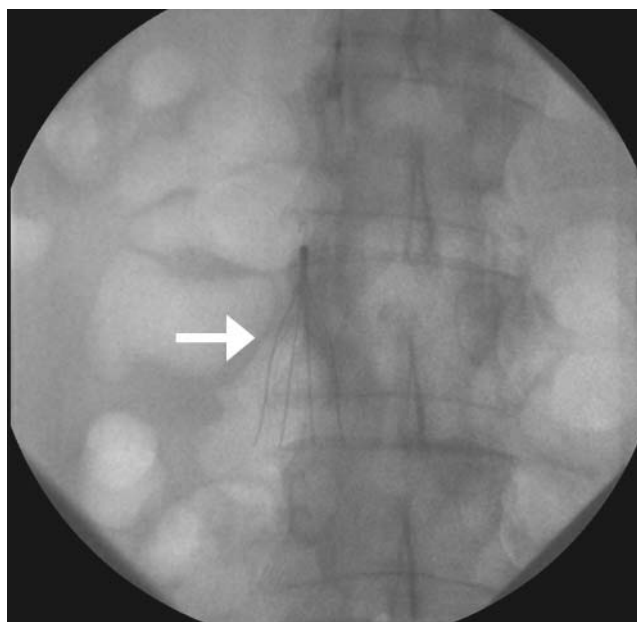


Figure 2 A 65-year-old female following intracranial aneurysmal clipping developed a pulmonary embolus but was unable to receive anticoagulation because of the recent intracranial surgery. Thus, a retrievable caval filter was placed. A plain film following filter insertion demonstrates a retrievable Cook Celect filter (Cook Medical, Bloomington, IN) within the infrarenal cava without any tilt (arrow).

and segmental and toe pressures. Drops in pressure correlate to luminal stenosis; for example, a normal ABI is 1.11 ± 0.1 ; for patients with intermittent claudication, the ABI is 0.59 ± 0.15 ; and patients with rest pain have a characteristic ABI of 0.26 ± 0.13 .⁷

Flow characteristics including peak systolic and end-diastolic velocity, pulse contour, and amplitude (waveform) may be determined using duplex US and plethysmography. Waveforms are useful in identifying a proximal occlusive stenosis. Mazzariol and colleagues reported that a severely abnormal common femoral artery waveform was 100% predictive for detecting iliac artery stenosis greater than 50%.⁸ Mildly abnormal common femoral artery waveforms unfortunately did not exclude significant proximal stenosis; therefore, additional imaging modalities were required. Mazzariol and colleagues concluded that duplex US was able to provide enough information for surgery in more than 83% of patients.⁸ For infrainguinal disease, a significant stenosis is defined as a twofold or greater increase in peak systolic velocity (PSV) or the absence of blood flow consistent with an occlusion. In similar studies, Proai and colleagues and Grassbaugh and colleagues reported that duplex US was predictive in 88% of patients compared with 93% of patients undergoing conventional angiography.^{9,10} Despite the fact that TASC II¹¹ does not recommend bypass graft surveillance with US, it is widely used for peripheral bypass graft surveillance, and many authors attest to its value¹² [see Figure 3].

A recent meta-analysis evaluated the diagnostic accuracy of MRA (time of flight [TOF]), contrast enhanced CTA, and duplex US for diagnosing arterial stenoses equal to or greater than 50% and arterial occlusions within the lower limb.¹³

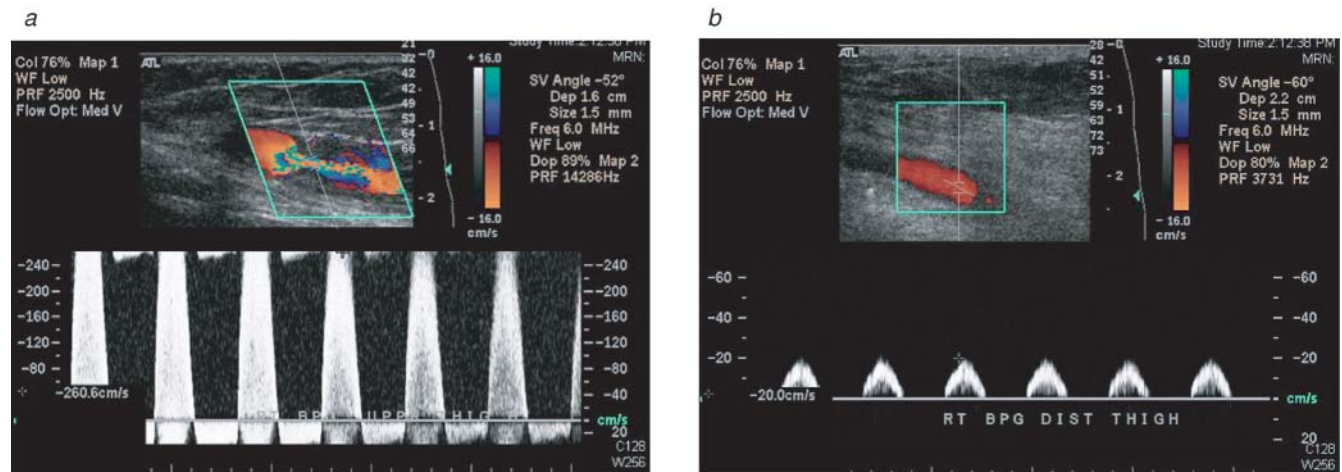


Figure 3 A 68-year-old female presented with two-block intermittent claudication, no rest pain, and no ulceration. A right femoropopliteal vein bypass was created 6 years previously. (a) A duplex sonogram of the vein bypass demonstrates a tight stenosis within the midvein bypass with markedly elevated peak systolic velocity (PSV) of 260 cm/s. (b) A duplex sonogram of the vein bypass distal to the stenosis demonstrates patency but a dampened waveform with a PSV of 20 cm/s.

Duplex US had a median sensitivity and specificity of 88% (80 to 98%) and 96% (89 to 99%), respectively, for lesions at all sites; 88% and 95%, respectively, for lesions above the knee; and 84% and 93%, respectively, for lesions below the knee.¹³ Another meta-analysis also demonstrated a lower sensitivity and specificity for duplex US compared with MRA as the authors concluded that the sensitivity for MRA was 97.5% compared with 87.6% for duplex US.¹⁴ The specificity of the two tests was similar, 96.2% versus 94.7%.¹⁴

DUPLEX US FOR AAA

Sixty percent of AAAs are asymptomatic and are diagnosed incidentally on physical examination or imaging. US is advocated as the imaging modality of choice for AAA screening.^{15,16} A sonographic diagnosis of an AAA is achieved when the diameter of the dilated segment of aorta is 1.5 times greater than the adjacent unaffected aorta. Ultrasound interrogation of an AAA involves taking longitudinal, transverse, and coronal views [see Figure 4a]. However, US has several shortcomings, including variability in transverse dimensions of the aneurysm sac, limitations in aneurysm neck assessment, and limited visualization of luminal thrombus.¹⁷ The Society for Vascular Surgery has launched a national program to screen large populations for carotid artery stenosis, AAAs, and PAD. The screening program consists of a truncated carotid artery scan, an abdominal ultrasound to detect AAAs, and an ABI. Flinn reported the finding of unsuspected aneurysms in 2.2% of patients, carotid stenosis greater than 50% in 7.6% of patients, and PAD in 7% patients.¹⁸

US is also important in the postoperative surveillance of patients. Endoleak is defined as the persistence of blood flow within the aortic sac following stent graft deployment. Despite continued improvement in stent graft design, the occurrence of endoleaks remains the Achilles heel of EVAR. Posttreatment surveillance is therefore necessary to detect endoleaks and identify the patients who may require reintervention.

Initially, CT was solely employed for this surveillance; however, many centers, in an effort to minimize patient radiation exposure, are now advocating the role of colour duplex US, either alone or in combination with plain films. Color Doppler examination in a patient following EVAR enables one to determine the presence of endoleak, identify the source of endoleak, measure maximum sac diameter, and assess the flow within the stent graft [see Figure 4, b and c].

Aortic duplex US can aid in the diagnosis of other aortic pathologies as well as aneurysmal disease, such as atherosclerosis causing stenoses, dissection with the characteristic finding of an intimal flap [see Figure 5], arteriovenous fistulae (AVF), and pseudoaneurysms.

DUPLEX US FOR CAROTID ARTERY STENOSIS

Patients with severe symptomatic carotid artery stenosis are at high risk for ipsilateral ischemic stroke; thus, appropriate intervention, surgical or endovascular, is vital to prevent disabling stroke. The North American Symptomatic Carotid Endarterectomy Trial (NASCET)¹⁹ and the European Carotid Surgery Trial (ECST)²⁰ measured the degree of internal carotid artery (ICA) stenosis with intra-arterial angiography and then determined if carotid endarterectomy (CEA) had a benefit in reducing the stroke rate in the less than 50%, 50 to 69%, and 70% or more ICA stenosis groups. The NASCET concluded that there was a sustained benefit in treating patients with CEA with 50% or greater symptomatic stenosis.¹⁹ Although DSA remains the gold standard, diagnostic DSA has a 1% risk of stroke and a less than 1% risk of death; thus, noninvasive imaging with duplex US, CTA, and MRA is now widely practiced, and DSA is usually reserved for indeterminate cases or prior to carotid arterial stenting.

Duplex US enables one to evaluate waveforms at the common carotid artery, prestenotic ICA, stenosis of ICA, and poststenotic ICA [see Figure 6]. Langlois and colleagues first correlated PSV and end-diastolic velocity, measured by duplex US, compared with the degree of ICA stenosis

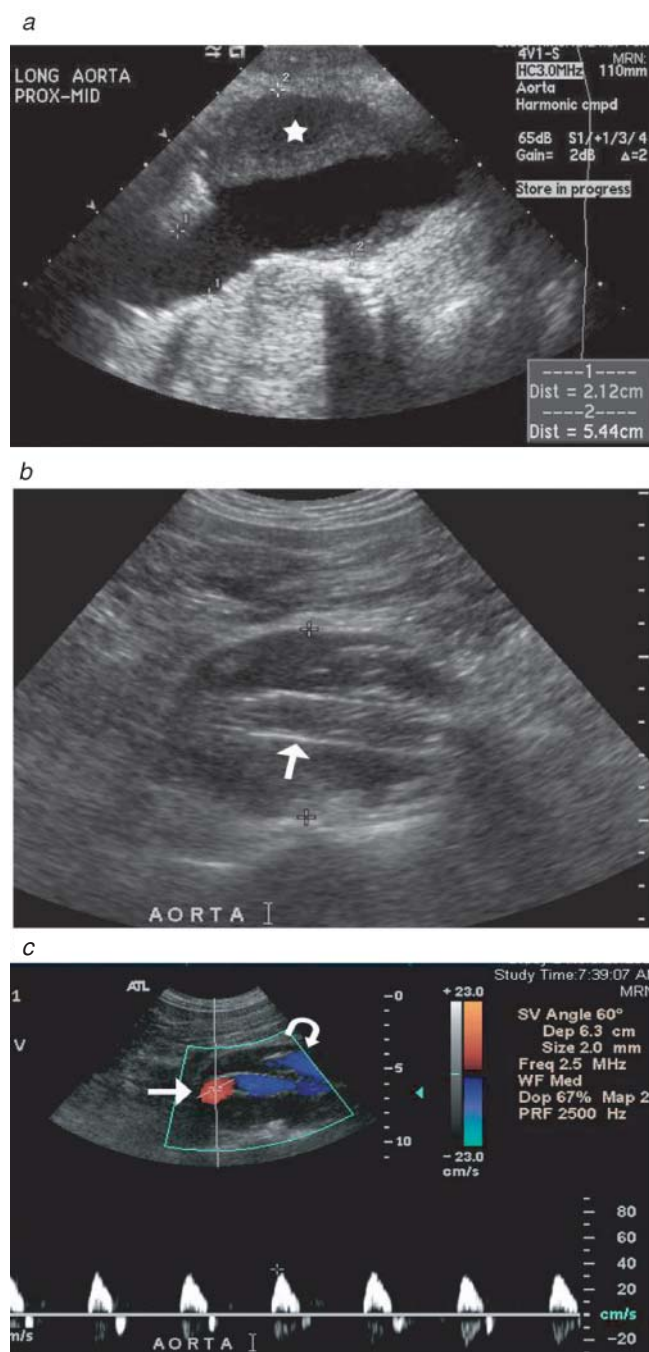


Figure 4 A 59-year-old male smoker underwent aneurysm screening ultrasonography. (a) A longitudinal view demonstrates a 5.5 cm infrarenal abdominal aortic aneurysm with thrombus (star) within the sac. (b) Ultrasonography was used for follow-up post-endovascular aneurysm repair. Note the stent graft (arrow) excluding the aneurysmal sac with an overall reduction in sac size compared with the initial sonogram. (c) A color duplex sonogram demonstrates patency of the main body of the stent graft (arrow) and the contralateral iliac limb (curved arrow). No endoleak was identified on this surveillance duplex ultrasound examination.

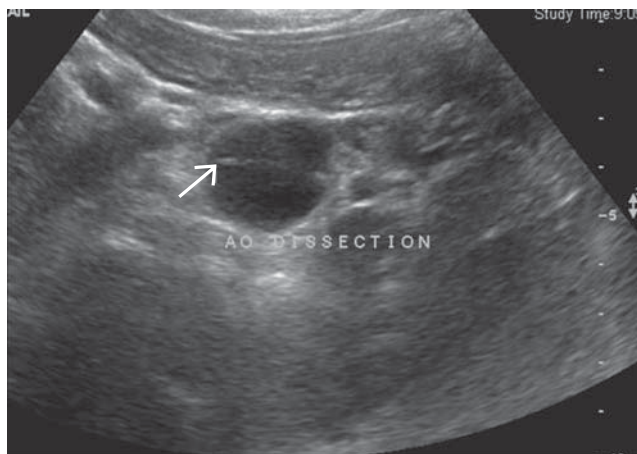


Figure 5 A 67-year-old male with sudden-onset back pain underwent duplex ultrasonography. The initial sonogram demonstrated a flap within the lumen of the abdominal aorta consistent with a dissection flap (arrow).

determined by DSA.²¹ Following the NASCET and the ECST, this correlation has subsequently been revised by the Society of Radiologists in Ultrasound Consensus Committee.²² Each vascular laboratory needs to develop its own internally validated criteria. Duplex US assessment of ICA stenosis using the consensus and internally validated criteria also obviates the confusion that occurs when assessing stenosis angiographically as three different methods are commonly used (the NASCET, ECST, and common carotid artery methods). These different methods and calculations explain the differences found between the NASCET and the ECST; for example, a 50% ICA stenosis determined by the NASCET method correlates to a 75% ICA stenosis by the ECST method.

In addition to calculating ICA stenosis, duplex US also provides important information regarding plaque characterization: ulcerated versus nonulcerated surface, hypoechoic (fibrofatty) versus echogenic (calcified), stability of the overlying cap, and homogeneous versus heterogeneous plaque. The external carotid artery and proximal vertebral and subclavian arteries are also visualized when completing the duplex US. Diagnosis and assessment of nonatheromatous conditions including carotid dissection, carotid body tumor, carotid artery kinks, and fibromuscular dysplasia may be elicited using duplex US.

Duplex US may be limited in differentiating near and complete occlusion, investigating heavily calcified lesions, and evaluating for in-stent restenosis.

DUPLEX US FOR RENAL AND MESENTERIC DISEASE

Color and pulsed Doppler evaluation of splenic and renal vessels can be used to evaluate for chronic mesenteric ischemia or renal artery stenosis (RAS). Examination may be limited by patient obesity or operator experience. The technique used to complete the evaluation of these vessels is beyond the scope of this chapter, but in brief, patients are best examined early in the morning after overnight fasting to minimize scatter and attenuation by intra-abdominal bowel gas and

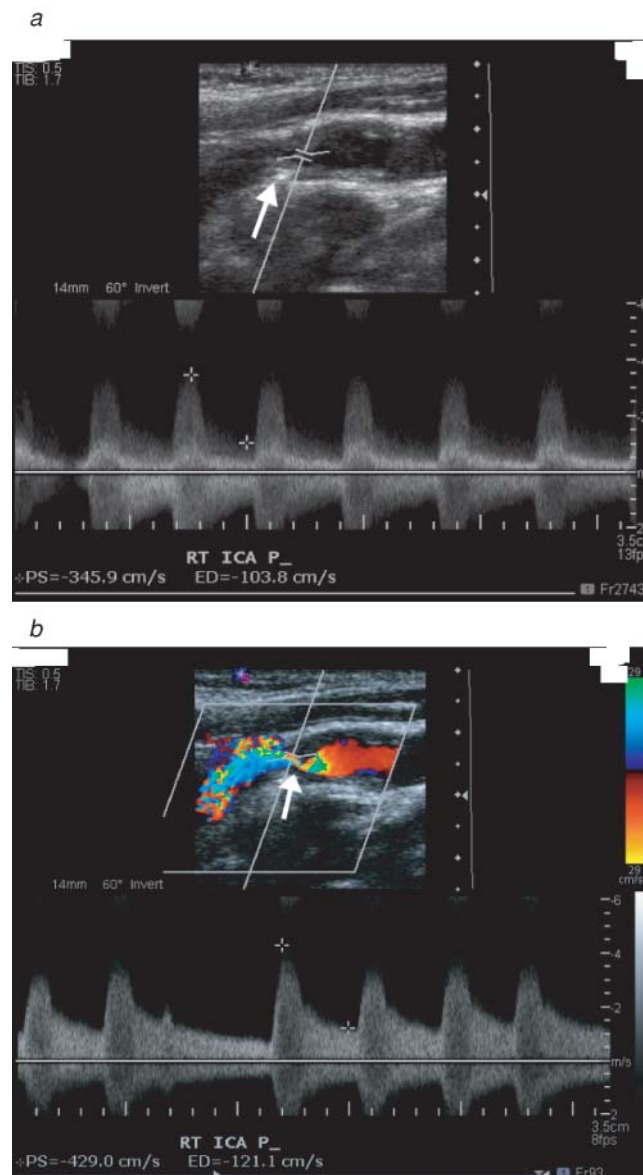


Figure 6 A 69-year-old male with a history of two transient ischemic attacks presented for investigation. (a) Duplex ultrasonography of both carotid arteries was performed. The longitudinal B-mode ultrasound demonstrates an eccentric echogenic plaque (arrow) within the right internal carotid artery (ICA) causing a marked stenosis. There is no evidence of shadowing and thus no significant calcification. Thus, this is consistent with a soft, lipid-rich plaque. (b) When the color Doppler is placed over the stenosis, there is marked luminal compromise (arrow). The peak systolic velocity is 429 cm/s. These findings are consistent with a significant greater than 70% stenosis. This patient went on to digital subtraction angiography and was treated with a carotid stent.

are examined in the supine and lateral positions using a low-frequency (2 to 5 MHz) transducer. The vessels are located by identifying and following the abdominal aorta. Blood flow velocity, particularly PSV, and a ratio of mesenteric vessel PSV to aortic PSV are calculated. Moneta and colleagues

compared velocities to angiograms in 34 patients with mesenteric stenosis and found that a PSV greater than 200 cm/s in the celiac artery and greater than 275 cm/s in the superior mesenteric artery (SMA) was predictive of a greater than 70% stenosis on an angiogram.²³ A mesenteric-aortic ratio greater than 3 indicates a hemodynamically significant stenosis. A PSV greater than 180 cm/s correlates to significant RAS, and a renal:aortic velocity ratio greater than 3.5 conforms to a greater than 60% RAS.

DUPLEX US FOR VENOUS DISEASE

Lower limb venous disease most commonly involves venous thromboembolism (VTE) and chronic venous insufficiency, with up to one in 20 people being diagnosed with VTE over the course of a lifetime.^{24–26} US forms the mainstay of diagnosis for both of these venous conditions. Normal lower extremity veins have characteristic findings on duplex US, including thin, nonechogenic walls, normal valves, and compressibility; the diameter is usually larger than that of the corresponding artery, and the diameter of the large veins changes with respiration (increases with deep inspiration or Valsalva maneuver). Blood flow within medium to large veins is described as spontaneous (occurs without extrinsic compression), phasic (changes in response to respiration, that is, flow cessation with Valsalva maneuver), augmented (increases in flow with manual compression of the limb distal to the ultrasound probe), and unidirectional [see Figure 7].

Venous thrombus originates focally within the vein and then begins to propagate along the vein. In the acute phase, an acute inflammatory response is initiated and typically lasts 7 to 14 days. Thrombus in the acute phase is loosely attached to the vein wall and subsequently is at the highest risk of embolization. Several key characteristic findings on US in acute thrombosis include low thrombus echogenicity identified by a flow void and lack of vein compressibility, venous distention, loss of compressibility, free-floating thrombus, diminished or absent flow augmentation, and phasisty and venous collateralization [see Figure 8]. It is clinically important to diagnose an acute thrombosis to prevent thrombus propagation and embolization and potentially limit the

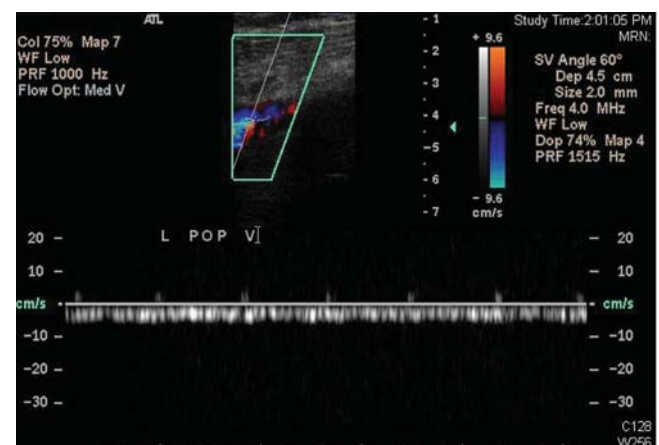


Figure 7 An ultrasound demonstrating a normal venous flow pattern within the popliteal vein.

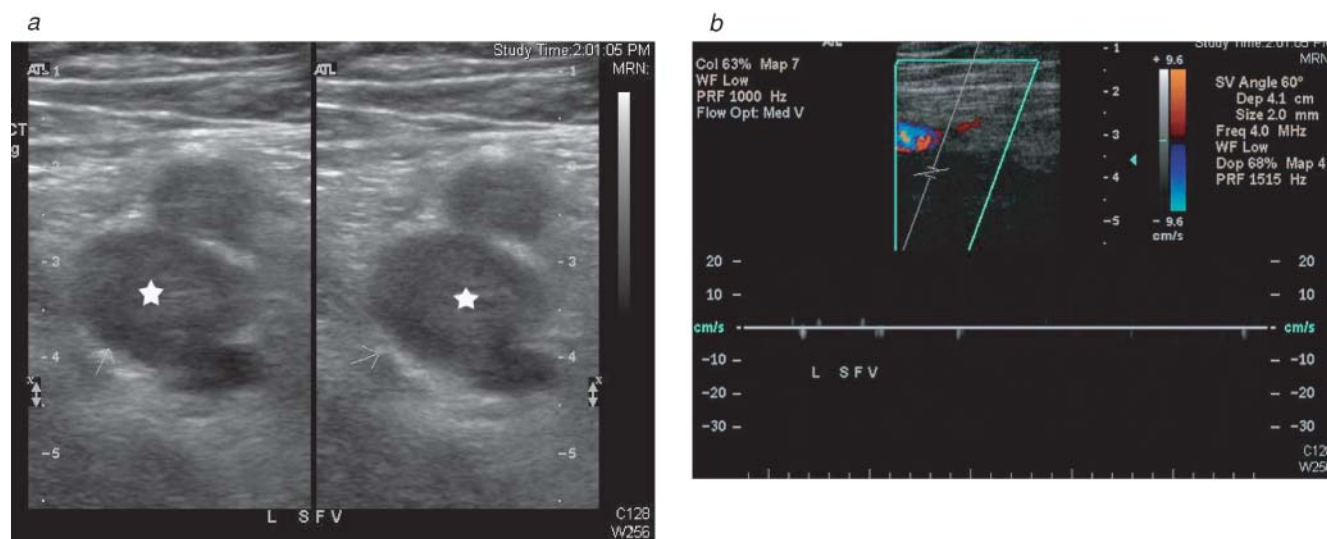


Figure 8 A 46-year-old male presented with left lower limb swelling and tenderness. (a) An ultrasound of the deep venous system of the left leg demonstrates echogenic material within the left superficial femoral vein (LSFV) (white star). There is noncompressibility of the LSFV (right panel). (b) On a color duplex ultrasound, there is no venous flow within the LSFV consistent with occlusive deep venous thrombus.

injurious effects of acute inflammation to veins and valves. Subacute thrombosis occurs between 2 weeks and 6 months, during which the thrombus becomes more echogenic and adherent to the vein wall and retracts, the diameter size decreases, and flow is restored. The chronic phase occurs after 6 months and is characterized by infiltration of the vein and thrombus by fibroblasts. Chronic thrombus is seen on a ultrasound as thickening and fibrosis of the vein wall, hyper-echoic calcified thrombus, valve thickening, and rigidity with reflux and lack of spontaneous, phasic, or augmented flow.

In patients with evidence of varicose veins or chronic venous insufficiency, US is used to demonstrate and locate sites of reflux in the superficial and deep venous systems. A valve reflux time greater than 0.5 seconds suggests venous insufficiency.

Within the upper extremity, venous duplex US is also valuable for the investigation of VTE, albeit performed less frequently than in the lower limb. A meta-analysis determined that upper limb duplex US had an excellent specificity (94 to 100%) but a variable sensitivity (56 to 100%) for diagnosis of arm VTE.²⁷ Venous mapping prior to hemodialysis AVF creation is performed with duplex US in many centers, with venography being reserved for problem solving. Established hemodialysis AVF can be interrogated with duplex US in the setting of poor flows, difficulty with cannulation, or prolonged bleeding following needle removal or in the dreaded situation of loss of the thrill.

Multidetector Computed Tomographic Angiography

BASIC PRINCIPLES

The basic principle of CT is to use multiple projections of an object to reconstruct the internal structure of that object

and produce a two-dimensional image. The generation of a CT image can be broken down into three stages: (1) data acquisition involving the exposure of the patient to ionizing radiation, (2) image reconstruction, and (3) image display.

DATA ACQUISITION

A CT scanner is composed of an x-ray tube, an array of detectors, and associated electronics, all mounted on a frame called a gantry. The x-ray tube produces a fan-shaped beam of x-rays that interact with the patient, some of which pass through the patient to interact with the detectors. During data acquisition, both tube and detectors rotate around the patient and the detectors repeatedly measure the number of x-rays transmitted through the patient. The amount of radiation transmitted to each detector and the gantry angle at the time of the measurement are recorded. Typically, the detector array contains 500 to 1,000 detectors, each of which is sampled approximately 1,000 times per revolution. Each line of this information reflects the summation of the attenuation coefficients (how difficult it is for an x-ray to pass through) of all structures in that x-ray path. The entire data set forms the raw data from which an image is reconstructed.

IMAGE RECONSTRUCTION

From the raw data, a digital image is created. A variety of mathematical techniques can be used to accomplish this; these rely on the principles of back-projection, iterative formulas, or analytic formulas, either with or without Fourier transformation. The result is a matrix of numbers; generally, a 512×512 matrix is employed in vascular CT. Each number in this matrix is called a pixel, and each pixel corresponds to a volume of tissue or voxel within the patient. The average density of the tissue within each voxel is represented by the

pixel value. The dimensions of the voxel in the scan plane are set by the field of view (FOV) and matrix; the dimensions of the pixel in these axes can be calculated by dividing the FOV by the matrix size. The third dimension, representing the voxel depth, is the image thickness, which is determined by the collimation width of the fan beam. The difference in attenuation of the contents of a voxel relative to water is defined as the CT attenuation number and expressed in Hounsfield units (HU). A 12-bit number scale (2^{12}) is used, which defines water as 0 and air as $-1,000$; therefore, each pixel is a number from $-1,000$ to $+3,095$.

IMAGE DISPLAY

This digital image or number matrix is converted to a visual format for interpretation. A grayscale is used, with the densest materials, such as bone (highest Hounsfield units), being assigned lighter shades (white), whereas the least dense, such as air (black) (most negative Hounsfield units), are assigned darker shades of gray. The source images are acquired and displayed in the axial plane; however, because of the large volume of data obtained with multidetector computed tomographic angiography (MDCTA), image postprocessing to enable disease interpretation is necessary. The axial image plane is no longer the only plane available for image interpretation. With multidetector computed tomography (MDCT) acquisition, near-isotropic (spatial resolution is approximately equal in all planes) data sets can be obtained and thus manipulated in all imaging planes and projections without significant loss of image quality, to enable eloquent display of the arterial anatomy and pathology. Therefore, a dedicated three-dimensional (3D) workstation to enable a real-time interactive approach to image manipulation and interpretation has now become a necessity. Available image postprocessing techniques on the clinical 3D workstations include multiplanar reconstruction, maximum-intensity projection (MIP), volume rendering, and shaded surface display.

ADVANTAGES OF MDCTA

With the advent of MDCTA, noninvasive angiography has become a viable option as a result of increased speed of acquisition, spatial resolution, and volume coverage compared with the older generation of single-detector CT scanners. Isotropic data sets can now be acquired with MDCTA, allowing for 3D reconstruction and many postprocessing methods to enable both diagnostic interpretation and eloquent anatomic and pathologic arterial display.

The alternative noninvasive imaging techniques to MDCTA are MRA and duplex US, both of which are widely used clinically. MRA has been shown to have diagnostic accuracy similar to that of MDCTA^{28,29}; however, direct comparison studies in the literature are lacking, likely attributable to the fact that each modality is usually compared with DSA for the purpose of a reference standard. Although MRA lacks the need for ionizing radiation, its major advantage over MDCTA, MRA is limited because of cost, scanner availability, local expertise, and the need for a gadolinium contrast agent, which has recently been shown to cause nephrogenic systemic fibrosis in patients with impaired renal function. Duplex US, although readily available, cheap, and safe, has a reduced

sensitivity compared with both MRA and MDCTA¹⁴ and a lower physician confidence.³⁰

LIMITATIONS OF MDCTA

CT contributes to 75% of the total collective dose from ionizing radiation to the public from medical imaging.³¹ With the increasingly widespread use of CT and individual patients having multiple scans over their lifetime, low-dose techniques are increasingly desired. The goal is to keep doses “as low as reasonably achievable” (ALARA). This represents a practice mandate adhering to the principle of keeping radiation doses to patients and personnel as low as possible. The average effective dose for peripheral arterial CTA was reported at 12.2 mGy by Catalano and colleagues,³² and a CT dose index of 12.97 mGy, with an effective dose index of 9.3 mSv, was reported by Rubin and colleagues.³³ Interestingly, the effective dose index for MDCTA of the peripheral arteries was 3.9 times lower than that for DSA, 9.3 mSv versus 36.2 mSv, respectively.³³ Of note, for comparison, a chest radiograph has an effective dose of 0.1 mSv. Low-dose techniques, involving image acquisition at a reduced milliamperage, that is, 50 mA, have been reported to be feasible and accurate when compared with DSA.³⁴ MDCTA also necessitates the intravenous administration of contrast medium, which is a potentially nephrotoxic agent; thus, care needs to be employed in administering contrast to patients with renal impairment. There is a lack of dynamic information with MDCTA in comparison with time-resolved MRA or DSA; this can even render the scan nondiagnostic if there are marked differential flow rates in the runoff arteries below the knee. An adaptive method of contrast administration described previously may prove to alleviate this issue.³⁵ Similar to most imaging techniques, patient motion will degrade MDCTA image quality and result in blurred images. A strategy to reduce this problem is to wrap a towel around the patient's lower limbs and fix them together with adhesive tape to reduce any inadvertent limb motion.³³ Image display and data storage are also limitations as vast amounts of data are acquired with each MDCTA examination. Remote access to large data sets is becoming more available with the use of “thin clients” and central servers for image processing.

ABDOMINAL AORTIC CTA

AAAs occur in up to 4% of the population above 50 years and 9% above 65 years of age. MDCTA can be used to diagnose and follow up stable aneurysms, as a tool to assist preoperative decision technique for aneurysmal repair (endovascular, open or hybrid techniques) and in the acute setting to confirm aneurysmal contained rupture. In the preoperative setting, CTA provides information on aneurysmal sac size, location, and extent; the relation of aneurysm to adjacent arterial origins; accessory arteries; and stenosis or occlusion of adjacent arteries; neck length, shape and angulation; size, tortuosity, and extent of calcification of noninvolved iliac arteries are all important characteristics that can be gleaned accurately from a CTA³⁶ [see Figure 9, a and b]. Orthogonal measurements of the aneurysm using a centerline provide accurate measurements for preprocedure planning [see Figure 9c].

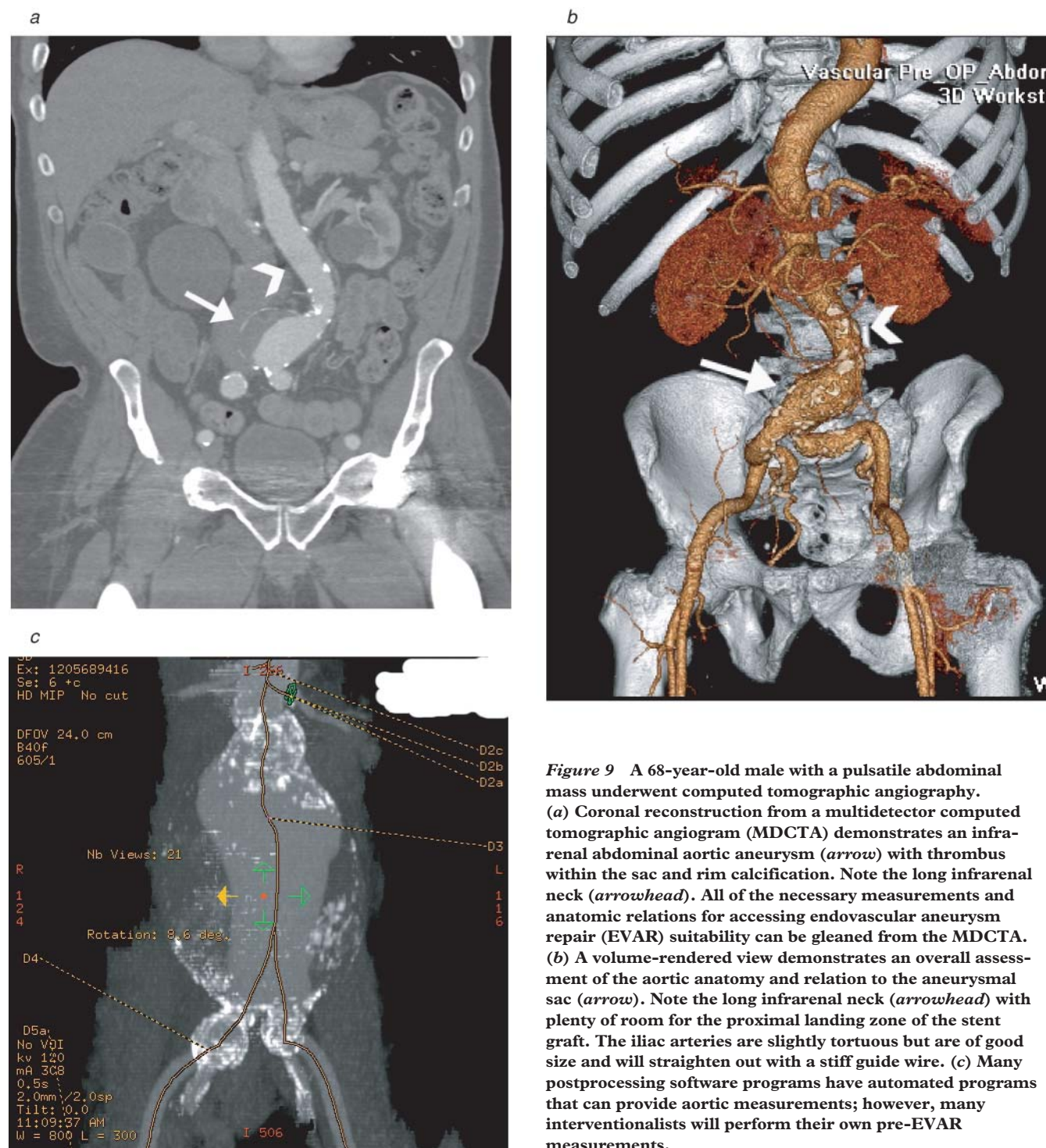


Figure 9 A 68-year-old male with a pulsatile abdominal mass underwent computed tomographic angiography. (a) Coronal reconstruction from a multidetector computed tomographic angiogram (MDCTA) demonstrates an infrarenal abdominal aortic aneurysm (arrow) with thrombus within the sac and rim calcification. Note the long infrarenal neck (arrowhead). All of the necessary measurements and anatomic relations for accessing endovascular aneurysm repair (EVAR) suitability can be gleaned from the MDCTA. (b) A volume-rendered view demonstrates an overall assessment of the aortic anatomy and relation to the aneurysmal sac (arrow). Note the long infrarenal neck (arrowhead) with plenty of room for the proximal landing zone of the stent graft. The iliac arteries are slightly tortuous but are of good size and will straighten out with a stiff guide wire. (c) Many postprocessing software programs have automated programs that can provide aortic measurements; however, many interventionalists will perform their own pre-EVAR measurements.

In the acute setting in a cardiovascularly stable patient, MDCTA is the imaging modality of choice for evaluation of suspected aneurysmal rupture because of its widespread availability, speed of acquisition, temporal and spatial resolution, and excellent sensitivity and specificity.³⁷ Imaging features of an AAA rupture include initial unenhanced CT demonstrating an aneurysm with adjacent high-attenuation periaortic hemorrhage extending posterolaterally into the perirenal and

pararenal spaces of the retroperitoneum [see Figure 10]. CTA will demonstrate the aneurysm with active contrast extravasation extending outside the aneurysmal sac consistent with active arterial bleeding. A draped aorta sign occurring when the posterior wall of the aorta is indistinct from adjacent structures or closely following the contour of adjacent vertebral bodies, may be seen in a contained rupture of the posterior aortic aneurysmal wall.³⁸ Impending aneurysmal

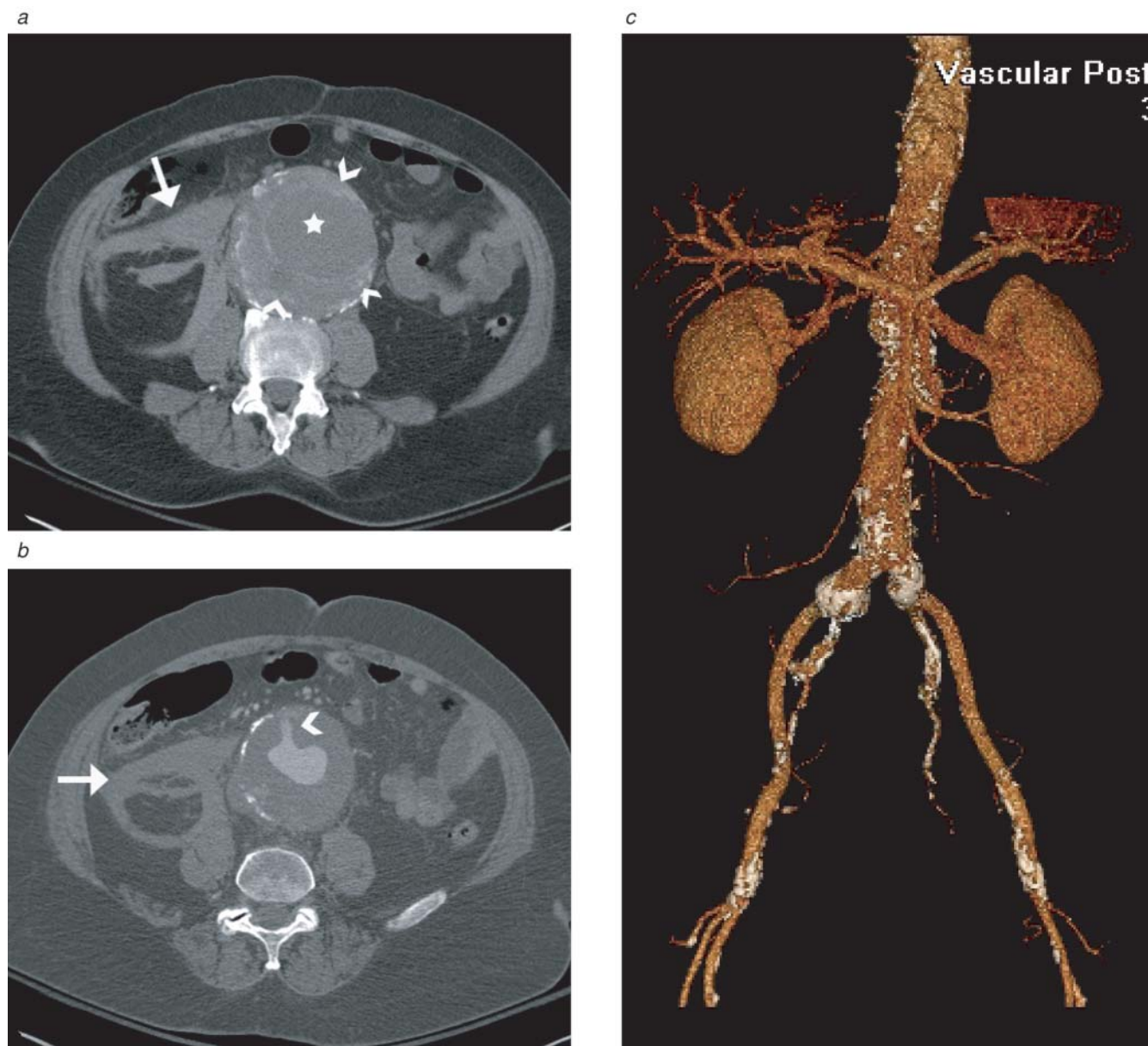


Figure 10 An 81-year-old male presented to the emergency department with acute onset of severe back pain and an episode of collapse. (a) An axial noncontrast computed tomographic scan demonstrates a large infrarenal abdominal aortic aneurysm (star) with evidence of retroperitoneal hemorrhage (arrow). Note the high-attenuation material (arrowheads) within the thrombus of the aneurysmal sac consistent with acute hemorrhage into the thrombus-filled sac. (b) Following administration of intravenous contrast, there is evidence of jets of contrast into the thrombus within the aneurysmal sac (arrowhead) and high attenuation within the retroperitoneal hemorrhage (arrow). These findings are consistent with rupture of the infrarenal aneurysm. (c) This was successfully treated by open repair, as shown by this volume-rendered multidetector computed tomographic angiogram postrepair.

rupture in both thoracic and abdominal aneurysms may be seen as a crescent of high-attenuation contrast material within the unenhanced mural thrombus.³⁹ An aortoduodenal fistula, which may be associated with recurrent and potentially catastrophic bleeding, can be detected by loss of the normal fat plane between the aorta and duodenum and the presence of air in the aorta.⁴⁰ Currently, in the setting of a ruptured AAA, EVAR is a viable treatment option provided that favorable

aortic anatomy, adequate operator skills, endovascular facilities, and protocols are in place.⁴¹ Measurements required for calculation of the optimal dimensions of aortic stent grafts are usually obtained with MDCTA encompassing 3D reconstruction. However, in the acute rupture setting, with an unstable patient, it may sometimes be necessary to bypass MDCTA, and then on-table angiography is used to assess EVAR suitability and for stent graft size selection.⁴¹ MDCTA

can eloquently diagnose many other aortic pathologies, including dissection; atherosclerosis causing stenosis, occlusion, or ulceration; and pseudoaneurysms and mycotic aneurysms.

Patients treated with EVAR undergo frequent imaging by CTA to monitor for endoleak, stent migration or fracture, and stability of aneurysm size.⁴² An increase in the diameter of an aneurysmal sac is associated with endoleak. Evaluation of an endoleak requires an unenhanced CT scan, as well as imaging during arterial and venous phases of contrast enhancement. Unenhanced images are used to detect artifact from calcification or embolization material that may mimic endoleak on the enhanced images and to evaluate stent graft material for any infolding or migration. Arterial phase imaging enables assessment of stent graft patency and endoleak identification. Delayed venous phase images have been shown to enhance the detection rate of endoleaks as some may not be appreciated in the arterial phase.

The CT scanning volume for imaging the abdominal aorta usually starts at the diaphragm and extends caudally to the symphysis pubis. Bolus tracking triggering can reliably obtain the optimal arterial phase by placing a region of interest (ROI) on the aorta at the level of the celiac artery. An injection volume of 100 mL of high-concentration contrast agent (350 mg iodine/mL) at a flow rate of 5 mL/s is typically used. Images are acquired in the cranial to caudal direction with a slice thickness of 2.0 mm, a slice interval of 2.0 mm, and 0.6 mm of collimation.

PERIPHERAL ARTERIAL CTA

The most common indication for peripheral CTA in many centers is for further evaluation of PAD. The diagnosis has already been established clinically and with ABIs, but the extent and severity of arterial involvement are of interest to the vascular surgeon or interventional radiologist. The TransAtlantic Inter-Society Consensus (TASC) guidelines recommend appropriate endovascular or surgical treatment of PAD based on lesion location, number, severity, length, and morphology.¹¹ Peripheral CTA is well positioned to evaluate all of these criteria to enable appropriate treatment planning. MRA is also a useful modality for diagnosing the extent and severity of PAD; however, cost, scanner availability, patient contraindications, local expertise, and the risk of nephrogenic systemic fibrosis can limit this tool.⁴³ CTA can also be employed to perform bypass or vein graft surveillance⁴⁴ or follow-up of lesions treated with percutaneous transluminal angioplasty.⁴⁵ Availability and rapid access place CTA at the forefront for fast and complete arterial assessment in lower limb injury, in both trauma settings and iatrogenic events.^{46,47} Lower limb aneurysmal and pseudoaneurysmal disease can be eloquently evaluated with CTA as sac size, relation to parent vessel, thrombus load, and distal runoff can all be demonstrated prior to covered stent placement or surgical repair.⁴⁵ Rarer indications encountered include vasculitis,⁴⁷ arteriovenous malformations (AVMs),⁴⁴ and popliteal entrapment syndrome.⁴⁸

Most institutions will initially perform a scout view from the diaphragm to the feet, an optional noncontrast acquisition from the celiac axis to the feet, and an arterial phase timed acquisition from the celiac axis to the feet, with the

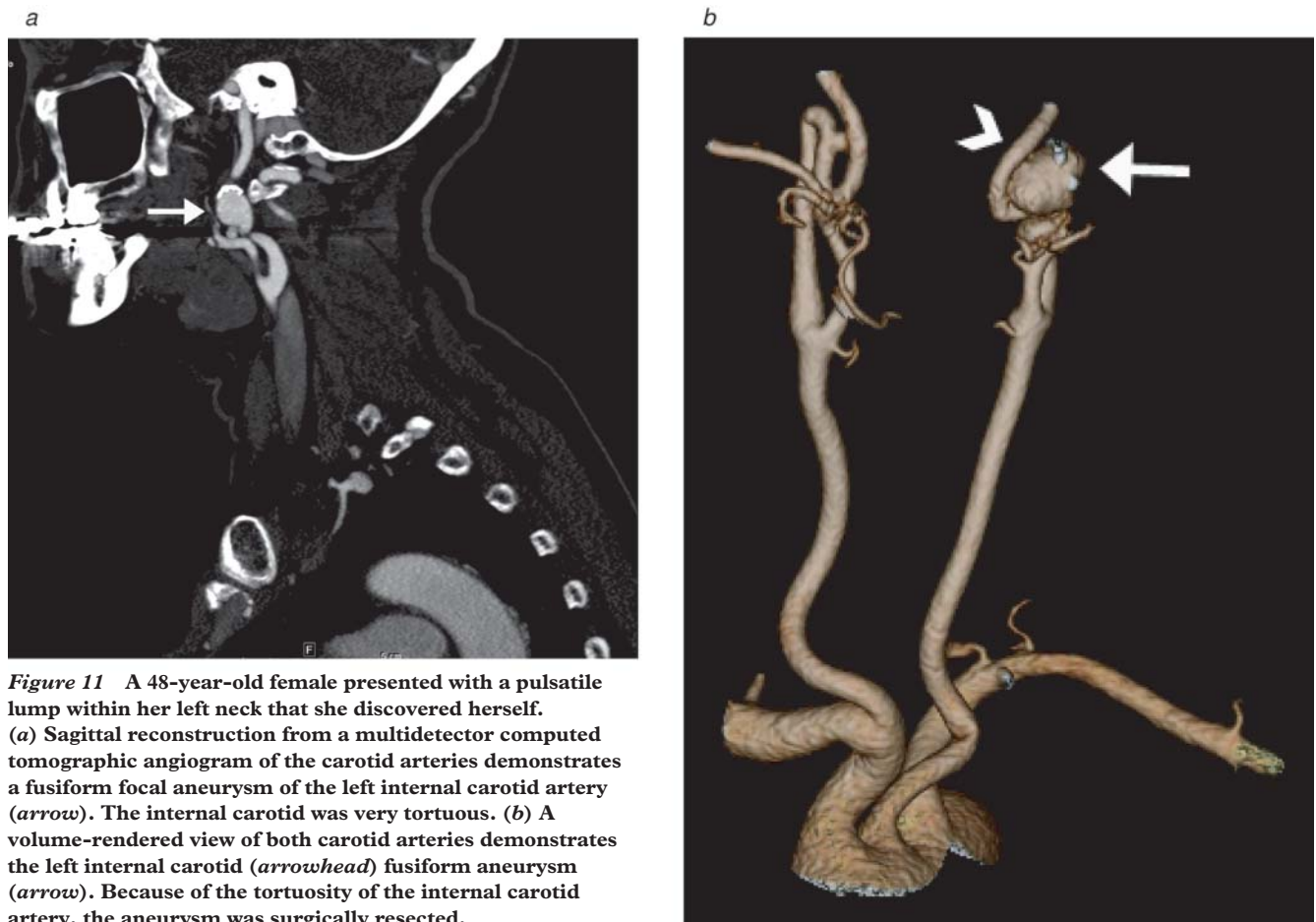
option of a second limited acquisition from the lower thighs to the feet in the event that the contrast has a slower transit time on the symptomatic side.

Bolus tracking triggering can reliably obtain the optimal arterial phase by placing a ROI on the aorta at the level of the celiac artery. An injection volume of 150 mL of high-concentration contrast agents (350 mg iodine/mL) at a flow rate of 5 mL/s is typically used. Images are acquired in the cranial to caudal direction with a slice thickness of 1.0 mm, a slice interval of 1.0 mm, and 0.6 mm of collimation.

CAROTID CTA

In the United States, stroke is the leading cause of adult disability and the third leading cause of death. About 80% of strokes are ischemic strokes. Conventional DSA remains the reference standard for the evaluation of carotid artery disease; however, DSA has significant risks. Thus, noninvasive methods are now widely used, usually in combination at present, with initial duplex US performed followed by cross-sectional imaging with CTA or MRA prior to intervention. There is an emerging role for CTA in the evaluation of carotid disease likely attributable to continued advances in CT technology, its noninvasive nature, and its lower cost than DSA. A recent meta-analysis assessed the accuracy of CTA versus DSA for assessment of symptomatic carotid artery disease.⁴⁹ Sensitivity and specificity for detection of a 70 to 99% carotid artery stenosis were 85% and 93%, respectively, rising to 97% and 99%, respectively, for 100% stenosis detection.⁴⁹ However, another meta-analysis comparing US, CTA, and MRA to DSA determined that contrast-enhanced MRA was the most accurate for assessing a 70 to 99% symptomatic carotid stenosis with sensitivity and specificity of 86% and 91%, respectively.⁵⁰ In this study, CTA performed poorly and was the least accurate noninvasive modality, with sensitivity and specificity for detection of 70 to 99% carotid artery stenosis of 68% and 77%, respectively, compared with 82% and 77%, respectively, for Doppler US.⁵⁰ These conflicting results from two meta-analyses should prompt further evaluation into the role of CTA in assessing carotid artery disease and should caution surgeons on the decision to proceed with intervention based solely on one noninvasive imaging modality of the carotid artery. Plaque composition can be evaluated by CTA, which is an important indicator of plaque stability and helps with the assessment of risk factors for thromboembolic events and in monitoring the effects of best medical therapy.

Other carotid pathologies can be eloquently diagnosed with CTA, including aneurysm disease [see *Figure 11*], dissection, vasculitis, and postoperative complications such as para-anastomotic aneurysms and infections. The scanning volume of carotid CTA is determined based on the initial anteroposterior and lateral topograms. The volume should include all the vascular structures from the aortic arch to the entire intracranial circulation to the level of the skull vault. This scan volume also serves to diagnose any preexisting cerebral infarcts. Automated bolus tracking or test bolus triggering techniques can reliably obtain the optimal arterial phase by placing an ROI on the aortic arch. An injection volume of 75 mL of high-concentration contrast agent (350 mg iodine/mL) at a flow rate of 5 mL/s is typically used. Images are acquired in the caudal to cranial direction with



a slice thickness of 1 mm, a slice interval of 0.5 mm, and 0.6 mm of collimation.

THORACIC CTA

The disease processes affecting the aortic root and thoracic aorta include aneurysmal dilatation and rupture, aortic dissection, intramural hematoma and penetrating ulcer, traumatic injury presenting early as transection or late as a pseudoaneurysm formation, inflammatory processes that can extend into the arch vessels, and congenital malformations. The diagnosis, surveillance, and monitoring with MDCTA play an important role in determining the timing and role for endovascular and surgical intervention.

Conventional DSA is regarded as the reference standard for evaluation of the thoracic arterial system. CTA of the thoracic aorta is currently the preferred method, however, for follow-up of patients with thoracic aortic aneurysms.⁵¹ In addition to evaluating luminal disease, CTA can also assess the vessel wall for plaque composition, hematoma, and dissections. The wall of the aneurysm is easily identified by intramural calcifications allowing for accurate size measurement. CT also allows for evaluation of the extent of mural thrombus and aneurysm wall for a contained leak, as well as any associated dissection, distal embolization, or pleural

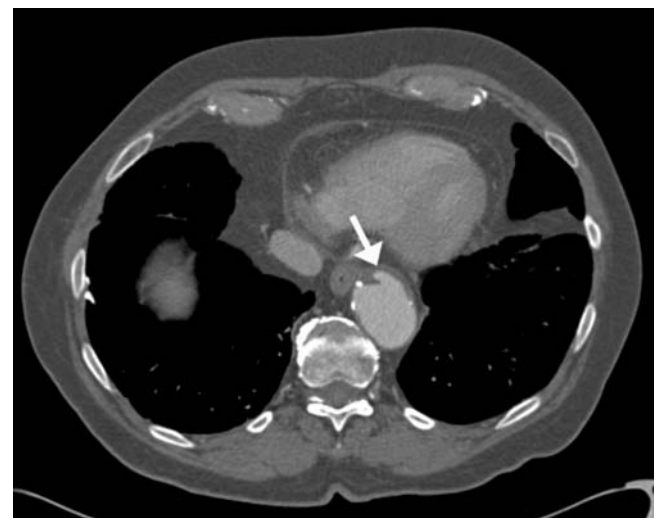


Figure 12 A 74-year-old male undergoing computed tomography for abdominal pain. Axial multidetector computed tomographic angiography through the lower descending thoracic aorta demonstrates a small outpouching from the thoracic aorta into the aortic wall consistent with an anterior small penetrating ulcer (arrow).

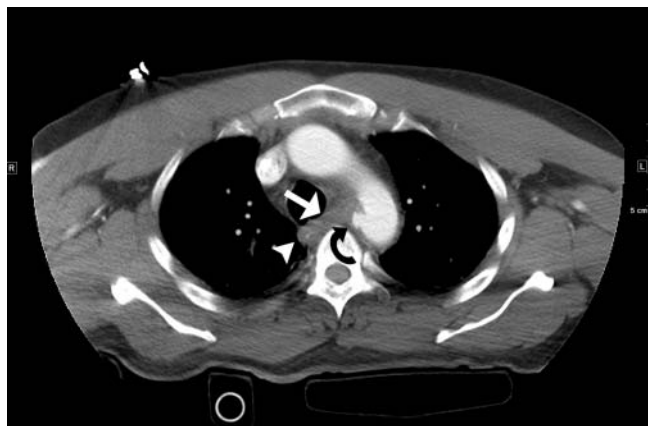


Figure 13 A 40-year-old male who presented to the emergency department following a high-velocity motor vehicle accident with crushing central chest pain. An axial multidetector computed tomographic angiogram at the level of the aortic arch demonstrates increased attenuation material (*white arrow*) within the mediastinum displacing the esophagus (*arrowhead*) to the right. On the medial aspect of the undersurface of the aortic arch, at the level of the relatively fixed aortic isthmus, there is a disruption in the smooth contour of the aortic wall (*curved black arrow*), with a small area of outpouching of contrast. The finding of mediastinal hematoma (*white arrow*), along with aortic disruption in the setting of a motor vehicle accident, is consistent with acute aortic injury known as aortic transection. This requires emergent repair, with many centers now favoring endovascular and/or hybrid methods. This patient underwent a left subclavian arterial transposition. The transposition was performed before covering the transection with a stent graft to preserve the dominant left vertebral artery.

effusion. Three-dimensional images demonstrate the normal anatomic relationship of the branch vessels, the mediastinal structures, and the extent of the disease process.

MDCTA has become the imaging modality of choice for the evaluation of thoracic aortic dissection at most medical centers. Magnetic resonance imaging (MRI) and transesophageal echocardiography (TEE) are widely used with sensitivities and specificities similar to those of MDCTA; however, ease of availability, lower cost, ability to evaluate arch vessels and the abdominal aorta, increased spatial resolution, non-operator dependence, and no limited acoustic windows mean that MDCTA is preferred by many. The pathognomonic imaging finding for thoracic aortic dissection on CT is two adjacent contrast-filled lumens, which represent a patent true lumen and the false lumen. The two lumens are separated by a thin band known as the intimal flap. The intimal flap can have unusual characteristics, which are detected by CT, including partial thrombosis, a circular or spiral orientation down the aorta, or multiple fenestrations. CT is also effective for visualizing more subtle signs of dissection such as internal displacement of intimal calcium, mural thickening, ischemia of end-organs supplied by aortic branches, or a left pleural effusion. CT also demonstrates the start point, course, and extent of the intimal flap in relation to the ascending aorta, aortic arch, abdominal aorta, and branch vessel ostia, which is vital for planning surgical or endovascular repair. The major limitations of CT for thoracic aortic dissection are technical factors that can cause a false positive reading. These include improper timing of contrast bolus injection, aortic wall or cardiac motion, streak artifacts, and periaortic structures. Motion or pulsation artifact in the region of the aortic root can be misinterpreted as the flap of an aortic dissection. Aortic motion from pulsation artifact has now been virtually

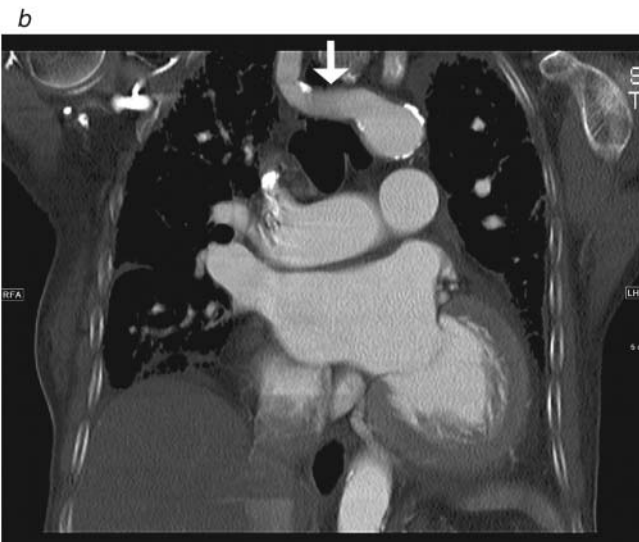
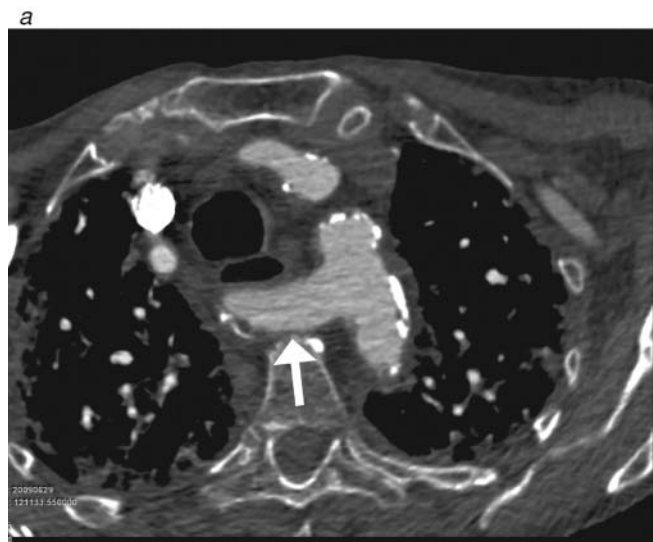


Figure 14 A 63-year-old female presented with dysphagia for solids with no significant weight loss. (a) An axial multidetector computed tomographic angiogram demonstrates an artery arising from the medial aspect of the aortic arch and coursing posterior to the esophagus consistent with an aberrant right subclavian artery (*arrow*). (b) Coronal maximum-intensity projection demonstrates the aberrant right subclavian artery (*arrow*) passing posterior to the esophagus, causing posterior indentation on the esophagus. The dysphagia associated with this anatomic variant is classically known as dysphagia lusoria. This is the most common embryologic abnormality of the aortic arch, occurring in up to 1.8% of the population.

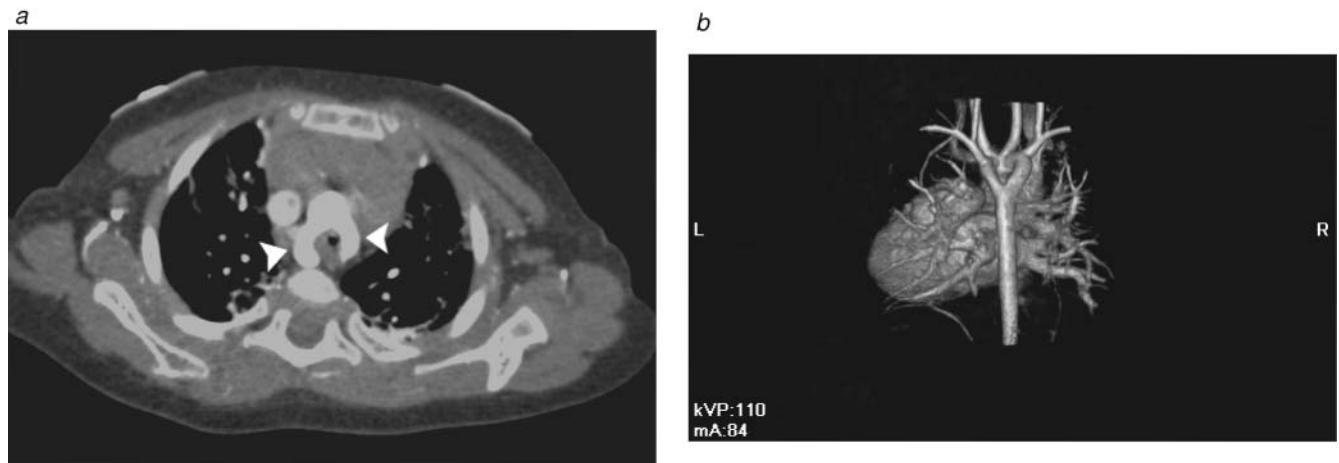


Figure 15 A 4-year-old male child with episodes of dyspnea and intermittent cyanosis and a widened mediastinum on a chest radiograph was referred for computed tomographic angiography. (a) Axial view from a multidetector computed tomographic angiogram shows a crescentic vascular ring (arrowheads) surrounding the trachea and esophagus. (b) A posterior coronal volume-rendered view demonstrates a complete vascular ring consistent with a double aortic arch with the right arch of larger caliber. The carotid arteries arise anteriorly from the common arch, and a subclavian artery arises from each of the right and left arches. This patient went on to have surgical correction because of the respiratory symptoms.

eliminated with the advent of electrocardiographic (ECG) gating and faster acquisition times, allowing for near-complete suppression of cardiac and thoracic aortic motion. ECG gating consists of image acquisition only in the diastolic phase

of the cardiac cycle when the heart, and consequently the ascending thoracic aorta, is in its most quiescent phase.

Intramural hematoma, which can also cause an acute aortic syndrome similar to dissection, may be overlooked if an initial



Figure 16 A 78-year-old male presented with acute-onset abdominal pain and one episode of diarrhea. (a) Coronal reconstruction of a noncontrast abdominal computed tomographic (CT) scan demonstrates thickened loops of small bowel (arrow). (b) An axial postcontrast T₁ fat saturation magnetic resonance image demonstrates a filling defect within the superior mesenteric vein (SMV) with expansion of the SMV (arrow) consistent with SMV thrombus, which correlates with the noncontrast CT findings.



Figure 17 A 36-year-old female presented with intermittent midline abdominal pain, weight loss, postprandial vomiting, and food avoidance. Despite her young age, symptoms were suggestive of mesenteric ischemia; thus, multidetector computed tomographic angiography (MDCTA) was performed. An axial image from the MDCTA demonstrates dilatation of the stomach (*star*) and the first and second parts of the duodenum (*x*), with a compressed third part of the duodenum (*arrowhead*) crossing the midline between the aorta and the superior mesenteric artery (SMA) (*arrow*). Note the presence of little intraperitoneal fat. The entity where the duodenum is compressed between the SMA and the aorta is known as SMA syndrome.

noncontrast scan of the thoracic aorta is not performed. This hematoma is usually attributable to bleeding of the vasa vasorum within the aortic media and results in chest pain radiating to the back, with a clinical history almost identical to dissection. The imaging features of intramural hematoma are a crescentic area of high attenuation within the aortic wall extending longitudinally and nonspirally on the noncontrast scan, which simply looks like a thickened aortic wall with a preserved lumen on the CTA. The imaging features, however, may be identical in the setting of a dissection with a small thrombosed false lumen. Also, the noncontrast images for intramural hematoma may be identical to those of a penetrating ulcer; however, the CTA will differentiate these two conditions as a penetrating ulcer appears as a contrast-filled outpouching, diverticulum-like structure penetrating into the aortic wall [see Figure 12]. Many authors regard intramural hematoma, penetrating ulcer, and aortic dissection as a spectrum of the same disease process.

CTA is now regarded as the first-line modality for evaluating traumatic disruption or transection of the thoracic aorta, replacing DSA. CTA is the cornerstone diagnostic tool because of its accessibility, noninvasiveness, rapid acquisition, and ability to evaluate the entire thorax and other body regions in a single examination.⁵² MDCTA has been shown to be nearly 100% sensitive, with, accordingly, high negative predictive value for the detection of acute thoracic injury.⁵³ CTAs can be used to plan appropriate intervention for acute thoracic transection, with many centers now advocating endovascular repair as first line treatment[see Figure 13].

Some congenital variant anatomy can be eloquently demonstrated with thoracic MDCTA, often incidentally diagnosed [see Figure 14 and Figure 15].

The scanning volume of CTA is determined by the indication. It is typical to start at the lung apices, which provides adequate coverage of the supra-aortic vessels. The end position is typically at the level of the midkidney; however, if a dissection is suspected, the coverage can be extended to the groin. Full assessment of aortic dissection by CT requires unenhanced CT followed by arterial phase contrast-enhanced CT. The unenhanced CT is useful for detection of dense intramural hematoma that may be mistaken for chronic thrombus on the enhanced images. ECG gating is usually reserved for the evaluation of aortic dissections, along with aortic root and ascending thoracic aortic aneurysmal disease,

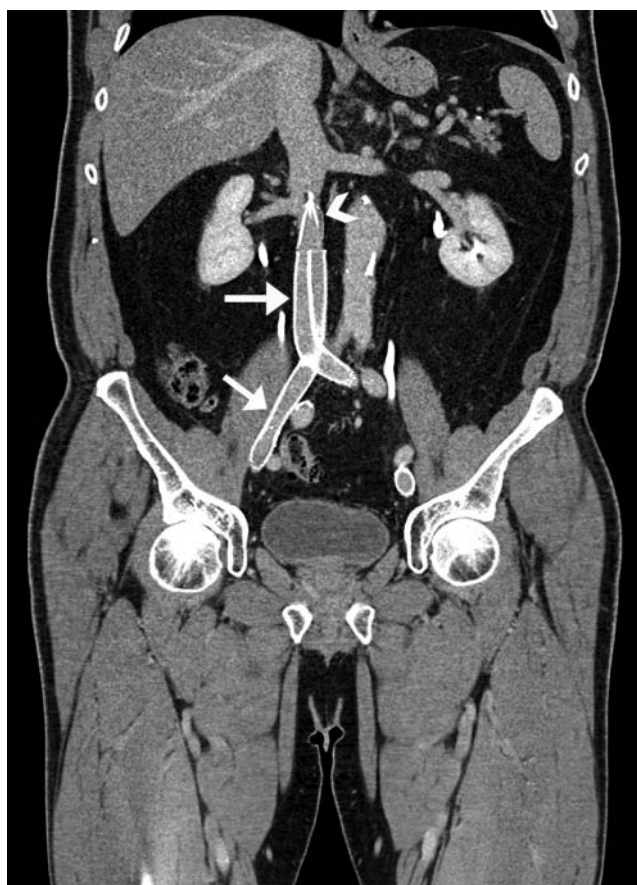


Figure 18 A 45-year-old male presented with bilateral lower limb swelling and tenderness. Duplex ultrasonography diagnosed bilateral deep vein thrombosis extending above the inguinal ligaments. Because of the severity of limb symptoms, catheter-directed lysis was initiated, with a safety retrievable caval filter also inserted. On check venography, cavoileal stenosis was unmasked. A coronal computed tomographic scan acquired during the portovenous phase following iodinated contrast administration demonstrates the postprocedure result. There are bilateral kissing cavoileal stents in situ (*arrows*), along with the caval filter (*arrowhead*). Note that the thrombus has completely cleared following lysis.

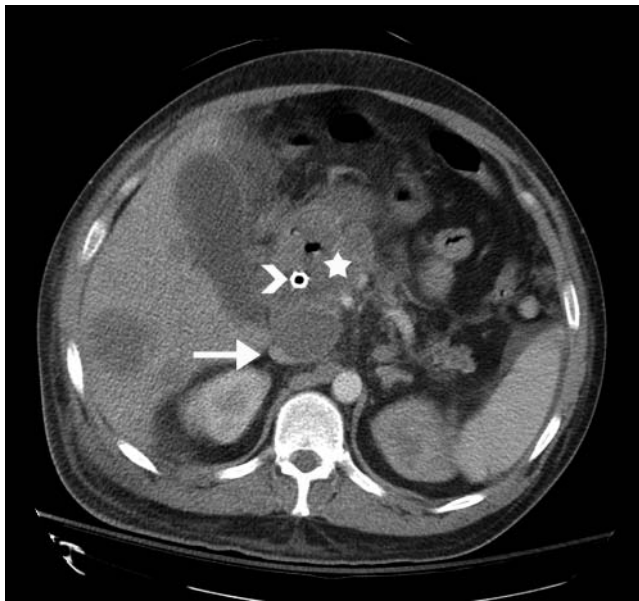


Figure 19 A 36-year-old male with metastatic pancreatic cancer undergoing palliative care presented with gross bilateral lower limb painful edema. Duplex ultrasonography showed no evidence of deep vein thrombosis. An axial multidetector computed tomographic scan acquired in the portovenous phase demonstrates a metal biliary stent (arrowhead) in situ passing through the large pancreatic malignancy (star). There is marked anterior extrinsic compression of the inferior vena cava by the pancreatic tumor, with only a small residual caval lumen remaining (arrow).

as gating reduces cardiac and aortic motion and therefore reduces pulsation artifact.

Automated bolus tracking or test bolus triggering techniques can reliably obtain the optimal arterial phase by placing an ROI on the ascending thoracic aorta. An injection volume of 100 mL of high-concentration contrast agent (350 mg iodine/mL) at a flow rate of 5 mL/s is typically used. Images are acquired in the cranial to caudal direction with a slice thickness of 1.5 mm, a slice interval of 1.0 mm, and 0.6 mm of collimation.

CTA OF THE MESENTERIC ARTERIES

CTA allows excellent visualization of the mesenteric vasculature.⁵⁴ Aneurysms, thrombosis, stenosis or occlusion, dissection, and inflammatory processes affecting the mesenteric vasculature have been evaluated by MDCTA.

Mesenteric ischemia comprises three categories: acute arterial occlusion, nonocclusive ischemia (mesenteric angina), and venous thrombosis. Acute mesenteric ischemia is a life-threatening event that may be caused by a variety of etiologies. These include embolic phenomenon, severe hypoperfusion, thrombosis of an underlying arterial stenosis, dissection, hypercoagulable states (in situ thrombosis formation), and vasculitis. MDCTA with optimally timed contrast bolus can often readily delineate the site of arterial occlusion manifested by an abrupt cutoff of arterial contrast enhancement with complete occlusion or thrombus identified as a filling defect with contrast surrounding it in a nonocclusive thrombus. A combination of imaging planes, including the axial source images and the sagittal and coronal reformatted images, together with some curved multiplanar reformatted images, can increase the diagnostic yield. Although DSA remains the gold standard, it is usually reserved for cases

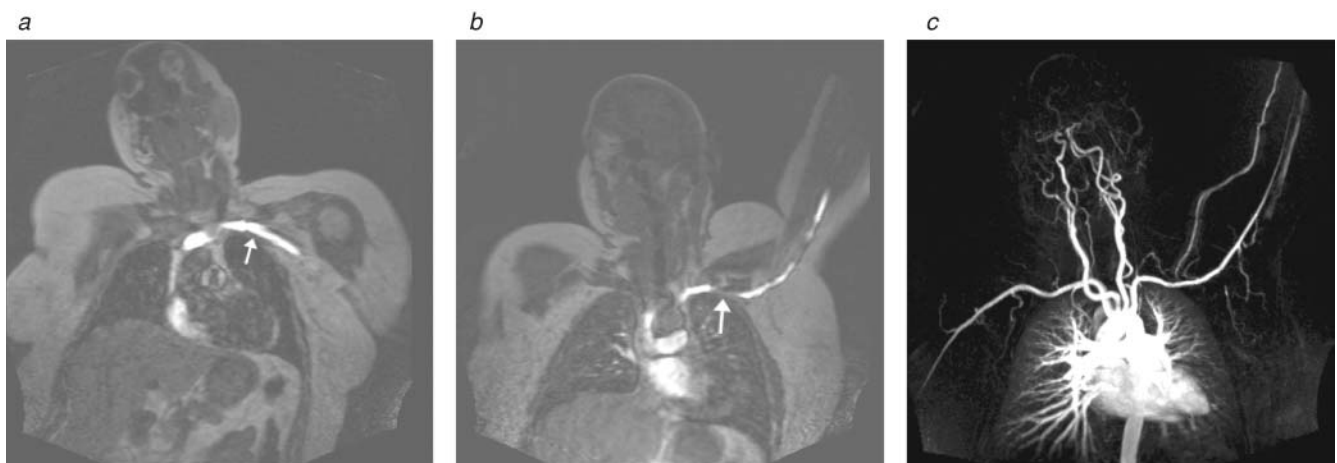


Figure 20 A 29-year-old female swimmer presented with left arm pain and intermittent swelling. (a) Coronal image from a direct magnetic resonance venogram (MRV) with injection of dilute gadolinium contrast via a left peripheral intravenous canula with the left arm adducted. There is no evidence of subclavian venous compromise at the level of the thoracic outlet (arrow). (b) Coronal image from a direct MRV with the left arm abducted demonstrates subclavian venous compromise with luminal narrowing at the level of the thoracic outlet (arrow). (c) Coronal maximum-intensity projection from a high-resolution magnetic resonance angiogram demonstrates no arterial compromise with the left arm abducted. Incidental note is made of a four-vessel aortic arch, with the right subclavian and the right common carotid arteries arising separately from the aortic arch.

requiring concurrent endovascular intervention, which is less likely in the acute setting as open surgery with embolectomy and bowel inspection is more desirable to restore mesenteric perfusion as rapidly as possible. CT accurately visualizes the portal, splenic, and superior mesenteric veins and can be used to diagnose mesenteric venous thrombosis.⁵⁵ Diagnosis of mesenteric venous thrombosis requires delayed images in the venous phase to avoid unopacified mesenteric veins, which can mimic thrombosis. Unenhanced images are also beneficial because they may show a hyperdense thrombus.⁵⁶ A pathognomonic finding of mesenteric venous thrombosis on CT includes an enlarged mesenteric vein with a low-density

center surrounded by an enhancing wall along with marked edema of the mesentery with bowel wall thickening [see *Figure 16*]. When evaluating for mesenteric vascular pathology, close attention to the morphology of the bowel is important as thickened bowel loops with thumbprinting, the presence of a sentinel loop or an ileus, secondary bowel wall hemorrhage or edema, pneumatosis (air within the bowel wall—a late sign that usually indicates dead infarcted bowel), and altered enhancement (either hyper- or hypoenhancement of the affected bowel) are signs of ischemia or infarction. Portal venous air is a late and often premonitory sign that can occur with a long segment of infarcted bowel.

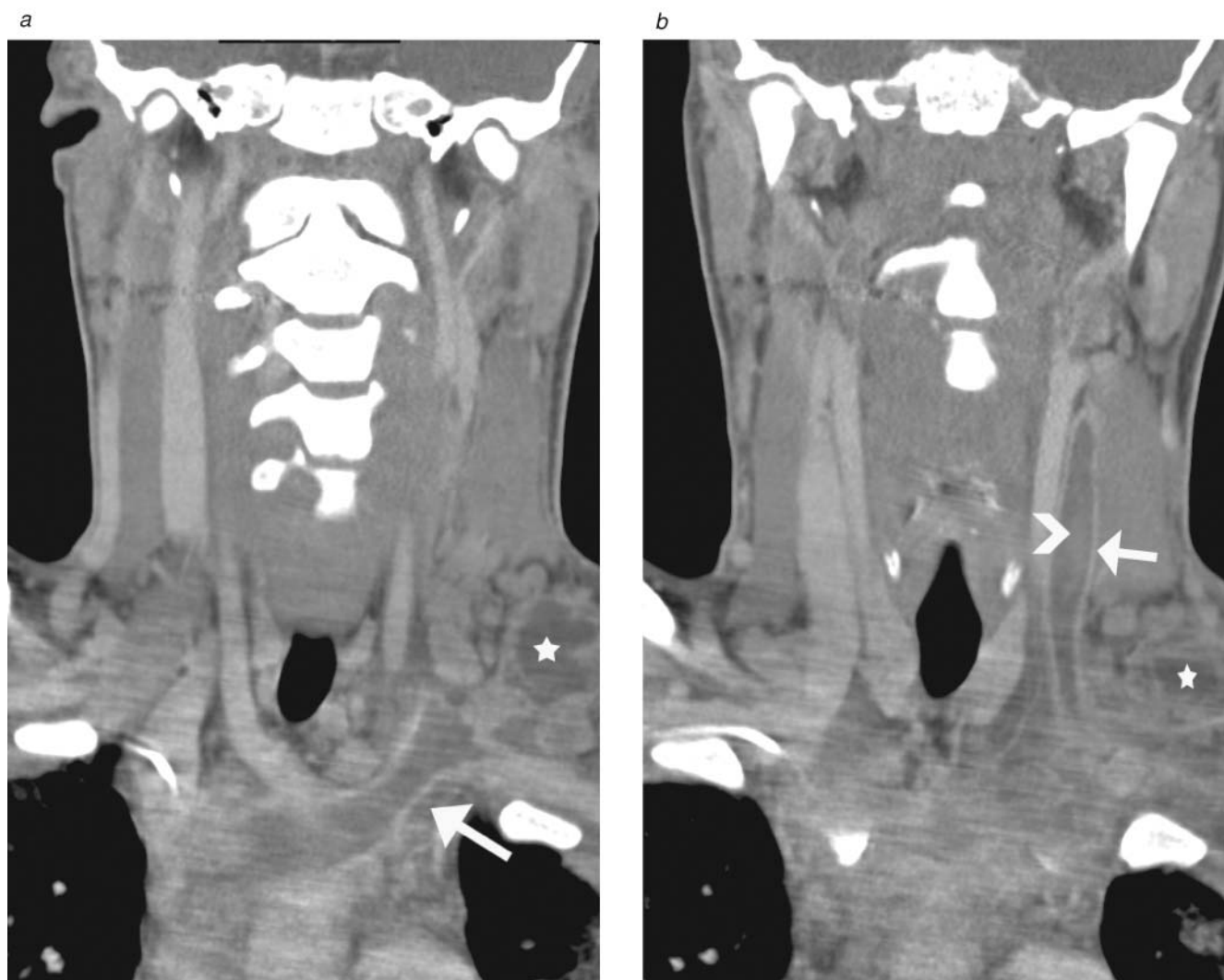


Figure 21 An 18-year-old male presented with a painful mass in the left side of his neck and low-grade fevers. (a) Coronal reconstruction of a multidetector computed tomographic venogram was obtained and demonstrates a focal mass in the left supraclavicular region with a low-attenuation center (*star*) and an enhancing rim. There is extensive low-attenuation material within an expanded left brachiocephalic vein (*arrow*). (b) More posterior coronal reconstruction demonstrates further low-attenuation material within an expanded left internal jugular vein (LIJV) (*arrow*). Note that the material is also enhancing within the vein lumen (*arrowhead*). The focal mass in the left supraclavicular region with a low-attenuation center (*star*) and an enhancing rim is also seen. These findings are consistent with a septic thrombus within the LIJV extending into the left brachiocephalic vein as a result of the left supraclavicular abscess. This constellation of findings is known as Lemierre syndrome. The neck abscess was drained percutaneously under ultrasound guidance, and the patient was treated with intravenous antibiotics, with resolution of fevers.

Chronic mesenteric ischemia classically manifests clinically with the triad of postprandial abdominal pain, weight loss, and food avoidance. Atherosclerosis, causing severe stenosis or occlusion in at least two mesenteric arteries, is the usual etiology. CTA can accurately demonstrate the stenoses or occlusions, degree of calcification, and number of mesenteric vessels involved and serves as a pretreatment roadmap prior to stenting or bypass. The advantage of CTA over MRA is in the follow-up of stented patients as a result of the superior spatial resolution and lack of stent-related artifacts with CTA to determine stent patency and detect any in-stent restenosis. Other etiologies of chronic mesenteric angina can also be diagnosed with CTA, including fibromuscular dysplasia, vasculitis, radiation arteritis, and, albeit rarely, SMA syndrome [see Figure 17].

Celiac axis compression by the median arcuate ligament is known as median arcuate ligament syndrome and can lead to mesenteric angina; however, it is often asymptomatic. Additionally, this entity has been reported to predispose patients who have undergone orthotopic liver transplantation to hepatic artery thrombosis. If median arcuate ligament syndrome is suspected, imaging should be obtained during full inspiration to avoid artifactual stenosis.⁵⁷ Celiac and mesenteric stenoses are best visualized by sagittal thin-slab MIP or volume-rendered images. However, a thin-slab coronal MIP image also provides an excellent overview of the mesenteric vascular structures and the bowel loops. Treatment is surgical, consisting of release of the ligament, with no real

role for an endovascular option as a result of stent compression or even fracture. Although surgical treatment can lead to clinical improvement in symptomatic patients, the importance of celiac artery compression in asymptomatic patients is not established.

Most institutions will initially perform an arterial phase scan from the lower third of the chest above the diaphragm to the pubic symphysis; an optional initial noncontrast acquisition may be useful to see a high-attenuation thrombus, and venous phase timed acquisition covering the same scan range should also be obtained. Bolus tracking triggering can reliably obtain the optimal arterial phase by placing an ROI on the descending thoracic aorta above the diaphragm. An injection volume of 150 mL of high-concentration contrast agent (350 mg iodine/mL) at a flow rate of 5 mL/s is typically used. Images are acquired in the cranial to caudal direction with a slice thickness of 1.0 mm, a slice interval of 1.0 mm, and 0.6 mm of collimation.

COMPUTED TOMOGRAPHIC VENOGRAPHY

Duplex US is regarded as the first-line tool for diagnosis of lower and upper limb deep vein thrombosis (DVT); however, in certain clinical scenarios, particularly when interrogating the pelvic veins, computed tomographic venography (CTV) may be necessary to aid diagnosis for suprainguinal DVT. Venous phase contrast-enhanced CT can also be valuable in cases of May-Thurner syndrome with extensive thrombus prior to intervention with pharmacologic or mechanical

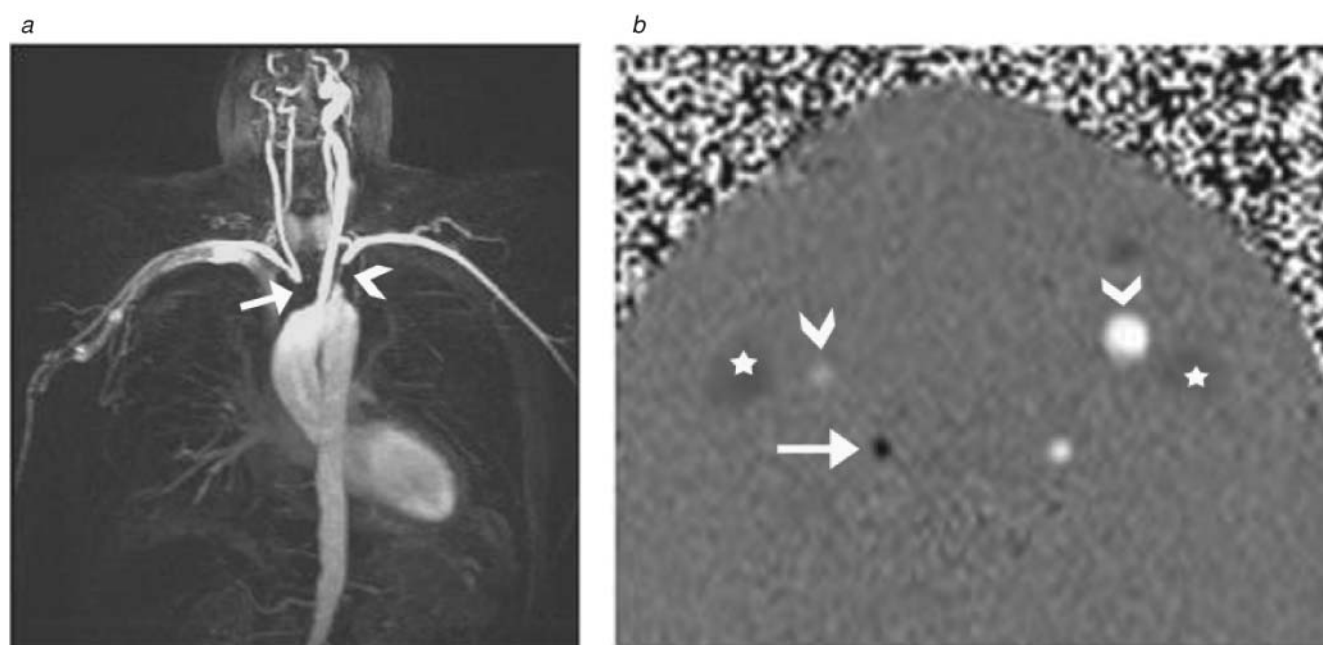


Figure 22 A 63-year-old female presents with lightheadedness and dizziness, particularly when grocery shopping. (a) Coronal maximum-intensity projection from a high-resolution contrast-enhanced thoracic aortic magnetic resonance angiogram demonstrates an occlusion of the right innominate artery (arrow) and a focal tight stenosis of the left subclavian artery (arrowhead). (b) Axial phase contrast magnetic resonance image obtained for flow directional information. Note that the antegrade flow is white in color and retrograde flow is black in color. There is forward flow (white) within both carotid arteries (arrowheads); note the smaller caliber of the right carotid artery compared with the left. There is reverse or retrograde flow (black) within the right vertebral artery (arrow) consistent with a right subclavian artery steal phenomenon. Note the normal retrograde flow within both internal jugular veins (stars).

thrombolysis and venoplasty and stenting [see *Figure 18*]. CTV can eloquently demonstrate the classical May-Thurner finding of left-sided common iliac vein compression by the overlying right common iliac artery, as well as the extent of thrombus and degree of venous stenosis.⁵⁸

Occlusion of the inferior vena cava (IVC) can be caused by both intrinsic and extrinsic [see *Figure 19*] diseases, and CT is sensitive for both thrombosis of the IVC and adjacent tumors causing caval compression. CT also clearly demonstrates caval anatomy, particularly congenital venous abnormalities such as duplication of the cava, circumaortic and retroaortic renal veins, left-sided cava, and, albeit rarely, persistent sciatic veins. These anatomic findings are most important to be aware of prior to any intervention; that is, the presence of a circumaortic or retroaortic renal vein will affect clamp position during open AAA repair, and the presence of a double IVC will potentially require two caval filters to prevent pulmonary embolus.

However, CTV can be technically difficult to perform as the timing of the contrast bolus is not as standard as for

arterial imaging, where an ROI is used to obtain the optimum contrast density within the artery of interest. Often a standard imaging delay is used, for example, 120 seconds after contrast administration; however, this does not take into account individual patient factors such as cardiac output, blood pressure, and body habitus. This contrast timing problem has been largely overcome with the use of MRV, where a time-resolved sequence can be used, analogous to the concept of DSA, where multiple acquisitions can be acquired at multiple time points, enabling imaging in both optimal arterial and venous phases with a number of phases in between [see *Magnetic Resonance Venography, below*].

CTA AND CTV OF THE THORACIC OUTLET

The thoracic outlet comprises a complex anatomic region with the brachial plexus, subclavian vein, and subclavian artery situated in a small enclosed space liable to compression. The most common symptoms occur from compression of the brachial plexus, followed by compression of the subclavian vein and least of all compression of the subclavian

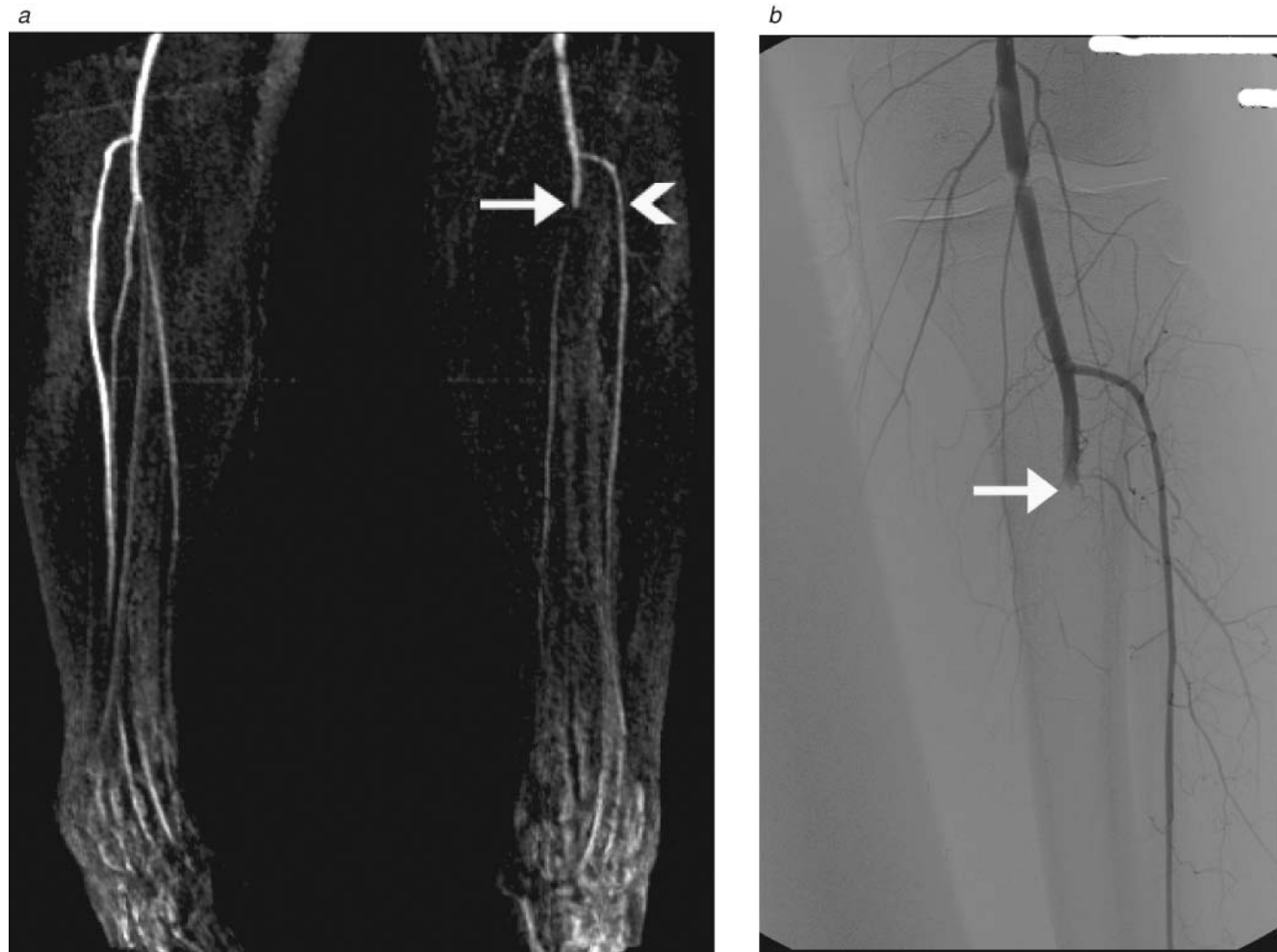


Figure 23 A 59-year-old female presented with an acutely ischemic left leg. (a) Coronal maximum-intensity projection from a time-resolved magnetic resonance angiogram demonstrates an abrupt cutoff at the left tibioperoneal trunk (arrow). Note the patency of the left anterior tibial artery (arrowhead). (b) Thrombus was confirmed at angiography (arrow), and catheter-directed lysis was commenced.

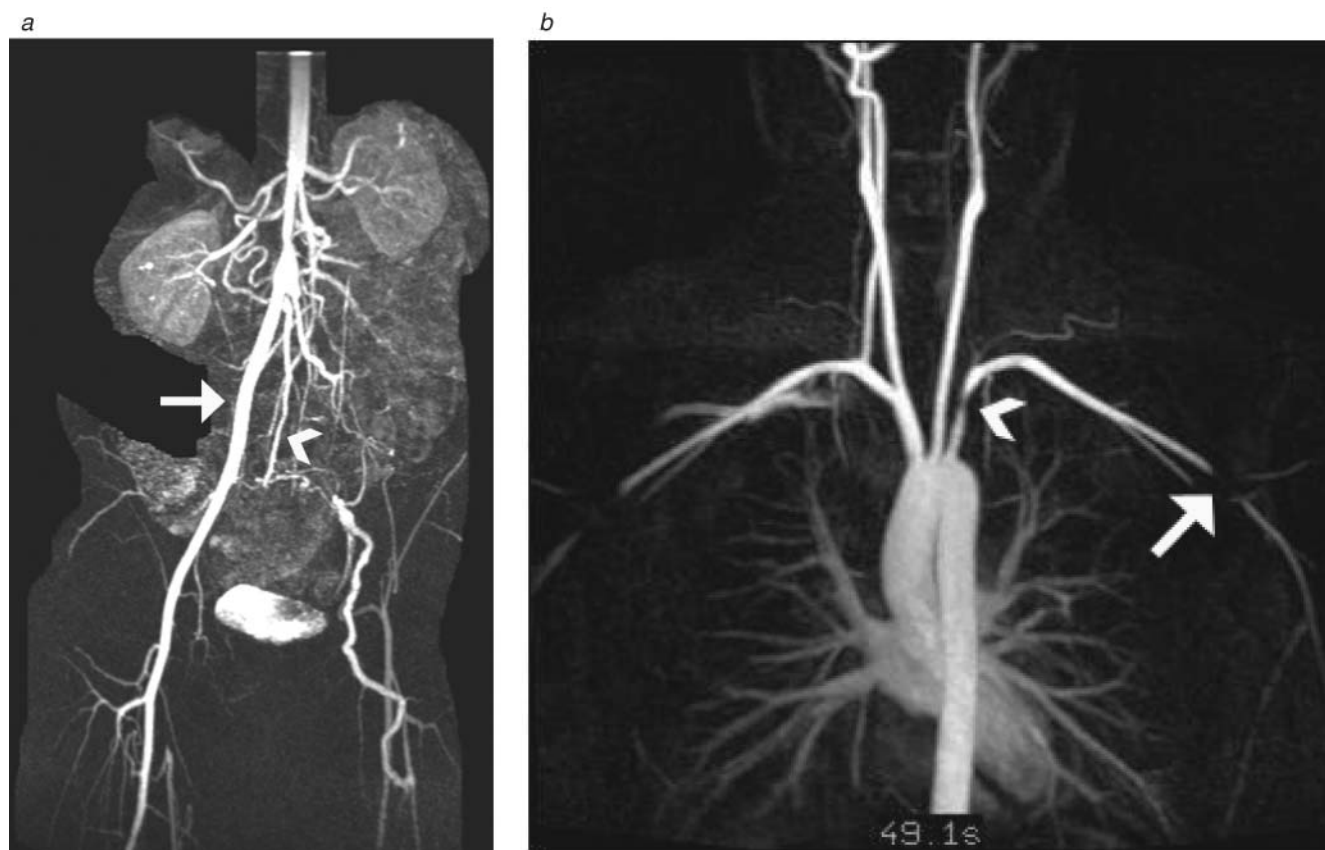


Figure 24 A 41-year-old Asian female presented with left-sided claudication and an elevated erythrocyte sedimentation rate. (a) Coronal maximum-intensity projection (MIP) from a high-resolution abdominal magnetic resonance angiogram (MRA) demonstrates a mid-aortic narrowing with evidence of previous surgery with an aortobifemoral bypass (arrow). Note that the left limb of the aortobifemoral graft is occluded. There is enlargement of the median sacral artery (arrowhead), and large collaterals are present, allowing reconstitution of the left common femoral artery. (b) The same patient also underwent thoracic MRA. Coronal MIP from this high-resolution chest MRA shows evidence of a focal high-grade stenosis of the left subclavian artery (arrowhead), along with a short segment occlusion of the left axillary artery (arrow). This combination of findings, along with the elevated inflammatory markers, was consistent with Takayasu arteritis.

artery. As a result of the complex interrelation between muscles and neurovascular structures, CTA and CTV are particularly useful in the diagnosis of thoracic outlet syndrome and in preoperative planning. Matsumura and colleagues demonstrated the utility of CT in the sagittal plane and 3D reconstruction in patients with thoracic outlet symptoms and controls.⁵⁹ Three-dimensional CT reconstruction provides accurate details of cervical and abnormal first ribs, along with the presence of muscular hypertrophy of the scalene muscle occurring in thin athletic patients. Sagittal reconstruction was performed before and after abduction external rotation of the arm. Abduction external rotation allows the clavicle to pass upward on the first rib, producing occlusion of the subclavian vein, followed by subclavian artery occlusion. Three-dimensional CT reconstruction may also demonstrate abnormalities of the clavicle. Malunion and callous formation of clavicular fractures compromises the costoclavicular space, producing neurovascular compromise of the thoracic outlet. MRA and MRV may also be advantageous in the diagnosis of thoracic outlet syndrome [see Figure 20].

CTA AND CTV OF OTHER SITES

Rare etiologies are encountered on imaging intermittently, and although every syndrome or clinical condition is beyond the scope of this chapter, one such example presented is that of Lemierre syndrome [see Figure 21]. This consists of a septic thrombus within the internal jugular vein, which can cause severe life-threatening sepsis, including septic pulmonary emboli, and can be associated with neck abscesses.⁶⁰ Treatment consists of identification of the septic source, often necessitating abscess drainage and intravenous antibiotics, and may even require involved venous segmental resection.⁶⁰

Magnetic Resonance Angiography

With advancements in hardware and software over the last decade, MRI of the entire arterial tree has grown exponentially. Although DSA still remains the gold standard, there is no arterial or venous bed where MRA or MRV cannot be

used to establish a diagnosis of arterial or venous disease. The single most important advantage of MRA over CTA is that MRA does not require the use of ionizing radiation, thereby enabling serial examinations to be performed, particularly for aneurysmal surveillance over the life of the patient, and the lack of radiation is also of importance in scanning young patients. Moreover, MRA does not necessitate the use of nephrotoxic iodinated contrast medium; however, the gadolinium contrast agent used is not suitable for patients already in established renal impairment or failure because of the risk of nephrogenic systemic fibrosis (NSF), with the highest risk in patients with a glomerular filtration rate less than 30 mL/min.⁶¹ MRA, unlike CTA, can yield dynamic flow information analogous to that of DSA, with the use of time-resolved magnetic resonance (MR) techniques, which is particularly useful for the evaluation of below-knee arteries. Also, MRI can be used to glean physiologic information as phase contrast imaging can demonstrate arterial flow velocity and direction, which is most useful in diagnosing arterial steal phenomena. The common problem of calcification with its blooming artifact on CTA is also overcome by MRA as the calcium in atherosclerotic plaque manifests as a low signal on

MRA without the obscuring blooming artifact. In addition, MRA acquisition can be performed in a number of different imaging planes depending on the vessel of interest; that is, the thoracic aorta can be imaged in a left anterior oblique plane, analogous to the images one would acquire with conventional DSA.

However, MRA has its own limitations with respect to artifacts, particularly occurring in the setting of arterial or venous stents. Susceptibility artifact leads to signal dropout around the site of the stent, which leads to a signal void within the vessel lumen and thus limits the accuracy of assessing that particular arterial segment and the ability to diagnose in-stent restenosis. Although this problem is more pronounced for stainless steel stents compared with nitinol stents, stent geometry and strut orientation can also affect the degree of susceptibility artifact. Copper has been found to be a more desirable stent component to limit the degree of susceptibility artifact.⁶² Patients with certain implanted devices are not suitable to undergo MRA, such as intracranial clips and certain cardiac defibrillators; however, many centers have now successfully scanned patients with permanent cardiac pacemaker devices using a truncated scan technique. Currently, the obtained

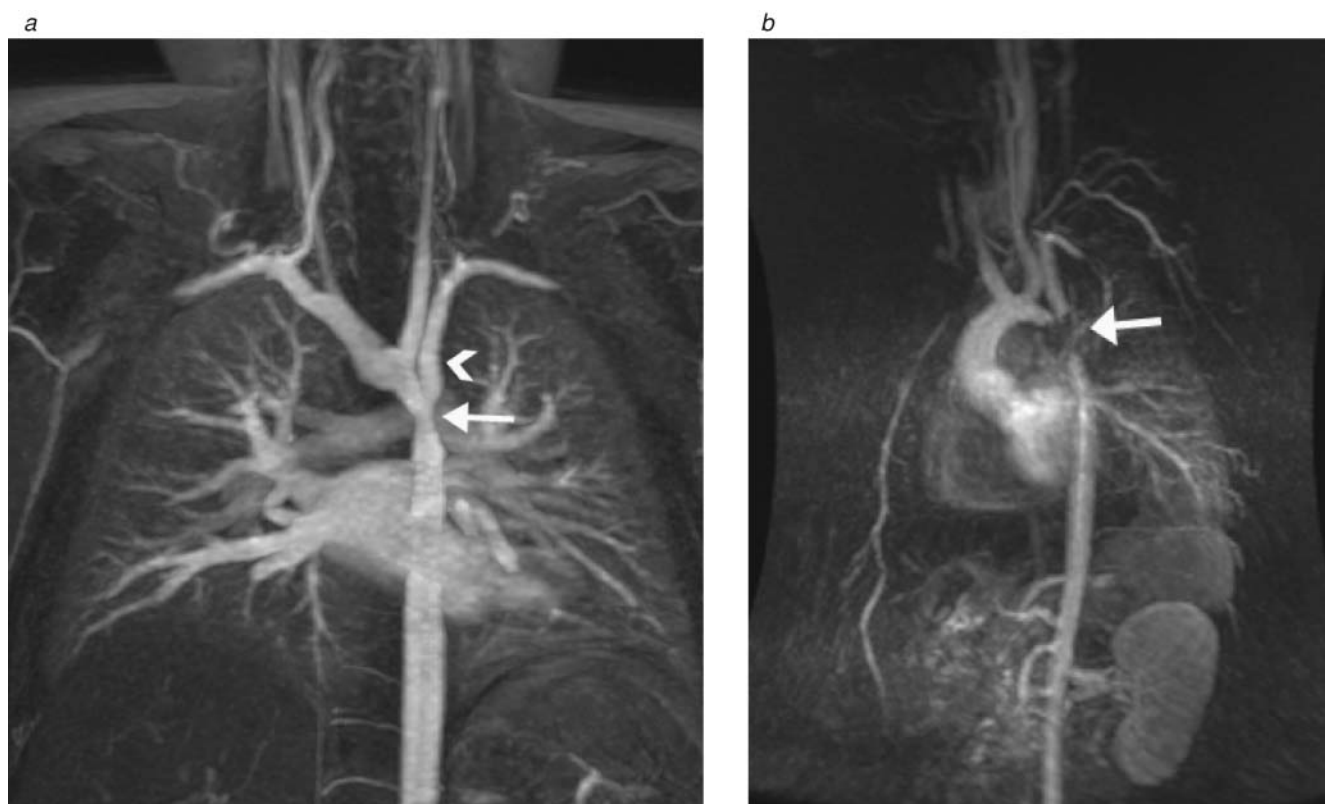


Figure 25 A 59-year-old male with a previous open repair of a coarctation at 8 years of age. He presented again with bilateral claudication and underwent magnetic resonance angiography (MRA). (a) Coronal maximum-intensity projection (MIP) from a high-resolution MRA demonstrates recurrence of the coarctation (arrow) at the expected location within the descending thoracic aorta beyond the left subclavian artery (arrowhead). It was elected to treat his recurrent coarctation endovascularly. (b) Sagittal MIP from a time-resolved MRA poststenting demonstrates susceptibility artifact manifesting as signal dropout from the stent across the coarctation (arrow).

spatial resolution of MRI is inferior to that of CT, but with higher field strengths, spatial resolution can approach that of CT.

The most recent exciting advance in arterial MRA is the development of sequences that do not require administration of contrast media to obtain eloquent accurate MRAs, thus avoiding the risk of NSF development. Both CT and MRI are currently being extensively used for plaque imaging, where individual components of atherosclerotic plaque can be characterized and followed post-medical therapy or intervention.

BLACK BLOOD MRI

Black blood imaging is currently not heavily relied on in most vascular MRI practices. It is of use, however, to examine the wall of the aorta to evaluate atherosclerotic plaque and aortic wall thickening occurring in inflammatory

conditions such as large vessel vasculitides such as Takayasu arteritis and giant cell arteritis. Black blood imaging uses spin-echo (SE) and fast spin-echo (FSE) pulse sequences, which take advantage of the inherent contrast between rapidly flowing blood and the aortic wall and thus require no administration of intravenous contrast medium. Signal void occurs within the vessel lumen because of the movement of spins and dephasing of turbulent flow. A detailed description of MRI physics and pulse sequences is beyond the scope of this chapter.

BRIGHT BLOOD MRI

A number of bright blood techniques are used without the need for administration of intravenous contrast medium, with the most widely practiced method being the TOF technique. TOF is based on the phenomenon of flow-related enhancement of proton spins entering into a partially saturated



Figure 26 A 31-year-old male presented for follow-up for a coarctation corrected when the patient was a child. A coronal maximum-intensity projection image from a time-resolved magnetic resonance angiogram demonstrates a stenosis (arrowhead) of the proximal descending thoracic aorta just distal to the origin of the left subclavian artery. There is a large shunt identified from the apex of the left ventricle to the descending thoracic aorta consistent with a surgical bypass created to correct for the presence of this coarctation (arrow).

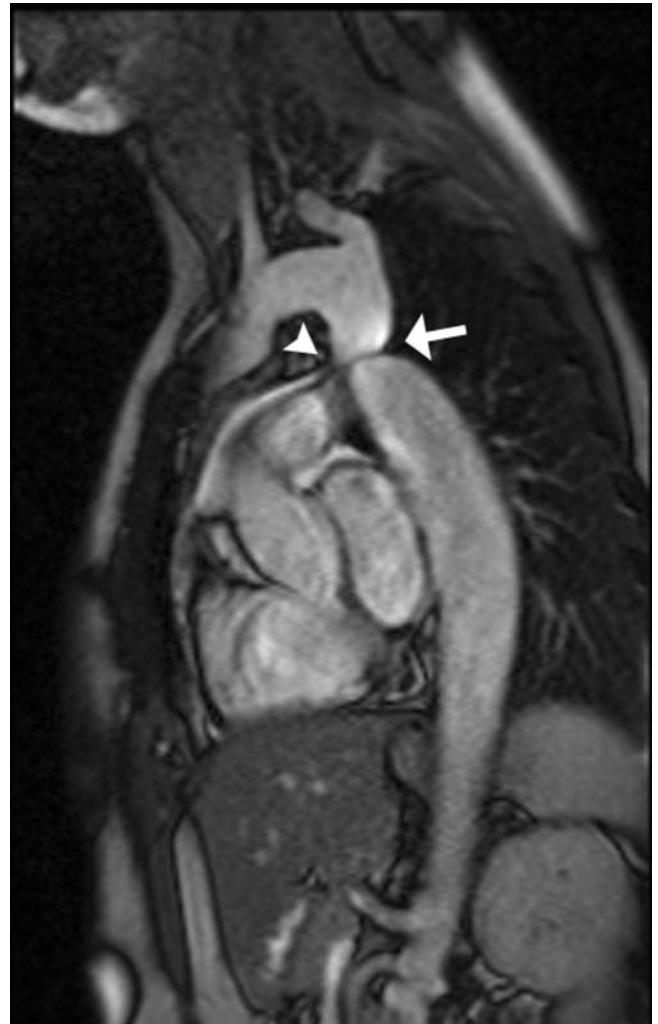


Figure 27 A 25-year-old male presented with claudication on running. A sagittal fast imaging with steady-state precession (FISP) magnetic resonance image of the thoracic aorta demonstrates a coarctation (arrow) and a persistent patent ductus arteriosus (arrowhead).

imaging slice. The protons that enter are unsaturated spins that give more signal than stationary spins within the previously saturated slice. Thus, in simple terms, a section of tissue is partially saturated with a radiofrequency pulse, which eliminates production of signal; arterial blood, which is unsaturated, then flows into this slice, and its spins are then able to produce a signal. During the acquisition, multiple thin, sequential sections are acquired in two-dimensions by using a flow-compensated gradient echo (GRE) sequence. These sections can be reformatted with the MIP technique to obtain a 3D image. Although the use of no contrast has inherent benefits, TOF has several limitations, including loss of signal if laminar flow is not present, resulting in false positives, poor performance in tortuous vessels, inability to appreciate retrograde flow in collaterals, and long imaging times. Despite these limitations, some advancements in the sequences have allowed vendors to develop two-dimensional cine mode TOF sequences, namely cine GRE, which are ECG gated and result in higher temporal resolution. These newer TOF sequences, known differently depending on the

vendor (true fast imaging with steady-state precession = FISP [Siemens], fast imaging employing steady-state acquisition = FIESTA [GE], and balanced fast field echo = FFE [Philips]), are useful in emergency settings as an aneurysm, rupture, large vessel thrombus, or dissection flap can be eloquently demonstrated.

Cine phase contrast is another noncontrast bright blood technique that can be used for dynamic evaluation of blood flow to demonstrate flow velocity and direction. Cine phase contrast depends on the phase shifts that flowing protons experience as they travel along the gradient field. Direction is manifest by bright or dark pixels, and velocity is represented by relative signal intensity. This technique is particularly useful for diagnosing steal phenomena such as subclavian steal [see Figure 22].

CONTRAST-ENHANCED MRA

Contrast-enhanced magnetic resonance angiography (CE-MRA) has revolutionized the use of MRI in the diagnosis of vascular disease as this technique can yield good-quality,



Figure 28 A 79-year-old female presented with three episodes of right-sided transient ischemic attacks. Maximum-intensity projection from a contrast-enhanced carotid and aortic arch magnetic resonance angiogram demonstrates a tight, greater than 90% stenosis of the left internal carotid artery (arrow). This was repaired surgically.



Figure 29 A 56-year-old male presented with right-sided one-block intermittent claudication 1 week following coronary angiography. A coronal maximum-intensity projection image from a time-resolved magnetic resonance angiogram demonstrates a short focal occlusion of the right common femoral artery (CFA) (arrow). Note that some small collaterals are present, allowing reconstitution of the right profunda femoris and superficial femoral artery. There is a discrepancy in the contrast density between the two limbs being denser on the left, consistent with poorer flow on the right side. This short focal occlusion was secondary to a closure device and required surgical repair with a right CFA patch plasty.

accurate angiograms that can be manipulated, via post-processing techniques, in all imaging planes, in a fast timely manner with no radiation dose to the patient.

The principle used by CE-MRA is that of T_1 shortening produced by the gadolinium contrast agent. Intravenously administered gadolinium circulates within the bloodstream and shortens the T_1 so much that blood is rendered bright irrespective of the flow patterns or velocities, thus avoiding the limitations of the bright blood TOF technique. Signal enhancement and overall image quality of CE-MRA depend on the intra-arterial concentration of the contrast agent; therefore, correct timing of imaging after contrast material injection is crucial. Thus one must image when the contrast bolus is within the desired vessel of interest, analogous to the concept of contrast timing for CTA. Similar to CTA, a number of methods are available to optimize contrast timing, including injection of a test bolus using a small amount of contrast material, automatic triggering using an ROI, and



Figure 30 A 61-year-old male with three-block intermittent claudication presented for evaluation. Coronal maximum-intensity projection from a high-resolution magnetic resonance angiogram demonstrates a mid-superficial femoral arterial complete occlusion (arrow) with a large collateral (arrowhead) and multiple small collaterals. This was treated endovascularly with a 6 mm stent.

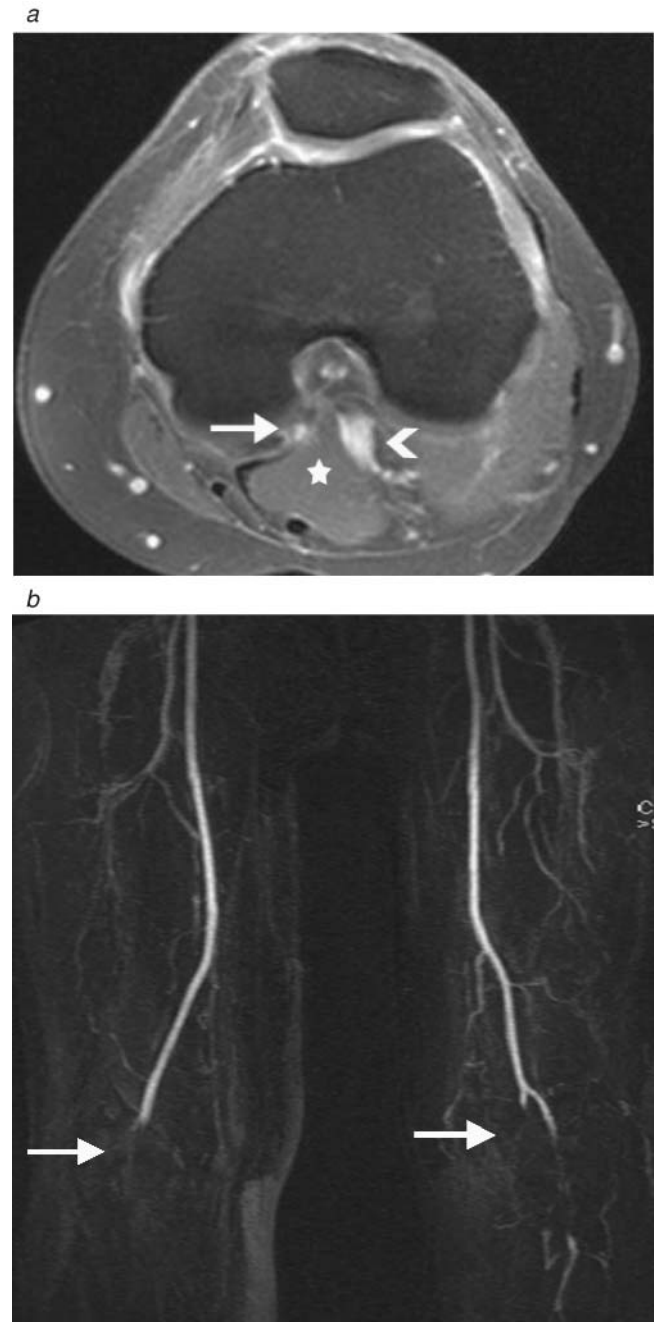


Figure 31 A 39-year-old male athlete with bilateral claudication when running. (a) An axial contrast-enhanced magnetic resonance image at the left popliteal fossa demonstrates the popliteal artery (arrow) separated from the popliteal vein (arrowhead) by a muscular band (star), which is from the medial head of the gastrocnemius muscle. This finding is consistent with popliteal arterial entrapment syndrome. (b) Coronal maximum-intensity projection from a time-resolved magnetic resonance angiogram with the patient in plantar flexion demonstrates occlusion of both right and left popliteal arteries (arrows) with some reconstitution distally. This is consistent with bilateral popliteal arterial entrapment.

MR fluoroscopy. Contrast volume is determined on an individual patient basis per weight, with a single dose being 0.1 mmol/kg; for CE-MRA, at least double the dose is usually administered. Based on the Fourier nature of MRI data acquisition, image contrast depends mainly on central k-space data; thus, collection of the central lines of k-space during the plateau phase of arterial enhancement is essential for optimal CE-MRA. Image fine detail depends on peripheral k-space data, which may be collected before and/or after the gadolinium peak to enhance MRA image resolution.

Repetition times (TRs) used for CE-MRA are approximately 5 milliseconds or less, with echo times (TEs) of 1 to 2 milliseconds and total scan times ranging from 10 to 30 seconds, thus fast enough to acquire all of the data in one breath-hold. Many other tricks can be employed to perform time-resolved MRA, which is a dynamic MRA technique almost analogous to the concept of rapid imaging frames obtained during DSA. A combination of ultra-short TR, parallel imaging, partial Fourier transform, sharing of peripheral k-space data, and sliding window reconstruction with

radial or spiral trajectories makes time-resolved (TR) CE-MRA possible at subsecond temporal resolution. TR-MRA is particularly useful in evaluating the peripheral runoff arteries, where traditional high-resolution CE-MRA can be limited by discordant flow bilaterally, contrast bolus timing issues, and consequent venous overlay [see Figure 23].

Postprocessing of the CE-MRA source data is somewhat easier and less time consuming than that of CTA data as the contrast-filled vessel is the brightest structure for the MRA MIP image because the calcium is of low signal on MR, unlike the high attenuation of calcified plaque and bone on CT. As with CTA, image interpretation is performed on a computer workstation, where the source images are analyzed and postprocessing techniques, including multiplanar reformation, MIP reformation, and volume rendering, are used.

THORACIC AORTIC MRA

Thoracic aortic aneurysmal disease is particularly suited to diagnosis and follow-up with CE-MRA as MRA is highly accurate, is reproducible, and incurs no radiation dose for

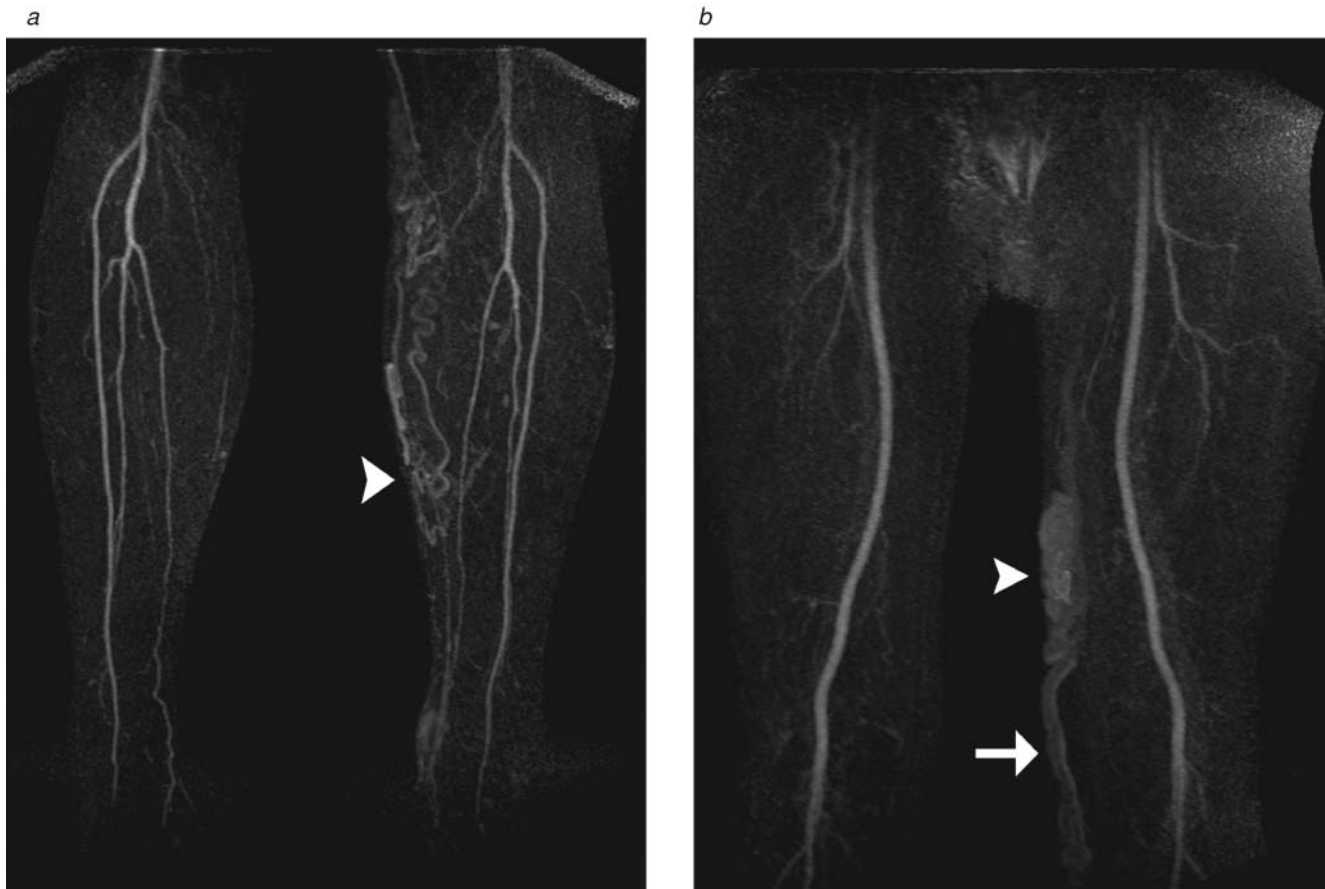


Figure 32 A 29-year-old male presented with a painful left lower limb with some skin discoloration. (a) Coronal maximum-intensity projection (MIP) from a time-resolved peripheral magnetic resonance angiogram (MRA) demonstrating both lower limb runoff vessels. Although this is within the arterial phase of contrast injection, early draining veins are identified on the medial aspect of the left lower limb with a small nidus (arrowhead). (b) Coronal arterial phase time-resolved MIP more proximal within the thighs demonstrates a large left great saphenous vein (arrow) with varicosity (arrowhead). As directionality of the flow can be determined with dynamic time-resolved MRA, it was noted that the direction of flow was from the nidus in the cephalad direction, confirming arteriovenous malformation with varicosity, as opposed to reflux from the saphenofemoral junction or perforators, which would result in flow in a caudal direction and manifest as venous insufficiency with varicose veins.

the patient. Also, MRI can be used to evaluate the adjacent aortic valve for anatomy (bicuspid or trileaflet), stenosis, or regurgitation, all of which are vital to know prior to an ascending aortic aneurysm repair to determine if the surgery is valve sparing or necessitates a concomitant aortic valve replacement. Acquiring the CE-MRA images in the oblique sagittal plane allows for almost the entire aorta to be visualized, which is useful for thoracoabdominal aneurysms and type B dissections.

Aortic dissection, along with its complications of coronary artery involvement, aortic valve rupture, pericardial hemorrhage with tamponade, branch vessel involvement, visceral ischemia, and peripheral ischemia, can be reliably diagnosed with MR using both noncontrast bright blood imaging techniques—mainly the new steady-state free precession (SSFP) techniques such as FISP, FIESTA, and FFE—and CE-MRA. Techniques such as FISP can rapidly diagnose and determine the extent of aortic dissection in a few minutes, without the need for breath-hold, contrast, or radiation. Cine FISP through the aortic valve can rapidly assess function, and a stack of short axis slices through the heart can determine any ventricular wall motion abnormalities that may be seen with coronary artery involvement resulting in myocardial infarction, along with tamponade physiology; however, there are obviously other methods to diagnose these complications, such as transthoracic or transesophageal echocardiography. Previously, SE black blood sequences were also used to demonstrate the intimal flap, usual signal void in the true lumen, and high signal attributable to slow flow or thrombus within the false lumen. CE-MRA can eloquently confirm the diagnosis, differentiate thrombus from slow flow within the false lumen, and diagnose complicated type B dissection with visceral or peripheral ischemia that may need endovascular or surgical intervention.

The limitations of MRI are availability, MR-compatible vital sign monitoring equipment, and fear of placing an unstable patient in the magnet. However, in high-volume centers with 24-hour access to magnets and staff experienced in monitoring unstable patients within the MRI scanner, this modality offers a viable alternative to CTA and TEE, especially in the setting of an iodinated contrast allergy or renal impairment.

Intramural hematoma, regarded by many as a spectrum in the same disease process as dissection, can be differentiated from dissection with thrombosis of the false lumen with the use of different sequences, namely cine GRE. SE can be used to age the thrombus with intermediate signal attributable to oxyhemoglobin in the acute setting and high signal attributable to methemoglobin in the more subacute setting.

Large vessel vasculitides such as Takayasu arteritis and giant cell arteritis are well suited to evaluation with MRI and CE-MRA. Aortic and branch vessel wall thickening can be diagnosed even before the occurrence of luminal compromise and/or dilatation. Aortic wall thickness can be demonstrated readily on fat-suppressed T_1 -weighted (T_1W) MRI, and edema is seen as a hyperintense intramural signal on T_2 -weighted (T_2W) imaging. Mural hyperenhancement of the aortic or arch vessel wall on fat saturation T_1W images after injection of contrast material is considered to indicate active inflammation; thus, a delayed postcontrast T_1W image is

obtained after the CE-MRA portion when considering large vessel vasculitis. The CE-MRA portion of the study identifies the involved segments of the aorta and its branch arteries. Takayasu arteritis classically causes proliferation of the intima, with medial and adventitial fibrosis, which subsequently leads to segments of arterial stenosis, occlusion, and/or poststenotic dilatation, usually affecting the aorta and its arch branches in a patchy distribution [see Figure 24].

Coarctation usually presents in childhood but occasionally can present in adulthood or recur in adulthood. MRA is an eloquent way to demonstrate the coarctation or the previous repair [see Figure 25a, Figure 26, and Figure 27]. However, once a coarctation is stented, MRA becomes limited in its ability to follow up the patient because of the susceptibility artifact encountered [see Figure 25b].

ABDOMINAL AORTIC MRA

CE-MRA has been shown by a number of authors to have a high sensitivity and specificity, both 100%, for the diagnosis of AAA.⁶³ The important information for preprocedural planning can be gleaned from MRA, including location, size, extent, adjacent arterial branch anatomy, thrombus load, and 3D spatial relations. Importantly, when measuring the size of an AAA on MRA, the source images and not the MIP images should be used to see the wall of the aorta and thus not underestimate the size of the aneurysm on the MIPs. However, to date, most centers continue to perform pre-EVAR planning with CTA. Post-EVAR follow-up can be performed with CE-MRA to detect endoleaks and monitor sac size; however, the stainless steel stent grafts cause marked susceptibility artifact and are contraindicated for MRI per the manufacturer's guidelines. Open aneurysm repair is not without its flaws, and CE-MRA can be used to detect potential complications such as para-anastomotic aneurysms, infections, graft occlusions, and venous or enteric fistulae. Graft infections, when confirmed, usually require complex surgical intervention with removal of the graft material and extra-anatomic bypass grafting; however, infection can often be difficult to diagnose. MRI can aid in the diagnosis by using fat-suppressed T_1W and T_2W imaging, along with delayed contrast enhanced fat-suppressed T_1W images. The presence of fluid surrounding the graft (bright on T_2W , dark on T_1W), surrounding muscle edema (bright on T_2W), and delayed peripheral contrast enhancement on fat-suppressed T_1W images are all signs of graft infection.⁶³

MRI is rarely used in the acute setting of suspected AAA rupture, again for the reasons outlined in the section on thoracic aortic MRA above.

CAROTID MRA

A recent meta-analysis examining noninvasive imaging modalities for diagnosis of carotid artery stenosis determined that contrast-enhanced MRA seems to be the most accurate noninvasive imaging test,⁵⁰ compared with US and MDCTA, and this finding is concordant with that of an earlier systematic review.⁶⁴ Sensitivity and specificity for CE-MRA for the diagnosis of 70 to 99% NASCET stenosis were in the order of 85% (95% CI 0.69 to 0.93) and 85% (95% CI 0.76 to 0.92), respectively,⁵⁰ and 94% (95% CI 0.88 to 0.97) and 93% (95% CI 0.89 to 0.96), respectively.⁶⁴ The results were not as accurate, in either meta-analysis, in the diagnosis of

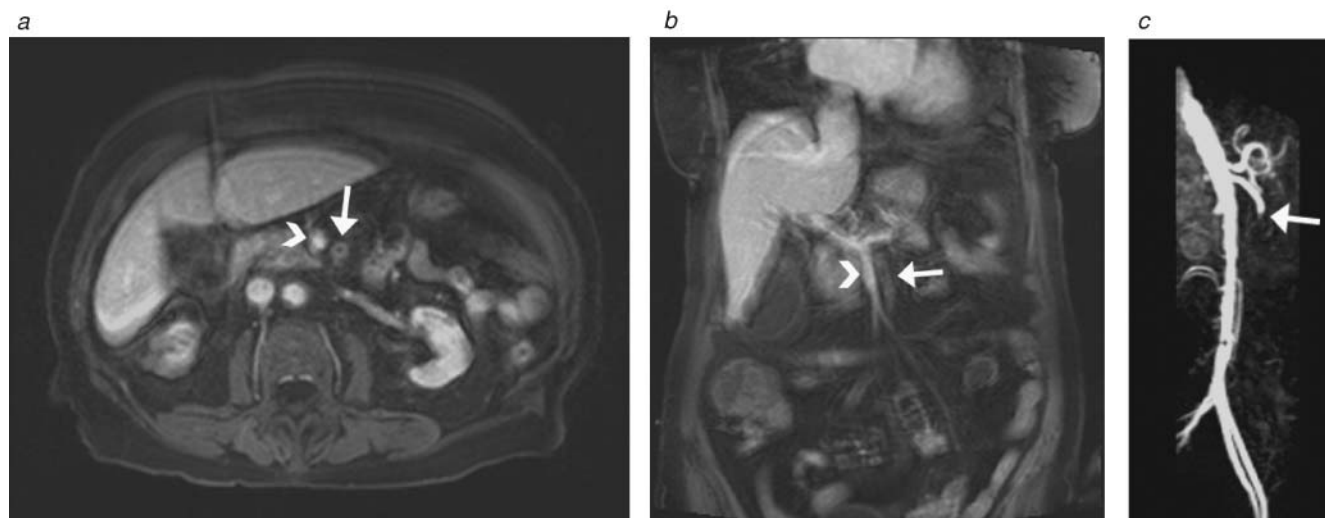


Figure 33 A 69-year-old male presented with acute onset of diffuse abdominal pain. Axial (a) and coronal (b) postcontrast fat saturation T₁-weighted magnetic resonance images through the upper abdomen demonstrate a filling defect within the superior mesenteric artery (SMA) (arrows) with contrast enhancement of the adjacent superior mesenteric vein (arrowheads). (c) Sagittal maximum-intensity projection from a high-resolution contrast-enhanced magnetic resonance angiogram demonstrates an abrupt cutoff of the SMA (arrow) consistent with an embolus or in situ thrombus. This was successfully treated with surgical embolectomy.

carotid artery stenosis in the order of 50 to 69% per NASCET reporting criteria.^{50,64}

MRA, including the aortic arch and circle of Willis, can provide an excellent preprocedural extra- and intracranial roadmap, which can reduce the number of DSA runs and total contrast volume used during carotid stenting, thereby

reducing catheter dwelling time within the aorta and carotid artery [see Figure 28].

Again, MRI is limited in the stented patient because of susceptibility artifact; however MRI is an excellent tool for the post-CEA patient to detect any postoperative complications. Carotid patch infection, along with its complications of



Figure 34 A 45-year-old female presented for evaluation of menorrhagia and underwent pelvic magnetic resonance imaging (MRI). Of note, she had an episode of blunt trauma 5 months earlier. (a) Coronal T₁-weighted fat saturation postcontrast pelvic MRI demonstrates a 1 cm focal area of enhancement within the left posterior pelvis (arrow) with evidence of a feeding vessel (arrowhead). (b) Axial T₁-weighted fat saturation postcontrast pelvic MRI confirms the presence of a 1 cm pseudoaneurysm from the inferior gluteal artery (arrow). This was successfully coil embolized.

abscess formation, pseudoaneurysms, and blowout, is universally feared. MRI can be useful in this setting, similar to the diagnosis of infected abdominal aortic grafts, as described above.

PERIPHERAL MRA

A large meta-analysis determined that the sensitivity and specificity of CE-MRA in diagnosing peripheral arterial stenoses is 94% and 90%, respectively.²⁸ When compared with MDCTA and duplex US for diagnosing peripheral arterial stenoses greater than 50% in another large meta-analysis, CE-MRA had a sensitivity and a specificity of 95% and 97%, respectively, with MDCTA at 91% and 91%, respectively, and duplex US at 88% and 96%, respectively.¹³ Where patients indicated a preference for imaging modality, MRA, with or without contrast, was chosen.¹³ Therefore, many centers are now using MRA as the first-line imaging tool for

determining the extent of PAD. The ABI remains the first-line noninvasive test to diagnose PAD; however, the ABI has a limited role in determining the extent of disease and in preprocedural planning. MRA has the ability to produce conventional “angiogram”-like images, which are easy to interpret and provide an accurate roadmap prior to open or endovascular intervention, thereby eliminating the need for DSA in the vast majority of cases [see Figure 29].

The usual MRA imaging protocol consists of initial scout images of the abdomen, pelvis, and lower limbs, usually with a dedicated peripheral coil. At our institution, a time-resolved MRA of the runoff vessels is obtained first to eliminate the problem of venous overlay and missed timing of the contrast bolus. This time-resolved technique uses parallel imaging and k-space under sampling with echo-sharing to increase temporal resolution at the expense of spatial resolution. This technique produces a dynamic “run,” analogous to a DSA “run,” which yields information on asymmetrical arterial contrast opacification, flow direction, collateral filling, and retrograde filling of diseased arterial segments [see Figure 30]. A three-station (pelvis, thigh, and runoff) high-resolution MRA is then acquired with a mask image performed at each station followed by a rapid acquisition with peak arterial gadolinium enhancement at each station with incremental table movement between stations. Usually, a double dose of gadolinium (0.2 mmol/kg) is required.

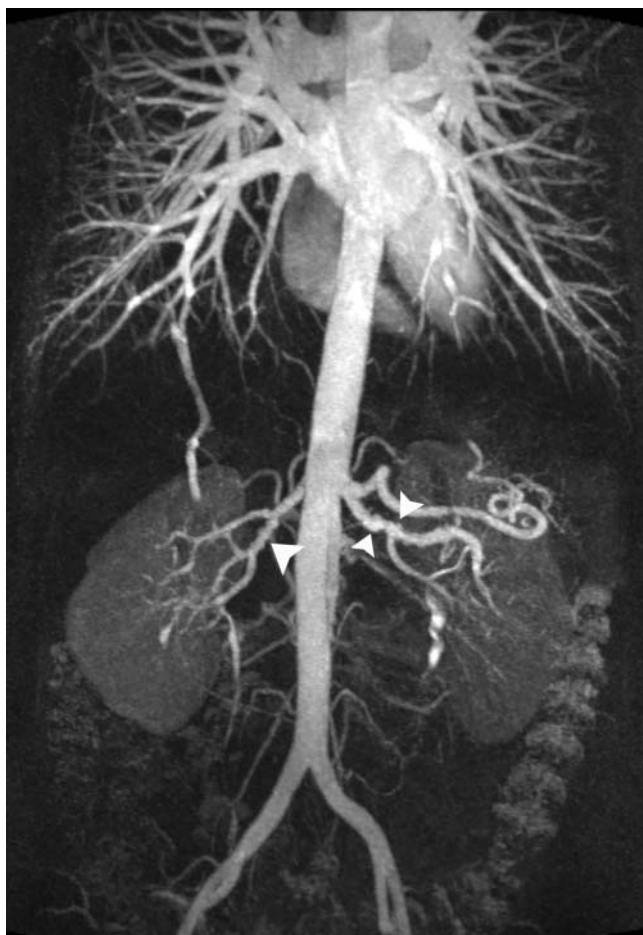


Figure 35 A 32-year-old female with hypertension undergoing workup for cause. Coronal maximum-intensity projection from a high-resolution contrast-enhanced magnetic resonance angiogram. There is evidence of bilateral nonostial beading of both main renal arteries (*arrowheads*), with no significant stenosis. This finding is consistent with fibromuscular dysplasia. This was successfully treated endovascularly with balloon angioplasty.

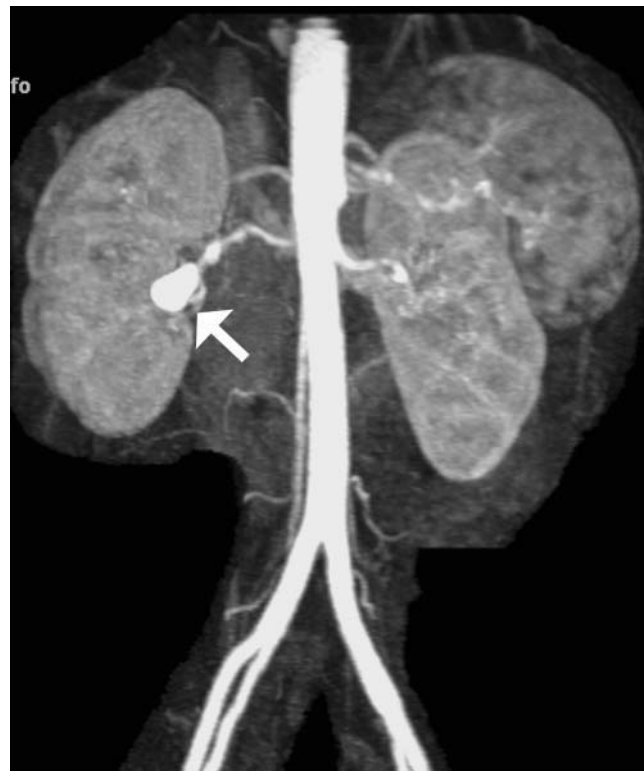


Figure 36 A 34-year-old female undergoing workup to donate a kidney to her sister. Coronal maximum-intensity projection from a time-resolved magnetic resonance angiogram demonstrates a 2.1 cm right renal artery saccular aneurysm (*arrow*).

MRI is well suited to evaluate nonatherosclerotic conditions such as popliteal entrapment syndrome because of its ability to demonstrate the vessel lumen and the surrounding popliteal fossa anatomy to determine if the artery-muscle relation is normal. [see Figure 31]. Dynamic MRA can be performed with the foot in both dorsiflexion and plantar flexion to elicit the popliteal arterial compression, which is characteristic of the syndrome. MRA commonly shows a normal popliteal arterial lumen with the foot in the relaxed neutral position, with narrowing of the arterial lumen during stress maneuvers. Venous compression, stenosis, or occlusion with or without thrombus can also be clearly demonstrated by acquiring images in the venous phase.

Limb AVMs and venous malformations are eloquently characterized with MRI⁶⁵; in particular, time-resolved MRA with the high temporal resolution can demonstrate the high- or slow-flow characteristics and nidus localization, and any connections to deep veins can be identified [see Figure 32]. This information is vital for treatment planning with percutaneous alcohol or sclerotherapy for the low-flow malformations and with intra-arterial embolization therapy reserved for high-flow malformations.

MESENTERIC MRA

Previously, a small study demonstrated that CE-MRA had a 100% sensitivity and a 95% specificity for diagnosis of significant stenosis (> 75%) or occlusion of a mesenteric artery, compared with the gold standard of DSA.⁶⁶

In acutely unwell patients suspected of acute mesenteric ischemia, simple noncontrast MR using an SSFP sequence such as FISP can identify arterial occlusion without the need for contrast or breath-hold; also, bowel wall evaluation can be performed [see Figure 33]. However, in most centers, CTA is the preferred imaging option for the acute setting.

Occasionally, contrast-enhanced MRI, which is performed for other indications, can incidentally identify arterial pathology [see Figure 34].

RENAL MRA

A meta-analysis evaluating five noninvasive methods to diagnose RAS concluded that CE-MRA and MDCTA were significantly better at diagnosing RAS than duplex US, captopril renal scintigraphy, and captopril testing.⁶⁷ Also, there was no significant difference in diagnostic performance between CE-MRA and MDCTA.⁶⁷ However, when CE-MRA and MDCTA were compared with DSA in 402 patients with hypertension suspected of RAS, the combined sensitivity and specificity were 62% and 84%, respectively, for MRA versus 64% and 92%, respectively, for MDCTA.⁶⁸ The authors concluded that both CE-MRA and MDCTA were not reproducible or sensitive enough to rule out RAS; however, the specificity was adequate.⁶⁸ Therefore, when the study is negative, a conventional angiogram is not needed, but when a study is positive, then an angiogram may be needed prior to intervention. However, recent results from the ASTRAL trial demonstrated no significant clinical benefit on renal function or blood pressure control with renal stenting compared with best medical management in the majority of patients.⁶⁹ Therefore, given the lack of significant benefit from endovascular intervention, one can argue that noninvasive imaging is sufficient for the evaluation of RAS as CE-MRA can confidently

rule out RAS. If RAS exists, noninvasive imaging can overcall the degree of stenosis rather than miss the disease. Overcalling is relevant only if one is planning an intervention as one would not perform angioplasty or stent a true 30% stenosis (called as 60% on MRA); however, one would treat a 30%

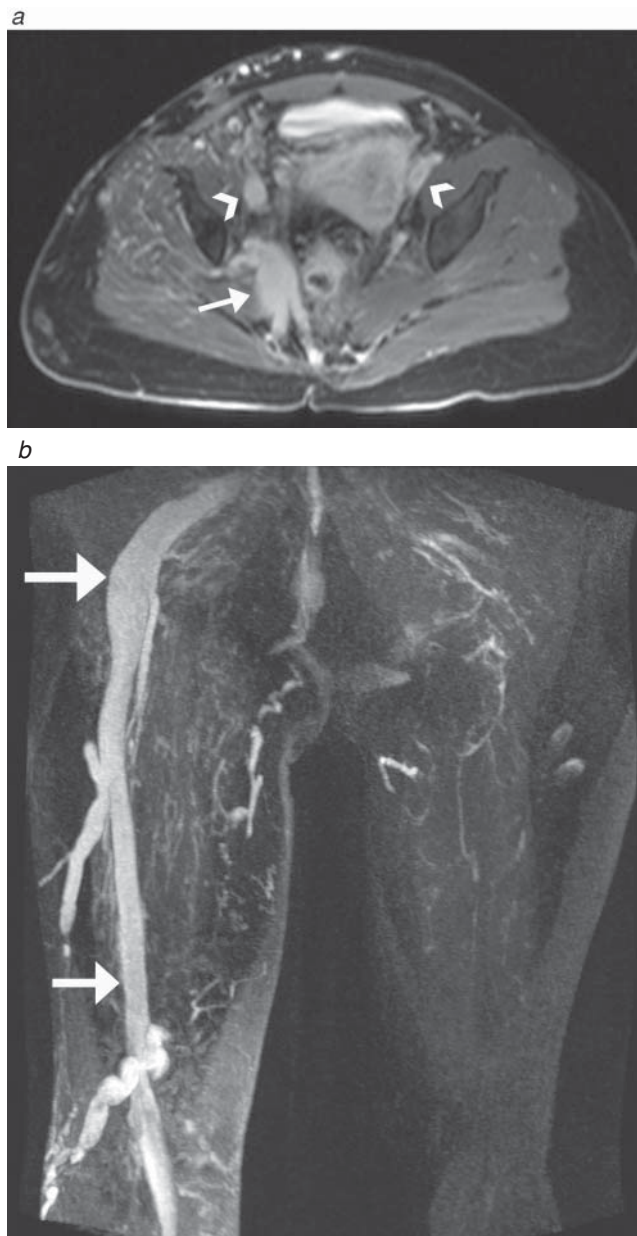


Figure 37 A 29-year-old female presented with a swollen right lower limb. (a) Axial contrast-enhanced fat saturation T₁-weighted magnetic resonance image through the pelvis, acquired in the venous phase, demonstrating an enlarged enhancing venous structure posterior within the right pelvis consistent with a congenital anatomic variant of a persistent sciatic vein (arrow). Note the presence of both iliac venous systems (arrowheads). (b) Coronal maximum-intensity projection from the time-resolved magnetic resonance venogram demonstrating the right persistent sciatic vein (arrow).

stenosis medically. Thus, now perhaps the function of noninvasive imaging is to rule in or out the disease, with less importance on the absolute degree of stenosis, and to rule out other etiologies of hypertension [see *Figure 35* and *Figure 36*].

MAGNETIC RESONANCE VENOGRAPHY

A small study comparing CE-MRV with DSA determined that the overall sensitivity, specificity, and accuracy for the detection of portal, splenic, or superior mesenteric venous thrombosis were 100%, 98%, and 99%, respectively, for MRV and 91%, 100%, and 96%, respectively, for DSA.⁷⁰

MRV can be useful for problem solving for venous disease within the lower limbs. In patients with extensive upper thigh varicose veins in conjunction with perineal varicosities, MRV can be useful to diagnose pelvic venous congestion syndrome. Occasionally, unusual anatomic venous variants can present, and as these often manifest in young patients, the lack of ionizing radiation necessary for MRV makes it a better choice than MDCTV [see *Figure 37*].

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33 ANTERIOR RETROPERITONEAL SPINE EXPOSURE

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Anterior surgical exposure of the lumbar spine is a technique that has been increasingly performed by a host of general and vascular surgeons over the past decade to aid spinal surgeons. Whereas anterior spinal approaches were once reserved for rare spinal disorders such as tumors or infections, the development of spinal instrumentation has led to many commonly encountered spinal disorders, such as lumbar disk disease and spondylolisthesis, being treated through an anterior approach. Owing to the predominance of spinal pathology at the lower lumbar levels and the spinal surgeons' need for assistance with anterior approaches, the "exposure surgeon" has emerged.

The knowledge and expertise in dealing with the structures encountered in the anterior exposures lie within the field of general surgery. Manipulation of diverse structures, including the small bowel, colon, ureter, aorta, and iliac vessels, must be done with precision and is an excellent opportunity for the surgeon to provide added expertise to aid the spinal surgeon in obtaining a successful outcome.

This chapter covers the aspects of anterior surgical exposure of the spine relevant to the exposure surgeon. A brief review of the background, pathophysiology, and clinical presentation of lumbar spine disease is presented, followed by a review of the treatment options and preoperative evaluation. The technical aspects, including the relevant anatomy, exposure techniques, and conduct of the operation, are presented. The routine postoperative management of these patients and frequently encountered complications are reviewed. Important but rare situations, such as redo anterior approaches, are discussed. These areas are all important for the exposure surgeon to understand and master to safely provide optimal anterior spinal exposures and offer an important avenue for the surgical trainee to gain experience with open surgical techniques.

Background

Anterior lumbar interbody fusion was first described for Pott disease of the spine.¹ This approach has gained popularity in treating a variety of diseases of the spine. Over the past decade, a broad range of lumbar pathology has been treated with instrumentation requiring an anterior approach. General, vascular, and trauma surgeons are often enlisted to provide exposure of the spine. Anterior fusion and disk replacement procedures have become common, especially with the development of anterior lumbar interbody fusion and total disk arthroplasty. The spinal pathology addressed during the anterior exposures may be divided into diseases that affect the intervertebral disk and diseases that involve the

vertebral bodies along with the disk. The most common sites of involvement are the fourth and fifth lumbar vertebrae and the intervertebral disks between L4 and L5 and L5 and the sacrum (S1).

Knowledge of retroperitoneal anatomy is essential to the successful performance of these procedures. The iliac vessels will often need to be mobilized to gain access to the anterior aspect of the lumbar spine. During this mobilization, injury to the vessels may occur. Injuries to the iliac vessels are uncommon; however, when these injuries occur, life-threatening hemorrhage may result. Having a surgeon who can repair these injuries and perform the exposure can potentially reduce the chances of complications and optimize patient outcomes.

Pathophysiology

Isolated intervertebral disk disease is believed to be a major cause of chronic low back pain. The intervertebral disk is generally an avascular, fluid-rich structure that consists of the outer collagenous annulus fibrosus and the inner gelatinous nucleus pulposus. The intervertebral disk serves to absorb and dissipate loads on the spinal column and allows motion. With aging, desiccation and loss of disk height are universal. Back pain may result from internal disk disruption (IDD), disk herniation, or degenerative disk disease (DDD).

Discogenic pain is primarily attributable to IDD and DDD. IDD is marked by the presence of normal disk anatomy. This generally affects younger patients who present with back pain without radiculopathy. As the intervertebral disk is avascular and poorly innervated, pain is postulated to result from the leak of noxious chemicals.² In this manner, the disk serves as a "pain generator," and removal of the disk can lead to relief of pain. In contrast, DDD is marked by changes in the intervertebral disk architecture. In this setting, neurovascular ingrowth into the degenerated disk may lead to pain. The adjacent end plates and vertebral bodies may also serve as pain generators. Mechanical changes occur with DDD, which can lead to pain as a result of loading and alignment changes.

Bony abnormalities of the lumbar spine frequently treated by the exposure surgeon include lumbar spondylolisthesis. Spondylolisthesis exists when there is actual forward translation of one vertebral body over another with an intact neural arch. This misalignment and change in mechanical stress can lead to back pain secondary to muscular strain as well as potential nerve impingement with radicular pain. Often with these processes, the changes in alignment can lead to a change in disk structure and worsening pain. The pain is mechanical and aggravated by back extension or on arising from a bent

posture. Radicular leg pain or neurogenic claudication may exist. For spondylolisthesis to exist, there must be both disk disruption and ligamentous disruption. Therefore, therapies to treat this address both the disk and the vertebral alignment.

Clinical Presentation

Most of the types of lumbar spine pathology discussed above typically present with back pain. Radicular pain indicates nerve root impingement. These processes are more common in women and present in the fourth decade.² Back pain without radiculopathy, sitting intolerance, and increased pain with flexion, rotation, and bending are common complaints. Symptoms include low back pain, which is often made worse with long periods of standing or sitting. The postural relation and alleviating factors are important in differentiating lumbar disease from other pathologies. DDD may be accompanied by radiation to the sacroiliac joints, buttocks, and thighs. Spinal stenosis attributable to disk herniation may lead to lower extremity complaints but can be differentiated from vascular claudication by (1) the long time needed for recovery and (2) alleviation of pain by leaning forward and removing pressure on the spine. The presence of any atherosclerotic risk factor is a very important historical consideration. Physical examination in a patient with spinal stenosis may reveal pain with straight leg elevation, limited mobility, significant kyphosis, and tenderness over the lower spine.

Imaging modalities play a large role in the diagnosis of lumbar pathology. Plain x-rays may demonstrate a loss of disk height, bony abnormalities, and spondylolisthesis. Flexion and extension views are important. Magnetic resonance imaging (MRI) may demonstrate the “black disk” phenomenon. The significance of this finding is debated as this may often be seen in asymptomatic patients.² Discography is frequently performed to elicit the pain and to correlate the findings with other imaging studies. A computed tomographic (CT) scan can be combined with the discogram for additional information on disk architecture, and spinal stenosis. Imaging abnormalities may have a high false positive rate as 30% of asymptomatic patients will have abnormal imaging. Therefore, the diagnosis of lumbar spine disease must be based on sound clinical judgment, taking into account the history and physical examination and all imaging studies.

Treatment Options

Although the treatment of lumbar disk disease and spondylolisthesis has undergone significant evolution, the stepwise approach is needed. Nonoperative therapy is an essential first step. Patient education and activity modification are important initial treatments. Physical therapy and antiinflammatory medications are important cornerstones in patient management. The importance of appropriate pain control is clear; escalation of therapy is dependent on the response of the patient. Surgical therapy is reserved for failures of all less invasive therapies. Several less invasive surgical procedures may be offered to the patient, such as intradiscal electrothermal therapy, nucleus replacement, kyphoplasty, and other evolving treatments within the armamentarium of the spinal surgeon. However, the most invasive treatments, such as

anterior lumbar interbody fusion and disk arthroplasty, are the procedures of interest to the exposure surgeon.

Intervertebral disk disease is approached with two options: motion preservation or fusion. Lumbar fusion has been traditionally performed with a posterior approach. However, with new developments in instrumentation, the fusion can also be performed with an anterior approach.^{2,3} The anterior approach offers several advantages over posterior instrumentation and fusion. Anterior lumbar interbody fusion (ALIF) avoids the disruption of the muscular stability of the back and potential nerve root injury. Anterior fusion also produces a larger fusion surface, more complete disk decompression, and improved outcomes. ALIF was initially reserved for failures of posterior fusion, but with the improved results, ALIF may now be offered as the primary surgical treatment. The goal of all fusion procedures is to eliminate motion at the intervertebral space, restore alignment, and alleviate pain.

Although fusion has been successful in treating isolated intervertebral disk disease, recent investigations have established the options for motion-preserving therapy in affected patients.⁴ The development of total disk replacement (TDR) has the potential to preserve motion at the treated disk space while eliminating the disk as a source of pain. Preservation of motion at the disk space can avoid the late sequelae of adjacent-level degeneration seen above a previous spinal fusion. Prospective, randomized trials have demonstrated the superiority of TDR to ALIF in selected patients.⁵⁻⁸ This has important implications for the exposure surgeon: although fusions may be performed from a posterior approach, all currently available TDR systems in the United States require an anterior approach to the lumbar spine.

The treatments available for spondylolisthesis include decompression alone and decompression with fusion. Simple decompression may be chosen in high-risk patients and those with limited slip. However, prospective, randomized trials have demonstrated that the addition of fusion to decompression leads to improved outcomes.⁹ This has led to increased use of fusion for the treatment of spondylolisthesis, with anterior fusion demonstrating greater success than posterior fusion. Along with the fusion, anterior instrumentation with plates and screws is necessary when anterior columnar support is inadequate.³

Preoperative Evaluation

A thorough understanding of the background and treatment options for lumbar spine disease enables the exposure surgeon to fully participate in the treatment of these patients and not function as a mere technician. The importance of teaming with an experienced spinal surgeon with sound judgment cannot be overemphasized. Exposure surgeons must develop their own preoperative approach to the patient that maximizes the opportunity for success.

Once a patient has been selected as a candidate for anterior spinal surgery, a thorough evaluation by the exposure surgeon should be performed in a preoperative office visit. Given the magnitude of the operation and the central role the exposure surgeon plays, establishing a relationship with the patient is very important. Given the different perspectives of the spine and exposure surgeons, important additional information may be gleaned from the exposure surgeon's assessment.

A thorough medical history is an essential first step. Most patients who require this type of surgery tend to be young and otherwise healthy. Some patients will be overweight because of inactivity from their spine disease. Significant comorbidities that may place the patient at high risk for surgery must be considered at this point. General health issues, with an emphasis on atherosclerotic risk factors such as diabetes, hypertension, and tobacco use, should be queried. Previous surgical interventions, including previous abdominal operations, must be reviewed. Previous spinal surgery, even procedures from a posterior approach, can have implications related to scarring, instrumentation, and infection that can complicate an anterior approach.

A physical examination with special attention to body habitus, planned incision site, and previous surgical incisions should be performed. In all patients, a thorough pulse examination must be documented. The presence of significant vascular disease should be a relative contraindication to any anterior approach given the potential for vascular calcification and injury. If aortoiliac occlusive disease is suspected, noninvasive vascular studies may aid in the evaluation of patients with the potential presence of vascular disease by history or physical examination.

A review of all available imaging studies should be performed by the exposure surgeon. This will ensure that the approach surgeon understands and reviews the relevant anatomy. Available x-rays will demonstrate any vascular calcification, which may then suggest the need for further vascular imaging. The relevant vascular anatomy demonstrating the relation of the lumbar level of interest and the aortic bifurcation, confluence of iliac veins, and course of the iliac arteries and veins can often be determined from MRIs or CT scans. These scans can also demonstrate the presence of arterial calcification, surgical clips from previous operations, and other findings that may alter the considered approach. This will allow the exposure surgeon to have the clearest understanding possible to formulate an effective surgical plan.

A key part of any surgical procedure involving more than one specialist is communication. After the preoperative visit, the exposure surgeon should contact the spine specialist and review the case. This will minimize any potential for confusion at the time of surgery. At all stages, the exposure surgeon must be open and forthcoming, with both the patient and the spine surgeon, regarding expectations of the proposed surgery. It is important to remember that not all patients are good candidates for anterior spinal surgery. Previous colon surgery, retroperitoneal dissection, pelvic irradiation, or the presence of aortoiliac occlusive disease should be considered relative contraindications. Overall physiologic status is important and should be carefully considered prior to committing the patient to any major operation. The spine disorders treated via the anterior retroperitoneal approach are almost never life threatening; therefore, if the surgeon performing the exposure feels that the surgery will carry excessive risk, the procedure should be reconsidered.

Vascular Anatomy and Variations

The arterial anatomy is relatively simple, and variations rarely pose any difficulty in exposure of the disk levels. The arterial structures of importance include the aorta and the

bilateral common iliac arteries. Most mobilization involves the left common iliac artery, but exposure usually does not require division of any significant branches. If exposure of the disk levels cephalad to the L4-L5 level is necessary, then division of segmental lumbar arteries may be required.

Although the arterial anatomy is simple, the venous anatomy will require intraoperative assessment to determine the best method for exposure. At certain levels, typically L4-L5, mobilization of the iliac veins is essential to gain proper exposure to the lumbosacral spine. The venous anatomy in this area can be variable, and if there is improper mobilization of the veins, injury can occur, and this can lead to large blood loss.

The inferior vena cava originates at the confluence of the left and right common iliac veins. This usually occurs at the L4-L5 disk level; however, this can be variable. The left common iliac vein has tributaries that are known as the ascending lumbar vein (ALV) and the iliolumbar vein (ILV) [see Figure 1]. The ALV commonly arises from the lateral aspect of the common iliac vein. This vein will need to be divided to properly mobilize the left common iliac vein. The ILV can arise near the ALV or may arise more distally. Unruh and colleagues demonstrated that the venous anatomy can be variable and categorized the tributaries of the left common iliac vein into three types.¹⁰ More than half of the patients will have a common origin of a venous branch from the left common iliac vein, which then divides into the ALV and ILV. The other common variants both include two distinct origins for the ALV and ILV. The authors have proposed referring to these veins as the lateral lumbosacral veins because of the variation often encountered.¹⁰ The importance of this anatomy lies in the fact that these veins can be easily torn with medial retraction of the left common iliac vein and result in severe hemorrhage that is difficult to control. Mobilization and division of these key branches are necessary for full retraction of the left common iliac vein. It is important to note that although there can be significant variation of the venous anatomy in this area, careful dissection can avoid serious venous injuries in nearly all cases, and usually no more than two veins in this area need to be divided.

Operative Approach

GENERAL CONSIDERATIONS

The lumbar spine is most frequently diseased at the levels of the fourth lumbar vertebra through the sacrum (L4-S1). The anterior approach to the spine at these levels will therefore have to address the peritoneal and retroperitoneal structures overlying the spine at these levels. Employing an extraperitoneal approach can minimize the need to directly address the intraperitoneal structures. The external landmark for the aortic bifurcation is generally the umbilicus, although this can vary with age and body habitus. The L4-L5 disk space is generally located near the aortic bifurcation [see Figure 1]. The L4-L5 disk lies in a plane that is generally axial but may be angulated in a slightly caudal direction. In a thin person, the step-off between L5 and S1 can be palpated and identifies the L5-S1 disk space. In the supine patient, the L5-S1 disk lies roughly halfway between the umbilicus and the pubis. However, the L5-S1 disk space is often angulated

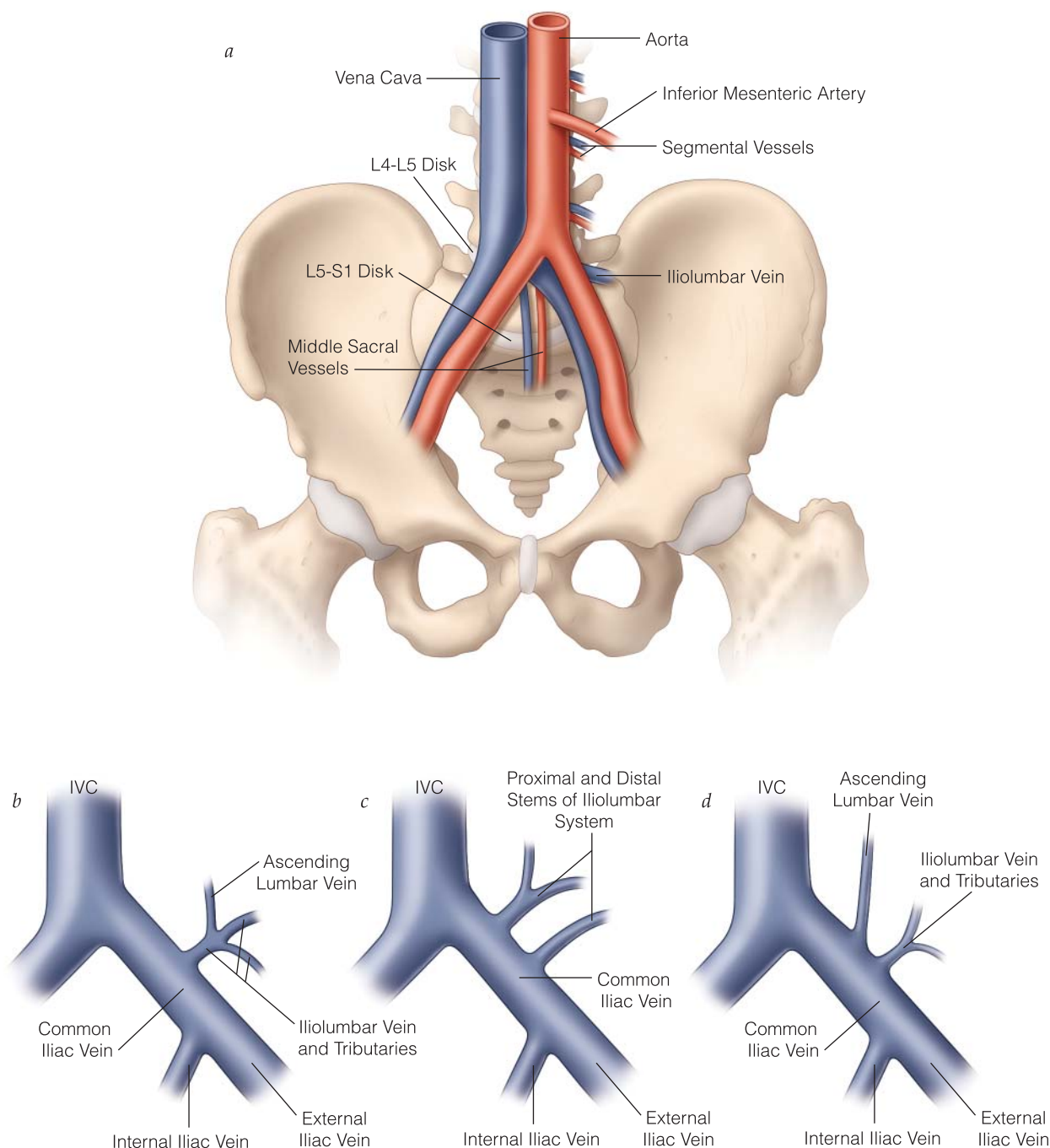


Figure 1 (a) The important anatomic relations of the disk spaces to the aorta, vena cava, and iliac arteries and veins are depicted. (b to d) The three differing patterns of venous tributaries into the left common iliac vein are demonstrated. IVC = inferior vena cava.

in a more caudally directed plane than L4-L5. These are all important aspects to keep in mind when planning the surgical approach.

The vascular manipulations necessary during exposures of the lumbar spine are the most critical aspects of the exposure. Exposure at L4-L5 generally involves mobilization of the left common iliac artery and vein. The disk space may be exposed above the vessels, between the vessels, or below the vessels

[see Figure 2]. Chiriano and colleagues reviewed 243 cases of L4-L5 exposure.¹¹ The exposure was achieved superolateral to the left common iliac artery in 44% of cases. Mobilization of the left common iliac artery laterally and left common iliac vein medially was necessary in 45% of cases. The ALV and/or ILV will have to be divided to mobilize the vein medially. In 11% of cases, the exposure was achieved between left and right common iliac veins as described for L5-S1.¹¹ The

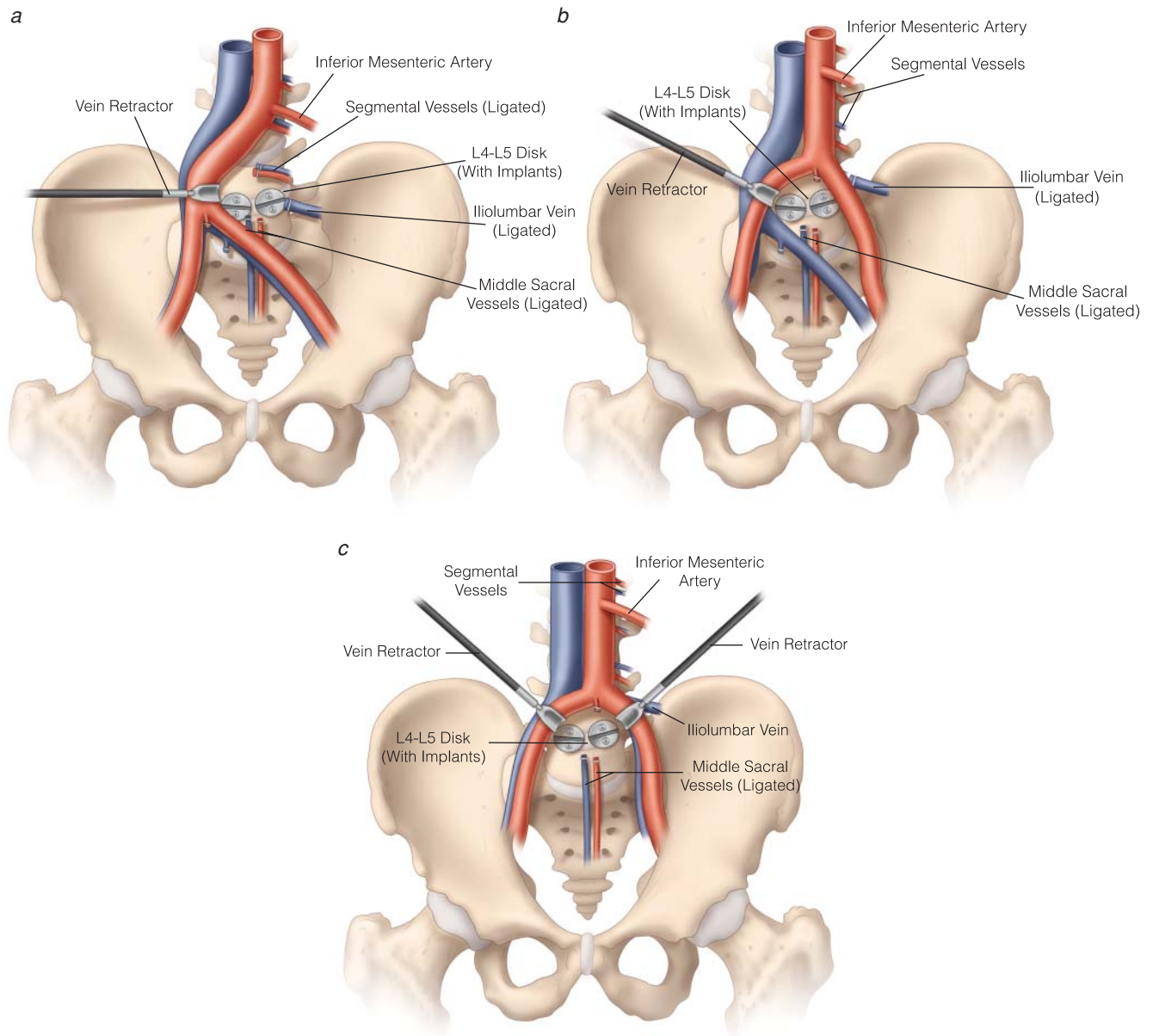


Figure 2 The manipulations necessary to expose the L4-L5 disk space are determined by the relation of the disk space to the iliac vessels. (a) Exposure obtained above the left common iliac artery and vein. (b) Exposure obtained between the left common iliac artery and vein. (c) Exposure obtained below the left common iliac vein.

exposure of the L5-S1 disk space is typically obtained between the right and left iliac veins without the need for significant vascular mobilization [see Figure 1]. The median sacral vessels serve as a consistent landmark on the anterior disk surface for the centerpoint of the disk.

Overlying nervous structures within the area of the aortic bifurcation include the sympathetic plexus, which often lies over the origin of the left common iliac artery. Care in this area is important to prevent damage and preserve sexual function, primarily ejaculatory function, in the patient. Also in this area, the ureter must be identified and protected from injury.

CONDUCT OF OPERATION

Anterior approaches are all performed with the patient placed supine on a radiolucent table. Care must be taken to ensure that the patient is not rotated as this will affect the ability to accurately place the instrumentation. The patient's arms are placed on armboards extending out at a 90° angle as arms tucked at the sides will interfere with lateral fluoroscopic imaging. Appropriate monitoring lines are placed by the anesthesia and neurology services. Prior to preparing the operative field, fluoroscopy is performed to identify the levels of interest and mark the level on the skin [see Figure 3]. This simple step avoids malpositioning of the incision and limits

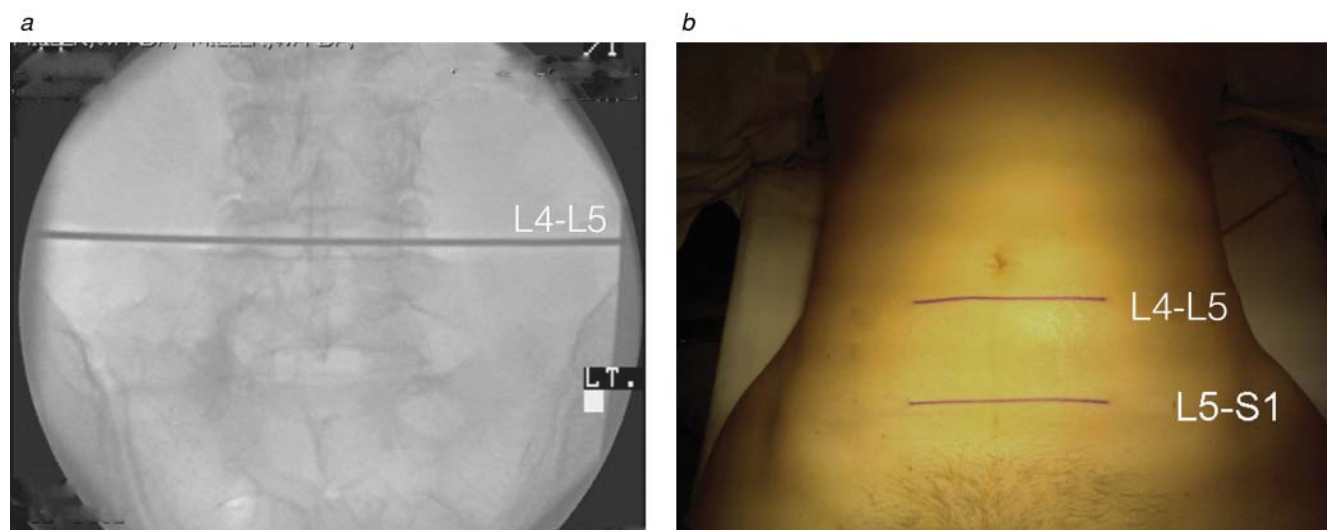


Figure 3 Intraoperative incision planning: (a) fluoroscopy is used to identify the disk space, and (b) the level is marked on the skin.

the size of the incision. The choice of a lower transverse abdominal or vertical paramedian incision typically depends on two factors: the upper level of exposure necessary and the number of levels to be exposed. For exposures involving L4-L5 and/or L5-S1, we prefer a lower abdominal transverse incision. For exposures involving L3-L4 or higher or for all three-level approaches, we prefer a left vertical paramedian incision [see Figure 4]. Both incisions allow for excellent extraperitoneal exposure.

When a transverse incision is made, the incision is generally approximately 3 cm below the umbilicus when the L4-L5 disk is to be exposed. Because of the more caudal angulation of the L5-S1 disk space, isolated L5-S1 exposure can be obtained with a transverse incision a few fingerbreadths above

the pubis. When both L4-L5 and L5-S1 are to be exposed, the incision generally is made slightly favoring the upper level because of the importance of adequate exposure to address vascular manipulations, which are frequently required at L4-L5. The soft tissues are divided with cautery down to the anterior rectus sheath. The sheath is divided transversely, with the lateral aspect extending no further than the lateral aspect of the rectus muscles. The anterior rectus sheath is then mobilized away from the rectus muscles in a cephalad and caudal direction. This will allow lateral retraction of the muscles and superior-inferior retraction of the fascia. The muscle bellies are separated in the midline, and the muscles are mobilized laterally. The midline plane may be somewhat scarred if the patient has had a previous cesarean section

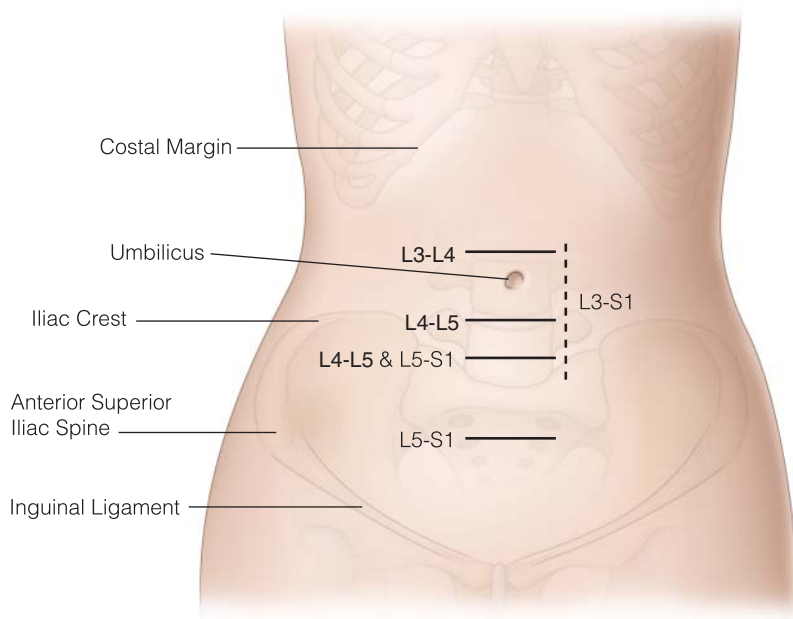


Figure 4 General guideline for planning skin incision.

or hysterectomy, but these muscles can almost always be separated and retracted. The extraperitoneal plane is then developed, with dissection being carried out behind the rectus muscles. The inferior portion of the posterior rectus sheath may be encountered and is divided in a vertical direction to then allow entry into the extraperitoneal plane. In the midline, the peritoneum may be adherent to the linea alba, and careful sharp dissection is necessary. When there has been a previous lower midline or Pfannenstiel incision, the extraperitoneal plane can generally be developed slightly laterally toward the left, away from any scarring. Dissection can then be carried back toward and across the midline. At any point, if a hole is made in the peritoneum, dissection can be carried out in another location and the extraperitoneal plane developed while keeping the peritoneum mostly intact. The dissection proceeds downward and toward the patient's left with mobilization of the peritoneum and its contents toward the right.

When a left paramedian incision is chosen, the dissection begins as above. Once the anterior rectus sheath is identified, the sheath is incised vertically 2 to 3 cm lateral to the midline. The fascia is mobilized away from the left rectus abdominus muscle. The left rectus is then dissected to the midline and mobilized laterally. The posterior rectus sheath is then identified and incised vertically. The extraperitoneal plane is then entered. Given the vertical orientation, this incision allows for more optimal access when three-level exposures are necessary and is favored for any lumbar exposure above L4-L5.

Once the extraperitoneal plane is developed via either the transverse or paramedian approach, dissection is generally unencumbered downward and to the patient's left [see Figure 5]. Care should be taken to avoid injury to the inferior epigastric vessels, which should be left anteriorly attached to the posterior aspect of the rectus. The round ligament may be identified and divided during this portion of the procedure. In males, the spermatic cord is mobilized and retracted inferomedially. The psoas muscle can be identified at this point.

Blunt dissection is used to mobilize the peritoneal contents medially while keeping the peritoneum intact. Cephalad dissection in a retronephric plane will allow creation of a larger dissection space. The ureter is identified and rotated medially along with the peritoneal structures. The external iliac artery will be seen and can be traced to the left common iliac artery and the aorta. This dissection anterior to the arteries can be done bluntly, but there may be some small veins coursing anteriorly that can be cauterized. The distal dissection typically then occurs medial to the iliac vessels. Occasionally, the obliterated umbilical artery (a branch of the internal iliac artery) will be encountered and should be ligated and divided. The bladder is typically caudal to the area of dissection and is not directly identified. At this point, a self-retaining retractor system is essential. We prefer the Omni-Tract surgical retractor system (St. Paul, MN) with radiolucent blades. This allows the maintenance of exposure throughout the instrumentation process with minimal interference.

Often multilevel exposures are required, and exposure of the disk spaces usually proceeds in a cephalad to caudal direction. When multiple disk levels need to be treated, it is safer to expose one level at a time. Adequate exposure often

requires retraction of the vessels, and optimal exposure of one level may compromise the exposure of the other disk levels. The dissection at each level should be carried out sequentially. After one level has been adequately exposed, the retractors can then be adjusted to expose the subsequent (typically more caudal) level. For proper instrumentation to take place, wide exposure of the anterior aspect of the intervertebral disk must be achieved. The placement of an artificial disk requires clear identification of the midline of the disk and extensive side-to-side exposure of the anterior aspect of the disk. The performance of fusion with anterior instrumentation typically involves less side-to-side exposure of the disk but does require exposure of several millimeters of the vertebral bodies adjacent to the disk. Thus, it is important for the exposure surgeon to be aware of the surgical plan.

The most common intervertebral disk levels that require exposure are the L4-L5 and the L5-S1 disks. The L4-L5 disk level will often be more difficult to expose. The key intraoperative decision is what relation the disk space holds to the iliac vessels [see Figure 2]. This can often be anticipated in light of preoperative imaging (when available). Palpation of the disk will often clearly identify the important relations determining whether the window should be created above the left common iliac artery, between the left common iliac artery and vein, or below the left common iliac vein. During all manipulations of the left common iliac vein, careful dissection and control of the ilio-lumbar and ascending lumbar veins are key.

For exposure of the L5-S1 disk, the sacral promontory can be easily palpated in the retroperitoneal space. Dissection is carried out medially to the left common iliac vessels. The left common iliac vein can generally be carefully retracted laterally, and the soft tissues over the L5-S1 disk can be divided. The middle sacral artery will be identified and serves as an excellent mark for the midline of the disk. The middle sacral artery and vein can be divided with ligature, the harmonic scalpel, electrocautery, or clips. Blunt dissection can then be used to retract the tissues toward the right, medial to the right common iliac vein, and complete the exposure of the anterior aspect of the disk.

Once all levels have been exposed, radiopaque markers are placed in the disk spaces. This allows confirmation of the appropriate level by the exposure surgeon and confirmation by the spine surgeon [see Figure 6]. By obtaining anteroposterior and lateral views, this also allows the identification of the centerline, which is very important during instrumentation.

Instrumentation is then performed by the spinal surgeon. Clearly orienting the spinal surgeon about the relevant anatomy, retractor positioning, and centerline will help avoid any potential for injury. As a result of the observation that nearly all serious vascular injuries occur during the instrumentation portion of the procedure, we have adopted the policy of remaining scrubbed and assisting with the instrumentation. Often at L4-L5, compression of vascular structures is necessary to obtain adequate exposure [see Figure 7]. Periodic relief of compressing retractors will help avoid any thrombotic complications. Compression of vascular structures is rarely necessary at L5-S1 [see Figure 8]. Following completion of instrumentation at each level, the retractors should be readjusted to optimize exposure.

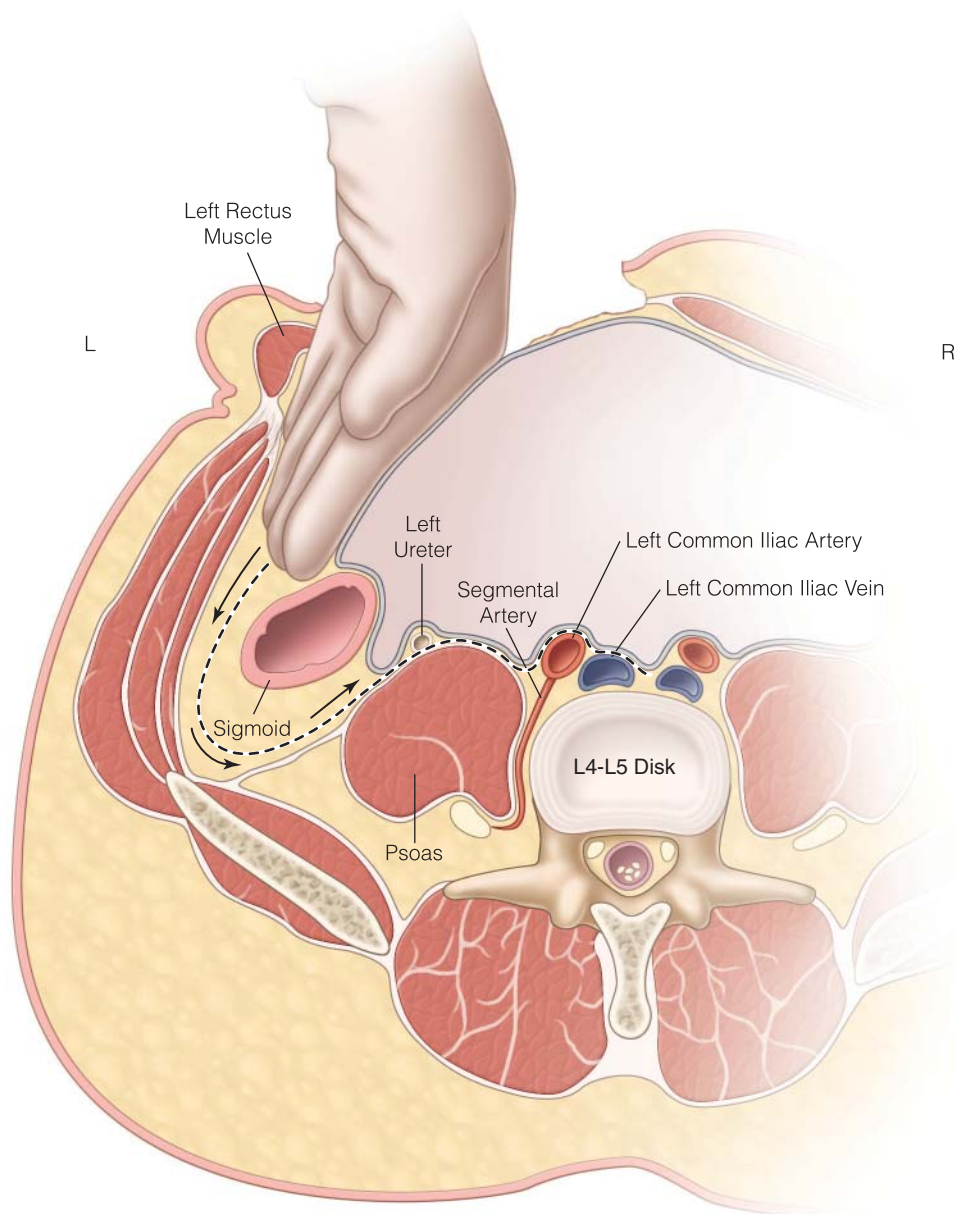


Figure 5 The avascular retroperitoneal plane is developed by blunt dissection. Initial dissection may be carried out lateral to the rectus muscle, but once retractors are placed, lateral retraction of the left rectus is performed to facilitate midline exposure of the disk space.

After completion of the spine portion of the procedure, hemostasis is initially confirmed with the retractors in place. Careful removal of the individual retractor blades is necessary to inspect for hemostasis as a retractor blade may have provided a tamponade effect on a venous injury. To aid in hemostasis, we use spray fibrin sealant (Tisseel, Baxter Biosurgery, Deerfield, IL). The myofascial layers are reconstructed in a layered fashion.

The exposure of the L2-L4 disks is relatively simple because major veins will not need to be mobilized. A left-sided, vertical paramedian incision is useful for this exposure. At higher levels (L2-L3), the genitofemoral nerve can be identified on the anterior aspect of the psoas muscle and should be left in

situ. The aorta can then be mobilized medially off the spine. Lumbar arteries and veins need to be divided on the left side to gain full anterior exposure of the spine. It is important to ligate the lumbar veins prior to retraction, or these veins can be avulsed off the vena cava, and this will result in hemorrhage that is difficult to control. Care must be taken when there is atherosclerotic disease in the aorta. If the aorta is calcified, injuries can occur with retraction as it is often necessary to retract the aorta at a fairly acute angle to obtain exposure of the spine at these levels.

Once the procedure is completed, it is essential to perform a pulse examination of the lower extremities. Early detection of arterial occlusions is crucial for the best possible outcomes.

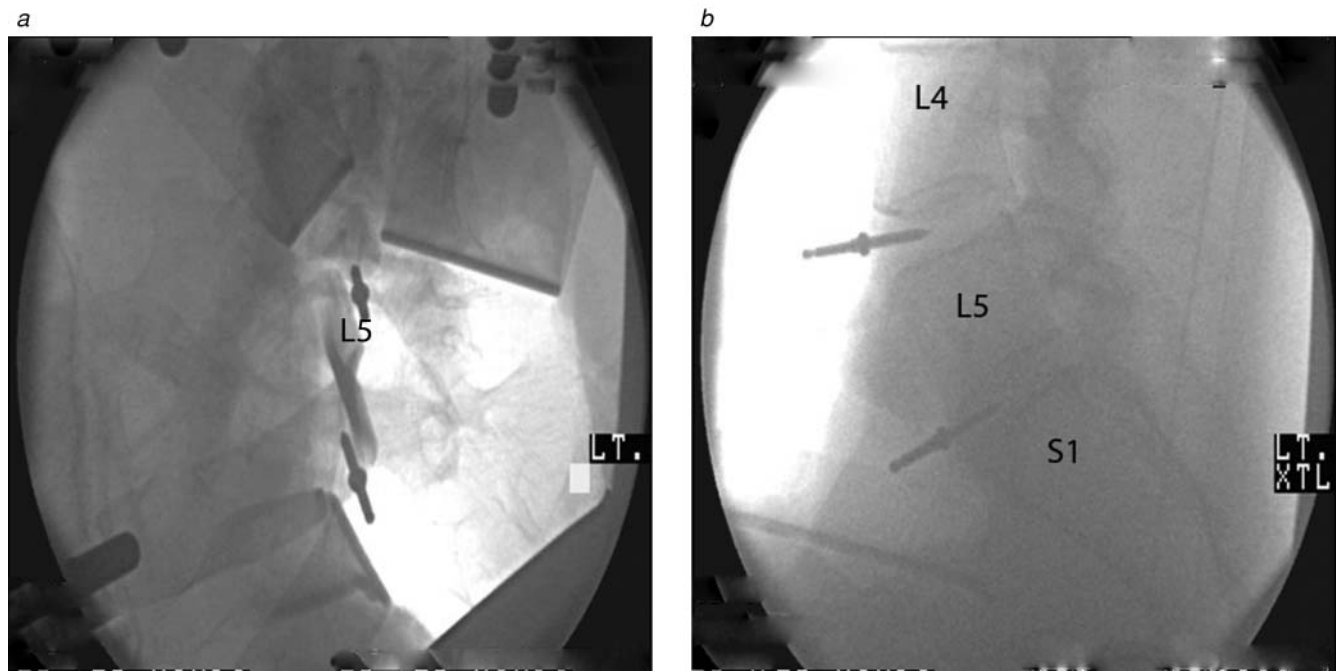


Figure 6 Intraoperative fluoroscopy is used to confirm the appropriate level and to identify the midline. (a) The anteroposterior view demonstrates the radiopaque markers in the L4-L5 and L5-S1 disk spaces. The relation of the marker to the spinal process helps determine the midline. (b) A lateral view clearly confirms the disk levels. (Note that the radiolucent retractor blades can be left in place during imaging.)

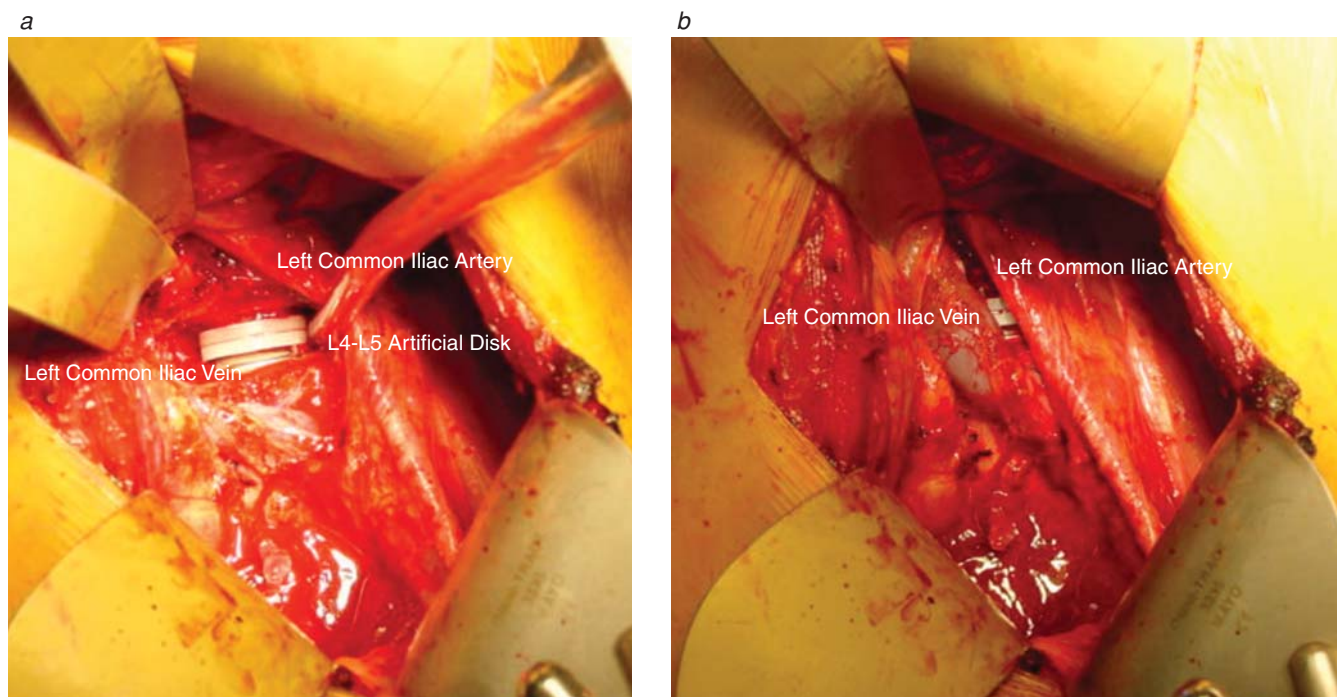


Figure 7 The exposure obtained at L4-L5 often requires extensive mobilization of the left iliac vessels. (a) Extensive side-to-side exposure is generally necessary for placement of the artificial disk. (b) Periodic relaxation of the retraction during preparation of the disk space is suggested.



Figure 8 The exposure obtained at L5-S1 rarely requires vascular manipulations. (Note that the middle sacral vessels have been divided.)

Again, it is incumbent on the exposure surgeon to have an accurate assessment of the preoperative pulse examination to identify significant changes. In our practice, we have not found pedal pulse oximetry probes or somatosensory evoked potentials to be of use in identifying arterial injuries.

Postoperative Care

The patients should have neurovascular checks postoperatively. If the peritoneum is entered, the patient may experience a transient ileus. Most patients can be started on a clear liquid diet on postoperative day 1 and advanced as tolerated. Patients with multilevel reconstructions and those with paramedian incisions tend to have a more prolonged ileus than patients who undergo single-level exposures, but this is unpredictable. Depending on the number of levels treated and method of instrumentation, the patient may be in a soft corset or rigid spinal brace postoperatively. Early mobilization is encouraged, and the patients are often ambulating with the physical therapists on the first postoperative day.

Pain control is often a major issue in the perioperative period. Many patients will be on a significant amount of oral analgesia preoperatively, and this should be considered when attempting to control postoperative pain. Consultation from a pain specialist is often helpful in the management of patients on chronic narcotics. Patients will experience pain not only from the anterior incision but also from the instrumentation of the spine. The Foley catheter should be removed as soon as possible. Prophylaxis against venous thromboembolic disease should be continued until the patient is able to ambulate well.

Complications

VASCULAR INJURIES

During the exposure of the intervertebral disk spaces, mobilization of the iliac veins and sometimes mobilization of the iliac arteries are necessary. Injuries to these vessels can

occur during this mobilization or during the spinal instrumentation. Arterial injury is rare. When calcified atherosclerosis is present in the iliac arteries, associated plaque can be injured during retraction. This can lead to bleeding or thrombosis. Tears are usually amenable to primary suture repair; arterial reconstruction is rarely necessary. Vessel thrombosis is also rare but amenable to repair using standard vascular techniques. Castro and colleagues described a case of distal aortic thrombosis after spinal surgery.¹² Bilateral iliofemoral thrombectomies were performed, but, ultimately, the patient expired following bilateral amputations. Raskas and Delamater described thrombosis of the left iliac artery in a patient with calcified atherosclerosis of the aorta.¹³ This injury required bypass of the artery with a Dacron graft.

Venous injuries are usually minor; however, the lack of exposure can make control of these injuries difficult. Simple suture repair of the venous injuries can frequently control the bleeding and fix simple injuries. Often major venous injuries occur as a result of attempts to repair smaller injuries. This can occur during attempts to clamp the vein or when there is an unsuccessful attempt at suture repair. The iliac veins can be controlled by proximal and distal compression without full mobilization of the veins, which allows direct suture repair and avoids collateral injuries.

Hamden and colleagues reviewed their experience of 480 patients who had anterior exposure of the spine.¹⁴ Vascular injuries occurred in 11% (54 of 480) of patients. Only two injuries were arterial. The majority of the injuries were venous, with the left common iliac vein being most frequently injured. Only 1.9% of the injuries were severe, which was defined as injuries that required blood transfusion or vascular reconstruction or resulted in greater than 300 cc of blood loss. As suggested previously, the L4-L5 level was associated with more vascular injuries.

In our experience with 405 anterior exposures, several trends have been identified in vascular injuries.¹¹ Minor injuries to venous structures requiring simple repair with monofilament suture occur in nearly one quarter of cases and are more common when L4-L5 exposure is performed. These injuries are easily repaired and of minimal consequence and occur when the exposure surgeon is establishing the initial exposure. Major vascular injuries occurred in 3% of cases, with two arterial and 10 venous injuries. All major vascular injuries occurred during the instrumentation portion of the procedure. This observation suggests that the exposure surgeon should remain present and participate throughout the entire procedure and not merely for the opening and closure.

DEEP VEIN THROMBOSIS

Although the iliac veins are commonly manipulated and retracted during anterior spine exposures, deep vein thrombosis (DVT) is rare. Although direct manipulation is felt to play a role in the development of DVT in these cases, other factors are clearly at play, as in all types of major operative procedures. Of three episodes of DVT in our experience, two were associated with a major ipsilateral venous injury, whereas one had no identified injury.¹¹ An episode of DVT following anterior exposure was reported in the setting of a retroperitoneal hematoma that caused compression of the inferior vena cava.¹⁵ Pulmonary embolus is also a rare occurrence,

with Brewster and colleagues reporting one case of pulmonary embolism in their series of 128 cases of anterior retroperitoneal exposure of the lumbar spine.¹⁶ Appropriate perioperative thromboembolic prophylaxis is important in these patients.

LYMPHOCELES

Lymphoceles are rare complications after anterior spinal exposures. The lymphatics are generally either cauterized or, in the case of larger identified lymphatics near the left common iliac artery origin, ligated. There are only a few cases of this complication in the literature following this procedure. If the lymphoceles are large and symptomatic, they may have to be drained surgically. If the symptoms are minimal, conservative management can be attempted.¹⁷

NERVE DYSFUNCTION

The lumbar sympathetic nerves lie lateral to the spine and may be injured during the dissection or from retraction when the spine is exposed. Injury to the sympathetic nerves results in vasodilation of the left lower extremity. Because most exposures approach from the left side, the observation is often made that the right foot is cool. Examination will demonstrate palpable pulses bilaterally, and, in fact, it is the left foot that is abnormally warm from the sympathectomy, whereas the right foot is cool as a result of normal sympathetic tone. This tends to be a self-limiting process with no long-term sequelae.

Of more concern to the surgeons and patients is the potential for sexual dysfunction following anterior spinal surgery. Sexual dysfunction can occur in males (usually retrograde ejaculation as opposed to impotence) as a result of disruption of the intermesenteric nerve plexus and superior hypogastric nerve plexus that course over the left common iliac artery origin.^{18–21} The incidence of retrograde ejaculation after anterior fusion ranges from 0.5 to 6%. With a retroperitoneal approach, the incidence appears to be less than 1%, and half of the cases are temporary.²² The transperitoneal approach appears to have a much greater incidence of retrograde ejaculation, presumably because of the division of the tissues overlying the left common iliac vessels without identification and sparing of the nerve fibers. With the retroperitoneal approach, the tissues overlying the left iliac vessels are generally kept intact and swept with the peritoneal contents toward the right. Although the intermesenteric and superior hypogastric nerve plexuses have bilateral innervations, redo exposures from the right side in a patient with a previous left-sided approach markedly increase the risk of retrograde ejaculation.

BOWEL AND GENITOURINARY INJURIES

Bowel injuries are rare and can be avoided by keeping the peritoneum intact. In our series, one bowel injury occurred during disk removal when the bowel moved into the surgical field through a small defect in the peritoneum.¹⁹ The bowel injuries may be repaired primarily, but as in any case with bowel violation, the potential for hardware infection must be recognized.

The left ureter can be injured during the dissection or mobilization. If there has been previous surgery in this area,

a ureteral stent can be considered. Gumbs and colleagues reported a ureteral injury that was repaired by a urologist intraoperatively.²³ Interestingly, this injury occurred in a patient who had a stent placed preoperatively. Again, this is a rare complication but needs to be distinguished from a lymphocele. If a urinary leak is discovered postoperatively, urologic evaluation is necessary.²³

RARE INJURIES

There are a variety of other rarely reported complications related to the anterior retroperitoneal spine exposure. The incidence of incisional hernias is quite low (zero in our experience) but may be a source of chronic postoperative discomfort. Other rarely reported complications include postoperative pancreatitis and the development of retroperitoneal fibrosis.

Exposure Options

The goal of the anterior retroperitoneal spine exposure is to gain the best access to the spine to optimally perform the spinal procedure. There are three main approaches to this: the conventional exposure, the mini-open muscle-splitting exposure, and the laparoscopic approach. All three techniques involve the same dissection of the pelvic vasculature. The main difference is the skin incision, violation of the peritoneum, and the approach to the myofascial layers.

CONVENTIONAL RETROPERITONEAL APPROACH

The conventional anterior retroperitoneal approach is our preferred approach, as described in detail above. Although the incision typically ranges from 10 to 15 cm in length, the exposure attained is excellent. The iliac vessels can be carefully mobilized and protected as the exposure allows for adequate access. In the case of vascular injuries, no further extension of the exposure is necessary. As a bonus, the cosmetic results appear quite good with the standard transverse incision.

MINI-OPEN APPROACH

Brau has described his mini-open approach for exposure of the L3-L4, L4-L5, and L5-S1 levels.²⁴ For a single level, a small transverse incision on the left side of the abdomen is performed. For multiple levels, an oblique incision is performed. The spinal levels to be exposed determine the position of the incision. The anterior rectus sheath is incised, and the left rectus muscle is circumferentially mobilized, allowing medial and lateral retraction. The retroperitoneal space can then be entered. The iliac vessels are then mobilized. The technique allows for a smaller incision than the standard transverse or paramedian incisions, but the exposure is admittedly limited. Compression of the iliac vessels is common as a result of the limited exposure. Brau acknowledges that this technique cannot be used in all patients. When used, an incision of 6 to 10 cm for single-level exposures and 8 to 18 cm for multilevel exposures is possible. The length of the incision and the ease of exposure vary with the patient's body habitus. Obviously, a thinner patient's lumbar spine can be easily exposed with a smaller incision.

LAPAROSCOPIC APPROACH

Laparoscopic anterior spinal exposure was first described in 1995 by Zuckerman and colleagues.²⁵ The laparoscopic approach for the L5-S1 levels can be relatively straightforward. Given that the only vessels that need to be divided are the middle sacral vessels, this can be achieved in most cases using a laparoscopic approach. There is extensive experience in the literature that shows that the laparoscopic approach to L5-S1 disk level is effective.^{26–33} The exposure of the L4-L5 level can be more challenging. Kleeman and colleagues described their experience using laparoscopy to expose the L4-L5 disk level.²⁸ They were successful in 135 of 139 cases. All of their failures were in the first 30 cases, which demonstrates that this approach has a significant learning curve. Their experience mobilizing the iliac arteries and veins was very similar to standard open techniques. All methods of vein mobilization that Chiriano and colleagues described were necessary using the laparoscopic approach.¹¹ Kleeman and colleagues used preoperative CT or MRI to determine the venous anatomy and therefore aid in planning the laparoscopic approach.²⁸ They also experienced the vascular complications that are seen with open surgery, including arterial embolization, venous bleeding, and DVT.

TRANSPERITONEAL APPROACH

A standard, transperitoneal open approach to the lumbar spine has been described. In general, the approach may use a lower midline or transverse incision. Instead of dissection proceeding in an extraperitoneal plane, the peritoneum is entered and the bowel is packed. The retroperitoneum is then entered, and the disk spaces are exposed. This dissection has the drawback of bowel manipulation and has been shown to have a markedly elevated incidence of retrograde ejaculation.²² We have reserved this approach for remedial operations following previous anterior retroperitoneal approaches when the removal of hardware is necessary.

COMPARISON OF APPROACH OPTIONS

Kaiser and colleagues compared their experience using the mini-open and laparoscopic approaches.²⁷ Operative times were longer with the laparoscopic approach. In the mini-open group, the hospital stay was marginally longer, but this was statistically significant. The complication rate was higher in the mini-open group; however, this was driven by the occurrence of mild ileus. Importantly, the incidence of retrograde ejaculation was significantly higher in the laparoscopic group—a finding supported by others.²²

Zdeblick and David compared mini-open and laparoscopic approaches.²⁹ They found no difference between the two groups when a single disk level was exposed. In contrast, when more than one level was exposed, the operative time and complication rates were higher with the laparoscopic approach. Most importantly, inadequate exposure was seen in 16% of patients. This led to only a single cage being placed, which may compromise the long-term results of the procedure. The mini-open group had no patients with inadequate exposure.

When considering all of the approaches, the surgeon must take into account the primary goal of the spine surgeon. The

incision length, approach, and risks should be explained to the patient at the initial evaluation as informed consent regarding the exposure is the responsibility of the exposure surgeon. Personal preference often plays a role, but the virtues of the various approaches should be understood. In our experience with the retroperitoneal approach, we have always been able to accomplish the exposure safely and allow for the optimal placement of instrumentation.

Special Considerations

REPEAT ANTERIOR EXPOSURE

If the patient has had previous surgery via the anterior or posterior approach, the dissection will be more difficult as a result of scarring in the operative field. Infections of previous instrumentation of the spine can also make the dissection more treacherous. For redo operations, different approaches should be considered. If there was a previous exposure via the left retroperitoneal approach, the redo operation via the right retroperitoneal approach may be considered for L5-S1. When the retroperitoneum is too scarred for development of a dissection plane, a transperitoneal approach can be used, but the risk of retrograde ejaculation may be higher.^{19,22} Previous left colon surgery often leads to extensive inflammation in the area of L4-L5 and should be considered a contraindication for anterior exposure. The previous performance of a hysterectomy or cesarean section has not prevented successful anterior retroperitoneal exposure in our experience.

Placement of a prosthetic polytetrafluoroethylene patch around the iliac vessels at the time of initial spinal instrumentation has been suggested as an aid for redo procedures. In theory, this should provide a plane of repeat dissection between the instrumentation and the patch while protecting the vessels. Although this sounds appealing, the utility of this is unknown. Given the high risk of repeat anterior approaches, other alternatives should be sought. For removal of infected instrumentation at L4-L5, we have employed a lateral approach to lessen the risk of vascular injury.

THORACOLUMBAR EXPOSURE FOR SPINAL FRACTURE

Exposure of the distal thoracic and proximal lumbar spine (T12-L2) is often necessary in the setting of trauma. T12-L1 pathology is most often a result of blunt trauma. These patients present all of the challenges of a trauma patient. The surgeon performing the exposure will often have more experience dealing with trauma patients; therefore, it is that surgeon's responsibility to ensure that the patient is stable enough to undergo the procedure. These patients will often have concomitant chest trauma, the left chest may be entered, and there may be some compromise of pulmonary function. The fracture site can often bleed significantly intraoperatively, and it is essential that blood products are available.

The patient is placed in the lateral decubitus position using a bean bag. Fluoroscopy is used to identify the fracture and plan the incision. A left thoracoabdominal incision over the ninth, 10th, or 11th rib typically allows exposure of the T11 through L1 vertebral bodies. The myofascial layers are incised, including the serratus anterior and the latissimus dorsi muscles. This will expose the rib, and the dissection is carried out with care to avoid injuring the neurovascular

bundle. Harvest of the rib for use as a bone graft can be performed at this point. Care should be used to avoid entry into the pleural space. If violation of the pleura occurs, a chest tube should be placed at the completion of the procedure. The external and internal oblique muscles are then divided, followed by the transversalis layer, and the retroperitoneal space is entered. The dissection is carried in the retronephric plane, and the peritoneal contents are mobilized anteriorly with complete dissection off the undersurface of the diaphragm. Care must be taken when performing this dissection to avoid injury to the spleen. The crus of the diaphragm may be incised to gain access to the spine. With division of the crus, the pleural space may again be entered.

When treating spinal fractures, the exposure needs to provide access to the vertebral body above and below the fractured vertebra to allow for instrumentation. Typically, the body of T12 can be reached by mobilizing the left crus of the diaphragm from the retroperitoneum. The thoracic cavity may be entered cephalad to the diaphragm if more superior exposure is necessary, as is typical for the T11 level. In this case, dissection can be carried out above and below the diaphragm without division of the diaphragm. The lateral aspect of the vertebral bodies can then be obtained by lateral retraction of the psoas muscle. Segmental vessels are frequently encountered and require division with ligation or cautery. Exposure of the spine at these levels for adequate

decompression and fixation typically requires a lateral approach, and the anterior portion of the vertebral body is not exposed. The level is then confirmed fluoroscopically, and the instrumentation is then performed. Once the spine is treated, the crus and the diaphragm will be repaired. A chest tube can be placed, or the pleural cavity can be aspirated as the closure is performed.³⁴ The fascia is then closed in layers.

Improving Resident Training

The increasing use of laparoscopic and endovascular procedures has made open surgery less common than in the past. As endovascular aneurysm repair has become widespread, surgery trainees have less experience with exposure of the aorta and iliac vessels. Anterior retroperitoneal spine exposure offers an opportunity to increase the experience of surgeons in training in open surgery. This applies not just to vascular trainees but also those in general surgery, urology, and gynecology who may all benefit from this experience. Trauma surgeons may infrequently encounter difficult pelvic venous injuries, and experience in elective treatment in a nonstressful environment will add to more confidence. All of this experience can be gained while ensuring patient safety in the performance of anterior spine exposures.

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34 AORTIC DISSECTION

Mark F. Conrad, MD, MMSc, and Richard P. Cambria, MD

Acute aortic dissection is the most common catastrophic event affecting the aorta. However, its overall prevalence is rare, occurring in three of every 1,000 patients who present to the emergency department with chest and/or back pain.¹ Acute aortic dissection is a lethal disease: early studies showed that in the absence of treatment, the majority of patients died within 3 months of presentation. Reported mortality rates of untreated patients approached 75% within the first 2 weeks after the onset of symptoms.² Few survived the chronic phase more than 5 years as a result of progressive aneurysmal degeneration and rupture of the outer wall of the false lumen.^{3,4} Despite improvements in both medical and surgical therapies, overall mortality associated with acute dissection in contemporary practice remains significant: mortality was 27% in a recent report from the International Registry of Acute Aortic Dissections (IRAD).⁵ Early death attributable to an acute dissection of the ascending aorta is usually secondary to the central cardioaortic complications of aortic rupture into the pericardium, acute aortic regurgitation, and coronary ostia compromise,^{6,7} whereas descending aortic dissections are more commonly associated with death from end-organ compromise attributable to visceral or extremity malperfusion.^{8,9}

General Features

CLASSIFICATION

Aortic dissections are classified according to the anatomic location of the entry tear and the time between onset of symptoms and patient presentation. A dissection is considered acute when the diagnosis is made within 2 weeks of the initial onset of symptoms and thereafter becomes chronic. Although such a designation appears arbitrary, it is based on autopsy studies that showed that 74% of patients who die from aortic dissections do so in the first 14 days.¹⁰

Anatomically, aortic dissection is classified based on the location of the intimal tear and the extent of the dissection along the aorta. Two classification schemes are used to describe aortic dissections. The DeBakey classification delineates both the origin of the entry tear and the extent of the descending aortic dissection as follows [see Figure 1].¹¹

- Type I: dissection originates in the ascending aorta and extends through the aortic arch and into the descending aorta and/or abdominal aorta for a varying distance
- Type II: dissection originates in and is confined to the ascending aorta
- Type IIIa: dissection originates in the descending aorta and is limited to the same
- Type IIIb: dissection involves descending and variable extents of the abdominal aorta

The Stanford classification simplified the anatomic classification according to the origin of the entry tear alone. A

Stanford type A dissection originates in the ascending aorta and therefore encompasses DeBakey type I and II dissections, whereas a Stanford type B dissection originates in the descending aorta distal to the origin of the left subclavian artery and includes DeBakey types IIIa and IIIb [see Figure 1].

INCIDENCE AND EPIDEMIOLOGY

Recent population-based studies have estimated the incidence of acute aortic dissection to range from 2.9 to 3.5 per 100,000 person-years.^{12,13} Men are more frequently affected, with a male-to-female ratio of 4:1 reported in a recent IRAD series.¹⁴ In our cumulative experience, type A dissections account for 60% of cases, and this is consistent with the IRAD data, wherein 62.5% of 1,417 patients presented with a type A dissection.¹⁵ The incidence of type A dissection peaks between 50 and 60 years of age, whereas type B dissections occur more frequently in older patients, between 60 and 70 years of age.⁵

Hypertension is common and was present in 70% of patients in the IRAD database [see Table 1].¹⁴ Aortic wall structural abnormalities and the presence of a bicuspid aortic valve with or without its accompanying aortic root dilatation are well-established risk factors for ascending aortic dissections. Indeed, the presence of a bicuspid aortic valve has been documented in 7 to 14% of all aortic dissections.^{5,16} Other aortic diseases, such as coarctation of the aorta, annuloaortic ectasia, chromosomal abnormalities (Turner syndrome, and Noonan syndrome), aortic arch hypoplasia, and hereditary conditions (Marfan syndrome and Ehlers-Danlos syndrome), are also risk factors for the development of acute aortic dissection.¹⁷ Marfan syndrome accounts for 50% of cases of acute aortic dissection in patients under 40 years of age.¹⁴

It has been previously reported that in women under 40 years of age, 13 to 50% of aortic dissections occur during pregnancy.^{14,18} Preeclampsia with resultant hypertension is the most common etiology of peripartum aortic dissection, but pregnant women with Marfan syndrome are also at high risk. The presence of a dilated aortic root (>4 cm) is the best predictor of dissection in the pregnant patient with Marfan syndrome.¹⁹ Cocaine ingestion is a rare cause of acute aortic dissection in otherwise healthy individuals, with an incidence as high as 37% in an urban setting but less than 1% in the IRAD population.^{14,20,21} These patients are typically young (average age 47 years), male (75%), and smokers (100%) with a history of hypertension (70%) and no particular trend toward dissection type.²¹

Pathologic Anatomy

INTIMAL TEAR

The process of aortic dissection is dynamic and can occur anywhere along the course of the aorta, resulting in a wide

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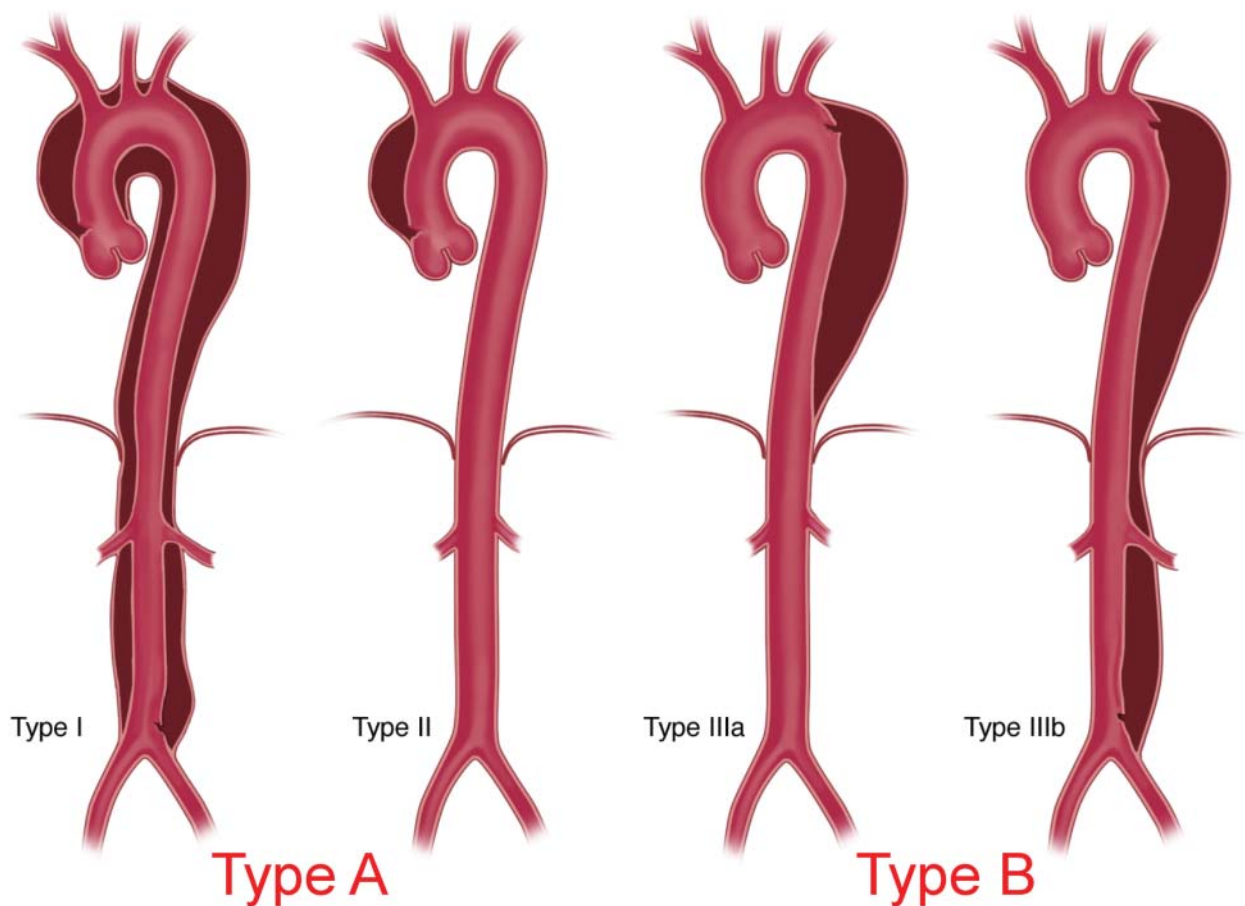


Figure 1 Acute aortic dissection can be classified by the original DeBakey system (*black*) based on the location of the proximal tear and distal extent of the dissection flap or by the Stanford system (*red*), which uses the location of the proximal tear alone.

spectrum of clinical manifestations. The pathognomonic lesion is one of an intimal tear followed by blood surging either antegrade (typically) or retrograde (depending on the hemodynamic gradient between the true and false lumina) and cleaving the intima and media layers of the aortic wall longitudinally for a variable distance.^{22,23} The typical tear is transverse, not circumferential, but the intimomedial layer can be cleaved both longitudinally and circumferentially.²² The adventitially bound, blood-filled space created between the dissected layers of the aortic wall becomes the false

lumen. Fenestrations (connections between the true and false lumina) occur within the intimal flap downstream, usually at branch vessel ostia, which are cleaved by the dissection process: these serve as sites of reentry of blood flow into the true lumen, thus maintaining false lumen patency. The presence of an “intimal flap,” representing the intimomedial septum between the true and false lumen, is the most characteristic pathology in acute aortic dissection. The origin of the intimal flap or tear is in the ascending aorta in 65%, in the descending aorta in 25%, and in the arch or abdominal

Table 1 Demographic and Clinical Features of Combined MGH and IRAD Experience with Acute Aortic Dissection			
Variable	MGH, n (%) ⁸	IRAD, n (%) ²⁷	Total, n (%)
Patients	512	1078	1590
Age, yr (mean)	62	62.4	
Male	347 (67.8)	732 (67.9)	1,079 (67.9)
Type A	278 (54)	674 (62.6)	952 (60)
Hypertension	361 (70.5)	755 (71.8)	1,116 (70.2)
VC/pulse deficit	159 (31)	259 (27.7)	418 (26.3)

IRAD = International Registry of Acute Aortic Dissections; MGH = Massachusetts General Hospital; VC = vascular complication.

aorta in 10% of patients.⁵ In the descending aorta, the intimal tear typically originates within a few centimeters of the left subclavian artery because this segment of the aorta is subject to the greatest fluctuations in left ventricular pressure.^{2,10,24} In the usual pattern of a Stanford type B dissection, the cleavage plane will progress with the distal false lumen on the left posterolateral aspect of the aorta (80% of patients); the celiac, superior mesenteric, and right renal arteries typically emanate from the true lumen, and the left renal artery arises from the false lumen [see Figure 2].¹⁰ It is to be emphasized, however, that variations in this pattern are frequently encountered.

ASSOCIATED PROCESSES

One pathologic process that is associated with increased risk of aortic dissection is medial degeneration of the aortic wall (cystic medial necrosis) that diminishes the structural integrity (collagen and elastin fibers) of the aortic layers.²⁴⁻²⁶ This process appears to be an essential feature of several hereditary conditions, such as Ehlers-Danlos syndrome and Marfan syndrome.¹⁷ Although specific connective tissue diseases account for only 10 to 15% of all acute aortic dissections, the degree of medial degeneration in otherwise normal patients with aortic dissection is greater than that of age-matched controls.⁵ Atherosclerosis has not been

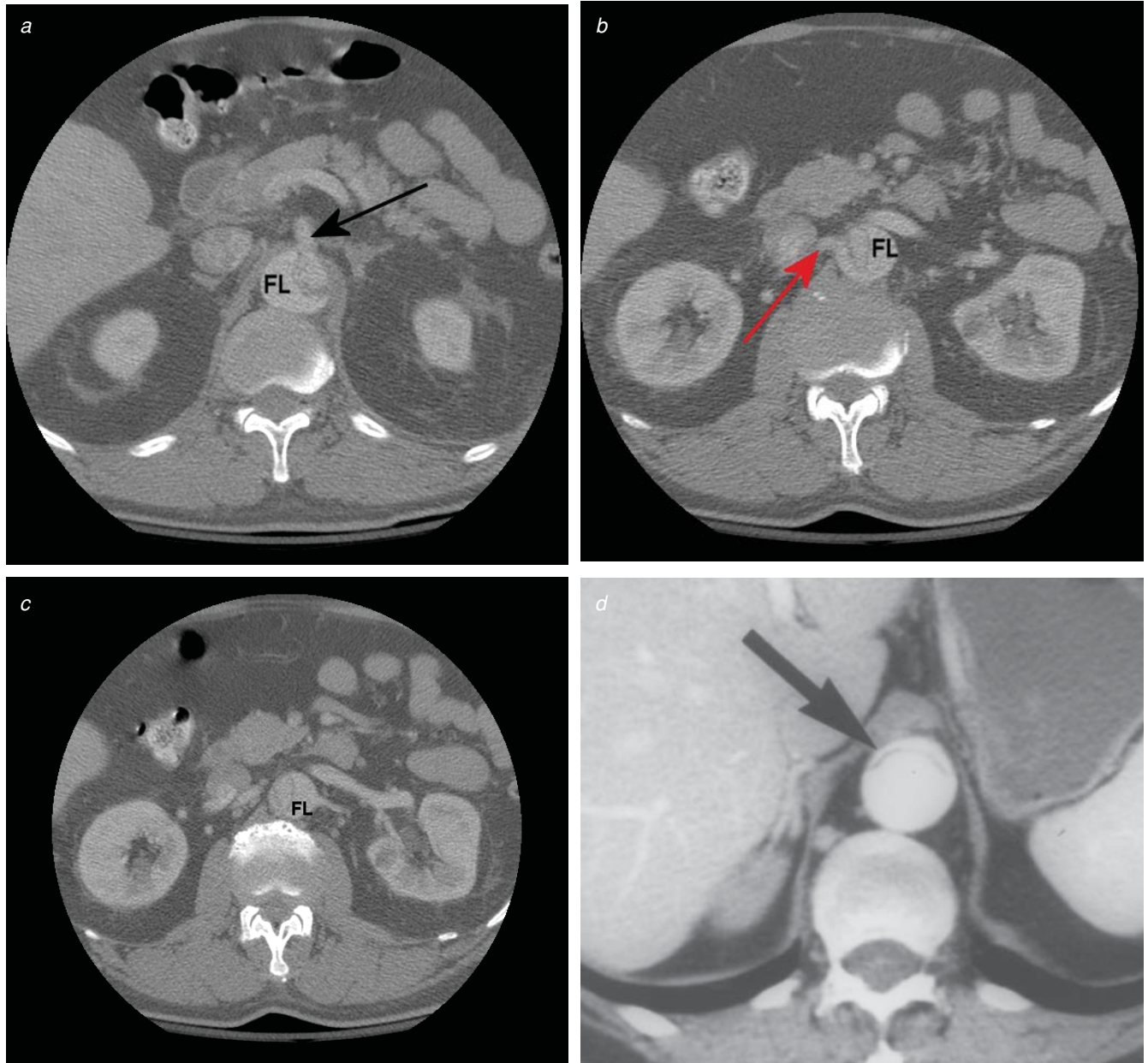


Figure 2 Computed tomographic angiogram findings of acute aortic dissection. (a) Axial image of aortic dissection with the superior mesenteric artery arising from the true lumen (*black arrow*). (b) Axial image of aortic dissection with the right renal artery (*red arrow*) arising from the compressed true lumen. (c) Axial image of aortic dissection with the left renal artery originating from the false lumen. (d) Axial image of aortic dissection with compressed true lumen (*thick arrow*). FL = false lumen.

considered to be an important etiologic feature of acute aortic dissection and was present in only 31% of patients in the IRAD.²⁷ However, Jex and colleagues noted either gross or microscopic atheroma in 83% of patients in their series.²⁸ The presence of an atherosclerotic aneurysm presenting with concurrent aortic dissection is uncommon, occurring in only 14 to 15% of patients in recent series.^{27,29} The unusual coexistence of an aortic dissection that originates in and/or involves a preexistent atherosclerotic aneurysm appears to change the natural history; rupture is the likely scenario. To wit, in a review of 325 patients with aortic dissection, rupture in the abdomen occurred only in the setting of antecedent degenerative, atherosclerotic aneurysm.³⁰ These findings support the posture of treating such type B dissections as “complicated,” and initial surgical priority should be given to the aorta where both entities are present (usually the infrarenal abdominal aorta).

Malperfusion Syndromes

Malperfusion syndrome occurs when there is end-organ ischemia secondary to aortic branch compromise from the dissecting process. This can involve one or more vascular beds simultaneously. Early symptoms are often subtle and of varying severity over the hours and days after the initial onset of symptoms. Consistent over several series, aortic branch compromise is present in up to 31% of patients with acute aortic dissection,^{9,27,31,32} with progression to the malperfusion syndrome correlating with early mortality.^{8,9,27} Virtually any aortic branch can be affected, and as intuitively suspected, the morbid clinical events will vary as a function of the vascular territory involved.

Identifying the mechanisms of branch compromise is a critical step in formulating effective treatment plans. The anatomic and physiologic variables underpinning any compromised vascular bed include (1) the percentage of aortic circumference dissected, (2) the presence of a distal reentrant focus in the false lumen or true lumen outflow, and (3) the topography of branch ostia to the true versus the false lumen.⁶ In the minutes after an aortic dissection is initiated, the true lumen (representing the remnant of the original aortic lumen) collapses to a variable degree and the false lumen expands.³³ The adventitially bound outer wall of the false lumen must expand to a larger diameter to accommodate the same wall tension at a given blood pressure, as governed by the law of LaPlace. In contrast, the true lumen, which contains the majority of the elastic components of the aortic wall, undergoes radial elastic collapse.³³ Therefore, the degree to which the true lumen recoils and the false lumen expands (i.e., their respective cross-sectional area) is dependent on the percentage of the total aortic circumference involved with the dissection. In the presence of a deep proximal tear and the absence of distal fenestrations, the mean false lumen pressure increases, leading to compression of the true lumen³⁴ [see Figure 2]. A compressed true lumen will lead to impaired perfusion of distal structures and should increase the index of suspicion for visceral and renal ischemia. Two mechanisms for aortic branch vessel compromise have been identified, each of which has specific treatment implications in the management of malperfusion syndromes.³³

DYNAMIC OBSTRUCTION

In dynamic obstruction, the dissection flap prolapses into the vessel ostium and impedes blood flow with each cardiac cycle [see Figure 3]. This is the more common mechanism of branch compromise and is responsible at least in part for some 80% of malperfusion syndromes.³⁵ The severity of the true lumen collapse and the degree of aortic-level ostial vessel occlusion are determined by the circumference of the dissected aorta, cardiac output, blood pressure, heart rate, and peripheral resistance of the outflow vessel.³⁶ Pulse deficits based on dynamic obstruction may wax and wane over time because of variability in the aforementioned

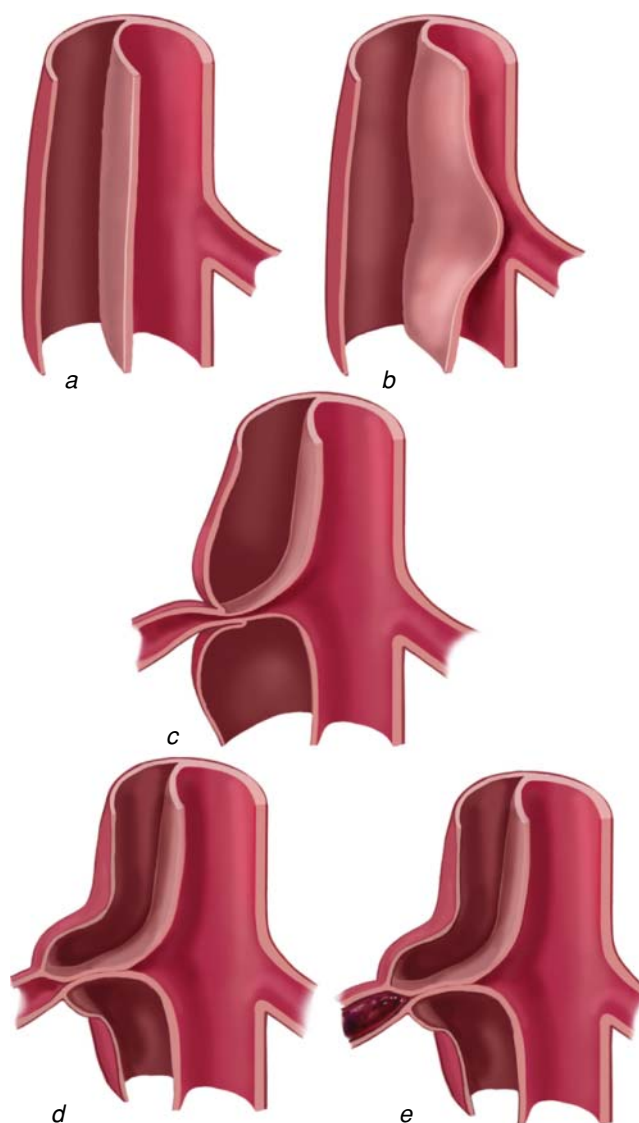


Figure 3 Mechanisms of aortic branch obstruction in acute dissection. (a and b) In dynamic obstruction, the septum may prolapse into the vessel ostium during the cardiac cycle, and the compressed true lumen flow is inadequate to perfuse branch vessel ostia, which remain anatomically intact. (c, d, and e) Near-complete circumferential dissection with static obstruction; the cleavage plane of the dissection extends into the ostium and compromises inflow. Thrombosis beyond the compromised ostia may further worsen perfusion.

factors.^{6,37} Chung and colleagues modeled the anatomy and physiologic conditions of a Stanford type B aortic dissection in vitro and concluded that the movement of the dissection flap to produce dynamic obstruction of any branch vessel is related to the size of the entry tear, the limitation of false lumen outflow, and increased true lumen outflow produced by falling peripheral resistance.³⁶

STATIC OBSTRUCTION

In acute dissection, the false lumen is highly thrombogenic as a result of the exposed adventitial and medial layers. Thrombus formation may occur in the blind end of the dissection column; more often, “reentrant” foci maintain false lumen flow.³⁸ If the blind end or the propagating end of the dissection column enters and constricts the ostia of a branch vessel, organ injury can occur by thrombosis or hypoperfusion of the involved vessel. This mechanism for malperfusion syndrome involves the dissecting process extending into the branch vessel proper, narrowing it to a variable degree, and has been termed *static obstruction*.³⁵ This obstruction is unlikely to resolve with restoration of aortic true lumen flow alone, and some manipulation of the vessel itself (e.g., stent, bypass graft) will typically be required [see Figure 3].

Clinical Presentation

PAIN

The most common presenting symptom of acute aortic dissection is pain (located in the back, abdomen, or chest), reported in over 93% of patients, with 85% specifying an abrupt onset.^{5,39} Whereas the pain is typically described as anterior in location in type A dissections, for type B dissections, pain is more often experienced in the back (78% versus 64%, respectively).^{5,16} The classic presentation of an “acute aortic syndrome” is severe chest or back pain that causes the patient to seek medical attention within minutes to hours of onset and has been described as “the worst ever” by nearly 90% of patients.⁵

HYPERTENSION

On initial physical examination, arterial hypertension is present in 70% of type B dissections but only in 25 to 35% of type A dissections. The presence of hypotension complicating a type B dissection is rare (<5% of patients) but may be present in 25% of dissections that involve the ascending aorta, potentially as a result of aortic valve disruption or cardiac tamponade.⁵ The malperfusion of brachiocephalic arteries by the dissection may falsely depress brachial cuff pressures.⁴⁰ Hypertension that is refractory to medical management is common in type B dissections, occurring in 64% of patients.⁴¹ However, as this refractory hypertension is usually not associated with renal artery compromise or aortic dilatation, continued medical management is warranted.

PERIPHERAL VASCULAR COMPLICATIONS

Peripheral vascular complications are common and occur in 30 to 50% of patients in whom the aortic arch and/or the

thoracoabdominal aorta is involved.^{9,31,32} In patients with peripheral vascular complications not involving the ascending aorta, the brachiocephalic trunk is involved in 15% patients, the common carotid arteries in 20%, the left subclavian artery in 15%, and the iliofemoral arteries in 35%.^{9,42} In this population, mortality is clearly linked to the number of pulse deficits at the time of presentation. Indeed, within the first 24 hours, the mortality increases from 9.4% in patients with no deficits to 35.3% in patients with three or more deficits.⁴² Although it is uncommon for isolated lower extremity pulse deficits to cause mortality as a result of lower extremity ischemia or its sequelae, leg ischemia remains a marker of extensive dissection.⁹

OTHER COMPLICATIONS

Syncope may complicate the presentation of acute aortic dissection in 5 to 10% of patients, and its presence often indicates the development of cardiac tamponade or involvement of the brachiocephalic vessels.⁴³ Overall, patients in the IRAD who presented with syncope were more likely to have a type A dissection than a type B (19% versus 3%, $p < .001$), more likely to have cardiac tamponade (28% versus 8%, $p < .001$), and more likely to die in the hospital (34% versus 23%, $p = .01$).⁴⁴ Spinal cord ischemia from the interruption of intercostal vessels is clearly more common with type B aortic dissections, occurring in 2 to 10% of all patients.⁴⁵ In addition, direct compression of any peripheral nerve can occur, albeit rarely, resulting in paresthesia (lumbosacral plexopathy), hoarseness of voice (compression of recurrent laryngeal nerve), or Horner syndrome (compression of sympathetic ganglion).^{46–48}

Diagnosis

In the United States, acute chest pain is the chief complaint in 8.2% of all emergency department visits. This translates to almost 4.6 million patients annually.⁴⁹ The majority of these patients do not have an aortic dissection, and it would be inefficient, unrealistic, and costly to obtain axial imaging on all patients with acute chest pain. Indeed, the indiscriminate application of thoracic imaging to patients with a low pretest probability of having an aortic dissection has been predicted to yield an 85% false positive rate.⁵⁰ However, aortic dissection often affects younger patients (in their 50s) and thus is often not readily apparent. Indeed, physicians correctly suspect the entity in only 15 to 43% of presentations as aortic dissection is often identified as an incidental finding during evaluation of another pathologic process.^{13,51} A recent review of the IRAD population showed that the average time between presentation and confirmation of the diagnosis was 24 to 34 hours depending on the patient’s age.¹⁴ This underscores the importance of clinical suspicion for early identification, and aortic dissection should be considered in patients who present with persistent chest pain, a normal chest x-ray, and a negative cardiac workup.

IMAGING

The goal of imaging is to first confirm the diagnosis of acute aortic dissection and then determine the extent of dissection, the potential involvement of branch vessels, and the presence of immediate life-threatening complications,

such as tamponade. Historically, retrograde aortography was considered the reference standard in the evaluation of acute aortic dissection. However, the improvement of other techniques, such as contrast computed tomographic angiography (CTA), transesophageal echocardiography (TEE), and magnetic resonance imaging (MRI), has shifted the role of aortography from diagnostic to adjunctive during endovascular management. An evaluation of the IRAD data showed that worldwide from 1996 to 1999, CTA was the initial test performed in 63% of patients and 75% underwent CTA as part of the workup.⁵² TEE was also routinely used (72%), although it was the first test obtained in only 32% of patients. More than two thirds of patients required two or more imaging tests, with MRI (19%) and aortography (19%) used with the same frequency.⁵²

COMPUTED TOMOGRAPHIC ANGIOGRAPHY

CTA has become the test of choice for the identification and characterization of acute aortic dissections. It is readily available and noninvasive and has a reported sensitivity of 83 to 95% and a specificity of 87 to 100% for the diagnosis of acute aortic dissection.^{53–55} The chief limitation of CTA is the ascending aorta, where the sensitivity may drop to less than 80%, but this is readily overcome by the addition of TEE.⁴⁰ A dedicated protocol to image the entire aorta is usually sufficient to provide the necessary diagnostic information. A helical CT dissection protocol will give excellent aortic imaging of the true and false lumina, approximate entry tear sites, and aid in planning intervention. In most cases, the true lumen may be localized by its continuity with an undissected segment of the aorta.⁵⁶ However, in circumferential dissection of the aortic root or when imaging of the aortic arch is omitted, this rule may be difficult to apply. The finding of greatest significance is that in the descending thoracic aorta, the false lumen is larger than the true lumen in over 90% of cases ($p < .05$).⁵⁶ As displayed in Figure 2, a slitlike, compressed true lumen is perhaps the key radiographic finding that should substantially raise the index of suspicion for renal/visceral/lower extremity malperfusion syndrome.

Three-dimensional computed tomographic (CT) scan reconstructions can aid treatment planning, but axial imaging affords the best opportunity to detect topographic relations of the true and false lumina and potential aortic branch compromise. Although it is appropriate to operate on acute type A dissections based on CT findings alone, the IRAD data show that most patients undergo preoperative CT (71%) and TEE (77%) (either preoperative or intraoperative) in circumstances where the clinical and/or laboratory signs dictate the need for urgent revascularization.⁵⁷ In comparison with other modalities, CT scanning is the least operator dependent, provides useful anatomic correlates for surgical and endovascular therapy, and most reliably collects information for follow-up analysis and measurement.

ECHOCARDIOGRAPHY

The sensitivity of TEE has been reported to be as high as 98%, and the specificity ranges from 63 to 96%.^{58–60} The advantages of TEE include wide availability, ease of use, and bedside capability. In addition, TEE possesses the ability to detect entry tear sites, false lumen flow or thrombus,

involvement of the arch or coronary arteries, degrees of aortic valvular regurgitation, and pericardial effusions. The addition of color flow Doppler patterns may decrease false positive results by recognizing differential flow velocities in the true and false lumina.⁶¹ The chief limitation of TEE is the anatomic blind spot in the distal ascending aorta and arch secondary to the air-filled trachea and left mainstem bronchus and inability to document dissection extension beyond the diaphragm.⁶² Despite these shortcomings, TEE can be particularly useful in delineating dissection and relevant surgical pathology in the ascending aorta and therefore is chiefly applied in this territory.⁶³ Moreover, in the unstable patient with a suspected acute dissection in the ascending aorta, TEE may be performed in the operating room to expedite diagnosis and definitive therapy.

OTHER IMAGING

Plain chest radiography is often the first imaging study obtained during the workup of acute chest pain, but the findings of aortic dissection on chest radiography are non-specific and never diagnostic. These include widening of the cardiac or aortic silhouette, displacement of aortic calcifications, and effusions.^{5,16} However, in many cases, the initial chest film is negative. Aortography, although rarely used for diagnosis, has a sensitivity of 86 to 88% and a specificity of 75 to 94% for the diagnosis of thoracic aortic dissection, but false negative angiograms can occur when the false lumen has thrombosed.^{64–67} The aortographic findings considered supportive of a diagnosis of aortic dissection include distortion of the normal contrast column, flow reversal or stasis into a false channel, failure of major branches to fill, and aortic valvular regurgitation.⁶⁶

MRI has an overall sensitivity and specificity for diagnosis of aortic dissection in the range of 95 to 100%.^{52,68,69} MRI can detect the site of the entry tear, the extent of the dissection, potential branch vessel involvement, and differential true versus false lumen flow. The overall sensitivity and specificity for diagnosis of branch vessel involvement are 90% and 96%, respectively.⁷⁰ The chief limitations of MRI include lack of immediate availability, long examination times, and lack of monitoring for critically ill patients. In addition, patients who have had pacemakers, aneurysm clippings, or ocular implants are not candidates for MRI.

Treatment

Optimal treatment of acute dissection is predicated on timely diagnosis and a thorough understanding of the anatomic extent of the pathology. Prompt institution of intravenous antihypertensive medications to lower systemic blood pressure and pulse (dP/dT) is a key element of initial therapy for all patients, with the goal of stabilizing the extent of the dissection, reducing intimal flap mobility, relieving dynamic aortic branch obstruction, and decreasing the risk of rupture. Mortality in the acute phase of a proximal dissection may exceed 1% per hour related to the central cardioaortic complications of tamponade, acute aortic valvular insufficiency, and coronary obstruction. Thus, prompt ascending aortic graft replacement with or without aortic valve repair or replacement is the treatment of choice for the majority of patients with acute type A aortic dissection.

For patients with type B dissections, the catastrophic complication of rupture is uncommon, except in those patients who present with advanced false lumen dilatation or the equivalent of aneurysm formation at the aortic entry site.⁶ Furthermore, in patients with uncomplicated type B dissections, surgical therapy (i.e., graft replacement of the aortic entry tear site) has not demonstrated superiority over medical or interventional therapy for stable patients, whereas those with malperfusion usually require urgent intervention.³⁹

MEDICAL MANAGEMENT

Currently, medical management in an intensive care unit is the initial therapy for virtually all patients with the tentative diagnosis of aortic dissection. The immediate management of acute aortic dissection is directed toward reducing the hemodynamic forces that have initiated and propagated the intimal tear and cleavage of the aortic wall. The goal of medical therapy is to reduce systolic blood pressure and dP/dT and thereby reduce the forces predisposing the dissected aorta to rupture or compromise of branch vessels.⁴⁰ Intravenous antihypertensive therapy should be started in all patients in whom acute aortic dissection is suspected, with the exception of those with hypotension.⁴⁰ For those patients with hypotension in the setting of acute dissection, an expeditious evaluation for tamponade is warranted, but percutaneous pericardiocentesis as a temporizing measure is not advised as it often accelerates bleeding or shock.⁷¹ In contemporary practice, a combination of a beta blocker and a vasodilator is standard medical therapy. In addition, the beta blocker should be initiated before the direct vasodilator (i.e., sodium nitroprusside); otherwise, the reflex sympathetic stimulation from direct vasodilation will stimulate catecholamine release and resultant increases in dP/dT, opposite of the desired effect. Once the patient's blood pressure has been controlled to a systolic of 105 to 120 mm Hg (or a mean of 60 to 70 mm Hg) and the pain has resolved, the patient can be transitioned to oral antihypertensive medications. Patients who are managed medically should be followed with serial surveillance CT scanning because during the first 4 to 7 years after acute aortic dissection, aneurysmal degeneration of the false lumen in the thoracic aorta may develop in 14 to 40% of patients treated with medical therapy alone.^{5,72,73}

OPEN SURGICAL TREATMENT OF TYPE A DISSECTIONS

A complete review of the surgical literature and state-of-the-art management of acute type A dissection is beyond the scope of this chapter. Medical therapy alone has been associated with a 60% in-hospital mortality in type A dissections, and urgent surgical repair is the treatment of choice unless major neurologic deficits or peripheral vascular complications of the dissection pose greater overall risk (i.e., visceral ischemia) than the threat of proximal rupture. However, following repair of the ascending thoracic aorta, 90% of patients who present with type A dissection and peripheral vascular compromise have resolution of their peripheral symptoms without additional vascular procedures.⁷⁴ In addition, patients who present more than 2 days after symptom onset have already survived the initial high-risk period and as many as half can be treated nonoperatively, with a trend toward improved long-term survival compared with those who undergo immediate operative intervention.⁷⁵

The type A dissection arm of the IRAD was recently used to develop a risk model to predict surgical mortality.⁵⁷ The authors reported an in-hospital mortality of 23.9% and identified age over 70 years, previous cardiac surgery, hypotension or shock at presentation, cardiac tamponade, any pulse deficit, and myocardial ischemia as independent predictors of poor outcome.

The anatomic goal of open repair is resection of the aortic intimal tear with graft replacement and reconstruction of the aortic wall layers in the distal anastomosis so as to eliminate false lumen flow [see Figure 4]. Persistent false lumen flow continues in many patients after ascending aortic graft replacement despite liberal use of circulatory arrest and technical adjuncts such as glue aortoplasty.⁷⁶

OPEN SURGICAL TREATMENT OF TYPE B DISSECTIONS

Threatened or actual rupture at the aortic intimal tear in the proximal descending aorta remains, in our view, the only indication for acute open graft replacement in distal dissection. Unless an extensive aneurysm is present, resection should be confined to the proximal descending aorta as mortality and spinal cord ischemia risk increase dramatically with extensive aortic replacement in the setting of an acute dissection.⁷⁷ Although the anatomic goal of central aortic replacement is reconstruction of the aortic wall layers in the distal anastomosis and obliteration of false lumen flow, 25 to 50% of patients with type B aortic dissections who are treated surgically can be expected to have persistent false lumen flow.^{78,79} Central aortic repair is less commonly performed in contemporary practice because of substantial surgical morbidity, the equivalent results of medical therapy in uncomplicated patients, and the variable success in relieving distal malperfusion. The mortality rate for the open repair of acute type B aortic dissection has ranged from 6 to 69% in several large series.^{80–84} In a recent IRAD review of 476 patients with type B dissection, 82 (17%) underwent open repair of the descending thoracic aorta, with a contemporary in-hospital mortality of 29.3%.⁸³ Given the variable results with open repair, it seems logical that thoracic endovascular aortic repair (TEVAR) will be preferred over open repair even in circumstances where the indication includes actual or threatened aortic rupture.

Although presently rarely indicated, central aortic graft replacement for type B aortic dissection presents significant technical challenges. To ensure anastomotic integrity, strips of polytetrafluoroethylene felt can be placed inside the true lumen and outside the aortic wall and sewn together with the aortic wall “sandwiched” in between.⁸⁵ In contradistinction, the introduction of glue aortoplasty is an important contribution to modern-day aortic dissection surgery. With the aorta transected and a sponge inserted in the true lumen to protect its diameter, the glue is applied for a length of 2 cm between the dissected layers, at a thickness of 2 mm. After 2 minutes, the aortic layers are fused and strengthened to accept a collagen-impregnated woven polyethylene terephthalate graft with a running polypropylene suture. The complexity of repair of the friable proximal aorta will lead to a prolonged cross-clamping time such that distal aortic perfusion with partial left heart bypass should be used to maintain visceral and spinal cord blood flow.

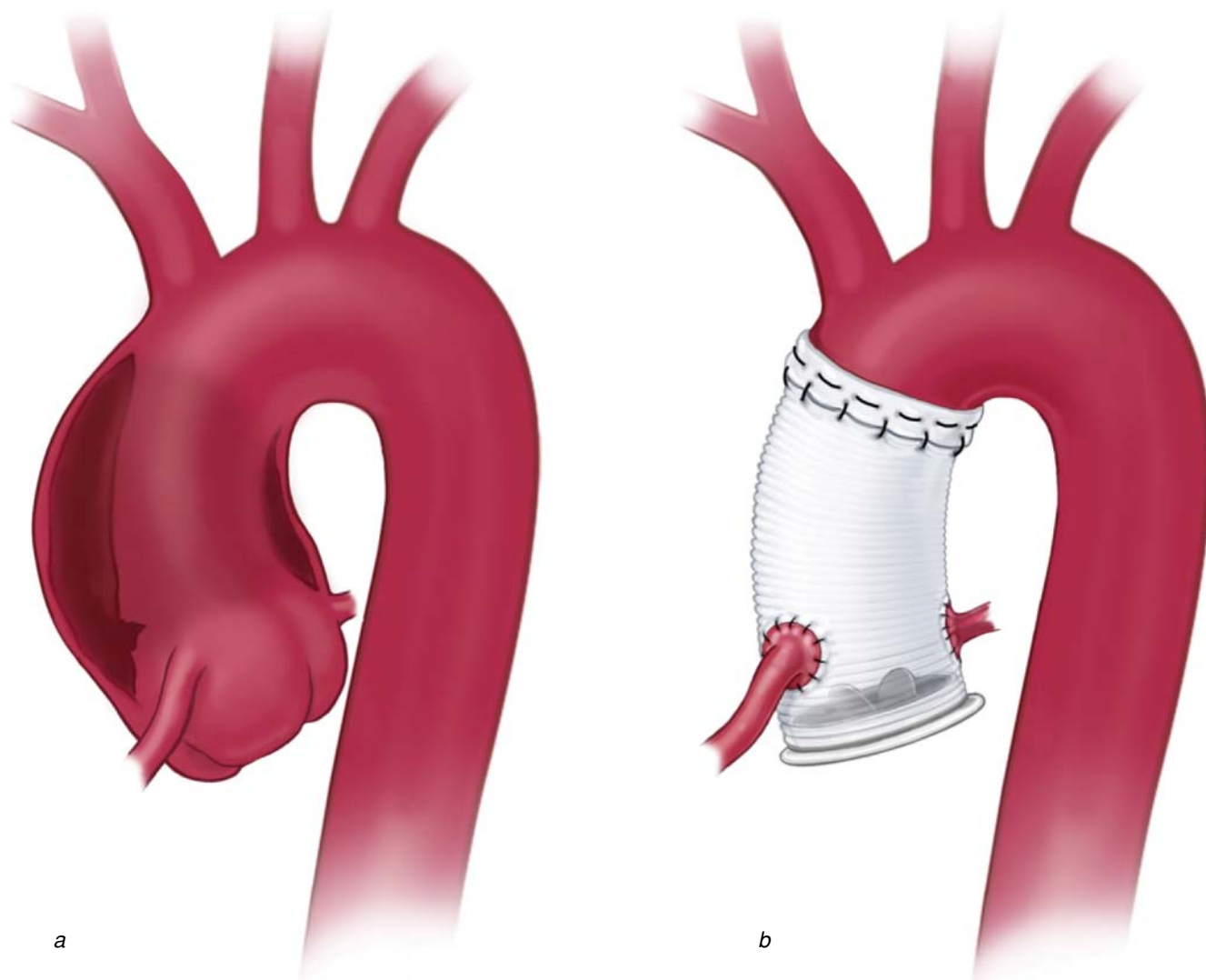


Figure 4 (a) Cartoon depiction of type A dissection limited to the ascending aorta. (b) Repair of type A dissection with replacement of the ascending aorta. Anatomic goals of replacement include (1) resection of aortic tear, (2) resuspension/repair or replacement of the aortic valve as necessary, (3) routine use of circulatory arrest to perform at least the distal anastomosis, and (4) reconstruction of the aortic layers so as to redirect flow into the true lumen and eliminate false lumen flow (this is successful only 50% of time).

ENDOVASCULAR TREATMENT OF AORTIC DISSECTION

Although medical therapy remains the current standard of care for uncomplicated type B aortic dissections, stent graft coverage of the aortic entry tear may ultimately prove to be the best solution to correct malperfusion syndromes in the acute phase and reduce late aortic-related complications by minimizing aneurysmal degeneration of the false lumen. When indicated, the goals of TEVAR for acute type B dissection include coverage of the proximal entry tear, expansion of the true lumen with restoration of flow to the visceral vessels, and obliteration of false lumen flow with subsequent complete thrombosis [see Figure 5]. When these components of therapy are successfully achieved, aortic remodeling should occur with subsequent prevention of future aneurysmal degeneration of the outer wall of the false lumen.

There are particular technical points of stent graft repair of aortic dissection that deserve emphasis. First, the placement

of uncovered stents over the entry tear within the proximal true aortic lumen is ill advised as this may lead to a retrograde dissection into the arch or ascending aorta.⁸⁶⁻⁸⁸ If a patient is to be considered a candidate for stent graft treatment, the location of the entry tear and proper recognition of the proximal zone of fixation are fundamental to procedural success, and the operator should have definitive knowledge of the three-dimensional aortic topography displayed on the preintervention CT scan prior to embarking on endovascular therapy. Endovascular repair of acute aortic dissection should be performed in an operating room with adequate fluoroscopic imaging. True lumen access should be obtained from either a brachial or femoral approach; typically, since the tear in type B dissection is distal to the left subclavian artery, rapid true lumen access is easily obtained through a right brachial approach. The proper true lumen position should then be confirmed

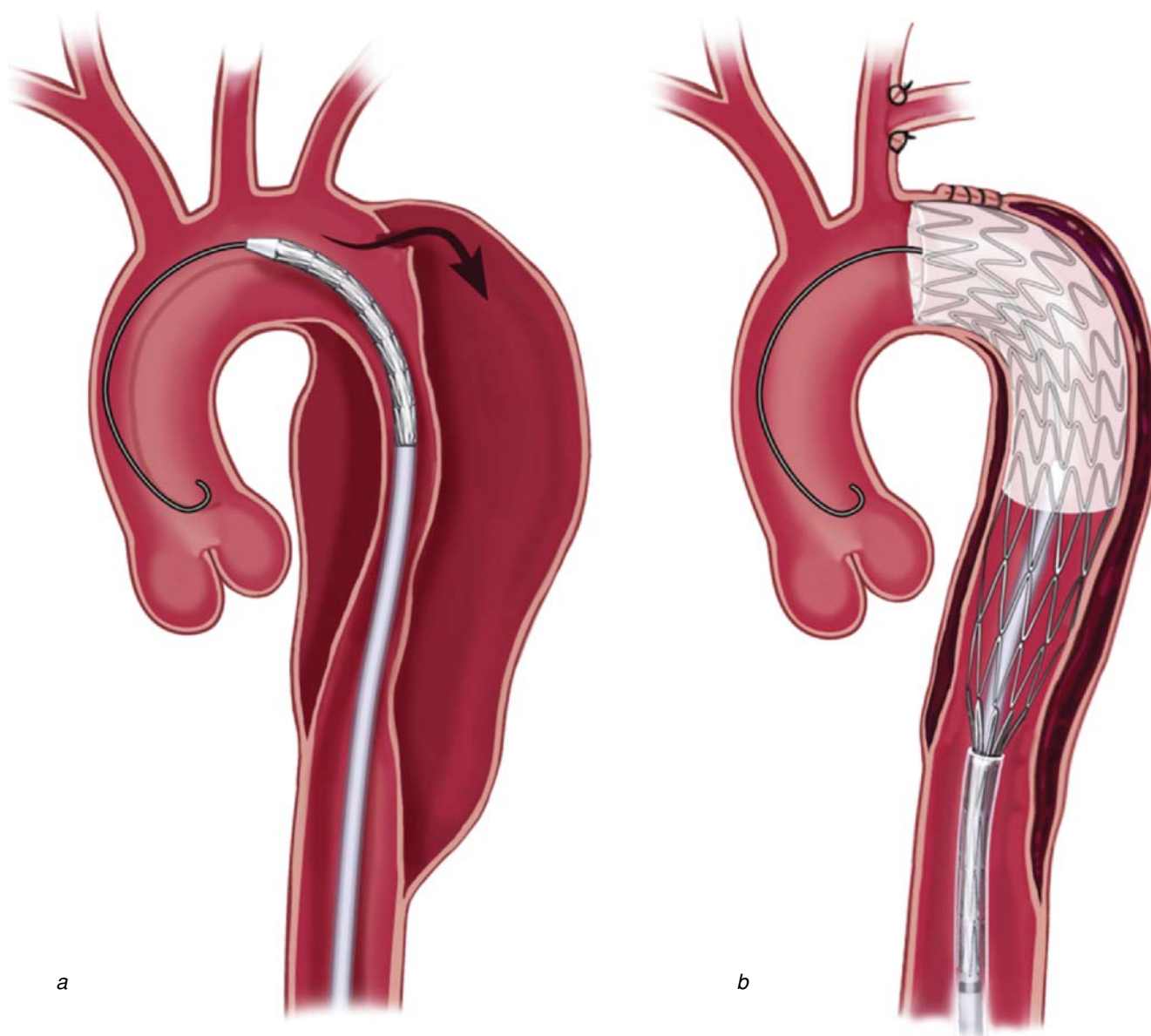


Figure 5 (a) Cartoon depiction of type B dissection with undeployed stent graft advanced to the level of the left carotid artery to ensure appropriate coverage of the entry tear. (b) Stent graft deployment to cover the proximal entry tear in the hope of inducing false lumen thrombosis and true lumen reexpansion. The latter should also alleviate “downstream” branch compromise caused by dynamic obstruction mechanisms. False lumen thrombosis in the thoracic aorta should, in theory, minimize subsequent aneurysmal expansion of the outer wall of the false lumen.

using intravascular ultrasonography to avoid inadvertent deployment of the stent in the false lumen [see Figure 6].

The Eurostar/United Kingdom registry report is the largest compendium of patients treated with thoracic aortic stent grafts to date.⁸⁹ In the combined registry, 131 patients with aortic dissection (5% proximal, 81% distal, 14% not classified) were treated with stent grafts; 57% had symptoms of rupture, aortic expansion, or side branch occlusion. Although no meaningful long-term data are available, primary technical success was achieved in 89% and 30-day mortality was 8.4%. Paraplegia occurred in 0.8% of those treated, and survival at 1 year after treatment was reported in 90% of 67 patients who had such follow-up.

A recent meta-analysis of stent graft repair for aortic dissection prior to 2005 identified 609 patients with a procedural success of 98.2%.⁹⁰ The 30-day mortality was 5.3% and was threefold higher in patients with acute dissection. The neurologic complication rate was 2.9%. A more recent review of the Nationwide Inpatient Sample (from 2005 to 2007) identified 5,000 patients who underwent repair of type B aortic dissections (3,619 open versus 1,381 TEVAR) and found that the TEVAR group had a significantly lower 30-day mortality (10.6% versus 19% for open repair).⁹¹

The Investigation of Stent-grafts in Aortic Dissection (INSTEAD) trial was a prospective, randomized, multicenter trial of stent grafting versus medical therapy for the treatment

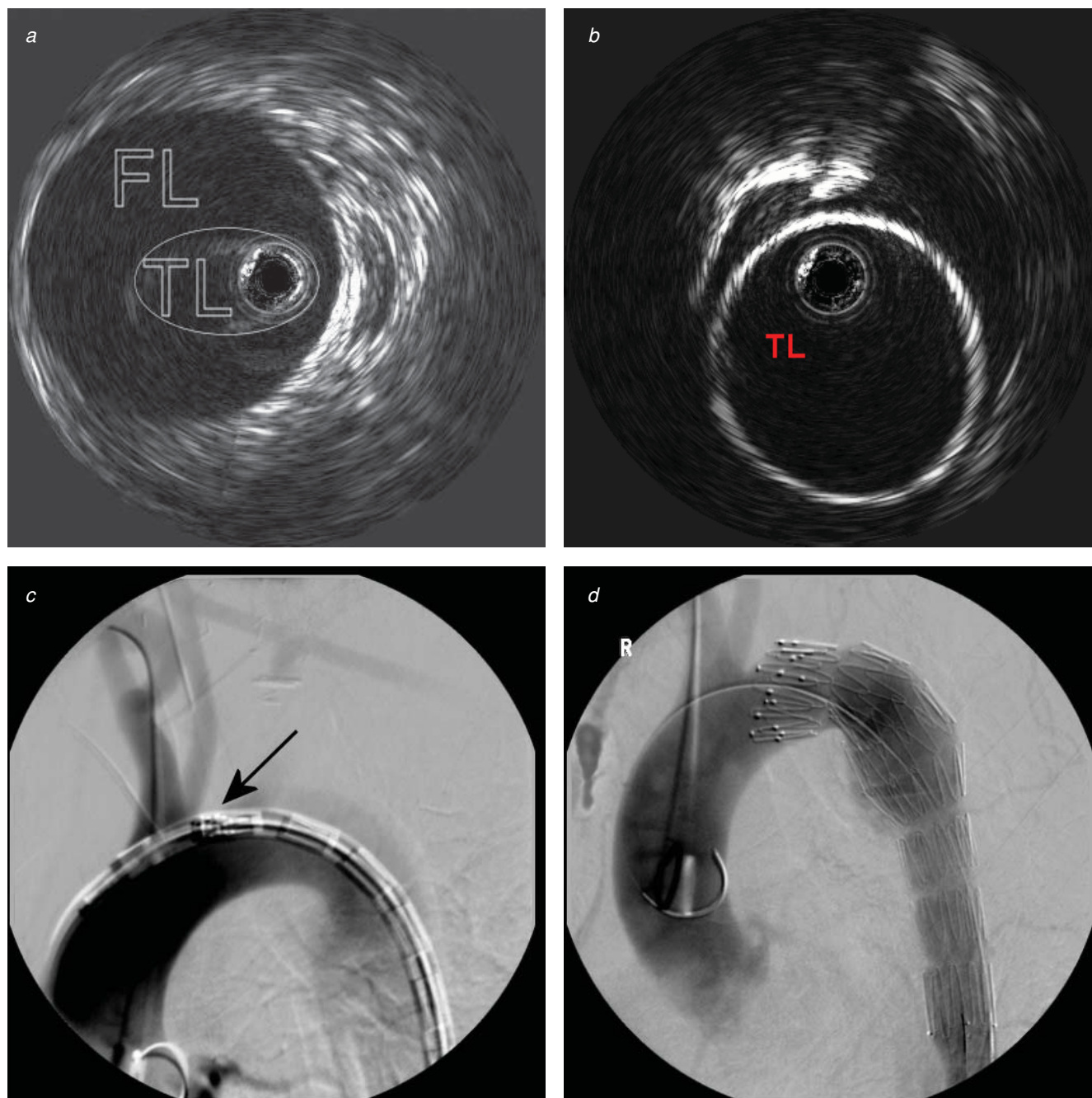


Figure 6 (a) Intravascular ultrasonography (IVUS) of acute type B dissection with “floating” true lumen (TL) that is enhanced by the circle. Endovascular repair of acute type B aortic dissection. (b) IVUS of expanded TL after endovascular repair of acute type B dissection. (c) Thoracic aortography showing the stent graft in the descending thoracic aorta. The proximal portion of the graft (*black arrow*) is placed at the level of the left common carotid artery, covering the left subclavian artery to obtain proximal seal in normal aorta. (d) Thoracic aortography showing stent graft deployed with obliteration of the proximal false lumen. FL = false lumen.

of chronic, uncomplicated type B aortic dissection that found no difference in mortality between the two treatment arms. However, the stent graft group achieved false lumen thrombosis in over 90% of patients at 1 year (significantly higher than the medically treated group). This is significant because false lumen thrombosis and true lumen expansion (so-called aortic remodeling) may be considered a surrogate for prevention of late aneurysm formation. In addition, a recent study of 33 patients with acute type B dissections treated

with TEVAR showed aortic remodeling at 1 year with a decrease in total aortic volume, an increase in true lumen diameter, and a decrease in false lumen diameter, with thrombosis occurring in 90% of patients.⁹²

These preliminary data suggest that stent graft repair may ultimately become the treatment of choice for the majority of patients with distal dissections; the available data consisting largely of registry and/or single-center retrospective reviews permit only the conclusion that stent graft repair

of the aortic entry tear can afford effective treatment of complicated type B dissections, with the inherent advantages of a minimally invasive approach. The use of stent graft repair in the treatment of acute dissections holds promise to reduce both early complications and the progression over time to aneurysmal degeneration. The instantaneous and dramatic occurrence of false lumen thrombosis by coverage of the aortic entry tear appears to be a key determinant in the process; the significance of small distal fenestrations remains unknown. Furthermore, early treatment in the window of acute type B dissection appears to be associated with improved technical outcomes, consistent with the hypothesis that true lumen or septum malleability may diminish in the chronic phase of the disease. However, the available data are insufficient to apply TEVAR to all acute type B dissections, and medical therapy remains first-line therapy in uncomplicated patients. Clearly, comparative clinical trials are needed to clarify the role of stent graft repair in acute distal dissections.

OTHER ENDOVASCULAR APPROACHES

Mossop and colleagues from Australia described their experience in 25 patients with a staged thoracoabdominal and branch vessel endoluminal repair.⁹³ Initial treatment involved endograft closure of the proximal entry tear and bare metal, self-expanding Z-stenting of the true lumen, thereby supporting the true lumen and stabilizing the dissection flap. At the 1-week follow-up, secondary reentry tears were then sealed by a variety of endovascular approaches, including placement of branch vessel covered stents, short segment covered aortic endografts, and coil embolization of the false lumen [see Figure 7]. In their series over 4 years, they reported no Z stent migration or stent-related intimal trauma resulting in rupture. Induction of false lumen thrombosis was achieved in 85%. Survival at a mean follow-up of 2.5 years was 100%.

PERCUTANEOUS FENESTRATION

Fenestration of the intimal flap may be performed by several techniques using the combination of ultrasonography and fluoroscopy. Most commonly, fenestration is performed from the smaller (usually the true lumen) to the larger false lumen. Using a Roesch-Uchida, Brockenborough, or Colopinto needle or the back end of a 0.014 wire, a fenestration is created close to the compromised aortic branch. After the needle and a stiff wire are advanced from the true to the false lumen, a 5 French catheter is advanced into the alternate lumen. Confirmation of the position across the membrane is performed by contrast injection. Subsequently, an angioplasty balloon of at least 12 to 15 mm in diameter and 20 to 40 mm in length is used to create a fenestration tear [see Figure 8].

An alternative technique of fenestration has been termed the “scissors technique.”⁹⁴ Stiff guide wires are placed in each lumen from a single femoral access. A single long sheath is advanced over the two wires, thus dividing the membrane over this distance. Those familiar with use of the scissors technique have reported both clean longitudinal tears (the ideal result) and circumferential separation of the flap from the aortic wall with aorto-aortic intussusception (not ideal).⁹⁵

Lastly, the use of a snare to deliver a wire from one femoral access through the flap and down the contralateral femoral access has been described. By pulling this “U” down the distal aorta, a fenestration defect may be created with the same potential risk of intimal dehiscence described above. In light of these dramatic and unpredictable alterations in intimal flap anatomy and flow dynamics incurred by overly aggressive fenestration in the visceral aorta, the investigators with the largest series of patients currently recommend that percutaneous fenestration be limited to the distal aorta.⁹⁶ The ideal hemodynamic result for fenestration of the dissected intima is realized when there is equalization of peak systolic pressures between the two lumina in the aorta and the false lumen is decompressed.^{36,97,98}

In a series of 40 patients with malperfusion syndromes, 14 patients underwent combined stenting and balloon fenestration, 24 underwent stenting alone, and two underwent fenestration alone.⁹⁶ The location of the balloon fenestration was in the thoracic aorta in eight patients, in the upper abdominal aorta in three patients, and just above the aortic bifurcation in seven patients. Flow was restored to the ischemic territories in 37 of 40 patients (93%), but the 30-day survival was 75%. In follow-up past the 30-day perioperative period, five additional patients expired, with one of these deaths related to false lumen rupture and two of unknown etiology. This 30-day death rate of 25% compares favorably with the historical surgical series wherein operative mortality was reported to be up to 50%.⁹⁹ However, contemporary surgical series have demonstrated substantially improved operative mortality, even for those patients with mesenteric compromise⁸; thus, it is worth emphasizing that mortality in such patients is more often referable to delayed diagnosis than the morbidity of the intervention itself.

The effect of fenestration on the long-term outcome of false lumen expansion in patients with distal dissections is unknown as the false lumen remains pressurized and therefore at risk for continued progression to aneurysm. Beregi and colleagues reported a series of 46 patients treated by either stent graft therapy ($n=12$) or balloon fenestration ($n=34$) for peripheral ischemic complications of acute aortic dissection and found that a decrease in aortic diameter occurred in patients treated with stent grafts, whereas the aortic diameter in those with balloon fenestration grew.¹⁰⁰ Indeed, it is likely that as further experience with TEVAR of the proximal entry tear is gained, fenestration and stenting of branch vessels will be used as an adjunct to stent grafting rather than definitive therapy.

OPEN SURGICAL REPAIR

Since dynamic obstruction at the aortic level is the most common mechanism of malperfusion syndromes, surgical fenestration has been the most commonly applied procedure.⁶ Because the threat of proximal aortic rupture is rare, many surgeons have favored a complication-specific approach in which the intervention is directed toward restoring flow to acutely affected organs.^{8,101} The fundamental technique of surgical fenestration is wide resection of the dissected septum to relieve aortic obstruction by equalizing flow between the true and false lumina [see Figure 9]. It may be desirable to extend the septectomy into the visceral segment,

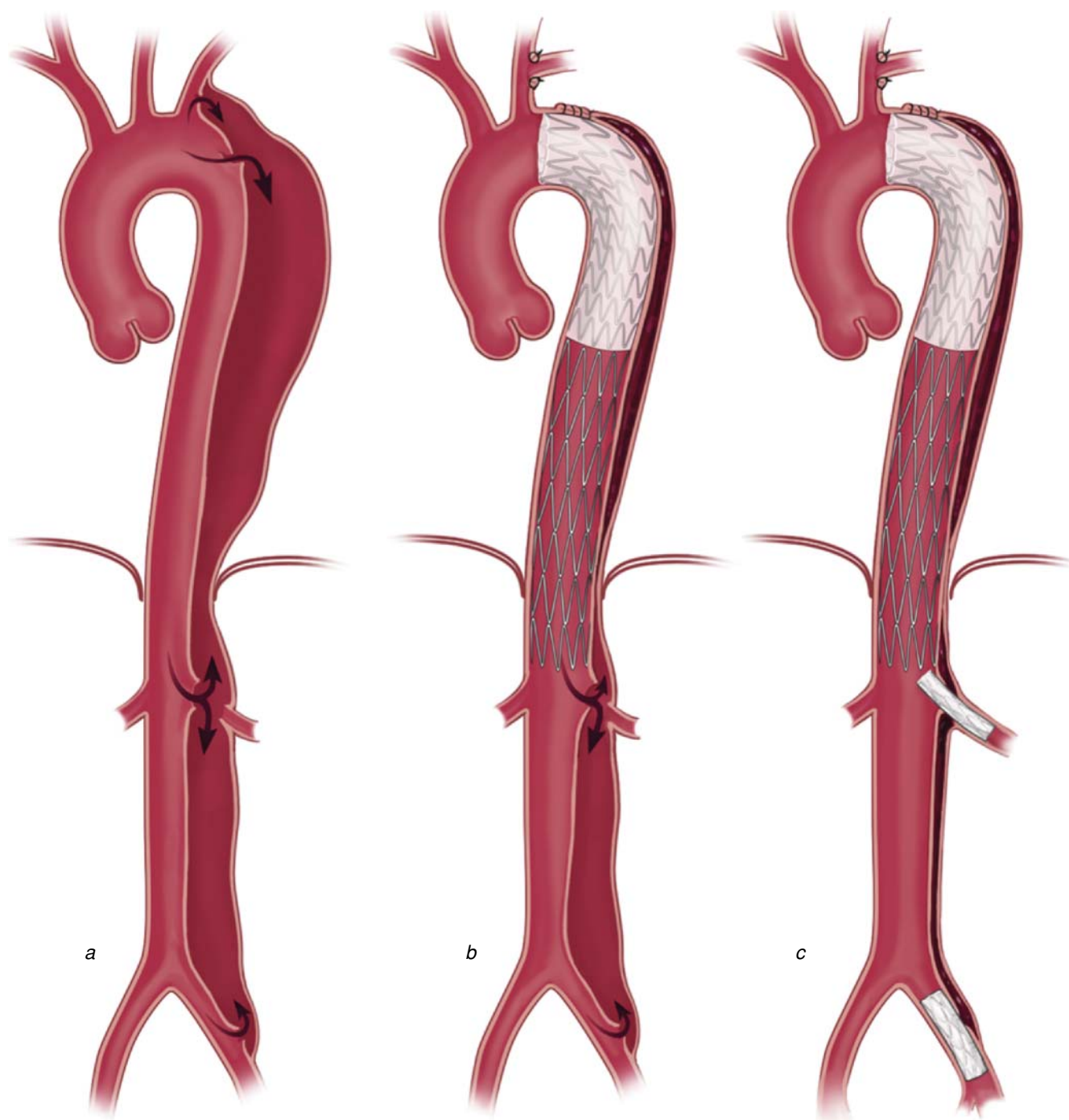


Figure 7 Cartoon depiction of the use of a combination of covered and bare metal stents to completely obliterate the false lumen in acute type B dissection. (a) Stanford type B dissection with entry tear distal to the left subclavian artery and fenestrations at branch artery ostia. (b) Covered stent graft used to seal the proximal entry tear (with coverage of the left subclavian artery to obtain adequate seal). Bare metal stents then obliterate the thoracic false lumen to the level of the renal arteries. False lumen flow remains in the abdominal portion of the dissection as a result of multiple entry points. (c) Interval placement of covered stents over false lumen entry points with complete obliteration of the false lumen.

permitting direct inspection or repair of the ostia of the mesenteric and renal vessels.¹⁰² Experience has demonstrated that the duration of supraceliac clamping can be limited to the 20-minute range, with repositioning of the clamp to an infrarenal location following closure of the visceral segment aortotomy. Interposition of a short segment polyester graft in the infrarenal aorta facilitates reconstruction of the aortic

layers at the distal anastomosis with the double-layer polytetrafluoroethylene felt technique. Our posture relative to extending the fenestration or septectomy into the visceral aortic segment is dictated by the anatomic complexity displayed on the CT scan. Small aortic diameter, total absence of visceral artery flow, the dissected septum extending directly to or beyond a vital branch orifice, and radiographic

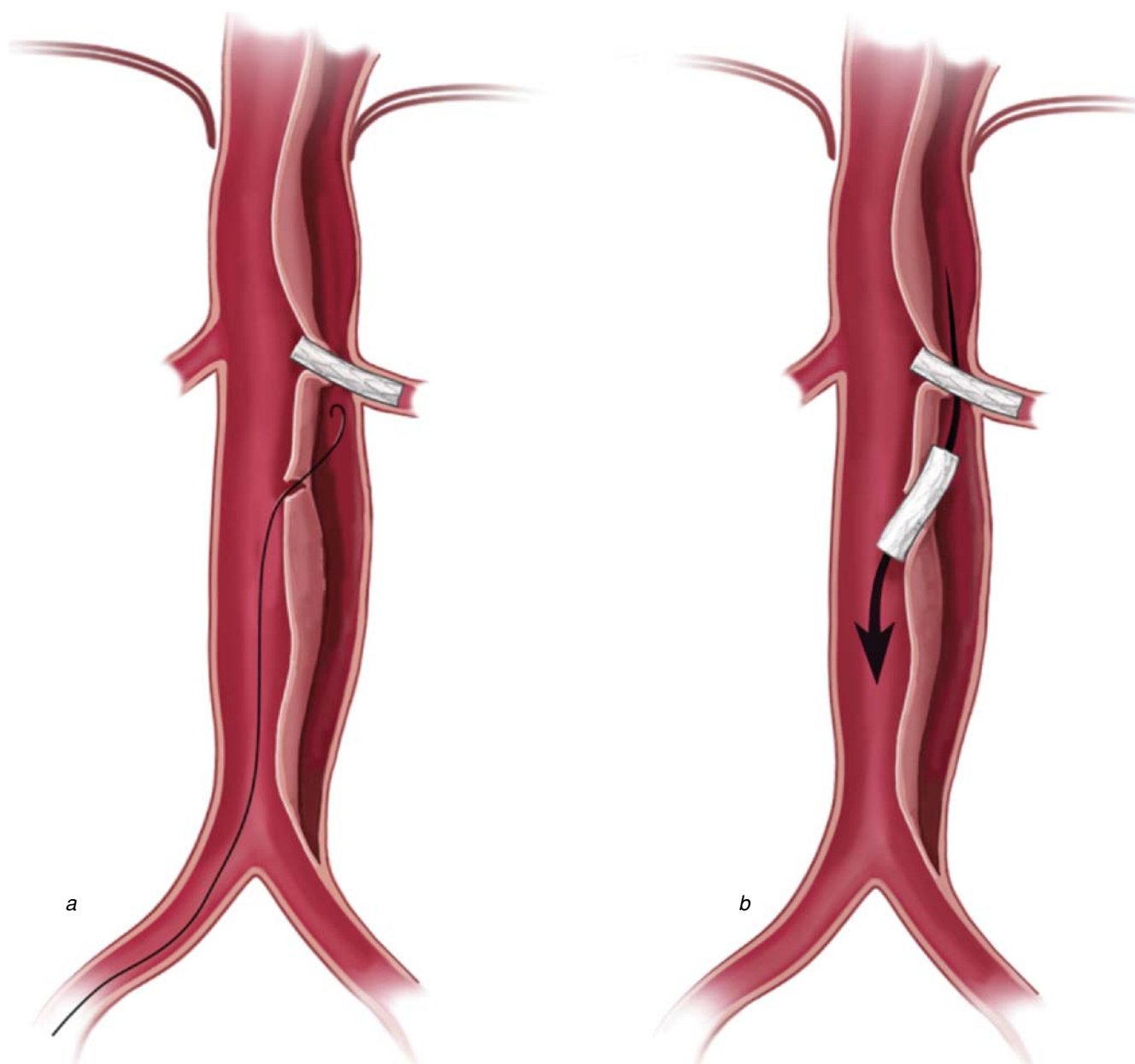


Figure 8 Cartoon depiction of endovascular fenestration. (a) The left renal artery (coming off the false lumen) made to originate from the true lumen. This requires stenting using either a covered or bare metal stent. (b) A balloon is then used to enlarge natural fenestrations in the dissection flap, and a stent can be used to keep this fenestration open.

evidence of intussuscepted septum into a renal/mesenteric vessel are all considerations that prompt extension of the aortotomy into the visceral segment. Such an approach also permits direct repair of a static obstruction, that is, where the branch vessel itself is dissected. This can be accomplished by circumferential suture of the vessel intima to the aortic wall at the ostia. Since continuous exposure of the visceral segment is desirable in surgical treatment of malperfusion syndrome, we prefer left flank approaches for this procedure. Depending on body habitus, a ninth or 10th interspace thoracoabdominal approach is used to allow for complete infradiaphragmatic aortic exposure and transperitoneal inspection of the viscera and palpation of the superior mesenteric artery pulse caudal to the mesocolon. At a median

follow-up of 19 months, no significant aortic dilatation occurred with such aortic tailoring as a surgical technique.¹⁰²

Advocates of surgical fenestration for malperfusion syndromes have asserted that the “surgical” morbidity and mortality rates quoted to support endovascular therapies are outdated and strongly influenced by delays in diagnosis and treatment.¹⁰³ Elefteriades and colleagues reported a survival of 65% at 1 year, 57% at 3 years, 50% at 5 years, and 28% at 10 years for patients treated with a “complication-specific” approach.¹⁰⁴ Overall, of the 14 patients in the total experience treated by open fenestration, their actuarial survival was 77%, 77%, and 53% at 1, 3, and 5 years, respectively. None of the surgically fenestrated patients were noted to have expansion of their aortic diameters on follow-up.

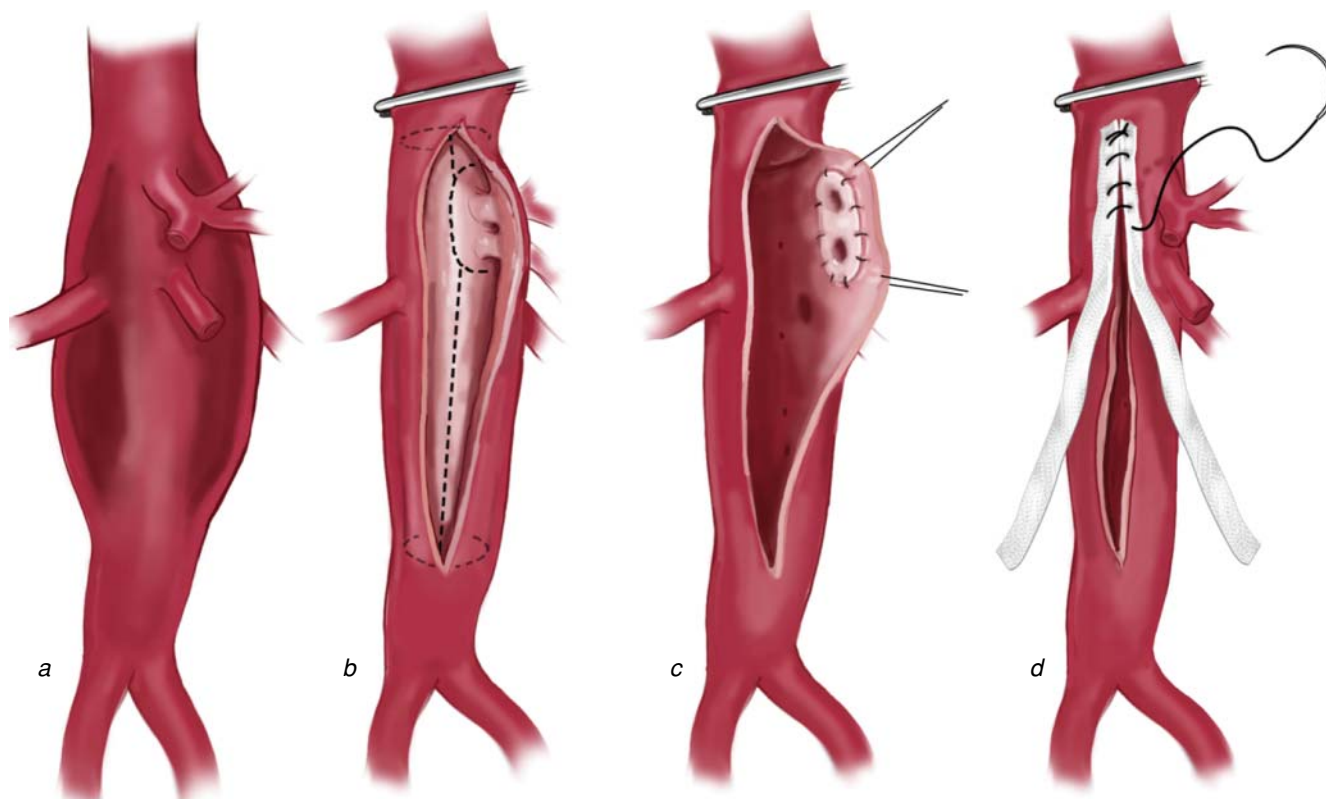


Figure 9 Technique of surgical abdominal aortic fenestration. (a) Dissection involving the visceral segment of the aorta. (b) If static obstruction of the renal or visceral vessels is suspected based on axial imaging studies, the fenestration can be carried onto the visceral aortic segment. The left kidney has been swept anteriorly; note that the left renal artery is perfused from the false lumen. The septum is incised to expose the origins of the celiac/superior mesenteric/right renal artery perfused via the true lumen. (c) Direct suture repair of the vessel ostium may be required, herein shown at the left renal origin, whose orifice abuts the circumferential terminus of the dissection. (d) After septectomy in the visceral segment, the outer aortic wall is closed over Teflon felt and the clamp is moved to the infrarenal aorta, which is most conveniently reconstructed with a tube graft.

A recent report from the Mayo Clinic affords perspective on both the infrequent need for and the durability of surgical fenestration.¹⁰⁵ From their database of 857 patients with a diagnosis of aortic dissection, only 321 patients underwent surgical intervention of any kind and only 14 patients underwent surgical fenestration during the study period—1.6% of the total study population. Surgical fenestration relieved the malperfusion syndrome for all patients with organ or limb ischemia. Operative mortality was 43% (3 of 7) in the acute dissection group; seven patients were treated in the chronic phase of the disease, with no mortality. Follow-up at a mean of 5.1 years for the 11 survivors revealed no evidence of aneurysm formation at the site of fenestration. The authors noted that in comparison of surgical fenestration with series of endovascular fenestration, the likelihood of subsequent aortic complications related to expansion or rupture of the false lumen may be greater in those patients treated by endovascular means. Therefore, although endovascular fenestration may offer more rapid restoration of perfusion, its durability would seem less than surgical fenestration techniques (see below).¹⁰⁵

Our cumulative experience affords a perspective over a 35-year period involving some 200 patients with acute aortic dissection treated during the 1990s and in part clarifies the role of open surgical fenestration and peripheral endovascular intervention in patients with malperfusion

syndromes.⁸ Nearly a third of the patients had evidence of branch occlusion; 17 (32%) of these 53 patients underwent peripheral vascular intervention to restore circulation. The overall mortality rate in the interval 1990 to 1999 was significantly lower when compared with an earlier report from 1965 to 1986 (18% versus 37%, $p < .006$).⁸ In discerning the factors associated with improved results over time, three variables were important: (1) aortic rupture occurred in just 6% of patients versus 18% in the previous interval; presumably, patients were being diagnosed and referred more promptly; (2) the impact of branch occlusion on mortality was no longer significant, implying that recognition and treatment of malperfusion syndromes had improved overall results; and (3) mortality in patients with mesenteric ischemia had improved to 37%, whereas an 87% mortality rate was observed in our earlier report. Recently, the IRAD data implicated mesenteric ischemia as responsible for 15% of all deaths related to acute dissection.⁵ For patients with mesenteric or renal malperfusion syndromes, surgical fenestration was used in nine patients. Restoration of flow was successful in all patients, and all patients so treated survived, whereas two deaths occurred in patients with mesenteric ischemia managed with percutaneous fenestration.

Open aortic fenestration is an excellent method of restoring circulation to vascular territories affected by malperfusion syndromes, especially when mesenteric and renal beds

are involved, and affords the opportunity to assess bowel viability and plan second-look procedures. Treatment priority should be assigned to the most life-threatening condition in patients with acute aortic dissection. The presence of mesenteric ischemia assumes such priority in virtually all patients, and constitutes an exception to prompt central aortic repair in those with type A dissections.

Natural History

The primary late complication of aortic dissection is aneurysmal dilatation of the outer wall of the false lumen; of patients surviving acute dissection, 25 to 40% will progress to have aneurysmal dilation of the dissected aorta despite medical therapy.^{106,107} In most clinical series of thoracoabdominal aneurysms, some 20% of cases are the sequelae of chronic dissection, for which conventional open repair is typically the only treatment option in contemporary practice.¹⁰⁸ Indeed, a variety of technical and anatomic considerations indicate that stent graft repair of aneurysms of chronic dissection etiology remains a major challenge.¹⁰⁹ Factors that appear to have a significant impact on chronic aneurysm development after dissection include poorly controlled hypertension, maximal aortic diameter of at least 4 cm in the acute phase, and continued patency of the false lumen.¹¹⁰ Furthermore, some 10 to 20% of those with dissection will subsequently experience late rupture of the aneurysm,¹¹⁰ and conventional surgical repair of such lesions is considerably more complex than with degenerative aneurysms.

LONG-TERM SURVIVAL

A recent review of the IRAD data focused on long-term survival of patients with acute aortic dissection. In an examination of 242 consecutive patients discharged alive after type B dissections, Tsai and colleagues found that the 3-year survival for patients treated medically was 77.6%; for those treated surgically, it was 82.8% and 76.2% for those treated with stent graft repair.¹¹¹ Independent predictors of long-term mortality included female gender, a history of previous aortic aneurysm, atherosclerosis, renal failure, and in-hospital hypotension or shock.¹¹¹ An examination of the 273 type A dissection patients discharged alive found that survival for patients treated with surgery was 90.5% at 3 years versus 68.7% for those treated medically.¹⁵ Independent predictors of mortality in this cohort included atherosclerosis and previous cardiac surgery.¹⁵ These studies show that although posthospital survival is excellent after type A dissection, nearly one quarter of those with type B dissections died within 3 years, suggesting that current treatment strategies are inadequate.

LATE THERAPY

Aneurysms that are the sequelae of chronic dissection tend to be more extensive and occur in younger patients compared with degenerative aneurysms. Treatment with effective beta blockade is an essential feature of long-term therapy and follow-up. The rationale of such therapy is based on the recognition that patients with aortic dissection have a systemic illness that places their entire aorta at risk for further dissection, aneurysm, or rupture. Guidelines

recommend progressive upward titration of beta blockade to achieve a blood pressure less than 125/80 mm Hg in usual patients and less than 120 mm Hg in those with Marfan syndrome. In addition, aggressive beta blockade has been shown to retard the growth of the aortic root in Marfan syndrome patients and may have a similar effect on the thoracoabdominal aorta.¹¹² Serial imaging is the cornerstone of long-term follow-up, and axial imaging modalities should encompass the entire aorta. Although in the developmental stages at present, branched stent graft technologies will likely have an important role in the future management of patients with aneurysms of chronic dissection etiology.¹¹³

Intramural Hematoma and Penetrating Aortic Ulcer

Two aortic entities related to aortic dissection deserve mention. An intramural hematoma (IMH) represents a collection of blood that is confined to the aortic media, whereas a penetrating aortic ulcer (PAU) is a defect in the elastic lamina of the aortic wall that leads to localized medial disruption and potential rupture. These are two closely related (possibly the same) aortic conditions that commonly cause diagnostic confusion with classic aortic dissection [see Figure 10]. Such confusion is related to the fact that these entities share the feature of an intimal violation with the flowing blood gaining entry and/or propagating between the aortic wall layers (usually within the media), and IMH and PAU may present concurrently. PAU is often noted as a radiographic curiosity on CT scans obtained for evaluation of the thoracic aorta, whereas IMH is a dissection process wherein the defining features include absence of an “intimal flap” and (as implied by the name) a thrombosed false lumen.

ETIOLOGY AND DIAGNOSIS

In both conditions, symptomatic patients present with the abrupt onset of severe pain in the chest, neck, back, and/or abdomen that is typical of acute aortic syndrome. Paradoxically (and unlike classic aortic dissection), both are manifestations of degenerative aortic pathology, typically occurring in older patients with significant hypertension and often with diffuse degenerative atherosclerotic disease of the thoracic aorta. IMH of the thoracic aorta has been characterized as a distinct clinical entity whose distinguishing radiographic features are the absence of direct communication between the thrombus in the false lumen and the true lumen and the absence of a definable intimal flap (as seen with classic aortic dissection) or penetrating ulcer.^{114,115} IMH extent is variable in terms of the length of the aorta involved, circumference, and direction of propagation. The etiology of IMH was initially thought to involve spontaneous rupture of the vasa vasorum within the medial layers of the aortic wall, which will occasionally evolve into a PAU (a rare event). More consistent with our own observations, a PAU phenomenon is usually the origin of IMH, and whether the ulcerlike projection is radiographically demonstrated is mere serendipity.¹¹⁶ Indeed, in the Mayo Clinic series, approximately 80% of patients with PAU had an associated IMH.¹¹⁷ PAU is used to describe those lesions when a caplike projection of contrast is seen (on CT scan) beyond the usual luminal aortic boundary [see Figure 11]. In this instance, the atherosclerotic

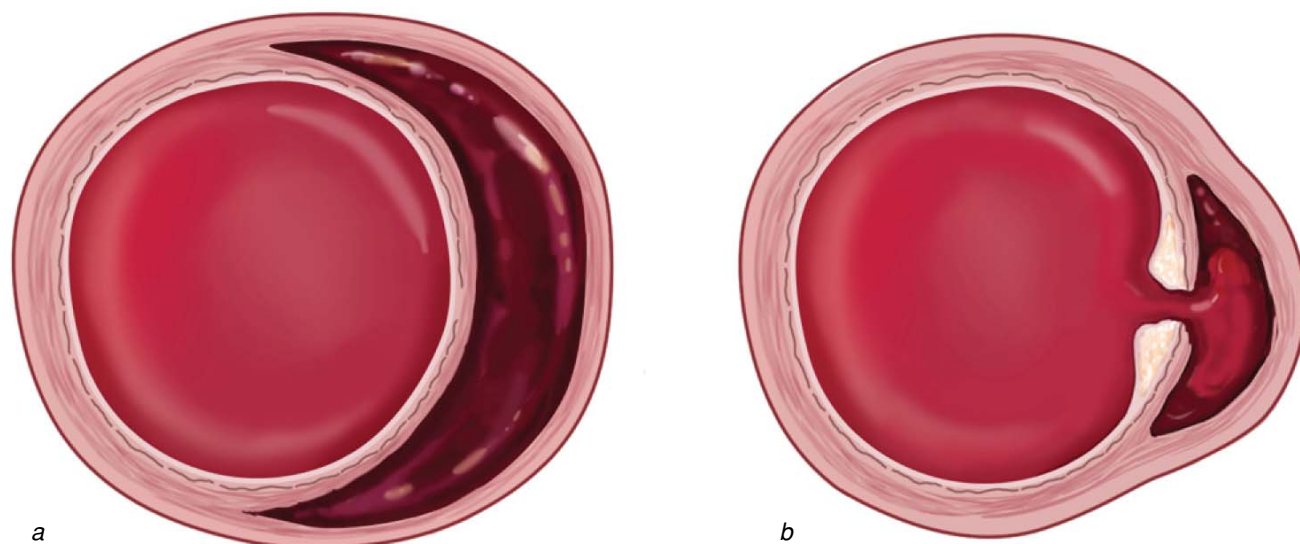


Figure 10 (a) Cartoon depiction of intramural hematoma. (b) Cartoon depiction of penetrating aortic ulcer.

lesion penetrates the internal elastic lamina and facilitates hematoma formation within the media. Further propagation of this flap is thought to be prevented by the presence of atherosclerotic disease in the aorta (a rare finding in classic aortic dissection).¹¹⁸

TREATMENT

Although the natural history of asymptomatic type B IMH and PAU has been complete resolution in 50 to 80% of patients,¹¹⁸ progression to classic dissection or aneurysmal degeneration of the aorta can occur.^{116,119} The IRAD database

examined 1,010 patients who presented with symptoms of the acute aortic syndrome and identified a 5.7% incidence of IMH. This affected the descending aorta in 60% of cases, whereas classic aortic dissection more commonly affected the ascending aorta (65% of cases). The overall mortality of IMH was similar to that of classic aortic dissection, 20.7% versus 23.9%, both for proximal (39.1% versus 29.9%) and distal (8.3% versus 13.1%) locations. Among the 51 patients whose initial diagnostic study revealed IMH, eight (16%) progressed to aortic dissection on a second imaging study. A normal aortic diameter in the acute phase was the best predictor of IMH regression without complications. The IRAD investigators recommended prompt surgical therapy for IMH involvement of the ascending aorta. Intense medical therapy (goal of systolic blood pressure <120/80, heart rate <60 beats/min) with serial imaging was recommended for involvement of the arch and descending aorta.¹²⁰

A recent report of 35 patients with IMH detailed a significant correlation between disease progression and initial aortic diameter and/or hematoma thickness. Those patients with an initial aortic diameter greater than 40 mm had a 30-fold increased risk of progression to either aneurysm formation or rupture. In addition, hematoma thickness greater than 1 cm was associated with a ninefold increased risk of progression. This suggests that the degree of separation of the aortic wall layers may contribute to chronic aneurysmal degeneration.¹²¹

Although such focal pathology may be ideally suited for stent graft repair, patients with incidental asymptomatic IMH or PAU of the descending aorta are currently managed with medical therapy. Tittle and colleagues detailed their experience with 45 patients with symptomatic PAU and IMH.¹²² In this cohort, 33% had rupture on admission and 53% required operation. Patients with lesions involving the ascending aorta were more likely to undergo surgical repair (83%), whereas only 50% of patients with involvement of the descending thoracic aorta were operated on. Indications for intervention include aortic diameter greater than 6 cm,



Figure 11 Computed tomographic angiogram of penetrating aortic ulcer (red arrow) in the descending thoracic aorta.

rupture, impending rupture, or major progression in size despite medical therapy.¹¹⁶ Those patients with involvement of the ascending aorta are usually treated surgically because of the high risk of cardioaortic complications. Surveillance imaging of patients with IMH or PAU treated medically should be frequent, especially those with evidence of aneurysmal dilation.

Conclusion

Considerable progress has been demonstrated in the overall results of treatment of acute aortic dissection. A broad clinical awareness of aortic dissection and improved methods of diagnosis have helped reduce the morbidity and mortality associated with this disease process. Indeed, clinicians who understand the principles of both medical and surgical management of aortic dissection can effectively separate patients who require surgical intervention from those who can be managed medically with serial imaging studies. Although open surgery has been the standard of care for many years, it is clear that a wide variety of thoracic aortic pathologies are amenable to endovascular therapy. As stent graft technology continues to evolve, it is likely that it will become the primary method of treatment of acute aortic dissection in the future.

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1 INITIAL MANAGEMENT OF LIFE-THREATENING TRAUMA

Frederick A. Moore, MD, FACS, and Ernest E. Moore, MD, FACS

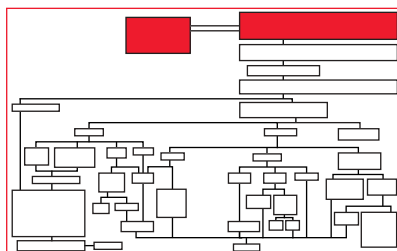
Initial Approach to the Critically Injured Patient

Salvage of the critically injured patient is optimized by a coordinated team effort in an organized trauma system. Management of life-threatening trauma must be prioritized according to physiologic necessity for survival—that is, active efforts to support airway, breathing, and circulation (the ABCs) are usually initiated before specific diagnoses are made. In this chapter, we outline a systematic approach to severely injured patients within the so-called golden hour. The discussion is divided into prehospital care and emergency department (ED) management; the ED component is further divided into (1) primary survey with initial resuscitation, (2) evaluation and continued resuscitation, and (3) secondary survey with definitive diagnosis and triage.

Prehospital Care

INTERVENTION AT INJURY SITE

Resuscitation and evaluation of the trauma patient begin at the injury site. The goal is to get *the right patient to the right hospital at the right time* for definitive care. First responders (typically, firefighters and police) provide rapid basic trauma life support (BTLS) and are followed by paramedics and flight nurses with advanced trauma life support (ATLS) skills. Medical control is ensured by preestablished field protocols, radio communication with a physician at the base hospital, and subsequent trip audits. Management priorities of BTLS on the scene are to (1) assess and control the scene for the safety of the patient and the prehospital care providers, (2) tamponade external hemorrhage with direct pressure, (3) protect the spine after blunt trauma, (4) clear the airway of obstruction and provide supplemental inspired oxygen, (5) extricate the patient, and (6) stabilize long-bone fractures. Whereas the benefits of BTLS are undisputed, the merits of more advanced interventions remain controversial.¹ Airway access, once considered a major asset of the care provided by paramedics and flight nurses, has now been questioned, not only because missed tracheal intubation is a concern but also because unintentional hyperventilation (hypocarbica) is detrimental in the setting of traumatic brain injury (TBI) and during cardiopulmonary resuscitation (CPR).² Moreover, the value of intravenous (IV) fluid administration remains controversial.^{3,4}



FIELD TRIAGE

When it is geographically and logistically feasible, critically injured patients should be taken directly to a designated level I trauma center or to a level II trauma center if a level I trauma center is more than 30 minutes away. The currently available field trauma scores, however, are not reliable in making this triage decision. The development of field triage criteria has paralleled the development of trauma centers. The decision is based on a practice algorithm called a “decision scheme.” The first field triage decision scheme was published by the American College of Surgeons in 1986, with subsequent updates in 1990, 1993, 1999, and 2006.⁵ The decision scheme has four steps that the emergency medical service (EMS) provider proceeds through after measuring vital signs and level of consciousness to decide if the patient should be transported to a higher level trauma center [see Table 1]. Because the potential harm associated with undertriage is high and could result in death or substantial morbidity and disability, criteria were initially chosen to err on the side of minimizing undertriage rather than minimizing overtriage. However, overtriage results in an overuse of financial and human resources, overcrowding of trauma centers, and increased EMS transport times. Target levels for undertriage rates within a trauma system range from 0 to 5% of patients requiring level I or level II trauma center care, whereas levels of overtriage vary from 25 to 50%. As field triage continues to evolve on the basis of new research findings, overtriage rates might be reduced while maintaining low undertriage rates.

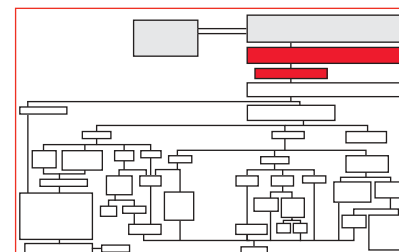
DECLARATION OF DEATH AT SCENE

The determination that care is futile during prehospital evaluation is best made on the basis of the cardiac rhythm. Asystole justifies declaration of death at the scene, and profound bradycardia (heart rate [HR] < 40 beats/min) has been shown to signal an unsalvageable situation.⁶

ED Management

ARRIVAL AT HOSPITAL UNDER ACTIVE CPR

When a patient arrives in the ED after prehospital CPR has been initiated,



Initial Approach to the Critically Injured Patient

Communicate with base hospital

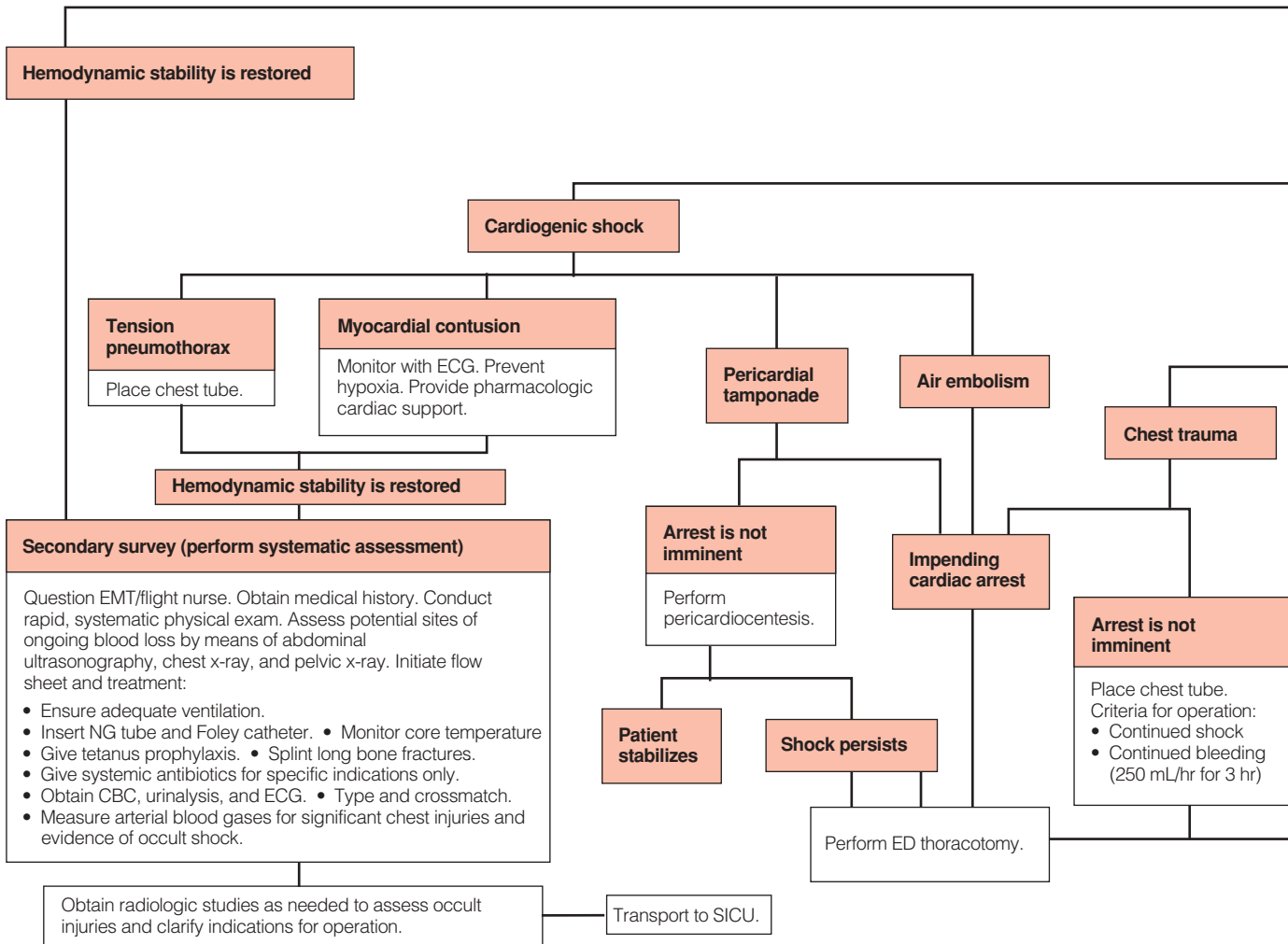
Field triage: Level I, II, or III facility

Assemble trauma team:

- Trauma surgeon
- ED physician
- Surgical specialist
- Radiology technicians
- Nurses
- Respiratory technicians

Ensure ancillary services:

- OR
- CT scanning
- Blood bank
- Interventional radiology



ED = emergency department; CT = computed tomography; ECG = electrocardiogram; EMT = emergency medical technician; NG = nasogastric; SICU = surgical intensive care unit; BP = blood pressure; CVP = central venous pressure; DPL = diagnostic peritoneal lavage; OR = operating room

Urban: < 15 minutes (Rural: > 30 minutes)

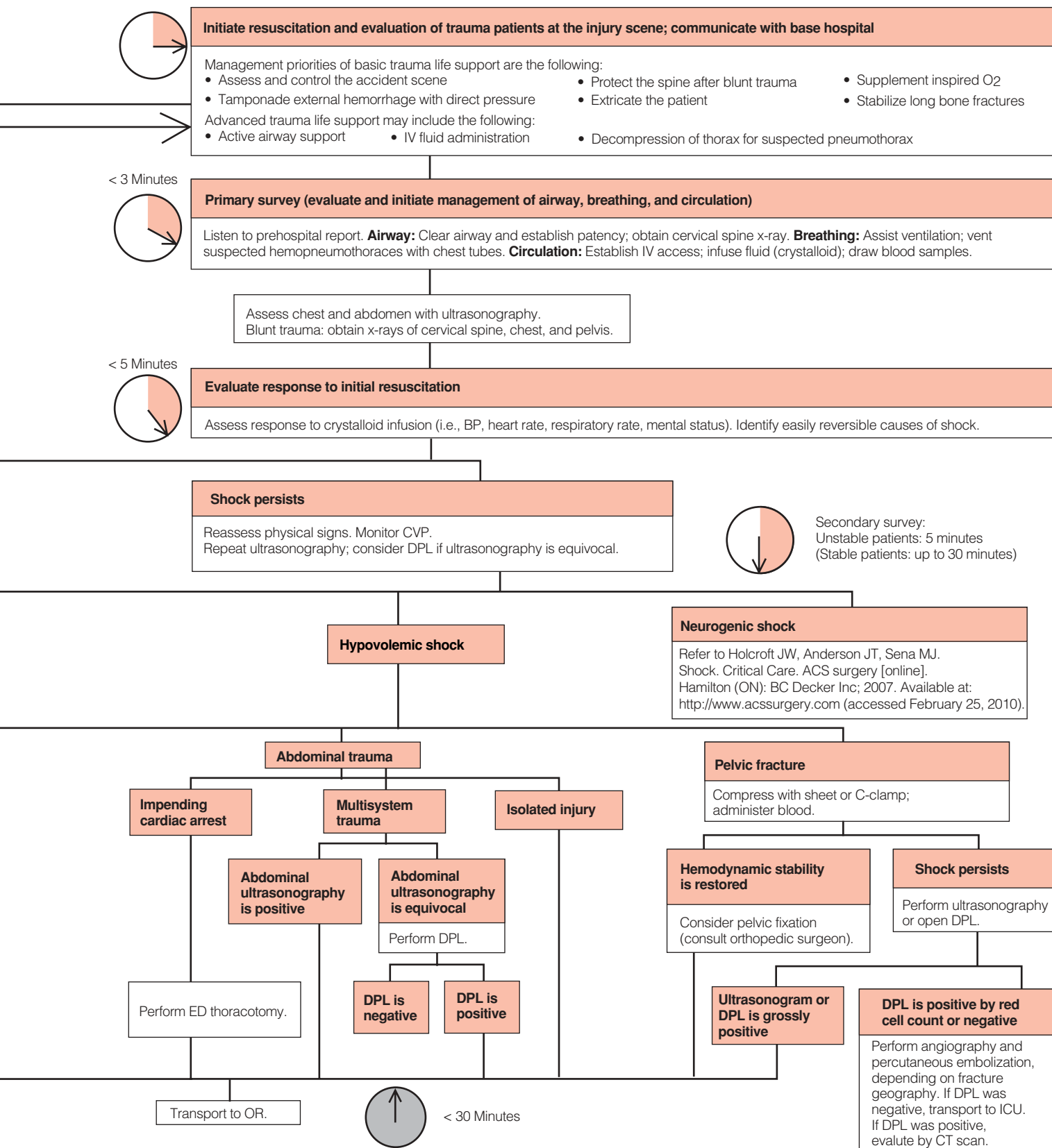


Table 1 2006 Field Triage Decision Scheme Recommendations

Step one: physiologic criteria - Glasgow Coma Scale of < 14 - Systolic blood pressure of < 90 mm Hg - Respiratory rate of < 10 or > 29 breaths per minute (< 20 in infant aged < 1 year) Step two: anatomic criteria - All penetrating injuries to head, neck, torso, and extremities proximal to elbow and knee - Flail chest - Two or more proximal long-bone fractures - Crushed, degloved, or mangled extremity - Amputation proximal to wrist and ankle - Pelvic fractures - Open or depressed skull fracture - Paralysis Step three: mechanism-of-injury criteria - Falls - Adults: fall > 20 feet (one storey = 10 feet) - Children aged < 15 years: fall > 10 feet or two to three times child's height - High-risk automobile crash - Intrusion: > 12 inches to the occupant site or > 18 inches to any site - Ejection (partial or complete) from automobile - Death in same passenger compartment - Vehicle telemetry data consistent with high risk of injury - Automobile versus pedestrian/bicyclist thrown, run over, or with significant (> 20 mph) impact - Motorcycle crash > 20 mph Step four: special considerations - Age - Adults aged > 55 years - Children aged < 15 years - Anticoagulation and bleeding disorders - Burns - Without other trauma mechanism: triage to burn facility - With trauma mechanism: triage to trauma center - Time-sensitive extremity injury - End-stage renal disease require dialysis - Pregnancy > 20 weeks - EMS provider judgment
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EMS = emergency medical service.

Table 2 Guidelines for Declaring Patients Dead on Arrival to the Hospital

Penetrating trauma - Prehospital CPR for > 15 min with no signs of life - Asystole without pericardial tamponade Blunt trauma - Prehospital CPR for > 10 min with no signs of life - Asystole

CPR = cardiopulmonary resuscitation.

ultimate goal is to establish adequate oxygen delivery to the vital organs. This is accomplished by first progressing through the ABCs: airway control with cervical spine precautions, assisted breathing with ventilation, and empirical tube thoracostomy to relieve a pneumothorax if indicated. These maneuvers are carried out to maximize oxygen delivery to the alveoli. Support of the circulation (tamponade of external bleeding and fluid administration) is instituted to restore effective blood volume, thereby enhancing myocardial performance and thus oxygen delivery to the tissues.

Unstable patients fall into two categories: those who respond to initial intervention and those who do not. Early nonresponders are challenging because they require an immediate lifesaving intervention. The key is to perform the correct intervention before the patient dies. Patients who respond to initial interventions can be demanding because a subset of them have only a finite time window before shock recurs. Multiple diagnoses must be considered before definitive triage is possible. The clinician must rapidly formulate a differential diagnosis and then sequentially initiate the appropriate diagnostic tests.

Airway and Breathing

After blunt trauma, airway control should proceed on the assumption that an unstable cervical spine fracture exists; thus, hyperextension of the neck must be avoided. Airway management in the seriously injured victim can usually be accomplished with simple techniques, but it is occasionally stressful. Evaluation begins by asking the patient a question such as "How are you?" A response given in a normal voice indicates that the airway is not in immediate jeopardy; a breathless, hoarse response or no response at all indicates that the airway may be compromised.

Airway obstruction and hypoventilation are the most likely causes of respiratory failure. The critical decision is whether active airway intervention is needed. The first maneuver is to clear the airway of debris and to suction secretions. In the obtunded patient, this procedure is followed by elevation of the angle of the mandible to alleviate pharyngeal obstruction and placement of an oropharyngeal or nasopharyngeal tube to maintain airway patency. Supplemental oxygen is given via a nasal cannula (6 L/min) or a nonrebreathing oxygen mask (12 L/min). Airway patency, however, does not ensure adequate ventilation, nor does a normal arterial oxygen saturation (Sao₂) on pulse oximetry. Clinical evidence of hypoventilation includes poor air exchange at the nose and mouth, diminished breath sounds, and decreased chest wall excursion; the most likely causes are head injury, spinal cord transection, hemopneumothorax, flail chest, and profound

the critical question is whether to perform a resuscitative thoracotomy. The prognosis for blunt trauma patients is poor because the major causes of cardiopulmonary arrest after blunt trauma (e.g., massive brain injury, high spinal cord injury, and exsanguination from multiple injuries) are difficult to reverse. In contrast, patients with stab wounds to the heart are frequently salvageable if cardiac arrest occurs because of cardiac tamponade. In most cases, the heart can be resuscitated by simply decompressing the pericardium, given that blood volume is usually maintained. Guidelines for terminating resuscitation are based on the mechanism of injury, the duration of CPR, the presence of signs of life (e.g., pupillary response, respiratory effort, or motor activity), and the presence of asystole documented by cardiac monitoring [see Table 2].⁷

PRIMARY SURVEY AND INITIAL RESUSCITATION

During initial assessment, an empirical sequence of lifesaving therapeutic and diagnostic procedures is pursued. The

shock. Suspected hemopneumothoraces should be vented immediately with large-bore chest tubes inserted via the midlateral thorax.

Cervical spine protection is integral to airway management but should not be allowed to delay necessary intervention. The majority of significant spinal injuries in adults arriving alive at the ED are at the C5 to C7 levels. In children 8 years old or younger, the most frequent site of spinal injury is between the occiput and the C3 level. Significant spinal cord injury without radiographic abnormalities (i.e., the SCIWORA syndrome) is a relatively rare event (0.5% of patients undergoing radiography), and the data on its relative frequency in children and in adults are conflicting.⁸ A fractured cervical spine is usually tender to direct palpation in alert patients, but pain may be masked by distracting injuries.⁹ Even good-quality cross-table lateral cervical spine films may not detect 15% of unstable fractures. Accordingly, in patients who cannot have C-spine injury ruled out by clinical criteria, a cervical collar is left in place until the cervical spine has been evaluated for bony and ligamentous integrity by computed tomographic (CT) scanning.¹⁰

Bag-mask ventilation is an effective temporizing measure, but it consumes the attention of a skilled trauma team member, it may insufflate air into the stomach, and it can be resisted by spontaneously breathing patients. It is also ineffective in the presence of severe maxillofacial trauma. The decision for urgent airway control is made on clinical grounds; there often is no time to obtain a confirmatory arterial blood gas (ABG) analysis. Persistent airway obstruction or signs of inadequate ventilation mandate prompt intervention. Patients with expanding neck hematomas, deteriorating vital signs, or severe head trauma are also best managed with an aggressive airway approach.

The method of airway control depends on (1) the presence of maxillofacial trauma, (2) overall patient condition, and (3) the experience of the physician. Patients in respiratory distress with severe maxillofacial trauma warrant operative intervention. Cricothyrotomy is the preferred approach in adults and has replaced tracheostomy in the ED [see *Figure 1*]; the rare exceptions are in patients with major laryngeal trauma or extensive tracheal disruption. Percutaneous transtracheal ventilation may be safer than both of these surgical procedures for temporary airway management, particularly in children. In all other patients, the current standard approach is rapid sequence intubation (RSI) of the trachea orally with inline immobilization [see *Table 3*].⁹ In adults, a large (8 mm internal diameter) cuffed endotracheal tube is inserted to a distance of 23 cm from the incisors. In children, tube size is gauged to equal the diameter of the little finger. The proper depth (in centimeters) to which the tube should be inserted can be estimated by multiplying the tube's internal diameter (in millimeters) by 3. A chest x-ray should be obtained as soon as possible to rule out the possibility of right mainstem intubation.

Intubated patients should be placed on a high fraction of inspired oxygen ($F_{I}O_2$), and their SaO_2 should be monitored by pulse oximetry. Generally, a low SaO_2 is easily treated by increasing the $F_{I}O_2$. Patients who do not respond when the $F_{I}O_2$ is increased to 100% should be treated with low levels of positive end-expiratory pressure (PEEP) once adequate volume status is ensured. Positive-pressure ventilation

impedes return of blood to the heart; as a result, emergency intubation of a hypovolemic patient can adversely affect cardiac output. Hyperventilation should also be avoided. This can cause auto-PEEP, which can adversely affect cardiac output. Additionally, a low arterial carbon dioxide tension ($Paco_2$) can cause cerebral vasoconstriction, which can be deleterious in patients with TBI. An ABG analysis should be obtained to assess pH, $Paco_2$, and base deficit. The use of end-tidal capnography ($EtCO_2$) has been recommended as a surrogate measure of ventilation. However, trauma patients frequently suffer from impaired pulmonary ventilation/perfusion, and a recent study showed that $EtCO_2$ had low correlation with $Paco_2$. Therefore, $EtCO_2$ should not be used to guide ventilation in intubated trauma patients in the ED.¹¹

Circulation

Once alveolar ventilation is ensured, the next priority is to optimize oxygen delivery by maximizing cardiovascular performance. External hemorrhage is controlled by means of manual compression, and empirical volume loading for presumed hypovolemia via large-bore IV cannulas is initiated. The size, number, and sites of IV catheters depend on the degree of shock present and on estimates of injury severity. If the patient arrives in shock or has obvious multiple injuries, a short 14 French catheter should be placed in each antecubital vein. When vascular collapse precludes peripheral percutaneous access in an adult, the alternative is cannulation of the femoral or the subclavian vein by means of the Seldinger technique. We have found the supraclavicular subclavian approach to be useful in the ED.¹² Venous access should be avoided in regions with potential penetrating vascular injuries (e.g., lower neck, upper chest, pelvis, or groin).

Intraosseous infusion through a cannula placed in the medullary cavity of a long bone is a safe and efficacious method for emergency vascular access in infants and children younger than 6 years. This procedure is typically performed in the anteromedial aspect of the tibial plateau in an uninjured extremity; the distal femur, the distal tibia, and the sternum are other potential sites. Intraosseous infusion generally allows administration of sufficient fluid to facilitate subsequent cannulation of the venous circulation.¹³ If access remains problematic in children, great saphenous vein cut-down at the groin is the preferred route because inadvertent femoral artery injury with the percutaneous approach may result in limb-threatening vasospasm. With establishment of the first IV line, blood should be drawn for hematocrit, white blood cell (WBC) count, electrolyte concentrations, blood-group typing, coagulation profile, and toxicology screen as indicated.

Isotonic crystalloid is used for initial resuscitation in the ED.¹⁴ Lactated Ringer (LR) solution is preferred to normal saline (NS) unless the patient has an obvious brain injury. Excessive early administration of crystalloids has been identified as a risk factor for adverse outcomes; accordingly, the amount infused should be monitored closely.¹⁵ If the patient does not respond to crystalloid infusion at levels exceeding 30 mL/kg, blood should be administered. LR solution and banked blood should not be infused through the same IV line.

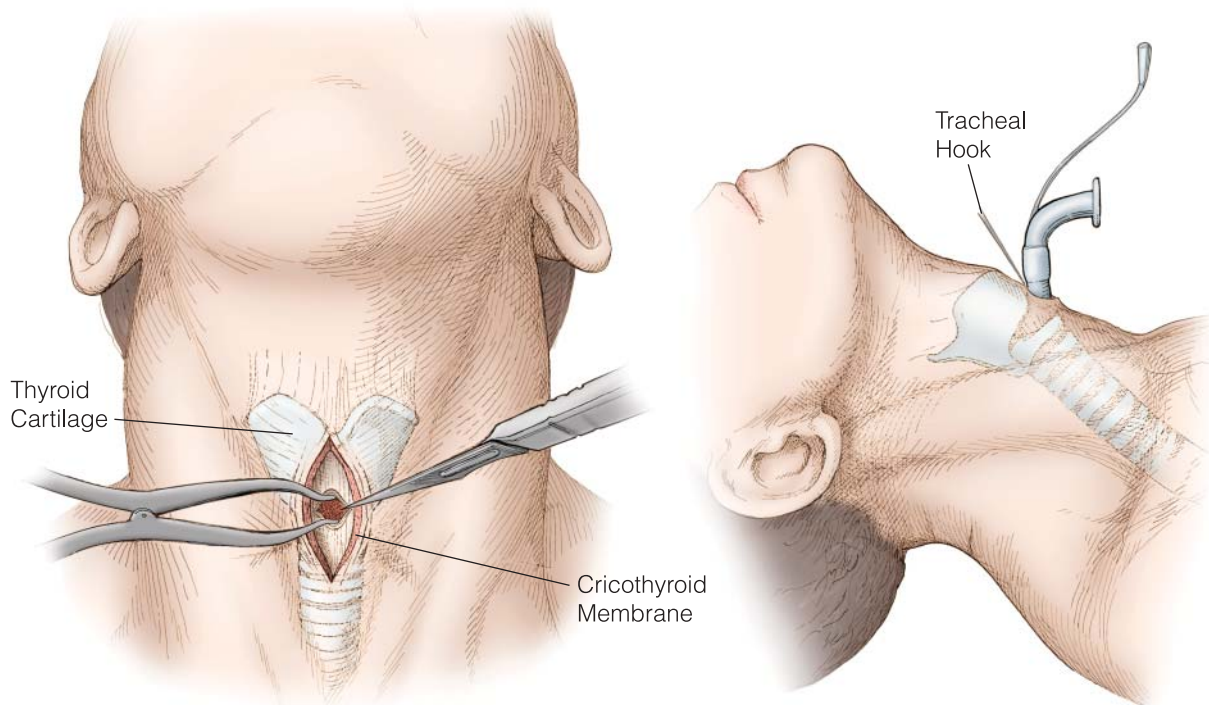


Figure 1 The technique for cricothyrotomy is illustrated here. The larynx is stabilized with one hand, and a 2 cm vertical incision is made over the cricothyroid space. The cricothyroid membrane is palpated and incised horizontally. A Trousseau dilator is inserted and spread vertically for visualization of the subglottic space (left). A tracheal hook is used to retract the inferior border of the thyroid cartilage as a tracheostomy tube with a 6 mm internal diameter is inserted into the trachea (right).

Early empirical blood transfusions are indicated in patients who arrive in severe shock or who have injuries associated with significant bleeding (e.g., a vertical shear pelvic fracture or bilateral femur fractures), especially if the patients are elderly. Type-specific blood should be available within 20 minutes. If type-specific blood is not available, reconstituted O-negative packed red blood cells (PRBCs) may be used. Type O-negative PRBCs have no cellular antigens; therefore, the risk of major hemolytic reactions caused by patient antibodies attacking donor RBC antigens is minimal. When O-negative PRBCs are unavailable, O-positive PRBCs

may be used. The patient will become sensitized to the Rh factor, which is significant for women of childbearing age. Protocols for massive transfusions (defined as > 10 units PRBCs in 6 hours) should be established with the blood bank to ensure prompt availability of blood products for patients arriving with life-threatening bleeding.¹⁶ Recent studies demonstrate that patients arriving with severe bleeding are coagulopathic and benefit from early administration of fresh frozen plasma (FFP).

Also germane to the initial period of massive blood transfusion are the potential complications of acidosis, hypothermia, and hypocalcemia. Moderate hypothermia (< 32°C) causes platelet sequestration and inhibits the release of platelet factors that are important in the intrinsic clotting pathway. In addition, hypothermia has consistently been associated with poor outcome in trauma patients. Core temperature often falls insidiously because of exposure at the scene and in the ED and because of administration of resuscitation fluids stored at ambient temperature. The first step is to prevent further heat loss by covering the body (including the head) and infusing warm blood and fluid. Another simple technique is to heat and aerosolize ventilator gases. Active external rewarming with heating blankets and increased room temperature should also be employed. These techniques are not, however, very effective in reversing established hypothermia.

The use of bicarbonate in the treatment of systemic acidosis remains controversial. Moderate acidosis (pH < 7.20) impairs coagulation, myocardial contractility, and oxidative metabolism. Acidosis in the trauma patient is caused

Table 3 10 Steps in Rapid-Sequence Intubation

1. Preparation of equipment and supplies
2. Preoxygenation
3. Sedation to decrease anxiety
4. Premedication to mitigate adverse effects: vecuronium bromide (1 mg) to prevent defasciculations, lidocaine (1.5 mg/kg) to prevent increased ICP with TBI
5. Cricoid pressure
6. Administration of paralytic agent: succinylcholine (1.0–1.5 mg/kg), vecuronium bromide (0.6–1.2 mg/kg) if succinylcholine contraindicated
7. Intubation
8. Confirmation of tube position by auscultation and capnography
9. Securing of airway
10. Chest x-ray to confirm optimal tube position

ICP = intracranial pressure; TBI = traumatic brain injury.

primarily by a rise in lactic acid production secondary to tissue hypoxia and usually resolves when the volume deficit has been corrected. Administration of sodium bicarbonate may cause a leftward shift in the oxyhemoglobin dissociation curve, reducing tissue oxygen extraction, and it may worsen intracellular acidosis caused by carbon dioxide production. On the other hand, adrenergic receptors may become desensitized with protracted acidosis. Studies indicate that vasopressin may be more effective than epinephrine as hemorrhagic shock approaches irreversibility. Bicarbonate infusion, therefore, should be limited to persons with protracted shock.

Hypocalcemia caused by citrate binding of ionized calcium does not occur until the blood transfusion rate exceeds 100 mL/min (1 U/5 min). Decreased serum levels of ionized calcium depress myocardial function before impairing coagulation. Calcium gluconate (10 mg/kg IV) should be reserved for cases in which there is electrocardiographic (ECG) evidence of QT interval prolongation or, in rare instances, for cases of unexplained hypotension during massive transfusion.

EVALUATION AND CONTINUED RESUSCITATION

Identification of Hemodynamic Instability

Recognizing the presence of shock and assessing its severity are key factors in early decision making. During the initial ABCs, palpation for the presence of pulses can be used to generate an estimate of systolic blood pressure (SBP). In general, a radial pulse is detected when SBP is higher than 80 mm Hg, a femoral pulse when SBP is above 70 mm Hg, and a carotid pulse when SBP exceeds 60 mm Hg. The initial blood pressure (BP) measurement should be made with a manual cuff; automatic cuff BP measurement machines may overestimate SBP in hypovolemic trauma patients.¹⁷ An SBP lower than 90 mm Hg (or an age-adjusted decrease in SBP that exceeds 30 mm Hg) in conjunction with an HR higher than 130 beats/min is generally considered indicative of major shock. Most patients, however, especially young ones, can compensate for hypovolemia and maintain a normal BP even in the face of significant ongoing hemorrhage. It should be kept in mind that because acute massive blood loss may paradoxically trigger a vagal-mediated bradycardia, the traditional inverse correlation between increased HR and reduced effective blood volume may not hold in the early resuscitation period.¹⁸ The initial hemoglobin level is notoriously misleading, either because the patient has not yet been volume loaded or because there has not been sufficient time for influx of interstitial fluid into the intravascular space. It is more informative to measure the hemoglobin level again after initial volume loading for purposes of comparison; a decrease greater than 2 g/dL should be grounds for concern.

The size of the base deficit can be a useful measure of the depth of hemorrhagic shock.¹⁹ Whether the base deficit is persisting or declining is more important than its absolute

value, but generally a base deficit greater than 8 mEq/L is indicative of severe shock. Measurement of central venous pressure (CVP) is helpful in identifying severe hypovolemia, and serial CVP measurements may be helpful to assess volume loading, but the correlation between circulating blood volume and CVP value is relatively poor.²⁰ Although arterial lines are of limited value in initial ED management, they become increasingly useful as time passes. The end points of initial resuscitation during the time of critical diagnostic testing and triage are as follows: (1) SBP higher than 90 mm Hg, (2) HR lower than 120 beats/min, (3) hemoglobin concentration equal to or greater than 10 g/dL, and (4) CVP equal to or greater than 10 cm H₂O.²¹

Management of Nonresponsive Unstable Patients

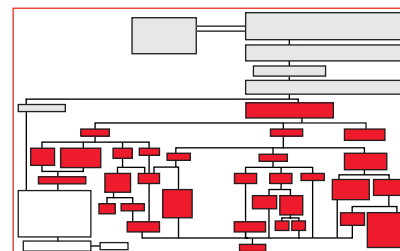
Shock that persists despite initial volume loading may derive from severe hypovolemia, cardiogenic causes, or neurogenic causes. Given that neurogenic shock is fairly well tolerated, the key concern at this point is to quickly distinguish hypovolemic shock from cardiogenic shock because cardiogenic shock may necessitate immediate ED intervention. This distinction can usually be made by measuring CVP in conjunction with physical examination. In hypovolemic shock, CVP is generally less than 5 mm Hg, whereas in clinically significant cardiogenic shock, CVP usually exceeds 20 mm Hg.

The differential diagnosis of traumatic cardiogenic shock depends on the mechanism of injury and may include (1) tension pneumothorax, (2) pericardial tamponade, (3) myocardial contusion, and (4) air embolism. Telltale physical signs may be difficult to discern in a noisy ED, especially when compounded by persistent hypovolemia. Timely diagnosis requires a high index of suspicion. Tension pneumothorax, the most common cause of cardiogenic shock in both blunt and penetrating trauma, is often first confirmed with emergency chest tube placement [see Figure 2].

In traumatic pericardial tamponade, the classic components of the Beck triad (hypotension, muffled heart sounds, and jugular venous distention) are frequently absent, and pulsus paradoxus is rarely detectable. ED ultrasonography is the first test employed by trauma surgeons in patients with high-risk penetrating wounds.²² However, the ultrasonogram may appear normal, with clotted blood in the pericardium, and CVP measurement is a helpful addition. Occasionally, a blunt trauma patient can be salvaged through timely diagnosis of a blunt atrial tear.

Myocardial contusion should be suspected in any blunt trauma patient with unexplained cardiogenic shock or persistent arrhythmia. ECG changes and elevated troponin levels are usually nonspecific.^{23,24} Fundamental interventions include correction of acidosis, hypoxia, and electrolyte abnormalities; judicious administration of fluid; and pharmacologic suppression of life-threatening arrhythmias.

Bronchovenous air embolism into the left atrium from a pulmonary laceration typically occurs after penetrating trauma and is more common than is generally recognized.²⁵



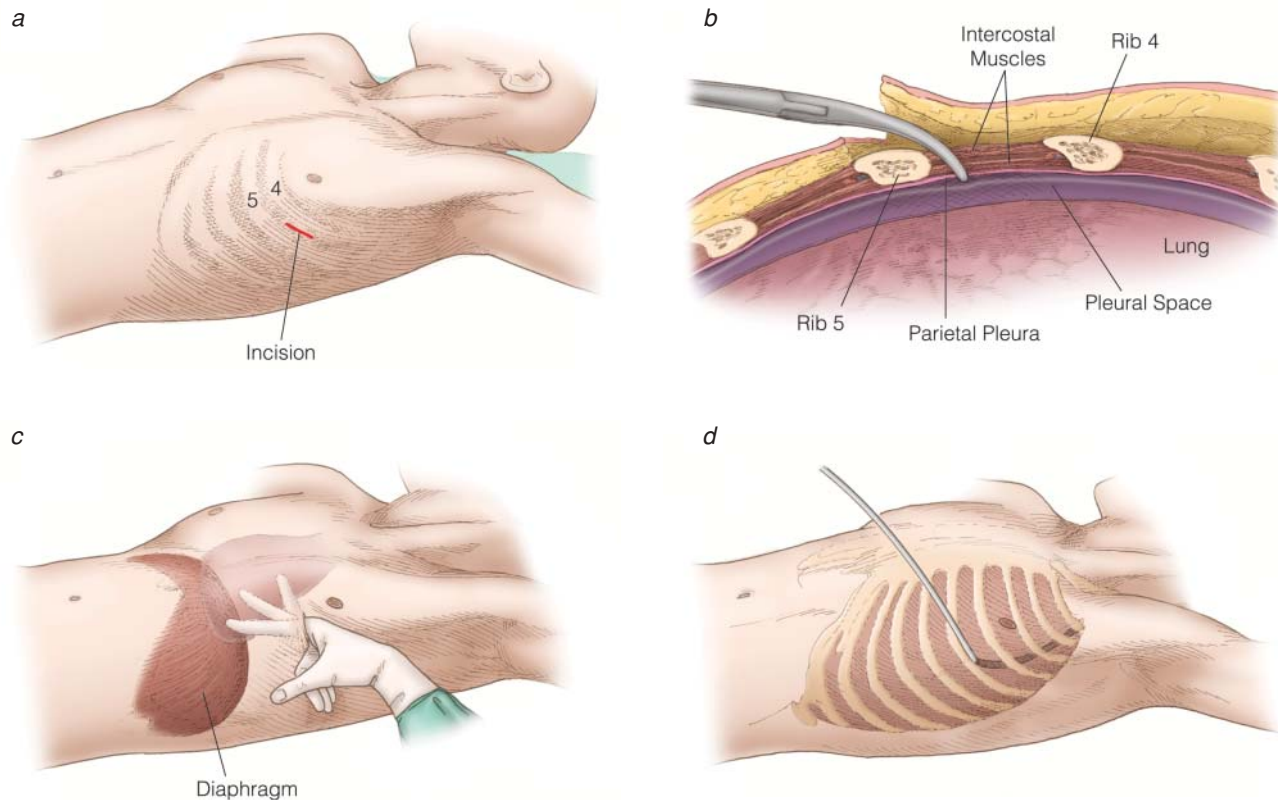


Figure 2 In acute trauma, a tube thoracostomy is performed through the fourth or fifth interspace at the midaxillary line, well above the diaphragm (a). A short subcutaneous tunnel is fashioned over the superior edge of the rib, and the overlying fascia and intercostal muscle are divided sharply. The pleural space is entered by incising the intercostal muscle and the pleura with a heavy scissors (b). A gloved finger is then inserted to confirm penetration of the thoracic cavity and to free up intrapleural adhesions (c). A large-bore tube (36 French) is directed posteriorly toward the pleural apex; the proximal port must be well inside the chest (d). The tube is then secured to the chest wall with No. 5 braided polyethylene suture and connected to a standard collection apparatus.

Hemodynamic instability develops after positive pressure ventilation is initiated as air is forced from the pulmonary bronchioles into the adjacent open pulmonary veins and, ultimately, into the coronary arteries. ED thoracotomy is essential for pulmonary hilar cross-clamping, air aspiration from the left ventricle, and cardiac massage. The patient is then transferred to the operating room (OR) for definitive management of the pulmonary lesion before the hilar clamp is released.

ED thoracotomy is an integral part of the initial management of the patient who arrives in extremis and deteriorates to imminent cardiac arrest [see Figure 3].²⁶ The physiologic rationale is to minimize the duration of profound shock. ED thoracotomy permits (1) release of pericardial tamponade, (2) internal cardiac massage, (3) cross-clamping of the descending thoracic aorta to enhance coronary and cerebral perfusion and to reduce subdiaphragmatic bleeding, and (4) control of intrathoracic blood loss. Internal cardiac massage should be done bimanually; otherwise, a forceful thumb may rupture the relatively thin right ventricle as it becomes distended. When blood volume is depleted or pericardial tamponade is present, closed-chest compression is ineffective in maintaining systemic blood flow, whereas open cardiac massage maintains coronary and cerebral perfusion for as long as half an hour. Adjunctive thoracic aorta occlusion

enhances both coronary and cerebral perfusion by maintaining aortic diastolic pressure and increasing carotid systolic pressure. Aortic cross-clamping also decreases subdiaphragmatic bleeding in the event of associated abdominal injury. These benefits are obtained at the expense of increased myocardial oxygen demand and poor perfusion of the lower torso. Clinical experience suggests that 30 minutes is the limit for prevention of splanchnic ischemic sequelae. The possibility of patient salvage is largely determined by the mechanism of injury, as well as by the patient's condition at the time of thoracotomy. Success rates approach 50% in patients arriving in shock from a penetrating cardiac wound and 20% in patients with penetrating wounds as a whole. On the other hand, patient outcome is dismal when ED thoracotomy is performed in the setting of blunt trauma; it is now considered futile in patients lacking cardiac activity. Ventricular lacerations of the heart are repaired with pledgeted horizontal mattress sutures, whereas atrial injuries are controlled with a partially occluding vascular clamp and repaired with a continuous suture [see Figure 4]. Small left ventricular wounds can be closed without pledgets. For large ventricular wounds, skin staples are an alternative means for rapid closure. Extensive injuries to the lung with ongoing major hemorrhage may require temporary hilar clamping to enable transport to the OR.

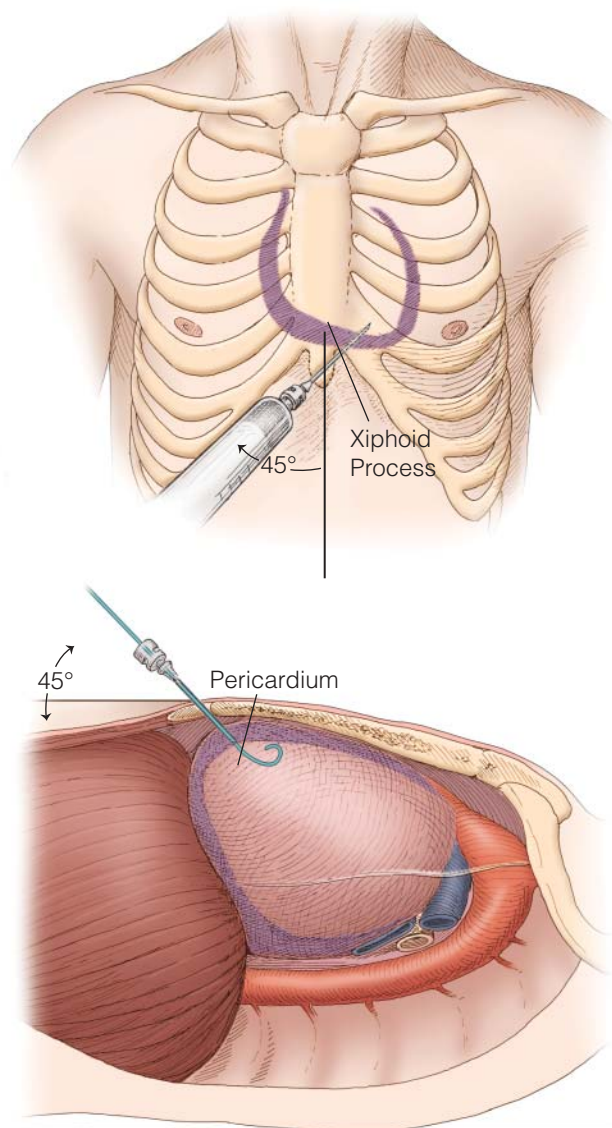
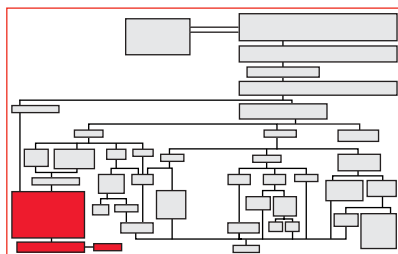


Figure 3 For pericardiocentesis, an 18-gauge spinal needle is inserted at the left xiphoid-costal junction and inserted toward the inferior tip of the left scapula (angled 45° to the patient's right and 45° from the chest wall). The needle is advanced until blood or air is encountered; a "pop" may be appreciated as the needle tip traverses the pericardium. If air is withdrawn, the needle tip should be directed more toward the patient's midline. If blood is withdrawn, 50 mL should be aspirated and injected onto a sheet so that it can be inspected for clots. As a rule, intraventricular blood will clot, whereas defibrinated pericardial blood will not clot.

SECONDARY SURVEY WITH DEFINITIVE DIAGNOSIS AND TRIAGE DECISIONS

Fortunately, most acutely injured patients arriving in shock can be rendered



hemodynamically stable enough to undergo a secondary survey. Diagnosis and treatment proceed simultaneously. Prioritization is imperative and is governed by the initial severity of shock and its response to ongoing resuscitation [see Table 4].²⁷ Easily correctable life-threatening injuries should be addressed first before a search is made for occult trauma. Prioritization is also guided by the mechanism of injury. Penetrating trauma typically results in a localized injury, whereas blunt trauma frequently results in multiple injuries involving several body regions. When hemodynamic instability recurs, its cause must be identified and corrected promptly.

The length of time spent in the ED, the decision for urgent operation, and the ordering of special radiologic studies are critical decisions that must take into account the mechanism of injury, the severity of shock, and the availability of a staffed OR. A patient in refractory shock with a central abdominal gunshot wound (GSW), for example, clearly should be transported to the OR in a matter of minutes, but the management of a previously unstable victim of a motor vehicle crash who has a positive abdominal ultrasonogram combined with altered mental status, a widened mediastinum on chest x-ray, and an unstable pelvic fracture requires a far more complex decision. In general, however, when priorities conflict, the safest arena for managing critically injured patients is the OR.

Penetrating Trauma

Systematic assessment The secondary survey is more focused in cases of penetrating trauma, but the most common problem error is failure to identify multiple injuries. The priorities are (1) to identify all of the wounds, (2) to decide whether an urgent operation is indicated, and (3) to determine whether additional testing is needed to assist with intraoperative management. The decision-making process is driven by hemodynamic stability and the location of the wounds. Efforts should focus not on resuscitating the patient until vital signs are normal but, rather, on obtaining adequate IV access, ensuring that blood products are available, and notifying the OR. Hemodynamically unstable patients should be rapidly sent to the OR with minimal testing. The most valuable tests are plain x-rays to determine missile trajectory.

Neck Patients who have an obvious life-threatening penetrating injury (e.g., a gurgling wound, pulsatile bleeding, or a compromised airway) or are in severe shock should undergo operation promptly. ED management should be limited to airway control, external compression to control bleeding, IV access, and chest x-ray. A neurologic examination should be performed and documented in the event of a spine or carotid artery injury.

Management of hemodynamically stable patients without obvious injury is selective.²⁸ Patients with zone I wounds should undergo computed tomographic angiography (CTA) scanning or angiography to rule out occult vascular injuries. Alert patients with zone II injuries but without significant hematoma, crepitation, dysphonia, or dysphagia may be managed expectantly.²⁹ The exception is a transverse GSW where CT scanning is usually done because of the high risk of an occult injury. Symptomatic patients with zone III injuries should undergo CTA scanning or angiography to assess for arterial injury that may warrant angioembolization.³⁰

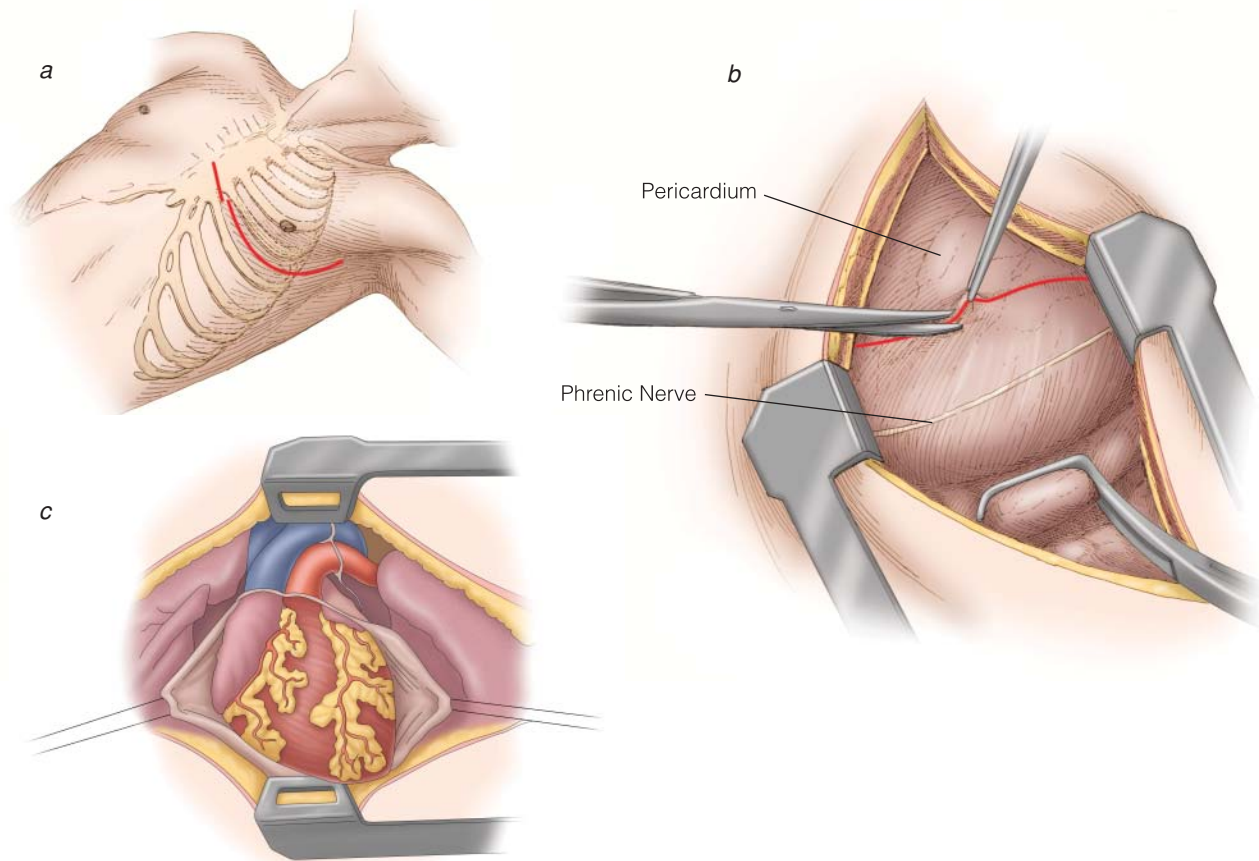


Figure 4 (a) A left anterolateral thoracotomy is performed through the fifth intercostal space. (b) The lung is reflected superiorly for placement of a Satinsky vascular clamp on the descending thoracic aorta. A pericardiotomy is performed with scissors anterior to the phrenic nerve. (c) A so-called butterfly extension across the sternum creates a bilateral anterolateral thoracotomy, providing access to both thoracic cavities and to the pulmonary hila, the heart, and the proximal great vessels.

Chest In unstable patients with thoracic injuries, a chest tube should be placed into the wounded hemithorax, followed by a chest x-ray to confirm tube placement, lung expansion, hemothorax evacuation, and the presence of foreign bodies. If a cardiac wound is suspected, ED ultra-

sonography should be performed.²² Persistent instability without evidence of intrathoracic bleeding or pericardial tamponade should raise the suspicion of intra-abdominal bleeding. Occasionally, a thoracic spinal cord injury contributes to hemodynamic instability.

The challenge in this setting is to quickly identify those patients who require an urgent operation. Patients with ultrasonographically documented hemopericardium and persistent tachycardia should undergo pericardiocentesis to relieve any ongoing subendocardial ischemia even if the SBP is normal, and a pigtailed catheter is inserted for repeated aspiration during transport to the OR [see Figure 5]. Patients who exhibit persistent signs of pericardial tamponade (e.g., CVP > 20 mm Hg) despite negative results from ultrasonography should be transported to the OR for creation of a subxiphoid pericardial window. If the patient is in extremis or deteriorates suddenly, ED thoracotomy should be performed promptly [see Figure 3]. Most patients diagnosed with intrathoracic bleeding outside the pericardium stabilize after tube thoracostomy and modest volume loading. Urgent thoracotomy is indicated for (1) so-called caked hemothorax [see Figure 6], (2) an initial chest tube output higher than 20 mL/kg, (3) a persistent output higher than 3 mL/kg/hr

Table 4 Hemodynamic Instability Score²⁷

Grade 0: No significant hypotension (systolic blood pressure < 90 mm Hg) or serious tachycardia (heart rate > 130)
Grade 1: Hypotension or tachycardia by report but none recorded in emergency department
Grade 2: Hypotension or tachycardia responsive to initial volume loading with no ongoing fluid or PRBC requirement
Grade 3: Hypotension or tachycardia responsive to initial volume loading with modest ongoing fluid (< 250 mL/hr) or PRBC requirement
Grade 4: Hypotension or tachycardia only responsive to > 2 liters of volume loading and the need for vigorous ongoing fluid infusion (> 250 mL/hr) and/or PRBC transfusion
Grade 5: Hypotension unresponsive to fluid and/or PRBC transfusion

PRBC = packed red blood cell.

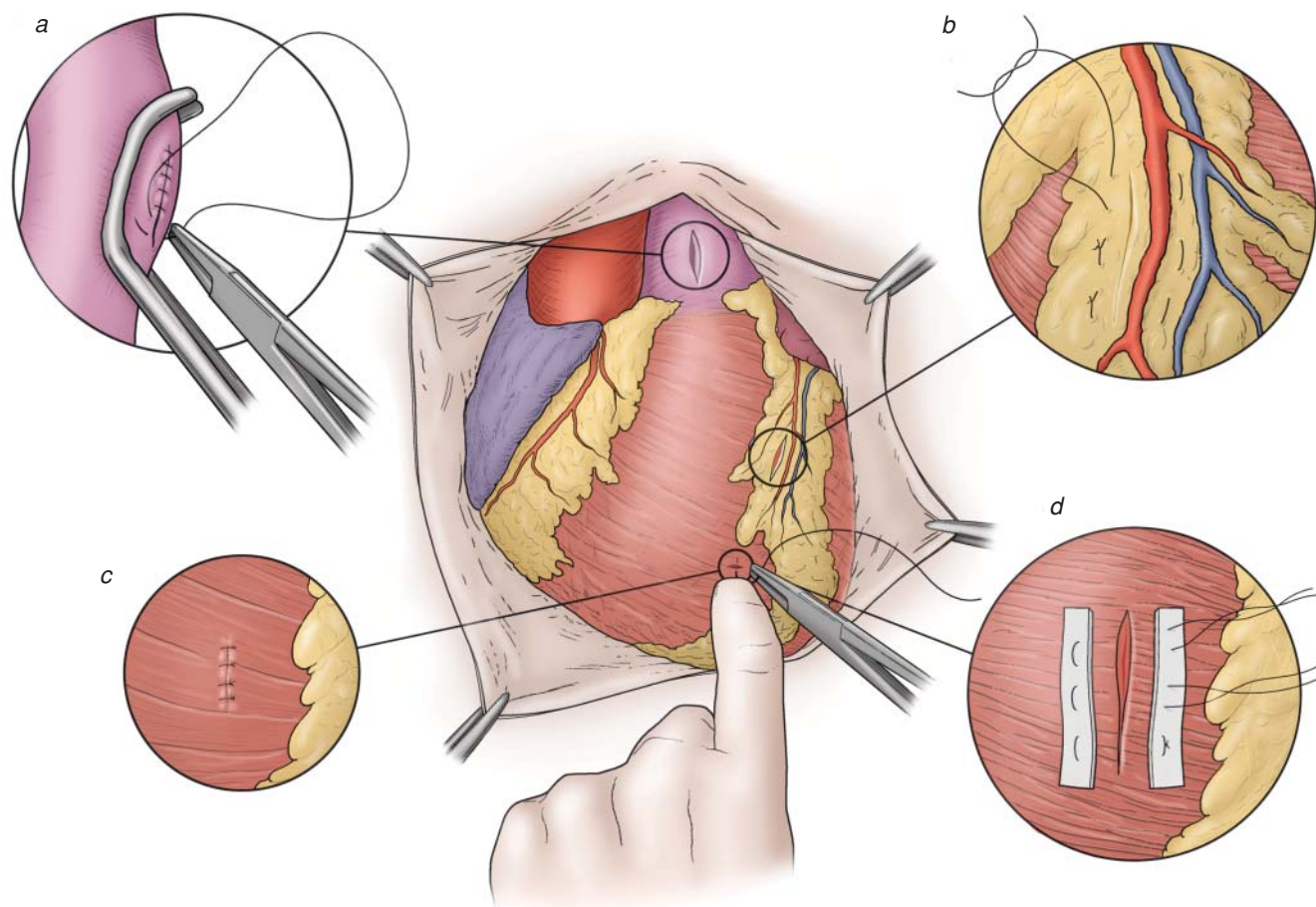


Figure 5 (a) A Satinsky vascular clamp is used to control arterial and major vessel injuries while they are closed with a running suture. (b) For wounds close to coronary arteries, horizontal mattress sutures should be used to spare the arteries. (c) Small wounds to the thick left ventricle can be closed with interrupted simple sutures. (d) Larger wounds should be closed using pledgets; staple closure may be preferred for larger ventricular wounds.

for 3 consecutive hours, or (4) a 12-hour output exceeding 30 mL/kg. Patients with an initial chest tube output higher than 10 mL/kg should be closely observed for hemodynamic instability in the intensive care unit (ICU). Abrupt cessation of chest tube output may be deceptive; if hypotension persists or recurs, a second chest tube should be inserted and another chest x-ray obtained.³¹

Patients with large air leaks, massive subcutaneous emphysema, or a persistent pneumothorax should undergo bronchoscopy to exclude a tracheobronchial injury. Patients with transmediastinal GSWs or penetrating wounds close to the great vessels should undergo CT scanning, and angiography should be done if the trajectory delineated on the CT scan is in proximity to a major artery.³²

Lower chest Wounds located below the nipples anteriorly or the tips of the scapulas posteriorly may penetrate the diaphragm and cause significant intra-abdominal or retroperitoneal injuries. Such penetration occurs in 10% of stab wounds and 30% of GSWs.³³ If the patient is unstable, tube thoracostomy, chest x-ray, and abdominal ultrasonography

are indicated. If instability persists, the patient should be transported to the OR. If the patient stabilizes after tube thoracostomy, additional testing must be done to exclude associated injuries. Diagnostic peritoneal lavage (DPL) is a good screening test for intra-abdominal injuries. The red blood cell (RBC) threshold for OR interventions to rule out diaphragmatic injuries is lowered because the injury may not bleed substantially.³⁴ Thoracoscopy is performed for RBC counts between 1,000 and 10,000/ μ L and laparoscopy or laparotomy is performed for RBC counts greater than 10,000/ μ L. Left-sided penetrating injuries should be pursued more aggressively because of the increased risk of delayed visceral herniation. CT scanning may assist in diagnosing occult retroperitoneal injuries but is not reliable for excluding penetrating diaphragmatic injuries.

Anterior abdomen Unstable patients should be transported to the OR with minimal resuscitation and testing. Biplanar abdominal x-rays are often helpful in clarifying bullet trajectories; entrance and exit wounds should be



Figure 6 An emergency department chest x-ray shows a massive hemothorax. If the chest tube fails to evacuate the blood, this is a so-called caked hemothorax, which is an indication for emergency thoracotomy in the operating room.

marked with radiopaque objects. Management of stable patients depends on the mechanism of injury. Although there is some enthusiasm for selective management of GSWs, laparotomy is generally recommended for GSWs that violate the peritoneal cavity.³⁵ CT scanning or laparoscopy is indicated for suspicious tangential GSWs. Laparotomy is indicated in patients with overt peritonitis after a stab wound. In other patients, the stab wound should be explored. If there is no violation of the anterior fascia, the patient can safely be discharged. If the fascia is violated, the patient should be admitted for serial clinical assessments.³⁶

Retroperitoneal structures Unstable patients with injuries to the flank, the back, or the pelvis should undergo immediate laparotomy. Stable patients are difficult to evaluate. With the exception of blood on rectal examination, the findings from physical examination are unreliable. Gross hematuria is indicative of bladder or kidney injury. Triple-contrast CT scanning may be helpful in patients with high-risk wounds.³⁷ Most retroperitoneal colon injuries are identified on the basis of extraluminal gas or fluid rather than of contrast extravasation. Sigmoidoscopy should be performed if a rectal injury is suspected. High-risk wounds should be explored to ensure that retroperitoneal colon injuries are not missed; delayed diagnosis is associated with significant morbidity.

Extremities Unstable patients with isolated penetrating injuries to the extremities should be managed with external compression to control bleeding. Blind clamping for vascular injuries should not be done because of injury risk to adjacent nerves. IV access with modest volume loading, and prompt triage to the OR for exploration and definitive treatment. Recent war experience indicates that tourniquet use was a valuable adjunct in saving lives in the setting of explosions that caused mangled or amputated extremities; however, the follow-up studies related to limb morbidity were limited.³⁸ How this practice transcends into civilian trauma is conjectural, but it is important to emphasize that the inappropriate

use of tourniquets can cause considerable harm. It is important to note that although extremity injuries are common in civilian trauma, death from extremity exsanguination is rare.

Management of stable patients with penetrating extremity injuries begins with a search for “hard” signs of arterial injury (e.g., an expanding or pulsatile hematoma, absent distal pulses, a palpable thrill, an audible bruit, or signs of distal ischemia). The presence of any of these hard signs prompts further evaluation. If signs of distal ischemia exist, the patient should be taken to the OR, where on-table angiography is performed to identify the injury site. If knowledge of the patient’s specific vascular anatomy is needed and no signs of ischemia exist, a formal angiogram is reasonable. If “soft” signs (i.e., a history of arterial bleeding prior to ED admission, wound proximity to an artery, small nonpulsatile hematoma over the artery, nerve deficit originating in a nerve adjacent to the artery) of vascular injury are present, distal blood pressures should be measured in the injured extremity, the contralateral extremity. If the ratio of the BP in the injured extremity to that in the contralateral extremity is 0.90 or higher, arterial injury is virtually excluded and no additional testing is needed. These patients can be discharged from the ED but should follow up in the outpatient clinic because a small percentage will eventually come to operation as the original undetected injury progresses rather than heals. These ratios are not, however, reliable for excluding arterial injuries in the axilla or the groin. Furthermore, the presence of a “good” Doppler signal does not exclude an arterial injury.

Blunt Trauma

Systematic assessment The goal is to identify all potentially life- and limb-threatening injuries. A comprehensive assessment is crucial to facilitate triage from the ED to the OR, the CT scanning suite, the interventional radiology suite, or the ICU. The details of the patient’s medical history, as well as the details specifically related to the injury, are critical. The prehospital emergency medical technicians are encouraged to provide a comprehensive account of the event and a thorough patient assessment. A minimal review of the patient’s medical history should include preexisting medical illnesses, current medications (especially anticoagulation status in the elderly), allergies, tetanus immunization status, and the time of the last meal.³⁹ A helpful method to recall this list is the ATLS AMPLE: Allergies, Medications, Past illness, Last meal and Events/Environment. A rapid, systematic physical examination is done, literally from head to toe. Patients are completely disrobed and, once spinal injury is excluded, are rolled from side to side so that the back and the flanks can be inspected. A rectal examination is done to look for blood and to evaluate sphincter tone; the perineum and the axillae are inspected; and neurologic function and peripheral pulses are documented.

The cervical spine is rigidly immobilized, and long-bone fractures are splinted to minimize pain, blood loss, and soft tissue damage. Insertion of a gastric tube decompresses the stomach and reduces the risk of pulmonary aspiration; because maxillofacial injury may provide a pathway into the cranial vault,⁴⁰ the tube should be placed orally when midfacial fractures are present. Blood in the gastric aspirate may be the only sign of an otherwise occult injury to the stomach or the duodenum.

Placement of a Foley catheter empties the bladder, discloses hematuria, and permits the physician to monitor urinary output. The Foley catheter should not, however, be inserted until abdominal ultrasonography is completed, and it should not be placed on an urgent basis in male patients with suspected urethral injuries (i.e., those with blood at the meatus, a perineal hematoma, a high-riding prostate, or an extensively displaced anterior pelvic fracture). If urethral injury is suspected, a retrograde urethrogram, followed by a cystogram (to exclude bladder injury), is obtained, prioritized in accordance with the given setting. In females, the urethra is shorter and better protected and thus is rarely injured.

Routine x-rays performed simultaneously with the ABCs include anteroposterior chest and pelvic films. CT scanning has virtually replaced plain x-rays for diagnosing potential spinal injuries. Once life-threatening injuries have been addressed, x-rays of extremities with suspected fractures (including the joint above and the joint below) should also be obtained, but preferably with guidance from an orthopedic surgeon.

Given that trauma victims are uniquely susceptible to hypothermia, a rectal or bladder temperature probe is essential in those who have been exposed to a cold environment or who require massive volume replacement. A core temperature reading lower than 32°C (89.6°F) should be confirmed with an esophageal probe, and rewarming measures appropriate for the degree of hypothermia should be initiated. Tetanus prophylaxis is routine. Systemic antibiotics should be withheld until a specific indication arises.⁴¹ An ECG is obtained after blunt chest trauma, and an ABG analysis is done in select patients to confirm adequate ventilation and metabolic balance. In patients with evidence of significant hypovolemia, a blood sample should be sent for blood-group typing and coagulation studies.

Rapid hemorrhage control Blunt trauma patients who arrive in shock and remain hemodynamically unstable pose difficult triage decisions. Initial screening must be directed at identifying life-threatening bleeding that necessitates immediate OR intervention. Most hospitals do not have an interventional radiology suite immediately available; early notification is crucial in assembling the team. At our institutions, after normal working hours, this process consumes more than 1 hour.

Initial screening focuses on the chest, the abdomen, and the pelvis. A chest x-ray is the most reliable screening test for intrathoracic bleeding; it also confirms the location of endotracheal, nasogastric, and thoracostomy tubes, as well as that of the central venous catheter. The presence of pleural fluid may be difficult to confirm on a supine chest x-ray: 1 L of blood may produce only a hazy appearance in a hemithorax. Hemothoraces should be drained promptly via tube thoracostomy [see Figure 2]. Continued bleeding must be monitored carefully by measuring chest tube output, obtaining serial chest films to detect retained intrapleural blood, and observing vital signs. The criteria used to decide when thoracotomy is indicated are similar to those used in cases of penetrating trauma, but far fewer blunt trauma patients meet these criteria, and intrathoracic bleeding is rarely a reason for immediate OR triage.

The abdomen is notoriously difficult to evaluate and is much more likely than the chest to harbor occult life-threatening bleeding. The peritoneal cavity may sequester as much as 3 L of blood with only minimal abdominal distention. Head injury or intoxication frequently alters the patient's response to acute injury, and pain from associated fractures may overshadow peritoneal irritation secondary to bleeding. Ultrasonography [see Figure 7 and Figure 8] is the most rapid method of identifying free blood, but it may yield false negative results in as many as 15% of patients on initial examination.⁴² Diagnostic peritoneal aspirate (DPA) [see Figure 9] remains the most reliable method of identifying significant intraperitoneal hemorrhage in patients with life-threatening bleeding.⁴³ In patients presenting in high-grade shock, a grossly positive aspirate (> 10 mL of blood) warrants emergency laparotomy.²⁷

Assessment of bony stability by means of physical examination and plain films of the pelvis is crucial for the early identification of major pelvic fractures. Life-threatening hemorrhage occurs most commonly with fracture patterns involving the posterior columns [see Figure 10]. Appropriate initial management of unstable patients who have a high-risk pelvic fracture on the initial pelvic x-ray includes blood volume replacement (including early blood and FFP) and

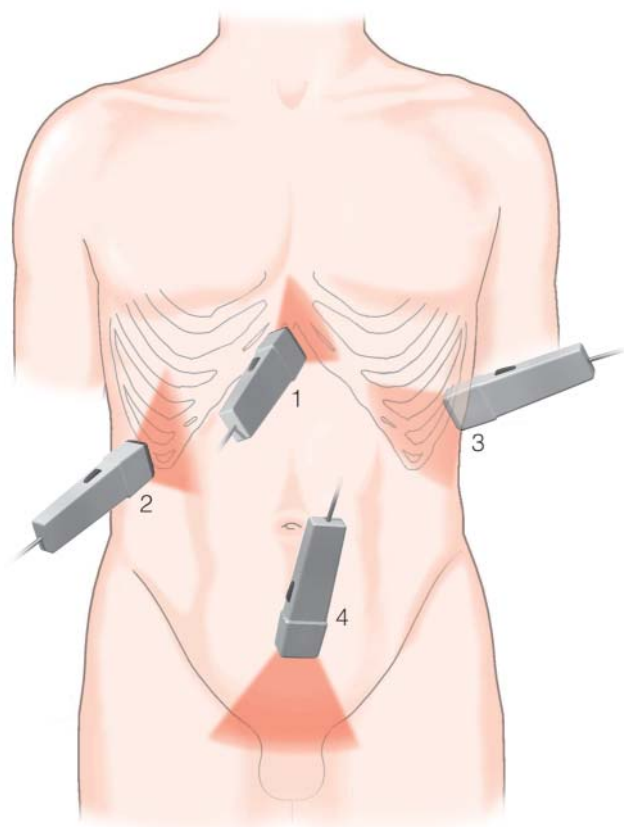


Figure 7 Shown are four transducer positions in the FAST (focused assessment with sonographic evaluation of the trauma patient): (1) pericardial area, (2) right upper quadrant, (3) left upper quadrant, and (4) pelvis.

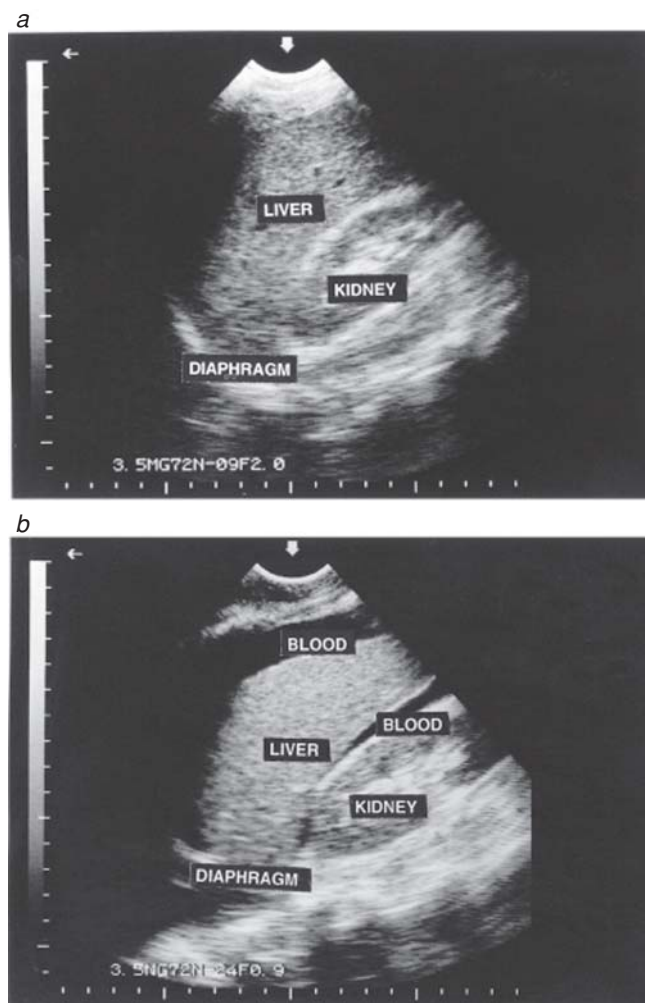


Figure 8 (a) A sagittal ultrasound image of liver, kidney, and diaphragm yields normal findings. (b) A sagittal ultrasound image of the right upper quadrant shows blood between the liver and kidney and between the liver and diaphragm.

application of a pelvic binder; wrapping with a sheet is also effective [see Figure 11].

The next step is to evaluate the response to initial resuscitation and then perform ultrasonography or DPA to determine whether significant intra-abdominal bleeding is present.^{44,45} An unstable patient with clearly positive findings from ultrasonography or DPA should undergo laparotomy because of the high probability of major hepatic, splenic, or mesenteric bleeding. If there is a large pelvic hematoma at the time of laparotomy and the patient is unstable, extraperitoneal pelvic packing should be done [see Figure 12].⁴⁶ The role of pelvic packing versus angioembolization is controversial, but these modalities should be viewed as complementary.⁴⁷

Fast-track CT scanning to refine triage In unstable patients who respond to initial interventions, the priorities are to (1) identify and quantitate ongoing sources of bleeding; (2) identify TBI, especially in those patients who require immediate craniotomy; and (3) identify any other injuries that call for urgent intervention (e.g., thoracic aortic injury

[TAI]) or special precautions (e.g., spine fractures). With the widespread availability of multidetector CT scanners in proximity to the ED, rapid whole-body imaging is now feasible, permitting accurate triage for these competing priorities.⁴⁸ The decision to order CT scanning is made early, while the ABCs are being addressed and ultrasonography and initial plain x-rays are being performed, and depends on the age of the patient, any obvious injuries identified, and the patient's hemodynamic stability. The decision is less clear-cut in the common situation in which a previously unstable patient has a positive abdominal ultrasonogram. The key issue here is which injuries identified by CT scanning would alter the decision to perform an urgent laparotomy. Some institutions make much larger "cuts" so that the scan can be done faster, and the final CT scans lacks the detail needed to describe injuries well and may miss injuries in the abdomen and pelvis.

Identification of abdominal injuries The decision to perform an urgent laparotomy in a patient with a positive ultrasonogram depends on the patient's hemodynamic stability. A CT scan can be helpful in refining triage by identifying extravasation of IV contrast (i.e., a blush) and in diagnosing hollow viscus injuries. A blush should prompt consideration of angiography. Early angiography is a helpful adjunct in managing liver and kidney injuries, although its role in managing acute splenic injuries remains to be established.^{27,49,50} Hollow viscus injury is notoriously difficult to diagnose; extravasation of oral contrast is rare.^{51,52} When all signs (e.g., unexplained free fluid, bowel wall thickening, mesenteric streaking, and free air) are considered, however, the sensitivity of CT in making the diagnosis approaches 90%. In questionable cases of hollow viscus injury in stabilized patients, we advocate delayed DPL to search for elevations in WBC count, amylase level, and alkaline phosphatase level. Pancreatic injury is also poorly defined on the initial CT scan. A rising lipase warrants repeat CT scanning (and consideration for endoscopic retrograde cholangiopancreatography or magnetic retrograde cholangiopancreatography).⁵³

Identification of TBI Approximately 20% of blunt trauma patients who arrive in shock have a TBI.⁵⁴ During the initial evaluation, it is important to identify TBI patients who might benefit from an emergency craniotomy. The neurologic examination is of utmost importance. The initial Glasgow Coma Scale (GCS) score in the field should be confirmed with prehospital personnel, and short-acting sedatives or paralytics should be given sparingly. A GCS score lower than 8 and a lateralizing neurologic examination indicate a significant risk that emergency craniotomy will be needed and, therefore, justify obtaining a CT scan of the head if hemodynamic stability permits.^{55,56}

Identification of TAI Initial plain films should be examined for evidence of TAI. We use the overpenetrated mediastinal view and specifically look for evidence of a mediastinal hematoma. In the multi-institutional study from the American Association for the Surgery of Trauma (AAST) however, 7% of patients with TAI had a normal ED chest x-ray. We therefore obtain a chest CT scan on the basis

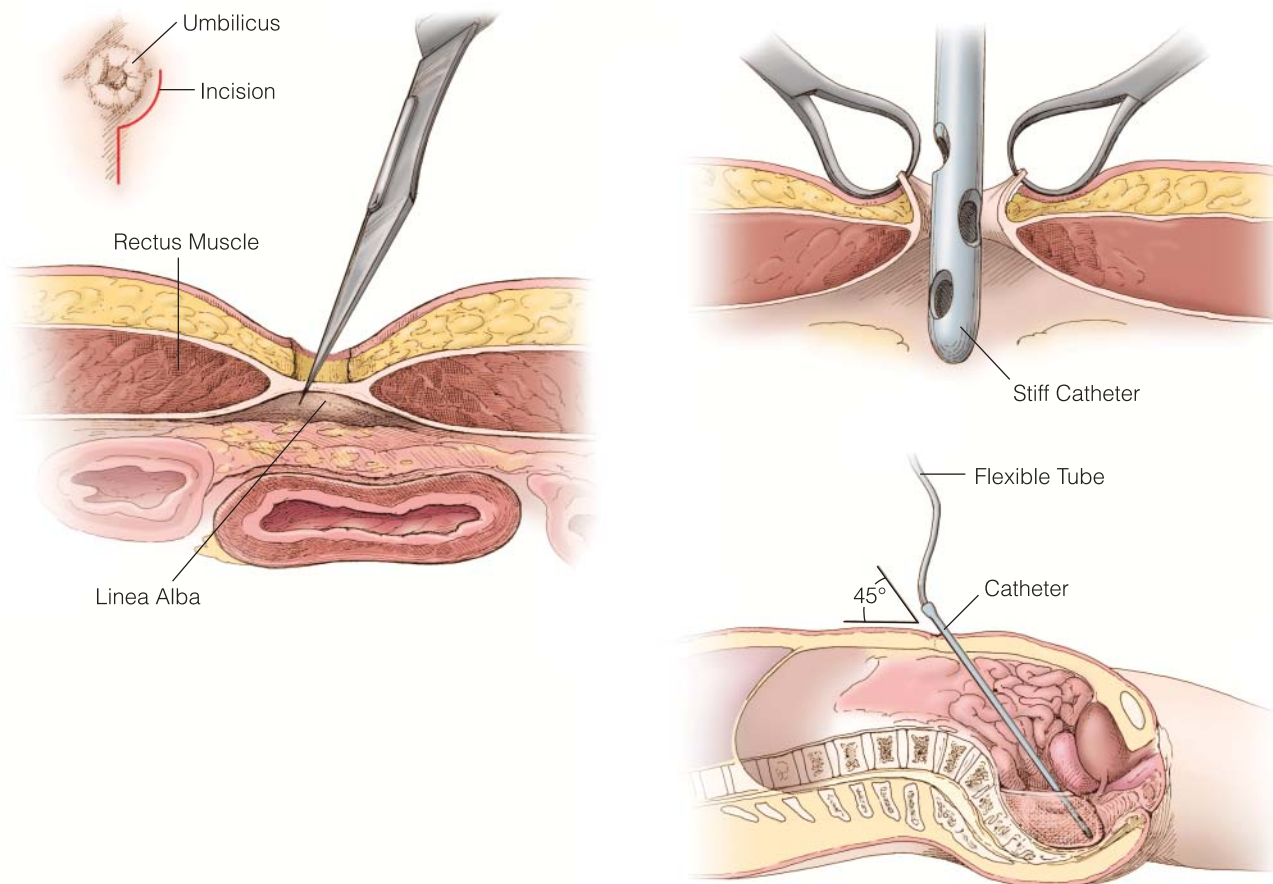


Figure 9 Illustrated here is the semiopen technique for peritoneal lavage. A 3 to 4 cm incision is made over the infraumbilical ring, and the linea alba is incised vertically for 1 cm. The fascial edges are grasped with towel clips and elevated. A standard peritoneal dialysis catheter is introduced into the peritoneum at a 45° angle and then advanced into the pelvis without use of the trocar. If 10 mL of gross blood is aspirated, the study is considered to be positive. Otherwise, 1 L of normal saline (10 mL/kg for children) is infused. The lavage fluid is retrieved by gravity siphonage; the empty saline bag is dropped to the floor. Ultrasonography is helpful for confirming intraperitoneal fluid infusion. A 50 mL sample of the fluid is submitted for laboratory analysis.

of the mechanism of injury.⁵⁷ CT scanning has replaced angiography for the diagnosis of TAI. An occasional angiogram is done to confirm the diagnosis of great vessel injury or to clarify the vascular anatomy before thoracotomy.

The management of TAI has changed markedly over the past decade. Traditionally, a diagnosis of TAI mandated urgent thoracotomy. Currently, however, antihypertensive therapy and ICU monitoring allow delayed repair in patients with significant associated injuries.⁵⁸ Additionally, endovascular stenting has become preferred over open repair for favorable lesions.⁵⁹

Identification of limb ischemia The absence of distal pulses in a fractured or dislocated extremity should be addressed urgently. Fractures and dislocations should be reduced, and the extremity should be closely examined for signs of ischemia.⁶⁰ Distal SBP measurements comparing injured limbs with noninjured limbs (i.e., the ankle-ankle index [AAI] or the ankle-brachial index [ABI]) should be obtained. If the ABI or AAI is less than 0.90 after reduction, CTA should be performed to exclude the presence of an arterial injury.^{61,62} A pulseless extremity is best evaluated in the OR by means of on-table angiography.

Discussion

Prehospital Care

ADVANCED TRAUMA LIFE SUPPORT

The growing sophistication of EMS has expanded the scope of prehospital care, but the extent of prehospital

interventions remains a highly controversial issue.¹ In trauma, advocates of the so-called scoop-and-run philosophy argue that resuscitative efforts in the field unnecessarily delay provision of definitive care and have detrimental effects on physiology and survival when overzealously applied. At

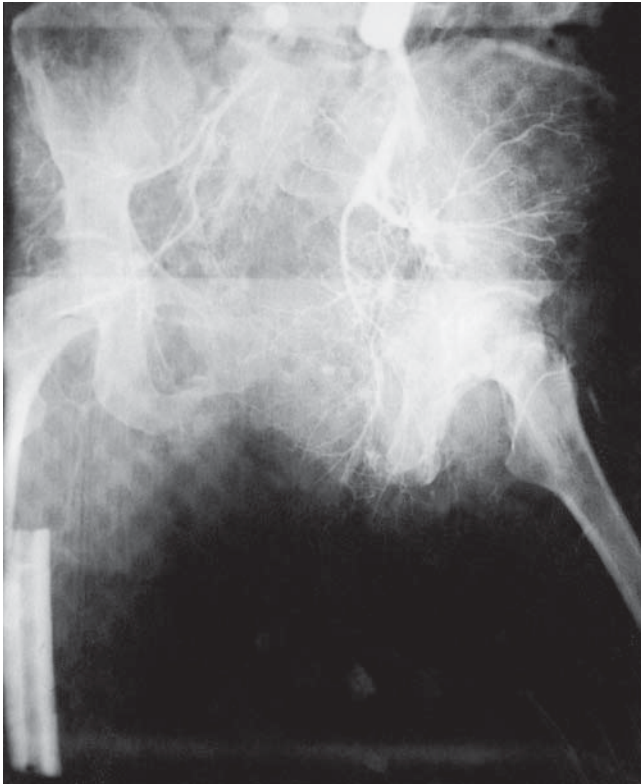


Figure 10 Pelvic angiography with selective embolization may be an integral component in the early management of a major pelvic crush injury with continuing hemorrhage.

present, there is little evidence to support the use of ATLS in prehospital management of urban trauma patients. ATLS skills may be of value in rural areas where transport time exceeds 30 minutes, but, unfortunately, the limited volume of serious trauma in such areas makes it difficult to gain the experience necessary to maintain this expertise.

Prehospital Airway Management

The goal of initial resuscitation is to restore adequate oxygen delivery to vital organs. Efforts to improve tissue perfusion will be unproductive unless the oxygen content of the circulating blood is sufficient. Airway patency and maintenance of adequate ventilation are thus the initial priorities. However, intubation and positive pressure ventilation inhibit venous return to the heart and detrimentally decrease cardiac output in hypovolemic patients.⁶³ Furthermore, patients intubated in the field are often hyperventilated, and the resulting low P_{aCO_2} causes cerebral vasoconstriction. Routine end-tidal capnometry for TBI patients undergoing field intubation has been proposed as the standard of care for preventing excessive hyperventilation.² In addition, emergency airway control after blunt trauma should be performed with the assumption that an unstable cervical spine fracture exists until such injuries are excluded radiologically, but this policy does not preclude RSI. The current recommendation—oro-tracheal intubation with in-line manual stabilization of the head and neck—has proven safe. When oro-tracheal intubation fails, the laryngeal mask airway is a rapid, safe, and effective technique

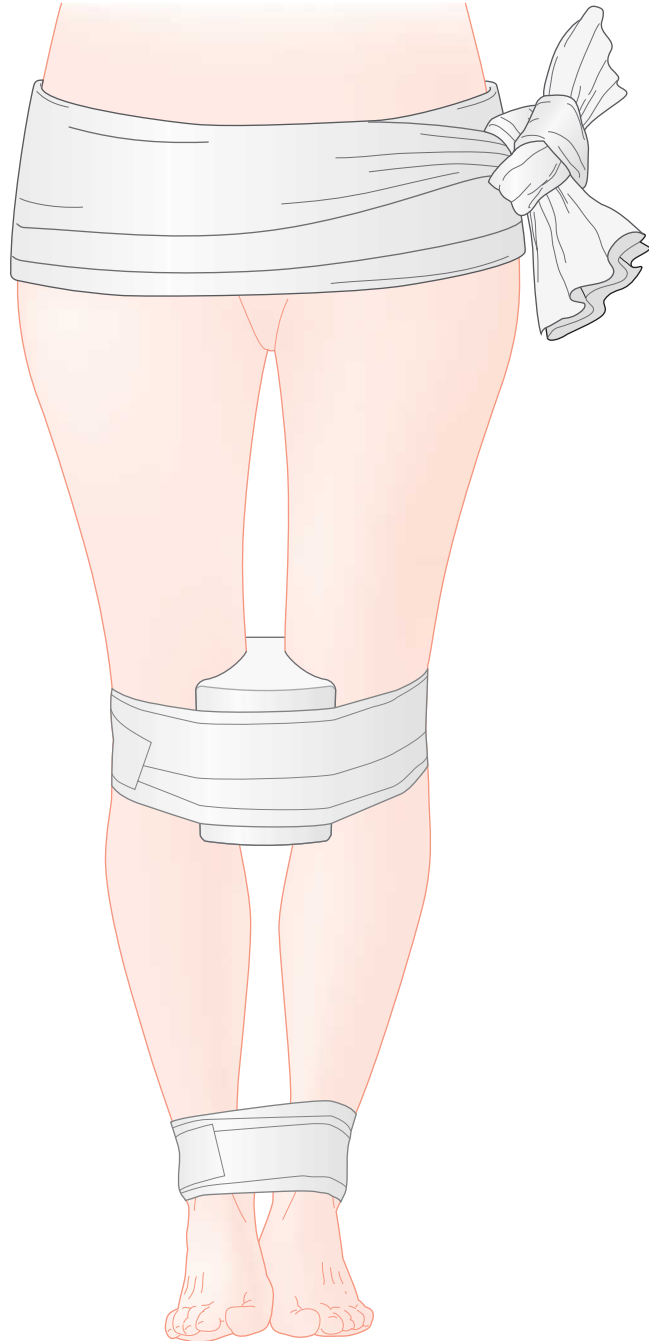


Figure 11 Shown is the wrapping technique currently used for support of a mechanically unstable pelvic fracture.

for maintaining temporary airway control until definitive medical care becomes available.¹¹ For patients with extensive maxillofacial trauma that precludes oral intubation, cricothyrotomy has been the traditional alternative, but this procedure has some risks, particularly in children.

Prehospital Volume Resuscitation

A provocative 1994 clinical trial found that for hypotensive patients with penetrating torso injuries, survival improved when fluid resuscitation was delayed until surgical intervention

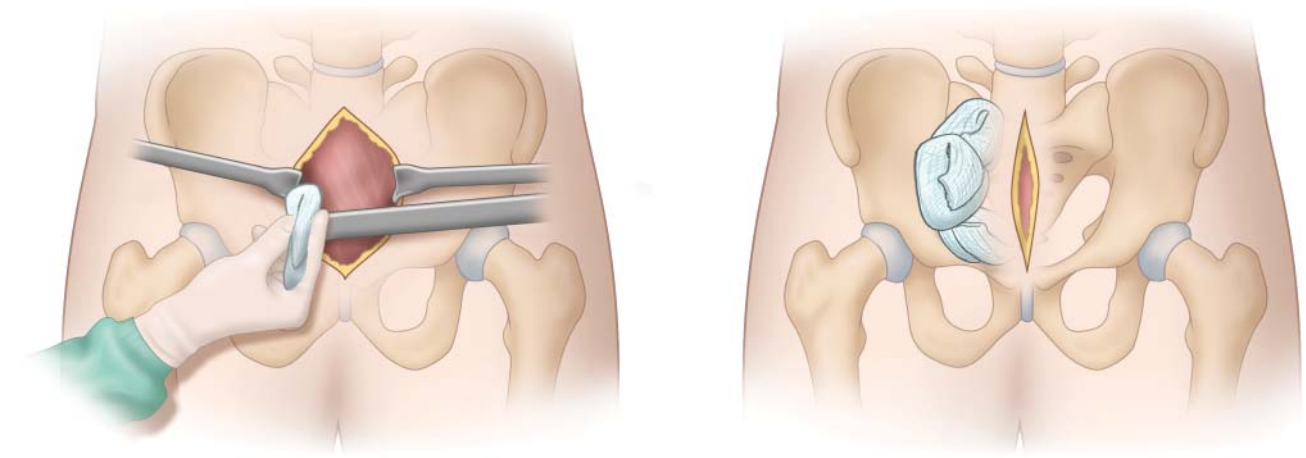


Figure 12 Preperitoneal pelvic packing (PPP) is performed through a 6 to 8 cm midline incision made from the pubic symphysis cephalad, with division of the midline fascia. The pelvic hematoma often dissects the preperitoneal and paravesical space down to the presacral region, facilitating PPP; alternatively, blunt digital dissection opens the preperitoneal space for packing. Three standard surgical laparotomy pads are placed on each side of the bladder, deep within the preperitoneal space, and the fascia is closed with O-PDS suture and the skin with staples.

had controlled the source of hemorrhage.³ A subsequent subset analysis, however, revealed that survival was improved only in patients who had sustained cardiac injuries, not in patients who had sustained major vascular, abdominal solid organ, or noncardiac thoracic injuries.⁶⁴ Although this clinical trial had some methodologic flaws, it was important because it emphasizes that source control of hemorrhage is an overriding priority in hemodynamically unstable patients.

Whether fluid resuscitation should be withheld until control of hemorrhage is achieved is doubtful; such an approach is clearly not the current standard of care. The critical issue is whether it is preferable to administer fluids to restore oxygen delivery to tissue, but potentially causing hemodilution and disruption of early hemostatic clots, or to withhold fluid resuscitation, prolonging cellular shock to the point where it may be irreversible by the time operative control is accomplished. At present, the rational compromise between these two extremes is hypotensive resuscitation with limited volume loading with the goal of maintaining SBP > 90 mm Hg.^{65,66} This approach is becoming the standard of care for penetrating trauma, but its application to blunt trauma is not as clear as 20% of patients with major torso trauma have a serious concomitant TBI and hypotension is a well-documented risk factor for poor outcomes with TBI.

Resuscitation with Hypertonic Saline

A report by Velasco and colleagues in 1980 spurred renewed research interest in hypertonic saline (HS).⁶⁷ Small-volume HS was shown to be as effective as large-volume crystalloids in expanding plasma volume and enhancing cardiac output in hemorrhagic shock in animals. Furthermore, HS increased perfusion of the microcirculation, presumably by selective arteriolar vasodilatation and by decreasing swelling of the endothelium. This improved microcirculation, however, could lead to increased bleeding. Consequently, HS was tested in animal models of uncontrolled hemorrhagic shock and was shown to increase bleeding, but mortality was model

dependent, and the best survival was obtained when HS was given with high-volume isotonic crystalloids. Additionally, the resuscitative effectiveness of HS was found to be enhanced by combination with dextran (hypertonic saline dextran [HSD]). In view of the small volume needed to achieve these effects, there was great interest in the use of HS in resuscitation in the field for both military and civilian use. From the late 1980s through the early 1990s, prospective randomized controlled trials (PRCTs) were performed.¹³ Individually, these trials found survival outcome to be inconsistently improved but did document that a bolus of HS is safe. Meta-analysis of these data suggests that HS is no better than standard-of-care isotonic crystalloid fluids.⁶⁸ Subgroup analysis of the data showed that the patients who benefited most from HSD were those who presented with shock and concomitant severe TBI. The results of this analysis agreed with laboratory data showing that in comparison with isotonic crystalloid, both HS and HSD raised cerebral perfusion pressure, lowered intracranial pressure, and reduced brain edema. However, one well-executed trial that tested HS for field resuscitation of TBI patients in shock did not demonstrate any benefits.⁶⁹

Recent laboratory studies have again renewed interest in the use of HS in early traumatic shock resuscitation. Numerous basic laboratory investigators have convincingly shown that HS resuscitation markedly decreases the inflammatory response (specifically neutrophil cytotoxicity) in animal models of hemorrhagic shock, ischemia/reperfusion, and sepsis. One very interesting clinical PRCT from Toronto showed that an immunomodulatory effect occurs in humans who are undergoing shock resuscitation.⁷⁰ The researchers showed that HS promotes a more balanced inflammatory response to hemorrhagic shock. This raises the possibility that, similar to observations made in experimental models, HS might also decrease the incidence and severity of post-traumatic acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF). This hypothesis was tested in

a recent clinical PRCT from Harborview Medical Center in Seattle.⁷¹ The study was stopped for futility after the second interim analysis. Intent-to treat analysis demonstrated no significant difference in ARDS-free survival. Most recently, a National Institutes of Health (NIH)-sponsored Resuscitation Outcomes Consortium multicenter trial testing HS demonstrated similar disappointing results.⁷² This involved two parallel studies. The first (which enrolled trauma patients in shock with severe bleeding) was stopped in March 2009 because of safety concerns noted in an interim analysis. Although overall 28-day mortality was not different, more of the patients receiving HSD were dying earlier than those who received NS. The second study (which enrolled TBI patients) was stopped after interim analysis of 1,073 patients who were followed for 6 months and demonstrated no differences in outcomes. In summary, although the experimental data supporting HS resuscitation in the setting of traumatic shock with or without TBI are very compelling, HS resuscitation has been very extensively tested in the clinical setting for these indications, and there are no conclusive data to support its routine use.

ED Management

BLOOD VOLUME RESTITUTION

Traditional Crystalloid versus Colloid Debate

Since the early 1940s, restoration of blood volume has been embraced as a pivotal intervention in shock resuscitation; however, considerable controversy has persisted concerning optimal fluid to use.¹⁴ Plasma and serum were considered the best substitutes for whole blood and, in some cases, better than blood itself. This was the resuscitation strategy used in World War II, and renal failure was noted to be a major cause of late deaths in soldiers who survived shock resuscitation. Isotonic crystalloids became the standard of care in the late 1960s based on the laboratory work of Shires and colleagues and Dillon and colleagues, as well as others.^{73,74} Their basic concept was that during hemorrhagic shock, interstitial fluid is redistributed into both the intravascular and intracellular spaces; thus, large-volume resuscitation with isotonic crystalloids is needed to replenish losses from both the intravascular and interstitial spaces. These investigators empirically observed that optimal resuscitation to correct this extracellular fluid deficit required infusion of isotonic crystalloid fluid and shed blood in a ratio of three volumes of crystalloid to one of blood.⁷⁵

As a result of this experimental work, isotonic crystalloid fluids were used in the Vietnam conflict. For various reasons, mortality and acute renal failure decreased, but a new entity called “shock lung” emerged as a major cause of late deaths. This complication was soon described in civilian publications as ARDS and was shown to be the major source of morbidity and mortality in the ICU. The pathogenesis was not known, but controversy existed over whether ARDS was an iatrogenic complication of resuscitation with isotonic crystalloids.

Beginning in the mid-1970s, PRCTs were done to compare crystalloids with colloids in resuscitation, with pulmonary dysfunction as the primary end point. The results were conflicting and in large part were attributable to shortcomings

in study design (i.e., small numbers of patients, heterogeneous populations, and different resuscitation end points and sodium loads), as well as difficulty in defining pulmonary dysfunction. These data have been assessed by meta-analysis, and no difference in the incidence of pulmonary dysfunction has been found.⁷⁶ However, when mortality is used as the end point and the data are subgrouped, the use of crystalloids in trauma patients is associated with improved survival.

The same subgroup analysis was done in the most recent SAFE trial, and again the use of isotonic crystalloids compared to albumin in trauma patients was associated with improved survival.⁷⁷ Although these subgroup data are not definitive, they are consistent with the early laboratory work and do support the current use of crystalloids in US trauma centers. Additionally, it has been difficult to justify the standard use of colloid solutions because they are considerably more expensive than crystalloid solutions. The relative costs per 500 cc of intravascular volume expansion is \$130 for albumin 25%, \$88 for albumin 5%, \$78 for plasmonate 5%, \$20 for dextran 70%, \$20 for hetastarch 6%, and 17% for Hextend compared to \$3 for LR solution.

Choice of Crystalloid

The selection of a crystalloid engenders less controversy than the choice between crystalloid and colloid. Although newer formulations (e.g., Ringer ethyl pyruvate) are being tested clinically,⁷⁸ NS and LR solution remain the most commonly used fluids. In theory, LR solution is preferable to NS because it provides a better buffer for metabolic acidosis, but to date, investigators have not documented any important differences in outcome. One laboratory study found that NS and LR solution were equivalent in the setting of moderate hemorrhagic shock but that, in the setting of massive hemorrhage, NS was associated with greater physiologic derangement (e.g., hyperchloremic acidosis) and higher mortality.⁷⁹ Clinical experience confirms the adverse effects of iatrogenic hyperchloremia.⁸⁰ NS is preferred, however, when blood is being transfused simultaneously. There is some concern that the calcium in LR solution could exceed the chelating capabilities of the citrate in the stored blood, resulting in the formation of clots that could enter the circulation and compromise the microcirculation, although there is no objective clinical evidence to substantiate these concerns.

Transfusion Trigger

Banked RBCs have been widely available since World War II, but the indications for administration continue to be debated.¹⁴ Animals with hemorrhagic shock were shown to have improved survival with hemoglobin concentration ([Hb]) maintained in the range of 12 to 13 g/dL. However, animal models of isovolemic hemodilution demonstrated that the optimum [Hb] for maintaining systemic oxygen delivery (DO₂) is 10 g/dL, but in healthy human volunteers, isovolemic hemodilution is tolerated at concentrations as low as 5 g/dL. Until recently, clinical studies in critically ill patients concluded that 10 g/dL hemoglobin was optimum for shock resuscitation, but more recent consensus panels have judged that a lower concentration is adequate. The American Society of Anesthesiologists recommends maintaining hemoglobin at greater than 6 g/dL, whereas the NIH recommends a concentration of greater than 7 g/dL. A PRCT has shown

that ICU patients randomized to restrictive blood transfusions (transfuse if hemoglobin concentration is < 7 g/L and maintain between 7 and 9 g/dL) did as well and possibly better than patients who were liberally transfused (transfuse if < 10 g/dL and maintain between 10 and 12 g/dL).⁸¹ We and others have reported that transfusion of PRBCs is a strong risk factor, independent of shock severity, for bad outcomes (i.e., infections, MOF, and deaths) in trauma patients (a patient population most likely to benefit from PRBC transfusion).⁸² The observation that transfusion of PRBCs is associated with adverse outcomes has now been consistently observed across a broad spectrum of high-risk hospitalized patients.⁸³ The choice of transfusion trigger is dependent on the clinical scenario. During active shock resuscitation with ongoing bleeding, shooting for a higher hemoglobin level is preferred. Blood is a good volume expander and will limit isotonic crystalloid infusions, and the higher hemoglobin level provides a margin of safety. Once bleeding is controlled, the lower transfusion trigger should be used unless there is evidence of high oxygen extraction (i.e., SaO_2 minus mixed venous hemoglobin oxygen saturation $< 50\%$).

The adverse outcomes of PRBC transfusion are attributed to the age of stored RBCs. The concept of transfusion-related immunosuppression dates from the early 1970s with the observation that greater pretransplantation transfusion was associated with improved renal allograft survival. Subsequently, perioperative PRBC transfusion was associated with cell-mediated immunosuppression, tumor recurrence, and postoperative infections. The capacity of banked PRBCs to provoke neutrophil cytotoxicity is a key mechanism in MOF.⁸⁴ Focused clinical studies have shown that severely injured patients at high risk of MOF have circulating neutrophils that are primed for cytotoxicity within the first 6 hours after injury, increased expression of adhesion receptors, activation of p38 mitogen-activated protein kinase, and delayed apoptosis. The precise mechanisms linking PRBC transfusion and neutrophil priming remain to be established, but it is generally believed that passenger leukocytes accompanying RBCs in storage are important in the generation of proinflammatory agents that progressively increase from 14 to 42 days of storage. Some investigators have implicated cytokines (tumor necrosis factor, interleukin-1, interleukin-6, interleukin-8), but our focus has been on proinflammatory lipids presumably generated from the degradation of the RBC membrane. Although prestorage leukoreduction of PRBCs decreases the generation of cytokines, this process does not eliminate neutrophil priming. Another emerging concern regarding stored cells is that substantial shape changes and impaired deformability occur by the second week of storage and progress during further preservation. The effects of decreased deformability on microcirculation have been documented experimentally and include impaired tissue access and entrapment, resulting in microvascular obstruction.⁸⁵ These findings might account for the observation that blood transfusion failed to improve oxygen consumption in critically ill and injured patients and, in one study, appeared to induce splanchnic ischemia.^{86,87}

Blood Substitutes

As a consequence of the limited supply of stored blood and the recognition that transfusions contribute to adverse patient outcomes, there has been a resurgence of interest in blood

substitutes. Hemoglobin-based oxygen carriers (HBOCs) date back to 1933, when it was shown that hemolysates could transport oxygen in mammals. Unfortunately, when these solutions were infused into humans, they had excessively toxic effects (i.e., vasoconstriction, acute renal failure, and abdominal pain), which were attributed to stromal contamination.

Although the next generation of HBOCs were stroma-free, toxic effects persisted and were attributed to the instability of the hemoglobin tetramer, which spontaneously dissociates into dimers and monomers. The next generation of HBOC formulations focused on stabilizing the hemoglobin tetramer. One of these products, diaspirin cross-linked hemoglobin, was authorized for a phase III study in trauma patients.⁸⁸ However, the trial was prematurely stopped because of the unexpectedly high mortality in the treatment group (24 of 52 [46%] compared with 8 of 46 [17%] in the control group). Although this event was judged a major setback for clinical implementation of HBOCs, the product used had already been shown to increase pulmonary and systemic vascular resistance in animals. Tetrameric hemoglobin extravasates from the vascular space, binds nitric oxide within the vessel wall, and thereby results in unopposed vasoconstriction. This issue has been effectively addressed by polymerizing the hemoglobin tetramer.⁸⁹ The additional benefit of these larger moieties is that they exert less colloid osmotic activity, which means that a higher dose can be administered.

A further limitation of earlier HBOCs was that because of the loss of 2,3-diphosphoglycerate, oxygen affinity was greatly increased; the partial pressure of oxygen required to produce 50% saturation (P_{50}) decreased from the normal 26 mm Hg to 12 mm Hg. This problem was addressed by pyridoxylation of the hemoglobin tetramer, which raised the P_{50} to 29 mm Hg. One such polymerized hemoglobin solution has been tested extensively in phase I and phase II trials in trauma patients, where it proved to be safe and effective. A phase III prehospital trial has recently been completed where this polymerized hemoglobin solution appeared to provide equivalent outcomes to stored PRBCs.⁸⁹ Unfortunately, the Food and Drug Administration did not agree with the investigators' conclusions, thus apparently ending another chapter in the history of blood substitutes. A new generation of HBOCs is being developed, but, unfortunately, these will unlikely be available for clinical use in the next decade.

EARLY IDENTIFICATION OF NONRESPONDERS

BP and HR are the current standard-of-care monitors of shock resuscitation in the field and in the ED. Both, however, are insensitive markers of early compensated shock; alternative monitors are badly needed for assessing the adequacy of tissue perfusion with a view to avoiding both underresuscitation and overresuscitation. Near-infrared spectroscopy, a simple technique that monitors oxygen saturation in tissue, has been shown to track oxygen delivery reasonably well during shock resuscitation and has been tested as an ED monitor.⁹⁰ Transcutaneous oxygen tension monitoring and central venous oxygen saturation monitoring have also shown promising results in the ED environment.⁹¹

The challenge is to identify as early as possible those patients who are not responding to early interventions. Blind and aggressive volume loading in the hope of normalizing

BP and HR, without appropriate emphasis on control of hemorrhage, sets the stage for the so-called bloody vicious cycle [see Figure 13] or the abdominal compartment syndrome (ACS).⁹²

CONTROVERSIES IN POSTINJURY COAGULOPATHY

Most deaths in injured patients arriving to the hospital with major blood loss are attributable to progressive coagulopathy. Thus, identifying the patient at risk for coagulopathy and treating the factors associated with defective coagulation are integral to initial management. Factors predictive of severe coagulopathy include persistent hemorrhagic shock reflected by metabolic acidosis (base deficit [BD] > 14), refractory core hypothermia (< 34°C), and massive transfusion (> 10 U PRBC/6 hr). During the Vietnam war, coagulation abnormalities were recognized to be associated with prolonged shock and, ultimately, a poor prognosis. However, extensive prospective studies by the Puget Sound Blood Bank found a relatively poor correlation between prothrombin time (PT), partial thromboplastin time (PTT), and bleeding times with coagulation status in patients requiring massive transfusion.⁹³ Consequently, when whole blood transfusion was changed to blood component management, it was acknowledged that FFP should be given empirically with packed RBCs in patients anticipated to need a massive transfusion. Despite 40 years

of investigation, three interrelated areas of controversy exist: (1) the pathogenesis of the acute coagulopathy of trauma, (2) the optimal ratio of blood components to be administered empirically for resuscitation of the critically injured patients (i.e., damage control resuscitation), and (3) the end points for blood component management (i.e., goal-directed therapy).

ACUTE COAGULOPATHY OF TRAUMA

Recent work by Brohi and colleagues suggests that coagulopathy develops very early postinjury and that it is principally driven by thrombin binding to endothelial thrombomodulin resulting in activated protein C-mediated anticoagulation.⁹⁴ This acute coagulopathy appears to be related mechanistically to tissue ischemia from pronounced shock. Such a process may be teleologically protective by inducing an auto-anticoagulation state that prevents thrombosis in critical tissue beds during prolonged periods of low flow while exposed tissue factor is promoting clot formation at the injury site. An alternative hypothesis is that early clotting derangement is due to disseminated intravascular coagulation and fibrinolysis. The importance of this debate is the determination of whether the early coagulopathy following injury is attributable to clotting factor deficiency requiring immediate blood component replacement.

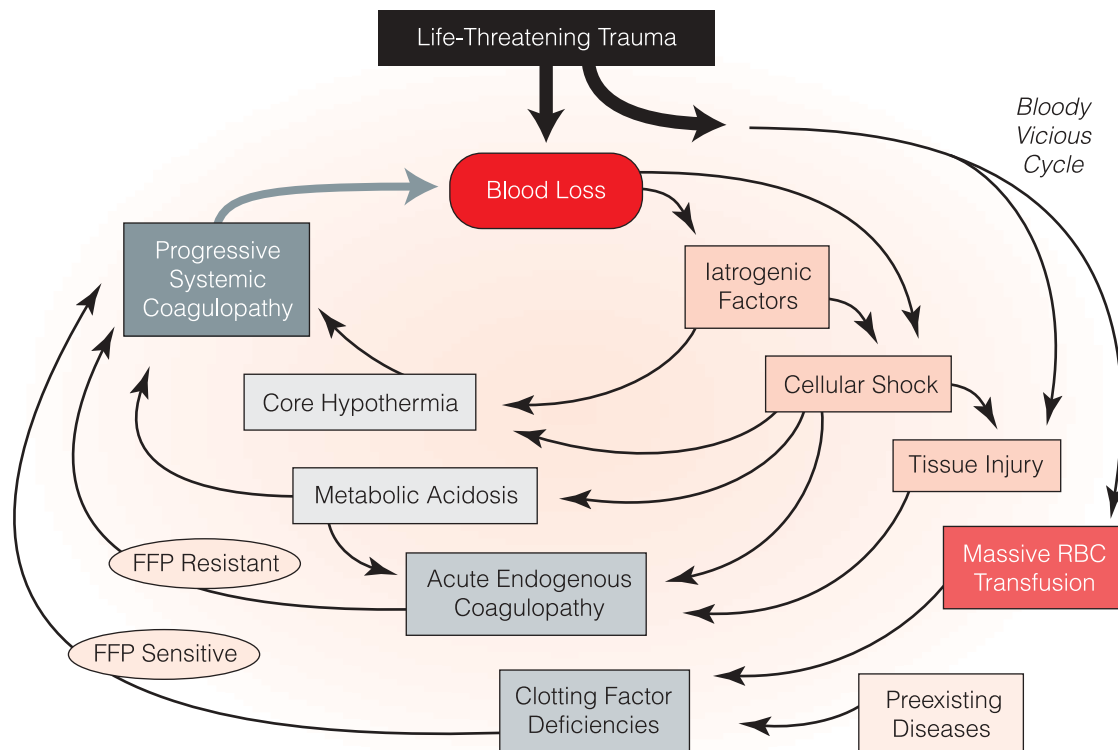


Figure 13 The so-called bloody vicious cycle is a syndrome that has a multifactorial pathogenesis. The usual manifestations include coagulopathy, hypothermia, and metabolic acidosis.⁹² FFP = fresh frozen plasma; RBC = red blood cell.

PREEMPTIVE BLOOD COMPONENT ADMINISTRATION

Although there is a general consensus that clotting factors should be administered concurrently with PRBCs in patients anticipated to require a massive transfusion, the optimal composition of these components remains unclear. For effective hemostasis, the conversion of prothrombin to thrombin requires factors XII, XI, IX, and VIII as well as activated factors X and V. FFP provides these factors and up to 400 mg of fibrinogen. Traditionally, FFP was prepared by isolating the plasma from the cellular components via centrifugation of whole blood within 8 hours of collection. With the advent of apheresis methods, most FFP is now platelet-rich plasma, which is then frozen. The hemostatic activity of most coagulation factors is maintained for long periods, although factors V and VIII decrease with thawing. For nearly 30 years, empiric transfusion of FFP has been recommended, but the ratio of FFP to RBC remains controversial. Early experimental work and subsequent clinical observations indicated that ratios of FFP to RBC $< 1:4$ were warranted to avoid factor deficiency, but platelets were not justified for initial RBC resuscitation. Recently, the military has promulgated a preemptive platelet to FFP to RBC ratio of 1:1:1 based on the argument that this represents the composition of shed whole blood.⁹⁵ A retrospective review of this policy appears to demonstrate a survival benefit in critically injured soldiers requiring massive transfusion. However, a more recent subanalysis suggests that this benefit may be primary in those with extensive blast injury. Furthermore, concurrent civilian data suggest that an FFP to RBC ratio of 1:2 to 1:3 may be adequate.⁹⁶ The rationale for preemptive platelet transfusion is similarly controversial. Clinical studies to date, including the extensive Puget Sound Blood Bank work, do not substantiate initial platelet repletion. The resolution of these ongoing debates requires a better understanding of the scientific basis for achieving postinjury hemostasis.

GOAL-DIRECTED HEMOSTATIC THERAPY

A recent paradigm shift to the cell-based concept of hemostasis underscores the need for a rapid comprehensive assessment of coagulation. Resurgent interest in thromboelastography (TEG) suggests that this technology may provide a real-time viscoelastic analysis of blood clotting that includes the interaction of the enzymatic cascade with platelets. Whole blood (0.35 mL) is placed in a rotating metal curette heated to 37°C. A piston is suspended in the sample, and the rotational motion is transferred to the piston as fibrin strands form between the wall of the curette and the piston. TEG assesses clot strength from the time of initial fibrin formation to clot retraction, ending in fibrinolysis. In contrast, the standard battery of coagulation studies (PT, PTT, and bleeding time) is based on isolated, static end points. Rapid TEG is further advantageous as the addition of tissue factor to the whole blood specimen stimulates a rapid reaction. The resulting coagulation tracing can be transmitted from the blood bank to the OR or surgical ICU, exhibiting a functional profile within 5 minutes of blood sampling. This point-of-care monitoring offers the possibility of goal-directed coagulation management, analyzing virtually in real time the impact of specific component administration. Experimental work and nonrandomized clinical studies thus far appear to support this concept.

ACS AND REVISITING THE CRYSTALLOID VERSUS COLLOID DEBATE

Unfortunately, the above-described PRCTs comparing crystalloid and colloid resuscitation were done long before the ACS had become recognized as an important clinical entity. ACS emerged as an epidemic in the mid-1990s in US level I trauma centers as a result of changes in a number of processes of care that started in the 1980s, including the following: (1) trauma system development, which triaged badly injured patients into high-volume centers with specialized shock trauma ICUs; (2) ATLS-endorsed high-volume isotonic crystalloids to achieve a normal BP as a standard of care for initial resuscitation; (3) damage control surgery allowed patients to survive who previously exsanguinated on the OR table; and (4) the widespread availability and use of pulmonary artery catheters to pursue goal-oriented resuscitation to supranormal levels of oxygen delivery.⁹² ACS is an early event, and its clinical trajectory can be accurately predicted within 3 to 6 hours after ED admission. On admission to the ICU, high-risk patients have significant intra-abdominal hypertension and are in persistent shock. Contrary to conventional wisdom, they do not respond well to preload-directed resuscitation. In fact, continued aggressive resuscitation precipitates the full-blown syndrome [see Figure 14].

As we studied its epidemiology, it became apparent that ACS starts in the ED in patients arriving with severe bleeding who require a massive transfusion. Fundamental changes are needed in pre-ICU care of these patients. Failure to recognize the severe shock, ongoing bleeding, an indiscriminate crystalloid infusion, and failure to prioritize definitive measures for hemorrhage control have been identified as key issues in the ED. In our experience, early overzealous crystalloid resuscitation in the setting of severe bleeding sets the stage for ACS, which we demonstrated to be a modifiable link in the cascade to MOF. Additionally, albumin was the principal colloid used in the early PRCTs, but other types of colloids (starches and gelatins) are now available.

Because of their higher molecular weights, these colloids are confined to the intravascular space, and their infusion results in more rapid and sustained plasma volume expansion. In severe hemorrhagic shock, however, the permeability of capillary membranes increases, allowing colloids to enter the interstitial space, which can then worsen edema and impair tissue oxygenation. The theory that these high-molecular-weight agents plug capillary leaks that occur during neutrophil-mediated organ injury, although enticing, has not been established. Furthermore, Lucas proposed that resuscitation with albumin induces renal failure and even impairs pulmonary function.⁹⁷ Similarly, hetastarch has been shown to induce renal dysfunction in patients with septic shock and in recipients of kidneys from brain-dead donors. Hetastarch (Hespan) also has a limited role in massive resuscitation because it causes a coagulopathy and hyperchloremic acidosis attributable to its high chloride content. Newer hydroxyethyl starch preparations (Hextend, pentastarch) purportedly do not cause these adverse effects but have not been studied in massive resuscitation.⁹⁸

Although we share the belief that colloids might reduce the incidence of ACS, this possible benefit must be weighed

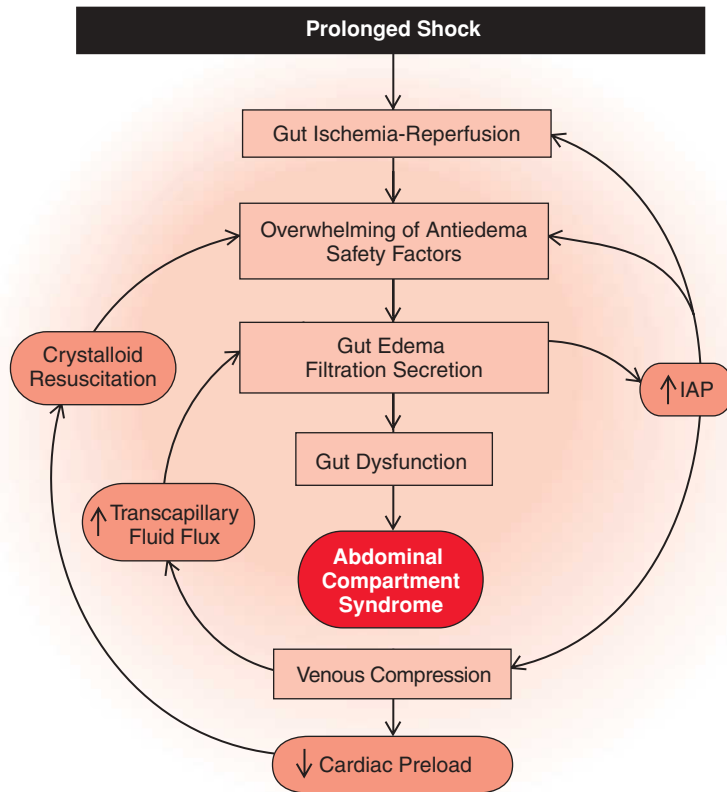


Figure 14 Depicted is the so-called saltwater vicious cycle, which results in the development of abdominal compartment syndrome. The term “filtration secretion” refers to the process by which increasing gut edema causes interstitial pressure to rise to high levels, leading to disruption of the interstitial matrix. Ultimately, as a result, the villus tips spring leaks, through which interstitial fluid passes into the gut lumen. IAP = intra-abdominal pressure.

against the potentially detrimental effects of colloids already reported. ACS occurs in a small subgroup of patients (< 1%) who arrive with severe bleeding and require a massive transfusion.¹⁴ Early prediction models can identify these high-risk patients and an alternative resuscitation strategy that limits isotonic crystalloids and uses massive transfusion protocols that emphasize that early FFP will be beneficial in this subgroup of patients. Finally, alternative crystalloid solutions are being developed that not only expand the intravascular space and replete the extracellular fluid but also have anti-inflammatory properties (e.g., Ringer ethyl pyruvate).⁷⁸ Given

the current evidence that excess fluid resuscitation is harmful, there has been interest in the early use of vasopressors after trauma.⁹⁹ However, a recent multi-institutional epidemiology study showed that patients who had early vasopressors within 12 hours of injury had an 80% increased risk of dying.¹⁰⁰

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 Figure 12 Seward Hung

2 INJURIES TO THE CENTRAL NERVOUS SYSTEM

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Traumatic brain injury (TBI) is a leading cause of death and disability in the world. In the United States, over 1.5 million people suffer TBI each year, resulting in over 50,000 deaths and 80,000 permanent disabilities.¹ As a result, over 5.3 million people in the United States currently live with TBI-related deficits, making this an epidemic that dramatically affects patients, their families, and society at large. Although neurosurgeons and neurointensivists are best trained to manage patients with TBI,^{2,3} resuscitation and stabilization of patients in the early period after head injury are typically performed by paramedics, emergency department physicians, general surgeons, and trauma surgeons. These professionals are at the forefront of care for patients with TBI and have the potential to dramatically affect patient outcome.

In the first few hours after head injury, rapid diagnostic evaluation and appropriate neurosurgical consultation are of the utmost importance for patients with TBI. In the hours, days, and weeks following injury, maximal neurologic recovery is achieved by aggressively maintaining adequate cerebral blood flow (CBF) and oxygenation to prevent secondary insults to the injured brain. To optimize outcome in patients with TBI, particularly in the context of significant multisystem injuries, a collaborative, multidisciplinary, evidence-based, protocol-directed approach to patient care should be used by modern-day trauma centers.

According to the National Spinal Cord Injury Statistical Center, approximately 12,000 people present to a hospital in the United States each year with a new spinal cord injury (SCI). As of 2008, it is estimated that between 229,000 and 306,000 in the United States live with SCI-related deficits. Most injuries result from motor vehicle accidents (42.1%); 15 to 20% are attributable to falls, 15 to 20% result from interpersonal violence, and the remaining 15 to 20% are associated with sports and recreational activities. Over the past two decades, the proportion of injuries associated with sports has decreased, whereas the proportion attributable to falls has increased. The average age at SCI continues to steadily rise; since 2005, the average age of patients suffering SCI is 40.2 years (between 1973 and 1979, it was 28.7 years). Although there continues to be a slight trend toward an increasing percentage of females, the vast majority of patients suffering SCI are males (80.9%). Between 45 and 50% of patients with SCI have other injuries that seriously affect their prognosis.

The cervical spine is most often involved in SCI (55%), followed by the thoracic (30%) and lumbar levels (15%). In an analysis of 358 patients with SCI, complete neurologic injury occurred in 78% of the 71 cases of thoracic injury, 65% of the 85 cases of thoracolumbar injury, and 60% of the 202 cases of

cervical injury.⁴ Average direct costs of SCI (including hospitalization, rehabilitation, residence modification, and long-term care) are tremendous. According to the National Spinal Cord Injury Statistical Center, the lifetime costs of a 25-year-old suffering low (C5 to C8) or high (C1 to C4) quadriplegia is \$3,160,137 or \$1,786,836, respectively; the average yearly expense of a patient with high quadriplegia is \$801,161 in the first year and \$143,507 each subsequent year.

Initial resuscitation and evaluation of injured patients are discussed more fully elsewhere. In this chapter, we outline approaches to the management of severe head injury and acute SCI. In addition, we address the pathophysiology of such injuries to provide the reader with the understanding required for making appropriate decisions about diagnosis and treatment of injured patients [see Discussion, *below*].

Head Injury

EMERGENCY DEPARTMENT MANAGEMENT

Hypoxia and hypotension are two of the worst secondary insults following TBI and should be avoided at all costs during initial patient management. Severe oxygen desaturation (< 60%) during transport to the hospital is associated with a 3.5-fold increase in mortality,⁵ and duration of in-hospital oxygen desaturation (< 90%) is an independent predictor of mortality.⁶ One episode of post-TBI hypotension doubles mortality risk, whereas two or more episodes increase the relative risk of mortality to 8.1,⁷ and the total duration of hypotensive episodes is a significant predictor of morbidity and mortality.⁶ Patients with SCI above T5 are particularly prone to severe hypotension as a result of vasogenic spinal shock and should be aggressively treated with volume resuscitation and administration of alpha-adrenergic vasopressors. Therefore, aggressive and complete physiologic resuscitation is the highest priority for patients with head and spinal cord injuries.

A multidisciplinary team should provide an adequate airway, deliver sufficient oxygenation and ventilation (intubation, ventilation, and detection of hemothorax or pneumothorax), and establish hemodynamic stability (with adequate fluid replacement and detection and treatment of any bleeding), all according to the principles developed by the advanced trauma life support system. The ABCs of emergency care (airway, breathing, and circulation) always take precedence, and patients' neurologic injuries should not distract caretakers from these important principles of trauma management. The initial neurologic assessment, which should take no more than a few seconds, consists of rating the patient's level of consciousness on the Glasgow Coma Scale (GCS) [see Table 1] and assessing the

Table 1 Glasgow Coma Scale

Test	Response	Score
Eye opening (E)	Spontaneous	4
	To verbal command	3
	To pain	2
	None	1
Best motor response (arm) (M)	Following verbal command	6
	Localization to pain	5
	Withdrawal response to pain	4
	Abnormal flexion response to pain (decorticate rigidity)	3
	Extension response to pain (decerebrate rigidity)	2
	None	1
Best verbal response (V)	Oriented conversation	5
	Disoriented conversation	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
	Intubated	"T" (1)
Total score	Total (E + M + V)	3–15*

*3T–11T when intubated.

diameter and reactivity of the pupils. Although the same assessment is made after resuscitation as a guide for prognosis and therapy, it should also be made (and recorded) before resuscitation to permit evaluation of the effect of resuscitative measures and differentiation between primary and secondary neurologic injury.

Early orotracheal intubation and ventilation are recommended for patients with a GCS score of 8 or lower or a motor score of 4 or lower. Other indications for immediate intubation are loss of protective laryngeal reflexes and ventilatory insufficiency, as manifested by hypoxemia (arterial oxygen tension $[P_{aO_2}] < 60$ mm Hg), hypercarbia (arterial carbon dioxide tension $[P_{aCO_2}] > 45$ mm Hg), spontaneous hyperventilation (causing $P_{aCO_2} < 26$ mm Hg), and respiratory arrhythmia. Indications for intubation before transport are deteriorating consciousness (even if the patient is not in a coma), bilateral fractured mandible, copious bleeding into the mouth (as occurs with fracture of the base of the skull), and seizures. Patients with TBI should be normoventilated ($P_{aCO_2} \approx 40$ mm Hg) unless they clearly demonstrate signs of raised intracranial pressure (ICP) (see below).

Fluid replacement should be performed with isotonic solutions such as normal saline or packed red blood cells when appropriate. Although appropriate in certain clinical scenarios, lactated Ringer (LR) solution should generally be avoided in patients with TBI as it has been shown to increase ICP⁸ and decrease intracranial compliance.⁹ Hypertonic saline (HS) may be more appropriate in patients with TBI as it has been shown to improve intracranial compliance and lower ICP, and in a randomized prospective trial of pediatric TBI, HS was shown to result in lower ICP, higher cerebral perfusion pressure (CPP), higher serum sodium, and fewer complications and shorter intensive care unit (ICU) stays when compared with patients receiving LR solution.¹⁰

Glucose-based solutions should be avoided in adult patients with TBI. Elevated serum glucose in the first 24 hours

after TBI or following surgical intervention is associated with worse neurologic outcome.^{11,12} In a recent review from the IMPACT study, hyperglycemia on admission or during hospital course is an independent prognostic indicator of outcome 6 months following TBI.^{11,13} A recent review of 77 patients with severe TBI identified early hyperglycemia as a strong predictor of poor outcome and death.¹⁴

Intracranial hypertension should be treated aggressively as it is a primary predictor of outcome in the acute period following TBI. Hyperventilation reduces ICP by decreasing cerebral blood volume (CBV) and does not interfere with volume resuscitation. Because it can result in iatrogenic cerebral ischemia, however, it should be used only in patients with acute neurologic deterioration with lateralizing signs (e.g., anisocoria, unilateral motor posturing). Hyperosmolar therapies are also effective agents for reduction of ICP but have differing effects on volume status. Mannitol is an osmotic diuretic that has long been used in the setting of TBI and is thought to reduce ICP by drawing free water out of the brain as well as improving blood rheology, resulting in improved CBF and reduced CBV.¹⁵ It has been shown that pupillary abnormalities following TBI not only result from oculomotor nerve compression but also reflect brainstem ischemia attributable to compression. Therefore, administration of mannitol is effective because it not only decreases ICP but also increases CBF through modulation of viscosity. Given that mannitol results in diuresis and dehydration, its use in hypotensive patients may not be prudent and should be preventively followed with intravenous fluid boluses. HS may be a preferable hyperosmolar agent in this setting as it promotes fluid resuscitation while providing all of the ICP-lowering benefits of mannitol.^{16,17} It is important to note that arterial hypertension following severe head injury may reflect intracranial hypertension (Cushing phenomenon), especially when accompanied by bradycardia; it should not be directly treated, because it may be the sole mechanism permitting the brain to maintain perfusion despite increasing ICP.

In the absence of signs of herniation, sedation should be used when required for safe and efficient transport of the patient. Transport time should be kept to a minimum because transport is often accompanied by secondary insults (e.g., hypoxia or hypotension). Pharmacologic paralysis, which interferes with neurologic examination, should be used only if sedation alone is inadequate for safe and effective transport and resuscitation. When pharmacologic paralysis is used, short-acting agents are preferred. As noted above, prophylactic hyperventilation may exacerbate early ischemia and should not be used in patients with suspected TBI. Guidelines for the resuscitation and initial treatment of patients with severe head injuries have been established that facilitate management [see Figure 1].

After hemodynamic stability is achieved, unenhanced computed tomography (CT) of the head should be performed in all patients with persistent impairment of consciousness. In most institutions, a CT scan of the cervical spine is also obtained for evaluation of cervical spine injury in patients with severe head injury. Various criteria have been described to determine the necessity of head CT scan in patients with suspected TBI, including the Canadian Head CT Rule and the New Orleans Criteria. A summary of these guidelines is presented in Table 2.

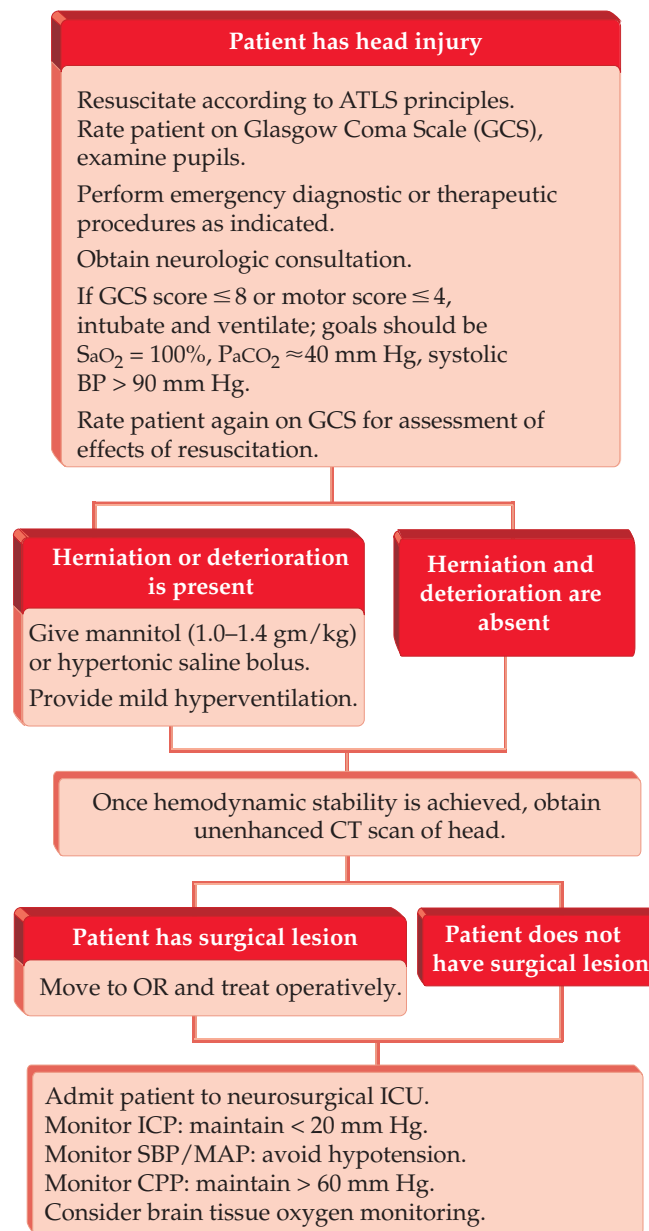


Figure 1 ATLS = advanced trauma life support; BP = blood pressure; CPP = cerebral perfusion pressure; CT = computed tomography; ICP = intracranial pressure; ICU = intensive care unit; OR = operating room; PaCO₂ = arterial carbon dioxide tension.

OPERATIVE MANAGEMENT

Guidelines for the surgical management of severe TBI were recently published in a supplement to the journal *Neurosurgery*.¹⁸ In general, extra-axial hematomas (e.g., subdural and epidural) that result in at least 5 mm of midline shift are candidates for surgical evacuation and should be immediately evaluated by neurosurgical consultants. Evacuation of epidural or subdural hematomas can dramatically reduce ICP, improve CPP, and optimize CBF so as to prevent secondary insults to the injured brain. Evacuation of subdural

Table 2 Indicators Necessitating Non-contrast Head CT Scan in Patients with Loss of Consciousness and GCS Score of 14 or 15

Sign and symptoms Headache Somnolence Mental status changes or confusion Nausea or vomiting Seizure	Perseveration Neurologic deficit Blurred or double vision Vertigo Hemotympanum, raccoon eyes, CSF leak, Battle sign
Clinical history Dangerous mechanism Drug or alcohol intoxication	Age over 60 years

CSF = cerebrospinal fluid; CT = computed tomography; GCS = Glasgow Coma Scale.

hematomas has been shown to dramatically decrease elevated ICP¹⁹ and reverse cerebral ischemia,²⁰ and surgical evacuation of subdural hematomas within 4 hours of injury has been shown to improve clinical outcome.²¹ With widespread accessibility of emergent CT scans, routine exploratory burr holes are no longer appropriate in the management of TBI. In cases of progressive neurologic deterioration with suspected intracranial hematoma, therefore, moderate hyperventilation (PaCO₂ ≈ 30 mm Hg) and high-dose mannitol (1.0 to 1.4 g/kg) should be administered while the patient receives a CT scan and is prepared for surgical evacuation.

Posterior fossa hematomas, which are rare, also require urgent evacuation because obstructive hydrocephalus and brainstem compression can result in rapid neurologic deterioration. Current guidelines recommend surgical evacuation of posterior fossa hematomas with associated neurologic dysfunction or those that result in mass effect on CT scan, including “distortion, dislocation, or obliteration of the fourth ventricle.”¹⁸

ICU MANAGEMENT

Once patients are adequately resuscitated, evaluated, and treated for urgent indications (e.g., hematoma evacuation), they should be rapidly transferred to an ICU for neurocritical care management. Efforts should be made to manage patients with severe TBI in neuroscience ICUs as studies have shown that outcome from TBI is significantly improved when patients are managed in a specialized unit with direct involvement of neurosurgery and/or neurocritical care services.²

The focus of ICU management is the prevention of secondary insults to the injured brain. To ensure optimal cerebral oxygenation, efforts should be made to control cerebral metabolic demand (prevent fevers and seizures, induce sedation or coma) and support CBF and oxygenation (optimize hemoglobin concentration, oxygen saturations, and CPP; maximize cerebral vessel diameter; limit blood viscosity). Despite these efforts, admission to an ICU does not eliminate the occurrence of secondary insults. In a series of 124 patients admitted to a neurosurgical ICU, more than one episode of hypotension occurred in 73% of all patients, and more than one episode of hypoxia occurred in 40%.⁶ In another study, online monitoring of CPP, jugular venous

oxygen saturation (S_{rO_2}), local CBF, and brain tissue oxygenation was performed in 14 patients who had sustained a severe head injury; 37% of the episodes involving decreased CBF, CPP, and saturation were related to clinical and nursing procedures.²² Nonetheless, limiting the occurrence and duration of secondary insults significantly improves neurologic outcome in patients with severe TBI.

Monitoring

A variety of bedside devices are currently available for monitoring ICP, local CBF, and local and global cerebral oxygenation.

ICP monitoring ICP monitoring is indicated in all salvageable patients with a GCS score less than or equal to 8 (after resuscitation) with an abnormal head CT scan. In patients with a normal head CT scan but a low GCS, ICP monitoring is indicated if two of the following are present: age above 40 years, motor posturing, or hypotension (< 90 mm Hg).²³ It is important to note that a “negative” head CT scan does not reliably predict ICP. In patients with two of the three above characteristics and a negative head CT scan, 53 to 63% had ICP above 20 mm Hg. Narayan and colleagues reported a 13% incidence of elevated ICP in patients with a “normal CT scan on admission,”²⁴ and Eisenberg and colleagues found that severe TBI patients with an initial negative head CT had a “10-15% chance of developing elevated pressure.”²⁵ As a result, currently published guidelines recommend protocol-directed placement of ICP monitors rather than subjective placement based on CT scan results alone.

Current guidelines continue to recommend aggressively maintaining ICP below 20 mm Hg in patients with severe TBI. ICP above 20 mm Hg is a significant independent determinant of outcome, and a recent study of 233 patients found ICP greater than 15 mm Hg to be one of five independent risk factors for death.²⁶ Patients whose ICP is maintained below 20 mm Hg have significantly better outcome, and a recent systematic review found that ICP 20 to 40 mm Hg increased mortality by 3.5-fold and ICP above 40 mm Hg increased mortality by 6.9-fold; raised but reducible ICP increases mortality by 3- to 4-fold, and refractory ICP was associated with an odds ratio for death of 114.3.²⁷ Although monitoring of ICP has never been subjected to a prospective, randomized clinical trial, it continues to play a fundamental role in neurocritical care management of patients with severe head injury. Implementation of an ICP-based protocol for TBI patients has been shown to significantly improve outcome,²⁸ and patients whose ICP responds to pharmacologic therapy have a better outcome.

Brain tissue oxygen monitoring Direct measurement of local brain tissue oxygen tension (P_{btO_2}) has become increasingly popular in the management of severe TBI and has been adopted as an adjunct or replacement to jugular bulb oximetry by many neurotrauma centers (see below). Used in Europe for many years before its approval by the US Food and Drug Administration in 2001, these probes are typically inserted into radiographically uninjured subcortical white matter and used as indicators of global cerebral oxygenation.²⁹ These probes measure oxygen tension in brain tissue and are most sensitive to changes in

system arterial oxygenation (P_{aO_2}) and CBF.³⁰ Normal values range between 25 and 30 mm Hg.

One impetus behind P_{btO_2} monitoring is the observation that brain oxygen does not always correlate with CPP and is often reduced after successful resuscitation of TBI patients, even when hemodynamically stable. ICP and CPP monitoring, which has long been used to ensure adequate CBF, may not be sufficient for providing adequate cerebral oxygenation. In fact, Stiefel and colleagues at the University of Pennsylvania found that 29% of patients with ICP less than 25 mm Hg and 27% of patients with CPP greater than 60 mm Hg experience severe cerebral hypoxia ($P_{\text{btO}_2} < 10$ mm Hg), and 47% of patients who seem to be “optimally managed” (ICP < 25 mm Hg and CPP > 60 mm Hg) experience P_{btO_2} less than 20 mm Hg and 21% P_{btO_2} less than 10.143 mm Hg.³¹ P_{btO_2} closely and linearly correlates with regional CBF; levels below ischemia (18 mL/100 g/min) correlate with P_{btO_2} of 22 mm Hg.

Another reason for P_{btO_2} monitoring is the observation that neurologic outcome is significantly worse in patients with reduced P_{btO_2} .³¹ P_{btO_2} values less than 8 to 10 mm Hg represent a high risk of ischemia and increased mortality, and any episode of P_{btO_2} less than 7 mm Hg is associated with risk of death regardless of duration.³² In a study of 60 patients, P_{btO_2} strongly correlated with good outcome ($P_{\text{btO}_2} > 35$ mm Hg), moderate or severe disability (P_{btO_2} 26 to 35 mm Hg), and a vegetative state or death ($P_{\text{btO}_2} < 26$ mm Hg).³³ P_{btO_2} is a very strong predictor of outcome (diagnostic sensitivity 92%, specificity 84%) and directly correlates with GCS on admission, CPP, and brain glucose levels; P_{btO_2} below 19 mm Hg was invariably associated with a vegetative state or death in this study.³⁴ A prospective study of 101 patients found a worse outcome if P_{btO_2} was below 10 mm Hg for over 30 minutes; a 50% risk of death was found in patients with P_{btO_2} below 15 mm Hg for 4 hours.³⁵

Although a clinical trial of ICP/ CPP- versus ICP/ CPP/ P_{btO_2} -directed therapy has not been completed (one is currently under way), there is evidence that efforts to increase P_{btO_2} may result in improved neurologic outcome. In a report by Stiefel and colleagues, adopting an oxygen-directed severe TBI protocol to maintain P_{btO_2} greater than 25 mm Hg coincided with a significant decrease in mortality from severe TBI at their institution (25% versus 44%), prompting the design of a prospective, randomized clinical trial.³¹

One potential mechanism of decreased P_{btO_2} despite normal ICP and CPP is posttraumatic vasospasm (PTV), a significant source of secondary insult that occurs in 19 to 50% of patients with severe TBI.³⁶⁻³⁸ PTV typically develops between 12 hours and 5 days after injury, lasts anywhere between 12 hours and 30 days, and is an independent predictor of permanent neurologic deficit and poor outcome in many studies. Recently, the use of brain tissue oxygen probes to detect and direct therapy for PTV was described,³⁹ further supporting the role of brain tissue oxygen monitoring in the management of severe TBI.

Current TBI guidelines do not address indications for brain tissue oxygen monitoring in severe TBI but do recommend that P_{btO_2} be maintained above 15 mm Hg at all times.⁴⁰ The treatment algorithm used at our institution to maintain P_{btO_2} levels above this threshold is presented in Figure 2.

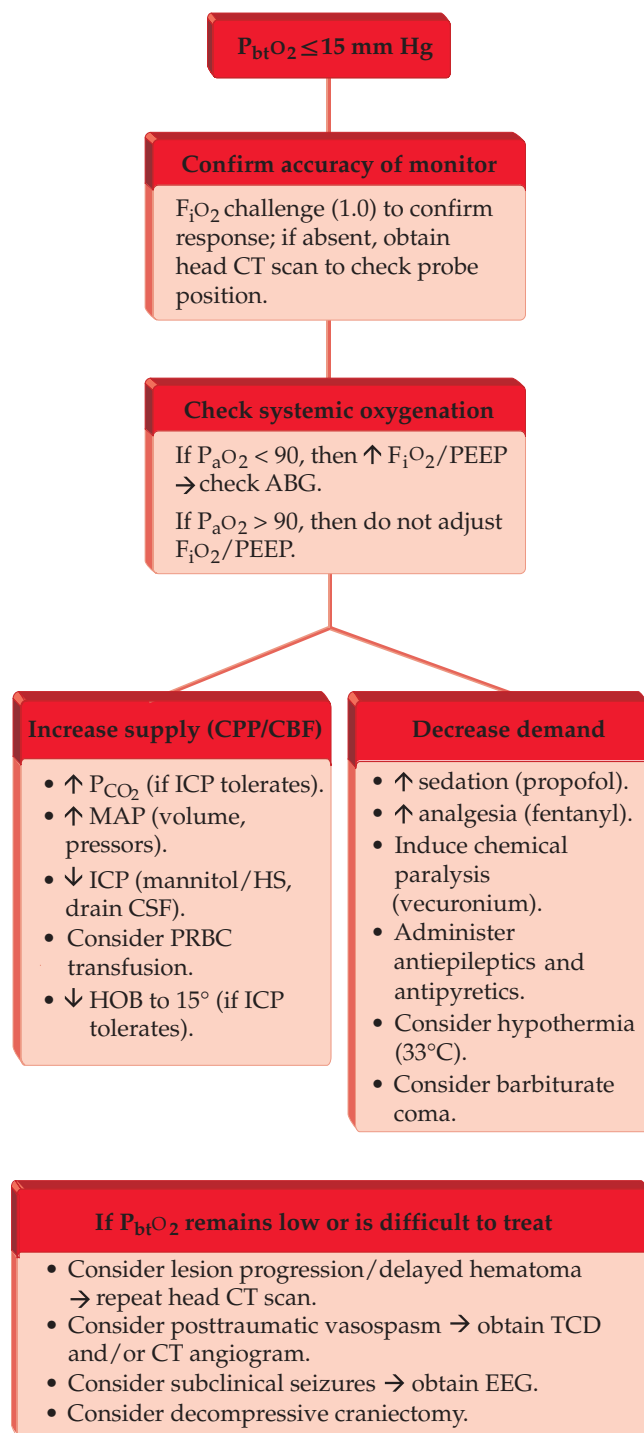


Figure 2 P_{bt}O₂ = brain tissue oxygen; ABG = arterial blood gas; CBF = cerebral blood flow; CPP = cerebral perfusion pressure; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalogram; F_iO₂ = fraction of inspired oxygen; HOB = head of bed; HS = hypertonic saline; ICP = intracranial pressure; MAP = mean arterial pressure; P_aO₂ = arterial oxygen tension; P_{CO₂} = carbon dioxide tension; PEEP = positive end-expiratory pressure; PRBC = packed red blood cell; TCD = transcranial Doppler.

Jugular bulb oximetry Simultaneous monitoring of arterial (S_aO₂) and S_{jv}O₂ can be used to estimate the arterial-jugular venous oxygen difference (AVDO₂), an important

indicator of the adequacy of CBF. S_{jv}O₂ is monitored by percutaneous retrograde insertion of a fiberoptic catheter in the internal jugular vein, with the tip of the catheter located in the jugular bulb. The catheter is usually inserted into the jugular vein with the dominant cerebral venous drainage (the right jugular vein in 80 to 90% of the population), but some prefer to insert the catheter ipsilateral to the most brain damage. AVDO₂ is calculated according to the following formula:

$$AVDO_2 = (S_{aO_2} - S_{jvO_2}) \times 1.34 \times Hb + [(P_{aO_2} - P_{jvO_2}) \times 0.0031]$$

The contribution of the variables within the brackets, which is small, is usually ignored for practical purposes. Because calculation of AVDO₂ requires the drawing of blood samples, it can be done only intermittently.

Continuous monitoring of S_{jv}O₂ can be performed, with normal values ranging between 50 and 70%. Episodes of S_{jv}O₂ less than 50% for > 15 minutes correspond with desaturations, which may result from insufficient arterial oxygenation (S_aO₂), inadequate oxygen-carrying capacity (Hb concentration), or inadequate CBF. These episodes of desaturation are strongly associated with neurologic outcome and mortality.

The limitations of jugular bulb oximetry should be kept in mind when S_{jv}O₂ values are interpreted.^{41,42} Because S_{jv}O₂ represents global oxygenation, regional ischemia may go undetected if the ischemic region is too small to be represented in the total hemispheric S_{jv}O₂ value. Ischemia may also occur in a part of the brain being drained by the opposite jugular vein. In addition, extracerebral veins drain into the internal jugular vein approximately 2 cm below the jugular bulb. With low flow values, significant extracerebral contamination may occur, resulting in deceptively high S_{jv}O₂ values. Finally, artifactual readings are often encountered as a result of reduced light intensity when the catheter lodges against the vessel wall. Technical improvements in catheters, however, have markedly reduced the number of artifacts observed.

Management of CPP

CPP is calculated from mean arterial pressure (MAP) and ICP (CPP = MAP – ICP), and is used as an indicator of CBF. Maintaining adequate CPP following TBI has been shown to improve outcome in many studies, although the “ideal” CPP level seems to vary among and within patients over time. Early studies seemed to suggest that neurologic outcome directly correlated with elevated CPP, with several studies suggesting that CPP 70 to 80 mm Hg was the clinical threshold below which mortality and morbidity increase.^{43–45} A retrospective analysis of 392 patients with TBI found that MAP below 70 mm Hg and/or CPP below 60 mm Hg were independent predictors of poor outcome.⁴⁶ Cerebral microdialysis studies shed further light on this topic, suggesting that ischemic insults to the brain occurred when CPP dropped below 50 mm Hg.⁴⁷ These studies suggested that maintaining an elevated CPP was an effective strategy for optimizing outcome following severe TBI.

However, a randomized clinical trial of “CPP-targeted therapy” (CPP > 70) versus “ICP-targeted therapy” (CPP > 50, ICP < 20) highlighted the importance of considering other organ systems when managing severe TBI patients. In this study, Contant and colleagues found no significant

difference in neurologic outcome between the two strategies but reported a higher morbidity in patients receiving CPP-targeted therapy because of a fivefold increased risk of acute lung injury (ALI).⁴⁸ At the same time, a separate large, international trial reported that maintaining CPP greater than 60 mm Hg was not beneficial.⁴⁹

As a result, current published guidelines recommend against aggressively maintaining CPP above 70 mm Hg (because of the risk of ALI) but also recommend aggressive measures to keep CPP above 50 mm Hg at all times.⁵⁰ As a result, most centers have adopted a CPP goal of 60 mm Hg, although this can be adjusted by the neurosurgical or neurocritical care service based on the patient's pressure autoregulation status. Management strategies for CPP therapy include reduction of ICP and support of MAP. MAP support is first accomplished with optimization of fluid status to central venous pressures (CVPs) of 8 to 10 mm Hg (pulmonary arterial wedge pressure 12 to 14 mm Hg). If this is insufficient to maintain an adequate CPP, an alpha-adrenergic infusion should be used. Phenylephrine is an optimal agent for management of CPP following severe TBI as it has minimal vasopressive effects on cerebral vasculature.

Management of ICP

Elevated ICP can significantly compromise CPP and promote herniation syndromes, and current guidelines recommend initiation of therapies when measurements reach 20 mm Hg.⁵¹ As mentioned above, ICP values above 20 mm Hg independently determine outcome, and patients whose ICP is maintained below 20 mm Hg during their hospital stay have significantly better neurologic recovery.²⁵ Therefore, it is important to institute preventive measures in all patients with severe TBI, and therapeutic measures for ICP elevations above 20 mm Hg should be instituted in a timely and aggressive manner. Prophylactic measures to prevent elevation of ICP include patient positioning, temperature management, seizure prophylaxis, electrolyte balance, and choice of intravenous maintenance fluids. Therapeutic measures include cerebrospinal fluid (CSF) drainage, sedation, chemical paralysis, hyperosmolar therapy, hypothermia, hyperventilation, decompressive surgery, metabolic coma.

Prophylactic measures *Patient positioning* Patient positioning can have a dramatic effect on ICP and should be optimized for each patient. A neutral head position allows for maximal venous outflow through the jugular veins, and any deviation from neutral (neck flexion, extension, lateral deviation, rotation) can result in elevation of ICP. Placement of a cervical collar can also cause a significant increase in ICP; in one series, the mean rise in ICP attributed to collar placement was approximately 4.5 mm Hg.⁵² A study in patients undergoing lumbar puncture found a significant increase in CSF pressure from 17.7 to 24.8 cm H₂O with placement of a rigid Philadelphia collar.⁵³

Elevation of the head of the bed from 0 to 30° significantly decreases ICP without changing CPP, CBF, cerebral metabolic rate of oxygen (CMRO₂), arteriovenous difference of lactate (AVD_{lactate}), cerebrovascular resistance (CVR), or brain tissue oxygenation.⁵⁴ Ninety-three percent of the ICP-lowering effects of head elevation are achieved at 30°;⁵⁵ and head elevation above 45° can result in reduced CPP with a resultant increase in ICP. It is recommended, therefore, that

elevation of the head of the bed should be maintained at 30 to 45° for patients with severe TBI.

Temperature management Hyperthermia following TBI can increase ICP and reduce CPP and is associated with worsened outcome. Hypothermia produces a balanced reduction in energy production and use, decreasing CMRO₂ and CBF proportionally. In a study of 846 patients with severe TBI, pyrexia was one of six factors strongly associated with outcome at 1 year,⁵⁶ and studies have shown that fevers are particularly common in patients with head injury. An analysis of 4,259 patients managed in a neurology/neurosurgery ICU found that elevated body temperature is an independent predictor of ICU stay, hospital stay, functional outcome, and mortality following TBI.⁵⁷

Prophylactic mild hypothermia has been advocated by some authors,⁵⁸ and prophylactic moderate hypothermia has been studied in randomized clinical trials with inconclusive results (studies are still ongoing with more select patient subgroups).^{59,60} The main side effects of hypothermia are cardiac arrhythmias and coagulation disorders, reported after cooling to 32° to 33°C. Other drawbacks of hypothermia include the difficulty of detecting infection because of the lack of warning signs (e.g., spiking and elevated temperature) and the need for specialized equipment (e.g., rotor beds with cooling control) and personnel to induce and maintain the condition. At present, evidence is insufficient to support prophylactic moderate hypothermia, but aggressive support of euthermia (or mild hypothermia to 35°C) may be appropriate in patients with severe TBI.

Seizure prophylaxis Posttraumatic seizures can cause a dramatic increase in CBF, CBV, and ICP, and prevention may also reduce the risk of chronic epilepsy. In a large randomized, double-blind, placebo-controlled trial by Temkin and colleagues, phenytoin therapy was found to significantly reduce the incidence of early (days 0 to 7) seizures from 14.2 to 3.6% but had no effect on late seizures or long-term survival rates.^{61,62} Patients treated with phenytoin demonstrated impaired neuropsychological test performance 1 month after injury; however, this difference was not present at the 12-month evaluation.⁶³ Of note, Young and colleagues performed a randomized, double-blind trial of 244 TBI patients and found no effect of dilantin on preventing early or late post-traumatic seizures.⁶⁴ However, the incidence of posttraumatic seizures was low in both groups, and it is unclear if therapeutic phenytoin levels were achieved: no patient with serum phenytoin greater than or equal to 12 µg/mL experienced a seizure. In the Temkin and colleagues study, over 70% of patients treated with phenytoin had therapeutic serum levels.⁶² Current guidelines by the Brain Trauma Foundation, the American Academy of Neurology Quality Standards Subcommittee, and the Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation recommend the use of phenytoin for 7 days following severe TBI, with efforts made to target therapeutic levels.⁶⁵

Electrolyte and IV fluid management Hyponatremia can promote secondary insults to the injured brain by promoting cerebral edema and lowering seizure threshold. Hyponatremia occurs in 17.4 to 33% of patients suffering severe TBI, and is often attributed to cerebral salt wasting and/or syndrome of inappropriate antidiuretic hormone (SIADH).^{66,67} An IMPACT database review of 5,270 TBI patients

identified hyponatremia on admission as strongly correlating with poor outcome.¹¹ Given that sodium concentration is 77 mg/dL in 0.45% saline and 130 mg/dL in LR solution, normal saline is the intravenous fluid of choice for management of patients with severe TBI. Use of “half-normal” (0.45%) saline has been shown to promote cerebral swelling and increased ICP,⁶⁸ and failure to rapidly correct hyponatremia has been associated with cognitive impairments during the recovery phase, although the threshold of effects varies significantly among individuals. Cerebral salt wasting following TBI is likely attributable to release of brain natriuretic peptide, a potent vasodilator and natriuretic that is elevated in serum during the acute phase of TBI.⁶⁹

Similarly, fluid imbalance (either hyper- or hypovolemia) can also result in increased ICP, albeit by different mechanisms. Hypovolemia can compromise cardiac output and CPP, triggering cerebral vasodilation (in patients with intact autoregulation) that results in increased CBV and elevation in ICP. Hypervolemia may also result in increased ICP, particularly in patients with impaired cerebral autoregulation who are unable to vasoconstrict in response to increased MAP. Therefore, euvolemia is the safest and most prudent treatment strategy for patients with severe TBI.

Therapeutic measures Patients who experience elevated ICP despite the above prophylactic measures should be managed by a protocol-directed, tiered approach [see Figure 3].

Therapies within a tier should be maximized before moving to a higher tier, and careful consideration should be given to repeat head CT scans when a patient requires escalation of therapy (to evaluate for intracranial lesion progression). It is generally not advisable for escalation of tiered therapy to occur without careful assessment by the treating neurosurgeon or neurointensivist as some etiologies of elevated ICP may result from reversible events (e.g., hypoventilation) that require more specific treatment strategies.

Hyperosmolar therapy Mannitol and HS can be delivered in boluses for acute control of ICP, but in adults, it is not typically used as a regular, intermittent therapy. They can be used across all tiers of therapy but are limited by their side effects of induced serum hyperosmolality and induced hyponatremia.

Mannitol is usually administered in intravenous boluses of 0.25 to 1 g/kg over 10 to 15 minutes, until either ICP is controlled or serum osmolality reaches 320 mOsm/L. There is some evidence suggesting that higher doses (e.g., 1.4 g/kg) may be more effective,^{70,71} although the integrity of these studies has been questioned. Because volume depletion is an important side effect of mannitol therapy, urine losses should be replaced. HS (3 to 10%) may be used in place of mannitol: it appears to be equal or superior to mannitol for ICP control and can be delivered in varying concentrations (e.g., 3%, 7.5%, 23.4%).⁷² In addition, HS is not associated with volume depletion but actually increases intravascular volume, which

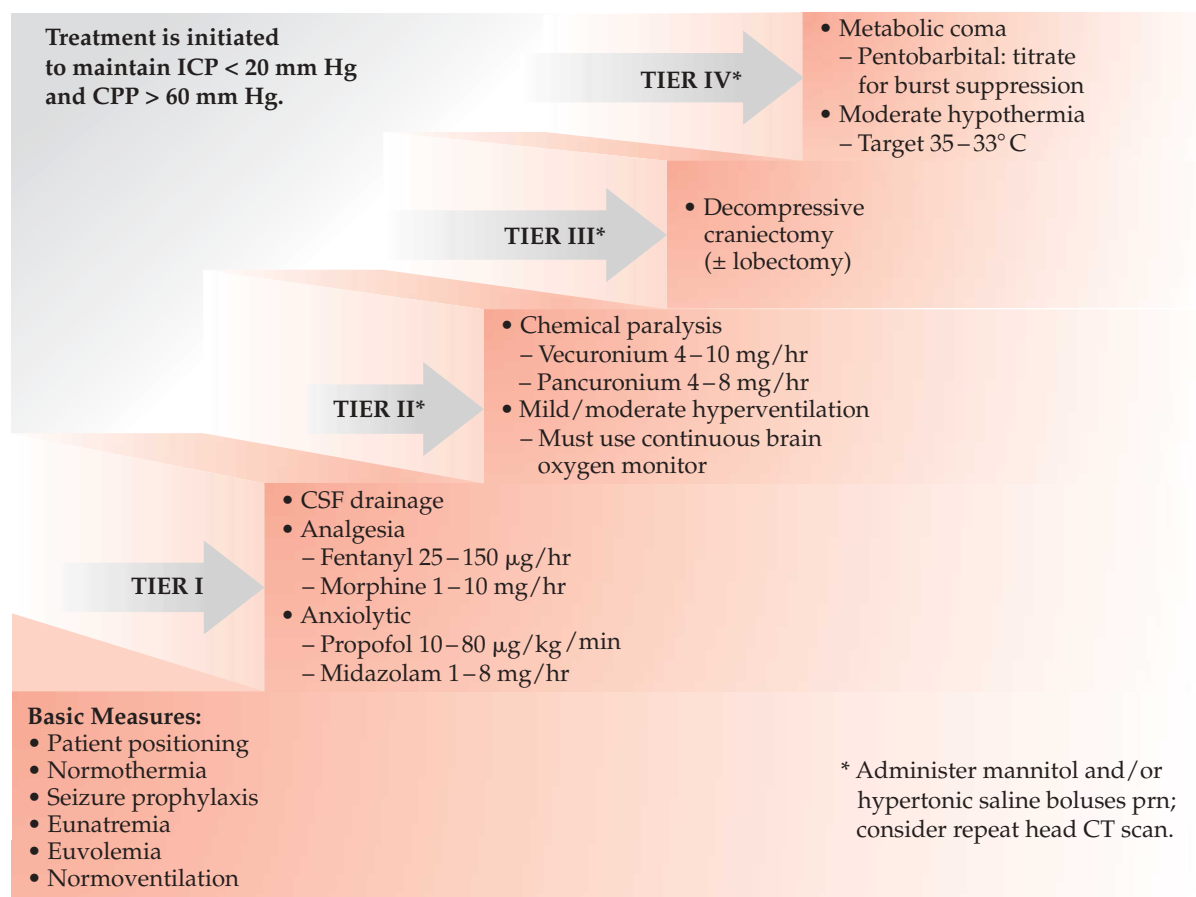


Figure 3 ICP = intracranial pressure; CPP = cerebral perfusion pressure; CSF = cerebrospinal fluid; CT = computed tomography.

may be preferable during resuscitation or in patients with decreased CVP. As mentioned above, the therapeutic effects of hyperosmolar therapies likely involve both osmotic and rheologic mechanisms.

TIER I CSF drainage has no known deleterious side effects but does have the potential risk of aggravating brain shift (depending on the side of its insertion relative to the side of injury). In general, it is best to drain the minimal amount of CSF necessary to maintain ICP below 20 mm Hg.

Various sedation strategies have been described for patients with severe TBI, all of which aim to reduced cerebral metabolic demand and, in turn, CBV and ICP. Most strategies include analgesic and anxiolytic drug infusions. Bolus delivery of these medications should be avoided in patients with severe TBI as this can result in induced hypotension, reduction of MAP and CPP, and reflexive cerebral vasodilation that causes elevation in ICP and further compromise of CPP and CBF. Agents with short half-lives and few active metabolites are preferable as they permit intermittent interruption of sedation to assess neurologic function, a strategy that has been shown to reduce ICU stay, ventilator dependence, and the need for repeat imaging and diagnostics.^{73,74} It is important to note, however, that these interruptions in sedation should not be performed in patients with elevated ICP and poor intracranial compliance as the risks of ICP spikes far outweigh the benefits of intermittent neurologic examination.

Many neuroscience ICUs prefer the use of fentanyl and propofol for ICP control as they are relatively shorter-acting agents that have demonstrated success in management of severe TBI. Propofol is a sedative hypnotic with a rapid onset and a short duration of action.^{75,76} In patients requiring more than 48 hours of sedation, propofol infusion results in significantly fewer ventilator days than treatment with intermittent lorazepam⁷⁷ and has a more favorable economic profile and shorter weaning time than midazolam.⁷⁸ In moderate and severe TBI patients, a prospective trial found significantly improved ICP control with propofol infusion (versus morphine).⁷⁹ In a recent multicenter, retrospective study, a propofol-based protocol resulted in lower ICP, higher CPP, and significantly improved survival (81.8% versus 46.7%).⁸⁰ Because propofol can have deleterious side effects after prolonged use (i.e., > 48 to 72 hours), adults should be closely monitored for “infusion syndrome” and children requiring prolonged sedation should be managed with midazolom infusion. Propofol is delivered via a preservative-free, lipid-base vehicle, which carries a high caloric content (1 kcal/mL) and should be accounted for when determining caloric balance.

As sedation is maximized for ICP control, patients may experience relative hypotension with CPPs dropping below 60 mm Hg. Intravenous volume expansion should be used to target CVPs of 8 to 10 mm Hg, after which a phenylephrine infusion should be instituted and titrated to CPP (and not MAP) goals.

TIER II After maximizing sedation and supporting CPP, many clinicians will institute muscular paralysis for ICP control. Although its efficacy may vary among patients, pharmacologic paralysis can be used in conjunction with maximal sedation to further reduce ICP. Paralysis is also achieved using continuous intravenous infusion and should be titrated

to effect (using percutaneous peripheral nerve stimulation). Although muscular paralysis compromises most of the neurologic examination, it is important to remember that neuromuscular blockade does not interfere with pupillary response, which is mediated by smooth muscle contraction.

Hyperventilation can be used as a strategy for ICP lowering despite maximal sedation and chemical paralysis but carries the risk of iatrogenic cerebral ischemia.⁸¹ Therefore, mild to moderate hyperventilation should *only be used in patients with a continuous brain oxygenation monitor*, such as a brain tissue oxygen probe or jugular bulb oximetry monitor.

TIER III Decompressive craniectomy is an important component of protocol-driven therapy for patients with severe TBI and should be performed in patients who have exhausted TIER I and II therapies and do not have adequate ICP control with intermittent hyperosmolar therapies. The effects of decompressive craniectomy on ICP are often dramatic: Olivecrona and colleagues performed decompressive craniectomy in 21 patients with elevated ICP despite evacuation of hematomas, sedation, CSF drainage, and pentothal infusion and found that mean ICP decreased from 36.4 to 12.6 mm Hg; they reported a trend toward improved outcome in these patients.⁸² Aarabi and colleagues found that 85% of patients have ICP below 20 mm Hg following decompressive craniectomy (mean ICP 23.9 mm Hg versus 14.4 mm Hg), and outcome at 3 months was significantly better than expected in patients who underwent craniectomy.⁸³ Timofeev and colleagues reported 49 patients who underwent craniectomy for refractory ICP; at the 6-month follow-up, 61.2% had a favorable outcome, 20.5% remained severely disabled, and 18.4% were left in a vegetative state.⁸⁴

Historically, decompressive craniectomy has been thought of as a TIER IV therapy, but there is significant evidence advocating its earlier use in protocol-directed TBI management. Albanese and colleagues studied very severe TBI patients with a high risk of brain death and performed decompressive craniectomy either before or after placement of an ICP monitor (based on injury severity, patients with absent pupillary responses underwent immediate craniectomy).⁷² Overall, they found that 25% of patients attained social rehabilitation at the 1-year follow-up. The size of craniectomy is also an important consideration when performing these procedures. A large multicenter study in China compared the effects of a standard trauma craniectomy (frontotemporoparietal, 12 × 15 cm, $n = 241$) to a limited craniectomy (temporoparietal, 6 × 8 cm, $n = 245$) for refractory ICP and found significantly increased “good outcome” at 6 months (39.8% versus 28.6%) with more extensive bone removal.⁸⁵ Currently, a prospective, randomized, multicenter, international trial (RESCUEicp study) is under way to more definitively establish the role of early decompressive craniectomy in TBI.⁸⁶

TIER IV Moderate hypothermia and barbiturate metabolic coma are highly effective means of reducing ICP but are associated with significant morbidity. As a result, many centers are considering surgical intervention prior to inducing barbiturate coma. Decompressive craniectomy, with or without lobectomy, can carry increased morbidity and mortality in patients who are receiving barbiturate infusion as they are often dependent on pressors to maintain adequate CPP and are less able to tolerate significant blood loss. It is important

to note, however, that many experts still advocate maximizing medical therapies (including barbiturate coma) prior to surgical intervention. In the absence of more definitive data on early decompressive craniectomy, it is important to have neurosurgical consultants intimately involved in patient care as TIER III and IV therapies are being considered.

High-dose barbiturate infusion for TBI was first described in the 1930s and is the most effective medical therapy for ICP control. In patients whose ICP does not respond to conventional therapy, barbiturate treatment is two to four times more likely to control ICP, and the likelihood of survival in patients who respond to barbiturates is 92% at 1 month (versus 17% for nonresponders).²⁵ Barbiturates appear to protect the brain and lower ICP through several mechanisms, including alteration of vascular tone, suppression of metabolism, and inhibition of free radical lipid peroxidation. The most important effect may involve coupling of CBF to regional metabolic demands, so the lower the metabolic requirements are, the lower the CBF and the related CBV, with subsequent beneficial effects on ICP and global cerebral perfusion. Barbiturate therapy (usually pentobarbital to a blood level of 4 mg/L) is instituted when other measures to control ICP fail. In one series of 25 patients with an ICP higher than 40 mm Hg, barbiturates not only controlled ICP but also improved outcome.⁸⁷ In a separate study, however, 54% of patients placed on barbiturate therapy experienced hypotension (compared with 7% of control subjects),⁸⁸ and others have attributed barbiturate therapy with worse neurologic outcome.^{88,89} Barbiturates are a powerful tool for control of ICP, but their use should be carefully scrutinized and monitored.

Hemoglobin, hematocrit, and blood viscosity Hematocrit and viscosity are inversely related, and a balance must be established to optimize oxygenation. If the hematocrit is too high, viscosity increases; if the hematocrit is too low, the oxygen-carrying capacity of blood decreases. Historically, neurosurgeons and neurointensivists have felt that the ideal balance between these factors is a hematocrit around 30%; below this, oxygen-carrying capacity may fall without a significant change in viscosity, and above this, viscosity may increase out of proportion to oxygen-carrying capacity. Despite this evidence, however, recent clinical trials have suggested that a lower hematocrit goal may be appropriate.

In 1999, the Canadian Critical Care Trials Group published the results of the “Transfusion Requirement in Critical Care” (TRICC) study, an investigation of 838 ICU patients who were randomized to a “restrictive” (trigger Hb 7.0 g/dL, target Hb 7.0 to 9.0 g/dL) or “liberal” (trigger Hb 10.0 g/dL, target 10.0 to 12.0 g/dL) strategy.⁹⁰ Overall, hospital mortality was decreased in the “restrictive group,” whereas 30-day mortality was similar between the two groups. Patients who were less acutely ill (APACHE-II score < 21) or younger (< 55 years) had a significantly lower mortality with a “restrictive” transfusion strategy, whereas patients with clinically significant cardiac disease (unstable angina, myocardial infarction)⁹¹ had a higher mortality rate with the “restrictive” strategy. Only a small subset of these patients had moderate or severe TBI, but a subgroup analysis of these patients also revealed no significant difference in outcome between a

“restrictive” or “liberal” strategy (this analysis was limited in power because of small patient groups).⁹² A retrospective review of 169 patients with severe TBI found that number of days with hematocrit less than 30% was associated with improved neurologic outcome, although very low levels were associated with worse outcome.⁹³ In this study, administration of a blood transfusion was associated with worse outcome. Others have suggested that outcome may be associated with the age of blood; a recent study by Leal-Noval and colleagues found that packed red blood cell units that have been banked for less than 19 days have more favorable effects on cerebral oxygenation following severe TBI.⁹⁴

At present, the “ideal” hematocrit for patients with severe TBI is not known and may lie between 21 and 30%.

Spinal Cord Injury

DIAGNOSIS AND INITIAL MANAGEMENT

In the field, all patients with significant trauma, any trauma patients who lose consciousness, and any patients suffering minor trauma who have complaints referable to the spine or the spinal cord should be treated as if they had an SCI until proven otherwise [see Figure 4]. If cardiopulmonary resuscitation is necessary, it takes precedence. The objectives are to maintain adequate oxygenation and maintain blood pressure (BP) by administering fluids and vasopressors. The main concerns of management in the field are immobilization before and during extrication from a vehicle (or removal from the scene of another type of accident) and immobilization during transport to prevent active or passive movement of the spine. Subsequently, the patient may require a rigid Philadelphia collar, support from sandbags and straps, a spine board, or a log-roll for turning. A brief motor examination may detect possible deficits.

When the patient arrives at the hospital, care should be taken to provide adequate oxygenation, prevent hypotension, and maintain immobilization. Patients with an injury above C4, who may have respiratory compromise, may need ventilatory assistance. Lesions above T5 may be accompanied by loss of sympathetic tone and ensuing venous pooling and arterial hypotension. Because paralytic ileus is common, usually lasting several days, a nasogastric tube should be placed to prevent vomiting and aspiration. A Foley catheter should be inserted because urinary retention is also a common occurrence. Vasomotor paralysis may cause poikilothermia (uncontrolled temperature regulation), and normothermia should therefore be maintained.

A detailed neurologic examination is required to determine whether the injury is complete or incomplete and at what level of the spinal cord the injury occurred. If possible, a history should determine the mechanism of injury (e.g., hyperflexion, extension, axial loading, or rotation). The American Spinal Injury Association (ASIA) (www.asia-spinalinjury.org) has developed a protocol for sensory and motor examination of patients with SCIs that is precise and relatively easy to follow [see Figure 5].

Spinal shock consists of loss of all or most motor, sensory, and autonomic functions below the level of the lesion. It usually develops in the setting of a severe SCI that occurs over a brief

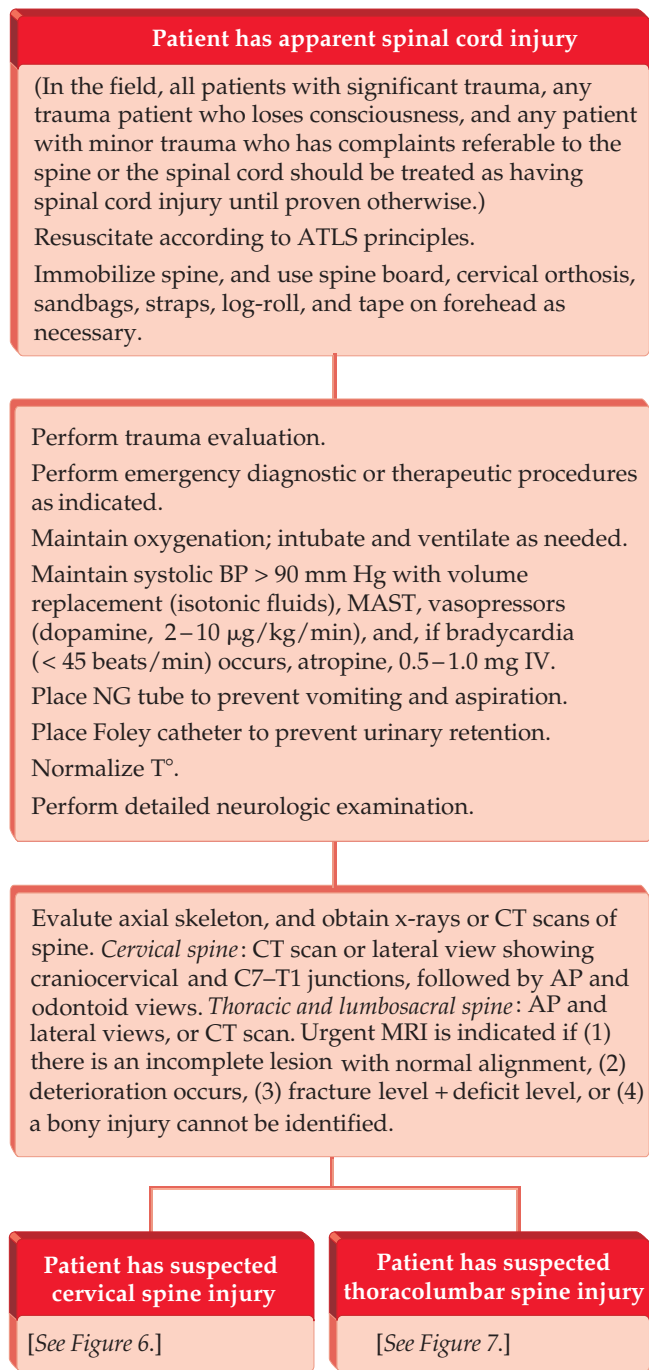


Figure 4 AP = anteroposterior; ATLS = advanced trauma life support; BP = blood pressure; CT = computed tomography; MAST = military antishock trousers; MRI = magnetic resonance imaging; NG = nasogastric.

period and is most commonly witnessed immediately after the injury (although it may also appear hours later in cases of progressive injury). As originally defined, the term “spinal shock” referred to arterial hypotension resulting from loss of sympathetic tone after SCI. Currently, however, most authors use the term to refer to the complex of symptoms associated with the loss of spinal reflex activity below the level of the lesion, which

may or may not include arterial hypotension. The motor component of spinal shock may consist of paralysis, flaccidity, and areflexia. The sensory component may involve both spinothalamic and dorsal column sensory function, and the autonomic component may include systemic hypotension, bradycardia, skin hyperemia, and warmth.

Spinal shock should be differentiated from spinal concussion. Spinal concussion is a poorly understood phenomenon. It is defined as partial spinal cord sensory or motor deficits that resolve completely within 24 to 72 hours and that are never associated with permanent SCI. Spinal concussion is rare and has never been described in conjunction with spinal shock.

All patients with possible spine injuries should be examined radiologically. Roentgenography of the cervical spine with the patient in a rigid collar includes a lateral view showing both the craniocervical and the cervicothoracic (C7 to T1) junction. If the lateral view is normal and the patient is coherent and has no neck tenderness or neurologic deficit, the collar can be removed for anteroposterior and odontoid views. If the lower cervical spine or the cervicothoracic junction is not well visualized, a lateral view with caudal traction on the arms, or a swimmer’s view, is required. If areas of the spine are still not visualized or if there is a neurologic deficit, a CT scan with sagittal reconstruction should be obtained through the poorly visualized levels.

The use of flexion-extension films (i.e., testing of the active range of motion of the cervical spine from maximal anteroposterior flexion to extension) is typically limited to patients who are awake and able to cooperate.⁴⁵ Although spinal instability is probably best demonstrated with this type of imaging, it should be noted that in patients with neck pain, muscle spasm can limit range of motion and thereby mask a subluxation. Accordingly, it is recommended that patients with posttraumatic neck pain who are neurologically intact, whose plain radiographs are normal, and who are capable of limited flexion and extension effort (i.e., < 30° of motion) be placed in a rigid cervical collar and reevaluated 1 to 2 weeks later. In comatose patients, dynamic films are sometimes obtained under direct fluoroscopic guidance, although magnetic resonance imaging (MRI) appears to render such studies unnecessary.

CT is particularly helpful in the further evaluation of fractures diagnosed on plain films: it shows bone in greater detail and at higher resolution than plain films or MRI. It achieves better visualization of fixed subluxations and allows more accurate assessment of the central bony canal and the neuronal foramina. CT is highly accurate in visualizing body fractures, Jefferson (C1) and hangman (C2) fractures, and bilateral locked facets. It appears to be less accurate, however, in visualizing transverse C2, posterior element, and nondisplaced spinous process fractures and sometimes misses superior articular process fractures.⁹⁵

MRI of the cervical spine is the study of choice for evaluating injury to the soft tissues and ligaments. Intrinsic cord damage (e.g., edema, hematoma, or contusion) and injury to the surrounding ligaments, disks, and paravertebral soft tissues are well visualized. In addition, MRI is helpful in the assessment of brachial plexus injury, although a series of special coronal images is usually required. A fat suppression image usually identifies ligamentous injury to the posterior elements quite well, and fine-cut gradient echo imaging of the



STANDARD NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

MOTOR

KEY MUSCLES

	R	L	
C2			
C3			
C4			
C5			Elbow flexors
C6			Wrist extensors
C7			Elbow extensors
C8			Finger flexors (distal phalanx of middle finger)
T1			Finger abductors (little finger)
T2			
T3			
T4			
T5			
T6			
T7			
T8			
T9			
T10			
T11			
T12			
L1			
L2			Hip flexors
L3			Knee extensors
L4			Ankle dorsiflexors
L5			Long toe extensors
S1			Ankle plantar flexors
S2			
S3			
S4-5			

0 = total paralysis
 1 = palpable or visible contraction
 2 = active movement, gravity eliminated
 3 = active movement, against gravity
 4 = active movement, against some resistance
 5 = active movement, against full resistance
 NT = not testable

TOTALS ☐ + ☐ = ☐
 (MAXIMUM) (50) (50) (100)

☐ Voluntary anal contraction (Yes/No)

SENSORY

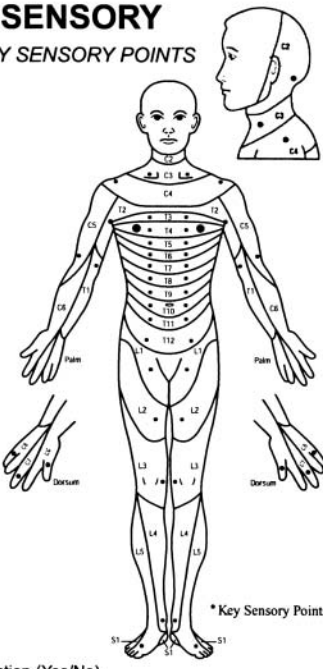
KEY SENSORY POINTS

	R	L	
C2			
C3			
C4			
C5			
C6			
C7			
C8			
T1			
T2			
T3			
T4			
T5			
T6			
T7			
T8			
T9			
T10			
T11			
T12			
L1			
L2			
L3			
L4			
L5			
S1			
S2			
S3			
S4-5			

TOTALS ☐ + ☐ = ☐
 (MAXIMUM) (56) (56) (56) (56)

☐ Any anal sensation (Yes/No)

0 = absent
 1 = impaired
 2 = normal
 NT = not testable



☐ PIN PRICK SCORE (max: 112)
☐ LIGHT TOUCH SCORE (max: 112)

NEUROLOGICAL LEVEL The most caudal segment with normal function	R	L	COMPLETE OR INCOMPLETE? Incomplete = Any sensory or motor function in S4-S5	ZONE OF PARTIAL PRESERVATION Caudal extent of partially innervated segments	R	L
	SENSORY ☐	MOTOR ☐			SENSORY ☐	MOTOR ☐

ASIA IMPAIRMENT SCALE ☐

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2000 Rev.

Figure 5 For the motor examination, 10 key muscles are tested (left). For the sensory examination, 28 key dermatomes are tested (right). CT = computed tomography; MRI = magnetic resonance imaging.

transverse ligament of C2 is extremely sensitive in detecting disruption.⁹⁶ The major drawbacks of MRI are the length of the imaging time, which may be a problem in the critically ill trauma patient, the susceptibility to movement artifacts, and the need for MRI-compatible monitoring devices and traction equipment. Moreover, in this setting, it is often difficult to obtain an adequate medical history with regard to implanted medical devices or old bullet fragments, both of which preclude MRI. Radiologic evaluation and clearance of the cervical spine can be facilitated by the use of an established protocol [see Figure 6].

Anteroposterior and lateral views of thoracic and lumbosacral vertebrae should be obtained for all trauma patients who were thrown from a vehicle or fell more than 2 meters to the ground, complain of back pain, are unconscious, cannot reliably describe back pain or have altered mental status preventing adequate examination, or have an unknown mechanism of injury or other injuries that suggest the possibility of spinal injury. If a fracture or subluxation is

found on the plain films, a CT scan with sagittal reconstruction extending from one level above the fracture or subluxation to one level below it is recommended.

Indications for urgent MRI include the following: an incomplete lesion with normal alignment (to rule out the possibility of compression); deterioration (worsening deficit or ascending level); a fracture level different from the level of deficit; and neurologic deficit but inability to identify a bony injury on CT (to rule out the possibilities of soft tissue compression, disk herniation, or hematoma that would necessitate surgery). Radiologic evaluation of patients with suspected thoracolumbar spine injuries is also facilitated by use of a protocol [see Figure 7].

In most patients, the spine can be cleared on the basis of plain x-rays and neurologic examination. Obtunded or comatose patients whose plain x-rays are normal but who are at high risk for spine injury (e.g., those injured in high-speed motor vehicle accidents or by falls from great heights) should be evaluated by a spine specialist before spine clearance.

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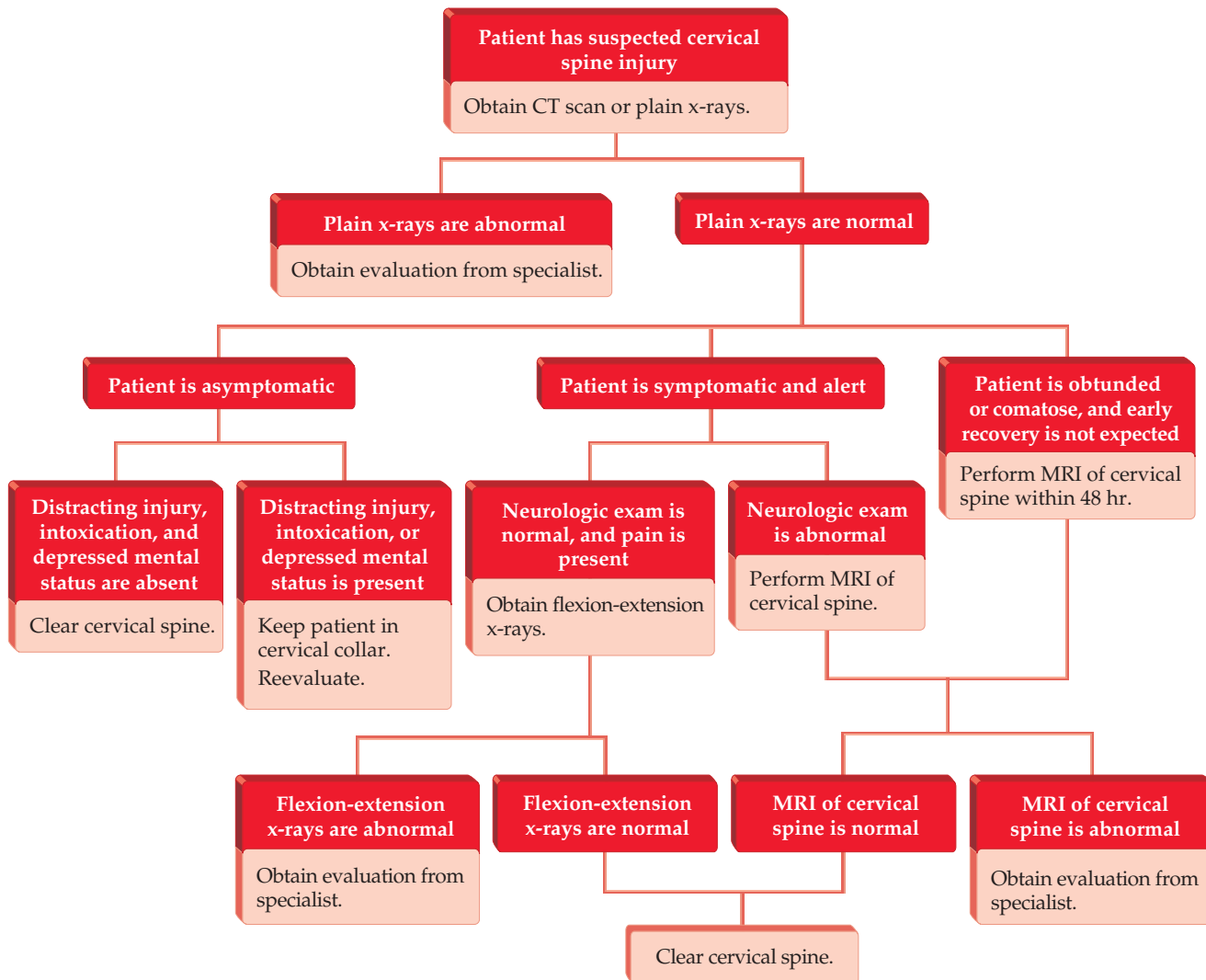


Figure 6 CT = computed tomography; MRI = magnetic resonance imaging.

TREATMENT

Traction

The objectives of craniocervical traction are to reduce fracture-dislocations, to maintain normal alignment or immobility of the cervical spine to prevent further injury, to decompress the spinal cord and roots, and to facilitate bone healing. A common technique is placement of Gardner-Wells tongs, a U-shaped device with pins that are anchored to the skull just above the pinna. Traction is applied with the patient in the supine position by adding weights to the traction ring. Alternatively, traction may be applied with the patient in a halo ring. A special traction triangle is then added to the ring. The advantage of this approach is that the patient can be stabilized in a halo vest as soon as reduction is obtained. Furthermore, the halo vest is helpful in dealing with a highly unstable spine that requires instrumentation because the patient can be easily turned onto the operating table without the risk of significant movement of the spine.

Traction should always be applied under strict neurologic monitoring. If the patient's condition deteriorates when the weight is increased, additional weight should be removed and the patient should immediately undergo imaging (e.g., with plain films, MRI, or both). In the case of a highly unstable fracture, traction should be guided by fluoroscopy rather than serial x-rays.

Pharmacologic Treatment

A number of drugs are known to interfere with the processes of secondary injury. The challenge is to identify the most effective treatment or combination of treatments with the fewest severe side effects—a task requiring many experiments for each treatment tested. Methylprednisolone (MP), thought to act by scavenging free radicals, has been reported to be neuroprotective in patients with SCIs.^{97–99} Considerable controversy remains, however, regarding the clinical benefit of MP administration after acute SCI.

Three multicenter, randomized, controlled clinical trials carried out in the United States evaluated MP in this setting:

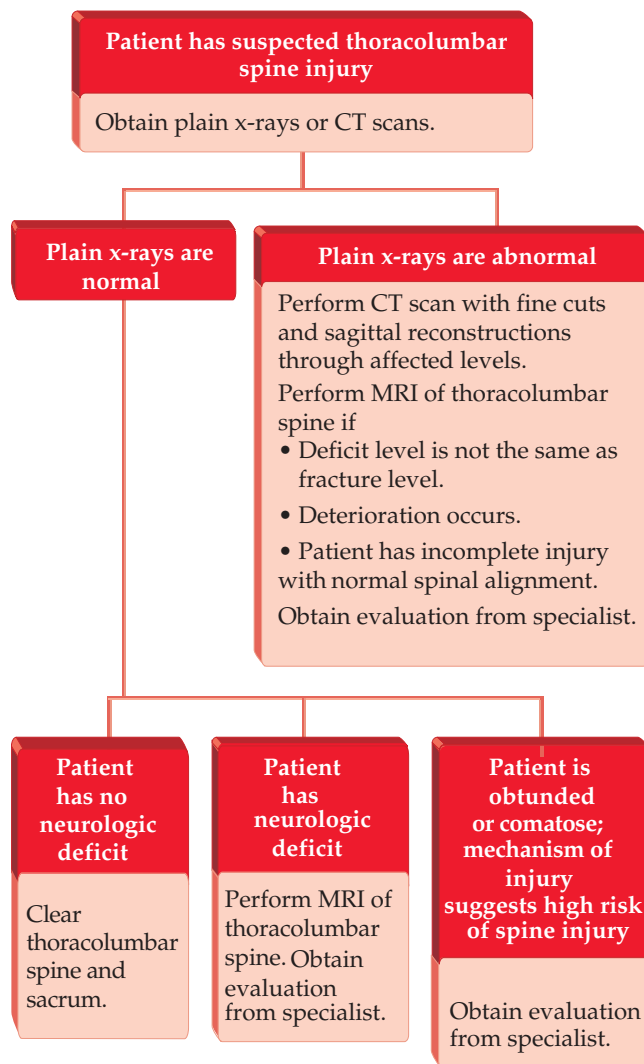


Figure 7 CT = computed tomography; MRI = magnetic resonance imaging.

the National Spinal Cord Injury Study (NASCIS) I, NASCIS II, and NASCIS III.⁹⁷⁻⁹⁹ In NASCIS I, reported in 1984, the administration of a 100 mg MP bolus followed by 100 mg/day for 10 days was compared with administration of a 1,000 mg MP bolus followed by 1,000 mg/day for 10 days. There was no placebo group. No difference was noted between the two MP groups with respect to motor or sensory outcome at 6 weeks, 6 months, and 1 year.

Because data from animal studies suggested that the MP doses used in NASCIS I were too low to yield a significant difference in outcome, NASCIS II was initiated in 1985. In this trial, administration of high-dose MP (i.e., a 30 mg/kg bolus followed by 5.4 mg/kg/hour for 23 hours) was compared with administration of naloxone (a 5.4 mg/kg bolus followed by 4 mg/kg/hour for 23 hours) and with placebo. Neurologic outcome was graded by evaluating sensory and motor function at 6 weeks and 6 months after injury. Fourteen muscle groups were examined and graded on a scale of 0 to 5. The scores were added, with a total score

of 0 indicating no motor activity below the level of the lesion and a total score of 70 representing normal motor function. For sensory assessment, 29 spinal cord segments were similarly evaluated and graded on a scale of 1 to 3. A total score of 29 indicated no response in any segment, and a total score of 87 indicated that all sensory segments were normal. The authors reported a statistically significant mean motor and sensory improvement after MP administration. In the MP group, there was a mean improvement of 16.0 in the motor score, compared with a mean improvement of 11.2 in the placebo group. The mean changes in sensory scores were 11.4 (MP) and 6.6 (placebo) for sensation to pinprick and 8.9 (MP) and 4.3 (placebo) for sensation.

In NASCIS III, patients who received a 24-hour regimen of MP (a 30 mg/kg bolus followed by 5.4 mg/kg/hr), a similar 48-hour regimen, or a 48-hour regimen of tirilazad mesylate (2.5 mg/kg every 6 hours) were evaluated. There was no placebo group. No differences in sensory or motor recovery were observed between groups. In a subgroup analysis, it was noted that in patients whose treatment was initiated more than 3 hours after injury, motor function improved more with the 48-hour MP regimen than with the 24-hour regimen. The Functional Independence Measurement (FIM) did not show any statistically significant differences between groups.

NASCIS II and III have been criticized for flaws in research design and data analysis. For example, patients with a normal motor examination and patients with a combined conus-cauda injury were included. Furthermore, only motor and sensory scores from the right side of the body were reported. Moreover, in the statistical analysis, only the results of a post hoc analysis were statistically significant.

A 2000 study presented a statistical reanalysis of the NASCIS II and III data.¹⁰⁰ In this reanalysis, no difference in neurologic recovery between the placebo, 24-hour MP, and 48-hour MP groups was found, but an increased mortality was documented in the 48-hour MP group—a finding that was not reported in the NASCIS studies. Current guidelines take the position that the available medical evidence does not conclusively establish the existence of a significant clinical benefit from administration of MP for either 24 or 48 hours and that the harmful side effects may actually outweigh any clinical benefits.¹⁰¹ MP administration is therefore considered a treatment option to be used at the discretion of the treating physician.

The calcium channel blocker nimodipine causes significant increases in blood flow in the spinal cord,^{102,103} but, paradoxically, the dosage necessary to exert this effect is accompanied by significant systemic hypotension. Administration of GM₁ ganglioside, a compound that occurs naturally in the membranes of mammals and is particularly abundant in the central nervous system (CNS), has been shown to have short-term neuroprotective effects and long-term regenerative effects in animal models. In a prospective, placebo-controlled, double-blind study, some improvement in motor, sensory, and bladder function was seen in patients treated with GM₁ ganglioside, but no overall improvement in neurologic outcome was noted.¹⁰⁴ This agent is currently an optional treatment for patients with SCIs. Treatment with GM₁ ganglioside is started after the completion of MP therapy and continued for 56 days.

Surgical Treatment

The role of neurosurgery in the treatment of spinal fractures and SCI remains controversial. There is considerable disagreement as to whether surgery should be performed, what type of surgery, and when. The primary goals of treatment are to decompress and protect underlying neural structures, to restore spinal stability and alignment, to facilitate early mobilization and rehabilitation, and to maximize neurologic recovery.

There is general agreement among physicians that immobilization of the patient to prevent further injury and early stabilization of fractures and dislocations of the spine are necessary. The single widely accepted indication for early urgent surgical treatment is ongoing neurologic deterioration in the presence of spinal canal compromise from bone and disk fragments, hematoma, or unreduced subluxation. Surgical indications still under debate include incomplete SCI (with persistent spinal cord compression) and complete SCI with the possibility of some neurologic recovery.

In some studies, early surgical intervention has been associated with an increased risk of systemic complications (especially pulmonary complications) and neurologic deterioration. One group of investigators found that one third of all cases of neurologic deterioration could be attributed directly to surgical intervention; four of 26 patients who underwent spinal surgery within 5 days experienced deterioration, whereas none of the patients treated after 5 days had any neurologic sequelae.¹⁰⁵

Other studies, however, have not found an increased risk of deterioration with early intervention. One study evaluated 110 patients with cervical SCI, of whom 88 underwent surgery for spinal stabilization; in the 39 patients treated within 24 hours, the incidence of systemic complications was reduced by 50% in comparison with the incidence in the 49 patients treated 24 hours to 3 weeks after injury.¹⁰⁶ In addition, the incidence of neurologic deterioration was 0% in the early-stabilization group compared with 2.5% in the late-stabilization group. Data from NASCIS II showed improved outcome in patients undergoing surgery within 24 hours of injury compared with patients treated after 200 hours, but the difference was not statistically significant.¹⁰⁷

We adhere to the following protocol in treating patients with cervical spine fracture-dislocations. After systemic stabilization, patients are placed in a halo ring and traction as soon as possible. We prefer to set up traction in the neurologic ICU, but this can be done in the emergency department when necessary. Closed reduction is attempted under the guidance of fluoroscopy or serial x-rays, depending on the degree of spinal cord compromise or expected instability. Patients are then secured in their halo vests and undergo MRI evaluation, regardless of whether reduction attempts succeeded or failed. Patients with reduced and realigned injuries and no cord compromise are kept in their halo vests and offered nonurgent surgical stabilization, depending on the nature of the injury. Patients with irreducible fractures or continued compromise of the neural elements are taken to the OR promptly for urgent surgical decompression and fixation, regardless of whether the neurologic injury is complete or incomplete.

The efficacy of early surgical decompression in patients with thoracolumbar fractures is not established, except in cases where the neurologic examination reveals deterioration. Most surgeons, however, advocate urgent decompression in patients who have canal compromise and an incomplete injury; patients who do not fall into this category can be kept on strict spinal precautions, with definitive therapy instituted on a nonurgent basis.

Diagnosis and Treatment of Specific Fractures and Dislocations

Cervical spine Injuries to the cervical spine include atlas fractures, axis fractures, fractures of the lower cervical spine, and atlanto-occipital and atlantoaxial dislocations. Atlanto-occipital dislocation (AOD) is rare, occurring in approximately 1% of patients with cervical spine injuries. Many of these patients die immediately after trauma as a result of brainstem injury and respiratory arrest. Since the 1980s, advances in emergency patient management in the field, reduced transport time, and better recognition of the condition have improved the survival rate after AOD. Nevertheless, since 1966, fewer than 100 survivors of AOD have been reported in the literature. Patients who survive AOD often have neurologic deficits, such as lower cranial neuropathies, unilateral or bilateral weakness, and quadriplegia. Some 20% of patients, however, exhibit no abnormalities on neurologic examination at presentation. AOD is difficult to diagnose and is often missed on the initial cervical radiograph. Accordingly, a high index of suspicion for this condition should be maintained, particularly when signs such as prevertebral soft tissue swelling on the plain cervical radiograph or subarachnoid hemorrhage at the craniovertebral junction on CT are present. Additional investigation with MRI may be necessary.

Because AOD mostly involves ligamentous injury, treatment generally consists of operative fusion. Traction is rarely employed because even a small weight may cause distraction injury with these highly unstable dislocations.

Atlantoaxial dislocations are often fatal as well. Like AODs, they are highly unstable lesions associated with severe ligamentous injury.

Atlas (Jefferson, or C1) fractures, which represent 5 to 10% of all cervical spine fractures, result from axial loading. Because of the large diameter of the spinal canal and the tendency of fragments to move outward, these fractures usually are not accompanied by significant neurologic injury. However, 40% of patients with an atlas fracture have another cervical fracture as well (usually involving C2). The integrity of the transverse ligament largely determines whether the fracture is stable.¹⁰⁸ Injuries that involve the midportion of the transverse ligament or the periosteal insertion (e.g., types Ia and Ib) will not heal spontaneously and must be treated with surgical fixation of the C1-C2 complex. In contrast, type II injuries (e.g., avulsion injuries or comminuted lateral mass fractures) will usually heal in a rigid external orthosis (e.g., a halo vest). Most other atlas fractures can be managed in a rigid cervical collar, except for widely displaced or comminuted fractures, which also require that the patient be immobilized in a halo vest.

Axis (C2) fractures account for 10 to 20% of all cervical spine fractures in adults and 70% of cervical fractures in

children. The odontoid process is the part of C2 that is most commonly fractured (accounting for 60% of axis fractures). The management of odontoid fractures remains controversial: only class III data are available, which are insufficient to establish practice guidelines.¹⁰⁹

Three different types of odontoid fractures are recognized. Fractures of the tip of the odontoid process (avulsion fracture, type I) are uncommon but are thought to be stable in most cases. They can be treated by using a hard cervical collar with or without preceding cervical traction or by immobilizing the patient in a halo vest.

Fractures of the neck (type II) and fractures at the junction of the odontoid process and the axis body (type III) are more common (accounting for 65 to 80% and 20 to 35% of odontoid fractures, respectively). Management of type II fractures depends on the degree to which the dens is displaced: fractures with more than 5 mm of displacement are typically managed surgically, whereas fractures with less than 5 mm of displacement can be treated nonsurgically with a halo vest or a semirigid orthosis (e.g., a sterno-occipito-mandibular immobilizer [SOMI] brace).¹¹⁰ The management of type II fractures also depends on the age and general medical condition of the patient. Halo-vest immobilization is associated with a significantly increased risk of pulmonary complications and death in elderly patients and thus should be used with caution in this population. Surgical stabilization and fusion are recommended for type II fractures in patients older than 50 years.¹¹⁰

The type IIa subcategory of odontoid fracture warrants special mention. These fractures have either anterior or posterior chip-fracture fragments at the base of the dens and are considered unstable. They are often widely displaced and have a nonunion rate of 75 to 85% with halo-vest immobilization. Accordingly, surgical management is recommended. The integrity of the transverse ligament should be evaluated in patients with type II injuries; fixation with an odontoid screw is contraindicated, and C1-C2 fixation should be performed instead.

Most type III odontoid fractures will fuse with rigid external mobilization (i.e., either cervical traction followed by placement in a rigid cervical collar or placement in a halo vest). Again, more than 5 mm of displacement is an indication for surgical stabilization.¹¹⁰

Traumatic spondylolisthesis, or hangman's fracture, accounts for approximately 20% of C2 fractures. Injury usually results from axial compression in combination with hyperextension of the occipitoatlantoaxial complex on the lower spine, resulting in bilateral fracture of the pars interarticularis. Fractures affecting the ring of the axis without C2-C3 angulation are stable and can be treated with immobilization in a Philadelphia collar or a SOMI brace. Halo-vest immobilization is recommended in unreliable patients or patients with both C1 and C2 fractures. The average healing time is 12 weeks. Fractures with angulation, subluxation, or C2-C3 locked facets are treated with halo-vest immobilization if they are adequately reducible and with surgical intervention if they are nonreducible, are associated with disruption of the C2-C3 disk space, or are subject to recurrent subluxation.^{96,110}

Approximately 80% of all fractures of the lower cervical spine are produced by indirect forces. The vertebra most

commonly involved is C5, and dislocations are most frequent at the C5-C6 level. The following injury mechanisms are observed: flexion and distraction (approximately 40% of cases), flexion and compression (22%), vertical compression (8%), extension and compression (24%), extension and distraction (6%), and lateral flexion (3%).

Flexion and distraction injuries usually result from a blow to the occiput from below. The initial disruption is within the posterior ligamentous complex, leading to facet dislocation and an abnormally large divergence of the spinous processes. Unilateral facet dislocation and facet interlocking result when a rotatory component is involved. Bilateral facet dislocation with anterior translation of the superior vertebra results from severe hyperflexion; the translation is usually at least 50% in such cases. Cord and root involvement vary with the degree of subluxation and translation: 50% of patients with unilateral facet dislocation present with moderate cord and root injury, and 90% of patients with bilateral facet dislocation and a full translation of the vertebral body have a neurologic deficit (most often a complete cord lesion). Teardrop fractures (characterized by a bone chip just beyond the anterior inferior edge of the vertebral body) result from severe hyperflexion injury, and the fractured vertebra is usually displaced posteriorly on the vertebra below; these patients are often quadriplegic.

Flexion and compression injuries, usually observed at the C4-C5 and C5-C6 levels, typically result from a blow to the back of the head. The effect on the anterior vertebral body varies from a moderate rounding or loss of anterior height to a wedge shape with an oblique fracture from the anterior surface to the inferior subchondral plate. Approximately 50% of patients with the latter type of injury have a neurologic deficit. More severe injuries are accompanied by translation of the inferior posterior margin of the vertebral body into the neural canal. About 75% of patients have neurologic involvement. Translations of more than 3 mm result in a complete spinal cord lesion in most cases.

Extension and compression injuries are usually caused by a blow to the forehead and result in fractures of the posterior complex. About 40% of patients with unilateral vertebral arch fractures (articular process, pedicle, or lamina) have a neurologic deficit (most often a radiculopathy). Bilaminar fractures are accompanied by a complete cord lesion in 40% of cases. Bilateral vertebral arch fractures with complete anterior translation of the vertebral body present with radiculopathy (30% of cases), central cord syndrome (30%), or an incomplete cord lesion (30%). In one series, no complete cord lesions were observed with this type of injury.¹¹¹

Treatment of injuries to the lower cervical spine has not been standardized. As a general rule, severe ligamentous involvement and severe vertical compression call for surgical intervention. Severely comminuted vertebral body fractures may also necessitate surgery because of the high risk of progressive kyphosis. Isolated spinous process fractures and unilateral lamina and pedicle fractures are usually managed conservatively with placement in a rigid cervical collar. If there is a fracture through the transverse foramen above C6, the vertebral artery should be evaluated for dissection by means of magnetic resonance angiography, CT angiography,

or catheter angiography.¹¹⁰ Surgical intervention should be carefully considered, especially in young trauma victims. In a series from 1988, 87% of patients with distractive flexion injury and 88% of those with compressive flexion injury healed with halo-vest immobilization.¹¹²

Thoracolumbar spine Approximately 64% of fractures of the spine occur at the T12-L1 junction, and 70% of these fractures are unaccompanied by immediate neurologic injury. Evaluation according to Denis's three-column principle [see Figure 8] is useful for determining whether a fracture is stable, although the precise definition of stability remains controversial.¹¹³ Fractures of the thoracic spine are more stable because of support from the surrounding rib cage and the strong costovertebral ligaments. When two of the three columns are affected, the fracture is considered unstable, and surgical intervention is generally required.

The four major types of thoracolumbar spine injuries are compression fractures, burst fractures, seat-belt fractures (Chance fractures), and fracture-dislocations. These four types of fracture involve the anterior, middle, and posterior columns

of the spine in different ways [see Table 3]. Transverse process fractures are rarely unstable and are typically managed conservatively with analgesics or muscle relaxants.

Minimal to moderate compression fractures (< 50% loss of height or < 30° of angulation) with an intact posterior column can be treated with analgesics and bed rest. Ambulation should be started early, and depending on the degree of kyphosis, external immobilization (with a thoracolumbar orthosis or a Boston brace) may or may not be indicated. Severe compression injuries should be treated with external immobilization in extension. If the loss of anterior height of the vertebral body exceeds 50%, there is an increased risk of progressive kyphosis; evaluation with follow-up radiographs is indicated. Occasionally, surgical intervention is required. An anterior injury is considered unstable if it involves more than three adjacent elements or if height loss in a single element exceeds 50% with more than 30° of angulation.¹¹⁴

Burst fractures are considered unstable even if there is no initial neurologic deficit. Early ambulation should be avoided because the axial loading may result in progressive collapse or angulation, with concomitant neurologic damage. Indications

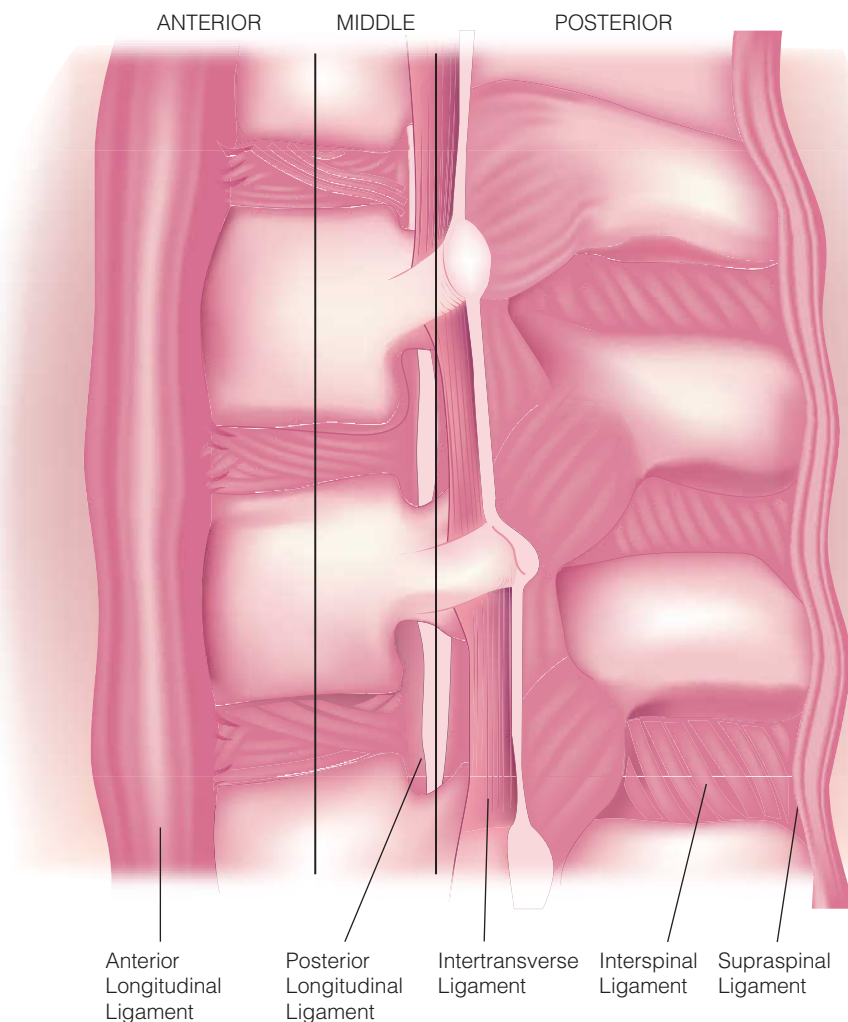


Figure 8 If two or more columns are destroyed or nonfunctional, instability is likely.

Table 3 Column Failure in the Four Types of Major Thoracolumbar Spinal Injury¹¹³

Fracture Type	Anterior Column	Middle Column	Posterior Column
Compression	Compression	Intact	Intact, or distraction if severe
Burst	Compression	Compression	Intact, or involved
Seat belt	Intact or mild compression of 10–20% of anterior vertebral body	Distraction	Distraction
Fracture-dislocation	Compression, rotation, shear	Distraction, rotation, shear	Distraction, rotation, shear

for the surgical treatment of burst fractures include the following:

1. Loss of more than 50% of body height
2. Retropulsed bony fragments narrowing the canal by more than 50%
3. Kyphotic angulation of 25° or more

A Chance fracture is a horizontal fracture through all three columns. It occurs most commonly in the lower lumbar spine and is a highly unstable injury. Chance fractures are now less frequent than they once were because of the widespread use

of shoulder belts in addition to lap belts, which prevents upper torso flexion during deceleration. Chance fractures are treated with surgical stabilization, and decompression and correction of spinal alignment may be required as well.¹¹⁴

Fracture-dislocations, also known as fracture subluxations, are three-column injuries that usually involve disruption of the ligamentous structures or the disk space. Dural lacerations and neurologic injury are common with such injuries. Fracture-dislocations are considered unstable and are treated with surgical decompression and stabilization.

Discussion

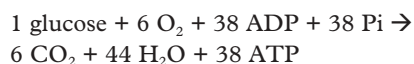
Pathophysiology

HEAD INJURY

Cerebral Metabolism

At 1,200 to 1,400 g, the brain accounts for only 2 to 3% of total body weight and does not do any mechanical work, yet it receives 15 to 20% of all cardiac output to meet its high metabolic demands. Of the total energy generated, 50% is used for interneuronal communication and the generation, release, and reuptake of neurotransmitters (synaptic activity); 25% is used for maintenance and restoration of ion gradients across the cell membrane; and the remaining 25% is used for molecular transport, biosynthesis, and other, as yet unidentified, processes.

Cell metabolism involves the consumption of adenosine triphosphate (ATP) during work and the ensuing consumption of metabolic substrates to resynthesize ATP from adenosine diphosphate (ADP). ATP is generated both in the cytosol (via glycolysis) and in the mitochondria (via oxidative phosphorylation). Glucose is the sole energy substrate, unless there is ketosis, and 95% of the energy requirement of the normal brain comes from aerobic conversion of glucose to water and CO₂. ATP generation is highly efficient. Glycolysis and subsequent oxidative phosphorylation result in the generation of 38 molecules of ATP for each molecule of glucose:



In the absence of oxygen, anaerobic glycolysis can proceed, but energy production is much less efficient. Two molecules

of ATP and two molecules of lactate are generated for each molecule of glucose:



Regulation of Blood Flow

Because the reserves of glucose and glycogen within the astrocytes of the brain are limited and there is no significant storage capacity for oxygen, the brain depends on blood to supply the oxygen and glucose it requires. More specifically, substrate availability is determined by its concentration in blood, flow volume, and the rate of passage across the blood-brain barrier.

Under normal circumstances and with certain physiologic alterations, an adequate supply of substrates can be maintained by regulation of CBF. CBF increases with vasodilatation and decreases with vasoconstriction. Caliber changes take place mainly in cerebral resistance vessels (i.e., arterioles with a diameter of 300 µm down to 15 µm).¹¹⁵ Control of CBF by influencing vessel caliber is commonly referred to as autoregulation of blood flow.

Metabolic autoregulation CBF is functionally coupled to cerebral metabolism, changing proportionally with increasing or decreasing regional or global metabolic demand. Thus, the brain precisely matches local CBF to local metabolic needs. Because 95% of the energy in the normal brain is generated by oxidative metabolism of glucose, CMRO₂ is considered to be a sensitive measure of cerebral metabolism. The relation between CBF and metabolism is expressed in the Fick equation:

$$\text{CMRO}_2 = \text{CBF} \cdot \text{AVDO}_2$$

CMRO₂, expressed in milliliters per 100 g of brain tissue, is normally about 3.2 mL/100 g/min in awake adults. The average CBF value for mixed cortical flow is 53 mL/100 g/min in a healthy adult. AVDO₂, a measure of cerebral oxygen extraction, can be calculated by subtracting the oxygen content of jugular venous blood (6.7 mL/dL) from that of arterial blood (13 mL/dL), resulting in a value of 6.3 mL/dL; this value can then be corrected for hemoglobin content according to the formula discussed earlier [see Head Injury, ICU Management, *above*]. Under conditions of increasing metabolic demand (increased CMRO₂), such as seizures or fever, CBF increases proportionally, thus keeping AVDO₂ constant. With decreasing metabolism (anesthesia, deep coma), CBF decreases.

Pressure autoregulation Another important physiologic property of the cerebral circulation is maintenance of a constant supply of substrates at the level set by metabolism. According to the Poiseuille equation,

$$CBF = k \frac{CPP \cdot d^4}{(8 \cdot l \cdot v)}$$

in which k is a constant of proportionality, d is vessel diameter, l is vessel length, and v is blood viscosity; changes in CPP (e.g., arterial hypotension or increases in ICP) are followed by changes in CBF, unless diameter regulation (pressure autoregulation) takes place.¹¹⁶ In humans, the limits of pressure autoregulation range from 40 to 150 mm Hg of CPP.

Viscosity autoregulation In accordance with the Poiseuille equation, CBF can vary with changes in the viscosity of blood. Blood viscosity changes with variations in hematocrit, γ -globulin, and fibrinogen components of plasma protein. Increased viscosity would increase cerebrovascular resistance ($8 \cdot l \cdot v/d^4$). By means of diameter adjustment (viscosity autoregulation), cerebrovascular resistance is decreased and CBF can be kept constant.¹¹⁷

CO₂ reactivity Vascular caliber and CBF are also responsive to changes in Paco₂. CBF changes 2 to 3% for each mm Hg change in Paco₂ within the range of 20 to 60 mm Hg. Hypercarbia (hypoventilation) results in vasodilatation and higher CBF, and hypocarbia (hyperventilation) results in vasoconstriction and lower CBF. Autoregulation is a compensatory or adaptive response adjusting CBF to metabolism; with CO₂ variation, vessel caliber changes and CBF follow passively. The vessels respond not to changes in Paco₂ but to the pH in the perivascular space. CO₂ can cross the blood-brain barrier freely, thus changing the pH, but over 20 to 24 hours, with a constant new level of Paco₂, the pH in blood and in the perivascular space returns to baseline, and the diameter of the cerebral blood vessels also returns to baseline.¹¹⁸ With CO₂ reactivity, changes in CBF are compensated for by changes in AVDO₂, so that a constant supply of substrates is maintained at the level set by metabolism (CMRO₂). A constant AVDO₂ is a common feature of metabolic, pressure, and viscosity autoregulation; because CBF is tuned to metabolism, AVDO₂ can be kept constant.

Cerebral Circulation and Metabolism after Severe Head Injury

Arterial hypoxia and hypotension It is known from eyewitness reports of head injury and experimental studies immediately after the impact that arterial hypotension and interruption of normal respiration, sometimes with a period of prolonged apnea, are common findings. In the days after a head injury, there are many occasions and opportunities for hypoxic and hypotensive insults. As noted above, hypotension (systolic BP < 90 mm Hg) and hypoxia (Pao₂ < 60 mm Hg) are major determinants of poor outcome.

The effect of hypotension on the brain depends on the status of autoregulation. If autoregulation is defective, decreased BP leads directly and linearly to a reduction in CBF. If autoregulation is intact, arterial hypotension can lead to a considerable increase in ICP, which interferes with CBF by decreasing perfusion pressure.

Elevated ICP According to the Monro-Kellie doctrine, ICP is governed by three factors within the confines of the skull: brain parenchyma plus cytotoxic edema, CSF plus vasogenic edema, and CBV. When the volume in one compartment increases, ICP increases unless there is a compensatory decrease in volume in the other compartments. The relation between intracranial volume and ICP is expressed in the pressure-volume index (PVI).¹¹⁹ PVI is defined by the volume that must be added to or withdrawn from the craniospinal axis to raise or decrease ICP 10-fold:

$$PVI = \frac{\Delta V}{\log ICP_i / ICP_o}$$

where ΔV is the change in volume, ICP_o is ICP before the volume change, and ICP_i is ICP after the volume change. PVI is thus a measure for the compliance ($\Delta V/\Delta P$) or tightness of the brain. Under normal circumstances, PVI is 26 ± 4 mL; 26 mL of volume will raise ICP from 1 to 10 mm Hg, but the same volume will also raise ICP from 10 to 100 mm Hg. Conversely, a change in volume of only 6.4 mL is necessary to increase ICP from 10 mm Hg (normal) to the treatment threshold of 20 mm Hg. Thus, small changes in volume have a relatively large effect on ICP. PVI values as low as 5 mL have been reported in patients with head injuries.

Apart from mass lesions, ICP typically increases after severe head injury because of cerebral edema. Initial compensation is by displacement of CSF from the cranium, which is visualized in a CT scan of the head as small ventricles and basal cisterns. Subsequent compensation would be by a decrease in CBV, which can be accomplished by means of vasoconstriction.

Relation between vessel diameter, CBV, and ICP The total diameter of the cerebrovascular bed determines CBV. Cerebral veins contain most of the total blood volume, but their diameter and thus their volume are relatively constant. Approximately 20 mL of blood (i.e., one third of total CBV) is located in the cerebral resistance vessels (which range in diameter from 300 μ m down to 15 μ m).¹¹⁸ Because most autoregulatory and CO₂-dependent variations in diameter take place in these vessels, CBV is determined mainly by their diameter. Typically, the diameter ranges from 80 to 160% of baseline, resulting in volume changes between 64 and 256%

of baseline. With a baseline value of 20 mL in the resistance vessels, CBV will range from 13 mL (maximal vasoconstriction) to 51 mL (maximal vasodilatation). Given a PVI of 26, change from maximal vasoconstriction to maximal vasodilatation will be accompanied by an almost 29-fold change in ICP.

CBV, ICP, and CBF CBF and CBV are governed by vascular diameter. Thus, depending on other parameters influencing CBF (such as mean arterial BP, ICP, and blood viscosity), changes in vascular caliber also affect CBF.

Hypocarbica reduces ICP by means of vasoconstriction, consequently improving CPP. However, net CBF is decreased because in the Poiseuille equation, vessel diameter is carried to the fourth power. A randomized clinical trial has shown that preventive hyperventilation retards clinical improvement after severe head injury, perhaps through reduction of CBF to ischemic levels.¹²⁰ However, its rapid effect on ICP is a great advantage in cases of acute neurologic deterioration (e.g., in the presence of an expanding mass lesion before evacuation can take place) and should be reserved for these situations.

There are two methods of reducing ICP by means of vasoconstriction without affecting CBF. The first is to reduce blood viscosity. As can be deduced from the Poiseuille equation, decreasing the blood viscosity will, by itself, lead to vasoconstriction, provided that viscosity autoregulation is intact. With impaired autoregulation, decreased viscosity will result in an increase in CBF but no decrease in ICP. However, this effect can be used to maintain CBF under vasoconstriction with hypocarbica. As discussed above, the effect of mannitol on ICP is thought to be mediated in part by lowering blood viscosity.

The second method of reducing ICP without affecting CBF is to increase CPP, which can be done by raising BP. Again, with intact autoregulation, an increase in CPP will lead to vasoconstriction, with net CBF remaining constant. With impaired autoregulation, CBF will follow CPP passively, and maintenance of normal BP may be indicated in these cases. More important, however, is the avoidance of hypotension under these circumstances; the effect of CPP therapy may be attributable in part simply to prevention of hypotension.

Cerebral ischemia Cerebral ischemia, defined as CBF that is inadequate to meet the metabolic demands of the brain, is an important mechanism of secondary injury in patients with severe head injury, and the adequacy of CBF

has been associated with neurologic outcome. In autopsy findings from patients dying after severe head injury, histologic damage indicative of cerebral ischemia was seen in 80% of cases.¹²¹ One group of investigators found that ischemia (CBF < 18 mL/dL with abnormally high AVDO₂ values) occurred in 20 to 33% of patients with severe head injuries within 4 to 12 hours of injury and that the ischemia was associated with a poor prognosis.¹²² Of the intracranial lesions, acute subdural hematoma and diffuse cerebral swelling were most often associated with ischemia.

The relation between cerebral metabolism and CBF is expressed in the Fick equation [see Metabolic Autoregulation, above]. The normal brain tends to keep AVDO₂ constant and to react to changes in metabolism by adjusting blood flow. When CBF decreases in response to metabolism (as with hyperventilation or decreasing CPP with impaired autoregulation), oxygen supply is maintained by increasing oxygen extraction (i.e., AVDO₂ increases). A rising AVDO₂ is thus a sensitive marker of insufficient cerebral perfusion. However, the extent to which oxygen extraction can be increased is limited, and this limit is reached when AVDO₂ is doubled (13.2 mL/dL). Consequently, any further reduction in CBF results in neuronal dysfunction (i.e., CMRO₂ decreases). Because 50% of the energy is used for synaptic activity, a reversible and functional loss is usually observed first. Further decline, however, will result in ion pump failure, loss of membrane integrity, consequent cell swelling (cytotoxic edema), and cell death (irreversible infarction). The occurrence of irreversible infarction depends on both the level and the duration of ischemia. When CBF falls to approximately 18 mL/100 g/min for more than 4 hours, it reaches the threshold for irreversible infarction.

Maintenance or improvement of CBF is thus essential to the treatment of severe head injury, and AVDO₂ is a sensitive marker of the adequacy of therapy. When therapeutic measures fail to sustain CBF, CMRO₂ can be decreased to reinstate the match between CBF and metabolism. CNS suppression can be achieved by administering hypnotic agents (e.g., barbiturates or propofol) or inducing hypothermia. Decreasing cell metabolism will result in reduced production of CO₂, lactic acid, or both and (with blood vessels almost always remaining responsive to perivascular pH changes) in vasoconstriction accompanied by reductions in both CBF and ICP. The relations between CMRO₂, CBF, CBV, CPP, and AVDO₂ are complicated. An overview is available elsewhere [see Table 4].¹²²

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Table 4 Changes in CBF, CBV, ICP, and AVDO₂ Associated with Primary Reduction of Selected Variables¹²²

Variable Reduced	CBF	CBV (ICP)	AVDO ₂
CMRO ₂	↓	↓	NC
CPP (autoregulation intact)	NC		NC
CPP (autoregulation defective)	↓	↓	
Blood viscosity (autoregulation intact)	NC	↓	NC
Blood viscosity (autoregulation defective)	↑	NC	↓
Paco ₂	↓	↓	↑
Conductance vessel diameter (vasospasm above ischemia threshold)	↓	↑	↑

AVDO₂ = arteriovenous oxygen content difference; CBF = cerebral blood flow; CBV = cerebral blood volume; CMRO₂ = cerebral metabolic rate of oxygen; CPP = cerebral perfusion pressure; ICP = intracranial pressure; Paco₂ = arterial carbon dioxide tension; NC = no change.

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Acknowledgments

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3 INJURIES TO THE FACE AND JAW

Mark E. Engelstad, DDS, MD, and Richard A. Hopper, MD, MS

Assessment and Management of Maxillofacial Injuries

The human face is vulnerable to injury. It is frequently the target of interpersonal violence or inadequately restrained within a motor vehicle accident. Injuries to both the soft tissues and skeleton of the face are frequent sources of emergency department admissions and consultations. Isolated maxillofacial trauma is rarely life threatening or an immediate cause of death unless associated with airway compromise.¹ However, approximately 20% of all patients with facial soft tissue, dentoalveolar, or facial fracture trauma have associated injury to additional body systems.² Motor vehicle crash victims with facial injuries have a high associated rate of neurologic (32%), orthopedic (31%), visceral (24%), and ophthalmologic (14%) injuries. Personal assault has a lower association with neurologic (11%) and ophthalmologic (4%) injuries.³ When facial fractures are present in patients suffering an occupational injury, an average of four associated injuries are seen for every facial fracture present and 2.4 associated injuries for every facial fracture present in a victim of a motorcycle crash.

In the 21st century, facial injuries still result in devastating permanent defects in function and appearance, but advanced craniomaxillofacial (CMF) techniques are steadily improving outcomes. In the past 40 years, techniques in CMF surgery have evolved significantly. Advancement in minimally invasive access, internal fixation with plates and screws allowing immediate function, reconstruction of defects with primary bone grafting and patient-specific implants, and computer-assisted surgical planning are improving results and decreasing treatment time.

It is now widely recognized that a coordinated, multidisciplinary treatment strategy achieves better outcomes for facial trauma patients. CMF trauma patients return to function and a normal quality of life far sooner than when long periods of intermaxillary fixation (IMF) and gruesome external appliances were the norm.

Initial Evaluation

Maxillofacial injuries result from energy transfer that is usually blunt or penetrating in nature. Blunt trauma to the face, most commonly secondary to motor vehicle accidents or assault, results in bony and dental injury, whereas penetrating trauma causes neurovascular injury and soft tissue defects. Gunshot wounds can show surprisingly few external signs of injury while causing extensive damage to the hard tissues of

the face as the bones and teeth absorb energy from the passing projectile. Shotgun wounds result in obvious and extensive avulsion of both hard and soft tissues. Firearm injuries that cause avulsion of large portions of the face are quite survivable if the airway is secured.

Maintaining an airway is the primary consideration in facial trauma. Bony maxillofacial injury does not usually require immediate surgical attention but is a sign that significant force has been sustained and that the cervical spine and airway should be evaluated and monitored.⁴ The surgeon must maintain vigilance because patients who present soon after injury can, over subsequent minutes or hours, lose their airway as edema progresses [see Figure 1].

The initial maxillofacial assessment should include documentation of the presence or absence of vision in each eye. Soft tissue injuries causing significant hemorrhage should be dealt with; palpating the scalp and looking behind the ears and under the cervical collar will reveal hidden lacerations. The facial skeleton should be evaluated for mobility or malocclusion and the oropharynx inspected for loose teeth or foreign bodies that could obstruct the airway.

Assessing the occlusion for changes can be confusing because there are so many normal variants of dental anatomy. If there are step-offs in the dental arch, then a fracture is likely; asking the patient if the bite feels abnormal is also helpful. In the intubated patient, the diagnosis of facial fractures can be delayed, so the patient should be reexamined after extubation. The presence of numbness on the face, especially around the upper and lower lips, is also suggestive of facial fracture.

The initial survey should proceed with the following priorities, in decreasing importance: airway, hemorrhage, vision, bony trauma, soft tissue injuries.

AIRWAY ASSESSMENT

Facial trauma can result in immediate or delayed airway compromise. The caliber of the airway can decrease subsequent to displacement of facial bones, expanding edema or hematoma, loose dentition and debris, foreign bodies, or laryngeal injuries. A heightened level of awareness is needed when monitoring the airway after facial trauma. Most low- to moderate-energy facial trauma does not result in significant airway compromise over time. However, edema from injuries with high-energy transfer, such as gunshot wounds or high-speed blunt trauma, can steadily worsen over time. If the patient feels that he or she must sit up to breathe comfortably, this can be taken as a sign of current or pending airway compromise.

In patients who cannot maintain their own airway, an endotracheal tube should be inserted at the first opportunity, both to maintain ventilation and prevent aspiration. In the

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Assessment and Management of Maxillofacial Injuries

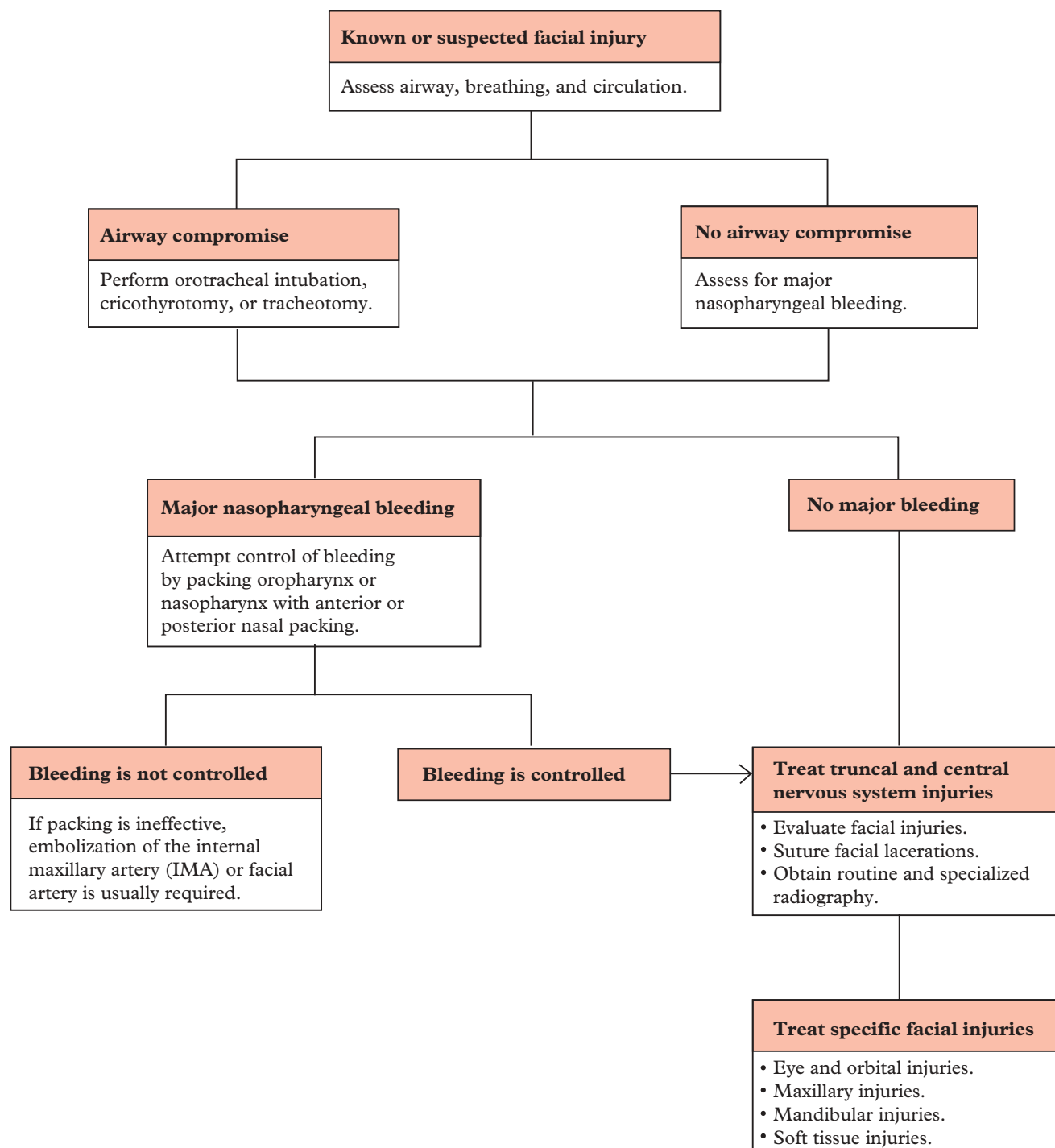




Figure 1 This patient suffered a combination of blunt and penetrating trauma to the central face. Note the unstable maxilla, missing bone, endotracheal tube, and intracranial bolt monitor. Clamps had been placed in the field to control arterial bleeding. This patient will require tracheostomy, reduction and fixation of bone fragments, bone grafting of missing bone, and soft tissue reconstruction.

presence of midface and skull base fractures with or without cerebrospinal fluid (CSF) leakage, an airway is more safely established by orotracheal intubation or cricothyrotomy. Both of these routes minimize the likelihood of inadvertent submucosal or intracranial tube placement, as may occur with nasal intubation in the trauma setting. However, nasotracheal intubation is not absolutely contraindicated in the presence of these injuries; the use of fiberoptic intubation techniques can provide safe transnasal endotracheal tube passage. Alternatively, a stylet to maintain the direction of passage, along with direct oropharyngeal visual confirmation of the tube passing over the soft palate, can allow safe nasotracheal intubation. Blind nasotracheal intubation should be avoided in patients with cribriform plate fractures.

Treatment of the compromised airway is complicated by the likelihood that 10% of patients with facial trauma have a cervical spine injury.⁵ A cervical collar or need to maintain in-line traction makes intubation in the emergency setting even more difficult. In the uncooperative trauma patient in need of a safe airway, only a brief attempt should be made to insert an endotracheal tube. If unsuccessful, cricothyrotomy should be performed. If time and urgency allow, a more deliberate tracheotomy may be done instead.

Maxillofacial fractures alone, even when extensive, are not usually an indication for a surgical airway. Internal fixation of maxillofacial injuries minimizes the need for IMF (wiring the upper and lower teeth together) and significantly shortens the recovery period. The decision to accept the morbidity and potential complications from tracheostomy or cricothyrotomy should be based on airway deterioration and inability to intubate or the anticipated need for a long duration of intubation.

MAXILLOFACIAL HEMORRHAGE

Once an airway has been established, the next maxillofacial priority is to control bleeding from the face, scalp, or deeper wounds. Firm compression with moist packs is an effective way to stop most arterial and venous facial bleeding. Definitive ligation or cautery of a single bleeding point is sometimes necessary. Blind clamping and suture ligation in deep wounds should be avoided in areas where the facial nerve may be injured.

Blood loss from scalp laceration, much of which may have occurred at the scene of injury, can be severe enough to cause hypovolemic shock.⁶ Continuous scalp hemorrhage often comes from arteries just superficial to the galea, where they are surrounded by dense connective tissue, which prevents scalp arteries from retracting after injury.⁷ Single-layer suture wound repair or application of Raney clips can minimize scalp blood loss until definitive wound repair is possible.

Persistent nasal hemorrhage is first treated by direct pressure with anterior nasal packing. In the trauma setting, epistaxis may have a number of sources; packing both the anterior and the posterior nasal cavity is sometimes required to provide sufficient direct pressure, but extensive comminution of the midfacial skeleton will make nasal packing less effective. Most commercially available nasal packs involve an anterior balloon and a posterior balloon with separate ports for differential inflation pressures. In a fully mobile Le Fort fracture, IMF may be required to prevent the maxilla from being inferiorly displaced during nasal packing. If packing is ineffective, embolization of the internal maxillary artery (IMA) or facial artery is usually required.⁸

There is a large amount of evidence that early transarterial embolization is the most effective treatment for significant persistent facial hemorrhage that does not respond to direct pressure or other methods.^{8–11} Reduction and fixation of bony injuries are often not effective at controlling significant bleeding. Likewise, ligation of the external carotid artery is unreliable because of the rich collateral vascular supply to the head and face.¹² In unstable patients with ongoing significant facial hemorrhage that cannot be controlled by packing, embolization should be considered as soon as possible.¹³

Comprehensive Survey

In the multisystem trauma patient, maxillofacial injuries have relatively low priority. Unless airway compromise, deteriorating visual acuity, or severe hemorrhage exists, the definitive diagnostic maxillofacial evaluation can be delayed until the stabilization of more life- and limb-threatening injuries. A definitive maxillofacial trauma examination should proceed in a consistent sequence.

INSPECTION

Facial swelling or facial asymmetry is a sign of underlying bony injury. The face can swell quickly and dramatically, even with minimal skeletal injury. Trauma can be hidden in easy-to-overlook areas underneath cervical collars, behind the ears, and in the hair. Look inside the mouth for injured dentition or ecchymosis under the tongue or on the mucosa, which are signs of mandibular or maxillary fracture. If the patient can bite, look for gross malocclusions or step-offs in the dental arch and ask the patient to open and close the mouth.

If the bite feels abnormal to the patient, a mandibular or midfacial fracture is likely [see Figure 2]. Inspect the interior of the nose for CSF leakage, septal deviation, or septal hematoma. Septal hematomas are rare but should be drained to decrease the chance of septal cartilage necrosis and resulting nasal deformity [see Figure 3].

Periorbital ecchymoses are associated with zygomatic, orbital, or skull base fractures; ecchymosis in the mastoid region, the so-called Battle sign, is also a sign of skull base fracture. Facial nerve injuries are initially localized by asking the patient to lift the eyebrows, close the eyes, and purse the lips.

Inspect the external auditory canal and the tympanic membrane for blood or ecchymoses, which are signs of skull base or mandibular condyle injury. Confirm that gross hearing is intact by rubbing your fingertips together near both ears.

Ocular and periorbital evaluation is an important part of the facial trauma examination. If lacerations exist around the eye, closely inspect the lid margin and the nasolacrimal duct for injury; both would require specialized repair. The normal distance between medical canthi in adults is 33 to 35 mm. An increase in this distance is called telecanthus and is a sign of significant bony trauma between the orbits, the so-called naso-orbitoethmoid (NOE) fracture.

Ocular pain, decreased vision, and the appearance of spots before the eyes are all highly suggestive of globe damage. One prospective study reported a 29% incidence of ocular injury in 49 patients with orbital fractures.¹⁴ Gross visual acuity

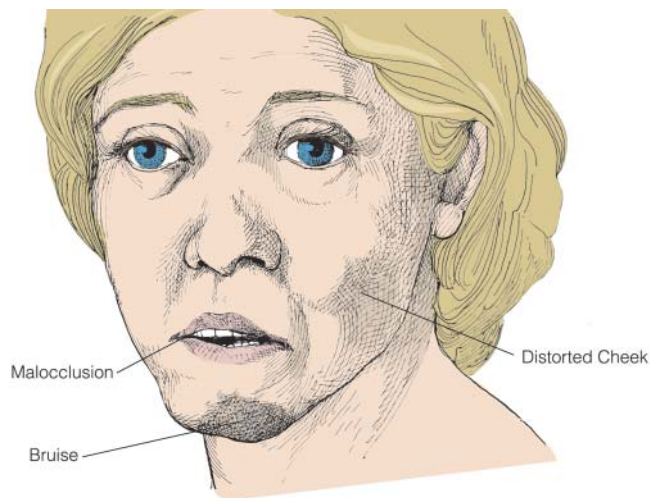


Figure 2 **Fractured mandible.**

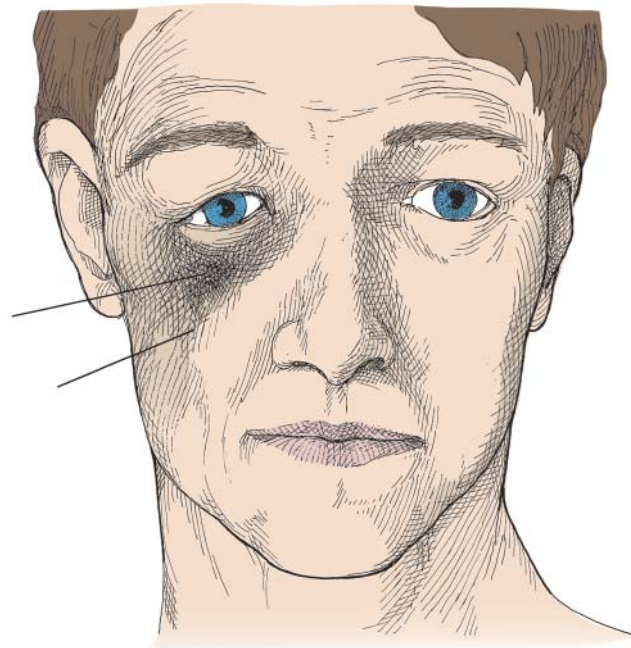


Figure 3 **Fractured zygoma.**

and the presence of diplopia should be assessed for each eye separately and both eyes together. Documentation of acuity (i.e., “can count fingers at 2 meters” or “light perception only”) allows comparison over time and makes detection of progressive visual loss more likely.

Evaluate the eyeball for extraocular movement. Note that in fractures involving the orbit, some decrease in extraocular range of motion is expected; this differs from true inferior rectus muscle entrapment, which prevents any movement in superior gaze and is often accompanied by pain and nausea. Vertical or anteroposterior changes in globe position relative to the other eye are a sign of orbital fracture. Check pupils for symmetry, light reactivity, hyphema (blood in the anterior chamber of the eye), and subconjunctival ecchymoses. If globe disruption is suspected, never press on or around the eye and always protect it from further disruption with a shield.

If the trauma sustained was significant enough to fracture the orbital bones, then the possibility of globe injury exists, even when no external signs of ocular trauma are visible.¹⁵ Although the threshold for requesting an ophthalmology consultation varies by institution, it is absolutely indicated in the presence of decreasing visual acuity, anisocoria not accounted for by central nervous system injury, lens displacement, hyphema, or globe disruption. Relative indications include subconjunctival ecchymosis and diminished ocular range of motion.

PALPATION

Touch lightly around the lips and cheeks to assess for diminished sensation from the trigeminal nerve, which is a sign of fracture. Palpate the entire scalp for signs of injury.

Bimanual palpation works best for examining the rest of the craniofacial skeleton. Palpate the bony prominences of the zygomas, zygomatic arches, and orbital rims and assess

them for tenderness, asymmetries, step-offs, or crepitus. Simultaneously palpating both sides allows comparison and makes detection of injury more likely. Assess mandibular integrity with bimanual manipulation while closely observing the teeth for movement, a sign of fracture. Newly missing teeth should be noted, along with the possibility that they may be in the airway [see Figure 4].

Gently palpate the nose for asymmetry, tenderness, or crepitus. Significant nasal fractures will often present with gross deformity visible on inspection alone [see Figure 5].

The maxilla should be evaluated for mobility relative to the skull base, an indication of the Le Fort fracture, discussed below. This is usually done by placing one hand on the forehead or bridge of the nose for stability and the other inside the mouth to grasp and mobilize the maxilla. If a Le Fort-type injury exists, the maxilla will move independent of the stable skull base.

Lastly, if the patient is able to speak, perceived changes in the quality of voice are indicative of laryngeal or cranial nerve X or XII injury. The presence of ecchymosis over the larynx or subcutaneous air in the anterior neck is an indication of significant laryngeal injury. In this situation, due consideration should be given before attempting intubation, which may turn a partial laryngeal or tracheal separation into a complete disruption. Fiberoptic intubation in a controlled surgical setting or proper surgical airway should be pursued if the suspicion of significant laryngeal trauma exists.

IMAGING

The facial skeleton is complex; it has varying degrees of osseous thickness and a large amount of three-dimensional (3D) complexity. The accurate diagnosis of fractures in the deeper areas of the midface, such as the orbit and frontal sinus, is not possible without computed tomography (CT).

Plain Radiography

Because of the complex anatomy of the face and its inability to image discrete areas, plain radiography of facial trauma is no longer useful, with one exception: the orthopantomogram (OPG), otherwise known as the panoramic radiograph

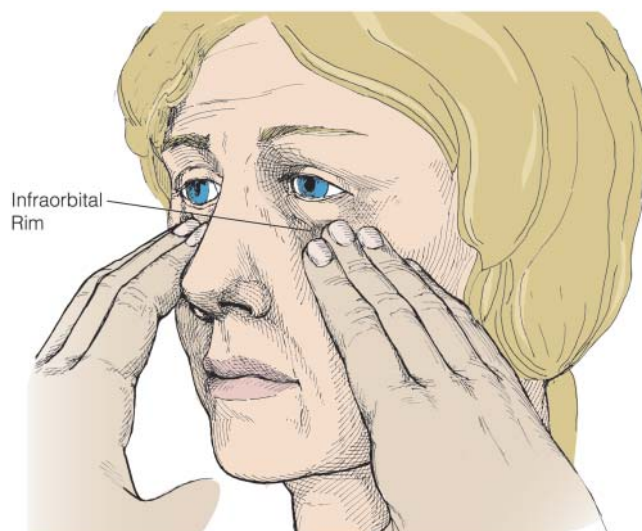


Figure 4 **Infraorbital fracture.**



Figure 5 **Broken nose.**

of the upper and lower jaw. Where available, the OPG is useful for diagnosis and treatment planning of mandibular and dentoalveolar fractures.

Computed Tomography and Magnetic Resonance Imaging

Overall, CT is the gold standard imaging modality for maxillofacial trauma. It has a range of sensitivity to visualize subtle injuries to thin bones and orbital soft tissues. CT allows volumetric (3D) rendering of the entire skull and mandible, which can be used for patient-specific 3D treatment planning and implant development. However, many maxillofacial injuries are visible only in standard axial, coronal, and sagittal cross-sectional format. 3D maxillofacial CT can simplify conceptual understanding of the injury, but cross-sectional windows should always be assessed.¹⁶ Outside its use for vascular imaging, magnetic resonance imaging is not often used in the evaluation of maxillofacial trauma.

CT angiography and magnetic resonance angiography are effective techniques to evaluate vascular injuries associated with maxillofacial trauma. Published regimens to manage vascular maxillofacial injuries are evolving toward selective surgical intervention based on combined clinical examination and angiography findings.¹⁷

Treatment of Soft Tissue Injuries

BASIC CONCEPTS

Maxillofacial soft tissue injuries are very common. They are the result of blunt or penetrating trauma and can involve finely detailed structures such as the facial nerve, parotid duct, or lacrimal drainage system. During initial examination,

signs of injury to these structures are an indication for specialist consultation.

All wounds should be thoroughly inspected for the presence of foreign bodies or broken teeth before irrigation, cleansing, and débridement. Irrigation with normal saline is usually adequate. If other agents are added, they should not pose any danger if they get into the eye. If the presence of deeper foreign bodies is suspected, plain radiography can be used to localize them before closure. After automobile accidents, broken glass, which is often radiolucent, may be found in the wound. Failure to adequately remove all loose fragments and foreign material can result in persistent local inflammation and residual cosmetic deformities.

Because of rich facial blood flow, even dusky tissues on small pedicles will often survive and may prove to be useful later on; conservative débridement of injured facial soft tissues is usually recommended.

To enhance hemostasis, an epinephrine-containing local anesthetic should be locally infiltrated for repair, except in areas of significantly compromised blood flow. Where possible, regional nerve blocks should be used because they will not distort the wound margins, which is preferable in areas such as the eyebrows, forehead, and lips, where specific tissue alignment is required. The infraorbital nerve, for example, can be blocked to provide anesthesia to the upper lip, side of the nose, and nearby soft tissues. Supraorbital nerve and mental nerve regional blocks are also useful.

Many soft tissue injuries of the face and scalp can be repaired with local anesthesia and standard layered closure in the emergency department, with good results. However, non-cooperative children and adults or patients with extensive or complex soft tissue injuries should be treated in the operating room under general anesthesia. If associated bony injuries will require future repair, then temporary closure of soft tissue injuries is sufficient. Lacerations are frequently used for access to underlying bony injuries, so definitive repair should be done after bony reconstruction.

Facial lacerations are usually closed in layers. Subcutaneous sutures should be placed to remove dead space and reapproximate the skin surface without tension. The purpose of skin surface sutures is not to pull open skin margins together but to gently reapproximate them. Tight skin sutures that strangulate the wound margins should be avoided. Always consider resorbable skin sutures in small children; the safe removal of these sutures can be very challenging in the uncooperative child.

Routine antibiotic use for simple nonbite facial soft tissue injuries is not indicated. When careful wound preparation is performed before repair, simple lacerations do not appear to benefit from prophylactic antibiotic therapy.^{18,19} A home care regimen of daily wound cleansing and coverage with a topical antibiotic ointment will usually suffice.

In more complex and grossly contaminated wounds, antibiotic coverage should be considered. Patients should be reminded to use sunblock with a sun protection factor of 15 or more on facial wounds for several months after initial healing to minimize darkening of the wound margins.

FACIAL AND TRIGEMINAL NERVE INJURIES

Injuries to the proximal facial nerve result in obvious and serious functional disabilities. When evaluating soft tissue

injuries around the facial nerve, its function must be assessed and documented before giving any local anesthetic. Evaluate the temporal branch by asking the patient to lift the eyebrows, the zygomatic branch by tightly closing the eyes, the buccal branch by smiling, and the marginal mandibular branch by pursing the lips or frowning. If the patient is unconscious, a nerve stimulator can be used to grossly assess the integrity of the facial nerve.

When evaluating the facial nerve, imagine a vertical line extending superiorly and inferiorly from the lateral canthus of the eye [see Figure 6]. Nerve injuries posterior to this line can be considered for nerve repair. Injuries to the nerve anterior to this line are generally too small to repair and will have adequate contralateral crossover innervation.

Patients with deep penetrating soft tissue injuries that involve the parotid gland, especially the deep posterior parotid gland, should be assumed to have a facial nerve injury until proven otherwise. Clean, sharp divisions of one of the proximal nerve branches should be identified and repaired with direct neurorrhaphy as soon as possible. If a defect in the nerve trunk of several millimeters or more exists, the ends of the nerve should be tagged for later repair by grafting.

Sensory nerve injury usually involves the trigeminal nerve; results in hypoesthesia or anesthesia of the facial brow, nose, lids, lips, and skin; and is a sign of associated bony injury. Altered sensation in these areas is often temporary; even when it is permanent, long-term disability from sensory nerve injury is usually minimal.

PAROTID DUCT INJURIES

The parotid duct extends anteriorly 2 to 3 cm from the anterior parotid gland and drains saliva into the mouth

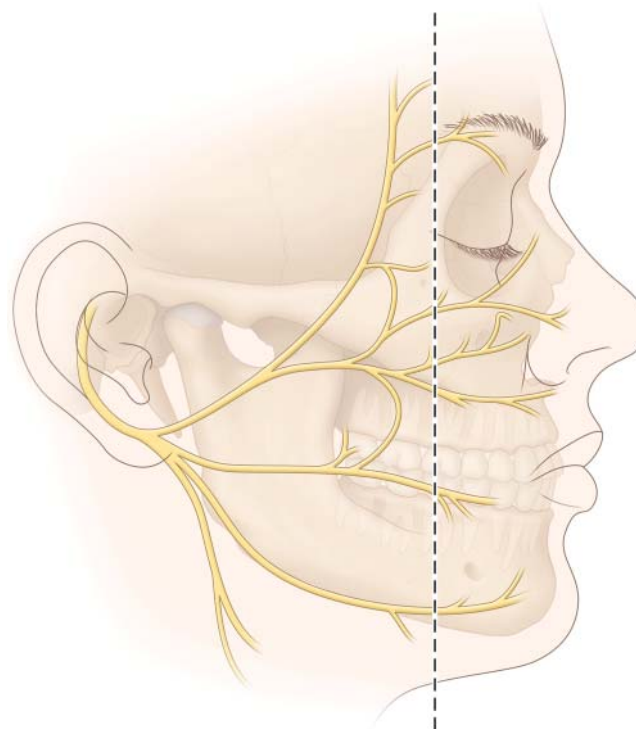


Figure 6 Soft tissue injuries involving the facial nerve distal to the vertical line are likely too small for primary repair.

through an orifice found on the buccal mucosa just opposite the maxillary molars. Deep lacerations between the anterior parotid gland and this orifice can potentially damage the parotid duct.

If a ductal injury is suspected, a slender and flexible probe can be inserted retrograde through the duct orifice and back toward the parotid gland; if the probe is found protruding into the wound, then the duct has most likely been severed. If both ends of the severed duct can be located, then careful anastomosis over a stent or catheter can be performed to maintain duct continuity [see Figure 7]. Some studies demonstrate that normal wound closure without specific duct repair provides similar outcomes and that specific repair of the duct may not be necessary.²⁰

SCALP INJURIES

Shaving the scalp is not routinely necessary for laceration repair. The blood supply in this area is rich, and infection is very uncommon. When using cautery for hemostasis, remember that bleeding scalp vessels are deep to the hair follicles, at the level of the galea. Avoid excessive cautery in the superficial layers, which can lead to alopecia. Scalp lacerations are repaired in one or, at most, two layers.

Scalp injuries can create significant potential space between the scalp and the skull, allowing hematoma accumulation, so drain placement or head wrap may be necessary. Never use an active drain over a skull fracture. Primary repair of partial scalp avulsion will require extensive releasing incisions and local flap rotation; some can be left to granulate secondarily.

EYELID INJURIES

Laceration of the eyelid region should raise suspicion for penetrating ocular injury, which can exist with no external signs. Globe rupture or retained intraorbital foreign bodies may be present with only very small external signs of injury. Eyelid injuries come in two main types: those that involve the margin of the lid and those that do not. The former are more complex, and their repair is the domain of the subspecialist. Repair of lid margin injuries requires meticulous three-layer closure and close postoperative monitoring. Injuries that do not involve the lid margin should still be carefully examined and then closed in layers.

Mobilizing nearby soft tissue to repair areas of eyelid avulsion is difficult, and soft tissue débridement around the eyelids should be kept to a minimum, even if the tissue appears poorly perfused.

LACRIMAL DUCT INJURIES

Lacerations involving the medial quarter of the eyelids should be assumed to compromise the lacrimal drainage system. Repair of the ducts is highly specialized and involves microscopic identification and repair over a flexible stent. Identification of these ducts can be tedious; inaccurate probing in search of them will only further damage the drainage system, leading to epiphora (poor drainage and pooling of tears) later. Successful repair usually requires specialist consultation.

EYEBROW INJURIES

The eyebrows should never be shaved; they are required for accurate alignment of the tissue margins and usually will

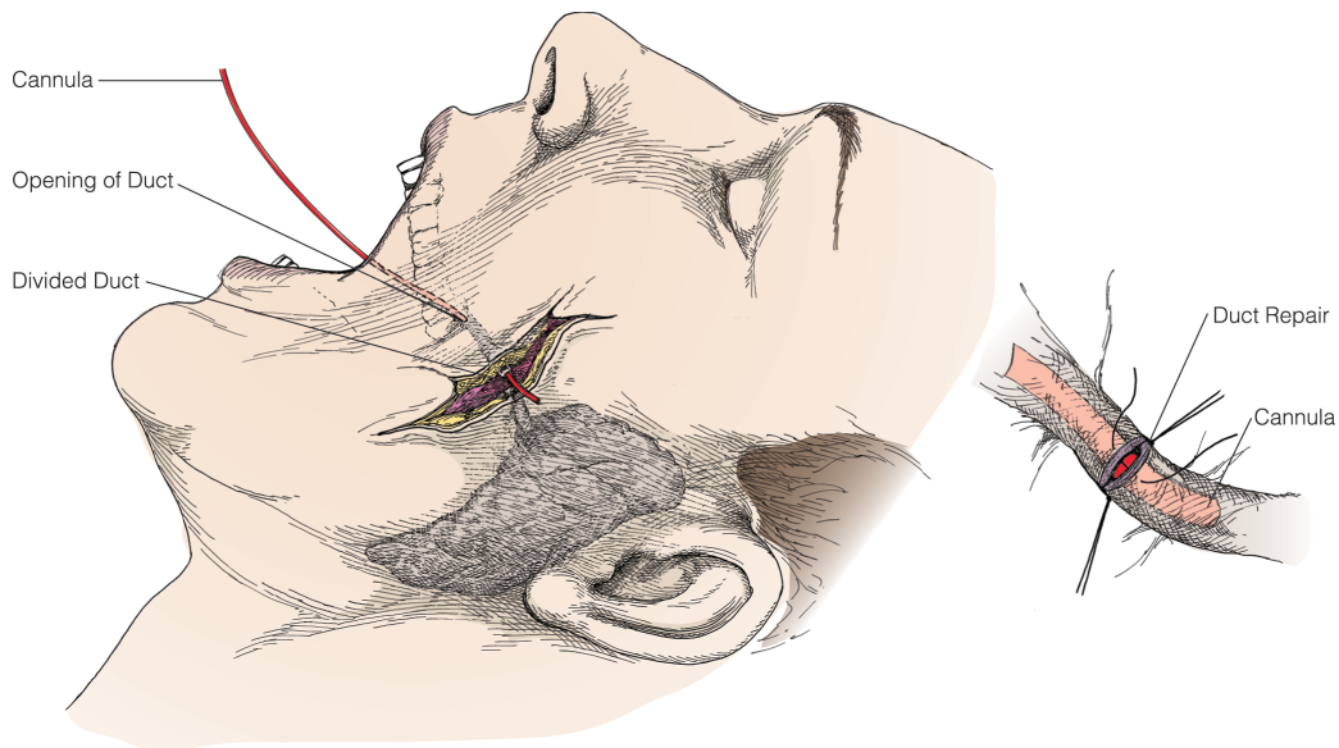


Figure 7 Injuries to the parotid duct are repaired by passing a catheter through the Stensen duct and through the area of laceration and then repairing the parotid duct over the catheter.

not grow back. If débridement is necessary, incisions should be made parallel to the eyebrow hair follicles, which run obliquely under the skin surface. Doing so will minimize eyebrow alopecia, which is quite noticeable if it occurs.

EXTERNAL EAR INJURIES

Because of their prominence, external ear injuries are common. The ear is highly vascular, and circulation is often maintained, even in cases of partial avulsion when only a small pedicle is present.

Full-thickness auricle lacerations should be aligned and repaired in layers, but suturing of the cartilage layer is not always necessary. If total avulsion occurs, the cartilage should be deepithelialized and buried in a retroauricular subcutaneous pocket for use in later reconstruction.

Shearing of the vascular mucoperichondrium from the underlying cartilage can lead to hematoma formation. To maintain normal skin-cartilage contour and prevent cauliflower ear, these hematomas should be evacuated early followed by placement of a conforming pressure dressing on both sides of the auricle.

NASAL INJURIES

Soft tissue injuries of the nose create cosmetic concerns, but malalignment of injured supporting cartilage can also create functional problems. Mucosa should be repaired first, with resorbable suture; then both cartilage and skin should be repaired with fine nonresorbable suture. Structures with linearity (like the alar rim) or transition points (such as the skin-mucosa junction) should be carefully aligned or noticeable deformity will result.

LIP INJURIES

When repairing lip injuries, identification and alignment of the vermilion border on both sides of the laceration are critical. Direct infiltration of epinephrine or local anesthesia into the wound margins will make identification of the vermilion much more difficult. If direct injection is necessary, tattoo or mark the vermilion first. Through-and-through lip lacerations should be closed in layers. A key point is identification and direct suturing of the orbicularis oris layer, which reconstructs the oral sphincter and prevents notching at the lip margin. If ragged wound margins exist, sharp wedge excision will allow direct, well-aligned closure and a better cosmetic result. If dental injuries exist, lip lacerations should be examined for embedded tooth fragments.

Treatment of Maxillofacial Fractures

BASIC CONCEPTS

Maxillofacial fracture treatment paradigms differ from those of the axial skeleton. There are two windows for optimum treatment of maxillofacial injuries. The first 6 to 12 hours following injury, before the onset of edema, is typically reserved for urgent comorbidities (e.g., optic nerve compression, uncontrollable facial bleeding, pediatric trapdoor orbital fractures). In the multisystem trauma victim, this early treatment phase may not be possible because of the higher priority of other injuries. The most common timing for repair is 3 to 7 days postinjury, after the initial edema has subsided and the

patient is cleared for the operating room. If complicating injuries do not exist, most bony facial repair is done on an outpatient basis. Blood supply in the face is relatively rich, so, generally speaking, infection is less common and antibiotics are less necessary than when treating extremity fractures, even when repair is delayed.

The most common maxillofacial fractures are nasal, mandibular, orbital, and zygomaticomaxillary complex fractures. The paranasal sinuses (maxillary, ethmoid, frontal) are frequently involved. Surgeons with maxillofacial trauma expertise exist in the specialties of oral and maxillofacial surgery, otolaryngology, and plastic and reconstructive surgery. A multidisciplinary approach is frequently required, especially for complicated repair, with involvement of neurosurgery and ophthalmology.

PRINCIPLES OF MAXILLOFACIAL FRACTURE REPAIR

Successful surgical repair of facial fractures requires adequate exposure and visualization, mobilization and reduction, and stable internal fixation of the fractured segments, especially along the facial buttresses.¹⁶ Facial buttresses meet the following critical criteria: (a) they are all linked either directly or through another buttress to the cranium or cranial base as a stable reference point; (b) they have sufficient bone thickness to accommodate metal screw fixation; and (c) they are accessible through standard limited surgical incisions. Examples of vertical buttresses include the thickened bone that runs from the alveolus up the side of the nose to the frontal bone. An example of a horizontal buttress is the one that runs from the temporal bone, along the zygomatic arch and inferior orbital rim to the other side. Thin nonbuttress bone such as the anterior wall of the maxillary sinus does not require reduction and fixation.¹⁶

Accurate reduction and fixation of the facial buttresses restore projection, width, and height of the facial skeleton relative to the cranial base and, more importantly, establish functional support for the teeth and globes. Once this has been accomplished, the soft tissues of the face, such as the dissected periosteum, nasal cartilages, and ligamentous attachment of the eyelids, are resuspended in their correct position.

DENTOALVEOLAR INJURIES

Dentoalveolar trauma refers to isolated fracture or displacement of the teeth or its supporting bone, the alveolus. These injuries are very common, and the possibility of missing teeth or tooth fragments in the airway should be kept in mind.

Treatment usually involves reduction and splinting to nearby stable teeth. In some cases, extraction is necessary, but this is cosmetically devastating to the patient. Reconstruction of lost teeth and alveolar bone is expensive and time consuming, so efforts to stabilize and salvage existing teeth and bone are important.

MANDIBULAR FRACTURES

Gross mobility, malocclusion, and numbness of the lower lip are signs of mandibular fracture. Ecchymoses in the floor of the mouth or vestibule are also suggestive, and CT will confirm the diagnosis. Mandibular fracture alone is not usually an indication for emergent intubation. Even bilateral

mandibular fracture will not usually compromise the airway, except with severe displacement or in obtunded patients. Mandibular fractures are named by region, as in Figure 8.

Historically, all mandibular fractures were treated with several weeks of IMF and still are today in many places. However, open reduction and internal fixation (ORIF) offers more immediate mobility and, in many cases, the prospect of avoiding IMF altogether. Given that IMF inhibits respiratory function,²¹ avoiding it can be helpful for successful ventilator weaning.

Because it has teeth, complicated movement patterns, and relatively less vascularity, the mandible has a higher complication and infection rate than other facial fractures. Most infections are secondary to inadequate fragment stabilization or the presence of necrotic teeth and bone. In addition, the teeth fit in an extremely precise arrangement with the upper jaw, and failure to reestablish this relationship is often unacceptable to the patient.

Mandibular fractures are a result of the force sustained. Direct injury to the chin will fracture the symphysis along with the thin subcondylar area as the force is transmitted through the mandible. In any case, because the mandible is ring-shaped, the presence of one fracture should raise suspicion for a contralateral injury.

The goals of treatment are bony union and a normal occlusal relationship. Many simple fractures can be treated with closed techniques and limitation of function. More severe injuries requiring ORIF are approached and repaired through transoral or transcuteaneous incisions. The condylar fracture is the most controversial mandibular injury, largely because the facial nerve inhibits access to it. Because facial nerve injuries can be devastating, there is a bias toward closed treatment of the condyle, even when open treatment might be beneficial.

Mandibular fractures should be treated sooner rather than later, but many factors can lead to delayed treatment. In

general, open mandibular fractures should be treated within 2 to 3 days of injury, whereas closed fractures can be treated 7 to 10 days after injury if necessary.

MAXILLARY FRACTURES

The midface, like the front of a car, is designed to crumple in the presence of blunt force, absorbing energy and protecting the cranium and cervical spine. In 1901, Rene Le Fort performed a series of experiments on cadaver heads, demonstrating that blunt force fractures the midface along certain lines of inherent weakness: the Le Fort I, II, and III level fractures [see Figure 9 and Figure 10]. The Le Fort classification is universal and very helpful for communication and documentation, but Le Fort injuries can occur on multiple levels simultaneously and asymmetrically and in any combination. A fractured palate indicates significant energy transfer.

The lowest of these fractures, the Le Fort I, horizontally separates the palate and tooth-bearing maxilla from the rest of the midface. The Le Fort II, the so-called pyramidal fracture, includes the lower maxilla plus the medial infraorbital rim, orbital floor, and nasal bones [see Figure 9]. Le Fort III fractures, the craniofacial disjunction, pass through the upper portions of the orbits and include the zygomas; they are characterized by complete separation of the entire midface from the cranium [see Figure 10 and Figure 11].

Depending on the level of the Le Fort fracture, various incisions will be required. In general, higher-level fractures are more complicated and require additional access. The principles of treatment are the same, however: reestablish proper occlusion, line up the facial bony buttresses, and apply internal fixation at key structural points.

The midface is relatively vascular and immobile (unlike the mandible), so infection and nonunion are less common.

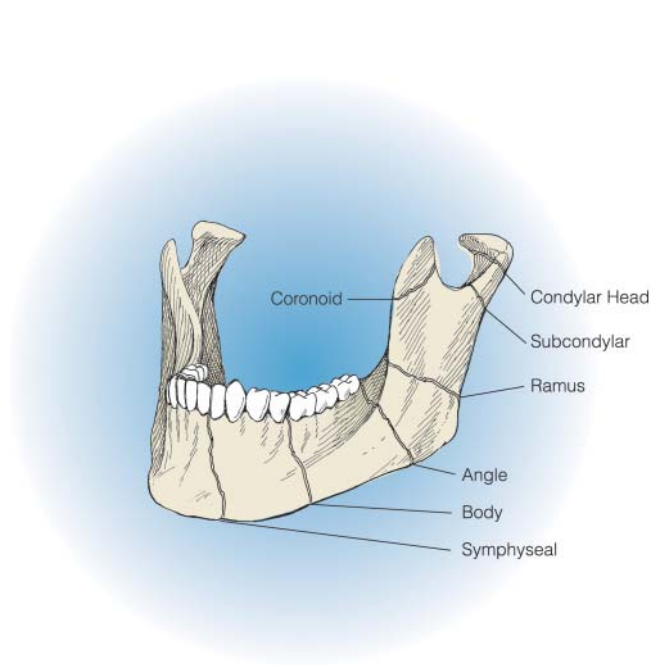


Figure 8 Mandibular fracture.

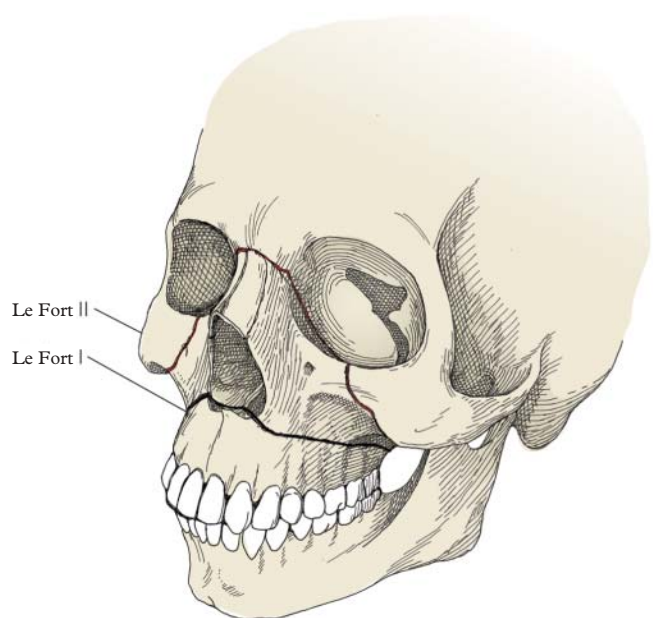


Figure 9 Le Fort I fractures (black line) affect the upper jaw alone. In Le Fort II fractures (red line), the upper jaw and the central portion of the face are separated from the skull.

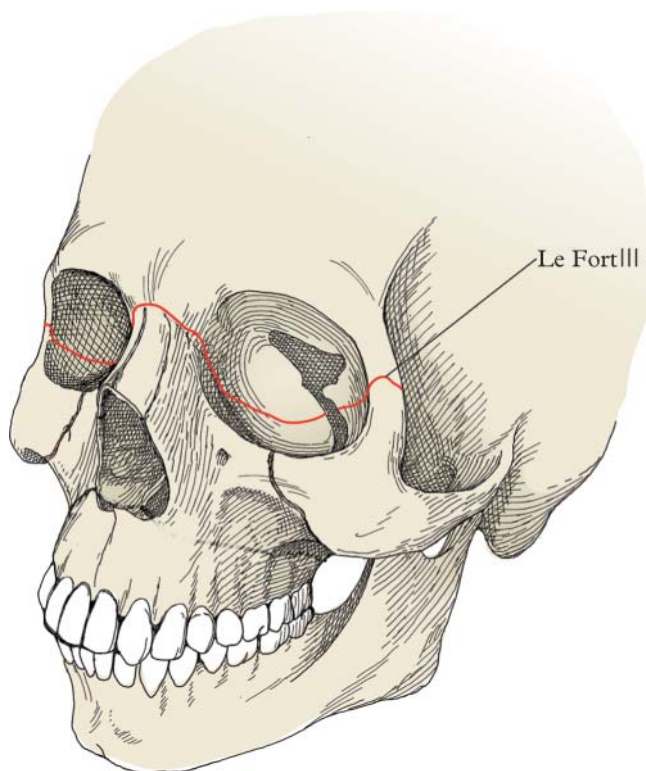


Figure 10 In Le Fort III fractures, all of the facial bones are separated from the skull.

ZYGOMATIC FRACTURES

The zygoma forms the prominence of the cheek (the malar eminence) and a large part of the orbit. After nasal fractures, zygomatic fractures are the most common bony injury from blunt trauma. To prevent noticeable flattening of the face or impingement of mandibular opening, even minimal zygoma displacement can require repair [see Figure 12].

The degree of displacement and the difficulty of repair depend on the amount of energy absorbed. Simple low-energy injuries can often be treated by oral access alone, whereas high-energy injuries are fragmented at the margins, requiring both oral and orbital access with multiple-point fixation. Accurate alignment of the zygomatic fracture can be challenging because of the combination of rotary and translational displacement of the bone fragments.

It is important to remember that any injury severe enough to displace the zygoma and change the shape of the orbit has the potential for ocular injury or globe malposition. An ophthalmology consultation should be considered for every zygomatic fracture, especially when associated with other ocular findings. If the globe is injured, bony surgery may need to be postponed.

ORBITAL FRACTURES

Orbital injuries can occur in isolation or as a component of more extensive injuries. The main concern in orbital trauma should always be injury to the globe and visual loss. The orbit is lined with thin bone that fractures when blunt force meets the globe, as in an assault. The globe is prevented from

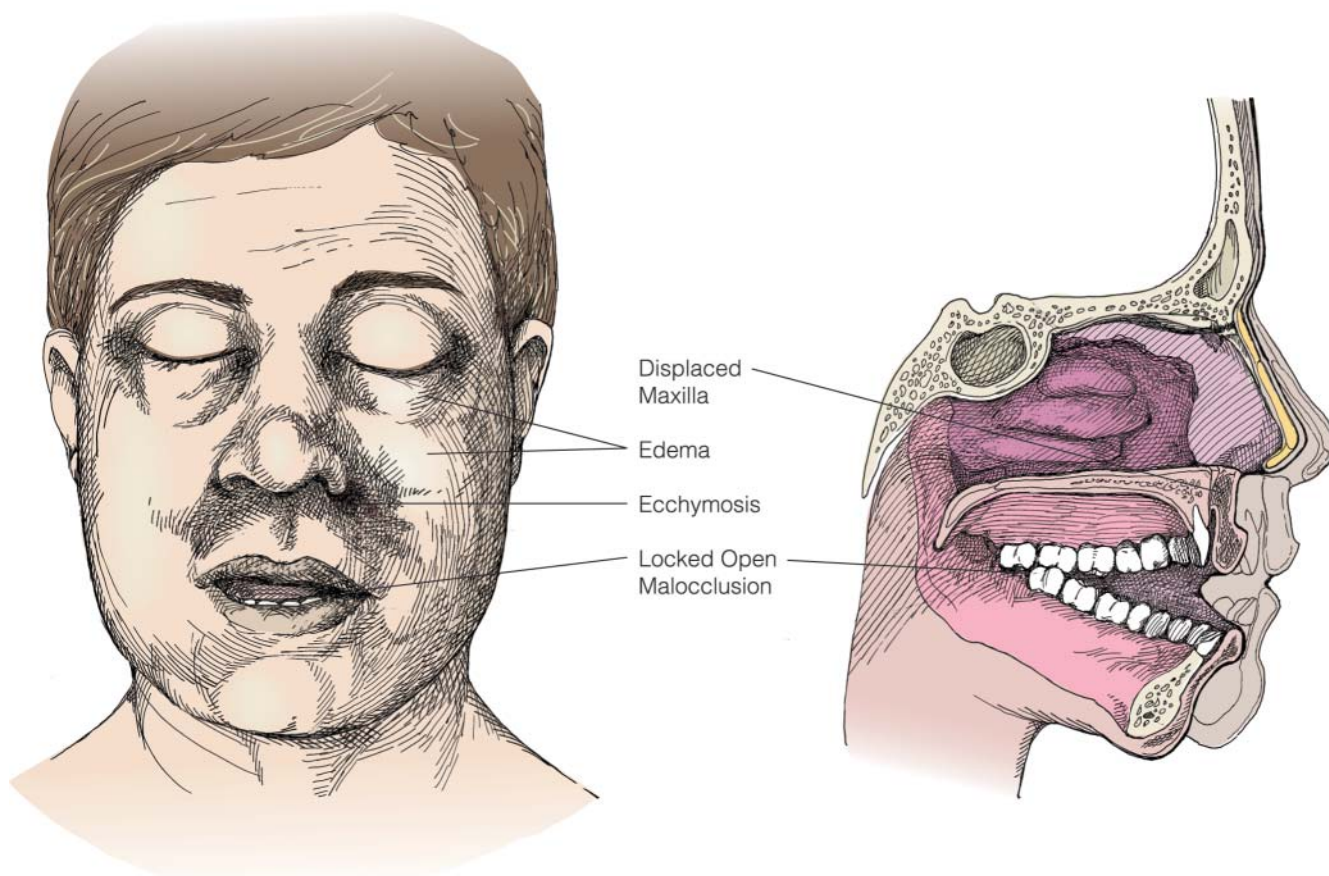


Figure 11 Findings in patients with Le Fort III maxillary fractures immediately after injury, before obliterative edema develops.

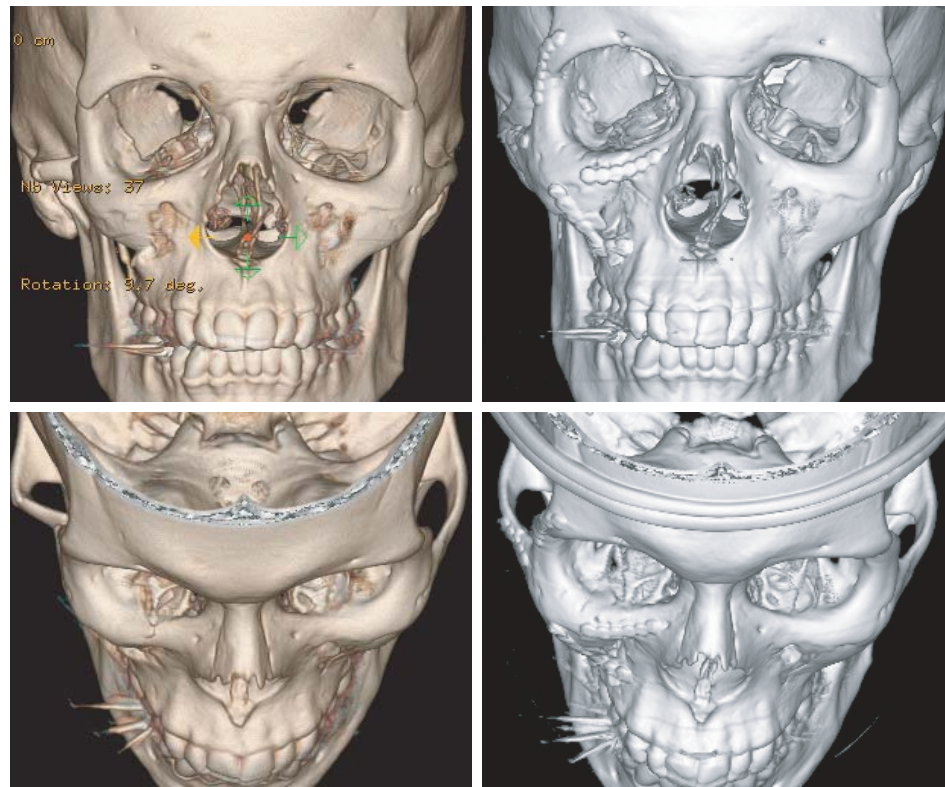


Figure 12 Preoperative (*left*) and postoperative (*right*) orbitozygomatic fracture on the patient's right side. Note the decreased width and projection of the zygoma position preoperation, which is a combination of rotation and translation deformity. Postoperation, anatomic reduction has been achieved, along with titanium plate fixation along the facial buttresses.

rupturing by fracture of this thin bone, instantly increasing the volume of the orbit. This traumatically acquired increase in orbital volume needs repair to prevent permanent posterior-inferior displacement of the eyeball within the distorted orbit (enophthalmos) and associated diplopia.²²

Orbital repair is achieved through a transconjunctival or periorbital transcutaneous approach and the restoration of normal orbital shape and volume with implants or bone grafting. Both zygoma and orbital fractures can be repaired any time within 2 to 3 weeks of injury.

The exception to this timing is pediatric trapdoor fractures.²³ Entrapment of the inferior rectus in children can easily be missed because the flexible bone can spring back into place like a trapdoor and look normal on a CT scan, except for the entrapped muscle under the bone in the maxillary sinus. These children can often present to emergency departments with abdominal pain as a result of the visceral response from the muscle entrapment. If a vision check is not performed at the initial evaluation, the underlying injury can be missed as the abdominal pain is worked up. This trapdoor fracture requires urgent treatment within 24 to 72 hours to minimize the chance of motility problems.

NASAL FRACTURES

Nasal fractures are the most common type of maxillofacial fracture. The vast majority of isolated nasal fractures can be treated with good results by simple closed reduction within 2 to 3 weeks of injury. This is accomplished with a blunt

instrument placed inside the nose, under the nasal bones, combined with external digital forces as required to realign the fractured segments. Internal nasal packing or external splinting is sometimes required. If these simple techniques do not achieve an acceptable result, a proper rhinoplasty may be required after a period of initial healing.

NOE FRACTURES

A significant NOE injury is devastating to the appearance and difficult to repair; in this region, even small discrepancies can significantly alter a patient's appearance. The thin bone of the NOE region provides nasal projection and a point of attachment for the medial canthi of the eyelids. When significantly injured, nasal projection is lost, and the distance between the medial canthi widens (telecanthus). Repair is challenging because of the number of thin, specialized structures and difficult access. Unless bony architecture and normal intercanthal distance are reestablished, the patient will have a permanent deformity that cannot be disguised.^{24,25} If CSF rhinorrhea is present, a neurosurgical consultation should be obtained. Injuries to the dura in the anterior cranial fossa can result in persistent CSF leakage and can be difficult to repair. In certain cases, transnasal endoscopic repair is possible.²⁶ By definition, the ethmoid sinus and walls are damaged in NOE fractures. If there is bilateral injury in this region, the nasofrontal ducts that drain the frontal sinus are also likely disrupted. This disruption of frontal sinus outflow can require obliteration of the frontal sinus. Failure

to diagnose and treat severe disruption and obstruction of the nasofrontal ducts increases the risk of the patient developing delayed complications, such as frontal sinus mucocele.

FRONTAL SINUS FRACTURES

Fractures of the frontal sinus are signs of significant cranial energy transfer. Isolated anterior table fractures with significant displacement will require repair to prevent a visible frontal deformity. Combined anterior-posterior table fractures with significant posterior table displacement disrupt the barrier that normally separates the brain from the aerodigestive tract. Injuries to the frontal sinus can also compromise the sinus outflow tract, as mentioned above.²⁷ Injuries to the frontal sinus area often require a combined CMF-neurosurgical approach. The goal of frontal sinus treatment is to create a “safe sinus,” one that drains into the nose and does not communicate with the brain. If this is not possible, the sinus may be removed entirely, performing a procedure called cranialization, which involves removing the posterior

wall of the sinus and separating its remnants from the cranium. Additionally, the frontal sinus can be “obliterated” by blocking the drainage ducts and filling the sinus with material such as bone or fat. Patients with posterior table injuries require long-term follow-up care because potentially life-threatening complications, such as meningitis or mucocele, may develop long after the original injury.²⁸

Summary

Facial trauma should be considered an indicator of associated critical injuries. The initial evaluation needs to include consideration of airway management, cervical spine injury, visual assessment, control of bleeding, identification of CSF leaks, and neurologic injury. The definitive diagnosis of maxillofacial injuries follows a structured history and physical examination and close evaluation of CT imaging.

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Acknowledgment

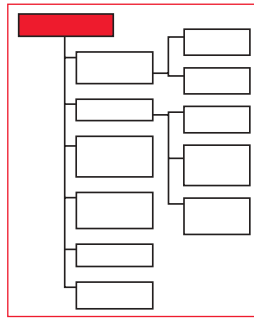
Figures 2 through 5 and 7 through 11 Carol Donner.

4 INJURIES TO THE NECK

David H. Wisner, MD, FACS, and Joseph M. Galante, MD*

Assessment and Management of Neck Injuries

Injuries to the neck can be the result of blunt and penetrating trauma. Both mechanisms can cause devastating injuries, with high associated morbidity and mortality rates. Although penetrating neck trauma can be dramatic, blunt injuries may present in a more subtle or delayed manner, such as blunt cerebrovascular injuries, that create a diagnostic challenge. Having an understanding of anatomy and potential injuries can assist in developing a simple systematic approach to patients with injuries to the neck. Airway management in trauma does not differ based on the mechanism of injury. The principles that dictate airway management are universal; unfortunately, the management of blunt and penetrating injuries is not. After discussing airway management, the management of these patients will be separated into penetrating and blunt mechanisms to accommodate the unique considerations specific to each of these different mechanisms.



Airway

INITIAL MANAGEMENT

The initial priority, as with all trauma patients, should be to ensure an adequate airway.¹ Assessment of the airway can be done easily by talking to the patient. **Attention should be paid to signs of an injury, for example, dysphonia, stridor, or gurgling. In these patients, orotracheal intubation is required.** During intubation, blood and edema in the airway should be noted. In more extreme cases, a surgical airway may be needed by means of either cricothyrotomy (in emergency cases) or tracheotomy (in less extreme cases). Nasotracheal intubation is not advisable in the majority of trauma settings.

Patients with major airway injuries (i.e., penetrating laryngeal injuries) who are awake will position themselves to best protect their airway. They may want to sit upright and lean forward to keep their airway patent and allow for drainage of blood and secretions. In these patients, one may forgo cervical and spinal precautions to maintain an airway. Attempts to reposition them should be avoided until a definitive airway

can safely be accomplished, even if it means going to the operating room.

Cricothyrotomy

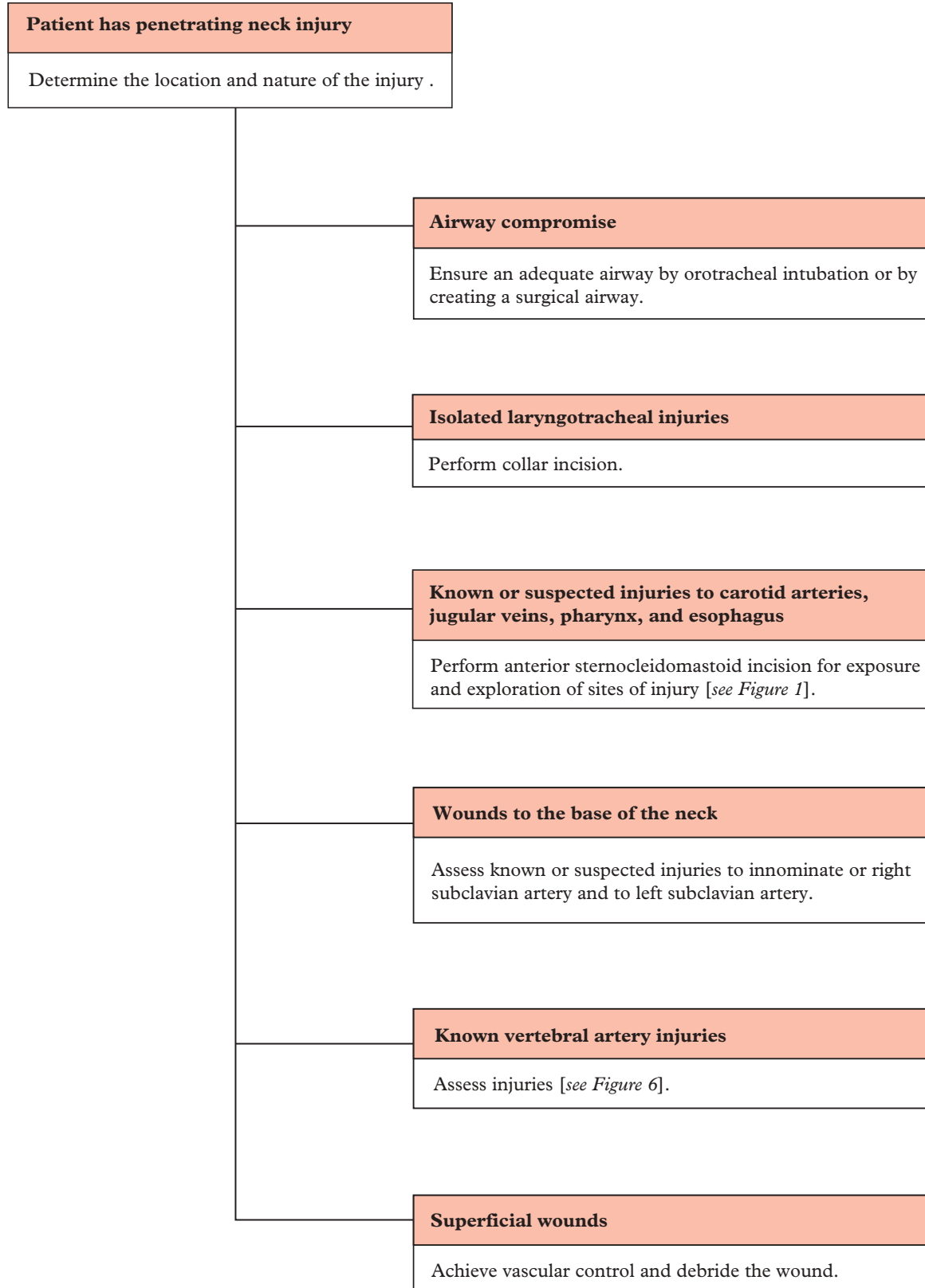
In emergency situations, when oral intubation is not successful or feasible, a cricothyrotomy should be done. The landmarks of the superior (notched) and inferior borders of the thyroid and the cricoid cartilage should be palpated. It is helpful to stand on the patient's right side (for a right-handed surgeon) and to stabilize the cartilaginous framework by holding the thyroid cartilage in place with the left hand. A transverse incision should be made at the level of the cricothyroid membrane and developed rapidly through the subcutaneous tissue. As with any transversely oriented incision of the anterior neck, the anterior jugular veins are at risk for injury. A vertical incision should be used if there is a suspected injury to the trachea but the exact location is unknown. This incision allows access to as much of the anterior surface of the airway as possible and improves visualization by decreasing the chance of injury to the anterior jugular veins.

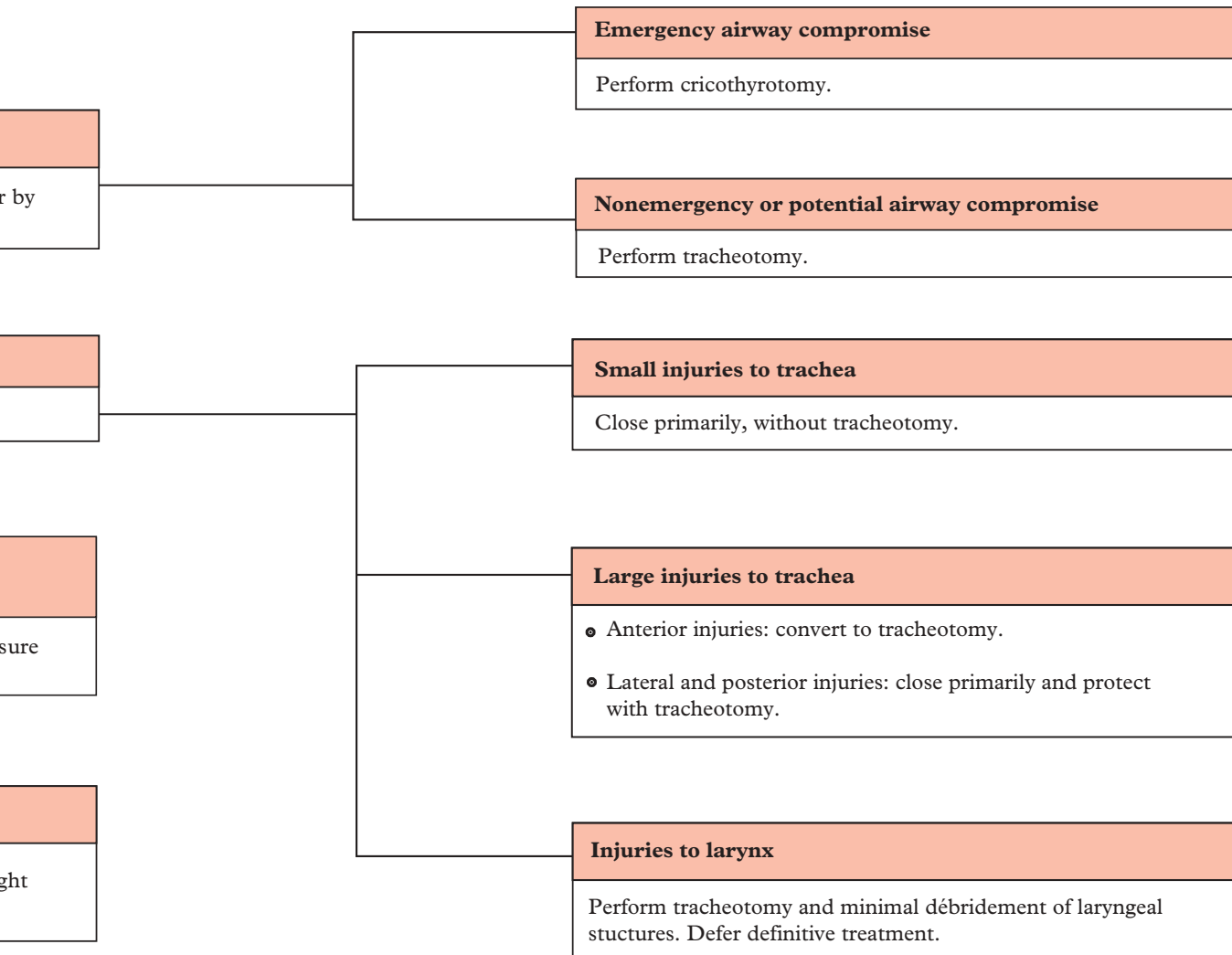
After the skin and the subcutaneous tissue have been divided, an incision should be made through the cricothyroid membrane. This is most rapidly done with a No. 11 knife blade. It is important to avoid pushing the knife blade too far and causing injury to the posterior wall of the airway or to the posteriorly located hypopharynx and esophagus. After the incision has been made, it can be enlarged by using a tracheotomy hook on the thyroid cartilage or by placing the knife handle in the incision and twisting it 90°. At this point, an indwelling definitive airway should be placed and secured. In most adults, a No. 4 or larger endotracheal tube or tracheotomy tube is adequate for initial placement. Any incisional bleeding from veins or other vessels should be controlled at this time; bleeding during the initial portion of the procedure should not distract from an appropriate focus on first establishing the airway. As with all procedures, and in particular with cricothyroidotomy, a face shield is imperative for the providers' protection from blood or secretions coughed out on entering the airway.

Controversy exists over the conversion of emergency cricothyrotomies to tracheotomies. The traditional view, initially promulgated by Chevalier Jackson in 1921, is that cricothyrotomy is more likely than tracheotomy to result in airway stricture or damage to more proximal structures in the larynx.² On the basis of this rationale, cricothyrotomies were converted to tracheotomies on a semielective basis within 24 to 48 hours of admission if the patient's general condition permitted.^{3,4} This practice continued until Brantigan and Grow published an article in 1976 showing a low complication rate

* The authors and editors gratefully acknowledge the contributions of the previous author, Robert C. Jacoby, MD, FACS, to the development and writing of this chapter.

Assessment and Management of Neck Injuries





with elective cricothyroidotomies.⁵ Recent studies in trauma patients show that there is a higher rate of complications in patients who had their cricothyroidotomy converted rather than left as a cricothyroidotomy.⁵ Some have even advocated that elective cricothyroidotomies may be used preferentially in critically ill patients with difficult neck anatomy because of the low complication rates.⁶ In patients with median sternotomies, the higher placed cricothyroidotomy is preferred to avoid secretions at the incision site. Although more data are becoming available showing similar or improved outcomes with cricothyroidotomy, it is still typical to convert a cricothyroidotomy to a tracheostomy in 1 to 2 days in a stable patient.

Tracheotomy

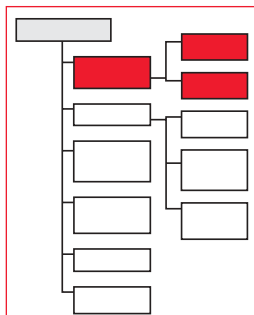
In some instances, airway compromise may not be extreme but a surgical airway may still be necessary for safety or subsequent management (i.e., laryngeal injury). In such circumstances, a tracheotomy rather than a cricothyrotomy should be done because cricothyrotomy may make definitive treatment more difficult.

The initial approach for urgent tracheotomy is similar to that for tracheotomy, the difference being that a so-called collar incision is made at a point two fingerbreadths inferior to the level of the cricothyroid membrane rather than above the sternal notch. The incision should be wide enough to provide rapid exposure and should extend as far as the anterior border of the sternocleidomastoid bilaterally. Anteriorly located injuries at the level of the cricoid or the trachea may already have created a hole in the airway. In such cases, if the need for a surgical airway is immediate, the wound should be enlarged and used as a route of access to the airway.

Penetrating Neck Trauma

INITIAL MANAGEMENT

Once an airway has been established, patients with penetrating trauma need to be evaluated in accordance with Advanced Trauma Life Support (ATLS) guidelines.⁷ Management of penetrating neck trauma starts by determining the depth of the wound. If the wound did not violate the platysma, injury to major underlying structures can be ruled out. If the wound clearly violated the platysma or its depth cannot be determined, further investigation is warranted. Patients with any obvious hard signs of vascular injury⁸ (e.g., pulsatile bleeding from the wound, an expanding hematoma, a bruit, or a neurologic deficit), shock, or air bubbling from the wound require immediate operative exploration. If the patient is stable and has no obvious signs of underlying vascular injury, a nonoperative workup should be obtained regardless of the location of the skin wound [see Figure 1].



Historically, management of penetrating neck injuries included categorizing them on the basis of their location in the neck. In this schema, the neck was divided into three distinct zones [see Figure 2], and management was determined by the zone in which the patient happened to have wounds in the skin. Zone I was from the clavicles to the inferior aspect of the cricothyroid cartilage and included the trachea, esophagus, aortic arch, great vessels (subclavian and carotid arteries as well as jugular veins), and cervical spine. Zone II, the largest of the three zones, extended from the inferior aspect of the cricothyroid cartilage to the angle of the mandible and included the aerodigestive tract, great vessels of the neck, and cervical spine. Zone III was from the angle of the mandible to the skull base and included the aerodigestive tract (the oral cavity, pharynx, and larynx), great vessels, cervical spine, and cranial vault.

The idea was that hemodynamically stable patients with zone II injuries presumably had underlying injuries to either the vasculature or the aerodigestive tract that were easily accessible via a sternocleidomastoid incision; such patients would therefore undergo mandatory neck exploration if the wound had violated the platysma. Zone I and III injuries, because of potential difficulties in obtaining proximal or distal control of the vessels through a standard incision,⁹ were worked up radiographically, and if no injury was identified, the patients were observed.

This concept of mandatory exploration of patients with zone II injuries and nonoperative workup of zones I and III has a number of problems. Division of the neck into three distinct areas results in extremely small zones I and III, and even zone II, in the middle of the neck, is not very long in most patients. As a result, determining that a given wound is clearly in only one of the zones is often very difficult. Description of a wound as being on the border of zones I and II or on the border of zones II and III is a common and confusing occurrence. Moreover, the location of the skin wound is not a reliable guide to the location of injuries to underlying structures. In penetrating trauma, the path of the missile or blade is clearly as important as the location of the skin wound. An object that enters the skin in zone II can easily injure structures in zone I or III, depending on the direction in which it entered the skin. A selective approach regardless of zone reduces the rate of negative neck explorations. Therefore, the zones of the neck are useful as descriptors but not as a guide for management.

Patients with wounds at the base of the neck should be identified early because of the high likelihood of an intrathoracic injury. A median sternotomy should be done for unstable patients with injuries at the base of the right neck or patients in whom the superior mediastinum is the most likely site of injury. Arterial injuries in such circumstances are usually to either the innominate artery or the right subclavian artery. Exposure of injuries to the proximal left subclavian artery is difficult via sternotomy because of the artery's posterior location; in patients with such injuries, a left thoracotomy is needed.

PENETRATING TRAUMA: STABLE PATIENT

Patients who do not require immediate operative intervention need a logical diagnostic approach to prevent missing an

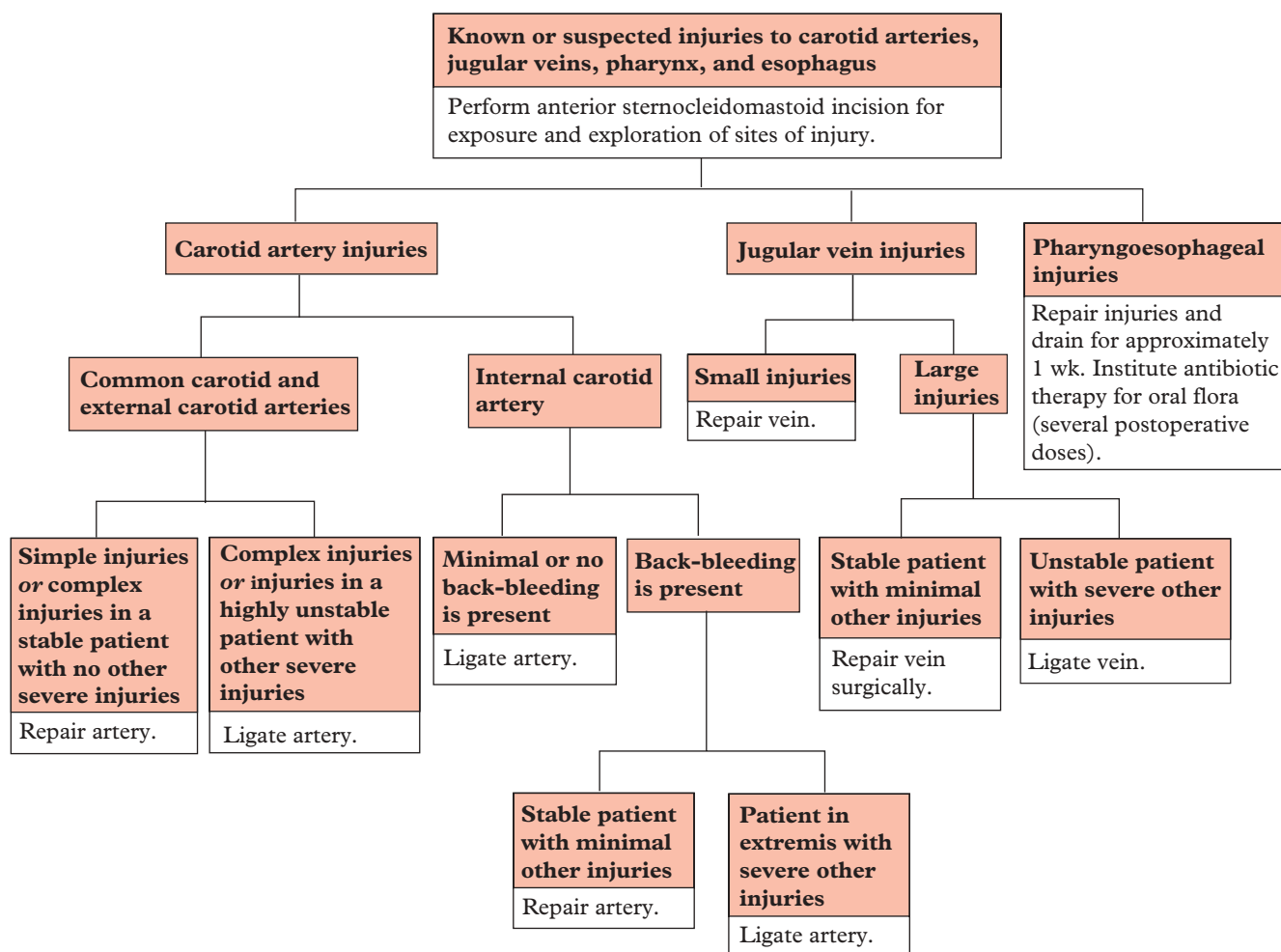


Figure 1 Algorithm outlining operative management of known or suspected injuries to the carotid arteries, jugular veins, pharynx, and esophagus.

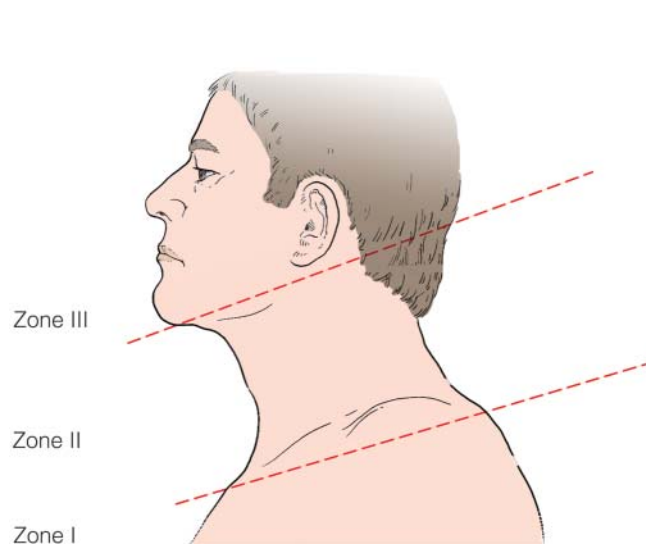
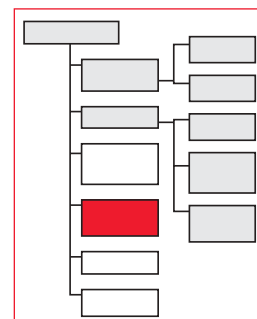


Figure 2 The traditional division of the neck into three separate zones. This division has been used as a basis for decision making with respect to penetrating cervical injuries.

injury. Evaluation modalities are needed for each of the structures of the neck, including vascular, aerodigestive, and bony structures. Computed tomography (CT) is used to evaluate the bony structures. With reconstruction technology, multidetector CT scanners can provide three-dimensional images of the cervical spine and facial bones.¹⁰

CT scanners are not as effective as screening tools for aerodigestive injuries. These structures, the larynx, pharynx, hypopharynx, cervical esophagus, and trachea, should be directly visualized. This evaluation may take many forms, including indirect laryngoscopy, flexible fiberoptic nasopharyngolaryngoscopy, flexible bronchoscopy, and rigid or flexible esophagoscopy.¹¹ Flexible endoscopy, although the preferred method for airway assessment,¹² may miss small injuries in redundant tissue when evaluating the hypopharynx and cervical esophagus.¹³ If the patient has a cleared cervical spine and there is an extremely high index of suspicion for



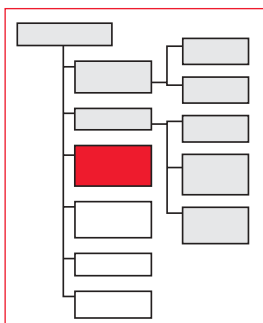
missed injury, rigid esophagoscopy should be done. If the cervical spine is not cleared and the patient can swallow contrast, esophagoscopy may be performed but does not provide visualization of the proximal oropharynx and hypopharynx. It is important to emphasize that injuries to the pharynx are much more common than those to the cervical esophagus and that such injuries are best diagnosed by laryngoscopy and pharyngoscopy rather than by esophagoscopy or esophageal contrast studies.

SCORE For vascular injuries, conventional angiography was for many years the gold standard for ruling out vascular injury, but it is invasive, can be time consuming, and is resource intensive. With the advent of multidetector CT scanners, CT angiography has sensitivities and specificities that approach those of conventional angiography.¹⁴ CT can be quite helpful in determining the course that a knife or bullet took within the neck. If CT defines a knife or bullet tract that is clearly remote from major vascular or aerodigestive structures, no further workup is needed. If CT clearly shows an injury that should be repaired, exploration of the neck is indicated. If CT can neither establish nor rule out the presence of a vascular or aerodigestive injury, further imaging should be performed.

SCORE Retained projectiles cause scatter or air in the tissue planes, which may disrupt the quality of the images, and alternative diagnostic modalities need to be used. The air may be from the projectile or from an aerodigestive tract injury, and further imaging or endoscopic studies should be done.^{15,16}

Carotid Artery Exploration and Repair

SCORE The operative approach requires access to all structures in the neck, especially if the exact location of injury is not known. This is best accomplished with an incision along the anterior border of the sternocleidomastoid muscle [see Figure 3]. The sternocleidomastoid incision has three advantages. First, it provides exposure of the carotid sheath, the pharynx, and the cervical esophagus. Second, it can be lengthened to provide more extensive proximal or distal exposure. Finally, if bilateral exploration is necessary, separate sternocleidomastoid incisions can be done.



The patient is placed in the supine position, with the head turned away from the side of exploration and the neck extended. In this regard, it is helpful to clear the cervical spine before operation if possible. If both sides of the neck are to be explored, the head is left in the midposition, facing up. The entire neck and the appropriate side of the face and head are prepared. The anterior chest is also included in the preparation in case a median sternotomy is necessary for proximal control. The patient is draped so that the lateral neck is left as the primary field while the chest is kept easily accessible. The lateral chin and the tip of the earlobe are also kept in the field to provide landmarks. If the possibility exists that the injury is to the distal subclavian artery or the axillary artery, the patient's arm should be draped in a way that allows it to be manipulated.

The skin incision is carried through the dermis and the platysma. After the platysma is divided in the direction of the incision, the investing fascia overlying the anterior border of

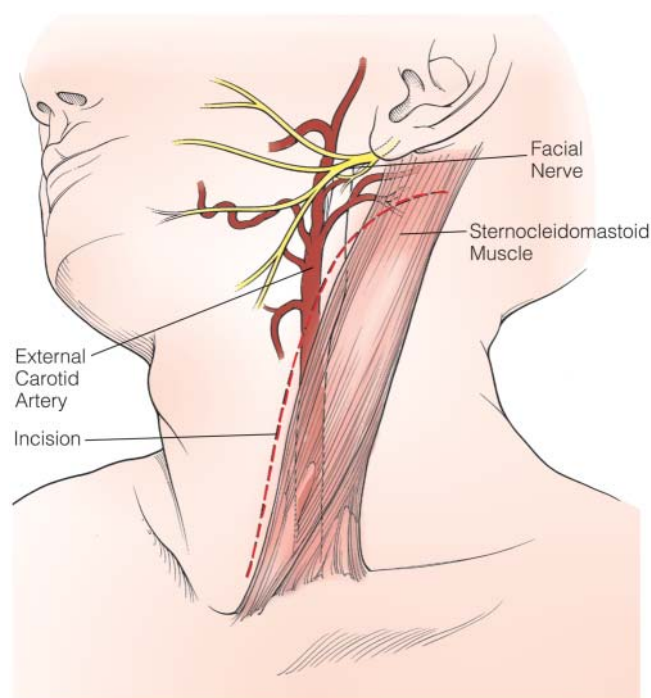


Figure 3 In general, exposure of structures in the anterior areas of the neck is best done through an incision oriented along the anterior border of the sternocleidomastoid muscle.

the sternocleidomastoid muscle is incised, and the muscle is retracted laterally and posteriorly to expose the carotid sheath. It is often necessary to divide a venous branch that connects the external jugular vein posterolaterally to the anterior jugular vein anteromedially. This vein lies in a plane immediately deep to the platysma.

Classic principles of vascular surgery apply; proximal and distal control should be obtained before exploration of a carotid artery injury. Obtaining proximal control before entering a perivascular hematoma is more important than having distal control, and if necessary, distal bleeding can be controlled with digital pressure while the dissection of the injured vessel is completed. Although it is often difficult to obtain control before addressing the area of injury, proximal and distal control of the vessel should be obtained at some point before any attempts at definitive repair. For injuries near the carotid bifurcation, it is necessary to control the common, internal, and external carotid arteries, as well as the proximal branches of the external carotid artery. This should be done with vessel loops; ligation of vessels should be avoided.

The initial exploration should attempt to rule out arterial or venous injury unless an overt airway injury is present and requires immediate attention. The location of the carotid artery can be confirmed by the presence of a pulse. **SCORE** The carotid sheath contains the jugular vein, carotid artery, and vagus nerve. During dissection of the carotid sheath and retraction of the jugular vein, care must be taken to keep from injuring the associated vagus nerve. Division of the facial vein, which is superficial to the carotid bifurcation, facilitates jugular vein retraction. The severed ends of the facial vein should be suture-ligated to ensure that the ties will not come

off with increased intravenous pressure in the postoperative period—for example, secondary to a cough or a Valsalva maneuver [see Figure 4].

Exposure of the proximal common carotid artery at the base of the neck is easier after division of the omohyoid muscle at the point where its superior and inferior bellies are joined. Division of the omohyoid muscle results in minimal functional deficit postoperatively. For proximal control of the common carotid artery, it may be necessary to enter the chest via median sternotomy. To minimize blood loss, the decision to do a sternotomy should be made without undue delay. Control of the proximal right common carotid artery via this route is relatively easy and is accomplished by dissecting distally along the innominate artery. Proximal control of the left common carotid artery via median sternotomy is more difficult because its origin from the aortic arch is more posterior than the origin of the innominate artery. Left thoracotomy should be done when the proximal left internal carotid artery is injured, especially if the patient is in extremis. If a proximal left common carotid injury (or proximal left subclavian artery injury) is known or suspected preoperatively, it is helpful to bump up the patient's left hip and shoulder to position the left chest 20° to 30° anteriorly. The head is turned to the right, and the left arm is prepared as far as the elbow and draped to allow it free movement. Moving the arm is helpful when proximal exposure and control are obtained through the chest and distal exposure and control are obtained through a supraclavicular incision. Moving also allows improved exposure of the axillary artery if necessary.

If a median sternotomy has been done for exposure of an innominate artery or right subclavian artery injury, it may prove necessary to extend the incision into the right neck to obtain adequate distal control and exposure. Either a right supraclavicular or an anterior sternocleidomastoid extension can be used. Although both are easily accomplished, the anterior sternocleidomastoid extension is the more versatile of the two.

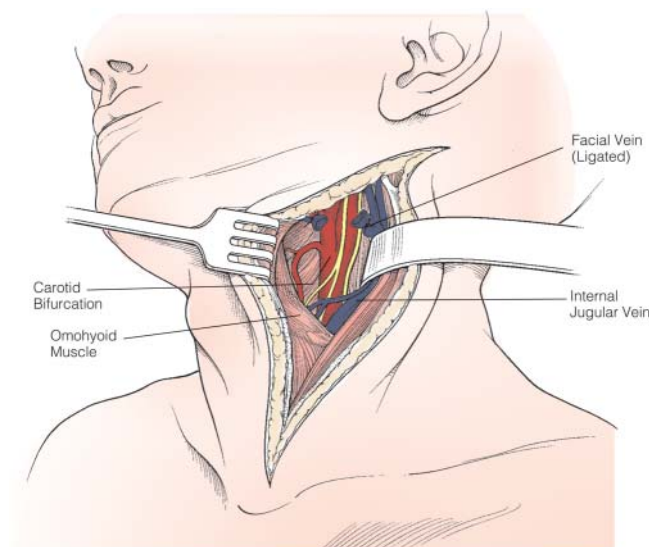


Figure 4 After a plane along the anterior border of the sternocleidomastoid muscle has been developed, dissection is carried down to the level of the carotid sheath. Suture ligation of the facial vein facilitates this dissection. Lateral retraction of the internal jugular vein improves exposure of the carotid bifurcation.

For wounds to the distal internal carotid artery, exposure can be difficult. A 3 to 5 French Fogarty balloon catheter can be placed through the area of injury or through a proximal arteriotomy to help with distal control. The catheter should be advanced distally and the balloon inflated to provide a dry field for arterial repair. Repair can be done around the catheter; the balloon is deflated near the conclusion of the repair, and the catheter is removed before the final several sutures are tied.

If exposure of the distal internal carotid artery is needed, a number of important structures should be identified and protected [see Figure 5]. The hypoglossal nerve is usually encountered within several centimeters of the carotid bifurcation and should be dissected free of the internal carotid and retracted upward. This is facilitated by division of the occipital artery, which crosses superficial to the hypoglossal nerve on its course from the external carotid artery toward the occiput. It is also helpful to divide the ansa cervicalis branches that run inferiorly from the hypoglossal nerve to supply the muscles of the neck. Injury to the hypoglossal nerve results in impaired motor function of the tongue and can lead to dysarthria and dysphasia. Injury to or sectioning of the ansa cervicalis causes little or no morbidity.

Further distal exposure of the internal carotid artery may require unilateral mandibular subluxation or division of the ascending ramus of the mandible.⁴ Such maneuvers are somewhat easier when the patient is nasotracheally intubated. They increase the size of the small area immediately behind the condyle and allow easier division of the stylohyoid ligament and the styloglossus and stylopharyngeus muscles. These three structures can be divided together adjacent to their common origin at the styloid process. If this is done, care should be taken to preserve the facial nerve, which lies superficial to these muscles and must be dissected free of the muscles before they are divided. The underlying glossopharyngeal nerve, which lies deep to these muscles and superficial to the internal carotid artery, should also be protected by dissecting it free of the muscles before their division. Injury to the facial nerve results in loss of function of the muscles of facial expression. If the glossopharyngeal nerve is injured, loss of motor and sensory supply to parts of the tongue and pharynx increases the risk of aspiration.

Once the muscles originating from the styloid process have been divided, the styloid process itself can be resected to gain a further short distance of distal exposure. In very rare instances, it may prove useful to remove portions of the mastoid bone to provide even more distal exposure of the internal carotid artery as it enters the carotid canal. For more distal lesions, it is necessary to place a posterolateral scalp incision, reflect a medially based scalp flap, and divide the ipsilateral external auditory canal. This approach results in better exposure of the mastoid process and allows exposure of the intrapetrous portion of the internal carotid after removal of the overlying bone of the mastoid with a high-speed bone drill.

During dissection of the external carotid artery, the branches should be identified. They can be ligated if necessary but should be preserved if possible (this usually depends on whether they can be temporarily occluded with vessel loops, a looped suture, or clips). During dissection around the common and internal carotid arteries, care should be taken to avoid cutting or clamping the posterolaterally located vagus nerve; the recurrent laryngeal nerve runs with the vagus nerve at this level, and damage to the laryngeal nerve can lead to paralysis of the ipsilateral vocal cord.

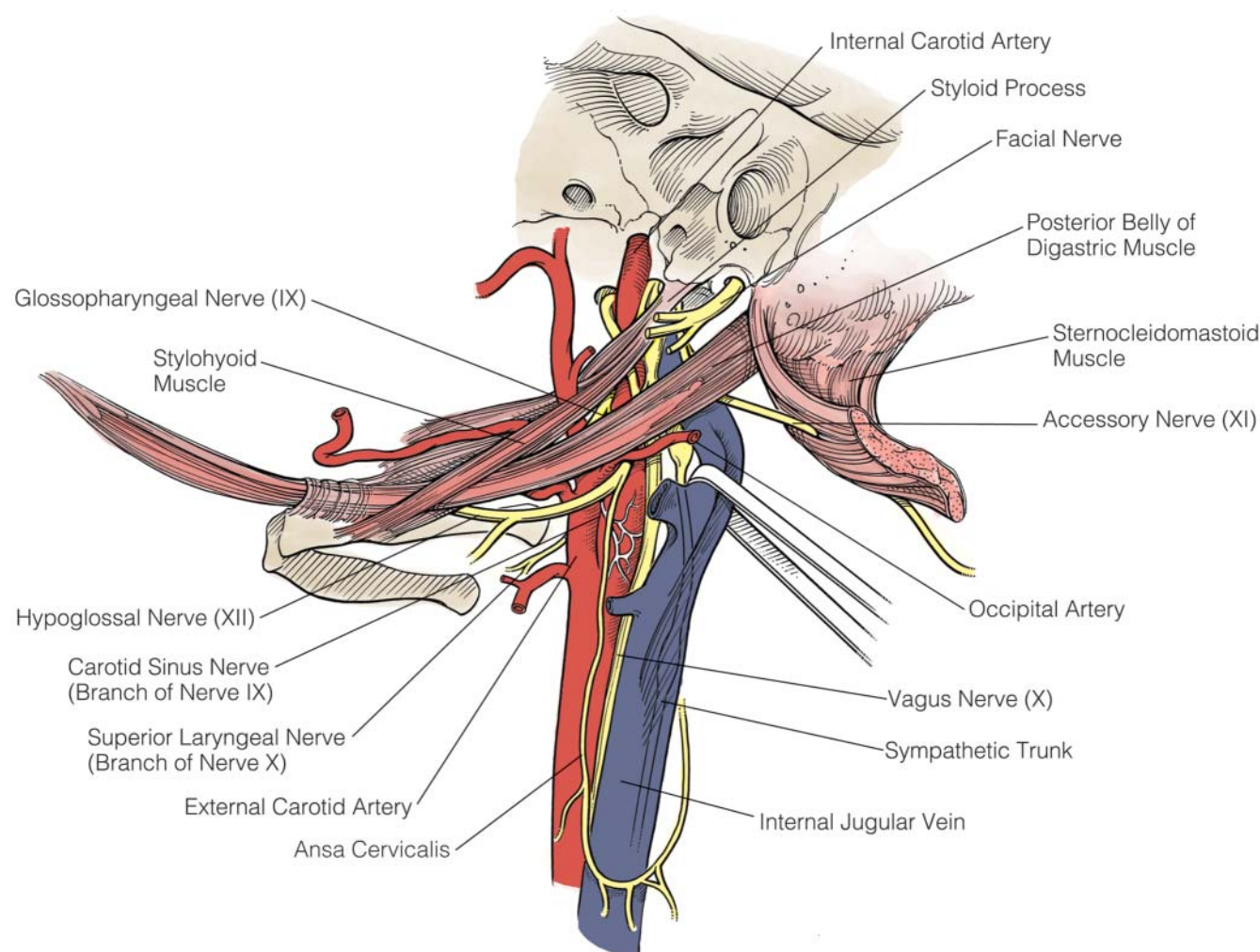


Figure 5 During distal dissection of the internal and external carotid arteries, a number of important structures are encountered, including the hypoglossal nerve and the occipital artery.

If associated injuries allow, a 5,000- to 10,000-unit bolus of heparin should be given before any of the arteries in the neck are occluded. Because they have no branches, the common and internal carotid arteries can be safely mobilized for some distance from the injury to ensure a tension-free repair.

Management of common or external carotid artery injuries is governed by the extent of injury and the overall status of the patient. Simple injuries to the external carotid artery should be repaired, whereas complex injuries should be ligated given that the external carotid artery normally has such good collateral flow. Even in cases with complex injuries to the common carotid artery, if the patient has no neurologic deficits, ligation can be done. The internal carotid will be reconstituted with flow from the external carotids.

Injuries to the internal carotid artery are more problematic. If the injury is simple and there is no suggestion that flow in the vessel has been interrupted, repair should always be undertaken. An example of such an injury is a simple stab wound of part of the circumference of the artery with an associated pseudoaneurysm and good distal flow. In this circumstance, lateral repair can be done quickly and easily with a short cross-clamp time.

After proximal and distal control of the vessel is obtained, a check should be made for back-bleeding. If the back-bleeding from the distal circulation is brisk, as it usually is, repair can be done safely.

If an injury to the common carotid artery or the internal carotid artery has interrupted flow in the vessel, repair creates a theoretical disadvantage. Interruption of flow may lead to focal brain ischemia and partial disruption of the blood-brain barrier. Sudden restoration of blood flow may cause hemorrhage in the area of the ischemia and worsen the extent of brain injury; an anemic, or white, infarct of the brain may be converted to a hemorrhagic, or red, infarct. Whether this pathophysiology is important after traumatic injury is unclear and controversial.

Deciding whether to repair or ligate when flow has been interrupted is often difficult. One approach is to base the decision on the patient's preoperative neurologic status. If there is no neurologic deficit, it is presumed that there are no areas of brain ischemia and that repair is safe. Conversely, a focal neurologic deficit is presumed to be related to ischemia, and in such cases, the risk of worsening the patient's neurologic status with restoration of blood flow is increased. Even though this approach

is rational, it is not applicable in cases in which a detailed neurologic examination before surgery is not possible. Furthermore, this approach may be applicable only to patients in coma or with severe neurologic deficits. There are indications that milder neurologic deficits respond favorably to revascularization.

Yet another approach is to gauge the appropriateness of repair according to the nature of the injury itself. In this approach, large, complicated injuries requiring involved and lengthy procedures for repair are ligated, whereas simple injuries requiring only simple and quick repairs are repaired. Similarly, repair is not indicated in patients with severe or multiple associated injuries. There is also a difference between the management of injuries of the common carotid artery and the management of injuries of the internal carotid artery. Common carotid injuries are more accessible and easier to repair, and repair is generally associated with a good outcome. Continued antegrade flow in the internal carotid artery is more likely after injury to the common carotid artery than after injury to the internal carotid artery because of the possibility of collateral flow via the external carotid artery.

A reasonable way to deal with repair dilemmas is to make the decision on the basis of distal back-bleeding. Interruption of blood flow to the brain is tolerated only for a short time, and restoration of flow is unlikely to be accomplished quickly enough to improve outcome. It is therefore logical to base the decision about revascularization on the state of back-bleeding from the internal carotid artery. If back-bleeding is brisk, the patient is presumed to have good collateral flow, and the chances that there is an area of ischemia are low. Repair rather than ligation is safe in such circumstances. If internal carotid artery back-bleeding is minimal or absent, an ischemic infarct is more likely and restitution of arterial inflow is more dangerous. A corollary to this reasoning is that if back-bleeding is poor, a clot distal to the area of injury may be present, and return of flow with repair may dislodge the clot distally.

If a carotid artery injury involves minimal loss of vascular wall, primary repair is straightforward and can be done with either a continuous or an interrupted technique; interrupted sutures will not purse-string the vessel. In younger patients who are still growing, interrupted sutures should be used to prevent later stenosis. As in elective vascular surgery, nonabsorbable sutures should be used; the carotid arteries generally require a 5-0, 6-0, or 7-0 monofilament suture, depending on the location of the injury and the type of suture material employed.

Defects longer than 1 to 2 cm should not be repaired primarily, because this will place excessive tension on the repair. For large defects limited to one surface of the vessel, a patch repair should be done. Either a venous patch or a synthetic patch can be used; when available, a venous patch is preferred for better long-term patency and to avoid placing a foreign body in a potentially contaminated wound. Saphenous vein from the groin is preferable for patches because of its durability; a saphenous vein from the ankle is easiest to harvest when time is of the essence. Although the jugular vein is in the operative field and can be easily harvested, it is better not to interfere with venous outflow in a neck in which the arterial inflow is to undergo repair; in addition, the jugular vein is very thin and difficult to handle.

For repairs near the carotid bifurcation, an alternative to venous patches and synthetic patches is the use of the proximal external carotid artery. This approach is especially appropriate

when the origin of the external carotid artery is itself involved in the area of injury. If the injury is to the proximal internal carotid artery and the origin of the external carotid artery is free of injury, it is better to leave the external carotid artery patent and to use a venous patch or a synthetic patch instead; if the repair fails, the external carotid artery provides collateral distribution to the internal carotid artery via the ophthalmic artery. An alternative approach is to transpose the proximal external carotid artery to replace the proximal internal carotid.

Repair of circumferential loss of the common or internal carotid arteries is difficult. In this circumstance, if the defect is too long for primary anastomosis and the patient's general and neurologic condition permits, an interposition graft is indicated. As with patch grafts, although either venous or synthetic material can be used, saphenous vein from the groin is generally the donor material of first choice because of its strength. The saphenous vein from the groin is also well suited for reconstruction of the common carotid artery.

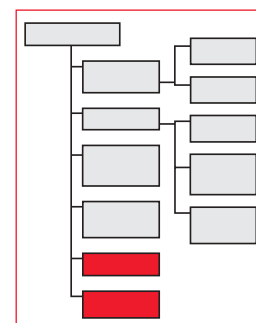
Completion angiography should be done after interposition graft placements and complex repairs of the common or internal carotid arteries. In general, patients with carotid artery injuries should be admitted postoperatively to an intensive care unit (ICU). ICU observation need not be prolonged but should be continued for at least 12 to 24 hours postoperatively. In the early postoperative period, the patient should be observed for bleeding or for the development of a neck hematoma; large postoperative hematomas may compromise the airway. If a tense hematoma develops postoperatively, reexploration is mandatory. Acute changes in the neurologic examination are a potential sign of thrombosis or embolism from the site of injury and should prompt further investigation or reexploration.

Labile blood pressure—particularly in patients with extensive dissection around the carotid bifurcation—is another potential postoperative problem. It is related to manipulation of the carotid body, and control may require pharmacologic intervention. Labile blood pressure is usually self-limiting and disappears over the first 1 to 3 days after operation, but this is another reason why patients with carotid artery repairs should be monitored initially in the ICU.

Antibiotics should be administered preoperatively to cover common skin flora and should generally not be continued postoperatively unless there has been violation of the aerodigestive tract.

Vertebral Artery Exploration and Repair

In the rare case of a patient who presents with active, severe bleeding and in whom the most likely source of bleeding is the distal vertebral artery, surgical exposure of the vertebral artery is necessary. Initial exposure should be obtained via an anterior sternocleidomastoid incision. This approach can be used for exposure of both the proximal and the distal vertebral artery. The incision is developed down to the level



of the carotid sheath. The lateral margin of the internal jugular vein is developed sharply, and the internal jugular vein and the other contents of the sheath are retracted medially. After retraction of the carotid sheath, the plane just superficial to the

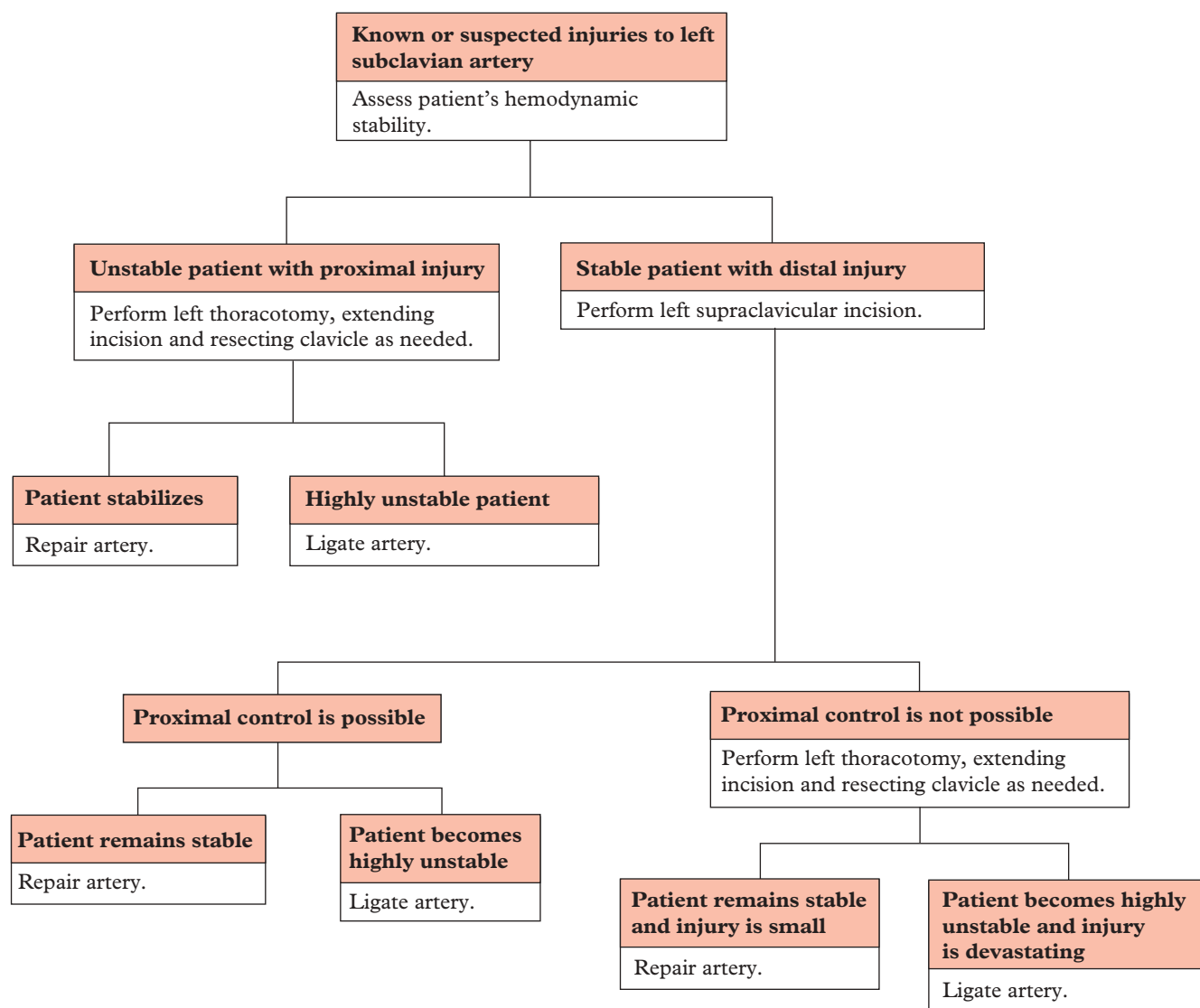


Figure 6 Algorithm outlining management of known injuries to the vertebral artery, which are most often discovered by angiography.

prevertebral muscles is encountered. The ganglia of the cervical sympathetic chain are located here and should be protected, although this is not always possible in emergency circumstances. The anterior longitudinal ligament, located deep in the medial aspect of the wound, is incised longitudinally. The ligament, the underlying periosteum, and the overlying longus colli and longissimus capitis are mobilized anterolaterally with a periosteal elevator [see Figure 7]. The elevation is carried laterally along the lateral margin of the bodies of the cervical vertebrae and along the anterior aspect of the transverse processes of the cervical vertebrae. To avoid injury to the laterally and posteriorly placed cervical nerve roots, the dissection should not be extended laterally beyond the tips of the transverse processes.

After the anterior aspects of the transverse processes of the cervical vertebrae have been exposed, they can be removed with a small rongeur. This should be done distal to the area of injury only; proximal ligation of the vertebral artery can be done in its more easily exposed proximal portion. Although the vertebral artery is also accessible in the spaces between the transverse

processes, there are a number of venous branches in these regions, and it is therefore safer to approach the artery within the confines of the bony foramina.

The third and most distal portion of the vertebral artery is most easily approached between the atlas and the axis. The segment of the artery between the transverse processes of these two vertebrae is longer and more exposed than the segments between the other cervical vertebrae and is therefore, in theory, somewhat easier to expose.

Exposure of the proximal vertebral artery at the base of the neck can also be achieved via an incision along the anterior border of the sternocleidomastoid muscle. Initial exposure is identical to that used for exposure of the carotid arteries. At the level of the carotid sheath, however, dissection is carried lateral to the internal jugular vein, which is retracted medially to expose the supraclavicular fat pad. The proximal vertebral artery can then be controlled after dissection deep to the fat pad, as described for the supraclavicular approach to isolated proximal vertebral artery injuries [see Figure 8].

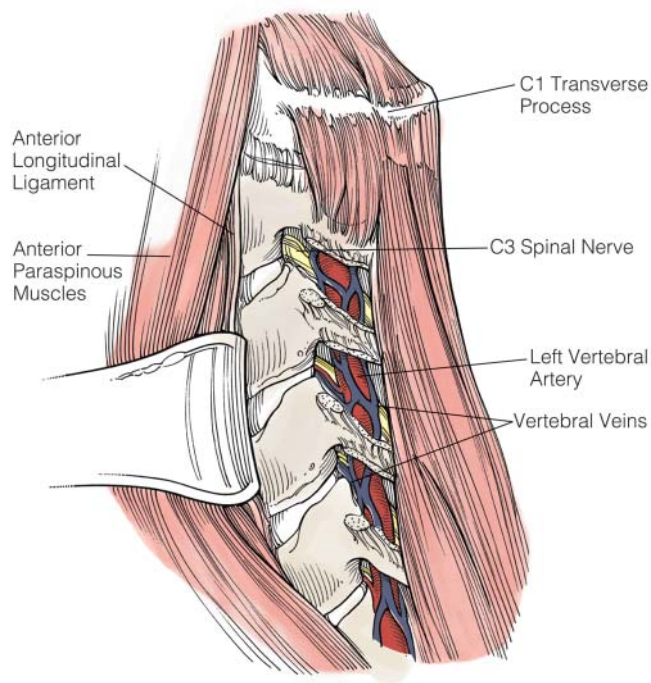


Figure 7 Throughout most of their course, the vertebral artery and the vertebral veins are surrounded by the transverse processes of the cervical vertebrae. Exposure of this portion of the vertebral artery is best done with anterior and lateral mobilization of the longus colli and the longissimus capitis.

As opposed to injuries of the carotid arteries, in which either repair or ligation is an option, injuries to the vertebral arteries should always be treated with interruption of flow by surgical or other means. Proximal ligation should usually be done at the

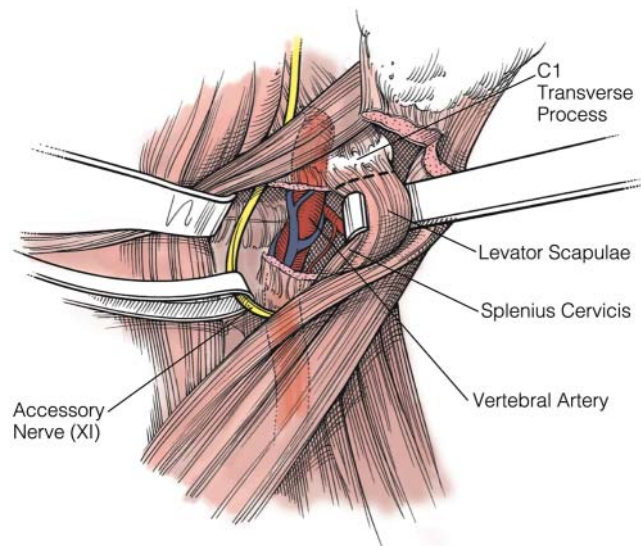


Figure 8 Exposure of the distal vertebral artery is done via an incision along the anterior border of the sternocleidomastoid muscle. The sternocleidomastoid muscle is then divided near its origin at the mastoid process. The spinal accessory nerve is mobilized anteriorly. The vertebral artery is accessible after division of the levator scapulae and the splenius cervicis.

origin of the vertebral artery because the approach to the artery at this point is easier than the approaches to the more distal segments. The artery should be suture-ligated as close to its origin as possible so as not to create a thrombogenic blind pouch off the subclavian artery. Distal ligation can be accomplished by first exposing the artery and then ligating with ligatures, suture ligatures, or surgical clips. The use of clips minimizes dissection around the artery, which, in turn, decreases the likelihood of further injury to surrounding veins.

In emergency circumstances, a useful technique is to approach the proximal artery surgically at the base of the neck and pass a thrombectomy catheter distally to the site of injury [see Figure 9]. First, the proximal vertebral artery is exposed and ligated at its origin. Next, the thrombectomy catheter is passed distally via an arteriotomy. The catheter balloon is then inflated, and the wound is checked to determine whether bleeding has been controlled. If bleeding has been controlled, the distal end of the catheter is left in place, and the proximal end is brought out through the wound. The catheter is left in situ for approximately 48 hours, at which time the balloon is deflated and the wound is again checked for bleeding. If there is no bleeding for 4 to 6 hours, the catheter can be withdrawn. Use of a thrombectomy catheter can also serve as a bridge to angiographic embolization. If the thrombectomy catheter technique is unsuccessful, a direct surgical approach to the second or third portion of the artery is necessary. A potential disadvantage of a surgical approach, however, is that proximal ligation of the vertebral artery precludes angiographic embolization except via the contralateral vertebral

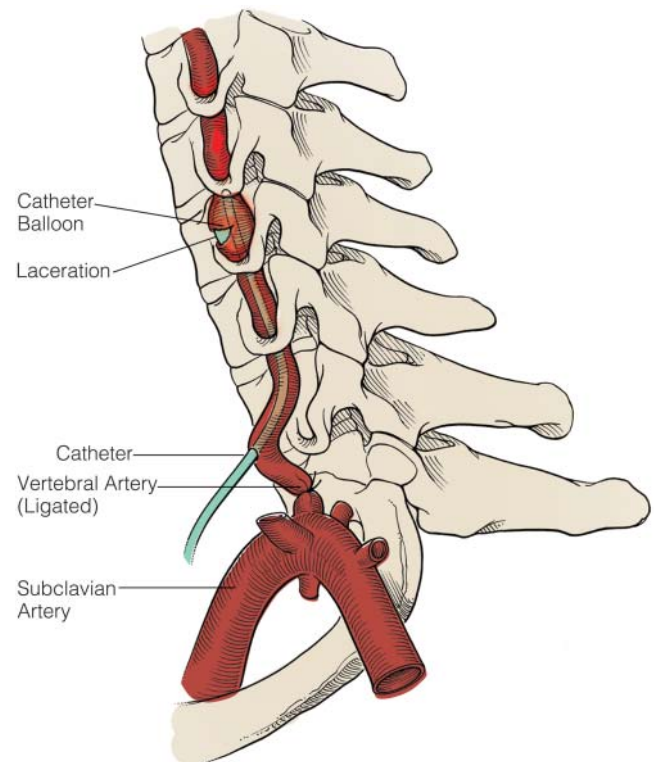


Figure 9 Bleeding from vertebral artery injuries located within the transverse process of the cervical vertebrae can sometimes be controlled by exposing the proximal vertebral artery at the base of the neck, passing a thrombectomy catheter distally, and inflating the balloon at the site of injury.

artery. Embolization via the contralateral vertebral artery is difficult and may result in ischemia or uncontrolled embolization.

If the injury is shown by preoperative angiography to be confined to the first portion of the vertebral artery, both proximal and distal ligation may be possible via a supraclavicular incision [see Figure 10]. The patient is positioned with the head turned away from the side of the injury, and the chest and ipsilateral neck are prepared and draped. Preparation and draping include the chest so that a left thoracotomy can be done later if necessary for proximal control of the left subclavian artery. In such cases, it is helpful to bump the patient up on the left so that an anterolateral thoracotomy incision can be carried further posteriorly.

A supraclavicular incision is made approximately one fingerbreadth superior to the clavicle and is extended medially to the midpoint of the sternocleidomastoid insertion and laterally to the juncture of the middle and lateral thirds of the clavicle. The skin, the subcutaneous tissue, and the platysma are incised. The external jugular vein, if in the operating field, is suture-ligated. The clavicular head of the sternocleidomastoid muscle is encountered next, and its lateral aspect is divided with the electrocautery at its insertion on the clavicle. The muscle is then retracted superiorly and medially. In the plane deep to the

sternocleidomastoid muscle, the omohyoid muscle is divided in its middle tendinous portion with the electrocautery.

At a level just deep to the sternocleidomastoid and omohyoid muscles, the carotid sheath is encountered in the medial aspect of the wound. The lateral border of the internal jugular vein is dissected free of adjacent tissue and retracted medially. If the operation is on the left, the thoracic duct may be found in the medial portion of the wound. The thoracic duct is easily injured with retraction and should be divided and ligated if it is obviously in the way.

Just lateral to the internal jugular vein at the same depth is the supraclavicular fat pad, which is dissected from the supraclavicular fossa in which it lies. Exposure is further enhanced by dissection and division of the anterior scalene muscle. The phrenic nerve, which is closely applied to the anterior surface of the anterior scalene muscle, is dissected free of the underlying muscle and retracted out of the field with a vessel loop. The anterior scalene muscle is then divided with the electrocautery. During dissection of the supraclavicular fat pad, it may be necessary to divide branches of the thyrocervical and costocervical trunks. The most prominent of these branches is the inferior thyroid artery, which stems from the thyrocervical trunk and courses medially toward the thyroid.

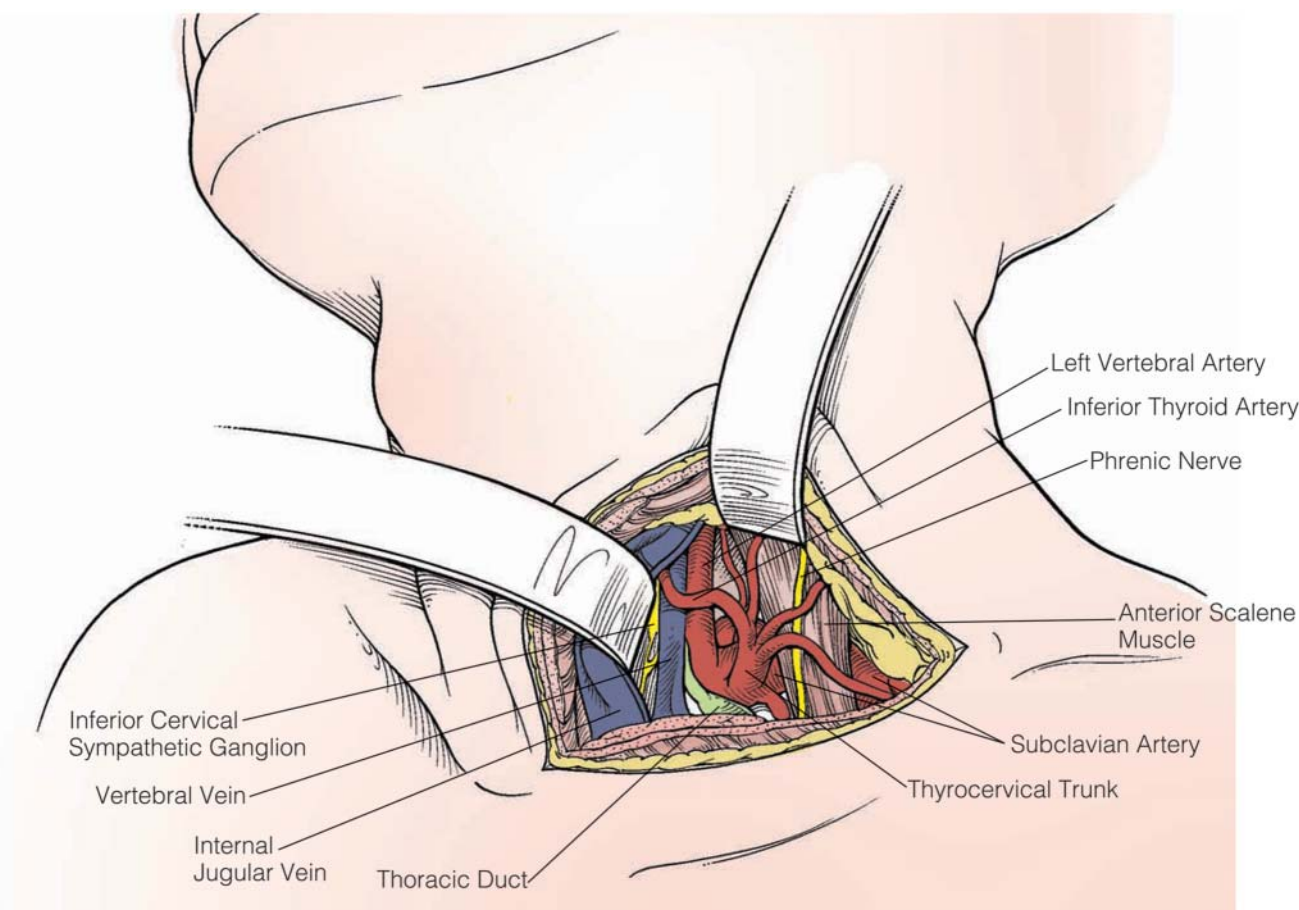


Figure 10 The proximal vertebral artery can be approached via a supraclavicular incision. Dissection of the supraclavicular fat pad reveals the underlying vertebral artery, where it diverges from the subclavian artery. During dissection, care should be taken to avoid injuring the phrenic nerve.

After the supraclavicular fat pad has been dissected, the proximal portion of the vertebral artery is reached. The vertebral vein, which usually lies slightly superficial and medial to the vertebral artery, is divided and suture-ligated to provide better exposure. Care should be taken not to retract the vertebral vein too vigorously before suture ligation so that this vessel is not avulsed from the subclavian vein. At the depth of the vertebral artery, the white, cordlike elements of the brachial plexus are often visible in the superolateral aspect of the wound. If possible, traction should not be placed on the brachial plexus, and use of the electrocautery around the plexus should be minimized. After exposure, the proximal vertebral artery is ligated both proximal and distal to the site of injury. No attempts at repairing the injury should be made.

Endovascular Repair

Endovascular repair of penetrating carotid artery injuries is still controversial. Advocates have identified it to be beneficial in hemodynamically stable patients with injuries in either the proximal common carotid or the distal internal carotid arteries. Operative exposure of these vessels can be difficult, and instead, a stent graft is used to exclude the injured portion of the artery. Validation of this technique is difficult because of the small number of studies in trauma patients coupled with the challenge of applying the vascular surgery literature to the trauma patient population. Little is known about the long-term effects of carotid stents in relatively young patient populations. Recently, a study has looked at long-term follow-up in a small number of trauma patients.¹⁷ The 30-day stroke rates and mortality were similar to the authors' previously reported open rates. Further study is needed for this technique to gain more widespread acceptance for carotid artery injury.

The use of endovascular embolization in the treatment of distal vertebral artery injuries is more widely accepted than endovascular treatment of carotid artery injuries. Like any endovascular technique, its success depends on the availability of equipment for and expertise with the procedure. Stable patients who have angiographically documented injuries to the distal vertebral artery should be treated if possible with embolization.¹⁸ If angiographic expertise is not available and the patient is stable enough for transfer, it is preferable to send the patient to a center with angiographic embolization capability. In urgent circumstances, an angiographic approach is not practical, and a direct surgical approach is necessary. In practice, rapid exposure of the vertebral artery is very difficult, particularly in an actively bleeding patient.

In cases where angiographic embolization of the vertebral artery has been employed, a postprocedure angiogram should be done several days to weeks after the procedure to ensure that the artery remains occluded and that an arteriovenous fistula has developed between the injured vertebral artery and the surrounding venous plexus. Duplex scanning has also been used to a limited extent for follow-up screening. It can serve as an alternative to angiography, but its sensitivity relative to that of angiography remains to be established.

Jugular Vein Injuries

Any of the veins in the neck can be ligated when necessary. An exception to this rule is the rare instance when both internal jugular veins have been injured, in which case an attempt should be made to repair one of the veins, if possible. Even

in such cases, however, bilateral internal jugular ligation, if necessary, is usually tolerated. It is particularly important to use suture ligatures rather than simple ligatures on the cut ends of the internal jugular vein.

If the injury to the internal jugular is simple, the vein should be repaired. Large jugular vein injuries should be repaired only if the patient's general condition and associated injuries allow; if the patient is hemodynamically unstable or has severe associated injuries, large jugular vein injuries should be treated with ligation.

It is not always necessary to encircle the jugular vein completely both proximal and distal to the site of injury; pressure with a finger or a sponge stick sometimes suffices to control bleeding while simple lateral venorrhaphy is done. In the case of more elaborate repairs, it is better either to encircle and occlude the proximal and distal vein or to place a side-biting vascular clamp for control during repair. Nonabsorbable 4-0 or 5-0 sutures should be used.

Pharynx and Esophagus

The oropharynx, hypopharynx, and cervical esophagus are exposed via the same anterior sternocleidomastoid incision used for arterial and venous injuries. If the patient has a known right-sided injury, the incision should be made in the right neck. If the injury is on the patient's left side or if the exact site of injury is unknown, the exposure should be made from the left because the cervical esophagus is located slightly to the left of the midline. After the initial incision, the contents of the carotid sheath are retracted laterally to expose the lateral aspects of the pharynx and the esophagus. This maneuver is made easier if the anesthesiologist places a large colored esophageal dilator through the mouth. The dilator makes identification of the otherwise flat esophagus easier, and the colored tubing of the dilator can sometimes be seen through defects in the esophageal wall.

Sometimes, a pharyngoesophageal injury is suspected but cannot be confirmed preoperatively. In such cases—especially when the injury is more than 1 or 2 hours old—salivary amylase may be present in the wound, giving the surgeon's gloves a greasy feel. The presence of salivary amylase can be a valuable clue to the existence of an otherwise unknown occult injury.

Injuries to the pharynx and the esophagus may be repaired in either one or two layers with either 3-0 or 4-0 absorbable sutures. Attempts should be made to repair nearly all injuries, even when they are severe or their discovery is delayed. In extreme cases of very large injuries or very delayed operative intervention, it may be necessary simply to drain the neck widely and turn the injury into a cervical esophagostomy. Esophageal diversion with distal esophageal ligation is rarely necessary in patients with isolated cervical esophageal injuries, except when the injury is very low in the neck or in the thoracic esophagus.

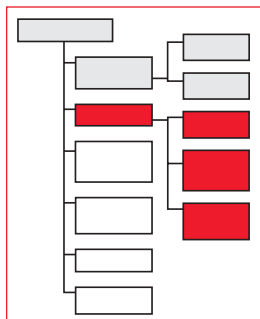
Pharyngoesophageal injuries should be drained; either closed or Penrose drainage can be used. The drains should be left in place for approximately 1 week, at which time a radiographic contrast study should be obtained to determine whether the repair is competent. If the contrast study is negative for extravasation and the patient's general status permits, feeding can begin. If the feedings are well tolerated, the drains can be removed.

Patients with pharyngoesophageal injuries should receive several postoperative doses of antibiotics appropriate for oral

flora. If the repair is inadequate or breaks down, the resultant fistula often heals with nonoperative management, provided that drainage is adequate. A high index of suspicion for mediastinitis should be maintained¹⁹; the prevertebral space provides a ready route of access from the pharynx and the cervical esophagus into the mediastinum. Missed or inadequately drained injuries may result in profound infection and a septic response.

Larynx and Trachea

The presence of an isolated laryngotracheal injury is commonly not recognized preoperatively. On occasion, however, isolated injuries to the larynx and trachea are recognized preoperatively on the basis of a suspicious history and the results of diagnostic studies, such as laryngoscopy and bronchoscopy.



Injuries to the larynx that result in airway compromise should be treated initially with a collar incision for the creation of a surgical airway; however, definitive treatment should be deferred. Minimal débridement of laryngeal structures should be carried out during the initial operative procedure. Injuries to the larynx should be handled on a semielective basis by otolaryngologists with expertise in laryngeal repair and reconstruction. Further investigation of the larynx, including laryngeal x-rays, laryngoscopy, and CT, may be necessary. On rare occasions, the injury is in the distal cervical or proximal intrathoracic trachea. In such circumstances, access to the trachea may not be possible through a cervical incision alone. Median sternotomy and lateral retraction of the innominate artery and the left internal carotid artery allow exposure of the anterior surface of the trachea at the thoracic inlet. Right thoracotomy provides access to the more distal intrathoracic trachea.

Small injuries of the trachea should be repaired primarily and may be treated without tracheotomy. These injuries, if not repaired, may lead to drainage of secretions into the mediastinum and result in mediastinitis. Absorbable 3-0 or 4-0 sutures should be placed transversely, if possible, and should include tracheal rings above and below the site of injury. Large anterior defects should be converted to a tracheotomy, whereas defects to the lateral or posterior aspects of the trachea should be closed primarily and protected with a tracheotomy. Tension can be relieved from a repair by mobilizing the trachea proximally and distally. During this mobilization, the recurrent laryngeal nerves are subject to injury if the dissection is carried into the tracheoesophageal groove. Laryngotracheal injuries do not require routine drainage unless there is an associated injury to the pharynx or esophagus.

If a large segment of trachea has been destroyed, primary anastomosis can be accomplished for defects up to five or six tracheal rings in length. A tension-free anastomosis is created by mobilizing the intrathoracic trachea inferiorly and laryngeal complex superiorly.

Patients with laryngeal injuries should be watched carefully in the postoperative period for signs of mediastinitis, which may result from persistent airway leak or a missed pharyngo-esophageal injury. The chest x-ray should also be checked for pneumomediastinum as a sign of continued airway leakage,

particularly in patients who remain on positive pressure ventilation.

Blunt Trauma

Blunt trauma to the neck may not be as dramatic as penetrating trauma, especially with respect to vascular injuries, but may carry just as high morbidity. The basic principles of initial management apply, in accordance with ATLS guidelines: airway, breathing, circulation.⁷ The blunt trauma patient who is unstable with either airway compromise or hard signs of vascular injury needs immediate operative intervention. But, for the majority of patients, a systematic diagnostic workup is required. Patients at highest risk for neck injuries in blunt trauma are those with a direct blow to the neck, signs and symptoms of airway compromise, neurologic deficits, and facial trauma. The approach is similar for penetrating trauma and focuses on the aerodigestive tract, vascular injuries, and the cervical spine.

AERODIGESTIVE TRACT

Blunt injuries to the aerodigestive tract are suspected if there is any subcutaneous air in the neck or mediastinum on the chest radiograph or if any air is seen on CT scan. Once an injury is suspected, endoscopic evaluation similar to that done for penetrating injuries is performed. In contrast to penetrating trauma, injuries to the esophagus after blunt trauma tend to be blowout injuries with larger holes. Contrast esophagrams can detect these injuries easily. Pharyngoscopy and flexible endoscopy can be used to evaluate the oropharynx and airway.

When injuries are discovered with panendoscopy or contrast esophagoscopy, repair is done in a fashion similar to that described in the penetrating trauma section. The basics include débridement of devitalized tissue, repair, and drainage. There is a risk of abscess and mediastinitis if aerodigestive injuries go unrecognized or are not treated. The exceptions are small oropharyngeal injuries.

Small oropharyngeal injuries, if they are detected, can be treated with antibiotics and observation for developing infection. These injuries can be difficult to approach operatively and usually heal on their own. If the wounds are large or there is an associated cervical spine injury that requires open reduction and internal fixation, operative repair should be undertaken.

CEREBROVASCULAR INJURIES

Blunt injuries to cervical arteries, although relatively rare, can be difficult to diagnose and can lead to devastating complications (e.g., stroke and bleeding). Most such injuries result from stretching of the vessels as a consequence of hyperextension of the neck.²⁰ Motor vehicle collision is a common cause of this sort of stretch injury. Injury may also be caused by direct trauma to the artery, such as with a seat belt or by fracture fragments, particularly cervical transverse foramen or basilar skull fractures.²⁰ Arterial stretching leads to endothelial tearing, with subsequent intimal flaps, dissections, or emboli.

The true incidence of blunt cervical vascular injury is unknown. Recently, aggressive screening has put the incidence at 1 to 2% of all blunt trauma patients, with higher rates in specific patient populations.²¹ Patient populations at

highest risk for blunt cervical artery injury are those with signs and/or symptoms of injury (i.e., seat-belt mark, expanding hematoma,²² neurologic deficit²²), with certain mechanisms of injury (i.e., near-hanging), or with other specific head or neck injuries (basilar skull fracture).²³ When aggressive screening is employed, approximately 3 to 5% of blunt trauma patients undergo workup and approximately 30% of the workups reveal an injury.²⁴

Four-vessel angiography has historically been the gold standard for imaging the cervical vasculature but is invasive and expensive and has largely been replaced as a screening modality by CT angiography.²⁵ CT angiography is noninvasive can be performed relatively rapidly and can be done in the course of CT scanning of the head and other parts of the body. Improvements in CT technology, particularly the use of multidetector CT scanners, have resulted in sensitivity and specificity rates similar to those of formal angiography.^{26,27}

Biffi and colleagues developed a grading scale for blunt cervical arterial injury based on the angiographic appearance of the lesion.²⁸ On this scale, grade I and II lesions show less than 25% and greater than 25% luminal narrowing, respectively; grade III lesions are pseudoaneurysms; grade IV lesions demonstrate thrombosis; and grade V lesions are transections with extravasation. Grade I to III lesions may progress to a higher grade over time.²⁰

Treatment of blunt cervical arterial injury reduces morbidity and mortality. Groups in Denver and Memphis have shown a dramatic decrease in stroke rates (54% to 2.6% and 64% to 6.8%, respectively) for carotid artery injuries in treated versus untreated patients.²⁹ Although treatment of some sort seems to be beneficial, the exact means of treatment is debated. The primary goal of treatment is to decrease embolic events, and the most common treatment is some means of interfering with clotting, which can be challenging in trauma patients with contraindications to anticoagulation, such as intracranial hemorrhage, solid organ, or pelvic injuries. The risks and benefits of anticoagulation versus simple observation and expectant management need to be weighed.

Asymptomatic patients with small intimal flaps or minimal dissection who have no contraindication to antiplatelet agents should be given aspirin. If a contraindication to aspirin exists, the patient should be treated expectantly. More than half of low-grade injuries heal within 2 weeks, and anticoagulation can be stopped after 14 days. If the patient is asymptomatic but has an acute dissection with no contraindications to anticoagulation, then either heparin or antiplatelet agents should be given. Patients with neurologic symptoms need to be anticoagulated. If there is an enlarging pseudoaneurysm or

a contraindication to anticoagulation, operative or endovascular intervention should be performed.²⁰

Endovascular techniques have been used increasingly for the treatment of blunt carotid injuries, most commonly for pseudoaneurysms, especially in the distal portions of the internal carotid, where open repairs are made difficult by the skull base. DuBose and colleagues reported 76% success rates in the placement of endovascular stents in the carotid artery, with close to 80% patency rates at follow-up.³⁰ They reported a stroke rate of 3.5%, which is similar to that seen after open procedures.

Follow-up for blunt carotid injuries is based on grade and treatment modality. Grade 1 and 2 injuries can be reevaluated at discharge, if at all, because the majority heal. Grade 3 injuries require anticoagulation or antiplatelet treatment for up to 8 weeks and then should be reimaged. Approximately a third of all grade 3 injuries progress and may require delayed endovascular or operative intervention.²⁰ Grade 4 and 5 injuries, because of their devastating nature, are typically treated at presentation and should have routine and regular follow-up of the repair.

VERTEBRAL ARTERY

Blunt vertebral artery injuries are often associated with cervical spine fractures.³¹ Most patients with blunt vertebral artery injuries are stable, experience no external bleeding, and have their injuries discovered by angiography or CT angiography. A number of such lesions have been successfully treated with angiographic embolization. Given the difficulties of surgical exposure, lesions of the distal vertebral artery, if characterized by active extravasation, pseudoaneurysm, or arteriovenous fistula, should be treated angiographically when the patient's general condition permits and when the necessary expertise is available. If the patient is bleeding profusely, such an approach is not possible and a rapid surgical approach is indicated, with ligation of the proximal vertebral artery and an attempt at thrombectomy catheter control or packing of the wound until an angiographic approach is attempted. If this is unsuccessful, the lesion should be approached directly. If a patient with a distal vertebral artery lesion is stable—particularly when the lesion is otherwise silent and has been detected angiographically—an attempt should be made at angiographic embolization if the necessary expertise is available. If the patient is stable, transfer to the nearest center with cerebral angiographic embolization capability is appropriate. Embolization is done via the ipsilateral proximal vertebral artery. Detachable balloons or coils can be used.

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Acknowledgments

Figures 2 through 5 and 7 through 10 Liz Done

5 INJURIES TO THE CHEST

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Chest trauma as a result of blunt or penetrating mechanisms is highly prevalent and associated with significant morbidity and mortality. Thoracic injuries are a primary or contributing cause of death in up to 75% of all trauma-related deaths.^{1,2} Fortunately, the majority of thoracic injuries can be treated effectively, and often definitively, by relatively simple maneuvers that can be learned and performed by most physicians involved in early trauma care. However, approximately one in six patients has severe, life-threatening injuries that necessitate urgent operative repair. These extremes in injury severity are unique to the chest and require a correspondingly broad range of knowledge and skills on the part of the treating surgeon.

Initial Evaluation and Management

PRIMARY SURVEY

Initial evaluation and treatment of patients with thoracic injuries are guided by the same principles and priorities as initial evaluation and treatment of patients with other injuries. Evaluation begins with an organized and rapid primary survey aimed at recognizing and treating immediately life-threatening problems.

The first priority is to ensure an adequate airway. An airway often can be established by clearing any blood or debris from the oropharynx and pulling the mandible or the tongue forward. Severely injured patients commonly require nasotracheal or orotracheal intubation, and some, especially those with severe maxillofacial trauma, may require cricothyroidotomy or tracheostomy. The second priority is to ensure adequate ventilation. If the patient is not breathing, he or she must be intubated promptly. If ventilation is inadequate because of open or tension pneumothorax, these problems should be addressed at this stage of care.

The next priority is control of external hemorrhage and restoration of circulation. External hemorrhage is best controlled by direct pressure. Inadequate perfusion generally results from either hypovolemia or pump (i.e., cardiac) problems. Hypovolemia from hemorrhage, by far the most common cause of inadequate perfusion in the traumatic setting, often must be treated operatively as part of the resuscitative effort. Pump problems are signaled by distended neck veins and are caused by one of four conditions: (1) tension pneumothorax, (2) pericardial tamponade, (3) coronary air embolism, or (4) cardiac contusion or myocardial infarction (MI). These conditions are discussed in detail elsewhere (see below). At this early stage of treatment, they should be addressed sufficiently to ensure adequate perfusion.

In most blunt trauma patients, urgent treatment of thoracic injury is accomplished during the primary survey because the most common blunt chest injuries can be controlled with

endotracheal intubation or tube thoracostomy. In this setting, thoracotomy is indicated for cardiac tamponade, a massive hemothorax, or uncontrolled massive air leaks. Neither pulmonary nor cardiac contusions should delay diagnosis or definitive treatment of extrathoracic injuries resulting from blunt trauma.

TUBE THORACOSTOMY: INDICATIONS AND TECHNIQUE

During initial resuscitation, chest tube placement can be both therapeutic and diagnostic. The two most common indications for tube placement in this setting are pneumothorax and hemothorax; however, signs and symptoms of these conditions may not be readily apparent during the initial evaluation of the patient. In addition, when the patient is in shock, the surgeon often cannot afford to take the time to differentiate between various possible causative conditions. Because tube thoracostomy is quick, relatively safe, and simple, it should be liberally used for patients in extremis or with pulseless electrical activity.

Tension pneumothorax, the most common and easily treated immediately life-threatening thoracic injury, results when blunt or penetrating trauma disrupts the respiratory system and allows air to escape from the lung parenchyma or the tracheobronchial tree into the pleural space, thereby increasing intrathoracic pressure. This increased pressure is transmitted to all the cardiac chambers and retards venous return to the heart, resulting in hypotension. The classic signs of tension pneumothorax—decreased breath sounds, tympany on the ipsilateral side, tracheal shift, and distended neck veins—are commonly absent or are incompletely manifested in a busy emergency department (ED). The diagnosis is often suggested by the presence of shock accompanied by evidence of inadequate venous filling on physical examination and recognition of diminished breath sounds and asymmetrical motion of the two sides of the chest. Treatment of a suspected tension pneumothorax should not be delayed in patients with hemodynamic compromise.

Chest tube placement in the trauma setting requires the chest to be prepared and draped in a sterile fashion. A local anesthetic (e.g., 1% lidocaine) is not required in unconscious patients but should be used in alert patients. On the midaxillary line in approximately the fifth interspace, a scalpel is used to make a 2 to 3 cm incision, oriented in the direction of the interspace, through all layers of the skin and subcutaneous tissue. A finger or a blunt clamp is inserted to penetrate the intercostal muscles and the parietal pleura. The wound is explored with the index finger (in adults) or the fifth finger (in children) to ensure that the pleural space has been entered. In adults, a 36 French chest tube is then inserted and advanced posteriorly, toward the apex of the thoracic cavity, for optimally effective drainage of air and blood. The desired tube position is best achieved through appropriate

orientation of the skin incision relative to the entrance into the chest cavity: the straight line between these two points defines the direction of the tube once it is in the chest. The tube is then attached to 20 cm of suction with a water seal and a collection chamber. Visual inspection of air passing through the water seal yields an estimate of the size of the air leak, an important consideration with suspected airway injuries.

Collection chambers for hemothoraces should be of the same design. Those associated with autotransfusion devices (e.g., cell savers) have immense theoretical potential for rapid retrieval and processing of shed blood. However, their utility is limited. For example, with a small to moderate-size hemothorax (< 1,000 mL), the red cell yield of an autotransfusion device would be small and not worth the associated time and expense. With a large hemothorax, the most important goal of therapy is control of bleeding, and arranging for autotransfusion could delay or hinder the achievement of this goal. In addition, the collection system uses heparin, and delivery of the products is limited by the pore size of the filtration device (40 to 100 μ m), making rapid delivery difficult. Furthermore, products of autotransfusion may contain harmful cytokines, damaged cells, and debris, while lacking platelets and other important proteins and coagulation factors. Given these factors, in our practice, autotransfusion is rarely used in the acute setting.³ Antibiotic prophylaxis after tube thoracostomy is controversial.⁴ Practice guidelines from the Eastern Association for the Surgery of Trauma currently recommend use of a first-generation cephalosporin for no more than 24 hours, ideally starting before the initial tube placement in cases of isolated chest trauma.

After the primary survey, less dramatic pneumothoraces may be recognized on diagnostic images, along with hemothoraces on various imaging studies. Treatment of occult pneumothoraces (i.e., those seen only on computed tomography [CT]) deserves special mention. In general, patients with occult pneumothoraces who require positive pressure ventilation, those who are hypotensive or have respiratory distress of any etiology, and those who have associated complex injuries or hemothorax should be treated with tube thoracostomy. One group, however, has questioned the need for tube thoracostomy in patients requiring positive pressure ventilation on the basis of findings from a small number of patients.⁵ Patients with occult pneumothoraces who are treated without tube thoracostomy should be observed for at least 24 hours with repeat chest radiography to ensure that the pneumothorax has not enlarged.

Retained Hemothorax and Empyema

 In treating a hemothorax with tube thoracostomy, the goal is complete evacuation of blood from the pleural space and complete expansion of the lung. Complications such as atelectasis and empyema after chest trauma are clearly related to the presence of residual blood, fluid, and air, as can occur secondary to improper positioning (i.e., within a fissure) or obstruction of the tube. A retained hemothorax is suggested by the presence of a persistent opacification in the pleural space in a patient with a known previous hemothorax. However, plain chest radiography can be misleading, often underestimating the amount of fluid in the chest, and the radiodensity seen can be confused with adjacent pulmonary

contusion or atelectasis. Chest CT confirms the diagnosis, providing information about the size and location of the hemothorax that can be used intraoperatively to make the appropriate incision. Because retained blood serves as a nidus for infection and empyema,⁶ aggressive attempts at removal are justified. Particularly after penetrating trauma, placement of additional chest tubes is rarely effective in removing clotted blood from the pleural space and may increase the risk of infection.⁷ Thus, an operative approach is needed. When used early (less than 5 days after injury), video-assisted thoracic surgery (VATS) is a cost-effective method for managing clotted hemothoraces and free-flowing blood in patients who ideally can tolerate single-lung ventilation.^{8–10} However, VATS may limit the surgeon's ability to control bleeding and perform definitive repair of injuries; thus, in patients who have ongoing bleeding, posterolateral thoracotomy is required. It is our practice to routinely obtain chest CT within 48 hours of injury when patients have persistent pleural effusion on chest radiography within 48 hours of injury. In patients confirmed to have a persistent pleural effusion limiting lung expansion, we proceed directly to VATS. It is well documented that delaying the operation increases the technical difficulty of the procedure and rate of conversion to thoracotomy.¹¹

Empyema thoracis is a relatively common complication after chest trauma, occurring in 5 to 10% of patients.^{12,13} Possible causes include retained hemothorax, pneumonia with parapneumonic effusion, persistent foreign body, ruptured pulmonary abscess, bronchopleural fistula, esophageal leakage, and tracking through the intact or injured diaphragm from an abdominal source. Empyema may be difficult to diagnose in the posttraumatic setting and must be differentiated from pleural thickening, pulmonary contusion, and an uninfected effusion. Chest CT with intravenous (IV) contrast usually demonstrates a fluid collection with loculations or an enhancing rim. Such findings, coupled with a clinical scenario of low-grade sepsis, worsening respiratory function, or failure to thrive, are diagnostic. Analysis and culture of fluid obtained at thoracentesis or chest tube placement typically confirm the diagnosis, but the fluid may be sterile if the patient is already receiving antibiotics.

Antibiotic therapy, either broad spectrum or specifically directed against cultured organisms (usually gram-positive pathogens), is certainly an important component of therapy for empyema thoracis, but the primary goal is removal of the infection while the fluid is still thin. When this goal is met, a more modest therapeutic procedure can be performed, there is less risk that a restrictive pulmonary peel will develop, and the injured patient recovers faster overall. Rarely, in the early stages, tube thoracostomy may suffice for treatment; however, more commonly, the infected pleural process cannot be completely evacuated via chest tube because of thicker fluid, loculations, or pleural adhesions. In these cases, VATS or a formal thoracotomy with decortication is generally required.

Decortication is the cornerstone of effective therapy for posttraumatic empyema. Emphasis should be placed on completely removing the visceral pleural peel to allow complete lung expansion postoperatively. Decortication should not be undertaken in the face of severe sepsis. Instead, antibiotics and drainage (via tube thoracostomy, CT-directed catheter

placement, or open rib resection) should be employed until sepsis is controlled. Once the patient's condition has stabilized, decortication may be performed. In cases of early empyema, VATS has been successfully used for lysis of adhesions and removal of fluid.^{14,15} Because of the limited capacity for performing pleurectomy with this procedure, VATS should not be used when thick peel or a trapped lung is present. In adult patients with posttraumatic empyema, there is no proven role for intrapleural fibrinolytic therapy.

EMERGENCY DEPARTMENT RESUSCITATIVE THORACOTOMY

Emergency department resuscitative thoracotomy (EDRT) is a drastic step in the treatment of the injured patient. If possible, the patient should be stabilized and transported to the operating room (OR), where better facilities are available for definitive care. EDRT is best reserved for patients who arrive at the ED and deteriorate rapidly and those who have undergone cardiac arrest just before arrival. EDRT is futile care when performed in the face of prehospital cardiopulmonary resuscitation of greater than 10 minutes in the setting of blunt trauma and 15 minutes after penetrating trauma or when the presenting rhythm is asystole. Overall, the survival rate for patients undergoing EDRT for blunt trauma is approximately 1%.¹⁶ Survival rates are better for patients undergoing EDRT after penetrating trauma, with reported rates from 16 to 57%, and those for patients with cardiac wounds range from 57 to 72%.^{17–19} Better outcomes are seen when performed for stab wounds rather than gunshot wounds.

The technique of EDRT ideally requires that an antiseptic solution be splashed on the chest, but skin preparation is not required. A left anterolateral thoracotomy incision is made from the sternal border to the midaxillary line in the fourth intercostal space. A chest retractor is inserted and opened widely. The costochondral junctions of the fifth, the fourth, and sometimes the third rib are divided quickly with the scalpel to provide exposure. The six main therapeutic goals are (1) confirming endotracheal intubation; (2) control of hemorrhage; (3) relief of cardiac tamponade if present; (4) effective cardiac compression; (5) cross-clamping the pulmonary hilum in the case of major lung hemorrhage, air embolism, or massive bronchopleural fistula; and (6) cross-clamping of the descending aorta for lower torso hemorrhage control. Attention is directed first to the injury. If there is exsanguination from a great vessel, the hemorrhage is controlled with pressure. If air embolism is the cause of the arrest, the hilum is clamped and air is evacuated from the aorta. Otherwise, the pericardium is opened anterior and parallel to the phrenic nerve. The hemopericardium is evacuated, the cardiac injury is controlled with digital pressure, and a temporary repair is performed. After the cause of the arrest has been addressed, the descending thoracic aorta is occluded with a vascular clamp or digital pressure and intrathoracic cardiac compression is initiated. The patient's intravascular volume is restored, and electrolyte imbalances are corrected. If the patient can be saved, he or she is transported to the OR for definitive repair and closure.

SECONDARY SURVEY AND DEFINITIVE DIAGNOSIS

The secondary survey should focus on more subtle evidence of injury that may be detected on physical examination

and chest x-ray. Simple rib fractures are clinically relevant when associated with pain and are better diagnosed by palpation than by most imaging studies. Pneumothorax and hemothorax often go undetected during the primary survey but are common findings later in the workup.

Echocardiography can be an important adjunct for assessing proximity wounds to the heart or evaluating a new murmur. Because of continuing improvements in CT technology, this modality is increasingly being used in the evaluation of thoracic trauma in stable patients.²⁰ Indeed, CT angiography is now routinely employed for definitive diagnosis of aortic and great vessel injuries, rendering standard angiography unnecessary in most cases.²¹ Additionally, CT is also useful in the diagnosis of tracheobronchial and esophageal injuries.^{22,23}

Operative Considerations

INDICATIONS FOR OPERATIVE MANAGEMENT

Indications for operative treatment of thoracic injuries fall into five broad categories: (1) hemorrhage, (2) major airway disruption, (3) cardiac and vascular injuries, (4) esophageal disruption, and (5) diaphragmatic disruption. **The extent and location of hemorrhage can sometimes be determined from open wounds but are more often established after chest tube insertion. If 1,500 mL of blood or more is obtained initially or ongoing bleeding at a rate of 300 mL/hr or higher for 3 hours is noted, thoracotomy is generally indicated.**²⁴ Caveats to the use of chest tube drainage as an indicator for chest explorations are chest trauma with a delayed presentation and the presence of a coagulopathy. Patients presenting with chest trauma in a delayed fashion may have a significant hemothorax that has accumulated in the time it has taken the patient to arrive in the ED. Furthermore, previously placed chest tubes may become clotted, allowing accumulation of a hemothorax prior to arrival. In these situations, placement of a second chest tube and/or evidence of ongoing bleeding rather than an absolute amount may be a more reliable indicator of the need for thoracic operation.²⁴ Additionally, another group of patients in whom caution should be exercised are those who have significant chest wall injury and a coagulopathy attributable to closed head injury or preinjury medication. Thoracotomy in this setting is frequently not therapeutic.

Massive air leakage and the presence of gastric or esophageal contents in the chest tube effluent also necessitate surgical intervention. **The severity of an air leak can be estimated by examining the amount of air traversing the water seal chamber. Intermittent bubbling signifies a small leak, whereas a continuous stream of bubbles signifies a large leak. A continuous leak seen in conjunction with inability to expand the lung completely or with inadequate tidal volumes is considered a massive air leak. In stable patients with no evidence of bleeding, specific diagnostic measures may be performed to evaluate the thoracic viscera. The likelihood of associated intra-abdominal injuries must not be overlooked.**

CHOICE OF INCISION

The choice of thoracic incision obviously depends on many factors, including the indication for operation, the

urgency of the situation, the presence of associated injuries, the mechanism of injury, and the results of preoperative studies. For injuries that are suspected or diagnosed preoperatively, the choice of the appropriate approach to the affected thoracic structure is greatly simplified [see Table 1]. For exploratory surgery, the choice of incision is more complex and should depend on the mechanism, the instrument, the location (of the entire injury, not just the entry site), and the symptoms. Stab wounds generally have a lower potential for deep penetration than missile injuries do.

A median sternotomy is one of the more versatile thoracic incisions. It can be opened and closed more quickly than a thoracotomy, is associated with less postoperative pain, and may be less likely to result in contamination of the dependent hemithorax. In general, a median sternotomy provides the best exposure of the right-side cardiac chambers, the ascending aorta, the aortic arch, and the arch vessels (excluding the left subclavian artery), and it provides adequate exposure of both lungs and both hemidiaphragms. In the setting of exploratory surgery, a median sternotomy is the best incision for mantle stab wounds and some precordial gunshot wounds whose trajectory can be reliably determined. Its main

limitation is that it does not provide exposure of the posterior mediastinal structures.

For exploration of lateral stab or gunshot wounds, a posterolateral thoracotomy on the side of the injury is the incision of choice. Besides being the best incision for exploratory purposes, the fifth interspace thoracotomy is the most versatile approach to ipsilateral pulmonary and mediastinal pathologic states. Exposure can be markedly enhanced by removal of the fifth rib, which yields an incision that is as long as the rib itself and extends as high as the fourth interspace and as low as the sixth interspace. In general, it is unwise to perform an exploratory thoracotomy below the fourth interspace or above the sixth. A transverse anterior thoracotomy (clamshell incision) is occasionally useful for undetermined or transmediastinal injuries in urgent situations. When exposure of both hemithoraces is required in nonurgent situations, both staged bilateral posterolateral thoracotomies and median sternotomy provide better exposure; one or the other is therefore preferred.

The role of VATS in the trauma setting continues to evolve. In acute situations, VATS is useful for ruling out diaphragm injury and may be preferable to laparoscopy insofar as it is

Table 1 Surgical Approaches for Traumatic Injuries to Thoracic Structures

Site of Injury	Incision		
	Sternotomy	Right Thoracotomy	Left Thoracotomy
Right atrium	+++	++	0
Right ventricle	+++	+	+
Left atrium	+++	+	+
Left ventricle	++	0	+++
Superior vena cava	+++	++	0
Azygos vein	++	+++	0
Inferior vena cava	+++	++	0
Aortic root	+++	+	0
Aortic arch	+++	0	++
Right subclavian artery	++	++	0
Proximal right carotid artery	+++	+	0
Innominate artery	+++	++	0
Left subclavian artery	+	0	+++
Proximal left carotid artery	++	0	++
Descending aorta	0	+	+++
Main pulmonary artery	+++	0	++
Right pulmonary artery	++	+++	0
Left pulmonary artery	++	0	+++
Right upper lobe	++	+++	0
Right middle lobe	++	+++	0
Right lower lobe	+	+++	0
Left upper lobe	+	0	+++
Left lower lobe	0	0	+++
Right hilum	++	+++	0
Left hilum	++	0	+++
Pericardium	+++	++	++
Right internal mammary artery	++	+++	0
Left internal mammary artery	++	0	+++
Proximal esophagus	0	+++	0
Distal esophagus	0	++	+++
Proximal trachea	++	+	+
Carina	0	+++	+
Right main stem	0	+++	0
Left main stem	0	++	++
Right hemidiaphragm	+	+++	0
Left hemidiaphragm	+	0	+++
Cardiopulmonary bypass	+++	++	++

+ = site accessible with difficulty; ++ = acceptable; +++ = preferred; 0 = site inaccessible.

less likely to cause tension pneumothorax. VATS may also have a role to play in the management of persistent intercostal or internal mammary artery bleeding, but this application demands some degree of experience with thoracoscopic surgery. **Later after injury, VATS can be employed for evacuation of retained hemothorax or for management of the early stages of empyema.**

DAMAGE CONTROL TACTICS

Whereas the concept of damage control is critically important in abdominal trauma, it is less important in thoracic trauma. In most instances, serious bleeding from thoracic structures is unlikely to be controlled with packing; however, severe coagulopathy occasionally prevents definitive repair and necessitates abbreviation of surgery and temporary closure of the chest by suturing or stapling the skin incision only.²⁵ The two most common locations of injury in these scenarios are the lung and the chest wall. Hemorrhage from lung lacerations in patients with metabolic exhaustion generally should not be treated with formal anatomic resection: stapled wedge resection, tractotomy, or simple suture repair is more appropriate. In patients with persistent chest wall bleeding that is not associated with a major vessel, treatment with lung reexpansion for local tamponade and correction of coagulopathy usually suffices. Patients in whom an air embolus occurs, most commonly immediately after intubation, or who have massive bronchopleural fistula will require clamping or “twisting” of the pulmonary hilum on the affected side so that the patient may be stabilized prior to proceeding with definitive operation. In rare circumstances, complex esophageal injuries may be associated with extensive loss of tissue, necessitating rapid exclusion and proximal diversion. In most patients with any chance of survival, however, the surgeon should attempt primary closure of the injury, buttressing the repair with autologous tissue and employing wide drainage. Even with large defects, this approach has a surprisingly high rate of ultimate success.

ANESTHETIC CONCERNS

Air embolism seen in the acute traumatic setting is a left heart embolus rather than the more commonly seen right-side embolus. In the setting of traumatic air embolus, there are no anesthetic concerns that should be addressed in contradistinction to right heart emboli.

Airway management can be extremely complex in patients with thoracic injuries, especially when tracheobronchial injury is involved. Whenever operative management is required for a thoracic trauma patient, operative planning should begin with a discussion with the anesthesiology team about airway issues.

In general, double-lumen and bronchial-blocker endotracheal tubes, which allow better exposure by partially or completely deflating a selected lung, should be strongly considered for any thoracic operation. For any given patient, the improved exposure achievable with such tubes must be weighed against the disadvantages, namely, the additional time needed for placement and the requirement that single-lung ventilation be tolerable from a cardiopulmonary standpoint. Hemodynamic stability, therefore, is usually a prerequisite for the use of these devices. The extent of the advantage gained with lung isolation must also be considered.

For example, surgery on the mediastinum or the hilum is greatly facilitated by lung deflation, whereas surgery on the chest wall is not.

If, at presentation, a patient with an otherwise adequate airway has signs of airway injury (e.g., a massive air leak, subcutaneous air, or hemoptysis), further evaluation with bronchoscopy in the OR is indicated before a decision is made to replace the existing adequate airway. In the absence of massive air leakage, bronchial tearing, or hemorrhage into one mainstem bronchus, a double-lumen tube should be advanced into the left mainstem bronchus. Otherwise, the tube should be placed so as to protect the uninjured side.

When a patient with a double-lumen tube in place requires continued intubation after operation, the tube generally must be replaced with a standard endotracheal tube or a tracheostomy because an adequate pulmonary toilet cannot be performed through a double-lumen tube. In contrast, a bronchial-blocker tube may be left in place after surgery because a suction catheter can be passed down it. A disadvantage of the bronchial-blocker tube, however, is that intraoperative lung isolation may be less complete than that obtained with a double-lumen tube.

When a patient requiring a thoracic operation presents with an inadequate airway, specific airway management depends on the nature of the injuries. Most of these patients can be intubated in the standard fashion. If intubation is unsuccessful, however, cricothyroidotomy should be attempted without delay. In cases of tracheal transection, the distal segment must be controlled quickly through a neck incision and selectively intubated through the wound. In cases of known or suspected thoracic airway injuries, an endotracheal tube should be inserted over a bronchoscope past the injury or into an uninjured mainstem bronchus.

Intraoperative management of the airway in patients with complex tracheobronchial injuries can be challenging and is discussed in detail elsewhere [see Tracheobronchial Injuries, *below*]. Injuries to the thoracic trachea may necessitate placement of temporary tubes within the operative field to provide ventilation [see *Figure 1*]. After repair of a tracheobronchial injury, the patient should be extubated if at all possible to prevent stress on the repair.

The locations of arterial catheters should be considered as well. In general, radial arterial lines should be placed in the extremity opposite the side of the intended thoracotomy and not (obviously) in vessels distal to anticipated cross-clamps. Placement of an epidural catheter for postoperative pain management should also be considered in patients undergoing nonurgent thoracotomy.

Control of body temperature is critical for both operative and nonoperative management. Most thoracic trauma patients are hypothermic and require a warm OR, warm IV fluids, and warming blankets. Occasionally, controlled hypothermia is a useful adjunct to procedures involving the thoracic aorta when spinal cord injury and paraplegia are risks. For patients with severe coagulopathy and a core temperature lower than 33.5°C (92.3°F), extracorporeal warming can be lifesaving. This procedure involves placement of a 21 French femoral venous cannula and a 17 French internal jugular cannula and use of a centrifugal pump and a heat exchanger. Heparin is not necessary.

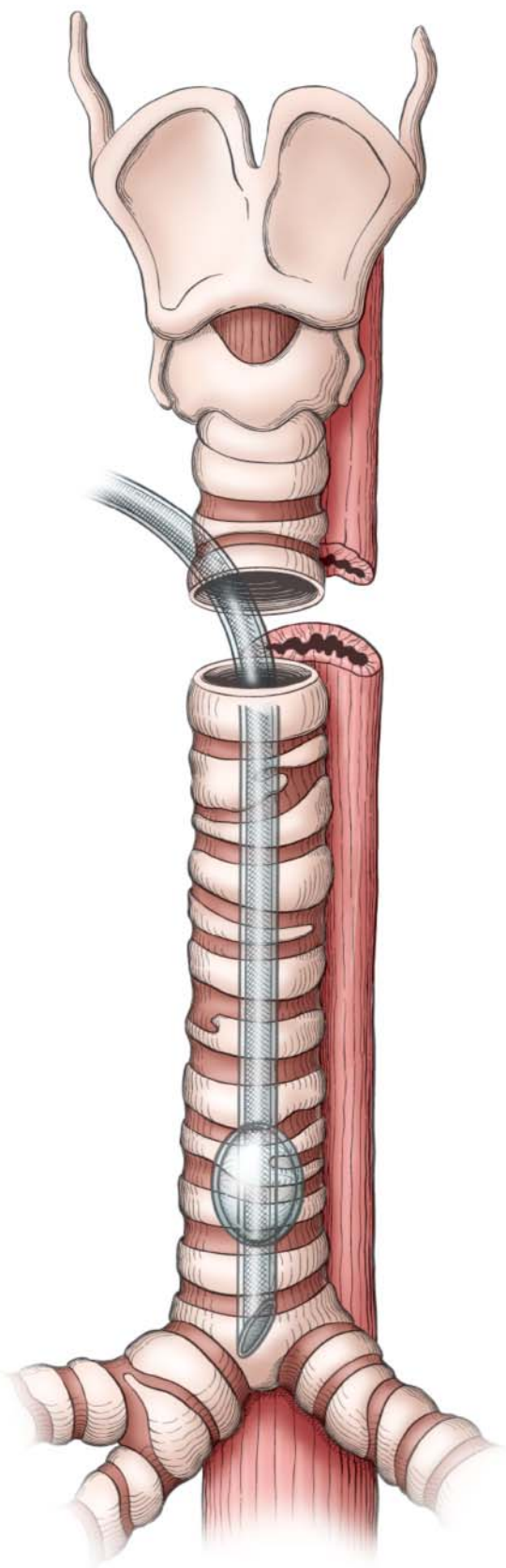


Figure 1 Intraoperative placement of an endotracheal tube is useful for airway management in patients with tracheobronchial injuries.

Chest Wall Injuries

BLUNT

The greatest significance of certain chest wall injuries is their frequent association with other, more life-threatening injuries. These so called sentinel injuries include first rib fractures, scapular fractures, sternal fractures, bilateral rib fractures, and lower fractures.

Simple Rib Fractures

Rib fractures are the most common chest wall injuries resulting from blunt trauma. The main pathophysiologic consequences of rib fractures are pain, splinting, and prevention of adequate cough. The diagnosis should be suspected if pain or splinting occurs on deep inspiration and is confirmed by careful physical examination, consisting of anterior-posterior and lateral-lateral manual compression. If an alert patient feels no pain when these maneuvers are done, clinically significant rib fractures can be excluded. Although rib fractures are often identified on routine chest radiographs, they are more likely to be undetectable except on rib-detail films, which are rarely indicated. A variant of rib fracture that falls into the same physiologic category is costochondral or costosternal separation. This condition is usually detected during physical examination but is not seen on routine chest radiographs.

Management Pain control for isolated rib fractures can usually be adequately accomplished with oral analgesics, encouraging good pulmonary toilet, and use of thoracic epidural anesthesia (discussed below) in select patients. We mention chest wall strapping, taping, and bracing only to condemn these practices. Binding devices generally restrict tidal volume and thus promote rather than prevent atelectasis and pulmonary complications. Increasingly, reports have demonstrated the feasibility of rib fracture repair using a variety of different methods, including wire sutures, intramedullary wires, staples, and various plating systems.²⁶ Potential indications for operative repair of rib fractures include flail chest (as discussed below), painful moveable rib fractures that are refractory to conventional management, chest wall deformity or defect, rib fracture nonunion, and during thoracotomy for other indications. In isolated reports, clinical outcomes have been excellent when repair is undertaken, and most trauma surgeons feel that there is a role for rib repair; however, there is a need for clinical trials documenting the superiority of rib fracture repair versus conventional management in select patient populations.^{27,28}

Special mention should be made of rib fractures in the elderly. The mortality associated with rib fractures is twice as high in patients older than 65 years as in younger patients, and the relative increase in the incidence of pneumonia in older patients is even higher, even after the increased comorbidity is taken into account.^{29,30}

Sternal Fractures

The vast majority of sternal fractures result from motor vehicle accidents and are associated with the use of three-point restraints. Isolated sternal fractures in this setting are relatively benign, with a low incidence of associated cardiac, great vessel, and pulmonary injuries. Sternal fractures in

unrestrained occupants and victims of crush injuries, however, are commonly associated with underlying visceral injuries, which must be excluded.³¹

The diagnosis of sternal fracture is based on the presence of severe pain, often associated with instability on sternal palpation. In many cases, physical examination can clarify the nature of the fracture. Sternal fractures are almost invariably transverse, with the majority occurring at the sternomanubrial joint or in the midbody of the sternum. They may be characterized as simple (two fragments) or comminuted (multiple fragments), as displaced or aligned, or as stable or unstable. The fragments of an unstable fracture move substantially with activity.

Management Initial management of a sternal fracture is directed toward resuscitation and identification or exclusion of other life-threatening injuries. In patients with isolated sternal fractures, a normal electrocardiogram (ECG) and a normal chest radiograph suggest that associated serious injuries are unlikely. If the pain is controlled with oral analgesics, these fractures can usually be managed on an outpatient basis. Displaced fractures may be reduced by the simple (albeit painful) maneuver of having the patient simultaneously raise his or her head and legs from the bed. Such a position requires contraction of the rectus abdominis, which distracts the caudad segment inferiorly, and the sternocleidomastoid muscles, which retract the cephalad segments superiorly. The physician can then depress the anterior segment and allow the patient to relax. This measure often suffices for alleviation of subsequent pain and sometimes constitutes adequate long-term treatment.

The vast majority of sternal fractures heal with nonoperative management. Those that are unstable or are displaced by more than 1 cm of overlap are more likely to exhibit malunion or nonunion and subsequent chronic pain; they should be treated with open reduction and internal fixation. Occasionally, a patient with a clinically stable, minimally displaced sternal fracture associated with lower extremity injuries who requires crutches for ambulation experiences such disabling sternal pain during ambulation that fracture repair is necessary.

Sternal fractures may be repaired with either of two operative techniques. In both, the sternum is approached via either a vertical midline incision or a sweeping transverse inframammary incision similar to that used for repair of pectus excavatum. The fracture is exposed, and the ends are mobilized and fixed with either reconstruction plates or No. 6 sternal wires. Reconstruction plates provide a more stable and less painful fixation and can be used in the management of comminuted and crush fractures. Wire repair is unsatisfactory in patients with comminuted or crush fractures and in many patients requiring crutches for ambulation. Both wire fixation and plate fixation are well tolerated and, in fact, greatly appreciated by properly selected patients.

Flail Chest

Flail chest is the most serious of the blunt chest wall injuries. It is common after any form of blunt thoracic trauma, and although it may occur as an isolated finding, it is usually associated with other significant injuries.³² Flail chest represents a disruption of the stability and normal respiratory

mechanics of the rib cage. It involves fractures of adjacent ribs, each of which is fractured in two or more places, so that a panel of chest wall moves independently of, and in the opposite direction to, the remainder of the chest. When it occurs in conjunction with separation of the costochondral or costosternal joints, the sternum can also be part of the flail segment, and the condition is termed a sternal flail chest.

The following are the three components of the pathophysiology of flail chest:

1. *Alteration of chest wall mechanics.* The paradoxical motion of a large flail segment occasionally impairs the patient's ability to achieve an adequate tidal volume or an effective cough.
2. *Underlying pulmonary contusion.* In the vast majority of serious flail chest injuries, this is the most significant physiologic aberration. In the contused portion of the lung, there is extravasation and accumulation of blood and fluid in the alveolar air space, which results in sufficient shunting to produce hypoxemia.
3. *Pain.* The extreme pain of multiple rib fractures leads to profound splinting and diminution of tidal volume and prevents adequate coughing and pulmonary toilet in most alert patients. The combination of depressed tidal volume and inadequate coughing leads to hypoventilation, atelectasis, and often pneumonia.

The diagnosis is typically suspected on the basis of the presence of numerous adjacent rib fractures on a chest radiograph [see Figure 2] but can be conclusively confirmed only by

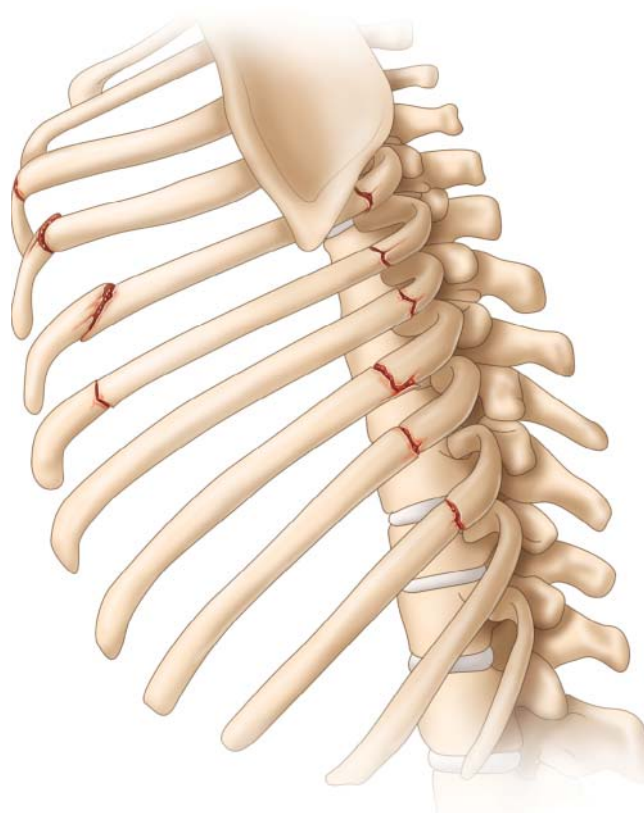


Figure 2 Chest x-ray and three-dimensional reconstruction of a patient with flail chest.

the presence of a paradoxical motion observed in the involved segment in a spontaneously breathing patient. A flail segment may be overlooked in a patient on positive pressure ventilation because there may be no paradoxical motion without inspiratory effort. Therefore, in an intubated patient, the diagnosis must be sought through careful examination and palpation of the rib cage for stability.

Management Proper management of flail chest hinges on the recognition that the injury is not a static condition but, rather, an evolving process. Frequent reevaluation and timely, appropriate intervention are essential. During the initial assessment, the patency of the airway and adequacy of ventilation must be established or confirmed. Immediate intubation is rarely required for patients with isolated flail chest injuries. When early intubation is indicated, it is usually for associated injuries, most commonly to the central nervous system (CNS).

In virtually all awake and alert patients, management without intubation should be attempted. To this end, early and aggressive pain management is essential. Pain cannot be eliminated entirely, but it usually can be diminished sufficiently to allow an adequate tidal volume and a forceful cough. Oral analgesics rarely suffice for patients with even a small flail segment; stronger agents are required for all but the most stoic of patients. Parenteral narcotics are effective, especially when administered in a patient-controlled analgesia (PCA) device. Intercostal nerve blocks occasionally provide dramatic pain relief, but only for short periods. If the patient is encouraged to cough vigorously during pain relief, intermittent nerve blocks may be helpful, despite the inherent risk of pneumothorax.

The mainstay of pain control in patients with flail chest is thoracic epidural anesthesia, in which a solution containing 0.002 to 0.005% morphine sulfate and 0.075 to 0.2% bupivacaine is infused through a small catheter in the thoracic epidural space at a constant rate of 0.15 to 0.75 mg morphine/hr. At this low dosage, bupivacaine acts synergistically with morphine and does not exert a local anesthetic effect on the spinal cord; in addition, it generally does not give rise to the respiratory depression frequently observed with systemic narcotics. Epidural anesthesia provides immediate comfort, dramatically improves vital capacity and tidal volume, and, most important, enables the patient to produce a forceful cough.³³

The most common serious adverse effect of epidural anesthesia is transient hypotension at the time of insertion. This complication can be prevented by providing adequate volume resuscitation before creating the chemical sympathectomy. Urinary retention occurs in 30 to 50% of cases; in practical terms, this means that most flail chest patients should not have their urinary catheters removed until the epidural analgesics are no longer required. Patients who have head injuries and are thus at risk for increased intracranial pressure should not undergo epidural catheterization, because an unintentional dural puncture could alter cerebrospinal pressure sufficiently to induce or contribute to cerebral herniation. Relative contraindications to epidural catheter placement include spine fractures and infection; however, fever may be a relative indication if it is thought to be secondary to splinting with atelectasis or pneumonia.

The decision-making process for management of flail chest should begin with assessment of the patient's ability to cough [see Figure 3]. If the patient is able to clear tracheal secretions—that is, actually cough them up into the oropharynx—then observation in an acute care setting, in conjunction with small, infrequent doses of narcotics, is appropriate. If the patient has no cough or has a very truncated cough that moves secretions but does not propel them into the oropharynx, an aggressive program to promote pulmonary toilet should be instituted. If a sufficiently vigorous cough cannot be achieved and there is no specific contraindication, an epidural catheter is inserted and the patient is followed closely with frequent physical examinations in the intensive care unit. Ambulation is encouraged, and frequent coughing is required. It is important that management decisions be made early and followed closely so that effective therapy can be started expeditiously. There is no role for antibiotic prophylaxis or steroid use in the management of patients with flail chest or pulmonary contusion.

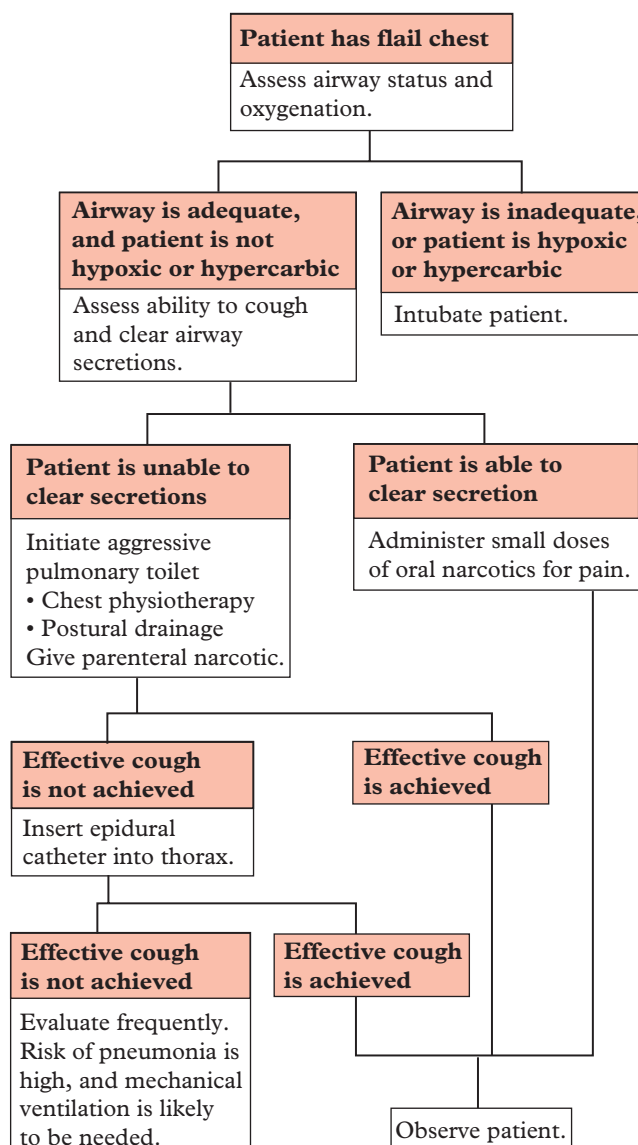


Figure 3 Algorithm illustrating approach to the management of flail chest.



Depending on the presence and severity of an underlying pulmonary contusion and adequate pulmonary toilet, many flail chest victims can avoid intubation.³⁴ However, any patient with flail chest who demonstrates further deterioration of pulmonary function and who becomes hypoxic or hypercarbic should undergo mechanical ventilation aimed at (1) ensuring a tidal volume adequate for establishing normal chest wall excursion and (2) maintaining a respiratory rate adequate for achieving normocarbica. Hypoxia is managed by increasing the fraction of inspired oxygen (FiO₂) and applying sufficient positive end-expiratory pressure to achieve adequate oxygenation (usually defined as arterial oxygen saturation greater than 90%) with nontoxic levels of FiO₂.

A few patients with severe disruption of chest wall mechanics as a result of flail chest continue to require positive pressure ventilation even though adequate pain control has been achieved and the pulmonary contusions are beginning to resolve. Some of them may benefit from internal fixation of the multiple rib fractures, which restores chest wall stability and eliminates much of the fracture-related pain. A variety of methods have been described to stabilize the ribs and obtain compression osteosynthesis of each fracture site. An isolated, single-institution series described the efficacy of this procedure in patients with flail chest.^{35,36} Further clinical trials are needed.

PENETRATING

In most cases of penetrating thoracic trauma, the injury to the chest wall is vastly overshadowed by the injury, or potential for injury, to the intrathoracic structures. The notable exceptions to this general rule are hemorrhage and open chest wounds.

Hemorrhage

Stab wounds and low-caliber gunshot wounds to the anterior chest are common in urban areas. Once serious injury to intrathoracic organs has been excluded, such injuries often can be managed with tube thoracostomy or observation alone. Indications for urgent thoracotomy are discussed elsewhere [see Operative Considerations, Indications for Operative Management, *above*].

In patients with persistent hemorrhage from chest tubes who require thoracotomy, the most common source of the bleeding is a lacerated internal mammary or intercostal artery. Attempts to control bleeding from these vessels nonoperatively usually fail. Angiography to localize the bleeding vessel is unnecessary and delays definitive care: coupled with embolization of the lacerated vessel, it is more time consuming than surgical intervention and does not address associated injuries and hemothorax.

Penetrating wounds to the midportion of the pectoral muscle occur with surprising frequency, possibly as a result of an assailant's erroneous conception of the location of the heart. Such injuries often lacerate the pectoral branch of the thoracoacromial artery, which courses along the posterior surface of the pectoral muscle. Control of this troublesome bleeding is extremely difficult to achieve if exploration is attempted directly through an extension of the entrance wound, but exposure is much improved if exploration is attempted through an oblique wound along the lateral pectoral margin after entry into the subpectoral plane.

Open Chest Wounds

The diagnosis of an open chest wound is usually obvious, and their treatment depends on the size of the wound and the size of the chest wall defect. Most small open pneumothoraces can be managed initially with occlusive dressings, but there is usually an underlying pulmonary injury with air leakage, which necessitates early tube thoracostomy to prevent tension pneumothorax. Once the patient's condition is stable, the wound can be debrided and closed. Occasionally, primary skin closure must be delayed.

Larger chest wall defects pose a challenging therapeutic problem. Such wounds usually result from high-velocity missiles or shotguns fired at close range. Initial management is directed toward restoration of respiratory mechanics with early intubation and mechanical ventilation.

The next priority is to address any underlying intrathoracic injuries, which may range from mild pulmonary contusion to massive hemorrhage in conjunction with severe lung or hollow viscus injury. When associated intrathoracic injuries are present, the first step in the closure of the defect is to select an appropriate operative approach. Although the primary objective in this situation is to provide excellent exposure for repair of what may be life-threatening injuries, whenever possible, the thoracotomy should be performed in such a way as to preserve the blood supply and muscle mass of the chest wall adjacent to the defect.

After definitive repair of intrathoracic injuries and débridement of devitalized chest wall tissue, the next step is to plan the closure. Such planning requires a degree of familiarity with current and developing techniques and an understanding of pleural drainage, respiratory mechanics, and techniques of tissue transfer. Collaboration with plastic and thoracic surgeons is often helpful. Most chest wall defects can be closed with viable autogenous tissue, usually through rotation of local myocutaneous or myofascial flaps of the pectoral muscle, the latissimus dorsi, or the rectus abdominis.

Pulmonary Injuries

Because of their size, the lungs are commonly injured in cases of thoracic trauma. Mortality from pulmonary lacerations is directly proportional to the amount of blood lost. A 1,500 mL hemothorax, regardless of causative mechanism, should always prompt exploration.

LACERATIONS

Bleeding pulmonary lacerations can be oversewn, resected, or explored via pulmonary tractotomy. Bleeding from small or shallow lacerations can be controlled with an over-and-over repair using a continuous monofilament suture. Bleeding from deeper lacerations is controlled with resection or tractotomy. Most pulmonary resections for trauma should be stapled, nonanatomic resections; however, anatomic lung resection is required in rare instances, and trauma surgeons should remain familiar with the technical aspects of this procedure.³⁷ Mortality is proportional to the amount of lung tissue resected: with suture repair alone, mortality is 9%; with tractotomy, 13%; with wedge resection, 30%; with lobectomy, 43%; and with pneumonectomy, 50%.^{38,39}

Tractotomy is especially useful for deep through-and-through injuries that do not involve the hilum.⁴⁰ In this

technique, the injury tract is opened with a linear stapler [see Figure 4] or between two aortic clamps. If clamps are used, the cut lung edges are oversewn and the tract left open. Tractotomy exposes bleeding vessels and air leaks inside the tract and permits selective ligation. Occasionally, it exposes an injury to a major vascular or airway structure that must be treated with a formal resection. Because of the risk of exsanguination or excessive devitalization of lung tissue, tractotomy is not indicated when the injury traverses the hilum or when the entire thickness of a lobe will be cut.

Central lung injuries often cause massive hemorrhage. In addition, they may be sources of pulmonary venous air emboli when both a major pulmonary vein and a large airway are disrupted. A common scenario involves an intubated patient who exhibits sudden deterioration of CNS and cardiac status shortly after being placed on positive pressure ventilation. Emergency thoracotomy must be performed and the pulmonary hilum clamped or twisted. The diagnosis is confirmed by visualizing air in the epicardial coronary arteries. Aspiration of air from the left-side cardiac chambers and elevation of central blood pressure are also useful maneuvers. Most central lung injuries are associated with extensive parenchymal injury in gravely ill patients. Selective repair of hilar structures is usually impractical in this setting, and lobectomy or pneumonectomy is the salvage procedure of choice.

CONTUSIONS

Pulmonary contusions are bruises to the lung that usually are caused by blunt trauma to the chest but sometimes result from penetrating injury by high-velocity weapons. The contused segment of the lung has a profound ventilation-perfusion mismatch, which produces an intrapulmonary right-to-left shunt and hypoxia. The clinical sequelae of lung contusion may vary from simple shortness of breath to respiratory failure requiring mechanical ventilation. There is systemic activation of the innate immune system as a result of lung contusion as evidenced by the local and systemic production of various inflammatory mediators such as the interleukins, prostaglandins, and chemokines. This resultant

inflammatory response contributes to the evolution of pulmonary and remote organ dysfunction.⁴¹ Typically, the bruise is not fully appreciated on a chest x-ray, but it is fully evident on a chest CT scan [see Figure 5]. In fact, the size of the contusion as measured on a chest CT scan is directly proportional to the risk of developing posttraumatic acute respiratory distress syndrome (ARDS).⁴² Lung contusion is a well-established risk factor for pneumonia, and the bruised lung also may serve later as a source of sepsis.

Most pulmonary contusions that are not complicated by excessive attempts at resuscitation or by superinfection resolve over 3 to 5 days. Supportive care in the form of cardiovascular and, if necessary, ventilatory support must be provided. In general, pulmonary contusion is treated in much the same fashion as flail chest. Patients with rib fractures and painful chest wall excursions must be given sufficient analgesic support to allow them to produce a cough forceful enough to maintain pulmonary toilet. Intubated patients should undergo suctioning frequently. Patients with pulmonary contusions who require substantial volume resuscitation should be considered for pulmonary arterial catheter monitoring. Steroids are not indicated, because they have no effect on the development or resolution of the contusion and because they set the stage for subsequent infection. Diuretics and prophylactic antibiotics are also unnecessary.

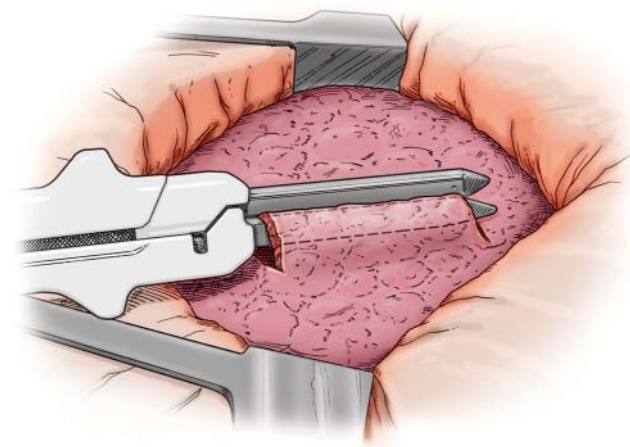


Figure 4 Pulmonary tractotomy is useful for controlling hemorrhage associated with deep through-and-through injuries to the lungs.

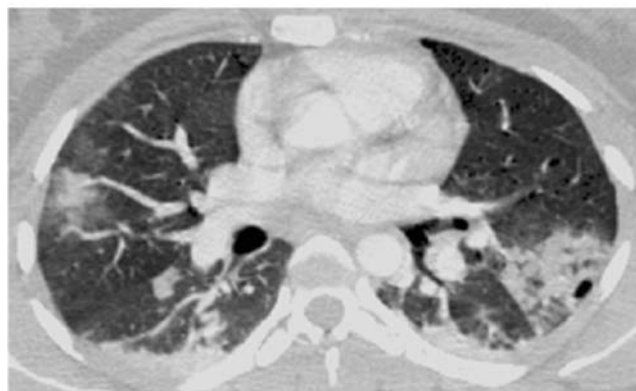
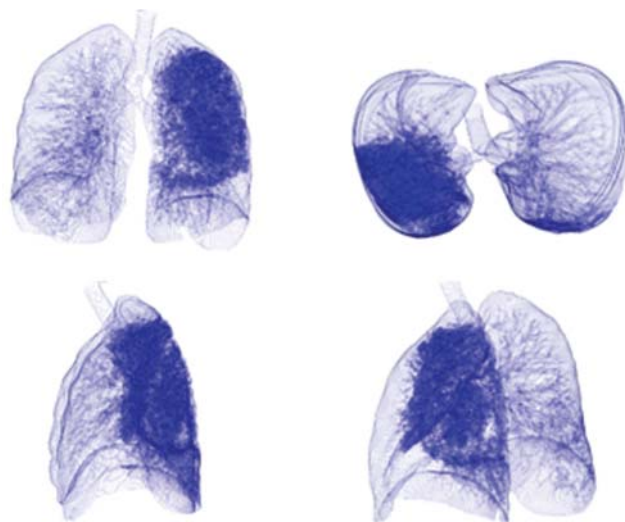


Figure 5 Chest computed tomographic scan of a pulmonary contusion with three-dimensional reconstruction.

Tracheobronchial Injuries

Although tracheobronchial injuries are rare and often lethal, a high index of suspicion for the existence of the injury, a timely diagnosis, and appropriate intervention can improve the chances of a successful outcome. The reported incidence of tracheobronchial injury in blunt chest trauma patients ranges from 0.2 to 8%.^{43–45} Concomitant injury is the rule rather than the exception, but the patterns of associated injury vary widely.⁴⁶ More than 80% of tracheobronchial ruptures occur within 2.5 cm of the carina. Mainstem bronchi are injured in 86% of patients and distal bronchi in only 9.3%, whereas complex injuries are seen in 8%.

Various clinical presentations result after injury to the tracheobronchial tree, generally depending on the severity and the location of the injury. In the neck, airway involvement may create severe respiratory distress that causes death before emergency care can be given. Alternatively, patients with cervical tracheal injuries may present with stridor and severe respiratory distress or with hoarseness, hemoptysis, or cervical subcutaneous emphysema.

The presentation of thoracic tracheobronchial injury depends on whether the injury is confined to the mediastinum or communicates with the pleural space. Thoracic tracheobronchial injuries confined to the mediastinum usually present with a massive pneumomediastinum. Injuries that do extend into the pleural space usually create an ipsilateral pneumothorax that may or may not be under tension. A pneumothorax that persists despite adequate placement of a thoracostomy tube and that leaks air continuously is suggestive of tracheobronchial injury and bronchopleural fistula. Dyspnea may actually worsen after insertion of the chest tube because of the loss of tidal volume via the tube. Several radiographic clues to possible airway injury may be observed with endotracheal intubation, such as abnormal migration of the tube tip and distention of the endotracheal tube balloon beyond the normal tracheal diameter.

In only 30% of cases is a definitive diagnosis of tracheobronchial injury made within 24 hours. More often, the diagnosis is made late, when pulmonary collapse distal to the injury and sepsis occur. As many as 10% of tracheobronchial tears give rise to no initial clinical or radiologic signs and are not recognized until months later, after stricture occurs. Immediate intubation of patients with multisystem trauma can mask laryngeal or high cervical tracheal injuries and thereby delay the diagnosis. After tracheobronchial transection, the peribronchial connective tissues sometimes remain intact and allow continued ventilation of the distal lung in much the same way that perfusion is maintained after traumatic aortic transection. If unrecognized, this injury heals with scarring and granulation tissue and occasionally creates bronchial obstruction.

The diagnosis is typically suspected on the basis of the clinical history and the characteristic signs and symptoms [see Figure 6]. The advent of spiral CT with multiplanar reconstruction has led to renewed interest in the use of this modality to evaluate tracheobronchial injury. An increasing number of reports demonstrate the utility of CT technology in diagnosing tracheobronchial injuries, with a sensitivity approaching 100%.^{47,48} Thus, because of its excellent negative

predictive value, CT may be employed as a screening tool to look for these injuries in stable patients; however, at present, diagnostic bronchoscopy remains necessary to reliably exclude the diagnosis of tracheobronchial injury. In stable patients with transmediastinal gunshot wounds, chest CT may be used to detect the proximity of the missile tract to mediastinal structures, directing subsequent evaluation.²³ Indications for bronchoscopy in this setting include a large pneumomediastinum, a refractory pneumothorax, a large air leak, persistent atelectasis, and possibly marked subcutaneous emphysema.⁴⁶

Bronchoscopy, either rigid or flexible, is the most reliable means of establishing the diagnosis and determining the site, nature, and extent of the tracheobronchial disruption. Whichever type of scope is used, the signs and symptoms should be correlated with the endoscopic findings. The most critical determinant seems to be the endoscopist's level of experience and comfort with the procedure. An experienced bronchoscopist can perform either technique with a high degree of sensitivity, specificity, and accuracy.⁴⁴ Often the lesions are missed initially, or their severity is underestimated, or they evolve into more obvious or severe lesions. For this reason, bronchoscopy should be liberally repeated as needed.

MANAGEMENT

With tracheobronchial injuries, as with all injuries, airway management is the first priority in treatment. If the patient is maintaining his or her own airway and is adequately ventilated, a cautious noninterventional approach is probably the best initial choice until further diagnostic workup is performed or other life-threatening injuries are stabilized. Careless handling or mishandling of the airway (e.g., inadvertently placing an endotracheal tube through a transected or ruptured airway and into soft tissue) can be disastrous and may compound the injury. ED tracheostomies are difficult and may be dangerous, to say the least.

How best to secure an airway in a patient with neck trauma and possible tracheal injury is a matter of debate. With blind endotracheal intubation, the path of the tube distal to the larynx is unknown, and it is possible to lose the lumen or create a false passage. With intubation over a flexible bronchoscope, the tube can be visualized as it passes beyond the site of injury, and some of the dangers of blind intubation are thereby mitigated; however, some degree of sedation is usually required, and if the patient is oversedated, the airway that was being spontaneously protected may be lost. Paralytic medications should generally be avoided in this setting, for the same reason. Urgent tracheostomy or cricothyrotomy, performed in the OR, is advocated by many as the safest and securest way of obtaining airway control. If the trachea is completely transected, the distal trachea can usually be found in the superior mediastinum and grasped for insertion of a cuffed tube. The approach taken to airway control must vary with the resources and expertise available at each institution. One must also keep in mind that even after the airway is secured, it may still be possible to exacerbate the injury by means of aggressive ventilation with high airway pressures. Tube thoracostomies should be appropriately placed at this time and connected to suction, even though dyspnea may worsen.

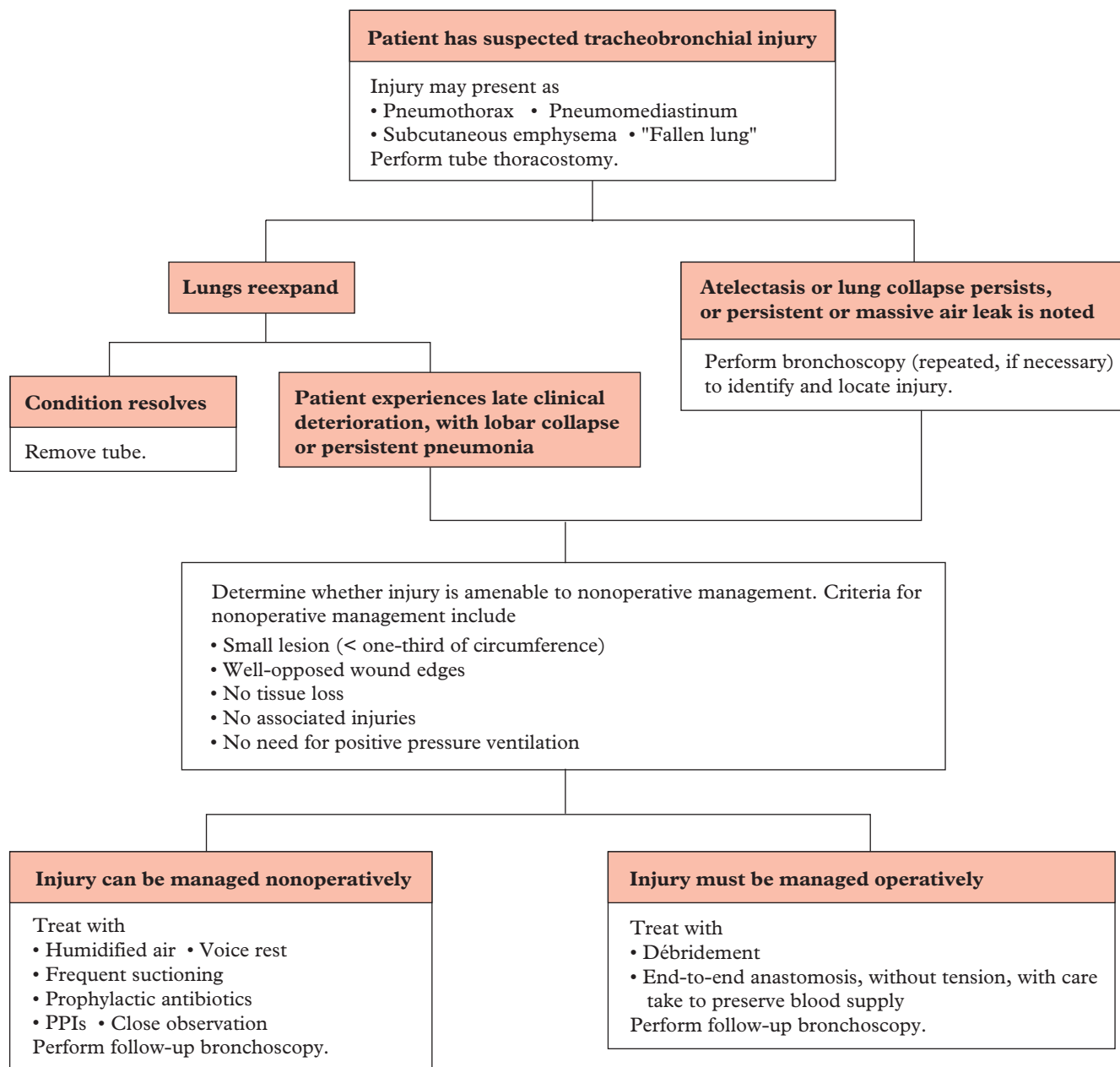


Figure 6 Algorithm illustrating approach to management of suspected tracheobronchial injury. PPI = proton pump inhibitor.

Once the airway is controlled, there is time for orderly identification of concurrent injuries, esophagoscopy, laryngoscopy, arteriography, transport to definitive care areas, and, if necessary, celiotomy.

Nonoperative

On occasion, asymptomatic tracheobronchial tears are found incidentally in the course of bronchoscopy or other imaging procedures. Nonoperative management is reserved for highly selected patients with unsuspected small injuries of this type. Lesions suitable for observation must involve less than one third of the circumference of the tracheobronchial tree. For patients to be candidates for nonoperative care,

their lungs should be fully reexpanded with tube thoracostomy, and any air leaks should stop soon after insertion of the tube. There must be no associated injuries and no need for positive pressure ventilation. Prophylactic antibiotics, humidified oxygen, voice rest, frequent suctioning, and close observation for sepsis and airway obstruction are required.

Small penetrating wounds with well-opposed edges and no evidence of loss or devitalization of tracheal tissue may be effectively treated with temporary endotracheal intubation.⁴⁹ The cuff of the endotracheal tube should be inflated below the level of injury and left undisturbed for 24 to 48 hours while the wound seals. If a conservatively managed patient's clinical condition deteriorates, bronchoscopy should be

liberally repeated. Even small tears may produce substantial amounts of granulation tissue on healing, which may necessitate late endobronchial excision.

Operative

Like emergency airway management, intraoperative airway management requires close coordination with the anesthesiologist. After the airway is initially secured, manipulation during the repair creates additional challenges. A sterile anesthesia circuit and tube must be available to pass off the table once control of the airway at the level of transection has been regained. In especially difficult cases, in which airway management is unsatisfactory or the repair is complex, cardiopulmonary bypass or venovenous extracorporeal membrane oxygenation (ECMO) may be instituted. Both techniques require systemic anticoagulation, and their potential risks and benefits in multiply injured patients remain to be determined. Once the repair is complete, the endotracheal tube ideally should be removed immediately after the operation.

Intrathoracic tracheal, right bronchial, and proximal left mainstem bronchus injuries are best repaired through a right posterolateral thoracotomy at the fourth or fifth intercostal space because this approach is blocked from the left by the heart and the aortic arch. Complex or bilateral injuries are also approached through the right chest, for the same reason. Distal left bronchial injuries more than 3 cm from the carina are approached through a left posterolateral thoracotomy in the fifth intercostal space.

Optimal repair includes adequate débridement of devitalized tissue (including cartilage) and primary end-to-end anastomosis of the clean tracheal or bronchial ends [see Figure 7]. The anastomosis can be accomplished without tension by mobilizing the structures anteriorly and posteriorly, thereby preserving the lateral blood supply. On occasion, bronchial sleeve resection, lobectomy, or pneumonectomy is urgently

required for more extensive or distal injuries to lobar or segmental bronchi.

Esophageal Injuries

Injury to the esophagus, although relatively rare, poses particular problems for the treating physician because of the complexity of the presentation, the workup, and the treatment options. Despite diagnostic and therapeutic advances, the morbidity and mortality associated with esophageal injury remain high. Preoperative evaluation is still a subject of debate, as is the question of mandatory surgical exploration versus selective nonoperative management. Currently, most esophageal injuries are iatrogenic or endoluminal; however, we will concentrate here on injuries specifically related to external trauma—namely, penetrating injury and blunt esophageal rupture.

Whereas the cervical esophagus is relatively unprotected from external trauma, the thoracic esophagus, being surrounded by the bony thorax, is well protected. The esophagus lies in close proximity to the heart, the great vessels, and the entire membranous portion of the trachea. Consequently, simultaneous injury to several of these intrathoracic organs is common, which greatly increases associated morbidity and mortality. The esophagus has no serosal covering; rather, it is entirely surrounded by loose areolar connective tissue, which makes suture placement less secure and increases the overall difficulty of surgical repair. **The planes of the paraesophageal and prevertebral spaces communicate freely with the mediastinum. As a result, spillage from the esophagus readily tracks into the mediastinum, leading to mediastinitis, causing sepsis, and accounting for much of the increased morbidity and mortality seen with delayed diagnosis and treatment of esophageal injuries.**

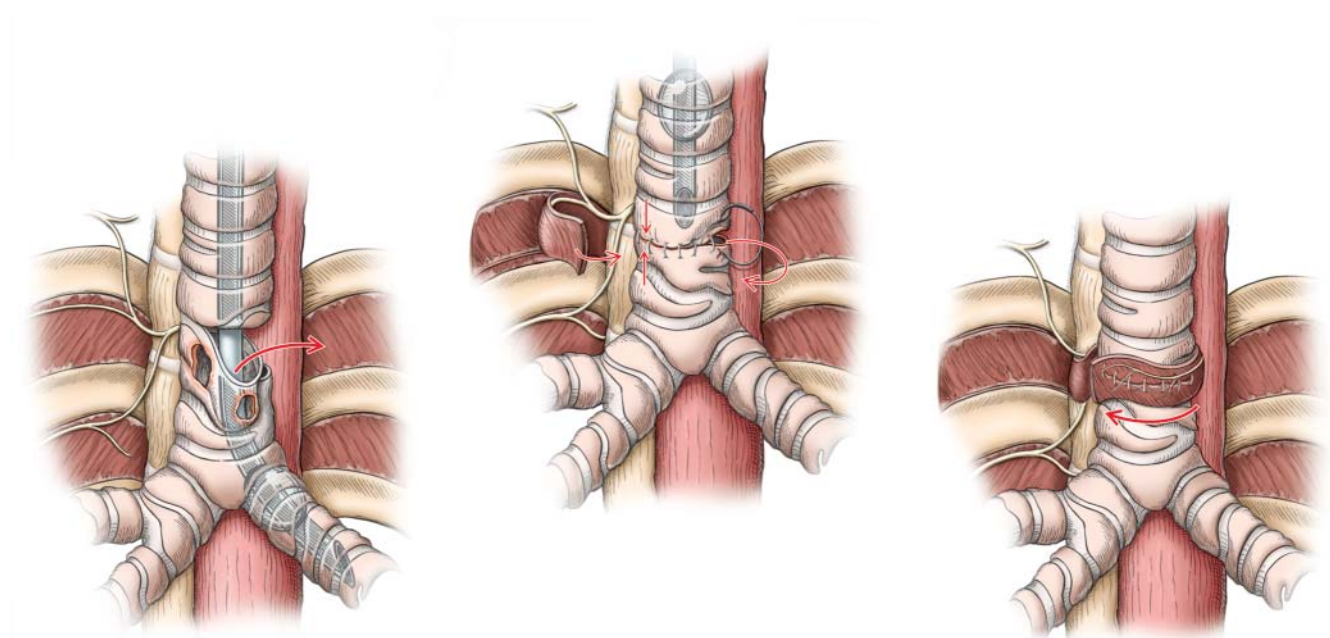


Figure 7 Tracheal injury may be repaired by means of segmental resection, with the suture line buttressed with an intercostal muscle flap.

SCORE Most esophageal injuries result from penetrating trauma. If surgical exploration is performed for all penetrating cervical wounds that violate the platysma, the esophagus is found to be injured approximately 12% of the time. Penetrating intrathoracic esophageal injuries are less common, however, occurring in about 0.7% of all penetrating chest wounds.⁵⁰ Blunt esophageal trauma is relatively uncommon, tending to occur just proximal to the esophagogastric junction on the left side, where the esophagus is less well protected.

SCORE Between 60 and 80% of esophageal injuries give rise to clinical signs or symptoms, the sensitivity and specificity of which depend on the location of the injury, the size of the perforation, the degree of contamination, the length of time elapsed after injury, and the presence of associated injury. Odynophagia, dysphagia, hematemesis, oropharyngeal blood, cervical crepitus, pain and tenderness in the neck or chest, resistance to passive motion, dyspnea, hoarseness, bleeding, cough, and stridor are commonly noted. Fever, subcutaneous emphysema, abdominal tenderness, and mediastinal crunching sounds (Hamman sign) may be observed. Pain is the most common presenting symptom (71% of patients), followed by fever (51%), dyspnea (24%), and crepitus (22%).⁵¹ Overall, the signs and symptoms associated with esophageal injury are fairly nonspecific, and a high index of suspicion must be maintained to make the diagnosis.

SCORE Evaluation of potential penetrating trauma to the esophagus is based on the trajectory and path of the missile. For penetrating injuries near the organ, it is necessary to prove that the esophagus is uninjured. Generally, this is done in one of two ways: (1) surgical exploration demonstrates a missile path inconsistent with esophageal injury or (2) direct examination of the esophagus reveals no injury. If neither option is feasible, proof is obtained through diagnostic testing. Plain x-rays, CT scans, and contrast esophagograms have all been used for this purpose, with varying sensitivity and specificity [see Table 2]. Endoscopy may add to the diagnosis, but the results depend on the operator's technique and experience, and there is a risk that it may exacerbate an esophageal tear or further injure an unstable cervical spine.

In an otherwise asymptomatic patient who is awake, alert, and able to cooperate, a simple contrast swallow is usually sufficient to exclude injury. Injuries resulting from low-velocity projectiles and stab wounds do not cause large tissue defects; for these injuries, barium gives superior anatomic detail and is the agent of choice. Injuries from large-caliber or high-velocity projectiles usually cause more damage; thus, the contrast agent tends to spread more widely throughout

the mediastinum during a diagnostic swallow. If contrast studies are indicated in this setting, a water-soluble agent may be used first. Such agents cause pulmonary damage when aspirated, however, and should not be used if tracheo-esophageal fistula is suspected.

For patients who are going to the OR for another reason (e.g., vascular repair or laparotomy), it may be most expedient to perform esophagoscopy simultaneously with the operation. If the entire esophagus is well visualized and no injury is identified, no further evaluation is required. If the study is suboptimal for any reason, or if the possibility of an injury persists, a contrast study should be done as soon as the patient's condition permits.

Regardless of the diagnostic studies obtained, evaluation must be carried out expeditiously. Significant delays in management can increase the incidence of esophageal injury-related morbidity by as much as a factor of two.⁵²

In cases of blunt trauma, determining when further study is needed is a vexing task. In general, whenever a patient has pneumomediastinum that is extensive or is associated with any of the symptoms of esophageal injury (e.g., odynophagia or blood in the esophagus), the esophagus should be evaluated. Simple pneumomediastinum rarely warrants evaluation of the esophagus. Chest CT may also be useful in delineating who needs further workup as it identifies patients with high risk of aerodigestive injury.⁵³ In the absence of suggestive signs, symptoms, and radiographic findings, pneumomediastinum associated with blunt trauma is much more likely to be from a distal small airway disruption or from a bronchial injury, the evaluation of which should take precedence over evaluation of the esophagus.

MANAGEMENT

Although injuries to the thoracic esophagus caused by external trauma are less common than those to the cervical esophagus, they are more likely to be fatal.⁵⁰ Trauma to the thoracic esophagus is almost exclusively caused by gunshot wounds; the location of the organ within the chest protects it from most stab wounds. Care of any associated injuries to surrounding structures (e.g., major airways and blood vessels) takes precedence in the management scheme; thus, by necessity, diagnosis and definitive therapy of intrathoracic esophageal injuries are often delayed. Guidelines have been formulated for the evaluation of transmediastinal penetrating wounds [see Figure 8].

SCORE Injuries to the distal third of the thoracic esophagus are most easily approached via the left chest. More proximal injuries are best approached through the right chest or via a combination of chest and cervical incisions. The incision should be made so as to facilitate subsequent buttressing of the repair (e.g., with a pedicle from an intercostal muscle or the latissimus dorsi).

Surgical repair entails local débridement, wide drainage, primary repair of the perforation, and buttressing of the repair with a viable muscle flap. Primary repair can usually be accomplished when the perforation is operated on within 24 hours of occurrence. Many investigators recommend two-layer repair of esophageal injuries; however, a secure single-layer repair performed with a continuous absorbable monofilament suture (e.g., 3-0 polydioxanone) allows excellent visualization of each bite and good mucosa-to-mucosa

Table 2 Diagnostic Measures for Evaluating Suspected Esophageal Injuries

Diagnostic Measure	Sensitivity (%)	Specificity (%)	Accuracy (%)
Assessment of clinical signs and symptoms	80	64	72
Contrast esophagography	80–100	94–100	90–95
Rigid esophagoscopy	67–100	89–95	86–94
Flexible esophagoscopy	67–100	67–100	82–97

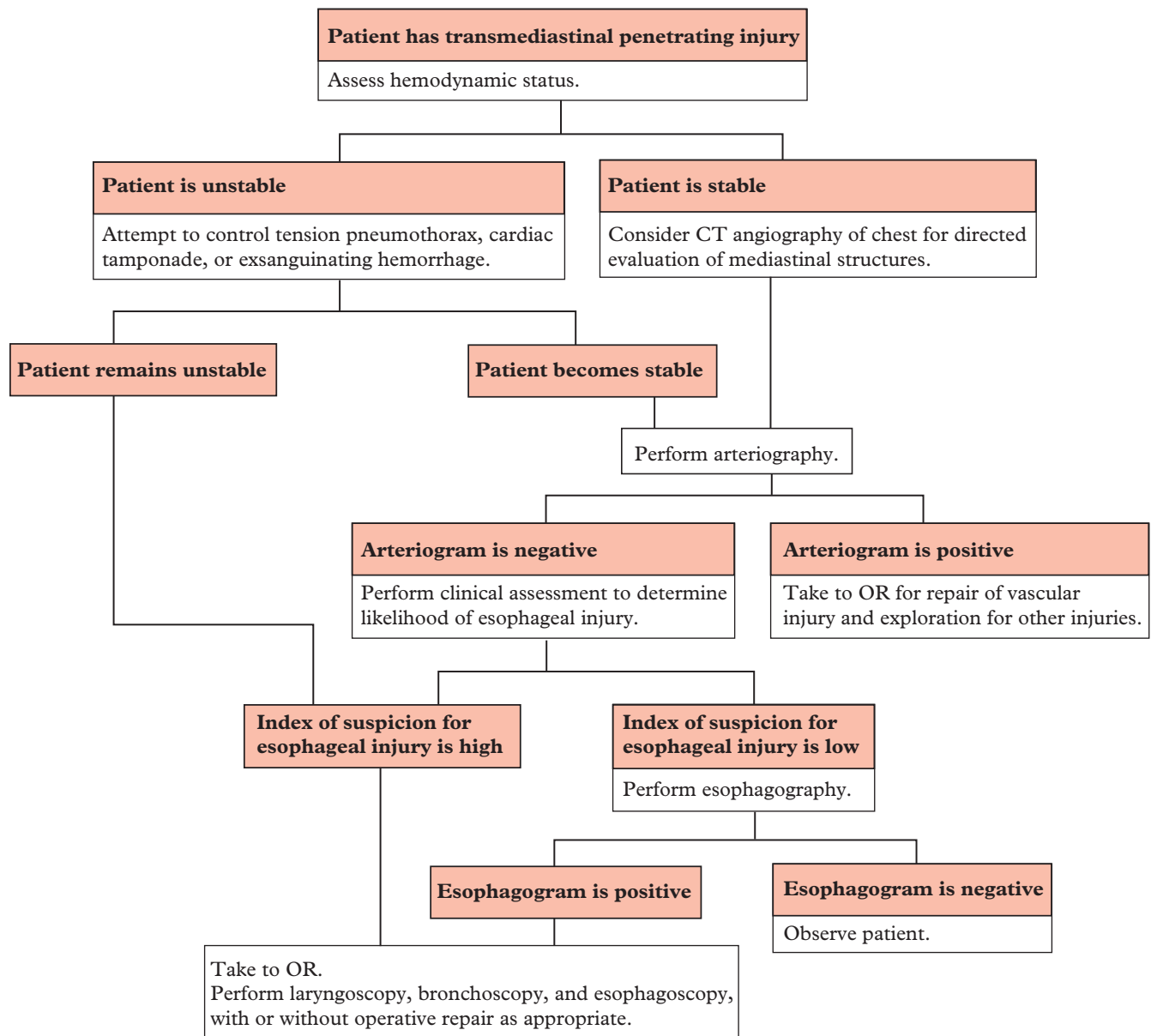


Figure 8 Algorithm illustrating approach to management of transmediastinal penetrating injury. CT = computed tomographic; OR = operating room.

approximation. A number of different tissue flaps—free pericardium, pleura, intercostal muscle, diaphragm, rhomboid muscle, lung, and gastric fundus (as in a Thal patch)—have all been used, with varying success. Placement of a gastrostomy tube for gastric drainage and jejunal feeding tube for enteral feeding access should be considered in all of these patients.

Depending on the interval before exploration, the severity of the injury, the degree of contamination, and the extent of the local inflammatory response, primary repair may not be feasible, although an attempt at primary repair with autologous tissue coverage is recommended. If this is the case, several techniques may be employed, including esophageal diversion, total esophageal exclusion, esophagectomy, and T tube drainage. Most of the experience with these delayed repairs has been acquired in patients who have perforations

caused by instrumentation or by iatrogenic esophageal rupture, neither of which is entirely analogous to the injuries seen with external trauma.

In the absence of distal obstruction, almost all late-presenting esophageal perforations heal after primary repair and tissue flap coverage. Generally speaking, techniques such as esophageal exclusion, diversion, and resection should be needed only when perforation occurs in the setting of a primary esophageal pathologic condition (e.g., cancer); esophageal perforation in this setting is rarely managed by trauma surgeons.

Complications

Complications seen after esophageal repair include esophageal leakage and fistula, wound infection, mediastinitis, empyema, sepsis, and pneumonia. Long-term complications

(e.g., esophageal stricture) also occur, but they are more common after iatrogenic perforation of an already diseased esophagus.

Esophageal anastomotic leakage is the most common complication associated with repair of perforations, occurring in 10 to 28% of repairs.⁵⁴ The causes are primarily technical and include inadequate débridement, devascularization, closure under tension, and the presence of associated infection. As many as 50% of these leaks are asymptomatic; in this setting, they are usually associated with prompt flow of oral contrast back into the esophageal or gastric lumen. Continued abstinence from oral intake, supplemental nutrition, and antibiotic therapy usually suffice for successful treatment.

In patients who have sepsis and esophageal leakage after repair of an esophageal perforation caused by external trauma, treatment should focus on wide local drainage and creation of a controlled fistula, which is usually best accomplished by resecting a segment of a rib posteriorly at the level of the perforation and then packing the wound open. Because there is usually no underlying esophageal or gastric pathologic condition and no forceful distribution of mediastinal contamination, these fistulas generally heal well without resection, diversion, or replacement of the esophagus.

Thoracic Duct Injuries

Chylothorax after blunt or penetrating chest trauma is rare; only case reports and small case series are found in the literature. Much of the management of this condition is extrapolated from management of iatrogenic thoracic duct injuries, which are much more common. Most patients with traumatic chylothorax show evidence of other axial injuries to the chest, especially spine fractures.⁵⁵ The diagnosis is made by finding chylomicrons and high levels of triglycerides in a typically large pleural effusion of milky appearance. Drainage of as much as 1,000 mL/day is not unusual and results in severe nutritional and immunologic derangements, which are the main causes of the high mortality associated with this condition.

MANAGEMENT

Treatment usually begins with limiting oral intake of short- and long-chain triglycerides, which cause increased flow of chyle. Diets high in medium-chain triglycerides must often be given enterally because they are not palatable. Some clinicians recommend instituting total parenteral nutrition with complete abstinence from oral intake. Administration of octreotide may also help decrease chyle production.⁵⁶ These modalities, in conjunction with adequate pleural drainage and lung expansion, are successful in approximately 50% of cases after 2 to 6 weeks.

Operative strategies for managing thoracic duct injuries are generally undertaken only after conservative measures fail. Preoperatively, patients are fed cream, with or without dyes such as Sudan black, to increase chyle flow and enhance visualization of the site of injury. The thoracic duct is then ligated above and below the injury; this may be performed by means of VATS on the hemithorax ipsilateral to the effusion.⁵⁷ Fibrin glue and talc pleurodesis may be used as adjuncts to ligation. Because there are usually multiple areas

of injury and because the thoracic duct is friable by nature, surgical treatment is not always successful. Continued nutritional management and reoperation may be required.

Cardiac Injuries

The incidence of cardiac trauma continues to rise as a consequence of growing urban violence, improved detection of cardiac injuries, and an increase in the percentage of patients with such injuries who arrive at trauma centers alive. Improved prehospital transport, along with the continuing evolution of diagnostic, surgical, and anesthetic techniques, has contributed to an increase in overall survival in this population. Although the overall mortality associated with cardiac trauma remains high, survival rates of 50 to 95% are not uncommon in patients who arrive at the hospital with vital signs.^{58–60}

PENETRATING

Patients with penetrating cardiac injuries generally present in one of three ways. In approximately 20% of patients, the injury is clinically silent, at least initially, and is subsequently diagnosed at operation or on diagnostic imaging. In approximately 50%, there is evidence of pericardial tamponade, including one or more of the signs in the Beck triad (hypotension, distended neck veins, and muffled heart sounds). In the remaining patients, hemorrhagic shock develops after free bleeding from an atrial or ventricular wound into one or both hemithoraces.

Diagnosis of penetrating injuries to the heart often requires a high index of suspicion. The locations of entrance and exit wounds, the trajectory and path of the wounding object, and the locations of any retained missiles on radiographs are helpful in predicting heart injuries. Proximity wounds to the heart are defined as those that penetrate the chest wall in the area bounded superiorly by the clavicles, laterally by the midclavicular lines, and inferiorly by the costal margins. Any crossing of the anterior mediastinum by a missile or an instrument is also considered a proximity wound. Because cardiac injuries are present in 15 to 20% of patients who present with proximity wounds, these injuries must be definitively excluded.

Physical examination is often unreliable in detecting pericardial tamponade. It is rare for all three signs in the Beck triad to be found; in fact, only about half of patients with tamponade show even two of the three. Moreover, detection of muffled heart sounds and distended neck veins amid the commotion typical of the trauma bay can be extremely difficult, especially when (as is often the case) the patient is agitated or intoxicated. Accordingly, whenever tamponade is suspected, additional diagnostic modalities should be employed.

As more surgeons become familiar with the use of ultrasonography in the trauma setting, two-dimensional surface echocardiography is gaining acceptance as a means of diagnosing cardiac injuries. When performed by appropriately trained surgeons, this modality detects blood within the pericardial sac with a sensitivity of 96 to 100% and a specificity of 100%—results essentially equivalent to those achieved with a pericardial window.⁶¹ However, the sensitivity of echocardiography for detecting cardiac injuries is diminished in

the presence of a hemothorax; thus, when clinic suspicion of a cardiac injury is present in conjunction with a hemothorax in a stable patient, alternative diagnostic modalities should be considered (pericardial window). When the requisite equipment is readily available, this test can be performed in approximately 2 minutes. It is of vital importance that the trauma surgeon who is attending to the patient performs and interprets the test: the results will be available sooner, the clinical correlation will be more accurate, and the information obtained will be more rapidly applied to treatment decisions. The main limitations of two-dimensional surface echocardiography are the high cost of the equipment and the specialized training required.

Although cardiac ultrasonography has many advantages, the subxiphoid pericardial window remains the gold standard for diagnosis of cardiac injury. For otherwise stable patients with proximity wounds or suggestive signs and symptoms, a pericardial window should be considered when ultrasonographic findings are equivocal or when ultrasonography is unavailable. This procedure is usually performed in the OR with the patient under general anesthesia, often in combination with abdominal exploration.

A subxiphoid pericardial window is performed through a 10 cm vertical midline incision that is made over the xiphoid, slightly favoring the epigastrium. The xiphoid is grasped with a clamp and dissected away from the abdominal fascia and the diaphragmatic fibers, and the substernal plane is accessed. As the inferior portion of the sternum is being elevated, the prepericardial adipose tissue is dissected to provide exposure of the acute margin of the pericardium. The pericardium is then retracted inferiorly into the wound and incised sharply. The presence of blood or clot within the pericardial sac indicates a positive result, necessitating immediate repair of the injury. A pericardial window can also be accomplished during thoracoscopy of the left hemithorax, and examination of the pericardium can be performed, although less reliably, during laparoscopy via a transdiaphragmatic view.

Some authorities advocate using pericardiocentesis to detect cardiac injuries, especially where rapid access to the OR, trauma surgeons, and anesthesiologists is not available. Drawbacks to this approach include the high rate of false positives and false negatives and the potential for iatrogenic cardiac injuries. Furthermore, pericardiocentesis is of limited use in treating tamponade because blood within the pericardial sac often is clotted and is not amenable to removal through a needle.

Management

Treatment of penetrating cardiac wounds depends on the urgency of the presentation. In patients who are in shock from suspected cardiac injuries, the distinction between the two most likely causes, pericardial tamponade and free hemorrhage, is important. If the patient exhibits distended neck veins and the characteristic plethoric, dusky facial expression, chest tubes should immediately be placed bilaterally. If shock does not then resolve, the diagnosis of tamponade should be made and a pericardial window performed, either in the ED with local or no anesthesia or in the OR as described (see above). If there is a suspicion of free hemorrhage into one or both hemithoraces, which can usually be detected by means of physical examination and chest x-ray, the patient should

be transported to the OR for definitive treatment. In patients who are in extremis from either causative condition or who go into cardiac arrest in the ED, an emergency left anterior thoracotomy should be performed.

In planning the surgical approach to the repair of cardiac injuries, the location of the entrance and exit wounds, the path of the wounding object, the type of wound created, the associated signs and symptoms, and the level of suspicion for other thoracic visceral injuries are important considerations. A median sternotomy is a logical extension of a subxiphoid pericardial window and provides access to all four chambers of the heart. It is appropriate for most precordial stab wounds and some low-caliber gunshot wounds. Its main limitations are that it does not allow repair or cross-clamping of the descending aorta or examination or repair of the esophagus and bronchi and that it provides limited exposure of the lower lobes of the lungs and the hemidiaphragms. A left thoracotomy is appropriate for patients who may require cross-clamping of the thoracic aorta and for those with suspected cardiac injuries in conjunction with other complex thoracic visceral injuries. Only occasionally is a right thoracotomy required; this incision generally does not provide adequate exposure of the heart.

Atrial wounds are generally amenable to early control by finger pressure or by exclusion with a vascular clamp and simple oversewing. Right or left ventricular free wall injuries away from the coronary arteries may be treated by applying digital pressure over the entrance wound for hemostasis and then placing horizontal mattress sutures under the wound, reinforced with an epicardial continuous suture along the site of injury. All left ventricular wounds should be repaired with felt-pledgeted or pericardial-pledgeted sutures. Many right ventricular stab wounds can be closed primarily without pledgets if the sutures are tied accurately.

Injuries near coronary arteries must be closed without the coronary artery being incorporated within the suture. This can be accomplished by placing horizontal mattress sutures lateral and deep to the coronary artery across the cardiac laceration. If the sutures are tied with careful attention to the function of the myocardium distal to the injury and equally careful attention to the ECG, the laceration can be closed without coronary artery occlusion and subsequent ischemia.

An alternative method of repair of cardiac lacerations employs a skin stapler, which is effective in controlling hemorrhage from stab injuries and low-velocity gunshot wounds.⁶² The stapler can be used on all chambers of the heart, and in some instances, staple repair can be quicker than suture repair.

With all penetrating cardiac wounds, it is important to recognize the possibility of associated intracardiac injuries. The surgeon should palpate the heart along the pulmonary outflow tract for a thrill that would indicate a traumatic ventricular septal defect. This diagnosis can be confirmed by performing co-oximetry on a sample of blood aspirated from the pulmonary artery and the right atrium and demonstrating a step-up. Digital palpation through atrial wounds should be routinely employed to identify atrioventricular valvular insufficiency or, occasionally, an atrial septal defect. Intraoperative surface echocardiography and transesophageal echocardiography are also excellent at diagnosing intracardiac injuries, but they are not readily available in the urgent trauma setting.



Postoperatively, all patients with cardiac wounds should receive a thorough cardiovascular examination aimed at detecting murmurs or evidence of cardiac failure and should undergo echocardiography if either of these is detected. Repair of intracardiac lesions usually can wait until the patient's condition is stable and cardiac catheterization has been performed, although some patients experience such profound heart failure that immediate operative repair, with cardiopulmonary bypass, must be performed.

BLUNT



Blunt cardiac injuries range from disruption of myocardium, septa, or valvular structures to cardiac contusion. Both cardiac disruption (also known as cardiorrhexia) and cardiac contusion are common; the former is seen most often in patients who die at the scene and the latter in those who survive to reach the hospital.

Blunt cardiac injury typically involves a direct blow to the chest, usually sustained in a motor vehicle collision or a fall. Cardiac injuries generally are associated with sternal or rib fractures, although they may occur in the absence of any chest wall fracture; however, sternal fractures do not predict the presence of blunt cardiac injury. The most common location of blunt cardiac injury is the anterior heart, which consists primarily of the right ventricle. A blow that causes the sternum to exert a direct impact on the myocardium may result in direct injury to myocardial cells, sometimes leading to cell death, mechanical dysfunction, or dysrhythmias.

The diagnosis of myocardial contusion is elusive. Many tests have been proposed, but none have proved definitive, except for direct visualization of the heart at surgery or autopsy. For practical purposes, the clinically significant sequelae of myocardial contusion are myocardial dysrhythmias and pump failure. Both of these sequelae must be treated, regardless of whether the diagnosis of blunt cardiac injury can be made. Guidelines have been proposed that may facilitate the workup of this condition.⁶³



As an initial test, a 12-lead ECG should be obtained whenever blunt cardiac injury is suspected. If the ECG is normal, no further workup is required. If there is an ECG abnormality that does not necessitate treatment (e.g., non-specific ST-T wave changes), the patient should undergo monitored observation for 12 hours and then be discharged if there are no dysrhythmias and the ECG is normal at that time. If there is a more serious ECG abnormality (e.g., dysrhythmia, ST-segment elevation, or heart block), the patient should undergo observation for at least 24 to 48 hours and may require further testing and treatment, depending on the sequelae of the abnormality. In patients with hemodynamic instability and suspected blunt cardiac injury, echocardiography should be performed promptly. There is no role for cardiac enzyme analysis or cardiac troponin assay in this setting. The latter test may detect myocardial injury, but this information does not complement ECG and echocardiographic findings and has no clinical utility. Similarly, there is no role for nuclear medicine studies.

Management



Pump failure associated with cardiac contusion is usually the result of right heart failure, in that most hemodynamically significant cardiac contusions are caused by injury to the

anterior right ventricular free wall. Treatment of right heart failure from cardiac contusion consists of inotropic support and reduction of right ventricular afterload. Dysrhythmias secondary to cardiac contusion are treated in the same manner as dysrhythmias of any other etiology.

The commonly repeated adage that cardiac contusion should be treated similarly to MI is incorrect. Therapy for MI is based on the premises that the patient is likely to have concomitant coronary artery disease and that increased myocardial oxygen demand may result in extension of the evolving infarct or the creation of an additional infarct. However, most young trauma patients have normal coronary arteries, and increased myocardial oxygen demand is unlikely to extend cardiac contusion unless the heart sustains an additional blow. Generally, the goal in resuscitation of injured patients is to increase systemic oxygen delivery, which may increase cardiac work. In addition, unlike patients with MI, patients with myocardial contusion appear not to be at increased risk for cardiac complications from general anesthesia and surgery.

In the rare patient with cardiorrhexia who presents to the hospital with signs of life, the most common injury is right atrial perforation. Other lesions seen in patients with vital signs, in order of decreasing incidence, are left atrial perforation, right ventricular perforation, atrial septal perforation, ventricular septal perforation, coronary artery thrombosis, and valvular insufficiency (most commonly involving the tricuspid and mitral valves).^{58–60} Patients with cardiac rupture generally present with signs of pericardial tamponade and require rapid decompression. Placement of an intra-aortic balloon pump is often an effective temporizing measure while preparations are made for definitive repair.

Patients with blunt cardiac trauma who lose vital signs in the field or who go into cardiac arrest before arrival at the hospital generally should not be subjected to ED thoracotomy, because virtually none of these patients can be saved. Patients admitted with vital signs after suffering blunt cardiac rupture, however, have about a 50% chance of survival, and much of the mortality in these patients is attributable to associated injuries.

Blunt Aortic Injuries

Traumatic rupture of the aorta may account for as many as 10 to 15% of all traffic fatalities, and the majority of such injuries are fatal at the scene. Of those who survive the initial injury, 50% die in the first 24 hours and 90% die within the first month if the aorta is not repaired. Traumatic disruption of the thoracic aorta results from rapid deceleration and is produced by a shearing effect caused by differences in the mobility of the aorta above and below a point where the vessel is fixed. Most thoracic aortic disruptions in survivors occur at the aortic isthmus just distal to the origin of the left subclavian artery, where the aorta is fixed to a significant degree by the ligamentum arteriosum. Autopsy series reveal that as many as 40% of aortic injuries in nonsurvivors are not located at the isthmus, and the injuries tend to be complex.⁶⁴

Suspicion of an aortic injury is most often triggered by abnormal findings on a chest x-ray in a patient with a high-speed mechanism of injury and multiple other injuries. Most patients show no signs or symptoms on physical examination,



but some complain of interscapular pain or hoarseness, and some exhibit a difference in blood pressure or pulse fullness between the upper and lower extremities or between the right and left upper extremities. Accordingly, the diagnosis is usually made radiographically, often beginning with the recognition of mediastinal hemorrhage on a screening chest x-ray.

Numerous radiographic signs of a torn thoracic aorta have been described, all of which are manifestations of hemorrhage within the mediastinum that alters or obliterates the shadows seen on a normal chest radiograph. Mediastinal widening is the most frequent indicator of mediastinal hematoma from a torn thoracic aorta. Other important signs are obscuration of the detail of the contour of the aortic knob, opacification of the aortopulmonary window, depression of the left mainstem bronchus, apical cap, deviation of the nasogastric tube, and displacement of the esophagus to the right. These signs may be present in any combination or may be entirely absent.

Currently, high-speed CT with IV contrast is being liberally used for diagnosis of thoracic vascular injuries. Appropriately, this modality is employed in virtually all patients with abnormal chest x-rays and in many patients with normal x-rays whose injury mechanisms include a high degree of energy transfer. CT findings that are diagnostic of aortic injury include mediastinal hematoma, periaortic hematoma, intraluminal irregularity (intimal flap), acute coarctation, and abnormal aortic contour [see Figure 9]. Depending on the experience of the interpreting clinician, aortography may be eliminated in most of these patients before surgical repair; the sensitivity and specificity of CT in this setting approach 100%.^{21,65,66} Aortography should continue to be used for equivocal cases or cases in which spiral CT is not available.

MANAGEMENT

Essentially all aortic injuries associated with mediastinal hematomas should be repaired. The timing of repair, however, is less urgent than the timing of certain associated maneuvers that must be done, such as attainment of an adequate airway, control of external or cavitory hemorrhage, and evacuation of intracranial mass lesions. In general, if there is active bleeding from a blunt aortic injury, it will be massive; lesser amounts of bleeding from a chest tube often derive

from associated injuries. If intra-abdominal bleeding is present, laparotomy is indicated before repair of the torn thoracic aorta and before aortography. Similarly, in patients with intracranial hemorrhage that necessitates operative evacuation, craniotomy should take precedence over repair of the torn thoracic aorta.

While one is temporizing, stringent efforts must be made to prevent hypertension and reduce shear forces across the injury, ideally by means of IV beta blockade. Esmolol, because of its short half-life, is the best agent to use in these patients, who are at risk for sudden hypovolemic episodes of hypotension. The goals of medical therapy are a heart rate lower than 100 beats/min and a systolic blood pressure of approximately 100 mm Hg (in young and middle-aged patients) or 110 to 120 mm Hg (in elderly patients).²¹ Nitroprusside may have to be given to achieve these goals, but it should not be used until after adequate beta blockade is achieved, because it can increase intravascular shear forces when used alone. During pharmacologic treatment of aortic injuries, pulmonary arterial catheter monitoring is essential to prevent deleterious reductions in cardiac output and mixed venous oxygen saturation. With careful delayed operative management of aortic injuries, the risk of rupture is low but is not completely eliminated.^{21,67}

Traditional repair techniques include exposure of the aorta and arch through a left thoracotomy and direct repair or interposition graft placement. Although excellent results have been obtained with so-called clamp-and-sew techniques, most guidelines recommend use of some form of distal aortic perfusion (e.g., left atrial–distal aortic bypass or partial cardiopulmonary bypass with femoral cannulation). Systemic heparinization is required for cardiopulmonary bypass and has been shown to be safe with respect to hemorrhagic complications.^{68,69} The aortic arch is clamped between the common carotid and left subclavian arteries after these vessels and the distal aorta have been controlled. An interposition graft is required for most of these injuries, although 15 to 20% can be treated with suture repair alone. With distal aortic perfusion, the risk of paraplegia is approximately 5% and is independent of clamp time; without distal aortic perfusion, ischemic times longer than 30 minutes are associated with an exponential rise in the incidence of spinal cord injury.

Another potential advantage to using cardiopulmonary bypass is the ability to institute deep hypothermic circulatory arrest if needed. This technique involves cooling to a core temperature lower than 20°C (68°F) to induce cardiac standstill, turning off the pump, and operating on the unclamped aorta in a relatively dry field. Circulatory arrest can be safely maintained in this setting for approximately 30 to 45 minutes. This technique may be useful for patients who have previously undergone thoracic aortic surgery or who have complex tears involving the arch.

An evolving modality for the treatment of aortic injury is endovascular stent grafting. The rationale for the insertion of a stent graft in this population is that the aorta above and below the injury is usually normal, which is not the case in the atherosclerotic population. Toward this end, several reported series have described the use of this technique in both early and delayed settings.^{70–72} The results of these studies are very promising, demonstrating equivalent results when

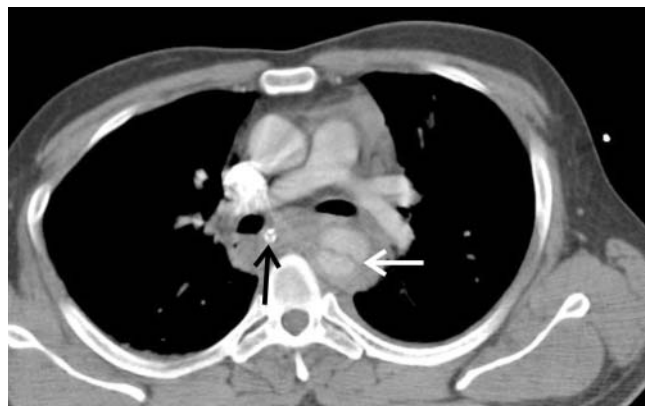


Figure 9 Shown is an injury to the descending thoracic aorta (white arrow). A nasogastric tube can be seen in the esophagus, which is deviated to the right (black arrow).

compared with surgical repair, and are superior to those obtained with endovascular repair of aortic aneurysms and dissections.⁷³ However, caution must be used when interpreting these results as these are single-institution, primarily retrospective studies rather than randomized controlled trials, and long-term outcomes, including the incidence of late stent migration, erosion, thrombosis, and infection, are unknown. Furthermore, there are limitations with the current level of stent graft technology; however, this field is advancing rapidly to overcome these deficiencies, and reports on newer devices are encouraging.⁷⁴ Although endovascular stenting may eventually prove to be a durable and excellent long-term therapy in the treatment of traumatic aortic disruption, currently, its application should be reserved for those patients enrolled in a prospective trial, or who are a poor operative risk, or who refuse conventional surgery.

Great Vessel Injuries

Except for tears in the descending aorta, injuries to the thoracic great vessels, by any mechanism, are rarely seen in clinical practice; the best descriptions come from wartime and autopsy series. Indeed, postmortem studies reveal that patients with nonisthmus aortic and great vessel injuries rarely reach the hospital alive.⁷⁵ As many as 14% of patients have multiple great vessel injuries. Diagnosis and management of these injuries cover a wide spectrum of possibilities, depending on the mechanism of injury, presenting features, and associated injuries.

PENETRATING

Penetrating thoracic great vessel injuries are usually obvious. The presence of an entrance wound at the base of the neck or in the chest should alert the clinician to this possibility. If the patient is in shock, urgent operation is required. If the patient's condition stabilizes with resuscitation, an arteriogram should be performed to localize the injury.

Management

Exposure is most often obtained via a median sternotomy, with or without neck extension as needed for innominate, right subclavian, or carotid arterial injuries [see Table 1]. Exposure of the left subclavian artery can be more difficult, even through a sternotomy with a trap-door extension. For isolated injuries to the proximal subclavian artery, a fourth-interspace left posterolateral thoracotomy is most useful. For injuries to the middle and distal thirds, supraclavicular incisions or deltopectoral incisions—or, occasionally, a combination thereof—are appropriate, provided that inflow control can be achieved. When inflow control may not be achievable, as in cases involving injury at the thoracic outlet or the presence of a large hematoma, endovascular control of the proximal subclavian artery by means of a balloon catheter placed percutaneously through the femoral artery may be necessary. Moreover, a growing body of literature supports endovascular management of great vessel injuries.^{76–80} Endovascular repair may be considered in stable patients with arteriovenous fistula or pseudoaneurysm. As with endovascular repair of blunt aortic injuries, concerns with this modality primarily center on the lack of long-term outcomes in a typically young patient population.

Most penetrating wounds of the middle and distal segments of the great vessels are amenable to lateral repair or end-to-end anastomosis; injuries involving greater tissue destruction, for which grafts might be indicated, usually prove fatal before the patient arrives at the hospital. The subclavian artery is a notable exception to this general rule because the lack of elastic fibers in its tunica media makes it extremely friable. End-to-end anastomosis of an injured subclavian artery under any tension is doomed to failure. Accordingly, many subclavian injuries should be repaired with an interposition graft. Proximal injuries to the great vessels are best repaired by exclusion and bypass grafting with prosthetic material from the ascending aorta. Because bleeding is usually active, there is rarely enough time to arrange for cardiopulmonary bypass. In any case, cardiopulmonary bypass generally is not needed, except for rare cases of associated ascending or aortic arch injury.

BLUNT

Blunt injuries of the great vessels are typically the result of high speed and rapid deceleration. In postmortem examinations, pedestrians struck by motor vehicles have the highest rate of great vessel injuries. Patients with such injuries are rarely seen in the ED with signs of life.⁷⁶ Superior mediastinal hematoma is the most common finding during workup; its presence is an indication for further imaging with spiral CT or angiography. Besides vessel laceration with hematoma, presentations of blunt thoracic great vessel injury include dissection and thrombosis, which may be asymptomatic if localized to the proximal segments. Central neurologic injury may also be present, especially with carotid dissection. Associated stretch injury of the brachial plexus or the cervical nerve roots is common with subclavian artery injuries.

Management

Once the diagnosis is made, all great vessel injuries require intervention, typically surgical therapy; however, as mentioned above, an increasing number of reports describe successful endovascular treatment of these injuries in select patients. The exceptions to this are small intimal defects that are found incidentally as these typically require observation with repeat imaging and antiplatelet therapy. Surgery is contraindicated if neurologic injury is present, the injury is deemed unsurvivable, or a common carotid dissection has extended into the distal internal carotid artery. As with blunt aortic injuries, the timing of surgery should be tailored to the treatment priorities mandated by the associated injuries. When time permits, proximal lesions are best managed with cardiopulmonary bypass and hypothermic circulatory arrest. Arranging for these techniques is mandatory with injuries involving the ascending aorta and the arch.

Mediastinal blood seen on a chest CT scan probably more often derives from mediastinal venous injuries than from arterial injuries. These isolated venous injuries need not be repaired unless they are associated with cardiac tamponade or massive hemorrhage into a pleural space, both of which are uncommon. An exception is injury to the intrapericardial venae cavae, which is usually associated with tamponade. These injuries are caused by tearing of the mobile heart against the relatively fixed veins, particularly the inferior vena cava. In most cases, they can be repaired primarily.

Associated venous injuries are commonly encountered during exploration for great vessel arterial injury. If possible, they should be treated with lateral repair or patch venorrhaphy with pericardium or saphenous vein. However, ligation of these veins sometimes proves necessary and is generally well tolerated.

Conclusion

Thoracic trauma is a contributing factor in a majority of trauma-related deaths. With thorough physical examination and appropriate radiographic evaluation, the majority of these

injuries can be identified early and appropriate therapy can be initiated. Most thoracic injuries do not require operative intervention; rather, they may be treated with simple, lifesaving bedside procedures. However, when considering surgical intervention, many variables must be considered in this decision process, and each injury has unique issues to be addressed. Once the need for intervention is apparent, the critical decision for an appropriate surgical approach is based on a complete understanding of the location and nature of the injury.

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Acknowledgments

Figures 1 and 7 Alice Y. Chen
Figure 4 Tom Moore

6 OPERATIVE EXPOSURE OF ABDOMINAL INJURIES AND CLOSURE OF THE ABDOMEN

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Over the past two decades, the advent of nonoperative management techniques for many solid-organ injuries has led to a significant shift in the care of patients who have sustained abdominal trauma. The ever-improving accuracy of diagnostic modalities (computed tomography in particular) has also contributed to this shift.¹⁻⁴ Today, fewer patients require operative intervention for treatment of abdominal injuries. Those who do require such intervention make up a select group who continue to pose a significant challenge to surgeons. In our view, these patients are best managed by following a standardized operative approach, the aim of which is to diagnose, prioritize, and treat the injuries in an expeditious fashion so that the patient is not kept in the operating room any longer than necessary [see Figure 1]. Such an approach optimizes patient care by minimizing the risk of missed injuries and ensuring a rapid and efficient response by the members of the surgical team. Naturally, every patient’s care should be individualized as necessary. In general, however, a standardized operative approach, complemented by a solid knowledge of a variety of exposures and techniques, should allow the surgeon to deal with virtually any abdominal injury. In this chapter, we outline our recommended approach to operative intervention in patients with abdominal trauma.

Patient Preparation

The key to success in this setting is advance preparation aimed at covering all eventualities. Such preparation involves both the environment and the patient. The room should be warmed to ensure that the patient does not lose too much heat and become hypothermic. The instruments should be open on the back table, and specific instruments should be available when specific injuries are anticipated (e.g., a vascular set should be available when a vascular injury is suspected). A sufficient number of laparotomy pads should be on hand, and a retracting device with which the surgical team is familiar should be employed. Cell saver systems and rapid infusion systems can be useful adjuncts; if desired and available, they should be requested in advance.⁵

Patient preparation begins with the insertion of a nasogastric or orogastric tube and a Foley catheter. Invasive monitoring lines may have to be placed, and resuscitation should continue as the patient is being prepared. A broad-spectrum antibiotic should be administered intravenously before the initial incision is made. When the patient is correctly positioned on the operating table, skin preparation should extend from the sternal notch superiorly to include the anterior thorax. Thus, no further preparation will be required if a thoracic injury is identified or vascular control in the thorax is necessary. Thoracostomy, if required, can also be performed without the drapes being changed. Inferiorly, skin preparation should extend to the upper anterior thighs so that the proximal saphenous veins are available if a vascular reconstruction is required and so that distal vascular control can be achieved without undue delay.

All areas of the body that are not included in the skin preparation should be covered so as to prevent excessive heat loss, and warming devices should be placed if available. Sterile draping should be placed so as to allow access to all potential injuries. If the patient is in extremis and in danger of expiring, however, patient preparation should be limited to a rapid skin cleansing and surgery should commence immediately.

Incision and Initial Exploration

CHOICE OF INCISION

A midline celiotomy is the incision of choice. Its advantages are that it allows rapid and easy access to the abdominal cavity, with good exposure of the majority of the intra-abdominal organs and structures, and that it can be extended into a median sternotomy if necessary. Its main disadvantage is that it may not provide adequate exposure of injuries in the deep recesses of the upper quadrants.

Patients with previous midline incisions pose a challenge to the surgeon. If at all possible, an attempt should be made to enter the abdomen above or below the previous incision, in an area less likely to have adhesions. If this is not possible, an alternative incision, such as a chevron (bilateral subcostal) incision, should be considered. A chevron incision provides entry into the abdomen while avoiding any viscera that are adherent to the undersurface of the previous laparotomy scar. However, this incision takes more time, does not provide ideal exposure, and is associated with a higher morbidity; accordingly, it should be considered only when the circumstances are dire. Paramedian, subcostal, retroperitoneal, and flank incisions are not recommended, for much the same reasons.

INITIAL EXPLORATION

Once the peritoneal cavity has been entered, initial exploration proceeds in an orderly fashion so as to minimize hemorrhage and contamination, prevent iatrogenic injury, and facilitate the expeditious identification of injuries. The intestines are eviscerated, and gross blood is rapidly evacuated. Laparotomy pads are then rapidly placed in all four quadrants to pack the abdomen; the right upper quadrant is packed first, then the left upper quadrant, and finally the lower two quadrants. Care should be taken not to tear the falciform ligament or the fibrous capsule of the liver during this maneuver. Blood pressure may drop when the abdomen is decompressed. Anesthesia should be given the opportunity to catch up with resuscitation efforts at this point.

Once hemodynamic stability has been achieved, the intraperitoneal portion of the exploration is begun. In cases of blunt trauma, the temporary packs (except for those around the solid viscera) may now be carefully removed and any remaining blood evacuated. In cases of penetrating trauma, it is often easier initially to address the site of ongoing hemorrhage via a direct approach. Vascular injuries are controlled manually until proximal and distal

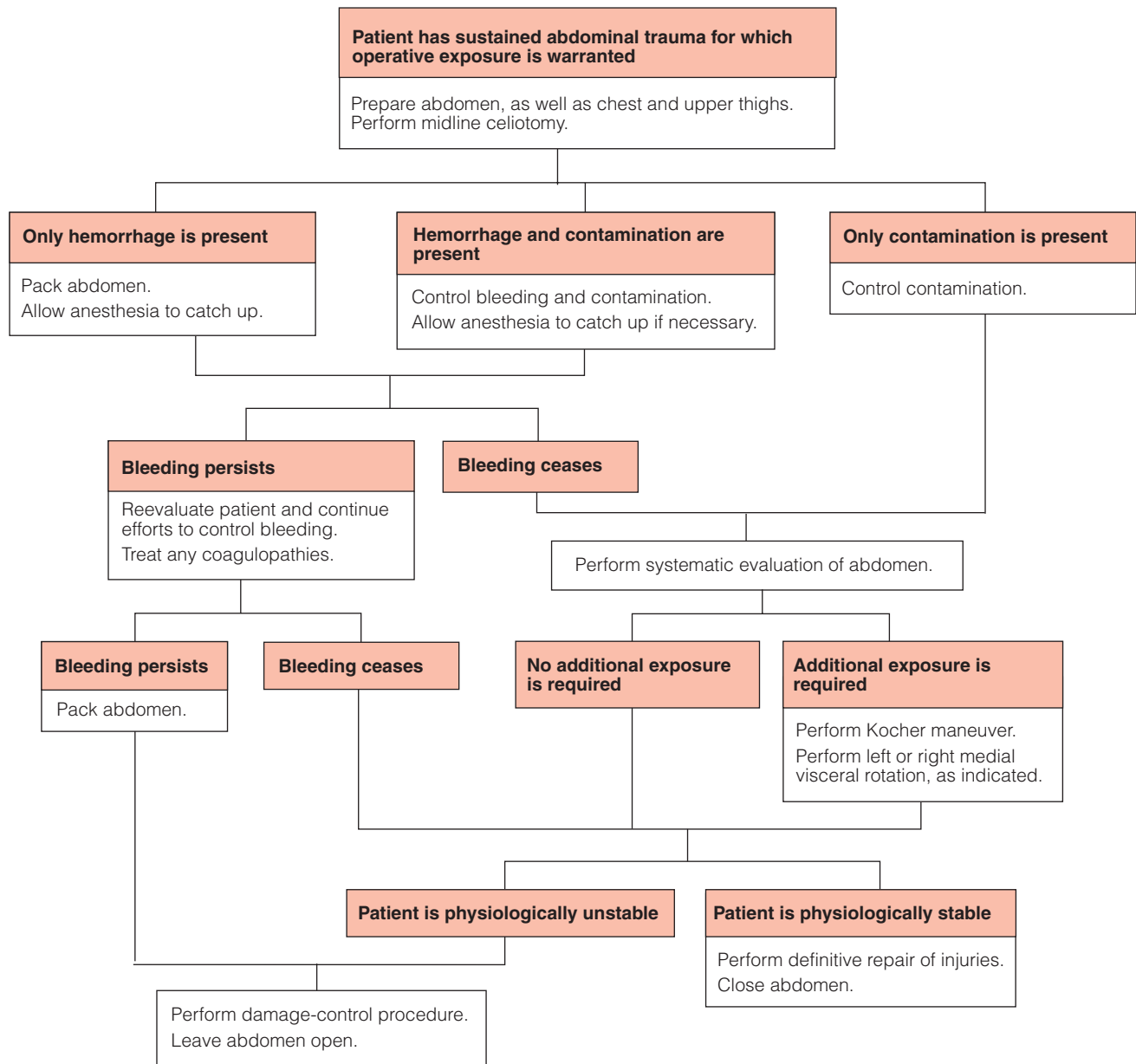


Figure 1 Algorithm outlines the approach to initial operative exposure in abdominal trauma patients.

control can be achieved. Mesenteric bleeding sites are clamped. Solid organs are initially packed as for blunt trauma, then treated with directed repair. In either scenario, bleeding that remains uncontrolled by packing requires immediate attention.

The enteric viscera are then examined in an orderly fashion. The anterior aspect of the stomach is inspected from the esophagogastric junction down to the pylorus. If an injury is present or is strongly suspected on the basis of the mechanism of injury or the presence of a hematoma or soilage, the posterior aspect of the stomach is examined by opening the gastrocolic omentum; this measure also permits examination of the anterior surface of the body of the pancreas. The exploration then continues distally along the course of the GI tract. If duodenal or pancreatic injury is a possibility, the duodenum is mobilized fully by means of a Kocher maneuver. The duodenojejunal junction at the ligament of Treitz is then inspected, and the small intestine is inspected all the way to the ileocecal valve. Both sides of the small intestine must

be examined, and particular care must be taken not to miss an injury at the mesenteric border. Careful consideration should also be given to the possibility of mesenteric vascular injuries, which may be manifested as mesenteric hematomas.

Next, the colon is inspected from the cecum to the rectum. If injuries are present or missile tracts are noted in proximity to a portion of the ascending or descending colon, the retroperitoneal portion of the colon is inspected by incising the white line of Toldt (the retroperitoneal reflection) so as to allow access to the posterior surface of the colon. Finally, the laparotomy pads around the solid organs are removed, one organ at a time, to permit inspection for hemorrhage or injury.

Once the peritoneal survey is complete, the retroperitoneum is inspected for potential injuries. Retroperitoneal hematomas are classified on an anatomic basis: zone 1 is the central area, bounded laterally by the kidneys and extending from the diaphragmatic hiatus to the bifurcation of the vena cava and the aorta; zone 2

comprises the lateral area of the retroperitoneum, from the kidneys laterally to the paracolic gutters; and zone 3 is the pelvic portion [see Figure 2]. Whether exploration is warranted for a retroperitoneal hematoma depends on the mechanism of injury and the location of the hematoma [see Priorities in Management, Repair of Retroperitoneal Injuries, *below*, and 7:10 *Injuries to the Great Vessels of the Abdomen*]. A careful evaluation is performed to identify possible occult injuries to organs (e.g., the pancreas, the duodenum, the retroperitoneal colon, the kidneys, and vascular structures).

The initial exploration concludes with a brief pelvic survey aimed at excluding injuries to the rectum or the distal urogenital tract (including the bladder). At the end of the operation, this initial inspection should be repeated, following the same sequence, to confirm that no injuries have been missed.

Operative Exposure

To expose the various organs that may be injured in patients who have sustained abdominal trauma, the surgeon must be familiar with a number of different techniques. In what follows, we detail the operative exposures that enable the surgeon to perform

the necessary repairs. The repairs themselves are described in greater detail elsewhere [see 7:7 *Injuries to the Liver, Biliary Tract, Spleen, and Diaphragm*; 7:8 *Injuries to the Stomach, Small Bowel, Colon, and Rectum*; 7:9 *Injuries to the Pancreas and Duodenum*; 7:10 *Injuries to the Great Vessels of the Abdomen*; and 7:11 *Injuries to the Urogenital Tract*].

AORTA AND BRANCHES

Control of the aorta can be gained at several different levels, depending on the site of injury. The supraceliac aorta can be exposed by incising the gastrohepatic ligament, retracting the left hemiliver laterally and cephalad, and retracting the stomach caudally. The esophagus and periesophageal fat pad are then mobilized laterally to permit identification of the abdominal aorta at the diaphragmatic hiatus, at which point the aorta can be encircled, clamped, or compressed. This exposure allows control of the aorta, but it is inadequate in terms of providing vascular access for definitive repair. Better exposure of the supraceliac aorta and its branches can be obtained by means of a left medial visceral rotation [see Figure 3]. To perform this maneuver, the splenorenal ligament is mobilized with a combination of sharp and blunt dissection. The left peritoneal reflection is incised from the splenicocolic flexure down the paracolic gutter to the level of the distal sigmoid colon. The left-side viscera are then gently mobilized to the midline (mostly with blunt dissection) in a plane anterior to Gerota's fascia. This technique allows exploration of the entire length of the abdominal aorta, the origin of the celiac axis, the origin of the superior mesenteric artery, the left iliac system, and the origin of the right common iliac artery. In addition, it facilitates control of the left renal vascular pedicle before exploration of a left-side zone 2 retroperitoneal hematoma. Alternatively, a variation on the standard left medial visceral rotation (the Mattox maneuver⁶) may be employed, in which the left kidney is also included in the organs that are rotated (the plane being anterior only to the muscles of the posterior abdominal wall). This variant may afford better access to the origin of the left renal artery.

If the injury is more distal, the aorta may be approached in a transperitoneal fashion. The small intestine is retracted to the right, the transverse colon is retracted cephalad, and the descending colon is retracted laterally. The peritoneum is then incised directly over the aorta, and the third and fourth portions of the duodenum are mobilized cephalad. The proximal limit of this dissection extends to the left renal vein, which may be divided if necessary to provide more cephalad access to the aorta. If ligation of the left renal vein is called for, it should be done at a point where the gonadal vein will be left intact to drain the kidney. A more limited dissection may suffice to expose the distal infrarenal aorta. Depending on the injury, distal control may or may not be required. Control may be achieved at the level of the distal infrarenal aorta, above the bifurcation.

Once again, if the patient is in extremis, formal dissection may be curtailed and proximal control achieved either by manually compressing the aorta against the spine at the level of the esophagogastric junction or by using an aortic occluder [see 7:10 *Injuries to the Great Vessels of the Abdomen*].

VENA CAVA AND BRANCHES

Access to the suprahepatic inferior vena cava can be gained only by either incising the central tendon of the diaphragm or by performing a median sternotomy and opening the pericardium. The infrahepatic inferior vena cava is exposed by performing a right medial visceral rotation (the Cattell-Braasch maneuver) [see Figure

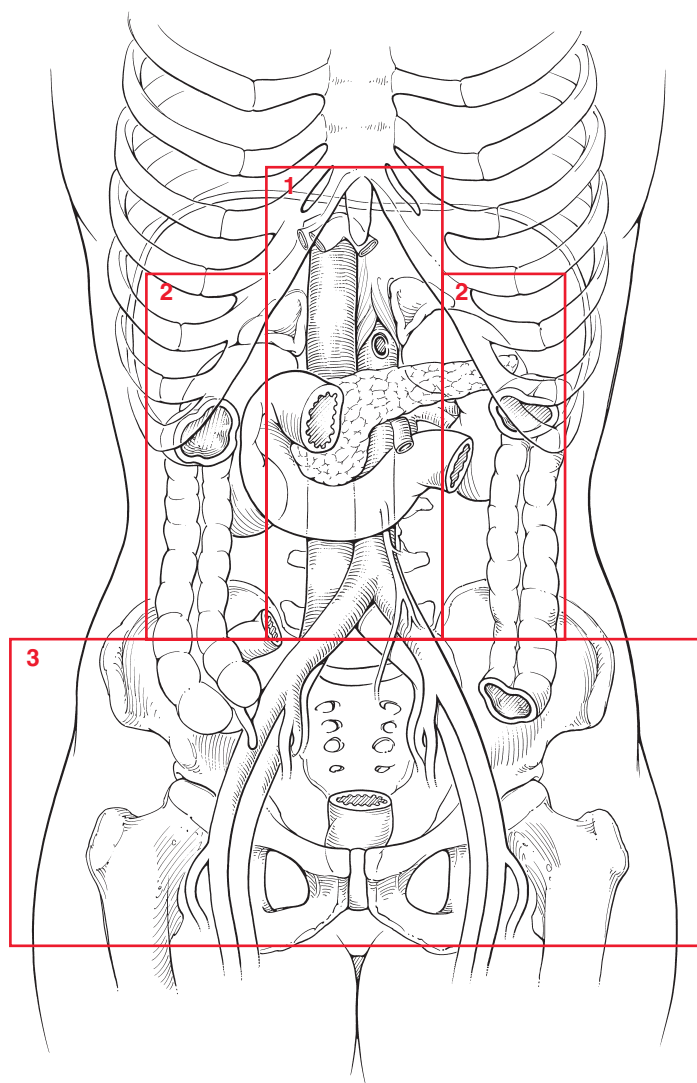


Figure 2 Shown are the anatomic zones of the retroperitoneum: zone 1 (central), zone 2 (flank), and zone 3 (pelvic).

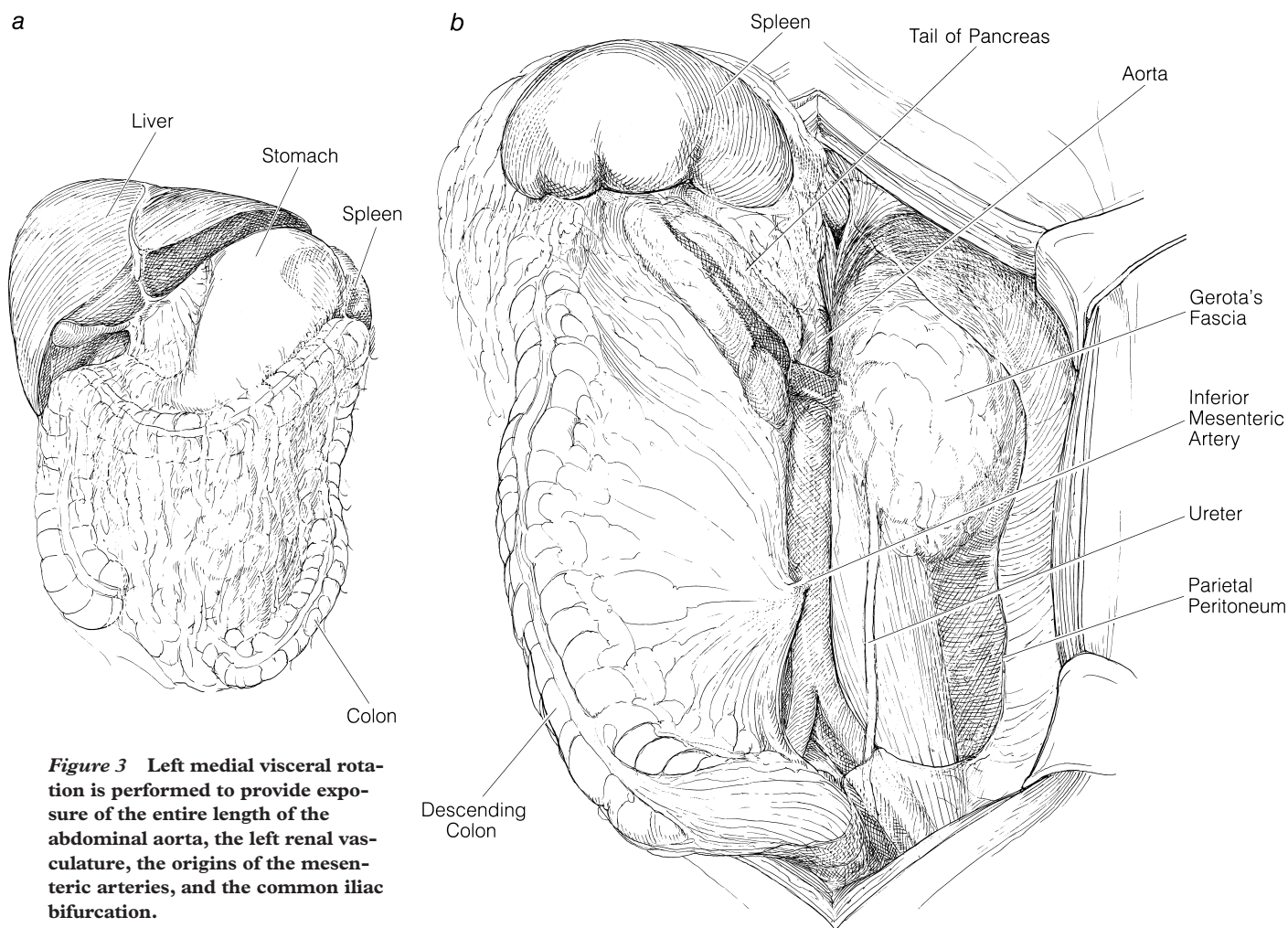


Figure 3 Left medial visceral rotation is performed to provide exposure of the entire length of the abdominal aorta, the left renal vasculature, the origins of the mesenteric arteries, and the common iliac bifurcation.

4]. The right colon is mobilized by taking down the hepatic flexure and then incising the right peritoneal reflection along the paracolic gutter. The colon is once again reflected medially toward the aorta in a plane anterior to Gerota's fascia with careful blunt dissection. If additional exposure is necessary, the inferior margin of the peritoneal incision may be extended to the root of the mesentery—and even beyond, if the inferior mesenteric vein is sacrificed. This exposure permits visualization of both the aorta below the origin of the superior mesenteric artery and the vena cava below the third portion of the duodenum. Exposure of the portion of the vena cava directly below the liver alone can be achieved by performing a Kocher maneuver [see Figure 5] with medial mobilization of the duodenum and the head of the pancreas.

LIVER

Mobilization of the liver begins with division of the round ligament (ligamentum teres), followed by takedown of the falciform ligament (to prevent iatrogenic trauma to the liver capsule during exposure and identification of other intraperitoneal injuries). This mobilization may be extended as far cephalad as is necessary. Further mobilization can be achieved by incising the left triangular ligament, with care taken not to injure the suprahepatic inferior vena cava at the diaphragmatic hiatus during the dissection. When visualization of the right hemiliver is required, the falciform ligament should be incised to its most superior extent, and the right triangular ligament should then be carefully divided. This

step is challenging and may have to be performed partly by palpation, with care taken not to injure the inferior vena cava, the hepatic veins, or the phrenic vessels [see 7:7 *Injuries to the Liver, Biliary Tract, Spleen, and Diaphragm*].

SPLEEN

The spleen can be mobilized into the midline by dividing the phrenicosplenic and splenorenal ligaments with a mixture of sharp and blunt dissection. In cases where the spleen has been injured by blunt trauma, these ligaments often are already disrupted, and this disruption facilitates the dissection. The splenocolic ligament often contains sizeable blood vessels that must be controlled, and the gastrosplenic ligament contains the short gastric arteries. Once the spleen is mobilized into the midline, control of the vascular pedicle can be achieved, the splenic injury can be assessed, and splenorrhaphy or splenectomy can be performed as appropriate [see 7:7 *Injuries to the Liver, Biliary Tract, Spleen, and Diaphragm* and 5:25 *Splenectomy*].

PANCREAS

Intraoperative evidence of a central hematoma, peripancreatic edema, or bile staining in the retroperitoneum or the lesser sac raises the possibility of pancreatic injury. The contents of the lesser sac can be visualized by performing a direct inspection through the gastrohepatic ligament or by dividing the ligament. Alternatively, access can be gained by dividing and ligating two or three gas-

troepiploic arcades of the gastrocolic ligament. If it proves necessary to explore the pancreas, the stomach is separated from the transverse colon by completing the division of the gastrocolic ligament, and a Kocher maneuver is performed to reflect all portions of the duodenum medially, along with the head of the pancreas. The peritoneum lateral to the duodenum is incised, and careful blunt dissection is employed to mobilize the duodenal loop from the common bile duct superiorly to the superior mesenteric vein inferiorly. This mobilization allows inspection of the anterior and posterior surfaces of the head of the pancreas, as well as the uncinate process. If injury to the body or tail of the pancreas is suspected, the splenorenal and splenocolic ligaments are incised. At this point, the spleen and then the pancreas can be mobilized medially to a position near the level of the superior mesenteric vessels, and the anterior and posterior aspects of the body and tail of the pancreas can be examined [see 7:9 *Injuries to the Pancreas and Duodenum*].

KIDNEYS

Operative exposure of the kidneys starts with either a left or a right medial visceral rotation, depending on which kidney is involved. The renal vascular pedicle should be controlled before any hematoma in Gerota's fascia is opened [see 7:11 *Injuries to the Urogenital Tract*]. Repair of the kidney may be facilitated by mobilizing the organ out of Gerota's fascia and retracting it medially.

DUODENUM, BILIARY TRACT, AND SMALL INTESTINE

Exposure of the posterior surface of the duodenum is achieved by means of a Kocher maneuver [see *Pancreas, above, and Figure 5*]. This technique is also used when injury to the distal extrahepatic biliary system is suspected. The proximal extrahepatic biliary tree is visualized by using a Kocher maneuver in conjunction with local exploration of the porta hepatis. In patients with injuries to the distal duodenum or the proximal jejunum, division of the ligament of Treitz may also be necessary for accurate identification of the site of injury. Because of the mobility of the small intestine, injuries to this structure generally are readily identified and repaired without additional mobilization.

COLON AND RECTUM

Evidence of staining, pneumatosis, or hematoma in proximity to a portion of the ascending or descending colon, particularly in the setting of related injuries or missile tracts, should prompt a full evaluation of the colon. Because the colon is a partially retroperitoneal structure, the retroperitoneal reflection must be incised to allow inspection of the posterior surface of the colon. Sometimes, rectal injuries are not accessible via an intraperitoneal approach; in this situation, consideration should be given to a diverting colostomy and presacral drainage [see 7:8 *Injuries to the Stomach, Small Bowel, Colon, and Rectum*].^{7,8}

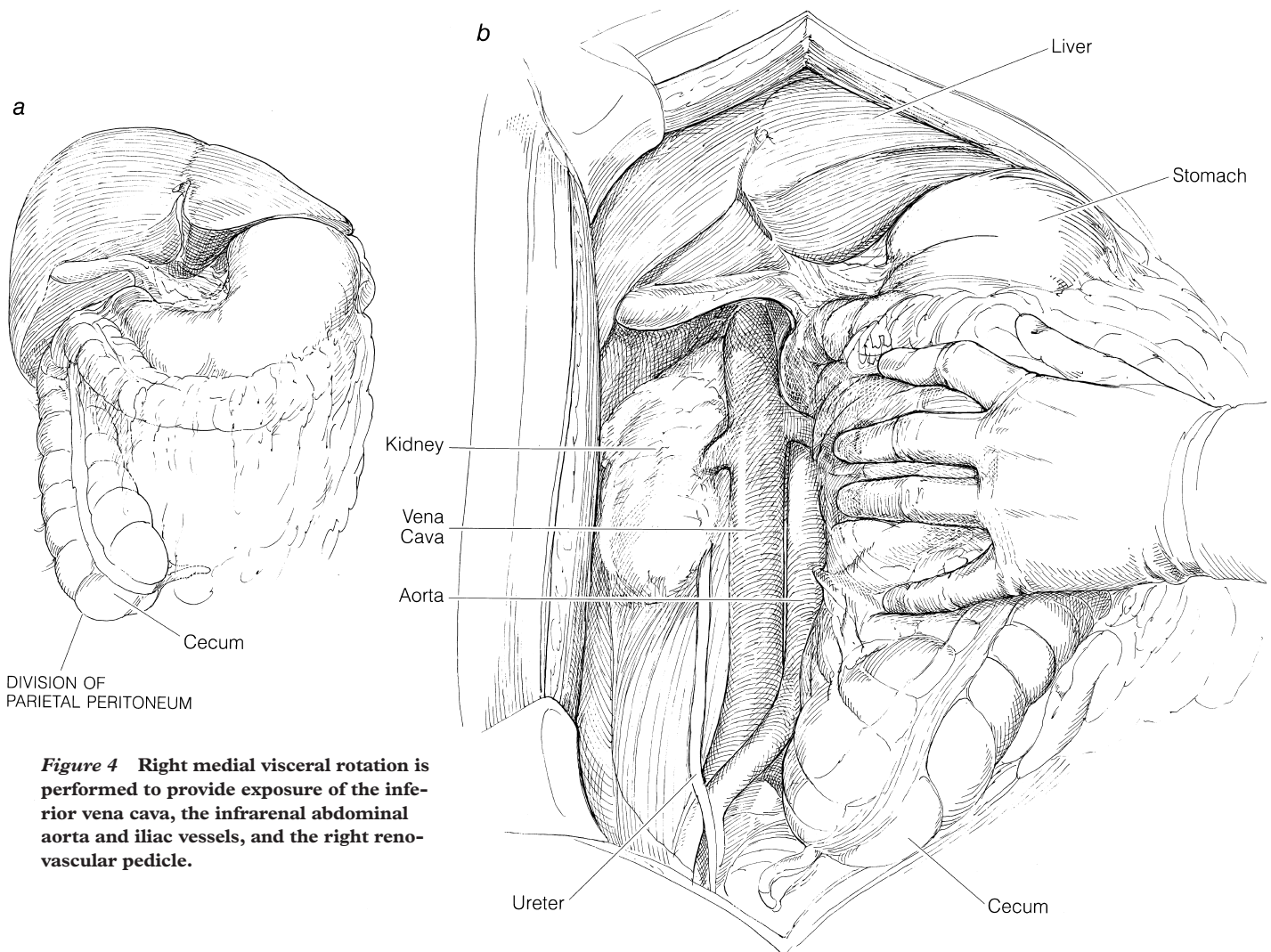


Figure 4 Right medial visceral rotation is performed to provide exposure of the inferior vena cava, the infrarenal abdominal aorta and iliac vessels, and the right renovascular pedicle.

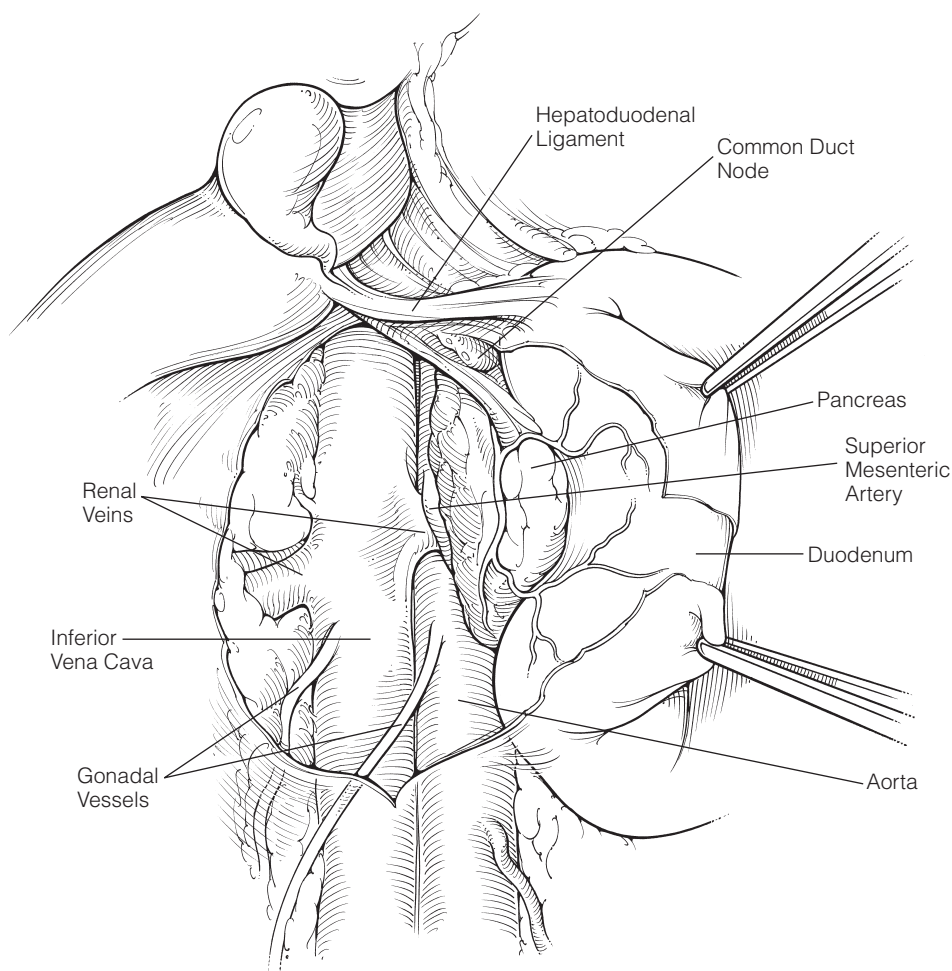


Figure 5 The Kocher maneuver reflects the duodenum and the pancreatic head from the retroperitoneum, allowing access to the infrahepatic inferior vena cava as well as to the distal common bile duct, the duodenum, and the pancreatic head.

Priorities in Management

CONTROL OF HEMORRHAGE

In the event that the patient remains hemodynamically unstable because of persistent uncontrolled hemorrhage, the primary focus of the initial exploration is control of bleeding. As noted (see above), the approach to hemorrhage control differs depending on whether the patient sustained blunt trauma or penetrating trauma. In cases of blunt trauma with bleeding from a solid organ, the first thing that should be done is to attempt repeat packing of the specific bleeding site with a sufficient number of laparotomy pads. This is an important skill to master and can be effective as a temporizing measure until either more definitive vascular control can be achieved or coagulopathy can be corrected. In cases of penetrating trauma, bleeding is more effectively managed by means of either vascular control just proximal and distal to the site of injury or direct control at the bleeding site.

When significant hemorrhage is anticipated, control of the injured vessel should be obtained by the operative techniques discussed previously [see *Operative Exposure, above*]. Given the possibility of exsanguinating hemorrhage, the surgeon must be prepared to gain proximal aortic control at the diaphragmatic hiatus or even within the chest via a left lateral thoracotomy. For immediate control, the aorta can be manually compressed at the hiatus; a padded Richardson retractor, an aortic compressor, or an assistant's hand can then take over this function to allow the surgeon to continue the exploration. If a need for prolonged proximal aortic control is anticipated, an atraumatic aortic vascular clamp should

be placed. Injuries to the proximal abdominal aorta often necessitate that the vessel be controlled in the chest to permit repair.

In patients who have sustained parenchymal injuries to solid viscera, control of the vascular inflow is crucial as both a diagnostic and a therapeutic maneuver. Gaining control of the splenic hilum effectively arrests further splenic hemorrhage. Similarly, use of the Pringle maneuver [see 7:7 *Injuries to the Liver, Biliary Tract, Spleen, and Diaphragm*] to control the vessels in the porta hepatis (the hepatic artery and the portal vein) helps determine the source of perihepatic hemorrhage. This maneuver is initially performed by digitally compressing the portal structures; if digital compression causes the hemorrhage to diminish, the surgeon's hand is replaced with an atraumatic vascular clamp or a Rumel tourniquet. Although the Pringle maneuver can be maintained for at least 30 to 45 minutes without causing permanent liver damage, the clamp or tourniquet should be removed as soon as is feasible. In the vast majority of cases of liver trauma—aside from those involving an injury to the retrohepatic vena cava—the use of the Pringle maneuver, combined with perihepatic packing, should arrest hemorrhage.

In patients who have sustained injuries to the retrohepatic vena cava, it may be necessary to gain vascular control by performing hepatic exclusion before definitive repair can be attempted [see 7:7 *Injuries to the Liver, Biliary Tract, Spleen, and Diaphragm*]. Hepatic exclusion may be achieved by means of either atriocaval shunting (which is rarely if ever used^{9,10}) or occlusion of the inferior vena cava both above and below the liver. The latter may lead to significant hemodynamic instability, particularly in volume-depleted

patients; however, it may reasonably be considered in patients whose volume status is adequate. Complete hepatic exclusion involves both (1) atriocaval shunting or clamping of both the infrahepatic and the suprahepatic inferior vena cava and (2) control of hepatic arterial and portal venous inflow.¹¹ In general, injuries to the retrohepatic vena cava are best dealt with by means of damage-control procedures.

Hepatic parenchymal hemorrhage can be challenging, and any of a number of techniques may be used to control it, depending on the location, type, and degree of bleeding. These techniques range from simple electrocauterization and parenchymal suturing to argon beam cauterization, direct vessel ligation, hepatotomy, and even resection [see 7:7 *Injuries to the Liver, Biliary Tract, Spleen, and Diaphragm*].^{12,13} In difficult cases, it may be advisable to perform an abbreviated laparotomy, pack the liver extensively, and transport the patient to the angiography suite, where selective embolization can be performed; the patient can then be transported to the ICU, undergo warming, and have any coagulopathy corrected before returning to the OR to have the packs removed.

Mesenteric bleeding can usually be controlled with manual compression of the vessel followed by suture ligation. Retroperitoneal hematomas are often harbingers of vascular injury, and proximal and distal vascular control should be obtained before exploration is initiated [see 7:10 *Injuries to the Great Vessels of the Abdomen*]. Typically, bleeding from injured hollow viscera is minor and can be controlled by repairing the injury; on occasion, however, temporary hemostatic suturing or stapling may be required.

CONTROL OF CONTAMINATION

Once hemorrhage has been controlled, the next priority is to control contamination. All gross spillage should be removed from the abdomen with suction and laparotomy pads, and further contamination should be prevented by temporarily closing small enterotomies with Babcock clamps (or, alternatively, with a continuous suture or skin staples). When multiple enterotomies are present, suture closure is preferred (to ensure that multiple clamps are not present in the operative field). If the injuries are in close proximity, the preferred method of controlling intestinal spillage is to apply atraumatic bowel clamps at both the proximal and the distal end of the injury site. Alternatively, if the injured segment will have to be resected, rapid control of further spillage can be obtained by firing a GI stapler at each end of the injured segment.

REPAIR OF VASCULAR INJURIES

Once intestinal contamination has been dealt with, the next priority is definitive vascular repair [see 7:10 *Injuries to the Great Vessels of the Abdomen*]. If proximal and distal control of the injured vessel has not already been obtained, it is obtained at this point. The extent of the vascular injury is determined, dead or devitalized tissue is carefully debrided, and vessel continuity is reestablished if possible. If the injury is not amenable to primary repair and the vessel cannot be ligated, autogenous tissue should be obtained (usually from the proximal greater saphenous vein) and used for either patch angioplasty or interposition grafting. If no suitable autogenous venous tissue is available, synthetic material may be considered as an alternative vascular conduit. For aortic or iliac arterial injuries, primary ligation with subsequent extra-anatomic bypass is an acceptable alternative. In cases in which an abbreviated laparotomy is necessary, vascular shunting may serve as a substitute for definitive repair until hypothermia, coagulopathy, and acidosis are corrected.

REPAIR OF DAMAGED OR DEVITALIZED BOWEL

Once vascular injuries have been addressed, the next priority is to repair any enteric injuries [see 7:8 *Injuries to the Stomach, Small Bowel, Colon, and Rectum*]. Because the stomach is a large and well-vascularized organ, gastric injuries are usually amenable to primary repair. Injuries to the small intestine that involve less than 50% of bowel circumference after debridement of devitalized edges can be repaired with either a single-layer or a two-layer closure; single-layer closure, being less likely to compromise the lumen of the bowel, is generally preferred. In cases involving multiple enterotomies in close proximity or a large area of devitalized tissue, a segmental enterectomy with primary anastomosis is preferable. The anastomosis may be either hand-sewn or stapled; the latter tends to be more expeditious but less cost-effective.

Solitary injuries to the colon that do not necessitate resection after debridement and are not associated with multiple transfusions or significant gross contamination are managed by means of primary closure. Large or multiple injuries to the right colon are best managed with a right hemicolectomy followed by an immediate ileocolic anastomosis. Similar injuries to the left colon are generally treated with resection and proximal diversion. The distal limb may be exteriorized as a mucous fistula, or, if inadequate bowel length renders diversion impossible, a Hartmann procedure may be performed.¹⁴⁻¹⁶

REPAIR OF RETROPERITONEAL INJURIES

Once all injuries within the peritoneal cavity have been addressed, the next priority is to inspect the retroperitoneum once more, paying particular attention to the possibility of hematoma expansion. The decision whether to explore a retroperitoneal hematoma is based on the mechanism of injury and on the zone in which the injury is located. All zone 1 hematomas should be explored regardless of the injury mechanism: they signal possible aortic, vena caval, duodenal, or pancreatic injury. Zone 2 and 3 hematomas should be explored in cases of penetrating trauma but not, as a rule, in cases of blunt trauma (with the exception of expanding zone 2 hematomas).

Before a retroperitoneal hematoma is opened, proximal vascular control should be obtained so that hemorrhage will be minimized once the effect of the tamponade has been lost. Injuries to retroperitoneal organs (e.g., the kidneys, the pancreas, and the adrenal glands) are treated by means of debridement or resection, with drainage as indicated. Vascular injuries are repaired as discussed previously [see *Repair of Vascular Injuries, above, and 7:10 Injuries to the Great Vessels of the Abdomen*].

Closure

GENERAL TECHNIQUE

Once the abdominal exploration has been completed, the abdomen is copiously irrigated with an isotonic crystalloid solution. The closure method employed is typically determined on the basis of five main considerations: (1) the degree of blood loss, (2) the volume of resuscitation fluid received, (3) the degree of contamination, (4) the patient's perceived nutritional status, and (5) the patient's hemodynamic stability. In cases that necessitate an abbreviated or damage-control procedure, the speed with which the closure can be performed may be the most important factor. Provided that the risk of subsequent abdominal compartment syndrome (ACS) is considered to be low, every effort should be made to close the fascia. Fascial closure is usually accomplished with a continu-

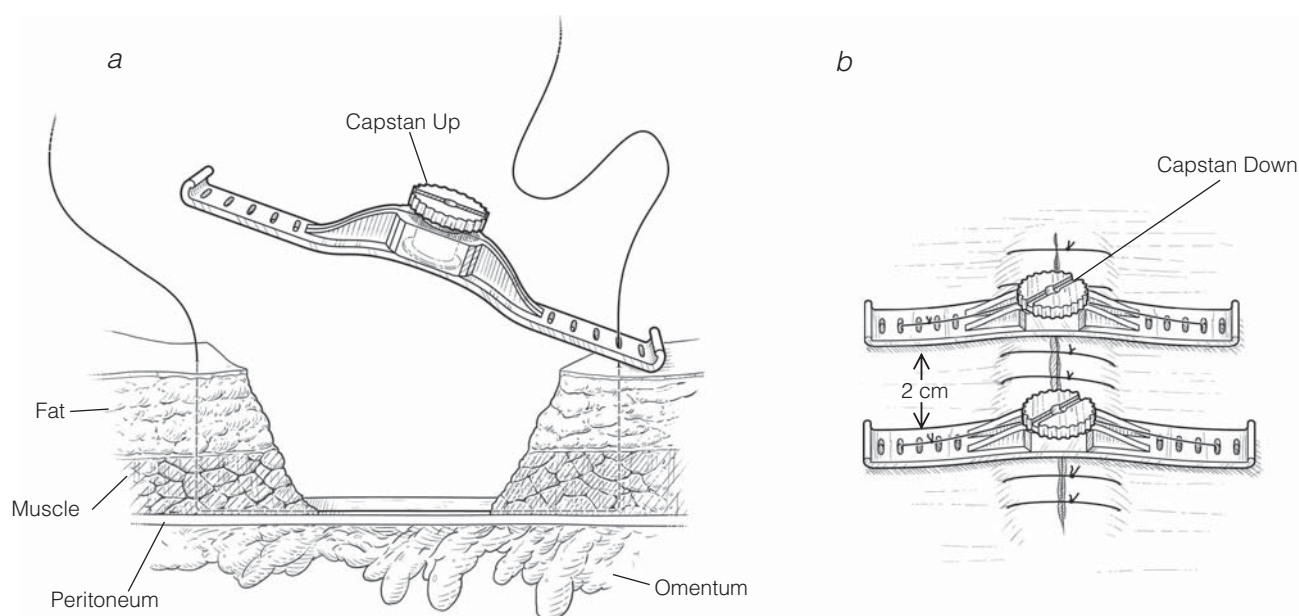


Figure 6 Retention sutures may be used to bolster fascial closure in wounds at high risk for breakdown. (a) Sutures are placed in the subfascial plane. (b) The defect is approximated, and the sutures are tied over skin bridges.

ous absorbable or nonabsorbable monofilament suture, though it may also be accomplished with interrupted sutures. The rate of fascial dehiscence is essentially the same for the two techniques; however, the extent of dehiscence is more limited when closure is done with interrupted sutures.^{17,18} With either technique, it is important not to place excessive tension on the fascial tissues.

In cases where there is a specific reason to be concerned about possible dehiscence (e.g., in patients who are malnourished or obese or are receiving steroid therapy), large monofilament sutures may be placed at intervals within the standard closure to serve as retention sutures. They may be tied over bolsters created from a red rubber catheter or over plastic skin bridges [see Figure 6]. If rapid closure is required, the abdomen may be closed with four or five retention sutures of this type that are placed through the abdominal wall and just above the peritoneum. These sutures must be checked daily and should be loosened if there is evidence that they are cutting through the abdominal skin as a consequence of edema creating increased tension on the wound.

SKIN CLOSURE

If the patient has minor injuries without evidence of enteric contamination, the skin may be closed primarily. Stapled closure is most expeditious, but suture closure is also acceptable. A degree of clinical judgment is required in assessing a wound's suitability for closure. If the skin is closed primarily, it should be inspected daily, and the wound should be opened without delay if there is concern about subsequent infection. Alternatively, primary delayed closure may be performed by leaving the wound open, packed with moist gauze. If the wound shows no evidence of infection when examined after 3 to 5 days, it may be closed with Steri-Strips or with interrupted sutures that are placed (without being tied) during the original operation. If intraperitoneal contamination has occurred, either primary delayed closure should be performed or the wound should be packed and left to heal by secondary intention.

ABBREVIATED OR DAMAGE-CONTROL LAPAROTOMY

If a patient remains unstable after surgical bleeding and contamination have been controlled or is cold and coagulopathic, an

abbreviated or damage-control procedure is indicated. It may be necessary to perform a rapid abdominal closure—with the proviso that further exploration, as well as definitive repair of injuries that have been temporarily controlled, will be required. The decision to perform a damage-control procedure should be made at an early stage, before the so-called lethal triad (hypothermia, acidosis and coagulopathy) has had time to develop. Damage control has undoubtedly led to improved survival for trauma patients, but it has also led to an increase in the number of patients whose abdomens are left open.¹⁹

TEMPORARY ABDOMINAL CLOSURE

When a damage-control procedure is required, it is often most expedient to perform a rapid temporary abdominal closure, then to transport the patient to the intensive care unit. This measure may also be necessary in patients whose abdomens cannot be closed because of intestinal and organ edema caused by intraoperative fluid resuscitation. The simplest form of temporary abdominal closure is the use of towel clips to close only the skin [see Figure 7], in conjunction with the application of a bioocclusive dressing to control fluid loss and contamination. This closure, however, leaves the patient still at risk for subsequent ACS.

The first temporary abdominal dressing described was the so-called Bogotá bag—that is, an empty intravenous fluid bag that was cut in half and sewn to the wound edges. This dressing can still be used in circumstances where no other equipment is available. The so-called vacuum pack technique involves the placement of a sterile plastic drape over the bowel contents and under the fascia, followed by insertion of two or more suction drains, over which sterile towels or open laparotomy pads may be placed. To minimize heat loss and insensible fluid loss, an adherent bioocclusive dressing is placed over the entire dressing and the abdominal wall, with the drains attached to suction. Several commercial devices are now available that can be used to facilitate temporary closure of the open abdomen; these include the VAC Abdominal Dressing System (Kinetic Concepts Inc., San Antonio, Texas) and the Wittmann Patch (Star Surgical, Burlington, Wisconsin).^{20,21}

MANAGEMENT OF THE OPEN ABDOMEN

Once the patient's physiologic status has stabilized, he or she should be returned to the OR for reexploration and definitive repair of any remaining injuries [see Figure 8], preferably within 48 hours after the first operation. At this juncture, the abdomen should be assessed for the feasibility of closure. In some patients, the fascial edges cannot be approximated, because of edema; in others, reapproximation may cause a significant rise in intra-abdominal pressure, as evidenced by a rise in pulmonary inspiratory pressures. These patients are at risk for ACS, and their abdomens should be left open.

At this point, if temporary abdominal coverage continues to be required, a temporary abdominal dressing should be placed that attempts to prevent fascial retraction and the associated increased risk of nonclosure of the abdomen. Options include dynamic retention sutures, the Suture Tension Adjustment Reel (STAR) (WoundTEK, Inc., Newport, Rhode Island), the Wittmann Patch, nonabsorbable mesh, fascial zippers, and the VAC Abdominal Dressing System.²⁰⁻²⁵ Once the dressing is placed, it should be

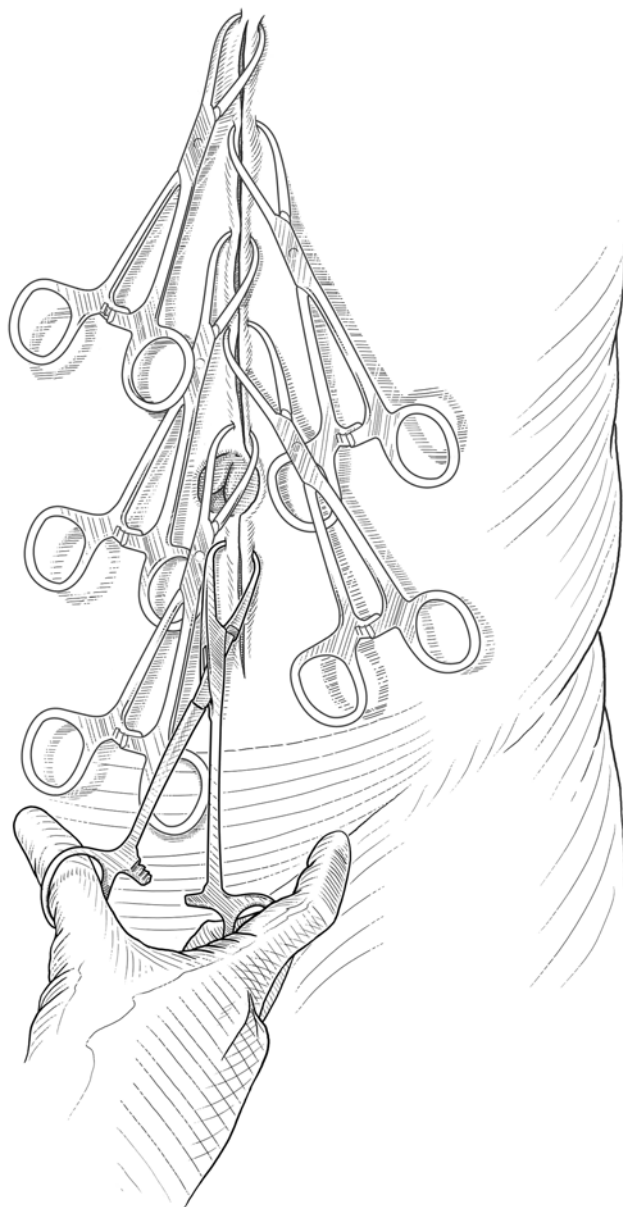


Figure 7 Shown is a “quick out” closure with surgical towel clips.

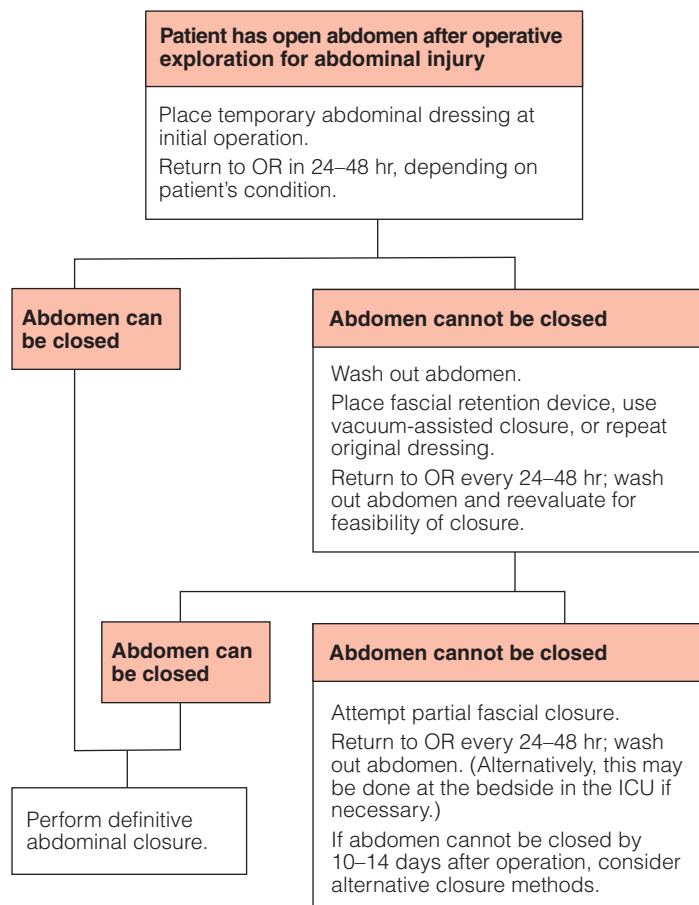


Figure 8 Algorithm outlines the approach to the open abdomen in a patient with abdominal injuries.

examined every 24 to 48 hours, depending on the degree of contamination; this is often best done in the OR, but it may also be done in the ICU if the patient remains unstable. At every subsequent procedure, the fascia should be assessed for the possibility of closure. Partial closure of the incision (i.e., closure of the cephalad and caudad portions) should be considered, even if full closure cannot be accomplished. In approximately 50% of patients, closure of the fascia is not possible; however, there is some evidence to suggest that this figure may be lowered by employing some of the devices now commercially available.^{20,26,27}

ABDOMINAL COMPARTMENT SYNDROME

Patients who undergo fascial closure are at risk for ACS as a consequence of ongoing resuscitation efforts and associated bowel and organ edema. ACS is defined as intra-abdominal hypertension greater than 25 mm Hg in conjunction with dysfunction of one or more organ systems (e.g., pulmonary, renal, or cardiac).^{28,29} Intra-abdominal pressure is determined indirectly by measuring bladder pressure. Bladder pressure can be measured by using an arterial transducer at the level of the symphysis pubis that is connected to the urinary catheter after 30 to 50 ml of sterile water has been introduced. Alternatively, an idea of the intra-abdominal pressure can be gained by raising the Foley tubing above the bed after instillation of the water, then measuring the column.³⁰ A rising trend in pressure can be as significant as a single elevated measurement. Patients who have undergone a long operation, have been the object of vigorous resuscitation efforts, or who have sustained mul-

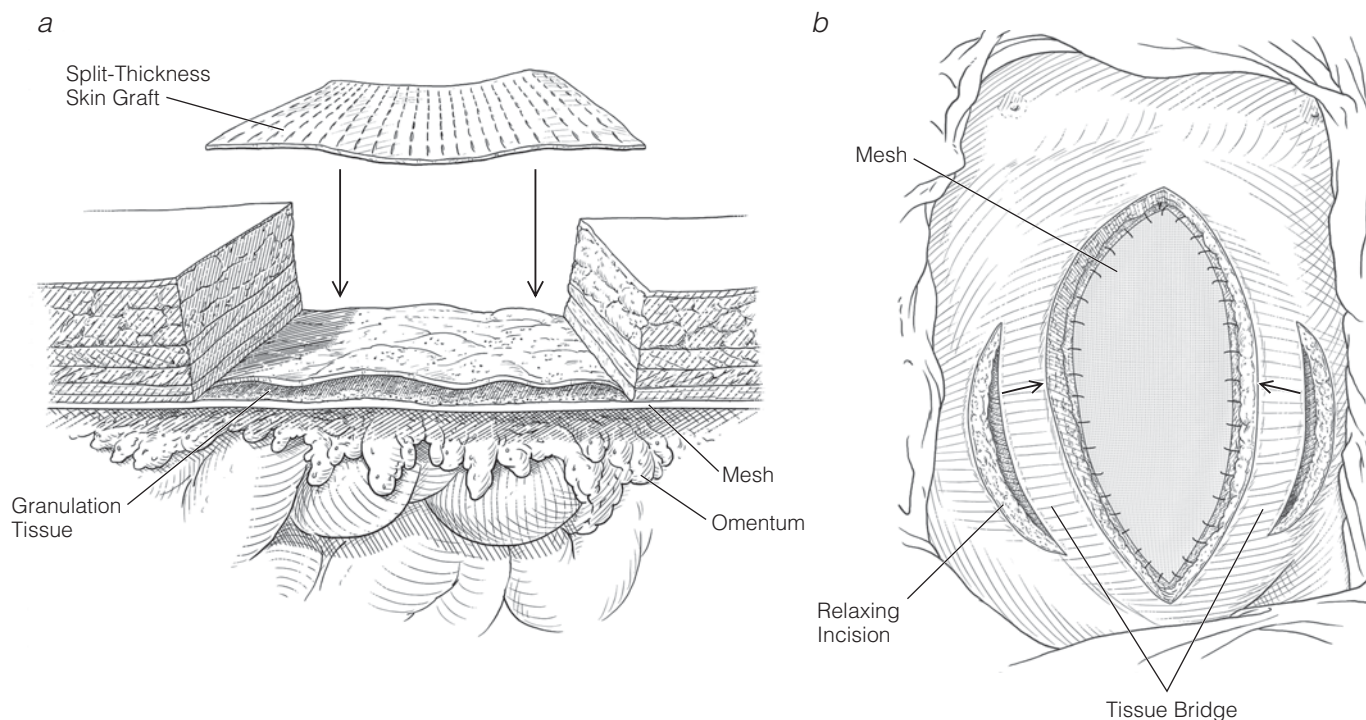


Figure 9 Mesh may be used for temporary or permanent abdominal closure in patients at risk for increased abdominal pressure. (a) Mesh is sutured into the fascial plane, then covered with a split-thickness skin graft. (b) The abdominal defect is closed with mesh.

multiple injuries should be monitored closely for the development of ACS. If the diagnostic criteria for ACS are met, prompt abdominal decompression is indicated. On occasion, this measure may have to be carried out at the bedside in the ICU.

Occasionally, ACS develops in patients who have a temporary abdominal dressing in place (so-called tertiary ACS). Accordingly, it is mandatory to continue to monitor intra-abdominal pressure in these patients.²⁹

CLOSURE OF THE OPEN ABDOMEN

It is important to close the abdomen as early as possible: an open abdomen carries an increased risk of desiccation of the intestines and subsequent fistula formation. In certain patients, however, despite aggressive efforts to close the fascia, it proves impossible to accomplish primary closure, even after many days and repeated procedures. There are several techniques that may be employed to obtain final closure in this situation.

The simplest method is to allow granulation tissue to form over the omentum and the exposed intestines and later, when there is a good clean granulation bed with no evidence of infection, to place a split-thickness skin graft. Alternatively, a piece of absorbable mesh may be placed; this helps facilitate dressing changes, provides a modicum of protection to the intestines, and serves to control evisceration [see Figure 9]. A skin graft can then be placed in the same fashion, once a granulation bed has developed.

Another option is to employ relaxing incisions, either to allow a skin-only closure or to allow the skin to be closed over absorbable mesh. Open skin wounds should be left open to heal by secondary intention. Unfortunately, the use of relaxing incisions will not prevent the formation of large ventral hernias, which will have to be repaired at a later date.

Abdominal fascial defects may also be closed with sheets of nonincorporable synthetic material (e.g., Gore-Tex; W. L. Gore and Associates, Inc., Newark, Delaware). The advantages of these nonabsorbable materials are that they do not react with tissue and that they are associated with a low incidence of complications (e.g., fistula formation). The disadvantages are that they are expensive and that they must ultimately be removed unless the skin can be closed over them to prevent contamination.

Another option for achieving primary closure of the abdomen is component separation of the rectus sheath. The external oblique aponeurosis is incised and mobilized, along with the rectus sheath, to bring the fascia to the midline. Defects as wide as 14 to 20 cm can be bridged in this fashion, but recurrent hernia rates remain high.³¹

Several biosynthetic materials are now available to be used for bridging abdominal fascial defects. One such material is Surgisis (Cook Biotech Inc., West Lafayette, Indiana), a porcine submucosal matrix that can provide scaffolding for the ingrowth of fibrous tissue while supporting abdominal contents and permitting skin closure.³² Another is AlloDerm (LifeCell Corp., Branchburg, New Jersey), a denatured human cadaveric product that can be used in a similar fashion to replace denuded fascia or to bridge the fascial gap in cases where primary closure cannot be accomplished.^{33,34} At present, long-term follow-up data are lacking for both products, and their use is further limited by their very high cost.

Morbidity is very high in these patients; subsequent complications range from prolonged ventilator dependence to enteric fistulas to massive ventral hernias.^{35,36} Major ventral hernias represent a significant technical challenge and should not be repaired until the patient's recovery from injury is complete and his or her nutritional and general status has returned to normal. This may take as long as 12 months from the time of the initial trauma.

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Acknowledgments

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7 INJURIES TO THE LIVER, BILIARY TRACT, SPLEEN, AND DIAPHRAGM

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Injuries to the Liver

The liver is the most commonly injured solid organ in blunt trauma, comprising 5% of all trauma admissions, and because of its size is frequently involved in penetrating trauma. Following blunt trauma, the most commonly injured structures are the parenchyma and hepatic veins. Blunt forces dissipate along segments of the liver and along the fibrous coverings of the portal triad structures; the hepatic veins, however, are not so insulated. Given its size and location within the abdomen, the liver is also commonly involved in penetrating trauma. Stab wounds typically result in direct linear tears, whereas gunshot wounds or shotgun wounds result in significant cavitory injuries attributable to blast effect and the “tumbling” of the missile within the liver parenchyma. Thus, arterial injury is more common with penetrating trauma.

Over the past 20 years, nonoperative management (NOM) of liver injuries has evolved to become the prevailing therapeutic strategy for blunt hepatic trauma. Several concurrent changes resulted in this paradigm change. First was the realization that diagnostic peritoneal lavage (DPL) was sensitive but not specific for identifying intraperitoneal hemorrhage that necessitated operative management. Surgeons recognized that many laparotomies undertaken for a positive DPL were associated with liver injuries that did not require intervention for bleeding.¹ Second, trauma surgeons noted that nonbleeding hepatic venous injuries, if manipulated at laparotomy, often resulted in more hemorrhage and sometimes even death.² Furthermore, it became conspicuous that with hemostasis achieved in the operating room, recurrent postoperative bleeding was rare. Therefore, surgeons queried whether hepatic venous injuries, which are low-pressure system injuries, could heal without intervention. Finally, computed tomography (CT) provided a reliable method for diagnosing and grading liver injuries.

INITIAL EVALUATION

The first step in patient management in the emergency department (ED) is the primary survey and evaluating the patient's response to resuscitation. Patients with hemodynamic instability and either a penetrating abdominal wound or intra-abdominal hemorrhage noted on focused abdominal sonography for trauma (FAST) examination should undergo urgent laparotomy. Although the definitive diagnosis of a hepatic injury may not be made, laparotomy should be

undertaken [see Operative Exposure and Hemorrhage Control, *below*]. For hemodynamically stable patients, further evaluation is warranted. Abdominal examination includes inspection for abdominal wall abrasions or ecchymosis and assessing for distention, rigidity, tenderness, or rebound. Although DPL was used routinely to evaluate abdominal trauma in the ED a decade ago, it has been supplanted by FAST in most hospitals over the past decade. The advantage of FAST is that it is noninvasive, portable, rapid, and easily repeatable over the patient's ED course. Any of the three standard views of the abdomen—right and left upper quadrants and pelvis—can reveal intra-abdominal fluid, which is presumed to be hemorrhage unless the patient has liver disease with known ascites. Although ultrasonography is sensitive for detecting intraperitoneal fluid greater than 400 mL, it does not reliably determine the source of hemorrhage or extent of solid-organ injuries and does have limitations in some settings, such as subcutaneous emphysema, morbid obesity, and retroperitoneal hemorrhage from pelvic fractures.^{3,4}

Patients with evidence of intra-abdominal fluid should undergo CT unless laparotomy is indicated. Occasionally, the first ultrasound views of the abdomen may be normal; repeating the ultrasonography as a second snapshot in time is critical for patients at high risk for injury. FAST is not 100% sensitive⁵; therefore, diagnostic peritoneal aspiration (DPA) is warranted in hemodynamically unstable patients without a defined source of blood loss to rule out abdominal hemorrhage, and some prefer DPA as the initial screening tool in the presence of pelvic fractures as well. The diagnostic measures advocated for the severely injured or unstable patient (FAST, DPA) are those that can easily be performed in the trauma bay. Transport of a hypotensive patient out of the ED for CT scan evaluation is hazardous; monitoring is compromised, and the environment is suboptimal for dealing with acute problems. On the other hand, CT is very desirable in the hemodynamically stable patient at risk for liver injury because laparotomy may provoke further hepatic bleeding.

IMAGING AND INJURY GRADING

Since its initial use in the early 1980s, CT has become a routine part of trauma evaluation. With multislice helical scanning, the entire torso can be scanned in under 5 minutes. Patients with fluid on a FAST examination, considered a “positive FAST,” who do not have immediate indications for laparotomy and are hemodynamically stable undergo CT to quantify their injuries. Additionally, patients with persistent abdominal tenderness, significant abdominal wall trauma, distracting injuries, or altered mental status should undergo CT. Although the majority of abdominal penetrating injuries that violate the peritoneum require laparotomy, the exception

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is penetrating trauma isolated to the right upper quadrant. In hemodynamically stable patients with the trajectory of penetrating trauma confined to the liver by CT scan, nonoperative observation is an option.^{6,7}

The American Association for the Surgery of Trauma (AAST) developed a grading scale to provide a uniform definition of liver injuries [see Table 1 and Figure 1].³ Solid-organ injury grading permits effective transfer of information between treating physicians and predicts failure rates and complication rates of NOM. In addition to grading the liver injury, specific findings that should be noted on a CT scan in patients include contrast extravasation (i.e., a “blush”), the amount of intra-abdominal hemorrhage, and the presence of pseudoaneurysms [see Figure 2]. Additionally, associated enteric injuries mandating laparotomy should be excluded.

NONOPERATIVE MANAGEMENT

Indications for Nonoperative Management

Nonoperative management of blunt solid-organ injuries is appropriate in hemodynamically stable patients who do not have overt peritonitis or other indications for laparotomy. High-grade injuries, a large amount of hemoperitoneum, contrast extravasation, and pseudoaneurysms are not absolute contraindications for NOM; however, these patients are at high risk for failure and are more likely to need angioembolization.^{8–12} Likewise, there is no patient age cutoff for the NOM of solid-organ injuries. In fact, in contrast to splenic trauma, where age over 55 years is considered a relative indication for operative intervention, older patients appear to be more likely to survive NOM. A multidisciplinary approach including angiography with selective angioembolization has improved NOM success rates as well as survival.^{2,10,11} Patients with grade III or higher injuries should be admitted to the surgical intensive care unit (ICU) with frequent monitoring of their hemodynamics, abdominal examination, and hemoglobin level. Ultrasound surveillance for fluid collections (blood or bile) is warranted for grade IV and V injuries.

Over 80% of patients with liver injuries may be managed nonoperatively. Patients who require laparotomy typically fail NOM in the first 24 to 48 hours.^{2,8} One of the early studies to test the application of nonoperative therapy in 1995 supported its broad application with an overall success rate greater than 85% in hemodynamically stable patients, despite substantial hemoperitoneum documented by CT.⁸ Of the 8% of patients who failed NOM, half required operation as a result of associated injuries (i.e., enteric or pancreatic injuries), whereas half underwent laparotomy for hepatic-related hemorrhage. Perhaps not surprisingly, those patients who failed NOM had increasing rates of failure associated with increasing grades of hepatic injury, with grade V injuries having a greater than 20% failure rate. Subsequent studies have reported failure rates of 14% in grade IV injuries and 23% in grade V injuries.⁹ Similarly, the amount of hemoperitoneum appears to correlate with successful management; patients with a large amount of hemoperitoneum (i.e., blood extending into the pelvis) are more likely to fail NOM. However, predicting which patients will ultimately require laparotomy has yet to be accomplished.

An indication for angioembolization to address ongoing hepatic bleeding is transfusion of 4 units of red blood cells

(RBCs) in 6 hours or 6 units of RBCs in 24 hours. Recurrent hemodynamic instability, however, often requires laparotomy with perihepatic packing for hemostasis. Patients with contrast extravasation identified on CT scan, indicating arterial hemorrhage, should also be considered as a candidate for hepatic angiography. Originally, evidence of extravasation was an indication for laparotomy; however, the advent of endovascular techniques has resulted in effective hemostasis in selected cases. Angioembolization is particularly helpful in hemodynamically stable patients with contrast pooling within the hepatic parenchyma.¹⁰ Patients with contrast extravasation into the peritoneal cavity are more likely to require laparotomy,¹¹ but cases of successful embolization have been reported.¹²

Although not universally embraced, selected patients with penetrating injuries to the right upper quadrant may be candidates for NOM.^{6,7,13,14} Patients must have a CT scan that documents confinement of the injury to the liver [see Figure 3]. Additionally, the patient must be hemodynamically stable, have a reliable physical examination without evidence of peritonitis (i.e., cannot have depressed mental status), and not require blood products. Patients should be admitted for serial examination and hemoglobin monitoring; any alteration should prompt laparotomy. Violation of the diaphragm has the risk of a biliopleural fistula. An alternative approach is to perform laparoscopy to confirm trajectory of the missile or knife and to repair the diaphragm. In addition to avoiding the morbidity of a laparotomy, the success of NOM for penetrating trauma has resulted in decreased hospital stays, lower transfusion requirements, and diminished abdominal infection rates.

Follow-up Imaging

Based on the available literature, clear indications for repeat imaging in asymptomatic patients are lacking, although patients with grade IV or higher injuries are at substantial risk of complications.^{15,16} Repeat imaging in patients with complex hepatic injuries should be performed with bedside ultrasonography. Patients with evidence of right upper quadrant fluid collections or clinical deterioration (increasing abdominal pain, worsening liver function tests, unexplained fever) should undergo CT to exclude a biloma, an abscess, necrosis, or hemorrhage.^{15,16} In asymptomatic patients, the trend in several institutions has been to repeat CT scans in patients with all high-grade injuries, that is grade IV or higher. The rationale is to exclude a delayed pseudoaneurysm, which may rupture, and to document healing, which may be used to guide activity limitations. If postdischarge routine imaging is performed, it is typically done more than 4 weeks after injury.

OPERATIVE EXPOSURE AND HEMORRHAGE CONTROL

In penetrating abdominal injuries not suitable for NOM and in blunt abdominal injuries when NOM is contraindicated or has failed, exploratory laparotomy is performed.

Exposure

Visualization of the right hemiliver [see Figure 4] is hindered by the posterior attachments and by the right lower costal margin. Exposure of the right hemiliver is facilitated by

Table 1 AAST Organ Injury Scales for Liver, Biliary Tract, Diaphragm, and Spleen

Injured Structure	AAST Grade	Characteristics of Injury	AIS-90 Score
Liver*	I	Hematoma: subcapsular, nonexpanding, < 10% surface area	2
		Laceration: capsular tear, nonbleeding, < 1 cm parenchymal depth	2
	II	Hematoma: subcapsular, nonexpanding, 10–50% surface area; intraparenchymal, nonexpanding, < 10 cm in diameter	2
		Laceration: capsular tear, active bleeding, 1–3 cm parenchymal depth, < 10 cm in length	2
	III	Hematoma: subcapsular, > 50% surface area, expanding; ruptured subcapsular hematoma with active bleeding; intraparenchymal, > 10 cm or expanding	3
		Laceration: > 3 cm parenchymal depth	3
	IV	Hematoma: ruptured intraparenchymal hematoma with active bleeding	4
		Laceration: parenchymal disruption involving 25–75% of hepatic lobe or 1–3 Couinaud segments within a single lobe	4
	V	Laceration: parenchymal disruption involving > 75% of hepatic lobe or > 3 Couinaud segments within a single lobe	5
		Vascular: juxtahepatic venous injuries (i.e., injuries to retrohepatic vena cava or central major hepatic veins)	5
	VI	Vascular: hepatic avulsion	5
Extrahepatic biliary tree*	I	Gallbladder contusion/hematoma	2
		Portal triad contusion	2
	II	Partial gallbladder avulsion from liver bed; cystic duct intact	2
		Laceration or perforation of gallbladder	2
	III	Complete gallbladder avulsion from liver bed	3
		Cystic duct laceration	3
	IV	Partial or complete right or left hepatic duct laceration	3
		Partial common hepatic duct or common bile duct laceration (< 50%)	3
	V	> 50% transection of common hepatic duct or common bile duct	3–4
		Combined right and left hepatic duct injuries	3–4
		Intraduodenal or intrapancreatic bile duct injuries	3–4
Diaphragm†	I	Contusion	2
	II	Laceration < 2 cm	3
	III	Laceration 2–10 cm	3
	IV	Laceration > 10 cm, with tissue loss < 25 cm ²	3
	V	Laceration with tissue loss > 25 cm ²	3
Spleen*	I	Hematoma: subcapsular, nonexpanding, < 10% surface area	2
		Laceration: capsular tear, nonbleeding, < 1 cm parenchymal depth	2
	II	Hematoma: subcapsular, nonexpanding, 10–50% surface area; intraparenchymal, nonexpanding, < 5 cm in diameter	2
		Laceration; capsular tear, active bleeding, 1–3 cm parenchymal depth, not involving a trabecular vessel	2
	III	Hematoma: subcapsular, > 50% surface area or expanding; ruptured subcapsular hematoma with active bleeding; intraparenchymal, > 5 cm or expanding	3
		Laceration: > 3 cm parenchymal depth or involving trabecular vessels	3
	IV	Hematoma: ruptured intraparenchymal hematoma with active bleeding	4
		Laceration: laceration involving segmental or hilar vessels producing major devascularization (> 25% of spleen)	4
	V	Laceration: completely shattered spleen	5
		Vascular: hilar vascular injury that devascularizes spleen	5

AAST = American Association for the Surgery of Trauma; AIS-90 = Abbreviated Injury Scale—1990 Revision.

*Advance one grade for multiple injuries, up to grade III.

†Advance one grade for bilateral injuries, up to grade III.

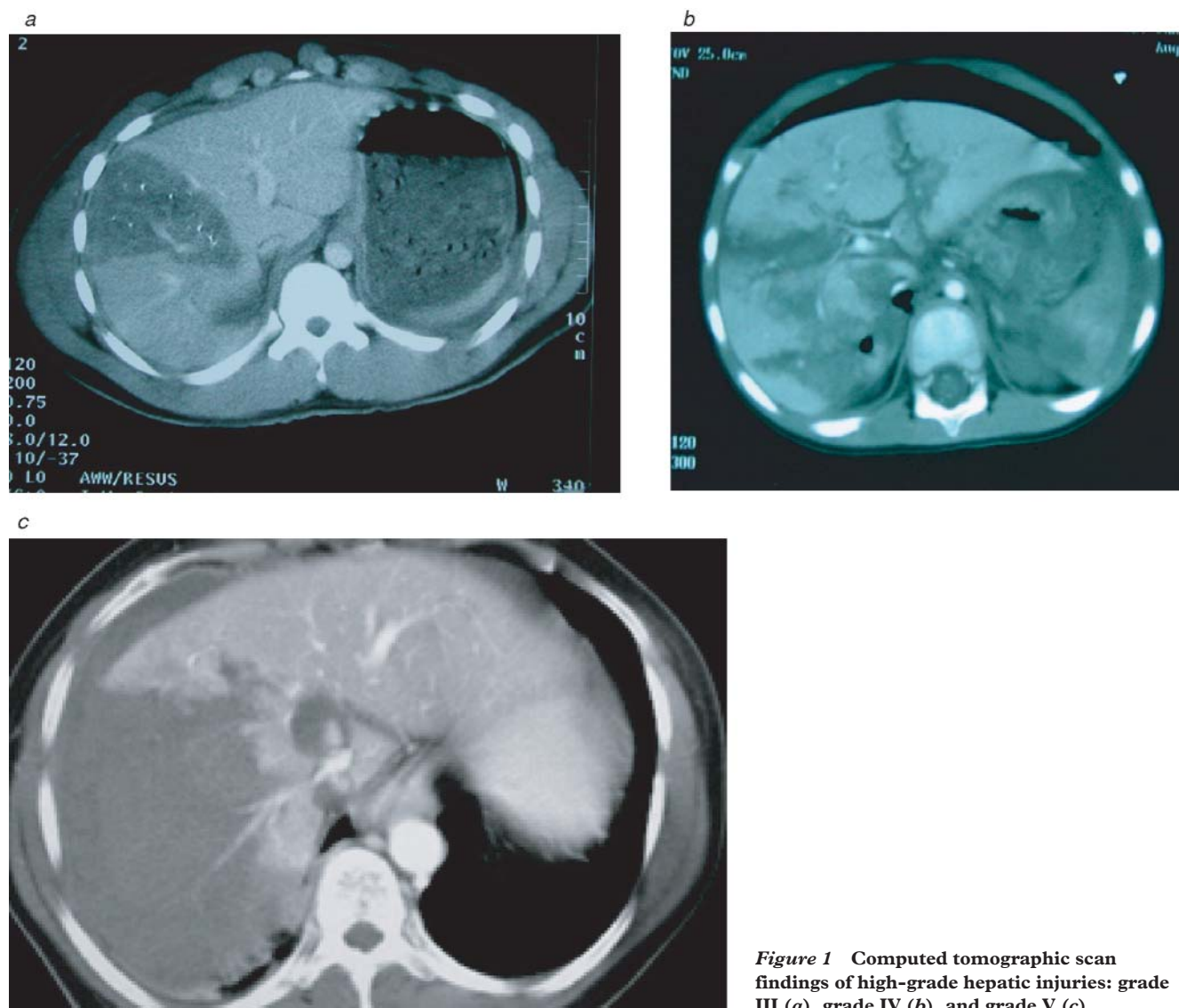


Figure 1 Computed tomographic scan findings of high-grade hepatic injuries: grade III (a), grade IV (b), and grade V (c).

elevating the right costal margin with a large Richardson retractor. Further exposure can be achieved with mobilization, which requires division of the right triangular and coronary ligaments. In dividing the superior coronary ligament, care must be taken not to injure the lateral wall of the right hepatic vein; in dividing the inferior coronary ligament, care must be taken not to injure the right adrenal gland (which is vulnerable because it lies directly beneath the peritoneal reflection) or the retrohepatic vena cava. When the ligaments have been divided, the right hemiliver can be rotated medially into the surgical field. Mobilization of the left hemiliver poses no unusual problems other than the risk of injury to the left hepatic vein, the left inferior phrenic vein, and the retrohepatic vena cava.

If wide exposure of the junction of the hepatic veins and the retrohepatic vena cava is necessary, the midline abdominal incision can be extended by means of a median sternotomy. The pericardium and the diaphragm can then be divided toward the center of the inferior vena cava, minimizing injury to the phrenic nerve. This combination of incisions provides

superb exposure of the hepatic veins and the retrohepatic vena cava while avoiding injury to the phrenic nerves.

Temporary Control of Hemorrhage

Temporary control of hemorrhage is essential for two reasons. First, during treatment of a hepatic injury, ongoing hemorrhage may pose an immediate threat to the patient's life, and temporary control gives the anesthesiologist time to restore the circulating volume before further blood loss occurs. Second, bleeding sites other than the liver are common with both blunt and penetrating trauma, and if the liver is not the highest priority, temporary control of hepatic bleeding permits attention to other life-threatening injuries. The most useful techniques for the temporary control of hepatic hemorrhage are manual compression, perihepatic packing, and the Pringle maneuver.

Manual compression of the liver with laparotomy pads will control the majority of parenchymal hemorrhage [see Figure 5].^{17,18} Manual compression is best suited for immediate attempts to prevent exsanguination and for periodic

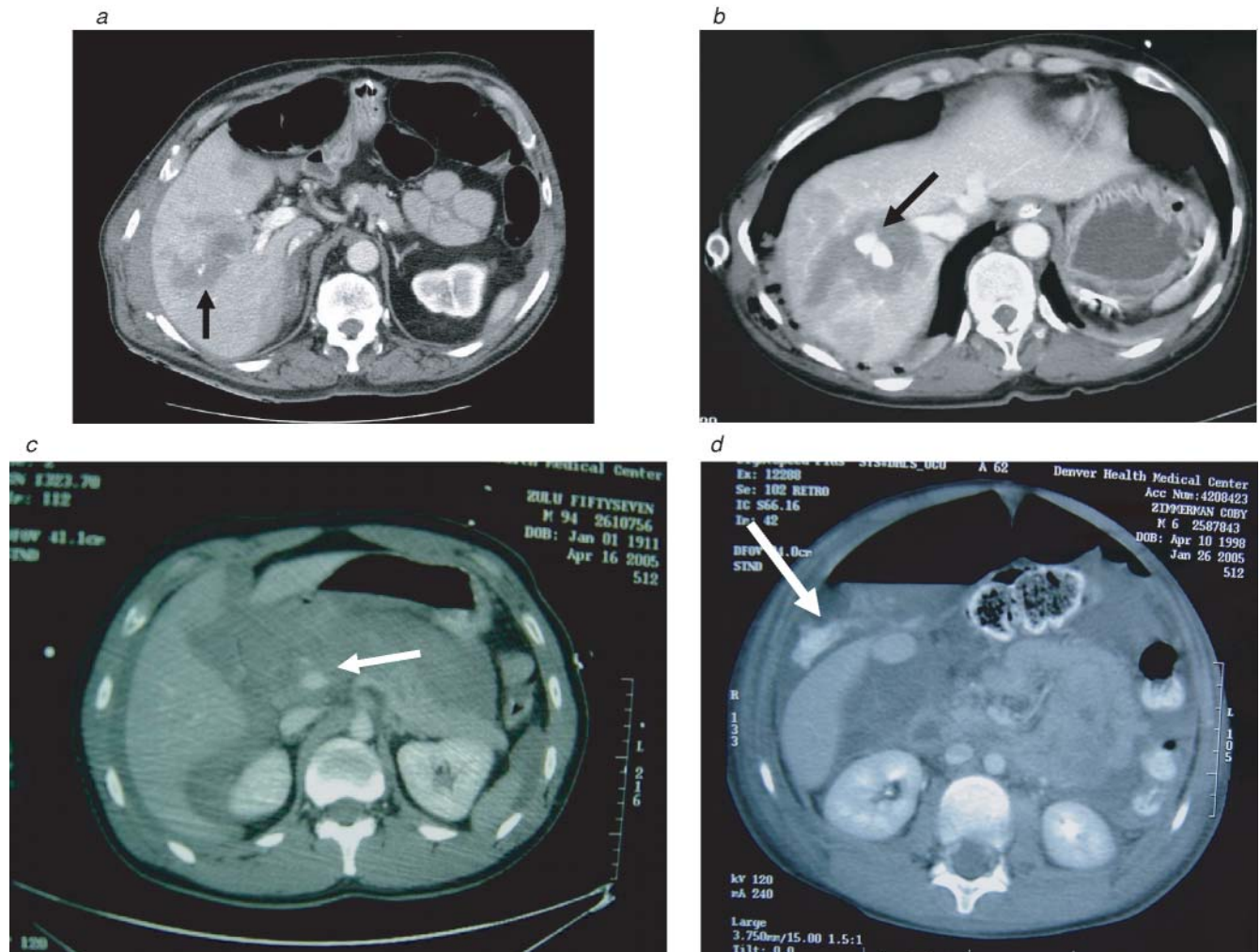


Figure 2 Contrast extravasation (arrows), indicating arterial hemorrhage, can be intraparenchymal (a, b) or intraperitoneal (c, d).

evaluation of bleeding sites during a complex procedure. The goal of this technique is to reapproximate the lacerated edges of the liver to their preinjury conformation.

Perihepatic packing with carefully placed laparotomy pads is capable of controlling hemorrhage from almost all hepatic injuries.¹⁹ The right costal margin is elevated, and the pads are strategically placed over and around the bleeding site [see Figure 6]. Additional pads should be placed between the liver,

diaphragm, and anterior chest wall until the bleeding stops. Ten to 15 pads may be required to control the hemorrhage from an extensive right lobar injury. Packing is not as effective for injuries to the left hemiliver, because with the abdomen open, there is insufficient abdominal and thoracic wall anterior to the left hemiliver to provide adequate compression. Two sequelae may be encountered with the packing of hepatic injuries. First, excessive packing compresses the



Figure 3 Nonoperative management of penetrating abdominal trauma (arrows) may be considered if the wound is isolated to the liver as documented by computed tomographic scan.

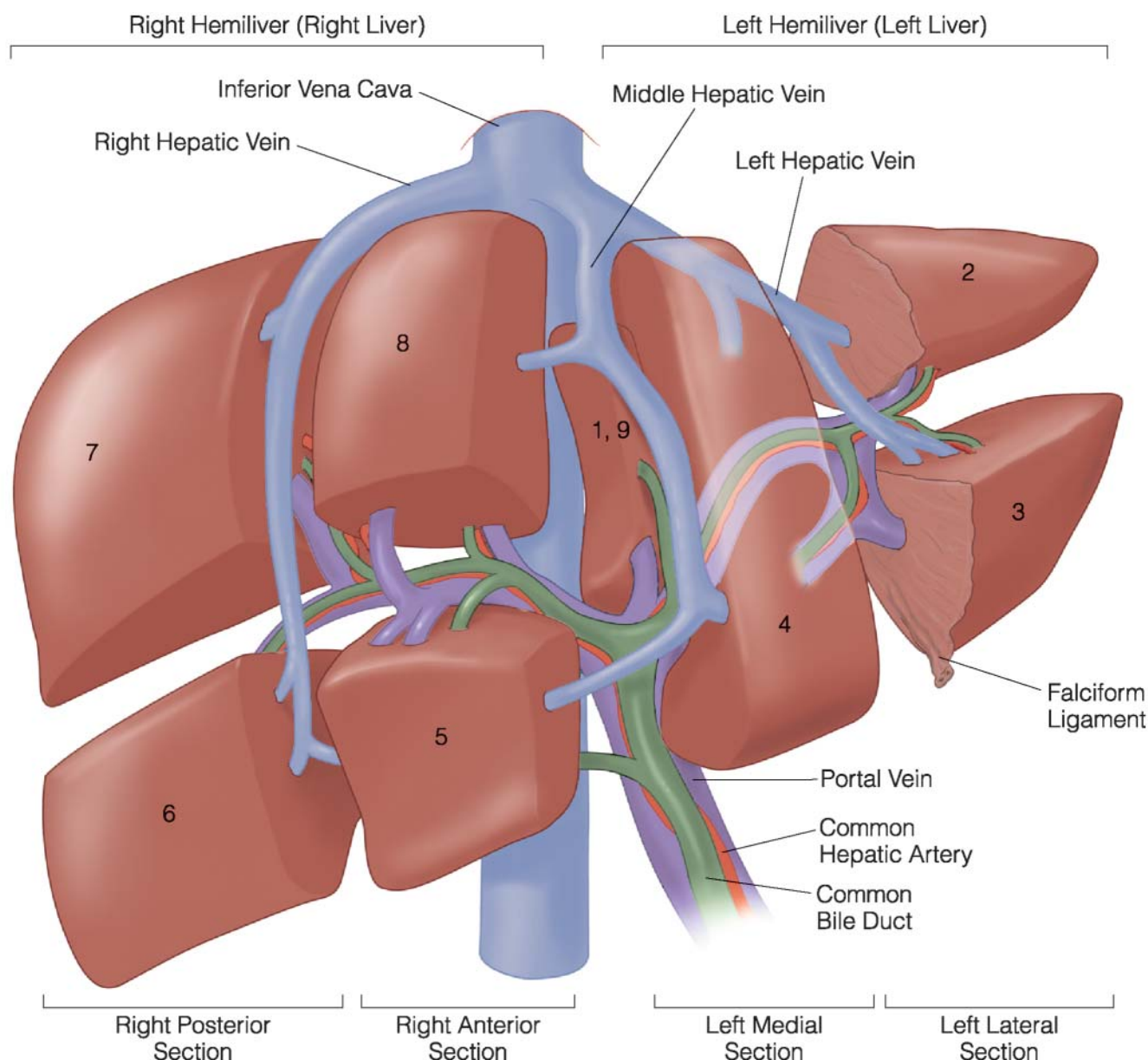


Figure 4 The anatomic divisions of the liver.

inferior vena cava, decreases venous return, and reduces left ventricular filling; hypovolemic patients may not tolerate the resultant decrease in cardiac output. Second, perihepatic packing forces the right diaphragm superiorly and impairs its motion; this may increase airway pressures and thus reduce tidal volume. If the patient has persistent bleeding despite packing, injuries to the hepatic artery, portal vein, and retrohepatic vena cava should be considered.

The Pringle maneuver,²⁰ which is the occlusion of the portal triad using a vascular clamp, can help delineate the source of hemorrhage and provide temporary control [see Figure 7]. We prefer to manually tear the lesser omentum and place the clamp from the patient's left side while guiding the posterior blade of the clamp through the foramen of Winslow with the aid of the left index finger. The advantages of this

approach are as follows: (1) it avoids injury to the hepatic pedicle structures, (2) it includes any aberrant or accessory hepatic arteries, and (3) the handle of the clamp sits over the stomach rather than the right lobe of the liver, hence providing better visualization and access. The length of time that a Pringle maneuver can remain in place without causing irreversible ischemic damage to the liver is unpredictable. Although cases in which a Pringle maneuver has been applied for more than 60 minutes without appreciable hepatic damage have been reported, the goal of warm ischemia time should be less than 30 minutes. An alternative is to release the Pringle maneuver intermittently to allow temporary revascularization. Ideally, one should attempt to perfuse the liver every 15 minutes for 5 minutes. Identification of the source of recurrent massive hemorrhage is clarified with application

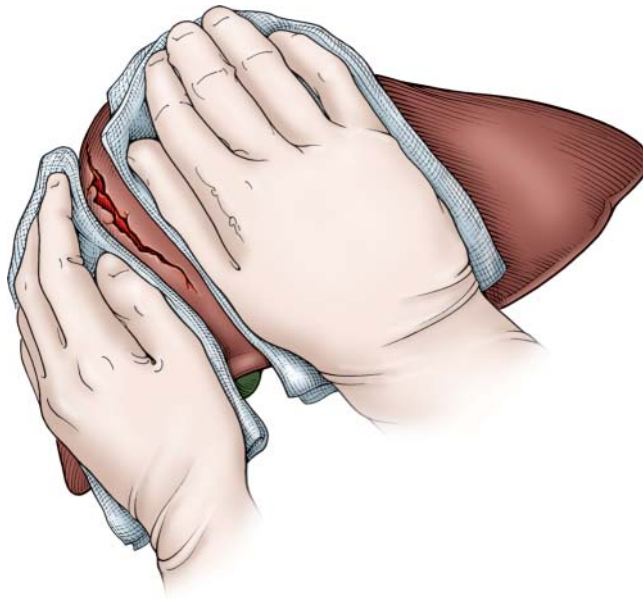


Figure 5 Manual compression, with cooptation of the liver edges, temporarily controls blood loss in hypovolemic patients until the circulating blood volume can be restored.

of the Pringle maneuver; hemorrhage from hepatic artery and portal vein injuries should halt with the application of a vascular clamp across the portal triad (including accessory hepatic arteries), whereas hepatic veins and retrohepatic vena caval bleeding will continue.

Other, less commonly used techniques for hemorrhage control include the application of a tourniquet or a liver

clamp. A 2.5 cm Penrose drain may be used as a tourniquet; once the bleeding hemiliver is mobilized, the Penrose drain is wrapped around the liver near the anatomic division between the left hemiliver and the right hemiliver. The drain is stretched until hemorrhage ceases, and tension is maintained by clamping the drain. Unfortunately, tourniquets are difficult to use: they tend to slip off or tear through the parenchyma if placed over an injured area. An alternative is the use of a liver clamp; however, the application of such devices is hindered by the variability in the size and shape of the liver. We have not had consistent success with either of these methods.

To control hemorrhage from juxtahepatic venous injuries not controlled with perihepatic packing, complex interventions may be required to achieve hepatic vascular isolation. Three techniques that have been employed include (1) use of venovenous bypass with hepatic vascular isolation using clamps on the suprarenal vena cava and the suprahepatic vena cava, (2) the atriocaval shunt, and (3) the Moore-Pilcher balloon shunt. All techniques are performed with an associated Pringle maneuver. Of the three techniques, venovenous bypass is currently used by the authors.

Venovenous bypass²¹ offers several theoretical advantages in the trauma arena: it does not require systemic heparinization, it maintains good venous return to the heart, and it potentially allows decompression of the portal system to minimize bowel edema and avoid the reperfusion of toxic gut-derived products of ischemia. Venovenous bypass is accomplished by placing an 18 French catheter in the inferior vena cava via the femoral vein and a second 12 French catheter in the superior mesenteric vein via the inferior mesenteric vein [see Figure 8]. A centrifugal pump (Biomedicus pump,

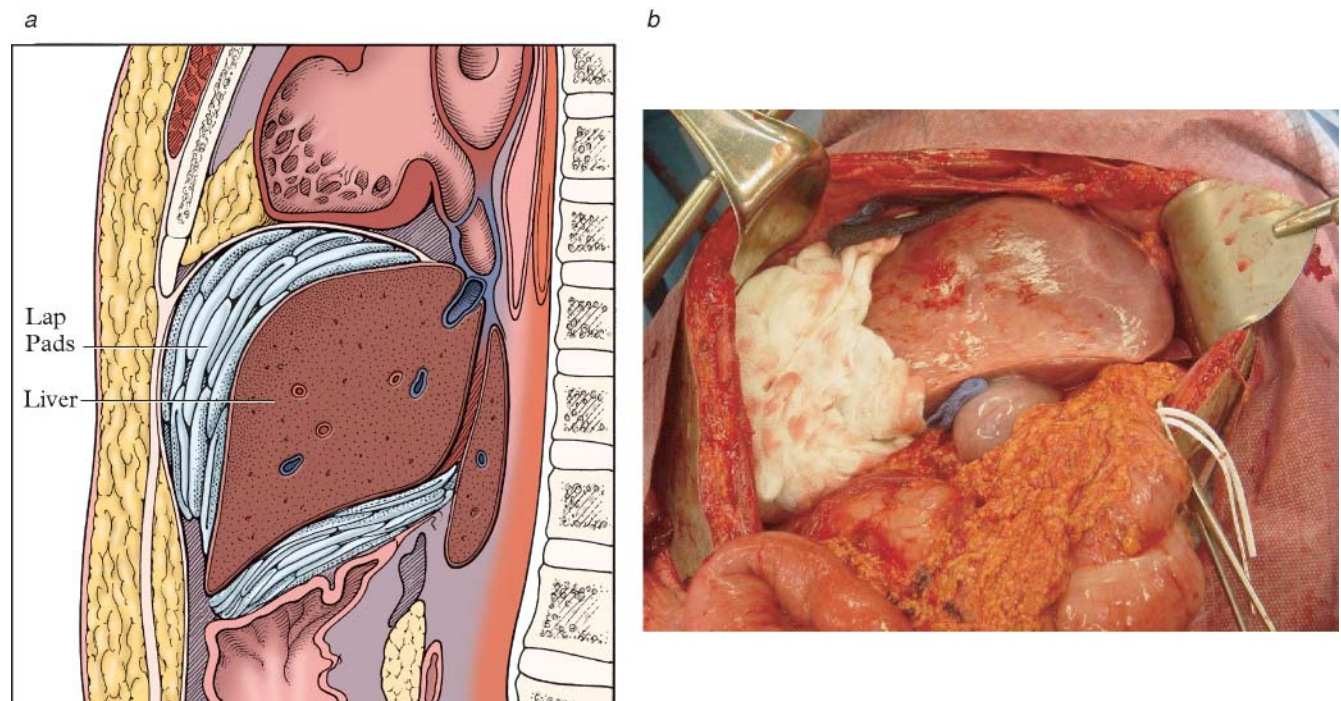


Figure 6 Perihepatic packing is effective in managing the majority of parenchymal injuries. Multiple laparotomy pads are placed between the liver and diaphragm, followed by packs underneath the liver as seen on this sagittal illustration (a) and intraoperative picture (b).

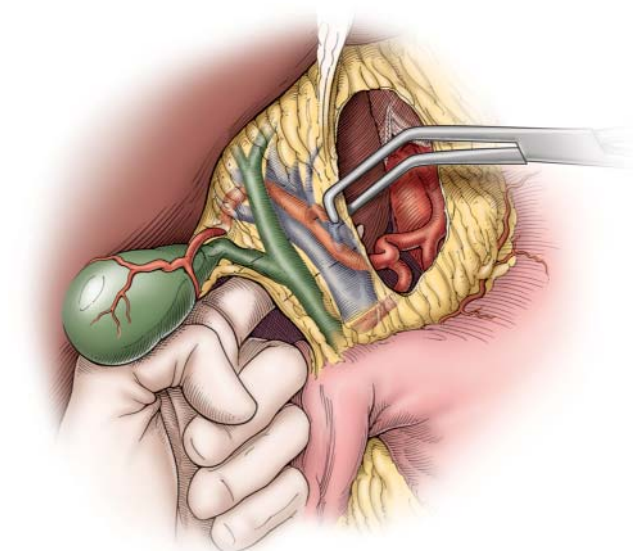


Figure 7 The Pringle maneuver. The portal triad is occluded by guiding the posterior blade of the clamp through the foramen of Winslow with the aid of the left index finger.

Bio-Medics, Inc., Minneapolis, MN) withdraws blood from these veins and pumps it into the superior vena cava through a third 22 French catheter placed in the internal jugular vein. Flow rates of 1 to 2 L/min are maintained by the pump technician, who should limit the risk of air embolus. Hepatic

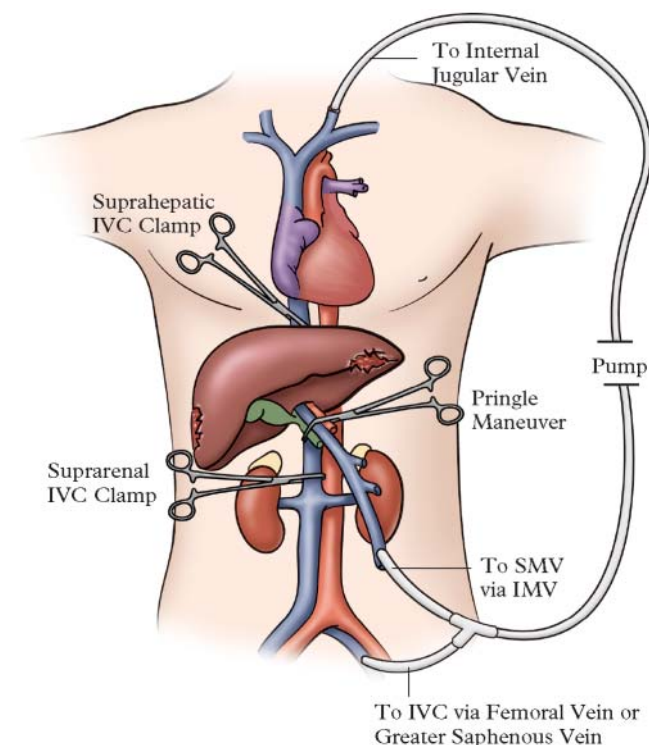


Figure 8 Venovenous bypass permits hepatic vascular isolation with continued venous return to the heart. IMV = inferior mesenteric vein; IVC = inferior vena cava; SMV = superior mesenteric vein.

isolation is achieved by clamping the inferior vena cava just above the renal veins and in a suprahepatic position, followed by a Pringle maneuver using standard vascular clamps.

The atriocaval shunt was designed to achieve hepatic vascular isolation while permitting venous blood to enter the heart from below the diaphragm.²² To place the shunt, the suprarenal and suprahepatic vena cava are encircled, and a 36 French chest tube is passed into the cava from a purse-string-controlled hole in the right atrial appendage. A variation of the original atriocaval shunt has been the substitution of a 9 mm endotracheal tube for the large chest tube [see Figure 9]. Although this change may seem trivial, surrounding the suprarenal vena cava with a snare tourniquet is extremely difficult because exsanguinating hemorrhage must be controlled by posterior compression of the liver, which severely restricts access to that segment of the vena cava. A historical alternative to the atriocaval shunt is the Moore-Pilcher balloon, which is no longer commercially available.²³ This device was inserted through the femoral vein and advanced into the retrohepatic vena cava. When the balloon was inflated, the hepatic veins and vena cava were occluded,

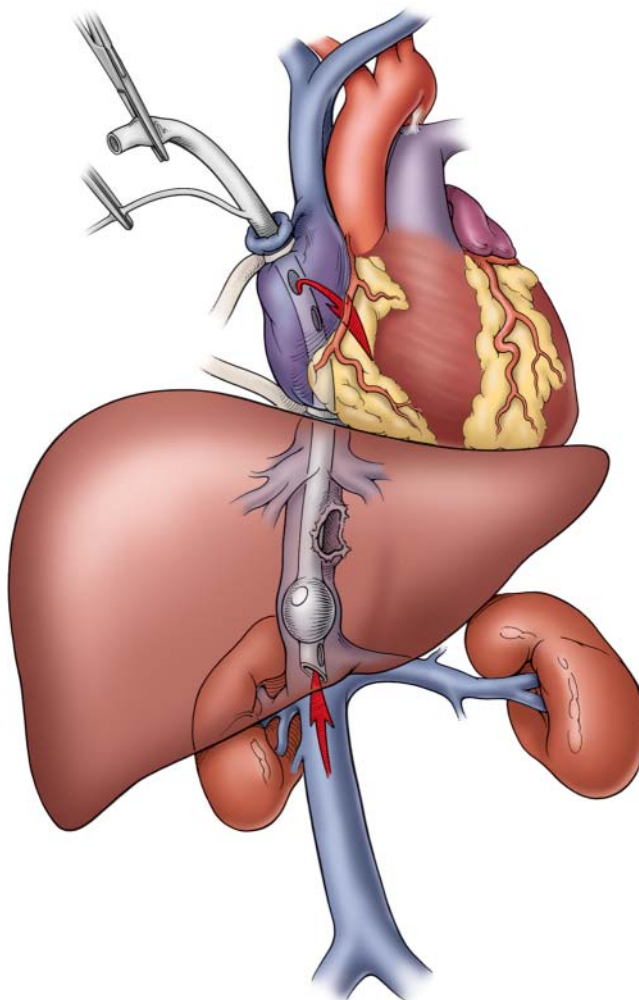


Figure 9 An endotracheal tube can be adapted to become an atriocaval shunt by cutting proximal holes to allow flow of blood into the atrium.

thereby achieving vascular isolation. The catheter itself was hollow, and holes placed below the balloon permitted blood to flow into the right atrium from the inferior vena cava. Despite a theoretically easier approach, there was no documented improvement in survival with this balloon occlusion technique.²⁴

Even in experienced centers with readily available equipment, however, such techniques carry a mortality rate greater than 80%. Surgeons who attempt hepatic vascular isolation should be aware that none of the techniques provide complete hemostasis. Because of the technical challenge and high mortality associated with hepatic vascular isolation, there has been a recent trend to avoid a direct operative approach to the injured vessels. If massive venous hemorrhage is seen from behind the liver, and if reasonable hemostasis can be achieved with perihepatic packing, the patient can be transferred to the interventional radiology suite, where hemorrhages from arterial sources are embolized and stents are placed to bridge venous injuries.²⁵

DEFINITIVE MANAGEMENT OF INJURIES

Parenchymal Injuries

A number of effective methods for the definitive control of hepatic parenchymal hemorrhage have been developed. Minor lacerations may be controlled with manual compression applied directly to the injury site. Topical hemostatic techniques include electrocautery (set at 100), the argon beam coagulator (set at 100), microcrystalline collagen, thrombin-soaked gelatin foam sponge, fibrin glue, and BioGlue (BioForm Medical, San Mateo, CA). Suturing of the hepatic parenchyma with large, liver stitches is generally discouraged because of the obligatory hepatic necrosis but remains an effective hemostatic technique in selected cases. The preferred suture material is 2-0 chromic catgut attached to a large, blunt-tipped, curved needle; the large diameter prevents the suture from pulling through the Glisson capsule. If, however, the capsule of the liver has been stripped away by the injury, this technique is far less effective. Interrupted simple or horizontal mattress sutures are placed parallel to the edge of the laceration. When tying sutures, adequate tension is achieved when hemorrhage ceases or the liver blanches around the suture. This technique of placing large liver sutures controls bleeding through reapproximation of the liver laceration rather than direct ligation of bleeding vessels. Aggressive finger fracture to identify bleeding vessels followed by individual clip or suture ligation was advocated previously but currently has a limited role in hemostasis. Hepatic lobar arterial ligation may be appropriate for patients with recalcitrant arterial hemorrhage from deep within the liver and is preferable to a deep hepatotomy, particularly in unstable patients. Omentum can be used to fill large defects in the liver. The tongue of omentum not only obliterates potential dead space with viable tissue but also provides an excellent source of macrophages. Additionally, the omentum can provide buttressing support for parenchymal sutures. Perihepatic packing following hepatic artery ligation is associated with an increased risk of hepatic necrosis. Several studies have demonstrated that the use of Penrose or sump drains is associated with a greater risk of intra-abdominal sepsis when compared with those treated with closed suction drains or no

drains.²⁶ Closed drains, however, are indicated if bile is seen emanating from the liver.

Resectional débridement is indicated for peripheral portions of nonviable hepatic parenchyma. Except in rare circumstances, the amount of tissue removed should not exceed 25% of the liver. Resectional débridement is performed by means of the finger-fracture technique or a modified stapled technique and is appropriate for selected patients with grade III to grade V lacerations. Because additional blood loss occurs during removal of associated viable tissue, this procedure should be reserved for patients who are in sound physiologic condition and can tolerate additional blood loss.

The final alternative for patients with extensive injuries to one hemiliver is anatomic hepatic resection. In elective circumstances, anatomic hemihepatectomies can be performed with excellent results; however, in the setting of trauma, the mortality associated with this procedure exceeds 50% in most series. Consequently, hepatic resection is rarely performed in trauma patients, having been largely replaced by perihepatic packing. Nonetheless, there are two circumstances in which anatomic resection may still be a reasonable choice. The first is prompt resection in patients with extensive injuries of the left lateral section of the liver because there is a much smaller area of parenchyma to traverse compared with lobectomy. The second is delayed anatomic hemihepatectomy in patients whose hemorrhage has been controlled but whose left or right hemiliver is nonviable as a result of ligation or thrombosis of critical blood supply. Because of the large mass of necrotic liver tissue, there is a high risk of subsequent infection or persistent hyperinflammation, setting the stage for multiple organ failure (MOF). The necrotic hemiliver should be removed as soon as the patient's condition permits.

Portal Triad Vascular Injuries

Injuries of the portal triad vasculature must be addressed immediately to control potential massive hemorrhage and minimize hepatic reperfusion injury. In general, ligation from the celiac axis to the level of the common hepatic artery at the gastroduodenal arterial branch is tolerated as a result of extensive collaterals, but the proper hepatic artery should be repaired. The right or left hepatic artery, or, in urgent situations, the portal vein, may be selectively ligated; occasionally, lobar necrosis will necessitate delayed anatomic resection. If the right hepatic artery is ligated, cholecystectomy should also be performed. Initial control of vascular injuries is accomplished digitally by applying enough direct pressure to stop the hemorrhage. Sharp dissection is used to define the injury and mobilizes sufficient length for proximal and distal control. Heparinized saline (50 U/mL) is injected into the proximal and distal ends of the injured vessel to prevent clot formation on the exposed intima. Ragged edges of the injury site should be judiciously débrided using sharp dissection.

The type of operative repair is based on the extent of injury. Lateral suture repair is preferred for arterial injuries with minimal loss of tissue. If the vascular injury is a stab wound with clean transection of the vessels, a primary end-to-end anastomosis is done. If the injury is destructive, temporary intravascular shunting should be used to reestablish inflow

while preparing for definitive repair. Interposition grafts are used in such cases when end-to-end anastomosis cannot be accomplished without tension despite mobilization. For the hepatic artery, autogenous saphenous vein from the groin should be used because polytetrafluoroethylene (PTFE) grafts less than 6 mm have a prohibitive rate of thrombosis. The portal vein, however, can be bridged with a PTFE graft. Portal triad injuries may be complicated with enteric contamination from colon or small bowel injuries. There is natural reluctance to place artificial grafts in such circumstances, but graft infections are rare. Therefore, following the control of hemorrhage, bowel contamination is contained and the abdomen irrigated before placing PTFE grafts. Blunt avulsions of the portal structures are particularly problematic if located at the hepatic plate, flush with the liver; hemorrhage control at the liver can be attempted with directed packing or Fogarty catheters. If the avulsion is more proximal, flush with the border of the pancreatic body or even behind the pancreas, the body of the pancreas must be transected to gain access for hemorrhage control and vascular repair. Overall mortality in patients with portal triad injuries is greater than 50%, with mortality approaching 80% in patients with combined injuries.²⁷ With the majority of deaths related to exsanguination in the operating room or postinjury refractory shock in the ICU, early hemorrhage control is paramount.

Penetrating Injuries

Simple lacerations can often be managed with interrupted simple liver sutures of 0-chromic. Translobar penetrating injuries are particularly challenging because the bullet frequently traverses a major blood vessel and the extent of the injury cannot be visualized. Management options include intraparenchymal tamponade with a Foley catheter or balloon occlusion.²⁸ A homemade balloon can be fashioned by placing a red Robinson catheter inside a 1-inch Penrose drain, ligating each end of the drain [see Figure 10]. The

deflated balloon is then inserted into the bleeding tract, and, once positioned, a contrast agent is injected through the red Robinson catheter to fill the Penrose balloon. If control of the hemorrhage is successful, a stopcock or clamp is used to occlude the catheter and maintain the inflation. Another option for hemorrhage control, particularly for deep lacerations, is Foley catheter occlusion [see Figure 11]. Using a Foley catheter with a 30 cc balloon, the tip is placed deep within the tract; the balloon is inflated sequentially along the length of the tract until hemorrhage stops. If tamponade is successful with either modality, the balloon is left inflated for 24 to 48 hours followed by judicious deflation in the surgical ICU and removal at a second laparotomy. If recurrent hemorrhage occurs, selective angioembolization should be pursued. Hepatotomy, using the finger-fracture technique, with ligation of individual bleeders may occasionally be required. However, division of the overlying viable hepatic tissue may cause considerable blood loss in the coagulopathic patient.

Gallbladder and Extrahepatic Duct Injuries

Injuries to the gallbladder or extrahepatic ducts may occur in isolation or in combination with more complex hepatic injuries.^{1,2} Cholecystectomy is performed for injuries to the gallbladder and following operative ligation of the right hepatic artery. Injuries of the extrahepatic bile ducts are a challenge because of their small size and thin walls. Because of the proximity of other portal structures and the vena cava, associated vascular injuries are common. Small lacerations, with no loss or devitalization of adjacent tissue, can be treated by the insertion of a T tube through the wound or by lateral suture using an absorbable 6-0 monofilament. Virtually all transections, and any injury associated with significant tissue loss, will require a Roux-en-Y choledochojejunostomy. The anastomosis is performed using a single-layer, interrupted technique using 6-0 monofilament absorbable suture. To reduce anastomotic tension, the jejunum should be tethered to the areolar tissue of the hepatic pedicle or porta hepatis.

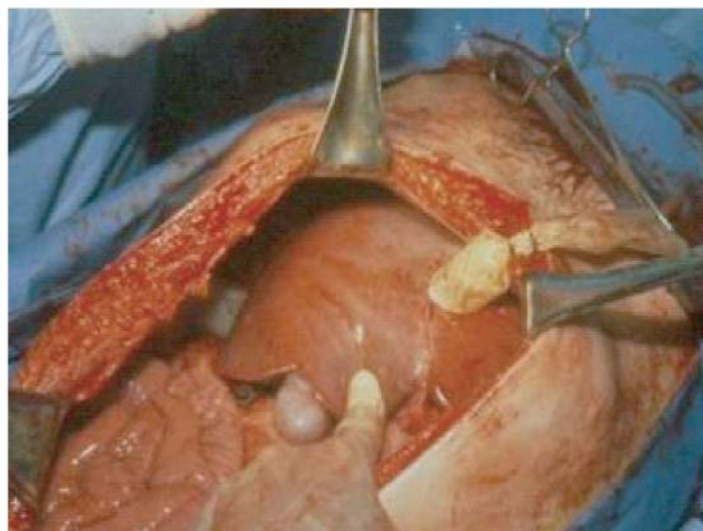
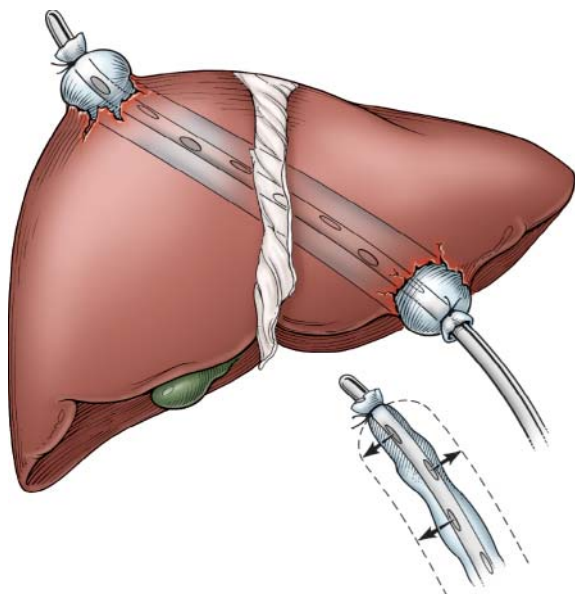


Figure 10 Penrose expansion into a balloon with injection of saline (arrows), as described by Poggetti and colleagues, effectively controls translobar penetrating wounds.²⁸

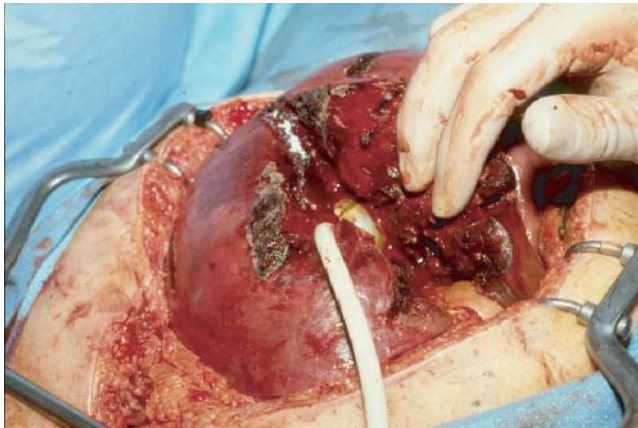


Figure 11 Using a Foley catheter with a 30 cc balloon can also effectively tamponade deep laceration following blunt or penetrating trauma.

Injuries to the major hepatic ducts may not be possible to repair under emergent circumstances. One approach is to intubate the duct for external drainage and attempt a repair when the patient recovers. Alternatively, the lobar duct can be ligated if the opposite lobe is normal and uninjured.^{27,29}

POSTOPERATIVE CARE

Patients undergoing perihepatic packing for extensive liver injuries are typically returned to the operating room for pack removal 24 to 36 hours after the initial injury. Earlier exploration may be indicated in patients with evidence of ongoing hemorrhage. Signs of rebleeding are a falling hematocrit, blood clots accumulating under the temporary abdominal closure device, and bloody output from the Jackson-Pratt drains placed under the abdominal Ioban covering (3M, St. Paul, MN); the magnitude of hemorrhage is reflected in transfusion requirements and refractory acidosis. Patients with hepatic ischemia, as a result of a prolonged intraoperative Pringle maneuver, have an expected elevation but subsequent resolution of their transaminases; alternatively, patients requiring hepatic artery ligation may develop hepatic necrosis. Although patients should be evaluated for potential infectious complications, patients with complex hepatic injuries frequently have intermittent “liver fever” for the first 5 postinjury days. If perihepatic drains were placed intraoperatively, the quantity and quality of output should be evaluated. Persistent bilious output should prompt investigation for a bile leak. Alternatively, abrupt cessation of drainage with an associated fever should prompt consideration for diagnostic imaging.

In general, outcome following vascular injuries of the portal triad is related to the early technical success of the operation. Following hepatic artery interposition grafting, the patient’s systolic blood pressure should not exceed 140 mm Hg for at least the first 72 hours postoperatively. Conversely, following hepatic artery ligation, hypotension should be avoided. Midline laparotomy wounds are inspected 48 hours postoperatively by removing the sterile surgical dressing. If a wound infection is identified—evidenced by erythema, pain along the wound, or purulent drainage—the wound should be

opened by removing skin staples. After ensuring that the midline fascia is intact with digital palpation, the wound is initially managed with wet-to-dry dressing changes.

MORTALITY AND COMPLICATIONS

Overall mortality for patients with hepatic injuries is approximately 10%. The most common cause of death is exsanguination, followed by MOF and intracranial injury. Complications following major hepatic trauma include delayed hemorrhage, bilomas, perihepatic abscesses, hepatic necrosis, arterial pseudoaneurysms, and various fistulae.^{15,16} In patients requiring perihepatic packing, postoperative hemorrhage is not unusual. Ideally, patients should undergo reexploration once their coagulopathy is corrected; however, unstable patients should be returned to the operating room emergently for evaluation and repacking. Alternatively, angioembolization is appropriate in select cases, particularly for central lesions.

The most common sequelae of hepatic trauma are biliary fistulas, complicating up to 20% of injuries.^{8,16,30} Clinical presentation includes abdominal distention, pain and tenderness on examination; intolerance of enteral feeding; and abnormal liver function tests. Bedside ultrasonography should be used liberally. Bilomas, loculated collections of bile, can have a variable clinical course. Small, sterile bilomas will eventually be reabsorbed, but larger fluid collections should be drained percutaneously [see Figure 12]. Bilomas may become infected, particularly after penetrating trauma, and should be treated much like any other intra-abdominal abscess. If operative drainage becomes necessary for loculated collections, a twelfth rib resection approach provides optimal drainage for posterior infections. Biliary ascites, attributable to the disruption of a major bile duct, often requires reoperation. If the patient was initially treated nonoperatively, a laparoscopic approach may be considered for abdominal washout and drain placement.³¹ Primary repair of the injured duct is unlikely to be successful and is rarely attempted. Endoscopic retrograde cholangiography should be relied on for both diagnosis and treatment³² [see Figure 12]. Occasionally, the ductal injury can be stented, with adjunctive sphincterotomy to reduce pressure within the biliary system.^{30,33} The vast majority of ductal injuries, particularly in patients managed nonoperatively, heal within 4 to 6 weeks. Patients undergoing hepatic artery ligation, either operatively or with angioembolization, may develop hepatic necrosis. Resectional débridement is indicated for the removal of peripheral portions of nonviable hepatic parenchyma.³⁴

Pseudoaneurysms are rare complications of patients with hepatic injuries. Given that hemorrhage from hepatic injuries is often treated without isolating individual bleeding vessels, arterial pseudoaneurysms may develop, with the potential for rupture. Rupture into a bile duct results in hemobilia, which is characterized by intermittent episodes of right upper quadrant pain, upper gastrointestinal hemorrhage, and jaundice. If the aneurysm ruptures into a portal vein, portal venous hypertension with bleeding esophageal varices may occur. Either scenario is best managed with hepatic arteriography and embolization.^{35,36} Biliovenous fistulae, causing jaundice as a result of rapid increases in serum bilirubin levels, should

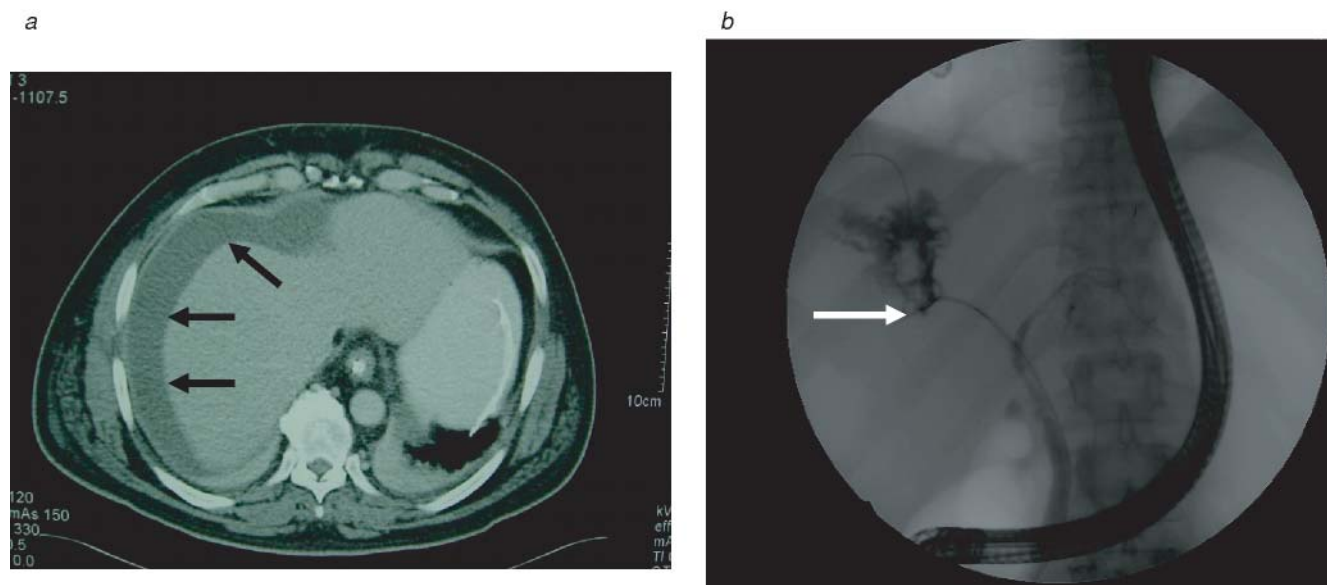


Figure 12 A biloma, evident on a computed tomographic scan (a), with an associated right hepatic duct injury evident on endoscopic retrograde cholangiography (b).

be treated with endoscopic retrograde cholangiopancreatography and sphincterotomy.³⁷ Rarely, a biliary fistulous communication will form with intrathoracic structures in patients with associated diaphragm injuries, resulting in a bronchobiliary or pleurobiliary fistula. As a result of the pressure differential between the positive biliary tract and the negative pleural cavity, the majority require operative closure. Occasionally, endoscopic sphincterotomy with stent placement will effectively address the pressure differential, and the pleurobiliary fistula will close spontaneously.

Injuries to the Spleen

The spleen is the second most commonly injured abdominal organ in blunt trauma patients. Historical studies have reported a 10% mortality with all splenic injuries; however, isolated splenic injury mortality is less than 1%. The mechanisms of injury are similar to those seen with liver injuries: motor vehicle collisions, autopedestrian accidents, and falls. Similar to penetrating trauma to the liver, stab wounds to the spleen typically result in direct linear tears, whereas gunshot wounds result in significant cavitory injuries.

Until the 1970s, splenectomy was considered mandatory for all splenic injuries. Recognition of the immune function of the spleen refocused efforts on splenic salvage in the 1980s.^{38,39} Following success in pediatric patients, NOM of splenic injuries was adopted in the adult population and has become the prevailing strategy for blunt splenic trauma.⁴⁰

INITIAL EVALUATION AND INJURY GRADING

Addressing the patient's ABC's, examining the patient's abdomen, and performing adjunctive imaging with FAST and CT are the initial steps of diagnosing a patient's splenic injury. Hypotension with a positive FAST scan should prompt emergent laparotomy. For patients with an identified blunt splenic injury on a CT scan, the injury should be graded

according to the AAST injury grading scale [see Table 1].³ Similar to liver injuries, the grade of splenic injury predicts failure rates and complication rates of NOM. Other findings that should be searched for on a CT scan include contrast extravasation (is the contrast blush contained within the spleen, or does it spill into the peritoneum?), the amount of intra-abdominal hemorrhage (is it isolated to the splenic fossa, or does blood extend into the pelvis?), and the presence of pseudoaneurysms [see Figure 13].

NONOPERATIVE MANAGEMENT

Indications for Nonoperative Management

NOM of solid-organ injuries is pursued in hemodynamically stable patients who do not have overt peritonitis or other indications for laparotomy.^{41–45} There is no age cutoff for patients for the NOM of solid-organ injuries.^{46,47} High-grade injuries, a large amount of hemoperitoneum, contrast extravasation, and pseudoaneurysms are not absolute contraindications for NOM; however, these patients are at high risk for failure.^{48–51} The identification of contrast extravasation as a risk factor for failure of NOM led to liberal use of angioembolization. The true value of angioembolization in splenic salvage has not been rigorously evaluated. Patients with intraparenchymal splenic blushes who are otherwise asymptomatic may be considered for a period of observation rather than empiric angioembolization⁵²; it is thought that the contained hemorrhage within the splenic capsule may result in tamponade of the bleeding [see Figure 14].

It is clear, however, that 20 to 30% of patients with splenic trauma deserve early splenectomy and that failure of NOM often represents poor patient selection.^{53,54} In adults, indications for prompt laparotomy include initiation of blood transfusion within the first 12 hours considered to be secondary to the splenic injury or hemodynamic instability. In the pediatric

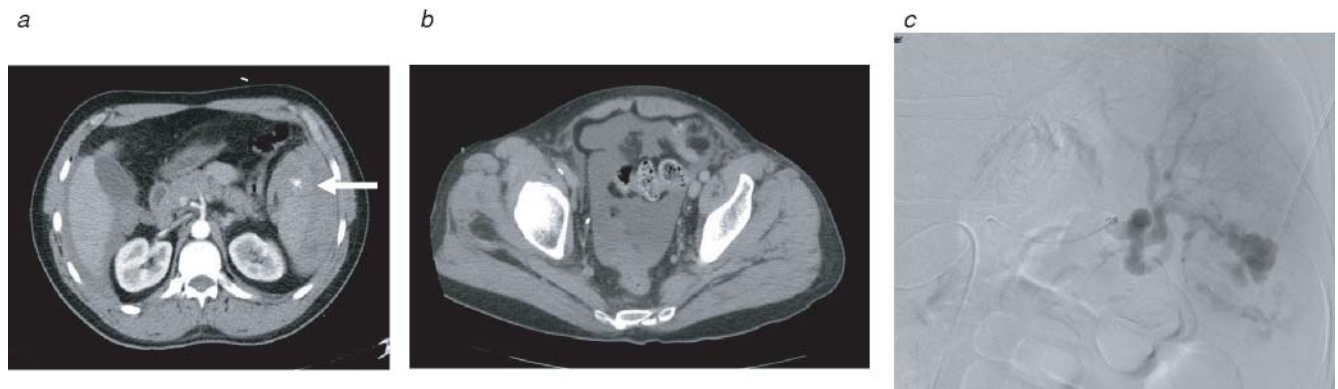


Figure 13 Findings on imaging that are associated with failure of nonoperative management for splenic injuries: contrast extravasation or “blush” (arrow) (a), intra-abdominal hemorrhage extending into the pelvis (b), and pseudoaneurysms (c).

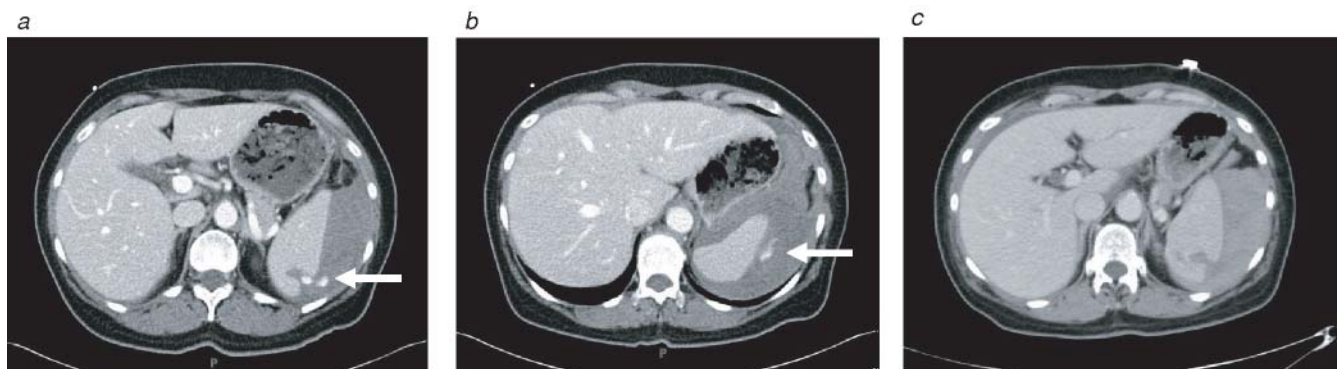


Figure 14 Intraparenchymal splenic blush (arrows) noted on an initial computed tomographic scan (a, b) may resolve following a period of close observation (c).

population, blood transfusions up to half of the patient’s blood volume are used prior to operative intervention. Following the first 12 postinjury hours, indications for laparotomy are not as black and white. Determination of the patient’s age, comorbidities, current physiology, degree of anemia, and associated injuries will determine the use of transfusion alone versus intervention with either embolization or operation. Unlike hepatic injuries, which rebleed in 24 to 48 hours, delayed hemorrhage or rupture of the spleen can occur up to weeks following injury. Algorithms for the management of pediatric splenic injuries exist,⁵⁵ and the patient’s physiologic status is the key determinant. Rapid mobilization in patients who are hemodynamically stable with a stable hematocrit and no abdominal pain is generally successful. Overall, nonoperative treatment obviates laparotomy in more than 90% of cases.

Follow-up Imaging

Out of concern over the risk of delayed hemorrhage or other complications, follow-up CT scans have often been recommended; unfortunately, there is no consensus as to when or even whether they should be obtained. Patients with grade I or II splenic injuries rarely show progression of the lesion or other complications on routine follow-up CT scans;

it is reasonable to omit such scans if patients’ hematocrits remain stable and they are otherwise well. Patients with more extensive injuries often have a less predictable course, and CT may be necessary to evaluate possible complications. Routine CT before discharge, however, is unwarranted. Outpatient CT, however, in patients who participate in vigorous or contact sports should be performed at 6 weeks to document complete healing before resuming those activities. A more convenient and less expensive alternative to follow-up CT is ultrasonographic monitoring of lesions.

OPERATIVE EXPOSURE AND HEMORRHAGE CONTROL

In penetrating abdominal injuries not suitable for NOM and in blunt abdominal injuries when NOM is contraindicated or has failed, exploratory laparotomy is performed.

To ensure safe removal or repair, the spleen should be mobilized to the point where it can be brought to the surface of the abdominal wall without tension. An incision is made in the peritoneum and the endoabdominal fascia, beginning at the white line of Toldt along the descending colon and continuing cephalad 1 to 2 cm lateral to the posterior peritoneal reflection of the spleen; this plane of dissection is continued superiorly until the esophagus is encountered [see Figure 15a]. Posteriorly, blunt dissection is performed to

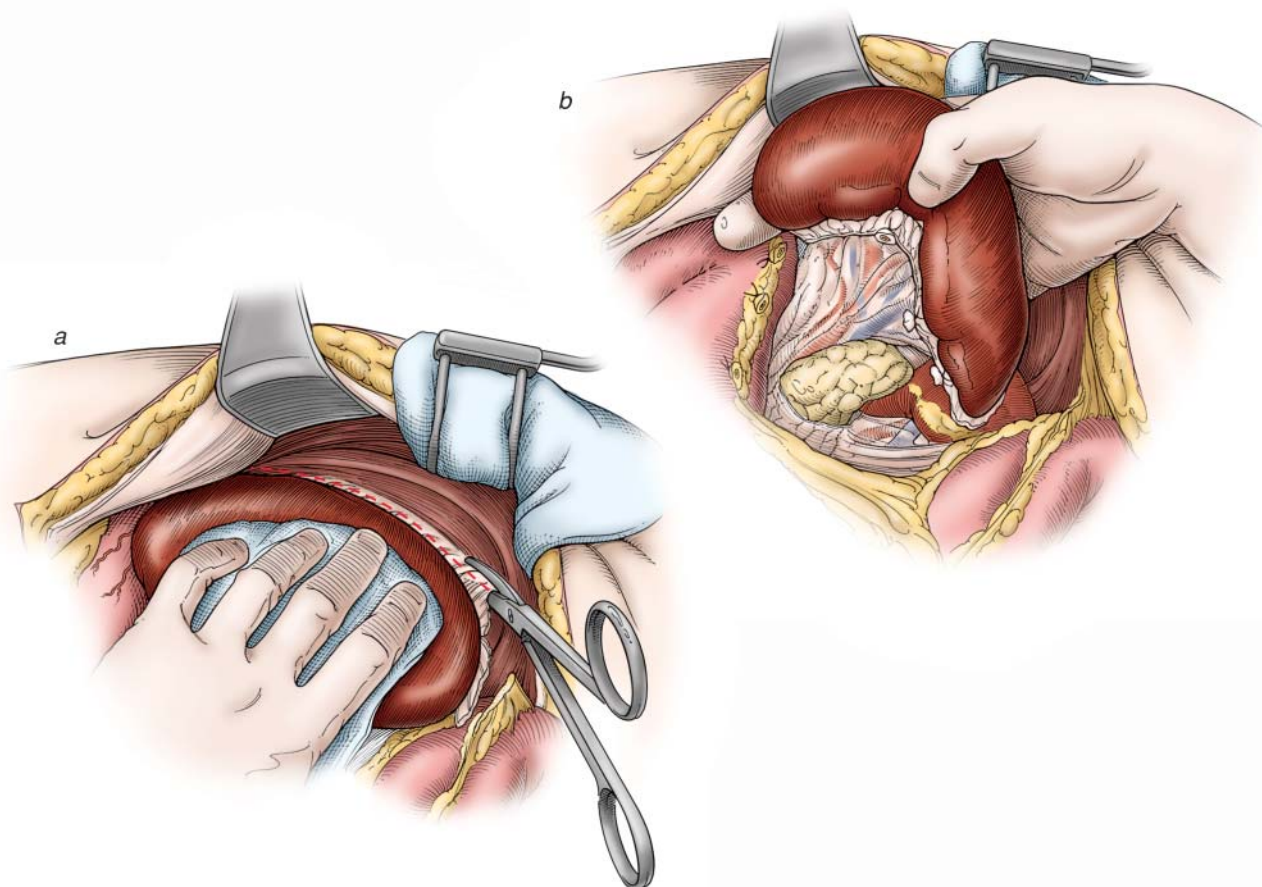


Figure 15 The first step in mobilizing the spleen is to make an incision in the peritoneum and the endoabdominal fascia, beginning at the inferior pole and continuing posteriorly and superiorly (a). The correct plane of dissection is between the pancreas and Gerota fascia (b).

mobilize the spleen and pancreas as a composite away from Gerota fascia and up and out of the retroperitoneum; this posterior plane may be extended to the aorta if necessary [see Figure 15b]. Additionally, the attachments between the spleen and the splenic flexure of the colon may be divided to avoid avulsion of the inferior splenic capsule. Care must be taken not to pull on the spleen; otherwise, it will tear along the posterior peritoneal reflection, causing significant hemorrhage. It is often helpful to rotate the operating table 20° to the patient's right so that the weight of the abdominal viscera facilitates viscera retraction. Any ongoing hemorrhage from the splenic injury may be temporarily controlled with digital occlusion of the splenic hilar vessels. Once mobilization is complete, the spleen can be repaired or removed without any need to struggle to achieve adequate exposure.

DEFINITIVE MANAGEMENT OF INJURIES

Splenic injuries are treated operatively by splenectomy, partial splenectomy, or splenic repair (splenorrhaphy), based on the extent of the injury and the physiologic condition of the patient. Splenectomy is indicated for hilar injuries, pulverized splenic parenchyma, or any grade II or higher injury in a coagulopathic or multiply injured patient. We

employ autotransplantation of splenic implants [see Figure 16] for partial immunocompetence in younger patients.⁵⁶ Drains are not used. Partial splenectomy can be employed in patients in whom only the superior or inferior pole has been injured. Hemorrhage from the raw splenic edge is controlled with a horizontal mattress suture, with gentle compression of the parenchyma [see Figure 17]. Similar to hepatic injuries, splenorrhaphy techniques to achieve hemostasis include topical agents (electrocautery, argon beam coagulation, thrombin-soaked gelatin foam sponge, fibrin glue, BioGlue), enveloping the injured spleen in absorbable mesh, and pledgeted suture repair.

POSTOPERATIVE CARE AND COMPLICATIONS

Enthusiasm for splenic salvage was driven by the rare but often fatal complication of overwhelming postsplenectomy sepsis (OPSS). OPSS is caused by encapsulated bacteria, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*, which are resistant to antimicrobial treatment. In patients undergoing splenectomy, prevention against these bacteria is provided via vaccines administered optimally at 14 days but definitely prior to hospital discharge.⁵⁷ Vaccines to be administered include Pneumovax (Merck & Co.,

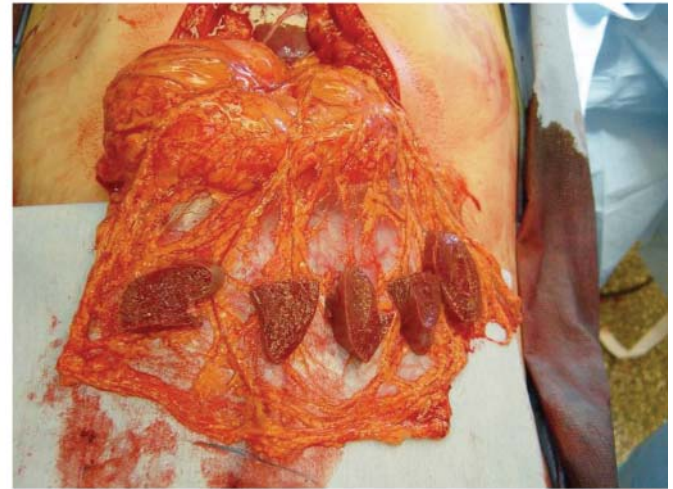
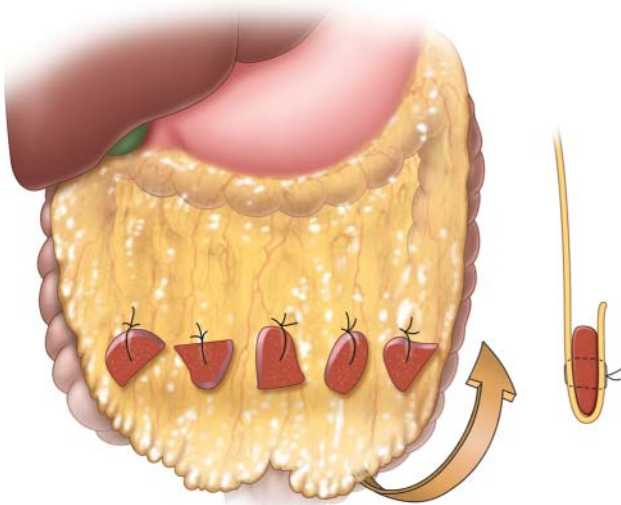


Figure 16 Autologous splenic transplantation is performed by placing sections of splenic parenchyma, $40 \times 40 \times 3$ mm in size, into pouches in the greater omentum.

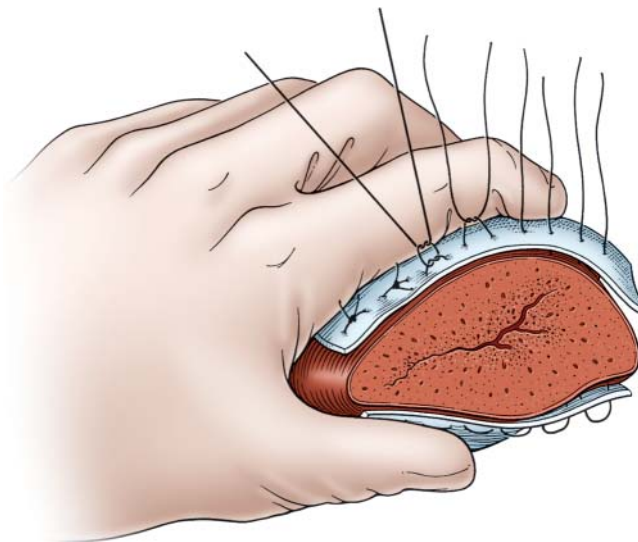


Figure 17 Splenorrhaphy is performed using interrupted mattress sutures through pledgets along the raw edge of the spleen.

Inc., Whitehouse Station, NJ), Menactra (Sanofi Pasteur, Swiftwater, PA), and Fluvirin (Novartis, East Hanover, NJ). Revaccination remains open to debate, but some argue for revaccination every 6 years.

An immediate postsplenectomy increase in platelets and white blood cells (WBCs) is normal; however, beyond postoperative day 5, a WBC count above $15,000/\mu\text{L}$ and a platelet to WBC ratio less than 20 are highly associated with sepsis and should prompt a thorough search for underlying infection.^{58,59} A common infectious complication following splenectomy is a subphrenic abscess, which should be

managed with percutaneous drainage. Following splenectomy or splenorrhaphy, postoperative hemorrhage may be attributable to loosening of a tie around the splenic vessels, a missed short gastric artery, or recurrent bleeding from the spleen if splenic repair was used. Additional sources of morbidity include a concurrent but unrecognized iatrogenic injury to the pancreatic tail during rapid splenectomy, resulting in pancreatic ascites or fistula.

Injuries to the Diaphragm

In cases of blunt trauma to the diaphragm, the injury is on the left side 75% of the time, presumably because the liver diffuses some of the energy on the right side. Blunt diaphragmatic injuries result in a linear tear in the central tendon, whereas penetrating injuries are variable in size and location depending on the weapon. With blunt, and occasionally with penetrating, injuries, the diagnosis is suggested by an abnormality of the diaphragmatic shadow on a chest radiograph [see Figure 18]. In patients without clear imaging results in the trauma bay, a CT scan may identify a diaphragmatic injury.

Regardless of the etiology, acute injuries are repaired through an abdominal incision or with thoracoscopy or laparoscopy. Following delineation of the injury, the chest should be evacuated of all blood and particulate matter, and tube thoracostomy should be placed if not previously done. Using Allis clamps to approximate the diaphragmatic edges, the defect is closed with a running No. 1 polypropylene suture [see Figure 19]. Occasionally, large avulsions or shotgun wounds with extensive tissue loss will require polypropylene mesh or AlloDerm (LifeCell, Branchburg, NJ) to bridge the defect. Alternatively, transposition of the diaphragm cephalad one to two intercostal spaces may allow repair without undue tension.⁶⁰

Financial Disclosures: None Reported

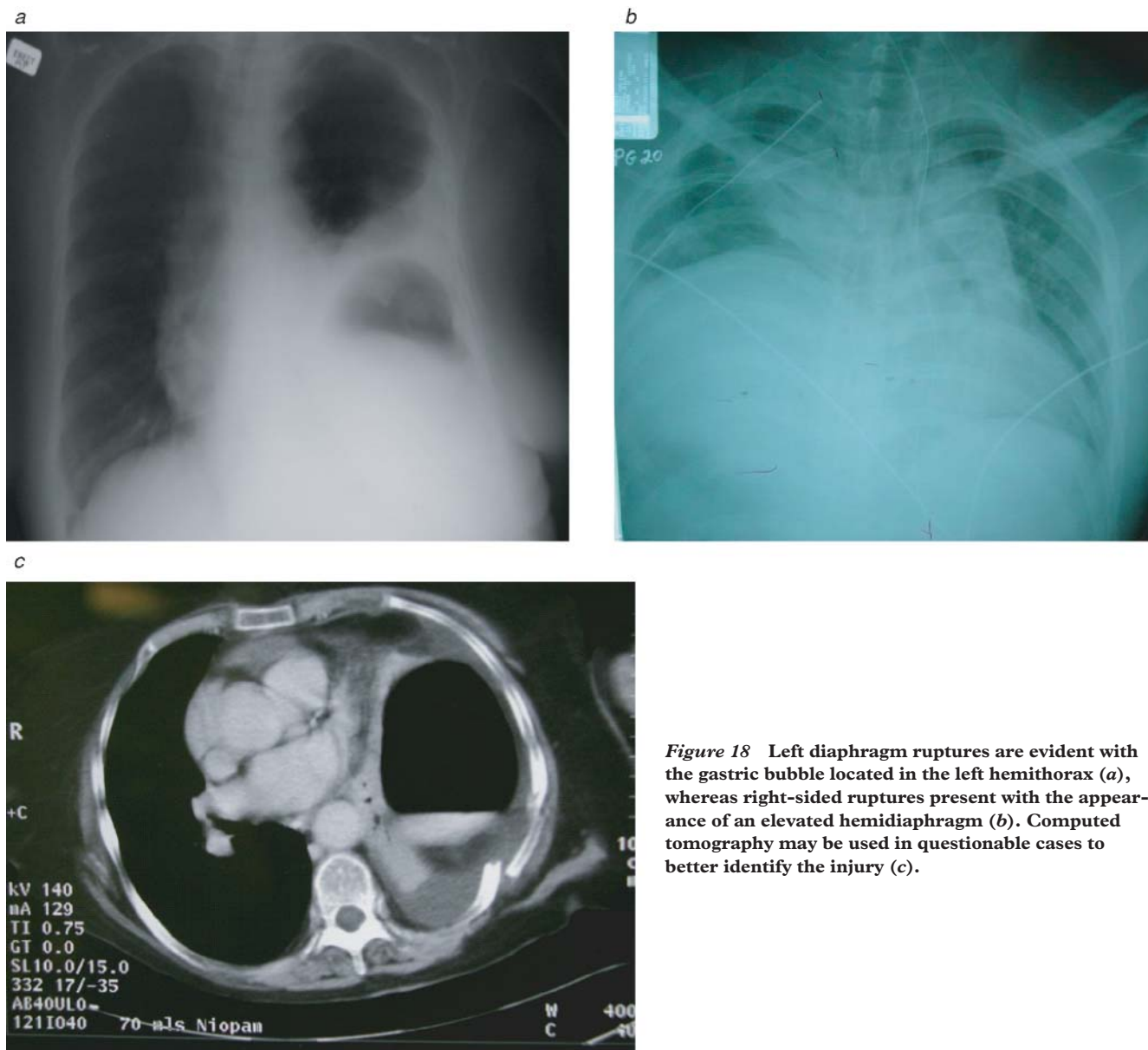


Figure 18 Left diaphragm ruptures are evident with the gastric bubble located in the left hemithorax (a), whereas right-sided ruptures present with the appearance of an elevated hemidiaphragm (b). Computed tomography may be used in questionable cases to better identify the injury (c).

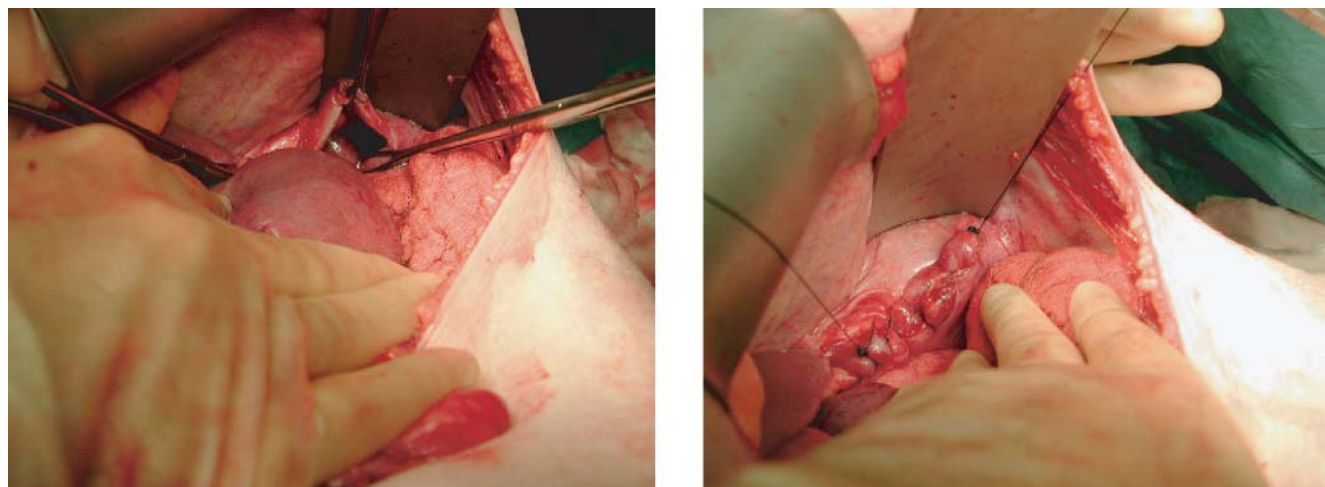


Figure 19 Using Allis clamps to approximate the diaphragmatic edges, the defect is closed with a running No. 1 polypropylene suture.

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Acknowledgments

Figure 4 Tom Moore
Figure 8 Thom Graves
Figures 5 through 7, 9, 10, 15, 17 Susan Brust

8 INJURIES TO THE STOMACH, SMALL BOWEL, COLON, AND RECTUM

Jordan A. Weinberg, MD, FACS, and Timothy C. Fabian, MD, FACS

Hollow viscus injury is most commonly the result of penetrating abdominal trauma. It is relatively infrequent in the setting of blunt trauma: in one multi-institutional analysis, only 1.2% of blunt trauma admissions were associated with a hollow viscus injury.¹ Initial resuscitation of the patient with abdominal trauma is described in detail elsewhere. The diagnosis of hollow viscus injury remains a challenge in abdominal trauma patients, and subsequent evaluation is determined by the mechanism of injury. Regardless of the specific injury mechanism, however, the principles of operative management are the same.

Determination of Need for Operation

BLUNT TRAUMA

Hollow viscus injury after blunt trauma, although uncommon, can have serious consequences if the diagnosis is missed or delayed. In a multi-institutional study of 198 patients with blunt small bowel injury, delay of as little as 8 hours in making the diagnosis resulted in increased morbidity and mortality.² Mortality increased in parallel with time to operative intervention (< 8 hours to operation, 2% mortality; 8 to 16 hours, 9%; 16 to 25 hours, 17%; > 24 hours, 31%), as did the complication rate.

Particular consideration should be given to lap- and shoulder-restraint injuries, which may be associated with an increased risk of hollow viscus injury. The so-called seat-belt sign (i.e., ecchymosis of the abdominal wall secondary to the compressive force of the lap belt) is associated with a more than doubled relative risk of small bowel injury.³ Flexion-distraction fractures of the spine (Chance fractures) are also associated with lap-belt use, and the presence of such fractures should raise the index of suspicion for associated hollow viscus injury.

Physical examination findings such as abdominal tenderness or tachycardia may suggest the presence of hollow viscus injury. Reliability of the examination, however, may be compromised by distracting chest or long bone injury, closed head injury, spinal cord injury, or intoxication. Laboratory abnormalities including elevations in white blood cell (WBC) count, amylase, and/or lactic acid may also point toward the presence of hollow viscus injury, but are relatively nonspecific. Provided that the patient has suffered a low-risk mechanism of injury (such as a fall from standing or a low-speed motor vehicle collision), hollow viscus injury is extremely unlikely given a normal, reliable physical examination and normal laboratory results, and further investigation

along this path is unwarranted. However, the presence of abdominal complaints, an abnormal or nonreliable physical examination, abnormal laboratory results, or a high-risk mechanism of injury warrants further evaluation.

Ultrasonography is routinely performed early in the evaluation of blunt abdominal trauma. It is highly specific and moderately sensitive in identifying intra-abdominal fluid, the presence of which in a hemodynamically unstable patient is an indication for laparotomy (in that it strongly suggests the presence of significant intra-abdominal hemorrhage).⁴ Ultrasonography does not, however, reliably distinguish solid-organ injury from hollow viscus injury—a distinction that is critical for determining subsequent management (i.e., operative versus nonoperative) in a hemodynamically stable patient. Computed tomography (CT) and/or diagnostic peritoneal lavage (DPL) may help differentiate one type of injury from the other.

Helical (spiral) CT is currently the imaging modality of choice in stable patients who have undergone blunt abdominal trauma. Our experience indicates that it is useful for identifying blunt hollow viscus injury. In a review of over 8,000 CT scans performed to evaluate cases of blunt abdominal trauma, we found that the number of abnormal radiologic findings suggesting blunt injury to the bowel, the mesentery, or both [see Table 1] was correlated with the true presence of injury.⁵ A CT scan demonstrating a solitary abnormality was associated with a true positive rate of 36%, whereas a scan demonstrating more than one abnormality was associated

Table 1 Incidence of Findings Suggestive of Blunt Mesenteric and Bowel Injury in True Positive and False Positive CT Scans⁵

Finding	Incidence	
	True Positive CT Scans (%)	False Positive CT Scans (%)
Unexplained intraperitoneal fluid	74	79
Pneumoperitoneum	28	2
Bowel wall thickening	30	8
Mesenteric fat stranding	9	4
Mesenteric hematoma	19	19
Extravasation of luminal content	4	0
Extravasation of vascular content	9	0

CT = computed tomographic.

with a true positive rate of 83%. Unexplained intraperitoneal fluid (i.e., fluid appearing in the absence of solid-organ injury) was the most common radiographic finding associated with blunt bowel or mesenteric injury but often proved to be a false positive finding [see Table 1].

On the basis of this experience, we developed an algorithm for the evaluation of blunt hollow viscus injury in patients with unreliable physical examinations [see Figure 1]. If CT scanning demonstrates no suspicious findings, the patient is observed. No further diagnostic workup of hollow viscus injury is performed, and the duration of the observation period depends on both the overall condition of the patient and clinical judgment. It is worth noting that the 2003 multi-institutional review of 2,457 cases carried out by the Eastern Association for the Surgery of Trauma (EAST) reported a 13% incidence of blunt small bowel injury in patients with an initial negative CT scan. These results indicate that caution should be exercised in dismissing the presence of hollow viscus injury on the basis of a negative scan.³ This concern is echoed by our own institutional experience, in which the incidence of injury in patients with an initial negative CT scan was 12%.⁵

If CT demonstrates a solitary suspicious finding, DPL is performed for further evaluation. If DPL yields positive results (WBC count > 500 cells/ μ L, alkaline phosphatase level > 10 IU/L, or amylase level > 20 IU/L), exploratory laparotomy is performed. It must be kept in mind, however, that DPL results may be falsely negative or equivocal in the early period after trauma.⁶ This phenomenon may be attributable to a time lag between the intestinal perforation and the subsequent development of intraperitoneal leukocytosis. If a high degree of suspicion of hollow viscus injury remains even after a negative DPL result, DPL may be repeated. Alternatively, exploratory laparotomy may be performed. The choice between the two options is largely based on the individual surgeon's clinical judgment.

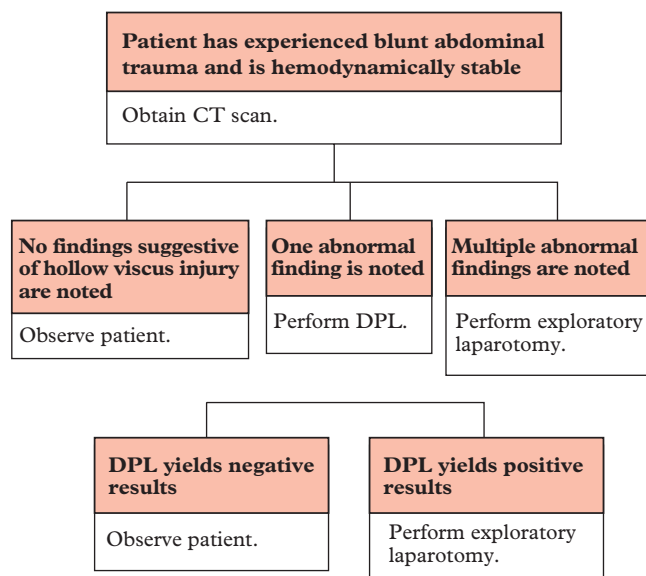


Figure 1 Algorithm outlining the evaluation of blunt injury to a hollow viscus. CT = computed tomographic; DPL = diagnostic peritoneal lavage.

If CT demonstrates multiple abnormalities, DPL is omitted from the workup and exploratory laparotomy is performed.

PENETRATING TRAUMA

Gunshot Wounds

Gunshot wounds to the abdomen generally necessitate exploratory laparotomy, given the high incidence of intra-abdominal injury. The exception to this rule is the case of a tangential wound that is believed to be traversing the soft tissues of the abdominal wall without entering the peritoneal cavity. In this scenario, we usually perform laparoscopy to look for peritoneal penetration. If the peritoneum has been violated, a laparotomy is done to permit systematic evaluation of the peritoneal cavity. If the peritoneum has not been violated, the operation may be terminated and the patient discharged after recovery from anesthesia, provided that there are no other extra-abdominal injuries necessitating hospital admission.

Stab Wounds

Stab wounds to the abdomen are associated with a lower incidence of intra-abdominal injury than gunshot wounds. Accordingly, there has been a shift toward selective management algorithms that rely on diagnostic tests, serial abdominal examination, or some combination of the two. When the peritoneum has obviously been penetrated (as with omental or bowel evisceration) or the patient presents with hemodynamic instability, we perform a laparotomy to evaluate the entire peritoneal cavity for organ injury. When it is unclear whether the peritoneum has been penetrated in a hemodynamically stable patient, we proceed with a definitive evaluation to rule out peritoneal violation. Anterior wounds (i.e., those anterior to the midaxillary line) are evaluated for fascial penetration by means of local wound exploration. In the emergency department, with sterile technique and local anesthesia, the wound is sharply extended to allow retraction of the subcutaneous tissue and visualization of the anterior fascia. If local wound exploration demonstrates the absence of fascial penetration, no further evaluation is necessary. If peritoneal violation is obvious on local wound exploration, we proceed with exploratory laparotomy. Often, however, fascial penetration is evident, but it is difficult to determine whether the peritoneum has been violated. In such cases, laparoscopy is performed in the operating room to look for peritoneal penetration. If peritoneal penetration is confirmed, we proceed with laparotomy.

Other centers have reported favorable experiences with expectant management of anterior stab wounds that penetrate the peritoneum.⁷⁻⁹ Patients without evidence of peritonitis are admitted and monitored with serial physical examinations. Development of abdominal pain, peritoneal signs, or hemodynamic instability heralds the presence of hollow viscus injury, and the patient should be taken to surgery immediately. Should the patient remain stable with an unremarkable physical examination, serial examinations may be discontinued after 24 hours.

The rationale for this approach is based on both the high incidence of nontherapeutic laparotomy for stab wounds that has been historically observed and the recognition that nontherapeutic laparotomy is not without risk, with reported

complication rates from 8 to 41%.^{10–12} Expectant management has been demonstrated to be relatively safe, and delayed intervention (within 24 hours) does not seem to portend the same risk as observed in blunt trauma.^{7–9,13} Nonetheless, it is inevitable that with the expectant approach, a significant injury on occasion will be missed. A prospective randomized trial comparing the safety and cost-effectiveness of mandatory laparotomy versus selective nonoperative management of abdominal stab wounds demonstrated lower morbidity (although not statistically significant) in the selectively managed group (8% versus 19%, $p = .26$).⁸ It is notable, however, that one patient in the selectively managed group developed empyema secondary to a missed diaphragmatic injury with associated gastric perforation.

Should expectant management be undertaken, it should be emphasized that appropriate patient selection is critical. Expectant management is not appropriate for the patient with an altered sensorium or unreliable physical examination. As noted (see above), we prefer to determine the presence of peritoneal penetration at the time of presentation and proceed with open exploration as indicated. The rationale for this approach is to avoid any delay in diagnosis of hollow viscus injury and to allow early discharge of patients with no peritoneal violation. Other centers have described the use of both CT and DPL to facilitate the decision to perform laparotomy, observe, or discharge the patient.^{14,15}

Wounds to the lower back or the flank (posterior to the midaxillary line), which carry a lower risk of intra-abdominal injury, are evaluated with CT, augmented by intravenous, oral, and rectal contrast studies. CT scanning has proved to be a reliable means not only of identifying posterior intraperitoneal violation but also of evaluating injury to retroperitoneal structures.^{16,17}

Operative Management of Injuries at Specific Sites

When hollow viscus injury is suspected, antibiotics with broad-spectrum aerobic and anaerobic coverage should be administered before the skin incision. If injury is confirmed, the antibiotics should be continued for a 24-hour period. The EAST Practice Management Guidelines Workgroup has reviewed the available evidence regarding perioperative antibiotic use in the trauma setting.¹⁸ Data from prospective studies clearly indicate that prolonging antibiotic administration beyond 24 hours provides no additional protection against surgical site infection (SSI).

Abdominal exploration is generally performed through a midline incision that is sufficiently extensive to permit evaluation of the entire peritoneal cavity. Once initial control of any significant bleeding has been obtained, the next step is to control any contamination from spilled gastrointestinal contents. Babcock clamps are useful for temporarily controlling contamination from bowel perforations without causing injury to the bowel wall. Inspection commences in a systematic fashion, with any holes in the bowel controlled as they are found. In the setting of penetrating injury, when an odd number of hollow viscus perforations is encountered, a diligent search for an additional perforation is essential. An odd number of perforations implies that one of the wounds is tangential (or that the projectile is intraluminal); this is a diagnosis of exclusion.

INJURIES TO THE STOMACH

Intraoperative evaluation of the stomach begins with full visualization of the anterior gastric surface from the pylorus to the esophagogastric junction. Proximal exposure is facilitated by incising the triangular ligament and retracting the left lateral section of the liver to the patient's right. The posterior aspect of the stomach is assessed by opening the gastrocolic ligament, which provides access to the lesser sac. Care must be taken to avoid injuring the vascular arcade of the greater curvature. While the stomach is elevated superiorly, the transverse colon is retracted inferiorly to expose the posterior gastric wall. Frequently, light adhesions between the posterior gastric wall and the retroperitoneum overlying the pancreas must be freed to provide full exposure. Alternatively, the greater omentum may be detached from its avascular attachment to the transverse colon to afford access to the lesser sac. Care must be taken to avoid placing excess tension on the greater curvature of the stomach and the short gastric vessels so as not to cause iatrogenic injury to the spleen. The greater and lesser curvatures should be closely inspected because the omental attachments may obscure an underlying gastric wound. Such inspection is particularly important in the setting of a small-caliber missile wound: the perforation can be remarkably small, and the serosal tissue damage in such cases is often subtle.

Treatment of a gastric injury is dictated by its severity [see Figure 2], which is classified according to the grading system developed by the American Association for the Surgery of Trauma (AAST) [see Table 2]. Intramural hematomas (grade I) are managed by means of unroofing and evacuation, followed by seromuscular closure with interrupted sutures. The great majority of gastric perforations are amenable to primary repair (grades II and III). In view of the propensity of the richly vascularized gastric wall to bleed at the site of injury, a two-layer technique is recommended to achieve adequate hemostasis. When the wound involves the pylorus, conversion to pyloroplasty to prevent stenosis is often beneficial. Suture repair of wounds at the cardioesophageal junction is reinforced by gastric fundoplication.

Some extensive wounds are not amenable to primary repair (grades IV and V). Such injuries include significant tissue loss or gastric devascularization and often are associated with major vascular injury as a consequence of the proximity of the major vessels and the force necessary to cause such a significant injury. Patients with grade IV or V injuries often do not survive long enough to undergo laparotomy; consequently, these extensive gastric wounds are rarely encountered. Grade IV injuries can usually be managed by means of a partial gastrectomy. Restoration of gastric outflow is accomplished with either a gastroduodenostomy or a gastrojejunostomy; the choice is dictated by the extent of the resection and the presence or absence of an associated duodenal or pancreatic injury. In the exceedingly rare event of complete gastric devascularization or destruction, a total gastrectomy is required; we have yet to encounter such a situation.

In fasting patients, the stomach harbors low numbers of bacteria because of its low pH. In trauma victims, however, who, it seems, often arrive with full stomachs, a more neutral pH and a higher bacterial count can be expected. If a gastric perforation with significant contamination is encountered,

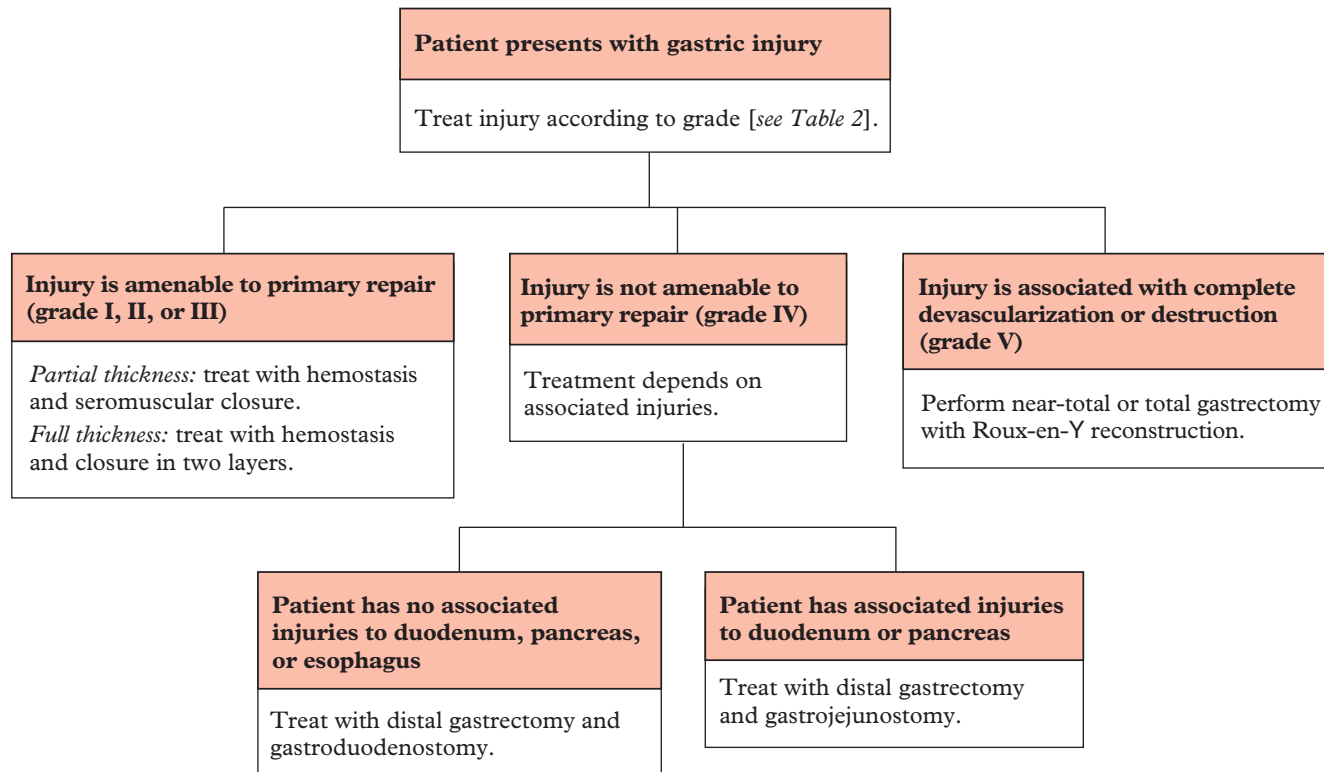


Figure 2 Algorithm outlining the treatment of gastric injury.

secondary or delayed primary skin closure should be performed in view of the increased risk of SSI; this is particularly true when significant hemorrhage or associated injury is present, in which case, the rate of intra-abdominal abscess formation may be as high as 24%.¹⁹

INJURIES TO THE SMALL INTESTINE

Injury to the small intestine is evaluated intraoperatively by “running the bowel”: the small bowel and its mesentery are inspected in a systematic and comprehensive fashion from the ligament of Treitz caudad to the ileocecal valve. As active mesenteric bleeding is encountered, it is controlled by isolation and individual ligation of the bleeding vessels rather than by mass ligation of the mesentery, which may produce ischemia. Likewise, as bowel perforations are found, temporary control measures are rapidly initiated in an effort to prevent excessive or ongoing soilage. Once all bowel injuries are accounted for, the decision must be made whether to perform primary repair, resection of the injured segment, or some combination of the two. Primary repair of multiple injuries preserves bowel length and is generally preferred. At the discretion of the operating surgeon, resection of a segment containing multiple injuries may be performed to expedite the operation, provided that the amount of bowel to be resected is small enough that its loss would have only a negligible effect on digestive function.

In contemporary surgical practice, the patient with severe abdominal injuries is routinely managed with “damage control” or staged laparotomy. The damage control approach has evolved from a realization that the critically injured patient

often requires rapid, lifesaving bailout techniques to arrest hemorrhage and control enteric spillage to preempt the combined physiologic insult of the trauma and surgery from progressing to irreversible shock and death.²⁰ With respect to small bowel injuries managed in this scenario, reconstruction of intestinal continuity following bowel resection is not performed at the initial operation and is instead deferred to subsequent laparotomy following resuscitation of the patient (typically 24 to 48 hours following the initial operation). The damage control approach is employed to prevent or mitigate the development of acidosis, coagulopathy, and/or hypothermia secondary to major blood loss and resuscitation. This decision should be made early in the operative course and be based on the rapid recognition of injury patterns rather than the onset of physiologic derangement, which may herald the onset of irreversible shock.²⁰

Management of each wound is determined by its severity according to the AAST grading system [see Figure 3 and Table 2]. Small partial-thickness injuries (grade I) are managed by reapproximating the seromuscular layers with interrupted sutures. Small full-thickness wounds (grade II) are repaired with limited débridement and closure. Closure is performed in either one or two layers (we prefer a single-layer closure), and transverse closure is preferred to avoid luminal narrowing. Larger full-thickness wounds (grade III) may be repaired primarily if luminal narrowing can be avoided; otherwise, resection and anastomosis should be performed. Extensive wounds and wounds associated with devascularization (grades IV and V) are treated with resection and anastomosis. When mesenteric injury is encountered in the absence

Table 2 AAST Organ Injury Scales for Gastrointestinal Tract and Pancreas

Injured Structure	AAST Grade*	Characteristics of Injury	AIS-90 Score
Stomach	I	Intramural hematoma < 3 cm; partial-thickness laceration	2
	II	Intramural hematoma ≥ 3 cm; small (< 3 cm) laceration	2
	III	Large (> 3 cm) laceration	3
	IV	Large laceration involving vessels on greater or lesser curvature	3
	V	Extensive (> 50%) rupture; stomach devascularized	4
Duodenum	I	Single-segment hematoma; partial-thickness laceration	2; 3
	II	Multiple-segment hematoma; small (< 50% of circumference) laceration	2; 4
	III	Large laceration (50–75% of circumference of segment D2 or 50–100% of circumference of segment D1, D3, or D4)	4
	IV	Very large (75–100%) laceration of segment D2; rupture of ampullary or distal bile duct	5
	V	Massive duodenopancreatic injury; devascularization	5
Pancreas	I	Small hematoma without duct injury; superficial laceration without duct injury	2
	II	Large hematoma without duct injury or tissue loss; major laceration without duct injury or tissue loss	2; 3
	III	Distal transection or parenchymal laceration with duct injury	4
	IV	Proximal transection or parenchymal laceration involving ampulla	4
	V	Massive disruption of pancreatic head	5
Small bowel	I	Contusion or hematoma without devascularization; partial-thickness laceration	2
	II	Small (< 50% of circumference) laceration	3
	III	Large (≥ 50% of circumference) laceration without transection	3
	IV	Transection	4
	V	Transection with segmental tissue loss; devascularized segment	4
Colon	I	Contusion or hematoma; partial-thickness laceration	2
	II	Small (< 50% of circumference) laceration	3
	III	Large (≥ 50% of circumference) laceration	3
	IV	Transection	4
	V	Transection with tissue loss; devascularized segment	4
Rectosigmoid and rectum	I	Contusion or hematoma; partial-thickness laceration	2
	II	Small (< 50% of circumference) laceration	3
	III	Large (≥ 50% of circumference) laceration	4
	IV	Full-thickness laceration with perineal extension	5
	V	Devascularized segment	5

AAST = American Association for the Surgery of Trauma; AIS-90 = Abbreviated Injury Score, 1990 version.

*Advance one grade for multiple injuries, up to grade III.

of bowel injury, the associated bowel must be closely assessed for evidence of vascular compromise. If the bowel appears viable, the rent in the mesentery should be reapproximated after bleeding is controlled to prevent an internal hernia. If there is evidence of vascular compromise, bowel resection and anastomosis are indicated.

Determination of intestinal viability begins with assessment of the bowel's appearance. Adjunctive measures, such as the use of a handheld Doppler device or fluorescein infusion with Wood lamp illumination, may facilitate assessment of perfusion in segments where viability is questionable. We generally prefer to use a handheld Doppler device because it is easy to

use and is available at short notice in the operating room. A probe applied directly to the antimesenteric side of the bowel wall effectively detects the presence of arterial flow, which reliably demonstrates viability.

Small bowel anastomoses are usually handsewn in one or two layers, although stapling devices may also be employed. The choice of technique depends largely on surgeon preference. One multicenter retrospective study suggested that in the setting of trauma, stapled anastomoses had a higher complication rate than did sutured anastomoses²¹: overall, 13% of stapled anastomoses were associated with an intra-abdominal postoperative complication, compared with 5% of sutured

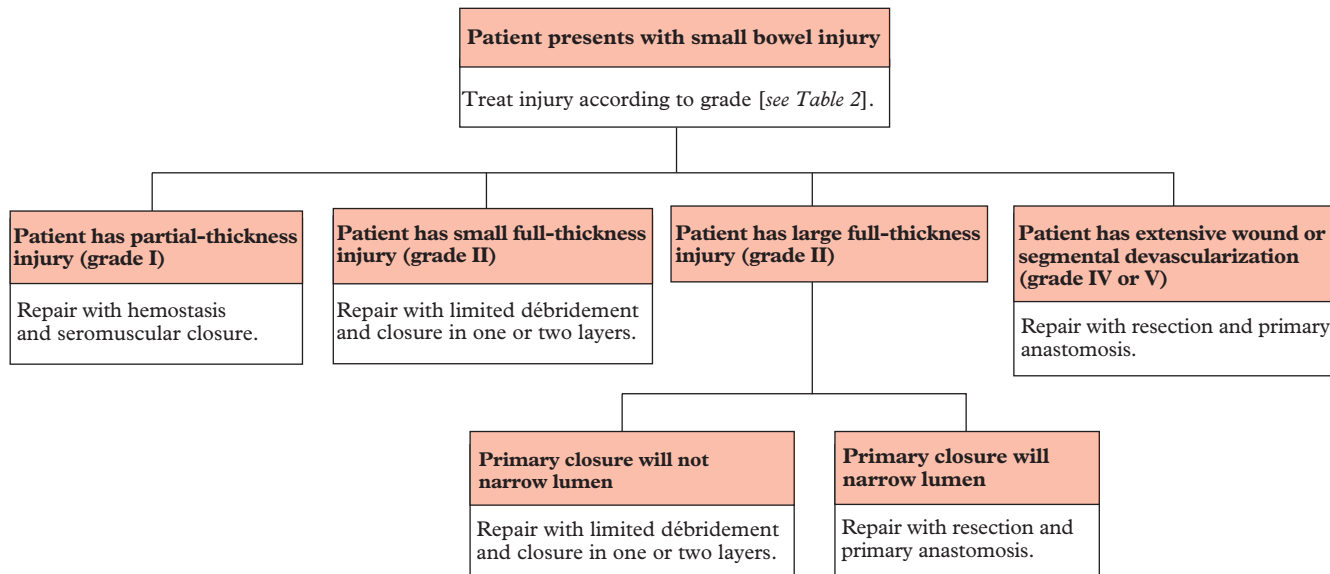


Figure 3 Algorithm outlining the treatment of small bowel injury.

anastomoses. Because this study did not separate small intestinal anastomoses from colonic anastomoses, it is unclear to what extent the results apply specifically to small bowel anastomoses. It is likely, however, that bowel edema contributes to staple line failure. If bowel edema is evident or anticipated, it may be prudent to perform a sutured anastomosis.

INJURIES TO THE COLON

In World War II, colostomy was mandatory for penetrating colon trauma because of the significant morbidity associated with anastomotic suture line dehiscence.²² In the ensuing years, experience with primary repair of penetrating colonic injuries in civilian settings suggested that primary repair could be performed safely and perhaps, in select cases, with less morbidity than colostomy.^{23,24} This suggestion was confirmed in the late 1970s by a randomized, prospective study that demonstrated significantly lower rates of intra-abdominal infection in patients treated with primary repair than in those treated with colostomy.²⁵ In that early trial, high-risk patients (i.e., those with shock, hemorrhage, associated injuries, delayed presentation, significant peritoneal soilage, destructive wounds of the colon, or loss of abdominal wall integrity) were excluded from randomization and treated with colostomy. Currently, there is less concern for such risk factors, and primary repair is gaining wider acceptance.²⁶

To direct management decisions, it is helpful to categorize penetrating colonic injuries as either nondestructive or destructive [see Figure 4].²⁷ Although blunt colonic injuries are considerably less common, we manage them in a similar fashion.

Nondestructive colonic injuries are defined as wounds that involve less than 50% of the bowel wall without devascularization. Such wounds account for approximately 80% of colon wounds and are amenable to primary suture repair with limited amounts of débridement. Sufficient data have been accumulated over the past 30 years to support primary repair as standard treatment for nondestructive colon wounds in the

absence of peritonitis, regardless of associated injuries or comorbid conditions. Evaluation of the available prospective and retrospective data indicates that the suture line failure rate for primary repair is approximately 1%, which is less than the rate generally reported for elective colon and rectal surgery. Mortality associated with suture line failure in this setting is uncommon. The favorable morbidity and mortality profiles, along with the inherent benefits of avoiding colostomy, support primary repair as standard therapy for nondestructive wounds. Partial-thickness lacerations (grade I) are repaired with inverting seromuscular sutures. Full-thickness lacerations (grade II) may be closed in one or two layers.

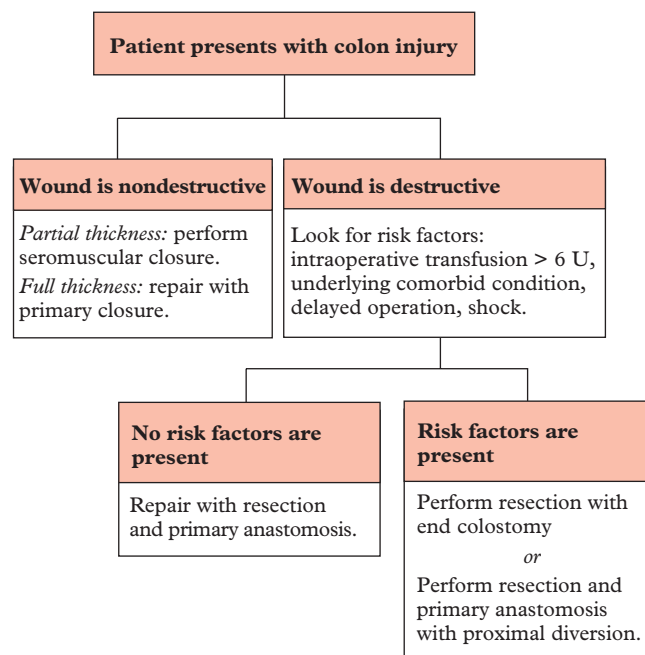


Figure 4 Algorithm outlining the treatment of colon injury.

Destructive colonic injuries are defined as wounds that completely transect the colon (grade IV) or involve tissue loss and devascularized segments (grade V). Optimal management of such wounds is less certain than optimal management of nondestructive wounds. Data from randomized and prospective trials demonstrate that resection and primary anastomosis can be performed safely.^{28–31} It should be kept in mind, however, that these results are derived from a relatively small number of reported cases. The retrospective data indicate a higher incidence of suture line failure and a significant incidence of associated mortality, suggesting that resection and primary anastomosis may not be the optimal treatment for all colonic wounds.²⁷

A 1994 report from our institution (University of Tennessee) concluded that patients with destructive colonic injuries who had comorbid medical conditions or transfusion requirements greater than 6 units of blood were at significantly higher risk for suture line breakdown when the wounds were managed with resection and primary anastomosis.³² Other reported risk factors that may direct the surgeon toward fecal diversion include a Penetrating Abdominal Trauma Index (PATI) score greater than 25, shock, and a delayed operation.³³ It is our practice to manage these patients as high-risk patients and perform fecal diversion. Diversion may be accomplished by means of either loop colostomy (with an open or closed distal stoma) or end colostomy (with a mucous fistula or closure of the rectal stump). The diversion technique is dictated by both surgeon preference and the nature of the colonic injury. In most civilian clinical practices, destructive wounds account for approximately 20% of all colon wounds encountered. Between 50 and 75% of destructive wounds do not have risk factors that prompt diversion. Thus, the overall diversion rate ranges from 5 to 10%. In our experience over the past several years, 90 to 95% of all colon wounds have been managed with primary repair or resection and anastomosis.

Destructive colon wounds managed in the context of damage control laparotomy are typically initially resected with the bowel left in discontinuity. On return to the operating room following resuscitation of the patient, the surgeon is faced with the decision to restore bowel continuity via a colonic anastomosis versus performing diversion via end colostomy or ileostomy. A third alternative is to perform anastomosis and proximally divert with a loop ileostomy. Relatively small clinical series concerning this scenario have suggested that delayed anastomosis in this context is relatively safe.^{34,35} In the largest reported series to date (56 patients), however, a relatively high anastomotic leak rate (12%) was observed, and the authors recommended that delayed colonic anastomosis be performed with caution.³⁶ It is notable, however, that stoma construction may present its own problems in the open abdomen scenario as these patients often have significant abdominal wall and bowel edema, potentiating the risk for stoma-related complications such as retraction or ischemia/necrosis. In general, we recommend that in the setting of the open abdomen, fecal diversion should be considered on a case-by-case basis, balancing the risks of anastomotic complications against the challenge of a potentially difficult stoma.

The potential risk of postoperative SSI associated with colonic injury should be considered at the time of the initial

laparotomy. Retained bullets or other projectiles that have penetrated the colon or rectum may act as nidus for abscess formation and should be removed when it is technically feasible to do so. Approximately 10% of these retained missiles result in soft tissue infection or osteomyelitis.³⁷ Delayed primary or secondary skin closure is recommended.

If colostomy is performed, it will eventually have to be closed in most cases. The mortality associated with colostomy closure is low, but the reported morbidity has varied considerably, ranging from 5 to 25% in single-institution studies.^{38–40} We typically perform closure 2 to 3 months after hospital discharge to allow time for the resolution of the dense inflammatory adhesions that may form after laparotomy. Before closure, a contrast enema is obtained to confirm that no distal strictures or fistulas are present. Some surgeons maintain that early closure (within 2 weeks) is as safe as the traditional late closure (3 months), with a shorter operating time and less intraoperative blood loss, and suggest that it may also allow colostomy closure during the patient's initial hospitalization.⁴¹ To date, however, this practice has not garnered wide enthusiasm.

Occasionally, blunt abdominal trauma associated with lap-belt use results in a large deserosalization injury to the cecum and ascending colon or to the sigmoid colon. In such cases, the serosa may be reapproximated with interrupted silk sutures in an accordion-type fashion, provided that the lumen is not significantly compromised by the imbrication of the submucosa. It is likely that subclinical luminal narrowing occurs frequently after such repairs, of which we rarely see sequelae. If significant luminal narrowing is anticipated or the serosal disruption is extensive enough to preclude reapproximation, resection of the injured segment with primary anastomosis is indicated.

INJURIES TO THE RECTUM

Recognition of rectal injuries requires diagnostic vigilance. All patients with a penetrating wound to the pelvis, perineum, buttock, or upper thigh should be evaluated for rectal injury. Digital examination for the presence of rectal blood is mandatory, but the absence of blood does not definitively rule out injury. Rigid proctoscopy should be performed whenever there is any suspicion of rectal injury. In our most recent experience with penetrating rectal injuries, sensitivities for digital rectal examination and rigid proctoscopy were 51% and 78%, respectively.⁴²

It is our practice to classify rectal injuries according to anatomic criteria, which then dictate management [see Figure 5].^{43,44} The anterior and lateral sidewalls of the upper two thirds of the rectum are serosalized; injuries in this region are classified as intraperitoneal and are managed in the same manner as colonic injuries [see Figure 4]. The upper two thirds of the rectum posteriorly and the lower one third of the rectum circumferentially are not serosalized; injuries in these regions are classified as extraperitoneal.

Extraperitoneal wounds in the upper two thirds are usually amenable to exploration and suture repair. Fecal diversion is also performed as an adjunctive measure and may be accomplished with either loop or end colostomy. In select cases in which the wound is primarily intraperitoneal with minimal extraperitoneal involvement, diversion may be omitted.

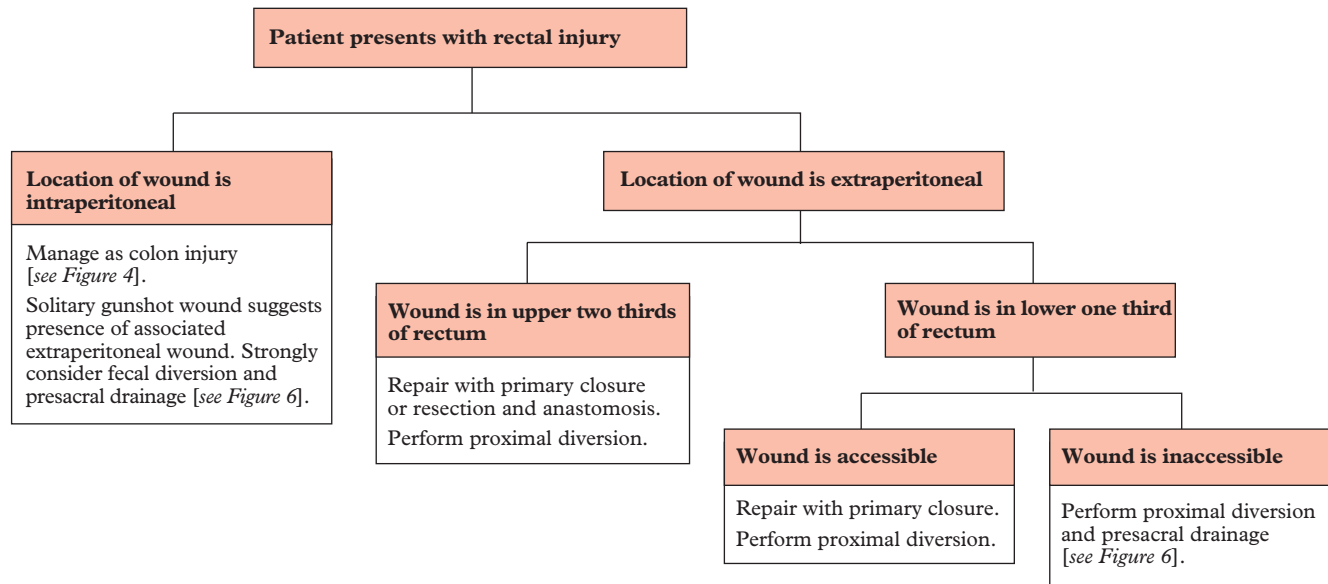


Figure 5 Algorithm outlining the treatment of rectosigmoid or rectal injury.

Extraperitoneal wounds to the lower third of the rectum are usually explored and repaired, provided that the wound is easily accessible without risk to the associated neurovascular and genitourinary structures. Fecal diversion is recommended. Wounds that are difficult to reach are not explored and instead are managed with proximal fecal diversion and presacral drainage. Presacral drainage is performed with the patient in the lithotomy position [see Figure 6]. A curvilinear incision is made in the skin between the coccyx and the anus, and blunt dissection is employed to gain entry into the presacral space. Generally, we place one or two Penrose drains into this space and gradually withdraw them between postoperative days 5 and 7.

Whether presacral drainage is necessary is controversial. There is published prospective evidence to suggest that presacral drainage does not lessen morbidity⁴⁵; however, this study did not make a distinction between accessible and inaccessible extraperitoneal wounds. Our view is that for inaccessible extraperitoneal wounds, presacral drainage is required to prevent retroperitoneal abscess formation, which results from fecal contamination of a relatively closed space and can produce significant morbidity in the form of retroperitoneal infection that may also track downward into the thighs. Accessible extraperitoneal wounds that are explored and repaired become effectively intraperitonealized; thus, presacral drainage is not required for these injuries.

As emphasized (see above), a tangential gunshot wound is a diagnosis of exclusion. This point is of particular importance when the wound involves the rectum because mobilization and visualization may be limited by a narrow pelvis, a fat-laden mesorectum, and, in many cases, a patient who is unstable as a result of associated injuries. Although a solitary proximal rectal gunshot wound may truly be tangential (or the projectile may be intraluminal), an associated distal extraperitoneal wound is often present. After primary repair of the proximal wound, fecal diversion and presacral drainage should be performed, as with inaccessible extraperitoneal rectal injuries.

Distal rectal washout was initially advocated on the basis of experience gained during the Vietnam War.⁴⁶ In the majority of civilian studies since then, however, distal rectal washout has had no significant effect on morbidity.^{43,47–49} It may

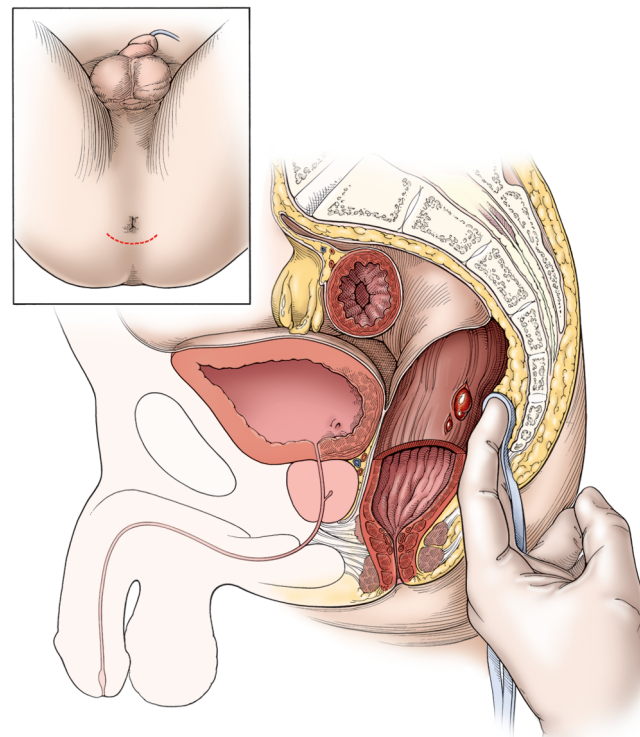


Figure 6 Presacral drainage is provided through a curved incision midway between the anus and the tip of the coccyx. With blunt dissection, two fingers are inserted between the rectum and the hollow of the sacrum. Penrose drains are inserted and sutured to the skin.

be useful in cases of severe wound contamination or fecal impaction, but, in general, it does not seem to be an important adjunct to the management of rectal injuries. Typically, distal rectal washout involves lavage of the rectum distal to the injury with 3 to 6 L of irrigant via an irrigation tube placed into the distal limb of a loop colostomy. The irrigant may be normal saline, a genitourinary irrigant, or an antiseptic

solution. Digital rectal dilatation is performed to facilitate drainage of the irrigant. Care should be taken to protect the midline wound with a polyethylene or similar barrier to reduce the risk of wound contamination during the washout.

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Acknowledgment

Figure 6 Susan Brust, CMI

9 INJURIES TO THE PANCREAS AND DUODENUM

Gregory J. Jurkovich, MD, FACS

Duodenal and pancreatic injury continues to challenge the trauma surgeon. The relatively rare occurrence of these injuries, the difficulty in making a timely diagnosis, and high morbidity and mortality rates justify the anxiety these unforgiving injuries invoke. These issues also likely explain the hesitancy of many to address pancreatic injuries with operative intervention and the most recent literature exploring the options and consequences of nonoperative management.¹⁻³ Mortality rates for pancreatic trauma range from 9 to 34%, with a mean rate of 19%. Duodenal injuries are similarly lethal, with mortality rates ranging from 6 to 25%. Complications following duodenal or pancreatic injuries are alarmingly frequent, occurring in 30 to 60% of patients.⁴⁻⁶ Recognized early, the operative treatment of most duodenal and pancreatic injuries is straightforward, with low morbidity and mortality. Recognized late, these injuries result in a protracted, difficult clinical course, often ending in a devastating outcome.⁷⁻¹¹

History

An 1827 report of a traumatic transection of the pancreas as a result of a stagecoach wheel running over a patient is generally recognized as the first literature on pancreatic trauma.¹² By 1903, Mickulicz was able to identify 45 cases of pancreatic trauma in the literature, of which 21 involved penetrating and 24 blunt injuries.^{13,14} He noted that all 20 patients not operated on died, and 18 of the 25 (72%) who were operated on survived—a remarkable success for the time. Mickulicz recommended a thorough exploration through a midline incision, suture control for hemostasis, and the placement of drains in all cases, recommendations that still hold today.¹³ In 1930, Stern reviewed 62 reported cases of pancreatic trauma, in which 30 of the patients survived and 32 died.¹⁴ His treatment recommendations were essentially the same as Mickulicz's, although Stern perhaps foresaw the role of diagnostic peritoneal lavage in his recommendation to use "abdominal puncture" to aid in the diagnosis of pancreatic trauma.

The occurrence of complications was also noted early. In 1982, Kulenkampff reported what was likely a pancreatic pseudocyst following blunt trauma.¹⁵ In 1905, Korte reported a case of isolated pancreatic injury with total transection and resultant pancreatic fistula.¹⁶ The fistula closed spontaneously (as most do), and the patient survived. In 1946, Whipple reported that the catgut sutures used in and about the pancreas were likely to dissolve, leading to hemorrhage, fistula formation, duodenal leaks, and peritonitis; the use of silk was recommended.¹⁷

Wartime experience with pancreatic trauma emphasizes the high morbidity and mortality but also the infrequent

occurrence of this injury. There were only 5 case reports of pancreatic injury from the American Civil War, with an 80% mortality¹⁸; 5 reported cases from British troops in World War I, with an 80% mortality; 62 cases (of 3,154 abdominal injuries) reported by the 2nd Auxiliary Surgical Group in 1944 and 1945 during World War II, with a 56% mortality¹⁹; and 9 cases from the Korean War, with a 22% mortality.²⁰ More direct surgical management of pancreatic wounds also occurred in each of these wartime experiences.

Diagnosis

The two most important determinants of outcome following pancreatic injury are the status of the main pancreatic duct and the time from injury to definitive management of a ductal injury. This was probably first recognized and emphasized by Baker and colleagues in 1962.²¹ Two subsequent reviews of the experience with pancreatic trauma at the University of Louisville confirmed and emphasized the importance of determining the status of the pancreatic duct. Heitsch and colleagues found that resection of distal ductal injuries as opposed to drainage alone significantly lowered postoperative morbidity and mortality,²² and Smego and colleagues confirmed this observation one decade later by noting that pancreatic resection distal to the site of ductal injury resulted in a decrease in the mortality rate at that institution from 19 to 3%.²³ Our experience at Harborview Medical Center in Seattle supports this in that accurate determination of the status of the pancreatic duct with intraoperative pancreatography results in a decrease in complications from 55% to 15%.²⁴ Although improvements in image quality have been noted,²⁵ cross-sectional body imaging techniques currently used in the multitrauma patient (computed tomography [CT] of the abdomen) do not routinely have adequate sensitivity to assess the ductal status, and magnetic resonance imaging (MRI) is usually too unwieldy in the acute trauma patient.²⁶ Hence, the challenge remains in making an early determination of the status of the pancreatic duct.

The diagnostic techniques of most use in a patient with a possible pancreatic injury depend on the mechanism of injury, other indications for early laparotomy, and the time interval following the initial abdominal insult. Patients with clear indications for laparotomy need little or no preoperative evaluations directed at identifying a possible pancreatic injury as the diagnosis of pancreatic injury must be made intraoperatively. However, establishing the presence of pancreatic injury in those not requiring immediate laparotomy for hemorrhage or bowel perforation is a challenge made more difficult by the knowledge that a missed pancreatic duct injury has dire consequences.²⁷⁻³⁰

Although there are isolated reports of patients with complete ductal transection being asymptomatic for weeks to months to years following the initial injury,^{23,27,29,31} it is more common for patients with initially missed pancreatic injuries to manifest an abdominal crisis within a few days of their injury.³²⁻³⁴ The failure of physical signs and symptoms to develop promptly is related to the retroperitoneal location of the pancreas, pancreatic enzymes remaining inactive following an isolated injury, and decreased secretion of pancreatic fluid after injury. Early identification of a subtle pancreatic injury therefore requires a high index of suspicion, a carefully planned approach, and close observation.

A high index of suspicion is warranted in all patients with high-energy direct blows to the epigastrium. The classic examples are a crushed steering wheel with an adult driver and a handle bar injury in a child.^{35,36} The energy of impact results in a crushing of the retroperitoneal structures against the spine and typically transecting the pancreas at this point. Soft tissue contusion in the upper abdomen and disruption of the lower ribs or costal cartilage are physical findings that should suggest possible pancreatic injury. Epigastric pain out of proportion to the abdominal examination is often another clue to a retroperitoneal injury.

HYPERAMYLASEMIA

Although the highest concentration of amylase in the human body is in the pancreas, hyperamylasemia is not a reliable indicator of pancreatic trauma. In one series, only 8% of blunt abdominal injuries with hyperamylasemia had pancreatic injury.³⁷ Conversely, as many as 40% of patients with a pancreatic injury may initially have a normal serum amylase.^{38,39} In addition, there is evidence that isolated brain injury can cause elevated amylase⁴⁰ or lipase⁴¹ via an unclear central mechanism. Nonetheless, the presence of hyperamylasemia should heighten suspicion for pancreatic injury. The time between pancreatic injury and serum amylase determination may be critical. In a report of 73 patients with documented blunt injury to the pancreas, serum amylase was elevated in 61 patients (84%) and normal in 12 (16%).⁴² All 12 patients with a normal amylase were evaluated within 3 hours of injury. Patients with an elevated amylase were assayed 7 ± 1.5 hours after injury compared with 1.3 ± 0.2 hours after injury in those patients with normal serum amylase. These investigators concluded that serum amylase levels determined within 3 hours of injury are not diagnostic.

Our review of the available data led us to conclude that the sensitivity of serum amylase in detecting blunt pancreatic trauma varies from 48 to 85% and the specificity varies from 0 to 81%.⁵ The negative predictive value of serum amylase following blunt trauma is about 95%.^{38,39,43} Sensitivity and positive predictive value may improve if serum amylase is assayed more than 3 hours after injury. What this means is that 95% of patients with blunt trauma with a negative amylase will indeed not have a pancreatic injury. An elevated serum or peritoneal lavage effluent amylase does not necessarily confirm the presence of a pancreatic injury, but it does mandate further evaluation.

IMAGING STUDIES

Blunt abdominal trauma patients with hyperamylasemia who present with a reliable, benign abdominal examination

are carefully observed and serial amylase is remeasured after several hours. Persistent elevation or the development of abdominal symptoms is grounds for further evaluation, which may include abdominal CT scan, endoscopic retrograde cholangiopancreatography (ERCP), or surgical exploration. If the abdominal examination is initially equivocal or unreliable, hemodynamically stable patients with hyperamylasemia should undergo a dual-contrast (intravenous and oral) abdominal CT scan as part of the initial evaluation. If the patient subsequently develops abdominal symptoms or the amylase fails to normalize, a directed evaluation of the pancreas is warranted, either by repeat abdominal CT, ERCP, or surgical exploration.

Abdominal CT scans have a reported sensitivity and specificity of 70 to 80% in diagnosing pancreatic injury, although the accuracy of this examination is largely dependent on interpreter experience, the quality of the scanner, and the time from injury.⁴⁴⁻⁴⁶ The CT findings of pancreatic injury include direct visualization of a parenchymal fracture [see Figure 1], an intrapancreatic hematoma, fluid in the lesser sac, fluid separating the splenic vein and pancreatic body, thickened left anterior renal fascia, and retroperitoneal hematoma or fluid. These findings are often subtle, and rarely are they all present in one patient.⁴⁷ Some of the CT signs of pancreatic injury may not yet be apparent if the patient is examined immediately after injury, perhaps attributing to the reports of false-negative CT scans in up to 40% of patients with significant pancreatic injuries.⁴⁸ This, however, is not grounds for delaying a CT evaluation but is an argument for repeating a CT scan if symptoms persist.

Although ERCP has no role in the acute evaluation of the hemodynamically unstable patient, there has been a flurry of reports over the past decade regarding the utility of ERCP in diagnosing and managing pancreatic trauma. ERCP is currently the best imaging technique of the pancreatic duct and its divisions but usually requires anesthesia and is not readily or widely available. Most experience has been with ERCP in the late or missed diagnosis of pancreatic duct injury, occasionally with transducal stenting used to manage the injury, particularly in children.⁴⁹⁻⁵³ This is an evolving issue that will continue to foster investigations, but the principle of timely diagnosis and recognition and management of ductal injury remains.^{22,54} Early ERCP showing intact pancreatic ducts, including the secondary and tertiary radicals, without any extravasation permits nonoperative therapy if no associated injuries are present.⁵⁵ The difficulty in this management scheme is determining which patients warrant ERCP and getting the ERCP accomplished promptly.^{56,57}

MRI has emerged as a potential technique in the evaluation of the pancreatic duct in the earliest part of the 21st century.^{26,58} Although primarily used to date in elective circumstances, magnetic resonance pancreatography (MRCP) has been reported as a noninvasive alternative to determine the status of the main pancreatic duct in a small series of patients with pancreatic injury. To date, most reports suggest that MRCP is either unreliable or too unwieldy in the very acute phase after injury, but MRCP appears to be gaining increased interest in delayed diagnosis and management.⁵⁹ Further study of its sensitivity and specificity in this setting is warranted, but the initial enthusiasm appears to have been tempered.

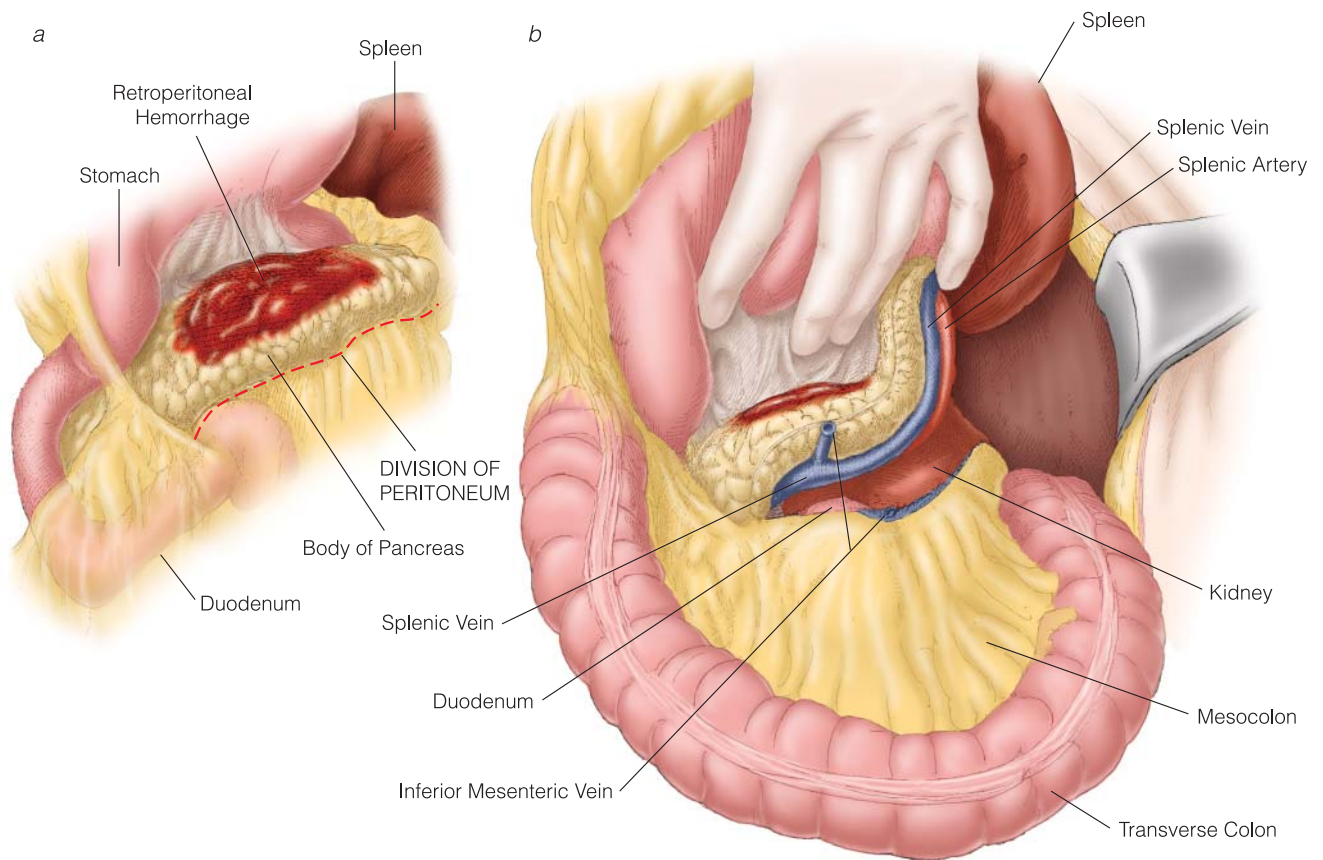


Figure 1. Contusion to the body of the pancreas. Illustrated is the appearance of a contusion to the body of the pancreas overlying the vertebral column, as seen from the lesser sac (a). The pancreas is mobilized to determine whether a fracture is present and to assess the likelihood of a duct injury. This exposure is best accomplished by dissecting along the inferior border of the gland, dividing the inferior mesenteric vein if necessary, and reflecting the pancreas superiorly (b).

INTRAOPERATIVE EVALUATION

Classification of pancreatic injuries is based on the status of the pancreatic duct and the site of injury relative to the neck of the pancreas. Careful pancreatic inspection and injury classification are often complicated by the extent and severity of associated injuries and occasionally by the reluctance of the surgeon to mobilize retroperitoneal structures. Clues suggesting potential pancreatic injury include the injury mechanisms previously described, the presence of upper abdominal wall contusion or abrasion, and concomitant lower thoracic spine fractures. The presence of a upper abdominal central retroperitoneal hematoma, edema about the pancreatic gland and lesser sac, and retroperitoneal bile staining mandate thorough pancreatic inspection.

Inspection of the pancreas requires complete exposure of the gland. The initial steps in exposure are to open the lesser sac through the gastrocolic ligament just outside the gastroepiploic vessels. Carry this exposure far to the patient's left, fully opening the lesser sac and freeing up the transverse colon. The transverse colon is retracted downward and the stomach upward and anteriorly [see Figure 1]. Frequently, a few adhesions between the posterior stomach and the anterior surface of the pancreas need to be incised. A complete Kocher maneuver is required next to provide adequate visualization

of the pancreatic head and uncinate process. In addition, mobilization of the hepatic flexure of the colon (a frequently overlooked maneuver) greatly facilitates visualization and bimanual examination of the head and neck. Inspection of the tail of the pancreas requires exposure of the splenic hilum. If injury involves the tail of the pancreas, mobilization is achieved first by division of the peritoneal attachments lateral to the spleen and colon. The colon, spleen, and body and tail of the pancreas are then mobilized forward and medially by creating a plane between the kidney and the pancreas with blunt finger dissection. This maneuver permits bimanual palpation of the pancreas and inspection of its posterior surface.

It is worth noting that injuries to the major duct occur in perhaps 15 to 20% of pancreatic trauma. In our institution, we managed 193 pancreatic injuries over a 15-year time frame.⁴ Only 27 (14%) had grade III injuries and 10 (5%) grade IV or V injuries. In the 1970s and 1980s, penetrating wounds were documented as more likely to cause pancreatic duct injury,^{60,61} but more recent reviews have not substantiated that observation.^{4,62} Regardless of the mechanism, the majority of pancreatic duct injuries can be diagnosed by careful inspection of the tract of injury following adequate exposure. All penetrating wounds should be traced from their

entry point through the surrounding tissue to the point of exit or lodging of the missile. If the pancreas has been damaged by a knife or a bullet, it is necessary to determine the integrity of the major pancreatic duct. Most penetrating wounds to the margins of the gland can be inspected directly and duct integrity confirmed. However, penetrating wounds in the head or neck or central portion of the pancreas often require further evaluation. Occasionally, intravenous injection of 1 to 2 μ g of cholecystokinin pancreatozymin (1 to 2 mL of sincalide) may stimulate pancreatic secretions enough to localize an otherwise unrecognized major duct injury. The remaining few injuries may require the more elaborate investigative techniques, including intraoperative pancreatography (see below).

Minor blunt contusions or lacerations of the pancreatic substance usually do not require further evaluation of the pancreatic duct and are effectively managed with closed suction drainage. An intact pancreatic capsule, however, does not necessarily rule out complete division of the pancreatic duct, and, rarely, blunt impact to the pancreas can result in transection of the major duct without complete transection of the gland.²³ Establishing the status of the major ductal system under these circumstances remains an important step in determining therapy and in anticipating late morbidity and mortality. Routine performance of intraoperative pancreatography when proximal duct injury was suspected decreased the postoperative morbidity rate from 55% to 15% at our institution.²⁴

Intraoperative imaging of the pancreatic duct can be performed by one of three techniques: ERCP, direct open ampullary cannulation, or needle cholangiopancreatography. Intraoperative ERCP is cumbersome and often difficult to coordinate during an emergency operation, but it has been used and reported.⁶³ Duodenotomy and direct ampullary cannulation, or even transection of the tail of the pancreas and distal duct cannulation, have been reported as useful techniques in the past, but current perioperative imaging, improved exposure and direct visualization of the pancreas, and effective use of wide closed-suction drainage and postoperative ERCP have largely abolished the use of these very invasive diagnostic techniques of imaging the pancreatic duct.⁶⁴ Needle cholecystocholangiopancreatography remains a useful intraoperative adjunct in the evaluation of the pancreatic duct. This technique involves cannulating the gallbladder with an 18-gauge angiocatheter and injecting 30 to 75 mL of three-quarter-strength water-soluble contrast under fluoroscopic imaging. Clear images of the biliary tree are readily obtained, and in our experience, this technique is successful in imaging the pancreatic duct 64% (7 of 11) of the time.⁴ Contracture of the sphincter of Oddi with intravenous morphine may enhance the likelihood of pancreatic duct visualization. A cholecystectomy is not necessary following this procedure.

Classification of Pancreatic Injuries

Although a number of classification systems have been devised to catalogue pancreatic injuries,^{60,64,65} the American Association for the Surgery of Trauma (AAST) Committee on Organ Injury Scaling addresses the key issues of treatment of parenchymal disruption and major pancreatic duct status by focusing on the anatomic location of the injury for the more severe (grade III to V) injuries [see Table 1].⁶⁶ Table 1

also defines the Abbreviated Injury Scale (AIS) value that corresponds to the AAST grading system.⁶⁷ The AIS has undergone a revision in 1998 and again in 2005. These differences are important since most commercially available trauma registries use AIS coding. The AIS coding system is sponsored and owned by the Association for the Advancement of Automotive Medicine. Duct injuries have different management alternatives than distal duct and parenchymal injuries [see Figure 2]. Parenchymal contusions or lacerations with minimal or no parenchymal tissue loss and no ductal injury (grade I or II) need only be externally drained. Combined duodenal and pancreatic head injuries that include the major duct or ampulla require a combined pancreatoduodenectomy, commonly known as the Whipple procedure, but uncommonly required for trauma. The difficult decisions in managing pancreatic trauma involve patients with parenchymal disruption and major duct injury. By focusing on the anatomic location of the duct and parenchymal injury (proximal versus distal), this classification provides a useful management guide.

Treatment of Pancreatic Injuries

CONTUSIONS AND LACERATIONS WITHOUT DUCT INJURY

Minor pancreatic contusions, hematomas, and capsular lacerations (grade I) account for about 50% of all pancreatic injuries; lacerations of the pancreatic parenchyma without major ductal disruption or tissue loss (grade II) account for an additional 25% of pancreatic injuries. These injuries are the injury pattern commonly managed nonoperatively. If identified at operation, they require only hemostasis and adequate external drainage.^{2,68} No attempt should be made to repair capsular lacerations because closure may result in a pancreatic pseudocyst, whereas a controlled pancreatic fistula is usually self-limiting. Soft closed-suction drains (Jackson-Pratt) are preferred over Penrose drains or sump drains as intra-abdominal abscess formation is less likely, effluent is more reliably collected, and the excoriation of the skin at the exit site is significantly less with closed-suction drains.^{35,69,70} Drains are removed when the amylase concentrations in the drain are less than that of serum, generally within 24 to 48 hours. An international consensus group definition of pancreatic fistula is the persistence of any measurable volume of drain output on or after postoperative day 3 with an amylase content greater than three times serum amylase activity.⁷¹ As described below, there are three grades of pancreatic fistula complications [see Complications, below]. Drains are generally left in situ until there is no evidence of pancreatic leak.

Nutrition should be provided via the oral or gastric route as soon as possible. However, a prolonged gastric ileus or pancreatic complications may preclude standard gastric feeding in patients with severe injuries. Also, since most tube feeding formulas are high in fat and increase pancreatic effluent volume and amylase concentration, the low fat and higher pH (4.5) of elemental diets are preferred as they tend to be less stimulating to the pancreas.^{72,73}

DISTAL TRANSECTION AND DISTAL PARENCHYMAL INJURY WITH DUCT DISRUPTION

The anatomic distinction between proximal and distal pancreas is generally defined by the superior mesenteric

Table 1 AAST Organ Injury Scales for Pancreas and Duodenum

Injured Structure	AAST Grade*	Characteristics of Injury	AIS-90 Score	AIS-2005 Score
Pancreas	I	Small hematoma without duct injury; superficial laceration without duct injury	2	2
	II	Large hematoma without duct injury or tissue loss; major laceration without duct injury or tissue loss	2; 3	2
	III	Distal transection or parenchymal laceration with duct injury	3	3
	IV	Proximal [†] transection or parenchymal laceration involving ampulla	4	4
	V	Massive disruption of pancreatic head	5	5
Duodenum	I	Single-segment hematoma; partial-thickness laceration without perforation	2; 3	2
	II	Multiple-segment hematoma; small (< 50% of circumference) laceration	2; 4	2
	III	50–75% disruption (laceration) of segment D2 or 50–100% disruption of segment D1, D3, or D4	4	3
	IV	Very large (75–100%) laceration of segment D2; rupture of ampulla or distal CBD	5	4
	V	Massive duodenopancreatic injury; devascularization of duodenum	5	5

AAST = American Association for the Surgery of Trauma; AIS-90 = Abbreviated Injury Score, 1990 version; AIS-2005 = Abbreviated Injury Score, 2005 version; CBD = common bile duct.

*Advance one grade for multiple injuries, up to grade III.

[†]Proximal pancreas is to the patient's right of the superior mesenteric vein.

vessels passing behind the pancreas at the junction of the pancreatic head and body. Although there is no anatomic distinction in the gland itself between the head, body, or tail, this anatomic division is useful in estimating residual pancreatic endocrine and exocrine function. Innes and Carey have shown that a distal pancreatic resection at the portal vein removes an average of 56% (range 36 to 69%) of the gland by weight.⁷⁴ Since most blunt trauma pancreatic injuries occur at the spine, which is just to the patient's left of the portal vein as it crosses behind the pancreas, a "distal pancreatectomy" in this circumstance averages as a 56% gland resection. A resection at the common bile duct removes an average of 89% (range 64 to 95%) of the gland. Although reports of normal endocrine and exocrine function after 90% pancreatectomy do occur, every effort should be made, if possible, to leave at least 20% residual pancreatic tissue to minimize postoperative complications.^{75,76}

Distal parenchymal transection, particularly with disruption of the main pancreatic duct, is best treated by distal pancreatectomy. This is true in children and adults. CT, particularly if done more than 4 hours after the injury has occurred, is usually accurate enough to confirm complete transection. Operative intervention in this case is superior to nonoperative management in that the operation is definitive, the residual gland is adequate to preserve exocrine and endocrine function, and the recovery is relatively short. Nonoperative management is typically fraught with the complications of pseudocysts, abscess, prolonged and recurrent hospital admissions, and repetitive drainage procedures, including the technically challenging and invasive attempts at endoscopically traversing a transected distal duct.^{1,10,77}

If at celiotomy there is any concern regarding the status of the remaining proximal main pancreatic duct, intraoperative pancreatography should be performed through the open end of the proximal duct. If the remaining proximal duct is normal, the transected duct should be identified and closed with a direct "U"-stitch suture ligature with a nonabsorbable monofilament suture.⁷⁸ The parenchyma can be closed with the large (4.8 mm) TA-55 staple,^{78,79} but we find that this excessively crushes the residual pancreas, so we prefer mattress sutures placed through the full thickness of the pancreatic gland from anterior to posterior capsule to minimize leak from the transected parenchyma. Although most surgeons prefer nonabsorbable suture for pancreatic stump closure, one report suggests that a lower complication rate is obtained with absorbable polyglycolic acid suture to oversee the pancreatic stump.⁵⁴ A small omental patch can be used to buttress the surface, and a drain should be left near the transection line.

Concern for the possibility of postsplenectomy sepsis and subphrenic abscess formation following splenectomy has prompted several authors to describe distal pancreatectomy without splenectomy [see Figure 3]. The technical challenge in pancreatectomy with splenic salvage is in isolating and ligating the pancreatic branch vessels off the splenic vein and artery yet preventing injury to the splenic hilum and thrombosis of the splenic vein. Generous mobilization of the entire pancreatic gland and spleen is a prerequisite. An average of 22 tributaries of the splenic vein and seven branches of the splenic artery must be ligated.⁸⁰ One report suggests that this maneuver will add an average of 50 minutes (range 37 to 80 minutes) to the operative time.⁸¹ Patton and colleagues reported splenic salvage in 21 of 33 patients (64%) who

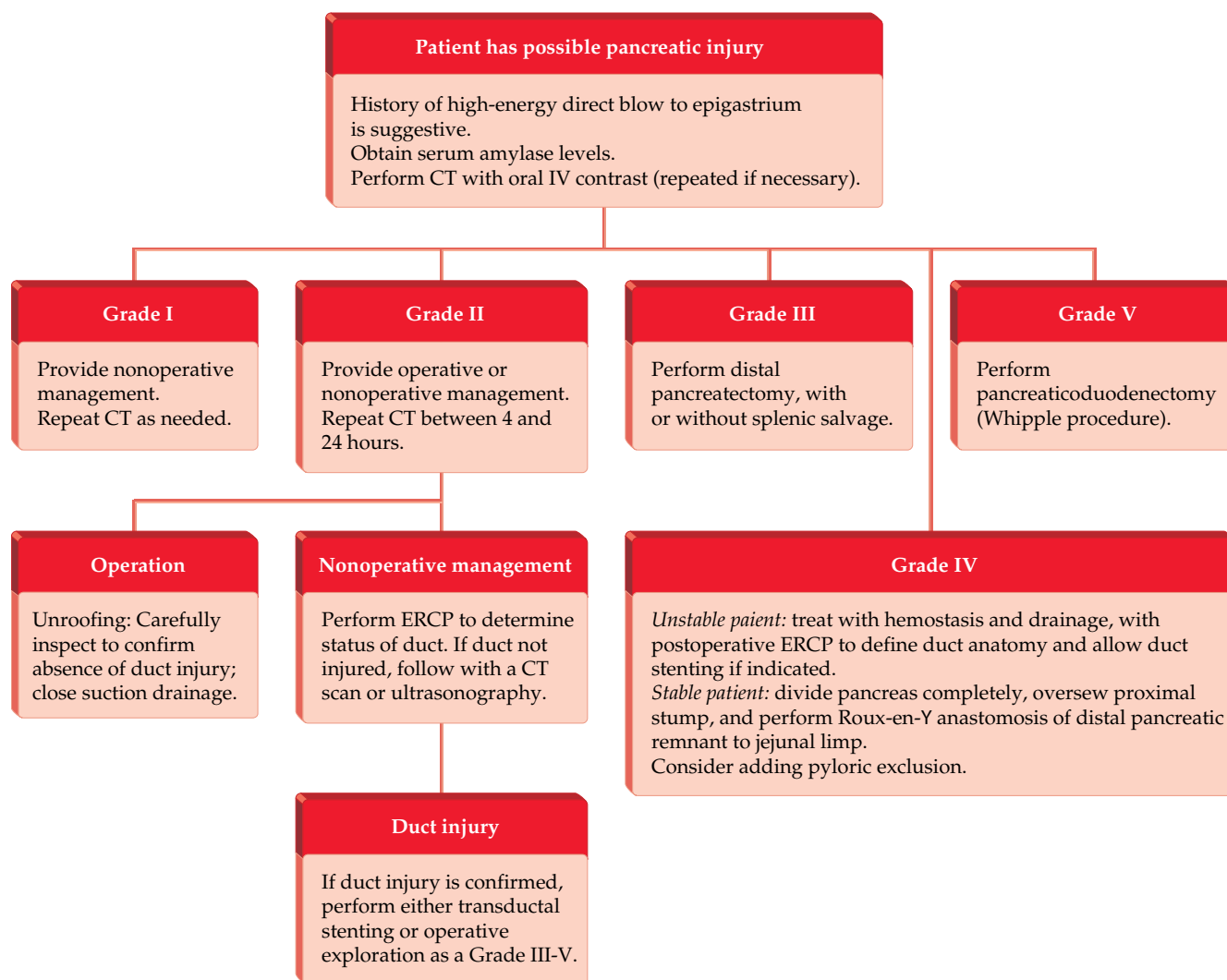


Figure 2. Treatment of pancreatic injury. Algorithm outlining the treatment of pancreatic injury. CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography.

underwent distal pancreatic resection (8 blunt, 13 penetrating).³⁴ The increased operative time and potential blood loss incurred while performing pancreatectomy without splenectomy must be balanced against the slight risk of overwhelming postsplenectomy sepsis. The balance would seem to favor splenic salvage only when the patient is completely hemodynamically stable and normothermic and the pancreatic injury is isolated or present with only minor associated injuries.

PROXIMAL TRANSECTION OR INJURY WITH PROBABLE DUCT DISRUPTION

Injuries to the pancreatic head represent the most challenging management dilemmas. The key principles of immediate management are, in order, control bleeding, halt contamination, and define the anatomy of the injury. Effective management can only follow these steps. It is essential that the surgeon define the pancreatic duct anatomy in proximal pancreatic injuries. This can usually be accomplished by local inspection and exploration of the defect to determine the duct status. Techniques of intraoperative pancreatography

have been described above and are strongly recommended if local exploration alone is inadequate to determine the status of the main pancreatic duct. The only exception to this approach is the hemodynamic unstable patient with hypothermia, acidosis, and coagulopathy, in which case, simple damage control surgery is advised. Most experienced surgeons express reservations regarding performance of a duodenotomy to perform pancreatography, but a needle cholecystocholangiopancreatography can often image the pancreatic duct along with the distal common bile duct (64% in our experience).⁴ If this proves unsuccessful, then wide external drainage with several closed-suction drains should be performed with planned early postoperative ERCP (preferred), or MRCP should be the plan. If major proximal duct injury is confirmed by postoperative ERCP, pancreatic duct stenting rather than near-total pancreatectomy may be an option depending on local expertise.^{1,49,50,53} However, at least one report has had discouraging results with stenting, notable for long-term stricture development and acute sepsis.³⁰

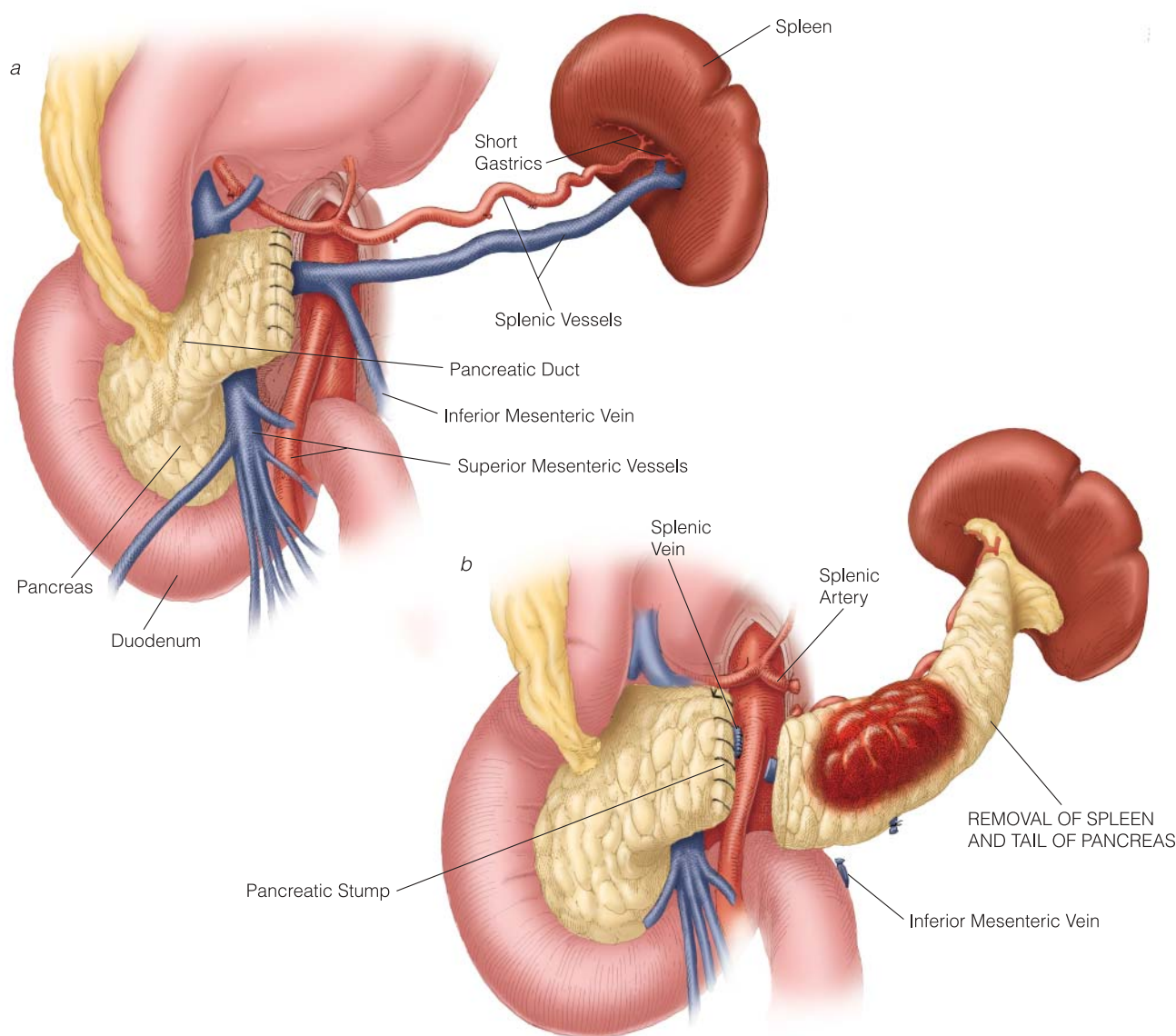


Figure 3. Distal pancreatectomy with and without splenic salvage. Illustrated is distal pancreatectomy with salvage of the spleen (a) and without splenic salvage (b).

If the proximal duct is injured, but the ampulla and duodenum are spared (rare), two options are available. One option is extended distal pancreatectomy, resulting in subtotal removal of the gland. The proximal residual gland will drain into the duodenum in a normal fashion if the duct is intact. Wide external drainage of the residual pancreatic surface must be provided. We have not added pyloric exclusion or duodenal defunctionalization or diverticulization to this procedure, although others advocate its use in this circumstance.^{72,82} If there is concern that the residual proximal pancreatic tissue is inadequate to provide endocrine or exocrine function, the second option is to preserve the pancreatic tail distal to the injury using a Roux-en-Y pancreaticojejunostomy [see Figure 4]. This requires division of the pancreas at the site of injury, débridement of injured parenchyma, secure closure of the proximal duct and parenchyma,

and anastomosis of the open end of the divided distal pancreas to the Roux-en-Y jejunal limb. A review of 399 patients with pancreatic injury from four separate publications revealed that only 2 (0.5%) patients underwent Roux-en-Y drainage of the distal segment of a transected pancreatic gland.^{34,54,83,84} Although rarely employed and complicated by the need for a combination of pancreatic resection, pancreatic-jejunal anastomosis, and construction of the Roux-en-Y limb, this operation needs to be in the armamentarium of trauma surgeons.

The report by Patton and colleagues from Memphis, supported by the experience of University of Mississippi reported by Duchesne and colleagues, is compelling for the effectiveness of drainage alone rather than extended pancreatectomy, particularly for proximal pancreatic gland injury in which the duct status is unclear.^{2,34} In the Patton and

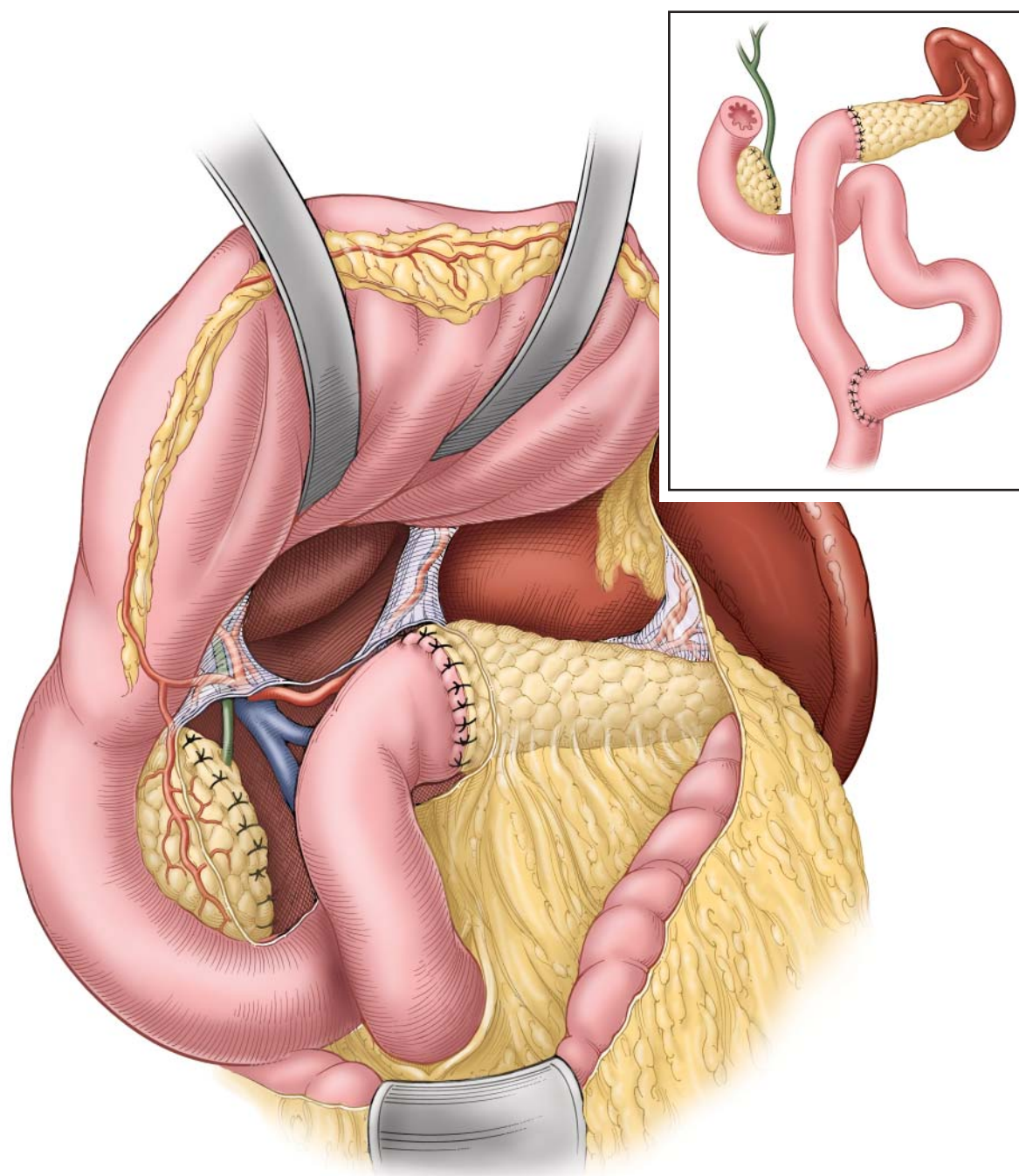


Figure 4. Roux-en-Y pancreaticojejunostomy. If a patient has a grade IV injury to the pancreatic head and there is concern regarding whether the proximal residual gland would have adequate endocrine and exocrine function if the distal gland is resected in an extended distal pancreatectomy, an option is to preserve the uninjured portion of the distal gland. This is done by dividing the pancreas at the site of the injury and performing a Roux-en-Y pancreaticojejunostomy to allow the distal pancreas to drain into the jejunal limb.

colleagues' study, 37 patients with proximal pancreatic injury were managed by closed-suction drainage alone, resulting in a modest 13.5% fistula and abscess rate. Pancreatography was not performed in these patients, so the status of the pancreatic duct was not defined, and it remains unclear whether this technique is truly effective in the presence of a major

pancreatic duct injury. In the Duchesne and colleagues report, 35 patients had AAST grade I or II pancreatic injuries by CT scan and were intentionally managed nonoperatively. Five (14.3%) failed nonoperative management because of missed bowel injury ($n = 2$) and pancreatic abscess ($n = 3$), all classified as AAST grade II injuries. These failures of

nonoperative management survived but had a significantly longer length of stay (19 days versus 9 days). Operative exploration and drainage of even low-grade pancreatic injuries remain a prudent approach.

Both of these reports emphasize the importance of determining the status of the pancreatic duct. If the duct and its branches are not injured, nonoperative management is likely to be successful, and the role for detailed description of pancreatic duct anatomy advocated by Takishima and colleagues is relevant.⁸⁵ If no effort is made at determining the status of the pancreatic duct, at least wide drainage is mandatory. This approach is likely to be successful most of the time since injury to the main pancreatic duct is unusual; when it fails, however, the consequences are significant and morbid.^{4,6}

If the main pancreatic duct is injured or transected, distal resection is preferred, with the option of Roux-en-Y drainage of a long or significant distal pancreas that the surgeon is loath to sacrifice. Damage control drainage remains a viable lifesaving first operation. Finally, postoperative ERCP and transductal injury stenting appear to be another viable option, particularly in children, and particularly with very experienced endoscopists.^{1,53}

In the case of an incomplete pancreatic parenchymal transection, some surgeons have described an end jejunum-to-side pancreas anastomosis. This technique is not recommended because of the difficulty in ensuring the integrity of the anastomosis and potential for a high-output pancreatic fistula from the posterior pancreatic wound. Stone and colleagues from Emory University illustrated the high complication rate associated with this dated technique. Of 7 patients in whom the technique was used (among 283 patients), 5 (71%) developed a fistula and 3 (43%) died.⁶⁸

Insertion of a needle catheter jejunostomy or small feeding tube jejunostomy at the time of initial celiotomy should be considered for all patients with grade III to V pancreatic injuries. This allows early postoperative enteral nutrition, rather than committing the patient who cannot tolerate oral or gastric feedings to total parenteral nutrition.⁸⁶ There is some morbidity related to surgically placed feeding tubes. Our experience is that feeding jejunostomies have a major complication rate of 4% in severely injured patients.⁸⁷ Needle catheter jejunostomies were associated with fewer complications than the larger, Witzel tube jejunostomy—hence, our preference for this smaller-caliber feeding tube and elemental or short-chain polypeptide feeding formulas, which we prefer.^{73,87}

Combined Pancreatic-Duodenal Injuries

Fortunately, severe combined pancreatic head and duodenal injuries are rare. Forty-eight of 1,404 patients (3%) with pancreatic injuries reported between 1981 and 1990 underwent pancreatoduodenectomy.⁸⁸ These injuries are most commonly caused by penetrating wounds and occur in association with multiple other intra-abdominal injuries. In fact, these associated injuries are the primary cause of mortality and emphasize again the priorities of hemorrhage control and contamination control in dealing with pancreatic or duodenal injury. The major immediate mortality in patients with combined pancreatic and duodenal injuries is attributable to major vascular injury in the vicinity of the head of the

pancreas. If immediate control of hemorrhage and resuscitation can be obtained, the Whipple resection remains the preferred option in that select group of patients with unreconstructable injury to the ampulla or proximal pancreatic duct or with combined massive destruction of the duodenal and pancreatic head. Essentially, in these patients, pancreatoduodenectomy is the completion of surgical débridement of devitalized tissue. For patients with hemodynamic instability, hypothermia, coagulopathy, and acidosis, a staged operative approach (damage control surgery) is advocated, first obtaining control of hemorrhage, then managing bowel and bacterial contamination, and, lastly, identifying the anatomy of the injury, followed by resuscitation in the intensive care unit. The patient is returned to the operating room for definitive reconstruction and anastomoses when stabilized, generally 24 to 48 hours later.

Because of the large number of possible combinations of injuries to the pancreas and duodenum, no one form of therapy is appropriate for all patients. In Feliciano and colleagues' review of 129 cases of combined pancreatic-duodenal injuries, 24% of the patients were treated with simple repair and drainage, 50% underwent repair and pyloric exclusion, and only 10% required a Whipple procedure.⁸² The best treatment option is predicated on the integrity of the distal common bile duct and ampulla, as well as the severity of the duodenal injury [see Figure 5]. For that reason, every patient with a combined pancreatic-duodenal injury requires a cholangiogram, a pancreatogram, and evaluation of the ampulla. When the common bile duct and ampulla are intact (as is the situation in the majority of the cases), the duodenum can be closed primarily and the pancreatic injury treated as previously described. If the status of the pancreatic duct cannot be made intraoperatively, wide external drainage of the pancreatic head with closed suction drains should be performed rather than a total pancreatectomy and early postoperative ERCP or MRCP performed.

It may be advisable to divert gastric contents away from the duodenal repair in the presence of severe injury to the duodenum. Duodenal "diverticulization" employs primary closure of the duodenal wound, antrectomy, vagotomy, end-to-side gastrojejunostomy, T-tube common bile duct drainage, and lateral tube duodenostomy. The concept is to completely divert both gastric and biliary contents away from the duodenal injury, provide enteral nutrition via the gastrojejunostomy, and convert a potential uncontrolled lateral duodenal fistula to a controlled fistula [see Figure 6]. A less formidable and less destructive alternative is the "pyloric exclusion," which does not employ antrectomy, biliary diversion, or vagotomy [see Figure 7].^{72,89-91} This procedure is performed through a gastrotomy and consists of grasping the pylorus with a Babcock clamp and suturing closed the pylorus with an absorbable size 0 polyglycolic acid or Maxon suture and constructing a loop gastrojejunostomy. This diverts gastric flow away from the duodenum for several weeks while the duodenal and pancreatic injuries heal. The pylorus eventually opens (2 weeks to 2 months), and the gastrojejunostomy functionally closes. Fang and colleagues at Chang-Gung Memorial Hospital in Taiwan described a technical method of controlled release of the pyloric exclusion knot, thereby timing the opening of the pyloric

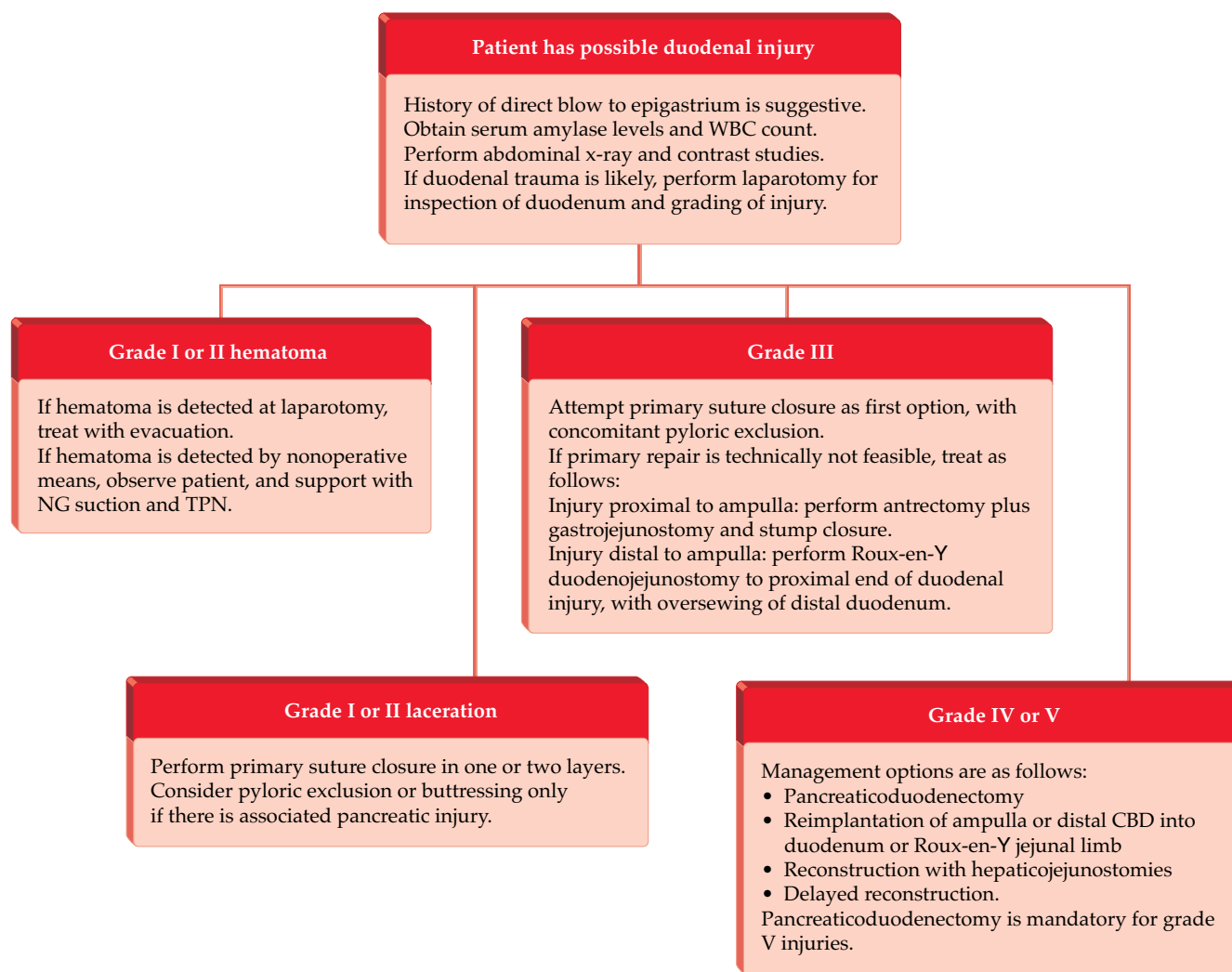


Figure 5. Treatment of duodenal injury. Algorithm outlining the treatment of duodenal injury. CBD = common bile duct; NG = nasogastric; TPN = total parenteral nutrition; WBC = white blood cell count.

occlusion.⁹² Marginal ulceration at the site of gastrojejunostomy has been reported from 5 to 33% of patients in whom a vagotomy was not performed.⁹⁰⁻⁹³ Pyloric exclusion is generally reserved for severe combined duodenal and pancreatic head and duodenal injuries in which a Whipple procedure is not required. Few advocate pyloric exclusion for isolated pancreatic injuries.

In very massive injuries of the proximal duodenum and head of the pancreas, destruction of the ampulla and proximal pancreatic duct or distal common bile duct may preclude reconstruction. In addition, because the head of the pancreas and the duodenum have a common arterial supply, it is essentially impossible to entirely resect one without making the other ischemic. In this situation, a pancreatoduodenectomy is required. Between 1961 and 1994, 184 Whipple procedures were reported for trauma, with 26 operative deaths (14%) and 39 delayed deaths, for a 64% overall survival rate.⁸⁸ However, more recent experience suggests that with appropriate selection criteria, pancreatoduodenectomy for injury can be performed with morbidity and mortality similar to those described for resections done for cancer.⁹⁴⁻⁹⁶

Nonoperative Management in Children

Major pancreatic duct injury in children is rare, with an incidence of 0.12% of children with blunt abdominal trauma.⁵² Most pediatric pancreatic injuries are grade I or II injuries, without major pancreatic duct injury. As a result, several authors have advocated managing all blunt pediatric pancreatic injuries nonoperatively, with bowel rest, serial abdominal CT to observe for pseudocyst formation, and subsequent percutaneous drainage as required.^{7,97-99} However, the high morbidity and prolonged hospital course of these patients may not be justified given the good recovery from distal pancreatectomy with splenic salvage.¹⁰ Pseudocysts develop in 40 to 100% of children with major ductal injury,^{7,8,100} and recurrent episodes of pancreatitis can occur remote to the time of injury.^{36,101} ERCP with proximal stenting of ductal injuries is an additional adjunct to care in these patients but requires the availability of a skilled pediatric endoscopist. A report from Toronto details the management of 35 children with pancreatic trauma over a 10-year time period.⁷ Twenty-three had early diagnosis (< 24 hours), whereas in 12, the diagnosis was initially missed. Twenty-eight were managed

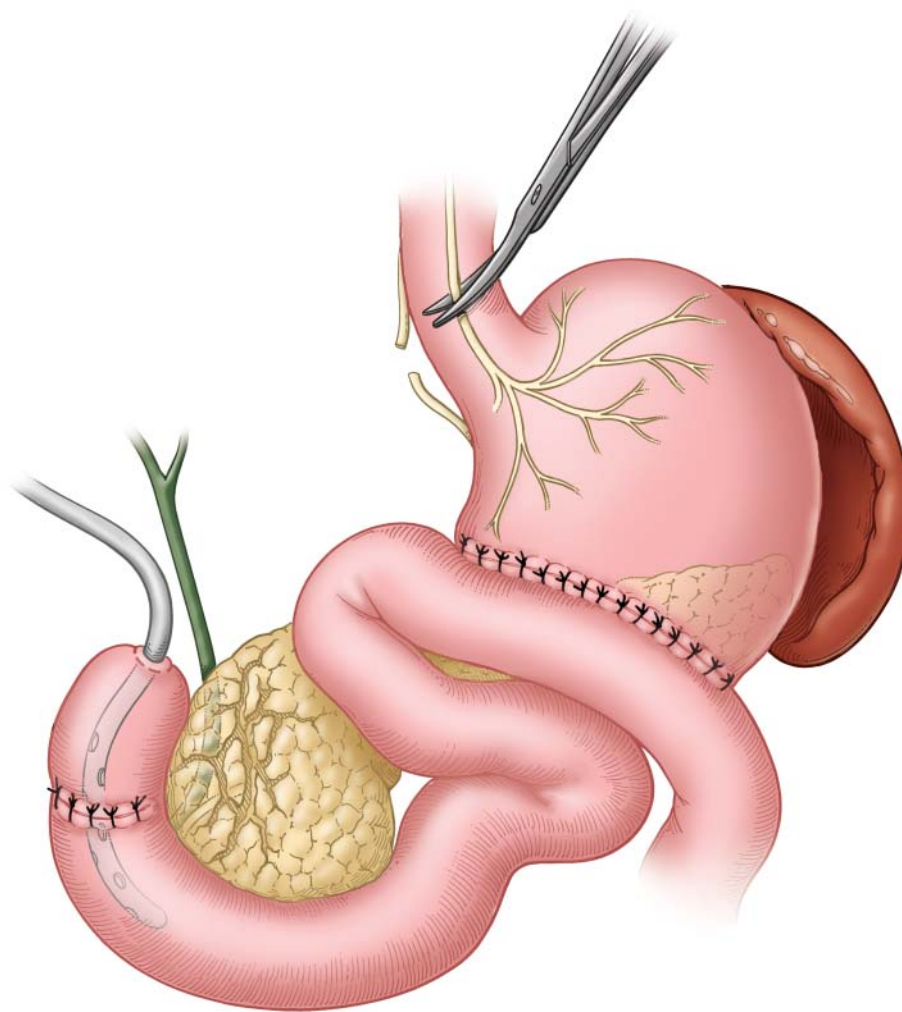


Figure 6. Duodenal diverticularization. Duodenal diverticularization consists of antrectomy with gastrojejunostomy, tube duodenostomy, vagotomy, and peripancreatic drainage.

nonoperatively. A subsequent report examined in more detail 10 of these patients having a pancreatic duct transection.⁹⁹ Forty-four percent developed pseudocyst, and all were managed with percutaneous drainage; 75% had atrophy of the distal pancreatic remnant, but there was no evidence of endocrine or exocrine dysfunction. A report from Japan demonstrated 100% pseudocyst development in five children with pancreatic duct injury managed nonoperatively.⁸ The data seem to suggest that pediatric pancreatic injuries can be successfully managed nonoperatively, but with a high incidence of pseudocyst formation requiring further hospitalization and interventions and with atrophy of the distal remnant. Other pediatric surgical authors point out the benefits of distal pancreatectomy in terms of shortening hospital stay and interventions.^{10,52,102}

Complications

The incidence of complications following pancreatic injury remains uncomfortably high. Between 20 and 40% of patients who undergo surgical intervention of a pancreatic injury have a complicated postoperative course and even higher if a combined pancreatoduodenal wound has occurred [see Table 2].⁵

Although the majority of complications related to pancreatic injury are self-limiting or treatable, sepsis and multisystem organ failure are responsible for nearly 30% of the deaths in pancreatic trauma. In some series, up to one half of the postoperative complications could have been avoided with careful inspection of the pancreas and accurate determination of the status of the main pancreatic duct.²⁸

FISTULA

Postoperative pancreatic fistula has been defined as any measurable drain output with an amylase greater than three times serum.⁷¹ This is the most common complication following pancreatic injury, with an incidence of 7 to 20%, rising to 26 to 35% after combined pancreatoduodenal injury.^{34,61,103,104} Direct suture closure of the main pancreatic duct may help minimize this complication, but fibrin sealants do not seem to provide any advantage.¹⁰⁵ The vast majority of these are minor (less than 200 cc/day) and spontaneously resolve within 2 weeks of injury, providing that adequate external drainage has been provided. In a multicenter review of distal pancreatectomy for trauma, the postoperative fistula rate was 14% (10 of 71), with spontaneous fistula closure in 89% (8 of 9) of survivors in 6 to 54 days.⁸³ One patient required

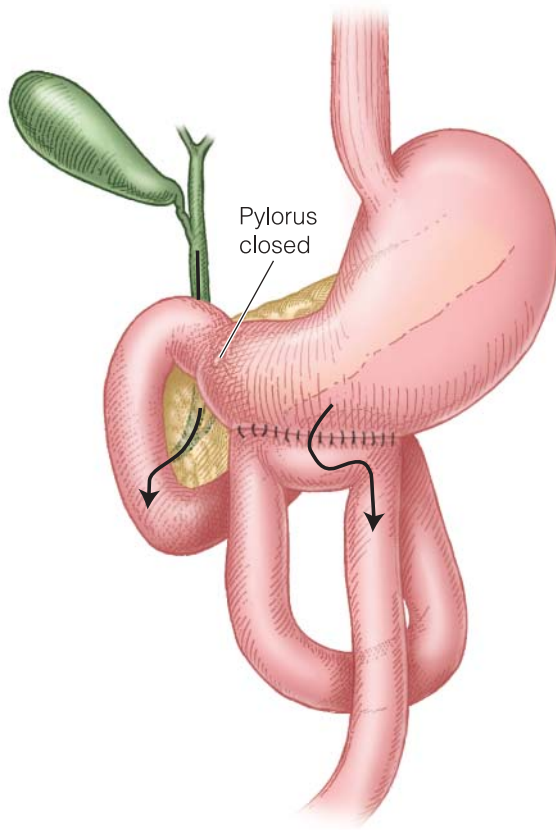


Figure 7. Pyloric exclusion. Pyloric exclusion consists of closure of the pylorus from within the stomach, followed by gastrojejunostomy. The procedure eliminates discharge of gastric acid into the duodenum, thus minimizing the stimulation of pancreatic secretion and reducing morbidity if there is breakdown of a repair.

extirpation of a residual pancreatic sequestrum to facilitate fistula closure. This compares with a 3.3% fistula rate in elective distal pancreatectomy for chronic pancreatitis.⁷⁶ High-output fistulae (greater than 700 cc/day) are rare and generally require longer periods of external drainage or surgical intervention for resolution. If a high-output fistula fails to progressively decrease in volume or persists more than

10 days, ERCP is indicated and can be most helpful in establishing the cause of the persistent fistula and planning further therapy. Nutritional support must be provided throughout this period. The surgeon's foresight in placing a feeding jejunostomy at the time of initial trauma laparotomy is now rewarded. Low-fat, higher pH elemental feeding formulas cause less pancreatic stimulation than standard enteral formulas and should be tried prior to committing the patient to total parenteral nutrition.⁷³ A somatostatin analogue (octreotide acetate [Sandostatin]) has shown promise in treating prolonged, high-output pancreatic fistulae, but only after eradicating any infection and in the absence of pancreatic duct obstruction or stricture.¹⁰⁶

Octreotide as an adjuvant to standard fistula management probably diminishes fistula output, but its shortening of the time to fistula closure remains to be proven.¹⁰⁷ Somatostatin analogues do seem to prevent postoperative complications and fistula formation in patients undergoing elective pancreatic resection, although nonrandomized reports on the efficacy of somatostatin analogues in pancreatic trauma patients are contradictory.^{108,109} In addition, the trials demonstrating a decrease in postoperative complications with octreotide use in elective pancreatic resection initiated octreotide in the preoperative period, a time frame not applicable to the trauma setting.¹⁰⁹ Treatment typically begins with 50 µg subcutaneously every 12 hours but can increase to 1,000 µg/day. Octreotide has been included in total parenteral nutrition solutions, although this remains controversial and is not recommended by the 1997 package insert because of the formation of glycosyl octreotide conjugates that may decrease efficacy.¹¹⁰ Major side effects are unpredictable changes in serum glucose, pain at the injection site, and a variety of nonspecific gastrointestinal complaints.

ABSCESSSES

The incidence of abscess formation after pancreatic trauma ranges from 10 to 25%, depending on the number and type of associated injuries. Early operative or percutaneous decompression or evacuation is critical, although the mortality rate in this group of patients remains about 25%.^{82,111} The intra-abdominal abscess is most often subfascial or peripancreatic; a true pancreatic abscess is unusual, resulting from inadequate débridement of dead tissue or inadequate initial drainage.^{61,84,104,112} True pancreatic abscesses are often not amenable or responsive to percutaneous drainage, and prompt surgical débridement and drainage are required. Percutaneous decompression may be helpful in distinguishing between abscess and pseudocyst.

Table 2 Factors Determining Severity of Duodenal Injury

Factor	Degree of Injury	
	Mild	Severe
Means of injury	Stab	Blunt force or missile
Size of injury	≤ 75% of circumference	> 75% of circumference
Location of injury in duodenum	D3, D4	D1, D2
Interval between injury and repair	≤ 24 hr	> 24 hr
Adjacent injury to CBD	Absent	Present

CBD = common bile duct.

PANCREATITIS

Transient abdominal pain and a rise in the serum amylase concentration may be anticipated in 8 to 18% of postoperative patients.^{23,84,113} This type of pancreatitis is treated with nasogastric decompression, bowel rest, and nutritional support and can be expected to resolve spontaneously. A much more infrequent but deadly complication is hemorrhagic pancreatitis. The first sign of this complication may be bloody pancreatic drainage or a fall in the serum hemoglobin concentration, with the patient rapidly becoming desperately ill. It is fortunate that this complication occurs in less than 2% of operative pancreatic trauma patients since mortality may approach 80% with no effective treatment.^{61,75}

SECONDARY HEMORRHAGE

Postoperative hemorrhage requiring blood transfusion may occur in 5 to 10% of pancreatic trauma patients, particularly when inadequate external drainage has been afforded after pancreatic débridement or when intra-abdominal infection has developed.^{113,114} These patients generally require reoperation for control, although angiographic embolization may be an effective alternative.

PSEUDOCYSTS

Missed blunt pancreatic injuries, or those intentionally managed nonoperatively, often result in the formation of a pseudocyst. One report tabulated 22 pseudocysts in 42 blunt pancreatic trauma patients managed nonoperatively.²⁷ The status of the pancreatic duct is the key determinant to

treatment of a pancreatic pseudocyst. If the pancreatic duct is intact, percutaneous drainage of the pseudocyst is likely to be effective. If the pseudocyst is secondary to a major pancreatic ductal disruption, percutaneous drainage will not provide definitive therapy but will convert a pseudocyst to a chronic fistula. ERCP should therefore precede any percutaneous drainage. If pancreatic duct stenosis or injury is demonstrated, treatment options include (1) reexploration and partial gland resection, (2) distal gland internal Roux-en-Y drainage, and (3) endoscopic transpapillary stenting of the pancreatic duct.⁴⁹ The experience of Kouchi and colleagues of Japan suggests that a pseudocyst greater than 10 cm in size will require surgical decompression.⁸

EXOCRINE AND ENDOCRINE INSUFFICIENCY

Both exocrine and endocrine insufficiency are unusual after pancreatic trauma. Animal and human studies suggest that a residuum of 10 to 20% of normal pancreatic tissue is adequate for pancreatic function,^{24,115} implying that any resection distal to the mesenteric vessels should leave adequate functioning pancreatic tissue. The multicenter study of 74 cases of distal pancreatic resection described earlier documented only 1 case of endocrine deficiency (diet-controlled hyperglycemia following 80% pancreatectomy) and no instance of exocrine insufficiency.⁸⁴ Balasegaram reported no pancreatic insufficiency after resections of up to 90% of the pancreas.¹⁰³ In contrast, patients with chronic pancreatitis who undergo distal pancreatectomy have an incidence of diabetes ranging from 15% (0 to 33% gland resected) to 64% (50 to 75% gland resected).⁷⁶

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10 INJURIES TO THE GREAT VESSELS OF THE ABDOMEN

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In patients who have injuries to the great vessels of the abdomen, the findings on physical examination generally depend on whether a contained hematoma or active hemorrhage is present.¹ In the case of contained hematomas around the vascular injury in the retroperitoneum, the base of the mesentery, or the hepatoduodenal ligament, the patient often has only modest hypotension in transit or on arrival at the emergency center. The hypotension can be temporarily reversed by the infusion of fluids and may not recur until the hematoma is opened at the time of laparotomy. This is usually the situation when an abdominal venous injury is present. In the case of active intraperitoneal hemorrhage, the patient typically has significant hypotension and may have a distended abdomen on arrival. Another physical finding that is occasionally noted in association with an injury to the common or external iliac artery is intermittent or complete loss of a pulse in the ipsilateral femoral artery; this finding in a patient with a transpelvic gunshot wound is pathognomonic of an injury to the iliac artery.

Injuries to the great vessels of the abdomen are caused by penetrating wounds in 90 to 95% of cases; accordingly, they are often accompanied by injuries to multiple intra-abdominal organs, including those in the gastrointestinal (GI) tract.²⁻⁵ The general principles governing the sequencing of repairs of injuries to the great vessels and the GI tract are outlined elsewhere.

A hematoma [see *Figure 1* and *Figure 2*] or hemorrhage associated with an injury to a great vessel of the abdomen occurs in one of the three zones of the retroperitoneum or in the portal-retrohepatic area of the right upper quadrant. The magnitude of injury is usually described according to the Abdominal Vascular Organ Injury Scale, devised in 1992 by the American Association for the Surgery of Trauma [see *Table 1*].⁶

Injuries in Zone 1

SUPRAMESOCOLIC

It is helpful to divide midline retroperitoneal hematomas into those that are supramesocolic and those that are inframesocolic.¹ Hematoma or hemorrhage in the midline supramesocolic area of zone 1 is cause to suspect the presence of an injury to the suprarenal aorta, the celiac axis, the proximal superior mesenteric artery, or the proximal renal artery.

When a hematoma is present in the midline supramesocolic area, one usually has time to perform left medial visceral rotation [see *Figure 3*].^{7,8} The advantage of this technique is that it allows visualization of the entire abdominal aorta, from the aortic hiatus of the diaphragm to the common iliac arteries [see *Figure 4*].

Obvious disadvantages include the 5 to 7 minutes required to complete the maneuver when the surgeon is inexperienced; the risk of damage to the spleen, the left kidney, or the posterior left renal artery as the maneuver is performed; and the anatomic distortion that results when the left kidney and the left renal artery are rotated anteriorly. When the hematoma is near the aortic hiatus of the diaphragm, it may be advisable to leave the left kidney in its fossa, thereby eliminating potential damage to the structure as well as the distortion resulting from rotation. Because of the density of the celiac ganglia and nerve plexus and the lymphatic vessels surrounding the upper abdominal aorta, this portion of the aorta is difficult to visualize even when left medial visceral rotation has been performed. It is frequently helpful to transect the left crus of the aortic hiatus in the diaphragm at the 2 o'clock position to allow exposure of the distal descending thoracic aorta above the hiatus. Visualization of this portion of the vessel is much easier to achieve than visualization of the diaphragmatic or visceral abdominal aorta below, and an aortic cross-clamp can be applied much more quickly at this level.

Active hemorrhage from the midline supramesocolic area is controlled temporarily by packing with laparotomy pads or using an aortic compression device [see *Figure 5*].^{9,10} A definitive approach is to divide the lesser omentum manually, retract the stomach and esophagus to the left, and manually dissect in the area just below the aortic hiatus of the diaphragm to obtain rapid exposure of the supraceliac abdominal aorta.¹¹ An aortic cross-clamp can then be applied. Distal control of the upper abdominal aorta is difficult to obtain because of the presence of the anteriorly located celiac axis and superior mesenteric artery. In young trauma patients who are otherwise healthy, ligation and division of the celiac axis allow easier application of the distal aortic clamp and better exposure of the supraceliac area for subsequent vascular repair.¹²

Small penetrating wounds to the supraceliac abdominal aorta are repaired with a continuous 3-0 or 4-0 polypropylene suture. If two small perforations are adjacent to each other, they can be connected and the defect closed in a transverse fashion. If closure of a perforation would result in significant narrowing of the aorta or if a portion of the aortic wall is missing, patch aortoplasty with polytetrafluoroethylene (PTFE) is indicated. On rare occasions, in patients with extensive injuries to the diaphragmatic or supraceliac aorta, resection of the area of injury and insertion of a vascular conduit are indicated. Even though many of these patients have associated gastric, enteric, or colonic injuries, the most appropriate prosthesis with such a life-threatening injury is a 12, 14, or 16 mm woven Dacron, albumin-coated Dacron, or PTFE graft [see *Figure 6*].¹³ Provided that vigorous intraoperative irrigation is performed after repair of GI tract perforations, that proper graft coverage is ensured, and that

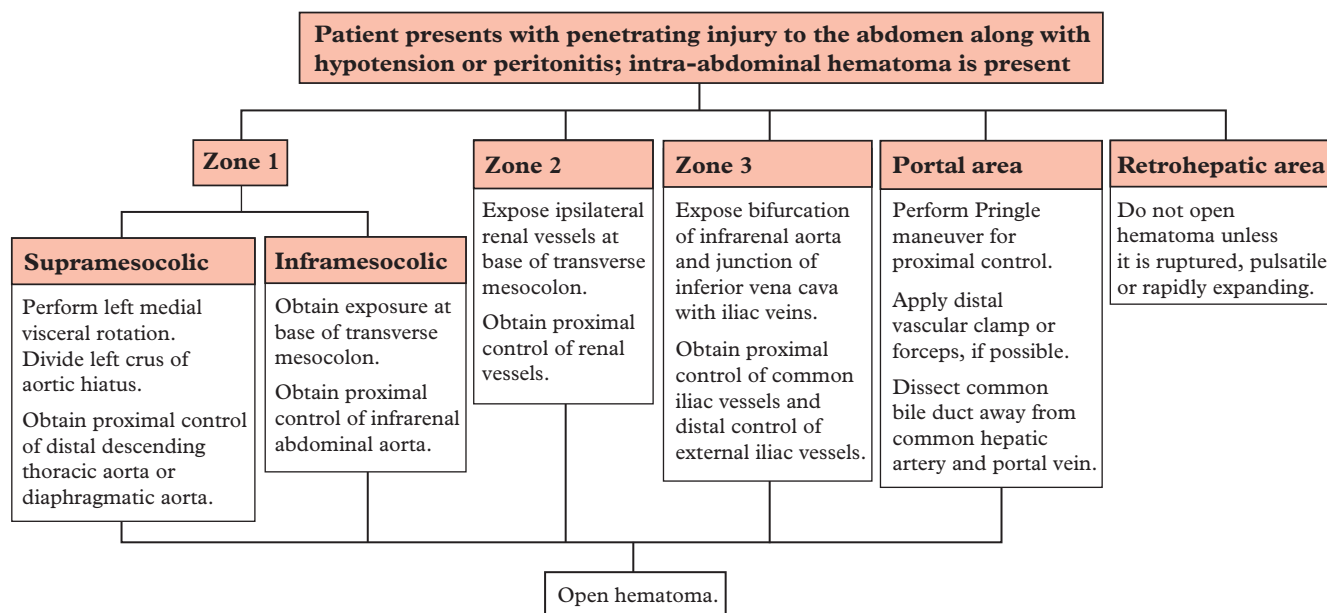


Figure 1 Algorithm illustrating management of intra-abdominal hematoma found at operation after penetrating trauma.

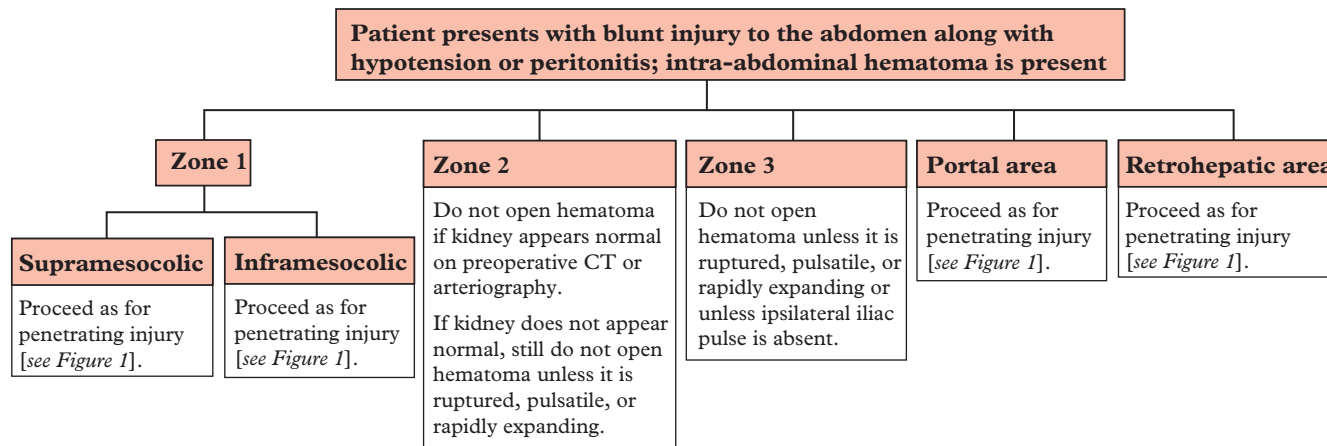


Figure 2 Algorithm illustrating management of intra-abdominal hematoma found at operation after blunt trauma.
CT = computed tomography.

perioperative antibiotics are appropriately employed, it is extraordinarily rare for a prosthesis inserted in the healthy aorta of a young trauma patient to become infected.

The aortic prosthesis is sewn in place with a continuous 3-0 or 4-0 polypropylene suture. Both ends of the aorta are flushed before the distal anastomosis is completed, and the distal aortic cross-clamp is removed before the final knot is tied to eliminate air from the system. The proximal aortic cross-clamp is removed very slowly as the anesthesiologist rapidly infuses fluids and intravenous bicarbonate to reverse so-called washout acidosis from the previously ischemic lower extremities. The retroperitoneum is then irrigated with an antibiotic solution and closed over the graft in a watertight fashion with an absorbable suture.

Cross-clamping of the diaphragmatic or supraceliac abdominal aorta in a patient with hemorrhagic shock results in severe ischemia of the lower extremities. Restoration of flow through

the repaired abdominal aorta may then cause a reperfusion injury in addition to the ischemic edema that develops in the muscle compartments below the knee. In a patient who is hemodynamically stable after repair of the suprarenal abdominal aorta and other injuries, measurement of compartmental pressures below the knees should be performed before the patient is moved from the operating room (OR). Pressures in the range of 30 to 35 mm Hg are likely to rise in the intensive care unit; accordingly, at many centers, bilateral below-the-knee two-incision four-compartment fasciotomies would be performed in this situation.¹⁴

The survival rate in patients with injuries to the suprarenal abdominal aorta had been 30 to 35% but was lower than 10% in one 2001 review.^{4,13}

Injuries to branches of the celiac axis are often difficult to repair because of the amount of dissection required to remove the dense neural and lymphatic tissue in this area. Because

Table 1 AAST Abdominal Vascular Organ Injury Scale

Grade	Characteristics of Injury	OIS Grade	ICD-9	AIS-90
I	Unnamed superior mesenteric artery or superior mesenteric vein branches	I	902.20/902.39	NS
	Unnamed inferior mesenteric artery or inferior mesenteric vein branches	I	902.27/902.32	NS
	Phrenic artery or vein	I	902.89	NS
	Lumbar artery or vein	I	902.89	NS
	Gonadal artery or vein	I	902.89	NS
	Ovarian artery or vein	I	902.81/902.82	NS
	Other unnamed small arterial or venous structures requiring ligation	I	902.90	NS
II	Right, left, or common hepatic artery	II	902.22	3
	Splenic artery or vein	II	902.23/902.34	3
	Right or left gastric arteries	II	902.21	3
	Gastroduodenal artery	II	902.24	3
	Inferior mesenteric artery, trunk, or inferior mesenteric vein, trunk	II	902.27/902.32	3
	Primary named branches of mesenteric artery (e.g., ileocolic artery) or mesenteric vein	II	902.26/902.31	3
	Other named abdominal vessels requiring ligation or repair	II	902.89	3
III*	Superior mesenteric vein, trunk	III	902.31	3
	Renal artery or vein	III	902.41/902.42	3
	Iliac artery or vein	III	902.53/902.54	3
	Hypogastric artery or vein	III	902.51/902.52	3
	Vena cava, infrarenal	III	902.10	3
IV*†	Superior mesenteric artery, trunk	IV	902.25	3
	Celiac axis, proper	IV	902.24	3
	Vena cava, suprarenal and infrahepatic	IV	902.10	3
	Aorta, infrarenal	IV	902.00	4
V†	Portal vein	V	902.33	3
	Extraparenchymal hepatic vein	V	902.11	3 (hepatic vein) 5 (liver + veins)
	Vena cava, retrohepatic or suprahepatic	V	902.19	5
	Aorta, suprarenal and subdiaphragmatic	V	902.00	4

AAST = American Association for the Surgery of Trauma; AIS = Abbreviated Injury Scale; ICD = International Classification of Diseases; NS = not specified; OIS = Organ Injury Scale.

This classification is applicable to extraparenchymal vascular injuries. If the vessel injury is within 2 cm of the parenchyma of a specific organ, one should refer to the injury scale for that organ.

*Increase grade by I if there are multiple injuries involving more than 50% of vessel circumference.

†Reduce grade by I if laceration is less than 25% of vessel circumference.

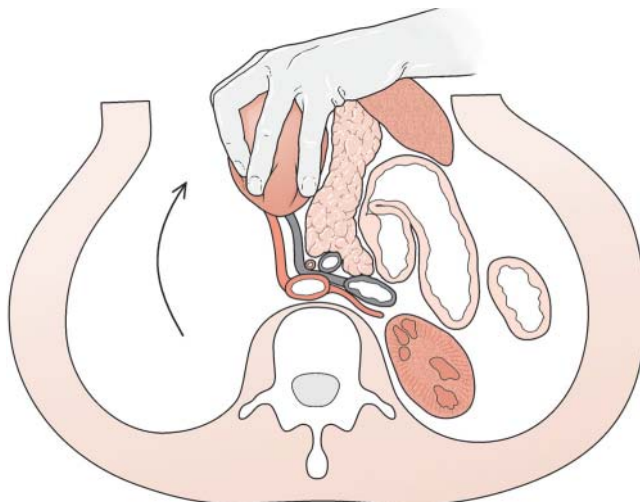


Figure 3 Left medial visceral rotation is performed by means of sharp and blunt dissection with elevation of the left colon, the left kidney, the spleen, the tail of the pancreas, and the gastric fundus.

most patients have excellent collateral flow in the upper abdomen, major injuries to either the left gastric or the proximal splenic artery generally should be ligated. Because the common hepatic artery may have a larger diameter than either of these two arteries, an injury to this vessel can occasionally be repaired by means of lateral arteriorrhaphy, an end-to-end anastomosis, or the insertion of a saphenous vein graft. One should not worry about ligating the hepatic artery proper proximal to the origin of the gastroduodenal artery as there is extensive collateral flow to the liver from the midgut. When the entire celiac axis is injured, it is best to ligate all three vessels and forgo any attempt at repair. In one recent review of 13 patients with injuries to the celiac axis, the overall survival was 38%.¹⁵

Injuries to the superior mesenteric artery are managed according to the anatomic level of the perforation or thrombosis.¹⁶ On rare occasions, in patients with injuries beneath the neck of the pancreas, one may have to transect the pancreas to obtain proximal control. Another option is to perform left medial visceral rotation (see above) and apply a clamp directly to the origin of the superior mesenteric artery. Injuries to the superior mesenteric artery in this area or just beyond the base of the mesocolon are often associated with injuries to the pancreas.

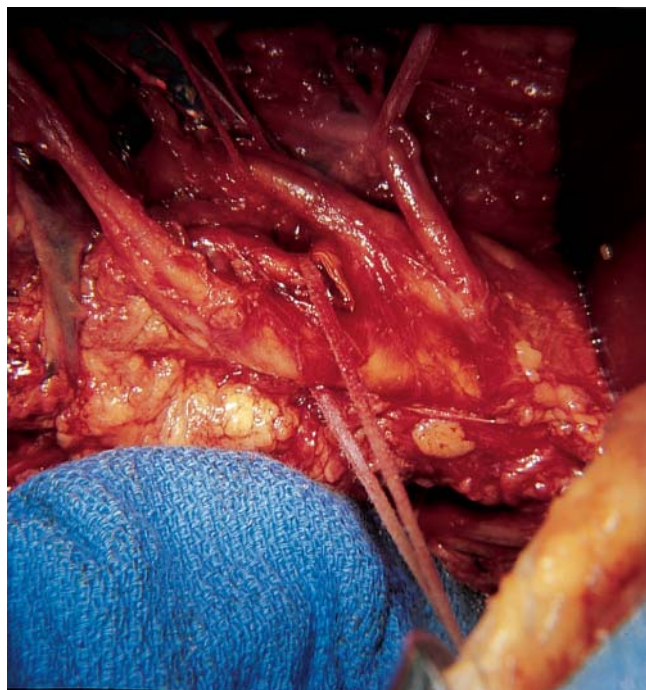


Figure 4 Shown is an autopsy view of the supraceliac aorta and the celiac axis, the proximal superior mesenteric artery, and the medially rotated left renal artery after removal of lymphatic and nerve tissue. Reproduced with permission from Feliciano DV. Abdominal vascular injury. In: Moore EE, Feliciano DV, Mattox KL, editors. Trauma. 5th ed. New York: McGraw-Hill; 2004.

The potential for a postoperative leak from the injured pancreas near the arterial repair has led numerous authors to suggest that any extensive injury to the artery at this location should be ligated [see Figure 7].

Because of the intense vasoconstriction of the distal superior mesenteric artery in patients who have sustained exsanguinating hemorrhage from more proximal injuries treated with ligation, the collateral flow from the foregut and hindgut is often inadequate to maintain the viability of the organs in the distal midgut, especially the cecum and the ascending colon. Therefore, it is safest to place a saphenous vein or PTFE graft on the distal infrarenal aorta, away from the pancreatic injury and any other upper abdominal injuries.¹⁷ Such a graft can be tailored to reach the side or the anterior aspect of the superior mesenteric artery, or it can be attached to the transected distal superior mesenteric artery in an end-to-end fashion without significant tension [see Figure 8]. Soft tissue must be approximated over the aortic suture line of the graft to prevent the development of an aortoenteric fistula in the postoperative period.

In patients with severe shock from exsanguination caused by a complex injury to the superior mesenteric artery, damage-control laparotomy is indicated [see Damage-Control Laparotomy, below]: the injured area should be resected and a temporary intraluminal Argyle, Javid, or Pruitt-Inahara shunt inserted to maintain flow to the midgut during resuscitation in the surgical intensive care unit (SICU).¹⁸ When ligation is indicated for more distal injuries to the superior mesenteric

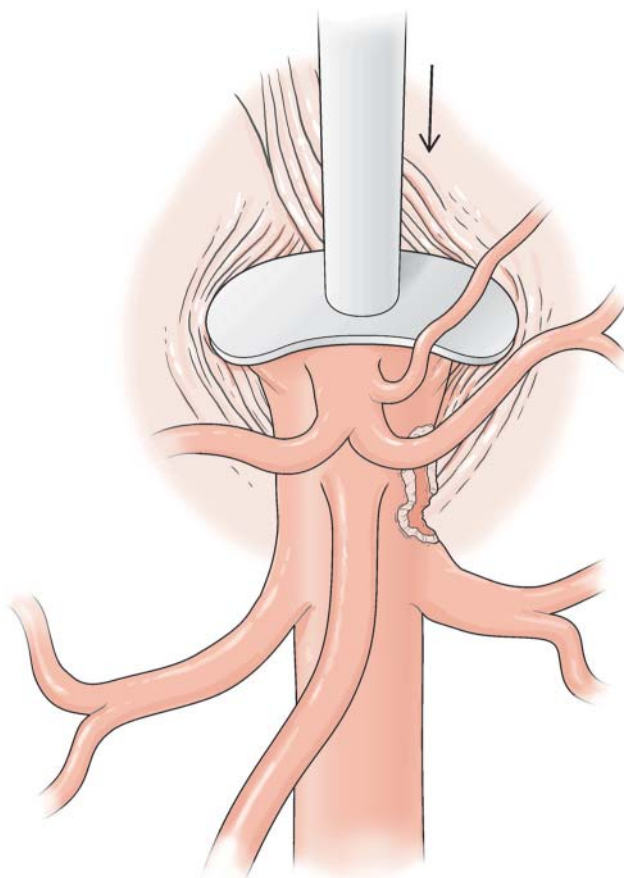


Figure 5 An aortic compression device is used to control hemorrhage from the visceral portion of the abdominal aorta.

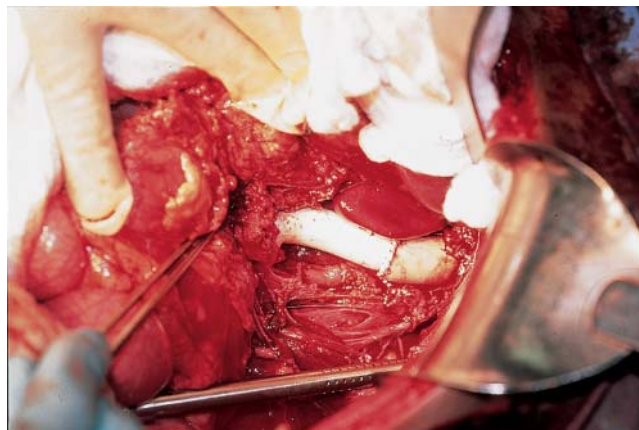


Figure 6 A 22-year-old man with a gunshot wound to the right upper quadrant had injuries to the prepyloric area of the stomach and to the supraceliac abdominal aorta. The aortic injury was managed by means of segmental resection and replacement with a 16 mm polytetrafluoroethylene graft. The patient went home 46 days after injury. Reproduced with permission from Feliciano DV. Abdominal vascular injury. In: Moore EE, Feliciano DV, Mattox KL, editors. Trauma. 5th ed. New York: McGraw-Hill; 2004.

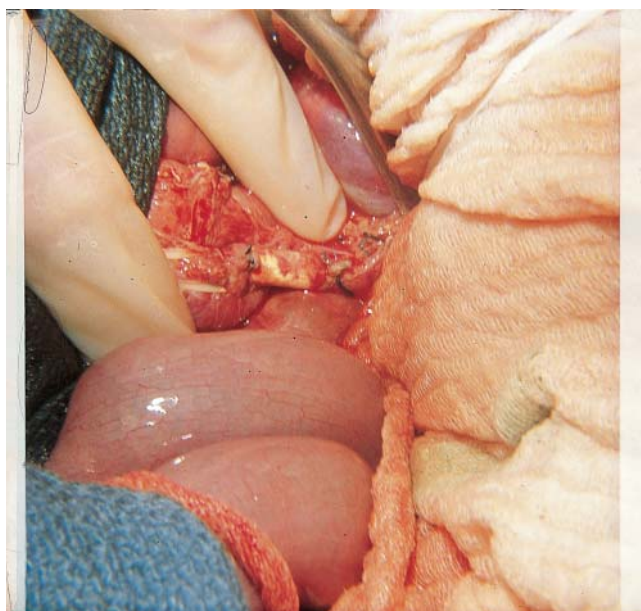


Figure 7 An 18-year-old man experienced a gunshot wound to the head of the pancreas and the proximal superior mesenteric artery. A Whipple procedure was performed, and a 6 mm polytetrafluoroethylene graft was placed in the artery. The artery-graft suture line dehiscenced secondary to a pancreatic leak on day 30 after injury, and the patient died on day 42.

artery, segments of the ileum or even the right colon may have to be resected because of ischemia.

The survival rate in patients with penetrating injuries to the superior mesenteric artery is approximately 55 to 60% overall [see Table 2] but only 20 to 25% when any form of repair more complex than lateral arteriorrhaphy is necessary.^{1-4,17,19}

An injury to the proximal renal artery may also be present under a supramesocolic hematoma or bleeding area. When active hemorrhage is present, control of the supraceliac abdominal aorta in or just below the aortic hiatus must be obtained. When only a hematoma or a known thrombosis of the proximal renal artery is present, proximal vascular control can be obtained by elevating the transverse mesocolon and dissecting the vessel from the lateral aspect of the abdominal aorta. Options for repair of either the proximal or the distal renal artery are described elsewhere [see Injuries in Zone 2, below].

The superior mesenteric vein is the other great vessel of the abdomen that may be injured in the supramesocolic or retro-mesocolic area of the midline retroperitoneum. Because of the overlying pancreas, the proximity of the uncinate process, and the close association of this vessel with the superior mesenteric artery, repair of the superior mesenteric vein is quite difficult. As with injuries to the superior mesenteric artery (see above), one may have to transect the neck of the pancreas between non-crushing vascular or intestinal clamps to gain access to a perforation of the superior mesenteric vein. An injury to this vein below the inferior border of the pancreas can be managed by compressing it manually between one's fingers as an assistant places a continuous 5-0 polypropylene suture to complete the repair. When a penetrating injury to the vein has a posterior component, one must ligate multiple collateral vessels entering the vein in this area to achieve proper visualization.

There is excellent evidence that young trauma patients tolerate ligation of the superior mesenteric vein well when vigorous postoperative fluid resuscitation is performed to reverse the peripheral hypovolemia that results from splanchnic hypervolemia.^{20,21} Typically, ligation is followed almost immediately by swelling of the midgut and discoloration suggestive of impending ischemia. In such cases, temporary coverage of the midgut with a silo, followed by early reoperation, may be necessary to reassure the operating surgeon that the ischemia has not become permanent.

The survival rate in patients with injuries to the superior mesenteric vein ranges from 36 to 71%, depending on whether other vascular injuries are present [see Table 3].^{1-4,20} In three reviews in 2001, the survival rate was 58%.²⁻⁴

INFRAMESOCOLIC

The lower area of the midline retroperitoneum in zone 1 is known as the midline inframesocolic area. Injuries to either the infrarenal abdominal aorta or the inferior vena cava occur in this area.

An injury to the inframesocolic abdominal aorta that is under a hematoma is controlled by performing the same maneuvers used to gain proximal control of an infrarenal abdominal aortic aneurysm. The infrarenal abdominal aorta is exposed by pulling the transverse mesocolon up toward the patient's head, eviscerating the small bowel to the right side of the abdomen, and opening the midline retroperitoneum until the left renal vein is exposed. A proximal aortic cross-clamp is then placed immediately inferior to this vessel [see Figure 9]. When the entire inframesocolic area is distorted by the presence of a large pulsatile hematoma, the inexperienced trauma surgeon should remember that the hole in the infrarenal abdominal aorta is under the highest point of the hematoma (the so-called Mt. Everest phenomenon). When there is active hemorrhage from this area, rapid proximal control is obtained in the same fashion or, if necessary because of the need to apply compression, by dividing the lesser omentum and applying the cross-clamp just below the aortic hiatus of the diaphragm. Distal control of the infrarenal abdominal aorta is obtained by dividing the midline retroperitoneum down to the aortic bifurcation, taking care to avoid the origin of the inferior mesenteric artery on the left side.

Injuries to the infrarenal aorta are repaired by means of lateral aortorrhaphy, patch aortoplasty, an end-to-end anastomosis, or insertion of a Dacron or PTFE graft. Much as with injuries to the suprarenal abdominal aorta in young trauma patients, it is rarely possible to place a tube graft larger than 12, 14, or 16 mm. Because the retroperitoneal tissue is often thin at this location in young patients, an important adjunctive measure after the aortic repair is to mobilize the gastrocolic omentum, flip it into the lesser sac superiorly, and then bring it down over the infrarenal aortic graft through a hole in the left transverse mesocolon. An alternative is to mobilize the gastrocolic omentum away from the right side of the colon and then swing the mobilized tissue into the area just below the ligament of Treitz to cover the graft. With either technique, it is mandatory to suture the viable omental pedicle superior to the aortic suture line to prevent a postoperative aortoduodenal fistula.^{22,23}

The survival rate in patients with injuries to the infrarenal abdominal aorta had been approximately 45% in series published from 1974 to 1992 but was 34% in a 2001 review [see Table 2].¹⁻⁴

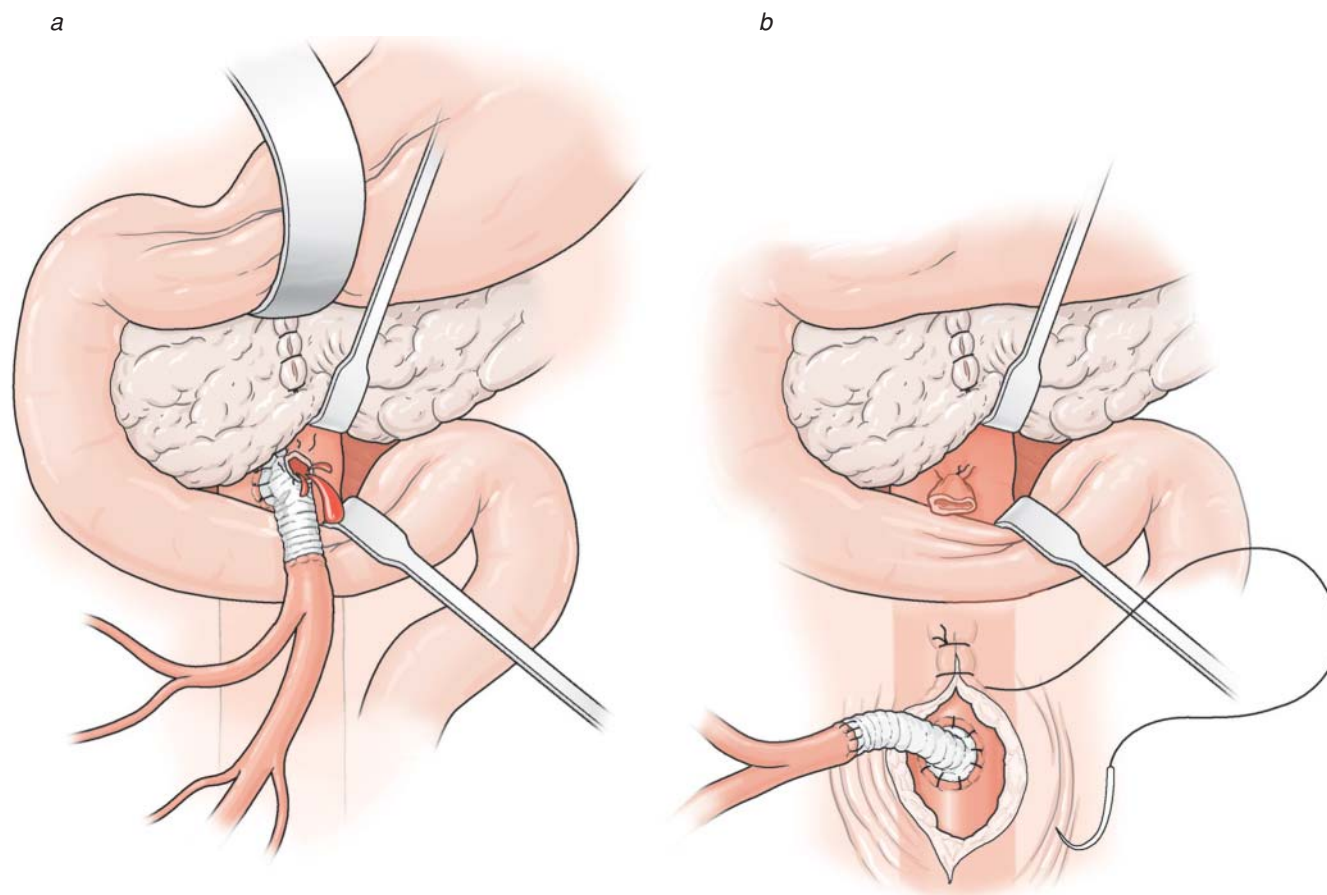


Figure 8 (a) When complex grafting procedures to the superior mesenteric artery are necessary, it may be dangerous to place the proximal suture line near an associated pancreatic injury. (b) The proximal suture line should be on the lower aorta, away from the upper abdominal injuries, and should be covered with retroperitoneal tissue.

Injury to the inferior vena cava below the liver should be suspected when the aorta is found to be intact underneath an inframesocolic hematoma, when such a retroperitoneal hematoma appears to be more extensive on the right side of the abdomen than on the left, or when there is active hemorrhage coming through the base of the mesentery of the ascending colon or the hepatic flexure. It is certainly possible to visualize

the inferior vena cava through the midline retroperitoneal exposure just described (see above); however, most surgeons are more comfortable with visualizing the vessel by mobilizing the right half of the colon and the C loop of the duodenum.¹ With this right medial visceral rotation maneuver, the right kidney is left in situ unless there is an associated injury to the posterior aspect of the right renal vein, to the suprarenal vena cava, or to

Table 2 Survival after Injuries to Arteries in the Abdomen

Injured Artery	Asensio et al ² (2000)		Davis et al ³ (2001)*	Tyburski et al ⁴ (2001)
	Isolated Injury	With Other Arterial Injury		
Abdominal aorta as a whole	21.7% (10/46)	17.6% (3/17)	39.1% (25/64)	21.1% (15/71)
Pararenal to diaphragm	—	—	—	8.3% (3/36)
Infrarenal	—	—	—	34.2% (12/35)
Superior mesenteric artery	52.4% (11/21)	28.6% (2/7)	53.3% (8/15)	48.8% (20/41)
Renal artery	62.5% (5/8)	33.3% (2/6)	56.2% (9/16)	73.7% (14/19)
Iliac artery				
Common	—	—	55.5% (5/9)	44.7% (17/38)
External	—	—	65.2% (30/46)	62.5% (20/32)

*Excludes patients who exsanguinated before repair or ligation.

Table 3 Survival after Injuries to Veins in the Abdomen

Injured Vein	Asensio et al ² (2000)		Davis et al ³ (2001)*	Tyburski et al ⁴ (2001)
	Isolated Injury	With Other Venous Injury		
Inferior vena cava as a whole	29.3% (12/41) [†]	22.2% (8/36) [†]	56% (47/84)	43% (61/142)
Pararenal to diaphragm	—	—	—	40.3% (31/77)
Infrarenal	—	—	—	46.2% (30/65)
Superior mesenteric vein	47.4% (9/19)	35.7% (5/14)	71.4% (15/21)	56.3% (18/32)
Renal vein	—	44.1% (15/34)	70% (21/30)	68.8% (22/32)
Iliac vein (all)	62.2% (23/37)	33.3% (5/15)	—	—
Common	—	—	81% (17/21)	49% (24/49)
External	—	—	74.5% (41/55)	66.7% (16/24)

*Excludes patients who exsanguinated before repair or ligation.

[†]Excludes retrohepatic vena cava.

the right kidney itself. Right medial visceral rotation, in conjunction with the Kocher maneuver, permits visualization of the entire vena caval system from the confluence of the iliac veins to the suprarenal vena cava below the liver. Local exposure of the iliac vein–vena cava junction in the lower abdomen and of the renal vein–vena cava junction in the upper abdomen is appropriate before completion of right medial visceral rotation. This measure allows rapid application of proximal and distal vascular clamps on the inferior vena cava in the event that exsanguinating hemorrhage results when the caval injury is exposed.

For proper exposure of a hole in a large vein such as the inferior vena cava, the loose retroperitoneal fatty tissue

must be dissected away from the wall of the vessel. Active hemorrhage coming from the anterior surface of the inferior vena cava is best controlled by applying a Satinsky vascular clamp. If it is difficult to apply this clamp, one should try grasping the area of the perforation with a pair of vascular forceps or several Judd-Allis clamps; this step may facilitate safe application of the Satinsky clamp.²⁴ When the perforation in the inferior vena cava is more lateral or posterior, it is often helpful to compress the vessel proximally and distally around the perforation, using gauze sponges placed in straight sponge sticks. On occasion, an extensive injury to the inferior vena cava can be controlled only by completely occluding the entire inferior vena cava with large DeBakey aortic cross-clamps. This maneuver interrupts much of the venous return to the right side of the heart and is poorly tolerated by hypotensive patients unless the infrarenal abdominal aorta is cross-clamped simultaneously.

There are two anatomic areas in which vascular control of an injury to the inferior vena cava below the liver is difficult to obtain: (1) the confluence of the common iliac veins and (2) the junction of the renal veins with the inferior vena cava. One interesting approach to an injury to the inferior vena cava at the confluence of the iliac veins is temporary division of the overlying right common iliac artery, coupled with mobilization of the aortic bifurcation to the patient's left.²⁵ This approach yields a better view of the common iliac veins and the proximal inferior vena cava and makes repair considerably easier than it would be if the aortic bifurcation was left in place. Once the vein is repaired, the right common iliac artery is reconstituted via an end-to-end anastomosis. The usual approach to injuries to the inferior vena cava at its junction with the renal veins involves clamp or sponge-stick compression of the infrarenal and suprarenal vena cava, as well as control of both renal veins with Silastic loops to facilitate the direct application of angled vascular clamps. As noted, medial mobilization of the right kidney may permit the application of a partial occlusion clamp across the inferior vena cava at its junction with the right renal vein as an alternative approach to an injury in this area. Another useful technique for controlling hemorrhage from the inferior vena cava at any location is to insert a 5 or 30 mL Foley balloon catheter into the caval laceration and then inflate it in the lumen.^{26–28} Once the bleeding is controlled, vascular clamps are positioned around

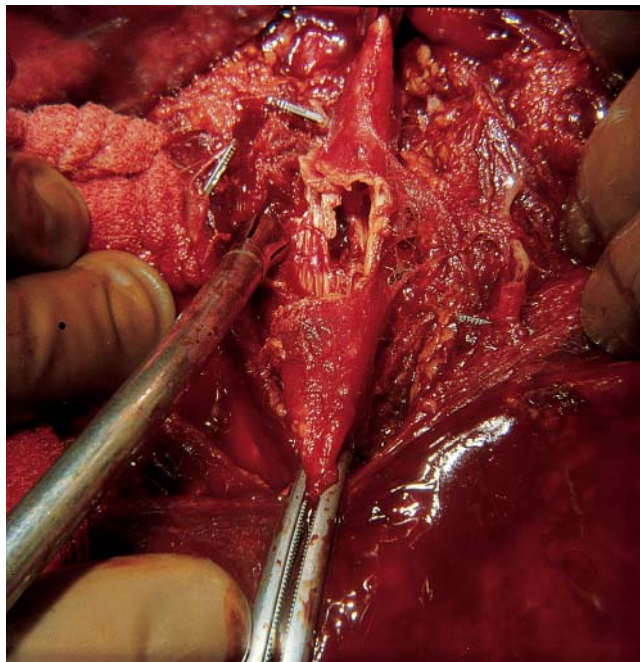


Figure 9 Shown is a gunshot wound to the infrarenal abdominal aorta viewed through standard inframesocolic exposure. The patient's head is at the bottom of the photograph. Reproduced with permission from Feliciano DV, Burch JM, Graham JM, editors. *Abdominal vascular injury*. In: *Trauma*. 3rd ed. Stamford (CT): Appleton & Lange; 1996.

the perforation, and the balloon catheter is removed before repair of the vessel.

Anterior perforations of the inferior vena cava are managed by a transverse repair with a continuous 4-0 or 5-0 polypropylene suture. Much has been written about visualizing posterior perforations by extending anterior perforations, but in my experience, opportunities to apply this approach have been rare. It is often easier to roll the vena cava to one side to complete a continuous suture repair of a posterior perforation. When both anterior and posterior perforations have been repaired, there is usually a significant degree of narrowing of the inferior vena cava, which may lead to slow postoperative occlusion. If the patient's condition is unstable and a coagulopathy has developed, no further attempt should be made to revise the repair. If the patient is stable, there may be some justification for applying a large PTFE patch to prevent this postoperative occlusion [see Figure 10].

Ligation of the infrarenal inferior vena cava is appropriate for young patients who are exsanguinating and in whom a complex repair of the vessel would be necessary. After the damage-control abdominal procedure has been completed and a silo has been used to cover the midgut, it is, once again, worthwhile to measure the compartmental pressures below the knees before the patient is moved from the OR. Below-the-knee two-incision four-compartment fasciotomies are performed when pressures exceed 30 to 35 mm Hg.¹⁴ Three-compartment fasciotomies in the thighs have proved necessary in some surviving patients after caval ligation. Patients who have undergone ligation of the infrarenal inferior vena cava require vigorous resuscitation with crystalloid solutions in the postoperative period; in addition, both lower extremities should be wrapped with elastic compression wraps and elevated for 5 to 7 days after operation. Patients who have some residual edema during the later stages of hospitalization despite the elastic compression wraps should be fitted with

full-length custom-made support hose. Ligation of the suprarenal inferior vena cava is occasionally necessary when the patient has an extensive injury at this location and appears to be in an irreversible shock state during operation.²⁹ If the patient's condition improves during a brief period of resuscitation in the SICU, reoperation and reconstruction with an externally supported PTFE graft are usually necessary to prevent renal failure.

The survival rate in patients with injuries to the inferior vena cava depends on the location of the injury; in the past, it ranged from 60% for the suprarenal vena cava to 78% for the infrarenal vena cava but decreased to approximately 33 to 56% if injuries to the retrohepatic vena cava were included. Current studies indicate survival rates of 22 to 56% for inferior vena cava injuries taken as a whole.^{1-3,30-32} A 2001 review reported survival rates of 46.1% for the infrarenal inferior vena cava and 40.3% for more superior injuries.⁴ In a recent review of 25 patients undergoing ligation of the infrahepatic inferior vena cava (22 infrarenal, three suprarenal), survival was 41%. One-year follow-up was available in seven of nine survivors, and no patient had more than trace edema.³²

Injuries in Zone 2

Hematoma or hemorrhage in zone 2 is cause to suspect the presence of injury to the renal artery, the renal vein, or the kidney.

In patients who have sustained blunt abdominal trauma but in whom preoperative intravenous pyelography, renal arteriography, or abdominal computed tomography (CT) confirms that a reasonably intact kidney is present, there is no justification for opening a perirenal hematoma if one is found at a subsequent operation [see Figure 11].³³

In highly selected stable patients with penetrating wounds to the flank, there are some data to justify performing preoperative CT. On occasion, documentation of an isolated minor renal injury in the absence of peritoneal findings on physical examination makes it possible to manage such patients nonoperatively.³³ In all other patients with penetrating wounds, when a perirenal hematoma is found during initial exploration, the hematoma should be unroofed and

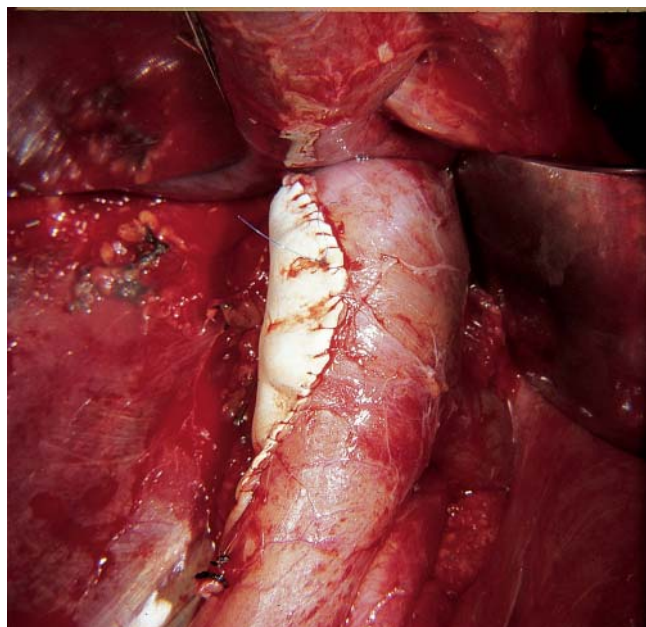


Figure 10 Shown is a polytetrafluoroethylene patch repair of an injury to the infrarenal inferior vena cava.

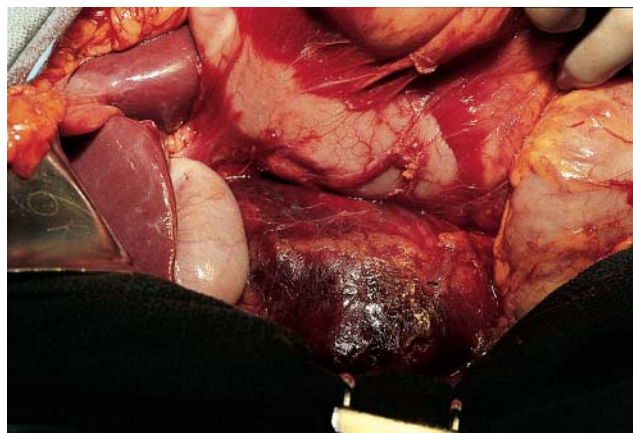


Figure 11 A right perirenal hematoma was not opened at operation because preoperative abdominal computed tomography documented a reasonably intact kidney.

the wound tract explored. If the hematoma is not rapidly expanding and there is no active hemorrhage from the perirenal area, some surgeons control the ipsilateral renal artery with a Silastic loop in the midline of the retroperitoneum at the base of the mesocolon.^{34,35} Control of the left renal vein can be obtained at the same location; however, control of the proximal right renal vein requires mobilization of the C loop of the duodenum and dissection of the vena cava at its junction with this vessel.

If there is active hemorrhage from the kidney through Gerota fascia or from the retroperitoneum overlying the renal vessels, no central renal vascular control is necessary. In such a situation, the retroperitoneum lateral to the injured kidney should be opened, and the kidney should be manually elevated directly into the abdominal incision. A large vascular clamp should then be applied directly to the hilar vessels of the elevated kidney to control any further bleeding until a decision is reached on repair versus nephrectomy.

On rare occasions, a small perforation of the renal artery can be repaired by lateral arteriorrhaphy or resection with an end-to-end anastomosis.³⁶ Interposition grafting and replacement of the renal artery with either the hepatic artery (on the right) or the splenic artery (on the left) have been used on rare occasions, but such approaches ordinarily are not indicated unless the injured kidney is the only one the patient has. In patients who have sustained multiple intra-abdominal injuries from penetrating wounds or have undergone a long period of ischemia while other injuries were being repaired, nephrectomy is the appropriate choice for a major renovascular injury, provided that intraoperative palpation has confirmed the presence of a normal contralateral kidney.

The role of renal revascularization in patients who have intimal tears in the renal arteries demonstrated on an abdominal CT scan or renal arteriogram after deceleration-type trauma remains controversial. If a circumferential intimal tear is noted on preoperative CT or conventional arteriography but flow to the kidney is preserved, the decision whether to repair the artery depends on whether laparotomy is necessary for other injuries and whether the opportunity for anticoagulation is available. If there are no other significant injuries and flow to the kidney is preserved despite the presence of an intimal tear, anticoagulation and a repeat contrast-enhanced CT within the first several days may be justified. An alternative approach involves insertion of an endovascular stent in the renal artery, followed by a period of anticoagulation (see below).³⁷ If occlusion of the proximal renal artery from blunt deceleration-type trauma is documented, the critical factor for renal salvage is the time from occlusion to revascularization. Renal artery occlusion from deceleration-type trauma that is detected within 6 hours of injury may be treated with immediate operation, resection of the area of intimal damage, and an end-to-end anastomosis performed by an experienced vascular trauma team. Given proper exposure and medial mobilization of the kidney, this operation is not technically difficult in a young trauma patient whose renal artery is otherwise normal. In a 1998 review, fewer than 20% of kidneys revascularized in this manner regained any significant degree of function.³⁸ Hypertension develops in some patients who undergo observation only after thrombosis is detected.

The survival rate in patients with injuries to the renal arteries has been 65% in recent reviews [see Table 2].^{1,3,4}

Many patients with penetrating wounds to the renal veins are quite stable as a result of the retroperitoneal tamponade described earlier (see above). Once vascular control is obtained with the direct application of clamps, lateral venorrhaphy is the preferred technique of repair. If ligation of the right renal vein is necessary to control hemorrhage, nephrectomy should be performed, either at the initial laparotomy or at reoperation after a damage-control laparotomy; the medial left renal vein may be ligated as long as the left adrenal and gonadal veins are intact. It should be noted, however, that in some vascular series, more postoperative renal complications were noted when this maneuver was used on the left side.³⁹

The survival rate in patients with injuries to the renal veins ranged from 44.2 to 70% in three recent reviews, with a mean of 60.4% [see Table 3].^{1,3,4}

Injuries in Zone 3

Hematoma or hemorrhage in either lateral pelvic area is suggestive of injury to the iliac artery or the iliac vein. When lateral pelvic hematoma or hemorrhage is noted after penetrating trauma, compression with a laparotomy pad or the fingers should be maintained as proximal and distal vascular control is obtained. The proximal common iliac arteries are exposed by eviscerating the small bowel to the right and dividing the midline retroperitoneum over the aortic bifurcation. In young trauma patients, the common iliac artery usually is not adherent to the common iliac vein, and Silastic loops can be passed rapidly around these vessels to provide proximal vascular control. Distal vascular control is most easily obtained where the external iliac artery and vein come out of the pelvis proximal to the inguinal ligament. Even with proximal and distal control of the common or the external iliac artery and vein, there is often continued back-bleeding from the internal iliac artery. Such bleeding is controlled by elevating the Silastic loops on the proximal and distal iliac artery and then either clamping or looping the ipsilateral internal iliac artery, which is the only major branch vessel that descends into the pelvis.

For transpelvic bilateral iliac vascular injuries resulting from a penetrating wound, a technique of total pelvic vascular isolation has been described. Proximally, the abdominal aorta and the inferior vena cava are cross-clamped just above their bifurcations, and distally, both the external iliac artery and the external iliac vein are cross-clamped, with one clamp on each side of the distal pelvis. Back-bleeding from the internal iliac vessels is minimal with this approach.

Ligation of either the common or the external iliac artery in a hypotensive trauma patient leads to a greater than 50% amputation rate in the postoperative period; consequently, injuries to these vessels should be repaired if at all possible. The standard options for repair—lateral arteriorrhaphy, completion of a partial transection with an end-to-end anastomosis, and resection of the injured area with insertion of a conduit—are feasible in most situations [see Figure 12].⁴⁰ On rare occasions, it may be preferable either to mobilize the ipsilateral internal iliac artery to serve as a replacement for the external iliac artery or to transpose one iliac artery to the side of the contralateral iliac artery.⁴¹ When a patient is in severe shock from exsanguination caused by a complex injury to the common or the external iliac artery, damage-control

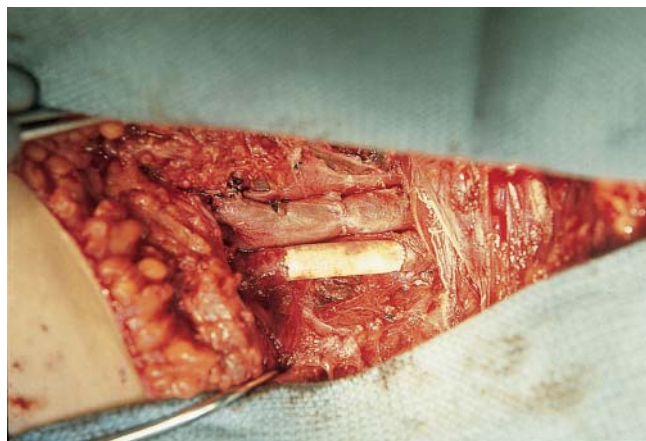


Figure 12 A 24-year-old man experienced a gunshot wound to the left external iliac artery and vein. The arterial injury was repaired with segmental resection and insertion of an 8 mm polytetrafluoroethylene graft; the venous injury was repaired with segmental resection and an end-to-end anastomosis.

laparotomy [see Damage-Control Laparotomy, *below*] is indicated.⁴² The injured area should be resected and a temporary intraluminal Argyle, Javid, or Pruitt-Inahara shunt inserted to maintain flow to the ipsilateral lower extremity during resuscitation in the SICU.¹

One unique problem associated with repair of the common or the external iliac artery is the choice of technique when significant enteric or fecal contamination is present in the pelvis. In such cases, there is a substantial risk of postoperative pelvic cellulitis, a pelvic abscess, or both, which may lead to blowout of any type of repair. When extensive contamination is present, it is appropriate to divide the common or external iliac artery above the level of injury, close the injury with a double row of continuous 4-0 or 5-0 polypropylene sutures, and bury the stump underneath uninjured retroperitoneum. If a stable patient has obvious ischemia of the ipsilateral lower extremity at the completion of this proximal ligation, one may perform an extra-anatomic femorofemoral crossover bypass with an 8 mm externally supported PTFE graft to restore arterial flow to the extremity.¹ If the patient is unstable, one should take several minutes to perform an ipsilateral four-compartment below-knee fasciotomy; this step will counteract the ischemic edema that inevitably leads to a compartment syndrome and compromises the early survival of the leg. After adequate resuscitation in the SICU, the patient should be returned to the OR for the femorofemoral graft within 4 to 6 hours.

Injuries to the internal iliac arteries are usually ligated even if they occur bilaterally because young trauma patients typically have extensive collateral flow through the pelvis.

The survival rate in patients with isolated injuries to the external iliac artery in older series exceeded 80% when tamponade was present. If the injury was large and free bleeding had occurred preoperatively, however, the survival rate was only 45%. Current studies report overall survival rates of approximately 45 to 55% for injuries to the common iliac artery and 62 to 65% for injuries to the external iliac artery [see Table 2].^{1,3,4,43}

Hemorrhage from injuries to the iliac veins can usually be controlled by means of compression with either sponge sticks or the fingers. As noted, division of the right common iliac artery may be necessary for proper visualization of an injury to the right common iliac vein or inferior vena cava at the confluence of the iliac veins. Similarly, ligation and division of the internal iliac artery on the side of the pelvis will yield improved exposure of an injury to an ipsilateral internal iliac vein.⁴⁴

Injuries to the common or the external iliac vein are best treated by a lateral venorrhaphy with continuous 4-0 or 5-0 polypropylene sutures. Significant narrowing often results, and a number of reports have demonstrated occlusion on postoperative venography. For patients with narrowing or occlusion, as well as for those in whom ligation was necessary to control exsanguinating hemorrhage, the use of elastic compression wraps and elevation for the first 5 to 7 days after operation is mandatory.⁴⁵

In some centers, once the patient's perioperative coagulopathy has resolved, anticoagulation with a low-molecular-weight heparin is initiated to prevent progression or migration of a venous thrombus. The patient is then discharged on a regimen of oral warfarin sodium, and serial measurement of the international normalized ratio (INR) is continued for 3 months.

The survival rate in patients with injuries to the iliac veins ranges from 33 to 81%, depending on whether associated vascular injuries are present [see Table 3].^{1-4,42,46} In three recent series, the survival rate (location not specified or combined injury) was 65%.²⁻⁴

Injuries in the Porta Hepatis or Retrohepatic Area

PORTA HEPATIS

Hematoma or hemorrhage in the area of the portal triad in the right upper quadrant is cause to suspect the presence of injury to the portal vein or the hepatic artery or of vascular injury combined with an injury to the common bile duct.

If a hematoma is present, the proximal hepatoduodenal ligament should be occluded with a vascular clamp (the Pringle maneuver) before the hematoma is entered.⁴⁷ If the hematoma is centrally located in the porta, one may also be able to apply an angled vascular clamp or vascular forceps to the distal end of the portal structures at their entrance into the liver.

If hemorrhage is occurring, compression of the bleeding vessels with the fingers should suffice until the vascular clamp is in place. Once proximal and distal vascular control is obtained, the three structures in the hepatoduodenal ligament must be dissected out very carefully because of the danger of blindly placing sutures in proximity to the common bile duct.

Injuries to the common hepatic artery in this location are occasionally amenable to lateral repair, although ligation of the right or left hepatic artery is ordinarily well tolerated because of the extensive collateral arterial flow and perfusion of oxygenated blood through the ipsilateral branch of the portal vein.⁴⁸⁻⁵¹ If an associated hepatic injury calls for extensive suturing or débridement, ligation of the common hepatic artery or artery to the injured lobe will certainly lead to

increased postoperative necrosis of the hepatic repair. Moreover, ligation of the common hepatic artery or the right or left hepatic artery and the portal vein branch to that lobe will lead to necrosis of the lobe and will necessitate hepatectomy. Finally, ligation of the right hepatic artery to control hemorrhage should be followed by cholecystectomy.

Because of the large size of the portal vein and its posterior position in the hepatoduodenal ligament, injuries to this vessel are particularly lethal. Once the Pringle maneuver has been performed, mobilization of the common bile duct to the left and of the cystic duct superiorly, coupled with an extensive Kocher maneuver, allows excellent visualization of any injury to this vein above the superior border of the pancreas. When the perforation extends underneath the neck of the pancreas, it may be necessary to have an assistant compress the superior mesenteric vein below the pancreas and then to divide the pancreas between noncrushing intestinal clamps to obtain exposure of the junction of the superior mesenteric vein and the splenic vein.

The preferred technique for repairing an injury to the portal vein is lateral venorrhaphy with continuous 4-0 or 5-0 polypropylene sutures.^{52,53} Complex repairs that have been successful on rare occasions include end-to-end anastomosis, interposition grafting with externally supported PTFE, transposition of the splenic vein, and a venovenous shunt from the superior mesenteric vein to the distal portal vein or the inferior vena cava. Such vigorous attempts at restoration of blood flow are not justified in patients who are in severe hypovolemic shock, for whom ligation of the portal vein is more appropriate. In addition, if a portosystemic shunt is performed in such a patient, hepatic encephalopathy will result because hepatofugal flow will be present in the rerouted or bypassed portal vein. As with ligation of the superior mesenteric vein, it is necessary to infuse significant amounts of crystalloids to reverse the transient peripheral hypovolemia that occurs secondary to the splanchnic hypervolemia resulting from ligation of the portal vein.^{20,53}

Since the early 1980s, the survival rate in patients with injuries to the portal vein has been approximately 50%.^{1,3,52,53}

RETROHEPATIC AREA

Retrohepatic hematoma or hemorrhage is cause to suspect the presence of injury to the retrohepatic vena cava, a hepatic vein, or a right renal blood vessel. In addition, hemorrhage in this area may signal injury to the overlying liver.

If there is a hematoma that is not expanding or ruptured and clearly has no association with the right perirenal area, a tamponaded injury to the retrohepatic vena cava or a hepatic vein is present. Perihepatic packing around the right lobe of the liver for 24 to 48 hours has been shown to prevent further expansion and should be considered.

If hemorrhage is occurring that does not appear to be coming from the overlying liver, the right lobe of the liver should be compressed posteriorly to tamponade the caval perforation. The Pringle maneuver is then applied, and the surgical and nursing team, the anesthesiologist, and the blood bank are notified. Once the proper instruments and banked blood are in the OR, the overlying injured hepatic lobe or the lobe closest to the presumed site of injury is mobilized by dividing the triangular and coronary ligaments and then lifted

out of the subdiaphragmatic area.⁵⁴ On occasion, an obvious perforation of the retrohepatic or suprahepatic vena cava or an obvious area where a hepatic vein was avulsed from the vena cava may be grasped with a forceps or a series of Judd-Allis clamps; a Satinsky clamp may then be applied.²⁴ Because of the copious bleeding that occurs as the liver is lifted and the hole in the vena cava sought, the anesthesiologist should start blood transfusions as the lobe is being mobilized.

If the retrohepatic hemorrhage is not controlled after one or two direct attempts, another technique must be tried. The most common choice is the insertion of a 36 French chest tube or a 9 mm endotracheal tube as an atriocaval shunt.⁵⁵ The shunt can reduce bleeding by 40 to 60%, but vigorous hemorrhage persists until full control of the perforation is obtained with clamps or sutures. An alternative approach is to isolate the liver and the retrohepatic vena cava by cross-clamping the supraceliac aorta, the porta hepatis, the suprarenal inferior vena cava, and the intrapericardial inferior vena cava.⁵⁶ Because profoundly hypovolemic patients usually cannot tolerate cross-clamping of the inferior vena cava, this approach is rarely employed. Some experienced hepatic surgeons have successfully used extensive hepatotomy to expose and repair an anterior perforation of the retrohepatic vena cava.⁵⁷

The retrohepatic vena cava is repaired with continuous 4-0 or 5-0 polypropylene sutures. When the atriocaval shunt is removed from the heart after the vessel has been repaired, the right atrial appendage is ligated with a 2-0 silk tie.

The survival rate in patients not in cardiac arrest who undergo atriocaval shunting and repair of the retrohepatic vena cava has ranged from 33 to 50%.^{55,56}

Damage-Control Laparotomy

Patients with injuries to the great vessels of the abdomen are ideal candidates for damage-control laparotomy⁵⁸: they are uniformly hypothermic, acidotic, and coagulopathic on completion of the vascular repair, and a prolonged operation would lead to their demise. Shunting, repair, or ligation of this abdominal vascular injury, packing of minor or moderate injuries to solid organs, packing of the retroperitoneum, stapling and rapid resection of multiple injuries to the GI tract, and consideration of diffuse intra-abdominal packing are all appropriate, as is silo coverage of the open abdomen, in which a temporary silo made from a urologic irrigation bag is sewn to the skin edges with a continuous 2-0 polypropylene or nylon suture.^{59,60}

The patient is then rapidly moved to the SICU for further resuscitation. Priorities in the SICU include rapid restoration of normal body temperature and administration of red blood cells, fresh frozen plasma, and platelets in the military paradigm of "1:1:1" and cryoprecipitate when indicated.⁶¹ It is usually possible to return the patient to the OR for removal of clot and packs, reconstruction of the GI tract, irrigation, and reapplication of silo coverage or application of a vacuum-assisted closure device within 48 to 72 hours.^{59,60}

When massive distention of the midgut persists after 10 to 14 days of intensive care and use of the vacuum-assisted closure device (10 to 25% of patients), the safest approach is to convert the patient to an open abdomen (i.e., without closure of the midline incision) and cover the midgut with a double-thickness layer of absorbable mesh. With proper nutritional support and occasional use of Dakin solution to minimize bacterial contamination of the absorbable mesh, most patients

are ready for the application of a split-thickness skin graft to the eviscerated midgut within 3 to 4 weeks of the original operation for an injury to a great vessel.

Endovascular Therapies

Endovascular techniques are now used selectively in patients with traumatic and iatrogenic abdominal vascular injuries. Examples of arterial repairs in zone 1 have included the insertion of endostents in patients with the following injuries: (1) blunt intimal injuries in the abdominal aorta,^{62–64} (2) late hemorrhage from the abdominal aorta and a hostile abdomen,^{65,66} and (3) the presence of an aortocaval fistula.^{67,68} Even with the obvious concern about thrombosis of endostents placed in the abdominal venous system, such repairs have been performed with injuries to the inferior vena cava.^{69–71}

In zone 2, where angiographic techniques have long been used to control bleeding from or fistulas in the renal parenchyma after trauma,^{72,73} wall stents are now used routinely to control intimal flaps in blunt injuries to the renal arteries.^{74–76}

A significant number of patients with endostent or endograft treatment of iatrogenic and traumatic injuries to the iliac arteries in zone 3 have now been reported.^{77–79} The endostents have been particularly useful in controlling intimal injuries from blunt trauma to the iliac arteries.

Complications

Besides those already mentioned, major complications associated with repair of injuries to the great vessels in the

abdomen include thrombosis, dehiscence of the suture line, and infection. Because of the risk of occlusion of repairs in small vasoconstricted vessels (e.g., the superior mesenteric artery), it may be worthwhile to perform a second-look operation within 12 to 24 hours if the patient's metabolic state suggests that ischemia of the midgut is present. Early correction of an arterial thrombosis in the superior mesenteric artery may permit salvage of the midgut.

As noted [see Injuries in Zone 1, *above*], dehiscence of an end-to-end anastomosis or a vascular conduit inserted in the proximal superior mesenteric artery when there is an injury to the adjacent pancreas may be prevented or the incidence lowered by inserting a distal aorta–superior mesenteric artery bypass graft. To prevent adjacent loops of small bowel from adhering to the vascular suture lines, both lines should be covered with soft tissue (retroperitoneal tissue or omental pedicle for the aortic suture line and mesenteric tissue for the superior mesenteric arterial suture line). Also as noted [see Injuries in Zone 3, *above*], when an extensive injury to either the common or the external iliac artery occurs in the presence of significant enteric or fecal contamination in the pelvis, ligation and extra-anatomic bypass may be necessary.

On occasion, vascular-enteric fistulas occur after repair of the anterior aorta or the insertion of grafts in either the abdominal aorta or the superior mesenteric artery.¹ In my experience, such fistulas most commonly occur at suture lines; hence, proper coverage of suture lines with soft tissue should eliminate or lower the incidence of this complication.^{22,80}

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Figures 1 and 2 Marcia Kammerer
Figures 3, 5, and 8 Tom Moore

11 INJURIES TO THE UROGENITAL TRACT

Alex J. Vanni, MD, and Hunter Wessells, MD, FACS

The World Health Organization (WHO) predicts a dramatic worldwide rise in the burden of disease caused by road traffic accidents and war.¹ This rise will directly influence the incidence of urogenital trauma, in that motor vehicle crashes (MVCs) and firearm injuries are responsible for the overwhelming majority of major renal and pelvic injuries.² In one population-based study, the percentage of trauma patients in the United States who had renal injuries was 1.2% (incidence 4.9 per 100,000 population).³ Thus, in 1 year, some 14,000 patients with renal injuries are hospitalized nationwide. Approximately 45,000 pelvic fractures occur each year in the United States, 15 to 25% of which are associated with urologic injury. Urogenital injuries, although rarely fatal, can cause profound morbidity and permanently impair quality of life. Early identification and treatment can reduce the long-term disability associated with these injuries.

Blood in the urine is the hallmark of injury to the urogenital system; however, as an isolated indicator, it is not specific for injury location or severity. In penetrating abdominal trauma, hematuria is a signal that the kidneys, the ureters, and the bladder must be evaluated. Urethral and genital injuries are suspected only in the setting of wounds to the pelvis, the perineum, or the buttocks. When hematuria occurs in association with blunt trauma, the entire urogenital system must be evaluated: the forces associated with high-speed MVCs and falls can cause injuries to both the upper and the lower regions of the urogenital tract.

In what follows, each of the major urogenital organs is treated separately. New imaging modalities and a growing emphasis on nonoperative management of upper and lower urinary tract injuries have dramatically changed the field of urologic trauma. Concomitant injury to both the upper and the lower urinary tract is rare, but extra vigilance must be maintained to detect such injury when it does occur. Evaluation and management of trauma to the female reproductive organs require special expertise, particularly when the patient is the victim of a sexual assault.

Injuries to the Kidneys

INITIAL EVALUATION

The most reliable sign of injury to the kidney is hematuria [see Figure 1], except in patients with renal artery thrombosis or pedicle avulsion, who may have no blood in their urine. However, the degree of hematuria correlates poorly with the severity of renal injury,⁴ and as a result, criteria for imaging in these patients must take into account both the mechanism of injury and the probability of severe kidney injury.⁵ Accordingly, a consensus statement from a renal trauma subcommittee convened by the WHO proposed guidelines for imaging

renal injuries [see Table 1].⁶ As with all guidelines, exceptions exist. A high degree of suspicion for renal trauma is required for patients who do not meet the hematuria criteria for imaging but who have experienced a fall from a height, have sustained a direct blow to the flank, or have other indicators (e.g., persistent flank pain or severe associated injuries).

Computed tomography (CT) is the first-line imaging modality for all cases of suspected renal trauma in hemodynamically normal and stable patients. A standard examination includes helical (spiral) CT with a portal venous phase (from the diaphragm to the ischial tuberosities) to visualize active arterial bleeding [see Figure 2a], followed after 10 minutes by delayed images (from the kidneys to the ischial tuberosities) to identify urinary contrast extravasation [see Figure 2b]. CT should not be used as the primary evaluation method in hemodynamically unstable patients: other diagnostic tests, such as diagnostic peritoneal lavage (DPL) or ultrasonography, should be performed before renal imaging with CT.

The American Association for the Surgery of Trauma (AAST) Organ Injury Scale is used to classify blunt and penetrating renal injuries and corresponds closely to the appearance of the kidney on CT [see Figure 3 and Table 2].⁷

MANAGEMENT

Differences in the management of blunt and penetrating renal trauma are a result of the greater instability of the patient after penetrating trauma and the higher likelihood of severe renal injuries after firearm and stab wounds.

Nonoperative

The goal in the management of renal trauma is to safely preserve the maximal number of renal units, avoiding unnecessary explorations, repairs, and nephrectomies. Increasing numbers of renal injuries, including grade IV and V injuries, are being managed nonoperatively. The accuracy and rapidity of helical CT, combined with the improvements achieved in resuscitation methods, have reduced the number of renal explorations performed.⁸ Currently, 36% of all penetrating renal injuries and fewer than 5% of blunt injuries necessitate operative management.⁹ All grade I and II renal injuries, regardless of the mechanism of injury, can be managed with observation alone because the risk of delayed bleeding is extremely low. Most grade III and IV injuries, including those with devitalized parenchymal fragments and urinary extravasation, can be managed nonoperatively with close monitoring, serial hematocrit measurement, and repeat imaging in selected cases. Active arterial bleeding, in the absence of other associated injuries, can be treated with emergency arteriography and selective angioembolization.

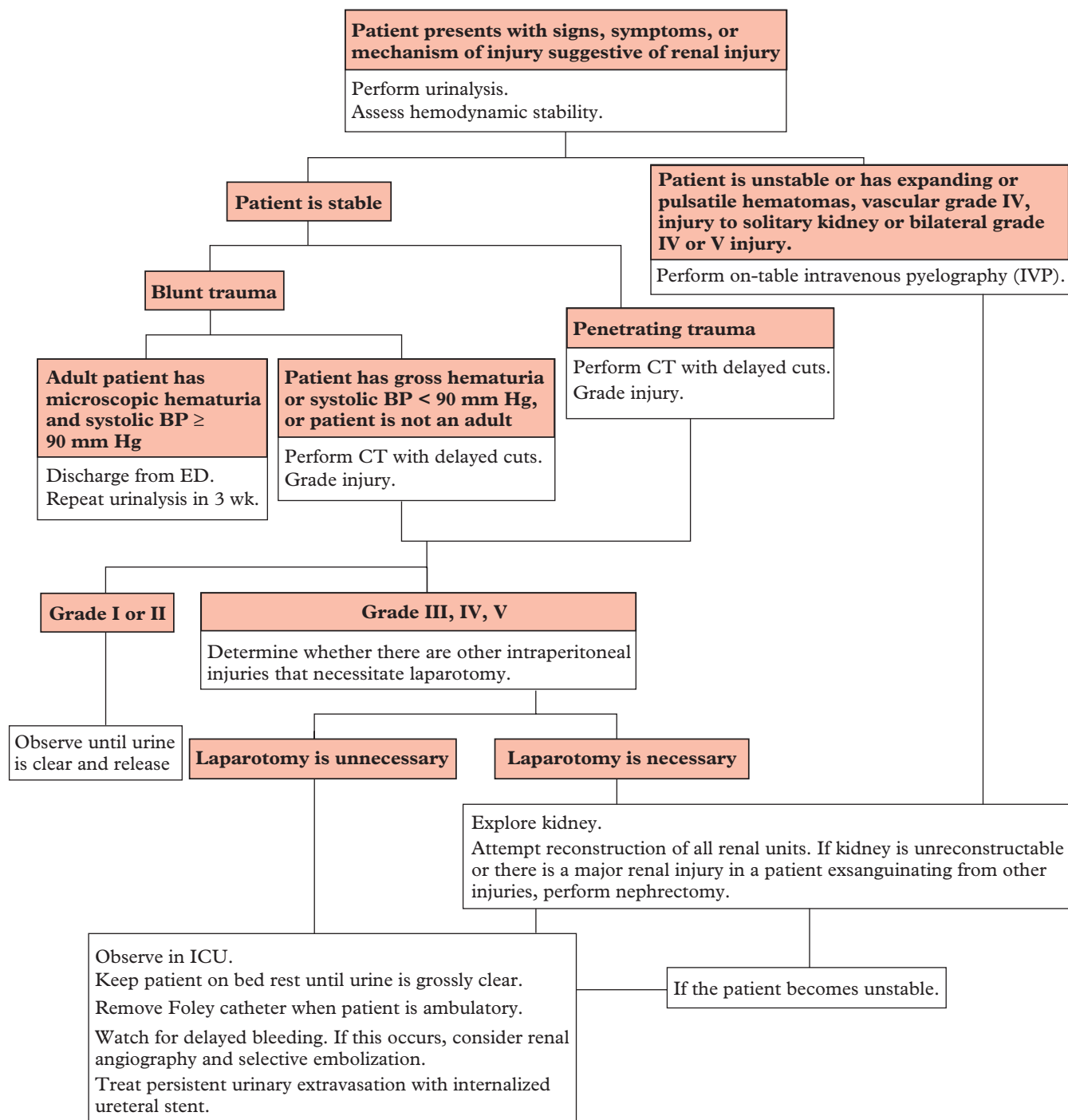


Figure 1 Algorithm outlining management of renal injuries. BP = blood pressure; CT = computed tomography; ED = emergency department; ICU = intensive care unit.

Thrombosis of the renal artery or its branches is treated expectantly unless the contralateral kidney is absent or injured, in which case, emergency revascularization is indicated. Endoluminal stenting and thrombolytic therapy are promising but still experimental approaches with limited long-term follow-up.^{10,11}

Critics of nonoperative management cite the potential risk of delayed complications avoided by nephrectomy or renorrhaphy. To date, there are no prospective, randomized, controlled trial data comparing operative versus nonoperative management of renal trauma injuries. However, a number of studies have shown a decrease in the number of renal

Table 1 Criteria for Imaging of Renal Injuries	
Type of Trauma	Criteria for Imaging
Blunt	Gross hematuria (visibly blood-tinged urine)
	Adult with microhematuria (defined as ≥ 1 + RBC on dipstick or > 3 RBC/hpf) with a period of hypotension (systolic BP < 90 mm Hg)
	Child (< 15 yr) with > 50 RBC/hpf
Penetrating	Stable patient with any degree of hematuria and injury near urinary tract

hpf = high-power field; RBC = red blood cells.

explorations performed with minimal morbidity and without increasing mortality.¹²

Operative

The only absolute indications for renal exploration are pedicle avulsion, pulsatile or expanding hematoma, and hemodynamic instability resulting from renal injury.⁶ Significant numbers of shattered kidneys (grade V) and renal vascular injuries (grades IV and V) are now managed nonoperatively. The strongest predictor for nephrectomy is severity of renal injury; however, roughly one third of all penetrating and 44% of blunt grade IV and V renal injuries are now managed nonoperatively.^{9,13,14} In patients who require laparotomy for associated injuries, renal exploration and reconstruction of grade III and IV injuries may reduce the likelihood of delayed complications. However, the need for laparotomy and surgery for other intra-abdominal organs is associated with a higher likelihood of nephrectomy. Thus, exploration of suspected kidney injuries (as determined by previous imaging or on-table evaluation) in patients undergoing laparotomy for major splenic or bowel injury should be attempted by surgeons experienced in repairing an injured kidney.⁹ In reality, the success of nonoperative management for most grade III and IV injuries means that operative intervention

in cases of blunt trauma is typically limited to patients with the most severe renal injuries, in whom conservative management fails either because of bleeding or because of ongoing urinary extravasation despite ureteral stenting.¹⁵

A significant number of patients with a penetrating injury and a minority of those with blunt trauma require immediate laparotomy before radiographic evaluation.^{9,13} Hematuria should alert the surgeon to the possibility of renal injury, and the presence of a perinephric hematoma visible through the mesocolon should prompt further evaluation. If a major renal injury is suspected on the basis of the size of the hematoma or an abnormal intraoperative intravenous pyelogram (IVP), exploration is indicated.

Intraoperative IVP (so-called one-shot IVP) is indicated when exploration of a kidney is planned and no preoperative imaging is available. The main purpose of a one-shot IVP in this setting is to confirm the presence of a contralateral functioning kidney; a potential benefit is the ability to rule out major injury. The plain abdominal film is obtained 10 minutes after injection of a 150 mL bolus of iodinated contrast material. If the injured kidney is adequately imaged and found to be normal, exploration may be omitted¹⁶; otherwise, the kidney should be explored. In critically ill patients with multiple associated injuries, renal exploration is indicated only if a pulsatile or expanding hematoma is present, in which case, expeditious nephrectomy is necessary. If exploration is not done, staging with CT should be completed once the patient is stable; angioembolization and percutaneous drainage can be used to manage bleeding and urinary extravasation, respectively.^{17–19}

The priorities of operative management for grade III, IV, and V injuries are hemorrhage control and definitive repair of the collecting system. A midline transabdominal incision permits exploration of the kidneys and provides optimal access to the renal hilum. After intraperitoneal sources of bleeding have been controlled, preliminary isolation of the renal artery and vein should be achieved before Gerota's fascia is opened. There is some controversy regarding the value of early vascular control, with one randomized controlled trial showing no benefit from

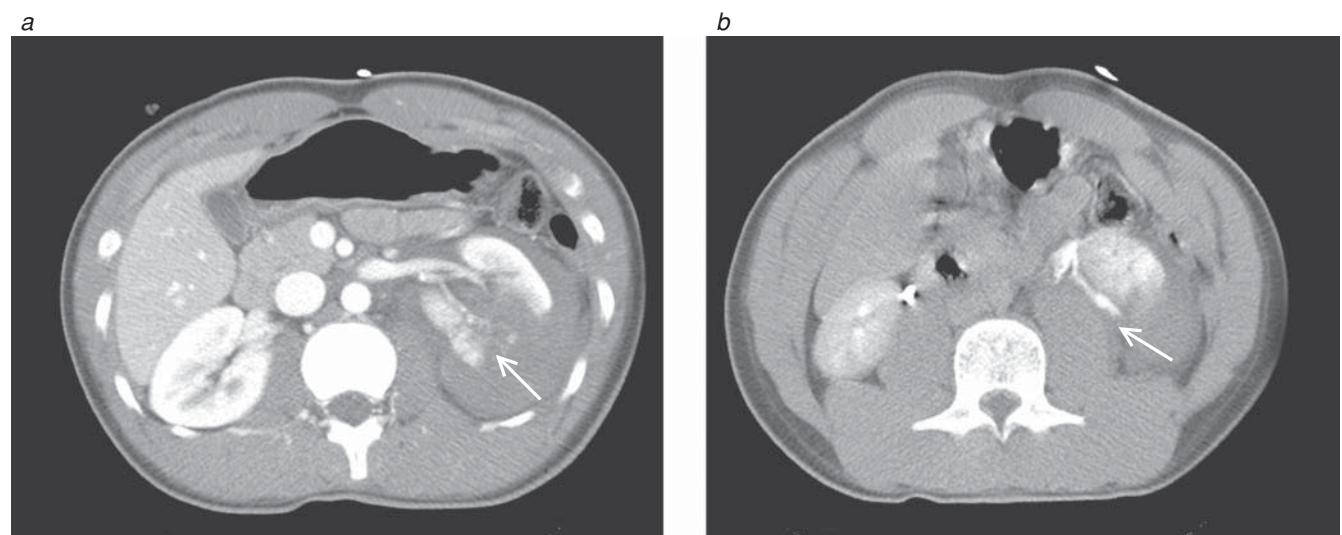


Figure 2 Shown are (a) a deep laceration with vascular contrast extravasation (arrow) and (b) a deep laceration with urinary contrast extravasation (arrow).

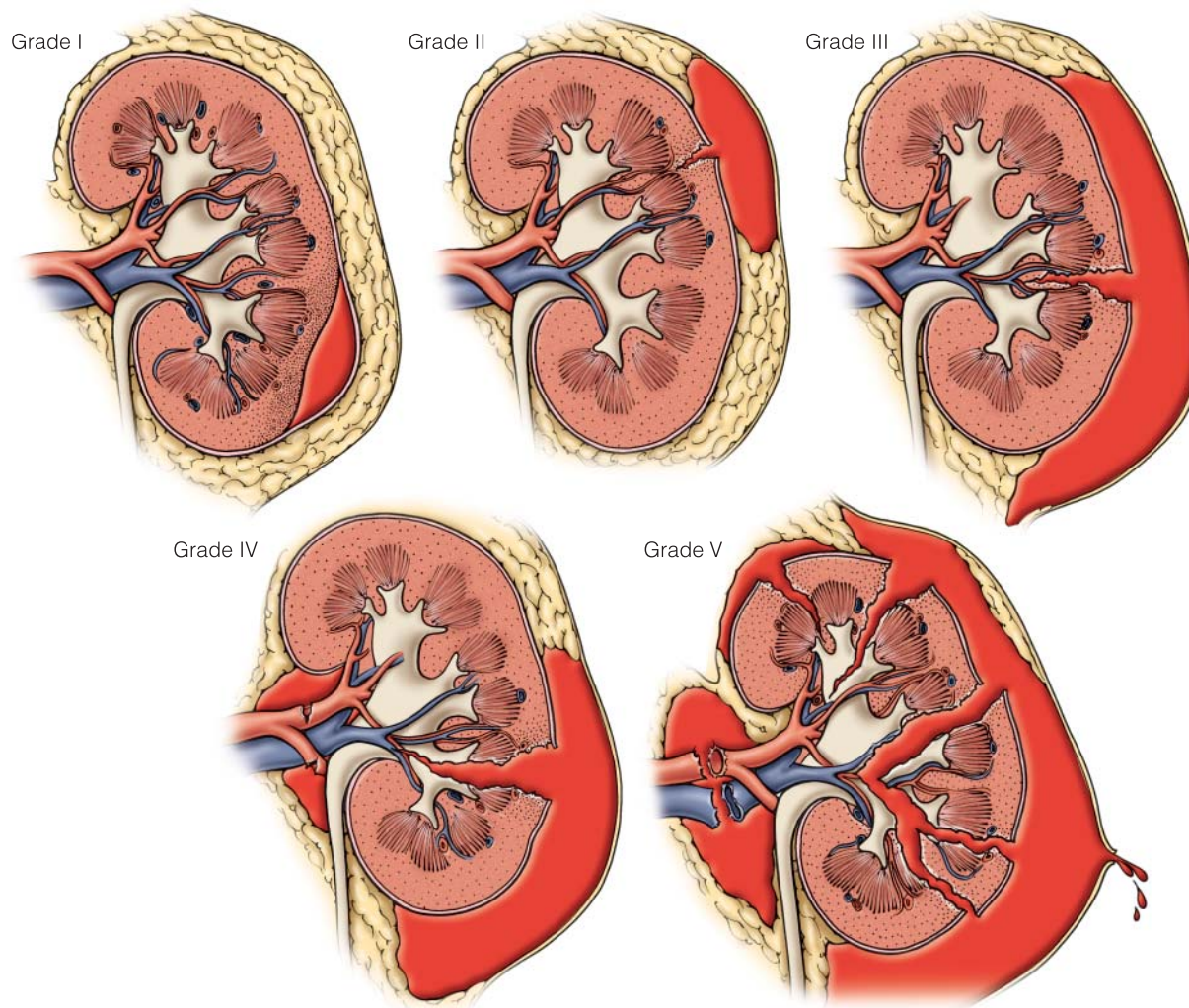


Figure 3 Illustrated is the American Association for the Surgery of Trauma (AAST) classification of renal injuries into grades I through V.

early isolation of the vessels in cases of renal gunshot wounds²⁰; however, the weight of the remaining evidence suggests that this technique is still valuable if renal reconstruction is the goal of exploration with an expected renal salvage rate of 85%.^{6,21,22} Isolation of the renal vessels is accomplished by opening the posterior peritoneum medial to the inferior mesenteric vein or by reflecting the ipsilateral colon (provided that the perinephric hematoma is left undisturbed).

Once vessel loops have been placed around the renal artery and vein, Gerota's fascia is opened. If massive bleeding occurs when the hematoma is entered, Rumel tourniquets or vascular clamps are applied to occlude the renal artery. If this maneuver does not stop the bleeding, one should suspect a venous injury and occlude the renal vein as well. Surface cooling of the kidney is not advocated, because of time constraints and concerns about possibly exacerbating hypothermia. Total exposure of the kidney by means of sharp and blunt dissection facilitates identification of injury to the parenchyma, the renal pedicle, or the collecting system. The renal capsule should not be pulled off the parenchyma: doing so would complicate subsequent repair.

Renal reconstruction includes sharp débridement of all devitalized tissue, achievement of hemostasis, closure of the collecting system, coverage of the defect, and drainage [see Figure 4]. Renal salvage should be possible in nearly 90% of grade III and IV injuries. Nephrectomy is reserved for destroyed kidneys that cannot be reconstructed or for cases of serious renal injury associated with other life-threatening injuries (e.g., vascular or hepatic trauma) in which taking the time required for attempted renal repair would jeopardize the life of the patient.^{3,22,23}

A number of sophisticated products are available for enhancing surgical hemostasis and reducing the need for tedious ligation of individual small arterioles on the parenchymal surface. Such products include a hemostatic bandage applied directly to the cut surface of the kidney,²⁴ polyethylene glycol-based hydrogels, fibrin glue, and a gelatin matrix–thrombin tissue sealant (FloSeal, Baxter International, Inc., Deerfield, IL).^{25–28} To date, none of these products have been evaluated in the setting of blunt renal injuries, but the results in elective partial nephrectomy models are encouraging.²⁸

Table 2 AAST Organ Injury Scales for Urinary Tract

Injured Structure	AAST Grade	Characteristics of Injury	AIS-90 Score
Kidney*	I	Contusion with microscopic or gross hematuria, urologic studies normal; nonexpanding subcapsular hematoma without parenchymal laceration	2; 2
	II	Nonexpanding perirenal hematoma confined to renal retroperitoneum; laceration < 1.0 cm parenchymal depth of renal cortex without urinary extravasation	2; 2
	III	Laceration > 1.0 cm parenchymal depth of renal cortex without collecting system rupture or urinary extravasation	3
	IV	Parenchymal laceration extending through renal cortex, medulla, and collecting system; injury to main renal artery or vein with contained hemorrhage	4; 4
	V	Completely shattered kidney; avulsion of renal hilum that devascularizes kidney	5; 5
Ureter*	I	Contusion or hematoma without devascularization	2
	II	< 50% transection	2
	III	≥ 50% transection	3
	IV	Complete transection with < 2 cm devascularization	3
	V	Avulsion with > 2 cm devascularization	3
Bladder†	I	Contusion, intramural hematoma; partial-thickness laceration	2; 3
	II	Extraperitoneal bladder wall laceration < 2 cm	4
	III	Extraperitoneal bladder wall laceration > 2 cm or intraperitoneal bladder wall laceration < 2 cm	4
	IV	Intraperitoneal bladder wall laceration > 2 cm	4
	V	Intraperitoneal or extraperitoneal bladder wall laceration extending into bladder neck or ureteral orifice (trigone)	4
Urethra*	I	Contusion with blood at urethral meatus and normal urethrography	2
	II	Stretch injury with elongation of urethra but without extravasation of urethrography contrast material	2
	III	Partial disruption with extravasation of urethrography contrast material at injury site with visualization in the bladder	2
	IV	Complete disruption with < 2 cm urethral separation and extravasation of urethrography contrast material at injury site without visualization in the bladder	3
	V	Complete transection with ≥ 2 cm urethral separation or extension into the prostate or vagina	4

AAST = American Association for the Surgery of Trauma; AIS-90 = Abbreviated Injury Score, 1990 version.

*Advance one grade for bilateral injuries, up to grade III.

†Advance one grade for multiple injuries, up to grade III.

Once hemostasis is satisfactory, the collecting system is scrutinized for evidence of injury. If the extent of the injury is unclear, 2 to 3 mL of methylene blue is directly injected into the renal pelvis while the ureter is occluded with a vessel loop to identify any openings in the collecting system. Open calyces or infundibula are closed with 4-0 absorbable sutures, whereas the renorrhaphy is completed with interrupted 2-0 absorbable sutures. Often the renal capsule can be used to cover exposed renal parenchyma and provide additional hemostasis. The defect in the parenchyma can be filled with folded absorbable gelatin sponges as the capsule is closed over the bolsters. If the capsule has been destroyed, coverage may be obtained with an omental or perinephric fat flap tacked down over the defect, a patch constructed from polyglycolic acid or peritoneum, or an entire sac of polyglycolic acid wrapped around the kidney, with the parenchymal edges kept well apposed.²⁹

At the end of the procedure, the kidney is returned to its location within Gerota's fascia, which is not reapproximated. Closed-suction drainage of the renal fossa is recommended only after repair of the collecting system; internalized stents are

reserved for complex injuries (e.g., large lacerations of the renal pelvis or the ureteropelvic junction [UPJ]).

Postintervention Care

Management of patients after operative or nonoperative intervention for renal trauma depends to a large extent on the presence and severity of associated injuries. The most significant urologic complications are urinary leakage, urinoma formation, and delayed bleeding.

After nonoperative management Bed rest is prescribed until the urine becomes grossly clear. Drainage of the bladder with a Foley catheter is necessary only until other injuries are stable and the patient can void spontaneously. For grade IV injuries with large amounts of urinary extravasation, follow-up imaging 48 to 72 hours after the initial scan is recommended to evaluate the degree of ongoing extravasation.^{15,30} CT is recommended, although in children, protocols that reduce the radiation exposure should be used. If at 72 hours the amount of extravasation has not decreased from

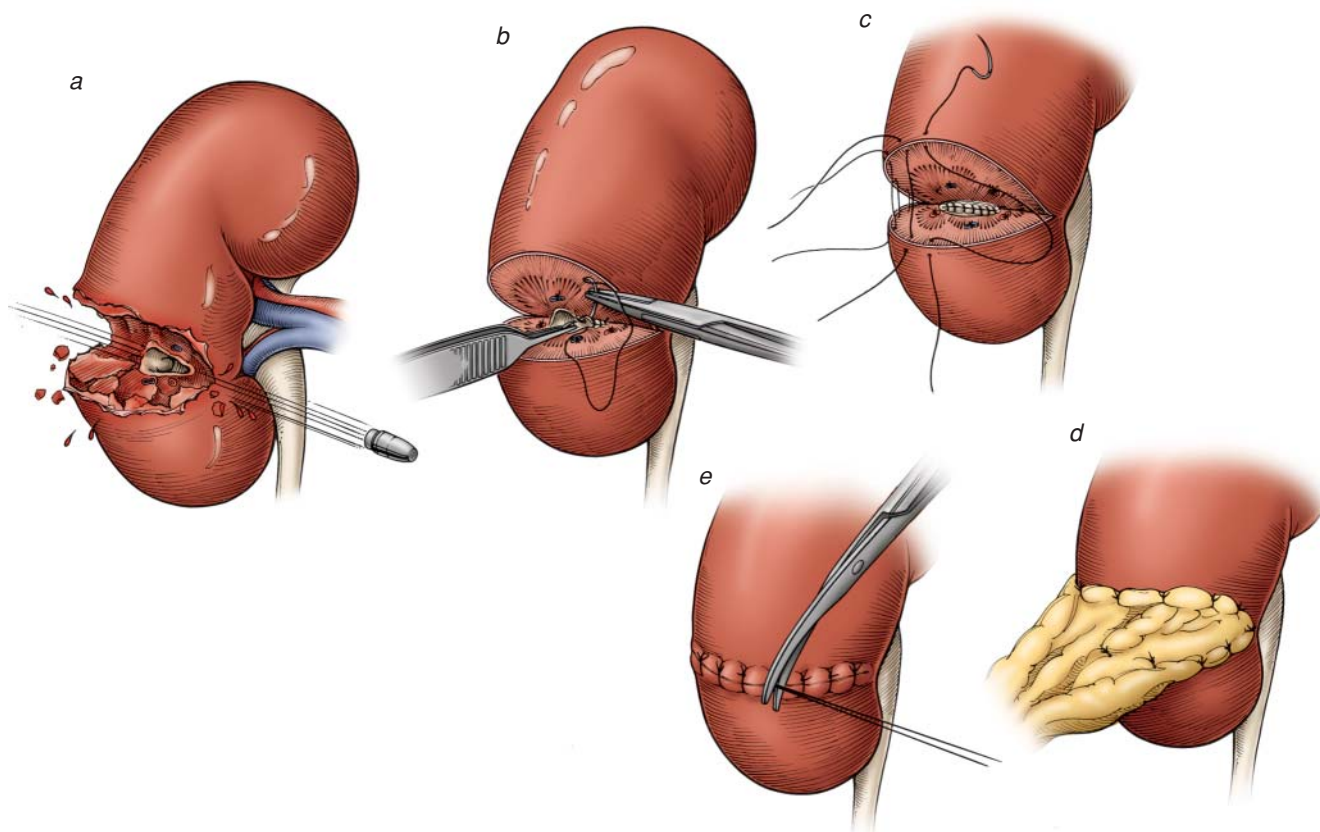


Figure 4 Depicted are the steps in renal reconstruction. (a) The patient has suffered a deep midrenal laceration into the renal pelvis. If the renal capsule is present at the wound margins, it should be peeled back and preserved for subsequent closure. The devitalized renal parenchyma is removed with a scalpel until bleeding occurs at the margin. Polar injuries can be débrided by guillotine amputation of the parenchyma. (b) The collecting system having been closed, vessels are ligated. Manual compression usually controls bleeding during ligation. Ligation of individual vessels with absorbable monofilament suture material achieves hemostasis. Temporary release of renal artery occlusion for the assessment of hemostasis is not recommended. Ligation of venous bleeding points generally controls adjacent arterial sources. (c) Sutures are placed to close the defect. (d) An absorbable gelatin sponge is placed. (e) Alternatively, the defect may be closed with an omental pedicle flap.

that seen on the initial scan, stenting is indicated. The presence of urinary extravasation within or outside Gerota's fascia is inconsequential in the decision to proceed with renal exploration or ureteral stenting. Cystoscopy and internal double J stenting allow successful treatment of the small percentage of cases in which the injury does not close spontaneously.³⁰ When a double J stent is used to manage persistent extravasation, the urinary bladder should be decompressed with a Foley catheter.

Parenchymal fragmentation and arterial thrombosis cause ischemia and often delay resolution of urinary leakage.³¹ Nevertheless, internal stenting almost invariably suffices, although resolution of extravasation can take weeks to months. Ultrasonography is useful for following such collections and for reducing the patient's radiation exposure. For small uninfected collections adjacent to the kidney, no intervention is needed. If a perinephric fluid collection is large enough to compress the ureter or becomes infected, additional percutaneous drainage is indicated [see Figure 5]. The drain fluid is tested for creatinine, and if the findings are consistent with a urine leak, the drain is left in place until the collection resolves

and leakage can no longer be demonstrated on contrast imaging.

Delayed bleeding is a rare but serious complication of nonoperative management of major lacerations.³² Pseudoaneurysm formation is the most common cause of delayed bleeding [see Figure 6].³³ Gross hematuria usually, but not invariably, accompanies the bleeding. If it is seen in conjunction with hypotension or a decreasing hematocrit, urgent angiography is the best initial approach; selective embolization is an effective treatment that renders exploration unnecessary in most instances.

Nonspecific low-grade fever, flank pain, and elevated white blood cell count can be seen with nonoperative renal injury management; thus, care must be taken to exclude an infected retroperitoneal hematoma or urinoma.

After operative management Retroperitoneal drains are removed within 48 hours after renal exploration unless the creatinine concentration in the drained fluid is higher than that in the serum. Persistent urinary leakage is best evaluated by means of repeat CT with delayed cuts. As with

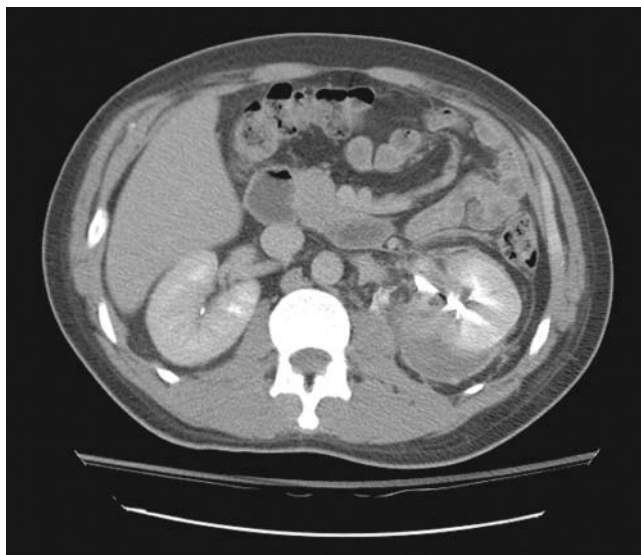


Figure 5 Computed tomographic scan showing an infected urinoma in a patient with left grade IV injury who presented 7 days after injury with fever and sepsis and subsequently underwent ureteral stenting. The urinoma was drained percutaneously.

nonoperative management, internal stenting and percutaneous drainage are the mainstays of treatment for leaks and urinomas, respectively. Postoperative hemorrhage is rare if the injured parenchyma has been adequately débrided and repaired. Angiographic evaluation with embolization is the best approach for postoperative renal bleeding.

Functional Imaging

Postoperative nuclear imaging correlates with AAST renal injury grade and is recommended in patients with grade IV and V injuries involving significant parenchymal loss or



Figure 6 Shown is a pseudoaneurysm of the left kidney after blunt injury.

vascular injury.³⁴ The goal is to identify patients with significant loss of functioning renal tissue who are at potential risk for chronic renal insufficiency. Grade III, IV, and V renal injuries result in a mean decrease in renal function of 15%, 30%, and 65% respectively.³⁴ Patients whose level of residual function in the injured kidney, as determined by radionuclide scintigraphy, is less than 25% should be considered as having a solitary kidney. This information is useful in counseling patients who participate in high-risk sports activities (e.g., skydiving, motocross, and hang gliding). The optimal timing of postoperative nuclear imaging has not been determined, but by 3 months, the hematoma and inflammation related to the injury usually have resolved.

Hypertension is a rare late complication of renal reconstruction and nonoperative management, usually renin mediated and deriving from an ischemic segment of renal parenchyma (also referred to as a Goldblatt kidney). Occasionally, angiography delineates the ischemic segment of the kidney, and excision of the nonperfused segment or complete nephrectomy may be required.

Injuries to the Ureters

INITIAL EVALUATION

Ureteral trauma [see Table 2] is rare, accounting for fewer than 1% of genitourinary injuries. Furthermore, the absence of physical signs of injury makes diagnosis difficult, and a delayed presentation is not uncommon. Gross or microscopic hematuria may be absent in 25 to 83% of patients with ureteral injuries, and as many as one half of all ureteral injuries resulting from blunt trauma are not recognized immediately. A high index of suspicion and a high degree of vigilance are necessary if the diagnosis is to be made early enough to prevent late consequences such as urinoma, sepsis, and nephrectomy.^{35–37}

The mechanism of injury has a particular bearing on the diagnosis and management of ureteral injury. The complexity of ureteral repair and number of associated injuries increase with the severity of AAST grade.³⁷ Overall, penetrating wounds are the predominant cause of these injuries. CT with delayed cuts should be performed when ureteral injury is suspected and the patient is stable. Imaging is of variable usefulness in the detection of ureteral injuries, but extravasation of the contrast agent is diagnostic.³⁸ Only 4 to 20% of ureteral injuries are caused by blunt trauma, and within this category, MVCs predominate.^{35,37} In children, ureteral injury at the UPJ often occurs after severe deceleration.³⁹ Children's ureters are particularly prone to injury at this location because the hyperextensibility of their spines can result in ureteral avulsion at the UPJ.^{37,38,40}

MANAGEMENT

All injuries to the ureter should be repaired surgically [see Figure 7] unless a delay in diagnosis has resulted in an abscess or a urinoma [see Figure 8]. If an abscess or a urinoma is present, drainage by means of percutaneous nephrostomy, coupled with ureteral stenting, allows infection and inflammation to resolve before definitive management; in this setting, an operative approach is likely to result in nephrectomy.

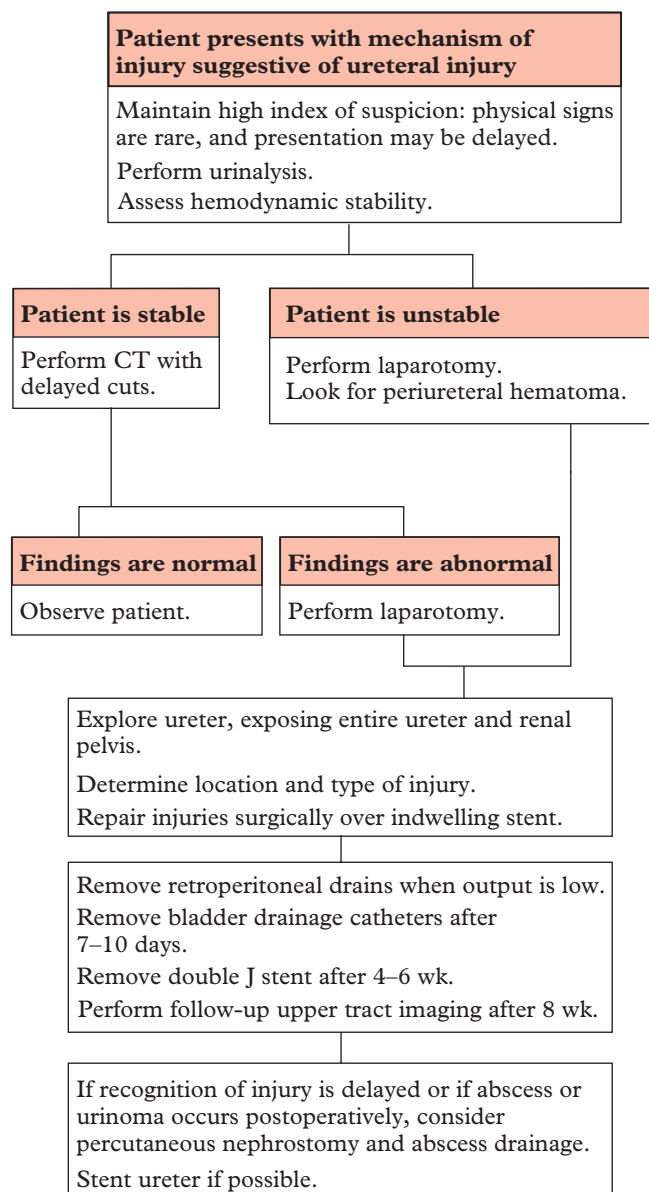


Figure 7 Algorithm outlining management of ureteral injuries. CT = computed tomography.

Ureteral Exploration

In stable patients, blunt ureteral injuries are typically identified by preoperative radiographic studies, which allow directed exploration and repair (see below). With penetrating trauma, ureteral injury may not be suspected until the time of laparotomy, when a hematoma is found near the kidney or ureter. Direct inspection of the entire trajectory of the offending agent requires particular vigilance for direct injury to or contusions of the ureter. Injection of indigo carmine into the collecting system identifies extravasation. Direct injection saves time and ensures that injuries are not missed as a result of low urine output from shock or renal injury. One study found that all penetrating ureteral injuries were detected at laparotomy without previous imaging.³⁶



Figure 8 Computed tomographic scan showing extravasation and urinoma caused by unrecognized right upper ureteral injury.

Reconstruction and Repair

Ureteral injuries should undergo surgical reconstruction as soon as they are recognized unless associated injuries prevent such a strategy. For example, gunshot injuries to the iliac vessels or the ureters may necessitate heroic vascular reconstruction. Ligation of the ureter with subsequent nephrostomy tube drainage or exteriorization of a ureteral stent allows elective reconstruction months later. Percutaneous and endoscopic approaches can also be used to establish urinary drainage if ureteral exploration is not feasible.

In the event that the operating surgeon is unfamiliar with acute ureteral reconstruction, several options are available before definitive repair. One option is to exteriorize a ureteral stent, suturing the ureter to the stent with a 2-0 silk suture, to facilitate locating the ureter during subsequent delayed reconstruction. Another approach is to ligate the injured ureter with a 2-0 silk suture with subsequent percutaneous nephrostomy tube drainage. An 8 French nephrostomy tube should be placed in the ipsilateral kidney after the patient has been stabilized to ensure maximal urinary drainage, avoiding the complications of urinary infection and nephron loss. No trauma data exist defining the maximum safe time interval of ureteral ligation on kidney function; however, timely nephrostomy tube placement after occlusion is likely to minimize potential complications secondary to obstruction. Once urinary drainage has been attained with either a ureteral stent or nephrostomy tube, definitive ureteral reconstruction by an experienced urologist should be performed within the first few days after injury or else delayed for a minimum of 3 months, or longer, until the patient has fully recovered.

Reconstructive steps in ureter repair include débridement of devitalized tissue, creation of a spatulated tension-free anastomosis, watertight mucosal approximation (5-0 or 6-0 absorbable sutures—knots inside or outside), stenting, coverage of the repair with vascularized tissue when feasible, and appropriate drainage.⁴¹ Stab wounds generally cause less

tissue damage than gunshot wounds and are more easily repaired; partial transections may be closed primarily.

Upper ureter Disruption or transection of the upper ureter or the UPJ is repaired by means of débridement and primary anastomosis of the renal pelvis and the ureter. Mobilization of the ureter is limited to ensure that the blood supply is not compromised. Interrupted 5-0 or 6-0 absorbable sutures are preferred, and a double J ureteral stent or a nephrostomy tube is inserted before completion of the anastomosis.

Medial ureter Injuries to the abdominal ureter between the UPJ and the pelvic brim are repaired by means of ureteroureterostomy [see Figure 9]. After débridement, the ends are spatulated on opposite sides, and an interrupted approximation is completed with 5-0 or 6-0 absorbable sutures over a double J stent. In cases of overlying colonic, duodenal, or pancreatic injury, the anastomosis should be covered with omentum or retroperitoneal fat. Large defects

in the abdominal ureter may necessitate transureteroureterostomy, in which the injured ureter is passed behind the mesocolon to the contralateral side. Anastomosis of the injured ureter to a 1 to 2 cm opening in the medial side of the normal ureter can be achieved without tension. With transureteroureterostomy, a stent (usually a 5 French pediatric feeding tube) should cross the anastomosis and be brought out through the normal lower ureter or bladder.

Distal ureter Ureteral injuries in the pelvis should be managed with reimplantation into the bladder. The distal stump is ligated, and after the anterior bladder wall is opened, the proximal end of the ureter is brought through a new hiatus on the back wall of the bladder. The ureter is then spatulated and approximated to the bladder mucosa with interrupted chromic sutures. One 3-0 anchoring stitch brings the distal apex of the ureter to the muscle and mucosa; the rest of the sutures approximate the mucosa. A refluxing reimplantation is acceptable in adults. Larger defects can be bridged by performing a vesicopsoas hitch, in which the bladder is sewn to the central tendon of the psoas muscle. The dome is mobilized by dividing the obliterated umbilical arteries bilaterally and, if necessary, the contralateral superior vesical artery. Three interrupted nonabsorbable sutures that enter the detrusor muscle (but not the bladder lumen) anchor the dome above the iliac vessels. Complex bladder or vascular injuries in the pelvis make transureteroureterostomy a more attractive option for avoiding further dissection in the injured area. A ureteral stent should be used in all ureteral reimplantations. The bladder is closed in two layers with a continuous 2-0 absorbable suture. Closed-suction retroperitoneal drainage and Foley catheter decompression of the bladder are essential.

Postintervention Care

Postoperative care of ureteral trauma relates mainly to the manipulation of drains and the management of complications. Retroperitoneal drains may have significant output for several days but are removed after 2 to 3 days unless output is consistent with a urine leak as determined by creatinine measurement (see above). Bladder catheterization is necessary for 7 days after ureteral reimplantation. In combined bladder and ureteral reconstructions, contrast cystography is indicated before catheter removal. Cystoscopic removal of the double J stent is usually performed with local anesthesia 4 to 6 weeks after operation. CT, IVP, or renal scintigraphy 3 months after removal of the stent rules out the possibility of asymptomatic obstruction.

Fistula formation, usually the result of distal obstruction or necrosis of the ureter, should be managed by means of antegrade or retrograde drainage of the collecting system with percutaneous or endoscopic techniques. Drainage of periureteral fluid collections may also be necessary. If recognition of an injury or a complication is delayed, reconstruction should be deferred for at least 3 to 6 months until all inflammation has subsided.

Injuries to the Bladder

INITIAL EVALUATION

Bladder injury [see Table 2] is most often caused by blunt injuries, with penetrating trauma accounting for 14 to 33%

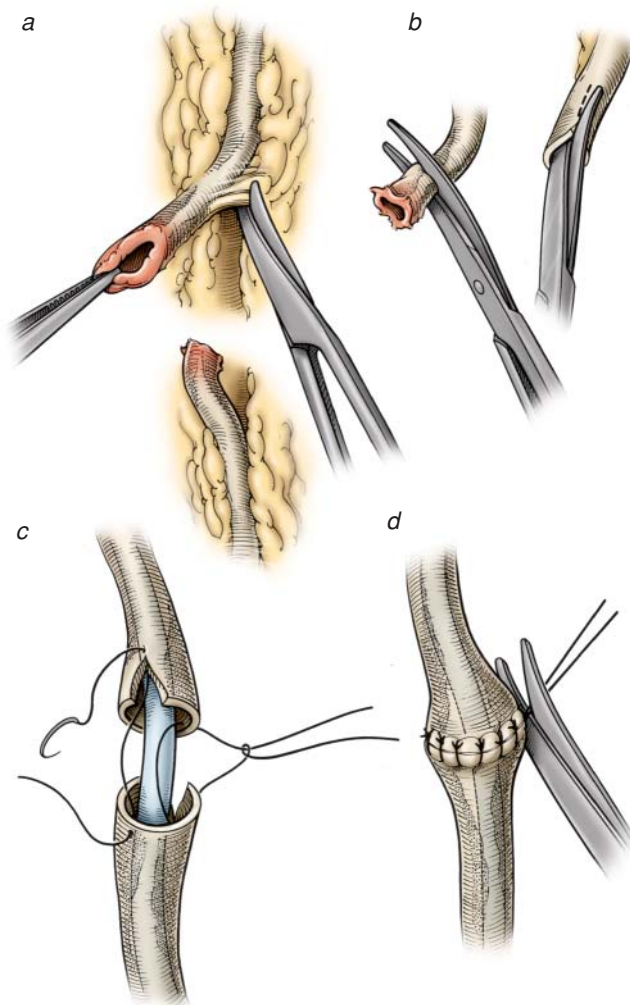


Figure 9 Depicted are the steps in a ureteroureterostomy. (a) The injured ureter is dissected free. (b) The ends are débrided and spatulated. (c) A stent is placed, and the anastomosis is begun. (d) The anastomosis is completed.

of civilian cases. About 3 to 9% of patients with a pelvic fracture have an associated injury to the bladder, with an elevated risk of bladder rupture occurring in disruptions of the bony pelvic ring.^{42,43} Because the fracture type has a poor predictive value for the type of associated genitourinary trauma, all patients with pelvic fractures and any degree of hematuria should be suspected of having a bladder injury. Approximately two thirds of bladder injuries are extraperitoneal and one third are intraperitoneal, a distinction that has important management ramifications.

The signs and symptoms of bladder injury are generally nonspecific [see Figure 10], although 95% of patients with bladder rupture present with gross hematuria. Patients may complain of suprapubic pain, dysuria, or an inability to void. Physical examination may reveal tenderness in the suprapubic region, ileus, or an acute abdomen. The percentage of patients without any hematuria ranges from 0 to 3%.^{44,45} Laboratory studies are usually inconclusive unless significant reabsorption of urine causes elevated serum creatinine levels, hyperkalemia, or hyponatremia.⁴⁶

Bladder rupture can be accurately diagnosed with either retrograde CT cystography or plain-film retrograde cystography. The indications for cystography include blunt trauma with gross hematuria in the presence of low-density free abdominal fluid on CT (< 25 HU); blunt trauma with a pelvic ring fracture and any degree of hematuria (> 30 red blood cells [RBCs] per high-power field [hpf]); stable penetrating trauma with any degree of hematuria; and an injury to the pelvis. The appearance of intraperitoneal and extraperitoneal rupture with each modality is characteristic [see Figure 11]. CT cystography is performed with 5 mm cuts after the bladder is filled. Contrast is instilled to tolerance in responsive patients, whereas 40 cc of water and 350 cc of contrast agent are instilled in intubated patients as insufficient bladder filling can yield false negative results. At one large center, the sensitivity and specificity of CT cystography for bladder rupture caused by blunt trauma were 95% and 100%, respectively.⁴⁵ With current patterns of CT use for trauma evaluation, including imaging of pelvic bony fractures, CT cystography appears to be more efficient than plain-film studies. Furthermore, CT cystography clearly identifies the location of many bladder injuries and may be able to identify bladder neck injuries [see Figure 11a]. With penetrating trauma, there must be a higher level of suspicion for bladder injury because the sensitivity and specificity of cystography (CT or conventional) in this setting have not been determined. If bladder injury is associated with a pelvic fracture in a male patient, the possibility of a urethral injury is 5 to 29% and must be excluded.^{43,47} A successfully placed Foley catheter rules out a complete urethral disruption.

MANAGEMENT

Nonoperative

Extraperitoneal bladder injuries caused by blunt trauma are generally managed nonoperatively with 10 days of catheter drainage.^{47–49} Contraindications to nonoperative management include urinary infection; pelvic fractures requiring internal fixation; the presence of bony fragments in the bladder; bladder neck injury, which may compromise continence; rectal injury; and female genital lacerations associated with

pelvic fracture. After 10 days, plain-film or CT cystography is performed to document healing. Once the extravasation has resolved, catheter removal can be based on the patient's overall status and mobility. If extravasation persists, cystography is repeated at appropriate intervals until healing occurs.

Operative

All penetrating injuries and all intraperitoneal ruptures of the bladder are managed by means of bladder exploration and repair. If the patient requires laparotomy for associated injuries and can tolerate the extra operating time, repair of extraperitoneal bladder injuries is also recommended. Conversely, in severely unstable patients, catheter drainage can be used as a temporizing measure until the patient is able to undergo exploration.

Bladder exploration can be performed via an intraperitoneal approach or by entering the extraperitoneal space of Retzius in the anterior pelvis. Intraperitoneal injuries present as a stellate rupture of the dome of the bladder. By enlarging this opening, one can inspect the interior of the bladder to exclude concomitant extraperitoneal injuries.⁵⁰ In cases involving orthopedic reconstruction of the pelvis, the bladder may be approached extraperitoneally through the incision used to expose the pubic symphysis. Although extensive hemorrhage has been described in this scenario, it is a rare occurrence. Most extraperitoneal bladder injuries associated with pelvic fractures are anteriorly located, small in size, and easily closed without a more extensive bladder exploration.

Penetrating injuries and unrecognized blunt injuries discovered at laparotomy without previous CT cystography call for systematic evaluation. By opening the bladder vertically at the dome or along the anterior surface, one can identify sites of injury intravesically and inspect the ureteral orifices and the bladder neck. Lacerations are closed with 3-0 absorbable sutures, which approximate detrusor muscle and mucosa in one layer and provide hemostasis. In patients with penetrating injuries, entrance and exit sites must be identified. The cystotomy is then closed with two layers of continuous 2-0 slowly absorbable sutures.

Postintervention Care

Adequate urinary drainage is essential to successful healing of the repaired bladder. There is no evidence that suprapubic catheters are superior to urethral catheters in this context.^{49,51} However, the catheters placed during trauma resuscitation are not of sufficient caliber to allow easy bladder decompression; therefore, a 20 French urethral catheter should be substituted at the end of the operation. A closed-suction drain near the bladder closure (but not overlying the suture line) is recommended. Cases of severe hematuria resulting from extensive injuries or coagulopathy warrant additional drainage with a suprapubic cystostomy tube to allow irrigation of clots and proper decompression of the bladder.

The perivesical drain can be removed after 48 hours unless the creatinine level in the drained fluid indicates ongoing urinary leakage. In the majority of patients with a bladder repair, 7 days of catheter drainage is sufficient to allow healing. Because bladder repair is reliable, any complications of bladder injury are usually related to a delay in diagnosis rather than to postoperative morbidity. Azotemia, ascites, and sepsis can result from an unrecognized intraperitoneal

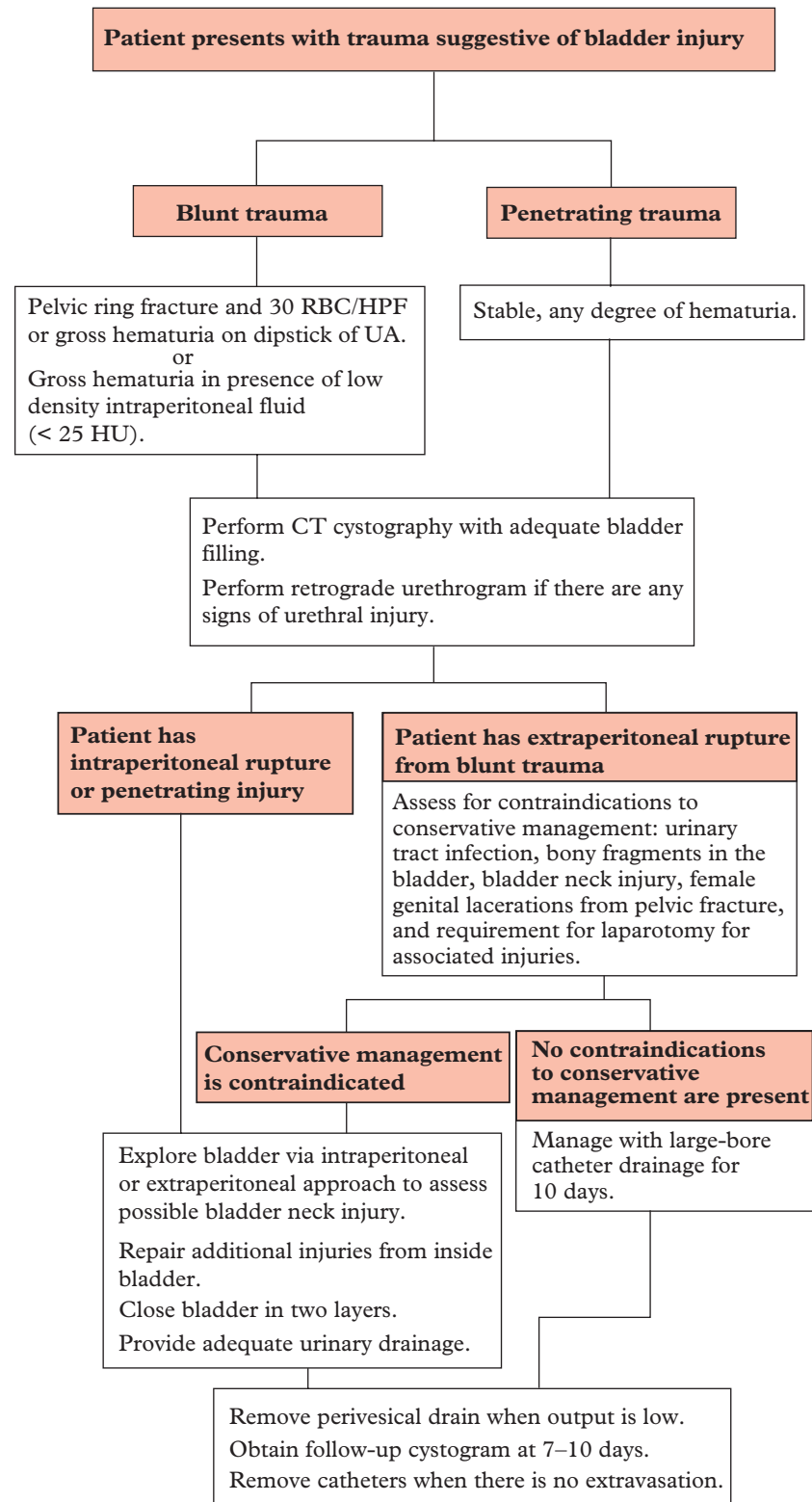


Figure 10 Algorithm outlining the management of bladder injury. CT = computed tomography.

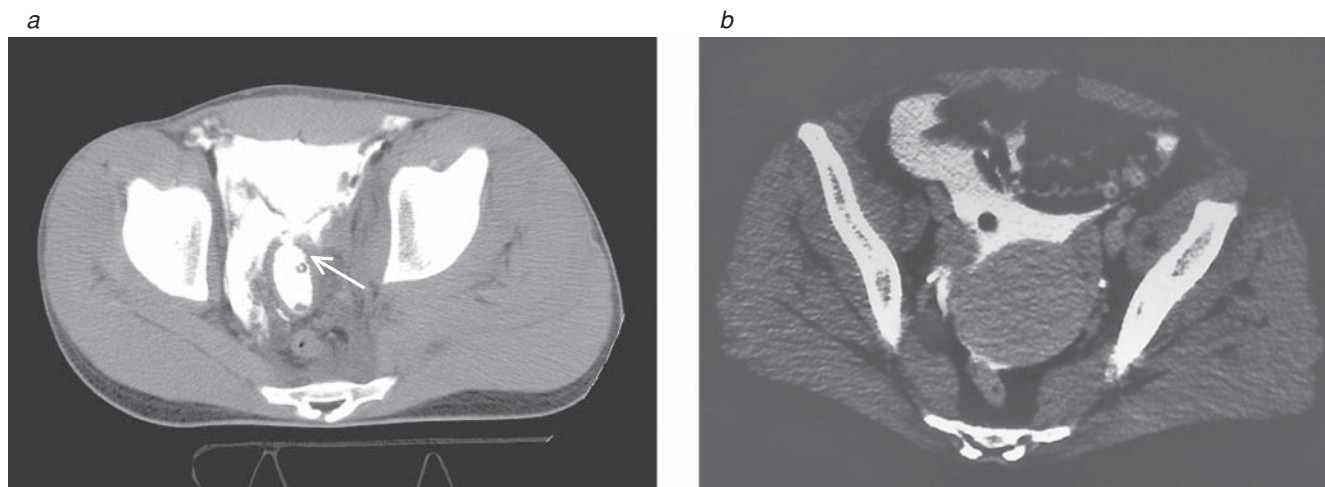


Figure 11 (a) Computed tomographic (CT) cystogram showing extraperitoneal bladder rupture. A definitive discontinuity in the bladder wall is visible (arrow). (b) CT cystogram showing intraperitoneal bladder rupture.

injury. Bladder neck injury, if overlooked, leads to scarring and incompetence of the proximal sphincter mechanism, with resultant incontinence, especially in females.

Injuries to the Urethra

INITIAL EVALUATION

Almost all injuries to the male urethra [see Table 2] are caused by blunt trauma. Prostatomembranous urethral distraction injuries in males occur in 1.5% of pelvic fractures, which are the most common cause of posterior urethral injury.⁴³ Pelvic fractures with a displaced inferomedial pubic ramus and pubic symphysis diastasis have an increased risk of urethral injury. For every 1 mm increase in pubic diastasis, the risk of urethra injury increases 10%.⁵² Anterior urethral (penile and bulbar urethral) injuries are commonly caused by straddle injury but may be the result of penile fracture or penetrating injuries to the genitalia. The female urethra is rarely injured, but when such injury occurs, it is usually associated with bladder injury and pelvic fracture. Up to 40% of female urethral injuries are missed in the emergency department, emphasizing the need for a high index of suspicion in women with gross hematuria and pelvic fracture.⁵³

Blood at the urethral meatus—the classic sign of injury to the male urethra—is an indication for immediate urethrography. Attempts at catheter placement risk converting an incomplete injury to a complete disruption and are to be discouraged if urethral injury is suspected.

Because signs of urethral injury are variable, retrograde urethrography is the essential diagnostic test used for documenting the location, nature, and extent of injury. Extravasation of the contrast agent is evidence of urethral injury [see Figure 12]. In the absence of extravasation, a Foley catheter should be passed. If a catheter has been placed but its position is unclear, contrast injection will confirm its placement in the bladder. In such cases, the catheter should be left in place until a pericatheter contrast study can fully evaluate the urethra. In cases of pelvic fracture and complete

posterior urethral injury, bladder injury must be excluded by open bladder exploration or via cystography through a percutaneously placed suprapubic tube.

MANAGEMENT

Traumatic urethral injuries have traditionally been managed by means of suprapubic cystostomy, with reconstruction delayed for 3 to 6 months; however, most urethral trauma patients can undergo immediate realignment, with or without sutured repair. The exception is the patient with a straddle-type crush injury to the bulbar urethra, which should always be treated with urinary diversion and delayed repair. The recommended treatment is based on the location and mechanism of injury [see Figure 13 and Table 3].

Posterior Urethra

Posterior urethral (prostatic and membranous urethral) injuries can be managed with suprapubic cystostomy or early primary urethral realignment. Realignment without sutured repair renders definitive reconstruction unnecessary in a significant percentage of patients.⁵⁴ Bladder neck injury and wide separation of the bladder from the urethra warrant immediate surgical intervention.⁵⁵ Simultaneous rectal injury often occurs in this setting and necessitates evacuation of the pelvic hematoma, irrigation, placement of drains, and primary realignment of the urethra. Primary realignment is also preferred in cases of open reduction and internal fixation of pelvic fractures because the risk of hardware contamination is considered to be lower with a urethral catheter than with suprapubic cystostomy.⁵⁶

Primary realignment is usually performed through a lower midline abdominal incision, which allows antegrade passage of instruments through the bladder at the same time as retrograde passage of instruments from the urethral meatus. Flexible cystoscopes or magnetic-tipped catheters advanced under fluoroscopic guidance are used to place a wire into the bladder beyond the injury, and a Council-tip Foley catheter is then advanced over the wire. Neither mucosal approximation nor direct anastomosis is the goal. Suprapubic catheter

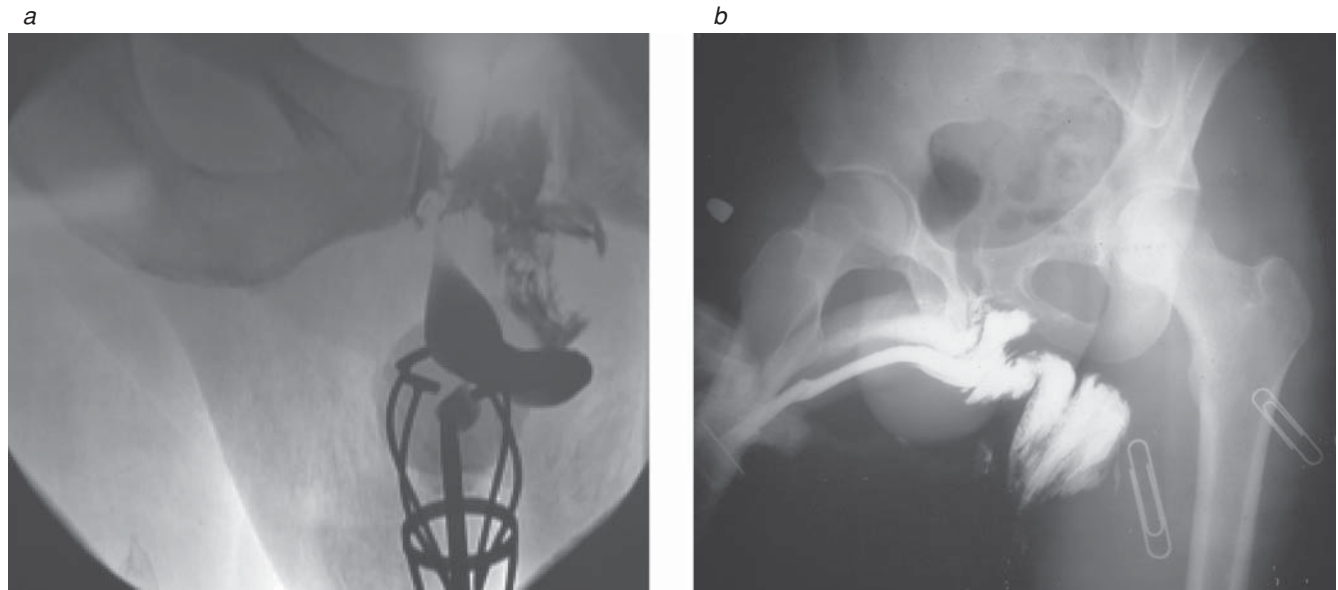


Figure 12 (a) Retrograde urethrogram of a posterior urethral injury after pelvic fracture shows extravasation at the level of the urogenital diaphragm. (b) Retrograde urethrogram of an anterior urethral injury caused by a gunshot wound shows extravasation at the level of the bulbar urethra.

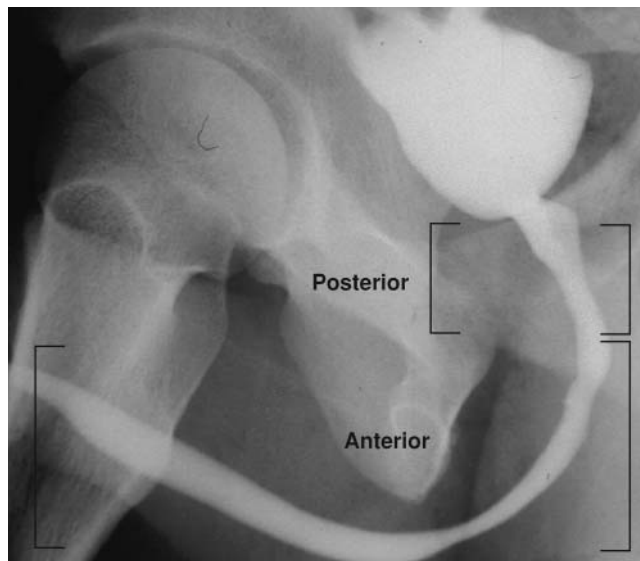


Figure 13 Shown are the posterior and anterior portions of the urethra. The posterior portion comprises the prostatic urethra and the membranous urethra; the anterior portion comprises the bulbar urethra and the penile urethra. Treatment of urethral injury depends on the location and mechanism of injury.

drainage is not required, but a perivesical drain should be left in place for 48 hours.

Anterior Urethra

Immediate surgical reconstruction is preferred for penetrating injuries of the bulbar and penile urethra and for urethral injuries associated with penile fracture. For these grade III and IV injuries, primary repair is associated with a lower stricture rate than simple realignment.^{57,58} Wounds accompanied by major tissue loss and defects larger than 2 cm (e.g., grade V injuries) or major associated injuries are best treated with suprapubic tube urinary diversion (see below) and subsequent reconstruction at a tertiary referral center.

Suprapubic Cystostomy

Many centers continue to use suprapubic cystostomy as the primary management of prostatomembranous urethral disruption and straddle injuries to the bulbar urethra. Suprapubic cystostomy, with the tube percutaneously placed under fluoroscopic guidance, allows temporary urinary diversion for initial stabilization and evaluation of the patient. Cystography can then be performed via the suprapubic tube to rule out associated bladder injury. Straddle injuries must be treated with suprapubic diversion unless the urethral disruption is only partial and allows passage of a guide wire or catheter

Table 3 Management of Urethral Trauma

Location of Injury	Mechanism of Injury		
	Blunt	Penetrating	Penile Fracture
Posterior (prostatic and membranous urethra)	Realignment or suprapubic cystostomy	Realignment	—
Anterior (bulbar and penile urethra)	Suprapubic cystostomy	Surgical repair	Surgical repair

under fluoroscopic guidance. Finally, suprapubic cystostomy is also recommended for penetrating injuries to the anterior urethra if the injuries were caused by high-velocity weapons and are characterized by extensive tissue loss; if serious associated injuries are present; or if bony fractures prevent proper placement of the patient in the lithotomy position.

Female Urethra

Prompt surgical reconstruction of the bladder neck and urethra are warranted when possible. Urethral injuries distal to the external sphincter can be left unrepaired. However, proximal and midurethral injuries should be closed primarily over a catheter, with all overlying vaginal lacerations repaired concomitantly to minimize the risk of urethrovaginal fistula formation or vaginal stenosis. Placement of a suprapubic tube with delayed repair is reserved only for unstable patients.⁵³

Postintervention Care

Catheter care is of great importance after urethral reconstruction or suprapubic cystostomy. Urethral catheters should be secured to the abdominal wall in the early postoperative period. After immediate reconstruction of the anterior urethra, the Foley catheter should remain in place for 3 weeks, at which time a contrast voiding cystourethrogram should be obtained. If extravasation is present, the catheter should be replaced for 1 week and the study repeated. After primary realignment of urethral injuries, the urethral catheter is left in place for 6 weeks, at which time a pericatheter retrograde urethrogram is obtained, with the expectation that any extravasation will have resolved.

If the patients initially underwent diversion with a suprapubic tube alone, the tube should be changed after a tract has formed (usually about 4 weeks after the procedure) and then monthly until reconstruction can be performed. Stricture formation or complete obliteration of the urethra may be the final result of this nonoperative approach. Subsequent radiographic studies will indicate whether secondary endoscopic or open procedures are needed.

Injuries to the Vagina, Uterus, and Ovaries

Injuries to the female genitalia [see Table 4 and Figure 14] must be regarded as especially morbid because of their association with sexual assault and interpersonal violence, as well as because of the potential medical complications (infection and bleeding). Genital trauma is reported in 20 to 53% of sexual assault victims.^{59,60} Blunt unintentional trauma, including pelvic fracture and straddle injuries, often results in perineal and vaginal injuries and, less commonly, cervical and uterine trauma.^{61–64} Enlargement of a reproductive organ predisposes that organ to injury.^{65,66} Penetrating injuries account for almost all injuries to the fallopian tubes, the ovaries, and the nongravid uterus.⁶⁷

INITIAL EVALUATION

A history of sexual trauma must be sought; if such a history is elicited, appropriate police and support services must be notified.⁶⁸ In addition, if sexual assault has occurred, informed consent for the rest of the patient assessment must be obtained. This assessment includes a history, a physical examination, collection of evidence and laboratory specimens, and treatment, as outlined by the American College of

Obstetricians and Gynecologists.⁶⁹ The percentage of assault victims with identifiable spermatozoa in the vaginal specimens is lower than 50%.⁷⁰

All female patients with evidence of lower urinary tract and urethral injury should undergo examination of the external genitalia, as well as speculum examination of internal organs. The finding of blood implies vaginal laceration. In the presence of pelvic fracture or impalement injury, vaginal laceration warrants complete evaluation (with cystourethrography, proctoscopy, and laparotomy, as indicated) to rule out associated urinary tract and gastrointestinal tract injuries. Failure to identify vaginal injury associated with pelvic fracture may lead to abscess formation, sepsis, and death.

MANAGEMENT

Perineal lacerations in the absence of associated urinary tract and rectal injury can be managed in the emergency department. Only large hematomas must be incised and drained, with ligation of vessels. Lacerations of the vulva may be closed primarily after irrigation and débridement. Interrupted absorbable sutures allow any accumulated fluid to drain and eliminate the need for suture removal. Drains are used if there is a large cavity; if hemostasis is suboptimal, the wound may be packed.⁶⁴

Vaginal and cervical lacerations from either blunt or penetrating injury will bleed extensively if the pudendal vessels are injured.⁶⁴ If bleeding is not severe, examination and repair with local anesthesia are possible in the emergency department. If large lacerations are associated with bleeding and hematoma, speculum examination under anesthesia permits more complete assessment and repair of injuries. Vaginal lacerations should be closed with continuous or interrupted absorbable sutures that include mucosal and muscular layers. Antibiotic-soaked vaginal packing should be left in place for 24 hours. Perioperative administration of broad-spectrum antibiotics is sufficient, unless injuries are more complex.

Complex vaginal and perineal lacerations associated with pelvic fracture must be managed much more aggressively to prevent the morbidity and mortality characteristic of open fractures.⁷¹ Evaluation of vaginal injuries with the patient under anesthesia, cystography, and rigid proctoscopy are mandatory. The vaginal laceration should be closed with absorbable sutures. Even in the absence of injury to the bladder or the rectum, diversion of the urinary and fecal streams should be considered to facilitate care of the perineal wound; however, we rarely divert the fecal stream unless the perineal injury extensively involves the rectum or the sphincter.⁷² Extraperitoneal bladder rupture associated with vaginal lacerations must be repaired operatively to prevent infection of a pelvic hematoma or formation of a vesicovaginal fistula. Urologic, gynecologic, and orthopedic consultations are necessary for care of associated injuries.

Injury to the pelvic genital organs is rare in a nongravid patient. Penetrating trauma is the most common cause, and the majority of patients have associated injuries necessitating laparotomy.⁶⁶ Blunt injury of the nongravid uterus and the pelvic organs occurs in the face of preexisting abnormalities; DPL demonstrates hemoperitoneum in these instances.⁶⁷ The uterus, the organ most commonly injured, is repaired with figure-eight sutures or a two-layer closure using slowly

Table 4 AAST Organ Injury Scales for Female Reproductive Tract

Injured Structure	AAST Grade	Characteristics of Injury	AIS-90 Score
Vagina*	I	Contusion or hematoma	1
	II	Superficial laceration (mucosa only)	1
	III	Deep laceration (into fat or muscle)	2
	IV	Complex laceration (into cervix or peritoneum)	3
	V	Injury to adjacent organs (anus, rectum, urethra, bladder)	3
Vulva*	I	Contusion or hematoma	1
	II	Superficial laceration (skin only)	1
	III	Deep laceration (into fat or muscle)	2
	IV	Avulsion (skin, fat, or muscle)	3
	V	Injury to adjacent organs (anus, rectum, urethra, bladder)	3
Nongravid uterus*	I	Contusion or hematoma	2
	II	Superficial laceration (< 1 cm)	2
	III	Deep laceration (≥ 1 cm)	3
	IV	Laceration involving uterine artery	3
	V	Avulsion or devascularization	3
Fallopian tube†	I	Hematoma or contusion	2
	II	Laceration < 50% of circumference	2
	III	Laceration ≥ 50% of circumference	2
	IV	Transection	2
	V	Vascular injury or devascularized segment	2
Ovary†	I	Contusion or hematoma	1
	II	Superficial laceration (depth < 0.5 cm)	2
	III	Deep laceration (depth ≥ 0.5 cm)	3
	IV	Partial disruption of blood supply	3
	V	Avulsion or complete parenchymal destruction	3
Gravid uterus*	I	Contusion or hematoma (without placental abruption)	2
	II	Superficial laceration (< 1 cm) or partial placental abruption (< 25%)	3
	III	Deep laceration (≥ 1 cm) in second trimester or placental abruption > 25% but < 50%; deep laceration in third trimester	3; 4
	IV	Laceration involving uterine artery; deep laceration (≥ 1 cm) with > 50% placental abruption	4; 4
	V	Uterine rupture in second trimester; uterine rupture in third trimester; complete placental abruption	4; 5; 4–5

AAST = American Association for the Surgery of Trauma; AIS-90 = Abbreviated Injury Score, 1990 version.

*Advance one grade for multiple injuries, up to grade III.

†Advance one grade for bilateral injuries, up to grade III.

absorbable sutures.⁶⁶ Avulsion of the uterine artery or extensive blast destruction of the uterus may necessitate hysterectomy.⁶⁴ When hysterectomy is necessary for trauma, the vaginal cuff should be left open to allow drainage of the operative bed.⁷³ Lacerations to the ovary or the fallopian tube are managed by primary closure or salpingo-oophorectomy if contralateral structures are normal.

After hysterectomy or repair of vaginal lacerations, a vaginal pack should remain in place for 24 hours. Hemorrhage caused by uterine injury has been treated with oxytocin,

which increases uterine tone and controls bleeding. Fertility after injury to the female reproductive organs is not well documented, but patients must be counseled about the possible adverse consequences of uterine and adnexal trauma.

Injuries to the Penis

Traumatic injuries to the penis are unusual, with variable etiology. Injury to the flaccid penis is rare, occurring mainly

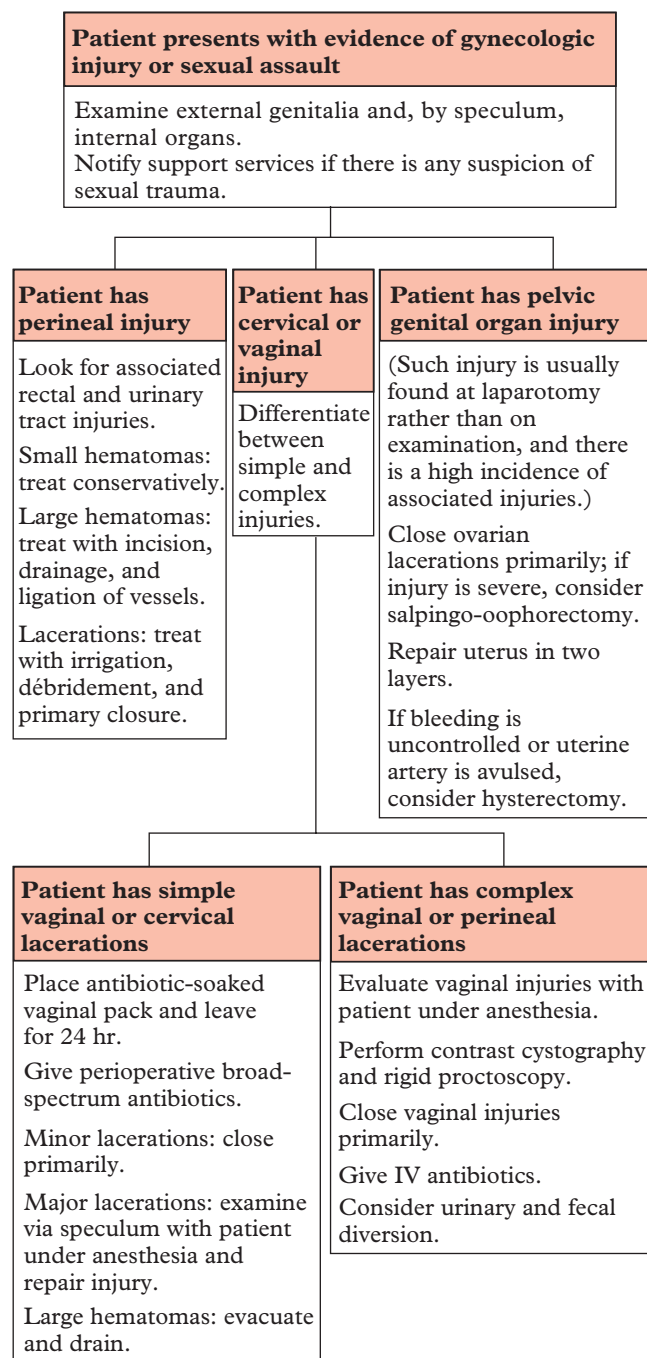


Figure 14 Algorithm outlining management of injuries to the female genitalia. IV = intravenous.

as a result of penetrating trauma and machinery accidents.^{58,74,75} However, the incidence of battlefield pelvic and genital organ injury has increased as a result of fragmentation devices and changing pattern of warfare. With the use of protective armor on the torso, 6% of contemporary genitourinary battlefield injuries affect the penis.^{76,77} Penile fracture is an uncommon injury of the tunica albuginea that occurs only with full penile rigidity, whereas penile amputation is a

devastating injury requiring immediate surgical treatment.^{78–81} Prompt operative treatment allows recovery of erectile function after most penile injuries [see Table 5]. Remarkably, in many cases, penile replantation successfully restores erectile capability.

INITIAL EVALUATION

Penile Fracture/Penetrating Injury

Missed intromission, acute bending of the penis, and a snapping or popping sound followed by acute pain and immediate detumescence are characteristic of penile fracture. Delayed presentation, attributable to embarrassment, is common. Penetrating injuries to the penis may result from deliberate attempts at mutilation, as well as from accidental firearm injury (typically occurring when a handgun goes off while in a man's pants pocket). Because of the pliability of the flaccid penis, entry and exit wounds may be complex. Penile swelling is usually limited to the shaft of the penis by the Buck fascia; scrotal and perineal ecchymosis develop if the deep investing fascia of the penis is disrupted. Imaging of the corpora cavernosa with contrast cavernosography has limited sensitivity and specificity and thus is not recommended.⁸² Associated urethral, scrotal, bladder, and rectal injuries must be excluded.

Inability to void, gross hematuria, and blood at the meatus all imply urethral injury and warrant further investigation. A uniform policy of exploration for all penile fractures and penetrating injuries will ensure that urethral injuries are identified. Passage of a catheter in the operative field with inspection of the involved urethra allows identification and primary repair of a lacerated or transected urethra.

Penile Amputation

Whether caused by a jealous lover or by self-mutilation, penile amputation is a catastrophic event.⁸³ Proper preservation of the amputated organ is critical for successful restoration of function. The amputated part should be placed on saline-soaked gauze inside a clean bag, which should then be sealed and placed inside a second bag containing ice slush.⁸¹ Cold ischemia times longer than 24 hours are acceptable and allow transport of the patient to tertiary centers, where replantation can be performed. Even at normal temperatures, replantation 16 hours after injury has been successful.⁸¹ Microsurgical repair techniques have certain advantages, including better preservation of the penile shaft skin and the possibility of a sensate glans and normal orgasmic function. However, astonishing results have also been reported with the conventional technique of corporal reattachment without microvascular reanastomosis of the dorsal neurovascular structures.

MANAGEMENT

Penile Fracture/Penetrating Injury

A circumferential subcoronal incision provides exposure after penile fracture and most penetrating injuries of the shaft and permits corporal and urethral repair. The superficial layers and skin are bluntly degloved back to the base of the penis. For deeper injuries, proximal to the suspensory ligament or in the crura, a penoscrotal or perineal incision is required to provide access to the corpus cavernosum. Rupture of the corpus cavernosum as a result of a fracture, a

Table 5 AAST Organ Injury Scales for Male Genitalia

Injured Structure	AAST Grade	Characteristics of Injury	AIS-90 Score
Scrotum	I	Contusion	1
	II	Laceration < 25% of scrotal diameter	1
	III	Laceration ≥ 25% of scrotal diameter	2
	IV	Avulsion < 50%	2
	V	Avulsion ≥ 50%	2
Testis*	I	Contusion or hematoma	1
	II	Subclinical laceration of tunica albuginea	1
	III	Laceration of tunica albuginea with < 50% parenchymal loss	2
	IV	Major laceration of tunica albuginea with ≥ 50% parenchymal loss	2
	V	Total testicular destruction or avulsion	2
Penis†	I	Cutaneous laceration or contusion	1
	II	Laceration of Buck fascia (cavernosum) without tissue loss	1
	III	Cutaneous avulsion, laceration through glans or meatus, or cavernosal or urethral defect < 2 cm	3
	IV	Partial penectomy or cavernosal or urethral defect ≥ 2 cm	3
	V	Total penectomy	3

AAST = American Association for the Surgery of Trauma; AIS-90 = Abbreviated Injury Score, 1990 version.

*Advance one grade for bilateral injuries, up to grade III.

†Advance one grade for multiple injuries, up to grade III.

stab wound, or a bullet wound is signaled by the presence of active bleeding and a defect in the fibrous tunica albuginea. Careful exploration and inspection of the corpus spongiosum are mandatory, even if urethrography shows no extravasation. Tunical ruptures caused by fracture are transversely oriented [see Figure 15] and sometimes extend behind the spongiosum; this structure may have to be mobilized and retracted for adequate visualization of the injury.

The tunica albuginea is closed with interrupted 3-0 slowly absorbable sutures. Débridement and curettage have occasionally been used in this setting but generally are reserved for late presentations. Skin closure is possible with most penetrating injuries to the penis. The extensive vascular supply to the skin is rarely compromised. Interrupted chromic sutures provide a cosmetic closure and allow drainage of residual blood between the sutures. A lightly compressive dressing is sufficient; tight wraps are to be avoided because they may lead to necrosis of swollen shaft skin. Catheter drainage is mandatory if urethral injury is present. Sexual intercourse is contraindicated for 1 month after penile injury.

Penile Amputation

Microsurgical replantation differs from simple corporal reattachment in that the neurovascular structures are reanastomosed in addition to the urethra and the tunica albuginea. With corporal reattachment, a spatulated end-to-end urethral anastomosis is performed with interrupted absorbable sutures over a urethral catheter. The adventitia of the corpus spongiosum is reapproximated in a second layer, and the tunica albuginea and its septum are then connected. The restored cavernosal blood flow preserves the distal corpora, the glans,

and the urethra. Ischemic skin loss is expected without reanastomosis of the dorsal artery and vein. When microsurgical techniques are available, the dorsal nerves, the dorsal arteries, and the deep dorsal vein are each reanastomosed with fine nonabsorbable sutures. Meticulous closure of the superficial tunica dartos and the skin completes the repair.

Temporary ectopic replantation of the penis has been described in cases where the perineum is heavily contaminated or too extensively damaged for immediate replantation.⁸⁴ Postoperative care includes urinary diversion, bed rest, anticoagulation (in selected cases), hydration, and monitoring of arterial flow in the distal penis.

Injuries to the Scrotum and Testes

INITIAL EVALUATION

Scrotal trauma may result in testicular injury or genital skin loss [see Table 5]. Because blunt injuries to the testicle are difficult to recognize, high-resolution ultrasonography has become a key element in the evaluation of scrotal trauma [see Figure 16]. When a straddle injury or penetrating mechanism suggests the possibility of urethral injury, retrograde urethrography is indicated.

Penetrating scrotal injuries commonly involve not only the testis but also the corpora cavernosa, the urethra, and the spermatic cord. Ultrasonography is useful to ascertain the integrity of the arterial inflow to the testis.⁸⁵ The excellent blood supply of the scrotal skin allows most penetrating injuries to be débrided and closed. Even simple bite injuries can be irrigated and closed with appropriate antibiotic coverage. Exceptions to this general rule include complex contaminated



Figure 15 Shown is a case of penile fracture. A linear tear in the tunica albuginea can be seen (arrow).

human and animal bites, which are left open and are treated with intravenous antibiotics and local wound care (or débridement in cases of severe soft tissue infection).⁸⁶

Rupture of the testicle is often immediately painful, with rapid onset of swelling. Falls, straddle injuries, and direct blows are common mechanisms of injury.⁸⁷ However, seemingly minor degrees of trauma may be associated with delayed onset of pain; in this scenario, testicular torsion must be included in the differential diagnosis. Physical signs of rupture include scrotal swelling, tenderness, and ecchymosis. Injury to the scrotal wall or the tunica vaginalis may cause significant swelling without rupture of the tunica albuginea of the testis; pelvic hematoma caused by fracture can result in massive scrotal swelling. For these reasons, blunt injury to the scrotum should be evaluated by ultrasonography unless the findings from the physical examination are normal.

The ultrasonographic characteristics of testicular rupture [see Figure 17] include loss of normal homogeneity of the testicular parenchyma, loss of continuity of the tunica albuginea, and intraparenchymal hematoma.⁸⁵ A discrete break in the tunica is relatively rare. In cases of pelvic fracture with massive scrotal edema, ultrasonography can document the integrity of the testis and allow conservative management of

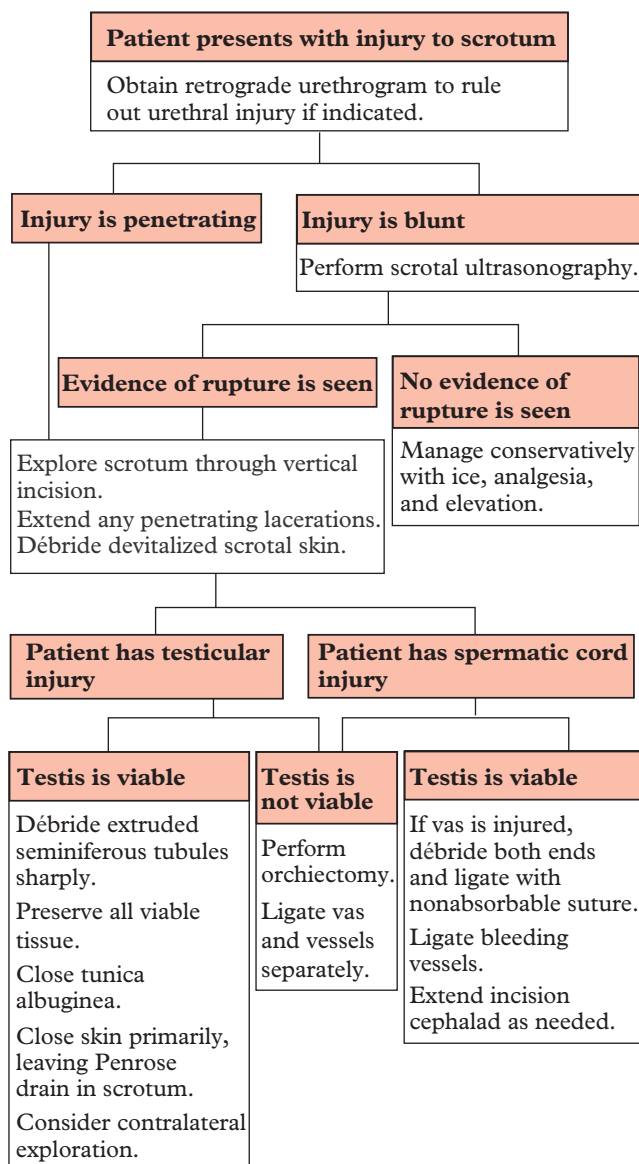


Figure 16 Algorithm outlining management of injury to the scrotum or testes.

the swelling. If rupture is not documented, treatment with ice packs, analgesics, and elevation allows resolution of swelling.

MANAGEMENT

Exploration of the scrotum through a vertical incision allows inspection of the scrotal contents; when spermatic cord injury is discovered, the incision can be extended cephalad to the groin. The goal is preservation of testicular parenchyma for endocrine and cosmetic purposes; normal sperm production and transport are not expected after repair of rupture. Clots and extruded seminiferous tubules are débrided with scissors to allow closure of the tunica albuginea over the edematous parenchyma. A continuous 3-0 slowly absorbable suture is sufficient.

When spermatic cord injury is detected, the first priority is determination of the viability of the testis. A small incision into

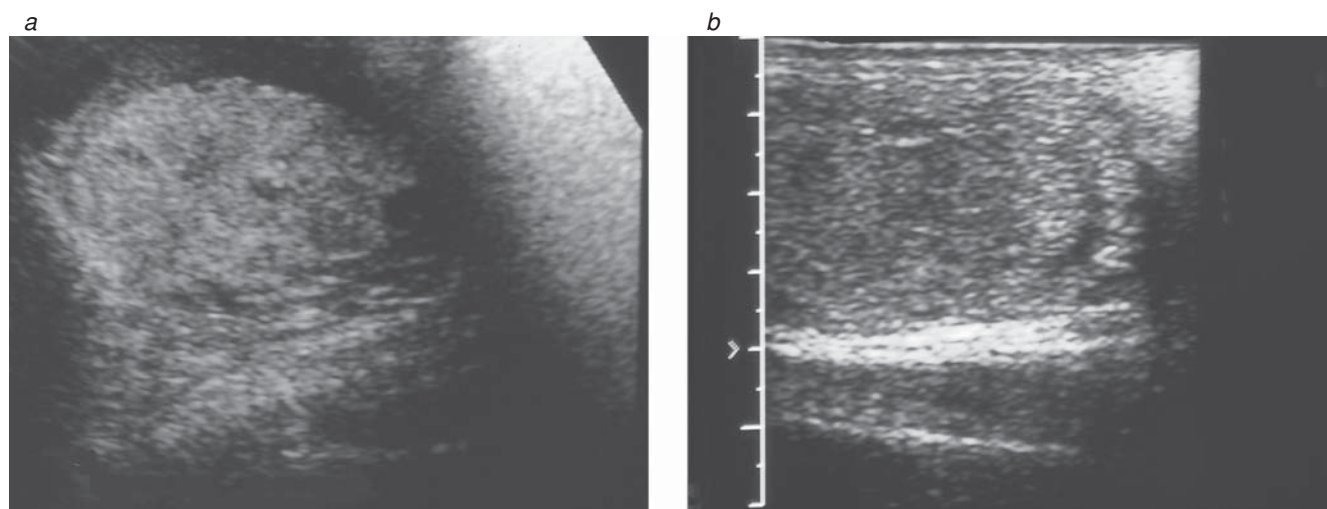


Figure 17 (a) Ultrasonogram of ruptured testes shows intraparenchymal hematoma and heterogeneous echotexture. (b) Ultrasonogram of ruptured testes shows indistinct testicular contour and abnormal echotexture.

the tunica albuginea should cause some bleeding; if the testis is cyanotic and does not bleed when cut, orchiectomy should be performed. If only the vas deferens or spermatic vessels are injured, the testis will remain viable. Ligation of the spermatic vessels is performed in the standard fashion; if vasal ligation is necessary, use of nonabsorbable suture with long tails enables later identification for reconstruction if infertility ensues.

Scrotal skin lacerations can be closed primarily in most instances. Exceptions arise if there is a prolonged delay between injury and definitive care or if grossly contaminated wounds are associated with rectal injuries. Hemostasis should be meticulous. Interrupted suture closure of the tunica dartos and skin in separate layers, with a Penrose drain brought out through a separate dependent stab wound, limits postoperative hematoma formation. Fluffed gauze should be used for dressing, and a scrotal supporter should be used to keep the scrotum elevated. The Penrose drain is removed on postoperative day 1. There are no major restrictions to activity after scrotal surgery, and patients can be discharged once they have recovered from associated injuries.

Scrotal avulsion can be devastating and must be differentiated from complex lacerations. Skin avulsed by shear forces in MVCs may be suitable for cleansing and preparation for full- or split-thickness grafts; however, when high-speed rotating machinery is the mechanism, as when clothing and skin are caught in a power takeoff, this approach is not recommended. The intrinsic microvasculature of the skin is probably damaged. Scrotal skin loss caused by burns or electrical or mechanical injury usually spares the testis, which has a separate blood supply. Conservative débridement is possible if there is no infection, but the demarcation between viable and nonviable tissue should be identified before extensive débridement.⁸⁸ Management depends on the amount of skin remaining. Options include primary closure, immediate coverage with meshed split-thickness skin grafts, and placement of the testes in subcutaneous pouches in the thigh.

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12 INJURIES TO THE PELVIS AND EXTREMITIES

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Injuries to the pelvis and extremities are common, occurring in approximately 85% of patients who sustain blunt trauma. Improper management can have devastating consequences. Major long bone fractures are a sign that substantial force has been applied to the body, and they are frequently associated with torso injuries. Trauma to the pelvis or the extremities can result in injuries that are potentially life-threatening (e.g., pelvic disruption with hemorrhage, major arterial bleeding, and crush syndrome) or limb-threatening (e.g., open fractures and joint injuries, vascular injuries and traumatic amputation, compartment syndrome, and nerve injury secondary to fracture dislocation). In this chapter, we outline the basic knowledge the general or trauma surgeon requires for initial management of injuries to the pelvis, the extremities, or both.

Evaluation and Assessment

INITIAL PRIORITIES

In the surgical management of musculoskeletal injury, the priorities are (1) to save the patient's life, (2) to save the endangered limb, (3) to save the affected joints, and (4) to restore function; these priorities are pursued in accordance with advanced trauma life support (ATLS) guidelines.¹ The musculoskeletal injury that it is most important to identify during the primary survey is an unstable pelvic injury, which can lead to massive and life-threatening internal bleeding. If manual compression-distraction of the iliac crests elicits abnormal movement or pain, a pelvic fracture is probably present. In this case, a prefabricated splint or sheet wrap is applied around the pelvis to reduce the intrapelvic volume, and the legs are wrapped together to induce internal rotation of the lower limbs. Grossly deformed extremities are reduced by means of manual traction to reduce motion and to enhance the tamponade effect of the muscles. In the initial phase, control of hemorrhage from deep soft tissue lesions and vessel injury is best achieved with direct compression.

During the secondary survey, the rest of the musculoskeletal system is assessed to identify fractures, dislocations, and soft tissue injuries. It is advisable to perform a tertiary survey 24 to 48 hours after admission to detect any missed injuries, especially in multiply injured patients whose condition at admission precluded the completion of a full secondary survey.²

IMAGING

Diagnostic imaging usually begins with conventional x-rays. The pelvis is imaged during the primary survey, but x-rays of the extremities typically are obtained only after life-threatening injuries have been corrected and the patient's general condition is such that the surgeon can afford to spend the time necessary to complete extremity and spine imaging (which is often as long as several hours). Conventional x-rays of the affected limb are guided by the injury mechanism, the history, and the physical examination and

are always done in two planes (anteroposterior [AP] and lateral). Long bones should be visualized over their entire length, including the adjacent joints. After reduction of fractures and dislocations, x-rays should be repeated, unless no time is available (e.g., because of the presence of limb-threatening vascular injury).

Computed tomographic scanning is frequently used as an adjunct to conventional x-rays, especially in patients with periarticular fractures and dislocations or pelvic fractures. Axial, sagittal, coronal, and three-dimensional reconstructions allow exact determination of the extent of the fracture and the position of fracture fragments. CT scanning also helps in the process of deciding between operative and nonoperative treatment, and it facilitates preoperative planning when a surgical therapy is adopted. In addition, CT scanning may play a role in detecting bleeding sources in the pelvis, though hemodynamic instability or ongoing blood loss in the presence of a pelvic fracture usually is best managed with immediate angiography rather than CT.

Magnetic resonance imaging can be helpful with complex malunions, soft tissue injuries, and certain fracture types (e.g., scaphoid fracture).³ Bone scintigraphy and ultrasonography are less frequently employed in the setting of pelvic and extremity trauma. Triphasic bone scanning is primarily used to detect osteomyelitis, avascular necrosis, and malignant lesions, whereas ultrasonography is mostly used to assess soft tissue injuries.

CLASSIFICATION OF INJURIES

Fracture

Of the many existing fracture classification systems, the one that is most frequently used is the system developed by two Swiss organizations, the Association for Osteosynthesis (AO) and the Association for the Study of Internal Fixation (ASIF) [see Figure 1].⁴ The AO-ASIF fracture classification system serves both as a means of documenting fractures (e.g., for research purposes) and as an aid to the surgeon in assessing the severity of the fracture and determining the appropriate treatment.

In the AO-ASIF system, any given extremity fracture can be described in terms of a five-place alphanumeric designation [see Figure 1a]. The first place represents the bone injured. The second represents the segment affected by the injury (proximal, middle or diaphyseal, or distal, with malleolar a fourth category that is sometimes employed). The third represents the fracture type (A, B, or C). In middle-segment long bone fractures, type A refers to simple fractures with two fragments, type B refers to wedge fractures with contact between the main proximal and distal fragments after reduction, and type C refers to complex fractures without contact between the main fragments after reduction [see Figure 1b]. In proximal and distal long bone fractures, type A refers to extra-articular fractures with the articular surface intact, type B refers to partial articular fractures in which there is some articular involvement but part of the articular surface remains attached to the diaphysis, and type C refers to complete articular fractures in which

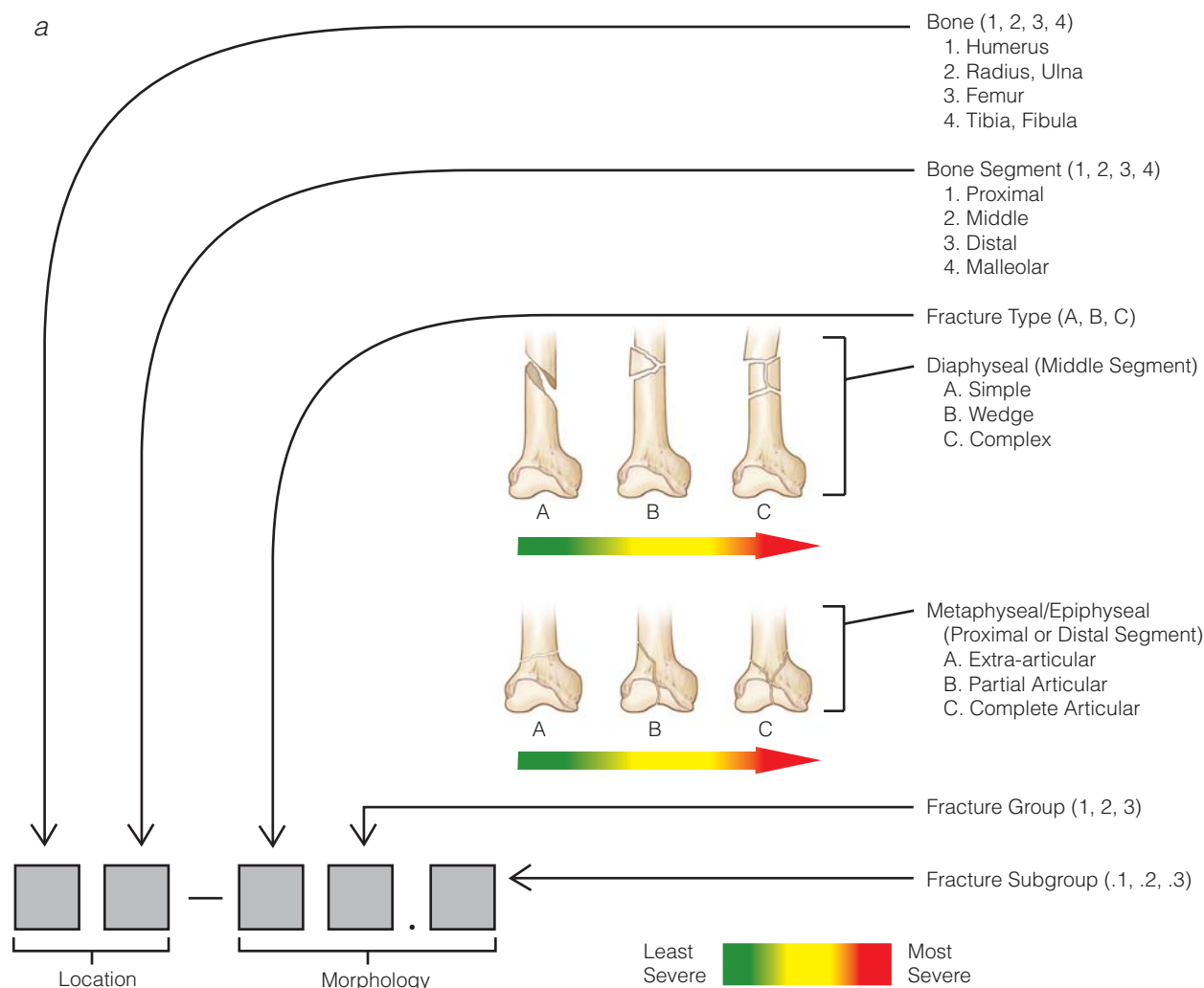


Figure 1 (a) Shown is the AO-ASIF classification system for fractures, as expressed in a five-place alphanumeric designation. (b) Illustrated are the three types of diaphyseal long bone fractures, along with the three groups into which each type is divided. (c) Depicted are the three types of metaphyseal or epiphyseal long bone fractures.

the articular surface is disrupted and completely separated from the diaphysis [see Figure 1c]. The fracture types are then further subdivided into three groups (1, 2, or 3), represented by the fourth place, and (mainly for scientific purposes) three subgroups (.1, .2, or .3), represented by the fifth place.

For the fracture types, groups, and subgroups, increasing letter and number values represent increasing severity, as determined by the complexity of the fracture, the difficulty of treatment, and the prognosis. Thus, an A1 fracture is the simplest injury with the best prognosis, and a C3 fracture is the most complex injury with the worst prognosis. For practical purposes, the first four places of the AO-ASIF alphanumeric designation are usually sufficient for treatment planning; the fifth (the subgroup) adds little to the process.

Pelvic ring and acetabular fractures are classified in essentially the same fashion [see Management of Pelvic and Acetabular Injuries, below].

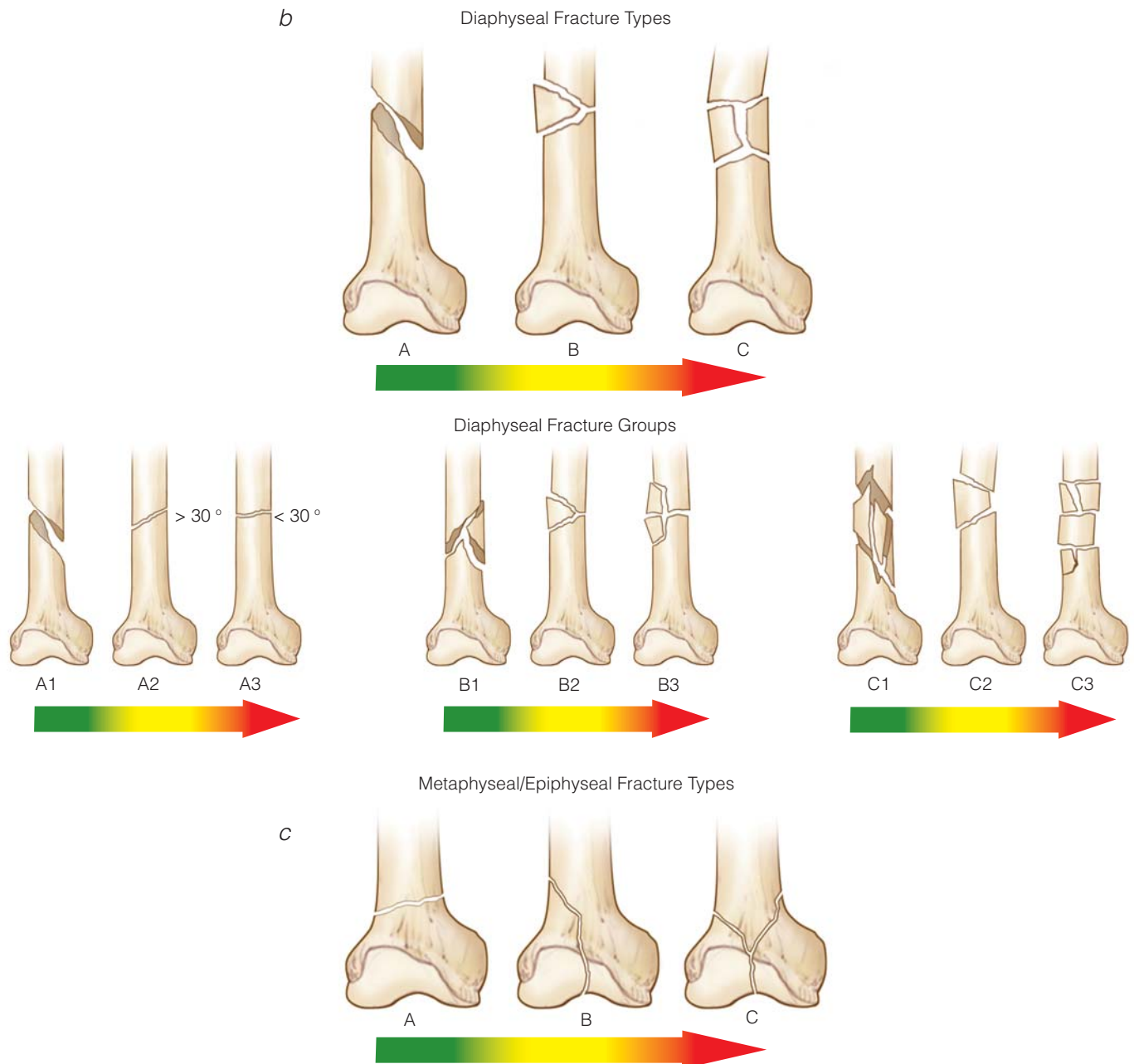
Soft Tissue Injury

The type of soft tissue injury present and its extent are determined by the type of insult sustained (e.g., blunt, sharp, or crush), the degree and direction of the force applied, the area affected, and

the extent of contamination (if any). With closed injuries, the intact skin prevents direct assessment of the subcutaneous tissues, and as a result, soft tissue injuries are frequently underestimated. In the emergency department, a single inspection is made, and the wound is covered by a sterile dressing; at this point, it may be helpful to take pictures with a digital camera. Exact grading of the soft tissue injury is best done in the operating room by an experienced surgeon who can also decide on a treatment plan.

The system most commonly used for classification of open fractures is the one developed by Gustilo and Anderson, which divides these fractures into three types as follows [see Figure 2]^{4,5}:

1. Type I: the wound is smaller than 1 cm and results from an inside-out perforation, with little or no contamination; the fracture type is simple (type A or B).
2. Type II: the skin laceration is larger than 1 cm but is associated with little or no contusion of the surrounding tissues; there is no dead musculature, and the fracture type is moderate to severe (B or C).
3. Type III: extensive soft tissue damage has occurred, with or without severe contamination, frequently in association with compromised vascular status; the fracture is highly unstable (type C) as a result of comminution or segmental defects. Type



III fractures are further divided into the following three sub-categories:

- a. IIIA: adequate soft tissue coverage of the bone is still possible.
- b. IIIB: extensive soft tissue loss occurs with periosteal stripping and exposed bone; contamination is usually massive.
- c. IIIC: an arterial injury is present that requires repair; any open fracture accompanied by such an injury falls into this category, regardless of fracture type.

Closed fractures are less frequently classified according to the type and extent of soft tissue injury, though this does not mean that such injury is not an important consideration with closed fractures. The classification system most commonly used for closed fractures is that of Tscherne, which recognizes the following four grades:

1. Grade 0: soft tissue injury is absent or minor; the fracture type is simple.
2. Grade I: superficial abrasion or contusion is present as a result

of pressure applied by the fragment from the inside; the fracture type is simple or moderate.

3. Grade II: deep contaminated abrasions and localized skin or muscle contusion are present as a consequence of direct trauma, possibly leading to compartment syndrome; the fracture type is moderate to severe.
4. Grade III: extensive skin contusions, destruction of musculature, and subcutaneous tissue avulsion have occurred; the fracture is severe and mostly comminuted.

Timing and Planning of Intervention

In multiply injured patients, the timing of operative treatment of injuries to the pelvis and extremities depends both on the condition of the patient and on the particular combination of skeletal and soft tissue injuries sustained [see Table 1]. In such cases, the threshold for adoption of a damage-control strategy [see Damage-Control Surgery, below] to minimize operating time and tissue

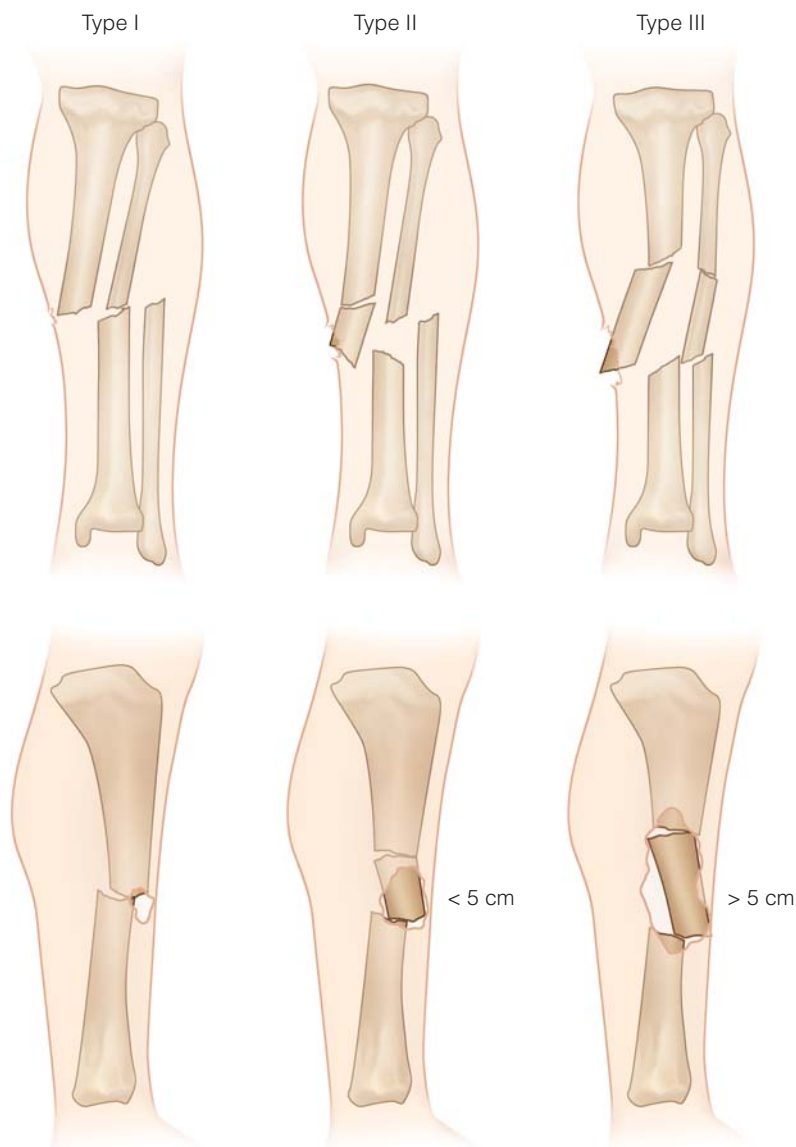


Figure 2 Illustrated is the Gustilo-Anderson classification system for open fractures.

insult should be low.^{6,7} The performance of multiple definitive osteosyntheses is an option only in patients who have been successfully resuscitated (as indicated by stable hemodynamic status without a need for inotropes; absence of hypoxia, hypercapnia, and acidosis; normothermia; normal coagulation parameters; and normal diuresis).

In other cases, the timing and extent of operative treatment of musculoskeletal injuries may be more complex. Generally, if open reduction and internal fixation are indicated, the sooner the operation is performed, the better. With early operation, fracture surfaces are more easily cleaned of blood clots and other material, and reduction is facilitated by the absence of prolonged dislocation and shortening. After 6 to 8 hours, swelling develops, making both the operation and the subsequent closure more difficult and thereby increasing the risk of infection and other wound complications. There are some cases, however, in which it might be preferable to postpone a complex articular reconstruction in order to ensure that the surgical team is optimally prepared. If, for any reason, significant swelling precludes a definitive operation, it is usually safer to stabilize the fracture temporarily (e.g., with splinting or external fixation), then wait 5 to 10 days for the swelling to subside. Temporary stabilization usually allows the surgeon to achieve a

reasonable provisional reduction; however, complete joint dislocations are not acceptable. Clinically, sufficient reduction of swelling has occurred when the skin has regained its creases and is wrinkled over the operative site. Early definitive surgery may also be contraindicated when abrasion or degloving injury is present at the fracture site on admission.

Swelling is less of a problem with shaft fractures that will be treated with intramedullary nailing. If, however, it is not possible to perform nailing within 24 to 48 hours after the injury, it is better to postpone the operation for 7 to 10 days; patients operated on between days 3 and 7 are at higher risk for the acute respiratory distress syndrome (ARDS).^{8,9} If the procedure must be delayed for more than 2 to 3 weeks (e.g., because of sepsis and organ failure), reconstruction of bones and joints will be substantially more difficult. If such delay leads to suboptimal axial alignment and nonanatomic reconstruction of the articular surface, the long-term prognosis will be worse.

Thorough preoperative planning is necessary for any operation done on the musculoskeletal system. Depending on the procedure to be performed, logistical considerations may include availability of the appropriate operating team, availability of the correct operating table, availability of the specific instruments needed, avail-

ability of the appropriate implants, and availability of intraoperative imaging. Technical considerations include the operative approach to be followed and the fixation method to be used, which are determined on the basis of an understanding of the extent of the injuries and a detailed knowledge of the anatomy in the area to be exposed. For example, awkward placement of fixator pins could seriously obstruct soft tissue reconstruction if the pins are in the area that should be used for a soft tissue flap. Before operation, the correct operative site is verified (with the patient awake) and marked with a permanent marker pen. A drawing of the planned reduction maneuvers and fixation techniques may be helpful for the surgeon while also serving as an educational tool for the assisting team members. Correct documentation is important for both medical and legal reasons.

DAMAGE-CONTROL SURGERY

Immediate and complete care of all fractures, dislocations, and soft tissue injuries may seem the ideal treatment strategy for patients with musculoskeletal injuries. However, this is not always the case. Major trauma leads to a systemic inflammatory response syndrome (SIRS) characterized by increased capillary leakage, high energy consumption, and a hyperdynamic hemodynamic state. Especially in the setting of severe single-organ injury or multiple injuries, the physiologic and immunologic impact of extend-

Table 2 Goals of and Indications for Damage-Control Surgery in Management of Pelvic and Extremity Trauma

Goals	Control of hemorrhage Control of contamination Removal of dead tissue and prevention of ischemia-reperfusion injury Facilitation of ICU treatment Pain relief
Indications	Clinical parameters Multiple trauma (ISS > 15) and additional chest trauma Pelvic ring injuries with exsanguinating hemorrhage Multiple trauma with abdominal or pelvic injuries and hemorrhagic shock (BP < 90 mm Hg) Radiographic findings indicating (bilateral) lung contusion Femoral fractures in polytrauma patient Polytrauma in geriatric patient Resuscitation, operation, or both expected to last > 90 min Physiologic parameters Severe metabolic acidosis (pH < 7.20) Base deficit (< -6 mEq/L) Hypothermia (T° < 35° C) Coagulopathy (PT > 50% of normal) Multiple transfusions

ISS—Injury Severity Score PT—prothrombin time

Table 1 Time Frames for Operative Treatment of Pelvic and Extremity Trauma*

Category I: immediate	(Imminent) hemodynamic instability (e.g., pelvic fracture) Neurovascular injury with compromised vitality of extremity (Imminent) compartment syndrome
Category II: urgent (within 6–12 hr)	Open fractures (increased risk of infection) Joint dislocations that cannot be reduced in ED Primary stabilization (e.g., external fixation) in multiply injured patients who are hemodynamically stable Femoral neck fractures in patients < 65 yr (to prevent femoral head necrosis) Long bone fractures (to prevent complications and immobilization) Severe soft tissue injury (e.g., degloving caused by rollover accident) Closed fractures with compromised skin Dislocated talar neck fractures
Category III: semiurgent (within 12–24 hr)	Femoral neck, intertrochanteric, and subtrochanteric fractures Closed reduction of fractures in children Treatment of soft tissue injuries (e.g., to tendons of wrist and hand) Closed fractures that benefit from early treatment (e.g., to prevent swelling with ankle fractures) Spine fractures that are unstable or associated with neurologic deterioration Wound debridement and irrigation or washout
Category IV: semielective (within 24–72 hr or delayed)	Achilles tendon ruptures Stable spine fractures Other fractures Revision procedures other than those done for infection

*These time frames are general guidelines and may be modified in accordance with individual patient parameters (e.g., physiologic condition, soft tissue injury, and fracture type) and local preferences.

ed surgical procedures on the patient's general condition can increase the risk of the multiple organ failure syndrome (MODS), ARDS, and other complications. Balanced against this risk is the understanding that early fracture fixation in polytrauma patients is beneficial in terms of mortality and morbidity. Improved understanding of the physiologic response to major trauma over the past decade has led to the approach known as damage-control surgery (DCS) or staged surgery, the purpose of which is to keep the patient from having to deal with the "second hit" imposed by the operation right after experiencing the "first hit" imposed by the initial trauma.

Currently, DCS is widely promoted for management of intra-abdominal, vascular, and musculoskeletal injuries. It can be divided into three main phases: (1) a resuscitative phase, (2) an intensive care phase, and (3) a reconstructive phase.¹⁰ The initial focus is on control of bleeding, contamination, and temporary stabilization of fractures; time-consuming reconstructions and osteosyntheses are avoided at this point. At a later stage, when vital functions have been restored, definitive reconstructions are performed during one or more planned reoperations.

The decision whether to employ DCS should be made before the operation to avoid a scenario in which the patient's general condition of the patient deteriorates seriously during a difficult operation (e.g., a complex femoral nailing procedure) [see Table 2]. An experienced and judicious surgeon will make an appropriate decision about DCS more often than not. If, as sometimes happens despite the surgeon's best efforts, the patient's condition does show serious deterioration unexpectedly during operation, the surgeon should immediately choose a bailout option, usually involving external fixation.

As applied to musculoskeletal trauma, DCS begins with debridement of open wounds and irrigation with pulsed lavage (so-called washout). Amputation of the injured limb or limbs is considered if it appears potentially lifesaving [see Management of Life-Threatening or Limb-Threatening Injuries, Mangled Extremity, below]. During the initial debridement, osteochondral

fragments in open joint fractures are retained—provided that they are not severely contaminated—to allow later reconstruction of the joint surface. Dislocations and diaphyseal fractures are reduced and stabilized with simple external fixator frames (if necessary, placed so as to span the adjacent joint or joints), and wounds are provisionally closed. Fixator pins are placed through stab incisions in safe zones. Fractures need not be reduced anatomically under image intensifier control; the only goals at this point are to restore length and align long bone fractures and joints, to reduce contamination, and to enable postoperative wound management in the intensive care unit while definitive treatment is pending. The more complex the fixator frame, the more time-consuming its application usually is. Muscle compartments believed to be at risk for compartment syndrome are widely decompressed.

At all times, the operating surgeon must keep the goals of DCS clearly in mind. The main aim of this strategy is not necessarily a nice-looking postoperative x-ray showing parallel fixator pins and a perfectly reduced tibia; rather, it is the survival of the patient in stable physiologic condition. Depending on the severity of the injuries, the reconstructive procedures likely to be performed, and the availability of specialists or subspecialists, consultation with a plastic surgeon during the initial operation may be advisable to optimize operative and logistical planning.^{6,7}

Careful attention must be paid to the logistical aspects of DCS. As soon as the decision for DCS is made, OR personnel should be notified of the type of procedures to be performed and the implants required. It may be helpful to have a dedicated DCS equipment trolley with all the materials and equipment necessary for the first hour.¹¹ Once the patient and the operating team are in the OR, the injuries sustained, the operative plan, and the injuries (known or suspected) that need special attention (e.g., a small pneumothorax) are written down or sketched on a whiteboard so that all persons present in the OR know what is to be done.

During the operation, the surgeon should stay in close contact with the anesthesiologist regarding the condition of the patient and the procedure currently under way. If operative procedures are required in more than one organ system (e.g., laparotomy and external fixation of the femora), they should, whenever possible, be performed simultaneously by multiple teams working together. The end of the procedure should be announced well ahead of time so that the anesthesiologist can take the precautions necessary for transport of a potentially unstable patient and so that the ICU can be notified of the patient's arrival. In this way, unnecessary waiting times in the OR can be kept to a minimum.

The second phase of DCS is restoration of vital functions in the ICU. This phase is crucial for ensuring that the patient is fit to undergo a second procedure.¹⁰ Close cooperation between surgeon and critical care physician is required to outline an aggressive strategy for ventilation, circulatory support, and reversal of hypothermia, coagulopathy, acidosis, and other abnormalities. Administration of large volumes of fluid will be necessary as a consequence of massive tissue swelling and bowel edema. Cardiac monitoring with central venous access should usually be employed. Application of external fixators allows the nursing staff to place the patient in the position that is most suitable for intensive care of head, chest, and abdominal injuries, while still allowing wound inspection and dressing changes as required. During this phase, imaging studies may be performed (or, if already performed, repeated) to allow planning for repeated washouts and definitive reconstructive procedures.

The third phase in the DCS sequence is the performance of one or more planned reoperations. This usually takes place at least 24

to 48 hours after the initial procedure, when the patient is stable and normothermic and has normal or near-normal coagulation parameters.¹⁰ Subsequent visits to the OR are used to continue wound debridement and coverage and to exchange external fixators for definitive fixation (e.g., with intramedullary nails).^{12,13} During these operations, multiple teams can work simultaneously on the repair of abdominal, musculoskeletal, and other injuries. The period from postinjury day 5 to day 10 is often referred to as the window of opportunity for reconstruction of intra-articular or periarticular fractures and of upper-limb fractures.

Management of Life-Threatening or Limb-Threatening Injuries

LIFE-THREATENING PELVIC TRAUMA

Pelvic fractures are frequently associated with significant hemorrhage, not only because of the fracture itself but also because pelvic trauma is often accompanied by serious injuries to other parts of the body (e.g., the chest or the abdomen). Significant arterial hemorrhage is present in approximately 25% of patients with unstable pelvic fractures.^{4,5,10,14,15} Bleeding from pelvic trauma can be quite severe: as much as 4 L of blood may accumulate in the retroperitoneal space. Whether hemorrhagic shock is associated with certain fracture types remains a matter of debate, but there is certainly a link between the severity of the pelvic injury and the incidence of hemorrhagic shock. Hemorrhagic shock in patients with pelvic fracture strongly influences outcome and necessitates immediate evaluation and treatment.

Hemorrhage may originate either from within the fractured pelvic bones themselves or from torn arteries and veins in the pelvis, which are in close proximity to the bony structures of the pelvis. In particular, the presacral venous plexus and the internal iliac arteries and side branches may be lacerated. The most commonly injured anterior branches of the internal iliac artery are the internal pudendal artery and the obturator artery, whereas the most commonly injured posterior branches are the superior gluteal artery and the lateral sacral artery.^{16,17}

Given that bleeding in pelvic fracture patients can occur in other body compartments besides the pelvis and can be arterial as well as venous, it is of the utmost importance to identify its source and, ideally, determine its nature as soon as possible. This information is crucial in determining what the next steps in management should be [see Figure 3].

The first step after diagnosing a pelvic fracture should be the immediate application of some type of external stabilization device (e.g., a sheet wrap or a device such as the Pelvic Binder [Pelvic Binder Inc., Dallas, Texas]) [see Figure 4].¹⁸ The rationale behind this step is that approximating the fractured bones and thereby decreasing the volume of the pelvis may reduce blood loss, particularly from the fractured bones and the lacerated venous plexus. In addition, stabilization may minimize further damage to blood vessels and prevent dislodgment of recent clots. It is doubtful, however, whether this procedure actually reduces arterial hemorrhage to a significant degree.

In hemodynamically unstable patients with clinical signs of a pelvic fracture, the next step (immediately after—or, preferably, while—x-rays of the chest, the pelvis, and the cervical spine are obtained according to ATLS protocols) should be the FAST (focused assessment for sonographic evaluation of the trauma patient) to rule out a significant intra-abdominal bleeding source. If the FAST is negative and no other obvious sources of hemorrhage (e.g., chest or extremities) are found, the pelvis is the most

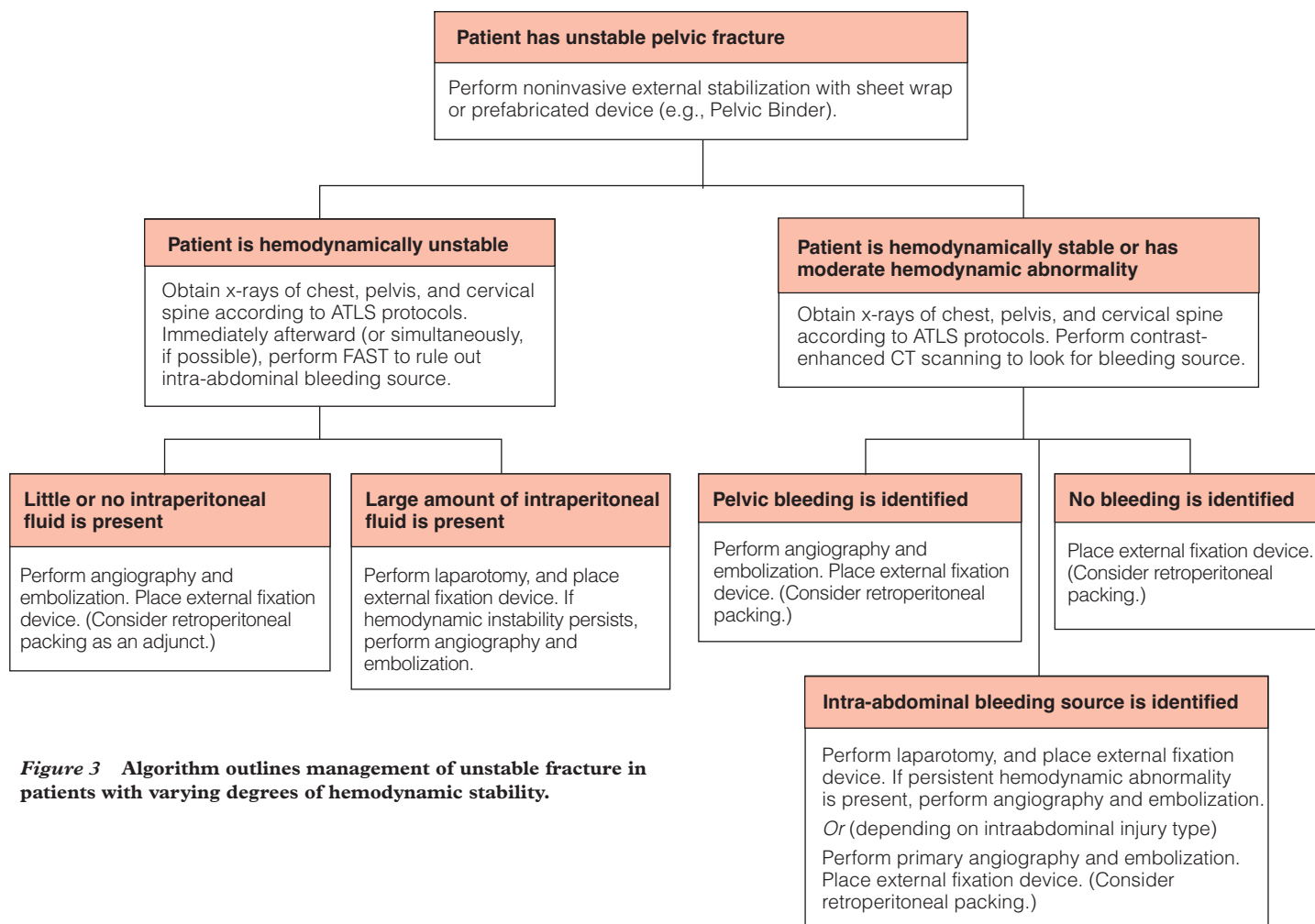


Figure 3 Algorithm outlines management of unstable fracture in patients with varying degrees of hemodynamic stability.

likely source of the bleeding. The question then arises whether the pelvic hemorrhage is predominantly arterial or venous. An arterial bleeding source in the pelvis is found in 73% of hypotensive patients who do not respond to initial fluid resuscitation.¹⁹

Contrast-enhanced CT scanning is extremely helpful in determining the presence of arterial hemorrhage in cases of pelvic fracture, but it can be performed only if the patient is stable enough to undergo the time-consuming transfer to the imaging suite. If a CT scanner is available in the shock room, it may be possible to extend the use of this modality to unstable patients. Extravasation of contrast medium, a large retroperitoneal hematoma, or abrupt cutoff of an artery on CT indicates that angiographic embolization is necessary. Contrast extravasation (so-called contrast blush) is a particularly good predictor of arterial hemorrhage necessitating embolization, having a sensitivity and specificity of well over 80%.²⁰ Thus, CT is an ideal means of identifying patients who should be treated with angiographic embolization and ideally should be performed in all pelvic fracture patients who are stable enough to undergo this procedure.

Arterial hemorrhage should preferably be treated by angiographic embolization, which has shown excellent results in current studies [see Table 3].^{21,22} Several authors have argued that in unstable patients, angiographic embolization should be done immediately, before operative placement of an external fixation device, because the chance of finding an arterial bleeding source is high and because the duration of the interval between arrival in the ED

and the performance of embolization strongly influences outcome. Angiographic embolization with gel foam or coils can almost always be performed via the common femoral artery approach, even with a sheet wrap or an external fixation device in place. Success rates exceed 90%, and major complication rates are below 5%. This technique does, however, require a skilled, experienced, and permanently available interventional radiology service.

In patients with unstable fractures, venous hemorrhage is treated with operative placement of an external fixation device. This measure requires specific expertise on the part of the trauma surgeon; in experienced hands, it should take no longer than 20 minutes to perform. Patients with more severe pelvic fractures (e.g., AO-Tile type B and C fractures and higher grades of lateral compression and anteroposterior compression fractures [see Management of Pelvic and Acetabular Injuries, Pelvic Ring, below]) probably benefit most from this procedure. Retroperitoneal packing may be employed as an adjunct to external fixator placement.²³ It is unlikely that external fixation has a significant impact on arterial hemorrhage; consequently, it is vital to decide whether angiographic embolization should precede placement of an external fixation device in the OR.

The optimal strategy for controlling bleeding in patients with life-threatening pelvic injuries remains subject to debate.^{24,25} We favor a prominent role for CT scanning and angiographic embolization, whereas others favor more liberal use of surgical retroperitoneal packing of the pelvis.

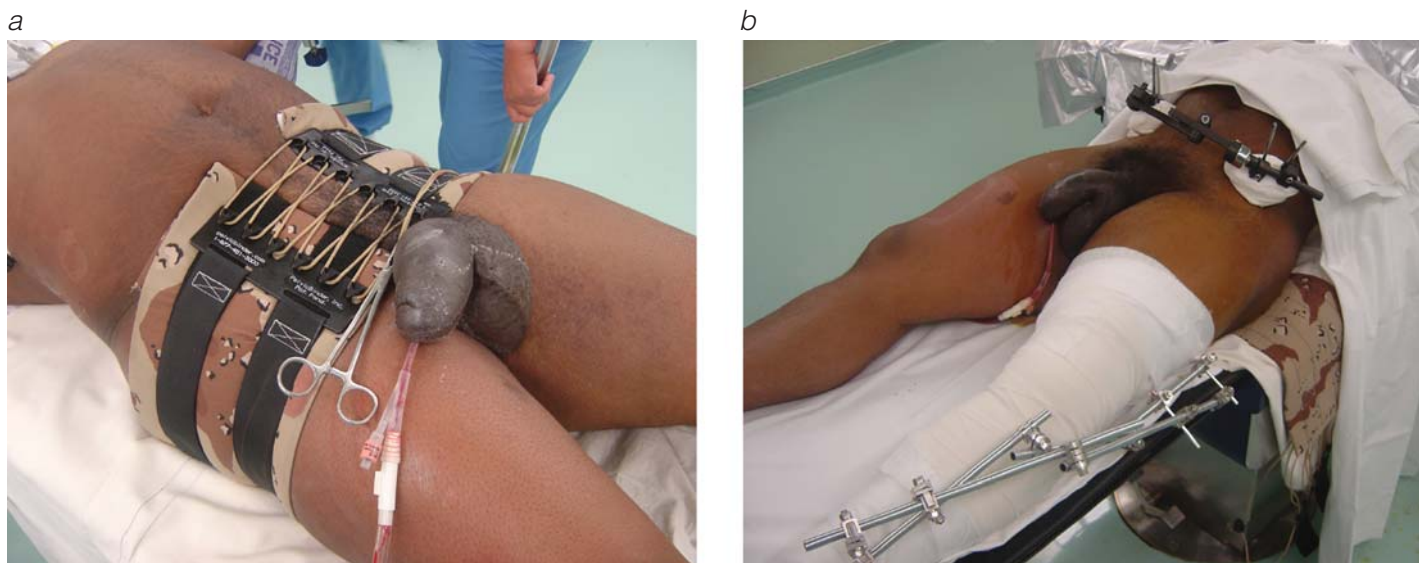


Figure 4 (a) Shown is initial stabilization of pelvic fracture in a patient with severe head injury, life-threatening unstable pelvic fracture, distal femoral fracture, and proximal tibial fracture. (b) Shown is the same patient after DCS.

OPEN FRACTURES AND SOFT TISSUE RECONSTRUCTION

Approximately 3% to 5% of all fractures and 10% to 15% of all long bone fractures are open. The prognosis after an open fracture is very different from that after a closed fracture; treatment of open fractures is much more complex than treatment of simple fractures or traumatic wounds. The existence of an open fracture means that a great deal of energy has been delivered to the bone to produce soft tissue disruption. Accordingly, it can be inferred that there has been considerable stripping of muscle, periosteum, and ligament from the bone, resulting in relative devascularization, and that varying degrees of contusion, crushing, and devascularization of the associated soft tissues have occurred. All of these events greatly influence the rate of healing, the incidence of nonunion, and the risk of infection (most commonly by *Staphylococcus aureus*, *Enterococcus*, or *Pseudomonas*). As noted [see Evaluation and Assessment, Classification of Injuries, Fracture, above], open fractures are typically classified according to the system formulated by Gustilo and Anderson.^{4,5,26}

Management of open fractures in the ED starts with a detailed history that includes the patient's medical condition before the injury, the mechanism of injury, and the time elapsed since the injury. A careful physical examination is then performed, with particular attention paid to neurovascular status, muscle function, and the presence or absence of associated injuries. Compartment syndrome [see Management of Life-Threatening or Limb-Threatening Injuries, Mangled Extremity, below, and 7:13 Injuries to the Peripheral Blood Vessels] should be ruled out in patients at risk; as many as 10% of open tibial fractures are associated with compartment syndrome as a result of severe soft tissue injury. If the limb is malaligned, gentle gross reduction should be performed to relieve any vascular compromise. The wound is then inspected, and a sterile dressing is applied. Once this is done, the dressing should not be removed until the patient is in the OR and preparation for operation has begun. The need for repeated inspections by various specialists can be eliminated by taking pictures of the fractured limb with a digital camera. A temporary splint is applied to the limb to relieve pain and prevent further soft tissue injury. X-rays are obtained in two planes, with the adjacent joints included. Antibiotic treatment is started in the ED, and antitetanus measures

are instituted according to local protocols.

The goals of treatment are to prevent infection, achieve adequate soft tissue coverage, allow bone healing, and promote early and full functional recovery. The basic principles of management consist of aggressive debridement, open wound treatment, soft tissue and bone stabilization, and systemic administration of antibiotics.^{4,5} These principles have reduced the formerly high mortality associated with open fractures to acceptable levels.

High-velocity gunshot wounds and open fractures must be approached differently from closed fractures because of the force imparted to the soft tissues. Open fractures call for emergency surgical treatment. Ideally, such treatment should begin within 6 hours of injury; the incidence of infection is directly related to the time elapsed before initiation of treatment. Typically, a second-generation cephalosporin is administered for 48 to 72 hours; prolonged administration is not necessary. For grade III open fractures, gentamicin should be added to cover gram-negative bacteria; for farmyard injuries, which are at risk for contamination with *Clostridium*, penicillin should be added.^{27,28}

The first stage of operative treatment consists of thorough irrigation of the wound with 6 L of normal saline; pulsed or jet lavage

Table 3 Indications for Angiographic Embolization in Patients with Pelvic Fracture

Hemodynamic instability; FAST negative for intra-abdominal bleeding source; inadequate response to fluid resuscitation
Contrast blush on contrast-enhanced pelvic CT scan
Large retroperitoneal hematoma on CT scan; expanding retroperitoneal hematoma on sequential CT scans
Persistent hemodynamic instability after operative placement of external fixator, laparotomy, or both
Hemodynamic stability with prolonged transfusion requirement (> 3 units of RBCs/24 hr) or other clinical signs of ongoing hemorrhage

FAST—focused assessment for sonographic evaluation of the trauma patient
RBCs—red blood cells

can be helpful for this purpose. Cultures are ordered at this time. To determine the true extent of the soft tissue damage, it is frequently necessary to enlarge the skin wound. Foreign contaminants, as well as dead bone and other devitalized tissues, predispose to infection and should therefore be removed. It is good practice to perform a routine second-look operation 48 to 72 hours after the initial debridement; debridement should be repeated until the soft tissues appear healthy and clean.

Although grade I open fractures may sometimes be treated in much the same way as similar closed fractures, grade II and grade III open fractures must be surgically stabilized during the second stage of the initial operation. Restoring of the normal anatomy through reduction and stabilization improves circulation; promotes healing of bone and soft tissue; reduces inflammation, bleeding, and dead space; and increases revascularization of devitalized tissue. It also results in earlier mobilization of multiply injured trauma patients and improves their overall status.

Internal fixation is preferred for most open fractures, with plates and screws mostly used for articular and metaphyseal fractures and intramedullary nailing for femoral and tibial shaft fractures. It is not always necessary, however, to achieve definitive fixation in the first operation. In the case of complex fractures for which additional imaging or a specialized operative team is required, a correctly placed external fixator is a safe and sensible option. External fixation as a temporary bridge to definitive fixation is also frequently used for severely contaminated grade III open fractures. Surgically created wound extensions may be closed; however, the traumatic wound itself should be left wide open. If the wound is small, a portion of the surgical extension should be left open to allow adequate drainage and to prevent the traumatic wound from sealing off prematurely. Every attempt should be made to cover bone, joint surfaces, implants, and sensitive structures (e.g., tendons, nerves, and blood vessels) with available local soft tissue, but such coverage must be achieved without tension. As an alternative to soft tissue coverage, a temporary method of wound coverage may be chosen (e.g., traditional wet dressings, synthetic membranes, allografts, or other skin substitutes).^{4,5,29,30}

Because leaving a wound open for prolonged periods increases the risk of infection, skin coverage and soft tissue reconstruction should ideally be achieved within 1 week after the injury. In the case of a grade I or II open fracture for which the initial culture is negative, the wound may be allowed to close by granulation and secondary intention, or the patient may be returned to the OR in 5 to 7 days for delayed primary closure. For larger wounds, split-thickness skin grafts are often required. For grade III open fractures, some type of flap is often required for soft tissue coverage [see 3:7 *Surface Reconstruction Procedures*]. Local fasciocutaneous flaps are suitable for smaller defects with intact surrounding skin. Muscle flaps have the advantage of adding vitality to exposed bone and can cover substantial defects; they are frequently covered with a split skin graft. Large wounds and those for which a local flap is not suitable require a free flap that is anastomosed to the local vessels. The flap procedure should preferably be done early, 5 to 10 days after the injury; some authors have even reported good results with definitive soft tissue reconstruction completed during the initial operation (so-called fix and flap).^{4,5,31}

A comparatively new method of wound coverage is negative-pressure wound therapy (NPWT) with a vacuum-assisted closure device (VAC Abdominal Dressing System; Kinetic Concepts, Inc., San Antonio, Texas).^{32,33} The perceived advantages of this approach include provision of a moist wound healing environment, reduction of the wound volume, minimization of bacterial colonization, removal of excess fluid, and (most important) pro-

motion of granulation tissue. Sponges are available in different sizes and can be further trimmed to fit the size of the wound, filling all dead space. An airtight seal is created with an adhesive drape covering the wound and the sponge. Dressings are changed every 2 to 4 days until the desired goals are reached. NPWT has proved to be a viable adjunct for treatment of various soft tissue injuries, including open tibial fractures and pelvic injuries). It is also a useful means of securing skin grafts and is reported to lead to improved graft survival. Although NPWT has yielded promising results in several case series, it should still be regarded primarily as a method of providing temporary coverage of soft tissue defects, not as a replacement for surgical debridement. Surgeons using NPWT should take care not to delay definitive closure, even if such closure involves a complex free muscle transfer.

Rehabilitation should be started soon after the operation. It is facilitated by following an aggressive treatment algorithm consisting of adequate fracture stabilization and early soft tissue coverage to prevent prolonged immobilization of joints and soft tissues. Infection is the most common complication after an open fracture and can be the result of inadequate surgical technique, incomplete debridement, or delayed soft tissue coverage. Open fractures are also associated with a higher incidence of delayed union and nonunion, which often necessitate placement of a cancellous bone graft or, in the case of a large defect, a free fibular graft.

MANGLED EXTREMITY

One of the more difficult decisions for a trauma surgeon is whether to amputate a severely injured or mangled extremity [see 7:13 *Injuries to the Peripheral Blood Vessels*]. The Mangled Extremity Severity Score (MESS) is frequently used as an aid in making this decision,^{4,5} with a score of 7 or higher generally considered an indication for amputation. The final decision whether to amputate or to attempt salvage, however, is based on the individual patient's overall condition, level of neurovascular function, and expected functional result.^{34,35}

The decision between amputation and salvage does not necessarily have to be made immediately; often, it can wait until the involved specialists have discussed the matter in the hours or days following the initial operation. If a mangled extremity does not pose an acute threat to the patient during the initial resuscitation, it may be best treated with irrigation and debridement (as with open fractures), some form of external stabilization, and temporary soft tissue coverage. Amputation in the acute phase should be performed at a safe level by means of a guillotine technique, combined with open wound management.

The functional prognosis after limb salvage is based on the presence or absence of nerve injury and the surgeons' judgment of whether adequate vascularization, soft tissue coverage and long-term bony stabilization are likely to be achievable. Often, multiple operations must be performed over several months, and even then, the outcome may be uncertain. In patients with limbs at high risk for amputation, the 2-year outcomes after reconstruction typically are about the same as those after amputation.³⁶ Accordingly, some patients may be better served by early amputation as definitive treatment.

COMPARTMENT SYNDROME

Compartment syndrome is defined as high-pressure swelling within a fascial compartment [see 7:13 *Injuries to the Peripheral Blood Vessels*]. Many physicians still believe, incorrectly, that compartment syndrome cannot develop in conjunction with an open fracture, because the break in the skin provides decompression. This is a dangerous assumption: compartment syndrome occurs in

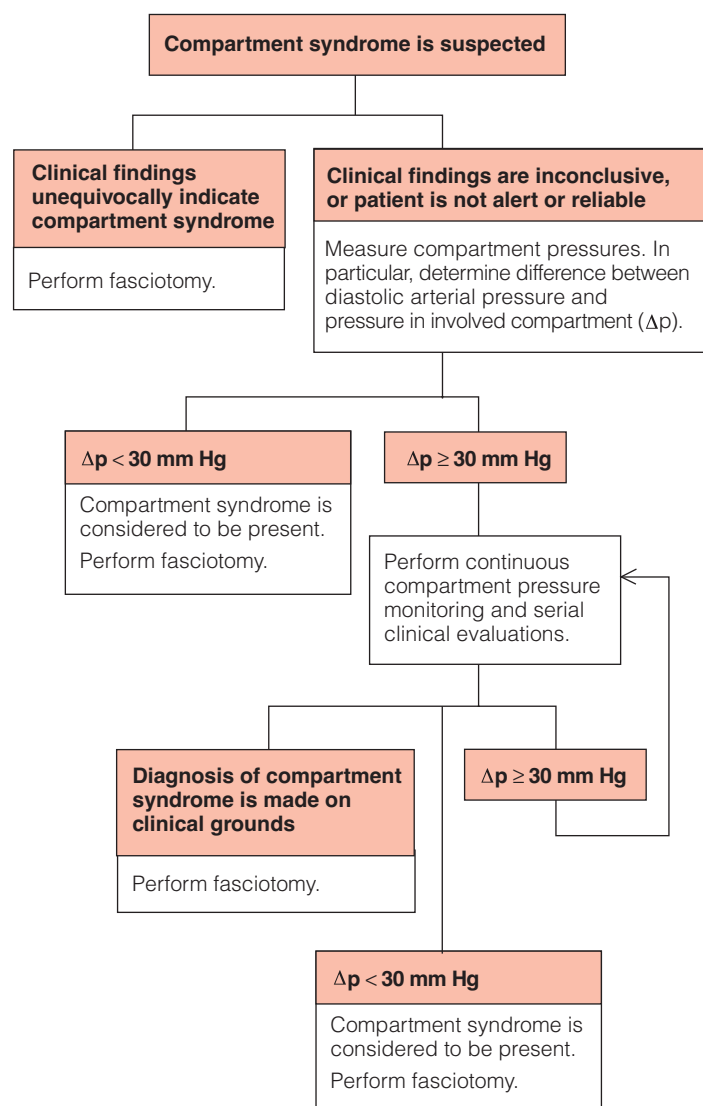


Figure 5 Algorithm outlines diagnosis of suspected compartment syndrome.

a significant number of patients with open fractures—for example, as many as 10% of patients with open tibial fractures. The most common cause of compartment syndrome is hemorrhage and edema in the damaged soft tissues seen with fractures. Other causes include a too-tight dressing or cast, disruption of the limb's venous drainage, advanced ischemia, and eschar from a circumferential burn. Multiply injured patients with hypovolemia and hypoxia are predisposed to compartment syndrome.^{4,5,10}

The key to diagnosis of compartment syndrome [see Figure 5] is to maintain a high level of suspicion in any situation involving an extremity injury where there is a significant chance that this syndrome might develop (e.g., tibial fractures, forearm fractures, and all comminuted fractures associated with severe soft tissue injury). The diagnosis is primarily a clinical one, with the five Ps—pain, pallor, paresthesia, paralysis, and pulselessness—constituting the classic signs. The surgeon should not wait until all these signs are present; the prognosis is much better if they are not. Severe ischemic muscle pain occurs that is unrelieved by the expected amounts of analgesia. On palpation, the compartment is tense and swollen, and passive stretching of the digits of the extremity

increases the pain. Paresthesia occurs early and should be actively watched for; paralysis develops when ischemia has caused permanent damage. Pulselessness occurs late and is a relatively rare sign; it has been shown that irreversible damage can occur in a patient who still has palpable pulses.^{4,5,10,37}

Measurement of compartment pressures is also employed in the diagnosis of compartment syndrome. Monitoring can be particularly helpful in patients who are not alert or are difficult to examine.³⁸ There is no agreement on what constitutes the critical pressure threshold for a definitive diagnosis. An absolute value of 30 to 35 mm Hg has frequently been adopted as a diagnostic indicator; however, the evidence suggests that the difference between the diastolic arterial pressure and the pressure in the involved compartment (delta pressure, or Δp) is more important than any particular absolute value. Currently, a diagnosis of compartment syndrome is usually made if Δp is less than 30 mm Hg, depending on the clinical signs and the level of suspicion.

If compartment syndrome is suspected, the first step is to remove all circumferential bandages to relieve any pressure. If a plaster cast is present, it should be split, spread, or removed; if necessary, maintenance of reduction should be sacrificed. If the clinical picture does not improve after these measures are taken, then a decompressive fasciotomy is indicated. Fasciotomy is described in greater detail elsewhere [see 7:13 *Injuries to the Peripheral Blood Vessels*].

PERIPHERAL VASCULAR INJURY

Vascular injuries can result from either blunt or penetrating trauma to the extremities, though the vascular injuries seen in urban trauma centers tend to be caused more often by penetrating trauma. Early diagnosis and prompt multidisciplinary treatment are crucial for successful management. The severity of the vascular injury and the length of the interval between injury and restoration of perfusion are the major determinants of outcome.^{37,39–42} Diagnosis and management of such injuries are outlined in greater detail elsewhere [see 7:13 *Injuries to the Peripheral Blood Vessels*].

There has been considerable discussion regarding the optimal order of repair in cases of combined musculoskeletal and vascular trauma—that is, whether fracture stabilization should precede vascular repair or follow it.⁴³ Fracture stabilization facilitates the exposure needed for vascular repair and reduces the risk of subsequent disruption of a fresh arterial repair, but it inevitably takes time to perform. Rapid application of an external fixator is a good alternative for extensive fracture repairs. Insertion of a temporary intraluminal shunt can be valuable and limb-saving when DCS is performed in a patient with severe vascular extremity injury or when a patient has a grossly unstable fracture that must be stabilized before arterial repair is possible.⁴⁴ Endovascular repair plays a limited, albeit growing, role in the treatment of arterial injuries associated with extremity trauma.⁴⁵

PERIPHERAL NERVE INJURY

Injury to a peripheral nerve can result in loss of motor function, sensory function, or both; it is the principal factor accounting for limb loss and permanent disability. Because the upper extremities have less muscle and bone mass and more neurologic structures than the lower extremities do, upper-extremity injuries are twice as likely to result in nerve damage as lower-extremity injuries are. Penetrating injuries from cuts or stab wounds that result in a clean laceration of a nerve are amenable to early intervention and repair; penetrating injuries from gunshot wounds are more difficult to assess and manage. Blunt

injuries result primarily from compression or stretching.^{4,5,46-48}

Nerve injuries are generally categorized according to the Seddon classification system, which divides them into three types: (1) neurapraxia, (2) axonotmesis, and (3) neurotmesis. Complete recovery from neurapraxia and axonotmesis can usually be achieved, but neurotmesis usually necessitates surgical intervention. How quickly and successfully nerves regenerate depends on several factors, including age, type of nerve (sensory or motor), level of injury, and duration of innervation.

Careful assessment of motor and sensory function is essential for diagnosis. Additional diagnostic information can be obtained by means of electromyography (EMG), MRI, and nerve conduction studies.

In the setting of blunt trauma, surgical treatment is recommended for closed injuries when the injured nerve shows no evidence of recovery either clinically or on electrodiagnostic studies done 3 months after the injury. It is also recommended for gunshot wounds without vascular or bony problems; such wounds have relatively good potential for neurologic recovery. For most open injuries (e.g., laceration with neurotmesis), surgical exploration at the earliest opportunity is recommended. If possible, the nerve is reapproximated primarily and the epineurium is sutured, or (sural) nerve grafts are employed.^{4,5,46}

Physical therapy should be started soon after nerve injury to maintain passive range of motion in the affected joints and preserve muscle strength in the unaffected muscles. Splinting of affected joints may be necessary to prevent contractures and minimize deformities.

CRUSH SYNDROME

Crush syndrome (also referred to as traumatic rhabdomyolysis) is a clinical syndrome consisting of rhabdomyolysis, myoglobinuria, and subsequent renal failure. It is caused by prolonged compression of muscle tissue (frequently in the thigh or the calf) and is usually seen in victims of motor vehicle accidents who required a long extrication procedure or in earthquake victims who are rescued from beneath rubble after being trapped for several hours or days. Once released from entrapment, crush syndrome patients are likely to exhibit agitation, severe pain, muscle malfunction, swelling, and other systemic symptoms.^{4,5,10,49,50}

The pathophysiologic process underlying this syndrome begins with muscle breakdown from direct pressure, impaired muscle perfusion leading to ischemia and necrosis, and the release of myoglobin. As long as the patient is entrapped, the ischemic muscle is isolated from the circulation, and this isolation affords some protection against the systemic effects of the released myoglobin and other toxic materials. Extrication and the resulting reperfusion of necrotic and ischemic muscle lead to the second insult, the reperfusion injury. This injury is caused by the formation of toxic reactive oxygen metabolites, which leads to failure of ion pumps and increasing permeability of cell membranes and microvasculature. When large amounts of muscle are involved, the resulting fluid changes can rapidly induce shock. The large quantities of potassium, lactic acid, and myoglobin that are released into the circulation can lead to renal failure, disseminated intravascular coagulation, and circulatory arrest.^{49,50}

Treatment should begin at the time of extrication so as to anticipate the onset of the syndrome. The first step is initiation of I.V. fluid therapy, starting with a 2 L crystalloid bolus and continuing with crystalloid infusion at a level of 500 ml/hr (the dosage must be adjusted in pediatric and cardiac patients). Cardiac monitoring is essential (T waves indicate hyperkalemia). Intravascular fluid expansion and osmotic diuresis, by maintaining high tubular vol-

ume and urine flow, may prevent renal failure. Forced diuresis can be achieved by giving mannitol or other diuretics. Alkalization of the urine with sodium bicarbonate (1 mEq/kg I.V. to a total of 100 mEq) is a controversial measure but is recommended by some on the grounds that it should, in theory, reduce intratubular precipitation of myoglobin. If compartment syndrome is suspected, compartment pressures should be measured [see Compartment Syndrome, *above*].^{49,50}

General Management of Fractures

FIXATION METHODS AND IMPLANT TYPES

Fracture fixation can be accomplished either nonoperatively (by means of external splinting) or surgically. Surgical fixation can be achieved with many different techniques, which yield varying degrees of stability. Screws, metal wires (e.g., Kirschner or cerclage wires), plates, nails, and external fixators have all been used for this purpose. Surgical fixation methods may be broadly divided into techniques of absolute stability and techniques of relative stability.⁴

Treatment of fractures with techniques of absolute stability was widely promoted by the ASIF. Anatomic reduction and achievement of absolute stability by means of interfragmentary compression plating were advised for treatment of articular, metaphyseal, and diaphyseal fractures. This method reduces strain at the fracture site and allows bone healing without visible callus formation (so-called direct bone healing). However, obtaining interfragmentary compression usually necessitates a fairly extensive surgical approach, which disturbs the local blood supply.

Unlike techniques of absolute stability, techniques of relative stability (e.g., intramedullary nailing, use of bridging plates across a comminuted fracture, and external fixation) allow small interfragmentary movements to occur when a load is applied across the fracture site. Such movements can stimulate callus formation and lead to union of the bone in four stages: (1) inflammation, (2) soft callus, (3) hard callus, and (4) remodeling. The various techniques of relative stability (also referred to as splinting or bridging techniques) yield varying degrees of stiffness.

Both biologic factors (fracture healing) and biomechanical factors (strength and stiffness) are important for recovery after a fracture. Over the past two decades, clinical experience and data from basic studies have led to a shift in focus away from the mechanical aspects of fracture treatment and toward the biological aspects. Today, a common practice is so-called biologic osteosynthesis, which means careful handling of the soft tissues to take advantage of the remaining biologic support, coupled with the use of techniques of relative stability to stimulate callus formation. Anatomic reduction is no longer considered a goal in itself, except in the case of intra-articular fractures.⁴

Conventional dynamic compression plates are applied tightly against the bone. Their application can compromise the blood supply and thereby induce partial necrosis of the underlying bone. The presence of avascular tissues may reduce the healing potential and lower the local resistance to infection. To overcome some of these disadvantages, plates with smaller contact areas were developed. This process has culminated in the introduction of locking compression plates (e.g., LCP; Synthes, West Chester, Pennsylvania), which can be regarded as noncontact plates. The LCP is a plate-and-screw system in which the screws are also locked in the plate by means of an extra thread in the head of the screw; thus, the plate is no longer tightly fixed to the bone and the periosteum. Locking compression plates (also referred to as locked internal fixators) are designed in such a way that both conventional dynamic compres-

sion techniques and bridging techniques can be used, depending on the fracture type. They may be applied via a less invasive approach using closed reduction techniques.^{4,5}

Intramedullary nails are placed within the medullary canal and therefore have the same biomechanical properties in both the frontal and the sagittal plane. They differ from plates in that the latter are attached eccentrically to the bone. Intramedullary nails may be inserted in either an unreamed or a reamed fashion; both techniques have advantages and disadvantages. With unreamed nailing, the nails are inserted without widening the medullary canal. This approach causes somewhat less operative trauma than reamed nailing, but it places some limitations on the diameter and strength of the nail and the locking bolts. If larger-diameter nails (> 9 mm) are needed, the medullary canal must be reamed to accommodate them. Reaming takes time, leads to increased intramedullary pressure, and produces debris that may be embolized in the pulmonary circulation. The clinical consequences of reamed intramedullary nailing have not yet been fully clarified. Current evidence suggests, however, that reamed nailing is associated with significantly lower rates of nonunion and implant failure than unreamed nailing is.^{4,5,51}

External fixators consist of metal pins (Schanz screws) that are placed in the bone proximal and distal to the fracture and connected outside the skin by one or more rods. Most external fixators are used only on one side of the limb, but in specific instances, multiplanar or circular devices may be used. The stability of the frame depends primarily on the stiffness of the rods, the distance between the rod or rods and the bone (the smaller the distance, the greater the rigidity), and the number, placement, and diameter of the fixator pins. As a general rule, two pins proximal and distal to the fracture are sufficient for fixation of long bone fractures. The main advantage of external fixators is that their use minimizes additional surgical trauma. The main disadvantages are the occurrence of pin-tract infections and the frequent lack of stability for definitive fracture treatment. Appropriate placement of fixator pins requires a detailed knowledge of the cross-sectional anatomy of the injured limb.^{4,5}

BASIC PRINCIPLES OF TREATMENT

Although most fractures heal readily with casting, long periods of immobilization with restriction of muscle activity, joint motion, and weight bearing are known to lead to so-called fracture disease, characterized by muscle atrophy, joint stiffness, disuse osteoporosis, and persistent edema. Accordingly, the goals of fracture treatment should include not only the achievement of bony union but also the early restoration of muscle function, joint mobility, and weight bearing.^{4,5}

Currently, there are seven main indications for operative treatment of fractures:

1. Preservation of life (e.g., decreasing morbidity and mortality through fixation of femoral shaft fractures);
2. Preservation of a limb (as with open fractures, fractures associated with vascular injury, and fractures complicated by compartment syndrome);
3. Articular incongruity;
4. Facilitation of early mobilization and rehabilitation;
5. Inability to maintain reduction with conservative treatment;
6. The presence of more than one fracture in the same limb (so-called floating joint); and
7. The presence of additional fractures in other limbs (e.g., bilateral humeral or tibial fractures).

Improved understanding of the biology of fracture repair and

the importance of the soft tissues has led to substantial changes in the treatment of diaphyseal fractures. It is now widely recognized that anatomic reduction of each fracture fragment is not always a prerequisite for restoration of normal limb function (see above). For most long bone fractures, radial and ulnar fractures excepted, the most important goal is restoration of the mechanical axis of the limb without significant shortening, angulation, or rotational deformity. Good functional results may be expected even if fracture fragments lying between the proximal and distal main fragments are not anatomically reduced.^{4,5}

In the upper extremity, both plates and intramedullary implants are frequently used for operative fixation of fractures. In the lower extremity, intramedullary nails are generally preferred because they allow early weight bearing, in contrast to plates and screws, which are more susceptible to failure. However, intramedullary nailing may not be suitable for shaft fractures that extend into the metaphysis or the adjacent joint. The treatment plan may also be influenced by the local condition of the soft tissues (e.g., the presence or absence of contusions or wounds), the quality of the bone (e.g., the presence or absence of osteoporosis), and the origin of the fracture (pathologic or nonpathologic).^{4,5}

For intra-articular fractures, alignment alone is insufficient. Anatomic reduction of the articular surface is required to restore joint congruity, and rigid fixation is necessary to allow early motion and thereby prevent the joint stiffness resulting from prolonged immobilization. Impacted osteochondral fragments are elevated, and the resulting metaphyseal defect underneath is filled with cancellous bone or a bone substitute. Fracture fragments may be reduced either via direct exposure or via more limited approaches, with the assistance of an image intensifier or arthroscope, or both. Regardless of which approach is followed, care must be taken not to devascularize bone fragments. Fixation may be achieved with metal wires, screws, and plates. The reconstructed articular surface is connected to the diaphysis with plates or, alternatively, external fixators.^{4,5}

Nonoperative treatment usually consists of application of casters or (less frequently) traction and may be employed as either temporary or definitive therapy. It reduces the risk of infection and eliminates operative risk, but it also frequently results in a longer time to union, a higher risk of malunion, and a greater likelihood of stiffness of the involved joints. Accordingly, nonoperative management is mostly reserved for extra-articular and minimally displaced fractures.^{4,5}

Autologous bone grafting remains the gold standard for improving and accelerating fracture healing. In recent years, however, various other methods have been developed and evaluated for this purpose. There is some evidence from randomized trials indicating that low-intensity pulsed ultrasonography may shorten the healing time for fractures treated nonoperatively.^{52,53} Ultrasound treatment does not, however, appear to confer any additional benefit after intramedullary nailing with prior reaming. The discovery of specific bone growth factors (bone morphogenetic proteins [BMPs]) was an important step forward in the understanding of bone physiology and raised the possibility that these factors could be locally applied to enhance fracture healing. However, clinical trials have not yet determined the most appropriate indications for the use of BMPs in managing specific fractures or nonunions.⁵⁴

The indications for implant removal are not well established. There are few definitive data to guide the decision as to whether an implant should be removed or left in place. In general, implants in most adult patients may be left in place; the same is true of implants in the upper extremity. When implants are removed for relief of pain and mitigation of presumed functional impairment

alone, the results are unpredictable and depend on both the implant type and its anatomic location. Implant removal is often technically challenging and may lead to complications such as infection, neurovascular injury, or refracture. Current data do not support routine removal of implants to protect against allergy, carcinogenesis, or metal detection. The decision for or against implant removal is therefore based on individual patient and surgeon preferences, as well as on the clinical circumstances.^{55,56}

Management of Upper-Extremity Injuries

SHOULDER

Fractures of the clavicle are common and are usually caused by falling on the shoulder. Approximately 80% of clavicular fractures occur in the middle third of the bone, 15% in the lateral third, and 5% in the medial third. Dislocation results from traction of the pectoral and sternocleidomastoid muscles. Neurovascular injury is uncommon, but the patient should always be evaluated for such injury nonetheless. Treatment is primarily conservative, employing a collar and cuff or a sling; union rates approach 95%. Operative fixation is indicated only when there is impending perforation of the overlying skin, an associated injury to the subclavian artery and brachial plexus, an ipsilateral scapular neck fracture (so-called floating shoulder), a dislocation greater than 2 cm (a relative rather than absolute indication), or painful nonunion. Fixation methods include plate osteosynthesis and intramedullary osteosynthesis.⁵⁷

Scapular fractures result from high-energy trauma and are frequently accompanied by life-threatening injuries to the head, the chest, or the abdomen. CT scanning is usually required to determine the fracture pattern. Most scapular fractures can be treated conservatively. Severely ($> 40^\circ$) dislocated scapular neck fractures and dislocated intra-articular glenoid fractures are treated with open reduction and internal screw or plate fixation.

HUMERUS

Proximal

Fractures of the proximal humerus are common, especially in elderly women. Correct positioning of the four main bony structures of the proximal humerus (the head, the greater tuberosity, the lesser tuberosity, and the shaft) and their muscle attachments is important for a good shoulder function. Consequently, fractures of this segment of the humerus may have significant functional consequences. Damage to the blood supply of the head may lead to avascular necrosis of this part of the bone. Conservative treatment with a sling is preferred for elderly patients with minimally displaced fractures, and early range-of-motion exercises are encouraged. Operative treatment is indicated for patients with dislocated two-, three-, or four-part fractures and fracture-dislocations. The optimal fixation method has not been established, but plate osteosynthesis is frequently employed; alternatives include intramedullary techniques and prosthetic replacement.^{58,59} Rehabilitation usually takes several months, and continuing impairment of shoulder function is a common complaint.

Shoulder (glenohumeral joint) dislocations mostly occur in young persons participating in sports. The size difference between the large articular surface of the humeral head and the small surface of the glenoid renders the shoulder particularly vulnerable to dislocation. The majority (95%) of patients have anterior dislocations, resulting from abduction and exorotation. The relatively few posterior dislocations that occur tend to be difficult to diagnose and are frequently missed initially. A particularly rare and severe

type of shoulder dislocation is luxatio erecta, characterized by inferior dislocation of the abducted arm. Injuries associated with shoulder dislocation include injury to the axillary nerve, injury to the labrum (Bankart lesion), and a depression in the humeral head (Hill-Sachs lesion); the last two predispose to recurrence. Radiographs should be obtained in AP, axillary, and Y-scapular views to determine the position of the humeral head and detect any fractures. Treatment consists of gentle and closed reduction. This can usually be done in the ED; if necessary, it can be done in the OR with the patient under general anesthesia. Reduction is followed by immobilization in a sling.⁵

Dislocations of the sternoclavicular joint are rare, but they are potentially life-threatening when they occur posteriorly (anterior dislocations are far less dangerous). Diagnosis of these injuries is difficult with conventional x-rays; accordingly, CT is recommended when sternoclavicular joint dislocation is suspected. Compression of the mediastinal vessels and trachea can sometimes lead to respiratory and circulatory failure. In such cases, urgent operative reduction, performed with an eye to potential vascular emergencies, is warranted.^{5,10}

Dislocations of the acromioclavicular joint result from falling on the shoulder and are frequently classified according to the system formulated by Tossy. Tossy 1 dislocations (sprains) and Tossy 2 dislocations (subluxations) are treated conservatively with a collar and a cuff. For Tossy 3 dislocations (complete separations), operative treatment may be considered, though the optimal technique remains to be determined and the results of operative fixation are still uncertain.⁵

Shaft

Fractures of the humeral shaft typically result from direct trauma. Depending on the level of the fracture, dislocation mainly results from traction placed on the deltoid or pectoral muscles. Fractures of the middle and distal thirds of the humeral shaft can result in injury to the radial nerve, which is the most severe functional complication. Most closed AO-ASIF type A1 and A2 fractures can initially be treated conservatively with functional bracing techniques (rather than hanging casts); this approach yields good or excellent results in the majority of cases. Moderate angulation, rotation, and shortening are well tolerated. Generally accepted indications for operative treatment include open fractures, AO-ASIF type B and C fractures, associated vascular injury, multiple trauma, bilateral fractures, combined humeral shaft and forearm fractures (so-called floating elbow), pathologic fractures, secondary radial nerve palsy, and nonunion.⁶⁰ The standard technique is open reduction and plate fixation; the main alternative is locked intramedullary nailing, either antegrade (entering in the proximal humerus) or retrograde (entering in the distal humerus).^{61,62} External fixation is employed in the presence of severe soft tissue injuries and in polytrauma patients as part of DCS.

Distal

Fractures of the distal humerus result from falling on the elbow with the forearm flexed. In elderly persons, many of whom are osteoporotic, a fall from a standing position is often sufficient to cause such a fracture, whereas in young patients, high-energy trauma is required. Extra-articular injuries usually have a good prognosis. Intra-articular fractures are more difficult to manage: limitation of flexion and extension and pain often occur, even after optimal treatment. In addition to AP and lateral x-rays, it may be advisable to obtain CT scans to help clarify the fracture pattern. For minimally displaced AO-ASIF type A fractures, conservative treat-

ment is appropriate, but for all other fractures, open reduction and plate osteosynthesis are required, frequently in conjunction with an olecranon osteotomy to provide adequate exposure. In comminuted fractures, the articular surface can be difficult to reduce. In osteoporotic bone, finding good bone stock can be a serious problem.^{4,5,63,64}

ELBOW

Olecranon fractures are the most common fractures in the area of the elbow and usually are caused by falling directly on the elbow. They frequently lead to impaired extension as a consequence of the discontinuity between the triceps and the proximal ulna. All dislocated olecranon fractures are treated operatively, with Kirschner wires and a tension band employed for simple fractures and plate osteosynthesis for comminuted fractures. Both methods allow early functional therapy postoperatively.

Fractures of the radial head are caused by falling on the outstretched arm and may occur either in isolation or in combination with an elbow dislocation, an ulnar shaft fracture (Monteggia fracture), a coronoid process fracture, or a medial collateral ligament rupture. In addition, the interosseous membrane between the ulna and the radius may be disrupted over its entire length, thereby disturbing the distal radioulnar joint at the wrist (Essex-Lopresti injury). Fractures with dislocations smaller than 2 mm can be treated conservatively with early range-of-motion exercises; external support is usually unnecessary. Dislocated fractures and fractures causing mechanical blockage (e.g., of pronation or supination) are mostly treated operatively, with plate or screw fixation. When the fracture is comminuted, adequate reduction and fixation may be impossible. If the elbow is otherwise stable, radial head excision may be performed; if not, a radial head prosthesis may be inserted to stabilize the joint. Active and passive range-of-motion exercises should be started soon after the operation.

Elbow dislocations are typically caused by falling on the outstretched hand. Posterior dislocations, characterized by dorsal displacement of the radius and the ulna, are more common than anterior dislocations. Associated injuries may include coronoid process fractures and collateral ligament injuries, as well as neurovascular injuries. Most elbow dislocations can be treated with closed reduction by applying traction with the forearm flexed 30°. After reduction, the stability of the elbow should be carefully evaluated. Plaster immobilization should not be continued beyond 3 weeks. Operative reduction is necessary only when the dislocation is associated with an open fracture, when interposing fragments preclude adequate closed reduction, or when neurovascular injury is present.^{4,5}

FOREARM

The bones in the forearm have a complex relation with each other and with the elbow and the wrist, and this complex relation allows numerous different combinations of flexion, extension, pronation, and supination. The mechanism of a forearm injury is a frequently a vehicular accident or a fall; isolated fractures of the radius or the ulna are rare and usually result from a direct blow. The goal of treatment is to achieve anatomic restoration of length, axial alignment, and rotation with stable fixation in a manner that permits free movement (especially pronation and supination) of the elbow and the wrist postoperatively [see Figure 6]. Only nondisplaced fractures may be treated nonoperatively; all other forearm fractures must be treated operatively. The standard technique is open reduction with plate fixation; intramedullary fixation is an alternative. The radial nerve is at risk during plate fixation of the proximal radius.⁶⁵⁻⁶⁷

Approximately 10% of ulnar fractures are accompanied by a

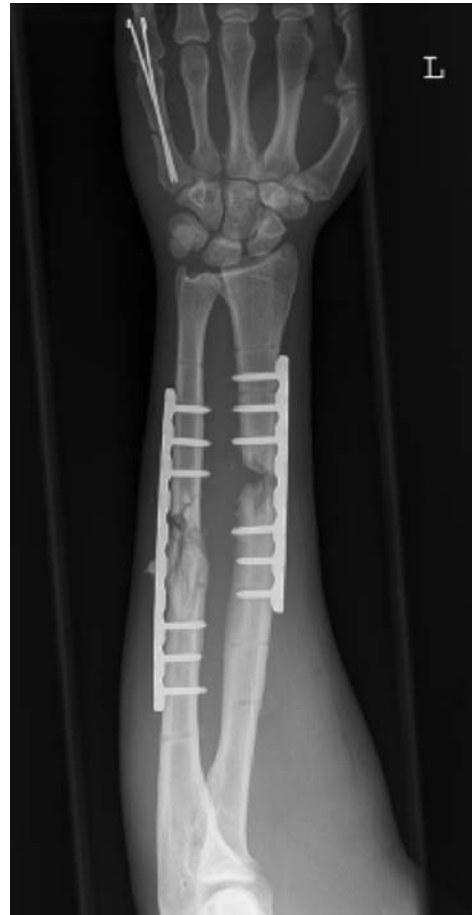


Figure 6 Shown is grade II open forearm fracture with segmental bone loss in the radius, initially stabilized with debridement and external fixation. Injury is treated with secondary plate osteosynthesis and Kirschner wire fixation of metacarpal fracture.

radial head dislocation (Monteggia fracture). Appropriate x-rays must be obtained to ensure that this injury is not missed. The radial head is reduced by closed or open methods during plate fixation of the ulna. Radial shaft fractures are sometimes associated with a dislocation of the ulna in the distal radioulnar joint (Galeazzi fracture). If the distal radioulnar joint remains unstable after plate fixation of the radius, temporary transfixation is necessary.^{4,5}

WRIST

Distal radial fractures are among the most commonly encountered fractures. Like elbow dislocations, they are usually caused by falling on the outstretched hand. The incidence rises sharply with increasing age, especially in osteoporotic women. Associated injuries include ulnar styloid process fractures and ligamentous carpal injuries. Dislocations are classified as dorsal (Colles type) or volar (Smith type); the former are more common. Partial articular fractures (AO-ASIF type B) are also referred to as dorsal or volar Barton fractures. Diagnostic imaging plays an important role in assessment; the critical radiographic parameters are radial angle, radial length, and dorsal angulation. Radiologic signs of instability include initial dorsal angulation greater than 20°, greater than 5 mm reduction in radial length, intra-articular involvement, and metaphyseal comminution. An articular stepoff greater than 2 mm is associated with a poor prognosis.

Minimally displaced AO-ASIF type A distal radial fractures and stable impacted fractures may be treated conservatively in plaster for 4 to 6 weeks. If necessary, this can be done after closed reduction, though loss of reduction may occur after an initial satisfactory position has been achieved. For all other fractures, operative treatment is advised, depending on fracture type and patient status [see Figure 7]. AO-ASIF type B fractures are best treated with open reduction and screw or plate fixation; however, optimal treatment of AO-ASIF type C fractures remains to be determined. External fixation combined with Kirschner wires and plate osteosynthesis is frequently employed. In some cases, it may be necessary to fill a subchondral or metaphyseal defect with a cancellous bone graft or a bone substitute. Reflex sympathetic dystrophy develops in some patients [see Special Considerations, Complications, Reflex Sympathetic Dystrophy, *below*]. Treatment of this syndrome can be difficult, and complete functional loss is occasionally the final result.^{4,5,68}

Fracture of the scaphoid typically is caused by falling on the outstretched or dorsally flexed hand. It tends to be difficult to diagnose and is easily missed. Signs such as pain, functional impairment, and tenderness at the anatomic snuff box are often absent initially, and standard AP and lateral x-rays of the wrist may be insufficient to identify the injury. If special scaphoid views do not confirm the presence of a fracture, the wrist is immobilized and x-rays are repeated after 7 to 10 days. Alternatively, CT, MRI, or bone scintigraphy may be performed to confirm the diagnosis.³ Undisplaced fractures may be treated conservatively in plaster. Immobilization should be continued for 6 to 12 weeks to minimize the risk that disturbance of the delicate blood supply of the scaphoid might result in avascular necrosis or pseudarthrosis. Dislocated fractures (with dislocation greater than 2 mm or angulation greater than 25°) are treated with screw osteosynthesis.^{4,5,69}

Perilunate dislocations result from high-energy trauma and include a spectrum of severe ligamentous wrist injuries, fractures, and dislocations characterized by dorsal dislocation of the distal carpal row, the scaphoid, and the triquetrum with respect to the lunate. Perilunate dislocations may be missed initially in multiply injured patients if the physical examination is incomplete or the x-rays of the wrist are inadequate or not carefully examined. Treatment consists of closed or open reduction; additional fixation may be performed as needed, depending on the degree of stability achieved after reduction. Associated fractures of the radius or the scaphoid are treated operatively.⁵

HAND

Fractures of the hand can result from direct blows, twisting injuries, crush injuries, and gunshot wounds. Neurovascular status, wounds (e.g., bites), and tendon function should all be carefully evaluated. Most fractures can be detected on posteroanterior, lateral, and oblique views.

Metacarpal neck fractures, most frequently of the fourth or fifth metacarpal (so-called boxer's fracture), can usually be treated conservatively with 3 to 4 weeks of immobilization and early range-of-motion exercises.⁷⁰ Fracture healing may result in cosmetic deformity but good function. Severely dislocated fractures are typically treated with Kirschner wires or plate fixation. Most fractures of the metacarpal shafts can be treated nonoperatively with immobilization in a cast or splint for 4 weeks. If the wrist is immobilized in plaster, it should be positioned in 20° of extension, with the the metacarpophalangeal joints in 70° to 90° of flexion and the interphalangeal joints in complete extension to prevent shortening of ligaments. Rotation (as indicated by nail position) should be checked frequently. Indications for operative treatment include angulation greater than 10° to 30°, shortening, malrotation (more



Figure 7 Illustrated is treatment of distal radial fracture with (a) volar plate osteosynthesis and (b) external fixation.

frequent in the second and fifth metacarpals), and multiple fractures. Bennet's fracture (an intra-articular fracture of the base of the first metacarpal with a small ulnar fragment that remains attached to the second metacarpal) should be treated with reduction or, if unstable, fixation with percutaneously placed Kirschner wires or screws. Other metacarpal base fractures are less frequent but may also be associated with carpometacarpal dislocations. Treatment focuses on reduction of the joint and restoration of alignment and the articular surface, if necessary by means of open reduction.^{5,71,72}

Phalangeal fractures are common. In the distal phalanx, fractures often result from crush injury and may be associated with subungual hematoma (which should be drained) and soft tissue injury. The vitality of the fingertip may be compromised. Nondisplaced fractures may be treated with immobilization in plaster or a splint for 3 weeks, followed by active range-of-motion exercises. Dislocated fractures may be treated with closed or open reduction and fixation with Kirschner wires or small screws or plates.^{71,72}

Dislocations of the interphalangeal joints usually are easily recognized by the obvious deformity they cause, but x-rays must still be obtained to exclude fractures. Dorsal dislocations are associated with injuries to the volar plate or collateral ligaments, which tend to increase instability. Treatment consists of closed or open reduction, followed by testing through the range of motion to check stability and x-rays to ensure adequate reduction. If reduction is unstable, transarticular Kirschner wire fixation may be necessary.⁵

So-called gamekeeper's thumb is an injury to the ulnar collateral ligament of thumb metacarpophalangeal joint that causes instability at that joint; the ulnar collateral ligament frequently becomes dislodged between the adductor pollicis aponeurosis and its normal position (Stener lesion). Partially unstable lesions (< 20° to 30° opening at stress examination in comparison with the uninjured side) may be treated in a plaster splint for 3 to 4 weeks. Completely unstable lesions are treated with surgical repair to prevent chronic instability.⁵

TENDONS

Injuries to the rotator cuff reduce the shoulder's strength and impair its function. Most ruptures occur in cuff muscles or tendons that are already affected by degenerative changes. Operative treatment is advised for young patients and for patients who have experienced substantial ruptures as a result of recent trauma.

Rupture of the distal biceps tendon occurs mainly in middle-aged men. The tendon is torn off the radial tuberosity during flexion against resistance. The muscle belly is visibly retracted proximally, and flexion and supination are reduced by 30% to 40%. In cases where the diagnosis is not clear, MRI or ultrasonography may be helpful. Treatment consists of reattaching the tendon to the radius with suture anchors or drill holes.

In the case of tendon injuries around the wrist and the hand, appropriate clinical testing and diagnosis depend on a solid knowledge of the exact anatomy and function of the various tendons. The extensor tendons are located just under the skin, directly on the bone, on the back of the hands and the fingers; their superficial location makes them easily injured even by a minor cut. The flexor tendons pass through fibrous rings called pulleys, which guide the tendons and keep them close to the bones; because of the more complex anatomy, flexor tendon injuries are usually more challenging than extensor tendon injuries. Partial injuries with intact function may be treated conservatively, but most injuries, especially sharp lacerations, are treated with surgical repair followed by

protected motion. Postoperative treatment and rehabilitation of tendon injuries are very important and require the services of a special hand therapist.

A commonly encountered extensor tendon injury is so-called mallet finger, which results from forcible flexion of the extended distal interphalangeal joint. The extensor tendon is torn off the distal phalanx, with or without an intra-articular fragment of its base. Clinically, the distal interphalangeal joint is in flexion, and active extension of the distal phalanx is impossible. Most lesions can be treated with a special splint that keeps the distal interphalangeal joint in extension for 4 to 6 weeks.⁵

Management of Pelvic and Acetabular Injuries

PELVIC RING

Pelvic fractures occur in about 3% of trauma patients. These injuries can have a devastating influence on the outcome of trauma care and therefore must be identified as early as possible. Internal retroperitoneal bleeding is the main concern in the early management of these patients because over 40% of the mortality from pelvic trauma is attributable to persistent bleeding. Accordingly, the initial physical examination and the AP pelvic x-ray (which is diagnostic in 90% of cases) during the primary survey are essential for placing the focus on the potential risk of internal bleeding. Additional inlet and outlet views (taken at a 45° angle from cephalad and caudal) may be useful for accurate classification and determination of dislocation.^{4,5} CT scanning is performed in nearly all cases but not necessarily as an emergency evaluation. The CT scan facilitates fracture classification and provides additional information on active bleeding and associated injuries. Administration of I.V. contrast material during CT scanning helps in detecting active arterial bleeding, which suggests the need for early angiographic embolization. Angiographic embolization may be lifesaving in patients with pelvic arterial bleeding.

Pelvic injuries are frequently associated with other serious injuries. Fractures of the anterior pelvic ring, especially when seen in combination with blood from the urethral meatus, are an indication for retrograde urethrography before placement of a transurethral catheter to detect or exclude urethral and bladder injuries. Vaginal and rectal examinations are components of the standard workup for detecting or excluding fracture perforations and abnormalities of prostate position (indicative of urethral injury).

Posterior pelvic ring injuries may be accompanied by sacral plexus nerve injuries. Perineal and groin wounds often are in continuity with fracture components and pose a serious threat of further complications. With open pelvic injuries, early surgical debridement and fecal deviation must be considered.

The AO-Tile classification of pelvic ring and acetabular fractures is based on the degree of pelvic stability or instability. The pelvis is divided into an anterior section (comprising the symphysis pubis and the pubic rami) and a posterior section (comprising the ilium, the sacroiliac joint complex, and the sacrum).⁴ Determination of whether and to what extent the posterior section is displaced is crucial for estimating the stability of the injury. Depending on the degree of posterior bony or ligamentous instability, pelvic ring injuries may be classified into three types as follows:

1. Type A: injuries where the mechanical stability of the pelvic ring is intact—the most common type, seen in 50% to 70% of pelvic fracture patients.
2. Type B: injuries characterized by partial posterior stability (i.e., injuries that are rotationally unstable but vertically stable)—seen in 20% to 30% of pelvic fracture patients.

3. Type C: injuries characterized by combined anterior and posterior instability (i.e., injuries that are both rotationally and vertically unstable)—seen in 10% to 20% of pelvic fracture patients.

Another system used to categorize pelvic fractures is the Young-Burgess classification, which is based on the force vectors causing the fracture. In this system, pelvic ring fractures are divided into the following four major groups: (1) lateral compression, (2) anteroposterior compression, (3) vertical shear, and (4) combined mechanical injury. The stability or instability of the fracture can be determined on the basis of knowledge of the ligamentous anatomy of the pelvis coupled with assessment of the fracture pattern and the direction of the injuring force.^{4,5}

Provisional stabilization is advised after manual reduction of pelvic ring disruption, especially in open-book fractures with significant dislocation. External fixation is one means of achieving provisional stabilization; however, it is more time consuming than applying a sheet wrap or a similar device for temporary stabilization. For this reason, many institutions prefer the latter approach during initial management in the ED. The Pelvic C-Clamp (Synthes, West Chester, Pennsylvania) is also employed for external stabilization, primarily in hemodynamically unstable patients with unstable (i.e., type B or C) pelvic ring injuries. This device acts by exerting direct compression on the posterior part of the pelvic ring, thereby reducing the intrapelvic volume, compressing fracture parts, and providing stability. Application of this device should also be considered if operative retroperitoneal pelvic packing is necessary.

Definitive treatment of pelvic injuries depends on the type of injury, the classification (stability), the local soft tissue situation, and the general condition of the patient [see Figure 8]. Type A fractures are stable and usually need not be treated operatively. Functional treatment, with early ambulation and weight bearing as tolerated, usually suffices.

Type B1 (open-book) injuries with minimal dislocation of the

symphysis may be treated conservatively. If symphyseal dislocation is less than 2.5 cm, anterior plate fixation of the symphysis is usually sufficient. If the patient cannot undergo formal internal fixation, an external fixator (which may have been applied initially for bleeding control) is a reasonable alternative for definitive treatment. However, the discomfort and the complications (e.g., infection) caused by external fixator pins motivate many surgeons to convert to internal plate fixation after the initial stabilization phase. In the setting of an emergency laparotomy, early anterior plate fixation may be considered during the same laparotomy, provided that patient is or has been rendered physiologically stable. Type B2 (lateral compression) injuries with minimal anterior dislocation often have good intrinsic stability and can frequently be treated conservatively.

For type C injuries, both anterior and posterior stabilization is required. Of the many techniques currently in use, plate fixation of the anterior pelvic ring combined with either percutaneous sacroiliac screws or plate fixation of the posterior pelvis provides the best mechanical stability. The main goals are to restore the anatomy and prevent any leg-length discrepancy while encouraging allowing early mobilization of the patient to prevent the complications of prolonged bed rest.^{4,5,73-75}

Percutaneous placement of iliosacral screws under fluoroscopic guidance is already the preferred technique for stabilization of the majority of unstable sacroiliac injuries. The continuing development and growing availability of modern surgical tools (e.g., computer-assisted intraoperative navigation) are providing ever more opportunities for minimally invasive approaches to pelvic fracture fixation. Nevertheless, stabilization of the pelvis through open surgical reduction and internal fixation using standard plate and screw techniques are still proper alternatives and are the treatment of choice for many pelvic ring fractures.

ACETABULUM

Traumatic acetabular fractures may occur either in isolation or as part of a pelvic ring injury [see Figure 8a]. On occasion, they occur in combination with hip dislocation; in such cases, urgent

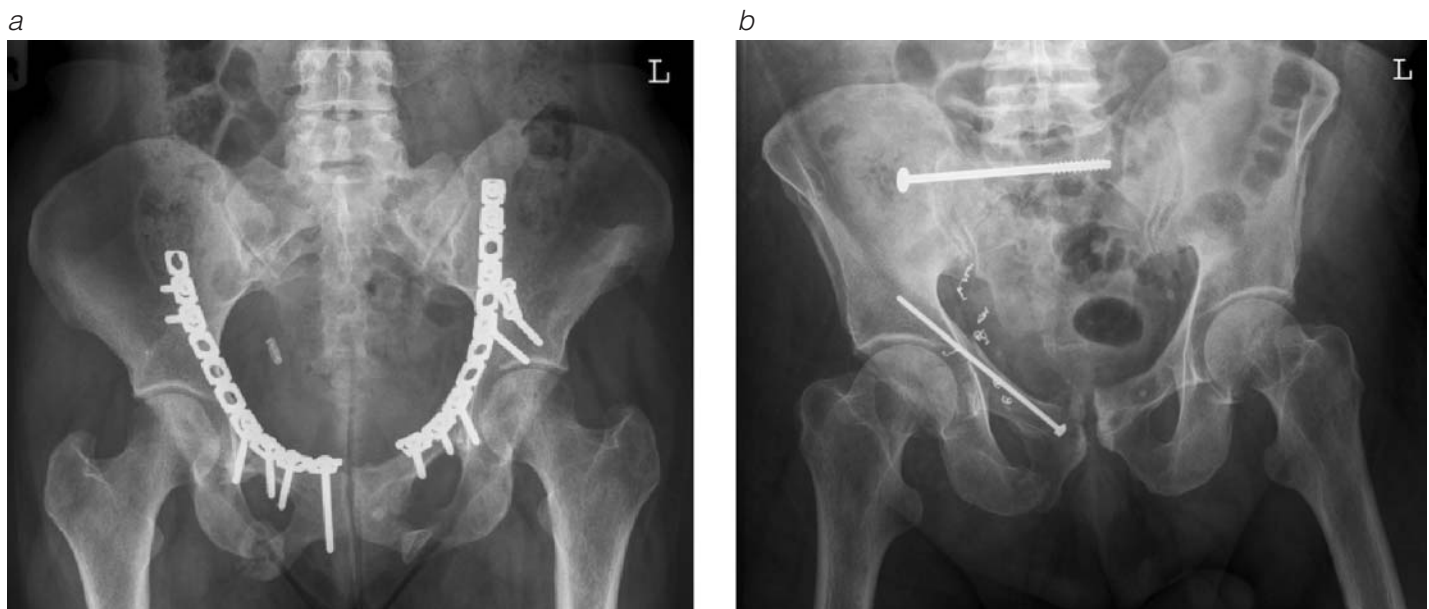


Figure 8 Shown are (a) plate osteosynthesis for combined pelvic ring injury and left-side acetabular fracture in a multiply injured patient and (b) treatment of type C unstable pelvic ring injury with initial angioembolization (coils visible) and external fixation, followed by secondary percutaneous placement of sacroiliac and pubic screws.

reduction of the dislocated hip is essential for restoring blood flow to the femoral head. For adequate fracture classification, x-rays must be obtained in Judet views (oblique views taken with the beam stationary and with the patient rolled 45° to both sides along the vertical axis). CT scanning with axial and three-dimensional reconstructions can greatly clarify the extent of the injury and help identify the number and size of fracture fragments. An accurate neurologic examination that includes assessment of the integrity of the sciatic nerve should also be part of the initial workup.

Until the 1960s, the vast majority of patients with acetabular fractures were treated conservatively. Thanks to the impressive efforts of Letournel and Judet (who also introduced the most frequently used classification system), operative treatment has become standard for dislocated acetabular fractures.^{76,77} The most important goal of operative treatment is to restore the articular surface so that a congruent hip joint can be obtained. Achievement of this goal nearly always requires open reduction and internal fixation with plates or screws through anterior or posterior approaches. Extensive experience on the part of the operating team is necessary to ensure optimal long-term results. After the operation, the patient should be able to take part in non-weight-bearing exercises.

The majority of acetabular fractures can be treated in a delayed fashion between 3 and 14 days after the injury. Acute operative fracture treatment may be indicated if a dislocated hip cannot be reduced, if redislocation of the hip cannot be prevented, or if interposition of intra-articular fracture fragments occurs. In many instances, however, initial skeletal traction (if indicated after hip reduction) will be applied.

Adequate prophylaxis of deep vein thrombosis (DVT) is essential for both patients with pelvic fractures and those with acetabular fractures. Functional outcome after acetabular fracture surgery is determined by many factors, the most important of which are anatomic fracture reduction, the development of osteoarthritis, avascular necrosis, and heterotopic ossification.^{4,5,77-79}

Management of Lower-Extremity Injuries

FEMUR

Proximal (Hip Fracture)

Fracture of the proximal femur (hip fracture) is one of the most common conditions seen by orthopedic and trauma surgeons. It is particularly common in the elderly. Substantial force is required to fracture a hip in a young person, whereas a minor trauma or fall may be sufficient to do so in an elderly osteoporotic woman. Almost 90% of patients with proximal femoral fractures are older than 65 years. Between 5% and 10% of these elderly patients die during hospital admission; 25% die within the first year after the accident.

Hip fractures are typically classified into four broad categories according to their anatomic site: (1) femoral head fractures, (2) intracapsular (femoral neck) fractures, (3) intertrochanteric fractures, and (4) subtrochanteric fractures. Within these broad categories, they may be further divided into subcategories according to various classification systems (see below). Such classifications can be helpful in guiding decision making with respect to treatment, which necessarily differs from one type of hip fracture to another.^{4,5} In general, the choice of treatment is influenced by a range of patient-related factors that includes age, the presence and severity of comorbid medical conditions, previous mobility, cognitive status, fracture classification, and the status (i.e., preserved or disrupted) of the all-important blood supply to the femoral head. Failure of treatment frequently results from inappropriate choice of a

fixation method or misinterpretation of the fracture configuration.

Fractures of the femoral head are the most devastating of hip injuries and must be handled as surgical emergencies. They are generally classified according to Pipkin's system. Because substantial force is required to produce femoral head fractures, they are often seen in association with hip joint dislocations and acetabular fractures, most commonly in multiply injured patients who were involved in motor vehicle accidents. The diagnosis is made on the basis of pelvic and acetabular x-rays, supplemented by CT scans. Concomitant hip dislocations (most often posterior) should ideally be reduced with the patient under general anesthesia and with muscle relaxation achieved by upward traction with the hip in 90° of flexion.⁸⁰ If possible, this should be done in the ED to minimize delay in restoring blood flow to the femoral head. After reduction, the stability of the joint is tested clinically, and CT scanning is performed to assess impaction fractures, loose fragments in the hip joint, and the integrity of the acetabulum.

Most femoral head fractures are treated operatively if the patient's condition permits. For optimal results, this should be done within 24 to 48 hours after the injury, if possible. Closed treatment of dislocated fractures yields uniformly poor results. Internal fixation of these injuries is technically demanding and should allow early passive and active motion exercises postoperatively. Indomethacin is administered to prevent heterotopic ossification around the hip. Weight bearing is allowed after 10 to 12 weeks. In some patients, particularly physiologically older patients with major fractures, it may be best to insert a hip prosthesis primarily. Although operative treatment is usually necessary to provide the best chance of recovery, the magnitude of the initial trauma is generally such that good results can be obtained in only 50% to 70% of cases.^{4,5,81}

A typical patient with an intracapsular (femoral neck) fracture presents with a shortened, externally rotated, and abducted lower extremity. These fractures are often classified according to Garden's system. Treatment is determined by the fracture type and associated patient factors. Especially in young patients, because of the risk of nonunion and avascular necrosis, dislocated femoral neck fractures should preferably be treated on an emergency basis within 12 hours after the injury.⁸² In otherwise healthy and ambulatory patients, incomplete and impacted fractures (intact trabeculae of the inferior neck; Garden 1) may be managed with conservative treatment, consisting of early mobilization with crutches or a walker (to the extent permitted by the pain experienced) and supervised by a physical therapist. Secondary dislocation occurs in 10% to 50% of cases, leading to secondary operative treatment. Complete but undislocated fractures (Garden 2) are mostly treated operatively with cannulated screws or a sliding hip screw (e.g., Dynamic Hip Screw [DHS]; Synthes, West Chester, Pennsylvania). Sliding hip screws allow controlled compression of the fracture to be obtained during weight bearing as the lag screw slides into the plate. Complete fractures with partial (Garden 3) or complete displacement (Garden 4) are treated by means of early anatomic reduction with fixation to eliminate the risk of displacement and permit rapid mobilization. When the patient is physiologically older than 70 years, placement of a primary hip prosthesis is often indicated instead of internal fixation; however, this procedure is associated with higher perioperative morbidity and mortality.^{4,5,81,83}

Trochanteric fractures are the most common fractures of the proximal femur. They do not threaten the blood supply to the femoral head, because they occur below the extracapsular ring of vessels. Trochanteric fractures are classified according to the AO-ASIF system. Almost all patients with such fractures are candidates for internal fixation. The main exceptions are elderly patients who

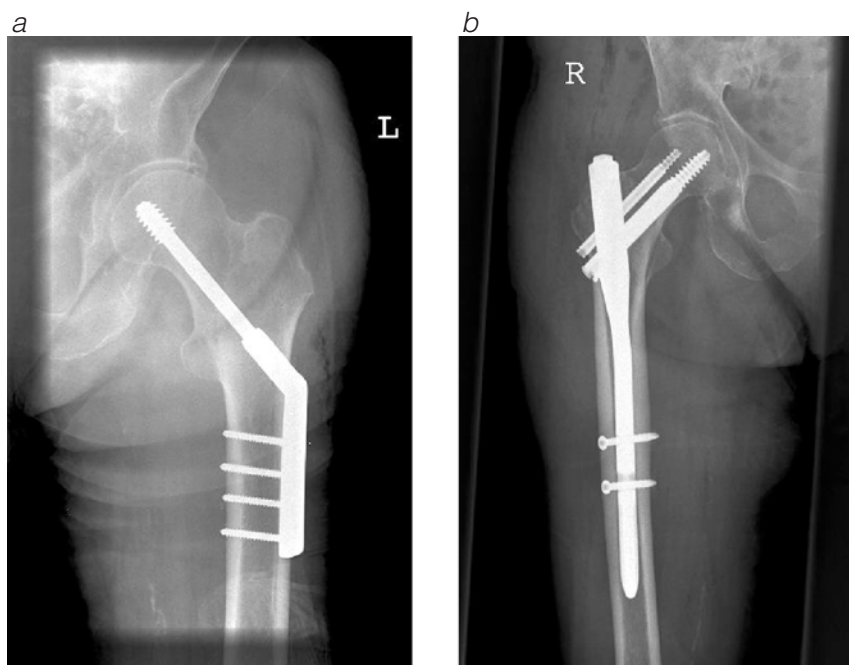


Figure 9 Shown are (a) fixation of AO-ASIF type A1 fracture with the Dynamic Hip Screw and (b) fixation of AO-ASIF type A2 fracture with the Proximal Femoral Nail.

had significant arthritis of the hip before sustaining the fracture; for these patients, placement of a hip prosthesis is an alternative.

The lesser trochanter provides crucial support for the medial femoral cortex; thus, assessment of its integrity is important for determining the stability of the fracture, which, in turn, helps determine treatment. The main treatment options are extramedullary and intramedullary implants. Extramedullary implants include sliding hip screws (see above), which are relatively easy to insert and also allow open reduction of the fracture if necessary. These implants are most suitable for stable (AO-ASIF type A1) fractures [see Figure 9a]. For unstable (AO-ASIF type A2 and A3) intertrochanteric fractures, intramedullary fixation is the treatment of choice because of the favorable position of the implants in the biomechanical loading axis of the femur. Examples include the Proximal Femoral Nail (PFN; Synthes, West Chester, Pennsylvania) [see Figure 9b], the Intramedullary Hip Screw (IMHS; Smith & Nephew, London, England), and the Gamma Nail (Stryker, Kalamazoo, Michigan). The operative technique for intramedullary fixation is more complex and unforgiving than that for extramedullary fixation, and various complications may arise, including malpositioning and femoral shaft fractures during insertion. Intramedullary implants are usually inserted percutaneously on a traction table with one or more screws in the femoral head and one or more distal locking screws. Internal fixation of trochanteric fractures should allow mobilization from postoperative day 1, preferably with full weight bearing or the use of a walker.^{4,5,84}

Subtrochanteric (AO-ASIF type A3) fractures are inherently unstable. Operative treatment may be difficult because high bending forces in the region (resulting from the angular shape of the proximal femur) often lead to implant failure before union. The preferred management approach is intramedullary nailing; the use of angled blade plates is an alternative, especially in young patients who require anatomic reduction.^{4,5}

Shaft

In most adults, considerable force is necessary to fracture the

femoral shaft; a simple fall seldom results in this type of fracture unless the bone has been weakened by osteoporosis or other disease. A patient with a femoral shaft fracture should therefore be considered a victim of high-energy trauma and evaluated accordingly.

Most fractures of the femoral shaft are easily recognized clinically on the basis of pain and abnormal position or movement. Because of the shape of the thigh, more than 1 L of blood may be lost into this space with little or no external indication. Neurovascular injuries are relatively uncommon in this setting; however, when the fracture is in the distal third of the femoral shaft, injury to either the superficial femoral artery or the popliteal artery may ensue as a consequence of the tethering of these vessels against the shaft at the level of the adductor canal. Femoral shaft fractures are often associated with injuries to knee ligaments, which are difficult to assess in the presence of the femoral fracture. Thus, when the patient is under anesthesia for treatment of the fracture, the stability of the knee should be assessed as well. Imaging consists of AP and lateral x-rays, with the hip and knee joints included.

In the ED, a fractured femur is immobilized with a vacuum splint or a Thomas splint. This measure reduces blood loss and lessens patient discomfort, and the splints need not be removed for x-rays to be taken. Ideally, femoral shaft fractures should be treated within 12 to 24 hours after the injury; preoperative skeletal traction is therefore superfluous. The main goal is stable fixation that yields correct length, rotation, and alignment, with full weight bearing possible within a few days of the operation.

Femoral shaft fractures of AO-ASIF types A to C are best treated with locked intramedullary nailing [see Figure 10]. In isolated instances, a plate or an external fixator may be indicated. Nailing lowers the incidence of respiratory distress syndrome, blood loss, and tissue trauma and reduces the patient's need for narcotics. In the setting of DCS, femoral fractures are initially stabilized by means of external fixation. The external fixator can then be exchanged for an intramedullary nail 2 to 10 days later without a significant increase in complications.^{12,13,85} Nailing can be performed with the patient supine on a fracture table or in a lateral



Figure 10 Illustrated (a through e) is treatment of comminuted AO-ASIF type C femoral fracture with intramedullary nailing. No attempt was made to reduce fracture fragments in order to preserve their vascularization. Healing was uneventful, with complete restoration of function.

decubitus position with closed reduction (or, if necessary, open reduction) of the fracture. Most nails are inserted in an antegrade manner through the greater trochanter or piriform fossa, though retrograde nailing through the intercondylar notch is becoming increasingly popular for distal shaft fractures. Reaming is generally advised because it reduces the rate of nonunion.⁵¹

Most complications with femoral shaft fractures are secondary to technical problems at the time of nailing and can therefore be prevented by paying close attention to technical details (in particular, the entry point of the nail and correct rotation). In rare instances, embolization of debris from reaming may lead to fat embolism syndrome (FES) [see Special Considerations, Complications, Fat Embolism Syndrome, *below*]. Infections occur mostly in open fractures and fractures where there is substantial soft tissue involvement. Compartment syndrome of the thigh may occur after femoral shaft fracture, albeit infrequently; it should be suspected if severe swelling is present.^{4,5}

Distal

Supracondylar (AO-ASIF type A) and intercondylar (AO-ASIF type B and C) fractures of the distal femur typically occur in young patients who have sustained high-energy trauma or in elderly patients with osteoporotic bone. Careful assessment of neurovascular status is important. X-rays focused on the knee should be supplemented with x-rays of the femoral and tibial shafts. CT can provide additional information on the fracture pattern and help in preoperative planning. Standard treatment consists of operative reduction and internal fixation, followed by partial-weight-bearing or non-weight-bearing active or passive exercises.

Supracondylar fractures can be treated with retrograde

intramedullary nailing or plating, depending on the surgeon's preference. Open reduction with extensive techniques for applying angled blade plates, condylar plates, sliding hip screws, and similar devices is currently being replaced by less invasive plating techniques using screws that are locked into the plate. An example of the latter is the Less Invasive Stabilization System (LISS; Synthes, West Chester, Pennsylvania), which allows submuscular fixation and percutaneous placement of self-drilling unicortical fixed-angle screws. The focus with this system is more on correction of length and alignment and less on anatomic reduction.

Intercondylar fractures are treated with anatomic reduction and screw fixation of the articular surface to allow early motion and thereby facilitate cartilage healing. Either open methods or image intensifier-assisted closed methods may be employed. The reconstructed articular surface is then connected en bloc to the femoral shaft with one of the previously described techniques (usually plating).^{4,5,86}

KNEE

Patellar Fracture

Knee injuries are common in multiply injured patients, in large part because of the vulnerability of this joint to dashboard injuries in automobile accidents and to direct trauma in motorcycle accidents. Patellar fractures usually result from a fall on the knee, a sudden forceful contraction of the quadriceps muscle with knee flexion, or a combination of the two. Other injuries (e.g., cruciate ligament failure and femoral fracture) may be present as well. The most important task in the examination is to confirm that the extensor mechanism is intact by asking the patient to raise the leg with the knee fully extended. X-rays should include AP, lateral, and

(optionally) tangential views.

Transverse and stellate fractures with minimal (< 1 to 2 mm) displacement and an intact extensor mechanism may be treated conservatively by keeping the joint in a cast for 6 weeks, with weight bearing allowed. All other fractures are treated by open reduction with internal fixation, typically with Kirschner wires and tension bands or cerclage wires. Postoperatively, early active motion and partial weight bearing are allowed. Severely comminuted patellar fractures may be irreparable; in such instances, a partial or total patellectomy with reconstruction of the extensor apparatus may be required. Ligamentous patellar injuries (e.g., to the quadriceps tendon or the patellar tendon) are treated by means of operative repair and reinsertion to the patella.^{4,5}

Dislocation

Knee dislocations, though potentially severe injuries, are generally rare, with only a few small series having been reported. They result primarily from motor vehicle and pedestrian accidents, falls, and sports activities, though they also occur spontaneously in morbidly obese persons. Their severity is determined by the complexity of the ligamentous injury and any associated trauma, including popliteal artery and vein injury (20% to 30% of cases) and peroneal nerve injury (25% to 35%). Failure to recognize vascular injury can lead to muscle necrosis and amputation. It is therefore essential that reduction of knee dislocations be carried out immediately, either before arrival at the hospital or in the ED, followed by vascular examination and x-rays. Anterior dislocation (30% to 40% of cases) is often caused by severe knee hyperextension, whereas posterior dislocation (25% to 30%) occurs with the application of force to the proximal tibia in an anterior-to-posterior direction, as in a dashboard-type injury or a high-energy fall on a flexed knee.

Physical examination reveals gross deformity around the knee with swelling and immobility. Occasionally, the knee will have relocated spontaneously before the patient arrives at the ED. Attention should be focused on the presence or absence of hard signs of vascular injury [see 7:13 *Injuries to the Peripheral Blood Vessels*]; if preferred, the ankle-brachial index (ABI), duplex scanning, or both may be employed in addition.^{5,37} Although many authors recommend mandatory arteriography or operative exploration for all knee dislocations, this recommendation is increasingly being questioned.⁸⁷⁻⁸⁹ The current literature indicates that the absence of hard signs reliably excludes a significant arterial injury that necessitates operative repair. The presence of hard signs of vascular injury, however, is an indication for arteriography; because about 25% of patients with hard signs actually have no vascular injury, arteriography serves to prevent many unnecessary vascular explorations. Another potentially valid (and timesaving) approach may be to take those with hard signs directly to the OR and obtain an on-table angiogram. In some instances, noninvasive tests may be able to distinguish patients who have vascular injuries requiring repair from those who do not.

Asymptomatic intimal injuries visualized by angiography do not call for surgical exploration, and the clinical value of interventional radiology techniques (e.g., stent placement) in this context is questionable. If there is a vascular injury that requires surgical repair, an external fixator that spans the knee joint should be quickly placed. Restoration of circulation has absolute priority in this situation; the amputation rate exceeds 80% when vascular repairs are done more than 8 hours after injury. Operative repair of nerve injuries is controversial. Optimal treatment of multiple ligament ruptures is also subject to debate. Many authors recommend early operative ligamentous repair followed by functional bracing and mobilization for

optimal results, whereas others recommend primary immobilization followed, if necessary, by late reconstructions.^{4,5,90}

Ligamentous Injury and Meniscal Tearing

Distortions of the knee are common injuries; most involve varus, valgus, or rotational deformities. The history should focus on the mechanism of injury, the type and location of pain, any associated symptoms, the amount of immediate dysfunction, the presence and onset of joint edema, and any history of past knee problems. The physical examination should include inspection, active motion, and stress testing to detect instability. Hemarthrosis is a sign of possible cruciate ligament injury. If pain and swelling preclude reliable examination, the examination should be repeated in 5 to 7 days. Collateral ligament injuries are graded on a scale of I to III. A grade I injury is a sprain (with stretching but no tearing of the ligament, local tenderness, minimal edema, and no gross instability on stress testing), a grade II injury is a partial ligament tear (with moderate local tenderness and mild instability on stress testing), and a grade III injury is a complete tear (with discomfort on manipulation, a variable amount of edema, and clear instability on stress testing).

X-rays of the knee are obtained to detect any fractures of the tibial plateau or the intercondylar eminence. The number of unnecessary x-rays may be substantially and safely reduced by applying the so-called Ottawa knee rule. This rule specifies the following indications for x-rays: age 55 years or older, tenderness at the head of the fibula, isolated tenderness of the patella, inability to flex the knee 90°, and inability to walk four weight-bearing steps immediately after the injury and in the ED. MRI is useful for detecting ligamentous, meniscal, and cartilage injuries but is rarely indicated on an emergency basis.

Treatment depends on the patient's age and activity level and should always include appropriate reeducation and strengthening of the relevant muscles (hamstrings and quadriceps). Grade I and II collateral ligament injuries (which are usually medial) may be treated conservatively with early active motion, with or without a knee brace. Grade III medial collateral ligament injuries may be treated in a knee brace for 6 weeks, but grade III lateral collateral ligament injuries must be treated surgically because conservative treatment frequently leads to chronic instability. Anterior cruciate ligament ruptures are increasingly being treated by operative means in serious athletes and other physically active persons. The ligament is arthroscopically reconstructed with a section of the patellar tendon or the semitendinous tendon. Isolated posterior cruciate ligament ruptures, which are considerably less common, are primarily treated nonoperatively.^{4,5,91}

Meniscal tears occur mainly in physically active persons, though they may also result from simple distortions experienced during activities of daily living, especially if the meniscus has previously undergone some degeneration. Complaints include mild pain, swelling, grinding, locking, and "giving way." Clinical diagnosis is aided by provocative tests (e.g., the McMurray and Appley tests), but when symptoms persist, MRI is often performed. Mild meniscal tears may be treated conservatively, whereas symptomatic lesions usually call for surgical treatment. In general, meniscal repair is indicated when the tear is in the vascular outer one third of the meniscus, and partial excision is indicated when the injury is in the avascular inner two thirds.⁵

TIBIA

Proximal

Tibial plateau fractures are intra-articular fractures that mostly

result from indirect varus or valgus trauma. The amount of displacement and comminution is determined by the magnitude and direction of the forces applied. High-energy fractures may be associated with severe soft tissue injuries, as well as ligamentous and meniscal tears. It is important to recognize that severe proximal tibial fractures can represent a reduced fracture dislocation of the knee, and thus, the neurologic and vascular concerns that accompany knee dislocations can apply to these fractures as well [see Knee, Dislocation, *above*].

Tibial plateau fractures are characterized by local pain, swelling from hemarthrosis, and, in some cases, instability of the knee joint. Aspiration of a tense hemarthrosis is sometimes required to decompress the joint and relieve pain. Only 6% of patients with knee trauma have a fracture. The need for x-rays is generally determined according to the Ottawa knee rule [see Knee, Ligamentous Injury and Meniscal Tearing, *above*].⁹² If a fracture is confirmed, CT scanning with axial, coronal, and sagittal reconstructions is done to delineate the severity and orientation of the fracture lines. This measure also helps the physician decide whether operative or nonoperative treatment is indicated and, if the former, which operative approach should be taken. If the condition of the soft tissues precludes early definitive operative treatment, a plaster splint or temporary external fixation may be employed to allow the soft tissues time to heal or to give the surgeon time to plan an operative procedure for soft tissue coverage.

Proximal tibial fractures are classified according to the AO-ASIF system or the Schatzker system. Extra-articular AO-ASIF type A1 and A2 fractures and minimally (< 2 mm) displaced intra-articular fractures (AO-ASIF type B and C) may be treated conservatively; all others should be treated operatively. Operative treatment consists of anatomic reduction of the articular surface, either under direct vision (arthrotomy) or via a less invasive approach (with arthroscopic or fluoroscopic assistance). Reduction is held with screws, plates, or both, and often, the use of iliac bone grafts or bone substitutes (e.g., calcium phosphates) is required to maintain the elevation of the articular surface. The articular “block” is connected to the tibial shaft by means of plates and screws; if soft tissue injuries preclude plating, special external fixation devices (i.e., ring fixators with tensioned wires) may be employed instead. Fixed-angle plating systems that allow less invasive insertion methods are also gaining popularity for use in the proximal tibia. Early motion is appropriate after operation, with weight bearing allowed after 8 to 12 weeks. Disabling complications include infection, posttraumatic arthritis, and instability of the knee.^{4,5}

Shaft

Fractures of the tibial shaft are among the most common serious fractures. The subcutaneous location of the tibia affords little protection from direct violence, and high-energy fractures are associated with longer healing times. Tibial fractures can be fraught with complications (e.g., compartment syndrome, nonunion, delayed union, malunion, and infection), and in their most severe manifestations, they can end in amputation. Tibial shaft fractures are easily diagnosed clinically in the ED. Examination includes palpation for signs of possible compartment syndrome and assessment of the neurovascular status. If the fracture is grossly angulated or malaligned, gentle restoration of axial alignment helps relieve vascular kinking and compromise. The extremity should be splinted, and appropriate x-rays should then be obtained to allow full assessment of the fracture.

Selected closed fractures without dislocation and minimally displaced AO-ASIF type A fractures may be treated conservatively

with an above-the-knee cast for 2 to 4 weeks, followed by functional bracing for 10 to 16 weeks. Bracing relies on the intact soft tissues, primarily the interosseous membrane, to prevent shortening and dislocation.⁹³ Displaced and unstable AO-ASIF type A, B, and C fractures, as well as all open fractures, are treated operatively. The severity of any associated soft tissue injury is a crucial factor in deciding how to manage of tibial shaft fractures. The standard treatment for such fractures—closed reduction with reamed, interlocking intramedullary nailing—has a high success rate and a low complication rate [see Figure 11]. In those unusual circumstances in which the fracture pattern does not permit insertion of an intramedullary rod (e.g., certain fractures in the proximal or distal third of the shaft), plate fixation may be employed instead; unfortunately, this procedure is associated with a high rate of nonunion.^{4,5,51}

For open fractures associated with complex wounds, the standard treatment has been external fixation, which permits stabilization of the fracture, affords ready access to large open wounds, and facilitates nursing care. Currently, however, nailing appears to be superior to external fixation for grade 1 and 2 open fractures: the infection rate is no higher, the complication rate is lower, and the functional end results are better. Grade 3 open fractures are highly complex injuries, and an expert team that includes a plastic surgeon is required for optimal management. Aggressive irrigation and debridement are followed by either external fixation or intramedullary nailing, depending on the state of the surrounding soft tissue factors, the fracture pattern, time-related factors, and the surgeon's preference. If secondary soft tissue procedures involving a pedicle or a free flap are warranted, they should be planned at an early stage in treatment. In multiply injured patients who require DCS, tibial shaft fractures are initially stabilized with external fixation, with care taken to place the fixator pins strategically, in anticipation of subsequent soft tissue coverage procedures. Once the patient is physiologically stable, the fixator may be removed and intramedullary nailing performed. In these patients, a combination of retrograde femoral nailing and antegrade tibial nailing done through a single knee incision offers an elegant and less invasive means of stabilizing a floating knee.

One of the most severe complications that may develop after a tibial fracture is compartment syndrome [see 7:13 *Injuries to the Peripheral Blood Vessels*]. When the fracture is in the distal third of the shaft, delayed union or nonunion is a particular risk as a consequence of the limited vascularization provided by the predominantly posterior soft tissue envelope.^{4,5}

Distal

Fractures of the distal tibia mostly result either from vertical loading that drives the talus into the tibia (as in a fall from a height or a motor vehicle accident) or from low-energy trauma with torsion (as in skiing). Intra-articular fractures in this region are called tibial plafond (ceiling) or pilon fractures. Pilon fractures are frequently accompanied by severe soft tissue swelling and comminution of the articular surface and the metaphysis; the fibula may or may not be fractured. Standard AP and lateral x-rays are obtained in conjunction with CT scans to define the fracture pattern and aid in preoperative planning. The goals of treatment are to restore ankle joint integrity, congruency, and stability; to achieve bony union; and to allow functional painless motion. In cases where there is substantial soft tissue involvement, staged surgery may be advisable. A safe option is to apply a bridging external fixator from the midtibia to the foot, leaving enough distance between the fixator pins to allow future incisions in the distal tibia; this may be done with or without primary percutaneous screw fixation of the joint

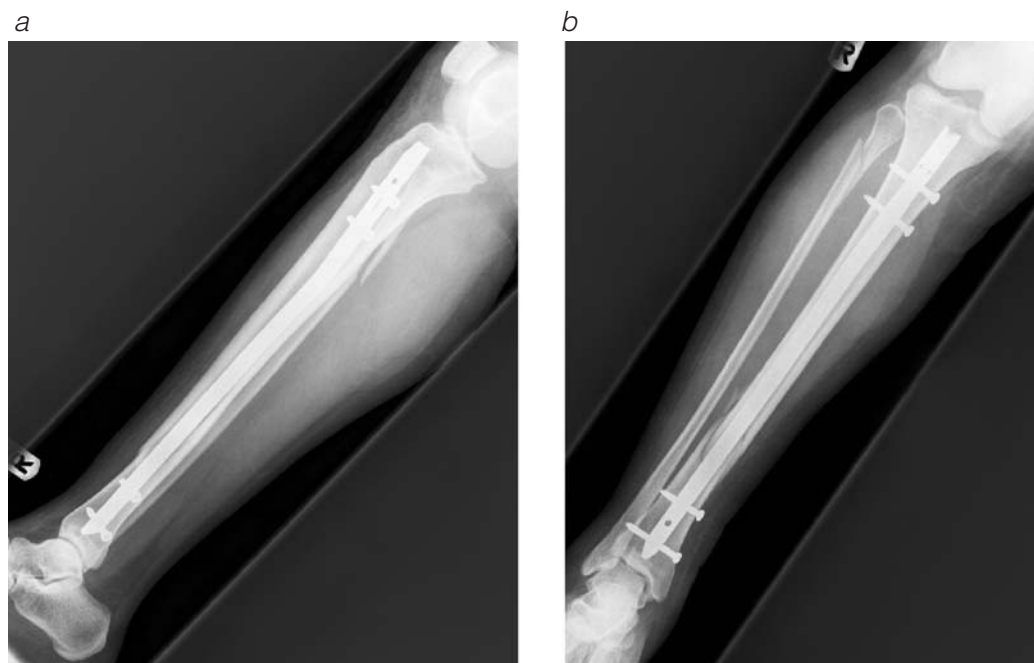


Figure 11 Shown (*a, b*) is treatment of closed AO-ASIF type A1 tibial fracture with reamed intramedullary nailing.

surface and with or without primary fixation of the fibula to restore the length of the ankle.

Fractures that are not accompanied by dislocation (mostly AO-ASIF type A1) may be treated conservatively in a cast for 8 weeks. All other distal tibial fractures generally require operative treatment, the basic principles of which resemble those appropriate for proximal tibial fractures. Because of the typical swelling and the frequent presence of fracture blisters, optimal timing of the procedure is critical. For extra-articular (AO-ASIF type A) fractures, a minimally invasive approach involving percutaneous insertion of a plate with locking screws (e.g., the LCP) may be feasible. For intra-articular (AO-ASIF type B and C) fractures, anatomic reduction of the articular surface and internal fixation are required, preferably performed by an experienced surgeon. As a rule, the fibula is fixed first through a lateral incision, and the tibia is then fixed via an anterior or medial approach. Dissection should be minimized to prevent further soft tissue injury. Any debris present in the joint is removed. After reconstruction of the articular surface, a connection with the tibial shaft is made, most frequently with a plate and screws or with a hybrid ring fixator. With most AO-ASIF type C distal tibial fractures, the use of a bone graft or bone substitute is required to support the articular surface. After the procedure, the patient is allowed to engage in active movement without weight bearing for 8 to 12 weeks. The outcome of treatment of pilon fractures depends primarily on the quality of the articular reduction and the recovery of the soft tissues. Such fractures frequently give rise to severe posttraumatic arthritic pain, and delayed ankle fusion may be required.^{4,5}

FIBULA

Shaft

Generally, fibular shaft fractures may be ignored. Such fractures heal readily, sometimes so readily that they interfere with the union of associated tibial fractures. Isolated midshaft fibular fractures that do not involve the ankle joint may be treated symptomatically, often without a cast. In some instances, plating the fibular fracture

provides additional stabilization for an unstable distal tibial shaft fracture; however, rendering the fibula stable may diminish the cyclic compression that occurs with weight bearing at the site of the tibial fracture and thus may delay healing. For this reason, in most cases of combined tibial and fibular fracture, the fibula is not stabilized.⁵

ACHILLES TENDON

Achilles tendon ruptures are mainly caused either by sudden forceful dorsiflexion of the foot with the knee extended (placing the soleus and gastrocnemius muscles on maximal stretch) or by sudden takeoff during athletics. They are frequently seen in weekend athletes, as well as in more regular participants in active sports (e.g., football, volleyball, tennis, and squash). A common scenario is one in which the patient wrongly believes that someone has hit him or her on the heel; sometimes, the patient hears a snap as well. On physical examination, a visible or palpable dent is apparent in the tendon 2 to 6 cm above the calcaneus. The Thompson test is useful for confirming or ruling out an Achilles tendon rupture. For this test, the patient is placed in the prone position with both feet extending past the end of the examining table. If squeezing of the calf muscles on the affected side does not result in plantar flexion of the foot, the tendon is ruptured; if this maneuver does result in plantar flexion, the tendon is intact. If the patient does not present until several days after the injury, diagnosis may be more difficult. In such cases, ultrasonography or MRI may be helpful.

Treatment may be nonoperative (i.e., immobilization in plantar flexion) in certain patients, but it is operative in most. Operative treatment consists of surgical repair of the tendon either via full exposure of the tendon or via a minimally invasive approach (e.g., suture anchors); the latter may be preferable for minimizing wound healing problems. After the procedure, the injured area is kept in a soft cast for 6 weeks, during which period the patient is allowed active movement with weight bearing. Surgical treatment substantially reduces the incidence of recurrent ruptures; however, it is also associated with an increased risk of wound healing problems and surgical site infection.^{5,94}

ANKLE

Fracture and Dislocation

Ankle fractures are usually caused by indirect trauma. They are generally categorized according to the AO-ASIF classification system, which also guides treatment decisions. The factors that determine the type of fracture present include age, bone density, the position of the foot at the time of injury (pronation or supination), and the direction of the forces that acted on the joint to produce the injury (adduction, abduction, exorotation, or axial loading). The history and physical examination reveal pain, swelling, functional impairment, and inability to bear weight. Conventional x-rays usually suffice for diagnosis. A true AP (mortise) view requires 20° of internal rotation for adequate assessment of the joint. If the fracture is particularly complex, CT scanning should be performed to obtain additional information. The two main factors to consider in the management of ankle fractures are the congruency of the ankle joint medially, laterally, and superiorly (i.e., with respect to the tibia, the fibula, and the talus) and the presence of soft tissue injury (because there is little muscle coverage in this area). Even small disturbances of ankle congruity (e.g., widening of the mortise) can lead to overloading of the cartilage and predispose to posttraumatic arthritis.

Type A fractures are transverse lateral malleolar fractures that occur distal to the syndesmosis, at or just below the level of the ankle joint. They may be treated either conservatively in a plaster cast or functionally in a soft cast for 4 to 6 weeks with full weight bearing allowed.

Type B fractures are oblique or spiral fractures of the lateral malleolus that occur at the level of the syndesmosis, with or without a fracture of the medial malleolus. Whereas nondislocated type B fractures may be treated conservatively, all other type B fractures are treated by means of open reduction and internal fixation with a plate or screws, followed by protected weight bearing. The best time for operative treatment is within the 8 hours following admission. After 24 hours, edema increases, and surgery is best postponed until 5 to 7 days later, when the condition of the soft tissue has improved. In the meantime, the fracture or dislocation is reduced, and a splint is applied.

Type C fractures occur above the syndesmosis. Sometimes, a fracture is located near the fibular head proximally. In such cases, the interosseous membrane and the syndesmosis are ruptured between the fibular fracture and the ankle joint (Maisonneuve fracture). This type of injury is easily missed if a careful examination is not performed and the appropriate proximal x-ray obtained. Type C fractures are generally treated surgically with plating or with one or two fibulotibial syndesmotomic positioning screws, which allow the syndesmosis to heal with a correct length and position relative to the talus of the fibula.

Malleolar fractures are frequently associated with fractures of the posterior lip of the tibial plafond (trimalleolar fractures). Large fragments (> 20% of articular surface) should be reduced and fixed to prevent posterior dislocation of the talus. Early complications include inadequate reduction and fixation, wound problems, and infection. Long-term results are primarily determined by the presence and extent of cartilage damage and by the congruency of the ankle joint. Approximately 30% of patients experience persistent symptoms around the ankle.^{4,5,95}

Isolated ankle dislocations without fractures are rare; 30% of these injuries are associated with an open wound extending into the joint. A dislocated ankle should immediately be reduced—before x-rays are taken if possible—to minimize further neurovascular compromise. After closed or open reduction, wound care is

provided and immobilization instituted.⁵

Ligamentous Injury

Ankle ligament injuries are among the most common injuries seen in the ED. They often occur during sports activities as a result of inversion during plantar flexion of the ankle. Approximately 85% of ligamentous ankle injuries involve one or another of the three lateral ligaments: the anterior talofibular ligament, the calcaneofibular ligament, and the posterior talofibular ligament. Approximately 65% of ankle sprains resulting from inversion occur in the anterior talofibular ligament alone. Ankle sprains are commonly classified into three grades: grade I is a sprain with stretching of the ligament, grade II is a partial ligament tear, and grade III is a complete tear. This classification does not, however, guide treatment. Diagnosis is based on the history and the physical examination (including the anterior drawer test). X-rays are obtained if a fracture is suspected. The number of unnecessary x-rays can be markedly and safely reduced by applying the so-called Ottawa ankle rule [see Figure 12], which is analogous to the Ottawa knee rule described earlier [see Knee, Ligamentous Injury and Meniscal Tearing, above].⁹⁶

The main treatment options for ankle ligament injuries are immobilization in plaster, functional treatment (early mobilization with the joint in tape or a soft cast), and surgical repair. Current evidence indicates that functional treatment is the recommended strategy for most patients.^{97,98} Approximately 20% of patients experience varying levels of recurrent or chronic symptoms.

FOOT

The foot is a complex system consisting of numerous bones, ligaments, and tendons. Accordingly, many different types of foot injury are seen. The history plays an important role in identifying the mechanism of injury. Foot injuries do occur as isolated events, but they also frequently occur in conjunction with distant injuries and thus may easily be missed initially in cases of polytrauma. Physical examination includes assessment of the soft tissues of the foot and ankle, the degree of pain felt on compression, the stability of the injured area, and the neurovascular status of the foot. Conventional x-rays are often supplemented with CT scans; MRI and bone scintigraphy are also sometimes employed, though less frequently.^{4,5} The pain, swelling, functional impairment, and deformity associated with foot injuries can markedly limit the patient's mobility. In recent years, it has become clear that function can be improved by restoring the normal anatomy and avoiding prolonged immobilization in plaster.

Talus

The talus plays an important role in the transmission of force to the rest of the foot, with 60% of its surface covered by cartilage. This cartilaginous covering, in combination with a delicate blood supply, makes talus fractures complex injuries. Fractures and dislocations of the talus typically result from high-energy trauma (as in motor vehicle accidents or falls). Most talus fractures are intra-articular; sometimes, the only damage consists of an osteochondral flake (e.g., from an ankle sprain).

Most talus fractures are treated operatively. Ideally, surgical treatment should be carried out as early as possible, especially if the fracture involves the talar neck. Screw fixation may be accomplished either via open reduction or percutaneously (if displacement is minimal). After the operation, active motion is allowed, and weight bearing is started after 8 to 12 weeks. The outcome of treatment is determined primarily by the presence or absence of open wounds, the fracture type, and the status of the remaining

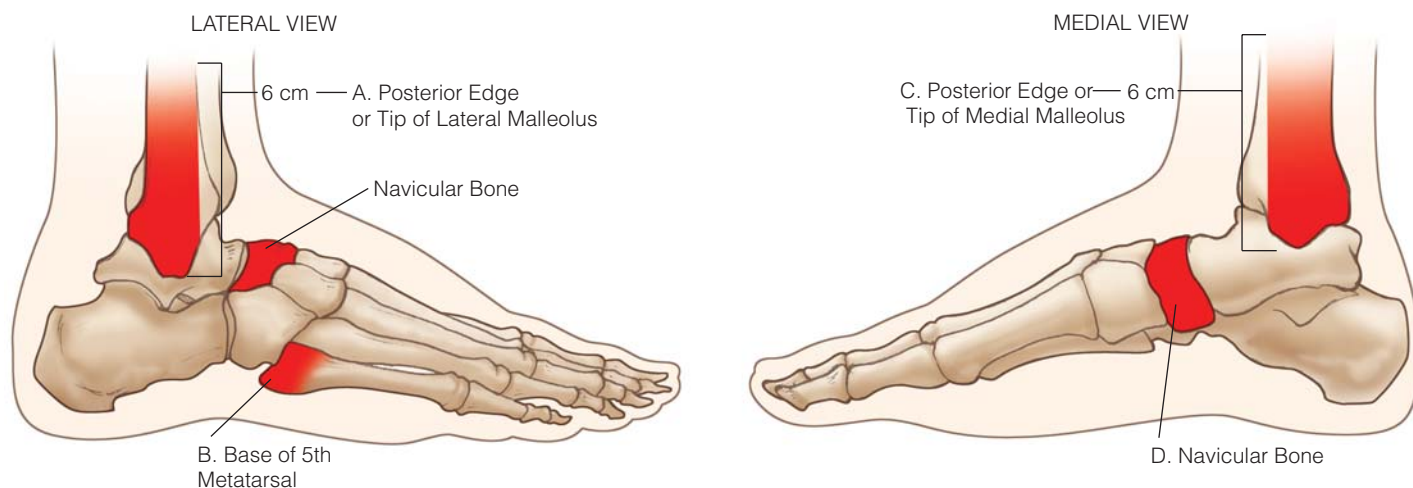


Figure 12 Illustrated is the Ottawa ankle rule. According to this rule, an ankle or foot x-ray series is required only if (1) palpation of the marked areas is painful or (2) the patient is completely unable to bear his or her own weight both immediately after the injury and for four steps in the ED.

blood supply. Avascular necrosis, infection, and posttraumatic arthritis can lead to severe disability.^{4,5,99}

Calcaneus

The calcaneus is the most frequently fractured bone in the foot. Fractures of the calcaneus are primarily caused by falling or jumping from a height and thus are commonly seen in combination with other injuries (e.g., spine fractures). Examination typically reveals marked swelling of the foot, with or without deformity. Lateral x-rays of the foot show a reduction in Böhler's angle (the posterior angle formed by the intersection of a line from the posterior to the middle facet with a line from the anterior to the middle facet) from the normal range of 20° to 40°. Conventional x-rays are always supplemented with CT scans to delineate the extent of the fracture.

Most extra-articular and nondislocated intra-articular fractures can be treated conservatively with non-weight-bearing mobilization of the ankle and the foot over a period of 6 to 12 weeks; there is no need for a splint or a cast. Optimal treatment of intra-articular fractures—in particular, the role of surgery—remains subject to debate, however. Depending on the fracture configuration, reduction and internal fixation of the joint surfaces may be accomplished either via an open approach or percutaneously. The same measures recommended as conservative treatment are then carried out as postoperative treatment. Whether this strategy yields better functional results than conservative treatment is not clear. However, there is currently a trend toward operative treatment in situations where anatomic reconstruction of the subtalar and calcaneocuboidal joints can be achieved. Smoking, advanced age, diabetes, and noncompliance are relative contraindications to surgical management. A substantial percentage of patients heal with malunion or experience posttraumatic arthritis. These patients are candidates for arthrodesis of the subtalar joint.^{4,5,100,101}

Midfoot

The midfoot contains the navicular bone, the cuboid bone, and the three cuneiform bones (medial, intermediate, and lateral). Proximally, the navicular and the cuboid articulate with the talus and the calcaneus (Chopart's joint); distally, the cuboid and the cuneiforms articulate with the metatarsals (Lisfranc's joint). Fractures and ligamentous injuries in these joints are easily missed

and can lead to prolonged deformity, pain, and functional impairment. Restoration of the anatomy both medially and laterally is important for a good outcome.

The majority of nondislocated fractures, extra-articular fractures, and ligament avulsion fractures of the midfoot can be treated nonoperatively in plaster or with functional therapy and early motion. Dislocated fractures are generally treated operatively with screw or plate fixation unless such treatment is precluded by severe comminution. Fractures in Lisfranc's joint mainly result from high-energy trauma and are often associated with dislocation of one or more metatarsal bones. Such fractures are treated by means of operative reduction and fixation with Kirschner wires or screws.^{4,5,102,103}

Metatarsals and Toes

Most metatarsal fractures result from direct trauma (e.g., from a heavy object falling on the foot); however, they can also occur with chronic repetitive loading in the absence of obvious trauma (so-called stress or march fracture).

For the most part, fractures of the second through fourth metatarsals and nondislocated fractures of the first and fifth metatarsals can be treated nonoperatively by using a plaster cast or a heavy supportive shoe for 4 to 6 weeks. With the majority of displaced fractures, closed reduction can be achieved, but maintenance of the reduction requires internal fixation; malunion can disturb ambulation. Many fractures of the lesser metatarsals and subcapital fractures can be treated with percutaneous pinning. Fractures with joint involvement and multiple fragments frequently necessitate treatment with open reduction and plate fixation. Fractures of the base of the fifth metatarsal form a special group. The mechanism of injury is identical to that seen in ankle sprains. These fractures are generally divided into two types: avulsion fractures (involving the insertion of the peroneus brevis tendon) and transverse fractures of the base of the fifth metatarsal (Jones fracture). Both types may be treated nonoperatively if displacement is minimal, but delayed healing is common with Jones fractures. Operative treatment consists of tension-band wiring or screw or plate fixation.^{4,5,104}

Fractures and dislocations of the toes result from direct trauma. Virtually all toe fractures can be treated conservatively by taping the injured toe to an adjacent, uninjured toe (so-called buddy tape). On

rare occasions, reduction and Kirschner wire fixation of a dislocated toe fracture are indicated. Toe dislocations are reduced with traction and are treated in much the same way as toe fractures.⁵

Special Considerations

GERIATRIC TRAUMA

Musculoskeletal injuries in the elderly are a rapidly growing health problem and cause considerable morbidity and mortality. Advanced age, increased risk of falling, and reduced bone mineral density are the most important risk factors for the occurrence of osteoporotic fractures. Although many standard principles of extremity trauma management apply to the elderly, there are also certain concerns that are specific to this population. Hence, in evaluating an elderly person who has sustained an extremity injury, it is essential to assess the entire patient, not just the affected bone or joint.

One issue is that injured elderly persons often have one or more comorbid conditions, the presence of which increases perioperative risk. Advances in medical and anesthetic techniques have made it safe for many patients to undergo surgical procedures that previously would have been contraindicated; however, the timing of surgery can still pose problems. Ideally, sufficient time should be taken to ensure that patients receive optimal preoperative preparation, but such preparation should be provided with the understanding that delaying surgery unnecessarily will increase mortality. Inadequate nutrition is common in the elderly and should receive appropriate attention. The presence of osteoporosis can be confirmed by measuring bone mineral density (e.g., with dual-energy x-ray absorptiometry). Treatment of osteoporosis consists of a combination of physical exercise, dietary supplementation (with calcium and vitamin D), and administration of bisphosphonates (e.g., alendronate). Elderly patients have special needs with regard to rehabilitation, in that dependence or immobility may necessitate institutional care.¹⁰⁵⁻¹⁰⁷

REHABILITATION

The care of a patient with musculoskeletal injuries does not stop when the last operation is performed. Adequate rehabilitation is critical for ensuring the best possible functional outcome. Physical therapists, occupational therapists, speech trainers, dietitians, social workers, and psychologists may all play roles in this process. To ensure optimal continuity of treatment from the hospital to the rehabilitation center, rehabilitation experts should be involved early after the admission of a patient who has sustained severe pelvic or extremity trauma.^{4,5}

COMPLICATIONS

Systemic complications of pelvic and extremity trauma include FES, ARDS, hemorrhagic complications, crush syndrome, and thromboembolism. Severe local complications include compartment syndrome, acute and chronic infection, infected nonunion, malunion, and posttraumatic reflex sympathetic dystrophy.

Fat Embolism Syndrome

FES is most commonly associated with fractures of long bones of the lower extremity. The classic clinical triad consists of respiratory distress, cerebral dysfunction, and petechial rash. The pathophysiology is not clear, but there is some evidence to suggest that extravasation of fat particles from long bone fractures may play an important part. Furthermore, early stabilization of long bone fractures has been shown to decrease the incidence of FES. Signs and

symptoms of clinical FES usually begin within 24 to 48 hours after trauma. Treatment is primarily prophylactic and supportive, consisting of early fracture fixation, careful volume replacement, analgesia, and respiratory support. The role of corticosteroids in this setting is controversial.^{4,5,108,109}

Thromboembolism

Both symptomatic and asymptomatic DVT can pose serious problems in trauma patients. DVT is an important cause of pulmonary embolism (PE) and often results in major morbidity or death. The incidence of DVT ranges from 4% in patients with conservatively treated lower-extremity injuries to between 20% and 35% in patients with pelvic and acetabular injuries and patients with hip fractures. All trauma patients should therefore receive DVT prophylaxis. Once a thromboembolic event has occurred, the patient should be immediately treated with I.V. anticoagulants according to local protocols. Prevention and treatment of DVT and PE are discussed in greater detail elsewhere [see 6:6 *Venous Thromboembolism*].^{4,5,10,110-113}

Infection

Infections that develop after osteosynthesis are nearly always caused by exogenous bacteria. Contamination may occur in the course of the injury (as with an open fracture), during surgical treatment, or postoperatively (as a result of disturbed wound healing). Most infections manifest themselves within the first 7 days after the operation. Some become apparent only after a longer period has elapsed; these are often preceded by an unnoticed low-grade infection. The infection types most frequently associated with osteosynthesis are implant-related infections (involving colonization of fixation materials), osteomyelitis (a bone infection), and infectious arthritis. Diagnosis is based primarily on clinical signs (e.g., redness, fever, and pain), laboratory studies (e.g., C-reactive protein level and leukocyte count), and bacteriologic tests. In patients with late-developing infections, x-rays, CT, and MRI can provide additional useful information. Treatment consists of surgical debridement, open or closed wound management, and supplemental local or systemic antibiotic coverage. For cases of chronic osteomyelitis, advanced soft-tissue coverage procedures are frequently required. Implant removal is generally unnecessary as long as the implant provides stable fixation.

Gas gangrene is the most serious infection seen in traumatic wounds; *Clostridium perfringens* is the classic causative pathogen. Other gas-forming organisms common seen include coliforms, anaerobic streptococci, and *Bacteroides*. Pain is the initial symptom of gas gangrene, followed by edema and exudation of a thin, dark fluid. The wound acquires a bronze discoloration and a musty smell, and crepitations develop in the muscles. Symptoms progress rapidly, and profound shock and MODS usually ensue. The diagnosis is made on clinical grounds, supported by Gram's staining. Successful treatment depends on early diagnosis, radical surgical debridement, fasciotomy, and I.V. antibiotic therapy.^{4,5,114}

Delayed Union, Nonunion, and Malunion

At present, there is no consensus among surgeons on how best to assess fracture healing—and, therefore, no consensus on precisely what constitutes delayed union, nonunion, or malunion. In general, delayed union refers to a fracture that heals more slowly than the average. “Average” depends on the fracture's location and type, but 3 months is a frequently accepted time limit for delayed union.

Nonunion refers to a failure of bone healing that results from an arrested growth process; 6 months is the usual time limit. Nonunion has numerous potential causes, but the most important

factors leading to nonunion are disturbance of the blood supply and insufficient fracture stability. The blood supply is disturbed both by the injury itself and by the surgical procedure performed to treat the injury. Instability results from inadequate fixation technique, a suboptimal implant choice, or implant failure. In some nonunions, a false joint with a fibrocartilaginous cavity lined with synovium is formed (a condition also referred to as pseudarthrosis). Treatment of hypertrophic nonunions focuses primarily on achieving adequate stability, whereas treatment of atrophic nonunions requires not only achieving stability but also reversing the atrophy to the extent possible. The gold standard for treatment of atrophic nonunions is placement of a cancellous autologous bone graft, which has the advantage of being osteogenic, osteoinductive, and osteoconductive. Unfortunately, the morbidity from cancellous bone harvesting can be considerable.

Malunion is a deformity characterized by abnormal length,

rotation, or angulation. The degree of malunion that is acceptable with respect to function and cosmesis varies with the age of the patient and the location of the fracture.^{4,5}

Reflex Sympathetic Dystrophy

Posttraumatic reflex sympathetic dystrophy (also referred to as complex regional pain syndrome) is a poorly understood complication that may develop in any of the extremities after an operation or even minor trauma. It is capable of causing severe disability^{4,5,115,116} Symptoms include unexplained diffuse pain, skin changes, edema, temperature changes, and functional impairment. The optimal treatment regimen has not been established; common therapeutic measures include free radical scavenger treatment (e.g., with systemic acetylcysteine and local dimethyl sulfoxide cream), administration of vitamin C, analgesia, vasodilatation, and careful physical therapy.

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13 INJURIES TO THE PERIPHERAL BLOOD VESSELS

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Before and during World War II, the management of extremity vascular trauma consisted of vessel ligation, which resulted in amputation rates as high as 70%. As surgical techniques improved and primary arterial repair became standard, amputation rates declined to approximately 30%. By the time of the Vietnam War, the use of routine angiography and repair had reduced amputation rates to 15%.¹ On the modern battlefield, the incidence of extremity injury remains high, with 88% of vascular injuries occurring in the extremities.^{2,3} Current management of extremity arterial trauma yields amputation rates ranging from 5 to 20%.^{2,4,5}

This chapter outlines the current standard of care for vascular injuries in the extremities and incorporates the influx of endovascular modalities for the management of vascular trauma. Management of such injuries requires knowledge of the mechanism of injury, awareness of high-risk injury patterns, familiarity with modern diagnostic techniques and their indications, and a comprehensive understanding of the assessment, triage, and management decisions that influence outcome in this setting.

Mechanisms and Sites of Extremity Vascular Injury

BLUNT VERSUS PENETRATING TRAUMA

Arterial trauma is typically classified according to the general mechanism of injury—that is, blunt or penetrating—because different mechanisms tend to produce different types of injuries. After blunt trauma, the vascular injury most commonly seen is avulsion. This stretching type of damage can result in the disruption of either the intima or both the intima and the media, leaving a highly thrombogenic adventitia to maintain temporary vessel continuity [see Figure 1]. Complete occlusion typically occurs when significant intimal damage leads to thrombosis of the artery. Injuries that do not produce occlusion may give rise to an intimal flap, a pseudoaneurysm (secondary to partial arterial injury), or an arteriovenous (AV) fistula.

Penetrating trauma can transect the vessel completely, which may be manifested as a thrombosis (resulting from vessel spasm) or frank bleeding. If the vessel is only partially transected, it may contract and continue to bleed; even if it is initially controlled, it may rebleed as the patient is resuscitated and arterial pressure rises toward normal. In many cases of penetrating trauma, the location of a presumed vascular injury may be determined simply by following the path of the penetrating object. If there is evidence of ongoing bleeding from a penetrating vascular injury, prompt operative intervention, without further evaluation, is indicated. The risk of amputation varies: stab wounds

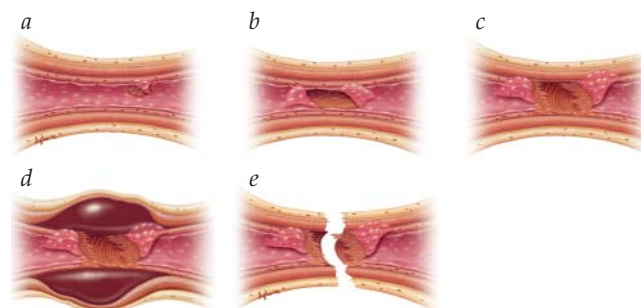


Figure 1 An avulsion injury, in which the artery is stretched, resulting either in partial (a) or complete (b) intimal disruption or in complete intimal or medial disruption (c), with or without pseudoaneurysm formation (d) and complete separation of all layers of the vessel wall (e).

are unlikely to lead to amputation, whereas high-velocity firearm injuries with concomitant blast effect and tissue loss are considerably more likely to do so.⁶ In modern military contexts, blast injuries account for 50 to 70% of cases of vascular trauma.² Vascular trauma from blast wounds may present as thrombosis (related to intimal injury resulting from the application of kinetic force to the tissue) or as deep cavitary injuries with vessel disruption and even segmental arterial loss.

LOCATION OF INJURY AND RISK OF AMPUTATION

Extremity vascular trauma is commonly encountered by surgeons in both urban and rural practices. In urban settings, upper and lower extremity injuries account for 40% and 20% of all vascular injuries, respectively.⁷ In rural settings, extremity injuries account for approximately 50% of all vascular injuries.⁴

Current military data indicate that the most frequently injured lower extremity vessel in the setting of penetrating trauma is the superficial femoral artery (SFA), followed by the popliteal artery, the deep femoral artery, the tibial arteries, and the common femoral artery (CFA); the most frequently injured upper extremity vessel is the brachial artery, followed by the radial artery and the ulnar artery.² In civilian settings, injuries leading to limb loss often include damage to bones and nerves.

Stepwise logistic regression analysis demonstrates that the following are independent risk factors for amputation: occluded grafts, combined above-the-knee and below-the-knee injuries, tense compartments, arterial transections, and associated compound fractures.⁶

Initial Assessment

HISTORY

Assessment of an injured extremity starts with a history, which can be obtained in parallel with the physical

Financial disclosure information is located at the end of this chapter before the references.

examination. The information that should be collected includes the patient's bleeding history at the scene, the time of injury, and the mechanism of injury.

PHYSICAL EXAMINATION

The physical examination is the most important part of the assessment. A careful evaluation of the extremities can provide information on the location and severity of vascular injuries, identify the trajectory and the entrance and exit points of wounds, and suggest appropriate triage and management of vascular injuries.

The initial part of the examination should follow Advanced Trauma Life Support (ATLS) guidelines with attention paid to the ABCs (airway, breathing, and circulation). Areas of obvious hemorrhage should be addressed in the primary survey; more specific evaluation of the extremities for vascular injury can be carried out during the secondary survey. Blood pressure, temperature, and distal pulses are evaluated. Side-to-side symmetry is important; thus, injured extremities should be compared with their uninjured counterparts.

If pulses are absent and a joint or fracture dislocation is present, then reduction should be performed. Frequently, a pulseless extremity regains pulses once the fracture or dislocation is reduced. If pulses return after reduction, the assessment may move on to the next priority. If pulses do not return, a vascular injury is assumed and treatment of such an injury becomes the immediate priority.

Once the initial part of the examination has been carried out, a neurologic examination should be performed. Motor and sensory functions should be assessed in a distal-to-proximal direction on each extremity. Any gross limb deformities should be reduced and splinted to yield a more anatomic alignment of the extremity and relieve any compromise of neural or vascular structures.

CLINICAL CATEGORIZATION OF VASCULAR INJURY

Traditionally, clinical evidence of vascular injury has been divided into hard and soft signs. Hard signs of extremity vascular injury include arterial bleeding, ongoing hemorrhage with shock, an expanding or pulsatile hematoma, a palpable thrill or audible bruit over the injured area, absent distal pulses, and limb ischemia. When a patient presents with hard signs of vascular injury, immediate surgical exploration and vascular repair are warranted. The exception to this rule is the case where the patient presents with multilevel trauma to an extremity and the level of arterial injury is in question. In this situation, arteriography is indicated. This is preferably done intraoperatively to minimize delay in repairing the injury and to facilitate operative decision making.

Soft signs of vascular injury include a history of severe hemorrhage at the scene, hypotension, a small stable hematoma that is not expanding or pulsatile, diminished or unequal pulses, a neurologic deficit (primary nerve injury occurs immediately after injury, whereas the onset of ischemic neuropathy may be delayed for minutes to hours), and a wound that is in proximity to vascular structures.⁸ Management of patients with soft signs of injury presents a more difficult diagnostic dilemma and is discussed in more detail elsewhere (see below).

It is important to keep in mind that palpation of a pulse is a subjective measure and is thus prone to wide inter-observer variation. Furthermore, pulses may be palpable distal to major arterial lesions, including complete arterial disruptions.^{8,9} These limitations notwithstanding, a precise and well-documented physical examination is an appropriate screening tool for vascular injuries.

NONINVASIVE EVALUATION IN CONJUNCTION WITH PHYSICAL EXAMINATION

In patients with soft signs of arterial injury, the ankle-brachial pressure index (ABI) is a highly useful adjunct to the physical examination. The ABI is obtained by placing a standard arm blood pressure cuff on the supine patient proximal to the ankle for lower extremity injuries or just proximal to the wrist for arm injuries. The systolic pressure is determined with a Doppler probe at the respective posterior tibial and dorsalis pedis arteries or at the ulnar and radial arteries. The ratio of the highest systolic pressure obtained in the affected extremity to the systolic pressure in an unaffected upper extremity is the ABI¹⁰ [see Figure 2].

In a preliminary study, Lynch and Johansen evaluated the ABI as a screening tool for patients with injured extremities.¹⁰ They found that an ABI of less than 0.90 had a sensitivity and a specificity of 95% and 97%, respectively, for major arterial injury. The negative predictive value for an ABI greater than 0.90 was 99%.

In follow-up, a 1991 prospective study assessed the sensitivity and specificity of Doppler-derived arterial pressure measurements in trauma patients undergoing evaluation for possible extremity vascular injury from both penetrating and blunt mechanisms.¹¹ An ABI was obtained in 100 consecutive injured limbs, and all patients then underwent contrast arteriography. An ABI that was less than 0.90 was 87% sensitive and 97% specific for arterial injury. The authors concluded that in the absence of hard signs of arterial injury, the ABI is a reasonable substitute for screening arteriography, particularly if continued observation can be ensured.

The use of the ABI has been extended to the management of blunt extremity trauma associated with high-risk fractures and dislocations. In a controlled trial that included 75 consecutive patients with blunt high-risk orthopedic injuries, the negative predictive value of a Doppler-derived ABI higher than 0.90 was 100%. In the 70% of patients who had an ABI higher than 0.90, clinical follow-up revealed no major or minor arterial injuries. Of the 30% who had an ABI lower than 0.90, 70% had an injury that was diagnosed by arteriography, and 50% of these injuries necessitated operative repair.^{12,13}

It is important to remember that there are several situations in which a vascular injury may not lead to an abnormal ABI. For example, an injury that is considered nonaxial (e.g., an injury to the deep femoral artery in the thigh or the profunda brachii in the arm) may not lower the ABI and thus may be missed. In addition, a lesion that does not disrupt arterial flow (e.g., an intimal flap or a transected artery that is maintained in continuity by connective tissue) may yield a normal ABI. Finally, an AV fistula may be associated with a normal ABI.

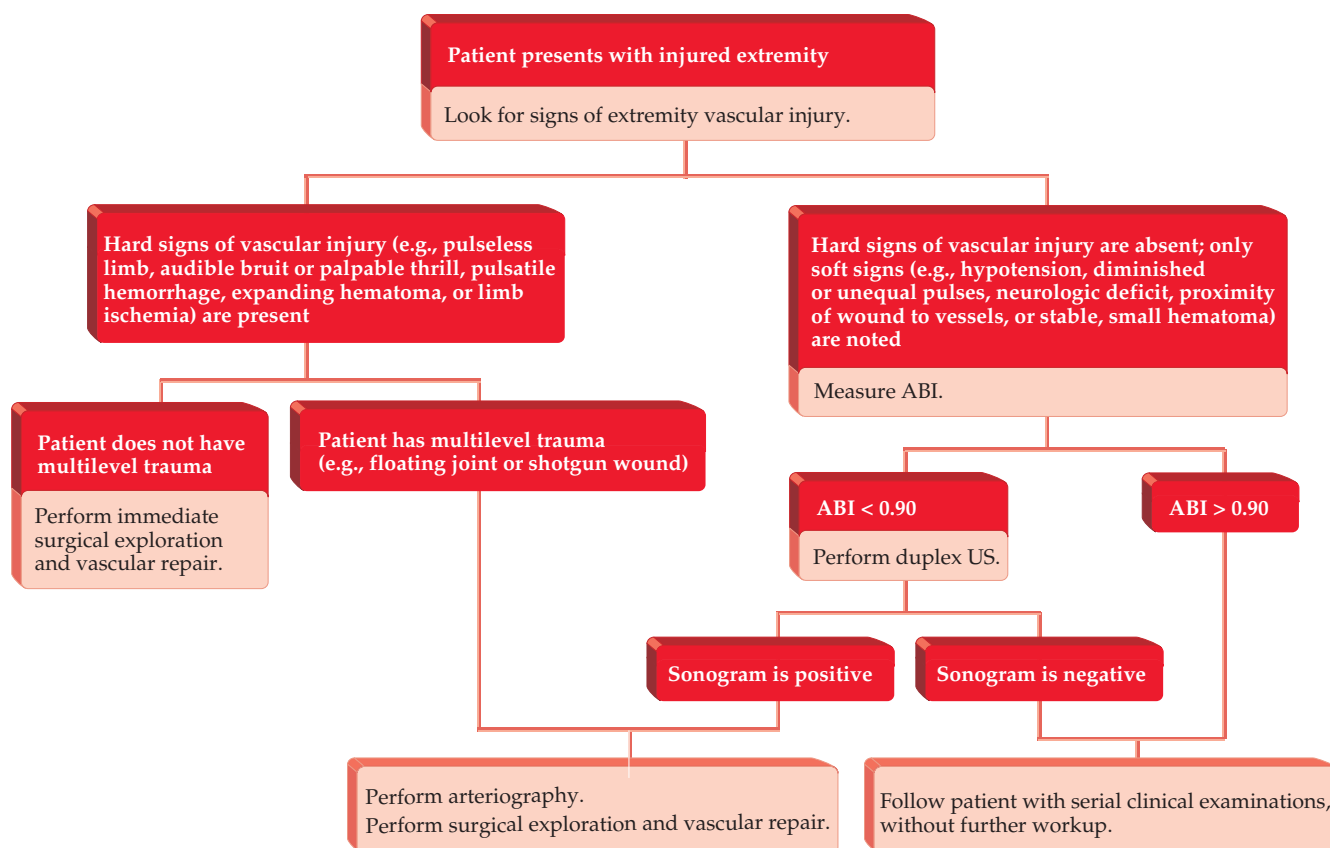


Figure 2 An algorithm for the workup of a patient with potential extremity vascular injury. ABI = ankle-brachial pressure index; US = ultrasonography.

Certain patient characteristics may affect the ABI as well. For example, measurement of the ABI may fail to detect an injury if the patient is severely hypotensive or in shock or if the clinical circumstances do not permit placement of a cuff around an injured site or extremity. Moreover, elderly patients may have abnormal preinjury ABIs as a consequence of atherosclerosis. In these situations, the concept of symmetry is crucial. It is also important to consider the possibility that the patient may have previously undergone peripheral vascular surgery, although this is rarely the case in the typical trauma population.

IMAGING

Diagnostic Angiography

Arteriography has a sensitivity of 95 to 100% and a specificity of 90 and 98% and is therefore considered the gold standard for evaluation or confirmation of arterial injury.^{14,15} In the setting of extremity injury, however, nonselective angiography has not been found to be cost-effective and is often overly sensitive, detecting minimal injuries that do not call for further management.^{16–18} Furthermore, arteriography can be time consuming, can delay definitive treatment, and can give rise to complications of its own, including renal contrast toxicity and pseudoaneurysm formation.¹⁸

Angiography should be reserved for patients with soft signs of vascular injury and an abnormal ABI; there is little reason to perform angiography in a patient with hard signs

of injury unless an intraoperative angiogram is needed to delineate the anatomy. In no case should transport to the operating room for definitive treatment be delayed so that arteriography can be performed. Several reviews have supported reserved use of arteriography in this setting. A 2002 report concluded that physical examination in conjunction with measurement of the ABI was an appropriate method of identifying significant vascular injuries caused by penetrating extremity trauma.¹⁹ Patients with normal physical examinations and normal ABIs could safely be discharged; angiography was indicated only for asymptomatic patients with abnormal ABIs.¹⁹

Duplex Ultrasonography

Several studies have evaluated the efficacy and accuracy of duplex ultrasonography in the setting of extremity vascular trauma. The sensitivity of duplex ultrasonography is between 90 and 95%, the specificity is in the range of 99%, and the overall accuracy is between 96 and 98%. These figures approach those reported for arteriography in the evaluation of similar vascular trauma patients. Duplex ultrasonography has no inherent risks and may be more cost-effective for screening certain injuries than either arteriography or exploration. Duplex ultrasonography has been shown to be a reliable method of diagnosis in patients with potential peripheral vascular injuries.^{20,21}

The advantages of duplex ultrasonography notwithstanding, it is important to remember that this imaging modality

may not be equally appropriate in all scenarios. As an example, given that duplex ultrasonography is highly operator dependent, the results of duplex examination may not be reliable in situations where the examiner has not had sufficient access to the technology or experience with the technique. As another example, injuries in certain anatomic locations (e.g., injuries in regions where bone structures interpose themselves, injuries in areas with concomitant soft tissue injuries, injuries that dive into the pelvis or chest, and injuries in patients with a large body habitus) may not be well visualized with duplex ultrasonography. Such considerations are important in assessing patients with potential extremity vascular injuries; if either applies in a given case, angiography may be required.

Computed Tomographic Angiography

Ongoing radiologic advances have led some centers to consider using computed tomographic angiography (CTA) to evaluate arterial injury. To date, this approach has been formally evaluated in only a modest number of studies, although there is reason to believe that it will be more widely used in the future. A few small series found CTA to have a sensitivity and specificity of approximately 90% in the evaluation of large arteries; other studies suggested that this modality might be a reasonable alternative to conventional arteriography for diagnosis of traumatic arterial injuries. Before CTA can be considered equivalent to the gold standard, large randomized trials will have to be performed.^{22,23}

MANAGEMENT ALGORITHMS

On the basis of the data available on noninvasive assessment and diagnostic imaging, an effective management algorithm can be created [see Figure 2].^{24,25} If the ABI is higher than 0.9, the patient may be followed clinically without further workup. If the ABI is lower than 0.9, arteriography or duplex ultrasonography should be performed, the results of which will dictate the final plan of action. It is impossible to define every single clinical scenario that could possibly give rise to arterial trauma. The ABI fulfills the requirements of a useful screening tool in that it is sensitive, specific, reproducible, noninvasive, and inexpensive.

Management of complex extremity trauma involving soft tissue, nerve, and arterial injury must include consideration of primary amputation to increase patient survival. This issue is well addressed by an algorithm for complex extremity trauma created by the Committee on Trauma of the American College of Surgeons (ACS) [see Figure 3].²⁶ The algorithm incorporates the environment, the type of injury sustained, and the stability of the patient into the process of deciding whether to attempt limb salvage or perform amputation.

HIGH-RISK LOWER EXTREMITY INJURIES

Certain lower extremity injuries—such as knee dislocations, displaced medial tibial plateau fractures and other displaced bicondylar fractures around the knee, open or segmental distal femoral shaft fractures, floating joints, gunshot wounds in proximity to neurovascular structures, and mangled extremities—are associated with a particularly high incidence of concomitant vascular trauma.²⁷ The most

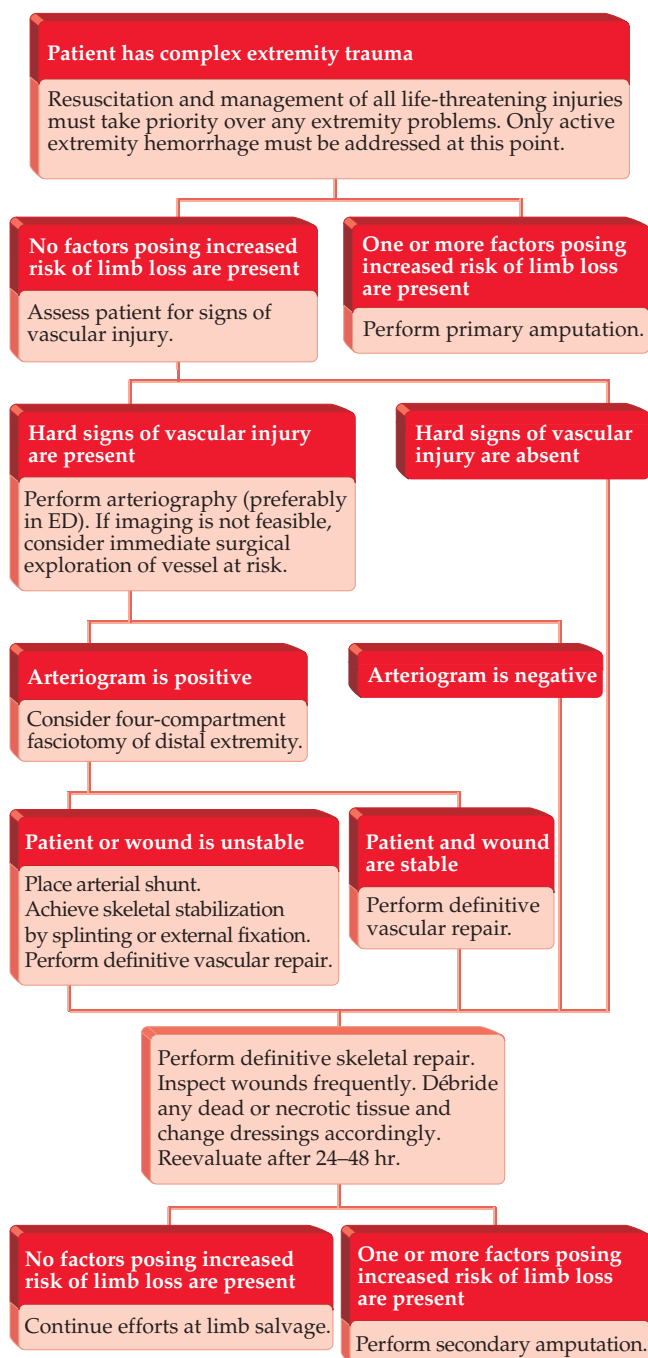


Figure 3 An algorithm for the management of complex extremity trauma, adapted from an algorithm developed by the ACS Committee on Trauma. The full annotated version of the ACS algorithm is available at the ACS Web site (<http://www.facs.org/trauma/publications/mancompexttrauma.pdf>). ED = emergency department.

commonly injured lower extremity artery in the setting of blunt trauma is the popliteal artery, which starts below the adductor hiatus and ends at the soleus arch. Because the vessel's start and end point areas are relatively fixed, there is a potential for significant stretch injury at the knee joint. A purely ligamentous knee dislocation is associated with a high risk of arterial injury, despite the lack of sharp fracture

fragments. The risk of popliteal injury may be as high as 40% in patients with knee dislocations. Although the arterial disruption may be only a minor intimal tear and examination may reveal no evidence of injury, such internal tears are thrombogenic and may result in delayed thrombosis. Because lower extremities are often splinted and covered during stabilization, delayed thrombosis may not be recognized in a timely fashion.

Workup of a patient with a posterior knee dislocation may or may not require angiography. Some authors maintain that angiography is unnecessary in routine evaluation of patients with blunt lower extremity trauma who present with a normal neurovascular examination and that angiography or duplex ultrasonography should be used selectively for patients with diminished pulses who lack associated indications for mandatory operative exploration.²⁸ In addition, the use of the ABI has been validated in the setting of blunt lower extremity trauma. The ABI has proved to be a rapid, reliable, noninvasive tool for diagnosing vascular injury associated with knee dislocation. At present, the evidence suggests that routine arteriography for all patients with knee dislocation is not indicated but that a secondary study should be ordered when the ABI is low or the neurovascular examination yields abnormal results.^{12,14,29} When managing a posterior knee dislocation, one should have a high index of suspicion for vascular injury and a low threshold for obtaining secondary studies.

Management

INITIAL TREATMENT CONSIDERATIONS

Time to Repair

A warm ischemia time of less than 6 hours is generally accepted as the standard interval within which arterial continuity must be restored to prevent permanent damage to the soft tissues.^{30,31} This interval may vary depending on several factors, including the level of injury, previous vascular disease, the presence of collateral vessels, and previous extremity surgery.

Vascular Control

As has long been a dictum in vascular surgery, it is important to gain proximal control of the injured vessel—meaning control at a point one level higher than the injured area—before assessing the site of the injury. This maneuver reduces blood loss from the injury during repair and minimizes hematoma formation and subsequent loss of tissue planes. Entering an injured area without first obtaining proximal control can be dangerous, can cause additional injury to other neurovascular structures, and can result in belated attempts to gain proximal control in a hurried fashion, which may cause secondary injury to the vessel. In situations where proximal control has not yet been obtained or cannot be obtained, an intraluminal or intra-arterial balloon (e.g., a Fogarty catheter or even a Foley catheter in the larger arteries) may be used to achieve temporary control. This simple technique sometimes proves to be lifesaving.

Use of Tourniquets

Surgeons have long debated the use of tourniquets in the management of vascular trauma.^{32–34} Undoubtedly, the

tourniquet can be a lifesaving addition to the surgeon's armamentarium if used correctly and appropriately. Proximal application of a tourniquet may facilitate examination, permit definitive control of a bleeding point, and help determine whether significant nerve, muscle, or tendon injury has occurred. Even if a tourniquet is kept in place for only a short period, it may be invaluable for the control of hemorrhage.

When a tourniquet is used, it must be applied correctly. Incorrectly applied tourniquets actually increase bleeding from an extremity wound and increase the risk of early exsanguination. This paradoxical effect results from occlusion of the lower-pressure venous outflow and inadequate occlusion of the higher-pressure arterial inflow. In addition, an improperly applied tourniquet may cause surrounding tissue damage, leading to nerve palsies, tissue loss, and amputation shortening. With a properly applied tourniquet, there can be substantial associated pain, which should be managed with intravenous or intramuscular analgesics.³⁵ Of greater consequence, however, is the appropriate timing of the tourniquet's application. In reviewing military data looking at the emergency use of tourniquets, Kragh and colleagues found that survival was strongly associated with tourniquet application prior to the arrival to the emergency department but, more importantly, prior to onset of shock.³⁶ In addition, the speed at which the device could be successfully placed was of the utmost importance. Of note, no amputations resulted solely from tourniquet use.

Tourniquets are often placed on hypotensive patients before resuscitation, and these patients can start to bleed through their tourniquets when resuscitation is initiated. Accordingly, tourniquets should be continuously monitored and tightened for maximal effectiveness during resuscitation. In the hospital setting, pneumatic tourniquets may be used as temporizing proximal clamps in patients with multiple injuries as well as in patients with blast injuries, massive soft tissue destruction, or mangled extremities.³⁵

EXPOSURE OF INJURY

Once the decision has been made to transport the patient to the operating room, the next step is to determine the operative approach that will optimize exposure of the injury. Often exposures of upper extremity arteries prove more challenging than exposures of lower extremity vessels, primarily because they are performed less frequently. A thorough discussion of all extremity vascular exposures is beyond the scope of this chapter. Accordingly, in what follows, we discuss those exposures of the upper and lower extremities that are particularly useful in the trauma setting.

Upper Extremity

Operative exposure of potential vascular injuries in the upper extremity requires detailed knowledge of the anatomy of the axillary and brachial arteries. The axillary artery is surrounded by muscle on all sides, including the chest wall, the pectoral girdle, and the brachium. The vessel itself is divided into three segments by the pectoralis minor: the medial segment, the posterior segment, and the lateral segment. The specific operative approach depends on which of these three segments has been injured.

To gain access to the first (medial) segment of the axillary artery, the infraclavicular region must be exposed [see Figure 4]. This approach may also be useful for proximal control of more distal injuries, depending on the location and type of injury being treated. A horizontal incision is made 2 cm below the middle third of the clavicle, and dissection continues through the subcutaneous fascia, the pectoral fascia, the pectoralis fibers, and the clavipectoral fascia. At this level, the neurovascular bundle can be identified with the artery lying superior and deep to the axillary vein. Exposure and control of the artery are obtained by means of sharp dissection. To gain access to the second (posterior) and third (lateral) portions of the axillary artery, an incision is made along the lateral border of the pectoralis major from the chest wall to the biceps. The coracobrachialis muscle can then be identified with the neurovascular sheath located at the posterior border of this muscle.³⁷

As an alternative, the deltopectoral approach may be employed to gain access to any of the segments of the axillary artery. An incision is made from the midpoint of the clavicle along the anterior border of the deltoid muscle. The incision is deepened through subcutaneous tissue to reach the intramuscular groove. The cephalic vein is retracted, and the axillary artery may then be traced both proximally and distally.

To expose the brachial artery, a longitudinal incision is made in the medial arm between the biceps and the triceps [see Figure 5], and dissection is carried out through the subcutaneous tissue. The basilic vein can then be identified. This vein is retracted inferiorly, and the neurovascular bundle is exposed by opening the deep fascia at the medial border of the biceps. To expose the brachial artery along with the arteries in the forearm, an S-shaped incision is

made over the antecubital fossa. The superior portion of the incision follows the medial border of the biceps muscle and extends horizontally in the antecubital fossa; the inferior portion is made laterally on the volar aspect of the forearm. Such an incision affords complete exposure of all of the target vessels. On subcutaneous dissection, multiple veins can be seen, including the median cubital, the cephalic, and the basilic veins. Exposure of the deep fascia and entrance into the bicipital aponeurosis allows exposure of the median nerve, the brachial artery, and two deep veins. The incision can be extended to track the radial and ulnar arteries.³⁷

Lower Extremity

In addressing potential vascular injuries in the lower extremity, it is essential to be able to expose the CFA and the popliteal artery. To gain access to the femoral artery, a vertical skin incision is made midway between the superior iliac spine and the pubic tubercle [see Figure 6]. This incision is opened to expose the superficial epigastric and superficial circumflex branches. The fascia lata is incised along the medial portion of the sartorius muscle up to the inguinal ligament, and the femoral sheath is exposed and opened. In an emergency situation where retroperitoneal or abdominal exposure is not warranted, the inguinal ligament can also be divided if necessary for more proximal control. The CFA can then be identified lateral to the femoral vein and can be tracked downward to the point where it bifurcates into the profunda femoris and the SFA. Typically, the profunda femoris branches laterally off of the CFA 3 to 5 cm distal to the inguinal ligament; the SFA lies superior to the profunda femoris. The incision may be extended inferiorly as necessary to locate more distal vascular injuries.³⁷

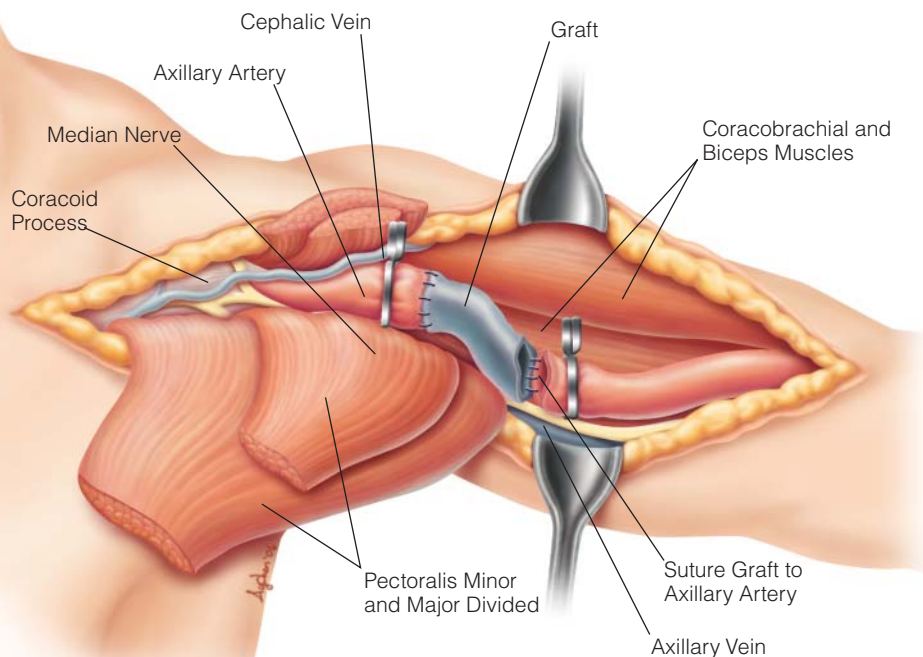


Figure 4 Exposure of the axillary artery.

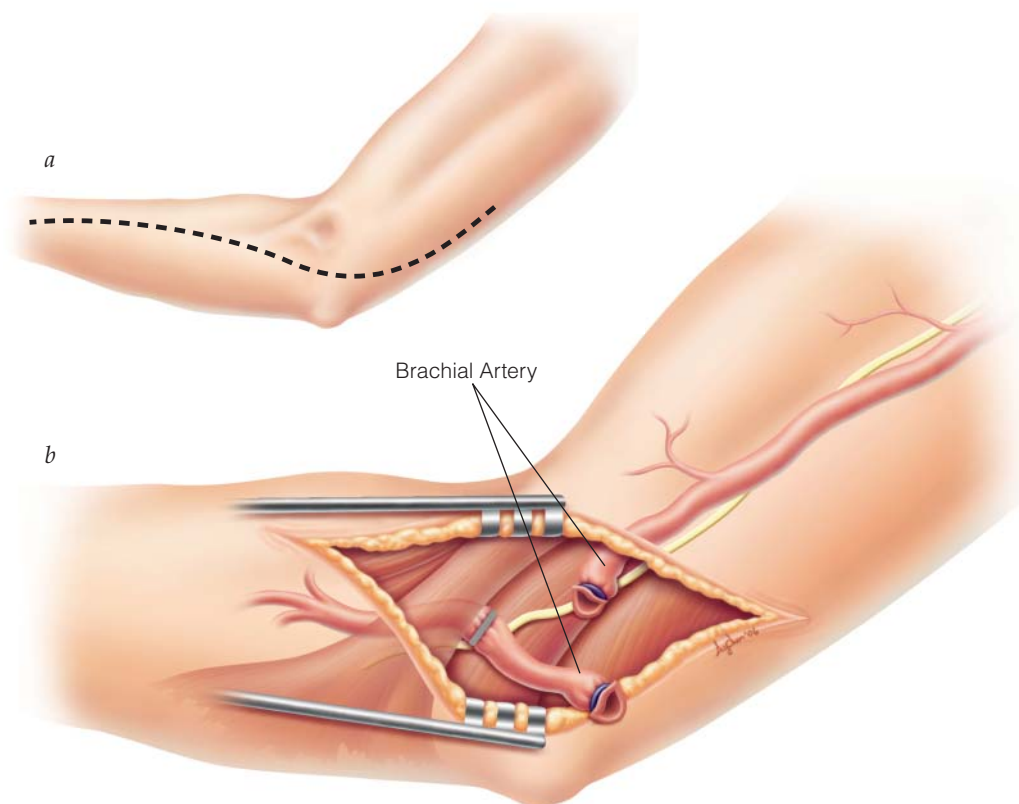


Figure 5 (a) Exposure of the brachial artery, with removal of an occluded segment to restore blood flow to the hand and forearm. (b) The incision is extended onto the forearm in an S shape to afford complete exposure.

In the setting of trauma, exposure of the popliteal artery is best accomplished via a medial approach. To expose the proximal (supragenicular) popliteal artery, an incision is made in the distal portion of the thigh along the anterior border of the sartorius muscle [see Figure 7]. The fascia can be incised, the muscle can be retracted posteriorly, and the popliteal vessels may be identified. It may be necessary to divide the adductor tendon or the semimembranous muscle for exposure. If necessary, this incision can be extended down the leg for exposure of the tibial vessels. To expose the distal (infragenicular) popliteal artery, an incision is made just behind the posteromedial surface of the tibia [see Figure 8]. The gastrocnemius muscle is retracted posteriorly, and the semitendinous, gracilis, and sartorius muscles are retracted superiorly. These muscles may also be divided if more exposure is needed. The popliteal vein is the first and most superficial portion of the neurovascular bundle. The tibial nerve is posterior and medial to the popliteal artery and should always be identified and protected during the dissection. If necessary, this exposure can be extended inferiorly to the tibial peroneal trunk for control of the distal arteries.³⁷

DEFINITIVE REPAIR OF INJURY

Primary Repair versus Grafting

Once the need for operation has been established and the exposure chosen, the next step is to determine which type of repair will be performed. Primary repair is preferred when possible. However, substantial proximal and distal mobilization of the artery may be required to allow a tension-free anastomosis.

Choice of Conduit

Often the extent of the injury is such that primary repair is impossible and a conduit (autogenous or prosthetic) must be placed. It is crucial that the contralateral leg be prepared so that a venous segment can be harvested if required. In view of the possibility that the extremity arterial injury may be accompanied by significant venous injury, harvesting vein from the ipsilateral leg is discouraged. The most commonly used conduit is the great saphenous vein (GSV), which can be cut and made to form a larger conduit by using a spiral technique or a panel graft technique.³⁸ The superficial femoral vein (SFV) may also be used as a conduit,³⁹ but the dissection required is tedious and time-consuming and may be associated with significant morbidity.

Autogenous conduits should be used in contaminated wounds when direct vascular repair is not feasible. Nonautogenous conduits (e.g., polytetrafluoroethylene [PTFE] or Dacron grafts) may also be employed, but as a rule, they should be reserved for extreme situations in which native vein are not available. For patients with severe peripheral vascular injuries but without adequate available vein, PTFE appears to be an acceptable choice for primary reconstruction; graft infection is rare if the graft is covered with healthy tissue.^{40,41}

Management of Arteries in Distal Extremity

On occasion, arteries in the distal extremities (e.g., the radial, ulnar, or tibial arteries) may have to be repaired or ligated after trauma. In most patients, there is little need for repair of these arteries, which can typically be ligated without deleterious effects. The safety of ligation is predicated on

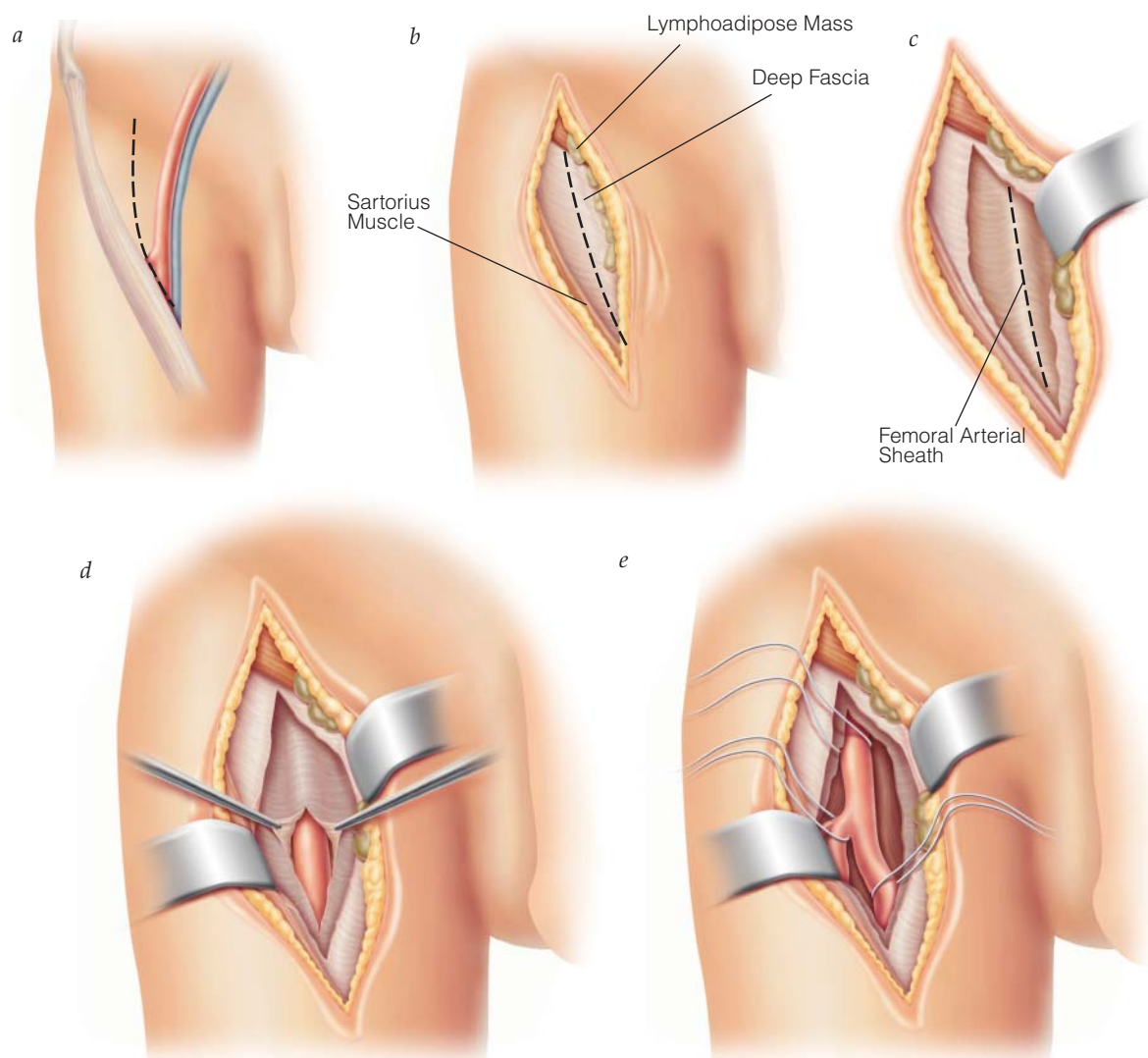


Figure 6 Exposure of the femoral artery. (a) A curved 10 to 12 cm skin incision is made slightly lateral to the pulsation of the femoral artery. (b) Lymphoadipose tissue is retracted to expose the deep fascia overlying the course of the femoral artery. (c) The deep fascia is incised, exposing the femoral arterial sheath, which is then opened along its axis (d). (e) The common and superficial femoral arteries are mobilized and encircled with Silastic vessel loops.

the presence of adequate arterial flow from the nonaffected arteries, as well as retrograde blood flow from an intact palmar or plantar arch.^{42,43} Repair of injuries to these arteries is associated with the possibility of embolization or other surgical problems. In addition, the patency rate for grafts in the distal extremities tends to be low.⁴⁴

Repair of Venous Injuries

In most regions of the extremities, repair of any concomitant venous injuries is recommended, on the grounds that it may help keep an arterial repair open and prevent post-operative edema. Primary repair involves closing the venotomy transversely; this may be facilitated by mobilizing the proximal and distal venous structures. If primary repair is not possible, a patch is recommended. To augment venous flow and help maintain patency, an AV fistula may be created and then electively ligated at a later date. The administration of heparin and the use of a foot pump may

also help maintain the patency of a venous repair and reduce the hypercoagulability associated with the Virchow triad and venous occlusion.

If the vein cannot be repaired, it may have to be ligated. For injuries to the tibial vein and some injuries to the brachial vein or a more distal arm vein, ligation may be chosen over repair with few deleterious consequences. For injuries to the popliteal vein or the SFV, repair is recommended when possible to optimize continued venous drainage of the extremity. As noted [see Choice of Conduit, above], if vein is harvested, it should come from the contralateral leg so as to permit continued outflow from the injured lower extremity.^{45,46}

If proximal ligation of a lower extremity vein is required, it should be performed on the common iliac vein rather than the external iliac vein. Higher ligation allows cross-pelvis collateral circulation via the internal iliac veins. In addition, ligation of the external iliac vein is fraught with difficulty.

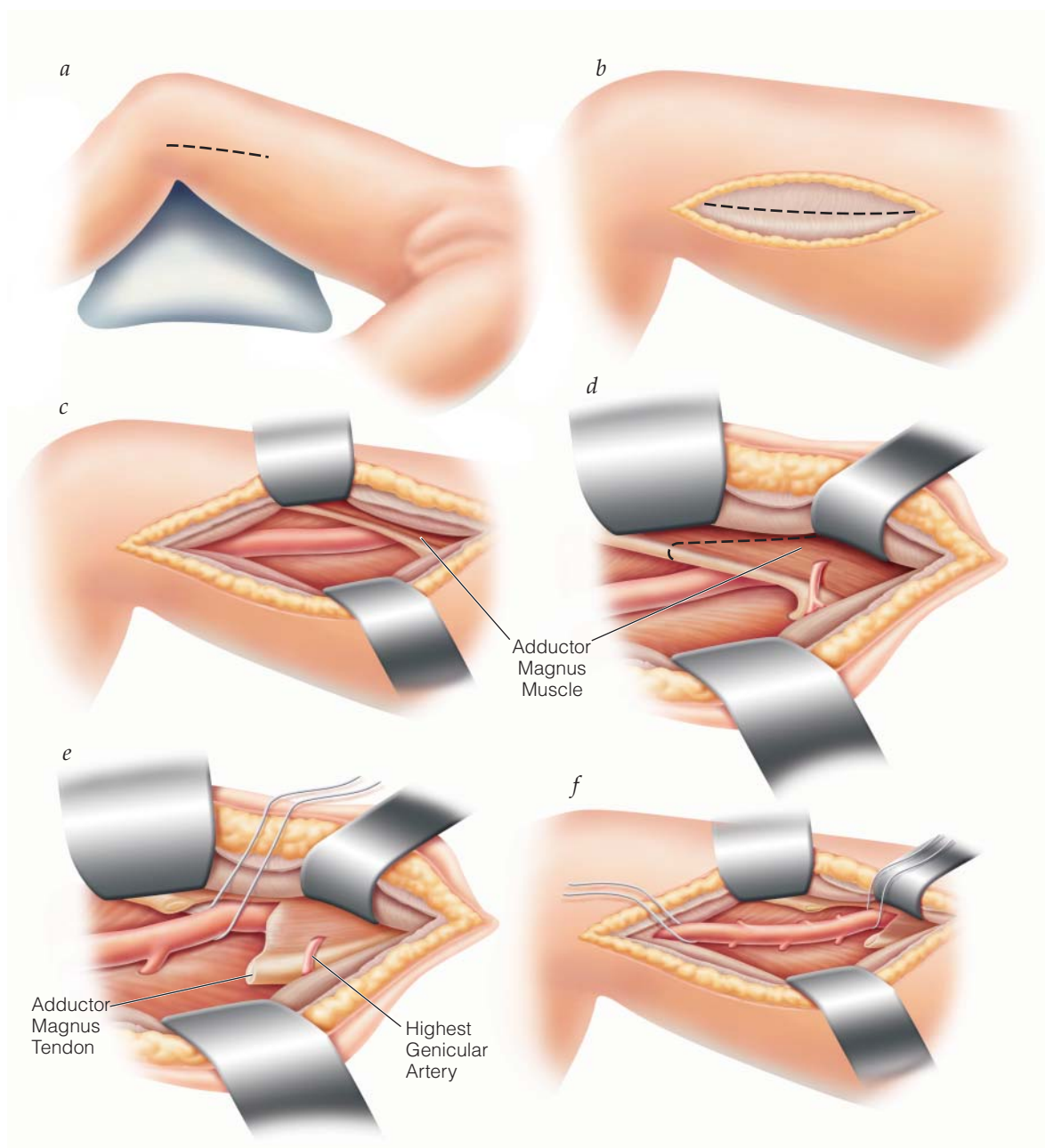


Figure 7 Medial exposure of the proximal popliteal artery. (a) An incision is made in the lower third of the thigh, anterior to the sartorius muscle. (b) The deep fascia is incised, and the sartorius muscle is retracted posteriorly, allowing the popliteal artery to be readily palpated. (c) The popliteal arterial sheath is opened, exposing the vessel and its surrounding venules. The adductor magnus tendon may be seen covering the proximal end of the artery (d), and it may have to be divided (e) to provide better exposure of the artery. (f) The popliteal artery, freed of the venous plexus, is mobilized between two vessel loops.

Every attempt should be made to repair the vein to prevent major morbidity, including poor venous return and resultant severe edema. Ligation of the common femoral vein (CFV) is also not ideal because of the risk of leg edema; however, if ligation at the level of the CFV proves necessary, it does allow some venous return flow via the cruciate collateral vessels, the obturator vein (from the medial circumflex femoral vein), and the gluteal vein (from the lateral circumflex femoral vein).

Postoperative Care

After repair of a vascular injury, patients require 24 hours of monitoring in the intensive care unit for serial pulse and Doppler assessments, monitoring of hemodynamic status, and evaluation of the site of the repair. In addition, patients must be watched for the development of metabolic derangements (e.g., metabolic acidosis, hyperkalemia, myoglobinuria, and renal failure) after hemorrhagic shock and reperfusion of ischemic limbs. Any changes in the physical

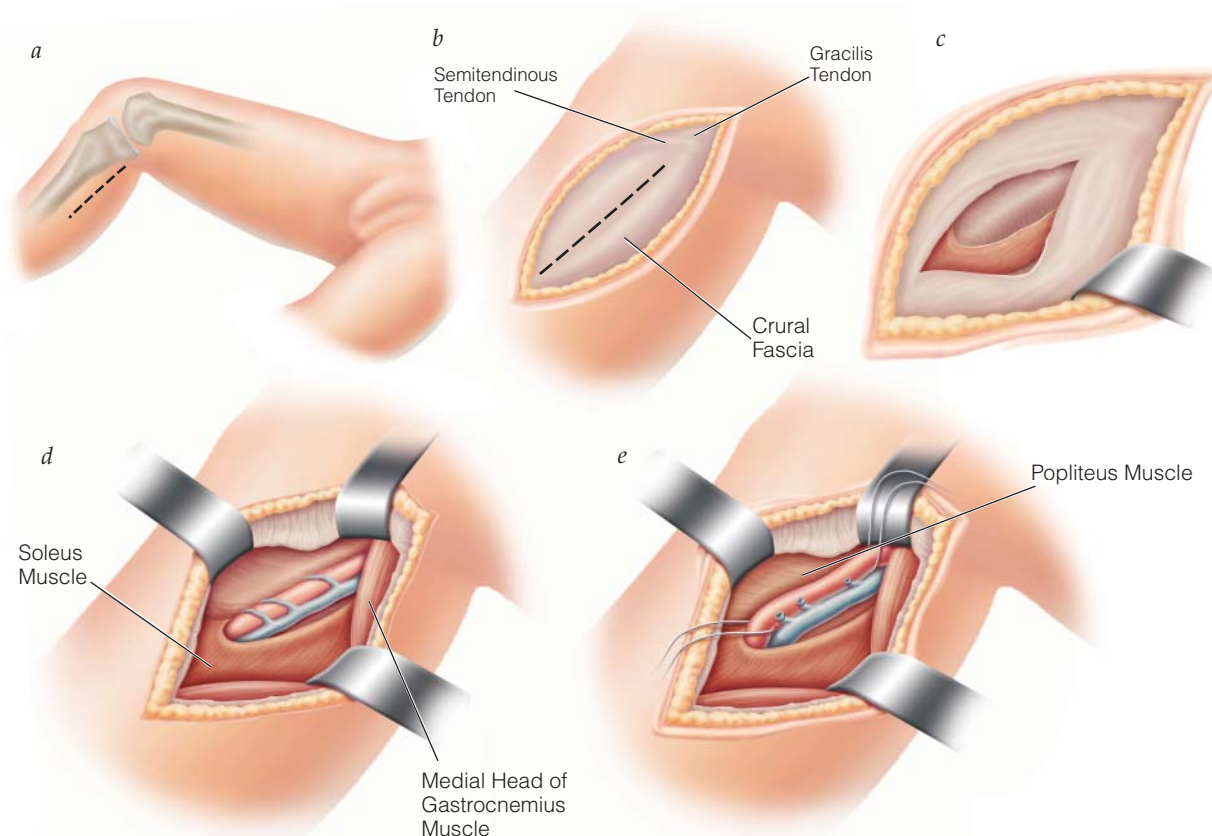


Figure 8 Medial exposure of the distal popliteal artery. (a) An incision is made just behind the posteromedial surface of the tibia. (b) The crural fascia is exposed. (c) The fascia is incised, exposing the vascular bundle. (d) The medial head of the gastrocnemius muscle is retracted posteriorly, exposing the distal popliteal vessels and the arcade of the soleus muscle. (e) The distal popliteal artery is freed and mobilized between vessel loops.

examination or ABI warrant immediate investigation, usually beginning with duplex ultrasonography. Typically, a duplex examination is also performed in the early post-operative period to establish a baseline for subsequent surveillance of the graft or repair.

MANAGEMENT OF COMPARTMENT SYNDROME

Compartment syndrome is a condition characterized by abnormally high pressure within a closed space. The elevated tissue pressure leads to venous obstruction within that space. When the pressure continues to increase, the intramuscular arteriolar pressure is eventually exceeded. At that point, blood can no longer enter the capillary space, and the result is shunting within the compartment. If the pressure is not released, muscle and nerve ischemia occurs, leading to irreversible damage to the contents of the compartment.⁴⁷

Underlying pathologic processes that reduce the size or increase the contents of a compartment include hemorrhage, reperfusion edema, a tight cast, constrictive dressings, and pneumatic antishock garments. In addition, crush injury may be associated with the development of rapid swelling and rigid compartments. The key to the diagnosis of compartment syndrome is continuous assessment of any extremity injury in which elevated pressures may develop. To directly assess the actual pressure in any one compartment

requires the use of invasive monitoring. The most commonly used device is the Stryker Intra-Compartmental Pressure Monitor System (Stryker Surgical, Kalamazoo, MI). This tool measures the pressure that is necessary to inject a small amount of saline into the desired compartment. For example, to evaluate the most commonly affected compartment of the lower extremity, the anterior compartment, the needle of Stryker device is inserted at the junction of the proximal and middle third of the calf approximately 1 cm medial to the tibia. If required, measurements may be repeated at predetermined intervals to trend any changes in the pressures. It must always be remembered that the diagnosis is a clinical one; although compartment pressures may be measured, clinical suspicion and findings suggestive of compartment syndrome on physical examination should suffice to mandate therapy.

Current management of compartment syndrome is derived from a 1970 review by Patman and Thompson in which fasciotomy was performed after arterial reconstruction in 164 patients with peripheral vascular disease.⁴⁸ The investigators concluded that fasciotomy could result in limb salvage and implied that it should be considered after restoration of arterial inflow to an extremity. Indications for fasciotomy included pain on palpation of the swollen compartment, reproduction of symptoms with passive muscle stretch, a sensory deficit in the territory of a nerve

traversing the compartment, muscle weakness, diminished pulses (a very late sign), and compartment pressure exceeding 30 to 35 mm Hg.

It has been noted that the difference between the diastolic pressure and the measured compartment pressure may be a more reliable clinical indicator of compartment syndrome than the compartment pressure by itself. A difference of less than 30 mm Hg between the two pressures is significant and may be the most reliable indicator of when fasciotomy is warranted.

There are a number of clinical situations in which fasciotomy should be considered: when there is a 4- to 6-hour delay before revascularization, when arterial injuries are present in conjunction with venous injuries, when crush injuries or high-kinetic energy injuries have been sustained, when vascular repair has already been performed (reperfusion), when an artery or vein has been ligated, and when tense compartments or elevated compartment pressures are noted in a comatose or head-injured patient. In these scenarios, fasciotomy should be considered a prophylactic maneuver.

The lower leg contains four osseofascial compartments: the anterior compartment, the lateral compartment, the superficial posterior compartment, and the deep posterior compartment. The thigh contains three osseofascial compartments: the quadriceps, the hamstrings, and the adductors. For fasciotomies of the lower leg, there are two techniques: perifibular fasciotomy and the double-incision technique. Perifibular fasciotomy affords access to all four compartments of the leg via a single lateral incision that extends from the head of the fibula to the ankle following the general line of the fibula. The double-incision technique employs two vertical skin incisions that are separated by a bridge of skin at least 8 cm wide [see Figure 9]. The first incision extends from knee to ankle and is centered over the interval between the anterior and lateral compartments; the second also extends from knee to ankle and is centered 1 to 2 cm behind the posteromedial border of the tibia.⁴⁷ Although decompression in the lower extremity may be achieved via either of the two techniques, the double-incision technique is preferred in the setting of trauma because it readily ensures that all four compartments have been adequately decompressed.

The forearm consists of three osseofascial compartments: the superficial flexor compartment, the deep flexor compartment, and the extensor compartment. To decompress the upper extremity, a volar fasciotomy and/or a dorsal fasciotomy may be performed. A volar fasciotomy decompresses the superficial and deep flexor compartments of the forearm via a single skin incision.⁴⁷ This incision begins medial to the biceps tendon, crosses the elbow crease, proceeds toward the radial side of the forearm, and extends distally along the medial border of the brachioradialis muscle, continuing across the palm along the thenar crease [see Figure 10]. After the superficial and deep flexor compartments of the forearm are decompressed, intraoperative pressure measurements may be obtained to help determine whether fasciotomy is necessary to decompress the extensor compartment. If the pressure continues to be elevated in the extensor compartment, a dorsal fasciotomy should be performed.

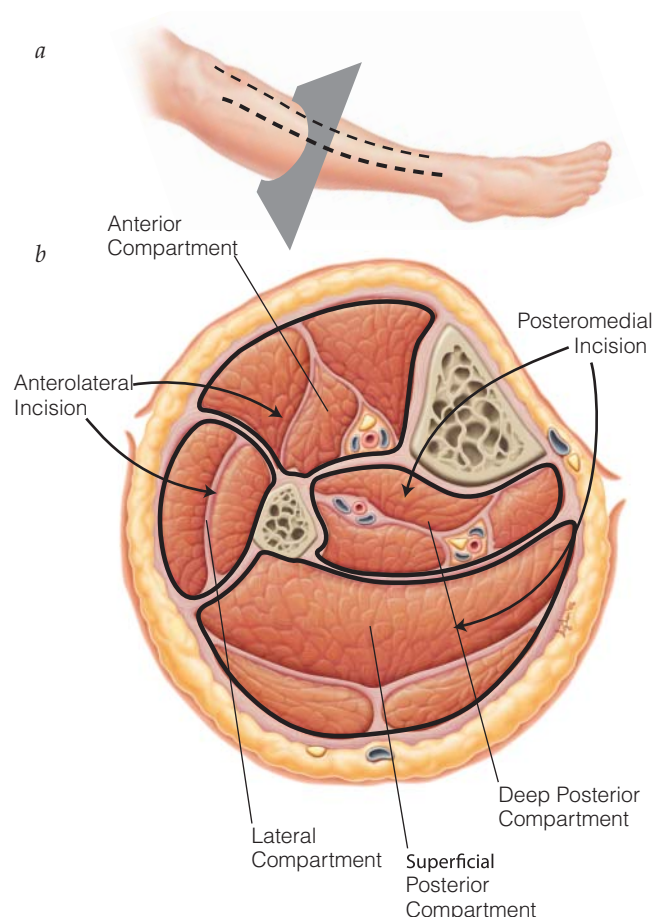


Figure 9 (a) The two-incision technique for lower leg decompression in compartment syndrome. Two vertical skin incisions are made from knee to ankle, separated by a skin bridge at least 8 cm wide. (b) Fasciotomies are then performed in all four compartments along the dashed lines.

With the arm pronated, a straight incision is made from the lateral epicondyle to the midline of the wrist.⁴⁷

After fasciotomy, both the fascia and the skin are typically left wide open. Failure to leave the skin wide open may lead to secondary compartment syndrome. The skin defects may be closed with skin grafts at the time of original operation provided that this can be done without excessive tension or pressure. Alternatively, the patient may be returned to the operating room after the swelling resolves for delayed skin closure (with the fascia left open) or split-thickness skin grafting as indicated. Recent literature has suggested that use of the vacuum-assisted closure (VAC) device can result in higher rates of fasciotomy closure compared with traditional wet-to-dry dressings and should be considered in the armamentarium of fasciotomy site management.⁴⁹

It is important to consider fasciotomy in patients with arterial injuries associated with crush injury and venous injury or occlusion. These secondary injuries may be associated with a higher risk of compartment syndrome than either isolated arterial injuries or ischemia-reperfusion alone.⁵⁰ In any setting, the most important concerns in performing a fasciotomy are that the procedure must be

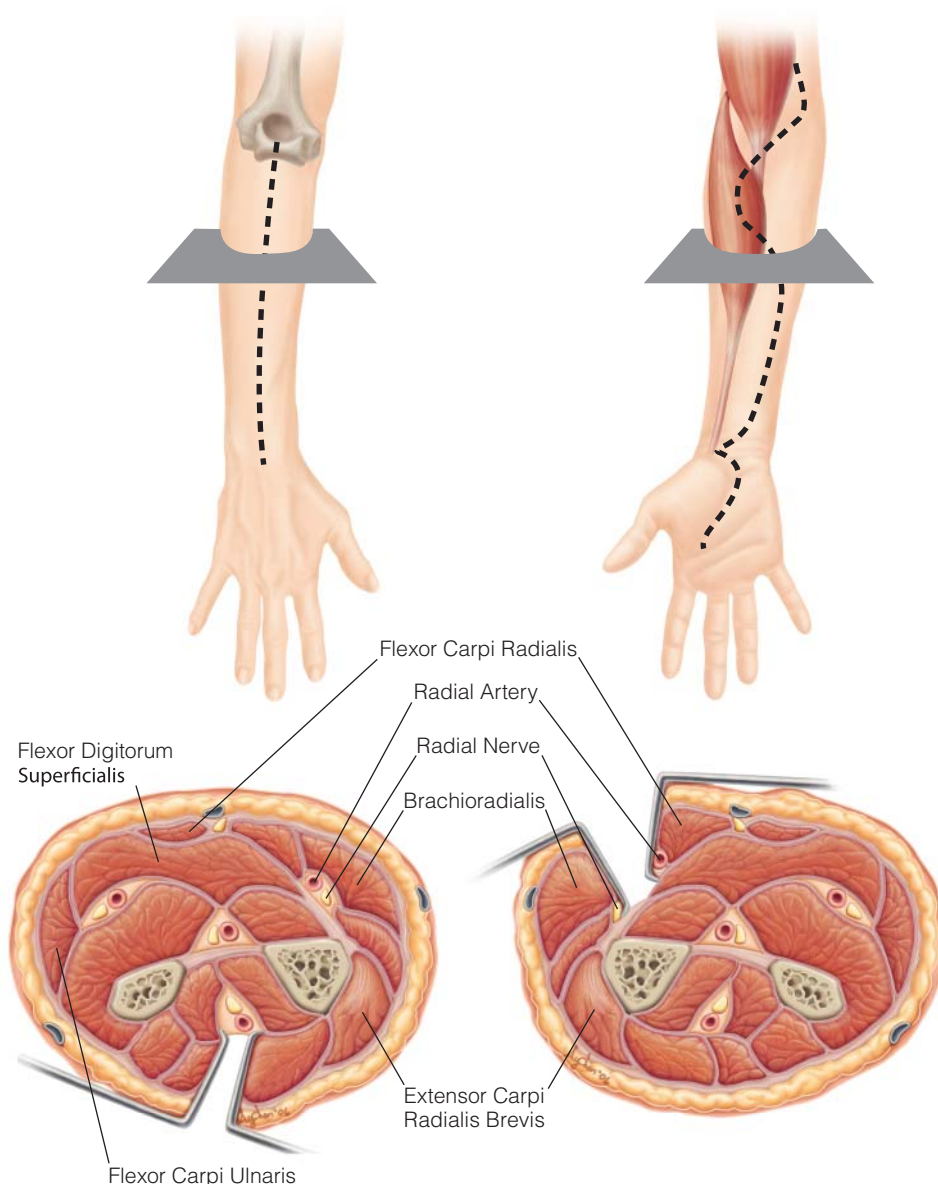


Figure 10 Incisions for forearm decompression in compartment syndrome.

done in a timely manner and that all of the compartments must be completely decompressed.

Special Considerations

MANAGEMENT OF INTIMAL INJURIES

How best to manage small traumatic intimal injuries identified by means of angiography has been the subject of considerable debate. In general, patients who have injuries shorter than 2 mm and involving less than 50% of the vessel circumference with no noted pulse deficits may be placed on an antiplatelet regimen and followed clinically; evidence from animal studies supports this approach.⁵¹ There is some clinical evidence to suggest that antiplatelet medication (e.g., acetylsalicylic acid) and observation alone may be adequate treatment in such patients; however, additional follow-up studies are required before this recommendation can be confirmed.⁵²

Even though some cases can be treated conservatively, it is important not to underestimate the potential importance of angiographically identified intimal injuries. Patients with such injuries are at risk for the development of a pseudoaneurysm, AV fistula, dissection, or even thrombosis.^{51,53,54}

ANTICOAGULATION

Whether anticoagulation is indicated in patients with vascular trauma is also debatable. It has been suggested that early administration of systemic anticoagulant therapy (heparin, 100 U/kg) may reduce amputation rates by preventing microvascular thrombosis. There is some evidence that anticoagulation may improve limb salvage rates while posing only a minimal risk of bleeding complications.⁵⁵ Systemic anticoagulation may be contraindicated in certain situations, such as active hemorrhage, coagulopathy, and craniocerebral injury. If heparin cannot be given systemically, it may be administered locally during the operation at the site of the arterial repair.

ENDOVASCULAR INTERVENTION

The landscape of vascular surgery has evolved dramatically over the past several decades with the introduction of catheter-based therapies. As the endoluminal techniques and equipment have become much more commonplace, the scope of endovascular surgery has expanded outside its traditional boundaries (e.g., aneurysmal and atherosclerotic diseases) and into other areas, including trauma. As such, the treatment of peripheral vascular injuries has advanced with the introduction of endovascular surgery. In some cases, this minimally invasive approach can complement the time-honored open surgical method and, in other cases, can completely replace it.

The benefits of endovascular surgery over conventional surgical techniques are numerous. Endovascular therapy affords the ability to approach injuries from uninjured sites with limited operative exposure, leading to less blood loss and less surgical stress.^{56,57} Endovascular approaches allow access and treatment of difficult to expose areas and can be performed under local or regional anesthesia, allowing for accurate neurologic assessment.^{58,59} In addition, endovascular approaches can be used as a temporizing measure to allow for adequate resuscitation and ultimately delayed treatment of injuries after the patient has stabilized^{60,61}—in essence, percutaneous damage control. An example of this is the use of an aortic occlusive balloon to obtain proximal vascular control and hemostasis while fluids and/or blood are transfused for resuscitation.

Shortcomings with endovascular therapy include access-site complications, retroperitoneal hemorrhage, and endograft issues such as stent stenosis and fracture, thrombosis, and infection.⁶¹ In regards to trauma, the major disadvantages of endovascular surgery are twofold. The first lies in the fact that many of the endoluminal therapies were originally designed to treat traditional vascular diseases so that the experience in trauma is relatively new and still developing.⁵⁶ The second deals with the durability of the procedures themselves. Although the immediate and short-term patency of the endovascular prosthesis is promising, long-term data are limited in the trauma patient.⁵⁸

Axillary/Subclavian Vessel Trauma

Exposure and treatment of these vessels provides a major operative challenge, particularly in the acutely injured and hemodynamically unstable trauma patient. However, endovascular balloon tamponade via either the groin or the brachial artery can provide the necessary time and hemostasis to allow for angiographic diagnosis, exposure with avoidance of iatrogenic damage to surrounding structures, and treatment of the primary injury.^{59,62} In addition, definitive treatment via an endovascular technique may also be attempted. Covered stents can provide a lower rate and severity of complications when used for such injuries.^{59,63,64} In cases of thrombosis, catheter-directed thrombolysis may improve outflow prior to placement of a stent given that the thrombolytics are not contraindicated.⁶⁵ Moreover, endovascular repair does not preclude an open repair at a later date.⁵⁷

Brachial/Radial/Ulnar Vessel Trauma

Treatment of brachial, radial, and ulnar vascular injuries is usually best approached surgically as these vessels are

easily accessible and amenable to direct therapy. However, such injuries can be managed through an endovascular approach. Brachial artery intimal dissections secondary to blunt trauma have been repaired with prolonged angioplasty balloon inflation times with resolution of the injuries.⁶⁶ Follow-up over a 4-year period suggests that this is a successful and durable procedure. Use of covered stents has also been reported for brachial transections, but concern remains over the small vessel diameter and the propensity for stenosis or thrombosis.^{65,67}

Femoral Vessel Trauma

These injuries are typically approached directly through a groin incision extending distally as necessary. However, when more proximal control is warranted, the incision is extended above the inguinal ligament in the form of a flank incision to expose the iliac vessels in the retroperitoneum. Using an endovascular approach, balloon tamponade of the iliac vessels may be performed via the ipsilateral or contralateral groin, providing hemostasis and thus avoiding dissection into the retroperitoneum.⁵⁸ As in the upper extremity, covered stents may also be placed with low morbidity and mortality.^{56,63,68} Covered stent placement can also be used during repair of concomitant complex orthopedic injuries, where it is important to maintain distal perfusion.⁶¹ For the difficult to expose deep muscular branches of the profunda femoral artery, coil embolization may provide a viable alternative in the face of significant life-threatening hemorrhage.⁶⁹

Popliteal Vessel Injury

A common finding associated with posterior knee dislocations, this injury is at significant risk for thrombosis and limb loss.⁶⁵ Even in the endovascular era, this type of trauma has been approached via a medial incision above and below the knee due to concerns of stent fatigue and fracture in this highly mobile area.⁷⁰ However, both angioplasty⁷¹ and covered stent placement⁷² have been reported, with excellent immediate results. These approaches may offer a temporizing or permanent solution in the unstable patient or in the patient with difficult anatomy or other significant secondary injuries precluding open surgery.

Tibial Vessel Injury

Traditionally, infrapopliteal vessels are not treated as long as there is no extensive hemorrhage and the circulation to the foot is intact through at least one vessel.⁷³ Pseudoaneurysms, however, can develop necessitating intervention. Surgical techniques include ligation, direct repair with or without a vein patch, interposition grafting, or primary repair.^{74,75} The use of an endovascular stent is now another viable option.⁷⁶ In dealing with subsequent traumatic AV fistulas, treatment is easily managed with transcatheter coils or balloons, which may reduce reoperative wound complications.⁵⁹

TIMING OF ORTHOPEDIC REPAIR VIS-À-VIS VASCULAR REPAIR

Another issue that continues to evoke controversy is the timing of repair of concomitant vascular and orthopedic injuries—in particular, the order in which these injuries

should be repaired. In general, vascular repair should take precedence over orthopedic reconstruction when possible. Vascular surgeons have long been concerned about the instability of knee dislocations and distal femoral or proximal tibial fractures, fearing that a fragile vascular reconstruction might be undone by subsequent orthopedic maneuvers; however, the data do not support this fear. There is some evidence that in patients with combined injuries, giving priority to revascularization over orthopedic fixation leads to shorter hospital stays and a trend toward lower fasciotomy rates. In a 2002 study, revascularization before fracture fixation was not found to result in iatrogenic disruption of the vascular repair.⁵⁰

When an extremity has been substantially destabilized as a consequence of bony injury, short-term external fixation may be employed to facilitate vascular repair. A temporary intraluminal shunt is often used to maintain perfusion during initial orthopedic stabilization. One study demonstrated that routine use of intraluminal shunts in patients with complex extremity vascular injuries had the potential to reduce excessive morbidity (e.g., the need for fasciotomy and the resultant prolonged hospital stay) from prolonged arterial insufficiency.⁷⁷ In selected patients with combined skeletal and vascular injuries to the upper or lower limb, temporary vascular shunting may reduce complications resulting from prolonged ischemia and permit an unhurried and reasonable sequence of treatment.⁷⁸

SALVAGE OF SEVERELY INJURED OR MANGLED EXTREMITIES

When an extremity is severely injured or mangled, a decision must be made whether to attempt salvage or perform amputation. Because of the need to take the patient's emotional and medical concerns into account, evaluation of an extremity for potential salvage is a difficult undertaking. Several scoring systems have been developed to help make this decision-making process somewhat easier. The most commonly used system is the Mangled Extremity Scoring System (MESS), which uses four objective criteria to predict the likelihood of amputation after lower extremity trauma: skeletal/soft tissue injury, limb ischemia, shock, and patient age. A MESS score of 7 or higher predicts amputation with an accuracy approaching 100%. However, it is essential to remember that each patient must be carefully evaluated and that attempts at limb salvage must not be based solely on a high MESS score.^{79,80}

The need for amputation may be best predicted by the occurrence of severe injuries to the sciatic or tibial nerves, the presence of associated fractures, and the failure of arterial repair.⁶ Often the decision to amputate is not made at the time of presentation or during the initial operation. If, after revascularization and skeletal stabilization, the extremity is clearly nonviable or remains insensate, then delayed amputation may be performed under more controlled circumstances.⁸¹

The optimal approach to evaluating a severely injured extremity involves a multispecialty approach, including the trauma surgeon, the vascular surgeon, and the orthopedic surgeon. With full knowledge of the patient's condition, an attempt at limb salvage may be appropriate. In some cases, however, amputation may be preferable to preservation of an insensate, nonfunctional limb.

Conclusion

The management of vascular trauma has evolved significantly in recent years with the advent of endovascular therapy and its use in vascular trauma. It is crucial to remember that the mainstay of vascular trauma relies initially on a physical examination and the ABI. Time-honored approaches to vascular injury remain the gold standard of management, but the incorporation of endovascular techniques as adjunctive methods should be considered as a viable option to temporize injury and offer vascular control in difficult anatomic areas for traditional open procedures. Vascular trauma will require a multispecialty approach to allow the influx of newer techniques but will ultimately rely on early recognition and the time-honored physical examination to minimize ischemic time and allow for optimal patient outcomes.

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Figures 1, 4 through 10 Alice Y. Chen

14 MANAGEMENT OF THE PATIENT WITH THERMAL INJURIES

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Optimal care of the burn patient requires not only specialized equipment but also, more importantly, a team of dedicated surgeons, nurses, therapists, nutritionists, pharmacists, social workers, psychologists, and operating room staff. Burn care was one of the first specialties to adopt a multidisciplinary approach, and over the past 30 years, burn centers have decreased burn mortality by coordinating prehospital patient management, resuscitation methods, and surgical and critical care of patients with major burns. Detailed practice guidelines for burn patients, as well as lists of the resources needed in a burn center, have been developed.^{1,2}

Where to Treat Burn Patients

Patients with critical burns, as defined by the American Burn Association [see Table 1], should be transferred to a specialized burn center as soon as possible after their initial assessment and resuscitation. A community general or plastic surgeon with an interest in burns could manage moderate burns that do not involve functionally significant body sites. However, even patients with small burns benefit from the expertise of a specialized burn care team. Furthermore, the burn center's focused approach facilitates patient and family education, reentry into society, long-term rehabilitation needs, and reconstructive surgical needs.

OUTPATIENT VERSUS INPATIENT MANAGEMENT

Outpatient management may be appropriate for small burns (1 to 5% of total body surface area [TBSA]) that do not involve joints or vital structures. However, successful outcomes in such cases require a well-organized plan and clear communication with the patient and family. Many outpatient management plans fail because insufficient teaching during a

short visit to an emergency department leads to inadequate pain control, wound infection, and limited movement.

Three important reasons for hospitalizing a patient with a burn injury are wound care, physical therapy, and pain management. A short hospital stay immediately after the injury gives the burn team the opportunity to teach the patient how to properly clean and dress the burn; this is especially important for burns to the extremities. A therapist should assess patient movement and educate the patient about expected activity levels and exercise programs. Background pain (pain experienced with ordinary daily activities) and procedural pain (pain experienced during wound care) should be carefully assessed, and analgesic medications should be titrated to the individual patient's pain levels.

Complex burn wound management is discussed in detail elsewhere. For outpatient management, however, simplicity is the key to success. Patients and their families are unlikely to manage complicated dressing plans. For outpatient burn care, once-daily dressing changes are adequate. A common misconception is that these wounds must be cleaned with sterile saline. In fact, burns can be effectively washed during a daily shower or bath with regular tap water and nonperfumed soap. A second misconception is that the patient must scrub the wound to débride all the superficial exudates. Simply wiping the wound with a soapy washcloth to remove the topical ointment and wipe away the bacteria that have accumulated over the past day provides adequate care. Intact blisters can be left as a protective wound cover if they do not prevent movement of a joint. Dressings must allow full range of motion.

Physical therapy is an essential component of burn management. A common misconception is that burns over joints should be immobilized to promote healing. Actually, immobilization of extremities leads to swelling, which worsens burn wound pain and increases the risk of wound infection. Patients with hand burns must be taught exercises to maintain range of motion. Likewise, patients with foot burns must ambulate without assistive devices so that normal muscle contraction can facilitate lymphatic drainage of the lower extremity. Patients must be taught to elevate burned extremities when they are not actively exercising.

Inadequate pain management is a frequent reason for return visits to the emergency department or readmission to the hospital. Often inadequate pain control results from poor patient understanding of how to care for the burn (e.g., excessive scrubbing during wound care or inactivity and subsequent swelling). Although a healing partial-thickness burn may become more painful as the epithelial buds begin to emerge and healing progresses, an acute increase in stinging

Table 1 American Burn Association Criteria for Burn Injuries that Warrant Referral to a Burn Unit

Partial-thickness burns of greater than 10% of total body surface area
Third-degree burns
Electrical burns, including lightning injury
Chemical burns
Inhalation injury
Burn injury in patients with preexisting medical disorders that could complicate management, prolong recovery, or increase mortality
Burns with concomitant trauma

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pain may be the first sign of a superficial wound infection. This is an indication that the burn should be evaluated for signs of infection, including erythema and breakdown of a previously epithelized wound; cellulitis may or may not surround an infected burn. Systemic antibiotics and a change in the topical antimicrobial agent are indicated in this situation.

Socioeconomic issues can be important contraindications to outpatient management of a burn wound [see Table 2]. Any suggestion of abuse—of a child or an adult—mandates admission for full evaluation of the home situation by the burn team; if the history and the burn distribution are consistent with a nonaccidental injury or potential neglect, the patient must be referred to protective services. Likewise, suggestion of a self-induced burn injury should trigger admission for psychological evaluation. For example, the presence of multiple small cigarette burns in various phases of healing is an absolute indication for admission to the hospital for psychological evaluation, even though the burns themselves may be easily cared for at home with small adhesive bandages. Although language barriers are not an absolute indication for hospital admission, there must be assurance that patients fully understand the treatment plan before they leave the emergency department. Underinsured and homeless patients may not have the resources to care for a wound outside the hospital and should be admitted for initial wound care and planning for transfer to a facility where they have access to a daily shower. Finally, the success of outpatient burn wound management depends on the ability to arrange a follow-up visit with an outpatient health care provider who can assess the outcome.

For patients with large burns, transition from inpatient to outpatient status is based on the same principles listed above. When burn pain can be controlled with oral medication and the patient and family can provide wound care, perform range-of-motion exercises, and manage splints and other assistive devices, outpatient management is appropriate. In some cases, daily or weekly outpatient therapy sessions to maintain range of motion may be included. If there are concerns about nonhealing wounds, weekly follow-up visits with the burn surgeon may be indicated initially. Because of possible long-term sequelae—scarring, contractures, and rehabilitation difficulties—the burn team should follow burn patients for 1 to 2 years after injury; longer follow-up may be necessary for patients with persistent contractures and scar formation. Prolonged follow-up is especially important with young children, who may encounter difficulties as they grow and may therefore require periodic monitoring until adulthood.

Table 2 Criteria for Outpatient Management of Burn Patients

Outpatient Management Appropriate	Outpatient Management Inappropriate
Patients with small burns* who have demonstrated understanding of wound care, pain control, and therapy	Abused patients Demented patients Intoxicated patients Homeless patients Patients with comorbid conditions Patients with a language barrier

*1–5% of total body surface area.

Fluid Management

In the late 1960s, Charles Baxter developed objective criteria for resuscitation of the thermally injured patient.^{3,4} The Baxter formula (also known as the Parkland formula) calls for the infusion, over 24 hours, of 3 to 4 mL of crystalloid per percentage of TBSA burned. Half of this volume is delivered during the first 8 hours after injury, and the other half is delivered over the subsequent 16 hours. It is important to remember that this is an estimate of need; individual patients may have higher or lower fluid requirements depending on their overall condition and comorbidity. Continuous monitoring and reliance on objective clinical outcomes must dictate patient management.

The reliability of the Parkland formula directly depends on accurate assessment of burn depth and percentage of TBSA affected.⁵ There are two formulas for quick estimation of burn size. One is the commonly used Rule of Nines: each arm is considered to be 9% of TBSA, each leg 18%, the anterior trunk 18%, the posterior trunk 18%, and the head 9% [see Figure 1]. Another easy method involves using the patient's full palm, including digits, to represent 1% of TBSA. First-degree burns should not be included in the calculation of burned areas.

Despite improvements in invasive monitoring techniques, the most reliable measures of adequate tissue perfusion for burn resuscitation continue to be mean arterial pressure (MAP) and adequate urine output (UOP). MAP should be maintained above 60 mm Hg to ensure adequate cerebral perfusion. For an otherwise healthy adult, a UOP of 30 mL/hr should be adequate; for a child, 1.0 to 1.5 mL/kg/hr should suffice. No evidence supports the use of pulmonary arterial (PA) catheter measurements for routine resuscitation; in fact, reliance on PA catheters may lead to overresuscitation and contribute to the development of fluid-related complications (see below). Use of diuretics and inotropes should be restricted to patients with underlying comorbidity, especially preexisting cardiac disease. Use of inotropes will not stop the leak of plasma into the extravascular space but may lead to ischemia in the wound, resulting in conversion of a partial-thickness wound into a full-thickness wound. Use of mannitol may be appropriate for patients with myoglobinuria who require an osmotic diuretic to maintain a UOP of 100 mL/hr.

Although the first 24 hours after a burn is usually considered the resuscitative phase of a burn injury, stabilization of the flux of mediators and closure of capillary leaks, in fact, take place on a continuum, occurring gradually from 12 to 48 hours after the burn injury. As capillary leakage resolves, the amount of fluids needed to maintain a MAP of 60 mm Hg and a UOP of 30 mL/hr should progressively decrease. A patient with both a large, deep burn and a profound inhalation injury or a patient in whom resuscitation has been delayed may require significantly more fluid than predicted by the Parkland formula to maintain blood pressure and UOP. It is common for a patient with combined thermal and inhalation injury to require 1.5 times Parkland or more.

Baxter's early work showed that capillary leak may persist for up to 24 hours postburn⁴ and that plasma expansion during this period was independent of the type of fluid given.³ More recently, however, it has been suggested that although endothelial dysfunction and capillary leak are present within

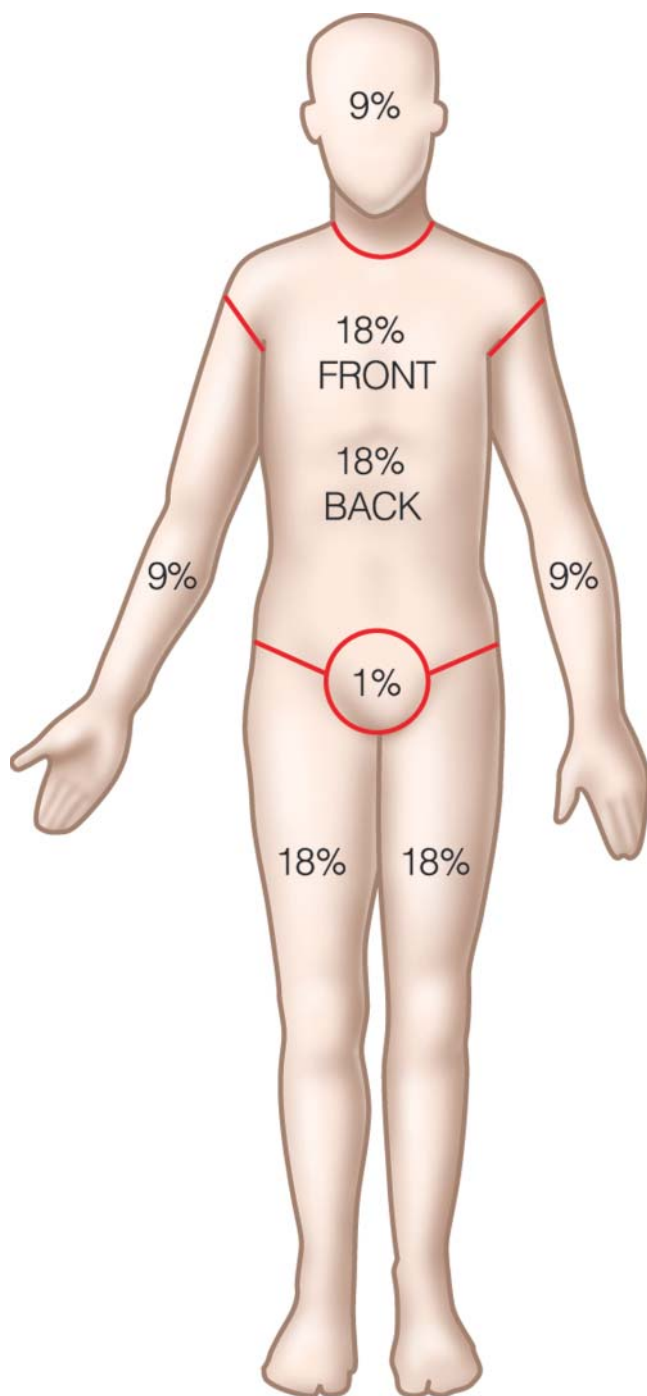


Figure 1 The size of a burn can be estimated by means of the Rule of Nines, which assigns percentages of total body surface to the head, the extremities, and the front and back of the torso.

2 hours of burn injury, they last for a median of 5 hours, a period that is much shorter than previously described.⁶ Colloid administration (albumin or fresh frozen plasma) after the capillary leak has closed (12 to 48 hours) may facilitate resuscitation in the patient with persistent low UOP and hypotension despite adequate crystalloid delivery. In such cases, the formula used is 5% albumin, 0.3 to 0.5 mL/kg/%

TBSA burned over 24 hours. Alternatively, plasmapheresis may reduce intravenous fluid requirements in patients who are not responding to resuscitation.⁷ Indications for plasmapheresis include a sustained MAP of less than 60 mm Hg and a UOP less than 30 mL/hr in a patient with ongoing fluid needs that exceed twice the estimated volume requirements. Early plasmapheresis (12 to 24 hours after injury) may decrease the incidence of complications from administration of excessive fluid (see below). Why plasmapheresis works is unknown, but, theoretically, the process should remove inflammatory mediators that cause vasodilatation and capillary leak.

Once resuscitation is complete (24 to 48 hours after injury), insensible losses and hyperthermia associated with a hyperdynamic state may indicate the need for ongoing fluid administration. The route of administration can be intravenous or, preferably, enteral. Reliable daily weights can be extremely valuable for the detection and measurement of insensible fluid loss or fluid retention.

Along with MAP and UOP, several laboratory variables can be used to ensure that patients are receiving appropriate amounts of resuscitation fluid [see Table 3 and Table 4].

COMPLICATIONS OF FLUID ADMINISTRATION

Before the development of current resuscitation formulas, inadequate resuscitation was a common cause of death in burn patients as a result of decreased tissue perfusion and subsequent multiorgan failure.⁸ In addition, this ischemia caused conversion of the burn to a deeper injury, thereby increasing surgical requirements. However, there are also complications associated with overresuscitation, or so-called fluid creep.^{9,10} Whereas Baxter suggested that 12% of patients would require more than 4.3 mL/kg/%TBSA resuscitation fluid,⁴ subsequent reports suggested that more than 55% of patients receive this amount of fluid.^{8,9,11} Excessive fluid resuscitation increases the risk of complications, including poor tissue perfusion, compartment syndrome involving the abdomen or extremities, pulmonary edema, and pleural effusion.

Abdominal compartment syndrome (ACS) is an increasingly well-recognized posttraumatic complication that occurs in patients who require extensive fluid resuscitation. Increased abdominal pressure decreases lung compliance and impedes lung expansion, resulting in elevated airway pressures and hypoventilation. The classic presentation includes high peak airway pressures, decreased venous return, oliguria, and intra-abdominal pressures exceeding 25 mm Hg.¹² Sustained intra-abdominal hypertension is often fatal. Bedside decompressive laparotomy can alleviate ACS and can be performed safely through burn wounds,¹³ and its use should be considered in patients with hemodynamic instability, hypoventilation, and elevated abdominal pressures. Whether the patient survives, however, depends on the comorbid conditions that led to the requirement for large resuscitative volumes.

To avoid potential complications of overaggressive fluid resuscitation, many institutions have developed protocols that guide the intensive care unit (ICU) nurse to adjust the amount of fluid given to a patient based on UOP and MAP, such that if the hourly UOP is low, the fluids are increased, and if the UOP is high, the fluids are decreased.

Table 3 Acute Physiologic Changes during Burn Resuscitation

Measurement	Comment	Goal	Signs of Underresuscitation	Signs of Overresuscitation
Fluid volume	Fluid input generally exceeds output during the early postburn period as edema develops	Urine output: adults, 30 mL/hr; children < 20 kg, 1.0–1.5 mL/kg/hr	Low urine output	Urine output > 30 mL/hr; hyperosmolar diuresis from hyperglycemia must be excluded
Body weight	An accurate dry weight is necessary for estimation of resuscitation fluid requirements	Weight will increase because of intravascular leak and resuscitation volume	Weight approaches dry weight	Massive weight gain from anasarca
Body temperature	Hyperthermia may indicate a hyperdynamic state	Normothermia	—	—
Electrocardiographic status	Dysrhythmias are uncommon in young patients but may complicate management of older patients	Normal sinus rhythm	Tachycardia may reflect intravascular contraction	Dysrhythmias may reflect poor oxygenation, electrolyte imbalance, or pH abnormality

Table 4 Acute Biochemical and Hematologic Changes during Burn Resuscitation

Measurement	Comment	Goal	Signs of Underresuscitation	Signs of Overresuscitation
Serum creatinine and blood urea nitrogen	Normal baseline values rule out preexisting renal disease, which reduces urine output reliability as an index of tissue perfusion	Normal values	Rising values may reflect underresuscitation or acute tubular necrosis	May be normal
Hematocrit and hemoglobin	Significant blood loss from incorrectly performed surgical interventions such as escharotomies or central venous line placement may lower values	Should approach normal	May be elevated with severe intravascular depletion; this is typical with delayed resuscitation	May be low in patients with excessive intravascular volumes
White blood cell count (WBC)	The initial WBC may vary, depending on the stress response and cell margination; the absolute value is not particularly useful during the early postburn period; once leukopoiesis increases, neutropenia resolves without treatment with stimulatory factors	Normal values	May increase	May decrease, but this generally represents margination of circulating neutrophils into the wound
Blood glucose	Increased release of catecholamines in burn patients may lead to hyperglycemia; diabetic patients may require insulin	Levels maintained at ≤ 120 mg/dL	Hyperglycemia, which may misleadingly increase urine output	Hypoglycemia, especially in infants (< 20 kg), who have decreased glycogen stores
Electrolytes	Electrolyte status depends on the type of crystalloid used for resuscitation; hypernatremia and hyponatremia can be avoided by resuscitation with lactated Ringer solution; use of normal saline should be avoided because it can lead to hyperchloremic acidosis	Normal electrolyte levels	—	—
Plasma protein and myoglobin levels	Patients with very deep burns or electrical burns may have elevated plasma myoglobin levels	Decreased albumin level within the first 8 hr after burn injury may be normal	Myoglobinemia may result from prolonged underresuscitation and tissue ischemia	Myoglobinemia may result if excessive resuscitation leads to compartment syndrome; escharotomy should be performed to minimize rhabdomyolysis
Prothrombin time, partial thromboplastin time, and platelet count	Initial values are useful to determine whether the patient has preexisting hepatic or hematologic disease	Normal	Prolonged shock and underresuscitation may lead to disseminated intravascular coagulation; coagulation factors and platelets may be needed in such cases	Unrecognized compartment syndrome and delayed escharotomy may cause tissue ischemia and disseminated intravascular coagulation; a dropping platelet count may indicate heparin-induced thrombocytopenia

Taken to the extreme, this includes creation of a computer program that titrates fluid rate according to UOP.^{14,15} Early reports are promising and suggest a low incidence of complications.

Airway Management

Abnormal pulmonary function commonly complicates the management of thermally injured patients. It may result from inhalation injury or from the systemic response to the burn. Understanding the management of pulmonary dysfunction in the thermally injured patient requires a working knowledge of pulmonary function measurements and of pulmonary pathophysiology [see Table 5 and Table 6].

INHALATION INJURY

Inhalation injuries occur in approximately one third of all major burns, and mortality is more than double that of cutaneous burns.^{16–18} Curiously, isolated inhalation injuries do not result in high mortality.¹⁹ Presumably, the combination of

inhalation injury and cutaneous thermal injury creates a double insult in which recurrent or persistent bacteremia aggravates the pulmonary injury.

Three distinct components of inhalation injury exist: carbon monoxide (CO) poisoning, upper airway thermal burns, and inhalation of products of combustion. Diagnosis of an inhalation injury requires a thorough history of the circumstances surrounding the injury and is often suggested by fire in a closed space, carbonaceous sputum, and an elevated carboxyhemoglobin level (> 15%).

Carbon Monoxide Poisoning

CO injury is the most commonly recognized form of inhalation injury and the most common cause of death in inhalation injury. Clinical signs and symptoms of CO toxicity correlate with arterial carboxyhemoglobin levels, which can be used to quickly and precisely determine the degree of CO intoxication [see Table 7]. CO intoxication can be easily treated with 100% inhaled oxygen, which rapidly accelerates the dissociation of CO from hemoglobin [see Table 8].

Table 5 Measures of Pulmonary Function

Measurement	Normal Values	Abnormal Values Indicating Need for Mechanical Ventilation
Tidal volume (V_T), mL/kg	5–8	< 5
Vital capacity (V_C), mL/kg	65–75	< 10; < 15*
Forced expiratory volume in 1 s (FEV_1), mL/kg	50–60	< 10
Functional residual capacity (FRC), % of predicted value	80–100	< 50
Respiratory rate (f), breaths/min	12–20	> 35
Maximum inspiratory force (MIF), cm H ₂ O	80–100	< 20; < 25; < 30*
Minute ventilation (V_E), L/min	5–6	> 10
Maximum voluntary ventilation (MVV), L/min	120–180	< 20; < (2 × V_E)*
Dead space fraction (V_D/V_T), %	0.25–0.40	> 0.60
Paco ₂ , mm Hg	36–44	> 50; > 55*
Pao ₂ , mm Hg	75–100 (breathing room air)	< 50 (room air); < 70 (mask O ₂)*
Alveolar-to-arterial Po ₂ gradient [P(A-a)O ₂], mm Hg	25–65 (breathing 100% O ₂)	> 350; > 450*
Arterial-alveolar Po ₂ ratio (Pao ₂ /P _A O ₂)	0.75	< 0.15
Arterial Po ₂ -inspired O ₂ (Pao ₂ /F _I O ₂) mm Hg	350–450	< 200
Intrapulmonary right-to-left shunt fraction (Qs/Qt), %	≤ 5%	> 20%; > 25% > 30%*

F_IO₂ = fraction of inspired oxygen; Paco₂ = arterial carbon dioxide tension; Pao₂ = arterial oxygen tension; P_AO₂ = alveolar oxygen tension.

*More than one value indicates lack of uniform agreement in the literature.

Table 6 Mechanisms of Pulmonary Dysfunction and Indications for Mechanical Ventilation

Mechanism	Best Indicator
Inadequate alveolar ventilation	Paco ₂ and pH
Inadequate lung expansion	Tidal volume, respiratory rate, VC
Inadequate respiratory muscle strength	MIF; MVV; VC
Excessive work of breathing	V_E required to keep Pco ₂ normal; V_D/V_T ; respiratory rate
Unstable ventilatory drive	Breathing pattern, clinical setting
Severe hypoxemia	P(A-a)O ₂ ; Pao ₂ /P _A O ₂ ; P _A O ₂ /F _I O ₂ ; Qs/Qt

F_IO₂ = fraction of inspired oxygen; MIF = maximum inspiratory force; MVV = maximum voluntary ventilation; P(A-a)O₂ = alveolar-to-arterial Po₂ gradient; Paco₂ = arterial carbon dioxide tension; Pao₂/F_IO₂ = ratio of arterial Po₂ to inspired O₂; P_AO₂/F_IO₂ = ratio of alveolar Po₂ to inspired O₂; Qs/Qt = intrapulmonary right-to-left shunt fraction; VC = vital capacity; V_D/V_T = dead space fraction; V_E = minute ventilation.

Table 7 Clinical Manifestations of Carbon Monoxide Poisoning

Carboxyhemoglobin Level (%)	Clinical Manifestations
< 10	None
15–25	Nausea, headache
30–40	Confusion, stupor, weakness
40–60	Coma
> 60	Death

Hyperbaric oxygen therapy has been touted as a superior treatment for quickly reducing carboxyhemoglobin levels,²⁰ but the data are controversial and the studies are generally poorly controlled.²¹ Hyperbaric oxygen therapy may be appropriate in a patient with impaired neurologic status and a markedly elevated carboxyhemoglobin level (> 25%). However, the risks (including barotrauma) associated with isolation in a hyperbaric chamber may be too significant for a burn patient (> 10% TBSA) undergoing resuscitation. In one study of 10 patients with combined inhalation injury and burns treated acutely with hyperbaric oxygen, seven patients survived, but the complications included aspiration (two cases), cardiac arrest (two cases), hypovolemia with metabolic acidosis (three cases), respiratory acidosis (four cases), cardiac dysrhythmia (three cases), and eustachian tube occlusion (two cases).²² Consensus is growing that when cardiac arrest complicates inhalation injury, the result is uniformly fatal regardless of aggressive therapy, including hyperbaric oxygen therapy.²³

Upper Airway Thermal Injury

Direct thermal damage tends to occur in the upper airway rather than in the lower airway because the oropharyngeal cavity has a substantial capacity to absorb heat. Upper airway thermal injury constitutes an important indication for intubation because it is mandatory to control the airway before airway edema develops during resuscitation.

The diagnosis of upper airway thermal injury is achieved with direct laryngoscopic visualization of the oropharynx. The decision whether to intubate should be based on visual evidence of pharyngeal burns or swelling or carbonaceous sputum coming from below the level of the vocal cords. If a patient is phonating without stridor, intubation can often be delayed. Singed facial and nasal hair does not constitute an adequate independent indication for intubation.

Treatment of upper airway injuries includes hospital admission for observation and provision of humidified oxygen, pulmonary toilet, bronchodilators as needed, and prophylactic

endotracheal intubation as indicated. Upper airway thermal burns usually manifest within 48 hours after injury, and airway swelling can be expected to peak at 12 to 24 hours after injury. A patient with a true upper airway burn will likely require airway protection for 72 hours. A short course of steroids may facilitate earlier resolution of airway edema in a patient with small cutaneous burns, but a patient with a burn larger than 20% TBSA should not be treated with steroids because of the risk of infection and failure to heal. The decision whether to extubate can be based on pulmonary weaning criteria but also on the presence of an air leak around the endotracheal tube.

Lower Airway Burn Injury

Burn injury to the tracheobronchial tree and the lung parenchyma results from combustion products in smoke [see Table 9] and, under unique conditions, inhaled steam. Numerous irritants in smoke or the vaporized chemical reagents in steam can cause direct mucosal injury, leading to mucosal slough and bronchial edema, bronchoconstriction, and bronchial obstruction. Tracheobronchial mucosal damage also leads to neutrophil chemotaxis and release of inflammatory mediators into the lung parenchyma, accentuating the injury with exudate formation and microvascular permeability. Inflammatory occlusion of terminal bronchioles and necrosis of the mucosa render the airway and pulmonary parenchyma susceptible to infection with resulting pneumonitis, which further increases mortality. Together, these may progress to pulmonary edema, pneumonia, and acute respiratory distress syndrome (ARDS). Reduced myocardial contractility secondary to smoke-toxin inhalation may also contribute to resuscitation failures in burn victims with concomitant inhalation injury.

Inhalation injury can often be a clinical diagnosis.¹⁸ Lower airway injury can be confirmed by bronchoscopy or xenon-133 ventilation-perfusion scan,²⁴ but these modalities have not traditionally changed therapeutic choices or clinical outcome.²⁵ There is no standard definition of inhalation injury, but a bronchoscopic grading scheme has been created, based on Abbreviated Injury Score criteria [see Table 10],²⁶ derived from findings on initial bronchoscopy. The scale grades the degree of airway injury based on progressively severe endoluminal damage. Interestingly, bronchoalveolar lavage findings on initial bronchoscopy have demonstrated a high incidence of bacterial contamination, typically gram-positive cocci that would commonly be associated with community-acquired pneumonia, and often in high quantitative colony counts.²⁷

ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

Understanding of the pathophysiology of ARDS has improved since its initial description in the late 1960s,²⁸ and ARDS-related deaths were lower in the period 1995 through 1998 than in the period 1990 through 1994; however, 40 to 70% of patients with ARDS still die of the disease.²⁹ ARDS is an independent risk factor for death in burn patients.³⁰ Mortality in burn patients with ARDS is attributable to overwhelming sepsis and multiple organ failure rather than to respiratory failure alone.³¹

Clinically, ARDS is characterized by pulmonary edema, refractory hypoxemia, diffuse pulmonary infiltrates, and

Table 8 Half-Life of Carbon Monoxide–Hemoglobin Bonds with Inhalation Therapy

Carboxyhemoglobin Half-Life	Treatment Modality
4 hr	Room air
45–60 min	100% oxygen
20 min	100% oxygen at 2 atm (hyperbaric oxygen)

Table 9 Clinical Findings Associated with Specific Inhaled Products of Combustion

Source	Product of Combustion	Clinical Effect
Organic matter	Carbon monoxide Carbon dioxide	Poor tissue oxygen delivery Narcosis
Wood, paper, anhydrous ammonia	Nitrogen oxides (NO, NO ₂)	Airway mucosal irritation, pulmonary edema, dizziness
Polyvinyl chloride (plastics)	Hydrogen chloride	Airway mucosal irritation
Wool, silk, polyurethane (nylon)	Hydrogen cyanide	Respiratory failure, headache, coma
Petroleum products (gasoline, kerosene, propane, plastics)	Carbon monoxide, nitrogen oxide, benzene	Airway mucosal irritation, coma
Wood, cotton, paper	Aldehydes	Airway mucosal irritation, lung parenchyma damage
Polyurethane (nylon)	Ammonia	Airway mucosal irritation

altered lung compliance. Pathologically, it is distinguished by diffuse alveolar epithelial damage with microvascular permeability and subsequent inflammatory cell infiltration into the lung parenchyma, interstitial and alveolar edema, hyaline membrane formation, and, ultimately, fibrosis.

The development of ARDS is presaged by high fluid resuscitation requirements, reflecting increased microvascular permeability and leading to increased pulmonary edema. ARDS commonly develops within 7 days after injury. The likelihood of death is significantly increased in patients with a multiple organ dysfunction score of 8 or higher and a lung injury score of 2.76 or higher. In one review, burn patients with inhalation injury had a 73% incidence of respiratory failure (with hypoxemia, multiple pulmonary infections, or prolonged ventilator support) and a 20% incidence of ARDS, whereas patients without inhalation injury had a 5% incidence of respiratory failure and a 2% incidence of ARDS.³⁰ Advanced age may also constitute an important risk factor for the development of ARDS; one small retrospective study has suggested that age is the only independent major predisposing factor for ARDS.³² Curiously, acute lung injury rarely develops in patients with inhalation injury without cutaneous burns.^{33,34}

Inflammatory Mediators in ARDS with Burn Injuries

Local and systemic inflammatory mediators released in response to burn injury include platelet-activating factor,

interleukins, prostaglandin, thromboxane, leukotrienes, hematopoietic growth factors, cell adhesion molecules, and nitric oxide (NO).^{35,36} Systemic levels of circulating tumor necrosis factor- α (TNF- α) and interleukin-1 correlate with ARDS severity. Clinical studies have correlated infection—but not isolated inhalation injury—with increased IL-2 levels, which reemphasizes the potential significance of the double insult inflicted by the combination of a burn and an inhalation injury.³⁷ Some data suggest that relative imbalances in levels of inflammatory mediators may be more important than absolute values.

An important cell in the inflammatory cycle is the pulmonary alveolar macrophage, which produces reactive oxygen intermediates (ROIs) as a means of killing microorganisms. In animal models, addition of a burn injury to a smoke insult exaggerates lipid peroxidation and hypoproteinemia, implicating reactive oxygen species in the pathophysiology of ARDS. With systemic inflammation, unchecked ROI production may lead to local tissue injury. ROIs damage cells by direct oxidative injury to cellular proteins and nucleic acids, as well as by inducing lipid peroxidation, which leads to the destruction of the cell membrane. ROIs are generated under conditions of ischemia-reperfusion (as with failed resuscitations), which occurs when the flow of oxygenated blood is restored to ischemic tissue such as unexcised eschar. During ischemia, there is increased activity of xanthine oxidase and increased hypoxanthine production; when reperfusion reintroduces oxygen, the xanthine oxidase and hypoxanthine generate ROIs, which cause more tissue injury.

Management of ARDS

In spite of 30 years of advances in ARDS treatment, patients with ARDS still must depend on mechanical respiratory support—not treatment—as the primary therapeutic intervention while the alveolar epithelium repairs itself, the capillary permeability resolves, and the lung heals. Restricting fluids to prevent further edema formation has increased survival.³⁸ The most encouraging strategy to prevent lung injury and increase survival has been low tidal volume mechanical ventilation, commonly called lung protective ventilation, with or without high levels of positive end-expiratory pressure (PEEP).^{39,40} Pharmacologic approaches to treating ARDS in burn patients parallel those used in other critically ill surgical patients and are addressed elsewhere.

For most patients with pulmonary complications from thermal injury, conventional ventilatory approaches will be

Table 10 Bronchoscopic Criteria Used to Grade Inhalation Injury

Grade	Bronchoscopic Findings
0 (no injury)	Absence of carbonaceous deposits, erythema, edema, bronchorrhea, or obstruction
1 (mild injury)	Minor or patchy areas of erythema, carbonaceous deposits in proximal or distal bronchi (any combination)
2 (moderate injury)	Moderate degree of erythema, carbonaceous deposits, bronchorrhea, with or without compromise of the bronchi (any combination)
3 (severe injury)	Severe inflammation with friability, copious carbonaceous deposits, bronchorrhea, bronchial obstruction (any combination)
4 (massive injury)	Evidence of mucosal sloughing, necrosis, endoluminal obliteration (any combination)

adequate. However, the population at risk for development of ARDS may need more sophisticated management to reduce barotrauma and pulmonary infection in the minimally compliant lung with increased airway pressures. In the past, conventional ventilator management of inhalation injury and ARDS, which emphasizes normalization of blood gases, promoted high rates of barotrauma—that is, ventilator-induced lung injury that is physiologically and histopathologically indistinguishable from ARDS itself. Overdistention and cyclic inflation of injured lung exacerbate underlying lung injury and perpetuate systemic inflammation. These effects can be minimized by maintaining low tidal volumes and plateau pressures and by applying PEEP. Hence, the use of alternative modes of ventilation (e.g., volume-limited ventilation with or without inverse-ratio ventilation, prone positioning, and tracheal gas insufflation) has increased in patients at risk for ARDS. No single approach is likely to benefit all patients, and adjustment of ventilatory controls must be based on individual clinical responses.

Lung-protective ventilation Lung-protective ventilation uses low inspiratory volumes (4 to 6 mL/kg) to keep peak plateau pressures below 30 cm H₂O. This strategy is limited by the accumulation of CO₂ (so-called permissive hypercapnia), although respiratory acidosis with a pH as low as 7.20 is tolerated.

The Acute Respiratory Distress Syndrome Network Study (ARDSNet) found that ARDS patients ventilated with low tidal volumes had a 22% lower mortality than patients ventilated with conventional means.^{40,41} The volume-preset, assist-control mode is recommended for tidal volume control, and the respiratory rate should be slowly increased as tidal volume is reduced to maintain minute ventilation and prevent acute hypercapnia. Tidal volume can be increased for severe acidosis (pH < 7.15). Alternatively, a sodium bicarbonate infusion may be initiated to correct pH and tracheal gas insufflation can be used to help clear CO₂ in cases of severe hypercarbia. Ventilator inspiratory flow should be optimized to minimize dyspnea. If dyspnea results in asynchronous breaths, sedation may be necessary or the tidal volume can be titrated to 7 to 8 mL/kg provided that plateau pressures are below 30 cm H₂O.

One study of children with burns found that low tidal volume ventilation was associated with low incidences of ventilator-induced lung injury and respiratory-related deaths,⁴² which supports the use of this modality in thermally injured patients. In fact, in patients with large burns and inhalation injury, it may be warranted to use low tidal volume ventilation before ARDS develops. The early resuscitative phase may be the optimal time to initiate this approach.

Positive end-expiratory pressure The ARDSNet comparing ventilation with lower tidal volumes to traditional tidal volumes for acute lung injury employed a PEEP ladder with increasing amounts of PEEP for increasing fraction of inspired oxygen (F_IO₂), from a low of 5 mm Hg PEEP to a high of 24 mm Hg PEEP.^{40,41} The higher respiratory rate associated with the smaller tidal volumes of the ARDSNet strategy has been found to generate a higher total PEEP as a result of the addition of intrinsic PEEP (from shortened expiration time), and this has been postulated as a possible

mechanism for the 22% reduction in mortality.⁴³ Acute lung injury is a heterogeneous disease, and different etiologies of lung injury likely benefit from different approaches to ventilatory management. In patients with a focal distribution of loss of aeration, there is a low potential for alveolar recruitment and susceptibility to alveolar hyperventilation with high levels of PEEP. In such patients, examination of static lung compliance and plasma concentrations of IL-6, IL-8, and tumor necrosis factor receptor were decreased with a more conservative PEEP strategy than the ARDSNet protocol.³⁹ In contrast, a patient with inhalation injury and significant truncal thermal burns undergoing fluid resuscitation exhibits a more diffuse lung injury pattern with significant decrease in the chest wall compliance and more pleural effusions. Talmor and colleagues have suggested that such patients may benefit from placement of an esophageal balloon and titration of the tidal volume and PEEP according to the measured transpulmonary pressure.⁴⁴

Prone positioning Changing a patient's position from supine to prone is emerging as a simple and inexpensive strategy to improve gas exchange in acutely injured lungs. Studies report that despite concerns about airway protection, this is a safe intervention that may improve the ratio of arterial oxygen pressure to fraction of inspired oxygen (PaO₂/F_IO₂) early in the course of ARDS.⁴⁵ Protti and colleagues used computed tomography to show that decreased arterial carbon dioxide tension (Paco₂) following prone positioning is related to lung recruitability and, accordingly, severity of lung injury.⁴⁶ Some data suggest that prone positioning in conjunction with NO administration may improve arterial oxygenation.⁴⁷ However, no clinical trials have examined the use of prone positioning in burn patients. If prone positioning has a significant effect, this positive result presumably would be evident during operative procedures when a patient with an acute lung injury is placed in this position (e.g., for excision of a posterior torso burn). Furthermore, prone positioning may be relatively contraindicated in a patient with a burned head who is at extreme risk for loss of control of the airway because of facial swelling and difficulty securing an endotracheal tube.

Extracorporeal membrane oxygenation Few centers have experience with extracorporeal membrane oxygenation (ECMO), and published information on its use for the treatment of ARDS in patients with inhalation injury and burns is mostly confined to anecdotal case reports.⁴⁸ Given its experimental nature and its high cost, ECMO is reserved for patients in whom other ventilatory modalities fail. Although ECMO has been shown to increase survival in some children with large burns and severe acute lung injury, patients with higher ventilator requirements before undergoing ECMO generally do not survive, suggesting that if ECMO is to be successful, it must be instituted early to prevent barotrauma and irreversible lung injury.⁴⁹ Early implementation of permissive hypercapnia and lung protective ventilation may be equally effective.

High-frequency percussive ventilation High-frequency percussive ventilation (HFPV) is another strategy for maintaining low peak pulmonary pressure and preventing alveolar overdistention. HFPV has the added advantage of

facilitating mucosal clearance of tracheobronchial casts that occlude the airway and predispose to pulmonary infection. Although HFPV is usually described as rescue therapy for patients in whom conventional therapy has failed, there is some evidence that it can reduce mortality and the incidence of pneumonia in patients with inhalation injury.^{50,51} Improved oxygenation and pulmonary toilet have been reported in patients treated early with HFPV,⁵² which suggests that a larger-scale prospective trial is warranted to determine whether the benefits of HFPV justify the added cost and effort of maintaining multiple types of ventilators and credentialing for respiratory therapists.

A similar method, high-frequency oscillatory ventilation, may have no impact on burn mortality. However, it may have a role in the supportive management of burn patients with severe oxygenation failure that is unresponsive to conventional ventilation.⁵³

NO inhalation Endogenously produced NO plays an important role in the changes in systemic and pulmonary microvascular permeability seen in an animal model of combined smoke inhalation and third-degree burn.³⁶ Clinically, inhaled NO may be useful in burn patients with severe acute lung injury causing refractory hypoxemia in whom conventional ventilatory support is failing.⁵⁴ Low methemoglobin levels and absence of hypotension attributable to the NO indicate the safety of inhaled NO in these patients. Strong, immediate, and sustained improvement in the $\text{PaO}_2/\text{F}_i\text{O}_2$ and reduction in PA mean pressure in response to NO seem to correlate with survival. However, many studies have failed to show a survival advantage with inhaled NO, and a prospective study is warranted.

Corticosteroids The use of corticosteroids in the treatment of burns is potentially problematic because of the negative effect these agents have on wound healing. Nevertheless, there is evidence that early initiation of low- to moderate-dose corticosteroids for severe ARDS continued for 14 to 21 days before tapering may decrease the mortality and morbidity outcomes without increased adverse reactions.⁵⁵ Encouragingly, comparison of the effects of dexamethasone, methylprednisolone, and hydrocortisone on wound healing in an animal model has shown that unlike dexamethasone and hydrocortisone, methylprednisolone did not significantly impair wound healing.⁵⁶ Thus, in a patient with severe ARDS, methylprednisolone may be the corticosteroid of choice to lessen the morbidity and mortality of severe lung injury. Larger multicenter studies, particularly those including burn patients, could strengthen the findings from meta-analyses of the existing studies and more definitively answer questions about risks and benefits.

Nebulized heparin Numerous pathologic airway alterations occur with inhalation injury and acute lung injury/ARDS. Augmented bronchial circulation, bronchospasm, and airway obstruction from cast formation from mucus secretions, denuded epithelial cells, inflammatory cells, and fibrin act to impair pulmonary function. Therefore, prevention or dissolution of fibrin cast formation with its resultant ventilation/perfusion mismatch, increased atelectasis, and

associated inflammation could significantly improve pulmonary function.⁵⁷ Desai and colleagues have reported that nebulized heparin combined with *N*-acetylcysteine significantly decreased reintubation rates, incidence of atelectasis, and mortality in children with massive burn and smoke inhalation injury.⁵⁸

TRACHEOSTOMY VERSUS ENDOTRACHEAL INTUBATION

Transmural airway inflammation from inhaled gases and heat necessitates endotracheal airway protection, yet the use of endotracheal tubes in such cases may be complicated by tracheal pressure necrosis. Hence, survivors of inhalation injury may develop laryngotracheal strictures. One report suggests that there is a 5.5% incidence of tracheal stenosis in patients with burns and inhalation injury.⁵⁹ The relative risks and benefits of tracheostomies and endotracheal intubation have been debated since the early 1970s. Each modality has its own advantages and complications. Nasotracheal intubation is the least advantageous form of airway protection because of its association with paranasal sinusitis,⁶⁰ as well as pressure necrosis of the alar rim of the burned nose, which is nearly impossible to reconstruct. Therefore, nasotracheal intubation should be avoided unless absolutely necessary.

Tracheostomies are also associated with complications, including tracheal malacia, tracheal stenosis, tracheoinnominate artery fistulas, tracheoesophageal fistulas, and posttracheostomy dysphagia.⁶¹ However, complications associated with tracheostomy may relate to previous long-term endotracheal intubation and to the underlying pathophysiology, suggesting that if tracheostomy is to be done, it should be done early on. Furthermore, the tracheostomy tube should be removed at the earliest possible time. In a 1985 study of airway management, tracheal stenosis and tracheal scar granuloma formation were reported to be more frequent and more severe after tracheostomy than after translaryngeal intubation.⁶² As expected, the duration of tube placement significantly affected the development of permanent damage, leading to the conclusion that initial respiratory support with translaryngeal tubes is preferable for up to 3 weeks. Burn patients who undergo tracheostomy before postburn day 10 may have a lower incidence of subglottic stenosis with no difference in pneumonia incidence when compared with orally intubated patients.⁶³ Nevertheless, tracheostomy has been reported to provide no benefit for early extubation or overall outcome for burn patients.⁴⁹ A major consideration in deciding whether to perform a tracheostomy has been the presence of eschar at the insertion site, which complicates tracheostomy-site care and increases the risk of airway infection. Several investigators reported the use of percutaneous tracheostomy in burn patients to be safe and cost effective; in one study, percutaneous tracheostomy had a lower incidence of stoma-site infections and pulmonary sepsis.⁶⁴ Thus, percutaneous dilatational tracheostomy may provide a reasonable, less invasive approach for patients who are likely to need prolonged ventilatory support.⁶⁵ This procedure can be safely performed at the bedside, at one quarter the cost of a conventional tracheostomy. Given ongoing controversies over the relative risks and benefits of endotracheal intubation and tracheostomy in burn patients and the rarity of complications from intubation in our own practice, we perform tracheostomies only when multiple attempts at extubation have failed;

these failures usually occur because the patients cannot protect their airway.

Temperature Regulation

Because the burn patient has lost the barrier function of the skin, temperature regulation is an important goal of successful management. Keeping a patient warm and dry is a major goal during resuscitation, especially during the pre-burn center transport of patients. This includes maintaining a warm ambient temperature. Large evaporative losses⁶⁶ combined with administration of large volumes of intravenous fluids that are at room temperature or colder may accentuate the hypovolemia, which will complicate the patient's overall course and may lead to disseminated intravascular coagulopathy. Mild hyperthermia may occur in the first 24 hours as a result of pyrogen release or increased metabolic rate⁶⁷ and may cause tachycardia that misleadingly suggests hypovolemia. Because infection is unlikely early on, especially within the first 72 hours after injury, elevated temperatures should be treated with antipyrogens to control the energy expenditure associated with increased catabolism.⁶⁸ About 72 hours after injury, patients with thermal injuries commonly develop a hyperdynamic state, the systemic inflammatory response syndrome (SIRS), which is characterized by tachycardia, hypotension, and hyperthermia—classic signs of sepsis that in this case do not have an infectious source.

Although patients with burns are likely to have elevated temperatures and may even have elevated white blood cell counts, fevers in burn patients are not reliable indicators of infections.⁶⁹ At least one study has demonstrated that in pediatric burn patients, physical examination is the most reliable tool for evaluating the source of fever.⁶⁹

Infection Control

Infection is a major potential problem for patients with large thermal injuries. In one review, up to 100% of such patients developed an infection from one or more sources during the hospital stay. It is important to apply sound epidemiologic practice to treating infections, both to limit development of opportunistic infections in individual patients and to achieve good infection control in the burn unit itself.

Tetanus prophylaxis has been standard for patients admitted for any type of trauma, primarily because the disease is so devastating and its prevention so simple. There are a few cases in the modern medical literature of tetanus in patients who received immunization during childhood.⁷⁰

For many years, all patients admitted with burn injuries received antibiotic prophylaxis against gram-positive organisms. This practice often led to the development of gram-negative bacterial infections or, even worse, fungal infections. Studies have now verified that prophylactic antibiotics not only are unnecessary but also may well be contraindicated in patients with burns.⁷¹ Therefore, treatment of infections in patients with burns should be based on clinical judgment and supportive laboratory and radiologic findings.

The wound is a primary source of infection for patients with burns. The mainstay of both prevention and treatment is daily washing with soap and water and application of a topical broad-spectrum antimicrobial agent. As soon as it

becomes evident that a burn wound will not heal, excision and grafting should be performed. Preferably, the decision to proceed with surgery should be made before postburn day 21. For patients who undergo surgery, perioperative antibiotics may reduce postoperative wound infection.⁷¹

Nutrition

In the early 1970s, Curreri and Luterman recognized that patients with major thermal injury experience hypermetabolism, with an increased basal metabolic rate, increased oxygen consumption, negative nitrogen balance, and weight loss; hence, these patients have exaggerated caloric requirements.⁷² Furthermore, inadequate caloric intake can be associated with delayed wound healing, decreased immune competence, and cellular dysfunction.

A patient with a large burn may lose as much as 30 g of nitrogen a day because of protein catabolism. Not only is urinary excretion of urea nitrogen increased, but also large amounts of nitrogen are lost from the wound itself. Therefore, total urea nitrogen levels do not accurately reflect all nitrogen losses in burn patients.⁷³ A patient with a small burn (< 10% TBSA) may lose nitrogen at a rate of 0.02 g/kg/day. A moderate burn (11 to 29% TBSA) may be associated with nitrogen losses equaling 0.05 g/kg/day. A large burn (≥ 30% TBSA) may result in the loss of as much as 0.12 g/kg/day, which may be equivalent to daily losses of 190 g of protein or about 300 g of muscle. Thus, a highly catabolic patient with a large burn will typically require 2 g/kg/day of protein to maintain a positive nitrogen balance.

Catabolism generally continues until wounds have healed. However, once a patient becomes anabolic, preburn muscle takes three times as long to regain as it took to lose.^{74,75} Therefore, a patient in whom it takes 1 month for burn wounds and donor sites to heal may need 3 or more months to regain preburn weight and muscle mass. These statistics underscore the importance of accurately estimating each patient's caloric needs during hospitalization. Over the years, a number of equations have been developed to estimate caloric needs [see Table 11]. Probably the most widely used formula is the Harris-Benedict equation, which estimates basal energy expenditure according to gender, age, height, and weight:

$$\text{Men BEE: } 13.75 \times \text{Weight} + 5.00 \times \text{Height} - 6.76 \times \text{Age} + 66.5$$

$$\text{Women BEE: } 9.56 \times \text{Weight} + 1.85 \times \text{Height} - 4.68 \times \text{Age} + 65.5$$

Table 11 Formulas for Estimating Caloric Needs in Burn Patients

Harris-Benedict Formula
Basal energy expenditure (BEE)* × activity factor [†] = calories needed daily
Curreri Formula
25 kcal / kg + 40 kcal/% TBSA burned = calories needed daily

TBSA = total body surface area.

*Women: BEE = 65.5 + 9.6 (weight in kg) + 1.8 (height in cm) – 4.7 (age in years). Men: BEE = 66.5 + 13.8 (weight in kg) + 5.0 (height in cm) – 6.8 (age in years).

[†]For burns, the activity factor is 2, which may overestimate caloric needs for patients with smaller burns.

The basal energy expenditure is then multiplied by an activity factor that reflects the severity of injury or the degree of illness; for burns, this multiplier is 2, the maximal factor for this formula. The limitation of the Harris-Benedict equation is that it may overestimate caloric needs for patients with burns smaller than 40% TBSA. A formula specific for patients with burns is the Curreri formula,⁷⁶ which is based on patient weight and burn size; this formula may overestimate caloric needs for patients with large burns and therefore is best used for patients with burns less than 40% TBSA.^{77,78}

Ongoing evaluation of metabolic status of the burn patient is necessary to take into account changes in wound size and clinical condition. Metabolic demands decrease with burn healing or grafting; on the other hand, donor sites create new wounds, which may increase catabolic rates. Development of infection or ARDS greatly increases catabolism and may alter caloric needs.⁷⁹ Simple assessment of nitrogen requirements can be determined by measuring 24-hour total urea nitrogen levels in the urine. However, this does not account for nitrogen lost from the wound itself. Serum albumin levels are notoriously unreliable markers of adequate nutrition because they lag behind clinical progress; they are especially known to be low in patients with burns larger than 20% TBSA.⁸⁰ Transthyretin (also known as prealbumin, although it is not related to albumin in structure or function) levels correlate more closely with catabolic status,⁸¹ and a trend over several weeks may indicate whether the patient's caloric needs are being met.⁸² C-reactive protein levels also provide an indication of the patient's general inflammatory state; high levels may correlate with increased catabolism.⁸³ For intubated patients, indirect calorimetry may be helpful in measuring caloric needs but may not be more exact than the Curreri formula.⁸³ The so-called metabolic cart is a portable gas analyzer that quantifies volumes of inspired O₂ and expired CO₂ and calculates nutritional requirements according to the following formula:

$$\text{kcal/day} = ([3.9 \times \dot{V}_{O_2}] + [1.1 \times \dot{V}_{CO_2}]) \times 1.44$$

where $\dot{V}_{O_2}$ is the volume of oxygen consumed and $\dot{V}_{CO_2}$ is the volume of carbon dioxide consumed. This result can also be indirectly measured in patients with PA catheters in place by using the Fick equation:

$$\text{kcal/day} = \text{cardiac output} \times (\text{arterial } PO_2 - \text{venous } PO_2) \times 10 \times 6.96$$

ENTERAL NUTRITION

As early as 1976, the benefits of enteral nutrition over parenteral nutrition had already been identified for patients with functional gastrointestinal systems.⁸⁴ The problems of prolonged ileus and Curling stress ulcers in burn patients have been largely eliminated by early feeding.⁸⁵ Multiple studies have shown that patients with major thermal injury can receive adequate calories within 72 hours after injury.⁸⁶ At the University of Washington Regional Burn Center, tube feeding is started a median of 5 hours after admission.

There is ongoing debate about the benefits of gastric feeding versus duodenal feeding. Although feeding distal to the pylorus should pose less aspiration risk, one study found evidence of enteral formula in pulmonary secretions of 7% of patients receiving gastric feeds compared with 13% of patients

receiving transpyloric feeding.⁸⁷ Hence, for burn patients with high caloric needs, the benefit of decreased aspiration with transpyloric feeds may only be theoretical and may be offset by the delay in feeding for confirmation of tube placement; such confirmation is necessary because these tubes can easily flip back into the stomach.

Continuation of tube feedings during surgery in intubated patients who require multiple operations is a safe way to maximize caloric intake and decrease wound infection. There is no need to stop feedings for anesthesia induction and endotracheal intubation in the patient with a secure airway⁸⁸; however, intraoperative positioning, especially if the patient will be prone during surgery, may necessitate stopping feedings preoperatively. Mayes and colleagues have presented data that support continuation of tube feedings in critically ill burn patients undergoing decompressive laparotomy.⁸⁹

GLUCOSE LEVELS

Both hyperglycemia and hypoglycemia are associated with increased mortality and morbidity in critically ill patients. Improved survival in surgical ICU patients maintained with tight blood glucose control of 80 to 110 mg/dL⁹⁰ led to the widely practiced policy of tight glycemic control. The association of poor glucose control with bacteremia, reduced graft take, and higher mortality in pediatric burn patients has further supported this practice.⁹¹ Based on the current literature, it is our policy to maintain blood glucose levels as close to normal as possible, without evoking unacceptable glucose fluctuations, hypoglycemia, or hypokalemia, and therefore aim for a range of 100 to 180 mg/dL.

ALBUMIN LEVELS

Burn patients characteristically have hypoalbuminemia that persists until wounds are healed and the rehabilitation phase of recovery has begun. In fact, patients with large burns have serum albumin levels that average 1.7 g/dL and never exceed 2.5 g/dL.⁸⁰ Management of hypoalbuminemia is controversial, but there is general agreement that once burn resuscitation is complete, infusion of exogenous albumin to serum levels above 1.5 g/dL does not affect burn patient length of stay, complication rate, or mortality.⁹²

NUTRITIONAL SUPPLEMENTS

Specialized nutritional formulas with purported effects on metabolic rate and immunologic status have garnered a great deal of interest as adjuncts in the management of critically ill and injured patients.⁹³ Much of the information on nutritional requirements for critically ill patients was derived from an animal burn model,⁹⁴ however, and studies on the efficacy of specialized nutritional supplements in humans have generated contradictory data. A randomized trial of nutritional formulas that were intended to enhance immune status and that included essential amino acids and omega-3 fatty acids showed no clinical advantage in burn patients.⁹⁵ However, the addition of glutamine supplementation to an enteral nutrition regimen has been shown to decrease hospital and ICU length of stay as well as mortality in adult burn patients, perhaps explained by its trophic influence on intestinal epithelium and on maintenance of gut integrity.⁹⁶ Other nutritional or metabolically active supplements that have demonstrated promise in promoting anabolism in burn

patients include insulin, recombinant human growth factor, the anabolic steroid oxandrolone, and propranolol.⁹⁷ Oxandrolone in particular has produced marked improvements in weight gain, return to function, and length of hospital stay⁹⁸; however, its use should be cautioned in nonburn patients as surgical patients have not shown the same benefit.⁹⁹ Early administration of antioxidant supplementation with α -tocopherol and ascorbic acid has been shown to reduce the incidence of organ failure and shorten ICU length of stay in critically ill surgical patients.¹⁰⁰ Whether this is true for burn patients remains to be demonstrated, but the relatively low cost and the low risk of complications make this an attractive intervention for burn patients at risk for ARDS.

Anemia

Because acute blood loss is uncommon in a patient with an isolated burn injury, a rapidly decreasing hematocrit during resuscitation should prompt an evaluation for associated injuries. Procedures during resuscitation, such as central venous line placement or escharotomies, should not be associated with significant blood loss.

Anemia was a major problem in burn management before early excision and grafting became commonplace. As excision techniques have become more sophisticated, operative blood loss has decreased, as has the need for transfusion.^{101,102} Nevertheless, excision and grafting may be associated with large blood loss, and the operating team must be prepared for intraoperative blood transfusion.

Decisions about transfusion must be based on the patient's age, overall condition, and comorbidity. The risks of viral transmission and transfusion reactions, as well as the cost, must also be carefully considered. Based on the findings of the Transfusion Requirements in Critical Care (TRICC) trial, for an otherwise healthy patient who does not need surgery, a hematocrit as low as 20% may be tolerated.¹⁰³ Patients with inhalation injury or ARDS may benefit from the greater oxygen-carrying capacity afforded by a higher hematocrit. Studies of the effects of prolonged storage of blood have shown that storage alters corpuscle and cytosol and thereby impairs oxygen-carrying capacity. Blood transfusion can lead to impaired oxygen uptake and can be proinflammatory. Additionally, each transfusion has been shown to have an associated increased infectious risk. Therefore, for patients with large burns who require multiple operations for excision and grafting, every effort should be made to limit blood loss and decrease phlebotomy to conserve blood and decrease the need for blood transfusions. Additionally, patients with large burns and anticipated blood loss during hospitalization should probably receive iron supplements.

Given that the literature contains some indication that erythropoietin levels may be elevated in patients with large burns, the benefit of exogenous erythropoietin is debatable.¹⁰⁴ At least one prospective study suggests that administration of recombinant erythropoietin in acutely burned patients does not prevent anemia or decrease transfusion requirements.¹⁰⁵

Pain Management

Pain management for patients with burn injuries can be challenging. The simplest approaches work best; polypharmaceutical drug administration is likely to confuse both

patients and health care providers and should therefore be avoided. Burn patients experience several different classes of pain: background, breakthrough, and procedural. Each patient responds to a different approach.

Background pain is the discomfort that burn patients experience day and night. It is best treated with long-acting pain relievers. For a hospitalized patient with large burns, methadone or controlled-release morphine sulfate may be the most appropriate choice for background pain. In an outpatient with a small burn, a nonsteroidal antiinflammatory drug (NSAID) may be optimal; if excision and grafting are planned, the NSAID should be stopped at least 7 days before surgery to permit recovery of platelet function.

Breakthrough pain results when activities of daily living exacerbate burn-wound discomfort. Short-acting narcotics or acetaminophen is used to alleviate breakthrough pain. Persistent breakthrough pain indicates that the dose of the long-acting medication should be increased.

Procedural pain is the discomfort that patients experience during wound care and dressing changes. This usually requires treatment with a short-acting narcotic. For inpatients with larger burns, oral narcotics or transmucosal fentanyl citrate¹⁰⁶ works well for wound care; intravenous morphine or fentanyl is used for uncontrolled pain. For outpatients, oxycodone (5 to 15 mg) works well for daily wound care.

Anxiety related to wound care is an underdiagnosed and undertreated source of discomfort that is often construed as pain, especially in children. Therefore, patients with large burns requiring wound care once or twice a day should be evaluated to determine whether they would benefit from a short-acting anxiolytic agent for procedures. Reports have suggested encouraging results in treating neuropathic hyperalgesia and allodynia in the burn wound or donor site with gabapentin, finding rapid reduction in neuropathic pain with no severe adverse reactions.¹⁰⁷

Learning to accurately assess pain in burn patients can help prevent complications related to excessive narcotic use, such as prolonged sedation, delirium, and, more urgently, loss of airway control. This is especially true in young children and elderly patients, who may have decreased ability to tolerate narcotics.^{108,109}

Nonpharmacologic approaches are also an important component of pain management in burn patients. Hypnosis—administered either by trained health care providers or, more efficiently, by patients themselves—has proved to be a useful tool for reducing narcotic use in patients with burns.¹¹⁰ Another distraction modality that has shown promise and garnered significant publicity has been virtual reality. Although it is not a standard of care for all patients admitted with burn injuries, preliminary observations suggest that use of virtual reality can enhance patient comfort during wound care and intense therapy.

Discomfort in the healed wound may persist for months after injury. In general, narcotics do not control such symptoms; exercise and deep massage are more effective. Itching can be a pervasive long-term symptom for which there is no reliable topical or systemic therapy. Diphenhydramine, cyproheptadine, cetirizine, and gabapentin may relieve itching. There are also promising data on the use of doxepin ointment as a topical treatment for itching of healed wounds.¹¹¹ Keeping the wound moist with a topical salve may be as effective as other pharmacologic approaches.

Deep Vein Thrombosis Prophylaxis

The incidence of deep vein thrombosis (DVT) and, thus, the need for DVT prophylaxis in patients with thermal injury have never been clearly defined. Whereas some studies report DVT in as many as 25% of all hospitalized burn patients and advocate DVT prophylaxis,¹¹² others report that thromboembolism is responsible for only 0.14% of deaths in burn patients and does not warrant the potential complications of anticoagulation therapy.¹¹³ At the University of Washington Regional Burn Center, a quality assurance review found that

in patients with burns larger than 20% TBSA, clinically evident thromboembolic disease occurred in 9% of those who received prophylaxis with unfractionated heparin and in 18% of those who received low-molecular-weight heparin, perhaps as a result of a greater tendency for the low-molecular-weight heparin to be held. On the basis of these data, patients with burns larger than 20% TBSA receive prophylaxis with subcutaneous unfractionated heparin, 5,000 U three times a day.

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15 MANAGEMENT OF THE BURN WOUND

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Advances in resuscitation and critical care have significantly improved survival after thermal injury. Ultimately, survival remains contingent on effective wound management and complete wound closure. Current approaches to burn management are based on an understanding of the biology and physiology of human skin and the pathophysiology of the burn wound.

Anatomic and Physiologic Considerations

BIOLOGY OF THE SKIN

The skin is a complex organ composed of two distinct layers, the epidermis and the dermis; these layers are integrated by a structure known as the basement membrane zone (BMZ) [see Figure 1]. It provides containment, structure, protection, homeostasis, excretion, temperature regulation, biosynthesis, sensory perception, and appearance.

The epidermis is the outer layer and acts as the barrier between body tissues and the environment. This layer protects against infection, ultraviolet light, and evaporation of fluids and provides thermal regulation. The epidermis is derived from fetal ectoderm and, thus, like other ectodermal derivatives, is capable of regeneration. Repair of epidermal wounds is achieved through regeneration of epidermal cells both from the perimeter of the wound and from the adnexal structures of the epidermis (i.e., hair follicles, sweat glands, and sebaceous glands).¹ Accordingly, pure epidermal injuries heal without scarring.

The principal cell of the epidermis is the keratinocyte. These cells are arranged into five progressively differentiated layers, or strata: the stratum basale, the stratum spinosum, the stratum granulosum, the stratum lucidum, and the stratum corneum. The outermost of these layers—the relatively impermeable stratum corneum—provides the barrier mechanism that protects the underlying tissues. These layers are derived from continued cell division and maturation of the basal keratinocyte stem cells at the stratum basale, the deepest level of the epidermis.

Besides keratinocytes, the epidermis contains cells from other embryologic layers that carry out specific functions. These cells include melanocytes and Langerhans and Merkel cells. Melanocytes, derived from fetal neuroectoderm, migrate to the ectoderm during normal embryogenesis and populate the interfollicular stratum basale and hair follicles. These send dendritic processes between the basal cells to the epidermis, anchoring them to the keratinocytes. Through these dendritic processes, melanosomes are transferred via phagocytosis to the adjacent keratinocytes. The melanosomes synthesize the pigment melanin through the action of the

enzyme tyrosinase. Melanin provides the skin with its pigment and absorbs harmful ultraviolet radiation. Melanocytes are terminally differentiated cells without reproductive ability.² Hence, deep dermal injuries often lead to cutaneous hypopigmentation.

Langerhans cells, derived from bone marrow cells, play a critical role in the immune function of the skin. These cells recognize, phagocytize, process, present foreign antigens, and, through their expression of class II antigens, initiate the rejection process in skin transplantation.³ Merkel cells are neuroendocrine cells that reside near hair follicles and nerve endings. These cells are transducers of fine touch. Their embryonic origin and homeostasis are a source of great debate.⁴ However, their presence in the hand and feet must be considered when deciding whether to excise and graft the volar and plantar surfaces.

In contrast to the epidermis, the dermis is a complex network comprising cellular and acellular components. This layer provides skin with its durability and elasticity. Structurally, the dermis consists of two sublayers, a superficial one (the papillary dermis) and a deeper one (the reticular dermis). Collagen is the major structural matrix molecule, constituting approximately 70% of the skin's dry weight. Elastic fibers account for approximately 2% of the skin's dry weight and play an important role in maintaining the integrity of the skin after mechanical perturbation. Glycosaminoglycans (GAGs) and adhesion molecules are the third major extracellular components of the dermis. These molecules help regulate intracellular and extracellular events by binding to, releasing, and neutralizing cytokines and growth factors.^{4,5} Adhesion molecules are crucial for cellular migration and chemotaxis in and out of the wound.

The fibroblast is the principal cell of the dermis and is responsible for synthesis and degradation of fibrous and elastic dermal proteins. The dermis also contains various bone marrow–derived inflammatory cells and other poorly understood mesenchymal stem cells, mast cells, and cells associated with vascular, lymphatic, and nervous tissue.

The BMZ is a complex region of the extracellular matrix connecting the basal cells of the epidermis with the papillary dermis. At the light microscopic level, the dermal-epidermal junction consists of protrusions of dermal connective tissue known as dermal papillae, which interdigitate with epidermal projections known as rete ridges. The structure of the BMZ is best appreciated on electron microscopy, where it appears as a trilaminar zone consisting of a central electron-dense region (the lamina densa) flanked on both sides by regions of lower electron density [see Figure 2]. Within the basal cells of the epidermis are multiple sites of attachment to the basal lamina, which are known as hemidesmosomes. On the dermal

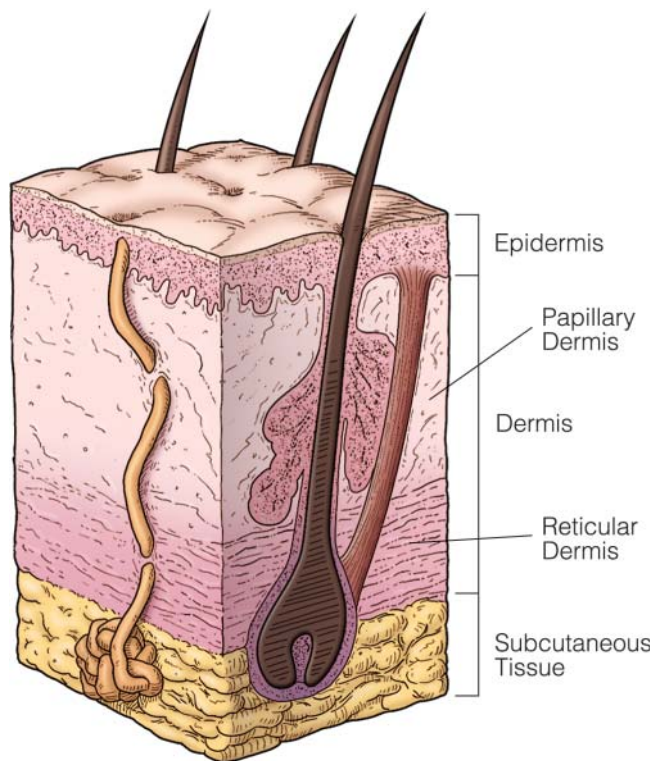


Figure 1 Cross-sectional diagram shows the two distinct layers of the skin—the epidermis and the dermis (papillary and reticular)—and the underlying subcutaneous fat.

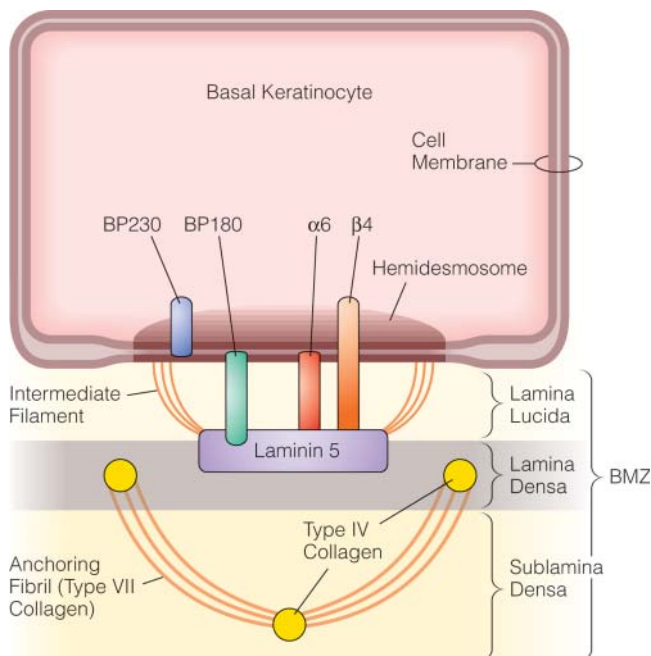


Figure 2 The basement membrane zone (BMZ) integrates the epidermis with the underlying dermis. On electron microscopy, the BMZ has three layers: a central electron-dense region known as the lamina densa and two regions of lower electron density to either side of this central region.

side of the basal lamina are numerous anchoring fibrils, which reach from the lamina into the connective tissue of the dermis. The BMZ plays a significant role in burn wound healing: epithelialized wounds undergo blistering until the anchoring structures of the BMZ mature and provide protection from shearing.⁶

PATHOPHYSIOLOGY OF THERMAL INJURY

Jackson's 1953 classification of burn wounds remains the foundation of our understanding of the pathophysiology of thermal injury to the skin.⁷ In this classification, there are three zones of tissue injury resulting from a burn [see Figure 3]. The central, most severely damaged area is called the zone of coagulation because the cells in this area are coagulated or necrotic. Tissue in this zone must be debrided. The zone of coagulation is surrounded by the zone of stasis, an area characterized by vasoconstriction and ischemia. Tissue in this zone is initially viable; however, it may convert to coagulation as a consequence of the development of edema, infection, and decreased perfusion. With good wound perfusion, tissue in the zone of stasis generally remains viable. Surrounding the zone of stasis is the zone of hyperemia, an area characterized by vasodilation resulting from the release of inflammatory mediators from resident cutaneous cells. Tissue in this zone typically remains viable.

Clinical Evaluation and Initial Care of Burn Wound

After admission to the burn center, the burn wound is cleaned with soap and water, blisters and debris are removed, and the extent and depth of the wound are assessed. Management of tar burns warrants special mention. When tar that has been heated to maintain a liquid form comes into contact with skin, it can transfer sufficient energy to cause a significant burn injury. As the tar cools on the skin, it solidifies, thereby becoming difficult to remove. Solvents such as petrolatum, petrolatum-based ointments, lanolin, and Medi-Sol (Orange-Sol, Inc., Gilbert, Arizona) are useful for tar removal. For optimal effect, 10 to 15 minutes should be allowed after

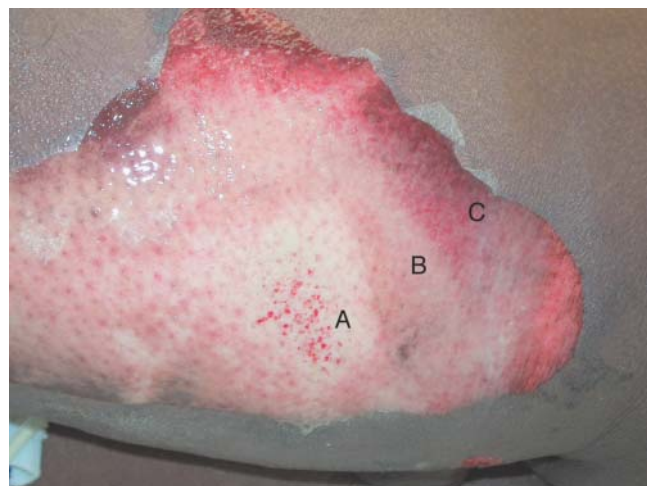


Figure 3 A burn wound is characterized by three zones of injury: A represents the zone of coagulation, B the zone of stasis, and C the zone of hyperemia.

solvent application before removal of the tar is attempted. Repeat applications may be necessary for complete removal.

ASSESSMENT OF BURN DEPTH

Thermal injury can damage the epidermis alone, the epidermis along with a portion of the dermis, or the entire skin and can even extend into the underlying subcutaneous tissue. The depth of the injury affects the subsequent healing of the wound; thus, assessment of burn wound depth is important for selection of wound dressings and, ultimately, for determination of the need for surgery [see *Table 1*].

Superficial burns involve only the epidermis. They typically are erythematous and painful, much as a sunburn would be. Most such burns heal within 3 to 4 days, without scarring. The usual treatment is a soothing moisturizing lotion (e.g., one containing aloe vera), which both optimizes the rate of epithelialization and provides comfort to the patient.

Partial-thickness burns extend through the epidermis and into the papillary dermis. Blistering is their hallmark [see *Figure 4*]. These burns can be further categorized as superficial or deep. Superficial partial-thickness burns are typically

pink, moist, and painful. They usually heal within 2 to 3 weeks, without scarring or functional impairment. Deep partial-thickness wounds extend into the reticular layer of the dermis. They are typically a mottled pink-and-white, dry, and variably painful. In some cases, they may be difficult to distinguish from full-thickness burns. Deep partial-thickness burn wounds, if they do not become infected, typically heal in 3 to 8 weeks, with severe scarring, contraction, and loss of function. Therefore, if a partial-thickness burn has not healed by 3 weeks, surgical excision and skin grafting may be required.

Full-thickness burn wounds extend through the entire dermis and into the subcutaneous tissue. These burns are typically white or black, dry, and painless [see *Figure 5*]. Some full-thickness burns appear red, but they can be distinguished from superficial burns because they are not moist and do not blanch with pressure. Because all skin appendages are burned away, full-thickness burns can heal only by contraction or migration of keratinocytes from the periphery of the wound. Accordingly, all full-thickness burns, unless they are quite small (e.g., the size of a quarter or smaller), must be treated with excision and grafting.

As a rule, both superficial and full-thickness burns are easily recognized, and treatment decisions are relatively straightforward. It is frequently difficult, however, to determine the ultimate fate of intermediate partial-thickness burns soon after injury. For this reason, these wounds are often referred to as indeterminate-thickness wounds. Over the course of the first several postburn days, it usually becomes easier to determine which indeterminate-thickness wounds are likely to heal in a timely manner, without the need for grafting.

Various techniques for assisting the assessment of burn depth have been described, including the use of vital dyes, laser flowmetry, thermography, and magnetic resonance imaging.⁸ However, none of these adjuncts have been shown to replace the clinical evaluation of an experienced burn care provider.

<i>Table 1</i> Overview of Burn Wound Management		
Burn Wound Type	Clinical Features	Management
Superficial	Erythematous, painful	Soothing, moisturizing lotions (i.e., aloe)
Partial thickness	Blistered, pink, moist, painful	Silver sulfadiazine; greasy gauze once epithelial buds are present
Deep partial thickness	Dry, mottled pink-and-white, less painful	Silver sulfadiazine dressings daily; surgical excision and grafting if not going to heal within 3 wk
Full thickness	Dry, leathery, black or white, painless	Silver sulfadiazine; early excision and skin grafting

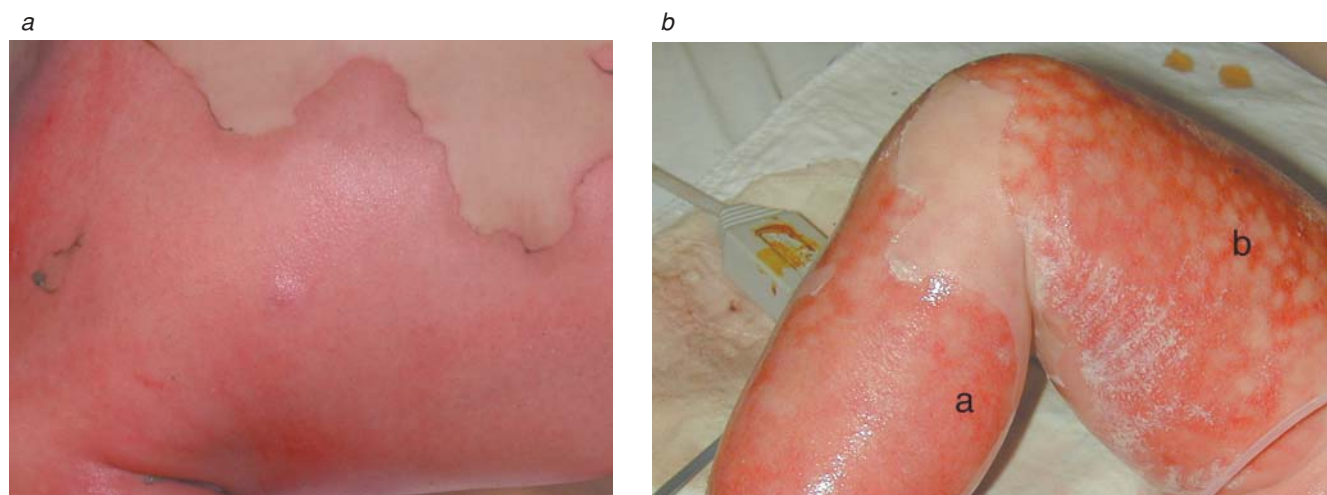


Figure 4 Shown at left is a shallow scald burn with the pink, moist appearance typical of a superficial partial-thickness burn wound. Such injuries typically heal without the need for excision and grafting. A superficial partial-thickness burn (a), which involves only the papillary dermis, is visually distinct from a deep partial-thickness burn (b), which is mottled in appearance, extends into the reticular dermis, and is more likely to require excision and grafting.



Figure 5 Shown is a full-thickness flame burn with a characteristic brown, leathery appearance. Such wounds require excision and subsequent skin grafting.

DETERMINATION OF NEED FOR ESCHAROTOMY

Burn wound eschar consists of dead skin, has the consistency of leather, and may restrict limb perfusion by creating a nonelastic exoskeleton. A key issue in assessing burn wounds is whether escharotomies are necessary. In general, escharotomies are required only for circumferential full-thickness extremity burns in which distal perfusion has been compromised or for chest burns in which eschar poses an external mechanical barrier to respiration. Escharotomies can be performed at the bedside with either a scalpel or an electrocautery. They should extend through the eschar only, not through the muscle fascia. Adequate release is signaled by separation of the eschar, improved distal perfusion, and, sometimes, a popping sound. Because an escharotomy is a superficial incision through dead tissue, only minimal doses of analgesics and anxiolytics are required.

DAILY BURN WOUND CARE

The use of hydrotherapy tanks, previously a standard component of burn unit wound care, has fallen from favor somewhat because of the risks of cross-contamination between one burn wound area and another. It is preferable to place the patient on a shower table, which is inclined so that water runs off the wounds and into a drain [see Figure 6]. Smaller wounds can often be managed with bedside wound care after a shower. Increasingly, partial-thickness burns are treated with biosynthetic and/or silver-impregnated materials that do not require daily wound care.⁹ Washing with tap water and regular soap suffices for daily burn wound cleansing. It is important to be cognizant of the need to provide adequate sedation and analgesia while performing daily wound care—a particularly challenging task with infants and elderly patients.

Topical Burn Wound Treatment

GENERAL PRINCIPLES

Because thermal injury disrupts the protective barrier function of the skin, dressings are needed to protect the body



Figure 6 Shower tables are generally preferred to Hubbard tanks for burn wound care. A clean plastic drape can be used to cover the shower table during patient care.

against environmental flora. Burn dressings also protect against evaporative heat loss. The ideal burn dressing would be inexpensive and comfortable and would not require frequent changing. Daily dressing changes allow the burn care provider not only to apply clean dressings but also to clean the wounds and débride fragments of separated eschar and devitalized tissue.

Numerous topical agents and dressings are available for use in burn patients; we limit our discussion to the ones that are most commonly employed and have proved most effective. Selection of an appropriate dressing for a given wound is governed by the specific goals of management. With purely superficial wounds, the goal is to create a moist environment that will optimize epithelialization. Typically, this is achieved by applying ointments or lotions. With partial-thickness and full-thickness wounds, however, it is necessary to include agents that protect against microbial colonization (see below). Once a partial-thickness burn demonstrates evidence of epithelialization, dressings should be changed to a regimen that facilitates healing (e.g., greasy gauze with ointment).

ANTIMICROBIAL AGENTS

It must be emphasized that systemic antibiotic prophylaxis plays no role in the management of acute burn wounds and provides no protection against microbial colonization of burn eschar¹⁰; in fact, use of prophylactic antibiotics in burn patients increases the risk that opportunistic infections will

develop. Because eschar has no microcirculation, it is impossible for systemically administered antibiotics to reach the eschar surface, where colonization occurs. Therefore, topical preparations, which are capable of supplying high concentrations of antimicrobial agents at the wound surface, must be used. In the early postburn period, the dominant colonizing organisms are staphylococci and streptococci—typical skin flora. Over time, however, the burn wound becomes colonized with gram-negative organisms.¹¹ Thus, topical antimicrobial agents used in early burn care should have broad-spectrum coverage to minimize colonization of the wound, but they need not be able to penetrate the burn eschar deeply.

Of the antimicrobial agents used in this setting [see Table 2], silver sulfadiazine is the one most commonly employed for partial-thickness and full-thickness burns. Silver sulfadiazine is soothing on application and is active against a broad spectrum of microorganisms. Because it does not penetrate eschar, very little is systemically absorbed; therefore, it is ineffective against already established burn wound infections. Wounds treated with silver sulfadiazine may form a tenacious yellow-gray pseudoeschar, which can be mistaken for true eschar. This pseudoeschar develops when silver sulfadiazine combines with the wound exudates; it can be gently débrided during daily wound care. It has been suggested that silver sulfadiazine may be responsible for the leukopenia that sometimes develops during the first week after a major burn. This attribution may not be entirely accurate, however, given that this leukopenia may also develop in patients treated with silver nitrate. It is possible that the leukopenia results not from either agent but from the margination of neutrophils secondary to the pathophysiology of the burn injury itself. In any case, the leukopenia is typically self-limited and necessitates no change in therapy. Patients with a history of sulfa allergy typically do not have adverse reactions to silver sulfadiazine; however, if there is concern about a possible reaction, a test patch can be applied to a small area of the wound. If the patient is allergic, silver sulfadiazine will cause pain on application or, in some cases, a rash.

Mafenide acetate is also commonly used in the management of burn wounds. It provides excellent coverage against gram-negative organisms, but it is not as active against staphylococci and has no antifungal activity. Unlike silver sulfadiazine, mafenide penetrates eschar very well, and this ability makes it effective in treating as well as preventing burn wound infections. Mafenide does, however, have some drawbacks. Because it is a potent carbonic anhydrase inhibitor, regular use and the consequent ongoing systemic absorption can lead to metabolic acidosis. In addition, because it is so well absorbed, twice-daily administration is necessary. Finally, topical application of mafenide, particularly to partial-thickness burns, is painful, which limits its utility in the routine management of burn wounds. Mafenide is frequently used on the ears and the nose because of its ability to penetrate eschar and protect against suppurative chondritis; however, silver sulfadiazine appears to be equally effective in this setting.¹² Mafenide is available both as a cream and as a solution. The solution is useful as a topical agent for skin grafts when the wound bed is considered likely to benefit from postoperative antimicrobial treatment.

Silver nitrate provides broad-spectrum antimicrobial coverage, including good activity against staphylococci and gram-negative organisms (e.g., *Pseudomonas*). It is relatively painless on administration and must be reapplied every 4 hours to keep the dressings moist. It does not readily penetrate eschar. Silver nitrate is used in the form of a 0.5% solution, which is bacteriostatic but is not toxic to epithelial cells. The hypotonic formulation (it is reconstituted in water) can cause osmolar dilution, resulting in hyponatremia and hypochloremia. Therefore, careful electrolyte monitoring and diligent replacement are necessary. In rare cases, use of silver nitrate solution can also lead to methemoglobinemia; if this condition is detected, administration of silver nitrate should be discontinued. A principal disadvantage of silver nitrate solution is that it stains everything it touches black.

Newer silver-containing dressings are now manufactured, improving care by decreasing the need for daily wound care. Some dressings contain nanocrystalline silver embedded on a high-density polyethylene mesh (Acticoat, Smith & Nephew,

Table 2 Topical Antimicrobial Agents Used in Burn Care

Agent	Antimicrobial Coverage	Advantages	Disadvantages/Precautions
Bacitracin	Gram-positive bacterial	Soothes and moisturizes; good for facial care and epithelializing wounds	Not appropriate for deeper wounds
Mafenide	Broad-spectrum antibacterial; antistaphylococcal	Penetrates eschar well; available as solution or cream	Painful on application; causes metabolic acidosis (via carbonic anhydrase inhibition)
Mupirocin	Anti-MRSA	Effective against MRSA	Narrow (poor gram-negative) antimicrobial coverage
Nystatin	Antifungal (<i>Candida</i>)	Provides fungal prophylaxis with swish-and-swallow solution	May interfere with activity of mafenide
Silver nitrate	Broad-spectrum antibacterial	Effective for both prophylaxis and treatment of wound infection	Penetrates eschar poorly; causes hyponatremia; stains linen and dressings; induces methemoglobinemia
Silver sulfadiazine	Broad-spectrum antibacterial; antipseudomonal	Soothes on application and causes no pain	Penetrates eschar poorly; causes leukopenia

MRSA = methicillin-resistant *Staphylococcus aureus*.

London, England), embedded in hydrofibers (Aquacel AG, ConvaTec Bristol-Meyers Squibb Company, Skillman, New Jersey), or attached to a soft silicone dressing (Mepilex Ag, Mölnlycke Health Care US, LLC, Norcross, Georgia). It is speculated that the nanocrystalline silver provides a sustained release of elemental silver, contributing to aerobic, anaerobic, gram-positive and gram-negative antimicrobial activity.¹³ Acticoat has been successfully used for coverage of partial-thickness burns, as well as for coverage of donor sites and meshed skin grafts.¹⁴ With burn wounds, the Acticoat dressing is typically changed every 3 days. The reduced frequency of dressing changes simplifies burn care somewhat but can hinder evaluation of evolving partial-thickness burns. With donor sites, Acticoat can be left in place until the underlying partial-thickness wound heals. Typically, an adhesive tape such as Hypafix (Smith & Nephew) is used to secure the dressing to the donor site for 7 days. Once the tape has been removed, the Acticoat usually is sufficiently adherent to allow patients to shower daily and towel-dry the dressing until it eventually peels off the healed wound. The development of nanocrystalline silver-embedded products has increased the treatment modalities of the burn patient.

Bacitracin, neomycin, and polymyxin B have all been used for coverage of superficial wounds in conjunction with Xeroform or petrolatum gauze to accelerate epithelialization and minimize colonization. These ointments also are commonly administered several times daily in the care of superficial face burns. Mupirocin has proved effective in treating methicillin-resistant *Staphylococcus aureus* (MRSA) colonization; however, because of the potential for the development of bacterial resistance, it should be employed only in MRSA-positive wounds.

Surgical Burn Wound Management

As noted [see Clinical Evaluation and Initial Care of Burn Wound, Assessment of Burn Depth, *above*], superficial burns and superficial partial-thickness burns typically heal without any need for surgical excision and grafting. Dressing changes and wound care can remove necrotic debris and provide an environment conducive to healing in a timely fashion (2 to 3 weeks), with minimal scarring. For deep partial-thickness and full-thickness burns, however, operative débridement with subsequent skin graft coverage is necessary. Timely removal of eschar is critical for successful management. Surgical excision removes necrotic tissue that serves as a nidus for microbial proliferation and the development of burn wound sepsis.^{15,16}

EARLY EXCISION AND GRAFTING

Surgical excision of burn wounds is a concept whose importance was not fully appreciated until the 1970s. Previously, the usual practice was to leave eschar intact over the wound surface, the idea being that proteolytic enzymes produced by migrating neutrophils and bacteria within the contaminated eschar would cause a natural separation of the eschar from the wound bed (sloughing) and that the resulting granulating wound would serve as the bed for grafting. The rationale for delaying surgical management was that it would presumably allow the burn care provider time to determine which wounds would heal spontaneously and which would have to be covered with skin grafts. It has since become clear,

however, that in cases of extensive burn injury, delayed management results in more extensive bacterial colonization, as well as an increased likelihood of burn wound sepsis, multiple organ failure, and, ultimately, death.

Early excision and skin grafting of small burn wounds were first described by Lustgarten in 1891.¹⁷ After the Coconut Grove fire in 1942, Cope and colleagues suggested that patients treated with early excision and grafting had better overall outcomes.¹⁸ In 1960, Jackson and colleagues reported discouraging results with early burn wound excision,¹⁹ and it was not until 10 years later, when Janzekovic reported good results with surgical burn wound excision,²⁰ that enthusiasm for early excision was rekindled. As clinical experience with early excision was accumulated, the benefits became clear.

Since Janzekovic's report, studies have repeatedly shown that early wound excision and closure improve survival, reduce the infection rate, and shorten hospital stay. Other studies have demonstrated that early removal of dead and severely damaged tissue interrupts and attenuates the systemic inflammatory response syndrome (SIRS).^{15,16,21–24} Early excision of deep burn wounds also appears to decrease hypertrophic scarring. Similarly, early excision and grafting have been shown to be beneficial for burns of indeterminate depth. In a study of patients with burns covering less than 20% of their total body surface area (TBSA), early excision and grafting reduced length of stay, cost of care, and time away from work in comparison with nonoperative treatment.²⁵

WOUND EXCISION

Early staged excision, beginning as early as postburn day 3 if feasible, is now conventional treatment for major burns. Operations are spaced 2 to 3 days apart until all eschar is removed and full wound coverage is achieved. Débrided wounds can be temporarily covered with biologic dressings or cadaveric allograft until autogenous donor sites are available.^{26,27}

Generally, the decision whether to perform operative wound excision is guided by whether spontaneous wound healing is likely to occur in a timely fashion (i.e., within 2 to 3 weeks after the burn). Burn wounds over joint surfaces, however, should undergo excision and grafting sooner so as to minimize healing by wound contraction, which can ultimately lead to disabling contractures. In patients with extensive burns, hemodynamic and pulmonary status must be considered in deciding on the timing of operation. Any critically ill burn patient will have some degree of respiratory dysfunction, but the patient should at least be capable of being safely transported from the intensive care unit to the operating room and back. The risk of hypothermia and the need for blood transfusion must be anticipated before operation and clearly communicated to the anesthesiologist.

There are two main technical approaches to surgical excision of the burn wound: fascial excision and tangential excision. Fascial excision, as the name suggests, involves excising the burned tissue and the underlying subcutaneous tissue down to the muscle fascia [see Figure 7]. A major advantage of fascial excision is that it yields an easily defined plane that is well vascularized and therefore can readily accept a graft. In addition, bleeding is generally easier to control at the fascial level of dissection because the vessels are easier to identify and coagulate. Furthermore, the entire excision can



Figure 7 Fascial excision involves excision of the burned skin and the underlying subcutaneous tissue down to the level of the muscle fascia. It is typically performed with the electrocautery. As shown (arrows), the edges should be tacked down to minimize the ledge at the edge where normal tissue adjoins the exposed fascia.

be performed with the electrocautery, and blood loss is thereby minimized. The principal drawback of this approach is that the excision inevitably includes some healthy, viable subcutaneous tissue. Another disadvantage is that the removal of subcutaneous tissue may create an unaesthetic contour deformity.

Tangential excision, as the name suggests, involves sequentially excising the layers of eschar in a tangential fashion until a layer of viable bleeding tissue capable of supporting a skin graft is encountered [see Figure 8].^{28,29} The goal is to remove only the nonviable tissue, particularly in the case of deep dermal wounds. Typically, tangential excision is performed with a handheld knife (a Watson knife or a Weck/Goulian blade). A back-and-forth carving motion is used, and very little force is applied. The guard on the knife can be used

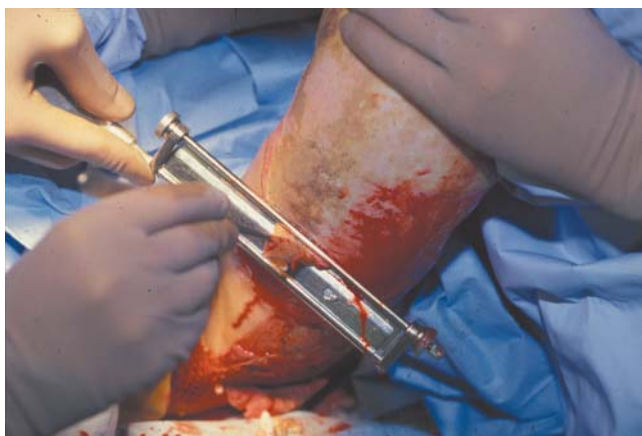


Figure 8 Tangential excision of the burn wound is carried out with a Watson knife (as shown here) or a Weck/Goulian blade. Eschar is tangentially excised until healthy, bleeding tissue that is suitable for skin grafting is reached.

to control the depth of excision. The appearance of diffuse punctate bleeding signals that viable tissue has been reached. The main disadvantages of tangential excision are that (1) it may be difficult to control the diffuse bleeding from the wound bed, and (2) it may be difficult to assess the suitability of the underlying fat for accepting a graft.

A water jet–powered instrument (VersaJet Hydrosurgery System, HydroCision, Andover, Massachusetts) is available that can be used for tangential burn wound excision. This device offers an easy and relatively precise way of excising eschar and is particularly useful for excising nonviable tissue from the concave surfaces of the hands and feet, as well as the eyelids and ears.³⁰

To minimize hematoma formation and graft loss, it is critical that adequate hemostasis be achieved before the placement of skin grafts, cadaveric grafts, or skin substitutes. Telfa pads (Kendall, Mansfield, Massachusetts) soaked in an epinephrine solution (1:10,000) are a mainstay of hemostasis, combined with topical pressure and cauterization when necessary. A fibrinogen thrombin delivery system (Tisseel Fibrin Sealant, Baxter, Deerfield, Illinois) is commercially available that improves the ability to control bleeding after excision.

Regardless of which excision technique is used, blood-conserving strategies should be used routinely to minimize transfusion requirements. These strategies include manual pressure, use of topical epinephrine and/or fibrin sealant, tumescence of burn wounds with vasoactive medications, and the use of tourniquets.^{31–33} The extremities can be suspended from operating room ceiling hooks [see Figure 9] to provide access to their entire circumference.

SKIN GRAFTING

The best replacement for lost skin is clearly skin itself. The first known report of skin grafting comes from the *Sushruta Samhita*, an ancient Indian surgical treatise that may date back as far as the seventh century BC. This text describes the use of both skin flaps and grafts for the repair of mutilations of the nose, the ears, and the lips. The Indian method of grafting was first introduced to Western medicine by English surgeons, who observed it during the late 18th century.³⁴



Figure 9 Extremities can be suspended from operating room ceiling hooks to facilitate exposure for burn excision and grafting.

It was not until 1804 that successful transplantation of free skin grafts was reported by Baronio of Milan, who successfully grafted large pieces of autogenous skin onto different sites on sheep.³⁴ In 1869, Jacques Reverdin, in a report to the Société Imperiale de Chirurgie, described the use of a small epidermal graft, which became known as the pinch graft.³⁵ This technique did not, however, gain wide recognition until 1870, when successful experiments in skin grafting for the treatment of burn patients were performed by George David Pollock.³⁶ In 1872, Ollier described the use of both full-thickness and split-thickness skin grafts and realized the possibility of covering large areas with such grafts if a satisfactory method of cutting them could be devised.³⁴

Currently, a 95% success rate is the standard of care for skin grafting. To achieve this level of success requires adequate wound bed preparation (see above), careful selection of suitable donor sites, and appropriate postoperative care.

Skin grafts are broadly classified as either full-thickness or split-thickness grafts, depending on whether they contain the full thickness of the dermis or a partial thickness. Split-thickness grafts are further categorized as thin, intermediate, or thick, depending on the amount of dermis harvested with the graft. The thinner the skin graft, the greater the degree of contraction that occurs at the recipient site after engraftment. Although thicker grafts have the advantage of contracting less, they leave a greater dermal deficit at the donor site, which can lengthen the time needed for healing and increase the risk of hypertrophic scarring at that site.

Full-thickness skin grafts can be harvested either through use of a dermatome or through direct excision of skin from the flank, the groin crease, the hypothenar eminence, or the forearm and can be used for coverage of small defects of the hand or the face. Standard (intermediate) split-thickness grafts are typically harvested at a thickness of 0.010 to 0.012 in. Thin (0.006 in.) split-thickness skin grafts are generally used in conjunction with skin substitutes, whereas thick (0.018 to 0.025 in.) split-thickness grafts are typically used in grafting of the hand and the face. The thickness of the graft depends both on the dermatome setting and on the pressure the harvester applies to the dermatome during harvesting.³⁷

Donor-site selection for split-thickness skin grafts is based on the distribution of the burn. The anterolateral thigh, when available, is the donor site of choice for most adult patients: it can be harvested in the supine position, it can easily be left open to the air so the donor-site dressing can dry, and it can be covered by shorts if desired. When larger grafts are needed or the thighs are burned, the back, the buttocks, and the abdomen can serve as donor sites. Subcutaneous infiltration of a physiologic salt solution yields a smooth, firm surface that facilitates the harvesting of these areas. If this is done, the anesthesiologist should be informed that additional fluid is being administered. In children, the buttocks and the scalp are commonly employed as donor sites. Once healed, these sites are usually inconspicuous: the buttock donor site can be harvested in such a way that it can be covered by a bikini, and the scalp donor site is typically covered by regrown hair. It is important to reassure the patient's parents that if the graft is harvested appropriately, the donor site will not exhibit alopecia and the recipient site will not grow hair. Generally, however, these sites are sufficient only for the grafting of small wounds.

Skin grafts can be applied as sheet (or unmeshed) grafts, or they can be meshed at ratios ranging from 1:1 to 4:1. Meshing allows the egress of serum and blood from wounds, thereby minimizing the risk that hematomas or seromas will form that could compromise graft survival. In addition, meshed grafts can be expanded or stretched to cover larger surface areas. When grafts are meshed at ratios of 3:1 or higher, allograft skin or another biologic dressing can be applied over them to prevent the interstices from becoming desiccated before they close.³⁸ Because of the lack of dermis in the interstices, widely expanded mesh always scars, takes a long time to close, and results in permanent unattractive mesh marks. In our center, widely spread mesh is never used unless it is grafted onto a dermal template to minimize scarring (see below).

Sheet grafts should be used on the face, the neck, the hands [see Figure 10], and, whenever possible, the forearms and the legs. In these exposed areas, the superior cosmetic and functional results obtainable with sheet grafts make such grafts preferable. Because sheet grafts have no interstices, they must be closely monitored and periodically rolled with a cotton-tipped applicator to drain any fluid collection. Any serous or bloody blebs that form beneath the graft should be incised with a No. 11 scalpel and drained expeditiously. A common practice known as pie-crusting, which involves making incisions in a sheet graft at the time of surgery, actually does not yield much improvement in graft survival, because blebs often form in areas without incisions. Use of fibrin sealant at the time of grafting may lower the incidence of blebs.³⁹

GRAFT AND DONOR-SITE DRESSINGS

Once the graft is secured in place, a dressing may be applied to protect it from shearing, as well as to accelerate closure of meshed graft interstices. Numerous options for graft dressings exist, including wet dressings and greasy gauze. The use of a nonadherent dressing such as Conformant 2 (Smith & Nephew) along with an outer antimicrobial wet dressing allows the overlying dressings to be periodically removed without dislodging the graft from the wound bed. Bolsters consisting of cotton and greasy gauze are employed to help grafts conform to concave wound surfaces, and splinting of extremities may be necessary for safe graft immobilization, especially over joints. A vacuum-assisted closure system can



Figure 10 Sheet grafts are the gold standard for skin grafting of the face, the neck, and, whenever possible, the forearms and the legs. This 1-month follow-up demonstrates the aesthetic superiority of sheet grafts.

be used as another option for promoting graft healing. Alternatively, an Unna boot can be placed on both the upper and the lower extremity to immobilize the graft and provide vascular support, allowing mobilization of the extremity in the immediate postoperative period.⁴⁰

Sheet grafts can be either left open to the air to allow continuous monitoring or wrapped with dry dressings, which can be removed if necessary to allow interval inspection and deblebbing.

There are also various options for donor-site dressings. The ideal donor-site dressing would not only minimize pain and infection but also be cost-effective. Greasy gauze or a nanocrystalline silver-embedded material is often employed for this purpose. Typically, these dressings are left in place until the donor site epithelializes, at which time the dressing is easily separated from the healed wound. Op-Site (Smith & Nephew), a transparent polyvinyl adherent film, is also commonly used. With Op-Site, the underlying wound is easily examined without removal of the dressing; however, intermittent drainage of the wound fluid that accumulates is necessary. Op-Site does not work well over joint surfaces and concave or convex areas (e.g., the back). Silver sulfadiazine in a diaper is an excellent covering for buttock donor sites in children; dressing changes can be done with each diaper change.

POSTOPERATIVE WOUND CARE

Even with complete graft take and timely donor-site epithelialization, several wound management issues may still arise in the early postoperative period. Physical therapy must be initiated in this period, and management of scarring must be addressed. Blisters are common on newly healed donor sites and ungrafted wounds. The new epithelial layer of these wounds lacks the connections to the underlying wound bed normally provided by the BMZ, which protect the epidermis from shearing. During the months it takes for these structures to reconstitute, their absence frequently leads to blistering. These blisters are usually best managed by draining them with a clean pin, reapplying the epithelial layer to the wound surface, and covering the site with adhesive bandages. The bandages can be soaked off in the shower to ensure that the adhesive causes no additional injury.

Inclusion cysts may develop in healed grafts that were placed over excised wound beds that still contained a thin layer of dermis with adnexal structures. The secretions from the adnexal structures collect beneath the skin graft to form the cysts. Inclusion cysts are treated by unroofing the affected area with a needle.

A condition known as sponge deformity (so called because the skin looks like a bridge of coral sponge [see Figure 11]) may occur if a skin graft is placed over a wound that heals underneath the graft in multiple small areas, with or without sloughing of the overlying graft.⁴¹ Where the graft does not slough, a bridge forms. This unsightly deformity can be treated by incising the bridges over the healed tissue with sharp scissors.

Healed donor sites, skin grafts, and ungrafted burns can also break down as a result of infection—a process referred to as melting. Such melting can occur quite rapidly: a graft or healed wound that demonstrates complete take one day may exhibit significant breakdown the next day. Wound cultures should be obtained from these areas, and the open sites

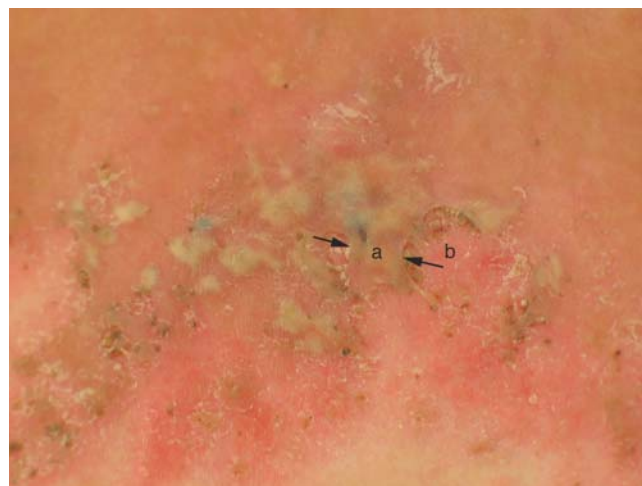


Figure 11 Sponge deformity can occur if a skin graft is placed over a wound that heals beneath without sloughing of the overlying graft. Arrows depict the bridge of skin graft (a) that forms over healed skin (b).

should be treated with topical antibiotic ointment and, if the problem worsens, systemic antibiotics.⁴¹

Malignant degeneration can occur in healed burn wounds decades after the initial injury. These tumors—known as Marjolin ulcers—are usually squamous cell carcinomas and are more aggressive than typical skin cancers. Marjolin ulcers have a high metastatic potential and are associated with a high mortality. New or chronic ulcers in burn wounds should raise the suspicion of malignancy and be considered an indication for biopsy.⁴³

BIOLOGIC DRESSINGS AND SKIN SUBSTITUTES

As noted [see Early Excision and Grafting, *above*], conventional burn wound management dictates early, aggressive excision of burn wound eschar to minimize the chances of sepsis or progression of burn wound depth.^{15,16,21–24} In some cases, the body surface area to be excised is larger than can be covered by autografts from the available donor sites. The solution is to strategically select areas for autograft coverage and then temporarily cover the remaining open areas with biologic dressings. Donor sites typically epithelialize within about 2 weeks, after which time they can be reharvested, allowing temporary dressings to be serially removed and covered with new autograft.^{26,44}

Biologic dressings perform several important functions. By adhering to the wound bed, they provide a physical covering that controls water vapor transmission, thus minimizing loss of water, electrolytes, and proteins and preventing desiccation and maceration of wounded tissue (which can lead to extension of the depth of injury). In addition, biologic dressings help prevent microbial invasion from the environment.^{26,45,46}

ALLOGRAFT AND XENOGRAFT SKIN

Although the technique of skin grafting is thousands of years old, skin grafting between individuals was not reported until the late 19th century. In 1869, Reverdin published a report on the transplantation of small epidermal grafts from his own arm onto a patient's burn wound.³⁵ In 1881, Girdner described transplantation of skin grafts from a cadaver to a

burn patient and reported a 75% immediate take rate. It was widely noted that these grafts initially performed well but survived for only 6 to 8 weeks.³⁴ The mechanisms underlying the rejection of these grafts were eventually elucidated by the efforts of Sir Peter Medawar, who received the Nobel Prize in 1960 for his seminal work on defining the basis of allograft rejection and tolerance induction.

The use of allograft was popularized by James Barrett Brown in the 1940s and 1950s,⁴⁷ and with the subsequent development of skin banking, allograft became the standard temporary graft for excised burn wounds when sufficient autograft is unavailable or autografting is not indicated.^{26,27,46,48,49}

Ultimately, allograft skin is always rejected unless the donor and the recipient are immunologically identical. The rejection process usually begins within 10 days in an immunologically competent host, but allografts can be tolerated for up to 1 month in a host who is severely immunocompromised (e.g., as a result of extensive burn injury).^{26,49,50} The use of immunosuppressive agents such as cyclosporine has led to the achievement of prolonged allograft tolerance,^{24,50–53} but it also exposes the burn patient to the risks inherent in prolonged systemic immunosuppression.

In addition to providing temporary wound closure, allograft has been used as an overlay for meshed autograft with the aim of accelerating epithelialization of the interstices. Allograft has also been used to cover donor sites after autograft harvesting and to cover wounds after excision as a means of assessing the suitability of a bed for autograft placement.²¹

Recognition of the weaker immunogenicity of the dermal layer of cadaver allograft stimulated various attempts to employ allograft for permanent dermal replacement. Jackson and colleagues were the first to report the use of alternating strips of autograft and allograft for definitive closure of large burn wounds.¹⁹ In 1985, Heck and colleagues constructed the first deliberate combination of allogeneic dermis with autologous epidermis.⁵⁴ This basic idea was subsequently expanded on by Cuono and colleagues, who used cryopreserved allogeneic dermis as a bed for autologous keratinocyte cultures.^{3,55} These investigators demonstrated long-term survival and documented the reconstitution of a normal-appearing BMZ with anchoring fibrils.

Use of allograft skin as a temporary cover or as the permanent dermal replacement in the composite technique does have several drawbacks, including the limited availability of suitable skin, the variable quality of the skin obtained, the substantial cost of allograft procurement and preservation, and the significant potential for disease transmission.^{56,57} In addition, the cryopreservation process significantly compromises the viability, and therefore the efficacy, of the allograft.^{58,59}

Xenografts from a number of species have also been used as biologic dressings. Porcine xenograft has been used in the management of exfoliative skin disorders (e.g., toxic epidermal necrolysis) as well as for temporary wound coverage after excision and before definitive autografting.^{26,60–62}

Since the 1980s, research efforts have focused on the development of skin replacements that could serve as either a temporary or a permanent substitute for human skin. Conceptually, any skin replacement must recapitulate the native skin biology—that is, it must include an epidermal component, a dermal component, and a BMZ equivalent linking the two.

CULTURED EPIDERMAL AUTOGRAFTS

Replacement of the epidermis alone was successfully accomplished in the 1970s with the development of cultured epidermal autografts (CEAs). In 1975, Rheinwald and Green reported the successful isolation and culture of epidermal keratinocytes,⁶³ and several years later, O'Connor and colleagues reported the first clinical use of CEAs to cover burn wounds.⁶⁴ In 1984, Gallico and colleagues described the use of CEAs to resurface the burn wounds of two children who had sustained injuries over 95% of their TBSA.⁶⁵ CEAs are grown in the laboratory from a biopsy of the patient's own skin. A current example is Epicel (Genzyme Biosurgery, Cambridge, Massachusetts), which has been approved by the Food and Drug Administration (FDA) for use in the United States but requires Institutional Review Board approval and separate informed consent because of concern that the feeder layer for the keratinocytes is of murine origin.

CEAs are most commonly applied to the granulation tissue of chronic wound beds. As more clinical experience with CEAs was amassed, the drawbacks of using epidermal components alone to replace full-thickness skin loss became evident.^{27,66–68} The lack of a dermal component made the CEAs extremely fragile and led to high rates of sloughing and infection.^{27,69,70} Even when CEA engraftment occurred, the BMZ structures critical to graft durability were poorly reconstructed.^{69–71} Compton and colleagues compared the outcome of wounds covered with CEAs alone with the outcome of wounds covered first with allograft dermis and then with CEAs. They found that in wounds containing the allograft dermal component, there was greater initial take, better long-term durability, and accelerated formation of important BMZ structures.⁷² It is now well recognized that CEAs are capable of replacing the epidermis but are not effective when used alone to resurface deep partial-thickness and full-thickness wounds. Bilayer skin substitutes consisting of both dermal and autologous epidermal cultured cells are being developed to reduce the time for maturation on the patient.²⁷ Although the theoretical applications are vast, the successes of these products have never been demonstrated in prospective randomized trials. Another potentially promising concept is use of dispersed cells in conjunction with widely meshed grafts to decrease time to closure and decrease scarring.⁷³

In vitro development of an epidermal replacement was made possible by the simpler biology of the epidermis. Development of a dermal replacement has proved a more formidable challenge. Dermis consists mainly of extracellular matrix, and its complex structure is not amenable to growth in culture.

SKIN SUBSTITUTES

The drawbacks of allograft and xenograft skin have further underscored the need for an off-the-shelf dermal replacement. Yanniss, Burke and colleagues described a pioneering approach to the development of a skin replacement containing both an epidermal and a dermal component in the early 1980s.^{74–77} Recognizing the importance of the dermis in skin replacement, they developed a bilayer construct that is now commercially available under the name Integra (Integra LifeSciences Corporation, Plainsboro, New Jersey). The epidermal component of this construct consists of a layer of Silastic film, which acts as a protective barrier against infection and evaporation from the wound bed; the dermal layer

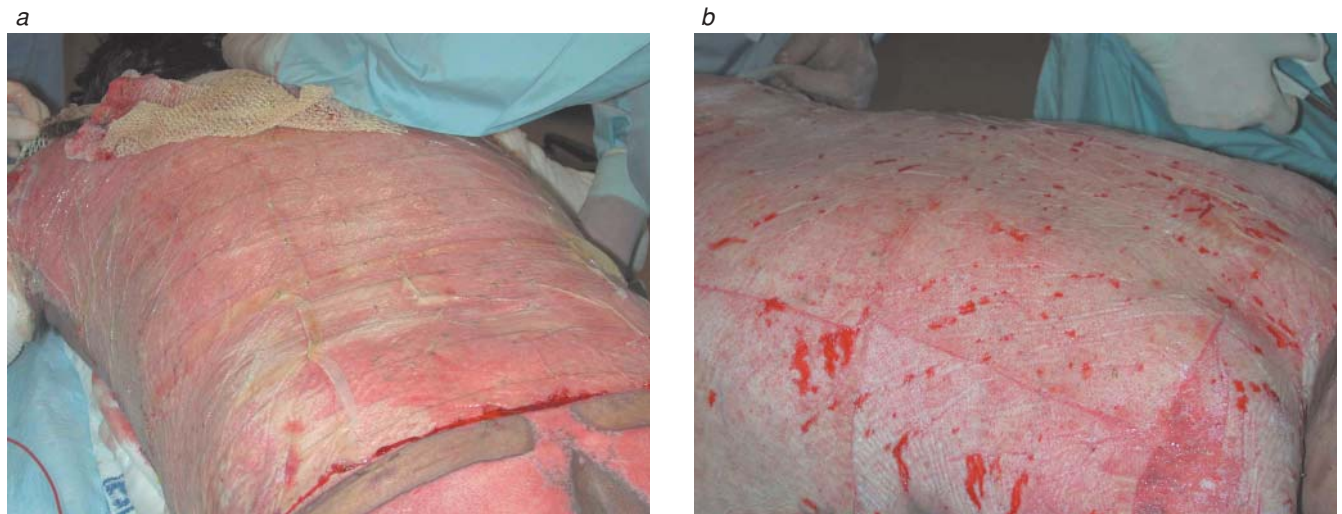


Figure 12 A bilaminar skin substitute is placed on the excised burn wound (a) and secured with staples. The skin substitute typically vascularizes in 2 weeks, at which point the Silastic outer layer is removed (b) and the neodermis can be autografted.

consists of a porous matrix of fibers composed of cross-linked bovine collagen and a single type of GAG (chondroitin-6-sulfate). Integra can be placed on a completely excised, noninfected wound bed. Initial studies indicated that a neodermis forms, created by the ingrowth of fibroblasts and endothelial cells into the dermal matrix template provided by the Integra. Once this neodermis forms and the dermal scaffold is well incorporated into the wound (typically, after 14 days), the Silastic component is removed. A thin (0.006 in.) split-thickness autograft is then placed on the neodermis [see Figure 12].^{27,78,79} Integra not only is a useful adjunct in the management of large burn wounds but also can play an important role in the management of hand and facial burns requiring excision and grafting.^{80–82} It must be emphasized, however, that for Integra to vascularize completely, it must be applied to a viable, noninfected wound bed. In addition, meticulous surgical technique and appropriate postoperative care are critical for a successful outcome.

Another product marketed for dermal replacement is Alloderm (LifeCell, Branchburg, New Jersey), which is an acellular dermal matrix produced from human cadaveric skin. The cadaveric skin is first stored in normal saline for 15 hours to remove the epidermal component. The cadaveric dermis is then incubated in sodium dodecyl sulfate to extract any remaining cellular components. The decellularized substrate is freeze-dried and reconstituted by soaking it in crystalloid solution before use.²⁶ Alloderm can be used for immediate wound coverage in combination with a thin split-thickness autograft. Data from multicenter trials indicate that Alloderm works best with thin (0.006 to 0.008 in.) autografts: the

thicker the autograft, the lower the take rates.^{26,27,83} Alloderm has also been used for abdominal wall reconstruction and for soft tissue augmentation in the face.

A product known as TransCyte (Smith & Nephew)—formerly Dermagraft-TC—is approved by the FDA as a temporary (as opposed to permanent) cover for full-thickness wounds after excision. TransCyte is produced by seeding neonatal fibroblasts isolated from foreskin onto Biobrane, a synthetic dressing consisting of Silastic attached to a nylon mesh, which is coated with porcine peptides prepared from type I collagen. The Silastic layer of Biobrane serves as a temporary impermeable barrier, whereas the fibroblast-impregnated nylon mesh serves as a dermal component.^{26,27}

Dermagraft (Smith & Nephew), in contrast, is employed as a permanent dermal replacement. Dermagraft consists of human neonatal fibroblasts seeded onto an absorbable polyglactin mesh scaffold, which is intended to mimic the native dermal architecture.^{26,27} It is approved by the FDA for treatment of venous stasis ulcers, but it was developed for coverage of excised burn wounds in conjunction with a split-thickness autograft.

Although a permanent off-the-shelf skin replacement has yet to be developed, the available products have already significantly influenced the management of burn wounds. In addition, the shortcomings of each product and strategy have improved our understanding of skin biology and physiology and confirmed the importance of both the epidermis and the dermis in the structure and function of skin.

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Acknowledgments

Figure 1 Tom Moore
Figure 2 Seward Hung

16 MISCELLANEOUS BURNS AND COLD INJURIES

David M. Heimbach, M.D., F.A.C.S., and Nicole S. Gibran, M.D., F.A.C.S.

Electrical Injury

Three main forms of electrical injury exist: low-voltage burns (i.e., burns resulting from contact with circuits of less than 440 volts [V]), high-voltage burns (i.e., burns resulting from circuits of greater than 1,000 V), and super-high-voltage burns (caused by lightning). There is also a poorly defined “intermediate-voltage” category, which includes burns caused by contact with industrial circuits of 440 to 800 V; these burns have characteristics of both high-voltage and low-voltage burns, depending on the circumstances.

A common “electrical,” though noncontact, injury is an intense flash burn resulting from the short-circuiting of an industrial circuit by an electrician with a metal tool. Such a short-circuiting causes the metal part of the tool to vaporize, as if it were an uncontrolled arc welder; this vaporization results in a very high temperature flash that causes deep burns to the hand holding the tool and less deep burns to the upper body and face. Clothing can catch fire, compounding the problem. These burns are not, however, associated with the problems of contact electrical burns, and they should be treated in much the same way as other thermal burns.

An electrical burn is managed in essentially the same way as any other burn except that a higher urinary output is necessary in the presence of myoglobinuria. In addition to the potentially devastating tissue destruction seen with high-voltage injury, electrical injuries can lead to chronic and debilitating nonsurgical conditions that must be addressed.

LOW-VOLTAGE INJURIES

The human body is three to four times as sensitive to alternating current as it is to direct current. Alternating current has generally replaced direct current for all commercial power applications because it is cheaper to transmit and can be more easily transformed to any required voltage. The amount of 60-cycle alternating current that can just be perceived in the hand is about 1.1 milliamperes (mA), which produces a tingling sensation. Skin resistance, however, varies according to the thickness of the epidermal keratin layer, as well as the cleanliness and dryness of the skin. The calloused hand may provide resistance of as much as 1,000,000 ohms/in² while dry; normal skin provides resistance of 5,000 ohms/in²; and wet skin provides resistance of only 1,000 ohms/in². With currents higher than 2 to 4 mA, the tingling gives way to muscle contractions, which get stronger as the current increases. The “let go” current is reached at approximately 15 mA, above which the victim cannot release his or her grasp of the conductor. Above 20 mA, there is sustained spasm of the respiratory muscles. If the passage of current lasts less than 4 minutes, respiration will resume; however, if it lasts longer than 4 minutes, asphyxiation may occur, and mouth-to-mouth resuscitation may be required. At levels above 30 to 40 mA, ventricular fibrillation (VF) may be induced. As the current is increased, the heart’s susceptibility to fibrillation first increases and then decreases. At 1 to 5 A, the heart goes into sustained contraction, and the likelihood of VF becomes

negligible. When the high current is terminated, the heart usually reverts back to sinus rhythm, just as happens in cardiac defibrillation, when such high currents are deliberately applied to the chest to depolarize the entire heart.

In the event that the victim of electric shock is unconscious, the initial responder should remove the source of the current (taking care not to become a victim of shock himself or herself) and then provide cardiopulmonary resuscitation (CPR); paramedics may then begin defibrillation. If a sinus rhythm has not been established on arrival at the emergency department (ED), the physician should treat the patient as he or she would any other dysrhythmia patient. If sinus rhythm has been established, the patient should be treated as a sudden death victim, with evaluation for anoxic damage and cardiac monitoring.

Many patients come to the ED after receiving an electric shock from household current. If the electrocardiogram and rhythm strip are normal, the patient should be reassured and discharged without hospital admission. Muscle soreness will resolve spontaneously in 24 to 48 hours and may be treated with analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs).

Cutaneous burns with significant tissue necrosis rarely result from contact with low-voltage current. Usually, the area of contact is large enough to dissipate the heat of the current, and underlying tissue destruction is minimal.

Mouth Burns in Children

The exception to this rule is a child who may chew on the end of a live electric extension cord. The child’s saliva completes the circuit between the positive and neutral leads; the resulting electrical short may cause significant tissue destruction of the lips, tongue, or both [see Figure 1]. These burns should be evaluated and treated by a plastic surgeon or a burn surgeon. The patient is often admitted to ensure he or she receives proper nourishment and that the parent is comfortable with pain management and wound cleansing. The parent should be forewarned that the eschar might separate in a few days, resulting in bleeding from the labial branch of the facial artery. In an emergency setting, this bleeding can be easily treated by pinching the lip between thumb and forefinger while the child is brought to the ED for suture ligation.

There are two plans for definitive care.¹⁻³ Long-term results appear to be about equal for nonoperative and operative acute management. If nonoperative management is chosen, splinting is usually recommended to keep the mouth stretched to prevent contracture, but patients and parents do not always comply fully with splint use. Immediate coverage with flaps hastens the healing but leaves a permanent scar and may result in the sacrifice of some normal tissue.

HIGH-VOLTAGE INJURIES

Current in wires containing 1,000 V or more may cause massive tissue destruction. The tissue destruction results from electrical energy being converted to heat as it meets resistance in the tissues.



Figure 1 Shown is an electrical burn caused by a 110-volt household current. The injury resulted from the patient's sucking on an extension plug. The burn was treated conservatively with a mouth splint, which resulted in a nearly normal-appearing mouth with good function.

The smaller the size of the body part through which the electricity passes, the more intense the heat and the less the heat is dissipated. Fingers, hands, forearms, feet, and lower legs frequently are totally destroyed; areas of larger volume (e.g., the trunk) usually dissipate enough current to prevent extensive damage to viscera unless the contact wound is on the abdomen or the chest. As current passes through the body, arc burns, as well as the usual contact wounds, are common. These deep wounds, which may be as destructive as contact wounds, occur when current takes a direct path, often between joints in close apposition to one another at the time of injury. Burns of the volar aspect of the wrist, the antecubital fossa when the elbow is flexed at the time of injury, and the axilla are most common. Such injuries should always be seen immediately by a surgeon with a special interest in burns. The immediate evaluation of the patient with a major electrical burn is similar to that of any severely injured patient and includes evaluation of the ABCs (*A*irway, *B*reathing, and *C*irculation).

In addition to burns, which may be obvious, the patient may have other associated injuries resulting from falls or may have broken bones resulting from the tetanic spasms of major muscle groups. Common potential fractures include those of the lumbar spine and hip.

RESUSCITATION

Flash and flame burns without electrical contact injuries are treated in the same manner as all thermal burns are. For patients with electrical contact injuries, fluid requirements are considerably greater than are predicted by the various formulae used for thermal burn victims; the reason is that the cutaneous injury is usually only the "tip of the iceberg," and underlying deep tissue damage may be extensive. A good general starting point is to administer lactated Ringer solution at two to three times the quantity specified by the Baxter (Parkland) burn formula. This would initially require providing 8 to 10 ml/kg/% of total body surface area (TBSA) that is burned. Fluid administration should be adjusted, with the aims of correcting metabolic acidosis, normalizing vital signs, and attaining a urinary output of approximately 100 ml/hr

in adults, especially in the presence of myoglobinuria. With significant myonecrosis, rhabdomyolysis results in increased levels of circulating myoglobin and hemoglobin, as well as cell fragments, which can plug the renal tubules and cause acute tubular necrosis. Myoglobin precipitation is accentuated by acidic urine and decreased by alkaline urine. There has never been a report of a correlation between exact myoglobin levels in the urine or the blood and development of renal failure.^{4,5} Because urinary myoglobin levels can be significantly elevated even when the urine is clear, the clinical relevance of quantifying such levels is unclear. However, gross myoglobin in the urine should be treated with aggressive fluid hydration. If the urine is red or reddish black, urinary flow of at least 1 ml/kg/hr is indicated until the pigment clears, and acidosis should be corrected. An osmotic diuretic such as mannitol (25 g bolus, followed by 12.5 g every 2 to 4 hours) may be necessary to maintain adequate urinary output. Use of sodium bicarbonate to maintain urinary pH above 7 without raising blood pH above 7.5 theoretically may minimize protein precipitation in the urine.

SURGICAL CONSIDERATIONS

There are two indications for early operation in a patient with a high-voltage electrical burn. If the burn is making the patient sick (e.g., myoglobin will not clear or acidosis will not resolve), the wound should be explored and all grossly necrotic tissue removed. If the burn is making an extremity sick (e.g., there are signs of a compartment syndrome), early escharotomy, fasciotomy, or both should be performed. Otherwise, delaying surgical exploration by a few days can often allow definitive debridement and wound closure through a single operation.^{6,7}

Escharotomy and Fasciotomy

In general, an escharotomy is indicated for a circumferential deep burn when there is evidence of impaired distal perfusion. Fasciotomy is indicated for concomitant electrical injury to underlying muscle when there is evidence of increased compartment pressure, myoglobinuria, tense muscle compartments, or nerve or vessel compression. Careful monitoring, including measurement of compartment pressures, is mandatory, and escharotomies and fasciotomies should be performed at the slightest suggestion of progression. Routine compartment pressure measurements may be helpful, but any of the signs of impending compartment syndrome (i.e., increased pain, pallor, absence of pulse, decreased sensation, and tense swelling) mandate prompt compartment release in the operating theater.

One unique injury that must be considered in patients with electrical injuries to the hand is a carpal tunnel injury.⁷ With the associated swelling, relatively small electrical injuries can lead to swelling in the carpal tunnel that manifests as increasing paresthesias and numbness in the distribution of the median nerve. If the injury is sufficiently devastating to create a mummified hand, carpal tunnel release probably has no role in the treatment plan.

CONTACT SITES

Because most electrical injuries result from alternating current, entrance and exit sites are better referred to as contact points. These are thermal burns resulting from heat generation, but unlike flame burns, they are often associated with significant injury to the deep tissues. The amount of heat generated depends on the resistance to current flow. A dry hand or foot in contact with high voltage may generate heat in excess of 1,000° C, leading to mummification at the contact site [see *Figure 2*].

With the passage of a large current, multiple contact sites may be seen along the route of the current, resulting in injuries that

suggest the effects of an explosion. Sites of current arcing (see above) should be treated in the same manner as primary contact sites because the underlying damage can be just as severe.

WOUND MANAGEMENT

In general, if there are large amounts of necrotic muscle as a result of high-voltage electrical contact, aggressive surgical debridement to decrease myoglobinemia is indicated. This intervention may minimize subsequent organ dysfunction. If gross myoglobinuria does not resolve after several hours of aggressive hydration, diuresis, and compartment release, the presence of a large amount of dead muscle is a virtual certainty. Muscle of indeterminate viability should be spared, but if a limb is obviously unsalvageable, guillotine amputation may be appropriate and life-saving. The goal of subsequent surgical procedures is to conserve viable tissue while removing neighboring dead tissue. The uneven nature of the injuries makes this approach difficult and time-consuming. If they are not exposed, small, scattered areas of injured muscle will be replaced by fibrous tissue. A high fever and tachycardia, however, may be physiologic evidence that remaining nonviable muscle has become infected. Because bone resists current and becomes very hot, there may be a substantial amount of nonviable necrotic muscle tissue along the bone that must be debrided. It is not uncommon for superficial forearm muscles to appear viable while necrotic muscle surrounds the radius and ulna. Use of vascular grafts to replace clotted arteries is sometimes an option. However, such grafts may actually increase morbidity and prolong recovery; amputation followed by use of one of the newer prostheses may result in better function than would be available in a hand or foot that has poor sensation and motor function.

In accordance with the principles used for thermal burns, devitalized tissue below the skin at the contact sites should be debrided within 7 days after injury [see Figure 3]. Sequential debridement of residual necrotic tissue may be necessary over the ensuing 3 to

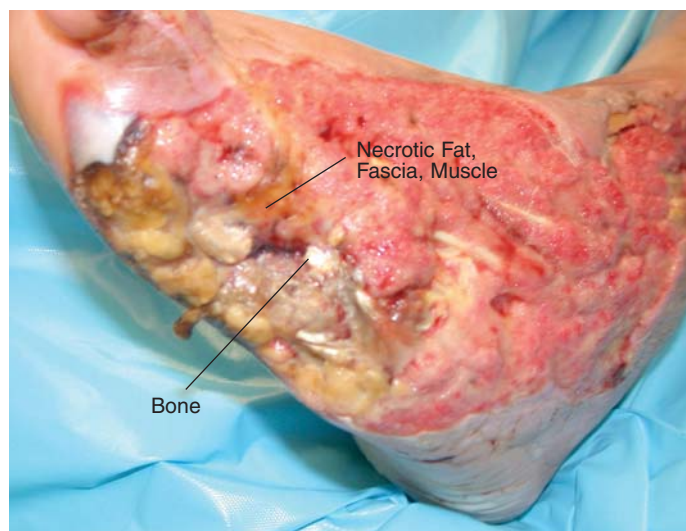


Figure 3 Shown is the same injury seen in Figure 2 just before a second debridement on day 7. Because this patient's right leg was amputated, every attempt was made to salvage as much of the left foot as possible. At initial debridement, it is difficult to tell precisely how much of the foot is possibly viable; note that there is still considerable nonviable soft tissue under the metatarsals and that the metatarsals are considerably exposed. After the second debridement, the foot was treated in a Wound Vac to stimulate vascularization.



Figure 4 Shown is the same foot as in Figures 2 and 3 at the time of discharge (day 21 after injury). Two toes and the fifth metatarsal were removed, leaving a stable, sensate foot with satisfactory cover.



Figure 2 Shown is a contact-point injury caused by a 15,000-volt current, seen on day 1. Although the injury looks relatively simple, a similar injury to this patient's right foot led to a below-the-knee amputation. Careful monitoring for compartment syndrome in the leg is mandatory in such injuries.

5 days. Early aggressive debridement, followed immediately by reconstructive surgery with tissue transfer by rotation or free flaps to cover remaining viable tissue, nerves, vessels, and bone, may facilitate early recovery [see Figure 4].

To help determine the optimal timing and results of operation, one group reviewed the charts of 62 patients who underwent treatment for high-voltage electrical burns of the upper extremities.⁶ A total of 100 upper extremities were treated. Of these, 22% underwent decompression within 24 hours because of progressive nerve dysfunction, clinical compartment syndrome, or failure of resusci-

tation. This subset required a mean of 4.2 operations; the amputation rate was 45%, which was similar to that reported in other series. For another 35% of the burned extremities, the first operative procedure was delayed until resuscitation was complete. This subset required a mean of 2.1 operations and no amputations. For the remaining 43% of the extremities, no operations were required to achieve healing. Overall results showed a 10% amputation rate and a mean hospital stay of 27 days; these results were better than the results reported by others.

NONSURGICAL PROBLEMS RELATED TO ELECTRICAL INJURY

Cardiac Injuries

Immediate cardiac arrest is the most common cause of death from electrical injury. Low-voltage exposure is likely to induce ventricular fibrillation, whereas high-voltage exposure is more likely to produce cardiac standstill. Cardiac standstill and respiratory arrest may revert spontaneously if CPR prevents anoxia; VF is more likely to necessitate defibrillation. Conventional wisdom states that patients who have sustained high-voltage injuries should be admitted for 24-hour telemetry monitoring and that cardiac isoenzyme levels should be followed. Studies have shown that if the ECG is normal on admission, subsequent cardiac dysrhythmias are rare and intensive monitoring is probably not necessary.^{8,9} The transient interest in isoenzyme and troponin levels has now waned, and assessment of these variables has not proved useful in predicting cardiac damage.^{8,10-13}

Myocardial infarction is uncommon, but it has been reported in a small percentage of cases in each series. In one patient at the University of Washington (UW) Burn Center, a papillary muscle ruptured within 24 hours; this led to immediate, fatal congestive heart failure.

Neurologic Complications

Neurologic complications are common sequelae of high-voltage electrical injuries and can affect the brain, spinal cord, and peripheral nerves. Immediate but frequently transient symptoms include varying levels of unconsciousness, respiratory paralysis, and motor paralysis. Permanent changes include cortical encephalopathy, caused by the electrical injury itself or resulting from hypoxia at the time of the accident. Spinal cord injuries are rare but may present as progressive muscular atrophy, amyotrophic lateral sclerosis, or transverse myelitis. These conditions may occur days to months after the injury and progress slowly.¹⁴⁻¹⁶

A study of 90 patients (82 male and 8 female) with electrical burns was conducted at the UW Burn Center to identify and evaluate neurologic consequences.¹⁷ There were four deaths. Of the 86 remaining patients, 22 sustained low-voltage injury. Of these 22, 11 had immediate neurologic symptoms; these symptoms resolved in nine of the 11 patients. A total of 64 patients sustained high-voltage injury; of these, two thirds had immediate central or peripheral neurologic symptoms (or both). Loss of consciousness accounted for the largest percentage of central nervous system sequelae in the high-voltage group (45%). Of the 29 patients who lost consciousness, 23 (79%) regained consciousness before arrival at the hospital. Six patients remained comatose, three died, and three awoke but had neurologic sequelae. One third of the patients in the high-voltage group had one or more acute peripheral neuropathies; of these neuropathies, 64% resolved or improved. Five patients had transient initial paralysis, but there were no delayed spinal cord symptoms. Eleven patients experienced one or more delayed peripheral neuropathies; half of these delayed neuropathies resolved or improved.

Peripheral neuropathies are relatively common in burned extremities, resulting either from direct nerve injury or from fibrosis occurring around the nerves. Reflex sympathetic dystrophy is not uncommon. Many patients suffer aches, headaches, chronic pain, and various nonanatomic neurologic complaints for some months after injury.¹⁸⁻²⁰

Cataracts

The incidence of premature cataract development may be as high as 5% to 10% after electrical injury.²¹⁻²³ Surprisingly, cataracts occur equally in patients who have obvious contact points on the face or head and in those who do not. The latent period may range from weeks to years, with the average being 6 months.²³ Therefore, complete ophthalmologic examination for cataracts at the time of hospitalization and, subsequently, with any subjective decrease in visual acuity is warranted. For workers' compensation claims, an eye examination shortly after the injury is indicated to document normal lens transparency in case cataracts occur as an injury-related disease and not from preexisting problems.

Psychological Effects

Posttraumatic stress syndrome is more common after electrical burns than after thermal burns.²⁴ However, general rehabilitation and self-assessed quality of life are comparable after thermal burns and after electrical burns.²⁵

LIGHTNING INJURY

A lightning strike is an extraordinarily high-voltage discharge of brief duration. The current generated may reach 300,000 A and 100 million V. Fortunately, the current often flows around the surface of, rather than through, the body; this "flashover" permits an overall survival rate of 65% or higher.²⁶⁻²⁸ The most common immediate potentially fatal complications are paralysis of the respiratory center and cardiac standstill. Cardiac activity will usually resume spontaneously, but apnea may be present for 15 minutes or longer—long enough to cause anoxic brain injury in the absence of pulmonary resuscitation. A rare but fascinating complication is keraunoparalysis, which is a transient paralysis associated with extreme vasoconstriction and sensory disturbances of one or more extremities. It usually lasts only an hour (in rare instances, as long as 24 hours); a lifeless appearance should not result in the patient's being treated as a victim of sudden death.²⁹ Cardiac and neurologic complications are frequent and are generally similar to those resulting from man-made high-voltage injuries.³⁰ Dendritic superficial skin burns, known as Lichtenberg's flowers or fractals,³¹ are sometimes seen. These superficial burns heal rapidly without sequelae. Ruptured tympanic membranes and vertigo are common accompaniments.^{32,33} Treatment of systemic effects is generally supportive; tissue injuries are treated in the same manner as other high-voltage injuries.

Chemical Burns

GENERAL EMERGENCY CARE

Immediate treatment of chemical burns involves the immediate removal of affected clothing; the burns should then be thoroughly flushed with copious amounts of water at the scene of the accident. The only exception to this is for chemical burns involving dry powder; for such burns, the powder should be brushed from clothing and skin. Chemicals will continue to burn until removed; washing for at least 15 minutes under a stream of running water may limit the overall severity of the burn. No thought should be given to

searching for a specific neutralizing agent. Delay results in deepening of the burn, and neutralizing agents may cause burns themselves; they frequently generate heat while neutralizing the offending agent, adding a thermal burn to the already potentially serious chemical burn.

Chemical burns, usually caused by strong acids or alkalis, are most often the result of industrial accidents, assaults, or the improper use of harsh solvents and drain cleaners. In contrast to a thermal burn, chemical burns cause progressive damage until the chemicals are inactivated by reaction with the tissue or are diluted by being flushed with water. Individual circumstances vary, but acid burns may be more self-limiting than alkali burns. Acid tends to tan the skin, creating an impermeable barrier that limits further penetration of the acid. Alkalis combine with cutaneous lipids to create soap and thereby continue dissolving the skin until they are neutralized. A full-thickness chemical burn may appear deceptively superficial, seeming to cause only a mild brownish discoloration of the skin. The skin may appear to remain intact during the first few days after the burn and only then begin to slough spontaneously. Chemical burns should be considered deep dermal or full-thickness burns until proved otherwise. In general, definitive treatment of these burns is the same as for thermal injuries—shallow burns heal with infection prevention; deep burns are excised and grafted as soon as their depth is determined.

Some chemicals, such as phenol, cause severe systemic effects; others, such as hydrofluoric acid, may cause death from hypocalcemia even after moderate exposure. Unless the characteristics of the chemical are well known, the treating physician is advised to call the local poison control bureau for specifics on treatment.

ALKALIS

Lime (calcium oxide/hydroxide) and sodium or potassium hydroxide are examples of common alkalis used in industry and around the home.

Sodium or potassium hydroxide (drain cleaner) is ingested by children accidentally and by adults attempting suicide. Mouth burns are the tip of the iceberg. Emergency treatment should be directed to the oropharynx and the upper GI tract; description of such treatment is beyond the scope of this chapter. Sodium or potassium hydroxide is also used in assaults, especially in areas where people cannot afford handguns.³⁴ Teen hoodlums sometimes fill water pistols with sodium hydroxide and squirt sleeping homeless people. Contact of concentrated sodium hydroxide with the cornea results in prompt and permanent corneal destruction and blindness. Drain and oven cleaners are also favorite substances of patients who deliberately and repeatedly inflict injury on themselves (Munchausen syndrome).³⁵⁻³⁷

The unwitting homeowner or novice construction worker who does not protect the skin when working with concrete cement (calcium hydroxide) is often surprised at day's end with painful red contact areas on the hands, feet, knees, and forearms. By bedtime, these injuries have become excruciating and require emergency treatment and, frequently, excision and grafting.^{38,39}

Strong alkali burns are invariably deep, though they may seem deceptively shallow at their onset.

ANHYDROUS AMMONIA

Anhydrous ammonia is a colorless, pungent gas that is stored and transported under pressure in liquid form. Ammonia injury is uncommon, but it is associated with high morbidity and mortality. Particularly devastating is severe acute respiratory distress syndrome (ARDS) and long-term restrictive disease with bronchiectasis. Most of the literature consists of case reports, but all empha-

size the severity and long-term sequelae of the respiratory and ocular problems.⁴⁰⁻⁴⁴

ACIDS

As noted (see above), acid burns tend to denature (tan) the skin. Although they may be full-thickness burns, destruction of deeper tissues is often limited as a result of the formation of an impervious carapace of the dermis.

Hydrochloric and Nitric Acids

Hydrochloric and nitric acids are strong acids that denature proteins but usually do not result in systemic poisoning unless inhaled or ingested.

Chromic Acid

Some acids, such as chromic acid and dichromate, cause both systemic and cutaneous problems. Chromium poisoning is characterized by complete anuria, hepatic damage, and progressive anemia. It can occur from the cutaneous absorption of chromium from chromic acid burns that are as small as 1% of TBSA. Aggressive surgical excision and prompt hemodialysis may be lifesaving.⁴⁵⁻⁴⁸

Formic Acid

Similarly, formic acid causes metabolic acidosis, intravascular hemolysis, and hemoglobinuria when ingested or when concentrated solutions contact the skin.^{49,50}

Carbolic Acid

Phenol (carbolic acid) is used as a hospital, industrial, and home disinfectant. Exposure may lead to rapid CNS depression, vomiting, coughing, stridor, and, in rare instances, seizures.⁵¹ The cutaneous burns are usually first degree.

Hydrofluoric Acid

Hydrofluoric acid burns are unique in terms of their presentation and current treatment. Hydrofluoric acid is used in industrial cleaners and rust removers. It is used in concentrated form in the etching of circuit boards and in dilute form as a cleaner for glass and milk cans. Hydrofluoric acid is a very strong acid that coagulates skin and allows entry of fluoride ions, which then chelate calcium and magnesium in tissue and plasma. Local cell death results; with severe exposure, severe systemic hypocalcemia and hypomagnesemia can result in fatal cardiac dysrhythmias.⁵²⁻⁵⁴ Fluoride, as the most electronegative element, tightly binds many cations essential to hemostasis, inhibiting normal blood coagulation. As a metabolic poison, it stimulates some enzymes (e.g., adenylate cyclase) and severely inhibits others (e.g., Na^+ , K^+ -ATPase and the enzymes of carbohydrate metabolism).⁵⁵ Treatment of severe poisoning requires careful monitoring in an ICU, replacement of magnesium and calcium, and consideration of dialysis.

More commonly, industrial exposure is limited to the hand.⁵⁶ Exposure to concentrated solution will cause immediate symptoms, but the more common dilute solutions may not cause symptoms for hours. Often, the worker will go home and experience increasingly severe pain, which will prevent sleep and lead to a nighttime visit to the ED. The worker will likely be unaware of the cause of the pain; the emergency physician should question the patient about solvents used that day.

Conventional treatment of burns to the hand and digits has consisted of local application of calcium liquids and gels. Direct injection of calcium gluconate into the injury site is somewhat

effective but may cause pressure necrosis of fingers that are already swollen. A much better treatment that can yield almost magical results is direct intra-arterial infusion of a dilute calcium gluconate solution through the radial or brachial artery. The sooner the infusion is started after the onset of pain, the better the result. Pain is immediately mitigated if not cured, and tissue destruction is often minimal.^{57,58} This measure has become the treatment of choice in the UW Burn Center and has yielded good results with no complications to date. However, therapy must be started within the first 24 hours; after this point, tissue damage is permanent. An alternative is intravenous infusion of calcium gluconate with the Bier block technique (i.e., a venous tourniquet applied proximal to the infusion site),⁵⁹⁻⁶¹ but this measure can increase swelling in the extremity.

War and Chemicals of Mass Destruction

NAPALM

Napalm is jellied gasoline that is generally ignited and sprayed on material and combatants in wartime. It causes devastating burns because the gasoline sticks to clothing and skin while it is burning. Injuries are usually fourth-degree thermal burns, which are treated in the same manner as other very deep thermal burns.

WHITE PHOSPHORUS

White phosphorus is used in many types of military munitions, as well as in fireworks and in industrial and agricultural products. In the presence of oxygen, it ignites spontaneously; when in contact with skin, it causes deep thermal injuries. It may also give rise to multiple organ dysfunction syndrome (MODS) because of its toxic effects on erythrocytes, the liver, the kidneys, and the heart. Treatment of the injured patient is difficult. The particles must be debrided to prevent continued burning and systemic poisoning. Conventional wisdom was to use a solution of copper sulfate to convert the elemental phosphorus into copper phosphate. However, this approach has fallen into disfavor because copper poisoning may result, the effects of which are often as bad as those of phosphorus poisoning.^{62,63} During debridement in the operating theater, exposure of the particles to air can reignite the phosphorus and thereby endanger the patient and the operating team.

MUSTARD GAS, LEWISITE, AND PHOSGENE

Sulfur mustard is a vesicant that alkylates DNA. In liquid or gas form, its main targets are the skin, the eyes, and the lungs.⁶⁴⁻⁶⁸ Its clinical effects are similar to those of burns, with loss of immunity, respiratory failure, and ophthalmic, gastrointestinal, and hematologic signs. In the Iraq-Iran war (1981–1989), extensive use of chemical weapons such as mustard gas caused injuries with high mortality and morbidity, as well as chronic side effects in vital organs, especially the respiratory tract. In a study that examined long-term effects of mustard gas exposure in 220 survivors, nearly all the victims complained of cough, dyspnea, and suffocation. Hemoptysis was found in six victims. Respiratory distress with use of accessory muscles was observed in four. Two thirds of the subjects had wheezing and coarse rales. Most had obstructive patterns on pulmonary function testing.⁶⁹ Cutaneous exposure is manifested by a delayed erythema of skin occurring after about 4 hours, followed by blistering in 12 to 48 hours. The blisters rupture, leaving shallow, painful ulcers. Other vesicants are more corrosive: lewisite (arsine) and phosgene are both more potent than mustard gas, and symptoms appear sooner with these agents.⁷⁰

Rescuers should be protected with suitable clothing, respirators,

gloves, and boots. The victim's clothing is removed, and extensive water lavage is provided, along with copious isotonic eye irrigation. Once decontamination has been completed, there is no danger to attendants; blister fluid does not contain chemicals.⁷¹ Burns are usually of partial thickness and can be treated in the same manner as other partial-thickness burns.

Cold Injury

Cold injuries limited to digits, extremities, or exposed surfaces are the result of either direct tissue freezing (frostbite) or more chronic exposure to an environment just above freezing (chilblain or pernio; trench foot). Cold injury has been a major cause of morbidity during war, and it is described as being the single major injury sustained by British soldiers in the Falklands expedition. Cold injury resulted in over 7 million soldier fighting days lost by Allied forces in World War II.⁷²

CHILBLAIN, PERNIO, AND TRENCH FOOT

Chilblain and pernio are descriptive terms for a form of local cold injury characterized by red-purple, pruritic skin lesions (papules, macules, plaques, or nodules) that are often associated with edema or blistering. These lesions are caused by a chronic vasculitis of the dermis, and their development appears to be provoked by repeated exposure to cold, though not freezing, temperatures. The injury typically occurs on the face, the anterior tibial surface, or the dorsum of the hands and feet—areas that are poorly protected or are subject to long-term exposure to the environment. With continued exposure, ulcerative or hemorrhagic lesions may appear and progress to scarring, fibrosis, and atrophy. Treatment consists of sheltering the patient, elevating the affected part on sheepskin, and allowing gradual rewarming at room temperature. Rubbing or massage is contraindicated, because further damage and secondary infection may result.⁷³⁻⁷⁵

Trench foot or cold immersion foot (or hand) describes a non-freezing injury of the hands or feet, typically sustained by sailors, fishermen, or soldiers as a consequence of long-term exposure to wet conditions (e.g., water or mud) and temperatures just above freezing.⁷⁶⁻⁸⁰ Alternating arterial vasospasm and vasodilatation appear to occur, with the affected tissue first cold and anesthetic and then becoming hyperemic after 24 to 48 hours of exposure. With the hyperemia comes an intense, painful burning and dysesthesia, as well as tissue damage characterized by edema, blistering, redness, ecchymosis, and ulceration. Complications consisting of local infection and cellulitis, lymphangitis, and gangrene may occur. After 2 to 6 weeks, a posthyperemic phase ensues, resulting in tissue cyanosis with increased sensitivity to cold. Treatment is best started during or before the reactive hyperemia state; it consists of immediate removal of the extremity from the cold, wet environment and exposure of the extremity to warm, dry air. The limb is elevated to minimize edema, pressure spots are protected, and local and systemic measures to combat infection are undertaken. Massage, soaking of the feet, and rapid rewarming are not indicated.

FROSTBITE

Frostbite is a common, severe form of cold injury that involves local freezing of tissues. Frostbite is classified into four grades of severity^{81,82}:

1. First-degree injury involves the freezing of tissue with hyperemia and edema but without blistering.
2. Second-degree frostbite involves the freezing of tissue with hyperemia, edema, and characteristic large, clear blisters.

3. Third-degree frostbite involves the freezing of tissue with the death of subcutaneous tissues and skin, resulting in hemorrhagic vesicles that are generally smaller than those seen in second-degree frostbite.
4. Fourth-degree frostbite is notable for tissue necrosis, gangrene, and, eventually, full-thickness tissue loss.

The degree of severity of frostbite is often not apparent for several days. For all forms of frostbite, the initial presentation is pain or discomfort, as well as pruritus if the injury is mild. With more severe injury, there is a progressive decrease in range of motion, and edema becomes prominent. The injury progresses to numbness and eventual loss of all sensation in the affected tissue. The involved area appears white or blue-white and is firm or even hard (frozen) to the touch. The tissue is cold and insensate. Although the initial symptoms may be mild and may be overlooked by the patient, severe pain, burning, edema, and even necrosis and gangrene may appear with rewarming.

Weather conditions, altitude, degree of protective clothing, duration of exposure, and degree of tissue wetness are all contributing external factors to the development of frostbite. Acclimation to cold may be protective, whereas a previous history of frostbite probably does predispose an individual to another cold tissue injury. Smoking and a history of arterial disease also are contributing factors. In urban environments, more than 50% of frostbite injuries are alcohol related, and a significant percentage (16%) of patients have an underlying psychiatric illness.^{83,84}

Current evidence suggests that frostbite injury may in fact have two components: (1) the initial freeze injury and (2) a reperfusion injury that occurs during rewarming.⁸⁵⁻⁸⁷ The initial response to tissue cooling is vasoconstriction and arteriovenous shunting, relieved intermittently (every 5 to 7 minutes) by vasodilatation. With prolonged exposure, this response fails, and the temperature of the freezing tissue will approximate ambient temperature until a temperature of -2°C is reached. At this point, extracellular ice crystals form; as these crystals enlarge, the osmotic pressure of the interstitium increases, resulting in the movement of intracellular water into the interstitium. Cells begin to shrink and become hyperosmolar, disrupting cellular enzyme function. If freezing is rapid (i.e., if the temperature falls by more than $10^{\circ}\text{C}/\text{min}$), intracellular ice crystal formation will occur, resulting in immediate cell death. Intravascularly, endothelial cell disruption and red cell sludging result in cessation of circulation.⁸⁸⁻⁹¹

During rewarming, red cell, platelet, and leukocyte aggregation is known to occur; this results in patchy thrombosis of the microcirculation.⁹² These accumulated blood elements are thought to release, among other products, the toxic oxygen free radicals and the arachidonic acid metabolites prostaglandin F_2 and thromboxane A_2 , which further aggravate vasoconstriction and platelet and leukocyte aggregation. However, the exact mechanism of tissue destruction and death after freeze injury remains poorly defined. Animal studies suggest that vascular injury, in the form of endothelial cell damage and subsequent interstitial edema (but not vessel thrombosis) is the primary initial event in rewarming injury. It has been demonstrated that a marked amelioration of the frostbite injury can be achieved in a rabbit ear model by treating the animals (after cold injury and before rewarming) with a monoclonal antibody to the neutrophil CD18 glycoprotein complex.⁹³ The implication of this observation is that neutrophil adherence to the endothelium of frostbitten tissue during rewarming (reperfusion) is at least partially responsible for the subsequent tissue injury. Clinical application of these experimental observations remains untested.

TREATMENT

Prehospital or field care of a victim of cold injury should focus on removing the patient from the hostile environment and protecting the injured body part from further damage. Rubbing or exercising the affected tissue does not augment blood flow and risks further cold injury or mechanical trauma. Because repeated bouts of freezing and thawing worsen the injury, it is preferable for the patient with frostbite of the hands or feet to seek definitive shelter and care immediately rather than to rewarm the tissue in the field and risk refreezing. Once rewarming has begun, weight bearing should be avoided.

The ED treatment of a frostbite victim should first focus on the basic ABCs of trauma resuscitation [see 7:1 *Initial Management of Life-Threatening Trauma*] and on identifying and correcting systemic hypothermia. Frostbitten tissue should be immersed in a large water bath of 40° to 42°C (104° to 108°F). The bath should be large enough to prevent rapid loss of heat, and the water temperature should be maintained. This method of rapid rewarming may significantly decrease tissue necrosis caused by full-thickness frostbite.^{88,90,91} Dry heat is not advocated, because it is difficult to regulate and places the patient at risk for a burn injury. The rewarming process should take about 30 to 45 minutes for digits. The affected area appears flushed when rewarming is complete and good circulation has been reestablished. Narcotics are required, because the rewarming process may be quite painful.

The skin should be gently but meticulously cleansed and air-dried, and the affected area should be elevated to minimize edema. A tetanus toxoid booster should be administered as indicated by the immunization history. Sterile cotton should be placed between toes or fingers to prevent skin maceration, and extreme care should be taken to prevent infection and to avoid even the slightest abrasion. Prophylactic antibiotics and dermal blister debridement are both controversial; most clinicians debride blisters and reserve antibiotics for identified infections. A 2005 study reported a lower than expected digit amputation rate when rapid rewarming was followed by treatment with heparin and tissue plasminogen activator (tPA), but to date, this finding has not been confirmed by other studies.⁹⁴

After rewarming, the treatment goals are to prevent further injury while awaiting the demarcation of irreversible tissue destruction. All patients with second- and third-degree frostbite should be hospitalized. The affected tissue should be gently cleansed in a warm (38°C) whirlpool bath once or twice a day; some clinicians add an antiseptic such as chlorhexidine or an iodophor to the bath. On the basis of findings of arachidonic acid metabolites in the blisters of frostbite victims, some authors advocate the use of topical aloe vera (a thromboxane inhibitor) and systemic ibuprofen or aspirin. After resolution of edema, digits should be exercised during the whirlpool bath, and physical therapy should begin. Tobacco, nicotine, and other vasoconstrictive agents must be withheld.

Numerous adjuvants have been suggested and tried in an effort to restore blood supply to frostbitten areas. Because of the intense vasoconstrictive effect of cold injury, attention has been focused for many years on increased sympathetic tone. Sympathetic blockade and even surgical sympathectomy have been advocated as early therapy, the theoretical rationale being that sympathetic blockade should release the vasospasm that may precipitate thrombosis in the affected tissue. Unfortunately, this method of treatment has produced inconsistent results in experimental studies and is difficult to evaluate clinically.^{89,95} Experience with intra-arterial vasodilating drugs such as reserpine and tolazoline has also failed to verify this hypothesis. In a controlled clinical study, immediate (mean, 3 hours) ipsilateral intra-arterial reserpine infusion coupled with early (mean, 3 days) ipsilateral operative sympathectomy failed to

alter the natural history of acute frostbite injury.⁸⁹ Sympathectomy may, however, mollify the chronic pain, hyperhidrosis, and vasospasm of cold injuries; some clinicians also suggest that it reduces the risk of subsequent cold injury. Heparin, low-molecular-weight dextran, thrombolytic agents, and hyperbaric oxygen have failed to demonstrate any substantial treatment benefit (despite the suggestive results of the 2005 study by Twomey and associates⁹⁴).

The difficulty in determining the depth of tissue destruction in cold injury has led to a conservative approach to the care of frostbite injuries. As a general rule, amputation and surgical debridement are delayed for at least 1 month unless severe infection with sepsis occurs. The natural history of a full-thickness frostbite injury leads to the gradual demarcation of the injured area; dry gangrene or mummification clearly delineate nonviable tissue. Often, the permanent tissue loss is much less than originally suspected. In one review, only 39% of urban frostbite victims required debridement and skin grating or amputation.⁸⁴ Emergency surgery is unusual, but during the rewarming phase, vigilance should be maintained to detect the development of a compartment syndrome necessitating fasciotomy. Open amputations are indicated in patients with persistent infection and sepsis that is refractory to debridement and antibiotics.

Frostbitten tissues seldom recover completely. Some degree of cold insensitivity invariably remains. Hyperhidrosis (occurring in as many as 72% of patients), neuropathy, decreased nail and hair growth, and persistent Raynaud phenomenon in the affected part are frequent sequelae of cold injury.⁹⁶ The affected tissue remains at risk for reinjury and should be carefully protected during any cold exposure. Treatment with antiadrenergics (e.g., prazosin hydrochloride, 1 to 2 mg/day) or calcium channel blockers (e.g., nifedipine, 30 to 60 mg/day) and careful protection from further exposure are often helpful. However, there is little that appears to afford significant relief to the chronic symptoms that follow tissue freeze injury; sympathectomy, beta- and alpha-adrenergic blocking agents, calcium channel blockers, topical and systemic steroids, and a host of home remedies have all been tried, with only occasional individual success.⁷⁸

Toxic Epidermal Necrolysis

Toxic epidermal necrolysis (TEN) is a devastating, though (fortunately) rare, exfoliative disease of the skin and mucous membranes that results in full-thickness epidermal necrosis. The first published report of adult TEN appeared in 1956, when Lyell, in Lyon, France, compared four cases to scald burns.⁹⁷ Some authors describe a similar skin sloughing but with lesser involvement, termed the Stevens-Johnson syndrome. In reality, the two diseases are exactly the same: Stevens and Johnson anticipated Lyell by 34 years when they described the same pathology in two children in South Africa.⁹⁸ Dermatologists have long known the disease as erythema multiforme majus exudativum. Thus, even though only one disease process is involved, various names continue to be used: Europeans refer to this condition as Lyell disease, pediatricians call it the Stevens-Johnson syndrome, dermatologists refer to it as erythema multiforme majus, and American surgeons and internists call it TEN.

TEN can be precipitated by the administration of medications, most commonly sulfonamides, antibiotics, and anticonvulsants. It can also be caused by events such as immunizations, systemic diseases, and viral illnesses. Some cases have no known precipitating cause.

The molecular etiology of TEN remains unclear. According to

one theory, certain offending drugs that should be metabolized are instead deposited in the epidermis, leading to an immune response, which causes the body to reject the skin. In 1998, Viard pointed out that keratinocytes normally express the death receptor Fas (CD95); keratinocytes from TEN patients were found to express lytically active Fas ligand (FasL). Antibodies present in pooled human intravenous immunoglobulins (IVIg) blocked Fas-mediated keratinocyte death in vitro. In a pilot study, 10 consecutive individuals with clinically and histologically confirmed TEN were treated with IVIg; disease progression was rapidly reversed, and the outcome was favorable in all cases. The implication was that Fas-FasL interactions were directly involved in the epidermal necrolysis of TEN and that IVIg might be an effective treatment.⁹⁹ This report sparked numerous small clinical series, the results of which have been, at best, inconclusive.¹⁰⁰⁻¹⁰⁴ A 2005 study of the effect of IVIg on ocular complications was unable to demonstrate any benefit.¹⁰⁵ There may be a role for γ -globulin, but current data indicate that it is no miracle cure. Because of the high cost of γ -globulin and its potential for inducing renal damage, we no longer use it to treat TEN at the UW Burn Center.

TEN should be distinguished from a somewhat similar disease, staphylococcal scalded skin syndrome (SSSS). This entity is caused by a bacterial exotoxin, which splits the epidermis above the dermal-epidermal junction. Although patients with SSSS experience severe erythema, the skin exfoliates rather than blisters. SSSS does not involve mucosa, and the patients are in a septic state from the underlying staphylococcal infection. SSSS usually affects newborns, becoming much less common as people get older. This unusual disease is treated with antibiotics directed against staphylococci.¹⁰⁶

The TEN-induced areas of denudation are comparable to those affected by a very shallow second-degree burn. Oropharyngeal, esophageal, anal, urethral, and vaginal^{107,108} mucosal sloughing are also characteristic of TEN. The disease attacks squamous epithelium, so the remainder of the GI tract is usually spared. There is only one case report of intestinal epithelial sloughing.¹⁰⁹ Complications such as infection, malnutrition, negative nitrogen balance, severe wound pain, and MODS are identical to those seen in patients with major burns. The most common causes of death in TEN patients are systemic infection and pneumonia. The potential mortality from TEN is high, but it is reduced by treatments and protocols common in burn centers (e.g., wound coverage with biologic dressings). There is good evidence that patients affected with TEN should be referred early for management in a burn center.¹¹⁰⁻¹¹² The role of the dermatologist is to define the diagnosis and determine the potential cause.

CLINICAL MANIFESTATIONS

A prodrome of TEN usually consists of fever, sore throat, and malaise; 1 to 2 days after these symptoms appear, the skin of the face and extremities usually becomes tender and erythematous. Lesions appear either as large areas of red skin or as target lesions that are about 2 cm in diameter and consist of concentric rings of erythema. At the same time, ulcerations in the lips and mouth appear, making oral intake painful.

In 24 to 96 hours, the involved skin begins to form both small blisters and bullae. Moderate traction of the erythematous skin results in separation of the epidermis from the dermis—a positive Nikolsky sign.¹¹³ When the bullae rupture, large denuded areas of skin become apparent. Fingernails, toenails, and the skin of the palms and soles may also slough.

One hallmark of this disease is severe inflammation of the mouth. Blisters develop on the oral mucosa, leaving a very raw, red

surface. The lips quickly become swollen and crusted with clotted blood. The oral lesions may be confined to the oral cavity or may extend to the larynx or even to the trachea and the esophagus. The patient is usually unable to eat. The eyelids swell as conjunctival inflammation develops. Conjunctival infection, usually caused by *Staphylococcus aureus*, may lead to scarring and permanent blindness.¹¹⁴ The nasal and urethral mucosa may also become inflamed, and erosions can develop on the genital and perianal skin.

Renal failure can occur as a result of hypovolemia, the septic response, or membranous glomerulonephritis. In as many as 50% of cases, there are abnormalities in liver enzymes, including modest increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Bilirubin levels often show modest to severe increases.¹¹⁵ The mechanism of these increases, which appear to be a part of the toxic component of TEN, is unknown.

TREATMENT

The initial focus of treatment is on restoration and maintenance of cardiopulmonary stability. Because TEN does not induce the intense cytokine reaction that is associated with similar-sized burns, massive anasarca is unusual; resuscitation need not proceed in the manner recommended for burns. Maintenance of normal vital signs and adequate urinary output (0.5 ml/kg) is satisfactory. Because of the high incidence of catheter infection in the absence of epidermis, use of Swan-Ganz catheters is usually avoided when possible.¹¹⁶

Treatment involves aggressive wound management, similar to that of a massive second-degree burn, in which the emphasis is on optimizing healing and controlling infection. A crucial feature of TEN is an intact and uninjured dermis, which, if protected, rapidly reepithelializes from sweat glands and hair follicles, which appear to remain intact. Treatment must, therefore, protect the dermis from desiccation and infection. Routine use of ointments and salves not only creates intense pain but also increases the risk of the formation of a “pseudo eschar” of crusts and devitalized dermis that impairs wound healing.

Biologic or manufactured covers have formed an important role in wound treatment.^{111,117,118} Emergency operative wound cleansing and application of commercially available pigskin (porcine xenograft) has been the standard of care at the University of Washington Burn Center in more than 130 cases. The pigskin is stapled in place, the patient is treated for several days in a fluidized bed, and the pigskin is removed as the denuded areas heal. The pigskin is relatively inexpensive, adheres well, is nontoxic, and probably provides some growth factors to hasten healing. With this management plan and meticulous systemic care, mortality at the UW Burn Center has been below 20% for the past 15 years.¹¹⁹ Alternative covers include Acticoat¹²⁰ (Smith & Nephew, London, United Kingdom) and Biobrane¹²¹⁻¹²⁴ (Mylan Laboratories, Canonsburg, Pennsylvania), which follow the same principle of dermal protection to permit uninfected healing.

In addition, associated physiologic and psychological care must be meticulous. Lung function is often impaired as a result of the aspiration of secretions from involved oral mucosa and a reduction in the clearance of secretions as a result of oral pain and overall weakness. Pain control and aggressive pulmonary toilet to assist the patient's cough are the first line of defense. Suctioning can lead to significant bleeding and should be used either sparingly or only after an endotracheal tube is in place. The patient should be intubated if lung function is progressively impaired. If the patient is intubated, partial ventilatory assistance is often required because chest wall pain, systemic toxicity, and weakness can severely impair spontaneous ventilatory efforts.

Cardiovascular function is initially impaired as a result of hypovolemia caused by plasma leaking from the blisters, increased skin evaporative losses, and decreased oral intake. Controlling the febrile response will also help decrease fluid losses, vasodilatation, and the resulting hyperadrenergic response. Careful use of NSAIDs is often necessary to keep the patient's temperature below 102° F (38.9° C). Adequate pain control is essential. Methadone is effective for long-acting pain control, and morphine is a good choice for procedural pain.

Aggressive oral care is critical because of the high risk of local mouth infection and consequent wound and lung infection. Early and continued assessment and aggressive management of corneal involvement are required. Administration of ophthalmic antibiotic ointments and gentle breaking of adhesions between conjunctiva and eyelids with a small glass rod are the standard treatment.¹²⁵

OPTIMIZING NUTRITION

Nutrition is a major component of care, and it often cannot be delivered orally because of oral lesions. A small gastric feeding tube is preferred, as the GI tract between stomach and anus is usually intact and is normally functional.¹²⁶ In general, standard tube-feeding formulas for an individual under moderate stress are sufficient because the full ravages of postburn hypermetabolism are probably not present. When sepsis is avoided, it is very unusual for the gut to fail and for intravenous parenteral nutrition to be needed.

The role of corticosteroids in the treatment of TEN remains unclear. Although some patients who were receiving steroids before the development of TEN still get severe disease,¹²⁷ a number of dermatologists feel that the administration of steroids when the disease process is just beginning, before skin sloughing occurs, can attenuate the process and thereby reduce subsequent sloughing. However, once vesicles have formed and the separation has occurred, corticosteroids no longer effectively attenuate skin sloughing; in fact, the use of corticosteroids retards the rate of healing. In one study, the complication rate was found to be higher in patients who received steroids.¹²⁸ This study, however, did not take into account the patients whose disease might have been sufficiently limited by steroid use to make burn center treatment unnecessary.

FOLLOW-UP CARE

Fortunately, when treatment is successful, the disease usually resolves without hypertrophic scarring, though some mismatching of epidermal pigmentation may be evident. Nails may remain deformed, and eyes are usually dry, requiring periodic lubrication. Obviously, patients must not again contact the medication that caused the disease; for common medications, a Medic Alert bracelet is useful.

Ionizing Radiation Burns

The burn surgeon may encounter ionizing radiation injuries in three settings. Of these, by far the most common involves deliberate exposure to radiation (i.e., radiation used in treatment) or accidental radiation in a hospital, a laboratory, or an industrial complex. In such settings, a single individual is likely to be injured. The second scenario involves failure of a nuclear energy plant, such as occurred at Chernobyl; in this scenario, dozens to hundreds of exposures may occur. The third setting is that resulting from a nuclear explosion through military or terrorist action. In such a scenario, thousands of casualties will immediately overwhelm all resources.

LOCALIZED INJURY

A gray (Gy) is the current unit of radiation, defined as 1 joule (J) of energy deposited in 1 kg of tissue; 1 Gy is the equivalent of 100 rads.

Localized injury is produced by local irradiation of a small area; no systemic effects are produced. As with thermal burns, the degree of injury is dependent on the type of radiation encountered, the radiation dose delivered, and the susceptibility of the tissue. An initial erythema appears within minutes or hours of exposure and subsides over 2 to 3 days. Secondary erythema occurs 1 to 3 weeks after exposure and is associated with hair loss and desquamation of the epidermis. At about 3 weeks, blisters (after doses of about 20 Gy) or ulcerations (after doses in excess of 25 Gy) may occur. Ulceration may recur months to years after injury. Blood vessels become telangiectatic, and deeper vessels become occluded, leading to fibrosis, atrophy, and necrosis.¹²⁹

Wounds are generally treated in a manner similar to the treatment of thermal burns, with the additional caveat that radiation sickness is accompanied by immunosuppression, and that endarteritis obliterans will markedly diminish the blood supply. Infection is common, and the optimal timing of excision and grafting of deep ulcers is not known.

WHOLE-BODY IRRADIATION AND RADIATION SICKNESS

A detailed description of whole-body radiation exposure and its treatment is beyond the scope of this chapter. Radiation sickness, also known as the acute radiation syndrome, may begin within hours of exposure. It is initially characterized by nausea, vomiting, diarrhea, and lethargy; this is followed by the hematopoietic syndrome (neutropenia and thrombocytopenia) and the gastrointestinal syndrome (severe diarrhea, bowel ischemia, bacterial translocation, and sepsis).¹³⁰ Treatment is mainly supportive.

A nuclear explosion is characterized by a supersonic blast, a fireball extending miles from the epicenter, and immense amounts of ionizing radiation. These three components interact, causing severe mechanical injury, flash and flame burns from the ignition of clothing, and, of course, severe radiation exposure.¹³¹ The flash has been described as being so intense that the side of a victim facing the flash will be charred to bone while the opposite side is unburned. Doctors in Hiroshima after the atomic bombing there observed that for a time, thermal burns appeared to be healing, but in the second and third weeks, the wounds broke down and infection set in as the acute radiation syndrome became manifest.

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17 REHABILITATION OF THE BURN PATIENT

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Of all of the different processes that a burn patient undergoes, rehabilitation is the longest: it begins on the day of the injury and never really ends. As burn patients survive larger, more debilitating burns, the measure of success and the goal of quality burn care are the return of injured patients to a level of function they had prior to injury. Highly trained and knowledgeable physical and occupational therapists, under the direction of rehabilitation physiatrists, are needed to deliver this care to achieve high-quality functional and cosmetic results.

The specific objectives of a rehabilitation program change throughout the patient's course. In the early stages, the program focuses on return to baseline cardiopulmonary status and avoiding musculoskeletal dysfunction. The later stages of rehabilitation focus on return to baseline function, return to work or school, and adjustment to possible aesthetic and psychological changes. This changing focus emphasizes the need for an integrated team approach. Determining the qualifications and capabilities of rehabilitation programs for burn patients, as well as other injury and neurologic disorders, is the Commission on Accreditation of Rehabilitation Facilities (CARF). This independent, not-for-profit organization will review and grant accreditation on the request of the facility. CARF-accredited programs and services have demonstrated that they meet internationally recognized standards and have made a commitment to continually enhance the quality of their services and programs. More information and a complete list of accredited providers can be found on the CARF Web site, <http://www.carf.org>.

A national agenda for addressing rehabilitation and recovery is spearheaded by the National Institute on Disability and Rehabilitation Research (NIDRR). Created in 1978, NIDRR is a national leader in sponsoring research. NIDRR is located in Washington, DC, and is one of the three components of the Office of Special Education and Rehabilitative Services at the US Department of Education. NIDRR operates in concert with the Rehabilitation Services Administration and the Office of Special Education Programs. Its mission is to generate, disseminate, and promote new knowledge to improve options available to disabled persons. The ultimate goal is to return individuals to integrated members of their community. NIDRR supported 294 projects in 2008 with a budget of \$89 million.¹ NIDRR funds projects to advance knowledge in burn rehabilitation by providing grants to national centers of excellence. More information can be

found at the Web site <http://www.ed.gov/rschstat/research/pubs/index.html>.

Quality of Life after Burn Injury

The improvement in the acute care of patients who sustain a massive burn injury has been one of the major advances in trauma care over the last 20 years. Prior to 1970, a person sustaining a burn covering more than 30% of the body surface nearly always died. Today, only about 12% of those with a 30% total body surface area burn die.²

It is not surprising that patients with larger injuries require longer hospital stays, incur more expenses, and usually require years of rehabilitation to attempt to regain their level of function prior to the injury. This leads to the question of whether a person who sustains a massive burn injury, and who may suffer irreparable loss of function, has good quality of life after recovery. Unfortunately, few data compare the perceived quality of life of severely burned individuals with that of unburned healthy individuals.³

A massive burn injury has both physical and psychological consequences. The physical consequences include pain, itching, and loss of function. The psychological consequences include but are not limited to depression, anxiety, loss of self-esteem, and inability to socialize. The Burn Specific Health Scale was developed in 1982 in an attempt to quantitate and evaluate quality of life for all burn survivors.⁴ This 114-item inquiry was shortened to an 80-item questionnaire in 1987⁵ and again revised in 1992 and became the Revised Burn Specific Health Scale (BSHS-R),⁶ which measures seven domains: simple functional abilities, work, body image, interpersonal relationships, affect, heat sensitivity, and treatment regimens. The BSHS-R is a valid and reliable outcome scale for those patients with burn injuries. It has also been translated into Finnish and Spanish and has been proven reliable and valid in those languages also. A portion of the BSHS-R is shown in Table 1 to demonstrate the types of questions asked. The results of the BSHS-R give a clinician an idea of how an individual patient is affected by the injury and where to focus therapy and treatment. Follow-up evaluations can be used to quantify improvements in quality of life. This was shown in a study by Cromes and colleagues, in which they analyzed 110 burn-injured patients with the BSHS.⁷ Patients had an improved quality of life when there was reduced overall stress and lower level of pain. Patients at 6 months from injury had an improved physical quality of life than at 2 months.

Table 1 Selected Items from the Revised Burn Specific Health Scale ⁶
Heat Sensitivity
Being out in the sun bothers me
Hot weather bothers me
I can't get out and do things in hot weather
It bothers me that I can't get out in the sun
My skin is more sensitive than before
Work
My burn interferes with my work
Being burned has affected my ability to work
My burn has caused problems with my working
Working in your old job performing old duties

Response format: 0 = extreme(ly); 1 = quite a bit; 2 = moderate(ly); 3 = a little bit; 4 = none (not at all).

Less than 50% of patients who suffer a major burn injury return to the same job with the same employer without accommodations.⁸ Given that most health insurance is connected with employment, prolonged time off work can cause significant hardship to patients and their families. There are few data on the factors that influence return to work after burn injury. This information could have a positive impact on quality of life after injury.

Quality of life remains difficult to measure. Several studies have demonstrated that burn survivors are able to return to their preinjury functional status after their injuries.^{3,7,9,10} Freedom from emotional and physical distress and being involved in preburn activities positively affect recovery after injury.^{7,11} Other factors affecting positive outcome include comprehensive multidisciplinary aftercare¹⁰ and supportive and healthy family dynamics.⁹

Components of Rehabilitation

EXERCISE AND AMBULATION

The underlying principle of the recovery of the burn patient is return to normal function. Through exercise, the patient can try to maintain normal activity from admission and beyond. It takes proper patient education and understanding of the importance of exercise to get through the long and typically painful process of rehabilitation. The goals of exercise are to reduce the effects of edema, maintain range of motion, stretch the eschar and scar, and return the patient to an optimal level of function.¹²

Scar is the limiting factor for proper range of motion. As burns or grafted areas heal, some scar is always made. They can form bands of fibrous tissue that cross joints, and if left untreated, this can lead to irreversible loss of range of motion and joint dysfunction. Range of motion of all joints should be monitored on a daily basis, starting on admission, so that attention can be directed to those joints at risk. Trained therapists are needed to properly instruct the patient about exercise methods unique to each patient and level of understanding.

Range of motion exercises should begin on the day of admission. Patients with large burns may be incapacitated and unable to participate in the exercises. Passive stretching of all extremities should occur during times when the patient cannot perform the activity. Ideally, this is done twice a day on all joints



Figure 1 Range of motion exercises being done on the hand.

of the upper and lower extremities [see Figure 1]. Care needs to be taken on especially painful and newly grafted areas.

Coordination with administration of pain control medications is optimal. Patients frequently undergo general anesthesia for excision and grafting multiple times during the early post-burn period. This is a good time to evaluate the patient for range of motion limitations as pain will not hinder the activity. As the patient begins to participate, the therapist can begin passive resistance exercises. This will be the beginning of strength training, in which the amount of resistance is increased until the patient returns to his or her preinjury state.

Patients will assume a position of comfort while at rest. Burns and burn scars lead to contractures, and the skin that overlies joints is at the highest risk for loss of function.¹³ A patient with full range of motion may lose a great deal of range overnight.

Patients with large burns are immobilized for a long period of time because of their critical illness. This can range from only a few days to several weeks. The benefits of early mobilization are well established, but it cannot occur in critically ill patients. When a patient has improved such that mobilization is possible, it usually takes maximal assistance to perform this task [see Figure 2]. Factors such as severe weakness, impaired motor control, and decreased cognitive status are to blame. Several bed rest studies have identified that the antigravity muscles of the lower extremities are the first muscles to weaken during periods of inactivity.¹⁴ A tilt table can be a bridge to ambulation by allowing a patient to perform a weight-bearing exercise in a gravity-reduced environment.¹⁵

The benefits of early ambulation are to help maintain range of motion, maintain strength in the lower extremities, and prevent thromboemboli.¹² Ambulation is also known to maintain bone density and promote functional independence.¹² It is important to have all wounds properly dressed and lower extremity wounds supported with elastic wraps. Wrapping the gravity-dependent areas can decrease edema and thus minimize pain during periods of ambulation.

An aggressive exercise program has also been shown to improve the pulmonary function in severely burned children,¹⁶ reduce the need for scar release after burn,¹⁷ and improve muscle strength, power, and lean body mass.¹⁶



Figure 2 Patients who have sustained major burn injuries typically cannot be mobilized for days to weeks after their injury. Even when they have improved sufficiently to permit mobilization, they usually require considerable assistance.

The patient should be kept well informed of the progress made during exercise and ambulation session. Prior to starting any intervention, the goals of each session should be outlined and the patient informed that the goals will be advanced at each session. Many patients do well when there is a visual goal, such as walking to a specific location. The use of a toy or game can sometimes help younger patients reach the desired goal.

Many clinicians discontinue range of motion exercises and ambulation for 3 to 14 days after autografting to minimize graft trauma. It is my practice to begin range of motion exercises of grafted hands and faces at 5 days and at 7 days after grafting for other areas. One must remember to weigh the risks of graft loss with the possible loss of function when ordering a period of inactivity.

PRESSURE GARMENTS

The use of pressure garments in grafted burns or those that take longer than 14 days to heal is considered standard of care in most burn care centers despite literature that questions the efficacy and pressure delivered.^{18,19} The proponents of the use of pressure advocate its use to aid in the reduction of hypertrophic scarring by reducing blood flow and oxygen delivery, which leads to a reduction in the collagen deposition in the healing wound. This allows a balance in the production and breakdown of collagen and leads to a flatter scar.²⁰ Clinical studies do not find the same result and have shown that pressure garments do not alter wound maturation time.¹⁹ Patients have very poor compliance with the use of pressure garments,^{21,22} and medical insurance coverage for the cost of the garments is often lacking.²³

Those that use pressure garments for the treatment of burns scars and tissue edema follow this simple plan. If a burn heals in less than 14 days, pressure is not used. With burns that take 14 to 21 days to heal, the use is limited to those wounds that begin to show signs of hypertrophy. Pressure therapy is always used in grafted burns and those that take longer than 21 days to heal. Pressure garments deliver pressure from 10 to 40 mm Hg.

The optimal pressure is recommended to be around 25 mm Hg to oppose the capillary pressure.²⁴

Pressure garments come in many colors and are custom-made for every patient for use on any part of the body. They should be worn 23 hours a day and are quite durable, lasting about 3 months. When the garments no longer feel tight to the patient, they should be replaced. The garments conform to body movements and can be worn during therapy or other activities.

SILICONE

Another treatment for burn-related scarring is topical application of silicone. Silicones are entirely synthetic polymers based on a dimethyl siloxane monomer. The most common example is polydimethyl siloxane. Silicone fluids, gels, and elastomers have been used in burn wound care. Elastomer sheets are the most commonly used today.²⁵ They easily conform to the patient and can be used in conjunction with pressure garments or alone. Silicones are not thought to apply pressure to the wound but are thought to increase the wound temperature, which changes the oxygen tension to diminish scarring.²⁶ Another thought is that the silicone provides a water barrier that allows the scar to remain hydrated, which decreases blood flow, thereby reducing collagen deposition and scar hypertrophy.²⁷

Much information is known about the effect of silicone, but as with pressure garments, there are no randomized controlled trials that prove that these therapies minimize hypertrophic scarring.

SPLINTING

Splinting can be used as an adjunct to range of motion therapy throughout all phases of burn care. Splints are also used postoperatively to protect newly placed autografts. The reason for splinting is to oppose the contracting force of the healing burn and not compromise positive functional outcomes. There are many ready-made splints, but most therapists mold splints to each individual patient. This allows changes to be made as the needs of the patient change. In each case, the overall medical status of the patient and any associated injuries must be included in the decision process.

When splinting is applied, there are general recommendations to follow for how to position the patient for each area of the body. The neck is splinted in extension; the arms are externally rotated, abducted, and supinated; the trunk is straight; the hip and knee are in neutral rotation and straight; and the feet are in dorsiflexion. Each patient may have slightly different needs, but this overall plan should be followed.

Along with passive splints, the use of continuous passive motion devices can provide an additional therapeutic option to increase the range of motion of certain joints.

Regardless of the specific therapy applied, the goal is to bring about the best functional outcome at the completion of therapy. There are several principles one needs to follow when designing a splint, and these are listed in Table 2. All devices should not cause pain and need to be easily applied and removed. They also need to be lightweight and allow for adequate ventilation to avoid skin breakdown.

PAIN CONTROL

Although quantifying pain is difficult, a burn injury is most likely the most painful trauma a person can sustain. Proper treatment of a burn requires daily wound care,

Table 2 Purpose of General Splinting Design ¹²
Allows for edema reduction
Maintains joint alignment
Supports, protects, and immobilizes joints
Maintains and/or increases joint range of motion
Maintains tissue elongation
Remodels joint and tendon adhesions
Promotes wound healing
Relieves pressure points
Protects newly placed grafts
Does not disallow dysfunction of nonsplinted joints
Counteracts gravity to assist in functional activity
Strengthens weak muscles

exercise, and ambulation, all of which are painful. This is followed by months of rehabilitation, which often makes patients feel that their pain is unending. All patients have different thresholds for pain and different abilities to cope with their pain and long-term rehabilitation. Poor pain control can lead to a patients' inability to complete required tasks during therapy.

A generalized treatment plan for pain follows a structured approach that is unique to each burn patient. The plan needs to cover the three types of pain: background pain, breakthrough pain, and procedural pain. This plan should employ the use of narcotics and anxiolytics as needed but also include nonpharmacologic therapies. The plan also needs to be flexible and conform to the changing needs of the patient. Each institution needs to develop a guideline-based approach to pain control, such as the one listed in Table 3.²⁸ The American Burn Association has published guidelines for the management of pain.²⁹

Opioid agonists are the cornerstones of the treatment of burn-related pain. They provide flexibility through variable routes of administration, doses, and durations of action. Nonsteroidal anti inflammatory agents and acetaminophen have few indications in the acute setting but are very useful throughout the rehabilitation period.

There have been many nonpharmacologic adjuncts to pain control studied for use during the acute phase of burn care, including hypnosis, virtual reality, and cognitive interventions. Each has been proven beneficial, but there are few data on their use in the rehabilitation and recovery phases. One could surmise that learned pain management techniques, such as distraction and relaxation, would assist patients throughout their entire course of therapy.

Table 3 Guideline-Based Approach to Pain Control in Burn Patients ²⁸
Promise attentive patient care
Chart and display assessment of pain and pain relief
Define pain and relief levels to trigger a review
Survey patient satisfaction
Monitor treatment efficacy

Satisfactory pain control is not always achieved, but each institution should develop treatment plans that include opioids, anxiolytics, and nonpharmacologic therapies in the management of burn patients.

WEIGHT GAIN AND RECOVERY

Severe catabolism and loss of lean body mass is a well-recognized complication of major burn injury. Thirty percent of the calories burned during the hypermetabolic state are from muscle. Weight loss of one pound per day has been described.³⁰ Continued loss of lean body mass can lead to further complications from depressed immune function, increased rates of pneumonia, and decreased rates of wound healing.³¹

The mainstay of treatment is avoidance of weight loss with a diet high in calories and proteins. A typical daily intake ranges from 30 to 35 cal/kg/day with 1.8 to 2 g/kg/day of protein. Close monitoring of daily intake of nutrition and daily weight measurements is necessary. A dietitian with specialty training in the nutritional needs of burn patients can provide daily monitoring and be a great asset to the burn care team.

In no other disease or trauma is the hypermetabolic response as severe as it is following a burn injury. A person with a 40% total body surface area burn may have metabolic requirements twice normal.³² This response begins on post-burn day 5 and continues up to nearly 1 year postburn.³³ Severe catabolism in a burn patient is the result of increased catabolic hormones, decreased anabolic hormones, and direct cell injury from inflammatory mediators.^{34–36} Oxandrolone, an anabolic steroid and testosterone analogue, when used in cooperation with an aggressive exercise program and appropriate nutrition, can increase the rate of weight gain,³¹ and its use is not age dependent in adults.³⁷ These positive effects have not yet been shown in children.

SPEECH THERAPY

Speech pathologists form another important component of the multidisciplinary burn care team. They bring special skills in the early clinical evaluation and management of dysphagia. They can also evaluate the efficacy of the pharyngeal phase of swallowing to determine the adequacy of airway protection.³⁸ Their skills should also be used in the stretching and muscle strengthening of the facial and oral musculature.³⁹

Dysphagia is the inability of a patient to accept and safely transport food and liquid from the mouth to the stomach. It is a consistent and prominent impairment associated with all types of burn injuries.⁴⁰ Patients with larger burns may also require prolonged mechanical ventilation; in this case, the initial dysphagia assessment is delayed until extubation. A recent retrospective review found the initial assessment to be on postburn day 20 and first safe oral intake to be around postburn day 30, and 90% of patients were able to safely tolerate a regular diet at discharge.⁴¹

SKIN CARE

Chapping

Grafted and healed burn skin is not as durable as noninjured skin. The injury itself depletes the skin of its native ability to remain moisturized, which increases the likelihood of chapped skin. Liberal use of skin moisturizing products that contain lanolin can help keep the skin moisturized and

prevent dry, cracked, and easily injured skin. Itching may also be lessened with the use of moisturizers and thus decrease the likelihood of trauma caused by scratching.

Hyperpigmentation

Healed and grafted burns are also at risk for hyperpigmentation if exposed to direct sunlight during the postinjury inflammatory phase, which may last up to 2 years after a burn.⁴² Sunblock should be used at all times during sun exposure, in combination with appropriate clothing coverage. The use of clothing alone as sunblock is not sufficient as a significant amount of ultraviolet light penetrates clothing and can lead to skin damage.⁴³

Itching

Patients recovering from burn injuries can suffer severe discomfort caused by itching. Itching does not stop when the wound is closed but continues throughout the healing process. Histamine released during the inflammatory phase of wound healing and during the prolonged phase of collagen deposition is thought to be the main cause of itching, but stress and opioid medications have also been implicated.

A number of studies have been done to identify the treatment for itching. These have included antihistamine medication, skin moisturizers, distraction therapy, special bath oils, and low-dose antibiotics. None of these treatments alone or in combination have been shown to be effective.

There may be a light at the end of the tunnel. Two topical creams have promising preliminary data to support their use for burn itch. Topical 5% doxepin cream, applied three times a day to healed burns wounds, significantly decreased burn itch compared with oral antihistamines.⁴⁴ Also, topical dapson gel, applied one to four times a day, was shown in a pilot study to significantly reduce itching in 84% of the patients.⁴⁵ Dapsone is now in phase II trials with, it is hoped, more promising results to follow.

MASSAGE THERAPY

Massage has been a part of burn care for the past 400 years.⁴⁶ There are, however, few randomized controlled data to suggest its effectiveness for the reduction of burn scars. One thorough study suggests no difference in scarring when comparing a group receiving scar massage to a control group,⁴⁷ but even the authors admitted that a 10-minute treatment may not be long enough. Massage has been shown to be an effective adjunct to burn treatment and rehabilitation by decreasing itching,⁴⁸ pain,⁴⁸⁻⁵⁰ anxiety,⁴⁸⁻⁵⁰ anger,⁵⁰ and depression.^{48,50}

BODY TEMPERATURE REGULATION

The core body temperature is regulated through changes in cutaneous blood flow and through the dissipation of heat by the evaporation of sweat. A full-thickness burn destroys the dermis and the elements that are the basis of temperature regulation. The body can compensate for this through excessive sweating in the nonburned areas of the body, but this is thought to be limited to those with a burn that covers < 40% of the patient's total body surface area.⁵¹ New data suggest that patients with larger burns can compensate for this with improved cardiovascular fitness.⁵² Healed and grafted burns have less cutaneous blood flow and the inability for vasodilation to allow effective conductive heat loss.^{51,53} Sweat in these

areas cannot aid in evaporative heat loss because of an isolation effect of the hypovascularized area.⁵⁴ Patients exercising in hot and humid climates will have the greatest difficulty maintaining their thermoequilibrium because of the inability of effective evaporative and conductive heat loss.

The control of the ambient temperature is most concerning during the acute phase of burn care and in the operating room [see 7:15 *Management of the Burn Wound*]. In my experience, burn patients in the rehabilitation phase are not uniform in their tolerance to heat and cold. Some require more clothing to tolerate the cold, whereas others have the same exercise tolerance after their burn. I also know of one burn patient whose temperature tolerance changed so drastically that he moved to a snow belt state to get away from the heat and another who moved from a snow belt state to get away from the cold.

When patient temperature tolerance negatively affects burn rehabilitation efforts, the ambient environment needs to be changed to meet the individual patient needs.

Hypertrophic Scar

The formation of hypertrophic scars is considered common after a burn injury; surprisingly, there are few published data on the prevalence of hypertrophic scar after burn injury.⁵⁵ Estimates vary from 4% in burns that heal spontaneously⁵⁶ to 75% in grafted areas.⁵⁷ Injured skin heals through scar formation in an attempt to quickly return the protective covering to the injured area. During this attempt to form the new covering, new connective tissue is created; this gives the scar strength. When scar formation becomes extensive, it leads to a hypertrophic scar. The reason why scar is formed as opposed to regeneration of original tissues is not known.

A hypertrophic scar is a raised, erythematous, pruritic, and inelastic mass of tissue that is the result of a large amount of extracellular matrix of altered composition and organization compared with normal dermis. Microscopically, there is a whorl-like pattern of collagen, abundance of immature connective tissue, and prolonged chronic inflammatory reaction.⁵⁸ The extracellular matrix is composed of a multitude of cell types that are maintained in a hyperactive state by inflammatory mediators. Eventually, all hypertrophic scars undergo some spontaneous resolution, but it is unpredictable.

Contraction of a wound is a normal and necessary part of wound healing. Contraction is the result of long-term shrinkage of a scar. This abnormal process of wound healing can continue indefinitely. The uncontrolled progression of a contracture can lead to a loss of function in that area. Contracture will continue until it achieves a comfortable position or meets an equal opposing force.⁵⁹

One way to possibly reduce hypertrophic scar and contracture is to minimize the time that wound contraction takes place. Early excision and grafting has been shown to reduce the amount and intensity of inflammation⁶⁰ and the development of hypertrophic scarring by shortening the time the wound is in the inflammatory phase.⁶¹ When grafting a wound, it is best to use an adequate amount of tissue to cover all of the wound edges and use sheet grafts whenever possible.⁶⁰ A full-thickness skin graft will lead to less skin contraction during the healing process than a split-thickness graft. The thinner the split-thickness graft, the more contraction will occur.

The treatment options for hypertrophic scar include aggressive range of motion therapy and surgical excision. When therapy to stretch the scar fails and a lifestyle-limiting contracture develops, surgical excision may become necessary. Many times, the scar is excised and the defect is covered with another skin graft. The scar can also be excised and the wound closed primarily if there is enough tissue to cover the wound with a tension-free closure. Corticosteroid injection into the postsurgical wound after scar excision has been studied, with a reduction of scars in 30 to 100%.⁶² No randomized prospective trials have studied the use of corticosteroid injections, but the initial results seem promising.

Heterotopic Ossification

Heterotopic ossification (HO) is a condition in which mature lamellar bone is laid down in tissues that do not usually ossify. This was first described in the early 20th century and usually occurs in medical conditions with poor prognoses. As the survival rate of patients with major burns increases, so does the incidence of HO, about 3% overall.⁶³ The most common site of HO is in joints underlying areas of full-thickness burns in patients with burns that cover greater than 20% of their total body surface area,⁶³ but HO can occur anywhere. It more likely occurs in the upper extremities, with the elbow most frequently involved.⁶⁴

Treatment techniques that contribute to the successful surgical and medical management of this condition are as unclear as the factors that influence the development of HO. Outcomes of surgical treatment remain less than optimal. The medical treatment of HO incorporates the use of steroids and nonsteroidal anti inflammatory medications for prophylaxis and treatment.⁶⁵ Even though etidronate, an inhibitor of osteoclast bone resorption, has been effective in reducing HO that developed after spinal column⁶⁶ and hip injuries,⁶⁷ it should not be used to treat HO acutely⁶⁸ and should not be used to prevent HO in thermally injured patients.⁶⁹ All treatment modalities remain controversial.

Psychological Support

A burn injury can be the most aesthetically devastating of any traumatic event. With society's emphasis on youth and beauty, a burn injury can be socially incapacitating. Patients with burn injuries lose control of their life on arrival at the burn center. Every moment of every day is planned for them with necessary therapy, wound care, nutritional supplementation, and operations, for an indeterminate amount of time.

Previous psychiatric diagnoses have been shown to both increase mortality and prolong length of stay.⁷⁰ Preexisting psychological disorders can be exacerbated during rehabilitation. Any previous psychiatric diagnosis needs early and effective intervention in the acute phase of burn care. The clinician, pharmacist, and psychiatrist must have an understanding of burn physiology and burn pharmacokinetics to ensure that an effective medical treatment plan is established.

Depression, anxiety, and guilt are symptoms that will often arise during the early course of rehabilitation. Posttraumatic stress disorder (PTSD) can arise during the hospital phase of burn care, and the incidence can be up to 43%. Alteration of the patient's self-image is thought to be the most common

predisposing factor for the development of PTSD. Other factors include poor pain control and associated physical impairments. PTSD may develop only after hospital discharge, and it is difficult to identify patients at risk.⁷¹ Therefore, it is imperative for clinicians to provide education and psychological intervention to all patients during the hospital course and aggressive follow-up after discharge.

The most effective way to attempt to treat PTSD is to try to minimize its occurrence. This includes effective pain and anxiety control, and, as stated above, opioids are the cornerstone of effective pain control. The addition of benzodiazepines can be a great asset to pain control, but the withdrawal from these medications can produce symptoms similar to PTSD. This, however, should not dissuade their use. Nearly every psychotropic medication has been tried as treatment of PTSD, with no one medication showing better efficacy than another.

Psychological problems are identified in a significant number of burn patients. Premorbid psychological problems can be exacerbated, and others can develop significant problems without risk factors. Effective treatment includes psychological debriefing, use of appropriate pharmacologic interventions, exposure therapy, and desensitization.⁷² It is important to include psychiatric services as soon as the need arises so that early and effective interventions can support the patient through this traumatic event.

Neurologic Complications

Peripheral neuropathy is a well-known complication after a major burn injury, but its incidence is unknown. When first described in 1971, the incidence was reported to be 15% in the 249 burn patients studied.⁷³ There have been multiple studies since then, reporting incidence rates of 2 to 84%.⁷⁴⁻⁷⁸ All reported correlation with increased length of stay, increased total body surface area burned, and electrical injury.

A more recent retrospective review of cross-sectional data from 572 patients with major burn injury found an incidence of 11%. Those more likely to develop peripheral neuropathy were those with greater than 15% total body surface area burns, greater than 20 days in the intensive care unit, and electrical injuries.⁷⁹

The exact mediator of this complication is not known. It is important for all patients, especially ones with the above risk factors, to receive comprehensive neurologic examinations to diagnose this complication. Limiting the progression and possible prevention of this devastating complication are possible with specific attention to the following areas: avoiding compartment syndrome, proper patient positioning to avoid nerve compression, limiting tourniquet times, and avoiding prolonged compressive dressings.

Special Considerations after Electrical Injuries

Even though electrical injuries account for only 7% of admissions to burn centers, these injuries incur a disproportionate amount of morbidity and mortality.² Electrical injuries lead to a multitude of injuries other than direct cutaneous, as seen in other burns, such as massive tissue necrosis resulting in amputation, cardiac arrhythmias, cataracts, and respiratory dysfunction. The probably least understood yet most common complication following electrical injury is the

neurologic sequelae that occur in up to 70% of patients.⁸⁰ The most common symptoms include numbness, weakness, memory problems, and chronic pain.⁸¹ Unlike the obvious injuries incurred after electrical injuries, these symptoms may not present themselves until months later.⁸¹ These symptoms are not limited to high-voltage injuries. These neurologic sequelae have been found to be more common in low-voltage injuries⁸¹; therefore, it could be suggested that all patients with electrical injuries, no matter the amount of cutaneous damage, be followed to identify those patients with neurologic symptoms. No randomized trials have studied rehabilitation of patients with neurologic sequelae following electrical injury or studies of early intervention to minimize morbidity.

Burn Reconstruction

The timing of reconstruction is postponed until the wound is fully matured, which can take up to 2 years.⁶⁰ If the contracture is causing a severe functional deficit, early reconstruction is planned to correct the problem.

The first priority in burn reconstruction is to avoid the need for further reconstruction through proper postoperative care. The second is return of active function, and the final priority is return of passive function. The process of reconstruction demands a systematic approach that includes all members of the multidisciplinary burn team and the patient. Following a rational and orderly plan of possible reconstruction and considering the patient as a whole will make the order of what is to be reconstructed clearer.

Primary closure of any wound is optimal, whether it is repairing a direct injury or a reconstructive procedure. Many times, the wound is too large to allow for this technique. Occasionally, large hypertrophic scars that are surrounded by uninjured tissue can be excised through multiple excisions and primary closure. This is a time-consuming process, but it will lead to a good result.

The Z-plasty is a technique by which two triangular skin flaps are interchanged in position to gain length along a scar or skin fold at the expense of surrounding tissues. An understanding of skin blood supply and geometry techniques is necessary to accomplish the desired results. The incisions of the flaps are three lines of equal length. The angles of the limbs of the flaps dictate the gain in length from the original scar. There is an approximate gain of 25% for 30° angles, 50% for 45° angles, and 75% for 60° angles.

If the above-mentioned techniques are not possible, the alternative is excision of the scar or contracture and placement

of a skin graft. After excision of the scar, the wound will usually retract quite widely, leaving a much larger skin deficit. The thickness of the replacement graft depends on the need for the reconstruction. A thinner graft has a higher likelihood of survival but also a higher chance of wound contracture during the maturation phase. Full-thickness grafts have the best color match and hair pattern but require near-perfect conditions to survive, and the donor sites will not heal spontaneously. If a full-thickness graft is needed for reconstruction and the donor site cannot be closed primarily, the donor site can be closed using a split-thickness skin graft.

A flap is used for reconstruction when the above methods are not possible or may not be desirable. Exposed bones or tendons need to be covered with a vascularized section of tissue as they lack the vascular supply to support a skin graft. Flaps are also desired to fill contour defects.

A random flap is based on the blood supply from musculocutaneous arteries penetrating its base. The Z-plasty described above is an example of this flap. An axial flap receives its blood supply from a direct cutaneous artery. The pivot point of the flap is the artery itself. This flap is very useful in burn reconstruction, and an exact knowledge of cutaneous arterial anatomy is necessary to design one. A radial forearm flap is the classic example of this type of flap.

A free flap can be divided from its vascular pedicle and used to cover a distant defect. This is highly useful with burn patients because tissue surrounding a defect is also damaged and cannot be used for reconstruction.

Tissue expanders are another way to achieve wound coverage. An expandable device is surgically placed beneath the skin and gradually increased in size to stretch the uninjured skin so that it may be used to cover the defect. This technique is best used in parts of the body with a bony background, such as the skull or chest wall.

Summary

The goal of caring for burn patients is to return them to their preinjury levels of function. The process of rehabilitation is the mechanism to achieve that end. A multidisciplinary team approach that outlines specific and measurable goals with the patient's input will be the most effective plan. When reconstruction is needed, it is essential to involve the patient and all members of the multidisciplinary burn team to plan appropriately. Continued frequent evaluation of the goals, along with modifications as needed, is essential to return the patient to a good quality of life.

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19 TRAUMA IMAGING

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Imaging of the trauma patient has evolved significantly over the past few decades, driven by the development of faster computed tomographic (CT) scanners and placement of imaging equipment in the emergency department. The most common imaging performed for trauma in the United States is radiography (x-rays) and CT. Except for limited abdominal and cardiac applications, ultrasonography plays a limited role for trauma evaluation in the United States but is used more extensively in other countries.¹⁻³ Magnetic resonance imaging (MRI) is used selectively and much less frequently than CT, most often for secondary evaluation of spine and neurologic injuries.

Radiographs are commonly available, are inexpensive, can be performed portably, and can often be rapidly obtained. Their disadvantages include overlap of structures, low contrast resolution compared with CT and MRI, and ionizing radiation.

CT provides excellent spatial and contrast resolution, especially when intravenous (IV) contrast is administered. The location of structures (such as bullets) can be accurately determined in the anterior-posterior (AP) dimension, allowing three-dimensional (3D) localization. In addition to evaluation of osseous abnormalities and the presence of foreign bodies (e.g., bullets, knives), CT provides excellent detail of many soft tissue injuries. With modern equipment, the CT acquisition time is short once the patient has been positioned and the scanner protocol has been entered. With the exception of some fluoroscopy, catheter angiography, and nuclear medicine studies, CT results in the highest radiation dose to the patient and should be used judiciously to limit radiation exposure.

MRI provides detail unavailable from other studies such as radiography, CT, or ultrasonography. It can detect early cerebral infarctions, hemorrhage, or edema (e.g., diffuse axonal injury); identify ligamentous injuries of the spine or musculoskeletal system that are not visible on CT; and better visualize spinal cord compression from hemorrhage or a disk. A tremendous advantage of MRI over CT is its lack of ionizing radiation. However, an MRI usually requires even more time to obtain than a CT scan, and there are MRI compatibility issues limiting the type of equipment that can be brought into the scanner. These limitations preclude routine use of MRI for trauma patients.

Ultrasonography for trauma in the United States is largely limited to the FAST (focused assessment with sonography for trauma) scan to evaluate for free intraperitoneal fluid or pericardial fluid.

In this chapter, we focus on an approach to imaging and briefly discuss some common imaging findings that are useful for the surgeon to recognize.

Initial Imaging

Traditionally, the initial imaging typically obtained for a polytrauma patient are three radiographs together referred to as the “trauma series”: cross-table lateral cervical spine radiograph, supine AP chest radiograph, and supine AP pelvis radiograph. These three images are obtained to assist in the initial evaluation of the ABCDs of the Advanced Trauma Life Support (ATLS) system.

The lateral cervical spine radiograph permits evaluation of the following:

Airway—for endotracheal tube (ETT) or nasogastric tube (NGT) malposition

Breathing—as a high cervical spine injury can affect the phrenic nerve

Circulation—as a high cervical spine injury can affect the sympathetic nervous system

Disability—as it may identify an unstable or potentially unstable spine injury

The chest radiograph permits evaluation of the following:

Airway—for ETT or NGT malposition or foreign bodies in the airway

Breathing—which may be compromised by a large pneumothorax or hemothorax, pulmonary contusions, diaphragm injury, or flail chest

Circulation—demonstrated as hemothorax or mediastinal hematoma potentially attributable to cardiac or great vessel injuries

The AP pelvis is not specifically obtained early in the trauma evaluation to identify orthopedic injuries but is included at this time to identify a pelvic ring disruption that can be difficult to identify clinically and that may result in a large extraperitoneal hematoma that may be a cause of hemorrhagic shock.

If ETTs, chest tubes, or central lines are placed or adjusted, another chest radiograph is usually obtained to help confirm (along with clinical findings) that the intervention was successful.

If the blunt trauma patient is unstable, a FAST scan may be performed. This is a limited sonogram designed to be performed rapidly to determine if there is free intraperitoneal fluid (presumed to represent hemoperitoneum) or more than the expected physiologic quantity of pericardial fluid (presumed to represent hemopericardium). Although FAST scans are performed at many trauma centers, a Cochrane analysis reports that “there is insufficient evidence from [randomized controlled trials] to justify promotion of ultrasound-based clinical pathways in diagnosing patients with suspected blunt abdominal trauma,”⁴ and the reliability of the scan depends on the operator’s experience. However, this remains an unsettled issue as other reports demonstrate a significant

reduction in time to complete the diagnostic algorithm and implement definitive care, as well as decreased complications and length of stay.⁵

If a hemodynamically unstable patient has a pelvic ring disruption but otherwise demonstrates no other significant injury, the most common trauma management algorithm sends them to angiography to evaluate for retroperitoneal arterial pelvic hemorrhage and for embolization if bleeding is detected. Supplemental or alternative treatments include “sheeting the pelvis” and external fixation, as well as retroperitoneal pelvic packing.⁶

If a hemodynamically unstable patient demonstrates hemoperitoneum or hemopericardium on a FAST scan but otherwise demonstrates no other significant injury, he or she is typically taken to surgery for evaluation and repair.

If a hemodynamically unstable patient demonstrates both injuries, then the initial treatment may depend on the severity of the pelvic ring disruption and the amount of hemoperitoneum or hemopericardium, as well as the availability of an operating room and surgeon or an angiography suite and angiographer.

Imaging Approaches

If the patient is stable and is not taken to surgery or angiography following initial imaging, then additional imaging may be indicated. For low-mechanism trauma with a normal physical examination, little to no additional imaging may be obtained, depending on local protocols. For other patients with isolated or polytrauma, additional imaging may be indicated. We focus on the workup of these patients in the remainder of this chapter.

There are two primary approaches to completing the imaging workup. Some institutions implement standard head to pelvis CT on all trauma patients. If this protocol is followed for all patients, then no additional decisions need to be made. The advantage of this approach is that the patient is fully imaged in an efficient standardized manner, and it can be quicker than selective CT. The potential disadvantages are increased radiation and nonoptimal contrast enhancement and body positioning. If a single contrast-enhanced phase study is performed, the neck and chest components may not demonstrate the high degree of enhancement that can be achieved with a dedicated computed tomographic angiogram (CTA), whereas the abdomen and pelvis components may be scanned earlier than ideal, resulting in less enhancement and more heterogeneous enhancement, both of which can limit evaluation for injury. If a multiphase contrast-enhanced study is performed (e.g., arterial and portal venous phase), patients will incur a significant increase in their radiation dose, which is inappropriate for low-risk patients.

The more traditional approach is selective CT based on the clinical examination and previous imaging findings. This approach is selected to limit the radiation dose to patients, many of whom have no significant traumatic injury, and is discussed in the sections below. In the future, it may be appropriate to implement a head to pelvis scan in selected patients without clinical or radiographic findings if we can identify the subset of high-risk patients in whom the risk from additional radiation dose is offset by the benefit of more rapid and complete CT.

If a trauma patient obtains a CT scan of the neck, chest, or abdomen, a dedicated spine CT scan of the imaged region (cervical, thoracic, or lumbar spine) is generated. This saves the additional time, cost, and radiation exposure from a separate CT or radiographic examination of the spine. The dedicated spine CT consists of an image reconstructed to optimize identification of spinal injuries using a small field of view centered around the spine, narrow slice thickness, and bone algorithm reconstructions. Multiplanar reformations (MPRs) in the sagittal and coronal plane are also generated to improve evaluation of alignment and detection of injuries that can be missed on just the axial images. Similarly, bony pelvis CT scans can be reconstructed from (soft tissue) pelvic CT scans obtained in conjunction with abdominal CT scans for trauma.

Brief Introduction to CT

Iodinated contrast agents can be injected intravenously to produce enhancement of vessels and parenchyma. High concentrations of contrast, such as that seen in the vascular system during the early portions of the study, are visualized as white (or bright) on CT. Less concentrated contrast within organs results in “enhancement” (or increased whiteness or brightness) of the organ, increasing our ability to evaluate anatomy and pathology.

CT scans obtained without IV contrast are referred to as noncontrast CT scans, whereas those obtained after administration of contrast are referred to as contrast-enhanced CT scans (or can be more specifically described by the phase of contrast enhancement, as described below).

CT scans obtained while most of the contrast is still in the arteries are referred to as arterial phase CT scans and are usually obtained 15 to 30 seconds after the start of contrast injection to evaluate the arterial system and specific lesions, which enhance early. The most common time to evaluate the abdomen and pelvis is during the portal venous phase (70 seconds after the start of contrast injection), when the liver and spleen demonstrate bright and homogeneous enhancement, and most other structures also enhance well. Delayed phase images may also be obtained to evaluate for a change in enhancement of lesions over time (such as hemangiomas or adrenal nodules), for a change in the appearance of extravasated vascular contrast (to confirm that findings represent extravasation), or for demonstration of urinary extravasation. Delayed phase images are typically obtained after a 5- to 10-minute delay.

When a CT scan is ordered by the clinician, the radiologist protocols it, typically to one of a number of predefined protocols that specify the region to be scanned, the technical parameters to use, the contrast phases during which the patient should be scanned, and whether IV, oral, or rectal contrast should be used. The clinician should not usually have to concern themselves with most of these technical details but should provide the appropriate clinical history, specify the reason for the study, and identify any special circumstances or contraindications (such as contrast allergy), which would allow the radiologist to protocol the study appropriately. If other information is available, such as indeterminate findings on previous studies that the radiologist may or may not be aware of (e.g., if it was performed at an

outside facility), it is helpful to communicate these findings to the radiologist as they may alter the selected protocol or result in modification of the preset protocols.

Prior to the widespread use of helical multidetector computed tomographic (MDCT) scanners over the past decade, the original sequential (or step and shoot) CT technique required significant time to physically scan the patient. With current helical MDCT scanners, the actual time required to scan patients constitutes only a tiny fraction of the entire time required to obtain CT imaging. Commonly available MDCT scanners can image 2.5 cm or more of patient length per second, and newer MDCT scanners can scan up to 15 cm of patient length per second, and even faster. Thus, the actual scan time constitutes only a tiny portion of the total imaging time, which is largely taken up with transportation of the patient; transfer to the CT table; positioning of arms, tubes, lines, and monitoring equipment; connection of IV contrast injector and testing of the contrast injection; obtaining scout images to determine which portions of the patient to scan; entering scan parameters into the scanner to obtain the appropriate study; and processing the images after the scan has been completed. Fast scans of limited areas of the body, without contrast injection, can be performed in 5 to 10 minutes, but complete scanning and processing of patients with more complex imaging requirements (including contrast injection and the need to move the arms or other structures between scans) can take significantly longer, typically 15 to 30 minutes or more. Although the initial axial CT images are available almost immediately after scanning is completed, many of the CT scanners currently in widespread use may still require up to 10 to 30 minutes to further process the images to allow optimal evaluation of the patient. Newer scanners and consoles are more powerful and should significantly reduce this postprocessing time.

Images reviewed primarily for soft tissue detail such as abdominal viscera, brain, vasculature, and peritoneal fluid are reconstructed using a “standard” or “soft tissue” algorithm. The resulting images appear less grainy or noisy and provide better interpretation of these structures.

Images reviewed primarily for osseous detail or fine lung detail (such as pulmonary fibrosis) or dense structures such as metal are reconstructed using a “bone” algorithm. The resulting images provide better visualization of these structures but would appear too noisy for optimal evaluation of the soft tissues.

Both sets of images can be reconstructed from the data acquired from a single scan of a patient; thus, patients do not need to be radiated twice to obtain both sets of images. A CT scan of the chest, abdomen, and pelvis is reconstructed using the soft tissue algorithm. A thoracic and lumbar spine CT scan can be reconstructed from the same scan data using the bone algorithm to better visualize the osseous structures. In addition, these images are reconstructed using a smaller field of view, generating images of a smaller diameter through the patient, centered around the spine, which results in higher spatial resolution images.

CT Image Processing

Coronal and/or sagittal MPR images are now obtained for most CT examinations and have proven invaluable in many

applications. For example, sagittal and coronal reformations can clearly depict horizontally oriented fractures that may be missed on axial images.

3D reconstructions have a powerful visual impact and may be preferred by viewers not experienced in the evaluation of cross-sectional imaging. 3D images can provide supplementary information and improve appreciation of spatial relationships. Whereas some authors report improved evaluation with 3D images,⁷ others demonstrate improved accuracy using the standard two-dimensional (2D) axial images, and most radiologists use the 3D images to supplement the 2D images,⁸ which should always be reviewed.

Modern CT scanners and postprocessing workstations can semiautomatically reconstruct 3D images of bones, contrast-enhanced blood vessels, and other high-density structures using “thresholding” techniques. When the density difference between the object of interest and surrounding structures is small (e.g., a liver laceration), 3D reconstructions need to be manually generated. Newer, more intelligent workstations may overcome these limitations.

Volume rendering can be used to generate CT images that simulate radiographs from varying projections by manipulating the opacity of different tissues. Volume-rendered transmission display images of spine and pelvic injuries [see Figure 1a] can eliminate the need for additional radiographs⁹ that were obtained in the past to provide surgical guidance and/or a baseline for comparison with follow-up radiographs.

Alternatively, a 3D surface display of an object simulates viewing of an opaque object rather than a CT scan or radiograph [see Figure 1b]. Structures “behind” the object are not visible on this image, and multiple projections that simulate the viewer rotating around the object are generated to provide visual information about structures hidden by the opaque object in certain projections. These images are often used in evaluation of musculoskeletal and vascular injuries but are not as commonly used elsewhere in the torso.

Radiation Dose

The biologic effects of ionizing radiation produced by radiography, CT, and fluoroscopy are controversial and depend on which dose-effect relationship is accepted. One model is the “linear no threshold” model, in which the risk of radiation-induced cancer increases linearly with the dose absorbed and in which there is a (low) risk of radiation-induced cancer even at extremely low doses. Another model is the “threshold” model, in which there is no risk of radiation-induced cancer below a certain dose. A variety of other models have been proposed.

Even if a single model is universally accepted, another challenge is calculating the dose absorbed by the patient. This can vary tremendously depending on the protocol implemented, the size of the patient, and other factors.

Radiologists follow the ALARA principle (as low as reasonably achievable) and attempt to keep the radiation dose as low as reasonably achievable. Although thin-slice high-quality images can be obtained with modern equipment, resulting in images that look pleasing to the eye and allow for beautiful reconstructions, the cost of these images is often a high radiation dose. Radiologists should protocol their studies to

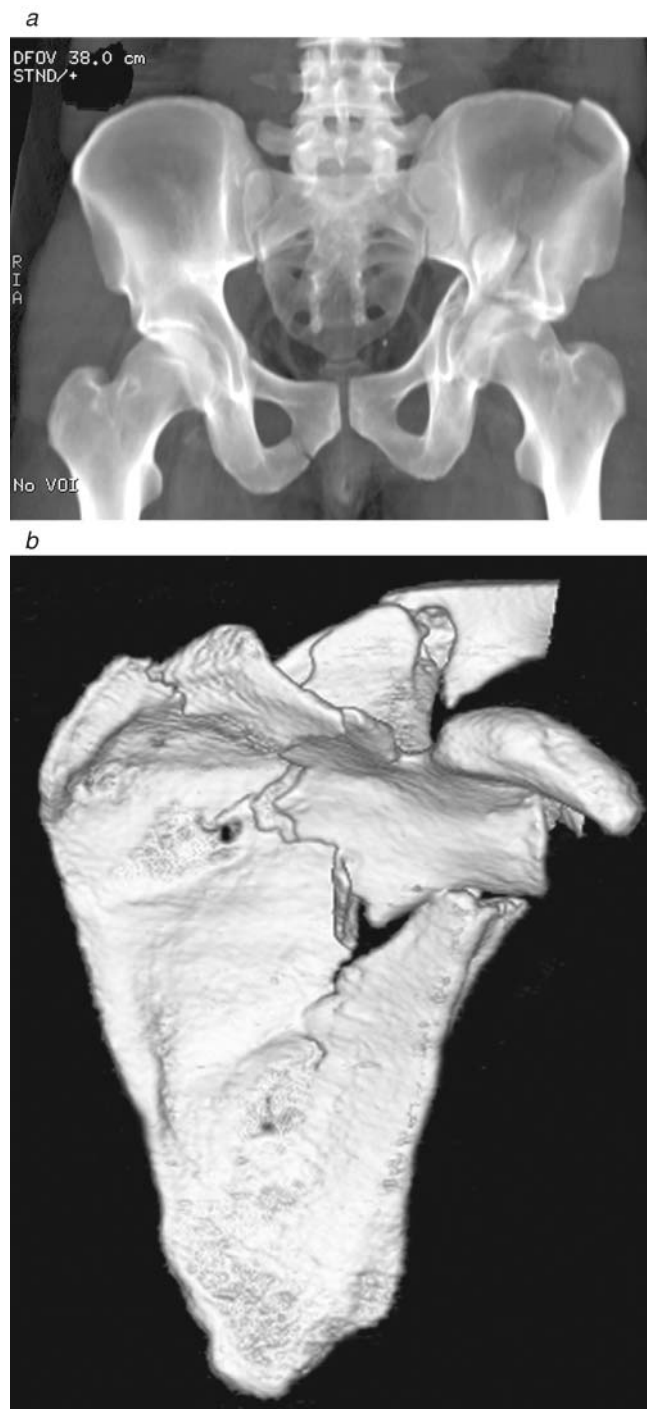


Figure 1 (a) Volume-rendered transmission display image of the pelvis processed to provide an appearance similar to that of a pelvic radiograph. Note that the iliac portions of the sacroiliac joints can be visualized through the sacrum, similar to the effect seen with a radiograph. (b) Volume-rendered surface display image of the scapula, visualized from the front. Note that we cannot see through the scapula, and objects posterior to the visualized portion of the scapula are invisible on this view.

provide diagnostic information with the minimum radiation dose, which may result in images that appear a little noisier or grainier than images that can be produced with a higher dose.

The risk of radiation-induced cancer decreases with increasing age. A recent study estimated the risk of developing cancer for several common CT scans¹⁰:

Head CT: 20-year-old female, one in 4,360; 60-year-old female, one in 12,250

Single-phase abdomen-pelvis CT: 20-year-old female, one in 470; 60-year-old female: one in 1,320

Single-phase abdomen-pelvis CT: 20-year-old male, one in 620; 60-year-old male, one in 1,250

Brief Introduction to Reviewing a CT Scan

There are a number of approaches to reviewing a CT scan (or any other type of imaging study), but they all require a systematic approach to ensure that the reader is not distracted by any initial significant findings detected, leading to incomplete review of the remainder of the study. The section below describes one approach to review of an abdominal CT scan.

To fully visualize all the information on a study, one needs to review the images using several different windows. The window settings control what range of CT densities you see and the contrast of the image. These values are usually pre-programmed on the picture archiving and communication system (PACS), and the user can simply pick the desired named window.

The soft tissue window provides a general overview of most soft tissue structures and is the primary window for evaluation of the abdomen. However, normal lungs appear completely black, as does a pneumothorax, and this window is not reliable for excluding pneumothoraces. Similarly, gas could appear similar in density to fat, and pneumoperitoneum or retroperitoneal gas could be missed using this window.

The lung window demonstrates the pulmonary parenchyma well, allowing detection of nodules, contusions, lacerations, atelectasis, etc., and clearly demonstrates a pneumothorax. A lung window, or similar window, can also be used to look for abnormal gas in the abdomen, pelvis, and soft tissues. However, the soft tissue details are completely or almost completely obscured by this window, and extensive (otherwise obvious) pathology can be missed using this window alone to evaluate the abdomen.

The bone window best evaluates osseous structures and allows detection of subtle fractures and other osseous pathology that may be missed on other windows.

One approach to the review of an abdominal CT is as follows:

1. Start by reviewing the axial images.
 - Using lung windows, review the lung bases for pneumothorax, pulmonary injury, nontraumatic pulmonary abnormality, or abnormal gas.
 - Switch to soft tissue windows.
 - Review lung bases for mediastinal abnormalities, pleural fluid, incidental pulmonary emboli, or other vascular abnormalities.
 - Review the liver, spleen, biliary system, pancreas, adrenals, kidneys, renal collecting systems and ureters,

diaphragm, bowel, bladder, and male- or female-specific structures.

- Review peritoneal spaces and retroperitoneum for abnormal fluid or blood.
 - Review the aorta and major branches, inferior vena cava and major branches, splenic and portal veins, and hepatic veins.
 - Review body wall and soft tissues.
 - Review for tubes and lines and the presence of foreign bodies.
 - Switch to bone windows.
 - Evaluate osseous structures of the chest, abdomen, and pelvis.
 - Using a lung window, modified lung window, or modified soft tissue window, evaluate for abnormal gas anywhere—in vessels or bowel wall, pneumoperitoneum, retroperitoneal gas, pneumomediastinum, soft tissue gas, etc.
 - If multiple phases of imaging have been obtained, review all phases (e.g., noncontrast, arterial phase, portal venous phase, delayed phase), paying special attention to vascular abnormalities, abnormal enhancement of structures, and vascular or urinary extravasation.
2. Review the sagittal and/or coronal images, as well as any other reformations provided, such as 3D images.

Head Imaging

HEAD CT

Head CT is the study of choice for initial evaluation for traumatic brain injury (TBI). Symptoms of TBI are classified as mild, moderate, or severe depending on the extent of the injury. In general, a Glasgow Coma Scale (GCS) score of 13 or higher (of a maximum 15) is considered mild TBI, whereas 9 to 12 is considered moderate TBI and 8 or below is classified as severe TBI. The timing, urgency, and type of brain imaging are influenced by the suspected degree of injury.

Access to head CT has revolutionized management of patients with TBI. Head CT can be obtained quickly at relatively low cost and can provide vital diagnostic information for early evaluation of TBI in the emergency setting. For these reasons, all patients with TBI classified as moderate or severe undergo head CT for the initial assessment of TBI. In general, head CT is also obtained in all cases where loss of consciousness has occurred and in cases where intoxication, distracting injuries, overt craniofacial trauma, and/or a high-energy mechanism for TBI are present, regardless of mental status. However, head CT is not performed without expense or radiation dose; therefore, several prediction rules exist for triage of patients in the setting of minor head trauma, including the New Orleans Criteria (NOC),¹¹ the Canadian CT Head Rule (CCHR),¹² and CT in Head Injury Patients (CHIP)¹³ [see Table 1, Table 2, and Table 3]. Each of these prediction rules has a reported 100% sensitivity for detection of lesions that require neurosurgical intervention, yet differences in their approach exist. For example, the goal of the CCHR is to identify patients who would benefit from undergoing head CT, whereas the NOC and CHIP are likely to be more useful for identifying patients who would not benefit from head CT.

Table 1 New Orleans Criteria¹¹

Computed tomography is required for patients with minor head injury with any one of the following findings. The criteria apply only to patients who also have a Glasgow Coma Scale score of 15.

- Headache
- Vomiting
- Older than 60 years
- Drug or alcohol intoxication
- Persistent anterograde amnesia (deficits in short-term memory)
- Visible trauma above the clavicle
- Seizure

Table 2 Canadian CT Head Rule^{*12}

CT is required only for patients with minor head injury[†] with any one of the following findings:

High risk for neurosurgical intervention:

- Glasgow Coma Scale score lower than 15 at 2 hours after injury
- Suspected open or depressed skull fracture
- Any sign of basal skull fracture[‡]
- Two or more episodes of vomiting
- 65 years or older

Medium risk for brain injury detection by CT

- Amnesia before impact of 30 or more minutes
- Dangerous mechanism[§]

CT = computed tomography.

*The rule is not applicable if the patient did not experience a trauma, has a Glasgow Coma Scale score lower than 13, is younger than 16 years, is taking warfarin or has a bleeding disorder, or has an obvious open skull fracture.

[†]Minor head injury is defined as Glasgow Coma Scale score of 13 to 15 after witnessed loss of consciousness, amnesia, or witnessed disorientation.

[‡]Signs of basal skull fracture include hemotympanum, “raccoon” eyes, cerebrospinal fluid otorrhea or rhinorrhea, and Battle sign.

[§]Dangerous mechanism is a pedestrian struck by a motor vehicle, an occupant ejected from a motor vehicle, or a fall from an elevation of three or more feet or five stairs.

Table 3 CHIP Prediction Rule¹³

CT is required in the presence of 1 major criterion:

- Pedestrian or cyclist versus vehicle
- Ejected from vehicle
- Vomiting
- Posttraumatic amnesia ≥ 4 hr
- Clinical signs of skull fracture*
- GCS score < 15
- GCS score deterioration ≥ 2 points (1 hr after presentation)
- Use of anticoagulant therapy
- Posttraumatic seizure
- Age ≥ 60 yr

A CT is required in the presence of at least 2 minor criteria:

- Fall from any elevation
- Persistent anterograde amnesia[†]
- Posttraumatic amnesia of 2 to < 4 hr
- Contusion of the skull
- Neurologic deficit
- Loss of consciousness
- GCS score deterioration of 1 point (1 hr after presentation)
- Age 40–60 yr

CHIP = CT in Head Injury Patients; CT = computed tomography; GCS = Glasgow Coma Scale.

*Any injury that suggests skull fracture, such as palpable discontinuity of the skull, leakage of cerebrospinal fluid, “raccoon eye” bruising, and bleeding from the ear.

[†]Persistent anterograde amnesia is any deficit of short-term memory.

Head CT for evaluation of TBI is generally acquired without iodinated contrast from the foramen magnum through the vertex of the skull. Slice thickness of 5 mm enables adequate differentiation of gray matter from white matter structures; thinner sections may be retroactively rendered for evaluation of specific abnormalities, but gray-white matter discrimination may be impaired. The initial head CT scan acquired in the emergency department is rendered in standard algorithm to optimize radiologic evaluation of the intracranial contents and overlying soft tissue structures, and bone algorithm for evaluation of osseous structures and possible radiodense (e.g., metallic) foreign bodies. Follow-up head CT scans obtained for serial evaluation of TBI lesions are oriented parallel to the orbital roof to spare radiation exposure to the lens of the eye because of the known dose-dependent risk of cataract formation.¹⁴ Serial follow-up head CT scans are generally rendered in standard algorithm only for repeat evaluation of the intracranial contents and soft tissue lesions, with repeat bone algorithm reserved only for cases where detailed reevaluation of the osseous structures is desired.

If a TBI lesion has been identified on the initial head CT [see Figure 2], serial head CT follow-up is often part of the management plan. The frequency of serial head CT scans is

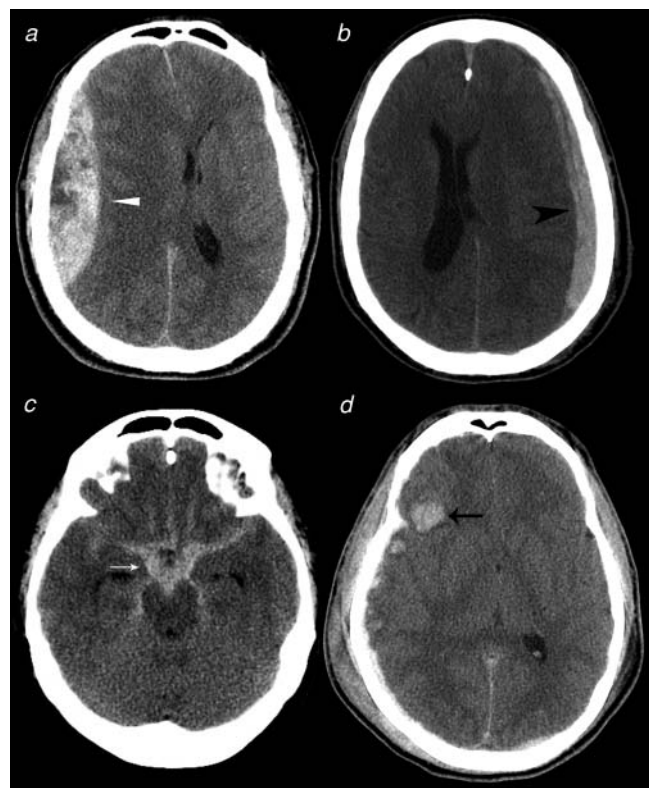


Figure 2 Head computed tomography remains the initial imaging test of choice for detection of acute intracranial bleeding, which may occur in the epidural space (a, epidural hematoma, *white arrowhead*), the subdural space (b, subdural hematoma, *black arrowhead*), the subarachnoid space (c, subarachnoid hemorrhage, *white arrow*), within the brain parenchyma (d, hemorrhagic contusion, *black arrow*), or any combination of the above.

dictated by the nature of the TBI lesion. The detection of any acute intracranial bleeding generally necessitates a minimum of two additional follow-up scans to confirm lesion stability or worsening, although this approach may vary based on the clinical scenario and clinician preferences. In cases of moderate and severe TBI, the morphologic abnormalities on head CT imaging can also be used to predict clinical outcomes using scoring systems such as the Marshall CT score¹⁵ [see Table 4] and the more recent Rotterdam score¹⁶ [see Table 5]. Such classification systems are particularly useful in the setting of early sedation, intubation, and mechanical ventilation in patients with moderate or severe TBI as the GCS score may be unreliable or impossible to obtain in such patients.

Table 4 Marshall CT Classification¹⁵	
Category	Definition
Diffuse injury I (no visible pathology)	No visible intracranial pathology seen on CT scan
Diffuse injury II	Cisterns are present with midline shift of 0–5 mm and/or: lesion densities present; no high- or mixed-density lesion > 25 cc; may include bone fragments and foreign bodies
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift 0–5 mm, no high- or mixed-density lesion > 25 cc
Diffuse injury IV	Midline shift > 5 mm, no high- or mixed-density lesion > 25 cc
Evacuated mass lesion	Any lesion surgically evacuated
Non-evacuated mass lesion	High- or mixed-density lesion > 25 cc, not surgically evacuated

CT = computed tomography.

Table 5 Rotterdam Classification¹⁶	
Predictor Value	Score
Basal cisterns	
Normal	0
Compressed	1
Absent	2
Midline shift	
No shift or shift ≤ 5 mm	0
Shift > 5 mm	1
Epidural mass lesion	
Present	0
Absent	1
Intraventricular blood or tSAH	
Absent	0
Present	1
Sum score	+1

tSAH = traumatic subarachnoid hemorrhage.

The sum score can be used to obtain the predicted probability of mortality from the formula below. We chose to add +1 to make the grading numerically consistent with the grading of the motor score of the Glasgow Coma Scale and with the Marshall CT Classification. The corresponding probabilities are calculated with the formula probability (mortality) = $1/[1 + e^{-(2.60 + 0.80 \times \text{sum score})}]$.

BRAIN MRI

MRI of the brain is generally more sensitive and specific than CT for detection and characterization of TBI lesions. One clear exception is the superiority of CT for detection and delineation of skull fractures. MRI is also less widely available, more expensive, more time consuming, and more difficult to perform in critically ill or injured patients than CT, all of which limits its utility in the emergent evaluation of TBI. In addition, safety concerns can preclude access to MRI if incompatible hardware implants (e.g., cardiac pacemakers) and/or metallic foreign bodies are present. The MRI compatibility of all devices external to the patient (e.g., mechanical ventilation equipment, external fixation devices) must also be ensured prior to positioning the patient within an MRI scanner. The topic of MRI safety is too large to cover in this brief chapter. Nevertheless, an important MRI safety principle is to screen each patient for identifiable causes of MRI incompatibility, and this may include obtaining radiographs and/or limited CT scans targeted to the anatomy in question for detection of possible metallic foreign bodies and/or implants. For example, any concern for a potential metallic foreign body within the orbits (such as patient history of sheet metal working) is typically investigated with limited noncontrast CT of the orbits to exclude or identify such foreign bodies prior to placing the patient within the magnetic field. Patients with implanted hardware devices should also have their specific hardware (e.g., manufacturer, year, model and/or serial number) recorded, researched, and cleared by the radiologist or MRI technologist on duty prior to entry into the scanner.

Brain MRI for TBI at our institution includes standard multiplanar T₁-weighted, T₂-weighted, and fluid attenuation inversion recovery (FLAIR) sequences for characterization of brain anatomy and detection of brain injuries. In general, T₁-weighted images are useful for depicting anatomy; therefore, T₁-weighted images in both axial and sagittal planes are routinely obtained. Cerebrospinal fluid is dark on T₁-weighted images, whereas fat, proteinaceous fluid, methemoglobin, melanin, and enhancement from gadolinium contrast agents are all bright on T₁-weighted images. T₂-weighted images are most useful for detecting pathology in the central nervous system (CNS) because of the high sensitivity of T₂-weighted imaging for detection of fluid. However, the intrinsic bright signal of normal fluid on T₂-weighted images can potentially obscure a subtle lesion; therefore, FLAIR imaging is useful in that it suppresses normal cerebrospinal fluid signal while highlighting edematous brain lesions and extra-axial bleeding. FLAIR sequences in particular may be useful for detection of intracranial bleeding, such as subdural hematomas, subarachnoid hemorrhage, and hemorrhagic contusions, as well as nonhemorrhagic lesions such as nonhemorrhagic contusions and shear injuries. T₂*-weighted gradient echo (GRE) sequences are sensitive to magnetic susceptibility from blood degradation products, which result in a “blooming” effect that highlights even very small parenchymal hemorrhages [see Figure 3]. GRE sequences are useful for detection of hemorrhagic shear injuries, particularly in cases where diffuse axonal injury is suspected clinically. Diffuse axonal injury is typically suspected when the clinical severity of TBI is disproportionate to relatively mild findings on head CT in such patients.

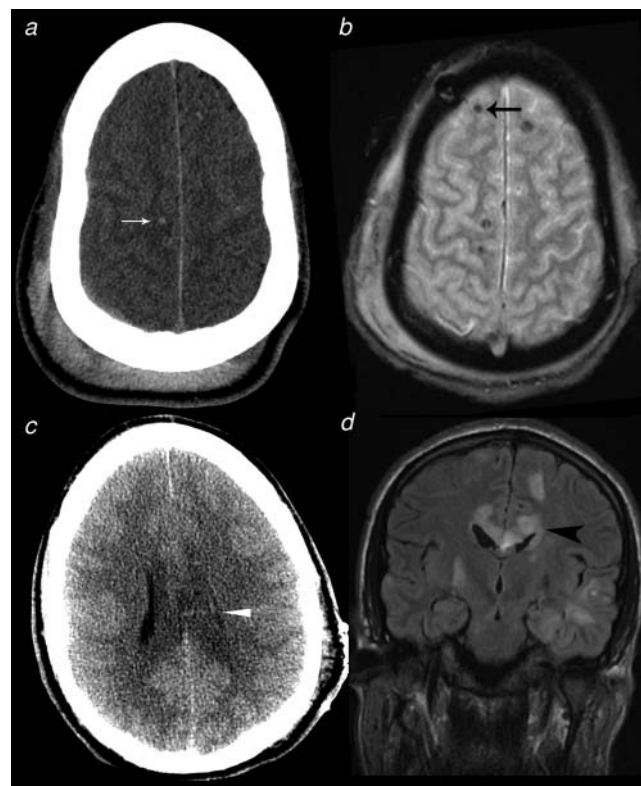


Figure 3 Magnetic resonance imaging (MRI) is more sensitive for detection of shear injuries in diffuse axonal injury. Whereas computed tomography (CT) may reveal characteristically small foci of hemorrhagic shear injury (a, white arrow), gradient echo MRI frequently shows “blooming” foci of low signal, indicating hemorrhagic shear even in locations where the CT scan appears normal (b, black arrow). Similarly, nonhemorrhagic shear injuries are frequently less apparent on CT (c, white arrowhead) than on fluid attenuation inversion recovery MRI (d, black arrowhead).

Gadolinium contrast agents may be administered intravenously to improve detection and characterization of brain lesions through contrast enhancement. Gadolinium contrast increases bright signal on T₁-weighted imaging within tissues that lack an intact blood-brain barrier (such as the pituitary gland, the nasopharyngeal mucosa, CNS metastases and abscesses). However, the majority of lesions seen in the setting of TBI do not exhibit gadolinium enhancement or do so only in the subacute phase (e.g., subacute hematoma), wherein the lesion may be misinterpreted for another etiology in which the blood-brain barrier is disrupted (e.g., CNS metastasis or abscess). Therefore, the role of IV gadolinium contrast agents for evaluation of TBI is limited.

Maxillofacial Imaging

In cases where clinical suspicion for craniofacial injury exists, a maxillofacial CT scan with thin sections in axial and coronal planes for improved evaluation of craniofacial fractures can be acquired either separately or at the same time as the initial head CT scan. TBI patients with a high suspicion for significant craniofacial injuries (i.e., acute fractures other than a nondisplaced nasal bone fracture) can be initially

imaged with a single combined head CT for evaluation of TBI and maxillofacial CT for evaluation of maxillofacial trauma. The combined scan is performed using a multidetector scanner to acquire the scan information in contiguous thin sections (on the order of 0.5 to 1.0 mm) from just below the mandible through the vertex of the skull. From this data set, both the head CT and the maxillofacial CT can be rendered. However, this combined scan results in additional radiation exposure, either from just below the mandible to the foramen magnum (for maxillofacial CT coverage) or from just above the frontal sinuses to the vertex of the skull (for head CT coverage); therefore, a combined scan is not routinely performed in all cases.

Cerebrovascular Imaging

High-energy trauma can result in blunt cerebrovascular injury (BCVI). BCVI is commonly graded according to the Biffl scale¹⁷ [see Table 6]. The Biffl scale is based on findings of arterial injury (e.g., arterial dissection) at catheter angiography. Although the risks of serious morbidity and mortality from catheter angiography are low, they remain higher than for CTA, which uses IV iodinated contrast administered via peripheral IV rather than intra-arterial contrast via selective vessel catheterization. Patients with suspected BCVI, identified by the signs, symptoms, or mechanisms listed in the modified Denver criteria [see Table 7], are initially evaluated

using neck CTA, with catheter angiography reserved for dedicated evaluation and/or endovascular treatment of abnormalities detected on the initial neck CTA.

Neck CTA is obtained from the origins of the great vessels from the aortic arch through the circle of Willis using a multidetector scanner to acquire thin sections in the axial plane during peak arterial phase of iodinated contrast enhancement. The iodinated contrast is administered intravenously as a rapid bolus (e.g., 5 cc/s) via a power injector; therefore, a large-bore IV catheter (20 gauge or larger) is required. From this data set, the cervical arterial anatomy may be examined in exquisite detail. However, CTA cannot provide information regarding flow-related phenomena such as arteriovenous shunting, although clues to the presence of arteriovenous shunting may be inferred from early venous opacification. The imaging protocol for neck CTA typically includes both pre- and postcontrast head CT for improved detection and characterization of intracranial vascular injuries and bleeding.

Magnetic resonance angiography (MRA) of the neck is an alternative to neck CTA for evaluation of the cervical arterial vessels. MRA can be acquired using either noncontrast techniques (time-of-flight or phase contrast) or IV gadolinium-enhanced techniques. Noncontrast MRA can be performed in cases where IV contrast administration is contraindicated but results in decreased signal-to-noise images compared with contrast-enhanced studies. However, the spatial resolution of either MRA technique is generally not superior to that of CTA, and for the additional reasons of relatively greater costs, longer imaging times, and greater technical difficulty in traumatically injured patients, MRA remains a secondary evaluation for BCVI.

Catheter angiography remains the gold standard test for evaluation of the cervical vasculature and is often the initial test of choice for evaluation of penetrating trauma, particularly if clinical suspicion for severe vascular injury favors the potential need for embolization.

Table 6 Biffl Carotid Artery Injury Grading Scale¹⁷

Injury Grade	Description
I	Luminal irregularity or dissection with < 25% luminal narrowing
II	Dissection or intramural hematoma with ≥ 25% luminal narrowing, intraluminal thrombus, or raised intimal flap
III	Pseudoaneurysm
IV	Occlusion
V	Transection with free extravasation

Table 7 Modified Denver Criteria for BCVI Screening

Symptoms or signs of BCVI
Massive epistaxis
Central or lateralizing neurologic deficit that is unexplained or incongruent with CT scan
Expanding neck hematoma
Acute or subacute cerebral infarction on CT scan
Transient ischemic attack or stroke after blunt neck trauma
Horner syndrome (disruption of the sympathetic chain, with ipsilateral ptosis, miosis, and anhidrosis)
Cervical vascular bruit in a patient < 50 years old with blunt neck trauma
Injury mechanisms/patterns identified as risk factors for BCVI
Midface fracture with cervical hyperextension/rotation/flexion injury
Complex mandible fracture with cervical hyperextension/rotation/flexion injury
Closed-head injury with diffuse axonal injury and cervical hyperextension/rotation/flexion injury
Cervical spine fracture with cervical hyperextension/rotation/flexion injury
Displaced midface fracture (Le Fort II or III) from high-energy mechanism
Skull base fracture involving foramen lacerum, sphenoid, mastoid, or petrous bones
Complex mandible fracture from high-energy mechanism
Seatbelt abrasion, hanging bruise, or unexplained contusion or hematoma of neck, resulting in significant cervical swelling or altered mental status
Cervical vertebral fracture extending through the transverse foramen
Cervical vertebral subluxation
Upper cervical vertebral fracture (C1–C3)

BCVI = blunt cerebrovascular injury; CT = computed tomographic.

Adapted from Biffl WL, Moore EE, Offner PJ, et al. Optimizing screening for blunt cerebrovascular injuries. *Am J Surg* 1999;178:517–22; Cothren CC, Moore EE, Biffl WL, et al. Cervical spine fracture patterns predictive of blunt vertebral artery injury. *J Trauma* 2003;55:811–3.

Spine Imaging

SPINE RADIOGRAPHY AND CT

If an abnormality of the spine is detected on the trauma series, placing the patient at risk for cervical vascular injury (such as bilateral jumped facets), CTA of the neck is performed, and the bony cervical spine CT scan is generated from this study. Otherwise, if spine imaging is indicated, radiographs or CT scans are obtained for further evaluation.

In the 1990s and earlier, radiographs were used for imaging evaluation of cervical spine injury, and a CT scan was obtained if a definitive neurologic deficit or abnormality on radiographs was identified. Hanson and colleagues demonstrated a clinical decision rule to distinguish patients at high risk for cervical spine injury, for whom it was cost-effective to bypass radiographs and instead obtain a CT scan of the cervical spine.¹⁸ These criteria include a high-speed motor vehicle collision, a crash with death at the scene, a fall from more than 10 feet, a significant closed-head injury or hemorrhage identified on CT, neurologic symptoms or signs referable to the cervical spine, and pelvic or multiple extremity fractures.

Whereas some institutions may perform CT on anyone requiring cervical spine imaging, others do not routinely perform cervical spine CT evaluation of children under the age of 9 but instead image them with radiographs unless CT is required to further evaluate specific clinical or radiographic findings as radiographs have been demonstrated to be highly sensitive in detecting injury in young children.¹⁹ In children 4 years of age or younger, only AP and lateral radiographs are obtained. In children 5 to 8 years of age, an odontoid view is also obtained. In both age groups, if a head CT imaging is obtained, it is extended inferiorly to include C1 and C2, and the odontoid view is no longer needed.

Two major studies provide guidance on which patients should undergo cervical spine “radiography” (x-rays): the Canadian C-Spine Rule (CCSR) and the NEXUS criteria.^{20,21} Many institutions use these rules to determine if cervical spine imaging is indicated, and if so, CT imaging is obtained. We continue to obtain cervical spine radiographs on many patients, especially low-mechanism patients, and usually follow the criteria proposed by Hanson and colleagues¹⁸ to determine when to image with CT. This is done to limit radiation dose as most cervical spine CT scans are negative for injury but result in a much higher radiation dose to patients (up to a 14 times higher thyroid dose²²), which is especially important for younger patients. However, cervical spine CT scans are obtained in patients with appropriate mechanism who are intubated (or otherwise unable to cooperate with the radiographic examination) or patients with severe degenerative changes or other findings that would limit evaluation of the spine with radiographs.

Using the NEXUS criteria, patients who meet all five of the following criteria are considered to have a low probability of injury and do not require imaging: no midline cervical tenderness, no focal neurologic deficit, normal alertness, no intoxication, and no painful distracting injury.

Using the CCSR, there are three sequential decisions to make to determine if imaging is not indicated:

1. If there are any high-risk factors, then radiography is performed. High-risk factors include patients 65 years of age or older, a dangerous mechanism, and extremity paresthesias.
2. If no low-risk factors are present that would allow assessment of range of motion, then radiography is performed. Low-risk factors include a simple rear-end motor vehicle collision, sitting position in the emergency department, ambulatory patient at any time, delayed onset of neck pain, and absence of midline cervical tenderness.
3. If the patient is not able to actively rotate the head 45° to the left and to the right, then radiography is performed.

Cervical spine CT scans are typically extended down to T4 as T1–T4 are often inadequately visualized on thoracic spine radiographs, especially on the lateral view.

If thoracic or lumbar spine imaging is indicated and cannot be extracted from a torso CT, then spine radiographs or CT scans could be obtained. If there are focal neurologic deficits, or severe focal pain that would lead the clinician to order a spine CT even in the presence of negative radiographs, then CT of the appropriate region is indicated. Otherwise, radiographs are obtained.

SPINE MRI

Emergent spine MRI is indicated as a secondary evaluation in patients with traumatic spinal injuries. The goal of imaging is to exclude or identify treatable spinal injuries, such as unstable ligamentous injury, epidural hematoma, and/or traumatic disk herniation that may result in cord compression, before cord injury has occurred, and to characterize spinal cord injuries for prognosis [see Figure 4]. A standard protocol for evaluation of acute spinal trauma can be applied to the

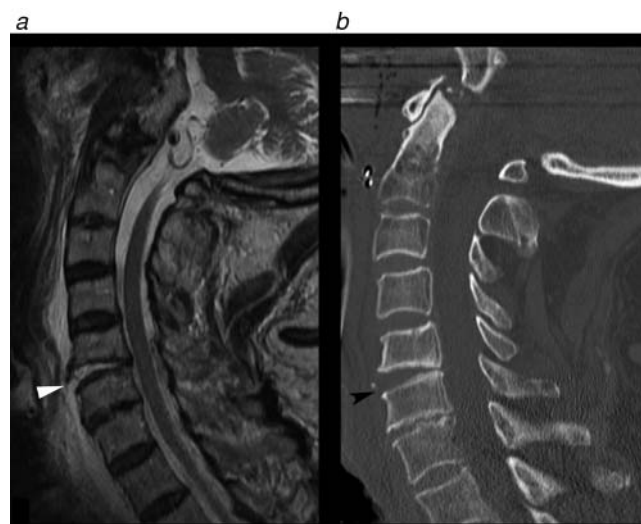


Figure 4 Magnetic resonance imaging may be performed in the setting of cervical spine trauma as a secondary test to evaluate for soft tissue injuries, such as ligamentous injury and disk injury (*a*, disruption of the anterior longitudinal ligament and C5–C6 disk injury with associated prevertebral fluid collection, *white arrowhead*). Signs of ligamentous injury on a computed tomographic scan may be relatively subtle by comparison (*b*, anterior widening of the C5–C6 intervertebral disk space, *black arrowhead*).

cervical, thoracic, and lumbar regions of the spine as indicated by initial radiographic and/or CT evaluation. Standard MRI sequences include axial and sagittal T1 and T2, as well as sagittal short-tau inversion recovery (STIR) and axial GRE sequences. T₁ and T₂ sequences provide excellent anatomic resolution, and T₂ is generally most reliable for identification of cord edema. Sagittal STIR is also highly sensitive for edema, both within the cord and within the osseous structures, as it suppresses the bright signal from normal marrow that is observed on both T₁ and fast spin echo T₂ sequences. Axial GRE sequences are most useful for detection of “blooming” artifact as a result of blood degradation products, particularly within the spinal cord. Detection of spinal cord hematoma is a poor prognostic sign in spinal cord injury.

MRI is relatively expensive and time consuming to perform. Performing MRI of the complete spine to “screen” for spinal injuries frequently results in poor image quality and impaired sensitivity. To cover the entire spine in a single MRI session, the sagittal images are often acquired over an expanded field of view (e.g., cervical through upper thoracic spine and lower thoracic through lumbar spine) that decreases image resolution. Axial images similarly must be acquired at larger slice gap intervals, resulting in a greater chance of “skipping over” (and hence missing) small lesions. Despite these efforts to reduce acquisition time, the complete spine MRI examination time overall remains long enough that unsedated patients may become uncomfortable and restless in the scanner, resulting in patient motion artifact that degrades image quality and further impairs diagnostic accuracy. For these reasons, it is generally recommended to target MRI of the spine to the anatomy of greatest clinical concern—cervical, thoracic, or lumbar spine—unless inclusion of the entire spine is unavoidable.

Chest Imaging

The chest is initially imaged as part of the trauma series. If interventions are performed, follow-up radiographs may also need to be obtained.

Less complex injuries such as rib fractures, hemothorax, and pneumothorax are usually evaluated with radiographs, but if there is concern for more complex injuries such as major airway or mediastinal injury, a chest CT scan is obtained for further evaluation.

If the mediastinum is not normal on a chest radiograph, in a patient with appropriate mechanism for aortic or great vessel injury, a mediastinal view is obtained. This consists of a radiograph coned down to image the mediastinum and with radiographic technique modified to better visualize the mediastinum. If the mediastinum is not normal on this study, a mediastinal vascular injury is suspected.

In the past, suspected injuries of the aorta and great vessels were evaluated with catheter angiography. Over the past decade, CTA of the chest, integrated with other CT scans of the body, has replaced catheter angiography for diagnostic purposes, allowing more rapid imaging to be obtained, without the added risk (low as it is) of catheter angiography. In addition to evaluating the aorta [see Figure 5] and great vessels, chest CTA provides evaluation of the remainder of the chest for spine, pulmonary, and musculoskeletal injuries, regions not evaluated with catheter angiography.

Abdominal and Pelvic Imaging

The clinical indications for abdominal CT following trauma are discussed in other chapters of this text.

CT of the abdomen and pelvis for trauma should use IV contrast if at all possible as it allows the solid organs to enhance, increasing our ability to detect lacerations, infarctions, and surrounding hematoma. On a noncontrast scan, a solid-organ laceration filled with hematoma may be difficult (if not impossible) to identify if the hematoma has density similar to that of the organ and if no identifiable contour defect or hematoma is adjacent to the organ. Oral contrast is not routinely administered for trauma imaging, as discussed later in this chapter.

CT of the abdomen and pelvis is performed during the portal venous phase of IV contrast enhancement as this is the best single phase in which to evaluate the abdominal contents. During this phase, the liver enhances well, as does the spleen (without the heterogeneous appearance commonly seen earlier in arterial phase imaging). The kidneys enhance fairly homogeneously, and most other structures demonstrate adequate enhancement to allow identification of injury.

Some institutions routinely add other phases, such as arterial phase and/or delayed phase imaging. Others do not routinely perform arterial phase imaging (CTA) as part of their initial evaluation of the abdomen and pelvis as they find the yield to be low and choose instead to minimize the radiation dose to their larger population without vascular injury and perform selective additional imaging in the few patients requiring it. However, if predictors of vascular injury are developed and the value of arterial phase imaging is proven to outweigh the consequences of the additional radiation, it may be appropriate to image these selected patients during the arterial phase of enhancement as well as during the venous phase. Newer MDCT scanners are fast enough to allow arterial phase imaging prior to portal venous phase imaging using just one injection of contrast.

Some institutions have their CT scanner and radiologists in their emergency department and review the abdomen and pelvis CT scans while the patient is on the scanner to determine if delayed images are necessary. Delayed images can be selectively obtained to minimize radiation. Other institutions without the ability to review images while the patient is still on the scanner may elect to routinely obtain delayed images on all patients, but this will result in a higher radiation dose to their population.

Low radiation dose delayed images are obtained for one of the following reasons:

- To further characterize potential vascular injuries such as pseudoaneurysm, arteriovenous fistula, or vascular extravasation
- To evaluate for urinary extravasation
- To further characterize nontraumatic (incompletely characterized) lesions such as liver hemangiomas or adrenal masses (assuming that the patient is stable enough to undergo this elective delayed imaging)

Injury Grading and Common Injury Appearances

The American Association for the Surgery of Trauma (AAST) organ injury scale (OIS)²³ is generally based on

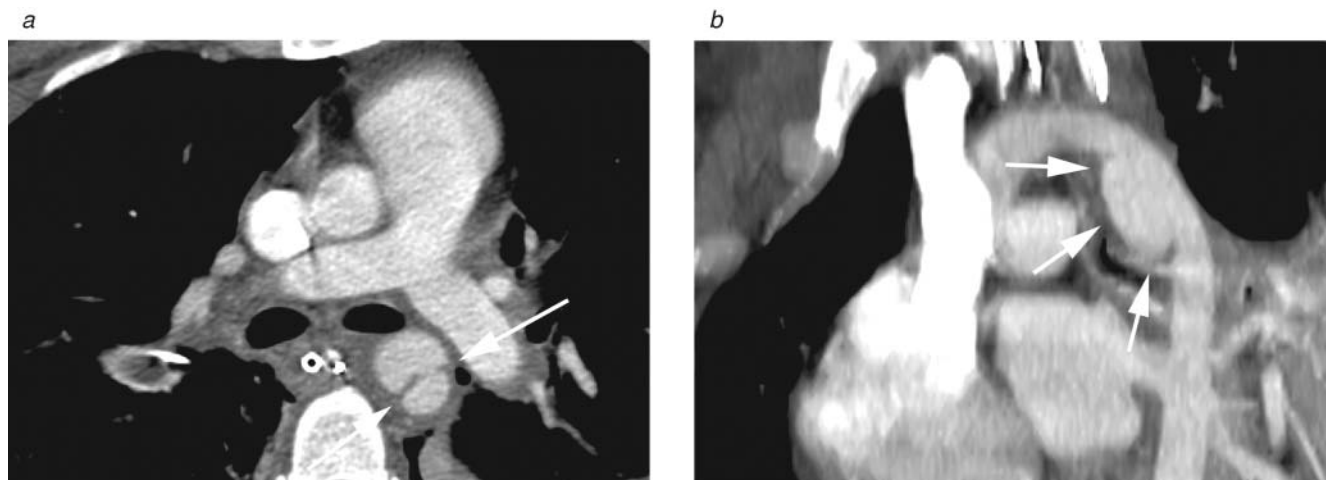


Figure 5 (a) Linear defect (arrows) may be interpreted as an aortic dissection. (b) Oblique multiplanar reformation images oriented similar to the “candy cane” images obtained with angiography demonstrate that the lesion represents a traumatic aortic pseudoaneurysm, which protrudes beyond the normal contour of the aorta (arrows).

anatomic abnormalities that can be identified on CT or at surgery: hematoma, contusion, laceration, shattered organ, and partial or complete devascularization.

Croce and colleagues demonstrated poor correlation of CT with surgical grading; however, this study was based on CT imaging obtained from 1986 to 1990,²⁴ which was quite limited compared with imaging available today. Injury grading was consistent on CT and at surgery in only 16% of patients. In another 11% of patients, CT identified intrahepatic hematomas that were missed at surgery. The remaining 73% of patients had incorrect injury grading by CT (using surgery as the gold standard). In 56% of these remaining patients, CT underestimated the injury grade, whereas in 44%, CT overestimated the injury grade. However, these results must be interpreted with caution as images were obtained with 8 mm thickness, with 2 mm gaps between images and without the benefit of MPRs. Thus, injuries may have been missed as a result of suboptimal enhancement attributable to slower CT scanning, volume averaging attributable to the thicker images, or missed injuries in the plane of the scan attributable to gaps between images and/or absent MPRs (which would better demonstrate these findings).

Consistent injury grading using the AAST OIS can be challenging as it may be difficult to interpret some of the grading criteria.²⁵ In a study of CT grading of pediatric hepatic trauma,²⁶ only moderate intraobserver agreement was found for all investigators, except for the senior radiologist who demonstrated good intraobserver agreement. Interobserver correlation suggested agreement on the general severity of the injury but not on the exact grading of the injury.

Common Injury Appearances

We briefly describe some of the common solid-organ CT imaging findings below and review other imaging findings in their specific sections of this chapter.

A subcapsular hematoma typically presents as a crescentic or biconvex fluid collection located between the organ and its capsule. A small collection of fluid adjacent to an organ can

be difficult to distinguish as subcapsular or extraparenchymal, but if the capsule is clearly indentified, or if there is a smooth, well-margined peripheral contour to the fluid and/or compression of the underlying parenchyma [see Figure 6], then a subcapsular hematoma can be diagnosed.

A contusion typically presents as an area of decreased attenuation on portal venous phase imaging and may demonstrate increased attenuation on delayed imaging.

A laceration typically presents as a linear or jagged defect in the parenchyma, with decreased attenuation on contrast-enhanced images compared with the surrounding normal tissue [see Figure 7]. On noncontrast images, the laceration may present with higher density than surrounding paren-

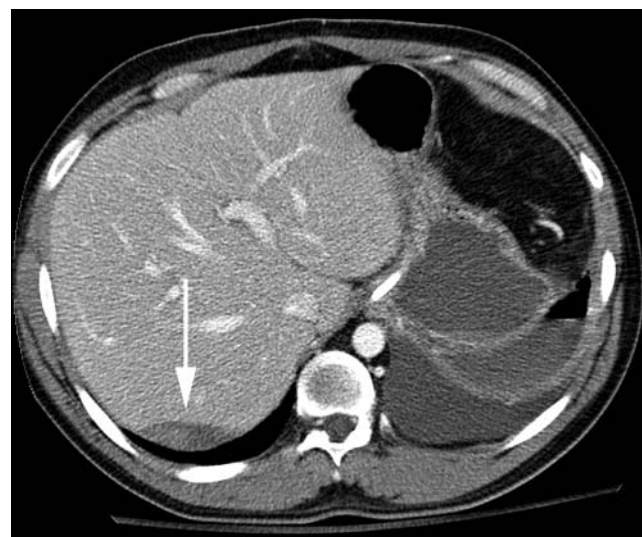


Figure 6 Small subcapsular hematoma (arrow) is present along the posterior margin of the right lobe of the liver, characterized by a well-defined peripheral border and mild compression (indentation) of the underlying hepatic parenchyma.



Figure 7 Arrows identify the more anteriorly located linear laceration and the more posteriorly located jagged laceration of the right lobe of the liver, evident as regions of decreased density compared with the uninjured portions of the liver on this contrast enhanced computed tomographic scan.

chyma as a result of hemorrhage within the laceration. The depth of the laceration can be measured on CT.

A shattered organ presents as multiple small fragments separated by multiple deep lacerations, usually surrounded by extensive hematoma [see Figure 8].

A devascularized organ demonstrates no enhancement on contrast-enhanced CT [see Figure 9] unless collateral vessels are able to provide some perfusion following disruption of the major supplying vessels.

Specific Findings in Abdominal Solid-Organ Injuries

Most injuries demonstrate the common imaging findings described above. Several specific abdominal organ features are briefly described below.

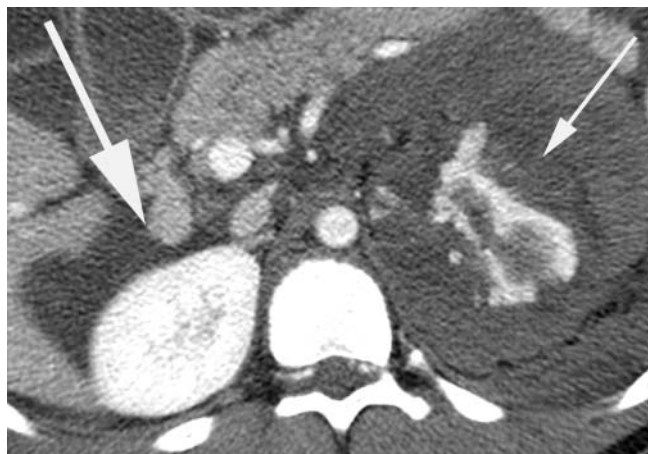


Figure 8 A small arrow identifies enhancing fragments of the shattered left kidney surrounded by a large amount of hematoma and/or urinoma. Compare with the normal right kidney (large arrow).



Figure 9 The arrow identifies the nonperfused right kidney attributable to a traumatic renal artery injury resulting in renal infarction. Compare with the normally enhancing left kidney.

LIVER TRAUMA

Although hemorrhage extending from liver injury usually results in hemoperitoneum, retroperitoneal extension of hemorrhage can result in a negative FAST scan and diagnostic peritoneal lavage but can be identified on CT. CT is not reliable for detecting the presence of bile duct injury, but suspicion should be raised when deep hepatic lacerations or lacerations extending to the gallbladder fossa are identified. These can be worked up further with hepatobiliary scintigraphy.

PANCREATIC TRAUMA

Diagnosis of pancreatic injury can be challenging. Focal findings may not be evident on initial imaging and may take up to 24 hours to become apparent on CT.²⁷ Hence, repeat imaging using a pancreatic protocol is often requested 8 to 24 hours after the initial nonconclusive CT in patients with a high suspicion of pancreatic injury. Conversely, fluid adjacent to the pancreas is not infrequently present in patients without pancreatic or duodenal injury. The clinical examination and laboratory results are critical in deciding which patients with nonspecific initial imaging findings require further imaging. Whereas some authors claim that pancreatic ductal injury can be accurately diagnosed with CT,²⁸ others would consider endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) for further evaluation.

Esophageal and Bowel Injury

Identification of esophageal injury on CT is challenging. Given that esophageal injury is rare in blunt trauma, unless specific findings are present suggesting esophageal injury (such as focal esophageal thickening and/or focal paraesophageal gas or fluid out of proportion to other mediastinal findings), it is usually assumed that paraesophageal gas is attributable to extension of a pneumothorax. In penetrating injury to the mediastinum, this assumption cannot be made, and further evaluation of the esophagus is indicated. Esophagography can then be performed to evaluate for perforation.

Oral and rectal contrast are not usually administered for initial CT imaging of blunt abdominal trauma as they are rarely required.^{29–31} However, in the few cases in which bowel

injury is suspected, directed follow-up CT to evaluate the area of concern may use oral contrast (e.g., for suspected duodenal injury based on wall thickening and surrounding fluid) or rectal contrast (e.g., for suspected colon injury near a displaced pelvic fracture). Although extravasation of bowel contrast definitively makes the diagnosis of bowel perforation, it is rarely seen, and bowel injury may exist in the absence of contrast extravasation (if the perforation is occluded by hematoma or other bowel contents or by spasm). Intraperitoneal or retroperitoneal gas near the area of suspected bowel injury [see Figure 10] is assumed to arise from bowel perforation if other sources for the gas are not identified (such as extension of pneumothorax).

In penetrating trauma, however, fluid and gas near the bowel could represent hematoma and gas from the track of the penetrating object or evidence of bowel injury. Oral and rectal contrast are administered to victims of penetrating trauma as they may be helpful to confirm bowel disruption (if extravasation is demonstrated). The patient is imaged shortly after administration of oral contrast, and imaging is not delayed to allow contrast to pass to the terminal ileum as it is more desirable to determine the extent of other injuries acutely so that they can be addressed rapidly.

When free air or contrast extravasation is not identified, focal bowel wall thickening with surrounding stranding raises concern for injury. However, this is a nonspecific finding as bowel can be thickened as a result of peristalsis, and stranding may extend from other injuries or be unrelated to trauma. Absent enhancement of the expected region of bowel wall, when the remainder of the bowel demonstrates normal enhancement, indicates bowel wall infarction or disruption. High-density fluid consistent with hematoma that is present only within the mesentery or that is predominantly located



Figure 10 A focus of gas (arrow) and stranding adjacent to the lateral wall of the ascending colon is identified. If this was noted following blunt trauma and no other source for the gas was identified, the gas and stranding would provide presumptive evidence of bowel rupture. However, if this was noted following penetrating trauma, the gas and fluid may both result from the penetrating injury and track, and bowel injury could not be confirmed with imaging without other imaging signs such as bowel wall disruption or contrast extravasation.

within the mesentery rather than in the more accessible regions of the peritoneal cavity is suggestive of mesenteric hematoma. Occlusion of or extravasation from a mesenteric vessel identifies mesenteric injury.

Urinary System Injury

The urinary system differs from other abdominal and pelvic organs as fluid around these structures may represent urinary leakage and not simply hemorrhage.

If an injury to the kidney is identified with adjacent fluid or if there is unexplained or suspicious fluid around the kidney or ureter, delayed images should be obtained. The delay allows renal excretion of contrast into the urine to occur, permitting detection of contrast-enhanced urine leakage from the kidney or ureter [see Figure 11].

Delayed imaging is obtained at 5 to 10 minutes. If the patient is stable, a longer delay before imaging allows more contrast extravasation to occur, which may increase the chance of detecting a small leak or identifying its extent. The delay can always be shortened to accommodate the needs of

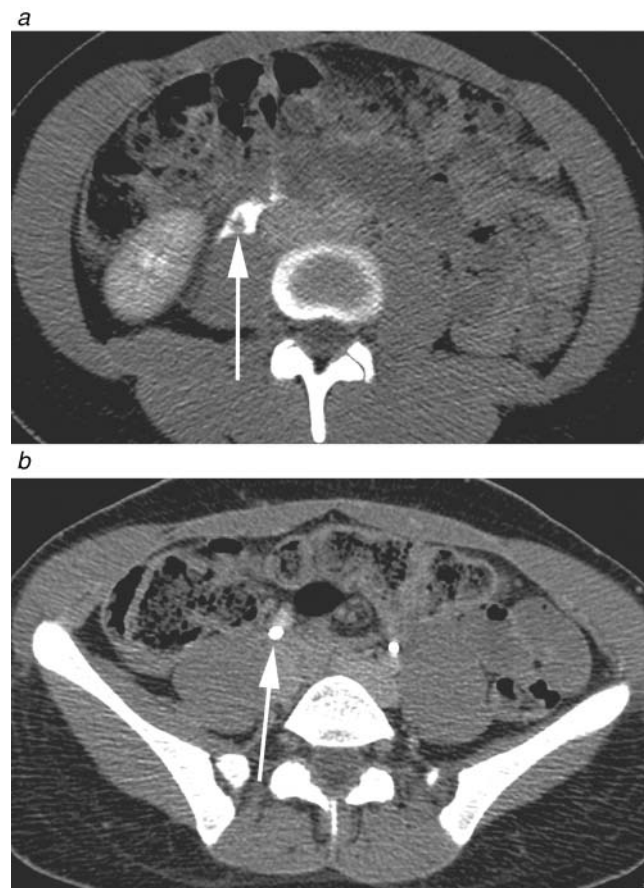


Figure 11 (a) Extravasated urinary contrast (white material) surrounding the proximal right ureter (arrow) is noted, indicating ureteral laceration or transection if no other source of contrast is identified. (b) Contrast is present in the distal right ureter (arrow), confirming that the proximal and distal ureter are in contiguity and that the injury represents a laceration and not a transection.

the surgical team (e.g., if the patient becomes unstable or needs to be transported to surgery or angiography), with the understanding that shorter delays may limit evaluation.

When gross hematuria and free intraperitoneal fluid are present, an intraperitoneal bladder rupture should be suspected, and computed tomographic cystography (CTC) can be obtained for evaluation of the bladder [see Figure 12]. If a high level of microhematuria (≥ 30 red blood cells per high-power field on microscopic urinalysis)³² or gross hematuria are present, in conjunction with a pelvic ring disruption, then further evaluation for bladder rupture with CTC is indicated.

When delayed images of the pelvis are indicated, CTC is obtained in conjunction with the delayed images. Using a urinary catheter and dilute iodinated contrast, the bladder is filled while waiting to obtain the delayed images. The patient is scanned once rather than radiated twice: once for the delayed images and again for the CTC. This allows faster completion of the study as time is not taken to fill the bladder and set up the scan for the CTC following the delayed images.

Penetrating Trauma

In penetrating trauma patients, it is helpful to follow the visualized or expected path of the penetrating object. Knife tracks can be challenging to visualize. If there is little hematoma or gas, the majority of the track may be poorly or not visualized. But careful review, using CT windows that demonstrate gas, often reveals at least a portion of the proximal and distal aspects of the track.



Figure 12 Coronal image from a computed tomographic cystogram demonstrating an intraperitoneal bladder rupture, with contrast (large arrow) extending superiorly from the disrupted dome of the bladder into the intraperitoneal spaces (small arrows) adjacent to bowel.

Unfortunately, the track is usually not entirely visualized in a single axial plane CT image, and the superior and inferior images should be reviewed to identify an oblique course of the track.

Another challenge to be aware of is the change in the position of structures between the time of injury and the time of imaging, possibly exacerbated by a change in patient position. Thus, a patient who was stabbed through the lateral chest wall while in deep inspiration may demonstrate a pulmonary laceration far more superiorly than expected when compared with the chest wall laceration as a result of the decreased lung volumes at the time of imaging secondary to patient splinting and supine position.

If a track is identified, injury along the course of the track should be considered, even if there is no direct visualization of injury. For example, a stab wound through the dome of the liver and into the lung base should be assumed to involve the diaphragm, even if the diaphragmatic injury cannot be directly visualized.

Isolated Free Intraperitoneal Fluid

Free intraperitoneal fluid in the absence of identifiable solid-organ injury on CT raises concern for occult bowel injury or devitalizing mesenteric injury. This frequently prompts further evaluation, typically diagnostic peritoneal lavage or exploratory laparotomy. With modern CT scanners and techniques, small amounts of isolated intraperitoneal fluid are detected more commonly than in the past, even in males, and more conservative approaches to the management of these patients have been proposed,^{33,34} with variable success reported.

Vascular Injury

Vascular contrast beyond the normal confines of a vessel may represent a pseudoaneurysm [see Figure 5b], arteriovenous fistula, or active extravasation. A pseudoaneurysm will closely match the density of adjacent vessels during the contrast-enhanced portion (arterial or portal venous phase) of the CT scan but will “wash out” on the delayed phase and continue to match surrounding vessels as the contrast in the pseudoaneurysm remains contiguous with the intravascular space and flows away from the injury. An arteriovenous fistula may demonstrate contrast enhancement and washout similar to those of a pseudoaneurysm but represents posttraumatic communication between an artery and a vein. When small, both lesions may simply appear as small focal areas of extraluminal contrast [see Figure 13] and be difficult to differentiate, and catheter angiography may be necessary to differentiate between these lesions.

Active contrast extravasation [see Figure 14a] represents contrast leaking beyond the vessel, not contained by either the vessel wall or the surrounding tissue that produces a pseudoaneurysm. The extravasated contrast mixes with unopacified hemorrhage, and the density and appearance of the extravasated contrast depend on the rate of extravasation and the amount of mixing that occurs with surrounding hemorrhage. Delayed images demonstrate an accumulation of contrast [see Figure 14b] versus the washout seen with pseudoaneurysms and arteriovenous fistulae.



Figure 13 Round lesion (arrow) is identified within the liver, which on sequential images (not shown) does not follow the normal course of a vessel. It has density similar to that of surrounding vessels but is larger than adjacent vessels. The round, smooth contours suggest that this represents a pseudoaneurysm, which was proven at angiography.

Transection or avulsion of a vessel may demonstrate active extravasation from the proximal portion of the vessel, with absent enhancement of the distal vessel (assuming no collateral flow). However, if there is spasm or dissection of the proximal vessel, no contrast extravasation may be present.

Stretching of a vessel can produce a traumatic dissection, which may result in partial or complete occlusion attributable to thrombosis.

In recent years, CTA of the extremities has begun to replace or supplement diagnostic catheter angiography in screening for injury. CTA may be considered a reasonably accurate screening tool for suspected injuries such as posterior knee dislocations, gunshot injuries near a vessel, or other injuries resulting in abnormal pulses or abnormal distal pressures demonstrated with Doppler ultrasonography. Although catheter angiography or surgery is sometimes required for treatment, CTA provides a noninvasive rapid mechanism to evaluate for the presence of injury and to determine if further intervention is required. Performing isolated CTA of the extremities is relatively straightforward, but performing CTA of the extremities in conjunction with torso imaging can be challenging because of the length of the area imaged (potentially more than 6 feet if we image from the arms above the head down to the feet), timing of contrast injection and imaging (as the CT table may have to rapidly move from the neck down to the legs and then back up to the chest), position of the arms, and site of contrast injection (as injected venous contrast in the upper extremities and chest may obscure portions of the arteries we wish to examine).

Musculoskeletal Injury

Most suspected orthopedic injuries are initially imaged with radiography. Complex injuries, especially those involving or suspected to involve the joints, may require CT for

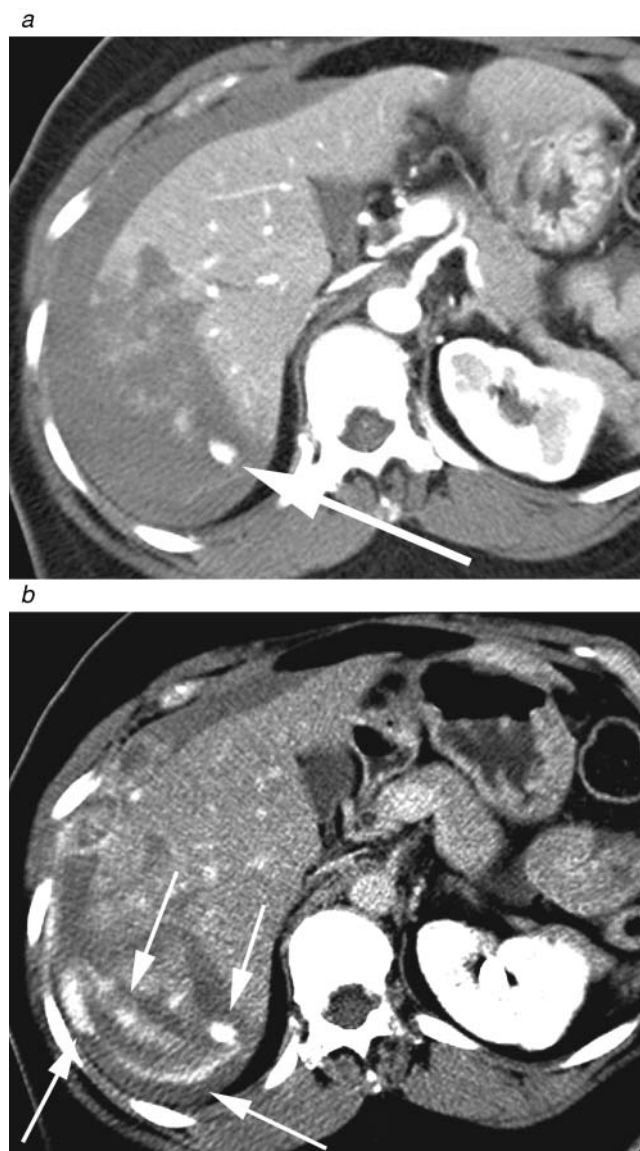


Figure 14 (a) In addition to the liver laceration and surrounding hematoma demonstrated on portal venous phase images, a small collection of contrast is identified (arrow) beyond the expected confines of the normal vessels. This may represent active extravasation, pseudoaneurysm, or arteriovenous fistula. (b) Delayed images demonstrate contrast extravasation as areas of high-density material (arrows) mixed with parenchymal and perihepatic hematoma.

further evaluation,³⁵ and MRI may be helpful in selected cases. Some of the more common orthopedic CT examinations obtained include shoulder fractures extending into the glenoid fossa, pelvic ring and acetabular fractures, tibial plateau fractures, and hindfoot and midfoot fractures. CT is not limited by the presence of casts or dressings, and positioning is usually not as critical as it is for radiographs.

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1 CARDIAC RESUSCITATION

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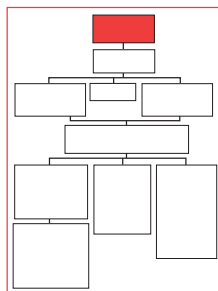
Approach to Cardiovascular Resuscitation

Out-of-hospital sudden cardiac arrest claims the lives of more than 300,000 persons in the United States each year, making it the leading cause of death.¹⁻⁴ In fact, approximately 50% of all cardiac deaths are sudden deaths.⁵ In hospitals, a minimum of 370,000 patients also suffer a cardiac arrest, followed by an attempted, but only sometimes successful, resuscitation.⁶ Although most victims of sudden death have underlying coronary artery disease (70 to 80%), sudden death is the first manifestation of the disease in half of these persons.² Other causes and contributing factors include abnormalities of the myocardium (i.e., chronic heart failure or hypertrophy from any cause), electrophysiologic abnormalities, valvular heart disease, congenital heart disease, and miscellaneous inflammatory and infiltrative disease processes (e.g., myocarditis, sarcoidosis, and hemochromatosis).⁷⁻⁹

The pathophysiology that culminates in a sudden cardiac death is complex and poorly understood. It likely represents a mix of electrical abnormalities combined with acute functional triggers, such as myocardial ischemia, central and autonomic nervous system effects, electrolyte abnormalities, and even pharmacologic influences.¹ Classically, most sudden deaths that occur in adults in the community are thought to be secondary to ventricular tachycardia (VT) that quickly degenerates into ventricular fibrillation (VF). In a 10-year study in the Seattle area, the different arrhythmias found in prehospital cardiac arrest patients presumed to have underlying cardiovascular disease were VF (45%), asystole (31%), pulseless electrical activity (PEA; 10%), VT (1%), and other arrhythmias (14%).³ Studies indicate that the out-of-hospital incidence of VF has decreased in recent years, probably because of the decrease in mortality from coronary artery disease.¹⁰

The Chain of Survival

The resuscitation of an adult victim of sudden cardiac arrest should follow an orderly sequence, no matter where the patient's collapse occurs. This sequence is called the chain of survival.¹¹ It comprises four elements, all of which must be instituted as rapidly as possible: activation of the emergency medical service network, cardiopulmonary resuscitation (CPR), early defibrillation, and provision of advanced care.



ACTIVATION OF EMERGENCY MEDICAL SERVICES

A person in cardiac arrest is unresponsive and pulseless, although agonal respirations may last for minutes. Confirm unresponsiveness by speaking loudly and gently shaking the patient. If the patient is truly unresponsive, immediately call for help by activating the emergency medical service in the community (in most locales, this means calling 911). If an automated external defibrillator (AED) is available, have it brought to the resuscitation scene. AEDs are both easily used and lifesaving.¹²⁻¹⁶ If the patient is already in the hospital, call a code (e.g., code blue, code 199). The concept of a rapid response system (RRS), known as a rapid response team or a medical emergency team, has been developed to improve the outcome of in-hospital emergency.¹⁷ The identification of medical emergency based on the activation criteria and immediate response by a dedicated team are major components of this system. The implementation of an RRS has been shown to be associated with a reduction of the incidence of in-hospital cardiac arrest and subsequent mortality.^{18,19}

INITIATION OF CPR

While awaiting the arrival of a defibrillator and advanced help, the rescuer assesses the patient's airway, breathing, and circulation [see The Primary Survey, *below*] and initiates CPR [see Table 1]. When CPR is started within 4 minutes of collapse, the likelihood of patient survival at least doubles.^{20,21}

INITIATION OF DEFIBRILLATION

When the AED or monitor-defibrillator arrives, attach it appropriately to the patient and analyze the patient's rhythm; if the patient is in VF or pulseless VT, a defibrillatory shock should be rapidly applied [see Table 2 and Table 3]. The importance of rapid access to defibrillation cannot be over-emphasized. In a patient who is dying from a shockable rhythm, the chance of survival declines by 7 to 10% for every minute that defibrillation is delayed.²² Chest compression should be resumed immediately after a defibrillation to minimize the interruption of CPR.

INITIATION OF ADVANCED CARE

If the patient remains pulseless despite the steps described above, resume CPR; establish a definitive airway, confirm its correct placement, and then secure it; establish intravenous (IV) access; and then administer appropriate medications as determined by the rhythm and the arrest circumstances. If the patient is in VF or pulseless VT, repeated attempts at

Approach to Cardiovascular Resuscitation

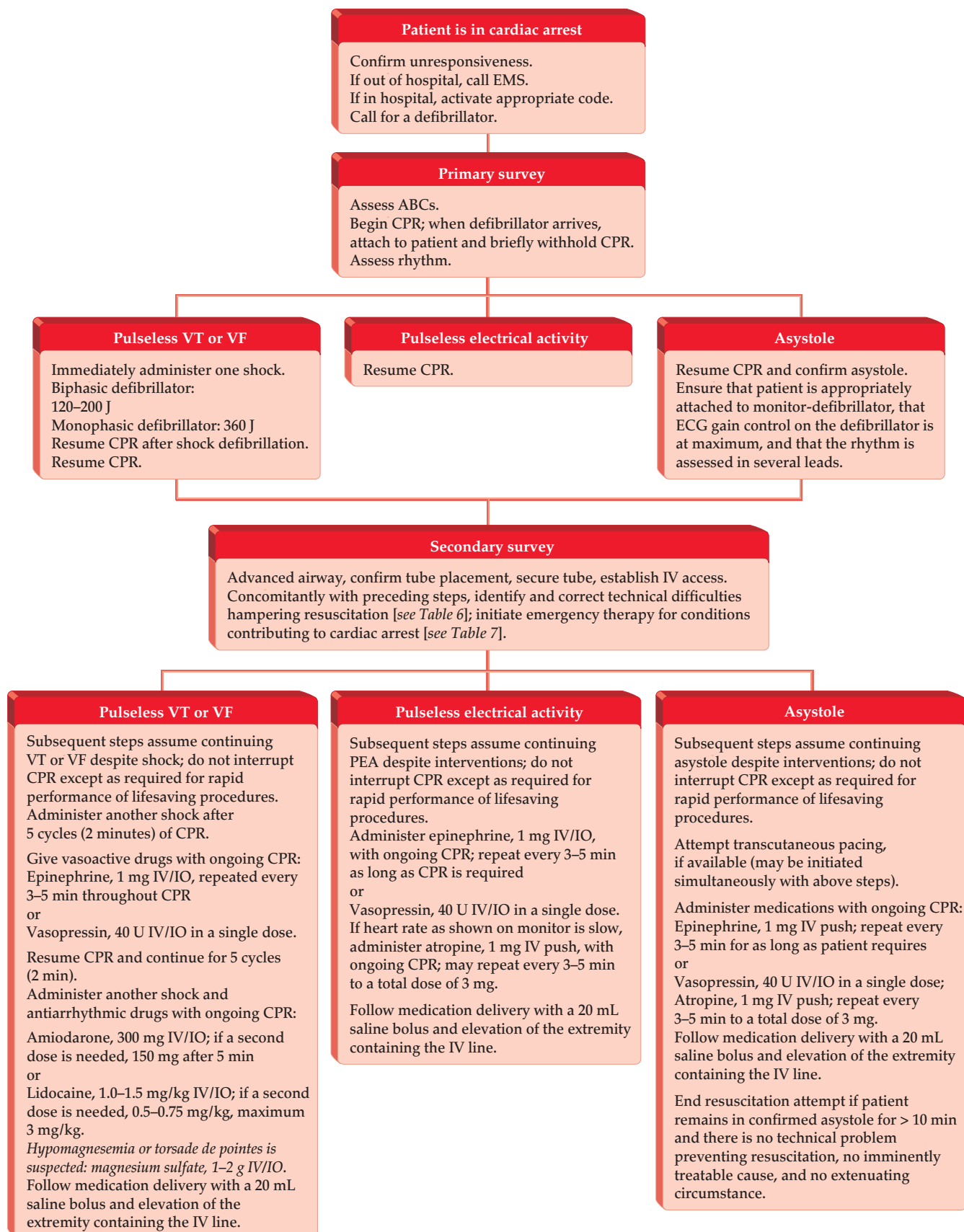


Table 1 Initial Resuscitation Steps in the Unresponsive Patient

Confirm unresponsiveness
Activate the emergency medical system
In most community locales, call 911
In the hospital, activate the appropriate code response
Call for an automatic external defibrillator (AED) or a manual defibrillator
Begin basic life support (CPR)
Open airway
Check breathing; if not breathing, deliver two initial breaths
Check for carotid pulse; if pulseless, do the following:
Begin chest compressions at the rate of 100 compressions/min, depressing the sternum 1.5–2.0 inches per compression
In pediatric patients,* compress approximately one third to one half the depth of the chest at the rate of 100 compressions/min
Intersperse ventilations with chest compressions: in nonintubated patients, deliver 30 compressions, pause for two breaths, then repeat; in intubated patients, deliver one breath every 6 to 8 sec, with no pause in compressions
In pediatric patients,* 30:2 for single rescuer and 15:2 for two rescuers for nonintubated patients; in intubated patients, deliver one breath every 6 to 8 sec, with no pause in compressions
Reassess for return of spontaneous circulation every 5 cycles or 2 minutes of CPR
When defibrillator arrives, immediately analyze and treat arrhythmia
Attach patient to AED [see Table 2] or the monitor-defibrillator [see Table 3]
Analyze arrhythmia and treat as appropriate

CPR = cardiopulmonary resuscitation.

*Lay rescuers: 1 to 8 years; health care providers: 1 year to adolescent.

Table 2 Using an Automatic External Defibrillator

Automatic external defibrillator (AED) arrives (CPR is in progress).
Place AED beside patient.
Turn on the AED.
Attach the electrodes to the AED (they may be preattached).
Attach the electrode pads to the patient (as diagrammed on the pads). In pediatric patients,* use child pads and system if available.
AED analyzes patient's rhythm
Stop CPR (and ensure no one is touching the patient).
Press the Analyze button on the AED (some devices analyze the rhythm automatically as soon as the pads are placed on the patient).
AED instructs rescuers (via an audible voice prompt and/or on-screen instructions)
Shock is indicated: clear the patient (ensure no one is touching the patient) and push the Shock button. Resume CPR starting with chest compressions, immediately after shock, for 2 minutes. Then analyze the rhythm.
or
Shock is not indicated: reassess the patient for signs of circulation; if present, assess the adequacy of breathing; if there are no signs of circulation, resume CPR.

CPR = cardiopulmonary resuscitation.

*Lay rescuers: 1 to 8 years; health care providers: 1 year to adolescent; AED for infants < 1 year is not recommended.

Table 3 Using a Manual Defibrillator

Defibrillator arrives (CPR is in progress)
Place defibrillator beside patient.
Turn defibrillator on.*
Set Lead Select switch to Paddles. Alternatively, if patient is already attached to monitor leads, set Lead Select switch to lead I, II, or III; ensure that all three leads are correctly attached to the patient and the defibrillator: white to right shoulder, black to left shoulder, red to ribs on left side.
Apply gel to paddles or place conductor pads on the patient's chest. Some devices use disposable electrode patches that are prepaste with a conducting gel. In either case, the appropriate positions of the paddles with applied gel, conductor pads, or disposable paddles are as follows: sternal paddle is placed to the right of the sternum, just below the right clavicle; apex paddle is placed to the left of the left breast, centered in the left midaxillary line at the fifth intercostal space.
Analyze rhythm
Briefly withhold CPR
If using paddles to assess rhythm, apply paddles as described with firm pressure (25 lb of pressure to each paddle) and visually assess rhythm on monitor (if using leads, briefly withhold CPR and assess rhythm in lead I, II, or III). If rhythm is either pulseless VT or VF, proceed as follows:
Defibrillate, then reassess
Announce to resuscitation team, "Charging defibrillator, stand clear!" and press Charge button on either paddles or defibrillator.*
Warn resuscitation team that a defibrillatory shock is coming:
"I am going to shock on three! ONE, I'm clear; TWO, you're clear, THREE, everybody's CLEAR!" Simultaneously with these statements, visually ensure that no resuscitation team member is in contact with patient.
Press the Discharge buttons on both paddles simultaneously to deliver a defibrillatory shock. Resume CPR starting with chest compressions, immediately after shock, for 2 minutes (about 5 cycles). Then analyze the rhythm.

Adapted from Levine RL et al⁵² and Cummins RO et al.⁸⁹

CPR = cardiopulmonary resuscitation; VF = ventricular fibrillation; VT = ventricular tachycardia.

*Biphasic defibrillator: device specific (120 to 200 J), monophasic defibrillator: 360 J; in patients ≤ 8 years: 4 J/kg

defibrillation are interspersed with delivery of vasoactive and antiarrhythmic drugs [see Table 4].

RESUSCITATION OUTCOME

When every link in the chain of survival is quickly and sequentially available, the patient is provided with an optimal opportunity for return of spontaneous circulation.^{22,23} In the United States, individual communities report survival rates of 4 to 40% or more in cases of sudden cardiac death.^{24–27} Pre-hospital victims of VF have had survival rates to hospital discharge of greater than 50% when an AED was expeditiously used.²⁸ Many other factors also influence patient survival, however; these include whether the patient's collapse was witnessed, the rapidity and effectiveness of bystander CPR, the rhythm associated with the cardiac arrest, and underlying comorbidities.^{29,30} With inpatient cardiac arrest, for example, overall survival rates vary from 9 to 32%,^{31–37} but in one study, survival to hospital discharge was 30% for patients with primary heart disease, 15% for patients with infectious diseases,

Table 4 Drugs Useful in Cardiac Arrest

Category	Drug and Doses Supplied	Indications in Cardiac Arrest	Adult Dosage	Comments
Vasopressors	Epinephrine, 1 mg in 10 mL emergency syringe; 1 mg/mL (1 mL and 30 mL vials)	Pulseless VT or VF unresponsive to initial defibrillatory shock; PEA; asystole	1 mg IV/IO push; may repeat every 3–5 min for as long as patient is pulseless; can also be given via the endotracheal route: 2–2.5 mg diluted with normal saline (NS) to 10 mL total volume	IV/IO boluses of epinephrine (1 mg) are appropriate only in pulseless cardiac arrest patients; if continued epinephrine is required after resuscitation, a continuous infusion should be started (1–10 µg/min) High-dose epinephrine (up to 0.2 mg/kg IV/IO per dose) does not improve survival to hospital discharge in cardiac arrest patients and is no longer recommended in adults
	Vasopressin, 20 IU/mL (1 mL vial)	Pulseless VT or VF unresponsive to initial defibrillatory shock; PEA; asystole	40 IU IV/IO push, single dose only; can also be given via endotracheal tube: same dose, diluted with NS to 10 mL total volume	If no response after 10 min of continued resuscitation, administer epinephrine, as above
Antiarrhythmics	Amiodarone, 50 mg/mL (3 mL vial)	Pulseless VT or VF unresponsive to defibrillatory shock, CPR, and vasopressor	VT/VF: 300 mg diluted in 20–30 mL; NS or D ₅ W rapid IV/IO push; a repeat dose of 150 mg may be given if required in 3 to 5 min; maximum dose in 24 hr should not exceed 2,200 mg	Side effects may include hypotension and bradycardia in the postresuscitation phase
	Lidocaine, 50 mg or 100 mg in 5 mL emergency syringes; premixed bag, 1 g/250 mL or 2 g/250 mL	Pulseless VT or VF unresponsive to defibrillatory shock, CPR, and vasopressor	Initial dose: 1–1.5 mg/kg IV/IO, may repeat 0.5–0.75 mg/kg IV/IO in 5–10 min; maximum dose, 3 mg/kg May also be given endotracheally: 2–4 mg/kg diluted with NS to 10 mL total volume	An alternative when amiodarone is not available
	Magnesium sulfate, 500 mg/mL (2 mL and 10 mL vials), or 10 mL emergency syringe	Pulseless VT or VF unresponsive to defibrillatory shock, CPR, and vasopressor, associated with torsades de pointes, and known or suspected low serum magnesium	Administer 1–2 g diluted in 10 mL D ₅ W IV/IO over 5–20 min Total body magnesium deficits should be replaced gradually after initial therapy has stabilized the emergency: administer 0.5–1 g/hr for 3–6 hr, then reassess continued need	Measured magnesium levels correlate only approximately with the actual level of deficiency Patients with renal insufficiency are at risk for dangerous hypermagnesemia; use appropriate caution Side effects may include bradycardia, hypotension, generalized weakness, and temporary loss of reflexes
Anticholinergic	Atropine, 1 mg in 10 mL emergency syringe	Asystole or PEA (if rate of rhythm is slow)	For asystole or PEA: 1 mg IV/IO every 3–5 min up to 3 mg May be given via ET tube: 2–3 mg diluted with NS to 10 mL	Avoid use in type II second-degree heart block or third-degree heart block
Miscellaneous	Bicarbonate, 50 mEq in 50 mL emergency syringe	Significant hyperkalemia Significant metabolic acidosis unresponsive to optimal CPR, oxygenation, and ventilation Certain drug overdoses, including tricyclic antidepressants and aspirin	Hyperkalemia therapy: 50 mEq IV/IO Metabolic acidosis: 1 mEq/kg slow IV/IO push; may repeat half initial dose in 10 min; ideally, ABGs should help guide further therapy Use in overdose: discuss with toxicologist	In non-dialysis-dependent hyperkalemic patients, bicarbonate is most useful if metabolic acidosis is also present; bicarbonate is less effective in dialysis-dependent renal failure patients. The use of bicarbonate in metabolic acidosis management in cardiac arrest patients is controversial. Side effects may include sodium overload, hypokalemia, and metabolic alkalosis
	Calcium chloride, 100 mg/mL in 10 mL prefilled syringe	Significant hyperkalemia Calcium channel blocker drug overdose Profound hypocalcemia of other causes	In hyperkalemia: 5–10 mL slow IV/IO push; may repeat if required In calcium channel blocker overdose: discuss with toxicologist	Do not use if suspected cause of hyperkalemia is acute digoxin poisoning Do not combine in same route with sodium bicarbonate Calcium chloride is not a routine medication in cardiac arrest

Adapted from Eisenberg MS and Mengert TJ³ and 2005 American Heart Association.⁹⁰

ABG = arterial blood gases; CPR = cardiopulmonary resuscitation; D₅W = 5% dextrose in water; ET = endotracheal; PEA = pulseless electrical activity; IV/IO = intravenous/intraosseous; VF = ventricular fibrillation; VT = ventricular tachycardia.

All medications used during cardiac arrest, when given via a peripheral venous site in an extremity, should be followed by a 20 mL IV saline bolus and elevation of the extremity for 10 to 20 seconds.

and only 8% for patients with other end-stage diseases (e.g., cancer, lung disease, liver failure, or renal failure).³⁸

Such statistics underline the importance of using cardiac resuscitation appropriately and with discrimination. Cardiac resuscitation provides rescuers with powerful tools that save the lives of thousands of people every year. These techniques are capable of returning patients who would otherwise die to productive and meaningful lives. However, cardiac resuscitation should not be employed to reverse timely and natural death. Under those circumstances, it has the potential to lengthen the dying process and to increase human suffering. All practitioners are well advised to remember that “death is not the opposite of life, death is the opposite of birth. Both are aspects of life.”³⁹ It is untimely death that requires immediate intervention with cardiac resuscitation.

The Primary and Secondary Surveys of Cardiac Resuscitation

A cardiac resuscitation is a stressful event for everyone involved. Too often, clinic and inpatient cardiac arrests and their management are episodes of chaos in the busy lives of resident and attending physicians. Yet it has been eloquently stated that a good resuscitation team should function like a fine symphony orchestra.⁴⁰ Such skill levels require dedicated individual and team practice and careful code team organization. Mastery in cardiac resuscitation is, in fact, a lifelong pursuit that requires training and retraining in basic life support (BLS) and advanced cardiovascular life support (ACLS); regular practice and review; and leadership and team skill development. Its key elements include not only the resuscitation itself but the response to the announcement of a code, postresuscitation stabilization of the patient, notification of the family and primary care provider, and code critique and debriefing. To help practitioners learn and apply some of the most essential techniques used in cardiac resuscitation more easily and effectively, the American Heart Association (AHA) has developed the concepts of the BLS primary and the ACLS secondary surveys of a patient in cardiac arrest.⁴¹

THE PRIMARY SURVEY

The primary survey for the victim of sudden cardiac arrest consists of the appropriate assessment of the patient’s airway (A), breathing (B), and circulation (C) and the simultaneous application of expert CPR until defibrillation (D) becomes possible (assuming the patient is in VF or pulseless VT). Thus, the primary survey includes the second and third links in the chain of survival (see above).

In 1958, Kouwenhoven noted that when his research fellow forcefully applied external defibrillating electrodes on a dog’s chest in the laboratory, an arterial pressure wave occurred.⁴² Further study and refinements led to the technique of closed-chest CPR, the careful description of which was published in 1960.⁴³ The first report of the use of this technique in patients was in 1961.⁴⁴ Since those early days, the fundamentals of closed-chest CPR have remained relatively unchanged. Mouth-to-mouth, mouth-to-mask, or

bag-valve-mask ventilation oxygenates the blood. Chest compressions produce forward blood flow. This flow appears to result from a combination of direct compression of the heart and intrathoracic pressure changes.^{45,46}

CPR in isolation does not defibrillate the heart. Its main benefit is to extend patient viability until a defibrillator and advanced interventions become available and, one hopes, succeed in restoring spontaneous circulation in the patient. CPR is not nearly as effective as a contracting heart; systolic arterial pressure peaks of 60 to 80 mm Hg may be generated, but diastolic blood pressure remains low, and a cardiac output of only 25 to 30% of normal can be achieved even under optimal conditions.⁴⁷ Still, effective CPR is critical to keeping the patient alive. It is worth remembering that the most important rescuers at a cardiac resuscitation are those who are performing expert CPR because only through their efforts are the patient’s heart and brain kept viable until defibrillation and other advanced interventions can restore spontaneous circulation.

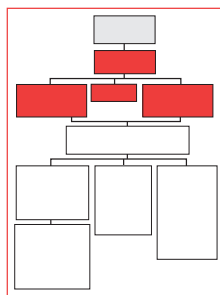
After unresponsiveness is confirmed, the emergency medical system is activated and an AED is called for; the primary survey (A, B, C, and D) proceeds as described (see below) until the AED arrives.

Airway Optimization

Open the patient’s mouth and optimize the airway in the nontrauma patient by use of the head-tilt and chin-lift maneuver. A jaw-thrust maneuver should be used instead of the head-tilt technique if cervical spine injury is suspected. In patients with suspected spine injury, proper spine alignment must be maintained throughout all phases of the resuscitation. In such circumstances, as equipment becomes available, the patient’s spine requires immobilization with a padded backboard, hard cervical collar, appropriate bolstering around the patient’s head to prevent movement, and strapping of the patient to the backboard.⁴⁸

Breathing Assessment

To assess breathing, the rescuer places his or her cheek close to the patient’s mouth and looks, listens, and feels for patient respirations. If adequate respirations are not detected within 10 seconds, the rescuer then delivers two initial breaths. Each breath is delivered over 1 second. The patient’s chest should rise with each delivered breath, and exhalation is allowed for between breaths. Breaths may be delivered using the mouth-to-mouth technique with appropriate barrier precautions (the patient’s nose should be pinched if the mouth-to-mouth technique is used), mouth-to-nose technique (if the mouth-to-mouth technique is difficult to achieve), or mouth-to-mask technique. The ideal device, if available, is a bag-valve-mask device with room air or oxygen; this allows the delivery of a substantially higher oxygen concentration to the patient. If the patient cannot be ventilated, the rescuer repositions the airway and attempts the technique again. If the airway is still obstructed, up to five abdominal thrusts are then applied, followed by a finger sweep of the oropharynx to relieve suspected obstruction, and then ventilation attempts are repeated. Definitive intervention for an obstructed airway in the hospital setting may involve laryngoscopic visualization of the cause of obstruction and foreign-body removal. If an adequate airway cannot be established by less invasive means, cricothyrotomy may be required.



CPR Initiation

The health care rescuer next checks for a carotid pulse in the unresponsive patient but should allow no more than 10 seconds to do so. (The AHA no longer recommends pulse checks for rescuers who are not health care providers.⁴⁹ Instead, lay rescuers should initiate chest compressions if the unresponsive patient is not breathing.) If the patient has no carotid pulse, begin chest compressions. The patient should be on a firm surface, and the heel of the rescuer's hand should be in the center of the inferior half of the patient's sternum (but cephalad to the xiphoid process). The rescuer's other hand is placed on top of the lower hand.

The rescuer's arms are held straight, with the force of each compression coming from the rescuer's trunk. The 2005 AHA guidelines emphasize "Push hard, push fast, allow full chest recoil after each compression, and minimize interruptions in chest compressions" to achieve effective chest compression.⁴⁹ The sternum is smoothly compressed by 1.5 to 2.0 inches and then released. The duration of the compression-release cycle is divided equally between compression and release. The recommended rate of chest compression is about 100 compressions/min. The chest should be allowed to rebound to its precompression dimensions between compressions, but the resuscitator's palm closest to the patient should remain in contact with the sternum.

In nonintubated patients, chest compressions are regularly interrupted for the delivery of ventilations. The sequence is the same, regardless of whether one-rescuer or two-rescuer CPR is being performed: the rescuer delivers 30 compressions, pauses for two breaths, and then resumes compressions. In endotracheally intubated patients, administer 8 to 10 breaths per minute by hand bagging while compressions continue.

The optimal timing and ratio of ventilations to compressions in CPR are an ongoing area of research. The current 30:2 ratio for the patient without an advanced airway is based on the experts' recommendation, which is supported by observational study, the theoretical mathematical model, and animal studies. In the porcine model, a compression to ventilation ratio of 30:2 during BLS was significantly associated with the shorter median time to a return of spontaneous circulation and improved arterial oxygenation.⁵⁰ Furthermore, using a physiologic and mathematical analysis, the maximum oxygen delivery and blood flow was achieved at a ratio near 30:2.⁵¹

Good technique is critical throughout CPR delivery. The patient should have carotid pulses with chest compressions and should have appropriate breath sounds and chest movement with ventilations. Interestingly, femoral pulsations with CPR do not necessarily indicate effective CPR; these pulsations often are venous rather than arterial. Quantitative end-tidal carbon dioxide levels can be monitored, if practical. Higher levels correlate with more effective CPR and increased survival.⁵² The patient should be reassessed for return of spontaneous circulation every 5 cycles or 2 minutes of CPR [see Table 1].

Defibrillation

When the monitor-defibrillator or AED arrives, it is attached to the patient; the rhythm is analyzed, and if the

patient is in VF or pulseless VT, defibrillation is provided [see Table 2 and Table 3].

Defibrillation is thought to work by simultaneously depolarizing a sufficient mass of cardiac myocytes to make the cardiac tissue ahead of the VT or VF wavefronts refractory to electrical conduction. Subsequently, the sinus node or another appropriate pacemaker region of the heart with inherent automaticity can resume orderly depolarization-repolarization, with return of a perfusing rhythm.^{15,53} The sooner defibrillation occurs, the higher the likelihood of resuscitation. When defibrillation is provided immediately after the onset of VF, its success rate is extremely high.⁵⁴ In a study of sudden cardiac arrest patients in Nevada gambling casinos, the survival rate to hospital discharge was 74% for patients who received their first defibrillation no later than 3 minutes after a witnessed collapse.²⁸ In this study, defibrillation was delivered via an AED operated by casino security officers.

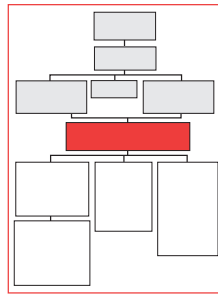
Early defibrillation is so critical that if a defibrillator is immediately available, its use traditionally takes precedence over CPR for patients in VF or pulseless VT of recent onset. If CPR is already in progress, it should, of course, be halted while defibrillation takes place. Newer defibrillators can compensate for thoracic impedance, ensuring that the selected energy level is, in fact, the energy that is delivered to the myocardial tissue. In addition, defibrillators that deliver biphasic defibrillation waveforms instead of the monophasic damped sinusoidal waveforms allow effective defibrillation at lower energy levels and without the need for energy-level escalation during subsequent shocks.^{15,55-58} In the Optimized Response to Cardiac Arrest (ORCA) study, which involved 115 patients with prehospital VF, the 150-joule biphasic shock AED was more effective than the traditional high-energy monophasic shock AED in four respects: it was more successful in producing defibrillation with the first shock (96% versus 59%); it led to a higher rate of ultimate success with defibrillation (100% versus 84%); it had a better rate of return of spontaneous circulation (76% versus 54%); and its use was associated with a higher rate of good cerebral performance in the survivors (87% versus 53%).⁵⁹ There were no differences, however, in terms of survival to hospital admission or discharge, and replication of the ORCA findings is lacking at this time. In current AHA guidelines, 360 J is recommended for the defibrillation using a monophasic defibrillator and 120 to 200 J (device specific) is recommended for a biphasic defibrillator for adult patients.⁴¹

The duration of VF is a consideration in deciding whether to defibrillate immediately and as soon as a defibrillator is available or to perform CPR for a brief period first to "prime the pump" before proceeding to defibrillation. In the porcine model in the setting of prolonged VF (> 10 minutes), CPR before defibrillation provides several physiologic benefits.⁶⁰ Studies have found that patients with VF of longer than 5 minutes' duration had better return of spontaneous circulation, survival to hospital discharge, and 1-year survival if ambulance personnel provided 3 minutes of CPR before performing defibrillation than if ambulance personnel performed defibrillation immediately after arriving at the scene; however, some experts question the validity of these results, on the basis of study design.^{61,62} Although three stacked shocks was recommended in the Emergency Cardiovascular Care 2000, to resume chest compressions right after defibrillation and continue for

2 minutes (about 5 cycles) without rhythm check is now recommended based on expert consensus.⁶³

THE SECONDARY SURVEY

The secondary survey for a victim of persistent cardiac arrest takes place after completion of the primary survey. Like the primary survey, the secondary survey follows an ABCD format, which in this case consists of advanced airway interventions (A); optimized oxygenation and ventilation by confirmation of proper airway device placement and repeated reassessment of the adequacy of delivered breaths (B); IV access and appropriate medication delivery to the patient's circulation (C); and definitive therapy based on a differential diagnosis (D) that considers the specific disease processes thought to be responsible for, or contributing to, the cardiac arrest. The secondary survey includes the fourth link in the chain of survival, rapid advanced care (see above).



Placement of an Advanced Airway

Patients who remain in cardiac arrest after completion of the primary survey require placement of an advanced airway. Depending on the setting and the experience of the rescuers, this advanced airway may be a laryngeal mask airway, an esophageal-tracheal Combitube (a tracheal tube bonded side by side with an esophageal obturator), or an endotracheal (ET) tube.^{36,64} The laryngeal mask airway and the Combitube can be placed by personnel with less training than that required for ET intubation, and they do not require additional special equipment or visualization of the vocal cords. Nevertheless, oral ET intubation is generally the preferred advanced airway technique for cardiac resuscitation, especially in the hospital setting, where experienced intubators are generally present; in the prehospital setting, the evidence supporting ET intubation remains inconsistent. ET intubation isolates the airway, maintains airway patency, helps protect the trachea from the ever-present risk of aspiration, helps permit optimal oxygenation and ventilation of the patient, allows for tracheal suctioning, and even provides a route for delivery of some medications to the systemic circulation (via the pulmonary circulation) if IV access is unobtainable or lost.⁶³ Interruptions in chest compressions should be minimized during the attempts at intubation.

Optimization of Breathing and Ventilation

When a cardiac arrest patient undergoes ET intubation, correct positioning of the ET tube must be immediately confirmed and regularly reconfirmed during and after the resuscitation [see Table 5]. Routine use of an esophageal detection device or end-tidal CO₂ detector is recommended, along with careful patient examination. Caution is necessary with qualitative colorimetric end-tidal CO₂ detectors because both false positive and false negative results have been documented during cardiac arrests.⁶⁵ Breath sounds should be present during auscultation over the anterior and lateral chest walls, and the patient's chest should rise and fall with delivered ventilations. No gurgling should be heard when the epigastrium is auscultated. The ET tube should be inserted to the appropriate depth marking: for average-sized adults, this is 21 cm at the corner of the

Table 5 Confirmation of Endotracheal Tube Placement

Intubation process

- Vocal cords are visualized by intubator
- Tip of ET tube is seen passing between the cords
- Cuff of ET tube also passes cords by 1 cm

Postintubation checks

- Breath sounds are symmetrical (auscultate over lateral anterior chest and in midaxillary line bilaterally)
- No gurgling with auscultation over epigastrium
- Patient's chest rises and falls appropriately with ventilation
- Esophageal detector device or end-tidal CO₂ detector* to obtain the additional confirmation

Secure the ET tube to prevent dislodgment

Reassess the adequacy of oxygenation and ventilation throughout the resuscitation (bedside patient assessment; also obtain ABGs when feasible)

After resuscitation, obtain a portable chest radiograph

ABG = arterial blood gas; ET = endotracheal.

*Undetectable level of end-tidal CO₂ can be caused by a low cardiac output status during cardiopulmonary resuscitation; end-tidal CO₂ may be initially detectable in an esophageal intubation because of the air from the stomach.

mouth in a woman and 23 cm in a man. The patient's skin color should be reasonable (i.e., not dusky or cyanotic) provided that the patient's pigmentation allows such assessment.

Once correct positioning is confirmed, the ET tube is then appropriately secured to prevent its dislodgment. When feasible, an arterial blood gas (ABG) measurement will help further confirm the adequacy of oxygenation and ventilation as the resuscitation proceeds.

Establishment of Circulation Access

Access to the patient's venous circulation is mandatory; such access may be achieved by a code team member or members simultaneously while other resuscitators pursue steps A and B of the secondary survey. Ideally, a large IV cannula is placed in a prominent upper extremity vein or the external jugular vein to optimize delivery of needed medications. If a peripheral line is not achievable, additional access possibilities include central line placement via the internal jugular, subclavian vein (via the supraclavicular approach), or, less ideally, femoral vein; even intraosseous (IO) access is available as alternative route for fluid resuscitation, drug administration, and blood withdrawal. It is useful to remember, as already noted, that some important resuscitation medications can be delivered via the ET tube in cases of failed IV and IO access; such medications include naloxone, atropine, vasopressin, epinephrine, and lidocaine (mnemonic: NAVEL). Of note, approximately 2 to 2.5 times doses of drugs are required to obtain the adequate blood concentration.

The commonly used medications in cardiac resuscitation may be grouped into the following general categories: vasopressors (epinephrine or vasopressin), antiarrhythmics (amiodarone, lidocaine, or magnesium), anticholinergic agents (atropine, if the arrest arrhythmia is asystole or PEA is slow), and miscellaneous drugs used to treat specific problems contributing to the arrest state, such as sodium bicarbonate (for severe metabolic acidosis, hyperkalemia, and certain drug overdoses) and calcium

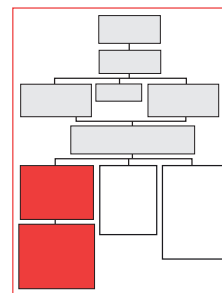


Table 6 Technical Problems That May Prevent a Successful Resuscitation

Problem	Patients at Risk	Recommendations
Ineffective CPR	All cardiac arrest patients	Ensure technically perfect CPR. Confirm carotid pulses with CPR. If arterial line was in place before cardiac arrest, confirm adequate arterial waveform with CPR on arterial line monitor. Monitor end-tidal CO₂ if available (higher levels correlate with better CPR and improved patient survival). Confirm adequate oxygenation with an ABG when feasible.
Inadequate oxygenation and ventilation	All cardiac arrest patients	Ensure optimal airway positioning and control. Have suction immediately available to manage pharyngeal and airway secretions. Ensure use of properly fitting, tightly sealed face mask for bag-valve-mask (BVM) ventilation until a definitive airway is established. Apply cricoid pressure to prevent gastric distention during BVM ventilation until a definitive airway is established. Ensure that supplemental oxygen is flowing to BVM at 15 L/min. Deliver an appropriate tidal volume per breath (6–7 mL/kg if oxygen is available) at the rate of 8–10 breaths/min. Confirm bilateral and equal breath sounds with ventilation. Confirm that patient's chest rises with each ventilation. Allow adequate time for exhalation between breaths. Confirm optimal oxygenation and ventilation with an ABG when feasible.
ET tube difficulties	All patients intubated with ET tube	Allow ≤ 20–30 sec/intubation attempt. Intubator should see tip of ET tube and cuff pass between vocal cords at time of intubation. After intubation, immediately confirm correct ET tube placement; regularly reconfirm ET tube placement throughout resuscitation. Confirm adequacy of oxygenation and ventilation with an ABG. After intubation, consider nasogastric tube placement to decompress stomach and optimize diaphragmatic excursions with ventilation.
IV line difficulties	All cardiac arrest patients	Place one or more 18-gauge or larger IV cannulas in an antecubital or external jugular vein site. Check for IV infiltration regularly throughout the resuscitation. Follow all medications administered through a peripheral IV site with a 20 mL saline bolus and elevation of the extremity containing the IV for 10–15 sec (if possible). Consider central line placement or IO route if the resuscitation is prolonged. Be aware of all IV/IO infusions the patient is receiving. Stop all nonessential medications that had been started before the cardiac arrest. During the resuscitation, the only infusions the patient should receive are normal saline, blood products (if clinically indicated), and pertinent medications necessary to assist with return of spontaneous circulation. Pulmonary artery catheters and central lines occasionally act as an arrhythmogenic focus within the right ventricle. If applicable, deflate all relevant balloons on the catheter and withdraw the catheter to a superior vena cava position.
Monitor defibrillator difficulties	All cardiac arrest patients	Make sure Synchronization Mode button is in the off position when defibrillating patients in pulseless VT or VF. Make sure electricity is not arcing over the patient's chest because of perspiration or smeared conducting gel; dry patient's chest with a towel except for areas directly beneath pads or paddles. Do not administer shock through nitroglycerin paste or patches. If the patient has an internal cardioverter-defibrillator (ICD) or a pacemaker, the patient may still be manually defibrillated, but do not shock directly over the internal device. Under these circumstances, place the pads or paddles at least 2.5 cm away from the patient's internal device. If the ICD is intermittently firing but not defibrillating the patient and if the ICD is thought to be compromising the resuscitation, turn the device off with a magnet so that manual defibrillation may take place without interference. Maximize the gain or electrocardiography "size" and check the rhythm in several leads (or change the axes of the paddles if reading the rhythm in Paddles mode) to confirm asystole when the initial rhythm appears to be asystole.

ABG = arterial blood gas; ET = endotracheal; IV/IO = intravenous/intraosseous; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 7 Potentially Treatable Conditions That May Cause or Contribute to Cardiac Arrest

Condition	Clinical Setting	Diagnostic and Corrective Actions
Acidosis	Preexisting acidosis, diabetes, diarrhea, drugs, toxins, prolonged resuscitation, renal disease, shock	Obtain stat ABG. Reassess technical quality of CPR, oxygenation, and ventilation. Confirm correct endotracheal tube placement. Hyperventilate patient (P_{aCO_2} of 30–35 mm Hg) to partially compensate for metabolic acidosis. If pH < 7.20 despite above interventions, consider IV sodium bicarbonate, 1 mEq/kg IV slow push.
Cardiac tamponade	Hemorrhagic diathesis, malignancy, pericarditis, post–cardiac surgery, post–myocardial infarction, trauma	Initiate large-volume IV crystalloid resuscitation. Confirm diagnosis with emergency bedside echocardiogram, if available. Perform pericardiocentesis. Immediate surgical intervention is appropriate if pericardiocentesis is unhelpful but cardiac tamponade is known or highly suspected clinically.
Hypoglycemia	Adrenal insufficiency, alcohol abuse, aspirin overdose, diabetes, drugs, toxins, liver disease, renal disease, sepsis, certain tumors	Consider clinical setting and obtain finger-stick glucose or stat blood glucose measurements (may be obtained on ABG specimen). If glucose < 60 mg/dL, treat: 50 mL = 25 g of D ₅₀ W IV. Follow glucose levels closely posttreatment.*
Hypomagnesemia	Alcohol abuse, burns, diabetic ketoacidosis, severe diarrhea, diuretics, drugs (e.g., cisplatin, cyclosporine, pentamidine), malabsorption, poor intake, thyrotoxicosis	Obtain stat serum magnesium level. Treat: 1–2 g magnesium sulfate IV over 2 min. Follow magnesium levels over time because blood levels correlate poorly with total body deficit.
Hypothermia	Alcohol abuse, burns, central nervous system disease, debilitated and elderly patients, drowning, drugs, toxins, endocrine disease, exposure history, homelessness, poverty, extensive skin disease, spinal cord disease, trauma	Obtain core body temperature. If severe hypothermia (< 30°C), limit initial shocks for pulseless VT/VF to three, initiate active internal rewarming and cardiopulmonary support, and hold further resuscitation medications or shocks until core temperature > 30°C.† If moderate hypothermia (30–34°C), proceed with resuscitation (space medications at intervals greater than usual), passively rewarm, and actively rewarm truncal body areas.
Hypovolemia, hemorrhage, anemia	Major burns, diabetes, gastrointestinal losses, hemorrhage, hemorrhagic diathesis, malignancy, pregnancy, shock, trauma	Initiate large-volume I.V. crystalloid resuscitation. Obtain stat hemoglobin level on ABG specimen. Emergently transfuse packed red blood cells (O negative if type-specific blood not available) if hemorrhage or profound anemia is contributing to arrest. Emergently consult necessary specialty for definitive care. Emergency thoracotomy with open cardiac massage is a consideration if experienced providers are available for the patient with penetrating trauma and cardiac arrest.
Hypoxia	All cardiac arrest patients are at risk	Reassess technical quality of CPR, oxygenation, and ventilation. Confirm correct ET tube placement. Obtain stat ABG to confirm adequate oxygenation and ventilation.
Myocardial infarction	Consider in all cardiac arrest patients, especially those with risk factors for coronary artery disease, a history of ischemic heart disease, or prearrest picture consistent with an acute coronary syndrome	Review prearrest clinical presentation and ECG. Continue resuscitation algorithm; proceed with definitive care as appropriate for the immediate circumstances (e.g., thrombolytic therapy, cardiac catheterization/coronary artery reperfusion, circulatory assist device, emergency cardiopulmonary bypass).
Poisoning	Alcohol abuse, bizarre or puzzling behavioral or metabolic presentation, classic toxic syndrome, occupational or industrial exposures, history of ingestion, polysubstance abuse, psychiatric disease	Consider clinical setting and presentation; provide meticulous supportive care. Emergently consult toxicologist (through regional poison center) for resuscitative and definitive care advice, including appropriate antidote use. Prolonged resuscitation efforts are appropriate. If available, immediate cardiopulmonary bypass should be considered.
Hyperkalemia	Metabolic acidosis, excessive administration, drugs and toxins, vigorous exercise, hemolysis, renal disease, rhabdomyolysis, tumor lysis syndrome, significant tissue injury	Obtain stat serum potassium level on ABG specimen. Treatment: calcium chloride 10% (5–10 mL IV slow push [do not use if hyperkalemia is secondary to digitalis poisoning]), followed by glucose and insulin (50 mL of D ₅₀ W and 10 U regular insulin IV); sodium bicarbonate (50 mEq IV); albuterol (15–20 mg nebulized or 0.5 mg IV infusion).‡
Hypokalemia	Alcohol abuse, diabetes, diuretic use, drugs and toxins, profound gastrointestinal losses, hypomagnesemia, excess mineralocorticoid states, metabolic alkalosis	Obtain stat serum potassium level on ABG specimen. If profound hypokalemia (K^+ < 2–2.5 mEq/L) is contributing to cardiac arrest, initiate urgent IV replacement (2 mEq/min IV for 10–15 mEq) and then reassess.§

Table 7 (continued) Potentially Treatable Conditions That May Cause or Contribute to Cardiac Arrest		
Condition	Clinical Setting	Diagnostic and Corrective Actions
Pulmonary embolism	Hospitalized patients, recent surgical procedure, peripartum, known risk factors for venous thromboembolism (VTE), history of VTE, prearrest presentation consistent with acute pulmonary embolism	Review prearrest clinical presentation; initiate appropriate volume resuscitation with IV crystalloid and augment with vasopressors as necessary. Attempt emergency confirmation of diagnosis, depending on availability and clinical circumstances; consider emergency cardiopulmonary bypass to maintain patient viability. Continue resuscitation algorithm; proceed with definitive care (thrombolytic therapy, embolectomy via interventional radiology, or surgical thrombectomy) as appropriate for immediate circumstances and availability.
Tension pneumothorax	Post-central line placement, mechanical ventilation, pulmonary disease (including asthma, COPD, necrotizing pneumonia), postthoracotomy, trauma	Consider risks and clinical presentation (prearrest history, breath sounds, neck veins, tracheal deviation). Proceed with emergency needle decompression, followed by chest tube insertion.

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ABG = arterial blood gas; COPD = chronic obstructive pulmonary disease; CPR = cardiopulmonary resuscitation; D₅₀W = 50% dextrose in water; ECG = electrocardiogram; ET = endotracheal; IV = intravenous; VF = ventricular fibrillation; VT = ventricular tachycardia.

*Unrecognized hypoglycemia can cause significant neurologic injury and can be life threatening, but caution with IV glucose is appropriate in the setting of cardiac arrest. Available evidence indicates that hyperglycemia may contribute to impaired neurologic recovery in cardiac arrest survivors.

†Active internal or core rewarming includes warm (42–46°C) humidified oxygen delivered through the ET tube; warm IV fluids; peritoneal lavage; esophageal rewarming tubes; bladder lavage; and extracorporeal rewarming if immediately available. Active external rewarming includes warming beds, hot-water bottles, heating pads, and radiant heat sources applied externally to the patient.

‡Glucose is not necessary initially if the patient is already hyperglycemic, but glucose levels should be followed closely after administration of IV insulin because of the risk of hypoglycemia (especially in patients with renal failure because of the long duration of action of IV insulin in such patients). Sodium bicarbonate is most helpful in patients with concomitant metabolic acidosis; it is less effective in lowering serum potassium in dialysis-dependent renal failure patients.

§High-dose nebulized albuterol should lower serum potassium by 0.5 to 1.5 mEq/L within 30 to 60 min, but administration during cardiac arrest may be difficult.

¶In a non-cardiac arrest situation, the usual IV potassium replacement guidelines for patients requiring parenteral therapy are generally 10 to 20 mEq/hr with continuous electrocardiographic monitoring. If profound hypokalemia is contributing to cardiac arrest, however, these usual replacement rates are not timely enough, given the critical nature of the situation. Under these circumstances, potassium chloride, 2 mEq/min IV for 10 to 15 mEq, is reasonable, but reassessment and careful attention to changing levels, redistribution, and ongoing clinical circumstances are essential to prevent life-threatening hyperkalemia from developing.

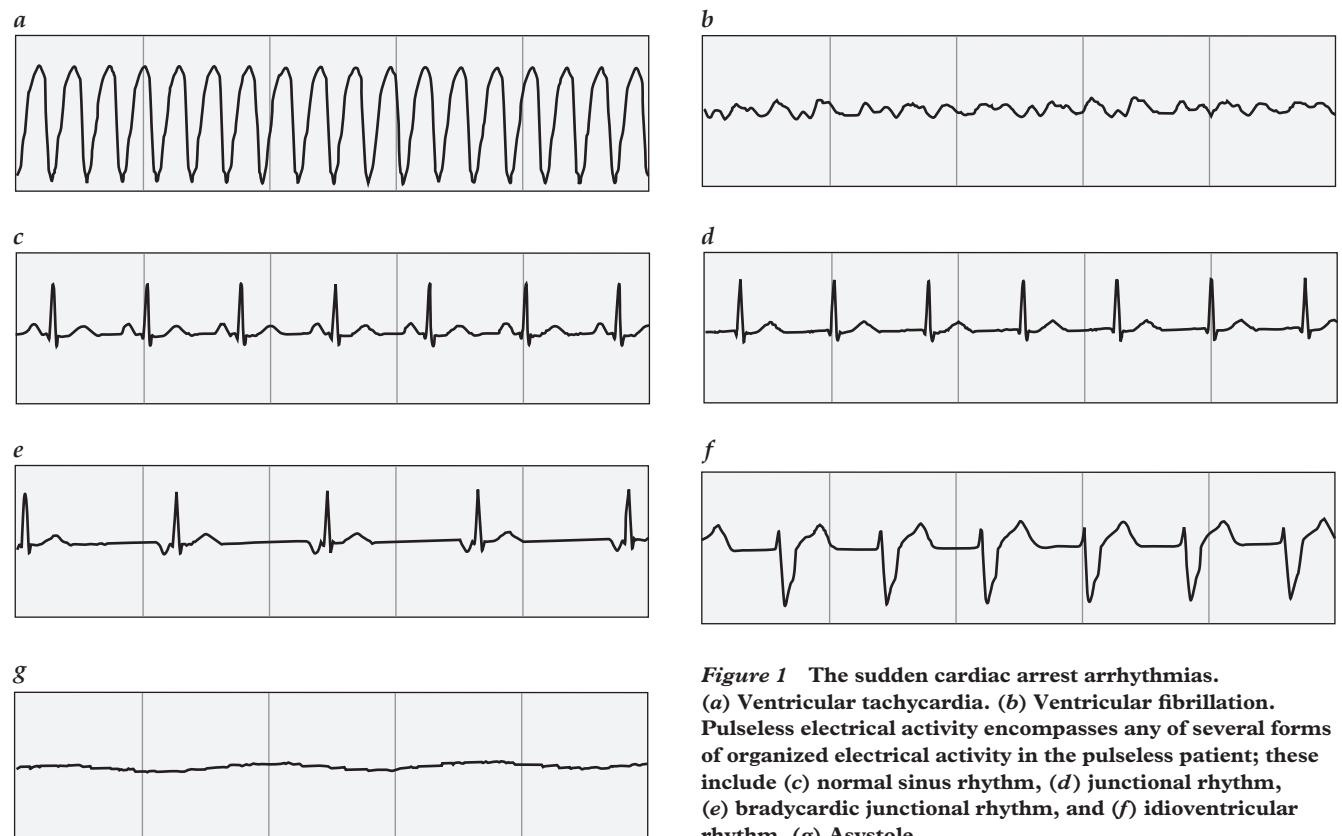


Figure 1 The sudden cardiac arrest arrhythmias. (a) Ventricular tachycardia. (b) Ventricular fibrillation. Pulseless electrical activity encompasses any of several forms of organized electrical activity in the pulseless patient; these include (c) normal sinus rhythm, (d) junctional rhythm, (e) bradycardic junctional rhythm, and (f) idioventricular rhythm. (g) Asystole.

Initiation of Defibrillation

Defibrillation with AED or manual defibrillator should be attempted immediately. However, if the time from onset of arrest, especially out-of-hospital, to CPR to the availability of defibrillation is estimated to be longer than 4 to 5 minutes, it may be reasonable to continue CPR for 2 minutes (about 5 cycles) before initiating defibrillation [see Defibrillation, above]. However, for in-hospital VF/VT sudden cardiac arrest, the health care provider should try to defibrillate as soon as possible.

Checking the displayed rhythm on the monitor and the patient's carotid pulse right after the initial shock is no longer recommended. Instead, 2 minutes (about 5 cycles) of CPR should be immediately resumed. If there are any doubts concerning the rhythm or if there is suspicion of a dysfunctional lead or paddle cable, then a manual pulse check would be appropriate.

Initiation of Drug Therapy

In patients with ongoing VF/VT after initial defibrillation and CPR, another shock and subsequent CPR are delivered. Simultaneously, drug therapy begins with the administration of a vasoconstrictor (either epinephrine or vasopressin) [see Table 4]. If there is no IV or IO access, the drug can be given endotracheally. After each IV dose, drug delivery is followed by a 20 mL saline bolus and the extremity containing the IV line is elevated. As long as the patient remains pulseless, epinephrine is administered every 3 to 5 minutes. When vasopressin is the chosen initial drug, only a single dose is given; if the resuscitation continues 10 minutes or longer after vasopressin is administered, epinephrine should be substituted for vasopressin for the remainder of the code. If VF or pulseless VT persists despite the initial administration of a vasoconstrictor and repeated defibrillation attempt, parenteral antiarrhythmic drug therapy is added; amiodarone or lidocaine is an appropriate agent [see Choice of Antiarrhythmic Drugs, below]. Throughout all of these steps, the code team leader is also actively looking for and correcting any technical and physiologic or anatomic problems that may be preventing a successful resuscitation [see Table 6 and Table 7].

Emergency Laboratory Tests

If spontaneous circulation does not return after the first round of antiarrhythmic drug therapy, the resuscitation team must also endeavor to identify and treat the clinically relevant conditions causing or contributing to the cardiac arrest [see Table 7]. In theory, the interventions conducted to this point should have resulted in a perfusing rhythm. The code team must ask why this has not occurred and then attempt to answer this question as the resuscitation continues. Emergency laboratory studies that may prove helpful include a stat ABG measurement and measurements of hemoglobin, potassium, magnesium, and blood glucose levels (most of which can be obtained from the ABG specimen).

Choice of Antiarrhythmic Drugs

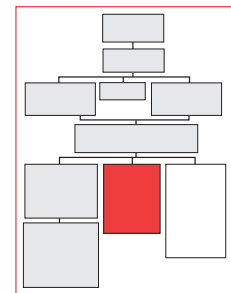
Three antiarrhythmic drugs are used in cardiac resuscitation: amiodarone, lidocaine, and magnesium (if persistent VT is associated with torsades de pointes or the patient is thought

or proved to be hypomagnesemic).⁷² It is not known which one of these drugs or which combination of them will optimize the chances of patient survival to hospital discharge. Despite many years of routine use, there are no controlled studies demonstrating a survival benefit with lidocaine, versus placebo, in the management of VF or pulseless VT. Two studies in patients with shock-refractory prehospital VF showed that survival to hospital admission was better with amiodarone than with placebo (44% versus 34%; $p = .03$)⁷³ or with lidocaine (22.8% versus 12.0%; $p = .009$).⁷⁴ Neither of these studies demonstrated an improved survival to hospital discharge in the amiodarone groups, but neither study had the statistical power to demonstrate such a difference. The optimal role and the exact benefit of antiarrhythmic medications in cardiac resuscitation are yet to be fully elucidated. According to AHA guidelines, although amiodarone is preferred to lidocaine, either is an acceptable initial antiarrhythmic drug for the treatment of patients with VF or pulseless VT that is unresponsive to initial shock, CPR, airway management, and administration of epinephrine or vasopressin plus shock. On the basis of available evidence, however, amiodarone may be the antiarrhythmic agent of first choice in the setting of prehospital refractory VF, allowing for optimal survival to hospital arrival.⁷²⁻⁷⁴

PULSELESS ELECTRICAL ACTIVITY

Community ACLS providers are encountering nonventricular arrhythmias (i.e., PEA and asystole) with increasing frequency. Classically, the prognosis for PEA has been poor, with outpatient survival rates generally reported as 0 to 7%.^{75,76} The sequence of resuscitation steps in the management of PEA is as follows:

activation of the emergency medical or code response, primary survey (CPR and rhythm evaluation), and secondary survey (confirmation of advanced airway, optimal oxygenation and ventilation, establishment of IV/IO access, epinephrine and atropine administration, and, finally, problem solving for technical difficulties and establishment of the cause of the cardiac arrest). The two core drugs for PEA management are epinephrine (repeated every 3 to 5 minutes for as long as the patient is pulseless) and atropine (up to 3 mg over time if the PEA rhythm on the monitor is inappropriately slow). Vasopressin is a reasonable alternative to a first or second dose of epinephrine. The best hope for a successful resuscitation is to find and treat the cause of PEA; therein lies the exceptionally challenging aspect of PEA resuscitation management [see Table 6 and Table 7]. Because coronary artery thrombosis and pulmonary thromboembolism are common causes of cardiac arrest, a trial evaluated the efficacy of tissue plasminogen activator (t-PA) in the setting of PEA of unknown or presumed cardiovascular cause in 233 patients in prehospital and emergency department settings.⁷⁷ No benefit was found with thrombolytic therapy for PEA in this study; the proportion of patients with return of spontaneous circulation was 21.4% in the t-PA group and 23.3% in the placebo group.



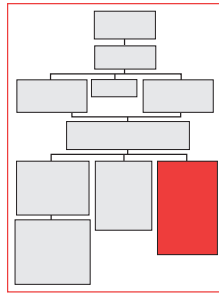
ASYSTOLE

The prognosis for asystole is generally regarded as dismal unless the patient is hypothermic or there are other extenuating but treatable circumstances. The sequence of resuscitation steps in the management of asystole is as follows: activation of the emergency medical or code response, primary survey (CPR, rhythm evaluation, and asystole confirmation), and secondary survey (confirmation of advanced airway, optimal oxygenation and ventilation, IV/IO access with epinephrine and atropine administration, immediate transcutaneous pacing, if available, and problem solving for technical difficulties and establishment of the cause of cardiac arrest). The two core drugs for asystole management are epinephrine (repeated every 3 to 5 minutes for as long as the patient is pulseless) and atropine (up to 3 mg over time). As with PEA, vasopressin is a reasonable and beneficial substitute for epinephrine in asystole. A single dose of aminophylline (250 mg IV) may also be beneficial in atropine-resistant asystole.⁷⁸ Potentially treatable causes of asystole include hypoxia, acidosis, hypothermia, hypokalemia, hyperkalemia, and drug overdose. Resuscitation efforts should stop if asystole persists for longer than 10 minutes despite optimal CPR, oxygenation and ventilation, and epinephrine or atropine administration; if extenuating circumstances (e.g., hypothermia, cold-water submersion, or drug overdose) are not present; and if no other readily treatable condition is identified.

Immediate Postresuscitation Care

Even when the resuscitation is successful, the patient's situation remains tenuous and continued meticulous patient care is essential. When the cardiac monitor indicates what should be a perfusing rhythm, the rescuer should immediately confirm that the patient has a palpable pulse. If there is a pulse, the patient's blood pressure is then obtained. Simultaneously, resuscitation team members need to quickly reassess the adequacy of the patient's airway, the ET tube position, oxygenation and ventilation, and the patient's level of consciousness and comfort.

If the patient is hypotensive, appropriate blood pressure management depends on the rhythm on a monitor and the presence or absence of fluid overload, as judged at the bedside. If the monitor shows tachyarrhythmia, immediate synchronized cardioversion is indicated irrespective of the duration of QRS wave. A transcutaneous pacing should be considered for the unstable bradycardia (Morbitz type II second-degree atrioventricular [AV] block or third-degree AV block). If the patient is clinically volume overloaded or in frank pulmonary edema and hypotensive, dopamine is started at inotropic doses (5 µg/kg/min IV) and titrated to a target systolic blood pressure of 90 to 100 mm Hg. If the patient's clinical status suggests normovolemia or hypovolemia, IV crystalloid boluses (in 250 to 500 mL increments) can be administered instead of dopamine to support adequate tissue perfusion. In patients who are regaining consciousness, their level of comfort mandates careful assessment and administration of analgesia and sedation, as appropriate.



If the arrest rhythm was either VT or VF, the parenteral antiarrhythmic drug used immediately before the return of spontaneous circulation is continued as a maintenance infusion (amiodarone, 1 mg/min for 6 hours, then 0.5 mg/min for 18 hours as blood pressure allows; or lidocaine, 2 to 4 mg/min). If an antiarrhythmic drug has not yet been administered, it is usually started at this point to prevent the recurrence of VF or pulseless VT. There are important exceptions to this guideline, however. If the perfusing postarrest arrhythmia is an idioventricular rhythm or third-degree heart block accompanied by an idioventricular escape rhythm, an antiarrhythmic medication should not be started at this time, because the antiarrhythmic agent could eliminate the ventricular perfusing focus and return the patient to a pulseless state.

Initial postresuscitation studies usually include an ECG; portable chest radiography; and measurement of ABGs, a serum electrolyte panel, finger-stick or blood glucose, serum magnesium and cardiac enzyme levels, and hemoglobin and hematocrit. The resuscitated patient requires urgent transfer to the optimal site for continued definitive care. Depending on the circumstances, this may be either the cardiac catheterization laboratory or the intensive care unit.

Ongoing research continues to look at optimal postresuscitation management strategies to improve neurologic outcome and survival to hospital discharge.⁷⁹ Hyperthermia, hyperventilation, and hyperglycemia compromise postresuscitation neurologic outcome, whereas mild to moderate induced hypothermia (32 to 34°C) for 12 to 24 hours after return of spontaneous circulation (ROSC) appears to improve neurologic outcome and decrease mortality.^{80–82} Current AHA guidelines state that mild to moderate hypothermia should be initiated for unconscious adult patients with ROSC after out-of-hospital VF sudden cardiac arrest.⁸³

Ending a Resuscitation Attempt

Throughout the resuscitation, the team leader must speak with calmness and authority, and all resuscitations should be orchestrated with clarity and finesse. If possible, the code captain should make clinical decisions without directly performing specific procedures. Cardiac arrests are emotionally charged, but the leader must insist on a composed, orderly, and technically sound resuscitation. It is appropriate to invite suggestions from team members and to ensure that all members are comfortable with the decision to stop the resuscitation should that time arrive.

The decision whether to stop a cardiac resuscitation is burdensome. Clearly, the circumstances of the event, patient comorbidities, the nature of the lethal arrhythmia, and the resuscitation team's ability to correctly identify and treat potential contributing causes of the arrest are all important considerations. Resuscitation efforts beyond 30 minutes without a return of spontaneous circulation are usually futile unless the cardiac arrest is confounded by intermittent or recurrent VF or pulseless VT, hypothermia, cold-water submersion, drug overdose, or other identified and readily treated contributing conditions.^{84,85}

With nontraumatic cardiac arrest in the prehospital setting (assuming proper equipment and medications are available and no extenuating circumstances suggest otherwise), full

resuscitation efforts take place at the scene of the arrest in preference to rapid transport to an emergency department. A prehospital resuscitation that has been appropriately conducted but has not resulted in at least temporary return of spontaneous circulation to the patient may be discontinued. It is important that certain criteria are adhered to, however, including the following: high-quality CPR provided, an adequate airway successfully placed, appropriate oxygenation and ventilation delivered, IV/IO access established, appropriate medications specific to the arrest scenario administered, and resuscitation attempted for at least 10 minutes; in addition, the patient must not be in persistent VF, and there can be no extenuating circumstances that mandate in-hospital continuation of the resuscitation (e.g., hypothermia, drug overdose). The decision whether to cease resuscitation efforts in the field is bolstered by direct discussion with emergency medical service physicians. It is also essential that social services be available to provide immediate assistance and support to the family and loved ones of the patient who has now died.

Discontinuing in-hospital resuscitations is advisable when three criteria are met: (1) the arrest was unwitnessed, (2) the initial rhythm was other than VF or VT, and (3) spontaneous circulation does not return after 10 minutes of ongoing resuscitation.⁸⁶ In a study of this three-component decision rule, only 1.1% of patients (3 of 269) who met these criteria

survived to hospital discharge, and none of the 3 survivors were capable of independent living.⁸⁷ In a study of 445 prospectively recorded resuscitation attempts in hospitalized patients, no patient survived who suffered a cardiac arrest between 12 am and 6 am if the arrest was unwitnessed and if it occurred in an unmonitored bed.³⁸

A resuscitation attempt in a persistently asystolic patient should not last longer than 10 minutes, assuming that all of the following conditions apply: asystole is confirmed through proper rhythm monitoring and assessment; high-quality CPR is taking place; ET intubation is correctly performed and confirmed; adequate oxygenation and ventilation are provided; IV access is secured; appropriate medications (epinephrine or vasopressin and atropine) have been administered; and the patient is not the victim of hypothermia, cold-water submersion, drug overdose, or another readily identified and reversible cause.

After all resuscitation attempts, the code team captain should debrief the team so that all may learn from the experience. Finally, marked empathy and skill are needed to carefully and compassionately inform family members about the outcome of the resuscitation.⁸⁸

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2 ACUTE CARDIAC DYSRHYTHMIA

Caesar Ursic, M.D., and Alden H. Harken, M.D.

Management of Acute Dysrhythmias

After successful cardiopulmonary resuscitation (CPR) or any myocardial ischemic event, the most common source of hemodynamic instability is an abnormal heart rhythm. This chapter outlines the approach to a patient with an apparent acute cardiac dysrhythmia.

The purpose of the heart's electrical activity is to induce mechanical activity. Abnormal electrical activity that occurs in the absence of hemodynamic compromise should be examined but treated with forbearance because therapy itself poses some hazards: all antidysrhythmic agents, except oxygen, are negatively inotropic. In the evaluation of a patient who appears to exhibit an acute cardiac dysrhythmia, four questions should be asked:

1. Does the patient actually have a cardiac dysrhythmia?
2. Does the patient require any therapy (i.e., is the patient sufficiently stable that treatment is NOT indicated)?
3. How soon should therapy be started (i.e., how unstable is the patient)?
4. Which therapy is the safest and most effective?

Patient Is Hemodynamically Unstable

The choice of therapy is determined by the stability of the patient and the origin of the dysrhythmia. An electrocardiogram is helpful but not required. Patients with asystole require CPR [see 8:1 Cardiac Resuscitation]. All hemodynamically unstable patients who have a dysrhythmia other than asystole should be treated immediately by cardioversion. Actually, cardioversion of asystole will do no harm; it just will not help, because there is no underlying rhythm to reorganize. If in doubt, therefore, one should proceed with cardioversion.

The two primary goals in the management of an acute dysrhythmia are to control the ventricular rate and to maintain a normal sinus rhythm. It is important to note that hemodynamic instability in a patient who has a ventricular rate between 60 and 100 beats/min is almost certainly not the result of a cardiac rhythm disturbance. Furthermore, heart rates in excess of 100 beats/min do not necessarily require therapy. Most patients can remain hemodynamically stable—and, in fact, increase their cardiac output—while raising their heart rate to 220 beats/min minus their age. In addition, it is not critical to reestablish normal sinus rhythm in all cases.¹ In a young, healthy patient with a nor-

mal heart, the so-called atrial kick adds almost nothing to cardiac output.² If normal sinus rhythm is abolished and atrial fibrillation is electrically induced in a young healthy patient, the ventricles and the rest of the cardiovascular system compensate almost immediately to prevent a fall in cardiac output.³ On the other hand, loss of synchronous atrial activity in patients with end-stage cardiac decompensation may decrease cardiac output by as much as 40%⁴; fortunately, such a degree of end-stage cardiac compromise is rare.

CARDIOVERSION

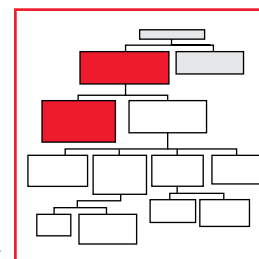
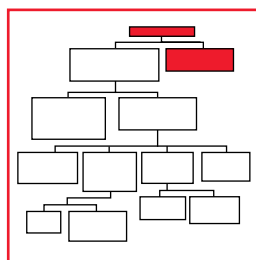
Cardioversion delivers sufficient electrical energy to the precordium (or directly to the heart) to depolarize cells, even those in a relatively refractory state. Cardioversion imposes electrical reorganization on the heart. In theory, after this massive depolarization, all the myocardial cells will repolarize simultaneously and then reinstitute a synchronous beat [see Sidebar The Intracardiac Cardioverter Defibrillator].

Certain precautions are necessary with cardioversion. The procedure is of no use in patients who are in asystole or who have fine ventricular fibrillation (VF), because these patients have no cardiac activity to organize—though, again, cardioversion does no harm in such cases (as it is said, “you cannot fall off the floor”). Supraventricular dysrhythmias such as atrial flutter can be converted with extremely low energy levels (e.g., ≤ 5 joules), but such low levels should not be employed in emergency situations. For a hemodynamically unstable patient, the initial cardioversion should be with 100 joules; if the dysrhythmia is not abolished, the voltage should be increased rapidly (to a maximum of 360 joules).

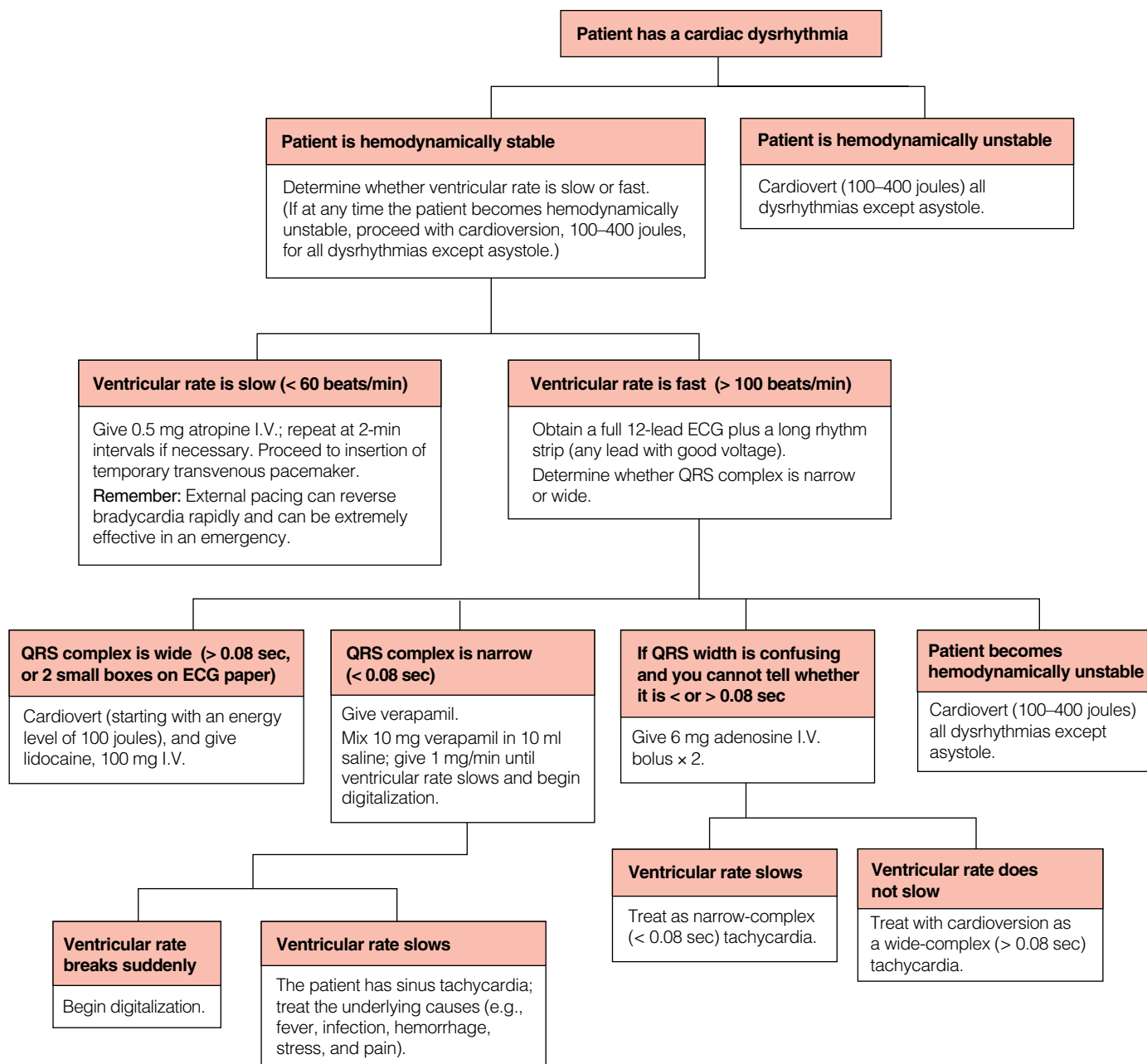
Patient Is Hemodynamically Stable

VENTRICULAR RATE IS SLOW

If the patient is bradycardic before or after cardioversion, atropine should be administered in a 0.5 mg I.V. push. This dose may be repeated at 2-minute intervals. Because the effects of atropine are transient, a temporary internal or external pacemaker should be used to maintain the heart rate. Insertion of an internal pacemaker consistently takes longer than predicted; an external pacemaker is a very effective temporizing maneuver [see Sidebar Troubleshooting a Pacemaker].



Management of Acute Dysrhythmias



The Intracardiac Cardioverter Defibrillator

Over 30 years ago, Michel Mirowski developed the first automatic intracardiac cardioverter defibrillator (ICD), a device that detects dangerous tachyarrhythmias and delivers a cardioverting shock.⁵⁵ In the intervening time, it has become abundantly clear that some of the 400,000 Americans who die “suddenly” of tachyarrhythmias each year could have been identified as high risk, although they could not have been saved by pharmacologic or surgical treatment. For these patients, an ICD can be lifesaving.⁵⁶

The ICD identifies dangerous rhythm patterns by means of two algorithms. The first of these algorithms analyzes the patient's heart rate. The patient's maximum attainable sinus rate must be determined by exercise testing before the device is implanted; the ICD is then programmed to detect heart rates above this value. (The ICD can be externally programmed to detect rates between 155 and 200 beats/min.⁵⁷)

Using rate criteria alone, however, the ICD cannot discriminate between sinus tachycardia and ventricular or supraventricular tachycardia. Inappropriate shocks are the Achilles heel of the ICD: almost one third of patients experience at least one inappropriate shock annually, when the device detects an episode of sinus tachycardia in which the rate exceeds the threshold programmed earlier. The ICD misinterprets the event as ventricular tachycardia and delivers a shock to the hemodynamically stable patient.⁵⁸ Patients like this to being punched hard in the chest. Although rarely of electrophysiologic significance, an inappropriate shock can be psychologically crippling.⁵⁹

Although computer circuitry is facile and rapid, an ICD recognizes patterns poorly. Fine (or even coarse) VF may not exhibit enough positive spikes to be recognized as a tachyarrhythmia by the ICD. A second algorithm (the probability density function algorithm) was developed to analyze electrophysiologic data and improve the specificity of the ICD's sensing circuitry. A unique feature of ventricular fibrillation is the virtual absence of isoelectric time. Conversely, during sinus tachycardia and supraventricular tachycardia, the ECG is at the isoelectric baseline much of the time. The probability density function algorithm enables the ICD to determine the proportion of time that the ECG is spending at the isoelectric baseline and thereby to detect ventricular fibrillation.

The ICD typically requires more than 5 seconds to appreciate ventricular tachycardia or fibrillation. It then charges its energy storage capacitors for 15 seconds and delivers a 30-joule cardioverting shock. If necessary, the device will deliver a second, third, fourth, and fifth countershock. If the rhythm disorder persists after the fifth countershock, the device will not recycle.

ICD systems are not complex. The device consists of a battery, which is

heavy (though newer batteries are becoming lighter), and circuitry, which is light, with a total weight of less than 100 g. Most implanted defibrillators are currently placed without a thoracotomy. A sensing and defibrillating lead system (14 French) is inserted percutaneously via the subclavian vein into right ventricular–right atrial position. The distal electrode tip senses ventricular fibrillation and tachycardia. The cardioverting energy is then discharged between a coil electrode on the diaphragmatic surface of the right ventricle and another coil electrode positioned in the superior vena cava.

It is now clear that ICDs really do work and are capable of extending life. The most effective predictor of outcome in patients with ICDs is the severity of heart failure.⁶⁰ The ICD does not prevent malignant arrhythmias: it is, in essence, a safety net that cardioverts ventricular tachycardia or VF when it occurs. Therefore, it must still be used in conjunction with antidysrhythmic drugs.^{61,62}

It is easy for a surgeon to become spooked by an ICD. The most effective strategy for managing a patient with an ICD is simply to ignore the ICD. If such a patient is being transported to the OR, however, the device should be inactivated before the electrocautery is used: the ICD will misinterpret the cautery current as VF and respond by delivering a shock to the patient.

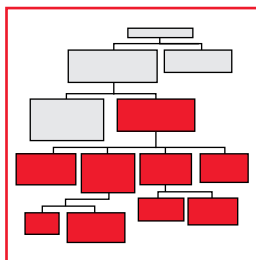
The aura of mystery surrounding the ICD may be instantly eliminated by turning off the device (see below). Once the ICD is inactivated, the patient can be treated as any other patient would be. If external cardioversion is indicated, the ICD can be disregarded; external cardioversion will not harm or activate it.

How to Turn the ICD Off

1. If you can find the industry representative to program the device to remain off, do so. Then treat the patient exactly as you would if the ICD were not present.
2. If you cannot find the representative or the situation is urgent:
 - a. Palpate the ICD generator, which is typically implanted in the left subcostal region.
 - b. Place a heavy pacemaker (or, better yet, an ICD magnet) over the upper corner of the device, toward the patient's left shoulder. Older devices used to emit a soft beep (synchronous with the heartbeat) in response to a magnet when they were active. Unfortunately, that feature has since been engineered out, and newer ICDs are silent.
 - c. Tape the magnet in place over the upper border of the device. As long as the magnet is in place, the ICD is off and the electrocautery can be used safely.

VENTRICULAR RATE IS FAST

If a patient is hemodynamically stable, a full 12-lead electrocardiogram is helpful; a long rhythm strip should be obtained as well. The best ECG lead to use for evaluating acute dysrhythmias is one that has good-voltage QRS complexes and maximal P waves, if the latter are present at all.



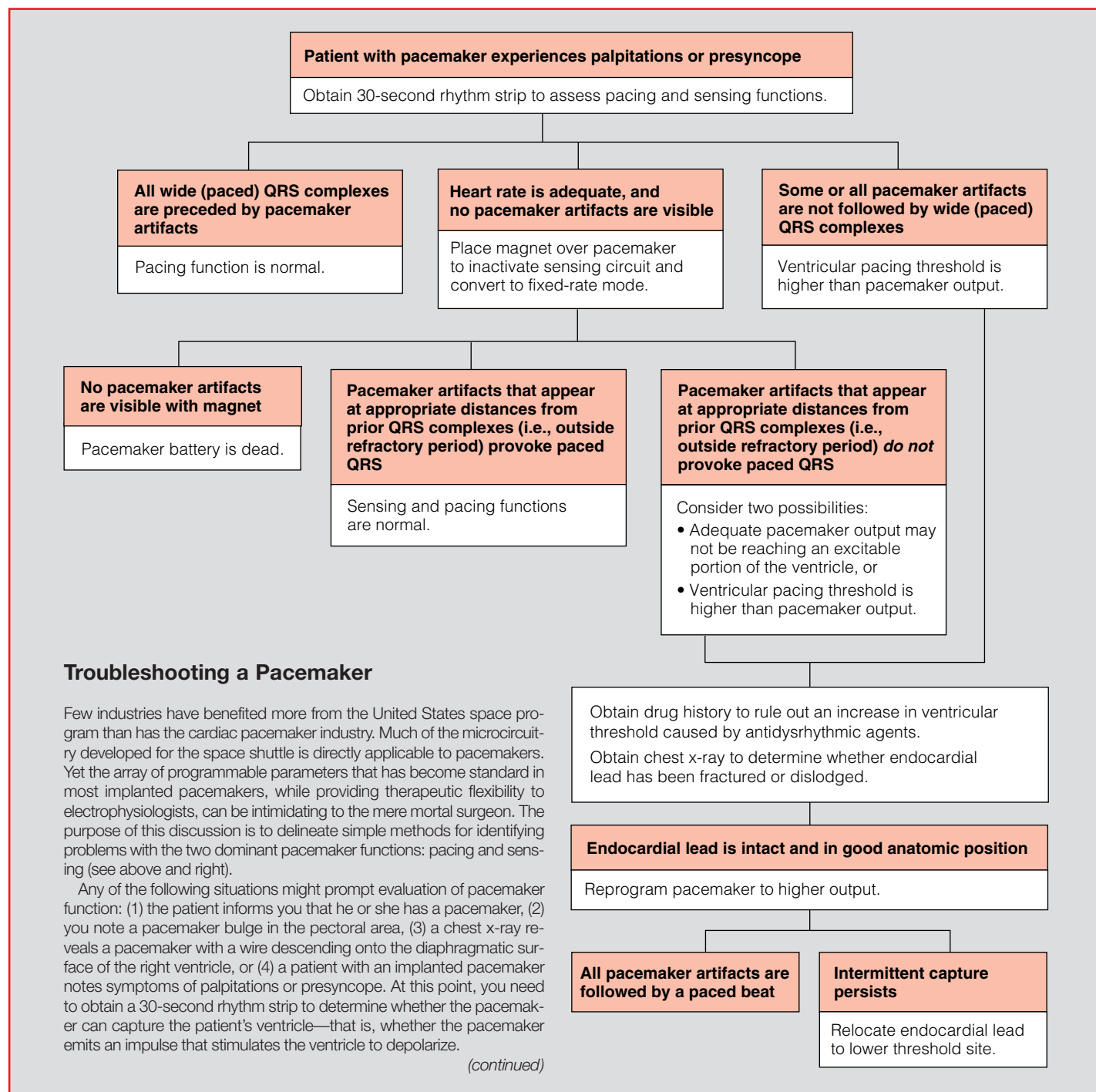
Electrocardiography

A cardiac impulse produces a positive, or upward, deflection on the monitor or oscilloscope as it approaches an ECG electrode and a negative, or downward, deflection as it moves away from the electrode. The important factor in dysrhythmia recognition, however, is not the direction of the impulse but its duration and location. Normal conduction velocity is fast: an impulse is transmitted by healthy Purkinje fibers at a rate of 2 to 3 m/sec.³ Hence, when an impulse that arises in the atrium (supraventricular) is transmitted via the atrioventricular (AV) node to the high-velocity Purkinje system, the entire ventricle is electrically activated in 0.08 second (80 milliseconds; or two small boxes on ECG paper). An impulse that is generated at an ectopic ventricular site, however, cannot

access the high-velocity Purkinje fibers as rapidly as a normal impulse, and ventricular activation is delayed. The QRS complex arising from an ectopic ventricular locus is therefore wider, signifying aberrant ventricular conduction [see Figure 1].

Because dysrhythmias of supraventricular origin typically display a narrow QRS complex, the width of the QRS can generally be used to distinguish dysrhythmias of ventricular origin from those of supraventricular origin [see Figure 2]. A wide QRS, however, may also be produced by an impulse that originates in the atrium and is aberrantly conducted to or through the ventricles (supraventricular rhythm with aberrancy). Such rhythms are relatively uncommon, constituting approximately 10% of all wide-complex tachycardias; more important, these patients will not suffer if their dysrhythmias are treated as though they were of ventricular origin.

When the ventricular rate is fast and the QRS is narrow, the 12-lead ECG should be searched for P waves, which indicate the presence of atrial activity. If P waves are absent and the QRS complexes occur at irregular intervals [see Figure 3], the patient probably has atrial fibrillation. It is not crucial to know this, however; the focus should be on the width of the QRS complex. A calcium channel blocker (verapamil or diltiazem) should be administered to control the ventricular rate. For verapamil, 10 mg is



mixed into 10 ml of saline, and 1 mg/min is given until the ventricular rate slows. For diltiazem, 0.25 mg/kg—15 to 20 mg is a reasonable dose for the average patient—is given over 2 minutes; the dose can be repeated in 15 minutes at 20 to 25 mg (0.35 mg/kg) over 2 minutes. A patient with a wide-complex tachycardia—or any patient who is hemodynamically unstable—is treated by cardioversion (see above), commonly followed by administration of lidocaine, 100 mg I.V., whereas a patient with a narrow-complex tachycardia should be treated with verapamil^{3,5} or diltiazem to retard impulse conduction through the AV node. Therefore, it is not necessary to identify the specific type of dysrhythmia in order to treat it effectively.

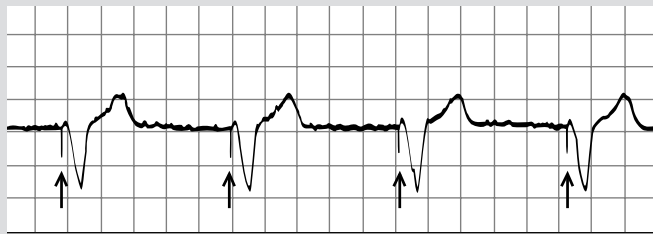
Verapamil and diltiazem act by producing profound AV nodal blockade (see below); however, they are also peripheral vasodilators.⁶ Moderate to profound systemic hypotension can be anticipated until the patient converts to sinus rhythm.

Much has been written about the risks of using calcium channel blockers in patients who are already receiving beta blockers. Abrupt and complete AV block rarely occurs, however, and in the vast majority of patients, persistent supraventricular tachycardia poses a greater risk than the possibility of third-degree heart block. Therefore, previous beta blockade should not be considered a contraindication to the use of a calcium channel blocker. Some clinicians may prefer to use adenosine.

Troubleshooting a Pacemaker (continued)

Ventricular Capture

a



Note the pacemaker artifact (↑) that precedes each wide QRS complex in rhythm strip a, above. The QRS complex is wide because ventricular activation does not originate from the AV node, and ventricular conduction is therefore aberrant. At this point, you know that your patient is pacing, and you can determine the pacing rate. You do not, however, know the pacing threshold (i.e., the minimum voltage required for ventricular capture) or the safety margin between pacemaker output and pacing threshold. At this moment (and presumably yesterday and tomorrow), this pacemaker is appropriately discharging its most important function—pacing the heart and maintaining an adequate rate.

Ventricular Sensing

b



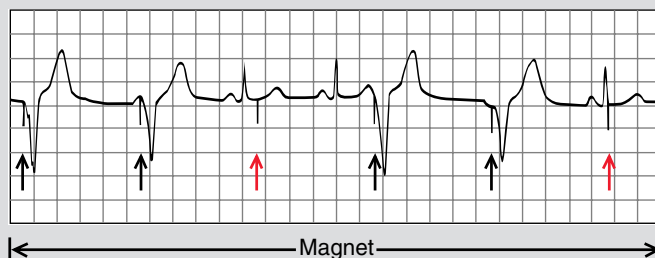
In rhythm strip b, above, normal P waves are followed by regular QRS complexes, and no pacemaker artifacts are evident. It is most likely that this patient's pacemaker has been programmed to fire at a paced rate that is slower than this patient's intrinsic heart rate, and the pacemaker is thus appropriately sensing each QRS complex. It is unlikely but possible, however, that the pacemaker is not sensing appropriately. Instead, one of the following problems may be occurring: (1) the pacemaker battery is dead, which is unlikely unless the battery was implanted more than 5 years ago, (2) the intracardiac electrode has been fractured, which is also unlikely, because current leads are remarkably durable, (3) the intracardiac electrode has been dislodged (this is an uncommon late problem that typically results in pacemaker artifacts unrelated to each QRS complex), or (4) the patient is taking an antidysrhythmic drug that has profoundly depressed ventricular excitability below threshold level for capture (this problem is very rare and can be excluded by taking a drug history). It is overwhelmingly likely, therefore, that rhythm strip b simply demonstrates that the pacemaker is sensing appropriately.

Assessing Ventricular Capture When the Spontaneous Heart Rate Is High

Typically, by the time you see the syncopal patient in the emergency department or recovery room, the patient is sufficiently excited that his or her

heart rate has recovered, and the rhythm strip will look like rhythm strip b. In a patient in whom heart rate is adequate and no pacemaker artifacts are visible, it is necessary to override the pacemaker's sensing circuit to determine whether the pacemaker is capable of emitting a pacing impulse that will capture the ventricle. The pacemaker's sensing circuit may be inactivated by placing a magnet over the pacemaker. Alternatively, the pacemaker may be reprogrammed to a paced rate that is faster than the patient's intrinsic heart rate. In this fashion, capture may easily be assessed. (Unfortunately, the programmers are expensive and are therefore often locked in some inaccessible closet. Programmers have great theoretical value but very little practical value to the surgeon.)

c



In rhythm strip c, above, a magnet has converted the patient's pacemaker from the demand mode to the fixed-rate mode. The pacemaker artifacts that precede the wide (paced) QRS complexes in this rhythm strip (black arrows) show that the pacing function of this pacemaker is intact. Occasionally, a pacemaker artifact occurs during the electrical refractory period that immediately follows the QRS complex (red arrows). Pacing during the refractory period will not result in ventricular capture. Pacing during the refractory period should not result in ventricular capture and must not be interpreted as intermittent capture. In a patient whose pacemaker seems to be sensing appropriately (as in rhythm strip b), the magnet permits assessment of ventricular capture. Rhythm strip c demonstrates normal ventricular capture in the presence of a magnet.

Some or All Pacemaker Artifacts Are Not Followed by Wide QRS Complexes

If a pacemaker impulse that occurs outside the refractory period is not followed by a wide QRS complex, two possibilities should be considered. First, an adequate pacemaker impulse may not be reaching an excitable portion of the ventricle because of fracture or dislodgment of the endocardial lead. This problem can usually be identified by a chest x-ray. Second, if the chest x-ray shows that the lead is intact and in good anatomic position, the pacemaker output is not sufficient to reach the pacing threshold. Occasionally, this problem is caused by fibrosis at the endocardial electrode tip. If the pacemaker can be reprogrammed to a higher output, the capture problem should resolve. Otherwise, the lead must be repositioned to a site at which the pacing threshold is lower.

Occasional Pacemaker Artifacts Closely Follow a Spontaneous QRS Complex

If the patient's rhythm strip looks like rhythm strip c, *in the absence of a magnet*, the pacemaker is not sensing properly. In the demand mode, most pacemakers require at least a 2.5 mV signal to suppress output. Thus, if the pacemaker emits stimuli in spite of a normal spontaneous heart rate, an adequate QRS signal either is not being sensed (the lead tip may be lodged at the site of a prior myocardial infarction or scar) or is not being transmitted to the pacemaker (because of lead fracture or dislodgment).

Adenosine (see below) produces conduction delay in the AV node and deserves recognition as a second very good option (albeit only a transiently effective one) for treatment of paroxysmal narrow-complex tachycardia or for diagnosis of supraventricular tachycardia with aberrancy (including Wolff-Parkinson-White syndrome). Adenosine is given in a 6 mg I.V. push, followed 2 minutes later by a 12 mg I.V. push and then, after another 2 min-

utes, by a final 12 mg I.V. push over 2 seconds.^{2,7}

Patients receiving adenosine complain of a frightening feeling of breathlessness and pressure that is not angina or dyspnea. This feeling typically resolves within 30 seconds. Facial flushing is also common. Unlike verapamil, adenosine is associated with hypotension in fewer than 1% of patients. Transient atrial or ventricular ectopy, with varying degrees of AV block, occurs in more

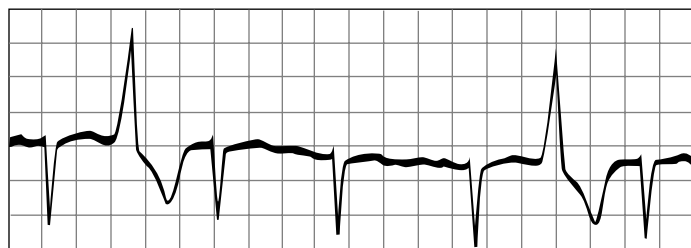


Figure 1 This tracing depicts frequent ventricular ectopic depolarizations interspersed among depolarizations from a supraventricular source. Note that the QRS depolarizations of supraventricular origin are narrow, whereas the QRS complexes of ectopic ventricular origin are wide.

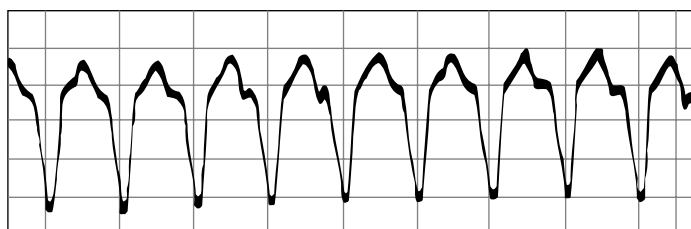


Figure 2 In a wide-complex tachycardia, each impulse is conducted aberrantly through the ventricles. The QRS complex is therefore prolonged to more than 0.08 second and occupies more than two small boxes on the ECG tracing.

than half of patients. None of the side effects of adenosine necessitate therapy.

Compared with calcium channel blockers, adenosine has certain advantages. Because of its rapid onset and short duration of action, and because its side effects are trivial and self-limited, adenosine can be used diagnostically. If, as is often the case, the QRS width is confusing and it is therefore uncertain whether the rhythm disorder is supraventricular (QRS < 0.08 second) or ventricular (QRS > 0.08 second), a 6 mg I.V. bolus of adenosine may be infused, and repeated if necessary. If the dysrhythmia slows or breaks, it was supraventricular. If it does not break, proceed to cardioversion (see above). On the other hand, even if a dysrhythmia responds to adenosine, the profound neuroendocrine and electrolyte perturbations that provoked the dysrhythmias in the first place—perturbations that are very common in the surgical intensive care unit—are likely to persist, and the dysrhythmia disorder typically recurs. Continuous (therapeutic) infusion of adenosine (150 to 300 $\mu\text{g/kg/min}$) is rational from a physiologic standpoint but is frighteningly expensive. Therefore, if adenosine works transiently, it is appropriate to follow with one of the longer-acting calcium channel blockers.

Calcium Channel Blockers

Both the sinoatrial (SA) node and the AV node are activated by the movement of calcium through the so-called slow calcium channels.⁸ Calcium channel blockers are the most powerful agents currently available for blocking the transmission of impulses across the AV node. A supraventricular dysrhythmia produces an acceleration in the ventricular rate because impulses generated by an ectopic source above the AV node are transmitted too rapidly to the ventricle [see Figure 4]. Calcium channel blockers produce a pharmacologic blockade of the AV node, reducing the number of impulses reaching the ventricles and thereby controlling the ventricular rate (Remember, keeping the

ventricular rate between 60 and 100 beats/min is the ultimate goal of antidysrhythmia therapy).

Adenosine

Adenosine is an endogenous nucleoside that has differential antidysrhythmic effects in both supraventricular and ventricular tissue. The appeal of adenosine as a therapeutic and diagnostic tool is that it depresses automaticity and conduction within the SA and AV nodes.⁹ Two clinically relevant types of adenosine receptors are present in cardiac tissue: (1) A_1 receptors, which are present on AV nodal tissue and cardiomyocytes and which thus mediate AV block and even bradycardia; and (2) A_2 receptors, which reside on vascular endothelial and smooth muscle cells and mediate coronary vasodilatation.¹⁰ A_3 receptors are present in the myocardium, and selective activation of these has a cardioprotective (cardiac preconditioning) effect; however, these receptors are not relevant in antidysrhythmic therapy.¹¹

Adenosine and acetylcholine exhibit identical cardiac effects and share similar receptor-effector coupling systems. Adenosine and acetylcholine provide an opposing balance to the sympathetic neurotransmitters norepinephrine and epinephrine. Thus, predictably, the adenosine antagonists caffeine, theophylline, and aminophylline provoke tachycardia and ectopy.

Because of the rapid intravascular metabolism of adenosine (half-life, 6 seconds), an intravenous bolus of adenosine (6 mg or 100 $\mu\text{g/kg}$) produces a negligible effect on systemic blood pressure, as confirmed by multiple clinical studies. Thus, adenosine is safe, but its effects are transient.

Adenosine is useful in blocking AV nodal conduction. Intracardiac recordings exhibit prolongation of the A-H interval with no alteration in conduction distal to the His bundle and on into the ventricular myocardium (the His-Purkinje system is unaffected).

In more than 90% of cases, adenosine is effective in terminating supraventricular tachycardia. Interestingly, adenosine has proved as effective at terminating atrioventricular reentry (85%) as at terminating atrioventricular node reentry (86%).⁹ Because of adenosine's short half-life, however, the supraventricular dysrhythmia is likely to recur within minutes in up to one third of patients. For that reason, adenosine is often used diagnostically, to discriminate supraventricular from ventricular dysrhythmias (see above).

Several clinical studies have compared adenosine with verapamil for therapeutic AV nodal blockade, with predictable results. Both agents block the AV node and control the ventricular rate: cumulative efficacy with either agent is more than 90%. Postconversion dysrhythmias in the two groups were similar. Spontaneous reinitiation of supraventricular dysrhythmias occurs more frequently with adenosine, whereas systemic hypotension is more commonly associated with verapamil (at least until the dysrhythmia breaks). Thus, for help in seconds (approximately 20 seconds), use adenosine (6 mg I.V. bolus, may be repeated); for help in minutes (3 to 5 minutes), use verapamil (1 mg/min I.V. up



Figure 3 P waves are absent and the QRS complexes are narrow and irregular in this ECG tracing from a patient with atrial fibrillation.



Figure 4 In a narrow-complex tachycardia, the entire ventricle is activated in less than 0.08 second. Presumably, the impulse originated at a supraventricular source and accessed the ventricle via the high-velocity Purkinje system.

to 10 mg); and for help in hours, infuse digoxin, 0.5 mg I.V. Although digitalis effectively blocks the AV node, it should be remembered that digitalis actually increases automaticity and excitability in both the atrium and the ventricle. The calcium channel blockers are superior to digoxin in controlling the ventricular rate.⁸

The adverse effects of adenosine, like the beneficial effects, are transient.⁹ Facial flushing, chest pressure (adenosine has been implicated in the sensation of angina), and transient third-degree heart block are very common. Significant side effects are rare. Nebulized adenosine can cause bronchoconstriction, especially in asthmatic patients. Bronchoconstriction has not been reported after intravenous administration of adenosine.

Magnesium

Magnesium is the second most abundant cation in humans. It is involved in many enzymatic reactions that influence the production and utilization of cellular energy. Abnormalities in electrolyte homeostasis (potassium and calcium in particular) are associated with a robust increase in cardiac myocellular excitability and automaticity, especially when these abnormalities are concurrent with myocardial ischemia.¹² Multiple clinical studies confirm the efficacy of intravenous magnesium infusion even when the measured serum values are normal. The mechanism is unknown. When confronted with a patient exhibiting either supraventricular or ventricular ectopy, it is safe (and often effective) to administer magnesium chloride at a dosage of 7 g or 100 mg/kg I.V. over 1 to 3 hours. It is not necessary to measure the serum magnesium concentration first; the serum value will not influence therapy.

Amiodarone

Amiodarone is a class III antiarrhythmic drug that exerts its primary effect by prolongation of the myocardial action potential and refractory period and by delay of both SA node function and AV conduction. Amiodarone is also unique among these compounds by virtue of exhibiting, to varying degrees, the pharmacologic traits of all four classes of antiarrhythmic drugs [see Discussion, Antidysrhythmic Agents, *below*].¹³ Among these is its ability to inhibit alpha- and beta-adrenergic stimulation without the classic side effects associated with beta receptor blockade. It also reduces transmural proarrhythmic heterogeneity (which predisposes to arrhythmias) in the human heart [see Discussion, Pathophysiology of Cardiac Dysrhythmias, Reentrant Dysrhythmias, *below*].¹⁴

Intravenous amiodarone was approved in the United States for use against malignant ventricular tachyarrhythmias in 1995. Rates of effective suppression for ventricular arrhythmias have been reported to be as high as 91% in uncontrolled trials.¹⁵ Intravenous amiodarone has also proved effective against refractory ventricular tachycardia and VF. In one double-blind, randomized, placebo-controlled trial, amiodarone significantly improved survival in patients suffering out-of-hospital cardiac

arrest.¹⁶ Amiodarone also proved superior to lidocaine (78% versus 27%) for termination of ventricular tachycardia in a randomized, prospective study of 29 patients with ventricular tachycardia refractory to external shock therapy.¹⁷

Another prospective, double-blind study comparing amiodarone with ibutilide (another class III antiarrhythmic agent) showed the drugs to be equally efficacious in the conversion of atrial fibrillation to sinus rhythm and in the subsequent maintenance of sinus rhythm.¹⁸ Although two patients (10%) in the amiodarone group experienced hypotension during treatment, long-term maintenance therapy using the oral form of amiodarone may make it the drug of choice for this purpose, given ibutilide's lack of oral bioavailability. Amiodarone was also found superior to both sotalol and propafenone in preventing the recurrence of atrial fibrillation in a randomized, prospective multicenter study of 403 patients with a mean follow-up period of 16 months.¹⁹

Although gratifyingly effective, amiodarone has significant side effects.²⁰ In trials of low-dose amiodarone (200 mg/day), thyroid, neurologic, cutaneous, ocular, bradycardic, and hypotensive problems were statistically more frequent; interestingly, pulmonary fibrosis was not.²¹

For the first 24 hours, the recommended dosages for adults are a loading dose of 150 mg I.V. over the first 10 minutes (15 mg/min) followed by 360 mg I.V. over the next 6 hours (1 mg/min); a maintenance infusion of 540 mg (0.5 mg/min) is given over the remaining 18 hours. The maintenance infusion may be continued for up to 3 weeks, at the rate of 0.5 mg/min, or the patient may be converted to oral dosing at 400 to 1,600 mg daily, depending on the duration of the preceding I.V. infusion.

Cardiac Dysrhythmias during Pregnancy

Fortunately, cardiac dysrhythmias are not frequent in young women of childbearing age. When rhythm problems do occur, they tend not to be hemodynamically destabilizing. The most commonly used obstetric drug with electrophysiologic side effects is magnesium sulfate.²² When magnesium is infused intravenously into the mother, the fetus may exhibit a dose-dependent bradycardia and a progressive decrease in healthy heart rate variability.^{23,24} Antidysrhythmic (indeed, any) drugs should be avoided during the first trimester of pregnancy, although most antidysrhythmic agents carry relatively little risk.²² Quinidine, procainamide, lidocaine, digoxin, adenosine, and beta blockers all have a long record of safety during pregnancy. Flecainide has proved to be effective in treating fetal supraventricular tachycardia complicated by hydrops. Phenytoin and amiodarone have been associated with congenital abnormalities.²²

The important point is that if the mother is hemodynamically unstable and exhibits a dysrhythmia, direct current cardioversion is safe and effective.

Proarrhythmia with Antidysrhythmic Drugs

Proarrhythmic manifestations of ostensibly antiarrhythmic drugs have been linked primarily to agents that prolong repolarization. Early afterdepolarizations associated with agents that retard repolarization or an increase in spatial and temporal dispersion of repolarization are the putative mechanisms of drug-induced or drug-enhanced arrhythmias.^{25,26}

The class III antidysrhythmic agents have traditionally been the agents most likely to cause dysrhythmias.²⁶ The best way of preventing dysrhythmias, however, is to follow the general policy of not using drugs at all if they are not needed.²⁷

Discussion

Antidysrhythmic Agents

Verapamil (or another calcium channel blocker), lidocaine, and adenosine are the only drugs essential for the acute treatment of cardiac dysrhythmias. Because patients may already be taking oral agents for chronic dysrhythmias, however, it is important to be aware of the actions and side effects of these drugs when treating an individual with an acute dysrhythmia. Antidysrhythmic drugs have been classified on the basis of their dominant electrophysiologic effect²⁸; this classification has been reviewed and placed in a clinical context.⁵ Adenosine has a unique receptor that modulates cyclic adenosine monophosphate (cAMP), resulting in cholinergic activity. It is not similar to other antidysrhythmic agents and is therefore unclassified.

CLASS I AGENTS (MEMBRANE ACTIVE)

Class I agents are fast sodium channel blockers. All class I agents—which include lidocaine, procainamide, quinidine, and disopyramide—are local anesthetics. These agents block the fast inward sodium current and thereby decrease both the amplitude of the action potential, or phase 0 depolarization (see below), and conduction velocity. These agents also depress the rate of spontaneous phase 4 depolarization, or automaticity, and thus are useful for abolishing premature ventricular contractions (PVCs); class I agents are sometimes termed PVC killers. Because these agents slow the conduction velocity, they can actually increase the likelihood of reentrant cardiac dysrhythmias in some patients.^{25,27}

CLASS II AGENTS (BETA BLOCKERS)

Class II agents are beta blockers and include such drugs as propranolol. Sympathetic hyperactivity, marked by increased release of catecholamines, is one of the major causes of cardiac dysrhythmias that result from increased automaticity (hyperexcitability).^{25,27,29} Beta-adrenergic blockade has produced a decrease in such automatic dysrhythmias under both clinical and experimental conditions.²⁹

CLASS III AGENTS (TO PROLONG REPOLARIZATION)

Class III agents, such as bretylium, act directly on the myocardial cell membrane to delay phases 2 and 3 of repolarization and thereby prolong refractoriness. Bretylium is effective in terminating reentrant dysrhythmias because it prolongs the refractory period of the ectopic focus to beyond the point at which an impulse reenters the circuit.^{1,2} Bretylium apparently has no effect on either automaticity or conduction velocity.³⁰

CLASS IV AGENTS (CALCIUM CHANNEL BLOCKERS)

Class IV agents, of which verapamil and diltiazem are the most effective, block the movement of calcium across the slow calcium channels but have virtually no effect on the so-called fast sodium channels.²⁸ Because both the SA node and the AV node are composed of slow-response fibers that are activated by the movement of calcium ions across the slow channels, the class IV agents are particularly effective in preventing unwanted supraventricular impulses from reaching the ventricles. These agents decrease the conduction velocity through the AV node and increase the refractory period of the AV node.

CLASS V AGENTS (UNCLASSIFIED)

The vagus nerve innervates the SA node, the atria, and the AV node, but it has almost no influence over the His-Purkinje system

or ventricular muscle. At therapeutic levels, digitalis has an anti-dysrhythmic action that is mediated almost exclusively via the vagus nerve. Toxic doses of digitalis, however, may produce an increased automaticity characterized by multifocal premature ventricular depolarizations [see Pathophysiology of Cardiac Dysrhythmias, *below*]. Caution must be observed in digitalizing a patient who is prone to atrial dysrhythmias, because digitalis increases atrial excitability and hence increases the risk of atrial ectopy. Because digitalis also induces AV nodal blockade mediated by the vagus nerve, however, any atrial dysrhythmias produced by digitalization will be less clinically significant.^{31,32}

Cellular Electrophysiology

Electromechanical activity of all muscle, including the heart, is determined by the concentration and flow of ions, particularly calcium, potassium, and sodium. Knowledge of cardiac electrophysiology can serve as a conceptual framework on which to build a rational therapeutic program. Direct observation of cellular electrical activity using a glass microelectrode reveals that the cell membrane is semipermeable: it permits easy passage of cations such as sodium, potassium, and calcium but provides a barrier to anions and proteins. Negatively charged intracellular proteins that cannot cross the cell membrane create a transmembrane potential in which the interior of the cell is negatively charged relative to the exterior. The membrane potential of a cell, E_K , is proportional to the difference between the logarithms of the intracellular potassium concentration, $[K]_i$, and the extracellular potassium concentration, $[K]_o$:

$$E_K = c(\log [K]_i - \log [K]_o)$$

The proportionality constant, c , varies with temperature, but at 37° C it is -60 mV. Thus, under physiologic conditions,

$$E_K = -60 \text{ mV} \times \log [K]_i / [K]_o$$

This relation, termed the Nernst equation, can be used to calculate the myocardial cell membrane potential if the potassium concentrations are known. For example, if the potassium concentration is normal—that is, 150 mEq/L intracellularly and 3.8 mEq/L extracellularly—then the membrane potential is

$$\begin{aligned} E_K &= -60 \text{ mV} \times \log 150 / 3.8 \\ E_K &= -90 \text{ mV} \end{aligned}$$

If, however, the serum potassium concentration rises to 6.0 mEq/L, then the membrane potential also changes:

$$\begin{aligned} E_K &= -60 \text{ mV} \times \log 150 / 6.0 \\ E_K &= -80 \text{ mV} \end{aligned}$$

Thus, the resting membrane potential is determined primarily by the concentration gradient for potassium across the cell membrane. The transmembrane potential can be calculated if the transmembrane potassium concentrations are measured with a glass microelectrode. Under clinical conditions, however, only the serum potassium level can be measured. This value does not provide an adequate guide to the transmembrane electrical voltage, because many physiologic factors are capable of altering the intracellular potassium concentration.¹³ Such factors include electrolyte and acid-base balance, the level of osmotic and metabolic activity, and the serum levels of glucose and insulin.

Any factor that causes osmotic movement of water into the cell

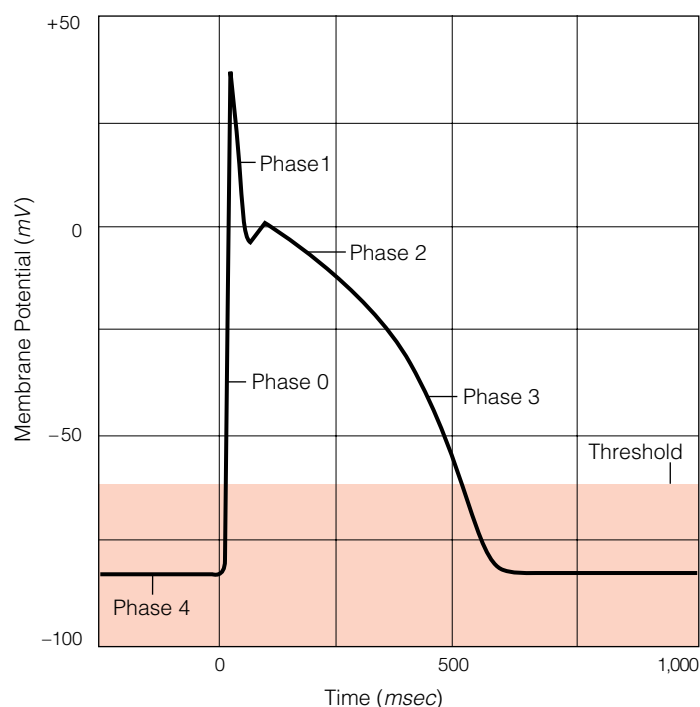


Figure 5 The standard Purkinje (or ventricular muscle) action potential has five distinct phases: phase 0, rapid depolarization; phase 1, early repolarization; phase 2, plateau; phase 3, rapid repolarization; and phase 4, diastole.

will dilute and thus decrease the intracellular potassium concentration. The transmembrane gradients of sodium and calcium are maintained by energy-requiring pumps in the cell membrane. When these pumps are inactivated, as during myocardial ischemia,¹² sodium and calcium can leak into the cell. If, as often occurs, sodium leaks into the cell faster than potassium leaks out, water will be drawn in, producing myocardial edema. Tissue acidosis can also alter the transmembrane potassium gradient. In acidosis, hydrogen ions can leak into the cell in exchange for potassium, thereby decreasing the intracellular potassium concentration and increasing the membrane potential. Variations in glucose transport can also affect the potassium gradient. Under the influence of insulin and epinephrine, glucose may move across the membrane into the myocardial cell, drawing in water by osmosis. The decline in intracellular potassium concentration stimulates the sodium pump to exchange extracellular potassium for intracellular sodium. Concurrent administration of glucose and insulin is the standard method for treating hyperkalemia because it shifts potassium from the extracellular fluid back into the cells.

ACTION POTENTIAL GENERATION

Stimulation of either cardiac muscle or skeletal muscle produces an action potential. Unlike a skeletal muscle action potential, which lasts only several milliseconds, a cardiac action potential may persist for as long as several hundred milliseconds.³³ The standard Purkinje, or ventricular muscle, action potential has five discernible phases [see Figure 5].

Phase 4

In phase 4, the resting membrane potential, or diastolic potential, of the cell is generated by active metabolic processes that produce substantial transmembrane potassium and sodium gradi-

ents. An energy-dependent (ATP-dependent) sodium-potassium pump counteracts a significant influx of sodium and efflux of potassium in the resting cell to maintain this resting membrane potential. As noted, when the extracellular potassium concentration rises from a typical value of 3.8 mEq/L to 6.0 mEq/L, the resting membrane potential increases from -90 mV to -80 mV. This effect would tend to increase automaticity, but it is superseded by the effect of hyperkalemia on the sodium current. A rise in the extracellular potassium level progressively impairs the flux of sodium through sodium-specific channels, leading to an overall decrease in myocardial excitability.³⁴

Phase 0

During phase 0, an electrical stimulus causes the sodium-specific fast channels and the calcium-specific slow channels to open, usually for no longer than 1 msec. As positive ions rush in, depolarization occurs as the membrane potential rises to threshold, or -60 mV, and an action potential is generated [see Figure 5]. Under normal physiologic conditions, the stimulus that produces an action potential is electrical, but any stimulus—electrical, physical (such as a precordial thump), or chemical—that depolarizes a membrane up to threshold (again, -60mV) can generate an action potential. There are various abnormalities that can cause the resting membrane potential to move toward threshold. For example, conditions that produce a decrease in energy supply (or, alternatively, an increase in energy demand) will have this effect because energy is required to maintain the potassium and sodium gradients across the resting membrane. Under such conditions, automaticity is enhanced because lesser stimuli can achieve the threshold potential, and the cardiac muscle is said to be hyperexcitable, or irritable.

Phases 1 and 2

Phase 1 is characterized by repolarization to the plateau phase, or phase 2. During phase 2, the slow calcium channels as well as the fast sodium channels are activated, and the membrane potential remains relatively constant for as long as 100 msec.³⁵ The long duration of this plateau phase is the most dramatic difference between an action potential in cardiac muscle and one in skeletal muscle. During this interval, termed the effective refractory period, the myocardium is relatively resistant to further excitation.

Phase 3

During phase 3, potassium channels reopen to promote efflux of potassium from the cell. Rapid repolarization ensues, and the resting membrane potential is reestablished at -90 mV.

Spontaneous Phase 4 Depolarization

Unlike ordinary atrial and ventricular muscle, the Purkinje fibers do not have a stable phase 4 diastolic potential [see Figure 6]. Instead, these fibers undergo continuous depolarization during diastole as a result of deactivation of the potassium efflux current.^{35,36} If the Purkinje fibers reach the threshold voltage, they will fire an action potential. Under normal conditions, however, the SA and AV nodes exhibit faster diastolic depolarization and reach threshold sooner than the Purkinje fibers. Because the cells in the SA node normally reach threshold first—winning the race, so to speak—the SA node typically assumes the pacemaker function of the heart. Premature ventricular contractions develop when a hyperexcitable cell or fiber in ventricular myocardium undergoes rapid diastolic depolarization and reaches threshold before the cells in the SA node. This cell or fiber then assumes the pacemaker function of the heart for that beat. The PVCs (or,

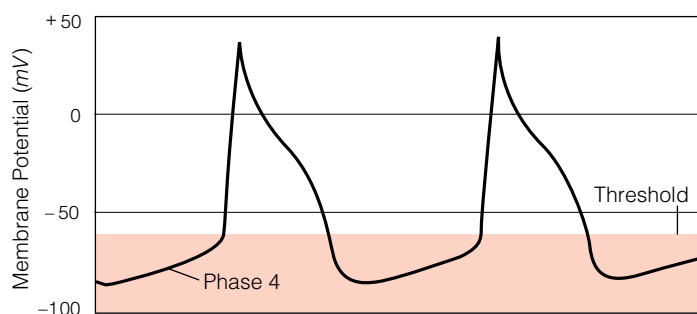


Figure 6 In normal cardiac Purkinje fibers, the membrane potential does not remain flat during phase 4 but instead rises gradually. This spontaneous phase 4 depolarization is the result of a resting potassium current.

more accurately, premature ventricular depolarizations) that result from such ventricular ectopy can be abolished by overdrive pacing. In this situation, a mechanical pacemaker is used to pace the heart at a rate faster than that of the PVC (i.e., the R-R interval is shorter). The artificial device thereby wins the race; it assumes the pacemaker function and regularizes the heart rate, producing a beneficial cosmetic effect on the ECG without altering the hyperexcitability of the diseased cell.

Pathophysiology of Cardiac Dysrhythmias

All dysrhythmias are caused by enhanced automaticity, reentry, or a combination of these two mechanisms.

AUTOMATIC DYSRHYTHMIAS

Any area of myocardial tissue that independently depolarizes, reaches threshold, and fires is termed automatic, and the electrical impulse that activates the adjacent myocardium generates an automatic rhythm. Acute dysrhythmias tend to be automatic; such automatic dysrhythmias are frequently seen in patients in emergency departments and coronary care units and in patients undergoing surgery. Five common clinical phenomena that tend to increase automaticity have been identified: local myocardial hypoxia, hypokalemia, hypercalcemia, increased catecholamine levels, and drugs (most commonly digitalis).

Local Myocardial Hypoxia

Energy-dependent cell membrane pumps maintain the resting membrane potential, and when oxygen supply to myocardial tissue is inadequate because of ischemia, the pumps fail to function properly. Consequently, the potassium gradient declines, and the membrane potential drifts closer toward threshold. Small membrane potential fluctuations or stimuli of less than normal magnitude are then sufficient to bump the membrane potential up to threshold and initiate an action potential. Ventricular muscle cells, not only those cells in specialized conduction tissue, can spontaneously generate electrical fluctuations, or oscillations, in membrane potential [see Slow Afterdepolarizations, *below*]. If the resting membrane potential is initially closer to normal because of local myocardial hypoxia, then these spontaneous oscillations are more likely to achieve threshold and fire an action potential.³⁷

Hypokalemia

Extracellular hypokalemia increases the resting membrane potential, drawing it further away from threshold and producing hyperpolarization. This effect tends to decrease tissue excitability,

or automaticity.^{37,38} Hypokalemia also increases the size of the sodium channels, however, thereby promoting more rapid influx of sodium during phase 0. Because the net result of hypokalemia is increased automaticity, the effect of hypokalemia on sodium influx appears to override its effect on membrane hyperpolarization. Hypokalemia is one of the most easily treated (and overtreated) forms of hyperexcitability.

Hypercalcemia

Calcium is a potent inotropic agent, mediating the interaction between actin and myosin that produces muscle contraction.³⁵ High extracellular calcium levels may cause myocardial work to exceed the energy supply and thus impair the function of the membrane pump. As a result, the resting membrane potential drifts up toward threshold, enhancing automaticity. Excess calcium also appears to promote spontaneous oscillations in membrane potential [see Slow Afterdepolarizations, *below*].³⁹ Because of calcium's inotropic effect, such oscillations are accompanied by muscle activity.

Elevated Catecholamine Levels

Increased catecholamine levels also appear to predispose to automaticity, as evidenced by an increase in the incidence of multiple PVCs reported in patients who have been infused with high doses of catecholamines, such as epinephrine or dopamine. Catecholamines increase both heart rate and contractility. As with hypercalcemia, elevated catecholamine levels may increase cardiac work beyond the limits of energy supply and cause the membrane potential to move closer to threshold. This effect on the energy-dependent membrane pumps has been observed in isolated preparations of Purkinje muscle fibers. The addition of catecholamines to preparations of Purkinje muscle fibers has decreased the outward potassium current to the point that the resting membrane potential was shifted as much as 25 mV toward depolarization, enhancing automaticity.^{36,37} In addition to affecting the operation of the membrane pumps, catecholamines can produce large spontaneous oscillations in membrane voltage.^{36,40} Catecholamines are elaborated endogenously; a patient who is in pain, for example, may be releasing large amounts of epinephrine into the circulation. In such cases, morphine can be used effectively as an antidysrhythmic agent.⁴⁰

Drugs

Digitalis is the prototypical cardiac stimulant. Typically, any

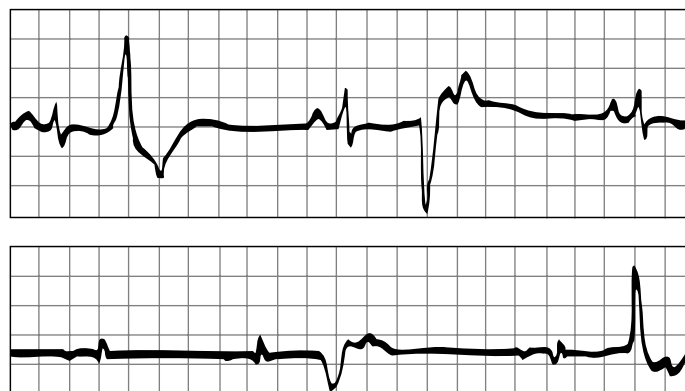


Figure 7 ECG demonstrates multifocal PVCs, indicating a diffuse hyperexcitability of the ventricles. Such hyperexcitability may arise from a metabolic abnormality such as hypokalemia or a pharmacologic cause such as digitalis toxicity.

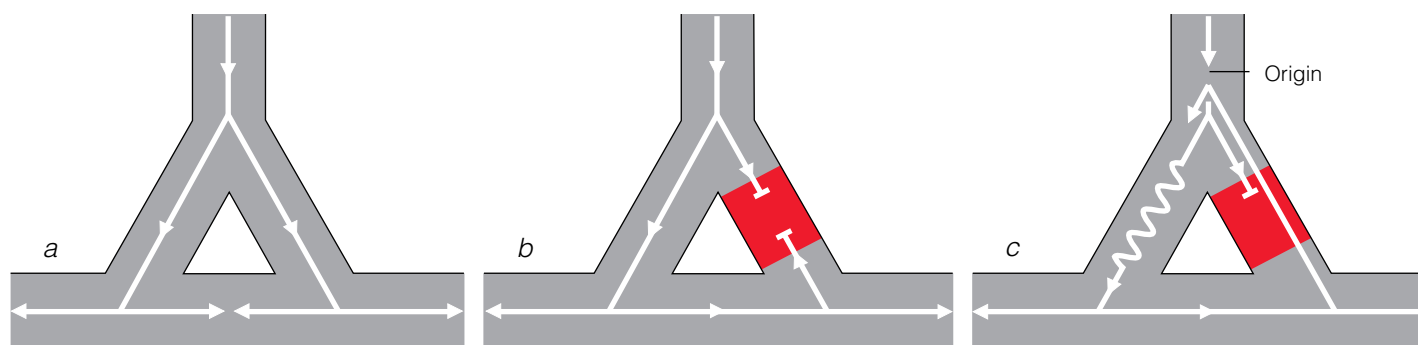


Figure 8 Schematic diagram portrays a conceptual framework for understanding the generation of reentrant dysrhythmias. In normal conduction (a), as in sinus rhythm or ventricular pacing, an impulse is propagated along two different anatomic pathways and is extinguished at the bottom. In (b), one pathway has a region of slow conduction (red area), which results in a rate-dependent block. In (c), the impulse is also blocked in the right limb (red area), but it travels over the alternative pathway sufficiently slowly (zigzag line) for the origin to be able to repolarize before the initial impulse returns; the conducted impulse then depolarizes the origin and reenters the circuit.

agent other than oxygen that causes the heart to pump harder and faster also increases cardiac excitability. Digitalis toxicity can produce diffuse myocardial hyperexcitability, manifested by so-called automatic ventricular ectopy. In this condition, the cardiac impulse originates from multiple sites in the ventricle. In patients with ventricular ectopy caused by digitalis intoxication, the whole myocardium becomes hyperexcitable and spontaneous depolarizations derive from multiple different sites. When the QRS complex originates at multiple loci, the ECG will exhibit multiple morphologies, and multifocal PVCs are apparent on the ECG—the classic multifocal ectopy of digitalis toxicity [see Figure 7].⁴¹⁻⁴³

REENTRANT DYSRHYTHMIAS

In the normally functioning heart, the rich cell-cell conduction pathways promote uniform activation of the atria or ventricles in waves. Because activation occurs by means of large electrical wave

fronts and because all cardiac tissue has a long refractory period, it is highly unlikely that any cells will remain excitable at the completion of each beat. However, disorders such as myocardial ischemia, fibrosis, and necrosis slow electrical conduction and also produce nonconductive areas that interrupt the normal electrical wavefront.⁴⁴ These conditions set up one of the requirements for reentry: areas of differential myocardial repolarization.⁴⁵

A circuit whose length exceeds the duration of the reentrant impulse circuit is required for the initiation of reentry (i.e., in order to sustain continuous conduction); such a circuit may develop because of anatomic or physiologic heterogeneity in myocardial tissue.^{44,45} Slow conduction, a shortened refractory period, and anatomic heterogeneity all favor reentry [see Figure 8]. The circuit wavelength of an impulse is the product of the conduction velocity and the duration of the longest refractory period in the circuit.⁴⁶ For example, for normal myocardium, the

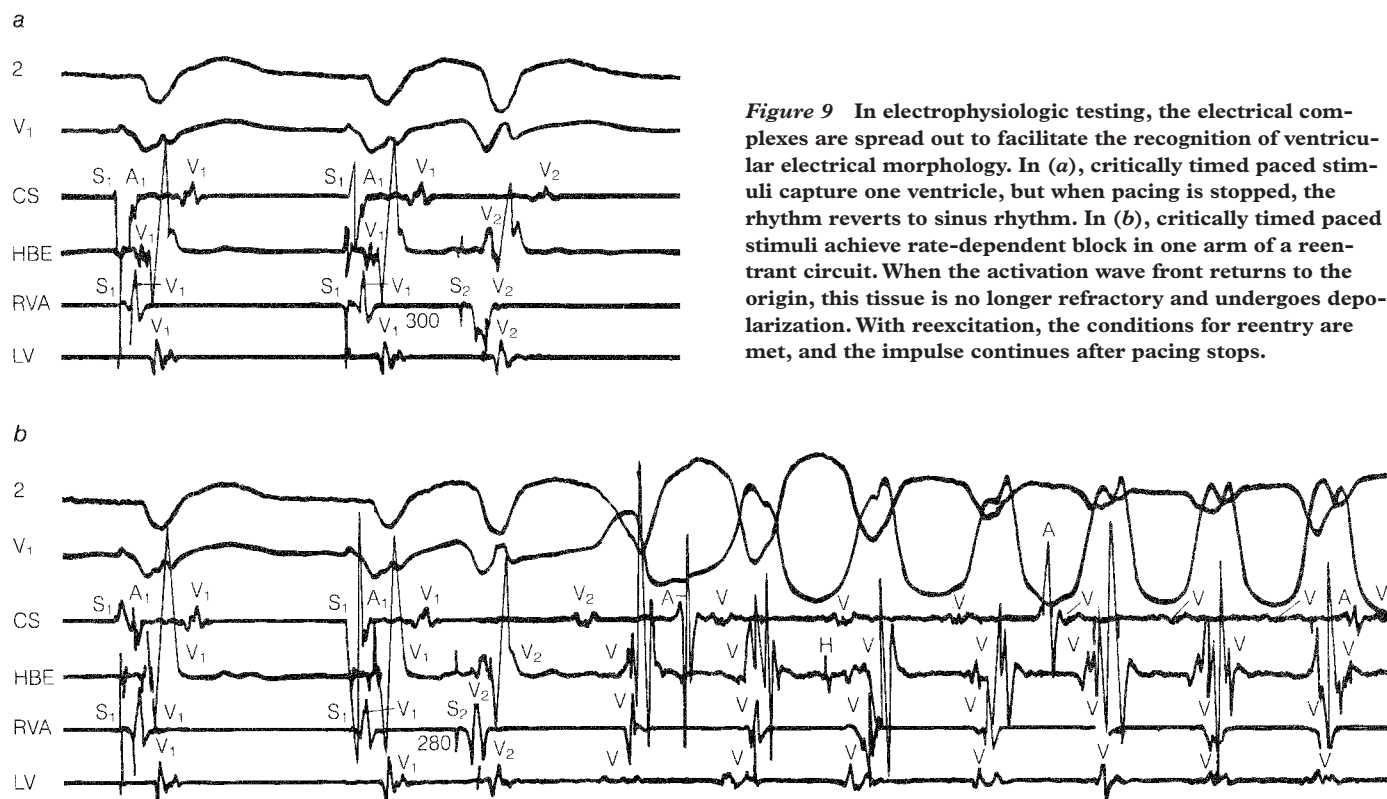


Figure 9 In electrophysiologic testing, the electrical complexes are spread out to facilitate the recognition of ventricular electrical morphology. In (a), critically timed paced stimuli capture one ventricle, but when pacing is stopped, the rhythm reverts to sinus rhythm. In (b), critically timed paced stimuli achieve rate-dependent block in one arm of a reentrant circuit. When the activation wave front returns to the origin, this tissue is no longer refractory and undergoes depolarization. With reexcitation, the conditions for reentry are met, and the impulse continues after pacing stops.

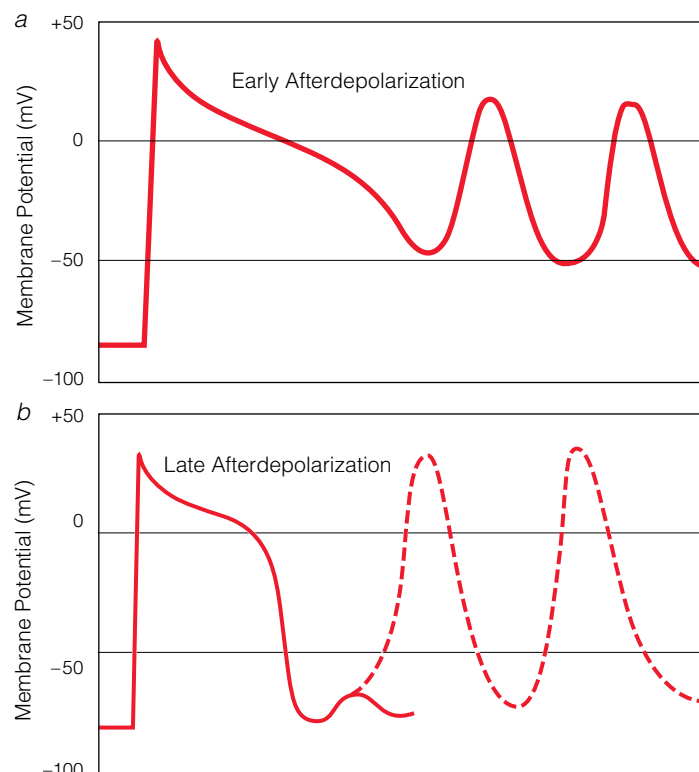


Figure 10 Membrane oscillatory instability may be manifested by either (a) early afterdepolarizations or (b) late afterdepolarizations. If the late afterdepolarizations achieve the threshold voltage, they can fire an action potential (dotted lines).

conduction velocity is 200 cm/sec and the refractory period is 0.4 second; therefore, the circuit length for a normally conducted myocardial impulse would have to be 80 cm. Because the reentrant circuit would have to be extraordinarily tortuous to encompass 80 cm, it would appear that concomitant slow conduction is essentially mandatory to shorten the circuit wavelength and permit initiation of a reentrant dysrhythmia. Regions such as the AV and SA nodes normally exhibit slow conduction, and therefore, any disturbance that produces minor additional slowing in these areas predisposes to reentry. It has also been suggested that extreme anatomic heterogeneity might permit microreentry.⁴⁵ For example, a tortuous path over stunned, slowly conducting ventricular muscle in an individual with heterogeneous myocardial infarction might achieve the prerequisites for reentry.

In vitro studies have investigated physiologic factors that might produce changes in conduction and excitability that predispose to reentrant dysrhythmias. For example, abnormal conduction has been observed in a Purkinje network subjected to local changes in potassium concentration.^{33,40} The decrease in conduction velocity can vary in different areas of the Purkinje network, leading to functional conduction block.^{37,38} In T- or X-shaped Purkinje preparations, the impulses either summate electrically or, conversely, inhibit each other when they arrive at the same junction simultaneously. It is difficult to study the cardiac microenvironment in living animals or humans, but in these studies,⁴⁷ electrical instability results when the Purkinje network is subjected to potassium fluctuations (which certainly occur with induced cardioplegia during cardiac surgery, and probably occur in myocardial ischemia).

Electrophysiologic testing with programmed stimulation in a

patient with a history of cardiac dysrhythmias can reveal whether latent substrates of reentry are present. Because organized ventricular reentry does not occur in normal myocardium, all reentrant dysrhythmias, whether they are induced or spontaneous, are pathologic. Rapidly paced stimuli may provoke a decrease in action potential duration and shorten refractoriness in myocardium in which the conduction velocity has already been reduced. Critically timed premature paced stimuli may then penetrate selective zones of myocardium, leading to a reentrant dysrhythmia [see Figure 9].⁴⁸ A ventricular tachydysrhythmia that can be induced by programmed stimulation carries an ominous prognosis unless it can be abolished by pharmacotherapy or surgery.⁴⁸

SLOW AFTERDEPOLARIZATIONS

Damaged atrial and ventricular muscle exhibits resting membrane potential instability.⁴⁹ The oscillations in membrane potential may at times be large enough to raise the membrane voltage to threshold level and cause the cell to fire. The phenomenon of oscillatory instability, which was first recognized in the 1940s,⁵⁰ is now thought to play an important role in the genesis of cardiac dysrhythmias. Injury,⁴⁹ elevated calcium levels,³³ digitalis,^{41,42} and catecholamines all promote membrane oscillatory instability, which may be manifested as either early or late afterdepolarizations. Both phenomena occur after an action potential; however, an early afterdepolarization occurs before repolarization of the cell, whereas a late afterdepolarization occurs after repolarization [see Figure 10]. Both early and late afterdepolarizations may be followed by extreme membrane oscillatory instability that leads to slow-response action potentials [see Figure 11]. If any of these slow potentials reach threshold, they may result in either organized electrical activity (premature ventricular depolarization) or disorganized electrical activity (fibrillation).

The recognition of slow potentials, depressed fast responses, and very slow conduction was originally based on in vitro studies of cardiac tissue.⁵¹ For example, bathing superfused Purkinje fibers in a solution with a high potassium concentration inactivates the fast sodium channels and markedly alters normal phase 0 depolarization. Under such circumstances, slow potentials that are less than 80 mV in amplitude, that depolarize at a rate of 1 to



Figure 11 Early afterdepolarizations may lead to slow-response action potentials. If any of these potentials reach threshold, they may lead to either organized electrical activity (premature ventricular depolarization) or disorganized electrical activity (fibrillation).

2 V/sec, and that last for up to 1 second are frequently documented.^{40,51} The amplitude and the overshoot of these slow potentials can be magnified by increasing the extracellular calcium concentration and can be abolished by adding manganese, an agent that blocks the slow calcium channels. These results suggest that the slow potentials are mediated by the slow calcium channels rather than by the fast sodium channels responsible for routine phase 0 depolarization. Although extraordinary nonphysiologic conditions are employed to induce such slow potentials in the laboratory, the myocardial microenvironment during the peri-infarction and postinfarction periods as well as after cardioplegia may well be similarly bizarre and equally nonphysiologic.

For example, even after extensive myocardial infarction, there are often healthy Purkinje fibers overlying areas of damaged, ischemic myocardium.⁵² Slow conduction and slow potentials are characteristic of stunned myocardium.^{53,54}

Slow potentials have been incriminated in the generation of reentrant dysrhythmias for three reasons: (1) because they are caused by an active calcium influx that produces 40 to 80 mV depolarizations, they may be conducted long distances; (2) because the conduction velocity may be 1,000 times slower than normal, the circuit wavelength is reduced accordingly; and (3) because slow potentials leave a long refractory wake, they set up zones of functional conduction block.^{53,54}

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3 SHOCK

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Management of Shock

In thermodynamic terms, the purpose of the heart is simple enough. Its sole function is to generate useful energy (as opposed to heat, which it also generates) and then transfer that energy into the pulmonary artery and the aortic root as efficiently as possible. The useful energy transferred into the pulmonary artery from the right ventricle moves the blood through the lungs and into the left atrium and ventricle during diastole. The useful energy transferred into the aortic root from the left ventricle moves the blood throughout the body. The blood delivers nutrients (including oxygen) to metabolizing tissues, removes waste products from those tissues, carries heat from those tissues to the skin (where the heat is dissipated into the environment), and transports hormones and intermediate products of metabolism from one part of the body to another. The remaining energy in the blood pushes the blood into the right atrium and ventricle during diastole.

This useful energy has two components: flow and pressure. Flow, in the case of the cardiovascular system, is cardiac output. The pressures of interest are the mean pressures in the roots of the pulmonary artery and the aorta [see Figure 1]. These pressures, like all those we describe in this chapter, are expressed as being above (or occasionally below) atmospheric pressure and are measured with transducers placed at the level of the right atrium.

The formula for calculating the amount of useful energy transferred into the root of the pulmonary artery from the right ventricle (per unit time—typically 1 minute) is the cardiac output multiplied by the mean pressure in the pulmonary artery. The useful energy transferred into the aortic root from the left ventricle (per unit time) is the cardiac output multiplied by the mean aortic root pressure.¹⁻³

If the amount of useful energy transferred into the roots of the pulmonary artery and the aorta is insufficient to meet the body's basic metabolic needs, the patient is said to be in shock. Shock can

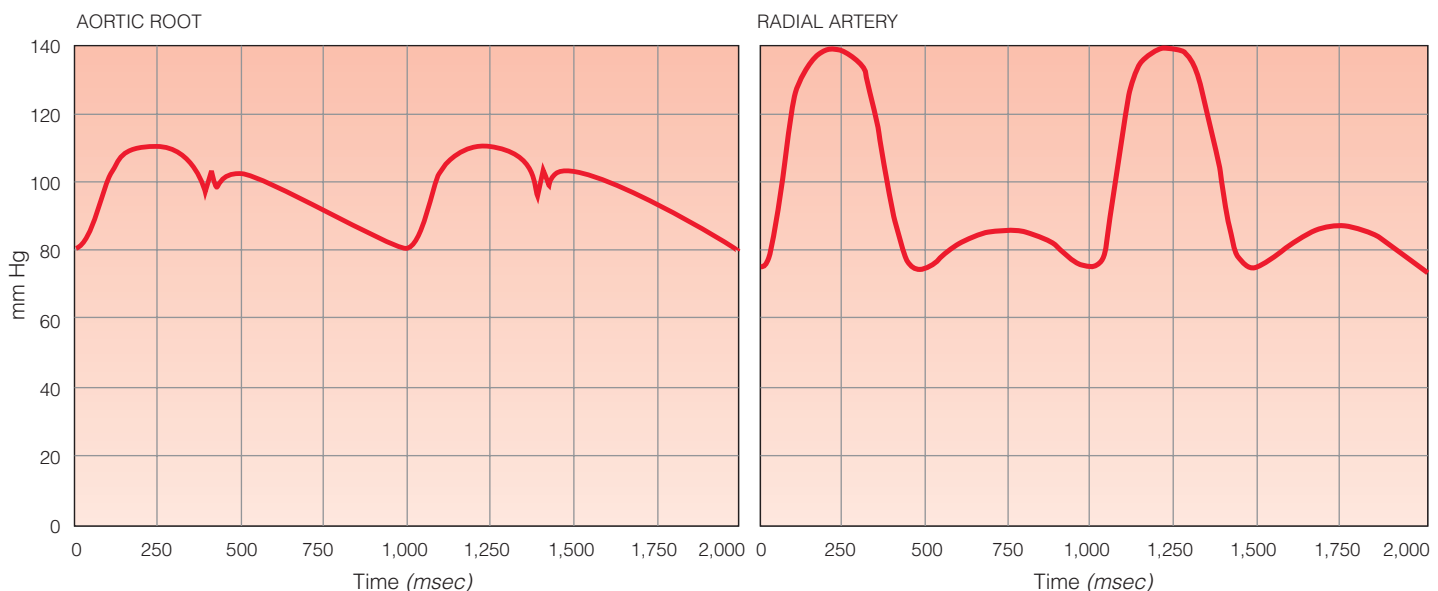
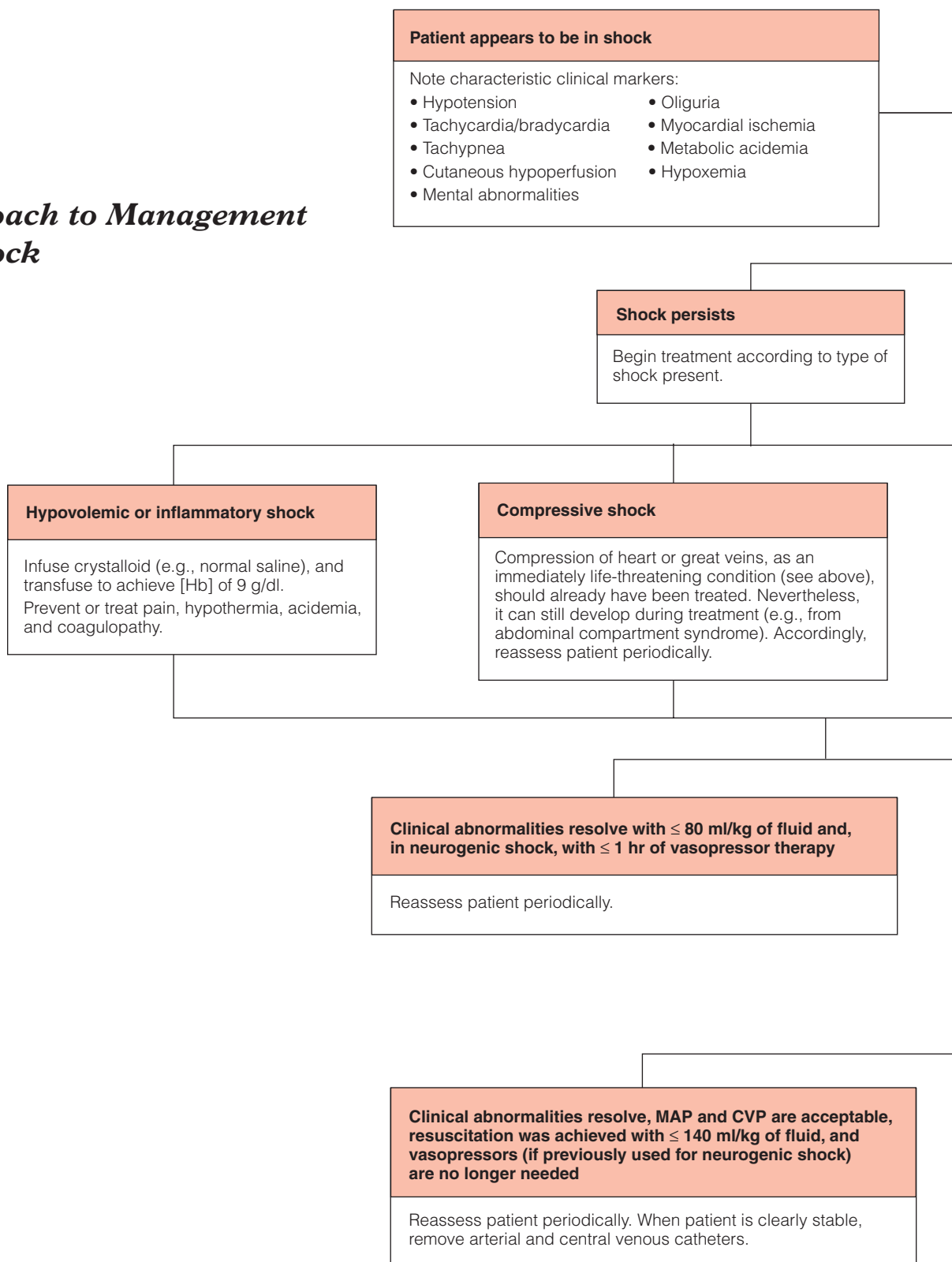
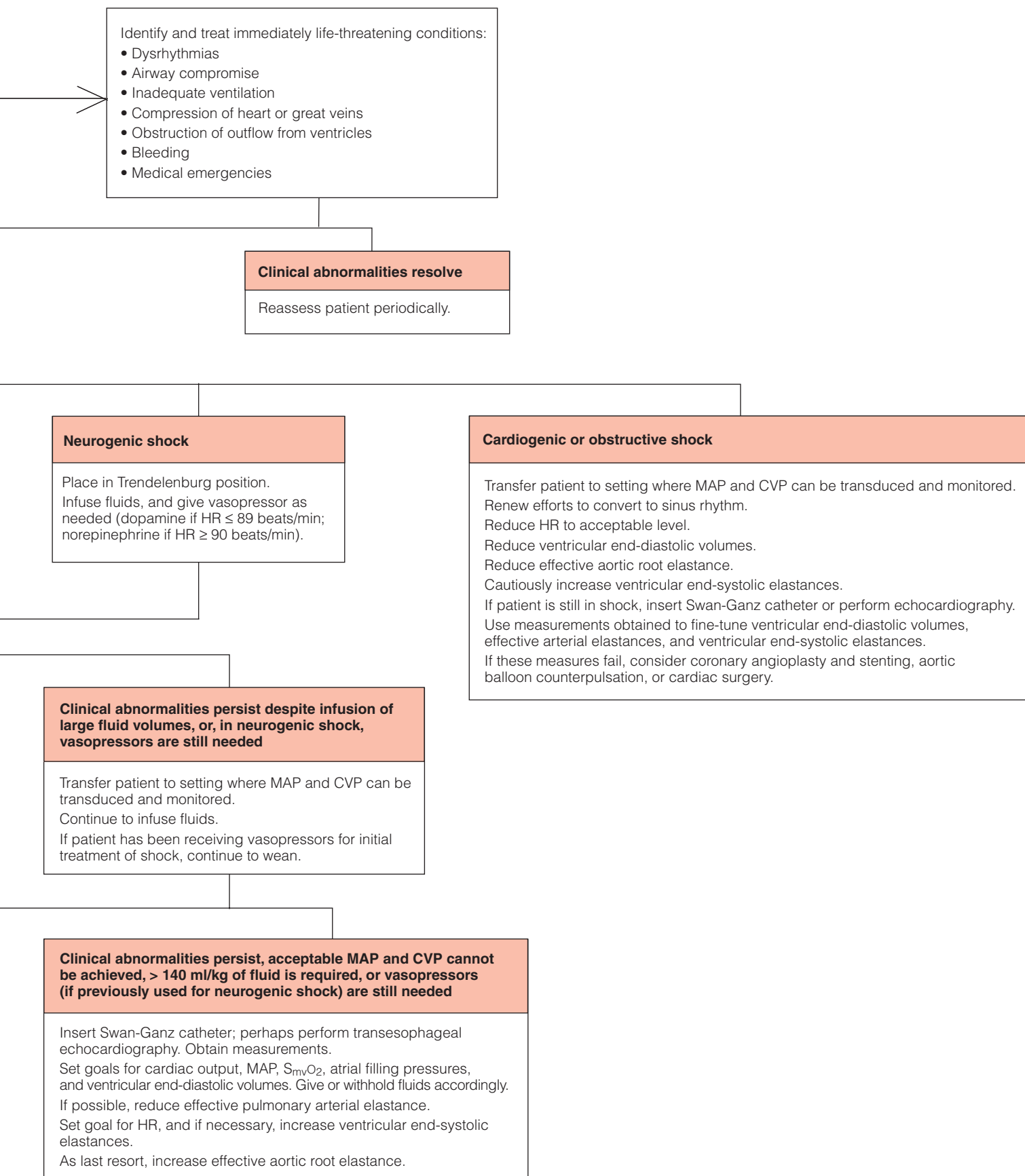


Figure 1 The mean pressure is defined as the area under a pressure tracing divided by the time needed to produce the tracing. A pressure wave in the ascending aorta with a blood pressure of 110/80 mm Hg will have the same mean pressure as a pressure wave in the radial artery of the same patient, even though the radial artery pressure might be 140/75 mm Hg. The systolic pressure in the radial artery is usually inscribed more rapidly. Therefore, even though the peak pressure in the radial artery is greater than that in the aorta, the areas under the tracings will be the same for the two vessels. Sometimes, the mean pressure can be approximated by taking one third of the difference between the systolic and diastolic pressures and adding that value to the diastolic pressure. Frequently, however, the formula does not work. In this example, the mean aortic pressure would be approximated at 90 mm Hg, whereas the mean radial artery pressure would be approximated at 97 mm Hg. Such results would be impossible: if the mean pressure in the radial artery were greater than the mean pressure in the aorta, blood would flow backward. This confusion is avoided by measuring the area under the curve and calculating the mean pressure exactly, which can be done with computer circuits that are available in all modern pressure-monitoring systems. It should also be noted that the systolic pressure in the radial artery is about 30 mm Hg higher than the systolic pressure in the aortic root. In extreme cases, it can be as much as 80 mm Hg higher [see Sidebar Energy Propagation throughout the Arteries and Its Effect on Pressures in Those Arteries].

Approach to Management of Shock





be caused by myriad different clinical conditions, which can be grouped into six broad categories [see Classification, below]. In all cases of shock, regardless of the category, one of two things has gone wrong, or else both have: either the cardiac output is inadequate or the mean central arterial pressures are inadequate, or else both are inadequate. When thinking about shock, one must keep these two possibilities in mind, both for assessment of the underlying problem and for treatment.

Classification

HYPOVOLEMIC SHOCK

The major physiologic derangement in hypovolemic shock (i.e., shock secondary to loss of blood volume) is a left ventricular end-diastolic volume (LVEDV) that is so small that the heart cannot produce adequate amounts of useful energy. Causes include bleeding, protracted vomiting or diarrhea, fluid sequestration in obstructed gut or injured tissue, excessive use of diuretics, adrenal insufficiency, diabetes insipidus, and dehydration. In severe cases, the hypovolemia is worsened by the loss of sodium, chloride, and water from the plasma to the interstitium and the intracellular space, which occurs as compensation for the intracellular acidosis created by lack of perfusion.

In all cases of hypovolemic shock, the cardiac output will be low. In mild cases, the pressure may be normal, depending on the degree of compensatory arteriolar constriction, but the product of the cardiac output and the pressure will be low. In severe cases, the mean arterial pressure (MAP) will be low, and the product of the output and the pressure will be very low.

INFLAMMATORY SHOCK

Any clinical condition that is associated with ischemia-reperfusion or infection can cause inflammatory shock (which is sometimes called septic shock if caused by an infection). Clinical conditions capable of causing inflammatory shock include pneumonia, peritonitis, cholangitis, pyelonephritis, soft tissue infection, meningitis, mediastinitis, crush injuries, major fractures, high-velocity penetrating wounds, major burns, retained necrotic tissue, pancreatitis, anaphylaxis, and wet gangrene.

This type of shock is caused by inflammatory and coagulatory mediators that are released from the damaged or infected tissues into the systemic circulation. Thus, for the shock state to develop, the infected or traumatized or reperfused tissues must be in proximity to a robust drainage of blood from the tissues. An avascular infection (e.g., a contained abscess), in which the inflammatory mediators do not have access to the circulation, will not cause inflammatory shock, whereas an uncontained abscess (e.g., a ruptured appendiceal abscess or an acutely drained subphrenic abscess), which allows vascular dissemination of the mediators, can do so. Similarly, dry gangrene, because of its poor vascular supply, will not cause inflammatory shock, whereas wet gangrene can.

The cardiovascular derangements in inflammatory shock are caused by three basic mechanisms. The first mechanism arises from the need to keep the body's temperature from becoming excessively high. In the case of inflammatory shock caused by infection, inflammatory mediators released from the infected tissue increase the metabolic rate and heat production by a factor as high as 2. The excess heat is carried by the blood to the skin, where it is dissipated to the environment by convection, conduction, radiation, and evaporation. Under resting, nonseptic conditions, in a thermoneutral environment, the heat can be dissipated and the body temperature controlled with a modest amount of

blood flow to the skin—on the order of 300 ml/min in a 60 kg subject.^{4,5} In an extremely cold environment, however, blood flow can drop to negligible levels, probably as low as 100 ml/min. In the case of extreme hypermetabolism, as occurs during exercise, blood flow can increase to 6 L/min.⁵ In the case of severe sepsis, blood flow is probably on the order of 3 L/min—enough to necessitate increasing the cardiac output by a factor of 1.5.

To maximize the delivery of heated blood to the skin, the cutaneous arterioles dilate. To maximize the surface area of the blood vessels in the skin (and thereby facilitate transfer of heat from the blood to the skin), the cutaneous venules and veins dilate. The blood pressure drops, both because of the arteriolar dilation and because pooling of blood in the cutaneous venous capacitance bed reduces the ventricular end-diastolic volumes (if the patient's blood volume has not been adequately replenished). Small end-diastolic volumes lead to a reduced stroke volume, which, in turn, lowers the cardiac output and exaggerates the fall in the blood pressure.

The second mechanism, also related to the release of inflammatory mediators (either from infected tissue or from tissue that has undergone ischemia and reperfusion), arises from the contraction of actin and myosin filaments in the endothelial cells of the microvasculature, both at the site of infection or ischemia-reperfusion and at distal sites as a consequence of blood-borne mediators. Intercellular gaps open up in the capillaries, venules, and small veins. These gaps give immunoglobulins and inflammatory cells access to the interstitium and allow protein-rich plasma to leak into the interstitium. As a result, blood volume is depleted and the ventricular end-diastolic volumes decreased.

The third mechanism, as in severe hypovolemic shock, is movement of sodium, chloride, and water from the plasma into the interstitium and the intracellular space as a means of controlling intracellular acidosis. Loss of fluid from the plasma into the cells reduces blood volume and thus decreases ventricular end-diastolic volumes.

These three mechanisms give rise to the characteristic clinical findings of inflammatory shock. The blood pressure will be low, for three possible reasons: (1) small ventricular end-diastolic volumes (if the patient has not been resuscitated), (2) lowered hindrance to ventricular ejection (because of the cutaneous arteriolar dilation), and (3) potential myocardial depression.⁶ The heart rate usually rises in an effort to increase the cardiac output; occasionally, it does not increase very much, in an effort to allow more time for ventricular filling and for perfusion of the coronary vasculature during diastole.

If the predominant feature of the shock state is loss of plasma volume into the interstitium through a permeable microvasculature and through intracellular accumulation of sodium, chloride, and water, the patient's skin will be cool and clammy (hence the terms cold septic shock and cold inflammatory shock). The cardiac output and the mean blood pressure will both be inadequate, and the patient's condition will meet the definition of shock—namely, inadequate perfusion because of inadequate generation of useful energy (cardiac output multiplied by mean pressure).

If, however, the blood volume has been restored or the predominant feature of the shock state is cutaneous vasodilatation, the patient's skin will be flushed and warm (hence the term warm inflammatory shock). The cardiac output will be high but the mean pressure will be low, as a consequence of the cutaneous arteriolar dilatation. If the product of the two—that is, the useful energy, or power—is inadequate to provide perfusion for the body, the patient is in shock. If the product of the two is adequate to provide perfusion, the patient will not be in shock, but the prob-

lem causing the systemic inflammatory state will still have to be corrected.

NEUROGENIC SHOCK

The cardiovascular derangements in neurogenic shock arise from the loss of autonomic innervation of the vasculature, caused by conditions such as spinal cord injury, regional anesthesia, administration of drugs that block the adrenergic nervous system (including some systemically administered anesthetic agents), and certain neurologic disorders. In some patients (e.g., those who have a low spinal cord injury or have received a regional anesthetic), the denervation is localized, which means that only the vasculature in the denervated areas will be blocked. In other patients (e.g., those who have a high spinal cord injury or have received a general anesthetic), the heart and the vasculature throughout the body will be blocked.

In all cases of neurogenic shock, the MAP will be low as a consequence of arteriolar dilation. In some cases of denervation, the cardiac output will increase because of the decreased hindrance to ventricular contraction and, in instances where the denervation does not involve the heart, an elevated heart rate. If the increased cardiac output is enough to compensate for the low pressure, the patient will not be in shock.

In most cases of denervation, however, the cardiac output will not increase enough to overcome the adverse effects of the low blood pressure. In some cases, the cardiac output will fall: blood will pool in the denervated venules and small veins; the ventricular musculature will lose its sympathetic tone (in the case of a generalized or high denervation); and the heart rate will not be able to respond with a tachycardia (in the case of a high blockade). When both the MAP and the cardiac output are low, the shock can be profound.

COMPRESSIVE SHOCK

The cardiovascular derangements in compressive shock arise from external forces that compress the thin-walled chambers of the heart (the atria and the right ventricle), the great veins (systemic or pulmonary), or both, compromising the filling of the chambers and resulting in inadequate ventricular end-diastolic volumes. Clinical conditions capable of causing compressive shock include pericardial tamponade, tension pneumothoraces, positive-pressure ventilation with large tidal volumes or high airway pressures (especially in a hypovolemic patient), an elevated diaphragm (as in pregnancy), displacement of abdominal viscera through a ruptured diaphragm, the abdominal compartment syndrome (e.g., from ascites, abdominal distention, abdominal bleeding, retroperitoneal bleeding, or a stiff abdominal wall, as in a patient with deep burns to the torso), and, perhaps, the thoracic compartment syndrome, caused by positive-pressure ventilation, the stiff lungs of the adult respiratory distress syndrome (ARDS), or the elevated diaphragm of the abdominal compartment syndrome.

OBSTRUCTIVE SHOCK

The cardiovascular derangements in obstructive shock arise when excessive stiffness of the arterial walls, compression of the arterial walls, or obstruction of the vasculature imposes an undue burden on the heart, so that the contractile apparatus of the ventricular musculature is no longer matched to the compliance and resistance of the vasculature into which it pumps. The obstruction to flow can be on either the right or the left side of the heart. Causes include pulmonary valvular stenosis, pulmonary embolism, air embolism, ARDS, aortic stenosis, calcification of the systemic arteries, thickening or stiffening of the arterial walls

as a result of the loss of elastin and its replacement with collagen (as occurs in old age), and obstruction of the systemic microcirculation as a result of chronic hypertension or the arteriolar disease of diabetes. The mean pressure in the pulmonary artery or the aorta will be high, and the systolic pressures will be disproportionately higher. The cardiac output will be low, and the heart will be working inefficiently.

CARDIOGENIC SHOCK

The cardiovascular derangements in cardiogenic shock arise from intrinsic cardiac abnormalities that prevent the heart from delivering blood into the vasculature with adequate energy. Sometimes, the problem is with the muscle; sometimes, it is with the rhythm. In all cases, the problem is a mismatch between the contractile or rhythmic characteristics of the myocardial musculature and the compliance and resistance of the vasculature into which the musculature pumps its contained blood. Causes include bradyarrhythmias, tachyarrhythmias, myocardial ischemia, myocardial infarction, cardiomyopathies, myocarditis, myocardial contusion (rare), cardiac valvular insufficiency, papillary muscle rupture, and septal defects. The MAP is usually low, depending on the degree of compensatory constriction of the systemic arterioles; the cardiac output is always low.

Characteristic Clinical Markers

The presence of a shock state is typically signaled by one or more characteristic clinical markers [see Table 1].

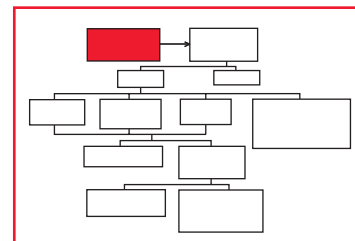


Table 1 Clinical Markers of Possible Shock State

Clinical Marker	Value or Findings Indicative of Shock
Systolic blood pressure	
Adult	≤ 110 mm Hg
Schoolchild	≤ 100 mm Hg
Preschool child	≤ 90 mm Hg
Infant	≤ 80 mm Hg
Sinus tachycardia	
Adult	≥ 90 beats/min
Schoolchild	≥ 120 beats/min
Preschool child	≥ 140 beats/min
Infant	≥ 160 beats/min
Cutaneous vasoconstriction	Pale, cool, clammy skin with constricted subcutaneous veins
Respiratory rate	
Adult	≤ 7 or ≥ 29 breaths/min
Child	≤ 12 or ≥ 35 breaths/min
Infant	≤ 20 or ≥ 50 breaths/min
Mental changes	Anxiousness, agitation, indifference, lethargy, obtundation
Urine output	
Adult	≤ 0.5 ml • kg ⁻¹ • hr ⁻¹
Child	≤ 1.0 ml • kg ⁻¹ • hr ⁻¹
Infant	≤ 2.0 ml • kg ⁻¹ • hr ⁻¹
Myocardial ischemia or failure	Chest pain, third heart sound, pulmonary edema, abnormal ECG
Metabolic acidemia	[HCO ₃ ⁻] ≤ 21 mEq/L Base deficit ≥ 3 mEq/L
Hypoxemia (on room air)	
0–50 yr	≤ 90 mm Hg
51–70 yr	≤ 80 mm Hg
≥ 71 yr	≤ 70 mm Hg

Pressures in Those Arteries]; the diastolic pressure in a peripheral artery is almost always lower than that in the aortic root. The approximated MAP, calculated as being one third of the way between the diastolic and systolic pressures, is not a reliable value. The formula is only an approximation to begin with, and the two pressures used in the calculation are unreliable and sometimes hard to obtain, particularly the diastolic pressure. Furthermore, in shock, the flow of blood through the brachial artery can be so minimal that very little turbulence is created and very little sound generated; hearing these faint sounds in a busy emergency department or intensive care unit can be difficult, and hearing their disappearance can be even more difficult.

Assessment of the blood pressure should take into account the patient's age [see Table 1]. In an adult, a low brachial peak systolic pressure (≤ 110 mm Hg) frequently indicates shock; a very low brachial peak systolic pressure (≤ 89 mm Hg) almost always does, especially in a patient who is under stress. (Admittedly, many normal patients, especially young women, may have a systolic pressure of 89 mm Hg or lower when supine, but only when in an unstressed state. The pain or stress associated with an injury or acute illness will drive that normally low pressure to much higher levels.) A sustained (> 30 seconds) systolic pressure drop greater

than 10 mm Hg in a patient who has arisen from a supine to an upright position can also be an indicator of underlying shock.

A normal blood pressure, however, does not rule out shock. Adrenergic discharge and the release of circulating vasoconstrictors (e.g., vasopressin and angiotensin) often sustain blood pressure during shock, especially during its early stages. As a result, visceral hypoperfusion, arising from arteriolar constriction, may precede changes in the supine brachial blood pressure. In addition, some forms of shock can even be associated with hypertension (as in a hypertensive crisis) if the cardiac output is low. Finally, the definition of hypotension can vary, depending on the patient's usual blood pressure, which the physician may not know. A systolic brachial pressure that might be normal for a young healthy patient might be low for an older patient who had severe hypertension before his or her injury or illness.

TACHYCARDIA OR BRADYCARDIA

The pulse rate—perhaps the most evident of all the physical findings in clinical medicine—can increase in shock, and the possibility of shock should be considered in any patient with a tachycardia. An abnormally high pulse rate—with “high” determined in relation to the patient's age [see Table 1]—can serve as an indicator of shock.

A normal or slow heart rate, however, does not rule out shock.^{10–12} On the contrary, a normal or slow rate might indicate severe shock, even imminent decompensation. (The heart rate slows down in severe hypoxemia. In most persons, it also slows down before death; and during childbirth, obstetricians worry about slow heart rates, not rapid ones.) In severe shock, the pulse rate may have to slow down to reduce myocardial oxygen requirements; to allow more time for ventricular filling during diastole; to allow more time for coronary perfusion of the myocardium; and to match the energy-producing capabilities of the ventricles with the compliance and resistance of the vasculatures into which they pump their blood.

TACHYPNEA OR BRADYPNEA

Any patient with tachypnea must be promptly evaluated not only for possible pulmonary insufficiency but also for possible shock [see Table 1]. The rapid respiratory rate may be a response to a metabolic acidemia; it may also be a means of compensating for inadequate filling of the ventricles, in that it will lower the mean intrathoracic pressure and facilitate the diastolic influx of blood into the heart from the capacitance venules and small veins in the periphery. In severe decompensated shock, the respiratory rate may fall to very low levels, perhaps because of ischemia in the muscles providing the ventilation.¹³

CUTANEOUS HYPOPERFUSION

Diminished skin perfusion is often the first sign of shock. In all types of shock other than warm inflammatory shock and neurogenic shock, blood flow to the skin is reduced because of adrenergic discharge and high circulating levels of vasopressin and angiotensin II. The result is the pale, cool, and clammy skin of a person exhibiting the fight-or-flight reaction. Cutaneous hypoperfusion is not specific for shock—it can also be the result of hypothermia, for example—but it can be a warning that the patient may decompensate at any time.

MENTAL ABNORMALITIES

Patients in severe shock frequently exhibit mental abnormalities, which can range from anxiousness to agitation to indifference to obtundation. These findings are not sensitive—indeed, they

Energy Propagation throughout the Arteries and Its Effect on Pressures in Those Arteries

The contraction of a ventricle and the ejection of its blood into a standing column of blood in the root of the pulmonary artery or the aorta create an energy wave that propagates throughout the arterial system. The wave travels distally until it reaches the arterioles, which reflect some of the energy back to the heart. The summation of the antegrade and retrograde energy waves at any given point in the arterial system creates a specific pressure and volume at that point.

Stiff arteries result in increased velocities of wave propagation, both outgoing and returning, and thus early return to the measurement site; compliant arteries result in late return. Distal arteriolar constriction increases the amplitude of the reflected wave; dilation decreases it. Symmetrical spatial distribution of arterioles results in uniform reflection of waves that coalesce in phase with one another; the summed reflected wave is compact with sharp contours and is short in duration. Asymmetrical arteriolar distribution results in reflection of waves that are out of phase with one another; the summed reflected wave is slurred and spread out. Arterioles that are distant from the measurement site create a composite reflected wave that returns late; arterioles that are close create a wave that returns quickly.

If the arterioles distal to the measurement site are constricted, symmetrically distributed, or nearby or if the conducting arteries are stiff, systolic pressures in the peripheral arteries increase and diastolic pressures decrease slightly. In this case, the amplitude of the reflected wave will be large (constricted arterioles), its components will be in phase (symmetrical arteriolar distribution), and the retrograde wave will return quickly (stiff arteries). If the measurement site is close to the arterioles, the reflected wave will return very quickly and will pass through the antegrade wave before diastole begins. The duration of systole will be short. The pressure contour created by the superposition of the antegrade and retrograde waves will be sharp, with a rapid upswing and downswing. The systolic pressure will be increased, sometimes substantially, and the diastolic pressure will be slightly decreased.

The opposite occurs if the distal arterioles are dilated, asymmetrically distributed, or distant from the measuring site or if the conducting arteries are compliant. Under these conditions, the amplitude of the reflected wave will be small, its components will be out of phase, and the retrograde wave will be delayed. Unless the measuring site is very close to the arterioles, the wave will return during both systole and diastole. The duration of systole will be lengthened, and the upswing and downswing of the waveform will be smoothed out. The systolic pressure will be minimized, sometimes substantially, and the diastolic pressure will be slightly augmented.

These general characteristics of the arterial vasculature have specific implications for the pressures in the aortic root and the radial artery. In the aortic root, the typical pressure waveform is blunted (damped) and is characterized by lower systolic pressures and higher diastolic pressures than the distal waveforms. The arterioles in the heart, brain, liver, and kidneys are chronically dilated, diminishing the amplitudes of the reflected waves. The arterioles supplied by the aorta are asymmetrically distrib-

uted: those in the upper part of the body are close to the aortic root, whereas those in the lower extremities are distant. Thus, the reflected waves return to the aortic root at varying times, with the result that some of their pressure oscillations cancel one another out. Finally, the arteries that come off the aorta have varying degrees of stiffness. The arteries supplying the upper body are compliant (slow wave propagation velocities and late return), whereas those supplying the lower body are stiff (high propagation velocities but delayed return because of the long distances the waves must travel). The blunted contour of pressure in the aortic root enhances cardiovascular efficiency: the low systolic pressure results in minimal hindrance to ventricular emptying, and the high diastolic pressure results in maximal perfusion of the coronary vasculature [see Figure 1].

In the radial artery, systolic pressures are almost always higher and diastolic pressures usually somewhat lower than in the aortic root [see Figure 1]. The duration of systole is shorter, with a sharper upswing and a more precipitous downswing. The arterioles in the hand are usually constricted, symmetrically distributed, and close to the measurement site. The normal radial artery is compliant, which decreases the velocity of wave propagation, but its compliance is outweighed by the closeness of the arterioles. Thus, waves return quickly.

The spiked pressure waveform in the peripheral arteries has no adverse effect on distal perfusion. It is the mean pressure in the artery that is important for perfusion, and that pressure is independent of the reflected pulsatile energy wave. The exaggerated peripheral arterial waveform does, however, make it difficult to extrapolate from distally measured systolic pressures back to the central aortic pressures. Such extrapolation must rest on certain assumptions. For example, in a patient with normally constricted arterioles in the hand, the peak systolic pressure in the radial artery is approximately 10 mm Hg higher than that in the brachial artery, which is approximately 10 mm Hg higher than that in the aortic root.

If the arterioles in the hand are constricted more than the arterioles in the central portions of the body (as may be the case in hypovolemic or cardiogenic shock), the peak systolic pressure in the radial artery can be much higher than that in the aortic root because of reflected waves with large amplitudes. On the other hand, severe shock may constrict the arteries between the aorta and the hand sufficiently to decrease all of the distal pressures (mean, systolic, and diastolic).

If the arterioles in the hand are dilated with respect to the central arterioles (as may be the case in inflammatory or generalized neurogenic shock), the peak systolic pressure in the radial artery and that in the aortic root come closer to each other. A warm hand means dilated cutaneous arterioles; accordingly, the reflected waves will have minimal amplitudes.

When managing a patient in shock, one would like to know the pressures in the aortic root, but one must be cautious in trying to estimate those pressures on the basis of pressures in peripheral arteries.

develop only in the late stages of shock—nor are they specific. They are, however, a strong warning to the physician that something must be done quickly. The body protects the blood supply to the brain at all costs. Changes in mental status as a result of severe shock suggest impending circulatory collapse.

OLIGURIA

The stress imposed by all forms of shock—in the absence of diuretic use, high alcohol levels, or administration of radiographic contrast agents—stimulates the release of vasopressin (antidiuretic hormone) and aldosterone (through activation of the angiotensin system).^{14,15} The result is oliguria, which is a sign of stress

at the very least and may be a sign of decreased blood flow to the kidneys in extreme cases [see Table 1].

Whenever the diagnosis of shock is being entertained, a Foley catheter should be placed. Successful treatment should reduce the stress and decrease the plasma levels of vasopressin and aldosterone. It should also increase renal blood flow, if the shock is indeed so severe that inadequate blood flow to the kidneys is compromising their viability. With successful treatment, the urine output should improve; if it does not, further therapeutic measures are necessary.

MYOCARDIAL ISCHEMIA

Electrocardiography is indicated whenever the suspicion of

shock arises. The electrocardiogram may show signs of ischemia, which may be caused either by a primary myocardial problem or by a secondary extracardiac problem (e.g., hypotension resulting from hemorrhage). In either case, the presence of myocardial ischemia should prompt quick action.

METABOLIC ACIDEMIA

Metabolic acidemia, as a sign of shock, may be manifested by an increased respiratory rate. Serum chemistry may demonstrate a decrease in the total concentration of carbon dioxide (bicarbonate plus dissolved CO_2), but analysis of blood gases is usually required for confirmation. The acidosis may take the form of either a low calculated bicarbonate level or a base deficit.¹⁶ Often, it does not become evident until after the shock has been recognized and treatment is under way. In severe, untreated shock, the anaerobic products of metabolism are confined to the periphery; they may not be washed into the central circulation until resuscitation has reestablished some flow to the ischemic tissues. The degree of acidosis after resuscitation can, however, provide information about the duration and severity of the initial insult. This knowledge can be useful in determining how aggressive subsequent management should be.

HYPOXEMIA

Shock may be associated with significant arterial hypoxemia, a finding that, like several of the other variables being discussed, should be evaluated in the context of the patient's age [see Table 1]. Low flow results in marked desaturation of the blood leaving the metabolizing peripheral tissue, which eventually ends up in the pulmonary artery (yielding a low mixed venous oxygen saturation [S_{mvO_2}]). In patients with coexisting pulmonary dysfunction and an intrapulmonary shunt, the markedly desaturated pulmonary arterial blood is only partially saturated as it passes through the lungs, ultimately mixing with fully saturated blood. The increased admixture of oxygen-poor blood results in a reduced oxygen saturation in the systemic arterial blood.

Identification and Treatment of Immediately Life-Threatening Conditions

If the patient shows signs suggestive of shock, the next step is to search for and treat conditions that could be immediately fatal, such as (1) dysrhythmias; (2) airway compromise; (3) inadequate ventilation; (4) compression of the heart, the great veins, or both; (5) acute obstruction of the large arteries into which the ventricles pump their blood; (6) bleeding; and (7) certain life-threatening medical conditions (e.g., anaphylaxis, severe electrolyte disturbances, and life-threatening endocrine abnormalities). Identification frequently requires pattern recognition.

DYSRHYTHMIAS

Given that an ECG is obtained promptly in any case of suspected shock, dysrhythmias will be recognized early in the course of resuscitation. A nonagonal patient should be treated in accordance with standard resuscitation routines [see 8:1 *Cardiac Resuscitation and 8:2 Acute Cardiac Dysrhythmia*]. A sinus rhythm will have to be established, but one can go about this in a deliberate manner.

An agonal patient should undergo cardioversion. In this situation, cardioversion takes precedence even over making a definitive

diagnosis of the particular type of dysrhythmia; one should not even obtain a 12-lead ECG. There are three agonal dysrhythmias that can be treated definitively within seconds: ventricular fibrillation, ventricular tachycardia, and atrial fibrillation. All can be converted to a sinus rhythm with cardioversion. If this measure is successful, patients may reasonably hope for restoration of life with full neurologic function. Admittedly, there are other dysrhythmias besides these three (e.g., asystole) that can produce an agonal state, and cardioversion is of no use for these conditions. There is, however, no treatment for asystole or these other dysrhythmias that is likely to produce survival with reasonable neurologic function. Thus, there is no point in making the differential diagnosis.

Cardioversion also takes precedence over all other potential resuscitative efforts, including gaining airway control, obtaining I.V. access, and performing chest compressions (though if the team taking care of the patient is able to perform cardioversion, secure the airway, and gain I.V. access at the same time, it should do so). The goal is to get blood flowing again to the brain. Even if the initial reperfusion is with partially desaturated blood, it is better than no perfusion at all. Furthermore, perfusion of the brain from a heart in sinus rhythm is many times more effective than perfusion from chest compressions.

COMPROMISE OF AIRWAY

If a patient can talk in a full voice without undue effort, the airway can be assumed to be intact. Supplemental oxygen should be given via a mask or nasal prongs; nothing else need be done.

If the patient cannot talk in a full voice, possible compromise of the airway must be assumed. Causes range from loss of protective reflexes to mechanical obstruction of the trachea or major bronchi. Sometimes, a jaw thrust is all that is needed for diagnosis and treatment of the problem. In cases of profound shock, however, the patient should be intubated and ventilated, either with an Ambu bag or with a mechanical ventilator.

If increasing abdominal distention is apparent, esophageal intubation or displacement of the endotracheal tube into the hypopharynx is a possibility. The tube should be replaced. Reintubation is hazardous in these circumstances, but leaving a tube in the esophagus or hypopharynx is more hazardous.

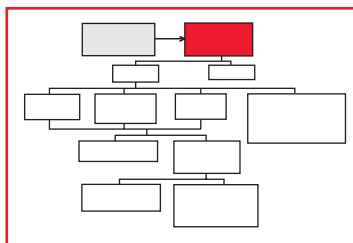
If breath sounds are absent on the left, right mainstem bronchial intubation is a possibility. The tube should be withdrawn into the trachea (or into what one believes to be the trachea).

If the endotracheal tube is obstructed by clotted blood or inspissated secretions, the obstruction can usually be cleared by suctioning. If this measure is unsuccessful, the patient should be reintubated.

Bleeding in the tracheobronchial tree (from injuries or from friable bronchial mucosa or tumor tissue) can eliminate ventilation from the lung segment supplied by the injured or obstructed bronchus and flood the initially uninjured lung with blood. If the bleeding is thought to be coming from the left lung, the endotracheal tube should be advanced into the right mainstem bronchus. Bleeding from the right lung is more problematic. Selective left mainstem intubation is usually impossible under emergency conditions. If selective mainstem intubation is not feasible or substantial bleeding continues on either side, definitive control of the bleeding will have to be obtained by means of either endobronchial techniques or open surgical intervention.

INADEQUATE VENTILATION

In the patient who has just been intubated, ventilation should begin with 100% oxygen, delivered through an Ambu bag. The patient should then be switched over to mechanical ventilation,



again with 100% oxygen. The ventilator should be set up so as to produce a minimal mean airway pressure (mean pressure being defined as the integral of the pressure over time divided by the time over which the pressure is produced [see Figure 1]). The respiratory rate should be set at 15 breaths/min and the tidal volume at 8 ml/kg lean body weight [see Table 2 and Sidebar Expectations for Cardiopulmonary Values in Patients of Different Sizes and Ages]. The end-expiratory pressure should be set at 0 mm Hg. Blood gas values should be obtained, and the settings on the ventilator should be adjusted as needed. The blood should be kept fully saturated. The patient should be mildly hyperventilated if the arterial pH is less than 7.20.

In some respects, these guidelines run counter to those used for long-term support of the mechanically ventilated patient. A fractional concentration of inspired oxygen (F_{iO_2}) of 100% can damage the alveolar epithelium and cause absorption atelectasis, and withholding positive end-expiratory pressure can facilitate the formation of atelectasis. A lung-protective ventilation strategy will ultimately be desirable [see 8:5 *Mechanical Ventilation and 8:4 Pulmonary Insufficiency*].¹⁷ In the initial resuscitation of the patient in shock, however, minimizing adverse effects on the cardiovascular system is the goal.¹⁸ Protecting the lungs can come later.

Many problems can arise with the use of mechanical ventilation. Even though modern ventilators are highly reliable, they can malfunction on occasion. If the chest wall does not rise with inspiration, the patient should be removed from the ventilator and ventilation recommenced with the almost foolproof Ambu bag. If ventilation proceeds normally with the Ambu bag, then the ventilator must have been at fault, and it should be replaced.

Pneumothoraces may arise from injuries to the lung, from attempts to place a central venous line, or from positive-pressure ventilation. They are treated with needle decompression followed by insertion of a chest tube.

Tension pneumothoraces sometimes develop in a patient who is breathing spontaneously; more often, however, they are created by the superimposition of positive-pressure ventilation on a previously existing pneumothorax. The tension pneumothorax not only eliminates ventilation on the side of the pneumothorax but also limits ventilation on the uninjured side. In addition, it compresses the heart and great vessels (see below). Characteristic signs include decreased or absent breath sounds on the involved side, a hyperresonant hemithorax, and, if the patient is normovolemic, distended neck veins. (A tracheal shift—a commonly described feature in patients with tension pneumothoraces—is hard to detect and, in our experience, rarely helpful in making the diagnosis.) A tension pneumothorax should be the first diagnosis considered in any patient who suddenly decompensates when placed on positive-pressure ventilation. Treatment consists of needle decompression followed by tube thoracostomy.

Air leaks always signify loss of at least some ventilation on the side of the leak. If they are large, they also signify loss of ventilation on the uninjured side, in that the administered air preferentially exits the airway through the chest wall defect or the chest tube on the injured side. A left-side leak can sometimes be treated by advancing the endotracheal tube into the right mainstem bronchus; a right-side leak usually necessitates surgical intervention, as does any large leak that does not close quickly.

Bleeding into the pleural cavity can eliminate ventilation of the affected side and push the mediastinum into the nonbleeding side. Treatment consists of insertion of a chest tube and, if the bleeding persists, surgical intervention.

COMPRESSION OF HEART OR GREAT VEINS

Acute pericardial tamponade is usually manifested by muffled heart tones and occasionally by an exaggerated (> 10 mm Hg) decrease in systolic blood pressure on spontaneous breathing. If the patient is not hypovolemic, the neck veins are typically distended. Nowadays, the diagnosis is frequently confirmed by echocardiography (if that modality is immediately available). Treatment consists of needle decompression or surgical creation of a pericardial window. Decompression in a patient with a chronic tamponade can also cause shock but may not give rise to the findings characteristic of acute tamponade. The diagnosis usually is made by means of echocardiography. Treatment is the same as for acute tamponade.

Diaphragmatic rupture and the ensuing intrusion of abdominal viscera into the chest can compress the venae cavae, the right side of the heart, the pulmonary arteries, the pulmonary microvasculature, the pulmonary veins, the left atrium, and the lungs. Treatment consists of operative reduction and repair.

The abdominal compartment syndrome can be caused by ascites, intestinal distention, intestinal edema, intra-abdominal or retroperitoneal bleeding, or noncompliance of the abdominal wall (as in patients with deep burns of the torso). The result is compression of the vasculature of the organs within the abdomen and intrusion of the diaphragm into the chest, which compromises ventilation and decreases ventricular end-diastolic volumes. If the patient is hypovolemic, the hemodynamic consequences can be devastating. Infusion of fluid can restore ventricular end-diastolic volumes but can also worsen the underlying problem, either by increasing the central venous pressure (CVP) and encouraging the development of ascites or edema or by exacerbating bleeding.¹⁹⁻²¹ The situation is made even worse because the increased venous pressures further reduce the perfusion pressures (calculated as MAP minus the venous pressure) in the organs at risk.

Initial treatment of ascites consists of paracentesis of just enough fluid to decrease the abdominal pressure, but no more. Treatment of intestinal edema may necessitate opening the

Table 2 Selected Cardiopulmonary Variables in Resting Subjects of Different Age-Adjusted Weights

Height (ft, in)	Lean Weight (kg)	Approximate Lean Weight (kg)	O ₂ Consumption (ml/min)	Cardiac Output (L/min)	Tidal Volume (ml)
5'0"	48.9	50	175	5.0	350
5'6"	59.1	60	210	6.0	420
6'0"	70.4	70	245	7.0	490
6'6"	82.6	83	290	8.3	580

Expectations for Cardiopulmonary Values in Patients of Different Sizes and Ages

Some numerical descriptors of physiologic variables that can be altered in shock (e.g., blood pressure, body temperature, and arterial pH) are independent of the amount of metabolically active tissue the patient has. For example, although it may well be that a large person in a given degree of shock will produce more lactic acid than a small person in a similar degree of shock, the amount of acid produced will be distributed in a larger volume of extracellular water, and the concentration of the acid in the water (and the resulting pH) will be independent of the patient's size. Thus, the interpretation of the arterial pH need not take into account the size of the patient.

Other descriptors, however (e.g., tidal volume, minute ventilation, ventricular end-diastolic volumes, stroke volume, cardiac output, oxygen consumption, carbon dioxide production, and caloric needs) do have to take the patient's size into account.

The question of how to interpret, or index, these size-dependent variables dates back at least to the 1800s. It seemed logical at that time (and still seems so today) to index the variables to body surface area.¹⁰⁷ The area of the body surface, as the site where the body dissipates its heat into the environment, must correlate with the efficiency with which the body offloads its generated heat. (During resting conditions, the amount of heat generated is minimized; during exercise or illness, more heat is generated from the same mass of tissue. Under any conditions, however, the body must be able to dissipate its heat; if it cannot, it will become hyperthermic to the point where its enzyme systems become dysfunctional.) The generated heat must correlate with the mass of oxidizing tissue, which must correlate with oxygen consumption and carbon dioxide production, which must correlate with the caloric needs. Thus, body surface area should correlate with all of these variables.

In the 1920s, when it became possible to measure cardiac output as part of metabolic studies, many investigators began to express cardiac output, as well as metabolic rate, in terms of body surface area, on the grounds that these two quantities should also be correlated. Although it was recog-

nized that the relation was not necessarily a linear one, this approach to indexing worked, in the sense that it minimized some of the inherent variability observed in nonindexed values. By the end of the 1920s, body surface area had become the most commonly used parameter for indexing both metabolic rate and cardiac output to body size.^{108,109}

In the 1930s, however, Max Kleiber made the empirical observation that the metabolic rates—and presumably the cardiac outputs and some of the ventilatory parameters—of members of one species of animals could best be compared with those of another species by indexing to body weight raised to the three-fourths power. Such indexing seemed to reduce variability even more effectively than indexing to body surface area did, though it was difficult to explain why.

Over the ensuing six decades, more and more accumulated evidence came to support Kleiber's contention, but only in the past two decades have his observations been satisfactorily explained. It now seems established that the Kleiber hypothesis can be proved by using a mathematical model that takes into account not only the thermodynamic considerations just described but also the fractal geometry of the vasculature in metabolizing organs and the thermodynamic constraints placed on such systems.

Thus, the problem of correlating size-dependent cardiopulmonary variables between species seems to be settled, and the different metabolic rates, cardiac outputs, and minute ventilations in different species appear to be well explained. However, the practice of using body weight raised to the three-fourths power does not solve the problem of how to make comparisons between members of the same species (e.g., between a large mouse and a small one or between a linebacker and a ballerina). In addressing this second problem, some clinicians, particularly those with a primary interest in the cardiovascular system, continue to index cardiopulmonary variables to body surface area. Others, particularly those with a primary interest in the respiratory system, favor indexing to body weight instead. A few prefer to use body weight raised to the three-fourths power. Still others choose not to index at all.

(continued)

abdomen and leaving it open. Bleeding may be controllable by operative or endovascular means. Treatment of the burned abdominal wall may involve escharotomies.

Pregnancy can elevate the diaphragm and complicate a shock state. If a woman in the late stages of pregnancy is thought to be in shock, she should be turned onto her left side to relieve compression of the right common iliac vein and the inferior vena cava. If shock persists, one should perform a cesarean section. (The goal is to save the mother. In any case, a pregnant woman in shock is of no use to her fetus.)

OBSTRUCTION OF VENTRICULAR OUTFLOW

Obstruction of right ventricular outflow caused by mechanical ventilation, a tension pneumothorax, a ruptured diaphragm, and the abdominal compartment syndrome is treated as previously discussed [see *Inadequate Ventilation and Compression of Heart or Great Veins, above*]. To treat pulmonary thromboembolism, aggressive anticoagulation with heparin, at the very least, is required; fibrinolytics, sometimes infused through a catheter in the pulmonary artery, may also be necessary [see 6:6 *Venous Thromboembolism*].

Right-side air embolism can arise as a complication of insufflation of gas into the peritoneal cavity during laparoscopy.²² It can also arise from penetrating injuries to large veins in the upper part of the body, caused either by trauma or by puncture of a large central vein in the upper body with a large-bore needle (if the needle

is unintentionally left open to atmospheric pressure and air). In the case of penetrating injuries, the air typically gains access to the venous system during spontaneous deep breathing. Patients are particularly vulnerable when upright.

In all of these situations, the air that gains access to the veins can form an obstructing air bubble in the outflow tract of the right ventricle. Treatable sources of air should be searched for and eliminated, and 100% oxygen should be administered to wash out residual nitrogen in the trapped air. The patient should be placed in the Trendelenburg position with the left side down to induce translocation of air from the outlet of the right ventricle to the apex of the chamber. A long central venous catheter should then be advanced centrally into (what is thought to be) the right ventricle to aspirate any air that may be present.

Air in the right atrium can embolize to the left side of the heart if some of the right-side air first embolizes to the pulmonary microvasculature. Obstruction to outflow from the right ventricle causes blood to back up in the right atrium. If the patient has a potentially patent foramen ovale, the increased pressures in the right atrium will push blood containing the residual air into the left atrium and from there into the left ventricle and to the rest of the body. Left-side air embolism can also be the consequence of a penetrating injury to the lung parenchyma (either from trauma or from a needle puncture) in a patient placed on positive-pressure ventilation: the positive airway pressure can push air from an injured bronchus into an adjacent injured pulmonary vein.

Expectations for Cardiopulmonary Values in Patients of Different Sizes and Ages (*continued*)

Not only is there no consensus on the preferred indexing method, but there also is no agreement on how and whether to adjust for obesity and aging. Body surface area is typically calculated on the basis of height and weight. Usually, the measured weight is used, which includes the weight of the fat. Thus, the calculation gives equal emphasis to metabolically active muscle and to metabolically inactive fat. Old age introduces a similar problem: for a given weight, older patients have less lean muscle mass and more fat than younger patients do. Some authors make an adjustment for age; others do not.

Even though there is, at present, no unanimity on how best to deal with these issues, it is obvious that some form of indexing (or nonindexing) is necessary, both for the management of patients and for the creation of written reference sources. Our current practice is to start with the assumption that lean persons (e.g., those with a body mass index [BMI] of 21 or so) do not have very much body fat. Assuming a BMI of 21, we then use the patient's height to assign a weight, which we assume is mostly metabolically active tissue. This assigned weight is employed in interpreting the size-dependent variables. For patients 50 years of age or younger, we use the assigned weight as is. For patients 51 years of age or older, we calculate an age-adjusted lean weight based on the assumption that 1% of lean body weight has been lost each year after the age of 50.¹¹² (Although this loss is in fact exponential in nature, we have not found it necessary to reflect this fact in the calculation.) As an example, with an 83-year old patient, we subtract 33% from the lean weight that the patient would have had at 50 years of age. For older subjects who have kept themselves in particularly good condition, we assume that 0.5% of lean body weight has been lost each year after the age of 50. Finally, we make subjective adjustments if muscle mass appears to be either abnormally large (as in male patients who worked out extensively when young) or abnormally small (as in malnourished patients or patients with a preexisting prolonged critical illness).

This practice means that we do not use the patient's actual weight when setting up the ventilator or when managing the patient on the basis of other size-dependent variables. The weight at the time of measurement can be inflated by fluid resuscitation, the hardware used for fracture fixation, bedclothes, or obesity. It can also be difficult to measure accurately in critically ill patients, who often cannot easily be moved to a bed-

side scale. We also do not adjust for gender. For longevity and freedom from debilitating illnesses, a BMI of 21 is close to ideal for both men and women (though it appears that a higher fat percentage is acceptable or even favorable for women¹¹³). The value we use is also conveniently close to the predicted body weight that has been advocated for use in setting tidal volumes.¹⁷

We have found it useful to assign expected values for size-dependent cardiopulmonary variables in subjects of different age-adjusted lean weights who are resting, fasting, well conditioned, supine, spontaneously breathing, and in a thermoneutral environment [*see Table 2*]. We make three assumptions in assigning these values, using the age-adjusted lean weight for all of the calculations:

1. The normal resting oxygen consumption is $3.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.
2. The normal resting cardiac output is $100 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.
3. The normal resting tidal volume is 7 mL/kg .

In practice, we usually approximate the height to the nearest half-foot [*see Table 2*], then approximate the lean weight for that approximate height. Once this is done, the values for oxygen consumption, cardiac output, and tidal volume tend to come out in a pleasing, almost linear way. We then make any additional adjustments necessary—in particular, for age and cardiovascular variables.

An example will demonstrate how use of the age-adjusted lean weight can influence assessment and treatment. The hypothetical patient is an 83-year-old man with an admission weight of 80 kg and a height of 5 feet 6 inches. If a Swan-Ganz catheter were in place, one would expect a cardiac output of 8 L/min. The patient's age-adjusted lean weight, however, is 40 kg (60 kg was the lean weight at 50 years of age, minus 33% for the subsequent 33 years on the assumption the patient did not work out much over the past few decades). Accordingly, one would expect a resting cardiac output of 4 L/min. (We would accept this value unless the patient had excessive metabolic needs.) This is not an unusual example; one could easily think of more extreme cases. The patient in this example has a BMI of 28, and there are many patients in the ICU today with indices that exceed this level.

The air bubbles in the blood can occlude the vasculature of the brain and heart, as well as that of other organs. The diagnosis should be considered when a patient with a penetrating thoracic injury suddenly and catastrophically decompensates after the initiation of positive-pressure ventilation. The differential diagnosis in this case consists of tension pneumothorax and air embolism. Accordingly, the first therapeutic measure is to insert chest tubes on both the right and the left. If it turns out that the patient has not had a tension pneumothorax, the diagnosis of possible air embolism should be kept in mind as other conditions are ruled out.

Treatment consists of surgical control. In the case of a penetrating injury, the chest should be opened through an anterolateral thoracotomy on the side with the suspected injury. The hilum of the injured lung should be cross-clamped. Then, if the right side was opened first, the incision should be extended into the left chest. The diagnosis may be confirmed if air bubbles are seen in the coronary vasculature. The heart should be massaged while the descending thoracic aorta is compressed. Vasoconstrictors should be given to increase the aortic pressure and to drive the air bubbles through and out of the arterial circulation. If neither side of the chest is known to have had a penetrating injury, the left side should be opened first. If no injury to the lung is detected, yet the diagnosis is certain (based on the finding of bubbles of air in the

coronary arteries), the incision should be carried into the right chest in an effort to find a treatable injury there. One must keep in mind that the primary treatment of air embolism is to eliminate the source of the air.

BLEEDING

Bleeding should be controlled by any means necessary. Compression might suffice, at least initially, if the bleeding is from an easily accessible site in an extremity; immobilization might be enough in the case of a fracture; endoscopic control might be enough for GI hemorrhage; endovascular control might be enough for bleeding from a pelvic fracture. For any kind of bleeding from any site, operative control is usually definitive. In any case, control is paramount: it makes no sense to infuse fluid or blood or to persist with ancillary measures while controllable bleeding continues unabated.

MEDICAL EMERGENCIES

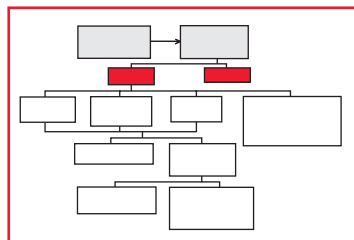
In the appropriate clinical circumstances, early consideration should be given to certain medical conditions that may cause shock. In diabetic patients, severe hypoglycemia should be considered. Rapid assessment with a bedside glucose monitor or empirical I.V. dextrose therapy may prevent the neurologic conse-

quences of prolonged hypoglycemia. Anaphylaxis can be treated with I.V. or subcutaneous epinephrine and antihistamine therapy. In patients with renal dysfunction, life-threatening electrolyte abnormalities should be considered. Finally, whenever standard resuscitative measures are unsuccessful in reversing shock, severe endocrine abnormalities (e.g., addisonian crisis and myxedema), though often difficult to diagnose, should be considered.

Specific Treatment Based on Category of Shock

If shock persists after immediately life-threatening conditions have been treated, the next step is to categorize the shock state on the basis of the underlying physiologic abnormality and treat the patient accordingly.

As a rule, all that is needed to make this preliminary classification is the history, the physical examination, a chest x-ray, an ECG, and, in some cases, a complete blood count, arterial blood gas analysis, electrolyte concentrations, and a glucose level. The categorization is seldom neat: more than one cause of cardiovascular inadequacy is usually present, as when a patient with a myocardial infarction requires mechanical ventilation or when a patient with a ruptured abdominal aortic aneurysm has a distended and tight abdomen. Nevertheless, classification is useful in that it focuses the physician's attention on the primary problem, which should be treated first.



Initial Management of Hypovolemic or Inflammatory Shock

CONTROL OF BLEEDING AND ONGOING INFLAMMATION

Control of bleeding, as the source of the problem in hemorrhagic shock, is the mainstay of treatment for the shock state. In the case of nonhemorrhagic hypovolemic shock or inflammatory shock, however, a temporary delay in source control (e.g., operative management of a bowel obstruction, abscess drainage, or tissue debridement) may be warranted until the patient has been adequately resuscitated. This is a particularly important consideration when the process of source control is likely to result in further cardiovascular compromise. An example is the patient who requires a laparotomy for a hollow viscus perforation. In this situation, briefly delaying administration of a vasodilating inhaled anesthetic while intravascular volume is restored may prevent cardiovascular collapse during anesthetic induction.

In the great majority of cases, source control and resuscitation will be carried out simultaneously. To this end, vascular access is required.

VASCULAR ACCESS

On the assumptions that an airway has been established, that the patient is being ventilated, and that bleeding is being controlled, the next step is to obtain vascular access. If possible, superficial veins in the upper extremities should be percutaneously cannulated with two large-bore catheters. If this is impossible, venous access can be achieved by means of cutdown on veins in the extremities or percutaneous puncture of central veins; access to

the bone marrow can be obtained by means of percutaneous insertion of a thick needle through cortical bone.²³

Cutdowns in the upper extremity cause little morbidity. They sometimes take time to perform, however, and the veins may be thrombosed from earlier use. The cephalic vein at the shoulder is less likely to be thrombosed, but it lies below the deep fascia and is sometimes difficult to isolate. The external jugular vein is deep to the platysma and can be difficult to identify when the lighting is poor. The saphenous vein at the ankle is readily exposed by cutdown and is large and easy to cannulate. It cannot be used, however, if there is extensive trauma to the extremity, and superficial thrombophlebitis is likely to develop if the cannula is left in place for more than 24 hours. The saphenous vein in the groin is large and easy to cannulate, but the end of the catheter inserted through this vein will lie in the external iliac vein. Iliofemoral deep vein thrombosis (DVT) or even septic DVT is common; either can be a potentially fatal complication in a patient who becomes critically ill.

Percutaneous cannulation of the internal jugular vein or the subclavian vein not only affords access for infusion of fluids and drugs but also provides a port for central venous monitoring. Obtaining central venous access with percutaneous techniques, however, can be risky,²⁴ particularly in a hypovolemic patient with collapsed central veins. The puncture can cause a pneumothorax. An artery adjacent to the vein may be punctured. At times, an arterial puncture may not be recognized, and the artery may even be dilated and cannulated. Once the vessel is cannulated, the problem may initially go undetected. Blood drawn from a cannulated artery in a shock patient may be flowing in a nonpulsatile fashion, giving the impression that the targeted vein has been successfully accessed. In severe shock, the arterial blood may be blue, thereby supporting this mistaken impression. A damaged artery can also bleed into the pleural cavity, an untamponaded space. If this occurs in a patient who is already compromised, the patient will probably die.

Percutaneous puncture of the common femoral vein is among the easiest of all venous access techniques and avoids the problems of pneumothorax and bleeding into a pleural cavity. The incidence of both nonseptic and septic DVT is very high, however, with this approach.²⁵⁻²⁷ If this vein is cannulated, the access site should be changed to a vein in the upper body as soon as the patient is stable.

If, in the course of attempting to cannulate the common femoral vein, the adjacent femoral artery is unintentionally cannulated, it is sometimes best to use the artery for vascular access. Intra-arterial infusion of fluids is as effective as I.V. infusion. Care must be taken, however, to ensure that no air enters the system. The catheter should be removed as soon as other access is gained.

In pediatric patients, intraosseous access (e.g., via the proximal tibia, the distal femur, the iliac crest, or the sternum) is a useful means of gaining vascular access under difficult conditions. On rare occasions, this approach may be used in adults when other sites are unavailable.^{28,29}

The first attempts at obtaining vascular access should be made in the upper extremities with a percutaneous technique. If these attempts fail, one should fall back on a technique with which one is comfortable. There is no single best approach.

INITIAL FLUID RESUSCITATION

Once vascular access is obtained, a 20 ml/kg bolus of normal saline should be infused. If the patient is in profound shock, the fluid bolus should be given within 5 minutes; if the situation is less urgent, the bolus may be given over a period of 15 minutes or so. If the shock does not resolve, two more boluses should be given. A rapid infuser might be necessary.

We consider normal saline (NS) the fluid of choice for initial resuscitation in most shock patients. Because it is slightly hyperosmolar, it may have some beneficial effect on the initial perfusion of ischemic tissues by drawing water out of red cells and reducing their rigidity; it may also decrease the swelling of the endothelial cells in the microvasculature of the injured or infected tissues. The chloride concentration of NS (154 mmol/L), however, can induce a hyperchloremic metabolic acidemia. If the patient already has a chloride concentration that exceeds 115 mmol/L, lactated or acetated Ringer solution is used instead. Some favor initial use of lactated Ringer solution to reduce the chance that a hyperchloremic acidosis will develop in the first place. Both lactate and acetate accept a proton to form an organic acid, which is converted in the liver to CO_2 and water. The CO_2 is excreted by the lungs; the water, by the kidneys. As long as hepatic function and pulmonary function are adequate, which is usually the case, the result of this process is buffering of the acidemia that can accompany the shock state. Both lactated and acetated versions of Ringer solution, however, are hyponatremic and hypo-osmotic; the latter is a potential problem in patients at risk for increased intracranial pressure and perhaps for swelling of the endothelial cells in the microvasculature.

Solutions containing glucose should not be used in the initial stages of resuscitation unless the patient is known to be hypoglycemic. Most patients in shock, in fact, are hyperglycemic as a result of high plasma levels of epinephrine, cortisol, and glucagon.³⁰ Excessively high plasma glucose concentrations can induce an inappropriate diuresis.

We do not use colloid solutions in the initial management of hypovolemic or inflammatory shock, and we think that the long-standing crystalloid-versus-colloid debate is now settled.³¹ At the same time, it must be admitted that factors such as the type of colloid used (albumin or hydroxyethyl starch), the timing of administration (early versus delayed), and the environment of care (prehospital, battlefield, or hospital) continue to be explored in laboratory, bedside, and field settings. Colloid solutions, compared with crystalloid solutions, have the advantage of producing a greater intravascular volume expansion for a given volume of fluid infused.³² This advantage may be significant in prehospital, mass-casualty, or battlefield environments.

As for albumin in particular, however, we do not believe it possesses any significant advantages for the purposes of resuscitation, in any environment. It is expensive and at times has been difficult to obtain. Moreover, a study that we consider definitive demonstrated that the use of this agent in critically ill patients provided no benefit and was perhaps even associated with a degree of danger.^{31,33} Accordingly, we see no reason why albumin should be used in any patient. It is possible, however, that other colloid solutions (e.g., hydroxyethyl starch solutions) may be of some use in environments where only limited amounts of fluid can be given. These agents are inexpensive and, in theory, may have some beneficial effects on inflammation and coagulation in the acutely injured patient.³⁴⁻³⁷ At the same time, no large, randomized trials have yet shown these solutions to be of any benefit when used in place of isotonic crystalloid.³⁸

Hypertonic saline solutions containing up to 7.5% sodium chloride (compared with 0.9% for normal saline) show promise for resuscitating patients in situations where large-volume resuscitation with isotonic solutions is impossible (e.g., combat, events involving mass casualties, and prehospital trauma care).^{39,40} Hypertonic solutions provide far more blood volume expansion than isotonic solutions and result in less cellular edema. In addition, they may have favorable effects on the inflammatory

response to injury.⁴¹⁻⁴⁶ These solutions are approved for use and commercially available in Brazil (where the idea originated), Chile, Argentina, and Europe; they are not currently approved for use in the United States or Canada.

TRANSFUSION

The ideal replacement for lost blood is probably fresh, warm, fully crossmatched, whole blood. In some settings (e.g., limited warfare), it is possible to type potential volunteers who are willing to provide the blood.⁴⁷ The volunteers with the appropriate blood type are called in as needed, and the recipients enjoy the benefits of fresh platelets, fresh clotting factors, fresh red cells with good longevity, minimal breakdown products produced by long storage, no cold-induced dysfunction of the infused cells, and no need for reconstitution.

In most settings, however, packed stored red blood cells (RBCs) should be given, supplemented with asanguinous fluids. In an emergency, O-negative cells should be given. There is no need for typing or crossmatching, and in the case of the confusion that can attend the treatment of multiple casualties, there is no danger that a patient will receive the wrong type of blood. If, however, the patient can wait a few more minutes and if there is minimal risk of giving the wrong type of blood, type-specific RBCs should be given. If large amounts of blood are required, as in a patient with extensive injuries or in the setting of multiple casualties, the blood bank will run out of O-negative cells. If the patient has initially been given a large number of O-negative cells and then must be given non-O-negative cells, the newly given cells can react with the initially given cells. Once time is available, typed and crossmatched RBCs should be given.

Transfusion of red cells restores intravascular volume and increases hemoglobin concentration, both of which improve oxygen delivery. On the face of it, it would seem that liberal transfusion of red cells should be ideal for resuscitation of a patient in shock. Unfortunately, allogeneic blood, especially old allogeneic blood, falls short of being the ideal resuscitation fluid.⁴⁸ Allogeneic leukocytes (an unavoidable component of transfused cells), and perhaps soluble factors as well, have been implicated in the observed association between RBC transfusions and poor patient outcomes.⁴⁸⁻⁵³ In critically ill patients who are not in shock, it would appear that limiting transfusions to keep the hemoglobin concentrations no higher than 8 or 9 g/dl might even improve survival, compared with administering transfusions more liberally to yield higher concentrations.⁵⁴

This sort of generalization, while providing useful guidance as to what an appropriate transfusion strategy might be for the average critically ill patient who is euvolemic, may not be applicable to the patient who is in shock. With patients in shock, the first priority is to achieve restoration of intravascular volume with some reasonable level of oxygen-carrying capacity. The second priority is to fine-tune that level of carrying capacity. Generally, in initial resuscitation, the hemoglobin concentration should be on the high side. One usually does not know the magnitude of blood loss in the initial management of shock, nor does one know if the patient is going to continue to bleed. In many cases, one also does not know whether the patient has coronary disease.

The following guidelines provide a reasonable approach to establishing a desirable hemoglobin concentration in the resuscitation of patients in all classes of shock. The key variables are (1) the possibility of a continued decrease in the hemoglobin concentration (from bleeding or hemolysis), (2) the possibility of coronary heart disease, and (3) the estimated or measured values for

the relation between oxygen supply and oxygen demand (determined via mixed venous or central venous oximetry).

1. A hemoglobin concentration of 7 g/dl is adequate in a young patient whose coronary arteries are in good shape and whose bleeding is known to be under control.
2. A hemoglobin concentration of 8 g/dl is adequate in a young patient who may be at slight risk for further bleeding.
3. A hemoglobin concentration of 9 g/dl is required if the risk of bleeding is substantial.
4. A hemoglobin concentration of 10 g/dl should be the goal if overt coronary disease is present or there is a significant risk of occult coronary disease (e.g., in a patient with peripheral vascular disease), even in the absence of ongoing myocardial ischemia.

From a conceptual perspective, the use of blood substitutes for resuscitation should limit the risk of transfusion reactions and could solve the problem of limited availability of allogeneic blood. Multiple preparations of hemoglobin-based oxygen carriers (HBOCs) have been developed, several of which have been tested clinically. Although the results obtained with early preparations have been disappointing, those obtained with newer, polymerized HBOCs have been encouraging. As of fall 2007, however, none had been approved for use.

MANAGEMENT OF PAIN, HYPOTHERMIA, ACIDEMIA, AND COAGULOPATHY

Once blood volume has been at least partially replenished, pain should be treated with small I.V. doses of narcotics. On the one hand, pain relief can reduce the stress response associated with shock and perhaps mitigate the severity of its late sequelae.³⁰ On the other, narcotics can also decrease tone in the venules and small veins, thereby exacerbating the shock state. Accordingly, one should titrate the doses and be ready to reverse the effect with a narcotic antagonist if necessary. A drop in blood pressure after administration of a narcotic suggests that the patient may still be hypovolemic, in which case more aggressive resuscitation may be indicated.

If hypothermia is present initially, it should be corrected; if not, it should be kept from developing. Hypothermia slows metabolic processes. In some situations (e.g., cold-water drowning), this effect may be beneficial, but in most cases, it is better for the patient to have a normal body temperature, normal myocardial function, and intact coagulatory and immune function.

The patient must be unclothed during the initial evaluation but should be covered afterward, with particular attention paid to covering the head. The room should be kept warm, and any fluids administered should be prewarmed either in an oven or with heating devices.

If the arterial pH is low, it should be raised to 7.20 by means of either modest degrees of hyperventilation or administration of bicarbonate. (Although agents other than bicarbonate can be given to correct a metabolic acidemia, it is not clear that they have any more to offer than bicarbonate does.) No efforts should be made to raise the pH above 7.20, other than through resuscitation. Moderate degrees of acidemia are well tolerated, and excessive administration of bicarbonate may worsen intracellular acidosis [see Initial Fluid Resuscitation, *above*].⁵⁵ Instead, efforts should continue to be directed toward managing the underlying cause of shock.

Coagulopathy should be treated with fresh frozen plasma and platelets [see 1:4 *Bleeding and Transfusion*]. The decision whether to use these components should be based on observation of bleeding and clotting in the patient, not on laboratory measurements of

coagulation or platelet counts, which can be normal even during exsanguination.

MODULATION OF INFLAMMATORY RESPONSE

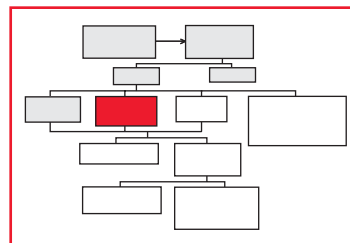
In the case of inflammatory shock, there has long been interest in therapeutic approaches aimed at blocking or counteracting inflammatory and coagulatory mediators released from the inflamed tissues. To date, almost all of these approaches have failed to show any benefit, and some have proved dangerous. A study published in 2001 yielded apparently more promising results, concluding that infusion of activated protein C seemed to improve survival in some patients with severe sepsis.⁵⁶ Since that study was published, several other trials have been carried out in an attempt to define the role of activated protein C in the treatment of severe sepsis with more precision.⁵⁷⁻⁵⁹ Taken as a whole, the current data do not convincingly demonstrate that this product has any real value. What is more, activated protein C is known to be associated with a risk of intracerebral bleeding. Accordingly, we do not use it, even in patients who are in severe sepsis and at high risk of death.

The use of corticosteroids in the treatment of sepsis has been studied extensively over the past several decades. Older regimens involved administering these agents in high doses, and the bulk of the evidence suggested that such regimens probably were, if anything, associated with increased death rates in comparison with placebo.⁶⁰ The authors of a multicenter study published in 2002 concluded that administration of modest doses of hydrocortisone and fludrocortisone to patients in septic shock with impaired adrenal function led to improvements in mortality.⁶¹ These conclusions notwithstanding, we remain unconvinced of the value of this measure, except in those rare patients who are truly addisonian. The possibility of harm is significant, in that corticosteroids have well-established potential side effects in the setting of shock (e.g., kidney damage and perhaps an increased risk of infection). In our view, confirmatory studies are required before this use of steroids in patients with septic shock can be recommended.

Initial Management of Compressive Shock

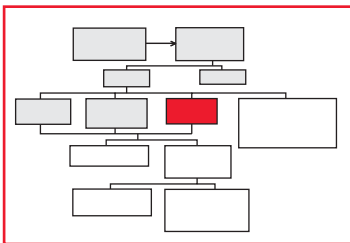
In many cases, extracardiac compressive and extracardiac obstructive shock, being conditions that can kill quickly, will already have been treated by this point in management.

It is wise, however, to keep these two causes of shock in mind as workup proceeds: they often develop secondarily. Examples of problems that can arise as treatment progresses are a tension pneumothorax that develops in a mechanically ventilated patient who is being worked up or treated for some nonpulmonary problem and an abdominal compartment syndrome that develops in a patient who is being resuscitated after a major injury or burn.



Initial Management of Neurogenic Shock

The initial management of neurogenic shock is the same as that of hypovolemic and inflammatory shock. If the shock is compounded by bleeding, the bleeding must



be stopped. Asanguinous fluids should be infused aggressively. Administration of RBCs may prove necessary.

Subsequent management of neurogenic shock, however, differs from that of hypovolemic or inflammatory shock, in that a patient in neurogenic shock may benefit from the use of the Trendelenburg position and the administration of a vasoconstrictor.

TRENDELENBURG POSITION

The Trendelenburg position is of no use in treating hypovolemic or inflammatory shock.⁶² It does increase the pressure in the carotid arteries (provided that the reference point for measurement—the right atrium—is held constant), but it increases the pressure in the internal jugular veins by an identical amount (because there are no valves in the internal jugular veins). The perfusion pressure for the brain, being the difference between these two pressures, is therefore unchanged. Nor, in hypovolemic or untreated inflammatory shock, is the Trendelenburg position of any value in translocating blood from the peripheral venous capacitance system to the heart. The systemic venules and small veins will already be depleted of their blood volume, which means that very little blood is available to be translocated. In the case of cardiogenic shock, the ventricular end-diastolic volumes are already too large; if anything, they must be decreased.

Patients in neurogenic shock, however, can benefit from being placed in the Trendelenburg position, provided that such placement does not compromise other aspects of care (e.g., securing the airway). This position causes blood to be rapidly translocated from the denervated, engorged venules and small veins back to the heart. Ventricular end-diastolic volumes will increase; stroke volumes will increase; the cardiac output will increase; and the blood pressure will rise.

ADMINISTRATION OF VASOCONSTRICTORS

Vasoconstrictors play no role in the initial management of hypovolemic or inflammatory shock, except perhaps for a minute or two in the initial management of a desperately sick patient. For these forms of shock, fluid replenishment is the crucial initial measure. Vasoconstrictors can shut off residual flow to organs already rendered ischemic by the shock state.

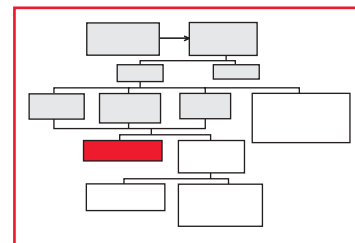
In the management of neurogenic shock, however, vasoconstrictors can be useful. The denervation of the arterioles, venules, and small veins can lead to profound hypotension; if the heart is denervated, the situation will be even worse. All of these ill effects of denervation can be overcome with the use of vasoactive drugs.

If the heart rate is slow, as it may be if denervation extends high enough to block the sympathetic nerves going to the heart, dopamine (in an initial dosage of 5 µg/kg/min) should be given. If the heart rate is rapid, phenylephrine (in an initial dosage of 100 to 180 µg/min, which is then decreased to 40 to 60 µg/min) or norepinephrine (in an initial dose of 0.5 µg/min, which can be increased to 15 µg/min under extreme conditions) should be used.

The danger in giving a vasoconstrictor to a patient in neurogenic shock is that the underlying condition that caused the shock state may also have caused occult bleeding. The vasoconstrictor, by maintaining the blood pressure, may reassure the physician while the patient continues to bleed. It is vital to be aware of this possibility when using vasoactive agents in these patients.

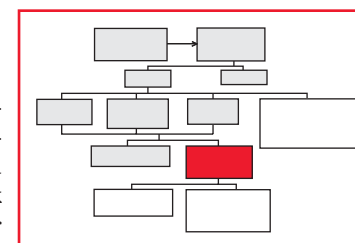
Subsequent Management of Hypovolemic, Inflammatory, Compressive, or Neurogenic Shock

CLINICAL ABNORMALITIES
RESOLVE WITH INITIAL
MANAGEMENT



If these initial maneuvers result in an acceptable blood pressure, heart rate, respiratory rate, skin perfusion, mental status, urine output, myocardial perfusion, acid-base balance, and arterial oxygenation, and if resolution is achieved with the administration of no more than 80 ml/kg of fluid—and, in the case of neurogenic shock, the use of vasopressors for no longer than 1 hour—nothing more need be done, except for periodic reevaluation of the patient for deterioration that might arise from an unexpected problem (e.g., a missed injury) or a complication induced by the initial management (e.g., a tension pneumothorax arising from positive-pressure ventilation).

CLINICAL ABNORMALITIES
PERSIST AFTER INITIAL
MANAGEMENT



Patients whose abnormalities persist despite the administration of 80 ml/kg of fluid and those in neurogenic shock who require vasopressors for longer than 1 hour should be

transferred to a setting in which arterial and central venous pressures can be transduced. Treatment should then be based on resolving the clinical abnormalities in the light of the information obtained via the arterial and central venous catheters.

Insertion of Arterial Catheter and Assessment of Mean Arterial Pressure

Arterial cannulation provides blood for analysis of blood gases and allows reliable measurement of the MAP [see Figure 1], the most useful of all of the peripheral arterial pressures for the assessment and treatment of shock. Morbidity with cannulation is unusual.^{63,64} The radial artery—an artery that usually has abundant collateral circulation—is most often used, at least in adults. The artery can become thrombosed, and portions of the thrombus can embolize distally, but distal tissue loss is rare. At times, larger arteries with less collateral circulation, like the brachial or femoral artery, must be used. The risk of tissue loss is greater when these arteries are cannulated. The perfusion of the limb distal to the insertion site must be assessed every 4 hours. Any suspicion of ischemia mandates removal of the catheter.

If, by chance, one cannot place an arterial catheter or must wait to achieve intra-arterial monitoring, one can use a blood pressure cuff equipped with software that allows measurement of the peripheral MAP using the so-called oscillometric methodology.^{65,66} In patients who are not too unstable, this approach is nearly as accurate as intra-arterial monitoring; however, it does not work well in the setting of hypovolemia, which is precisely where one most often would like to use it.

The mean pressure in the transducer used to monitor the pressure in the artery (or the mean pressure obtained via a properly functioning oscillometric cuff) is the same as the mean pressure in the artery being interrogated. In the absence of proximal obstruc-

tion caused by atherosclerosis in the subclavian or axillary arteries and in the absence of spasm of the proximal conducting arteries, the peripheral MAP is close to the mean pressure in the aortic root, the pressure that drives perfusion of the noncardiac tissues. It is also close to the mean diastolic aortic root pressure and is thus a good approximation for the pressure that perfuses the myocardium.

Thus, knowing the MAP is as close as one can get to knowing the pressure that is providing perfusion for the body. Accordingly, one should focus on the MAP, once it can be accurately determined. Once the MAP is known, there is no reason to pay attention to the systolic or diastolic pressures, as noted earlier [see Characteristic Clinical Markers of Apparent Shock, Hypotension, above]. It is difficult to extrapolate back to the aortic root end-sys-

tolic pressure (the systolic pressure that is of interest) from the peripheral systolic pressure [see *Sidebar* Energy Propagation throughout the Arteries and Its Effect on Pressures in Those Arteries],^{1,67} and the measuring system used to measure peripheral arterial pressures is frequently mismatched to the cannulated artery [see *Figure 2*].^{68,69} Later in the course of management, there will be a reason to try to extrapolate back from the peripheral systolic pressure to the central systolic pressure, but only for the purpose of evaluating the systolic pressure in the context of the stroke volume.

The MAP can be quite low and still be adequate for perfusing most of the tissues of the body. With the exception of the brain and spinal cord, all of the organs in a resting person with no obstructive arterial disease have some degree of chronic resting arteriolar

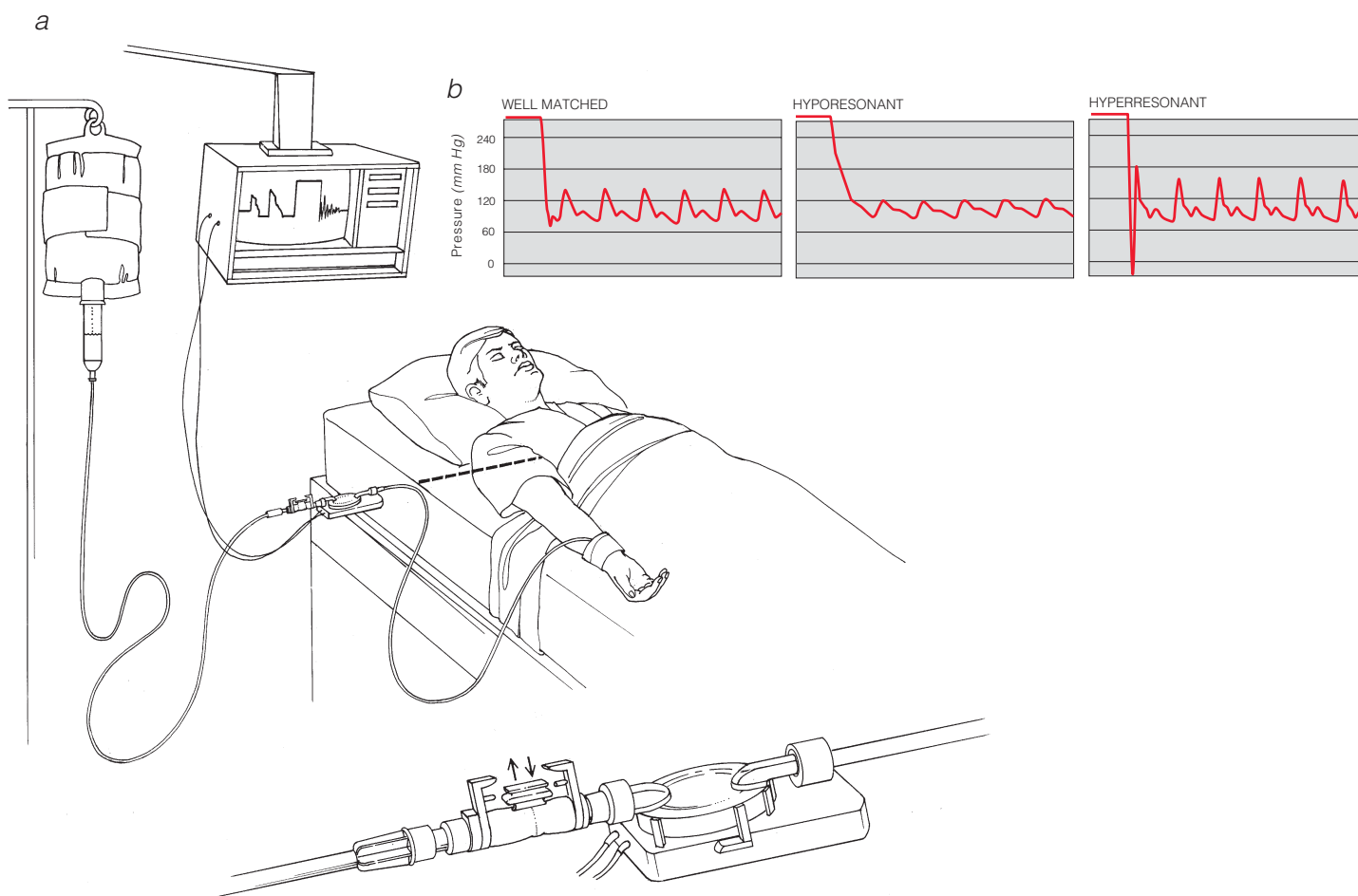


Figure 2 (a) The snap test will indicate if the pressure measured at the transducer is the same as the pressure measured at the tip of the catheter in the vasculature. A pressure of 250 mm Hg is superimposed on the pressure-measuring system by opening the flow-controlling device. The pressure is abruptly removed from the transducer system by snapping the device closed. (b) If the catheter-tubing-transducer system is well matched to the patient's vasculature, a normal arterial tracing (left) should resume promptly with minimal overshoot and oscillation. If the catheter-tubing-transducer system is excessively compliant or obstructed by a clot in the catheter or by a kink in the tubing, sudden closure of the flow-controlling device leads to a slurred, hyporesonant response (center). When the measuring system is excessively stiff in comparison with the vasculature, sudden closure of the device produces a hyperresonant arterial tracing (right), as manifested by an overshoot of the pressure to levels even below 0 mm Hg. In most patients the system used to measure pressures in the pulmonary artery, with a Swan-Ganz catheter, will be adequately matched. The systolic, diastolic, and mean pressures will all be accurately measured. One will be able to use the pulmonary arterial systolic pressure in assessing right ventricular end-systolic elastance, effective pulmonary arterial elastance, and ventricular oxygen requirements, and one will be able to use the mean pressure to assess the amount of useful energy produced by the ventricle. On the other hand, the catheters used to measure systemic arterial pressures will frequently generate a hyperresonant response. In this case, one will not be able to measure the peripheral systolic arterial pressure with adequate accuracy, although one will obtain an accurate measurement of the mean pressure in the artery, which assuming no obstruction or resistance to flow between the aortic root and the monitored artery, will be the mean pressure perfusing the body.

constriction. A fall in the perfusion pressure of an organ at risk in a patient in shock produces local ischemia and accumulation of metabolic waste products. These waste products cause reflex dilation of the arterioles in the organ at risk. Unless the hypotension is extreme, the dilation permits compensatory flow.

The reason why the brain and the spinal cord are exceptions is that their arterioles are chronically dilated. Under ordinary circumstances, this is not a problem, in that the cardiovascular system is designed to maintain a normal pressure for the brain. It is no accident that the primary baroreceptors for the system are placed at the carotid bifurcations. In severe shock, however, the body's cardiovascular reflexes may not be able to provide a MAP that is adequate for perfusion for the brain and the brain stem.

If the patient is awake and alert and there is no sign of spinal cord ischemia, one can be sure that the MAP is adequate for perfusion of the central nervous system. If the patient is obtunded, sedated, or anesthetized, however, assessing the adequacy of perfusion can be a challenge. In certain cases, one might know that at some previous point, perhaps during the same hospitalization, the patient was alert and neurologically intact with a given MAP (e.g., 50 mm Hg). If so, one can assume that the same pressure would still be adequate now. If, however, one does not have this information, one must err on the side of giving more fluids to keep the blood pressure high. In the case of an obtunded patient with no indications of possible carotid disease or of obstructed blood supply to the spinal cord, an arbitrary value can be assigned. A reasonable MAP might be 60 mm Hg for a younger patient (or somewhat higher for an older patient). In the case of a patient with possible carotid disease or compromised blood flow to the spinal cord, the pressure will have to be higher yet.

Determining the adequacy of the MAP for perfusion of non-CNS organs supplied by obstructed arteries is also a challenge. The microvasculature of the gut is maximally dilated in a patient with an occluded superior mesenteric artery. The same is true in a patient who has a kidney with an obstructed renal artery, an extremity with obstructed proximal arteries, or a heart with obstructed coronary arteries. In the face of hypotension, these organs cannot compensate with arteriolar dilation. A fall in the perfusion pressure can lead to a profound loss of flow.

In the case of a patient with possible obstruction of the arterial supply to susceptible organs, one must do one's best to assess the perfusion to the particular organ in question. For the heart, the absence or resolution of chest pain with resuscitation and the absence of ischemic changes on the ECG suggest that pressure and perfusion are adequate. For the gut, the absence of a history of cigarette smoking, the absence of pain, and the presence of bowel activity are reassuring. For the kidneys, adequate urine output and excretion of creatinine are generally indicative of acceptable pressure and perfusion. For the extremities, physical examination of the skin usually suffices.

Insertion of Central Venous Catheter and Assessment of Mean Central Venous Pressure and Right-Ventricular End-Diastolic Volume

The catheter used to measure the central venous pressure (CVP) is typically inserted percutaneously into either the subclavian vein or the internal jugular vein. As a rule, the tip of the catheter ends up in either the superior vena cava or the right atrium. The pressures at these sites vary both with the cardiac cycle and with ventilation. These variations can be substantial, depending on atrial activity and on the pressures produced by the labored breathing of the critically ill patient or by the effects of mechanical ventilation. Dealing with these fluctuations can be a challenge.^{70,71}

Nowadays, when considering the CVP, most physicians use the mean value, obtained over several ventilatory cycles [see Figure 1]. Typically, the number is read directly off the digital readout on the monitor. If the transducer is calibrated and zeroed properly (at the midaxillary line), interobserver variation should be nonexistent. The mean CVP gives a direct measure of the pressure that is most important in producing edema in the peripheral tissues. It is also close to the mean right ventricular end-diastolic pressure (RVEDP) (in the absence of tricuspid valvular stenosis) and thus can be used to derive a rough estimate of the right-ventricular end-diastolic volume (RVEDV) (i.e., for making an initial assessment of the adequacy of volume restoration).

Care must be exercised, however, in extrapolating from the CVP to the RVEDV. The CVP (or the RVEDP) is an intracavitary pressure, measured with respect to the atmospheric pressure present outside the body. To extrapolate from the intracavitary pressure to the cavity volume, one must consider that pressure with respect to the stiffness of all of the tissues from the inside of the chamber to the outside of the body. Many factors can increase the stiffness of these tissues. The stiffness of the ventricular wall itself during diastole (at this point, we are only considering diastolic volumes) will be increased by hypertrophy, scarring, and stretching. Ischemia, especially in association with a tachycardia, will also increase the stiffness of the ventricular wall during diastole. In addition, various factors can increase the stiffness of the tissues surrounding the ventricular cavity. The ventricle can be compressed by stiff, edematous lungs, lungs inflated with positive-pressure ventilation, or an elevated diaphragm. An edematous chest wall, in turn, can compress the lungs. All of these conditions will necessitate a high intracavitary pressure to produce an adequate end-diastolic volume.

Perhaps only one factor can actually reduce the stiffness of the tissues surrounding the ventricle. Spontaneous ventilation, with expansion of the chest wall and dropping of the diaphragm into the abdomen during inspiration, typically decreases the stiffness of the tissues around the lungs and thereby creates a negative pressure (with respect to atmospheric pressure). The result is a ventricle that fills easily with a low pressure.

Thus, in extrapolating from the intracavitary CVP to the RVEDV, one must do one's best to assess the stiffness of the ventricular wall and of the tissues surrounding the heart. For a normal subject breathing spontaneously, a CVP of 3 mm Hg is usually enough to support a normal RVEDV. For a healthy patient who is undergoing an elective operation and is on mechanical ventilation, a CVP of 6 mm Hg should be sufficient. For a modestly ill patient who has some edema in the lungs or chest wall and is on positive-pressure ventilation, a CVP of 9 mm Hg should be enough. For the usual patient sick enough to be in an ICU, who typically has more edema and perhaps an element of diaphragmatic elevation, the CVP should probably be around 12 mm Hg. For a patient who has ventricular ischemia, substantial edema, or greater than usual intrusion of the diaphragm into the chest, the CVP may have to be as high as 18 mm Hg.

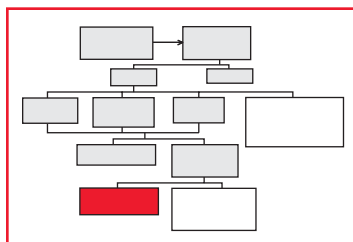
Treatment

Once the patient is in an environment where arterial and central venous monitoring is available, treatment consists of infusing more fluid. The goals are severalfold: to resolve the clinical abnormalities; to generate a MAP that appears to be adequate for perfusion of the brain and organs that might have an obstructed blood supply; to generate a CVP that is high enough to suggest an adequate RVEDV but is not unnecessarily elevated (we are aware of the potential conflict here); and, in the setting of neurogenic

shock, to wean the patient from vasopressors (which could shut off blood flow to the kidneys, the gut, or other organs with a high basal metabolic rate).

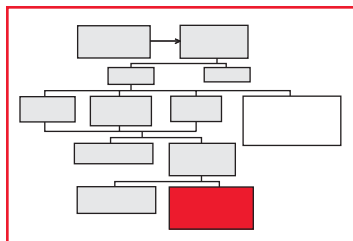
This fluid infusion can cause problems. On the one hand, it is important to be sure that at least the RVEDV is adequate to support ventricular production of useful energy. The values given (see above) can provide some guidance in this regard. On the other hand, it is also important to ensure that the CVP is no higher than necessary. High pressures create edema, and this edema can impair wound healing, make it difficult for tissues to fight off infection, and produce compartment syndromes in the brain, the liver, the kidneys, the abdomen, the chest, or an injured extremity. Furthermore, unnecessarily large end-diastolic ventricular volumes can increase ventricular oxygen requirements to an unacceptable extent.

CLINICAL ABNORMALITIES
RESOLVE AFTER ADMINIS-
TRATION OF ≤ 140 ML/KG OF
ADDITIONAL FLUID, WITH
ACCEPTABLE MEAN ARTERIAL
PRESSURE AND CENTRAL
VENOUS PRESSURE



If infusion of fluid of reasonable amounts of fluid (defined as no more than 140 ml/kg of crystalloid) leads to resolution of the clinical abnormalities with an acceptable MAP and an acceptable CVP (that is, with a CVP that should not produce edema unnecessarily and that should be associated with an estimated RVEDV that does not increase ventricular oxygen requirements unnecessarily), nothing more need be done. If the patient recovers completely from the problems that caused the shock, he or she might even be able to undergo diuresis—with the caveat that waiting for spontaneous mobilization of the administered fluid is usually safe, whereas giving a diuretic prematurely has the potential for pushing the patient back into a state of inadequate perfusion.

CLINICAL ABNORMALITIES
PERSIST DESPITE ADMINIS-
TRATION OF 140 ML/KG OF
ADDITIONAL FLUID



If, however, the clinical abnormalities do not resolve with the infusion of a reasonable amount of fluid, or if it is not clear that the patient has an acceptable MAP and CVP, or if vasopressors (in the case of neurogenic shock) are still thought to be necessary, then either insertion of a Swan-Ganz catheter or, in some cases, transesophageal echocardiography is indicated. Using the measurements obtained via a Swan-Ganz catheter (or from transesophageal echocardiography) can help one strike the optimal balance among fluid administration, use of drugs, edema formation, myocardial oxygen requirements, and peripheral perfusion.

There are few risks associated with transesophageal echocardiography, but the attendance of a physician is mandatory when the equipment is in use. Many anesthesiologists are comfortable with the technique, which can be very helpful in monitoring anesthetized patients. In the ICU, however, the required level of physician involvement is not likely to be available for any great length of time.

Insertion of a Swan-Ganz catheter requires gaining access to a central vein, which can cause problems [see Clinical Abnormalities

Persist after Initial Management, Insertion of Central Venous Catheter and Assessment of Mean Central Venous Pressure and Right-Ventricular End-Diastolic Volume, above].^{24,72} In addition, there are problems associated with passage and maintenance of a pulmonary arterial catheter [see Sidebar Problems Associated with Use of the Swan-Ganz Catheter].

The information obtained from a Swan-Ganz catheter, however, can give a nearly complete description of the status of the right ventricle. In some patients, it will give a good description of the left ventricle as well; in others, the Swan-Ganz information combined with the information obtained by means of echocardiography will yield a sufficiently good description.⁷³ In all patients, such monitoring will add significantly to the data that were already available [see Figures 3, 4, 5 and 6 and Sidebar Measurements That Can Be Obtained from Invasive Monitoring]. Understanding how this information is obtained and how it should be put into context is the most challenging part of treating the patient who is ill enough to need this sort of monitoring. Armed with the information obtained from invasive monitoring, one can set specific goals beyond that of resolution of the clinical abnormalities. Developing specific goals will help one strike the balance between generating power and minimizing edema formation and myocardial oxygen requirements.

Set Goals of Resuscitation, and Give or Withhold Fluids to Achieve Desirable Ventricular End-Diastolic Volumes

The goal in shock resuscitation is to achieve resolution of clinical abnormalities without creating excessive amounts of edema or imposing excessive demands on the heart. The first step is to decide on acceptable values for the cardiac output, the blood pressure, and the mixed venous oxygen saturation (S_{mvO_2}) in the context of the atrial pressures and the ventricular end-diastolic volumes.

In patients with major injuries or overwhelming infections, we aim for slightly higher than normal (but not excessively high) cardiac output values. Hyperthermia or systemic inflammation can raise oxygen consumption to values as high as twice those encountered in normothermic, uninjured, or uninfected persons [see 8:25 *Metabolic Response to Critical Illness*]. (To put these changes in perspective, oxygen consumption in a strenuously exercising young subject can increase by a factor of 15 to 20.) If the environment is cold enough to induce shivering, oxygen consumption can rise to levels several times higher than those observed in a thermoneutral environment. In these situations, a higher cardiac output is to be expected and presumably is desirable. By way of contrast, hypothermia in the absence of shivering decreases oxygen consumption. In this situation, the cardiac output can fall to quite low levels with no detrimental effect on survival. Efforts to increase cardiac output in severely cold patients can even induce fatal ventricular arrhythmias.

We also set different goals for the cardiac output, depending on the patient's premorbid cardiovascular capabilities. For example, cardiovascular conditioning increases the blood volume, increases the ventricular end-diastolic volumes, increases the stroke volume, and decreases the resting heart rate⁷⁴—that is, it prepares the cardiovascular system for stress. Accordingly, if we know that a patient was in good cardiovascular condition before the acute problem developed, we aim for a higher cardiac output. We do the same for pregnant patients, whose cardiovascular systems have adapted to deal well with hemorrhage and stress. With respect to age, we set higher goals for younger patients than for older ones.

Finally, we sometimes set goals for the cardiac output on the basis of trial and error. For example, if a supranormal cardiac output causes an abnormality (e.g., metabolic acidosis) to resolve when a normal output did not, we make an effort to keep the car-

Problems Associated with Use of the Swan-Ganz Catheter

Passage of a Swan-Ganz catheter can induce ventricular dysrhythmias, particularly in patients who have suffered recent myocardial infarctions or who have an irritable myocardium (as indicated by a preexisting arrhythmia or conduction defect). For some of these patients, prophylactic administration of lidocaine is indicated. Usually, the dysrhythmia subsides when the end of the catheter finally passes through the ventricle and enters the pulmonary artery. Sometimes, however, it can be eliminated only by complete removal of the catheter; in rare instances, aggressive pharmacologic treatment or even cardioversion is required. The balloon on the end of the catheter should be kept inflated during passage to cushion the tip and minimize myocardial irritability.

Passing a Swan-Ganz catheter in a patient with left bundle branch block can be particularly hazardous. The catheter can eliminate conduction through the right ventricle, producing complete heart block. If this condition does not resolve upon prompt withdrawal of the catheter, insertion of a transvenous pacemaker or the use of external pacing may be necessary. The time required to establish a rhythm, however, can be so long that the patient may die first. Swan-Ganz catheters should be placed in patients with left bundle branch block only when absolutely necessary.

Lodging of the catheter tip in the trabeculae of the right ventricle is a common problem during catheter passage. On rare occasions, the end of the catheter may puncture the right ventricular wall. The puncture site may not be immediately obvious and may in fact seal by itself; it is more likely, however, to lead to pericardial tamponade and, possibly, death. Measurements from the Swan-Ganz catheter will indicate pericardial tamponade, which mandates emergency operation.

Passage of the catheter through the tricuspid and pulmonic valves can damage them, especially if the device is roughly pulled back through the valves with the balloon inflated. In addition, if the catheter is left in place for more than a few days, valvular damage may result. Besides minimizing long-term use of the catheter, little can be done to prevent this problem.

A problem unique to the Swan-Ganz catheter is intracardiac knotting, which is most likely to develop during placement. The knot can occasionally be untied by manipulating the catheter under fluoroscopic guidance.

Passage of a J-wire into the right side of the heart from the groin can also be effective. If these approaches do not work, the catheter must be withdrawn to the site of entry and then removed, usually under direct surgical control.

Swan-Ganz catheters can migrate distally and cut off the blood supply to the pulmonary parenchyma, resulting in pulmonary infarction. This complication can usually be prevented by continuous monitoring of the pulmonary arterial waveform. Development of a permanently wedged wave pattern mandates immediate withdrawal of the catheter into a more proximal portion of the pulmonary vasculature. The catheter should never be allowed to have a wedge tracing (except, of course, when the wedge pressure is being measured); the tracing seen on the monitor should look like a tracing from the pulmonary artery or one of its large branches.

On rare occasions, the catheter can perforate the pulmonary artery. This event typically presents with hemoptysis but may present with acute cardiopulmonary collapse during or immediately after measurement of the wedge pressure. Risk factors include advanced age, pulmonary arterial hypertension, warfarin anticoagulation, clotting deficiencies, distal migration of the catheter into the pulmonary vasculature, and balloon overinflation. Patients with tumors surrounding the pulmonary artery are also at increased risk. The balloon itself may disrupt the pulmonary artery directly, or inflation of the balloon may force the tip of the catheter through the vessel wall.

Prevention consists of continuous monitoring of pulmonary arterial pressure tracings. The catheter location should be confirmed by chest x-ray at least once daily. Wedge pressures should be measured only when needed. The degree of balloon inflation necessary to obtain a wedge tracing should be noted and overinflation avoided. The balloon inflation port should be identified so that infusions are not misdirected into the balloon. The catheter should never be left in the wedge position. Rupture associated with mild hemoptysis can be treated by removing the catheter; rupture associated with cardiovascular collapse calls for lobectomy or pneumonectomy, which occasionally permits patient salvage.

diac output high for a while. Once the abnormality is resolved, we see whether the resolution can be maintained with a more normal cardiac output.

The goal for the systemic arterial pressure is one that is sufficient to perfuse the CNS and any organs that might have an obstructed arterial supply. In some cases, we might accept a lower value than the initial assessment if the cardiac output turns out to be high. Useful energy, in this context, is cardiac output multiplied by MAP. Thus, if the cardiac output is high enough, it is possible to maintain the desired level of energy with a low MAP.

In all cases, we aim for an $S_{mv}O_2$ of 60% or higher. As noted (see above), high $S_{mv}O_2$ values are not necessarily reassuring, but low values suggest that the heart, an organ that normally consumes a large amount of the oxygen delivered to it, is dangerously close to becoming hypoxic. Low $S_{mv}O_2$ values warrant immediate attention.

The initial goal with fluid infusion should be to achieve an RVEDV and an LVEDV that are at least normal. If either volume is less than normal, it will be close to impossible for the heart to generate adequate power for perfusion in an efficient manner. A CVP in the low teens with a pulmonary arterial wedge pressure (PAWP) in the midteens (on the assumption that the patient is undergoing mechanical ventilation) is a good start. As noted (see above), however, this is a complicated issue. On the one hand, one hopes that the filling pressures will be adequate to generate a sat-

isfactory cardiac output and an acceptable MAP. On the other hand, one does not want to raise these pressures any higher than necessary.

On the right side, the end-diastolic volume will be known. In a normal 60 kg subject who is breathing spontaneously, an RVEDV of 150 ml is enough to ensure adequate filling of the heart [see Table 3]. In a critically ill patient on mechanical ventilation, a larger volume is needed—closer to 200 ml. If possible, the RVEDV should not be too much larger than that figure: excessive volumes increase oxygen consumption unnecessarily, and perhaps right atrial pressure as well. In some patients, however, one has no choice. One must ensure that the ventricle has an adequate end-diastolic volume, even if the value turns out to be higher than desired. An inadequate volume will make it impossible for the ventricle to do its job, no matter how well tuned the rest of the cardiovascular system may be. No cardiovascular adjustment can overcome the problems produced by an inadequate end-diastolic volume.

On the left side, the judgment is far more complicated. The LVEDV will not have been directly measured and must therefore be estimated [see Sidebar Measurements That Can Be Obtained from Invasive Monitoring]. Trial infusions can sometimes help. If necessary, one can obtain echocardiography. In all cases, the goal is the same: an end-diastolic volume that is at least normal.

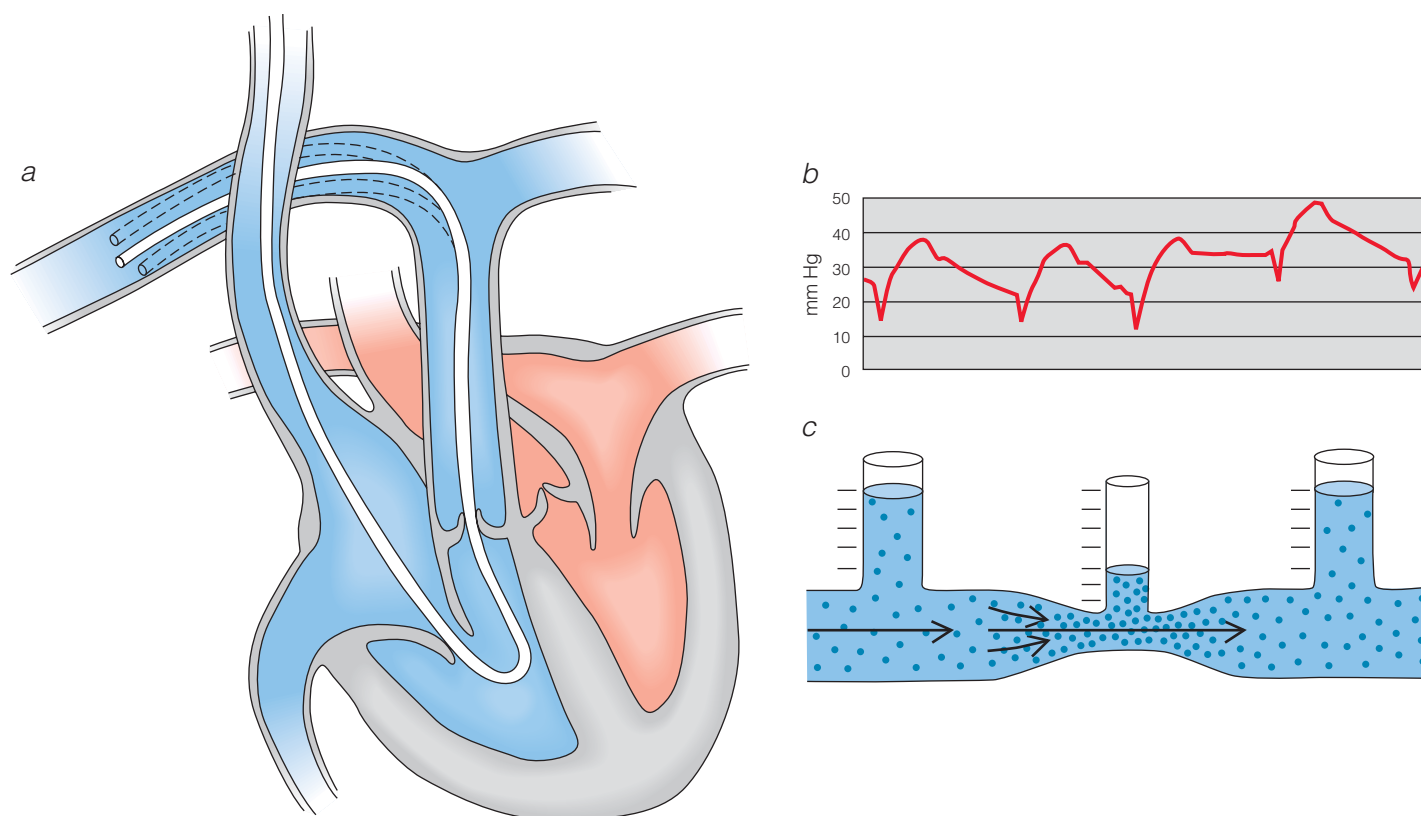


Figure 3 Catheter whip (or fling) results from movement of a catheter within the vasculature (a) that produces hydrostatic pressure changes at the tip of the catheter that are independent of any changes in hydrostatic pressure within the vessel itself. Pressure drops during diastole that are the result of catheter whip could be falsely interpreted as true vascular diastolic pressure. In the pressure tracing shown (b), the true diastolic pressure in the pulmonary artery is 24 mm Hg; catheter fling produces the lower pressure of 12 mm Hg at the tip of the catheter.

The total energy in a hydraulic system, such as the vasculature, is the sum of hydrostatic pressure and kinetic energy. The kinetic energy depends on the square of the velocity of the fluid. Because the velocity—and thus the kinetic energy—is greater the narrower the system (c), and because the total energy measured at any point in the system is constant, the hydrostatic pressure must be less in the narrow portion of the tube, where the velocity of flow is higher.

If a femoral or pulmonary arterial catheter moves within the vasculature as the heart beats, the velocity of blood across its orifice will increase; as the velocity increases and the kinetic energy increases, the hydrostatic pressure as measured at the tip will fall. This transient decrease in hydrostatic pressure at the tip of the catheter (as seen in the tracing) does not reflect the true hydrostatic pressure in the artery.

The radial artery catheter is best for determining the total energy in the systemic arterial vasculature. The catheter will not whip, because the artery is small and the catheter has no room to move about, and there will be no kinetic energy component in the blood, because the radial artery catheter is end-on (i.e., it faces into the direction of the flow), and thus, the velocity of the blood as it runs into the end of the catheter is zero. Therefore, the hydrostatic pressure will represent the total energy of the blood at that point of the arterial system. A catheter placed in the ascending aorta will be buffeted by the rapidly accelerating blood in the aorta, and catheter whip will be introduced. A pulmonary arterial catheter potentially has both the problem of catheter whip and the problem that it measures pressure in the direction of flow rather than end-on. The latter problem cannot be avoided. The problem of catheter whip can be dealt with by advancing the tip of a catheter that seems to be in the main pulmonary artery distally, into one of the branches of the artery. This will minimize whip and will be safe, as long as care is taken to be sure that the catheter is not placed so far distally that it becomes permanently wedged.

Minimize Effective Pulmonary Arterial Elastance

Once end-diastolic volumes that appear to be adequate but not excessive have been achieved, the next step is to determine whether the effective pulmonary arterial elastance can be decreased. In many surgical patients, the pulmonary arterial elastance is elevated as a consequence of stiff pulmonary arteries, a compressed pulmonary microvasculature,¹⁸ or a stiff left atrium. It can be measured quite accurately by means of the Swan-Ganz catheter (with some qualifications [see *Sidebar* Measurements That Can Be Obtained from Invasive Monitoring]). In general, the pulmonary arterial elastance should not exceed the right ventricular end-systolic elastance. This latter value will not be obtainable from the

Swan-Ganz catheter data, because the end-systolic unstressed volume will not be available, but it is known that the maximal end-systolic elastance for the right ventricle in a 60 kg subject is on the order of 0.8 mm Hg/ml [see *Table 4*]. As a rule, therefore, if the effective pulmonary arterial elastance exceeds 0.8 mm Hg/ml in a 60 kg patient, one should try to reduce it.

Treatment includes (1) adjustment of the ventilator to minimize compression of the vasculature and the atrium; (2) alteration of the patient's position so that the better of the two lungs is dependent (the goal being to maximize flow to the microvasculature that is least obstructed and to minimize flow to the microvasculature that is most obstructed); (3) diuresis, if possible, to decrease dis-

tention of the vasculature and atrium; and (4) decompression of the abdomen if the patient has a compartment syndrome (the elevated diaphragm of the syndrome and the resultant stiffness of the tissues in the chest are bad not only for the heart but also for the pulmonary vasculature).

In our experience, pharmacologic treatment of an elevated effective pulmonary arterial elastance has rarely worked, at least in adult surgical patients. In particular, we have not had much success with metabolites of arachidonic acid or analogues of these metabolites, nor have we had much success with inhaled nitric oxide. In the past few years, there have been several reports on the use of enteral sildenafil, 25 to 100 mg, in medical patients that appear to give grounds for optimism.⁷⁵ In surgical patients, however, the problem underlying elevated effective pulmonary arterial elastance is frequently mechanical. In such circumstances, one

cannot hold out too much hope for an intervention that works primarily on smooth muscle spasm. Admittedly, we do not have much experience with this use of sildenafil.

Set Goal for Heart Rate, and Increase Ventricular End-Systolic Elastances If Necessary

The next step, if necessary, is to increase the ventricular end-systolic elastances while taking into account the heart rate. Digoxin is a good choice for the occasional patient who is in atrial fibrillation, exhibits a rapid ventricular response, and also happens to be in shock. It can be given in a 0.5 mg loading dose, followed by increments of 0.25 mg every hour until the atrioventricular node is blocked sufficiently to yield the desired ventricular response. A guideline for an acceptable ventricular response might be a heart rate lower than 120 beats/min in a young

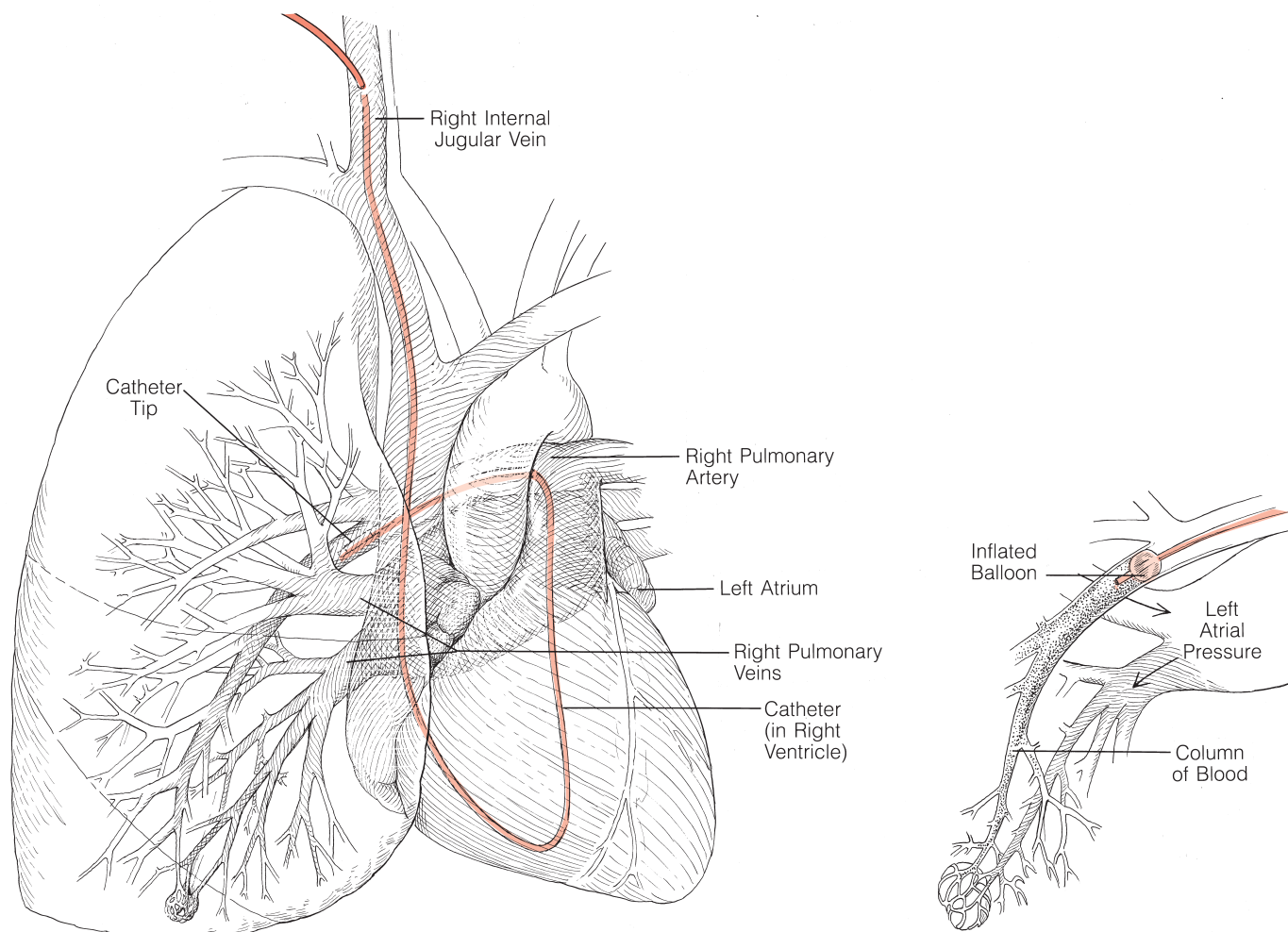


Figure 4 The pulmonary arterial catheter measures pressure in the pulmonary artery when the balloon is deflated. Because flow in the vascular system generates a pressure drop as the blood passes through the microvasculature, the pressure in the pulmonary artery has to be greater than that in the left atrium. When the balloon is inflated, flow in the vasculature distal to the tip is eliminated; therefore, there is no pressure drop. Because there is no pressure drop and because there are no valves between the left atrium and the pulmonary artery, the pressure in the pulmonary artery distal to the point of occlusion must equal the pressure in the left atrium, provided that there is an open column of blood between the end of the catheter and the left atrium. That is, pulmonary arterial wedge pressure will equal left atrial pressure as long as the catheter is in a dependent portion of the lung with a vasculature that remains open during ventilation. Because the catheter is flow directed, it usually will end up in such a dependent, well-perfused area. This is not a certainty, however. If inflated alveoli occlude the microvasculature, wedge pressure will equal alveolar pressure. This inaccuracy might not be easily detected.

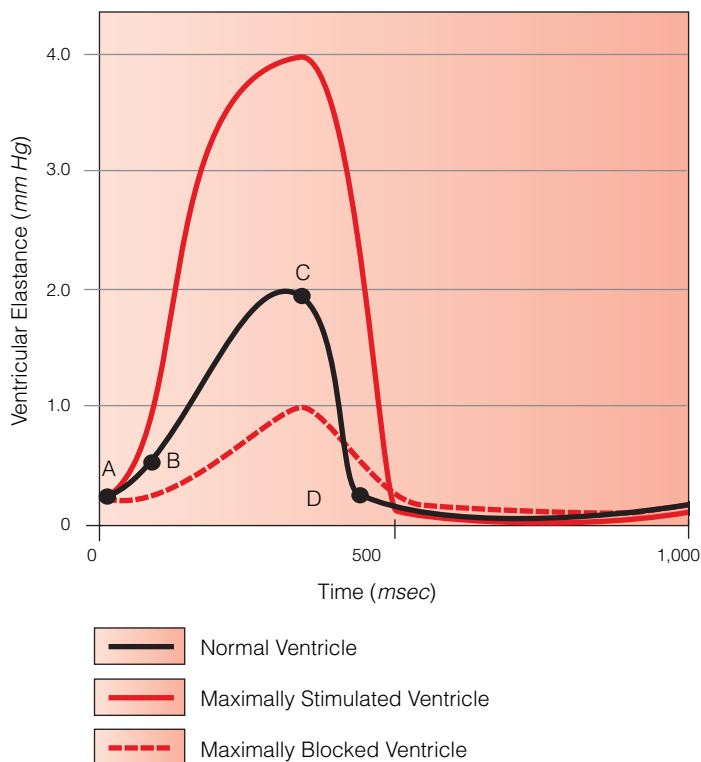


Figure 5 Illustrated is the elastance (stiffness) of the left ventricle over a cardiac cycle in a 60 kg person, as seen in a normal person under resting conditions, a person with a maximally contractile ventricle, and a person with profound beta blockade or congestive heart failure. Point A is the beginning of systolic contraction; point B is the opening of the aortic valve; point C is end-systole; and point D is the beginning of diastolic filling. During diastole, the stiffness typically increases from a minimum of 0.1 mm Hg/ml, in a 60-kg subject, at the beginning of diastolic filling, to a maximum of 0.2 mm Hg/ml at the end of diastole. The stiffness of the ventricle then dramatically increases, from the beginning of systole to the end of systole, where the stiffness under resting conditions is typically 2.0 mm Hg/ml. With maximal contractility, elastance rises more quickly than normal, and maximal stiffness, at end-systole, is twice the normal value. With congestive failure, elastance rises more slowly, and maximal stiffness is half the normal value. The elastance during diastole is lowest under conditions of maximal contractility, in the normal heart, leading to the ideal situation in which diastolic filling is maximized at the same time as maximum contractility. In the ischemic heart, diastolic stiffness increases under stress, so that filling is compromised at the same time that contractility is hampered.

patient, or lower than 90 beats/min in an older patient, or lower than 75 beats/min in a patient with coronary artery disease. Blood levels should not be monitored. The ventricular response will serve as a bioassay both for efficacy and for toxicity. Digoxin should not be used in patients who have any dysrhythmia other than atrial fibrillation: the toxicity will be unpredictable and difficult to monitor.

Dobutamine is the usual choice for most patients who might benefit from increases in ventricular end-systolic elastances. The dosage should be $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ initially. It can then be increased as needed, to an upper limit of $20 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. If necessary, milrinone may be added, first administered in a $50 \mu\text{g}/\text{kg}$ loading dose over 10 minutes and then infusion at a dosage of 0.375 to $0.75 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The two agents increase intracellular systolic calcium concentrations by different mechanisms. Neither has any vasocon-

strictor effects, and both are safe, at least for a short time. The usage of these drugs should be governed by consideration of the heart rate. As a rule, the heart rate will not increase very much with administration of either agent, but if it does rise to unacceptably high levels, one will have to reduce the dosage.

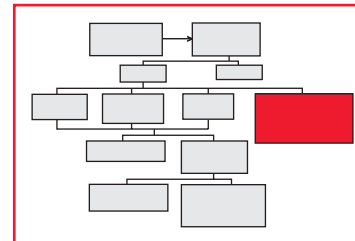
Last Resort: Increase Effective Aortic Root Elastance

As a rule, increasing the blood pressure is a trivial matter, except in the preagonal patient. One can always administer a vasoconstrictor, and one can almost always achieve any pressure desired. If the heart rate is not too rapid, dopamine can be given; if the rate is too fast, norepinephrine can be given. With either drug, the addition of vasopressin in low doses can facilitate its actions and allow one to minimize the doses.

A more difficult problem is knowing when one has no choice but to use a vasoconstrictor. In this situation, the Swan-Ganz catheter is invaluable. On occasion, use of dopamine or norepinephrine results in an increased cardiac output. If the increase in the blood pressure is caused primarily by an increase in the cardiac output, then the drugs are safe. If, however, the cardiac output is not increased, then the increased blood pressure must be the result of vasoconstriction. This means that at least some of the organs in the body must be experiencing reduced blood flow. Some organs (e.g., skin and fat) can withstand ischemia for a while, but no part of the body is expendable. Necrotic skin in an extremity means amputation of the limb; a necrotic gut means death.

The question of when to use a vasoconstrictor arises quite frequently in the treatment of warm inflammatory shock. There are no easy answers. We follow the guidelines described earlier [*see Insertion of Arterial Catheter and Assessment of Mean Arterial Pressure, above*]. In many cases, we find that a quite low MAP is adequate for perfusion, especially when associated with a generous cardiac output. We do everything we can to avoid using constrictors, resorting to them only when every other possible treatment has failed.

Management of Cardiogenic or Obstructive Shock



Many patients in hypovolemic, inflammatory, compressive, or neurogenic shock can initially be treated without invasive monitoring. Their problems may be manageable with fluid administration alone. Patients in cardiogenic or obstructive shock, however, probably have more complicated problems. These patients should be transferred to a unit where the cardiac rhythm can be monitored and arterial and central venous catheters can be used.

Treatment of cardiogenic or obstructive shock begins with renewed attempts to correct dysrhythmias (if this has not already been done). Every effort should be made to achieve a normal sinus rhythm. If myocardial damage is unlikely, as in a patient with uncomplicated valvular problems, the heart rate should not be allowed to reach or exceed 90 beats/min. If myocardial ischemia is a possibility, the heart rate should not be allowed to exceed 75 beats/min.

As noted earlier (see above), digoxin is excellent for controlling an unacceptably high heart rate in a patient in atrial fibrillation (in cases where the patient cannot be converted to sinus rhythm). Occasionally, it may be supplemented with a calcium channel blocker (e.g., diltiazem, 5 to 15 mg/hr).

For all other patients with an unacceptably high rate, a beta blocker should be given instead. Esmolol is a good first choice, in that it has a rapid onset of action and a short duration of action. A 500 $\mu\text{g}/\text{kg}$ loading dose is given, followed by a 50 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ infusion, which is increased as necessary. Metoprolol, 5 to 15 mg every 6 hours, may be given later if it is clear that beta blockade was needed and still is. If the heart rate is still excessively high, a calcium channel blocker should be added.

If the ventricular end-diastolic volumes seem excessively large, diuresis should be initiated or morphine sulfate, 1 to 4 mg/hr, should be given, both to relieve pain and stress and to allow pooling of blood in the systemic capacitance vessels.

If the effective aortic elastance is thought to be excessive, the stiffness of the arteries should be decreased by performing further diuresis, by adding an angiotensin-converting enzyme (ACE) inhibitor (e.g., enalaprilat, 1.25 to 5 mg every 6 hours), or by adding nitroglycerin, 5 to 200 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Nitroprusside is occasionally indicated, if the problem is believed to be exclusively on the arterial side of the circulation. As a rule, hydralazine should not be used. Because its principal effects are on the arterioles, not the arteries, it lowers the MAP but has substantially less effect on the stiffness of the arteries (which is more important for decreasing the ventricular oxygen requirements). Hydralazine can also increase the heart rate and thereby increase myocardial oxygen

requirements, thus defeating the very purpose for which it was originally given. The use of clonidine should also be avoided if possible. It, too, works mainly on the arterioles instead of the arteries, and it can cause nightmares and disorientation, side effects that can be a major problem in critically ill patients. With all of these drugs, dosages should be titrated as necessary.

If the energy-producing capabilities of the ventricles are still in question, an inotrope (e.g., dobutamine or milrinone) should be tried—albeit cautiously, in view of the effect these agents have on myocardial oxygen requirements. The inotrope can be added to digoxin if the patient is already receiving digoxin for treatment of a rapid ventricular response in atrial fibrillation.

The hemoglobin concentration should be kept at 10 g/dl or perhaps even higher, especially if the higher hemoglobin concentrations are associated with alleviation of symptoms. If transfusion is required, more aggressive diuresis will be needed as well.

If the clinical abnormalities still have not resolved, a Swan-Ganz catheter should be inserted. The measurements obtained from the catheter will allow more precise management of the ventricular end-diastolic volumes. Adjustments to these volumes can be directly correlated with their effects on the stroke volumes. The measurements might indicate that some of the problem is on the right side of the heart. If the effective pulmonary arterial elastance is excessively high, treatment should proceed in the same manner

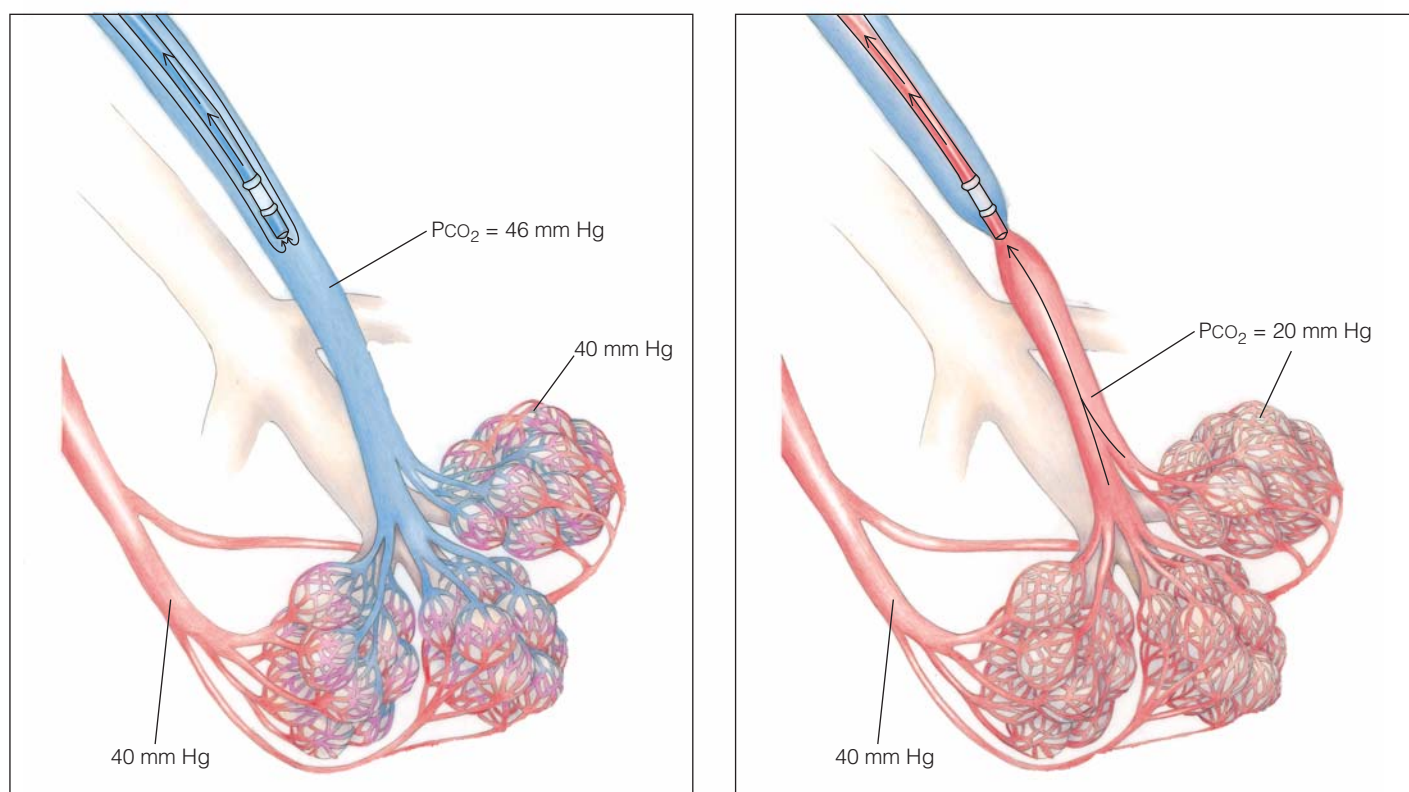


Figure 6 The Swan-Ganz catheter allows collection of mixed venous blood for measurement of S_{mvO_2} (left). If blood from the pulmonary artery is withdrawn through the catheter too forcefully, however, arterial walls can collapse around the tip of the catheter (right). The sample will in that case consist of blood from the distal pulmonary vasculature that has been pulled back past ventilated alveoli. To determine whether this has happened, the PCO_2 in the sample should be checked. P_{mvCO_2} is typically about 5 mm Hg greater than P_{aCO_2} . If the arterial walls have collapsed around the catheter, the sample will consist of blood from which much of the CO_2 will already have been removed by the ventilating alveoli, and the P_{mvCO_2} in the recovered blood may be as much as 20 mm Hg lower than a simultaneously obtained P_{aCO_2} . Specimens of this sort should be discarded and new specimens obtained. Taking care in obtaining true mixed venous blood is equally important when using a catheter with an oximeter mounted on its tip. Calibration of the oximeter requires direct measurement of S_{mvO_2} in a correctly obtained specimen.

Measurements That Can Be Obtained from Invasive Monitoring

Cardiac Output

Thermistor-tipped Swan-Ganz catheters can measure cardiac output by means of thermodilution [see Table 2].^{114,115} Originally, these values were obtained by injecting a known quantity of a cool solution into the right atrium and analyzing the temperature drop in the pulmonary artery as the cooled blood flowed past the thermistor. Nowadays, a heater coil is used to heat the blood in the right ventricle, and the resulting rise in temperature in the pulmonary artery is used to calculate the output. The temperature pulses are generated randomly. The measured outputs are obtained over the entirety of the respiratory cycle. Commercially available computers make the calculations on the basis of indicator dilution theory. Stroke volumes, obtained by echocardiography, can also be used to calculate the cardiac output, but cardiac outputs measured via the Swan-Ganz catheter are more accurate than those calculated from echocardiographic measurements.

Stroke Volume

The stroke volume is calculated as the cardiac output (measured by thermodilution) divided by the heart rate [see Table 3].

Right Ventricular End-Diastolic Pressure and Volume

The right ventricular end-diastolic pressure (RVEDP) is essentially the same as the central venous pressure, provided that there is no tricuspid stenosis. The proximal port on a Swan-Ganz catheter can be used to transduce that pressure.

The right ventricular end-diastolic volume (RVEDV) can be approximated from the end-diastolic pressure, but the introduction of pulmonary arterial catheters equipped with fast-response thermistors now allows direct measurement of the RVEDV.¹¹⁶ The measurements are accurate as long as the patient has a regular rhythm and a heart rate lower than 140 beats/min.

Measuring right ventricular volumes with echocardiography is difficult. The chamber is typically crescent-shaped; therefore, mathematical formulae based on linear measurements of the chamber will not be able to generate reliable estimates.

Right Ventricular End-Systolic Pressure and Volume

The right ventricular peak systolic pressure is the same as the peak pulmonary arterial pressure, provided that the pressures from the catheter are being accurately measured [see Figures 2 and 3]. The right ventricular end-systolic pressure (RVESP), which is the key pressure for evaluating the energy-producing capabilities of the ventricle and assessing the hindrance that the ventricle faces when it expels its blood into the root of the pulmonary artery (see below), can be approximated as 90% of the peak systolic pressure.³

The right ventricular end-systolic volume (RVESV) can be obtained by subtracting the stroke volume from the end-diastolic volume [see Table 3].

Left Ventricular End-Diastolic Pressure and Volume

The pulmonary arterial wedge pressure, measured with a Swan-Ganz catheter, will approximate the left atrial pressure, provided that there is no significant bronchial blood flow entering the vasculature distal to the end of the catheter and that the catheter is placed in a portion of the vasculature that is open to the left atrium throughout the ventilatory cycle [see Figure 4]. If no mitral valvular stenosis is present, the left atrial pressure will approximate the left-ventricular end-diastolic pressure (LVEDP). Thus, the wedge pressure will usually be close to both the left atrial and the left ventricular end-diastolic pressure. Knowing the left atrial pressure can be very helpful in making an estimate of the pulmonary microvasculature hydrostatic pressure. One will not be able to assign a specific number to that pressure on the basis of the left atrial or wedge pressure, but one will know that the microvascular pressure must be greater than the wedge

pressure. From the standpoint of preventing pulmonary edema, one would like to keep the wedge pressure as low as possible.

One can also use the wedge pressure—cautiously—to estimate the left-ventricular end-diastolic volume (LVEDV), but only if the ventricular wall is not abnormally stiff during diastole and if the tissues surrounding the left ventricle are not abnormally stiff.

Many different factors may influence the stiffness of the ventricular wall during diastole. A distended right ventricle under high pressure (a common finding in ARDS) can push the ventricular septum into the left ventricle during diastole and thus increase the diastolic stiffness of the walls of that chamber. (This situation will result in a large RVEDV in association with a small LVEDV—a frequent finding in patients in inflammatory shock. The situation can also go the other way: in patients with left-side congestive heart failure, left ventricular values can be substantially larger than right ventricular values.) The possibility of septal shift into the left ventricle can be ruled out if the measured RVEDV is reasonably small and the measured CVP is reasonably low.

The diastolic stiffness of the left ventricle can also increase if the wall is (1) thick (which can be ruled out with reasonable certainty if it is known that the patient has no aortic valvular disease and is not chronically hypertensive), (2) ischemic (which might become a problem with a tachycardia; a normal electrocardiogram usually suffices to rule out the possibility); or (3) scarred, as from an old myocardial infarction (which can be ruled out with a history and an electrocardiogram). If the left ventricular wall is none of these things, one can assume that it is probably normally compliant during diastole.

To assess the possibility of increased stiffness of the tissues surrounding the left ventricle, one can compare the RVEDV (measured with the Swan-Ganz catheter) with the CVP. If a low CVP is associated with a reasonably large end-diastolic volume, then it is clear that the tissues surrounding the heart cannot be excessively stiff (if they were, the low intracavitary CVP would not be able to produce a reasonable volume).

If the clinical assessment suggests that the walls of the left ventricle are normally compliant during diastole and if the assessment of the CVP and the RVEDV suggests that the tissues surrounding the ventricle are not excessively stiff, one can extrapolate from the wedge pressure to the ventricular end-diastolic volume. If, however, there is a question about the stiffness either of the left ventricular wall during diastole or of the tissues surrounding the ventricle, one cannot make this extrapolation.

Under these circumstances, one can make a rough estimate of the LVEDV by giving a fluid bolus in an amount that is sufficient to increase the wedge pressure by at least several mm Hg. If this measure increases the stroke volume, especially if the increase is associated with increased systemic arterial pressure, the initial LVEDV was probably small. If, however, increasing the wedge pressure has minimal effects on the stroke volume and the arterial pressure, there are two possibilities. The first is that the LVEDV was already generous. To test this possibility, a diuretic can be given; if the stroke volume and blood pressure do not decrease, one can assume that the left ventricular volume was probably adequate, perhaps even more than adequate. The second possibility is that the volumes were small but the diastolic compliance was poor.

In a 60 kg subject, a normal LVEDV is on the order of 150 ml (the same as for the right ventricle) for a wedge pressure of 6 mm Hg. If an essentially normal subject undergoes mechanical ventilation, as for an elective operation, a wedge pressure of 9 mm Hg is usually enough to produce an adequate LVEDV. If the patient is moderately ill, the pressure will probably have to be 12 mm Hg; if he or she is seriously ill, it will have to be 15 mm Hg, if not higher. Under no circumstances, however, should the pressure exceed 24 mm Hg: that level of left atrial pressure will give rise to fulminant pulmonary edema, even in a patient with completely normal pulmonary microvascular permeability.

(continued)

Measurements That Can Be Obtained from Invasive Monitoring (continued)

It must be kept in mind, however, that these generalizations are only that. Their accuracy suffers from the effort to extrapolate from an intracavitary pressure to a volume without any sure knowledge regarding the stiffness of the structures around the volume being considered. For accurate measurements of the LVEDV, transesophageal echocardiography is necessary.

Left Ventricular End-Systolic Pressure and Volume

Estimating the peak aortic root pressure is as difficult a process as estimating the LVEDV. Nevertheless, the effort is worth making. The systolic pressures in the aortic root and the left ventricle are the same. To have at least some idea of what these pressures are would be useful if one is to make an estimate of the energy-producing capabilities of the left ventricle and if one wants to know the hindrance that the ventricle faces when it pushes its blood into the aortic root.

One approach in estimating the systolic pressures in the aortic root is to measure the peak systolic pressures in the radial artery and then to cautiously extrapolate back to the corresponding pressures in the root of the aorta [see *Sidebar Energy Propagation throughout the Arteries and Its Effect on Pressures in Those Arteries*]. Another approach is to estimate the peak aortic root pressure by extrapolating from the MAP. In young patients with compliant arteries and no abnormal arteriolar constriction, the peak systolic pressure in the aortic root is usually about 20 mm Hg higher than the MAP.¹ In patients with stiff or calcified arteries, the central peak systolic pressure can be much higher than the MAP. In patients who are in warm inflammatory shock or neurogenic shock, the central systolic pressure may be only 10 mm Hg higher than the MAP. Usually, the aortic root end-systolic pressure is about 90% of the peak aortic root pressure.³

The left ventricular end-systolic volume (LVESV) (end-diastolic volume minus stroke volume) cannot be obtained with any reasonable accuracy from measurements obtained via the Swan-Ganz catheter. Estimates of the end-diastolic volume on the basis of the wedge pressure are very rough; at times, there might be some inaccuracy in measuring the stroke volume from the thermodilution cardiac output. If one needs to know the end-systolic volume, it is necessary to use echocardiography, which is usually quite accurate. Alternatively, one can use echocardiography to measure the end-diastolic volume and then subtract the stroke volume calculated from the heart rate and the cardiac output obtained by thermodilution.

Effective Arterial Elastances

Of the many cardiovascular descriptors that can be derived from the variables just described, four are of particular importance in considering how to treat a patient in shock: the two effective arterial elastances (one for the pulmonary artery and one for the root of the aorta) and the two ventricular end-systolic elastances. It is also valuable to have some feeling for the concept of the ventricular end-systolic unstressed volume.

The so-called effective arterial elastance is a single number used to describe the total hindrance that the ventricle faces as it ejects its blood during systole. It is calculated as the proximal arterial (or ventricular) end-systolic pressure divided by the stroke volume and is expressed in mm Hg/ml. In the case of the pulmonary vasculature, the effective arterial elastance can be calculated quite accurately, provided that a pulmonary artery catheter is in place and that the system used to measure the pulmonary arterial pressures is satisfactorily matched to the vasculature [see *Figures 2 and 3*]. In the case of the systemic vasculature, however, the calculation becomes problematic because of the difficulty in determining the pressures in the root of the aorta [see *Figure 2 and Sidebar Energy Propagation throughout the Arteries and Its Effect on Pressures in Those Arteries*]. Nevertheless, the effective arterial elastance for the aortic root remains the best single-number approximation for the hindrance faced

by the left ventricle. The values for the elastances depend on the patient's size [see *Table 4*].

The effective arterial elastance takes into account the stiffness of the arteries faced by the ventricles, the resistance of the arterioles in the circuit, the stiffness of the atrium and ventricle into which the blood is driven during diastole, and the interaction of all of these elements in conjunction with the heart rate. The systemic vascular resistance, as one part of this hindrance, can be calculated as the difference between the mean aortic pressure and the right atrial pressure divided by the cardiac output. One can also calculate a resistance for the pulmonary vasculature, but the calculation depends on the difference between two small numbers. In our view, calculated pulmonary vascular resistance is too unreliable to be a useful clinical descriptor.

The units used to express vascular resistances vary from hospital to hospital. It is simplest, as well as perfectly acceptable scientifically, to use arbitrary units. We prefer mm Hg·L⁻¹·min. That is, we use the number obtained through the simple calculation described without making any further corrections. Some multiply this raw number by 80 to convert the resistances to units in the centimeter-gram-second (CGS) system.

Ventricular End-Systolic Unstressed Volumes

The unstressed volume of a chamber is the minimal volume in the chamber that will generate a positive pressure. In the case of a cardiac ventricle, the end-systolic unstressed volume is the unstressed volume in the chamber when the ventricle is maximally stiff, at the end of systole. These volumes cannot be determined with currently available ICU monitoring, but one must nonetheless be mindful of the concept of end-systolic unstressed volume when assessing the energy-producing capabilities of the ventricles.

In normal subjects, the left ventricular end-systolic unstressed volume, measured with sophisticated echocardiography or in the cardiac catheterization laboratory, is on the order of 0.1 ml/kg lean weight. In patients with congestive heart failure, it can increase by a factor of 10, to 1.0 ml/kg. That is, left ventricular end-systolic unstressed volume is close to zero in a normal human heart, compared with other heart volumes (e.g., the end-diastolic volume, which is on the order of 2.5 ml/kg), but it can become substantial in a flabby heart.

To our knowledge, the right ventricular end-systolic unstressed volume has not yet been satisfactorily measured in human beings, even in the catheterization laboratory. This volume is very small in normal dogs, and there are reasons why it should be small in normal human beings as well. There are also reasons why the right ventricular end-systolic unstressed volume is likely to be very large in a patient with a failing right ventricle—probably even larger than the unstressed volume in the left ventricle of a patient in left-side failure.

Ventricular End-Systolic Elastances

The ventricular end-systolic elastance is a single number that represents the maximal stiffness of a ventricle, which occurs at end-systole. (The ventricles are quite compliant during diastole; they become much stiffer during systole [see *Figure 5*].) It is expressed in mm Hg/ml. Nowadays, ventricular end-systolic elastances are the most frequently used single-number approximations for describing the energy-producing capabilities of the ventricles. Large elastances correlate with good capabilities for energy production; low elastances correlate with poor capabilities.

Ventricular end-systolic elastances do not provide a complete description of energy-producing capabilities; for that, one also needs the ventricular end-systolic unstressed volumes. Nonetheless, they are good descriptors and are ideally suited for analysis of how a ventricle interacts with its vasculature.

(continued)

Measurements That Can Be Obtained from Invasive Monitoring (continued)

The right ventricular end-systolic elastance, in a patient who does not have unusually large end-diastolic volumes, can be approximated as the ventricular (or pulmonary arterial) end-systolic pressure divided by the end-systolic volume. The left ventricular end-systolic elastance cannot be approximated very well in the ICU, but studies done in the catheterization laboratory have yielded known values for both normal subjects and patients in congestive heart failure. One can sometimes assign a number to a patient if the clinical circumstances make it obvious that the patient's heart is clearly in good condition or clearly failing. These numbers can then be used in making decisions about adjustment of the effective aortic elastance.

Values for ventricular end-systolic elastance in a spontaneously breathing normal subject depend on body size [see Table 4]. In a maximal state of ventricular function, the values can double; in profound beta blockade or profound heart failure, the values can fall to 50% of normal.

Mixed Venous Oxygen Saturations

The mixed venous oxygen saturation (S_{mvO_2}) can be measured with appropriately equipped Swan-Ganz catheters [see Figure 7]. It will be

high if the cardiac output is high, if the hemoglobin concentration is high, if the arterial oxygen saturation is high, and if the oxygen consumption is low. It may be the best single-number descriptor of the adequacy of shock resuscitation.

Saturations lower than 60% should always be considered grounds for concern. The heart consumes much of the oxygen delivered to it. Low mixed venous values raise the possibility that the heart might not be receiving the oxygen it needs. Saturations higher than 80% are reassuring, in the sense that they suggest that it is not necessary to increase the oxygen delivery to the body (because the body, as a whole, is only using 20% of the oxygen delivered to it). On the other hand, there are situations in which a high S_{mvO_2} can be worrisome. The high value might arise from excessive amounts of blood being shunted to the skin, as in the case of sepsis, or it might arise from failure of metabolic activity either generally or in specific organs, resulting in minimization of oxygen consumption. As with all of the cardiovascular descriptors discussed, S_{mvO_2} values must be considered with respect to the specific clinical context in which they are determined.

as for hypovolemic or inflammatory shock (see above). If the effective aortic elastance still seems excessively high in relation to the estimated left ventricular end-systolic elastance, more aggressive efforts either to reduce the effective aortic elastance or to augment the left ventricular end-systolic elastance are warranted. The goal is to manage the patient so that the estimated effective aortic elastance is approximately one half of the estimated left ventricular end-systolic elastance—in other words, to achieve as much efficiency as possible.⁷⁶⁻⁷⁸

In some patients with acute myocardial ischemia and shock, all of the aforementioned treatments will fail. Such patients should undergo emergency coronary angiography, as should any patient with an acute coronary syndrome that becomes unstable

or that is associated with ST-T segment elevation. The purpose of the angiography is to find a correctable lesion that can be treated with coronary angioplasty, stenting, or surgical revascularization. If necessary, an intra-aortic balloon pump may be placed before or at the time of angiography, angioplasty, or stenting; it can then be left in place while the underlying problem awaits possible surgical correction (if indicated). The pump can be extraordinarily effective: there is no better means of dealing with the reflected energy waves generated by the transmission of energy into these vessels. It does, however, put the perfusion of the limb with the cannulated artery at risk. Furthermore, the pump is only a short-term solution: eventually, the underlying problem will have to be dealt with.

Discussion

To the best of our knowledge, the thermodynamic characterization of the cardiovascular system was first described in the 1880s, by Otto Frank in Germany. Frank compared the ventricles to Carnot engines and used that analogy to account for how the heart generated its energy. He was unable, however, to confirm his theory experi-

mentally—it was too complex to be evaluated with the measurements available at the time—and he was unable to account for how the ventricles transferred their generated energy into their respective vasculatures.

In the early 1900s, Ernest Starling, who had worked in Germany in his younger days and was aware of Frank's work,

Table 3 Influence of Body Size on Selected Cardiovascular Parameters in a Resting Subject*

Lean Weight (kg)	Cardiac Output (L/min)	Stroke Volume (ml)	End-Diastolic Volume (ml)	End-Systolic Volume (ml)
50	5.0	83	125	42
60	6.0	100	150	50
70	7.0	117	175	58
80	8.0	133	200	67

*On the assumptions that (1) cardiac output is 100 mL·kg⁻¹·min⁻¹, (2) heart rate is 60 beats/min (or, equivalently, stroke volume is 1.67 mL/kg), and (3) end-diastolic volume for the two ventricles is 2.5 mL/kg.

Table 4 Derived Descriptors of Energy-Producing Capabilities of Ventricles and of Hindrance That Ventricles Face When Injecting Blood into Their Respective Vasculatures*

Lean Weight (kg)	Right Ventricular End-Systolic Elastance (mm Hg/ml)	Effective Pulmonary Arterial Elastance (mm Hg/ml)	Left Ventricular End-Systolic Elastance (mm Hg/ml)	Effective Aortic Root Elastance (mm Hg/ml)
50	0.52	0.26	2.4	1.2
60	0.44	0.22	2.0	1.0
70	0.38	0.19	1.7	0.85
80	0.33	0.17	1.5	0.75

*On the assumptions used in Table 3 and on the additional assumptions that (1) right ventricular end-systolic pressure is 22 mm Hg, (2) left ventricular end-systolic pressure is 100 mm Hg, and (3) ventricular end-systolic unstressed volumes are zero.

expanded on that work both experimentally and theoretically. Using isolated muscle strips contracting against a suspended weight, he was able to demonstrate that the resting length of a muscle was a determinant of the amount of work that the muscle could produce. Going on to experiments in anesthetized dogs, he introduced the concepts of contractility and afterload and was then able to describe the energy produced by a ventricle and transferred into the vasculature as the result of the interaction between the ventricular end-diastolic volume, the contractility of the ventricle, and the afterload facing the ventricle.

This Frank-Starling model of the heart was elegant and parsimonious and could qualitatively describe much of normal cardiovascular physiology, but for a long time, two of its variables—contractility and afterload—could not be satisfactorily described in mathematical terms. As a consequence, the model could not deal with quantitative problems like heat dissipation throughout the system, nor could it address the issue of ventricular-arterial coupling.

These problems have now been solved. Modern models, using engineering concepts developed in the midportion of the 20th century and applied to the cardiovascular system in the latter part of the century, have succeeded in mathematically describing how a ventricle interacts with its vasculature. Like Frank's original description, these models begin by comparing a ventricle (either the right or the left) to a Carnot engine (or to an oscillating electrical energy source). They then compare the vasculature (including the contralateral atrium and the contralateral ventricle during its diastole) into which the ventricle pumps its blood to a system of pipes with compliant and resistive elements (or to an electrical circuit with capacitive and resistive elements). The interaction between the pulsatile energy source and the hindrance or impedance imposed by the vasculature determines the amount and type of energy that is transferred from a ventricle into its vascular bed.

The modern models use five variables to account for generation and transfer of energy in the cardiovascular system: (1) ventricular end-diastolic volumes, (2) ventricular end-systolic unstressed volumes, (3) ventricular end-systolic elastances, (4) effective elastances of the roots of the pulmonary artery and the aorta, and (5) heart rate. These variables determine how the ventricles interact with their complex vasculatures. They determine the pressures that will be generated in the system; the stroke volumes that will be produced; the cardiac output that will be produced (as the product of the heart rate and the stroke volume); the work that will be done by the heart on the vasculature; the total, mean, and oscillatory power that will be delivered into the vasculature; the heat that will be dis-

sipated into the walls of the heart during the cardiac cycle; the heat that will be dissipated in the walls of the arteries as the arteries expand and recoil during the cardiac cycle; the heat that will be dissipated in the arterioles of the microvasculature; the amount of oxygen that myocardium will require to produce all of this energy; and the efficiency with which the heart generates and transfers the energy into the vasculatures. In other words, by reasoning from the modern models, one should be able to predict, at least theoretically, all that one needs to know about managing a patient in shock. Thus, a knowledge of cardiovascular thermodynamics is not only of intellectual interest (to some) but also of therapeutic value. The goal of studying this material is to reach an informed understanding of how to deal with the basic problem of managing the patient in shock—that is, the problem of helping the heart produce and transmit energy without producing too much edema and without putting excessive demands on the myocardium.

We begin our discussion of cardiovascular thermodynamics by describing the various types of power generated by the heart and transferred into the vasculature. On the assumption that some useful energy is present in the cardiovascular system, we then describe how that energy accounts both for the distribution of blood in the various parts of the system and for the flow of blood through the various organs in the system. Next, we describe more specifically how a ventricle interacts with the root of its vasculature (either the root of the pulmonary artery or the root of the aorta) to generate and transfer its energy into the blood vessels. Finally, we describe the factors that determine how much energy is produced and how efficiently it is produced.

Analysis of Cardiovascular Thermodynamics

TYPES OF POWER PRODUCED BY HEART AND TRANSFERRED INTO VASCULATURE

The total power generated by a ventricle and transferred into its vasculature over time can be calculated as the cardiac output multiplied by the end-systolic pressures in the ventricle.^{2,79} It typically is expressed in units of volume divided by time multiplied by pressure. (It can also be expressed in units of heat divided by time or in terms of amounts of oxygen used for oxidation divided by time.) The total power is the major determinant of the ventricle's oxygen requirement.³

The total power has two components: the mean power and the oscillatory power. The mean power transferred into the vascula-

Table 5 Influence of Interventions on Goals of Shock Resuscitation, as Determined by Graphical Mathematical Analysis

Goal	Interventions
To increase stroke volume	Increase ventricular end-diastolic volume Increase ventricular end-systolic elastance Decrease effective arterial elastance
To increase arterial pressures	Increase ventricular end-diastolic volume Increase ventricular end-systolic elastance Increase effective arterial elastance
To increase work done by ventricle on its vasculature	Increase ventricular end-diastolic volume Increase ventricular end-systolic elastance Adjust effective arterial elastance so that it equals the ventricular end-systolic elastance
To decrease ventricular oxygen requirements	Decrease ventricular end-diastolic volume Decrease ventricular end-systolic elastance Decrease effective arterial elastance
To optimize efficiency*	Increase ventricular end-diastolic volume Adjust effective arterial elastance so that it is approximately one half the ventricular end-systolic elastance

*Defined as work done on the aortic root per heart beat divided by the sum of work done plus heat dissipated during isovolumetric relaxation.

ture is the useful power. The mean power generated by the heart and delivered into the roots of the pulmonary artery and the aorta is the power that moves the blood throughout the cardiovascular system, as described earlier (see above). The oscillatory power is an unavoidable consequence of coupling a pulsatile energy source with a circuit containing stiff and resistive elements. It is dissipated as heat in the walls of the arteries as the arteries expand and recoil during the cardiac cycle. It does no useful work and hence is not considered useful power.

Just as the mean power generated by the left side of the heart and delivered into the aortic root can be calculated as the cardiac output multiplied by the mean aortic root pressure, the oscillatory power generated by the left ventricle and delivered distally can be calculated as the difference between the total power generated (the cardiac output multiplied by the left ventricular end-systolic pressure [LVESP]) and the mean power. A similar calculation can be used for the right side of the heart.

In a well-conditioned normal person, one third of the total power generated and transmitted by the right ventricle into the pulmonary artery is in the form of oscillatory power; two thirds is in the form of mean power. (The right ventricular end-systolic pressure [RVESP] is on the order of 22 mm Hg; the mean pressure in the pulmonary artery is on the order of 15 mm Hg.) This level of efficiency (defined, in this case, as mean power divided by total power) is good, compared with that of most mechanical systems. (There are many definitions of efficiency [see Table 5].) Because the load faced by the right ventricle is usually minimal, an efficiency of two thirds is more than adequate to allow the ventricle to move the blood through the pulmonary vasculature and into the left side of the heart during diastole.

On the left side of the circulation in a normal person, the efficiency is extraordinarily good. Only 10% of the power transferred into the aortic root of a young individual is in the form of oscillatory power; 90% is in the form of mean power. (The LVESP is on

the order of 100 mm Hg; the mean pressure in the aortic root is on the order of 90 mm Hg.) The load imposed on the left ventricle is substantial, but the strength of the ventricle and its excellent matching with its vasculature allow it to carry out its functions easily and enable it to do far more than meet basal needs at times (as during exercise).

DISTRIBUTION AND FLOW OF BLOOD WITHIN AND THROUGH COMPONENTS OF CARDIOVASCULAR SYSTEM

Working on the assumption that the ventricles are capable of generating and transferring some mean power into the pulmonary and systemic arterial vasculatures, one can deduce how the blood volume is distributed throughout the vasculature and can determine the blood flow to the various parts of the vasculature. To make these deductions and determinations, however, one must understand the engineering concepts of unstressed volume, elastance, and resistance.

The unstressed volume of a hollow structure is the volume within the structure that is just large enough to generate a positive pressure (in reference to the atmosphere). The unstressed volume of the systemic venules and small veins is on the order of 1,000 ml; the unstressed volume of the right atrium during most of its cycle is probably on the order of 50 ml; the unstressed volume of the right ventricle at the end of diastole is probably on the order of 30 ml; the unstressed volume of the right ventricle at the end of systole is probably on the order of 5 ml; the unstressed volume of the left atrium is probably on the order of 30 ml; the unstressed volume of the left ventricle at the end of diastole is on the order of 30 ml; and the unstressed volume of the left ventricle at the end of systole is on the order of 5 ml. Whereas a quite large volume of blood is necessary to produce energy in the venules and the small veins, a quite small volume is adequate in the normal left ventricle at end-systole. The unstressed volumes in the other parts of the cardiovascular system fall between these two extremes.

The deformation of a hollow structure with changes in volume can be described in terms of compliance, capacitance, distensibility, elasticity, stiffness, or, to use the engineering term, elastance. All of these terms refer to the same mechanical characteristic of the structure, though some of them refer to changes in volume divided by changes in pressure, whereas stiffness and elastance refer to changes in pressure divided by changes in volume. A large elastance denotes a stiff structure; a small elastance, a compliant structure. Arteries have a large elastance; veins, a small elastance. The ventricles have a large elastance during systole and a small elastance during diastole.

The elastances of hollow structures (e.g., blood vessels) are usually thought of in terms of changes in pressure (referenced to the atmosphere) divided by changes in volume. The typical unit for the cardiovascular system would be mm Hg/ml. The pressure measured will be the pressure generated by the interaction of the energy inside the structure with the components of the structure itself and the components of the tissues surrounding the structure out to the body surface.

In mathematical terms, the elastance of a chamber with a given volume and pressure is the slope of the line that is drawn tangentially to the pressure-volume relation in the chamber around that point. In terms of the calculus, it is the first derivative with respect to volume of the pressure-volume relation. If the pressure-volume relation in the chamber is a straight line, the elastance is equivalent to the difference between the pressures at any two points on the line divided by the difference between the volumes associated with those two pressures.

Traditionally, in plotting the pressure-volume relation, physiologists, engineers, and cardiovascular physiologists have preferred to assign volume to the x-axis as the independent variable and to assign pressure to the y-axis as the dependent variable. Pulmonary physiologists, however, have generally preferred to reverse this assignment. Neither way is right or wrong: the assignment of variables to axes is arbitrary. Nevertheless, for the purposes of consistency and clarity, one must make a decision about how these concepts are to be represented. Accordingly, in the ensuing discussion, we will treat volume as the independent variable and, for the most part, will address stiffness or elastance rather than compliance, distensibility, or elasticity.

Many factors influence the elastances of the different parts of the cardiovascular system—activation of receptors in the walls of the vessels for adrenergic agonists, angiotensin, and vasopressin; the thickness of the walls; the amount of collagen in the walls versus the amount of elastin or scar; stretching of the walls; calcification of the walls (as in diabetes); compression of the vessels by surrounding tissues; linking of actin and myosin in contracted muscle in the walls; viscoelasticity of the walls; and ischemia.

The resistance of a conduit in a dynamic system refers to the hindrance to flow (as opposed to the elastance of the conduit, which refers to the hindrance to changes in shape). The resistance offered by a vessel in the cardiovascular system depends on its cross-sectional area, its length, and the viscoelasticity of the blood (which, in turn, depends on the temperature of the blood, the hematocrit, the fibrinogen concentration, and the velocity of the blood within the vessel).

On the arterial side of the systemic circulation, the great majority of the resistance present in a normal person with no obstructive arterial disease comes from the arterioles. The total cross-sectional area of the arterioles is smaller than that of the arteries. In contrast, on the venous side of the circulation, the great majority of the resistance comes from the great veins—namely, the superior and inferior vena cavae, the hepatic veins, and the pulmonary veins. The total cross-sectional area of these vessels is smaller than that of the venules and the small veins. In the pulmonary circulation, the majority of the resistance to flow comes from the microvasculature of the lungs, and the majority of the resistance to drainage of blood from the lungs comes from the pulmonary veins.

The resistance in the systemic arteries, the large systemic veins, the pulmonary microvasculature, and the pulmonary veins depends on a number of factors, many of which are the same as those that affect the elastance of the arteries. These factors include responses to adrenergic agonists, angiotensin, vasopressin, thromboxane, endothelin, and nitric oxide; external compression, as in a compartment syndrome; and mechanical blockage, as in embolism.

On the basis of these concepts, one can begin to consider the distribution of blood within the various parts of the cardiovascular system and the variation in flow to different organs under different conditions. A good initial example is the distribution of blood between the venous side of the systemic circulation and the right atrium and ventricle during diastole. The portion of the blood contained within the venules and the small veins that exceeds the unstressed volume of these vessels interacts with the elastance to create a pressure. This pressure drives the venous blood through the resistance posed by the hepatic veins, the inferior vena cava, and the superior vena cava and into the right atrium and right ventricle during diastole. If both the resistance of the large veins and the elastance of the right atrium and ventricle are low during diastole, a large amount of blood will end up in the

heart at this point. If the pressure in the venules and the small veins is low (as, for example, in hypovolemic shock), it will not be strong enough to drive the blood centrally. If the large veins are compressed and acquire a high resistance (as typically happens to the inferior vena cava and the hepatic veins in the abdominal compartment syndrome), filling of the right side of the heart will be slowed. If the right side of the heart is stiff during diastole (as, for example, in a patient with a pericardial tamponade or an ischemic right ventricle or even a patient on high levels of positive-pressure ventilation), its capacity for accepting blood from the venules and small veins will be limited.

Similar reasoning can be applied to the filling of the coronary vasculature during diastole. The volume of blood in the aortic root over and above the unstressed volume interacts with the elastance to create a pressure in the root. This pressure drives the blood through the coronary vasculature and into the coronary sinus. If there is minimal resistance in the ostia of the coronary arteries, if the thickness of the ventricular wall through which the arteries pass is not excessive, and if the elastance of the coronary sinus and right atrium is low, a large amount of blood will flow through the vasculature during diastole. If the ostia of the arteries are obstructed or if the arterial resistance is high because of ventricular hypertrophy, blood flow will be slow and there will not be adequate time for perfusion of the myocardium. In addition, there will be insufficient time for myocardial perfusion if the right atrium is stiff during diastole (as in the case of overdistention, external compression, or ischemia).

In the case of organs that are perfused evenly throughout the cardiac cycle (i.e., all of the noncardiac organs), blood flow depends on the difference between the pressures on either side of the organ (the MAP minus the pressure in the veins draining the organ) divided by the resistance of the arterioles in the organ. A large pressure differential creates a large flow, as does a low resistance.

Under ordinary, resting circumstances, a minimal pressure differential is adequate for perfusion of all of the noncardiac organs, provided that their arterial inflow is unobstructed. All of these organs, with the exception of the brain and the spinal cord, have at least some chronic constriction of their arterioles. All of them, again with the exception of the brain and the spinal cord, will be protected if the MAP falls for some reason. If the pressure falls, the arterioles will dilate and the resistance to steady-state flow will decrease. Flow will thus be maintained. The brain and the spinal cord will be protected because the cardiovascular system is designed to maintain normal perfusion of the CNS. The baroreceptors for the cardiovascular system are not placed in the origins of the internal carotid arteries for no reason.

If an organ is supplied by an obstructed artery (as in atherosclerosis), it becomes vulnerable. Chronic preexisting ischemia leads to chronic arteriolar dilation. The arterioles in the organ thus lose their option of dilating in the face of hypotension. The arteries at particular risk for this adverse development are those supplying the heart, the brain, the kidneys, the viscera, and the lower extremities.

In the case of organs confined within a rigid structure or a capsule (e.g., the brain, the kidneys, the liver, the muscle in a patient with compartment syndrome, or the gut in a patient with abdominal compartment syndrome), swelling will increase the resistance of the microvasculature (through compression of the vessels) and will raise the pressures in the veins draining the organs (also through compression). This combination—a high resistance with a low perfusion pressure as a consequence of a high venous pressure—is particularly ominous: it may lead to obliteration of all flow into the swollen space.

GENERATION OF ENERGY BY VENTRICLES AND TRANSFER OF ENERGY INTO VASCULATURE

To describe the energy-producing capabilities of the heart, the modern models start by considering the unstressed volumes and elastances of the chambers of the heart throughout the cardiac cycle. In the case of a ventricle, the unstressed volume is the volume of blood that would be left behind in the chamber at any given time if the ventricle could empty itself against no hindrance. Large unstressed volumes and small elastances describe a chamber that will fill well during diastole; small unstressed volumes and large elastances during systole describe a chamber with a good capacity for generating energy.

The elastances of the ventricles depend on many of the same factors that determine the elastances of the rest of the cardiovascular system, such as myocardial wall thickness, scar tissue, and ischemia. They also depend, however, on the influx of calcium into the myocytes and the linking of actin and myosin within the cells. The greater the concentration of ionized calcium in the cytosol during systole, the greater the linking and the greater the systolic elastance. Factors increasing systolic ionized calcium concentrations include stimulation of beta₁ receptors in the myocardium, inhibition of the sodium-potassium adenosine triphosphatase (ATPase) in the cell membranes (as with digitalis compounds), inhibition of phosphodiesterase within the cells (as with milrinone), and elevation of the extracellular calcium concentration (as with administration of calcium chloride or gluconate). The influx of calcium into a cardiac myocyte during systole requires no energy: the calcium easily goes down its electrochemical gradient, traveling from the outside to the inside of the cell. During diastole, however, it is necessary to pump the calcium out of the cell, and this step does require energy. Thus, any process or drug that increases ventricular end-systolic elastance will also increase ventricular oxygen requirements.

The elastances of a ventricle during a cardiac cycle can be mathematically described through analysis of ventricular pressure-volume loops.^{1,3} This is done by simultaneously measuring ventricular volume (with implanted microsonographic crystals, conductance catheter techniques, contrast ventriculography, or echocardiography) and intraventricular pressure. These measurements are then repeated while either the end-diastolic volumes or the hindrances against which the ventricle contracts are altered, thereby yielding a “family” of pressure-volume relations. From this family, the elastances of the ventricle during an entire cardiac cycle can be calculated.

How ventricular elastance varies during a single cardiac cycle can be illustrated by considering typical values for the left ventricle in a normal 60 kg woman in a resting state [see Figure 5]. At the end of diastole (or the beginning of systole), the elastance is 0.2 mm Hg/ml. When systole begins, the elastance increases rapidly (within about 50 milliseconds) to 1.0 mm Hg/ml. At this point in the cardiac cycle, the pressure inside the ventricle is high enough to open the aortic valve. The elastance continues to increase as the ventricle pushes its blood into the aortic root, reaching its maximum at the end of systole. Typically, the end-systolic elastance is some 10 times greater than the end-diastolic elastance, or about 2.0 mm Hg/ml. The elastance rapidly decreases during isovolumic relaxation until the beginning of diastolic filling of the ventricle; it then gradually and slightly increases until the end of diastole, returning to the initial value of 0.2 mm Hg/ml.

It is worthwhile to compare these variations in elastance with those seen in a person with maximal adrenergic stimulation of the heart and in a person with profound beta blockade [see Figure 5]. In the former, the end-systolic elastance is double the normal

value, or 4.0 mm Hg/ml, and the ventricle reaches its maximal elastance more quickly. In the latter, the end-systolic elastance is half the normal value, or 1.0 mm Hg/ml, and the ventricle reaches its maximal elastance more slowly.

Thus, the end-systolic elastance can serve as a reasonably complete and simple measure of ventricular systolic function.^{3,80} It can be precisely measured, at least in the catheterization laboratory; it has been shown to be independent of end-diastolic volumes and the hindrance imposed on the ventricle by the vasculature in experimental animals; and it is ideally suited for dealing with one of the fundamental problems in managing critically ill patients—namely, the problem of predicting how a ventricle with a given capacity for energy generation will interact with a vasculature with a given hindrance [see Ventricular-Arterial Coupling, below].

The hindrance that the contracting ventricle encounters during systole is probably best described as the impedance of the vasculature.^{7,81} It is a quantifiable descriptor and can be determined by making measurements of flow and pressure in the aortic root in the cardiac catheterization laboratory. Vascular impedance is a concept that is ideally suited for dealing with the problem of ventricular-arterial coupling. It can, with reservations, be expressed as a single number. On the right side of the heart, it can, again with reservations, be approximated from values obtained from measurements made with a Swan-Ganz catheter; on the left side of the heart, it can, with further reservations, be approximated by using the stroke volume taken from use of the catheter and estimating the aortic root end-systolic pressure.

The impedance (hindrance) faced by the ventricle during emptying has three components, which then interact with one another in various ways, depending on the heart rate. (We use the left ventricle as an example here, but the same concepts apply to the right ventricle.) The first component is the elastance (stiffness) of the named arteries, including the aorta, which hinders the accommodation of blood in the arteries as the ventricle empties during systole. The second component is the resistance to steady-state flow offered by the arterioles throughout the body. The third component is the resistance to flow offered by the large veins as they enter the chest, coupled with the stiffness of the right atrium and ventricle as they accept blood returning from the body.

At first glance, the way in which these components relate to impedance appears simple. The stiffer the arteries, the higher the impedance; the greater the arteriolar constriction, the higher the impedance; and the greater the hindrance to the filling of the contralateral heart, the higher the impedance. The concept becomes more complex, however, when one tries to understand how these components interact with one another, as they do when connected to a pulsatile energy source (e.g., a contracting ventricle). One way of exploring this interaction is to consider the energy wave that is propagated throughout the vasculature when the ventricle pumps blood into the aortic root.

When the left ventricle contracts, it pushes the blood it contains into a standing column of blood in the aortic root. Initially, this column of blood remains stagnant; however, the energy impulse imparted to it by the inrush of ventricular blood generates an energy wave that propagates throughout the arteries until it reaches the arterioles, which are situated throughout the body at differing distances from the heart. Part of the propagated wave bounces off the arterioles, generating reflected waves that return to the aortic root and the heart.^{1,82,83}

The amplitude of the reflected waves that return to the root of the aorta depends on the degree to which the arterioles are constricted: the greater the constriction, the larger the amplitude. Some of the reflected waves return during systole, some during

diastole. The timing, as one might expect, depends to a large extent on the spatial distribution of the arterioles: waves from nearby arterioles return sooner, and waves from distant arterioles return later. The timing also depends on the propagation velocity of the waves, which depends on the elastance of the walls of the arteries through which the waves pass: compliant arterial walls generate waves with a slow (desirable) velocity, and stiff walls generate waves with a rapid velocity. Finally, the timing depends on the viscoelastic properties of the conducting medium (i.e., the blood), but aside from limiting blood transfusions and keeping the patient warm, there is little that one can do to influence these properties. There is, however, a great deal that one can do to influence arterial elastance (see below).

The velocity of the propagating energy wave can be measured quite simply in humans by means of Doppler technology. The velocities in the upper part of the body are slower than those in the lower part because the arterial walls in the upper extremities are thinner and more compliant than those in the lower extremities. The velocities are faster if arterial wall receptors for norepinephrine, vasopressin, or angiotensin II are activated; if the arteries are stretched; or if the walls are calcified (as in diabetes).

The pulse velocities on the left side of the heart are, on average, about 4 m/sec in young children and 18 m/sec in octogenarians.⁸⁴⁻⁸⁶ (The increased velocities in older persons are a result of stiffened arterial walls, caused by the replacement of elastin in the walls with collagen as part of the aging process.)

These propagation velocities are much faster than the velocities with which the blood moves through the arteries. Blood flow velocity is fairly constant throughout all of the arteries in the body and does not differ substantially between human beings of different sizes or animals of different species. The velocities at which blood flows during a cardiac cycle typically range from 0 to 50 cm/sec, depending on many factors (e.g., the stage in the cardiac cycle and the presence of pulse wave reflections from the organ or organs that the artery supplies). In most arteries, whether the ascending aorta of a human being or the common iliac artery of a wombat, the mean blood flow velocity is approximately 15 cm/sec. This value is determined by the amount of blood flowing through a vessel per unit time and the cross-sectional area of the vessel. Unlike the propagation velocity of the energy wave, it is not affected by arterial wall elastance.

Thus, for a child, the energy wave propagation velocity (4 m/sec) is more than 25 times faster than the mean blood flow velocity, whereas for an 80-year-old, the energy wave propagation velocity (18 m/sec) is more than 100 times faster. The differences between energy wave propagation velocity and blood flow velocity indicate that although the blood is indeed moved by the energy waves generated by ventricular contraction, it has inertia. The blood does accelerate and gain speed as the energy wave moves through it, but it cannot be expected to keep up with the wave.

As a general rule, a patient is better off with compliant arteries and slow propagation velocities for the energy wave.^{1,82,83} With high velocities, the waves return too rapidly to the aortic root, arriving even before the ventricle has finished contracting; as a result, the ventricle fights itself, pumping against the very pressure wave that it generated. Another problem with high propagation velocities is that the waves die out before diastole, and thus, pressure that could have been used for perfusion of the coronary vasculature is lost. The mean aortic root pressure may even fall, compromising peripheral perfusion.

In a young, unstressed patient, the propagation velocities are slow, and the waves return during diastole. The heart benefits enormously. Because the waves arrive back at the heart after the

aortic valve has closed, the ventricle does not have to pump against its own energy impulse, and the perfusion pressure of the coronary arteries is maximized. The augmented diastolic and mean pressures maintain peripheral perfusion.

The behavior of these reflected waves has many clinical implications for treatment of the patient in shock, first, with respect to measurement and interpretation of pressures throughout the cardiovascular system [see *Sidebar Energy Propagation throughout the Arteries and Its Effect on Pressures in Those Arteries*], and second, with respect to understanding and treating some of the abnormalities underlying the shock state. (The behavior of the reflected waves has additional implications for treatment of patients with certain medical problems, such as isolated systolic hypertension, but those issues lie outside the scope of this chapter.)

With respect to understanding and treating shock, if a patient's arteries are abnormally stiff (e.g., as a result of age, calcification, distention, activation of vessel wall receptors, or external compression), the propagation velocity will be high, which means that the waves will return early, the systolic pressure at the aortic root will rise, and the diastolic pressure will fall. The elevated systolic pressure will increase ventricular oxygen requirements; the unaffected MAP will do nothing for tissue perfusion.

If the propagation velocity can be reduced, then the systolic pressure will come down, and the MAP will stay the same. This is usually a desirable result for a patient in shock, in that myocardial oxygen requirements will decrease while perfusion pressures are maintained. Accordingly, in the treatment of shock, there is often a clinical benefit to be gained from interventions aimed at reducing arterial stiffness.

Several options are available for decreasing arterial stiffness on the left side of the circulation, including diuresis or fluid restriction, ACE inhibition, and the use of agents that increase the production of nitric oxide near the arterial walls. The aortic counterpulsating balloon pump can be extremely effective in dealing with systemic arterial stiffness. (In fact, that is its only function.) Options for treating stiff arteries on the right side of the circulation include adjustment of the ventilator, diuresis to decrease the vascular volumes, and, in extreme cases, operative decompression of the pulmonary vasculature in patients with an abdominal compartment syndrome. (The elevated diaphragm can compress the pulmonary vasculature and the left atrium.) In addition, pharmacologic interventions may provide some benefit on occasion.

As mentioned (see above), the arterial impedance facing the ventricles can be determined in the catheterization laboratory by using catheters that can precisely measure pressures and flows at the roots of the arteries. To describe this complex interplay of wave propagation and reflection with a single number, to quantify responses to interventions, and to do both of these things with numbers available in the intensive care unit, one can calculate the hindrance facing the right ventricle as the RVESP (or, equivalently, the pulmonary arterial end-systolic pressure) divided by the stroke volume.^{2,81}

The resulting value—the effective pulmonary arterial elastance—will be high if a given stroke volume creates a high systolic pressure and low if the stroke volume creates a low pressure. (It is worth mentioning that although this value is an elastance and is expressed in the units used for elastance, it reflects not only the properties of the arteries but also those of the arterioles, as well as the hindrance imposed on the right ventricle by the left side of the heart during diastolic filling. After all, the amplitude of the reflected waves depends on the arterioles and on the hindrance imposed by the left side of the heart. The value for effective elastance takes into account all of the factors that may hinder ventricular empty-

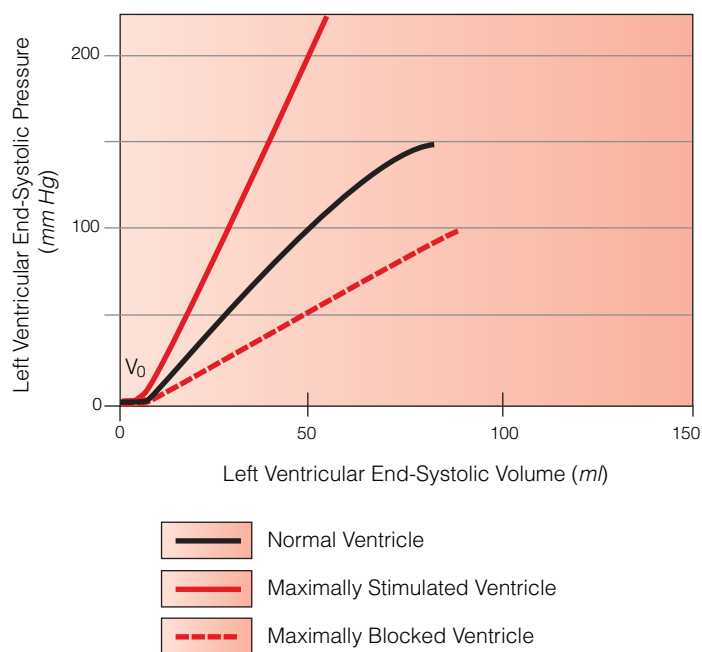


Figure 7 Shown is LVESP plotted against LVESV at end-systole, as seen in a normal ventricle, a maximally stimulated ventricle, and a maximally blocked ventricle. Once the LVESV exceeds the unstressed volume (V_0), the LVESP increases in a fairly linear way. The energy-generating potential of the three ventricles can be taken as the slopes of the relations: 2.0, 4.0, and 1.0 mm Hg/ml, respectively [see Figure 5].

ing.) A normal value for the effective elastance of the pulmonary artery in a 60 kg person is 0.2 mm Hg/ml. In severe pulmonary disease (as is seen with ARDS), the effective elastance can increase by as much as a factor of 8. The hindrance faced by the ventricle can be enormous.

It is difficult to measure the effective aortic root elastance in the ICU, but accurate measurements can be made in the catheterization laboratory.⁷ The problem is estimating the aortic root end-systolic pressure. In the ICU, however, one will know that the pressure in the aortic root at end-systole (and the LVESP) must be higher than the mean pressure. One can make an educated guess as to how much higher it will be, based on the patient's age, the presence or absence of underlying disease processes (e.g., diabetes), and whether the patient is receiving any agents (e.g., an alpha agonist) that would be expected to increase the elastance of the arteries in the systemic circulation. Once one has a reasonable estimate of the aortic root end-systolic pressure, one can use the stroke volume, obtained from measurements made by the Swan-Ganz catheter, to calculate the effective elastance of the aortic root. A normal value is 1.0 mm Hg/ml.² In a patient who is experiencing a severe hypertensive crisis or a patient who has been given pressors (perhaps without full consideration of the consequences), it might increase by a factor of 4. With inflammatory states, it might be as low as 0.5 mm Hg/ml.

VENTRICULAR-ARTERIAL COUPLING

In addressing the problem of ventricular-arterial coupling, it is useful to start by considering the pressure-volume relations in a ventricle and in the root of the artery receiving the energy from the ventricle. We will use the left side of the circulation for illustration, though we could just as well use the right side, which in some surgical patients is the critical side (and which is easier to analyze by

using data from a Swan-Ganz catheter). There is more information in the literature about the left side of the circulation, however, and more options are available for intervention on that side. Regardless of which side of the heart is considered, the concepts are the same.

The left ventricle is stiffest at end-systole.³ If the intraventricular pressure is plotted as a function of the intraventricular volume at end-systole, a fairly straight line will be generated [see Figure 7]. The slope of this line is the end-systolic elastance, which, as noted (see above), can serve as a descriptor for the energy-producing capabilities of the ventricle.

The x-intercept of the relation is not 0 but a value slightly greater than 0. This is an example of an unstressed volume. A typical value for the end-systolic unstressed volume in a 60 kg person is quite low, on the order of 6 ml. In patients with severe congestive heart failure, the unstressed volume can be as high as 60 ml, as a manifestation of a globally flabby heart, but in most patients, it can be assumed to be close to 0 ml.

The slope of the line can then be approximated as the LVESP divided by the LVESV.⁸⁰ Other points on the line can also be used to make this calculation, but they will not be known unless one is in the catheterization laboratory and can make sophisticated measurements of both pressure and volume as end-diastolic volumes or vascular impedances are altered. Accordingly, the aforementioned approximation is the most clinically useful calculation. The plot will look quite different in a person with maximal beta-adrenergic stimulation or a person with maximal beta blockade [see Figure 7].

The pressure-volume relation for the aortic root can be plotted on a graph in a similar fashion [see Figure 8]. In this case, the LVESV is still plotted on the x-axis, whereas the end-systolic pressure in the aortic root is plotted on the y-axis. This relation depends on the LVEDV. The example of a normal, resting 60 kg

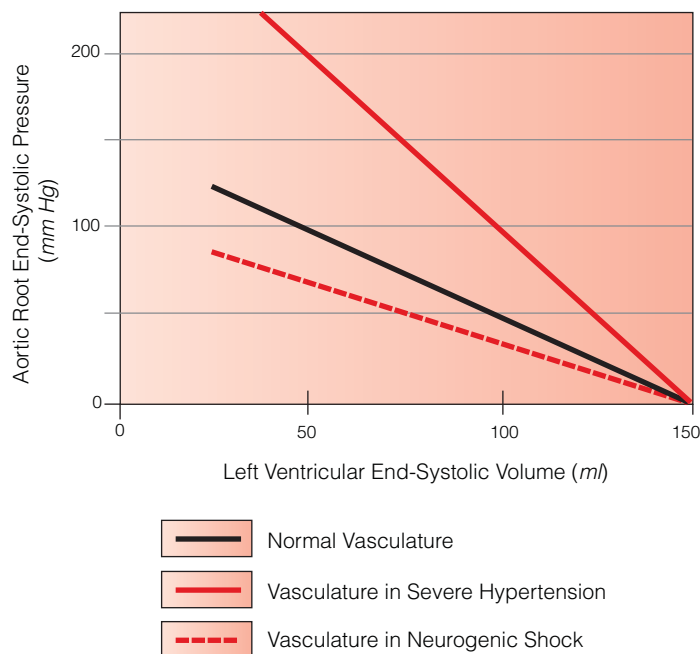


Figure 8 Shown is aortic root end-systolic pressure plotted against LVESV, as seen in a normal vasculature, the vasculature of a patient with severe hypertension, and the vasculature of a patient in neurogenic shock. The LVEDV is assumed to be 150 ml. The magnitudes of the slopes of the relations for the three vasculatures (1.0, 2.0, and 0.75 mm Hg/ml, respectively) can be taken to represent the hindrances facing the ventricles.

person with an LVEDV of 150 ml will illustrate this point. If the LVESV is 150 ml, the stroke volume will be 0 ml; if the stroke volume is 0 ml, the heart will generate no energy for filling the aortic root, and the end-systolic aortic root pressure will be 0 mm Hg. If, however, the LVESV is 50 ml (a normal value) and the LVEDV is held constant at 150 ml, the stroke volume will be 100 ml; a stroke volume of 100 ml in a normal, resting person will generate an aortic root end-systolic pressure of 100 mm Hg.

If points representing these two scenarios are plotted on the graph, a line can be drawn between them to represent the relation between the end-systolic pressure in the aortic root and the LVESV. The magnitude of the slope of this line is calculated by dividing the aortic root end-systolic pressure by the stroke volume. In this case, the calculation yields a value of 1.0 mm Hg/ml. This value can be taken as the effective elastance of the aortic root at end-systole, which, in turn, can be taken as a single-number representation of the hindrance (impedance) facing the left ventricle. Different values will be obtained in a patient with severe hypertension or a patient in neurogenic or warm septic shock [see Figure 8].

To deal with the problem of ventricular-arterial coupling, one then plots the two pressure-volume relations (for the left ventricle and the aortic root) at end-systole on the same graph [see Figure 9]. The LVESP must equal the end-systolic pressure in the aortic root. (In fact, the pressures throughout most of systole, with the exception of isovolumic contraction, are about the same.) The only point on the graph where the two pressures are equal is the point where the two lines intersect. This point defines the specific end-systolic volume and pressure for a patient with a specific unstressed ventricular end-systolic volume, a specific ventricular end-systolic elastance, a specific end-diastolic volume, and a specific effective aor-

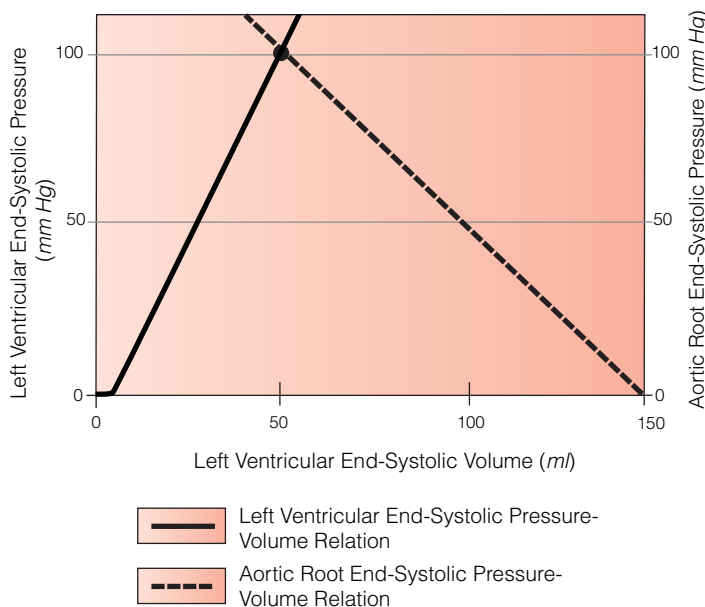


Figure 9 Illustrated is the superposition of the normal pressure-volume relation for the left ventricle at end-systole [see Figure 7] onto the normal pressure-volume relation for the aortic root at end-systole [see Figure 8]. The two pressures must be the same. Thus, in this case, the LVESV must be 50 ml, and both the LVESP and the aortic root end-systolic pressure must be 100 mm Hg (point C in Figures 5 and 10). That is, the end-systolic point is determined by the end-systolic unstressed volume, the ventricular end-systolic elastance, the ventricular end-diastolic volume, and the effective arterial elastance.

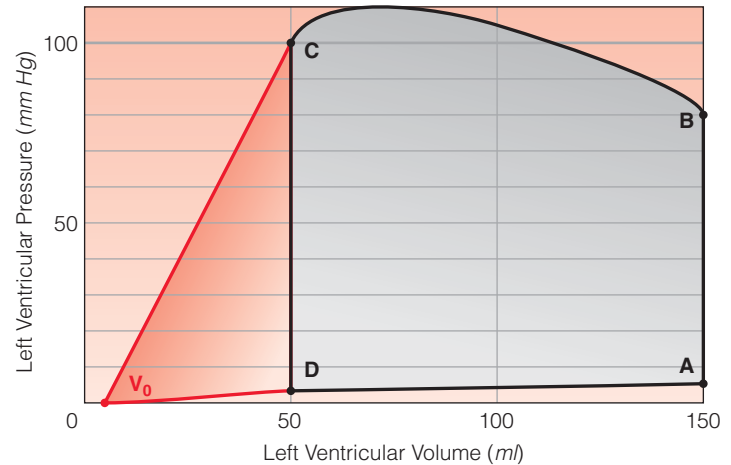


Figure 10 Illustrated is the pressure-volume relation for the left ventricle over an entire cardiac cycle. The work done on the left ventricle during diastole (or, equivalently, the energy added to the ventricle during systole) is the area under the curve DA. The energy added to the aortic root by virtue of ventricular contraction is the area contained within the loop ABCD. The total energy added to the aortic root during a single heartbeat is the sum of these two areas. The heat dissipated in the ventricular wall during isovolumic relaxation is equal to the area contained within the triangle CV₀D.

tic elastance. That is, this graphic analysis allows one to predict how a particular ventricle with particular characteristics will interact with an arterial system with a particular impedance.¹⁻³

PRESSURE-VOLUME LOOPS AND THERMODYNAMICS OF VENTRICULAR CONTRACTION

The next step is to draw a pressure-volume loop for the ventricle, working on the assumption that the unstressed end-systolic volume, the ventricular end-systolic elastance, the end-diastolic volume, and the effective aortic elastance are known. Typical values would be 6 ml, 2 mm Hg/ml, 150 ml, and 1 mm Hg/ml, respectively. From the analysis previously described (see above), it follows that the end-systolic volume will be 50 ml and the end-systolic pressure will be 100 mm Hg [see Figure 10].

At the beginning of systole (point A), the ventricle has a volume of 150 ml and an end-diastolic pressure of 8 mm Hg (if the patient is breathing spontaneously). The ventricle then contracts until the pressure in the chamber exceeds the pressure in the aortic root and the aortic valve opens (point B).

As the blood contained in the ventricle is pushed into the aortic root, ventricular volume decreases until end-systole (point C) is reached. It should be kept in mind that the pressure inside the ventricle at any time during ventricular emptying is determined by the balance between the volume and the stiffness of the chamber at that time. The pressure increases from the beginning of ventricular emptying to, roughly, the midportion of systole. That is, the effect of the rapidly increasing stiffness of the ventricle [see Figure 5] overcomes the effect of the decreasing volume as the ventricle empties. From the midportion of systole to end-systole, the effect of the decreasing volume starts to dominate as it overcomes the still-increasing stiffness, and the pressure gradually falls.

No work is done on the aortic root during isovolumic contraction, from point A to point B. (The volume of the ventricle is unchanged.) Work is, however, done on the aortic root from the opening of the aortic valve to end-systole, from point B to point C. (In fact, this is the only time during the cardiac cycle when work is being done on the aortic root.)

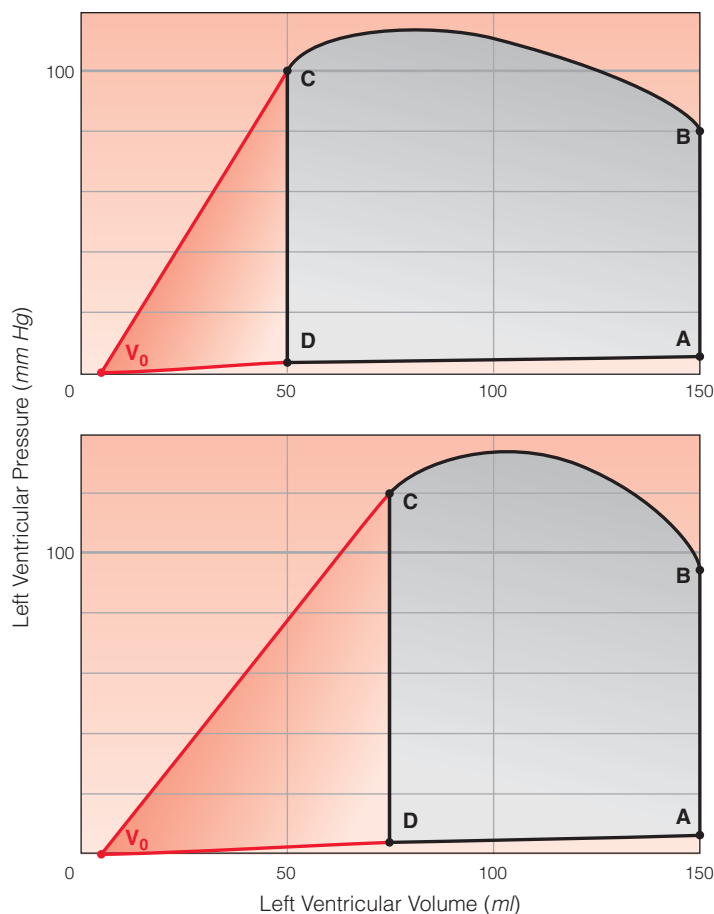


Figure 11 Shown are two pressure-volume loops generated by different ratios of effective aortic elastance to left ventricular end-systolic elastance. If the aortic root elastance is approximately half the ventricular end-systolic elastance (a), as in a normal resting subject, the ventricle will produce its work with optimal efficiency. If the aortic elastance equals the ventricular elastance (b), as when the same subject is given a vasoconstrictor, the pressure will increase and the ventricle will produce slightly more work, but substantially more energy will be wasted in the form of heat dissipation during isovolumic relaxation. If the vasoconstrictor is given to produce a higher pressure that is even higher, the work will begin to fall off, and the energy wasted as heat dissipated in the ventricular wall will increase even more.

The actin and myosin myofilaments then suddenly disengage at end-systole (point C), and the ventricle switches from its maximally contracted state to an increasingly compliant one. The result is another isovolumic phase as the ventricular pressure drops to its lowest value during the cardiac cycle at the beginning of diastolic filling (point D).

Although no work is done during isovolumic relaxation (the phase involves no change in volume), the ventricle loses energy: it started out, at end-systole (point C), with a high pressure and a set volume, but it ended up, at the beginning of diastole (point D), with a low pressure and the same volume. This energy was not used for work, did not generate any appreciable sound, and did not produce any kinetic energy; therefore, it must have been lost in the form of heat, as the actin and myosin filaments lost the chemical energy that was binding them together.

Finally, the chamber fills again and returns to its initial state, from point D to point A. During this time, work is being done on the ventricle by the energy produced from contraction of the left

atrium and by the residual energy pushed into the left side of the heart from contraction of the right ventricle.

The work done on the ventricle during diastole is represented by the area under the diastolic pressure-volume curve and the x-axis, which is approximately equal to the mean diastolic pressure multiplied by the stroke volume. The work done on the aortic root by the contraction of the ventricle is represented by the area contained within the curve, or the difference between the end-systolic and mean diastolic pressures multiplied by the stroke volume. The total work done on the aortic root with each cardiac cycle is represented by the entire area under the curve, down to the x-axis. It can be approximated as the end-systolic pressure multiplied by the stroke volume.

Also illustrated is the wasted energy associated with the loop (i.e., the energy lost in the form of heat dissipated in the ventricular wall during isovolumic relaxation). This variable is represented by the area contained within a triangle whose apices are the points V₀, D, and C (i.e., the unstressed volume, the beginning of diastolic filling, and end-systole).

The major problem in managing the patient in shock is to balance cardiac energy production against edema formation and myocardial oxygen requirements. The total amount of energy transmitted into the aortic root per minute is the total work done on the root per heartbeat multiplied by the heart rate. The total amount of heat dissipated in the ventricular wall during isovolumic relaxation is the area of the aforementioned triangle multiplied by the heart rate. The left-side oxygen requirements for the myocardium are directly proportional to the sum of the total amount of power produced and the total amount of heat dissipated in the ventricular wall. Thus, in considering cardiac energy production in the context of edema formation and myocardial oxygen requirements, the pressure-volume loop, along with the heart rate, tells one everything that one needs to know.

Construction of the pressure-volume loop for a ventricle requires knowledge of the ventricular end-systolic unstressed volume, the ventricular end-systolic elastance, the end-diastolic volume, and the effective arterial elastance. Even if exact values for these variables are not available, one will generally have some feeling for them, both on clinical grounds and from measurements made with invasive monitoring. One can then predict how these variables will affect the loop [see Figures 7, 8, 9, 10, and 11], as well as envision how intervention will affect the loop, for better or worse [see Figure 11].

The analysis can be done either graphically [see Figure 11] or mathematically [see Table 5]. In either case, it will allow one to predict how an intervention will affect the abnormality (given the uncertainty of some of the measurements that will be available) and the costs of correcting the abnormality by a particular intervention. Once the analysis is complete, the remaining task is to decide what the goals of resuscitation should be and how they should be achieved.

Goals for Cardiovascular Resuscitation in Treatment of Shock

Efforts have been made to avoid using any invasive cardiovascular measurements in resuscitation from severe shock (e.g., by using gastric mucosal pH as an end point for resuscitation), but to date, such efforts have not proved helpful outside carefully controlled research environments. There is wide agreement that invasive monitoring is still needed in the treatment of severe shock; however, there is no consensus on what to do with the values obtained from monitoring.

Table 6 Effects of Position and Strenuous Exercise on Cardiovascular Volumes and Pressures in a Young, Well-Conditioned 60 kg Woman

Variables	Supine (Resting)	Upright (Resting)	Upright (Exercising)
Lower-body venular volume (ml)	1,920	> 1,920	< 1,920
Lower-body venular pressure (mm Hg)	20	> 20	< 20
Upper-body venular volume (ml)	960	< 960	> 960
Upper-body venular pressure (mm Hg)	10	< 10	> 10
Right ventricular end-diastolic volume (ml)	150	133	145
Right ventricular end-diastolic pressure (mm Hg)	5	5	5
Right ventricular and pulmonary arterial end-systolic pressure (mm Hg)	22.5	22.5	35
Mean pulmonary arterial pressure (mm Hg)	15	15	20
Left ventricular end-diastolic volume (ml)	150	133	145
Left ventricular end-diastolic pressure (mm Hg)	8	8	8
Left ventricular and aortic root end-systolic pressure (mm Hg)	100	100	145
Mean aortic pressure (mm Hg)	90	90	110

One approach is to try to find a single parameter that can serve as the goal of resuscitation. The best candidate parameter is probably the $S_{mv}O_2$, measured with a pulmonary arterial catheter. This value can be quite helpful in minute-to-minute management during resuscitation from hemorrhagic shock. It is considerably less helpful, however, for resuscitation of patients in inflammatory shock, who often have quite high $S_{mv}O_2$ values, partly because of peripheral shunting through the cutaneous vasculature and partly because of functional shunting by cells that cannot metabolize the oxygen presented to them. In the setting of inflammatory shock, a high $S_{mv}O_2$ may even indicate a severe metabolic derangement rather than resolution of shock.

Another approach is to attempt to determine whether the patient's oxygen consumption (measured with a pulmonary arterial catheter and based in part on measurements of cardiac output) depends on oxygen delivery (the product of cardiac output, hemoglobin concentration, and arterial oxygen saturation). Unquestionably, at very low levels of oxygen delivery, oxygen consumption must decrease. At excessively high levels, however, oxygen consumption may continue to rise if oxygen delivery is increased by the administration of inotropes. These agents usually have beta-adrenergic effects and can increase peripheral oxygen metabolism; they also increase myocardial oxygen requirements. Thus, the act of increasing delivery can increase overall consumption.

Yet another approach is to maintain all patients at very high levels of oxygen delivery without making any attempt to ascertain whether there is a correlation between delivery and peripheral consumption. Two randomized trials evaluated this approach; neither found any evidence of benefit.^{87,88}

Our approach is to start, as any clinician would, by attempting to resolve the clinical abnormalities observed without subjecting the patient to invasive monitoring. If this attempt is unsuccessful, we insert monitoring catheters and use the information obtained from them to try to achieve reasonable ventricular power production with acceptable efficiency while minimizing the formation of edema. This approach is supported by a compelling study that underscored the value of taking a thermodynamic approach to resuscitation and indicated that the goal for resuscitation of the typical shock patient need be little more than a reasonable blood pressure and a reasonable cardiac output.

We do, however, set different treatment goals for different patients, depending on individual patient requirements and capabilities (see above). In general, the hearts of well-conditioned per-

sons can do more than those of poorly conditioned persons, and young hearts are more capable than old ones. Measurements of organ blood flows from the exercise physiology literature can help put this observation in perspective [see Tables 6 and 7].^{4,5,74,89-106} As

Table 7 Effects of Position and Exercise on Organ Blood Flow and Oxygen Consumption in a Young, Well-Conditioned 60 kg Woman

Variables	Supine (Resting)	Upright (Resting)	Upright (Exercising)
Whole body			
Blood flow (L/min)	6.0	5.0	22.0
Venous O ₂ saturation	76%	71.6%	11%
O ₂ consumption (ml/min)	210	210	3,180
Splanchnic viscera			
Blood flow (L/min) (% of total)	1.50 (25%)	1.25 (25%)	0.30 (1%)
Venous O ₂ saturation	77%	73%	18%
O ₂ consumption (ml/min)	50	50	40
Kidneys			
Blood flow (L/min) (% of total)	1.20 (20%)	1.00 (20%)	0.25 (1%)
Venous O ₂ saturation	91%	90%	65%
O ₂ consumption (ml/min)	12	12	12
Brain			
Blood flow (L/min) (% of total)	0.90 (15%)	0.75 (15%)	0.75 (3%)
Venous O ₂ saturation	67%	60%	59%
O ₂ consumption (ml/min)	45	45	45
Heart			
Blood flow (L/min) (% of total)	0.24 (4%)	0.20 (4%)	0.80 (4%)
Venous O ₂ saturation	46%	35%	1%
O ₂ consumption (ml/min)	20	20	130
Skeletal muscle			
Blood flow (L/min) (% of total)	1.20 (20%)	1.00 (20%)	19.5 (89%)
Venous O ₂ saturation	61%	54%	8%
O ₂ consumption (ml/min)	70	70	2,940
Skin			
Blood flow (L/min) (% of total)	0.30 (5%)	0.25 (5%)	0.30 (1%)
Venous O ₂ saturation	93%	91%	88%
O ₂ consumption (ml/min)	2	2	2
Other organs			
Blood flow (L/min) (% of total)	0.66 (11%)	0.55 (11%)	0.10 (0%)
Venous O ₂ saturation	87%	85%	31%
O ₂ consumption (ml/min)	11	11	11

an example, in strenuous exercise, cardiac output can increase by a factor of 3 to 4. Blood flow to the splanchnic viscera and the kidneys can fall to levels as low as 20% of normal, with no long-term ill effects. (The organs survive by extracting a higher percentage of the oxygen delivered to them.) During strenuous but not exhausting exercise in a warm environment, blood flow to the skin can increase from a baseline of 300 ml/min to levels as high as 6 L/min in an effort to offload heat and keep body temperature within acceptable limits. (We are not aware of any studies that have measured blood flow to the skin of patients in inflammatory shock, but we suspect that it may be as high as 3 L/min for a 60 kg person.)

To achieve the treatment goals, we begin by establishing adequate ventricular end-diastolic volumes. An inadequate end-diastolic volume cannot be compensated for, no matter what is done with the ventricular end-systolic elastance or effective aortic elastance. Inadequate ventricular end-systolic elastances can be compensated for with volume administration, up to a point, and low arterial impedances often do not require any compensation at all—the low hindrances may represent a compensatory response aimed at optimizing the efficiency with which energy is transmitted from the ventricle into the aortic root.

Surgeons are ideally suited to managing the problems associated with inadequate ventricular end-diastolic volumes. They know how to control bleeding; their technical training allows them to gain vascular access safely; they can decompress compartments subjected to excessively high pressures; and they appreciate the adverse consequences of not promptly addressing inadequate ventricular end-diastolic volumes. No surgeon likes dealing with an anastomotic breakdown, and no surgeon enjoys having to treat an overwhelming infection.

At the same time, it is important to remember that one must be judicious when administering fluid in an attempt to ensure adequate ventricular end-diastolic volumes. There is no thermodynamic free lunch. Unnecessary administration of fluid creates edema; excessively large end-ventricular volumes increase myocardial oxygen requirements unnecessarily. If one is unsure how best to balance the competing requirements of treatment, one should employ invasive monitoring to obtain additional information.

Invasive monitoring will allow one to adjust the RVEDV and LVEDV more precisely and to proceed with the next step—namely, adjusting the effective arterial elastances so that they are appropriately matched to the ventricular end-systolic elastances. The goal is to achieve adequate production of useful power while minimizing myocardial oxygen requirements. If the effective arterial elastance is adjusted so that it equals the estimated ventricular end-systolic elastance, maximum work per heartbeat will be achieved, but a substantial amount of heat will be dissipated in the ventricular wall during isovolumic relaxation [see *Figure 11 and Table 5*]. If the effective aortic elastance is adjusted so that it is approximately half the ventricular end-systolic elastance, less work will be done, but substantially less heat will be dissipated; thus, useful power will be produced much more efficiently. If the effective aortic elastance is allowed to exceed the ventricular end-systolic elastance, the pressure will increase, but the work produced will fall off and the myocardial oxygen requirements will increase—a situation that is rarely good for the patient.

For cases of hypovolemic and inflammatory shock, we start with the effective pulmonary arterial elastance. In these settings, this value frequently is excessively high: it is not unusual to see pulmonary arterial elastances that exceed the maximal right ventricular end-systolic elastance, which typically is on the order of 0.8 mm Hg/ml. There is no benefit to such a mismatch. Accordingly, we try to decrease the pulmonary arterial elastance through adjustment of

the ventilator, diuresis (if feasible), and, possibly, surgical decompression of the abdomen. We do not try to work on the effective aortic root elastance at this juncture; we do that later, if at all.

For cases of cardiogenic shock, we generally start with the effective aortic root elastance instead. In this setting, this value frequently is greater than the left ventricular end-systolic elastance. If the myocardium is badly compromised, the ventricular end-systolic elastance may be as low as 1.0 mm Hg/ml. If the effective aortic root elastance exceeds this value, the heart will be working inefficiently. Accordingly, we try to decrease the effective aortic elastance if possible, either with diuretics or with vasodilators. In some cases, this cannot be done. For example, a high systemic arterial pressure may be required for perfusion of the myocardium, especially in a patient who has coronary disease or a hypertrophied ventricle. It is important to remember, however, that a high aortic elastance comes at a price. One can always maintain a high arterial pressure, either by not trying to reduce it or by giving vasoconstrictors, but if the high pressure results in excessive myocardial oxygen requirements, one may be doing more harm than good.

After dealing with the end-diastolic volumes and the effective arterial elastances on both sides of the circulation, we turn to the ventricular end-systolic elastances. We find inotrope therapy to be advantageous at this stage. Increasing the ventricular end-systolic elastances will increase the stroke volume, the blood pressure, and the work done per heartbeat by the ventricle on the vasculature. If the inotrope increases the heart rate, it will increase the power generated by the ventricle (by increasing the cardiac output—the stroke volume multiplied by the heart rate).

In the case of hypovolemic and inflammatory shock, inotrope therapy usually does not have much of a downside. Most patients' ventricles will be able to deal with the increased oxygen requirements. In the case of cardiogenic shock, however, one might be willing to sacrifice some of the ventricular end-systolic elastance in order to reduce the elevated oxygen requirements induced by high intracellular calcium concentrations and to bring down the heart rate. The heart rate can be an extremely important consideration in this setting, for several reasons. To begin with, myocardial oxygen requirements are a linear function of the heart rate: doubling the heart rate doubles the oxygen requirements. Furthermore, increasing the heart rate may increase the impedance of the vasculature; the heart may beat so rapidly that the energy wave created by the previous ventricular contraction returns during the systole of the current contraction. In addition, a rapid heart rate may limit the time available for ventricular filling during diastole.

As a final measure, we increase the effective aortic root end-systolic elastance. It should be clear from the preceding discussion, however, that we prefer not to do this if it can be avoided. Most surgical patients have intact autonomic nervous systems and are not anesthetized. Furthermore, most surgical patients have good hearts. In the case of trauma or an emergency, any patient with a hopelessly failing heart would never have survived the injury or the initial insult imposed by the illness. In the case of elective surgery, a failing heart would usually have been noticed by the surgeon, who then would probably have attempted to modify the surgical approach to the problem or, perhaps, declined to operate on the patient in the first place. The low blood pressure in the upper extremity might be a manifestation of adjustments to a physiologic state that has complex undercurrents. It might reflect the need to offload heat to the environment; it might reflect the need to optimize the efficiency with which the heart interacts with the vasculature; or it might reflect a peculiarity of the measurement of the pressure (e.g., the pressure in the root of the aorta might be adequate even though the pressure in the arm might suggest other-

wise). One must pay attention to the blood pressure when managing a patient in shock, but not to the exclusion of other critical considerations. A balanced perspective is needed.

Vasoconstrictors will increase the blood pressure, but they may do so at the cost of reducing the amount of useful energy delivered into the arterial system if the effective arterial elastance already exceeds the ventricular end-systolic elastance. They will always increase the amount of oxygen required by the ventricle. Moreover, on the assumption that the effective aortic elastance ends up being greater than one half of the left ventricular end-systolic elastance, vasoconstrictors will always reduce the efficiency of energy production.

Conclusion

We thank those readers who have followed us thus far. We admit that none of this material is easy going, and we acknowledge that not everyone has the same love for the topic that we do. Moreover, we concede that the practical utility of some of the concepts we have discussed may not always be immediately obvious. At the same time, however, we maintain that these concepts, correctly understood and properly applied, can be of great value in the treatment of shock, and we hope we have given some indication as to why we believe this to be so.

Cardiovascular physiology is close to unique among the biologic sciences, in that it is one of the few biologic disciplines that are based on the physical sciences (the others might be membrane physiology and pulmonary physiology), as well as one of the few

that can be described mathematically. The cardiovascular system has an elegance all its own. One can readily think about it in theoretical, even mathematical, terms and then apply that thinking to understanding and treating abnormalities. This is not to say that one's theoretical analysis will always be on target. Currently available measurements in the ICU still do not provide all of the information that one would like to have, as is illustrated by the problems associated with not knowing the ventricular unstressed volumes and the difficulties associated with making reliable measurements on the left side of the heart.

To us, the uncertainties surrounding cardiovascular physiology are a large part of what makes cardiovascular problems interesting. There are some problems that can only be addressed through trial and evaluation. If the patient is being monitored, it is relatively easy to determine the correctness of an intervention. In general, all one need do is try the intervention and then see what happens to the cardiac output and the vascular pressures. If the intervention fails, one can then try something else. If the intervention is successful, one knows that the hypothesis that led to the intervention was probably correct. (We say "probably" because there is still a possibility that the favorable response was a coincidence; one may just have been lucky.)

In any case, the response, whether favorable or not, will usually be evident within a short time. Sometimes, one will know in a matter of minutes that the chosen intervention was the right thing for the patient. The satisfaction to be gained from quick and definitive management of a complicated and serious cardiovascular problem can be enormous.

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4 EARLY MANAGEMENT OF SEPSIS, SEVERE SEPSIS, AND SEPTIC SHOCK IN THE SURGICAL PATIENT

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Sepsis continues to be a common and serious problem. It is currently the 10th leading cause of death in the United States and the leading cause of death in noncardiac intensive care units (ICUs).¹ The incidence of sepsis among hospitalized patients continues to increase as the population ages. The current incidence of severe sepsis among hospitalized patients in the United States is 208 cases/100,000 patients.² It was estimated that there would be nearly 1 million cases of sepsis in the United States in 2010, with an associated mortality rate of greater than 30% based on a projected 1.5% increase in incidence per year based on the growth and aging of the US population.³ But subsequent studies have shown this estimate to be low, with increases in sepsis rates subsequently reported to be as high as 10% per year.^{4,5} These epidemiologic studies document that severe sepsis remains a major challenge and an increasing burden on health care systems worldwide.

Among surgical patients, sepsis is a leading cause of morbidity and mortality. A large epidemiologic study from Angus and colleagues determined that surgical patients account for nearly one third of sepsis cases in the United States.³ A recent analysis of the National Surgical Quality Improvement Project (NSQIP) database determined that sepsis and septic shock were 10 times more common than perioperative myocardial infarction and pulmonary embolism.⁶ The incidence of sepsis was highest in patients requiring emergency surgery, and colon perforation was the predominant source of sepsis. The development of septic shock was associated with a 30% mortality rate among elective surgical patients and a 39% mortality rate among emergent surgical patients. Risk factors for both the development of sepsis and death from sepsis included age older than 60 years, the need for emergency surgery, and the presence of comorbid conditions.⁷

Definition of Sepsis, Severe Sepsis, and Septic Shock

A clear and accurate definition of sepsis is critical for clinicians and researchers. A standard definition allows us to identify patients, leads to a better understanding of the disease process, and facilitates clinical research. Sepsis syndrome was first defined in the literature by Balk and Bone in 1989.⁸ This was followed by the American College of Chest Physicians and the Society of Critical Care Medicine's (ACCP/SCCM) Consensus Conference in 1991 that defined the systemic inflammatory response syndrome (SIRS) [see Table 1] and multiple organ dysfunction syndrome (MODS).⁹ In

response to ongoing criticism from experts in the field, a second consensus conference was convened in 2001 to revise the original definitions. The updated consensus conference definitions included an expanded list of the signs and symptoms of sepsis.¹⁰ Although the definitions included in the 2001 update are widely accepted, they do not specifically define the concept of surgical sepsis. In addition, the consensus conference definitions remain nonspecific and allow for some variability, especially with regard to defining organ dysfunction.

In an attempt to better define the categories of sepsis, severe sepsis, and septic shock for the surgical patient, we modified the ACCP/SCCM consensus conference definitions. We defined surgical sepsis as SIRS plus an infection requiring surgical intervention for source control or SIRS plus an infection within 14 days of a major surgical procedure. A major surgical procedure is defined as any procedure requiring general anesthesia for more than 1 hour.

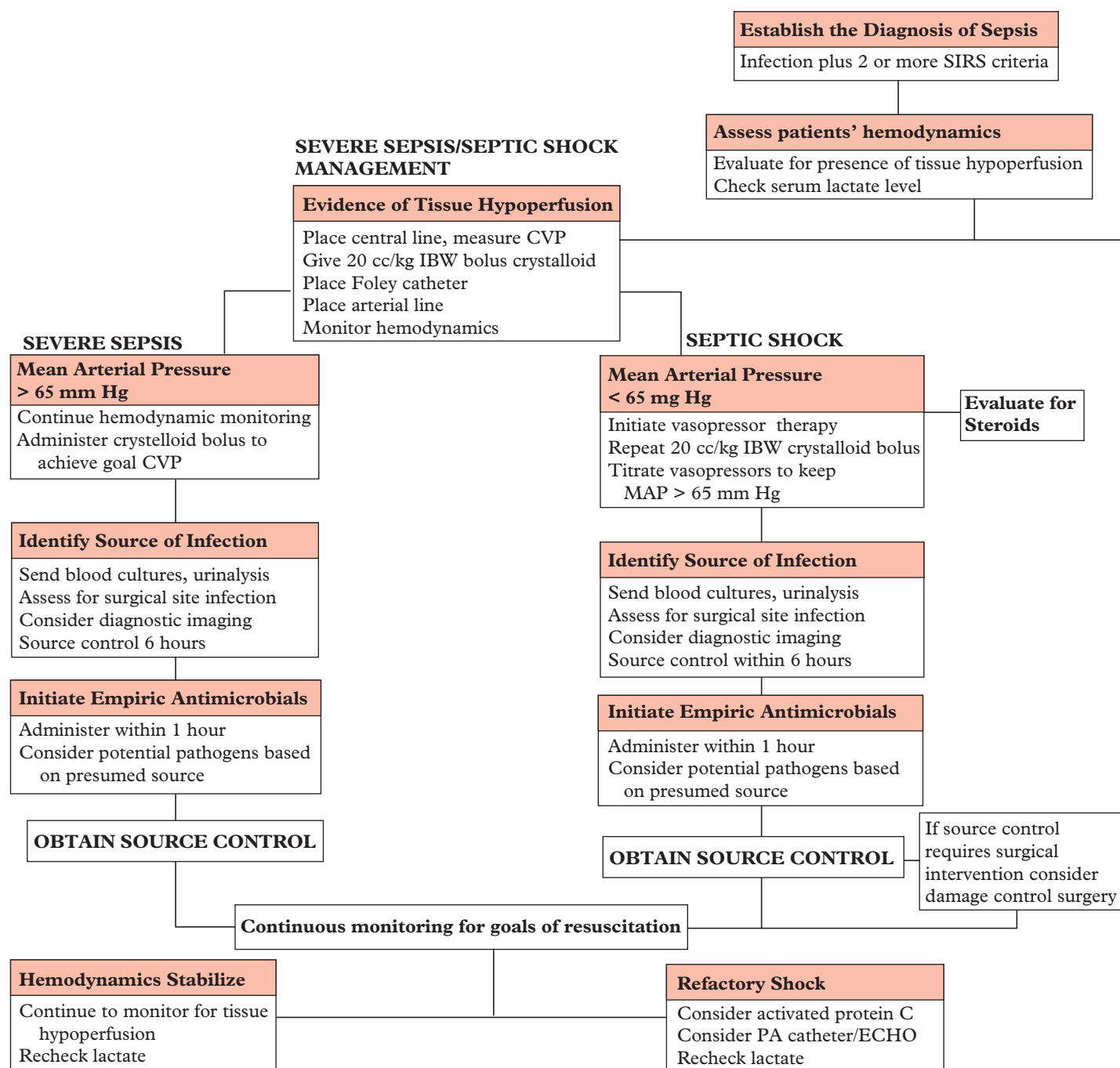
Severe sepsis is defined as SIRS plus infection plus acute organ dysfunction. The types of acute organ dysfunction are defined as follows:

1. Neurologic: a Glasgow Coma Scale (GCS) score less than 13 on recognition of sepsis or a deteriorating GCS score to less than 13 during the first 24 hours
2. Pulmonary: arterial oxygen tension (P_{aO_2}) to fraction of inspired oxygen (F_{IO_2}) ratio less than 250 (< 200 if the lung is the primary site of infection) and pulmonary capillary wedge pressure (PCWP) (if available) not suggestive of fluid overload
3. Renal (one of the following): urine output less than 0.5 mL/kg for 1 hour or more despite adequate volume resuscitation, an increase in serum creatinine 0.5 mg/dL or

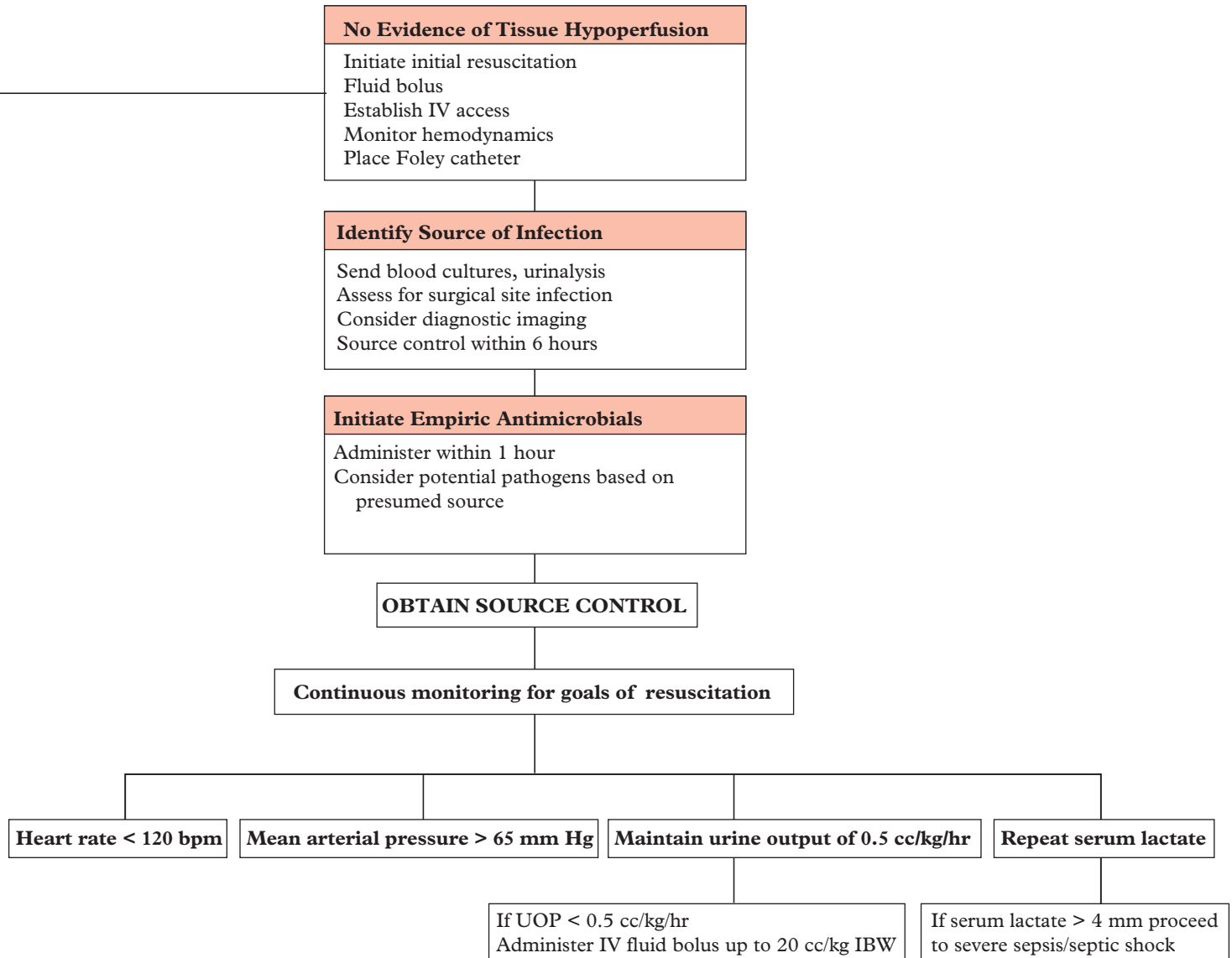
Table 1 Systemic Inflammatory Response Syndrome (SIRS) Criteria

Two or more of the following criteria must be present:

- Body temperature $< 36^{\circ}\text{C}$ or $> 38^{\circ}\text{C}$
- Heart rate > 90 beats per minute
- Tachypnea, with > 20 breaths per minute, or an arterial partial pressure of carbon dioxide < 4.3 kPa (32 mm Hg)
- White blood cell count $< 4,000$ cells/ μL (4×10^9 cells/L) or $> 12,000$ cells/ μL (12×10^9 cells/L) or the presence of $> 10\%$ immature neutrophils (band forms)

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SEPSIS MANAGEMENT



more from baseline (measured within 24 hours of starting sepsis resuscitation) despite adequate volume resuscitation or an increase in serum creatinine 0.5 mg/dL or more during the first 24 hours of sepsis management despite adequate volume resuscitation. Adequate volume resuscitation is defined as a minimum intravenous (IV) fluid infusion of 20 mL/kg/ideal body weight (IBW) or central venous pressure (CVP) 8 mm Hg or greater or PCWP 12 mm Hg or greater.

4. Coagulation (one of following): international normalized ratio (INR) greater than 1.5, platelet count less than 80,000 μ L, or 50% or greater decreased platelet count compared to 24 hours before instituting sepsis resuscitation or in the 24 hours after starting sepsis resuscitation in the absence of chronic liver disease
5. Hypoperfusion: lactate level less than 4 mmol/L

Septic shock is defined as SIRS plus infection plus acute cardiac dysfunction, which is defined by the following (must meet both criteria): (1) intravenous fluid challenge greater than or equal to 20 mL/kg/IBW of isotonic crystalloid infusion or CVP greater than or equal to 8 mm Hg or PCWP greater than or equal to 12 mm Hg and (2) requires vasopressors to increase mean arterial pressure (MAP) to greater than or equal to 65 mm Hg.

Initial Assessment and Evaluation of the Septic Patient

EARLY IDENTIFICATION OF SEPSIS

At our institution, we identified sepsis as a major cause of morbidity and mortality in our general surgery patients. As bedside nurses and other team members focus on multiple priorities and tasks, early signs of sepsis were often missed and interventions were delayed. In addition, many of the early signs and symptoms of sepsis may be subtle and in the surgical population are often attributed to other problems. For example, oliguria is commonly seen in surgical patients and is often attributed to underresuscitation in the operating room or volume loss from the gastrointestinal tract. However, oliguria can also be an early finding in patients with sepsis. Altered mental status, which is often attributed to narcotic administration or ICU psychosis, can also be an early warning sign of sepsis. Likewise, acute hypoxia on the surgical wards spurs a workup for pulmonary embolism, but acute hypoxia may herald the onset of severe sepsis or septic shock.

Identifying patients in the early stages of sepsis is imperative. If patients are allowed to progress into septic shock, their mortality is prohibitively high (> 30%) despite aggressive interventions. When you consider these factors, the benefit of routine, accurate screening of patients for sepsis quickly becomes apparent. In an attempt to increase the early identification of sepsis, we developed a sepsis screening tool in our surgical intensive care unit (SICU) [see Figure 1].¹¹ Our initial experience with this mandatory sepsis screening tool in our SICU showed promising results. The screening tool yielded a sensitivity of 96.5%, a specificity of 96.7%, a positive predictive value of 80.2%, and a negative predictive value of 99.5%. In addition, sepsis-related mortality decreased from 35.1% to 23.3%. Subsequent expansion and statistical validation of the screening on the surgical floor yielded similar

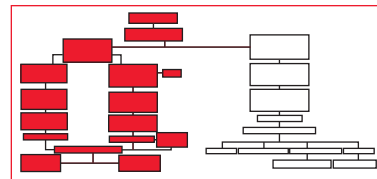
results.¹² Since implementing mandatory sepsis screening, we have seen a significant decline in our severe sepsis and septic shock-related mortality. Regardless of the method used to screen patients, all members of the patient care team must be aware of the early signs and symptoms of sepsis.

INITIAL ASSESSMENT

A clinical suspicion for the presence of sepsis should prompt further evaluation of the patient. The initial evaluation should focus on determining the degree of physiologic derangement that the patient is experiencing. Specifically, it is important to assess for the presence of tissue hypoperfusion. Several clinical and laboratory variables can be used to evaluate tissue perfusion status. The following variables are indicators that the patient is experiencing tissue hypoperfusion: (1) urine output less than 0.5 mL/kg of IBW, (2) MAP less than 65 mm Hg, (3) GCS score less than 12, and (4) serum lactate greater than or equal to 4 mmol/L. The presence of tissue hypoperfusion should prompt aggressive resuscitative measures that are focused on restoring tissue perfusion. Based on the definitions outlined above, those patients who do not have evidence of tissue hypoperfusion would fall into the category of sepsis. Those patients who do have evidence of tissue hypoperfusion would be categorized as having severe sepsis or septic shock. The initial resuscitation and management of these patients are discussed below.

INITIAL RESUSCITATION OF SEPSIS

The initial resuscitation phase of sepsis should begin immediately on recognition of sepsis. The goals of the resuscitation phase include restoring intra-



vascular volume, diagnosing the source of infection, initiation of broad-spectrum antimicrobial therapy, and source control. Many institutions have developed order sets that specifically address each of these issues. The use of standardized protocols for the initial management of sepsis has been demonstrated to improve patient outcomes in multiple settings.^{13–18}

The major tenets of initial resuscitation can be initiated in any area of the hospital and should not be delayed pending arrival in the ICU. Establishing IV access is a critical first step as this allows for the administration of IV fluid and antimicrobials. For those patients without evidence of tissue hypoperfusion, a large-bore peripheral IV line should be sufficient. In the event that peripheral IV access is not attainable, a central venous line should be inserted in a timely fashion.

The initial resuscitation fluid of choice still remains extremely controversial. There are no prospective, randomized, controlled trials evaluating crystalloid versus colloid resuscitation in surgical patients with sepsis. If colloids are given, the initial fluid bolus should be 300 to 500 mL of colloid over 30 minutes. If crystalloids are given, the initial fluid challenge should be 1,000 cc of crystalloid over 30 minutes. Additional fluid boluses should be repeated based on the patient's response. Fluid resuscitation should be initiated with the following goals in mind: (1) a target CVP (if available) of 8 to 12 mm Hg in nonintubated patients and a target CVP of 12 to 15 mm Hg in mechanically ventilated patients¹⁹;

Bedside Nurse
SIRS score

current heart rate _____ time _____
 T min _____ time _____
 T max _____ time _____
 current resp rate _____ time _____
 latest WBC count _____ date, time _____

patient label

10232007

points	0	1	2	3	≤ 4
heart rate (bpm)	70 - 109		55 - 69 110 - 139	40 - 54 140 - 179	≤ 39 ≥ 180
T (°C) min		34 - 35.9	32 - 33.9	30 - 31.9	≤ 29.9
T (°C) max	36 - 38.4	38.5 - 38.9		39 - 40.9	≥ 41
T (°F) min		93.1 - 96.6	89.6 - 93.0	86 - 89.5	≤ 85.9
T (°F) max	96.8 - 101.1	101.2 - 102.0		102.1 - 105.6	≥ 105.7
resp rate (br / min)	12 - 24	10 - 11 25 - 34	6 - 9	35 - 49	≤ 5 ≥ 50
latest WBC (kcell / mm ³)	3 - 14.9	15 - 19.9	1 - 2.9 20 - 39.9		≤ 1 ≥ 40
score (total points)					

If SIRS score ≥ 4, then notify Nurse Practitioner to complete sepsis screening form.

Completed by: _____, RN

Date / time: _____

Performance improvement review by PHYSICIAN:

sepsis
(Phase 1)severe sepsis
(Phase 2)septic shock
(Phase 2)

Start sepsis management protocol

Yes

No

Comments:

Signature: _____, MD

Date / time: _____

Figure 1 (a) Secondary Screening form to identify source of infection.

Nurse Practitioner/Resident Physician Sepsis Screening

1. Vascular access?

1. Vascular access?			Yes	No	Suspicion of:	
type	dialysis	triple / quad	PICC	port	tunneled	other (IV, art)
date placed						
site						
local finding						
blood culture finding						

line infection?

Yes No

2. Clinical pulmonary infection score (CPIS)

Variable	points	score
temperature (°C) time (hhmm)		
36.5 – 38.4	0	Intubated / mech vent support? Yes No date intubated:
38.5 – 38.9	1	
> 39.0 or < 36.0	2	
blood leukocyte count (# per mm ³) time (hhmm)		
4,000 – 11,000	0	
< 4,000 or > 11,000	1	
tracheal secretions time (hhmm)		
small	0	
moderate	1	
large	2	
purulent (add 1 point if purulent)	+1	
oxygenation (PaO ₂ /FiO ₂) time (hhmm)		
≥ 240 or presence of ARDS	0	
< 240 and absence of ARDS	2	
chest radiograph time (hhmm)		
no infiltrate	0	
patchy or diffuse infiltrate	1	
localized infiltrate	2	

pneumonia?

Yes No

3. Abdomen

recent abdominal surgery?	Yes	No
abdominal pain?	Yes	No
abdominal distention?	Yes	No
purulent drainage from surgical drains?	Yes	No
intolerance to enteral nutrition?	Yes	No

abdominal
infection?

Yes No

4. Skin / soft tissue

erythema / drainage from other surgical site?	Yes	No
site		

cellulitis / soft
tissue infection?

Yes No

5. Urinary tract

urinary catheter?	Yes	No
date placed		
latest urinalysis / urine culture results		

UTI?

Yes No

6. Other site

site	
------	--

other infection?

Yes No

Completed by: _____, NP

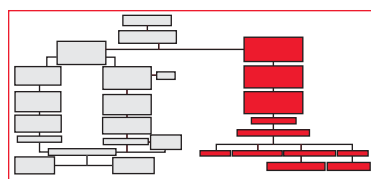
Date / time: _____

Figure 1 (b) Bedside Nurse SIRS Score.

(2) a MAP of 65 mm Hg or greater²⁰; (3) urine output of 0.5 mL/kg/hour or greater; and (4) central venous oxygen saturation (Scvo₂) of 70% or greater or mixed venous oxygen saturation (Svo₂) of 65% or greater (if available).²¹ These goals of resuscitation should be achieved within 6 hours of the recognition of sepsis. In addition, a baseline serum lactate should be sent on the identification of sepsis. A repeat serum lactate level should be sent 4 hours later to monitor the progress of the initial resuscitation.

The Saline versus Albumin Fluid Evaluation (SAFE) study randomized nearly 7,000 critically ill patients who required fluid resuscitation to receive albumin or normal saline, and no difference in mortality was identified. Interestingly, in the SAFE study, a subgroup analysis of the 1,218 patients with severe sepsis documented that albumin was associated with a trend toward reduced mortality (relative risk of death 0.87; 95% confidence interval 0.74 to 1.02).²² Two randomized clinical trials are ongoing to further investigate this finding: (1) Volume Replacement with Albumin in Severe Sepsis (ALBIOS)²³ (Italy) and (2) Early Albumin Resuscitation during Septic Shock (France).²⁴

INITIAL RESUSCITATION OF SEVERE SEPSIS AND SEPTIC SHOCK



For those patients presenting with severe sepsis and septic shock, the timely restoration of tissue perfusion is critical. The concept of early goal-directed

therapy (EGDT) in severe sepsis and septic shock [see Figure 2] was initially developed and validated in the emergency department (ED) setting in a single-center trial.²¹ The ED is frequently the point of entry into the hospital for many septic patients. Unfortunately, many of these patients may wait for prolonged periods of time in the ED. The end result is often a delay in the implementation of early sepsis resuscitation.

The use of EGDT has been shown to improve survival in patients presenting with severe sepsis and septic shock.^{16,21,25,26} The basic tenets of EGDT are to identify tissue hypoperfusion and institute therapies to reverse global tissue hypoxia by optimizing oxygen delivery. Tissue perfusion can be monitored by measuring Svo₂, Scvo₂, or peripheral muscle hemoglobin oxygen saturation (Sto₂). An Svo₂ of 65% or less, an Scvo₂ of 70% or less, and an Sto₂ of 75% or less can all be considered indicators of tissue hypoperfusion. Once tissue perfusion has been identified, specific therapies should be instituted to reverse tissue hypoxia by restoring adequate perfusion. The determinants of oxygen delivery are cardiac output, hemoglobin, and percent arterial hemoglobin oxygen saturation (Sao₂). EGDT attempts to restore tissue hypoperfusion by addressing these variables. The evidence-based sepsis resuscitation bundle was established with the goal of performing all indicated tasks 100% of the time within the first 6 hours after the diagnosis of sepsis was established and is used to assist with the provision of prompt resuscitation efforts in the treatment of sepsis [see Table 2].

To restore intravascular volume and enhance cardiac output, an initial crystalloid fluid bolus of 20 mL/kg of IBW

is recommended. This fluid bolus can be initially administered through existing peripheral IV lines; however, placement of a central venous line for monitoring of CVP is recommended. In addition, an arterial line should be placed in those patients presenting with hypotension who do not rapidly respond to volume loading. The use of noninvasive blood pressure monitoring for patients in septic shock often produces inaccurate measurements and should not be used for titrating vasoactive medications. A Foley catheter should also be inserted to allow for close monitoring of urine output, and bladder pressures should be monitored in patients requiring vigorous volume loading.

The goals of resuscitation remain the same as those listed above: (1) a target CVP (if available) of 8 to 12 mm Hg in nonintubated patients and a target CVP of 12 to 15 mm Hg in mechanically ventilated patients¹⁹; (2) a MAP of 65 mm Hg or greater²⁰; (3) urine output of 0.5 mL/kg/hour or greater; and (4) Scvo₂ of 70% or greater or Svo₂ of 65% or greater.²¹ In the event that an Scvo₂ of 70% or greater or an Svo₂ of 65% or greater cannot be achieved with restoration of intravascular volume and MAP of 65 to 90 mm Hg, red blood cells should be transfused to achieve a hematocrit of 30% or greater.

Multiple international randomized, controlled trials of EGDT for patients with severe sepsis are under way to validate the findings of the single-center Rivers trial.²¹ These include Protocolized Care for Early Septic Shock (ProCESS), Australian Resuscitation in Sepsis Evaluation (ARISE), and Protocolized Management in Sepsis (ProMISe). The ProCESS trial will randomize 1,950 patients who present to the ED in septic shock to three arms: (1) the EGDT Rivers protocol described above, (2) a simpler, less invasive protocol using an esophageal Doppler monitor and no blood transfusion, and (3) usual care.²⁷ The ARISE trial will randomize 1,600 patients to EGDT versus standard care and assess 90-day mortality in patients presenting to the ED with severe sepsis.²⁸ The ProMISe trial will randomize 1,260 patients to EGDT versus standard care and assess 90-day mortality in patients presenting to the ED with septic shock.²⁹ Furthermore, an individual, patient data meta-analysis will be performed across the three trials.

If the goal CVP, the goal MAP, and the goal hematocrit are all reached but there is still evidence of tissue hypoperfusion, inotropic agents should be initiated to improve cardiac output. In patients presenting with septic shock, the initial fluid bolus may not restore their MAP to 65 mm Hg or greater. A repeat fluid bolus of 20 mL/kg of IBW can be given to correct hypovolemia. However, transient vasopressor therapy may need to be initiated, even if volume resuscitation is still ongoing.

VASOPRESSOR THERAPY

Septic shock is primarily a vasodilatory shock, associated with a high cardiac output and a low systemic vascular resistance. Therefore, initial vasopressors therapy should be targeted at restoring vascular tone. Both norepinephrine and dopamine are acceptable first-line agents for treatment of septic shock. These agents should be administered through a central venous catheter. Norepinephrine is primarily an alpha-receptor agonist that promotes widespread vasoconstriction

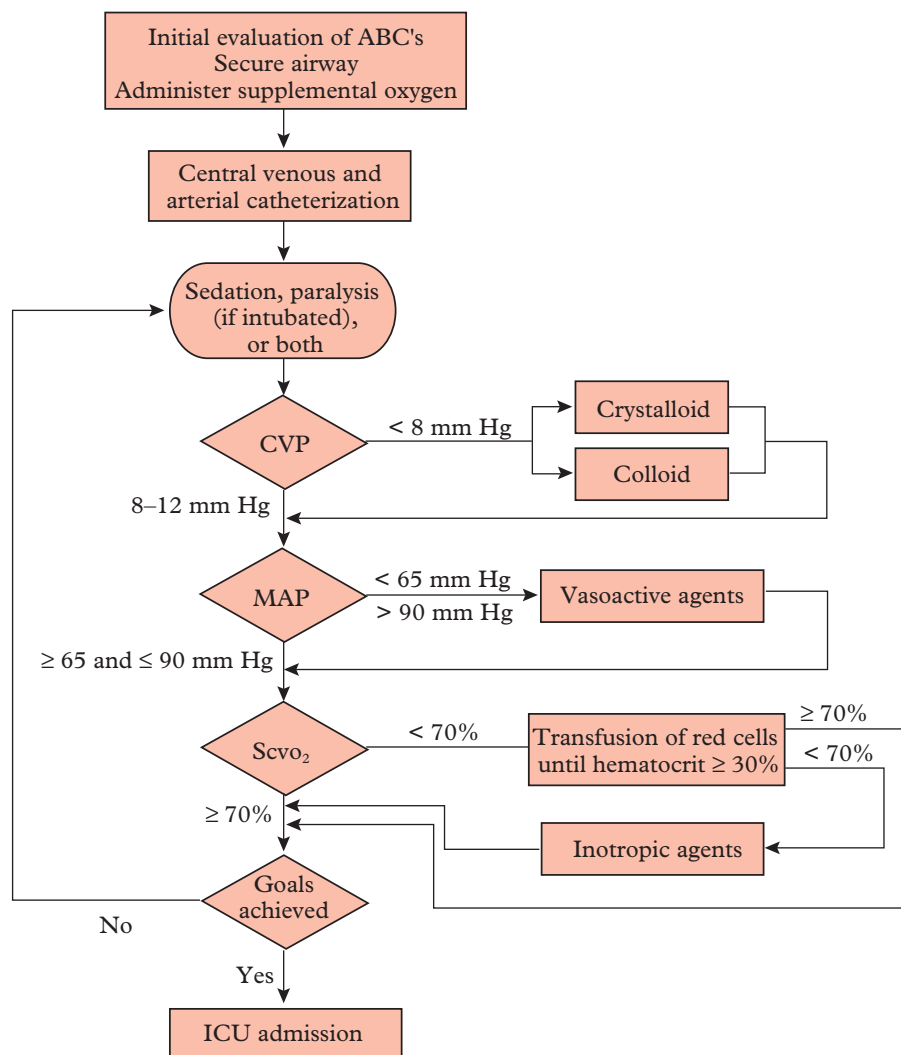


Figure 2 Protocol for early goal-directed therapy (EGDT). Adapted from Rivers E et al.²¹ CVP = central venous pressure; MAP = mean arterial pressure; Scvo₂ = central venous oxygen saturation.

and has little effect on heart rate or stroke volume. Dopamine has dose dependent effects on alpha, beta, and dopaminergic receptors. The initial increase in blood pressure seen with dopamine is related to increasing cardiac output. At higher doses ($> 7.5 \mu\text{g/kg/min}$), dopamine does activate alpha receptors, with resultant vasoconstriction.

In those patients with septic shock that is refractory to first-line vasopressors, the addition of vasopressin may be beneficial. Vasopressin is a stress hormone that has vasoactive effects. Recent work by Landry and colleagues suggested that in septic shock states, there is a relative deficiency of vasopressin.³⁰ The administration of vasopressin in this patient population has been shown to improve responsiveness to catecholamines and potentially reduce the dose of catecholamine needed to maintain blood pressure.³¹

The Vasopressin and Septic Shock Trial (VASST) randomized 779 patients in septic shock requiring norepinephrine ($5 \mu\text{g/min}$) for at least 6 hours and at least one organ system dysfunction present for less than 24 hours to vasopressin (0.01 to 0.03 U/min) versus norepinephrine at a higher

dose (5 to $15 \mu\text{g/min}$).³² No difference in 28-day or 90-day mortality was identified. In the prospectively defined stratum of less severe septic shock, the mortality rate was lower in the vasopressin group than in the norepinephrine group at 28 days (26.5% versus 35.7% ; $p = .05$), which persisted to 90-day mortality (35.8% versus 46.1% ; $p = .04$). A post hoc analysis of the VASST identified that the combination of low-dose vasopressin and corticosteroids was associated with decreased mortality and organ dysfunction compared with norepinephrine and corticosteroids.³³ Based on the results of studies to date, clinicians should consider the addition of low-dose (up to 0.03 U/min) continuous infusion vasopressin in individual septic shock patients who are adequately resuscitated and still require high doses of vasopressors.

Our current practice is to initiate a vasopressin drip at a rate 0.04 U/min in those patients requiring norepinephrine infusion at $15 \mu\text{g/min}$ or greater. The dose of vasopressin should not exceed 0.04 U/min because of the possibility of myocardial ischemia and decreased cardiac output at higher doses.³⁴ The evidence-based Surviving Sepsis Campaign

Table 2 Sepsis Bundles*

Sepsis Resuscitation Bundle (to be started immediately and completed within 6 hours)

- Serum lactate measured
- Blood cultures obtained prior to antibiotic administration
- Broad-spectrum antibiotics administered within 3 hours for ED admissions and 1 hour for non-ED ICU admissions
- In the event of hypotension and/or lactate > 4 mmol/L:
 - Deliver a minimum of 20 mL/kg of crystalloid (or colloid equivalent)
 - Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) $\geq$ 65 mm Hg
- In the event of persistent arterial hypotension despite volume resuscitation (septic shock) and/or initial lactate > 4 mmol/L (36 mg/dL):
 - Achieve central venous pressure (CVP) of $\geq$ 8 mm Hg
 - Achieve central venous oxygen saturation (ScvO₂) of $\geq$ 70% (achieving a mixed venous oxygen saturation of 65% is an acceptable alternative)

Sepsis Management Bundle (to be started immediately and completed within 24 hours)

- Low-dose steroids administered for septic shock in accordance with a standardized ICU policy
- Drotrecogin alfa (activated) administered in accordance with a standardized ICU policy
- Glucose control maintained $\geq$ lower limit of normal, but < 150 mg/dL (8.3 mmol/L)
- For mechanically ventilated patients, inspiratory plateau pressures maintained < 30 cm H₂O

ED = emergency department; ICU = intensive care unit.

*The goal is to perform all indicated tasks 100% of the time within the first 6 hours (sepsis resuscitation bundle) or first 24 hours (sepsis management bundle) of the diagnosis of severe sepsis.

guidelines regarding vasopressor use in sepsis are provided in Table 3.

Although most patients with sepsis initially present with increased cardiac output, a subset of patients will develop myocardial depression from sepsis. The exact mechanism for this reversible myocardial dysfunction is still under investigation. B-type natriuretic peptide (BNP) is secreted in response to stretching of myocardium and has been used clinically to assess volume overload and predict death in acute congestive heart failure. More recently, BNP has been shown to be elevated in early septic shock and likewise predict death. We

Table 3 Surviving Sepsis Campaign Guidelines Recommendations regarding Vasopressors⁷⁰

- Maintain MAP $\geq$ 65 mm Hg (1C).
- Norepinephrine and dopamine centrally administered are the initial vasopressors of choice (1C).
- Epinephrine, phenylephrine, and vasopressin should not be administered as the initial vasopressor in septic shock (2C).
- Vasopressin 0.03 U/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone.
- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B).
- Do not use low-dose dopamine for renal protection (1A).
- In patients requiring vasopressors, insert an arterial catheter as soon as practical (1D).

MAP = mean arterial pressure. Parens represent level of evidence for the recommendation.

recently showed that BNP increases with initial sepsis severity and is associated with early left ventricular dysfunction, which in turn is associated with later death.³⁵ Monitoring BNP in early sepsis to identify occult left ventricular dysfunction might prompt earlier use of inotropes, which are not commonly used in early sepsis resuscitation.

For those patients with suspected or documented cardiac dysfunction, the addition of inotropic therapy is recommended. Dobutamine is the first-line agent for treatment of cardiac dysfunction in patients with sepsis. The management of patients with a cardiac component to their shock state presents a unique challenge to the managing clinician because they require the titration of vasopressors and inotropic agents. In this subset of patients, a pulmonary artery catheter can be extremely useful. This allows for the specific titration of vasopressors based on systemic vascular resistance and inotropic agents based on cardiac output. There is no evidence to support increasing cardiac index to predetermined supranormal levels.

STEROIDS IN SEPTIC SHOCK

The use of steroids for the management of septic shock has been debated for several decades. In recent years, the concept of relative adrenal insufficiency in septic shock has received renewed attention. In spite of several large clinical trials addressing the issue of steroid use in patients with septic shock, the topic remains controversial. Much of the ongoing debate surrounds the definition of relative adrenal insufficiency in critically ill patients and the “gold standard” for diagnosing adrenal insufficiency in this population.

It had previously been a common practice to perform a low-dose adrenocorticotrophic hormone (ACTH; cosyntropin) stimulation test on all patients with septic shock as a means to identify those patients with relative adrenal insufficiency. To perform the cosyntropin stimulation test, a baseline serum cortisol is drawn that represents time zero (T₀). The patient is then given 250 µg of IV cosyntropin. Subsequent serum cortisol levels are measured at 30 (T₃₀) and 60 (T₆₀) minutes after the cosyntropin. If the delta cortisol is 9 µg/dL or less, then the patient is considered to have relative adrenal insufficiency and steroids are initiated. Based on the current evidence to date, we now recognize that the ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone. A number of factors interfere with the ACTH stimulation test, and our current diagnostic tests are not accurate. The administration of etomidate causes a temporary suppression of the hypothalamic-pituitary-adrenal axis, resulting in transient adrenal insufficiency. In addition, patients who have received steroids at any time during the 6 months preceding the presentation of septic shock should not undergo testing of their adrenal function. These patients should be empirically initiated on steroid therapy. The current edition (2008) of the Surviving Sepsis Campaign guidelines recommends that intravenous hydrocortisone be considered for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors [see Table 4]. The literature indicates that low-dose corticosteroids decrease the time to cessation of vasopressors,³⁶ increase the systemic vascular resistance and MAP,³⁷ and decrease the risk of death.³⁸ The dose of hydrocortisone should be 300 mg/day or less. We currently give hydrocortisone 50 mg IV every 6 hours. The

Table 4 Surviving Sepsis Campaign Guidelines regarding Steroids⁷⁰

- Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors (2C).
- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone (2B).
- Hydrocortisone is preferred to dexamethasone (2B).
- Fludrocortisone (50 µg orally once a day) may be included if an alternative to hydrocortisone is being used that lacks significant mineralocorticoid activity. Fludrocortisone is optional if hydrocortisone is used (2C).
- Steroid therapy may be weaned once vasopressors are no longer required (2D).
- Hydrocortisone dose should be ≤300 mg/day (1A).
- Do not use corticosteroids to treat sepsis in the absence of shock unless the patient's endocrine or corticosteroid history warrants it (1D).

ACTH = adrenocorticotropic hormone. Parentheses represent level of evidence for the recommendation.

duration of steroid administration also remains controversial. The current recommendation is that steroids be discontinued once vasopressors are no longer required.

IDENTIFYING THE SOURCE OF INFECTION

Identifying the source of infection is a key element to the initial management of sepsis. Whenever possible, cultures should be obtained prior to initiation of empirical antimicrobial therapy. Current recommendations include obtaining a minimum of two blood cultures, including one blood culture from each vascular access device and one blood culture from a peripheral puncture. Additional cultures from other sites (respiratory system, urinary tract) and radiographic imaging should be dictated by clinical suspicion. In the surgical population, this may include obtaining cultures from surgical drains and performing pertinent imaging to identify an undrained abscess.

To improve the chances of detecting bacteremia, it is crucial to obtain the appropriate volume of blood for the culture medium. Several studies have demonstrated that the volume of blood cultured is the single most important factor in the detection of bacteremia.^{39–41} The recommended volume of blood per culture tube is 10 mL or greater. Obtaining blood cultures from all vascular access devices, along with simultaneous collection of blood cultures from a peripheral site, is beneficial in diagnosing catheter-related infections. This concept of differential time to positivity has been well described in the literature.^{42,43} The differential time to positivity is defined as the difference in time necessary for the blood culture drawn simultaneously from a peripheral site and a central venous catheter to become positive. A differential time to positivity is considered to be positive if the blood culture that is drawn through the vascular access device becomes positive at least 120 minutes before the peripheral culture. If a patient has an indwelling vascular access device and the cultures drawn from that device become positive at least 120 minutes before the peripheral cultures become positive, it is recommended that the device be removed as it is likely infected.⁴²

INITIATION OF EMPIRICAL ANTIMICROBIAL THERAPY

Another key component of the initial resuscitation of the septic patient is the administration of IV antimicrobial

therapy. Antimicrobials should be administered after appropriate cultures have been sent but within 1 hour of sepsis recognition. The time to antimicrobial administration has been identified as a critical determinant of survival in patients presenting with sepsis. A recent study by Kumar and colleagues found that each hour in delay of antimicrobials was associated with an average decrease in survival of 7.6%.⁴⁴ Delayed administration of antifungal therapy in patients with *Candida* bloodstream infections was an independent predictor of hospital mortality.⁴⁵ Maintaining an adequate supply of commonly used antimicrobial agents in the ED and ICU can aid in the timely administration of these agents. The Surviving Sepsis Campaign guidelines recommend initiation of IV broad-spectrum antibiotics within the first hour of recognizing severe sepsis and septic shock [see Table 5].

The choice of antimicrobial therapy should take into account the patient's history (including drug allergies and recent antimicrobial exposure), suspected source of infection, and hospital-specific antibiograms. Within our SICU, our multidisciplinary sepsis team has developed antimicrobial regimens based on the suspected source of infection and the current antibiogram for our institution [see Table 6]. When selecting empirical antimicrobial therapy, a few general rules should be applied. The initial antimicrobial coverage should be broad enough to cover all potential pathogens. There is substantial evidence that administering inadequate antimicrobial coverage is associated with increased morbidity and mortality.^{46–49} Any antimicrobial that the patient has recently received should be avoided. Vigilant monitoring of culture data and de-escalation of the antimicrobial regimen based on culture results and sensitivities will reduce the risk of superinfection and the emergence of resistant organisms.

OBTAINING SOURCE CONTROL

The final component of the initial resuscitation bundle is identifying and controlling the source of infection. This can be as simple as removing an infected vascular access device. However, in our experience, in surgical patients, the abdomen is the site of infection in ≥50% of cases. These patients frequently require diagnostic imaging to identify the source and an operative procedure for source control. This includes

Table 5 Surviving Sepsis Campaign Guidelines regarding Antimicrobial Therapy

- Begin intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis (1D) and septic shock (1B).
- Broad spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source (1B).
- Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs (1C).
- Consider combination therapy in *Pseudomonas* infections (2D).
- Consider combination empirical therapy in neutropenic patients (2D).
- Combination therapy not more than 3–5 days and de-escalation following susceptibilities (2D).
- Duration of therapy typically limited to 7–10 days—longer if response slow or there is undrainable foci of infection or immunologic deficiencies (1D).
- Stop antimicrobial therapy if cause is found to be noninfectious (1D).

Parentheses represent level of evidence for the recommendation.

Table 6 Recommendations for Source-Specific Empirical Antibiotic Selection

Source of Infection	Antibiotic Drug	Regimen
Indication	If vancomycin allergy (not intolerance), then use linezolid	600 mg IV q. 12 hr
	1. Preferred therapy 2. Severe β -lactamase allergy	Monitor; adjust if renal dysfunction* Kinetic monitoring†
Pneumonia		
Community acquired (CAP)	1. Ceftriaxone and Levofloxacin	1 g IV q. 24 hr 750 mg IV q. 24 hr*
	2. Aztreonam and Levofloxacin	2 g IV q. 8 hr* 750 mg IV q. 24 hr*
Aspiration (not chemical pneumonitis)	Piperacillin-tazobactam	4.5 g IV q. 6 hr*
Ventilator associated (VAP)		
Early VAP (< 5 days)	1. Cefepime	2 g IV q. 12 hr*
	2. Ciprofloxacin	400 mg IV q. 12 hr*
Late VAP ($\geq$ 5 days; <i>Pseudomonas</i> risk: previous hospital or broad-spectrum antibiotic exposure; positive <i>Pseudomonas</i> culture)	1. Cefepime and Vancomycin and Tobramycin	2 g IV q. 8 hr* 15 mg/kg IV q. 12 hr* 7 mg/kg IV*†
	2. Ciprofloxacin and Vancomycin and Tobramycin	400 mg IV q. 8 hr* 15 mg/kg IV q. 12 hr* 7 mg/kg IV*†
Catheter-related infections		
Catheter-associated urinary tract infection (CAUTI)	1. Cefepime	1 g IV q. 12 hr*
	2. Ciprofloxacin	400 mg IV q. 12 hr*
IV, arterial catheter; bloodstream	Vancomycin	1 g IV q. 12 hr*
Candidemia high risk (TPN, steroid therapy, diabetes, hepatic failure)	Fluconazole	800 mg IV q. 24 hr*
Wound/soft tissue infections		
Necrotizing soft tissue infection (NSTI)	1. Piperacillin-tazobactam and Vancomycin and Clindamycin	4.5 g IV q. 6 hr* 15 mg/kg IV q. 12 hr* 900 mg IV q. 8 hr
	2. Ciprofloxacin and Vancomycin and Clindamycin	400 mg IV q. 8 hr* 15 mg/kg IV q. 12 hr* 900 mg IV q. 8 hr
Surgical site infection (SSI)	1. Ertapenem and Vancomycin	1 g IV q. 24 hr* 15 mg/kg IV q. 12 hr*
	2. Ciprofloxacin and Vancomycin	400 mg IV q. 12 hr* 15 mg/kg IV q. 12 hr*
Intra-abdominal infections		
<i>Pseudomonas</i> low risk	1. Ertapenem and Vancomycin	1 g IV q. 24 hr* 15 mg/kg IV q. 12 hr*
	2. Ciprofloxacin and Metronidazole and Vancomycin	400 mg IV q. 8 hr* 500 mg IV q. 8 hr 15 mg/kg IV q. 12 hr*
<i>Pseudomonas</i> high risk (previous hospitalization or broad-spectrum antibiotic exposure; positive <i>Pseudomonas</i> culture)	1. Imipenem-cilastatin and Vancomycin	500 mg IV q. 6 hr* 15 mg/kg IV q. 12 hr*
	2. Ciprofloxacin and Metronidazole and Vancomycin	400 mg IV q. 8 hr* 500 mg IV q. 8 hr 15 mg/kg IV q. 12 hr*
Candidiasis high risk (TPN, steroid treatment, diabetes, hepatic failure, upper GI perforation + H ₂ blocker, age $\geq$ 75 yr, prolonged antibiotic, long-term care)	Consider fluconazole	800 mg IV q. 24 hr*

GI = gastrointestinal; TPN = total parenteral nutrition.

emergent débridement of necrotic tissues, abscess drainage, removal of infected vascular access devices, and exploratory laparotomy. In the setting of septic shock, these procedures, although necessary, can present a unique challenge to the surgical team.

The concept of damage control laparotomy (DCL) was first used for the care of critically injured trauma patients.^{50–52} Damage control is defined as initial control of hemorrhage and contamination followed by intraperitoneal packing as needed and rapid, temporary abdominal closure. This concept was employed on those patients who presented with severe physiologic derangements such as coagulopathy, acidosis, and hypothermia. Rather than persist for hours performing definitive surgery in the operating room, a patient's critical surgical needs should be addressed in an abbreviated fashion so that the patient may be taken to the ICU for further resuscitation. Once their physiologic derangements have been corrected, they are taken back to the operating room for a definitive surgical procedure. The decision to use DCL should not be viewed as a bailout. Instead, it is a deliberate decision to truncate the surgical procedure to minimize the time away from the ICU. The decision to perform DCL is often made prior to arriving in the operating room and is based on the severity of the patient's physiologic derangements at the time of presentation.

The concept of DCL has now evolved to include critically ill patients with surgical sepsis. Much like the trauma patient with the lethal triad of acidosis, hypothermia, and coagulopathy, many patients with septic shock present in a similar fashion. For those patients presenting with septic shock and a source of infection that requires surgical intervention, the use of DCL can be lifesaving.

The first priority is to initiate resuscitation. The patient needs to undergo preoperative optimization, during which time the airway is secured, central venous and arterial lines are placed, volume resuscitation and broad-spectrum antimicrobial agents are administered, and vasopressors are titrated to the appropriate end points. Within 6 hours, the patient is taken to the operating room for emergency laparotomy and potential damage control. The surgeon needs to assess the degree of physiologic derangement early in the operation, and if severe physiologic derangements exist, then the operative interventions need to be truncated. The primary aim is to control the source of infection (e.g., resect dead bowel, manage bowel perforations [resection versus primary closure], drain abscesses, and wash out the abdomen). We do not create ostomies, and bowel may be left in discontinuity at this first operation. The abdomen is then managed with a temporary abdominal closure device (via a variety of techniques), and the patient is rapidly returned to the ICU, where he or she undergoes postoperative optimization. This includes optimizing volume resuscitation and mechanical ventilation, correction of coagulopathy and hypothermia, and monitoring for abdominal compartment syndrome (ACS). Over the next 24 to 48 hours, abnormal physiology is corrected so that the patient can safely return to the operating room for a definitive operation and abdominal closure. Septic shock is a tremendous metabolic insult, and it is very important to provide optimal nutritional support (this often requires combined enteral and parenteral nutrition) and early mobilization to prevent the loss of lean body mass, which impairs recovery.

One of the problems with this “damage control” strategy is that in some patients, the midline abdominal fascia cannot be closed at the second operation because of bowel distention and edema, and they require multiple additional laparotomies for definitive abdominal wall closure. The midline fascia is progressively closed with the use of a vacuum-assisted closure (VAC) device. For this technique to work, it is important that the bowel not become adherent to peritoneum of the anterior abdominal wall lateral to the paracolic gutters; otherwise, the abdomen becomes “frozen” and the fascia cannot be brought to midline. The VAC device actively removes fluid and decreases edema; provides medial tension, which helps minimize fascial retraction and loss of domain; and protects the abdominal contents by providing separation between the abdominal wall and viscera, with no fascial damage because it does not require fascial suture placement. Traditionally, abdominal wall defects in these “frozen” abdomens were closed by mobilizing skin or subcutaneous tissue flaps to cover the defect (i.e., accepting a large hernia defect and the need for delayed reconstruction) or by bridging the defect with mesh with later split-thickness skin grafting once granulation tissue has developed. This is associated with a 20% gastrointestinal fistula rate, which is a terrible complication. Additionally, many of these patients required delayed complex abdominal wall reconstructions. Recently, there has been a lot of enthusiasm for acute reconstruction with biologic mesh. However, long-term follow-up studies show that many of these patients require delayed hernia repairs of large defects.⁵³ In our published experience of treating the open abdomen with the VAC device, we achieved primary fascia closure in 87% at a mean of 7 days with a 2% fistula rate and no intra-abdominal abscess.^{54,55} These results are nearly identical to the results reported by Miller and colleagues from Wake Forest University, who taught us how to do this type of closure.⁵⁶ More recently, Cothren and colleagues reported a 100% primary fascial closure rate using a modified VAC device technique.⁵⁷ The long-term outcomes are not known, but in short-term follow-up (mean 180 days), ventral hernia was 2.3%. However, as is true with all emergency laparotomies, this rate will increase with time, but the hernia defects will be small and more easily repaired.

In addition to damage control scenarios, there are other reasons for leaving the abdomen open and planning a staged relaparotomy:

1. Patients with ischemic bowel who have undergone a resection will be taken back the next day to assess the viability of the remaining bowel before we attempt an anastomosis or ostomy. We have been quite successful in completing the small bowel to colon anastomosis at the second operation; thus, these patients have avoided the need for a temporary ileostomy.
2. Patients who have massive bowel distention that cannot be closed without causing significant intra-abdominal hypertension (IAH) will undergo temporary abdominal closure. Intra-abdominal hypertension sets the stage of ACS, which occurs with subsequent ICU resuscitation.⁵⁸ Avoiding ACS significantly improves survival.
3. In patients with necrotizing pancreatitis, we try very hard to avoid operative interventions but are occasionally forced to do so.
4. Patients who develop ACS will require a decompressive laparotomy and temporary abdominal closure. As a result

of advances in trauma care starting in the 1980s, this entity emerged as an epidemic in the mid-1990s in trauma centers worldwide. As we began to understand this new entity, it has been increasingly recognized to occur in nontrauma ICU patients.^{59–61} Unfortunately, if you do not look for ACS by monitoring bladder pressures, you will not find it, and these patients will die of refractory shock.

Within our SICU, we have been using DCL for our patients with septic shock. Over 2 years, we had 22 patients who underwent DCL for source control. Sources of intra-abdominal infection were the colon (11 patients), small bowel (four patients), stomach (two patients), and pancreas (one patient). Four patients had peritonitis with no identified source. Of the 22 patients, six died from multiple organ failure, for an actual mortality rate of 27%. The mean P-POSSUM predicted mortality was significantly higher at 69.4% ($p < .02$), as was the predicted mortality of 76% based on a mean Acute Physiology and Chronic Health Evaluation (APACHE) II score of 31.8 ($p < .02$).⁶² These data suggest that the use of DCL for patients with surgical sepsis is saving lives and is a viable option for patients with septic shock and the need for immediate operative source control.

ACTIVATED PROTEIN C FOR SEVERE SEPSIS AND SEPTIC SHOCK

In the normal physiologic state, anticoagulation predominates. The major anticoagulant factors are protein C, protein S, antithrombin, and tissue factor (TF) pathway inhibitor. Protein C is activated by the binding of thrombin to thrombomodulin on the surface of the endothelium. Once activated, protein C directly inhibits factor Va and factor VIIIa in the clotting cascade. In patients with severe sepsis and septic shock, there is a decreased expression of thrombomodulin on the vascular endothelium. As a result, there is decreased production of activated protein C (APC). This results in a shift toward the procoagulant state. This shift to a procoagulant state results in microvascular thrombosis, impaired fibrinolysis, and endothelial dysfunction. The microvasculature becomes occluded with resultant tissue hypoxia and direct tissue damage, which ultimately results in organ dysfunction or failure. The extent of coagulation disturbance ranges from mild laboratory abnormalities to disseminated intravascular coagulation (DIC). This underlying disruption of the intrinsic production of APC served as the physiologic impetus for the administration of APC as a means to reverse the procoagulant state seen in severe sepsis and septic shock.

As a result of the expense and potential bleeding complications associated with APC, its use should be restricted to patients meeting specific criteria. The administration of APC is currently recommended in those patients who are at highest risk of death from sepsis. This includes patients with an APACHE II score of 25 or greater, multiple organ failure (two or more organs), septic shock, or acute respiratory distress syndrome (ARDS) from sepsis. Because of the inherent risk of bleeding from the administration of APC, its use in surgical patients must be carefully considered. Current absolute contraindications to the use of APC include active internal bleeding, hemorrhagic stroke within the preceding 3 months, severe head trauma or intracranial surgery in the preceding 2 months, trauma patients with an increased risk

of life-threatening hemorrhage, the presence of an epidural catheter, the presence of an intracranial neoplasm, a platelet count less than 30,000/ μ L, an INR less than 3, or administration of other anticoagulant therapies (warfarin, heparin). The current guidelines for the use of APC in surgical patients include discontinuing the agent 2 hours prior to an invasive surgical procedure and restarting infusion 12 hours after an invasive surgical procedure. The use of APC has been shown to improve survival in surgical patients with a high risk of death. A recent review of current literature by Barie and colleagues revealed a significant reduction in mortality (odds ratio 0.66; 95% confidence interval 0.45 to 0.97) with the administration of APC in surgical patients with an APACHE II score of 25 or greater.⁶³ Although there is an increased risk of bleeding in surgical patients who receive APC, this survival benefit afforded by the administration of APC is believed to outweigh the risk. However, in those patients with a lower risk of death from sepsis, the administration of APC outweighs the potential benefits because of the increased risk of bleeding complications. The 2008 Surviving Sepsis Campaign guidelines recommend consideration of APC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II > 25 or multiple organ failure) if there are no contraindications (grade 2B; grade 2C for postoperative patients). They recommend that adult patients with severe sepsis and a low risk of death (e.g., APACHE II < 20 or one organ failure) should not receive APC.

Discussion

PATHOPHYSIOLOGY OF SEPSIS: A COMPLEX PROCESS

The clinical manifestations of sepsis are the result of a complex series of interactions between the inciting organism and the host's innate immune response. This intricate cellular interaction involves numerous signaling pathways as well as the production of cytokines and chemokines. A detailed discussion of each of these pathways is beyond the scope of this text. However, a few key elements are discussed.

Characteristics of the Pathogen

The host response to infection can be triggered by bacterial, viral, and/or fungal infection. The specific characteristics of the inciting organism play a role in the body's response to the infectious stimuli. Each organism has specific virulence factors that enable the organism to evade the host's defenses. These virulence factors include antigenic variation of surface molecules, inhibition of complement activation, resistance to phagocytosis, production of exotoxins, and scavenging of reactive oxygen intermediates.⁶⁴ Cell-to-cell communication between organisms allows for signaling and upregulation of virulence factors. Perhaps one of the best described virulence factors is lipopolysaccharide (LPS), also known as endotoxin, which is a component of the outer cell wall of all gram-negative bacteria. The presence of LPS provokes local and systemic inflammation, including proliferation of cytokines and activation of macrophages. The presence of LPS is essential to maintaining the integrity of the outer membrane of gram-negative bacteria, acting as a protective barrier against lysozymes, antimicrobial agents, and host phagocytic cells.

Characteristics of the Host

The human body is equipped with a variety of defense mechanisms against microorganisms. These include physical barriers such as the skin and mucosal surfaces, the innate immune response, and the adaptive immune response. Dysfunction of any of these components can lead to the development of sepsis. The recognition of pathogens by the innate immune response initiates a complex cascade of events that are intended to remove the pathogen from the host. This includes the release of reactive oxygen metabolites to destroy the pathogen, the release of chemokines to recruit additional lymphocytes, and the generation of a variety of systemic cytokines to further activate the host immune response. We are just beginning to understand the potential impact of genetic polymorphisms and the impact these may have on patient survival.^{65,66}

Effect of Sepsis on Coagulation

Proper function of the coagulation system is of critical importance, particularly in the surgical patient as it plays an important role in hemostasis. Extensive laboratory research has furthered our understanding of the relationship between inflammation and coagulation. In the septic patient, dysregulation of the coagulation system can result in derangements in laboratory tests of coagulation, increased bleeding risk, and DIC. A basic understanding of this relationship is essential to understanding the pathophysiology of sepsis.

A key factor in the interaction between coagulation and inflammation is TF expression. Under normal circumstances, TF is found only on adventitial structures, myocytes, and fibroblasts. When tissue injury occurs, these subendothelial structures that express TF are exposed and the clotting cascade is initiated when TF binds with circulating factor VII. During sepsis, proinflammatory mediators induce the expression of TF on the endothelium. The expression of TF by the endothelium not only activates the coagulation cascade but also is a potent stimulus for excess thrombin generation. Thrombin is a procoagulant molecule that converts fibrinogen to fibrin and promotes platelet activation. The formation of fibrin is followed by consumption of clotting factors and the formation of fibrin clots in the microcirculation. These fibrin clots serve as filters, trapping platelets to form larger clots. All of these actions combined shift the coagulation system into a procoagulant state. In addition, there is a loss of anticoagulant factors, such as thrombomodulin. Proinflammatory cytokines downregulate the production of thrombomodulin on the surface of the endothelial cells. Thrombomodulin is an essential cofactor in the conversion of protein C into APC. Clinically, this imbalance in the coagulation system is reflected as tissue hypoxia secondary to microvascular thrombosis. This disruption in the coagulation system and the resulting microvascular thrombosis have been the target of potential pharmacologic interventions, including APC.

SEPSIS SCREENING: INCREASING AWARENESS AND IMPROVING OUTCOMES

The early identification and management of sepsis remain a significant challenge to health care providers. In the recent past, multiple organizations have focused their efforts on providing evidence-based guidelines (EBGs) in an attempt to

decrease the morbidity and mortality associated with sepsis. Several recent studies in the literature have highlighted the correlation between early sepsis intervention and patient survival. The use of EGDT as described by Rivers and colleagues has emphasized the importance of early intervention during the “golden hours” of sepsis.²¹ A recently published study by Kumar and colleagues demonstrated a significant correlation between time to appropriate antimicrobial administration and patient survival.⁴⁴ In this study of 2,154 patients with septic shock, administration of effective antimicrobial therapy within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in administration of effective antimicrobial therapy was associated with an average decrease in survival of 7.6%.

In spite of strong evidence that the early implementation of evidence-based, sepsis-specific therapies saves lives, the early identification of sepsis remains challenging. The signs and symptoms of sepsis are nonspecific, particularly in the early phases of sepsis. As bedside nurses and other health care providers focus on multiple priorities and tasks, early signs of sepsis are often missed and time-critical interventions are delayed. Lack of awareness of the signs and symptoms of impending sepsis may contribute to the problem. In the surgical patient, some of the early signs of sepsis are often attributed to other common problems seen in the postoperative period. A recent audit of ward nurses’ knowledge of sepsis demonstrated a lack of awareness of the standard definitions of sepsis, severe sepsis, and septic shock; the significance of increased blood lactate concentration as an indicator of severe sepsis; and the basic tenets of EGDT.⁶⁷ The conclusion of this audit was that these deficits could result in missed or delayed diagnosis of severe sepsis or septic shock and seriously delayed therapy. Physicians also struggle with the early identification and evidence-based management of sepsis. A recent international survey of physicians regarding their knowledge about sepsis reported that 83% of physicians surveyed had missed the diagnosis of sepsis.⁶⁸ The reasons listed for missing the diagnosis of sepsis included a lack of monitoring, a lack of a common definition for sepsis, and a lack of knowledge. Of the 1,058 physicians surveyed, only 140 (13.2%) were able to give the definition of sepsis from the ACCP/SCCM consensus statement.

Our experience with the sepsis screening tool in the SICU prompted us to further evaluate sepsis in general surgery patients within our own institution. We conducted a quality improvement review of patients admitted to our SICU over a 5-month period with an admitting diagnosis of sepsis, severe sepsis, or septic shock. Of the 55 patients with sepsis, severe sepsis, or septic shock, 26 (47%) were admitted to the SICU from an inpatient surgical ward. Of these 26 patients admitted from the surgical ward, 15 (58%) presented to the SICU with severe sepsis or septic shock. Of the 15 patients who presented to the SICU in severe sepsis or septic shock, six died (40%). There were no deaths among the 11 patients who presented with sepsis. For each of these 26 patients, the first step of our sepsis screening tool was performed in a retrospective fashion. Of the 26 patients, 20 (77%) had a positive retrospective SIRS screen (SIRS score ≥ 4). On average, the screen became positive 25 hours before the diagnosis of sepsis was made (range 30 minutes to 114.75 hours, SD 35.8, interquartile range 33.75). The Surviving Sepsis Campaign guidelines place great emphasis on the speed with

which sepsis-specific interventions are initiated and the impact this has on sepsis-related mortality. The average delay of 25 hours between the initial recognition of sepsis using this screening tool and the initiation of appropriate therapy is well beyond the recommended time for intervention. This would indicate that the use of this nurse-initiated sepsis screening tool could significantly improve sepsis recognition on the inpatient surgical floor.

We subsequently implemented and validated our sepsis screening tool on the inpatient surgical ward.¹² The screening tool yielded a sensitivity of 99.9%, a specificity of 91.3%, a positive predictive value of 16.3%, and a negative predictive value of 99.9%. The sepsis-related mortality in those patients who screened positive for sepsis was 6.3%. Of the 16 patients who developed sepsis, four (25%) required transfer to the SICU. Of the 16 true positive screens, 14 (87.5%) had sepsis and two (12.5%) had severe sepsis at the time of the screen. These results emphasize the importance of sepsis screening for the identification of sepsis before the patient progresses into septic shock.

IMPLEMENTING EVIDENCE-BASED GUIDELINES: USE OF COMPUTERIZED CLINICAL DECISION SUPPORT

In the recent past, multiple organizations have focused on providing EBGs in an attempt to decrease the morbidity and mortality associated with sepsis.⁶⁹⁻⁷¹ These EBGs provide a comprehensive list of therapies and include several time-sensitive interventions. In spite of strong evidence that the early implementation of evidence-based, sepsis-specific therapies saves lives, the complexity of these recommendations makes bedside implementation difficult and subsequent compliance poor. A recent study by McGlynn and colleagues evaluating compliance with implementation of evidence-based care in a variety of acute and chronic health conditions found that only 55% of patients currently receive appropriate evidence-based care.⁷² This failure of health care providers to consistently implement evidence-based care is multifactorial. Busy clinicians struggle to keep up with the information overload that has resulted from the recent explosion in health care-related guidelines. As a result, it often takes 15 or 20 years for a newly proven therapy to become standard of care.⁷³ In addition, guidelines are often difficult to implement at the local level because they are not patient specific and rarely provide explicit directions for use at the bedside. All of these factors result in a significant hurdle that clinicians must overcome to provide up-to-date, evidence-based care.

In the case of EBGs for sepsis management, the number and complexity of the recommendations make it difficult to consistently implement these interventions. In addition, many of the interventions are time sensitive and need to be prioritized. Patients with an intra-abdominal source of surgical sepsis are at particularly high risk because of the severity of illness and treatment complexity. These patients often require emergent operation for source control, with damage control techniques employed for the most severely ill. Integration of surgical intervention with ICU resuscitation introduces even more variables in sepsis management. This necessitates having a system that ensures adequate timely resuscitation and adherence to EBGs for sepsis.

Our previous experience with computerized clinical decision support (CCDS) has proven valuable in implementing

other complex EBGs for critically ill patients.⁷⁴ A computer-based algorithm has the ability to accurately and precisely manage clinical interventions, often more consistently than the bedside clinician. Previous studies evaluating the use of CCDS to implement EBGs for ARDS management and hemorrhagic shock resuscitation have demonstrated that the use of CCDS improves compliance with EBGs at the bedside.⁷⁵⁻⁷⁸ Based on this experience, we developed a CCDS protocol for the management of sepsis. This bedside CCDS program includes an algorithm for goal-directed volume resuscitation, with subsequent real-time prompts for specific therapies such as antimicrobials, vasopressors, and further modalities within the initial 24 hours after sepsis identification. Acknowledgment of administered therapies allows the computer logic to proceed to the next step, ensuring compliance with all aspects of the EBGs.

Implementation of CCDS for the management of sepsis has significantly improved our ability to consistently implement EBGs in our SICU. Since implementing our CCDS sepsis management protocol, we have increased our compliance with all components of the 6-hour resuscitation bundle from 29 to 79%. In addition, our overall severe sepsis/septic shock mortality has declined from 24% to 12%. We attribute this significant decrease in sepsis-related mortality to increased compliance with the EBGs, a finding that is consistent with other reports in the literature.^{21,44,79-81}

FLUID RESUSCITATION: CRYSTALLOID VERSUS COLLOID

Since the early 1940s, the restoration of intravascular volume has been embraced as a pivotal intervention in shock resuscitation. However, considerable controversy has persisted concerning the optimal resuscitation fluid to use. This is largely attributable to conflicting evidence within the literature. Because of a lack of large, randomized trials addressing the issue, a number of meta-analyses have been performed. One large meta-analysis of 1,419 patients by the Cochrane Injuries Group Albumin Reviewers revealed an increased risk of death in those patients resuscitated with albumin compared with those resuscitated with crystalloid.⁸² Another large meta-analysis of by Wilkes and Navickis revealed no difference in mortality between patients who were resuscitated with albumin compared with those resuscitated with crystalloid.⁸³

The SAFE trial was a large, multicenter, randomized, controlled trial that compared the effect of colloid versus crystalloid fluid resuscitation on mortality in patients admitted to the ICU.⁸⁴ The results of the study revealed similar outcomes for patients in the colloid and crystalloid groups, suggesting that there is no advantage to the use of either resuscitation fluid. A subgroup analysis of patients with severe sepsis showed a slight improvement in survival among patients who received albumin, but this difference was not statistically significant as this study was not specifically designed to evaluate patients with sepsis.

There are several basic differences between crystalloid (lactated Ringer solution, normal saline) and colloid (albumin, hydroxyethyl starch, hypertonic saline) as resuscitation fluid. The volume of distribution of crystalloids is significantly larger than that of colloids. Therefore, the ratio of crystalloid to colloid infusion is approximately 3 to 1. Proponents of the crystalloid resuscitation cite improved expansion of the

extracellular compartment, minimal risk of anaphylactoid reaction, replacement of volume loss with physiologically balanced solution, and decreased costs. Proponents of colloid resuscitation cite faster time to restoration of intravascular volume because of the decrease in fluid required and reduced risk of interstitial edema secondary to the high oncotic pressure. If colloids are used for resuscitation, one must be particularly vigilant about monitoring cardiac filling pressures and avoiding fluid overload. In addition, the expense and availability of albumin may be factors in some settings. The use of hydroxyethyl starch solutions is associated with alterations of the coagulation cascade and therefore should be used with caution in surgical patients. In addition, hydroxyethyl starch solutions have been associated with renal dysfunction and higher rates of acute renal failure in sepsis.⁸⁵

USE OF STEROIDS IN SEPTIC SHOCK

The administration of steroids in septic shock has been debated for decades. In the 1960s, high-dose steroid replacement therapy was found to improve survival in animal models of septic shock. However, a clinical study by Bennet and colleagues found no benefit to the use of steroids in sepsis, and the practice was largely abandoned.⁸⁶ In the 1970s, high-dose steroids were widely used for patients with septic shock. Schumer and colleagues demonstrated significant improvement in survival among patients who received high-dose steroids.⁸⁷ This practice continued into the 1980s, at which time new evidence emerged that high-dose steroids were associated with an increased risk of death and a higher frequency of secondary infections. However, because of the discrepancies in the medical literature regarding the use of steroids in sepsis, there was no clear consensus. The 1990s produced several meta-analyses evaluating the use of high-dose steroids in septic shock. The consensus of these studies was that high-dose steroids provided no survival benefit and, in fact, were associated with increased mortality. As a result of these studies, the use of high-dose steroids for patients with septic shock has been largely abandoned. However, the use of low-dose steroids for the management of septic shock remains a topic of intense discussion.

The concept of relative adrenal insufficiency in septic shock has been the focus of several recent clinical studies. To better understand the debate, a basic understanding of the role of the adrenal glands is required. The adrenal gland produces several substances, including sympathetic hormones and glucocorticoids, including cortisol. Cortisol has immunologic and antiinflammatory effects, including inhibition of many proinflammatory cytokines (interleukin-1 [IL-1], IL-2, IL-3, IL-6, interferon gamma, and tumor necrosis factor- α). It also stimulates the production of antiinflammatory mediators such as IL-10 and decreases the local inflammatory reaction. Cortisol also plays a vital role in maintaining vascular tone and endothelial integrity. In addition, cortisol potentiates the vasoconstrictor effects of catecholamines. During critical illness, the normal physiologic response results in the stimulation of the adrenal glands and an increase in cortisol production by up to sixfold. During sepsis, the adrenal glands' ability to increase cortisol production may be impaired. Multiple factors contribute to this, including high levels of circulating inflammatory cytokines, decreased glucocorticoid

sensitivity of receptors, and suppression of the hypothalamic-pituitary-adrenal axis by various medications. The end result is a state of relative adrenal insufficiency.

In the recent past, numerous trials have been undertaken to evaluate the use of low-dose steroids in sepsis. Low-dose steroid use is defined as 300 mg or less of hydrocortisone (or an equivalent steroid) over 5 days or less. In 2002, Annane published the results of a multicenter, randomized, double-blind, placebo-controlled trial evaluating the use of low-dose steroids in patients with septic shock.³⁸ All patients with septic shock were randomized within 3 hours of the onset of septic shock to either the treatment arm or the placebo arm. Patients underwent a low-dose cosyntropin stimulation test, and relative adrenal insufficiency was defined as a delta cortisol of 9 μ g/dL or less. Patients in the treatment arm received hydrocortisone 50 mg IV every 6 hours and 50 μ g of fludrocortisone orally daily or matching placebos. Patients who received low-dose steroids showed a decreased time to shock reversal and a decreased mortality compared with patients who received placebo. Subsequently, two smaller trials and two meta-analyses demonstrated similar results.^{88,89} The findings of these studies suggest that low-dose steroid use in patients with relative adrenal insufficiency significantly improves time to shock reversal and 28-day mortality. However, a follow-up study published in 2008 brought the use of low-dose steroids in septic shock back into question. The Corticosteroid Therapy of Septic Shock (CORTICUS) trial was a multicenter, randomized, double-blind, placebo-controlled trial that also evaluated the use of low-dose steroids in patients with septic shock.⁹⁰ Patients with septic shock underwent a low-dose cosyntropin stimulation test with a delta cortisol of 9 μ g/dL used to define relative adrenal insufficiency. Unlike the Annane study, patients in the CORTICUS trial were randomized up to 72 hours after the diagnosis of septic shock to receive either hydrocortisone 50 mg IV every 6 hours or placebo. No difference in 28-day all-cause mortality was identified, but earlier shock resolution was confirmed in the steroid group (median time to reverse shock 3.1 versus 5.7 days; $p = .003$). However, it is important to note that the patients enrolled in this trial had a lower placebo group mortality (63% in the Annane study; 31% in the CORTICUS trial). The Annane study enrolled only patients with vasopressor-dependent septic shock, whereas the CORTICUS trial enrolled all patients with septic shock. In the Annane study, patients were randomized within 3 hours of the onset of septic shock. In the CORTICUS trial, patients were randomized up to 72 hours after the onset of septic shock. In addition, patients in the Annane study received both hydrocortisone and fludrocortisone as opposed to only hydrocortisone in the CORTICUS trial. The CORTICUS trial patients were different as well, with more abdominal sepsis and more surgical patients and fewer pneumonia patients. The CORTICUS trial documented that 46.7% of patients did not have a response to the corticotropin stimulation test, and these patients had a higher mortality rate. CORTICUS was underpowered for the primary outcome measure, death within 28 days in patients who did not respond to corticotropin. Therefore, considerable controversy still remains. An important contribution of the CORTICUS trial was the identification that hospital-based immunoassays are not accurate for cortisol measurements in critically ill patients.

Despite the ongoing debate over the optimal use of low-dose steroids in patients with septic shock, the Surviving Sepsis Campaign guidelines still recommend that hydrocortisone be considered in patients with septic shock who are not responsive to volume resuscitation and vasopressor therapy. The dose of hydrocortisone given should not exceed 300 mg/day and should be administered in divided doses. The use of fludrocortisone is still considered to be optional. Although the optimal duration of steroids also remains in question, most would agree that steroid administration should continue until the patient is off vasopressor therapy.

IMPORTANCE OF EARLY BROAD-SPECTRUM ANTIMICROBIALS

The timely administration of empirical antimicrobial therapy is perhaps the most beneficial pharmacologic intervention in patients with sepsis. Although antimicrobial therapy has always been a mainstay in the treatment of infection, only recently has the importance of antimicrobial choice and rapid administration been demonstrated to significantly impact patient mortality. In a landmark study by Kumar and colleagues, the relationship between time to antimicrobial administration and patient mortality was clearly documented.⁴⁴ This multicenter, retrospective study evaluated 2,154 patients with septic shock over a 15-year period. The primary objective was to determine the prevalence and impact on mortality of delays in antimicrobial administration from the initial onset of septic shock. The results of this study demonstrated a 7.6% decrease in survival for each hour of delay in antimicrobial administration after the onset of shock. In addition, patients who received effective antimicrobial therapy within 1 hour of the onset of septic shock had the highest survival rate at 79.9%. The results of this study have subsequently been corroborated by other studies.^{91,92}

In spite of convincing evidence that early antimicrobial administration significantly improves outcomes in patients with sepsis, compliance with this recommendation remains problematic. In Kumar and colleagues' study, more than 50% of septic shock patients experienced a delay in antimicrobial administration of at least 6 hours.⁴⁴ A recent multicenter prospective analysis of compliance with antimicrobial administration revealed that only 60% of patients were receiving antimicrobials within 1 hour.⁹³ After a 2-year educational campaign and focused programs for performance improvement, compliance reached only 67%. Clearly, there must be some significant clinical hurdles that we must overcome to implement this seemingly simple intervention.

Several barriers to the timely administration of antimicrobials have been identified. One critical issue is the rapid availability of IV access. During active sepsis resuscitation, IV access is needed for fluid administration and antimicrobial therapy. In addition, appropriate cultures, often from various sites, must be sent prior to antimicrobial administration. Many antimicrobials are not readily available in patient care areas and must be transported from the pharmacy to the bedside. Most patients receive at least two empirical antimicrobials, which can result in additional delays if adequate IV access is not available. Performing this multitude of tasks, particularly in an unstable septic shock patient, can quickly overwhelm the clinical team. The end result is a delay in antimicrobial administration.

Although each institution has its own barriers to implementation, it is important to recognize the importance of administering IV antimicrobials within 1 hour. This simple task of administering an antimicrobial can significantly improve patient survival. To minimize the time to antimicrobial administration, a few basic clinical practices can be implemented to help overcome these barriers. Rapidly establishing IV access is critical to the success of the resuscitation. If peripheral IV access is not easily attainable, central venous access should be secured promptly. Central venous access has the benefit of providing the clinical team with multiple infusion ports and a way to monitor CVP. Working in conjunction with Pharmacy to establish a rapidly available, premixed supply of commonly administered antimicrobials will also help minimize delays. Many institutions have developed a "sepsis toolbox" containing IV fluids, culture materials, blood tubes for measuring serum lactate, and a premixed supply of antimicrobials. This toolbox can be taken to the bedside of the sepsis patient at any location in the hospital, avoiding potential delays in the initiation of resuscitation.

The choice of empirical antimicrobial therapy is as important as administering antimicrobials within 1 hour. Antimicrobial selection can be a complex process and should take into account the patient's history and comorbid conditions, recent antimicrobial exposure, and probable source of infection. With the recent emergence of several virulent, drug-resistant pathogens, the length of the patient's hospital course and the potential for infection with such organisms should be taken into consideration. Failure to provide effective antimicrobial coverage for the causative organism significantly increases the risk of death from sepsis. The best practice is to provide broad coverage initially and de-escalate antimicrobial therapy based on culture data.

PLANNED LAPAROTOMY FOR ESTABLISHED PERITONITIS IS NOT DAMAGE CONTROL

The treatment strategy for patients with established peritonitis has been debated for three decades. After an initial emergency laparotomy, relaparotomy is frequently necessary to eliminate persistent peritonitis or a new infectious focus. There are two widely used relaparotomy strategies: relaparotomy when the patient's condition demands it ("on demand") and "planned" relaparotomy. In the planned strategy, a relaparotomy is performed every 48 hours for inspection, drainage, and peritoneal lavage of the abdominal cavity until the findings are negative for ongoing peritonitis. The planned strategy may lead to early detection of persistent peritonitis or a new infectious focus that reduces the risk of multiorgan failure but harbors the risk of potentially unnecessary reexplorations in critically ill patients, whereas the on-demand strategy harbors the risk of a potentially harmful delay in the detection of intra-abdominal infection with increased risk of multiorgan failure and the need for a delayed laparotomy at a time when intra-abdominal adhesions (days 10 to 14) create a hostile operative environment. Over the years, a number of case series have offered conflicting results. The consensus and meta-analysis conclusion is that for the non-critically ill patient (APACHE II < 10), use the on-demand strategy. Newer computed tomographic scan technology can accurately detect intra-abdominal infections in patients who clinically deteriorate or fail to improve, and with aggressive interventional radiology, greater than 95% of the

infections can be successfully treated without a repeat laparotomy. More recently, van Ruler and colleagues performed a prospective, randomized, controlled trial (PRCT) in patients with severe peritonitis (defined as APACHE II > 10) that confirmed that the practice of planned relaparotomy was associated with no difference in outcome compared with on-demand laparotomy and was associated with increased expenditure of hospital resources and length of hospital stay.⁹⁴ It is important to emphasize that this recent PRCT is not relevant to the previous discussion of “damage control” in patients with septic shock. Patients randomized into this PRCT had a mean APACHE II score of 15 (with predicted mortality of < 25%), whereas the patients we described had a mean APACHE II score of 32 (with a predicted mortality of

> 75%). We use damage control in patients in the “persistent septic shock cycle.” Its rationale is to appropriately time and limit the duration of source control to break the cycle and then optimize resuscitation in the ICU.

Conclusion

Sepsis continues to be a common and potentially lethal problem for surgical patients. The early identification and management of surgical patients with sepsis present a significant challenge to the surgical team. The implementation of rapid, evidence-based care in conjunction with timely surgical source control improves survival.

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5 MULTIPLE ORGAN DYSFUNCTION SYNDROME

John C. Marshall M.D., F.A.C.S., F.R.C.S.C.

Approach to Multiple Organ Dysfunction Syndrome

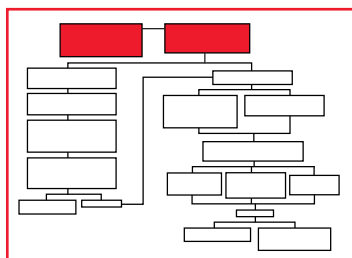
The multiple organ dysfunction syndrome (MODS)—also known as progressive systems failure,¹ multiple organ failure,² and multiple system organ failure³—is characterized by progressive but potentially reversible physiologic dysfunction of two or more organ systems that arises after resuscitation from an acute life-threatening event. The term MODS was introduced by a 1991 consensus conference of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM).⁴ The designation of MODS as a syndrome emphasizes that dynamic alterations in physiologic function in critically ill patients may have common pathophysiologic underpinnings. However, MODS is as much a paradigm as a syndrome—that is, it represents an approach to the care of the critically ill patient that emphasizes intensive monitoring and support of organ system function over specific therapies for isolated disease processes and that focuses on preventing or minimizing iatrogenic injury resulting from ICU interventions.

MODS evolves in the wake of a profound disruption of systemic homeostasis.^{5,6} It was originally described in patients with overwhelming infection, multiple injuries, or tissue ischemia; however, it has many overlapping risk factors [see Table 1]. Preexisting illness—in particular, chronic alcohol abuse⁷—predisposes to the development of organ dysfunction in patients exposed to these risk factors.

Clinical Definitions of Organ Dysfunction

Although MODS is readily recognized by experienced clinicians, there is still no clear consensus on its description with respect to either the systems whose function is deranged, the descriptors that best measure that derangement, or the degree of derangement that constitutes organ dysfunction or failure.

A systematic review of 30 published clinical studies evaluated the organ systems and variables used to describe MODS.⁸ Seven organ systems—the respiratory system (all 30 reports), the renal system (29 reports), the hepatic system (27 reports), the cardiovascular system (25 reports), the hematologic system (23 reports), the GI system (22 reports), and the CNS (18 reports)—were included in at least half of the studies. Scoring systems from both North America^{9,10} and Europe^{11,12} define MODS using six of these seven organ systems, eliminating the GI system because of the declining prevalence of stress-related upper GI bleeding and the lack of satisfactory measures of GI dysfunction. These scoring systems have many similarities [see Table 2].



In general terms, the dysfunction of a given organ system can be described in one of three ways:

1. As a physiologic derangement (e.g., an altered ratio of arterial oxygen tension [P_{aO_2}] to fractional inspiration of oxygen [F_{IO_2}] or an altered platelet count).
2. As the clinical intervention used to correct that derangement (e.g., mechanical ventilation or blood component replacement therapy).
3. As a discrete clinical syndrome incorporating several descriptive variables (e.g., acute respiratory distress syndrome [ARDS] or disseminated intravascular coagulation [DIC]).

Whichever of these three perspectives is adopted, common pathogenetic mechanisms underlie MODS, and common principles direct its prevention and management.

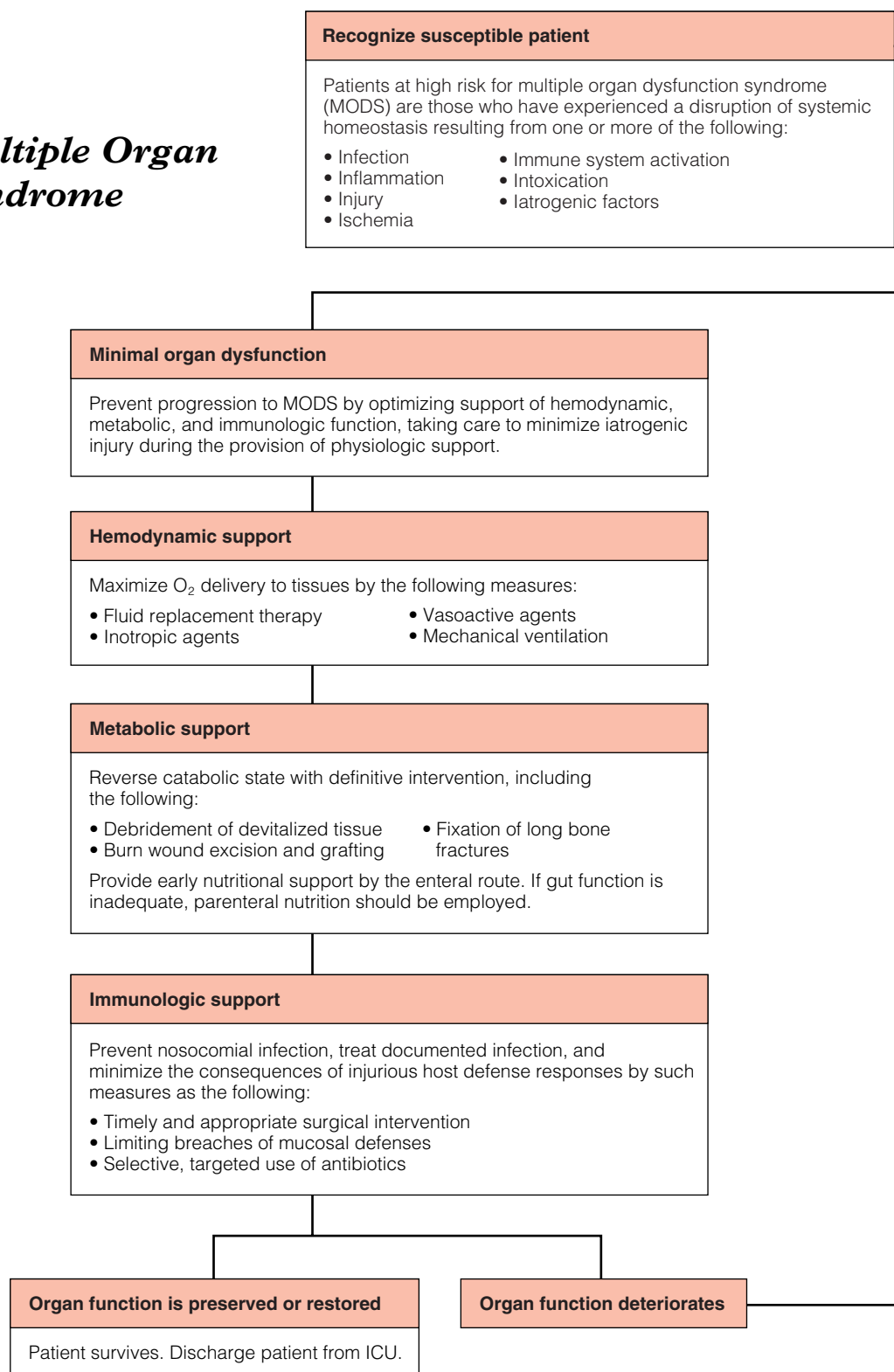
RESPIRATORY DYSFUNCTION

ARDS, initially described in the early 1960s,^{13,14} is the prototypical expression of respiratory dysfunction in MODS.¹⁵ In its

Table 1 Risk Factors for MODS

Infection	Peritonitis and intra-abdominal infections Pneumonia Necrotizing soft tissue infections
Inflammation	Pancreatitis
Injury	Multiple trauma Burn injury
Ischemia	Ruptured aneurysm Hypovolemic shock Mesenteric ischemia
Immune reactions	Autoimmune disease Transplant rejection Graft versus host disease
Iatrogenic factors	Delayed or missed injury Blood transfusion Injurious mechanical ventilation Total parenteral nutrition
Intoxication	Drug reactions Arsenic intoxication Drug overdose
Idiopathic factors	Thrombotic thrombocytopenic purpura Hypoadrenalism Pheochromocytoma

Approach to Multiple Organ Dysfunction Syndrome



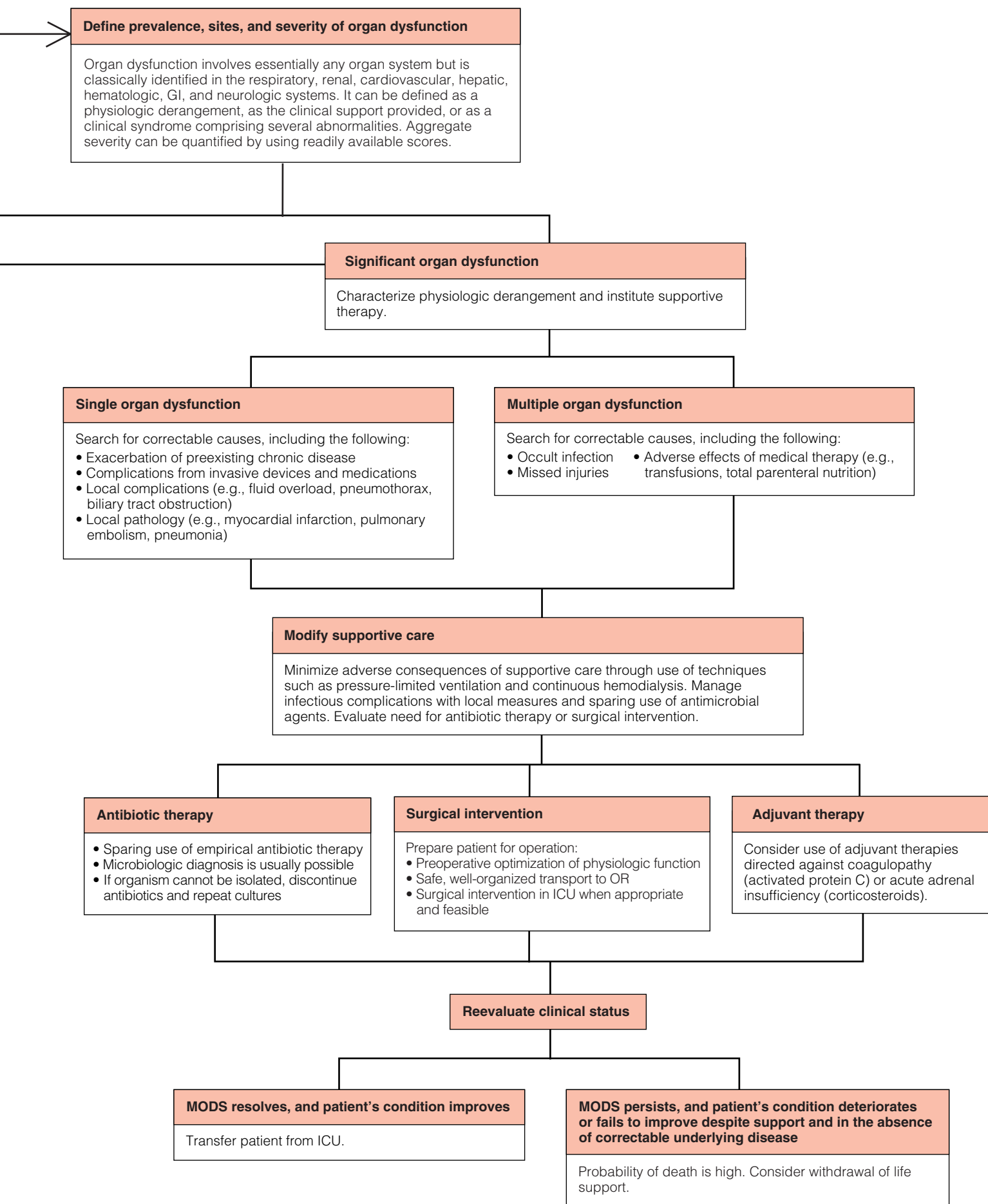


Table 2 Multiple Organ Dysfunction (MOD) Score⁹

Organ System	Indicator of Dysfunction	Degree of Dysfunction				
		None (0)	Minimal (1)	Mild (2)	Moderate (3)	Severe (4)
Respiratory	P _a O ₂ /F _i O ₂ ratio	> 300	226–300	151–225	76–150	≤ 75
Renal	Serum creatinine level	≤ 100 μmol/L	101–200 μmol/L	201–350 μmol/L	351–500 μmol/L	> 500 μmol/L
Hepatic	Serum bilirubin level	≤ 20 μmol/L	21–60 μmol/L	61–120 μmol/L	121–240 μmol/L	> 240 μmol/L
Cardiovascular	Pressure-adjusted HR*	< 10.0	10.1–15.0	15.1–20.0	20.1–30.0	> 30.0
Hematologic	Platelet count	> 120,000/mm ³	81,000–120,000/mm ³	51,000–80,000/mm ³	21,000–50,000/mm ³	≤ 20,000/mm ³
Neurologic	Glasgow Coma Scale score	15	13–14	10–12	7–9	≤ 6

*Calculated as the product of HR and central venous pressure (CVP), divided by mean arterial pressure (MAP): (HR · CVP)/MAP.

mildest form, respiratory dysfunction is characterized by tachypnea, hypocapnia, and hypoxemia. As lung injury evolves, a combination of worsening hypoxemia and increased work of breathing necessitates mechanical ventilatory support [see 8:6 *Mechanical Ventilator*].

Increased capillary permeability and neutrophil influx are the earliest pathologic events in ARDS. As the acute inflammatory process resolves, further lung injury results both from the process of repair, which involves fibrosis and the deposition of hyaline material, and from further lung trauma, resulting from positive pressure mechanical ventilation.¹⁶

Lung involvement in ARDS is inhomogeneous, with areas of functional and aerated alveoli interspersed with areas of non-functional alveoli.¹⁷ The distribution of injury reflects the sequelae of care in the intensive care unit: consolidation occurs in the posterior dependent regions of the lung, and cystic changes develop from overdistention by the ventilator in the antidependent regions.¹⁸

Impaired lung function is reflected in a reduced P_aO₂. To ensure adequate oxygen delivery to the tissues, mechanical ventilation must be instituted and F_iO₂ increased. The ratio of P_aO₂ to F_iO₂, therefore, provides a sensitive and objective measurement of the degree to which oxygenation is impaired and so is a reliable measure of physiologic respiratory dysfunction.¹⁹ Mechanical ventilation reflects the clinical intervention triggered by impaired oxygenation, and the additional criteria for ARDS—bilateral lung infiltrates and a normal pulmonary capillary wedge pressure—serve to exclude such primary causes of acute hypoxemia as pulmonary embolism, atelectasis, and congestive heart failure. By consensus, ARDS is defined as a P_aO₂/F_iO₂ ratio lower than 200 mm Hg in association with bilateral fluffy pulmonary infiltrates and a pulmonary capillary wedge pressure lower than 18 mm Hg.²⁰

ARDS is a robust model for the complex interactions that result in MODS. Lung injury in ARDS is the outcome of an interaction between an insult, a susceptible host, and the clinical therapeutic response, and its severity reflects not only the degree of the initial insult but also various poorly defined genetic influences in the host²¹ and the inadvertent adverse consequences of the mode of respiratory support employed.²²

RENAL DYSFUNCTION

Acute renal failure (ARF) [see 8:7 *Renal Failure*] was first described as a significant clinical problem during World War II,²³

but supportive care, in the form of dialysis, did not become available until the 1950s.

Clinical or subclinical renal dysfunction is common in MODS. Early-onset renal dysfunction typically results from hypotension and decreased renal blood flow. The etiology of late-onset renal failure is multifactorial and includes both pre-renal factors (e.g., decreased cardiac output and hypovolemia) and the cumulative renal effects of nephrotoxic agents (e.g., medications and radiocontrast material).²⁴ Intrarenal vasoconstriction results in a reduction in the glomerular filtration rate, hypoxic or oxidative injury to tubular epithelial cells, and desquamation of injured cells into the tubules, causing leakage of filtrate back into the renal interstitium and evoking neutrophil-mediated inflammation that causes further local tissue injury.²⁵ Intrarenal shunting of blood flow, coupled with occlusion of the renal microvasculature by thrombi or aggregated blood cells, further contributes to ischemia and physiologic dysfunction. The situation may be further aggravated by renal circulatory changes resulting from vasoactive agents administered to treat shock and by increased intra-abdominal pressure consequent to massive fluid resuscitation. Histologic studies show acute tubular necrosis with disruption of the basement membrane, patchy necrosis of the renal tubules, interstitial edema, and tubular casts; these microscopic changes correlate poorly with functional impairment.²⁶ Activated neutrophils have also been implicated in the pathogenesis of ARF,^{27,28} as has the induction of apoptosis in renal epithelial cells.²⁹

Renal dysfunction in MODS is reflected physiologically in a decreased urine output, biochemically in a rising serum creatinine level, and therapeutically as the introduction of exogenous renal replacement therapy or dialysis.

HEPATIC DYSFUNCTION

Hepatic dysfunction after trauma, like ARF, was first described during World War II [see 8:9 *Hepatic Failure*].³⁰ Two clinical syndromes have been described. The first, ischemic hepatitis, or shock liver, characteristically follows an episode of profound hypotension with splanchnic hypoperfusion. Early elevations of aminotransferase levels are striking and may be associated with an increased international normalized ratio and hypoglycemia; centrilobular necrosis is evident histologically. Successful resuscitation of the shock state results in rapid normalization of the biochemical abnormalities.³¹ The second syndrome, ICU jaundice, is much more common than ischemic

hepatitis and typically evolves many days after the inciting physiologic insult. Conjugated hyperbilirubinemia is a prominent feature, whereas elevation of aminotransferase levels and alterations of hepatic synthetic function are less pronounced.³² Histologic features include intrahepatic cholestasis, steatosis, and Kupffer cell hyperplasia. The pathogenesis is multifactorial and includes ongoing hepatic ischemia, total parenteral nutrition (TPN)-induced cholestasis, and drug toxicity.

An increased serum bilirubin level is the most commonly recognized feature of the hepatic dysfunction of MODS. Although extracorporeal support devices have been used for patients with end-stage liver disease, the hepatic dysfunction of critical illness is not considered to be life-threatening in itself, and no specific supportive therapy is indicated.

CARDIOVASCULAR DYSFUNCTION

Both peripheral vascular and myocardial function are altered in MODS. Characteristic changes in the peripheral vasculature include a reduction in vascular resistance and an increase in microvascular permeability, resulting in a hyperdynamic circulatory profile and peripheral edema. Both alterations jeopardize tissue oxygenation—reduced vascular resistance by facilitating shunting in the microvasculature and edema by increasing the distance across which oxygen carried in the blood must diffuse to reach the cell. Shunting also occurs as a result of occlusion of the microvasculature by thrombi and aggregates of nondeformable red cells³³; it is signaled by a reduction in arteriovenous oxygen extraction and an increase in mixed venous oxygen saturation ($S_{mv}O_2$). Biventricular dilatation with a reduction in the right and left ventricular ejection fractions has been described.³⁴ Right ventricular dysfunction is particularly prominent, perhaps as a consequence of increased pulmonary vascular resistance secondary to concomitant lung injury.³⁵ Finally, a loss of normal heart rate variability characterizes advanced cardiovascular dysfunction.³⁶

The cardiovascular dysfunction of MODS is apparent clinically as increased peripheral edema with hypotension that is refractory to volume challenge and therapeutically in the use of vasoactive agents to support the circulation. Nitric oxide (NO) has been implicated in both the peripheral vasodilatation³⁷ and the myocardial depression³⁸ associated with critical illness.

NEUROLOGIC DYSFUNCTION

Abnormalities of both central and peripheral nervous system function are common in critical illness. CNS dysfunction occurs in as many as 70% of critically ill patients, typically presenting as a reduced level of consciousness without localizing signs. Its pathophysiology is incompletely understood. Postulated mechanisms include the direct effects of proinflammatory mediators on cerebral function, the development of vasogenic cerebral edema, areas of cerebral infarction related to hypotension, and alterations in the blood-brain barrier resulting in changes in the composition of the interstitial fluid.³⁹ Electroencephalography typically shows one of four patterns indicating increasingly abnormal activity: diffuse theta wave rhythms, intermittent rhythmic delta waves, triphasic delta waves, and suppression or burst-suppression patterns.³⁹

Peripheral nervous system dysfunction, also known as critical illness polyneuropathy, is also common in MODS, though its clinical presentation tends to be more subtle than that of CNS dysfunction.^{40–42} Peripheral nervous system dysfunction may present as failure of weaning from mechanical ventilation⁴³ or as limb weakness with relative sparing of the cranial nerves. Endoneurial edema and axonal hypoxia⁴⁴ contribute to its pathogenesis, as do the iatrogenic sequelae of neuromuscular blockade.⁴⁵

HEMATOLOGIC DYSFUNCTION

The most common hematologic abnormality of critical illness is thrombocytopenia, which occurs in approximately 20% of all ICU admissions.^{46,47} Causes include increased consumption, intravascular sequestration, and impaired thrombopoiesis secondary to suppression of bone marrow function. In addition, heparin-induced thrombocytopenia resulting from antibodies to complexes of heparin and platelet factor 4 develops in as many as 10% of patients receiving heparin.⁴⁸ The most fulminant expression of hematologic dysfunction in MODS is DIC, which is characterized by derangements in platelet numbers and clotting times and the presence of fibrin degradation products in plasma.⁴⁹ The coagulopathy of critical illness is complex, involving multiple alterations in the biochemical mediators of coagulation and resulting in a shift to a procoagulant state.⁵⁰

Mild anemia is common in critical illness, though the nature of abnormalities in red cell production and removal are less well characterized in this setting.⁵¹ Transient leukopenia may develop in response to an overwhelming inflammatory stimulus, but neutrophilia is much more commonly encountered; total lymphocyte counts are reduced. Abnormalities in white cell populations reflect, at least in part, altered expression of apoptosis, which is inhibited in the neutrophil⁵² but accelerated in lymphoid cells.⁵³

GASTROINTESTINAL DYSFUNCTION

Upper GI hemorrhage after burn injury was first described by Curling in 1842.⁵⁴ Stress bleeding was once a relatively common complication, but improved techniques of resuscitation and hemodynamic support, earlier diagnosis of infection, and the widespread use of stress ulcer prophylaxis have reduced the frequency of this event, to the point where it now is seen in fewer than 4% of ICU admissions.⁵⁵ Other manifestations of GI dysfunction in MODS include ileus and intolerance of enteral feeding,^{56,57} pancreatitis,⁵⁸ and acalculous cholecystitis.⁵⁹

OTHER ORGAN SYSTEM DYSFUNCTION

MODS is associated with functional abnormalities of virtually every organ system. Endocrine abnormalities include impaired glucose regulation with hyperglycemia and insulin resistance⁶⁰ and hypercortisolemia with impaired responsiveness to adrenocorticotropic hormone (ACTH) stimulation.^{61,62} The sick euthyroid syndrome, characterized by reductions in serum T_3 , with or without an increase in reverse T_3 levels and a normal T_4 level, is another manifestation of the endocrine dysfunction of MODS.⁶³

Numerous derangements of immune function have been described in MODS patients. Cell-mediated immunity is impaired, as reflected by anergy to delayed hypersensitivity recall skin testing⁶⁴ and impaired *in vitro* lymphocyte proliferative responses.⁶⁵ The development of ICU-acquired infections caused by organisms of low intrinsic virulence can also be considered a manifestation of impaired immunity in MODS.⁶⁶

Abnormal wound healing also occurs in MODS. Common manifestations of impaired wound healing are the failure of an open wound to develop satisfactory granulation tissue and the development of decubitus ulcers.⁶⁷

Quantification of Organ Dysfunction

Physiologic instability is the major indication for ICU admission, and support of failing organ function is the ICU's *raison d'être*. The degree of physiologic derangement present at the time of ICU admission is a potent determinant of ICU survival,^{68,69} and irreversible organ dysfunction is the preeminent

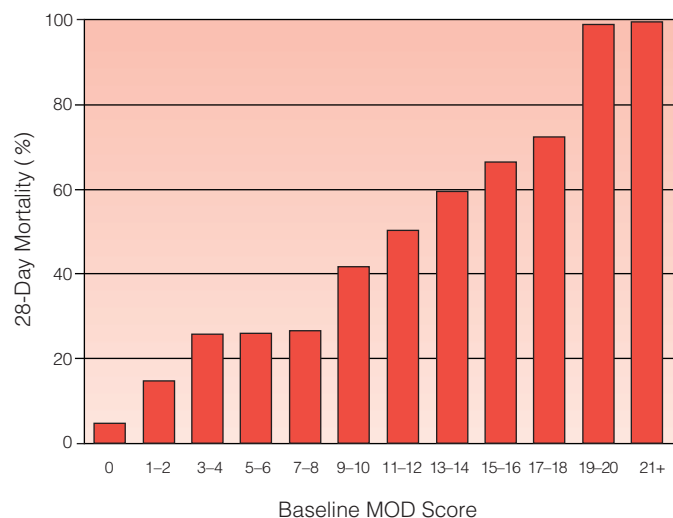


Figure 1 Increasing severity of organ dysfunction is directly correlated with increasing ICU mortality.

mode of ICU death.^{6,70} Formal quantification of the severity of physiologic derangement or of the evolution of organ dysfunction over time is not generally incorporated into individual patient care in the ICU. However, validated scoring systems have proved invaluable in describing patient populations, stratifying patients for entry into clinical trials, and assessing ICU morbidity in patient groups.

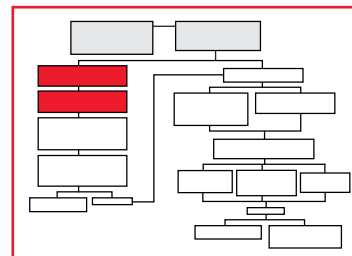
There are a number of published systems for quantifying the severity of organ dysfunction in the critically ill.^{9,10,12,66,71-74} These systems are all structurally similar, evaluating dysfunction in each of six or seven organ systems on a numerical scale in which more points are assigned for greater degrees of physiologic severity; they vary primarily with respect to the variables used to describe dysfunction. A representative example of such a scoring system is the Multiple Organ Dysfunction (MOD) score [see Table 2].⁹

The numerical scores can be obtained and applied in a variety of ways.⁷⁵ Scores can be calculated on the day of ICU admission or at the start of the institution of a novel therapy during the ICU stay; such scores provide a measure of baseline illness severity and correlate in a graded manner with the risk of ICU mortality [see Figure 1]. Scores can also be calculated daily, allowing the clinician to track net clinical improvement or deterioration over time⁷⁶ and to assess the progression or resolution of organ dysfunction (expressed as the area under the curve for the daily

scores).⁷⁷ Alternatively, the aggregate severity of organ dysfunction over time can be quantified by summing the worst values over time in each of the component systems. Such an approach permits quantitation of attributable ICU morbidity as the difference between the aggregate score and the score at baseline—thus identifying that component of ICU morbidity that can be prevented by an effective ICU intervention. Finally, morbidity and mortality can be combined into a single value by using a mortality-adjusted score that assigns a maximum number of points plus 1 to any patient who dies [see Table 3].

Prevention of Organ Dysfunction in Critically Ill Patients

Acute organ dysfunction is the most common indication for admission to an ICU, and any patient with significant physiologic instability is at risk for MODS. A number of risk



factors for the development of organ dysfunction have been identified [see Table 1]: these reflect a common pathogenesis for the syndrome through the activation of an innate immune response to tissue injury.

The first priority for optimal ICU care is to halt the progression of existing organ dysfunction while preventing the development of new organ dysfunction. Prevention of organ dysfunction is perhaps best approached from the perspective of optimization of hemodynamic, metabolic, and immune homeostasis. There are a number of interventions for which level 1 evidence of efficacy in reducing mortality or preventing organ dysfunction exists [see Table 4].

OPTIMIZING HEMODYNAMIC HOMEOSTASIS

The ability of the heart to pump blood is determined by (1) the preload delivered to the right atrium, (2) the intrinsic contractility of the myocardium, and (3) the afterload against which the heart must work—all of which may be deranged in critical illness. First, reduction of intravascular volume as a consequence of hemorrhage, third-space loss, and increased microvascular permeability reduces preload. Second, circulating mediators and NO depress myocardial contractility and thus impair the heart's intrinsic pumping ability. Third, reduced vascular tone, mediated by NO, reduces afterload. The first two abnormalities reduce cardiac output; the third increases it but may, by altering resistance gradients

Table 3 Approaches to Measuring Severity of MODS⁷⁵

Objective	Approach	Uses
To quantify baseline severity of organ dysfunction	Calculate organ dysfunction score on day of admission (admission MODS)	To establish baseline severity (e.g., for entry criteria for a clinical trial) or to ensure comparability of study groups
To quantify severity of organ dysfunction at point in time	Calculate score on particular ICU day (daily MODS)	To determine intensity of resource utilization or evolution or resolution of organ dysfunction at discrete point in time
To measure aggregate severity of organ dysfunction over ICU stay	Sum individual worst scores for each organ system over defined time interval (aggregate MODS)	To determine severity of physiologic derangement over defined time interval (e.g., ICU stay)
To quantify new organ dysfunction arising after ICU admission	Calculate difference between aggregate and admission scores (delta MODS)	To measure organ dysfunction attributable to events occurring after ICU admission
To provide combined measure of morbidity and mortality	Adjust aggregate score so that all patients dying receive maximal number of points (mortality-adjusted MODS)	To create single measure that integrates impact of morbidity in survivors and mortality for nonsurvivors

Table 4 ICU Interventions That Reduce Mortality or Attenuate Organ Dysfunction

Objective	Intervention
Resuscitation	Early goal-directed resuscitation ²⁴³
Prophylaxis	Selective digestive tract decontamination ⁹⁰
ICU support	Restrictive transfusion strategy ¹⁰⁷ Low tidal volume ventilation ²² Daily awakening ¹⁴⁴ Tight glucose control ⁶⁰ Enteral feeding ⁸⁶
Mediator-targeted therapy	Activated protein C ¹⁴⁶ Corticosteroids ¹⁴⁸ Antibody to TNF ²⁴⁴

in the microvasculature, alter nutrient flow to the tissues.

The first priority in supporting cardiovascular homeostasis, therefore, is to restore intravascular volume by administering fluids. There is no convincing evidence that any particular resuscitation fluid is superior in all patients, though crystalloid is associated with a lower mortality in trauma patients.⁷⁸ Either normal saline or lactated Ringer solution is an appropriate choice. The volume of fluid needed to restore optimal preload may be significant, reflecting not only acute losses but also the effective expansion of the vascular compartment because of vasodilatation and the loss of fluids into the extravascular compartment because of increased capillary permeability. Blood loss should be corrected by transfusing red cells, preferably in fresh, leukocyte-depleted blood. When hypotension is refractory to fluid administration, vasoactive agents, including vasopressors (e.g., dopamine and norepinephrine) and inotropes (e.g., dobutamine, epinephrine, and amrinone) may help increase blood flow to the tissues.⁷⁹

Given that the goal of hemodynamic stabilization is to support organ function rather than to restore physiologic or biochemical normalcy, the best measures of the success of resuscitation are those that reflect either return of function (in particular, urine output) or adequate blood flow to the tissues (e.g., $S_{mv}O_2$ or lactate concentration). Each of these measures, however, has shortcomings of which the clinician must be aware. Urine output may be decreased because of intrinsic renal damage even in the face of adequate renal flow. $S_{mv}O_2$ may be artefactually high because of shunting and abnormalities of oxygen uptake in the microvasculature. Lactate concentration is relatively insensitive to mild degrees of inadequate oxygen delivery and may be elevated in patients with liver disease.

Gastric production of CO_2 as measured with a gastric tonometer has been proposed as a means of evaluating splanchnic blood flow, but the benefits of tonometry in improving outcome are unproven.⁸⁰ Microvascular flow can also be directly visualized in the tongue or another exposed mucosal surface by using orthogonal polarization spectral imaging.⁸¹ Neither of these approaches has been widely used to guide resuscitation.

Blood pressure is widely used as an index of the initial adequacy of resuscitation, but pressure measurements may not reliably reflect flow in the microvasculature, particularly when systemic vascular resistance is low. Measurement of central venous or pulmonary capillary wedge pressures provides an estimate of the preload to the heart, though factors such as positive pressure ventilation, the extent of capillary leakage in the lungs, and

intrinsic myocardial dysfunction can all alter the pressure at which optimal preload is obtained.

In practice, resuscitation should be titrated to optimize the balance between several parameters rather than targeting any one parameter. It is sobering to recognize that current sophisticated approaches to resuscitation using the pulmonary arterial catheter have not been shown to yield net clinical benefit and may, in fact, cause harm [see 8:4 *Cardiopulmonary Monitoring*].⁸²

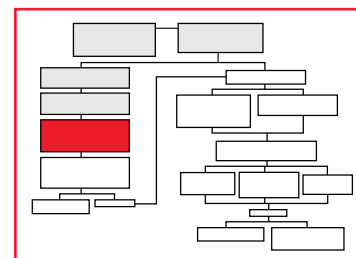
Hemodynamic resuscitation is most effective when it is early and rapid. A randomized trial of goal-directed therapy for sepsis, using a protocol comprising fluid administration, transfusion, and vasoactive support titrated to $S_{mv}O_2$ as measured from the superior vena cava through a central venous catheter, found that mortality was reduced from 46.5% to 30.5% when patients were resuscitated according to protocol in the emergency department within hours of their initial presentation. On the other hand, studies of goal-directed therapy initiated in the ICU have generally failed to demonstrate any evidence of benefit.^{83,84}

Optimization of oxygen delivery presupposes the ability to oxygenate blood adequately in the lungs. Increased pulmonary capillary permeability, atelectasis, altered consciousness, and intrinsic lung disease can all reduce oxygen uptake in acutely ill patients. Support can be provided through the administration of oxygen to the spontaneously breathing patient, through the use of positive pressure ventilation by mask, or through endotracheal intubation and mechanical ventilation. Positive pressure ventilation can cause further lung injury, however, particularly when the lung has been rendered vulnerable by early acute lung injury. Limiting tidal volume during mechanical ventilation to 6 ml/kg has been shown to improve survival in patients with early ARDS.²²

OPTIMIZING METABOLIC HOMEOSTASIS

The acute response to stress and injury is a complex, coordinated process characterized by increases in levels of catecholamines, glucocorticoids, antidiuretic hormone, and hormones that regulate intermediary metabolism, including insulin, glucagon, and growth hormone [see 8:25 *Metabolic Response to Critical Illness*].⁶ The activation of this response results in a predictable series of metabolic alterations, including retention of salt and water, increased production of glucose, enhanced lipolysis, increased protein catabolism, and an altered pattern of hepatic protein synthesis known as the acute-phase response, characterized by increased synthesis of C-reactive protein, α_1 -anti-trypsin, and fibrinogen and reduced synthesis of albumin.

Metabolic prophylaxis of MODS is directed toward reversal of the stimuli responsible for the catabolic hormonal milieu and toward the provision of adequate biochemical substrate at a time of increased metabolic demand. Early definitive surgical therapy in the form of debridement of devitalized tissue, burn wound excision and grafting, and rigid fixation of long bone fractures can attenuate the postinjury hypermetabolic state and minimize the subsequent development of MODS, though the benefits of early definitive therapy must be weighed against the additional stress of blood loss and hemodynamic instability. In the face of overwhelming injury, a policy of damage control to permit stabilization of the patient in the ICU is associated with an improved clinical outcome.⁸⁵



Nutritional support should be provided by the enteral route if possible [see 8:22 *Nutritional Support*]. Enteral nutrition is feasible in most patients, particularly if feedings are initiated early. The administration of even small quantities of enteral nutrition is considered advisable, even if it must be supplemented by some degree of parenteral nutrition. There is increasing evidence that immunologically enhanced enteral formulas can yield better clinical outcomes than standard enteral formulas.⁸⁶

Close regulation of glucose levels in accordance with an intensive policy of monitoring and insulin administration has been shown to improve clinical outcome.⁶⁰ On the other hand, there is no evidence that administration of growth hormone offers any significant benefit.⁸⁷

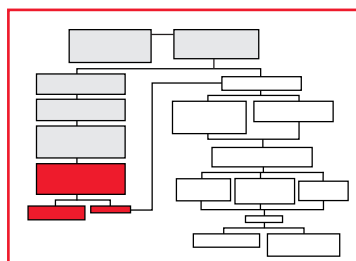
OPTIMIZING IMMUNOLOGIC HOMEOSTASIS

Infection is an important risk factor for MODS, but the converse is equally true: patients with MODS are at significantly increased risk for infection. This risk arises as a consequence both of impairment of normal host defense mechanisms and of colonization with potentially infectious nosocomial pathogens [see 8:16 *Nosocomial Infection*].

Of the numerous derangements of normal immune function with which critical illness is associated, impairment of mucosal defenses is probably the most important (and certainly the most preventable). Mucosal defenses are breached by surgical incisions and by invasive devices, including intravascular catheters, urinary catheters, and endotracheal and nasogastric tubes. Limiting the number of such devices in use and paying rigorous attention to their insertion and maintenance are important for minimizing nosocomial infection rates.⁸⁸ Gastric acid plays a primary role in maintaining the relative sterility of the stomach. Antacids ablate this defense and are a recognized risk factor for nosocomial pneumonia; they should not be used for stress ulcer prophylaxis. The declining incidence of clinically significant stress bleeding in the contemporary ICU suggests that prophylaxis should be limited to patients who are at increased risk for stress ulceration.⁵⁵ Cytoprotective agents (e.g., sucralfate) appear to have no significant advantages over H₂ receptor antagonists in reducing the risk of ventilator-associated pneumonia and are less efficacious in preventing bleeding⁸⁹; accordingly, H₂ receptor antagonists appear to be the prophylactic agents of choice.

An alternative strategy for preventing pathologic gut colonization and nosocomial infection involves prophylactic administration of a combination of systemic antibiotics (e.g., cefotaxime) and topical nonabsorbed antibiotics (e.g., tobramycin, polymyxin, and amphotericin B). This approach, known as selective decontamination of the digestive tract (SDD), has proved effective in reducing nosocomial infection rates and even ICU mortality⁹⁰; the effect is particularly evident in surgical patients who receive both systemic and topical therapy.⁹¹

Enteral feeding is beneficial in preventing nosocomial infection. Systemic antibiotics suppress the indigenous flora of mucosal surfaces, promoting pathologic colonization with resistant organisms.⁹² Therefore, use of antimicrobial agents in critically ill patients must be selective and targeted, and the use of broad-spectrum empirical therapy should be minimized by regular reviews of culture and sensitivity results and restrictions on antibiotic prescription practices.



Although nosocomial infections in critically ill patients usually arise from endogenous reservoirs, pathogens may also spread from patient to patient and from environment to patient. Certain organisms—in particular, *Acinetobacter*, *Xanthomonas*, and *Legionella*—are transmitted through aqueous sources in the ICU, and the isolation of these organisms from a critically ill patient is evidence of a potential problem in environmental infection control. Hand washing is an important but underutilized mode of infection prevention in the ICU [see 1:1 *Prevention of Postoperative Infection*]. There is no clear evidence that protective isolation of critically ill patients warrants the increased costs and increased demands on nursing staff.

The role of immunomodulation in the prophylaxis of MODS remains undefined. At present, there is no defined role for chemoprophylaxis of MODS beyond the specific effects of drugs such as heparin (prevention of deep vein thrombosis [DVT]) and H₂ receptor antagonists (prevention of upper GI bleeding).

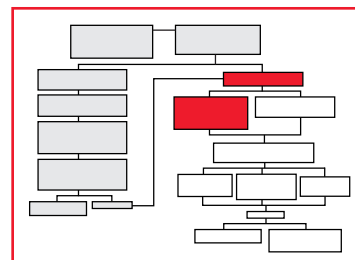
Evaluation of the Patient with Organ Dysfunction

SINGLE ORGAN DYSFUNCTION

Single organ dysfunction suggests local disease and should trigger a search for potentially correctable causes in the organ system involved. Isolated organ dysfunction may reflect preexisting chronic disease or a local problem such as fluid overload, atelectasis, biliary tract obstruction, or elevated intracranial pressure. Complications related to invasive devices or the adverse effects of medications are common causes of single organ dysfunction; the diagnosis is often presumptive, established on the basis of clinical improvement after discontinuance of the agent or removal of the device. Finally, single organ dysfunction may indicate acute disease in the involved organ, such as myocardial infarction, pulmonary embolism, or bone marrow suppression.

Acute respiratory dysfunction, for example, may be caused by pneumonia, atelectasis, pleural effusion, pneumothorax, or pulmonary embolism. Central venous and pulmonary arterial catheters may induce tachyarrhythmias as a result of mechanical irritation of the conducting system. Isolated renal dysfunction may be a consequence of abdominal compartment syndrome or of the nephrotoxic effects of medications (e.g., acute tubular necrosis caused by aminoglycosides and interstitial nephritis caused by penicillins and cephalosporins). Occasionally, renal dysfunction arises from a postrenal cause, such as blockage of a Foley catheter.

Medications are important causes of liver dysfunction in the critically ill patient. Erythromycin, ketoconazole, and haloperidol, for example, can induce cholestatic liver injury. Thrombocytopenia is an important adverse effect of a number of medications, including heparin flushes to maintain the patency of arterial lines. A decreased level of consciousness is usually the result of the poorly characterized metabolic encephalopathy of critical illness; however, it is necessary to rule out local causes such as meningitis, encephalitis, brain abscess, and subdural hematoma. Excessive or prolonged use of narcotics or sedative-hypnotics may lead to sustained alterations in level of consciousness, particularly when hepatic or renal function is impaired. Nondepolarizing muscle relaxants (e.g., vecuronium) may cause prolonged neuromuscular blockade and peripheral neuropathy.⁴⁵



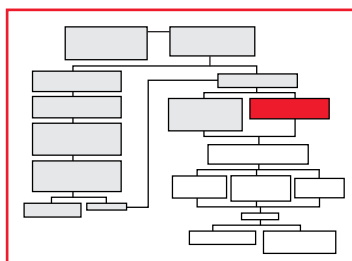
MULTIPLE ORGAN DYSFUNCTION

Although it has been suggested that there is a characteristic temporal sequence in the development of MODS [see Table 5],^{3,9} the clinical course tends to be variable and depends in part on the criteria used to define organ system dysfunction (see above). The specific pattern of dysfunction is much less important than the course of the evolving syndrome. Resolution of dysfunction suggests an appropriate response to specific and supportive therapy. Worsening of dysfunction, on the other hand, should prompt a search for potentially correctable causes and a reevaluation of the methods of supportive care in use. Not infrequently, a treatable cause of evolving MODS is found; often, however, no cause is evident. When no specific cause of the deterioration can be identified, therapy should focus on optimizing supportive measures to limit iatrogenic injury either until the patient recovers or, alternatively, until a considered decision is made that continuing active care is futile.

Search for Correctable Causes

Occult infection Uncontrolled infection, particularly infection arising within the abdomen, is an important risk factor for MODS.^{2,3,93} The development of otherwise unexplained organ dysfunction should trigger a careful radiologic search for an occult intra-abdominal focus.⁹⁴ However, MODS also develops in patients with pneumonia⁵⁸ and other life-threatening infections, and it sometimes evolves in patients in whom no infectious focus can be identified.^{66,95}

When MODS develops in the postoperative period, a careful search for infection must be undertaken, concentrating in particular on the operative site and on any invasive devices used. With appropriate attention to the clinical possibilities, aided by ultrasonography and CT scanning, the presence or absence of significant intra-abdominal pathology can usually be established. Local wound exploration may suggest the possibility of occult intra-abdominal infection through the demonstration of impaired wound healing or fascial dehiscence or through the isolation of typical intestinal microflora from a wound infection. The diagnosis of pneumonia in intubated ICU patients is notoriously difficult; however, the use of quantitative techniques (e.g., protected specimen brush bronchoscopy and bronchoalveolar lavage) can



aid in establishing or excluding the diagnosis.^{96,97}

MODS is rarely caused by urinary tract infections or device-related bacteremias, though these conditions are common in patients with significant organ dysfunction. *Clostridium difficile* colitis or disseminated fungal infection may also present as deteriorating organ function in critically ill patients.⁹⁸

Iatrogenic factors MODS can be considered the quintessential iatrogenic disorder, reflecting both the successes and the failures of contemporary ICU practice. On one hand, the syndrome arose only because the supportive care available today permits the prolonged survival of critically ill patients who, in an earlier era, would have died rapidly; on the other hand, potentially avoidable iatrogenic factors contribute prominently to the evolution of MODS.

Technical or judgmental errors often set the stage for MODS.⁹⁹⁻¹⁰¹ Whenever a patient manifests unexplained organ failure in the postoperative period, the surgeon must consider the possibility of an iatrogenic complication—for example, a missed intestinal perforation in a trauma victim, a leak from a tenuous anastomosis, or left colon ischemia after aneurysmectomy.

Many of the therapeutic interventions that are the mainstay of ICU care have the potential to cause local and remote organ injury. In the experimental setting, mechanical ventilation with high tidal volumes and low levels of positive end-expiratory pressure (PEEP) can induce both pulmonary and remote organ injury.^{102,103} A multicenter, randomized, controlled trial confirmed that mechanical ventilation of patients with acute lung injury in accordance with a lung-protective strategy (i.e., a tidal volume of 6 ml/kg) significantly improves survival²² and attenuates the local and systemic release of proinflammatory mediators [see 8:6 *Mechanical Ventilator*].¹⁶ Oxygen in high concentrations can produce pulmonary damage, probably as a result of the generation of toxic oxygen intermediates [see 8:26 *Molecular and Cellular Mediators of the Inflammatory Response*].¹⁰⁴

Blood transfusion has been implicated in the development of organ dysfunction, an effect that occurs independent of the effects of shock, blood loss, and fluid resuscitation.^{105,106} A multicenter, randomized, controlled trial demonstrated a significant reduction in the severity of new organ dysfunction in a heterogeneous population of critically ill patients when transfusion was withheld unless the hemoglobin concentration was less than 70 g/L (7 g/dl).¹⁰⁷ The age of the blood administered may be an underappreciated factor in defining optimal transfusion strategies. The effects of blood transfusion on splanchnic blood flow as measured with a gastric tonometer are significantly dependent on the age of the transfused blood. Transfusion of blood that is more than 12 days old can have an adverse impact on oxygen delivery.¹⁰⁸

TPN can also contribute to the de novo development of organ dysfunction. TPN-associated alterations in hepatic function with intrahepatic cholestasis and fatty infiltration are relatively common and are manifested by elevated aminotransferase and alkaline phosphatase levels.¹⁰⁹ TPN may also give rise to glucose intolerance and can aggravate ventilatory impairment through increased CO₂ production. In patients with borderline pulmonary function, this additional CO₂ production may prevent weaning from ventilatory support.¹¹⁰ Parenteral nutrition is also associated with higher rates of postoperative and nosocomial infections after multiple trauma.¹¹¹

Medications—in particular, analgesics, sedatives, and antibiotics—have also been associated with evolving organ dysfunction.

Table 5 Temporal Evolution of MODS^{3,9}

System	Time from ICU Admission to Onset of Significant Dysfunction (days)
Respiratory	1–2
Hematologic	3
Central nervous	4
Cardiovascular	4
Hepatic	5–6
Renal	4–11
Gastrointestinal	10–14

Inhaled NO is selectively delivered to ventilated lung segments and may effect early improvement of oxygenation in ARDS patients¹²¹; whether this early physiologic effect translates into an improved clinical outcome is unknown. Extracorporeal lung support by means of extracorporeal membrane oxygenation or extracorporeal CO₂ removal can be lifesaving in patients with isolated severe respiratory failure that is refractory to other forms of respiratory support.^{122,123} These techniques are resource intensive, however, and have not been convincingly shown to yield better outcomes than conventional mechanical ventilation.¹²⁴ If the patient remains hypoxemic despite optimization of

ventilatory support, it may be necessary to accept an arterial oxygen saturation (S_aO_2) as low as 80%.

Tissue oxygen delivery ($\dot{V}O_2$) is a function of three variables—cardiac output, hemoglobin concentration, and S_aO_2 (oxygen dissolved in the plasma makes only a negligible contribution). Tissue oxygen consumption ($\dot{V}O_2$) is a function of cardiac output and oxygen extraction (defined as the difference between arterial and venous oxygen content). In practice, multiple factors can impair oxygen delivery and consumption, and it is important that the clinician recognize these.

Oxygen uptake in the tissues is an entirely passive process, resulting from the diffusion of oxygen toward the relatively hypoxic extravascular space along an oxygen saturation gradient that is highest in the microvasculature and lowest at the cell. This passive diffusion can be reduced if there is interstitial edema, which makes the concentration gradient less steep, or if blood flow through the microvasculature is rapid. Alternatively, a reduction in the resistance of small arterioles may impede the diversion of blood into the microvasculature. Moreover, nutrient vessels in the microcirculation may be occluded by aggregates of neutrophils, platelets, and aged (and thus less deformable) red blood cells. The net result of these abnormalities is the shunting of oxygenated blood from the arterial side of the circulation to the venous side. This phenomenon is readily detected through measurement of $S_{mv}O_{2s}$ which is about 70% in normal persons but typically is much higher in patients with sepsis and organ dysfunction.

Paradoxically, each of the interventions commonly used to increase tissue oxygen delivery can also decrease it. Fluid resuscitation can increase cardiac output by increasing preload, but in patients with altered capillary permeability, it can create edema, thereby lengthening the distance across which oxygen must diffuse. Vasopressors can raise cardiac output by increasing peripheral vascular resistance, but at the cost of reducing flow through nutrient vessels in the microcirculation. Inotropes, on the other hand, directly increase cardiac output, albeit at the cost of increased myocardial oxygen consumption, but agents such as dobutamine may lead to further shunting by decreasing peripheral vascular resistance.

Currently, intensive invasive monitoring of critically ill patients with organ dysfunction is employed less frequently than it once was. The benefits of such monitoring remain somewhat uncertain. For example, a 1996 study suggested that the use of a pulmonary arterial catheter was associated with a 24% increase in mortality—not, presumably, because of complications of the catheter itself but rather because the decisions made on the basis of the data provided led to greater harm than benefit.¹²⁵ Although this estimate of harm may be exaggerated, there is little countervailing evidence of benefit to justify routine use of pulmonary arterial catheters. A 2003 study of 1,994 high-risk patients undergoing major elective surgery found that Swan-Ganz catheterization and preoperative optimization did not reduce mortality but was associated with a significant increase in the risk of pulmonary embolism.⁸⁴

Renal replacement therapy in critically ill patients with MODS serves three functions:

1. Regulation of fluid and electrolytes in patients in whom normal renal function is compromised and altered capillary permeability has led to total body fluid overload with edema.

2. Removal of products of metabolism, medications, and other toxins that the failing kidneys are unable to clear.
3. Removal of circulating mediators of inflammation.

The first two are classic indications for dialysis, though the therapeutic objectives may differ; the third lies more in the realm of promising experimental therapy.

Fluid overload is a common consequence of hemodynamic resuscitation during the early stages of acute illness. It results from increased capillary permeability, peripheral vasodilatation with expansion of the intravascular compartment, and impaired renal function. The use of continuous renal replacement therapies to titrate fluid balance and reduce uremia is conceptually appealing, but the benefits remain unproven. Both individual randomized trials^{126,127} and a systematic review¹²⁸ failed to show that early and aggressive continuous renal replacement improved clinical outcome. On the other hand, a multicenter randomized trial of more than 400 ICU patients with ARF showed that high-flow ultrafiltration (at a rate of 35 ml/kg/hr or higher) increased survival,¹²⁹ and a prospective study demonstrated that daily (as opposed to alternate-day) intermittent hemodialysis improved survival and hastened the resolution of ARF.¹³⁰ Another systematic review suggested that imbalances between study groups might have masked a potential benefit of therapy associated with early continuous hemodialysis.¹³¹

Whether it significantly improves outcome or not, early continuous renal replacement therapy does facilitate early management of the patient with MODS by permitting the removal of fluid, and it is generally better tolerated by hemodynamically unstable patients than is intermittent hemodialysis. Evidence that dialytic therapy can accelerate the clearance of circulating mediators of sepsis is scant.¹³²

SUPPORT OF OTHER ORGANS

Enteral nutritional support has been shown to reduce the rate of infectious complications in patients with multiple trauma^{111,133} and in those with pancreatitis.¹³⁴ A systematic review of 15 randomized trials found that early enteral feeding reduced the infectious complication rate and shortened the ICU stay without affecting mortality.¹³⁵ The use of immunologically enhanced enteral formulas appears to be associated with a further reduction in infectious complications, ventilator days, and length of hospital stay.¹³⁶ Paralytic ileus makes the provision of enteral feeding more difficult. Erythromycin, which is a motilin secretagogue, can facilitate bedside placement of enteral feeding tubes¹³⁷ and accelerate gastric emptying.¹³⁸

Techniques for extracorporeal support of the failing liver have been described, but their use is generally limited to a few centers with a particular interest in liver failure and organ transplantation.^{139,140} Unlike primary liver failure, the hepatic dysfunction of MODS does not lead to life-threatening organ system insufficiency and rarely calls for specific support. Hypoalbuminemia is common in MODS, occurring as a consequence of increased vascular permeability, loss through the GI tract, and reduced hepatic synthesis from the activation of an acute-phase response. Although hypoalbuminemia is associated with increased ICU morbidity and mortality, there is no convincing evidence that albumin supplementation improves clinical outcome.¹⁴¹

A randomized trial of transfusion strategies in the ICU demonstrated that organ function was improved by a restrictive transfusion policy that withheld transfusion unless the hemoglobin level dropped below 70 g/L,¹⁰⁷ a conclusion supported by a large European multicenter observational study.¹⁴² Benefit is also

seen in patients with underlying cardiovascular disease.¹⁴³ Thrombocytopenia is corrected by transfusion of platelet concentrates, but this generally is done only if the platelet count drops below 20,000/mm³. Coagulation factors can be replaced by giving fresh frozen plasma or cryoprecipitate.

Adequate analgesia and sedation are essential components of the care of MODS patients; however, the natural desire to alleviate pain and discomfort can lead to oversedation. A policy of daily awakening can reduce morbidity and shorten the ICU stay.¹⁴⁴

PHARMACOLOGIC THERAPY TARGETING HOST RESPONSE

Experimental studies implicate an activated inflammatory response in the pathogenesis of MODS. Despite extensive evaluation of a variety of novel strategies to target the host response in sepsis, to date, only two approaches have demonstrated an ability to improve survival.

Activated protein C is an endogenous anticoagulant molecule that inhibits factors V and VIII; in addition to its anticoagulant activities, it exerts significant anti-inflammatory activity [see 8:26 *Molecular and Cellular Mediators of the Inflammatory Response*].¹⁴⁵ Activated protein C has been produced as a recombinant protein (drotrecogin alfa activated) and has been evaluated in a multicenter randomized trial involving 1,690 patients with severe sepsis. In this trial, treatment resulted in a 6.1% improvement in 28-day survival¹⁴⁶ and a more rapid resolution of cardiovascular, respiratory, and hematologic dysfunction.¹⁴⁷ The benefit appears to be greatest in patients who have more severe illness (reflected in an elevated APACHE II [Acute Physiology and Chronic Health Evaluation II] score or a greater number of dysfunctional organs), community-acquired infection, or coagulopathy.

Critical illness is associated with multiple abnormalities of endocrine function, including reduced responsiveness to endogenous glucocorticoids,⁶² a state that predicts an increased risk of ICU mortality.⁶¹ In a 2002 study, administration of pharmacologic doses of corticosteroids (50 mg of hydrocortisone every 6 hours and 50 µg of fludrocortisone) to patients with refractory septic shock and an impaired response to a short-course ACTH stimulation test reduced mortality by 10%.¹⁴⁸ In contrast, earlier studies of high-dose corticosteroids in more heterogeneous groups of patients with sepsis found no evidence of benefit.¹⁴⁹

Systematic reviews have suggested that neutralization of tumor necrosis factor (TNF) or interleukin-1 (IL-1) can improve outcome in sepsis,¹⁵⁰ but neither of these approaches is clinically available at present. Other anticoagulant or anti-inflammatory strategies have been suggested but remain unproven.

MODS AND ICU-ACQUIRED INFECTION

Infection is a risk factor for organ dysfunction, but the converse is equally true: organ dysfunction is a risk factor for nosocomial infection, with the risk increasing as the severity of organ dysfunction increases.⁶⁶ The typical isolates are microbes of low intrinsic pathogenicity, including coagulase-negative *Staphylococcus*, *Enterococcus*, and *Candida* species and gram-negative organisms such as *Pseudomonas* and *Enterobacter*.¹⁵¹ These organisms commonly colonize the upper GI tract of the critically ill patient,¹⁵² they emerge under antibiotic pressures, and they form colonies on invasive devices—all of which may explain why they emerge as predominant infecting species in this setting. Studies of SDD have demonstrated that preventing such infections reduces ICU morbidity and mortality,^{90,153} but there is scant evidence that aggressive antimicrobial therapy to treat suspected nosocomial infection improves outcome. In fact, two reports from 2000 suggested that a more restrictive approach to the pre-

scription of antimicrobial agents reduced mortality and morbidity.^{97,154} Worsening organ dysfunction should prompt a careful search for untreated foci of infection, but empirical therapy should be used cautiously; if such therapy is started, it should be discontinued promptly as culture data are obtained. Often, mere removal of a colonized device (e.g., a central line or a urinary catheter) amounts to definitive therapy for these infections.

The association of organ dysfunction with occult intra-abdominal infection^{3,94} stimulated a period of enthusiasm for the practice of so-called blind laparotomy—that is, laparotomy undertaken to identify and treat an intra-abdominal infectious focus without radiographic evidence that infection is present.^{155,156} The uniformly disappointing results of such intervention,¹⁵⁷ coupled with improvements in diagnostic imaging techniques, led to abandonment of this approach except in certain unusual circumstances (e.g., clinically compelling evidence of a surgically correctable problem, suspicion of visceral ischemia, or the absence of the appropriate imaging facilities). It goes without saying that the classic physical findings of peritonitis—particularly when no abdominal operation has been done—may be the sole indication for surgical exploration. Moreover, in a complicated postoperative patient transferred from another institution because of worsening organ dysfunction, repeat laparotomy may legitimately be considered a component of the admission physical examination.

Outcome

PROGNOSTIC INDICATORS

The prognosis of MODS is directly related to the severity of the underlying organ dysfunction, which can be expressed in terms of either the number of failing systems^{3,73,158} [see Table 6] or the global severity of dysfunction as determined by an organ dysfunction score [see Figure 1]. It must be emphasized, however, that prognostic indicators reflect the expected outcome of a group of patients and are of limited use in making decisions about the care of an individual patient. Moreover, the prognostic weight of these scales reflects standards of care prevalent at a particular time and in a particular clinical setting. For example, at the time when Ranson's criteria were developed,¹⁵⁹ patients with pancreatitis and six or more

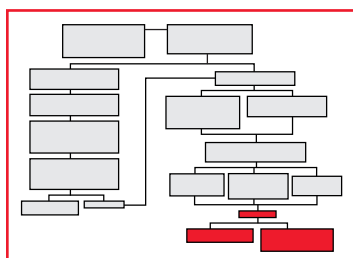


Table 6 Prognosis in MODS

Number of Failing Systems	Mortality (%)
0	3
1	15–30
2	50–60
3	60–100
4	70–100
5	100

positive indicators according to those criteria had a mortality of close to 100%; today, a majority of such patients survive.⁹³

Organ dysfunction is potentially recoverable when the factors responsible for the persistence or progression of MODS can be reversed. Identifying these factors, treating them appropriately, and providing optimal physiologic support can prove a daunting challenge, and it is often advisable to consider seeking independent advice or transporting the patient to a center with the clinical expertise and facilities to manage the multidisciplinary problems faced by MODS patients. Given that MODS often evolves as a consequence of medical misadventure, early consultation or referral may be a sound approach from a medicolegal perspective as well. On the other hand, it is a common contemporary ICU scenario that MODS evolves and worsens despite optimal care, necessitating a decision whether to continue or discontinue active care.

WITHDRAWAL OF LIFE SUPPORT

The most common mode of death for a patient with advanced MODS is limitation or withdrawal of life support in the face of a persistent failure to respond to full, aggressive ICU care.¹⁶⁰ The decision to withdraw or withhold life support is a complex one, and there are considerable differences of professional opinion and practice regarding how best to make it.¹⁶¹ Factors that must be taken into consideration include the nature of the underlying disease, the patient's premorbid health status, the wishes of the patient and the family regarding long-term ICU care, the patient's ultimate prospects for an independent existence, and the presence of active problems amenable to medical therapy. Although end-of-life deliberations may be difficult for medical staff and family alike, careful and realistic consideration of the expectations of all involved can facilitate a decision to discontinue active therapy in a manner that is dignified and humane rather than adversarial.

Discussion

MODS: Evolution of a Syndrome

The first ICU was established in Baltimore in the late 1950s.¹⁶² Its development marked much more than a simple advance in medical technology. The improvements in fluid resuscitation achieved during World War II, followed by the development of techniques of positive pressure mechanical ventilation, hemodialysis, and central venous catheterization over the subsequent decade, had set the stage for an entirely new disease paradigm—that of a disease that arose only in patients who would have died in the absence of resuscitation and exogenous support. The need for that support to sustain life became the metaphor that described this new disorder, originally described as sequential systems failure¹⁶³ and now generally known as

MODS.⁴ MODS is perhaps the classic instance of the new disease paradigm, in that it develops only in patients who would have died without medical intervention and evolves because of the inadvertent consequences of that intervention.

Earlier reports had described the physiologic failure of discrete organ systems after trauma or acute illness. Stress-related upper GI bleeding was described in 1842⁵⁴ and trauma-related renal²³ and hepatic³⁰ dysfunction during World War II. Description of respiratory failure awaited the widespread use of mechanical ventilators, but a process termed high-output respiratory failure was described in patients with peritonitis in 1963,¹³ anticipating the classic description of ARDS 4 years later.¹⁴ In each of these reports, however, the physiologic organ

abnormality was viewed as an isolated problem of a single organ, albeit one that could have broader secondary consequences. The suggestion by Baue¹ in 1975 that each organ abnormality was simply the local manifestation of a systemic process set the stage for attempts to identify common systemic pathologic processes and hence to develop therapies that were not merely supportive but also targeted fundamental mechanisms in the pathogenesis of MODS. The search for such therapies is, admittedly, still in its infancy. Not only is the disease process complex, but our ability to describe and characterize it is limited as well.

MODS is invariably preceded by evidence of systemic activation of an adaptive host stress response to infection or tissue injury. This response, which includes changes in cardiorespiratory function, increased microvascular permeability, evidence of activation of innate immune mechanisms, and alterations in intermediary metabolism, is termed sepsis when caused by infection and the systemic inflammatory response syndrome (SIRS) when considered independent of cause.^{4,164} SIRS is mediated through the release of a complicated network of host-derived mediator molecules (see below). The name notwithstanding, designation of SIRS as a syndrome may be somewhat presumptuous. There is no discrete or invariant pattern of clinical manifestations that identifies patients with activation of this complex response, nor is there convincing evidence that the response is common to all patients who meet the clinical criteria for SIRS.

It has been suggested that it is also possible to define a compensatory anti-inflammatory response syndrome (CARS) or a mixed acute response syndrome (MARS)¹⁶⁵; however, these “syndromes” are more conceptual entities than they are diseases that can be diagnosed and treated.¹⁶⁶

Theories of Pathogenesis

Organ dysfunction must ultimately be the consequence of the malfunctioning or death of cells in that organ. Although cellular derangements are readily documented under experimental conditions, it remains largely unknown how these derangements translate into the physiologic changes that define the clinical syndrome. Cellular dysfunction may reflect altered patterns of synthetic function, either because of activation of alternate patterns of gene expression or because of relative cellular oxygen deficiency from defective cellular respiration (so-called cytopathic hypoxia).¹⁶⁷ Mechanisms of fibrosis and repair may alter the normal cellular anatomic relationships and thereby impair function. Finally, cell death may result from mechanical or biochemical injury of sufficient severity to prevent oxidative metabolism and produce anatomic disruption of the cell or necrosis, but it may also occur through the activation of apoptosis (programmed cell death). Each of these abnormalities has been described in patients with sepsis, and each has multiple overlapping causes.

INFECTION AND HOST SEPTIC RESPONSE

The earliest descriptions of MODS emphasized its association with occult infection,^{58,94} prompting the hypothesis that organ dysfunction arises through the direct effects of one or more microbial toxins. However, the observations that MODS could also develop in patients with no identifiable focus of infection⁹⁵ and that treatment of infection did not necessarily reverse the syndrome¹⁶⁸ suggested that infection may be a cause of organ dysfunction in critical illness but is not necessarily the fundamental mechanism.

Microbial products, independent of bacterial viability, can evoke the clinical features of sepsis. Injection of endotoxin, or

lipopolysaccharide (LPS), derived from the cell wall of gram-negative bacteria reproduces the physiologic features of sepsis in human volunteers,¹⁶⁹ with larger doses producing life-threatening organ dysfunction.¹⁷⁰ Moreover, endotoxin can be detected in the circulation of patients at risk for MODS—not only patients with sepsis,^{171,172} but also those who have experienced traumatic¹⁷³ or thermal injury¹⁷⁴ and those who are undergoing cardiopulmonary bypass or repair of an abdominal aortic aneurysm.¹⁷⁵

Animal studies, however, have shown that the sequelae of endotoxemia are an indirect consequence of the activation of host innate immunity rather than a direct cytopathic effect of the endotoxin molecule. The C3h HeJ strain of mice arose through a spontaneous mutation of the parental C3h HeN strain, involving an alteration in a single gene product. This defect, later recognized as a point mutation in the gene encoding Toll-like receptor 4 (TLR4),¹⁷⁶ conferred complete resistance to endotoxin lethality in C3h HeJ mice. Studies involving bone marrow irradiation and crossover transplants of bone marrow cells between C3h HeN and C3h HeJ mice showed that endotoxin sensitivity was transferred with bone marrow cells¹⁷⁷ and confirmed that the sequelae of endotoxin challenge arose indirectly, through the activity of marrow-derived cells from the host. Microarray studies have demonstrated that literally hundreds of genes are expressed in macrophages, endothelial cells, and neutrophils after stimulation by LPS.^{178,179} The importance of this enormously complex response is underlined by the observation that the lethality of murine endotoxemia can be prevented by neutralizing any one of several dozen of these gene expressions before endotoxin challenge.¹⁴⁵

Endotoxin interacts with cells of the host innate immune system through TLR4. TLR4 is one of a family of 10 TLRs that have evolved to recognize danger signals in the extracellular environment and to activate cells to mount an appropriate response to a threat.¹⁸⁰ TLRs recognize not only microbial products (e.g., endotoxin) and components of the wall of gram-positive bacteria (e.g., lipoteichoic acid and peptidoglycan) (TLR2) but also bacterial DNA (TLR9) and even heat-shock proteins and structural components of damaged cells (TLR2) [see Table 7]. Thus, the response evoked appears not to be specific for the stimulus that elicited it, just as the clinical syndrome of systemic inflammation and organ dysfunction is not unique to patients with infection but can also be seen in association with other causes of tissue injury.^{164,181}

The binding of endotoxin to TLR4 triggers a cascade of intracellular signaling pathways leading to the expression of hundreds of genes whose products mediate innate immunity [see Figure 2]. The resulting alterations in normal patterns of cellular protein synthesis are profound: not only does the initial stimulus trigger a complex response, but the newly synthesized protein products of this response also, in turn, are capable of acting on the cell to induce a further cascade of mediator molecules. Any attempt to classify the mediators involved is inevitably arbitrary and simplistic. It is useful, however, to consider the response as involving (1) early inflammatory mediators (e.g., TNF and IL-1), (2) late inflammatory mediators (e.g., macrophage inhibitory factor and high-mobility group box [HMGB]–1), (3) counterinflammatory and tissue repair mediators (e.g., IL-10 and transforming growth factor [TGF]– β), (4) enzymes involved in the regulation of non-protein inflammatory mediators (e.g., inducible NO synthase, phospholipase A₂, and platelet-activating factor acetylhydrolase), (5) acute-phase reactants, and (6) cell surface adhesion or signaling molecules (e.g., intercellular adhesion molecule [ICAM]–1 and tissue factor).

Table 7 Toll-like Receptors and Their Ligands

Toll-like Receptor	Ligand(s)
TLR1	<i>Mycobacterium leprae</i> lipopeptide, <i>Borrelia</i> outer surface protein
TLR2	Peptidoglycan, lipoteichoic acid, bacterial lipoprotein, <i>Mycoplasma</i> lipopeptide, zymosan, CMV, <i>M. leprae</i> lipopeptide, lipoarabinomannans, injured cells
TLR3	Double-stranded RNA
TLR4	Endotoxin, HSP60, β -glucan, neutrophil elastase
TLR5	Flagellin
TLR6	<i>Mycoplasma</i> lipopeptide
TLR7	Imidazoquinolones, guanine ribonucleosides
TLR8	Unknown
TLR9	Bacterial CpG DNA
TLR10	Unknown

Blockade of any of these molecules prevents lethality in mice that are subsequently challenged with endotoxin. None of these mediators, however, is directly cytotoxic, which suggests that their role is to activate effector mechanisms of injury further downstream. The identity of those downstream mechanisms of cellular dysfunction or death is still speculative, though a number of attractive possibilities have been proposed.

GENETIC FACTORS IN HOST RESPONSE

A Scandinavian population-based study of causes of premature mortality in adoptees revealed that genetic factors play a significant role in the outcome of infection. When one of an adoptee's biologic parents died before the age of 50, the adoptee faced a six-fold increase in the risk of infectious mortality; this increased risk was substantially greater than that associated with premature death from cardiovascular disease or cancer.¹⁸² It is now known that polymorphisms in genes for TLRs and cytokines are common in the general population¹⁸³ and are associated with both altered expression of the gene product and enhanced susceptibility to sepsis and organ dysfunction. A mutation in the gene for TLR4 has been associated with a significantly increased risk of gram-negative infection in ICU patients.^{184,185} Polymorphisms in the genes for CD14,¹⁸⁶ TNF,^{187,188} heat shock protein 70,¹⁸⁹ IL-10,¹⁹⁰ and IL-1 receptor antagonist¹⁹¹ all have been associated with greater degrees of organ dysfunction and a worse clinical outcome in critical illness.

TISSUE INJURY MEDIATED BY PHAGOCYTIC CELLS OF INNATE IMMUNE SYSTEM

Polymorphonuclear neutrophils and monocytes form the first line of innate host defenses against invading microorganisms and injured tissue. Neutrophils are recruited to the site of tissue invasion or injury by locally released chemokines (e.g., IL-8). They adhere to the endothelium of the microvasculature through the interaction of the neutrophil adhesion molecule CD11b with ICAM-1 on the endothelial cell [see 8:26 *Molecular and Cellular Mediators of the Inflammatory Response*]. Adherent neutrophils are

then able to extravasate by degrading the tight junctions between endothelial cells, probably through the action of the neutrophil enzyme elastase; this process can cause injury to the cell as the neutrophil transits.¹⁹² Once localized to the site of challenge, the neutrophil releases a variety of molecules (e.g., proteases and reactive oxygen intermediates) that directly injure microorganisms and host tissue alike. Opsonization of bacteria by immunoglobulin or complement enables the neutrophil to phagocytose and kill invading pathogens. Activated neutrophils have been implicated in the pathogenesis of pulmonary,^{193,194} hepatic,¹⁹⁵ GI,¹⁹⁶ and renal²⁸ injury in experimental models of inflammation. Similarly, though ablation of fixed tissue macrophages increased the number of bacteria isolated from an animal model of peritonitis, it nonetheless reduced the severity of septic symptoms and improved survival.¹⁹⁷

Other studies have implicated natural killer (NK) cells^{198,199} and CD8-positive T cells²⁰⁰ in the lethality of experimental sepsis, though it is unclear whether lethality is a consequence of direct cellular cytotoxicity or of the activation of other biologic processes by secreted products of these cells.²⁰¹

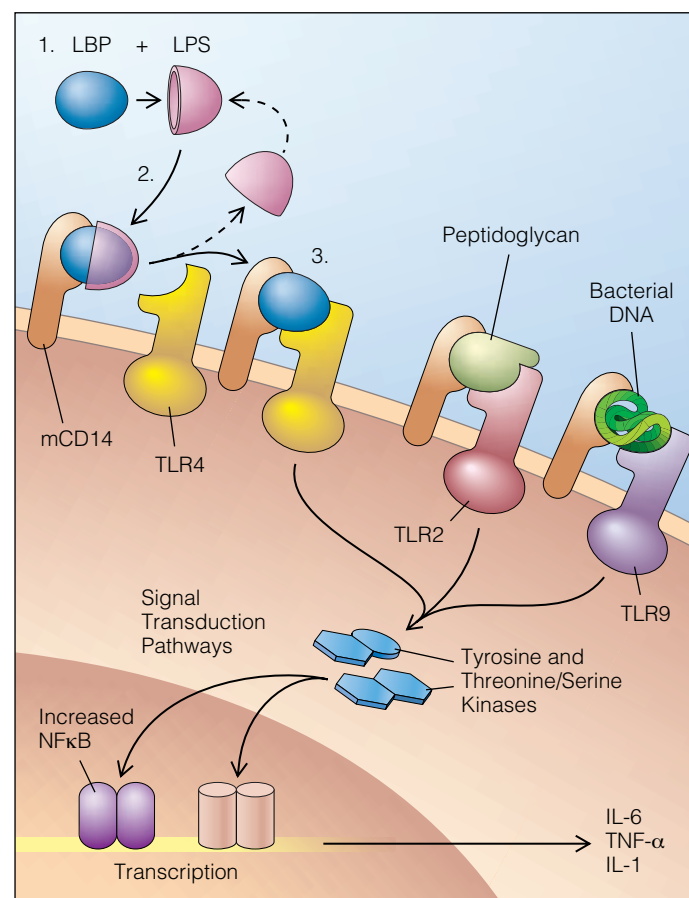


Figure 2 During lipopolysaccharide (LPS) signaling, (1) LPS binds to LPS-binding protein (LBP). (2) This complex is delivered to membrane-bound CD14 (mCD14). (3) The CD14-LPS complex interacts with Toll-like receptor 4 (TLR4), which initiates the intracellular signal transduction pathway. The signal transduction pathway leads to NFκB translocation into the nucleus, with increased transcription of proinflammatory cytokines. TLR2 is known to signal membrane compounds of gram-positive bacteria such as peptidoglycan. TLR9 recognizes bacterial DNA. (IL—interleukin; NFκB—nuclear factor κB; TNF-α—tumor necrosis factor-α)

ENDOTHELIAL INJURY

The network of endothelial cells lining the large and small vessels of the vascular tree is enormous, encompassing an area 600 times larger than that of the skin.²⁰² Far from being a passive conduit for blood cells and plasma, the endothelium contributes actively to the initiation, localization, and resolution of inflammation.²⁰³ Circulating inflammatory mediators evoke an endothelial cell response characterized by upregulation of adhesion molecules such as ICAM-1 and vascular cell adhesion molecule (VCAM), expression of TLR2 and tissue factor, and shedding of endothelial cell thrombomodulin.^{203,204} These changes result in neutrophil localization and local activation of coagulation with secondary tissue injury. In addition, healthy endothelial cells appear to play a role in limiting host injury during inflammation, as indicated by the observation that mice with a genetic deletion of syndecan-4 (a proteoglycan involved in endothelial cell adhesion and signaling) exhibit increased mortality and exaggerated release of IL-1 after endotoxin challenge.²⁰⁵

Postmortem studies of patients with ARDS show that ICAM-1 is upregulated throughout the lung, whereas VCAM is expressed in larger vessels,²⁰⁶ and that circulating markers of endothelial activation are present in critically ill patients with organ failure.²⁰⁷ Moreover, diffuse endothelial injury is suggested by the presence of circulating endothelial cells in the blood of patients in septic shock.²⁰⁸ Therapeutic strategies that target the adhesive interactions of lymphocytes and endothelial cells have shown promise against inflammatory conditions such as psoriasis and Crohn disease; studies of agents targeting the interaction of neutrophils with endothelial cells have so far yielded disappointing results.²⁰⁹

INTRAVASCULAR COAGULATION

Although plasma contains all the factors necessary to induce coagulation and formation of a fibrin clot, intravascular coagulation is limited in healthy persons by the absence of a trigger and the presence of endogenous anticoagulant mechanisms. This balance is disrupted in persons experiencing systemic inflammation, resulting in microvascular coagulation and obstructing oxygen delivery to the cell. Injury and inflammation can upregulate endothelial cell tissue factor expression and activate the coagulation cascade by catalyzing the conversion of factor VII to factor VIIa. Sequential activation of circulating coagulation factors results in the conversion of prothrombin to thrombin and, in turn, the conversion of fibrinogen to fibrin. The activation of coagulation is inhibited by three important endogenous anticoagulant pathways: the protein C pathway, the antithrombin pathway, and the tissue factor pathway inhibitor (TFPI) pathway. Each of these is impaired in critical illness, leading to a net procoagulant state.

Protein C is synthesized in the liver and circulates as an inactive precursor. It is activated in the vascular tree through its interaction with thrombomodulin on the endothelial cell; activated protein C blocks thrombin generation through its inhibitory interactions with factors V and VIII.²¹⁰ Hepatic production of protein C is impaired in sepsis. Moreover, shedding of endothelial cell thrombomodulin results in a reduction in the activation of available protein C, whereas acute-phase reactants such as α_1 -antitrypsin accelerate its degradation. The importance of this anticoagulant mechanism is underlined by a 2001 study of recombinant activated protein C in patients with severe sepsis, in which treated patients experienced a significant improvement in 28-day survival and those with the greatest degrees of organ dysfunction benefited most.¹⁴⁷

Antithrombin is a serine protease inhibitor that binds to and

inactivates thrombin and inhibits factors IXa, XIa, and XIIa. Levels of circulating antithrombin are reduced in sepsis. Administration of recombinant antithrombin failed to improve survival in a large multicenter study of patients with severe sepsis, though interaction with heparin may have masked a therapeutic effect.²¹¹

TFPI is synthesized by endothelial cells in response to cytokines and shear stress. It too is a serine protease inhibitor whose target is the complex of tissue factor, factor VIIa, and factor Xa that initiates the coagulation cascade. Recombinant TFPI has been evaluated as a therapy for sepsis; however, a large multicenter trial failed to show any survival benefit from such therapy.²¹²

The interactions between coagulation and inflammation are complex. Protein C binds to a receptor expressed on endothelial cells and neutrophils, and prevention of this interaction results in a disseminated inflammatory process.¹⁴⁶ Binding of activated protein C to its receptor in brain endothelium inhibits endothelial cell apoptosis and is neuroprotective during cerebral ischemia.²¹³

APOPTOSIS

Apoptosis, or programmed cell death, is a process through which cellular structural elements and DNA are degraded and residual cellular constituents are converted into membrane-bound vesicles (apoptotic bodies) that are cleared by macrophages. Phagocytosis of apoptotic bodies prevents the uncontrolled release of cellular constituents and so prevents an inflammatory response to the injured cell.²¹⁴ Apoptosis is also an intrinsically anti-inflammatory process, however, in that phagocytosis of an apoptotic cell by the macrophage evokes the expression of anti-inflammatory genes such as those for TGF- β and IL-10.^{215,216} Apoptosis, like cell replication, is a physiologic process that is essential for normal growth and development; either excessive or inadequate apoptosis can produce disease.

Increased rates of apoptosis of colonic epithelial cells and splenic lymphocytes are seen in autopsy specimens from patients dying as a consequence of sepsis or multiple trauma.²¹⁷ Conversely, whereas circulating neutrophils survive less than a day in vivo in healthy persons, neutrophils isolated from the blood of patients with sepsis show both phenotypic features of activation and prolonged survival (a consequence of the inhibition of a constitutively expressed apoptotic program).⁵² Animal studies have shown that inhibition of lymphoid cell apoptosis improves survival after septic challenge.²¹⁸ Conversely, induction of neutrophil apoptosis improved survival in a rodent model of intestinal ischemia-reperfusion injury.²¹⁹ The potential role of apoptosis in the pathogenesis of MODS is further suggested by animal studies of ventilator-induced lung injury, which demonstrated that injurious mechanical ventilation strategies can induce renal epithelial cell apoptosis and biochemical evidence of renal dysfunction.²²⁰

GASTROINTESTINAL DYSHOMEOSTASIS

Because MODS not infrequently evolves despite apparently adequate control of infection or other inciting triggers, it has been suggested that the GI tract may serve as the unseen motor of the pathologic state,²²¹⁻²²⁴ both as a reservoir of microorganisms and their products and as a mechanism for the evolution of inflammation.

The GI tract of a healthy human being harbors upward of 600 different microbial species, and bacteria outnumber human cells 10 to 1.²²⁵ The composition of the GI flora is stable over a person's lifetime, but intercurrent disease can produce profound changes in bacterial numbers and patterns of colonization. In critically ill surgical patients, the normally sterile proximal GI tract

becomes heavily colonized with the same organisms that predominate in nosocomial ICU-acquired infection—*Staphylococcus epidermidis*, *Pseudomonas*, *Candida*, and *Enterococcus*. Colonization is significantly associated with the development of nosocomial infection with the same organism.¹⁵² Extensive studies in animal models have shown that acute insults (e.g., endotoxemia, peritonitis, pneumonia, trauma, burns, biliary tract obstruction, malnutrition, and lack of enteral feeding) can induce bacterial overgrowth in the gut and translocation of enteric bacteria to regional lymph nodes of the peritoneal cavity.²²⁶ Similar stimuli result in translocation in humans,^{227,228} and prevention of colonization with topical nonabsorbed antibiotics reduces the incidence of nosocomial infections, including bacteremias.¹⁵³ Detection of circulating endotoxin after burns¹⁷⁴ or major vascular surgery¹⁷⁵ suggests that endotoxin is also absorbed from the gut under conditions of altered gut barrier function.

The role of the gut in MODS is not limited to that of a microbial reservoir. The GI tract and adjacent structures constitute the largest aggregation of immune cells in the body. Normal interactions between the indigenous flora and the gut immune system serve to prevent the generation of immune responses to luminal antigens. Loss of these tonic inhibitory interactions may, in turn, contribute to a state of systemically activated inflammation. Accordingly, hemorrhagic shock results in significantly elevated levels of TNF and IL-6 in portal venous blood,²²⁹ and portal endotoxemia replicates systemic features of MODS, such as hypermetabolism,²³⁰ impairment of cell-mediated immunity,²³¹ and activation of coagulation.²³² Ablation of the hepatic Kupffer cell population has improved survival in animal models of peritonitis.¹⁹⁷ Mesenteric lymph has been shown to contain factors that can evoke inflammatory changes in organs remote from the gut.²³³ Thus, dysfunction of normal microbiologic and immunologic homeostasis in the GI tract and the liver results in the gut serving as a secondary source of the stimuli that induce and perpetuate MODS.

A clinically relevant role for the gut in the pathogenesis of MODS is supported by the results of randomized trials of SDD.¹⁵³

Table 8 Characteristics of Linear and Complex Systems²⁴¹

Assumptions of Linear Systems	Assumptions of Complex Systems
Mediators have unique, consistent biologic effects	Mediators have redundant, variable, and context-dependent effects
Antagonism of effect is mediated by specific inhibitor	Antagonism of effect is not attributable to single mediator or process
Biologic processes occur sequentially	Biologic processes occur concurrently
Biologic response is reliably predicted by measurement of responsible mediator	Biologic response is not consistently predicted by measure of single mediator
Modulation of biologic process occurs in dose-dependent fashion; small intervention has small effect	Modulation of process is not predictably dose-dependent; small perturbation may have large effect
Normal behavior of system results in physiologic stability	Normal integrated behavior of system results in physiologic variability or oscillations over time

TWO-HIT HYPOTHESIS

A complementary hypothesis of MODS pathogenesis suggests that an acute insult, such as infection or trauma, primes the host so that a subsequent, relatively trivial, insult produces a markedly exaggerated host response.²³⁴ Such a model would account for the severity of MODS developing late after multiple trauma¹⁸¹ as well as the substantial morbidity associated with nosocomial infection in the ICU.¹⁵¹ Studies in animal models have revealed that previous hemorrhagic shock leads to an exaggerated response to subsequent endotoxin challenge.²³⁵

MODS and Complexity Theory

None of the various theories of pathogenesis described so far is adequate to explain the evolution of the clinical syndrome of MODS. These models are not mutually exclusive; rather, they reflect differing perspectives on a profoundly deranged state of systemic homeostasis—one that has evolved only because the health care team has intervened to subvert an otherwise lethal process. The enormously complicated interactions among multiple predisposing patient factors, a series of physiologic insults, and an endogenous response effected via multiple cell types and many hundreds of biochemical mediators is best modeled by means of complexity theory.^{236,237}

According to the precepts of complexity theory, a complex system cannot be understood through isolated analysis of its component parts: it can be understood only through an appreciation of the various interactions of those parts. The result of these multiple interactions is neither a state of anarchy nor a limitless series of unpredictable outcomes but, rather, a series of stable responses known as an emergent order. This stable order is dependent on the interactions of all its parts but is much more than their simple sum. It is characterized both by a resilience to potentially disruptive external influences and by a degree of intrinsic variability. Loss of intrinsic variability is a marker of a failing or diseased system. The healthy human heart exhibits normal variability in rate and rhythm, which is lost in patients with significant congestive heart failure.²³⁸ Loss of intrinsic heart rate and blood pressure variability is also evident in patients with septic shock.^{239,240}

The idea that concepts inherent in complex nonlinear systems can be applied to the understanding of MODS is compelling.²⁴¹ Clinicians are most familiar with linear models of disease, and the assumptions on which these models are based generally lead to effective clinical responses. For example, diabetes results from the deficiency of a single protein and is treated effectively by replacing that protein; cholangitis is the consequence of obstruction of the bile duct and is treated by relieving that obstruction. For linear diseases such as these, a single abnormality produces the clinical phenotype, and definitive therapy involves correcting that abnormality. Disorders of biologic pathways such as the coagulation cascade represent a somewhat more elaborate variation on the same theme. For example, pathologic coagulation resulting in DVT can be treated by means of a variety of different strategies aimed at disrupting the clotting cascade. Similarly, hypertension can be managed by means of various pharmacologic strategies that modify different aspects of the regulation of vasomotor tone.

Complex disorders such as MODS, however, are not so predictable, and the therapeutic modulation required is much more difficult [see Table 8]. The consequences of manipulating a particular mediator may be highly context dependent, varying with the nature of the insult, the predisposition of the host,

and the timing of administration.¹⁴⁵ Moreover, intervention carries the potential cost of inadvertent iatrogenic harm. A sobering consequence of high-quality clinical trials performed in the ICU over the past decade has been the realization that

making a normal or supranormal physiologic state the therapeutic target in a critically ill patient whose homeostasis is profoundly disrupted may, on occasion, be detrimental rather than beneficial.^{22,107,242}

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6 PULMONARY INSUFFICIENCY AND RESPIRATORY FAILURE

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Definition of Acute Lung Injury and Acute Respiratory Distress Syndrome



Pulmonary insufficiency is the most common complication after surgical procedures. It ranges in incidence from 5 to 50% and in severity from minor atelectasis to lethal acute respiratory distress syndrome (ARDS). The lung is extremely vulnerable to additional injury during the perioperative period as both ventilation and perfusion are affected by events associated with injury that accompanies surgery and anesthesia.

The clinical entities of acute lung injury (ALI) and ARDS are syndromes defined by a relatively limited set of descriptive pathophysiologic clinical findings, and patients are included regardless of the specific etiology of acute pulmonary dysfunction. The American-European Consensus Committee (AECC) in 1994 defined clinical ALI to require respiratory failure of acute onset with an arterial oxygen tension (PaO_2) to fraction of inspired oxygen (FiO_2) ratio less than or equal to 300 mm Hg (regardless of the level of positive end-expiratory pressure [PEEP]), bilateral infiltrates on a frontal chest radiograph, and a pulmonary capillary wedge pressure less than 18 mm Hg (if measured) or no evidence of left atrial hypertension.¹ ARDS was defined identically except for a lower limiting value of less than 200 mm Hg for $\text{PaO}_2/\text{FiO}_2$.¹ The AECC definitions of ALI/ARDS are widely used and simple to apply but at the same time have serious deficiencies in discrimination. There is often not a good correlation between these broad clinical definitions and diffuse alveolar damage, which is widely considered to be a major characteristic histologic feature of ALI/ARDS.² Regardless of the definition, ALI and ARDS affect a large number of patients, who have a poor prognosis.

In what follows, we discuss the care of patients at risk for pulmonary complications, including clinical presentation, pathogenesis, recognition, prevention, and treatment of pulmonary insufficiency. Atelectasis and lung edema are considered separate events, although it is obvious that both abnormalities can and do occur simultaneously after operation. The emphasis is on disorders of the pulmonary parenchyma as opposed to pulmonary insufficiency secondary to cardiac disease, thromboembolism, central nervous system depression, and other conditions. The discussion also involves specific conditions that can be associated with respiratory failure. Perioperative problems related to operations for

primary pulmonary disease are not fully addressed in this chapter.

Normal Pulmonary Physiology

VENTILATION AND PULMONARY MECHANICS

The term *pulmonary mechanics* refers to the gas volumes in the chest and the gas flow rates during forced inspiration and exhalation. These values are depicted in a normal spirogram [see Figure 1]. As noted, functional residual capacity (FRC) is approximately 2 L in a normal adult. During tidal breathing, the patient inhales about 500 mL, followed by exhalation back to FRC. During a maximal inspiratory maneuver, the patient inhales to total lung capacity (typically twice the FRC).³ During pulmonary function testing to measure gas flow and volume, the patient inhales to total lung capacity and then breathes out as hard and fast as possible. The volume that the patient exhales is referred to as the forced expiratory volume or vital capacity. The rate at which the gas is exhaled is measured as the timed vital capacity, or the maximal midexpiratory flow rate. The volume of tidal breaths multiplied by the respiratory rate yields the minute ventilation (typically 8 L/min in a normal adult). Approximately one third of this ventilation passes through the conducting airways (dead space), and two thirds reach the alveoli, where gas exchange takes place. Inspiration occurs when the diaphragm contracts, generating an intrapleural pressure that is negative relative to the atmosphere and resulting in the influx of air through the airway into the alveoli. Exhalation is largely a passive event, involving relaxation of the diaphragm and the accessory muscles of inspiration. Forced expiration requires the exertion of effort by the abdominal muscles.

The pulmonary parenchyma is highly elastic in nature; lung expansion is achieved either by internal distention of the alveoli or by generation of negative intrathoracic pressure. The relation between gas volume and alveolar inflating pressure is referred to as pulmonary compliance. Similar to the lungs, the chest wall is elastic in nature and behaves like a coiled spring; chest wall compliance is defined as a unit change of volume for change in pressure. At FRC, the tendency of the lungs to recoil back is balanced by the distending pressures at the alveoli [Figure 2]. Compliance relationships depend on the size of the patient. During diaphragmatic contraction, beginning at FRC, an intrapleural pressure of -10 cm H_2O is generated, which results in inspiration.³ During normal breathing, an inspiratory pressure of -5 to -10 cm H_2O results in inhalation of 500 to 1,000 mL. During

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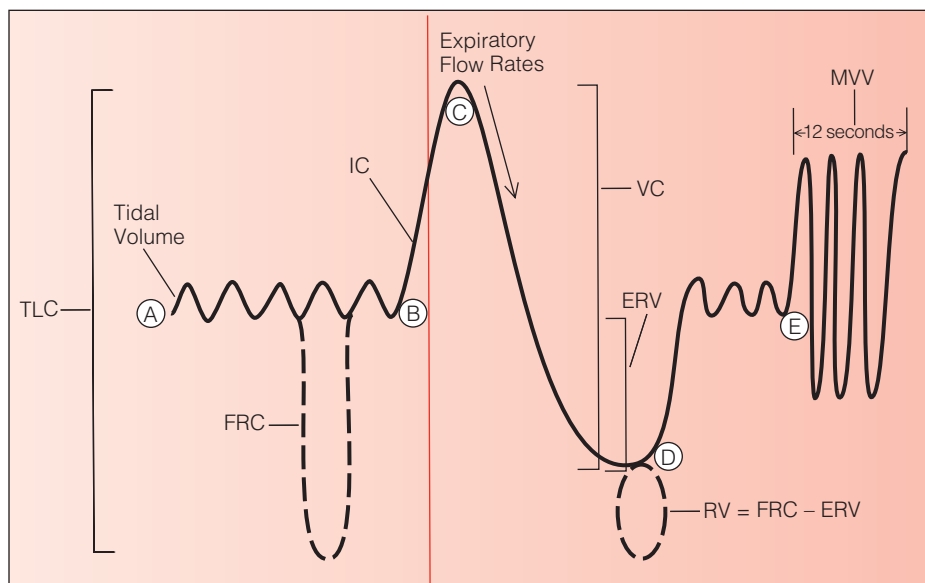


Figure 1 Depicted are gas volume and flow as demonstrated by spirometry. The subject is instructed to (A) breathe normally, (B) inhale as much as possible, (C) blow out as hard and fast as possible, (D) breathe normally, and (E) breathe as hard and fast as possible for 12 seconds. Functional residual capacity (FRC) is measured by a separate test, and residual volume (RV) is determined by subtracting expiratory reserve volume (ERV) from FRC.³ IC = inspiratory capacity; TLC = total lung capacity; VC = vital capacity.

forced inhalation against an open airway, intrathoracic pressures of -40 to -50 cm H_2O can be generated, resulting in inhalation to total lung capacity. Exhalation back to atmospheric pressure returns gas volume in the chest to FRC.

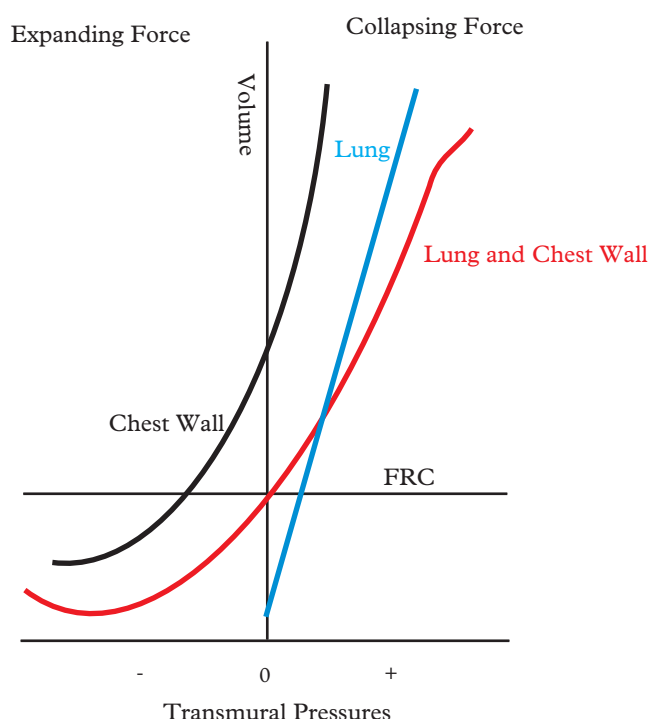


Figure 2 Relationship between functional residual capacity (FRC) and inspiratory/expiratory forces.

In other words, FRC represents the capacity at which the forces necessary to open the alveoli are balanced by the pressures that are intrinsic to the lung and chest wall that cause the lung to collapse.

The actual volumes for FRC, tidal volume, and total lung capacity related to inflating pressure are low for infants, children, and small adults and relatively high for normal large adults. An inspiratory pressure greater than -40 cm H_2O during spontaneous breathing (or greater than 40 cm H_2O during mechanical ventilation) causes overdistention of alveoli, stretching of alveolar capillaries, interstitial and pulmonary edema, and potentially severe lung injury. Patients with alveolar collapse, atelectasis, or interstitial pneumonia have an abnormally small FRC; consequently, their compliance characteristics tend to resemble those of a child. Under these circumstances, if a normal inflating tidal volume is used for such adult patients, high pressures are reached, overstretching occurs, and lung injury results.⁴

Minute ventilation (rate and depth of breathing) is controlled by the respiratory center in the brainstem to maintain arterial carbon dioxide tension (P_{aCO_2}) at 40 mm Hg. By definition and in practice, hypoventilation results in a P_{aCO_2} higher than 40 mm Hg and hyperventilation in a P_{aCO_2} lower than 40 mm Hg. If a patient is hypermetabolic because of exercise or fever, excess CO_2 is produced, and minute ventilation increases proportionately to keep the P_{aCO_2} at 40 mm Hg.

GAS EXCHANGE

Although O_2 exchange and CO_2 exchange occur simultaneously and at the same place in the lung, it is worthwhile to consider CO_2 clearance and O_2 uptake as if they were separate physiologic events. CO_2 , being highly soluble in water and very diffusible, is readily eliminated from the

pulmonary capillary blood to the alveolar gas space, even though the driving gradient is only about 45 mm Hg. The amount of CO_2 removed depends on the amount of alveolar ventilation [see Figure 3]. Minute ventilation (and hence alveolar ventilation) is regulated to remove all metabolically produced CO_2 each minute. Dissolved CO_2 combines with water to become carbonic acid (H_2CO_3), which is in equilibrium with the bicarbonate (HCO_3^-) in blood at a definite ratio. As long as this ratio is 1:20, the pH will be 7.4 (the Henderson-Hasselbalch equation).³ In postoperative patients, hypoventilation can be caused by respiratory-depressing drugs (e.g., narcotics and anesthetics), paralysis or weakness, obesity, and gastric distention, all of which result in CO_2 retention and respiratory acidosis.

Oxygenation of the blood depends more on matching of perfused alveoli to inflated alveoli than on minute ventilation. Under normal conditions, as long as inhaled alveolar gas contains at least 20% oxygen, red blood cells are fully oxygenated and exit the pulmonary capillaries at 100% saturation. During hypoventilation, the concentration of inspired oxygen in the alveoli does not reach 20% unless supplemental oxygen is given at the upper airway. In the recovery room, it is common practice to give supplemental oxygen; thus, a patient may be severely hypoventilated but remain fully oxygenated. The gradient for oxygen transfer from alveolar gas to red blood cells is much higher than that for CO_2 clearance. In a patient breathing room air, the oxygen tension (Po_2) in inhaled gas is approximately 150 mm Hg, and Po_2 in pulmonary capillary blood is approximately 40 mm Hg. Hence, the red blood cells are oxygenated during a single pass through the pulmonary capillary network. Oxygen in the blood is commonly measured in terms of either saturation (So_2) or Po_2 , but the most useful measure is oxygen content ($\dot{\text{C}}\text{O}_2$) because that is the major determinant of oxygen delivery at the tissue level. It is noteworthy that when $\dot{\text{C}}\text{O}_2$ is plotted against So_2 and Po_2 at different levels of hemoglobin concentration [see Figure 4],³ blood that is severely hypoxic because of anemia still exhibits normal So_2 and Po_2 .

Factors that impair oxygen delivery to blood include hypoventilation causing ventilation-perfusion mismatch,

diffusion block caused by chronic lung disease with fibrosis in the interstitial space, and complete atelectasis resulting in transpulmonary shunting of blood from the pulmonary arterial circulation to the venous circulation without participating in gas exchange. The first two generic causes of hypoxemia can be completely corrected by supplemental oxygen breathing, but supplemental oxygen has very little effect on oxygenation when the problem is caused by a transpulmonary shunt.

Assessment of Pulmonary Function

Given that identification of the high-risk patient can reduce the incidence of pulmonary complications, preoperative assessment of respiratory status is important. A detailed history is the most valuable step in the elucidation of a need for further workup. Factors indicating a need for more detailed study of pulmonary function include exercise intolerance, dyspnea on exertion, wheezing, cigarette smoking, cough, and sputum production.

Physical examination should include a general examination looking for cyanosis and the presence of carpopedal clubbing. Specific chest examination should focus on auscultation and percussion of the lung bases during tidal breathing and maximal inspiration to detect hypoventilation in weak or debilitated patients and hyperinflation in patients with chronic airway disease. Wheezing, rales, or rhonchi should trigger further examination. Cardiac insufficiency, obesity, clubbing, tobacco stains, and poor oral hygiene are all relative indications for more detailed pulmonary function testing. Chest x-ray should be considered part of the routine physical examination for any patient with an abnormality detected from the history or physical examination and any patient scheduled to undergo a thoracotomy. As part of the physical examination, the patient should be instructed to inhale to the maximum and then to perform a vigorous forced expiration. By observing the patient's chest and the sound of forced expiration, one can make a good guess at the volume of inspiration (which should be at least 1 L/50 kg), forced expiratory volume (which should be at least 2 L/50 kg), and expiratory

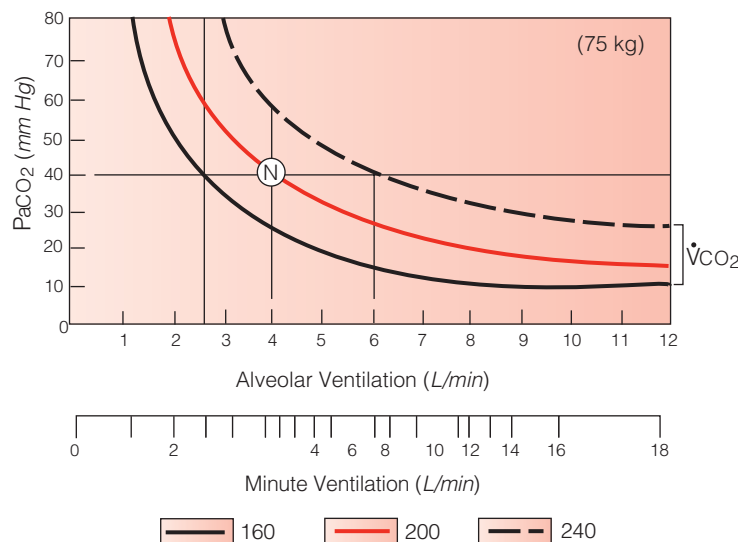


Figure 3 Illustrated is CO_2 excretion ($\dot{V}\text{CO}_2$) related to ventilation for a typical 75 kg adult subject. N = normal.³ PaCO_2 = arterial carbon dioxide tension.

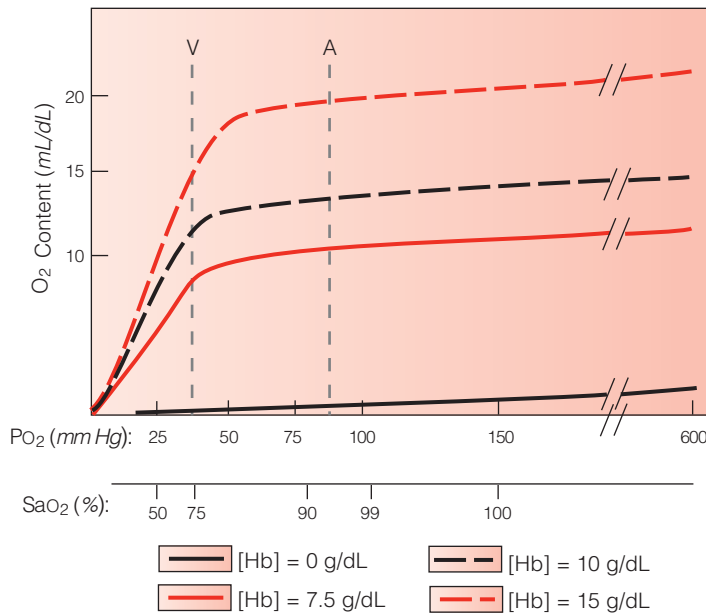


Figure 4 Shown is measurement of oxygen content in blood at four levels of hemoglobin (Hb) concentration. Dotted lines show values for arterial (A) and venous (V) blood. There is much more oxygen in normal venous blood with a oxygen tension (Po₂) of 40 mm Hg than there is in anemic arterial blood with a Po₂ of 150 mm Hg.³ SaO₂ = arterial oxygen saturation.

flow (most of the exhaled volume should come out in the first second without wheezing). Forced expiratory volume—or vital capacity (the two are different names for the same thing)—and maximum voluntary ventilation (MVV) can be directly measured with a handheld turbine spirometer.

The ability to climb one or two flights of stairs at a steady pace without dyspnea provides information about the patient that is not available in any other way short of treadmill or exercise testing. A patient who cannot do this simple exercise may have respiratory, cardiac, or joint disease or may be too obese, too weak, too sedentary, or too debilitated to manage mild exertion. Whatever the cause, an elective operation should be delayed if the patient cannot do the exercise.

Simple spirometry should be done whenever the history, the physical examination, or bedside tests yield findings indicating abnormal pulmonary function. Tidal volume, inspiratory capacity, vital capacity (total and timed intervals), forced expiratory volume, and MVV are measured, and the results are compared with tables for normal persons of the same age, sex, and size and then reported as percentages of predicted normal values. Results between 80 and 120% of predicted values are considered normal. If these tests of lung volume and flow are within the normal range, the risk of pulmonary complications is small (although the tests do not address endurance). Abnormally high values are not important; however, abnormal values below 70% of predicted levels indicate small airway or obstructive lung disease (if the expiratory flow rate is low), loss of lung volume (if vital capacity is low), or localized or generalized muscle weakness. If expiratory flow is abnormally low, spirometry should be repeated after the administration of aerosolized bronchodilators. Low expiratory flow that improves after bronchodilation indicates bronchospasm, which will require special management during and after operation. MVV values below 50% of the predicted level correlate well with postoperative pulmonary complications. However, the MVV may be abnormally low for many reasons, both pulmonary and nonpulmonary.

Arterial blood gas values are obtained if major pulmonary dysfunction is suspected, and they serve primarily as a baseline for postoperative comparison and for decisions about postoperative ventilation rather than as a screening test for adequacy of pulmonary function. PaCO₂ greater than 45 mm Hg at rest indicates significant alveolar hypoventilation. If the cause is muscle weakness, bronchospasm, or chronic bronchitis, it should be treated before any elective operation is undertaken. If the PaO₂ is less than 70 mm Hg, the patient has significant right-to-left shunting, diffusion block, or ventilation-perfusion mismatch—usually the last, although two or all three of these may occur together. These three causes of hypoxemia can be further identified by the response to breathing 100% oxygen, but this evaluation requires special equipment (a face mask or nasal catheter is not satisfactory), and the information gained is generally not worth the effort for the purposes of preoperative pulmonary assessment.

More detailed tests of pulmonary function are needed only in special situations. The most useful of these is measurement of FRC, which is done in association with simple spirometry using helium dilution or nitrogen washout. FRC is the most difficult lung volume to measure but also the most important: FRC is the most specific way of determining when the patient is in optimal pulmonary condition. An abnormally high FRC indicates air trapping from small airway disease or bronchospasm, which should be treated before any elective operation. An abnormally low FRC indicates loss of lung volume that may result from atelectasis, pneumonia, pleural effusion, or congestive heart failure, all of which should be treated until the FRC is normal.

Consensus guidelines for preoperative evaluation of patients undergoing resection for lung carcinoma were updated in 2007⁵ [see Figure 5]. A history suggesting dyspnea of minimal exertion or radiographic findings of diffuse parenchymal abnormalities should direct additional pulmonary function testing. The algorithm recommends formal pulmonary

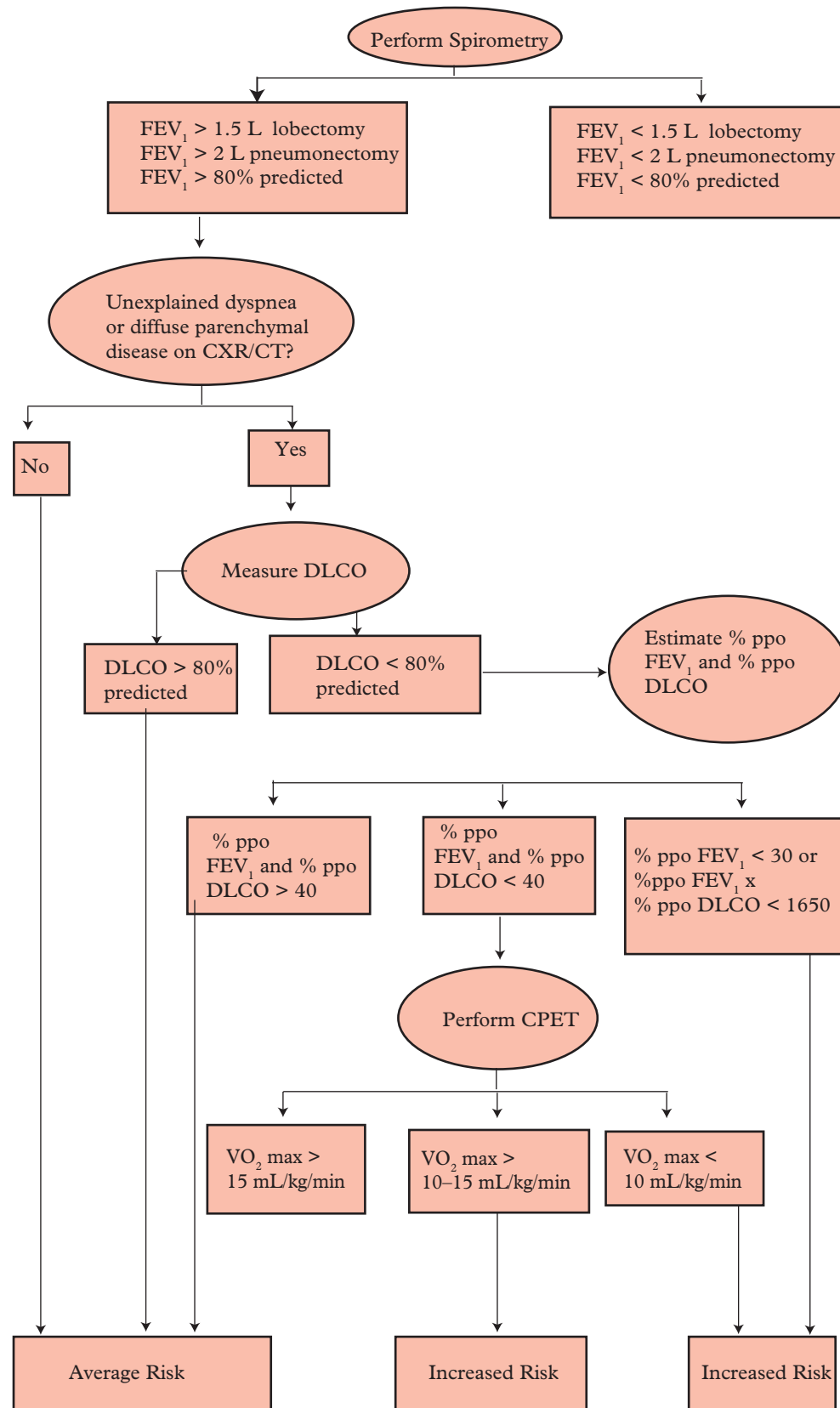


Figure 5 Preoperative evaluation of patients with lung cancer prior to resection. Adapted from Colice GL et al.⁵ CPET = cardio pulmonary exercise testing; DLCO = diffusion capacity of lung; FEV₁ = forced expiratory volume in 1 second; ppo = predicted postoperative; VO₂ max = maximal oxygen consumption.

function testing on optimal bronchodilator therapy and additional directed testing if the forced expiratory volume in 1 second (FEV₁) is below thresholds for safe resection (2.0 L for pneumonectomy, 1.5 L for lobectomy) or significantly decreased (< 80%). Diffusion capacity of the lung for carbon dioxide (DLCO₂), measurement, estimation of cardiopulmonary exercise tolerance, and calculation of the postoperative expected FEV₁ and DLCO₂ can further assist in risk stratification.

In summary, the history, physical examination, and chest x-ray constitute sufficient preoperative pulmonary assessment in almost all cases. Patients at risk for pulmonary complications, as identified by the history or examination, should undergo simple spirometry to identify abnormalities that can be corrected before elective operations. Arterial blood gases should be measured preoperatively in patients with major respiratory dysfunction to serve as a baseline for postoperative management.

Etiopathogenesis of Postoperative Pulmonary Insufficiency

CHANGES IN LUNG FUNCTION

After any major operation, changes occur in lung function. These changes occur in all patients but are not detected on routine examination. Aside from shallow tidal ventilation and some decreased breath sounds at the lung bases, the patient shows no signs of respiratory abnormality. On direct measurement, lung volumes are decreased (particularly residual volume, expiratory reserve volume, FRC, and vital capacity). Compliance is decreased because of the decrease in FRC. The work of breathing is increased for the same reason: more pressure is required to inhale a given volume into the decreased lung air space. Further evidence that alveoli are not being ventilated is absolute or relative arterial hypoxemia, which occurs with the patient breathing room air or 100% oxygen, indicating that nonventilated alveoli are being perfused (transpulmonary shunting).³

These changes in lung function are present immediately after operation, progress slowly over 1 to 2 days, and then return to normal in most patients [see Figure 6]. The extent and duration of abnormality are related to the site of operation, the duration of operation and anesthesia, the quality of postoperative care, and preexisting pulmonary status.

The extent and duration of postoperative pulmonary abnormalities are greatest for operations on the thorax and upper abdomen and progressively decrease as the site of operation moves more distally and more superficially on the body structures. These changes may occur after only 1 to 2 hours of general anesthesia if careful attention is not paid to maximal lung inflation during anesthesia. They are superimposed on the patient's preexisting lung status. If, for example, the patient requires operation for complication of pancreatitis 2 weeks after the onset of disease, he or she may already have pleural effusions, increased pulmonary capillary permeability, and existing transpulmonary shunting and thus may be unable to tolerate any further deterioration of lung function. Likewise, if the patient has preexisting chronic obstructive lung disease with high airway resistance, maximal work of breathing, and minimal functional lung tissue before

operation, CO₂ retention may develop if the work of breathing is even slightly increased after the procedure. Advanced age per se does not cause lung dysfunction, but elderly patients may have chronic lung disease or cardiac disease and thus be at higher risk for pulmonary failure. More important, elderly patients may be weak, and weak respiratory muscles predispose to alveolar collapse.

Several factors contribute to these changes in pulmonary function, but shallow breathing with incomplete alveolar inflation is the common denominator. If spontaneous deep breaths to maximal lung inflation are eliminated from the pattern of breathing, alveolar collapse begins within 1 hour and progresses rapidly to produce significant transpulmonary shunting [see Figure 7]. Several studies have shown that because of severe pain, anesthetics, or narcotic drugs, postoperative patients often lack the normal pattern of spontaneous deep breaths.^{6,7} This finding is further supported by the observation that the postoperative changes in lung function can be returned toward normal by instituting maximal-inflation deep breathing exercises at regular intervals.⁸ Excessive tracheobronchial secretions, aspiration of oral or gastric contents, and intraoperative fluid overload or blood transfusion may also contribute to postoperative changes in lung function.

The effects of an increased F_IO₂ and nitrogen washout are important to consider. The higher the concentration of oxygen in the alveoli, the lower the concentration of nitrogen. Nitrogen accounts for 80% of alveolar gas. Because nitrogen is inert, it merely occupies space, holding alveoli open as O₂ and CO₂ are rapidly exchanged during each breath. When nitrogen is washed out during O₂ breathing, alveoli tend to decrease in volume or collapse altogether with each breath, resulting in absorption atelectasis. Major atelectasis can occur with just a few minutes of 100% O₂ breathing. In one study, chest CT scans during O₂ breathing demonstrated major atelectasis occurring within minutes⁹ [see Figure 8]. Because a high F_IO₂ is commonly (and correctly) used during anesthesia with inhalational agents, it is important to minimize the risk of postoperative atelectasis through frequent recruitment of collapsed alveoli by inflation to total lung capacity and restoration of alveolar nitrogen at the end of the operation.

If the pattern of decreased lung volume and shunting is progressing rather than returning to normal, this development becomes clinically evident within 2 to 4 days after operation. Decreased lung volume is detectable as decreased breath sounds on physical examination, and atelectatic areas may be visible on chest x-ray. Hypoxemia as a result of shunting leads to an increased ventilatory rate and the sensation of dyspnea.

As noted, abnormal ventilation leads to altered pulmonary function; the abnormal pattern of tidal breathing without spontaneous deep breaths after operation is a good example of this phenomenon. A patient supine in bed preferentially ventilates the anterior superior lobes, whereas blood preferentially flows to the posterior dependent lobes. This ventilation-perfusion imbalance itself will result in hypoxemia. If it progresses over time, lower lobe alveoli begin to collapse in the pathogenetic pathway described earlier. Alveolar collapse will occur in any patient who remains in one position for a prolonged period and in whom the pattern of breathing is that of shallow tidal ventilation. It should be

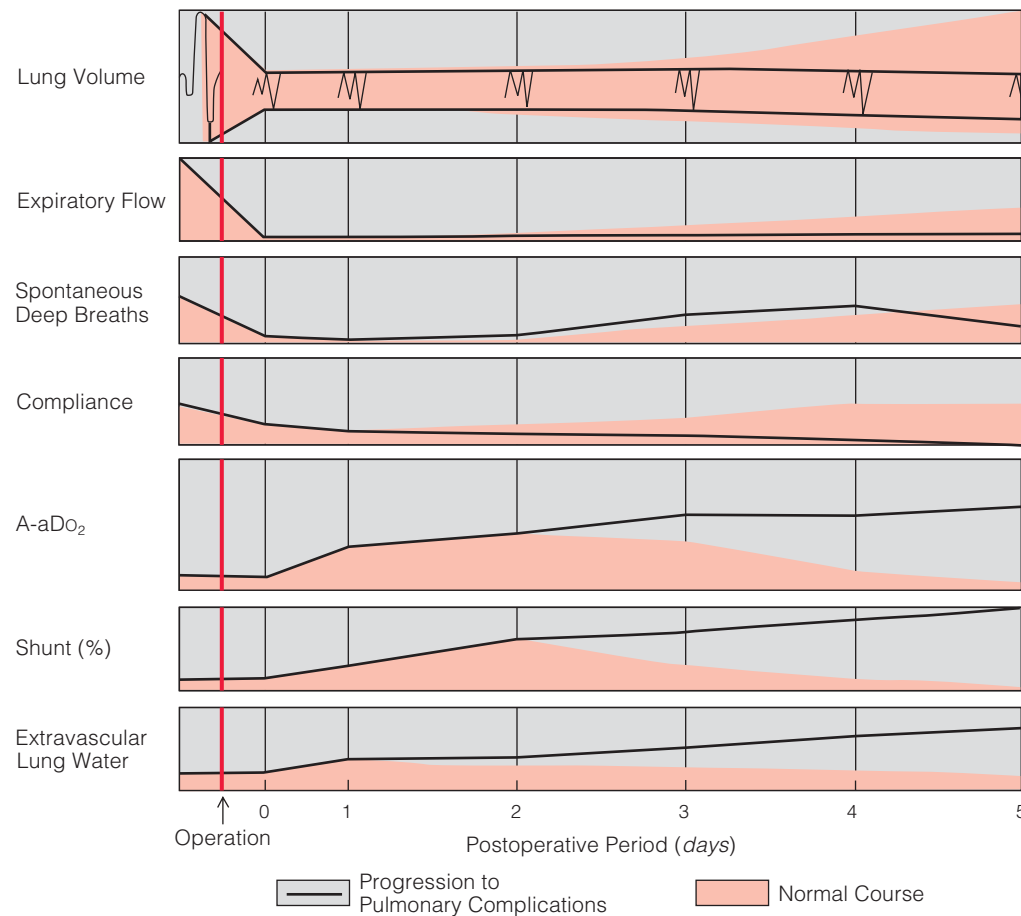


Figure 6 Shaded areas represent normal changes in pulmonary function after an operation. Solid lines represent progression to pulmonary insufficiency. A-aDO₂ = alveolar-arterial difference in oxygen.

emphasized that if regular maximal inflations are not carried out, small breaths delivered with a mechanical ventilator will lead to alveolar collapse, just as shallow spontaneous breathing will.

EDEMA AND THE PULMONARY INTERSTITIUM

Increased pulmonary hydrostatic pressure, decreased plasma oncotic pressure, and increased capillary permeability may all occur in the surgical patient. All of these states will cause increased pulmonary extravascular water and deterioration of lung function.

Fluid flux is a net function of the hydrostatic pressure that tends to force fluid out of the vascular space, on the one hand, and the oncotic pressure that tends to pull fluid in, on the other hand. High hydrostatic pressure or low plasma oncotic pressure results in accumulation of fluid in the extravascular space. If the pulmonary endothelium is damaged, fluid may leak into the extracellular space at normal hydrostatic or oncotic pressures (as in ARDS) [see Figure 9]. Pulmonary vascular resistance increases because of periarteriolar cuffing.³ Ventilation-perfusion imbalance is created by peribronchiolar and alveolar compression. Shunting occurs if the alveoli become completely collapsed or filled with fluid. Finally, boggy atelectatic areas of lung are ideal breeding grounds for bacterial pulmonary infection.

Well-intentioned therapy in the normal course of treatment or resuscitation may cause increased lung water. An example is replacement of lost blood or plasma with crystalloid, which must equilibrate into the entire extracellular space, including that in the lung. Excess exogenous fluid combines with increased endogenous production of the water of metabolism during hypermetabolic states to yield increased total body extracellular fluid—the major cause of pulmonary extravascular water collection. The effect is compounded by the decreased oncotic pressure that results when protein is lost or replaced with non-colloid-containing fluids. When plasma proteins are diluted in this way, lung interstitial proteins are also diluted; thus, the oncotic gradients stay unchanged, whereas the entire extracellular space expands.

The pulmonary capillary endothelium is the first major vascular bed to be exposed to any toxic substances arising from peripheral organ metabolism or perfusion of ischemic or infected tissue. The venous effluent from underperfused tissue (whether localized to a single organ, as in arterial embolism, or pervading the entire body, as in any type of shock) arrives directly at the lung, where pulmonary capillary damage occurs. Humoral products (e.g., lysosomal enzymes and bacterial endotoxin) or particulate materials (e.g., microemboli, major thromboemboli, platelet aggregates, and fat particles) may lodge in the pulmonary capillary bed. As these

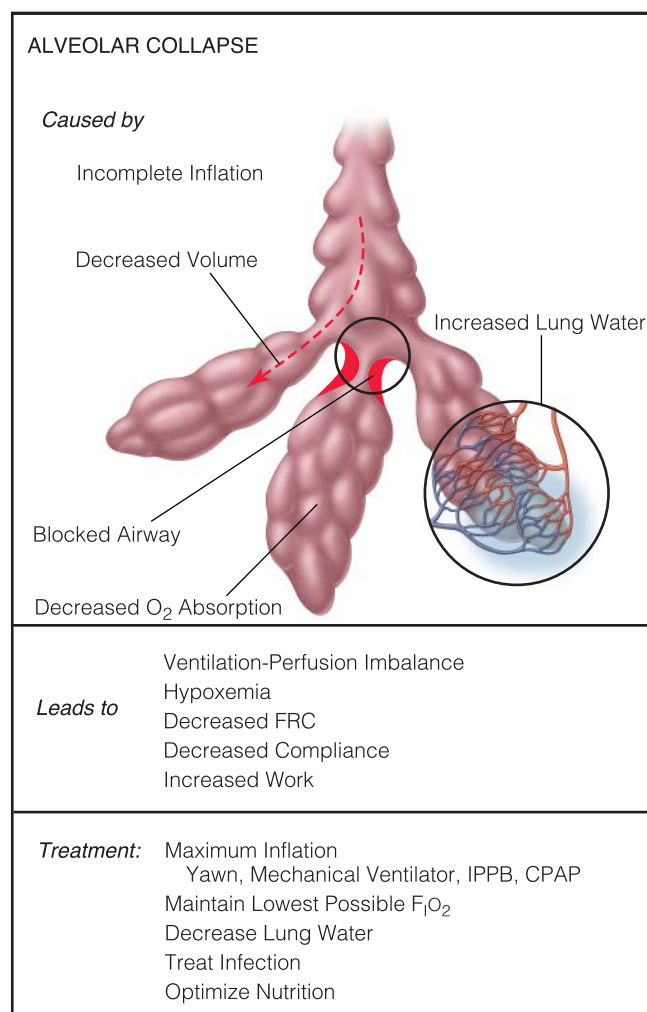


Figure 7 Illustrated are causes and effects of alveolar collapse in postoperative pulmonary insufficiency. CPAP = continuous positive airway pressure; F_IO₂ = fraction of inspired oxygen; FRC = functional residual capacity; IPPB = intermittent positive pressure breathing.

materials are cleared, leaky pulmonary capillaries are left behind, with the resultant accumulation of extravascular water. If the material trapped in pulmonary capillaries includes large amounts of platelets, secondary effects caused by platelet breakdown products (notably serotonin and thromboxane) are also seen.

Another characteristic unique to the pulmonary circulation is the phenomenon of hypoxic vasoconstriction. This compensatory phenomenon is seen to be diminished or completely lost in acute lung injury of different etiologies in animal models of acute lung injury, further contributing to hypoxia.^{10,11}

A phenomenon that may occur concurrently or in isolation is left ventricular failure with increased left atrial pressure results in pulmonary transcapillary transudation, as in congestive heart failure with overt pulmonary edema. Left ventricular pressures may waver at the point of high left atrial pressure for short periods—even minutes—resulting in a transient increase in lung water, and then return to a balanced state. This situation in itself may not lead to severe

pulmonary edema, but it probably makes the lung more vulnerable when minor capillary damage coexists.

OBESITY AS A RISK FACTOR

Obesity has not been consistently identified as an independent risk factor for postoperative pulmonary complications but does contribute physical challenges to normal ventilation. In the morbidly obese patient, the effort required to lift the chest wall and push the abdominal viscera and omentum aside during inspiration may be more than diaphragmatic contraction can handle. This condition is exacerbated after operation, when the patient may still be partially paralyzed, sedated from anesthetics or narcotics, and lying in the supine position (which allows the abdominal weight to push up on the diaphragm). In addition, obesity narrows the posterior pharyngeal space by the simple accumulation of fat in the submucosal tissues. This combination of factors makes hypoventilation a common problem in the obese patient. The hypoventilation can be profound but may be masked because the patients are receiving supplemental oxygen as Pao₂ remains normal, whereas Paco₂ may exceed 100 mm Hg. Moving the obese patient into a sitting position can minimize hypoventilation.

Clinical Approach to Postoperative Pulmonary Insufficiency

At any time during the first week after a major operation, a patient may manifest dyspnea, tachypnea, tachycardia, confusion, and cyanosis—the syndrome of pulmonary insufficiency. Although the most likely causes of this syndrome are atelectasis and edema, the first step in evaluation is to rule out mechanical limitation of breathing, acute bronchospasm (asthma), pulmonary thromboembolism, congestive heart failure, and hypovolemia.

Mechanical limitation of breathing may be caused by gastric or intestinal distention, ascites, pneumothorax, hydrothorax, or splinting of the chest wall to treat pain or rib fractures. It is diagnosed by physical examination and chest x-ray and treated by removing the limitation.

Bronchospasm occurs in patients with a history of asthma. The diagnosis is made by finding expiratory wheezes on physical examination and hyperinflation on x-ray. Treatment consists of bronchodilators.

Pulmonary embolism is the first consideration when the onset of pulmonary insufficiency is sudden but is the least common cause. Small (lobar) pulmonary emboli rarely cause symptoms. A patient who is symptomatic from embolism has had a major embolus (or a series of minor emboli) occluding more than 50% of the pulmonary circulation. It is usually easy to differentiate pulmonary embolism from atelectasis on the basis of clinical examination and blood gas measurements [see Table 1].

Congestive heart failure in the postoperative period may be either an exacerbation of a chronic condition or acute cardiac failure secondary to myocardial infarction. In either case, the diagnosis is made by physical and x-ray examination of the chest. In the patient who is fluid overloaded, the use of a pulmonary arterial catheter may be required to differentiate cardiogenic from capillary-injury pulmonary edema. The

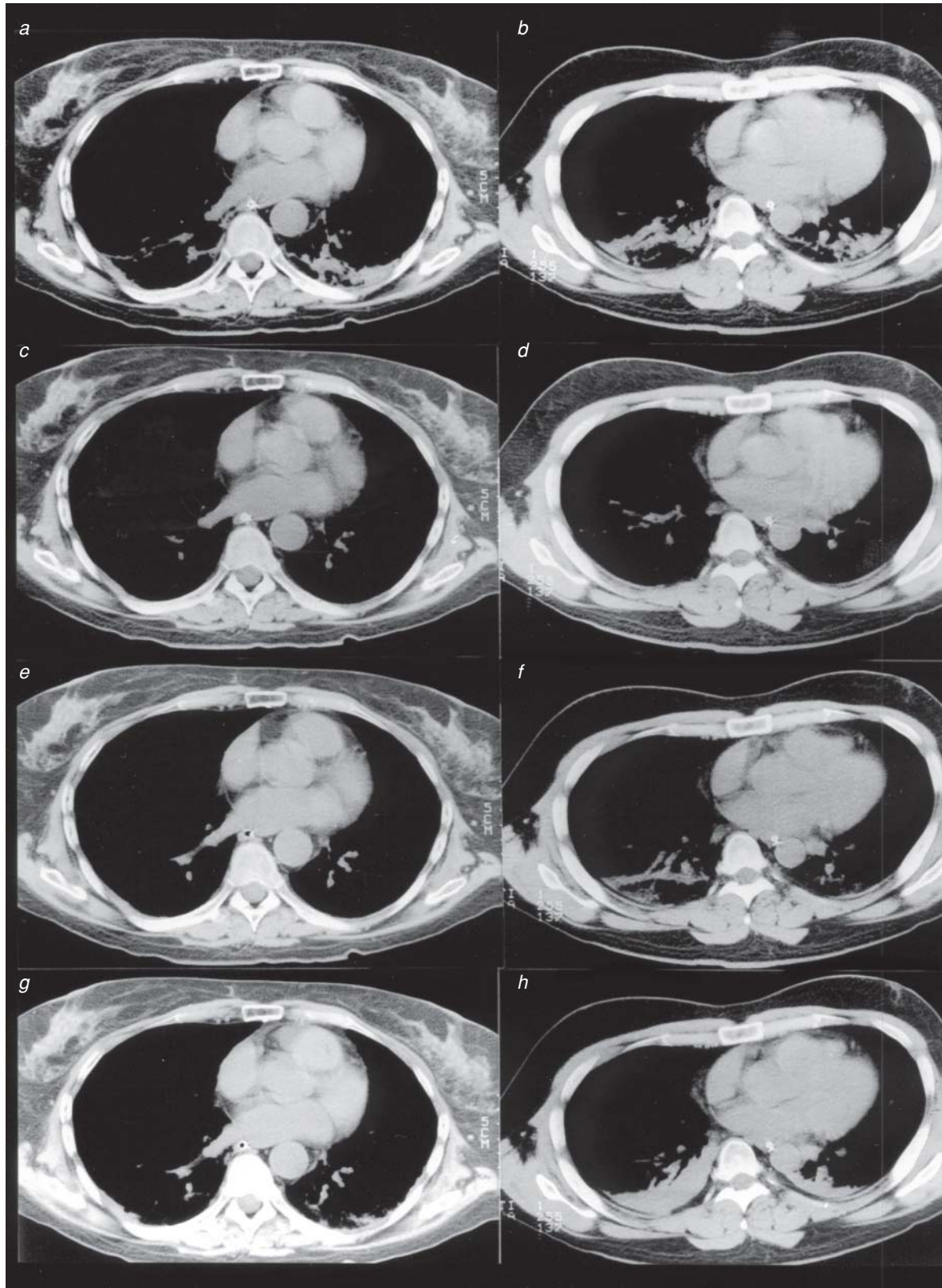


Figure 8 The subject on the left (*a, c, e, g*) is ventilated with 40% O₂ and the subject on the right (*b, d, f, h*) with 100% O₂. Atelectasis occurs (posteriorly) after induction and several minutes of tidal breathing (*a, b*) and is completely reversed by inflation to total lung capacity (plateau pressure 40 cm H₂O; *c, d*). Inflation was sustained for 5 and 40 minutes while the patient was breathing 60% nitrogen (*e, g*), but atelectasis recurred by absorption while the patient was breathing 0% nitrogen (*f, h*). Reproduced with permission from Rothen HU et al.⁹

INCREASED LUNG WATER

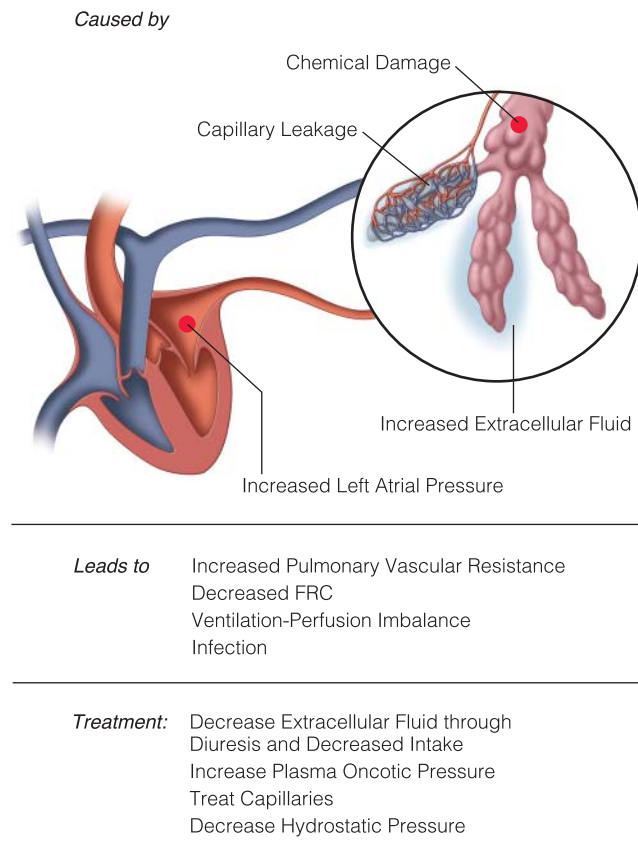


Figure 9 Illustrated are causes and effects of increased lung water in postoperative pulmonary insufficiency. FRC = functional residual capacity.

initial steps in management are the same, however, for the acutely ill patient: diuresis, supplemental oxygen, review of body weight and fluid balance records, and transfer to the intensive care unit (ICU) for more invasive monitoring.

Hypovolemia is often first manifested by dyspnea associated with metabolic acidosis, and postoperative shortness of breath should always raise the possibility of occult bleeding or third-space sequestration. Clinical examination elicits findings typical of hypovolemia. The chest x-ray is usually clear, and blood gases demonstrate normal oxygenation and CO₂ clearance. Serial measurements of serum lactate may not only be useful in diagnosis but also serve as a guide to resuscitation.

In postoperative pulmonary insufficiency caused by atelectasis and edema, physical examination shows diminished breath sounds over one or both lung bases. Rales and rhonchi may be heard in the middle and lower lung fields. Although tidal volume is normal, vital capacity (judged or actually measured) is abnormally small. Chest x-ray demonstrates incomplete lung inflation, usually with overt collapse or consolidation apparent in the lower lobes. If lung edema is the predominant cause of pulmonary insufficiency, a diffuse increase in lung density is seen, which, when combined with irregular inflation, is often described as diffuse fluffy infiltrates. This radiographic finding will usually differentiate this state from cardiogenic pulmonary edema, which is typically more apparent in the lower and middle lung fields when the x-ray is taken with the patient sitting or standing. Measurements of arterial blood gas values while the patient is breathing air demonstrate a pattern of normocapneic respiratory failure with hypoxemia, hypocarbia, and respiratory alkalosis.

Supplemental high-flow oxygen (10 L/min) supplied by nasal catheter or face masks supply approximately 40% inspired oxygen (regardless of the settings on the equipment) [see Table 2]. Supplemental oxygen substantially mitigates the hypoxemia resulting from ventilation-perfusion mismatch, pulmonary embolism, or cardiogenic pulmonary edema, typically resulting in a Pao₂ greater than 150 mm Hg. In contrast, supplemental oxygen has a minor effect on hypoxemia caused by atelectasis, yielding a Pao₂ typically rising from the 40s to the 80s. Fever and mild leukocytosis often accompany atelectasis, and the differential diagnosis between atelectasis and pneumonia is based primarily on continuing signs of infection without another obvious source, combined with pathogenic organisms on sputum culture. Thickened or

Table 1 Differential Diagnosis of Postoperative Dyspnea

	Atelectasis/Edema	Pulmonary Embolism	Bronchospasm	Congestive Heart Failure
Lung bases	Not aerated	Clear	Wheezes	Rales
Chest x-ray	Consolidation, general edema	Clear ↑ Diameter of main pulmonary artery	Hyperinflated	Hydrostatic edema ↑ Diameter of main pulmonary artery
Central venous pressure	Normal	Elevated	Normal	Elevated
Pulmonary arterial wedge pressure	Normal	Normal or low	Normal or high	High
Arterial Po ₂ (breathing air) (mm Hg)	40–60	40–80	70–90	40–60
Arterial Po ₂ (breathing O ₂) (mm Hg)	50–100	100–300	200–300	100–300
Arterial Pco ₂	Low	Normal or low	High	Normal or high
Lung scan	Regional ischemia	Regional ischemia	± Normal	± Normal
Pulmonary angiogram	Normal	Diagnostic	Normal	Normal

Pco₂ = carbon dioxide tension; Po₂ = oxygen tension.

Table 2 Intratracheal Concentration of Oxygen in Different Delivery Systems

Oxygen Delivery System	Intended $F_{I}O_2$	Tracheal Oxygen Concentration (%)	
		Quiet Breathing	Hyperventilation
Nasal cannula			
3 L/min		22.4	22.7
10 L/min		46.2	30.5
15 L/min		60.9	36.2
Face mask			
10 L/min	60	53.4	41.0
15 L/min	100	68.1	50.2
Venturi mask			
4 L/min	28	24.2	21.4
8 L/min	40	36.4	29.4

Adapted from Gibson RL et al.⁴⁸
 $F_{I}O_2$ = fraction of inspired oxygen.

Table 3 Prevention of Atelectasis during and after Operation

Ensure frequent inflation to total lung capacity
Deep breathing exercises facilitated by incentive spirometer
Mechanical ventilation after major operations until alert and awake
Positive pressure breathing for patients who cannot take deep breaths
Minimize respiratory depression
Adequate, but not excessive, narcotic dosage
Local and regional anesthesia
Minimize absorption atelectasis from increased $F_{I}O_2$
Add nitrogen (lowest $F_{I}O_2$ to keep $SaO_2 > 90\%$)
Use PEEP if $F_{I}O_2 > 50\%$
Avoid pulmonary edema
Clear pleural space of air and fluid
Use abdominal viscera to increase lung volume
Sitting or standing position
Avoidance of supine position and high abdominal pressure

$F_{I}O_2$ = fraction of inspired oxygen; PEEP = positive end-expiratory pressure; SaO_2 = arterial oxygen saturation.

copious bronchial secretions may be present in any patient after operation, particularly if the patient underwent endotracheal intubation, general anesthesia, or both during the procedure. Bronchial secretions rarely cause atelectasis.

Perioperative Measures to Prevent Pulmonary Insufficiency

INTRAOPERATIVE MEASURES TO PREVENT PULMONARY COMPLICATIONS

Intraoperatively, several factors may minimize the risk of postoperative pulmonary complications. The operation may directly improve pulmonary function (e.g., by repairing a mitral valve or a large abdominal wall hernia) or may mitigate or eliminate factors that of themselves are causing pulmonary insufficiency (e.g., by draining an empyema, removing a foreign body, or resecting dead tissue).

The operative procedure should be planned so as to simultaneously treat the patient and avoid any factors that may cause postoperative complications. With regard to the pulmonary system, planning includes various components, as follows.

Abdominal incisions should be planned to minimize postoperative pain and to maintain the strength of the abdominal wall for forced inspiration. Attempts should be made to avoid the use of prolonged nasogastric intubation. Veins under negative pressure (e.g., those in the brain) must be managed carefully to prevent air embolism. If the patient has a history of pulmonary embolism or existing deep vein thrombosis (DVT) in the legs, prophylaxis for these conditions is particularly important.

Ventilation with 100% O_2 before intubation is standard practice, and an $F_{I}O_2$ higher than 90% is commonly used during operation. However, elimination of inert nitrogen in the alveoli leads to absorption atelectasis very rapidly [see Table 3]. Accordingly, restoring normal alveolar nitrogen levels and volume through sustained inspiratory pressure with air before extubation is a valuable maneuver.⁹ By the same token, however, maintaining a high $F_{I}O_2$ throughout the

operation and during the early postoperative period significantly decreases the risk of a surgical site infection.¹²

Much of the intraoperative prevention of pulmonary complications is carried out by the anesthesiologist. Maintaining appropriate tidal volume ventilation (6 to 8 mL/kg) at a low respiratory rate during operation helps maintain alveolar integrity by reducing volutrauma and preventing atelectrauma.¹³ The anesthesiologist contributes greatly toward preventing pulmonary complications by avoiding crystalloid fluid overload during operation. Generally, blood or plasma lost during operation should be replaced with blood or plasma. Moderate amounts of isotonic solutions are permissible, but caution should be observed.

Mechanical ventilation should be continued postoperatively until adequate spontaneous ventilation has been clearly established. The action of paralytic drugs should be reversed completely, and a voluntary vital capacity at least twice the tidal volume should be documented before extubation.

PREVENTION OF ATELECTASIS AND EDEMA

In the recovery room, the endotracheal tube should be maintained in place as long as is necessary. Patients with preexisting pulmonary dysfunction or those at high risk for pulmonary complications may need to remain intubated and be maintained on mechanical ventilation for hours or days after operation. The balance of prolonged intubation has to be weighed against the cumulative risk of ventilator-associated pneumonia (VAP).¹⁴ Elderly, debilitated patients, patients who have undergone major cardiac procedures, and patients with extensive injuries, multiple fractures, pancreatitis, dead tissue, or severe peritonitis are commonly left intubated and maintained on mechanical ventilation for 12 hours or longer after operation. When the patient is fully alert and awake, hemodynamically stable, and appropriately resuscitated, the patient is ready for spontaneous ventilation trials and possible extubation. Spontaneous awakening and breathing trials are widely practiced as standard protocols in the care of the critically ill in most ICUs.^{15,16}

Abundant evidence suggests that well-ventilated alveoli are less susceptible to additional insults to the pulmonary

parenchyma than atelectatic alveoli are [see Table 4]. Lung expansion modalities have been extensively studied and are the only maneuvers demonstrated to reduce pulmonary risk.¹⁷ Incentive spirometry and deep breathing exercises are inspiratory maneuvers to recruit alveoli and counteract the postoperative reduction in FRC. Deep breathing exercises, clearing of sputum and mucus, and avoidance of prolonged periods in the supine position must begin in the recovery room. Profound hypoventilation, ventilation-perfusion imbalance, and resultant hypoxemia are the rule in patients awakening from anesthesia.

Airway cleaning, suctioning, expectorant drugs, mist inhalation, and mucolytic agents are all useful in patients with preexisting chronic bronchitis or thick, tenacious tracheo-bronchial secretions. However, these maneuvers and agents may not be necessary in patients who can inflate their lungs adequately by means of inspiratory maneuvers. In the past, a compulsion to force patients to cough dominated much of the thinking on postoperative pulmonary care. Currently, it is generally recognized that coughing maneuvers are painful in thoracotomy or laparotomy patients and should not be necessary if the lung remains well ventilated.

Breathing maneuvers and devices designed to encourage those maneuvers are important adjuncts to postoperative care. Because shallow breathing, the lack of spontaneous deep breaths, and alveolar collapse are the steps that lead to postoperative pulmonary complications, respiratory maneuvers must emphasize maximal lung inflation. Emphasis on breathing out (i.e., with coughing, tracheal stimulation, or so-called blow bottles) does nothing to accomplish alveolar inflation, aside from the preparatory inspiration the patient may take beforehand.

Deep inspiratory maneuvers can be done spontaneously or with the aid of a nurse or physical therapist but are better done with the aid of the incentive spirometer. This device allows the patient to see the inspired volume with each breath, thereby assuring the physician, the nurse, the respiratory therapist, and the patient that the maneuver is being done correctly and frequently enough to maintain alveolar inflation. Regular performance of deep breathing exercises using an incentive spirometer can decrease the incidence of pulmonary complications from about 30% to about 10%.⁸ Continuous positive airway pressure (CPAP) has been demonstrated to improve postoperative pulmonary outcomes.¹⁸ A few controlled studies in elective surgical patients

have demonstrated that reduction in pulmonary complications is obtained when high-risk patients are identified and interventions are initiated preoperatively.^{19,20} Concentrated efforts during preoperative sessions may result in increased patient compliance. The potential complications of mask CPAP—gastric distention, vomiting and aspiration, and patient discomfort—are rare but remain a cause for concern. This technique, perhaps combined with mask intermittent positive pressure breathing (IPPB), may prove useful in patients who are extubated but cannot or will not breathe deeply.

For patients requiring care in an ICU, keeping the head of the bed elevated at least 30° significantly decreases the risk of developing VAP.^{21–23} Accordingly, unless there is a contraindication (e.g., spinal fracture), semirecumbent positioning should be employed routinely. Frequent change of position and early ambulation will minimize fluid collection in the dependent portions of the lung. Postoperative nutrition should be maintained. If the patient must go without oral intake for more than 4 or 5 days, total parenteral nutrition is advisable for several reasons, not the least of which is to maintain the strength of the respiratory effort. Fluids must be managed carefully to avoid overloading the extracellular space and diluting the serum proteins.

Pulmonary thromboembolism from the deep veins of the leg or the pelvis is a constant threat after operation. Patients older than 40 years and patients with cancer are at particularly high risk. Several methods are used to prevent DVT, including anticoagulation, pharmacologic inhibition of platelet function, and application of pressure to the legs with elastic wraps or intermittent compression stockings. Regular muscle exercise is the easiest preventive maneuver, has the fewest complications, and is advised for all postoperative patients.

CORRECTION OF ABNORMALITIES

If a patient is scheduled for an elective operation, as much time as is necessary should be spent measuring lung function, correcting abnormalities where present, and changing conditions that may predispose to pulmonary complications. This is particularly true in patients with preexisting cardiopulmonary disease. Patients should be advised to train for a major operation as they would for an athletic event. The respiratory muscles should be exercised and specific breathing maneuvers learned.

Correction of factors that may decrease the efficiency of ventilation includes cessation of smoking, elective weight loss in grossly obese patients, and treatment of existing bacterial infection (chronic bronchitis) with culture-specific antibiotics where indicated. Cigarette smoking is directly toxic to respiratory ciliary epithelium and impairs normal intratracheal mucus transport. In addition, impaired wound healing and vasospasm increase postoperative local complications. Despite evidence in the cardiothoracic surgery population, surprisingly little evidence is available in the noncardiac population. Conflicting evidence exists regarding timing of discontinuation of smoking prior to surgery based on reports of increased airway reactivity following cessation.^{24,25} A general recommendation is that smoking should be stopped at least 6 to 8 weeks preceding elective surgery. Patients with a known reactive airway disease (e.g., asthma) should become

Table 4 Prevention of Pulmonary Edema during and after Operation

Avoid extracellular fluid overload
Routine intraoperative fluids limited to 3% of body weight
Low threshold for blood or colloid during resuscitation or blood loss
Treat or prevent left ventricular failure
Optimization of cardiac output with inotropes when filling pressures are elevated
Restore or maintain colloid osmotic pressure
Diuresis to concentrate proteins
Administration of 25% albumin or plasma if pulmonary edema is symptomatic
Minimize pulmonary capillary leakage
Drainage of pus and excision of dead tissue

accustomed to undergoing bronchodilator treatment preoperatively, and the effect of bronchodilators on pulmonary mechanics should be directly measured.

MEASURES IN PATIENTS WITH PREEXISTING LUNG DISEASE

Patients with chronic disease of the airways or the pulmonary parenchyma have less pulmonary reserve; consequently, in these patients, acute respiratory failure may develop after a minimal insult to the lung. The patient with emphysema or asthma presents an interesting problem. Because of the primary disease, residual volume and FRC are abnormally expanded. The patient is protected to some extent against alveolar collapse secondary to shallow breathing; however, the involved alveoli are difficult to ventilate, even with maximal effort. The dead space is abnormally large, so the minute ventilation must be higher than normal just to achieve normal CO₂ excretion. In addition, alveolar destruction, fibrosis, or bullae may be present, decreasing oxygenation and CO₂ excretion. The effect of shallow breathing in such a patient will not be atelectasis, as would occur with a normal lung, but rather CO₂ retention and hypoxemia. Supplemental oxygen may reverse the hypoxemia, but CO₂ narcosis may result, particularly if the patient is also sedated with narcotics or anesthetics.

Chronic bronchitis (daily production of purulent sputum) narrows the small airways, increasing susceptibility to inadequate inflation and alveolar collapse. Heavy cigarette smoking has the same effect. In these conditions, treating the airways before elective operation (with antibiotics or cessation of smoking) is advisable. Severe restrictive disease from pulmonary fibrosis, pleural thickening, fibrosis, or chest wall deformities predisposes to atelectasis.

Patients with acute respiratory failure may require operation; in fact, the respiratory failure may exist because of the indication for operation (e.g., sepsis, ischemic tissue, or shock). Such patients come to operation with a decreased FRC and increased pulmonary water, following the pathogenetic sequence of acute respiratory failure. The pulmonary problem may be mitigated or eliminated by the operation itself (e.g., when pus is drained or a fracture immobilized), but even if pulmonary function does not improve, these patients cannot afford any worsening of alveolar collapse or pulmonary edema. In such patients, further deterioration of pulmonary function must be prevented by means of prolonged postoperative intubation and mechanical ventilation and fine-tuning of hydrostatic pressure and colloid osmotic pressure in relation to cardiac output and blood volume.

Treatment of Postoperative Pulmonary Insufficiency

GENERAL SUPPORT

Beginning during the preliminary clinical and laboratory examinations and the differential diagnosis, supplemental oxygen should be supplied by nasal catheter or face mask. If the patient has a history of severe pulmonary disease with hypoxemia and hypercarbia, preoperative supplemental oxygen may correct the hypoxemia but diminish the respiratory drive and result in CO₂ narcosis; accordingly, special precautions should be taken. The patient should be

positioned so as to maximize diaphragmatic excursion—that is, sitting but not hunched forward, with care taken to ensure that the stomach and the abdomen are not distended.

TREATMENT OF ATELECTASIS

The cornerstone of treatment aimed at alveolar inflation [see Figure 7] is to establish large-volume inflation by instituting deep breathing exercises. The patient should be taught to carry out a sustained maximal inspiration (basically a yawn maneuver); as noted, an incentive spirometer will encourage and quantitate the patient's efforts. If adequate volumes cannot be generated in this manner, mechanical assistance is necessary. Noninvasive ventilation can be performed without intubation. This step must be done with direct measurement of exhaled volume, and it often requires high pressures (30 to 40 cm H₂O). All of the inflation techniques of mechanical ventilation (PEEP, sighs, inspiratory hold, CPAP) can be used in nonintubated patients. Again, coughing is not a treatment for pulmonary insufficiency: forced expiration collapses alveoli, does not clear small airways, and is painful and ineffective in the postoperative patient.

When an area of lung is not ventilated, mucus secreted in the bronchi draining from that lung segment may become thickened and impacted, hindering efforts at reexpansion. Chest physical therapy (percussion) and postural drainage should clear this mucus. Hydration and nebulized bronchodilator and mucolytic drugs may be used as well. Although coughing is not effective in preventing atelectasis, it is necessary for expelling mucus from airways that have been inflated distally. Coughing will not dislodge mucus from airways leading to nonventilated areas of the lung. In this situation, mucus must be removed directly with tracheal suction or bronchoscopy, preferably the latter.

Tracheal suctioning exacerbates hypoxia if not done properly. The catheter is inserted through the nose, passed through the larynx (with passage confirmed by a change in voice), and connected to oxygen administered at 5 L/min. Then 5 mL of saline is injected, and the oxygen is reconnected for several coughing breaths. Suction is applied for no longer than 10 seconds, after which oxygen is resumed. This process is repeated until the suction return is clear (1 to 5 minutes). Patients should be monitored for bradycardia as a manifestation of vagal stimulation secondary to deep suctioning. However, routine tracheal suctioning has no rational place in the care of postoperative adult patients. In infants, who have much narrower airways, even a very small amount of mucus may suffice to cause major tracheal or bronchial occlusion. Infants breathe rapidly, with large ventilation of the dead space; thus, their tracheal secretions tend to dry out, and they may have difficulty coughing material from the lower trachea or from the bronchi. Consequently, endotracheal suctioning can be valuable for infants who have undergone operations on the thorax or upper abdomen.

Flexible fiberoptic bronchoscopy is preferable to blind tracheal suctioning in the management of atelectasis in intubated patients. Bronchoscopy is performed to examine the airways and clear mucus from the atelectatic area. If adequate ventilation cannot be established with these methods, respiratory support is warranted. For reversible causes of respiratory failure, endotracheal intubation can be

avoided by using noninvasive mechanical ventilation.^{26–29} Mechanical ventilation is indicated if the respiratory rate is consistently higher than 30 breaths/min or if the patient is severely hypoxemic (oxygen saturation < 92% despite supplemental oxygen via nasal cannula or face mask). If either of these indications cannot be reversed by the measures described, intubation and mechanical ventilation are carried out.

TREATMENT OF EDEMA

The amount of lung water can be reduced by decreasing the entire extracellular fluid space, decreasing the hydrostatic pressure in the pulmonary capillary bed, and increasing plasma oncotic pressure without increasing oncotic pressure in the interstitial fluid of the lung [see Figure 9]. Mechanical positive pressure ventilation is not a means of decreasing lung water. In fact, positive pressure ventilation with PEEP actually increases lung water slightly, probably by stretching the pulmonary tissue.³⁰ Mechanical ventilation improves gas exchange in patients with pulmonary edema by overcoming the ventilation-perfusion mismatch associated with bronchodilators or alveolar thickening but does not decrease lung water itself.

Patients with simple atelectasis need no treatment for increased lung water other than avoidance of fluid overload and cardiac failure. Increased lung water warrants treatment when diffuse interstitial fluid collection is evident from x-rays and the hospital course. For example, patients who have had an episode of severe systemic infection, disseminated intravascular coagulation, or fat embolism; those with peritonitis; those experiencing revascularization of ischemic tissue; and those who received excess intravenous fluids during an operation are likely to have increased lung water in association with other pulmonary problems.

Total extracellular fluid volume is reduced by forced diuresis (or, if the patient is in renal failure, by dialysis or hemofiltration). Diuresis is induced with a potent agent such as furosemide. The course of diuresis is followed with careful daily measurement of body weight and hourly measurement of fluid intake and output. Usually, a patient with postoperative pulmonary insufficiency is 4 to 5 kg overloaded, primarily with extracellular fluid. Adequate treatment of increased lung water must include removing excess extravascular fluid (i.e., returning the patient to baseline weight). Diuresis is continued until the patient is close to dry weight and is maintained in this condition. Diuretic drugs remove water, sodium, and potassium at differing rates; thus, all of these must be monitored carefully and frequently. Usually, more water is removed than electrolytes, so extreme forced diuresis leads to a hypernatremic, hyperosmotic state. Serum sodium concentrations should be monitored closely.

Resuscitation with colloidal fluids cannot be routinely recommended based on current understanding of clinical data.³¹ However, treatment of individuals with colloid loading (and diuresis) can be highly successful.³² The technique should be used when capillary integrity has been restored, as determined by response to small initial doses.

Decreasing pulmonary hydrostatic pressure by improving left ventricular function is accomplished pharmacologically. The effectiveness of this treatment can be determined accurately only through direct measurement of cardiac output

and left atrial (or pulmonary capillary wedge) pressure, for which insertion of a pulmonary arterial catheter is required.

An effort should be made to establish and maintain normal pulmonary capillary permeability. The most common cause of pulmonary capillary leakage or ARDS is infection or inflammation at a site distant from the lungs. Any postoperative pulmonary insufficiency should trigger a search for wound infection, deep abscess, pancreatitis, and septic phlebitis. Although ALI and ARDS are “syndromes” caused by different injuries and conditions, their lung injury pathophysiology offers an array of potential specific targets for pharmacologic intervention. Pharmacotherapy for ALI/ARDS is complex because multiple aspects of inflammation, cell and tissue injury, vascular dysfunction, surfactant dysfunction, and oxidant injury are typically present in the lungs, with added multiorgan and systemic pathology in many cases. This necessitates the consideration not only of single-agent therapies but also combination or multimodal treatments. A number of pharmacologic agents have been studied in ALI/ARDS with limited or minimal success in improving survival in single-agent therapy.^{33,34} However, improved mechanistic scientific understanding coupled with the continuing identification of new agents and rational combination regimens increases the likelihood of successfully developing pharmacotherapies able to decrease mortality and improve long-term outcomes.

PROGRESSION TO ALI/ARDS AND PNEUMONIA

In the postoperative period, the lung is vulnerable as both of the essential components of lung function—ventilation (anatomy and physiology of breathing) and pulmonary circulation (anatomy and physiology of the pulmonary endothelium and interstitium)—are affected by all the events surrounding tissue injury, anesthesia, and tissue dissection.³ Abnormal ventilation leads to alveolar collapse, decreased FRC, and atelectasis. Abnormal capillary homeostasis leads to lung edema. ALI and ARDS are characterized by rapid-onset respiratory failure following a variety of direct and indirect insults to the parenchyma or vasculature of the lungs. The pulmonary pathology of ALI/ARDS can be divided conceptually into acute and fibroproliferative phases that have distinctive features but vary in detail depending on the etiology of injury. Mortality from ALI/ARDS is substantial, and current therapy primarily emphasizes lung-protective, low tidal volume mechanical ventilation and judicious fluid management plus standard treatment of the initiating insult or underlying disease.

Progression to pneumonia is common in the postoperative period, is responsible for a significant proportion of ARDS, and affects a substantial fraction of patients following surgery with general anesthesia.³⁵ The combination of atelectasis, edema, and pneumonia may necessitate intubation and mechanical ventilation. The subjective findings of dyspnea and confusion, combined with the objective findings of tachypnea and cyanosis, usually trigger ICU transfer, careful monitoring, and intubation. VAP, defined as a pulmonary infection occurring after at least 48 hours of mechanical ventilation, is the second most common nosocomial infection.³⁵ VAP is a leading cause of death in critically ill patients in the ICU, with estimated prevalence rates of 10 to 65% and mortality rates of 25 to 60% depending on the study, patient

populations, and medical/surgical conditions involved.^{14,36–40} Bacterial infection often complicates atelectasis and edema and may occur as a primary event after operation. The progression from atelectasis to pneumonia can be difficult to identify because pulmonary infiltration and consolidation, fever, leukocytosis, and sputum production occur in both conditions. This differential diagnosis is one of the most difficult in postoperative care; decisions must be based on repeated examination of the patient and quantitative culture results obtained from the lower respiratory tract.

Specific Conditions and Events Associated with Pulmonary Insufficiency

FAT EMBOLISM

In a small percentage of patients with long bone fractures, the clinical syndrome of fat embolism develops. This syndrome results from pulmonary embolization of neutral fat globules from the marrow cavity and is often associated with embolization of megakaryocytes and other marrow cells. Hypoxemia and bilateral patchy pulmonary infiltrates, beginning 12 to 36 hours after an injury or a bone operation, are typical of this lesion. Associated findings include a falling hematocrit, hemolysis, high fever, cerebral symptoms, petechiae (particularly in the anterior axillary folds, the sclerae, and the eyelids), and possibly fat globules in urine, blood, or sputum. Pulmonary capillary damage occurs, apparently as a consequence of sterile inflammation from fatty acids released as the triglyceride particles break down in the lung parenchyma. Care must be taken to keep the patient's fluid balance as dry as possible because the pulmonary capillaries leak even at normal hydrostatic pressures. This is often difficult in patients with multiple injuries, who may have active bleeding or oliguria concomitantly with the developing pulmonary lesion.

INHALATIONAL INJURY SECONDARY TO BURNS

Several investigators have demonstrated a generalized permeability increase in capillaries (including pulmonary capillaries) after a small burn; the more extensive the burn, the greater the capillary leakage.⁴¹ The pulmonary capillary bed shows signs of increased capillary permeability first, in the form of increased lung water. The pathogenesis of smoke inhalation has been recently shown to be multifactorial.⁴² The injury results in airway obstruction, increased pulmonary transvascular fluid flux, and loss of hypoxic pulmonary vasoconstriction. The changes in cardiopulmonary function are mediated by reactive oxygen and nitrogen species. Nitric oxide (NO) is generated by both inducible and constitutive isoforms of nitric oxide synthase (NOS). Toxic components of smoke include carbon monoxide, heat, various aldehydes and other organic materials, and a wide range of vaporized compounds. Materials that are totally combustible (e.g., natural gas and gasoline) burn to yield CO₂ and water, producing few toxic organic compounds and causing minimal lung damage when inhaled in smoke. On the other hand, materials that burn incompletely (e.g., wood, paint, and upholstery) yield a number of toxic vapors in addition to the usual products of combustion, and these vapors damage the respiratory epithelium and alveoli. The heat carried in smoke

is a relatively minor cause of lung damage because air is such a poor heat conductor. Deep lung damage from heat is unusual unless the thermal injury is conveyed by hot steam.

Carbon monoxide is the major toxic material in smoke. It does not damage the lungs but renders the brain hypoxic by associating with hemoglobin, thereby inducing potentially lethal brain damage. Patients with smoke inhalation injury who do not have a body surface burn usually pass through a period of mild pulmonary insufficiency and recover completely unless they have suffered irreversible brain damage or metabolic acidosis as a result of carboxyhemoglobinemia. Patients with the same degree of smoke inhalation injury who also have a moderate body surface burn are subject to serious pulmonary insufficiency with combined atelectasis and increased lung water; intubation, mechanical ventilation, and efforts to reduce lung water usually prove necessary.

CHEST TRAUMA AND LUNG CONTUSION

Direct injury to the chest may cause damage to the chest wall, the lung parenchyma, the diaphragm, the airway, and other intrathoracic structures (e.g., the heart and the great vessels). These injuries are usually associated with hemothorax or pneumothorax. Penetrating trauma may result in a sucking chest injury, in which air is inhaled into the pleural space during inspiration, filling the pleural space, eliminating the pressure gradient that would normally cause the lung to inflate, and resulting in atelectasis. Life-threatening hypoventilation may result from injuries to the chest wall or from alveolar collapse caused by fluid or blood in the pleural space. Emergency treatment includes placement of a large chest tube to empty the pleural space and reexpand the lung along with mechanical ventilation if spontaneous breathing is inadequate.

With blunt trauma, fracture of the ribs or sternum may create a segment of the chest wall that moves inward in response to the negative pressure created during spontaneous inspiration (so-called paradoxical motion); this floating segment is referred to as a flail segment, or flail chest. A small amount of paradoxical motion with no physiologic side effects does not warrant specific treatment. However, the physiologic consequences of this paradoxical motion, including hypoxia, hypercarbia, and respiratory failure, are usually attributable to the effects of underlying pulmonary contusion.

Lung contusion (LC) is also an important independent risk factor for the development of ALI, ARDS, and VAP in affected patients.^{43–45} The clinical pathophysiology of LC includes hypoxemia, hypercarbia, increased work of breathing, and decreased lung volumes and compliance in association with ventilation/perfusion mismatching, intrapulmonary shunting, edema, and segmental lung damage.^{43,46,47} As many as 30% of patients with LC progress to ALI/ARDS,⁴³ and more precise delineation of factors responsible for this is a subject of intense interest. One of the vexing clinical aspects of blunt trauma-induced LC is that there is often an unclear correlation between the volume of affected lung tissue and the severity and duration of hypoxemia,⁴³ indicating that cellular and subcellular injury and inflammation, as well as interactions with other insults occurring at or near the time of trauma, may be involved.

THORACOTOMY AND PULMONARY RESECTION

On the whole, patients experiencing pulmonary problems after thoracic operations are managed in much the same way as those with pulmonary insufficiency from other causes. Special attention should, however, be given to patients who have undergone resection of part or all of a lung as treatment for infection, cancer, congenital abnormalities, or, rarely, trauma. If the remaining lung is normal, removal of

lung tissue does not cause a major physiologic deficit. Nevertheless, pulmonary resection does give rise to certain unique concerns. If pleural space infection, leakage from the closed bronchus, or pulmonary failure occurs after pulmonary resection, challenging ventilatory problems can ensue.

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7 MECHANICAL VENTILATION

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This chapter is designed to enable the reader to manage the fundamentals of mechanical ventilation in both the emergent and the nonemergent setting. The chapter is constructed to provide a functional understanding of basic pulmonary physiology as a prerequisite knowledge base for grasping and manipulating the concepts central to basic, traditional, cyclical ventilation that is regularly employed in the air or ground ambulance, emergency department (ED), operating room (OR), and intensive care unit (ICU). Further conceptual and application additions allow the reader to explore advanced ventilation modes and techniques that are used in the ICU. Each segment is intended to build on the preceding one and therefore establishes a functional unit with regard to mechanical ventilation, whether it is provided in an invasive or a noninvasive fashion. The chapter concludes with examples of different approaches to ventilation and a section on special considerations in challenging circumstances.

Physiology

The two primary functions of the respiratory system are ventilation (removal of carbon dioxide) and oxygenation (uptake of oxygen). Although physiologically interrelated, ventilation and oxygenation are often considered distinct processes when discussing mechanical ventilation. To accomplish both functions, the respiratory system has to deliver gas from outside the body into the alveoli, where oxygen and carbon dioxide then diffuse in opposite directions across the alveolar-capillary membrane. The gas must then be exhaled from the alveoli back to the atmosphere.

The volume of air that moves in and out of a patient's lung per minute is termed minute ventilation ($\dot{V}_E$). It is the product of tidal volume (V_T) and the respiratory rate (f). The tidal volume in turn is the sum of dead space ventilation (V_D) and alveolar ventilation (V_A). Normal minute ventilation is approximately 5 to 8 L per minute and is controlled by the brainstem, primarily in response to medullary pH and the arterial partial pressure of CO_2 (PaCO_2). Dead space ventilation represents approximately 20 to 30% of the resting tidal volume. It is composed of anatomic dead space ventilation (conducting, non-gas-exchanging airways) and physiologic dead space ventilation (nonperfused alveoli). The physiologic dead space ventilation increases with increasing severity of pulmonary disease or lung injury.

The amount of CO_2 excreted is directly proportional to the alveolar ventilation and inversely proportional to the partial pressure of CO_2 in the alveoli. Oxygenation, on the other hand, is more dependent on the appropriate matching of alveolar ventilation and capillary blood flow ($\dot{V}/\dot{Q}$). Dead space ventilation represents excess ventilation relative to blood flow ($\dot{V}/\dot{Q} > 1$). Conversely, if the blood flow is

greater than ventilation ($\dot{V}/\dot{Q} < 1$), an intrapulmonary shunt occurs. In a true shunt ($\dot{V}/\dot{Q} = 0$), no gas exchange occurs in the nonventilated alveoli, which is equivalent to an anatomic right to left heart shunt. In intermediate situations, the excess blood flow does not fully participate in gas exchange, resulting in pulmonary venous blood that is not fully equilibrated with the alveolar gas (venous admixture). The shunt fraction and the efficiency of oxygen exchange can be estimated by a simple bedside assessment of the arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FIO_2) (P/F) ratio. Although not equally sensitive across all ranges of FIO_2 , the P/F ratio is part of the definition of acute lung injury (ALI) (P/F < 300) and acute respiratory distress syndrome (ARDS) (P/F < 200).

SPONTANEOUS NEGATIVE PRESSURE RESPIRATION

In spontaneous breathing, minute ventilation is generated by a "ventilator pump" consisting of the chest wall, the respiratory muscles, and the pleural space. During inhalation, expansion of the chest wall by the respiratory muscles causes an increase in alveoli volume and thus a decrease in alveolar pressure. The relation between the change in volume and the change in pressure is a function of lung compliance:

$$\text{Compliance} \approx \Delta V / \Delta P$$

Spontaneous breathing is referred to as negative pressure ventilation because during inspiration, the alveoli pressure drops below atmospheric pressure and establishes a transpulmonary pressure gradient. The decrease in pressure creates a pressure gradient from the upper airway to the alveoli. Gas, similar to fluid, flows from higher to lower pressure. Once the pressure difference is high enough to overcome airway resistance, gas flows into the alveoli until the alveolar pressure equalizes with the atmospheric pressure. During exhalation, the respiratory muscles relax and the elastic recoil of the chest wall and lung parenchyma decreases the alveoli volume, thus increasing the alveolar pressure. Gas then flows out of the lungs until the alveolar pressure again equalizes with the atmospheric pressure, unless active exhalation forces out additional gas.

The changes in intrathoracic pressure during the respiratory cycle also affect cardiac performance. During spontaneous inspiration, intrathoracic pressure and thus right atrial pressure decrease and the intra-abdominal pressure increases secondary to diaphragmatic descent. Both pressure changes increase venous return to the heart by increasing the pressure gradient between the periphery and the right atrium.

POSITIVE PRESSURE VENTILATION

In contrast to spontaneous ventilation, nearly all current mechanical ventilators generate airflow by increasing the proximal airway pressure above the alveolar pressure. Compared with spontaneous breathing, the intrathoracic

Financial disclosure information is located at the end of this chapter before the references.

pressure during mechanical inhalation is positive (instead of negative) and therefore has a different effect on cardiac performance.

Positive pressure ventilation lowers left ventricular afterload and augments left ventricular ejection fraction. This is, however, countered by an overall decrease in venous return because of an increase in thoracic pressure. Positive pressure ventilation has two opposing effects on venous return. The positive intrathoracic pressure increases the right atrial pressure and thus decreases the pressure gradient between the periphery and the heart. However, it also increases the intra-abdominal pressure, which partially counterbalances the decrease in the pressure gradient. The combined effect on cardiac performance is partly dependent on the patient's volume status. The decrease in venous return is especially pronounced in hypovolemic states, where initiation of positive pressure ventilation can lead to cardiovascular collapse.

PRESSURE-VOLUME RELATION

In both negative and positive pressure ventilation, the relation between the change in transpulmonary pressure and the resultant change in lung volume is described by the pulmonary compliance (lung and chest wall combined). Compliance is not a static constant; it varies with lung volume and with inspiration versus expiration. Figure 1 shows a static volume-pressure curve, which typically has a sigmoidal shape.

At the beginning of inspiration, initial increases in pressure result in small changes in lung volume (low-compliance part of the curve) until the lower inflection point (LIP) is reached. Above this point, which is commonly interpreted as the pressure required to recruit collapsed alveoli, the pulmonary compliance increases abruptly until it again levels off at the upper inflection point (UIP) as total lung capacity is reached. Various pathologic states affect pulmonary compliance. Emphysema commonly increases lung compliance, whereas fibrosis, pulmonary edema, ALI, ARDS, and pneumonia decrease it.

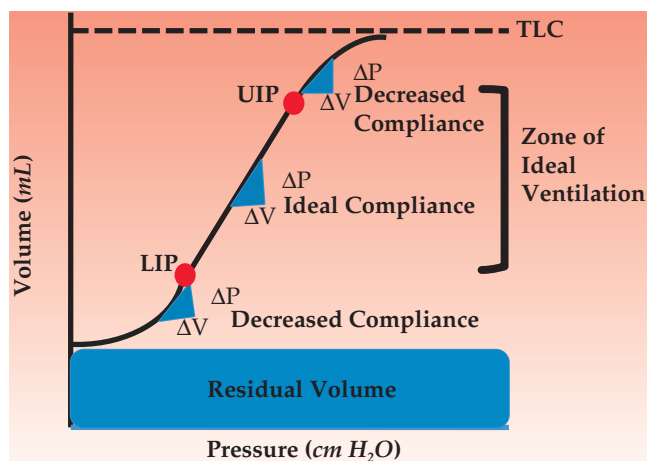


Figure 1 Static pressure-volume curve which demonstrates the relationship between the change in transpulmonary pressure (ΔP) and resultant change in lung volume (ΔV). TLC = total lung capacity; UIP = upper inflection point.

A true static pressure curve can be measured only when there is no airflow and pressures have equilibrated—a condition difficult to achieve in a patient secondary to the need for respiration. Most measurements are done under “quasistatic” conditions using a supersyringe method, the constant flow method, or the multiple-occlusion method.¹ In most clinical practice, static pressure curves are not routinely measured. A dynamic pressure-volume loop, easily obtainable on most ventilators, can be used to estimate LIP and UIP [see Figure 2]. Ventilation above the UIP can lead to overdistention, which will cause a birdlike beak shape to the pressure-volume loop [see Figure 2b].

INDICATIONS FOR MECHANICAL VENTILATION

Indications for mechanical ventilation can be broadly divided into two categories: airway compromise and respiratory failure. There are no absolute contraindications for initiating mechanical ventilation, and it should not be considered a last resort option. A planned, controlled intubation is much safer than an emergent procedure in a moribund patient. Airway instability can occur following injury, burns, or obstruction (internal or external). The need for a secure definitive airway may also arise from depressed mental status secondary to excessive sedation, incompletely reversed anesthesia, traumatic brain injury, and intoxication, as well as part of preparation for procedures or transport away from critical care areas.

Respiratory failure has a myriad of causes, both primary and secondary, and can result in failure of ventilation, oxygenation, or both. Patients may present with hypoxemia, hypercarbia, or increased work of breathing (WOB). Common causes of primary respiratory failure in surgical patients include ALI/ARDS, pneumonia, pulmonary edema, and aspiration. Secondary respiratory failure can occur from increased oxygen demand from increased metabolism seen in many inflammatory processes, such as septic shock or severe pancreatitis, as well as from decreased oxygen delivery during a variety of shock states. Inflammatory processes may also cause indirect ALI.

ACUTE LUNG INJURY

The pathophysiology of respiratory failure is in part dependent on the inciting etiology. In surgical patients, respiratory failure often occurs secondary to ALI/ARDS. In early stages of ALI, the alveoli demonstrate diffuse damage to the alveolar-capillary membrane, flooding with proteinaceous fluid, influx of neutrophils, formation of microthrombi, and deposition of hyaline membranes.² The mechanisms of the capillary endothelial and alveolar epithelium injury are not well known but are likely multifactorial and may vary depending on the inciting event. Mechanical ventilators can also initiate or exacerbate ALI, creating ventilator-induced lung injury (VILI). Ventilation even with “normal” tidal volumes can lead to alveolar overdistention in an injured lung secondary to the unequal and disproportionate distribution of gas flow into uninjured segments. The cyclical opening and closing of alveoli, where one alveolus is open and the other is partly open, can also cause lung injury along the common wall and is known as “intra-tidal shear.” The resultant changes in pulmonary

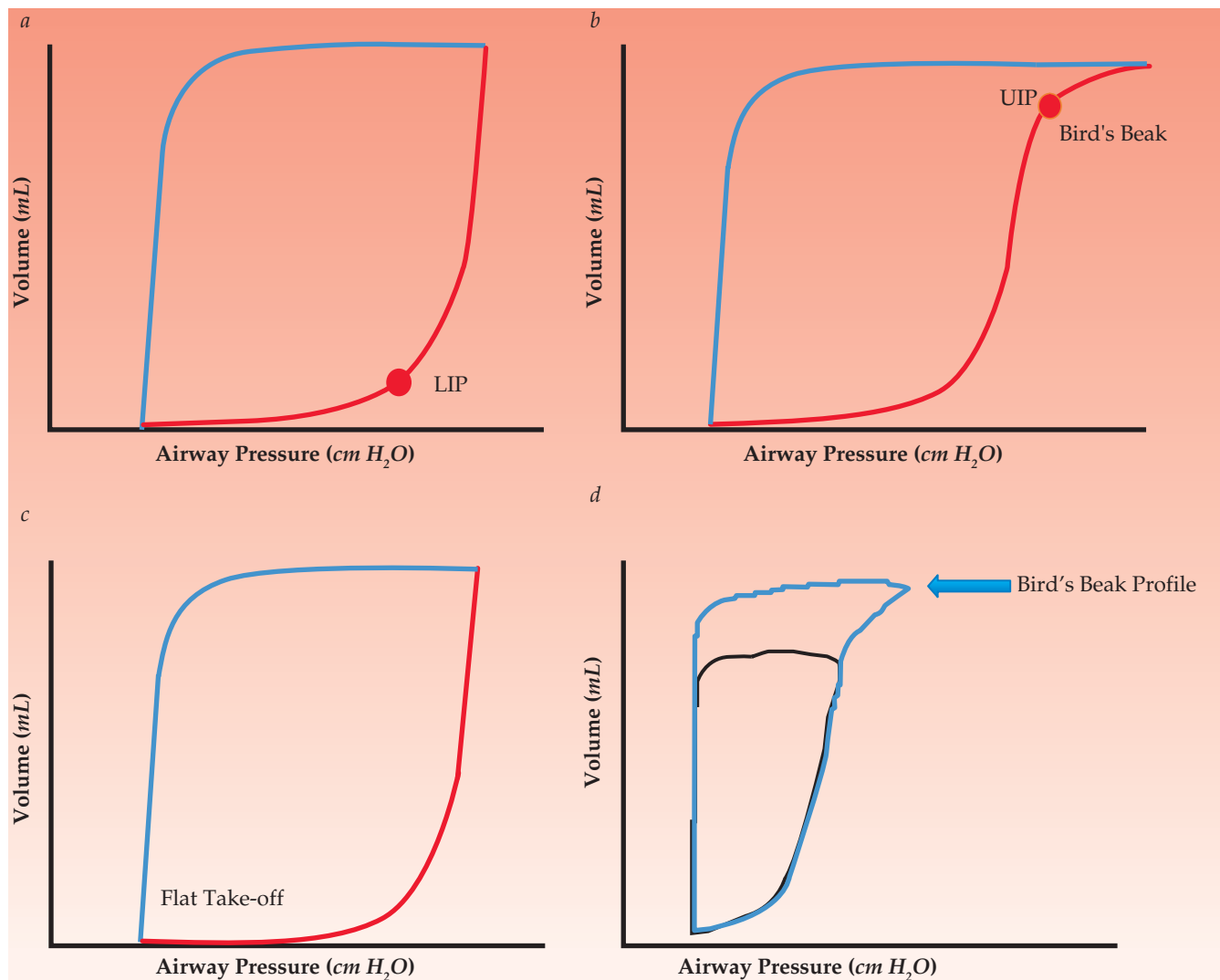


Figure 2 Dynamic pressure-volume curves, obtainable on most ventilators, can be used to estimate lower inflection point (LIP) and upper inflection point (UIP). (a) Normal (blue line = expiration; red line = inspiration). (b) Alveolar over-distension (blue line = expiration; red line = inspiration). (c) Under-recruitment (blue line = expiration; red line = inspiration). (d) Normal (black line) and over-distended (blue line) ventilation compared.

physiology include hypoxemia, hypercarbia, decreased lung compliance, and increased airway resistance.

Conventional Ventilation

ANATOMY OF A VENTILATOR

The first ventilator, the iron lung, was developed in 1928 and extensively used in the 1940s during the polio epidemics.³ The patient, except for the head and neck, was placed inside the machine, which was essentially a large cylinder with a rubber seal at the patient's neck. The machine would then generate a vacuum inside the tank and expand the chest wall through negative pressure. In comparison, the current mechanical ventilators are nearly all positive pressure ventilators; one negative pressure ventilator is available but is primarily used for pulmonary toilet in patients with cystic fibrosis. Although the design varies based on the model and manufacturer, certain features are common. The ventilator can be schematically segmented into a gas delivery engine, a monitoring system, and a user interface.⁴

Gas is delivered from a pressurized source and then blended to achieve the desired air/oxygen mixture. The gas is reduced to the desired pressure and then delivered by a gas- or electric-powered pneumatic system. The desired flow, volume, or pressure is achieved by a number of different control mechanisms depending on the selected ventilator mode. Gas exits the ventilator via the inspiratory port and travels through the Y connector tubing to the patient. Exhaled gas returns via the Y tubing back to the ventilator via the expiratory port. The machine typically monitors both the inspiratory and expiratory flows and pressures.

The goals of mechanical ventilation are to provide adequate oxygenation, CO₂ clearance, and management of the WOB. Commonly used quantitative targets include respiratory rate, Pao₂, oxygen saturation (Sao₂), and Paco₂. Qualitative targets include an assessment of the patient's comfort and WOB. Adequate Pao₂ and Sao₂ however, are not necessarily reflective of adequate tissue oxygenation. To achieve the goals of mechanical ventilation, the clinician must understand how each function of the mechanical ventilator works alone and in concert with the others.

MODES

Current mechanical ventilators use a wide array of positive pressure algorithms or modes to deliver the gas. The modes are traditionally classified based on the variable that terminates the inspiration cycle: pressure or volume. Each can be further subdivided by the method that initiates the inspiration cycle. Commonly, these include assist control ventilation (ACV), synchronized intermittent mechanical ventilation (SIMV), and pressure support ventilation (PSV).

In ACV, the machine delivers gas at a preset rate, referred to as mandatory or machine breaths. The patient can also initiate additional spontaneous breaths. Each spontaneous breath receives the same preset gas as the mandatory breath. The total minute ventilation is therefore the sum of the spontaneous and machine breaths multiplied by the delivered gas volume.

In comparison, in the SIMV mode, the machine will deliver a preset rate of machine breaths similar to the ACV mode, but any spontaneous breaths will receive a variable amount of gas flow and will do so without ventilator support. The delivered spontaneous tidal volume is a function of the patient's effort and inspiratory time. The spontaneous breaths may be augmented with pressure support (see below) to reduce the WOB and increase the delivered gas volume. In both ACV and SIMV, the machine and spontaneous breaths are coordinated or synchronized to prevent delivering machine breaths during a spontaneous breath or during exhalation.

TARGETS

Ventilator targets come in three forms: volume, pressure, or flow. The most commonly used target in the United States is volume and is known as volume-cycled ventilation (VCV). For this target, the ventilator delivers a preset volume of gas at a set rate. The airway pressure that subsequently develops is a function of the resistance and compliance of the respiratory system as well as the total volume, the maximal flow rate, and the waveform of gas delivery (see below). This target is most commonly combined with the ACV mode to create ACV-VCV. The next common target is pressure, and, indeed, the first US ventilator was a pressure ventilator, not a volume-cycled ventilator.

In pressure-cycled or pressure-controlled ventilation (PCV), the ventilator delivers gas to achieve a preset inspiratory pressure. The delivered volume is a function of the resistance and compliance of the respiratory system, as well as the fixed time for which the pressure is to be maintained (inspiratory time [T_i]), and varies with changes in lung mechanics. The resultant tidal volume will therefore vary on a breath-to-breath basis. A related target is PSV.

In PSV, there is no preset rate, and this mode cannot be used in patients without spontaneous respiration. All breaths are spontaneous and are assisted by the ventilator as it delivers gas to achieve a preset airway pressure that is above the set positive end-expiratory pressure (PEEP). Unlike PCV, which has a defined T_i (and therefore expiratory time [T_e]), PSV does not have predefined values. Instead, the gas flow terminates when the inspiratory gas flow needed to maintain airway pressure drops below 5 L/min or when the flow has declined to a preset percentage

of the maximal inspiratory flow rate at the start of inhalation. Newer devices allow the user to change the cutoff trigger to enhance patient-ventilator synchrony.

FLOW RATE

Flow rate ($\dot{Q}$) is the "speed" at which the gas is delivered and is reported in liters of gas/minute. The higher the rate, the faster the ventilator will reach the preset volume and therefore the shorter the T_i ; in PCV, the flow rate is adjusted to maintain the preset pressure and is therefore not fixed, as in VCV. A slower flow rate will increase T_i , which allows for better matching of regional time constant variations and thus results in enhanced recruitment of alveoli with long time constants. For a given respiratory rate (RR), an increase in T_i automatically results in a decrease in T_e . Usually, this is not a clinically relevant issue as VCV T_i are relatively short. However, at a high RR, where the T_e is already short, further decreases in T_e may lead to autoPEEP, CO_2 retention, increases in intrathoracic pressure, decreased venous return, and decreased cardiac performance noted as hypotension. AutoPEEP is readily detected on the flow-time trace as the failure of the trace to return to baseline during exhalation prior to the next breath being initiated [see Figure 3]. Common flow rates are from 40 to 75 L/min. The reader should note that higher flow rates are of necessity used during Acute Respiratory Distress Syndrome Network (ARDSNet) ventilation, where the tidal volumes are small and the RR is quite high. The higher the gas flow for a given tidal volume, the greater the peak airway pressure (Paw_{pk}) and the lower the mean airway pressure (Paw_{mean}). These observations are most readily understood within the context of the waveform of gas delivery.

WAVEFORM

Waveform describes how the ventilator manages gas flow rate as a function of time (flow-time curve). The two waveforms appropriate for adult ventilation are square and decelerating (ramp) [see Figure 4]; an accelerating waveform is appropriate only for neonates. In a square waveform, the maximal inspiratory flow rate is reached and then remains constant until the set volume of gas is delivered. The square waveform creates a shorter T_i , and a longer T_e but does so at the expense of a higher Paw_{pk} and a lower Paw_{mean} . This is important as T_i relates to recruitment and regional time constant matching and Paw_{mean} relates to oxygenation. A square waveform may be beneficial in patients with

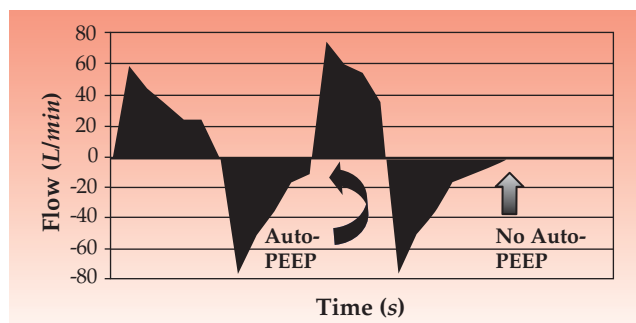
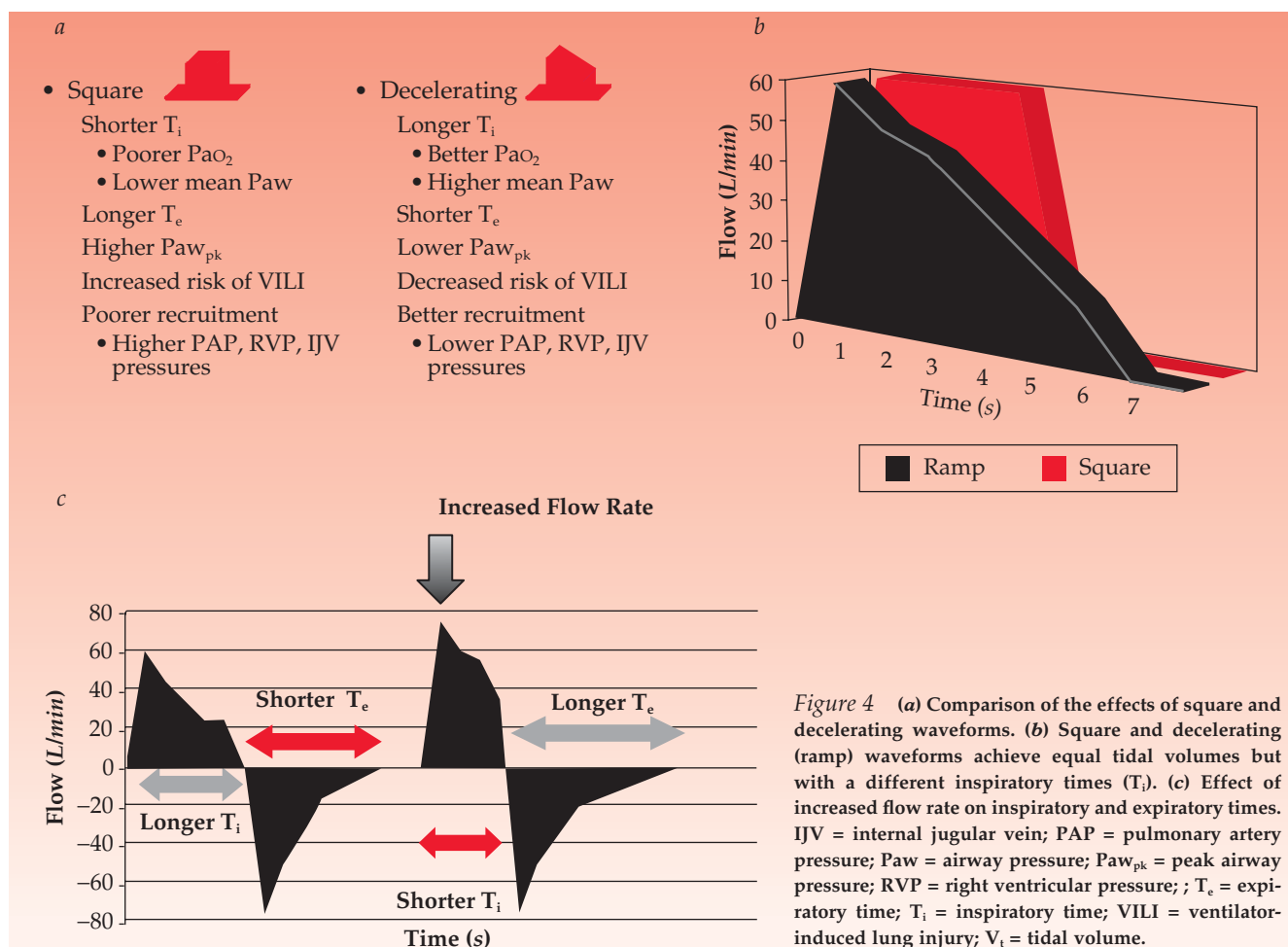


Figure 3 Detection of auto-positive end-expiratory pressure (autoPEEP) by examination of the flow-time trace.



restrictive airway disease who require longer expiration to maximize CO_2 clearance but may lead to inadequate oxygenation in patients with ALI.

In a decelerating or ramp waveform, once the maximal inspiratory flow is reached, the rate of gas delivery begins to decrease in a preprogrammed fashion. In comparison with the square waveform, more time is spent in inspiration for a similar volume of gas delivery, resulting in a longer T_i , increased Paw_{mean} , and decreased peak airway pressure. Accordingly, the use of a decelerating waveform supports alveolar recruitment and oxygenation. Conversely, the T_e is decreased in comparison with the square waveform for a given volume of gas delivery and at a similar respiratory rate.

The ventilator waveform determines the shape of the flow-time curve during inspiration. The expiratory curve is affected by the resistance and compliance of the respiratory system; therefore, inspection of the curve can assist in detecting pulmonary pathology. As discussed above, autoPEEP is detected if the flow does not return to baseline at the end of expiration. A decrease in the slope of the curve indicates increased expiratory resistance.

OXYGEN

One of the two primary functions of mechanical ventilation is to ensure adequate arterial oxygenation to support oxygen

delivery. Maintaining P_{aO_2} greater than 60 mm Hg will result in hemoglobin saturation greater than 90% in most patients. The simplest and quickest maneuver that can improve P_{aO_2} is to increase the percentage of inspired oxygen (F_{IO_2}) above that of room air (21%, or 0.21). This increases the oxygen diffusion gradient from the alveolus to the pulmonary capillary, resulting in an increase in P_{aO_2} unless an intrapulmonary shunt is present. However, breathing 100% oxygen can theoretically lead to nitrogen washout and alveolar collapse as no nonabsorbable gas remains to keep the alveolus open; this process is known as nitrogen absorption. In addition, prolonged high tension oxygen exposure ($F_{IO_2} > 0.6$) is thought to cause injury through formation of reactive oxygen species, including singlet oxygen, hypochlorous acid (HOCl), and hydrogen peroxide (H_2O_2).⁵ Despite such theoretical concerns, O_2 toxicity seems to be a laboratory phenomenon in nonhuman species or related to concomitant medication administration such as amiodarone or bleomycin in humans.⁶⁻⁸ Increasing the F_{IO_2} is most appropriately a temporary maneuver, whereas other adjustments are made to improve arterial oxygenation, and a search is made for the underlying cause and its remedy.

POSITIVE END-EXPIRATORY PRESSURE

Arterial oxygenation can also be improved by increasing the Paw_{mean} by increasing the PEEP. PEEP is the pressure in the airway at the end of exhalation, which prevents alveoli

collapse and thus helps maintain functional residual capacity (FRC). In normal patients, FRC is maintained by negative intrapleural pressure and the elastic recoil of the lungs. In mechanically ventilated patients, FRC is often reduced secondary to multiple etiologies. Patients in a supine position have as much as a 25% reduction in FRC from the pressure of the abdominal viscera on the diaphragm. FRC is also reduced by other external pressures on the diaphragm from ascites and/or abdominal distention as well as intrinsic lung processes such as alveolar collapse from secretions, pus, fluid, or blood. Decreases in FRC can also be related to intra-abdominal hypertension and an incipient abdominal compartment syndrome (ACS), either primary or secondary. Application of extrinsic PEEP can improve FRC by both preventing alveoli from collapsing and recruiting previously collapsed alveoli to participate in gas exchange. The improvement in FRC leads to improved $\dot{V}/\dot{Q}$ matching and oxygenation. On a mechanical level, increases in PEEP move the zero pressure point (ZPP) more proximally within the airway. Optimal PEEP is the PEEP that places the ZPP within a cartilaginous supported portion of the airway instead of a more distal, collapsible segment [see Figure 5].

Increasing PEEP, however, may have detrimental effects on cardiovascular performance, primarily through decreased venous return related to increased intrathoracic pressure. Although the P_{aO_2} may be improved, oxygen delivery may worsen secondary to a decrease in cardiac output. Optimal PEEP can be determined by several methods. Measurement of a static volume-pressure curve can determine the LIP, which corresponds to the pressure at which recruitable alveoli open. PEEP should be set slightly above this point. However, in practice, measuring the static volume-pressure curve is cumbersome and is not regularly done as it requires the use of a square waveform in a neuromuscularly blocked patient. Another method is to increase PEEP until there is no longer an increase in P_{aO_2} . Unfortunately, this approach may cause alveolar overdistention, decreased pulmonary blood flow and CO_2 clearance, and decreased venous return and cardiac output. PEEP can also be increased until there is no further increase in oxygen delivery measured by a pulmonary artery catheter (PAC). Alternatively, PEEP may be incrementally increased and the change in the $P_{aw_{peak}}$ noted. If the $P_{aw_{peak}}$ remains elevated, then no further increase in PEEP is likely helpful. If, however, the $P_{aw_{peak}}$

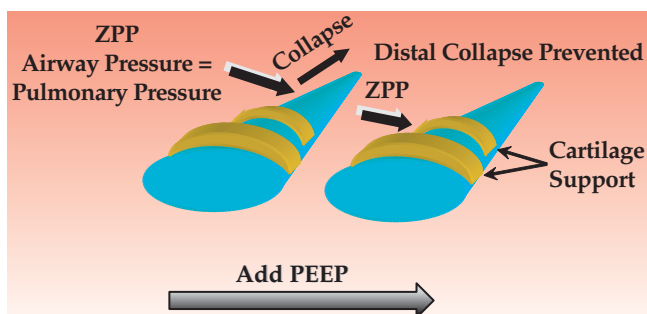


Figure 5 Positive end-expiratory pressure (PEEP) moves the zero pressure point (ZPP) proximal in the airway. Ideally, PEEP should be adjusted so that the ZPP occurs in the cartilage supported airway to prevent airway collapse.

falls after a short period of equilibration, this is taken as evidence of new alveolar recruitment and the potential for additional benefit from another increase in PEEP. In clinical practice, F_{iO_2} and PEEP are often increased simultaneously and adjusted based on empirical determinations of improvements in oxygenation and cardiovascular performance without the use of a PAC but instead may rely on other less invasive methods of cardiac output determination, including pulse pressure or stroke volume variation.

MINUTE VENTILATION

Minute ventilation is the amount of gas delivered to the patient over a minute. It is a product of the number of breaths and the delivered gas volume. Depending on the ventilator mode, minute ventilation can be adjusted by manipulating the number of machine breaths and the delivered tidal volume or the pressure change above PEEP. Normal minute ventilation is 7 to 10 L/min but varies with the patient's physiologic status, body mass, acid-base status, metabolic activity, and amount of dead space ventilation. An increase in minute ventilation will typically lead to improved CO_2 clearance. However, high minute ventilation may not allow enough time for alveolar emptying, leading to autoPEEP, CO_2 retention, and hypoxemia. Such a condition may be termed West Zone 1 ventilation, where alveolar pressure exceeds pulmonary arteriolar or venular pressures.

VENTILATOR PRESCRIPTION AND ARTERIAL BLOOD GASES

Mechanical ventilation is a therapy that may require constant adjustment. A common, although unsupported, practice is to obtain an arterial blood gas (ABG) 30 minutes after each adjustment; it has been demonstrated that 95% of CO_2 equilibration occurs within 7 minutes of a change in ventilator prescription on VCV.⁹ The ventilator prescription is then adjusted to optimize the patient's oxygenation and ventilation. However, ABGs are not necessary with every ventilator adjustment. Tissue oxygen delivery is mainly a product of cardiac output and oxygen saturation, with P_{aO_2} playing only a minor role. Oxygenation can therefore be followed with pulse oximetry. Similarly, trends in ventilation can be monitored using an end-tidal CO_2 monitor, which, however, should be periodically calibrated against the P_{aCO_2} .

Furthermore, an arterial sample need not be obtained for all pH- CO_2 analyses. For those without extreme pH variations (i.e., $7.2 < pH < 7.6$), pH and CO_2 may also be assessed using a venous blood gas (VBG). Given that the venous P_{CO_2} is generally 7 torr higher on the venous than the arterial side, the measured VBG P_{CO_2} should be decreased by 7 torr and the pH increased by 0.05 pH units ($\Delta pH = 0.08$ per 10 torr ΔP_{CO_2}). Thus, a VBG may "arterialize" quite readily. No such manipulation is possible for the P_{O_2} .

Moreover, the precise order of the ABG or VBG is directly related to the ventilator prescription. pH and P_{CO_2} are directly related to minute ventilation. Thus, the standard ventilator prescription should start with mode, rate, and then target (V_T for VCV or PC and T_i with $V_{T_{resultant}}$ for PCV). This provides the mandatory minute ventilation. The next ABG value is the P_{O_2} . Within the ventilator prescription, F_{iO_2} , PEEP, waveform (if appropriate), and flow rate (if appropriate) should follow as these all relate to oxygenation.

These values should be followed by the resultant Paw_{peak} , Paw_{mean} , RR, total minute ventilation (mandatory and spontaneous), and SaO_2 as a means of analyzing how the patient's lung is responding to the prescription. This should then be followed by an initial ABG for further assessment and documentation. By way of example, prescriptions for VCV or PCV might read as follows:

Assist control (AC) 10, V_T 700, F_{I,O_2} 0.4, +5;
 decelerating wave, $\dot{Q} = 40$ L/min
 Paw_{pk} 26, Paw_{mean} 10, RR 15, $\dot{V}_E$ 10.5 L/min; SaO_2 100%
 AC 10, pressure control (PC) 20, T_i 2.0 s;
 $VT_{resultant}$ 650, F_{I,O_2} 0.4, +5
 Paw_{pk} 25, Paw_{mean} 13, RR 15, $\dot{V}_E$ 9.75 L/min; SaO_2 100%

Advanced Ventilation

Advanced ventilation implies that either (1) the underpinning concepts or the application of the mode of ventilation is fundamentally different from traditional cyclical ventilation in some fashion or (2) the manner of gas delivery is sufficiently different from traditional methods to require a unique delivery system or unique monitoring consideration to be employed. In general, these advanced techniques are often used as “salvage” techniques when traditional methods fail to maintain oxygenation, CO_2 clearance, or, most commonly, both. We suggest that the reader consider some of these techniques for initial use in at-risk patient populations as a preventive measure instead of waiting for the need for rescue to be established. Furthermore, it is also appropriate for outlying facilities to occasionally refer patients to a tertiary care center for advanced ventilation based on the ability of the practitioner or the institution to support advanced ventilation.

AIRWAY PRESSURE RELEASE VENTILATION

In the setting of ALI, constant pressure and variable flow-based delivery is acknowledged as the optimal method of pulmonary recruitment. However, when the pressure is high and oxygenation is optimized, ventilation is compromised as it is difficult to exhale against a substantial pressure gradient [see Figure 6]. However, if the high pressure is released for a short period of time, ventilation is improved and respiratory acidosis is avoided. This short description aptly characterizes airway pressure release ventilation (APRV), where ventilation (CO_2 clearance) occurs during periods of pressure release [see Figure 7]. As a result, APRV is a seemingly counterintuitive mode that employs a high level of continuous positive airway pressure (CPAP) (P_{high}) that is maintained for a long period of time (T_{high}) coupled with a short period (T_{low}) during which the pressure is released (P_{low}). The prolonged period of high pressure facilitates oxygenation and pulmonary recruitment. Recruitment is maximized by a long period of CPAP as gas flow is present long enough to match widely disparate regional time constants and admit gas to alveoli with long time constants. The anticipated benefit from this significant recruitment is abrogation of hypoxic pulmonary vasoconstriction and an increase in right ventricular ejection fraction (RVEF) related to decreased mean pulmonary artery pressure.^{10,11} The increased RVEF leads to decreased right-sided pressures

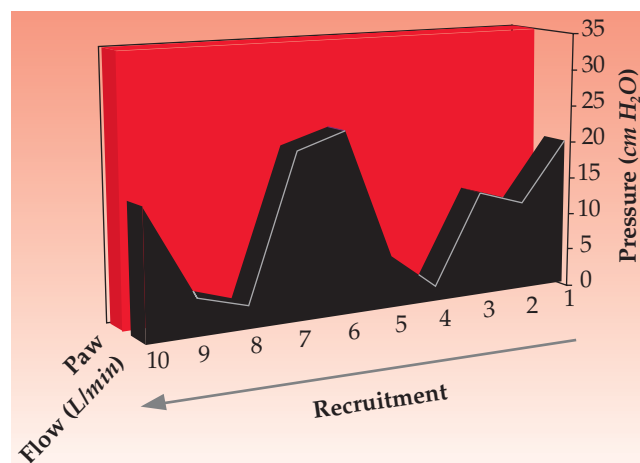


Figure 6 Constant pressure, variable gas flow can improve pulmonary recruitment. Paw = airway pressure.

and enhanced venous return and, thus, increased cardiac output.¹⁰⁻¹²

Understanding that physiology allows the physician to manipulate the ventilator settings to achieve maximal effect.^{13,14} Unlike traditional cyclical ventilation, APRV is best characterized by phase cycles instead of respiratory rates and inspiratory and expiratory times. A phase cycle is the time spent at the high pressure plus the time allowed for the release phase [see Figure 7]. Thus, one may calculate the number of phase cycles per minute. However, unlike cyclic ventilation, where inspiration and exhalation are sharply segregated, patients on ARPV may breathe within each breath, regardless of phase (high or low pressure), using a floating valve system. In fact, the spontaneous breathing allowed on ARPV is critical to its success.

Both animal and human data show that the readily demonstrated benefits of ARPV are decreased when spontaneous breathing is suppressed.^{15,16} Importantly, improvements in renal blood flow and the glomerular filtration rate are identifiable when using APRV instead of traditional modes of ventilation, and those improvements are tied to spontaneous breathing.¹⁷

HIGH-FREQUENCY OSCILLATION VENTILATION

Conventional ventilation is often limited by high airway pressures, leading some to use low tidal volume ventilation to ventilate only the available lung and avoid disproportionate gas distribution to compliant regions as one way to avoid VILI. When that strategy fails, and hypoxemia becomes unmanageable, one alternative besides APRV is high-frequency oscillation ventilation (HFOV). HFOV is a unique mode of positive pressure ventilation. The premise behind this mode is straightforward: increased Paw_{mean} enables oxygenation. What makes the mode unique is how HFOV achieves and sustains the increase. Recall that flow along the periphery of airways and at branch points is turbulent, whereas central column gas flow is laminar. Airway constriction, obstruction, and partial collapse further increase turbulent flow. HFOV delivers rather small volumes of gas at quite high frequency at a particular Paw_{mean} . A schematic of a HFOV system is presented in Figure 8. This gas delivery in essence

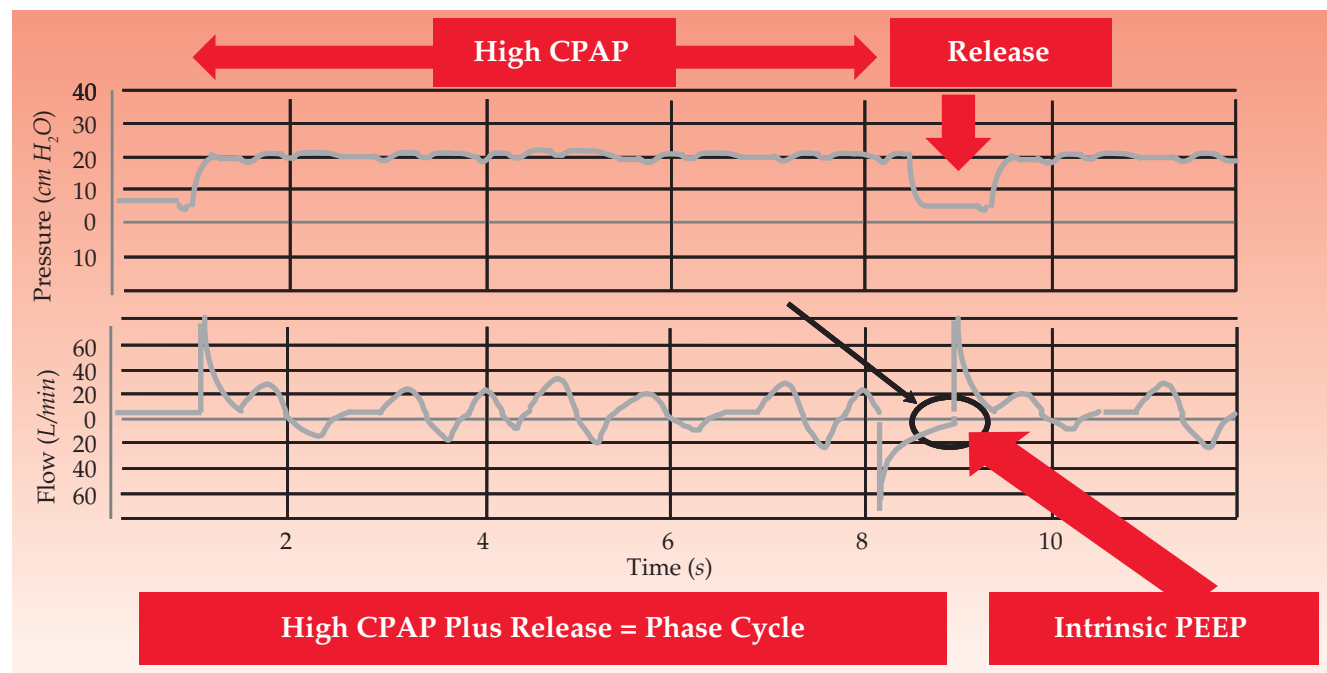


Figure 7 Airway pressure release ventilation (APRV). An APRV phase cycle consists of a time (T_{high}) of a continuous positive airway pressure (CPAP) (P_{high}) and a shorter release time (T_{low}) at a lower pressure (P_{low}). PEEP = positive end-expiratory pressure.

establishes a standing column of gas in the airways that creates a high $P_{\text{aw, mean}}$. It also provides gas flow in a fairly continuous fashion so as to meet widely disparate regional time constant variations. Gas transport occurs using different

mechanisms at different portions of the airway [see Figure 9]. Although HFOV excels at reversing hypoxemia because of the ability to achieve high $P_{\text{aw, mean}}$, it is poor at maintaining CO₂ clearance. Moreover, the adjustments to the driving pressure and the frequency (measured in hertz or cycles per second) are often counterintuitive. Therefore, a number of algorithms will aid the practitioner in adjusting HFOV settings.¹⁸ The user should be aware that heavy sedation and/or neuromuscular blockade are commonly required as HFOV is quite uncomfortable and the patient's respiratory efforts may be counterproductive in maintaining $P_{\text{aw, mean}}$. Transport out of the ICU for diagnostic testing or therapeutic undertakings is prohibitive because there is no portable HFOV mechanical ventilator. Several trials have demonstrated the salvage ability of HFOV for those who fail traditional ventilation and have unremitting hypoxemia, especially in the pediatric population.^{18–20} Anecdotal reports support its use in the management of bronchopleural fistula (BPF) or parenchymal-pleural (PPF), or as a component of simultaneous independent lung ventilation (SILV).^{21,22} However, no report proffers this mode as an initial mode or as one to be used for all patients with ALI/ARDS. The Oscillation for ARDS Treated Early (OSCILLATE) trial is a multicenter, randomized, controlled trial comparing HFOV with best current conventional ventilation to reduce ARDS mortality, initiated by the Canadian Critical Care Trials Group.

SIMULTANEOUS INDEPENDENT LUNG VENTILATION

SILV describes the process of independently ventilating the right and the left lung. It was once believed that one had to synchronize inspiration and exhalation for fear of compromising cardiac performance. This concept is outdated and false. We now know that each side may be ventilated

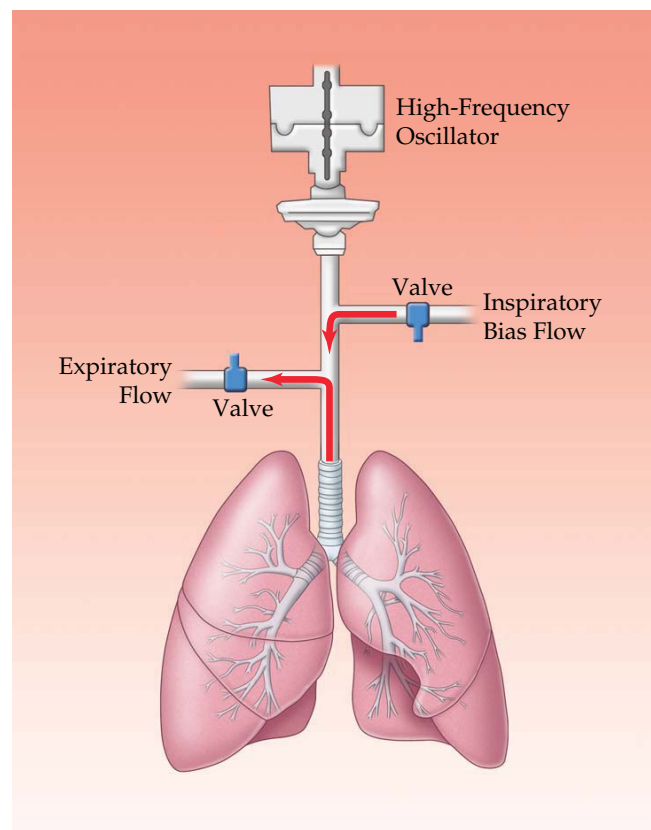


Figure 8 Schematic representation of a high-frequency oscillator.

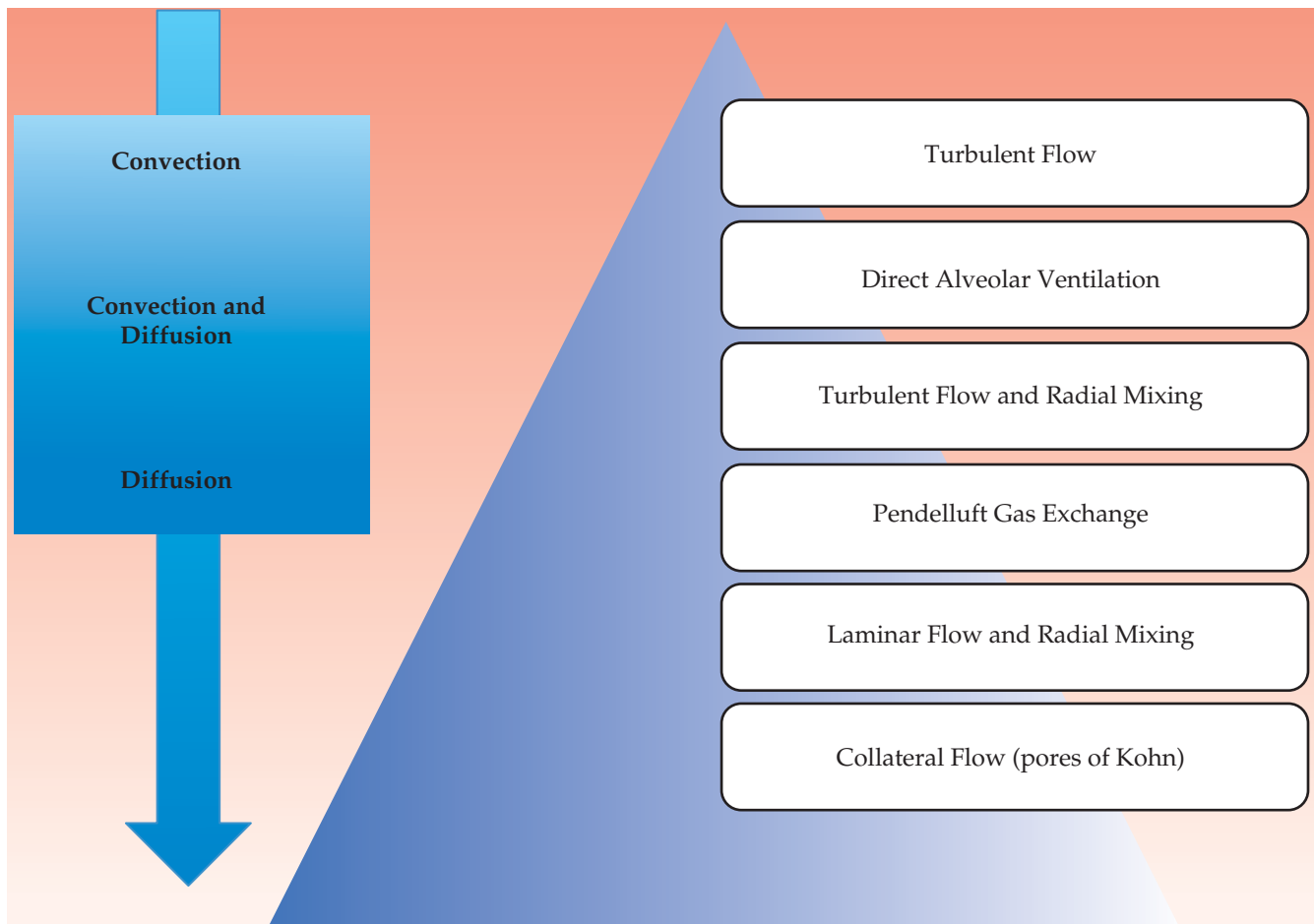


Figure 9 Mechanisms of gas exchange in high-frequency oscillation ventilation.

using different modes and at different rates.²³ SILV requires either a double-lumen oral endotracheal tube or, for those with a tracheostomy or a mediastinal stoma, separate bronchus cannulation using an internally ringed and nonkinking tube [see Figure 10]. Pairings may include any combination



Figure 10 Simultaneous independent lung ventilation using separate bronchus cannulation via a tracheostomy.

of VCV, PCV, APRV, or HFOV depending on the individual patient's needs, the experience and comfort level of the practitioner, and the capabilities of the institution. SILV may be considered for unilateral BPF/PPF, severe unilateral direct lung injury, management of a patient after single-lung transplantation (old and new lungs may require differential ventilation), and other less common conditions.²¹ This management technique is appropriately only rarely used. The oral endotracheal double-lumen tube is difficult to maintain in the correct position; suctioning is quite difficult as the lumina are small and readily plugged, and the patient often requires heavy sedation or neuromuscular blockade to ensure that the tube does not become dislodged. Separately cannulated bronchial orifices are even more problematic with regard to maintenance. As a result, routine nursing care is impeded and pressure ulceration is much more likely to occur from reduced turning and repositioning.

PROPORTIONAL ASSIST VENTILATION

Proportional assist ventilation (PAV) is a synchronized partial positive pressure ventilatory support mode that generates, on a breath-to-breath basis, inspiratory positive airway pressure proportional to the patient's inspiratory effort.²⁴ This unique method of unloading the WOB and providing inspiratory support is accomplished by amplifying the inspiratory airway pressure proportional to the patient's

spontaneous and instantaneous inspiratory flow rate and volume; gas flow is regulated by a proportional solenoid valve linked to a high-speed microprocessor. Although experience has been limited with this method of ventilation, its theoretical attractiveness as a noninvasive mode will likely translate into more widespread use as the mode becomes increasingly installed on modern ventilator systems. It achieves the desired end point of transitioning to spontaneous ventilation as quickly as possible to facilitate ventilator weaning. Noninvasive PAV has been used as an aid in exercise tolerance for patients with severe chronic obstructive pulmonary disease (COPD).²⁵

PRESSURE-REGULATED VOLUME CONTROL/GUARANTEE

ALI/ARDS is characterized in part by decreased compliance. As lungs heal and inflammation is reduced, compliance increases. Thus, for a given inspiratory pressure, the resultant volume of gas accepted by the lung will increase as compliance increases; conversely, decreasing compliance will yield a smaller volume. Pressure-regulated volume control/guarantee (PRVC/G) takes advantage of these relations. It also demonstrates that VCV is the most common form of mechanical ventilation used in the United States and other parts of the world.

This mode combines the best of both worlds in that the user can set a pressure limit but also identify a target volume to be delivered. The ventilator will adjust both pressure and flow rate (and therefore T_i) using a decelerating waveform to achieve the target tidal volume using the lowest possible pressure but not exceeding the preset pressure limit. Given that high peak and plateau pressures are associated with VILI and biotrauma, establishing a pressure limit helps reduce the likelihood of VILI. As the patient's compliance improves, the pressure required to generate the desired tidal volume and the length of time spent in positive pressure gas delivery both decrease [see Figure 11]. In this fashion,

PRVC/G is a “self-weaning” mode. Not all ventilators have this capability, and the software required has been developed and promoted by Siemens. Like a number of other modes (APRV and HFOV), PRVC/G seems to have been adopted in a niche fashion. This mode may have its optimal use in the neonate, whose lungs are more sensitive to gas maldistribution and volutrauma than those of an adult.²⁶

INVERSE-RATIO VENTILATION

The normal ratio of inspiratory time to expiratory time (I/E) is 1:3 (i.e., for each second of inspiration, 3 seconds are spent in expiration). A more prolonged inspiratory time (2:1, 3:1, 4:1) is used in inverse-ratio ventilation (IRV), either with pressure control or volume control. The prolonged inspiratory time has two effects on oxygenation: it improves gas distribution to lung regions with longer time constants and increases the Paw_{mean} , thus improving alveolar recruitment and oxygenation. Despite the theoretical benefits, there are no data to support the use of IRV in patients with ALI/ARDS.^{27,28} In addition, IRV has several distinctive disadvantages. The shortened expiratory time can potentially lead to incomplete expiration and autoPEEP, especially in patients with COPD. It is also an uncomfortable mode of ventilation for the patient and commonly requires heavy sedation and/or neuromuscular blockade.

Adjuncts

PRONE POSITIONING

Based on studies that have demonstrated improved oxygenation in animals with ALI, prone positioning has been used as an adjunct therapy in patients with severe ALI/ARDS and hypoxemia. Even healthy, supine patients often demonstrate dependent (dorsal) atelectasis from a multifactorial etiology. The weight of the heart and pressure from the abdominal contents compress the lung bases. In

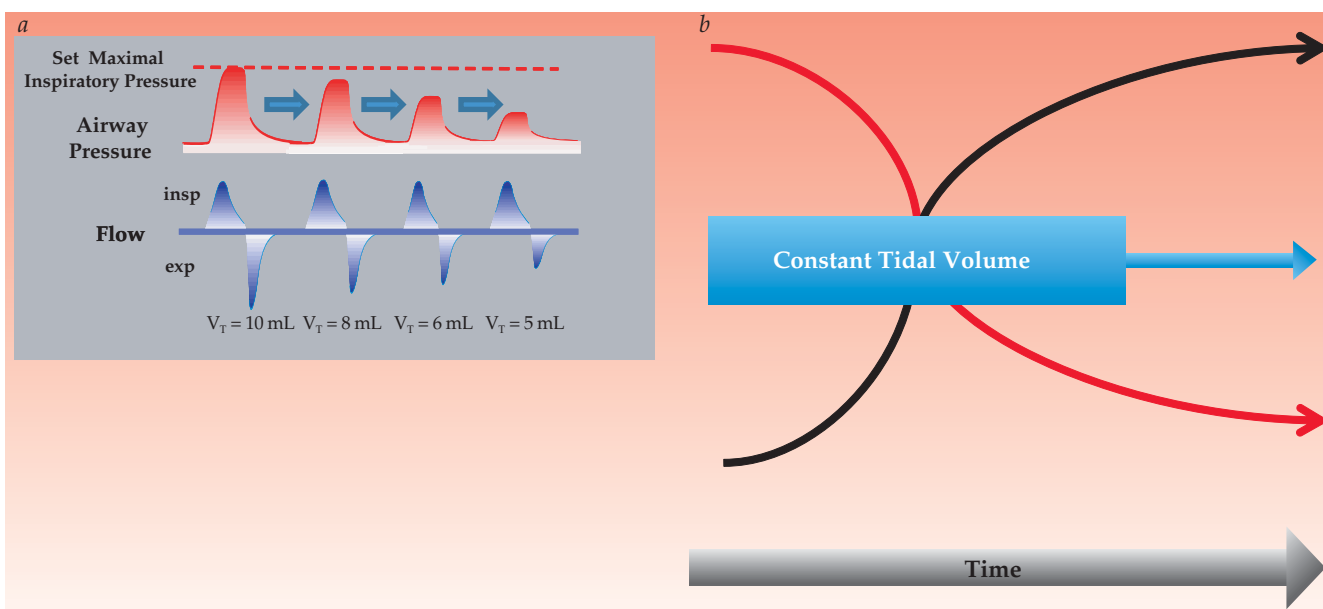


Figure 11 Pressure-regulated volume control / guarantee ventilation. (a) Peak inspiratory pressure (PIP) is adjusted (to a set maximum) by the ventilator based on the previous expired tidal volume to deliver the set tidal volume (V_T). (b) As lung compliance (black line) improves, the ventilator adjusts the PIP (red line) to keep the V_T constant. exp = expiration; insp = inspiration.

addition, there is a gravity-based increase in pleural pressure from the ventral to the dorsal lung that compresses the dependent alveoli. The combined result is a decrease in the FRC in the supine position.

In patients with direct or indirect lung injury, the ventilation of these dependent atelectatic areas is greatly reduced. Gas either does not enter these alveoli or does so only at high airway pressures that may cause hyperinflation of the nondependent alveoli and contribute to ALI or may require long inspiratory times to match regional time constant variations. Partially because of gravitational effects, pulmonary blood flow is also higher to the dependent areas. The increased perfusion of the nonaerated lung leads to increased $\dot{V}/\dot{Q}$ mismatch and hypoxemia.

Prone positioning reverses the gravitational pleural pressure gradient and alleviates the compression of the dorsal lung by the heart and abdominal contents. It improves aeration of the dorsal lung, and although the ventral lung is now less ventilated, the combined effect is usually less severe. Although variable depending on the patient's chest geometry, the volume of lung behind the heart is usually greater in the supine than in the prone position. Chest wall compliance is more uniform in a prone position, and the tidal volume and perfusion of the lung are more evenly distributed.²⁹ It appears that patients with an ovoid chest benefit less than those with a triangular chest [see Figure 12]. This observation is related to the fact that patients with ovoid chest geometry have relatively equal pulmonary volumes in the ventral and dorsal halves. Those with triangular chests have a greater volume in the dorsal half, thus providing recruitment, oxygenation, and often CO₂ clearance benefits when the dorsal half becomes nondependent.

Animal studies have demonstrated that prone positioning improves both $\dot{V}/\dot{Q}$ matching and oxygenation. In human studies, improved oxygenation was noted in about 70% of patients with ALI/ARDS. Improved oxygenation has, however, not translated to improved survival in several randomized, controlled trials.³⁰ Unfortunately, all the trials to date have had serious limitations, including being underpowered to detect small differences in outcome, nonstandardized mechanical ventilation protocols, use of low-“dose” prone positioning, and heterogeneous patient populations that included both mild and severe lung injury. In a recent trial, oxygenation improved in the prone position, but there was no difference in overall mortality at 28 days.³¹ However, in a subgroup of patients with severe hypoxemia, the relative risk of death was lower without reaching statistical significance.^{31,32}

Therefore, current evidence does not support prone positioning as a routine treatment for all patients with ALI/ARDS. It may be considered rescue therapy in patients with severe hypoxemia with limited treatment options. Further studies are needed to define the patient population that would benefit, the number of cycles, the duration of each cycle, and how long to continue prone positioning. The expanding use of open lung ventilation strategies such as APRV may also obviate the need for prone positioning in many patients.

Prone positioning should be approached with caution in facilities that do not have extensive experience as it can lead to adverse events, such as endotracheal tube (ETT)

obstruction, inadvertent extubation, death, premature removal of other care devices, and pressure ulcers. It should be noted that in facilities used to performing prone positioning, no increase in unintended device removal or untoward events has been reported.

NITRIC OXIDE

Nitric oxide (NO) is a naturally occurring colorless and odorless gas that is found in the body as endothelium-derived relaxing factor. It modulates vascular tone by decreasing calcium in smooth muscle cells via an NO-dependent increase in cyclic guanosine monophosphate. Inhaled nitric oxide (iNO) has been shown to be a selective pulmonary vasodilator in patients with pulmonary hypertension. It decreases pulmonary vascular resistance, pulmonary arterial pressure, and thus right ventricular afterload. iNO is rapidly inactivated by hemoglobin and therefore acts locally in ventilated lung regions, with little diffusion into surrounding tissue or systemic effects. iNO is administered mainly to ventilated patients but can also be given via a face mask or nasal cannula. A potential adverse effect of iNO is methemoglobinemia; levels should therefore be regularly monitored.

Theoretically, iNO should improve $\dot{V}/\dot{Q}$ matching in ARDS patients by improving blood flow only to ventilated areas. Low-dose iNO has been shown to improve oxygenation in the short term but in several trials has had no substantial impact on the duration of ventilatory support or patient outcome.^{33,34} Current data therefore do not support routine use, but iNO may be considered as a bridge therapy while other interventions are implemented to correct the underlying cause of hypoxemia.

HELIOX

Heliox is a mixture of helium and oxygen gas that has been used as a bridge therapy for upper and lower airway obstructive disease. Helium is a colorless, odorless, inert gas with a low atomic weight. Compared with oxygen or oxygen-nitrogen mixture, heliox has a lower density and therefore has improved flow through constricted airways by modulating turbulent to laminar flow. Heliox is commonly available as a 70/30 (O₂/He) mixture, although other mixtures, including an 80/20 mixture, are available. As an inert gas, helium has no known adverse effects. It is, however, more expensive than regular oxygen mixtures, requires special equipment and training, and invalidates tidal volume measurements by ventilators that are calibrated for oxygen/nitrogen mixtures. Data on its use in both adult and pediatric patients are limited to case reports and small series. The available data do support the use of heliox as a temporary therapy for patients with increased WOB secondary to upper airway obstructive disease.³⁵ The data for lower airway diseases such as asthma or COPD are mixed, likely because the flow in the lower airways is already laminar and the patient population characteristics are rather heterogeneous. Improvements in the WOB generally occur rapidly or not at all. Heliox is not a therapeutic drug and therefore serves only as a temporizing measure, whereas other treatments targeting the underlying cause are implemented.

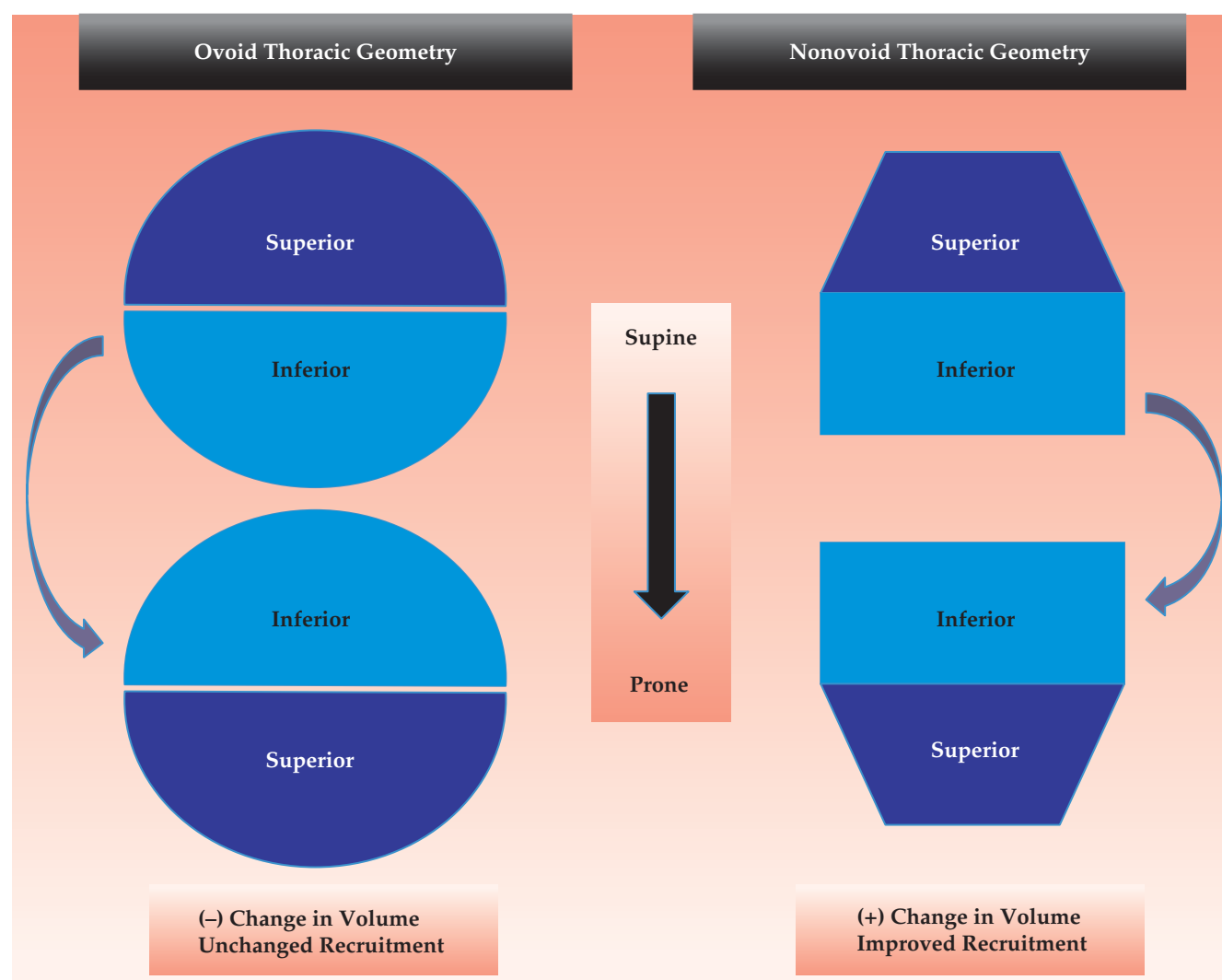


Figure 12 The effects of prone positioning are dependent on the patient's chest geometry. Patients with a triangular thoracic cage benefit more from prone positioning than patients with an ovoid thoracic cage.

RIB FRACTURE PLATING

Patients with multiple rib fractures and especially those with flail chest may present with respiratory distress or failure. In most centers, management is limited to pain control (intravenous, oral, local, or epidural analgesia), pulmonary toilet, and, when required, noninvasive and invasive mechanical ventilation. Selected centers have attempted rib fracture repair to improve both short- and long-term outcomes. The currently available literature, which is limited to case reports and small, randomized trials, suggests that patients with multiple rib fractures may benefit from operative repair. Operatively managed patients had fewer days on the ventilator, a lower incidence of pneumonia, and improved pulmonary function.^{36,37} A number of techniques have been described, but experience with each is limited, and indications for operation are not well established.³⁸ Further trials are necessary before rib fixation becomes a standard of care.

BRONCHOSCOPY

Mechanical ventilation bypasses or impairs the normal mechanism of secretion clearance. Accumulation of secretions can lead to atelectasis, pneumonia, $\dot{V}/\dot{Q}$ mismatching, hypoxemia, and elevated airway pressures. Conventional therapies such as endotracheal suctioning, chest physiotherapy, postural drainage, and recruitment maneuvers may not be sufficient to clear secretions and open collapsed segments. Therefore, more invasive techniques, such as therapeutic bronchoscopy, may be required. Flexible bronchoscopy can be performed at the bedside with mild sedation and topical lidocaine to blunt mucosal irritation and sympathetic discharge. Tachycardia, systemic hypertension, and bronchospasm are the most common complications, but cardiac dysrhythmia, pneumothorax, hemorrhage, and death have all been reported.

Therapeutic bronchoscopy has several potential applications in the mechanically ventilated patient. A microbiologic

specimen can be obtained via bronchoalveolar lavage or protected brush biopsy to help guide antibiotic therapy. Several studies have identified cost reductions when using invasive methods to diagnose pneumonia.^{39–42} Importantly, when there is no diagnosis of invasive infection, one may have confidence in the diagnosis of “no pneumonia,” discontinue antibiotics, and reduce the selection pressure for resistant pathogens. Bronchoscopy can also aid in secretion clearance and recruitment of collapsed units from mucus plugs. It can be used to confirm ETT position and diagnose tube malfunction. With prolonged intubation, biofilm deposition and desiccated secretions can narrow the lumen of an endotracheal or tracheostomy tube. This will manifest as increased resistance of the ventilator circuit and increased peak airway pressures. The bronchoscope will aid in the diagnosis and help guide therapy in this circumstance as well. Of course, fiberoptic intubation is also readily accomplished in skilled hands via flexible bronchoscopy, although other systems (i.e., Bullard) are also available. It is not yet clear what impact the seemingly widespread use of the GlideScope (Verathon Incorporated, Bothell, WA) will have on the need for fiberoptic bronchoscopy-directed intubation.

SEDATION, ANALGESIA, AND NEUROMUSCULAR BLOCKADE

Patients acutely requiring mechanical ventilation benefit from sedation and analgesia. This is optimally provided as a continuous infusion instead of intermittent boluses, consistent with the recommendations from the Society of Critical Care Medicine; a daily wake-up is included in this continuous regimen of sedation and analgesia. Commonly used agents for analgesia include morphine, fentanyl, and dilaudid. Common sedatives include midazolam, lorazepam, and diazepam and may be supplemented with typical antipsychotic medications, such as haloperidol. In many circumstances, especially traumatic brain injury, rapid onset and offset of a sedative are essential. In those circumstances, the drug of choice is the intravenous anesthetic propofol, which has no analgesic properties and must be combined with an analgesic to manage pain. Depth and adequacy of analgesia and sedation should be regularly assessed using established assessment scales such as the Richmond Agitation and Sedation Scale (RASS). Patients should undergo daily interruption of sedation, which has been shown to decrease the duration of mechanical ventilation.⁴³ As a caveat, noncompliance with the ventilator (i.e., patient-ventilator dyssynchrony) should not be solely attributed to inadequate sedation. The ventilator prescription should be reviewed and potentially adjusted for patient comfort and physiology.

The use of neuromuscular blockade in intensive care patients has dramatically decreased in the past decade. Its use has been associated with the recall phenomenon (chemical paralysis without adequate sedation), unrelieved pain (chemical paralysis renders pain assessment difficult), prolonged paralysis syndrome, and critical illness polyneuropathy. Neuromuscular blockade is currently useful to facilitate intubation, as a second-line agent for increased intracranial pressure management, but only rarely for the difficult to ventilate or oxygenate patient. Commonly used agents include pancuronium (untoward side effect is tachycardia), vecuronium (agent of choice for adults without

hepatic failure), and *cis*-atracurium (agent of choice in hepatic failure attributable to plasma degradation). All may be given via bolus or continuous infusion. When used by continuous infusion, the depth of paralysis should be monitored via a peripheral nerve monitor, usually applied over the ulnar nerve. Neuromuscular blockade is typically titrated to a goal of two twitches of a “train of four” as a means of trying to minimize the risk for prolonged neuromuscular blockade syndrome.

BETA AGONISTS

Patients on mechanical ventilation may develop bronchoconstriction without a prior history of reactive airway disease. Bronchospasm can be diagnosed based on physical examination with poor air movement or wheezing as well as increased (> 4 cm H₂O) peak to plateau gradient ($Paw_{peak} - Paw_{plat}$). Beta agonists (e.g., albuterol), which induce bronchial smooth muscle relaxation, are the most commonly used agents. Albuterol can be administered via a side port of the ventilator circuit using a metered-dose inhaler (cost-effective) or with an inline nebulizer. In general, long-acting beta-agonist preparations are used only as continuation therapy in those previously on such an agent prior to hospital admission. The data on continuing steroid use in combination with long-acting beta agonists are less clear in the acute setting, although there is clear benefit in the outpatient arena.

MAGNESIUM

Magnesium has been evaluated as an alternative and a complementary treatment option in patients with acute asthma exacerbation. Magnesium inhibits the release of calcium from the sarcoplasmic reticulum of smooth muscle and can result in bronchial smooth muscle relaxation. It is available as both an intravenous and a nebulized form. The available data on its efficacy are mixed. A meta-analysis of the available studies published in 2007 concluded that there is sufficient evidence that intravenous magnesium is associated with improvement in respiratory function in children.⁴⁴ The evidence in adults is weaker, but there may be some benefit. Although further trials are required, given the low risk of serious side effects from intravenous magnesium, it is often considered an adjunct in patients with acute asthma exacerbation and part of a regimen addressing an elevated peak-plateau gradient in the critically ill.

Approaches

PATIENT STATUS-GUIDED APPROACHES

Armed with the knowledge of how the ventilator works, as well as the different modes, targets, and adjuncts, it is appropriate to explore different working approaches to the patient with acute as well as chronic respiratory failure. The first major decision point in defining a ventilator strategy is based on the presence or absence of ALI/ARDS. Recall that ALI/ARDS represents a spectrum of illness that differs principally in severity and not causation much in the same way that sepsis, severe sepsis, and septic shock represent a spectrum of severity of illness. Also, note that the diagnosis of ALI/ARDS does not require a specific PEEP, ventilator

mode, or ventilator prescription (i.e., tidal volume, Q , waveform, T_i). As one transits from one ventilator strategy to another, it is entirely likely that a patient will fit the criteria for ARDS while on one mode, but within a few hours on another mode will no longer fit the definition. This likely indicates that the definitions are flawed and our understanding incomplete. Nonetheless, the existing definition represents a useful starting point from which to define a ventilator strategy.

PATIENTS WITHOUT LUNG INJURY

These patients may be successfully ventilated and oxygenated with virtually any strategy. Such patients include those who have incomplete reversal or washout of anesthetic agents and require a short period of mechanical ventilation in the postanesthesia care unit prior to liberation from mechanical ventilation. Similar patients may be found in the cardiothoracic intensive care unit after uncomplicated coronary artery bypass grafting as well. In general, these patients have near-normal or normal compliance and are commonly managed on ACV-VCV, SIMV-VCV, and PRVC/G as well as PSV. The diverse nature reflects local practice, and no mode has been definitively demonstrated to be superior to another. On occasion, these patients demonstrate a previously unidentified pneumonia, have a witnessed aspiration on induction or extubation, or have unanticipated hypotension or hemorrhage during their routine case, placing them at risk for ALI.

AT-RISK PATIENTS

The risks for ALI/ARDS include elements that cause direct as well as indirect lung injury and are too diverse to list within this chapter. However, certain common themes merit mention and include direct injury, pneumonia, shock of any etiology, massive plasma volume expansion, massive transfusion (especially fresh frozen plasma [FFP]), and hypotension and hypoperfusion followed by oxygenated reperfusion. In this patient population, it is unclear whether a particular mode confers a survival advantage by helping stave off the expected issues with derecruitment, atelectasis, and shunting that accompany burgeoning ALI/ARDS. Accordingly, many practitioners will engage in preemptive lung-protective ventilation based on risk alone or in response to particular parameters. These parameters may include a falling P_{aO_2}/F_{iO_2} ratio, rising $P_{aw_{peak}}$, increasing need for PEEP to maintain S_{aO_2} , or decreasing lung volumes on a portable chest x-ray as well as clinical events, such as the need for plasma volume expansion, vasopressors, severe sepsis, septic shock, or hemorrhagic shock. Thus, in the at-risk patient set, it is appropriate to obtain an ABG and a portable chest x-ray, calculate the P_{aO_2}/F_{iO_2} ratio, and evaluate the interaction of the ventilator prescription with the patient's lung as identified by $P_{aw_{peak}}$, $P_{aw_{mean}}$, the flow-time trace, and, for appropriate ventilator modalities, the dynamic pressure-volume loop.

Lung-protective strategies include ARDSNet, open lung ventilation using PCV, PRVC/G, and APRV. HFOV is not thought of as a primary ventilation modality, is typically reserved for salvage, and would be inappropriate for the at-risk patient population. Similarly, prone positioning is not generally appropriate for this population either as they

do not have an established lung injury that would benefit from prone positioning. The choice of strategy is user and institution dependent. However, the reader should be aware that the only modality that has thus far been demonstrated to confer a survival advantage is ARDSNet.⁴⁵ A note of caution is that the primary patient population in whom the benefit has been demonstrated is medical, not surgical. We commonly use APRV as a spontaneous breathing, open lung model approach to lung-protective ventilation but recognize that it is local and not a national standard of care. Regardless of management, many patients progress to ALI/ARDS.

PATIENTS WHO DEVELOP ALI/ARDS WHILE ON MECHANICAL VENTILATION

In this patient set, management depends on the ventilator mode on which the patient develops their lung injury. In the United States, a common progression is from ACV-VCV to ACV-PCV to ACV-PCV-IRV to prone positioning to HFOV or APRV; some centers transition their patients from optimized ACV/VCV directly to APRV, depending on local preferences. It is the rare patient who transitions to an extracorporeal support technique, even in centers of excellence that "regularly" provide these techniques. The rationale that underpins such transitions derives from the known pathophysiology of ALI/ARDS that positions fairly normal lung juxtaposed with quite abnormal pulmonary parenchyma. A significant difference between the two types of regions relates to alveolar collapse, disparate regional time constants, and shunting of blood as a result of hypoxic pulmonary vasoconstriction. Each maneuver in the progression of ventilator modalities is designed to progressively lengthen the T_i , better match regional time constants, recruit alveoli, and abrogate hypoxic pulmonary vasoconstriction, thereby increasing pulmonary flow. Improved pulmonary flow enhances CO_2 offloading and O_2 unloading but commonly requires support with plasma volume expansion, often at a time when the chest x-ray is read as being consistent with "pulmonary edema."

By way of examples, a series of transitions could follow the following prescription progression:

- Initial non-ALI prescription
 - AC 10/ V_T 800/40%/+5; $\dot{Q}$ = 50 L/min, decelerating; $P_{aw_{peak}}$ = 30, $P_{aw_{mean}}$ = 9; $\dot{V}_E$ = 9.2 L/min; S_{aO_2} 100%
- Optimized ACV/VCV (reduced V_T , reduced $\dot{Q}$, increased PEEP)
 - AC 10/ V_T 650/80%/+10; $\dot{Q}$ = 40 L/min, decelerating; $P_{aw_{peak}}$ = 38, $P_{aw_{mean}}$ = 11; $\dot{V}_E$ = 11.4 L/min; S_{aO_2} 92%
- Transition to ACV/PCV
 - AC 10/PC 25, T_i 2.5 s/60%/+10; V_{Tres} = 720; $P_{aw_{peak}}$ = 35, $P_{aw_{mean}}$ = 14; $\dot{V}_E$ = 9.4 L/min; S_{aO_2} 96%
- Progressive hypoxemia with S_{aO_2} < 90% leads to PCV-IRV
 - AC 8/PC 22, T_i 4.0 s/50%/+12; V_{Tres} = 780; $P_{aw_{peak}}$ = 35, $P_{aw_{mean}}$ = 16; $\dot{V}_E$ = 7.4 L/min; S_{aO_2} 99%
- Alternative transition from optimized ACV/VCV to APRV
 - P_{high} 30/ T_{high} 6.0 s/ P_{low} 2/ T_{low} 0.8 s/ F_{iO_2} 50%; $V_{Trelease}$ 640; $P_{aw_{peak}}$ = 30, $P_{aw_{mean}}$ = 24; $\dot{V}_E$ = 6.8 L/min; S_{aO_2} 100%

Note that one may use a P_{low} = 0 coupled with a significantly lower T_{low} = 0.4 s to avoid excessive volume exhalation during the release phase and loss of intrinsic PEEP.

ESTABLISHED ALI/ARDS

With some regularity, clinicians find patients with extant ALI/ARDS who are resident in their ICU, are transferred into their ICU from another ICU within their institution, or are transferred from an outside institution. The management of this subset of patients may be very similar to the examples above, especially when the mode on which the patient is being managed prior to your care is ACV/VCV. However, the more challenging subset is patients who have been optimized and are already on advanced ventilation but have persistent severe ALI/ARDS. For this subset, adjunctive maneuvers may be of assistance. These maneuvers may include prone positioning (in appropriately selected patients), bronchoscopy, and bronchoalveolar lavage to evaluate for undiagnosed infection, measurement of intra-abdominal pressure (to evaluate for intra-abdominal hypertension), and, in some patients, administration of glucocorticoids as part of a management scheme for late-stage ARDS to minimize fibrosis and permanent parenchymal destruction and distortion. For a small number of patients, management with an extracorporeal support technique may be of use.

LIBERATION FROM MECHANICAL VENTILATION

The term *liberation from mechanical ventilation* embraces the fact that some patients have their ETT (oral or nasal) removed when mechanical support is no longer needed, whereas others remain with an indwelling tube, typically a tracheostomy. The length of time a patient spends on mechanical ventilation is often used as a measure of the quality of care that is rendered in an ICU for a given disease process. Accordingly, many investigators have searched for the optimal method of determining when a patient is appropriate for reduced mechanical support and how best to accomplish liberation from mechanical ventilation. Quite often, the “best” method depends on local circumstance and physician preference. However, the overwhelming majority of the accumulated data agree on two elements: (1) one should have a weaning protocol and (2) it is best implemented by empowered respiratory therapists (i.e., nonphysicians) because of increased total contact time with patients and superior adherence to protocols compared with physician staff. With that in mind, note that there are many appropriate weaning protocols, and the protocol will depend on the ventilator mode that is used. Now let us examine the different elements that comprise the determination that a particular patient is ready for reduction of ventilator support.

READINESS FOR REDUCED OR ELIMINATED VENTILATOR SUPPORT

Airway Assessment

The clinician should understand the degree of difficulty in placing the oral or nasal ETT in a patient in whom reduction in ventilator support is contemplated. Those with “difficult” airways are commonly able to be extubated quite safely in the ICU, but some may benefit from extubation in the OR. Others, and they are clearly in the minority, may be more appropriate for tracheostomy prior to liberation from mechanical ventilation. Examples of this latter category may include those with unresectable cervical neoplasm, upper

airway injury, or physiognomy that renders reaccessing the airway rather difficult prior to reconstruction. Furthermore, patients should be able to protect their airway and be able to clear their own secretions once the artificial airway is removed. Thus, an acceptable mental status (Glasgow Coma Scale score > 8), appropriate muscular strength, and non-thick secretions are all reasonable prerequisites to be satisfied in the majority of cases. Although exceptions do exist, these guidelines serve to provide safety for the majority of patients. The next element that is commonly assessed is a series of performance measures investigating whether patients have the appropriate mechanics to support their own WOB.

Spontaneous Awakening Trial and Spontaneous Breathing Trial

A straightforward method of assessing whether patients may support their own WOB is to have them perform a spontaneous breathing trial (SBT) after daily interruption of sedatives (spontaneous awakening trial [SAT]). Paired SAT/SBT (wake up and breathe protocol) was compared with sedation per usual care plus a daily SBT in a randomized, controlled trial ($N = 336$). The use of SAT/SBT resulted in significantly increased ventilator-free days, increased ICU-free days, decreased hospital length of stay, and decreased 1-year mortality (hazard ratio 0.68, 95% CI).⁴⁶ For every seven patients treated with SAT/SBT, one life was saved. SAT/SBT has therefore become routine practice in mechanically ventilated patients in the ICU.

In an SBT, the patient is asked to breathe spontaneously for a proscribed period of time (generally no longer than 30 minutes) with minimal ventilator support. The amount of support provided by the ventilator is designed to eliminate any impedance during inspiration that is imposed by the ETT because its diameter is of necessity smaller than that of the patient’s native airway. This support is most commonly provided as either flow-by or a combination of PSV and PEEP. We typically adjust PSV according to ETT size as the WOB increases exponentially with reduced tube diameter. Thus, for a size 8.0 oral endotracheal tube (OETT), we provide PSV 5/+5, but for a size 7.5 OETT, we provide PSV 8/+5. The PEEP during an SBT should match the PEEP setting that was used during full ventilator support; higher PEEP is not a contraindication for SBT, especially in those with COPD who may have an intrinsic PEEP greater than 5 at baseline prior to intubation.

Special note is made of SBT in those who are managed on APRV. Given that APRV is a spontaneous breathing mode that resembles straight CPAP at low levels (i.e., at the end of weaning and immediately prior to liberation from mechanical ventilation), there is no need to switch to another mode for an “SBT.” Patients on APRV may be safely liberated from a P_{high} of 8 or 10 depending on their underlying condition. In some circumstances, it may be detrimental to switch such patients to a nonconstant pressure variable flow mode as alveolar recruitment may be compromised with the change. Relatedly, patients on HFOV should not be placed on an SBT as the transition from HFOV is to another full support mode once the $P_{\text{aw, mean}}$ has been decreased to 20 to 22 cm H₂O, not a liberation assessment.

Current data suggest that a once a day SBT is sufficient to assess appropriateness, with no identified benefit (or detriment) to twice or thrice a day SBTs. If a patient performs well on an SBT, then their appropriateness for liberation may further be assessed with weaning parameters.

Weaning Parameters

Weaning parameters may include a lengthy list of assessments that are readily provided by the ventilator with minimal or no adjustment of the settings. Table 1 provides a list of commonly assessed parameters used in determining the appropriateness for liberation from mechanical ventilation. Special note will be made of the following: minute ventilation, tidal volume, dead space to tidal volume ratio, respiratory rate, the rapid-shallow breathing index (also known as the Tobin Index), oxygen saturation, and cuff leak.

As a minute ventilation of 5 to 8 L/min is normal, deviations from the norm may preclude safe extubation. For instance, a minute ventilation of 3 L/min during an SBT in an 80 kg man is unlikely to provide adequate CO₂ clearance; instead, the low minute ventilation may reflect a substantial metabolic alkalosis with secondary respiratory acidosis compensation. Alternatively, the low minute ventilation could stem from an inappropriately high mandatory minute ventilation with a rather low Pco₂, and when the mandatory minute ventilation is removed, the patient has no need to breathe until the Pco₂ climbs to a sufficient level (generally 45 torr). Given that $\dot{V}_E = V_T \times RR$, one must evaluate each component.

Tidal volume is important in relation to body weight and the anatomic dead space of approximately 150 cc (100 cc with an OETT). One should calculate the V_D/V_T ratio as a ratio of 0.7 or greater is unsupportable with regard to spontaneous WOB. Moreover, a tidal volume less than 4 cc/kg ideal body weight will generally not support adequate alveolar ventilation and recruitment. Similarly, an RR greater than 25 generally indicates an unsupportable WOB with regard to liberation from mechanical ventilation. A common pattern is a high rate and a low tidal volume that often accompanies muscular deconditioning, is a good predictor (although not infallible) of failure of liberation from mechanical ventilation, and is identified as an inappropriately high Tobin Index. Note that some patients may be able to sustain the WOB during an SBT but fail from the accumulated WOB over time measured in hours.

The Tobin Index or rapid-shallow breathing index (RSBI) codifies the relation identified above between the RR and the tidal volume. The index is calculated as RR/V_T in liters; an index greater than 106 is associated with a greater likelihood of respiratory failure after liberation from mechanical ventilation compared with a lower index value. Although imperfect, the RSBI is a more durable and robust parameter than vital capacity or negative inspiratory force as both of these require active participation and are effort dependent.

Oxygenation is another key parameter to assess. Clearly, for those not habituated to relative hypoxemia (i.e., COPD patients with baseline Sao₂ < 90%), low Sao₂ is a strong contraindication to liberation from mechanical ventilation. The rationale is that there is an unrepaired condition that must be addressed prior to terminating positive pressure ventilation and alveolar recruitment. Patients should be able to maintain an Sao₂ greater than 92% on F_iO₂ less than 50% and, ideally, 40% prior to liberation from mechanical ventilation.

Furthermore, although not traditionally thought of as a “weaning parameter” per se, control or repair of the underlying condition that led to the acute respiratory failure is essential. For instance, if a patient is intubated for post-operative pneumonia and still requires suctioning every hour for thick, malodorous secretions, liberation from mechanical ventilation at that point in time is likely inappropriate. Controversy surrounds the management of patients managed with an open abdomen approach. Some clinicians are loath to have those patients liberated from mechanical ventilation because of the loss of the zone of apposition until the abdomen has been secured by adhesions, a Velcro fascial patch (Wittmann patch), or polyglycolic acid mesh plus a vacuum-assisted closure apparatus. Other clinicians will assess SBT on a daily basis and provide the patient with an opportunity at liberation from mechanical ventilation if weaning parameters and respiratory performance are acceptable. There are no definitive data to guide this circumstance.

The cuff leak test is one that is also surrounded by controversy. The premise behind the test is that in a nonedematous airway, when one deflates the ETT cuff and the patient is provided with positive pressure ventilation, some of the gas should pass retrograde around the ETT and be audible to the listening clinician. If no gas egress is heard, the cuff leak test is reported as negative and is thought by some to indicate airway edema and represent a contraindication to

Table 1 Modes of Ventilation

Mode of Ventilation	Support for Mandatory Breaths	Support for Spontaneous Breaths	Termination	Appropriate for Neuromuscularly Blocked or Nonspontaneously Breathing Patients
Assist control ventilation (ACV)	Full	Full	Target received	Yes
Synchronized intermittent mandatory ventilation (SIMV)	Full	None (can be added)	Target received	Yes
Pressure or volume support ventilation (PSV or VSV)	N/A	Yes	Flow < 5 L/min or below set % of maximal flow	No

ETT removal. The accuracy and utility of this test have been challenged and may be time sensitive, with greater accuracy and utility once a patient has been intubated for more than 48 hours. A note of caution in interpreting the test hinges on the relation between the patient's native airway and the size of the ETT. If the tube is rather large for the individual, there may be no edema but minimal to no leak attributable to simple mechanical tube luminal occupancy. No standard assessment of the ratio of ETT to airway diameter exists to guide cuff leak interpretation but may be obtainable using computed tomography (CT) or ultrasonography depending on local expertise. Either of these imaging techniques may ascertain whether the entirety of the airway lumen is occupied by the ETT. A clue that this is the case may be obtained if only a small volume of gas is required to fill the ETT cuff and obtain a normal cuff pressure (15 to 20 cm H₂O pressure).

A quantitative cuff leak test is more accurate and is performed as follows: measure the tidal volume delivered by the ventilator in a volume control mode with the ETT cuff inflated, then deflate the ETT cuff, and measure the expiratory tidal volume for six consecutive breaths. The leak can be calculated as the difference between the expiratory tidal volume with the cuff inflated and the expiratory tidal volume with the cuff deflated. If no leak is present, laryngeal edema or large ETT size for the airway is confirmed. If a leak is present, some have advocated the use of a threshold cuff leak volume of 140 mL when using a tidal volume of 10 mL/kg, with a positive predictive value and a negative predictive value of 83.8% and 93.1%, respectively. A low cuff leak volume (< 140 mL) was associated with high risk for severe laryngeal edema. Others advocate a cutoff of less than 15% leak as indicative of laryngeal edema.^{47,48}

THE DIFFICULT TO LIBERATE PATIENT

These patients may be the most vexing of all to manage in the ICU. These patients have generally been in the ICU for a prolonged period of time and are commonly difficult to liberate from mechanical ventilation for a variety of reasons. There are several methods of helping to manage such patients, which all share common features: (1) management of concomitant infection (increases minute ventilation needs for CO₂ clearance), (2) nutritional support (to help rebuild lean body mass), (3) avoidance of medications associated with ICU-acquired weakness (e.g., steroids, aminoglycosides, neuromuscular blocking agents),⁴⁹ and (4) progressive endurance training (pulmonary and total body). This section focuses on the last element as it directly influences ventilator prescription.

There are several standard methods of liberating the difficult to wean patient. These methods may be generally categorized as follows:

1. *Full ventilator support plus daily SBT.* This method relies on improved daily SBT performance as a signal to the clinician that the patient is finally ready to wean and leaves the patient on a full support mandatory mechanical ventilation mode between SBTs. This is likely the least successful method for the longer-term ventilated patient (>1 week) as there is no progressive training of all of the complex musculature involved in pulmonary mechanics, including the

diaphragm, intercostals, rectus abdominus, and sternocleidomastoid muscles. However, this method is successful for some, and patients are evaluated for liberation from mechanical ventilation using weaning parameters as above. Generally, such an approach is used for patients with an indwelling OETT.

2. *Progressive reduction in PSV with nighttime full ventilator support.* This method establishes a target $\dot{V}_E$, RR, and $V_{T\text{spont}}$ that is acceptable on PSV/PEEP and will leave that patient on that PSV/PEEP combination for as long as he or she will tolerate it until a predefined time has elapsed (commonly 0800 through 2200). At that time, the patient is returned to full support until the next day. On the next day, the PSV level is reduced by 1 to 2 cm H₂O pressure, and the pattern is repeated. When the patient reaches the target PSV/PEEP, he or she is assessed with weaning parameters as above. This approach may be used for patients with an OETT or, more commonly, a tracheostomy.
3. *Progressive time lengthening of minimal PSV/PEEP or CPAP.* This approach defines the PSV/PEEP that would be appropriate for liberation from mechanical ventilation based on ETT size and then assesses how long the patient can tolerate those settings prior to having an increased WOB. Increased WOB is then met with an intervening period of full support, and then the trial is again undertaken. For instance, a patient may tolerate PSV 8/+5 for 45 minutes, receive full support for 3 hours, and then perform a repeat trial. As the patient's endurance improves and the underlying condition is corrected, the length of time tolerated increases as well. Note that instead of PSV/PEEP, CPAP may also be used as the training mode; doing so is rather similar to low-level APRV. This approach is commonly used in patients with an OETT but may be equally well applied to those with a tracheostomy.
4. *Progressive time lengthening of tracheostomy trials.* This approach is only for those with tracheostomy tubes. Recall that when placing a patient on a tracheostomy tube trial, there is no positive pressure support for minute ventilation. Supplemental oxygen is provided by a tracheostomy mask. As such, the patient's lung is a system open to atmospheric pressure. Importantly, the patient is unable to close the glottis and generate PEEP. Derecruitment is predictable but may be manageable, especially in those who have been diuresed and have minimal extravascular lung water. One method of lengthening the time on tracheostomy mask or tracheostomy collar (TC) is to have a preplanned schedule that increases TC time and reduces full support time. A 7-day endurance training regimen example is provided below:
 - Day 1: TC 0.5 hr, ventilator 3.5 hoursx3 cycles, then full ventilator support
 - Day 2: TC 1.0 hr, ventilator 3.0 hoursx3 cycles, then full ventilator support
 - Day 3: TC 2.0 hr, ventilator 2.0 hoursx3 cycles, then full ventilator support
 - Day 4: TC 3.0 hr, ventilator 1.0 hoursx3 cycles, then full ventilator support
 - Day 5: TC 12 hr, then full ventilator support
 - Day 6: TC 18 hr, then full ventilator support
 - Day 7: TC 24 hr

Note that the regimen may be extended by progressing more slowly at any point. We regularly employ this regimen with success.

TRACHEOSTOMY

As one of the most commonly performed procedures in the United States, it is remarkable that so much controversy surrounds tracheostomy. The controversy surrounds the provider, timing, and technique but not the location. It has been firmly established that tracheostomy may be safely and appropriately performed at the bedside in the ICU instead of being exclusively performed in the OR.^{50,51} Traditionally performed by surgeons, tracheostomy is increasingly placed by nonsurgeons, predominantly anesthesia intensivists, but providers may also now include interventional pulmonologists. Instead of the standard “open” tracheostomy, nonsurgical providers virtually exclusively perform percutaneous dilatational tracheostomy (PDT). Despite some reports of increased tracheal scar and stenosis formation using the dilatational technique, little evidence supports this claim. The majority of issues surrounding PDT are related to tracheal access with the needle used to transmit the guide wire (akin to a Seldinger technique for central venous catheter insertion) puncturing and injuring surrounding vascular, neurologic, or aerodigestive tract structures; the key factor in avoiding such injuries is the regular and standard of care use of flexible bronchoscopic control of all aspects of PDT insertion. Thus, PDT is, at a minimum, a two-provider procedure. Success and good patient outcomes may be obtained with either the traditional or the PDT technique.

Therefore, the major controversy addresses timing. Tracheostomy insertion is arbitrarily defined as early (insertion < 7 days of mechanical ventilation) or late (insertion > 14 days of mechanical ventilation) and is insertion technique independent. The controversy stems from three observations: (1) tracheostomy placement typically facilitates liberation from mechanical ventilation, leading to a shortened ventilator length of stay; (2) patients with serious structural neurologic injury generally do not recover rapidly if they have made little improvement over the first 7 days of hospital care and typically benefit from secure airway access for ventilation, oxygenation, and pulmonary hygiene measures; and (3) indwelling oral or nasal endotracheal intubation for more than 4 weeks is associated with vocal cord injury and dysfunction, eustachian tube and sinus blockade, and postextubation dysphagia.

Proponents of early tracheostomy argue that even if an unnecessary tracheostomy is placed in a patient, the major benefits realized by all of the other patients who received an “early” tracheostomy would outweigh the downside of a few “inappropriate or unnecessary” tracheostomies. These putative benefits include but are not limited to reduced ventilator-associated pneumonia, ICU length of stay, and bloodstream infection risk as well as improved ICU throughput in systems with scarce ICU beds relative to total hospital bed capacity. Proponents of late tracheostomy counter that with waiting, some tracheostomies may be avoided as patients declare whether they require prolonged and durable airway access. Therefore, patients who avoid tracheostomy would enjoy reduced risk of structural injury, bleeding, and surgical site infection.

The guidelines for the timing of tracheostomy of the Eastern Association of the Surgery for Trauma provided an evidence-based review and include the following recommendations⁵²:

- *Level I:* There is no mortality difference between patients receiving early tracheostomy and late tracheostomy or extended endotracheal intubation.
- *Level II:* Early tracheostomy decreases the total days of mechanical ventilation and ICU length of stay in patients with head injuries. Therefore, it is recommended that patients with a severe head injury receive an early tracheostomy.
- *Level III:* Early tracheostomy may decrease the total days of mechanical ventilation and ICU length of stay in trauma patients. Therefore, it is recommended that early tracheostomy be considered in all trauma patients who are anticipated to require mechanical ventilation for more than 7 days, such as those with neurologic impairment or prolonged respiratory failure.

In the largest trial to date to evaluate tracheostomy timing, with 419 patients randomized in 12 Italian ICUs to receive percutaneous tracheostomy early (6 to 8 days) or late (13 to 15 days), no reduction in mortality (28 days or 1 year) or hospital length of stay was identified. There was a statistically nonsignificant trend toward a reduction in ventilator-associated pneumonia (14% versus 21%, $p = .07$) with early tracheostomy and a statistically significant reduction in ventilator days and ICU days.

This controversy remains unresolved. Instead, the timing of tracheostomy reflects local practice, and it is likely that no single “rule” or guideline adequately addresses all patient populations.

Special Problems

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

COPD-induced respiratory failure is one of the leading causes of admissions to the medical ICU. In surgical patients, COPD is less often the primary diagnosis and more often a comorbidity that complicates ventilator management. COPD is a disease of progressive and irreversible airflow limitation associated with an abnormal inflammatory response.⁵³ The diagnosis represents a wide spectrum of pathology that varies with the stage of the disease. In general, the peripheral airways demonstrate smooth muscle hypertrophy, peribronchial fibrosis, enlarged lymphoid follicles, and luminal obstruction by secretions. There is damage to the alveolar wall and a decrease in lung elastic recoil.⁵⁴

Physiologically, COPD is diagnosed by a reduced forced volume in 1 second (FEV_1) and reduced forced vital capacity (FVC). The end-expiratory lung volume is increased, and the chest wall geometry changes with a lower, flatter diaphragm and a more horizontal rib cage. The overall work of breathing is increased, and expiratory muscle use is common in severe COPD in contrast to normal, passive expiration.⁵⁵ The increase in both $\dot{V}/\dot{Q}$ mismatch and dead space ventilation and the relative alveolar hypoventilation result in baseline arterial hypoxemia and hypercapnea, the degree of which depends on the severity of the disease.

Ventilator and respiratory management of patients with COPD should primarily focus on treating the underlying cause of the respiratory failure. The outpatient pulmonary drug regimen should be continued and adjusted as required, often in consultation with a pulmonary specialist. Airway hyperreactivity can be treated with bronchodilators (see above) and often steroids. Superimposed COPD exacerbation may require a systemic steroid taper and antibiotics when associated with concomitant infection. Bronchial secretions should be managed aggressively and may benefit from bronchoscopic evacuation in cases associated with parenchymal volume loss on a chest radiograph.

Limitations in airflow from small airway obstruction can result in incomplete expiration, air trapping, and autoPEEP, requiring specific ventilator adjustments. The expiratory time should be maximized by decreasing the respiratory rate, increasing the inspiratory flow rate, and using the square flow rate waveform when recruitment is not an issue. In patients with airflow obstruction and dynamic hyperinflation, extrinsic PEEP should be adjusted to about 75 to 85% of the estimated autoPEEP to decrease the WOB.^{56–58} Furthermore, patients with COPD may not have “normal” baseline ABGs, and the oxygenation and ventilation targets should therefore be adjusted accordingly.

During weaning trials, COPD patients may not meet the conventional parameters, and the patient’s baseline status should again be taken into consideration. Unless contraindicated, noninvasive positive pressure ventilation (NIPPV) should be considered immediately after extubation to avoid reintubation in COPD patients.

ASTHMA

Sharing some similarities with COPD, asthma is another common comorbidity in surgical patients. Mechanical ventilation can induce bronchospasm in patients without a prior history of asthma. Furthermore, severe asthma exacerbation can occur in any asthma patient, even those with previously mild disease. The pathophysiology of asthma is marked by airflow obstruction from a combination of smooth muscle-mediated bronchospasm and airway inflammation. Common triggers for an acute exacerbation include allergen or irritant exposure (such as the ETT), medications, infections, perfumes, and increasingly recognized latex exposure. Often no specific trigger is discovered.

The main goal of therapy is to reduce small airway obstruction by reducing bronchospasm and airway inflammation. Inhaled beta agonists, such as albuterol, delivered via a nebulizer or a metered-dose inhaler using a spacer device, are first-line therapy. Higher doses are usually required for mechanically ventilated patients given loss of the drug in the ventilator circuit. Systemic steroids have been shown to be beneficial, and there may also be a role for inhaled corticosteroids in acute asthma exacerbations.⁵⁹ Other agents include ipratropium bromide (in those with concomitant COPD), heliox (in the nonintubated or the intubated patient with severe, acute life-threatening asthma), magnesium sulfate (see above), and leukotriene modifiers. Antibiotics are not recommended unless there is specific evidence of a bacterial infection.

Asthma patients also require longer expiratory times secondary to airflow obstruction. Initiation of mechanical

ventilation with an inappropriately short expiration may lead to lung hyperinflation from incomplete alveolar emptying. Hyperinflation can lead to decreased venous return, decreased cardiac output, and systemic hypotension. The ventilator prescription should be adjusted as discussed above for COPD patients with a lower respiratory rate and higher inspiratory flow rates. The minute ventilation should be adjusted to keep the plateau pressure below 30 cm H₂O; this may result in some degree of hypercapnea and may be buffered with a sodium bicarbonate-containing fluid when needed for pH maintenance. Most patients, with the exception of those with brain injury or cardiac dysfunction, can tolerate a moderate amount of hypercapnea as long as the increase is gradual.

BRONCHOPLEURAL FISTULA

BPF is a persistent air leak attributable to a breach in the visceral pleura that connects to the pleural space. It is an infrequent but severe complication of thoracic trauma and pulmonary resections. To be more precise, BPF is divided into a true BPF and a PPF or alveolar-pleural fistula. The classic BPF is a direct communication between the pleural cavity and a lobar or segmental bronchus.⁶⁰ On the other hand, a PPF can occur from a number of causes, including visceral pleural lacerations from trauma, iatrogenic injury associated with procedures such as central line placement or transbronchial biopsy, ventilator-associated biotrauma, or infectious etiologies. Whether from a BPF or a PPF, if the leak is large (> 100 mL/breath), it can lead to loss of PEEP and effective tidal volume, incomplete lung expansion, and false ventilator cycling. This will typically manifest as $\dot{V}/\dot{Q}$ mismatching, hypoxemia, and respiratory acidosis.

The initial treatment of a BPF or PPF is decompression of the pleural space with a tube thoracostomy to prevent the development of tension pneumothorax and to facilitate coaptation of the parenchyma and the pleura. Given that the flow through the fistula is dependent on the transpulmonary pressure, conventional chest tube management using negative suction may actually worsen the pressure gradient and increase the size of the leak. Chest tubes should therefore be placed on the minimal amount of suction required to maintain lung inflation and pleural space gas evacuation.

No specific ventilator management has been proven to be optimal, although certain modes may be ideal for BPF/PPF management. Although not directly equivalent to transpulmonary pressure, $P_{aw\text{mean}}$ should be minimized as tolerated. $F_{I}O_2$ may need to be increased to compensate for the resulting hypoxemia. PCV has a theoretical but unproven advantage in providing a fixed airway pressure and may use a lower pressure for a longer time. PSV should be avoided in large leaks. In this mode, the ventilator terminates the inspiratory cycle when there is a significant reduction in flow. With a large leak, this may never occur. Ideally, patients should be weaned and extubated as soon as possible. Alternative options described in case reports and small series include high-frequency jet ventilation, HFOV with low mean airway pressures, SILV, and extracorporeal membrane oxygenation. Importantly, SILV may use a different ventilator mode on each side; synchrony is not important (see above). Endoluminal and surgical options to control

the fistula may be required depending on its location and may include stenting, resectional therapy, or permanent occlusion of the affected lung segment.⁶¹

PLEURAL SPACE COLLECTIONS

Simple pleural effusions are very common in critically ill patients. They are caused by multiple processes, including hypoalbuminemia, heart failure, fluid overload, and systemic inflammation. Normally, most effusions improve or resolve with improvement in the underlying etiology. However, large effusions may contribute to respiratory failure and impair weaning from mechanical ventilation. Effusions cause alveolar atelectasis by direct compression and contribute to the decreased FRC, $\dot{V}/\dot{Q}$ mismatching, and hypoxemia seen in ICU patients. Drainage of a large effusion should be considered in patients who are not successfully weaning from the ventilator. The size of the effusion can be estimated by CT or ultrasonography.⁶² The procedure can be performed with or without radiologic guidance depending on the clinician's experience, size of the effusion, and presence of loculations. It was previously thought that effusions should only have 1,000 cc drained at a time to avoid the risk of postexpansion pulmonary edema or acute hypovolemia from fluid egress from the pleural space and a huge driving force for fluid reaccumulation. These events happen only rarely and quite uncommonly in those on mechanical ventilation.

For a transudative effusion, the technique and choice of a tube are a matter of personal preference; a pigtail catheter placed using a Seldinger technique will typically suffice. If the effusion is blood or an exudate, a standard chest tube is more appropriate because of a larger bore size, which facilitates draining thick fluid. For hemothorax, the largest tube available (typically a 36 or 40 French) is the most appropriate choice. For loculated effusions and the repeatedly accessed pleural space, an interventional radiology-guided catheter placement is quite appropriate to avoid iatrogenic injury; small catheters may be upsized as needed in this circumstance. Some data support drainage of pleural space collection after injury as a means of reducing ventilator length of stay.⁶³

ABDOMINAL AND THORACIC COMPARTMENT SYNDROME

Compartment syndrome is a well-described pathologic state that occurs when the pressure inside a closed compartment exceeds the lymphatic, capillary, venous, and, ultimately, arterial pressure. It is most commonly recognized in the muscle compartments of the lower extremity and in the abdomen. ACS can also contribute to respiratory failure through external pressure on the lung and diaphragm and its effects on venous return and cardiac performance.

Compartment syndrome can also develop in the thoracic cavity. Although not as well characterized as ACS, thoracic compartment syndrome has been reported.⁶⁴ It has been primarily described in postoperative cardiac, thoracic, and chest trauma patients. It is characterized by cardiac tamponade physiology, decreased cardiac output, hemodynamic instability, acidosis, hypotension, decreased lung compliance, and increased airway pressures. Treatment is with immediate decompression of the chest by reopening the incision and maintenance of an open chest with a temporary

closure until the underlying process (e.g., pulmonary, tissue edema, hematoma) resolves.

PREGNANCY

The respiratory system undergoes a number of physiologic changes during normal pregnancy. Upper airway edema may develop, potentially complicating endotracheal intubation. Oxygen consumption increases by 20%, and the metabolic rate increases by 15%.⁵³ Minute ventilation increases up to 50% through an increase in tidal volume but not respiratory rate. ABG analysis reveals a relatively compensated respiratory alkalosis. Closer to term, FRC is decreased 10 to 25%, with an associated mild decrease in total lung volume. The increase in oxygen consumption and decrease in FRC lead to a decrease in oxygen reserve. Pregnant women can therefore rapidly desaturate during periods of apnea or hypoventilation.⁶⁵

The literature on the management of respiratory failure with mechanical ventilation in pregnancy is limited. The low tidal volume ventilation used in ARDS patients has not been prospectively evaluated in pregnant patients. As a result of decreased chest wall compliance, it is difficult to fully understand the relation between plateau pressures and transpulmonary pressures. Higher airway pressures may therefore be acceptable to achieve appropriate tidal volumes.⁶⁶ Oxygenation should be optimized not only for adequate maternal but also fetal oxygen delivery. Hyperventilation should be scrupulously avoided because it adversely affects uterine blood flow.⁶⁷ It is also unclear whether permissive hypercapnea is safe for the fetus.

Noninvasive Positive Pressure Ventilation

Although lifesaving in patients with acute respiratory failure, invasive mechanical ventilation may be associated with significant complications. Endotracheal intubation can lead to upper airway trauma and requires sedation, which in turn may prolong ventilator duration. It bypasses the upper airway defense mechanisms with an increased risk of sinusitis, nosocomial pneumonia, and sepsis along with an associated increase in mortality. Noninvasive ventilation is an alternative method of providing positive pressure ventilator support. Its use in patients with acute respiratory failure was first described in 1990,⁶⁸ and it has been subsequently used in various patient populations.

DELIVERY ROUTES

Instead of an ETT, NIPPV uses six types of interfaces to connect the patient's airway to the ventilator.⁶⁹ These include a nasal-oral (full face) mask, a nasal mask, nasal plugs, a mouthpiece, a total face mask, and a helmet. Each has its own advantages and disadvantages. The larger interfaces such as the full or total mask or the helmet have fewer air leaks and require less patient cooperation but may cause more claustrophobia, discomfort, and a higher risk of aspiration. The nasal interfaces are often better tolerated and allow the possibility of speaking and drinking. However, they have greater air leaks (especially with mouth breathing) and require more patient cooperation. The most commonly used interfaces for acute indications are a face or nasal mask.⁶⁹

MODES

NIPPV typically uses pressure-cycled modes administered by conventional mechanical or portable bilevel ventilators. The most common modes include CPAP and bilevel positive airway pressure (BiPAP). Although CPAP does not specifically assist inspiration, it is often classified as an NIPPV mode. CPAP is the equivalent of PEEP. It is a continuously applied positive airway pressure that helps retard alveolar collapse and assists in alveolar recruitment with subsequent improvements in FRC and $\dot{V}/\dot{Q}$ matching. BiPAP is the equivalent of PSV combined with PEEP. The machine provides a patient-triggered positive pressure support of each breath. The patient is able to set the respiratory rate and the inspiratory and expiratory times; the clinician sets the amount of pressure during inspiration (IPAP) and during expiration (EPAP). Typically, IPAP is set greater than EPAP. BiPAP has achieved results superior to those obtained using CPAP alone in the management of impending acute respiratory failure in medical and surgical patients. The reader should note that when using a full face mask, one may also prescribe traditional mechanical ventilation such as ACV-VCV, ACV-PCV, or APRV, although this manner of gas delivery is much less common.

CONTRAINDICATIONS

Contraindications for NIPPV include respiratory arrest, hemodynamic instability, agitation, uncooperativeness, excessive secretions, inability to protect the airway, and significant upper gastrointestinal bleeding. There is a theoretical, unproven but well-entrenched concern regarding the use of NIPPV in patients with recent upper gastrointestinal anastomosis, especially when the patient is new to the mode, on sedatives or analgesics that may impair the sensorium, and unable to maintain a nasogastric tube in place to abrogate the untoward effects of aerophagia.

USES

Level 1 evidence supports the use of NIPPV in patients with COPD exacerbations, in maintaining extubation of COPD patients, and in the treatment of cardiogenic pulmonary edema. Its use in other areas, such as postoperative respiratory failure, prevention of reintubation, and pneumonia, is more controversial, but some recent data support the use of helmet-based BiPAP in this setting.⁷⁰ In patients with mild to moderate respiratory acidosis and distress from COPD exacerbation, NIPPV has been shown to prevent further deterioration, avoid the need for intubation, and improve survival.^{71,72} Additionally, in several meta-analyses, NIPPV has also been shown to decrease intubation rates and reduce mortality compared with standard therapy in patients with cardiogenic pulmonary edema.^{73–75}

In postoperative patients, NIPPV can be theoretically employed either prophylactically to prevent respiratory failure in higher-risk patients or as a bridge therapy in patients with established respiratory failure.⁷⁶ Although two multicenter randomized trials (performed in mixed surgical populations) failed to show a beneficial effect of NIPPV in established respiratory failure,^{77,78} other, smaller trials in more defined surgical subpopulations, such as thoracic patients, have demonstrated some advantage.^{79,80} Furthermore, the

preventive use of NIPPV has been shown to be beneficial in preventing atelectasis, hypoxemia, and respiratory failure in select high-risk postoperative patients.^{81,82}

Illustrative Case Scenario

A 62-year-old woman presents to an outside hospital with obvious septic shock and hypoxemia (Sao_2 82% on FiO_2 0.21). She is orally intubated and placed on ACV/VCV. She is febrile to 38.7°C (101.7°F), tachycardic (heart rate = 114 beats/min), and hypotensive (blood pressure = 82/66 mm Hg) and is started on crystalloid fluid resuscitation. Because of a distended and tender abdomen, and while awaiting transfer to your institution, she undergoes CT scanning, which demonstrates perforated diverticulitis with free fluid and air.

On arrival at your facility, she remains in shock and is started on norepinephrine and vasopressin while she is prepared for surgery. However, despite achieving a mean arterial pressure (MAP) greater than 65 mm Hg, she remains hypoxemic (Sao_2 90% on FiO_2 1.0). Her ventilator settings are as follows: AC 14/ V_T 650/100%/+5; $\dot{Q}$ = 65 L/min; Paw_{peak} 34, Paw_{mean} 9; decelerating waveform. Her initial ABG = 7.28/32/62; lactate = 5.2 mmol/L. Her chest x-ray indicates low lung volumes and a right lower lobe opacity consistent with early aspiration pneumonia. She does not have radiographic evidence of ALI but does have hypoxemia and a $\text{Pao}_2/\text{FiO}_2$ ratio of 62/1.0. Thus, she has a large A-a gradient (611; age-expected normal A-a gradient = 18) and is at high risk for developing ALI/ARDS. Her low lung volumes suggest underrecruitment, but her Pco_2 is already low.

The low Pco_2 in the setting of a 9.1 L/min minute ventilation (which is lower than anticipated for someone in septic shock) indicates a lack of O_2 use leading to underproduction of CO_2 ; this is supported by the increased arterial lactic acid concentration consistent with hypoperfusion. Thus, this patient needs plasma volume expansion to optimize O_2 delivery and use rather than a change in ventilator settings. However, her ACV/VCV prescription may be optimized by decreasing her $\dot{Q}$, increasing her PEEP, decreasing her RR, and increasing her tidal volume while keeping her Paw_{peak} and therefore her P_{plat} less than 35 cm H_2O pressure to avoid VILI and biotrauma. These later maneuvers are designed to increase T_i , avoid creating autoPEEP, decrease the V_D/V_T , increase FRC, and decrease the A-a gradient. It is anticipated that the Pco_2 may rise on the next ABG.

After additional plasma volume expansion (PVE) and the ventilator prescription changes to AC 10/ V_T 800/100%/+8; $\dot{Q}$ = 40 L/min; Paw_{peak} 32, Paw_{mean} 13 and decelerating waveform, her next ABG is 7.36/46/246. Thus, with minimal ventilator manipulation, her $\text{Pao}_2/\text{FiO}_2$ has significantly improved (246), as has her A-a gradient (409.5), allowing you to decrease her FiO_2 to 0.6 and retain a preserved Sao_2 of 100%. At this point, she undergoes operation under general anesthesia, where she requires a sigmoid colectomy and peritoneal débridement, and because of the degree of contamination and the need for additional débridement, she is left in discontinuity, and a temporary abdominal wall closure is placed. She is transferred to the surgical ICU, where she is again hypoxic after being returned to her previous ventilator settings.

At this point in time, her chest x-ray demonstrates additional loss of lung volumes and patchy infiltrates and the ventilator indicates high Paw_{peak} (38 cm H₂O pressure). The high airway pressures are consistent with burgeoning ALI with loss of compliance as she has an open abdomen and should have even more thoracic cage space than when her abdominal wall was intact. Thus, a ventilator strategy that establishes an airway pressure limit or manipulation of ventilator settings to decrease the volume of delivered gas (low tidal volume approach consistent with ARDSnet) to decrease the resultant airway pressure should be considered. However, with her decreasing lung volumes, and therefore worsened derecruitment, further decreasing her lung volumes will increase hypoxemic pulmonary vasoconstriction, decrease RVEF, impede venous return, and diminish cardiac performance. This may be an unsupportable series of events in a patient who is currently on vasopressors for MAP management. Thus, in this setting, a pressure-limited ventilator prescription may be more ideal.

Her prescription may be changed to PCV, APRV, or HFOV. However, because she is planned to return to the OR, HFOV is a poor choice as a result of transport and management issues with HFOV outside the ICU setting. An alternative, if HFOV is the mode of choice at your institution, is to operate at the bedside—an increasingly common decision across the United States and at our institution for patients on advanced modes of ventilation. Given that PCV is a mode available on every modern ventilator, let us explore this mode first.

A reasonable change to PCV may be accomplished by the following prescription, recalling that increased airway pressures and hypoxemia in a vasopressor-requiring patient are being addressed: AC 10/PCV 25, T_i 2.5 s/100%/+10; Paw_{peak} 35, Paw_{mean} 14, decelerating $V_{Tresulant}$ 720 cc, $\dot{V}_E$ 7.2 L/min with a 30-minute postchange ABG of 7.34/46/186. Her prescription significantly increases her T_i and limits her Paw_{peak} . She has a metabolic and respiratory acidosis, and her PCO_2 may remain above normal and her pH buffered with an altered fluid regimen (low or no chloride fluid to reduce the expected hyperchloremic metabolic acidosis that accompanies large-volume PVE) to avoid worsening her existing ALI by creating worsened intratidal shear. This strategy is termed permissive hypercapnia and is a successful means of managing hypoxemic salvage. A central venous pressure (CVP) monitoring catheter is placed indicating a CVP of 3, and additional PVE is initiated as she remains on high-dose vasopressors (norepinephrine at 0.25 µg/kg/min; vasopressin at 0.04 U/min); empirical steroids are also prescribed as part of a septic shock management protocol.

Despite PVE, her urine output begins to fall, and once again, her airway pressures begin to rise and her resultant tidal volumes begin to fall by about 100 cc from their baseline. Concomitantly, her MAP also declines from over 65 mm Hg on a stable dose of vasopressors to 50 mm Hg, and her SAO_2 has declined to 93% on an F_{IO_2} of 0.6. At this point in time, she is net positive 18 L of isotonic fluid, 4 units of packed red blood cells, and 8 units of FFP (principally because of dilution); her CVP is now 10 mm Hg. A repeat chest x-ray does not demonstrate new infiltrates, pneumothorax, ETT malposition, or full pulmonary hila but does identify decreased lung volumes consistent with the

decreased compliance and $V_{Tresulant}$ obtained from the ventilator. There is no change in her secretions, and her $Paw_{peak} - P_{plat}$ gradient remains elevated at 7 (normal = 4). Although the changes in pulmonary mechanics may simply represent progressive remote ALI from her septic shock, these changes do not routinely lead to hypotension unless there is myocardial demand ischemia and contractility compromise. Diuresis in the setting of hypotension is often difficult to support, especially while on vasopressors early in the course (postoperative days 0 to 1) of septic shock. Therefore, one must look for other correctable causes of all of the above findings. The next most appropriate site to investigate is her abdomen.

The observations above are all consistent with intra-abdominal hypertension and the ACS. Thus, measuring an intravesical pressure is ideal. Doing so, her measured intravesical and intra-abdominal pressure (IAP) is 24 mm Hg pressure, whereas a concomitant MAP is 52 mm Hg. Thus, her abdominal perfusion pressure (APP), which is equal to MAP-IAP is 28 mm Hg (normal = 50 mm Hg).⁸³ ACS can recur in patients with an already open abdomen with temporary abdominal closure. The pressure can often be alleviated by a “looser” temporary abdominal closure or further extending the incision. Performing a bedside relaparotomy for a presumed secondary ACS is appropriate, and anticipating both visceral edema and the presence of ascites is appropriate and expedient as the ACS is a surgical emergency. Having done so, her postrelaparotomy IAP is 12 mm Hg and her MAP is 70 mm Hg. Similarly, her ventilator parameters return to their previous baseline and her hypoxemia resolves.

Twelve hours later, and with a well-preserved urine output and an IAP of 16, her $V_{Tresulant}$ again falls and is accompanied by recurrent hypoxemia, necessitating an increase to F_{IO_2} of 100%, and is complicated by a rising PCO_2 . She remains on pressors and has a MAP over 65 mm Hg. There is worsening of infiltrates on a chest x-ray and even more decreased lung volumes. This pattern is consistent with worsening ALI secondary to ischemia and reperfusion at a site remote from the lungs; it is also consistent with a burgeoning pneumonia. It is likely that one could improve her PO_2 with another increase in T_i , and one would need to decrease the RR to avoid worsening the PCO_2 . However, because the PCO_2 is high and is associated with a low pH, one would also need to buffer the pH with intravenous $NaHCO_3$ or tromethamine, worsening her salt overload; also, given that the settings would inverse the I/E ratio, deep sedation or neuromuscular blockade would be needed and would be problematic given the high-dose pressors that are already in use. Therefore, a different ventilator mode would be most appropriate.

In this setting, APRV or HFOV would be appropriate. We prefer APRV given its ability to be transportable and used in the OR. Also, it is associated with improvements in cardiac performance, improvements in renal and intestinal blood flow, and abrogation of hypoxic pulmonary vasoconstriction. Furthermore, because this patient already has a high PCO_2 and HFOV uncouples oxygenation and ventilation, commonly resulting in an increased PCO_2 , HFOV is less than ideal in this scenario.

Initial APRV settings for this patient could be prescribed as P_{high} 30, P_{low} 2 seconds, T_{high} 6.0, T_{low} 0.8 seconds, and $F_{\text{I}O_2}$ 100%; alternatively, the P_{low} could be set at 0 and the T_{low} appropriately narrowed to 0.5 seconds. These settings generate a V_{Trelease} of 650 cc (initially) and rapidly resolve her hypoxemia, allowing one to decrease her $F_{\text{I}O_2}$ to 0.5. Her 1-hour postchange ABG is 7.36/46/212, leading to a further decrease in $F_{\text{I}O_2}$ to 0.4. By 4 hours, her V_{Trelease} is 820 cc and her ABG is 7.48/34/186. Her chest x-ray demonstrates improved lung volumes and a relatively narrow mediastinum, and her CVP falls from 14 to 8. This begins the weaning phase even while the patient is acutely ill. We typically reduce the P_{high} by 2 cm H_2O pressure and increase the T_{high} by 0.5 seconds every 2 to 4 hours as tolerated. Liberation from mechanical ventilation occurs as indicated above when the P_{high} is reduced to either 8 or 10 cm H_2O pressure. Further ABG analysis is unnecessary as one may follow the patient's weaning using an end-tidal CO_2 device. Alternatively, as many patients have a CVP monitoring catheter, venous blood gases may be obtained and "arterialized" by decreasing the P_{CO_2} by 7 torr and increasing the pH by 0.05 units; these adaptations hold true for those without severe metabolic acidosis or alkalosis (i.e., $7.2 < \text{measured pH} < 7.6$).

Conclusions

Mechanical ventilation is a complex intervention with a wide variety of components, each of which needs to be carefully integrated into a single, coherent approach to the patient's underlying pathophysiology, in particular volume status and cardiac performance. Much like medications that are titrated to a physiologic end point and used to achieve similar but distinct effects (i.e., vasopressors), different ventilation modes may have unique applications. Moreover, one must realize when it is appropriate to change from one mode to another, as well as when a nonpulmonary cause of acute respiratory failure is present, including intra-abdominal hypertension and the ACS.

Liberation from mechanical ventilation may be just as complex as the management while on ventilation. Multiple different approaches exist, without a clearly defined one that is superior to the rest. For those who have impending or recurrent respiratory failure, noninvasive ventilation may be appropriate for select surgical patients and may have its optimal application in the resolution of volume overload or atelectasis. Although standard ventilation may be managed by a wide variety of individuals, advanced ventilation techniques are optimally managed by intensivists with specialty training to best apply the variety of unique modes at the ideal time in the ICU course of patients with critical illness or injury.

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Acknowledgment

Figure 8 Christine Kenney

8 ACUTE RENAL FAILURE

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Acute renal failure (ARF) remains one of the major therapeutic challenges facing the modern physician. The term describes a syndrome characterized by a rapid decrease (occurring within hours to days) in the kidney's ability to eliminate waste products, regulate extracellular volume, and maintain electrolyte and acid-base homeostasis. This loss of excretory function is manifested clinically by the accumulation of end products of nitrogen metabolism (e.g., urea and creatinine). Other typical clinical manifestations include decreased urine output (which is not always present), the accumulation of nonvolatile acids, and an increased serum potassium concentration.

In the literature, the incidence of ARF has been variable, depending on the criteria used to define the condition. ARF has been reported to occur in approximately 5% to 8% of hospitalized patients and 15% to 30% of patients admitted to an intensive care unit. Despite the advances that have been made in understanding the pathophysiology of ARF and developing extracorporeal therapies, the mortality associated with this condition continues to be alarmingly high. Moreover, there is evidence to suggest that the mortality is even higher in patients with ARF that is severe enough to warrant initiation of renal replacement therapy (RRT).

The term acute tubular necrosis (ATN) has frequently been used in the context of ARF, but current evidence suggests that this term has limited clinical relevance, in that it describes only the histopathology and is not reliably linked with differences in patient management. The concept of ATN comes from animal models that do not accurately reflect clinical situations and from old biopsy data. Even in cases where the term seems appropriate, the so-called necrosis is frequently patchy and mostly isolated to the thick ascending loop of Henle. Furthermore, cells found in the urinary tubular casts of such patients are viable on staining studies, a finding that partly invalidates the use of the term necrosis.

General Principles

DEFINITION OF ACUTE RENAL FAILURE

A logical approach to organ failure might reasonably begin by defining what a particular organ does. In the case of the kidney, the list of functions is long. Many of these functions, however, are either shared with other organs (e.g., acid-base control, which is shared with the lung) or require complex neurohormonal interactions that involve other organs (e.g., the renin-angiotensin-aldosterone axis). Other renal functions are not routinely measured (e.g., small peptide excretion, tubular metabolism, and hormonal production).

There are only two functions that are routinely and easily measured in patients and are unique to the kidney: (1) production of urine and (2) excretion of waste products of nitrogen metabolism. Accordingly, clinicians have focused on these two functions in their efforts to define the presence of so-called ARF.

The two waste products whose levels are routinely measured in patients are urea and creatinine. The urea level is the one that is affected more by extrarenal factors (e.g., gastrointestinal blood,

changes in nitrogen intake, and changes in protein catabolic rate) and that varies more rapidly. The creatinine level is a more reliable marker of the glomerular filtration rate (GFR) and is commonly used to define the presence or absence of ARF; however, it does not change in direct proportion to the loss of nephron mass and is not a real-time descriptor of the GFR. Nonetheless, using urea and creatinine levels to define ARF seems a practical and reasonable approach to the biochemical definition of this condition. The problem, however, is that in current practice, there are too many essentially arbitrary biochemical cutoff values for the definition of ARF. This point was highlighted by a review of 28 studies of post-operative ARF, in which each study used a different definition of this condition.¹ The lack of agreement on the operative definition of ARF has significantly hindered research in this field, especially with regard to the design and execution of randomized, controlled trials. In 2004, however, the work of the Acute Dialysis Quality Initiative (ADQI) (<http://www.ADQI.net>) led to the development and publication of a consensus definition of ARF. It is hoped that acceptance and use of this definition will lead to more consistent, reproducible, and generalizable results from epidemiologic and interventional studies of ARF [see Figure 1].²

ASSESSMENT OF RENAL FUNCTION

Waste Product Levels

As noted (see above), to establish that ARF is present, one must be able to measure renal function and detect that it has been altered; however, the complexity of renal function can make this a difficult undertaking. Accordingly, in the clinical context, monitoring of renal function is limited to indirect assessment of the GFR through measurement of urea and creatinine levels in blood. These levels are relatively inaccurate markers of GFR and are heavily influenced by patient age, patient sex, nutritional status, steroid use, and the presence of GI bleeding or muscle injury. Furthermore, they generally only become abnormal once the GFR has fallen by 50% or more; they do not reflect real-time dynamic changes in the GFR and can be grossly modified by aggressive fluid resuscitation. Determining creatinine clearance by means of 2-hour or 4-hour collections or calculating clearance by means of formulas adjusted for body weight, sex, or age may increase the accuracy of the results, but it rarely, if ever, changes clinical management. Sophisticated radionuclide-based tests are available, but they are cumbersome and are useful only for research purposes.

Urine Output

Urine output is a commonly measured parameter of renal function and often is more sensitive to changes in renal hemodynamics than biochemical markers of solute clearance are. However, urine output is also of limited sensitivity and specificity; some patients have severe ARF, as indicated by a markedly elevated serum creatinine level, while maintaining normal urine output (so-called nonoliguric ARF). Because nonoliguric ARF has a lower

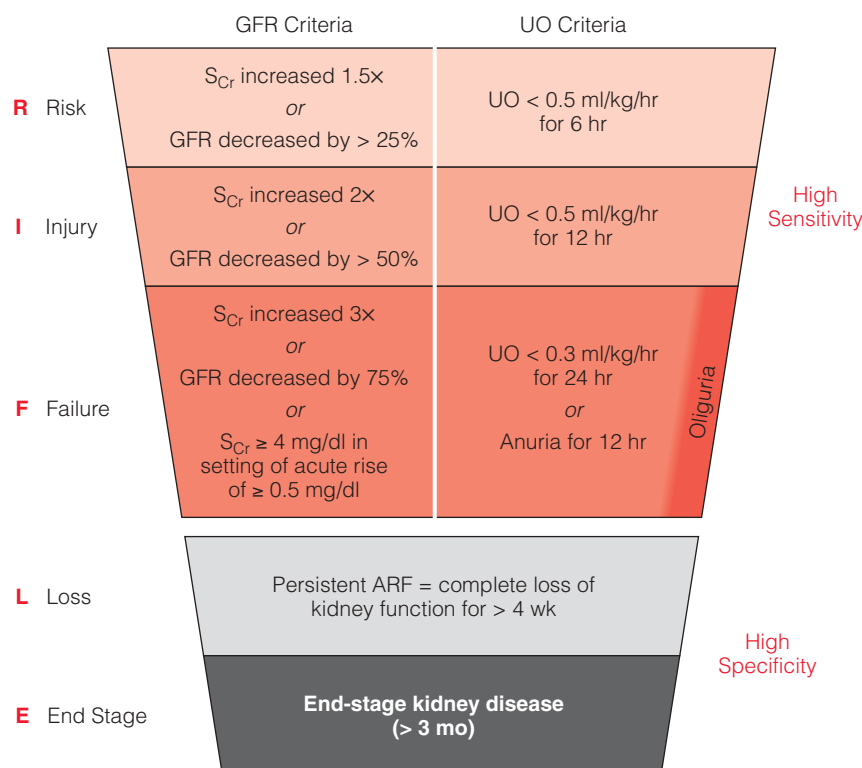


Figure 1 Depicted is the RIFLE (Risk, Injury, Failure, Loss, End stage) classification scheme for ARF.² The classification system includes separate criteria for GFR and urine output (UO). Those criteria that lead to the worst possible classification of renal failure should be used. The designation RIFLE-F (for failure) is appropriate even if there is a less than threefold increase in the serum creatinine concentration (S_{Cr}), provided that the new S_{Cr} is higher than 4.0 mg/dl (350 μ mol/L) in the setting of an acute increase of at least 0.5 mg/dl (44 μ mol/L). In this case, the designation RIFLE-FC should be used to denote acute-on-chronic disease. Similarly, when the presence of renal failure (RIFLE-F) is determined on the basis of urine output criteria only, the designation RIFLE-FO should be used to denote oliguria. The shape of the figure illustrates the point that more patients are included in the mild category (top), including some who do not have renal failure (higher sensitivity, lower specificity). In the severe category (bottom), the criteria are strict and therefore specific, but some patients with renal dysfunction may be missed (higher specificity, lower sensitivity).

mortality than oliguric ARF, urine output is frequently used as a means of distinguishing varieties of ARF.³ Classically, oliguria has been defined (approximately) as a urine output of less than 5 to 6 ml/kg/day or less than 0.5 ml/kg/hr. Often, changes in urine output can develop before biochemical changes in renal function become apparent.

Serum and Urine Biomarkers

Overall, it would be highly desirable to have markers of renal function that would enable physicians to diagnose true reductions in function associated with renal injury; the ability to diagnose such functional impairments would allow the identification of those patients in whom early intervention might be justified.

In the past few years, several serum and urine biomarkers have been developed for use in the detection of early renal dysfunction or injury. One such biomarker is cystatin C, a cysteine proteinase inhibitor of low molecular weight. This substance has many features that would make it an ideal tool for the assessment of renal function, especially its constant rate of production (which appears to be independent of any pathologic states), its exclusively renal excretion, and the good inverse correlation of its blood levels with radionuclide-derived measurements of the GFR.^{4,5} Another biomarker is kidney injury molecule-1 (KIM-1), a transmembrane protein that is present in the proximal renal tubule and is markedly upregulated and excreted in the urine in response to injury.⁶ Several other urinary biomarkers have been described that also appear to have potential for the detection of renal injury, including interleukin-18 (IL-18), Na^+/H^+ exchanger isoform 3 (NHE3), and neutrophil gelatinase-associated lipocalin (NGAL).⁷⁻⁹

These biomarkers are all promising; however, they are still relatively new, and thus, their roles in the diagnosis and management of ARF have not yet been assessed in large multicenter studies. At present, therefore, clinicians continue to rely on serum creatinine levels, plasma urea levels, and urine output as the three clinical pil-

lars of the diagnosis of ARF. They accept and understand the inaccuracy of these tests because they recognize that in this setting, obtaining absolute values is less important than detecting change and identifying the direction of change.

CLASSIFICATION OF ACUTE RENAL FAILURE

The classification of ARF into clinically useful etiologic categories remains challenging and problematic, for several reasons. First, several of the test results that are time-honored and commonly cited classifiers of ARF—such as a relatively high fractional excretion of sodium (FE_{Na}), a high urinary sodium level, a low specific gravity, the presence of casts, and a relatively low urinary osmolality—have yet to be validated against a widely accepted definition of ARF or a gold-standard test. Second, these test results have not been characterized in blinded, controlled, or standardized studies. Third, classification of ARF on the basis of these test results has not been shown to alter either patient management or outcome. Nevertheless, despite their limitations, these test results are widely used in the literature to classify and define ARF.

Unfortunately, there is no easy solution to the problems associated with classification of ARF. Clearly, more research is necessary before our understanding of ARF reaches the point where more reliable and objective subdivisions can be created (as has been done with pneumonia). The comprehensive process initiated by the ADQI (see above) should facilitate such research.²

These classification difficulties notwithstanding, there does exist a practical and useful approach to stratifying patients presenting with ARF. Traditionally, ARF is classified according to the probable source of renal injury: prerenal, renal (parenchymal), or post-renal (obstructive) [see Table 1].

Prerenal

Prerenal ARF is by far the most common type of ARF. The term prerenal typically indicates that the kidney is malfunctioning

predominantly as a result not of reasons intrinsic to the kidney but of systemic factors, which, through variable mechanisms, can alter renal blood flow (RBF) or intraglomerular hemodynamics and result in a decrease in GFR.

Clinicians frequently use terms such as prerenal azotemia or prerenal ARF to indicate not only that the cause or trigger of ARF is external to the renal parenchyma but also that a given patient has functional loss of GFR (i.e., loss of GFR without structural cell injury) as opposed to structural loss. In cases of suspected structural injury to the kidney, they typically use the term ATN instead. This clinical distinction probably does not reflect a true difference between two separate pathophysiologic states; more likely, these states simply represent two different points on a continuum of renal injury. Furthermore, no biopsy studies of ARF in patients treated in the ICU have been conducted to demonstrate that so-called ATN is the histopathologic basis of prolonged renal dysfunction.¹⁰

Common systemic causes of ARF include a low cardiac output state (e.g., myocardial infarction, tamponade, or valvular disease), cardiac surgery, major vascular surgery, trauma with hypovolemia, shock of any type (anaphylactic, hemorrhagic, or hypovolemic), hemodynamic instability associated with surgery, hepatic failure, increased intra-abdominal pressure, intra-abdominal hypertension, and rhabdomyolysis.^{3,11} The mechanisms by which these events induce ARF vary according to the causative trigger and are poorly understood; however, they are likely to be complex and to involve multiple pathways of renal injury. By far the most significant systemic factors contributing to ARF in developed countries

Table 1 Differential Diagnosis of Acute Renal Failure

Probable Source of Renal Injury	Differential Diagnosis
Prerenal	States of low cardiac output (myocardial, valvular, pericardial, or arrhythmic disease; pulmonary hypertension; pulmonary embolism; mechanical ventilation) States of decreased intravascular volume (dehydration; hemorrhage; burns; GI losses from vomiting, diarrhea, or surgery; renal losses from diuretics, osmotic diuresis, or diabetes insipidus) States of low systemic vasodilation (sepsis or septic shock; anaphylaxis; HRS) States of altered renal hemodynamics (from antiprostaglandin agents, ACE inhibitors, or exogenous vasopressors)
Renal (parenchymal)	Glomerulonephritis or vasculitis Renovascular disease (renal artery or vein occlusion; malignant hypertension) Exposure to toxins, either endogenous (myoglobin; hemoglobin; uric acid) or exogenous (radiocontrast media; antimicrobials; chemotherapeutic agents; immunosuppressive agents; ethylene glycol) Interstitial nephritis (from antimicrobials, diuretics, malignancy, or infection) Tubular deposition or obstruction (from bilateral cortical necrosis, multiple myeloma, or amyloidosis) Renal allograft rejection Trauma
Postrenal (obstructive)	Obstruction of ureter (from compression or kinking of ureters or pelvic/iceal area, calculi, malignancy, or external compression [e.g., retroperitoneal fibrosis]) Obstruction of bladder (from prostatic hypertrophy, calculi, malignancy, blood clot, or neurogenic bladder) Obstruction of urethra (from stricture, phimosis, or trauma)

ACE—angiotensin-converting enzyme HRS—hepatorenal syndrome

Table 2 Drugs Capable of Precipitating Acute Renal Failure

Radiocontrast media	ACE inhibitors
Aminoglycosides	Methotrexate
β-Lactam antibiotics	Cisplatin
Trimethoprim-sulfamethoxazole	Cyclosporine
Amphotericin	FK-506 (tacrolimus)
NSAIDs	

ACE—angiotensin-converting enzyme NSAIDs—nonsteroidal anti-inflammatory drugs

(especially in critically ill patients) are sepsis and septic shock, which account for more than 50% of all cases of ARF.¹²⁻¹⁴

If the systemic cause of prerenal ARF is rapidly removed or corrected, renal function usually improves, returning to near-normal or baseline levels over a period of days. If intervention is delayed or unsuccessful, however, renal injury can become established, and RRT may have to be initiated. In these circumstances, if the patient survives, it frequently takes several days or weeks to achieve renal recovery with independence from RRT.^{13,15-17}

Parenchymal

Parenchymal ARF is generally less common than prerenal ARF. The term parenchymal ARF is used to define a syndrome in which the principal source of damage is within the kidney and in which typical structural changes can be seen on microscopy. This syndrome can result from any of a number of disorders that affect the microvasculature, the glomerulus, the tubules, or the interstitium [see Table 1].

Nephrotoxic drugs are a particularly important cause of parenchymal ARF, especially in hospitalized patients.^{3,11} Many patients with drug-induced ARF show rapid improvement once the offending agent is removed. The drugs most commonly implicated in the development of ARF are aminoglycosides, penicillin or penicillin derivatives, nonsteroidal anti-inflammatory drugs (NSAIDs), trimethoprim-sulfamethoxazole, amphotericin B, cyclosporine, chemotherapeutic agents, and angiotensin-converting enzyme (ACE) inhibitors [see Table 2].¹¹ Not uncommonly, patients may be receiving several potentially nephrotoxic drugs concurrently. Accordingly, in all patients with ARF, a thorough history of drug administration is mandatory.

Other conditions that can cause parenchymal ARF include glomerulonephritis, vasculitis, interstitial nephropathy, malignant hypertension, pelvic/iceal infection, bilateral cortical necrosis, amyloidosis, and trauma.

Postrenal

Obstruction to urine outflow gives rise to postrenal ARF, which is the most common cause of functional renal impairment in the community (i.e., in nonhospitalized patients) and is usually secondary to prostatic hypertrophy. Obstructive ARF is also seen in hospitalized patients, albeit less commonly; typical causes in this population include prostatic hypertrophy, pelvic tumors, retroperitoneal fibrosis, papillary necrosis, and large calculi [see Table 1].

The clinical presentation of obstruction may be acute or acute-on-chronic in patients with long-standing renal calculi; oliguria is not always present. If obstruction is suspected, ultrasonography can be easily performed at the bedside. However, in some cases of acute obstruction, the ultrasonogram is abnormal, and in many cases, the obstruction occurs in conjunction with other renal

insults (e.g., staghorn calculi and severe sepsis of renal origin), so that the renal dysfunction is actually caused by a combination of factors.

Specific Syndromes

Hepatorenal syndrome Hepatorenal syndrome (HRS) is a form of ARF that typically occurs in the setting of advanced cirrhosis but can also occur in the setting of severe liver dysfunction caused by alcoholic hepatitis or in association with other forms of acute hepatic failure.¹⁸

The pathophysiologic hallmark of HRS is profound renal vasoconstriction in the setting of systemic and splanchnic vasodilation. The pathogenesis of HRS is incompletely understood; however, there are several mechanisms that may contribute to its development, including (1) activation of the renin-angiotensin system in response to systemic hypotension; (2) activation of the sympathetic nervous system in response to systemic hypotension and increased intrahepatic sinusoidal pressure; (3) increased release of arginine vasopressin in response to systemic hypotension; and (4) reduced hepatic clearance of various vascular mediators (e.g., endothelin, prostaglandins, and endotoxin).^{18,19}

HRS can occur spontaneously in patients with advanced cirrhosis. Much more frequently, however, it is caused by other precipitating conditions, including sepsis (specifically, spontaneous bacterial peritonitis), paracentesis-induced hypovolemia, elevated intra-abdominal pressure (from tense ascites), GI bleeding, diuretic-induced or lactulose-induced hypovolemia, and various combinations of these. Other contributing factors to ARF should be routinely sought, including cardiomyopathy related to alcoholism, nutritional deficiencies, viral infection, and exposure to nephrotoxins.

Typically, HRS patients have advanced cirrhosis and show evidence of portal hypertension with ascites in the absence of other apparent causes of ARF. They generally are oligoanuric, with progressive increases in serum creatinine or blood urea nitrogen levels and bland urinary sediment. These patients experience profound sodium and water retention, with significant hyponatremia, a urine osmolality higher than the plasma osmolality, and a very low urinary sodium concentration (< 10 mEq/L).

Rhabdomyolysis-associated ARF Rhabdomyolysis-induced ARF is estimated to occur in about 1% of hospitalized patients; however, it may account for close to 5% to 7% of cases of ARF in critically ill patients, depending on the setting.^{11,14,20} The pathogenesis of this condition involves the interplay of prerenal, parenchymal, and postrenal factors, including concurrent hypovolemia, renal ischemia, direct tubular toxicity mediated by the heme pigment in myoglobin, and intratubular obstruction.^{21,22}

The causes of muscle injury that can result in rhabdomyolysis include major trauma or compression, a drug overdose, vascular embolism, prolonged seizures, malignant hyperthermia, neuroleptic malignant syndrome, various infections (e.g., pyomyositis, necrotizing fasciitis, influenza, and HIV infection), severe exertion, alcoholism, and certain drug interactions (e.g., the combination of a macrolide antibiotic or cyclosporine with a statin).

Clinically, rhabdomyolysis is variably manifested by an elevated serum creatine kinase level, pigmented granular urinary casts, and a red-to-brown color in the urine. Various electrolyte disorders may also develop as a result of muscle breakdown, including hyperphosphatemia, hyperkalemia, hypocalcemia, and hyperuricemia.

Contrast-induced nephropathy Contrast-induced nephropathy (CIN) is currently the third most frequent cause of ARF in hospitalized patients, and its incidence is likely to increase further

with the broader utilization of radiocontrast media for diagnostic and interventional procedures.^{3,11} CIN results in prolonged hospitalization, higher mortality, excessive health care costs, and, possibly, long-term kidney impairment.²³⁻²⁵ In addition, CIN (or concerns regarding the risk of CIN) may result in delay or cancellation of important diagnostic or therapeutic procedures.

Experimental studies suggest that the pathophysiologic basis of CIN is the interplay among direct tubular epithelial cell toxicity, alterations in renal hemodynamics with ensuing ischemia, and concomitant atheroembolic showers of the renovasculature after procedures involving exposure to radiocontrast media.

Several different definitions of CIN appear in the literature. Generally, however, CIN is defined as an acute decline in kidney function occurring after the administration of intravascular radiocontrast media in the absence of other precipitants of renal dysfunction. Although it may seem obvious that CIN is the cause of the renal dysfunction, other important possible causes (e.g., atheroembolic disease, renal ischemia, and other nephrotoxic agents) should be considered before the diagnosis is made.²⁶ For research purposes and for better generalizability of results and outcomes across clinical studies, CIN has traditionally been defined as a 25% or greater (or ≥ 0.5 mg/dl [$44 \mu\text{mol/L}$]) increase in the serum creatinine level from the baseline value.^{27,28}

Patients with CIN typically present with an acute rise in the serum creatinine level within 24 to 48 hours after injection of a radiocontrast agent. Oliguria is usually absent, and FE_{Na} may be low initially.²⁹ Urine studies may reveal granular brown casts, tubular epithelial cells, and minimal proteinuria (< 300 mg/day). The presentation may vary, however. In some cases, there is no significant increase in the serum creatinine level, but urinalysis yields abnormal results or markers of renal tubular injury are present. In other cases, there is a clear increase in the serum creatinine level, but results of urinalysis are bland and nondiagnostic. As a rule, the serum creatinine level peaks within 3 to 5 days after radiocontrast injection and returns to baseline within 7 to 10 days. In some patients, however, kidney function does not return to baseline, and a degree of renal impairment persists.

Although transient declines in renal function have been reported after administration of radiocontrast media in almost all patients, clinically important declines are exceedingly uncommon in patients with normal baseline kidney function. In general, clinically important declines in renal function are associated with the presence of preexisting risk factors. In several epidemiologic studies, multivariate analyses suggested that the presence of preexisting chronic kidney disease ($\text{GFR} < 60$ ml/min/1.73 m²), a diagnosis of diabetes mellitus, the administration of a substantial quantity of radiocontrast media, the presence of hypotension or hypertension, increased age, anemia, a recent acute myocardial infarction, a history of congestive heart failure, the use of an intra-aortic balloon pump, and the presence of shock were independently associated with a risk of the development of CIN.³⁰⁻³⁴

Clinical Evaluation

In all patients presenting with renal failure, it is important to determine whether the reduction in kidney function is truly acute or whether chronic kidney disease was already present. In this context, it is worth noting that more than one third of patients in whom ARF develops have some degree of preexisting chronic kidney disease with chronic parenchymal changes (e.g., as a result of aging, long-standing hypertension, diabetes, or atheromatous disease of the renal vessels). Such patients may also have preexisting elevations of the serum creatinine concentration; however, this is

Table 3 Laboratory Tests Used to Help Diagnose Established Acute Renal Failure

Test	Result in Prerenal ARF	Result in Established ARF
Urine sediment	Normal	Epithelial casts
Specific gravity	> 1.020	< 1.020
U _{Na}	< 10 mEq/L	> 20 mEq/L
FE _{Na}	< 1%	> 1%
Urinary osmolality	> 500 mOsm/kg H ₂ O	< 300 mOsm/kg H ₂ O
U _{Cr} /P _{Cr} ratio	> 40	< 10
Plasma urea/creatinine ratio	High	Normal

ARF—acute renal failure FE_{Na}—fractional excretion of sodium P_{Cr}—plasma creatinine concentration U_{Cr}—urinary creatinine concentration U_{Na}—urinary sodium concentration

not always the case. Often, an insult that would be considered relatively trivial and incapable of fully explaining the onset of ARF in a normal patient is in fact sufficient to unmask a lack of renal functional reserve in another patient.

In general, diagnosis and management of ARF should always be based on four principles: (1) confirmation of the probable cause, (2) elimination of potential contributing factors, (3) institution of disease-specific therapy if appropriate, and (4) prevention and management of the complications of ARF.

In most cases, important clues to the cause of ARF in a given patient and an accurate working diagnosis can be obtained from a careful review of the medical record (with particular attention to medications administered, exposure to potential nephrotoxins, and recent events in the hospital, including any operative or other procedures undergone), in conjunction with physical examination and selected radiologic and laboratory investigations [see Investigative Studies, *below*]. In these cases, one can proceed to a therapeutic trial without having to resort to renal biopsy.

An important caveat in the workup of a patient with ARF is that one should not assume that ARF can always be correctly or simply attributed to a single mechanism. As an example, patients with postrenal obstruction frequently have some degree of sepsis, often are hypotensive, and sometimes are hypovolemic and underresuscitated. As another example, patients with crescentic glomerulonephritis are often systemically unwell and may have pulmonary disease with hypoxemia or hypotension (from volume depletion caused by inadequate oral intake or from the vasodilatory effect of inflammation). The possibility that several mechanisms can contribute to ARF in a single patient underscores the importance of careful clinical assessment in the approach to the patient with ARF of recent onset.

ARF patients frequently are critically ill and require admission to an ICU. Such patients often have sustained a major systemic insult. Upon transfer and admission to the ICU, fluid resuscitation either is well under way or has already been completed. Despite such efforts, patients often are profoundly oliguric or anuric, with a rising serum creatinine level and developing metabolic acidosis. Potassium and phosphate levels may be rising as well. Concomitant multiple organ dysfunction (signaled by the need for mechanical ventilation and vasoactive drugs) is common in ARF patients. Fluid resuscitation is typically continued or reinstituted under the guidance of invasive hemodynamic monitoring. Vasoactive drugs

are often used to restore mean arterial pressure (MAP) to acceptable levels (typically, 70 to 75 mm Hg or higher). Improvement may be noted over time, and urine output may return, with or without the assistance of diuretic agents. If urine output does not return, however, early implementation of RRT should be considered. If the cause of ARF has been removed or resolved and the patient has become physiologically stable, renal recovery may occur slowly, over a period as short as 4 to 5 days or as long as 3 or 4 weeks. In some cases, even after renal recovery occurs, urine output continues to be higher than normal for several days. If the cause of ARF has not been adequately remedied, the patient remains gravely ill, the kidneys do not recover, and death from multiple organ dysfunction syndrome (MODS) commonly ensues.

Investigative Studies

As noted (see above), it is vital to identify the underlying condition or conditions responsible for ARF. The diagnosis may be obvious from the results of the clinical assessment; however, in many patients, it is best to consider all possibilities and to exclude common treatable causes by performing some simple investigative studies.

LABORATORY TESTS

A key study is microscopic examination of the urinary sediment. Urinalysis is an essential and simple noninvasive test that can yield important diagnostic information and highlight patterns suggestive of specific syndromes. For example, the finding of dysmorphic red blood cells (RBCs) or RBC casts is virtually diagnostic of active glomerulonephritis or vasculitis. Similarly, the finding of heavy proteinuria suggests some form of glomerular disease. The finding of white blood cell (WBC) casts can suggest either interstitial nephropathy or infection. A urinalysis that yields no abnormal findings can also provide important diagnostic information, suggesting that ARF is prerenal or obstructive. Finally, examination of the urine helps the clinician determine whether a urinary tract infection is present.

Several measures of urine and blood biochemistry have traditionally been used to help clinicians distinguish between prerenal ARF and so-called ATN or established ARF [see Table 3]. One such measure is the FE_{Na}.^{35,36} In the setting of prerenal ARF, filtered sodium is avidly reabsorbed from glomerular filtrate in the renal tubules, resulting in an FE_{Na} lower than 1%, whereas in the setting of renal tubular injury in established ARF, the resulting FE_{Na} is higher than 1%. However, the diagnostic utility of FE_{Na} has been questioned, and several reports have concluded that FE_{Na} must be interpreted with caution.^{37,38} For example, FE_{Na} is often higher than 1% in patients who have received diuretic therapy, regardless of the effective circulating volume (ECV).^{39,40} Furthermore, FE_{Na} may be lower than 1% in patients with conditions associated with parenchymal ARF (e.g., sepsis, rhabdomyolysis, and exposure to radiocontrast media), perhaps reflecting non-homogeneous injury to the renal parenchyma and preservation of tubular function in some regions.⁴¹⁻⁴³

Overall, the clinical utility of these tests in hospitalized and critically ill patients who receive fluids in massive amounts, loop diuretics, or vasopressors is untested and questionable. Furthermore, it is important to keep in mind that, as noted [see Classification of Renal Failure, *above*], prerenal ARF and established ARF are part of a continuum of disease and that separating the two conditions, though conceptually valid, is of only limited clinical relevance. In general terms, therapy is the same for prerenal ARF as for established ARF: one treats the underlying cause while

promptly resuscitating the patient, using hemodynamic monitoring to guide therapy.

In certain circumstances, other laboratory investigations may be necessary to establish the diagnosis. Marked anemia in the absence of blood loss may suggest acute hemolysis, thrombotic microangiopathy, or paraproteinemia related to malignancy. If thrombotic-thrombocytopenic purpura or another cause of microangiopathic hemolytic anemia is suspected, a peripheral blood smear should be obtained and examined for evidence of hemolysis or schistocytes, and levels of lactic dehydrogenase, haptoglobin, unconjugated bilirubin, and free hemoglobin should be measured. If paraproteinemia from multiple myeloma or lymphoma is suspected, serum and urine protein electrophoresis should be done and the serum calcium concentration measured. A history of cancer or chemotherapy should prompt measurement of uric acid to detect possible tumor lysis syndrome.

In patients with a potential mechanism of muscle injury, creatine kinase and free myoglobin levels should be determined. If an elevated-anion gap metabolic acidosis is present and there is evidence that a toxin may have been ingested, ethylene glycol or methanol levels should be measured.

Systemic eosinophilia suggests the possibility of systemic vasculitis, allergic interstitial nephritis, or atheroembolic disease. Measurements of levels of specific antibodies (e.g., anti-glomerular basement membrane [GBM] antibodies, antineutrophil cytoplasmic antibodies [ANCA], antinuclear antibodies [ANAs], anti-DNA antibodies, or anti-smooth muscle antibodies) or cryoglobulins are extremely useful screening tests to support the diagnosis of vasculitis, certain types of collagen vascular diseases, or glomerulonephritis.

IMAGING

Renal ultrasonography is a rapid, noninvasive imaging modality that is designed primarily to look for evidence of obstruction, stones, cysts, masses, or overt renovascular disease. Doppler ultrasonography or magnetic resonance imaging can be useful in screening for renovascular occlusion. A chest x-ray may be indicated, either to assess possible pulmonary complications of ARF or to help confirm or rule out a diagnosis of systemic vasculitis.

BIOPSY

On rare occasions, percutaneous renal biopsy is necessary to confirm the diagnosis, determine the severity of renal injury, guide therapy, and estimate the potential for renal recovery.^{44,45} Renal biopsy is indicated when a thorough noninvasive investigation has failed to yield the diagnosis, after prerenal and postrenal causes have been excluded, and before aggressive immunosuppressive therapy is initiated. The biopsy is generally performed under ultrasonographic guidance, using local anesthesia. As a rule, the risk associated with performing a renal biopsy in a critically ill patient undergoing mechanical ventilation is comparable to that associated with performing a biopsy under standard conditions.⁴⁶

Prevention

GENERAL MEASURES

The fundamental principle of ARF prevention is to eliminate and treat precipitating causes of renal dysfunction. If prerenal factors are contributing to the problem, they must be identified, and hemodynamic resuscitation must be quickly instituted. Intravascular volume must be maintained or rapidly restored; this is often best done with the help of invasive hemodynamic monitoring. Oxygenation must be maintained. An adequate hemoglobin con-

centration (≥ 8 g/dl) must be maintained or immediately restored during the acute phase of resuscitation. Some patients remain hypotensive (MAP < 75 mm Hg) even after intravascular volume has been restored. In these patients, autoregulation of RBF may be impaired or lost. Restoration of MAP to near-normal levels is likely to improve RBF and increase GFR. Such restoration requires the administration of vasopressor drugs. In patients with hypertension or renovascular disease, a MAP of 75 to 80 mm Hg may still be inadequate.

Despite these measures, progressive ARF may still develop in patients whose cardiac output is inadequate. To improve cardiac output may require a variety of interventions, such as the addition of inotropic drugs or the application of ventricular assist devices. Whether additional fluid therapy in a patient with normal or increased cardiac output and adequate blood pressure provides any significant renal protection is questionable; such therapy may in fact contribute to excess accumulation of extravascular fluid, resulting in pulmonary edema.

Once hemodynamic resuscitation has been accomplished and nephrotoxins removed, it is unclear whether additional pharmacologic measures provide any further benefit to the kidneys. So-called renal-dose (or low-dose) dopamine therapy is still frequently used. There is little evidence that this regimen is effective in critically ill patients⁴⁷⁻⁴⁹; however, dopamine is a tubular diuretic that occasionally increases urine output,⁵⁰ and the increased output may be incorrectly interpreted as an increase in GFR.⁵¹ A large phase III trial that examined the use of low-dose dopamine in critically ill patients showed it to be no better than placebo for prevention of renal dysfunction.⁵² In patients with low cardiac output, however, higher-dose dopamine may increase cardiac output, RBF, and GFR (as might dobutamine or milrinone).

Fenoldopam is a selective D_1 dopamine receptor agonist with no affinity for adrenergic D_2 , α , or β receptors. It has been shown to reduce systemic vascular resistance while increasing RBF through reversal of the vasoconstrictive effects of angiotensin II and endothelin.⁵³ Fenoldopam improves both renal cortical and renal medullary blood flow and decreases sodium reabsorption in the proximal tubule.⁵⁴ In a randomized, controlled trial of prophylactic continuous infusion of fenoldopam in critically ill patients with sepsis, this measure led to a reduction in the incidence of ARF; however, it had no impact on the need for RRT or on mortality.⁵⁵ At present, the clinical implications of this study are uncertain; a clearer understanding of the role of fenoldopam prophylaxis will have to await the results of a larger clinical trial.

There is a biologic rationale for the use of mannitol in this setting, as there is for the use of dopamine. Whereas animal experiments have yielded some encouraging findings, there are as yet no data from controlled human studies to support the clinical application of mannitol.⁵⁶ The value of mannitol as a renal-protective agent remains questionable.

Loop diuretics may protect the loop of Henle from ischemia by reducing its transport-related workload through inhibition of the $Na^+/K^+/2 Cl^-$ pump.⁵⁷ The results of animal studies have been encouraging, as have those of ex vivo experiments.⁵⁸ To date, however, no double-blind, randomized, controlled studies of suitable size have definitively shown that these agents reduce the incidence of ARF in humans.⁵⁹⁻⁶² A few studies, however, have suggested that loop diuretics can induce polyuria, which may translate into prevention or easier control of volume overload, metabolic acidosis, and hyperkalemia—the three major triggers of RRT.^{59,60} When RRT can be avoided, treatment is simpler and less costly. Thus, loop diuretics may be useful for the purposes of prophylaxis, especially if given via continuous infusion.^{63,64}

Other agents, such as adenosine antagonists (e.g., theophylline) and atrial natriuretic peptides (e.g., urodilatin and anaritide), have also been suggested for prevention of ARF.⁶⁵⁻⁶⁸ In a randomized, controlled trial that included 504 critically ill patients with ARF, administration of atrial natriuretic peptide did not yield any overall improvement in dialysis-free survival.⁶⁶ Subgroup analysis suggested that this measure was of some benefit in patients with oliguric ARF; however, a follow-up study of 222 critically ill patients with oliguric ARF found no differences in dialysis-free survival or overall mortality between those who received atrial natriuretic peptide and those who received placebo.⁶⁷

SPECIFIC SYNDROMES

Rhabdomyolysis-Associated ARF

The principles of prevention of rhabdomyolysis-associated ARF are based primarily on animal studies, retrospective data, small case series, and multivariate logistic regression analyses; to date, no randomized, controlled trials have been conducted. These principles include (1) identification and elimination of potential causative agents or correction of underlying compartment syndromes; (2) prompt and aggressive fluid resuscitation to restore vascular volume and maintenance of polyuria (> 300 ml/hr) to flush obstructing cellular casts (if present); and (3) alkalization of the urine (to a pH > 6.5) to reduce renal toxicity from myoglobin-induced lipid peroxidation and improve the solubility of myoglobin.²² Experimental studies suggest that mannitol may act as a scavenger of free radicals and thereby reduce cellular toxicity; however, the role of forced diuresis with mannitol remains controversial.

Contrast-Induced Nephropathy

Measures aimed at preventing CIN have been studied in several randomized trials; to date, however, few prophylactic or therapeutic interventions have conclusively been shown to reduce the incidence of CIN, and no therapeutic intervention has been found to be efficacious once CIN is established. The most prudent method of preventing CIN is to identify patients with risk factors before radiocontrast media are administered, then to consider either delaying the diagnostic or interventional procedure until kidney function can be optimized or switching to an alternative imaging modality. At the same time, every effort should be made to identify and correct underlying volume depletion and discontinue potential nephrotoxins. If the procedure is performed, the volume of radiocontrast media employed should be kept to a minimum.

The adoption of periprocedural hydration protocols and the use of nonionic iso-osmolar radiocontrast media (e.g., iodixanol) have reduced the incidence and severity of radiocontrast-associated renal injury.⁶⁹⁻⁷² In the first few years of the 21st century, randomized trials assessed the efficacy of *N*-acetylcysteine for the prevention of CIN, with highly variable results.⁷³⁻⁸² These results were further analyzed in several meta-analyses, which concluded that there appears to be a potential reduction in renal injury with *N*-acetylcysteine (though this conclusion remains controversial).⁸³⁻⁸⁷ It is reasonable to use *N*-acetylcysteine for prevention of CIN in routine care, in view of its relative ease of use, its low cost, and its good safety profile, especially in patients at high risk for CIN. There is also some evidence to suggest that adenosine antagonists may confer some protection against CIN; however, further evidence is required to confirm that the benefit is real.^{88,89}

Management

The fundamental principles of the management of ARF are (1) to identify, treat, and remove any precipitating factors and (2) to maintain physiologic homeostasis while renal recovery takes place.

PREVENTION OR TREATMENT OF COMPLICATIONS

Complications of ARF such as encephalopathy, pericarditis, severe electrolyte disturbances (e.g., hyperkalemia), serious metabolic disturbances (e.g., severe metabolic acidosis), myopathy, neuropathy, or major fluid derangements should never be permitted to occur in a modern hospital setting. Prevention of these complications may entail several different measures, which may vary in complexity from fluid restriction to the initiation of extracorporeal RRT.

Extracellular fluid expansion is a common complication in patients with ARF, particularly in those who have a diminished capacity for sodium and water excretion as a consequence of oliguria. Accumulation of extracellular fluid is manifested by weight gain, dependent interstitial edema, elevated central venous pressure, pleural effusion and ascites, and pulmonary interstitial and alveolar edema. Extracellular fluid overload can be further exacerbated in patients who require large volumes of parenteral medications or nutritional formulas. If a patient is nonoliguric, fluid overload can generally be prevented through judicious use of loop diuretics. If a patient is oliguric, however, the only way of averting dangerous fluid overload is to institute RRT at an early stage.

Marked azotemia (urea concentration > 112 mg/dl [40 mmol/L] or serum creatinine concentration > 4.5 mg/dl [400 μ mol/L]) is undesirable and should probably be treated with RRT unless (1) recovery is imminent or already under way and (2) a return toward baseline or normal values is expected within 24 hours. It should be recognized, however, that to date, no randomized, controlled trials have defined the ideal time at which intervention with artificial renal support should be initiated.

Hyperkalemia (potassium concentration > 6 mEq/L) is another frequent complication of ARF. Obviously, patients with ARF and oliguria should never receive any potassium-containing solution, either orally or via continuous infusion. Spurious hyperkalemia secondary to hemolysis, thrombocytosis, and a very high WBC count may occur and must be excluded. Genuine hyperkalemia must be promptly treated to prevent the development of a life-threatening cardiac dysrhythmia. Patients should receive insulin with dextrose, bicarbonate (if acidosis is present), nebulized salbutamol, or all three together. If the serum potassium level exceeds 7 mEq/L or there are electrocardiographic signs of hyperkalemia, calcium gluconate (10 ml of a 10% solution I.V.) should also be immediately administered. These measures are temporizing actions only; urgent RRT should be arranged.

Metabolic acidosis is almost always present as a consequence of reduced excretion of nonvolatile acids produced through metabolism of dietary protein. In itself, the metabolic acidosis is rarely severe enough to necessitate treatment, but it can be greatly exacerbated by a host of concomitant processes when the kidney's capacity for generation of bicarbonate is diminished. Increased endogenous production of acid can occur in all types of shock, with elevated lactate production, severe sepsis, diabetic or starvation ketoacidosis, and liver disease. In addition, various exogenous sources can worsen metabolic acidosis, including toxins (e.g., ethylene glycol and salicylates) and solutions containing large amounts of chloride. When refractory severe metabolic acidosis (pH < 7.1) is present, early initiation of RRT should be considered.

ARF can also result in the development of anemia via any of several mechanisms, including bleeding, hemodilution, hemolysis, decreased RBC lifespan, and reduced erythropoiesis. One large randomized study suggested that a restrictive transfusion protocol for correction of hemoglobin levels higher than 7 g/dl in critically ill patients with anemia is adequate.⁹⁰ However, more liberal and aggressive transfusion may be necessary, depending on the results of individual patient assessments.

Nutritional support must be started early and must contain an adequate amount of calories (30 to 35 kcal/kg/day) in a mixture of carbohydrates and lipids. Sufficient protein (about 1 to 2 g/kg/day) must be administered. There is no evidence that specific renal nutritional solutions are useful. Vitamins and trace elements should be administered in amounts that at least match the recommended dietary allowance. The role of the newer immunonutritional solutions remains controversial. The enteral route is generally preferred to the parenteral route.

All drug regimens must be adjusted to take into account the effect of the decreased clearances associated with impaired renal function. Finally, assiduous attention should be paid to the prevention of infection.

MANAGEMENT OF HEPATORENAL SYNDROME

Management of HRS remains challenging. In general, it should include systematic identification and prompt treatment of any potentially reversible precipitating factors (especially infections and volume depletion). Prevention of hypovolemia by administering albumin to patients with spontaneous bacterial peritonitis has been shown to decrease the incidence of HRS and improve outcome.⁹¹

One small nonrandomized study found that treating HRS patients with a combination of midodrine and octreotide resulted in improved kidney function and outcome.⁹² Another small uncontrolled study suggested that I.V. *N*-acetylcysteine might improve GFR in patients with HRS through reductions in splanchnic vasodilatation achieved by decreasing the formation of nitric oxide and oxygen free radicals.⁹³

There is some evidence to suggest that vasopressin derivatives (ornipressin and terlipressin) may improve GFR in patients with HRS. In a small uncontrolled trial, administration of ornipressin, in conjunction with volume expansion, reduced plasma renin and norepinephrine levels and improved RBF, GFR, and urinary sodium excretion.⁹⁴ In other small studies, the combination of terlipressin and volume expansion led to similar improvements in systemic hemodynamics and kidney function, with a suggestion of improved short-term outcome.^{95,96} At present, however, the precise role of these agents in the management of HRS remains unclear.

Transjugular intrahepatic portosystemic shunting (TIPS) [*see 5:10 Portal Hypertension*] has been associated with modest improvements in kidney function in HRS patients, may improve outcome, and thus may be an option for patients who are not candidates for transplantation or are awaiting transplantation.⁹⁷⁻⁹⁹ In general, however, the ideal solution for reversal of ARF in HRS patients is to improve hepatic function by treating the underlying primary liver disease, to refer patients for orthotopic liver transplantation, or both.

RENAL REPLACEMENT THERAPY

When ARF is severe, resolution can take days to weeks. In these situations, extracorporeal techniques of blood purification often must be applied to prevent complications [*see Prevention or Treatment of Complications, above*]. Such techniques, collectively referred to as renal replacement therapy, include continuous renal replacement therapy (CRRT), intermittent hemo-

Table 4 Modern Criteria for Initiation of Renal Replacement Therapy*

Anuria (no urine output for ≥ 6 hr)
Oliguria (urine output < 200 ml/12 hr)
Serum urea concentration > 28 mmol/L or BUN > 80 mg/dl
Serum creatinine concentration > 3 mg/dl (265 μ mol/L)
Serum potassium concentration ≥ 6.5 mEq/L or rapidly rising
Pulmonary edema unresponsive to diuretics
Uncompensated refractory metabolic acidosis (pH < 7.1)
Any uremic complication (encephalopathy, myopathy, neuropathy, or pericarditis)
Temperature $\geq 40^{\circ}$ C (104° F)
Overdose with a dialyzable toxin (e.g., lithium or salicylates)

* If one criterion is met, RRT should be considered. If two criteria are met simultaneously, RRT is strongly recommended.
BUN—blood urea nitrogen

dialysis (IHD), and peritoneal dialysis (PD). The basis of all of these RRT techniques is the removal of unwanted solutes and water through a semipermeable membrane. Such a membrane may be either biologic (i.e., the peritoneum) or artificial (i.e., hemodialysis or hemofiltration membranes); each type has its advantages, disadvantages, and limitations.

In general, RRT for ARF should be initiated early, before complications develop. The commonly expressed concerns regarding early RRT stem from the adverse effects of conventional IHD with cuprophane membranes (in particular, hemodynamic instability) and from the risks and limitations associated with CRRT or PD. In the past few years, however, improved use of CRRT and the development of new hybrid techniques adapted from conventional IHD (e.g., sustained low-efficiency dialysis [SLED] and extended daily dialysis [EDD]) have reduced the incidence of these adverse effects.¹⁰⁰⁻¹⁰²

The criteria governing the initiation of RRT in patients with chronic renal failure may be inappropriate for patients with ARF, particularly if they are critically ill. Accordingly, a set of modern criteria for the initiation of RRT has been developed [*see Table 4*].

With either CRRT or IHD, the available data are insufficient to establish precisely what constitutes adequate intensity of dialysis; however, there is some evidence that a higher prescribed dose of RRT may improve survival.^{103,104} At a minimum, RRT should be of sufficient intensity to maintain homeostasis at all levels. An appropriate target urea level is 42 to 70 mg/dl (15 to 25 mmol/L), with a protein intake of about 1.5 g/kg/day. This target level can easily be achieved by using CRRT at urea clearances of 30 to 40 L/day (depending on patient size and catabolic rate).¹⁰⁴ If IHD is employed, daily treatment and extended treatment become desirable.¹⁰³

There remains considerable controversy regarding which modality of RRT is ideal for reducing mortality and enhancing renal recovery, in particular for patients who are hemodynamically unstable or critically ill. A major reason for the controversy is the difficulty of comparing the results of various small randomized, controlled trials that made use of different techniques.^{13,105-107} Large trials of sufficient statistical power would be hard to conduct and may never be performed. In the absence of such trials, RRT techniques should be judged on the basis of the following criteria: (1) biocompatibility, (2) hemodynamic side effects, (3) uremic control, (4) ability to control fluid status, (5) ability to control acidosis, (6) ability to allow full nutritional support, (7) risk of infection, (8) absence of specific side effects, and (9) cost.

CRRT and SLED may offer many advantages over conventional IHD and PD; however, the necessary technology and expertise are not available everywhere, and practice preferences vary widely from one country to another.¹⁰⁸ Therefore, it will be worthwhile to review certain salient features of CRRT and IHD.

Continuous Renal Replacement Therapy

CRRT was initially performed as an arteriovenous procedure (i.e., continuous arteriovenous hemofiltration [CAVH]), in which blood flow through the hemofilter was driven by the patient's blood pressure. A drawback of this approach was that the cannulation of an artery was associated with a morbidity of 15% to 20%. Accordingly, CRRT is now more commonly performed as a venovenous procedure using double-lumen catheters and peristaltic blood pumps (continuous venovenous hemofiltration [CVVH]), with or without control of the ultrafiltration rate. In a venovenous system, dialysate can also be delivered against the direction of blood flow (a technique known as continuous venovenous hemodiafiltration [CVVHDF]) to achieve either almost pure diffusive clearance or a mixture of diffusive and convective clearance. No matter which CRRT technique is used, the following outcomes are predictable: (1) a high level of biocompatibility, (2) hemodynamic stability, (3) continuous control of fluid balance, (4) control of acid-base status, (5) control of electrolytes (including phosphate and calcium), (6) the ability to provide protein-rich nutrition while achieving uremic control, (7) a minimal risk of infection, and (8) prevention of dangerous swings in intracerebral water balance.

Generally, performance of CRRT is restricted to ICUs and requires that specifically trained nursing and medical staff members be available 24 hours a day. Many small ICUs cannot provide this level of support. If CRRT is only performed five to 10 times a year, the cost of training may not be economically justifiable, and expertise may be hard to maintain. Furthermore, depending on how patient care is organized at a particular institution, CRRT may be more expensive than IHD.¹⁰⁹ In addition, the need for continuous anticoagulation of the extracorporeal circuit during CRRT raises the issues of possible hemorrhage, immune thrombotic thrombocytopenia, and increased transfusion requirements.¹¹⁰⁻¹¹² In view of these concerns, it is essential to consider the risks and benefits of more or less intensive anticoagulation and of alternative strategies.

In the vast majority of patients, low-dose heparin (< 500 IU/hr) is sufficient to achieve an adequate filter lifespan, is relatively easy and cheap to administer, and has almost no effect on coagulation test results. In some patients, a higher dose is necessary. In others (e.g., those with pulmonary embolism or myocardial ischemia), full heparinization may be indicated. Regional citrate anticoagulation is highly effective but somewhat complex, in that it requires a special dialysate or replacement fluid.¹¹³ Regional heparin or protamine anticoagulation is also somewhat complex, but it may be helpful if frequent filter clotting occurs and further anticoagulation of the patient is considered dangerous. Low-molecular-weight heparin (LMWH) is easy to administer but is more expensive than standard heparin.¹¹⁴ The LMWH dose must be adjusted for the loss of renal function, which is difficult to monitor. Heparinoids and prostacyclin may be useful if the patient has heparin-induced thrombocytopenia and thrombosis.¹¹⁵ Finally, in perhaps 10% to 20% of patients, anticoagulation is contraindicated because of endogenous coagulopathy or recent surgery. In such patients, mean filter lives longer than 24 hours can be achieved, provided that blood flow is kept at about 200 ml/min and reliable vascular access is maintained.¹¹⁶

Particular attention must be paid to the adequacy and ease of flow through the double-lumen catheter.¹¹⁷ Smaller (11.5 French)

catheters in the subclavian position pose particular problems; larger (13.5 French) catheters in the femoral position appear to function more reliably.¹¹⁸ The choice of membrane is a matter of some debate. There are several biosynthetic membranes on the market (e.g., those made of AN69, polyamide, polysulfone, or cellulose triacetate) that have excellent biocompatibility. To date, however, no controlled studies have shown any of them to possess a clinical advantage over any of the others.

Intermittent Hemodialysis

In IHD, as in CRRT, vascular access is typically obtained via a double-lumen catheter. Also as in CRRT, the circuit consists of venovenous blood flow driven by a peristaltic pump. As in CVVH, countercurrent dialysate flow is employed; however, standard IHD differs from CVVH in that it uses high dialysate flows (300 to 400 ml/min), generates dialysate by using purified water and concentrate, and is applied for short periods (3 to 4 hours). These differences have important implications. First, volume removal must be completed within a short time, and this process may be poorly tolerated by patients who are hemodynamically unstable or critically ill. There is a high incidence of hypotension in such patients, and repeated hypotensive episodes may contribute to delayed renal recovery.¹¹⁹ Second, solute removal is episodic, resulting in inferior uremic and acid-base control, decreased therapeutic efficacy, and a lower delivered dose of RRT. Suboptimal fluid and uremic control imposes unnecessary limitations on nutritional support. Furthermore, rapid solute shifts increase brain water content and raise intracranial pressure.¹²⁰

The issue of membrane bioincompatibility has given rise to a great deal of controversy. In comparison with high-flux synthetic membranes (also used for CVVH), standard low-flux dialyzing membranes made of cuprophane have been found to trigger the activation of several inflammatory pathways. It is possible that this proinflammatory effect contributes to further renal damage and delays recovery or even affects mortality. The controversy has not yet been resolved.

The limitations of conventional IHD in the setting of ARF led to the development of the new hybrid techniques SLED and EDD,^{100,101} which adapt IHD to specific clinical circumstances so as to make it easier to tolerate and more effective. At present, PD is rarely used in the treatment of adult ARF in developed countries; however, it may be a reasonable option in developing countries or in the treatment of children when alternatives are unavailable or are considered too expensive or invasive.¹⁰⁸

BLOOD PURIFICATION FOR INDICATIONS OTHER THAN ACUTE RENAL FAILURE

There is growing interest in the possibility that blood purification, by removing circulating mediators, may provide a clinically significant benefit for patients who are in a severe septic state.¹²¹⁻¹²³ Various techniques, including plasmapheresis, high-volume hemofiltration, very-high-volume hemofiltration, and coupled plasma filtration adsorption, are currently being assessed in animal studies and in phase I and II human studies.^{124,125} Initial findings suggest that continued exploration of this therapeutic option is worthwhile¹²⁶; however, randomized, controlled trials of sufficient statistical power have not yet been performed. Blood purification technology, in combination with the use of bioreactors containing either human or porcine liver cells, is also under active investigation as a form of artificial liver support for patients with fulminant or acute-on-chronic liver failure.¹²⁷ Some promising results have been reported.

Discussion

Pathogenesis of Acute Renal Failure

The pathogenesis of ARF varies, depending on the primary mechanism and contributing factors underlying the acute decline in kidney function.

For postrenal or obstructive ARF, the pathogenesis typically involves several humoral responses, as well as a host of mechanical factors. As a rule, a single functioning kidney has adequate capacity for clearance of daily nitrogenous waste and maintenance of water and acid-base homeostasis. Therefore, for postrenal ARF to develop, urinary flow must be obstructed in the urethra, in the bladder, or in both ureters (one ureter if the patient has only a single kidney). These mechanical factors can arise from within the genitourinary system (e.g., stones or strictures) or from extrinsic causes (e.g., ureteral compression or kinking) [see Table 1]. When urinary flow is obstructed, glomerular filtration initially continues, gradually elevating the intraluminal pressures proximal to the site of obstruction. Over time, the elevated pressures result in progressive distention and dilation of the proximal ureter, the renal pelvis, and the calyx and directly cause GFR to decline.

The pathogenesis of parenchymal ARF is typically immunologic. It is a complicated process that includes a wide variety of possible causative conditions (including glomerulonephritis, vasculitis, and interstitial nephropathy) and involves an extraordinary array of cell-mediated and humoral mechanisms, discussion of which exceeds the scope of this chapter.

The pathogenesis of prerenal ARF is of greater direct relevance to the surgeon. Traditionally, prerenal ARF is, by definition, the result of a reduction in ECV and a concomitant reduction in renal perfusion. A reduction in ECV is frequently accompanied by a reduction in MAP, which can stimulate several humoral and neural processes by activating arterial and cardiac baroreceptors. Increased activity in these baroreceptors stimulates the sympathetic nervous system and the renin-angiotensin-aldosterone system and triggers the release of arginine vasopressin from the posterior pituitary in an attempt to compensate for any reduction in GFR.

At the level of the kidney, there are several mechanisms that may play a major role in the development of prerenal injury, including (1) ischemia of the outer medulla, (2) activation of the tubuloglomerular feedback system (afferent arteriolar constriction), (3) tubular obstruction from cell casts, (4) interstitial edema secondary to back-diffusion of fluid, (5) inflammatory response to cell injury and local release of mediators, (6) disruption of normal cellular adhesion to the basement membrane, (7) oxygen free radical-induced apoptosis, and (8) phospholipase A₂-induced cell membrane injury. It must be kept in mind, however, that to date, most of these mechanisms have been demonstrated to be operative only in animal models. Because such models bear limited resemblance to the clinical scenarios in which ARF develops in humans, the relevance of these findings to human disease remains highly speculative. Even if these experimentally proven mechanisms are operative in humans, their hierarchy and their time sequence remain unknown, which makes the development of specific therapeutic targets for prevention and management a difficult task.

Epidemiology of Acute Renal Failure

As noted [see General Principles, Definition of Acute Renal Failure, *above*], defining ARF can be problematic. Even so, sever-

al useful observations can be made about the epidemiology of this condition.

First, some degree of acute renal injury (manifested by albuminuria; the loss of small tubular proteins; the inability to excrete a water, sodium, or amino acid load; or any combination of these) can be demonstrated in most ICU patients. The manifestations of renal injury may be seen in patients who are undergoing simple and successful cardiac surgery with cardiopulmonary bypass, as well as in patients who have severe sepsis but a normal serum creatinine concentration. Their significance is unclear, beyond the observation that some of them (e.g., albuminuria) have been associated with increased mortality.

Second, ARF is common in hospitalized patients, affecting between 5% and 8% (depending on the specific population being assessed and the criteria being used to define ARF).^{3,11} In a report from the Madrid ARF Study Group, the overall annual incidence of ARF was 209 cases/million, with ARF defined as either (1) a sudden increase in the serum creatinine concentration to 2.0 mg/dl (177 μ mol/L) or higher in a patient with normal premonitory renal function or (2) a 50% or greater increase in the serum creatinine concentration in a patient with chronic kidney disease.¹²⁸ In several other population-based epidemiologic studies, the annual incidence of ARF ranged from 20 to 187 cases/million (again, depending on the operative definition of ARF used).^{15,129-131} If these general observations are applied to the more economically developed countries, which have a total population of approximately 1 billion people, it may be estimated that about 200,000 cases of ARF occur in this population each year. Unfortunately, little information is available on the incidence of ARF in the less developed countries.

Third, current trends suggest that the incidence of and mortality attributable to ARF may actually be increasing, particularly in critically ill patients, despite advances in the understanding of the pathophysiology of ARF and the development of new and improved methods for its treatment. One explanation for this increase may be that ARF as a manifestation of single-organ dysfunction is becoming less common, whereas MODS with associated ARF is becoming more common.¹³² In a multinational, multicenter study carried out by the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) Investigators, it was estimated that ARF associated with admission to an ICU develops in approximately 6% of critically ill patients worldwide.¹² ARF was severe enough to warrant initiation of RRT in approximately 70% of the patients studied.¹² In other studies, the annual incidence of ARF severe enough to necessitate RRT has been estimated to range from 40 to 130 cases/million.^{12-14,132,133}

Fourth, large epidemiologic studies have identified a number of risk factors for the development of ARF, including greater age, male sex, preexisting illness, severe sepsis or septic shock, major surgery (in particular, cardiac surgery), cardiogenic shock, hypovolemia, and exposure to various nephrotoxic drugs.^{12,13} Smaller cohort studies have shown that ARF is common in the setting of MODS, specifically when there is concomitant acute circulatory, pulmonary, and hepatic organ dysfunction.¹³⁴⁻¹³⁷

Fifth, although the studies cited above suggest that ARF may in part be an expression of overall illness severity, there is evidence that ARF, in and of itself, significantly and independently increases mortality.¹³⁸ The overall hospital mortality for patients with ARF is estimated to be about 20%; however, the hospital mortality for

patients with more severe increasing renal injury (serum creatinine concentration ≥ 3.0 mg/dl [$265 \mu\text{mol/L}$]) ranges from 40% to 60%.^{3,11} There is also evidence that the short- and long-term prognosis is worse for patients who are critically ill and patients who require RRT. In these patients, the hospital mortality is 45% to 60%, and the long-term mortality is 60% to 70%.^{12-14,20,132,138-140}

Sixth, independence from RRT is associated with enhanced overall quality of life and improved functional status and probably has important health economic implications^{133,141}; thus, renal recovery after ARF or an episode of critical illness is an important

outcome to consider. Estimates of dependence on RRT at hospital discharge for survivors of ARF vary, ranging from 5% to 33%.^{12-14,16,20,109,133} Several factors may be associated with a higher likelihood of renal recovery with independence from RRT, including male sex, little or no preexisting comorbid illness, no evidence of preexisting chronic kidney disease, the use of CRRT rather than IHD, and earlier initiation of RRT.¹³ Despite the high overall mortality for survivors of ARF, there is evidence that the majority (70% to 80%) recover renal function and gain independence from RRT within 90 days to 1 year.¹³

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Acknowledgment

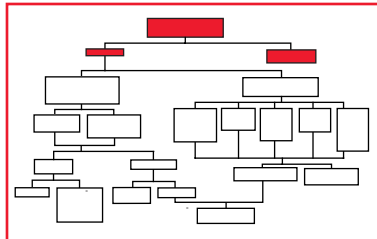
Figure 1 Seward Hung.

Juan R. Sanabria, M.D., M.Sc., F.A.C.S., and Achilles A. Demetriou, M.D., Ph.D., F.A.C.S.

Hepatic failure continues to be a frequent and major cause of morbidity and mortality in critically ill patients. In the past decade, new approaches to hepatic failure have been developed. Advances in critical care, the increasing use of sophisticated diagnostic modalities, and the adoption of a team approach to patient care (with active collaboration among intensivists, hepatologists, anesthesiologists, transplant surgeons, and other specialists) have resulted in improved overall outcomes.

Hepatic failure may be encountered as an instance of primary organ failure caused by a liver-specific disease process or as part of the multiple organ dysfunction syndrome (MODS). Typically, patients with secondary liver failure have no preexisting liver disease: their liver dysfunction is simply a reflection of their overall critical condition, and management usually involves treatment of underlying nonhepatic disorders. In what follows, we outline general management guidelines for primary hepatic failure and its complications.

Evaluation of patients with suspected liver disease is often complex and typically requires extensive patient workup—including a detailed history and physical examination, as well as various diagnostic studies—to establish the diagnosis and confirm the underlying cause of the disease. Common risk factors include a history of alcohol or I.V. drug abuse, previous transfusion of blood or blood products,¹ the use of certain medications, tattoos, sexual promiscuity, and incarceration. Less common risk factors include a family history of liver disease and exposure to various toxins and chemicals.



Liver disease gives rise to several easily recognizable manifestations. Jaundice and encephalopathy are common symptoms. In the early stages of liver disease, increasing fatigue, changes in sleep patterns, loss of short-term memory, inability to concentrate, and reduced libido may be noted. In the later stages, portal hypertension (PHT) is signaled by the development of ascites and upper or lower gastrointestinal bleeding. In addition, hypersplenism and abdominal wall collateral vessels may be detected on physical examination. Changes that occur primarily as a consequence of altered liver metabolism include palmar erythema, spider angiomas, gynecomastia, testicular atrophy, and encephalopathy. Many patients exhibit a degree of protein-calorie malnutrition, with muscle wasting and reduced physical activity.

Initial laboratory evaluation should include a complete blood count, a platelet count, liver function tests, a coagulation profile,

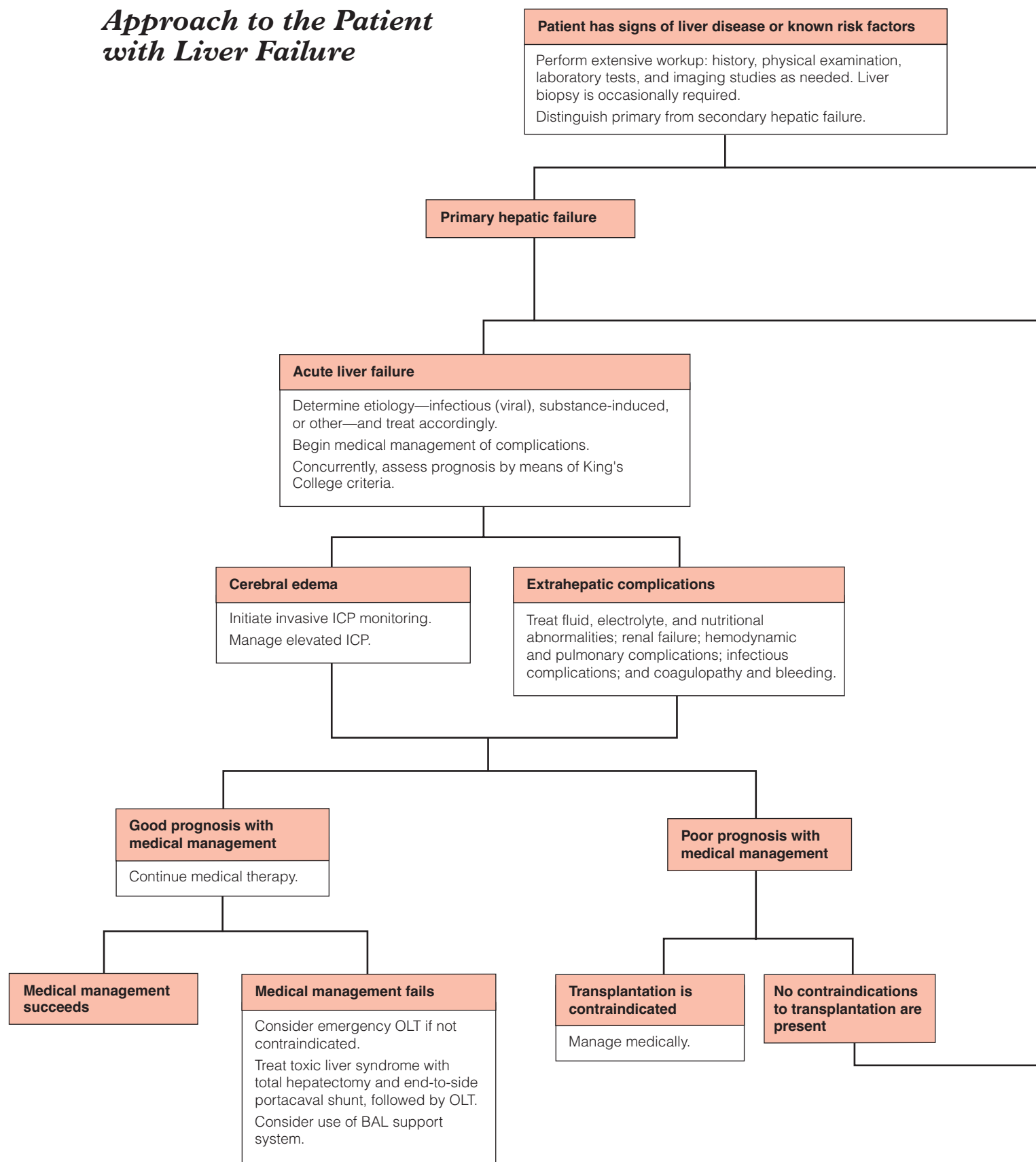
and assessment of renal function. In addition, a toxicology screen should be ordered and a sepsis workup initiated. Detection of one or more drugs in the urine or blood may help establish the diagnosis and direct treatment. Specific tests to detect other conditions (e.g., metabolic or autoimmune disorders) are ordered as needed. Blood and urine cultures are done to look for a concomitant or causative infectious agent; if ascites is present, analysis of the ascitic fluid (including a cell count with differential, Gram staining, and culture) is recommended. Serologic testing for hepatitis viruses and other viruses (e.g., herpesvirus, cytomegalovirus [CMV], and Epstein-Barr virus [EBV]) is indicated. In addition, a chest x-ray must be obtained, and additional imaging studies should be performed as indicated. At times, a liver biopsy is required to establish or confirm the diagnosis of liver disease.

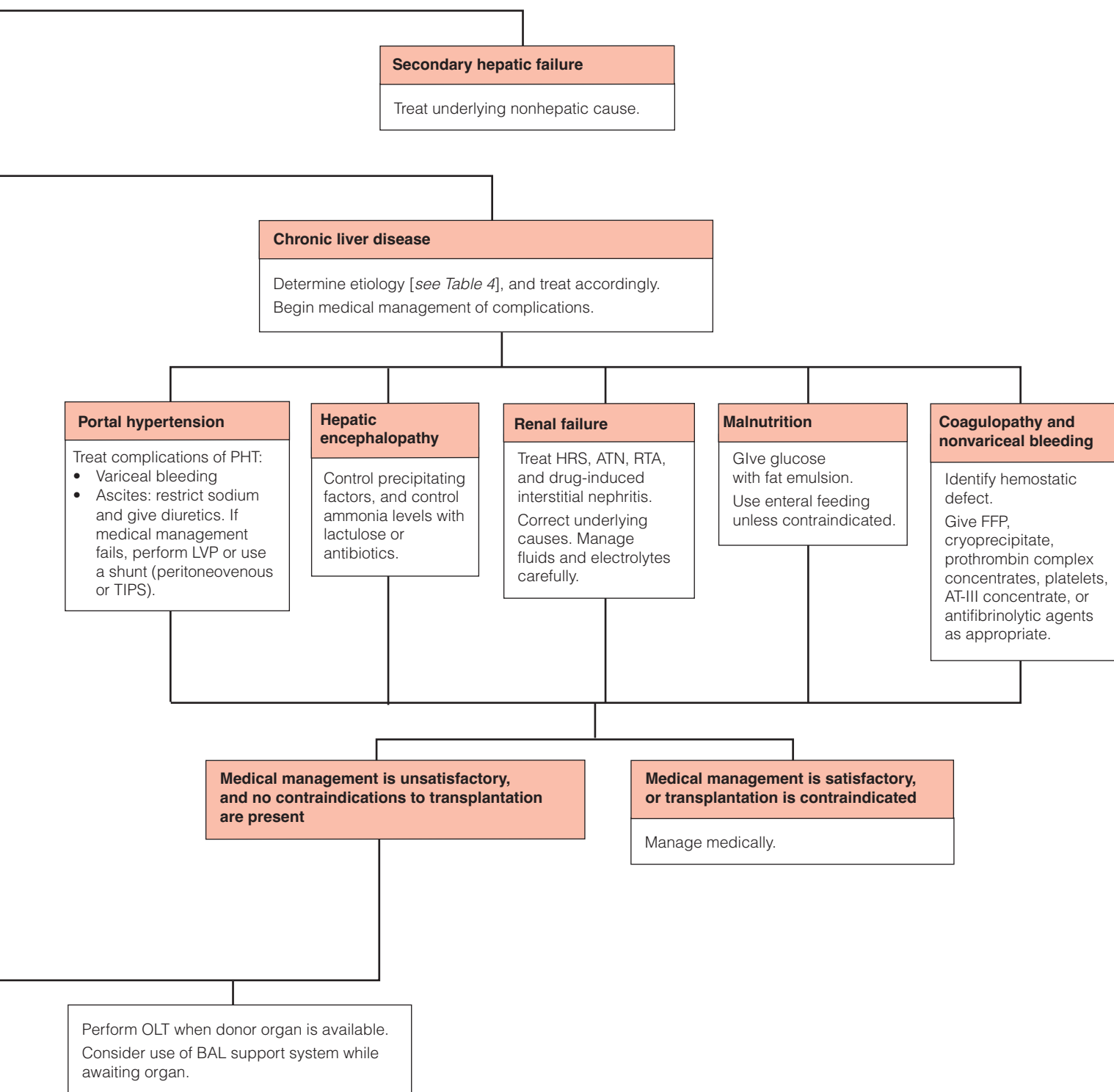
Most patients with primary hepatic failure have a history of pre-existing liver disease and possibly of cirrhosis, generally presenting with one or more complications of chronic liver disease (e.g., GI bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis [SBP], or renal failure). In one subgroup of patients, hepatic failure occurs as a result of an acute exacerbation of preexisting liver disease (e.g., acute reactivation of hepatitis B, acute decompensated Wilson disease, or autoimmune hepatitis). In another subgroup, primary hepatic failure develops acutely in the absence of any preexisting liver disease or known risk factors; this condition is known as fulminant hepatic failure (FHF). These patients present with massive liver necrosis, jaundice, and profound coagulopathy and often go on to experience deep coma and cerebral edema, which may lead to irreversible brain damage and death.

The distinction between an acute liver process and a chronic one is important. Acute liver failure (ALF) may be associated with severe multisystem organ involvement, as in the acute respiratory distress syndrome (ARDS) or MODS. The etiology of ALF includes the use of medications (in particular, acetaminophen), infection (specifically, viral hepatitis), miscellaneous conditions, and indeterminate causes. ALF may also develop after liver transplantation secondary to primary graft nonfunction (PNF) or hepatic artery thrombosis (HAT). It is manifested mainly by encephalopathy, progressive coagulopathy, poor urinary output, and elevated liver enzyme levels. Cerebral edema is uncommon in patients with PNF.

A thorough initial physical examination is important for establishing a baseline for comparison, so that trends toward improvement or deterioration can be detected during clinical evaluations subsequently conducted at 4- to 6-hour intervals. Worsening encephalopathy with rapidly deteriorating mental status is an indication for early endotracheal intubation. Reduced urine output in a euvolemic patient is a sign of impending renal failure. Elevated liver enzyme concentrations and an elevated international normalized ratio (INR) suggest that spontaneous liver recovery is unlikely.

Approach to the Patient with Liver Failure





ly. The development of hypoglycemia is a sign that only a limited amount of functional liver tissue remains. Metabolic acidosis may also reflect lack of functional liver reserve in a euolemic patient setting. In addition, factor V levels and the degree of hepatocyte necrosis observed at liver biopsy may help guide further therapy. Increasing levels of α -fetoprotein (AFP) have been associated with liver regeneration and liver recovery. Finally, the patient's overall medical status (e.g., the presence of severe coronary artery disease or a history of recent myocardial infarction) may determine the final outcome.

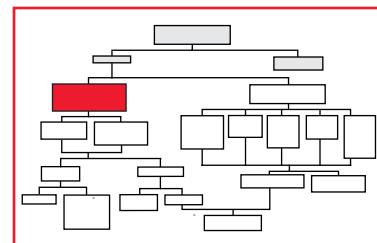
Initial Management

Initial management of a patient with hepatic failure includes the following components:

1. Airway protection. Airway management and maintenance should be established early in the course of the disease to prevent hypoxia with worsening brain edema or bronchial aspiration with pneumonitis, decreased gas exchange, and sepsis. Patients with cerebral edema require hyperventilation to lower the carbon dioxide tension (PCO_2) and reduce cerebral vasodilatation; however, the effect on PCO_2 is transient.
2. Monitoring of serum glucose levels. In patients who have experienced an acute loss of functional liver tissue, the lack of gluconeogenic pathways leads to decreased metabolism of lactic acid. The result is a high-anion gap metabolic acidosis with hypoglycemia, a state that is exaggerated in cases of sepsis with poor tissue perfusion.
3. Monitoring of cerebral perfusion pressure (CPP). The mental status of a patient with ALF should be followed by means of serial neurologic examinations, serial computed tomograms of the brain as indicated, and monitoring of intracranial pressure (ICP) and CPP. The signs detected by physical examination are not reliable, and changes in cerebral CT scans may develop late after the establishment of cerebral edema. Measuring CPP is the most reliable means of monitoring the degree of cerebral edema and can help guide early therapy.
4. Hemodynamic monitoring. Continuous assessment of central venous pressure is desirable in ALF patients to optimize fluid administration. Every effort should be made to establish adequate perfusion pressure without significantly increasing right-side cardiac pressures, diminishing venous return from the brain, and subsequently aggravating cerebral edema. Placement of a pulmonary artery catheter may be indicated in severely ill patients who may be hemodynamically unstable.
5. Correction of coagulopathy. The platelet count and the INR are the main variables monitored for assessment of coagulation. Because ALF patients typically are subjected to multiple interventions, invasive monitoring, and other procedures, fresh frozen plasma (FFP) and platelets are frequently administered.
6. Diagnostic workup. A rapid diagnostic workup is undertaken to allow appropriate disease management. Specific treatment should be instituted promptly to enhance liver recovery (e.g., administration of *N*-acetylcysteine to treat acetaminophen toxicity). It is of particular importance to identify any conditions that may rule out liver transplantation as a therapeutic option; such conditions include active infection, cancer, irreversible brain damage, and MODS. Evaluation of the patient for potential liver transplantation should begin early. To this end, it is important that the liver transplant team take part in the initial assessment and management of ALF patients.

Management of Acute Liver Failure

In the United States, ALF affects 2,300 to 2,800 patients each year.² How liver failure is defined depends largely on the temporal relation between the onset of illness and the



appearance of jaundice, encephalopathy, and coagulopathy. For example, some define FHF as ALF in which the interval between disease onset and the appearance of major symptoms is 8 weeks or less.³ In most cases, however, it is difficult to establish the precise time of onset of the disease process and thus hard to determine precisely how much time elapsed before hepatic failure developed. Recognizing that clinical findings and prognosis vary depending on the interval between the onset of jaundice and the appearance of encephalopathy, some authorities distinguish between FHF and subfulminant hepatic failure (SHF). Bernuau and coworkers defined FHF as an episode of ALF that was complicated by encephalopathy developing within 2 weeks of the onset of jaundice and defined SHF as ALF that was complicated by encephalopathy developing 2 to 12 weeks after the onset of jaundice.⁴ We use the term ALF for cases in which there is no evidence of chronic liver disease and in which liver disease develops within 8 weeks after the initial onset of illness.

CLASSIFICATION

ALF may be classified into three major categories on the basis of the underlying cause of the disease: infectious, substance-induced, and miscellaneous. In two multicenter studies, acetaminophen-induced toxicity was found to be the most common cause (20% and 39%) of ALF, followed by cryptogenic or indeterminate causes (15%).^{5,6}

Infectious (Viral Hepatitis)

Infectious ALF can be caused by several different viruses. Most cases are attributable to hepatitis viruses (types A through G), though herpesviruses (e.g., herpes simplex virus, varicella-zoster virus, CMV, and EBV), coxsackieviruses, echoviruses, adenoviruses, and parvovirus B19 are also capable of causing ALF.

Hepatitis A The incidence of FHF and SHF in patients with hepatitis A virus (HAV) infection is very low ($< 0.01\%$).⁴ The virus is transmitted orally. HAV infection usually occurs in children and typically gives rise to minimal manifestations that resolve uneventfully, resulting in detectable levels of antibodies. About 10% of patients experience a relapse, usually within 2 to 3 months after an initial clinical improvement. Relapse is signaled by increased serum transaminase and bilirubin levels and the reappearance of the virus in the stool. If encephalopathy develops during this period, the prognosis is poor.⁷ The clinical course of the disease tends to be more severe in older patients. Immunoglobulin therapy may reduce infection rates among young family members and HAV-naïve health care workers.

Hepatitis B ALF related to hepatitis B virus (HBV) occurs in fewer than 1% of HBV infections but is the most common form of virus-induced FHF.^{4,5,8} Like HAV infection, HBV infection leads to FHF more often than to SHF. HBV is transmitted by contact with blood or body fluids and by intercourse. Detection of hepatitis B surface antigen (HBsAg) and a quantitative polymerase chain reaction (PCR) for HBV DNA establish the diagnosis. In

some cases of FHF secondary to HBV infection, however, these markers may be absent,⁹ which indicates that in certain FHF patients, an enhanced immune response prevents further HBV replication and results in more rapid clearance of HBsAg. The survival rate is much lower for patients who are HBsAg-positive on presentation (17%) than for patients who are HBsAg-negative (47%).⁴ Clearance of HBsAg and HBV DNA results in better survival, as well as lower recurrence rates after emergency liver transplantation.¹⁰ Protocols based on antiviral therapy with lamivudine and anti-HBV immunoglobulin yield low rates of HBV recurrence after successful liver transplantation.

Hepatitis D Hepatitis D virus (HDV, also referred to as the delta agent) is a defective virus that uses HBsAg as its envelope protein. HDV RNA is detected in only 10% of patients with fulminant hepatitis D.¹¹ HDV infection can be either a coinfection (in conjunction with HBV infection) or a superinfection (in patients with previous HBV infection).¹² In FHF patients, HDV coinfection is more common than HDV superinfection; however, the latter is associated with a higher mortality than the former (72% versus 52%), as well as a stronger predisposition to subsequent chronic liver disease (54% versus 31%).¹³

Hepatitis C and indeterminate hepatitis Previously, FHF of indeterminate etiology was attributed to non-A, non-B viral hepatitis. It is now clear that some such cases are caused by hepatitis C virus (HCV) infection, though the precise extent to which HCV infection contributes to this indeterminate group is unclear. Unlike HAV and HBV infection, HCV infection is more likely to cause SHF than FHF. Despite the availability of advanced serologic testing, there are still many cases of FHF and SHF whose cause cannot be determined.^{14,15} These cases may be attributable to other, more recently described types of hepatitis viruses (e.g., hepatitis E virus [HEV], hepatitis F virus [HFV], and hepatitis G virus [HGV]). ALF caused by HEV infection, though rare in Western countries, is the most common form of FHF in India.¹⁶

Substance-Induced

Drugs Drug toxicity accounts for 35% of all cases of FHF and SHF and usually runs a subfulminant course.⁵ Drug ingestion causes hepatic injury in fewer than 1% of patients, about 20% of whom manifest FHF or SHF. In most cases of drug-induced hepatotoxicity, the degree of the toxicity correlates with the dose ingested and the serum drug level, but in others (e.g., certain cases of valproic acid-induced toxicity), patients manifest an idiosyncratic reaction with massive liver necrosis after exposure to the drug. As a general rule, however, increasing the total drug dose, simultaneously ingesting other drugs that induce or inhibit hepatic enzymes (synergistic toxicity), and continuing drug administration after the onset of liver disease all increase the risk of hepatic failure.⁴

Acetaminophen toxicity is the most common cause of drug-induced hepatic failure. The prognosis for patients with FHF caused by acetaminophen is usually better than that for patients with FHF caused by other drugs (e.g., isoniazid, psychotropic drugs, antihistamines, and nonsteroidal anti-inflammatory drugs).¹⁷ Halothane-induced FHF occurs within 2 weeks after general anesthesia and carries a high mortality.¹⁸

Toxins Most cases of toxin-induced FHF involve mushroom poisoning or exposure to industrial hydrocarbons. In mushroom poisoning, the active agents are heat-stable and are not destroyed

by cooking.¹⁹ Liver damage from mushroom toxins is delayed and is usually preceded by several days of vomiting and diarrhea. Mortality is high: up to 22% in one series. Emergency liver transplantation is sometimes successful.²⁰ Industrial hydrocarbons (e.g., carbon tetrachloride, trichloroethylene) are rare causes of FHF. In developing nations, aflatoxin and herbal medicines have been implicated as causes of FHF.

Acute, severe ethanol intoxication may result in the development of acute alcoholic hepatitis (AAH), a condition associated with high mortality. Treatment with steroids improves survival in AAH patients; other measures are instituted to treat complications and associated conditions (e.g., withdrawal syndrome and malnutrition). Liver transplantation has not been advocated for treatment of acute AAH.

Miscellaneous

ALF may be caused by any of a number of miscellaneous processes, including metabolic, vascular, and autoimmune conditions. The most frequent metabolic cause of ALF is Wilson disease, which may present as FHF or SHF with intravascular hemolysis and renal failure.^{21,22} A family history of hepatic and neurologic disease, the presence of Kayser-Fleischer rings, and low serum ceruloplasmin levels help establish the diagnosis. Acute decompensated Wilson disease carries a high mortality and is an indication for emergency liver transplantation.²³

Acute fatty liver of pregnancy is a rare cause of FHF associated with high mortality for both mother and infant. Delivery of the fetus results in regression of the microvesicular steatosis and improvement in liver function for the mother. The risk of FHF is increased with misdiagnosis and continuation of pregnancy. Liver transplantation has been successfully performed to treat this condition.²⁴

An unusual cause of ALF is the Budd-Chiari syndrome (acute hepatic vein thrombosis). The typical patient is a young woman who presents with right upper quadrant pain of acute onset, hepatomegaly, and ascites. The clinical course is usually benign, and liver enzyme levels normalize promptly. Occasionally, however, the syndrome progresses to FHF. Portal decompression sometimes treats this type of ALF successfully if done before massive hepatic necrosis occurs; once FHF develops, liver transplantation is the only option.

Acute autoimmune hepatitis can cause FHF. It is typically seen in female patients and may occur either with or without known autoimmune disorders. A panel of reactive antibodies confirms the diagnosis. High-dose steroid therapy usually arrests the process, resulting in rapid normalization of liver enzyme levels. In 10% to 20% of cases, urgent liver transplantation is necessary.

Several other conditions and disease processes are also known to cause ALF in both adults and children [see Table 1].

ASSESSMENT OF PROGNOSIS

Several prognostic criteria and indicators have been developed for predicting outcome after optimal medical management of FHF. The two main factors determining likelihood of survival are (1) the extent of liver necrosis and (2) the potential for hepatocyte regeneration. In a 1989 study, investigators at King's College Hospital in London compiled a set of indicators for predicting a poor outcome after medical therapy and hence the need for emergency liver transplantation.²⁵ The underlying cause of FHF was the single most important predictive variable. Accordingly, patients were divided into two groups, one comprising all cases of acetaminophen-induced FHF and the other all cases of FHF from other causes. Age, degree of encephalopathy, serum pH, prothrombin time (PT),

Table 1 Etiology of Acute Liver Failure**Infectious**

Viral: hepatitis A, B, C, D, E, F, and G and hepatitis of indeterminate etiology; infection by herpes simplex virus, cytomegalovirus, Epstein-Barr virus, or adenovirus

Bacterial: Q fever

Parasitic: amebiasis

Drugs**Toxins**

Mushrooms: *Amanita phalloides*, *verna*, and *virosa*; *Lepiota species*

Bacillus cereus

Hydrocarbons: carbon tetrachloride, trichloroethylene, 2-nitropropane, chloroform

Copper

Aflatoxin

Yellow phosphorus

Miscellaneous conditions

Wilson disease

Acute fatty liver of pregnancy

Reye syndrome

Hypoxic liver cell necrosis

Hypothermia or hyperthermia

Budd-Chiari syndrome

Veno-occlusive disease of the liver

Autoimmune hepatitis

Massive malignant infiltration of the liver

Partial hepatectomy

Liver transplantation

Postjejunoileal bypass

Galactosemia

Hereditary fructose intolerance

Tyrosinemia

Erythropoietic protoporphyria

Irradiation

α_1 -Antitrypsin deficiency

Niemann-Pick disease

Neonatal hemochromatosis

Cardiac tamponade

Right ventricular failure

Circulatory shock

Tuberculosis

time of onset of encephalopathy, and admission serum creatinine and bilirubin levels also proved to be significant variables [see Table 2]. Patients who met the criteria in either group had a 95% chance of dying with medical therapy alone and were identified as candidates for emergency liver transplantation. The major strength of the King's College study is that it based patient assessment on parameters that are easily obtained within a few hours of admission to the emergency department. This approach to assessment facilitates early transfer of patients with a poor prognosis to a specialized liver unit for evaluation for transplantation.

In another study, plasma factor V level and age were found to be independent predictors of survival.²⁶ The criteria for liver transplantation were the presence of hepatic encephalopathy (stage III or IV) and a factor V level either less than 20% of normal in patients younger than 30 years or less than 30% of normal in patients older than 30 years.

Other predictive models have been developed. A study of 59 patients with non-acetaminophen-induced FHF showed that plasma levels of albumin, lactate, valine, and pyruvate were predic-

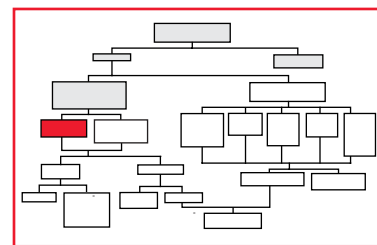
tive of survival when measured within 6 hours after admission.²⁷ Assessment of the residual functional reserve of the liver has been studied as an indicator of prognosis. The ratio of acetoacetate to β -hydroxybutyrate in an arterial blood sample (also known as the arterial ketone body ratio [AKBR]) is thought to reflect hepatic energy status.²⁸ Galactose clearance reflects both residual liver mass and hepatic blood flow.²⁹ This test has long been considered a standard test of hepatic functional reserve, and newer tests are routinely compared to it. At present, functional assessment tools are not widely used.

At our center, we apply the King's College criteria on admission to predict the likely outcome with medical therapy. Once the initial assessment is completed, the decision to proceed with emergency evaluation for liver transplantation is made. Evaluation, if indicated, is usually completed within 12 to 24 hours. The evaluation is similar to that of patients with chronic liver disease [see Chronic Liver Disease, *below*], with a few exceptions. Patients with FHF usually do not have preexisting liver disease; thus, it is vital that the evaluation [see Table 3] reveal the probable cause of liver failure. Unlike chronic liver disease, FHF is associated with cerebral edema and elevated ICP, which is the leading cause of death in these patients. Therefore, an extensive neurologic evaluation should be completed before a patient is listed for transplantation. Serial neurologic assessment is necessary to rule out irreversible brain damage and brain-stem herniation; use of short-acting sedatives make this evaluation less difficult.

TREATMENT OF COMPLICATIONS

Cerebral Edema

Cerebral edema develops in most patients with FHF, and its presence significantly influences management and outcome. Autopsy studies indicate that cerebral edema



is present in 80% of patients who die of FHF.^{30,31} It occurs in advanced stages of FHF and can be recognized by clinical, radiologic, or invasive means. Clinical findings include decerebrate posturing, myoclonus, spastic rigidity, seizure activity, systemic hypertension, bradycardia, hyperventilation, and mydriasis with diminished pupillary response. These findings initially are paroxysmal but later become persistent. Papilledema is a late finding and often does not occur at all, even in advanced stages of the disease.³² Noninvasive diagnostic modalities (e.g., CT scanning, electroencephalographic monitoring, and transcranial Doppler flow measurement) have not proved helpful for early detection and management of cerebral edema.^{33,34} CT scanning of the brain is not a sensitive test for detecting early cerebral edema: 25% to 30% of patients with elevated ICP exhibit no radiographic changes.³⁵ It is, however, useful for ruling out intracranial bleeding.

Currently, ICP monitoring is the best means of monitoring intracranial hypertension and is recommended for guiding treatment in patients with stage III or IV encephalopathy. ICP can be measured by using epidural, subdural, or intraventricular catheters. Although epidural catheters are slightly less sensitive to ICP changes, they have the lowest complication rate (3.8%) and the lowest rate of fatal hemorrhage (1%).³⁶ Despite a slightly higher complication rate, we prefer subdural catheters: in our view, they offer more reliable ICP monitoring. Institution of ICP monitoring is followed by aggressive treatment of any concomitant coagulopathy. FFP infusions are given to bring the PT below 25 seconds,

and platelet transfusions are given if the patient has severe thrombocytopenia (platelet count < 50,000/mm³). Once ICP monitoring is established, bolus administration of FFP is repeated as needed to keep the INR below 5 so as to reduce the risk of intracranial bleeding. To minimize the need for ICP monitoring, it has been suggested that patient selection should be based on reverse jugular oxygen saturation; saturations lower than 65% or higher than 80% are associated with a high likelihood of elevated ICP.³⁷

The goal of invasive monitoring is to keep the ICP below 15 mm Hg while keeping CPP, which is a better predictor of outcome, above 50 mm Hg. CPP is calculated by subtracting the ICP from the mean arterial pressure (MAP). ICP monitoring allows early detection of cerebral edema and hence earlier introduction of aggressive management. To date, no randomized, controlled trials have addressed the effect of high ICP and low CPP on outcome after liver transplantation; however, it appears that persistence of either an ICP higher than 25 mm Hg or a CPP lower than 40 mm Hg for more than 2 hours is associated with an increased risk of irreversible brain damage and a poor outcome.^{38,39}

Management of elevated ICP involves hyperventilation, minimization of external stimuli, deep sedation, elevation of the head, maintenance of hemodynamic stability, and infusion of mannitol. Patients are usually sedated with a short-acting agent (e.g., propofol) in small boluses before a procedure, nasotracheal suction, venipuncture, or line placement. Mechanical hyperventilation reduces ICP by lowering arterial carbon dioxide tension (P_aCO₂) to 25 to 30 mm Hg, thereby maximizing cerebral vascular constriction and reducing blood flow. This vascular effect diminishes progressively after 6 hours of therapy, though a clinical response is apparent for days. As many as 80% of patients without renal failure respond to mannitol infusions.⁴⁰ Serum osmolality should be measured frequently and maintained at 300 to 320 mOsm/L. Mannitol should be withheld if osmolality reaches or exceeds 320 mOsm/L, if renal failure occurs, or if oliguria and rising serum osmolality develop simultaneously. Repeated administration of mannitol may reverse the osmotic gradient. Mannitol should be discontinued if the ICP does not respond after the first few boluses.

Table 2 King's College Hospital Prognostic Criteria Predicting Poor Outcome for Patients with FHF

Acetaminophen-induced FHF	pH < 7.30 (irrespective of grade of encephalopathy)
	or
Non-acetaminophen-induced FHF	All of the following: PT > 100 sec (INR > 6.5) Serum creatinine > 3.4 g/dl Stage III or IV hepatic encephalopathy
	PT > 100 sec (INR > 6.5) (irrespective of grade of encephalopathy) or Any three of the following (irrespective of grade of encephalopathy): Age < 10 or > 40 yr Etiology: non-A, non-B hepatitis, halothane hepatitis, drug toxicity Duration of jaundice to encephalopathy > 7 days PT 50 sec (INR > 3.5) Serum bilirubin > 17.5 g/dl

FHF—fulminant hepatic failure INR—international normalized ratio
PT—prothrombin time

Table 3 Liver Transplant Evaluation and Workup for FHF Patients

Laboratory workup

CBC and differential count
Chemistry panel
Coagulation profile
24-hr creatinine clearance
Urinalysis
Arterial blood gases
ANA, AMA, ceruloplasmin, urinary copper, α_1 -antitrypsin
AFP
RPR
Thyroid function tests
Alcohol and drug toxicology screen

Viral serologies

Hepatitis A virus (IgM, IgG)
Hepatitis B virus (HBsAg, HBcAb, HBeAg, HBV DNA)
Hepatitis C virus (HCV antibody, HCV RNA-PCR)
Cytomegalovirus
Epstein-Barr virus
HIV

Cultures

Bacterial, fungal, and viral cultures
Blood
Sputum
Urine
Ascites

12-lead ECG

Chest x-ray

Pulmonary function tests

Abdominal Doppler ultrasonography

CT scans of head

AFP— α -fetoprotein AMA—antimitochondrial antibody ANA—antinuclear antibody RPR—rapid plasma reagent

Acute renal failure is a frequent complication. Fluid management is very difficult in this setting. Continuous hemofiltration or continuous venovenous hemodialysis (CVVHD) can be beneficial. Continuous hemofiltration is less deleterious than intermittent therapy in the management of patients with brain edema and renal dysfunction,¹⁶ probably because it does not cause the large fluid shifts that can occur with the intermittent technique.

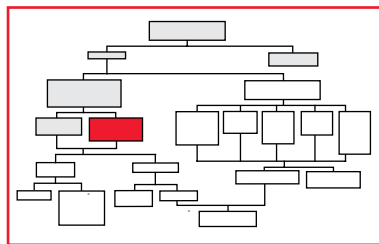
Patients who do not respond to conventional therapy may be placed in a barbiturate coma. Thiopental infusion decreases cerebral metabolic activity, lowers CNS oxygen demand, and protects the brain from ischemic injury secondary to decreased cerebral blood flow. In a retrospective, nonrandomized study, it lowered ICP and reduced mortality from FHF.⁴¹ In our experience, however, the effect of thiopental infusion on ICP is transient and unpredictable. Subclinical seizure activity has been detected in as many as 24% of ALF patients, but in a 2004 study, administration of phenytoin with control of the abnormal electrical activity did not affect overall outcome in ALF patients with seizures.⁴² In a study of 30 patients with ALF, the use of hypertonic saline led to significantly decreased ICP levels.⁴³ Administration of indomethacin or dexamethasone has led to modest reductions of ICP.

Studies evaluating the use of mild hypothermia (32° to 33° C [89.6° to 91.4° F]) in managing ALF reported significant decreases in ICP in all patients, some of whom were cooled for as long as 5 days.^{44,45} Bleeding and other coagulation disorders were not

observed; however, upon rewarming, a rebound effect was noted with an increase in ICP. In view of these findings, the authors suggested caution and recommended gradual, gentle rewarming. In addition, they found that liver implantation could be successfully performed under hypothermic conditions. Moderate hypothermia appears to be a promising experimental technique in ALF patients, but its utility in clinical practice remains to be determined.

Other Complications

In addition to cerebral edema and increased ICP, MODS and a variety of life-threatening complications are associated with FHF. Most of these complications are similar to those seen in chronic liver disease [see Chronic Liver Disease, Treatment of Complications, *below*]; however, the following complications are seen with particular frequency in FHF.



Fluid, electrolyte, and nutritional abnormalities Euvo-
lemia must be maintained to prevent fluid overload, pulmonary
edema, and dehydration; extreme fluid shifts should be avoided.
The presence of cerebral edema and intracranial hypertension calls
for careful fluid administration so as not to expand the intravascu-
lar space or exacerbate the edema. Electrolyte and acid-base
imbalances are frequent in FHF patients and should be managed
appropriately. Hyperkalemia may be multifactorial; usually it is
secondary to liver necrosis, massive transfusion, acid-base imbal-
ance, and renal failure. Acidosis results from increased lactic acid
production and decreased handling of lactate by the failing liver.
Compensatory respiratory alkalosis develops initially, but if
encephalopathy progresses, respiratory acidosis may result.
Sodium or potassium bicarbonate infusions should be adminis-
tered in cases of severe acidosis. Acetate provides twice the bicar-
bonate load and is metabolized outside the liver; thus, if sodium
and potassium intake is severely restricted, continuous infusion of
acetate salts may be useful.

Initially, amino acids should be withheld to prevent excessive
nitrogen loading; later, limited nitrogen supplementation (70 to 80
g protein/day) may be provided. Most patients present with severe
hypoglycemia that can be fatal and warrants aggressive therapy.
Hypoglycemia should be corrected rapidly by infusion of 50%
dextrose, followed by continuous infusion of a more dilute solution
at a rate of 4 mg/kg/min. A 10% solution is usually adequate; how-
ever, higher concentrations should be considered in patients whose
hypoglycemia persists or whose fluid intake is restricted. Caloric
supplementation has not been extensively studied in FHF.

Renal failure Renal failure occurs in as many as 55% of
FHF patients. Functional renal failure is a common cause of renal
failure in this population. However, acute tubular necrosis (ATN)
is more common in these patients than in those with chronic liver
disease and cirrhosis.⁴⁶ This is especially true in patients who have
not been resuscitated adequately, who have experienced prolonged
hypotension, or who have ingested hepatotoxins that are also
nephrotoxic (e.g., acetaminophen).

Adequate urine volume can be maintained by judicious volume
expansion, administration of loop diuretics, or both, along with
infusion of low doses of dopamine. Depleted intravascular volume
may be managed by giving blood products, volume expanders, or
both. Because plasma albumin levels are invariably low, salt-poor

albumin solutions may be preferable to carbohydrate-based vol-
ume expanders. If oliguria is present, especially if mannitol is
administered to treat ICP, hemodialysis or hemofiltration may be
needed to maintain optimal fluid volume.

Hemodynamic and pulmonary complications Circula-
tory disturbances tend to occur at an early stage of ALF and to
worsen over the course of the illness; they are characterized by gen-
eralized vasodilatation, resulting in increased cardiac output and
reduced systemic vascular resistance and MAP.⁴⁷⁻⁴⁹ The mech-
anisms of these hemodynamic disturbances are unclear, but
increased levels of nitric oxide and cyclic guanosine monophos-
phate (cGMP) have been demonstrated during the later stages of
the disease.⁵⁰ Fluids are managed so as to achieve euvo-
lemia (see above). A particular problem in managing hypotension related
to ALF is that autoregulation of cerebral blood flow is typically lost.⁵¹
Terlipressin (a vasopressin analogue) is widely used in patients
with end-stage liver disease (ESLD) and hepatorenal syndrome
(HRS). This agent acts through both V1 receptors, which are dis-
tributed in the systemic circulation and mediate vasoconstriction,
and V2 receptors, which are distributed in the cerebral vasculature
and mediate cerebral vasodilatation. The role of terlipressin in the
hemodynamic management of patients with ALF remains unclear.

Pulmonary complications, especially pulmonary edema, aspira-
tion pneumonia, and ARDS, are common in FHF patients.⁵²
Pulmonary edema is seen in as many as 40% of patients. Supple-
mental oxygen and mechanical ventilation are indicated. Sedative
and paralytic agents may be required to ensure tolerance of venti-
lation; however, they should be used sparingly because they may
hinder neurologic evaluation. Aspiration pneumonia is a potential
contraindication to transplantation and should therefore be treat-
ed aggressively.

Infectious complications Infection poses a serious threat to
FHF patients both by placing them at risk for sepsis and by being
a contraindication to liver transplantation. Immunologic defects
observed in this setting include impaired opsonization, impaired
chemotaxis, impaired neutrophil and Kupffer cell function, and
complement deficiency.^{53,54} Bacterial translocation through a
failed mucosal barrier has been implicated as one of the factors
responsible for a high incidence of septic episodes in this popula-
tion. Gram-negative organisms and the lipopolysaccharide derived
from their cell walls promote a systemic inflammatory response
that aggravates the patient's overall condition.⁵⁵ To lower the risk of
infectious complications, some groups advocate selective gut
decontamination. This practice appears to have no significant
advantages over systemic antibiotic prophylaxis alone.⁵⁶

Bacterial infection, usually originating from the respiratory or
the urinary tract or from a central venous catheter, occurs in more
than 80% of cases. In one study, bacteremia was documented in
25% of patients, with staphylococci, streptococci, and gram-neg-
ative rods the most common pathogens.⁵⁷ Because most FHF
patients have percutaneous lines and indwelling catheters in place,
iatrogenic sources must always be considered. Fungal infection is
less common than bacterial infection in this setting; however, one
series found a significant incidence of fungal infections, with
Candida albicans cultured in 33% of the patients studied.⁵⁸ The
majority of the patients had renal failure and had been treated with
antibiotics for longer than 5 days.

The high prevalence of infection notwithstanding, we do not
advocate antibiotic prophylaxis in this population unless either
there is strong suspicion of active infection or an ICP monitor is in
place. However, our decision threshold for initiating antibiotic

therapy is low, given that the usual clinical presentation (fever and leukocytosis) may be absent in as many as 30% of FHF patients.⁵⁷ Surveillance cultures for bacteria and fungi must be obtained at frequent intervals from blood (peripheral and central lines), urine, sputum, and open wounds. If ascites is present, the ascitic fluid should be cultured. In addition, chest radiographs should be obtained to identify developing infiltrates. Administration of broad-spectrum antibiotics should be initiated at the first sign of infection; as soon as an organism is identified, specific treatment may be focused more narrowly. Initiation of antifungal therapy with either fluconazole or another agent should be considered if a fungal culture is positive and if fever persists beyond 5 days while the patient is on antibiotics, especially if renal failure is present. The duration of antimicrobial therapy should be individualized for each patient. Follow-up cultures are recommended if a specific organism is isolated.

Coagulopathy and bleeding Bleeding is a frequent complication of FHF, typically resulting from massive liver necrosis, impaired hepatic synthesis of clotting factors, and platelet dysfunction. All clotting factors synthesized by the liver (i.e., factors II, V, VII, IX, and X) exhibit depressed plasma activity in FHF. Factor II, with a half-life of 2 hours, is the first to be depleted with hepatocellular dysfunction and also the first to be repleted during hepatocellular recovery. PT is invariably prolonged, reflecting a generalized clotting factor deficiency; it is used as one of the criteria for determining the likelihood of spontaneous recovery. At some centers, FFP transfusion is withheld and PT is followed carefully to determine upward or downward trends in the course of the disease and hence the likelihood of either spontaneous recovery or need for transplantation (unless the PT is greater than 25 seconds or the INR is greater than 5, especially if an ICP monitor is in place). Intracranial bleeding is the most devastating complication of coagulopathy in FHF patients with ICP monitors in place. In a 2003 study, administration of recombinant factor VIIa showed promising results in a group of patients with refractory coagulopathy.⁵⁹

Thrombocytopenia and abnormalities of platelet function are also common in FHF. Acute splenomegaly, consumptive coagulopathy, and bone marrow suppression all contribute to the development of thrombocytopenia. Conversely, clearance of older platelets from the blood by the reticuloendothelial system is hindered, resulting in an older, less effective platelet pool. In one study, a mean platelet count of 50,000/mm³ was associated with a higher incidence of GI hemorrhage.⁶⁰ Our current practice is to give platelets to patients who either are thrombocytopenic (platelet count < 50,000/mm³) or are actively bleeding.

MULTIDISCIPLINARY MEDICAL THERAPY AND INDICATIONS FOR LIVER TRANSPLANTATION

Because of the complexity of the underlying disease, medical management of FHF requires a multidisciplinary approach. Hemodynamic and respiratory support and prevention and treatment of cerebral edema are major goals. Complications of hepatic failure must be treated aggressively to prevent sepsis, ARDS, and MODS, which is the second most common cause of death in these patients if they survive the first few days. As noted [see Assessment of Prognosis, above], liver transplant evaluation must be carried out simultaneously with aggressive ICU care, and the patient's chances of spon-

taneous recovery must be assessed. In addition to determining the King's College prognostic score on admission, we follow the general trend in clinical course with respect to the development of encephalopathy, ICP elevation, coagulopathy, metabolic acidosis, and renal failure. The decision whether to continue with medical therapy or to perform liver transplantation must be made whenever a donor liver becomes available. In general, patients who appear to be deteriorating rapidly and who have no contraindications to liver transplantation should undergo emergency liver transplantation. Similarly, patients whose synthetic function does not improve within the first 48 to 72 hours should be considered for liver transplantation: the risk of complications and death from MODS if transplantation is not performed outweighs the risk of the procedure.

Toxic Liver Syndrome

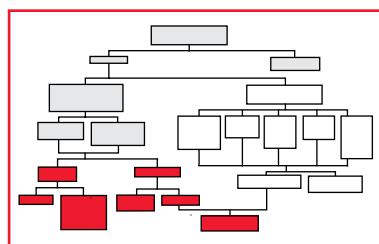
Even with a multidisciplinary, comprehensive approach to therapy, a few patients with FHF go on to manifest the so-called toxic liver syndrome, characterized by severe intracranial hypertension, profound lactic acidosis, hemodynamic instability, and MODS. It has been suggested that removal of the necrotic liver may improve the hemodynamic status of these patients and lower their ICP. In such extreme cases, a two-stage procedure has been performed: total hepatectomy with an end-to-side portacaval shunt, followed by liver transplantation when an allograft becomes available. In one large series,^{61,62} 32 adult patients with toxic liver syndrome underwent total hepatectomy with a portacaval shunt. The patients were anhepatic for 6.5 to 41.4 hours. Whereas 13 patients showed no signs of improvement after hepatectomy and soon died of MODS, 19 became more stable and underwent the full procedure. Only seven patients were alive at 46 months.

In the early 1990s, we used this approach to treat an 18-year-old female patient with uncontrollable cerebral edema secondary to FHF; she underwent total hepatectomy with a portacaval shunt, followed by orthotopic liver transplantation (OLT) 14 hours later.⁶³ During the anhepatic period, she was supported with the help of a bioartificial liver (BAL) [see Discussion, Bioartificial Liver Support System, below]. With artificial liver support, the severe neurologic dysfunction was reversed, ICP was normalized, and the serum ammonia level was reduced. The patient recovered completely, with no neurologic deficits. We subsequently used the same approach with another FHF patient, also successfully (unpublished data). It appears that for highly selected patients exhibiting severe toxic metabolic derangement and uncontrollable intracranial hypertension, total hepatectomy with a portacaval shunt—preferably accompanied by some form of artificial liver support—followed by OLT may be considered as a desperate salvage measure.

LIVER TRANSPLANTATION

With the introduction of orthotopic OLT as a treatment modality for FHF patients, overall patient survival improved from less than 20% to greater than 60%.^{64,65} As more experience was gained with OLT, it became apparent that optimal patient selection is essential for a successful outcome. FHF patients must be considered for OLT before irreversible brain injury, MODS, and sepsis develop. Patient selection should be based on a clear understanding of the natural history of the disease, the underlying cause, and the likelihood of spontaneous recovery without transplantation.

One of the most difficult aspects of managing FHF patients is the lack of reliable prognostic criteria predicting outcome. In our experience, the King's College criteria are less sensitive and specific in determining prognosis for patients with acetaminophen-induced FHF than for patients with FHF from other causes. As



a result, a small number of patients who either might have recovered spontaneously or might have sustained irreversible brain damage undergo unnecessary or unwarranted liver transplantation. Given the severe shortage of organ donors, as well as the cost and morbidity of liver transplantation and a commitment to lifelong immunosuppression, this is a significant problem.

Two interacting factors tend to influence the outcome of transplantation in the setting of ALF: (1) the severity of the illness before transplantation and (2) the condition of the graft used. The importance of the second factor was illustrated by the early experience with liver transplantation in France. Initially, French surgeons used the first available graft for ALF patients, regardless of its size, quality, or blood group compatibility. Subsequently, a study of 116 patients demonstrated that outcomes were significantly worse when adverse graft conditions (i.e., marginal quality, reduced size, and ABO incompatibility) were present.⁶⁶

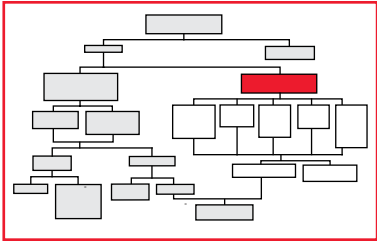
Some centers have successfully performed living donor liver transplantation in ALF patients.⁶⁷ This approach has been more commonly employed in pediatric patients.⁶⁸ Wider application has been limited by the risks this procedure poses to the donor in a setting where, because of the rapid progression of the disease, there is rarely enough time to evaluate potential donors appropriately and to eliminate the elements of pressure and coercion.⁶⁹ The potential for not just one but possibly two tragic outcomes must be emphasized.

Management of Chronic Liver Disease

Chronic liver disease usually develops as a result of long-standing, ongoing liver injury. The repeated injury and the ensuing repair usually result in deposition of an excessive amount of extracellular matrix (ECM), with or without accompanying inflammation. As the disease process progresses, excess ECM forms connective tissue bridges linking portal and central areas (so-called bridging fibrosis), eventually leading to cirrhosis. Cirrhosis is an irreversible state that gives rise to significant physiologic impairment, including poor exchange of nutrients and metabolites between sinusoidal blood and hepatocytes. Eventually, the lobular architecture becomes distorted and blood flow altered, leading to PHT and its numerous complications. In addition to PHT, repeated parenchymal injury results in the loss of a large number of functioning hepatocytes and subsequently leads to hepatic failure.

CLASSIFICATION

Like ALF, chronic liver disease is usually classified on the basis of the underlying cause [see Table 4]. According to the United Network for Organ Sharing (UNOS), the most common indication for liver transplantation in North America is chronic liver disease resulting from HCV infection. Other common indications are alcohol-induced liver disease, cholestatic liver disease (primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune liver disease), and cryptogenic cirrhosis. The occurrence of the metabolic syndrome (obesity, diabetes, and hypertension) is the most important risk factor for the development of nonalcoholic steatohepatitis (NASH), which is the most common cause of cryptogenic cirrhosis.

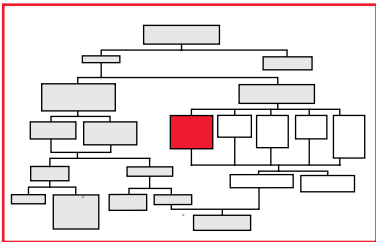


TREATMENT OF COMPLICATIONS

Chronic liver disease may be associated with a variety of complications, depending on the nature and extent of hepatocyte injury and regeneration. Most patients with chronic liver disease and possible cirrhosis are well compensated, maintain a relatively normal functional status, and remain essentially undiagnosed; however, a small percentage of patients become symptomatic. Hepatic failure secondary to cirrhosis is not an all-or-none process: patients may lose one or more specific liver functions while retaining the remainder. In addition to hepatic effects, cirrhosis and hepatic failure can exert a wide range of extrahepatic effects that involve virtually every organ system, leading to MODS and death in most cases if appropriate therapy is not instituted promptly. Consequently, treatment of cirrhosis and chronic hepatic failure must focus on treating both the underlying primary disease and all of its extrahepatic manifestations and complications.

Portal Hypertension

In most patients with chronic liver disease and cirrhosis, PHT develops as a result of increased resistance to portal venous blood flow within the liver. PHT is defined as a portal venous pressure higher than



12 mm Hg or a hepatic wedge venous pressure that exceeds the inferior vena cava pressure by more than 5 mm Hg. It is classified as prehepatic, hepatic, or posthepatic according to the anatomic site of increased portal venous resistance. Hepatic PHT is further classified according to the functional relationship to the hepatic sinusoids [see 5:10 Portal Hypertension]. Sinusoidal obstruction is more frequently seen with postnecrotic cirrhosis (e.g., cirrhosis resulting from HCV and HBV infection), whereas postsinusoidal obstruction is more common with alcoholic cirrhosis. Prehepatic and posthepatic causes of PHT are less often encountered in

Table 4 Etiology of Chronic Liver Disease

Alcoholic liver disease (exclude acute alcoholic hepatitis)
Viral hepatitis
Hepatitis B virus
Hepatitis C virus
Biliary cirrhosis
Primary biliary cirrhosis
Primary sclerosing cholangitis
Secondary sclerosing cholangitis
Biliary atresia
Autoimmune hepatitis
Metabolic abnormalities
Wilson disease
α ₁ -Antitrypsin deficiency
Hemochromatosis
Inborn errors of metabolism
Cryptogenic cirrhosis
Miscellaneous
Vascular anomalies (Budd-Chiari syndrome)
Toxin- or drug-induced
Inborn errors of metabolism
Other

patients with cirrhosis; however, efforts should always be made to rule out such causes, because these conditions all require different therapeutic approaches.

PHT is associated with numerous complications, most of which are life-threatening if not diagnosed and treated promptly. The most dramatic and catastrophic complication of PHT is bleeding from esophageal and gastric varices. Prompt diagnosis and management are vital. Since the early 1990s, management of variceal bleeding has evolved significantly, thanks to the advent of novel endoscopic therapies and nonoperative portosystemic shunt procedures. Although the esophagus and the stomach are the most common sites of bleeding varices, other sites within the GI tract may be involved as well, including the duodenum, the jejunum, the rectum, and ileostomy and colostomy sites.

One of the principal clinical manifestations of cirrhosis and PHT is ascites (i.e., leakage of lymph fluid into the peritoneal cavity). The appearance of ascites is indicative of advanced liver disease and is associated with a poor prognosis.⁷⁰ It is believed that increased hepatic sinusoidal pressure results in increased formation of lymph and causes hepatic lymph to weep from Glisson's capsule into the peritoneal cavity. As ascitic fluid accumulates, patients exhibit increasing abdominal distention, which in turn causes abdominal pain, decreased appetite, dyspnea, and, occasionally, pleural effusion (so-called hepatic hydrothorax).

An elevated WBC count in the ascitic fluid provides immediate information about possible bacterial infection. Cell counts higher than 500/mm³ suggest bacterial peritonitis, especially when the absolute neutrophil count exceeds 250/mm³.⁷¹ More than 20% of cirrhotic patients with ascites eventually manifest SBP. Patients with a low total protein level in their ascitic fluid (< 1.5 g/dl) appear to be at highest risk as a result of the reduced complement level and opsonic activity in the fluid. The diagnosis of SBP should be considered in any cirrhotic patient with fever, abdominal pain, worsening encephalopathy, or deteriorating renal function. Ascitic fluid analysis [see Table 5] distinguishes SBP from secondary bacterial peritonitis that develops as a consequence of an intra-abdominal abscess or a perforated viscus. Like ascites, SBP carries a grave prognosis: the estimated 1-year survival is less than 50% without liver transplantation.^{72,73}

Evaluation and management of PHT and its associated complications are addressed further elsewhere [see 5:10 Portal Hypertension].

Hepatic Encephalopathy

Hepatic encephalopathy is a complex neuropsychiatric syndrome that is seen in patients with severe hepatic insufficiency and cirrhosis. It is characterized by progressive alteration of cognitive function and coordination and depression of consciousness, leading to deep coma. Hepatic encephalopathy takes two main forms: (1) acute encephalopathy associated with FHF and (2) portosystemic encephalopathy (PSE) associated with cirrhosis and portosystemic shunts. It is classified into four stages according to the severity and extent of CNS impairment [see Table 6].

For accurate diagnosis of hepatic encephalopathy, it is necessary to recognize and correct all other disorders that affect cerebral function, including fluid and electrolyte abnormalities, hypoglycemia, azotemia, metabolic acidosis or alkalosis, hypoxia, and plasma hyperosmolality. Sedatives and paralytic agents should be

Table 5 Differentiation of Spontaneous Bacterial Peritonitis from Secondary Bacterial Peritonitis through Analysis of Ascitic Fluid

Fluid Assay	Spontaneous Bacterial Peritonitis	Secondary Bacterial Peritonitis
WBC (cells/mm ³)	> 500	> 500
Total protein (g/dl)	< 1.0	> 1.0
Glucose (mg/dl)	> 50	< 50
Lactic dehydrogenase (U/L)	< 225	> 225
Gram stain	Monomicrobial	Polymicrobial

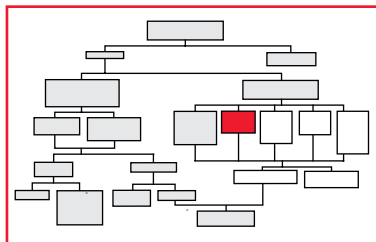
avoided during the initial assessment period if possible; if sedation or paralysis is required, the combination of poor hepatic function with the shunting of blood away from the liver may greatly lengthen drug elimination, thereby complicating patient assessment. Frequently, patients with PSE carry out normal activities while the disorder goes unrecognized, and PSE is diagnosed only when its presentation is exaggerated by infection or GI bleeding. PSE is also exacerbated by constipation, the onset of portal vein thrombosis, and the development of a liver malignancy.

Management of PSE begins with treatment of all potential precipitating factors: sedatives and other drugs with CNS effects should be discontinued, fluid and electrolyte abnormalities should be corrected, GI bleeding should be controlled, and underlying infections (especially SBP) should be treated. Early endotracheal intubation for airway protection may be needed in patients with stage III or IV encephalopathy because of the high risk of aspiration and subsequent pneumonia.

The therapeutic objectives in the management of hepatic encephalopathy are (1) to minimize ammonia formation and (2) to augment ammonia elimination [see Discussion, Mechanism of Hepatic Encephalopathy, below]. Lactulose and certain antibiotics are commonly employed to achieve these ends. Lactulose is a synthetic disaccharide cathartic that can be delivered orally, through a nasogastric tube, or via a high enema and can be administered early in the course of the disease. The dosage should begin at 25 g/day and then be titrated to a level at which the patient can produce three or four loose bowel movements daily. Lactulose is nei-

Table 6 Grading of Hepatic Encephalopathy

Encephalopathy Stage	Neurologic Changes
Stage I	Mild confusion, euphoria or depression, decreased attention span, slowing of ability to perform mental tasks, irritability, disorder of sleep pattern
Stage II	Drowsiness, lethargy, gross deficit in ability to perform mental tasks, obvious personality changes, inappropriate behavior, intermittent and short-lived disorientation
Stage III	Somnolent but arousable, unable to perform mental tasks, disorientation with respect to time or place, marked confusion, amnesia, occasional fits of rage, speech present but incomprehensible
Stage IV	Coma



ther absorbed nor metabolized in the upper GI tract. When it reaches the colon, the ensuing bacterial degradation acidifies the luminal contents and causes an intraluminal osmotic shift. The more acidic environment inhibits coliform bacterial growth, thereby reducing ammonia production. Additionally, the low intraluminal gut pH causes ammonia to be converted to ammonium ions, which do not enter the bloodstream easily. Finally, the cathartic action of lactulose clears ammonium ions from the bowel. Aggressive lactulose therapy may induce volume depletion and electrolyte imbalance; metabolic acidosis is a rare occurrence.

Neomycin, an agent commonly used for bowel preparation, alters gut flora, especially *Escherichia coli* and other urease-producing organisms, and reduces the production of ammonia. About 1% of neomycin is absorbed systemically; because of possible ototoxicity and nephrotoxicity, special care should be taken if it is administered on a continuous basis.⁷⁴ Other oral antibiotics used to treat hepatic encephalopathy are polymyxin B, metronidazole, and vancomycin, which affect gut flora in much the same fashion as neomycin.

Aromatic amino acids (AAAs) are known neurotransmitter precursors. It has been suggested that their products interfere with the activity of true neurotransmitters. It has also been shown that the ratio of branched-chain amino acids (BCAAs) to AAAs in plasma decreases steeply with worsening encephalopathy. Because AAAs and BCAAs compete for the same blood-brain barrier carrier transport sites, the relative paucity of BCAAs leads to increased cerebral uptake of AAAs, which in turn promotes synthesis of false neurotransmitters that then compete with the endogenous transmitters dopamine and norepinephrine.⁷⁵ Parenteral administration of BCAA-enriched formulas to patients with hepatic encephalopathy has been advocated, but it has not proved beneficial when compared with administration of conventional amino acid solutions.⁷⁶

Renal Failure

Liver disease and cirrhosis are commonly associated with functional renal failure—that is, impaired renal function in the absence of significant underlying renal pathology. The most common functional renal abnormality in cirrhotic patients is HRS, which is defined as a reversible state of renal failure characterized by azotemia, oliguria (< 10 mEq/L), and an increased urine-plasma osmolality ratio (U/P > 1.0) in the absence of urinary sedimentation. HRS occurs in 18% to 55% of cirrhotic patients with ascites and is typified by intense renal vasoconstriction, a decreased glomerular filtration rate (GFR), preserved tubular function, and normal renal histology.^{46,77} Although the exact cause of HRS is not known, current evidence suggests that it is multifactorial, involving systemic vasodilatation and reduced effective plasma volume, along with increased activity of the renin-angiotensin-aldosterone system, which causes further reduction of the GFR. HRS is classified as either type 1 or type 2. In type 1 HRS, renal failure is rapidly progressive, as defined by a doubling of the initial serum creatinine level to a value higher than 2.5 mg/dl or a 50% reduction in the initial creatinine clearance to a value lower than 20 ml/min in less than 2 weeks. In type 2 HRS, renal failure takes a slower, more gradual course.

The prognosis for patients with HRS is poor: to date, all therapeutic approaches have proved unsuccessful. Pharmacologic therapy has consisted of correcting effective volume status and attempt-

ing to reverse renal vasoconstriction through I.V. administration of vasodilators (e.g., dopamine, misoprostol, and aminophylline) or drugs that inhibit the synthesis or the effects of endogenous vasoconstrictors (e.g., captopril and thromboxane inhibitors). These approaches have not yielded effective and reproducible improvements in renal hemodynamics and renal function. Several investigators have reported improved renal function after OLT.^{46,77}

An approach to the management of HRS has been introduced that is aimed at correcting the primary underlying defect (i.e., systemic vasodilatation) instead of the secondary renal vasoconstriction. Two classes of drugs have been investigated: (1) agents that inhibit the effects of endogenous systemic vasodilators (e.g., prostacyclin, nitric oxide, and glucagon) and (2) agents that cause systemic vasoconstriction (e.g., ornipressin and terlipressin). In one small series of patients with type 1 HRS, a combination of an oral beta-adrenergic drug with midodrine and octreotide led to improved renal function and better long-term outcome.⁷⁸

Besides functional renal failure, various types of nonfunctional (i.e., organic) renal failure may occur in patients with cirrhosis (e.g., ATN, renal tubular acidosis [RTA], and drug-induced interstitial nephritis). ATN is especially common in patients with chronic liver disease or FHF and is usually seen in patients who are poorly resuscitated, have experienced prolonged hypotension, have undergone severe septic episodes, or have ingested hepatotoxins that are also nephrotoxic (e.g., acetaminophen). ATN is characterized by an abrupt rise in blood urea nitrogen (BUN) and serum creatinine levels, accompanied by oliguria or anuria. Unlike HRS, ATN leads to impairment of the concentrating ability of the tubular system and to excessive urinary sodium excretion; accordingly, a urine sodium concentration greater than 10 mEq/L is considered diagnostic for ATN in cirrhotic patients [see Table 7]. RTA is commonly seen in patients with primary biliary cirrhosis, autoimmune liver disease, and alcoholic cirrhosis. It is characterized by the inability of the renal tubules to acidify the urine in the presence of a normal GFR.

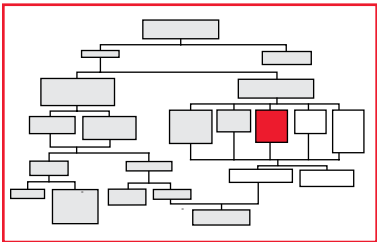


Table 7 Differentiation of Hepatorenal Syndrome from Acute Tubular Necrosis

Criteria	Hepatorenal Syndrome	Acute Tubular Necrosis
Underlying liver disease	Advanced liver damage with jaundice and impaired synthetic function	Mild or severe liver disease
Precipitant	GI bleeding, diuretics, paracentesis, sepsis, or none	Shock, nephrotoxins, sepsis
Onset	Days to weeks	Hours to days
Urinalysis	Renal epithelial cells with or without pigmented granular cells	Pigmented granular casts with or without RBCs, WBCs
Urinary sodium concentration	< 10 mEq/L	> 10 mEq/L
Urinary osmolality	> Serum osmolality	Isotonic
Urinary volume	Oliguric	Variable
Course	Progressive, unremitting	Deterioration followed by improved renal function

Management of renal failure is usually aimed at correcting the underlying precipitating causes. In patients with ascites, who experience ongoing loss of fluid and protein into the peritoneum, it is important to maintain an adequate intravascular volume. If intravascular volume is depleted, blood components, volume expanders, or both should be given. Given that the plasma albumin level is invariably low in these patients, salt-poor albumin solutions may be preferable to carbohydrate-based volume expanders. Albumin replacement has been effectively used for volume expansion after LVP.⁷⁹

Because of the complex physiologic liver-kidney interaction, fluid and electrolyte management often proves challenging. It is difficult to estimate the actual intravascular volume, which is depleted in most cirrhotic patients even though total body fluid volume is greater than normal. Sodium retention and free water retention are the two most common abnormalities of renal function that lead to ascites and dilutional hyponatremia. Typically, sodium retention is an early manifestation, whereas water retention and renal failure are late findings. Nephrotoxic drugs and I.V. contrast agents should be avoided, and dosages of antibiotics and other medications should be adjusted appropriately.

Hypernatremia and metabolic acidosis can develop secondary to excessive lactulose therapy and dehydration and result in renal function deterioration. Hypokalemia is also common; it develops secondary to increased serum aldosterone concentration, which leads to excessive excretion of potassium in exchange for sodium. Once renal failure develops, hyperkalemia, hypercalcemia, and hyperphosphatemia become significant problems, often necessitating dialysis.

Malnutrition

Most cirrhotic patients present with depleted glycogen stores, severe protein-calorie malnutrition, and wasting. Impaired hepatic synthetic activity, causing a deficiency of both visceral and structural proteins, is one of the hallmarks of advanced liver disease. In addition, poor appetite, tense ascites, abdominal pain, and excessive loss of protein through repeated LVP and overall increased energy expenditure tend to exacerbate malnutrition.

Excessive protein administration can induce hepatic encephalopathy; accordingly, protein intake should be limited to 1 to 1.2 g/kg/day. Glucose is the main energy source given to malnourished cirrhotic patients; however, its use is not without complications, in that these patients typically exhibit glucose intolerance. Lipid emulsion can be safely administered to most patients with hepatic failure and should be withheld only from patients with overt coma.⁸⁰ It is generally agreed that the ideal energy source should consist of a mixture of glucose and fat emulsion. Approximately 30% to 40% of all nonprotein calories can be provided in the form of fat. The total energy requirement should be 25 to 35 kcal/kg/day.

As noted [see Hepatic Encephalopathy, above], although AAAs have been implicated in the pathogenesis of hepatic encephalopathy, administration of BCAA solutions has not proved helpful, and current evidence does not support their routine use.^{76,81}

In general, the potential risks and complications associated with total parenteral nutrition (TPN) outweigh the benefits in patients with a functioning GI tract. When properly administered, enteral nutrition is safer, more physiologically appropriate, and significantly more cost-effective than TPN. It should therefore be considered the first choice for nutritional support in most patients with chronic liver disease unless a contraindication to enteral feeding is present.

Coagulopathy and Nonvariceal Bleeding

The spectrum of coagulation disorders in patients with liver disease ranges from minor localized bleeding to massive life-threatening hemorrhage. Abnormal bleeding may be spontaneous in some patients, but it is more often the result of a hemostatic challenge (e.g., surgical wounds or procedures, gastritis, portal hypertensive gastropathy, gastric or duodenal ulcers, or ruptured varices). The underlying anatomic lesion is believed to be as responsible for bleeding as the hemostatic defect; accordingly, therapy should be directed at correcting both. In addition, general physiologic monitoring is maintained. A physiologic pH and a normal core temperature optimize coagulation factors and platelet function. Poor nutrition and cholestatic diseases are associated with depleted levels of vitamin K. I.V. administration of vitamin K₁ can be accomplished with minor complications.

Although most bleeding episodes are secondary to decreased synthesis of clotting factors, other causes of bleeding (e.g., defective or dysfunctional factor synthesis and increased consumption of clotting components) must be ruled out. In most patients, the decreased levels of clotting factors parallel the progressive loss of parenchymal cell function. Usually, the levels of the vitamin K-dependent factors (i.e., prothrombin, factor VII, factor IX, factor X, protein S, and protein C) fall first, followed by the levels of other factors as cirrhosis progresses. Factor V is synthesized independently of vitamin K availability, and its concentration is of special interest because the plasma factor V level seems to be a predictor of the extent of liver cell damage. Impaired synthesis of coagulation proteins also has an impact on antithrombin III (AT-III), protein C inhibitor, plasminogen, and α_2 -antiplasmin, as well as on several other inhibitors and activators of both the extrinsic coagulation pathway and the intrinsic pathway. The combination of decreased factor levels and impaired synthesis of coagulation proteins explains the prolongation of the PT, the activated partial thromboplastin time (aPTT), and the thrombin clotting time (TCT) in these patients.^{82,83}

Given the complexity of hemostasis in cirrhotic patients, accurate diagnosis of a bleeding disorder is often hard to achieve. Several disorders and abnormalities may be present simultaneously, and one or more parameters of hemostasis and coagulation may be impaired. Therefore, any effective treatment approach should be broad-based and aimed at correcting several deficiencies or abnormalities at once. FFP contains all of the components of the clotting and fibrinolytic systems but lacks platelets. In most cases, transfusion of 6 to 8 units of FFP corrects severe clotting factor defects; however, the excess volume may not be well tolerated. Cryoprecipitate, the precipitate formed when FFP is thawed at 4° C, is rich in factor VIII, von Willebrand factor, and fibrinogen but lacks the vitamin K-dependent factors. Therefore, it should be given only when the fibrinogen level is lower than 100 mg/dl. Prothrombin complex concentrates contain only the vitamin K-dependent factors and proteins, and their use can provoke serious thromboembolic complications, including DIC. Therefore, their potential utility must be weighed carefully against the risk that thrombotic events may develop.⁸⁴

Other major disorders of hemostasis in patients with chronic liver disease and cirrhosis involve platelets and are manifested as thrombocytopenia, abnormal platelet function (thrombocytopathy), or both. In most cases, thrombocytopenia is related to sple-

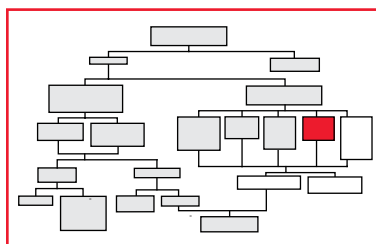
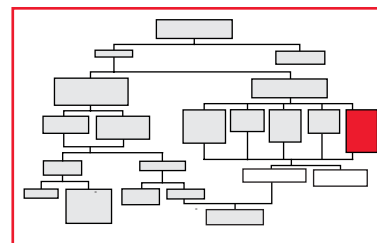


Table 8 Contraindications to Liver Transplantation

Absolute contraindications	Severe, irreversible brain damage
	HIV infection
	Extrahepatic malignancy
	Uncontrolled sepsis
	Severe pulmonary hypertension and advanced cardiopulmonary disease
	Active substance abuse or major psychosocial problems
Relative contraindications	Extrahepatic portal vein thrombosis in patients with hepatocellular carcinoma
	Elevated ICP or reduced CPP (in patients with FHF)
	Multiple organ dysfunction syndrome
	Hemodynamic instability
	Advanced age
	Portal vein thrombosis (except when secondary to hepatocellular carcinoma)

CPP—cerebral perfusion pressure ICP—intracranial pressure

nomegaly and hypersplenism (a common feature of PHT). Abnormal platelet function is attributed to many causes, including intrinsic platelet defects and abnormal interaction among platelets, endothelial surfaces, and clotting factors. It is manifested by a prolonged bleeding time, impaired platelet aggregation, and reduced adhesiveness. Some authorities attribute the inhibition of platelet aggregation to fibrin degradation products (FDPs); however, the FDP levels noted in the plasma of cirrhotic patients are not sufficient to impair platelet aggregation, nor do they correlate with the observed reductions in platelet aggregation.⁸⁵

Platelets should be transfused whenever a patient with either a quantitative or a qualitative defect experiences active bleeding. A normal response is a rise of 10,000/mm³ with each unit transfused; however, in cases of hypersplenism and accelerated consumption, such a response is rare. Transfusion should be continued until all serious bleeding has ceased, with the therapeutic goal being the maintenance of a platelet count near 50,000/mm³. Platelet transfusion is also indicated before any surgical or invasive procedure (e.g., paracentesis or liver biopsy). Indications for prophylactic platelet transfusion are less clear, and any potential gains must be balanced against potential side effects and development of antibodies. Most patients with advanced cirrhosis and liver failure have platelet counts lower than 100,000/mm³; however, prophylactic platelet transfusion is usually not recommended until the count falls below 15,000 to 20,000/mm³, at which point the risk of spontaneous bleeding is considerably increased.

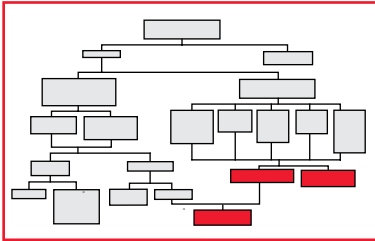
Another feature of severe liver disease is increased fibrinolytic activity, which may be either primary or secondary to DIC.⁸⁶ The precise causes of primary fibrinolysis and DIC remain unclear. Primary fibrinolysis appears to be a result of increased activity of tissue plasminogen activator and decreased levels of α_2 -antiplasmin.⁸⁷ DIC is believed to be triggered by the release of thromboplastic substances into the circulation as a consequence of liver cell damage or necrosis and by poor clearance of circulating activated tissue and clotting factors and FDPs by a defective reticuloendothelial system. Accelerated fibrinolysis is manifested by reductions in the whole blood clot lysis time and the euglobulin clot lysis time, as well as by elevated levels of fibrinolysis products (e.g., FDPs and D-dimer). Although enhanced fibrinolysis is relatively common in patients with cirrhosis, most of the characteristic abnormalities can occur after many types of physiologic stress and are not necessarily accompanied by a bleeding tendency.

At present, no satisfactory method of managing DIC is available. An extensive workup must be completed to rule out underlying causes (e.g., sepsis, ARDS, and MODS). FFP, platelet concentrates, and low-dose heparin (200 to 800 U/hr) may be given. AT-III concentrate has been used in an attempt to inhibit the action of thrombin, thereby decreasing procoagulant consumption, restoring normal levels of factors, and improving hemostasis. Clinical experience with AT-III therapy in this setting has been limited; however, there is evidence suggesting that AT-III may reduce hemostatic abnormalities and help control bleeding.⁸⁸

Antifibrinolytic agents (e.g., ϵ -aminocaproic acid and tranexamic acid) impede fibrinolysis and may be useful in treating bleeding in patients who have liver disease and show evidence of fibrinolysis.⁸⁹ In patients with DIC, administration of antifibrinolytic agents is contraindicated because of the potential for thrombotic complications. D-dimer levels should be determined to rule out DIC before use of these medications is considered. Because it is difficult to rule out DIC in patients with liver disease, the use of antifibrinolytic agents in liver disease is limited. Other antifibrinolytic compounds have been tested for use in liver transplantation. Of these, aprotinin has been shown to reduce the number of packed red blood cells given during liver implantation in selected patients.

LIVER TRANSPLANTATION

In 2005, 6,444 liver transplants were performed in the United States in 2004. The 1-year survival rates for patients and grafts have improved to greater than 90% and 85%, respectively. At present, the main limiting factor for the continued growth of liver transplantation is the scarcity of donors. Living related donor liver transplants account for approximately 5% of the total number of transplants.



End-Stage Liver Disease

Liver transplantation is an accepted therapy for ESLD. The standard indications for liver transplantation are well documented⁹⁰; they include PHT, poor hepatic synthetic function, hepatic encephalopathy, progressing jaundice, severe malnutrition, and excessive fatigue. PHT is manifested by variceal bleeding, hypersplenism, thrombocytopenia, ascites, hepatic hydrothorax, and SBP. Poor synthetic function is usually manifested by an elevated INR and low serum albumin and cholesterol levels. In general,

Table 9 Child-Turcotte-Pugh Scoring System

Points	1	2	3
Encephalopathy	None	Stage I or II	Stage III or IV
Ascites	Absent	Slight (or controlled by diuretics)	Moderate despite diuretic treatment
Bilirubin (mg/dl)	< 2	2–3	> 3
Patients with PBC or PSC	< 4	4–6	> 6
Albumin (g/L)	> 3.5	2.8–3.5	< 2.8
PT (prolonged sec)	< 4	4–6	> 6
INR	< 1.7	1.7–2.3	> 2.3

PBC—primary biliary cirrhosis PSC—primary sclerosing cholangitis

any concurrent medical or psychosocial condition that prohibits a major surgical procedure or subsequent immunosuppression constitutes a contraindication to liver transplantation [see Table 8].

UNOS currently regulates organ allocation to transplant candidates. In January 1988, minimal listing criteria for liver transplantation were implemented.⁹¹ These criteria were based on the Child-Turcotte-Pugh (CTP) scoring system [see Table 9], which includes five parameters: serum albumin and bilirubin levels, PT, ascites, and hepatic encephalopathy. Graft allocation had a subjective component, taking into account the time spent on the waiting list. The criteria currently used were implemented in February 2002 and are based on the Modeling for End-Stage Liver Disease (MELD) scoring system, which predicts patient survival without a liver transplant at 90 days.^{92,93} This scoring system was developed to predict survival in patients with cirrhosis after TIPS, and it has been shown also to predict patient survival after liver trans-

plantation.⁹⁴ The MELD score is calculated from three laboratory values that feed into a logistic regression formula: INR, serum creatinine level, and total bilirubin concentration. Modifications have been implemented to improve allocation, and exception policies are evolving. A similar scoring system, the Pediatric End-Stage Liver Disease (PELD) system, has been developed for pediatric patients, incorporating information on serum albumin levels and growth failure. A patient who has FHF is listed as status 1, and no MELD score is assigned.

Liver Cancer

Hepatocellular carcinoma (HCC) [see 5:9 *Tumors of the Pancreas, Biliary Tract, and Liver*] is 30 times more common in cirrhotic patients than in noncirrhotic patients. Its high growth rate and high mortality have prompted the development of exception points that favor HCC patients for rapid graft allocation.

Discussion

Mechanism of Hepatic Encephalopathy

The association between liver disease and altered mental status and consciousness has been recognized for centuries, but the exact underlying mechanism remains unknown. It appears that this syndrome has a multifactorial etiology and is associated with a number of complex changes, which are manifested collectively as hepatic encephalopathy. It is generally believed that hepatocerebral dysfunction is caused by an accumulation of cerebral toxins as a result of low hepatic clearance.⁹⁵

Of all the physiologic factors thought to contribute to the development of encephalopathy, the best known is ammonia. Arterial ammonia levels are frequently elevated in patients with hepatic encephalopathy; however, the clinical severity of hepatic encephalopathy correlates poorly with the ammonia level.⁹⁶ The precise contribution of ammonia to hepatic encephalopathy remains unclear; however, ammonia is known to inhibit the uptake of glutamate into astrocytes, thereby causing a rise in the extracellular glutamate level that appears to downregulate the postsynaptic glutamate receptors, resulting in decreased neuronal excitation.⁹⁷

Endogenous or exogenously ingested benzodiazepines may also play a role in the etiology of acute and chronic hepatic encephalopathy by interacting with the high-affinity γ -aminobutyric acid (GABA)-benzodiazepine receptor complexes. These substances are known to enhance inhibitory GABA-ergic tone. Animal studies suggest that gut flora may contribute benzodiazepine ligand activity,⁹⁸ as well as increased benzodiazepine receptor agonist activity.⁹⁹ Studies of FHF patients show increased benzodiazepine receptor ligands with enhanced GABA-ergic tone in all stages of encephalopathy.¹⁰⁰ Ammonia-induced activation of peripheral-type benzodiazepine receptors on astrocytes may cause the release of neurosteroids that enhance GABA-ergic neurotransmission. Hence, neurosteroids may potentiate the inhibitory actions of GABA at the receptor level, as well as lengthen the period during which the GABA ligand remains in the synaptic cleft. Ammonia also acts directly to potentiate GABA-ergic tone by enhancing the affinity of GABA for GABA-A receptors.¹⁰¹

These findings notwithstanding, there is no apparent correlation between benzodiazepine ligand activity and clinical stage of encephalopathy, nor is ligand elevation a consistent finding in all

patients. Furthermore, clinical and animal studies in which a benzodiazepine receptor antagonist has been administered have not shown consistent effects. The anecdotal success of flumazenil, the principal benzodiazepine antagonist, has been ascribed to the antagonism of benzodiazepines ingested by patients. Support for the concept of so-called endogenous benzodiazepines arising from the intestine can be found in a number of sources, including studies of dogs with congenital portacaval shunts, which document ligand activity in stool samples.¹⁰² Whether there is a causal relation to hepatic encephalopathy or whether this is merely a case of associated phenomena remains to be determined. Whatever the contribution of benzodiazepines to the pathophysiology of acute hepatic encephalopathy and cerebral edema, it appears likely that other mechanisms are involved.

Bioartificial Liver Support System

Despite the best management efforts, the morbidity and mortality associated with ALF remain exceptionally high. For most severe cases, liver transplantation is still the only effective therapeutic modality. Unfortunately, because of the severe organ donor shortage, the waiting period for transplantation is long, and patients consequently are at risk for the development of irreversible complications or contraindications to liver transplantation while awaiting a donor. In an effort to mitigate this problem, investigators have studied various artificial liver support systems designed to provide full metabolic, hemodynamic, and physiologic support until either the native liver regenerates or a liver becomes available for transplantation. From the 1970s to the 1990s, most therapeutic attempts focused primarily on detoxifying plasma. All such attempts either failed or had no significant impact on survival.¹⁰³

The ongoing severe organ shortage led several investigators to develop and test xenogeneic-based liver support systems employing whole-organ perfusion or isolated hepatocytes. We developed and tested a hybrid bioartificial liver (BAL) support system employing isolated porcine hepatocytes in an extracorporeal perfusion circuit. We subsequently initiated a clinical trial addressing the use of this system in patients with severe ALF as a bridge to either transplantation or spontaneous recovery.¹⁰⁴⁻¹⁰⁷

In 1997, the BAL our group developed (HepatAssist; Circe Biomedical, Inc., Lexington, Massachusetts) was tested in a phase I clinical trial.¹⁰¹ Patients were admitted to a dedicated liver support unit. Invasive hemodynamic monitoring (via peripheral arterial catheter and pulmonary artery catheter) was instituted after blood product administration for partial correction of coagulopathy. All patients received standard medical care, along with one to five BAL treatments (each lasting 6 to 7 hours). If signs of intracranial hypertension were observed, an ICP monitor was placed at the bedside for ICP and CPP monitoring. Patients were intubated endotracheally when in stage 4 encephalopathy and were placed on ventilatory support. The BAL treatments were well tolerated, and no technical problems were identified during BAL therapy. A total of 32 patients were treated with the BAL (29 patients with FHF and three with PNF after transplantation), of whom 84% survived with or without transplantation (unpublished data). Patients experienced remarkable neurologic improvement, with reversal of the decerebrate state after BAL treatments. Posturing, anisocoria, and sluggish pupil reactivity were reduced, and patients became more responsive to external stimuli. Brainstem function improved, and there was a significant reduction in ICP, with a concomitant increase in CPP. Other effects of BAL

treatment included a decrease in ammonia, transaminase, and bilirubin levels and a significant increase in the BCAA-AAA ratio.

Subsequently, the safety and efficacy of the BAL were evaluated in a prospective, randomized, controlled, multicenter trial that included 171 patients with severe ALF (86 in the control group and 85 in the BAL group).¹⁰⁷ Both patients with FHF or SHF and patients with PNF after liver transplantation were enrolled in this trial. Data were analyzed with and without consideration of the following confounding factors: liver transplantation, time to transplant, disease etiology, disease severity, and treatment site. In the study population as a whole, 30-day survival was 71% for the BAL group and 62% for the control group. In the FHF/SHF subpopulation (with PNF patients excluded), 30-day survival was 73% for the BAL group and 59% for the control group. When survival was analyzed so as to take into account the aforementioned confounding factors, there was no difference in survival between the BAL group and the control group in the study population as whole, but in the FHF/SHF subpopulation, survival was significantly higher in the BAL group than in the control group. This was the first prospective, randomized, controlled trial of an extracorporeal liver support system to demonstrate a significant survival advantage in patients treated with such a system.

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10 BRAIN FAILURE AND BRAIN DEATH

David Crippen, M.D., F.C.C.M.

He seems to be completely unreceptive
The tests I gave him show no sense at all
His eyes react to light; the dials detect it
He hears but cannot answer to your call
"Go to the Mirror Boy" (from *Tommy*, The Who, 1969)

Brain Failure

BRAIN FAILURE AND IMPAIRMENT OF CONSCIOUSNESS

As a type of organ system failure, brain failure invariably affects consciousness. Consciousness is structurally produced in the cerebral hemispheres, including the pons and the medulla.¹ These structures are all interconnected by the reticular formation, which begins in the medulla and extends to the midbrain, where it forms the reticular activating system. This pathway modulates the perception of events and controls integrated responses.²

Clinical evaluation of consciousness states is heavily dependent on the findings from physical examination. When the physical examination yields visual and palpable clues to the integrity of consciousness, impairment thereof may be classified into one of the following categories³:

1. Cloudy consciousness. This state is defined as a mild deficit in the speed of information processing by the brain, resulting from disruption of cell-to-cell connectivity at the histologic level. Cloudy consciousness may be noted after mild to moderate head trauma and may persist for several months. Memory of recent events is often diminished, but long-term memory typically remains intact.
2. Lethargy. This state is defined as a decrease in alertness, resulting in impaired ability to perform tasks that are normally accomplished without effort. Patients rouse briefly in response to stimuli, then settle back into inactivity when left alone. They retain awareness of their immediate environment.
3. Obtundation. This state is defined as a decrease in awareness and alertness, in which patients rouse briefly in response to stimuli and follow simple commands but are unaware of their immediate surroundings. When stimulation ceases, they settle back into inactivity.
4. Stupor. In this state, patients cannot communicate clearly but can be aroused by continued painful stimulation. Arousal may be manifested only as withdrawal from painful stimuli. As soon as stimuli are removed, patients settle back into inactivity.
5. Coma. In this state, patients do not respond to even the most vigorous stimuli.
6. Brain death. This state is equivalent to functional decapitation and is characterized by irreversible cessation of whole brain function and function of the hemispheres and the brain stem.

It should be kept in mind that the efficacy of the physical examination in the evaluation of consciousness diminishes when visual clues disappear (e.g., during heavy sedation or therapeutic musculoskeletal paralysis). In such situations, monitoring of cerebral

function is helpful in assessing the effect of therapy on neuronal function.

RELATION OF CARDIAC ARREST TO BRAIN FAILURE

In a substantial proportion of unconscious patients admitted to the intensive care unit, the brain failure resulted from metabolic and hemodynamic deteriorations that followed cardiac arrest.⁴ There is a great difference between surviving cardiopulmonary resuscitation (CPR) and walking out of the hospital unaided after such an event. It is relatively easy to restart the heart with traditional CPR; it is considerably harder to restart the brain.⁵ After several minutes of cardiac arrest, CPR will occasionally restore cardiac activity, but it will not necessarily restore useful brain function. Brain metabolism requires a constant high flow of oxygenated blood and nutrients. During cardiac resuscitation, cerebral perfusion decreases sufficiently to promote hypoxia and tissue edema. A number of mechanisms have been shown to underlie deteriorating and failed reflow. Hyperviscosity from hemoconcentration of plasma proteins and formed elements contributes to initial poor reperfusion at the capillary level. Endothelial cell swelling and edema of the pericapillary astrocytes also greatly inhibit reperfusion by reducing capillary diameter to less than 5 μm .

During reperfusion, abnormally high amounts of superoxide convert almost all available nitric oxide to peroxynitrite, which is regarded as the agent that causes most of the damage to brain capillary endothelial cells.⁶ As noted (see above), damage to the endothelium not only increases edema (tissue swelling resulting from leakiness) but also causes endothelial protrusions (blebs) that can block capillaries. Calcium-mediated vasospasm also plays a role. L-type calcium channel blockers, given before the insult, have been shown to prevent the no-reflow phenomenon in dogs and to result in an 80% survival rate (compared with an 86% mortality in the control group).⁷

During CPR, cerebral perfusion tends to decrease dramatically over time if adequate flow is not quickly reestablished.⁸ Maintaining a small amount of blood flow to the brain with CPR is not necessarily beneficial. Incomplete brain ischemia, which is created when only a small amount of blood is allowed into the brain after an anoxic insult (as in CPR), appears to result in more detrimental alterations in brain metabolism than does the complete anoxia resulting from the absence of any flow.⁹ When a small amount of blood is allowed to flow into an actively distorted and stressed metabolic system, the resulting cellular activity generates more toxic products of metabolism than complete anoxia would have produced.¹⁰ In other words, more brain damage seems to occur with prolonged CPR states than with no-flow states¹¹—especially if there is an increased level of glucose in the small quantities of blood supplied by CPR.¹² To date, this phenomenon has not been completely explained. Acidosis, in and of itself, is unlikely to be the only damaging factor, because severe respiratory acidosis does not damage the brain.¹³

PATHOPHYSIOLOGY OF BRAIN FAILURE

In vitro, central nervous system neurons can tolerate between 20 and 60 minutes of complete ischemic anoxia without irreversible injury.¹⁴ In vivo, however, injury occurs after a much shorter time and is much more severe. Immediately after the cessation of circulation to the brain, the cerebral vessels dilate in response to the local environmental factors and to increased arterial carbon dioxide tension ($P_a\text{CO}_2$). Because the brain has no stores of glucose, cellular metabolism quickly ceases. Absence of nutrients and hypoxia cause the most sensitive structures to lose their cellular integrity. This loss results in capillary leakage, edema, and cellular disruption and leads to the release of proteases and other damaging compounds into the surrounding tissues.¹⁵

These events, in turn, result in clogged microcirculation, stasis, and a vicious circle of worsening damage that backs up into the macrocirculation. If this process is allowed to continue for a substantial period and blood flow is then reestablished, the increased pressure gradient in the damaged area tends to disrupt the fragile architecture, much as the sudden bursting of a dam might do to downstream communities. The result is a progressive postresuscitative hypoperfusion state in which blood flow falls to less than 20% of normal within 90 minutes after reperfusion and remains at this low level for as long as 18 hours.^{16,17}

Two explanations for these phenomena have been proposed. The first is that massive overloading of the cells with calcium ions (Ca^{2+}) may be the initial stage of irreversible damage.¹⁸ Normally, the extracellular level of Ca^{2+} is high and the intracellular level is low. The damage to the cell membrane caused by hypoxia and loss of nutrient flow alters the gradient and allows Ca^{2+} to enter the cell, causing interference with enzymes, DNA, RNA, mitochondria, and energy production cycles. Infusion of high levels of Ca^{2+} into precapillary arterioles causes vasospasm and a vicious circle characterized by decreased flow and further depletion of oxygen and nutrients. The second theory is that during ischemia, abnormal metabolism may result in the creation of reactive oxygen metabolites, which attack DNA, RNA, and mitochondria, causing irreversible damage.¹⁹

Brain Death

DIAGNOSIS OF BRAIN DEATH

Brain death protocols have evolved to become highly specific and sensitive.²⁰ Brain death is a diagnosis of what is, not what might be. Initially, for an accurate diagnosis of brain death, there must be clear evidence of an acute, catastrophic, irreversible brain injury, and any reversible conditions that may obfuscate the clinical assessment (e.g., drug intoxication, hypothermia, and metabolic abnormalities) must be excluded.²¹ Subsequently, the physical examination must show coma, absent motor responses, absent brain stem reflexes, and apnea. Some protocols call for a second examination, performed after a variable interval.²² Further confirmatory studies (e.g., electroencephalography [EEG] or cerebral blood flow studies) may be ordered if there is any ambiguity in the clinical evaluation.²³

A typical brain death protocol may be summarized as follows:

1. Confirm that the patient is in a coma.
2. Evaluate the patient for seizure activity and decerebrate or decorticate movements.
3. Test for motor response to painful stimulation.
4. Test for pupillary response to light.
5. Test for the corneal reflex.

6. Test for the oculocephalogyric reflex (the doll's head reflex).
7. Test for the vestibulo-ocular reflex (the caloric test).
8. Test for upper and lower airway stimulation (e.g., pharyngeal and endotracheal suction).
9. Test for the gag reflex.
10. Perform the apnea test. This test should be the last test and should be conducted after two clinical examinations (separated by the mandatory observation period) have confirmed the absence of brain stem functions. The patient is disconnected from the ventilator while oxygenation of the lungs is continued passively. On the basis of calculation (whereby $P_a\text{CO}_2$ is assumed to rise 4 mm Hg in the first minute and 3 mm Hg every minute thereafter), the patient is allowed to build up to a $P_a\text{CO}_2$ of 60 mm Hg or more without becoming hypoxic. If there is no respiratory effort, the apnea test is considered confirmatory.²⁴
11. Consider ordering an EEG. The EEG should show electrocerebral silence for at least 30 minutes and must conform to established criteria for brain death.²⁵
12. If the cause of death cannot be determined with absolute accuracy, consider cerebral angiography. The absence of intracranial arterial circulation, as demonstrated by four-vessel angiography, confirms brain death.²⁶

THE NEW MEANING OF DEATH

The evolution of life support systems capable of prolonging vital signs indefinitely necessitated a more accurate definition of death, which arrived in 1968 in the form of the Harvard criteria.²⁷ In essence, these criteria considered the irreversible loss of certain organ functions, rather than whole body metabolic cessation, to be indicative of death. When the Harvard criteria were met, death was inevitable, even with continuing treatment. In a 1970 study in which all of the subjects met the Harvard criteria, all of the patients eventually died while undergoing continued medical treatment.²⁸ The Harvard criteria objectified the progression of disease, thereby making it possible for clinicians to predict inevitable death.

These early studies, however, only predicted with a reasonable certainty that patients meeting particular criteria would eventually die. A prognosis of death cannot necessarily serve as a diagnosis. In 1981, the President's Commission established brain death as a stand-alone criterion for determining death, not simply for predicting its inevitability.²⁹ The Uniform Determination of Death Act (UDDA) made brain death a criterion for death in 44 states.³⁰ This act states that an individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead and that a death certificate may then be filled out. Under the UDDA, death is pronounced at the time the criteria are met, and families may not demand continuing mechanical ventilation or other forms of ICU life support (except in the states of New York and New Jersey, both of which have conscience clauses).³¹

TECHNOLOGY AND DETERMINATION OF DEATH

The age of critical care medicine has changed the traditional concept of death. Before the postmodern technological revolution, determination of death was simple: a person was dead when a physician said so. The exact moment of death did not matter in the general scheme of things, because there was no postmortem treatment. In the new millennium, however, organ transplantation has changed the situation radically. Intensive care life support

systems can now create scenarios in which patients are dead enough for burial yet alive enough for recovery of viable organs for transplantation.³²

The traditionally accepted definition of death may be expressed as “the irreversible cessation of the integrated functioning of the organism as a whole.”³³ For practical purposes, this means that the organism dies when the central integrator of organ systems (i.e., the brain) reaches the point of functional irreversibility (not necessarily cellular death). For the organism to be pronounced dead, it is not necessary that each and every cell within the organism be dead: it is only necessary that the integrating organ function be irreversibly damaged. If the definition of death required that every single cell be dead, organ transplantation would be impossible because putrefaction would be the only benchmark of death.³⁴

At first glance, this definition of death would seem clear and unambiguous, but the clinical reality is that the brain dies in a progressive fashion, not instantaneously. Consequently, it is improbable that one will be able to discern the precise point at which death occurs. As Michael Darwin has written, “It is only the ideologue or the fool who acknowledges noon and midnight, but denies all the states of light and darkness that smoothly shade together to create day and night.”³⁵ As an analogy, we have arbitrarily decided on (and legally defined) the exact point at which a person is considered to have become intoxicated and legally incompetent to operate an automobile. But a particular blood alcohol level does not absolutely define drunkenness, any more than pronouncing a patient dead absolutely defines the exact point of death.

Resuscitative technology has muddied the waters further by creating additional uncertainty in the determination of death. As an example, in the United States, about 150 legally dead persons have undergone cryopreservation and are suspended in liquid nitrogen, awaiting a nanotechnology that will repair their fatal disease and restore them to life.^{36,37} In this practice, commonly known as cryonics,³⁸ a physician makes a pronouncement of death according to the usual cardiorespiratory criteria, whereupon the patient is medicolegally dead. Once this pronouncement has been made, the rules governing the procedures that can be performed change radically, in that the subject is no longer a living patient but a corpse. In the initial cryopreservation protocol, the subject is intubated and mechanically ventilated, and a highly efficient mechanical cardiopulmonary resuscitation device reestablishes circulation. Occasionally, subjects then begin to show what appear to be signs of life, including pupillary reaction and spontaneous motion.³⁹ Such cases raise crucial questions. Are these persons alive again, or were they ever really dead?

ARE THERE TWO KINDS OF DEATH?

The issue of determining death has become further confused by a creative interpretation of the UDDA, which, ironically, was drafted with the intention of clarifying this issue. As noted (see above), the UDDA guidelines declare that either “irreversible cessation of circulatory functions” or “irreversible cessation of the entire brain, including brain stem” constitutes death.³⁰ However, the UDDA does not elucidate how these two differing standards reflect the same phenomenon. The wording suggests that there are actually two kinds of death: brain and cardiac. This lack of a consistent standard for the determination of death, coupled with the intense demand for donor organs for transplantation, has promoted the evolution of a creative variation of organ procurement known as donation after cardiac death (DCD), which relies sole-

ly on the cessation of cardiorespiratory function, without reference to brain death.

This creative dichotomy between brain death and cardiac death is controversial. At a strictly functional level, it can be argued that the heart is irrelevant to the diagnosis of life or death because it fails the test of integration. The heart’s only purpose is to pump blood to the brain, which is the organ generally considered to be the integrator of the rest of the body. If cardiac standstill, in and of itself, constitutes death, then a patient whose heart is stilled during cardiopulmonary bypass is dead. Moreover, it is widely agreed that a patient who has a viable heart beating inside a brain-dead body is not alive. As W. H. Sweet stated three decades ago, “It is clear that a person is not dead unless his brain is dead. The time honored criteria of the stoppage of the heart beat and circulation are indicative of death only when they persist long enough for the brain to die.”⁴⁰

As noted (see above), brain death is defined in terms of irreversibility. A primary problem with the determination of death according to UDDA guidelines is the inability to establish precisely when it transitions from a reversible process to an irreversible event. Because the point of irreversibility is not known at the time death is declared, the exact time of death cannot be determined. Consequently, by a strict interpretation of the criteria, a patient may be still “alive” even though showing no demonstrable signs of life; if the brain is still functional, the patient cannot be dead. It does not matter if there is an intent to resuscitate or not. Neither the patient nor his or her family can consent to any procedure that will result in death, nor can the family consent to the patient’s being dead in a defined number of minutes, as has been suggested by proponents of DCD. Consenting to either of these options is tantamount to consenting to euthanasia.

Although the UDDA specifically required that death be irreversible, it failed to define the term. Accordingly, several ideological caucuses have developed around this issue, each with its own perspective. One caucus maintains that death is irreversible when the patient cannot “spontaneously” resuscitate. If so, how long must one wait to be sure that autoresuscitation will not occur? Long enough for a quorum of cells to die?

Another caucus maintains that death is irreversible when the patient cannot be resuscitated by any means or when resuscitation fails. If so, does this mean that every dying patient must be assaulted by every possible intervention before being declared dead?

A third caucus maintains that death is irreversible when the inherent order of the atoms that make up the brain is irrevocably destroyed. If, however, the overall structural integrity of the brain is preserved, there is no fundamental barrier, given our current understanding of physical law, to recovering the brain’s information content; regardless of how labor-intensive such recovery might be in practice, it is possible in principle. If the ultrastructure of the brain is physically destroyed, the laws of thermodynamics say that the information contained in the brain is irreversibly destroyed. With that consideration of irreversibility in mind, is a tobacco mosaic virus dead if its constituent parts can be broken up and shaken into solution and then reassemble themselves into a viable virus capable of self-replication?

THE FUTURE OF DEATH

There are disturbing differences between a corpse in a morgue and a brain-dead patient. If a whole-brain death (WBD) patient is a corpse, he or she is certainly a corpse with some unusual properties—one that breathes, circulates blood, digests food, filters wastes, and is capable of carrying a pregnancy to term.⁴¹ These

considerations raise the issue of whether there is a practical or ethical difference between being dead, being almost dead, or being in the process of dying, and they show that the precise moment when death occurs cannot be accurately pinpointed. It is clear that a WBD patient can be maintained on life-sustaining treat-

ment for much longer than was once thought and still retain definite characteristics of a living being. The organism as a whole, though disabled, is not yet dead and should not be represented as such—a fact that may have important consequences for our future conceptions of death and of life in death.

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11 COMA, COGNITIVE IMPAIRMENT, AND SEIZURES

Maxim D. Hammer, M.D.

Coma is the neurologist's favorite consultation: the history is usually straightforward, the neurologic examination is focused, and the differential diagnosis is limited. A good neurologic examination, in combination with a thoughtful battery of tests, will invariably achieve the correct diagnosis. It is vital for the intensivist to become equally comfortable with the rapid assessment of coma. Once initial stabilization of the patient has been achieved, management of coma is determined by the specific causative condition or conditions present. Rapid recognition of potentially reversible causes of coma (e.g., basilar artery occlusion [BAO], nonconvulsive status epilepticus, and herniation), followed by the appropriate emergency consultations, can often prevent or reduce morbidity and mortality.

This chapter is intended as a practical, rational, and efficient approach to the diagnosis and management of coma. To that end, an algorithmic approach to diagnosis is formulated, general treatment measures for comatose patients are outlined, specific causes of coma are reviewed, and prognostic issues are considered. Detailed discussions of neuroanatomy and cranial nerve pathways, which are readily available elsewhere,¹ are intentionally omitted, as are detailed descriptions of specific treatment of individual causes of coma (other than BAO, status epilepticus, cardiac arrest, increased intracranial pressure [IICP], and certain metabolic derangements).

Classification of Levels of Consciousness

AWAKENESS, ALERTNESS, AND AWARENESS

A patient's level of consciousness can usefully be described in terms of the three As of consciousness: *Awake*, *Alert*, and *Aware*. To be awake means to be fully roused and thus not asleep. To be alert means to be able to pay attention to one's environment or to an examiner. Finally, to be aware means to have an understanding of oneself and one's environment. Being oriented is a manifestation of being aware of one's environment.

A person who is awake, alert, and aware may be said to be fully conscious [see *Figure 1*]. One who is awake and alert but has lost awareness is severely demented. Someone who is merely awake and not alert or aware is delirious. A delirious patient's level of wakefulness may wax and wane. A person who is not awake, alert, or aware either is asleep (in which case he or she can be rendered awake—i.e., is arousable) or is somewhere along the so-called spectrum of coma (see below).

Admittedly, describing patients simply in terms of awakeness, alertness, and awareness omits many important nuances; nevertheless, it is an excellent and easily reproducible way of assessing level of consciousness.

UNRESPONSIVE PATIENT

The term unresponsive is used frequently, but often in a vague manner that does not yield a clear meaning. Fortunately, in the setting of coma management, there are only three possible meanings that need be considered [see *Figure 2*].

First, the term unresponsive may be applied to a patient who is actually fully conscious but is unable or unwilling to respond verbally. For example, a patient with aphasia (a common manifestation of stroke) may be awake, alert, and aware, yet unable to speak. As another example, a patient who is in a locked-in state (either from a brain stem injury or from generalized muscle paralysis) is fully conscious but cannot speak and cannot communicate except through subtle eye movements. Finally, patients with a psychiatric disorder may present with a so-called functional coma while remaining fully conscious; simple examination techniques quickly reveal that they are completely awake.

Second, the term unresponsive may be applied to a patient who has a waxing-and-waning level of wakefulness. This fluctuation between wakefulness and coma is what defines delirium, and it is invariably caused by infection, metabolic disturbances, or alcohol withdrawal.

Third, the term unresponsive may be applied to a patient who truly is not even awake. In this sense, the term could of course be applied to a person who is simply asleep, but for the purposes of this chapter, it should be understood as referring to a patient who is comatose.

SPECTRUM OF COMA

Patients who are not aware, alert, or even awake (except for those who are simply asleep) fall somewhere along the spectrum of coma. This spectrum reflects varying levels of impairment of the response to stimuli. On the high end of the spectrum, for example, is the patient who can be aroused (albeit perhaps only temporarily) by the sound of a voice. Somewhat farther down is the patient who can be temporarily aroused by a painful stimulus. Farther down still is the patient who cannot be aroused by a painful stimulus but at least exhibits some motor response to it. On the low end

			Aware
		Alert	
	Awake		
Sleep, Coma	Delirium	Dementia, Infant Consciousness	Normal Adult Consciousness

Figure 1 Awareness depends on alertness, which in turn depends on arousal (i.e., how awake one is). Normally cognizant adults are aware of themselves and their environment. Persons who have lost awareness but retain alertness and wakefulness may be characterized as severely demented. Persons who have lost alertness are delirious by definition, though their level of wakefulness may wax and wane. Finally, persons who are not aware, alert, or awake may be either asleep or in a coma.

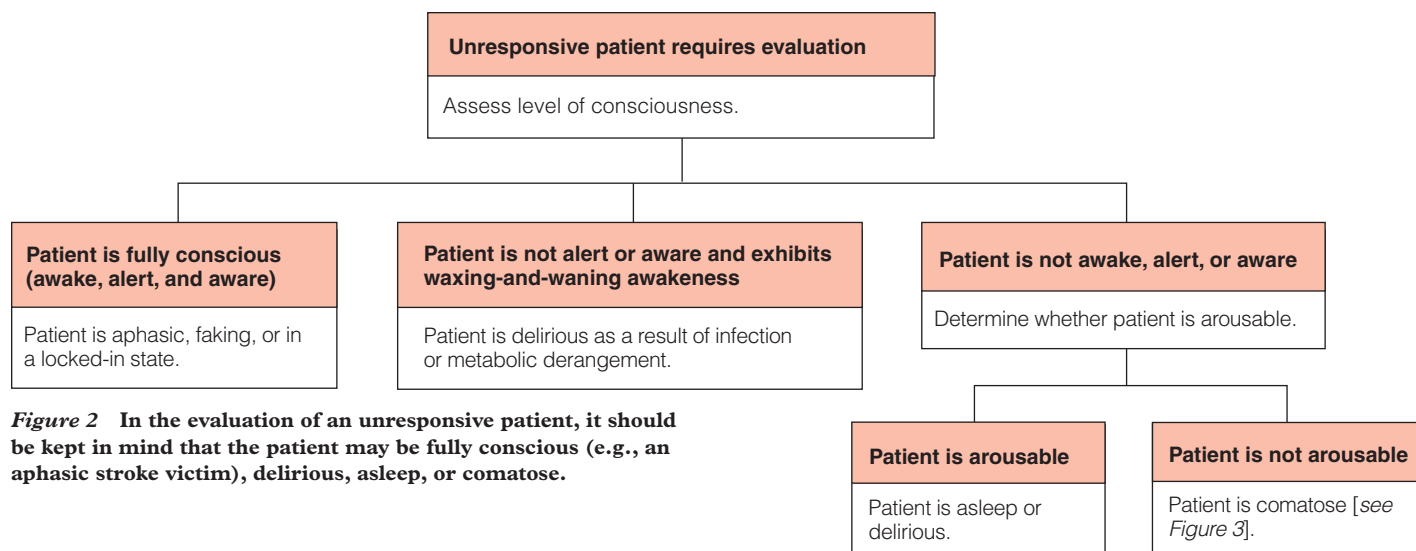


Figure 2 In the evaluation of an unresponsive patient, it should be kept in mind that the patient may be fully conscious (e.g., an aphasic stroke victim), delirious, asleep, or comatose.

of the spectrum is the patient who has no motor response to a painful stimulus; this is the generally accepted definition of coma.

The terms lethargy, stupor, and obtundation, though widely used, have come to signify different things to different people. Accordingly, to ensure precise communication, it is perhaps advisable to employ clear clinical patient descriptions rather than rely on these particular terms.

Initial Stabilization

The first step in dealing with coma is to stabilize the patient by addressing the ABCs of resuscitation (*A*irway, *B*reathing, and *C*irculation). The patient's airway must be cleared of all foreign material, and the patency of the airway must be verified. The spontaneous rate and rhythm of respiration should be noted. Endotracheal intubation is indicated in patients who are dyspneic, hypoventilating, or vomiting uncontrollably. If a patient is to be intubated, however, it is extremely helpful first to obtain a focused neurologic examination (which can be done in 60 seconds) because the information that can be gained from this examination will be lost when the patient is paralyzed for the intubation. Hyperventilation with a bag and mask and 100% oxygen should be performed before intubation to ensure adequate oxygenation during the procedure. If there is any possibility of cervical spine injury, intubation should be delayed, if possible, until fracture can be ruled out radiographically.

Circulation must be vigorously supported, especially in the setting of brain injury or hypoxia. This is accomplished by inserting a large-bore I.V. or central venous catheter and infusing isotonic fluids or volume expanders. The use of solutions containing free water (e.g., 5% dextrose in water) should be avoided, especially in the setting of brain injury or stroke, because such solutions have the potential to increase cerebral edema.

Clinical Evaluation

As the patient is being stabilized, evaluation should be initiated. A witness or someone else capable of providing a history should be sought. The differential diagnosis of coma is wide but limited [see Table 1]. Clues from the history, the focused neurologic examination, and the general physical examination are often helpful and sometimes diagnostic [see Figure 3].

HISTORY

The ideal historian is a person who knows the patient well. Optimally, if the coma was of sudden onset, a witness was present who can describe what occurred. A history of trauma, drug use, medications, recent febrile illness, heart disease, organ failure, or seizures often rapidly leads to the correct diagnosis [see Table 2]. Typically, the most challenging cases are those patients who are "found down"; such cases necessitate a clear diagnostic approach that begins with the physical and neurologic examinations.

FOCUSED NEUROLOGIC EXAMINATION

There are two good reasons for performing a neurologic examination on a coma patient. First, such an examination allows the physician to assign the patient a Glasgow Coma Scale (GCS) score [see Table 3], which may be used in making decisions about the necessity for intubation and which provides an objective means of following (at least superficially) the patient's neurologic status. Second, the neurologic examination may quickly yield important diagnostic information.

A complete and exhaustive neurologic examination is totally unnecessary. For the purposes of evaluating coma, a focused neurologic examination is preferable, being both valuable and rapid (~ 60 seconds). If intubation is indicated, the coma examination should be performed quickly before sedative and paralytic agents are given. This examination addresses a number of key findings [see Table 4], but in general, it may be thought of as assessing four neurologic variables: (1) spontaneous movements (~ 15 seconds), (2) pupillary response (~ 15 seconds), (3) ocular motility (~ 15 seconds), and (4) motor response (~ 15 seconds). A reflex hammer is not needed.

Spontaneous movements should be observed over a period of 10 to 20 seconds. Generalized seizures may present as tonic or tonic-clonic movements of one or both sides. Tonic seizures are characterized by sustained contractions with upper-extremity flexion and lower-extremity extension. Tonic-clonic seizures are characterized by tonic contractures alternating with periods of muscle atonia, resulting in rhythmic contractions. Myoclonus consists of motor jerks that are sudden, brief, shocklike, and randomly distributed; it may be seen in patients with hypoxic-ischemic encephalopathy (e.g., after cardiac arrest) or other metabolic disturbances. Other findings (e.g., a flaccid arm that hangs down the side of the stretcher or a leg that is extorted) may be indicative of

hemiparesis. The motor response to pain can be tested and assigned a GCS score. Asymmetry should be noted.

Pupillary responses are important in that their presence or absence distinguishes structural from metabolic coma (because

the pupils are generally resistant to metabolic insult); they also indicate the integrity of the brain stem [see Table 5]. The origin of the reticular activating system (RAS), the so-called on switch of consciousness, may be physically located adjacent to the brain stem nuclei that control pupillary response.

The pathways that control ocular motility also lie adjacent to the RAS. Roving eye movements usually indicate that the brain stem is intact and that a metabolic problem is affecting the brain. Minimal or absent eye movement in conjunction with reactive pupils also typically signifies a metabolic process. Gaze deviation may indicate a stroke: a cortical stroke will cause the eyes to look toward the damaged side of the brain, whereas a pontine stroke will cause the eyes to look away from the damaged side of the pons. Gaze deviation may also signify an ongoing seizure: the eyes look away from the hemisphere in which the seizure is occurring or, after the seizure is over, toward the postictal hemisphere. Vertical disconjugation of the eyes (skew deviation) is indicative of brain stem disease and frequently occurs during basilar artery thrombosis. Ocular bobbing (rapid downward movements with a slow drift back to the original position) is occasionally seen in the setting of extensive pontine damage.

GENERAL PHYSICAL EXAMINATION

Blood pressure, heart rate, and cardiac rhythm are key to the diagnosis of the various cardiovascular and hemodynamic causes of coma [see Table 1]. Hypothermia is noted in cases of exposure, drowning, methanol poisoning, and septic shock. Hyperthermia is obviously suggestive of an ongoing infectious process. A stiff neck is often caused by meningeal irritability resulting from infection or inflammation; it may be indicative of meningitis, but it also may be the only physical sign of subarachnoid hemorrhage. Various other physical findings may be observed in comatose patients as well [see Table 5].

A rise in intracranial pressure (ICP) occurs with any space-occupying lesion in the calvaria. Signs of rising ICP include increasing blood pressure, decreasing heart rate, and slowing or periodic respiration (Cushing phenomenon). Papilledema caused by IICP usually takes weeks to develop and is seldom a presenting sign.

Management

GENERAL MEASURES, TRIAGE, AND TEST BATTERY

As emergency management is being provided, laboratory studies should be obtained, including serum electrolyte, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), and creatinine levels, as well as liver function tests. A complete blood count (CBC), a urinalysis, and a urine toxicity screen should also be obtained. A lumbar puncture should be performed only if meningitis is suspected on the basis of clinical examination.

The so-called coma cocktail—consisting of dextrose, naloxone, and thiamine—is administered if the cause of coma is not immediately apparent from the brief history and physical examination; the addition of flumazenil is considered if benzodiazepine overdose is suspected [see Table 6].^{2,3} It should be kept in mind that administering dextrose to a thiamine-depleted patient (especially one who is malnourished or alcoholic) may precipitate the Wernicke-Korsakoff syndrome. As a rule, therefore, thiamine should always be given before dextrose.

Any comatose patient with focal signs on the coma examination should undergo head CT scanning. Any patient with signs of meningitis on the physical examination should receive emergency antibiotic therapy. When drug overdose or toxin ingestion is suspected, activated charcoal, 50 to 100 mg (with or without gastric

Table 1 Differential Diagnosis of Coma

Potential Cause of Coma	Differential Diagnosis
Cerebrovascular	Large brain stem stroke (with or without basilar artery occlusion) Massive stroke or hemorrhage with mass effect Subarachnoid hemorrhage Subdural or epidural hematoma Hypoxic-ischemic encephalopathy after cardiac arrest Hypertensive encephalopathy
Cardiovascular	Cardiac arrest Cardiac dysrhythmia Congestive heart failure Hypotension Myocardial infarction
Infectious	Bacteremia or sepsis Meningitis Encephalitis (e.g., herpesvirus, arbovirus)
Traumatic	Multiple severe concussions (diffuse axonal injury, second-hit syndrome) Subdural or epidural hematoma Multiple contusions Penetrating head injury
Toxic	Alcohol intoxication/withdrawal Opiate intoxication Anesthesia Overdose Antianxiety agents or antidepressants Anticholinergics Anticonvulsants Antihistamines Insulin Lithium Neuroleptics Opiates Salicylates Sedatives
Metabolic	Hyperglycemia or hypoglycemia Diabetic ketoacidosis Hyperosmolar nonketotic coma Hypernatremia or hyponatremia Osmotic demyelination syndrome: central pontine myelinolysis Hepatic failure Renal failure Hypoxia or hypercarbia Hypothermia
Epileptic	Grand mal status epilepticus Nonconvulsive status epilepticus Postictal state
Mass	Massive stroke or hemorrhage with mass effect Tumor or abscess with mass effect
Hematologic	Thrombotic thrombocytopenic purpura
Psychiatric	Conversion Malingering

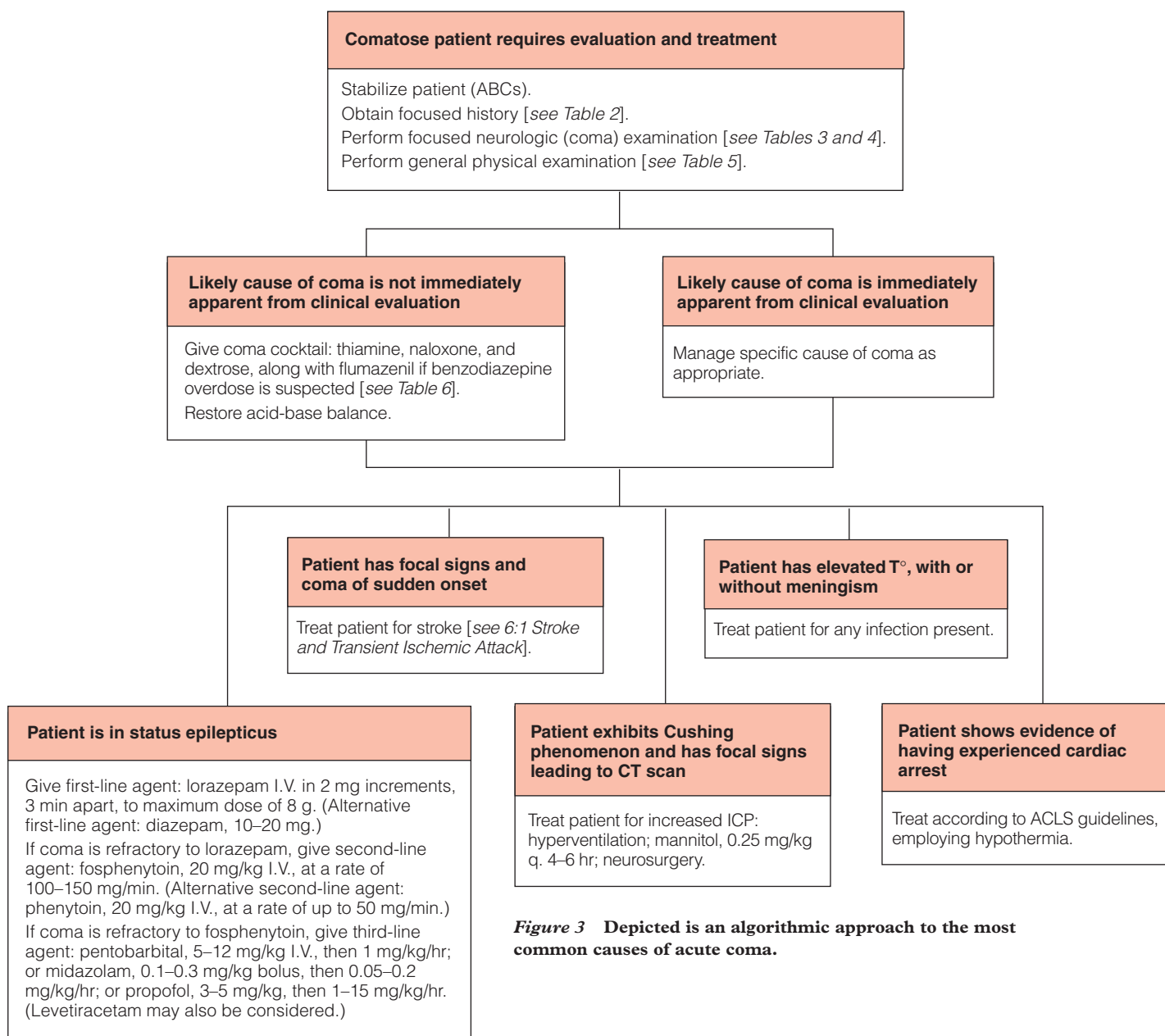


Figure 3 Depicted is an algorithmic approach to the most common causes of acute coma.

lavage), should be given to prevent systemic absorption. As noted, flumazenil may be given for suspected benzodiazepine overdose and may produce dramatic arousal; however, this agent is contraindicated in patients taking tricyclic antidepressants because of an increased risk of seizures.

Once the recommended general treatment measures have been carried out, the next step is to look for and address specific causes of coma.

MANAGEMENT OF SPECIFIC CAUSES OF COMA

Basilar Artery Occlusion

BAO is an uncommon cause of stroke but also an underrecognized one. Morbidity and mortality are high, with only about 15% to 45% of victims surviving.⁴ BAO may be caused by embolism (most often from the heart but sometimes from the vertebral arteries), by intrinsic atherothrombosis, or by vertebral dissection. It frequently presents with a stepwise accumulation of neurologic deficits that culminates in a coma.

A typical case scenario for BAO, occasionally heard by stroke neurologists, is as follows. A patient presents with double vision, followed hours later by ataxia. This may prompt an emergency department (ED) visit. The patient is admitted to the hospital but, on the nursing unit, becomes suddenly unresponsive and needs intubation for airway protection. In another typical scenario, a patient who has just undergone cardiac catheterization becomes suddenly unresponsive on the angiography table but is hemodynamically stable.

A comatose patient with BAO usually manifests obvious clinical signs of brain stem injury, such as quadriplegia, skew deviation, and diminished gag reflex (many physicians report that intubation is unexpectedly easy). On occasion, CT scanning may reveal an apparently hyperdense basilar artery [see Figure 4]; imaging of the posterior circulation invariably reveals the problem. Management of BAO should be aimed at immediate recanalization of the occluded artery. Thrombolysis, either intravenous (with tissue plasminogen activator) or intra-arterial (with urokinase or mechanical clot disruption), may be lifesaving.

As noted, patients with extensive brain stem injury resulting from BAO often die. Some enter what is known as the locked-in state, in which they remain conscious but are unable to move, breathe, or swallow. Occasionally, patients retain the capacity for subtle eye movements or eye blinking and thus are able to communicate through yes/no responses to questions. Most stroke neurologists consider the locked-in state a fate worse than death.

Seizures

A seizure disorder can cause coma in two different ways. First, the coma may be the initial manifestation of the immediate postictal state after a generalized seizure. In such cases, the coma resolves rapidly, and further management is unnecessary. The duration of the postictal coma may be directly correlated with patient age and inversely correlated with baseline functional status. Second, coma may develop when multiple generalized seizures occur in succession and there is not enough time between seizures to allow patients to recover. The resulting state is status epilepticus.

Generalized convulsive status epilepticus (GCSE) may be defined either as (1) continuous seizure activity lasting longer than 5 minutes or as (2) two or more discrete generalized seizures between which there is incomplete recovery of consciousness. GCSE is most frequently the result of noncompliance with an antiepileptic drug regimen, alcohol use or withdrawal, or drug toxicity. Less common causes include CNS infection, a cerebral tumor, trauma, refractory epilepsy, stroke, metabolic disorders, and cardiac arrest. If untreated, GCSE leads to cerebral edema, herniation, and death.

Table 2 Coma History

Questions to Be Asked	Possible Causes to Be Considered
Is there a witness?	[If no, see Table 4.]
Was it sudden?	Stroke If stepwise deterioration, consider BAO Seizure Cardiac arrest
Was there trauma?	Traumatic brain injury Subarachnoid hemorrhage Subdural or epidural hematoma with mass effect and herniation
Has there been drug use? If so, which drugs?	Recreational drug overdose Opioids, alcohol Prescription drug overdose Opioids, benzodiazepines, barbiturates, anticholinergics
Was there a recent febrile illness?	Meningitis or encephalitis Bacteremia or sepsis
Is there a history of heart disease?	Cardiac arrest Myocardial infarction Congestive heart failure Cardiac dysrhythmia Hypotension
Is there a history of organ failure?	Renal failure Hepatic failure
Is there a history of seizures?	Postictal from single seizure Convulsive status epilepticus Nonconvulsive status epilepticus

BAO—basilar artery occlusion

Table 3 Glasgow Coma Scale

Test	Response	Score
Eye opening (E)	Spontaneous	4
	To verbal command	3
	To pain	2
	None	1
Best motor response (arm) (M)	Obedience to verbal command	6
	Localization of painful stimulus	5
	Flexion withdrawal response to pain	4
	Abnormal flexion response to pain (decorticate rigidity)	3
	Extension response to pain (decerebrate rigidity)	2
	None	1
Best verbal response (V)	Oriented conversation	5
	Disoriented conversation	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
Total (E + M + V)		3–15

A tonic-clonic seizure begins with a tonic contraction that lasts as long as 30 seconds, followed by several minutes of repeated muscle contractions, loss of pupillary response to light, sweating, tachycardia, excessive bronchial secretion, and marked hypertension. Repeated seizures cause lactic and respiratory acidosis, rhabdomyolysis and myoglobinuria, aspiration and pulmonary edema, shoulder dislocations, rib fractures, and cardiac dysrhythmias. The neuronal damage induces an inflammatory response, and if seizures continue, cerebral edema ensues.

In the treatment of GCSE, the aim is not to stop the body from convulsing but to stop the abnormal cerebral electrical activity immediately. The longer GCSE continues, the more refractory it will be to treatment. Paralytics mask (but do not prevent) the seizures; therefore, intubation and paralysis should be avoided if possible.

Like all other coma victims, patients with GCSE should first be stabilized [see Initial Stabilization, above]. I.V. access should then be obtained. Glucose should be given empirically, along with thiamine, and blood should be drawn and sent for laboratory tests (including anticonvulsant levels).

Anticonvulsant management of status epilepticus is discussed in detail elsewhere^{5,6} and so need only be summarized here. The first-line treatment for GCSE consists of administration of lorazepam [see Figure 3]. Although there is no significant difference between the benzodiazepines with respect to rapidity of seizure control, lorazepam is thought to bind more tightly to brain receptors and thus is believed to have a longer duration of action. Lorazepam is given in 2 mg increments 3 minutes apart to a maximum dose of 8 mg before another agent is tried [see Table 7]. Diazepam may be employed as an alternative. The second-line agent is fosphenytoin, 20 mg/kg at up to 150 mg/min I.V.; phenytoin may be given as an alternative. If the patient does not respond to either lorazepam or fosphenytoin, a third-line agent—pentobarbital, midazolam, or propofol—should be given in a continuous infusion. Of the three third-line choices, midazolam may be the most effective, and it

Table 4 Focused Neurologic Examination (Coma Examination)

Neurologic Variable Assessed	Findings	Likely Cause of Coma
Spontaneous movement (15 sec)	Rhythmic movements	Seizure
	Random jerks (myoclonus)	Hypoxic-ischemic encephalopathy
Pupillary response (15 sec)	Unilateral fixed and dilated pupil	Brain herniation (mass) Posterior communicating artery aneurysm
	Midposition unreactive pupils	Midbrain lesion
	Pinpoint unreactive pupils	Pontine lesion
	Small and sluggishly reactive pupils	Drug intoxication
	Large and unreactive pupils	Atropine
	Unreactive pupils	Barbiturates, paralytics, lidocaine, phenothiazines, methanol, aminoglycoside antibiotics, hypothermia
Ocular motility (15 sec)	Roving eye movements	Metabolic insult to brain; brain stem is intact
	Gaze deviation	Stroke (eyes look toward damaged side of brain) Seizure (eyes look away from side of brain producing seizure)
	Skew deviation	BAO
	Ocular bobbing	Extensive damage to pons
	Unilateral weakness	Structural injury (e.g., stroke)
Motor response (15 sec)	Posturing (flexor or extensor)	Herniation (mass) Extensive cortical injury

certainly has the lowest side effect profile. Levetiracetam has also been successfully employed to treat some refractory cases of GCSE.^{7,8}

The goal of therapy is to achieve a burst-suppression pattern on electroencephalography for 12 to 24 hours before any attempt is made to taper medications.

Increased Intracranial Pressure

If ICP is suspected on the basis of clinical examination and herniation is identified, treatment must be initiated immediately.⁹ Medical management of ICP is a temporizing measure, aimed at slowing the process of herniation until the problem can be corrected neurosurgically.

The head of the patient's bed should be elevated to an angle of 30° to 45° to facilitate venous return from the head. If the patient is intubated, hyperventilation to bring the carbon dioxide tension below 25 mm Hg will rapidly, but only transiently, lower the ICP. Mannitol, 0.25 mg/kg every 4 to 6 hours, will also control ICP temporarily. Steroids may be used in the setting of tumors or abscesses of the brain. In most cases of ICP, the eventual treatment is neurosurgical decompression.

Cardiac Arrest

Cardiac arrest, if ongoing, is treated according to advanced cardiac life support (ACLS) guidelines. Several preliminary studies on the use of hypothermia for brain resuscitation after ventricular fibrillation (VF) cardiac arrest led to the publication of two randomized, controlled clinical trials in back-to-back issues of the *New England Journal of Medicine* in 2002.^{10,11} Both trials clearly demonstrated that hypothermia significantly improved survival and neurologic outcomes. As a result, the Advanced Life Support Task Force of the International Liaison

Committee on Resuscitation issued a guideline statement containing the following recommendation: "Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32° C to 34° C for 12 to 24 hours when the initial rhythm was VF. Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest."¹² This recommendation has spurred the implementation of hypothermia for resuscitation of cardiac arrest victims in many hospital centers.

Metabolic Derangements

Intoxication Many comatose patients who are seen in the ED are suffering from an overdose of alcohol, narcotics, sedatives, or some combination thereof. Most of these drugs induce depression of respiration and cardiovascular function, which is a major cause of mortality in comatose patients. Anticipation and early treatment of these complications may alleviate their effects. Early intubation, respiratory support, and maintenance of normal blood pressure are essential. Gastric lavage is effective when ingestion of a drug is discovered no more than 4 hours after the event (except in the case of salicylates, which may be removed in substantial amounts as long as 10 hours after ingestion). Accordingly, in most cases of drug overdose, little is gained by performing gastric lavage more than 4 hours after ingestion, unless the patient has been in shock and consequently manifests delayed gastric emptying and slowed absorption. When a patient is comatose or uncooperative, however, the examiner is rarely able to determine the exact time of ingestion; thus, gastric lavage is almost always indicated in this situation.

Patients are intubated with a cuffed endotracheal tube (to protect the airway from aspirated gastric contents) and placed in the left lateral decubitus position (to allow pooling of the gas-

Table 5 General Physical Examination

Physical Variable Assessed	Finding and Possible Causative Condition
Skin	Signs of trauma around head/neck Jaundice Hepatic failure Exanthema Viral infection Petechial rash Meningococcal infection
Head and neck	Brudzinski or Kernig sign Meningitis, meningoencephalitis Subarachnoid hemorrhage
Temperature	Fever Infection (meningitis, encephalitis, bacteremia, sepsis) Hypothermia Exposure Intoxication (alcohol, benzodiazepine, barbiturate) Myxedema coma Sepsis
Breath	Alcohol intoxication Fetor hepaticus Hepatic failure Uriniferous smell Uremia Ketoacidosis
Blood pressure	Hypotension Shock Sepsis Intoxication Myocardial infarction Addison disease Hypertension Hypertensive encephalopathy
Cardiac conduction and rhythm (ECG)	Dysrhythmia Acute myocardial infarction
Abdomen	Hepatomegaly Splenomegaly

tric contents) with the head down. Lavage is then performed with copious amounts of fluid until the returned fluid is clear. After evacuation, a slurry containing 10 g of activated charcoal in 30 to 50 ml is instilled into the stomach via a nasogastric tube. After lavage, cathartic agents may be used to shorten the transit time through the GI tract and thus to decrease absorption of the ingested material. Diuresis (saline, ionized, or osmotic), dialysis, and charcoal hemoperfusion all facilitate excretion of toxins. Specific antidotes exist for several common intoxicants; however, discussion of these antidotes is beyond the scope of this chapter.

Hypoglycemic coma Symptomatic hypoglycemia may occur when plasma glucose levels fall below 45 mg/dl. Symptoms may range from jitteriness with palpitations and diaphoresis to focal neurologic symptoms mimicking ischemic stroke to frank coma. The most common predisposing cause is diabetes; other common causes include alcoholism, hepatic failure, and renal failure.

If hypoglycemic coma is prolonged, it may result in permanent brain damage. Therefore, initial management involves urgent restoration of the patient to a euglycemic state. This may be accomplished through I.V. injection of glucose. Traditionally, injection of an ampule (50 ml) of a 50% solution is prescribed; however, this measure frequently results in loss of the peripheral I.V. site used. Alternatively, 250 ml of a 10% dextrose solution is rapidly injected; this measure provides the same amount of dextrose without causing any loss of venous access. If necessary, infusion of a 5% dextrose solution may be continued subsequently. As noted [see General Measures, Triage, and Test Battery, *above*], if the patient is thiamine depleted, 100 mg of thiamine should be given before dextrose so as not to precipitate Wernicke-Korsakoff syndrome.

Further treatment consists of prevention, in the form of educating patients in the use of insulin and encouraging them to carry glucose tablets or sweets with them at all times. A supply of glucagon (1 g I.M.) that can be administered by relatives may also be stored at home.

Diabetic ketotic coma Because patients who are comatose as a result of diabetic ketoacidosis often present in a profoundly dehydrated state, treatment must be initiated as soon as possible. The following are the key components of the management of diabetic ketoacidosis.

1. Replacement of fluid losses (the average fluid loss is approximately 7 L).
2. Normalization of electrolyte levels and careful monitoring of serum potassium.
3. Restoration of acid-base balance (bicarbonate infusion is reserved for severe cases).



Figure 4 In this noncontrast head CT scan, the basilar artery, which runs ventral to the pons and the lower midbrain, appears hyperdense. In the setting of acute coma, this finding suggests BAO.

Table 6 Coma Cocktail

Drug	Indications	Dosing (Adults)	Potential Adverse Effects
Thiamine	Wernicke-Korsakoff syndrome Ethylene glycol ingestion	100 mg I.V. over 5 min	Anaphylactoid reaction Hypotension Angioedema
Dextrose	Symptomatic hypoglycemia Altered mental status without ability to rapidly obtain serum glucose level	50–100 ml of 50% dextrose I.V. Alternatively, 250 ml of 10% dextrose (to prevent the phlebitis that frequently occurs with administration of 50% dextrose)	Phlebitis Cellulitis
Naloxone	Reversal of CNS depression and respiratory depression caused by overdose of opioid medication	0.1 mg I.V. initially (I.V. route is more effective than subcutaneous or endotracheal), aimed at producing subtle improvement in ventilation Repeat doses given in 2–3 min intervals, increased very slowly each time If no response after total dose of 10 mg, opioid toxicity ruled out	Hypersensitivity reaction Precipitation of sudden narcotic withdrawal syndrome (If heroin has been tainted with scopolamine, withdrawal of opioid can precipitate anticholinergic crisis) Lung injury, hypertension, and cardiac dysrhythmias (rarely reported)
Flumazenil	Benzodiazepine overdose	0.2 mg I.V. over 30 sec If no response, 0.3 mg I.V. over 30 sec If still no response, 0.5 mg I.V. every 30 sec to maximum dose of 3 mg	Contraindicated in patient experiencing seizure Benzodiazepine withdrawal, which may cause seizures and autonomic dysfunction

- Correction of insulin deficiency (4 to 6 U/hr).
- Replenishment of energy stores (e.g., through dextrose infusion with insulin coverage until the patient can resume oral feeding).
- Investigation to identify an underlying cause (infection is common).

Hyperglycemic hyperosmolar nonketotic coma Management of hyperosmolar nonketotic coma is essentially the same as that of diabetic ketotic coma. It is particularly important, however,

that meticulous rehydration be performed, given that many patients with this condition are elderly.

Vegetative State

Approximately 10% to 12% of comatose patients eventually lapse into a vegetative state (VS). Whereas comatose patients have closed eyes and do not respond to pain, VS patients have spontaneous eye opening according to sleep-wake cycles and may have minimal, purposeless movement. Specifically, the diagnosis of VS

Table 7 Drugs Used to Treat Status Epilepticus

Drug	Priority of Use	Dosing	Potential Adverse Effect
Lorazepam	First-line agent	2 mg increments I.V. 3 min apart to maximum of 8 mg	Respiratory depression Hypotension
Diazepam	Alternative first-line agent	10 mg I.V., 1 or 2 doses	Respiratory depression Hypotension
Fosphenytoin	Second-line agent	20 mg/kg, 150 mg/min	Dysrhythmia Hypotension
Phenytoin	Alternative second-line agent	20 mg/kg, 50 mg/min	Dysrhythmia Hypotension (Risk is lower than with fosphenytoin)
Pentobarbital	Third-line agent	5–12 mg/kg, 1–10 mg/kg/hr	Poor WBC chemotaxis Paralysis of respiratory cilia Poikilothermia
Midazolam	Third-line agent	0.1–0.3 mg/kg, 0.05–2.0 mg/kg/hr	Tachyphylaxis Death (mortality lower than with propofol)
Propofol	Third-line agent	3–5 mg/kg, 1–15 mg/kg/hr	Recurrent seizures after abrupt discontinuance Hypotension Hypertriglyceridemia Anemia Death (mortality higher than with midazolam)

WBC—white blood cell

can be made if there is intermittent wakefulness (sleep-wake cycles); no evidence of awareness of self or environment or ability to interact with others; no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to external stimuli; no evidence of language comprehension or expression; and sufficiently preserved hypothalamic and brain stem autonomic function to permit survival with medical and nursing care. VS that persists for more than 1 month is referred to as a persistent vegetative state (PVS); PVS that lasts for 1 year or longer is considered permanent VS.^{13,14}

Prognosis

At least 50% of patients who are in traumatic VS will recover consciousness within 1 year, compared with only 15% of patients in nontraumatic VS. In one series, 69% of nontraumatic VS patients died, 20% survived with severe disability, and 8% survived without severe disability. Indicators of poor prognosis in nontraumatic VS patients include the absence of pupillary reflexes for 24 hours after the event; no withdrawal from painful stimuli after 72 hours; the absence of roving eye movements after 7 days; and the absence of motor response to noxious stimuli after 72 hours.¹⁵⁻¹⁷

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12 ACID-BASE DISORDERS

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Anticipation and early identification of conditions that alter the body's ability to compensate for acid-base disorders are vital in the management of surgical and critically ill patients. A clear understanding of metabolic-respiratory interactions and a systematic approach aimed at identifying the separate components of acid-base disorders not only serves as a diagnostic tool but also helps in formulating therapeutic interventions. For example, abnormal acid-base balance may be harmful in part because of the patient's response to the abnormality, as when a spontaneously breathing patient with metabolic acidosis attempts to compensate by increasing minute ventilation. Such a response may lead to respiratory muscle fatigue with respiratory failure or diversion of blood flow from vital organs to the respiratory muscles, eventually resulting in organ injury. The increased catecholamine levels associated with acidemia may provoke cardiac dysrhythmias in critically ill patients or increase myocardial oxygen demand in patients with myocardial ischemia. In such cases, it may be prudent not only to treat the underlying disorder but also to provide symptomatic treatment for the acid-base disorder itself. Accordingly, it is important to understand both the causes of acid-base disorders and the limitations of various treatment strategies.

To treat acid-base disorders, it is not sufficient simply to return one or two laboratory parameters to normal values; one must understand the overall course of the disorder and the specific forces involved at any particular time. For example, in a patient with acute lung injury and moderate hypercapnia, allowing mild acidemia may be preferable to forcing the lung to achieve a normal carbon dioxide tension (P_{CO_2}). Similarly, prescribing bicarbonate therapy without anticipating the effects on the body's own compensatory efforts may induce an unwanted rebound alkalemia. A comprehensive understanding of the pathophysiology and a practical approach to bedside evaluation are complementary components of care and are equally necessary in the management of an acid-base disorder.

General Principles

DESCRIPTION AND CLASSIFICATION OF ACID-BASE DISORDERS

There are three widely accepted methods of describing and classifying acid-base abnormalities. Essentially, they differ from one another only with respect to assessment of the metabolic component of the abnormality; all three treat P_{CO_2} as an independent variable. The first method quantifies the metabolic component by using the bicarbonate ion (HCO_3^-) concentration (in the context of P_{CO_2}); the second, by using the standard base excess (SBE); and the third, by using the strong ion difference (SID). In practice, these three methods

yield virtually identical results when employed to quantify the acid-base status of a given blood sample.¹⁻⁷ Thus, the only significant distinctions between the methods are conceptual ones, related to how each one approaches the understanding of the mechanism of the disorder.⁶⁻¹⁰ In this chapter, we emphasize the physicochemical determinants of pH in the blood and the tissues; however, it is a simple matter to convert from one approach to the other if desired.⁵

There are three mathematically independent determinants of blood pH: (1) the SID, defined as the difference in concentration between strong cations (e.g., sodium [Na^+] and potassium [K^+]) and strong anions (e.g., chloride [Cl^-] and lactate); (2) the total concentration of weak acids (Atot), mainly consisting of albumin and phosphate; and (3) P_{CO_2} . These three variables, and only these three, can independently affect plasma pH. The H^+ and HCO_3^- concentrations are dependent variables whose values in plasma are determined by the SID, Atot, and P_{CO_2} . Changes in the plasma H^+ concentration occur as a result of changes in the dissociation of water and Atot, brought about by the electrochemical forces generated by changes in the SID and P_{CO_2} . The SBE is mathematically equivalent to the difference between the current SID and the SID required to restore the pH to 7.4, given a P_{CO_2} of 40 mm Hg and the prevailing Atot. Thus, an SBE of -10 mEq/L means that the SID is 10 mEq less than the value required to achieve a pH of 7.4.

The essential element of this physicochemical approach is the emphasis on independent and dependent variables. Only changes in the independent variables can bring about changes in the dependent variables. That is, movement of H^+ or HCO_3^- cannot affect plasma H^+ or HCO_3^- concentrations unless changes in the SID, Atot, or P_{CO_2} also occur. Several reviews of this approach are available in the literature.^{3,4,5-15} In what follows, we discuss the clinical application of this approach to the diagnosis and treatment of individual acid-base disorders.

ASSESSMENT OF ACID-BASE BALANCE

Acid-base homeostasis is defined by the plasma pH and by the conditions of the acid-base pairs that determine it. Normally, arterial plasma pH is maintained between 7.35 and 7.45. Because blood plasma is an aqueous solution containing both volatile acids (e.g., CO_2) and fixed acids, its pH is determined by the net effects of all these components on the dissociation of water. The determinants of blood pH can be grouped into two broad categories, respiratory and metabolic. Respiratory acid-base disorders are disorders of P_{CO_2} ; metabolic acid-base disorders comprise all other conditions affecting pH, including disorders of both weak acids (often referred to as buffers, although the term is imprecise) and strong acids (organic and inorganic) and bases. Any of the following indicators serves to identify an acid-base disorder:

1. An abnormal arterial blood pH (pH < 7.35 signifies acidemia; pH > 7.45 signifies alkalemia)
2. An arterial carbon dioxide tension (Paco₂) that is outside the normal range (35 to 45 mm Hg)
3. A plasma HCO₃⁻ concentration that is outside the normal range (22 to 26 mEq/L).
4. An arterial SBE that is either abnormally high (≥ 3 mEq/L) or abnormally low (≤ -3 mEq/L)

Once identified, an acid-base disorder can be classified according to a simple set of rules [see Table 1]. A disorder that does not fit well into the broad categories established by these rules can be considered a mixed (or complex) disorder. Some of the basic categories can be further divided into various subcategories (see below), but before the issue of classification is addressed in detail, three general caveats must be considered.

First, interpretation of arterial blood gas values and blood chemistries depends on the reliability of the data. Advances in clinical chemistry have improved the sensitivity of instruments used to measure electrolyte concentrations (e.g., ion-specific electrodes) and have greatly enhanced the speed and ease of analysis. Inevitably, however, prolonged exposure to the atmosphere results in a lowering of the Pco₂, and over time, there may be ongoing cellular metabolism. Accordingly, prompt measurement is always advisable. Even with prompt measurement, laboratory errors may occur, and information may be incorrectly reported. Samples drawn from indwelling lines may be diluted by fluid or drug infusions (a notorious source of error). When the situation is confusing, it is usually best to repeat the measurement.

Second, interpretation of arterial blood gas values may be problematic in patients with severe hypothermia (e.g., trauma patients undergoing damage-control interventions, who often are severely hypothermic and sometimes experience severe acidosis), in that the findings may not reflect the actual blood gas values present. Because blood samples are “normalized” to a temperature of 37°C before undergoing analysis, the results obtained in samples from a patient whose body temperature is significantly lower than 37°C (98.6°F) may not be sufficiently accurate. To obviate this potential problem, the results may have to be adjusted to take the patient’s actual temperature into account. At present, however, such temperature correction is not routinely done,

and there has been some controversy regarding whether it has real clinical value.^{16,17}

Third, whereas the aforementioned four indicators are useful for identifying an acid-base disorder, the absence of all four does not suffice to exclude a mixed acid-base disorder (i.e., alkalosis plus acidosis) in which the two components are completely matched. Fortunately, such conditions are rare. In addition, apart from distinguishing a respiratory acid-base disorder from a metabolic acid-base disorder, the four indicators and the rules previously mentioned [see Table 1] provide no information on the mechanism of an acid-base disorder.

Metabolic Acid-Base Disorders

Metabolic acid-base derangements are produced by a significantly greater number of underlying disorders than respiratory disorders are and are almost always more difficult to treat. Traditionally, metabolic acidoses and alkaloses are categorized according to the ions that are responsible (e.g., lactic acidosis and chloride-responsive alkalosis).

It is important to recognize that metabolic acidosis is caused by a decrease in the SID, which produces an electrochemical force that acts to increase the free H⁺ concentration. A decrease in the SID may be brought about by the generation of organic anions (e.g., lactate and ketones), by the loss of cations (as with diarrhea), by the mishandling of ions (as with renal tubular acidosis [RTA]), or by the addition of exogenous anions (as with iatrogenic acidosis or poisoning). By contrast, metabolic alkalosis is caused by an inappropriately large SID (although it may be possible for the SID to be inappropriately large without exceeding the normal range of 40 to 42 mEq/L). An increase in the SID may be brought about by the loss of more strong anions than strong cations (as with vomiting or diuretic therapy) or, in rare instances, by the administration of more strong cations than strong anions (as with transfusion of large volumes of banked blood containing sodium citrate).

Because metabolic acid-base disorders are caused by changes in the SID, their treatment necessarily involves normalization of the SID. Metabolic acidoses are corrected by increasing the plasma Na⁺ concentration more than the plasma Cl⁻ concentration (e.g., by administering NaHCO₃),

Table 1 Differentiation of Acid-Base Disorders⁶

Disorder	Physicochemical Parameter		
	HCO ₃ ⁻ Concentration (mEq/L)	Pco ₂ (mm Hg)	SBE (mEq/L)
Metabolic acidosis	< 22	= (1.5 × HCO ₃ ⁻) + 8 = 40 + SBE	< -5
Metabolic alkalosis	> 26	= (0.7 × HCO ₃ ⁻) + 21 = 40 + (0.6 × SBE)	> + 5
Acute respiratory acidosis	= [(Pco ₂ - 40)/10] + 24	> 45	= 0
Chronic respiratory acidosis	= [(Pco ₂ - 40)/3] + 24	> 45	= 0.4 × (Pco ₂ - 40)
Acute respiratory alkalosis	= 24 - [(40 - Pco ₂)/5]	< 35	= 0
Chronic respiratory alkalosis	= 24 - [(40 - Pco ₂)/2]	< 35	= 0.4 × (Pco ₂ - 40)

Pco₂ = carbon dioxide tension; SBE = standard base excess.

and metabolic alkaloses are corrected by replacing lost Cl^- (e.g., by giving sodium chloride [NaCl], potassium chloride [KCl], or even hydrochloric acid [HCl]). So-called chloride-resistant metabolic alkaloses [see Metabolic Alkalosis, Chloride-Resistant Alkalosis, *below*] are resistant to chloride administration only because of ongoing renal Cl^- loss that increases in response to increased Cl^- replacement (as with hyperaldosteronism).

PATHOPHYSIOLOGY

Disorders of metabolic acid-base balance occur in one of three ways: (1) as a result of dysfunction of the primary regulating organs, (2) as a result of exogenous administration of drugs or fluids that alter the body's ability to maintain normal acid-base balance, or (3) as a result of abnormal metabolism that overwhelms the normal defense mechanisms. The organ systems responsible for regulating the SID in both health and disease are the renal system and, to a lesser extent, the gastrointestinal (GI) tract.

Renal System

Plasma flows to the kidneys at a rate of approximately 600 mL/min. The glomeruli filter the plasma, producing filtrate at a rate of 120 mL/min. The filtrate, in turn, is processed by reabsorption and secretion mechanisms in the tubular cells along which it passes on its way to the ureters. Normally, more than 99% of the filtrate is reabsorbed and returned to the plasma. Thus, the kidney can excrete only a very small amount of strong ion into the urine each minute, which means that several minutes to hours are required to make a significant impact on the SID.

The handling of strong ions by the kidney is extremely important because every chloride ion that is filtered but not reabsorbed increases the plasma SID. Most of the human diet contains similar ratios of strong cations to strong anions; thus, there is usually sufficient Cl^- available for renal Cl^- handling to be the primary regulating mechanism. Given that renal Na^+ and K^+ handling is influenced by other priorities (e.g., intravascular volume and plasma K^+ homeostasis), it is logical that so-called acid handling by the kidney is generally mediated through management of the Cl^- balance.

Traditional approaches to the question of renal acid handling have focused on H^+ excretion, emphasizing the importance of ammonia (NH_3) and its add-on cation, ammonium (NH_4^+). However, H^+ excretion per se is irrelevant in that water provides an essentially infinite source of free H^+ . Indeed, the kidney does not excrete H^+ to any greater degree in the form of NH_4^+ than in the form of H_2O . The purpose of renal ammoniogenesis is to allow the excretion of Cl^- without Na^+ or K^+ . This purpose is achieved by supplying a weak cation (NH_4^+) that is "coexcreted" with Cl^- . The mechanisms of RTA are currently being reinterpreted by some authors in the light of a growing body of evidence showing that abnormal chloride conductance, rather than H^+ or HCO_3^- handling per se, is responsible for these disorders.³

Kidney-Liver Interaction

The importance of NH_4^+ to systemic acid-base balance, then, rests not on its carriage of H^+ or its direct action in the plasma (normal plasma NH_4^+ concentration < 0.01 mEq/L) but on its coexcretion with Cl^- . Of course, production of

NH_4^+ is not restricted to the kidney. Hepatic ammoniogenesis (as well as glutaminogenesis) is also important for systemic acid-base balance and, as expected, is tightly controlled by mechanisms sensitive to plasma pH.¹⁸ Indeed, this reinterpretation of the role of NH_4^+ in acid-base balance is supported by the evidence that hepatic glutaminogenesis is stimulated by acidosis.¹⁹ Metabolism of nitrogen by the liver can yield urea, glutamine, or NH_4^+ . Normally, the liver releases only a very small amount of NH_4^+ , incorporating most of its nitrogen into either urea or glutamine. Hepatocytes have enzymes to enable them to produce either of these end products, and both allow regulation of plasma NH_4^+ at suitably low levels. At the level of the kidneys, however, the production of urea or glutamine has significantly different effects in that the kidneys use glutamine to generate NH_4^+ and facilitate the excretion of Cl^- . Thus, production of glutamine by the liver can be seen as having an alkalinizing effect on plasma pH because of the way in which the kidneys use this substance.

Further support for this scenario comes from the discovery that hepatocytes are anatomically organized according to their enzymatic content.²⁰ Hepatocytes with a propensity to produce urea are positioned closer to the portal venule; those with a propensity to produce glutamine are positioned farther downstream. The upstream (urea-producing) hepatocytes have the first chance at the NH_4^+ delivered. However, acidosis inhibits ureagenesis, thereby leaving more NH_4^+ available for the downstream (glutamine-producing) hepatocytes. The leftover NH_4^+ is thus, in a sense, packaged as glutamine for export to the kidney, where it is used to facilitate Cl^- excretion.

Gastrointestinal Tract

The GI tract is an underappreciated component of acid-base balance. In different regions along its length, the GI tract handles strong ions quite differently. In the stomach, Cl^- is pumped out of the plasma and into the lumen, thereby reducing the SID of the gastric juice and thus the pH as well. On the plasma side, the SID is increased by the loss of Cl^- and the pH rises, producing the so-called alkaline tide that occurs at the beginning of a meal, when gastric acid secretion is maximal.²¹

In the duodenum, Cl^- is reabsorbed and the plasma pH is restored. Normally, only slight changes in plasma pH are evident because Cl^- is returned to the circulation almost as soon as it is removed. If, however, gastric secretions are removed from the patient, whether by catheter suctioning or vomiting, Cl^- will be progressively lost and the SID will steadily increase. It is important to remember that it is the loss of Cl^- , not of H^+ , that determines the plasma pH. Although H^+ is lost as HCl , it is also lost with every molecule of water removed from the body. When Cl^- , a strong anion, is lost without the corresponding loss of a strong cation, the SID is increased, and, therefore, the plasma H^+ concentration is decreased. When H^+ is lost as water rather than as HCl , the SID does not change; thus, the plasma H^+ concentration does not change either.

The pancreas secretes fluid into the small intestine that possesses an SID much higher than the plasma SID and is very low in Cl^- . Thus, the plasma perfusing the pancreas has its SID decreased, a phenomenon that peaks about 1 hour after a meal and helps counteract the alkaline tide. If large

amounts of pancreatic fluid are lost (e.g., as a consequence of surgical drainage), the resulting decrease in the plasma SID will lead to acidosis.

In the large intestine, the fluid also has a high SID because most of the Cl^- was removed in the small intestine and the remaining electrolytes consist mostly of Na^+ and K^+ . Normally, the body reabsorbs much of the water and electrolytes from this fluid, but when severe diarrhea occurs, large amounts of cations may be lost. If this cation loss persists, the plasma SID will decrease and acidosis will result.

In addition to the acid-base effects of abnormal loss of strong ions from the GI lumen, the small intestine, in particular, may contribute strong ions to the plasma. This contribution is most apparent when mesenteric blood flow is compromised and lactate is produced, sometimes in large quantities. Although global hypoperfusion may compromise the mesentery, the intestine does not appear to be a source of lactic acid in patients resuscitated from a septic state [see Metabolic Acidosis, Positive–Anion Gap Acidosis, Lactic Acidosis, *below*].²² Moreover, whether the GI tract is capable of regulating strong ion uptake in a compensatory fashion has not been well studied. There is some evidence that the gut may modulate systemic acidosis in experimental endotoxemia by removing anions from the plasma²³; however, the full capacity of the gut to affect acid-base balance remains to be determined.

METABOLIC ACIDOSIS

Traditionally, metabolic acidoses are categorized according to the presence or absence of unmeasured anions. These unmeasured anions are routinely detected by examining the plasma electrolytes and calculating the anion gap (AG) (see below). The differential diagnosis for a positive-AG acidosis includes various common and rare causes [see Table 2]. Generally speaking, non-AG acidoses can be divided into three types: renal, GI, and iatrogenic [see Table 3]. In the intensive care unit (ICU), the most common types of metabolic acidosis are lactic acidosis, ketoacidosis, iatrogenic acidosis, and acidosis secondary to toxins.

Even extreme acidosis appears to be well tolerated by healthy persons, particularly when the duration of the acidosis is short. For example, healthy individuals may achieve an arterial pH lower than 7.15 and a lactate concentration higher than 20 mEq/L during maximal exercise, with no lasting

Table 2 Causes of Positive–Anion Gap Acidosis

Common causes
Renal failure
Elevated ketone levels (ketoacidosis)
Elevated lactate levels (lactic acidosis)
Toxins (methanol, ethylene glycol, salicylate, paraldehyde, toluene)
Sepsis
Rare causes
Dehydration
Alkalemia
Decreased concentrations of unmeasured cations (Mg^{2+} , K^+ , Ca^{2+})
Sodium salts (lactate, citrate, acetate, penicillin, carbenicillin)
Rhabdomyolysis

Table 3 Differential Diagnosis for Normal–Anion Gap Metabolic Acidosis

Urine SID > 0 mEq/L	Renal Tubular Acidosis
Urine SID < 0 mEq/L	GI condition Diarrhea Pancreatic or small bowel drainage Iatrogenesis Parenteral nutrition Saline

GI = gastrointestinal; SID = strong ion difference.

effects.²⁴ Over the long term, however, even mild acidemia ($\text{pH} < 7.35$) may lead to metabolic bone disease and protein catabolism. Furthermore, critically ill patients may not be able to tolerate even brief episodes of acidemia.²⁵ There do appear to be significant differences between respiratory and metabolic acidosis (and even between different types of metabolic acidosis) with respect to patient outcome, and these differences suggest that the underlying disorder may be more important than the absolute degree of acidemia.^{26–28}

If prudence dictates that symptomatic therapy is to be provided, the likely duration of the disorder should be taken into account. When the disorder is expected to be a short-lived one (e.g., diabetic ketoacidosis), maximizing respiratory compensation is usually the safest approach. Once the disorder resolves, ventilation can be quickly reduced to normal levels, and there will be no lingering effects from therapy. If the SID is increased (e.g., by administering NaHCO_3), there is a risk of alkalosis when the underlying disorder resolves. When the disorder is likely to be a more chronic one (e.g., renal failure), therapy aimed at restoring the SID to normal is indicated. In all cases, the therapeutic target can be accurately determined from the SBE. As noted (see above), the SBE corresponds to the amount by which the current SID differs from the SID necessary to restore the pH to 7.4, given a PCO_2 of 40 mm Hg.¹³ Thus, if the SID is 30 mEq/L and the SBE is -10 mEq/L, the target SID is 40 mEq/L. Accordingly, the plasma Na^+ concentration would have to increase by 10 mEq/L for NaHCO_3 administration to correct the acidosis completely.

It should be noted that the target SID is the SID at the equilibrium point between the SID, PCO_2 , and Atot and that it may not be equal to 40 mEq/L, as in the example given. By convention, PCO_2 is set at 40 mm Hg, but the SBE is not corrected for abnormalities in Atot . In many hypoalbuminemic patients, Atot is lower than normal; thus, the SID at the equilibrium point will be less than 40 mEq/L.²⁹ Also, it is rare that the choice would be made to correct the acid-base abnormality completely. Therefore, the target SID should be used as a reference value, but in most cases, partial correction is all that is required.

If increasing the plasma Na^+ concentration is inadvisable for other reasons (e.g., hypernatremia), NaHCO_3 administration is inadvisable. It is noteworthy that NaHCO_3 administration has not been shown to improve outcome in patients with lactic acidosis.³⁰ In addition, NaHCO_3 administration is associated with certain disadvantages.³¹ Large (hypertonic) doses, if given rapidly, may actually reduce blood pressure³² and

may cause sudden, severe increases in PaCO_2 .³³ Accordingly, it is important to assess the patient's ventilatory status before NaHCO_3 is administered, particularly if the patient is not on a ventilator. NaHCO_3 infusion also affects serum K^+ and Ca^{2+} concentrations, which must be monitored closely.

To avoid some of the disadvantages of NaHCO_3 therapy, alternative therapies for metabolic acidosis have been developed. Carbicarb is an equimolar mixture of sodium carbonate (Na_2CO_3) and NaHCO_3 .^{31,34} Like NaHCO_3 , carbicarb works by increasing the plasma Na^+ concentration, except that it does not raise the PCO_2 . Results with carbicarb in animal studies have been mixed,³⁵ and experience in humans is extremely limited.

THAM (tris-hydroxymethyl aminomethane) is a synthetic buffer that consumes CO_2 and readily penetrates cells.^{31,36} It is a weak base ($\text{pK} = 7.9$) and, as such, is unlike other plasma constituents. The major advantage of THAM is that it does not alter the SID, which means that there is no need to be concerned about having to increase the plasma Na^+ concentration to achieve a therapeutic effect. Accordingly, THAM is often used in situations where NaHCO_3 cannot be used because of hypernatremia. Although THAM has been available since the 1960s, there is surprisingly little information available regarding its efficacy in humans with acid-base disorders. In small uncontrolled studies, THAM appears to be capable of reversing metabolic acidosis secondary to ketoacidosis or renal failure without causing obvious toxicity³⁷; however, adverse reactions have been reported, including hypoglycemia, respiratory depression, and even fatal hepatic necrosis, when concentrations exceeding 0.3 mol/L are used. In Europe, a mixture of THAM, acetate, NaHCO_3 , and disodium phosphate is available. This mixture, known as tribonate (Tribonat, Pharmacia & Upjohn, Solna, Sweden), seems to have fewer side effects than THAM alone does, but as with THAM, experience with its use in humans is still quite limited.

Anion Gap

Determination of anion gap The AG has been used by clinicians for more than 30 years and has evolved into a major tool for evaluating acid-base disorders.³⁸ It is calculated—or, rather, estimated—from the difference between the routinely measured concentrations of serum cations (Na^+ and K^+) and the routinely measured concentrations of anions (Cl^- and HCO_3^-). Normally, albumin accounts for the bulk of this difference, with phosphate playing a lesser role. Sulfate and lactate also contribute a small amount to the gap (normally, < 2 mEq/L); however, there are also unmeasured cations (e.g., Ca^{2+} and Mg^{2+}), which tend to offset the effects of sulfate and lactate except when the concentration of either one is abnormally increased. Plasma proteins other than albumin can be either positively or negatively charged, but in the aggregate, they tend to be electrically neutral,³⁹ except in rare cases of abnormal paraproteins (as in multiple myeloma). In practice, the AG is calculated as follows:

$$\text{AG} = (\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$$

Because of its low extracellular concentration, K^+ is often omitted from the calculation. In most laboratories, normal values fall into the range of 12 ± 4 mEq/L (if K^+ is considered) or 8 ± 4 mEq/L (if K^+ is not considered). In the past

few years, the introduction of more accurate methods of measuring Cl^- concentration has led to a general lowering of the normal AG range.^{40,41} Because of the various measurement techniques employed at various institutions, however, each institution is expected to report its own normal AG values.

Clinical utility of anion gap The primary value of the AG is that it quickly and easily limits the differential diagnosis in a patient with metabolic acidosis. When the AG is increased, the explanation is almost invariably one of the following five disorders: ketosis, lactic acidosis, poisoning, renal failure, and sepsis.⁴²

In addition to these disorders, however, there are several conditions that can alter the accuracy of AG estimation and are particularly frequent in critical illness.^{43,44} Dehydration increases the concentrations of all of the ions. Severe hypoalbuminemia lowers the AG, with each 1 g/dL decline in the serum albumin reducing the apparent AG by 2.5 to 3 mEq/L; accordingly, some recommend adjusting the AG for the prevailing albumin concentration.⁴⁵ Alkalosis (respiratory or metabolic) is associated with an increase of as much as 3 to 10 mEq/L in the apparent AG as a consequence of enhanced lactate production (from stimulated phosphofructokinase enzymatic activity), reduction in the concentration of ionized weak acids (A^-) (as opposed to Atot , the total concentration of weak acids), and, possibly, the additional effect of dehydration (which, as noted, has its own impact on AG calculation). A low Mg^{2+} concentration with associated low K^+ and Ca^{2+} concentrations is a known cause of an increased AG, as is the administration of sodium salts of poorly reabsorbable anions (e.g., β -lactam antibiotics).⁴⁶ Certain parenteral nutrition formulations (e.g., those containing acetate) may increase the AG. In rare cases, citrate may have the same effect in the setting of multiple blood transfusions, particularly if massive doses of banked blood are used (as during liver transplantation).⁴⁷ None of these rare causes, however, will increase the AG significantly,⁴⁸ and they usually are easily identified.

In the past few years, some additional causes of an increased AG have been reported. The nonketotic hyperosmolar state of diabetes has been associated with an increased AG that remains unexplained.⁴⁹ Unmeasured anions have been reported in the blood of patients with sepsis,^{50,51} patients with liver disease,^{52,53} and experimental animals that received endotoxin.⁵⁴ These anions may be the source of much of the unexplained acidosis seen in patients with critical illness.⁵⁵

The accepted clinical utility of the AG notwithstanding, doubt has been cast on its diagnostic value in certain situations.^{43,51} Some investigators have found routine reliance on the AG to be “fraught with numerous pitfalls.”⁴³ The primary problem with the AG is its reliance on the use of a supposedly normal range produced by albumin and, to a lesser extent, phosphate. Concentrations of albumin and phosphate may be grossly abnormal in patients with critical illness, and these abnormalities may change the normal AG range in this setting. Moreover, because these anions are not strong anions, their charge is altered by changes in pH. These concerns have led some authors to advocate adjusting the normal AG range on the basis of the patient's albumin⁴⁵ or even phosphate⁶ concentration. Each 1 g/dL of albumin carries a charge of 2.8 mEq/L at a pH of 7.4 (2.3 mEq/L, pH = 7.0; 3.0 mEq/L,

pH = 7.6), and each 1 mg/dL of phosphate carries a charge of 0.59 mEq/L at a pH of 7.4 (0.55 mEq/L, pH = 7.0; 0.61 mEq/L, pH = 7.6). Thus, the normal AG for a given patient can be conveniently estimated as follows⁹:

Normal AG = 2(albumin [g/dL]) + 0.5(phosphate [mg/dL])

or, in international units,

Normal AG = 0.2(albumin [g/L]) + 1.5(phosphate [mmol/L])

In one study, when this formula for calculating a patient-specific normal AG range was used to determine the presence of unmeasured anions in the blood of critically ill patients, its accuracy was 96%, compared with an accuracy of 33% with the routine AG (normal range = 12 mEq/L).⁹ This technique should be employed only when the pH is less than 7.35; even in this situation, it is accurate only within 5 mEq/L. When more accuracy is needed, a slightly more complicated method of estimating unmeasured anions is required.^{52,56}

Strong ion gap Another alternative to relying on the traditional AG is to use a parameter derived from the SID. By definition, the SID must be equal and opposite to the sum of the negative charges contributed by A^- and total CO_2 . This latter value ($A^- + \text{total } CO_2$) has been termed the effective strong ion difference (SIDE).⁴⁹ The apparent strong ion difference (SIDa) is obtained by measuring concentrations of each individual ion. The SIDa and the SIDE should both equal the true SID. If the SIDa differs from the SIDE, unmeasured ions must be present. If the SIDa is greater than the SIDE, these unmeasured ions are anions; if the SIDa is less than the SIDE, they are cations. The difference between the SIDa and the SIDE has been termed the strong ion gap (SIG) to distinguish it from the AG.⁵² Unlike the AG, the SIG is normally 0 and is not affected by changes in the pH or the albumin concentration. SIG has been shown to have prognostic value in the setting of trauma-related shock. In a study performed in 78 trauma patients, SIG measured early in the course of shock predicted mortality better than any other parameter, including AG, anion gap corrected (AGc), SBE, pH, and lactate with an area under the curve (AUC) of 0.96.⁵⁷

Positive-Anion Gap Acidosis

Lactic acidosis In many forms of critical illness, lactate is the most important cause of metabolic acidosis.⁵⁸ Lactate concentrations have been shown to correlate with outcomes in patients with hemorrhagic⁵⁹ and septic shock.⁶⁰ Traditionally, lactic acid has been viewed as the predominant source of the metabolic acidosis that occurs in sepsis.⁶¹ In this view, lactic acid is released primarily from the musculature and the gut as a consequence of tissue hypoxia, and the amount of lactate produced is believed to correlate with the total oxygen debt, the magnitude of hypoperfusion, and the severity of shock.⁵⁸ This view has been challenged by the observation that during sepsis, even in profound shock, resting muscle does not produce lactate. Indeed, various studies have shown that the musculature may actually consume lactate during endotoxemia.^{22,62,63}

The data on lactate release by the gut are less clear. There is little question that the gut can release lactate if it is underperfused. It appears, however, that if the gut is adequately

perfused, it does not release lactate during sepsis. Under such conditions, the mesentery either is neutral with respect to lactate release or takes up lactate.^{22,62} Perfusion is likely to be a major determinant of mesenteric lactate metabolism. In a canine model of sepsis induced by infusion of endotoxin, production of lactate by the gut could not be demonstrated when flow was maintained with dopexamine.⁶³

Both animal studies and human studies have shown that the lung may be a prominent source of lactate in the setting of acute lung injury.^{22,64–67} These studies do not address the underlying pathophysiologic mechanisms of hyperlactatemia in sepsis, but they do suggest that the conventional wisdom regarding lactate as evidence of tissue dysoxia is, at best, an oversimplification.⁶⁸ Indeed, many investigators have begun to offer alternative explanations for the development of hyperlactatemia in this setting [see Table 4].^{65,68–72} One proposed mechanism is metabolic dysfunction from mitochondrial enzymatic derangements, which can and do lead to lactic acidosis. In particular, pyruvate dehydrogenase (PDH), the enzyme responsible for moving pyruvate into the Krebs cycle, is inhibited by endotoxin.⁷³ Current data, however, suggest that increased aerobic metabolism may be more important than metabolic defects or anaerobic metabolism. In a 1996 study, production of glucose and pyruvate and oxidation were increased in patients with sepsis.⁷⁴ Furthermore, when PDH was stimulated by dichloroacetate, there was an additional increase in oxygen consumption but a decrease in glucose and pyruvate production. These results suggest that hyperlactatemia in sepsis occurs as a consequence of increased aerobic metabolism rather than of tissue hypoxia or PDH inhibition.

Such findings are consistent with the known metabolic effects of lactate production on cellular bioenergetics.⁶⁶ Lactate production alters cytosolic, and hence mitochondrial, redox states, so that the increased ratio of reduced nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide (NADH/NAD) supports oxidative phosphorylation as the dominant source of adenosine triphosphate (ATP) production. Finally, the use of catecholamines, especially epinephrine, also results in lactic acidosis, presumably by stimulating cellular metabolism (e.g., increasing hepatic glycolysis), and may be a common source of lactic acidosis in the ICU.^{67,75} It is noteworthy that this phenomenon does not appear to occur with either dobutamine or norepinephrine⁷⁶ and does not appear to be related to decreased tissue perfusion.

Table 4 Mechanisms Associated with Increased Serum Lactate Concentration

Tissue hypoxia
Hypodynamic shock
Organ ischemia
Hypermetabolism
Increased aerobic glycolysis
Increased protein catabolism
Hematologic malignancies
Decreased clearance of lactate
Hepatic failure
Shock
Inhibition of pyruvate dehydrogenase
Thiamine deficiency
? Endotoxin
? Activation of inflammatory cells

Although the source and interpretation of lactic acidosis in critically ill patients remain controversial, there is no question about the ability of lactate accumulation to produce acidemia. Lactate is a strong ion because at a pH within the physiologic range, it is almost completely dissociated. (The pK of lactate is 3.9; at a pH of 7.4, 3,162 ions are dissociated for every one ion that is not.) Because lactate is rapidly produced and disposed of by the body, it functions as one of the most dynamic components of the SID. Therefore, a rise in the concentration of lactic acid can produce significant acidemia. Just as often, however, critically ill patients have a degree of hyperlactatemia that far exceeds the degree of acidosis observed. In fact, hyperlactatemia may exist without any metabolic acidosis at all. This is not because acid generation is separate from lactate production (e.g., through “unreversed ATP hydrolysis”), as some have suggested.⁷⁶ Phosphate is a weak acid and does not contribute substantially to metabolic acidosis, even under extreme circumstances. Furthermore, the H^+ concentration is determined not by how much H^+ is produced or removed from the plasma but by changes in the dissociation of water and weak acids. Virtually anywhere in the body, the pH is higher than 6.0, and lactate behaves as a strong ion. Generation of lactate reduces the SID and results in an increased H^+ concentration; however, the plasma lactate concentration may also be increased without an accompanying increase in the H^+ concentration.

There are two possible explanations for these observations. First, if lactate is added to the plasma, not as lactic acid but rather as the salt of a strong acid (e.g., sodium lactate), the SID will not change significantly, because a strong cation (Na^+) is being added along with a strong anion. Indeed, as lactate is metabolized and removed, the remaining Na^+ will increase the SID, resulting in metabolic alkalosis. Hence, it would be possible to give enough lactate to increase the plasma lactate concentration without increasing the H^+ concentration. However, given that normal metabolism results in the turnover of approximately 1,500 to 4,500 mmol of lactic acid each day, rapid infusion of a very large amount of lactate would be required to bring about an appreciable increase in the plasma lactate concentration. For example, the use of lactate-based hemofiltration fluid may result in hyperlactatemia with an increased plasma HCO_3^- concentration and an elevated pH.

A more important mechanism whereby hyperlactatemia can exist without acidemia (or with less acidemia than expected) involves correction of the SID by the elimination of another strong anion from the plasma. In a study of sustained lactic acidosis induced by lactic acid infusion, Cl^- was found to move out of the plasma space, thereby normalizing the pH.⁷⁷ Under these conditions, hyperlactatemia may persist, but compensatory mechanisms may normalize the base excess and thus restore the SID.

Traditionally, lactic acidosis has been subdivided into type A, in which the mechanism is tissue hypoxia, and type B, in which there is no hypoxia.⁷⁸ This distinction may, however, be an artificial one. Disorders such as sepsis may be associated with lactic acidosis through a variety of mechanisms [see Table 4], some conventionally labeled type A and others type B. A potentially useful method of distinguishing between anaerobically produced lactate and lactate from other sources

is to measure the serum pyruvate concentration. The normal lactate-to-pyruvate ratio is 10:1,⁷⁹ with ratios greater than 25:1 considered to be evidence of anaerobic metabolism.⁷² This approach makes biochemical sense because pyruvate is shunted into lactate during anaerobic metabolism, dramatically increasing the lactate-to-pyruvate ratio. However, the precise test characteristics, including normal ranges and sensitivity and specificity data, have not yet been defined for patients. Accordingly, this method remains investigational.

Treatment of lactic acidosis continues to be subject to debate. At present, the only noncontroversial approach is to treat the underlying cause; however, this approach assumes that the underlying cause can be identified with a significant degree of certainty, which is not always the case. The assumption that hypoperfusion is always the most likely cause has been seriously challenged, especially in well-resuscitated patients (see above). Thus, therapy aimed at increasing oxygen delivery may not be effective. Indeed, if epinephrine is used, lactic acidosis may worsen.

Administration of $NaHCO_3$ to treat lactic acidosis remains unproven.³⁰ In perhaps the most widely quoted study on this topic, hypoxic lactic acidosis was induced in anesthetized dogs by ventilating them with gas containing very little oxygen.⁸⁰ These animals were then assigned to treatment with $NaHCO_3$ or placebo, and, surprisingly, the group receiving $NaHCO_3$ actually had higher plasma concentrations of both lactate and H^+ than the control group did. Furthermore, the $NaHCO_3$ -treated animals exhibited decreases in cardiac output and blood pressure that were not seen in the control group. One possible explanation for these findings is that the HCO_3^- was converted to CO_2 , and this conversion raised the P_{CO_2} not only in the blood but also inside the cells of these animals with a fixed minute ventilation; the resulting intracellular acidosis might have been detrimental to myocardial function. This hypothesis has not, however, been supported by subsequent experimental studies, which have not documented paradoxical intracellular acidosis or even detrimental hemodynamic effects after $NaHCO_3$ treatment of hypoxic lactic acidosis.⁸¹ Furthermore, it is not clear how this type of hypoxic lactic acidosis, induced in well-perfused animals, relates to the clinical conditions in which lactic acidosis occurs. The results of clinical studies have been mixed, but, overall, they do not support the use of $NaHCO_3$ therapy for lactic acidosis.³⁰

Ketoacidosis Another common cause of a metabolic acidosis with a positive AG is excessive production of ketone bodies, including acetone, acetoacetate, and β -hydroxybutyrate. Both acetoacetate and β -hydroxybutyrate are strong anions (pK 3.8 and 4.8, respectively).⁸² Thus, their presence, like the presence of lactate, decreases the SID and increases the H^+ concentration.

Ketones are formed through beta oxidation of fatty acids, a process that is inhibited by insulin. In insulin-deficient states (e.g., diabetes), ketone formation may quickly get out of control. The reason is that severely elevated blood glucose concentrations produce an osmotic diuresis that may lead to volume contraction. This state is associated with elevated cortisol and catecholamine secretion, which further stimulates free fatty acid production.⁸³ In addition, an increased glucagon level relative to the insulin level leads to a decreased

malonyl coenzyme A level and an increased carnitine palmityl acyl transferase level—a combination that increases ketogenesis.

Ketoacidosis may be classified as either diabetic ketoacidosis (DKA) or alcoholic ketoacidosis (AKA). The diagnosis is established by measuring serum ketone levels. It must be kept in mind, however, that the nitroprusside reaction measures only acetone and acetoacetate, not β -hydroxybutyrate. Thus, the measured ketosis is dependent on the ratio of acetoacetate to β -hydroxybutyrate. This ratio is low when lactic acidosis coexists with ketoacidosis because the reduced redox state characteristic of lactic acidosis favors production of β -hydroxybutyrate.⁸⁴ In such circumstances, therefore, the apparent degree of ketosis is small relative to the degree of acidosis and the elevation of the AG. There is also a risk of confusion during treatment of ketoacidosis in that ketone levels, as measured by the nitroprusside reaction, sometimes rise even though the acidosis is resolving. This occurs because the nitroprusside reaction does not detect β -hydroxybutyrate, and as β -hydroxybutyrate is cleared, ketosis persists despite improvement in acid-base balance. Furthermore, conversion of β -hydroxybutyrate to acetoacetate may cause an apparent increase in ketone levels—again, because the nitroprusside reaction detects the rising levels of acetoacetate but misses the falling levels of β -hydroxybutyrate. Hence, it is better to monitor the success of therapy by measuring the pH and the AG than by assaying serum ketones.

Treatment of DKA includes administration of insulin and large amounts of fluid (0.9% saline is usually recommended); potassium replacement is often required as well. Fluid resuscitation reverses the hormonal stimuli for ketone body formation, and insulin allows the metabolism of ketones and glucose. Administration of NaHCO_3 may produce a more rapid rise in the pH by increasing the SID, but there is little evidence that this result is desirable. Furthermore, to the extent that the SID is increased by increasing the plasma Na^+ concentration, the SID will be too high once the ketosis is cleared, thus resulting in a so-called overshoot alkalosis. In any case, such measures are rarely necessary and should probably be avoided except in extreme cases.⁸⁵

A more common problem in the treatment of DKA is the persistence of acidemia after the ketosis has resolved. This hyperchloremic metabolic acidosis occurs as Cl^- replaces ketoacids, thus maintaining a decreased SID and pH. There appear to be two reasons for this phenomenon. First, exogenous Cl^- is often provided in the form of 0.9% saline, which, if given in large enough quantities, will result in a so-called dilutional acidosis (see below). Second, some degree of increased Cl^- reabsorption apparently occurs as ketones are excreted in the urine. It has also been suggested that the increased tubular Na^+ load produces electrical-chemical forces that favor Cl^- reabsorption.⁸⁶

AKA is usually less severe than DKA. Treatment consists of administration of fluids and (in contrast to treatment of DKA) glucose rather than insulin.⁸⁷ Insulin is contraindicated in AKA patients because it may cause precipitous hypoglycemia.⁸⁸ Thiamine must also be given to keep from precipitating Wernicke encephalopathy.

Acidosis secondary to renal failure Although renal failure may produce a hyperchloremic metabolic acidosis,

especially when it is chronic, the buildup of sulfates and other acids frequently increases the AG; however, the increase usually is not large.⁸⁹ Similarly, uncomplicated renal failure rarely produces severe acidosis, except when it is accompanied by high rates of acid generation (e.g., from hypermetabolism).⁹⁰ In all cases, the SID is decreased and is expected to remain so unless some therapy is provided. An observational study on 64 maintenance hemodialysis patients and 14 control subjects showed that acidosis was secondary to three causes: hyperphosphatemia, hyperchloremia, and increased unmeasured anions.⁹¹ Hyperchloremia and the accumulation of unmeasured anions accounted for similar acidifying effects and for almost 90% of the acidosis in this type of patient. Hemodialysis permits the removal of sulfate and other ions and allows the restoration of normal Na^+ and Cl^- balance, thus returning the SID to a normal (or near-normal) value. However, those patients who do not yet require dialysis and those who are between treatments often require some other therapy aimed at increasing the SID. NaHCO_3 may be used for this purpose, provided that the plasma Na^+ concentration is not already elevated.

Acidosis secondary to toxin ingestion Metabolic acidosis with an increased AG is a major feature of various types of intoxication [see Table 2]. Generally, it is more important to recognize these conditions and provide specific therapy for them than it is to treat the acid-base imbalances that they produce.

Acidosis secondary to rhabdomyolysis The extensive muscle tissue breakdown associated with myonecrosis may also be a source of positive-AG metabolic acidosis. In this situation, the acidosis results from accumulation of organic acids. The myoglobinuria associated with the disorder may also induce renal failure. In most cases, the diagnosis is a clinical one and can be facilitated by measuring creatinine kinase or aldolase levels. Early identification and aggressive resuscitation may prevent the onset of renal failure and improve the prognosis.⁹²

Acidosis of unknown origin Several causes of an increased AG have been reported that have yet to be elucidated. An unexplained AG in the nonketotic hyperosmolar state of diabetes has been reported.⁴⁹ In addition, even when very careful measurement techniques have been employed, unmeasured anions have been reported in the blood of patients with sepsis,^{50,51,93} patients with liver disease,⁵² and animals to which endotoxin had been administered.⁵³ Furthermore, unknown cations also appear in the blood of some critically ill patients.^{13,51,94,95} The significance of these findings remains to be determined.

Prognostic significance of positive-AG metabolic acidosis Several studies have examined whether the presence of unmeasured anions in the blood is associated with particular outcomes in critically ill patients. Two such studies focused on trauma patients. In one, the investigators examined 2,152 sets of laboratory data from 427 trauma patients and found that the SIG altered the acid-base disorder diagnosis in 28% of the data sets.⁹⁶ Simultaneous measurements of blood gas, serum electrolyte, albumin, and lactate values

were used to calculate the base deficit, the AG, and the SIG. Unmeasured anions (defined by the presence of an elevated SIG) were present in 92% of patients (mean SIG 5.9 ± 3.3); hyperlactatemia and hyperchloremia occurred in only 18% and 21% of patients, respectively. The arterial SBE at ICU admission was poorly predictive of hospital survival, and its predictive ability was only slightly improved by controlling for unmeasured ions. In this data set, survivors could not be differentiated from nonsurvivors in the group as a whole on the basis of the SIG. However, in the subgroup of patients whose lactate level was normal at admission, there was a significant difference in the SIG between survivors and nonsurvivors, although no such differences were noted in the conventional measures (i.e., SBE and AG).

The poor predictive ability of the SBE, the AG, and even the SIG has been confirmed by studies of general ICU patients. In one study, analysis of data from 300 adult ICU patients demonstrated statistically significant but weak correlations between these measures and hospital mortality.⁹⁷ In another study, however, pretreatment SIG was found to be a very strong predictor of outcome in 282 patients who had sustained major vascular injury.⁹⁸ All but one of the nonsurvivors had an initial emergency department (ED) pH of 7.26 or lower, an SBE of -7.3 mEq/L or lower, a lactate concentration of 5 mmol/L or higher, and an SIG of 5 mEq/L or higher. All of the acid-base descriptors were strongly associated with outcome, but the SIG was the one that discriminated most strongly. The investigators concluded that initial ED acid-base variables, especially SIG, could distinguish survivors of major vascular injury from nonsurvivors. A subsequent prospective study in 78 trauma patients by the same group showed again the high predictive ability of SIG with an AUC of 0.96 (95% CI 0.89 to 0.99) when predicting mortality, which was superior to SBE (0.63), lactate (0.60), AG (0.8), AGc (0.86), and pH (0.50).⁵⁷

Even though the uncorrected AG and the SBE correlate poorly with the arterial lactate concentration in trauma patients,⁹⁹ several investigators have proposed that these parameters be used as surrogate measures of the severity of shock or lack of resuscitation. Various studies have shown that the SBE is a poor predictor of lactic acidosis and mortality in both medical patients and surgical or trauma patients and that it cannot be substituted for direct measurement of the serum lactate concentration.^{43,100,101} Some investigators, however, have found that the SBE can be used as a marker of injury severity and mortality and as a predictor of transfusion requirements.^{102–104} Unfortunately, the SBE can determine only the degree of acid-base derangement, never the cause. In many critically injured patients, abnormalities in body water content, electrolyte levels, and albumin concentration limit any potential correlation between SBE and lactate concentration, even when other sources of acid are absent.

Several reports in the trauma literature have focused on the prognostic value of persistently elevated lactic acid levels during the first 24 to 48 hours after injury. In one study, involving 76 patients with multiple injuries who were admitted directly to the ICU from the operating room or the ED, serum lactate levels and oxygen transport were measured at ICU admission and at 8, 16, 24, 36, and 48 hours.¹⁰⁵ In those patients whose lactate levels returned to normal within

24 hours, the survival rate was 100%, and in those whose lactate levels returned to normal between 24 and 48 hours, the survival rate was 75%. However, in those whose lactate levels did not return to normal by 48 hours, the survival rate was only 14%. Thus, the rate of normalization of the serum lactate level is an important prognostic factor for survival in a severely injured patient.

It is important, however, to understand that metabolic acidosis can no longer be considered as a generic term when trying to assess outcome early in the course of disease, given that the type of metabolic acidosis (i.e., lactic, hyperchloremic, SIG) influences outcome as pointed out by Gunnerson and colleagues.^{27,28}

Non-Anion Gap (Hyperchloremic) Acidoses

Hyperchloremic metabolic acidosis occurs as a result of either an increase in the level of Cl^- relative to the levels of strong cations (especially Na^+) or a loss of cations with retention of Cl^- . The various causes of such an acidosis [see Table 3] can be distinguished on the basis of the history and the measured Cl^- concentration in the urine.¹⁰⁶ When acidosis occurs, the kidney normally responds by increasing Cl^- excretion; the absence of this response identifies the kidney as the source of the problem. Extrarenal hyperchloremic acidoses occur because of exogenous Cl^- loads (iatrogenic acidosis) or because of loss of cations from the lower GI tract without proportional loss of Cl^- (gastrointestinal acidosis).

Renal tubular acidosis Most cases of RTA can be correctly diagnosed by determining urine and plasma electrolyte levels and pH and calculating the SIDa in the urine [see Table 3].¹⁰⁷ However, caution must be exercised when the plasma pH is greater than 7.35 because urine Cl^- excretion may be turned off. In such circumstances, it may be necessary to infuse sodium sulfate or furosemide. These agents stimulate excretion of Cl^- and K^+ and may be used to unmask the defect and to probe K^+ secretory capacity.

Establishing the mechanisms of RTA has proved difficult. It is likely that much of the difficulty results from the attempt to understand the physiology from the perspective of regulation of H^+ and HCO_3^- concentrations. As noted, however (see above), this approach is simply inconsistent with the principles of physical chemistry. The kidney does not excrete H^+ to any greater extent as NH_4^+ than it does as H_2O . The purpose of renal ammoniogenesis is to allow the excretion of Cl^- , which balances the charge of NH_4^+ . In all types of RTA, the defect is the inability to excrete Cl^- in proportion to excretion of Na^+ , although the precise reasons for this inability vary by RTA type. Treatment is largely dependent on whether the kidney will respond to mineralocorticoid replacement or whether there is Na^+ loss that can be counteracted by administering NaHCO_3 .

Classic distal (type I) RTA responds to NaHCO_3 replacement; generally, the required dosage is in the range of 50 to 100 mEq/day. K^+ defects are also common in this type of RTA; thus, K^+ replacement is also required. A variant of the classic distal RTA is a hyperkalemic form, which is actually more common than the classic type. The central defect in this variant form appears to be impaired Na^+ transport in the cortical collecting duct. Patients with this condition also respond to NaHCO_3 replacement.

Proximal (type II) RTA is characterized by defects in the reabsorption of both Na^+ and K^+ . It is an uncommon disorder and usually occurs as part of Fanconi syndrome, in which reabsorption of glucose, phosphate, urate, and amino acids is also impaired. Treatment of type II RTA with NaHCO_3 is ineffective; increased ion delivery merely results in increased excretion. Thiazide diuretics have been used to treat this disorder, with varying degrees of success.

Type IV RTA is caused by aldosterone deficiency or resistance. It is diagnosed on the basis of the high serum K^+ and the low urine pH (< 5.5). The most effective treatment usually involves removal of the cause (most commonly a drug, such as a nonsteroidal antiinflammatory agent, heparin, or a potassium-sparing diuretic). Occasionally, mineralocorticoid replacement is required.

Gastrointestinal acidosis Fluid secreted into the gut lumen contains more Na^+ than Cl^- ; the proportions are similar to those seen in plasma. Massive loss of this fluid, particularly if lost volume is replaced with fluid containing equal amounts of Na^+ and Cl^- , will result in a decreased plasma Na^+ concentration relative to the Cl^- concentration and a reduced SID. Such a scenario can be prevented by using solutions such as lactated Ringer solution (LRS) instead of water or saline. LRS has a more physiologic SID than water or saline and therefore does not produce acidosis except in rare circumstances [see Positive-Anion Gap Acidosis, Lactic Acidosis, *above*].

Iatrogenic acidosis Two of the most common causes of a hyperchloremic metabolic acidosis are iatrogenic, and both involve administration of Cl^- . One of these potential causes is parenteral nutrition. Modern parenteral nutrition formulas contain weak anions (e.g., acetate) in addition to Cl^- , and the proportions of these anions can be adjusted according to the acid-base status of the patient. If sufficient amounts of weak anions are not provided, the plasma Cl^- concentration will increase, reducing the SID and causing acidosis.

The other potential cause is fluid resuscitation with saline, which can give rise to a so-called dilutional acidosis (a problem first described more than 40 years ago).^{108,109} Some authors have argued that dilutional acidosis is, at most, a minor issue.¹¹⁰ This argument is based on studies showing that in healthy animals, large doses of NaCl produce only a minor hyperchloremic acidosis.¹¹¹ These studies have been interpreted as indicating that dilutional acidosis occurs only in extreme cases and even then is mild. However, this line of reasoning cannot be applied to critically ill patients, for two reasons. First, it is common for patients with sepsis or trauma to require large-volume resuscitation; sometimes, such patients receive crystalloid infusions equivalent to 5 to 10 times their plasma volumes in a single day. Second, critically ill patients frequently are not in a state of normal acid-base balance to begin with. Often they have lactic acidosis or renal insufficiency. Furthermore, critically ill patients may not be able to compensate for acid-base imbalance normally (e.g., by increasing ventilation), and they may have abnormal buffer capacity as a result of hypoalbuminemia. In ICU and surgical patients,^{112–114} as well as in animals with experimentally induced sepsis,¹¹⁵ saline-induced acidosis does occur and can produce significant acidemia.

The reason why administration of saline causes acidosis is that solutions containing equal amounts of Na^+ and Cl^- affect plasma concentrations of Na^+ and Cl^- differently.¹¹⁶ Although some authors continue to argue that a simple “dilutional” effect of fluids on the amount of base (HCO_3^-) is sufficient to explain the phenomenon,¹¹⁷ this concept has been discredited.¹¹⁸ The normal Na^+ concentration is 35 to 45 mEq/L higher than the normal Cl^- concentration. Thus, adding (for example) 154 mEq/L of each ion in 0.9% saline will result in a greater relative increase in the Cl^- concentration than in the Na^+ concentration. So much is clear; what may be less clear is why critically ill patients are more susceptible to this disorder than healthy persons are.

It appears that many critically ill patients have a significantly lower SID than healthy persons do, even when these patients have no evidence of a metabolic acid-base derangement.¹¹⁹ This finding is not surprising in that the positive charge of the SID is balanced by the negative charges of A^- and total CO_2 . Because many critically ill patients are hypoalbuminemic, A^- tends to be reduced. Because the body maintains PCO_2 for other reasons, a reduction in A^- leads to a reduction in SID so that a normal pH can be maintained. Thus, a typical ICU patient may have an SID of 30 mEq/L rather than 40 to 42 mEq/L. If a metabolic acidosis (e.g., lactic acidosis) then develops in this patient, the SID will decrease further. If this patient is subsequently resuscitated with large volumes of 0.9% saline, a significant metabolic acidosis will result.

The clinical implication for management of ICU patients is that if large volumes of fluid are to be given for resuscitation, fluids that are more physiologic than saline should be used. One alternative is LRS, which has a more physiologic ratio of Na^+ content to Cl^- content and thus has an SID that is closer to normal (roughly 28 mEq/L, compared with an SID of 0 mEq/L for saline). Of course, the assumption here is that the lactate in LRS is metabolized, which, as noted (see above), is almost always the case. Volume resuscitation also reduces the weak acid concentration, thereby moderating the acidosis. One *ex vivo* study concluded that administration of a solution with an SID of approximately 24 mEq/L will have a neutral effect on the pH as blood is progressively diluted.¹²⁰

Unexplained hyperchloremic acidosis Critically ill patients sometimes manifest hyperchloremic metabolic acidosis for reasons that cannot be determined. Often other coexisting types of metabolic acidosis are present, making the precise diagnosis difficult. For example, some patients with lactic acidosis have a greater degree of acidosis than can be explained by the increase in the lactate concentration,⁵⁰ and some patients with sepsis and acidosis have normal lactate levels.¹²¹ In many instances, the presence of unexplained anions may be the cause.^{50–52} However, anions such as amino acids, uric acid, and organic acids were shown to contribute to SIG only in 7.9% in critically ill patients with metabolic acidosis,¹²² whereas in other cases, there is a hyperchloremic acidosis.⁹³ Saline resuscitation may be responsible for much of this acidosis (see above), but experimental evidence from endotoxemic animals suggests that as much as a third of the acidosis cannot be explained in terms of current knowledge.¹¹⁵

One potential explanation for unexplained hyperchloremic acidosis is partial loss of the Donnan equilibrium between plasma and interstitial fluid. The severe capillary leakage that accompanies this loss of equilibrium results in loss of albumin from the vascular space, which means that another ion must move into this space to maintain the charge balance between the two compartments. If Cl^- moves into the plasma space to restore the charge balance, a strong anion is replacing a weak anion, and a hyperchloremic metabolic acidosis results. This hypothesis appears reasonable but, at present, remains unproven.

METABOLIC ALKALOSIS

Metabolic alkalosis occurs as a result of an increased SID or a decreased Atot , secondary either to loss of anions (e.g., Cl^- from the stomach and albumin from the plasma) or increases in cations (rare). Metabolic alkaloses can be divided into those in which Cl^- losses are temporary and can be effectively replaced (chloride-responsive alkaloses) and those in which hormonal mechanisms produce ongoing losses that, at best, can be only temporarily offset by Cl^- administration (chloride-resistant alkaloses) [see Table 5]. Like hyperchloremic acidosis, metabolic alkalosis can be confirmed by measuring the urine Cl^- concentration.

Chloride-Responsive Alkalosis

Chloride-responsive metabolic alkalosis usually occurs as a result of loss of Cl^- from the stomach (e.g., through vomiting or gastric drainage). Treatment consists of replacing the lost Cl^- , either slowly (with NaCl) or relatively rapidly (with KCl or even HCl). Because chloride-responsive alkalosis is usually

accompanied by volume depletion, the most common therapeutic choice is to give saline along with KCl . Dehydration stimulates aldosterone secretion, which results in reabsorption of Na^+ and loss of K^+ . Saline is effective even though it contains Na^+ because the administration of equal amounts of Na^+ and Cl^- yields a larger relative increase in the Cl^- concentration than in the Na^+ concentration (see above). In rare circumstances, when neither K^+ loss nor volume depletion is a problem, it may be desirable to replace Cl^- by giving HCl .

Diuresis and other forms of volume contraction cause metabolic alkalosis mainly by stimulating aldosterone secretion; however, diuretics also directly stimulate excretion of K^+ and Cl^- , further complicating the problem and inducing metabolic alkalosis more rapidly.

Chloride-Resistant Alkalosis

Chloride-resistant alkalosis [see Table 5] is characterized by an increased urine Cl^- concentration ($> 20 \text{ mmol/L}$) and ongoing Cl^- loss that cannot be abolished by Cl^- replacement. Most commonly, the proximate cause is increased mineralocorticoid activity. Treatment involves identification and correction of the underlying disorder.

Alkalosis from Other Causes

In rare situations, an increased SID—and therefore metabolic alkalosis—occurs secondary to cation administration rather than to anion depletion. Examples include milk-alkali syndrome and intravenous administration of strong cations without strong anions. The latter occurs with massive blood transfusion because Na^+ is given with citrate (a weak anion) rather than with Cl^- . Similar results ensue when parenteral nutrition formulations contain too much acetate and not enough Cl^- to balance the Na^+ load.

Table 5 Differential Diagnosis for Metabolic Alkalosis

Chloride loss ($\text{Cl}^- < \text{Na}^+$)
Chloride-responsive alkalosis (urine Cl^- concentration $< 10 \text{ mmol/L}$)
GI loss
Vomiting
Gastric drainage
Chloride-wasting diarrhea (villous adenoma)
Diuretic use
Hypercapnia
Chloride-resistant alkalosis (urine Cl^- concentration $> 20 \text{ mmol/L}$)
Mineralocorticoid excess
Primary hyperaldosteronism (Conn syndrome)
Secondary hyperaldosteronism
Cushing syndrome
Liddle syndrome
Bartter syndrome
Exogenous corticoids
Excessive licorice intake
Ongoing diuretic use
Exogenous sodium load ($\text{Na}^+ > \text{Cl}^-$)
Sodium salt administration (acetate, citrate)
Massive blood transfusions
Parenteral nutrition
Plasma volume expanders
Sodium lactate (lactated Ringer solution)
Other
Severe deficiency of intracellular cations (Mg^{2+} , K^+)

GI = gastrointestinal.

Respiratory Acid-Base Disorders

Respiratory disorders are far easier to diagnose and treat than metabolic disorders are because the mechanism is always the same, even though the underlying disease process may vary. CO_2 is produced by cellular metabolism or by the titration of HCO_3^- by metabolic acids. Normally, alveolar ventilation is adjusted to maintain the PaCO_2 between 35 and 45 mm Hg. When alveolar ventilation is increased or decreased out of proportion to the PaCO_2 , a respiratory acid-base disorder exists.

PATHOPHYSIOLOGY

CO_2 is produced by the body at a rate of 220 mL/min, which equates to production of 15 mol/L of carbonic acid each day.¹²³ By way of comparison, total daily production of all the nonrespiratory acids managed by the kidney and the gut amounts to less than 500 mmol/L. Pulmonary ventilation is adjusted by the respiratory center in response to PaCO_2 , pH, and PO_2 , as well as in response to exercise, anxiety, wakefulness, and other signals. Normal PaCO_2 (40 mm Hg) is attained by precisely matching alveolar ventilation to metabolic CO_2 production. PaCO_2 changes in predictable ways as a compensatory ventilatory response to the altered arterial pH produced by metabolic acidosis or alkalosis [see Table 1].

RESPIRATORY ACIDOSIS

Mechanism

When the rate of CO_2 elimination is inadequate relative to the rate of tissue CO_2 production, the Paco_2 rises to a new steady state, determined by the new relation between alveolar ventilation and CO_2 production. In the short term, this rise in the Paco_2 increases the concentrations of both H^+ and HCO_3^- according to the carbonic acid equilibrium equation. Thus, the change in the HCO_3^- concentration is mediated not by any systemic adaptation but by chemical equilibrium. The higher HCO_3^- concentration does not buffer the H^+ concentration. The SID does not change, nor does the SBE. Tissue acidosis always occurs in respiratory acidosis because CO_2 inevitably builds up in the tissue.

If the Paco_2 remains elevated, a compensatory response will occur, and the SID will increase to return the H^+ concentration to the normal range. The increase in the SID is accomplished primarily by removing Cl^- from the plasma space. If Cl^- moves into tissues or red blood cells, it will result in intracellular acidosis (complicated by the elevated tissue Pco_2); thus, to exert a lasting effect on the SID, Cl^- must be removed from the body. The kidney is designed to do this, whereas the GI tract is not (although the adaptive capacity of the GI tract as a route of Cl^- elimination has not been fully explored). Accordingly, patients with renal disease have a very difficult time adapting to chronic respiratory acidosis.

Patients whose renal function is intact can eliminate Cl^- in the urine; after a few days, the SID rises to the level required to restore the pH to a value of 7.35. It is unclear whether this amount of time is necessary because of the physiologic constraints of the system or because the body benefits from not being overly sensitive to transient changes in alveolar ventilation. In any case, this response yields an increased pH for any degree of hypercapnia. According to the Henderson-Hasselbalch equation, the increased pH results in an increased HCO_3^- concentration for a given Pco_2 . Thus, the “adaptive” increase in the HCO_3^- concentration is actually the consequence, not the cause, of the increased pH. Although the HCO_3^- concentration is a convenient and reliable marker of metabolic compensation, it is not the mechanism of the compensatory response. This point is not merely a semantic one: as noted (see above), only changes in the independent variables of acid-base balance (Pco_2 , Atot , and SID) can affect the plasma H^+ concentration, and HCO_3^- concentration is not an independent variable.

Management

Treatment of underlying ventilatory impairment As with virtually all acid-base disorders, treatment begins by addressing the underlying disorder. Acute respiratory acidosis may be caused by central nervous system (CNS) suppression; neuromuscular diseases or conditions that impair neuromuscular functions (e.g., myasthenia gravis, hypophosphatemia, and hypokalemia); or diseases affecting the airway or the lung parenchyma (e.g., asthma and acute respiratory dysfunction syndrome [ARDS]). The last category of conditions produces not only alveolar hypoventilation but also primary hypoxia. The two can be distinguished by means of the alveolar gas equation:

$$\text{P}_{\text{AO}_2} = \text{P}_{\text{I}\text{O}_2} - \text{Paco}_2/\text{R}$$

where R is the respiratory exchange coefficient (generally taken to be 0.8) and $\text{P}_{\text{I}\text{O}_2}$ is the inspired oxygen tension (approximately 150 mm Hg in room air). Thus, as the Paco_2 increases, the P_{AO_2} should also decrease in a predictable fashion. If the P_{AO_2} falls by more than the predicted amount, there is a defect in gas exchange.

In most cases, chronic respiratory acidosis is caused by either chronic lung disease (e.g., chronic obstructive pulmonary disease [COPD]) or chest wall disease (e.g., kyphoscoliosis). In rare cases, it is caused by central hypoventilation or chronic neuromuscular disease.

Control of hypoxemia Another aspect of respiratory acidosis that is illustrated by the alveolar gas equation is that the primary threat to life comes not from acidosis but from hypoxemia. In patients breathing room air, the Paco_2 cannot exceed 80 mm Hg before life-threatening hypoxemia results. Accordingly, supplemental oxygen is required in the treatment of these patients. Unfortunately, oxygen administration is almost never sufficient treatment by itself, and it generally proves necessary to address the ventilatory defect. When the underlying cause can be addressed quickly (as when the effects of narcotics are reversed with naloxone), endotracheal intubation may be avoidable. In the majority of patients, however, this is not the case, and mechanical ventilation must be initiated. Mechanical support is indicated for patients who are unstable or at risk for instability and patients whose CNS function is deteriorating. Furthermore, in patients who exhibit signs of respiratory muscle fatigue, mechanical ventilation should be instituted before respiratory failure occurs. Thus, it is not the absolute Paco_2 value that is the most important consideration in this situation but, rather, the clinical condition of the patient.

Chronic hypercapnia must be treated if the patient's clinical condition is deteriorating acutely. In this setting, it is important not to try to restore the Paco_2 to the normal range of 35 to 45 mm Hg. Instead, the patient's baseline Paco_2 , if known, should be the therapeutic target; if the baseline Paco_2 is not known, a target Paco_2 of 60 mm Hg is perhaps a reasonable choice. Overventilation can have two undesirable consequences. First, if the Paco_2 is rapidly normalized in a patient with chronic respiratory acidosis and an appropriately large SID, life-threatening alkalemia may ensue. Second, even if the Paco_2 is corrected slowly, the plasma SID may decrease over time, making it impossible to wean the patient from mechanical ventilation.

One option for treatment of hypercapnia is noninvasive ventilation with a bilevel positive airway pressure (BiPAP) system. This technique may be useful in the management of some patients, particularly those whose sensorium is not impaired.¹²⁴ Rapid infusion of NaHCO_3 in patients with respiratory acidosis may induce acute respiratory failure if alveolar ventilation is not increased to account for the increased CO_2 . Thus, if NaHCO_3 is to be given, it must be administered slowly, with alveolar ventilation adjusted appropriately. Furthermore, it must be remembered that NaHCO_3 works by increasing the plasma Na^+ concentration; if this effect is not possible or not desirable, NaHCO_3 should not be given.

Occasionally, it is useful to reduce CO₂ production. This can be accomplished by reducing the amount of carbohydrates supplied in feedings (in patients requiring nutritional support), controlling body temperature (in febrile patients), or providing sedation (in anxious or combative patients). In addition, treatment of shivering in the postoperative period can reduce CO₂ production. Rarely, however, can hypercapnia be controlled with these CO₂-reducing techniques alone.

Permissive hypercapnia In the past few years, there has been considerable interest in ventilator-associated lung injury. Overdistention of alveoli can result in tissue injury and microvascular permeability, which lead to interstitial and alveolar edema. In animal studies, prolonged use of elevated airway pressures and increased lung volumes resulted in increased pathologic pulmonary changes and decreased survival when compared with ventilatory strategies employing lower pressures and volumes.^{125,126} In a large multicenter clinical trial, simply lowering the tidal volume on the ventilator from 12 mL/kg to 6 mL/kg in patients with acute lung injury resulted in a 9% absolute reduction in mortality risk.¹²⁷ Although the protocol followed in this trial did not advocate a reduced minute ventilation and hence an elevated PaCO₂, this approach, often referred to as permissive hypercapnia or controlled hypoventilation, has become increasingly popular. Uncontrolled studies suggest that permissive hypercapnia may reduce mortality in patients with severe ARDS.²⁶ This strategy is not, however, without risks. Sedation is mandatory, and neuromuscular blocking agents are frequently required. Intracranial pressure rises, as does transpulmonary pressure; consequently, this technique is unusable in patients with brain injury or right ventricular dysfunction. There is controversy regarding how low the pH can be allowed to fall. Some authors have reported good results with pH values of 7.0 or even lower,²⁰ but most have advocated more modest pH reductions (i.e., ≥7.25).

RESPIRATORY ALKALOSIS

Respiratory alkalosis may be the most frequently encountered acid-base disorder. It occurs in residents of high-altitude

locales and in persons with any of a wide range of pathologic conditions, the most important of which are salicylate intoxication, early sepsis, hepatic failure, and hypoxic respiratory disorders. Respiratory alkalosis also occurs in association with pregnancy and with pain or anxiety. Hypocapnia appears to be a particularly strong negative prognostic indicator in patients with critical illness.¹²⁸ Like acute respiratory acidosis, acute respiratory alkalosis results in a small change in the HCO₃⁻ concentration, as dictated by the Henderson-Hasselbalch equation. If hypocapnia persists, the SID begins to decrease as a consequence of renal Cl⁻ reabsorption. After 2 to 3 days, the SID assumes a new and lower steady state.¹²⁹

Severe alkalemia is unusual in respiratory alkalosis. Management therefore is typically directed toward the underlying cause.¹³⁰ In general, these mild acid-base changes are clinically important more for what they can alert the clinician to, in terms of underlying disease, than for any direct threat they pose to the patient. In rare cases, respiratory depression with narcotics is necessary.

Pseudorespiratory Alkalosis

The presence of arterial hypocapnia in patients experiencing profound circulatory shock has been termed pseudorespiratory alkalosis.¹⁰⁹ This condition occurs when alveolar ventilation is supported, but the circulation is grossly inadequate. In such circumstances, the mixed venous Pco₂ is significantly elevated, but the PaCO₂ is normal or even decreased as a consequence of reduced CO₂ delivery to the lung and increased pulmonary transit time. Overall CO₂ clearance is therefore markedly decreased, and profound tissue acidosis—usually both metabolic and respiratory—ensues. The metabolic component of the acidosis comes from tissue hypoperfusion and hyperlactatemia. Arterial oxygen saturation may also appear adequate despite tissue hypoxemia. Pseudorespiratory alkalemia is rapidly fatal unless the patient's systemic hemodynamic status can be normalized.

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13 ENDOCRINE PROBLEMS

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Patients scheduled for operation may be receiving treatment with insulin, oral hypoglycemics, corticosteroids, thyroid hormone, or estrogen. The presence of any state calling for such treatment must be taken into consideration in planning operative management and perioperative care. In addition, glucose intolerance may develop in otherwise normal patients after operation, and this possibility must be taken into account as well. In what follows, we describe an approach to preventing and managing common endocrine conditions that occur as complicating factors in the perioperative period. We do not, however, address perioperative problems related to operations for primary endocrine disease.

Diabetes Mellitus

Diabetics have a 50% chance of undergoing a surgical procedure during their lifetime.¹ In the past, operation in these patients was associated with a mortality of 4% to 13%,² usually attributed to cardiovascular complications—clearly a significant operative risk. Any subsequent improvement in diabetes-related operative mortality has probably been offset by the increasing age of patients with diabetes and the larger variety of procedures they undergo.

Perioperative management of diabetic patients [see *Figure 1*] is complicated both by the metabolic abnormalities of the disease and by the effects of any diabetic complications that may be present. There is also an increased risk of postoperative surgical site infection (SSI).

EVALUATION OF THE DIABETIC PATIENT

History and Physical Examination

In taking a preoperative history from a diabetic patient, attention should be directed to any recent fluctuation in blood glucose level as well as to the type of therapy used to control the condition. The timing and dosage of medication should be considered, especially if the patient is taking long-acting insulin or an oral hypoglycemic. The extent to which diabetes is controlled in the perioperative period, which has a significant impact on postoperative recovery, may be affected by certain medications (e.g., antihypertensive agents). The presence of diabetic complications (e.g., atherosclerotic disease, diabetic nephropathy, and autonomic neuropathy) should be documented because these conditions may have serious effects during and after operation.

Medications used to control diabetes include the various forms of insulin as well as oral hypoglycemic agents. The most commonly used oral hypoglycemics are sulfonylurea, which acts by stimulating insulin secretion, and metformin, which acts by decreasing intestinal absorption. Patients should stop taking oral hypoglycemics before major operations, and their blood glucose should be controlled with insulin if necessary. Because sudden discontinuance of sulfonylurea can lead to hypoglycemia, blood

glucose levels should be carefully monitored in patients taking this medication who have experienced injury or undergone operation.

Laboratory Studies

The degree of control of diabetes can be assessed by recording blood glucose measurements at frequent intervals during fasting and at other times during the day and by determining what percentage of total hemoglobin is combined with carbohydrate (i.e., glycosylated). Normally, glycosylated hemoglobin (commonly called HbA_{1c}) accounts for 4% to 7% of total hemoglobin. HbA_{1c} levels increase when hyperglycemia occurs, and the increases are cumulative over time. The value of measuring HbA_{1c} in a preoperative patient known to be diabetic is that it gives the attending physicians some idea of how well hyperglycemic episodes are being controlled by insulin or oral hypoglycemics. Monthly measurements yield a good picture of the adequacy of glucose control over extended periods. HbA_{1c} percentages higher than 10% to 20% indicate that the hyperglycemic aspect of diabetes has been poorly controlled. Chronic diabetic complications are reduced when good control of blood glucose is maintained; diabetic patients are advised to measure their blood glucose levels frequently, which should result in normal HbA_{1c} levels. HbA_{1c} percentages higher than 15% suggest that the diabetes is quite brittle and that more frequent monitoring of blood glucose levels and closer control of insulin administration are indicated during and after operation. As long as the patient is carefully monitored, there is no evidence that high levels of HbA_{1c} are associated with any increased risk of impaired glucose control or complications after operation.

The other important laboratory study in diabetic patients is measurement of serum creatinine levels (or, perhaps, creatinine clearance) as an indicator of renal function. Renal insufficiency is a common complication of diabetes that may not be recognized during normal preoperative testing.

PREOPERATIVE MANAGEMENT

Metabolic Monitoring and Medications

All diabetic patients who are candidates for elective surgical procedures should undergo careful preoperative assessment, including metabolic monitoring. Ideally, glycemic control is achieved before a diabetic patient is admitted to the hospital. More realistically, however, admission may have to be scheduled for the day before the operation to allow time for optimizing metabolic control in all insulin-dependent patients as well as in non-insulin-dependent patients who have inadequate metabolic control. As a rule, target blood glucose levels before operation should be less than 125 mg/dl (6.9 mmol/L) during fasting and less than 180 mg/dl (10.0 mmol/L) postprandially. If emergency operation is required in patients with severe metabolic derangements (e.g., diabetic ketoacidosis or hyperosmolar nonketotic states), 6 to 8 hours of intensive treatment with insulin infusion

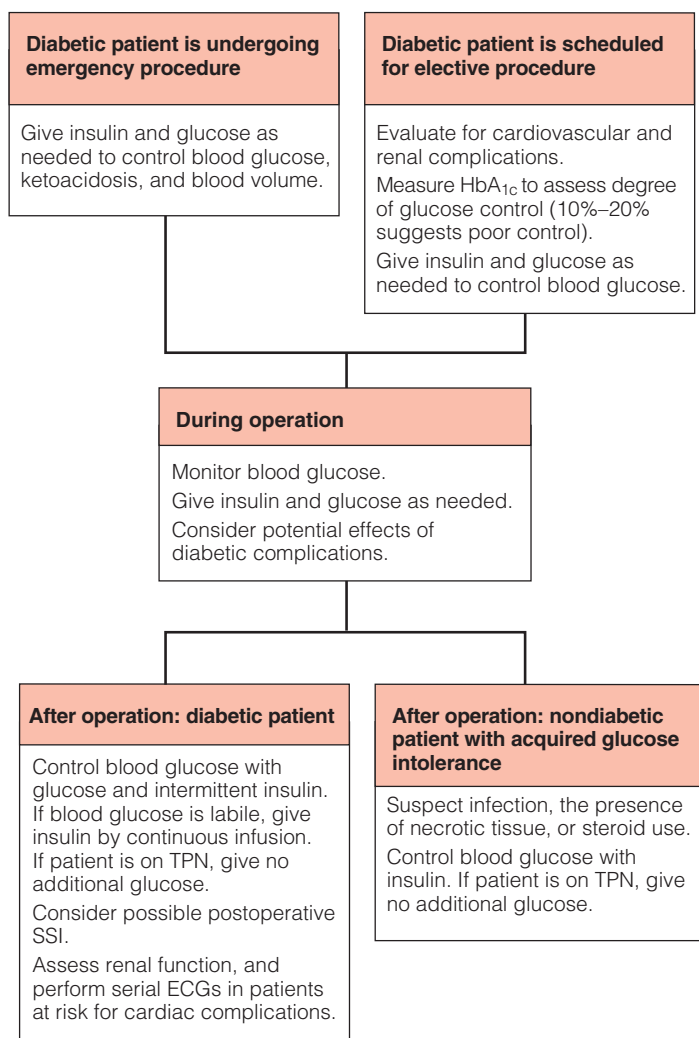


Figure 1 Shown is an algorithm outlining preoperative and postoperative management of the diabetic surgical patient.

and volume restoration usually improves their general condition. This brief period permits clarification of the diagnosis in patients with acute abdominal pain, which may be the consequence of diabetic ketoacidosis rather than a so-called surgical abdomen.

In preparing diabetic patients for operation, all long-acting insulins (i.e., Ultralente preparations) should be replaced with intermediate-acting insulins (i.e., neutral protamine Hagedorn [NPH] or Lente preparations). If the patient has type 2 (non-insulin-dependent) diabetes mellitus, use of long-acting sulfonylureas (e.g., chlorpropamide and glyburide) should be stopped because of the risk of hypoglycemia; a short-acting preparation should be substituted. Use of metformin should be stopped because of the risk of lactic acidosis when renal function is impaired, as it may be during any procedure requiring anesthesia. Chronically hyperglycemic patients are frequently dehydrated, and this condition should be corrected before operation.

INTRAOPERATIVE MANAGEMENT

Metabolic Effects of Operation and Anesthesia

During anesthesia and operation, endogenous insulin secretion is suppressed, but the plasma levels of counterregulatory hormones (glucagon, epinephrine, cortisol, and growth hor-

mone) increase in nondiabetic as well as diabetic patients. Increased secretion of these hormones in the setting of low insulin levels stimulates hepatic production of glucose. In nondiabetic persons, major procedures are frequently associated with blood glucose levels of 150 to 200 mg/dl (8.3 to 11.1 mmol/L). In diabetic persons, the metabolic abnormality varies according to the extent and duration of the surgical procedure and the degree to which insulin secretion is impaired.

A study in patients with stable type 1 (insulin-dependent) diabetes mellitus showed that blood glucose levels rose from about 180 mg/dl (10.0 mmol/L) to about 270 mg/dl (15.0 mmol/L) postoperatively.³ Ketone body levels increased by about 100%, as compared with levels in nondiabetic control subjects. Similar metabolic findings were reported even in patients with type 2 diabetes mellitus who underwent minor procedures that generated relatively little stress: blood glucose levels rose to 180 mg/dl (10.0 mmol/L), with higher than normal levels of ketone bodies and free fatty acids.⁴

Autonomic neuropathy can cause severe hypotension during induction of anesthesia. Diabetic nephropathy complicates fluid management and usually results in electrolyte abnormalities. All diabetic patients are at high risk for postoperative myocardial infarction, which is often asymptomatic. Poor nutrition and impaired phagocytosis make diabetic patients more susceptible to infection and slower to heal.

Insulin and Glucose Administration

Emergency procedures Diabetic patients may be more likely than nondiabetic patients to undergo emergency operation, which can cause rapid metabolic decompensation with dehydration, hyperglycemia, and ketoacidosis. In addition, a surgical emergency can precipitate uncontrolled diabetes in patients with no history of diabetes. Appropriate management depends, to a large extent, on the patient's metabolic condition. When one is faced with a so-called surgical abdomen, it is crucial to determine whether there is a metabolic abnormality that may be causing the condition. Given this possibility, it is sensible to manage the patient conservatively at first, with an emphasis on metabolic correction. If the underlying problem is in fact metabolic, it should resolve or improve in 3 to 4 hours; if the problem is surgical, it should remain the same or worsen over this period.

Elective major procedures In a patient undergoing general anesthesia, regardless of the duration of the operation, infusion of insulin and glucose is recommended if the patient is taking insulin for diabetes or is using drugs or diet therapy (or both) without achieving satisfactory control of type 2 diabetes mellitus.

Several methods of insulin administration may be used during the perioperative period. Most of the protocols include I.V. administration of short-acting insulin and 5% to 10% glucose. In some, glucose and insulin are administered together in a single infusion. The advantage of this approach is that if the glucose infusion is accidentally disconnected or obstructed, the insulin infusion is disconnected or obstructed as well, so that the risk of hypoglycemia is eliminated. The disadvantage of this method is that it is impossible to change the delivery rate of one agent without changing the delivery rate of the other. Administration of insulin and glucose in separate bags allows either infusion rate to be adjusted without the other being affected. The insulin infusion rate is progressively increased and the glucose infusion rate progressively decreased in accordance with the capillary blood glucose levels, measured hourly [see Table 1]. With this protocol,

Table 1 Representative Protocol for Insulin-Glucose Infusion during the Perioperative Period

1. Infuse 5% dextrose in water (D5W) I.V. via pump.
2. Make insulin solution with 0.5 U/ml of short-acting insulin (i.e., 250 U of regular insulin in 500 ml of normal saline). Administer in piggyback fashion via infusion pump into D5W infusion or through a separate I.V. site.
3. After initiating glucose-insulin infusion, stop all subcutaneous insulin therapy.
4. Measure capillary blood glucose levels every hour.
5. On the basis of hourly blood glucose levels, adjust each infusion according to the following schedule:

Blood Glucose (mg/dl)	Insulin Infusion		D5W Infusion (ml/hr)
	(ml/hr)	(U/hr)	
< 70*	1.0	0.5	150
71–100	2.0	1.0	125
101–150	3.0	1.5	100
151–200	4.0	2.0	100
201–250	6.0	3.0	100
251–300	8.0	4.0	75
> 300	12.0	6.0	50

*Give 10 ml D5W I.V. and repeat blood glucose measurement 15 min later.

a blood glucose level in the range of 125 to 200 mg/dl (6.9 to 11.1 mmol/L) can easily be maintained throughout the perioperative period. Close observation of blood glucose levels and prompt adjustment of insulin and glucose delivery are mandatory for achieving a stable blood glucose level. Electrolyte supplementation is administered via a separate infusion.

Minor procedures Diabetic patients who fast before minor operations (e.g., endoscopic procedures and operations performed with the patient under local anesthesia) should omit the morning dose of insulin or oral hypoglycemic agent, and their capillary blood glucose level should be measured every 2 to 4 hours. Supplemental subcutaneous short-acting insulin can be administered according to a variable insulin schedule, and the usual insulin or oral agent can be taken after the procedure [see Table 2]. This method of administration, which is associated with unpredictable absorption and variable plasma insulin levels, is restricted to surgical patients undergoing minor procedures and should not be used in those undergoing major operations.

POSTOPERATIVE MANAGEMENT

Insulin and Glucose Administration

After minor procedures, diabetic patients should receive I.V. glucose and insulin until their metabolic condition is stable and oral feeding can be tolerated. To prevent ketosis, the insulin and glucose infusions should be continued for at least 1 hour after the administration of subcutaneous short-acting insulin. After major procedures, patients should receive I.V. glucose and insulin until they are able to take solid food without difficulty. A regimen consisting of multiple subcutaneous injections of short-acting insulin before meals and intermediate-acting insulin twice

daily is recommended during the first 24 to 48 hours after cessation of the insulin and glucose infusions and before resumption of the patient's usual insulin regimen.

Total parenteral nutrition (TPN) [see 8:22 *Nutritional Support*], often required during the postoperative period, can cause serious metabolic derangements in diabetic patients. For a diabetic patient receiving TPN, a variable insulin infusion schedule [see Table 2] is recommended, with hourly determinations of blood glucose; however, additional glucose is not needed, because it is included in the TPN solution. Initially, the insulin should be given as a continuous infusion separate from the TPN solution. Once a stable dose of insulin is reached (usually within 24 to 48 hours), the total amount of insulin required over a 24-hour period can be added to the TPN bag. This amount may be high—often more than 100 units. At this point, capillary blood glucose levels can be measured every 2 to 4 hours.

Hypoglycemia can be difficult to detect in critically ill patients, in whom blood glucose levels are often elevated for any of a number of reasons. Accordingly, it has been common practice to accept blood glucose levels ranging from 150 to 200 mg/dl in these patients. This practice, however, was called into question by a 2001 randomized study of 1,548 ICU patients in which liberal glucose control (blood glucose level, 180 to 200 mg/dl) was compared with tight control (blood glucose level, 80 to 110 mg/dl).⁵ ICU survival was significantly better in the tight control group (95.4%) than in the liberal control group (92%). In addition, the tight control group had a lower incidence of systemic infection, had less need of antibiotic therapy, required fewer transfusions, and were less subject to hypobilirubinemia. These findings support the view that tight regulation of glucose and insulin to maintain normal blood glucose levels is desirable in critically ill patients.

Cardiovascular and Renal Assessment

Serial postoperative electrocardiograms are recommended for older diabetic patients, those with long-standing type 1 diabetes mellitus, and those with known heart disease. Postoperative myocardial infarction, which may be silent, is associated with a high mortality. Careful monitoring of blood urea nitrogen and serum creatinine levels facilitates the detection of acute renal

Table 2 Management of Diabetes in Patients Undergoing Minor Surgical Procedures³⁰

If patient fasted

1. Withhold morning dose of insulin or oral agent.
2. Measure capillary blood glucose level before procedure and every 2–4 hr thereafter.
3. Give short-acting insulin every 2–4 hr, as follows:

Blood Glucose (mg/dl)	Short-Acting Insulin (U)
< 150	0
151–200	2
201–250	3
251–300	5
> 300	6

4. After procedure, give usual dose of insulin or oral agent.

failure [see 8:6 Renal Failure]. If a contrast agent is used, the patient should be well hydrated before and after the procedure.

Infection

SSI is common in diabetic patients with poor metabolic control. Impaired granulocyte function resulting from hyperglycemia may predispose to bacterial infections. Autonomic neuropathy, if present, may lead to difficulty in postoperative voiding, which increases the risk of urinary tract infection. Poor circulation as a result of macroangiopathy or microangiopathy can also contribute to the likelihood of postoperative infection.

Tight metabolic control during the perioperative period can decrease the risk of postoperative infection. When SSIs do occur in the diabetic population, they are usually caused by mixed flora, including aerobic and anaerobic organisms such as *Escherichia coli*, Enterobacteriaceae, various streptococci, *Staphylococcus aureus*, and *Bacteroides fragilis*. Necrotizing infections (e.g., fasciitis, gangrene, and Fournier gangrene) are more common and spread more readily in diabetic patients.

Surgical debridement and drainage, if needed, should be performed early. Cultures should be obtained during drainage procedures. Ideally, antibiotic therapy awaits and is based on culture results; however, in practice, it is often preferable to initiate empirical therapy for the most likely organisms before the results are available. Swarming of *Proteus* organisms may obscure other pathogens on culture plates. Unless the patient is clearly manifesting a septic response, aminoglycosides should be avoided because of their nephrotoxicity and the likelihood that diabetic patients may have underlying renal disease. If severe infections do not respond to antibiotic therapy, the presence of *Candida* or other fungal species should be suspected.

Many factors play a role in the increased susceptibility of diabetics to infection, including macroangiopathy, microangiopathy, neuropathy, impaired neutrophil and lymphocyte function, increased capillary permeability, and impaired granulation and healing.⁶ An obvious example of this interaction of multiple contributing factors is a chronically infected nonhealing ulcer on a neuropathic foot. A less obvious but more serious example is the failure of host defenses against peritonitis, soft tissue infection, and bacteremia that develops in diabetic patients. Chemotaxis, adherence, phagocytosis,⁷ bacterial killing, and production of cytokines and complement are all impaired in patients with type 1 diabetes mellitus. The greater prominence of such abnormalities in patients with type 1 diabetes mellitus suggests that the most likely cause is related to chronic and irreversible glycosylation of many proteins, which limits the function of intracellular and intercellular messengers. The implication of this theory is that tight short- and long-term control of blood glucose should allow better control of infection.⁵

The impaired wound healing seen in diabetic patients clearly is related in part to increased susceptibility to infection; however, it is also observed with sterile wounds. Many animal studies have corroborated the clinical observation that skin, fascia, and bone all heal more slowly and with less strength in diabetic patients. Such studies have generally found that this impaired healing is partially mitigated by insulin control, which suggests that glycosylation of proteins is an important factor. A 1999 study indicated that the impaired healing is significantly mediated by endogenous corticosteroids.⁸ Local application of inflammatory substances or growth factors (e.g., platelet-derived growth factor, tissue growth factor, bacterial by-products, growth hormone, and hyperosmotic sugar) has been shown to stimulate healing in diabetic animals.^{6,9}

Adrenal Insufficiency

The anti-inflammatory properties of the glucocorticoid steroids [see Table 3] are commonly exploited to treat disease. Patients are often treated for long periods with large pharmacologic doses of steroids (commonly, prednisone by mouth) for inflammatory or autoimmune diseases such as arthritis, systemic lupus erythematosus, inflammatory bowel disease, and bronchial asthma. Primary failure of the hypothalamic-pituitary-adrenal (HPA) axis (as in Addison disease, Sheehan syndrome, and panhypopituitarism) is rare, but when it does occur, it must be treated with long-term administration of physiologic doses of corticosteroids. It is not uncommon for patients who are receiving such corticosteroid therapy to require operations, and this surgical population presents a unique perioperative management challenge [see Figure 2]. It is axiomatic that any patient treated with exogenous steroids may eventually manifest adrenal atrophy as a result of suppressed endogenous production of adrenocorticotrophic hormone (ACTH). Actual or relative adrenal insufficiency may occur during or after a major operation, resulting in a syndrome whose manifestations can range from nausea, vomiting, fever, abdominal pain, and electrolyte abnormalities to complete circulatory collapse.

The adrenal cortex is central to the maintenance of homeostasis both at rest and during stress.¹⁰ Cortisol, the predominant glucocorticoid hormone, is produced by the fascicular and reticular zones of the adrenal cortex. It is under the strict regulatory control of both the hypothalamus (via corticotropin-releasing hormone) and the anterior pituitary gland (via ACTH). Cortisol itself participates in its own regulation, imparting a potent negative feedback signal to both the hypothalamus and the ACTH-producing basophilic cells within the adenohypophysis of the pituitary. Together, these components, which constitute the HPA axis, form a finely regulated feedback loop for cortisol secretion.

Under unstressed physiologic conditions, the adrenal cortex constitutively produces approximately 20 to 25 mg of cortisol daily.¹¹ Cortisol secretion normally occurs in diurnal surges; consequently, simple measurements of serum cortisol levels in isolation generally do not suffice for accurate evaluation of the status of the HPA axis. Much of the daily variability in cortisol secretion can be tracked with 24-hour urinary measurements of the hydroxysteroid metabolites; however, there can be significant

Table 3 Selected Corticosteroid Preparations

Preparation	Equivalent Doses (mg)	Glucocorticoid Activity*	Mineralocorticoid Activity*
Short-acting (8–12 hr)			
Hydrocortisone	20	1	1
Cortisone	25	0.80	0.80
Intermediate-acting (12–36 hr)			
Prednisone	5	4	0.80
Prednisolone	5	4	0.80
Methylprednisolone	4	5	0
Triamcinolone	4	5	0
Long-acting (36–54 hr)			
Betamethasone	0.60	25	0
Dexamethasone	0.75	30	0
Mineralocorticoid			
Fludrocortisone	—	10	125

*Ranked on a scale rating hydrocortisone as 1.

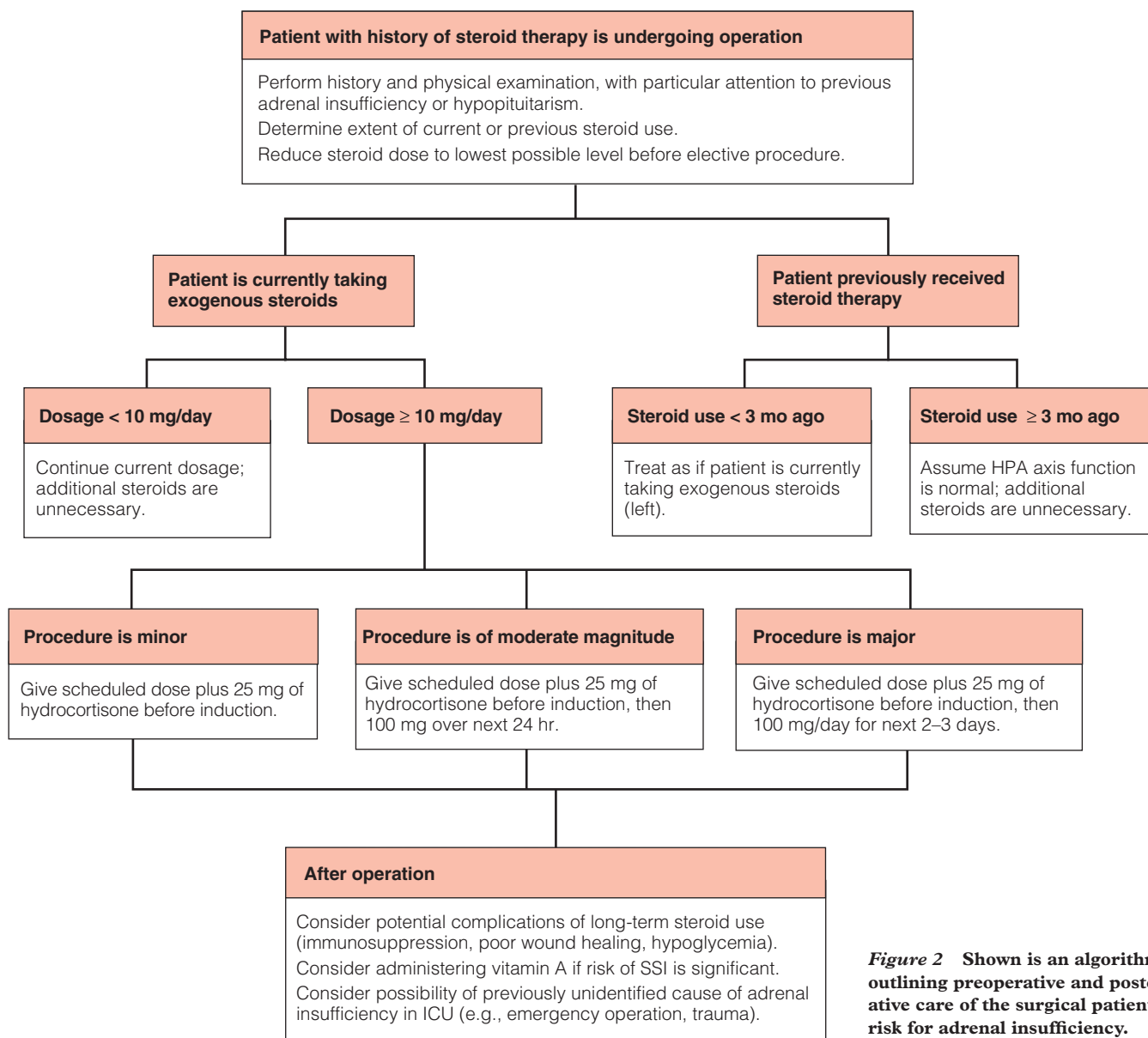


Figure 2 Shown is an algorithm outlining preoperative and postoperative care of the surgical patient at risk for adrenal insufficiency.

overlap between normal patients and those with clinical adrenal insufficiency.¹² Provocative testing of the HPA axis is based on the normal physiologic response of the adrenal gland to release cortisol in a receptor-mediated G-protein-coupled response to circulating ACTH.

Although there is some controversy regarding which laboratory evaluation is the best predictor of adequate adrenal response to a surgical stress, it is clear that ACTH stimulatory testing is more sensitive and specific than unprovoked steroid measurement alone. Hypoglycemia-induced release of ACTH in response to exogenous insulin infusion (the insulin tolerance test, or ITT) has long been considered the gold standard for determination of relative adrenal insufficiency, but various complications, including discomfort, seizures, and even death, limit its clinical usefulness as a routinely applied test.¹³ In several studies, strong correlations have been observed between the ITT and adrenal stimulation with a synthetic corticotropin construct.^{14,15} In this test, the plasma cortisol response is measured 0, 30, and 60 minutes after infusion of 250 µg of the ACTH analogue. Although there is no unanimously accepted cutoff value for stim-

ulated cortisol levels above which the HPA axis can be assumed to be intact, it has been suggested that a value higher than 600 mol/L at 30 minutes should be a sufficiently sensitive confirmation of an intact HPA axis.

Adrenal glucocorticoids are important modulators of the stress response: they play a complex role in the metabolic pathways for carbohydrates, fats, and proteins; modulate gluconeogenesis and lipolysis; mediate insulin resistance; and exert a host of well-documented effects on inflammation and wound healing. It is clear that physiologic stresses (e.g., burns, trauma, and iatrogenic tissue damage occurring during operations) result in an ACTH-induced surge in the adrenal steroid response.^{16,17} Serum measurements reveal that this response can produce cortisol elevations several times greater than those produced under basal conditions. It is becoming apparent that although this exaggerated adrenal stress response may have conferred a certain evolutionary benefit, prolonged exposure to high doses of steroids may nonetheless have deleterious consequences. The potential complications of long-term or high-dose administration of glucocorticoids are well described: they include hyper-

tension, cataracts, myopathy (especially when glucocorticoids are used in conjunction with nondepolarizing paralytic drugs), osteonecrosis (particularly on the femoral head), impaired wound healing, and immunosuppression.¹⁸

It was the observed (and presumably physiologic) magnitude of the cortisol response to stress that led to the long-held—albeit never corroborated—assumption that supraphysiologic levels of steroids were required to maintain homeostasis in the stressed environment. In the 1950s, two case reports were published that described perioperative deaths thought to result from untreated and unrecognized adrenal insufficiency.^{19,20} Thereafter, it became common practice to supply supraphysiologic doses of exogenous steroids (i.e., doses two to three times that expected under basal conditions) to patients believed to be at risk for adrenal suppression and therefore unable to mount the expected cortisol surge during operation. Subsequently, this practice came under scrutiny. Primary studies suggested that although HPA suppression could occur as a result of long-term steroid use, normal physiologic replacement doses were sufficient to maintain perioperative homeostasis; supraphysiologic doses were unnecessary.²¹ The concept that significantly lower doses of steroids are required to maintain homeostasis and normotension in the perioperative period than was once believed has been supported by prospective clinical studies in humans.²²

It is clear that ACTH is not only stimulatory but also trophic for the adrenal cortex. There is evidence that if the adrenal cortex is not exposed to ACTH, it is subject to hyposecretion and anatomic atrophy. It was once thought that exposure to even low doses of steroids (< 10 mg of prednisone equivalent) was sufficient to suppress the endogenous release of ACTH and thus to result in a state of adrenal insufficiency. This belief led to the common practice of administering so-called stress-dose steroids to surgical patients who had received exogenous steroids even in small doses or as long ago as 1 year before operation. Provocative studies on patients previously exposed to steroids demonstrated that the HPA axis usually remains intact despite either ongoing exposure to small doses of exogenous steroids (< 10 mg of prednisone equivalent daily) or earlier steroid use (if the time since discontinuance was longer than 2 to 3 months).^{23–26}

In summary, the glucocorticoids are essential components of human homeostasis both at rest and under stressful conditions

such as occur during surgery. Complete or even relative adrenal insufficiency is preventable; when it does occur, it can have disastrous consequences if not recognized and appropriately treated. Exogenous administration of steroids in sufficient doses is generally adequate to prevent the syndrome of adrenal insufficiency. The decision to administer supplemental perioperative steroids should be based on the specific details of the history of steroid use as well as on the magnitude of the proposed operation.

Hormone Replacement

Many surgical patients are receiving thyroid or ovarian hormone replacement therapy. In addition, the use of growth hormone, growth hormone precursors, and anabolic steroids has become more common in general practice. The effects of these hormone medications must be taken into account in any patient undergoing an elective or emergency operation. Because all of these substances have long half-lives, replacement is not necessary for the first 2 weeks after operation; however, if the illness or the operation itself prevents oral intake for more than 2 weeks, the possibility of hypothyroidism or estrogen depletion should be considered. Postoperative weakness, lack of energy, depression, and sleeping disorders can all be caused by the lack of long-term hormone supplements.

Some patients exhibit decreased endogenous thyroid function after operation, either because their thyroid-stimulating hormone (TSH) levels are depressed as a consequence of long-term thyroid medication or because they experience complications and become critically ill. Critical illness typically leads to reduced blood levels of triiodothyronine (T₃) and thyroxine (T₄). In addition, glucocorticoids, radiopaque dyes, propranolol, and amiodarone all lower plasma T₄ levels,²⁷ and dopamine decreases TSH secretion directly.²⁸ Most critically ill patients, however, do not exhibit metabolic or hemodynamic changes indicative of hypothyroidism. Measurement of TSH is helpful for determining the significance of thyroid function in critically ill patients. If the serum TSH level is lower than 5 μ U/ml and the patient is not on high-dose dopamine therapy, thyroid function is considered adequate regardless of other plasma markers. If the TSH level is higher than 20 μ U/ml, replacement with thyroxine is indicated.²⁹

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16 CLINICAL AND LABORATORY DIAGNOSIS OF INFECTION

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Infections are common complications treated in surgical and trauma intensive care units (ICUs).^{1,2} The Extended Prevalence of Infection in Intensive Care (EPIC II) study was a 1-day point prevalence study in 1,265 participating ICUs from 75 countries on the study day with data from 13,796 adult patients.³ On the day of the study, 7,087 patients (51%) were considered infected; 9,084 patients (71%) were receiving antibiotics. The infection was of respiratory origin in 4,503 (64%), and microbiologic cultures were positive in 4,947 (70%) of the infected patients; 62% of the positive isolates were gram-negative organisms, 47% were gram-positive organisms, and 19% were fungi. The ICU mortality rate of infected patients was more than twice that of noninfected patients (25% versus 11%, $p < .001$), as was the hospital mortality rate (33% versus 15%, $p < .001$). Patients who had longer ICU stays prior to the study day had higher rates of infection, especially infections attributable to multidrug-resistant pathogens. Studies have demonstrated that approximately 2 million nosocomial infections occur annually, and the cost of diagnosing and treating these infections exceeds 4.5 billion dollars each year.^{4,5}

The term “surgical infection” is a dynamic term that has changed over time. Classically, it implies that the infection is amenable to operative management through surgical source control, as in the case of complicated diverticulitis or necrotizing soft tissue infection. Currently, the term refers to any infection commonly seen in surgical patients (e.g., catheter-related bloodstream infection [CRBSI] or postoperative pneumonia). These infections are frequently acquired in the hospital, and their incidence is on the rise.

The presence of surgical infectious disease is usually determined clinically and confirmed microbiologically. Identification of an infection is rarely incidental: most often it is sought in response to a clinical signal. This signal is frequently fever, pain, change in physiologic function, or altered laboratory values but may be one or more of a number of other symptoms and signs.

Many surgical infections are outpatient conditions that are easily diagnosed and treated. Infections in hospitalized and especially critically ill patients, whether related to the primary surgical disease or resulting from surgical therapy, are less easily managed. Infections in critically ill patients are often difficult to diagnose, and the diagnostic workup may include unnecessary tests and procedures. Diagnosing infections in the ICU is a very inefficient process that is time consuming and costly.⁴ Key strategies must center around the following strategies:

1. In patients with severe sepsis, appropriate cultures should be obtained promptly and not delay the initiation of antibiotics.⁶
2. The diligence of diagnosing an infection should be directly related to the morbidity of missing that infection. For example, the diagnosis of bacteremia is more urgent than the diagnosis of a urinary tract infection (UTI).
3. If a clinician is concerned enough to order a culture or diagnostic test, a positive test should warrant treatment. Thus, if there is a low suspicion of a patient having an infection, tests should not be ordered.

Definitions

Traditionally, the terms “infection,” “sepsis,” “septicemia,” “bacteremia,” “endotoxemia,” and “septic shock” have borne similar connotations; this imprecision of terminology has led to considerable confusion about the specific role of microbial infection as a cause of the common clinical presentation of fever, tachycardia, and occasional hypotension. The traditional tendency to conflate these distinct concepts in this simplistic and unrefined manner has had major implications for how antibiotics are used—or, more bluntly, misused and overused commonly—in surgical patients.

The human body’s physiologic response to systemic infection is well characterized and is often referred to as sepsis. However, infection and sepsis are distinct entities: infection is a process, and sepsis is the response to that process. As a rule, infection, once diagnosed, needs a combination of antibiotics and source control for appropriate treatment.

The management of sepsis is more complicated, specifically in immunosuppressed patients who may not have the normal septic response to infection. Most surgeons, for example, have encountered a patient receiving high doses of steroids who has a perforated intra-abdominal viscus and fecal peritonitis but whose leukocyte count, temperature, and blood pressure are all normal. Conversely, a systemic inflammatory response syndrome (SIRS) may produce an exaggerated physiologic response with no infection.⁷

SIRS is the nonspecific clinical picture of temperature, heart rate, respiratory rate, and white blood cell (WBC) count abnormalities. SIRS may or may not be attributable to infection; when it is, it is referred to as sepsis [see Figure 1]. A SIRS response that mimics sepsis in noninfected patients commonly occurs in ICU patients and may manifest physiologic and metabolic changes that are indistinguishable from those associated with sepsis. When sepsis results in organ dysfunction, the ensuing state is referred to as severe sepsis; when it results in persistent cardiovascular decompensation and hypotension, the ensuing state is referred to as septic shock.

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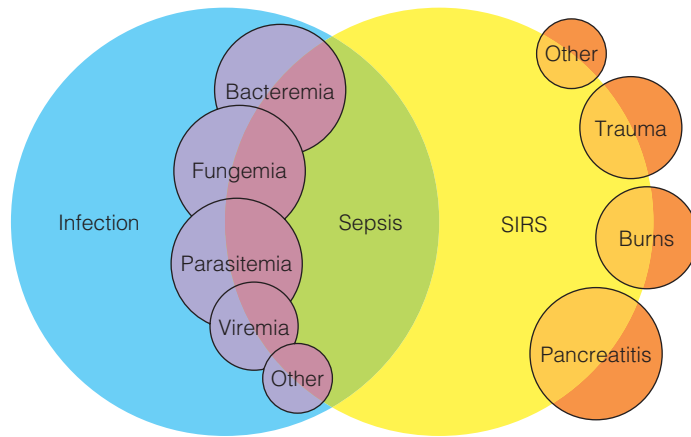


Figure 1 The interrelationships among infection, sepsis, and the systemic inflammatory response syndrome (SIRS).

Signs and Symptoms of Infection

INFLAMMATION

Rubor, calor, dolor, tumor, and functio laesa, which refer to redness, heat, pain, swelling, and loss of function, respectively, have been considered the cardinal signs of localized inflammation since the times of Hippocrates and Galen. They remain the primary signals leading to the concern of surgical infection and for many of the infectious complications of operation. They represent the host's effort to contain infection locally and may signal the presence of infection even in cases where the primary site of infection is superficial or deep surgical wound infection.

FEVER

Fever is perhaps the most common signal that concerns clinicians that an infectious process is present, although fever alone is most often not associated with an infection in ICU patients. Postoperative fever is a normal part of the recovery process; understanding the typical febrile course is important in differentiating normal from pathologic fever. Early postoperative and posttrauma fever is common and usually not related to infection. In fact, approximately 80% of critically ill trauma patients will develop a fever during the first week after the traumatic episode [see Figure 2].⁸ Infection usually begins to manifest itself with an altered physiologic prodrome (e.g., prolonged ileus after bowel surgery). Investigation should be started when there is clinical suspicion of an infection. A fever that appears after the normal postoperative temperature elevation has resolved should not be ignored. In the absence of a clear diagnosis, a thorough physical examination of the patient, laboratory tests, and appropriate imaging are required to identify occult infection.

The postoperative day (POD) on which the fever occurs historically gives insight into the likely cause. The “wind, water, walking, wound, and wonder drug” memorization tool is frequently used to remember causes of postoperative fever. “Wind” refers to atelectasis, which is a common cause of fever on PODs 1 and 2. “Water” refers to UTIs, which are common after POD 3 in patients who have had Foley catheters in place. “Walking” correlates with deep vein thrombosis (DVT), which occurs in postoperative patients usually

after POD 4. To reduce the risk of DVT, chemoprophylaxis and mechanical prophylaxis are recommended. “Wound” infections are another common cause of fever in surgery patients and are traditionally observed around POD 5. Finally, “wonder drug” medications can cause fever and should be kept in mind when working up a postoperative fever.⁹

Noninfectious causes must be considered with infectious causes in the ICU and postoperative patient because fever resulting from infection and trauma (i.e., surgery) is produced through the release of similar cytokines. Because fever can have many infectious and noninfectious etiologies, a new fever in a patient in the ICU should trigger a careful clinical assessment to determine whether infection is present.¹⁰

ALTERED HEART RATE

A heart rate that is either too high or too low may signal an infection. On rare occasions, a change in rhythm in the elderly (e.g., paroxysmal atrial tachycardia, flutter, or atrial fibrillation) indicates an infectious process. A patient with an infection does not always exhibit tachycardia. Patients on beta blockers or with gram-negative sepsis may have a so-called relative bradycardia, meaning that the resulting tachycardia is not as pronounced as one might expect. Tachycardia is often the first sign of infection after upper gastrointestinal surgery (e.g., gastric bypass).¹¹ An unexplained sustained increase in heart rate should not be ignored.

PAIN

Pain that persists or is out of proportion to the expected response deserves attention. Whenever a surgical wound that was healing favorably for the first 5 to 7 days becomes more painful, a deep or superficial surgical site infection (SSI) must be suspected and ruled out, even if other signs are absent. Unexplained muscular pain is often the first harbinger of deadly necrotizing soft tissue infection caused by gram-positive bacteria (e.g., group A streptococci), the early recognition of which may be lifesaving and limb preserving. Sometimes pain is referred, and the painful area appears normal on examination. Pneumonia that presents with upper abdominal pain is a classic example, as is the shoulder-tip pain with a normal range of motion seen in patients with a subphrenic abscess.

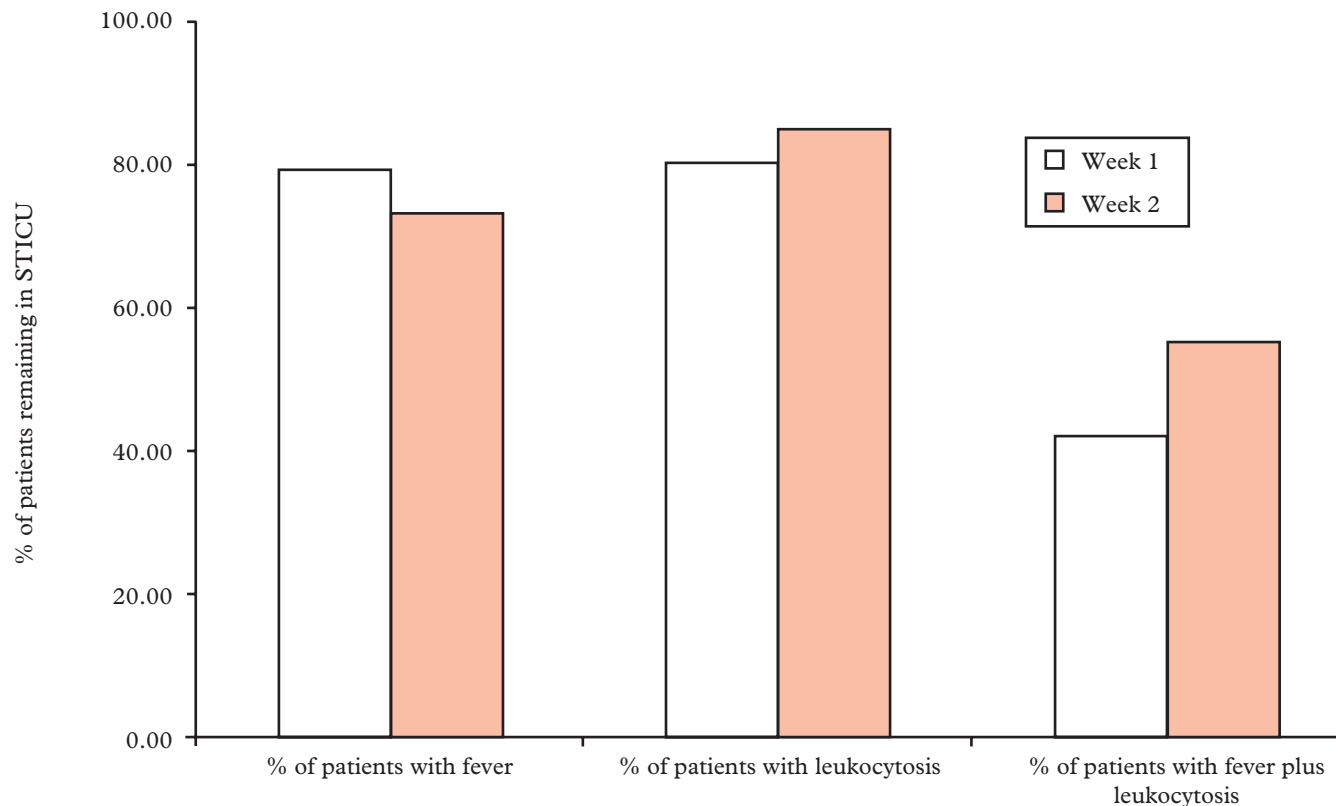


Figure 2 Percent of trauma patients who develop fever, leukocytosis, and fever plus leukocytosis during the first 2 weeks in the surgical and trauma intensive care unit (STICU).

CONFUSION

In the geriatric patient population, confusion is often the first sign of infection. With an increasing number of geriatric patients on surgical and trauma services, new-onset confusion must be taken seriously. The physician's first response to confusion in an elderly patient in the postoperative period must be to seek a cause, not to order sedation.¹²

Approach to Diagnosing Infections

EVALUATION FOR PRESENCE OF INFECTION

Once the surgeon suspects that a patient has an infection, an appropriate diagnostic workup is initiated. The diagnostic approach varies with the clinical situation and requires knowledge of specific condition-associated pathogens, as well as the prevalence of certain pathogens in a particular hospital or ICU [see Table 1]. The health of the host and the nature of the pathogen must be considered carefully in the diagnosis of surgical infection.

Relatively healthy patients without comorbidities likely have the characteristic symptoms of a disease. For example, a young, healthy patient with appendicitis is likely to present with fever, nausea, and right lower quadrant pain. If an elderly, demented patient with diabetes develops appendicitis, he or she is less likely to exhibit the classic symptoms.¹² It is important to assess these patients for more subtle signs of infection, such as changes in mental status or eating habits.

Extensive invasive monitoring and access devices frequently used in the care of critically ill patients predispose the patient to gram-positive infection, including methicillin-resistant *Staphylococcus aureus* (MRSA). The prevalence of resistant bacterial strains should be monitored in clinical settings to guide empirical therapy. MRSA, once an occasional finding, has become common in ICUs, wards, and the community.¹³ Early Gram stain microscopy is important to help direct treatment. It now must be assumed that Gram stains with gram-positive cocci in clusters indicate MRSA until proven otherwise, especially in ICU patients.

The ICU patient presents a particular conundrum. Nosocomial infection is identified in an estimated 20 to 30% of such patients.^{1,14} The prevalence of nosocomial infection has created a strong predisposition toward instituting empirical antibiotic therapy in ICU patients. Current recommendations are to start empirical antibiotics as early as possible on diagnosis of infection. In patients with severe sepsis, appropriate cultures should be obtained within the first hour prior to starting antibiotics but should not delay the administration of empirical antibiotic therapy.⁶

Although empirical antibiotics have been shown to improve mortality from nosocomial infections, the majority of surgical and trauma ICU patients who are started on empirical antibiotics are never found to have a confirmed infection.¹⁵ There are enormous inconsistencies in how infections are diagnosed, which has a tremendous effect on our ability to assess the efficacy of empirical antibiotic therapy.

The current approach to diagnosing infection in surgical patients, particularly those who are critically ill or compromised, is still in great need of clarification and standardization.¹⁶ Until these issues are resolved, the clinician must be familiar with the strengths and limitations of a variety of current diagnostic methodologies and then exercise thoughtfulness and disciplined diligence. The likelihood that a particular patient is infected (i.e., the pretest probability) is important in the decision to obtain diagnostic testing and initiating treatment.

HISTORY AND PHYSICAL EXAMINATION

The history should include all comorbid conditions (e.g., diabetes, lung disease, cirrhosis, hepatitis, kidney disease necessitating dialysis, and previous important infections) as well as a hospitalization history that covers health status, surgical diagnosis and therapy, additional therapeutic interventions (including interventional radiology, monitoring devices, drains, and drugs), and other related variables. This can be especially difficult in ICU patients who arrive too ill to be able to give a history of present illness, a review of symptoms, or a past medical history. It is hoped that immediate access of patient records with the use of electronic medical records will improve this process.¹⁷

The general physical examination is important, and a number of specific examinations should be carefully performed, with emphasis given to (1) all wounds and surgical sites; (2) all invasive monitoring or therapeutic devices and surrounding areas (notably central and peripheral intravenous [IV] lines); (3) all drainage systems and surrounding tissue, with particular attention paid to the nature of the drainage and whether it has recently changed in character or volume (particularly if it has stopped); (4) the rectal examination (for pelvic or prostatic infection); (5) areas of potential decubitus ulcers; (6) the neck (for central nervous system infection); (7) intravascular lines, surrounding tissue, and proximal vessels; (8) the lungs; and (9) the legs. The findings on physical examination should be a guide for selecting specimens for microbiologic analysis, particularly when there have recently been significant changes in wounds or drainage. Findings on physical examination may lead to obtaining radiologic imaging.

DIAGNOSTIC TESTS

Hematologic and Biochemical Tests

After physical assessment, laboratory blood tests are routinely relied on to orient the surgeon toward or away from a clinical diagnosis of infection. Leukocytosis, particularly with an increase in band forms, is a usual but inconsistent marker for infection. The WBC count is widely used to follow the response of infection to therapy and thus has been adopted as a surrogate indicator of the success or failure of therapy. Surprisingly, however, the documentation supporting this ubiquitous practice is sparse.^{18,19} The daily series of complete blood counts (CBCs) is routinely ordered in conjunction with the initiation of antibiotic therapy, but the results from these studies are often difficult for the bedside clinician to interpret. Leukocytosis is extremely common in ICU patients;

in fact, 80% of critically ill trauma patients have an elevated WBC during their first week of admission [see Figure 2].⁸ Therefore, we still need to determine better markers of infection besides daily fever and WBC.

Other biochemical cues that may help predict infection are changes in daily WBC, glucose levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and procalcitonin (PCT). Plasma CRP concentration, which has been extensively used in some European countries to monitor the evolution of infection, has been found to be significantly elevated in patients with pulmonary aspiration that has induced bacterial infection, compared with patients with sterile pneumonitis.²⁰ Some investigators have suggested that because CRP concentration appears to be particularly responsive to bacterial infection, it may be useful as a monitor of the efficacy of antibiotic use, thereby guiding discontinuance of treatment.²¹ A host of cytokines, cellular adhesion molecules, oxidants, and other biomolecules known to participate in systemic inflammation from numerous causes are being extensively investigated to establish both diagnostic and therapeutic functions. As yet, however, no single mediator of systemic inflammation has been validated as a reliable clinical tool for surveillance of the progression of infection or the response of infection to treatment.

Microbiologic Studies

As a rule, Gram stains and cultures of wound tissue, sputum, urine, and drainage effluent are useful studies. Bronchoalveolar lavage (BAL) with a quantitative culture is useful to diagnose ventilator-associated pneumonia (VAP) and has a higher sensitivity than sputum or blind endotracheal aspirate cultures.²² In some cases, a battery of cultures of potential sites of infection may be the only feasible approach. Culture techniques are discussed more thoroughly elsewhere.

Radiology

In patients who have not recently undergone an operation, the medical and surgical history combined with the radiologic examination may guide the clinician of a potential infectious focus (e.g., ulcer, diverticulitis, cholecystitis or cholangitis, or obstructed ureter). When an abdominal process is suspicious, computed tomography (CT) is the most sensitive radiologic study.²³ The evaluation for infection in a postoperative patient should include a chest x-ray. Ultrasonographic examination of the operative site may be useful to evaluate the possibility of a deep abscess. CT of the operative site is often more useful than ultrasonography because the presence of wounds, dressings, and drainage tubes may obscure ultrasonographic findings. CT is useful to diagnose postoperative intra-abdominal abscesses and can guide percutaneous aspiration of potentially infected fluid. Finally, the possibility of acalculous cholecystitis must be kept in mind and can be diagnosed by CT or ultrasound evaluation.

Diagnostic Approach to Specific Surgical Infection

ICU patients may develop common general surgery conditions while in the ICU. These infectious processes must be kept in mind when a complex ICU patient develops symptoms of infection.

APPENDICITIS

Patients with appendicitis classically present with right lower quadrant pain, anorexia, and fever. However, appendicitis should be considered in any patient with abdominal pain. Physical examination findings generally include focal tenderness over the appendix (usually found at the McBurney point). Pelvic and rectal examinations may elicit abnormal tenderness if the appendix is located in the pelvis. Patients with a perforated appendix have more exaggerated symptoms and may have peritonitis. Laboratory evaluation should include a CBC and a basic metabolic panel (BMP). Leukocytosis is seen in the majority of patients with appendicitis. The BMP is used to assess renal function and hydration status. A CT scan is often used to rule out appendicitis.²³ CT scans are particularly useful in female patients who may have an obstetric-gynecologic process that is mimicking appendicitis.

DIVERTICULITIS

Diverticulitis is an extraluminal infection caused by a perforated colonic diverticulum. The sigmoid colon has the most diverticuli and is where the vast majority of diverticulitis occurs. Patients with sigmoid diverticulitis commonly complain of left lower quadrant pain and changes in bowel function. Symptoms depend on the site of perforation and the extent of spillage. The spectrum of diverticulitis ranges from patients with a microperforation and minor symptoms to patients with peritonitis who require emergent surgery. CT scan confirms the diagnosis of diverticulitis and can show both the location of disease, the extent of inflammation, abscess formation, or involvement with adjacent organs.²⁴

Acute cholecystitis is one of the most common surgical infections in the United States. Patients classically present with right upper quadrant pain, low-grade fever, nausea, and a past history of biliary colic. Laboratory analysis should include a CBC and liver function tests. These laboratory results will help the clinician differentiate between biliary colic, acute cholecystitis, choledocholithiasis, and cholangitis. The diagnosis is then confirmed by a right upper quadrant sonogram, and the appropriate treatment is initiated.

In critically ill patients who develop signs of infection, the possibility of acalculous cholecystitis must be kept in mind. Acalculous cholecystitis is difficult to diagnose and secondary

to bile stasis and gallbladder ischemia. The diagnosis is difficult because the majority of critically ill patients are not able to express the classic signs of cholecystitis. If suspicion is high, then an ultrasound examination of the gallbladder is recommended. A nuclear imaging scan may be useful in assisting the diagnosis, as well as percutaneous drainage, which can be both diagnostic and therapeutic.

SKIN AND SOFT TISSUE INFECTIONS

The incidence of skin and soft tissue infections (SSTIs) has increased over the past two decades. These infections often lead to ICU admissions but can also develop in the ICU.²⁵ SSTIs can be categorized into necrotizing SSTIs and nonnecrotizing SSTIs.²⁶ SSTIs, especially necrotizing, have the potential to cause significant morbidity and mortality. The primary diagnostic challenge in patients with SSTIs is determining which infections require surgical débridement (i.e., source control). Physical examination should focus on the patient's constitutional symptoms and the appearance of the infected tissue. If the physical examination reveals evidence of abscess formation or necrotic tissue, then débridement is warranted. In many patients (particularly obese patients), the physical examination may be equivocal. These patients need a more extensive diagnostic workup, which involves CT scan or ultrasound evaluation to further define the extent and size of the infection. After the diagnosis and initial débridement of an SSTI, it is necessary to do rigorous daily examinations of the wound to evaluate for further necrosis or infection. These patients routinely require multiple débridements, and it is often difficult to determine resolution of infection in these patients. The first reexamination should occur within 12 hours of the initial débridement.

SURGICAL SITE INFECTIONS

An SSI is an infection that occurs somewhere in the operative field after a procedure. SSIs are classified as either incisional or organ space infections, with incisional SSIs having subclassifications of superficial and deep SSIs. SSIs are common hospital-acquired infections and a major contributor to hospital mortality and morbidity. Depending on the procedure, a patient has a 3 to 20% chance of developing an SSI.²⁷ Risk factors to develop an SSI are based on both inherent patient risk factors (e.g., chronic disease or immunosuppressive state) and the nature of the procedure. For example, a patient with diabetes undergoing a colon resection for perforated diverticulitis has a greater chance of developing an SSI than a relatively healthy patient undergoing an elective cholecystectomy for biliary colic. Perioperative antibiotics have been shown to decrease the incidence of SSIs for at-risk patients.

When there is concern for an SSI, the patient history should address the risk factors for SSI, such as previous diseases, and issues concerning the operation itself (e.g., duration, difficulty, urgency, use of drains, other details of the procedure, time elapsed since the operation). Physical examination should focus on the cardinal signs of infection and the absence or presence of a healing ridge. SSIs are particularly difficult to diagnose in obese patients and patients who have had primary closure of their wound. Frequent thorough examination

Table 1 Fundamental Approach to Diagnosis of Infection
Recognize clinical signal and observe its characteristics: 1. Nature 2. Intensity 3. Rapidity of development
Make best guess as to source and likely pathogen on the basis of 1. History of surgical disease 2. Physical examination 3. Microbiologic examination of stained specimens 4. Radiologic findings
Confirm presence of infection by means of 1. Laboratory results 2. Observation of clinical course 3. Invasive procedures (e.g., paracentesis, thoracentesis, interventional radiology, operation)

of these wounds for drainage or erythema is particularly important.

Deep and organ space infections tend to become apparent later in the postoperative course, often after a period in which the patient appears to be recovering, and are associated with a variety of signals, some of which can appear suddenly. The physical examination is complicated by the discomfort associated with the operation. Surgical site pain that increases or fails to resolve in the 7 to 10 days following surgery is an important yet subtle marker for occult infection that calls for investigation. Rectal examination is important because it may help detect a low pelvic abscess formation. Persistent diarrhea may also be a sign of pelvic abscess formation. Finally, return of ileus after an abdominal operation is a significant clue to the presence of abdominal infection. CT scan of the abdomen should be used to assess for a deep organ space infection in patients where there is considerable concern.

Ileus has many causes, some of which are not well understood. Prolonged ileus after abdominal operation—as well as almost any ileus after other operations—requires explanation. Infections at remote sites (e.g., SSI and pneumonia) can produce ileus.

The absence of wound healing can indicate the presence of a significant infection. Typically in such a case, wounds left for delayed primary closure or secondary closure do not exhibit the appropriate granulation tissue and appear pale, dry, and unhealthy. These patients should undergo an infection workup, including a careful physical examination to assess for a soft tissue infection. The development of good granulation tissue is a sign that infection has been appropriately treated.

Nosocomial Infections

Nosocomial infections are infections that result from treatment provided in the hospital. They are defined to occur 48 hours after admission or 30 days after discharge. The Centers for Disease Control and Prevention (CDC) estimates that there are 1.7 million nosocomial infections per year in the United States, which are attributed to 99,000 deaths. Nosocomial infection is identified in an estimated 20 to 30% of ICU patients.^{1,14} The most common nosocomial infections are UTIs, vascular catheter infections, VAP, SSTIs including SSIs, and *Clostridium difficile* infection.

URINARY TRACT INFECTION

UTI is the most common health care–associated infection in the ICU and predominantly occurs in patients with indwelling urinary catheters. Nearly all patients admitted to the ICU have a urinary catheter in place; of these, it is estimated that about 20% progress to UTI.²⁸ Bacteria adhere to urinary catheter surfaces, where they promote growth of a so-called biofilm composed of microorganisms, bacterial glycocalices, Tamm-Horsfall protein, and urinary salts. Eradication of this infectious nidus is essentially impossible without catheter removal.²⁹ The standard criterion for the diagnosis of UTI (10^5 bacteria/mL) is difficult to apply in catheterized patients because antibiotic therapy without removal of the catheter and the source of bacteriuria would be ineffective. Furthermore, it is well established that urine cultures demonstrating as few as 10^1 or 10^2 bacteria/mL increase 1,000-fold within

1 to 2 days³⁰; effectively, therefore, any bacterial growth on a urine culture from a catheterized patient signals heavy colonization, if not infection.

More important than quantifying the degree of bacteriuria is determining whether there is any evidence of tissue invasion by urinary bacteria, which would present as pyelonephritis, cystitis, prostatitis, epididymitis, bacteremia, or sepsis. The patient history should determine whether a Foley catheter was used and for how long; how, when, and why it was inserted; instrumentation (e.g., a so-called in-and-out catheter, cystoscopy, or transurethral resection of the prostate); and whether the patient has had any previous UTIs. The physical examination should ascertain whether there is any costovertebral angle tenderness or evidence of prostatic or epididymal tenderness.

Laboratory tests should include gross and microscopic urinalysis, urine culture, and sensitivity tests. Patients who have WBCs, leukocyte esterases, or nitrites in their urine often have a UTI. The commonly used threshold for diagnosing a UTI based on quantitative urine culture has been 10^5 colony-forming units per milliliter (CFU/mL), but the recent evidence-based Infectious Diseases Society of America guidelines state that “[catheter-associated] UTI in patients with indwelling urethral, indwelling suprapubic, or intermittent catheterization is defined by the presence of symptoms or signs compatible with UTI with no other identified source of infection along with $> 10^3$ cfu/mL of ≥ 1 bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours (A-III).”³¹ Blood culture is important because it may substantiate the diagnosis, identify the bacteria present, and determine the degree of invasiveness of the infectious process.

The predominant microorganisms causing catheter-associated urinary tract infection (CAUTI) in the ICU are enteric gram-negative bacilli, enterococci, *Candida* species, and *Pseudomonas aeruginosa*. Multidrug resistance is a significant problem in urinary pathogens.³² The duration of catheterization is the most important risk factor for the development of CAUTI. Diagnosis, particularly in the ICU setting, is very difficult as asymptomatic bacteriuria may be difficult to differentiate from symptomatic CAUTI. In general, asymptomatic bacteriuria should not be treated, and treatment of CAUTI often requires removal of the catheter along with systemic antimicrobial therapy. General strategies for the prevention of CAUTI apply to all health care–associated infections and include measures such as adherence to hand hygiene. Targeted strategies for prevention of CAUTI include limiting the use and duration of urinary catheterization, using aseptic technique for catheter insertion, and adhering to proper catheter care.

VASCULAR CATHETER INFECTION

The most frequent sites of infection postoperatively are IV catheters, particularly peripheral ones, especially if placed in the prehospital setting. Diagnosis of peripheral catheter infection is simple and is made on clinical grounds. Peripheral infections can be managed by removal of catheter and antibiotics alone if there is no purulent drainage from the site. If purulent drainage is present, incision and drainage of the infected area are recommended.

The diagnosis of central venous catheter (CVC) infection is more difficult. Hospitalized patients are increasingly being managed with monitoring or therapeutic modalities that depend on vascular access (e.g., total parenteral nutrition and dialysis); thus, central line–associated bloodstream infections (CLABSI) have become more common. Approximately 5 million central lines are placed in the United States per year, with 80,000 line infections. Central line infections increase mortality, morbidity, and health care costs. The combined pressures imposed by (1) the need to maintain vascular access in sicker and more complex patients and (2) the increasing predominance of gram-positive CVC infections observed since the late 1970s have led clinicians in many centers to administer empirical therapy without line removal to complex patients as a matter of course; some even advocate 10 to 21 days of vancomycin-based therapy. The problems associated with the latter approach—emerging vancomycin resistance, nephrotoxicity, and rash—are serious and relate specifically to the diagnostic strategy used to manage potential CVC infections. Distinguishing between contamination, colonization, and true infection is problematic; as a result, a number of diagnostic strategies have been advocated that are predicated more on practicality and cost-effectiveness than on microbiologic reality.³³

It is believed that CVC infection most commonly arises from invasion by skin microorganisms (*S. aureus* or *Staphylococcus epidermidis* in about 80% of cases), which may manifest itself as exit-site purulence with or without local cellulitis, as a tunnel infection that may be clinically difficult to detect, or as CRBSI. Of these, CRBSI, which complicates as many as 5% of line placements, is the most clinically important entity. It is strictly diagnosed by identification of the same microorganism (identical species and antibiogram) grown from both the catheter and a peripheral blood culture.

The catheter may be cultured in one of several ways, the most common of which is the roll-plate method. Growth of greater than 15 CFU from a 5 cm segment of the catheter tip by semiquantitative culture is considered positive and reflects catheter colonization. Because it is theoretically possible that this technique may fail to detect bacteria harbored within the catheter lumen, some authorities advocate the more sensitive sonication method, in which the catheter segment is immersed and agitated in a medium to produce a broth that contains bacteria from both the internal and the external surfaces of the line. This technique is both more costly and more time consuming in that it requires quantitative cultures that are deemed positive with growth of more than 10² CFU from a catheter by quantitative (sonication) broth culture.

The recent evidence-based update of the Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-related Infection states the following:

A definitive diagnosis of CRBSI requires that the same organism grow from at least 1 percutaneous blood culture and from a culture of the catheter tip (A-I), or that 2 blood samples be drawn (one from a catheter hub and the other from a peripheral vein) that, when cultured, meet CRBSI criteria for quantitative blood cultures or differential time to positivity (DTP) (A-II). Alternatively, 2 quantitative blood cultures of samples obtained through 2 catheter lumens in which the colony count for the blood sample drawn through one lumen is at least 3-fold greater than the colony count for the blood

sample obtained from the second lumen should be considered to indicate possible CRBSI (B-II). In this circumstance, the interpretation of blood cultures that meet the DTP criteria is an unresolved issue (C-III). For quantitative blood cultures, a colony count of microbes grown from blood obtained through the catheter hub that is at least 3-fold greater than the colony count from blood obtained from a peripheral vein best defines CRBSI (A-II).

A less costly method that renders quantitative cultures unnecessary relies on the speed of bacterial growth: if growth in catheter-drawn blood is faster than that in peripherally drawn blood, a primary line infection is likely. On its own, a line blood culture is not sensitive or specific enough to be diagnostically useful.

The National Healthcare Safety Network (NHSN) defines CLABSI as a primary bloodstream infection in a patient who had a central line within the 48-hour period before the development of the infection. “Criterion 1,” means that the patient has a recognized pathogen cultured from one or more blood cultures, and an organism cultured from blood is not related to an infection at another site. “Criterion 2” means that the patient has at least one of the signs or symptoms of fever, chills, and hypotension, that the signs or symptoms and positive laboratory results are not related to infection at another site, and common skin contaminant is cultured from two or more blood cultures drawn on separate occasions.³⁴

Prevention of CVC infections has recently become a national health care priority. The CDC now designates a CVC infection as an adverse event and has stated goals to reduce these complications by 50% over 5 years. Prevention is improved through use of sterile placement techniques, which involves antiseptic cleansing of the insertion site, appropriate hand washing, use of sterile gloves, and using a large sterile barrier. Other prevention techniques are avoidance of femoral vein catheters when possible and catheter care nursing protocols.^{10,14} An evidence-based intervention to reduce the incidence of CRBSI in ICUs (*N* = 103) in the state of Michigan documented a 66% reduction that was maintained throughout the 18-month study period.³⁵ A follow-up study confirmed that the reduced rates of CRBSI achieved in the initial 18-month period were sustained for an additional 18 months as participating ICUs integrated the intervention into practice.³⁶

SEPTIC SHOCK

Septic shock, which is often a complication of bacteremia, is sepsis with hypotension and severe perfusion abnormalities. Septic shock is often the first sign of multisystem organ failure and warrants early aggressive management.⁶ Fortunately, it rarely occurs without warning. Prior to the development of septic shock, the patient often has fever, tachycardia, recurring hypotension, and a change in laboratory values. Initial hypotension is usually not catastrophic and responds quickly to fluid resuscitation. Oliguria may accompany the hypotension. If this clinical state is allowed to progress, the hypotension will lead to renal failure. Multiorgan failure will result if the infection is not identified and treated with source control and appropriate antibiotics.

Both clinical assessment and laboratory studies are necessary to confirm the presence of septic shock, although florid septic shock is easily recognized on clinical examination

alone. Any or all of the following findings may be present in varying degrees: tachycardia, tachypnea, hypotension, generalized flushing, and other signs suggesting a hyperdynamic, hypermetabolic state. Pulmonary artery catheter measurements confirm high cardiac output and low peripheral vascular resistance. This hyperdynamic response is especially noted early. If the patient has low functional reserves or shock persists, cardiac function can deteriorate. If there is a high suspicion of septic shock, blood cultures should be acquired from two sites prior to starting broad-spectrum antibiotics. The results from the blood cultures assist with the choice of future antibiotics.

PNEUMONIA

The diagnosis and management of nosocomial pneumonia in surgical patients are addressed elsewhere. The central issue is that there is no universal agreement as to how pneumonia, particularly VAP, should be diagnosed. Of the innumerable diagnostic options, none can rely on demonstration of tissue invasion by microorganisms, as would be ideal: all are to some degree nonspecific, and any may be invoked to justify initiation of antibiotic therapy.³⁷ Bronchoscopic or nonbronchoscopic BAL with quantitative culture in our opinion is the most reliable method for diagnosis of VAP and should be performed on any patient for whom there is a high suspicion of VAP, especially critically ill trauma patients.

The Clinical Pulmonary Infection Score (CPIS) may be a useful tool in the diagnosis of VAP. The CPIS is based on fever, leukocytosis, tracheal aspirates, oxygenation, radiographic infiltrates, and semiquantitative cultures with Gram stain. The CPIS has been shown to effectively predict VAP in certain populations. However, the score has been shown not to be predictive of VAP in traumatically injured ICU patients,³⁸ thus further supporting the need for BAL quantitative cultures.

CLOSTRIDIUM DIFFICILE INFECTION

The definition of *C. difficile* infection includes the presence of symptoms (diarrhea, colonic ileus, toxic megacolon, abdominal pain, abdominal distention) and either a stool test result positive for *C. difficile* toxins or toxigenic *C. difficile* or colonoscopic findings demonstrating pseudomembranous colitis.³⁹ The incidence of *C. difficile* infection has increased over the past decade, and many epidemiologic studies have confirmed the importance of *C. difficile* as a transmissible nosocomial pathogen.^{40,41} *C. difficile* is an anaerobic spore-forming organism whose eradication is difficult. The incidence of *C. difficile* infection has risen tremendously over the past decade, and it is now the most common cause of nosocomial diarrhea.^{42,43} The increase in overall incidence has been highlighted by outbreaks of more severe disease than previously observed. A more virulent strain (NAP1/BI/027) has recently become highly prevalent.

C. difficile pseudomembranous enterocolitis is diagnosed by obtaining stool specimens for serology and culture. Stool culture is the most sensitive test but is not clinically practical as a result of its slow turnaround time. Enzyme immunoassay (EIA) testing for *C. difficile* toxins A and B is rapid but is less sensitive than the cell cytotoxin assay. A two-step method that uses EIA detection of glutamate dehydrogenase (GDH) as initial screening and then uses the cell cytotoxicity assay or

toxigenic culture as the confirmatory test for GDH-positive stool specimens only is increasingly being used for testing. Polymerase chain reaction (PCR) testing appears to be rapid, sensitive, and specific, but more data are necessary prior to recommending for routine testing. Proctosigmoidoscopy evaluation of the colon is useful to clinically diagnose pseudomembranous colitis prior to receiving culture or serology results.

The first step in the treatment of *C. difficile* infection is discontinuation of the inciting antimicrobial agent as soon as possible as this may influence the risk of recurrence. Initiation of antimicrobial treatment for *C. difficile* should not be delayed for test results if suspicion is high, particularly if severe or complicated *C. difficile* infection is suspected [see Table 2]. The 2010 *C. difficile* guidelines recommend first-line treatment with enteral vancomycin (500 mg q.i.d.) for patients with severe, complicated *C. difficile* infection, based on data that enteral metronidazole is inferior in efficacy. At present, enteral metronidazole is the drug of choice for the initial episode of mild-to-moderate *C. difficile* infection only.

Antibiotic therapy for *C. difficile* infection is usually successful in relatively healthy hosts if started early. Complex patients with chronic disease who develop *C. difficile* pseudomembranous colitis have a high risk of complication, including the development of fulminant colitis, which may require emergent total abdominal colectomy. If a patient does develop fulminant colitis, early colectomy is the best treatment.⁴⁴

The major risk factor for *C. difficile* infection is prior antibiotic use; therefore, the infection is most commonly seen in patients with extended hospital stays or patients in nursing facilities. Transmission is oral-fecal and commonly occurs within the hospital. The classic presentation is a patient who develops diarrhea a few days after receiving antibiotics, although occasionally patients may develop symptoms over a month after the antibiotics. Prevention programs that enforce proper hand hygiene among health care workers and conservative administration of antibiotics have been effective in reducing the incidence of *C. difficile*.⁴⁵

Difficulty in Diagnosing Infection and Empirical Antibiotic Use

In the surgical ICU, nosocomial infections have a considerable impact on patient mortality, morbidity, ICU and hospital length of stay, and cost. Patients with infections that are not treated precipitously can rapidly develop sepsis and multiorgan failure. Therefore, empirical antibiotics are started when there is a high suspicion for infection even when there is not a known source of infection. Prior to starting empirical therapy, cultures of all possible sources should be collected.

Empirical therapy with broad-spectrum antibiotics has been shown to improve outcomes.⁴⁶ However, the frequent presence of SIRS in complex or critically ill surgical patients makes the diagnosis of infection very difficult. Moreover, common clinical signs of infection such as fever and leukocytosis are not consistently associated with positive microbiologic culture results in critically ill patients. In fact, the vast majority of cultures sent from the ICU are negative.^{8,47,48} Studies have shown that approximately only 25% of patients started on empirical antibiotics are diagnosed with a confirmed infection.¹⁵ The aggressive use of empirical antibiotics

Table 2 Recommendations for the Treatment of *C. difficile* Infection³⁹

CDI Presentation	Clinical Definition	Recommended Treatment
Initial episode, mild or moderate	WBC < 15,000 cells/μL and Creatinine ≥ 1.5 × premorbid level	Oral metronidazole 500 mg t.i.d. for 10–14 days
Initial episode, severe	WBC ≥ 15,000 cells/μL or Creatinine ≥ 1.5 × premorbid level	Oral vancomycin 125 mg q.i.d. for 10–14 days
Initial episode, severe and complicated	Same as severe CDI and Hypotension, ileus, toxic megacolon, perfusion, need for colectomy, or ICU admission	No complete ileus: vancomycin 500 mg q.i.d. orally or via nasogastric tube and/or IV metronidazole 500 mg q. 8 hr Complete ileus: IV metronidazole 500 mg q. 8 hr and rectal installation of vancomycin (in 500 mg in normal saline every 6 hours via Foley catheter in rectum as a retention enema)
First recurrence		Same recommendations as for initial episodes
Second recurrence		Tapered/pulsed vancomycin

CDI = *Clostridium difficile* infection; ICU = intensive care unit; IV = intravenous; WBC = white blood cells.

may seem reasonable and is understandably difficult to resist but is potentially deleterious in many ways, and there are many sound objections to its reflexive use.⁴⁹

Empirical antibiotic therapy can obfuscate future cultures, predispose to the emergence of resistant organisms (which are associated with increased attributable mortality), promote derepression of homeostasis-maintaining endogenous flora, cause toxic reactions and secondary effects, alter the ecology of the unit in which it is used (as shown by the rising prevalence of MRSA, *C. difficile*, and vancomycin-resistant enterococci in both European and North American centers), and raise the cost of patient care. This widely used strategy is largely unvalidated.^{18,19} It must be emphasized that the paramount principle of therapy for infection is treatment focused on appropriate microbiologic cultures in the context of strict diagnostic criteria for infection.

Many authorities espouse streamlining of empirically begun broad-spectrum antibiotic therapy in response to microbiologic data once culture results are available. The practice of streamlining antibiotics has been shown to reduce the proliferation of antibiotic-resistant bacteria.⁵⁰ Although the benefits of antibiotic

streamlining are clear, it is frequently difficult to discontinue antibiotics once they have been started. Moreover, positive cultures do not automatically confirm infection, and great discretion must be exercised in determining how the microbiologic information obtained should be used. For example, tracheal aspirates from intubated patients routinely reveal gram-negative flora, but this finding in no way confirms pneumonia. A single blood culture growing *S. epidermidis* is similarly difficult to interpret and is often a contaminant.

Information technology may be a vital component to help physicians more accurately diagnose infections and use antibiotics more efficiently.^{9,27,51} Based on the vast amounts of clinical data and the increased risk of nosocomial infections, the ICU serves as an essential setting for implementing computerized data integration and clinical decision support systems. It is conceivable that in the near future, ICU physicians will rely on probabilities calculated from clinical decision support systems when making the decision to start empirical antibiotics.

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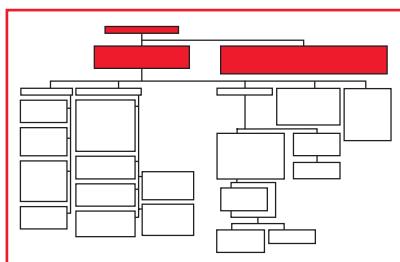
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17 NOSOCOMIAL INFECTION

E. Patchen Dellinger, M.D.

Approach to Postoperative Symptoms of Infection

Nosocomial infections are a potential threat to all hospitalized patients. They increase morbidity and mortality, prolong hospital stay, increase patient care costs,¹⁻⁵ and occur in almost every body site.



At any time during hospitalization, but especially postoperatively, the onset of fever or an elevated white blood cell count may signal an infectious process. Fever that begins or persists after postoperative day 4 is more likely to represent true infection. Although an infection will not develop in many febrile postoperative patients [see Discussion, below], a careful, directed examination of the patient, guided by history and operative procedure, should be undertaken, including inspection of the ears and the pharynx. Laboratory tests and x-rays are complementary. The use of empirical antibiotics or the prolonged administration of perioperative prophylactic antibiotics in the absence of a specific diagnosis is rarely efficacious. In fact, either may confuse the clinical picture and may lead to separate toxic or allergic complications. Antibiotics alone rarely constitute an adequate response to infectious complications, especially in the early postoperative period.

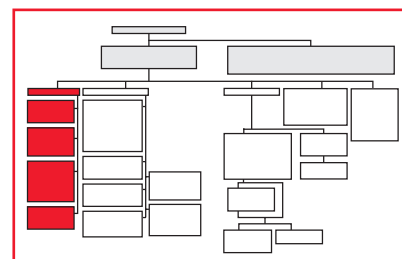
Respiratory infections are the most common early infection, with most wound infections presenting between postoperative days 4 and 7 and urinary tract infections (UTIs) occurring throughout hospitalization. However, if a high fever (temperature $> 38.9^{\circ}\text{C}$ [102°F]) develops in a patient within 48 hours of an operation, three diagnoses are most likely: atelectasis [see 8:5 *Pulmonary Insufficiency*], peritonitis caused by a leaking viscus after intra-abdominal operation [see 8:18 *Intra-abdominal Infection*], and invasive wound infection. Of these, atelectasis is most often diagnosed. It is not serious if recognized and treated. It can be diagnosed on the basis of decreased breath sounds, rales, or both on physical examination and on the basis of platelike densities or volume loss on chest x-ray. Atelectasis may be accompanied by hypoxemia and usually responds to standard physical measures. However, many patients with x-ray evidence of atelectasis are not febrile, and more than one third of patients with fever and no other apparent cause have no evidence of atelectasis.^{6,7}

Clues to the diagnosis of peritonitis caused by a leaking viscus are knowledge of problems in the conduct of the operative procedure, evidence of the hemodynamic and fluid balance changes that usually accompany a leaking viscus, and suggestive findings

on abdominal examination. Technical difficulties with anastomoses, excessive operative blood loss, and multiple bowel injuries can all increase the risk of leakage. Diffuse abdominal tenderness away from the incision, excessive fluid requirements in the early postoperative interval, and tachycardia all suggest iatrogenic peritonitis. Treatment always involves operative intervention and antibiotics. The least common cause of early high postoperative fever is an invasive wound infection, either with β -hemolytic streptococci or with clostridia. Diagnosis is made by local inspection of the wound and by a Gram stain of the wound's contents; treatment requires operative intervention in addition to antibiotics [see Infection Related to Operative Site or Injury, below].

Respiratory Infection

Pneumonia is the third most common nosocomial infection on surgical services and is the one most commonly associated with death



.8 Diagnosis

is not usually difficult in a patient without respiratory failure who is breathing spontaneously. In a patient with acute respiratory distress syndrome (ARDS) who is intubated and being ventilated, however, the diagnosis may be extremely difficult.⁹ This is because ARDS is associated with markedly abnormal chest x-ray findings and gas exchange abnormalities and may also include an elevated temperature without infection. A number of techniques for diagnosis, including bronchoalveolar lavage both with and without a bronchoscope and protected specimen brush cultures, have been reported to increase the sensitivity and specificity of diagnosis of pneumonia in this setting but have not been widely adopted.^{10,11}

The prevention of pneumonia in ventilated patients would be the best alternative, but there is not widespread agreement about the best means of prevention. Recommendations include standard infection control measures, elevation of the head of the bed, and possibly the use of endotracheal tubes that permit the aspiration of subglottic secretions.^{10,12-14}

The diagnosis of pneumonitis or atelectasis (see above) is frequently entertained during the workup of postoperative fever. It is important to remember that a common cause of basilar atelectasis and pleural effusion in the postlaparotomy patient is an inflammatory process below the diaphragm. Tracheitis or bronchitis, as indicated by purulent sputum in the absence of pul-

Approach to Postoperative Symptoms of Infection

Fever or an elevated WBC develops postoperatively

Fever begins or persists after 4th postoperative day

Identify source of infection:

- Perform physical examination guided by history and prior operations.
- Inspect all intravascular devices and urinary catheters.
- Order appropriate x-rays and laboratory tests.

Respiratory infection

Pneumonia, as suggested by ↑ WBC, ↑ temperature, purulent sputum, and lung infiltrate

Give appropriate antibiotics; provide supportive care.

Tracheitis or bronchitis, as suggested by purulent sputum, normal x-ray findings, and endotracheal or tracheostomy intubation

Give appropriate antibiotics if patient is febrile.

Paranasal sinusitis, as suggested by purulent nasal drainage, otitis media, and/or CT findings of fluid, air-fluid levels, and mucosal thickening

Identify pathogen via Gram stain and culture of sinus aspirate. Remove all nasal tubes; administer decongestants and appropriate antibiotics. Perform sinus irrigation or drainage for unresponsive cases.

Otitis media (associated with eustachian tube blockage from nasal tubes or inflammation)

Remove nasal tube, and give decongestants.

Infection related to operative site or injury

Wound infection (incisional SSI), as suggested by erythema, swelling, drainage, and increasing local pain and tenderness

Incise and drain. For minimal local soft tissue and systemic response, treat with dressing changes and no antibiotics. If antibiotics are required, give as follows. **Clean wounds:** Give cefazolin, 1 g I.V. q. 8 hr, or oxacillin, 1 g I.V. q. 6 hr. **Other wounds:** If infection is aggressive, give a third-generation cephalosporin or a quinolone plus clindamycin or metronidazole; or aztreonam plus clindamycin; or imipenem-cilastatin, meropenem, or piperacillin-tazobactam alone. If infection is less serious, give cefotetan, 1 g I.V. q. 12 hr, or cefoxitin, 1 g I.V. q. 6 hr. Invasive and necrotizing infection requires aggressive debridement. Stop antibiotics as soon as local inflammation and systemic signs of infection have resolved.

Intra-abdominal infection (organ/space SSI), as suggested by fever and abdominal tenderness

Confirm diagnosis by CT or ultrasonography. Perform appropriate operative or percutaneous procedure; give antibiotics.

Sternal and mediastinal infection, as suggested by sternal instability

Debride the sternum and affected mediastinal tissues. Consider transposition of viable soft tissue for wound closure.

Osteomyelitis (suggested by nonunion of a fracture, loosening of a prosthesis, or prolonged wound drainage)

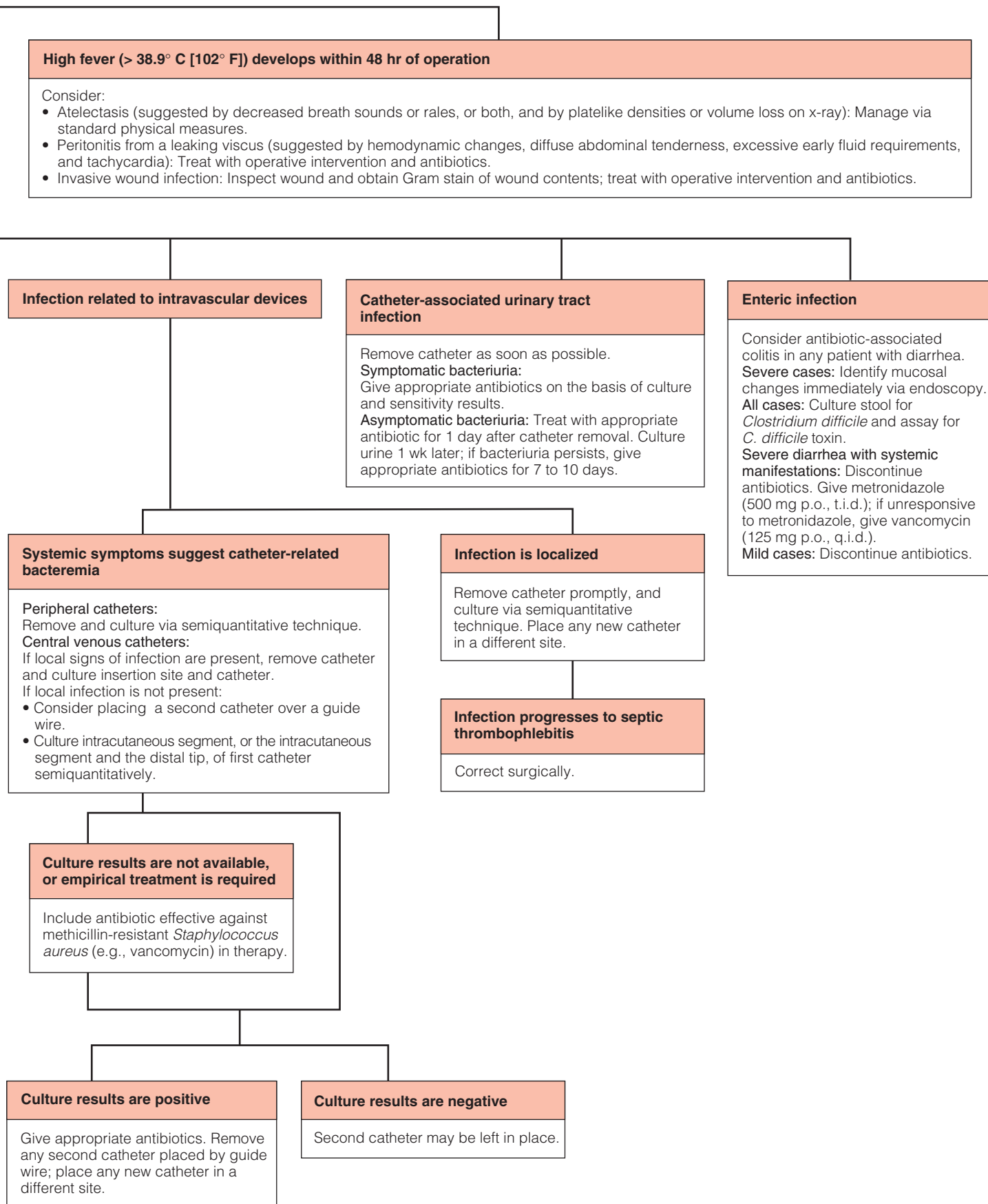
Repeated operative debridement, prolonged use of antibiotics, and fracture stabilization may be required.

Empyema, as suggested by systemic signs and pleural effusion

Examine and culture pleural fluid. Drain pleural space. Give appropriate antibiotics. If empyema fails to resolve, consider thoracoscopy, thoracotomy, and decortication.

Posttraumatic meningitis (anticipate if there is a history of CSF rhinorrhea or otorrhea)

Perform lumbar puncture for examination and culture of CSF if unexplained fever, headache, spinal pain or stiffness, or changes in mental status develop. Give appropriate antibiotics.



monary infiltrate, is often seen in modern ICUs, most commonly in association with an endotracheal or tracheostomy tube. Pneumonia may or may not follow. There is often a febrile response, in which case antibiotics may be appropriate on the basis of culture and sensitivity information. Sorting out the cause of purulent secretions in intubated patients is not easy but is important. Other causes of fever should be sought and an overall judgment rendered regarding the probable cause. If tracheitis or bronchitis is suspected, it can be treated with a brief course of antibiotics. A 2000 report described empirical treatment of patients for suspected pneumonia, followed by reevaluation at 3 days.¹⁵ By stopping antibiotic treatment at 3 days for patients without a confirmed diagnosis, the investigators were able to reduce antibiotic use threefold in that group, lower costs by more than half, and decrease the frequency with which resistant bacteria were isolated by more than half.

Paranasal sinusitis is a potentially lethal nosocomial infection, especially in ICU patients with nasogastric or nasotracheal tubes in place.¹⁶⁻¹⁸ In one report, it accounted for 5% of all nosocomial infections.¹⁶ The diagnosis of paranasal sinusitis should be considered in any febrile postoperative patient with nasal tubes or with facial fractures. Purulent nasal drainage is an important clue but may not be present. Plain films can be diagnostic but are often difficult to interpret in these patients because of superimposition of tubes, preexisting injuries, and suboptimal portable films. Fluid, air-fluid levels, and mucosal thickening are more easily detected by computed tomography. Diagnosis ultimately requires demonstration of white blood cells and bacteria on a Gram stain of sinus aspirate as well as culture for identification and sensitivity testing.

In one study of 67 patients with craniofacial injuries who underwent prospective otoscopy three times a week, 11 patients experienced either serous or purulent otitis media and were all found to have purulent paranasal sinusitis.¹⁹ Eleven of 12 patients who were ultimately diagnosed as having purulent paranasal sinusitis had coexistent otitis media.

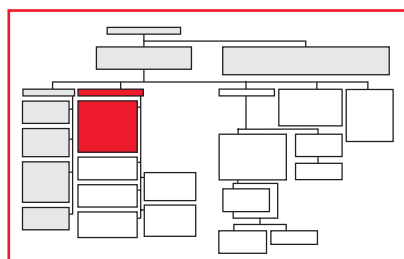
The spectrum of causative bacteria of paranasal sinusitis is similar to that of nosocomial pneumonia. Treatment includes removal of all nasal tubes and administration of decongestants and antibiotics. Occasionally, sinus irrigation, drainage, or both may be required. If empirical therapy must be initiated before specific culture results are known, the agents chosen should be effective against bacteria known to be present in sputum. The best method of prevention is to limit the number and the duration of use of nasal tubes.

Inflammation and infection of the nasopharyngeal mucosa can be significant in an ICU patient, though it is not often identified. Eustachian tube blockage, either from tubes or from inflammation, can be associated with either serous or infective otitis media. Prudent use of tubes is the most effective preventive measure. If clinical infection is recognized, tube removal and decongestants will usually provide adequate treatment.

Infection Related to Operative Site or Injury

SURGICAL SITE INFECTION

An infection of a surgical wound—that is, an incisional surgical site



infection (SSI)—traditionally reflects on a surgeon's care and skill and is the classic surgical nosocomial infection [see 1:1 *Prevention of Postoperative Infection*] Such infections are diagnosed primarily on the basis of local findings. Erythema, swelling, and drainage, as well as increasing local pain and tenderness in a site at which pain should be decreasing, all suggest infection. Fever and an elevated white blood cell count may or may not be present. An incisional SSI develops most commonly in the subcutaneous layer, though animal studies fail to explain this observation.²⁰ In an obese patient, however, a thick, overlying layer of uninfected tissue may obscure evidence of infection and thus delay diagnosis. Presentation may also be delayed if the infection begins in anatomic layers below fascial and muscular barriers, as may be the case after a thoracotomy or an operation on the femur.

Whether an infection will occur in a wound is probably determined within the first few hours of wounding^{21,22}; efforts to prevent wound infection are probably ineffective after this period.²³⁻²⁷ The incidence of SSI is reduced with appropriate use of perioperative antibiotics.^{28,29} However, there is no advantage to continuing prophylactic antibiotics beyond the perioperative period in response to fever or local wound erythema in the hope of preventing an overt SSI.³⁰⁻³²

The risk that an SSI will develop in an individual patient is best described by an index defined by the Centers for Disease Control and Prevention (CDC) in its National Nosocomial Infections Surveillance (NNIS) System. The index awards one point each for an American Society of Anesthesiologists (ASA) preoperative assessment score of III, IV, or V; an operation classified as either contaminated or dirty-infected; and an operation duration exceeding the 75th percentile for that procedure.^{33,34} Examination of the NNIS data demonstrates that in patients undergoing procedures commonly performed laparoscopically, SSI rates are decreased to levels comparable to those reported in patients with a one point lower risk index who undergo equivalent open procedures.³⁵ The CDC definitions for SSI were agreed to by a consensus panel representing the CDC, the Society for Hospital Epidemiology of America, the Association for Practitioners in Infection Control, and the Surgical Infection Society.^{34,36} In addition to appropriate use of prophylactic antibiotics, proper management of intraoperative temperature, oxygen concentrations, and blood glucose levels exerts a powerful influence on the risk of SSI and of other nosocomial infections.³⁷⁻⁴¹

Primary treatment of an SSI consists of opening the wound. When an SSI is suspected, the patient should not be given antibiotics without the wound having been opened. In most cases, the infection is confined to the incision. If the infection is of a superficial wound and if no major systemic manifestations are present, antibiotic therapy is unnecessary. If the local reaction around an infected wound is severe or extensive, administration of antibiotics is advisable until the reaction subsides (which usually takes no more than 3 days). In clean wounds that are away from the perineum and that are not associated with an operation that entered the bowel, the likely pathogens are *Staphylococcus aureus*, streptococci, or both. In such cases, treatment with cefazolin, 1 g I.V. every 8 hours, or oxacillin, 1 g I.V. every 6 hours, is satisfactory. By contrast, SSIs in the perineum and those that occur after bowel operations often involve mixed aerobic and anaerobic bacterial flora. If the infection is not very serious, it can be treated with cefoxitin, 1 g I.V. every 6 hours, or with cefotetan, 1 g I.V. every 12 hours. For more aggressive infections accompanied by evidence of tissue invasion or necrosis beyond the immediate

wound or by a severe systemic reaction, more comprehensive antibiotic treatment is indicated—that is, a third-generation cephalosporin or a quinolone combined with clindamycin or metronidazole; aztreonam combined with clindamycin; or imipenem-cilastatin, meropenem, or piperacillin-tazobactam alone. Infection of an abdominal incision may be a superficial manifestation of an underlying intra-abdominal abscess or of peritonitis.

Occasionally, infection is invasive and necrotizing. In surgical wounds, such an infection is most common after a GI procedure in which the wound was exposed to colonic microflora and in which wound closure was difficult. Necrotizing infection is also more likely in a patient who is seriously ill or who has evidence of multiple organ failure. Such infection should be suspected if there is undermining of the wound edges, extensive fascial necrosis, distant signs of infection, or a marked systemic response. It requires aggressive operative debridement and administration of antibiotics [see 3:2 *Soft Tissue Infection*].

Clostridium species, which can cause life-threatening postoperative necrotizing SSI, can also cause routine postoperative incisional infection limited to the wound and without myonecrosis.⁴² Such infection is marked by the absence of the systemic symptoms associated with clostridial myonecrosis and by the presence of intact white blood cells on a Gram stain of the wound contents. (Clostridial myonecrosis, on the other hand, is characterized by a Gram stain that shows gram-positive rods but few or no white blood cells [see 3:2 *Soft Tissue Infection*].)

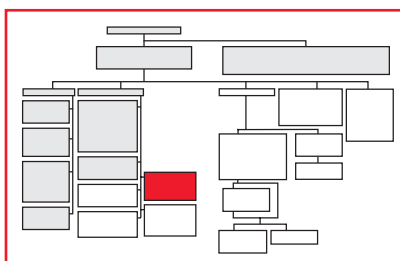
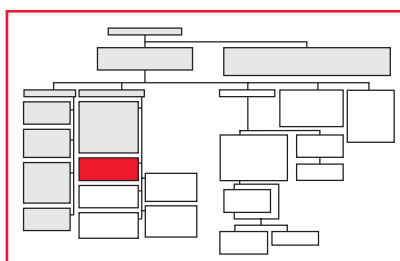
INTRA-ABDOMINAL INFECTION

Intra-abdominal infections—that is, organ/space SSIs—are a major cause of postoperative morbidity and mortality, particularly when diagnosis is delayed.^{43,44}

Suspected intra-abdominal organ/space SSI in a patient with fever or abdominal tenderness, or both, after an abdominal procedure or injury should not be treated with antibiotics alone; after a specific diagnosis, the appropriate operative or percutaneous procedure must be performed [see 8:18 *Intra-abdominal Infection*].

EMPHYEMA

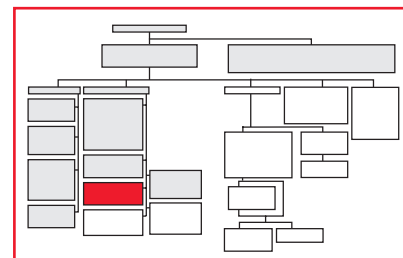
Empyema, which may follow thoracotomy or chest trauma necessitating tube thoracostomy, is a significant cause of posttraumatic infection.⁴⁵ Less commonly, empyema develops as a complication of pneumonia. Empyema should be suspected in any patient with systemic signs of infection, a pleural effusion, and no other obvious source of infection. Diagnosis requires thoracentesis of pleural fluid for a Gram stain and culture. The most common pathogen is *S. aureus*, though many other pathogens may be found as well. Initial treatment is by drainage with a chest tube and by administration of appropriate antibiotics based on the results of the Gram stain and culture. Because treatment is invasive, it should not be instituted until the diagnosis is confirmed.



Cases that do not resolve promptly and completely may ultimately require thoracoscopy or thoracotomy and decortication. Empyema after pulmonary resection or esophageal operation raises the possibility of a leaking bronchial closure or esophageal anastomosis. A leak is almost certain if an air-fluid level is present on chest x-ray. An esophageal leak is treated with repair or diversion.

STERNAL AND MEDIASTINAL INFECTION

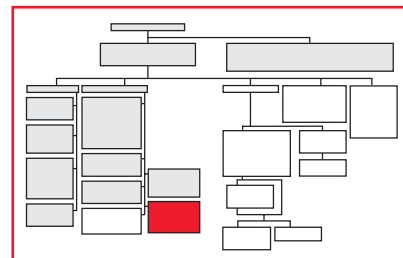
Sternal and mediastinal infections are the most serious infectious complications of operations that involve a median sternotomy.⁴⁶ The risk that a superficial infection will spread to involve the sternum and mediastinum is high because there is little soft tissue between the skin and the sternum. Infection may also start deep to the sternum without early superficial evidence. Sternal instability is an important indication of sternal infection. Computed tomography of the chest is sensitive and specific for the diagnosis of sternal osteomyelitis and mediastinitis.⁴⁷ All such infections require operative debridement of the sternum and of affected mediastinal tissues. Some wounds can then be closed. Many wounds require closure of the mediastinal space by transposition of viable soft tissue. Pectoralis or rectus muscle flaps, omental flaps, or both are commonly used.⁴⁸



POSTTRAUMATIC MENINGITIS

A basilar skull fracture with a cerebrospinal leak increases the risk of post-traumatic meningitis.⁴⁹ The most common pathogens are *Streptococcus pneumoniae*, *S. aureus*, other streptococcal species, and *Haemophilus influenzae*, but any oropharyngeal organism can be responsible.⁵⁰ Since the association between trauma and meningitis was first reported in 1970,⁴⁹ the appropriate use of antibiotics in these patients has been debated. Some researchers advocate prophylactic administration of antibiotics until any CSF leakage ceases,⁵¹ whereas others advocate them for an arbitrary period after injury (usually 5 days); however, controlled studies have failed to support a specific protocol.⁵⁰ Furthermore, experience in other clinical settings suggests that prophylactic antibiotics would be as likely to promote the development of resistant oropharyngeal flora and subsequent meningitis as they are to prevent it.^{52,53}

The ideal approach to patients with CSF rhinorrhea or otorrhea is to maintain a high index of suspicion for the development of meningitis. Fever not clearly attributable to another source or not immediately responsive to specific treatment for its presumed cause should prompt a lumbar puncture for examination and culture of spinal fluid. Lumbar puncture should also be performed to investigate headache, spinal pain or stiffness, or unexplained changes in mental status. Such an approach should result in a prompt diagnosis and permit early specific treatment of the responsible pathogen if meningitis is diagnosed.



OSTEOMYELITIS

Osteomyelitis is a relatively rare complication after elective orthopedic procedures. Its diagnosis and management are similar to those of infections involving other operative sites, but because the infection is deep and covered by muscular and fascial planes, diagnosis may be delayed. Nonunion of a fracture or loosening of a prosthesis may be the first sign of infection. Infection after open fractures is common; rates range from 5% to 50%.⁵⁴⁻⁵⁶ The primary determinants of infection after open fracture are the degree of soft tissue damage surrounding the fracture and the surgeon's ability to stabilize the fracture fragments.⁵⁵ Other important factors include the patient's age and overall condition, the severity of other injuries, the interval between injury and definitive management, and the use of prophylactic antibiotics. A brief course of perioperative antibiotics may prevent subsequent infection as effectively as a more prolonged course.^{30,57}

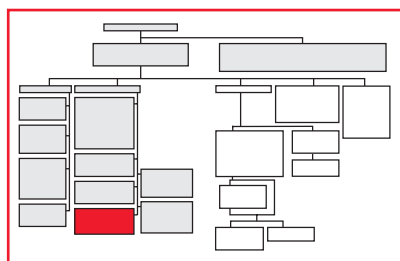
Treatment of osteomyelitis may require repeated operative debridement, prolonged use of specific antibiotics, and fracture stabilization. Pathogens include *S. aureus* for all grades of open fracture and, increasingly, gram-negative bacteria (e.g., *Pseudomonas aeruginosa* and *Klebsiella* and *Enterobacter* species) for grade III fractures.⁵⁷

Infection Associated with Intravascular Devices

Every type and location of intravascular device has been associated with clinically significant nosocomial bloodstream infection. The incidence of infection is highest with central venous catheters used for monitoring purposes.^{58,59}

It is important to specify the different definitions of catheter infection and catheter-related bloodstream infection (CRBSI). Infection at the catheter site is commonly defined as the presence of lymphangitis, purulence, or at least two of the following: erythema, tenderness, increased warmth, and a palpable thrombosed vein. However, many cases of phlebitis with no evidence of bacterial infection present with erythema and with tenderness, a palpable thrombosed vein, or both.⁶⁰ Few or no premonitory signs occur before phlebitis is obvious, and the first evidence of as many as 45% of phlebitis cases appears more than 24 hours after catheter removal. If a functional catheter remains in place for 12 hours after the onset of phlebitis symptoms, the duration and severity of symptoms increase markedly.⁶¹

CRBSI is characterized by (1) isolation of the same organism from the catheter and the blood, (2) clinical (or autopsy) and microbiologic data disclosing no other source of the bloodstream infection, and (3) clinical features of bloodstream infection (e.g., fever and leukocytosis).⁶² For indwelling, long-term central venous catheters (e.g., Hickman, Broviac, and Groshong), infections have been classified as exit-site and tunnel infections. Infections at the exit site are defined as the presence of erythema, tenderness, induration, or purulence within 2 cm of the skin around the exit site. They are presumably confined to the portion



of the catheter external to the subcutaneous Dacron cuff. Tunnel infections are defined as the presence of the same signs along the subcutaneous tract, at a distance more than 2 cm from the tract.^{63,64} The importance of this distinction is that many infections at the exit site are successfully treated with antibiotic therapy and local wound care, whereas tunnel infections usually necessitate removal of the catheter.^{63,64}

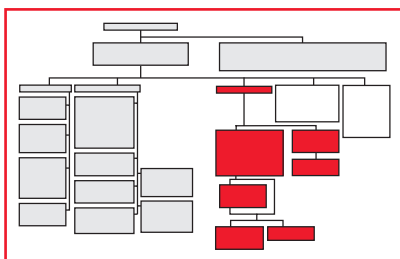
A semiquantitative technique for culturing intravascular catheters has been shown to distinguish between infection and contamination of the catheter and is more specific in the diagnosis of CRBSI than is broth culture of the catheter.⁶² The catheter is removed from the patient after antiseptic cleansing of the insertion site to prevent contamination from surrounding skin. A 5 to 6 cm segment of the catheter is aseptically removed; transported to the laboratory in a dry, sterile tube; placed on the surface of an agar culture plate; and rolled at least four times across the surface of the plate [see Figure 1]. If the plate grows at least 15 colonies, the culture is positive. Most catheters associated with bloodstream infection actually grow more than 1,000 colonies [see Figure 1]. For peripheral catheters, the entire catheter is cultured. For central catheters that are longer than 6 cm, either the distal tip or both the intracutaneous segment and the distal tip should be cultured [see Figure 2].

The most common source of bacteria involved in catheter infection is the skin around the insertion site.^{65,66} Patients who have a skin colonization at the insertion site of greater than 10^3 colony-forming units/25 cm² are 10 times more likely to have a catheter infection than those whose skin colonization is less. Of catheters that test positive with the semiquantitative culture technique, 16% to 44% appear to be primary sources of septicemia.^{62,67-69}

The catheter hub and lumen are recognized as important routes of infection. Colonization at these sites is detected not by roll-plate cultures but by sonication culture of catheter segments or by simultaneous cultures of blood drawn through the suspect catheter and from a distant site. Either sonication cultures recovering more than 10^2 colonies or catheter cultures more than five times the number recovered from distant sites are sensitive and specific indicators of catheter infection.^{70,71}

For catheters that are only locally infected and not responsible for CRBSI, removal is adequate treatment; the same is true for most catheters that cause bloodstream infection. If the patient's temperature and white blood cell (WBC) count return to normal within 24 hours after removal of the catheter and if local signs of inflammation at the catheter insertion site resolve within that period, antibiotics are not necessary. However, if the patient continues to show clinical signs of infection or has a documented bacteremia, a brief course of specific antibiotic therapy is indicated. Specific antibiotic therapy is also indicated if semiquantitative catheter culture reveals a large number of *S. aureus* organisms in conjunction with systemic signs of infection. If empirical therapy for CRBSI is undertaken before culture and sensitivity results are available, the antibiotic regimen should include vancomycin or another antibiotic known to be effective against methicillin-resistant *S. aureus* (MRSA): coagulase-negative staphylococci are the most commonly implicated pathogens,^{58,70,72} and there is a high rate of methicillin resistance among these organisms. In candidemic patients with I.V. catheters in place, candidemia resolves an average of 3 days earlier if the catheters are removed at the time of diagnosis and initiation of antifungal therapy.⁷³

For patients with documented catheter-associated bacteremia, treatment depends on the organism or organisms present. The available data on the necessary duration of treatment for coagulase-negative staphylococci are inconclusive. Often, good results



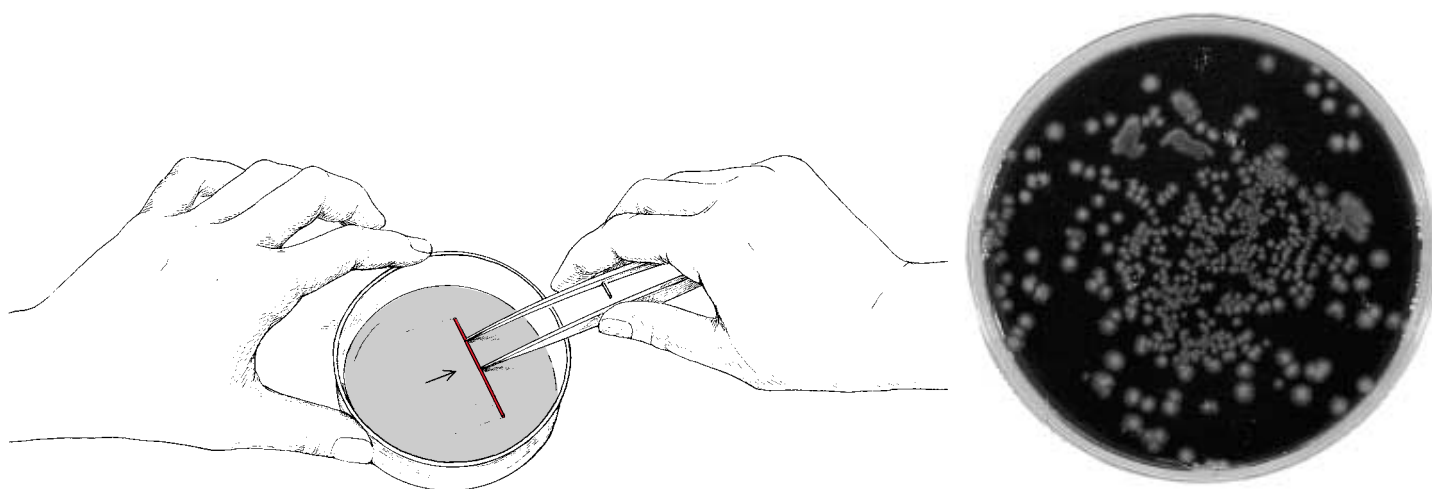


Figure 1 In a semiquantitative technique used to distinguish between infection and contamination of intravascular catheters, a 5 to 6 cm segment of the catheter is rolled at least four times across the surface of an agar culture plate (left). Typically, a positive culture grows far more than 15 colonies (right).

are achieved with catheter removal and either no antibiotics or a short course (1 to 3 days) of antibiotics; some experts recommend a 5- to 7-day course, but there is no compelling evidence that this is necessary. For *S. aureus* bacteremia, a 10- to 14-day antibiotic course is recommended if the infection is uncomplicated and a 4- to 6-week course if the infection is complicated. The relevant data on CRBSI caused by gram-negative bacilli or *Candida* are even sparser. Current recommendations call for antibiotic treatment lasting 10 to 14 days for gram-negative pathogens and 14 days or longer for *Candida*.⁷⁴

In a small proportion of patients, local catheter-related infection may progress to a life-threatening condition characterized by the formation of microabscesses within the cannulated vein and by persistent bacteremia after catheter removal. Septic thrombophlebitis can occur in a broad range of hospitalized patients and should be suspected when clinical signs of systemic sepsis, local signs of inflammation, and positive blood cultures persist after removal of the catheter. A surgical approach to the affected vein is required. When possible, the vein should be excised over the affected area and the wound left open. The presence of gross pus within the vein wall is not necessary for the diagnosis. The wall of the affected vein may simply appear thickened, with inflammation surrounding it and an edematous, pale thrombus enclosed within it. Fungal peripheral thrombophlebitis may be especially difficult to diagnose because the local site often does not appear infected. In the presence of continued candidemia without an obvious source, any palpably thrombosed vein near a site of present or previous catheterization must be suspected. Gram staining and hematoxylin-eosin staining of the vein contents or the vein wall are significantly less sensitive than silver staining and culture.⁵⁹

Even more rare is catheter-related septic central venous thrombosis. The diagnosis is made by the occurrence of (1)

thrombosis of the internal jugular, subclavian, or brachiocephalic vein proved by venography or duplex Doppler examination; (2) central venous catheter infection with positive catheter tip culture and positive peripheral blood cultures; and (3) persistent bacteremia or candidemia after catheter removal.^{75,76} Initial therapy consists of catheter removal, systemic antibiotics based on sensitivity testing and administered in a quantity and duration appropriate to treatment of endocarditis, and systemic anticoagulation during the same period. Surgical excision or drainage is reserved for failure of nonoperative measures.

At one time, it was common practice for both central and peripheral venous catheters to be either completely changed or exchanged over a guide wire at fixed intervals to reduce the risk of infection. Data from randomized, controlled, prospective trials did not demonstrate any advantage to this policy.^{60,70,77,78} These trials demonstrated that the risk of infection is linear, increasing with the duration of I.V. catheterization, whether one or multiple catheters are used.

Current practice is to change catheters when infection is suspected when the catheters are not working or not needed.^{60,70,77,79,80} Clearly, any catheter that is a cause of bloodstream infection must be removed, as should infected catheters that may not yet have caused such infection. The practical problem is that not all infected catheters show external evidence of infection. In addition, catheter culture and the subsequent clinical course confirm infection in only a small proportion of patients with central venous catheters or pulmonary artery catheters in place who are suspected on clinical grounds of having CRBSI.⁸¹ Changing central venous catheters over a guide wire circumvents most of the mechanical complications associated with central venous catheterization, saves time, and is more comfortable for the patient.⁸² However, if a culture of the first catheter is positive, the second catheter should be removed immediately, and any new

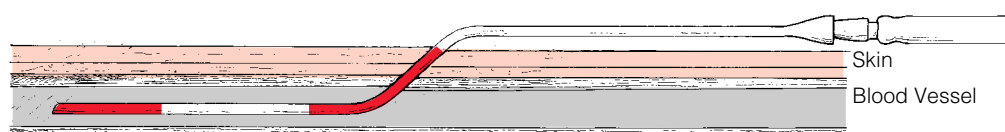
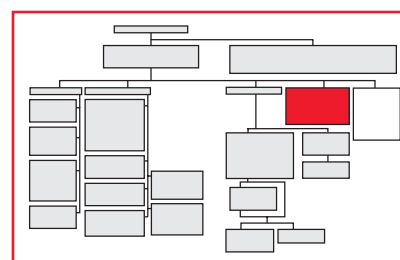


Figure 2 When a catheter is longer than 6 cm, either 5 to 6 cm of the catheter tip or both this segment and a 5 to 6 cm intracutaneous segment (red) can be cultured.



shown that of catheterized patients who have any detectable organisms in their urine (even $< 10^2/\text{ml}$), whose catheters remain in place, and who receive no specific antimicrobial therapy, 96% have organism counts higher than $10^5/\text{ml}$ within 3 days.¹⁰⁴ (By comparison, 27% of patients with sterile urine subsequently have colony counts higher than $10^5/\text{ml}$ before catheter removal.)

Although a catheter-associated UTI is a significant nosocomial infection with measurable morbidity and mortality [see Discussion, *below*], not all cases of bacteriuria should be treated with antibiotics. If a patient with bacteriuria is symptomatic, treatment should be initiated according to culture results and sensitivity testing. Although bacteriuria can sometimes be cleared without removal of the catheter, the risk of a new episode continues while the catheter is in place.¹⁰⁵ Ideally, the catheter should be removed as soon as possible. In one study, only 36% of untreated women with asymptomatic bacteriuria had sterile urine within 2 weeks after catheter removal, and 17% progressed to symptomatic bacteriuria; however, 81% of patients treated with a single dose of trimethoprim-sulfamethoxazole had sterile urine within 2 weeks after catheter removal.¹⁰⁶ Thus, it is prudent to obtain a culture at the time of catheter removal and to treat any bacteriuria detected.

A condom catheter is often used in male patients in place of a urethral catheter when neurologic injury or incontinence mandates long-term drainage. The available data are not sufficient to establish the ideal care of these devices and the true infection rate associated with their use. UTI rates as low as 0% in 79 patients managed with condom catheter drainage¹⁰⁷ and as high as 53%¹⁰⁵ to 63%¹⁰⁸ have been reported. Severe noninfectious local complications (e.g., ulceration and maceration of the penis) also can occur.^{107,108}

Because indwelling urinary catheters are a major source of nosocomial infection, they should be employed only when necessary and removed as soon as practicable. The most effective method of reducing infections among patients with urinary catheters is to use completely closed urinary drainage systems and to limit breaks in the closed system.¹⁰⁹ The incidence of new infections doubles on any day in which a closed urinary drainage system is opened.¹¹⁰ Urine samples for culture should be aspirated with a needle and syringe from the catheter lumen after antiseptic cleansing of the catheter sampling port. The catheter junction should not be disconnected to obtain a specimen. The use of a preconnected and sealed catheter and drainage bag system has been shown to result in a 2.7-fold reduction in the rate of catheter-associated UTIs and an adjusted risk ratio for death of 0.29.¹¹¹

Antibiotic irrigation systems do not reduce infections, but they do increase the incidence of resistant organisms.¹¹⁰ Systemic antibiotics reduce infections to a modest degree in the first 4 days of catheterization but at the expense of an increase in resistant organisms. The infection rate is higher in females than in males, in older patients than in younger ones, and in patients with critical illness than in those without critical illness.¹⁰⁹ Patients with nosocomial diarrhea and an indwelling bladder catheter have a ninefold higher risk of subsequent UTI than patients with an indwelling bladder catheter who do not have diarrhea.¹¹²

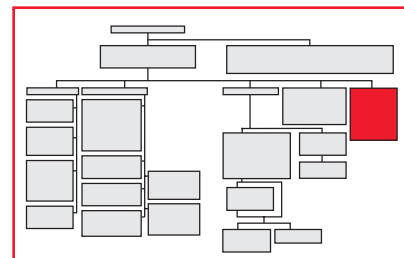
Although most UTIs acquired by hospitalized patients are assumed to be simple bladder infections, there is no strong correlation between location of infection and clinical symptoms.^{113,114} Many patients with upper UTIs do not have flank pain, fever, or other signs of systemic infection, and patients with a bladder infection may not have dysuria or suprapubic tender-

ness. Many patients with upper UTIs are treated without the diagnosis ever being made. Systemic infection and associated bacteremia or complications such as intrarenal or perinephric abscesses occur more commonly in immunocompromised patients (e.g., those with urinary tract obstruction or diabetes).¹¹⁵ In patients with a neurogenic bladder or indwelling bladder catheters, urinary sepsis may develop without symptoms referable to the urinary tract. However, symptoms of localized flank or low back pain, along with systemic signs, such as fever, rigors, sweats, and nausea, are relatively specific indicators of renal infection.¹¹⁶

If a patient has fever and bacteriuria during the postoperative period, the surgeon should perform a careful evaluation to determine whether he or she has pyelonephritis or a postoperative intra-abdominal infectious complication. Pyelonephritis can be treated solely with antimicrobial therapy in most cases, whereas all postoperative intra-abdominal infectious complications call for surgical intervention as well as antimicrobial therapy. No simple methods are available to distinguish between these diagnoses. The operating surgeon should carefully evaluate all of the patient's clinical signs and symptoms. A hospitalized patient with pyelonephritis should usually receive antimicrobial therapy for at least 14 days. An agent demonstrated to be effective against the causative organism by *in vitro* sensitivity testing should be used. In any patient who has severe signs of systemic infection or does not respond promptly to treatment, ultrasonography, renal scanning, or I.V. pyelography should be done to rule out obstruction. If obstruction is found, it must be corrected. If the patient has an indwelling bladder catheter, the catheter should be removed, appropriate therapy started, and a new, clean catheter inserted.¹¹⁶

Enteric Infection

Any organism that can cause food-borne enteric infection in the community can do so in the hospital,¹¹⁷ but cultures for routine enteric pathogens are not useful for patients



who have been hospitalized for more than 3 days.¹¹⁸ The most important nosocomial enteric disease to confront most surgeons is antibiotic-associated diarrhea, which can range from trivial, self-limited episodes of diarrhea to fulminant disease with systemic signs of sepsis, collapse, and death.

The first step in diagnosis is to consider antibiotic-associated colitis in any hospitalized patient with diarrhea. Mild cases may not be associated with any systemic signs or pathologic findings in the colon, and in the majority of mild episodes, there are no identifiable pathogens. More severe cases are marked by one or more of the following signs: nonspecific hyperemia, edema, granularity, or ulceration of colonic mucosa. The most severe cases are marked by pseudomembrane formation.

The single most efficient measure for detecting *C. difficile*-associated diarrhea is to send a stool sample for cytotoxin determination, a procedure that has a sensitivity of 70% to 100%. By sending a sample is sent for stool culture as well, one can increase sensitivity slightly (to 96%); however, if *C. difficile* is grown on the culture, the organism must still be tested for cytotoxin production, and this takes another day.^{118,119} Rectal swab cultures transported in anaerobic containers are at least as sensitive as conventional stool cultures,¹²⁰ but they are not adequate for detection of cytotoxin.¹¹⁹ Although it is possible that poly-

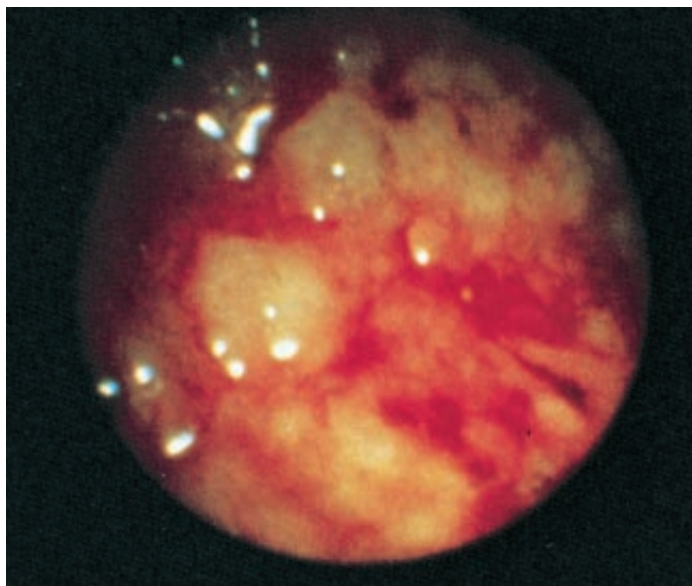


Figure 3 An endoscopic view of pseudomembrane formation is shown.

merase chain reaction assays for the cytotoxin gene in stool can eventually be developed, such assays are not available at present. Stool smears for detection of WBCs are not helpful.^{118,119} Endoscopy to detect pseudomembranes is indicated if the patient is seriously ill and a prompt diagnosis and initiation of specific treatment are desired. Administration of empirical therapy until a specific pathogen is identified is appropriate in this circumstance.¹¹⁹

Severe and persistent cases of antibiotic-associated diarrhea are most commonly associated with the recovery of *C. difficile* by culture and of *C. difficile* toxin by tissue culture assay.¹²¹ In more than 90% of patients who have pseudomembranous colitis, *C. difficile* toxin will be present on tissue culture assay. In antibiotic-associated diarrhea without pseudomembrane formation, positive toxin titers may be found in 70% of patients with signs of colitis and in 11% to 27% of patients without colitis.¹²²⁻¹²⁴

Pseudomembranes, present in about half of patients with *C. difficile*-associated diarrhea,¹¹⁹ are elevated, whitish plaques that vary in size from a few millimeters to 1 to 2 cm and may coalesce and slough. Histologically, the plaques show epithelial debris, polymorphonuclear infiltrate, chronic inflammatory cells, and fibrin deposition.¹²¹ The diagnosis of pseudomembrane formation is made by endoscopy [see Figure 3]. Most cases involve the rectum and the left colon, but as many as 25% may be missed by rigid sigmoidoscopy; by comparison, the false negative rate with flexible endoscopy is only 10%.¹²⁵ Although the great majority of cases involve only the colon, two fatal cases that primarily involved the ileum and the jejunum have been recorded.^{126,127} The clinical picture of pseudomembranous colitis includes watery diarrhea in 90% to 95% of cases, with bloody diarrhea in the remaining cases. Abdominal cramps, leukocytosis, and elevated temperature are present in approximately 80% of cases.¹²¹

All commonly employed antibiotics have been implicated in cases of antibiotic-associated pseudomembranous colitis, including vancomycin¹²⁸⁻¹³⁰ and antibiotics used for perioperative antibiotic prophylaxis, even in a single dose.¹³¹ Treatment should include cessation of the offending antimicrobial agent, if possible. In mild cases, this step may be all that is necessary: in 23% of

such cases, resolution occurs within 2 to 3 days of discontinuance of antibiotic therapy.¹¹⁹

A patient with systemic symptoms should also receive one of the agents with proven efficacy against the disease. The agent with which there has been the most recorded experience is vancomycin, but it is more expensive than the alternatives. The usual dosage is 500 mg/day orally in four divided doses. Metronidazole, 500 mg three or four times daily for at least 10 days, is an effective alternative.¹³² Bacitracin, 20,000 to 25,000 units four times daily, is also effective but should be considered the third choice.^{119,132} The current recommendation is to begin therapy with metronidazole to reduce the risk of inducing vancomycin-resistant enterococci [see Pathogens, below].^{119,133}

Relapses after treatment for *C. difficile* colitis are common, occurring in 5% to 30% of cases, perhaps because of persistence of the organism in spore form; 92% of these cases respond to a second course of treatment without relapse.^{119,132} Cases that do recur involve both persistent infection and new reinfection.¹³²

A profound ileus is sometimes associated with the severe form of the disease and may prevent the delivery of oral antibiotics to the site of infection. Limited experience suggests that parenteral metronidazole may be effective in these cases. However, there have been several cases of unsuccessful treatment of *C. difficile*-associated colitis with I.V. metronidazole and of the development of *C. difficile* colitis in patients receiving I.V. metronidazole alone or together with other antibiotics.^{132,134} In the most severe cases, the clinical evolution resembles that of toxic colitis associated with inflammatory bowel disease, and the patient may require a colectomy if the disease is unresponsive to nonoperative management. If operative treatment proves necessary, subtotal colectomy is preferred to hemicolectomy.¹³² In as many as 5% of cases, colitis may present as acute abdominal pain and tenderness and leukocytosis without diarrhea.^{135,136} Any patient with acute abdominal symptoms who has received antibiotics within the past 2 months should be considered for the diagnosis of *C. difficile*-associated colitis.¹³² If colitis is suspected because of previous antibiotic administration, sigmoidoscopy may facilitate the correct diagnosis and avert unnecessary abdominal exploration. CT may show thickening of the bowel wall, but operative exploration often does not yield significant findings.¹³⁶ Extraintestinal infections have also been reported.¹³⁷

Transfusion-Associated Infection

The transfusion of blood would seem to be an excellent method for transmitting blood-borne diseases; however, transmission of disease by blood transfusion is rare.^{138,139} Transfusion-associated malaria is occasionally reported in North America but occurs quite infrequently. The primary method for preventing malaria transmission is careful screening of donors by history. A handful of cases of babesiosis, Chagas disease, trypanosomiasis, toxoplasmosis, and infections with various herpesviruses, parvovirus, or West Nile virus have been reported over many years, but these are rare as well.¹³⁸⁻¹⁴¹

In the early years of blood collection and transfusion, cases of syphilis related to blood transfusion were reported infrequently. The practice of refrigerating blood, which kills circulating spirochetes within 1 to 2 days, is probably responsible for the absence of transfusion-associated syphilis today. Unfortunately, refrigerating blood does not kill all potential pathogens. Bacterial pathogens that can survive blood storage and cause subsequent symptomatic infection include *Yersinia enterocolitica*, *Pseudomonas fluorescens*, *P. putida*, *Campylobacter jejuni*, *Escherichia coli*, *Serratia*

species, *Salmonella* species, *Enterobacter* species, *Providencia* species, *S. aureus*, and streptococci. When transfusion-associated bacteremia or endotoxemia is suspected, the residual blood product in the bag should be examined by means of a hematologic stain, and the blood in the bag and samples of the recipient's blood should be cultured.

Bacterial contamination of transfused blood components accounted for 11% of all fatal transfusion reactions reported to the FDA between 1985 and 1999. In 2001, CDC investigators published a prospective survey of bacterial infections resulting from blood component transfusion in the United States between January 1998 and December 2000.¹⁴² This survey covered approximately 60% to 70% of all transfusions recorded in the United States during that period. The investigators identified 34 confirmed cases of bacterial infection from transfused blood components, nine (27%) of which were responsible for deaths. The estimated rates of transfusion-transmitted bacteremia were one per 100,000 single or pooled units of platelets and one per 5 million units of red blood cells. The estimated fatality rates were one per 500,000 units of platelets and one per 8 million units of red blood cells.

Until recently, the most severe and most common disease transmitted by blood transfusion in North America was viral hepatitis [see 8:20 *Viral Infection*]. With the development of specific and sensitive tests for detecting hepatitis B surface antigen (HBsAg), the incidence of posttransfusion hepatitis B dropped from 25% to 30% of all cases of transfusion-associated hepatitis to 5% to 10%. However, the advent of serologic tests for hepatitis B did not result in an overall decrease in posttransfusion hepatitis (PTH), because 80% to 90% of cases of PTH were caused by hepatitis C virus (HCV). Since the development of sensitive antibody tests for HCV, the incidence of PTH has dropped dramatically, and since the introduction in 1999 of nucleic acid amplification technology (NAT) (e.g., PCR and transcription-mediated amplification), it has fallen even further, to the point where the current estimated risk is one per 1.9 million transfused units.¹⁴³

The spread of AIDS [see 8:21 *Acquired Immunodeficiency Syndrome*] brought a new risk of transfusion-associated viral disease. The risk of acquiring transfusion-associated HIV infection is extremely low compared with posttransfusion hepatitis; transfusion-associated HIV infection is vastly less likely to occur and

has accounted for fewer deaths. Nevertheless, transfusion-associated AIDS is much more frightening to most patients and physicians than PTH because of its usually fatal prognosis. Prevention of HIV transmission during transfusion is accomplished by screening potential donors to eliminate those at high risk for infection and by testing all donated units for HIV with both antibody tests and NAT.¹⁴³⁻¹⁴⁵ It has been estimated that predonation screening is 98% effective in eliminating donation of positive units and that postdonation antibody testing is more than 95% effective, for a combined effectiveness of approximately 99.9%.¹⁴⁴ Overall, posttransfusion HIV infections were reduced by 76% between 1985 and 1988, a time during which the overall prevalence of the condition was increasing.¹⁴⁴

The continued concern about possible HIV transmission during transfusion arises from the so-called window of seronegativity between the time at which a potential donor becomes infected and the time at which the donor's antibody test becomes positive. A 1989 analysis of available data from most United States blood banks concluded that the risk of receiving a unit of blood that contained HIV but was negative for anti-HIV antibody in 1987 was approximately one per 153,000 transfusions on the basis of an average window period of 8 weeks.¹⁴⁴ A 2002 report, making use of data obtained since the introduction of NAT, established the current risk at one per 2.1 million transfusions.¹⁴³ In comparison, the risk of experiencing a fatal hemolytic transfusion reaction is one per 100,000 transfusions.¹⁴⁵ Thus, a transfusion recipient is much more likely to die of a hemolytic reaction than of infection.

Analysis of transfusion practices in the United States between 1982 and 1988 reveals a decrease in the number of blood, platelet, and plasma transfusions after 1986; before 1986, the number of these transfusions increased each year. In addition, between 1982 and 1987, the number of autologous units donated increased from 30,000 to 397,000 a year. In 1987, autologous units accounted for 3% of all blood transfused.¹⁴⁶ Since 1987, refinements of operative techniques have reduced the need for transfusion in many procedures, and research has demonstrated that in many cases, transfusion can safely be withheld until hemoglobin levels lower than 7 g/dl are reached [see 1:4 *Bleeding and Transfusion*].¹⁴⁷ In addition to the overall decline in transfusions since the late 1980s, the number of autologous units of blood transfused yearly has declined.¹⁴⁸

Discussion

Postoperative Fever

Many patients experience fever in the postoperative period without infection. In a prospective study of 871 general surgery patients, 213 (24%) had a documented infection or an unexplained fever in the postoperative period.¹⁴⁹ The most common occurrence was unexplained fever in 81 cases (38%), followed by wound infection in 55 (26%), UTI in 44 (21%), respiratory tract infection in 27 (13%), and other infections in 6 (3%). Of all unexplained fevers, 72% occurred in the first 2 days, and of all occurrences in the first 3 days, 67 (71%) of 95 were unexplained, with only 18 (27%) representing true infection. In another study, 73 (45%) of 162 patients experienced unexplained fever after general surgical or orthopedic procedures; 25% of the unexplained fevers were at least 38.3° C (101° F).¹⁵⁰

At Harborview Medical Center, 316 (98%) of 322 patients who underwent laparotomy for penetrating trauma had a temperature of at least 37.5° C (99.5° F) orally during the first 5 days after operation. Of these patients, however, only 67 (21%) actually acquired any infection during a 30-day follow-up. Even for the 80 patients whose temperatures were as high as 39° C (102.2° F) orally, only 48% actually acquired an infection before discharge. Fever that persisted or began after postoperative day 4 was more likely to represent true infection. Similarly, an elevated WBC count was nonspecific during the first 5 postoperative days: 89% of all patients had a WBC count greater than 10,000/mm³.^{151,152} A high fever should prompt examination of the patient, but in the absence of systemic signs of sepsis, an extensive laboratory or radiologic workup during the first 4 to 5 days is usually unhelpful.¹⁵³

Magnitude and Significance of Nosocomial Infection

An understanding of the prevalence of nosocomial infections and of the factors predisposing to their occurrence will help in prevention, diagnosis, and treatment. Since 1970, the NNIS system has collected and analyzed data on the frequency of nosocomial infections in a voluntary sample of hospitals (currently numbering 280) in the United States.¹⁵⁴ Although it has been suggested that the NNIS system underestimates the true incidence of nosocomial infections by 30% to 40%,^{3,155,156} the large number of cases studied during consecutive years provides a useful description of the most frequently encountered infections, their relative incidences, and the responsible pathogens.

INCIDENCE

In the 1986 NNIS report, the overall incidence of nosocomial infection was 33.5 per 1,000 discharges; the range extended from 13.3 per 1,000 pediatric discharges to 46.7 per 1,000 surgical discharges. Generally, the rate of infection is highest in large teaching hospitals and lowest in nonteaching hospitals. The higher incidence of infection among surgical patients is largely attributable to SSI. SSIs are the most frequent adverse events reported for hospitalized surgical patients and account for 38% of all nosocomial infections in surgical patients.¹⁵⁷ Two thirds of SSIs are incisional infections, and one third are organ/space infections.^{35,158} Some 38% of all SSIs result in readmission to the hospital.³⁵

Across all services, UTIs are the most common infections, accounting for 38.5% of all nosocomial infections, followed by lower respiratory tract infections (17.8%), surgical wound infections (16.6%), primary bacteremias (7.5%), and cutaneous infections (5.8%). All other categories combined account for 13.8% of nosocomial infections. The total incidence of nosocomial infection from all sites on surgical services ranges from 30.8 to 59.3 per 1,000 discharges. The risk that a surgical patient will acquire any infection varies according to the type of procedure performed as well as to the patient's underlying risk.¹⁵⁹

In the 1993 NNIS report, the most common nosocomial infections for surgical patients after an SSI were UTIs (27%), pneumonias (15%), primary bloodstream infections (7%), and all other sites combined (15%).¹⁵⁹ Of the infected surgical patients, 17% had more than one nosocomial infection, and 9% of surgical patients with nosocomial infections subsequently died; nosocomial infections were reported to have caused or contributed to 60% of the deaths. Of infections related to death, 38% were pneumonias, 21% occurred at the surgical site, and 20% were primary bloodstream infections. The likelihood that a specific infection will be related to death varies with the type of infection [see Table 1].

Urinary Tract Infection

With so many cases of bacteriuria occurring in catheterized patients, it would be easy to become complacent about the problem. Urinary tract catheterization is performed seven to eight million times a year in acute care hospitals in the United States.¹⁶⁰ Approximately 5% to 8% of catheterized, uninfected patients will acquire a urinary tract infection for each day of catheterization, leading to a cumulative infection rate of 40% to 50% after 10 days.¹⁰⁹ However, the great majority of catheterized patients with bacteriuria are asymptomatic.^{109,161} It has been estimated that only 0.7% of catheterized patients will acquire a symptomatic infection and that 8% to 10% of patients will have bacteriuria after the catheter has been removed.¹⁰⁹

In many of these patients, the bacteriuria resolves without specific therapy after the catheter has been removed. However, a

Table 1 Contribution of Nosocomial Infection to Death in Infected Surgical Patients Who Died¹⁵⁹

Type of Nosocomial Infection	Probability That Infection Was Related to Death (%)
Organ/space surgical site infection	89
Primary bloodstream infection	79
Pneumonia	77
Other	48
Incisional surgical site infection	46
Urinary tract infection	22

careful study of more than 1,458 patients clearly demonstrated that mortality is higher in catheterized patients who acquire bacteriuria than in those who do not.¹⁶⁰ In this study, 9% of all catheterized patients acquired catheter-related UTIs; these infections were associated with a threefold increase in deaths occurring during hospitalization, even after correction for other factors (e.g., age, severity of illness, hospital service, duration of catheterization, and renal function). In surgical patients between 50 and 70 years of age with normal renal function and without a fatal underlying disease, a 3% increase in the death rate per patient per hospitalization was associated with the occurrence of a UTI. Of all deaths occurring in catheterized patients, 14% were associated with a UTI.¹⁶⁰ By extrapolation, this mortality suggests that as many as 56,000 deaths a year in the United States may be related to catheter-acquired UTI.

Although the risk of bacteremia is small for any individual patient with bacteriuria, the large number of hospitalized patients with bacteriuria means that many bacteremic episodes are seen in this population. UTI is the most commonly diagnosed source of gram-negative sepsis, and the rate of bacteremia secondary to urinary catheters is estimated to be between 0.7% and 2%.¹⁰⁹ In a case-matched study from 1978, a postoperative UTI was associated with a 2.4-day prolongation of hospital stay and an excess cost of more than \$500.¹⁶² A subsequent study revealed that 2.3% of postoperative patients with UTIs were subsequently diagnosed as having a wound infection caused by the same organism responsible for the UTI.¹⁶³ This finding accounted for 3.4% of the wound infections occurring during the study.

Infection Associated with Intravascular Devices

Nosocomial infection associated with intravascular devices, which are placed for either monitoring or therapeutic purposes, assumed increasing importance during the 1970s and 1980s. In the United States, central venous catheters are in place for approximately 15 million patient-catheter-days per year, resulting in approximately 250,000 catheter-associated bloodstream infections.⁷⁰ Of all cases of nosocomial bacteremia occurring in NNIS hospitals between September 1984 and July 1986, 82% were associated with intravascular devices¹⁶⁴; 27% were associated with parenteral nutrition catheters and 55% with other vascular access devices. Reports from as early as 1963 called attention to the risk of serious systemic infections arising from peripheral I.V. catheters.¹⁶⁵ For ICU patients with bloodstream infections associated with central venous catheters, the attributable mortality is 25% to 35%, and the excess cost for survivors is \$34,000 to \$56,000 per patient, for a total annual cost of \$296 million to \$2.3 billion.⁷⁰

In terms of infection risk, pulmonary arterial catheters are no different from central venous catheters, except for their potential to cause right-side heart lesions that could predispose to right-side endocarditis.¹⁶⁶ Pulmonary arterial catheters can be responsible for bloodstream infection, and they require as much attention during insertion and subsequent care as central venous catheters do.^{68,167}

The arterial catheters used for monitoring purposes in the ICU have been thought to be less frequently associated with infection than central venous catheters are, but it is clear that life-threatening infections can originate with peripheral arterial lines.^{168,169} In early studies of radial artery catheters in which nonquantitative culture techniques were employed, catheter contamination rates of 4% to 39% were recorded, but there were no cases of CRBSI or clinical infection in 605 catheterizations.¹⁷⁰ In these studies, the majority of catheters were removed from patients within 3 days.

Prospective studies of arterial catheters demonstrated that 18% to 35% of the lines were locally infected, as reflected in semiquantitative cultures of at least 15 colonies.¹⁷¹ In one study, five cases of CRBSI occurred, representing an overall incidence of 4% and an incidence of 23% among locally infected catheters.¹⁷¹ The incidence of CRBSI was increased in catheters that were inserted by cutdown rather than by percutaneous puncture and in catheters with signs of local inflammation. In another, the clinical features of bloodstream infection arising from an arterial catheter were indistinguishable from the clinical features of episodes arising from a central venous line, and 12%

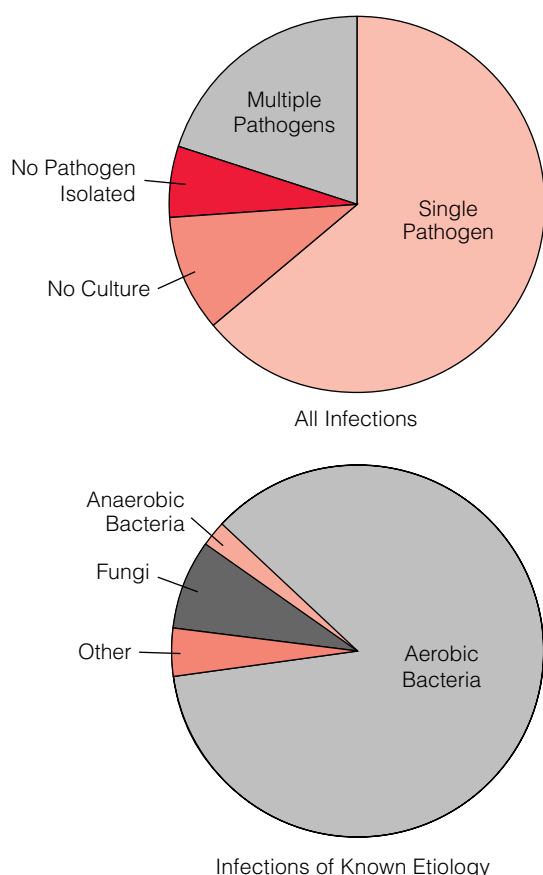


Figure 4 Illustrated is a breakdown of the etiology of 26,965 nosocomial infections from the National Nosocomial Infections Surveillance System.¹⁷³

Table 2 Five Most Common Pathogens Isolated from Surgical Patients and Percentage of Total within Each Site¹⁷³

Infection Site	Organism	Isolates at That Site (%)
Urinary tract infection	<i>Escherichia coli</i>	29
	<i>Pseudomonas aeruginosa</i>	16
	Enterococci	13
	<i>Proteus</i> species	7
	<i>Klebsiella</i> species	7
Surgical wound infection	<i>Staphylococcus aureus</i>	19
	Enterococci	12
	<i>E. coli</i>	12
	<i>P. aeruginosa</i>	10
	Coagulase-negative staphylococci	8
Lower respiratory infection	<i>P. aeruginosa</i>	17
	<i>S. aureus</i>	12
	<i>Enterobacter</i> species	11
	<i>Klebsiella</i> species	11
	<i>Serratia</i> species	7
Bacteremia	Coagulase-negative staphylococci	14
	<i>S. aureus</i>	10
	<i>Enterobacter</i> species	9
	Enterococci	9
	<i>Klebsiella</i> species	8
Cutaneous infections	<i>S. aureus</i>	19
	<i>P. aeruginosa</i>	13
	Enterococci	11
	Coagulase-negative staphylococci	10
	<i>E. coli</i>	8

of all nosocomial bacteremias in the ICU originated from an arterial catheter.¹⁷¹ Clearly, arterial lines as well as venous lines must be considered in the examination of a patient for the source of fever or bloodstream infection in the ICU.^{68,169,171,172} Twelve cases of radial artery rupture after arterial line infection have been reported. All but one were associated with *S. aureus* infection, and nearly all demonstrated systemic signs of infection for 2 days or longer after catheter removal.¹⁶⁹ Although there is no published experience with the use of guide wires to change and culture arterial lines in relation to possible catheter-related infection, the technique can be applied with the same rationale used for central venous catheters.

PATHOGENS

In 1984, the NNIS reported on 26,965 infections. Of these cases, 64% were caused by single pathogens, 20% were caused by multiple pathogens, 6% had no pathogen identified on culture, and 10% were not cultured [see Figure 4].¹⁷³ Of the 84% in which a pathogen was identified, 86% were caused by aerobic bacteria, 2% by anaerobes, and 8% by fungi [see Figure 4 and Table 2]. Overall on the surgical services, the most common pathogen isolated was *E. coli*, followed by *P. aeruginosa*, enterococci, *S. aureus*, *Enterobacter* species, *Klebsiella* species, coagulase-negative staphylococci, *Proteus* species, *Candida* species, and *Serratia* species. These 10 types of pathogens accounted for 84% of all isolates. Gram-negative rods were most common in UTIs

and lower respiratory tract infections, though *S. aureus* was the second most common pathogen isolated in lower respiratory tract infections. *S. aureus* was the most common isolate from surgical wound infections, whereas coagulase-negative staphylococci, followed closely by *S. aureus*, were the pathogens most often responsible for primary bacteremias.

As a consequence of changing hospital practices, hospitalized patients today tend to be more severely ill than was once the case. Large amounts of antibiotics are being used in hospitals, and antibiotic-resistant pathogens have become increasingly problematic. Current NNIS data indicate that the frequency with which antibiotics are administered to hospitalized patients who are not in an ICU is approximately 468 defined daily doses (DDD) per 1,000 patient-days.¹⁷⁴ For hospitalized ICU patients, the frequency is between 800 and 1,031 DDD per 1,000 patient-days. MRSA accounts for 51% of total *S. aureus* isolates in ICU patients, 40% in non-ICU patients, and 24% in outpatients with nosocomial infections; the corresponding figures for quinolone-resistant *P. aeruginosa* in relation to total *P. aeruginosa* isolates are 37%, 27%, and 27%.¹⁷⁴ In 2002, the second clinical isolate of vancomycin-resistant *S. aureus* in the United States was reported.¹⁷⁵

Nosocomial infections with resistant enterococci have become a serious problem. Enterococci were the third most common nosocomial bloodstream isolate reported by NNIS hospitals between 1990 and 1992.¹⁷⁶ The incidence of vancomycin-resistant enterococci (VRE) increased 26-fold between 1989 and 1993, from 0.3% to 7.9%, with a 34-fold rise in ICUs,¹⁷⁷ and the rate has continued to increase. The 2001 NNIS report stated that 13% of enterococci were resistant to vancomycin in ICU patients, 12% in non-ICU patients, and 5% in outpatients.¹⁷⁴ These strains arise from the patient's endogenous flora, but nosocomial spread within the hospital environment is also an important source.^{177,178} The environment around infected patients is heavily contaminated with VRE, and gown and glove isolation techniques are required to stop transmission.¹⁷⁸ Strict application of hand hygiene is also important for reducing the spread of VRE and other nosocomial pathogens. According to the available data and current CDC recommendations, the use of alcohol-based hand-rub solutions is superior to washing with soap and water: it can be performed more rapidly and is less damaging to the skin.¹⁷⁹

VRE are also highly resistant to other available antibiotics. Acquisition of VRE is significantly associated with prior hospitalization and with use of third-generation cephalosporins, vancomycin, or multiple antibiotics.^{180,181} In one study, 16% of stool specimens submitted for testing for *C. difficile* toxin were colonized with VRE, and all surgical patients in that study had the same strain.¹⁸²

High mortality can be associated with VRE infections. In a study comparing the outcome of patients having VRE bacteremia with the outcome of patients having bacteremia caused by vancomycin-sensitive enterococci (VSE), mortality was 2.3 times higher in those with VRE bacteremia, and 89% of patients with VRE bacteremia were colonized or infected with VRE at another site.¹⁸³ Prior treatment with third-generation cephalosporins is another risk factor for increased mortality.¹⁷⁶ Liver transplant patients with VRE bacteremia had a 92% higher mortality than comparable patients with VSE bacteremia, and those with VRE bacteremia also had a higher recurrence rate and greater need for invasive procedures.¹⁸⁴

Current recommendations include decreased—and possibly restricted—use of vancomycin, as well as aggressive infection control measures whenever VRE are isolated in a hospitalized patient.¹⁷⁷ In particular, vancomycin should not be used as pri-

mary treatment for *C. difficile*-associated diarrhea and should be avoided for surgical prophylaxis unless the hospital has a specific problem with MRSA or the patient cannot receive other appropriate antibiotics.

ENTERIC INFECTION

C. difficile is often found in patients with severe antibiotic-associated enteric infections. In one report, 691 (2%) of 32,757 consecutive postoperative patients experienced watery diarrhea significant enough to stimulate a request for *C. difficile* toxin assay.¹⁸⁵ Of this number, 75 (11% of patients with diarrhea) had a positive toxin assay. All cases were associated with antibiotic administration. Approximately 94% of the patients had received a cephalosporin either alone or in combination with other antibiotics; 29% of these responded to cessation of antibiotics and supportive measures, and the remainder were treated with vancomycin, metronidazole, or bacitracin. Six (14%) of the patients who required specific therapy relapsed after initial response to treatment and were subsequently cured with one or more additional courses of treatment. Two patients died, and the overall hospital stay for the remaining patients was prolonged by an average of 50%.

Most patients with mild cases of antibiotic-associated diarrhea do not have either positive cultures for *C. difficile* or positive toxin assays, and the etiologic role of *C. difficile* is unclear. Many hospitalized patients without diarrhea also have *C. difficile* in the stool, with or without toxin production,^{123,186} and the likelihood of isolating this pathogen increases with patients' increasing length of stay.¹¹⁸ A nonpathogenic yeast, *Saccharomyces boulardii*, when administered by mouth to hospitalized patients receiving antibiotics, significantly reduced the occurrence of antibiotic-associated diarrhea without affecting the rate of acquisition of *C. difficile*.¹²³

Some 3% of asymptomatic adults carry *C. difficile* in their stools, but 30% to 40% of healthy neonates may carry the organism. The rate of carriage declines after the age of 1 to 2 years. *C. difficile* can be spread in the hospital and has been isolated from 10% of inanimate objects in the environment of patients with *C. difficile* colonization, compared with 3% in hospital areas with no known cases.¹⁸⁷ In one report,¹⁸⁷ this organism was recovered from the hands of 13% of medical personnel working in a ward with affected patients; in another,¹⁸⁸ it was recovered from 60% of personnel immediately after they had cared for an affected patient. Soap-and-water washing was ineffective in preventing acquisition, but the combination of glove use and chlorhexidine washing was effective. In another medical center,¹⁸⁹ clusters of new nosocomial *C. difficile* diarrhea were prevented by screening all patients with diarrhea by active surveillance (using culture to identify *C. difficile* infection) and by instituting isolation precautions and daily disinfection of infected patients' rooms.

The prevalence of *C. difficile* in the environment is increased when a patient has diarrhea.^{187,188} In one prospectively studied cohort, 21% of patients without *C. difficile* in their stools on admission acquired the organism during hospitalization, and 37% of these patients experienced diarrhea; no cases of colitis occurred.¹⁸⁷ Diarrhea was more common in patients who received antibiotics. The rate of acquisition of *C. difficile* was 73% higher if a patient had a roommate colonized with *C. difficile*.

COST

The cost of nosocomial infections, both in dollars and in morbidity, is high. According to one estimate, 8.7 million extra hospital days and \$4.5 billion in hospital charges were attributable to nosocomial infections in United States hospitals in 1976.¹⁹⁰

Estimates of the number of deaths caused by nosocomial infections run as high as 58,000 a year; 9,700 of these deaths and 36% of all costs attributed to nosocomial infections are due to wound infections.¹⁹⁰ The actual numbers may be even higher. Another study found that 63 of 200 consecutive patients dying in the hospital had nosocomial infections; 18 (29%) of the 63 were judged causal and 26 (41%) contributory.⁸ Most of the causal and contributory infections were of the lower respiratory tract, and deaths were significantly associated with invasive devices (e.g., intra-arterial and central venous pressure monitoring devices and nasogastric tubes). Of the 57 deaths occurring on the surgical service, 27 (47%) were associated with nosocomial infections.

RISK

The risk of acquiring a nosocomial infection is clearly related to the reason for hospitalization as well as to the underlying dis-

ease.^{8,191} Patients admitted to the hospital with a fatal underlying disease have a nosocomial infection rate of 24%, compared with 10% in patients with ultimately fatal disease and 2% in those with nonfatal disease. Among 100 consecutive trauma patients admitted to the ICU at Harborview Medical Center in 1986, 42 acquired 64 nosocomial infections, including 23 lower respiratory tract infections, 17 urinary tract infections, and 6 wound infections.¹⁵² These 100 ICU admissions and 101 consecutive trauma admissions to the general ward were examined together. Of 153 patients admitted with injury severity scores of 25 or less, nosocomial infection occurred in 32 (21%). Of 48 patients with injury severity scores higher than 25, nosocomial infection occurred in 26 (54%).¹⁵² A statewide survey of hospitals in Virginia from 1978 to 1982 found that infections in ICU patients accounted for 25% of all cases of nosocomial infections, although fewer than 10% of the beds were in ICUs.¹⁹²

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Acknowledgments

Figures 1 and 2 Carol Donner.
Figure 4 Albert Miller.

18 POSTOPERATIVE AND VENTILATOR-ASSOCIATED PNEUMONIA

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Pulmonary complications are common after surgical procedures, accounting for nearly one of every four deaths that occur in the first postoperative week.¹ Overall, pneumonia is the third most common postoperative infection, after urinary tract infection and surgical site infection.² In critically ill patients, however, the respiratory tract is the most common site of nosocomial infection: in the intensive care unit (ICU), pneumonia accounts for 28 to 47% of all nosocomial infections.³

In discussing pneumonia occurring in surgical patients after operation, it is useful to distinguish between postoperative pneumonia and ventilator-associated pneumonia (VAP). Throughout this chapter, we make this distinction where appropriate [see *Incidence and Risk Factors and Diagnosis, below*]. Most of the literature published on the prevention, diagnosis, and treatment of VAP is not specifically aimed at surgical patients. The American Burn Association recently published practice guidelines specifically aimed at burn patients,⁴ but the majority of the studies on which their recommendations are based come from a mixed medical-surgical population.

Pathogenesis

Under basal conditions, the lower respiratory tract is sterile. Thus, for pneumonia to develop, bacteria must be introduced into the lungs, typically by being aspirated from either the upper respiratory tract or the gastrointestinal (GI) tract. This introduction of bacteria is generally associated with impairment of host defenses, both locally and systemically.

A leading hypothesis regarding the pathogenesis of VAP is that the oropharynx is overgrown by microbes, which are subsequently aspirated into the lungs and colonize the airway. This hypothesis is supported by the observation that whereas enteric gram-negative bacteria are absent from the oropharynx under basal conditions, they can be detected in the oropharynx in nearly 75% of critically ill patients.⁵ Additionally, a comparison of bacterial DNA samples in the tongues of critically ill patients with organisms recovered from bronchoalveolar lavage (BAL) samples supports this theory.⁶ Upper airway colonization by enteric bacteria occurs in 45 to 100% of intubated patients. Besides being colonized by aspirated endogenous flora, the airways may be colonized by exogenous flora as a result of cross-contamination from other ICU patients (through inadvertent transmission by health care workers).

A complementary hypothesis is that the upper GI tract plays a critical role in the pathogenesis of VAP. According

to this view, the stomach is a primary site of colonization that may subsequently infect the lung through retrograde movement of bacterial overgrowth, followed by aspiration of organisms from the oropharynx. The small decrease in mortality seen in certain ICU patient populations who undergo selective decontamination of the digestive tract (SDD) supports the possibility that endogenous gut flora plays a role in the pathogenesis of VAP, although this possibility remains controversial (discussed in detail below). Chronic infection of biofilms in an endotracheal tube may also play a role in the pathogenesis of VAP.⁷ Either suctioning or performing bronchoscopy in a patient with a biofilm may result in distal embolization of bacteria. The importance of biofilms in this setting, however, remains to be fully determined.

Incidence and Risk Factors

For an accurate assessment of the incidence of and risk factors for pneumonia in postoperative patients, it is helpful to consider postoperative pneumonia separately from VAP. Postoperative VAP, by definition, occurs in a patient who has undergone a surgical procedure and is on mechanical ventilation for longer than 48 to 72 hours; however, not every patient who acquires pneumonia after an operation is on a ventilator or in the ICU. The severity of an episode of pneumonia and its ultimate outcome are at least partially related to the comorbid conditions present; therefore, a surgical ICU patient with multiple organ dysfunction typically has a worse prognosis than a patient who acquires pneumonia while recovering from an operation on the surgical ward.

POSTOPERATIVE PNEUMONIA

A wide-ranging assessment of pneumonia in the postoperative setting was provided by a retrospective review of 160,805 patients who underwent major noncardiac surgical procedures at 100 Veterans Affairs Medical Centers between 1997 and 1999.² Pneumonia was diagnosed in a total of 2,466 (1.5%) of the 160,805. The 30-day mortality was 21% in patients who experienced postoperative pneumonia and 2% in those who did not. Multivariate analysis identified several risk factors that led to an increased risk of postoperative pneumonia, including type of surgery, age, functional status, recent weight loss, chronic obstructive pulmonary disease (COPD), type of anesthesia, impaired sensorium, history of a cerebrovascular accident, blood urea nitrogen (BUN) level, substantial transfusion, emergency surgical intervention, long-term steroid use, recent smoking, and significant recent alcohol use [see *Table 1*]. This review represents by far the most substantial effort yet made to quantify the incidence and risk factors of postoperative infections. However, it has two major limitations: (1) it was

Financial disclosure information is located at the end of this chapter before the references.

Table 1 Preoperative Predictors of Postoperative Pneumonia

Predictor	Odds Ratio (95% CI)
Type of surgical procedure	
AAA repair	4.29 (3.34–5.50)
Thoracic	3.92 (3.36–4.57)
Upper abdominal	2.68 (2.38–3.03)
Neck	2.30 (1.73–3.05)
Neurologic	2.14 (1.66–2.75)
Vascular	1.29 (1.10–1.52)
Other	1.00 (referent)
Age (yr)	
≥ 80	5.63 (4.62–6.84)
70–79	3.58 (2.97–4.33)
60–69	2.38 (1.98–2.87)
50–59	1.49 (1.23–1.81)
< 50	1.00 (referent)
Functional status	
Totally dependent	2.83 (2.33–3.43)
Partially dependent	1.83 (1.63–2.06)
Independent	1.00 (referent)
Weight loss > 10% in past 6 mo	1.92 (1.68–2.18)
History of COPD	1.72 (1.55–1.91)
Type of anesthesia	
General	1.56 (1.36–1.80)
Spinal, monitored, or other	1.00 (referent)
Impaired sensorium	1.51 (1.26–1.82)
History of cerebrovascular accident	1.47 (1.28–1.68)
BUN level	
< 2.86 mmol/L (< 8 mg/dL)	1.47 (1.26–1.72)
2.86–7.50 mmol/L (8–21 mg/dL)	1.00 (referent)
7.85–10.70 mmol/L (22–30 mg/dL)	1.24 (1.11–1.39)
≥ 10.70 mmol/L (≥ 30 mg/dL)	1.41 (1.22–1.64)
Transfusion > 4 units	1.35 (1.07–1.72)
Emergency operative intervention	1.33 (1.16–1.54)
Use of steroids for chronic condition	1.33 (1.12–1.58)
Current smoker within 1 yr	1.28 (1.17–1.42)
Alcohol intake > 2 drinks/day in past 2 wk	1.24 (1.08–1.42)

AAA = abdominal aortic aneurysm; BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease.

retrospective rather than prospective, and (2) more than 95% of the patients involved in the study were male.

VENTILATOR-ASSOCIATED PNEUMONIA

In contrast to postoperative pneumonia, VAP has been the subject of a good deal of epidemiologic study, although to date, surgical patients have made up only a subset of the patients studied. Although VAP can occur in any patient undergoing mechanical ventilation, it is substantially more common in surgical ICU patients than in medical ICU patients, reaching its highest prevalences in trauma and burn ICUs.⁸ As an example of how VAP disproportionately affects surgical patients, ventilator use in surgical ICUs is lower than that in respiratory ICUs (0.39 versus 0.46 ventilator days/patient days), but VAP develops nearly 10 times as often in the former as in the latter (4.9 versus 0.5 cases per 1,000 ventilator days).⁸ It should be remembered, however,

that patients in respiratory ICUs may have already had an episode of pneumonia while in the hospital, which may make diagnosis of secondary VAP more difficult in this population. Patients with burns are especially susceptible to developing VAP,⁹ especially the 10 to 20% of burn patients who are victims of inhalation injury.

The single greatest risk factor for VAP is related to the duration of mechanical ventilation. The risk peaks at day 5 on the ventilator, plateaus after day 15, and then declines significantly, with the result that VAP is uncommon in patients on long-term mechanical ventilation.

The absolute mortality in VAP patients ranges from 12% to more than 50%, with a substantially lower crude mortality in surgical patients than in medical patients.¹⁰ The attributable mortality associated with VAP has not been determined with certainty, although a review of observational studies suggests that it is not associated with increased mortality in either trauma or acute respiratory distress syndrome (ARDS) but is associated with increased mortality in other patient populations.¹⁰

Studies that demonstrate an increased relative risk of death with VAP frequently also demonstrate an increased prevalence of resistant organisms (e.g., *Pseudomonas aeruginosa* and *Acinetobacter baumannii*).¹¹ VAP patients as a group remain in the ICU approximately 6 days longer than comparable patients without VAP and incur more than \$40,000 in additional charges.¹² When the subgroup of surgical patients is considered on its own, however, the increase in length of stay in the ICU is closer to 1 day,¹² and the increase in hospital charges is almost certainly smaller (although still substantial).

Diagnosis

Pneumonia is commonly defined as distal airspace inflammation caused by microorganisms or products of microorganisms. Although this definition is simple, diagnosis of pneumonia is often complex, for two reasons. First, it is frequently difficult to isolate microorganisms from the lower respiratory tract, even if the patient has an active infection. Second, in the unlikely circumstance that a patient undergoes an open lung biopsy that demonstrates inflammation, this finding does not indicate that pneumonia is present, because a number of noninfectious insults can result in both local and systemic inflammation.

DIAGNOSTIC CRITERIA

Postoperative Pneumonia

Most postoperative fevers are of noninfectious origin, and even when an elevated temperature and an increased white blood cell (WBC) count result from an infection, pneumonia is still not the most likely diagnosis. It is therefore critical to establish objective criteria for diagnosing pneumonia after a surgical procedure. Of the several different diagnostic approaches that have been formulated, the most commonly used is the Centers for Disease Control and Prevention/National Healthcare Safety Network definition [see Table 2].¹³ This definition involves the combination of chest x-ray abnormalities in addition to the presence of at least three criteria that suggest the patient has an infection, and the

Table 2 CDC/NHSN Definition for Pneumonia

Two or more serial chest radiographs with at least one of the following: New or progressive and persistent infiltrate Consolidation Cavitation
<i>plus</i> At least one of the following: Fever ($> 38.4^{\circ}\text{C}$ [$> 100.4^{\circ}\text{F}$]) with no other recognized cause Leukopenia ($< 4,000$ WBC/ μL) or leukocytosis ($> 12,000$ WBC/ μL) Altered mental status with no other recognized cause in adults > 70 years of age
<i>plus</i> At least two of the following: New onset of purulent sputum or change in character of sputum or increased respiratory secretions, or increased suctioning requirements New-onset or worsening cough or dyspnea or tachypnea Rales or bronchial breath sounds Worsening gas exchange (O_2 desaturations, $\text{PaO}_2/\text{F}_i\text{O}_2 < 240$), increased oxygen requirements or increased ventilation demand

Adapted from Centers for Disease Control and Prevention.¹³
 CDC = Centers for Disease Control and Prevention; F_iO_2 = fraction of inspired oxygen; NHSN = National Healthcare Safety Network; PaO_2 = arterial oxygen tension; WBC = white blood cells.

infection is respiratory in origin. Importantly, the use of these criteria allows different institutions to benchmark their pneumonia rates against peer institutions and create a semi-objective method for diagnosing pneumonia. The criteria for diagnosing a patient with pneumonia are independent of whether a patient has had surgery, and in a surgical ward patient, the diagnosis is generally made when there is new onset of purulent sputum or a change in the character of the sputum in combination with a worsening chest x-ray that demonstrates either new or progressive infiltrate or consolidation.

Ventilator-Associated Pneumonia

Diagnosing VAP is more complicated than diagnosing postoperative pneumonia in a patient on the surgical ward, although with invasive quantitative cultures, it may be possible to make the diagnosis more accurately in a ventilated patient. In ICU patients, as in surgical ward patients, fever and leukocytosis are very common and are frequently of noninfectious origin. Unlike surgical ward patients, however, ICU patients often have chronically purulent secretions and abnormal chest x-rays that are not representative of pneumonia. There is no absolute gold standard for diagnosing VAP, and attempts to define VAP objectively for surveillance purposes have so far failed to reach any resolution.¹⁴ In addition to fever, leukocytosis, increased or changed sputum production, and an abnormal chest x-ray, indicators used to diagnose VAP may include sputum culture, the clinical pulmonary infection score (CPIS), and (less commonly) pleural fluid culture or open lung biopsy. Even though the Centers for Disease Control/National Healthcare Safety Network definition is commonly used for the diagnosis of VAP, it should be pointed out that a recent study of 253 patients who died in the ICU showed poor concordance when compared with autopsy findings.¹⁵

INVASIVE AND NONINVASIVE CULTURES

Samples for sputum culture may be obtained either non-invasively, via tracheal aspiration, or invasively, via bronchoscopy with either BAL or a protected specimen brush (PSB). Tracheal cultures, although commonly employed, may overestimate the rate of VAP and fail to diagnose some occurrences of pneumonia documented by postmortem pathologic study of the lung; these failings persist even when quantitative cultures are used. Moreover, the threshold used for documenting VAP with tracheal cultures changes both the sensitivity and the specificity of the test. In one study, reducing this threshold from 10^6 to 10^5 colony-forming units (cfu)/mL increased sensitivity from 55 to 63% while decreasing specificity from 85% to 75%, as determined by comparison with postmortem specimens in a sample of 28 patients who died within 3 days after culture.¹⁶

Invasive sampling has historically been felt to be significantly more accurate than tracheal aspiration in diagnosing VAP. However, this was called into question by a prospective, randomized trial comparing BAL and tracheal aspiration in 740 patients in 28 ICUs that demonstrated similar clinical outcomes and similar use of antibiotics, regardless of which strategy was used for diagnosing VAP.¹⁷ This study has been criticized, however, because patients whose airways were colonized, who were immunocompromised, or who received ciprofloxacin or meropenem were excluded from the trial; thus, a large segment of the population who may have benefitted from BAL screening was excluded from the study.¹⁸ Both BAL and PSB have sensitivities and specificities higher than 80% [see Table 3]. A study involving 22 patients with suspected VAP who had five samples taken from the same site during the same bronchoscopy procedure found that the two techniques yielded similar results.¹⁹ In this study, PSB isolated the same organisms each time, but quantitation with BAL varied within one log 59% of the time, leading to a change in diagnosis (from presence to absence of pneumonia or vice versa) in 13% of cases.

It must be noted that simply placing a bronchoscope through an endotracheal tube or a tracheostomy and obtaining a sample is still essentially tracheal aspiration, not BAL. As noted (see above), pneumonia is defined as the presence of microorganisms in the distal airways; thus, obtaining a sample from the proximal airways (even if access is obtained with a bronchoscope), although it can provide information about the microbial content of the proximal airways, suffers from the same limitations that obtaining a culture with a catheter placed down the endotracheal tube does.

Techniques for performing BAL vary somewhat among institutions. Generally, however, the bronchoscope is wedged in the most distal airway in the lobe of interest before cultures are obtained, and a 20 or 50 mL aliquot of normal saline is lavaged, returned, and discarded. Another aliquot of normal saline is then lavaged, and the returned fluid is sent off for quantitative culture.

Using invasive sampling techniques to obtain a diagnosis is especially important in trauma patients, who often have fever, leukocytosis, purulent sputum, and radiographic abnormalities as a consequence of the systemic inflammatory response syndrome (SIRS). A study of 43 trauma patients exhibiting all of these symptoms and signs who

Table 3 Diagnostic Techniques Used in Diagnosis of Ventilator-Associated Pneumonia

Diagnostic Technique	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
PSB cultures ($\geq 10^3$ cfu/mL)	82	89	90	89
BAL cultures ($\geq 10^4$ cfu/mL)	91	78	83	87
Microscopic examination of BAL fluid ($\geq 5\%$ intra-cellular organisms)	91	89	91	89

BAL = bronchoalveolar lavage; PSB = protected specimen brush.

underwent BAL found that 20 had culture results consistent with VAP, whereas 23 had bacterial growth amounting to fewer than 10^5 cfu/mL.²⁰ Antibiotics were stopped after culture results in all patients with low or no bacterial growth (average 3.3 days); 65% of patients showed improvement after discontinuance of antibiotics, and there was no difference in mortality between the SIRS group and the VAP group. These findings highlight the need to obtain invasive cultures in the trauma setting in that a high percentage of the patients in this study would have been incorrectly diagnosed as having pneumonia on clinical grounds alone.

Several nonbronchoscopic quantitative sampling techniques are now available, including mini-BAL and blind sampling PSB. These techniques involve blind passage of a catheter or telescoping catheters to a wedged position in the lung. Both mini-BAL and blind sampling PSB are slightly less accurate than their bronchoscopic counterparts, with sensitivities ranging from 58 to 100% and specificities ranging from 66 to 100%.²¹ In addition, these techniques may miss unilateral left-side pneumonia, presumably because blind insertion is more likely to result in wedging of the catheter in the right lung.

Regardless of the culture technique used, previous antibiotic therapy can reduce the chances of obtaining a positive culture. The determining factor appears to be the duration of such therapy. Initiation of antibiotic therapy within the preceding 24 hours decreases the chances of obtaining a positive culture and reduces the number of microorganisms recovered, although these effects are less pronounced with BAL than with other diagnostic techniques; however, in patients who have been receiving antibiotics for more than 72 hours, the sensitivity and specificity of BAL and PSB for the diagnosis of pneumonia are largely unaffected. These findings have clear implications for treating pneumonia in postoperative patients. Specifically, cultures should be accurate in a patient who is in the middle of a 1-week antibiotic course for complicated intra-abdominal infection, but starting antibiotic therapy immediately before obtaining a culture for suspected VAP will adversely affect the ability of the surgeon to diagnose this condition.

CLINICAL PULMONARY INFECTION SCORE

The CPIS quantifies a number of clinical findings suggestive of pneumonia—temperature, WBC count, tracheal secretions, tracheal cultures, oxygenation, chest x-rays, and the presence and progression of infiltrates on x-rays—in an attempt to diagnose pneumonia noninvasively [see Table 4]. A CPIS higher than 6 is associated with a high likelihood of pneumonia in some patient populations. Although some

studies suggest that a CPIS greater than 6 may correlate with VAP, most studies indicate that the CPIS has limited sensitivity and specificity.^{22–24} More recently, the value of pretest probability and modified CPIS to diagnose VAP was assessed by the Canadian Critical Care Trials Group.²⁵ In 740 patients enrolled in a multicenter randomized trial, intensivists prospectively rated the pretest probability of VAP as low, moderate, or high on the basis of clinical judgment. The modified CPIS was calculated without considering culture results. VAP diagnosis was determined by two adjudicators using standardized definitions. The receiver operating characteristic area under the curve for the modified CPIS was not significant (0.47; 95% CI 0.42 to 0.53), meaning that no CPIS threshold was clinically useful. The CPIS was of limited use in the diagnosis of VAP in this and many other studies and should not be used as a risk stratification tool in hospital-acquired pneumonia and/or VAP studies. Additional studies have shown the futility of CPIS use in trauma and burn patients.^{26,27} The main drawbacks of the CPIS are that (1) all of its elements are weighted equally (e.g., the presence of an infiltrate is given the same weight as a WBC count of $11,000/\mu\text{L}$, even though it is substantially more suggestive of pneumonia) and (2) assessment of chest x-rays and sputum production is necessarily subjective, meaning that an equivocal CPIS could lead to an inappropriate treatment decision.

OTHER MODALITIES FOR DIAGNOSING VAP

Although the use of invasive culture methods in conjunction with clinical judgment is the most common approach to diagnosing VAP, there are rare circumstances in which other diagnostic modalities may be useful. The most likely surgical situation in which pneumonia might be diagnosed without invasive cultures involves a patient with empyema in whom a positive purulent fluid culture is obtained at the time of either chest tube placement or thoracentesis. Histopathologic examination of tissue obtained at open lung biopsy that demonstrates the presence of both bacteria and inflammation is diagnostic of VAP. Rapid cavitation of a pulmonary infiltrate in a patient who has a negative workup for both cancer and tuberculosis, although extremely uncommon after operation, is likely to represent pneumonia when it does occur in this setting.

Although not currently of clinical benefit at the bedside, a number of biomarkers have been proposed to be potentially useful for the diagnosis of VAP.^{28,29} To date, none of these have shown adequate sensitivity or specificity to be incorporated into clinical practice, although the use of procalcitonin levels has been shown to reduce exposure to antibiotics in

Table 4 Calculation of Clinical Pulmonary Infection Score

Variable	Finding	Points
Temperature (°C)	≥ 36.5 and ≤ 38.4	0
	≥ 38.5 and ≤ 38.9	1
	≥ 39 or ≤ 36	2
Blood leukocytes (n/μL)	≥ 4,000 and ≤ 11,000	0
	< 4,000 or > 11,000	1
	Plus band forms ≥ 50%	Add 1
Tracheal secretions	Absent	0
	Nonpurulent secretions present	1
	Purulent secretions present	2
Oxygenation (Pao ₂ /F _i O ₂)	> 240 or ARDS*	0
	≤ 240 and no ARDS	2
Pulmonary radiography	No infiltrate	0
	Diffuse (or patchy) infiltrate	1
	Localized infiltrate	2
Progression of pulmonary infiltrate	No radiographic progression	0
	Radiographic progression (after CHF and ARDS excluded)	2
Culture of tracheal aspirate	Pathogenic bacteria cultured in very low to low quantity or not at all	0
	Pathogenic bacteria cultured in moderate or high quantity	1
	Same pathogenic bacteria seen on Gram stain	Add 1

ARDS = acute respiratory distress syndrome; CHF = congestive heart failure; F_iO₂ = fraction of inspired oxygen; Pao₂ = arterial oxygen tension; PAWP = pulmonary arterial wedge pressure.

*Defined as Pao₂/F_iO₂ ≤ 200 and PAWP ≤ 18 mm Hg, with acute bilateral infiltrates.

nonsurgical ICU patients.³⁰ Preliminary data on circulating RNA leukocyte profiles of 85 genes drawn at frequent time intervals were able to diagnose VAP 4 days prior to clinical diagnosis with a sensitivity of 57% and a specificity of 69% in 158 patients following blunt trauma.³¹ This strategy may be of use in further studies if validated in larger-scale trials.

Management

IDENTIFICATION OF PATHOGENS

For effective treatment of pneumonia in the postoperative patient, it is critical to know which organism or organisms are causing the disease. Overall, pneumonia in ICU patients is more frequently caused by gram-negative bacteria than by gram-positive bacteria. The most commonly isolated gram-negative pathogen is *P. aeruginosa* followed by *A. baumannii* (16.3% and 8.4% of total isolates, respectively).³² The most commonly isolated gram-positive pathogen is *Staphylococcus aureus* (24.4% of total isolates). Importantly, more than half of *S. aureus* isolates are methicillin resistant.

It is important to note that the microbes isolated in the first 3 to 4 days of an ICU stay are dramatically different from those isolated later. The pathogens found early (e.g., *S. aureus*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*) are typically sensitive to many classes of antibiotics, whereas the pathogens identified later (e.g., *P. aeruginosa*, *A. baumannii*, methicillin-resistant *Staphylococcus aureus* [MRSA], and *Stenotrophomonas maltophilia*) are more likely to be resistant. In more than 50% of VAP cases, more than one organism is isolated.³³ Isolation of an organism, in itself, does not establish the diagnosis of pneumonia, and colonization can occur at any time during the course of mechanical ventilation. It is

crucial to distinguish infection from colonization: the former calls for aggressive antimicrobial therapy, and the latter need not be treated at all—in fact, inappropriate use of antibiotics to treat colonization may adversely affect outcome. A study of 26 patients undergoing mechanical ventilation demonstrated that 22 were colonized by at least a single bacterial strain during their ICU stay, with 16 being colonized within 5 days after intubation.³⁴ Of these 22 patients, 21 were colonized by aerobes and 15 by anaerobes, and five went on to acquire VAP (three with aerobic pathogens, two with anaerobic pathogens).

The role of anaerobes in VAP is controversial: although they may represent as many as 23% of the isolated strains in patients with VAP (typically in early-onset cases in which aspiration was witnessed), their presence is not associated with an increase in mortality,³⁵ and there is no evidence that antianaerobic therapy changes outcomes in patients with VAP.

The role played by so-called commensal bacteria in the normally sterile lower respiratory tract is also unclear. Approximately 50% of isolates from ventilated patients are from bacterial species that are believed to be nonpathogenic except in immunocompromised patients; however, the significance of commensal bacteria in the airways of immunocompetent patients is unknown. The possible importance of commensal bacteria in the lower respiratory tract was highlighted by a study of 369 patients with VAP, a group comprising all patients diagnosed with the disease over a 10-year period in a mixed medical-surgical ICU.³⁶ The investigators identified 23 cases of VAP (through a combination of PSB and clinical signs) as resulting from a monomicrobial infection involving an organism typically considered to be commensal (most commonly, non-β-hemolytic *Streptococcus*, *Neisseria* species, and coagulase-negative *S. aureus*). Because

the idea that commensal bacteria could cause VAP was, and is, controversial, the diagnosis was reported only if agreed on by three independent experts. Mortality in these patients was not different from that in patients without VAP. At present, the importance of commensal bacteria in the pathogenesis of VAP remains undetermined.

ANTIMICROBIAL THERAPY

Importance of Rapid Initial Treatment

The cornerstone of therapy for hospital-acquired pneumonia is rapid institution of an appropriate broad-spectrum antibiotic regimen. Appropriate initial antimicrobial treatment is typically defined as an antibiotic regimen that is known to possess *in vitro* activity against the identified bacterial species.

The importance of rapid institution of appropriate antibiotic therapy has been highlighted in a number of trials involving postoperative patients. In one such trial, a group of 65 patients in a medical-surgical ICU who had positive BAL cultures and were diagnosed with VAP was retrospectively subdivided into a group that received adequate antibiotic therapy at the time of bronchoscopy and a group that received inadequate therapy.³⁶ Mortality in the adequate-therapy group was 38%, but that in the inadequate-therapy group was 91%. Similar results, albeit with substantially lower mortalities, were obtained in a study from a different medical-surgical ICU involving 113 patients with VAP diagnosed by means of either PSB or BAL.³⁷ Patients receiving inadequate initial antimicrobial therapy had a mortality of 37%, whereas those receiving adequate therapy had a mortality of only 15%.

A link between adequate initial antimicrobial therapy and mortality was also documented in a study of 2,000 consecutive ICU patients, including 793 surgical ICU patients.³⁸ In more than 60% of the 655 patients with documented infections, the respiratory tract was the source of the infection. Of the 655 infected patients, 210 had previously been operated on. Infection-related mortality was 42% in infected patients who initially received inadequate antimicrobial therapy, compared with 18% in those who received adequate therapy. Using a logistic regression model, the investigators found inadequate institution of antibiotic therapy to be the single most important independent determinant of hospital mortality. Similarly, delayed initiation of appropriate antimicrobial therapy has been associated with a fivefold decrease in survival in patients with septic shock.³⁹

Choice of Appropriate Antibiotic

When pneumonia is suspected on the basis of clinical and radiographic signs, there is no way of knowing precisely which bacteria are causing the disease, and culture results are usually not available until 2 to 3 days after a specimen is obtained. In the current era of increasing antibiotic resistance, it is critical to provide broad initial coverage of both sensitive and resistant microorganisms. This is especially important because multidrug-resistant pathogens have been demonstrated to be independent risk factors for inadequate therapy, which must be considered when picking initial antibiotics.⁴⁰ Because resistance patterns vary among countries, among institutions, and even among ICUs within a

single hospital, what constitutes adequate initial antibiotic therapy may be country specific, institution specific, or even ICU specific.^{41,42}

The makeup of the flora causing nosocomial infection tends to evolve as a patient's hospitalization proceeds, with bacterial resistance increasing in the later stages, and this evolution must be taken into account in prescribing the initial antibiotic regimen. Several other factors must be considered as well: (1) the hospital-specific (or, if available, ICU-specific) antibiogram documenting antibiotic resistance, (2) key patient-specific characteristics (e.g., an immunosuppressed liver transplant patient may be susceptible to microorganisms that a previously healthy trauma patient would not be), and (3) the efficacy, toxicity, and lung penetration of the antibiotics. If an antibiotic has poor lung penetration (as is the case with vancomycin and the aminoglycosides), a higher dosage may be needed for treatment of VAP than for treatment of other conditions. In addition, when different classes of drugs possess similar efficacy, those with higher side-effect profiles (e.g., aminoglycosides) should not be used as primary monotherapy.

As a rule, initial antibiotic treatment decisions must be tailored to local antibiograms. In 2005, however, the American Thoracic Society and the Infectious Diseases Society of America published consensus recommendations that outlined an evidence-based strategy for initiating antimicrobial therapy in patients with suspected VAP.⁴³ Patients with early-onset postoperative pneumonia or VAP who have no risk factors for multidrug-resistant pathogens may be treated with ceftriaxone, a quinolone (ciprofloxacin, levofloxacin, or moxifloxacin), ampicillin-sulbactam, or ertapenem. In contrast, patients with late-onset postoperative pneumonia or VAP and those with risk factors for multidrug-resistant organisms must be treated more aggressively. They should be started on combination therapy for gram-negative infections and should receive agents that provide broad coverage of gram-positive infections.

Gram-positive infections The optimal initial antibiotic regimen for gram-positive infections has not been established. A number of antibiotics can effectively treat infections caused by sensitive gram-positive organisms, but the options for treating infections caused by MRSA are limited. Historically, MRSA infection has been treated with vancomycin because no other commonly used antibiotic has been effective. Unfortunately, vancomycin has relatively poor lung penetration. For this reason, linezolid has been proposed as an alternative therapy for nosocomial pneumonia. Two prospective, randomized, multicenter trials comparing vancomycin with linezolid for the treatment of nosocomial pneumonia found the two agents to have similar clinical cure rates and microbiologic success rates in all of the patients studied, suggesting that these agents will be equally effective in the typical patient with gram-positive nosocomial pneumonia.^{44,45}

Two retrospective analyses pooled patients from the two trials just mentioned (see above), comparing vancomycin with linezolid in a subset of patients with MRSA nosocomial pneumonia⁴⁶ and in a smaller subset comprising patients with VAP from MRSA.⁴⁷ Both analyses demonstrated significantly improved survival and clinical cure rates in

patients treated with linezolid. A prospective, randomized trial of 149 patients with suspected MRSA VAP randomized to linezolid or vancomycin demonstrated no difference in clinical cure, survival rate, mean duration of ventilation, hospitalization, ICU stay, or microbiologic response assessed by a second bronchoscopic BAL culture.^{48,49} If vancomycin is used to treat MRSA, it should be given in an initial dose of 15 mg/kg, and trough levels should be maintained between 15 and 20 µg/mL.⁴³

Gram-negative infections The optimal initial antibiotic regimen for gram-negative infection involves starting the patient on combination therapy until culture results can be obtained. Options commonly employed include an antipseudomonal penicillin with a β-lactamase inhibitor, an antipseudomonal cephalosporin, or an antipseudomonal carbapenem combined with either an antipseudomonal fluoroquinolone or an aminoglycoside. If the patient has recently received antimicrobial therapy, the initial antibiotic regimen for VAP should employ a different class of antibiotic to avoid the risk of microbial resistance induced by previous antibiotic use.

A prospective study of 156 patients with VAP in two medical-surgical ICUs showed that treatment with antipseudomonal penicillin with β-lactamase inhibitors yielded better outcomes than treatment with cephalosporins, fluoroquinolones, or aminoglycosides (carbapenems were not given as first-line therapy).⁵⁰ The concept that even within the bounds of what constitutes appropriate initial antibiotic therapy there may be a single “most appropriate” antibiotic is intriguing and worthy of further study. At present, however, no single antibiotic class can be recommended over the others as optimal treatment of gram-negative infections.

Rotation of Antibiotics

VAP developing later in a patient’s ICU stay is more likely to be caused by resistant organisms. An increase in resistant organisms is associated with an increased relative risk of death in patients with VAP. Furthermore, patients who are isolated for infection control purposes because of MRSA experience more preventable adverse events and receive less documented care. Accordingly, scheduled rotation of antibiotics on a protocol basis has been proposed as a technique for hindering the emergence of resistant organisms by manipulating prevailing antibiotic pressures in the hospital environment.

Antibiotic rotation has been studied in both surgical ICUs and surgical wards. A study of 198 patients in a surgical ICU with VAP demonstrated that the type of pathogen did not influence mortality when a rotational antibiotic system was used, leading the authors to conclude that antibiotic rotation negates the impact of bacterial resistance.⁵¹ In addition, a study examined 2,088 patients both in a surgical ICU and in the ward they were transferred to, using a study design in which ICU patients (but not floor patients) were treated for 1 year without an antibiotic rotation protocol and for 1 year with such a protocol.⁵² In the first quarter of the year, patients received ciprofloxacin with or without clindamycin for pneumonia; in the second, piperacillin-tazobactam; in the third, carbapenem; and in the fourth, ceftazidime with or without clindamycin. The study demonstrated that the

overall number of hospital-acquired infections was decreased on the surgical ward in the year that antibiotic rotation was instituted in the ICU. Similarly, the incidence of resistant gram-positive and resistant gram-negative infections was reduced on the surgical ward when antibiotic rotation was practiced in the ICU. Perhaps surprisingly, the decrease in resistance came from patients who were not transferred from the ICU [see Table 5].

Although antibiotic cycling has not been definitively proved to be useful in postoperative patients, antibiotic cycling for VAP in the surgical ICU appears to be a strategy that is relatively easy to implement and that may not only decrease the incidence of resistant infection but also, possibly, decrease the overall incidence of infection.

Deescalation of Antibiotic Therapy

Although early initiation of adequate antimicrobial therapy has been demonstrated to reduce mortality in

Table 5 Differences in Infection-Related Outcomes for Non-ICU Ward Patients with and without ICU Antibiotic Rotation

Outcome	Nonrotation	ICU Rotation	p
Infections	407	213	—
Infected patients	333	161	—
Infections/infected patient	1.3 ± 0.04	1.2 ± 0.05	.1
Infections/100 admissions	19.7	9.8	< .0001
Infected patients/100 admissions	15.9	7.4	< .0001
Infections by service, n (%)			
Transplantation	95 (23)	39 (18)	.2
General surgery	292 (72)	155 (73)	.8
Trauma	21 (5)	19 (9)	.1
rGPC infections	52	34	—
rGPC infections/100 admissions	2.5	1.6	.04
rGNR infections	20	8	—
rGNR infections/100 admissions	1.0	0.4	.03
Time from intervention to discharge (days)	11.3 ± 0.8	13.5 ± 1.0	.1
Total use of antibiotics (days)	11.2 ± 0.9	8.7 ± 0.5	.02
Length of stay (days)	18.8 ± 1.3	26.4 ± 1.7	.0004
Deaths	28	23	—
Deaths/100 admissions	1.3	1.1	.5
rGPC deaths	6	5	—
rGPC deaths/100 admissions	0.3	0.2	.9
rGNR deaths	4	3	—
rGNR deaths/100 admissions	0.2	0.1	1.0

ICU = intensive care unit; rGNR = resistant gram-negative rod; rGPC = resistant gram-positive coccus.

patients with pneumonia, it is inappropriate to continue broad-spectrum agents for the entire treatment period. Instead, antibiotic therapy should be reassessed 2 to 3 days after initiation, when culture results become available, and specifically tailored in accordance with these results. If a single pathogen is identified in a culture, all antibiotics may be stopped except for a single agent to which the microbe is sensitive. The exception to this rule is *P. aeruginosa* infection, which many experts recommend treating with two synergistic agents.⁴³ Although there is little evidence that dual-agent therapy changes outcome, except in cases where VAP is accompanied by bacteremia, the recommendation is made because resistance frequently develops if a patient is treated with a single agent. There is no evidence that maintaining broad-spectrum antibiotic therapy after a positive culture has been obtained improves the outcome; however, there is abundant evidence that inappropriate antibiotic use breeds resistant organisms, which are a potential threat not only to the infected patient but also to nearby patients, who may become infected secondarily.

Unfortunately, even invasive quantitative cultures do not identify all pneumonia-causing organisms. How best to tailor antibiotic therapy in a patient with suspected VAP whose cultures are negative remains somewhat controversial. A common approach divides such patients into two broad groups: (1) those whose condition is improving with broad-spectrum therapy and (2) those whose condition is staying the same or becoming worse. In the first group, antibiotic therapy should be tailored to cover gram-negative (and, possibly, sensitive gram-positive) bacteria. MRSA is fairly easy to culture; thus, if invasive cultures are negative for this organism, vancomycin or linezolid that was started for coverage of resistant gram-positive organisms can be stopped. If there is good evidence of VAP (i.e., CPIS > 6 with both radiographic and sputum evidence of pneumonia), it is reasonable to continue gram-negative coverage for an appropriate period (see below). In the second group, treatment must be individualized. Repeat cultures should be obtained, and a search for nonpulmonary sources of infection, particularly those related to the patient's surgical procedure or to an indwelling central venous catheter, should be initiated. Depending on the clinical situation, all antibiotics may be discontinued, the current antimicrobial regimen may be continued, or a switch to a different class of antibiotic may be made.

Optimal Duration of Antibiotic Therapy

The length of the treatment period for VAP has long been a matter of controversy, thanks largely to the paucity of data on the subject. Historically, 7 to 10 days of treatment has been recommended for sensitive organisms and 14 to 21 days for multiresistant organisms that may be difficult to eradicate from the respiratory tract. Expert opinion also has suggested treating either multilobar or cavitary pneumonia for 14 to 21 days. To date, few recommendations have been published regarding postoperative pneumonia in surgical patients who are not in an ICU. Given that these patients are healthier than critically ill patients, the duration of antibiotic therapy in this population should be similar to or shorter than that in patients with VAP, although many surgeons treat any pneumonia for 10 to 14 days, regardless of the initiating organism.

In an attempt to resolve this issue, a prospective, randomized trial was undertaken that assessed mortality in 401 patients (including surgical patients) treated for VAP with antibiotics in 51 different ICUs.⁵³ All patients received adequate antimicrobial therapy within 24 hours of the diagnosis of VAP. Antibiotics were withdrawn after either 8 or 15 days, regardless of the patient's clinical condition, except in the case of a documented pneumonia recurrence that occurred before the conclusion of the study. At 28 days, mortality in patients treated with antibiotics for 8 days (18.8%) was comparable to that in patients treated for 15 days (17.2%) [see Table 6]. In addition, the two groups were comparable with respect to the overall recurrent infection rate (28.9% and 26.0%, respectively). The only exception to this latter finding arose in patients with infections caused by nonfermenting gram-negative bacilli (e.g., *P. aeruginosa*), in whom 8-day therapy was associated with a recurrence rate of 40.6%, compared with 25.4% for 15-day therapy; this increase in recurrence was not associated with excess mortality. Overall number of mechanical ventilation-free days and organ failure-free days, length of stay, and 60-day mortality were also similar in the two groups. Not surprisingly, patients receiving 8-day therapy had significantly more antibiotic-free days (13.1) than those receiving 15-day therapy (8.7). This increase was associated with a decrease in resistant organisms in patients who acquired recurrent infections: recurrence was associated with a 42.1% incidence of multiresistant pathogens in the 8-day group but a 62.0% incidence in the 15-day group. Such results are consistent with other observational studies documenting an increase in resistant organisms that is directly related to the duration of antimicrobial therapy.⁵⁴

On the basis of the evidence currently available in the literature, it is possible to formulate a treatment approach that is generally appropriate for the treatment of postoperative pneumonia and VAP [see Figure 1]. It should be noted that due to the increasing virulence of MRSA pneumonia (especially in patients with the Pantone-Valentine leukocidin gene), some experts recommend treating this specific organism for 15 days.^{55,56}

ADJUNCTIVE TREATMENTS

Patients with pneumonia (especially those with VAP) frequently have extrapulmonary manifestations of their infection. It is highly likely that patients within the ICU will have at least two criteria of SIRS (tachycardia, fever, tachypnea, elevated WBC count). Patients with two SIRS elements in the setting of known infection meet the American College of Chest Physicians/Society of Critical Care Medicine diagnostic definition of sepsis.⁵⁷ In addition to antimicrobial therapy targeted against the microorganism recovered from their lungs, they may also be candidates for adjunctive therapies for sepsis.⁵⁸

Although steroids are not indicated for pneumonia per se, they may play a role in the treatment of septic shock. There are two large, prospective, randomized trials of steroids (hydrocortisone 50 mg given every 6 hours) in septic shock. The first showed a mortality decrease from 63 to 53% in 300 patients treated with steroids.⁵⁹ A follow-up study with similar methodology showed no benefit to the use of

Table 6 Effect of Duration of Antibiotic Therapy for VAP on Outcomes 28 Days after Bronchoscopy

Outcome	8-Day Regimen (n = 197), n/Total (%)	15-Day Regimen (n = 204), n/Total (%)	Risk Difference between Groups (90% CI) (%)
Death from all causes			
All patients	37/197 (18.8)	35/204 (17.2)	1.6 (–3.7 to 6.9)
Nonfermenting GNB	15/64 (23.4)	19/63 (30.2)	–6.7 (–17.5 to 4.1)
MRSA	6/21 (28.6)	5/21 (23.8)	4.8 (–13.9 to 23.4)
Other bacteria	16/112 (14.3)	11/120 (9.2)	5.1 (–0.7 to 10.9)
Recurrence of pulmonary infection			
All patients	57/197 (28.9)	53/204 (26.0)	2.9 (–3.2 to 9.1)
Superinfection	39/197 (19.8)	38/204 (18.6)	1.2 (–4.3 to 6.6)
Relapse	33/197 (16.8)	23/204 (11.3)	5.5 (0.7 to 10.3)
Nonfermenting GNB	26/64 (40.6)	16/63 (25.4)	15.2 (3.9 to 26.6)
Superinfection	13/64 (20.3)	8/63 (12.7)	7.6 (1.1 to 14.2)
Relapse	21/64 (32.8)	12/63 (19.0)	13.8 (7.8 to 19.7)
MRSA	7/21 (33.3)	9/21 (42.9)	–9.5 (–30.1 to 11.1)
Superinfection	6/21 (28.6)	5/21 (23.8)	4.8 (–8.8 to 18.3)
Relapse	3/21 (14.3)	4/21 (19.0)	–4.8 (–9.9 to 0.4)
Other bacteria	24/112 (21.4)	28/120 (23.3)	–1.9 (–9.5 to 5.6)
Superinfection	20/112 (17.9)	25/120 (20.8)	–3.0 (–8.2 to 2.2)
Relapse	9/112 (8.0)	7/120 (5.8)	2.2 (–1.3 to 5.7)
	Mean n (SD)		Mean Difference (95% CI) (%)
Antibiotic-free days			
All patients	13.1 (7.4)	8.7 (5.2)	4.4 (3.1 to 5.6)
Nonfermenting GNB	12.0 (7.4)	7.5 (5.4)	4.5 (2.2 to 6.7)
MRSA	12.9 (7.0)	4.9 (5.7)	8.0 (4.6 to 12.1)
Other bacteria	13.7 (7.5)	10.0 (4.6)	3.7 (2.1 to 5.3)

GNB = gram-negative bacillus; MRSA = methicillin-resistant *Staphylococcus aureus*; VAP = ventilator-associated pneumonia.

hydrocortisone following septic shock in 498 patients treated with and without steroids.⁶⁰ One reason for the marked difference in results between these studies was the acuity of the patients in the study because baseline mortality was twice as high in the first study. In patients who have refractory shock from pneumonia-induced sepsis despite adequate fluid resuscitation, steroids may play a role as an adjunctive therapy but should be considered only in patients with a high mortality and refractory septic shock.

TREATMENT FAILURE

A 2004 study of 71 patients with ICU-acquired pneumonia in five medical-surgical ICUs found that 62% of patients did not respond 3 days after therapy was initiated.⁶¹ No cause of treatment failure could be identified in one third of the cases; in the remaining two thirds, the most common causes were inappropriate treatment (23%); concomitant infection (27%); misdiagnosis of infection, with the pulmonary disease being of noninfectious origin (16%); and superinfection (14%). When treatment fails, the patient should be reevaluated to look for a nonpulmonary source of fever, a noninfectious causative condition, or a pneumonia caused by organisms that are resistant to the empirical antibiotic regimen. Aerosolized antibiotics may have a role to play as adjunctive therapy in patients with multidrug-resistant pneumonia who do not respond to intravenous antibiotics.

Discussion

PREVENTION OF PNEUMONIA AFTER OPERATION

Before undergoing elective surgical procedures, patients should be instructed about taking deep breaths and ambulating

postoperatively (unless there is a medical contraindication to doing so). Such instruction is especially important in patients who are at high risk for pneumonia after operation. This group includes patients scheduled for abdominal aortic aneurysm repair or thoracic procedures, those older than 60 years, those undergoing general anesthesia, those whose functional status is poor, those with greater than 10% weight loss, those on long-term steroid therapy, those with COPD, smokers, those with abnormally low or high BUN levels, and those receiving more than 4 units of blood preoperatively.^{2,62} Patients who are also at high risk but are not candidates for preoperative respiratory instruction include those undergoing emergency surgical intervention, those with impaired sensoria, and those with a history of cerebrovascular accident with residual neurologic deficit (although, depending on the type of deficit, this patient population may benefit from preoperative teaching as well).

Incentive spirometry is valuable for preventing pneumonia after operation and is a cost-effective adjunct to early ambulation. It benefits a wide range of patients but is especially effective in moderate-risk and high-risk patients, who should receive extra attention in ensuring compliance with this simple intervention. Although chest physiotherapy has been proposed as a means of potentially decreasing postoperative pneumonia, a meta-analysis of 14 published studies assessing the usefulness of this modality after upper abdominal procedures did not support its routine use.⁶³

Like many other infections in critically ill patients, VAP is often preventable. Well-designed studies have found numerous interventions to be effective in lowering the incidence of VAP.⁶⁴ Some of these interventions are as simple as positioning the patient appropriately or educating health care workers about risk factors for VAP.

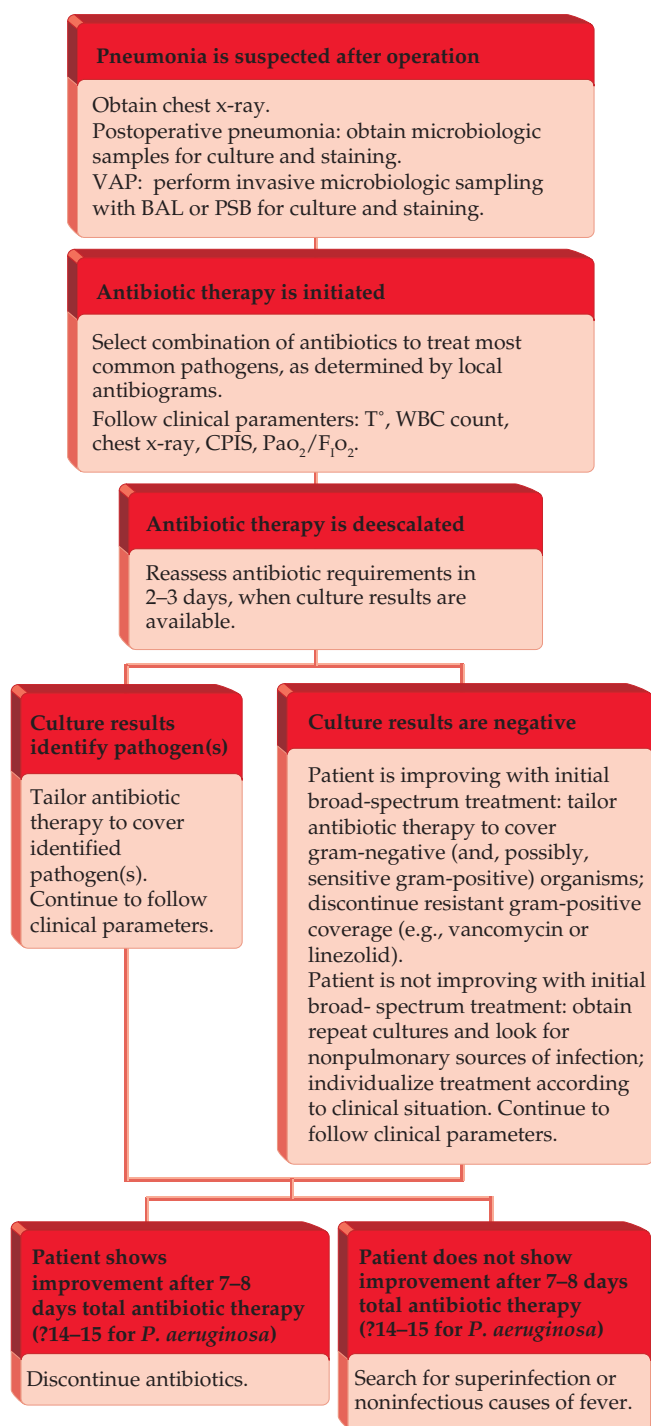


Figure 1 Algorithm outlining the recommended approach to antibiotic treatment of suspected pneumonia after operation. BAL = bronchoalveolar lavage; CPIS = clinical pulmonary infection score; Fio₂ = fraction of inspired oxygen; Pao₂ = arterial oxygen tension; PSB = protected specimen brush; T = temperature; VAP = ventilator-associated pneumonia; WBC = white blood cell.

Hand Hygiene

Appropriate hand hygiene is a simple but underused method of preventing nosocomial infection. Lack of attention to hand hygiene has been a persistent problem world-

wide for decades, and physicians often have the poorest compliance. The alcohol foams and gels currently available are more effective than hand washing in killing the bacteria present on the hands and take substantially less time to use, improving compliance with hand hygiene in the ICU.⁶⁵ Such preparations now represent the hand hygiene method of choice in most cases and should be readily available throughout the ICU. Hands that are visibly dirty or are soiled with blood or body fluids should still be washed with antimicrobial soap and water, however. Appropriate hand hygiene practices should be followed both before and after contact with a patient who has an endotracheal tube or tracheostomy in place, regardless of whether gloves are worn. In addition, hand decontamination is required before and after contact with any respiratory device that is used on a mechanically ventilated patient.⁶⁵

Gloves should be worn for handling respiratory secretions or objects contaminated with such secretions. They should be changed between contacts with different patients, after handling respiratory secretions. In addition, gloves should be changed between contacts with a contaminated body site and the respiratory tract or any portion of the ventilator circuit on the same patient. Gowns are also recommended when soiling with respiratory secretions is anticipated; they should be removed after the soiling occurs and before any contact with other ICU patients.

Patient Positioning

Aspiration of upper airway secretions occurs in healthy adults as well as in ill ones. It is, however, a matter of much greater concern in critically ill patients with decreased host defenses, who are at increased risk for VAP. Maneuvers to reduce aspiration of gastric contents therefore have the potential to decrease the incidence of VAP. Because the supine position is associated with an increased risk of aspiration (especially if the patient is receiving tube feedings via a nasogastric tube), placing the patient in a semirecumbent position—via the simple expedient of raising the head of the bed to an angle of 30° to 45° or greater—is recommended as a means of possibly preventing VAP (if not medically contraindicated).

A prospective, randomized trial involving 86 patients in two ICUs (neither of them surgical) was stopped at the first interim analysis because of the significant difference in the incidence of VAP between semirecumbent patients and supine patients.⁶⁶ The incidence of both clinically suspected VAP and microbiologically proven VAP was drastically reduced in patients positioned with the head of the bed at a 45° angle (from 34% to 8% and from 23% to 5%, respectively). Enteral feeding was also independently associated with the risk of VAP: supine patients receiving enteral feedings had a 50% chance of acquiring VAP. A subsequent prospective, randomized trial of 109 patients found that a target backrest elevation of 45° was not achieved 85% of the time, and the actual treatment position (28°) did not prevent the development of VAP compared with the standard position (10°).⁶⁷

The supine position has been identified as an independent risk factor for VAP in other observational studies of ICU patients as well. In addition, patients who require transport from the ICU are at substantially higher risk for VAP than those who do not (24.2% versus 4.4%).⁶⁸ It is possible that the

VAP rate is increased because patients requiring transport are sicker at baseline, but it is also possible that the rate is higher in this group partly because patients are supine for much or all of their transport time.

Because static bed rest is known to increase the risk of pulmonary (and nonpulmonary) complications, it has been theorized that postural oscillation and rotation may prevent VAP. Specialized kinetic beds are available that provide continuous movement and are capable of reducing pulmonary complications in surgical patients. A study of 106 blunt trauma patients in a surgical ICU demonstrated a significant decrease in VAP in patients randomly selected to undergo continuous postural oscillation.⁶⁹ A study of 65 surgical patients immobilized because of head injury or traction showed a nonstatistical trend toward a decreased risk of pneumonia in patients treated with kinetic beds.⁷⁰ Finally, a study of 69 liver transplant patients randomly assigned to either continuous lateral rotation or a conventional bed found that the incidence of lower respiratory tract infections was decreased in the study group, as was the length of time to the development of infection; however, the duration of mechanical ventilation and length of stay were unchanged.⁷¹

Overall, there appears to be a trend toward decreased VAP in surgical patients treated with kinetic beds. In addition, various accompanying nonpulmonary complications can also be prevented by this treatment (e.g., decubitus ulcers). Accordingly, kinetic beds should be used in surgical patients who are expected to have a prolonged ICU course.

Choice of Feeding Route

Although elevation of the head of the bed reduces aspiration, it does not prevent gastroesophageal reflux. Because gastric overdistention is also associated with an increased risk of aspiration, there has been considerable interest in identifying a route of feeding that is associated with a decreased incidence of VAP. This issue is directly relevant to the postoperative setting, in which many patients, as a consequence of the surgical procedure, experience ileus, which is often exacerbated by narcotics given for pain relief. The generally appropriate reluctance to feed a patient with a large gastric residuum in the ICU setting should be balanced against the desire to provide adequate nutrition as soon as is practicable after an operation, as well as against the multiple advantages of enteral feeding over parenteral feeding. Accordingly, the timing for initiating feedings postoperatively must be individualized on the basis of each patient's situation and condition. In addition, whereas feeding a supine patient greatly increases the risk of VAP, there is no documented benefit to postpyloric feeding or to using smaller nasogastric tubes⁷² and no clear recommendations can be made regarding how best to feed a postoperative patient enterally.

Minimization of Endotracheal Intubation

Extended mechanical ventilation is a major risk factor for VAP; it follows, then, that decreasing or eliminating the need for an endotracheal tube has the potential to lower the incidence of VAP. There are two major strategies by which this goal can be accomplished: (1) earlier extubation (i.e., removing an endotracheal tube when it is no longer needed)

and (2) noninvasive ventilation (i.e., continuing ventilatory support without the presence of an endotracheal tube). In addition, the route of intubation (oral versus nasal) can influence the development of pneumonia.⁷³

Although the optimal mode of weaning has not been definitively determined, it is clear that many patients are kept intubated even when they no longer require mechanical ventilation. The use of a weaning protocol, a sedation protocol, or both has been shown to reduce the duration of mechanical ventilation. In addition, daily interruption of sedation until a patient is awake has been demonstrated to decrease the number of ventilator days in a medical ICU population.⁷⁴ Importantly, a randomized, controlled trial of 336 patients demonstrated that the combination of a spontaneous awakening trial and a spontaneous breathing trial led to decreased time on the ventilator and ICU length of stay as well as decreased mortality for 1 year compared with a spontaneous breathing trial with "sedation per usual care."⁷⁵ This approach has not been extensively studied in the surgical ICU, where the issue is complicated by the greater need for postoperative narcotics. Regardless of the technique or protocol employed, patients should be assessed daily to determine whether ventilatory support is still necessary. Extubated patients have a substantially lower incidence of postoperative pneumonia than patients with an endotracheal tube in place.

The presence of an endotracheal tube in itself, independent of the need for mechanical ventilation, also appears to be a risk factor for VAP. The tube hinders both airway reflexes and coughing, allowing secretions that accumulate above the tube to enter the airways over time and serve as a nidus of infection. This problem is eliminated in patients who are ventilated noninvasively with bilevel positive airway pressure (BiPAP). Multiple studies have found noninvasive ventilation to be associated with lower pneumonia rates and mortalities than conventional ventilation. However, these studies were done in medical ICUs, predominantly on patients with COPD exacerbations, and it is unclear whether similar results are achievable in patients with postoperative respiratory failure.

Reintubation is also an independent risk factor for the development of VAP.⁷⁶ However, fear of the potential adverse consequences of reintubation should not prevent an awake patient who passes a spontaneous breathing trial from being extubated. Many postoperative patients who are extubated and have unexpected ventilatory problems can be managed without reintubation on BiPAP. In addition, although it is unclear what the correct percentage of extubation attempts that require reintubation would be, it is clear that the number is not zero. The decision to extubate is, in a way, comparable to the decision to perform an appendectomy. If every patient on whom an appendectomy is done has appendicitis, it is likely that too few operations are being done and that some patients are being allowed to experience a ruptured appendix needlessly. Similarly, if every patient who is extubated postoperatively does well, it is likely that too few extubations are being done and that some patients are being kept intubated inappropriately and thus experiencing preventable morbidity.

Nasal intubation increases the risk of sinusitis, which, even though only 10% of patients with opacified sinuses have recoverable bacteria, is associated with an increased incidence of VAP.⁷⁷ It is not clear whether sinusitis causes VAP or merely represents a marker of patients who are at higher risk for pneumonia. In either case, given the association between nasotracheal intubation and increased infection rate and mortality, nasotracheal intubation should not be considered a first-line method of obtaining airway control.

Ventilator Management

Although, in theory, ventilator tubing, suction catheters, and humidification systems could all play a role in the development of pneumonia, none of them have been convincingly shown to have an impact on VAP rates. Condensate in the ventilator tubing can become contaminated, but multiple randomized trials have demonstrated that routinely changing ventilator circuits in patients with respiratory failure does not lower the VAP rate.⁷⁸ Circuits should be changed when they are visibly soiled with vomit or blood or are malfunctioning. In addition, condensate should periodically be drained and discarded.

Heat moisture exchangers (HMEs) are frequently used instead of heated water humidification systems because HMEs are relatively inexpensive and require neither electricity nor active heating elements. HMEs minimize the formation of condensate within ventilator circuits, thereby, in theory, potentially decreasing VAP rates. One study found HMEs to yield lower infection rates than humidification systems,⁷⁹ but at present, there is no clear consensus in favor of either type of device. Either an open single-use catheter system or a closed multiuse catheter system may be used for suctioning. Although open systems are associated with increased environmental contamination, current evidence suggests that the incidence of VAP is not significantly affected by the type of suctioning system used.⁸⁰ In addition, when closed systems are used, routine changing of inline suction catheters does not reduce the incidence of VAP,⁸¹ nor is there convincing evidence that more frequent suctioning prevents VAP.

Ventilator Weaning

Given that the rate of VAP increases with increasing duration of mechanical ventilation, it is imperative to provide all attempts at ventilator weaning in the ICU as a VAP preventive strategy. Daily interruption of sedation, that is, spontaneous awakening trials, and daily spontaneous breathing trials are therefore recommended.^{75,82} It has been documented that a “wake up and breathe” protocol that pairs daily spontaneous awakening trials (i.e., interruption of sedatives) with daily spontaneous breathing trials results in better outcomes for mechanically ventilated patients in the ICU.

Prevention of Oropharyngeal Colonization

Oropharyngeal colonization can be decreased by means of either antiseptic therapy or a comprehensive oral hygiene program. Oral chlorhexidine gluconate (0.12%), given before and after cardiac procedures, has proved effective in

preventing postoperative pneumonia.⁸³ In a prospective, randomized, blinded trial, patients receiving a chlorhexidine rinse, which has documented activity against both aerobes and anaerobes, experienced a 69% decrease in the incidence of postoperative pneumonia. This decrease was not associated with a change in antibiotic resistance patterns after operation and was accompanied by a reduction in postoperative antibiotic use. Similar results were demonstrated in a study in the surgical ICU that demonstrated that an oral care protocol combining tooth brushing and twice-daily application of chlorhexidine gluconate decreased the VAP rate from 5.2 per 1,000 ventilator days to 2.4 per 1,000 ventilator days.⁸⁴ These results are consistent with a recent meta-analysis demonstrating that topical chlorhexidine is beneficial in preventing VAP, with the most significant benefit present in cardiac surgery patients.⁸⁵ An additional randomized trial with 2% chlorhexidine solution four times daily versus normal saline ($n = 207$) confirmed a VAP reduction (7 versus 21 per 1,000 ventilator days, $p = .04$), and a meta-analysis of two studies using 2% chlorhexidine revealed an overall relative risk of VAP for patients in the chlorhexidine group of 0.53 (95% CI 0.31 to 0.90; $p = .02$).⁸⁶ Interestingly, the addition of electric tooth brushing to oral care with 0.12% chlorhexidine was not effective for VAP prevention.⁸⁷

Drainage of Subglottic Secretions

Secretions that pool above an inflated endotracheal cuff may be a source of aspirated material that results in VAP. Specially designed endotracheal tubes are available that have a separate opening above the cuff of the tube to allow either continuous or intermittent suctioning and drainage of secretions that accumulate in the subglottic space.

A meta-analysis of five prospective, randomized trials evaluating the role of subglottic secretion drainage in 896 patients demonstrated that subglottic secretion drainage shortened the duration of mechanical ventilation and ICU stay and delayed the onset of pneumonia by 6.8 days and suggested that this could be an effective strategy in patients intubated for more than 72 hours.⁷⁶ Subsequent to the publication of this meta-analysis, however, the largest randomized trial of subglottic secretion drainage was performed in 714 cardiac surgery patients.⁸⁸ No statistically significant decrease in overall VAP rates was noted with continuous aspiration of subglottic secretions, although there was a decrease in hospital antibiotic use in the experimental group. For patients who required mechanical ventilation for more than 48 hours, VAP rates, ICU length of stay, and hospital antibiotic use were all decreased in patients treated with continuous aspiration of subglottic secretion, although this was not associated with an improvement in mortality.

In addition, a randomized trial of 280 patients in a medical-surgical ICU combining subglottic secretion drainage with an endotracheal tube with a polyurethane cuff demonstrated a decrease in both early and late VAP compared with a conventional endotracheal tube with a polyvinyl cuff without subglottic secretion drainage.⁸⁹ Most recently, a prospective trial at four French centers randomized adult patients intubated with a tracheal tube allowing drainage of subglottic secretions to undergo intermittent subglottic

secretion drainage (SSD) ($n = 169$) or not ($n = 164$). VAP, diagnosed by quantitative culture of distal airways, occurred in 14.8% of SSD patients versus 25.6% of control patients ($p = .02$, relative risk reduction 42.2%, 95% CI 10.4 to 63.1) but had no impact on the duration of mechanical ventilation or ICU mortality.⁹⁰

At present, use of subglottic secretion drainage is hindered by logistical difficulties. These specialized tubes require routine maintenance in the ICU to ensure that the suction lumen remains patent. In addition, any decision to place the tubes in patients undergoing surgery must also be made preoperatively and communicated to the anesthesiologist or emergency department physician before the patient is intubated.

Silver-Coated Endotracheal Tubes

There are significant data on preventing catheter-related bloodstream infection with antiseptic or antibiotic-impregnated catheters; however, until recently, there were no data as to whether a similar approach would be beneficial in preventing VAP.

Silver has broad-spectrum antimicrobial activity and has been used topically to prevent infections after thermal injury. Both animal and in vitro studies demonstrate that silver-coated endotracheal tubes are effective in decreasing bacterial colonization and adherence compared with standard tubes.⁹¹ Based on the antimicrobial efficacy of silver and an extensive clinical history without significant toxicity, a recent prospective, randomized trial compared the efficacy of silver-coated endotracheal tubes with that of conventional endotracheal tubes for the prevention of VAP in patients requiring mechanical ventilation for more than 24 hours (NASCENT trial).⁹² A total of 766 patients received endotracheal tubes coated on the inner and outer lumen with silver, whereas 743 patients were randomized to receive control endotracheal tubes. Patients who had emergency surgery or trauma made up 10% of the enrolled patient population, and over 30% of patients had their endotracheal tube placed in the operating room. Patients who received the silver-coated tubes had decreased incidence of VAP (7.5% versus 4.8%) and delayed occurrence of VAP. No statistically significant differences were noted in the duration of ICU or hospital stay or mortality. It should be noted that one controversial aspect of the study is the fact that 30% of positive BALs recovered organisms not typically considered to be pathogenic, and when the data were analyzed without these organisms, the p value between the silver-coated endotracheal tubes and control tubes increased to .06.⁹³

Despite this, an accompanying editorial to this trial suggested that silver-coated endotracheal tubes should “probably” be used in trauma patients, in light of the fact that the benefit seen with the tubes occurred during the first 10 days of mechanical ventilation and that they would most likely be effective in a high-risk patient population.⁹⁴ In addition, a cost-effectiveness analysis concluded that despite the increased cost of routinely placing silver-coated endotracheal tubes, their efficacy more than outweighed the cost, and they could potentially be a cost-saving strategy for preventing VAP.⁹⁵

Pharmacologic Approaches

Widely varying study results and significant infection control concerns have made SDD an extremely controversial practice. The term is actually a misnomer in that successful SDD protocols employ a combination of systemic antibiotics and nonabsorbable antibiotics given both orally and via a nasogastric tube. This is an important point: meta-analyses of SDD studies generally show that SDD is not effective if systemic antibiotics are not included.^{96,97}

Multiple recent meta-analyses examining the effect of SDD show decreased mortality in patients receiving SDD.^{98–100} A 2007 meta-analysis of 3,331 patients who received SDD including both parenteral and enteral antibiotics demonstrated a 26% decrease in overall mortality.⁹⁹ A follow-up meta-analysis from the same group examining 9,473 patients demonstrated a marked decrease in gram-negative respiratory tract infections with an odds ratio of 0.11 (95% CI 0.06 to 0.20) and a small decrease in gram-positive respiratory tract infections with an odds ratio of 0.52 (95% CI 0.34 to 0.78).¹⁰¹ These findings were consistent with a Cochrane meta-analysis that included 36 trials involving 6,922 patients.¹⁰⁰ In a subgroup analysis of 17 trials of 4,295 patients receiving both topical and systemic antibiotics, SDD decreased mortality with an odds ratio of 0.78 (95% CI 0.68 to 0.89), and respiratory infection was markedly decreased with an odds ratio of 0.35 (95% CI 0.29 to 0.41).

There is significant concern, however, that even if SDD is effective in ICUs with low endemic rates of vancomycin-resistant enterococcus, MRSA, and multidrug-resistant gram-negative bacteria (as is common in Europe), it might lead to enhanced selection of these and other resistant organisms in ICUs where they are endemic (as is common in the United States).¹⁰² A recent study in 13 ICUs demonstrated that even though SDD was effective,¹⁰³ intestinal colonization with gram-negative bacteria resistant to ceftazidime, tobramycin, or ciprofloxacin increased from 5, 7, and 7%, respectively, prior to the institution of SDD or selective oropharyngeal decontamination to 15, 13, and 13%, respectively, after treatment.⁹⁶ Furthermore, resistance levels in the respiratory tract were not more than 6% for all three antibiotics prior to the study but were greater than 10% for all three after initiating SDD. In addition, a study in a surgical ICU in Austria demonstrated an increase in oxacillin resistance in *S. aureus* isolates from 17 to 81% over a 5-year period where SDD was practiced.⁹⁷ A 6-year study of 360 trauma patients receiving SDD also reported a moderate increase in the development of resistant organisms.¹⁰⁴

Owing to infection control concerns, SDD is not widely accepted in the United States. It is noteworthy that routine use of SDD to prevent VAP is not recommended in most guidelines for preventing pneumonia or sepsis.^{21,58,104}

Another pharmacologic approach that has been proposed as a means of preventing VAP is avoidance of drugs that raise stomach pH, on the assumption that these agents may lead to bacterial overgrowth and, eventually, to VAP. The available data, however, indicate that this assumption is incorrect. A prospective, randomized trial involving 1,200 patients in 16 ICUs that compared the H_2 receptor antagonist ranitidine with sucralfate found no difference in the VAP rate between the ranitidine group and the sucralfate

group.¹⁰⁵ Notably, the rate of clinically important GI bleeding was higher in the sucralfate group. On the basis of this definitive study, drugs that raise stomach pH should not be avoided for infection control reasons.

Education of Health Care Workers

Obviously, to implement interventions that prevent VAP, health care workers must be aware that such interventions exist. Although ICU directors clearly play a major role in the overall direction of care, direct daily care of patients undergoing mechanical ventilation is provided by respiratory therapists and nurses, and these professionals stand to benefit most from educational efforts.

Multiple recent publications attest to the efficacy of educational programs in preventing VAP.^{106–108} In one of these, a program was initiated that was directed toward respiratory care practitioners and nurses in five ICUs at a single academic center.¹⁰⁶ Initially, 114 respiratory therapists and 146 nurses took a 20-question pretest to determine their level of knowledge about methods of preventing VAP. They then received a 10-page self-study module that provided information about VAP and outlined prevention strategies. Both immediately after the intervention and 6 months later, participants took a posttest that was identical to the original test. Test scores improved at both time points, demonstrating that the information taught was both learned and retained.

In the 12 months before implementation of the education program, 191 episodes of VAP were identified (12.6 per 1,000 ventilator days). In the 12 months following completion of the program, however, only 81 episodes of VAP (5.7 per 1,000 ventilator days) were identified [see Figure 2]. The greatest success in VAP prevention was achieved in the surgical/trauma/burn ICU, where VAP rates decreased from 18.1 to 6.6 per 1,000 ventilator days. These results

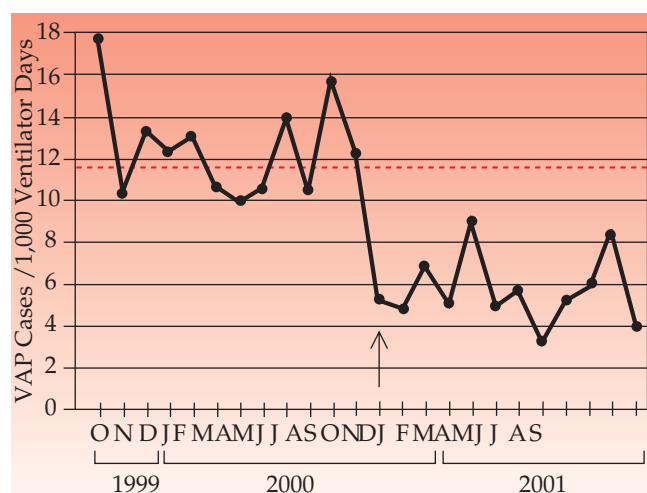


Figure 2 The influence of an education program for health care workers on the monthly rate of ventilator-associated pneumonia (VAP) per 1,000 ventilator days between October 1999 and 2001. The dotted line represents the VAP rate cited by the National Nosocomial Infection Surveillance system for intensive care units in the United States; the arrow represents the point at which the education program was initiated.

highlight the importance of disseminating information on VAP prevention to the health care workers who are providing the day-to-day care for patients at risk for VAP.

VAP Bundles

Pneumonia in the postoperative setting cannot be eliminated, but its incidence can be substantially decreased by following evidence-based prevention guidelines. Unfortunately, compliance with such guidelines is far from uniform.

Although multiple interventions have been demonstrated to prevent VAP, it is logical to assume that a strategy that stresses compliance with multiple evidence-based practices would be superior to a strategy focusing on a single intervention. This has led to the increasingly common practice of using bundles to prevent VAP. A recent review of VAP bundles analyzed four publications that included at least three components of the Institute for Healthcare Improvement (IHI) ventilator bundle (head of the bed elevation, sedation “holiday,” daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, and deep vein thrombosis prophylaxis).¹⁰⁹ Each article examining VAP bundles included a mix of surgical and medical patients. Each successfully brought down VAP rates. Although the authors could not rule out publication bias (because all studies showed an improvement with VAP bundles), implementing VAP bundles appears to be an effective method of decreasing VAP rates. It should be recognized, however, that not all of the elements of the IHI ventilator bundle are associated with VAP reduction, and some methods that have been definitively demonstrated to be effective in VAP reduction are not included in the current ventilator bundle.¹¹⁰ A European care bundle for VAP prevention was recently developed and includes the following: nonventilatory circuit changes unless specifically indicated, alcohol hand hygiene, appropriately educated and trained staff, incorporation of sedation control and weaning protocols into patient care, and oral care with chlorhexidine.¹¹¹

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19 INTRA-ABDOMINAL INFECTION

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Recognition and Management of Intra-abdominal Infection

The basic principles of rapid diagnosis, timely physiologic support, and definitive intervention for intra-abdominal infections have remained unchanged over the past century. Specific management of these conditions, however, has been transformed as a result of numerous advances in technology. Improved radiologic and laboratory techniques have led to more precise preoperative diagnoses, and newer procedures have led to treatment algorithms that cause less morbidity and permit faster recovery. Whereas the pathophysiology of these infections remains largely unchanged, their management is now marked by an ever-growing complexity. It is no longer true that the diagnosis of intra-abdominal infection, even in association with a perforated viscus, necessitates urgent surgical exploration, but it remains the case that decisions regarding the ultimate course of action for any individual patient are solely the responsibility of the surgeon.

Clinical Evaluation

HISTORY

The general approach to a patient suspected of having an intra-abdominal infection is much like that to a patient with any other acute surgical condition. Specific approaches to various intra-abdominal infections are addressed in more detail elsewhere [see *Infections of the Upper Abdomen* and *Infections of the Lower Abdomen*, below].

The first step is an accurate history. The acuteness and severity of the presenting symptoms may help localize the origin of the infection and allow appropriate triage of these patients. The specifics of the presenting episode (e.g., the onset, location, and nature of the pain and any changes in bowel habits) are crucial, as are the patient's medical and surgical histories. The question of whether a patient has presented with similar symptoms before (particularly if those symptoms led to a diagnosis) is important, and many patients arrive for medical treatment with a strong (and frequently correct) concept of the nature of their disease.

* The authors and editors gratefully acknowledge the contributions of the previous authors, Jeffrey S. Barkun, MD, FACS, Robert Smith, MD, Tae Chong, MD, and George Tzimas, MD, to the development and writing of this chapter.

PHYSICAL EXAMINATION

Once the history has been obtained, a thorough physical assessment is performed, with the emphasis on the abdomen, the pelvis (including the vagina), and the rectum. Inspection must include a careful search for scars indicating previous operations, given that any laparoscopic procedure can be undertaken by way of a variety of trocar sites. Percussion is valuable for assessing tenderness, as well as for differentiating abdominal distention caused by intraluminal gas or free air (signaled by tympany) from that caused by fluid in the peritoneum (signaled by dullness).

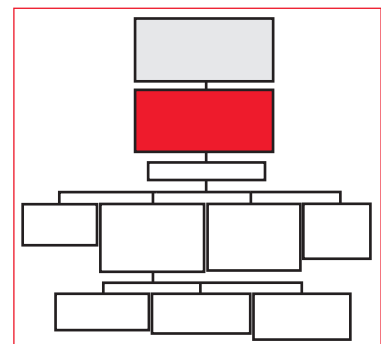
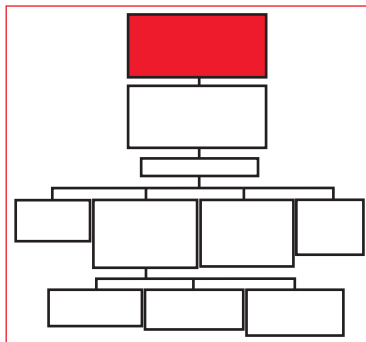
Proper assessment of the abdomen for tenderness via palpation can be learned only through extensive experience. Gaining the patient's trust is fundamental. Palpation should not be performed in a uniform manner from patient to patient; rather, the amount of tenderness present ought to be judged by the degree of pressure or indentation required to cause a given patient significant discomfort. In the setting of severe abdominal pain, elicitation of rebound tenderness by means of deep palpation followed by rapid release of pressure usually does not improve diagnostic accuracy or alter subsequent evaluation and should therefore be discouraged. Finally, administration of small doses of narcotics to patients with abdominal pain is unlikely to alter an experienced examiner's diagnostic ability for the worse.

Occasionally, a young patient whose history and physical examination (including vital signs) fit the classic clinical picture of appendicitis may be taken to the operating room without further assessment. Practically speaking, however, almost all patients with significant intra-abdominal infections undergo blood tests, and most also undergo some sort of radiologic evaluation.

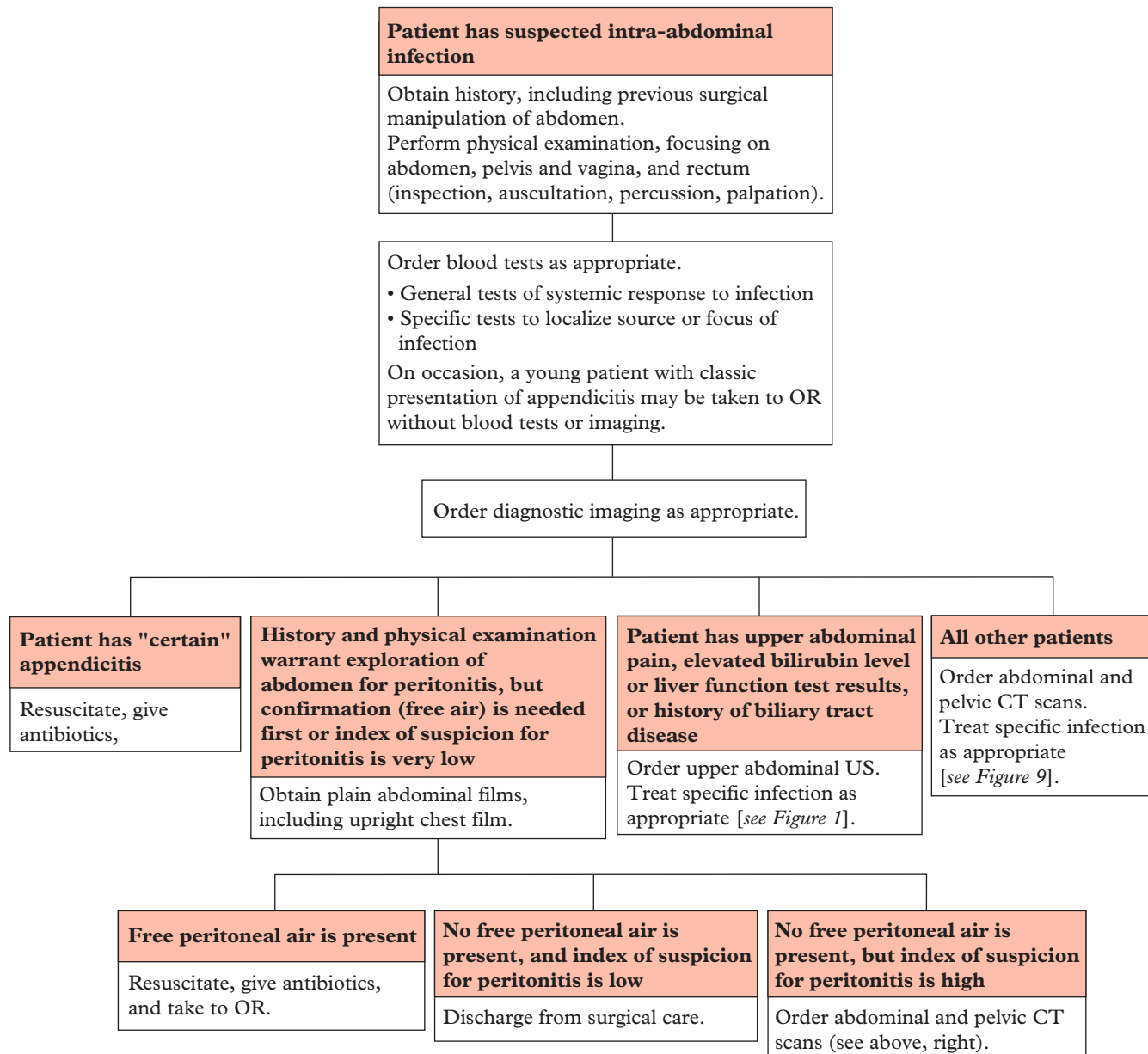
Investigative Studies

LABORATORY TESTS

Blood work can be divided into two categories: (1) general tests designed to assess the systemic response to infection and (2) specific tests designed to localize the source or site of infection. The former category includes serum chemistries and hematology studies. The latter category commonly includes amylase and lipase concentrations (in patients



Recognition and Management of Intra-abdominal Infection



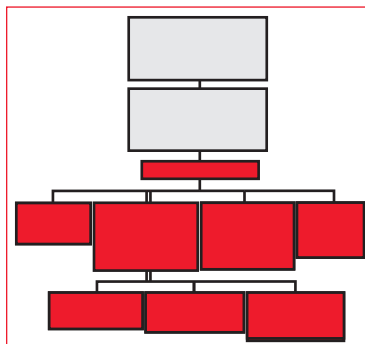
suspected of having pancreatitis), bilirubin levels and liver function tests (to evaluate hepatic or biliary tract disease), and lactate levels (when ischemic bowel is suspected). These tests are discussed further elsewhere, in connection with specific infections (see below). Urinalysis, of course, is necessary whenever urinary tract infection or urolithiasis is a possibility.

DIAGNOSTIC IMAGING

The use of various radiologic studies in the diagnosis of intra-abdominal infection continues to evolve rapidly. Outside the setting of trauma, it is now very rare for patients to undergo operations or other major interventions without first undergoing imaging. At one time, plain films of the abdomen (including an upright chest film) were routinely obtained whenever a significant intra-abdominal infection was suspected, principally to detect free peritoneal air, bowel obstruction, or fecaliths. Abdominal plain films proved to lack sensitivity, specificity, and anatomic definition in this setting and consequently have, in many cases, been supplanted by abdominal and pelvic computed tomography (CT). There are, however, two circumstances in which plain films of the abdomen remain a reasonable first study for a patient with suspected peritonitis: (1) when the surgeon has almost decided, on the basis of the history and physical examination, to explore the patient yet needs confirming evidence of perforation (i.e., free air) and (2) when the index of suspicion for peritonitis is so low that the plain film studies are intended to rule out an unexpected positive finding and will not be followed by an abdominal CT scan if negative.

Ultrasonography for intra-abdominal infection is useful only for focused examination of specific organ systems; it is inferior to CT for generalized surveillance of the abdomen because of the inability of sound waves to penetrate gas in the bowel. By far the best-delineated use of ultrasonography is in the diagnosis of liver and biliary tract disease, for which its ability to demonstrate cholelithiasis makes it superior to CT and for which it should almost always be the first radiologic test in the appropriate circumstances (e.g., a classic history of biliary colic or an elevated serum bilirubin level). Ultrasonography also visualizes the spleen, the kidneys, and the gynecologic pelvic organs well and has the additional benefit of using no ionizing radiation.

Abdominal and pelvic CT, appropriately, has become the key diagnostic test for evaluating patients with suspected peritonitis. This modality is widely available throughout much of the world, and newer scanners yield significantly higher resolution than older ones, with reduced scanning times and radiation exposure. CT is highly sensitive for free air, fluid collections, bowel wall abnormalities, and inflammatory changes. Now that significant intra-abdominal infections—perhaps even in the setting of a perforated viscus—are



no longer automatically considered to mandate operative intervention, the ability of CT to identify the source and assess the chronicity of an infection is critical to effective modern management. Multiple common conditions have now been defined for which an adequate CT scan allows nonoperative management either as definitive therapy (e.g., expectant treatment of a simple perforated duodenal ulcer) or as a means of temporizing (e.g., percutaneous drainage of a periappendiceal or peridiverticular abscess). In addition, in experienced hands, a negative CT scan of the abdomen and the pelvis virtually excludes any significant acute surgical illness.

It must be noted, however, that a CT scan is not necessary in all patients with abdominal pain, and the decision whether to obtain one should be made on the basis of predefined guidelines or with the input of a general surgeon. When the need for operative intervention has already been determined, imaging is unnecessary. In addition, some patients with an intra-abdominal infection amenable to nonoperative management (e.g., simple, mild diverticular disease that can be treated with oral antibiotics on an outpatient basis) do not necessarily benefit from CT.

In selected cases, other forms of imaging may be used. Magnetic resonance imaging (MRI), although usually more difficult to obtain in an emergency and logistically more complicated than CT, yields excellent tomographic images and has the added benefit of imaging vascular structures and the pancreaticobiliary tree more precisely. Nonetheless, MRI has no significant role in the evaluation of acute peritonitis, except in pregnant women and patients with iodine/contrast allergy. Nuclear medicine scans and fluoroscopic studies, although occasionally useful adjuncts for evaluating biliary tract and upper gastrointestinal (GI) disorders, also play no role in the assessment of acute peritonitis.

CLASSIFICATION OF PERITONITIS

Cases of peritonitis are broadly classified as primary, secondary, or tertiary; this classification provides a useful framework for suggesting general approaches to treatment. Primary peritonitis arises spontaneously, without a demonstrable source of contamination, and is generally treated with antibiotics alone; an example is spontaneous bacterial peritonitis in the setting of ascites. Secondary peritonitis is caused by a breach in the GI tract that leads to contamination of a normally sterile space. Control of the source of infection (“source control”) via drainage, resection, diversion, or some combination thereof is imperative for optimizing outcome. Tertiary peritonitis is a poorly defined entity associated with recurrence of intra-abdominal infection after the treatment of secondary peritonitis. It frequently features a diffuse infection in a critically ill patient and may be caused by any of a long list of health care–associated pathogens (e.g., *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Candida albicans*). Management of tertiary peritonitis is complex and must be individualized for each patient.

Options for Intervention

Once an intra-abdominal infection is diagnosed, there are multiple options for intervention. Not infrequently, an

approach combining several modalities is warranted. Occasionally, administration of systemic antibiotics is all that is necessary (or practical), as in cases of spontaneous primary bacterial peritonitis or of multiple infected fluid collections that are small but too numerous to drain. Single abscesses, particularly those without thick or particulate contents, can be adequately treated with simple aspiration and a short course of antibiotics. For discrete infected fluid collections in almost any setting, placement of a percutaneous indwelling drain (most commonly under radiologic guidance) is currently the treatment of choice. Operative management, either open or laparoscopic, is employed for resection of damaged or inflamed and unsalvageable organs, diversion of enteric contents, or drainage of collections that are too thick or numerous for percutaneous drainage. Beyond these general guidelines, therapy for specific intra-abdominal infections must be individualized (see below).

Infections of the Upper Abdomen

Biliary tract and pancreatic infections present as a systemic septic response or as infections localized in the upper abdomen [see Figure 1]. Typical findings include abdominal pain, a tender upper abdominal mass, fever and leukocytosis, and jaundice. Various combinations of these symptoms may occur, but it is convenient to consider three common clinical presentations. In each of the presentations, one or two symptoms dominate: (1) upper abdominal pain and fever, (2) fever and jaundice, and (3) an upper abdominal mass and fever. These clinical findings signal the need for a battery of screening tests, including a complete blood count (CBC); routine blood tests of liver function; determination of serum amylase level, prothrombin time (PT), and partial thromboplastin time (PTT); blood culture; chest and abdominal x-rays; and abdominal ultrasonography. When considered together, the clinical findings and the test results allow early differentiation of the three most common disease entities: acute cholecystitis, acute cholangitis, and acute pancreatitis.

UPPER ABDOMINAL PAIN AND FEVER

Patients with upper abdominal sepsis may present with epigastric or right upper quadrant pain and fever. Only two thirds of these patients admitted with a working diagnosis of acute cholecystitis have acute biliary inflammation.¹ In some patients, nonsurgical conditions (e.g., pneumonia, acute hepatitis, familial Mediterranean fever, herpes zoster of the intercostal nerves, and gastroenteritis) can be distinguished clinically from biliary disease. The most important screening test for acute biliary infection is the abdominal ultrasound examination: an abnormal image of the gallbladder or bile ducts supports a biliary etiology [see Figure 2].

The differential diagnosis should include acute cholecystitis, biliary colic, acute pancreatitis, and acute cholangitis, each of which requires specific management [see Table 1]. Clinical features and blood test results, although helpful, may be inconclusive. The abdominal ultrasonogram may provide specific clues. Stones appear in biliary colic [see Figure 2]; stones and thickening of the gallbladder wall in acute cholecystitis; gallstones and dilatation of the common bile duct (CBD) in acute cholangitis; and pancreatic enlargement and sonolucency in pancreatitis.

Pancreatitis

Diagnosis Differentiating acute pancreatitis from acute cholecystitis may be difficult. The serum amylase level lacks specificity, but if the clinical findings suggest acute pancreatitis, an elevated level of serum amylase clinches the diagnosis. In one study, the initial laboratory results in 100 patients with acute pancreatitis were compared with those in 100 patients with acute abdominal pain caused by acute cholecystitis, perforated peptic ulcer, or acute appendicitis.² The serum amylase concentrations were elevated in 95% of patients with acute pancreatitis but were normal in 95% of patients with acute abdominal pain from other causes. These concentrations peak within the first 48 hours and are almost always elevated in biliary pancreatitis³; in fact, a serum amylase concentration above 1,000 U/L strongly suggests a biliary origin of the pancreatitis.⁴ In addition, determination of serum lipase levels has been shown to be more specific than and at least as sensitive as determination of amylase levels for the detection of acute pancreatitis.^{5,6} Unless clinical findings and the results of biochemical tests and ultrasonography are unequivocal, contrast-enhanced spiral abdominal CT is usually performed to establish the diagnosis and stage acute pancreatitis. It has been suggested, however, that CT should be reserved for patients with clinically suspected severe acute gallstone pancreatitis on the grounds that the results would not change the recommended course of action in other patients.⁷ Occasionally, a very mild pancreatitis may give rise to no findings on a CT scan, and a normal technetium-99m (^{99m}Tc)-labeled HIDA (lidofenin) scan may help differentiate this condition from acute cholecystitis.

Treatment Pancreatitis encompasses a wide range of diseases, and treatment must be individualized for each patient. Possible therapeutic strategies range from outpatient management with temporary dietary modification (for very mild cases) to open débridement and complex intensive care (for severe cases). It is therefore useful to base possible treatment approaches in particular cases on the cause and severity of the pancreatitis.

Gallstone pancreatitis Standard therapy for gallstone pancreatitis includes intravenous (IV) fluids and narcotic analgesics. Nasogastric suction is useful in patients with significant ileus but need not be used routinely.⁸ The use of systemic antibiotics is controversial; they are of benefit in the 10 to 34% of patients who have concomitant cholangitis.⁹

Nutrition Enteral nutrition (EN) has been shown in a meta-analysis of seven randomized, controlled trials to be the preferred route of nutrition therapy, superseding the previous “gold standard,” parenteral nutrition (PN). Early EN modulates stress response, promotes rapid resolution of the disease processes, decreases disease severity of acute pancreatitis,^{10–12} and results in better outcomes, such as reduced infectious morbidity and hospital length of stay, although it does not affect mortality.¹³ The most recent nutrition guidelines set forth by the American Society for Parenteral and Enteral Nutrition suggest that on evaluation of disease severity, patients with severe acute pancreatitis need initiation of enteric feeds via nasoenteric tube (by the gastric or jejunal route) immediately following volume resuscitation. Those with mild to moderate acute pancreatitis do not require

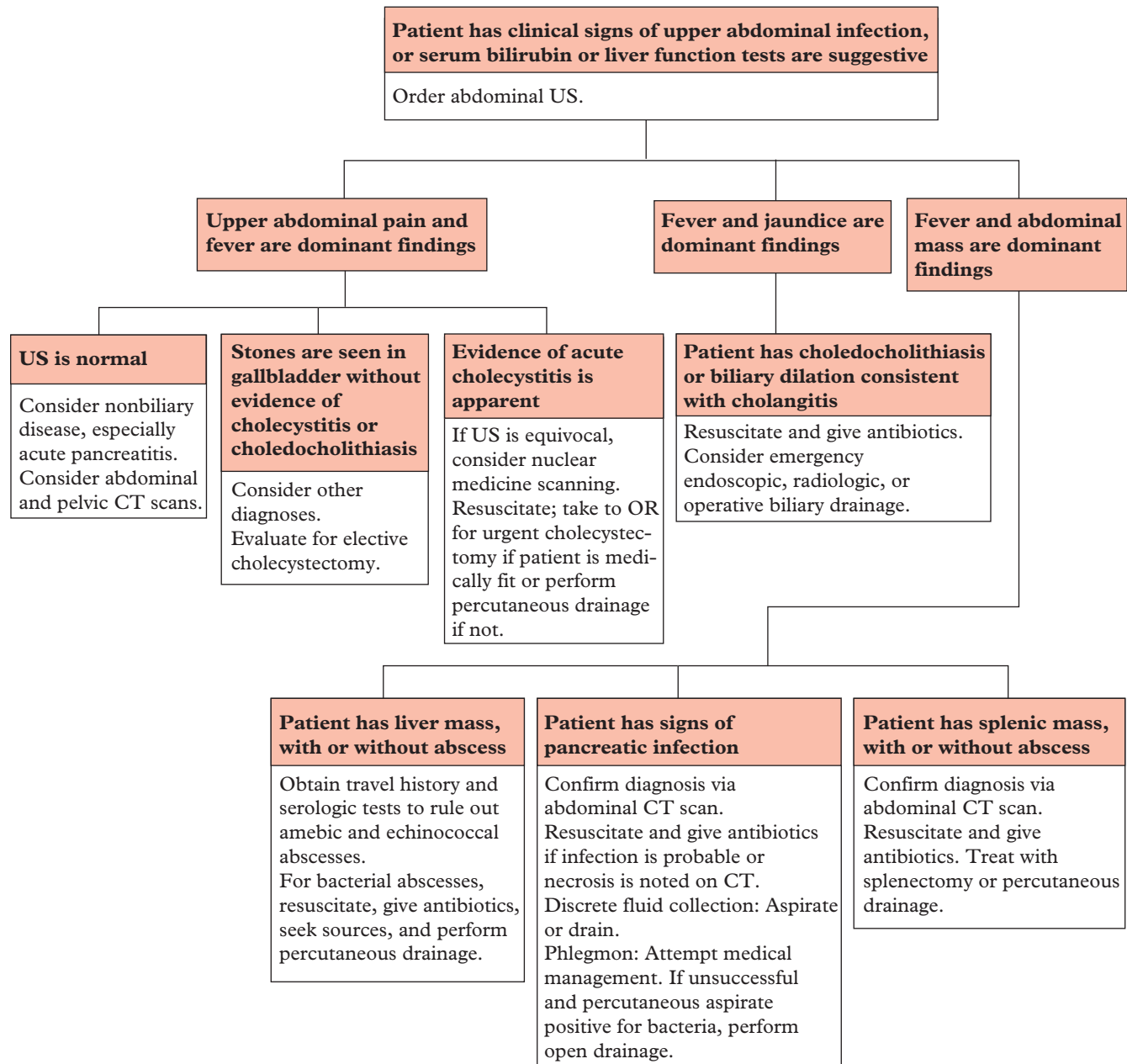


Figure 1 An algorithm outlining the approach to a patient with a suspected upper abdominal infection. CT = computed tomographic; OR = operating room; US = ultrasonography.

nutrition support therapy unless unexpected complications develop that lead to a delay in oral diet beyond 7 days. When EN is not feasible, parenteral nutrition should be initiated after the first 5 days of hospitalization only in severe acute pancreatitis.¹⁴

In clinical practice, the need for further treatment depends on the severity of acute pancreatitis. Severity determines both the risk of sepsis, which governs outcome, and the risk associated with early cholecystectomy. Ranson's criteria, APACHE-II (Acute Physiology and Chronic Health Evaluation II) and APACHE-III scores, and the Balthazar score have been shown to possess discriminatory value in identifying patients at high risk for complications.^{15,16}

Mild pancreatitis usually subsides within 1 week of onset. Most surgeons defer cholecystectomy until then; urgent operation should be reserved for cases complicated by biliary sepsis and may reveal acute cholecystitis in as many as 31% of patients.¹⁷

An attack of acute gallstone pancreatitis is initiated by obstruction at the confluence of the lower end of the CBD and the pancreatic duct by a stone or by edema at the ampulla of Vater resulting from stone migration. These stones may be found and removed in 63 to 78% of patients who undergo operation within 72 hours of admission¹⁷⁻¹⁹; by contrast, they are present in only 3 to 33% of patients explored after the first week.¹⁸⁻²² A randomized trial exploring the optimal



Figure 2 Abnormal abdominal ultrasound examination showing calculi in gallbladder casting shadows on underlying liver tissue.

timing of surgery for gallstone pancreatitis showed that early surgery (within 48 hours after admission) was not associated with a significant increase in morbidity or mortality in patients with mild pancreatitis but did not change the prognosis.²³

Endoscopic retrograde cholangiopancreatography (ERCP) Early ERCP and sphincterotomy have been suggested as an alternative to surgery of the CBD in patients with mild pancreatitis. However, randomized trials comparing endoscopic treatment with conservative treatment within the first 72 hours in patients with mild pancreatitis did not find that urgent endoscopic sphincterotomy improved outcome in this group of patients.^{24,25} Other studies showed that delaying surgery beyond 6 weeks may lead to a 32 to 57% risk of recurrent pancreatitis.^{26,27} Therefore, cholecystectomy and cholangiography should be delayed only until just before patients are discharged from the hospital, 5 to 15 days after the onset of symptoms. Laparoscopic cholecystectomy has facilitated this approach safely without prolonging hospital stay.

Severe pancreatitis Repeated clinical and radiologic evaluation is required in patients with severe pancreatitis to ensure early detection of complications because the outcome of an episode of pancreatitis depends on whether sepsis supervenes. When infection occurs, operative débridement and drainage may be required [see Fever and Abdominal Mass, below]. Some surgeons have attempted to alter the course of severe disease by early operation; however, urgent operation is associated with a high mortality.^{19,21,23,28} To avoid the mortality associated with early operative intervention, some clinicians advocate early diagnosis by ERCP [see Figure 3], followed by biliary decompression by means of endoscopic sphincterotomy and stone extraction. In a randomized trial comparing early ERCP and sphincterotomy with conservative therapy in patients with severe acute pancreatitis, ERCP and sphincterotomy decreased morbidity from 61% to 24% and lowered mortality from 18% to 4%.²⁴ The results of this trial, however, have been the subject of debate, and the success of this approach has been attributed by some authors to the treatment of a concomitant cholangitis rather than of the actual pancreatitis.²⁵ A well-conducted trial that excluded patients with concomitant cholangitis was published in 1997; unfortunately, this trial was unable to answer the question definitively, because too few patients with severe pancreatitis had been recruited.²⁹ It appears that ERCP is warranted mainly in cases of acute pancreatitis complicated by cholangitis and biliary sepsis.^{30,31}

Early use of antibiotics and selective decontamination have been proposed as a means of reducing septic complications, but neither has convincingly or reproducibly been shown to improve prognosis.^{32–36} Although prophylactic antibiotics have been shown to decrease the rate of infectious complications in severe acute pancreatitis, they have not clearly been shown to reduce overall disease mortality.^{32,33,37–39} A recent systematic review of seven studies with 404 patients confirmed no benefit of antibiotics in preventing infection of pancreatic necrosis or mortality, although none of the studies were adequately powered. Antibiotic prophylaxis should not be routinely recommended in patients with either alcoholic or biliary acute necrotizing pancreatitis unless further evidence demonstrates its efficacy.

Acute Cholecystitis

Diagnosis Acute cholecystitis is the most common diagnosis in patients presenting with upper abdominal pain and fever and is characterized by the clinical finding of a midinspiratory arrest on palpation of the right upper quadrant

Table 1 Diagnostic Indicators of Upper Abdominal Pain and Fever

	Biliary Colic	Acute Cholecystitis	Acute Pancreatitis
Duration	Short: 40% < 1 hr	Persistent	Persistent
Pathogenesis	Visceral	Somatic	Retroperitoneal
Signs	Tender	Guarding and spasm	Guarding and spasm
Laboratory tests			
Liver function tests	Occasionally abnormal	Abnormal	Abnormal
Serum amylase	Normal	Normal or slightly increased	Increased
Leukocyte counts	Often normal	Increased	Increased

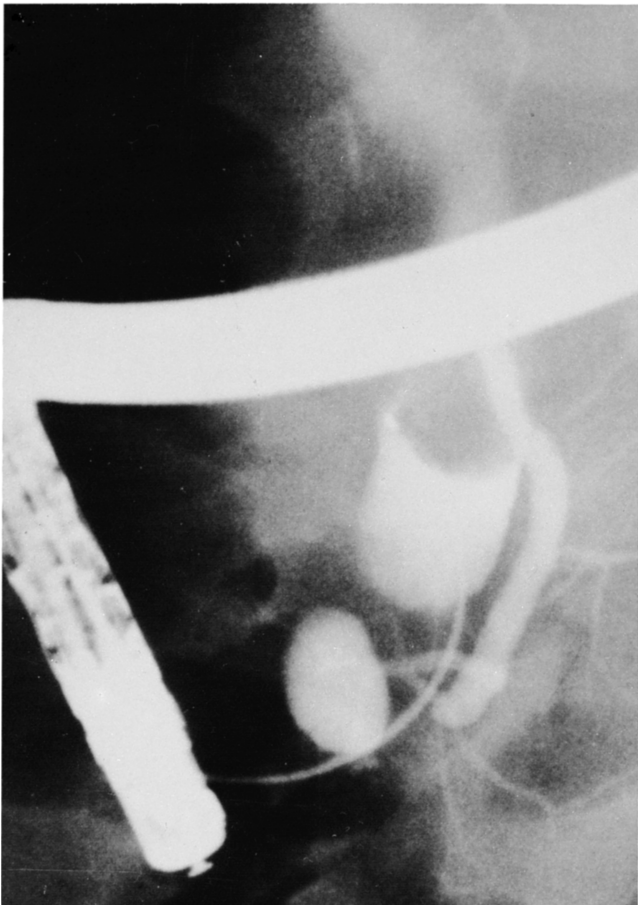


Figure 3 Endoscopic retrograde cholangiopancreatography showing a distal common bile duct stone in acute pancreatitis. A papillotome has been placed through the sphincter of Oddi in preparation for endoscopic sphincterotomy.

(Murphy sign). As noted (see above), with the widespread availability of ultrasonography, acute cholecystitis can usually be diagnosed rapidly on the basis of the findings of gallbladder wall thickening, pericholecystic fluid, and stones. Occasionally, more complex cases must be evaluated with nuclear medicine scanning to look for cystic duct obstruction. Concurrent acute obstructive cholangitis must also be considered in all patients with acute cholecystitis. Supportive laboratory data include a high serum bilirubin level and an increased alkaline phosphatase level. Dilated biliary ducts on abdominal ultrasonography usually confirm the diagnosis of acute cholangitis.

Emphysematous cholecystitis An uncommon and insidious variant of acute cholecystitis, emphysematous cholecystitis is characterized by gas in the gallbladder lumen or wall or in the pericholecystic soft tissue and biliary ducts secondary to gas-forming bacteria. The key to the diagnosis is the presence of air on an abdominal sonogram or x-ray [see Figure 4]. Compared with ordinary acute cholecystitis, emphysematous cholecystitis is associated with a fivefold increase in the risk of gallbladder perforation, as well as a 10-fold increase in mortality in patients younger than 60 years [see Table 2].⁴⁰

Acute acalculous cholecystitis Another variant of acute cholecystitis is acalculous cholecystitis; although still rare,



Figure 4 Air (arrows) outlining the gallbladder and bile ducts in emphysematous cholecystitis.

Table 2 Comparison of Acute Cholecystitis and Emphysematous Cholecystitis		
	Emphysematous Cholecystitis	Acute Cholecystitis
Gender (%)	70 male	70 female
Stones (%)	70	90
Bile culture positive (%)	95	66
Clostridia found (%)	46	1.2
Gangrenous gallbladder (%)	75	2.5
Perforation of gallbladder (%)	20	4
Mortality at age < 60 yr (%)	15	1.5
Pathogenesis	Ischemia, obstruction	Obstruction

it became more common from the 1950s through the 1990s. This disease was originally described as occurring after surgical treatment of unrelated disease but was subsequently identified in patients with multiple trauma, prolonged critical illness, and sepsis. Predisposing factors include gallbladder ischemia (in patients with shock or trauma) and biliary stasis (in prolonged fasting, hyperalimentation, and sustained narcotics therapy). A high index of suspicion is necessary. Acute

acalculous cholecystitis should be considered in any post-operative or acutely ill patient with upper abdominal pain and fever or with unexplained fever and leukocytosis. It is particularly common 2 to 4 weeks after injury. The diagnosis is confirmed by findings on abdominal ultrasound examination [see Figure 5] and occasionally ^{99m}Tc -labeled HIDA scanning coupled with infusion of cholecystokinin and morphine.^{41–43}

Treatment Standard treatment of acute cholecystitis consists of IV fluid administration, analgesics, and cholecystectomy. Although the timing of operation is somewhat controversial in ordinary acute cholecystitis, cholecystectomy should be performed at the earliest opportunity. This approach has been confirmed by at least one randomized trial comparing early with late laparoscopic cholecystectomy.⁴⁴ The delayed-surgery group had a greater need for conversion to open cholecystectomy (23% versus 11%), as well as a longer average total hospital stay and convalescence. Administration of systemic antibiotics is not required; however, single-dose antibiotic prophylaxis (e.g., cefazolin, 2 g IV) can be given at the start of the operation.^{45–47}

Some patients with acute cholecystitis are at high risk for gangrene and perforation of the gallbladder. It is crucial to identify these patients and perform cholecystectomy promptly because delay increases morbidity and mortality. Clinically, gangrene and perforation of the gallbladder in this high-risk population are suggested by marked systemic toxicity or by the radiologic demonstration of either emphysematous cholecystitis or acute acalculous cholecystitis.

With ordinary acute cholecystitis, body temperature is slightly increased in most patients—averaging 37.8°C (100.04°F)—but is normal in 20% of patients. By comparison, the risk of gangrene and perforation is reportedly higher in patients with marked systemic toxicity, manifested by a pulse rate greater than 120 beats/min, a body temperature higher than 39°C (102.2°F), and a left shift in the differential white blood cell count, showing more than 90% polymorphonuclear leukocytes. Unfortunately, findings of systemic toxicity are frequently absent in elderly patients.

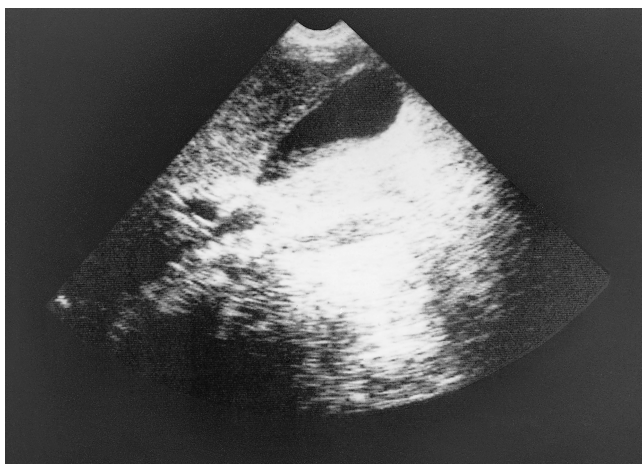


Figure 5 An abnormal abdominal ultrasound examination confirming the diagnosis of acute acalculous cholecystitis. When the image is compared with that in Figure 2, thickening of the gallbladder wall and intraluminal debris are obvious.

Patients with acute cholecystitis who have signs of systemic toxicity, emphysematous cholecystitis, or acalculous cholecystitis are at high risk for gallbladder gangrene and perforation and therefore require prompt and aggressive treatment. IV antibiotic therapy with a single agent can be given.^{48,49} Early cholecystectomy is the treatment of choice. Unfortunately, mortality may be as high as 20 to 30% with the traditional surgical approach.⁵⁰ If perforation and gangrene are not suspected but medical illness poses a high risk of mortality from operation, nonoperative supportive therapy may suffice. If this fails, another treatment option is percutaneous cholecystostomy.

A few patients with acute cholecystitis will have concurrent acute cholangitis. Cholecystostomy is contraindicated in these patients because of its high mortality; adequate drainage of the CBD is required in such cases [see Fever and Jaundice, below].

FEVER AND JAUNDICE

An alternative presentation of upper abdominal infection includes patients whose predominant symptoms are fever and jaundice, with pain a less marked component. Jaundice is almost always associated with obstruction of the biliary tree, either intrahepatic or extrahepatic. The combination of fever with jaundice always suggests acute cholangitis, a condition that can have a fulminant and fatal course if not treated promptly.

Acute Cholangitis

Diagnosis If a patient presents with a temperature higher than 38.5°C (101.3°F) in conjunction with jaundice, the possibility of acute cholangitis should always be investigated. If cholangitis is present, laboratory studies will reveal leukocytosis, and blood cultures will often be positive. A finding of gallstones and dilated biliary ducts on abdominal ultrasound examination supports the diagnosis. The Reynolds pentad is present in the full-blown syndrome.⁵¹ This syndrome includes upper abdominal pain, fever and chills, jaundice, hypotension, and mental status changes. Acute cholangitis is usually related to choledocholithiasis, recent biliary manipulation, biliary stenting performed for chronic obstruction, or previous biliary stenting.

Gallbladder infections Gallbladder empyema can duplicate most of the findings associated with acute cholangitis. In this condition, acute cholecystitis is complicated by suppuration within the gallbladder, which then becomes the focus of generalized sepsis. The distended gallbladder may be palpable and tender. When jaundice is associated with empyema of the gallbladder, it is less likely to be obstructive than when it is associated with acute cholangitis. True empyema of the gallbladder is rare. Treatment includes administration of IV fluids, systemic antibiotic therapy, analgesics, and early cholecystectomy.

In some patients with jaundice and inflammation, a stone impacted in the cystic duct or in the Hartmann pouch (infundibulum) may suggest choledocholithiasis, but preoperative diagnosis by ERCP shows an extrinsic compression of the duct known as Mirizzi syndrome. Two types of Mirizzi syndrome exist. In type I, a stone impacted in the cystic duct or Hartmann pouch compresses the common hepatic duct and

causes inflammation, thereby leading to jaundice. Treatment of this type consists of obliteration of the cystic duct and careful partial cholecystectomy, with the neck of the gallbladder left in place. In type II, protrusion of the stone into the hepatic duct erodes the septum between the cystic duct and the hepatic duct and causes a cholecystocholedochal fistula. Treatment of this type involves internal biliary drainage to the wall of the cholecystocholedochal defect, usually with a choledochojejunostomy, in addition to cholecystectomy.⁵²

Primary sclerosing cholangitis Patients with primary sclerosing cholangitis, especially those who have undergone internal or external biliary drainage, are at high risk for recurrent bouts of ascending cholangitis. Primary sclerosing cholangitis predominantly affects young males, particularly those with chronic ulcerative colitis. The diagnosis is suggested by the dominant cholestatic biochemical profile—that is, elevation of the serum bilirubin concentration, the serum alkaline phosphatase level, and aspartate aminotransferase activity. Because of the concomitant hepatic scarring, ultrasonography may not reveal the presence of dilated intrahepatic ducts. Definitive diagnosis requires visualization of the beaded appearance of the biliary tree by means of cholangiography. Cholangiocarcinoma and secondary sclerosing cholangitis in patients with Caroli disease or choledochal cysts may mimic these clinical, biochemical, and radiologic features, but this is an unusual occurrence and can be distinguished by careful follow-up of patients.

Currently, magnetic resonance cholangiopancreatography (MRCP) is the imaging modality of choice for elective management of patients with primary sclerosing cholangitis in that it yields results comparable to those of ERCP without being invasive.^{53–56}

Other causes of cholangitis An uncommon cause of recurrent cholangitis in North America is Oriental cholangiohepatitis, which is characterized by intrahepatic duct scarring, biliary strictures, and hepatolithiasis, as demonstrated by cholangiography. Irreversible intrahepatic and extrahepatic liver damage may result because of the overwhelming propensity of these patients to form calcium bilirubinate stones.

A few patients with cholangiocarcinoma causing bile duct obstruction or liver metastases causing intrahepatic bile duct obstruction may also present with a clinical picture suggestive of cholangitis. CT followed by MRCP can delineate the diagnosis in most such cases. Treatment consists of IV antibiotics and biliary drainage by radiographic or surgical means.

Treatment Once acute cholangitis is diagnosed, resuscitation is started with IV fluids and antibiotics, such as fluoroquinolones, or piperacillin/tazobactam.^{48,57–60} These antibiotics are required to deal with the various aerobic bacteria, of which *Escherichia coli*, *Klebsiella* species, and enterococci (including vancomycin-resistant strains [VRE]) are the most frequently encountered in this setting. Anaerobes may be isolated in 15 to 30% of patients and are particularly likely to be present in diabetics, the elderly, and patients who have previously undergone biliary manipulation. In patients with indwelling catheters, *Enterobacter* species, *Pseudomonas* species, and *Candida* species organisms are being isolated with increasing frequency. Indications of high risk include a serum bilirubin concentration higher than 3 mg/dL.

Approximately 75% of patients with acute cholangitis respond to conservative measures,⁶¹ and supportive treatment is continued. Subsequent investigations usually include CT followed by MRCP.^{62,63} Because of their invasive nature, ERCP and needle percutaneous transhepatic cholangiography (PTC) are reserved for cases in which a drainage procedure is anticipated or the information from the MRCP is deemed inadequate.

For the 25% of patients who do not respond to conservative treatment, early recognition may improve their prognosis. These high-risk patients often have systemic hypotension, mental confusion, a temperature higher than 39°C (102.2°F), or hypothermia.

Patients with refractory cholangitis who do not improve within 24 hours require urgent biliary decompression. Historically, urgent biliary decompression had been accomplished via surgical exploration of the CBD and T-tube drainage. Rarely, T-tube insertion alone may be lifesaving in a desperately ill patient; generally, however, definitive internal decompression is preferable. Unfortunately, any surgical decompression in these critically ill patients can result in a mortality of 30 to 40%.^{64–67} As a result, nonoperative methods of biliary decompression, including percutaneous transhepatic biliary drainage (PTBD) and endoscopic sphincterotomy at ERCP, are preferred.

Although PTBD can reduce the mortality associated with initial biliary decompression, many patients still require a definitive operation. Consequently, endoscopic sphincterotomy has been proposed for decompression of the biliary tree in patients with acute cholangitis from choledocholithiasis [see Figure 6]. In a study of 82 patients with acute cholangitis caused by CBD calculi, early operation was employed in 28 patients, endoscopic sphincterotomy in 43, and antibiotic therapy alone in 11.⁶⁸ Surgical mortality was 21% and morbidity 57%; by comparison, mortality for endoscopic sphincterotomy was 5% and morbidity 28%. Others confirmed these findings.⁶⁹ In patients whose gallbladder is still in place, endoscopic sphincterotomy alone, without cholecystectomy, may even be a reasonable long-term option. Of 23 patients whose gallbladders were left in situ,⁶⁸ only two required cholecystectomy in the 1- to 7-year follow-up period, one for empyema of the gallbladder and one for recurrent cholangitis.

An increasingly recognized cause of cholangitis is biliary sepsis after manipulation of the biliary tree with ERCP or PTBD. Treatment includes IV fluids and antibiotics. To prevent this complication, prophylactic antibiotics should be administered before every biliary manipulation.⁷⁰

FEVER AND ABDOMINAL MASS

A third group of patients with upper abdominal infection present with fever and an upper abdominal mass identified either by clinical signs or through diagnostic imaging. Even if the mass is only vaguely palpable, the mass effect is demonstrable on ultrasound examination of the abdomen. If the abdominal ultrasound examination is technically unsatisfactory because of intestinal gas, contrast-enhanced CT of the abdomen will facilitate the diagnosis.

The differential diagnosis is aided by the location of the mass. A mass in the right upper quadrant usually indicates acute cholecystitis, although the possibility of a liver abscess

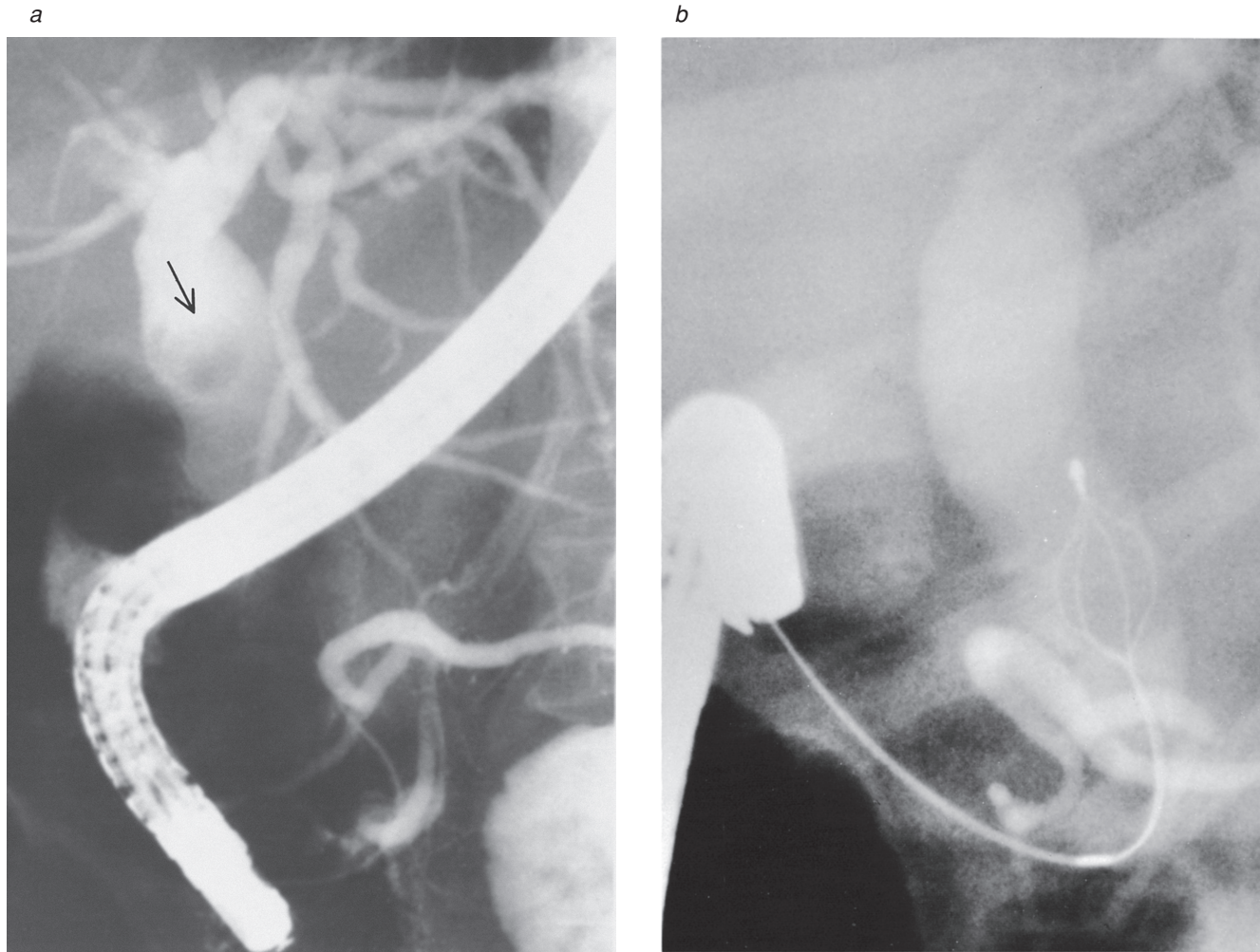


Figure 6 Endoscopic sphincterotomy for acute biliary decompression in acute obstructive cholangitis is shown. (a) The stone (arrow) is visible in the common hepatic duct, and the papillotomy has been passed through the sphincter of Oddi. (b) The stone is held within a Dormia basket before extraction. Reproduced with permission from Ranson JH et al.⁹⁹

must also be considered. A mass in the epigastrium or in the left upper quadrant usually signals a pancreatic infection; in rare instances, a solitary splenic abscess is found. Patients with an intra-abdominal abscess in the subphrenic space or an interloop abscess may also present in this manner.

Liver Abscess



Diagnosis In the setting of acute upper abdominal sepsis, a tender mass in the right upper quadrant is most likely an enlarged, inflamed gallbladder, possibly wrapped with omentum [see Upper Abdominal Pain and Fever, Acute Cholecystitis, above]. The next most common cause of fever and abdominal mass in the right upper quadrant, however, is liver abscess.

Pyogenic abscess Today, pyogenic liver abscess is most commonly related to biliary tract obstruction from gallstones or malignant disorders (35% of cases), and the ultrasound examination may reveal both the abscess and the dilated biliary ducts. Previously, portal pyemia from diverticulitis,

inflammatory bowel disease (IBD), or perforated appendicitis had been the most common cause; it now accounts for 20% of cases. Even less common is hematogenous spread via the hepatic artery. Approximately 20% of hepatic abscesses are cryptogenic. Ultrasonographic imaging of the liver may demonstrate lesions as small as 2 cm in the liver substance. CT, however, is superior to ultrasonography for evaluating the presence of air and abscesses as small as 0.5 cm in diameter, especially near the hemidiaphragms.⁷¹ Abdominal CT is also the diagnostic modality of choice in the postoperative patient.⁷² ERCP and PTC are indicated only when gallstone disease or a biliary malignancy is the potential source of the abscess. Most liver abscesses occur in the right lobe: 40% are 1.5 to 5 cm in diameter, 40% are 5 to 8 cm in diameter, and 20% are greater than 8 cm in diameter.

Amebic abscess Although pyogenic abscesses are commonly multiple, no imaging technique can reliably differentiate them from amebic abscesses. The best indication of a parasitic infection is a history of travel to an endemic area (e.g., Mexico, Central America, or Southeast Asia).

However, when a hepatic abscess is detected by an imaging technique, serologic tests should be performed to rule out active amebiasis or echinococcal infection. Examination of stool for amebae is insensitive; consequently, isoenzyme analysis, *Entamoeba histolytica*-specific antigen detection, or even polymerase chain reaction (PCR) is preferred to confirm the diagnosis of amebiasis.⁷³

SCORING *Echinococcal abscess* The diagnosis of echinococcal liver abscess can be confirmed by means of elevated indirect hemagglutination (IHA) titers (> 250). In the late 1980s, a combination of tests that included IHA for *Echinococcus granulosus* and enzyme-linked immunosorbent assay (ELISA) using *Echinococcus multilocularis* antigen yielded an 89% species-specific diagnosis of echinococcal disease.⁷⁴ Later work indicated that IgG ELISA and IHA were the best tests for follow-up after resection of the abscess. In patients with a favorable clinical outcome, the specific IgG level decreased toward the end of the first year, although in some cases, a positive serologic result persisted beyond 6 years.⁷⁵ Diagnostic aspiration is indicated when a diagnosis of pyogenic or amebic abscess is in doubt, but not in echinococcal disease. Aspiration may also be beneficial in patients with left-side abscesses and abscesses greater than 10 cm in diameter. The chest x-ray is abnormal in as many as 50% of cases of amebic abscess, and the plain abdominal x-ray may show calcification of an echinococcal cyst with secondary pyogenic infection.

It is essential to differentiate infected echinococcal cysts from pyogenic abscess: special precautions are required for drainage of echinococcal cysts because of the risk of spillage and anaphylaxis. Blood cultures are positive in as many as 50% of patients with pyogenic abscess, particularly in those with multiple abscesses; in fact, the presence of *Streptococcus milleri* in the blood suggests a visceral abscess.

SCORING **Treatment** *Pyogenic abscess* The preferred treatment of pyogenic abscess is closed continuous percutaneous drainage guided by CT or ultrasonography, provided that it is technically feasible and no other indication for laparotomy exists.⁷⁶ More than one catheter may be required for complete drainage. An alternative treatment is repeated percutaneous needle aspiration, the results of which are comparable to those of continuous drainage.⁷⁷ One advantage to repeated needle aspiration is the elimination of cumbersome, painful drainage tubes, which are prone to dislodgment. Although initial studies showed a good response rate with repeated needle aspiration,⁷⁸ the results were not duplicated in a subsequent randomized trial.⁷⁹

The abscess cavity dimensions are followed by serial imaging until the cavity collapses, and the catheter can usually be removed 2 to 3 weeks later. Continuous percutaneous drainage has been associated with a complication rate of 4% and a failure rate of 15%.^{80,81} However, operative drainage is the treatment of choice in patients with an identified intra-abdominal focus of infection and in patients in whom percutaneous drainage is not feasible or has failed.⁸¹ Operative drainage, especially via a laparoscopic approach, is a highly effective treatment option that is associated with low mortality and morbidity.⁸² In some patients, a limited hepatic resection may be required to eliminate multiple abscesses, particularly when an underlying intrahepatic stricture is the source.⁸³

Treatment of a pyogenic liver abscess should include systemic antibiotic therapy, with antimicrobial treatment alone being adequate in patients with a small hepatic abscess.^{84–86} Approximately 70% of pyogenic liver abscesses yield polymicrobial isolates,⁸⁷ and 25 to 45% of the organisms are anaerobic.⁸⁸ Multiple anaerobic isolates suggest the colon as a source, whereas a single isolate of *E. coli* suggests a nidus in the biliary tree. Antibiotic treatment should include initial coverage of both aerobes and anaerobes with either a single agent or multiple agents. The need to cover enterococci has been debated, but these organisms, including VRE, clearly are increasingly important health care-associated pathogens. Antibiotic therapy typically consists of a 4- to 6-week course of a single broad-spectrum agent (e.g., piperacillin/tazobactam or meropenem). Oral antibiotics may be initiated in stable patients following abscess drainage.^{84–88} It should be noted that significant changes have occurred in the etiology, bacteriology, and treatment of liver abscesses. There is a trend toward a higher incidence of pseudomonal and streptococcal infections, and the frequency of fungal infection is increasing as well.⁸⁹ The mortality from this disease remains high, and appropriate antibiotic coverage with drainage is of paramount importance. A follow-up CT is recommended approximately 1 to 2 months after initiation of treatment: antibiotics with or without percutaneous/open drainage.^{84–86}

The overall prognosis for multiple small hepatic abscesses is not as good as that for solitary abscesses, and the development of a pyogenic abscess in a patient with an underlying hepatobiliary or pancreatic malignancy has been identified as a preterminal event associated with a hospital mortality of 28% and survival of less than 6 months.⁹⁰

Amebic abscess Medical treatment is now the standard approach to management of amebic liver abscesses. Metronidazole, 750 mg orally three times a day for 10 days, is a highly effective regimen.⁹¹ A favorable response to treatment occurs within 4 to 5 days, and a decrease in the size of the abscess is apparent within 1 week on ultrasonographic examination, although a small residual cavity may persist for as long as 2 years. If the patient's condition does not improve, needle aspiration and culture are indicated. Secondary infection is treated as a pyogenic abscess. Otherwise, oral emetine, 65 mg/day, is added for up to 10 days.

Echinococcal abscess Symptomatic or secondarily infected echinococcal cysts are best treated by means of surgical excision or marsupialization. The use of oral anthelmintics (e.g., albendazole and mebendazole) has met with limited success. Nevertheless, preoperative treatment with albendazole or mebendazole for 1 month, combined with postoperative treatment, is indicated to reduce the risk of intraoperative seeding or postoperative recurrence.^{92,93}

Pancreatic Infection

Diagnosis When the mass is located in the epigastrium or the left upper quadrant, a pancreatic source is most likely. Prompt and accurate diagnosis is crucial because severe pancreatic infection is fatal if left untreated. The key to successful treatment is early diagnosis of infected pancreatic necrosis, infected pseudocyst, and pancreatic abscess. A high index of suspicion is required to diagnose these three infectious processes and to differentiate them from a pancreatic

inflammatory mass or phlegmon,⁹⁴ in which pancreatic edema and inflammation are present without necrosis or infection.

Correct diagnosis and treatment of infected pancreatic necrosis, infected pseudocyst, and pancreatic abscess require an understanding of their pathophysiology. It is generally assumed that infected pancreatic necrosis develops as a transmural, transductal, lymphatic, or hematogenous infection of a necrotic region of the pancreas. Infection develops in 40% of cases of pancreatic necrosis, usually in week 2 or 3 after development of the acute pancreatitis.⁹⁵ Surgical débridement is often required in these cases to prevent death. Pancreatic abscesses form by liquefaction of infected necrosis. They usually occur after week 5 of pancreatitis, when the acute phase of the disease has subsided.⁹⁶ Pancreatic abscesses are associated with a lower mortality than infected pancreatic necrosis. Like pancreatic abscesses, infected pancreatic collections and pseudocysts present late in the course of pancreatitis. They are associated with a lower mortality than pancreatic abscesses. Caused by infection in 13% of localized collections resulting from ductal blowout, infected pancreatic collections and pseudocysts may occur in the pancreas itself, in contiguous peripancreatic tissue, or in remote (extrapancreatic) tissue.

Clinical evaluation alone is generally insufficient to diagnose pancreatic infection. A clearly defined upper abdominal mass is palpable in only 50 to 75% of cases.⁹⁴ In most patients, the screening battery of tests reveals leukocytosis with leukocyte counts greater than 15,000/ μ L. Blood cultures are positive in 50% of cases. CT-guided percutaneous aspiration with Gram stain and culture provides the best method of diagnosing pancreatic infection. In one study of 75 patients with clinical toxicity suggestive of pancreatic sepsis, infection was confirmed in only 40%.⁹⁷ In another study of 21 patients with pancreatic infection, only five had specific signs on abdominal CT scan.⁹⁸ CT-guided diagnostic needle aspiration leads to a correct diagnosis within 72 hours in two thirds of patients, and the mortality associated with operative intervention is 19%; however, CT-guided needle aspiration is beneficial only if pancreatic infection is suspected and if the technique is used early in the course of disease.

Currently, the best indicator of infected pancreatic necrosis or abscess is a dynamic abdominal CT scan. The pancreatic findings on CT can be graded in five categories [see Figure 7]⁹⁹: (a) normal, (b) pancreatic enlargement alone, (c) inflammation of the pancreas and peripancreatic fat, (d) one peripancreatic fluid collection, and (e) two or more peripancreatic fluid collections. Only category e was associated with a high (61%) incidence of pancreatic abscess in one series. The number of objective prognostic signs present also predicted the subsequent development of an abscess: fewer than three signs, 12.5%; three to five signs, 31.8%; and more than five signs, 80%. However, the value of this method was limited because only five of the 83 patients evaluated had more than five prognostic signs. Specific definitive signs of infected pancreatic necrosis include air within the necrotic pancreatic tissue and evidence of pancreatic abscess with air/fluid level.

Treatment Once pancreatic infection is diagnosed, supportive measures are initiated, including nasogastric suction, withholding of oral feedings, meticulous attention to respiratory care and fluid and electrolyte balance, systemic antibiotic

therapy, and nutritional support. The key to successful treatment, however, is surgical, radiologic, or endoscopic drainage.

Pancreatic necrosis Sterile pancreatic necrosis alone is not an indication for surgical débridement. In one prospective study, 11 patients with sterile pancreatic necrosis were all followed successfully with conservative treatment.¹⁰⁰ However, once infected pancreatic necrosis is confirmed by Gram stain or culture, it can lead to sepsis and multiple organ failure, making secondary infection of necrotic pancreatic tissue virtually always an indication for intervention. Treatment of infected necrotizing pancreatitis consists of (1) open necrosectomy with complete removal of necrotic pancreatic tissue or (2) a step-up approach via percutaneous and/or endoscopic drainage and minimally invasive retroperitoneal necrosectomy.¹⁰¹ There is now consensus that the best outcomes from intervention for necrotizing infected pancreatitis are achieved when débridement is delayed until 3 to 4 weeks after the onset of pancreatitis, when the damaged area has been walled off and liquefaction has begun.

Open necrosectomy versus step-up approach The traditional approach to surgical treatment of infected necrotizing pancreatitis has been complete removal of infected necrotic tissue via an open approach. Unfortunately, this highly invasive approach leads to high rates of complications (34 to 95%), death (11 to 39%),^{101,102} and a risk of reoperation because of sepsis or GI complications^{94,103} and long-term pancreatic insufficiency. Less invasive, percutaneous, endoscopic (transgastric), and minimally invasive retroperitoneal necrosectomies were recently found by van Santvoort and colleagues to be associated with fewer complications and less mortality in these patients.¹⁰¹

Surgical treatment should be customized for each patient. An open approach may be used for massive necrosis (more than 100 g removed by débridement at operation or CT evidence of at least 50% pancreatic necrosis) or for extrapancreatic necrosis, with a 1990 meta-analysis of published surgical studies finding statistically better results with débridement and lavage compared with open packing after extensive débridement and sump drainage.¹⁰⁴ Additionally, to reduce the frequency of reoperation and lower mortality, some clinicians opt for open drainage or marsupialization of the infected pancreas. One modification involves the use of a prosthetic mesh and a zipper to facilitate reexploration in patients with severe intra-abdominal abscesses.^{105,106}

Pancreatic abscess Pancreatic abscess resulting from liquefaction of necrosis is also best treated by surgical drainage because residual necrosis may cause failure of treatment by percutaneous methods.¹⁰⁷ On the other hand, infected pancreatic fluid collections and pseudocysts can usually be treated nonoperatively. In one prospective study, percutaneous and surgical drainage were equally successful in treating infected pancreatic fluid collections and pseudocysts.¹⁰⁸ Clinical signs of progress rather than CT findings are the best indicators of the need for intervention, and nonoperative methods should be attempted before open surgery is planned.

Adjunctive procedures Cholecystectomy should be performed in cases of gallstone pancreatitis. Other operative procedures may be required to manage gastric or colonic complications. Gastric bleeding, gastric outlet obstruction, and gastric fistula necessitating reoperation are relatively

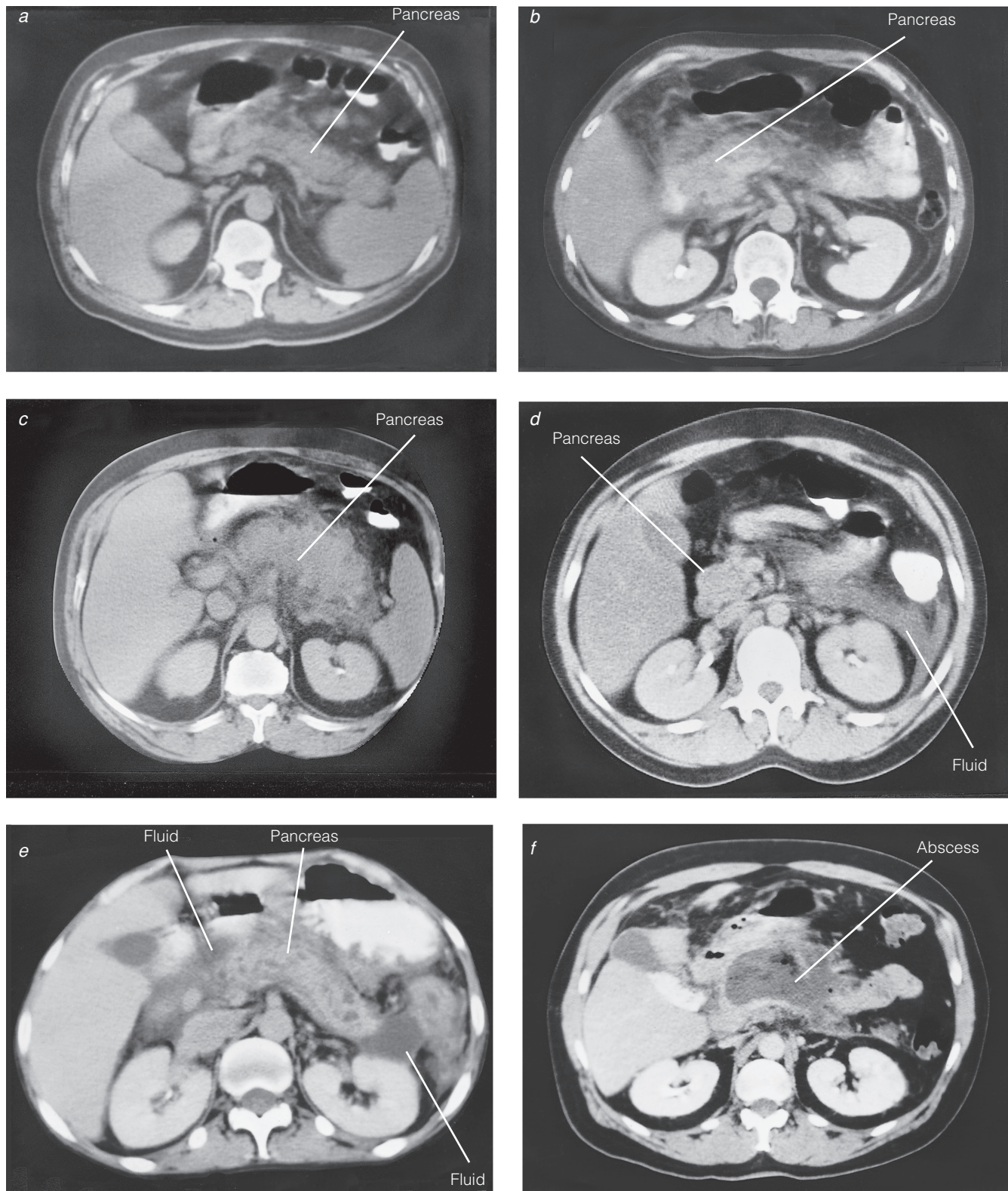


Figure 7 Pancreatic findings on a computed tomographic (CT) scan have been graded by Ranson into five categories: grade A, normal pancreas (a); grade B, diffuse enlargement of the pancreas and nonhomogeneous density of the gland (b); grade C, diffuse enlargement of the pancreas associated with peripancreatic inflammation (c); grade D, high-density fluid collection in the left anterior pararenal space (only the head of the pancreas is visualized at this level) (d); and grade E, diffuse enlargement of the pancreas with several intrapancreatic small fluid collections and poorly defined fluid collections adjacent to the tail and head of the pancreas (e). In the final CT scan (f), pancreatic abscess is demonstrated; partially encapsulated fluid collection containing bubbles of air represents a large abscess. Reproduced with permission from Berkman WA et al.¹¹⁵

infrequent in this setting. By contrast, colonic necrosis and fistula formation are relatively common and occur either spontaneously or as complications of treatment. The usual site of involvement is the splenic flexure or upper descending colon. Treatment consists of colonic resection or a diverting colostomy.

Antibiotic therapy The role of systemic antibiotic therapy in the prophylaxis of pancreatic infection is controversial. Experimental evidence suggests that antibiotics may sometimes decrease the severity of pancreatitis,¹⁰⁹ and endoscopic cannulation of the pancreatic duct has yielded bacteria in pancreatic secretions of patients with acute pancreatitis.¹¹⁰ In patients with pancreatic abscess, bacteriologic cultures are usually polymicrobial, the most common organisms being *E. coli*, enterococci, *Klebsiella pneumoniae*, *P. aeruginosa*, *S. aureus*, *Bacteroides fragilis*, and *Clostridium perfringens*. There is a growing trend toward early use of prophylactic antibiotics in cases of pancreatic necrosis, even though there are no data that convincingly demonstrate a clinical benefit. This trend may be partly responsible for the increasing prevalence of *Candida* species in pancreatitis-related sepsis; a 1996 report stated that *Candida* infection was detected in 21% of patients.¹¹¹

Nutrition Nutritional support of patients with pancreatic abscesses usually consists of small bowel tube feeds, although total parenteral nutrition (TPN) may be attempted occasionally. These patients have high metabolic demands and may experience glucose intolerance or hyperlipidemia. A 10-fold increase in mortality (from 2.5 to 21%) was reported in patients in whom a positive nitrogen balance could not be achieved.¹¹²

Splenic Abscess

Diagnosis A splenic abscess should be considered in patients who present with fever and a left upper quadrant mass, although it remains a rare cause of these symptoms. Most splenic abscesses encountered in clinical practice are solitary; multiple abscesses are usually covert and are typically found at autopsy in patients with disseminated malignancy, collagen vascular disease, fungemia, or chronic debility.

Because splenic abscess is rare, correct diagnosis requires a high index of suspicion. The main clue is the clinical setting: both bacteremia and local splenic disease are required to produce splenic abscess. In the preantibiotic period, this combination was seen most frequently in patients with bacterial endocarditis and typhoid. Even today, more than three quarters of splenic abscesses occur in patients who already have an infection elsewhere in the body; splenic abscesses can also occur in patients with splenic infarcts, splenic hematomas, or local splenic disease caused by hemoglobinopathies.

The diagnosis of splenic abscess may be supported by indirect radiologic signs, such as an elevated left hemidiaphragm or the finding of a left upper quadrant air-fluid level (mimicking the stomach). To clinch the diagnosis, an abdominal ultrasound examination or abdominal CT scan is required. The abdominal CT scan, enhanced with IV or oral contrast material, is preferred [see Figure 8].¹¹³ This technique provides a direct image of the spleen, on which abscesses appear as low-density areas that may contain gas.

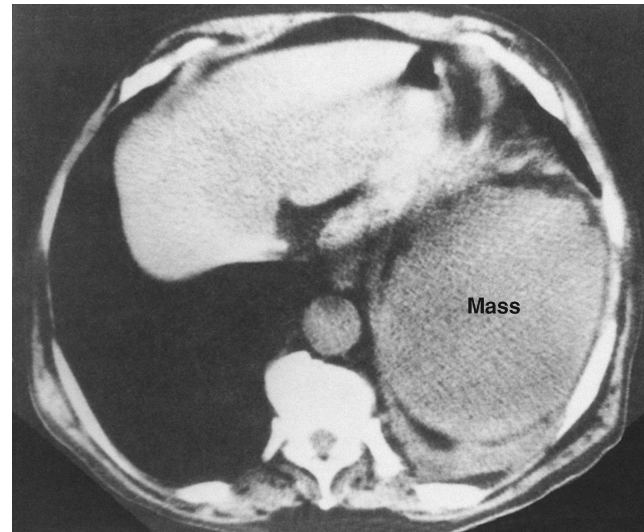


Figure 8 An abdominal computed tomographic scan, enhanced by contrast material, confirming the diagnosis of splenic abscess.

Treatment Treatment of splenic abscess includes IV administration of antibiotics and splenectomy. The usual pathogenic organisms found are staphylococci and streptococci, although gram-negative bacilli and anaerobes may also be present. When splenic abscesses are not drained, mortality approaches 100%. At one time, splenotomy was the preferred operative treatment, but splenectomy is currently the preferred approach. Percutaneous catheter drainage is being performed with increasing frequency and appears to be as effective as operative drainage.^{8,114,115}

Infections of the Lower Abdomen

Although enteric perforations, such as pancreatitis and cholecystitis, present most commonly with pain and fever, their diagnosis differs from that of upper abdominal infections of the solid organs. The pain associated with enteric perforation frequently is not well localized; consequently, CT is used more frequently than ultrasonography because it is superior for evaluating the entire abdomen [see Figure 9]. Moreover, a perforated viscus may present more acutely than other forms of infection do and is a common indication for emergency exploration. Thus, in the setting of a possible lower abdominal infection, the diagnostic emphasis is on confirming or ruling out the presence of an acute condition necessitating operation rather than on fine localization of a more chronic illness.

PEPTIC ULCER PERFORATION

The incidence of peptic ulcer perforation has decreased significantly as a consequence of the changes in disease progression and incidence of intractable ulcers brought about by the use of therapy targeting *Helicobacter pylori* and modern acid-blocking receptors. Still, a significant percentage of all hospital admissions are secondary to perforated peptic ulcers, and the patient population is becoming older and more evenly balanced between men and women, presumably because of increased use of nonsteroidal antiinflammatory drugs and cigarettes.¹¹⁶

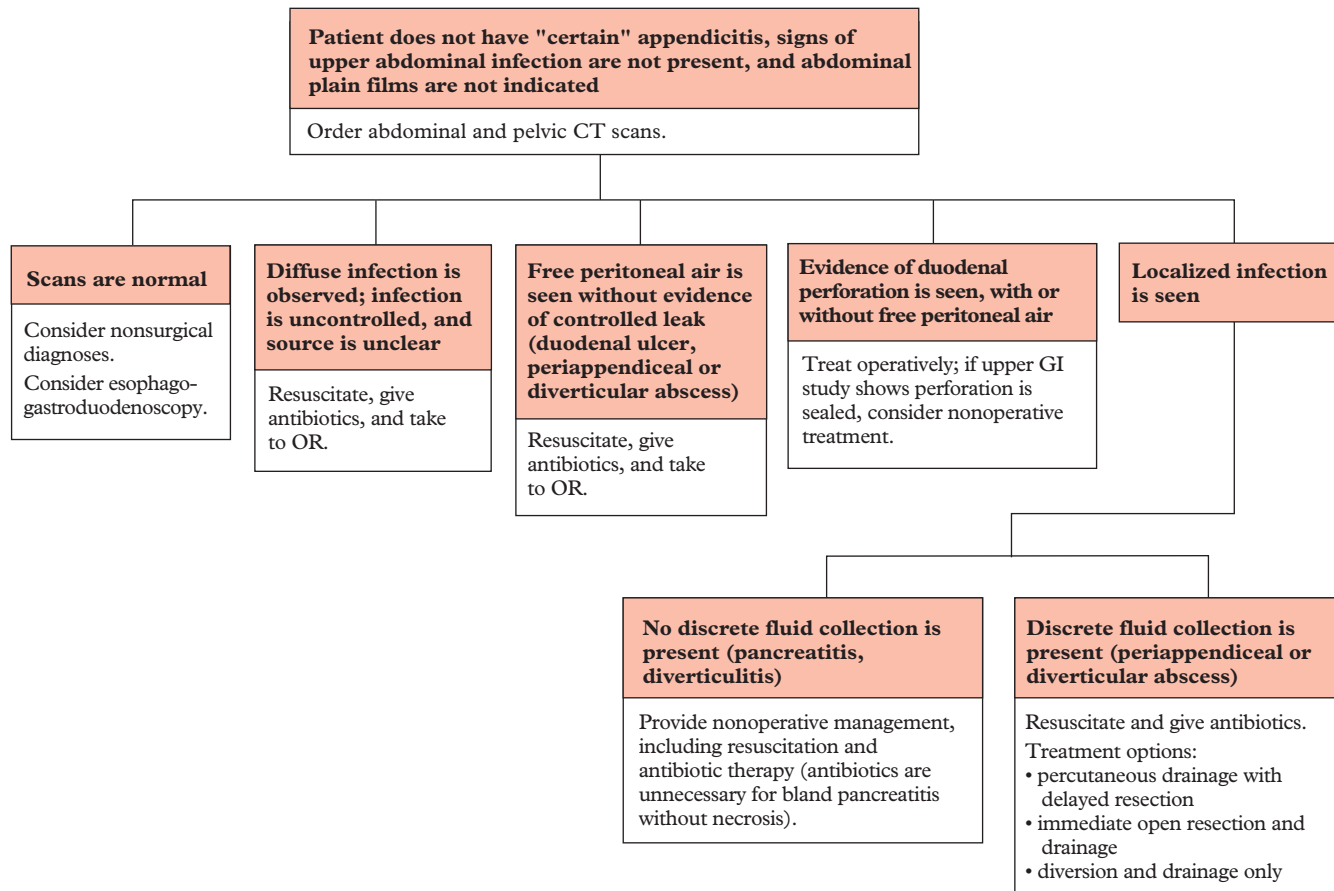


Figure 9 An algorithm outlining the approach to the patient with a suspected lower abdominal infection. CT = computed tomographic; GI = gastrointestinal; OR = operating room.

Diagnosis

A patient with a perforated peptic ulcer will complain of the sudden onset of intense abdominal pain and will often be able to pinpoint the exact time when the symptoms began. If the perforation has not spontaneously sealed or been managed with operative closure, the clinical picture can progress to florid sepsis and shock. Evidence of free air on plain upright and left lateral decubitus radiographs will be seen in as many as 70% of cases [see Figure 10a].¹¹⁷ Endoscopy should be avoided in the evaluation of peptic ulcer perforation, but equivocal cases or spontaneously sealed perforations can be evaluated with water-soluble contrast studies. CT can be used to localize an infection to the duodenum, particularly if communication of air or fluid with the duodenum is established [see Figure 10b] or if extravasation of contrast is seen [see Figure 10c].

Treatment

Surgical management centers on control of the site of perforation (via surgical closure or spontaneous sealing), with or without an acid-reducing procedure. Before this is done, IV fluids should be given, metabolic derangements corrected, appropriate antibiotics and an H₂ receptor blocker or proton pump inhibitor (PPI) administered, and a nasogastric tube placed for decompression.

Operative versus conservative management Several studies have shown nonoperative management to be safe and effective for perforations that have sealed spontaneously. A 1989 study evaluated 35 patients with acute duodenal perforations—excluding those with a history of chronic ulcer disease who ultimately went on to primary repair and acid-reducing surgery—who were managed nonoperatively after evidence of a sealed perforation was noted on a water-soluble upper GI study. The investigators reported one death, in a patient with a history of metastatic breast cancer, and one intra-abdominal abscess.¹¹⁸ In a 1989 prospective trial of 83 patients with perforated peptic ulcers randomly assigned to either conservative or operative management, the two groups experienced similar morbidity and mortality (≈ 5%), and 73% of the patients in the conservatively managed group experienced full resolution of their symptoms.¹¹⁹ The only significant difference between the groups was in the length of hospital stay. It has been suggested that patients with evidence of a sealed perforation confirmed by a Gastrografin upper GI study can be managed conservatively with a low incidence of reperforation and intra-abdominal abscess formation.¹²⁰ These patients must undergo repeated clinical examination and receive supportive therapy until clinical symptoms resolve.

Laparoscopic versus open repair A prospective, randomized trial of perforated peptic ulcers to either open or



Figure 10 An abdominal computed tomographic (CT) scan of a patient with a history of ulcer disease and a 1-week history of increasing abdominal pain showing retrogastric fluid collection with air that appears to be in communication with the duodenum (white arrow). The patient underwent laparotomy, and a perforated duodenal ulcer was repaired.

laparoscopic suture omental patch repair concluded that for perforations smaller than 10 mm, laparoscopic repair was associated with reduced operating times, less need for analgesics, fewer postoperative chest infections, earlier return to normal activities, and shorter hospitalizations.¹²¹ An earlier study also demonstrated reduced analgesic times and earlier return to normal activities but reported longer operating times.¹²² These studies confirm that small perforations can be adequately managed laparoscopically without exacerbation of bacterial sepsis. It must be emphasized, however, that biopsy of perforated gastric ulcers is critical for ruling out malignancies, and laparoscopic repair of the perforation may preclude biopsy.

Simple repair with medical management versus repair with acid-reducing procedure Definitive surgical management of ulcer disease during repair of a perforated peptic ulcer is contraindicated in patients who are hemodynamically unstable, have diffuse peritonitis, have an abscess, or have multiple underlying comorbid conditions.¹²³ The significant side effects associated with definitive surgery (dumping and diarrhea) and the success of medical management (PPIs, H₂ receptor blockers, and *H. pylori* eradication) have further contributed to the reduced popularity of proximal vagotomy at the time of repair. Now that fewer acid-reducing operations are being performed, there is some justifiable concern that younger surgeons will not be able to obtain the degree of training they would need to perform a definitive operation (highly selective vagotomy) in an urgent or emergency scenario.

A 1987 study found that simple closure with a Graham patch, without a concurrent operation to reduce ulcer recurrence, resulted in a higher recurrence rate than closure with proximal gastric vagotomy did (52% versus 16%; median follow-up, 54 months).¹²⁴ In a subsequent study of patients with acute perforations who were randomly assigned to undergo either simple closure or simple closure with proximal vagotomy, ulcer recurrence rates in the two groups after 2 years were 36.6% and 10.6%, respectively.¹²⁵ Both of these studies, however, were performed before PPIs and *H. pylori* therapy became routinely available.

Some 40% of patients with duodenal perforation treated with simple closure may experience recurrent duodenal ulcer. A 1995 series associated such recurrence with *H. pylori* infection.¹²⁶ To further study the role of *H. pylori* eradication in ulcer recurrence after peptic ulcer perforation, a randomized study was done in which patients with perforated duodenal ulcers and *H. pylori* infection after simple closure received either quadruple anti-*H. pylori* therapy (1 week of bismuth, tetracycline, and metronidazole with 4 weeks of omeprazole) or omeprazole alone.¹²⁷ After 1 year, 38.1% of patients managed with PPIs alone experienced ulcer recurrence, compared with 4.8% of patients managed with PPIs and *H. pylori* eradication. A similar study followed patients with perforated duodenal ulcers for up to 2 years after simple closure and randomization to either short-term H₂ receptor blockers or H₂ blockers with quadruple therapy; ongoing *H. pylori* infection correlated with recurrent ulcers for up to 2 years.¹²⁸

On the basis of these findings, definitive acid-reducing procedures should be considered only for (1) patients in whom medical management of peptic ulcers and *H. pylori* fails, (2) patients whose ulcer symptoms have persisted for longer than 3 months, and (3) patients with otherwise complicated ulcers (e.g., lesions that are bleeding or causing obstruction).¹²⁹

Antibiotic therapy In fasting persons, gastric juice contains as many as 10³ organisms/mL. These organisms are typically facultative gram-positive salivary bacteria (e.g., lactobacilli and streptococci) and fungi (e.g., *Candida* species). In induced states of achlorhydria (e.g., from treatment with H₂ receptor blockers or PPIs), there is an increase in the total number of organisms, including enterococci and nitrate-reducing organisms. This phenomenon suggests a proliferation of salivary and enteric organisms, but its clinical relevance is unknown.¹³⁰

Eradication of *H. pylori* in patients with uncomplicated ulcers and bleeding ulcers is now the standard of care.^{130,131} Infection with this organism is associated with a 1% per year risk of peptic ulcer disease, a level of risk approximately 10 times that seen in uninfected patients. Eradication of *H. pylori* with medical management typically results in resolution of the ulcer, and recurrence is rare. Consequently, acid-reducing procedures are not often required.¹³²

SMALL INTESTINAL PERFORATION

Diagnosis

Small intestinal perforation is a very difficult entity to diagnose, in large part because of its relative rarity. There are certain clinical scenarios (e.g., strangulated hernia and Crohn

disease) in which the likelihood of this condition is heightened, but in the setting of blunt small intestinal injury, the low incidental occurrence of perforation ($\approx 1\%$)¹³³ and the complexity of the presentation frequently lead to a delay in diagnosis. Such delay is associated with increases in the morbidity and mortality directly attributable to the injury.¹³⁴ The radiographic modality most useful in diagnosis is CT.¹³⁵

Treatment

The basics of treatment are the same for small bowel perforation as for all perforations: isolation and control of the source of contamination. In the acute setting, this is accomplished through laparotomy and excision of the disease segment, whether the perforation is the result of ischemic necrosis, of blunt injury, or of IBD. Primary reanastomosis is generally accepted in these patients. For patients with Crohn disease, perforation (usually presenting as a fistula) is a risk factor for postoperative disease recurrence¹³⁶; accordingly, close postoperative follow-up is indicated.

Two additional issues regarding small bowel perforations warrant special mention. The first has to do with small bowel perforation secondary to obstruction. When this event occurs, it is important not only that the perforated segment be resected but also that the cause of obstruction be identified to prevent recurrence. The second issue has to do with anastomotic leakage. Not all leaks call for surgical intervention. If the leak is a late complication, it is likely to have walled itself off into an abscess, in which case, CT-guided drainage of the abscess is the treatment of choice. Efforts at reducing the luminal transport are also made to improve healing.

Nutritional support plays a major supportive role in the treatment of patients with small bowel perforation. Many of these patients, either because of their underlying pathology (e.g., Crohn disease) or because of their hypermetabolic state (e.g., from trauma), lose some of their innate ability to heal and prevent anastomotic breakdown. The presence of a knowledgeable nutrition staff can dramatically enhance patient recovery in this setting.

Antibiotic therapy The small bowel flora is typically sparse (10^3 – 10^4 colony forming units/mL), with salivary organisms predominating. In conditions of stasis, obstruction, or impaired motility, however, colonic flora can proliferate, with *E. coli*, enterococci, and obligate anaerobes the dominant organisms. In the distal ileum, there are typically about 10^6 colony-forming units/mL, with an increasing proportion of enteric organisms and anaerobic bacteria, presumably as a result of backwash through the ileocecal valve.¹³⁷ Although there are generally far fewer bacteria in the small intestine than in the colon (which contains about 10^{12} organisms/mL), the standard antimicrobial therapy remains broad-spectrum coverage.¹³⁸

APPENDICITIS

Obstruction of the appendiceal lumen by a fecalith, a hyperplastic lymph node, or a foreign body is typically the inciting event in the pathogenesis of appendicitis. Luminal obstruction with continued secretion results in progressive distention, proliferation of luminal microorganisms, ischemia, gangrene, and subsequent perforation. The clinical history during this evolution is marked by diffuse epigastric pain with anorexia, nausea, and vomiting. The pain typically progresses

first to the periumbilical region and then to the right lower quadrant (at the McBurney point). Patients have a low-grade fever and exhibit direct tenderness at the McBurney point but may also manifest rebound tenderness, guarding, rigidity, and marked temperature elevation if the appendix perforates and results in diffuse peritonitis. As the viscera and the omentum localize and sequester the perforation, the symptoms may subside to a degree, with localized pain and a palpable abdominal mass the primary manifestations remaining.

Diagnosis

Classically, the diagnosis of appendicitis has been made primarily through clinical examination, with laboratory tests consistent with inflammation (i.e., an elevated leukocyte count with a left shift and an elevated C-reactive protein level) serving as confirmation. In as many as 20% of patients with appendicitis, however, the incorrect diagnosis is made, and the incidence of removal of a normal appendix can approach 40%.^{139–141} Early diagnosis of appendicitis can decrease the risk of postoperative complications from 39% to 8%, and one retrospective study found that the use of diagnostic CT lowered the rate of misdiagnosis to 7%.¹⁴² CT is reported to be 93 to 98% in diagnosing appendicitis, with significantly improved accuracy achieved by using an appendicitis protocol after retrograde water-soluble contrast administration.¹⁴³ CT findings suggestive of appendicitis [see Figure 11] include enlargement and dilation of the appendix (to > 6 mm), nonfilling of the appendix, and periappendiceal inflammation (fat stranding, abscess, phlegmon, and dependent fluid collections); these findings do not differ significantly between acute appendicitis and chronic, recurrent appendicitis.^{144,145}

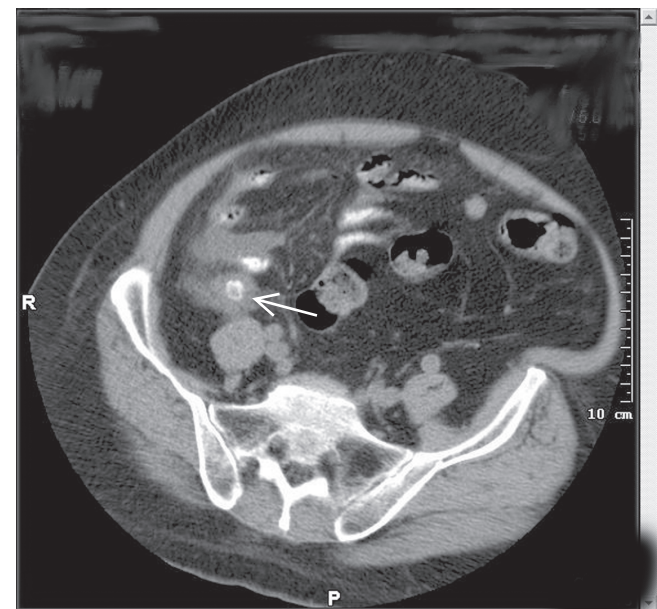


Figure 11 A pelvic computed tomographic scan of a patient with a distant history of right lower quadrant abdominal pain with recurrent acute attack demonstrating an inflamed and thickened appendix with surrounding fat stranding (white arrow). A gangrenous appendix was removed laparoscopically.

Current evidence supports the role of CT in the diagnostic evaluation of patients with suspected appendicitis. Studies have demonstrated decreases in the incidence of both normal appendectomies and prolonged, unnecessary observations.^{146–148} Furthermore, alterations in patient management attributable to diagnostic CT have been shown to decrease overall hospital and patient costs. Nevertheless, the utility of CT in young men whose history, physical examination, and laboratory test results fit the classic picture of appendicitis remains unproven; this subset of patients may be managed without confirmatory CT.¹⁴⁶ On the other hand, CT appears to be quite useful for diagnosing appendicitis in women, in which setting it decreases the incidence of normal appendectomies and facilitates diagnosis of other causes of the symptoms.^{147,148} Preoperative CT assists in planning an operation, identifying a periappendiceal abscess that may delay immediate appendectomy, and recognizing other sources of intra-abdominal pathology.^{149,150}

Treatment

Initial management consists of fluid resuscitation, appropriate prophylactic antibiotics, and preparation for surgery. Currently, acute nonperforated appendicitis, gangrenous appendicitis, and perforated appendicitis without an associated abscess are managed with urgent appendectomy. The main dilemmas in management center on the appropriate use of laparoscopic appendectomy and the role of conservative management for periappendiceal masses with interval appendectomy.

Laparoscopic versus open appendectomy In several prospective, randomized clinical trials that compared laparoscopic with open appendectomy, the consensus was that the former was associated with a lower incidence of wound infection, decreased use of pain medication, earlier return to normal activities, and reduced cost of hospitalization (although the data were conflicting on this last point).^{151–155} On the other hand, the trials found the laparoscopic approach to be associated with a significantly longer operating time, equivalent duration of hospitalization, and a possible increased risk of abscess formation.

There has been some debate with regard to laparoscopic appendectomy being associated with a higher incidence of intra-abdominal abscess formation in the setting of perforated appendicitis. However, the most recent systematic review and meta-analysis of 12 retrospective case-control studies of laparoscopic versus open appendectomy in adults with complicated appendicitis concluded that laparoscopy was associated with reduced surgical site infection rates and no difference with regard to intra-abdominal abscess rates.^{155–157} Furthermore, a prospective, randomized trial found that laparoscopic appendectomy was associated with reduced overall cost of hospitalization, decreased use of pain medication, and earlier return to functional status in patients with uncomplicated appendicitis.¹⁵¹

Two groups of patients clearly benefit from laparoscopic appendectomy: women and obese patients. In women, laparoscopy aids in the diagnosis of other pelvic pathologic conditions and lowers the incidence of negative appendectomies; in obese patients, it results in less postoperative pain and a shorter recovery time, even though it does not significantly

reduce the postoperative complication rate.^{158,159} Patients who present with evidence of perforated or complicated appendicitis may be better managed with the traditional open approach to minimize the risk of postoperative abscess formation.¹⁶⁰ Improvements in laparoscopic techniques, however, may eventually reduce the incidence of this complication to a level comparable to that seen with open management.

Periappendiceal abscess and interval appendectomy

The mainstays of conservative management have been parenteral antibiotics, supportive fluid resuscitation, and percutaneous drainage of radiographically amenable fluid collections. In a 2001 review of 155 patients with periappendiceal abscesses, the complication rate was 36% for patients managed with surgical incision and drainage and appendectomy compared with 17% for patients managed nonoperatively.¹⁶¹ The recurrence rate was 8% in the conservatively managed patients, and nonoperative management failed in five patients. Patients with perforated appendicitis and abscess or phlegmon diagnosed by CT but without a palpable mass were safely managed with conservative therapy. In a 2002 study, immediate appendectomy was associated with a higher postoperative complication rate and an increased incidence of more extensive initial operations (e.g., ileocecal resection, right hemicolectomy, and temporary ileostomy).¹⁶¹

The recurrence rate of appendicitis after conservative management ranges from 10 to 20%, although most of the studies have been small or have had short follow-up periods. Interval appendectomy has been typically performed between 6 weeks and 3 months after percutaneous intervention and clinical resolution [see Figure 12]. The risk of recurrence is greatest after the 6-month point in the clinical progression of acute appendicitis, which is managed conservatively.^{162,163}

In one study of patients managed with interval appendectomy for a periappendiceal mass, histologic evaluation revealed that a significant majority of samples had a patent appendiceal lumen and were at risk for recurrent appendicitis.¹⁶⁴ In a 2002 report, 45.8% of interval appendectomy pathologic samples showed evidence of chronic active inflammation.¹⁶⁵ But the low risk of recurrence clinically (5%), as found by Kaminski and colleagues, does not correlate with these findings. In addition, even when appendicitis did recur, patients tended to have milder clinical presentations with shorter lengths of hospital stay.^{166,167} As a result, interval appendectomy is currently not supported in the literature and should be discouraged.

Antibiotic therapy The pathogenic organisms recovered in peritoneal cultures derive from the colon and consist of aerobic or facultative bacteria and anaerobes. The most frequently isolated organisms are *E. coli*, enterococci, viridans streptococci, *B. fragilis*, *Lactobacillus* species, *Prevotella melaninogenica*, and *Bilophila wadsworthia*.^{168–170} It is noteworthy that the use of intraoperative peritoneal cultures has not been shown to affect the incidence of wound infection, abscess formation, or small bowel obstruction if patients are presumptively managed with antibiotics that cover gram-negative bacteria and enteric anaerobes.¹⁷⁰

Appropriate coverage can be obtained with any of the following: piperacillin/tazobactam, cefoxitin, cefotetan, ticagycline, ertapenem, moxifloxacin, and ciprofloxacin plus metronidazole.^{171–174} In a trial involving children with perforated

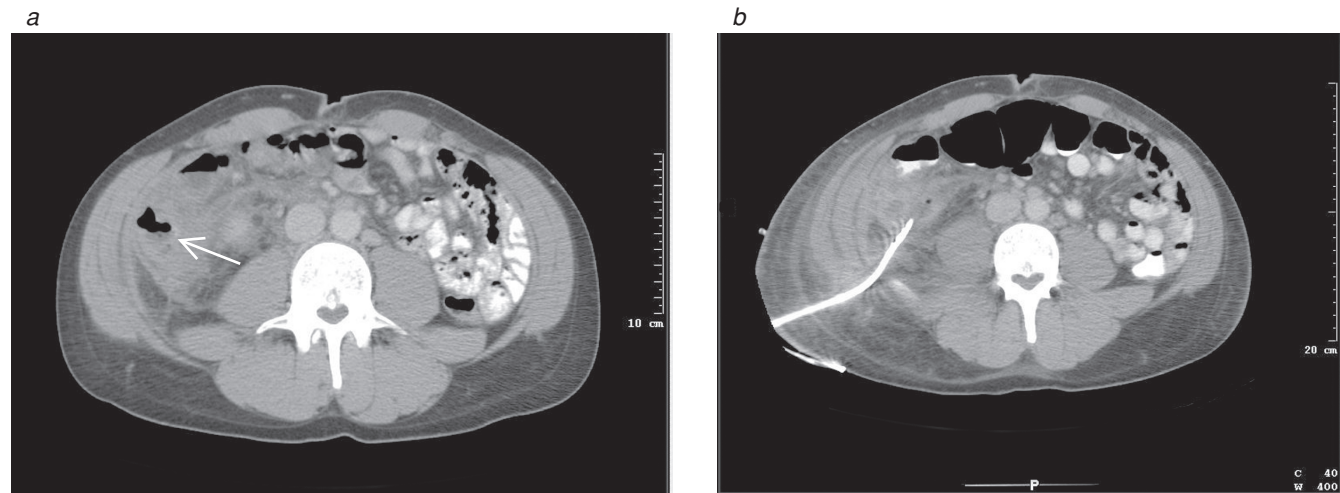


Figure 12 (a) A pelvic computed tomographic (CT) scan of a young patient with a 5-day history of right lower quadrant abdominal pain showing fluid collection containing air adjacent to the appendix and consistent with appendiceal perforation and abscess formation (*white arrow*). (b) A pelvic CT scan of the same patient after percutaneous ultrasound-guided placement of drainage catheter showing evacuation of air and much fluid. The patient underwent uneventful interval appendectomy 6 weeks later.

appendicitis, conversion to oral therapy after parenteral therapy was equivalent to parenteral therapy alone.^{175,176} In a study of patients with acute nonperforated appendicitis, preoperative administration of cefoxitin was superior to placebo in reducing the incidence of wound infection.¹⁷² In a study of children with acute nonperforated appendicitis, prolonged antibiotic administration (5 days) had no advantage over a single preoperative dose with respect to the incidence of wound infection or subsequent abscess formation.¹⁷⁷ The duration and timing of antibiotic administration in patients with nonperforated gangrenous appendicitis have not been shown to correlate with the wound infection rate.¹⁷⁸

COLONIC PERFORATION

Diagnosis

Diagnostic strategies for identifying colon lesions associated with intra-abdominal infection follow the general approach outlined earlier [see Clinical Evaluation, and Investigative Studies, *above*]. For unstable patients with generalized peritonitis, there is no need to delay operative intervention to wait for radiologic confirmation: the pathologic condition will be identified in the course of the operation. However, for patients who have localized peritonitis or those who are stable and whose physical examination is not conclusive for peritonitis, radiologic evaluation is pivotal in planning treatment.

Although plain films may reveal free air in the abdomen and prompt surgical intervention, CT may be a more valuable first study because of its ability to delineate the bowel wall and surrounding soft tissues with remarkable accuracy. In a 2002 study comparing abdominal radiography with CT for the evaluation of acute nontraumatic abdominal pain in the emergency department, the former was not nearly as diagnostically sensitive as the latter (a nonspecific diagnosis in 68% compared with a specific diagnosis in 80%).¹⁷⁹ The

investigators concluded that CT was the initial radiographic modality of choice for patients with acute abdominal pain in the emergency department. Another study found that CT scans frequently changed physicians' initial diagnoses, increased diagnostic certainty, and led to more appropriate treatment in patients with acute abdominal pain in the emergency department.¹⁸⁰

In view of the relatively high cost of CT, the concomitant radiation exposure, and the use of IV contrast agents to enhance the scans, some have suggested using ultrasonography to make diagnoses. However, the well-documented dependency of this modality on the skill of the individual technician makes it less attractive to the broader health care community, where full-time sonographers are not always available. Finally, it should be noted that there is no role for MRI in the acute setting except in a pregnant patient and patients with iodine allergy. Although it is both sensitive and specific, the logistic hindrances associated with its use greatly limit its applicability.

Treatment

Diverticulitis Diverticular disease ranges in severity from minor to serious. The focus of our discussion is on management of complicated (perforated) diverticular disease, for which resection should be considered after only one episode.

In the past, treatment of perforated diverticular disease involved a multistage surgical approach whereby the patient underwent three separate procedures: one for fecal diversion and drainage of the infection, a second for resection of the diseased segment, and a third for closure of the colostomy. This three-stage approach proved to be associated with high morbidity, high cumulative mortality, and prolonged hospitalizations.^{181–183} Since then, CT-guided percutaneous drainage, primary resection of the diseased segment, and improved patient selection for resection and primary anastomosis have

improved patient outcomes dramatically. Few adequately powered trials evaluating treatment of complicated diverticular disease have been done; accordingly, many of the current treatment standards have been derived by consensus on the basis of thorough review of the literature.

SCORE Therapy for perforated diverticular disease depends greatly on the patient’s condition at the time of presentation and on the stage of the disease. The Hinchey staging system¹⁸⁴ [see Table 3] classifies perforated diverticular disease according to the associated inflammatory process and is used to guide and compare treatment options.^{185–187}

In stage I disease, a small pericolic abscess [see Figure 13a] in a stable and otherwise healthy patient may resolve with conservative management, including broad-spectrum antibiotics and bowel rest. The patient can be evaluated for definitive surgical treatment later, after the episode resolves and the patient is in better condition for surgery. For larger abscesses or stage II disease [see Figure 13b], the standard of care is CT-guided percutaneous abscess drainage, if feasible. After drainage, resuscitation, and bowel preparation, a one-stage colectomy can be done (resection of the diseased segment with primary anastomosis) to avoid the potential increased morbidity of a two-stage procedure.¹⁸⁸

Table 3 Hinchey System for Classification of Perforated Diverticulitis ^{184,201}	
Stage	Description
I	Pericolic or mesenteric abscess
II	Pelvic or retroperitoneal abscess that is walled off
III	Purulent peritonitis
IV	Feculent peritonitis

For patients who have abscesses that are inaccessible to percutaneous drainage or who experience persistent symptoms despite drainage, operative correction is required. If adequate bowel preparation can be carried out, primary anastomosis at the time of surgery should be considered. If adequate bowel preparation is not possible, a two-stage approach, including a Hartmann procedure and subsequent stoma reversal, should be considered. Alternatively, depending on the patient’s condition, resection with primary anastomosis may be attempted. There is some evidence that employing intraoperative colonic lavage to reduce the fecal column and thus allow primary anastomosis may reduce morbidity, especially in patients with stage I or II disease.^{189–191} However, the studies supporting this view are not conclusive enough for such a regimen to be considered standard; further investigation is warranted before it is generally accepted. Finally, whether to add a diverting stoma to a primary anastomosis is a case-by-case decision that is usually guided by the presence of risk factors such as poor nutritional status, inadequate bowel preparation, blood loss, or intraoperative hypotension.¹⁹²

Stage III or IV diverticulitis is a surgical emergency that calls for prompt resuscitation and administration of broad-spectrum antibiotics, followed rapidly by surgical treatment. The Hartmann procedure is the most widely accepted operation for this presentation.^{193–195} It is associated with a substantially lower mortality than drainage followed by colostomy as a separate, delayed procedure (12% versus 28%).¹⁹⁶ In certain circumstances, with appropriate patient selection and low feculent contamination, primary anastomosis, with or without a covering stoma, may be feasible.^{197–199}

The goals of resection are to remove the focus of infection and to prevent recurrent attacks. Recurrent diverticulitis after resection is the result of incomplete removal of the diseased segment, especially at the rectosigmoid junction. Therefore,

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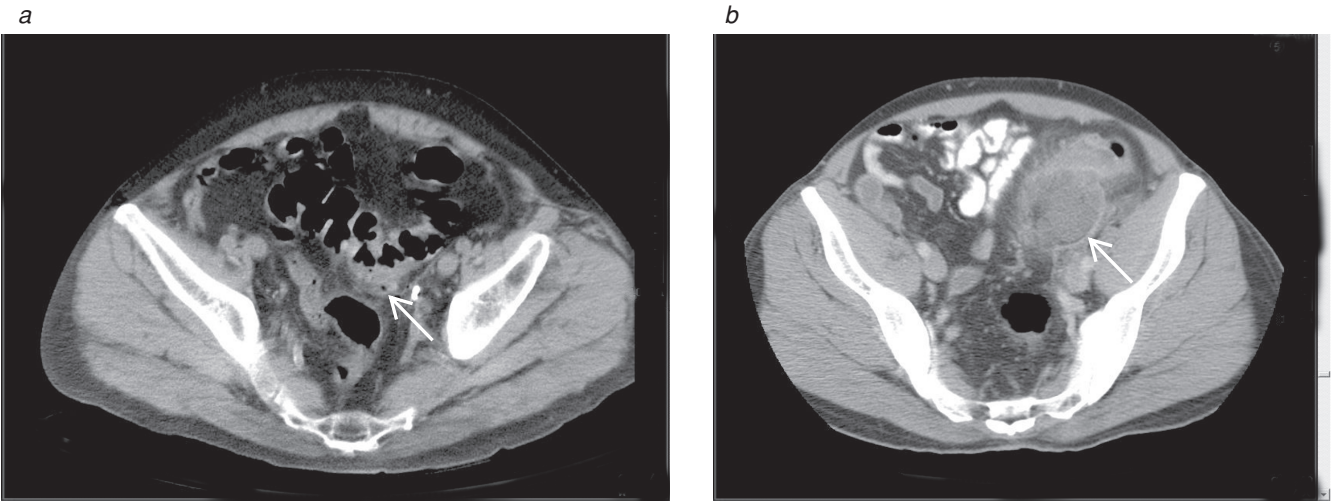


Figure 13 (a) A pelvic computed tomographic (CT) scan of an elderly patient with left lower quadrant abdominal pain of 2 days’ duration showing diverticulitis with a small amount of extraluminal air (white arrow). The patient was treated acutely with resuscitation and antibiotics alone and was discharged home without complications. (b) A pelvic CT scan of a middle-aged patient with a 1-week history of constipation and moderate pelvic pain showing left lower quadrant fluid collection consistent with peridiverticular abscess (white arrow). Proximal bowel is seen anterior to the abscess, distal bowel posterior. A percutaneous drain was placed, and elective colectomy with primary reanastomosis was performed 12 days later.

when the diseased segment is resected, the entire sigmoid must be removed, and the distal resection margin must extend below the confluence of the taeniae coli and onto pliable rectum.²⁰⁰ Proximally, the colon is mobilized until a margin of uninflamed bowel is identified. It is not, however, necessary to remove the entire colon affected by diverticuli.

Laparoscopy Laparoscopic treatment of diverticular disease is becoming more common but remains controversial. Many feel that there is no place for laparoscopic-assisted colectomy in the treatment of stage III or IV disease,¹⁸⁵ but there is growing acceptance of this approach in the treatment of stage I and II disease. A review of several small studies concluded that laparoscopic colectomy had a high potential for reducing hospitalization time and operative morbidity; however, the cost analysis data were conflicting, and some of the trials reported very high conversion rates.²⁰¹

Right-side disease Particular mention should be made of right-side diverticulitis. In the past, this condition was often misdiagnosed as appendicitis before exploration, but today, with the increased use of CT, this error is less frequently made. Given that diagnosis is difficult and the disease is surgically curable, some authors suggest that it should be treated with aggressive resection, ranging from simple diverticulectomy to right hemicolectomy.^{202,203} Others argue that the disease is relatively benign in the absence of perforation and suggest leaving the diseased bowel in situ, performing an incidental appendectomy, and then treating the patient conservatively.^{204,205} There is no standard therapy for cecal diverticulitis, mainly because of the small number of patients it affects annually, which translates into small series reported in the literature. In the course of follow-up, it is important that these patients undergo thorough evaluation for colon cancer.

Antibiotic therapy Appropriate antibiotic administration is an integral part of standard therapy for diverticular disease and is started at diagnosis. The most frequently isolated organisms are anaerobes, including *Bacteroides*, *Peptostreptococcus*, *Clostridium*, and *Fusobacterium* species. Gram-negative aerobes (predominantly *E. coli*) and facultative gram-positive bacteria (predominantly streptococci) are also associated with these infections.²⁰⁶ Parenterally administered broad-spectrum antibiotics are standard. A particularly common regimen is ciprofloxacin plus metronidazole, but other regimens are equally efficacious for treatment. According to a 2002 report from the Surgical Infection Society, the duration of therapy for complicated intra-abdominal infections should be no longer than 5 to 7 days.¹³⁹ If ongoing infection is suspected at the termination of treatment, investigation into a potential source of infection is warranted.

Other colon lesions associated with perforation and peritonitis A number of colonic conditions besides diverticular disease may be manifested by colonic perforation and secondary peritonitis. Whatever the specific cause, the general goals of therapy remain the same: (1) to identify and control the source of bacterial contamination, (2) to reduce the level of peritoneal contamination, and (3) to prevent recurrent infections.

Colon cancer After diverticular disease, colon cancer is the next leading cause of colonic perforation in uninjured patients.

In general, perforated colon cancer carries a high mortality,^{207,208} and the operative technique of choice is controversial. Perforation typically occurs at the site of the lesion but can also occur proximally (e.g., at the cecum) as a result of luminal obstruction.

Generally, perforations at the site of cancer in the ascending and transverse colon are treated with primary resection and anastomosis, with or without a diverting stoma, regardless of whether localized or diffuse peritonitis is present. When perforations occur at the site of cancer in the descending and sigmoid colon, however, there is some debate over the appropriate surgical approach, with some advocating primary resection and others staged procedures. Two studies from the early 1990s suggested improved long-term mortality after primary resection.^{209,210} A subsequent study, however, suggested that the improved mortality associated with primary resection was secondary to preselection and therefore could not be considered conclusive proof of the superiority of this approach. The authors of this latter study concluded that primary resection was appropriate for a select patient population with minimal comorbidity and that staged resection was beneficial for patients with a high degree of acute illness and comorbidity (e.g., elderly patients).²¹¹

Less common causes of colonic perforation Other diagnoses associated with colonic perforation and peritonitis (localized or diffuse) are ischemic necrosis as a result of vasculopathology [see Figure 14a] or volvulus, missed traumatic injury, and IBD [see Figure 14b]. Except for IBD, the standard therapy is excision of the affected segment and reanastomosis, with or without a covering stoma. For patients with numerous comorbidities, a high degree of feculent contamination, or very severe illness necessitating an extremely abbreviated operating time, a Hartmann procedure with a mucous fistula or an oversewn distal segment is the primary treatment. Because perforation associated with IBD is typically a self-limited disease, treatment is directed at the underlying pathophysiology and excision of the diseased segment is not always indicated.²¹²

Other Abdominal Infections

PELVIC INFLAMMATORY DISEASE

Because of the diverse clinical presentations of pelvic inflammatory disease (PID) and the significant sequelae associated with delayed diagnosis, women with this condition can pose a major diagnostic dilemma in the emergency department. In 2002, the Centers for Disease Control and Prevention (CDC) updated their established diagnostic guidelines for initiating therapy in patients with suspected PID.²¹³ According to these guidelines, empirical treatment should be started if a young, sexually active woman or any woman at risk for sexually transmitted diseases presents with symptoms [see Table 4] that cannot be attributed to another cause. To reduce undue treatment-associated morbidity, additional criteria are supplied to aid in specifying precisely who should receive treatment.

Treatment of PID, according to the CDC, includes broad-spectrum antibiotics directed toward *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, anaerobes, gram-negative facultative

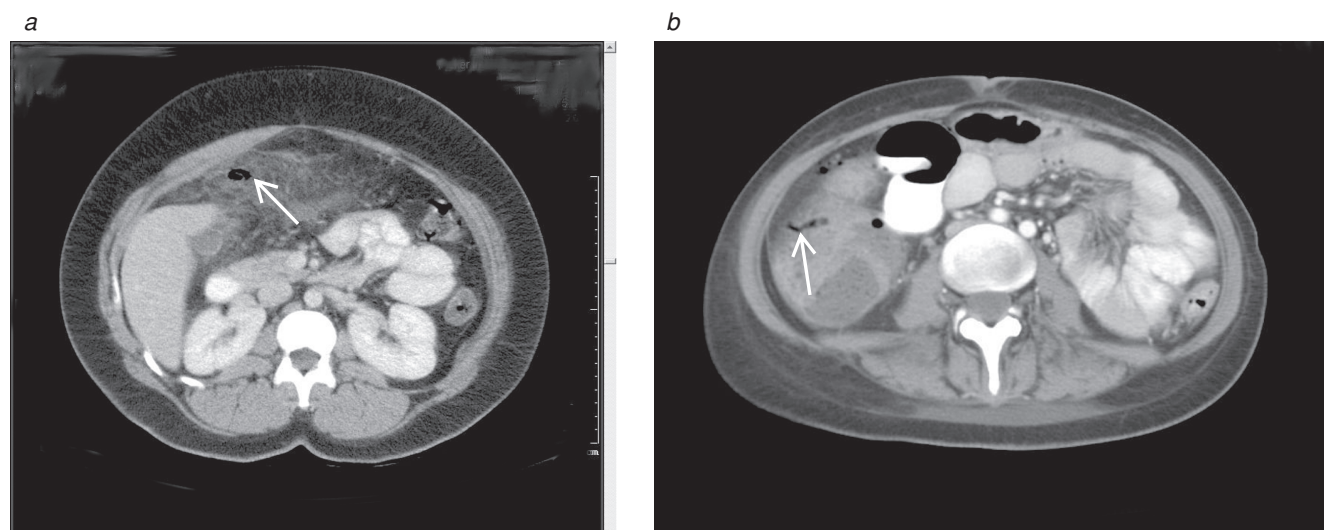


Figure 14 (a) An abdominal computed tomographic (CT) scan of an elderly patient with a history of vascular disease and worsening abdominal pain over a 3-day period showing diffuse inflammation and right upper quadrant extraluminal air (white arrow). The patient underwent emergency exploration, and ischemic perforation of cecum was found. Right hemicolectomy and temporary diverting ileostomy were performed. (b) An abdominal CT scan of a patient with a history of Crohn disease and worsening abdominal pain demonstrating thickening of the colonic wall with both intramural and extramural air (white arrow). The patient was treated with emergency total abdominal colectomy for pancolitis with creation of a temporary diverting ileostomy.

Table 4 CDC Guidelines for Diagnosis of Pelvic Inflammatory Disease²¹³

Minimal symptoms
Uterine/adnexal tenderness
Cervical motion tenderness
Additional supportive criteria (enhanced specificity of minimal symptoms)
Oral temperature > 38.3°C (>101°F)
Abnormal cervical or vaginal mucopurulent discharge
Presence of white blood cells on saline microscopy of vaginal secretions
Elevated erythrocyte sedimentation rate
Elevated C-reactive protein
Laboratory documentation of cervical infection with <i>Neisseria gonorrhoeae</i> or <i>Chlamydia trachomatis</i>
Most specific criteria
Endometrial biopsy with histopathologic evidence of endometritis
Transvaginal sonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex
Laparoscopic abnormalities consistent with PID

CDC = Centers for Disease Control and Prevention; PID = pelvic inflammatory disease.

bacteria, and streptococci [see Table 5]. Hospitalization is suggested when surgical emergencies (e.g., appendicitis) cannot be excluded or when the patient is pregnant; does not respond clinically to oral antimicrobial therapy; cannot follow or tolerate an outpatient oral regimen; has severe illness, nausea and vomiting, or high fever; or has a tubo-ovarian abscess. Surgical intervention for PID is generally limited to patients with symptomatic pelvic masses, ruptured tubo-ovarian abscesses, or draining abscesses that do not respond to antibiotic

therapy. Aspiration has also been considered as a treatment modality; it may limit morbidity and preserve fertility.²¹⁴

PYELONEPHRITIS

Pyelonephritis is a complication of urinary tract infection; consequently, it affects women more often than men. The diagnosis is typically made on the basis of systemic symptoms in the setting of a known, bacteriologically confirmed urinary tract infection. Pyelonephritis may be classified as either complicated or uncomplicated depending on patient factors (e.g., previous transplantation or an anatomic abnormality) and infectious characteristics (e.g., sepsis).

The typical pathogen in uncomplicated disease is *E. coli*, and outpatient treatment with trimethoprim-sulfamethoxazole or a fluoroquinolone usually suffices.²¹⁵ Complicated pyelonephritis, however, often is caused by microbes other than *E. coli*, including *Pseudomonas* species and enterococci. Hospitalization is required, and treatment usually involves parenteral administration of ceftriaxone²¹⁶ and/or piperacillin/tazobactam²¹⁷; vancomycin is indicated if the patient is allergic to penicillin. More aggressive therapies, including percutaneous nephrostomy or abscess drainage, may be considered on a case-by-case basis.

SPONTANEOUS BACTERIAL PERITONITIS

In adult patients, primary peritonitis usually accompanies cirrhosis and ascites²¹⁸; however, the presentation can be highly variable. To diagnose spontaneous bacterial peritonitis, paracentesis is performed and the fluid sent for Gram stain and culture (ascetic fluid inoculation, 10 mL, in blood culture bottles should be performed at the bedside); pH determination; measurement of glucose, protein, lactate, and lactic dehydrogenase levels; and a cell count with differential. According to a consensus statement from the International

Table 5 CDC Guidelines for Antibiotic Treatment of Pelvic Inflammatory Disease ²¹³	
Parenteral regimens	
A	Cefotetan, 2 g IV q. 12 hr or Cefoxitin, 2 g IV q. 6 hr plus Doxycycline, 100 mg p.o. or IV q. 12 hr
B	Clindamycin, 900 mg IV q. 8 hr plus Gentamicin, loading dose IV or IM (2 mg/kg body weight) followed by maintenance dose (1.5 mg/kg) q. 8 hr; single daily dosing may be substituted
Alternative	Ofloxacin, 400 mg IV q. 12 hr or Levofloxacin, 500 mg IV s.i.d. with or without Metronidazole, 500 mg IV q. 8 hr or Ampicillin-sulbactam, 3 g IV q. 6 hr plus Doxycycline, 100 mg p.o. or IV q. 12 hr
Enteral regimens	
A	Ofloxacin, 400 mg p.o., b.i.d., for 14 days or Levofloxacin, 500 mg p.o., s.i.d., for 14 days with or without Metronidazole, 500 mg p.o., b.i.d., for 14 days
B	Ceftriaxone, 250 mg IM in single dose or Cefoxitin, 2 g IM in single dose, and probenecid, 1 g p.o. administered concurrently in a single dose or Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) plus Doxycycline, 100 mg p.o., b.i.d., for 14 days with or without Metronidazole, 500 mg p.o., b.i.d., for 14 days

CDC = Centers for Disease Control and Prevention; IM = intramuscular; IV = intravenous.

Ascites Club, diagnostic paracentesis is recommended for every cirrhotic patient with ascites on admission to the hospital.²¹⁹ Empirical therapy is started if the neutrophil count is higher than 250/ μ L, the pH is lower than 7.35, and the lactate concentration is greater than 32 ng/mL. If the results of other studies suggest peritonitis, radiographic evaluation is indicated to rule out potential causes of secondary peritonitis.

Treatment consists of antibiotics, for example, cefotaxime at a minimum dosage of 2 g every 12 hours for 5 days, with follow-up paracentesis scheduled for 48 hours after the start of treatment.^{219–222} If the neutrophil count does not decrease significantly (to < 25% of the pretreatment value), treatment may be assumed to have failed. Surgical intervention is undertaken if the patient is refractory to medical management, the ascitic fluid grows mixed aerobes and anaerobes, or radiographic studies suggest secondary peritonitis, such as bowel perforation.

PERITONEAL DIALYSIS CATHETER-RELATED INFECTIONS

Peritonitis is a major cause of failure of peritoneal dialysis in long-term studies.²²³ Peritonitis is especially difficult to diagnose in dialysis patients because the presentation is usually vague. Accordingly, it is critical to maintain a low threshold for testing. The definition of peritonitis in this population includes satisfaction of two of the following three criteria: (1) a Gram stain demonstrating microorganisms or a positive culture of the dialysis effluent, (2) a dialysate white blood cell count higher than 100/ μ L, with at least 50% neutrophils, and (3) peritoneal signs or symptoms.²²⁴ The microbes most commonly identified are *Staphylococcus epidermidis* and *S. aureus* ($\approx$ 60% of isolates), followed by gram-negative bacteria ($\approx$ 30% of isolates); the remaining isolates are largely accounted for by fungi, anaerobes, and mycobacteria.

Treatment usually includes cefazolin and an aminoglycoside, with or without vancomycin (depending on local *S. aureus* resistance patterns). Antibiotics are administered via the catheter and allowed to dwell intraperitoneally. When treatment is complete, the antibiotic effluent is drained via the catheter. If infection continues despite antibiotic treatment, a recurrent infection with the same microbe is likely. If fecal contamination occurs, the catheter must be removed.

Discussion

Controversies and Special Cases

The controversies surrounding the management of intra-abdominal infections are numerous and ongoing, in large part because of the relative lack of well-organized, unbiased clinical evidence. There are several reasons for this information deficit. First, although in the aggregate, peritonitis is a common problem seen by general surgeons, any given practitioner sees most of the life-threatening forms of the disease (e.g., free perforation from colon cancer) infrequently. Second, advances in nonsurgical medicine and technology (e.g., laparoscopy)

have made new forms of treatment available and have improved outcomes from older techniques. As a result, conclusions drawn from older data may no longer be accurate. Third, many forms of intra-abdominal infection routinely present in such a complex and ill patient population (e.g., elderly patients with multiple comorbidities) that randomized studies with multiple exclusion criteria can rarely capture a high percentage of what is a highly heterogeneous group. Fourth, patients presenting with common causes of intra-abdominal infection that occur in relatively healthy and homogeneous populations (e.g., acute appendicitis and

cholecystitis) tend to do well no matter what reasonable therapy is applied. Consequently, it is frequently difficult to detect any significant differences between therapeutic modalities. For example, despite multiple randomized trials, it is still unclear whether a laparoscopic approach has any long-term superiority over an open approach in patients with right lower quadrant pain and suspected appendicitis: outcomes are excellent with either method. Finally, for almost any given argument, sufficient supporting data, whether in the form of randomized trials or—equally valuable—of large observational studies performed with statistical rigor, simply do not exist at present. Even simple questions, such as the optimum duration of antibiotic treatment for a patient with a single well-drained liver abscess, lack good answers.

In the end, most controversies in this area are not so much a matter of precisely determining the right or the wrong intervention for a disease as they are a matter of making a judgment about which of many possible interventions is likely to result in the lowest morbidity and mortality. For example, the decision to perform a primary colon reanastomosis in a patient with a perforated colon cancer cannot be considered either universally correct or universally incorrect; rather, it is subject to the surgeon's opinion about the specific patient involved. In what follows, we focus on several controversial decision points and discuss important factors that ought to be considered in attempting to optimize patient care.

NONOPERATIVE MANAGEMENT OF ACUTE APPENDICITIS

For over 120 years, appendectomy has been advocated as the treatment of choice in patients presenting with acute appendicitis. Occasional reports of conservative management with antibiotics or even herbal medications have been published in the United States and China, respectively, with a 7% recurrence of appendicitis at follow-up. Although current recommendations state that patients with acute appendicitis should always be treated with antimicrobials, the benefit and necessity of interval appendectomy have recently become a debatable issue. Two prospective randomized trials compared outcomes—pain, time to recovery, and adverse events—between medical and surgical (laparoscopic or open) treatment for acute appendicitis. Conservative treatment with antibiotics consisted of IV cefotaxime plus tinidazole for 2 days, followed by ofloxacin plus tinidazole for 8 days. Compared with open surgery, patients treated with antibiotics alone were found to have significantly lower subjective and objective pain scores and morphine consumption, although the recovery time was unaffected. Up to 12% of patients treated medically required an appendectomy after 12 hours of treatment and up to 35% of patients had surgery in the following year. The wound infection rate was reported as 14% after surgical treatment.^{225,226}

Current standard treatment for acute appendicitis is appendectomy with perioperative antibiotics. However, there is somewhat limited evidence to suggest that antibiotic treatment alone may reduce pain and narcotic consumption, although one third of patients are likely to be readmitted with acute appendicitis requiring surgery within 1 year.^{225,226}

CHANGING BACTERIOLOGY OF ACUTE BILIARY INFECTION

Most biliary infections are polymicrobial. The organisms most frequently cultured are *E. coli*, *Klebsiella* species,

Enterobacter species, and enterococci. Anaerobic bacteria are infrequently implicated in biliary infections. Peptostreptococci and clostridia are found occasionally; clostridia are especially common in patients with emphysematous cholecystitis.⁴⁰ Gram-negative anaerobic bacilli are rarely present in patients with biliary infection. In one study, only two of 28 patients with acute cholangitis had anaerobic bacteria in the bile; another investigator found anaerobic bacteria in 3 to 4% of cultures in similar patients.²²⁷ However, a higher incidence of anaerobic bacteria has been reported in patients who have acute cholangitis and acute cholecystitis than in patients who have chronic cholecystitis and cholelithiasis.²²⁸

One investigator noted an increased incidence of anaerobic bacteria in biliary infection and suggested that *B. fragilis* may play a more important role in the polymicrobial flora of biliary tract infection than was previously appreciated.²²⁹ These findings remain controversial. *Bacteroides* species are generally considered to be of limited importance in biliary tract infections, except in selected groups of patients. These groups include diabetics, the elderly,²³⁰ and those with acute cholangitis who have previously undergone biliary operation^{231,232}; in particular, malfunctioning biliary-intestinal anastomoses increase the risk of *Bacteroides* infection.²³³

NECESSITY OF DIVERSION AFTER EMERGENCY COLONIC PROCEDURES

The goal of safely repairing or resecting the colon in an emergency setting without leaving a patient with a temporary or permanent stoma for diversion has been pursued for decades. Through much of the 20th century, largely on the basis of wartime experience, diversion was routinely performed. Today, however, it is apparent that this approach is not always necessary either for trauma or for intrinsic colon disease. Thus, the question is no longer whether primary repair or reanastomosis can be achieved safely but, rather, in which individual patient a given treatment is prudent.

Traditionally, clinical studies have attempted to define patient characteristics associated with complications after attempted primary repair or reanastomosis. Not surprisingly, hypotension, blood loss, delay before treatment, and extensive contamination have all been associated with postoperative complications after primary repair; however, these risk factors are associated with complications after diversion as well. The nature of the colon injury is clearly an important consideration: multiple studies now support a one-step approach to traumatic colon injury in all except the most ill patients, but primary resection and reanastomosis for other causes of perforation (e.g., diverticulosis and cancer) remain controversial. Many nonrandomized studies have demonstrated that for nontraumatic causes of perforation, on-table lavage and primary resection yield outcomes equivalent to those of the Hartmann procedure, which suggests that both approaches are safe and that surgeons are capable of identifying the patients best suited to each one.

Perhaps more important than determining how likely a patient is to experience a complication after a given operation, however, is assessing how well the patient is likely to tolerate that complication in the early postoperative period. Thus, elderly patients with multiple comorbidities might be

better off undergoing diversion and thus avoiding the potential significant physiologic stress posed by an anastomotic leak in the early postoperative period, even though they will face the additional risk associated with reoperation if they subsequently choose to have a stoma reversed.

ROLE OF LAPAROSCOPY IN MANAGEMENT OF PERITONITIS

Laparoscopy has altered the surgical landscape by offering a minimally invasive approach that reduces the morbidity associated with a large incision, generally decreasing convalescence time and hastening return to normal activity. Nonetheless, laparoscopic management of intra-abdominal infection is still hindered somewhat by the difficulty of inspecting the entire bowel, the decreased tactile sensation, and the significantly greater expertise required for laparoscopic resection and reanastomosis of the bowel. These obstacles notwithstanding, almost every intra-abdominal procedure used to treat infection has been performed laparoscopically with acceptable results.

The single most important factor in the decision whether to take a laparoscopic approach is the skill and experience of the surgeon. From a theoretical point of view, it is almost always possible to treat a patient with peritonitis laparoscopically; the real question is whether the surgeon can perform the procedure most safely and efficiently via an open or a minimally invasive approach. The answer to this question will rely to a large extent on preoperative imaging studies. In addition, even if the surgeon does not plan to complete the operation laparoscopically, initial placement of the scope may aid in planning the most appropriate open incision and procedure by localizing the lesion of interest.

MANAGEMENT OF ANASTOMOTIC LEAKS

Dehiscence of a GI anastomosis is a common and too frequently fatal complication of modern GI surgery. Again, there is little debate regarding which therapeutic options are available to surgeons managing this problem. The options include the following: supporting the patient with medical care only, in the case of a tiny, radiographically evident but clinically insignificant leak seen on fluoroscopic study; reoperating and performing primary repair and drainage, in the case of a small early leak from an enteroenterostomy with minimal soilage; performing percutaneous drainage, in the case of a moderately symptomatic leak presenting in a delayed manner with an abscess; and reexploring and performing a diverting procedure, in the case of complete or near-complete disruption of an anastomosis with widespread fecal contamination. The only controversy has to do with which course (or combination of courses) to take in an individual patient.

Some general guidelines for the management of anastomotic dehiscence may be recommended, with the caveat that they have not yet been rigorously tested. Leaks diagnosed in the immediate postoperative period are easily approached because the relevant tissue planes have been dissected free. After 1 to 2 weeks, however, early adhesion formation makes reoperation more difficult, especially if the initial operation was for an infectious or inflammatory process, and increases the risk of complications, particularly inadvertent enterotomy and enterocutaneous fistula formation. Small, contained

leaks, if accessible, frequently respond to percutaneous drainage and antibiotics alone, with the small fistula resolving spontaneously. Medical management in such cases generally includes TPN, although EN is occasionally feasible if it is shown to have no effect on drain output. Larger leaks, on the other hand, are more likely to call for direct operative repair, resection and reanastomosis, or diversion. Once it is decided that surgical treatment is warranted and is not precluded by the state of the abdomen, definitive management should not be delayed. Exactly which operation is to be performed depends on the health of the bowel, the severity of abdominal contamination, and the level of overall physiologic dysfunction.

MANAGEMENT OF ENDOSCOPIC BOWEL PERFORATION

Large rents in a peritoneal portion of the bowel generally call for operative repair (most commonly to the colon), although it should be noted that simple repair or resection without diversion is almost always all that is required. Extra-peritoneal or retroperitoneal perforations, however, can be managed nonoperatively with antibiotics and IV fluids if the patient is stable. This situation occurs most frequently after ERCP or with low rectal perforations. Typically, CT demonstrates retroperitoneal air with minimal free peritoneal air. In these circumstances, patients can be safely observed as long as their condition does not deteriorate; oral intake can be restarted after 5 to 7 days. Endoscopic perforations of a normal distal esophagus can also be managed nonoperatively, although a perforation proximal to a tumor or stricture is unlikely to heal and almost always must be treated operatively.

NONOPERATIVE MANAGEMENT OF INFECTED FLUID COLLECTIONS

It is axiomatic that abscesses are best treated with drainage rather than with antibiotics, but there are certain circumstances in which drainage may not be possible. Pyogenic liver abscesses may not be amenable to either percutaneous or open drainage if they are multiple and involve both lobes. In such circumstances, aspiration or drainage of the largest abscess, followed by a long course of antibiotics, is generally successful. It has been argued that this approach works because of the liver's luxurious dual blood supply.

On the other hand, multiple peritoneal fluid collections (without a natural blood supply) are not infrequently seen even after successful management of diffuse or fecal peritonitis yet can occasionally be managed without drainage. Even if these collections are subsequently proved to be infected, they may be too numerous to approach percutaneously, and ongoing inflammation of the bowel may render an operative approach unsafe. Again, drainage of the largest accessible collection to establish a diagnosis and guide antibiotic management, followed by long-term antibiotic therapy, is the most feasible course. In this case, sampling is imperative because a hospital-acquired intra-abdominal infection is more likely to involve less common but more resistant pathogens, including fungi. Regardless of the situation, however, the optimal duration of antibiotic therapy for small undrained abscesses remains to be established.

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Acknowledgments

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20 FUNGAL INFECTION

Pamela A. Lipsett, M.D., F.A.C.S., F.C.C.M.

Approach to the Surgical Patient at Risk for Candidiasis

Fungal infections remain an important cause of morbidity and mortality in surgical settings, with critically ill patients, transplant patients, and sick neonates all being especially vulnerable. Over the past few decades, technological and scientific advancements have improved physicians' ability to sustain life in critically ill patients; developments in chemotherapeutics and immune-based therapies have yielded increased survival for many cancer patients; organ transplantation has evolved dramatically; and the use of invasive therapies (e.g., ventricular assist devices) has increased markedly. With these changes has come an increase in the incidence of serious *Candida* infections,¹ as well as an increase in the incidence of the less common (but nonetheless potentially fatal) noncandidal infections caused by *Aspergillus* and the Zygomycetes *Mucor* and *Rhizopus*.

Despite the significant progress in the supportive and intensive care of patients at risk, the development of a number of new and useful antifungal agents in the past decade, and the noteworthy improvements in therapeutic approaches to fungal infections, physicians' ability to diagnose these infections in a timely fashion remains limited, and patient outcomes remain poor. Antifungal prophylaxis has emerged as a potential means of reducing the occurrence of serious fungal infections. In patient populations estimated to be at high risk for acquiring a fungal infection, antifungal prophylaxis has reduced infection rates by about 50%; however, it has not been shown to improve mortality significantly.

This chapter outlines an approach to the workup and management of the nonneutropenic surgical patient with a suspected candidal infection, taking into account epidemiology, risk factors, diagnostic evaluation, and therapy. Noncandidal infections (aspergillosis and zygomycosis) are considered as well.

Definition and Classification

FUNGAL COLONIZATION VERSUS FUNGAL INFECTION

Colonization

Fungal pathogens can be isolated under a number of clinical conditions.²⁻⁷ Isolation of a fungal pathogen in the absence of any signs or symptoms of clinical infection is termed colonization. Fungal colonization, by itself, does not suffice to define fungal infection, but it remains an important risk factor for future invasive fungal infection. It is believed that once colonization has occurred, *Candida* pathogens can gain access to the bloodstream via three major routes: through the GI tract mucosal barrier, from an intravascular catheter, and from a localized source of fungal infection.²⁻⁷ A prolonged stay in an intensive care unit is associated with an increased risk of fungal infection. Depending on the patient population and the rigor and thoroughness with which sites are cultured, as many as 50% to 80% of critically ill patients

may experience *Candida* colonization at a single site.²⁻⁷ The colonization index (the number of sites tested divided by the number of sites colonized) and the corrected colonization index (the number of sites tested divided by the number of sites showing heavy growth) have been proposed as criteria for selecting a high-risk patient population to be considered for possible early preemptive or therapeutic intervention.^{3,8,9} When test results from multiple sites show no evidence of fungal colonization, it is almost certain that no fungal infection is present.^{3,6,9}

Infection

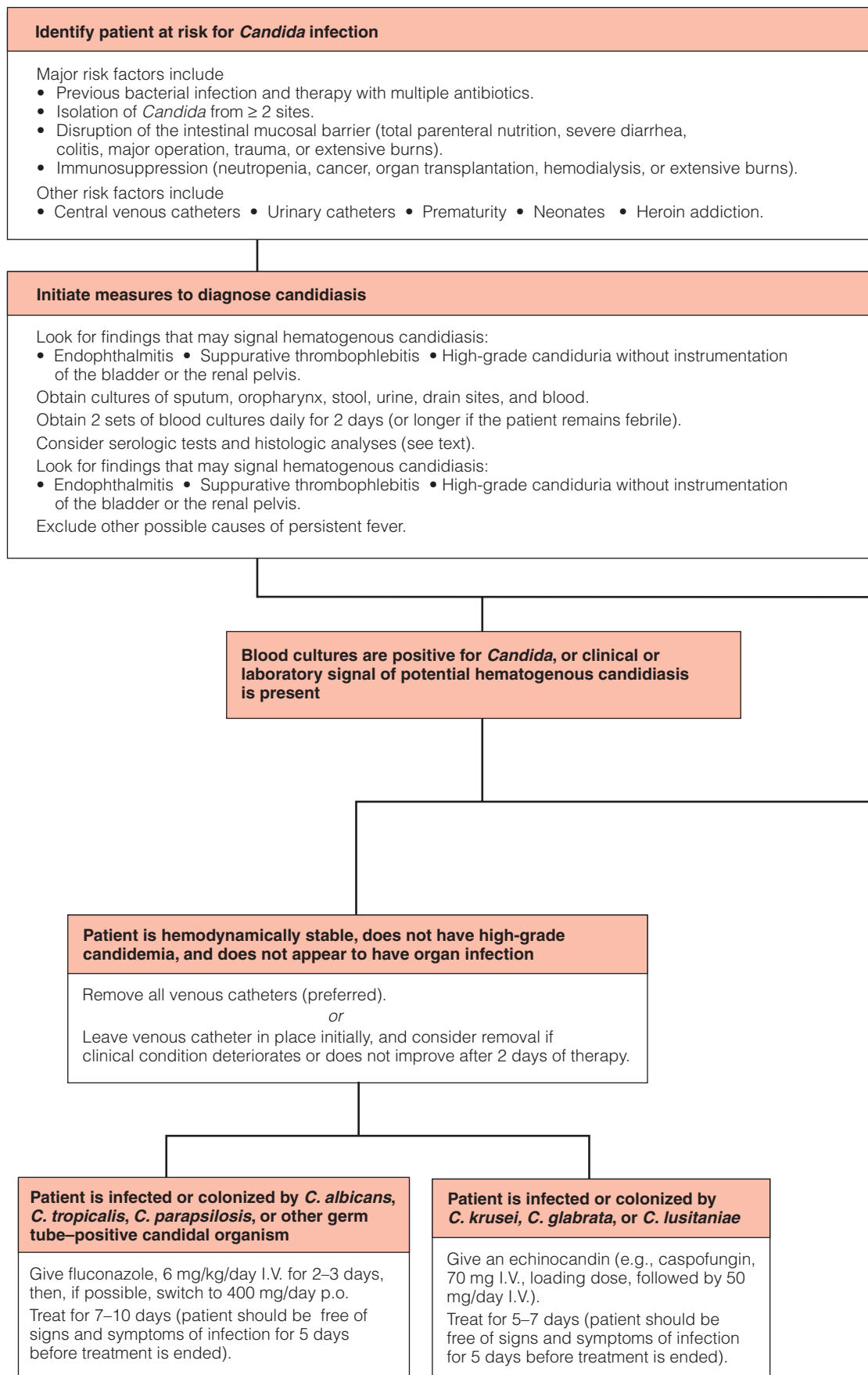
At a basic level, fungal invasion or infection might be defined as isolation of a fungal pathogen from a patient with signs and symptoms of an infection. As applied to fungal pathogens, however, this definition is an oversimplification. Clinicians relying on such a simplified definition would be prone to mistake some instances of fungal colonization for cases of true fungal infection. A degree of consensus has been reached regarding what constitutes a fungal infection in a neutropenic patient,¹⁰ but to date, no such consensus has been achieved as to what constitutes fungal infection in a nonimmunocompromised patient.^{2,8,11-18}

Given that it is not possible to establish a definitive diagnosis of fungal infection in all cases, it is often reasonable to express the diagnosis in terms of the degree of certainty about the presence of infection. Fungal infections can thus be classified as definite or probable.¹⁰ In brief, a definite fungal infection is present when deep tissue invasion is seen on a biopsy or culture from a sterile site in conjunction with clinical or radiologic abnormalities.¹⁰ Unfortunately, there is currently no agreement as to what signs and symptoms constitute a probable or possible fungal infection in a nonneutropenic patient.¹⁶⁻¹⁸

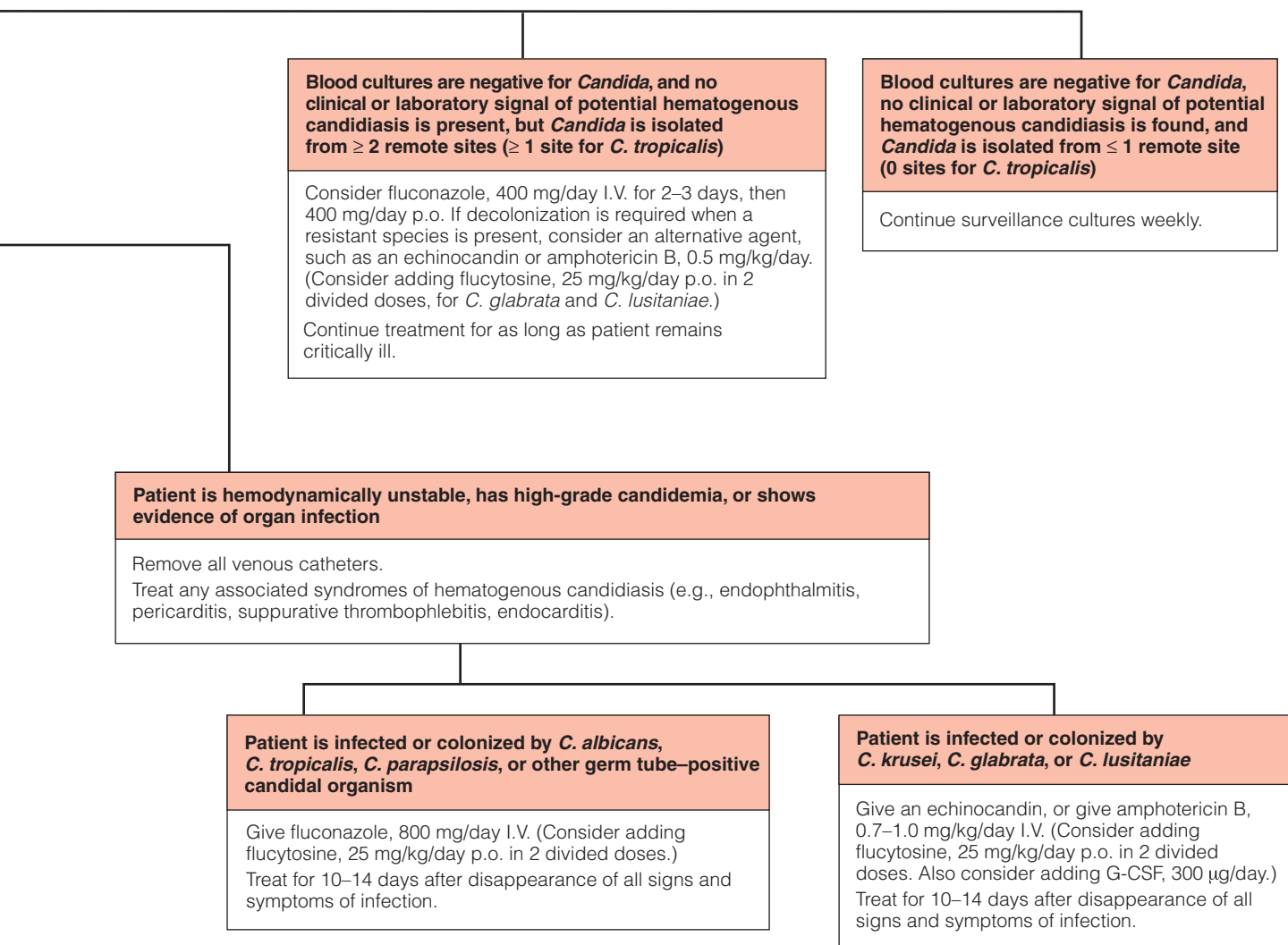
TYPES OF FUNGAL INFECTION

Candidemia

A positive blood culture has traditionally been the gold standard for the diagnosis of candidemia and is now universally accepted as establishing the presence of a fungal infection.^{16,17} Because blood-borne *Candida* can originate from a variety of different sites—including deep-seated infections (via hematogenous spread), catheter-related infections, and the gastrointestinal tract (via translocation), to name but a few—it is imperative that clinicians evaluating candidemic patients search carefully for all potential sources of infection. The search should include assessment of intravascular catheter sites, evaluation for peripheral septic thrombophlebitis, and examination of the abdomen as a possible site of infection. Because metastatic infection may develop from candidemia, new sources of fungal pathogens (e.g., endophthalmitis, infective endocarditis, hepatosplenic candidiasis, and arthritis) may arise over time.^{16,17}



Approach to the Surgical Patient at Risk for Candidiasis



A positive blood culture is an indication for initiation of anti-fungal therapy.^{16,17} However, systemic *Candida* infection may be present even in the absence of a positive blood culture. Blood cultures have a 50% false-negative rate and may take as long as 4 days to yield results. Accordingly, clinicians should not assume that the absence of a positive blood culture or tissue biopsy means that a fungal infection is not present; nearly 44% of patients with a negative blood culture have evidence of disseminated fungal infection at autopsy.¹⁹ Increasingly, candidal invasion is being observed on autopsy specimens in cases where the diagnosis had not been clinically suspected.²⁰

Disseminated Candidiasis

Patients in whom several noncontiguous organs are infected by *Candida* species are considered to have a disseminated infection acquired through hematogenous spread. To establish the diagnosis, the organism must be identified by means of histologic analysis, culture of tissue samples obtained from at least one internal organ, or both, and there should be radiographic, pathologic, or culture-derived evidence of infection in at least one other organ. The presence of candidemia in association with *Candida* skin lesions or of endophthalmitis in a setting consistent with a diagnosis of *Candida* infection is also diagnostic of disseminated candidiasis.¹⁷ Hepatosplenic candidiasis is a more chronic form of disseminated *Candida* infection that typically develops in neutropenic cancer patients.¹⁷

Epidemiology and Risk Factors

MAGNITUDE OF THE PROBLEM IN SURGICAL PATIENTS

Hospital-acquired, invasive *Candida* infections have become increasingly common causes of morbidity and mortality in hospitalized patients. Between 1979 and 2000, the incidence of *Candida* bloodstream infections increased by 207%.^{1,21,22} Data from the National Nosocomial Infections Surveillance System (NNIS) indicated that in the period from 1989 to 1998, *C. albicans* was the seventh most common cause of nosocomial infection in the ICU setting, accounting for 4.9% of bloodstream infections and 4.8% of surgical site infections.²³ Data from another national surveillance study, Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE), indicated that in the period from 1995 to 2002, *Candida* species, as a group, were the fourth most common cause of nosocomial bloodstream infection (after coagulase-negative staphylococci, *Staphylococcus aureus*, and enterococci).²⁴ In ICU patients, *Candida* species were the third most common cause of nosocomial bloodstream infection. Between 1995 and 2002, the percentage of bloodstream isolates accounted for by *Candida* species rose from 8% to 12%.

Population-based studies have identified certain demographic groups that appear to be at special risk for invasive *Candida* infection.^{1,25} One such group consists of patients at the extremes of age, with neonates being one of the most rapidly growing at-risk groups. Race appears to play a role as well. In one study, the incidence of fungal infections in neonates younger than 30 days was reported to be 466/100,000 (960/100,000 in black neonates and 238/100,000 in white neonates).²⁵ Surgical patients are also at particular risk for fungal infection: more than 50% of all fungal infections occur in this patient population.²⁴ In the National Epidemiology of Mycosis Survey (NEMIS), 42 *Candida* bloodstream infections were identified in 4,276 patients admitted to six surgical ICUs between 1993 and 1995, for an incidence of 9.8 such infections per 1,000 admissions.²⁶ *Candida* species caused

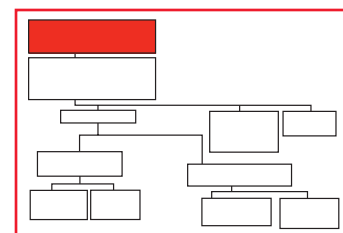
9.2% of all bloodstream infections diagnosed in the surgical ICUs, and more than half of the isolates were non-*albicans* species.

The morbidity and mortality associated with fungal infections are considerable.²⁷⁻³⁰ Between 1980 and 1997, multiple-cause mortality from mycoses in the United States rose from 1,557 deaths to 6,534 (most of which were associated with *Candida*, *Aspergillus*, and *Cryptococcus* species).²⁷ Two case-control studies performed at a single institution 15 years apart revealed no improvement in the mortality attributable to candidemia: the attributable mortality was 38% in the earlier study (1983–1986)³¹ and 49% in the later one (1997–2001).³²

Moreover, fungal infections place a substantial economic burden on the health care system.^{28-31,33} In one study, costs were, on average, \$41,000 (in 1993 dollars) higher for high-risk ICU patients than for low-risk ICU patients.³⁰ In a large European study, patients with *Candida* infection stayed longer both in the ICU (12.7 days) and in the hospital (15.5 days), and the direct costs associated with their care were higher by almost 16,000 euros.³⁰ In an earlier study from my institution (Johns Hopkins Hospital), the attributable increase in the cost of ICU care for surgical patients with fungal infections was \$21,590 (in 1996 dollars).²⁹

IDENTIFICATION OF AT-RISK SURGICAL PATIENTS

The risk factors associated with the acquisition of fungal infections have been well defined [see Table 1].^{2,11-14,34,35} General factors contributing to both the risk of incurring a fun-



gal infection and the outcome to be expected after such an infection include disruption of cutaneous or mucosal barriers, defects in the number and function of neutrophils or in cell-mediated immunity, metabolic derangements (as seen in preoperative and postoperative patients), and extreme youth or advanced age (see above). In an effort to create a rule for identifying a patient population with at least a 10% risk of fungal infection, a database of 2,890 patients who had stayed in an ICU for more than 4 days was subjected to retrospective review and statistical modeling.¹⁴ The best rule the authors were able to formulate included either the use of a systemic antibiotic or the presence of an intravenous central line, along with any two of the following: total parenteral nutrition, any dialysis, surgery, pancreatitis, or immunosuppressive agents. This rule captured 34% of patients with fungal infections. More important, it had a high negative predictive value and could be used to help exclude fungal infection as a likely possibility. Several other authors have attempted to predict a high-risk patient population, but to date, these models have not been used successfully in published papers or clinical trials and thus have not entered clinical practice.^{8,15}

Of surgical patients, those in the ICU, those who have sustained trauma or burns, and those who have received solid organ transplants (liver, pancreas, and small bowel transplant recipients, in particular) appear to be at higher risk for invasive fungal infection. The incidence of invasive *Candida* infection in liver transplant patients ranges from 1.3% to 15% for those receiving anti-fungal prophylaxis³⁶⁻³⁸ and may be as high as 23% for those not receiving prophylaxis.³⁹ In pancreas transplant recipients, the incidence of invasive fungal infection is approximately 9%⁴⁰; in small bowel transplant recipients, it may be as high as 59%.⁴¹ Longer stays in the ICU, GI surgery, and the presence of invasive central venous lines appear to impart special risk to surgical patients.^{3,26,42} One of the most important steps in treating fungal infection is rec-

Table 1 Clinical Presentation and Diagnostic Methods for Common Fungal Infections¹⁴⁷

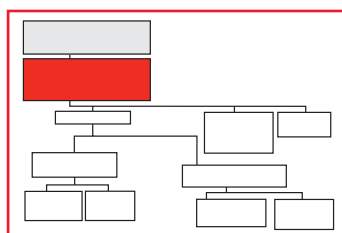
Host Fungus	Major Clinical Presentations	Diagnostic Methods
Normal host <i>Aspergillus</i> <i>Blastomyces</i> <i>Candida</i> <i>Coccidioides</i> <i>Cryptococcus</i> <i>Histoplasma</i>	Allergic bronchopulmonary Acute pneumonitis: chronic lung or skin Vaginitis, thrush, candidemia, I.V. catheter Acute pneumonitis, chronic cavitary, pulmonary nodule Pulmonary, meningitis Acute pulmonary, progressive dissemination in infants and elderly, chronic cavitary in chronic airway obstruction	Serum IgE, precipitins Culture, tissue Culture/smear Precipitins, complement fixation, culture Culture, latex agglutination Culture, antigen detection
Compromised host Diabetes mellitus <i>Candida</i> <i>C. glabrata</i> <i>Zygomycetes (Mucor, Rhizopus)</i>	Disseminated, pyelonephritis, vaginitis Pyelonephritis Rhinocerebral, paranasal, pulmonary, gastrointestinal, cutaneous	Culture/smear Culture Culture, tissue
Malignancy or corticosteroids <i>Aspergillus</i> <i>Candida</i> <i>Coccidioides</i> <i>Cryptococcus</i> Dematiaceous fungi <i>Fusarium</i> <i>Histoplasma</i> <i>C. glabrata</i> <i>Trichosporon</i> <i>Zygomycetes (Mucor, Rhizopus)</i>	Invasive/lung, sinuses, disseminated Fungemia, acute and chronic disseminated candidiasis Disseminated Pulmonary, meningeal, disseminated Lung, sinuses, brain, disseminated Lung, sinuses, cellulitis at site of onychomycosis, disseminated Progressive disseminated Disseminated Disseminated Rhinocerebral, paranasal, pulmonary, gastrointestinal, cutaneous, disseminated	Culture, tissue Culture, tissue Culture, precipitins, complement fixation Culture, latex agglutination, India ink preparation Culture, tissue Culture, tissue Culture, antigen detection Culture, tissue Culture, tissue Culture, tissue
Extensive surgery and previous antibiotic therapy <i>Candida</i> <i>C. glabrata</i>	Vaginitis, thrush, esophagitis, disseminated Disseminated	Culture, tissue Culture

ognizing that a particular patient is at risk for this condition.¹⁶⁻¹⁸ As noted [*see Definition and Classification, Fungal Colonization versus Fungal Infection, above*], fungal colonization is certainly an important risk factor for invasive fungal infection.²⁻⁷

Whereas most fungal infections probably originate from endogenous sources, some undoubtedly originate from interactions with patients' external environments—in particular, from interactions with health care workers.⁴³⁻⁴⁷ Cross-infection with *Candida* via hand transmission has been described in several studies.⁴³⁻⁴⁷ In one study, 6% of nurses' hand cultures contained fungal pathogens, with which 2 of 57 patients with candidemia could be linked by means of DNA fingerprinting.⁴⁸ In another, nail contamination in the operating room was linked to an outbreak of *C. tropicalis*-infected sternal wounds.⁴⁷ Parenteral nutrition has also been identified as a potential source of contamination with *Candida*.⁴⁹

Clinical Evaluation

Patients with candidemia or disseminated candidiasis can present with a wide variety of clinical signs and symptoms.^{11,17,18,50} Identification of high-risk patients is probably the single most important step in establishing the diagnosis of candidiasis.^{8,14,15,17,18,36,50} Although they are not very common presenting signs or symptoms, candidal endophthalmitis, suppurative phlebitis, and candiduria in the



absence of bladder instrumentation may each provide special clues suggesting an increased risk for fungal infection. A careful eye examination to identify the presence of candidal infection should be performed while the results of cultures of various sites are being awaited [*see* Investigative Studies, Culture, *below*], and a repeat examination should be performed after therapy for proven candidemia. Candidal endophthalmitis may remain asymptomatic until late in the course of infection.^{17,18,50,51}

The presence of peripheral suppurative phlebitis that fails to yield bacteria or does not respond to antibacterial agents may be an early clue to the presence of hematogenous candidiasis. Gentle squeezing of the venous catheter exit site may express pus that yields *Candida* species on a smear or culture. Surgical excision of the infected vein usually reveals *Candida* infection in its lumen.^{17,18,50,52}

The presence of high-grade candiduria in surgical patients who have not undergone instrumentation of the renal pelvis or the bladder suggests hematogenous candidiasis and should prompt a workup for this infection. In this setting, candiduria may result from seeding or filtering through the kidney.^{17,18,50,53-58}

Fever is sometimes the only sign of infection; however, it may be absent in infected patients who are receiving corticosteroids. Because fungal pathogens interact with the Toll-like receptors (TLRs), just as bacterial pathogens do, patients with fungal infections may present with the systemic inflammatory response syndrome (SIRS) or septic shock. Accordingly, the diagnosis should be seriously considered in high-risk patients who are persistently febrile. Because of the high mortality associated with fungal infection, empirical antifungal therapy is recommended

Table 2 Antimicrobial Agents of Choice for Candidal Infections*

Infection	Agent of Choice	Alternative Agents	Comments
Hematogenous			
Candidemia and acute disseminated candidiasis	Fluconazole, or echinocandin, or amphotericin B ± flucytosine	Lipid formulations of amphotericin B	Fluconazole should be given for <i>C. albicans</i> ; if a fluconazole-resistant species is known to be present or azole use has been prolonged, one of the echinocandins should be selected; amphotericin B should be selected in unusual cases when <i>Candida</i> is not the infecting pathogen; a two-drug regimen can be given to hemodynamically unstable patients with persistent high-grade fungemia
<i>Candida</i> endophthalmitis	Fluconazole	Amphotericin B + flucytosine; voriconazole; caspofungin	Patients with vitreal involvement require vitrectomy in addition to antifungal therapy
Suppurative phlebitis	Fluconazole + flucytosine	Amphotericin B + flucytosine	The central venous catheter should be removed and the infected vein excised
Endocarditis	Amphotericin B + flucytosine	Fluconazole + caspofungin	Surgical replacement or repair of valves is essential to prevent death from embolization or cardiac failure; oral fluconazole should be given after successful completion of a prolonged course of amphotericin B therapy; there is anecdotal evidence that fluconazole and caspofungin can be beneficial
Pericarditis	Amphotericin B	Fluconazole	—
Prosthetic device–related infection	Fluconazole or amphotericin B	—	Removal of device is required for successful therapy
Arthritis	Fluconazole	—	—
Osteomyelitis	Amphotericin B	Fluconazole	Surgical drainage of pus is required
Meningitis	Amphotericin B + flucytosine	Fluconazole + flucytosine	—
Nonhematogenous			
Oropharyngeal			
Otherwise normal host	Nystatin	Ketoconazole, fluconazole, clotrimazole troches	—
Patients at risk for hematogenous infection (e.g., cancer patients, surgical patients)	Fluconazole	Ketoconazole	—
Deep candidiasis			
Esophagitis and GI candidiasis	Fluconazole	Echinocandin; amphotericin B	Amphotericin B should be reserved for cases of failure of fluconazole therapy without endoscopic evidence of other causes of disease
Peritonitis and intra-abdominal	Fluconazole	Echinocandin; amphotericin B	—
Wound	Fluconazole	Amphotericin B	Antifungal therapy should be given to patients who do not respond to antibacterial therapy
Urinary tract			
Cystitis	Fluconazole	Amphotericin B	Fluconazole is preferable because of its high drug concentration in urine and because it is better tolerated; echinocandins appear to yield low urinary tract concentrations
Pyelitis			
Without papillitis	Fluconazole	—	—
With papillitis	Fluconazole + flucytosine	Amphotericin B	—
Pyelonephritis	Fluconazole + flucytosine	Amphotericin B	—

*Therapy is individualized on the basis of the patient's clinical condition and the infecting species.

for early treatment of a clinical occult infection or for prevention of a new infection.

Investigative Studies

CULTURE

The workup of a surgical patient with suspected hematogenous candidiasis begins with a complete set of cultures of sputum, oropharynx, stool, urine, all drain sites, and blood [see Table 2]. Candidiasis rarely develops in patients whose cultures show no evidence of *Candida* at any site.^{6,7,43} Obtaining more than six sets of blood cultures has little value, and there is no evidence to support obtaining arterial cultures. Once a blood culture has turned positive for *Candida*, the species must be rapidly identified so that the correct antifungal agent can be selected for treatment. A rapid and

inexpensive test is the germ tube test, which can distinguish *C. albicans* (positive result) from other *Candida* species. More than 90% of *C. albicans* isolates produce germ tubes when incubated in serum for 2 to 3 hours at 37° C. Several commercial products are now available to aid in the rapid identification of *Candida* species.^{59,60}

Positive cultures from nonsterile sites (sputum, urine, and wound drainage) must be interpreted with caution because of the frequent occurrence of *Candida* as a normal commensal of humans. Such cultures are useful mainly as an indication of colonization and, consequently, of the risk of infection in the appropriate setting.

ANTIBODY DETECTION, ANTIGEN DETECTION, POLYMERASE CHAIN REACTION, AND METABOLITE ASSAY

Many published papers and commercial products have touted the benefits of various auxiliary serologic tests in the identification of patients with fungal infection. At present, however, assays for

fungal wall elements (mannan), D-arabinitol (a cell membrane metabolite), or enolase (cell cytoplasm) appear to be of limited value, as do polymerase chain reaction (PCR)-based assays.^{50,59-67} These tests have mixed sensitivities and specificities that prohibit their widespread application. A 2005 study evaluated the assay for (1→3)-β-D-glucan, an important constituent of fungal cell walls that is absent from bacterial cell walls.⁵⁹ At a cutoff value of 60 pg/ml, the assay had a sensitivity of 69.9% and a specificity of 87.1%, with a positive predictive value of 83.8% and a negative predictive value of 75.1%. At a cutoff value of 80 pg/ml, it had a sensitivity of 64.4% and a specificity of 92.4%, with a positive predictive value of 89% and a negative predictive value of 73%. Of the 107 patients with proven candidiasis, 81.3% showed positive results at a cutoff value of 60 pg/ml, and 77.6% showed positive results at a cutoff value of 80 pg/ml. This screening test may be of some use in following high-risk patients, especially when performed serially.

HISTOLOGIC ANALYSIS

Analysis of fungal smears is a relatively insensitive method of diagnosing candidiasis and other fungal infections in otherwise sterile sites (e.g., joint fluid, peritoneal fluid, vitreous humor, or cerebrospinal fluid).⁶⁷ Centrifugation of these fluids and examination of the sediment may improve the diagnostic yield.⁵⁰ Conventional fungal stains, such as hematoxylin-eosin, periodic acid-Schiff (PAS), and Gomori methenamine-silver (GMS), are useful. The most sensitive stain is calcofluor white, but unfortunately, it requires fluorescent microscopy. Deep tissue biopsy provides a definitive diagnosis of candidiasis.

Management of Candidemia and Acute Disseminated Candidiasis

Patients who have *Candida* infections can now be treated with any of a number of antifungal agents, including amphotericin B, the azoles (fluconazole, itraconazole, voriconazole, and posaconazole), flucytosine, the lipid amphotericin products (see below), and the echinocandins (caspofungin, micafungin, and anidulafungin) [see Table 3].⁶⁸⁻⁷⁹ Randomized, controlled trials designed to determine noninferiority have demonstrated that several agents—namely, fluconazole, itraconazole, voriconazole, caspofungin, and micafungin—can be considered not inferior to the previous standard therapy—namely, amphotericin B or lipid formulations thereof.⁶⁸⁻⁷⁸

Because of the emergence of non-*albicans* species as significant pathogens, it is vital that surgeons be aware of the variety of *Candida* species that may be encountered and the relevant drug sensitivities.⁸⁰⁻⁸³ Most *C. albicans* isolates are sensitive to all of the currently available agents, but some low-level resistance has been reported, especially with previous long-term exposure to azoles at low dosages.⁸⁰⁻⁸³ *C. glabrata* may be resistant to fluconazole or require some modification of the dosage; *C. krusei* is resistant to fluconazole; and *C. lusitanae* may be resistant to amphotericin B.⁸⁰⁻⁸³ The selection of the initial antifungal agent to be used is based on estimation of the likelihood of infection, assessment of the probable sensitivity or resistance of the fungal species, consideration of specific patient risk factors (e.g., renal or hepatic insuff-

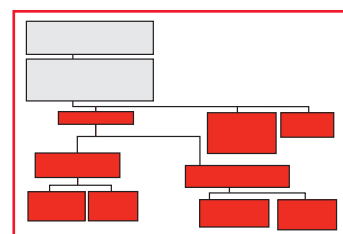


Table 3 Antifungal Chemotherapy⁶⁸⁻⁷⁹

Drug	Indications	Route of Administration	Major Side Effects
Amphotericin B	Hematogenous and deep-seated candidiasis; aspergillosis; blastomycosis; coccidioidomycosis; histoplasmosis; cryptococcosis	I.V., intrathecal	Anemia, headache, chills, fever, nausea, renal dysfunction, hypotension, tachypnea, hypokalemia, phlebitis
Clotrimazole	Oropharyngeal candidiasis	Oral	—
Flucytosine	Candidiasis (bloodstream infection, endocarditis, urinary tract infection); cryptococcosis	Oral	Leukopenia, thrombocytopenia, liver dysfunction, diarrhea
Fluconazole	Oropharyngeal and esophageal candidiasis; hematogenous candidal infection; other candidal infections (e.g., urinary tract infection, peritonitis); meningeal coccidioidomycosis; cryptococcosis	Oral, I.V.	Nausea and vomiting, skin rash, liver dysfunction
Itraconazole	Histoplasmosis; blastomycosis; aspergillosis	Oral	Nausea, vomiting, liver dysfunction
Ketoconazole	Candidiasis (chronic mucocutaneous candidiasis or oropharyngeal candidiasis); candiduria; blastomycosis; coccidioidomycosis; histoplasmosis; chromomycosis; paracoccidioidomycosis	Oral	Hepatotoxicity, nausea or vomiting, occasional suppression of adrenal function
Voriconazole	Aspergillosis (invasive); candidiasis (chronic mucocutaneous candidiasis or oropharyngeal candidiasis) and hematogenous candidal infection; candiduria; <i>Fusarium</i> or <i>Scedosporium</i> infection	Oral, I.V.	Photophobia, visual hallucinations, photosensitivity/rash, drug interactions, hepatotoxicity, nausea and vomiting, fever
Posaconazole	Disseminated candidiasis; prophylaxis of aspergillosis or oropharyngeal candidiasis in immunocompromised patients.	Oral	Abdominal pain, nausea or vomiting, diarrhea, drug interactions, prolonged QT interval, hyperbilirubinemia, hepatotoxicity, occasional suppression of adrenal function
Caspofungin	Candidiasis (chronic mucocutaneous candidiasis or oropharyngeal candidiasis); hematogenous candidal infection; aspergillosis (refractory)	I.V.	Rash, pruritus, nausea, vomiting, thrombophlebitis, headache, fever, increased liver enzymes
Micafungin	Candidiasis (chronic mucocutaneous candidiasis or oropharyngeal candidiasis); candidiasis prophylaxis; stem cell transplantation	I.V.	Rash, pruritus, nausea, vomiting, diarrhea, thrombophlebitis, headache, fever, increased liver enzymes
Anidulafungin	Candidiasis (chronic mucocutaneous candidiasis or oropharyngeal candidiasis); hematogenous candidal infection	I.V.	Hypokalemia, diarrhea

iciency), and determination of whether the patient should receive the agent orally or intravenously.⁶⁸⁻⁷⁹ In addition, selection of the best antifungal agent for a specific at-risk or infected patient is facilitated and enhanced by familiarity with the typical pathogens in the local community.

Several oral and intravenous azoles are available for clinical use.^{17,18,69,72,74-77} Clotrimazole and miconazole are not suitable for systemic therapy. Ketaconazole has very poor and erratic GI absorption and thus is not used for systemic therapy. Itraconazole also has very erratic GI absorption and therefore should not be used for systemic therapy either.^{17,18} A single trial conducted in a pediatric population found that itraconazole at a dosage of 10 mg/kg/day orally was clinically similar to fluconazole at a dosage of 200 mg/day orally for treatment of candidemia.⁸⁴ The I.V. agent fluconazole is a well-tolerated triazole that shows good activity in candidemic patients. Individual clinical trials involving nonneutropenic patients with candidemia, as well as a meta-analysis of these trials, indicate that amphotericin deoxycholate and fluconazole yield similar outcomes in terms of overall mortality, attributable mortality, and clinical and microbiologic response but differ in terms of toxicity, with fluconazole appearing to be less toxic.⁸⁵⁻⁸⁸ Thus, it is reasonable to use fluconazole to treat patients with candidemia.

The 2004 treatment guidelines published by the Infectious Disease Society of America suggest that physicians may choose among three alternatives for primary treatment of candidemia in nonneutropenic adult patients: (1) amphotericin B deoxycholate (0.6 to 1.0 mg/kg/day, or one of the lipid formulations); (2) fluconazole (400 to 800 mg orally or I.V.); and (3) caspofungin (loading dose of 70 mg I.V., followed by 50 mg/day I.V. or, if the patient has severe obstructive hepatic disease, 35 mg/day I.V.).¹⁷ If the species is known or believed to be *C. albicans*, fluconazole (loading dose of 12 mg/kg I.V., followed by I.V. infusion of 6 mg/kg/day) is appropriate. Fluconazole has excellent oral bioavailability and frequently can be delivered orally after the first few days. Dose adjustments must be considered if renal insufficiency is present.^{17,18,69,72,74-77} If the patient has received long-term azole therapy, is known to be colonized with *C. glabrata* or *C. krusei*, or both, then one of the echinocandins—either caspofungin (loading dose of 70 mg I.V., followed by 50 mg/day I.V.) or micafungin (100 mg/day I.V.)—should be administered.^{68,71,73,78,89} If the species then proves sensitive to fluconazole, this agent may then be given orally to continue therapy. Although clinical trials have shown voriconazole (6 mg/kg I.V. every 12 hours for the first 24 hours, then 3 mg/kg I.V. every 12 hours, p.o. switch 200 mg every 12 hours) to be an acceptable agent for treating candidemia,⁹⁰ there are many drug interactions and side effects of which the physician must be aware when using this drug. In particular, patients who have undergone transplantation and those with HIV infections are very likely to be taking agents that interact with voriconazole.

The current role of amphotericin B in the treatment of candidemia is limited by its toxicity [see Systemic Antifungal Agents, Amphotericin B, below]. The lipid-associated formulations of amphotericin B are less nephrotoxic than the parent compound.⁶¹ Three such formulations are available: (1) amphotericin B lipid complex (Abelcet), (2) amphotericin B colloidal dispersion (Amphocil, Amphotec), and (3) liposomal amphotericin B (AmBisome). A prospective, randomized trial found Abelcet to be as efficacious as conventional amphotericin B for treating hematogenous candidiasis.⁶² If, however, the patient is known to have a *Candida* infection, the infection can and should be treated with one of the agents previously mentioned. In a 2005 cost-effective-

ness analysis, both amphotericin B deoxycholate and its lipid products provided fewer discounted lives saved than either fluconazole or caspofungin did (according to the data available at the time of publication).⁸⁹

At present, there are no evidence-based guidelines concerning the optimal duration of therapy.^{17,18} This decision should be based in part on the severity of the patient's illness, as well as on his or her immune constitution. In general, therapy should be continued for at least 14 days after the last positive cultures and the resolution of all signs and symptoms of infection in the most seriously ill patients. Shorter courses of therapy may be appropriate in carefully selected patient populations without signs of hemodynamic instability or evidence of distant metastatic infection.

CATHETER MANAGEMENT

The fundamental controversy about whether central venous access lines should be removed when identified in patients with candidemia stems from the multiple routes by which infection occurs in different patient populations.⁹¹⁻⁹⁴ When the GI tract is the source of candidemia (as in cancer patients with mucositis),⁹⁵ catheter removal is unlikely to yield any significant benefit. On the other hand, when an I.V. catheter is a source of ongoing candidemia, there is some evidence to suggest that removal of the catheter may shorten the time to blood clearance and perhaps even improve overall survival. In a study examining catheter exchange in patients without cancer, replacement of all vascular catheters shortened the duration of candidemia from 5.6 days to 2.6 days.⁹¹ The current state of knowledge regarding the importance of biofilm, the penetration of antifungal agents, and the attachment of new pathogens tends to favor removal of catheters to the extent possible after candidemia. Given the available data, physicians should consider removing all intravascular catheters from inpatients who have candidemia with persistent fever, persistent or high-grade fungemia, or *C. parapsilosis* infection (which is more likely to be catheter related than infection with another *Candida* species would be).

IMMUNOTHERAPY

Despite the availability of newer antifungal agents, treatment failures remain significant problems. Physicians' familiarity with the roles of both innate and acquired immunity in the acquisition and resolution of fungal infections has grown substantially over the past several years.⁹⁶ The development of adjunctive immunotherapies based on an understanding of the host immune response has led to preliminary trials with cytokines such as interferon gamma and granulocyte colony-stimulating factor (G-CSF),⁹⁷ as well as with granulocyte transfusion.⁹⁸ Although these trials have demonstrated safety and (perhaps) proof of principle, they do not support clinical use of these agents, especially in nonneutropenic patients. Active investigation into the TLR-mediated pathogen recognition and signal transduction pathway and the means by which *Candida* evades the TLR-mediated host immune response may lead to new immunotherapies in the future. Because both persons at risk and host risk factors are identifiable, host vaccination remains a prime focus of investigation into prevention.⁹⁶

ANTIFUNGAL PROPHYLAXIS

The use of antifungal prophylaxis remains a controversial topic,^{3,99-108} though four recent meta-analyses¹⁰⁹⁻¹¹² and a Cochrane review¹¹¹ have all concluded that prophylactic administration of antifungal agents to high-risk critically ill or surgical patients reduces the incidence of invasive fungal infection but has no proven effect on mortality. These analyses illustrate the prob-

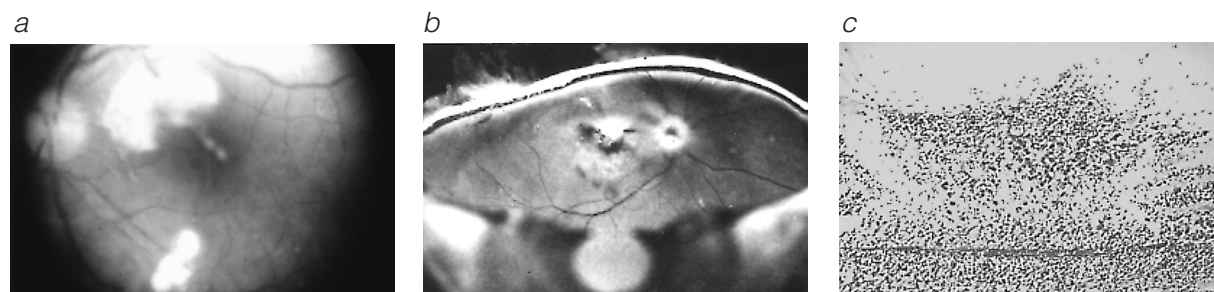


Figure 1 *Candida* endophthalmitis is common in patients with persistent fungemia. On funduscopy, a characteristic white, cotton-wool-like exudate can be seen (a). Cut section of an eye shows *Candida* retinitis (b). A microscopic view of *Candida* chorioretinitis is also provided (c).¹⁴⁶

lems inherent in attempting to combine data from small trials that employed different agents (ketoconazole and fluconazole) at different dosages in different at-risk patient populations. Perhaps the most difficult issue in determining whether antifungal prophylaxis should be employed involves the lack of a consensus on how fungal infection should be defined. Without a well-understood end point, it is impossible to decide whether a therapy should be widely applied.

To date, there have been eight major studies of antifungal prophylaxis that are applicable to the critically ill surgical patient population.^{3,102-108} The three largest of these are of particular relevance. In one study, a large number of liver transplant recipients were randomly assigned to receive either placebo or fluconazole for a period of 10 weeks (during which administration switched from I.V. to oral).¹⁰⁵ Definitions of fungal infections included both deep and superficial infections. The authors documented a significant decrease in fungal colonization and fungal infection (both superficial and deep) in the fluconazole group but reported no significant difference in mortality between groups. Although hepatotoxicity was absent in the fluconazole group, neurologic toxicity was higher than in the placebo group, presumably as a consequence of increases in cyclosporine levels, which must be adjusted in patients receiving prophylactic fluconazole.

In a large study that enrolled 220 patients in the medical or surgical ICU on or after their third day in the unit, prophylaxis with fluconazole, 100 mg I.V., was compared with placebo.¹⁰⁸ The patients enrolled in this trial were critically ill, were receiving respiratory support from a mechanical ventilator, and were undergoing selective decontamination of the GI tract. Candidemia was virtually eliminated in the fluconazole group. In addition, the incidence of invasive candidal infection was lower in this group (3.9% versus 8.9%), and fungal colonization was both less frequent and less intense.

Finally, in a single-institution, randomized, double-blind, placebo-controlled trial that compared enteral fluconazole (800 mg loading dose, followed by 400 mg/day) with placebo for prevention of fungal infections in high-risk critically ill surgical patients, the authors reported that fluconazole prophylaxis yielded a two- to threefold reduction in fungal infection but had no effect on mortality.³ Using a strict case definition that did not include fungal colonization, the intent-to-treat analysis demonstrated 20 patients with fungal infections (15.3%) in the placebo group and 11 such patients (8.5%), including four with infections that were unknown at enrollment, in the fluconazole group. The number needed to treat (i.e., the number of patients who would have to receive antifungal prophylaxis for a single fungal infection to be prevented) was 14.5, a low number that suggests a highly significant effect.

The data do not yet support widespread or routine use of antifungal prophylaxis. Accordingly, it is worthwhile to formulate some general conclusions regarding which patients should receive antifungal prophylaxis and which agent should be used. It is reasonable to consider antifungal prophylaxis in patients similar to those in the aforementioned studies (see above), including organ transplant patients^{3,17,109-112} and patients enrolled in referenced clinical trials. In most of these patient populations, fluconazole is the most appropriate agent for prevention of *Candida* infection: it has few side effects, it can be administered orally, and out of the agents that have been well studied, it is the most reasonably priced. In view of the increasing reports of resistance, however, the use of fluconazole should not be extended to additional patient populations, especially those who are less ill and certainly those who are at less risk. The key question in making the decision for or against antifungal prophylaxis should be whether the benefits achievable in the patient population being considered for prophylaxis are significant enough to outweigh the cost and the risk of eventual (and even expedited) resistance developing with excessive use.

ORGAN INFECTIONS

Candidal Endophthalmitis

The diagnosis of candidal endophthalmitis usually implies hematogenous spread to multiple organs and the need for systemic antifungal therapy. Identification of eye involvement early in therapy is crucial for preserving visual acuity [see Figure 1].⁵¹ Patients who have only chorioretinitis respond better to drug therapy alone than patients who show vitreal involvement. Treatment depends on achieving an adequate concentration of an agent effective against the fungal pathogen within the vitreous compartment.⁵¹ Because antifungal drugs do not penetrate the vitreous body as well as they do the other ocular compartments,¹¹³ patients with vitreal involvement require early vitrectomy in addition to antifungal therapy.

Fluconazole is currently the drug of choice because of its proven efficacy and its higher concentration (20% to 70% of the corresponding plasma level) in ocular tissue, including the vitreous body.^{51,114} Accordingly, I recommend 800 mg/day of fluconazole until a major response is observed, at which time it may be possible to reduce the dose to 400 mg/day. Many other *Candida* and non-*Candida* fungal species may also cause endophthalmitis, and in such cases, fluconazole may not provide effective coverage. If the infecting organism (especially *C. krusei*) is potentially resistant to fluconazole, the recommended therapy is amphotericin B (0.7 to 1.0 mg/kg/day I.V.), preferably in conjunction with flucytosine.¹¹⁵ Intravitreal injection of amphotericin B is recommend-

ed for vitreal infections. Both voriconazole and caspofungin have had limited success in patients with more resistant infections.⁵¹

The optimal duration of therapy for endogenous endophthalmitis is unknown. Ophthalmologic consultation is critical in establishing the diagnosis, assessing the patient's response to therapy, detecting complications, and determining whether early vitrectomy is indicated to prevent loss of sight.¹¹⁶

Suppurative Thrombophlebitis, Endocarditis, and Pericarditis

A rare but serious consequence of hematogenous candidemia is suppurative thrombophlebitis, which results from infection of a vessel traumatized by prolonged catheterization. Endothelial disruption exposes the basement membrane and leads to thrombus formation and propagation. Suppurative thrombophlebitis is particularly serious because intravascular infection results in a persistent high-density fungemia. Management of this disease consists of high-dose antifungal therapy, removal of the central venous catheter, and excision of the infected vein (when possible).^{52,117} Typically, blood cultures remain positive for several days; sometimes, they remain positive for as long as 3 to 4 weeks despite appropriate antifungal therapy, if the infected vein is not excised.

Fungal infections account for between 1% and 10% of all pathogens isolated from patients with infective endocarditis.¹⁷ In patients with prosthetic valves, the rate at which fungi are isolated may be as high as 10%. The overall outcome of candidal infective endocarditis is grim, carrying a reported mortality of up to 80%, especially when complicated by congestive heart failure and persistent fungemia.¹¹⁸ Embolic phenomena are more commonly associated with fungal endocarditis than with the nonfungal variety.

Candidal endocarditis is very difficult to treat. A 2005 review found that patients with candidal endocarditis who underwent adjunctive surgery had a lower reported mortality.¹¹⁸ Thus, surgical replacement or repair of valves is required to prevent death from embolization or cardiac failure in patients with complicated prosthetic valve endocarditis. Amphotericin B, with or without flucytosine, has been the therapy of choice; however, neither the optimal dosage nor the optimal duration of therapy has been determined. There is some anecdotal information suggesting that fluconazole, with or without caspofungin, may be successfully employed in this setting, primarily as long-term suppressive therapy after the initial administration of amphotericin B.¹¹⁹ Because of the high risk of late relapse, long-term maintenance therapy with oral fluconazole should be considered in patients unwilling or unable to undergo surgical treatment.

Candidal pericarditis is a very rare complication of hematogenous candidiasis. The surgical patients at risk for purulent pericarditis caused by *Candida* are those who have undergone a cardiac operation, those who have a malignancy and whose host defenses are impaired, and those who have a debilitating chronic disease.¹²⁰ Patients should be treated with surgical drainage or debridement and with high-dose amphotericin B or fluconazole.

Arthritis and Osteomyelitis

Candidal joint infections can develop via hematogenous spread as a consequence of inadvertent direct inoculation during joint procedures or intra-articular injection of corticosteroids. Such infections typically involve a single joint (most frequently the knee or the hip) and tend to occur in patients with rheumatoid arthritis or prosthetic joint devices.¹²¹ Local symptoms (i.e., pain on weight bearing or on full extension) may be present. Diagnosis is best achieved by visualizing the organisms or growing them from the joint fluid. Early diagnosis and systemic antifungal therapy are vital for preventing destruction of the cartilage or loosening of the prosthesis.

Successful treatment of fungal arthritis with fluconazole has been reported in several cases.¹²² I recommend giving fluconazole at a dosage of 400 to 800 mg/day for 6 to 12 months; others suggest giving amphotericin B first for 1 to 2 weeks, then switching to fluconazole.¹⁷ Fluconazole can be used for short-term therapy, either alone or in combination with surgery, as well as for long-term suppressive therapy in patients who are at risk for recurrence or who cannot undergo surgical debridement. In general, surgical resection of the involved joint is required.

Except for sternal infections complicating median sternotomy, most cases of candidal osteomyelitis develop through hematogenous spread. Vertebral body involvement is common. Back pain and fever may be followed by radiculopathy. Surgical drainage of all purulent collections is essential for a good response; however, surgical debridement of bony lesions may not be needed. Although amphotericin B has been the standard drug of choice for candidal osteomyelitis, fluconazole may be considered as an alternative. Amphotericin B should not be used for mediastinal irrigation after drainage and debridement of a mediastinal infection, because there is a high probability of chemical mediastinitis.

Meningitis

Candidal meningitis may follow hematogenous spread, or it may be a complication of neurosurgery or the implantation of ventriculoperitoneal shunts. In neonates, *Candida* infection may be present without previous surgery and without previously documented fungemia, but often, an intravascular catheter is present.¹²³ The infection is insidious and sometimes goes undiagnosed. Most patients with candidal meningitis have recently received antibacterial agents, and half have previously had bacterial meningitis. The overall mortality is around 10%.

The standard therapeutic regimen for candidal meningitis consists of amphotericin B with flucytosine. As an alternative, a combination of high-dose fluconazole (800 mg/day) and flucytosine (50 mg/kg/day) may be considered; this is a particularly attractive approach because of the high CSF concentrations achieved with both agents. Removal of the infected shunts, as well as the intravascular catheter, is recommended when possible.^{17,123} The duration of treatment should be based on the patient's clinical response and the culture results. In general, prolonged treatment (more than 4 weeks beyond the resolution of symptoms) is suggested.

Pneumonia

True candidal pneumonia is rare, but it can occur through hematogenous dissemination into the lung as one of many sites of infection.^{17,124,125} Oropharyngeal aspiration of oral and upper tracheal organisms does not typically cause pneumonia. The value of deep tracheal suction or even bronchoalveolar lavage in defining this disease should be questioned. Histopathologic confirmation is recommended.¹⁷ Laryngeal infection should be considered; some case reports suggest that it can be rapidly progressive.

Management of Nonhematogenous Candidiasis

SUPERFICIAL INFECTION

Oral candidiasis (thrush) appears as a whitish, patchy pseudomembrane covering an inflamed oropharynx; it commonly involves the tongue, the hard and soft palates, and the tonsillar pillars. Controlled trials have shown nystatin suspension, oral amphotericin B, clotrimazole troches, oral ketoconazole, fluconazole, and itraconazole to be efficacious for eradicating the clinical symptoms of oral candidiasis.¹⁷

Nystatin should be given as a 10 to 30 ml suspension five times daily, and the patient should be instructed to swish it around the mouth before swallowing; alternatively, the patient may take one or two troches five times daily. Clotrimazole is given five times daily in the form of a 10 mg troche that should be held in the mouth until dissolved. In surgical patients at risk for hematogenous infection, systemic therapy with ketoconazole (200 to 400 mg once daily), itraconazole (200 mg/day), or fluconazole (100 mg once daily) is preferred.¹⁷ Antifungal therapy should be administered for 7 to 14 days. Ketoconazole and itraconazole are slightly less effective than fluconazole because of variable GI absorption. Repeated episodes of oral candidiasis are common.

DEEP CANDIDIASIS

Esophagitis and Gastrointestinal Candidiasis

Superficial candidiasis involving only mucosal surfaces used to be a common finding at autopsy in surgical patients who had had a protracted hospital stay characterized by recurrent sepsis. Such lesions may arise at any site in the GI tract but appear most commonly in the esophagus and the small bowel; in some cases, they progress to hematogenous infection [see Figure 2].

In a minority of patients, the pathology of candidal infection of the lower GI tract may change from diarrhea without demonstrable tissue invasion to direct penetration into the submucosa, which eventually leads to pseudomembranous enterocolitis. Direct vascular invasion through the bowel wall may occur in immunosuppressed patients; these patients may exhibit extensive involvement of the GI tract from mouth to anus. Nonneutropenic surgical patients may exhibit more localized GI involvement.

The preferred therapy for esophageal candidiasis consists of fluconazole (100 mg/day orally) or itraconazole (200 mg/day) for 14 to 21 days.¹⁷ In patients who remain symptomatic after 7 days of therapy, endoscopy is indicated to rule out other causes of esophagitis. If endoscopy proves that esophagitis is being caused by candidal infection, low-dose amphotericin B (0.4 mg/kg/day) may be administered. Alternatively, caspofungin or voriconazole may be given,¹⁷ though it should be kept in mind that voriconazole causes more adverse events without being more efficacious. Therapy for esophageal candidiasis should be continued for at least 4 days after symptoms resolve; immunosuppressed patients generally require more extended therapy to prevent relapse.

Because stool cultures do not differentiate between colonization and infection, candidiasis in the lower GI tract is usually a postmortem diagnosis; hence, there are no reliable criteria governing when and how to treat this condition. It has been reported, however, that patients who have diarrhea that can only have been caused by heavy colonization with *Candida* species may respond dramatically to 2 to 4 days of nystatin therapy.

Peritonitis and Intra-abdominal Abscess

Perhaps the most controversial issue in the management of *Candida* infectious syndromes in surgical patients is the question of whether specific systemic therapy is required to eradicate the infection within intra-abdominal abscesses, peritoneal fluid, or fistula drainage.¹⁷ *Candida* is frequently cultured from intra-abdominal infectious foci but should be considered a serious threat only in high-risk patients.¹²⁶ Four risk factors for intra-abdominal candidiasis have been identified: (1) gastrointestinal perforations, especially in the upper GI tract, (2) anastomotic leakage, (3) surgery for acute pancreatitis, and (4) splenectomy.^{107,126} In patients with a localized fungal infection necessitating drainage, there is no replacement for adequate drainage and debridement.

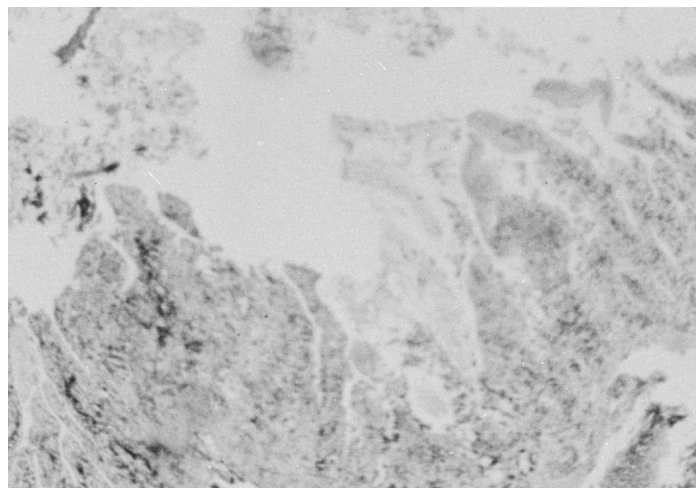


Figure 2 Superficial candidiasis may be found at all levels of the GI tract. Here, the esophagus of a patient found at autopsy to have disseminated candidiasis shows disrupted epithelium, submucosal inflammation, and the presence of yeast in the submucosa.

Such infections are often located in the abdomen, the liver, the biliary tree, the pancreas, or the peritoneal cavity. Percutaneous drainage can play an important role in the management of these difficult problems; however, one retrospective review of percutaneous drainage of fungal collections in the abdomen or thorax suggested that clinical failures occur more often when complex fluid collections are visible radiographically, when patients have a history of malignancy, and when patients are critically ill.¹²⁷

Patients with peritonitis and intra-abdominal abscesses should receive systemic antifungal therapy, usually in combination with antibacterial therapy (given that these infections are almost always polymicrobial in origin). The risk of dissemination is increased both by the recurrence of intra-abdominal infection and by the presence of extensive areas of communication between the abdominal cavity and the external environment via either fistulas or drain tracts. Because fluconazole is very safe and is capable of reaching high concentrations in peritoneal fluid, it is useful in the management of candidal peritonitis and should be considered the agent of choice in cases where the pathogens are susceptible to it.¹⁰⁷ Fluconazole should be given at a dosage similar to that employed in treating systemic disease (loading dose of 12 mg/kg I.V., followed by 6 mg/kg/day I.V.), with a 50% dosage reduction in cases of renal impairment. When pathogens are resistant to fluconazole, caspofungin and voriconazole at systemic dosages are acceptable alternatives.¹⁷

On rare occasions, candidal peritonitis occurs after long-term ambulatory peritoneal dialysis. This infection is not clinically distinguishable from bacterial peritonitis. In such cases, the infection tends to remain localized and to manifest with low-grade fever and abdominal pain and tenderness. The peritoneal dialysate is usually cloudy and contains more than 100 neutrophils/mm³. Therapy consists of systemic antifungal therapy and removal of the peritoneal catheter. The abdominal pain caused by the addition of amphotericin B to the dialysate has raised concern that chemical peritonitis might give rise to adhesions and thus impair the efficacy of dialysis. Accordingly, this agent should not be used for peritoneal irrigation. Immediate removal of the peritoneal catheter has been recommended. Fluconazole should be considered as the agent of choice and should be given for 1 to 14 days. A new catheter should not be placed for 4 to 6 weeks. In centers with a

high rate of fungal peritonitis secondary to peritoneal dialysis, nystatin prophylaxis may be considered. A prospective, randomized study of patients on continuous ambulatory dialysis found that *Candida* peritonitis was successfully prevented with oral nystatin (tablets containing 500,000 units given four times a day).¹²⁸

Occasionally, *Candida* species may cause cholangitis, biliary tract disease, pancreatic abscess, or liver abscess. This problem is increasingly found in cancer patients with percutaneously placed drainage catheters. Such patients must be given systemic therapy if there is any clinical evidence of infection (e.g., candidemia), and the drainage catheter must be changed. Diverticulitis complicated by candidal pyelphlebitis has also been reported.

Wound Infections

Diagnosis and treatment of candidal wound infections are problematic. Recovery of *Candida* species from drains and wounds does not necessarily mean that this organism is causing tissue infection; however, isolation of *Candida* or demonstration of invasive forms on biopsies at reoperation would suggest that invasive infection is present. Antifungal therapy should be administered to patients with demonstrated invasive infection and possibly to those in whom antibacterial therapy has failed and *Candida* has been isolated. If a deep sternal wound culture is obtained and is positive for *Candida* after coronary bypass surgery, antifungal agents should be given to prevent the establishment of candidal osteomyelitis of the sternum.

CANDIDURIA

Candida is either the most common or the second most common pathogen isolated from the urine in surgical ICU patients. The term urinary candidiasis refers to an ill-defined group of syndromes, many of which probably represent colonization rather than infection. Thus, the actual importance and meaning of candiduria are controversial.⁵³⁻⁵⁸ Candiduria is very common in hospitalized patients who have had urinary catheters in place for more than 14 days.⁵⁸ In this setting, it is more likely to reflect colonization than infection. In ICU patients, however, the significance of candiduria is less clear-cut: it may represent either upper tract disease or hematogenous disease and filtration of the pathogens into the urine.¹²⁹ Increasing concentrations of *Candida* in the urine, especially after a catheter exchange and particularly in a critically ill surgical patient with known risk factors, should raise concerns about possible upper-tract or disseminated disease.

Besides simple colonization, the spectrum of candidal urinary tract infection includes cystitis, pyelitis (i.e., infection of the renal pelvis), fungus ball of the ureter, and renal abscesses. The diagnosis of cystitis is based on the presence of symptoms of cystitis, diffuse erythema or fungal plaques on cystoscopy, candiduria, and pyuria. *Candida* cystitis warrants therapy. If a triple-lumen catheter is in place, bladder irrigation with amphotericin B (50 mg/L/day for 2 days) may be tried. Fluconazole (200 mg once daily) is a more attractive approach because of the convenience, the lower cost, and the very high drug concentrations achieved in the urine.⁵⁴ Flucytosine is excreted in the urine in high concentrations and may be particularly useful against *C. glabrata* infection.

Management of pyelitis depends on whether the renal papillae are invaded or the ureter is obstructed with a fungus ball. Patients with no papillitis and an open ureter usually respond to irrigation with amphotericin B through a ureteral or percutaneous catheter. If papillitis is present, systemic antifungal therapy with fluconazole (400 mg/day) is recommended. If fungus balls are present, surgical removal should be considered in addition to treatment with antifungal agents.⁵⁴

Hematogenous infections of the kidneys leading to multiple renal abscesses are treated as instances of hematogenous candidiasis. However, because both fluconazole and flucytosine are well tolerated, have good tissue diffusion, and are excreted in the urine in high concentrations, it is reasonable to assume that the combination of these two agents represents the therapy of choice for such infections.

GENITAL CANDIDIASIS

Fungal vulvovaginitis is a common problem in women and is often associated with antibiotic therapy and poor glucose control. It may be divided into simple and complex forms, with more than 90% of women having the simple form and the remaining 10% experiencing recurrent symptoms. The diagnosis is based on the clinical findings and on the presence of pseudohyphae on a fungal smear.

Antifungal agents, including oral azoles (fluconazole, 150 mg in a single dose; ketoconazole, 400 mg/day for 5 days; or itraconazole, 200 mg in a single dose) and topical medications (suppositories, creams, and vaginal tablets), are effective against more than 90% of uncomplicated infections. However, women who have experienced four or more episodes of vulvovaginal candidiasis during a 12-month period and those who have sustained acute severe attacks of candidal vaginitis are less likely to respond to conventional therapy. Preventive measures include control of host factors such as diabetes mellitus, antifungal prophylaxis during the course of antibiotic therapy and under other high-risk conditions, and avoidance of systemic corticosteroids, oral contraceptives, and antibiotics if possible. Therapy with oral fluconazole, itraconazole, or ketoconazole should be provided for approximately 14 days to ensure clinical remission and negative fungal cultures, followed by a maintenance regimen of fluconazole (150 mg once weekly for 6 months). Recurrence of vulvovaginal candidiasis is common, arising in 30% to 40% of patients after cessation of the maintenance regimen.¹³⁰

Management of Other Fungal Infections

ASPERGILLOSIS

Aspergillosis, a rare infection in general surgical patients, is now, unfortunately, becoming increasingly common in certain subpopulations, such as patients who experience marked immunosuppression after undergoing chemotherapy with cytotoxic agents, those being given adrenal corticosteroids, and those who have recently received antirejection therapy.⁸² Most cases of nosocomial aspergillosis are acquired via airborne transmission. Colonization of the respiratory tract is followed by invasive disease if the predisposing factors are present. Sources of airborne fungi in microepidemics frequently are associated with construction within the hospital or at adjacent sites. Other modes of transmission have also been reported for aspergillosis, including foreign bodies, catheters, and bandages.

Acute invasive pulmonary aspergillosis is the most common form of *Aspergillus* infection in immunocompromised surgical patients.⁸² The organisms tend to invade blood vessels and cause thrombosis and infarction of the surrounding tissues. The infection may manifest itself in the form of acute vascular events such as pulmonary embolisms or, more rarely, myocardial infarction, cerebral hemorrhage, or Budd-Chiari syndrome. Pulmonary *Aspergillus* infections include necrotizing bronchopneumonia and hemorrhagic pulmonary infarction, each accounting for about one third of these infections. Pulmonary aspergillosis may extend to contiguous organs or be disseminated. The rhinocere-

Table 4 Characteristics of Currently Available Azoles*⁶⁸⁻⁷⁹

	Ketoconazole	Fluconazole	Itraconazole	Voriconazole	Posaconazole
Spectrum	Narrow	Expanded	Expanded	Expanded	Expanded
Route(s) of administration	Oral	Oral, I.V.	Oral	Oral, I.V.	Oral
Bioavailability	Erratic, requires gastric acidity	Excellent	Erratic, requires gastric acidity	Excellent	With meals
Plasma half-life (hr)	6–9	30	20–40	Dose dependent, nonlinear	19–35
Hepatotoxicity	Occasional	Occasional	Occasional	Occasional	Occasional
GI intolerance	Frequent	Occasional	Occasional	Occasional	Occasional
CSF penetration	No	Yes	No	Yes	—
Renal excretion	No	Yes	No	Yes	No
Interaction with other drugs	Frequent	Occasional	Frequent	Very frequent	Very frequent

*Intravenous miconazole is also available but offers no advantage over the currently available azoles.

bral form of aspergillosis occurs less often than the pulmonary form. It originates in the sinuses and progresses through soft tissues, cartilage, and bone, causing lesions in the palate and the nose. Occasionally, the infection progresses through the base of the skull and involves the brain.

Diagnosis of *Aspergillus* infection is difficult. Computed tomography can be diagnostic¹³¹ and often allows early recognition of aspergillosis. In one study that used CT scans as a means of investigation, the mean time to diagnosis of invasive pulmonary aspergillosis fell from 7 days to less than 2 days, and this reduction was associated with a decrease in mortality. CT may also be combined with detection of *Aspergillus* antigen (galactomannan), an approach that shows promise for early diagnosis of invasive pulmonary aspergillosis.¹³² Often, however, diagnosis of *Aspergillus* infection depends on identifying the organism in culture or histopathologic specimens.⁸² Recovery of *Aspergillus* species from the respiratory tract culture of a surgical patient should be considered to represent contamination or colonization unless the patient is symptomatic and severely immunosuppressed.

All of the antifungal agents currently used for primary treatment of *Aspergillus* are associated with relatively high incidences of treatment failures and fairly poor outcomes. At present, voriconazole (at the dosage previously described [see Management of Candidemia and Acute Disseminated Candidiasis, above]) is the treatment of choice, with lipid amphotericin B formulations as secondary agents. In some institutions, combination therapy with an echinocandin is occasionally employed as an alternative.

ZYGOMYCOSIS (*MUCOR* AND *RHIZOPUS*)

Some of the most rapidly advancing forms of angioinvasive fungal infection are caused by the Zygomycetes *Mucor* and *Rhizopus*.¹³³ The reservoir, the mode of transmission, the pathogenesis, and the clinical presentations are similar to those of *Aspergillus* species. Zygomycosis is being seen with increasing frequency in stem cell transplant recipients who have been receiving voriconazole prophylaxis. In surgical patients, the major risk factors include diabetic ketoacidosis, immunosuppression after cytotoxic chemotherapy, adrenal corticosteroid therapy, organ transplantation, skin damage (e.g., from adhesive tape, an arm board, or severe burns), iron overload, and a prolonged postoperative stay.¹³³ Zygomycotic infections may be rhinocerebral, paranasal,

pulmonary, GI, cutaneous, or (very rarely) disseminated. Any patient with a necrotic lesion on the skin, soft, hard palate or nose should be considered to have an angioinvasive mold infection until emergency biopsy proves otherwise.

Appropriate management of zygomycosis consists of extensive surgical debridement of infected areas, rapid correction of the underlying disease, and administration of an appropriate antifungal agent. One of the lipid amphotericin products should be the first-line therapeutic agent, with high-dose amphotericin B deoxycholate a second choice.

EMERGING PATHOGENS

Fusarium and *Scedosporium* species are increasingly common causes of infections in surgical patients, especially in recipients of stem cell or organ transplants.^{82,134} Most cases of *Scedosporium* infection present as disseminated disease; skin lesions are common, and the lungs and the CNS are frequently involved. Surgeons may be tempted to use amphotericin B to treat these unusual molds, but voriconazole has been shown to yield better outcomes with both *Fusarium* and *Scedosporium*.

Many other mold species are also emerging as significant pathogens. In an at-risk patient, recovery of any fungus from any site should prompt an evaluation by an infectious disease specialist to determine the clinical significance of the isolate.

Systemic Antifungal Agents

AMPHOTERICIN B

Amphotericin B was the first systemic antifungal agent and has historically been considered the gold standard for antifungal therapy. Today, however, its usefulness in daily practice is substantially less than it once was, primarily because of the proliferation of many alternative agents that are less toxic (but that also may possess a more limited spectrum of activity) [see Table 4].^{17,135,136}

Amphotericin B is lipophilic and binds avidly to ergosterol, the principal sterol in the fungal cytoplasmic membrane. This binding disrupts the integrity of the membrane, resulting in leakage of intracellular contents and cell death. The clinical effectiveness of amphotericin B against fungi is believed to be attributable to the drug's stronger affinity for ergosterol (found in fungal cell membranes) than for cholesterol (the principal sterol found in mam-

malian cell membranes). Another proposed mechanism of action is oxidation-dependent amphotericin B–induced stimulation of macrophages.⁹⁹ Most of the fungal species that cause human infections are susceptible to amphotericin B.

Because amphotericin B is lipophilic, it must be complexed with a bile salt (deoxycholate) to be able to stay in solution. Unfortunately, about 20% of patients receiving amphotericin B deoxycholate experience an acute infusion-related reaction consisting of fever, hypotension, and tachycardia.¹³⁵ Premedication with acetaminophen may blunt this response; if it does not, premedication with hydrocortisone (25 to 50 mg I.V.) or meperidine (25 to 50 mg I.V.) is recommended. Hypotension, hypertension, hypothermia, and bradycardia have also been reported as infusion-related toxic effects of amphotericin B deoxycholate. Ventricular arrhythmias have been associated with rapid infusion of amphotericin B deoxycholate and with administration of this agent to patients with severe hypokalemia or renal failure. Through inhibition of erythropoietic production secondary to nephrotoxicity, amphotericin B suppresses the production of red blood cells, causing a normocytic, normochromic anemia. As a result of renal tubular loss, acidosis, hypokalemia, and hypomagnesemia are common. The need to replace lost electrolytes should be expected. Patients should be kept well hydrated.

Common practice is to give a 1 mg test dose and observe the patient for 1 hour in the hope of identifying patients at risk for severe acute reactions. The full dose of the drug (0.6 to 1 mg/kg/day) is then infused over a period of 4 to 6 hours, though there is evidence to suggest that much shorter infusion times (e.g., 1 hour in patients with adequate cardiopulmonary and renal function) may be acceptable. The total dose depends on the extent of the infection and the patient's condition. Patients must be monitored carefully during the first day of therapy. The infusion should be discontinued if the patient becomes hemodynamically unstable.

If acute reactions limit the amount of drug that can be infused, patients are premedicated with hydrocortisone (25 to 50 mg I.V.), either alone or in combination with meperidine (25 to 50 mg I.V.), 30 minutes before amphotericin B infusion is begun.

Renal toxicity and hypokalemia are the primary toxicities of amphotericin B [see Table 3]. Amphotericin B–induced nephrotoxicity may be glomerular (characterized by a decrease in glomerular filtration rate and renal blood flow) or tubular (with urinary casts, hypokalemia, hypomagnesemia, renal tubular acidosis, and nephrocalcinosis).¹⁰⁰ All of these abnormalities occur to varying degrees in almost all patients receiving the drug. In most patients, renal dysfunction gradually resolves after discontinuance of therapy. Amphotericin B nephrotoxicity may be minimized by refraining from using it with other agents that exert synergistic nephrotoxic effects¹³⁵ (e.g., aminoglycosides, vancomycin, cisplatin, and cyclosporine) and by providing sodium supplementation. Sodium supplementation consists of I.V. infusion of 500 ml of 0.9% saline solution 30 minutes before the administration of amphotericin B, followed by a second infusion of the same amount of saline after the amphotericin B infusion is completed.

To minimize synergistic nephrotoxicity when amphotericin B is used in conjunction with other nephrotoxic agents, use of one of the less nephrotoxic lipid formulations of amphotericin B—such as amphotericin B lipid complex (Abelcet), amphotericin B colloidal dispersion (Amphocil, Amphotec), or liposomal amphotericin B (AmBisome)—may be indicated.¹³⁶ These preparations differ from each other with respect to the amount of amphotericin B present and the type of lipid used, as well as with respect to their physical forms, pharmacokinetics, and toxicities. Of the three,

liposomal amphotericin B (AmBisome) is the one that is best tolerated. It should be noted that all of these formulations do still have some negative effect on renal function.

FLUCYTOSINE

Flucytosine can be useful for the treatment of hematogenous candidiasis. When used as a single agent, however, it is associated with a high failure rate and secondary emergence of resistance. Accordingly, flucytosine is usually employed in combination therapy, typically to treat *Cryptococcus* infections. Its major toxic effect is marrow suppression, especially when it is given at the prescribed dosage (i.e., 37.5 mg/kg every 6 hours).

Administration of flucytosine at a dosage of 25 mg/kg/day every 12 hours will often yield effective serum peak and trough levels. Peak serum concentrations should be monitored and the dosage adjusted so as to maintain a peak level of about 25 µg/ml. Flucytosine penetrates well into the eye and the CNS and thus may be used as a component of combination therapy for candidal endophthalmitis, meningitis, and endocarditis. It is removed by hemodialysis and peritoneal dialysis. Patients undergoing hemodialysis should receive a 37.5 mg/kg dose of flucytosine after each dialysis session unless their initial peak serum concentration is higher than 25 µg/ml or their postdialysis concentration is higher than 10 µg/ml. Patients undergoing peritoneal dialysis should receive a single 37.5 mg/kg dose daily.

FLUCONAZOLE

The mechanism of action of fluconazole is preferential inhibition of cytochrome P-450 enzymes in fungal organisms. Several *Candida* species, including *C. tropicalis*, are susceptible to this agent; however, *C. krusei* is highly resistant. *C. glabrata* may be susceptible, resistant, or susceptible–dose dependent (S-DD) (i.e., exhibiting dose-dependent sensitivity).⁸¹ Because fluconazole is relatively nontoxic at its recommended dosage, larger doses (up to 1,600 mg) may be given to achieve the higher minimum inhibitory concentrations (MICs) required to treat S-DD *C. glabrata* (16 to 32 µg/ml, compared with less than 8 µg/ml for susceptible strains). Fluconazole is not clinically active against *Aspergillus* species.

Fluconazole is available in both oral forms (pill and suspension) and an I.V. form. In any form, it is rapidly and almost completely absorbed from the GI tract: serum concentrations achieved after oral administration are almost identical to those achieved after I.V. infusion. This high degree of GI absorption, which is not affected by gastric acidity or the presence of food, is a major advantage that fluconazole has over ketoconazole. An initial loading dose that is twice the usual daily dose is recommended. Fluconazole is distributed evenly in body tissues, penetrates into the vitreous humor and the aqueous humor of the eye, and crosses the blood-brain barrier. It is excreted largely unchanged in the urine and undergoes only minimal metabolism in the liver. Consequently, dosage schedules must be adjusted in patients with renal impairment. Hemodialysis substantially reduces serum concentrations of fluconazole, and peritoneal dialysis also appears to remove the drug. A standard dose should be given after each course of dialysis.

The toxic effects of fluconazole are similar to those of other azoles, including nausea and vomiting (in about 2% of patients), headache, fatigue, abdominal pain, and diarrhea⁶⁸⁻⁷⁸; exfoliative dermatitis also occurs, but very rarely. Transient abnormalities of liver function are observed in approximately 3% of patients who receive fluconazole. Fatal hepatic necrosis was reported to have developed in two patients who were receiving fluconazole, but it was unclear whether the drug played a causal role. Fluconazole

does not induce adrenal suppression. On occasion, fluconazole administration may lead to prolongation of the QT interval.

Because fluconazole interacts with warfarin, phenytoin, and cyclosporine when given in a daily dose of 200 mg or higher, serum concentrations of these agents should be monitored when they are used in conjunction with fluconazole.

ITRACONAZOLE

Itraconazole is a synthetic triazole that is similar to other imidazoles (e.g., ketoconazole). Its mechanism of action involves inhibition of cytochrome P-450 and prevention of ergosterol synthesis in fungal cell membranes. Itraconazole is active against *Aspergillus* species and several of the endemic fungi (*Histoplasma*, *Cryptococcus*, and *Coccidioides*, to name a few). It is available in two oral forms: a capsule (100 mg) and a suspension (10 mg/ml). The bioavailability of the capsule is approximately 55%. Absorption is enhanced by the presence of food in the stomach but is significantly reduced by the presence of antacids or H₂-receptor blockers. The bioavailability of the suspension is higher; this formulation should be given on an empty stomach. In some patient populations, however, GI absorption of itraconazole is erratic, and oral administration might be ineffective. In such cases, I.V. infusion should be considered.

Itraconazole is metabolized to a large degree in the liver, and this process yields an active metabolite, hydroxyitraconazole. Accordingly, the dosage must be adjusted in patients with hepatic failure; however, the pharmacokinetics of itraconazole are not affected by renal impairment or hemodialysis. Serum concentrations of digoxin may increase when this agent is given with itraconazole,¹⁰⁴ and the metabolism of itraconazole may be accelerated when drugs that induce hepatic enzymes are given simultaneously.^{84,104} Serum concentrations of itraconazole should therefore be measured in patients with invasive infections. Itraconazole is a potent inhibitor of cytochrome P-450 3A4 and may increase the plasma concentrations of drugs metabolized via this pathway.

Itraconazole is generally well tolerated in dosages as high as 400 mg/day. The most common side effects are nausea, vomiting, diarrhea, and abdominal discomfort. Headaches, rash, pruritus, and dizziness occasionally occur. At higher doses, a mineralocorticoid excess syndrome (characterized by hypokalemia, hypertension, and edema) has been described, and hypokalemia develops in as many as 6% of patients who take 400 mg/day for several months.¹⁰⁴

The Federal Drug Administration (FDA) has issued a black box warning against the use of itraconazole in patients with congestive heart failure and those at risk for drug-drug interactions. Because itraconazole may be teratogenic, it should be avoided in pregnant patients as well. Itraconazole is currently approved only for treating blastomycosis, histoplasmosis, and aspergillosis, but it is also effective for treating candidiasis and cryptococcosis.

POSACONAZOLE

Posaconazole, the newest of the triazoles, also prevents synthesis of ergosterol by inhibiting lanosterol 14- α -demethylase. It is highly selective for fungal cytochrome P-450 systems, but unlike other azoles, it is not extensively metabolized by cytochrome P-450 enzymes.¹³⁷ Posaconazole is active against *Candida* and *Aspergillus* species, as well as against *Cryptococcus*, *Fusarium*, the Zygomycetes, and filamentous fungi.

Like the other azoles, posaconazole is well tolerated even with long-term administration.¹³⁷ The most common side effects are fever, nausea, vomiting, diarrhea, and headaches. Rash, thrombo-

cytopenia, and abdominal pain occasionally occur. As a consequence of hepatic metabolism, posaconazole has been associated with elevated liver enzyme levels, hyperbilirubinemia, and hepatocellular damage. Liver function test results should be monitored at baseline and throughout the course of posaconazole therapy. Prolongation of the QT interval and adrenal insufficiency may also be seen with administration of this agent.

Because posaconazole is an inhibitor of cytochrome P-450 3A4, it may be expected to increase the plasma concentrations of drugs metabolized via this pathway. Various drug interactions may occur, and it frequently proves necessary to adjust the dosages of other agents being given simultaneously with posaconazole. The adult dosage for posaconazole is 200 mg three times daily, taken with a full meal or a liquid nutritional supplement.¹³⁸ The use of this agent in pregnant patients is not recommended.

KETOCONAZOLE

Ketoconazole is effective against yeast infections of the skin and the mucous membranes; however, it should not be used to treat hematogenous candidiasis. Ketoconazole is not available in an I.V. form, and the serum levels it is capable of reaching depend largely on gastric acidity [see Table 4]. The same adverse events and drug-drug interactions observed with itraconazole occur with ketoconazole.

ECHINOCANDINS (CASPOFUNGIN, MICAFUNGIN, ANIDULAFUNGIN)

The echinocandins are lipopeptides that have been synthetically modified from the fermentation broths of various fungi.^{68-70,73,78} They act by weakening the fungal cell wall. More specifically, they bind to (1 $\rightarrow$ 3)- β -D-glucan synthase, thereby blocking synthesis of (1 $\rightarrow$ 3)- β -D-glucan, a substance that, along with chitin, provides shape and integrity to the fungal cell wall. The

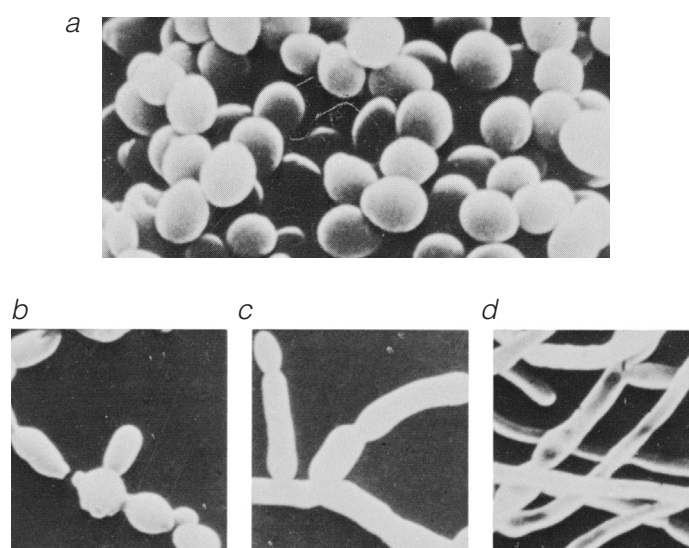


Figure 3 *Candida* takes several forms as it grows. A blastospore is a unicellular form (a). Blastospores divide by budding, a process in which new cellular material grows from a site on the blastospore (b). Nuclear division then occurs, and a septum forms between the two new cells. A hypha is a long tube of several cells divided by septa (c). A mycelium is a cellular aggregate that includes a hypha and its branches (d). A pseudohypha differs from a true hypha in that it is composed of morphologically distinct, elongated blastospores.

resulting loss of fungal cell wall integrity leads to osmotic lysis of the cell.

The echinocandins, as a class, are active against *Candida* species, including *C. krusei* and *C. glabrata*.^{68-70,73,78} In addition, they are active against *Aspergillus* species, including *A. fumigatus*, *A. flavus*, and *A. terreus*; in this setting, they show some synergism with itraconazole and voriconazole. None of the echinocandins are active against *Cryptococcus*, and none should be used for this indication. The emerging fungi *Fusarium*, *Rhizopus*, *Mucor*, *Scedosporium*, and *Pseudallescheria boydii* are all resistant to each of the echinocandins.

All of the echinocandins are available solely as I.V. formulations. Caspofungin is given in a loading dose of 70 mg I.V., followed by infusion of 50 mg/day.⁷⁰ Anidulafungin is given in a 200 mg loading dose on day 1, followed by infusion of 100 mg/day.⁷⁹ Micafungin does not require a loading dose and is given at a dosage of 100 mg/day.⁷¹ Caspofungin is slowly metabolized in the liver through

nonenzymatic peptide hydrolysis and N-acetylation to yield two inactive metabolites. Micafungin is metabolized into three metabolites⁷¹; cytochrome P-450 3A plays a minor role in this process. Anidulafungin undergoes spontaneous degradation into an inactive open ring peptide; no hepatic metabolism has been observed.

Both caspofungin and micafungin have been shown to be not inferior to lipid formulations of amphotericin B for the treatment of invasive candidiasis. In addition, they have been found to have fewer adverse effects, especially those effects that would necessitate discontinuance of therapy (e.g., renal toxicity). One study has found anidulafungin to be superior to fluconazole.¹³⁹

Overall, the echinocandins are well tolerated. They are all associated with essentially the same set of adverse effects, which on the whole are not serious. Phlebitis, fever, nausea and vomiting are among the most commonly reported adverse effects. Thrombocytopenia, hypokalemia, and abnormal liver function test results are occasionally reported.

Discussion

Pathogenesis of *Candida* Infection

For *Candida* to move from commensal to pathogen, it must invade either epithelial or endothelial cells. Even when this organism causes superficial disease, it is capable of eluding detection by the immune system. One way in which *Candida* avoids recognition is to assume an intraepithelial position. A key virulence factor for *C. albicans* is its ability to change from a blastospore to a filamentous hyphal form, and vice versa [see Figure 3]. Most of the evidence suggests that invasive disease is caused by the hyphal form, given that hyphae are found within cells¹⁴⁰ and blastospores on the epithelial surface or between cells (see below). *Candida* can gain entry to epithelial cells either through production of lytic enzymes¹⁴¹ or through endocytosis.¹⁴² The lytic enzymes produced include secreted aspartyl proteinases (SAPs), which are believed to digest the epithelial cell surface and thereby give *Candida* access to the interior of the cell. Mutated forms of SAPs and substances that inhibit SAPs can reduce the ability of *Candida* to enter epithelial cells. Hyphal forms of *Candida* have a greater capacity for inducing endocytosis than blastospores do, which suggests that the hyphae express invasinlike molecules on their cell surfaces¹⁴³; however, the exact identities of these molecules are not yet known.

In susceptible patients, *Candida* species can enter the bloodstream either through translocation across the GI mucosa or via an intravascular catheter. This invasion occurs through three gen-

eral pathways. The first such pathway is phagocytosis. Ingestion by phagocytes brings *Candida* into an intracellular position, and the leukocytes then move across the endothelial cell lining and into the bloodstream. *Candida* species have indeed been observed within circulating leukocytes; however, the observation that fungal infections are common in neutropenic patients argues that a mechanism other than phagocytosis must also play a major role. The second pathway is passage of *Candida* pathogens between endothelial cells and thence into the bloodstream. The fenestrated endothelium in the kidney is one site at which this process might occur. The final pathway is endocytosis by the endothelial cells themselves. The process of endocytosis requires intact endothelial cell microfilaments and microtubules and is in part governed by tyrosine phosphorylation of endothelial cell proteins. Both killed and live *Candida* are ingested by this mechanism. In vitro studies have shown that *Candida* hyphae induce their own endocytosis by expressing the invasinlike protein Als3, which binds to N-cadherin on the cell surface.¹⁴⁴ This binding then induces phosphorylation,¹⁴⁵ causing rearrangement of the microfilaments to produce pseudopods and initiate endocytosis.

It should be kept in mind that this is a highly simplified explanation and does not detail the many unknown specifics of the cellular processes involved. How *Candida* blastospores like those seen with *C. glabrata* gain access to the bloodstream is currently unknown.

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21 VIRAL INFECTION

Jennifer W. Janelle, M.D., and Richard J. Howard, M.D., Ph.D.

Approach to Viral Exposure

Compared with primary care physicians, such as internists, family physicians, and pediatricians, surgeons are seldom called on to treat viral infections. Viral infections nonetheless deserve the attention of surgeons because these infections can cause illness in patients after operation, albeit infrequently, and can spread to the hospital staff. Some viral infections (e.g., infections with the hepatitis viruses, HIV, and cytomegalovirus [CMV]) can result from administration of blood or blood products or can be transmitted to hospital personnel through needle-stick injury. Viral infections can also result from organ transplantation or trauma (e.g., rabies, which is transmitted by the bite of an infected animal). Some viruses, especially the herpesviruses, frequently infect immunosuppressed patients, in whom the viruses can cause severe illness and even death. In many surgical practices, there are increasing numbers of immunosuppressed patients, including organ transplant recipients; patients with cancer; patients receiving cancer chemotherapy, steroids, and other immunosuppressive drugs; the elderly; and the malnourished. Some viral infections can cause neoplastic disease for which operation may become necessary. Examples are hepatitis B virus (HBV) and hepatitis C virus (HCV), which are implicated in the etiology of hepatocellular carcinoma; Epstein-Barr virus (EBV), which can cause a lethal lymphoproliferative disorder in immunosuppressed patients; and human T cell lymphotropic virus type I (HTLV-I), which can induce a T cell leukemia. Viral infections very likely can cause other neoplasms as well.

Prevention of Transmission of HIV, Hepatitis B Virus, and Hepatitis C Virus

TRANSMISSION FROM PATIENTS TO HEALTH CARE WORKERS

The Centers for Disease Control and Prevention (CDC) has published extensive recommendations for preventing transmission of HIV, the etiologic agent of AIDS.¹⁻⁵ Applicable to clinical and laboratory staffs,^{3,4} to workers in health care settings [see Table 1]¹ and in other occupational settings,¹ and to health care workers performing invasive procedures,¹⁻⁵ these precautions are appropriate for preventing transmission not only of HIV but also of other blood-borne viruses, including HBV and HCV. The recommendations share the objective of minimizing exposure of personnel to blood and body secretions from infected patients, whether through needle-stick injury or through contamination of mucous membranes or open cuts.

Despite the apparently low risk of such exposure, the CDC recommends enforcement of these as well as other standard infection control precautions, regardless of whether health care workers or

patients are known to be infected with HIV or HBV. The CDC has taken the position that blood and body fluid precautions should be used consistently for all patients because medical history and physical examination cannot reliably identify all patients infected with HIV or other blood-borne pathogens and because in emergencies there may be no time for serologic testing. If these universal precautions are implemented, as the CDC recommends,¹⁻⁵ no additional precautions should be necessary for patients known to be infected with HIV.

The CDC does not recommend routine HIV serologic testing for all patients.¹⁻⁵ HIV serologic testing of patients is recommended for management of health care workers who sustain parenteral or mucous membrane exposure to blood or other body fluids, for patient diagnosis and treatment, and for counseling associated with efforts to prevent and control HIV transmission in the community.¹⁻⁵

Nevertheless, some hospitals and physicians are likely to perform serologic testing of patients if it is possible that health care workers will be exposed to the patients' blood or other body fluids, as would be the case with patients undergoing major operative procedures or receiving treatment in intensive care units. Those who favor routine preoperative testing of patients undergoing invasive procedures maintain that precautions are more likely to be followed and additional steps taken to lower the likelihood of virus transmission from patients to health care workers when it is known which patients are HIV positive.^{6,7} If such policies are adopted, the CDC advocates certain principles: (1) obtain consent for testing, (2) inform patients of results and provide counseling to seropositive patients, (3) ensure confidentiality, (4) ensure that seropositive patients will not receive compromised care, and (5) prospectively evaluate the efficacy of the program in reducing the incidence of exposure of health care workers to blood or body fluids of patients who are infected with HIV.

Although possible acquisition of HIV infection is the major concern for any health care worker who is exposed to blood products in the workplace, acquisition of viral hepatitis is actually much more likely. From a single needle-stick exposure, the estimated average risk of HIV transmission is 0.3%, whereas that of HCV transmission ranges from 0% to 10%.⁸ The risk that HBV will be transmitted from a single needle-stick exposure varies according to the hepatitis B e antigen (HBeAg) status of the source patient, ranging from 1% to 6% for HBeAg-negative patients to 22% to 40% for HBeAg-positive patients.⁹⁻¹¹ That health care workers are at increased risk for hepatitis B is indicated by the seroprevalence of HBV in this population, which is two to four times that in the general United States population (6% to 15% versus < 5%).^{9,12} This seroprevalence is expected to decrease with the availability of the hepatitis B vaccine and the mandate from the Occupational Safety

Table 1 Precautions to Prevent Transmission of HIV¹

Universal Precautions

1. All health care workers should use appropriate barrier precautions routinely to prevent skin and mucous membrane exposure when contact with blood or other body fluids of any patient is anticipated. Gloves should be worn for touching blood and body fluids, mucous membranes, or nonintact skin of all patients; for handling items or surfaces soiled with blood or body fluids; and for performing venipuncture and other vascular-access procedures. Gloves should be changed after contact with each patient. During procedures that are likely to generate aerosolized droplets of blood or other body fluids, masks and protective eyewear or face shields should be worn to prevent exposure of mucous membranes of the mouth, nose, and eyes. Gowns or aprons should be worn during procedures that are likely to generate splashes of blood or other body fluids.
2. Hands and other skin surfaces should be washed immediately and thoroughly if contaminated with blood or other body fluids. Hands should be washed immediately after gloves are removed.
3. All health care workers should take precautions to prevent injuries caused by needles, scalpels, and other sharp instruments or devices during procedures; when cleaning used instruments; during disposal of used needles; and when handling sharp instruments after procedures. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken by hand, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable syringes and needles, scalpel blades, and other sharp items should be placed in puncture-resistant containers for disposal; the puncture-resistant containers should be located as close as practical to the area of use. Large-bore reusable needles should be placed in a puncture-resistant container for transport to the reprocessing area.
4. Although saliva has not been implicated in HIV transmission, to minimize the need for emergency mouth-to-mouth resuscitation, mouthpieces, re-

suscitation bags, or other ventilation devices should be available for use in areas in which the need for resuscitation is predictable.

5. Health care workers who have exudative lesions or weeping dermatitis should refrain from all direct patient care and from handling patient care equipment until the condition resolves.
6. Pregnant health care workers are not known to be at greater risk for contracting HIV infection than health care workers who are not pregnant; however, if a health care worker acquires HIV infection during pregnancy, the infant is at risk for infection resulting from perinatal transmission. Because of this risk, pregnant health care workers should be especially familiar with and strictly adhere to precautions to minimize the risk of HIV transmission.

Additional Precautions for Invasive Procedures

1. All health care workers who participate in invasive procedures must use appropriate barrier precautions routinely to prevent skin and mucous membrane contact with blood and other body fluids of all patients. Gloves and surgical masks must be worn for all invasive procedures. Protective eyewear or face shields should be worn for procedures that commonly result in the generation of aerosolized droplets, splashing of blood or other body fluids, or the generation of bone chips. Gowns or aprons made of materials that provide an effective barrier should be worn during invasive procedures that are likely to result in the splashing of blood or other body fluids. All health care workers who perform or assist in vaginal or cesarean deliveries should wear gloves and gowns when handling the placenta or the infant until blood and amniotic fluid have been removed from the infant's skin and should wear gloves during postdelivery care of the umbilical cord.
2. If a glove is torn or a needle-stick or other injury occurs, the glove should be removed and a new glove used as promptly as patient safety permits; the needle or instrument involved in the incident should also be removed from the sterile field. In the event of an injury, postexposure evaluation should be sought as soon as possible.

& Health Administration (OSHA) directing that all health care workers potentially exposed to blood or other potentially infectious material either be offered hepatitis B vaccine free of charge, demonstrate immunity to hepatitis B, or formally decline vaccination.¹³ That vaccination has been effective in decreasing the incidence of hepatitis B in health care workers is shown by the decrease in infection rates from 174/100,000 in 1982 to 17/100,000 in 1995.¹⁴ Most series have not found the seroprevalence of HCV to be higher in health care worker groups at risk than in the general population.¹⁴ That hepatitis B and hepatitis C are much more common than HIV in health care workers is a strong argument for using universal precautions in all patients.

One reason why hepatitis B is so much more transmissible than HIV is the greater number of virus particles in the blood of hepatitis B carriers. These persons have blood concentrations of 10^8 to 10^9 virus particles/ml, compared with 10^2 to 10^4 /ml for persons with HIV infection and 10^6 /ml for persons with HCV infection.

The extensive guidelines that have been established by the CDC for the care of patients with HBV infection^{4,15-17} also apply to patients with HIV infection. Patients known to have hepatitis B, hepatitis C, or AIDS need not be put in a private room unless they are fecally incontinent or are shedding virus in body fluids. Health care workers should wear gloves and gowns when they have contact with or may have contact with a patient's blood, feces, or other body fluids. Needles used for drawing blood should be disposed of with special care: they must not be reused, recapped, or removed from the syringe. Hands must be washed before and after direct contact with the patient or with items that have been in contact with the patient's blood, feces, or body fluids.

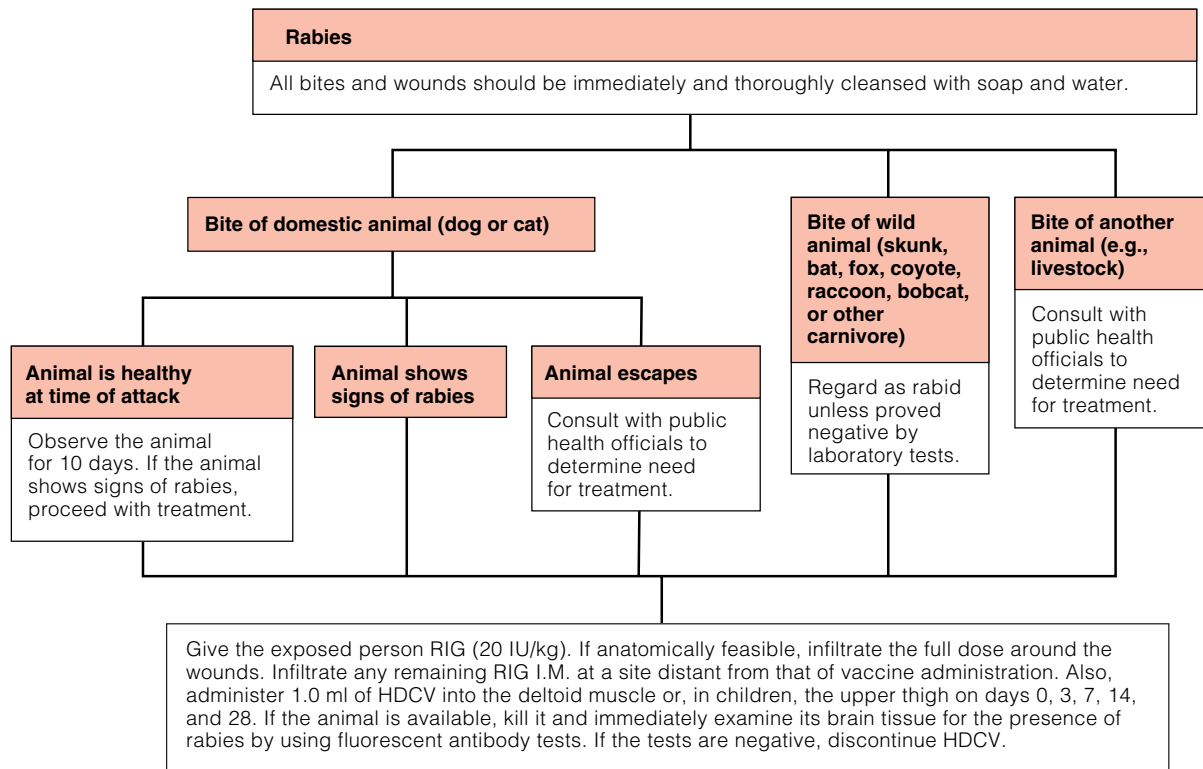
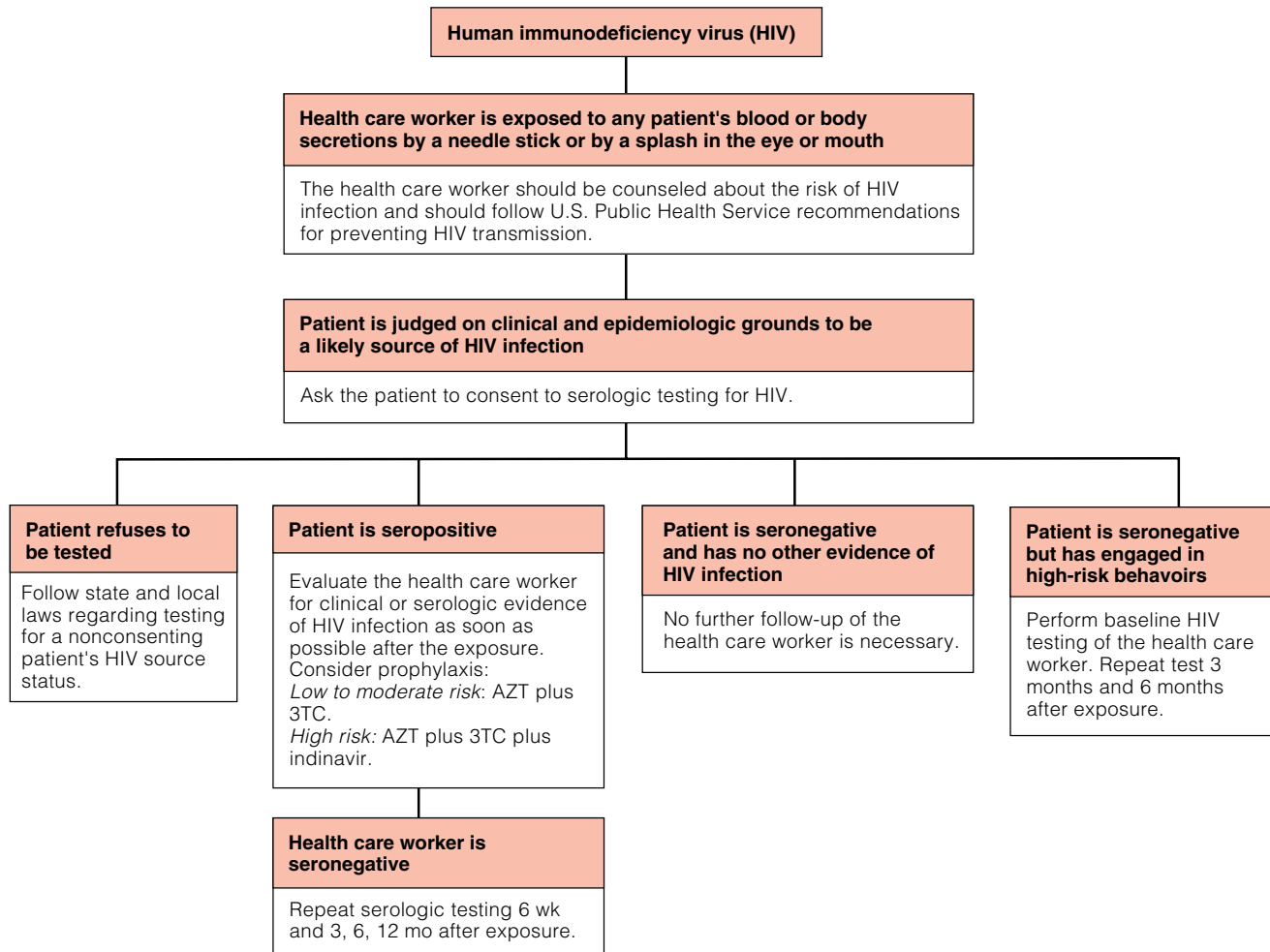
Published recommendations also provide guidelines for health care workers who are not directly involved in patient care (e.g., housekeeping personnel, kitchen staff, and laundry workers).¹⁻⁷

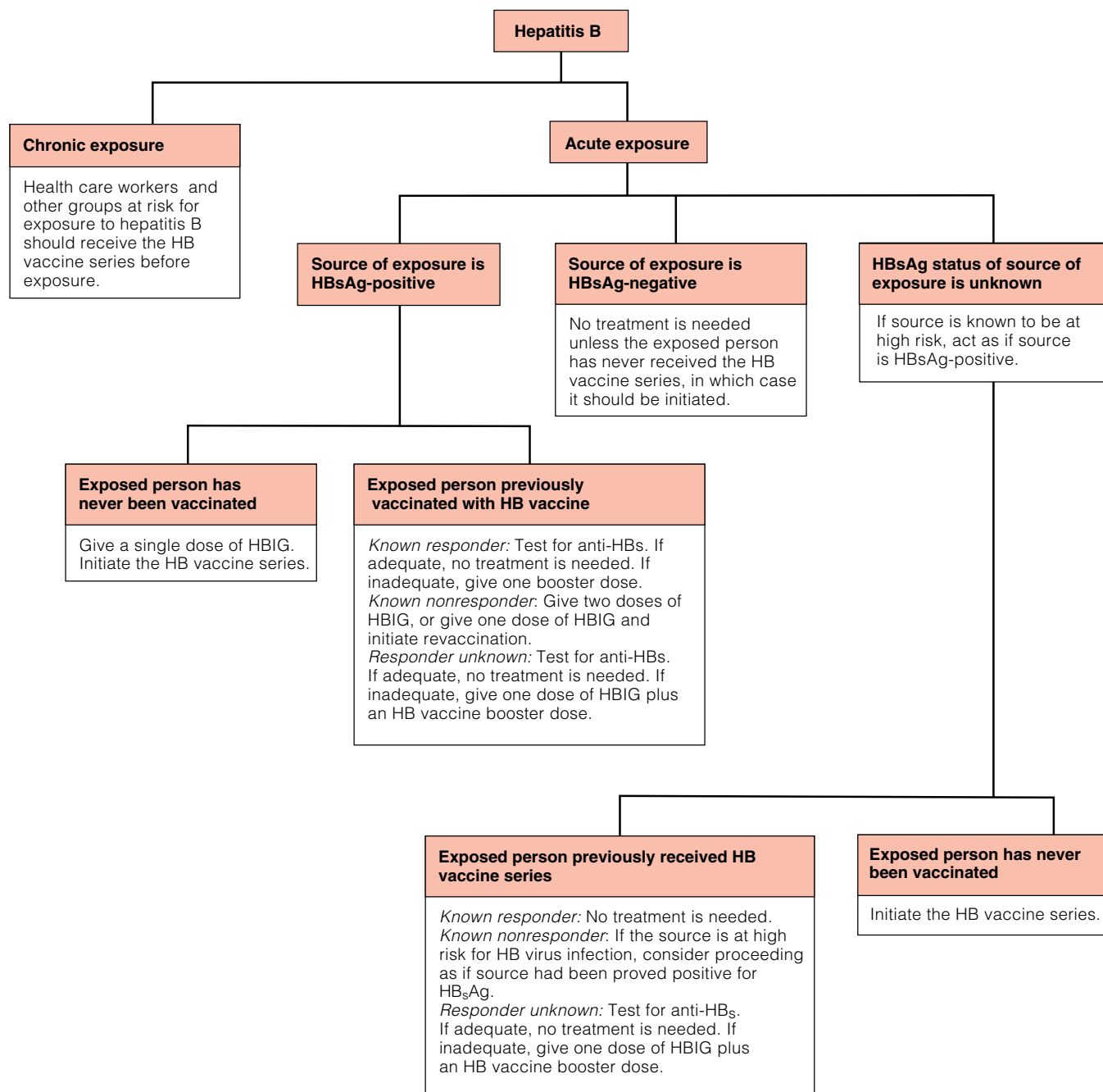
No additional precautions are necessary for these individuals because their risk of acquiring HIV, HCV, or HBV is so low; in fact, transmission to them has not been documented. However, staff should be educated about appropriate procedures. Workers should wear gloves when handling blood and body fluids of all patients and should wear masks in areas where blood may spatter (e.g., the dialysis unit or the obstetrics unit).

TRANSMISSION FROM HEALTH CARE WORKERS TO PATIENTS

To date, there have been only two reports of HIV transmission from infected health care workers to patients. In one report, DNA sequence analysis linked a Florida dentist with AIDS to HIV infection in six of his patients.¹⁸ In the other, an orthopedic surgeon in France may have transmitted HIV to one of his patients in the course of an operation.¹⁹ Despite extensive investigation, no break in infection control precautions was documented in either case, nor was any clear-cut means of transmission identified.

HBV transmission from health care workers to patients is known to occur. Nineteen case reports have documented physician-to-patient transmission.²⁰⁻³² Eighteen of the 19 physicians were surgeons; seven of the surgeons were gynecologists, three were cardiac surgeons, and one was an orthopedic surgeon. All of the physicians were positive for HBeAg. Three of the gynecologists made a practice of handling needle tips. Of the 135 patients studied, 121 had clinical hepatitis B, and 14 had only serologic evidence of infection. Forty-one of the 135 patients were accounted for by the only nonsurgeon, a family practitioner from rural Switzerland. There are many additional cases of HBV having been transmitted by dentists and oral surgeons. In addition, three patients' relatives, two members of a surgeon's family, and one laboratory technician became infected.





Approach to Viral Exposure

Hepatitis C

Perform serologic testing for ALT and HCV antibody at time of exposure and again at 6 months. If anti-HCV is detected, confirmatory testing with recombinant immunoblot is indicated. HCV immunoglobulin is no longer recommended.

In five studies, patients of 16 health care workers (including two surgeons) who were positive for hepatitis B surface antigen (HBsAg) were prospectively followed for evidence of hepatitis.³³⁻³⁷ A total of 784 patients were followed and were compared with 656 patients cared for by health care workers who were HBsAg negative. None of the patients acquired overt hepatitis or became seropositive for HBsAg. Eight (1.02%) of the 784 patients cared for by HBsAg-positive health care workers developed antibody to HBsAg (anti-HBs), but so did six (0.91%) of the 656 patients cared for by health care workers who were negative for HBsAg. These reports suggest that the likelihood of infected surgeons' or other health care workers' transmitting HIV or HBV to their patients is extremely low. Chronic carriers of HBsAg who are seronegative for HBeAg are much less likely to transmit HBV than persons who are HBeAg positive.

Before the cases of transmission of HIV from the dentist to six of his patients were reported, the CDC had not taken a position on whether HBV- or HIV-infected surgeons should be allowed to continue practicing medicine. After these cases were reported, the CDC held meetings of health care professionals and other interested parties and published its recommendations on July 12, 1991.³⁸ These recommendations called for physicians not to perform "exposure-prone invasive procedures" unless they sought counsel from an expert review panel and were advised under what circumstances, if any, they might be allowed to continue to perform these procedures. Physicians would have to notify prospective patients of their seropositivity. These recommendations were strongly resisted by the medical community because at that time, only one health care worker, the dentist, had been implicated in transmitting HIV to his patients, no mechanism of transmission had been elucidated, no other patients had HIV transmitted by a health care worker, and invasive procedures that were "exposure prone" (exposing the patient to blood of the health care worker) were impossible to define. After subsequent meetings, the CDC abandoned its attempts to define exposure-prone procedures but did not alter its recommendations. Rather, it left it up to the states to define exposure-prone procedures. Subsequently, the President's Commission on AIDS recommended that HIV-infected health care workers should not have to curtail their practices or inform their patients of their infection.

Transmission of HCV from health care workers to patients has been reported. In one such case, a cardiac surgeon transmitted HCV to at least five patients during valve replacement surgery.³⁹ In another, an anesthesiologist in Spain may have infected more than 217 patients by first injecting himself with narcotics, then giving the remainder of the drugs to his patients.⁴⁰ At present, no recommendations exist for restricting the professional activities of health care workers with HCV infection.

Management of Viral Exposure

HIV

The CDC has issued recommendations for the management of potential exposure of health care workers to HIV.^{1,4,41} If a health care worker is exposed by a needle stick or by a splash in the eye or mouth to any patient's blood or other body fluids, and the HIV serostatus of the patient is unknown, the patient should

be informed of the incident and, if consent is obtained, tested for serologic evidence of HIV infection. If consent cannot be obtained, procedures for testing the patient should be followed in accordance with state and local laws. Testing of needles or other sharp instruments associated with exposure to HIV is not recommended, because it is unclear whether the test results would be reliable and how they should be interpreted.⁴¹

Health care workers exposed to HIV should be evaluated for susceptibility to blood-borne infection with baseline testing, including testing for HIV antibody. If the patient who is the source of exposure is seronegative and exhibits no clinical evidence of AIDS or symptoms of HIV infection, further follow-up of the health care worker is usually unnecessary.⁴¹ If the source patient is seropositive or is seronegative but has engaged in high-risk behaviors, baseline and follow-up HIV-antibody testing of the health care worker at 6 weeks, 3 months, and 6 months after exposure should be considered.⁴¹ Seroconversion usually occurs within 6 to 12 weeks of exposure; infrequently, it occurs considerably later. Three cases of delayed HIV seroconversion among health care workers have been reported.⁴²⁻⁴⁴ In all three patients, an HIV antibody test yielded negative results at 6 months but positive results at some point during the following 1 to 7 months. In two cases, coinfection with HCV had occurred and took an unusually severe course. At present, it is unclear whether coinfection with these two viruses directly influences the timing or severity of either infection, but most experts recommend close monitoring for up to 1 year for health care workers exposed to both viruses in whom serologic evidence of HCV infection develops.

Treatment of the exposed health care worker should begin with careful washing of the exposure site with soap and water. Mucous membranes should be flushed with water. There is no evidence that either expressing fluid by squeezing the wound or applying antiseptics is beneficial, though antiseptics are not contraindicated. The use of caustic agents (e.g., bleach) is not recommended.

Any health care worker concerned about exposure to HIV should receive follow-up counseling regarding the risk of HIV transmission, postexposure testing, and medical evaluation, regardless of whether postexposure prophylaxis is given. HIV antibody testing should be performed at specified intervals for at least 6 months after the exposure (e.g., at 6 weeks, 3 months, and 6 months). The risk of HIV transmission is believed to depend on several factors: how much blood is involved in the exposure, whether the blood came from a source patient with terminal AIDS (thought to be attributable to the presence of large quantities of HIV), whether any host factors are present that might affect transmissibility (e.g., abnormal CD4 receptors for HIV), and whether the source patient carries any aggressive HIV viral mutants (e.g., syncytia-inducing strains). Factors indicating exposure to a large quantity of the source patient's blood (and thus a high risk of HIV transmission) include a device visibly contaminated with the patient's blood, a procedure that involved a needle placed directly in a vein or artery, and a deep injury.⁴⁵

During the follow-up period, especially the first 6 to 12 weeks, exposed health care workers should follow the U.S. Public Health Service recommendations for preventing further transmission of HIV.^{1,4} These recommendations include refraining from blood, semen, or organ donation and either abstaining from sexual intercourse or using measures to prevent HIV transmission during intercourse.⁴⁶

The circumstances of the exposure should be recorded in the worker's confidential medical record and should include the following:

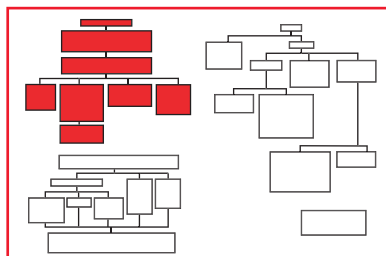


Table 2 Recommendations for Hepatitis B Prophylaxis after Percutaneous or Permucosal Exposure¹⁵

Hepatitis B Vaccination Status of Exposed Person	HBsAg Status of Source of Exposure		
	HBsAg-Positive	HBsAg-Negative	Untested or Unknown
Unvaccinated	Give single dose of HBIG Initiate HB vaccine series	Initiate HB vaccine series	Initiate HB vaccine series
Previously vaccinated	Test exposed person for anti-HBs If anti-HBs levels are adequate,* no treatment is needed; if they are inadequate, give an HB vaccine booster dose	No treatment is needed	No treatment is needed
Known responder			
Known nonresponder	No response to three-dose vaccine series: give two doses of HBIG or one dose of HBIG plus revaccination No response to three-dose vaccine series plus revaccination: give one dose of HBIG as soon as possible and a second dose 1 mo later	No treatment is needed	If source is at high risk for hepatitis B infection, consider proceeding as if source had been demonstrated to be HBsAg-positive
Response unknown	Test exposed person for anti-HBs If anti-HBs levels are adequate,* no treatment is needed; if they are inadequate, give one dose of HBIG plus an HB vaccine booster dose	No treatment is needed	Test exposed person for anti-HBs If anti-HBs levels are adequate,* no treatment is needed; if they are inadequate, initiate revaccination

*An adequate anti-HBs level is ≥ 10 mIU/ml, which is approximately equivalent to 10 sample ratio units (SRU) on radioimmunoassay or a positive result on enzyme immunoassay.

1. The date and time of the exposure.
2. Details of the exposure, including (a) where and how the exposure occurred, (b) the type and amount of fluid or other material involved, and (c) the severity of the exposure (for a percutaneous exposure, this would include the depth of injury and whether fluid was injected; for a skin or mucous membrane exposure, it would include the extent and duration of contact and the condition of the skin—chapped, abraded, or intact).
3. A description of the source of the exposure, including (if known) whether the source material contained HIV or other blood-borne pathogens, whether the source was HIV positive, the stages of any diseases present, whether the patient had previously received antiretroviral therapy, and the viral load.
4. Details about counseling, postexposure management, and follow-up.⁴¹

The data currently available on primary HIV infection indicate that systemic infection does not occur immediately. There may be a brief window of opportunity during which postexposure antiretroviral therapy may modify viral replication. Findings from animal and human studies provide indirect evidence of the efficacy of antiretroviral drugs in postexposure prophylaxis. The majority of these studies included zidovudine (AZT); consequently, all post-exposure prophylaxis regimens now in use include AZT. Combination treatment regimens using nucleoside reverse transcriptase inhibitors and protease inhibitors have proved effective. Accordingly, most experts now recommend dual therapy with two nucleosides (zidovudine and lamivudine) for low- to moderate-risk exposures. For high-risk exposures, most experts would add a protease inhibitor (usually either indinavir or nelfinavir) to the two nucleoside reverse transcriptase inhibitors. These medications should be started as soon as possible after the exposure (within hours rather than days) and should be continued for 4 weeks.

An important component of postexposure care is encouraging and facilitating compliance with the lengthy course of medication. Therefore, careful consideration must be given to the toxicity profiles of the antiretroviral agents chosen. All of these agents have

been associated with side effects, include GI (e.g., nausea or diarrhea), hematologic, endocrine (e.g., diabetes), and urologic effects (e.g., nephrolithiasis with indinavir). According to some early data, 50% to 90% of health care workers receiving combination regimens for postexposure prophylaxis (e.g., zidovudine plus 3TC, with or without a protease inhibitor) reported one or more subjective side effects that were substantial enough to cause 24% to 36% of the workers to discontinue postexposure prophylaxis.⁴⁷⁻⁴⁹

Whether antiretroviral agents should be chosen for postexposure prophylaxis on the basis of the resistance patterns of the source patient's HIV remains unclear. Transmission of resistant strains has been reported⁵⁰⁻⁵²; however, in the perinatal clinical trial that studied vertical transmission of HIV, zidovudine prevented perinatal transmission despite genotypic resistance of HIV to zidovudine in the mother.⁵³ Further study of the significance of genotypic resistance is necessary before definitive recommendations can be made.

HEPATITIS B

Both passive immunization with hepatitis B immune globulin (HBIG) and active immunization with hepatitis B vaccine (HB vaccine) are currently available for prophylaxis against hepatitis B [see Table 2].

Passive Immunoprophylaxis

HBIG is prepared by Cohn ethanol fractionation from plasma selected to contain a high titer of anti-HBs; this process inactivates and eliminates HIV from the final product. In the United States, HBIG has an anti-HBs titer of at least 1:100,000 by radioimmunoassay.⁵⁴ HBIG provides temporary, passive protection. It is indicated after low-volume percutaneous or mucous membrane exposure to HBV; it is not effective for high-

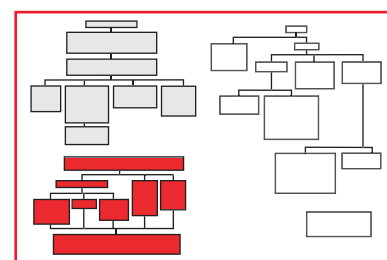


Table 3 Candidates for Hepatitis B Vaccine¹⁵

Preexposure vaccination	Persons with occupational risk (e.g., health care workers, public safety workers) Clients and staffs of institutions for the developmentally disabled Hemodialysis patients Sexually active homosexual men Users of illicit injectable drugs Recipients of certain blood products (e.g., patients with clotting disorders who receive clotting factor concentrates) Household and sexual contacts of HBV carriers Adoptees from countries of high HBV endemicity Other contacts of HBV carriers (vaccination is usually not required unless there are special circumstances, such as biting or scratching, or medical conditions, such as severe skin disease, that facilitate transmission) Populations with high endemicity of HBV infection (e.g., Alaskan natives, Pacific islanders, and refugees from HBV-endemic areas) Inmates of long-term correctional facilities Sexually active heterosexual persons with multiple sexual partners International travelers who spend more than 6 mo in HBV-endemic areas and have close contact with the local population All infants born in the United States Adolescents 11 to 12 years old who have not previously been vaccinated
	Perinatal exposure (infants born to HBsAg-positive mothers) Acute exposure to blood that contains (or might contain) HBsAg Sexual partners of persons with acute HBV infections Household contacts of persons with acute HBV infections (infants and older persons who have had identifiable blood exposure to the index patient)

volume exposure (e.g., blood transfusion). The recommended dose of HBIG for adults is 0.06 ml/kg I.M. Passive prophylaxis with HBIG should begin as soon as possible after exposure—ideally, within 24 hours.⁵⁴

Active Immunoprophylaxis

Two types of HB vaccine are currently licensed in the United States, plasma-derived vaccine (Heptavax-B) and recombinant vaccine (Recombivax HB and Engerix-B). Heptavax-B contains alum-adsorbed 22 nm HBsAg particles purified from human plasma and processed to inactivate the infectivity of HBV and other viruses. Plasma-derived vaccine is no longer being produced in the United States, but similar vaccines are produced and used in China and other countries. In the United States, use of Heptavax-B is limited to persons allergic to yeast. Recombivax HB and Engerix-B are prepared by recombinant DNA technology in common baker's (or brewer's) yeast, *Saccharomyces cerevisiae*.

For primary vaccination, three I.M. injections (into the deltoid muscle in adults and children and into the anterolateral thigh muscle in infants and neonates) are given, with the second and third doses 1 and 6 months after the first dose.⁵⁴ The dose for Heptavax-B and Engerix-B is 20 µg (volume, 1.0 ml) for persons older than 11 years, and that for Recombivax HB is 10 µg (1.0 ml) for persons

older than 19 years and 5 µg (0.5 ml) for persons 11 to 18 years of age. For immunologically impaired patients, including hemodialysis patients, the dose is 40 µg for all three vaccines. For postexposure prophylaxis with Engerix-B, a regimen of four doses given soon after exposure and 1, 2, and 12 months afterward has been approved.

HB vaccine is more than 90% effective at preventing infection or clinical hepatitis in susceptible persons. Protection is virtually complete in persons who develop adequate antibody. Routine testing for immunity after vaccination is not recommended, but testing should be considered for persons at occupational risk who require postexposure prophylaxis for needle-stick exposure.

Between 30% and 50% of persons who have been vaccinated will cease to have detectable antibody levels within 7 years, but protection against infection and clinical disease appears to persist.^{54,55} The need for booster doses has not been established. Revaccination of individuals who do not respond to the primary series will produce adequate antibody in 15% to 25% of cases after one additional dose and in 30% to 50% after three additional doses.⁵⁶

Although effective HB vaccines have been available since 1982, the incidence of hepatitis B in the United States continued to increase in the first decade of HB vaccine use. In 1991, the Advisory Committee for Immunization Practices (ACIP), citing the safety of the vaccine and the evidence of continuing spread of HBV, recommended universal vaccination of all infants born in the United States.⁵⁷

Recommendations for Exposure to Blood That Contains (or May Contain) HBsAg

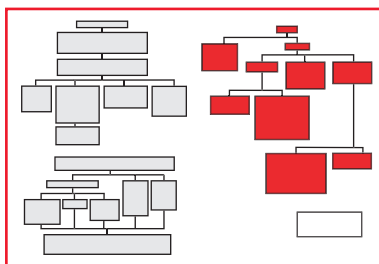
Acute exposure The U.S. Public Health Service has provided recommendations for hepatitis B prophylaxis after accidental percutaneous, mucous membrane, or ocular exposure to blood that contains (or may contain) HBsAg [see Table 2].⁴³ These recommendations are based on consideration of several factors: (1) whether the source of the blood is available, (2) the HBsAg status of the source, and (3) the hepatitis B vaccination and vaccination-response status of the exposed person. After exposure, a blood sample should be obtained from the person who was the source of the exposure and should be tested for HBsAg. The hepatitis B vaccination status and the anti-HBs response status (if known) of the exposed person should be reviewed. Because passive administration of antibody with HBIG does not inhibit the active antibody response to HB vaccine, the two can be given simultaneously

Chronic exposure The U.S. Public Health Service recommends that persons who are at risk for exposure to HBV receive the HB vaccine series [see Table 3].⁵⁴ Health care workers who are at increased risk for acquiring hepatitis B include all physicians (especially surgeons), dentists, and laboratory and support personnel, such as nurses and technicians who work in the operating room or who have contact with infected patients, blood or blood products, or excreta. Because of their frequent exposure to blood and their high risk of hepatitis B, all surgeons should receive HB vaccine. As of 1994, however, only 50% of surgeons had been vaccinated, despite the proven efficacy and safety of the vaccine and surgeons' increased risk of exposure.⁵⁸ Hospital personnel who do not have frequent contact with blood or blood products (e.g., the janitorial, laundry, and kitchen staffs) need not be vaccinated.

Screening of personnel and patients for anti-HBs before vaccination is indicated only for individuals in high-risk groups; it has not been found to be cost-effective outside these groups.

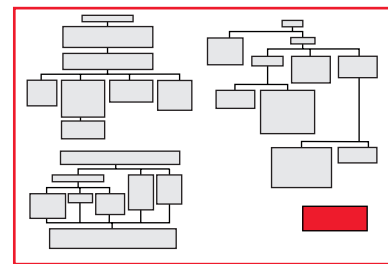
HEPATITIS C

The only tests currently approved by the U.S. Food and Drug Administration for diagnosis of hepatitis C are those that measure antibody to HCV. These tests detect anti-HCV in at least 97% of infected patients, but they cannot distinguish between acute, chronic, and resolved infection.⁵⁹ The positive predictive value of enzyme immunoassay (EIA) for anti-HCV varies depending on the prevalence of the infection in the population. Therefore, supplemental testing of a specimen with a positive EIA result with a more specific assay (e.g., the recombinant immunoblot assay [RIBA]) may detect false positives, especially when asymptomatic persons are being tested. Qualitative polymerase chain reaction (PCR) testing for HCV RNA can also be used to identify HCV. This test can detect HCV at concentrations as low as 100 to 1,000 viral genome copies/ml, and it can detect HCV RNA in serum or plasma within 1 to 2 weeks after viral exposure and weeks before alanine aminotransferase (ALT) levels rise or anti-HCV appears.⁵⁹ Under optimal conditions, the reverse transcriptase PCR assay for HCV can identify 75% to 85% of persons who are anti-HCV-positive and more than 95% of persons with acute or chronic hepatitis C.⁵⁹ Quantitative assays for measuring HCV RNA are also available but are less sensitive and should not be used as primary tests for confirming or excluding the diagnosis of HCV infection or monitoring the end point of treatment.⁵⁹ The data currently available on prevention of HCV infection with immune globulin (IG) indicate that this approach is not effective as postexposure prophylaxis for HCV infection.⁵⁹ Interferon may have a role in the treatment of acute hepatitis C: several studies have shown that interferon may delay or prevent the onset of chronic hepatitis C in patients treated early in the course of acute HCV infection.⁶⁰⁻⁶²



RABIES

The CDC has made recommendations for the prevention of rabies in people bitten by animals [see Table 4].⁶³ Bite wounds should always be thoroughly scrubbed with soap and water. Postexposure anti-rabies treatment includes both rabies immune globulin (RIG) and human diploid cell (rabies) vaccine (HDCV). The decision to administer such treatment should be based on the following considerations.



Species and Availability of Biting Animal

In the United States, rabies is most commonly transmitted by skunks, raccoons, foxes, and bats. Livestock occasionally transmit the virus, but rodents and lagomorphs (i.e., rabbits and hares) are rarely infected.⁶⁴ In different parts of the country, different animals predominate in the transmission of the virus. The likelihood that domestic cats or dogs in the United States will be infected varies from region to region. The chances of rabies transmission by a domestic animal that has been properly immunized are minimal.

Whether an animal is available for observation after biting someone also influences the need for antirabies prophylaxis. In certain cases, an animal that bites a person must be killed and tissue from its brain checked for the presence of rabies by fluorescent antibody tests as soon as possible [see Table 4].

Type of Exposure

Infected animals transmit rabies primarily by biting, although licking may introduce the virus into open cuts in skin or mucous membranes. Transmission occasionally occurs as a result of aerosol exposure: the virus may be excreted in the urine and feces of infected bats, aerosolized during urination and defecation, and then inhaled, for example, by spelunkers exploring caves.

Table 4 Rabies Postexposure Prophylaxis⁶³

Animal Species		Condition of Animal at Time of Attack	Treatment of Exposed Person*
Domestic	Dog, cat	Healthy and available for 10 days of observation	None, unless animal develops rabies [†]
		Rabid or suspected rabid	RIG (20 IU/kg) [‡] and HDCV [§] (five 1.0 ml doses intramuscularly, on days 0, 3, 7, 14, and 28)
		Unknown (escaped)	Consult public health officials. If treatment is indicated, give RIG [‡] and HDCV
Wild	Skunk, bat, fox, coyote, bobcat, raccoon, other carnivores	Regard as rabid unless proved negative by laboratory tests	RIG (20 IU/kg) [‡] and HDCV (five 1.0 ml doses intramuscularly, on days 0, 3, 7, 14, and 28)
Other	Livestock, rodents, lagomorphs (rabbits and hares)	Consider individually. Local and state public health officials should be consulted on questions about the need for rabies prophylaxis. Bites of squirrels, hamsters, guinea pigs, chipmunks, gerbils, rats, mice, other rodents, and lagomorphs almost never call for antirabies prophylaxis.	

*All bites and wounds should immediately be thoroughly cleansed with soap and water. If antirabies treatment is indicated, both rabies immune globulin (RIG) and human diploid cell rabies vaccine (HDCV) should be given as soon as possible, regardless of the interval from exposure. (The administration of RIG is the more urgent procedure. If HDCV is not immediately available, start RIG and give HDCV as soon as it is obtained.) Local reactions to vaccines are common and do not contraindicate continuing treatment. Discontinue vaccine if fluorescent antibody tests of the animal are negative.

[†]During the usual holding period of 10 days, begin treatment with RIG and HDCV at first sign of rabies in a dog or cat that has bitten someone. The symptomatic animal should be killed immediately and tested.

[‡]The full dose should be infiltrated around the wounds; any remaining RIG should be given I.M. at a site distant from that of vaccine administration. If RIG is not available, use antirabies serum, equine (ARS). Do not use more than the recommended dosage of RIG or ARS.

[§]HDCV should be administered into the deltoid (not the gluteus) muscle in adults and adolescents. In children, it may be administered into the upper thigh.

^{||}The animal should be killed and tested as soon as possible. Holding for observation is not recommended.

Circumstances of the Bite

An unprovoked attack is more indicative of a rabid animal than is a provoked attack.

If the animal shows signs of rabies or the patient has been bitten by a wild animal that is not captured, the patient should be treated as soon as possible with both RIG and HDCV. The recommended dose of RIG for postexposure prophylaxis is 20 IU/kg.⁶³ If anatomically feasible, the entire dose of RIG should be infiltrated into the area around the wound.^{65,66} Postexposure HDCV should be given I.M. in five 1.0 ml doses on days 0, 3, 7, 14, and 28.⁶³ Those with adequate preexposure immunization should receive two 1.0 ml doses of HDCV I.M. on days 0 and 3 but should receive no RIG. For adults, the vaccine should be administered in the deltoid area. For children, the anterolateral aspect of the thigh is also acceptable. The gluteal area should never be used for HDCV injections, because administration in this area results in lower neutralizing antibody titers.⁶³ HDCV must not be given in the same region as RIG.

The CDC recommends that preexposure immunization be considered for high-risk groups, such as animal handlers, certain labo-

ratory workers and field personnel, and persons planning to stay for more than 1 month in areas where canine rabies is highly prevalent and access to appropriate medical care is limited. The recommended preexposure regimen is 0.1 ml of HDCV on days 0, 7, and 21 or 28.⁶⁷ Testing for adequate antibody response is not necessary for persons at low risk for exposure, but administration of booster doses every 2 to 3 years is recommended for those at high risk for exposure. Postexposure treatment for persons who have received preexposure immunization consists of 1 ml HDCV on days 0 and 3 only, without RIG.⁶⁸

Although only a few cases of clinical rabies occur each year in the United States, approximately 30,000 persons a year are given postexposure prophylaxis. In 1992, 49 states, the District of Columbia, and Puerto Rico collectively reported 8,644 cases of animal rabies and one case of human rabies to the CDC.⁶⁹ The total expense associated with one rabid dog in California was \$105,790, even though no human contracted rabies.⁷⁰ This amount represents the costs of human antirabies treatment, vaccination of other animals, and animal-containment programs.

Discussion

Size and Structure of Viruses

Viruses are among the smallest and simplest of microorganisms. Human viruses can be as small as 18 to 26 nm in diameter (parvoviruses) or as long as 300 nm (vaccinia virus), slightly longer than *Chlamydia* (a bacterium). Viruses do not have the complex enzyme systems required for synthesis of nucleic acid precursors, they lack ribosomes for protein synthesis, and they have no energy-generating mechanism. Consequently, they cannot replicate outside cells.

The core of a virus is made of either RNA or DNA, but never both. The nucleic acid can be either single stranded or double stranded. This nucleic acid core is surrounded by the capsid, which is a protein coat made up of capsomers, repetitive subunits consisting of one protein or at most a few. Because the viral nucleic acid must code for coat proteins, a limitation in the number of capsid proteins conserves viral nucleic acid. The capsid protects the nucleic acid from nucleases in the environment, serves as its vehicle of transmission from one host to another, and plays a role in the attachment of the virus to the receptor sites on susceptible cells. The complete nucleic acid-protein coat complex is termed the nucleocapsid. For many viruses, the nucleocapsid is the complete virus particle, the virion. Other viruses, such as herpesviruses, may acquire an envelope, an additional lipid-containing membrane coat around the nucleocapsid, by budding through a membrane of the host cell [see Figure 1]. Some viruses may also have an enzyme associated with their core that replicates the nucleic acid. Examples are the DNA polymerase of the HBV and the reverse transcriptase of retroviruses.

Classification of Viruses

Viruses, like other organisms, are classified into families, genera, and species, but most viral species do not have formal names and in practice are referred to by common names (e.g., cytomegalovirus, coxsackievirus, Norwalk virus, and varicella-zoster virus). Viruses can also be classified by chemical characteristics and by

structural characteristics determined from electron microscopy (e.g., dimensions and site of assembly). Viruses are categorized into two broad groups depending on whether their nucleic acid is RNA or DNA. These two groups can be subdivided first according to whether the nucleic acid is single stranded or double stranded and then according to the presence or absence of an envelope. Single-stranded RNA viruses that replicate by means of a DNA step (i.e., retroviruses) are grouped separately from those that do not.

Identification of Viruses

Viruses can be identified by means of (1) serologic tests, (2) isolation of virus, (3) histologic examination, (4) detection of viral antigens, (5) detection of viral nucleic acid, and (6) electron microscopy. One or more of these techniques may be applicable to a given viral infection.

Specimens must be handled properly to maximize the likelihood of identifying the virus. If isolation of the virus is desired, blood and tissue samples should be taken promptly to the virology laboratory and inoculated onto the appropriate cell line. Samples obtained at night or on weekends can be placed in a balanced salt solution or tissue culture medium and kept in a refrigerator until taken to the laboratory. If microscopic identification of the virus is planned, specimens must be preserved appropriately. Routine preservation in formalin, for example, permits visualization of viral inclusions by routine staining and light microscopy. For identification of viral antigens by immunofluorescence techniques, the tissue specimen should be immediately frozen, preferably in liquid nitrogen. Specimens to be examined by electron microscopy must be placed in glutaraldehyde or another appropriate fixative.

SEROLOGIC TESTS

The antibody response to viral antigens can be detected in the serum of patients with viral infections. An IgM response usually indicates recent exposure to the virus, whereas the presence of IgG reflects past exposure.

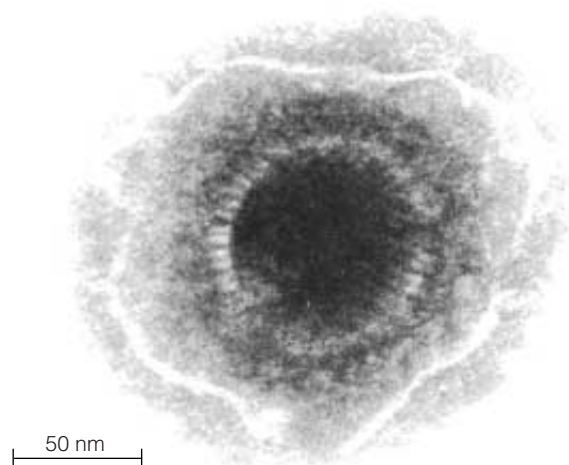
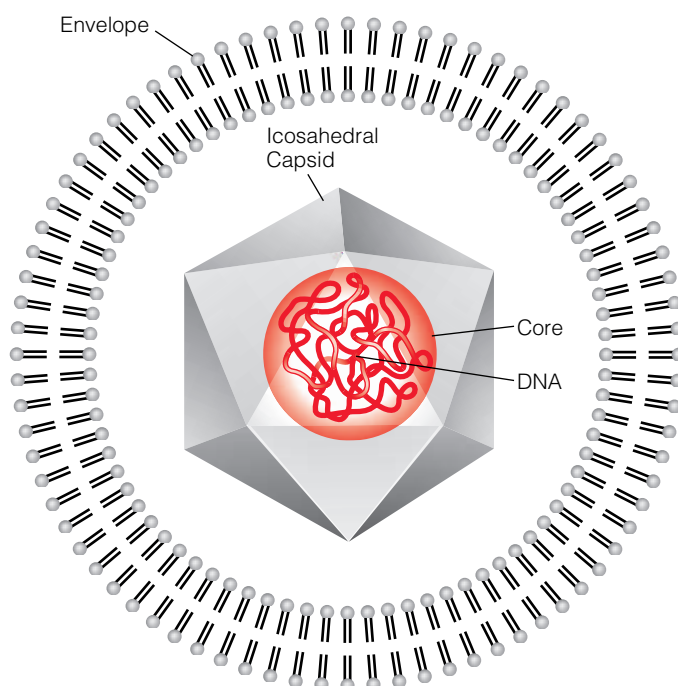


Figure 1 The capsomers and the irregularly shaped surrounding envelope of a cytomegalovirus are highlighted by negative staining with uranyl acetate (above). A typical herpesvirus (right) consists of a central core containing DNA; an icosahedral capsid, a surrounding layer of protein made up of 162 individual capsomers; and an envelope, a membrane coat acquired when the virus buds from the nuclear membrane of the host cell.



For most acute primary infections, serum obtained during late recovery or after recovery (convalescent serum) has an increased antibody titer, compared with serum obtained early in the course of the disease (acute serum). Most tests are performed on an initial serum dilution of 1:2 or 1:10 and on serial twofold dilutions thereafter. A fourfold increase in titer (indicated by reactivity of a two-tube dilution) usually represents a significant increase in antibody response and is considered to constitute seroconversion. An immunocompromised host may occasionally fail to mount an antibody response.

Some viruses are so common that patients may already have antibody titers when the disease is first suspected. Herpesviruses are ubiquitous and are present in many healthy people in latent form. At the onset of herpesvirus infections, patients may already have the corresponding antibody. Nevertheless, their antibody titer will almost always increase significantly after recovery.

A variety of serologic tests are available in the clinical laboratory: complement fixation, radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), immunofluorescence, immune precipitation, immune blotting, latex agglutination, virus neutralization, indirect hemagglutination, immune adherence hemagglutination, and hemagglutination inhibition. None of these serologic tests is appropriate for identification of all viruses.

ISOLATION OF VIRUS

The isolation of virus requires appropriate specimen collection and inoculation into animals or onto appropriate cell lines. Blood sent for virus isolation should be unclotted because some viruses, such as herpesviruses, are found primarily in lymphocytes. If cell-associated viruses are suspected, lymphocytes should be inoculated directly onto target cells. Several types of cells are available for growing viruses, and no single cell line is appropriate for all of them. Therefore, it is helpful to the laboratory to know which virus the clinician suspects.

Viruses that grow in cell monolayers in tissue culture have cytopathic effects that can be recognized under the microscope (e.g., rounding, transformation, or death) [see Figure 2]. Some viruses, such as rubella, produce no direct cytopathic effects but can be

detected because they inhibit the cytopathic effects of a second test virus. This phenomenon is called viral interference. Other viruses (e.g., myxoviruses) cause changes in the cell membrane so that red blood cells adhere to the cell surface (hemadsorption). The identity of isolated viruses can be confirmed by use of specific antisera that are known to inhibit viral growth.

Tissue suspected of containing an encephalitis or other neurotropic virus can be minced and the extract injected intracerebrally into an infant mouse. If the mouse dies and bacteria cannot be cultured from the brain, the injected material presumably contained such a virus. If antiserum of known specificity neutralizes the virus, the specificity of the antiserum indicates the specific identity of the virus. The criterion for neutralization is that inoculation of neutralized virus will not kill the mouse.

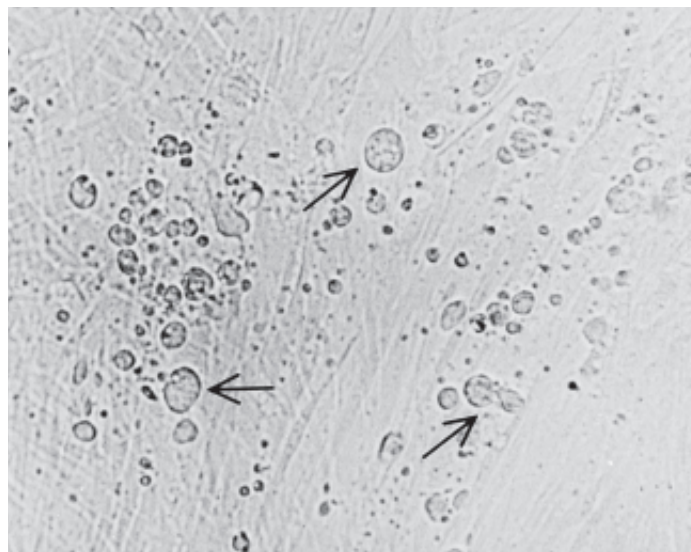


Figure 2 Cells infected with cytomegalovirus become large and round (arrows). Note the uniform appearance of adjacent uninfected cells.

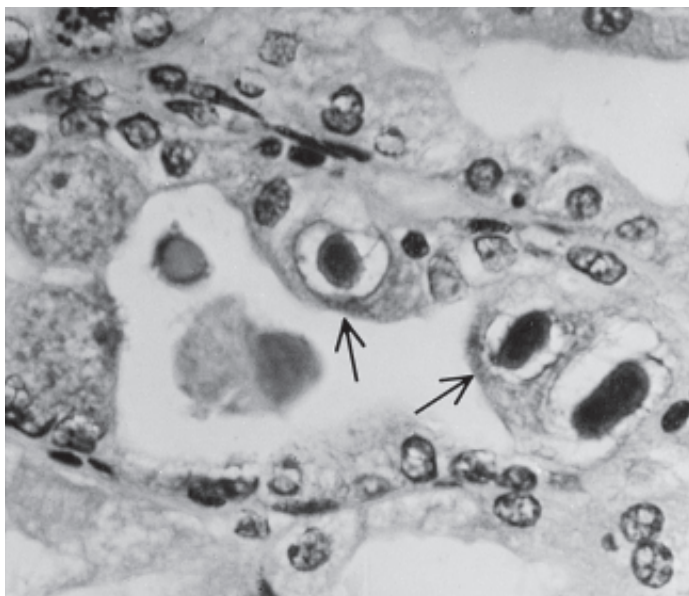


Figure 3 Kidney biopsy shows cytomegalovirus-infected tubular epithelial cells (arrows). In such cells, a dark intranuclear inclusion is surrounded by a clear halo. Inclusions usually indicate sites of previous or current viral replication.

HISTOLOGIC EXAMINATION

Histologic examination of biopsy and autopsy tissues may demonstrate changes that are typical of certain viruses. Members of the herpesvirus group can be characterized by intranuclear inclusions surrounded by a clear halo [see Figure 3]. RNA viruses usually produce inclusions in the cytoplasm; for instance, dark-staining intracytoplasmic inclusions in the brain tissue of animals or patients are diagnostic of rabies infection and are called Negri bodies. Inclusion bodies are either masses of closely packed virus particles or remnants of prior virus replication.

DETECTION OF VIRAL ANTIGENS

Viral antigens can be detected in tissues by techniques employing their corresponding antibodies. If virus is present, these antigens may be visible microscopically under ultraviolet light either by direct immunofluorescence (i.e., in tissue sections stained with fluorescein-labeled antiviral antibody) or by indirect immunofluorescence (i.e., in tissue sections exposed first to antiviral antibody and then to fluorescein-labeled anti- γ -globulin antibody). Fluorescence microscopy requires specimens that are fresh frozen (preferably in liquid nitrogen). Immunofluorescence staining of cells in tissue culture can detect viral antigens before cytopathic effects are evident. Viral antigens in formalin-fixed tissue can be identified by immunohistochemical microscopy (e.g., using peroxidase-labeled antibodies).

DETECTION OF VIRAL NUCLEIC ACID

Viral nucleic acids can be detected in body fluids and tissues at virus concentrations too low to be detected by other means. The PCR permits amplification of even a small number of copies of viral nucleic acid. In theory, even a single copy of a specific DNA can be detected by PCR. Before PCR is performed, DNA can be synthesized from viral RNA by means of reverse transcriptase. The PCR product can be detected by gel electrophoresis and compared with known viral DNA. This test is currently being used to diagnose CMV infection and is more sensitive than current serologic testing for HCV. Nucleic acid hybridization can detect viral nucleic acid in tissue specimens. Epstein-Barr virus genomes

can be detected in this way in EBV-related cancers and lymphoproliferative disorders.

ELECTRON MICROSCOPY

Although seldom used routinely, electron microscopy allows rapid identification (in a matter of hours) of viruses in body fluids, tissues, and tissue extracts. Identification of viruses in body fluids and tissue extracts by this method is easier if the samples are first concentrated by ultracentrifugation, evaporation, or ultrafiltration. HBV has been observed in specimens from hepatitis patients only after ultracentrifugation.

Epidemiology of Viral Infections of Interest to Surgeons

Viral infections are spread to humans via several patterns of transmission: (1) direct transmission from humans with symptomatic infection (e.g., HBV, HCV, herpesviruses, and HIV), (2) transmission from asymptomatic human carriers (e.g., HBV, HCV, HIV, and varicella-zoster virus), (3) transmission from arthropods (e.g., encephalitis and dengue viruses), and (4) transmission from other animals (e.g., rabies virus).

Viral infections are common in immunosuppressed patients in general and especially in recipients of organ transplants, who must take immunosuppressive drugs to prevent rejection. The overwhelming majority of these infections are caused by members of the herpesvirus family (e.g., CMV, herpes simplex viruses, varicella-zoster virus, and EBV); infections with HBV and with papovaviruses (e.g., human papillomavirus, which causes warts, and BK virus) are also frequent.

Because surgical patients are frequently given transfusions of blood or blood products and because hospital staff often incur accidental needle-stick injury, viruses that can be transmitted by these routes are of prime interest to surgeons and their patients. Examples of such viruses are HBV, hepatitis D, HCV, HIV, HTLV-I, and the herpesviruses, including EBV and CMV. These viruses can also be transmitted by organ transplantation either from the cells of the organ itself (e.g., HBV in liver cells or CMV in kidney cells) or from blood that has not been completely removed from the organ. Changes in donor acceptance and screening policies over time have increased the safety of the blood supply and should continue to do so in the future [see Table 5].⁷¹

HIV

Two serotypes of HIV, HIV-1 and HIV-2, have been identified. Both can cause AIDS. HIV-1 accounts for virtually all cases of AIDS in the United States and equatorial Africa. HIV-2 is found almost exclusively in West Africa; only a few cases of HIV-2 infection have occurred in the United States.

Because AIDS patients are immunodepressed, they are susceptible to opportunistic infections and neoplasms, especially non-Hodgkin lymphoma, *Pneumocystis carinii* pneumonia, and Kaposi sarcoma. AIDS is most prevalent in the United States among male homosexuals, abusers of I.V. drugs, and hemophiliacs. Since the implementation of testing for blood-borne HIV and the near-elimination of HIV from blood products, the incidence of HIV infection in the hemophiliac population has diminished markedly; however, in recent years, the incidence in the heterosexual population has been increasing rapidly.

HIV can be transmitted by transfusion of whole blood, packed red cells, plasma, factor VIII concentrates, factor IX concentrates, and platelets. The likelihood that a person will become infected with HIV after receiving a single-donor blood product that tests

Table 5 Changes in Donor Acceptance and Screening Policies Instituted to Reduce the Risk of Transmitting Infectious Diseases⁷¹

Policy	Implementation Date
Screening for HBsAg	July 1972
Voluntary exclusion of persons at high risk for AIDS	March 1983
Redefinition of high-risk behavior to include men who have had sex with more than one man since 1979	December 1984
Testing for antibody to HIV-1	Spring 1985
Redefinition of high-risk behavior to include any man who has had sex with another man since 1977	September 1985
Implementation of a mechanism to allow donors to indicate confidentially that their donations should not be used for transfusion	October 1986
Testing for alanine aminotransferase (ALT, formerly SGPT)	Winter 1986–1987
Testing for anti-HBc	Spring 1987
Testing for antibody to HTLV-1	January 1990
Testing for antibody to HCV	May 1990
Testing for antibody to HIV-2	April 1992
Testing for HIV-1 antigen	March 1996

positive for HIV approaches 100%.⁷²⁻⁷³ Before the advent of serologic testing for HIV in 1985, 0.04% of 1,200,000 blood donations in the United States were estimated to be HIV positive.⁷⁴ AIDS has developed in more than 8,500 recipients of blood transfusions, blood components, or transplanted organs or tissue.

Federal regulations now require that all prospective blood and plasma donors be screened for antibody to HIV by ELISA. Because this test yields a low rate of false positive results, assay by the more sensitive Western blot electrophoresis is always used to confirm positive ELISA results. Routine testing of blood donors has greatly reduced HIV transmission via blood transfusions, but infection can still occur if the donor has been infected with HIV but has not yet developed antibody.⁷⁵ The risk of HIV transmission via transfusion of screened blood that is negative for HIV is estimated to be one in 200,000 to one in 2,000,000 per unit transfused in the United States.⁷⁶ Antibody to HIV usually develops within 4 weeks to 6 months of HIV infection.⁷⁷ From the time of infection until the appearance of antibody, infected individuals will test negative by ELISA or Western blot, and their blood might still be used for transfusion.

HIV and AIDS can also be transmitted by organ transplantation.⁷⁸ So far, only a small number of patients have been found to be infected in this way, but more will undoubtedly be reported. These patients received transplants before HIV testing of potential donors became possible. All prospective organ and tissue donors now should be tested for HIV infection and other blood-borne viral infections.

HIV infection is also a potential problem in health care workers, who are exposed to a large and growing population of AIDS patients. In the United States, an estimated 1.0 to 1.5 million people are infected with HIV but as yet have no symptoms. HIV

transmission from blood, tissue, or other body fluids can occur in the health care setting as a result of percutaneous injury (e.g., from needles or other sharp objects), contamination of mucous membranes or nonintact skin (e.g., skin that is chapped, abraded, or affected by dermatitis), prolonged contact with intact skin, or contamination involving an extensive area.⁷⁹ HIV infection may be contracted through a variety of sources including blood, semen, vaginal secretions, visibly bloody fluids, and a number of other fluids for which the precise risk of transmission is undetermined (e.g., cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluid). Infection may also be contracted from concentrated HIV used in research settings.⁷⁹ The results of multiple prospective studies quantifying transmission risk associated with a discrete occupational HIV exposure indicate that the average risk of HIV transmission associated with needle punctures or similar percutaneous injuries is approximately 0.3%. The estimated risk of transmission from mucocutaneous exposure to HIV-contaminated material is 0.03%. As of December 1999, the CDC had received reports of 56 U.S. health care workers in whom documented HIV seroconversion was temporally related to occupational HIV exposure. Of these 56, 48 had percutaneous exposures, five mucocutaneous exposures, two both percutaneous and mucous membrane exposures, and one an unknown route of exposure.⁸⁰ Another 138 possible cases of occupational HIV transmission—six involving surgeons—have been reported in persons with no risk factors for HIV transmission other than workplace exposure; however, seroconversion after a specific exposure was not documented. There may be other health care workers who also have acquired HIV infection from needle-stick or mucous membrane exposure but have not been reported, either because they and their patients have not been tested or because they have other risk factors for HIV infection.

The concentration of virus in the blood or serum of antigen-positive individuals is several orders of magnitude less for HIV than for HBV. The number of needle-stick exposures to HIV that have actually led to a positive test result for HIV has been extremely small, whereas hepatitis B occurs in as many as 40% of health care workers exposed to the virus by needle-stick injury. Despite this relatively low infectiousness, AIDS is much more feared than hepatitis B because AIDS is often fatal. Although hepatitis B is usually not fatal and is often of short duration, several health care workers die of hospital-acquired hepatitis B and hepatitis C each year.

Hepatitis

Several viruses can cause hepatitis. Hepatitis A virus (HAV) and HBV cause what were formerly known as infectious hepatitis and serum hepatitis, respectively. HCV is the major cause of parenterally transmitted non-A, non-B hepatitis. Hepatitis E virus is a common cause of epidemic non-A, non-B hepatitis, which is chiefly found in developing countries in Africa and Asia. Hepatitis D virus (HDV, formerly called the delta agent) is defective or incomplete and is pathogenic only in the presence of HBV. The hepatitis viruses are the most common infectious agents to which hospital personnel may be exposed. Herpesviruses can also cause serious and sometimes fatal hepatitis, especially in severely immunocompromised patients, such as recipients of organ or bone marrow transplants and patients receiving intensive chemotherapy for cancer.

HEPATITIS A

HAV is a small (27 nm), single-stranded RNA virus belonging to the enterovirus subgroup of picornaviruses. Its almost exclusive transmission by the fecal-oral route is enhanced by poor personal

hygiene, poor sanitary conditions, and crowding. Transmission can be contained by careful hand washing and the isolation of excretions. Unlike other types of viral hepatitis, hepatitis A is rarely transmitted by blood, blood products, or needle sticks and is rarely transmitted among hemodialysis patients, health care workers, and I.V. drug abusers. The infrequent parenteral transmission of HAV is attributed in part to its lack of an asymptomatic carrier state. Hepatitis A can be transmitted percutaneously only during a brief period of viremia before the onset of symptoms and jaundice. The chance that an infected person will donate blood during this short period is small; also, patients are usually outside the hospital during this period.

HEPATITIS B

HBV is a member of the Hepadnaviridae family of DNA viruses. It is most prevalent in the Far East, the Middle East, Africa, and parts of South America, where as many as 15% of the general population are chronic carriers. Worldwide, the most common mode of transmission is from mother to child during the perinatal period. In the United States, however, sexual or parenteral transmission has been implicated in most infections. The high-risk groups for chronic HBV infection in the United States include I.V. drug users, men who have sex with men, other individuals with multiple sexual partners, household contacts and sexual partners of HBV carriers, health care workers, patients on long-term hemodialysis, and organ transplant recipients.⁸¹

Clinical Course

The clinical course of hepatitis B is extremely variable: infection ranges from the completely asymptomatic to the rapidly fatal. The incubation period averages 75 days but can last from 40 to 180 days. Exposure to HBV has five potential outcomes: (1) no infection occurs; (2) acute hepatitis develops, followed by clearance of infection; (3) acute fulminant infection develops, leading to hepatic necrosis and death; (4) acute hepatitis develops without clearance of infection, and a chronic carrier state ensues; and (5) no acute illness develops, but a chronic carrier state ensues.

Approximately 55% of adults infected with HBV have no symptoms despite serologic documentation of infection (see below), which explains why blood donors who seem to be in good health are capable of transmitting the virus. Other individuals infected with HBV may have such mild symptoms (e.g., slight malaise, fatigability, and loss of appetite) that they do not seek medical attention.

Approximately 45% of people infected with HBV experience typical acute, icteric hepatitis, which is characterized by fatigue, anorexia, nausea, vomiting, and hepatomegaly. In approximately 1% of adults infected with HBV, acute fulminant hepatitis develops. This condition is characterized by progressive hepatocellular destruction, encephalopathy, and deepening coma. Fulminant hepatitis causes death in approximately 80% of affected adults and 30% of affected children.

In approximately 5% to 10% of hepatitis B cases, the infection becomes chronic. Patients with chronic hepatitis may be asymptomatic or may have clinical and histologic evidence of the disease, as well as persistently elevated levels of serum aminotransferases [see Figure 4]. With time, many patients pass to an asymptomatic carrier state, and serum aminotransferase levels fall. The duration of the asymptomatic carrier state appears to be indefinite. Chronic HBV infection can result in hepatocellular carcinoma, which is especially common in China, Southeast Asia, and sub-Saharan Africa.

Because most patients remain asymptomatic until the development of end-stage liver disease, there are no specific clinical

findings that are indicative of chronic HBV infection. There are, however, several clinical syndromes linked to HBV infection that may provide a clue to the presence of chronic HBV infection. These syndromes include polyarteritis nodosa, membranous or membranoproliferative glomerulonephritis, leukocytoclastic vasculitis, erythema nodosum, arthritis, and serum sickness.

Antigens

HBV has a diameter of 42 nm and contains circular, double-stranded DNA. The protein coat on its outer surface is termed hepatitis B surface antigen. HBsAg is made in quantities greatly exceeding the amount required to coat the nucleic acid. The excess surface antigen appears in the serum as spheres 22 nm in diameter or tubules of the same diameter and of varying length. These spheres and tubules contain no nucleic acid and hence are not infectious. They may persist in the serum for prolonged periods, even for life, and in great quantities, up to 10^{12} to 10^{14} surface antigen particles (500 μ g protein) per milliliter.⁸²

The hepatitis B virus also has a nucleocapsid core, the outside of which contains the hepatitis B core antigen (HBcAg). HBcAg is not detected in hepatitis B during acute infection, because its antigenic determinants are hidden by the outer surface antigen of the intact virion.

Inside the hepatitis B nucleocapsid is a DNA-dependent DNA polymerase and the hepatitis B e antigen, which is thought to be either an internal component or a degradation product of the core antigen. HBeAg is found only in the serum of individuals whose serum also contains HBsAg, and it appears in the serum of virtually all patients early in the course of HBV infection. The presence of HBeAg in serum is indicative of the presence of large numbers of circulating intact virions: serum containing HBeAg is estimated to be one million times more infectious than serum containing HBsAg but not HBeAg.

Serology

HBsAg can be detected in the serum within a few weeks of viral exposure [see Figure 5]. It usually persists throughout the symptomatic period and does not disappear until after recovery. Anti-HBs appears shortly after the disappearance of HBsAg [see Table 6]. During this window period, neither HBsAg nor anti-HBs is detectable [see Table 7]. Anti-HBs persists for years and is associated with immunity to reinfection. HBV can be differentiated into eight serotypes on the basis of determinants of the surface antigen.

Hepatitis B core antigen (HBcAg) is not found free in the serum, but antibody to HBcAg (anti-HBc) becomes detectable at an early stage in the course of acute infections, 1 to 2 weeks after the appearance of HBsAg. Titers of anti-HBc fall after the disappearance of HBsAg but persist for life. In patients with chronic hepatitis B, HBsAg remains detectable indefinitely, and titers of anti-HBc remain high. Years after infection, titers of anti-HBs may have fallen to undetectable levels, and anti-HBc may be the only marker of previous infection. HBeAg is detectable immediately after the appearance of HBsAg. Antibody to HBeAg (anti-HBe) appears just after HBeAg becomes undetectable (usually before the disappearance of HBsAg) and persists for 1 to 2 years [see Figure 5].

HEPATITIS D

HDV is a defective, 35 to 37 nm RNA virus that can infect only persons who are also infected with HBV, because it uses HBsAg for its structural protein shell. HDV is found worldwide and is especially prevalent in the Amazon basin, central Africa, southern Italy, and the Middle East.⁸³ HDV infection is less common in the United States and Western Europe, where it is generally associat-

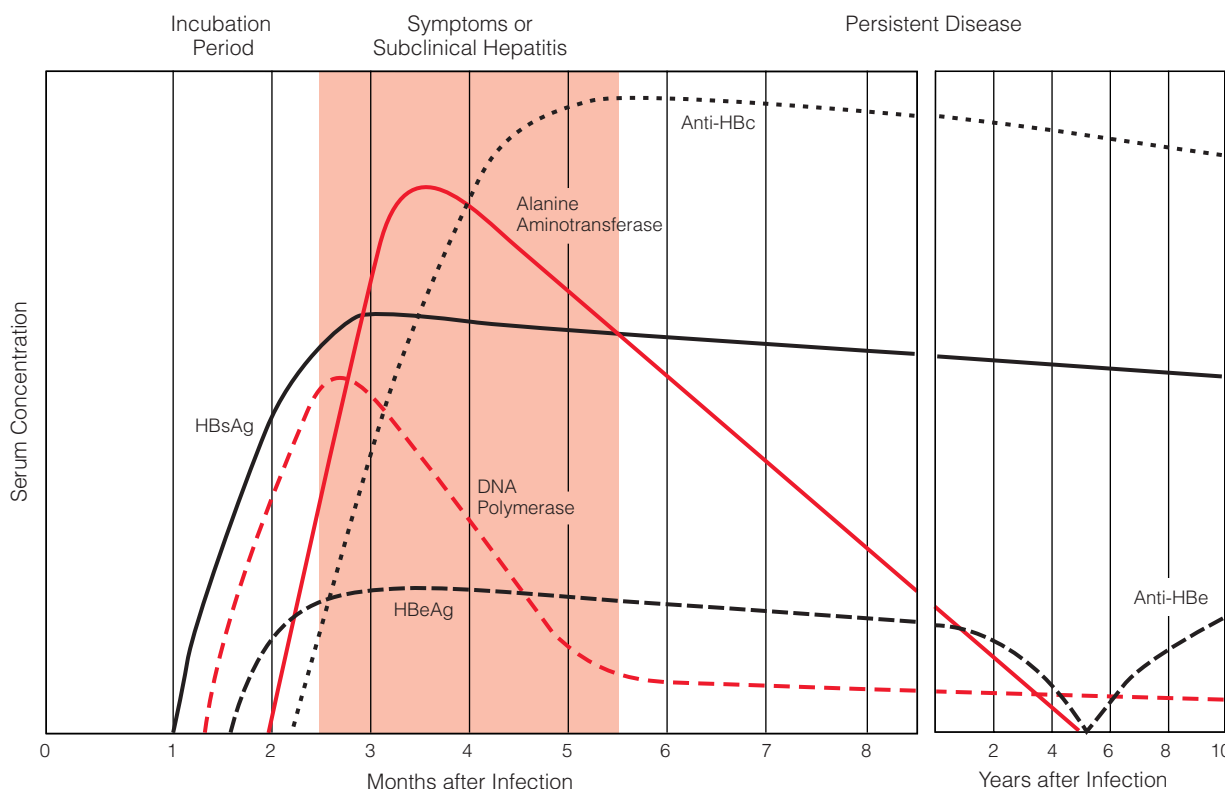


Figure 4 Schematic shows virologic, clinical, and serologic events of a hepatitis B infection that becomes persistent.

ed with parenteral blood exposure, typically in the setting of I.V. drug abuse or multiple transfusions.

Clinically, hepatitis D is found only in association with acute or chronic hepatitis B, and it cannot last longer than hepatitis B does. Depending on the state of the HBV infection, HDV infection appears either as a coinfection or a superinfection. Coinfection occurs when acute HDV infection and acute HBV infection are present simultaneously; superinfection occurs when acute HDV infection is superimposed on chronic HBV infection. Coinfection with HDV is associated with fulminant hepatitis and a mortality of 2% to 20%.⁸⁴ Fewer than 5% of cases of coinfection progress to chronic hepatitis D. In contrast, superinfection with HDV results in chronic HDV hepatitis, often with cirrhosis, in more than 70% of cases. The clinical and biochemical features of HDV infection resemble those of HBV infection alone. Chronic active hepatitis B progresses faster when hepatitis D is also present. Chronic HDV infection is more likely to result in severe morbidity and mortality than chronic HBV or HCV infection alone.

Diagnosis of acute HDV infection may be difficult: HDVAg appears in the circulation only briefly and often goes undetected. Antibody to HDV (anti-HDV) of the IgM class subsequently appears in serum in low titers. Because no anti-HDV IgG response occurs, no serologic marker of previous HDV infection may remain after recovery. Chronic HDV infection is easier to diagnose: high titers of anti-HDV in the serum indicate ongoing HDV infection, and HDV antigen is detectable in the liver by means of immunohistochemical techniques. Moreover, IgM anti-HDV remains detectable in serum.⁸³

NON-A, NON-B HEPATITIS: HEPATITIS E AND HEPATITIS C

Non-A, non-B hepatitis is divided into two varieties, an epidemic form (hepatitis E) and a parenterally transmitted form (hepatitis C).⁸⁵ Hepatitis E is an acute, self-limited disease whose

clinical features are similar to those of other types of hepatitis. Hepatitis E virus (HEV) is prevalent in the developing world, where it is spread by the fecal-oral route and has been associated with large outbreaks as well as sporadic cases. Outbreaks have been linked to contaminated water supplies. No cases of HEV infection acquired in the United States have been reported to date, but HEV acquisition has been reported in international travelers.

Hepatitis C is the most common cause of nonalcoholic liver disease in the United States. HCV is an RNA virus of the flavivirus family. It can be transmitted through parenteral exposure (usually in the setting of I.V. drug abuse), sexual contact, or the sharing of a household with an HCV-infected person; however, some persons with HCV infection have none of these risk factors, and there may be other means of transmission that have yet to be elucidated. Before the advent of antibody testing, HCV infection accounted for the majority (75% to 95%) of cases of posttransfusion hepatitis.⁸³ Since the spring of 1990, when a serologic test for HCV became available, all transfused blood has been screened for HCV, and the incidence of transfusion-associated hepatitis C has fallen precipitously. At present, however, I.V. drug use still accounts for a large proportion (60%) of HCV transmission in the United States.⁵⁹

The presence of anti-HCV IgG appears not to be protective: blood donors with anti-HCV antibody can transmit hepatitis.⁶² Surveys of HCV seropositivity indicate that 0.2% to 0.6% of volunteer blood donors carry anti-HCV IgG,⁸³ and the prevalence may be much higher among high-risk populations (e.g., residents of large inner-city communities). The prevalence of anti-HCV IgG is high among I.V. drug users, hemodialysis patients, and hemophiliacs.

Clinical Manifestations

The incubation period of hepatitis C averages 7 to 8 weeks in length but may be as short as 2 weeks or as long as 15. The clinical

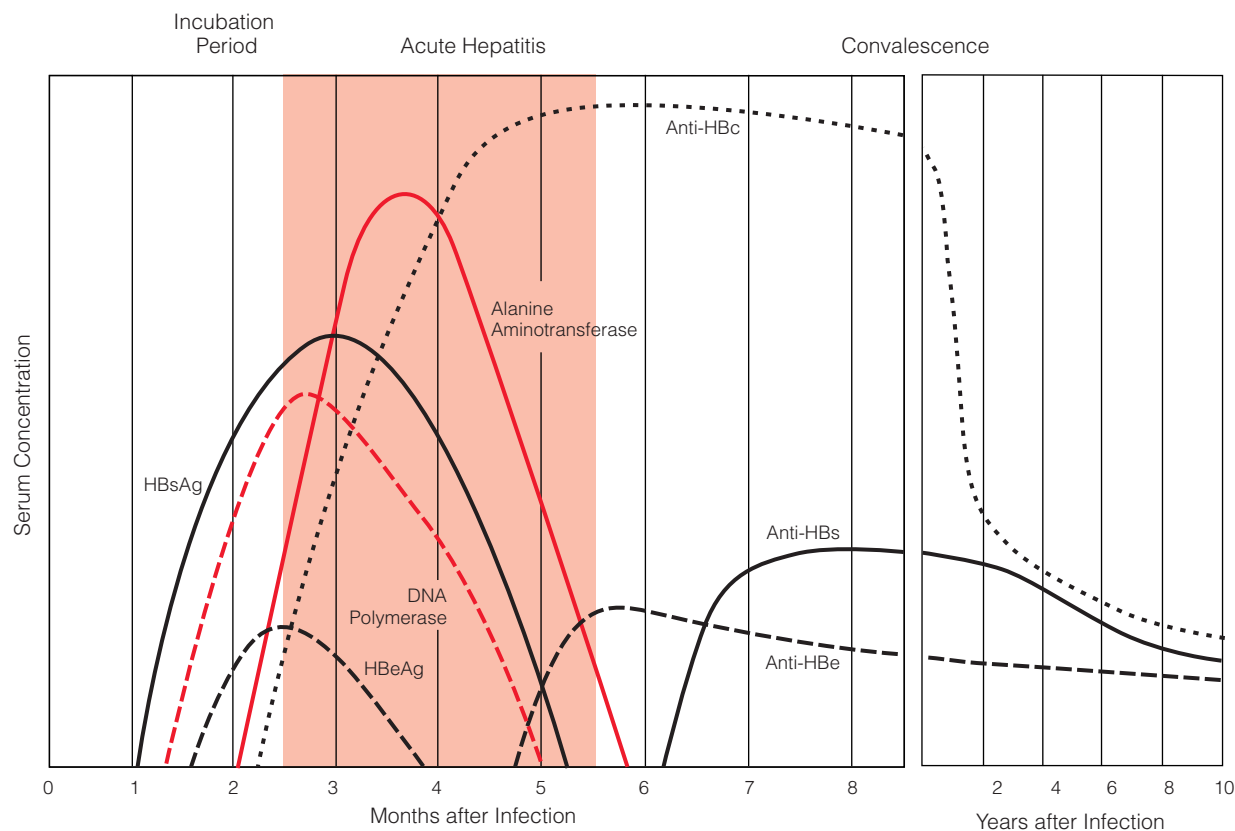


Figure 5 Schematic shows virologic, clinical, and serologic events during acute hepatitis B infection.

cal manifestations and biochemical alterations associated with acute hepatitis C are similar to but milder than those associated with hepatitis B. Serum aminotransferase levels can fluctuate widely; the peak levels are lower than those seen in hepatitis B (10 to 20 times normal as opposed to 20 to 50 times normal). Only about 25% of cases of acute HCV infection are icteric, and the mortality for acute infection is about 1%. Most patients have no acute illness suggestive of HCV infection. Antibody is not always present early in infection, and there are no clinically available assays for detecting IgM antibody to HCV. Thanks to improvements in the immunodetection of HCV, however, the interval before anti-HCV can be detected has decreased from the 6 to 12 months required with the first-generation tests to 8 to 12 weeks with the second-generation assays.⁸³

The most striking feature of HCV infection is its tendency to become chronic in as many as 50% to 75% of cases. One study found that even among the 1% to 10% of individuals with HCV whose bloodstreams had been cleared of HCV according to RT-PCR assay, as many as 90% still had HCV in the liver.⁸⁶ It is estimated that in the United States, nearly four million people are seropositive for HCV, and more than 30% of liver transplantations are performed to treat end-stage liver disease related to chronic HCV infection. The presence of anti-HCV IgG does not distinguish acute from chronic hepatitis. Within 10 years, cirrhosis may develop in as many as 20% to 25% of patients with active hepatitis⁸⁷; accordingly, these patients must be followed up carefully.

Chronic active hepatitis is characterized by elevated serum aminotransferase levels; however, other test results remain normal, and the patient is usually asymptomatic until end-stage liver disease develops. Liver biopsy shows inflammation around the portal triads. Recombinant interferons have been used to treat

chronic HCV infection, with mixed results: frequently, there is little response to treatment, or viremia returns after treatment. The combination of interferon with ribavirin has shown promise, however. Interferon treatment is generally reserved for patients who have chronic HCV infection and show evidence of active necroinflammatory liver disease with persistent ALT elevations.

HEPATITIS IN HOSPITAL PERSONNEL

Patients with hepatitis can infect hospital personnel with the

Table 6 Serologic Markers of Hepatitis B Infection

HBsAg	Present in acute and chronic infection Indicator that person is infectious
Anti-HBs	Appears 2 to 16 wk after HBsAg disappears from the serum Persists for years Confers immunity
HBeAg	Not present in the serum Found in the hepatocyte
Anti-HBc	Appears in serum with or shortly after HBsAg Persists for years May be only indicator of hepatitis B infection
HBeAg	Appears in the early acute phase Indicates serum is highly infectious Persistence beyond 10 wk suggests progression to chronic carrier state
Anti-HBe	Good prognosis for resolution of infection

virus via needle-stick injuries and other forms of accidental exposure. Conversely, physicians who are chronic carriers of HBV or HCV can infect their patients. According to a nationwide seroepidemiologic survey reported in 1978, approximately 19% of physicians have anti-HBs, compared with 3.5% of healthy volunteer blood donors [see Table 8].⁸⁸ Anti-HBs was found in 28% of surgeons, the highest prevalence in any medical specialty. For physicians, the likelihood of being positive for anti-HBs correlates with age and the number of years in practice. The risk of hepatitis is greatest among medical staff members in renal dialysis units, oncology units, and the clinical laboratory. Since 1978, when these data were reported, HBV vaccination has made it impossible to perform similar, more recent studies, because vaccination rather than previous infection would be responsible for the presence of antibodies.

Physicians and other staff members who care for hemodialysis patients with end-stage renal disease are at greater risk for acquiring HBV because of the high prevalence of hepatitis in such patients [see Table 9].^{89,90} Transmission of HBV decreases in dialysis centers when close attention is paid to hygienic technique. Isolation of patients who are carriers of HBsAg also reduces the incidence of HBV in hemodialysis patients and staff.⁹¹

From 0.28% to 9.3% of health care workers have antibody to HCV.⁹²⁻⁹⁴ In one study from Connecticut, five (12.5%) of 40 surgeons had antibody to HCV.⁹² In another study, from New York City, eight (1.75%) of 456 dentists had anti-HCV antibody.⁹³ The highest prevalence among dentists was found to occur in oral surgeons (9.3%). As use of vaccines for HBV becomes more widespread [see Management of Viral Exposure, Hepatitis B, *above*], HCV may come to predominate over HBV as the cause of the rare cases of hepatitis transmitted from hospital personnel to patients.

EPIDEMIOLOGY OF POSTTRANSFUSION HEPATITIS

Both HBV and HCV can be transmitted by percutaneous and other routes.⁸⁹ Rare cases of hepatitis have been attributed to the infusion of immune globulin, although its preparation by ethanol fractionization normally destroys hepatitis virus (as well as HIV). Albumin is pasteurized by heating at 60° C for 10 hours, which destroys hepatitis virus.

Because of the current criteria for acceptable blood donors, elimination of payment for blood donation, and serologic testing for HBV and HCV, the risk of contracting hepatitis B from a blood transfusion is now much lower than it once was. In the United States, it is now rare for either HBV or HCV to be transmitted via blood transfusion. According to the latest estimates available, the risk of HCV transmission via this route is approximately 1/103,000 (95% CI, 28,000 to 288,000), and that of HBV transmission is 1/63,000 (95% CI, 31,000 to 147,000).⁹⁵

HDV can also be passed by transfusion. In a study of 262 patients who had posttransfusion hepatitis and whose serum was positive for HBsAg, anti-HD was found in nine patients.⁹⁶ HDV can be detected in 24% of HBsAg-positive drug abusers and in approximately 50% of HBsAg-positive hemophiliacs.

LONG-TERM EFFECTS OF CHRONIC HEPATITIS

Chronic hepatitis can lead to problems requiring surgical intervention. It can cause cirrhosis, which in turn can cause portal hypertension and bleeding varices that necessitate portal systemic shunting. In addition, HBV and HCV predispose to hepatocellular carcinoma, the most prevalent visceral cancer in the world. The condition is especially prevalent in China, Southeast Asia, and sub-Saharan Africa. It is estimated that 25% of chronically infected persons die of cirrhosis or hepatocellular carcinoma.⁹⁷ HBV coinfection

Table 7 Serologic Patterns of Hepatitis B Infection

HBsAg	Anti-HBs	Anti-HBe	Interpretation
+	–	–	Early acute hepatitis B
+	–	+	Late acute hepatitis B
–	–	+	Window period between disappearance of HBsAg and appearance of anti-HBs <i>or</i> Chronic carrier with low HBsAg level <i>or</i> Infection in the remote past
–	+	+	Past hepatitis B infection
–	+	–	Infection in the remote past <i>or</i> Immunization with hepatitis B vaccine <i>or</i> HBIG received within the past 1 to 2 mo

+ = detectable – = not detectable

tion appears to increase the risk of hepatocellular carcinoma in HCV-infected persons. A widespread program of vaccination against HBV could greatly decrease the incidence of hepatocellular carcinoma. Epidemiology, molecular biology, and comparative pathology provide strong circumstantial evidence that hepatitis B is a significant factor in the etiology of hepatocellular carcinoma. The risk of primary hepatocellular carcinoma is more than 250 times greater in carriers of HBV than in noncarriers. HBV markers can be found in 80% to 90% of patients with hepatocellular carcinoma. Perhaps the best epidemiologic data indicating that hepatitis B precedes hepatocellular carcinoma were obtained in Taiwan from male civil servants between 40 and 60 years of age.⁹⁸ Approximately 3,500 HBsAg carriers were matched by age and place of birth (either mainland China or Taiwan) to 3,000 HBsAg-negative men, who served as control subjects. An additional group of 16,000 HBsAg-negative men between 40 and 60 years of age served as unmatched control subjects. After subjects were followed for 2 to 4 years, 50 cases of hepatocellular carcinoma were found, all but one of which occurred in chronic HBsAg carriers.

HCV is also associated with chronic infection in a high percentage (approximately 50%) of cases. In many countries, chronic HBV infection remains the leading factor in the development of hepatocellular carcinoma, whereas in Japan, Korea, and southern Europe, 50% to 75% of cases of hepatocellular carcinoma are

Table 8 Frequency of Antibody to Hepatitis B Surface Antigen (Anti-HBs) by Physician Specialty⁸⁸

Specialty	Number of Patients Tested	Positive Results (%)
Surgery	176	50 (28)
Pathology	37	10 (27)
Pediatrics	63	13 (21)
Internal medicine	259	46 (18)
Anesthesiology	59	10 (17)
Obstetrics-gynecology	63	10 (16)
Family practice	341	54 (16)
Nonpatient care	25	1 (4)
All others combined	169	26 (15)
Total	1,192	220 (18.5)

Table 9 Prevalence of Hepatitis B Virus (HBV) Serologic Markers in Various Populations⁹⁰

Population		Prevalence of Serologic Markers of HBV Infection (%)	
		HBsAg	All Markers
High risk	Immigrants or refugees from areas where HBV is highly endemic	13	70–85
	Clients in institutions for the mentally retarded	10–20	35–80
	Users of illicit parenteral drugs	7	60–80
	Homosexually active men	6	35–80
	Household contacts of HBV carriers	3–6	30–60
	Hemodialysis patients	3–10	20–80
Intermediate risk	Health care workers with frequent blood contact	1–2	15–30
	Prisoners (male)	1–8	10–80
	Staffs of institutions for the mentally retarded	1	10–25
Low risk	Health care workers with no or infrequent blood contact	0.3	3–10
	Healthy adults (first-time volunteer blood donors)	0.3	3–5

associated with chronic HCV infection.⁹⁹ In Japan, mortality from hepatocellular carcinoma increased approximately twofold in the 1980s, a change that may be attributable to a higher incidence of HCV-associated liver cancer.¹⁰⁰

Herpesviruses

CYTOMEGALOVIRUS

CMV is a member of the B herpesvirus family and is the largest virus known to infect humans. In some U.S. cities, the seroprevalence of CMV is 60% to 70%. Like other members of the herpesvirus family, CMV is capable of remaining within its host in a latent state, probably by down-regulating cell surface markers (e.g., HLA-1) and thus avoiding immune destruction. Latent CMV has been found in circulating mononuclear cells, polymorphonuclear cells, vascular endothelium, renal epithelial tissue, and pulmonary secretions. The virus may become reactivated in the setting of immunodeficiency, such as may arise with HIV infection, transplantation, or significant stress from operations or injuries. In non-immunocompromised patients, CMV typically causes a self-limited mononucleosis-like syndrome characterized by fever and mild hepatic transaminase abnormalities. In immunocompromised patients, however, CMV infection can be much more severe and even potentially life threatening, causing myelosuppression, pneumonitis, colitis, and retinopathy.

Posttransfusion Cytomegalovirus Infection (Posttransfusion or Postperfusion Syndrome)

The transmission of CMV by extracorporeal perfusion is responsible for the occasional development of a syndrome similar to mononucleosis in patients who have undergone open-heart operation. The syndrome characteristically appears 3 to 5 weeks after operation; its features are splenomegaly, fever, atypical lymphocytosis, and, occasionally, hepatomegaly, erythematous rash, and eosinophilia.⁸⁹ CMV can be isolated from the blood of virtually all patients with the typi-

cal posttransfusion syndrome and from the urine of half of these patients.⁸⁹ The condition is nonfatal and self-limited, but it may result in prolonged hospitalization and a long, expensive search for the source of fever. Although uncommon in adults 30 years of age and older, the syndrome can occur in as many as 10% of susceptible children and adults younger than 30 years.

This syndrome can also occur in patients who receive transfusions but who do not undergo open-heart operation. Occasional cases that develop postoperatively in patients who did not receive transfusions are thought to be the result of reactivation of latent infection. EBV can sometimes cause the syndrome.

The incidence of posttransfusion CMV infection is related to the kind of blood or blood product transfused. CMV is highly cell associated and is transmitted with leukocytes, which may be present in transfusions of packed red blood cells, platelets, or white blood cells; transmission from transfusion of fresh frozen plasma or cryoprecipitate has not been documented.¹⁴ Therefore, efforts to decrease the number of white blood cells in the transfused blood would be expected to decrease the rate of transfusion-associated CMV infection. Approximately 50% of patients who receive whole blood seroconvert to CMV, whereas only 10% of those who receive washed packed red blood cells seroconvert. The risk of seroconversion to CMV is between 12% and 100% when whole blood, either fresh or stored, is transfused.¹⁰¹ In one study, transfusion of frozen deglycerolized red blood cells resulted in seroconversion in only 3% of patients,⁸⁹ whereas in another, seroconversion occurred in 58% of 36 leukemic patients transfused with lymphocytes.¹⁰²

The risk of posttransfusion CMV infection is also related to the volume of blood received. In one study, 7% of patients receiving a single unit of whole blood seroconverted, whereas anti-CMV antibody titers rose in 21% of patients receiving more than one unit.¹⁰³ The risk of infection per unit of blood transfused is estimated to range between 2.7% and 12%.¹⁰⁴

Preexisting antibody to CMV does not protect transfusion recipients against reinfection. After transfusion of whole blood, titers of antibody to CMV will increase in 10% of recipients (an

indication of reinfection) and in 19% of patients who did not have antibody to CMV before transfusion (an indication of infection). Whereas a seronegative recipient of CMV-positive blood has a 21% chance of seroconversion, the risk of seroconversion from the receipt of one unit of CMV-negative blood is only 2%.⁸⁹ However, the sensitivity of the serologic test for CMV is such that even when blood that tests seronegative is used, there is still a residual 0% to 6% risk of CMV transmission.¹⁰⁵

Because so many patients receive blood transfusions during operation, it is understandable that evidence of posttransfusion CMV infection has been found in many patients postoperatively (e.g., after gynecologic surgery, cholecystectomy, appendectomy, lumbosacral fusion, splenectomy, and transplantation). It has also been found in surgical patients who are victims of trauma or burns.

However, it is surprising that infection with CMV, a ubiquitous virus, does not occur more frequently after transfusion. Between 30% and 54% of the adult population in the United States have antibody to CMV, an indication of previous infection.⁸⁹ Because infection with the virus is probably lifelong, a significant proportion of blood donors harbor the virus. The prevalence of antibody to CMV is 25% in units of blood from donors between 18 and 23 years of age and increases to 89% in blood from donors older than 60 years. The overall prevalence of seropositive blood donors is between 30% and 70%.

Cytomegalovirus in Transplant Recipients

CMV infection occurs not only in patients who have received blood transfusions but also in those who have suffered trauma, those receiving immunosuppressive therapy, and those with neoplastic disease. The groups at highest risk for CMV infection are probably recipients of organ transplants and of bone marrow transplants.¹⁰⁶⁻¹⁰⁸ Numerous studies have documented the high incidence of CMV infection after organ transplantation: the rates range from 26% to 100%.^{89,109,110} Primary CMV infection occurs in patients who do not have antibody to CMV before receiving transplants. Infections are considered to be reactivated if they occur in patients who did have antibody to CMV before receiving transplants. Rates of infection in patients receiving cardiac or bone marrow transplants are similar to those in patients receiving kidney transplants.

The high incidence of CMV infections after transplantation was recognized in the early days of such procedures. At autopsy of patients who died after renal transplantation, the intranuclear inclusions typical of CMV were found in tissue from the lungs, the parotid glands, the lymph nodes, the liver, the pancreas, the parathyroid, and the brain. CMV has been cultured repeatedly from the urine of transplant recipients, and the frequency of seroconversion among them has been high.

Likely sources of the virus are blood, because fresh blood can transmit CMV, and the organ transplant itself, because CMV can grow in renal tubular epithelial cells and can be transmitted as a latent virus. In several studies, recipients of kidney transplants had a much higher incidence of CMV infection when the donors had antibody to CMV than when the donors did not. In one study, 57% of recipients of kidneys from seropositive donors acquired CMV infection after transplantation, compared with 8% of recipients of kidneys from seronegative donors.¹¹¹ Even patients who have antibody to CMV can acquire new CMV infections as a result of transfusion or transplantation because there is more than one antigenic variety of the virus. Also, CMV that is latent in many patients who have antibody before transplantation may be reactivated after transplantation by host versus graft reactions, corticosteroids, or other immunosuppressive drugs. Hospital personnel, family members, and the environment play very small roles in transmission of CMV to transplant recipients.

Several systematic studies have demonstrated that CMV causes clinical illness in renal transplant recipients. In four studies, clinical illness developed in 83% of 76 patients with primary infection, compared with 44% of 268 patients with reactivation of a previous infection.^{89,109,110}

Recipients of renal transplants in whom CMV causes clinical illness most commonly present with fever. Fever occurs in 95% of patients with CMV infection and may be prolonged. Patients with CMV infection also frequently present with anorexia, arthralgias, and leukopenia. Other clinical features of the disease are diffuse pulmonary infiltrates, pancreatitis, transplant malfunction, and systemic bacterial and fungal superinfections. Invasion of the GI tract by CMV may cause gastritis and ulcers in both the duodenum and the colon, which in turn may lead to hemorrhage and perforation. Biopsies demonstrate CMV inclusions at the base of the ulcers. The virus appears to invade the vascular endothelium, and bleeding is possibly a result of vascular occlusion and ischemic necrosis of the overlying tissue.

Lethal CMV disease is characterized by the presence of most of the features listed above. Liver dysfunction is found in 100% of patients with lethal disease but in only 50% to 75% of patients with mild or moderate infection, and CMV viremia occurs in 46% to 48% of patients with severe CMV infection but in only 26% to 28% of patients with mild to moderate infection. Leukopenia and the presence of atypical leukocytes also correlate with the severity of the disease. CMV infection after renal transplantation is also associated with pneumonia, hepatitis, encephalitis, and retinitis.

Whether or not CMV infection causes or leads to graft rejection is uncertain. Both the highest incidence of CMV infection (> 80%)^{89,109,110} and the highest incidence of graft rejection occur within the first 3 months after transplantation. In several studies, young patients and recipients of second kidney transplants were at higher risk for graft loss if they had CMV than if they did not.^{89,109,110} In most studies, however, it is extremely difficult to demonstrate a relation between CMV infection and graft rejection.

Of the multiple factors affecting the risk of CMV infection in transplant recipients, the most important are (1) the familial relation and HLA matching between the kidney donor and the recipient and (2) the CMV serology of both the donor and the recipient. The presence of antibody in transplant recipients before transplantation seems to offer a small amount of protection against fever caused by CMV but does not protect against more serious consequences of the infection, such as leukopenia, graft failure, and death.

CMV infection is also a major problem in liver, heart, and bone marrow transplant recipients.^{106,108} In liver transplant recipients, CMV is a cause of hepatitis and liver dysfunction that can be confused with rejection or other causes of liver malfunction,¹⁰⁶ and it can lead to lethal infection. CMV pneumonitis in bone marrow transplant recipients is the most common life-threatening infectious complication after transplantation. The severity of infection in bone marrow transplant recipients may be attributable to the higher incidence of host versus graft disease in patients with CMV pneumonitis (82%) than in those without CMV pneumonitis (27%).¹¹²

Prevention and Treatment of Cytomegalovirus Infection

Several methods have been proposed to reduce the incidence of CMV infection after transfusion or transplantation. One method is to eliminate as many white blood cells as possible from transfused blood because CMV is almost certainly transmitted solely through these cells. From 90% to 100% of viable leukocytes in blood have been removed from frozen deglycerolized erythrocytes. In one study, transfusion of 24 hemodialyzed patients with leukocyte-free red blood cells from frozen deglycerolized blood prevented subsequent CMV infection.¹⁰⁴

Another approach is to transfuse blood only from CMV-negative donors. Because the majority of posttransfusion CMV infections are asymptomatic, however, the increased cost of performing serologic tests on all donated units might be difficult to justify.

Storage of blood to reduce infectiousness of CMV is another approach, but storage from 48 to 72 hours does not significantly reduce transmission of CMV infection. Irradiating the blood to render the CMV noninfectious is unacceptable because it causes cell transformation *in vitro*. Furthermore, in one study, administration of leukocytes previously exposed to 1,500 cGy (1,500 rads) of gamma radiation resulted in an increased incidence of CMV infection among recipients of these cells.¹⁰²

Because the incidence of CMV infection is higher in patients who receive kidney transplants from seropositive donors, some centers do not transplant kidneys from seropositive donors into seronegative recipients. However, no published reports indicate that this practice leads to a significant alteration in the outcome of renal transplantation with respect to graft rejection. Moreover, excluding kidneys from seropositive donors makes it more difficult to find kidneys for seronegative recipients.

Many attempts have been made to develop a CMV vaccine for administration before viral exposure by multiple passages of the virus in tissue culture. Two such vaccines have been used in clinical trials, one prepared from the AD169 strain and the other from the Towne 125 strain of the virus. Immunization with these vaccines can elicit both serum antibody and cell-mediated immunity. In one trial, the vaccine prepared from the Towne 125 strain lowered the incidence of clinical disease but not of infection, and the disease tended to be less severe in vaccinated patients than in control subjects who received placebo.¹¹³

Human IG has been administered after transfusion or transplantation in attempts to prevent associated CMV infection. In one study, it reduced life-threatening infection to a less severe form in most patients, but in other studies, not surprisingly, it provided no consistent benefit.¹¹⁴⁻¹¹⁷ In patients who are already seropositive, the virus is latent inside their cells, where it is probably not accessible to serum antibody. Patients with primary infections may not benefit from antibody treatment, because herpesviruses seem to transfer from cell to cell without ever existing free in serum. Even CMV hyperimmune globulin has no clear benefit in patients with clinical CMV infection.¹¹⁸ It may, however, help control severe infections, such as those seen in bone marrow transplant recipients.

Several antiviral agents have been used in attempts to reduce the incidence or lessen the effect of CMV infection. Among these agents are interferon, transfer factor, immune globulin, and nucleoside derivatives, such as cytarabine, vidarabine, and acyclovir (see below). Immune globulins, acyclovir, and ganciclovir are effective at preventing CMV infection in transplant recipients.^{109,110,114,119,120} Ganciclovir and foscarnet are active against CMV *in vitro*. Ganciclovir is currently being used to treat CMV and is the most effective agent in organ transplant recipients (see below).^{109,110,119-121}

EPSTEIN-BARR VIRUS

EBV is the herpesvirus responsible for infectious mononucleosis. It can be found in B cells in peripheral blood of infected patients and in tumor cells of patients with Burkitt lymphoma and nasopharyngeal carcinoma. It remains in a latent form in an infected host for years, probably for life. Most posttransfusion EBV infections are asymptomatic. Seroconversion to EBV will develop in approximately 8% of recipients transfused with between two and 14 units of blood. In as many as 5% of patients with preexisting antibody to EBV, significant elevations of antibody titers may develop, beginning

2 weeks after transfusion. These elevations indicate either reinfection or reactivation of a latent infection.⁸⁹ Because EBV is associated with cells and does not exist free in serum to any great extent, antibody to EBV in either donors or recipients is unlikely to provide substantial protection against infection resulting from blood transfusions or organ transplants. Among transfused patients who do not have preexisting antibody to EBV, the prevalence of EBV infection can reach 33% to 46%. In these patients, the absence of preexisting antibody presumably rules out reactivation of latent EBV infection as the source of infection.

EBV occurs worldwide. In the United States, nearly all adults and as many as 65% of persons of all ages have antibody to EBV. Infection is thought to occur in infancy, and as many as 17% of infants have antibody to EBV. By 5 years of age, 72% of children have antibody to EBV, and the prevalence in adults is similar.¹²² Thus, the majority of blood donors in the United States have been previously infected with EBV and probably have latent virus in their leukocytes. Although it is clear that EBV can be transmitted by blood when the transfusion occurs within 3 days of donation, it is not known whether blood stored for longer periods can transmit the virus. Because EBV is predominantly intracellular, plasma and its derivatives do not transmit the virus.

The diagnosis of EBV infection is made serologically. Tests both for IgM antibody to capsid antigens and for IgG antibody to the early antigens of EBV or tests of serial samples for IgG antibody to capsid antigens must be used. The heterophil antibody test (the Paul-Bunnell test) and a rapid slide test that is equivalent (the monospot test) are also used in most clinical studies to screen for EBV infection before more specific diagnostic tests are performed.

In cases of posttransfusion infection, IgG antibody to EBV can be detected at least 10 days before the onset of symptoms, and EBV can be cultured from circulating lymphocytes 11 days before the onset of symptoms. In patients with acute infection, EBV is found in approximately three of every 10⁴ peripheral blood lymphocytes.¹²³ In contrast, all recovered persons with antibodies to EBV are thought to have the virus in one of every 10⁷ circulating lymphocytes.

EBV is strongly implicated in the etiology of a posttransplantation lymphoproliferative disorder (PTLD).^{89,124,125} EBV has been isolated from the tissues of most cases of PTLD, but not all.^{126,127} Non-EBV-related cases of PTLD typically occur later after transplantation, and their etiology has not been elucidated.

PTLD comprises three general clinical presentations: (1) a mononucleosis-like syndrome involving the tonsils and the peripheral lymph nodes, (2) a diffuse polymorphous B-cell infiltration in many visceral organs, and (3) localized extranodal tumors in the GI tract, the neck, the thorax, or other parts of the body. Patients whose disease is limited to a single organ or to lymph nodes often respond to a reduction in immunosuppression or antiviral therapy; however, once the infection becomes widespread, the disease progresses rapidly and is fatal in more than 75% of cases.¹²⁸ In solid organ transplant recipients, PTLD may be limited to the allograft. There is some evidence to suggest that PTLD may have organ-specific features that promote lymphoproliferation: allograft involvement has been reported in 17% of renal transplant recipients, 8.6% of liver transplant recipients, and as many as 60% to 80% of lung or intestinal transplant recipients.¹²⁸

The persons at highest risk for PTLD are EBV-seronegative persons receiving EBV-positive organs or bone marrow. Most infections occur within the first 4 months after transplantation.¹²⁹ Several specific risk factors for the development of PTLD have been identified: a seropositive graft in a seronegative recipient, certain types of organ allografts (with intestinal transplants carrying the highest risk), any type of immunosuppression that blunts cellular immuni-

ty to EBV (with risk increasing as immunosuppression becomes more pronounced), and the presence of other infections (CMV in particular).

The optimal treatment of lymphoproliferative disorders remains unclear. Some early EBV-associated lymphoproliferative disorders in solid organ transplant recipients have regressed completely after reduction of immunosuppression.^{130,131} Early PTLTD may respond to antiviral therapy with acyclovir or ganciclovir, which may prevent infection of resting B cells, but such therapy is less likely to be effective in the face of high concentrations of latently infected circulating or tissue-invasive B cells. Some investigators also report resolution of PTLTD after treatment with interferon alfa.^{132,133}

Transmission of EBV can occur simultaneously with transmission of CMV or hepatitis virus. Although hepatitis accompanies EBV infections in sporadic cases, EBV alone has not been documented as a cause of posttransfusion hepatitis.

HERPES SIMPLEX VIRUS

Infection or reactivation of infection with herpes simplex virus type 1 (HSV-1) follows renal transplantation in 50% to 75% of patients, most often within 30 days after transplantation. Reactivation of infection is more common than primary infection: only 14% of patients who are seronegative before transplantation become infected, but infection is reactivated in 64% of patients who were already seropositive before transplantation.

Most cases of HSV-1 infection after transplantation are clinically inapparent and are indicated only by a significant rise in titer of antibody to the virus. The most prevalent clinical manifestation is herpes labialis, that is, fever blisters affecting not only the lips but also the mucous membranes of the oral cavity and the skin of the head and neck. Although these lesions are painful and may make eating, drinking, and taking oral medications difficult, they are usually self-limited and heal without treatment or reduction of immunosuppression. However, HSV-1 infection can take a much more malignant course, disseminating to cause pneumonitis, fulminant hepatitis, upper GI hemorrhage, encephalitis, aseptic meningitis, and death.

VARICELLA-ZOSTER VIRUS

Varicella-zoster virus (VZV), another herpesvirus, is the etiologic agent of herpes zoster and chicken pox. This virus resides in the dorsal root ganglia of adults who had primary varicella infection in childhood. Herpes zoster is more common in organ transplant recipients, in patients with cancer (especially those who have leukemia or lymphomas), in burn patients, and in patients receiving immunosuppressive drugs. Serologic evidence of VZV infection occurs in 8% to 16% of renal transplant recipients. The lesions of herpes zoster become evident 12 to 511 days after organ transplantation.

In children or adults who have not already had chicken pox and occasionally even in children who have, VZV can cause disseminated chicken pox in many organs, which may be fatal.

AGENTS EFFECTIVE AGAINST HERPESVIRUSES

Because the essential synthetic activities of viruses depend on the metabolic machinery of their host, it has been difficult to devise specific antiviral agents that interfere with viral replication but are not harmful to host cells.^{134,135} Many antiviral agents are too toxic to be used clinically. In contrast, antibacterial agents that are both toxic to bacteria and safe for human cells are easier to design because the structure and metabolic machinery of bacteria are distinct from those of host cells.

Although intracellular processes unique to viral replication have

been identified and specifically targeted for chemotherapeutic attack, very few agents have been effective against human viruses. Among these is amantadine, which is used for both prophylaxis and treatment of influenza A. Agents that were found to be effective for prophylaxis against smallpox, such as methisazone, now have no use, because the disease has been eradicated.

There are few effective chemotherapeutic agents for hepatitis or most of the other major viral diseases that concern surgeons, but several agents have been used for the treatment of herpesvirus infections, especially in immunosuppressed patients [see Table 10]. These agents, derivatives of purines and pyrimidines, interfere with viral nucleic acid synthesis.

Acyclovir and Valacyclovir

Acyclovir (acycloguanosine) is a nucleoside derivative that is used to treat herpesvirus infections, especially herpes simplex and varicella-zoster infections in immunocompromised hosts. Valacyclovir is the L-valyl ester prodrug of acyclovir. In cases of mucocutaneous herpes simplex and herpes zoster, acyclovir can shorten the period of virus shedding, decrease pain, and promote more rapid scabbing and healing of lesions. Acyclovir is also the drug of choice for encephalitis caused by herpes simplex, but it is not effective in patients with established neurologic damage resulting from herpes simplex or varicella-zoster infections or in patients infected with CMV. Acyclovir inhibits the replication of EBV in actively replicating cells but does not affect latent or persistent infection.

The total daily dose of acyclovir is 10 to 25 mg/kg, given by I.V. infusion lasting 60 minutes. The recommended length of parenteral acyclovir therapy ranges from 5 to 10 days, depending on the indication. A major side effect of such therapy is phlebitis at the injection site; rash, leukopenia, and neurotoxicity may also occur. Acyclovir applied topically as a 5% ointment is effective in immunocompromised patients for the treatment of limited cutaneous herpes infections and in patients with normal immunity for the treatment of initial episodes (but not recurrent episodes) of genital herpes simplex infection. Oral acyclovir seems to be effective as prophylaxis against reactivated herpes simplex infection in recipients of bone marrow transplants and in patients immunosuppressed as a result of HIV infection.

Penciclovir and Famciclovir

Penciclovir is a nucleoside analogue that is similar to acyclovir with respect to spectrum of activity and potency against herpesviruses. Famciclovir is the diacetyl ester of penciclovir. Penciclovir requires thymidine kinase (TK) for phosphorylation and thus is inactive against thymidine kinase-deficient strains of HSV or VZV; however, it may be active against some TK-altered or polymerase mutants that are resistant to acyclovir as well as against some foscarnet-resistant HSV isolates. In experimental settings, topical, parenteral, and oral penciclovir and oral famciclovir have been effective against HSV infection.

Vidarabine

Vidarabine (ara-A) is effective against herpes simplex and varicella-zoster viruses as well as poxviruses, oncornaviruses, and rhabdoviruses. It is used mostly to combat herpesvirus infections in immunosuppressed patients. In these patients, vidarabine accelerates healing of cutaneous herpes zoster, decreases its rates of cutaneous dissemination and of visceral complications, and shortens the duration of postherpetic neuralgia. For systemic use, a daily dose of 10 to 15 mg/kg of vidarabine is administered I.V. over a period of 12 hours. The duration of therapy for herpes zoster is

Table 10 Antiviral Therapy of Clinical Benefit

Virus	Condition	Regimen
Herpes simplex virus	Keratitis	3% Acyclovir ointment <i>or</i> 1% Trifluridine solution <i>or</i> 3% Vidarabine ointment <i>or</i> 0.5% IDU ointment <i>or</i> 0.1% IDU drops
	Herpes labialis	Treatment usually not indicated; may use 1% penciclovir cream <i>or</i> topical acyclovir q. 2 hr while patient is awake for 4 days
	Genital herpes Primary	Acyclovir, 200 mg p.o. 5 times daily <i>or</i> 400 mg p.o., t.i.d., for 10 days, <i>or</i> Valacyclovir, 500 mg–1 g p.o., b.i.d., for 10–14 days, <i>or</i> Famciclovir, 250 mg p.o., t.i.d., for 10 days*
	Recurrent	Acyclovir, 200 mg p.o. 5 times daily <i>or</i> 400 mg p.o., t.i.d., for 5 days, <i>or</i> Valacyclovir, 500 mg p.o., b.i.d., for 5 days, <i>or</i> Famciclovir, 125 mg p.o., b.i.d., for 5 days
	Prophylaxis	Acyclovir, 400 mg p.o., b.i.d., <i>or</i> Valacyclovir, 500 mg–1 g p.o., q.d., <i>or</i> Famciclovir, 250 mg p.o., b.i.d.
	Encephalitis	Acyclovir, 10 mg/kg t.i.d. I.V. for 14–21 days
	Neonatal HSV	Acyclovir, 10 mg/kg I.V. q. 8 hr for 10–21 days (20 mg/kg I.V. q. 8 hr if neonate is premature)
Varicella-zoster virus	Immunocompromised host	Acyclovir, 5 mg/kg I.V. q. 8 hr for 7 days <i>or</i> 400 mg p.o. 5 times daily for 14–21 days, <i>or</i> Famciclovir, 500 mg p.o., b.i.d., for 7 days,* <i>or</i> Valacyclovir, 1 g p.o., t.i.d., for 7 days*
	Immunocompetent host Eye infections Shingles	3% Acyclovir ointment Acyclovir, 800 mg p.o. 5 times daily for 7–10 days, <i>or</i> Valacyclovir, 1 g p.o., t.i.d., for 7–10 days, <i>or</i> Famciclovir, 500 mg p.o., t.i.d., for 7–10 days
Cytomegalovirus	Immunocompromised host Retinitis	Ganciclovir, 5 mg/kg I.V. q. 12 hr for 14–21 days,† <i>or</i> Foscarnet, 90 mg/kg (adjusted for renal function) I.V. q. 12 hr for 14–21 days, <i>or</i> Cidofovir, 5 mg/kg I.V. weekly for 2 weeks, then every other week
	CMV pneumonia	Ganciclovir, 2.5 mg/kg I.V. q.d. for 20 days

* Not approved by the FDA for this indication.

† An intraocular insert is also available.

5 days. Side effects include anorexia, weight loss, nausea, vomiting, weakness, anemia, leukopenia, thrombocytopenia, tremors, and thrombophlebitis at the site of administration.

Idoxuridine

Idoxuridine (5-iodo-2'-deoxyuridine) (IUdR, IDU) was the first clinically effective antiviral nucleoside. It is a halogenated pyrimidine that resembles thymidine in structure. Topical application of either a 0.1% solution or a 0.5% ointment of idoxuridine is effective treatment of herpes simplex keratitis but not of recurrent herpes labialis or localized zoster. In the United States, IDU is approved only for topical treatment of HSV keratitis. When combined with dimethyl sulfoxide (DMSO), IDU is active against herpes zoster and recurrent or primary genital HSV infection. In Europe, IDU is available in combination with DMSO for the treatment of herpes labialis, herpes genitalis, and herpes zoster.

Ganciclovir

Ganciclovir (DHPG, 2'-NDG, or BIOLF-62) is an acyclic nucleoside structurally related to acyclovir but with greater activity against CMV in vitro and in vivo. It is effective in treating CMV disease in transplant recipients and AIDS patients. The usual total daily dose of ganciclovir is 7.5 to 10 mg/kg, given in two or three divided doses. The dosage should be adjusted if the patient has decreased renal function. Myelosuppression is the principal dose-limiting toxic side effect.

Foscarnet

Foscarnet (trisodium phosphonoformate) is a pyrophosphate derivative that inhibits herpesvirus DNA polymerases and retroviral reverse transcriptases.^{134–136} In the United States, it has been used for the prevention and treatment of CMV retinitis in patients with AIDS. For patients who have received renal or bone marrow transplants,

foscarnet is given in a bolus injection of 9 mg/kg followed by infusion of 0.015 to 0.090 mg/kg/min I.V. for 7 days. Foscarnet is also used to treat acyclovir-resistant HSV infection. The major toxicity associated with foscarnet is nephrotoxicity; CNS side effects (e.g., headache, tremor, irritability, and seizures) can also occur.

Viral Infections from Animal and Human Bites

Surgeons are frequently called on to treat patients who have been bitten by either an animal or another person. Such bites can transmit several viruses and other infections. Certainly, rabies is the most feared viral infection transmitted in this way. Viruses that are found in saliva, such as HBV, herpesviruses, and possibly HIV, can be transmitted by a human bite, although such cases are most likely rare.

From zero to five cases of human rabies occur each year in the United States. Animal rabies is widespread and is found in every state except Hawaii. In 1992, more than 8,600 cases of animal rabies were reported to the CDC by 49 states, the District of Columbia, and Puerto Rico. The great majority of cases occur in

wild animals.⁶⁹ Before 1950, more than 8,000 cases of rabies in dogs were reported each year in the United States; the number is now fewer than 150 a year.

Rabies proceeds from a prodrome of fever, malaise, and headache, to hyperactivity and diffuse cerebral dysfunction, and then to coma and death. From 5% to 20% of patients may also show progressive paralysis. Occasionally, there is no history of an animal bite. Diagnosis can be confirmed by culture of saliva, cerebrospinal fluid, or brain tissue; demonstration of rabies antigen in the cornea or skin; or measurement of serum antibody to rabies virus. At post-mortem examination, typical intracytoplasmic inclusions (Negri bodies) can be seen in the brain cells.

Although the number of cases of human rabies is small, the disease is an important problem because of the large number of animal bites that occur each year. Surgeons may have to consider rabies prophylaxis in patients whom they treat for bite injuries [see Management of Viral Exposure, Rabies, *above*, and 1:7 *Acute Wound Care*]. Also, two fatal cases of rabies have occurred in recipients of corneal transplants from a patient whose cause of death was later found to be rabies.¹³⁷

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Acknowledgments

Figure 1 Micrograph courtesy of F. K. Lee, A. J. Nahmias, and S. Stagno, Emory University. Drawing by George V. Kelvin.

Figures 4 and 5 Albert Miller.

22 NUTRITIONAL SUPPORT

Rolando H. Rolandelli, MD, FACS, and Brian K. Siegel, MD, FACS

Nutritional Management of Hospitalized Patients

Evaluation of the Need for Nutritional Support

INDICATIONS FOR NUTRITIONAL INTERVENTION

Nutritional support is required in patients with various disease processes who fall into one of the following general categories:

1. The patient has been without nutrition for 10 days. In a well-nourished person, body stores are generally adequate to provide nutrients during shorter periods of stress without compromising physiologic functions, altering resistance to infection, or impairing wound healing. The provision of nutrients becomes more important as body stores become eroded because of inadequate food intake and accelerated catabolism. In general, deficits occur in surgical patients after 7 to 10 days of partial starvation; nutritional intervention should be initiated before this time.
2. The duration of illness is anticipated to be more than 10 days. In patients whose illness is known to have a moderately prolonged course, nutritional support should be considered essential care. Thus, individuals with severe peritonitis or pancreatitis, major injury (injury severity score [ISS] > 15), or extensive burns (> 20% total body surface area [BSA]) are candidates for nutritional support because of the known duration of their illness. (The duration of illness in chronically malnourished patients also would be expected to exceed 10 days.)
3. The patient is malnourished (loss of > 10% of usual body weight over 3 months). Several nutritional assessment tools are available to screen patients for malnutrition, but in general, the degree of weight loss can be used as an index of nutritional deficiency. Recovery may be compromised in patients who do not have adequate body nutrient stores because of an existing nutritional deficit [see Figure 1]. The patient should receive nutritional support when the weight loss approaches or exceeds 15% of usual body weight:

$$\% \text{ Weight loss} = \frac{(\text{Usual weight} - \text{present weight})}{\text{Usual weight}} \times 100$$

Patients who do not meet one of these three general indications should be reassessed after 7 days to identify individuals

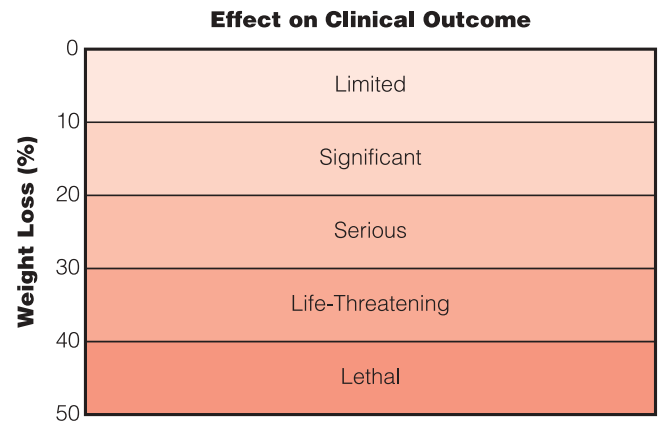
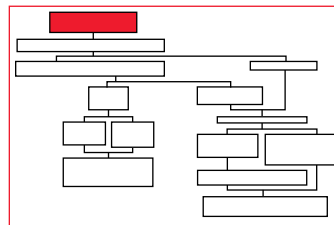


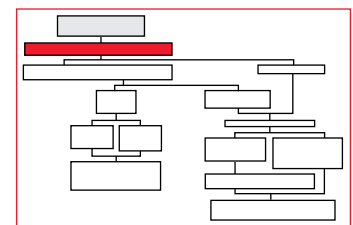
Figure 1 The magnitude of weight loss is a rough predictor of its effect on clinical outcome.

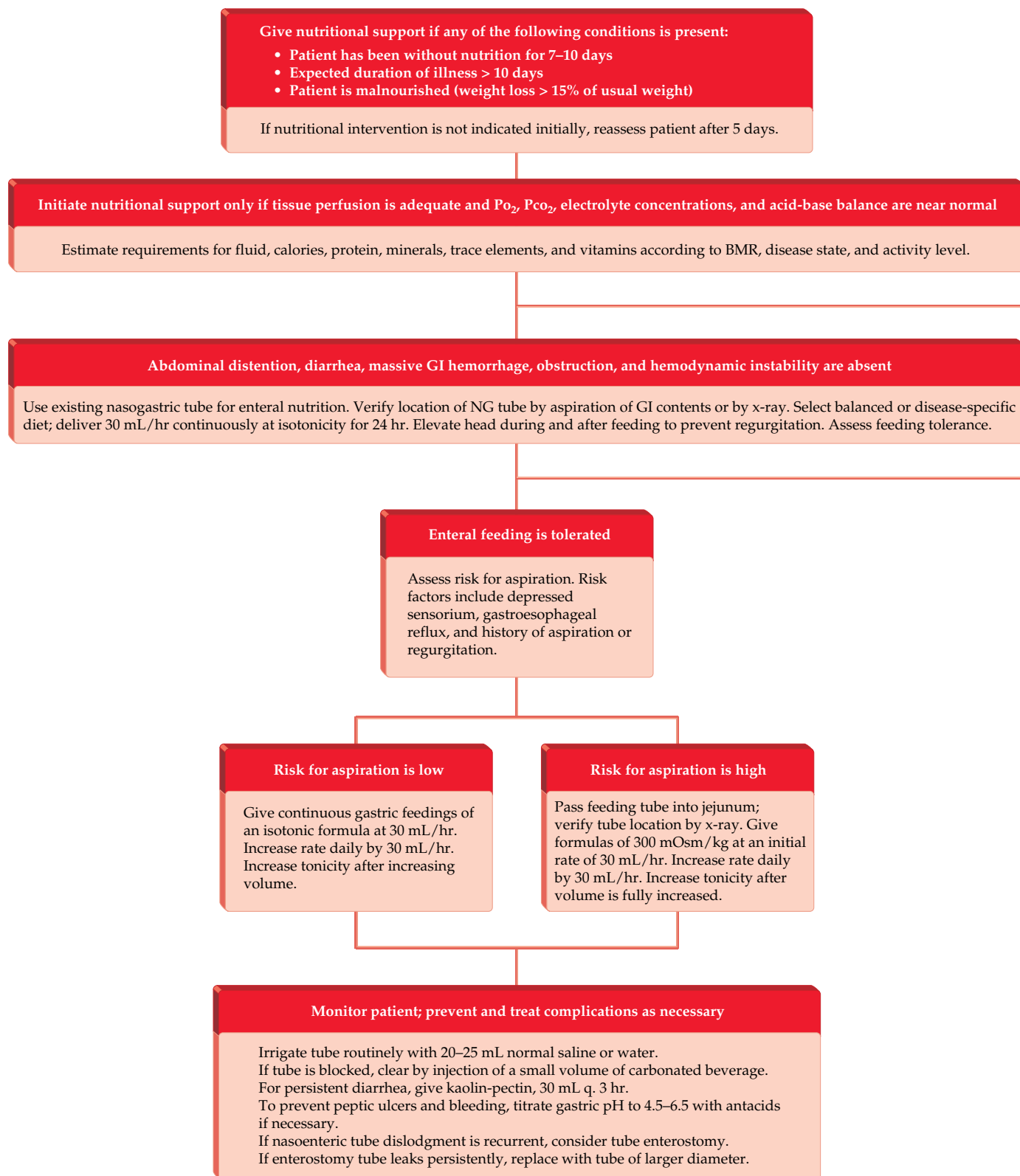
in whom complications develop after admission to the hospital and who require nutritional support. Serum proteins with a short half-life (e.g., prealbumin, transferrin, or retinol-binding protein) are useful markers for assessing the response to therapy.

PRIORITY OF CARDIOPULMONARY FUNCTION

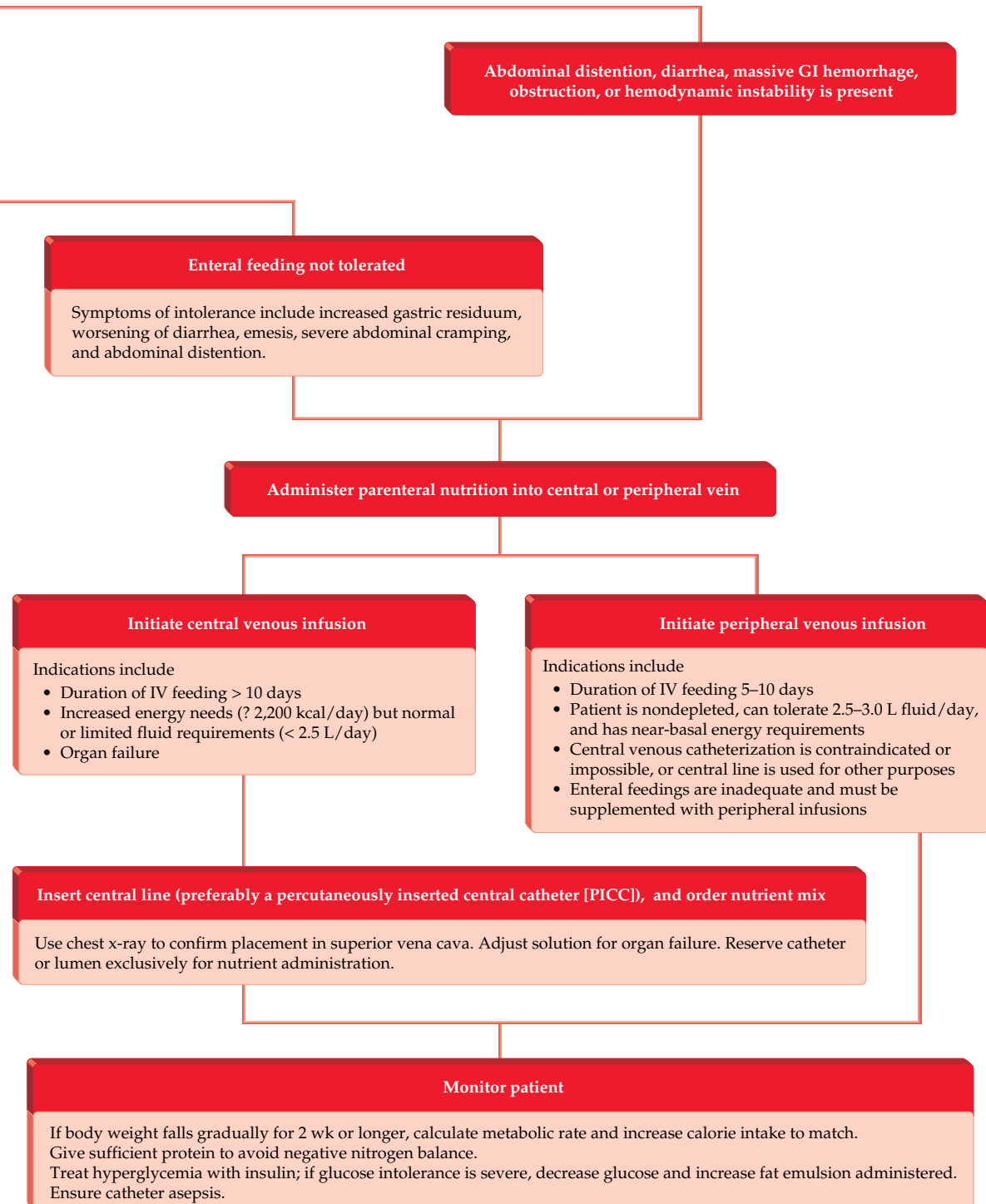
Intensive care unit (ICU) patients are frequently candidates for nutritional support but often have a number of complex medical and surgical problems

that may take precedence. In decreasing order of importance, the priorities are maintenance of airway, breathing, circulation, tissue oxygenation, acid-base neutrality, normal electrolyte concentrations, and adequate nutrition. The six functions that take priority over nutrition are usually impaired by acute and potentially life-threatening disorders that are often correctable over the short term. To optimize nutrient metabolism, circulation and tissue oxygenation must be adequate. In addition, hydrogen ion and electrolyte concentrations should be near normal in the extracellular fluid compartment, as reflected by blood or serum measurements.





Nutritional Management of Hospitalized Patients



If cardiopulmonary function is abnormal, nutrient administration may potentiate the abnormalities and create additional problems. For example, in a patient with respiratory insufficiency, infusion of moderate quantities of carbohydrate could increase carbon dioxide tension (PCO_2) and lower serum potassium concentration. These changes could initiate a life-threatening cardiac dysrhythmia. The need for nutritional support in the ICU patient should always be evaluated with respect to other care problems; acute disorders of cardiorespiratory function, disturbed acid-base status, and altered electrolyte concentrations should generally be corrected before nutritional support is initiated.

NUTRIENT REQUIREMENTS

The energy requirements of an individual are primarily related to body size, age, gender, and energy expenditure of activity (muscular work). In hospitalized patients who are generally inactive, the basal metabolic rate (BMR) accounts for the greatest amount of energy expenditure. The BMR in normal individuals is about 25 kcal/kg/day but can be calculated more precisely according to the Harris-Benedict formulas:

$$\text{Males: BMR (kcal/day)} = 66 + (13.7 \times \text{weight [kg]}) + (5 \times \text{height [cm]}) - (6.8 \times \text{age [yr]})$$

$$\text{Females: BMR (kcal/day)} = 665 + (9.6 \times \text{weight [kg]}) + (1.7 \times \text{height [cm]}) - (4.7 \times \text{age [yr]})$$

The BMR is influenced by the disease process. Hypermetabolism occurs in surgical patients with moderate to severe infection or injury. In these patients, the magnitude of the increase in the BMR depends on the extent of injury or infection. Patients generally fall into one of four categories according to their metabolic requirements [see Table 1].

Estimates that are based on normal basal metabolic requirements and adjusted only for the disease state of the patient reflect the energy needs of patients requiring mechanical ventilation or those at bed rest. However, further adjustments are necessary for patients who are out of bed and physically active: they should receive additional calories. To meet the energy needs of physically active patients, who are in a nonbasal state, calculated requirements should be increased an additional 15 to 20%. The metabolic response to stress and critical illness is complex and is mediated by interactions between the neuroendocrine system and circulating

cytokines. This interaction produces a metabolic milieu in which the body cannot utilize supranormal amounts of nutritional substrates (i.e., hyperalimentation). In fact, administering excessive nutrients with the purported goal of acutely correcting nutrient deficits is often harmful, leading to an abnormal accumulation of hepatic glycogen, enhancing total energy expenditure, and causing increased urea production and elevation of the blood urea nitrogen (BUN).

Weight gain usually should not be a priority for ICU patients. Complications of nutrient delivery are minimized and nutrient metabolism is generally optimized if the ICU patient receives only the energy necessary for weight maintenance throughout a complex and complicated clinical course. (This quantity of energy rarely exceeds 35 total calories/kg body weight/day in most general surgical patients who are admitted to the ICU for non-trauma-related care.) With resolution of the disease process, the hormonal environment is altered to favor anabolism. In addition, increases in spontaneous activity and in planned exercise stimulate rebuilding of lean body mass.

Protein

After energy requirements are determined, protein needs are calculated. The protein requirement for most individuals is 0.8 g/kg body weight/day (about 60 to 70 g protein/day). Critically ill patients may need 1.5 to 2.0 g/kg/day. Most standard enteral and parenteral feeding mixtures provide this increased quantity of protein if sufficient volume of formula is delivered to meet the increased caloric requirements of these patients. The nitrogen-to-calorie ratio for most feeding formulas prepared for surgical patients is 1:150 (i.e., 1 g of nitrogen for every 150 kcal).

The contraindications to this increased quantity of protein (a daily total of 100 to 150 g, which is equivalent to the amount of protein in a lean 16 oz. steak) are renal failure before dialysis ($\text{BUN} > 40 \text{ mg/dL}$) and hepatic encephalopathy. Patients with systemic inflammatory response syndrome (SIRS) often require increased quantities of dietary protein [see 8:13 *Multiple Organ Dysfunction Syndrome*]. Nutritional support reduces net nitrogen losses in such patients, but positive or even neutral nitrogen balance is generally not achieved, because of the disturbance in metabolism and the reduced intake of dietary protein.

Vitamins and Minerals

The requirements for vitamins, minerals, and trace elements are usually met when adequate volumes of balanced nutrient formulas are provided [see Table 2 and Table 3]. The requirements for most of the major minerals (sodium, potassium, chloride, phosphorus, magnesium, and zinc) are satisfied by monitoring serum concentrations of these elements and adjusting intake to maintain levels within the normal range. Some minerals and electrolytes are restricted in patients with renal failure. Although serum concentrations may not directly reflect total body deficits, sufficient quantities of these nutrients are available to support normal cellular functions if adequate blood concentrations are maintained. Most premixed enteral formulas provide adequate quantities of these substances if caloric needs are met. Vitamins and trace elements must be added to parenteral solutions.

Table 1 Alterations in Metabolic Rate

Patient Condition	Basal Metabolic Rate
No postoperative complications Fistula without infection	Normal
Mild peritonitis Long-bone fracture or mild to moderate injury	25% above normal
Severe injury or infection in ICU patient Multiorgan failure	50% above normal
Burn of 40–100% of BSA	100% above normal

Table 2 Vitamin Requirements

Vitamin	Units	Recommended Dietary Allowance (RDA) for Daily Oral Intake ¹		Tolerable Upper Intake Level ¹	Daily Requirement for IV Intake ⁹⁹
		Male	Female		
Vitamin A (retinol)	µg	900	700	3,000	990
Vitamin D (ergocalciferol)	µg	5–15*	5–15*	50	5
Vitamin E (tocopherol)	mg TE	15	15	1,000	7
Vitamin K (phyloquinone)	µg	120*	90*	Unknown	150
Vitamin C (ascorbic acid)	mg	90	75	2,000	200
Thiamine (vitamin B ₁)	mg	1.2	1.1	Unknown	6
Riboflavin (vitamin B ₂)	mg	1.3	1.1	Unknown	3.6
Niacin	mg	16	14	35	40
Pyridoxine (vitamin B ₆)	mg	1.3–1.7	1.3–1.5	100	6
Pantothenic acid	mg	5*	5*	Unknown	15
Folic acid	mg	0.4	0.4	1	0.6
Vitamin B ₁₂	µg	2.4	2.4	Unknown	5
Biotin	µg	30*	30*	Unknown	60

*Estimated to be safe and adequate dietary intakes.

Pharmacologic recommendations for stress in surgical patients The prescription of vitamins and minerals for therapeutic use should be based on the patient's nutritional history as well as on estimated requirements for the current disease state. These considerations are particularly important in prescription of the fat-soluble vitamins, which are stored in body fat and thus may become toxic at high levels. The upper levels of daily intake for vitamins and minerals have been published [see Table 2 and Table 3]. These are the maximum levels of intake from all sources likely to pose no risk of adverse effect.¹ Vitamins and minerals are sometimes given in large dosages to exert antioxidant effects.

Vitamins A, C, and E and the minerals zinc and selenium can attenuate the tissue-damaging effects of free radicals. In fact, a randomized prospective trial involving mostly trauma patients demonstrated a significant reduction in organ failure with the administration of vitamins C (1,000 mg) and E (1,000 IU).² Many physicians are giving these vitamins and minerals as supplements to injured and infected patients³; supplementation with glutamine should also be considered because of its ability to enhance intracellular glutathione stores, which also play a major antioxidant role [see Discussion, below].

Table 3 Trace Mineral Requirements

Mineral	Recommended Dietary Allowance (RDA) for Daily Oral Intake ¹ (mg)		Suggested Daily IV Intake ⁹⁹ (mg)	Tolerable Upper Intake Level ¹ (mg)
	Male	Female		
Zinc	11	8	2.5–5.0*	40
Copper	0.9	0.9	0.3–0.5	10
Manganese	2.3 [†]	1.8 [†]	0.06–0.1	11
Chromium	0.03–0.035 [†]	0.02–0.025 [†]	0.01–0.015	Unknown
Iron	8	18	0	45

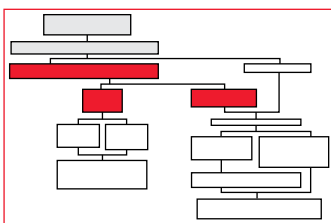
*Burn patients require an additional 2 mg.

[†]Estimated to be safe and adequate dietary intakes.

Enteral Nutrition

Enteral nutrition is the provision of liquid-formula diets by mouth or tube into the gastrointestinal (GI) tract. The GI tract is the preferred site for feeding the critically ill patient.

Enteral nutrition maintains and restores intestinal epithelium, whereas starvation or parenteral nutrition causes villous atrophy. It cannot be used safely, however, in patients who are hemodynamically unstable or who have abdominal distention, intestinal obstruction, or massive GI bleeding. For patients who are able to receive enteral nutrition, either a balanced or a modified diet is selected on the basis of diagnosis and nutritional requirements. An isotonic (approximately 300 mOsm/kg) diet is given continuously for a trial period of 24 hours. If the patient tolerates this regimen but is at increased risk for aspiration, feeding is delivered into the jejunum rather than into the stomach. A standard protocol is helpful in reducing complications.



SAFE USE OF THE GASTROINTESTINAL TRACT FOR FEEDING

Enteral nutrition should be prescribed only if safety and a low complication rate can be ensured. To determine whether the critically ill patient can be fed safely via the GI tract, a clinical assessment of intestinal function is performed. A good determinant of safe tolerance of enteral nutrition is a GI output lower than 600 mL/24 hr. For the purpose of these guidelines, GI output is defined as the volume of effluent from a nasogastric tube, an ostomy, or a rectal tube. Examples of conditions in critically ill patients that produce excessively high (> 600 mL/24 hr) GI outputs and therefore preclude the use of enteral nutrition are gastroparesis, intestinal obstruction, paralytic ileus, high-output enteric fistulas, antibiotic-induced colitis, severe idiopathic diarrhea, and the initial phase of short-bowel syndrome (SBS). Selected patients with enteric losses exceeding 600 mL/24 hr may receive enteral nutrition, however, if carefully monitored by an experienced team.

Another major cause of increased GI output is massive GI bleeding. Conditions that produce bleeding of this magnitude include peptic ulcer disease, esophageal varices, diverticulosis, and angiodysplasia of the colon. Mild bleeding such as that produced by stress gastritis may actually resolve with the delivery of enteral nutrition into the stomach because the liquid diet buffers gastric acid.⁴ Enteral nutrition does not exacerbate mild lower intestinal bleeding.

Although commonly used at the bedside as indicators of intestinal function, bowel sounds and passage of flatus are nonspecific and are unrelated to the eventual tolerance of enteral nutrition.

In the absence of excessively high GI output, abdominal distention, and massive GI bleeding, a trial of enteral nutrition is warranted to determine if the GI tract can be used safely for feeding.⁵

SELECTION OF DIET

Before delivery of enteral nutrition, the appropriate diet must be selected on the basis of the patient's nutrient

requirements [see Indications for Nutritional Intervention, above]. Most liquid-formula diets consist of either a balanced or a modified formula.

Balanced diets contain carbohydrates, proteins, and fats in complex (polymeric) forms in proportions similar to those of a regular Western diet. Frequently, however, the fat content is reduced to 10 to 15% of total calories, and the carbohydrate content is increased. Carbohydrates are present as oligosaccharides, polysaccharides, or maltodextrins; fats consist of medium-chain triglycerides (MCTs) or long-chain triglycerides (LCTs). The nitrogen source is a natural protein, which may be either intact or partially hydrolyzed. In general, balanced diets are isotonic, lactose free, and available in ready-to-use, liquid form. Flavored balanced diets can be used for oral supplementation as well as for enteral tube feeding.

Selection of a balanced diet is based on nutrient and fluid requirements. The caloric density of balanced diets can be 1.0, 1.5, or 2.0 kcal/mL. The largest number of commercially available diets provide 1.0 kcal/mL. The nonprotein caloric content of these diets is derived from either carbohydrates or lipids. Balanced diets formulated with carbohydrates as the main caloric source have higher osmolality than isocaloric diets containing lipids. These carbohydrate-based diets are well tolerated when administered directly into the stomach and may be helpful for patients with steatorrhea. Balanced diets that are fat based may be more appropriate for patients who have diarrhea caused by diet hyperosmolality, especially when feedings are infused directly into the small intestine. However, fat malabsorption is common in critically ill patients when the fat content of the diet exceeds 30% of total calories.

In modified formulas, the proportions and types of nutrients differ from those of a regular Western diet. Manufacturers of enteral diets have introduced these modifications to meet the special nutrient needs of patients with renal failure or SBS. Modified diets are also known as elemental diets or chemically defined diets. These diets contain crystalline amino acids or short peptides in compositions that differ from the reference composition of proteins of high biologic value, such as egg albumin. The fat-to-carbohydrate ratio of these modified diets varies depending on the purpose of the modification. The source of carbohydrate is either dextrose or oligosaccharides; fats are usually in the form of MCTs, essential fatty acids, or both. Because they are not palatable, modified diets are rarely used as oral supplements. Modified diets are further characterized according to the conditions for which they are formulated: stress, immunomodulation, and hepatic, renal, respiratory, or GI dysfunction [see Table 4].

Diets for patients with GI dysfunction have modified nitrogen and fat composition. Transport of dietary nitrogen across the intestinal mucosa is enhanced when nitrogen is provided in the form of short peptides rather than free amino acids. It is also well documented that the small-bowel mucosa utilizes glutamine as the preferred fuel [see Discussion, below]. Consequently, some modified diets contain nitrogen in the form of short peptides, whereas others have an extra amount of glutamine. MCTs are more easily absorbed and metabolized than LCTs are. Diets modified for improved absorption contain a higher proportion of MCT oil. These diets may be efficacious when used during the transition phase after a

Table 4 Composition of Modified Diets

Formula	Protein (g/L)	Carbohydrate (g/L)	Fat (g/L)	Ratio of Nitrogen (g) to Nonprotein Calories (kcal)	Caloric Density (kcal/mL)	Product* (Manufacturer)
Elemental	50	127	34	1:100	1.0	Subdue (Mead Johnson Nutritionals)
	40	127	39	1:131	1.0	Peptamen (Nestlé Clinical Nutrition)
Stress	56	130	28	1:71	1.0	Impact (Novartis)
	66	177	37	1:97	1.3	Perative (Ross Laboratories)
Hepatic	44	168	36	1:148	1.2	Hepatic Aid II (B. Braun Medical Inc.)
Renal	19	365	46	1:800	2.0	Amin-Aid (R&D Laboratories)

* Partial listing.

period of prolonged bowel rest or when the intestine is inflamed. Controlled trials are necessary to verify their clinical efficacy. Stress formulas are indicated for hypercatabolic patients whose nitrogen balance continues to be negative despite increased intake of a balanced diet. These diets usually contain more nitrogen and frequently have an altered amino acid composition. Little evidence supports the use of diets that provide branched-chain amino acids (BCAAs) in concentrations higher than 20 to 25% of total amino acid content for stressed patients.

The fat sources used for enteral diets are primarily omega-6 fatty acids (the arachidonic acid family). Published research suggests that supplementation with omega-3 fatty acids (the eicosapentaenoic acid family) results in the synthesis of eicosanoids (prostaglandins, leukotrienes, and thromboxanes) that enhance the immune response. Other substances that are said to be immunomodulating have also been added to enteral formulas [see Discussion, below].

ASSESSMENT OF FEEDING TOLERANCE

The selected formula is started at isotonicity and delivered continuously at 30 mL/hr for 24 hours. During this initial trial, the formula is delivered via a previously inserted Salem sump or rubber nasogastric (Levin) tube. If a nasogastric tube is not already in place, a soft tube made of either silicone rubber or polyurethane is inserted (see below).

Feeding tolerance is assessed for the first 24 hours. Poor tolerance is indicated by vomiting and severe abdominal cramps, gastric residuum greater than 50% of the volume administered during the previous 4-hour period of feeding, increased abdominal distention (a particularly important factor to assess in comatose patients and patients undergoing mechanical ventilation), and worsening of diarrhea. If any one of these conditions is present, parenteral nutrition is recommended. If there is no evidence of feeding intolerance, the patient is assessed for the risk of aspiration.

ASSESSMENT OF RISK OF ASPIRATION

Aspiration is a major complication in patients

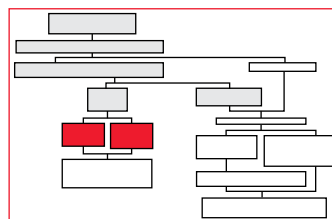
receiving enteral nutrition. The propensity to aspirate enteral feedings is often related to the patient's primary disease and neurologic status, as well as to the site of GI access and the method of delivery.

Important factors in assessing the risk of aspiration include depressed sensorium, increased gastroesophageal reflux, and history of previously documented episodes of aspiration. Depressed sensorium in the critical care setting is secondary to organic lesions of the central nervous system (CNS), metabolic encephalopathies, or medications. Head trauma, hypoxemia, hepatic and septic encephalopathies, and the use of H₂-receptor blockers are common causes of depressed sensorium in critically ill patients. Increased gastroesophageal reflux may be present in individuals with reduced lower esophageal sphincter (LES) pressure and increased intragastric pressure. Many medications used in the ICU, such as theophylline, anticholinergics, calcium channel blocking agents, beta-adrenergic agonists, and alpha-adrenergic antagonists, cause a reduction in LES pressure. Finally, a history of aspiration places the patient at increased risk for recurrent episodes.

For most enterally fed patients, safety demands that the head be elevated at feeding time and for some period thereafter to prevent regurgitation. If elevating the patient's head is not possible, an alternative site of nutrient delivery should be considered. Nasogastric intubation, in particular, requires elevation of the head because the tube may render the upper and lower esophageal sphincters incompetent and liable to reflux. Even the presence of a tracheostomy or endotracheal tube does not ensure that regurgitated gastric contents will not be aspirated. Liquid filling the pharynx will inevitably trickle past even an overinflated endotracheal tube cuff and into the lung. The lack of a truly reliable bedside method for detection of aspiration makes study of this complication difficult.

ACCESS FOR FEEDING

In most general and thoracic surgical patients, access for feeding is most commonly obtained via the stomach or the jejunum. Methods of access for intragastric feedings include nasogastric tubes and feeding gastrostomies placed through a laparotomy or percutaneously with the aid of endoscopy, fluoroscopy, or laparoscopy.



Nasogastric tubes provide the most common method of access for gastric feeding. Tubes made of polyurethane or silicone rubber are preferred because they are soft, nonreactive, and well tolerated by most patients. They are also less corrosive to the nasopharynx than tubes made of rubber or polyvinyl chloride. The soft consistency of these tubes often makes insertion into critically ill patients difficult and precludes the checking of gastric residuum. The difficulties of tube passage into the stomach are increased when thin, floppy tubes are inserted into obtunded patients. Useful aids include stylets, judicious use of gravity and positioning, and designation of especially experienced and certified nursing personnel to assist in this task [see Table 5].

Passage of a tube through the pylorus into the jejunum may be necessary if the patient is at increased risk for aspiration (see above). Our practice is to place the tube into the stomach, to position the patient on the right side for several hours once or twice in the next 24 hours, and then to obtain an abdominal x-ray. If the tube has not passed, metoclopramide, 10 mg IV, is given while the patient is still in the radiology department, and a repeat x-ray is obtained. If the location of the feeding tube is not evident, a small amount of contrast material can be injected through the tube to verify the position.

If the tube still has not passed through the pylorus, the aid of the fluoroscopist is enlisted. (Interventional radiologists take justifiable pride in their ability to cannulate almost any internal orifice.) Finally, if all else has failed and no alternative route for nutrition is appropriate, the endoscopist can capture the tube tip in the stomach with the biopsy forceps of the flexible endoscope (aided by a suture through the tube end) and guide the tube through the pylorus.

Table 5 Procedure for Inserting Nasoenteric Tubes

Provide privacy.
Explain procedure and its purpose.
Place patient in sitting position with neck flexed slightly and head of bed elevated to 45°.
Lubricate stylet and insert into feeding tube.
Inspect nares and determine optimal patency by having the patient breathe through one nostril while the other is temporarily occluded. Estimate the length of tubing required to reach into the stomach by measuring the distance from the tip of the nose to the earlobe and then from the earlobe to the xiphoid process. Add 25 cm to this length for nasoduodenal intubation.
If the patient seems uncooperative, instill generous amounts of lidocaine jelly into the nares and nasopharynx before tube insertion.
Lubricate the end of the tube and pass it posteriorly. Ask a cooperative patient to swallow water to facilitate passage of the tube.
Once the tube is beyond the nasopharynx, allow the patient to rest.
Have the patient continue neck flexion and swallowing while the tube is advanced.
If the patient begins to cough, withdraw the tube into the nasopharynx and then reattempt passage.
Confirm passage into the stomach by obtaining an abdominal x-ray.
Remove stylet.
Secure tube to bridge of nose or upper lip with nonallergenic tape and prevent undue pressure on external nares.

When any type of nasoenteric tube is placed to administer enteral nutrition, verification of the tube's location before feedings are started is mandatory. The simplest means of assessing proper tube placement in the GI tract is by the aspiration of gastric contents, the source of which can be confirmed by measuring the pH of the aspirate. Because small-bore, soft tubes tend to collapse under high negative pressure, a small syringe should be used to aspirate gastric contents. If gastric contents cannot be aspirated through the tube, radiographic confirmation of tube location is mandatory before enteral feedings are started. Because feeding tubes are often radiopaque, a simple plain film of the abdomen may be adequate. If the exact location of the tube is still in doubt, a small amount of contrast material can be injected through the tube. Placement of the distal tip of the tube in the duodenum is usually confirmed by an abdominal x-ray before transpyloric feedings are started. The tube should be inserted to a length sufficient to permit migration into the proximal jejunum.

Simple insufflation of air into the tube is not sufficient to verify the position of the tube. Auscultation over the stomach can detect sound transmitted through a tube that has been inadvertently passed into the bronchial tree. Many of these tubes are small enough to pass through the glottis and the trachea without markedly interfering with phonation or respiration. Enteral formulas delivered into the bronchial tree through a misplaced tube can cause severe pneumonitis and death.

The development of percutaneous techniques for the placement of gastrostomies has been a major contribution to enteral nutrition. Percutaneous endoscopic gastrostomy (PEG) [see 5:18 *Gastrointestinal Endoscopy*] and Witzel techniques for these procedures are well documented.

Concurrent decompression of the stomach and feeding into the small intestine have been used to reduce the risk of aspiration in critically ill patients. This combination of procedures requires either the insertion of a multilumen nasojejunum tube, the surgical placement of combined gastrojejunum tubes, modification of PEG, or insertion of a nasogastric tube in conjunction with a surgical jejunostomy. Such access to the GI tract also provides a route for the delivery of crushed medications and the option to provide cyclic nocturnal enteral nutrition with gastric decompression (i.e., the patient receives nutrients by mouth during the day).

FEEDING REGIMENS

If the patient tolerates the initial trial of enteral nutrition, then the delivery site for future feeding is chosen according to the risk of aspiration, and the feeding regimen is gradually intensified. If the risk of aspiration is minimal, intragastric feedings are preferred. These feedings are better tolerated physiologically, easier to administer, and less restrictive for the patient than continuous feeding into the small intestine. Patients fed into the stomach receive an isotonic formula delivered continuously at a rate of 25 mL/hr. The delivery is advanced by 25 mL/hr every 8 hours until the goal rate is reached.⁶ The level of gastric residuum that is of concern in the critically ill patient appears to be 400 mL.⁷ If the risk of aspiration is increased, feedings are delivered via nasoduodenal or nasojejunum tubes. Patients fed into either the duodenum or the jejunum receive formulas of 300 mOsm/kg delivered at an initial rate of 30 mL/hr with the aid of a

peristaltic pump. The rate is increased daily by 30 mL/hr until the goal rate is reached. It should be emphasized that only isotonic feedings should be administered into the small bowel. Hypertonic formulations have been associated with small-bowel injury and necrosis.

MONITORING AND PREVENTION OF COMPLICATIONS

Patients who receive enteral nutrition should be as carefully monitored as those who receive parenteral nutrition. Particular attention is directed to the patient's metabolic status and fluid and electrolyte balance. A protocol should be established and followed to ensure that nutritional goals are met and complications minimized. A standard checklist is helpful in starting and maintaining enteral nutrition and prevents omission of important details [see Table 6].

Four types of complications are related to enteral nutrition: GI, mechanical, metabolic, and infectious. The two most common types are GI and mechanical complications.

The most frequent GI complication is diarrhea, which may occur in as many as 75% of critically ill patients receiving enteral nutrition. Diarrhea is best defined as stool weight greater than 300 g/24 hr or stool volume greater than 300 mL/24 hr; however, these measurements are impractical and difficult to obtain. A more practical definition of diarrhea is more than three loose bowel movements during a period of 24 hours. There are many causes of diarrhea in critically ill patients receiving enteral nutrition, and the most frequent association (about 80% of cases) is with receipt of antibiotics

[see Figure 2]. The desired therapeutic approach is to adjust the enteral nutrition regimen accordingly rather than to discontinue it completely. Only one variable of the feeding regimen (i.e., osmolality, volume, rate, or type of diet) should be altered at a time. In our experience, critically ill patients tolerate a continuous feeding regimen better than intermittent feeding. If the patient still has diarrhea when being fed at a rate of 30 mL/hr and a concentration of 150 to 300 mOsm/kg, antidiarrheal treatment is indicated.

In many instances, antidiarrheal medication is given without a definite diagnosis; therefore, it is essential to select medications with both a wide therapeutic range and a low

Table 6 Standard Orders for Enteral Nutrition

Obtain abdominal x-ray to confirm tube location before feeding. Elevate head of bed 45° when feeding into the stomach. Record type and strength of diet and rate of infusion. Check gastric residuum every 4 hr in patients receiving gastric feedings. Withhold feedings if residuum is 400 mL or greater. Check gastric residuum every 2 hr after feedings held and restart gastric feedings when residuum is less than 400 mL. Check for abdominal distention. Check frequency, consistency, and volume of stool output. Weigh patient on Monday, Wednesday, and Friday. Record weight on graph. Record intake and output daily. For every shift, chart volume of formula administered separately from water or other oral intake. Change administration tubing and cleanse feeding bag daily. Irrigate feeding tube with 20 mL of water at the completion of each intermittent feeding, when tube is disconnected, after the delivery of crushed medications, or if feeding is stopped for any reason. When patient is ingesting oral nutrients, ask the dietitian to provide calorie counts daily for 5 days, then weekly thereafter. On a weekly basis, obtain complete blood count with red blood cell indices, SMA-12, serum iron, and serum magnesium. Obtain SMA-6 every Monday and Thursday. Once a week, collect urine for 24 hours, starting at 8:00 am, and analyze for urea nitrogen.

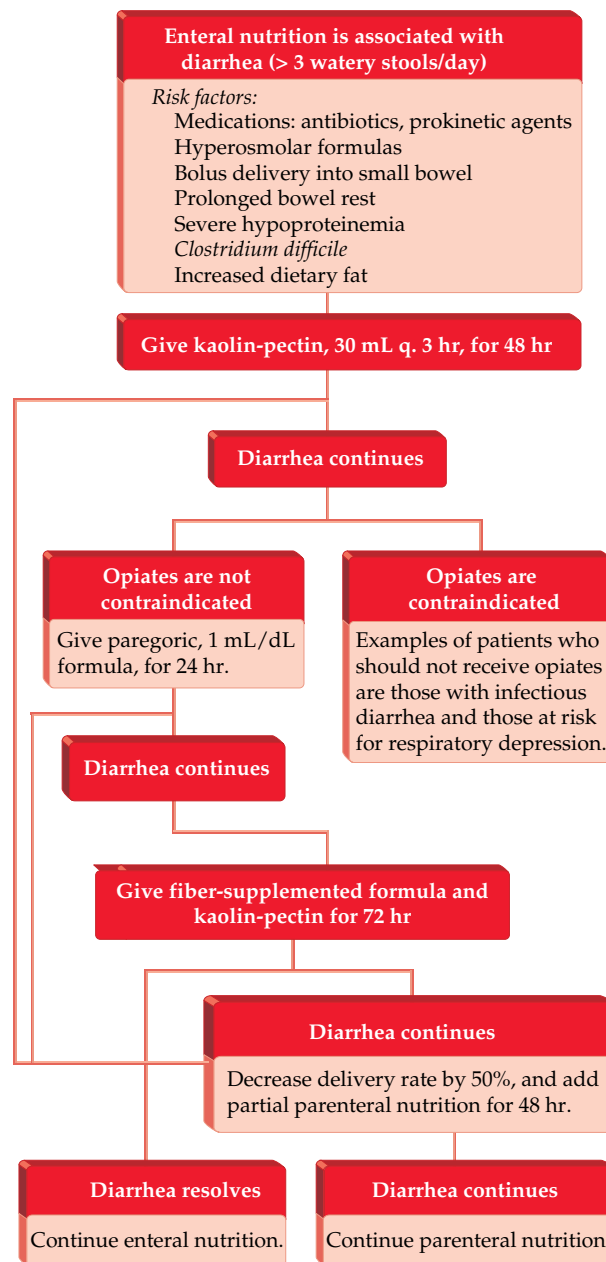


Figure 2 The decision-making approach for pharmacologic and dietary treatment of diarrhea associated with enteral nutrition is shown.

incidence of side effects. For these reasons, we prefer kaolin-pectin over opiates such as paregoric. Every 3 hours, 30 mL of kaolin-pectin solution is given through the feeding tube and followed by 25 mL of normal saline for irrigation. If this regimen is unsuccessful after 48 hours and opiates are not contraindicated, paregoric is added at a dose of 1 mL/100 mL of formula [see Figure 2]. Opiates act by slowing intestinal motility. Since the normal motility pattern is a defense mechanism for growth of bacteria in the small bowel, administering opiates to a patient with a contaminated small bowel can lead to bacterial overgrowth and worsen diarrhea. In addition, opiates are respiratory depressants and are also contraindicated in patients with infectious diarrhea.

Several diagnostic methods may help in identifying the cause of diarrhea associated with enteral nutrition. These include the assay of stool for *Clostridium difficile* enterotoxin, analysis of stool for fat malabsorption, the D-xylose test for carbohydrate malabsorption, and breath H₂ analysis for bacterial overgrowth. The D-xylose test and the breath H₂ analysis are more commonly used in non-critically ill patients with diarrhea associated with enteral feeding.

To prevent peptic ulcerations and bleeding, gastric acidity is controlled with H₂-receptor blockers in critically ill patients. Although these drugs help control hyperacidity, which is a cause of diarrhea, they also lead to bacterial overgrowth in the intestine.⁸ Therefore, the use of H₂-receptor blockers should be avoided in patients who receive feedings into the stomach, because the presence of the liquid formula in the stomach already provides a physiologic means of buffering acid. If necessary, antacids rather than H₂-receptor blockers should be used to titrate gastric pH to 4.5 to 6.5. The amino acid glutamine is also utilized to prevent or treat ulceration of the upper GI tract.

The most common mechanical complications that are related to enteral nutrition are tube dislodgment, clogging of the tube, and leakage of enteric contents around the exit site of the tube onto the skin. Tube dislodgment occurs more frequently in agitated patients and hypoxic patients. Inadvertent removal of the tube is usually prevented by adequate taping of the nasoenteric tube or, in agitated patients, by suturing the tube or using a Velcro abdominal wall binder.

Clogging or plugging of the tube often results from the failure to use saline irrigations after intermittent feedings or the inadvertent delivery of crushed medications through a small-bore tube. This complication is reduced by routine irrigations of 20 to 25 mL of normal saline or water after each intermittent feeding. Liquid medications may also help prevent this complication, although these medications are frequently hyperosmolar and may produce discomfort and diarrhea when delivered rapidly into the jejunum. The injection of a small volume of a carbonated beverage into a plugged tube will often clear the blockage. Occasionally, a guide wire and the help of the interventional radiologist will be needed.

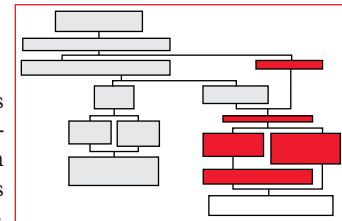
The leakage of enteric contents onto the skin around the exit site of a tube enterostomy is often uncomfortable for the patient and may produce a moderate amount of skin irritation. One cause of such leakage is insufficient approximation of the end of the tube (balloon or mushroom head) to the gastric wall. Leakage around a tube is prevented by proper fixation of the end of the tube with a retention disk or "bumper" at the skin level. The assistance of an enterostomal

therapist and the use of products such as karaya gum, zinc oxide, Stomahesive, and locally applied antacid are often helpful. Also problematic is the inappropriate use of urinary catheters for enteral access; these devices were not designed to function as gastrostomy or enterostomy tubes. The catheters currently preferred for these purposes are made of either silicone rubber or polyurethane and include a system designed to prevent migration of the tube into the stomach.

Parenteral Nutrition

CENTRAL VENOUS VERSUS PERIPHERAL VENOUS INFUSIONS

Central venous infusions [see 6:26 Vascular and Peritoneal Access] are indicated in most critically ill patients who receive parenteral nutrition because (1) patients in



the ICU often require increased quantities of energy and cannot tolerate large fluid volumes, and (2) solutions of much greater caloric density and tonicity can be infused into central veins than can be infused into peripheral veins. Nonetheless, peripheral venous infusions may be indicated in certain situations [see Table 7] (see below).

CENTRAL VENOUS NUTRIENT INFUSION

Hypertonic nutrient solutions are infused into the superior vena cava, where they are rapidly diluted. Usually, these solutions contain hypertonic glucose (25%), amino acids (5%), and other essential nutrients. The tonicity of the hypertonic nutrient solutions is so great (> 1,900 mOsm/kg) that administration of the mixture into peripheral veins would cause severe thrombophlebitis and venous sclerosis. These solutions contain at least 1 kcal/mL, and thus, infusion of 2.0 to 2.5 L/day provides 2,000 to 2,500 kcal of energy and all essential nutrients. This calorie load is sufficient to meet energy requirements in more than 90% of surgical patients.

Table 7 Indications for Central Venous or Peripheral Venous Infusions

Central venous infusions

- To provide adequate IV nutritional support for 10 days or more
- To satisfy nutrient requirements in patients with increased energy needs and normal or decreased fluid requirements
- To support the patient with single- or multiple-organ failure by infusing modified nutrient solutions in a limited fluid volume

Peripheral venous infusions

- To provide initial feeding (< 5 days) before catheter insertion in a patient who will require central venous feedings
- To infuse less concentrated solutions via a multiuse central catheter (i.e., a line for blood drawing, medication, and nutrients) into an individual in whom other venous access cannot be easily or safely obtained
- To supplement enteral feedings that are inadequate because of GI dysfunction
- To satisfy energy requirements that are near basal (1,500–1,800 kcal/day) in a nondepleted patient who can tolerate 2.5–3.0 L IV solution each day

Once positioned, the catheter is used exclusively for administration of the hypertonic nutrient solution. Drawing blood, monitoring central venous pressure, and administering medication through this dedicated lumen are to be avoided. Multiple-lumen central venous catheters are currently used in most patients; manufacturers suggest that at least one port be devoted to the infusion of hypertonic nutrient solutions and that other ports be used for drawing blood, monitoring pressure, and infusing medications. Reports suggest that the rates of catheter sepsis associated with use of these catheters are higher than the rates associated with single-lumen feeding catheters.^{9,10} In our experience, the infection rate associated with multiple-lumen catheters was similar to that observed with single-lumen catheters (3.3% versus 1.0%), but the multiple-lumen catheters were in place for a shorter period than the single-lumen catheters (7 versus 14 days).¹¹ Removal of the multiple-lumen catheters was indicated when multiple central access ports were no longer required or when one of the lumens became clotted or malfunctioned. It appears that multiple-lumen catheters can be used in the ICU for central venous nutrient infusions if strict protocols are maintained to ensure that one lumen is dedicated to nutrient infusion, that other lumens are handled safely, and that the catheters are removed when they are no longer required.

Occasionally, a patient may require the infusion of a hypertonic nutrient solution in a situation where percutaneous puncture of central veins is impossible or contraindicated. In such cases, catheterization of an antecubital vein and insertion of a peripherally inserted central catheter (PICC) with the tip positioned in the superior vena cava should be considered. These catheters are readily inserted by the interventional radiologist, and they eliminate the complications associated with subclavian and internal jugular vein insertions. The PICC line has become the primary route of central venous access in many institutions.

Catheters made of Silastic have been safely kept in place for extended periods and provide an additional option for care of patients who require central venous infusions. Catheterization of the femoral vein may provide a route for central venous access in some situations. Because of the high density of skin pathogens in the groin area, these catheters should be replaced every 2 to 3 days. If the catheter tip is positioned in the iliac vein or the inferior vena cava, the concentration of solution infused through the catheter should not exceed 15%. Strict care of the entrance site should be maintained because of the high complication rate associated with lines placed in the groin.

Central Venous Solutions

Central venous solutions are formulated in the hospital pharmacy. These solutions are commonly combinations of 500 mL of 50% dextrose and 500 mL of a 10% amino acid mixture [see Table 8] to which electrolytes, vitamins, and trace elements are added (see below). Each day, 2 L of the solution can be infused. Administration of fat emulsion (500 mL, 20%) 1 day a week meets essential fatty acid requirements. Alternatively, the three major nutrients may be mixed together in a 3 L bag (triple mix or three-in-one) and the entire contents of the single bag infused during the 24-hour period [see Table 8]. Another innovation is the use of an automated mixing device (Automix; Baxter International, Deerfield, IL)

Table 8 Composition of Central Venous Solutions

	Standard Solution	Triple-Mix Solution
Volume		
Amino acids 10% (mL)	500	1,000
Dextrose 50% (mL)	500	1,000
Fat emulsion 20% (mL)	—	250
Total (mL)	1,000	2,250
Contents		
Amino acids (g)	50	100
Dextrose (g)	250 (25%)	500
Total nitrogen (g)	8.4	16.8
Total calories (kcal)	1,050	2,600
Ratio of nitrogen to calories	1:125	1:154
Caloric density (kcal/mL)	1.0	1.15
Osmolarity (mOsm/kg)	1,970	1,900

that compounds various proportions of 70% glucose, 10% amino acids, and 20% fat emulsions into 3 L bags. This device allows the hospital pharmacy to manufacture a variety of nutrient combinations with minimal effort. More concentrated solutions can be made, and the computer will generate a label for the bag that allows nurses to verify the order.

Electrolytes and minerals are added to the base formula as required [see Table 9]. Sodium and potassium salts are added as chloride or acetate, depending on the acid-base status of the patient. The solution should usually consist of approximately equal quantities of chloride and acetate. If chloride losses from the body are increased, as in a patient who requires nasogastric decompression, most salts should be administered as chloride. Sodium bicarbonate is incompatible with the nutrient solutions, and acetate is administered when additional base is required (when metabolized, acetate generates bicarbonate). Phosphate is usually given as the potassium salt; sodium phosphate is used when potassium is contraindicated. Phosphate is also present in fat emulsions.

Commercially available preparations of vitamins, minerals, and trace elements are also added to the nutrient mix for

Table 9 Electrolytes Added to Central Venous Solutions

Electrolyte	Usual Concentration	Usual Range of Concentration
Sodium (mEq/L)	30	0–150
Potassium (mEq/L)	30	0–80
Phosphate (mmol/L)	15	0–20
Magnesium (mEq/L)	5	0–15
Calcium* (mEq/L)	4.7	0–10
Chloride (mEq/L)	50	0–150
Acetate (mEq/L)	70	70–220

*As gluconate.

daily administration unless they are contraindicated. A solution containing both fat- and water-soluble vitamins should be added. Vitamin K₁ (phytonadione), 10 mg, is given once a week to preparations without vitamin K but is contraindicated in patients receiving warfarin.

Trace elements are given daily. Usual requirements are satisfied by the addition of commercially available mixtures either to 1 L of standard solution or to the triple-mix bag each day. Trace elements are indicated for all patients receiving central venous nutrient solutions except those with chronic renal failure or severe liver disease. At especially high risk for zinc deficiency are alcoholics and patients who have pancreatic insufficiency with malabsorption, have undergone massive small-bowel resection, are in renal failure with dialysis, or have nephrotic syndrome; at high risk for copper deficiency are patients with SBS, jejunioileal bypass, malabsorptive conditions with severe diarrhea, or nephrotic syndrome. Copper and manganese are excreted primarily via the biliary tract. Therefore, in patients with biliary tract obstruction, excess retention of copper and manganese should be avoided by decreasing intake of these ions, monitoring blood levels, or both. Although the main excretory route for zinc and chromium is via the feces, renal excretion will minimize dangers from modest excesses of these elements. In patients with renal insufficiency, however, daily zinc and chromium administration may be contraindicated. ICU patients usually do not require iron. Iron is contraindicated in patients with sepsis because it supports bacterial growth. Iron may be required to treat iron deficiency anemia, particularly during convalescence from this condition. Rarely does the anemia that is associated with chronic disease and inflammation respond to iron therapy during the active stages of disease.

Like other invasive therapies, total parenteral nutrition (TPN) is associated with potential complications deriving either from central venous access or from the composition of the formula given. Most such complications are preventable with appropriate attention to detail [see Table 10].

PERIPHERAL VENOUS SOLUTIONS

Slightly hypertonic nutrient solutions (approximately 600 to 900 mOsm/kg) can be prepared for peripheral venous infusions from commercially available amino acid mixtures (5%), dextrose solutions (10%), and fat emulsions (20%). These nutrient mixtures have a low caloric density (approximately 0.3 to 0.6 kcal/mL) and thus provide only 1,200 to 2,300 kcal in 2,000 to 3,500 mL of solution. These solutions are particularly useful in patients who receive some but insufficient amounts of tube feedings; they must be supplemented with additional nutrients by venous infusion.

These dilute nutrient mixtures can be infused through plastic cannulas placed in large-bore peripheral veins. The catheter insertion site and surrounding tissue should be inspected periodically for signs of phlebitis or infiltration, and the infusion site should be rotated every 48 to 72 hours to prevent thrombophlebitis. Only fat emulsion can be administered simultaneously through the same IV site as a peripheral venous solution. The nutrient solution should be temporarily stopped if the catheter is used for administration of antibiotics, chemotherapeutic agents, blood, or blood products. The infusion line should then be flushed with saline and infusion of the nutrient solution resumed.

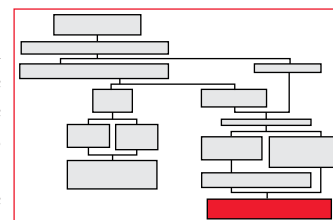
If the fat emulsion is infused in a piggyback manner, administration should be performed over a period of 8 to 12 hours and concluded in the early morning (3:00 am) to allow clearance of the emulsion from the bloodstream. Blood sampling should be avoided during short-term periods of fat infusion because the associated hypertriglyceridemia will interfere with many of the serum measurements. In patients who are receiving peripheral venous solutions by triple mix, hypertriglyceridemia is rare because the rate of infusion has been reduced and infusion extended over a 24-hour period.

Patients receiving peripheral venous feedings should be monitored as suggested for individuals receiving central venous feedings (see below). Mechanical and septic complications are uncommon. Fluid imbalances and alterations in serum electrolyte concentrations are similar to those seen in standard IV support, and corrections are made by altering the volume of the infusion or adding or omitting electrolytes. Hyperglycemia and glycosuria are rarely observed unless the patient is diabetic.

MONITORING THE PATIENT: OPTIMIZING NUTRITIONAL SUPPORT, PREVENTING COMPLICATIONS, AND RESOLVING COMMON PROBLEMS

General Measures

Patients receiving central venous feedings should be weighed daily, and accurate intake and output records should be maintained. Blood glucose should be monitored daily. Persistent abnormalities require that a more stringent schedule of monitoring blood glucose be instituted and specific therapy initiated (see below).



The quantity of energy administered to most ICU patients should minimize the loss of lean body mass and adipose tissues. Thus, variations in body weight usually reflect alterations in fluid balance. If sustained weight loss occurs (as characterized by a gradual fall in body weight over a period of 2 weeks or longer), caloric intake may be inadequate. Additional calories (500 to 1,000 kcal/day) should be administered to maintain weight. Alternatively, the metabolic rate could be calculated from the volume of oxygen consumed per minute ($\dot{V}O_2$) and calorie intake then matched to equal energy expenditure:

$$\text{Metabolic rate (kcal/hr)} = \dot{V}O_2 \text{ (mL/min)} \times 60 \text{ min/hr} \times 1 \text{ L/1,000 mL} \times 4.83 \text{ kcal/L}$$

This calculation is required in only 5% of our patients.

In non-ventilator-dependent patients, oxygen consumption and, in turn, the metabolic rate can be derived from measurements of respiratory gas exchange. Equipment (e.g., the metabolic cart) is commercially available that can make these measurements at the bedside. In a patient with a Swan-Ganz catheter in place, oxygen consumption can be calculated from cardiac output determinations and simultaneous measurements of mixed venous oxygen content (C_{mvO_2}) and arterial oxygen content (C_{aO_2}):

$$\dot{V}O_2 \text{ (mL/min)} = \text{cardiac output (L/min)} \times (C_{aO_2} \text{ [mL/dL]} - C_{mvO_2} \text{ [mL/dL]}) \times 1 \text{ L/10 dL}$$

Table 10 Diagnosis, Treatment, and Prevention of Potential Mechanical and Metabolic Complications Associated with TPN

Complications		Diagnosis	Treatment	Prevention
Mechanical	Pneumothorax	Dyspnea, chest x-ray	Tube thoracostomy Observation	Avoid emergency procedures Trendelenburg position
	Hemothorax	Dyspnea, chest x-ray	Remove catheter Observation	Insert catheter using appropriate technique
	Venous thrombosis	Inability to cannulate	Remove catheter Heparin therapy	Use silicone catheters Add heparin to solution
	Air embolism	Dyspnea, cyanosis, hypotension, tachycardia, precordial murmur	Trendelenburg position Left lateral decubitus position	Trendelenburg position Valsalva maneuver Tape IV connections
	Catheter embolism	Sheared catheter	Fluoroscopic retrieval	Never withdraw catheter through needle
	Dysrhythmias	Catheter tip in right atrium	Withdraw catheter to superior vena cava	Estimate distance to superior vena cava before insertion; confirm position with x-ray
	Subclavian artery injury	Pulsatile red blood	Remove needle Apply pressure Chest x-ray	Review anatomy
	Catheter tip misplacement	Chest x-ray	Redirect with a guide wire	Direct bevel of needle caudally
Metabolic	Hyperglycemic, hyperosmolar, nonketotic coma	Dehydration with osmotic diuresis, disorientation, lethargy, stupor, convulsions, coma, glucose 1,000 mg/dL, osmolality 350 mOsm/kg	Discontinue TPN; infuse D5 in 0.45% saline at 250 mL/hr Insulin 10–20 U/hr Bicarbonate Monitor glucose, potassium, pH	Monitor glucose
	Hypoglycemia	Headache, sweating, thirst, convulsions, disorientation, paresthesias	D50W IV	Taper TPN by one-half for 12 hr; then 12 hr of D5W at 100 mL/hr
	CO ₂ retention	Ventilator dependence, high respiratory quotient	Taper glucose	Provide 30–40% of calories with fat
	Azotemia	Dehydration, elevated BUN	Increase nonprotein calories	Monitor fluid balance
	Hyperammonemia	Lethargy, malaise, coma, seizures	Discontinue amino acid infusions Infuse arginine	Avoid casein or fibrin hydrolysate
	Essential fatty acid deficiency	Xerosis, hepatomegaly, impaired healing, bone changes	Fat administration	Provide 25–200 mg/kg/day of essential fatty acids
	Hypophosphatemia	Lethargy, anorexia, weakness	Supplemental phosphate	Treat causative factors; alkalosis, gram-negative sepsis, vomiting, malabsorption Provide 20 mEq/kcal
	Abnormal liver enzymes	Fatty infiltrate in liver	Evaluate for other causes	Provide balanced TPN solution
	Hypomagnesemia	Weakness, nausea, vomiting, tremors, depression, hyporeflexia	Infuse 10% MgSO ₄	Supply 0.35–0.45 mEq/kg/day
	Hypermagnesemia	Drowsiness, nausea, vomiting, coma, dysrhythmia	Dialysis Infuse calcium gluconate	Monitor serum levels

BUN = blood urea nitrogen; D50W = dextrose 50% in water; TPN = total parenteral nutrition.

Another objective of nutritional support in the ICU patient is the maintenance of lean body mass, which is reflected by nitrogen balance equilibration or positive nitrogen balance. Although complete nitrogen balance determination is a complex and sophisticated study, nitrogen equilibration can be estimated by using common analytic procedures. To estimate nitrogen balance, total nitrogen loss is subtracted from total nitrogen intake. Calculation of total nitrogen loss requires several steps. The urine urea nitrogen (UUN) concentration is multiplied by the total volume of urine output during a given day to yield the 24-hour UUN, that is, the total amount of urea excreted during that period. Because urea accounts for only approximately 80% of the nitrogen excreted in the urine, the value for the 24-hour UUN must be increased by an additional 20%. This quantity and an additional 2 g/day are added to the value for the 24-hour UUN to account for nonurea nitrogen, stool, and integumentary losses:

$$\text{24-hour UUN (g/day)} = \text{UUN (mg/dL)} \times \text{urine output (mL/day)} \times 1 \text{ g/1,000 mg} \times 1 \text{ dL/100 mL}$$

$$\text{Total nitrogen loss (g/day)} = \text{24-hour UUN (g/day)} + (0.20 \times \text{24-hour UUN [g/day]}) + 2 \text{ g/day}$$

Metabolic Monitoring

A wide variety of metabolic complications may occur during parenteral feeding [see Table 11]. These are minimized by frequent monitoring [see Table 12] and appropriate adjustment of nutrients in the infusion.

The most common metabolic problems occurring in ICU patients are hyperglycemia and glucosuria. The combination of excessive counterregulatory hormone release and overproduction of tumor necrosis factor- α (TNF- α), interleukin-1, and interleukin-6 characteristic of critical illness is a major factor responsible for stress-induced hyperglycemia in the nondiabetic host.¹² Hyperglycemia has been associated with infectious complications,^{13,14} worsened outcome after head injury and stroke,¹⁵ and increased proteolysis.¹⁶ Moreover, prevention of hyperglycemia by aggressive insulin treatment has been associated with a reduced mortality in ICU patients.¹⁷ Initially, elevated levels of blood glucose should be treated by the administration of subcutaneous insulin (5.0 U every 4 to 6 hours for glucose levels of 200 to 250 mg/dL; 7.5 U for 250 to 300 mg/dL; and 10.0 U for 300 to 350 mg/dL). When the nutritional solution is ordered for the next 24-hour period, half of the quantity of insulin administered subcutaneously is added to the mixture. At least 10 U of regular insulin per liter of solution should be given as the initial dose, and in some cases, as much as 40 U/L may be required. If larger doses of insulin are needed (> 100 U/day), a separate insulin infusion or drip should be used.

In most patients with severe glucose intolerance, the rate of glucose administered should not exceed 5 mg/kg/min (approximately 500 g/day). Additional calories should be administered as fat emulsion. The commercially available fat emulsions are all generally well tolerated by critically ill patients. Triglyceride levels should be monitored, and the rate of administration of the emulsion should be decreased or the emulsion temporarily discontinued if levels exceed 500 mg/dL. Fat emulsion should be used with caution in patients with known hypertriglyceridemia or in those with

gram-negative bloodstream infection that is associated with hyperlipidemia.

The infusion of excess glucose or lipid energy may alter pulmonary function and, in some patients, prevent weaning from a mechanical ventilator. Excessive carbohydrate loads (usually > 500 g/day) increase CO₂ production. If the quantity of CO₂ produced exceeds the ability of the lungs to excrete this oxidative end product, hypercapnia results. Fat emulsion may also interfere with diffusion of gas across the alveolar membranes. This interference is generally related to the concentration of the emulsion in the bloodstream; hence, monitoring triglyceride levels and preventing hypertriglyceridemia will minimize this complication.

Catheter Care and Catheter Infection

The most serious problem associated with central venous feedings is catheter infection [see 8:16 *Nosocomial Infection*]. Primary catheter infection is defined as the presence of signs and symptoms of infection (usually a febrile episode), with the indwelling catheter being the only anatomic focus of sepsis. After removal of the catheter, the symptoms usually attenuate. Cultures of the catheter tip with semiquantitative techniques yield at least 10³ organisms.¹⁸ The organisms are the same as those recovered from cultures of blood drawn from a peripheral vein during the initial evaluation of the infection.

Secondary, as opposed to primary, catheter infection is associated with a second infectious focus that causes bacteremia and thus seeds or contaminates the catheter. The microorganisms cultured from the catheter tip are similar to those cultured from the primary source. The infection clears after specific treatment of the primary infection.

Primary catheter infection is prevented or at least greatly reduced by following strict protocols to govern the use and manipulation of the central venous feeding catheter and by employing a systematic method of care and surveillance of the catheter entrance site. Usually, catheter care and its supervision and certification are performed by a nurse with expertise in maintenance of long-term IV access (the nurse may be assigned to the nutrition support service or may be experienced in IV access or infection control). Every 48 to 72 hours, the dressing that covers the entrance site of the catheter is removed, the site inspected, the area around the entrance site cleaned, a topical antibiotic or antiseptic ointment applied, and the site redressed with a new sterile dressing. This procedure is documented in the clinical record; if drainage or crusting appears at the entrance site, appropriate cultures are taken. In addition, the dressing is changed if it becomes wet or soiled or no longer remains intact. In patients who have either draining wounds in close proximity to the catheter entrance site or tracheostomies, the entire dressing should be covered with a transparent barrier drape to minimize contamination.

If signs and symptoms of infection develop in a recipient of central venous parenteral nutrition, a history should be taken and a physical examination performed [see Figure 3]. Appropriate tests (e.g., complete blood count and urinalysis) and diagnostic studies (including radiography) should also be performed. If blood cultures are needed, they should be

Table 11 Metabolic Complications of Total Parenteral Nutrition

Problems	Possible Causes	Solutions
Glucose Hyperglycemia, glycosuria, osmotic diuresis, hyperosmolar nonketotic dehydration and coma Ketoacidosis in diabetes mellitus Postinfusion (rebound) hypoglycemia	Excessive total dose or rate of infusion of glucose; inadequate endogenous insulin; increased glucocorticoids; sepsis Inadequate endogenous insulin response; inadequate exogenous insulin therapy Persistence of endogenous insulin production secondary to prolonged stimulation of islet cells by high-carbohydrate infusion	Reduce amount of glucose infused; increase insulin; administer a portion of calories as fat emulsion Give insulin; reduce glucose input Administer 5–10% glucose before infusate is discontinued
Fat Pyrogenic reaction Altered coagulation Hypertriglyceridemia Impaired liver function Cyanosis Essential fatty acid deficiency	Fat emulsion, other solutions Hyperlipidemia Rapid infusion, decreased clearance May be caused by fat emulsion or by an underlying disease process Altered pulmonary diffusion capacity Inadequate essential fatty acid administration	Exclude other causes of fever Repeat study after fat has cleared bloodstream Decrease rate of infusion; allow clearance before blood tests Exclude other causes of hepatic dysfunction Discontinue fat infusion Administer essential fatty acids in the form of one 500 mL bottle of fat emulsion every 2–3 days
Amino acids Hyperchloremic metabolic acidosis Serum amino acid imbalance Hyperammonemia Prerenal azotemia	Excessive chloride and monohydrochloride content of crystalline amino acid solutions Unphysiologic amino acid profile of the nutrient solution; differential amino acid utilization with various disorders Excessive ammonia in protein hydrolysate solutions; deficiency of arginine, ornithine, aspartic acid, or glutamic acid, or a combination of these deficiencies in amino acid solutions; primary hepatic disorder Excessive amino acid infusion with inadequate calorie administration; inadequate free water intake, dehydration	Administer Na ⁺ and K ⁺ as acetate salts Use experimental solutions if indicated Reduce amino acid intake Reduce amino acid intake; increase glucose calories; increase intake of free water
Calcium and phosphorus Hypophosphatemia Hypocalcemia Hypercalcemia Vitamin D deficiency; hypervitaminosis D	Inadequate phosphorus administration; redistribution of serum phosphorus into cells or bones, or both Inadequate calcium administration; reciprocal response to phosphorus repletion without simultaneous calcium infusion; hypoalbuminemia Excessive calcium administration with or without high doses of albumin; excessive vitamin D administration Inadequate or excessive vitamin D	Administer phosphorus (20 mEq potassium dihydrogen phosphate/1,000 IV calories); evaluate antacid or calcium administration, or both Administer calcium Decrease calcium or vitamin D Alter vitamin D administration
Miscellaneous Hypokalemia Hyperkalemia Hypomagnesemia Hypermagnesemia Anemia Bleeding Hypervitaminosis A Elevations in AST, ALT, and serum alkaline phosphatase	Potassium intake inadequate relative to increased requirements for protein anabolism; diuresis Excessive potassium administration, especially in metabolic acidosis; renal failure Inadequate magnesium administration relative to increased requirements for protein anabolism and glucose metabolism; diuresis; cisplatin administration Excessive magnesium administration; renal failure Iron deficiency; folic acid deficiency; vitamin B ₁₂ deficiency; copper deficiency; other deficiencies Vitamin K deficiency Excessive vitamin A administration Enzyme induction secondary to amino acid imbalance or to excessive deposition of glycogen or fat, or both, in the liver	Alter nutrient administration Alter nutrient administration Alter nutrient administration Alter nutrient administration Alter nutrient administration Alter nutrient administration Alter nutrient administration Reevaluate status of patient

ALT—alanine aminotransferase; AST—aspartate aminotransferase.

Table 12 Variables to Be Monitored during Intravenous Alimentation and Suggested Frequency of Monitoring

Variables	Suggested Monitoring Frequency	
	First Week	Later
Energy balance Weight	Daily	Daily
Metabolic variables		
Blood measurements		
Plasma electrolytes (Na ⁺ , K ⁺ , Cl ⁻)	Daily	3 × weekly
Blood urea nitrogen	3 × weekly	2 × weekly
Plasma osmolality*	Daily	3 × weekly
Plasma total calcium and inorganic phosphorus	3 × weekly	2 × weekly
Blood glucose	Daily	3 × weekly
Plasma transaminases	3 × weekly	2 × weekly
Plasma total protein and fractions	2 × weekly	Weekly
Blood acid-base status	As indicated	As indicated
Hemoglobin	Weekly	Weekly
Ammonia	As indicated	As indicated
Magnesium	2 × weekly	Weekly
Triglycerides	Weekly	Weekly
Urine measurements		
Glucose	Daily	Daily
Specific gravity or osmolality	Daily	Daily
General measurements		
Volume of infusate	Daily	Daily
Oral intake (if any)	Daily	Daily
Urinary output	Daily	Daily
Prevention and detection of infection		
Clinical observations (activity, temperature, symptoms)	Daily	Daily
WBC and differential counts	As indicated	As indicated
Cultures	As indicated	As indicated

* May be predicted from $2 \times \text{Na concentration (mEq/L)} + [\text{blood glucose (mg/dL)} \div 18]$.

drawn from a peripheral vein. If trained nurses have maintained the catheter and no evidence of infection at the exit site has been noted, the catheter dressing should not be removed, and the catheter should not be manipulated. Blood cultures should never be taken through the catheter. The one possible exception to this rule is the case in which the initial presentation of infection is characterized by marked hyperpyrexia, hypotension, or both. (In this case, contamination of the catheter is immaterial because the catheter will be removed.) If no other infectious focus is identified, the physician may elect to remove all indwelling lines, including the feeding catheter. In addition, either drainage around the catheter or a previous positive culture from the catheter exit site may warrant immediate removal. If another primary source of the infection is diagnosed, then specific therapy should be instituted, and parenteral nutrition should be continued. If no source of infection is identified, the catheter should be removed and the catheter tip cultured.

A dilemma arises if another source of infection is identified and if signs and symptoms of infection persist despite what appears to be appropriate therapy. If blood cultures are

positive, we favor removal of the catheter to prevent the complications that are associated with a contaminated indwelling catheter (e.g., septic emboli and endocarditis). If, however, peripheral blood cultures are negative, the catheter can be changed over a guide wire and the catheter tip cultured to confirm that no catheter infection exists. Central venous feeding can be continued during this interval. If the cultured catheter tip is positive ($\geq 10^5$ organisms), the catheter should be removed.

Changing the central venous catheter over a guide wire can aid in the diagnosis of primary catheter infection.¹⁹ Because most ICU patients have multiple potential sources for infection, this technique allows culture of the catheter tip but minimizes the risks associated with reinsertion of a new central catheter. Strict aseptic technique is used. The area surrounding the catheter entrance site is sterilized, the IV tubing is disconnected from the catheter, a guide wire is passed into the catheter, and the catheter is removed over the guide wire. A new catheter is inserted over the wire and sutured in place. The tip of the old catheter is cut, placed in a transfer vessel, and taken to the microbiology laboratory for semiquantitative culture. With strict care of catheters, the incidence of catheter infection should be less than 6%.²⁰ Bloodstream infection is most commonly caused by growth and invasion of organisms along the catheter tract. Occasionally, bacteria are infused through the catheter because of a breach in sterility during care of the infusion apparatus. The most common bacterial organisms causing catheter infection are the skin contaminants *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Candida albicans*. In some rare cases, the IV solutions may be contaminated. Moreover, most patients requiring central venous alimentation are immunocompromised hosts; their resistance is lowered further by disease, severe malnutrition, treatment, or some combination of these factors. Coexisting conditions (e.g., urinary tract infection, abscess, pneumonia, and mucositis secondary to chemotherapy) predispose these patients to bacteremia, which may contaminate the central venous catheter.

Immunosuppressed critically ill patients receiving multiple broad-spectrum antibiotics are also at risk for *Candida* bloodstream infection. Blood cultures positive for *C. albicans* in an ICU patient are an indication for catheter removal and treatment with fluconazole. An ophthalmologist should examine the eyegrounds of patients with proven candidemia to exclude the possibility of metastatic *Candida* ophthalmitis [see 8:19 Fungal Infection].

Home Nutritional Support

Home parenteral nutrition is indicated for patients who are unable to eat and absorb enough nutrients for maintenance. Most of the adult surgical patients who require home parenteral nutrition suffer from SBS caused by (1) extensive Crohn disease, (2) mesenteric infarction, or (3) severe abdominal trauma. Pseudo-obstruction, radiation enteritis, carcinomatosis, necrotizing enterocolitis, and intestinal fistulas are other indications for home nutritional support. Patients with these conditions cannot receive adequate nutrition enterally, though in some cases compensatory mucosal growth occurs that may either reduce or eventually eliminate the need for continued home parenteral nutrition.

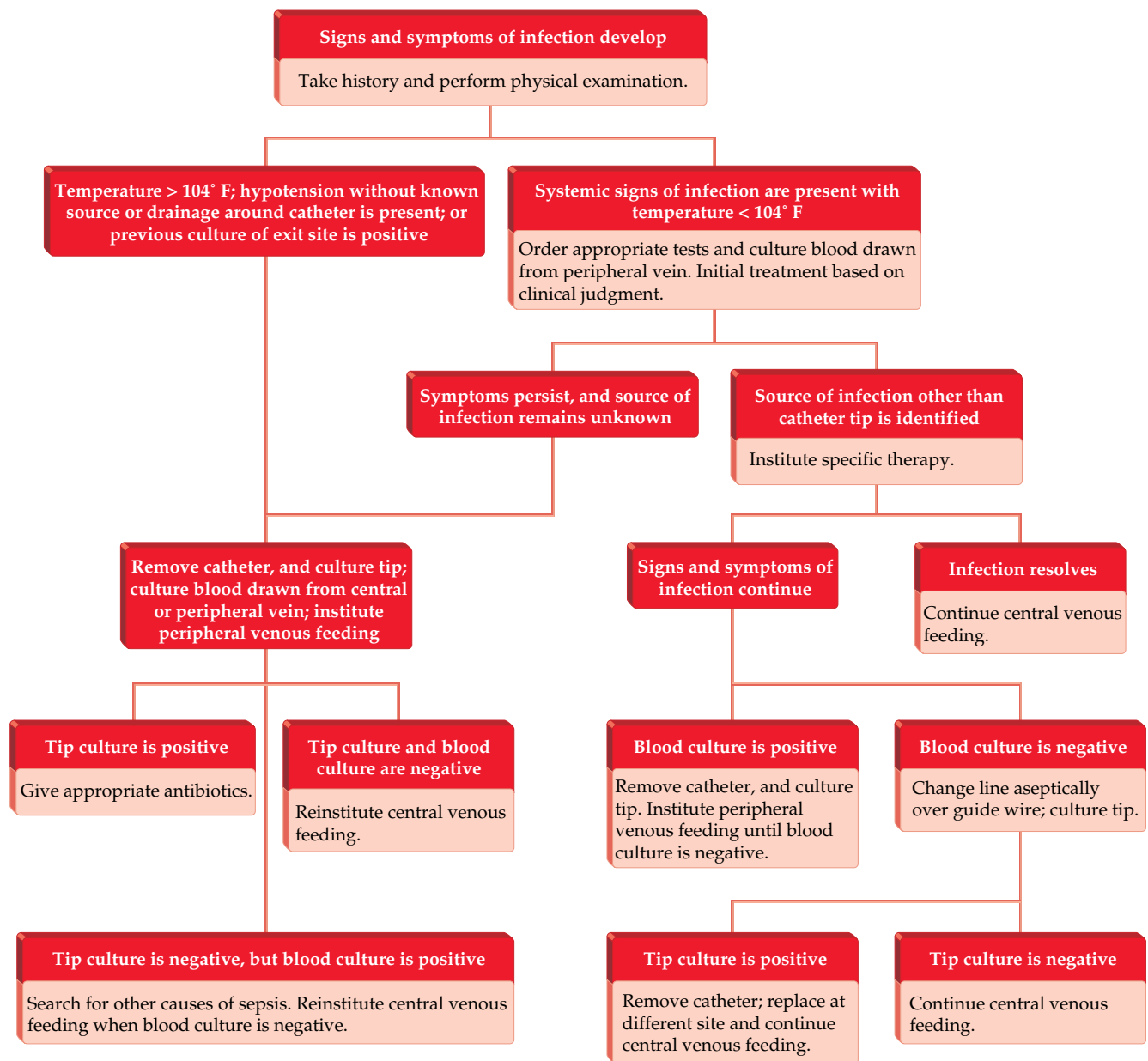


Figure 3 Shown is an algorithm for evaluating a febrile patient receiving central venous parenteral nutrition.

Patients must receive extensive evaluation, teaching, and training during hospitalization if home parenteral nutrition is to prove successful. These services should be provided by a team consisting of a physician, a nurse, a dietitian, a pharmacist, and a social worker. The team's instructions should be thorough and wide-ranging, covering the basic principles of parenteral nutrition as well as providing mechanical guidelines for catheter care, asepsis, and use of infusion pumps. Patients should be objectively evaluated before being discharged from the hospital to ensure that they have both an adequate understanding of the principles of IV nutrition and the technical ability to carry out home parenteral nutrition properly.

A patient who is judged by the nutrition support team to be a candidate for home TPN requires placement of a Silastic catheter designed for more permanent use than the central

venous catheter employed during hospitalization.²¹ The catheter is typically 90 cm long, with a thin 55 cm intravascular segment that is inserted either by venous cutdown into the internal or external jugular vein or the cephalic vein or directly into the subclavian vein by means of venipuncture. The intravascular portion of the catheter is cut so that its tip will lie at the junction of the superior vena cava and the right atrium. Placement of the catheter is carried out in the operating room by using local anesthesia (1% lidocaine) and adequate sedation. The catheter is tunneled subcutaneously from a small incision lateral to the sternum to the site of venous insertion. The catheter exit site is chosen on the basis of the patient's gender, physique, and hand dominance. In women, lower paraxiphoid or upper abdominal exit sites permit a more natural appearance. If the patient's coagulation status is abnormal, the cephalic vein is isolated in the deltapectoral

groove and tied distally, and the catheter is inserted proximally by means of venotomy. Otherwise, a percutaneous approach to the subclavian vein is taken. Proper positioning of the catheter is confirmed by fluoroscopy, and the incisions are closed with absorbable sutures. The catheter is sutured to the skin exit site, and the sutures are left attached for at least 2 weeks while tissue ingrowth into the Dacron velour cuff takes place. After the sutures are placed, sterile dressings are applied.

Calorie, protein, and fluid needs are carefully estimated for each patient, and the administration schedule is arranged so that the total volume may be infused nocturnally over 10 to 12 hours. Electrolytes, micronutrients, and trace minerals are added as indicated. Fat emulsions may be given either separately or admixed with glucose and protein and are used to reduce the requirement for dextrose calories and to prevent essential fatty acid deficiency.

The complications of home TPN are much the same as those of in-hospital TPN. They may be divided into four categories: mechanical, infectious, metabolic, and psychosocial. Mechanical complications, which are generally easy to remedy, include catheter occlusion and dislodgment and damage to the external portion of the catheter. Infectious complications that are superficial to the Dacron cuff usually respond well to antibiotics. Infections of the intravascular catheter may necessitate removal of the catheter after the diagnosis is confirmed by blood cultures obtained through the catheter, but the usual therapeutic approach is to initiate a trial of parenteral antibiotics. Metabolic complications related to individual nutrient deficiencies may be corrected by addition of the appropriate substance to the solution. The role of serum levels of trace minerals and micronutrients in the delineation of nutrient deficiency states remains unclear. In patients receiving insulin, hyperinsulinemia

after infusion may be prevented by reducing the rate of administration gradually over the last hour of infusion. Psychosocial complications may vary from slight depression to suicidal tendencies, which must be treated with appropriate counseling.

The costs of a home TPN program may also be divided into four categories: patient training, equipment, supplies, and follow-up. It has been estimated that the average annual cost of home TPN is 70% less than that of in-hospital TPN. The growth of private companies that deliver equipment and supplies to the home, maintain inventory, bill patients, and help with health insurance reimbursement has considerably facilitated home care.

Home enteral nutrition is frequently employed either as the sole source or as a partial source of nutritional support. It is the preferred method when GI tract function is adequate. In patients undergoing surgery of the aerodigestive tract for cancer, jejunostomy feedings can supplement oral feedings, especially during periods of adjuvant chemotherapy and radiation treatment. Patients are taught to cycle the feedings over 12-hour periods, using an enteral pump system to provide 20 to 30 kcal/kg/day. Use of an appropriate feeding tube and immediate flushing of the tube after use reduce the incidence of clogging at home. If blockage occurs, proteases or carbonated beverages can be introduced into the tube in an attempt to open it. Jejunostomy feedings reduce the risk of aspiration and help maintain nutritional status during periods of inadequate oral intake. Use of inexpensive nutritionally complete commercial formulas is encouraged. For patients who have more permanent disabilities that prevent adequate oral intake, a gastrostomy (or PEG [see 5:18 *Gastrointestinal Endoscopy*]) may be preferable. It reduces the GI complications of feeding by making use of the reservoir and admixing functions of the stomach.

Discussion

EVIDENCE-BASED NUTRITIONAL SUPPORT

Early Oral Feeding after Elective Operations

Anesthetics, prolonged bed rest, and fluid shifts make the intestine susceptible to ileus after most types of surgery, particularly after abdominal surgery. In the past, patients underwent gastric decompression with a nasogastric tube until they began to show obvious signs of bowel function. In recent years, however, several authors have questioned the necessity of postoperative nasogastric decompression that impedes early oral feeding. A study of 110 postoperative patients randomly assigned to receive either intraoperative orogastric decompression or postoperative nasogastric decompression found that patients in the latter group had more subjective complaints relative to the tube and more febrile morbidity, as well as longer times to passage of first flatus and tolerance of a diet.²² In another randomized study, 80 abdominal aortic aneurysmectomy patients had their nasogastric tubes either removed immediately upon tracheal extubation or left in place until passage of flatus. No intergroup differences were noted with regard to length of stay, time to

tolerance of a clear-liquid or regular diet, or necessity of replacing the nasogastric tube.²³

Other studies have suggested not only that nasogastric decompression is unnecessary but also that patients perhaps should be fed earlier than is traditionally practiced. In one study, 161 patients undergoing elective colonic or small-bowel resection without nasogastric decompression were randomly assigned to an early feeding group (clear-liquid diet on postoperative day 1, followed by regular diet as tolerated) or a traditional feeding group (nil per os [NPO] until passage of flatus).²⁴ The early feeding group was able to tolerate a regular diet earlier, without any increase in nausea or need for reinsertion of a nasogastric tube.²⁴ Two similar studies documented shorter hospital stays among patients who were fed early.^{25,26}

Traditionally, the initial diet given in the postoperative period has been either a clear-liquid diet or a full-liquid diet. Patients have generally been kept on these diets until they exhibit consistent flatus or pass bowel movements, then switched to regular diets. However, there is no evidence to suggest that this stepwise progression is justified or that this

approach leads to better outcomes. In fact, one randomized study of 254 patients who received either clear liquids (which were subsequently advanced to a regular diet) or a regular diet as the initial postoperative meal failed to show any significant differences in time to diet tolerance, complication rates, or hospital stays.²⁷

The use of opioids in the perioperative period (or, indeed, at any time when the patient is in pain) can have substantial deleterious effects on nutrition. Opioid-induced constipation can lead to lower abdominal discomfort, fecal impaction with diarrhea, nausea, and inadequate absorption of oral drugs. The resulting bowel dysfunction is attributable both to CNS-mediated alteration in autonomic flow to the gut²⁸ and to the direct local effect of opioids on the bowel.²⁹ Opioid receptor antagonists (e.g., naloxone and naltrexone) have the ability to reverse these changes, but this ability is limited by the inherent reduction in analgesia. Newer agents, such as methylnaltrexone (a quaternary derivative of naltrexone), are poorly lipid soluble, do not penetrate the CNS, and therefore do not antagonize the central effects of opioids.³⁰ A study involving healthy human volunteers demonstrated that IV methylnaltrexone could prevent opioid-induced delays in bowel motility without affecting analgesia.³¹ Such drugs may be particularly useful as adjunctive medications to minimize the side effects of opioids in those patients in whom their use is necessary.

Finally, early feeding has been combined with other therapies to enhance recovery [see 1:9 *Ambulatory and Fast Track Surgery*]. With the use of epidural anesthesia in conjunction with early oral feeding and an active exercise program, patients may experience much shorter periods of convalescent recovery and require less hospitalization.³²

ELECTRONIC ORDERING TO OPTIMIZE NUTRITIONAL SUPPORT

Nutritional care is often standardized in a hospital setting to optimize formula composition and delivery. An approach to nutritional prescription has been developed that may be reviewed at <<http://epen.kumc.edu>>.

PREOPERATIVE TPN

Multiple studies have been conducted to evaluate the effects of preoperative TPN, most of them involving patients with GI cancer who were considered to be at least moderately malnourished on the basis of weight loss, decreased plasma protein levels, or abnormal prognostic indices.³³ A pooled analysis of the data showed that patients who received preoperative TPN experienced 10% fewer postoperative complications than the control group did (i.e., the complication rate dropped from approximately 40% to 30%); in five studies, these differences reached statistical significance. The pooled analysis found no significant differences in mortality between the TPN groups and the control groups.

INTRAOPERATIVE TPN

Although intraoperative TPN has not yet been tested in clinical trials, our view is that it should be avoided. The stress associated with surgery and anesthesia results in hyperglycemia even without the infusion of dextrose. When infused during surgery, the dextrose in the TPN solution can elevate

blood glucose levels severalfold above normal values. These extreme levels of hyperglycemia have been associated with impaired immune function. Furthermore, experimental data has shown that hypotension or cardiac arrest during concentrated dextrose infusion results in more irreversible damage to the CNS.

POSTOPERATIVE TPN

Use of TPN in the immediate postoperative period without preoperative TPN has also been evaluated in multiple trials.³³ These studies included mostly patients with GI cancer who were considered to be at least moderately malnourished on the basis of weight loss, decreased plasma protein levels, or abnormal prognostic indices. In contrast to the pooled analysis of the preoperative data, a pooled analysis of the postoperative data showed that patients who received TPN after operation had an approximately 10% higher risk of ensuing complications (i.e., the complication rate rose from approximately 30% to 40%).

PERIOPERATIVE ENTERAL NUTRITION

Multiple trials have evaluated perioperative enteral nutrition, but the number of patients involved has been relatively small.³³ Two studies compared preoperative enteral nutrition with an ad libitum oral diet,^{34,35} and in one,³⁵ postoperative complication rates were significantly lower in patients who received enteral tube feeding. Other studies compared early postoperative jejunal tube feeding with a standard oral diet that was advanced as tolerated^{36–39}; no consistent differences in postoperative morbidity or mortality were identified. One study evaluated the use of postoperative jejunostomy tube feeding with a special formula enriched with arginine, ribonucleic acids, and omega-3 fatty acids after operation for upper GI tract cancer.⁴⁰ When only patients who were successfully fed were evaluated, those who received the enriched formula had fewer complications and shorter hospital stays than those who received the standard formula.

CANCER PATIENTS

Trials addressing perioperative nutritional support have been conducted in patients undergoing surgery for pancreatic, hepatocellular, GI, and head and neck malignancies. Many of those trials addressed the newer immunoenriched diets. In one, patients undergoing major pancreatic resection were randomly assigned either to a group that received TPN on postoperative day 1 or to a non-TPN group.⁴¹ No significant benefit from the use of adjuvant TPN could be demonstrated, and the incidence of complications (primarily those associated with infection) was significantly greater in the TPN group. It was concluded that routine use of postoperative TPN in patients undergoing major pancreatic resection for malignancy could not be recommended.

Another trial examined the effects of cyclic versus continuous enteral nutrition on postoperative gastric function after pylorus-preserving pancreaticoduodenectomy.⁴² Patients were evaluated with respect to gastric emptying, resumption of normal diet, and length of hospital stay. Nasogastric intubation was maintained for a shorter period in the enterally fed group than in the control group (6.7 days versus 9.1 days). The first day of normal diet came earlier for the enterally fed

group (12.2 days after operation versus 15.7 days). Hospital stay was shorter in the cyclic enterally fed group (17.5 days versus 21.4 days). It was concluded that cyclic enteral nutrition was clinically efficacious in this selected group of patients.

Studies using experimental models have shown that nutritional support reduces the catabolic response, improves protein synthesis, and enhances liver regeneration. One trial examined 64 patients who were randomly selected to receive perioperative IV nutritional support in addition to their oral diet, along with 60 patients (33 with cirrhosis, 12 with chronic active hepatitis, and 15 with no associated liver disease) who were randomly assigned to a control group.⁴³ The perioperative nutritional therapy consisted of an IV solution enriched with 35% BCAAs, dextrose, and a lipid emulsion (50% MCTs) that was given for 14 days perioperatively. Overall postoperative morbidity was lower in the perioperative nutrition group (34% versus 55%), mainly because the rate of infection-related complications was lower (17% versus 37%). These benefits were seen predominantly in patients with underlying cirrhosis who underwent major hepatectomy. It was concluded that perioperative nutritional support could reduce complications after major hepatectomy for hepatocellular carcinoma associated with cirrhosis.

An Italian study was designed to determine whether preoperative supplementation with a specialized diet improves outcomes in comparison with a standard formula.⁴⁴ In this study, 305 patients with a GI malignancy and preoperative weight loss were randomly assigned to three groups: (1) a group that received 5 days of preoperative oral supplementation and no postoperative nutritional support, (2) a group that received 5 days of preoperative oral supplementation with postoperative supplementation; and (3) a group that received no artificial nutrition before or after surgery. The results showed that preoperative nutritional support decreased the length of hospital stay and the incidence of postoperative infections.

A similar study done in China enrolled 468 malnourished GI malignancy patients and compared the outcomes of preoperative combined with postoperative nutrition with those of postoperative nutrition alone.⁴⁵ The results showed that the addition of preoperative nutrition decreased the duration of hospitalization and the incidence of postsurgical complications while also reducing mortality.

A study from Switzerland then addressed the question of whether the duration of preoperative nutrition was of any significance with respect to its effect on postoperative complications.⁴⁶ The investigators compared 2 days of a preoperative immunoenriched diet with 5 days of the same diet. They concluded that perioperative administration of an immunoenriched diet significantly reduces systemic perioperative inflammation and postoperative complications in patients undergoing major abdominal cancer surgery when compared to a postoperative diet alone; they also concluded that a 2-day preoperative feeding regimen is as effective as a 5-day regimen.

Patients with head and neck malignancies who undergo surgery have a high incidence of postoperative complications. A study was carried out to determine whether an arginine-enriched diet could improve outcomes.⁴⁷ In this study, 47 patients were randomly assigned to two groups, of which one received an arginine-based formula and the other a standard

formula. Fistulas were less frequent in the enriched-nutrition group. Wound infection was more frequent in the standard-formula group, but the difference was not statistically significant. The length of hospital stay was also shorter in the enriched nutrition group. It was concluded that enriched-formula diets improve local wound complication rates in postoperative head and neck cancer patients.

EARLY POSTOPERATIVE ENTERAL NUTRITION

A nonrandomized, uncontrolled study of 38 patients who underwent colorectal surgery over a 3-month period found that 31 of the 38 were able to tolerate an early feeding regimen.⁴⁸ Patients who tolerated early feeding had shorter postoperative stays (5.7 versus 10.6 days); those who did not had longer operative procedures and lost more blood intraoperatively. (Longer operating time and increased intraoperative blood loss may indicate a more difficult operation, which may in turn result in prolongation of recovery and decreased tolerance of early enteral feeding.) The investigators concluded (1) that early postoperative feeding is safe and is tolerated by the majority of patients and (2) that if early feeding is tolerated, it shortens hospital stay and may decrease health care costs.

In a study of 28 patients undergoing esophagectomy or pancreaticoduodenectomy who received either immediate postoperative enteral feeding via jejunostomy (13 patients) or no feedings during the first 6 days after operation (15 patients),⁴⁹ hand-grip strength, vital capacity, forced expiratory volume in 1 second (FEV₁), and maximal inspiratory pressure were measured before operation and on postoperative days 2, 4, and 6.⁴⁹ Postoperative vital capacity and FEV₁ were consistently lower in the fed group than in the unfed group, whereas there were no significant differences in grip strength and maximal inspiratory pressure. Postoperative mobility was lower in the fed group, and these patients tended to recover less rapidly. There were no significant differences in fatigue or vigor between the two groups. The investigators concluded that immediate postoperative jejunal feeding is associated with impaired respiratory mechanics and postoperative mobility and does not influence the loss of muscle strength or the increase in fatigue occurring after major surgery; they further concluded that immediate postoperative enteral feeding should not be routine in well-nourished patients who are at low risk for nutrition-related complications.

A 2005 study from Japan assessed 28 patients who underwent esophagectomy.⁵⁰ All of the patients received enteral nutrition immediately after the operation, but they were randomly assigned to two groups, of which one received a conventional enteral formula and the other a formula rich in omega-3 polyunsaturated fatty acids (PUFAs). The investigators found that early enteral nutrition with a large amount of omega-3 PUFAs resulted in reduced platelet aggregation, coagulation activity, and cytokine production. These effects would be expected to be beneficial in esophagectomy patients, but their clinical significance remains to be established.

A 1997 trial evaluated early enteral feeding after resection of upper GI malignancies.⁵¹ The purpose of the study was to determine whether early postoperative enteral feeding with an immune-enhancing formula could decrease morbidity, mortality, and length of hospital stay. A total of 195 patients with upper GI cancer were randomly selected to receive either

the immune-enhancing formula (supplemented with arginine, RNA, and omega-3 fatty acids) via jejunostomy or standard IV crystalloid solutions. There were no significant differences between the two groups with respect to the number of minor, major, or infectious wound complications; the length of the hospital stay; or mortality.

A similar study was published in 2005,⁵² involving 66 gastric cancer patients who were given early postoperative nutrition with either the immune-enhancing formula used in the previous study or a standard formula; the effect on the wound healing process was then examined. The investigators found that early postoperative enteral nutrition with a formula supplemented with arginine, omega-3 fatty acids, and RNA increased hydroxyproline synthesis and improved surgical wound healing in patients undergoing gastrectomy for gastric cancer.

Another trial investigated the effects of early postoperative enteral feeding in 43 patients with nontraumatic intestinal perforation and peritonitis.⁵³ After laparotomy, patients were randomly assigned to either a control group (22 patients) or a study group (21 patients). The study group received a feeding jejunostomy, and enteral feeding was started 12 hours after operation. Mortality was high in both groups (18% for the control group versus 19% for the study group). The control group had more septic complications than the study group (22 versus 8).

A 2008 study investigated early enteral feeding of septic patients with a pharmaconutrition supplement containing glutamine dipeptides, antioxidative vitamins and trace elements, and butyrate.⁵⁴ A total of 55 critically ill, septic patients from the adult ICU were enrolled. These patients received either an enteral supplement containing conditionally essential nutrients along with an immunoenriched formula or a standard formula. The study concluded that in medical patients with sepsis, early enteral pharmaconutrition with glutamine dipeptides, vitamin A and E, beta-carotene, selenium, zinc, and butyrate in combination with an immuno-enriched formula results in significantly faster recovery of organ function.

ICU PATIENTS

A meta-analysis of 26 relevant randomized clinical trials involving 2,211 patients cared for in ICUs demonstrated that the administration of parenteral nutrition did not reduce morbidity or mortality, though the data did suggest that there might be some benefit in the most malnourished groups of patients.⁵⁵ Therefore, use of this expensive therapy, which is often associated with complications if appropriate policies and procedures are not in place, should be reserved for ICU patients who have specific nutritional needs and cannot accept enteral feedings.

A 2002 study examined 60 ICU patients who were fed either via a nasogastric tube or via a nasojejunal tube.⁵⁶ The results led to the conclusion that gastric feeding is not associated with a higher incidence of aspiration or other adverse outcomes than small-bowel feeding is. In addition, gastric feeding can be started and advanced to the desired goal sooner and with fewer placement attempts than small-bowel feeding can.

CONCLUSIONS

Parenteral and enteral nutritional support is a valuable adjunctive—and sometimes life-saving—therapy in the management of selected types of surgical patients. It is generally agreed that patients who are unable to ingest adequate nutrients for a prolonged period require nutritional therapy to prevent the adverse effects of malnutrition. It is not entirely clear, however, precisely how “adequate” and “prolonged” should be defined. In practice, the definitions are likely to vary from patient to patient, depending on the amount of body energy stores and lean body mass, the presence or absence of preexisting medical illnesses, the number and severity of postoperative complications, and the nature of the surgical procedure. Summation of the data from numerous trials suggests that perioperative administration of immuno-enriched diets attenuates the perioperative inflammatory response and decreases postoperative infection complications. Severely malnourished patients (defined on the basis of percentage of body weight lost or nutritional risk index score) may derive greater clinical benefit from preoperative nutritional support, but this conclusion is based largely on retrospective analysis of prospective data. In addition, there are subsets of patients who may derive particular benefit from nutritional support, such as patients undergoing hepatic resection for hepatocellular carcinoma and elderly patients with hip fractures [see Guidelines, below]. The higher complication rates in patients given postoperative TPN and the case reports of small-bowel necrosis in patients who receive early postoperative enteral nutrition are evidence that nutritional support has risks and should not be given indiscriminately. Questions also remain as to the length of diet administration and the composition of the diet.

Nutritional Pharmacology and Immunonutrition

The role of nutrient administration to surgical patients has evolved from the maintenance of a positive energy and nitrogen balance to the use of nutrients to modulate tissue metabolism and organ system function. This new role is referred to as nutrition pharmacotherapy. Like other forms of adjuvant therapy, nutrition pharmacotherapy is usually a multitargeted therapeutic modality. For instance, one form of nutrition pharmacotherapy, immunonutrition, makes use of combinations of specific amino acids, fatty acids, and, in some enteral formulas, nucleotides. Another form, so-called bowel rehabilitation, uses an amino acid (glutamine) in combination with growth hormone and a modified diet. Inclusion of a specific nutrient as part of a plan of nutrition pharmacotherapy is based either on clinical studies or, more often, on extrapolations from experimental observations.

In what follows, we discuss each of the nutrients used, or proposed for use, in nutrition pharmacotherapy, with emphasis on chemical characteristics, physiologic effects, available forms for exogenous administration, and, if available, clinical data supporting its use for this purpose.

GLUTAMINE

Glutamine is the most abundant amino acid in the body and appears to be the most versatile. Most free glutamine is synthesized and stored in skeletal muscle, where

its concentration is 30 times greater than it is in plasma.⁵⁷ Skeletal muscle releases net glutamine for transport to the gut, immune cells, and the kidneys. The cells of the gut and those of the immune system proliferate rapidly, and glutamine acts as the main source of fuel and as a biosynthetic precursor. One of the compounds derived from glutamine is glutathione, a tripeptide (glutamate-cysteine-glycine) with potent antioxidant effects. Finally, glutamine participates in acid-base regulation via the release of ammonia, which combines with H^+ to form NH_4^+ and is lost in urine.

Catabolism induced by major injury, surgery, sepsis, or burns results in increased release of glutamine from skeletal muscle.⁵⁸ This output of glutamine into the circulation is associated with increased uptake and consumption by the gut, the immune system, the liver, and the kidneys. The net effect is a profound fall in intracellular muscle stores of glutamine. This deficit exceeds all other amino acid deficits and persists even when stores of all other amino acids have already been replenished.⁵⁹

Standard amino acid formulations have always included all of the essential amino acids and most of the nonessential ones. For a long time, glutamine was excluded from parenteral formulations because of its instability in aqueous solutions. As more knowledge of the potential benefits of glutamine became available, the pharmaceutical industry began to develop ways of keeping glutamine stable in an aqueous solution. For instance, Glamin (Fresenius Kabi, Bad Homburg, Germany), an amino acid formulation that is already commercially available in Europe, includes the dipeptide glycyl-L-glutamine, which is readily hydrolyzed to free glutamine in plasma and tissues. These dipeptide formulations are not yet approved for use in the United States.

Glutamine has been shown to promote the recovery of small-bowel and colon mucosa. In one human study, patients with high-output fistulas were given either TPN alone or TPN along with oral glutamine.⁶⁰ The multivariate regression analysis showed that resolution of the fistula was 13 times greater in the patients who received oral glutamine.

Several clinical studies addressing supplementation of parenteral formulas with glutamine have been published. The most striking results have been reported in patients undergoing bone marrow transplantation and in patients with SBS. The first randomized, double-blind, controlled study to investigate the effects of glutamine on metabolic parameters and clinical outcome in patients undergoing bone marrow transplantation was published in 1992.⁶¹ A total of 45 adults receiving allogeneic bone marrow transplants for hematologic malignancies were randomly selected to receive either L-glutamine, 0.57 g/kg/day, or a standard glutamine-free isonitrogenous formula for an average of 4 weeks after operation. The patients who received the glutamine-supplemented formula had a better nitrogen balance than the control group (-1.4 g/day versus -4.2 g/day); more important, they also had a lower incidence of microbial colonization and clinical infection and a shorter hospital stay. Subsequently, these findings were confirmed by a study performed by a different group of investigators.⁶²

One of the most challenging pathologic conditions for surgeons is SBS developing after massive small-bowel resection. Fortunately, the advent of parenteral nutrition has improved

survival for many patients with this condition who previously would have died of dehydration and malnutrition; however, it has also created a dependency on this therapy, which in the long term can have life-threatening complications. For this reason, many surgical scientists have searched for ways of augmenting these patients' intestinal absorption capacity so that their need for parenteral nutrition can be eliminated or at least greatly reduced. Having achieved a better understanding of the roles of glutamine, dietary fiber, short-chain fatty acids, and growth factors in the process of intestinal adaptation, investigators designed clinical trials with the aim of evaluating the effects of supplementation of these substances on patients with SBS.

In a randomized, double-blind, prospective multicenter trial, 41 SBS patients were given an optimal diet and then randomly selected to receive (1) oral glutamine (30 g/day) and placebo growth hormone, (2) placebo glutamine and growth hormone (0.1 mg/kg/day), or (3) both active agents.⁶³ The patients were weaned from TPN according to standard criteria based on daily measurements and laboratory values. At the end of 4 weeks, all subjects had lower IV nutrient requirements, with the glutamine-growth hormone group showing a greater reduction than the growth hormone group, which in turn showed a greater reduction than the glutamine group. These results demonstrate that specific growth factors and nutrients can be used to enhance nutrient absorption and adaptation after massive intestinal resection.

All of these studies were conducted according to research protocols that employed L-glutamine, which is not practical for IV use. As noted, glutamine is now commercially available (in Europe) in a dipeptide form that is stable in an aqueous solution. A recent meta-analysis of all the relevant studies involving IV glutamine showed that there was a significant reduction in postoperative infection associated with a decreased length of stay. In critically ill patients, there was a reduction in long-term (6-month) mortality, a finding that has not been recently associated with the administration of other specific nutrients.⁶⁴

ARGININE

Arginine is a nitrogen-dense amino acid that is considered a semiessential amino acid because it is required for growth.⁶⁵ The effect of arginine on growth seems to be mediated by its role in polyamine and nucleic acid synthesis. In addition, arginine is a potent secretagogue of growth hormone, insulin, glucagon, prolactin, and somatostatin.⁶⁶⁻⁶⁸ When the secretagogic effect of arginine is abolished by hypophysectomy, the stimulatory effect on wound healing is lost.⁶⁹ Supplemental dietary arginine has thymotrophic effects and enhances the responsiveness of thymic lymphocytes to mitogens in rats.⁷⁰ A similar response occurs in peripheral blood mononuclear cells of healthy human volunteers⁷¹ and postoperative patients,⁷² as evidenced by an enhanced response to concanavalin A and phytohemagglutinin.

Arginine enhances cellular immunity, as demonstrated by an increased delayed hypersensitivity response in animals with burns.⁷³ Dietary supplementation with arginine improves the response to dinitrofluorobenzene (DNFB) and enhances the survival of guinea pigs with burns on 30% of their BSA. In a model of acute peritonitis in guinea pigs, however,

supplemental arginine did not improve DNFB response or survival.⁷⁴

Studies using arginine in humans have yielded confounding results because the amino acid is often administered with other active substances (such as RNA and omega-3 fatty acids). However, oral arginine supplementation has been shown to enhance markers of wound healing in human volunteers.⁷⁵ Other small studies show that immunologic measures improve with both enteral and parenteral arginine administration.⁷⁶ Although this amino acid has shown antitumor properties in animals, the only relevant study done on humans to date demonstrated that supplementation stimulated growth of breast cancer.⁷⁷ Because there is currently some controversy over increased mortality in critically ill patients receiving arginine (see below), careful patient selection and full informed consent are essential when the use of this agent is planned.

NUCLEOTIDES

Purines and pyrimidines are precursors of DNA and RNA, which are essential for cell proliferation. Purines and pyrimidines are synthesized by the liver *de novo* from amino acids and reutilized by salvage pathways. Reduction of dietary nucleotides results in suppression of cellular immune responses and prolongation of allograft survival.⁷⁸ The mechanism of immunosuppression associated with nucleotide restriction seems to be an inability of T cells to undergo blastogenesis. Dietary supplements containing RNA or uracil (but not adenine) maintain resistance to infection by *C. albicans* or *S. aureus* in rodents.^{79,80} However, the immune response is not enhanced in comparison with a standard control diet.

On the basis of the immunosuppressive effect of dietary restriction of nucleotides, it has been postulated that nucleotide supplementation could provide an immunostimulant effect. This postulate has been tested in studies of the RNA–fish oil–arginine formula now available [see Enteral Formulations to Counteract Immunosuppression, *below*].

FATTY ACIDS

Fatty acids in the systemic circulation can be used in two forms: as fuels to be stored and oxidized as needed by the organism and as precursors for other essential compounds, such as eicosanoids (i.e., prostaglandins, leukotrienes, and thromboxanes). The eicosanoids are 20-carbon compounds derived from the essential fatty acids. They function as regulatory compounds in various physiologic processes, such as the immune response. Although organisms can oxidize other compounds to meet caloric needs, fatty acids in minimal amounts are essential as precursors for the synthesis of eicosanoids.

Fatty acids are classified in many different ways. One classification is based on chain length: short (two to five carbons), medium (six to 11 carbons), and long (12 to 26 carbons). Another classification is based on the presence of double bonds in the carbon chain: those with double bonds are called unsaturated and are further classified either as monounsaturated fatty acids or as PUFAs, depending on the number of double bonds. Another classification that has gained popularity is the omega classification, which indicates

where the first double bond is located when the carbons are counted from the noncarboxyl end of the chain (e.g., omega-3, omega-6, and omega-9).

Humans can synthesize only fatty acids with double bonds at position 7 (counting from the noncarboxyl end toward the carboxyl end). Therefore, fatty acids with double bonds at position 6 or position 3 must be supplied exogenously. Because humans can elongate and desaturate linoleic acid and α -linolenic acid to produce the remaining omega-6 and omega-3 PUFAs, these are considered the essential fatty acids. Providing 2% to 4% of total calories as fat prevents humans from developing essential fatty acid deficiency. The requirements for omega-6 PUFAs exceed the requirements for omega-3 PUFAs by a ratio of approximately 5:1.

PUFAs of the omega-6 series are abundant in vegetable oils, such as corn oil and soybean oil, and PUFAs of the omega-3 series are abundant in fish oils, such as menhaden oil. Other oils rich in omega-3 PUFAs are seed oils, such as black currant oil and canola oil (canola oil is derived from rape seeds and genetically modified to optimize the fatty acid composition).

The availability of 20-carbon PUFAs—arachidonic acid in the omega-6 series and eicosapentaenoic acid in the omega-3 series—is the determining factor for the synthesis of eicosanoids. There are two major metabolic pathways for the synthesis of eicosanoids. The cyclooxygenase pathway results in the production of prostanoids. Inasmuch as prostanoids contain two double bonds in the carbon side chain, they are also called dienoid products. These include prostaglandin E₂ (PGE₂), prostaglandin D₂ (PGD₂), prostaglandin F₂ (PGF₂), prostaglandin I₂ (PGI₂, also called prostacyclin), and thromboxane A₂ (TXA₂). The lipoxygenase pathway yields trienoic products (with three double bonds in the carbon side chain), such as thromboxane A₃ (TXA₃) and prostaglandin I₃ (PGI₃). All nucleated cells, with the exception of lymphocytes, can synthesize eicosanoids. Platelets are the major sources of thromboxanes, and the leukocytes mainly produce leukotrienes. Prostaglandins have various effects on the tone of blood vessels and the aggregation of platelets. Leukotrienes promote leukocyte migration (chemotaxis) and degranulation, release of lysosomal enzymes, and superoxide production.

Cells obtain arachidonic acid and eicosapentaenoic acid from degradation of phospholipids by phospholipase A₂ and phospholipase C or by elongation and desaturation of linoleic acid and α -linolenic acid. Mature immune cells, such as monocytes, macrophages, lymphocytes, and polymorphonuclear cells, lack D6 desaturase, the critical rate-limiting enzyme for transformation of 18-carbon PUFAs into 20-carbon PUFAs.⁸¹ Therefore, the availability of precursors for eicosanoid synthesis in immune cells depends largely on their lipid composition. Because lipid intake influences the lipid composition of immune cells, the type of PUFAs ingested can influence the immune response.^{82,83} Eicosanoids, especially PGE₂ and the lipoxygenase products leukotriene B₄ (LTB₄), 5-hydroxyeicosatetraenoic acid (5-HETE), and 15-hydroxyeicosatetraenoic acid (15-HETE), are immunomodulatory; when produced in excess (as in posttraumatic states), they are generally immunosuppressive.⁸⁴ Dietary supplementation with omega-3 PUFAs has improved survival of endotoxic shock in guinea pigs.⁸⁵ The reduced intake of

omega-6 PUFAs seems to be as important as the enrichment with omega-3 PUFAs. When animals are made deficient in linoleic acid, they have only a 24% mortality after endotoxin challenge; however, the mortality reaches 100% when arachidonic acid is given 2 days before endotoxin challenge.⁸⁶ Similar results have been reported in guinea pigs recovering from flame burns covering 30% of BSA.⁸⁷ When compared with animals fed dietary safflower oil (74% linoleic acid) or linoleic acid alone, animals fed fish oil had less weight loss, better skeletal muscle mass, lower resting metabolic expenditure, better cell-mediated immune responses, better opsonic indices, higher splenic weight, lower adrenal weight, higher serum transferrin levels, and lower serum C3 levels.

In conclusion, high intake of omega-6 PUFAs (e.g., linoleic acid) is associated with increased synthesis of PGE₂, which is immunosuppressive. A reduction in the intake of omega-6 PUFAs appears prudent in patients who are immunocompromised or in posttraumatic states. Dietary supplements with omega-3 PUFAs are associated with incorporation of eicosapentaenoic acid into leukocytes and with concurrent decreases in the incorporation of arachidonic acid. When these cells are challenged, there is significantly lower production of LTB₄, which exacerbates undesirable immune responses such as those seen in trauma and autoimmune diseases. Formulas for nutritional support should include omega-3 PUFAs, though the exact amount of omega-3 PUFAs and the precise ratio of omega-6 PUFAs to omega-3 PUFAs remain to be determined.

The fat emulsions currently available for IV use in the United States are made with LCTs derived either from soybean oil alone or from soybean oil and safflower oil. All of the fatty acids in LCTs are in the form of PUFAs, which include the essential fatty acids (i.e., linoleic and linolenic acids). As noted (see above), an excess of omega-6 PUFAs can have an immunosuppressive effect. Intravenously administered LCT emulsions are cleared in part through the reticuloendothelial system (RES).⁸⁸ When such emulsions are used as a calorie source, they may impair the ability of the RES to clear bacteria if given too rapidly or in excessively large amounts.

Moreover, the PUFAs in LCT emulsions require carnitine-mediated transport to cross the mitochondrial membrane for oxidation. Carnitine is a quaternary amine derived from two essential amino acids, lysine and methionine. During sepsis, urinary excretion of free carnitine rises significantly, and the plasma acylcarnitine level falls.⁸⁹ One way of circumventing these problems is to use emulsions that contain MCTs.

MCT-containing emulsions have long been used in enteral nutrition for their absorptive advantage over LCT-containing emulsions: whereas LCTs are absorbed via lacteals and the lymphatic system, MCTs are absorbed via the portal system. MCTs are obtained from coconut oil and contain saturated fatty acids (with octanoic acids predominating). Because MCTs are smaller than LCTs, they are more water soluble; they are also poorly bound to albumin and diffuse more easily across body compartments.

Several reports on IV administration of MCT fat emulsions have been published. One study evaluated the effect of a 75% MCT/25% LCT emulsion on RES function as demonstrated by technetium-99m-sulfur colloid (Tc-SC) clearance. Clearance of Tc-SC was significantly higher after 3 days of

MCT/LCT administration than after 3 days of LCT administration.⁹⁰ Another study investigated the metabolic effects of MCT-containing emulsions on surgical patients.⁹¹ The main finding of this study was the appearance of β -hydroxybutyrate in association with infusion of the MCT emulsion, which was indicative of a ketogenic effect. A tendency toward improved nitrogen balance was also observed but was not statistically significant.

In summary, specific fatty acids have significant potential for use in nutrition pharmacotherapy. Omega-6 fatty acids are potential immunosuppressants, whereas omega-3 fatty acids are potential immunostimulants. In the United States, the only emulsions commercially available for IV use at present are made of LCTs containing omega-6 fatty acids. MCTs offer some metabolic advantages over LCTs and obviate the side effects resulting from an excess of omega-6 fatty acids. Enteral diets containing omega-3 fatty acids appear to benefit stressed surgical patients, particularly those who are immunosuppressed as a result of therapy for cancer.

ENTERAL FORMULATIONS TO COUNTERACT IMMUNOSUPPRESSION

Impact (Sandoz Nutrition, Minneapolis, MN), a commercially available enteral formula enriched with omega-3 fatty acids, arginine, and RNA, was shown to reduce infectious complications in postoperative patients^{92,93} and in some critically ill patients.⁹⁴ Furthermore, it has been shown to reduce hospital stay in selected patient groups.⁹⁵ Concerns were raised, however, by data from a large meta-analysis of studies using these diets, which suggested that mortality was increased in patients exposed to these formulations.⁹⁶ The authors of the meta-analysis suggested that immunomodulation with the use of this diet may be beneficial in some patients (generally the less seriously ill) but may be harmful in others (generally the more critically ill patients who require nutritional support).⁹⁷ Until this issue becomes resolved, patient selection is extremely important if this diet is to be administered to surgical patients.

Guidelines

In 2002, the American Society for Parenteral and Enteral Nutrition (ASPEN) published an updated version of its guidelines for the use of nutritional support.⁹⁸ The following comprises brief excerpts from these guidelines.

GENERAL RECOMMENDATIONS

A nutrition screening incorporating objective data such as height, weight, weight change, primary diagnosis, and presence of comorbidities should be a component of the initial evaluation of all patients in ambulatory, hospital, home, or alternate care settings. A formal nutrition assessment should be carried out in any patient, independent of the care setting, who is identified by a nutrition screen as being nutritionally at risk.

Specialized nutrition support (SNS) should be used in patients who cannot meet their nutrient requirements by oral intake. When SNS is required, enteral nutrition should generally be preferred to parenteral nutrition. When SNS is indicated, parenteral nutrition should be used in patients whose GI tract is not functional or cannot be accessed and in

patients who cannot be adequately nourished by oral diets or enteral nutrition. SNS should be initiated in those patients whose oral intake has been inadequate for 7 to 14 days or in whom inadequate oral intake is expected over a 7- to 14-day period.

RECOMMENDATIONS FOR SPECIFIC DISEASE STATES

Cardiac Disease

Patients who have cardiac cachexia or experience complications after cardiopulmonary bypass are at nutritional risk and should undergo nutrition screening. In the cardiac surgery patient, enteral nutrition should be deferred until hemodynamic stability is achieved.

Pulmonary Disease

Patients with chronic obstructive pulmonary disease (COPD) or acute respiratory distress syndrome (ARDS) are at nutritional risk and should undergo nutrition screening. Energy intake should be kept at or below estimated needs in patients with pulmonary disease and demonstrated carbon dioxide retention. Routine use of modified carbohydrate and fat nutrition formulations is not warranted. Provision of a modified enteral formulation containing omega-3 fatty acids may be beneficial in patients with early ARDS. A fluid-restricted nutrient formulation should be used in patients with ARDS whose hemodynamic status necessitates fluid restriction. Serum phosphate levels should be monitored closely in patients with pulmonary disease.

Liver Disease

Patients with liver disease are at nutritional risk and should undergo nutrition screening. Nutrition assessment in patients with liver disease should include screening for deficiencies of micronutrients, including vitamins A, D, E, K, and zinc. Patients with cirrhosis should divide their meals into 4 to 6 meals per day, including a late evening snack. Protein restriction should be implemented for the acute management of overt hepatic encephalopathy. Protein restriction should not be implemented on a long-term basis in patients with liver disease. Use of BCAA-enriched diets and SNS formulas is indicated only in the setting of chronic encephalopathy unresponsive to pharmacotherapy. Perioperative nutritional support should be employed in patients undergoing liver resection for hepatocellular carcinoma associated with cirrhosis.

Renal Disease

Patients with renal failure are at nutritional risk and should undergo nutrition screening. Well-monitored patients who have advanced chronic renal insufficiency but are not on dialysis should receive diets restricted to 0.6 to 0.8 g protein/kg/day. Patients with chronic renal failure on hemodialysis or peritoneal dialysis should receive 1.2 to 1.3 g protein/kg/day. Patients undergoing continuous hemofiltration should receive at least 1.0 g protein/kg/day. Patients with acute renal failure should be given a balanced mixture of both essential and nonessential fatty acids. Patients with acute renal failure who are severely malnourished or hypercatabolic should receive 1.5 to 1.8 g protein/kg/day. Intradialytic parenteral nutrition should only be considered in the event of gut failure or other unusual circumstances where

enteral and parenteral nutrition are not feasible. Water-soluble vitamin supplementation is required for patients treated with dialysis. Vitamin A status should be carefully monitored in patients with chronic renal failure.

Pancreatitis

Patients with pancreatitis are at nutritional risk and should undergo nutrition screening. SNS should not be used routinely in patients with mild to moderate acute pancreatitis. SNS should be used in patients with acute or chronic pancreatitis to prevent or to treat malnutrition when it is anticipated that oral energy intake will be inadequate for 5 to 7 days. IV lipid emulsions are safe in acute pancreatitis, provided that triglyceride levels are monitored below 400 mg/dL.

Short-Bowel Syndrome

Patients with SBS are at nutritional risk and should undergo nutrition screening. Patients with SBS and an intact colon should receive diets rich in complex carbohydrates and low in fat. A low oxalate diet should be given to patients with SBS and an intact colon. Monthly vitamin B₁₂ injections should be given to patients in whom more than 100 cm of the terminal ileum has been resected.

Inflammatory Bowel Disease

Patients with inflammatory bowel disease (IBD) are at nutritional risk and should undergo nutrition screening. Enteral nutrition should be used in Crohn disease patients who require SNS. In cases of fistula associated with Crohn disease, a brief course of bowel rest and parenteral nutrition should be attempted. Perioperative SNS is indicated in patients with IBD who are severely malnourished and in whom surgery may be safely postponed. SNS and bowel rest should not be used as primary therapies for ulcerative colitis or Crohn disease.

Solid-Organ Transplantation

Patients in any stage of the transplantation process are at nutritional risk and should undergo nutrition screening. In the perioperative transplant period, patients should receive 1.5 to 2.0 g protein/kg/day. SNS should be provided to malnourished patients with complications or delayed oral intake after solid organ transplantation. Metabolic and nutritional complications of transplantation, including obesity, hypertension, diabetes mellitus, hyperlipidemia, and osteoporosis, should be treated with appropriate dietary and pharmacologic interventions.

Burns

Patients with second- or third-degree burns are at nutritional risk and should undergo nutrition screening. Adequate calories must be provided to address the hypermetabolism associated with acute thermal injury. When possible, the energy requirements of burn patients should be measured with indirect calorimetry. Severely burned patients require increased intake of protein until significant wound healing is achieved. There is no current role for the routine use of specific nutrients and anabolic agents (e.g., arginine, glutamine, omega-3 fatty acids, vitamins, trace minerals, antioxidants, growth hormone, and oxandrolone) in burn patients. Enteral nutrition should be initiated as soon as possible in patients with moderate to severe burns.

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Acknowledgments

Figure 2 Talar Agasyan.

23 CLINICAL PHARMACOLOGY

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Modern surgical care is dependent on the use of drugs, many of which can be harmful as well as beneficial. Polypharmacy is the norm, and, as a result, there is a high potential for adverse interactions between agents, including agents administered for anesthesia. In addition, surgical patients often exhibit alterations in drug metabolism, for various reasons. Overall, the incidence of drug-related adverse events in hospitalized patients is difficult to determine precisely because causality is often unclear. In one review, adverse drug events (defined as injuries caused by the use or nonuse of drugs) or adverse drug reactions (ADRs, defined as nonpreventable drug reactions resulting from the appropriate use of drugs) occurred in approximately 2 to 6% of hospital admissions.¹ These adverse occurrences increased the duration of hospitalization by 1.2 to 3.8 days and increased hospital costs by \$2,284 to \$5,640 per patient. A better understanding of pharmacokinetics, pharmacodynamics, and pharmacogenomics can help surgeons minimize the potential for harm associated with the use of pharmacologic agents.

Definitions of Key Terms

Pharmacokinetics may be defined in several ways. The word itself is a combination of the element *pharmaco-*, meaning “related to drugs” (from the Greek word *pharmakon*, “drug or poison”), and the word *kinetics*, meaning “the change in one or more variables as a function of time,” as Wagner succinctly put it.² In the discipline of pharmacokinetics, the variables in question relate to the time course and character of the body’s absorption, distribution, metabolism, and excretion of drugs.³ (These four processes are often collectively referred to by the abbreviation ADME.) Pharmacokinetics, then, can be thought of as the study of the actions of the body on a drug administered to it. The body’s pharmacokinetic handling of a drug depends on many factors, including the chemical characteristics of the drug, including chirality/different enantiomeric forms, dosage, route of administration, and the pharmaceutical preparation, as well as patient characteristics, including pathophysiologic alterations, comorbidities, and the effects of surgery and anesthesia.

Pharmacodynamics can be thought of as the study of the actions of a drug on the body. The variables in question relate to the time course and character of a drug’s effect at its site of action (i.e., at a receptor or another binding site). To ensure desired patient responses and prevent complications during the perioperative period, surgeons should possess a thorough understanding of both pharmacokinetics and pharmacodynamics.

Pharmacogenomics is a relatively new concept and is defined as the variability in pharmacokinetics and pharmacodynamics introduced by genetic variation within the

population. It has been estimated that 60% of ADRs to medications are associated with polymorphism in cytochrome P (CYP)-450 metabolizing enzymes.⁴ Not all variability is associated with toxicity. Examples of genomic-based effects on drug response include variability in: activation of prodrugs to active forms, conversion of administered drugs to active or inactive metabolites, receptor specificity to stereoisomers of drugs, and rapid inactivation of certain drugs. The goal of pharmacogenomic-based therapy is to individualize drug therapy to maximize therapeutic benefit while minimizing adverse drug reactions using a patient’s DNA profile.

Basic Pharmacokinetic Principles

ABSORPTION

Absorption is defined as the extent to which a substance moves into the systemic circulation from its site of administration. The pharmacokinetic parameter that is generally used to quantify drug absorption is bioavailability—that is, the fraction of an administered dose that becomes systemically available (often abbreviated as F). The bioavailability of a given drug in a given patient depends in large part on its route of administration. Inadequate bioavailability is a not uncommon cause of therapeutic failure but can be overcome in some cases by increasing the dose administered using the same route of administration or by changing the route of administration.

The absorption of a drug across any membrane or barrier is determined by blood flow to the tissue involved, the area of the membrane across which absorption occurs, and the solubility of the drug involved, which is affected by its relative lipophilicity, molecular size, and ionization status. In surgical or critically ill patients, regional blood flow may change, and diffusion across tissues may be limited by the presence of edema, inflammation, and tissue acidosis. As molecular size increases, diffusion decreases exponentially. The ionization of a drug can be estimated by means of the Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK}_a + \log(\text{base form/acid form})$$

where pH reflects the hydrogen ion concentration and pK_a represents the negative logarithm of the acid ionization constant. The ionized form of the drug is less lipid soluble; therefore, absorption across cell membranes by diffusion is less. For example, local anesthetics (which are weak bases) administered into or near inflamed areas or abscesses are not absorbed well into nerve membranes as they are protonated and thus less lipophilic. Some drugs may be actively transported across the cell membrane.

Routes of Delivery

Intravenous Many drugs, for example intravenous (IV) anesthetic agents and analgesics, are administered directly into the systemic circulation. IV administration, by definition, yields a bioavailability of 100%, rendering the process of absorption irrelevant. Systemic availability is most rapidly achieved when the drug is administered by IV bolus (also referred to as IV push). This mode of administration involves injecting relatively small volumes of drug directly into a vein, generally over a period of 1 to 5 minutes (although slower rates are sometimes called for and often preferred for some medications, e.g., vancomycin). Not surprisingly, there are many drugs that cannot be administered by IV bolus because of the potential for vein irritation and toxicity. With a few exceptions (e.g., propofol, dispersed in a lipid emulsion and lorazepam, solubilized in polyethylene glycol and propylene glycol), drugs are dissolved in aqueous solutions, sometimes with cosolvents such as propylene glycol and ethyl alcohol (e.g., phenytoin injection) for IV administration.

Many drugs that cannot be given as an IV bolus can be administered via IV infusion. Infusion may be either intermittent or continuous, depending on the drug's half-life or pharmacologic duration of action. Infusions can be administered via a peripheral vein or a central vein if the drug involved requires rapid dilution because of any irritative properties. For example, many antibiotics and IV anesthesia induction agents are administered via intermittent IV infusion. Drugs such as propofol, opioids, or dexmedetomidine in total IV anesthetic techniques or vasoactive agents such as dobutamine or norepinephrine in critical care settings are administered as continuous IV infusions. The flow rates used are dependent on the drug administered and patient response and vary widely. Use of precision IV infusion pumps is preferred when administering a continuous IV infusion.

Enteral Bioavailability is a critical consideration when a drug is being administered enterally because the rate and extent of absorption from the gastrointestinal (GI) tract need to be considered and will be altered by surgery, anesthesia, and comorbidities. The bioavailability of a drug after enteral administration depends on three major variables: the fraction of the dose absorbed across the apical cell membrane (i.e., the portion of the membrane bordering the intestinal lumen) into the cellular space of the enterocyte (f_a), the intestinal first-pass extraction of the drug (E_G), and the hepatic first-pass extraction of the drug (E_H). The relations among these factors may be described by the following equation⁵:

$$F = f_a \times (1 - E_G) \times (1 - E_H)$$

Most drug absorption after enteral administration occurs in the small intestine because of its large surface area. The value of f_a depends on several factors, including the dissolution rate of the drug formulation (for drugs given in a solid form, such as a tablet or capsule), gastric motility and emptying rate, and the solubility of the drug in GI fluids. Enteral feeding can also affect drug absorption. For example, tube feedings can impair absorption of phenytoin.⁶ Inflammatory bowel disease and low cardiac output states can reduce intestinal absorption by inducing edema. Drugs such as opiates and anticholinergic agents, anesthetics (e.g., neuraxial blockade), comorbidities such as gastroparesis, and the pathology

requiring surgery itself can affect intestinal motility. Poor motility can produce overgrowth of normal bowel flora, which can impair the absorption of some drugs. Postoperative nausea and vomiting affect absorption and preclude the enteral use of medication.

Once a drug molecule is absorbed through the intestinal cell membrane, it may be subject to intestinal first-pass metabolism by enzymes within the cells, as well as by efflux pumps embedded within the apical side of the cell membrane. Both CYP-450 and uridine 5'-diphosphoglucuronosyl-transferase (UGT) enzymes are found in the small intestine. These enzymes contribute to the metabolism of certain enterally administered drugs before they reach the systemic circulation and can exhibit genomic variability. Drugs whose oral absorption is significantly affected by the intestinal enzyme CYP3A4 include the immunosuppressive agents cyclosporine, tacrolimus, and sirolimus; calcium channel blockers such as diltiazem and verapamil; and some HIV protease inhibitors.

P-glycoprotein (Pgp) is a large protein that is the product of the multidrug resistance-1 (*MDR1*) gene. It is found on the apical membrane of enterocytes and acts as an efflux pump to remove exogenous substances.⁷ Pgp is found in many organs, including the kidneys, the brain (functions as part of the blood-brain barrier), the lungs, the liver, and the GI tract.⁸ Many clinically used drugs are Pgp substrates, including tacrolimus, sirolimus, cyclosporine, verapamil, diltiazem, digoxin, dexamethasone, and methylprednisolone; most Pgp substrates are also substrates for CYP3A4.^{9,10} The presence of the Pgp efflux pump keeps these drugs from undergoing enzymatic metabolism within the enterocytes. Some drugs are inhibitors or inducers of Pgp.

After a drug is absorbed into the intestine, it is transported to the liver via the portal vein. Variation is introduced by the effects of volatile anesthetic agents, hypovolemia, low cardiac output states, or cirrhosis, all of which tend to reduce portal vein flow. At this point, the drug may be subject to hepatic first-pass metabolism by enzymes within the liver. After passage through the liver, the drug, its metabolites, or both pass into the systemic circulation. If flow is reduced, then the risk for toxicity increases as less is metabolized or extracted. Drugs that are substrates of CYP2D6 and CYP3A4 are especially vulnerable to hepatic first-pass metabolism.⁶

Intramuscular Drug absorption after intramuscular (IM) injection is highly variable and depends on the properties of the drug molecule, the formulation, and the injection site. Because muscle is highly vascularized, drugs in aqueous solutions often are absorbed quite rapidly after IM administration (albeit more slowly than they are after IV administration). Any drug or condition that reduces blood flow to the muscle at the site of injection (such as volatile anesthetic agents, hypothermia, or shock) will decrease the rate of drug absorption after IM administration. Drugs in aqueous vehicles are absorbed more rapidly than those in lipid vehicles. In some cases, the slower absorption associated with lipid-based suspensions constitutes a practical advantage. For example, with certain medications (e.g., penicillin G benzathine, risperidone, and haloperidol), long-acting IM formulations are made by suspending the drug in a lipid vehicle specifically for the purpose of extending the duration of the therapeutic

effect to as long as 4 weeks. Some agents that use cosolvents for aqueous dispersion allow precipitation within muscle tissue and make IM absorption highly erratic (diazepam) and unreliable, as well as producing pain.

Subcutaneous In a subcutaneous injection, the drug is introduced into the connective tissue that lies underneath the dermal layer of the skin. This tissue is not as well vascularized as muscle. Consequently, a drug typically is absorbed more slowly after subcutaneous administration than after IM administration. Drugs commonly given via subcutaneous injection include insulin, unfractionated heparin (which, unlike most drugs, is rapidly absorbed via this route), and low-molecular-weight heparins (LMWHs). Generally, no more than 0.5 to 1 mL of a drug may be administered subcutaneously. Peripheral edema, inflammation, or hypoperfusion attributable to blood flow redistribution caused by volatile anesthetics, hypothermia, or shock may limit systemic absorption after subcutaneous injection.

Transdermal Although most topically administered drugs are meant to exert only local effects, some are meant to reach the systemic circulation. To be systemically distributed after topical application, drug molecules must pass through the stratum corneum and the epidermis to reach the blood vessels of the dermis. To traverse these outer layers of the skin, the molecules must be relatively lipophilic, low molecular weight, and nonionized. Drugs that are administered transdermally bypass both hepatic and intestinal first-pass metabolism and are absorbed continuously for as long as any available drug remains in the skin. Most transdermal patches are designed so that the rate of drug release is significantly slower than the rate of absorption through the skin, thereby permitting gradual and continuous absorption into the systemic circulation. Sometimes a loading dose is contained in the adhesive layer (as with the scopolamine patch for motion sickness or postoperative nausea and vomiting), allowing more rapid attainment of therapeutic blood levels. Examples of common transdermal formulations include the fentanyl patch, which releases the drug over a 72-hour period, and the clonidine patch, which releases the drug continuously for 7 days. Nitroglycerin paste is also used transdermally.

The main advantage of the transdermal method of administration is that it allows blood levels of a drug to be maintained at a desired level for a relatively long period without IV administration. One disadvantage is that after removal of the patch or other formulation, a residual amount of the drug may be left in the skin layer, and this residuum may continue to be absorbed into the systemic circulation even after therapy has been discontinued. Absorption may be limited by the same factors that limit IM or subcutaneous injections, as well as inflammation at the application site or the application of heat, which may actually increase the absorption rate.

Sublingual and transmucosal Some drugs (in particular those that are in a nonionized form and that exhibit high lipid solubility) are well enough absorbed via the oral mucosa that they may be given sublingually or simply dissolved in the mouth. This route of administration is especially advantageous for drugs that undergo significant hepatic first-pass metabolism when administered orally (e.g., nitroglycerin)

because when a drug is absorbed through the oral mucosa, it passes directly into the systemic circulation. Other drugs that are sometimes administered in this manner include buprenorphine and fentanyl.

Rectal Rectal administration of a drug may be convenient in clinical situations where (1) nausea and vomiting are present or enteral intake is restricted (e.g., before surgery), (2) IV administration is not desirable, and (3) the drug of interest is available in a suppository form. Unfortunately, drug absorption from the rectum is hard to predict and often incomplete. The rectum is drained distally by the systemic circulation and proximally by the portal circulation. From a pharmacokinetic standpoint, this means that a significantly large portion of a rectally administered dose will bypass the liver and reach the systemic circulation without undergoing hepatic first-pass metabolism.¹¹ Drugs available in rectal suppository form that are absorbed systemically include acetaminophen, aspirin, and the antiemetics promethazine and prochlorperazine. In addition, various drugs may be administered rectally with the intention of producing a local or colonic effect (e.g., anesthetic suppositories in patients with hemorrhoids, neomycin retention enemas in patients with hepatic failure, or antiinflammatory agents for ulcerative colitis).

Vaginal Vaginal administration of drugs is usually intended to produce local effects, except in the case of hormonal treatments (e.g., the vaginal contraceptive ring, the estradiol ring, and estradiol or progesterone creams), which are intended to have at least some degree of systemic absorption. An important consideration when prescribing topical vaginal products (e.g., antifungal agents) is the age of the patient. The pH of the vagina ranges from 3.5 to 4.2 in women of reproductive age, but it is either neutral or slightly basic in postmenopausal women and girls who have not yet reached puberty. These pH changes can alter the ionization state of antifungals such as ketoconazole. At an acidic pH, ketoconazole is protonated, but at a neutral or basic pH, it is nonionized and therefore able to cross the membranes of the vagina, undergoing unwanted systemic absorption and exerting undesired side effects, including the risk for drug interactions.

Nasal Most drugs that are administered nasally are topical agents employed to produce local effects, such as nasal steroids for environmental allergies. However, the nasal mucosa has much the same capacity for systemic absorption that the oral mucosa does: the area is highly vascularized, allowing rapid absorption of lipophilic and nonionized drugs. Currently, only desmopressin acetate (1-deamino-8-D arginine vasopressin, or DDAVP) and calcitonin are administered nasally for systemic therapy, although intranasal formulations of other drugs (e.g., insulin¹²) are in development. The mucosal membranes of the nose contain a number of drug-metabolizing enzymes, including CYPs, which may result in first-pass metabolism of certain drugs.

Inhalation The large surface area of the lung, the high permeability of the alveolar surfaces, and the highly vascular nature of lung tissue allow rapid systemic absorption of drugs,

especially those in gaseous form (e.g., inhaled general anesthetics). In terms of the onset of therapeutic effect, however, the partial pressure of these agents in blood and tissue is more important than the actual concentration.¹³ Inhalational anesthetics aside, most inhaled prescription drugs (e.g., β_2 agonists and corticosteroids for treatment of asthma and amphotericin B and tobramycin for treatment of lung infections) are designed to exert local effects on lung tissue. Systemic absorption does occur, but it is minimal and is partly attributable to swallowing of the drug during inhalation.

The pulmonary route of administration is also particularly effective at ensuring a high peak in drug concentration in the central nervous system (CNS). Currently, this property is used by cigarette smokers and users of cocaine, crystal methamphetamine, and even oxycodone. In the future, it may be used by developers of therapeutic drugs.

Nervous system In some situations, it is desirable to obtain therapeutic drug levels in the cerebrospinal fluid (CSF). However, under normal circumstances (i.e., in the absence of conditions such as inflammation and trauma), many drugs, especially those that are water soluble or ionized, have difficulty penetrating the blood-brain barrier. Even when a drug does cross this barrier and reach the brain, the choroid plexus may secrete it back into the blood, making it difficult to reach the desired drug levels in the CSF. To overcome this difficulty, certain drugs (typically local anesthetics or analgesics) may be injected into CSF or near the spinal canal in the vicinity of the nerve fibers that are to be blocked. Examples of this type of injection include spinal or epidural blocks. Paravertebral nerve blocks and nerve plexus blocks, such as brachial or lumbar plexus blocks, are placed into nerve sheaths surrounding these nerves outside the CNS. Systemic absorption does occur but is generally slow: it is not necessary for the therapeutic effect, and it may cause toxicity if large doses are used or if blocks are not placed with appropriate care.¹⁴ The vasoconstrictor epinephrine is sometimes administered along with a local anesthetic during a spinal, epidural, or peripheral nerve block because it decreases blood flow around the injection area, thereby reducing systemic absorption and prolonging the effects of the anesthetic. Epinephrine also acts on α_2 adrenoceptors on the nerve terminals to enhance the anesthetic effect by inhibiting the release of substance P and reducing nerve firing. Some chemotherapeutic agents are also directly placed into CSF, and other chemotherapeutic regimens purposefully disrupt the blood-brain barrier to allow passage of chemotherapy agents into the CNS.

DISTRIBUTION

While a drug is being absorbed into the systemic circulation, it may simultaneously be distributed into other physiologic fluids and tissues, depending on the physiology of the patient and the physiochemical properties of the drug. Patient variables that may affect distribution include body size, fluid distribution within the body, amount of adipose tissue, cardiac output, tissue blood flow, and levels of plasma proteins. Drug variables that affect distribution include lipophilicity, molecular weight, and affinity for plasma proteins and tissues. The distribution of a drug beyond the systemic circulation is typically described in terms of volume of distribution (V_d).

Termination of the clinical effect of some drugs, such as IV anesthetic induction agents, for example, propofol or sodium pentothal, rely on the phenomenon of redistribution from pharmacodynamically active sites to inactive sites. On IV administration, drugs are distributed to various tissues in proportion to the blood flow to these tissues. Seventy-five percent of cardiac output is distributed to the vessel-rich group of organs that comprise 10% of body weight, including the brain, heart, lungs, and kidneys. As tissue drug-binding sites in these areas are saturated, drug is distributed to less well-perfused organs, such as muscle, and to vessel-poor groups, such as fat, where they are considered to be pharmacologically inactive. When blood concentration of drug starts to decrease, they are eluted first from vessel-rich organs, terminating their pharmacologic action. Terminal elimination occurs via excretion and/or metabolism as drug is eluted from the less well-perfused sites.

Volume of Distribution

V_d is a pharmacokinetic parameter that relates the amount of a given drug in the body to the concentration of the drug in the area from which it was sampled (usually the bloodstream). It is not an actual physical volume; rather, it is estimated by means of pharmacokinetic techniques. There are several types of V_d parameters, the calculation of which depends on the route of administration of the drug and the pharmacokinetic model used to describe its disposition. V_d is usually expressed in liters and may range from a value approximately equivalent to blood volume (5 to 7 L), in the case of a drug such as warfarin, to values as high as 60 L/kg, in the case of amiodarone (which is extensively distributed to and readily binds to tissues outside the vasculature). In a clinical setting, V_d may be used to estimate the quantity of drug (A) needed to achieve a desired plasma concentration (C), as follows:

$$A = V_d \times C$$

Plasma Protein Binding

A number of commonly used drugs exhibit significant plasma protein binding [see Table 1]. Of the more than 60 different proteins that are found in plasma,¹⁵ three types are responsible for most instances of drug binding: albumin, α_1 -acid glycoprotein (AAG), and lipoprotein.

Albumin is a 66.3 kDa protein that comprises approximately 580 amino acid residues. It is made by the liver and broken down by the liver and reticuloendothelial system. Its half-life is approximately 19 days, and at any given point, 40% of the body's supply of albumin is circulating in plasma, with the remaining 60% located in interstitial fluid. The albumin molecule possesses two main drug-binding sites. The first site is called the warfarin-binding area, but it also binds other drugs, such as valproic acid, phenytoin, and sulfonamides. The second binding site is called the indole-benzodiazepine-binding area, which binds drugs such as certain penicillins and medium-chain fatty acids. Some drugs, such as the nonsteroidal antiinflammatory drugs (NSAIDs), bind to both sites. In addition to the main binding sites, separate binding sites for bilirubin, digitoxin, and tamoxifen have been discovered. Albumin binds mainly with weakly acidic (anionic) drugs, although it also binds with certain

Table 1 Commonly Used Drugs that Are Highly Bound to Plasma Proteins

Bound to albumin	Bound to AAG	Bound to albumin and AAG	Bound to albumin and lipoproteins	Bound to albumin, AAG, and lipoproteins
Ceftriaxone Citalopram Clofibrate Dexamethasone Diazepam Fluoxetine Fluvoxamine Ibuprofen Indomethacin Itraconazole Ketoconazole Ketorolac Losartan Mycophenolate Nafcillin Naproxen Paroxetine Phenytoin Prednisolone Sertraline Thiopental Tiagabine Valproic acid Warfarin	Diisopyramide Promethazine	Alfentanil Amprenavir Carbamazepine Clindamycin Erythromycin Fosphenytoin Lidocaine Lopinavir Meperidine Methadone Nelfinavir Olanzapine Ritonavir Saquinavir Verapamil	Amiodarone Cyclosporine	Amphotericin B Bupivacaine Chlorpromazine Diltiazem Felodipine Propranolol Quinidine

AAG = α_1 -acid glycoprotein.

basic drugs (e.g., benzodiazepines) and some neutral drugs (e.g., dexamethasone).

A few rare genetic polymorphisms are known to affect albumin levels or function. Certain disease states may induce alterations in the concentration or binding ability of albumin, such as cirrhosis, hepatic or renal failure, metabolic acidosis, or sepsis, thereby resulting in a higher free fraction of the drug (and thus an increased amount of drug available to exert pharmacologic or toxic effects) but, often, lower total drug concentrations as more drug is exposed to excretion mechanisms. In addition, drug displacement interactions may occur when a previously administered drug that is already bound to albumin is followed by a drug that has a higher affinity to the same binding site. Salicylates and sulfonamides are examples of drugs with high albumin-binding affinities that are capable of displacing other drugs from albumin-binding sites, thereby causing the unbound fraction of the displaced drug to increase. Nevertheless, the majority of displacements from binding sites on the albumin molecule result in the same free concentrations of the drug, although the total concentrations may decrease precipitously. In this situation, if the total concentrations are followed and the dosage is increased to achieve a specific total concentration, the increase in the unbound fraction that results from the drug interaction (or from a decreased albumin concentration caused by a disease state) may lead to toxicity. Because albumin levels can be low in patients with multiple comorbidities presenting for surgery, measurement of free drug levels is recommended if available.

AAG is an acute-phase protein that is both produced and metabolized by the liver. It is somewhat smaller than albumin (38 to 48 kDa) and has a half-life of 5 days. Approximately 60% of the body's supply of AAG circulates in plasma, with

the remaining 40% in interstitial fluid. AAG tends to bind basic drugs, such as local anesthetics, but it also binds some that are neutral or acidic. There are three known genetic variants of AAG, but it is unclear whether this variation is of any clinical significance. Low AAG levels can predispose patients to local anesthetic toxicity. Elevated AAG levels may lead to a decrease in the unbound fraction of a drug and thus to a reduction in the amount of drug available for pharmacologic activity.

The lipoproteins are a diverse group of proteins that vary significantly with respect to molecular weight, lipid content, and drug-binding affinity. Structurally, they comprise a lipid core made up of cholesterol and triglycerides, which is surrounded by an outer layer made up of phospholipids, cholesterol, and apolipoproteins. They are produced by the liver and the intestinal mucosa and are metabolized by the liver, the kidneys, and the intestine. Lipoproteins are classified into four groups: very low-density lipoproteins (VLDLs), low-density lipoproteins (LDLs), intermediate-density lipoproteins (IDLs), and high-density lipoproteins (HDLs). Of these, VLDLs, LDLs, and HDLs account for the bulk of lipoprotein drug binding. The most common mechanism by which drugs attach to lipoproteins is believed to be a non-saturable partitioning into the lipid core.^{15,16} Drugs that appear to exemplify this mechanism include cyclosporine,¹⁷ propranolol, digoxin, and tetracycline.¹⁵ Some drugs, however, such as propranolol and certain tricyclic antidepressants, are believed to bind to specific sites in a saturable manner.^{15,16} Lipoproteins may bind additional drug when albumin-binding sites become saturated.¹⁸

The amount of free (unbound) drug in plasma is considered the pharmacologically active fraction and is also the fraction exposed to mechanisms of elimination. Tissue and

plasma protein binding influence the apparent volume of distribution of a drug according to the following equation:

$$V_d = V_B + (f_B/f_T)V_T$$

where V_B is blood volume (0.07 L/kg), V_T is tissue volume, f_B is the unbound fraction of drug in the blood, and f_T is the unbound fraction of drug in tissue. For lipophilic drugs, tissue volume is calculated as total body water minus plasma volume (approximately 0.6 L/kg). For hydrophilic drugs, tissue volume is calculated as extracellular fluid minus plasma volume (approximately 0.13 L/kg). The degree of a drug's affinity for plasma proteins as opposed to tissue components is the main determinant of its volume of distribution. Changes in f_B , however, lead to changes in V_d only when a drug has a V_d of at least 30 L (i.e., when blood volume constitutes no more than a small fraction of the drug's total V_d).¹⁹

Uremia, cirrhosis, nephrotic syndrome, epilepsy, hepatitis, acidosis, sepsis, and various other disease states have been shown to decrease protein binding of drugs. Plasma protein binding is also reduced in pregnant women, neonates, and persons who have sustained severe burns. Accordingly, clinicians often assume that pregnant patients, newborns, or burn patients who are taking a highly protein-bound drug are automatically at risk for alterations in the unbound fraction of the drug; however, this assumption is not always valid.¹⁹ As noted (see above), V_d depends on several factors, including f_B , f_T , V_B , and V_T .

Increased binding of drugs to plasma proteins decreases the amount of drug available for diffusion into tissues, thereby limiting V_d . In contrast, increased binding of drugs to tissue proteins increases the apparent V_d . Increased protein binding also limits drug elimination because, for the most part, only unbound drug can be eliminated.

METABOLISM

With a few exceptions, drug metabolism (also known as biotransformation) consists of converting a lipophilic drug to a more hydrophilic metabolite, which is then more easily excreted by the kidneys. Metabolic reactions are generally divided into two phases: phase I reactions, which include oxidation, reduction, and hydrolysis, and phase II reactions, which include glucuronidation, sulfation, methylation, acetylation, and amino acid and glutathione conjugation.

From a clinical standpoint, the most important drug-metabolizing enzymes are the CYP enzymes. They are part of the microsomal mixed-function oxidase system and work in combination with CYP reductase, molecular oxygen, and reduced nicotinamide adenine dinucleotide phosphate (NADPH) to perform many of the phase I metabolic reactions. The CYP enzymes also help synthesize and metabolize endogenous substrates (including hormones) and break down nondrug xenobiotics (e.g., environmental pollutants). The liver, as the main metabolic organ of the body, contains more CYP enzymes than any other organ, but CYPs are also found in significant quantities in the small intestine, colon, kidneys, brain, lungs, heart, skin, nasal mucosa, heart, and eyes.

To date, 18 families of CYP enzymes and 42 subfamilies have been identified. These enzymes exhibit many genetic polymorphisms, some of which do not affect function, some of which restrict or enhance function, and some of which

Table 2 Common Substrates, Inducers, and Inhibitors of Cytochrome P-450

Substrates	Inducers	Inhibitors
Acetaminophen	Carbamazepine	Amiodarone
Caffeine	Cigarette smoke	Cimetidine
Cyclosporine	Dexamethasone	Ciprofloxacin
Diazepam	Ethanol (in chronic setting)	Diltiazem
Diltiazem	Isoniazid	Ethanol (in acute setting)
Fentanyl	Omeprazole	Fluconazole
Fluoxetine	Phenobarbital	Fluoxetine
Haloperidol	Phenytoin	Metronidazole
Midazolam	Rifampin	Omeprazole
Morphine		Propofol
Phenobarbital		
Phenytoin		
Tacrolimus		
Warfarin		

encode nonfunctional proteins. Particular polymorphisms may alter a person's ability to metabolize drugs. In addition, some persons have gene duplications that give rise to increased enzyme activity, which can render a drug ineffective because a therapeutic blood level is never achieved. These enzymes are also used as a therapeutic strategy in some cases to convert an inactive prodrug (formulated to improve bioavailability for example) to an active form in the body, as in proton pump inhibitors or clopidogrel. Thus, there is a great deal of interindividual variability dictated by genomic and other differences with respect to CYP-related metabolic capacity.

A number of common drugs are known to induce, inhibit, or serve as substrates for CYP [see Table 2]. Some of these drugs have multiple effects.

Other drugs, for example, succinylcholine and esteratic local anesthetic agents (such as procaine or tetracaine), are metabolized to inactive products by enzymes produced in the liver but circulate in the plasma (esterases such as pseudocholinesterase). Toxicity or prolonged action may occur as a result of low serum levels of these enzymes in severe hepatic failure. Other esterases exist in red blood cells and metabolize other drugs, such as esmolol.

ELIMINATION

Half-life

Half-life ($t_{1/2}$) is a pharmacokinetic parameter that represents the amount of time necessary for the amount or concentration of drug in the body to decrease by 50%. As a general rule, almost all (97%) of a drug will have been eliminated after five half-lives. For a first-order process, half-life is described by the following equation:

$$t_{1/2} = 0.693/k_e$$

where k_e is the elimination rate constant in inverse time units. It is important to remember that half-life should not be used as a measure of hepatic clearance or liver function, because it changes proportionately with clearance only when V_d remains constant.

Clearance of the drug [see Clearance, below] in volume units per unit of time (CL) and V_d are independent (albeit correlated) parameters that are related via k_e , as shown in the following equation:

$$CL = k_e \times V_d$$

Thus, k_e is equivalent to CL/V_d , which means that the equation for half-life (see above) can also be written as follows:

$$t_{1/2} = (0.693 \times V_d)/CL$$

Clearance

Clearance is an independent pharmacokinetic parameter that is defined as the volume of plasma, serum, or blood that is cleared of the drug per unit of time. The liver and kidneys are the organs primarily responsible for drug clearance. Clearance may be considered the most important of the pharmacokinetic parameters because it determines what the maintenance dose (MD) of a drug should be to achieve a desired steady-state plasma concentration (C_{pss}):

$$MD = C_{pss} \times CL$$

Renal Clearance

Renal clearance of drugs is the result of three processes: tubular secretion, tubular reabsorption, and glomerular filtration. The glomerular filtration rate (GFR) is generally considered the best overall indicator of kidney function. It may be determined through IV administration of a substance (e.g., inulin or iohalamate) that is freely filtered at the glomerulus but is not subject to reabsorption or secretion by the tubules. In a routine clinical setting, however, estimation of renal function by direct measurement of the GFR is impractical. A common alternative is to measure creatinine clearance (CrCL), which is generally accepted as a reasonably accurate estimate of the GFR (creatinine is filtered but also secreted to some extent) and therefore of renal function. This assumes constant production of creatinine by muscle and liver. A patient's urine is collected over a 24-hour period, and the concentration of creatinine in serum and urine is determined. CrCL is then calculated according to the following equation:

$$CrCL \text{ (mL/min)} = \text{rate of urinary creatinine excretion/serum creatinine concentration}$$

$$CrCL \text{ (mL/min)} = (U_{Cr}V \times 100)/(S_{Cr} \times 1,440)$$

where U_{Cr} is the urinary creatinine concentration (mg/mL), V is the volume of urine produced over a 24-hour period (mL), and S_{Cr} is the serum creatinine concentration (mg/dL) measured at the 12th hour (i.e., the midpoint) of the urine collection period.

For practical purposes, CrCL is usually estimated by applying any of a number of commonly accepted equations. The equation most frequently employed to estimate CrCL in patients with stable renal function is that of Cockcroft and Gault, which derives CrCL from the patient's age, ideal body weight (IBW), and S_{Cr} :

$$CrCL = [(140 - \text{age}) \times IBW]/(72 \times S_{Cr})$$

Because women have less muscle mass in relation to their body weight than men do, the value for CrCL in female patients is calculated by multiplying this equation by 0.85. The Cockcroft-Gault equation uses IBW rather than actual body weight because adipose tissue contains little, if any, muscle and therefore is believed to contribute little to the serum creatinine level; if actual body weight were used, CrCL might be overestimated.

It should be kept in mind that the various methods of estimating CrCL are necessarily imperfect, in that S_{Cr} may be abnormally high or abnormally low for reasons that have nothing to do with kidney function. For example, S_{Cr} may be decreased in elderly, bedridden, amputees, or wheelchair-bound patients (because of the loss of muscle mass), and it may be elevated in patients with increased muscle mass, those who have recently undergone strenuous exercise, trauma patients, and even persons who consume high quantities of red meat. Liver dysfunction can affect the accuracy of CrCL estimates by decreasing the conversion of creatine to creatinine.

Unbound drugs of low molecular weight are readily filtered by the glomeruli. The ionized fraction is then excreted. The nonionized fraction, however, can be reabsorbed by renal tubules and is typically metabolized by the liver to the ionized form. With some drugs, reabsorption is dependent on pH; consequently, when these drugs cause toxicity, manipulation of urinary pH to increase their elimination can be a useful therapeutic measure. Secretion of drugs into the renal tubules is an active process that is not particularly specific. Thus, drugs may compete with each other or with endogenous substrates for tubular secretion, and toxicities may result.

Metrics Reflecting Magnitude of Drug Exposure

AREA UNDER THE CURVE

Area under the curve (AUC) is a pharmacokinetic parameter that reflects the extent of a drug's bioavailability—that is, it reflects the total amount of active drug that reaches the systemic circulation after administration. The AUC is usually calculated from the actual area under a curve generated by plotting plasma concentrations of an administered drug over a period of time (whether from time 0 to infinity or from one dose to the next). For drugs exhibiting linear (i.e., first-order) kinetics, the AUC is proportional to the dose administered. With some drugs, however, this may not be the case at higher dosages, because drug elimination pathways may become saturated.

PEAK PLASMA CONCENTRATION

Peak plasma concentration (C_{max}) is a pharmacokinetic parameter that quantifies the highest level reached in the plasma after administration of a drug. Knowledge of C_{max} may be advantageous in certain situations. For example, some antibiotics (e.g., aminoglycosides) depend on a high C_{max} rather than on sustained drug levels for their bactericidal effects. Other drugs may cause toxicity if C_{max} reaches inappropriately high levels. C_{max} is expressed in units of concentration (e.g., $\mu\text{g/mL}$ or mg/L). It may be calculated in several ways. Which equation is used depends on the route of administration of the drug and the model used to describe its disposition.

TIME OF PEAK PLASMA CONCENTRATION

Time of peak plasma concentration (T_{max}) is simply the time at which the maximum plasma concentration is reached after extravascular drug administration. As such, it is also an indication of the time of peak drug absorption, at which absorption and elimination (expressed in mass units per time unit) are equal. Comparison of T_{max} between two extravascular

dosage forms allows determination of relative absorption rates. $T_{\max}$ decreases as the absorption rate increases.

Fundamental Pharmacokinetic Concepts

COMPARTMENTAL PHARMACOKINETIC MODELING

As the study of pharmacokinetics has progressed, various models for the disposition of drugs in the body have been proposed. Many of these models portray the body as a collection of spaces with volumes and elimination rates (clearance rates). These spaces, commonly referred to as compartments, are not actual anatomic realities, although they may have characteristics that are very similar to those of true anatomic spaces. They represent conceptual adaptations of monoexponential or multiexponential concentration versus time curves, in which the curves are converted to virtual spaces that have specific finite volumes and elimination rates.

The simplest compartmental model is the one-compartment model. This model assumes that the body is a single homogeneous unit in terms of a particular drug's pharmacokinetic profile. It therefore also assumes that the drug is instantaneously distributed throughout the compartment after administration. Obviously, this assumption is purely theoretical and, from a practical standpoint, impossible. Nevertheless, the one-compartment model adequately describes the disposition of many drugs that are rapidly distributed in the body. A concentration time profile that has a monoexponential character in the decline (see below) is often characterized as a one-compartment model. It is important to remember that the signal characteristic of the one-compartment model is not that the actual drug concentrations are the same in all body tissues as in blood or plasma (which is not necessarily the case) but that the rate at which drug or metabolite levels change is constant throughout the entire body.

Elimination from a compartment may be assumed to be a first-order or linear process. In a static first-order process, a constant proportion of the drug is eliminated over a given unit of time. The first-order elimination rate constant k (or k_e) is a proportionality constant that relates clearance to V_d . It is expressed in reciprocal time units (i.e., hr^{-1} or min^{-1}) because it is derived by dividing a rate (the volume from which all material is removed per unit of time, expressed in L/hr) by a volume (V_d , expressed in liters). The overall clearance of a drug is the sum of the clearances attributable to all of the routes by which the drug may be eliminated (e.g., $\text{CL} = \text{CL}_{\text{renal}} + \text{CL}_{\text{hepatic}} + \text{CL}_{\text{biliary}} \dots$); the precise value depends on the particular elimination pathways that are open to the drug. If a drug has nonlinear elimination characteristics, clearance will constantly change in conjunction with concentration.

As noted (see above), in a one-compartment model, whereas the rate of change in the drug concentration may be the same in all body tissues, the actual drug concentrations in particular tissues may be different from each other and from those in blood or plasma. The usual assumption, however, is that the ratios between tissue concentrations and plasma concentrations are constant. This assumption then leads to the further assumption that the relation between plasma concentration and the total amount of drug in the

body is also constant. The relation between these two factors is represented by the volume of distribution term V_d .

For many drugs, distribution can be more accurately described by employing a multicompartment model, which incorporates both a central compartment (as in the one-compartment model) and one or two (or, in rare cases, more than two) peripheral compartments. These peripheral compartments may represent more poorly perfused tissues of the body that have a different affinity for the drug. Peripheral compartments are hypothetical constructs in that the actual drug concentrations in tissues are not known, but their presence is often assumed on the basis of plasma concentrations measured over time after an IV bolus. When a concentration-time curve is plotted on a semilogarithmic graph after injection of an IV bolus, a drug that follows a one-compartment model shows a linear decline [see Figure 1a], whereas a drug that follows a two-compartment model shows two distinct phases, a distribution phase and an elimination phase [see Figure 1b]. The drug does not switch from one phase to the other in an on-and-off fashion; rather, the two phases predominate at different stages of drug disposition after administration.

The first phase of the two-compartment concentration-time curve, the distribution phase, primarily reflects the distribution of the drug from the vessel-rich group of tissues of the central compartment into the more poorly perfused tissues of the peripheral compartment. During this phase, the drug concentration in the peripheral compartment gradually increases until it reaches a maximum. At this maximum peripheral tissue concentration, the rate of drug input into the tissue is equal to the rate of drug output from the tissue, and the portion of drug in the central compartment is in equilibrium with the portion of drug in the peripheral compartment. This point in time is termed distribution equilibrium. After this point, the drug amounts in the central and peripheral compartments decline at similar rates, and the kinetics of the drug begin to resemble those of a one-compartment model.

The second portion of the concentration-time curve, the elimination phase, reflects the passage of the drug from the body. It is usually assumed that drug elimination occurs via the central compartment. This assumption is based on the observation that most drugs are eliminated mainly via the liver or the kidneys, both of which are highly perfused organs that are usually included in the central compartment.

The rate constants describing the rate of transfer between compartments in a two-compartment model are often referred to as microconstants because they cannot be determined by direct measurement; however, they can be estimated from a logarithmic graph of plasma concentration versus time after an IV bolus [see Figure 2]. Plasma (or central compartment) drug concentration (C_{central}) may be related to time by means of the following equation:

$$C_{\text{central}} = A e^{-at} + B e^{-bt}$$

where e is the base of the natural system of logarithms and A and B are intercepts on the y axis for each segment of the concentration-time curve. The hybrid constants A and B have no real physiologic significance, but they are useful for solving this equation as a sum of exponentials. The terms a and b represent the first-order rate constants for the distribution phase and the elimination phase, respectively. As may be seen from the concentration-time curve [see Figure 2],

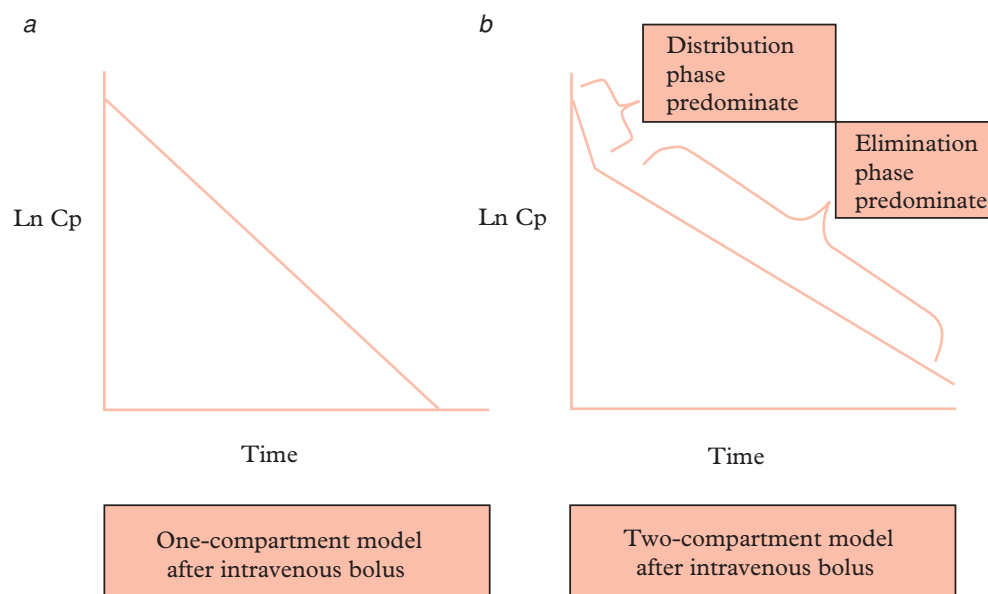


Figure 1 Depicted are (a) one-compartment and (b) two-compartment pharmacokinetic models. C_p = plasma concentration.

the decline in drug concentration is steeper in the initial (distribution) phase than in the second (elimination) phase.

Many agents are eliminated in a nonlinear manner (so-called zero-order elimination), and their elimination half-life lengthens as the dosage increases [see Figure 3]. This phenomenon is usually attributable to saturation of the enzyme systems responsible for metabolizing the drug. Such saturation can cause changes in the metabolite profile. When there is saturation of elimination, the area under the concentration-time curve ceases to be proportional to drug exposure, and the AUC does not increase linearly with increasing doses (as it does with first-order kinetic processes).

Saturable GI absorption may occur with drugs such as gabapentin, baclofen, and riboflavin, and saturation of intestinal metabolism may occur with propranolol. In addition, saturable plasma protein binding may occur with drugs such

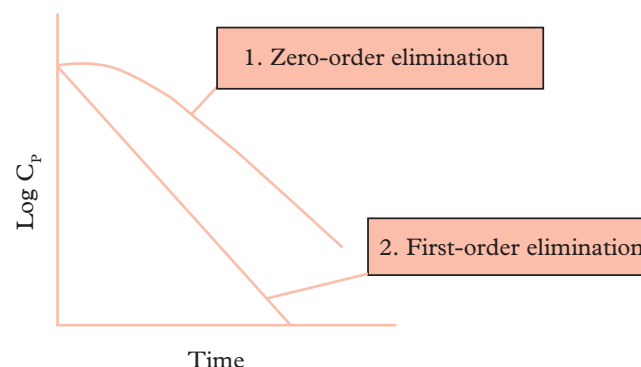


Figure 3 Plotting of plasma concentration against time illustrates the difference between zero-order (saturable) drug elimination and first-order elimination.

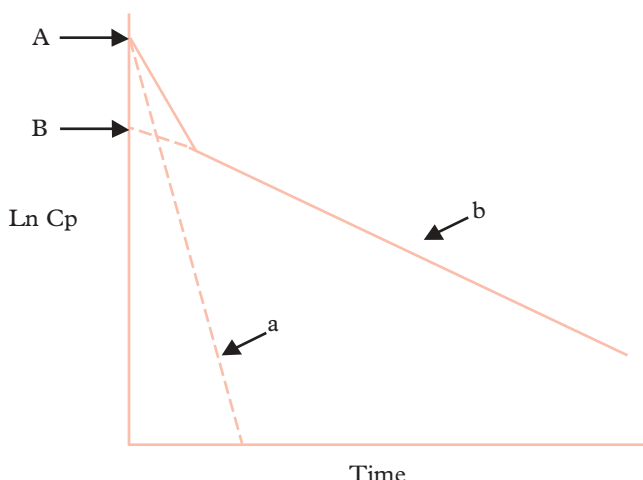


Figure 2 In a two-compartment model of pharmacokinetics, plasma concentration can be estimated by using intercepts A and B and microconstants a and b.

as lidocaine, ceftriaxone, warfarin, disopyramide, and phenytoin. Saturable tissue transport may occur with drugs such as methotrexate.¹⁸ The most clinically relevant zero-order processes, however, are those related to hepatic metabolism. Two drugs with narrow therapeutic indices whose metabolism follows zero-order kinetics are the antiepileptic medications phenytoin and valproic acid.

A drug with saturable elimination will, at a large enough dose, demonstrate a disproportionately large increase in AUC with a dose increase once the saturation point of the elimination system is reached. The term Michaelis-Menten kinetics is used to describe elimination of drugs by saturable enzymatic processes. The standard Michaelis-Menten equation for estimating the elimination rate (V) is as follows:

$$V = V_{\max} C_p / (K_m + C_p) = dC_p / dt$$

where $V_{\max}$ is the maximum metabolic rate of the enzymes, C_p is the plasma concentration, and dC_p/dt is the rate at which C_p changes over time. When $V_{\max}$ is reached, a constant

amount of drug is eliminated per unit of time, and elimination is truly a zero-order process. K_m , the so-called Michaelis constant, is a reflection of the metabolizing capacity of the enzyme system. It is equal to the drug concentration in the body when V is one half of V_{max} . This equation is appropriate at a wide range of drug concentrations because if C_p is much larger than K_m , the enzymatic processes become saturated, K_m can be considered negligible and drops out of the equation, and V is approximately equal to V_{max} .

PHYSIOLOGICALLY BASED PHARMACOKINETICS

A very useful pharmacokinetic modeling approach that is sometimes employed as an alternative to compartmental modeling is physiologically based pharmacokinetics (PBPK). PBPK is similar to compartmental modeling in that spaces are represented as instantaneously mixing compartments. However, it differs from classical compartmental modeling in that the compartments in a PBPK model are constrained to the actual space occupied by a particular tissue or organ. In addition, tissues are connected not by first-order rate constants or clearances but directly by blood flows originating in the arterial circulation and emptying into the venous system (with the exception of the lungs) [see Figure 4]. Drugs introduced into the vascular system circulate and are delivered to various tissues. Within tissues, any sort of transfer may be specified, from instantaneous transfer with a partition coefficient to linear or nonlinear transfer to or from a tissue space or within tissue subspaces. A great advantage of PBPK is that it permits modeling of tissue-specific concentrations and time courses of concentration changes. This advantage is especially important if the desired drug action depends on exposure within a particular space.

Pharmacodynamics

The discipline of pharmacodynamics aims to define the relation between pharmacokinetics and response to the drug.

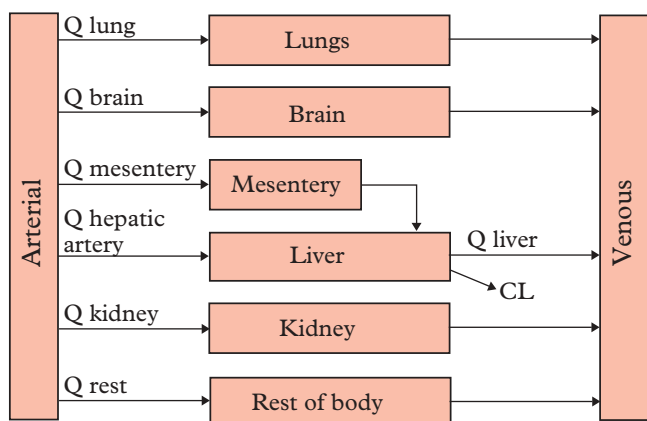


Figure 4 Shown is a schematic structural depiction of physiologically based pharmacokinetics (PBPK). In PBPK, unlike standard one- or two-compartment modeling, the compartments are restricted to the actual spaces occupied by particular tissues or organs. In this example, elimination occurs as clearance from the liver. Q = blood flow. CL = clearance.

PBPK modeling is very useful for capturing effect-site concentrations that can be linked to a particular drug effect. Effect-site concentrations are not directly measurable in clinical situations, but estimating such concentrations can help distinguish distributional effects that cause a dissociation between observed plasma concentration and physiologic response from tolerance-type or sensitization-type responses that occur at the site of action. With sensitization, a plasma concentration observed early in the exposure profile evokes a lesser response than the same concentration observed later (i.e., the patient becomes more sensitive to the drug). This development is often seen as a counterclockwise hysteresis when the drug's concentration is plotted against its effect over time. With tolerance, a concentration observed early in the exposure profile evokes a greater response than the same concentration observed later (i.e., the patient becomes tolerant to the drug). This development is seen as a clockwise hysteresis when concentration is plotted against effect over time.

BASIC PHARMACODYNAMIC MODELS

The linear-response pharmacodynamic model, as its name suggests, describes the relation between drug concentration (whether in plasma, in a particular compartment, or at the biophase) and physiologic response as a linear one [see Figure 5]. The general form of this model is as follows:

$$\text{Response} = \text{baseline} + (\text{concentration} \times \text{response factor})$$

The maximum-response model determines the relation between concentration and response on the basis of the maximum response (E_{max}), the concentration at which 50% of E_{max} is observed (EC_{50}), and, optionally, other factors (e.g., exponents applied to both E_{max} and EC_{50} that modify the steepness of the response). This model may also be modified to take into account the baseline response [see Figure 6]. The general form of the maximum-response model is as follows:

$$\text{Response} = (E_{max} \times \text{concentration}) / (EC_{50} + \text{concentration})$$

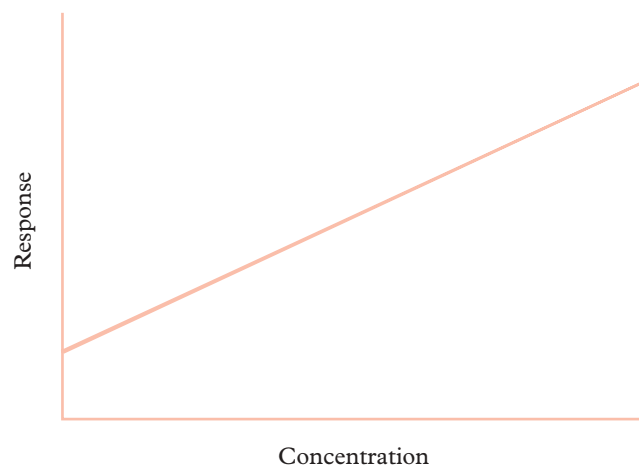


Figure 5 Illustrated is the linear-response pharmacodynamic model, in which the relation between drug concentration and physiologic response is a linear one.

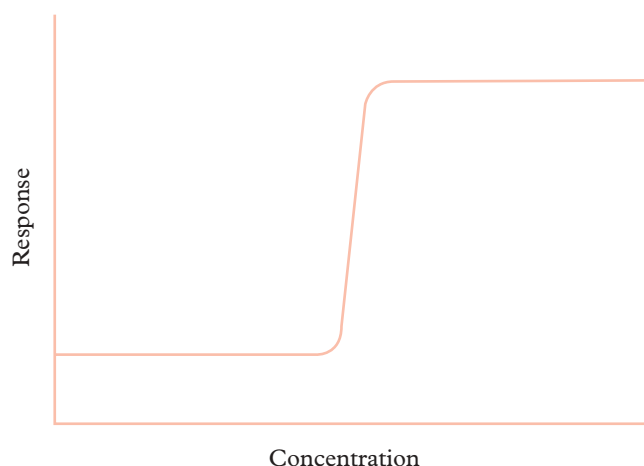


Figure 6 Illustrated is the maximum-response pharmacodynamic model, in which the relation between drug concentration and physiologic response is a nonlinear one that is determined by the maximum response ($E_{\max}$), the concentration at which 50% of $E_{\max}$ is observed (EC_{50}), and, sometimes, other factors.

Indirect-response models may be used to describe systems in which there is either constant production or constant elimination of the drug effect. In addition, however, the drug concentrations observed will have an impact on the elimination or production of the drug effect.

Concentration of drug at the receptor site is not the only factor involved in physiologic response. Drug-receptor interaction is required for cellular response to occur and may occur on the surface of the cell or intracellularly. This interaction sets in motion a cascade of molecular events that produces response. Receptor interaction with drugs is necessarily three-dimensional and introduces the concept of chirality to these interactions. Most drugs are manufactured as racemic mixtures, which are 50:50 mixtures of R and S stereoisomers. Usually, one of the isomers is much more physiologically active than the other. For example, most of the action of warfarin is based on receptor binding of the S-isomer. Some drugs are now produced as a single stereoisomer, such as esomeprazole (S-isomer of omeprazole), escitalopram (S-isomer of citalopram), and ropivacaine. Indeed, ropivacaine and levobupivacaine are formulated as single isomers to reduce the cardiac toxicity of local anesthetics because they are bound less avidly to cardiac tissue.

PHARMACOGENOMIC PRINCIPLES

The human genome contains approximately 3 billion base pairs, with around 35,000 coded genes. Polymorphism occurs in greater than 1% frequency. Polymorphism is caused by several types of mutation in DNA structure. Single nucleotide polymorphism (a change in sequencing from one base pair to another), alteration in sequencing (such as insertion, deletion, or inversion of base pairs), and duplication of single base pairs or segments of base pairs are responsible for encoding variant messenger RNA (mRNA) and, subsequently, non-wild-type proteins. Abnormal amounts of normal proteins can be produced in some variants. These proteins

form drug receptors, transporters, and enzymes, which ultimately determine pharmacokinetic and pharmacodynamic interaction.

A common example of polymorphism that partly explains wide variation in therapeutic response to a drug involves the vitamin K antagonist warfarin. Warfarin inhibits the enzyme VKORC1 (normally responsible for the carboxylation and activation of vitamin K and ultimately the active coagulation factors II, VII, IX, and X), which produces anticoagulant effects. Polymorphism produces variants of VKORC1 that alter its function and, subsequently, its anticoagulant activity. Another genetic alteration producing abnormal response to warfarin involves the CYP-450 metabolizing enzyme 2C9, which is normally responsible for inactivation of warfarin. The above pharmacokinetic alterations may by themselves or in interplay cause underresponse and thrombosis or overresponse and bleeding. The ability to test for these polymorphisms would allow more precise dosing and monitoring in warfarin therapy and, ultimately, the prevention of ADRs. A test does exist at this time, but the time to perform the test, as well as cost issues, limits its present use. Future advances in genetic testing will allow for more precise and safer drug therapy. Ultimately, patients would have a DNA profile done that would dictate not only dosage but also the actual choice of agent for any diagnosis.

Genetic polymorphism may also explain pharmacodynamic differences. For example, there are single nucleotide polymorphisms that encode different variants of the β_2 adrenoreceptor in the lung, which determine the degree of response or nonresponse to β_2 agonists in the treatment of bronchospasm.

Physiologic Factors that Alter Pharmacokinetics and Pharmacodynamics

For the most part, the pharmacokinetic and pharmacodynamic modeling methods used to determine dosing regimens are based on study data from normal subjects. For this reason, they may not be applicable to surgical patients without some modification. Such patients often have significant physiologic derangements that alter drug metabolism. If these physiologic derangements are not considered, patients may be at risk not only for drug toxicity and adverse events but also for inadequate drug response.

ORGAN SYSTEM DYSFUNCTION

Renal

Acute or chronic renal dysfunction can have pronounced effects on drug disposition, not only because of impaired excretion of drugs and metabolites eliminated by the kidneys but also because of other disease-induced physiologic alterations. Drugs themselves, such as antibiotics (aminoglycosides, vancomycin), NSAIDs, or IV contrast media, can cause renal dysfunction, especially when a concurrent insult to the kidneys occurs, such as surgical blood loss or sepsis. The degree of impairment is proportional to the decrease in the GFR. If the patient becomes oliguric, the GFR can be less than 10 mL/min. In surgical or critically ill patients, renal function may deteriorate rapidly. This is most commonly attributable to hypovolemia, blood loss, or hypotension produced by

volatile anesthetics or neuraxial anesthesia, causing renal hypoperfusion (and not intrinsic renal failure unless uncorrected). This is known as prerenal failure. Because actual measurement of the GFR is usually impractical, estimation of the GFR, based on serum and/or urine creatinine level and urine output is commonly used. In addition to lowering the GFR, renal failure reduces tubular excretion. The transport systems in the renal tubules may become saturated, further decreasing drug elimination and increasing the serum levels of the drug involved.

Other aspects of renal failure can affect pharmacokinetics. Renal failure may reduce gastric acid secretion, thereby decreasing the absorption of some drugs, and may inhibit hepatic metabolism, thereby decreasing the first-pass extraction and increasing serum drug levels.

Edema formation as a result of intrinsic renal failure or congestive heart failure and decreased plasma protein levels may have complex effects on V_d and $t_{1/2}$. Although V_d tends to be increased, decreased plasma protein binding may raise unbound drug levels and increase potential toxicity. The higher unbound drug concentrations may actually proportionally increase drug excretion as more drug is filtered, thereby reducing $t_{1/2}$.

Great care should be taken in administering drugs that are mainly excreted by the kidneys and have significant toxicity or a narrow therapeutic range. Typically, the initial loading dose is unaltered, but subsequent dosing should be based on estimates of the GFR. If possible, drug levels should be monitored. The timing of monitoring depends on the expected $t_{1/2}$. Trough drug levels are often used. Particular caution should be exercised with drugs whose levels or physiologic effects cannot be reliably monitored in a clinical setting (e.g., LMWHs). These drugs should be avoided in patients with significant renal impairment.

For patients who require renal replacement therapy, drug clearance varies from agent to agent. Intermittent hemodialysis and continuous renal replacement therapy can have substantial and varying effects on clearance. Knowledge of clearance rates can greatly facilitate the planning of dosing regimens.

Hepatic

The effects of hepatic dysfunction on pharmacokinetics are complex and difficult to predict. In general, hepatic impairment must be severe to have a significant direct effect on drug metabolism. It must be kept in mind, however, that hepatic dysfunction frequently leads to some degree of renal impairment, even in the absence of overt hepatorenal syndrome. Hypoperfusion induced by reduced hepatic artery or portal vein perfusion induced by blood loss, third spacing, hypovolemia, sepsis, cirrhosis, volatile or IV anesthetics, or neuraxial anesthesia superimposed on preexisting hepatic dysfunction or hepatitis, as well as exposure to hepatotoxic drugs, may convert mild or occult hepatic dysfunction to severe hepatic dysfunction.

How hepatic dysfunction affects the metabolism of a given drug is determined by how readily the drug is normally extracted by the liver (i.e., how high the extraction ratio is). For drugs with high extraction ratios (e.g., morphine and labetalol), hepatic extraction is dependent on hepatic blood flow. If blood flow is decreased as noted above, bioavailability

increases and elimination decreases, leading to a prolonged $t_{1/2}$ and increased C_p . For drugs with lower extraction ratios (e.g., diazepam and warfarin), decreased protein binding and reduced metabolism by hepatic enzymes have a greater effect on pharmacokinetics. Decreased protein binding is common in surgical patients, whether from decreases in total proteins (especially albumin) in cachectic, malnourished, or chronically ill patients or displacement of drugs from proteins by endogenous substances in sepsis, acidosis, or other drugs. The end result of decreased protein binding is an increase in the level of unbound, active drug, which leads to an increased potential for toxicity or prolonged effect.

Because there is no readily available method for measuring hepatic function, it is difficult to predict the impact of hepatic dysfunction on the pharmacokinetics of a given drug. Any attempt at such a prediction must begin with a high index of suspicion that hepatic function has deteriorated to the point where it may affect pharmacokinetics. Drug dosing must then be carefully planned on the basis of the estimated severity of the dysfunction. In practice, clinicians often do not consider the possibility that hepatic dysfunction is affecting pharmacokinetics until the patient exhibits signs of decreased drug metabolism (e.g., high sensitivity to opiates used for pain, prolonged sedation with benzodiazepines, slow recovery from propofol infusion, etc.).

Cardiac and Pulmonary

The major effects of cardiac dysfunction on pharmacokinetics can be attributed to hypoperfusion and organ ischemia, venous congestion, or both. Reduced gut perfusion and congestion can hinder absorption of enterally administered drugs. Hypoperfusion can also affect absorption via the intramuscular, subcutaneous, or transcutaneous route. Accordingly, to ensure appropriate systemic drug levels, the IV route is preferred. With many hydrophilic drugs, congestion and increased total body water can lead to an increase in V_d . With lipophilic drugs, however, V_d may be unaffected or even reduced.

The effects of cardiac dysfunction on renal and hepatic blood flow may result in diminished elimination of drugs. Hepatic congestion occurring as a result of right heart failure secondary to chronic pulmonary disease tends to have more severe adverse effects on hepatic function than it does on renal function. It is important to keep this difference in mind when administering drugs that are predominantly metabolized in the liver. Hemodynamically active agents (e.g., anesthetics, inotropes, vasopressors, and afterload reducers) or diuretics can have a significant impact on renal and hepatic blood flow and function.

Mechanical ventilation can exacerbate the effects of congestion and hypoperfusion because increased intrathoracic pressures reduce venous return to the right heart. This is especially true in patients with bronchospasm, interstitial lung disease, chronic obstructive pulmonary disease, or pulmonary emboli. The resulting venous congestion from the liver and kidneys can cause hepatorenal dysfunction and affect drug excretion. Hypoventilation (inducing respiratory acidosis), hyperventilation (inducing respiratory alkalosis), and hypoxemia all can induce changes in drug distribution, ionization, protein binding, and excretion, as well as electrolyte disturbances, which may affect the pharmacodynamics of drugs.

Systemic inflammatory responses, as in sepsis, trauma, or postoperative stress, can redistribute organ blood flow, causing organ thrombosis, ischemia, and acidosis, thereby affecting drug metabolism.

AGE

Renal function (specifically, the GFR) varies significantly with age. In neonates, the normal value for the GFR is only 2 to 4 mL/min, compared with a normal adult value of more than 100 mL/min. Over the 6 months following birth, however, the GFR increases to a level approximately twice the normal adult level and then slowly decreases. Consequently, many drugs may have a shorter $t_{1/2}$ in children than in adults. Hepatic function, particularly with regard to drug metabolism, follows a similar pattern in the first few months of life: an increase to supra-adult levels followed by a slow decline.

Gastric emptying is slower in neonates than in adults, and gastric acidity is lower as well; both of these differences may affect absorption of enteral medications. In addition, neonates have lower plasma protein levels, which may alter V_d . Common medications whose pharmacokinetics may be different in the pediatric population include antibiotics, narcotics, benzodiazepines, and anticonvulsants.

Increasing age leads to substantial changes in drug pharmacokinetics. Elderly persons have 10 to 15% less total body water than younger persons do, as well as a higher proportion of body fat and 20 to 30% less lean body mass. These changes in body composition can affect V_d . Renal function decreases with age, resulting in decreased clearance of many drugs. Intrinsic hepatic function is usually well preserved, although blood flow to the liver may diminish.

NUTRITIONAL STATUS

Severe malnutrition, as in critically ill, chronically ill, or cancer patients, leads to a relative increase in total body water as fat stores are depleted, as well as to a decrease in plasma protein levels. V_d increases, and the GFR decreases. Hepatic clearance of drugs is reduced, particularly in cases of protein malnutrition. Consequently, $t_{1/2}$ increases, thereby increasing the risk of drug toxicity. These abnormalities resolve with adequate nutritional support.

Obesity also can have significant effects on pharmacokinetics. To assess the potential implications, it is useful to compare total body weight (TBW) to IBW. IBW is calculated as follows:

Men: 50 kg + 2.3 kg for each 1 in. of height over 5 ft

Women: 45.5 kg + 2.3 kg for each 1 in. of height over 5 ft

For persons shorter than 5 ft, 2.3 kg is subtracted for each 1 in. below this height.

Because of the increased body fat in obese patients, lipophilic drugs can be distributed into and sequestered in adipose tissue. This effect becomes more pronounced with increasing lipid solubility. Deposition of drugs in fat increases V_d but also increases $t_{1/2}$. For highly lipophilic drugs (e.g., older volatile anesthetics, IV barbiturates, propofol, synthetic or semisynthetic opioids, and benzodiazepines), the doses required to achieve the desired effect may be quite high. For

hydrophilic medications, dosing adjustments generally are not necessary. Some agents, however, are relatively hydrophilic but are still distributed into fat stores to some extent. Ciprofloxacin is an example of such a drug; its partial absorption into fat has led many to recommend that the dose be based on 45% of TBW in addition to IBW. The initial dose of gentamicin should be increased by as much as 40% because of the risk of an increased V_d .

FLUID RESUSCITATION

Aggressive fluid resuscitation, as is performed after trauma or a major surgical procedure, increases interstitial and intracellular volume, as well as plasma volume, and reduces plasma protein levels. Third spacing attributable to peritonitis, burns, sepsis, and inflammation contributes to the need for fluid resuscitation. Consequently, V_d is significantly increased for many drugs.²⁰ The concentration of a drug can be estimated on the basis of the relative quantity of fluid sequestration and the degree of reduction in serum albumin concentration. Underdosing of medications is common in patients who have undergone aggressive fluid resuscitation.

Drug Dosing

INITIAL DOSING

In deciding on the initial dosing of a drug, particularly in the acute care setting, it is essential to strike a balance between the risk of causing toxicity, on the one hand, and the risk of failing to achieve therapeutic efficacy because of underdosing, on the other. For example, there is ample evidence that inadequate dosing of antibiotics in patients with pneumonia can lead to therapeutic failure.²¹ The relative risks for any particular drug can be determined by considering the therapeutic index for that agent. The therapeutic index is approximated as follows:

$$\text{Therapeutic index} = LD_{50}/ED_{50}$$

where LD_{50} is the dose that would cause death in 50% of cases and ED_{50} is the dose that would be effective in 50% of cases. If there is any overlap between the range of effective doses and the lowest lethal dose for a given drug (i.e., if the risk of death is substantial even in the drug's therapeutic range), it is worthwhile to consider the drug's standard margin of safety. This parameter is defined as follows:

$$\text{Standard margin of safety} = LD_1/ED_{99}$$

where LD_1 is the dose that would cause death in 1% of cases and ED_{99} is the dose that would be effective in 99% of cases. For drugs with a narrow margin of safety, it is critical to monitor their levels whenever possible [see Drug Level Monitoring, *below*]. These metrics (i.e., standard margin of safety and therapeutic index) are confounded if the slopes of the concentration effect and concentration toxicity relationships are different.

A common way of achieving therapeutic drug levels is to administer a loading dose. The size of the loading dose can be calculated on the basis of V_d , desired plasma concentration, and bioavailability:

$$\text{Loading dose} = (V_d \times C)/F$$

As noted (see above), F (i.e., bioavailability) equals 1 if the drug is administered intravenously. If there is concern about potential toxicity, the drug dose may be given over a prolonged period (e.g., a phenytoin load over 1 hour) or divided into smaller doses and given over an even longer period (e.g., a digoxin load over 24 hours). The optimal dosing interval for the maintenance doses is often close to the drug's expected $t_{1/2}$.

The goal of maintenance dosing is to achieve a steady-state plasma concentration that is within the therapeutic range. Generally, this goal is reached after five half-lives of the drug. From this point on, the amount of drug administered with each dose is equal to the amount of drug eliminated between doses. The steady-state plasma concentration may be approximately calculated from the drug's bioavailability, the maintenance dose (MD), the clearance rate, and the dosing interval (τ):

$$C_{\text{pss}} = (F \times \text{MD}) / (\text{CL} \times \tau)$$

C_{pss} may be too low if the MD is too small, if F is too low, if CL is too high, or if τ is too long. Should it prove necessary to adjust the dosing regimen, changes in one or more of these parameters will be indicated. For example, if a higher peak drug level is desired, the maintenance dose can simply be increased. However, if a lower trough level is desired to alleviate concern about toxicity, the dosing interval can be extended, or (depending on the peak level) the maintenance dose can be decreased.

In addition to monitoring drug levels when possible [see Drug Level Monitoring, *below*], it is crucial to monitor the clinical effect of a drug regimen. At times, this effect may be immediate, as when a vasopressor is administered to a patient in septic shock. At other times, the effect may be delayed, as when a course of antibiotics is administered for a patient with pneumonia. A one-size-fits-all approach to the duration of a therapeutic regimen may not suffice for all patients. Monitoring the clinical efficacy of a treatment regimen is essential for determining the appropriate timing of discontinuance.

DRUG LEVEL MONITORING

Monitoring of the plasma concentration is most commonly employed with drugs that have a low therapeutic index—that is, drugs for which there is a narrow margin between the level that is therapeutic and the level that causes toxicity. It should be kept in mind, however, that these therapeutic and toxic levels are not absolute indicators of safety or efficacy: they only represent values at which certain percentages of patients are treated effectively or certain percentages experience adverse events. Accordingly, such levels are not infallible guides for drug dosing. As an example, there are circumstances in which a clinician, knowing the drug levels and weighing the various risks and benefits, might elect to push the drug levels toward, or even into, the toxic range; for instance, in a patient with recalcitrant seizures, the plasma phenytoin level might be pushed to 25 $\mu\text{g/mL}$, which is above the standard therapeutic range. As another example, there are circumstances in which normal therapeutic drug levels are maintained, but the patient still experiences toxicity. Sometimes therapeutic benefit is obtained by levels below that considered to be in the therapeutic range.

The timing of drug monitoring is important if the results are to be accurately interpreted. The sample for the peak level should be drawn 30 to 60 minutes after a dose is administered; the sample for the trough level should be drawn just before the next dose is to be administered. If there is significant concern about a potentially toxic trough level, the next dose may be held until the level can be determined. The timing of these blood draws should be noted as precisely as possible. Ideally, samples should not be drawn until the drug has been administered for five half-lives. When a patient is critically ill, however, five half-lives may be too long to wait. If so, samples may be drawn before and after the third dose (for trough and peak levels, respectively). In such cases, the levels obtained must be interpreted carefully, first, because a true steady state may not have been achieved and, second, because these trough and peak levels are not from the same dose.

It should be kept in mind that standard drug level monitoring measures both the bound fraction and the unbound fraction of the drug. In certain circumstances (e.g., a patient with low plasma protein levels), the drug level can be misleading. Phenytoin is an example of a drug that is highly protein bound. If plasma protein levels are low, unbound drug levels can rise significantly even when total drug levels do not. In addition, a number of drugs are metabolized to an active metabolite that may contribute to toxicity. Some such metabolites, for example, the procainamide metabolite *N*-acetylprocainamide, can be measured.

Desired peak and trough ranges vary from one drug to another according to the desired effect and the risk of toxicity. With aminoglycosides, for example, toxicity is related to both the peak level (ototoxicity) and the trough level (renal toxicity), whereas efficacy is mostly based on the peak level (concentration-dependent bacterial killing). Once-daily administration of a large dose to achieve a high plasma concentration seems to be advantageous in terms of maximizing the efficacy of aminoglycosides and minimizing their toxicity. This approach differs from the once-daily dosing that may be necessary in a patient with renal insufficiency. In contrast, with vancomycin, efficacy depends on maintaining an adequate plasma level for as long as possible. Thus, the trough level is used to determine the adequacy of dosing, particularly in situations where higher than normal levels may be needed for adequate tissue penetration, for example, for patients with pneumonia or CNS infection.

Monitoring of the drug's effect is also important. For example, the international normalized ratio (INR)/prothrombin time may be measured in a patient receiving warfarin, or the activated partial thromboplastin time may be measured in a patient receiving heparin.

Drug Interactions

The more drugs a patient is given, the greater the potential for adverse drug interactions. This is particularly true for critically ill patients and patients undergoing major surgery. Not only do such patients receive multiple medications, but they also frequently experience transient organ system dysfunction induced by anesthesia, the original disease process, and the physiologic effects of surgery itself that can alter drug metabolism. They often have multiple comorbidities that may

make adverse drug effects more likely. Interaction between drugs may lead directly to toxic effects, or it may be indirectly harmful by decreasing the efficacy of one or both agents.

Drug interactions may affect any or all of the four primary pharmacokinetic parameters, that is, ADME. Absorption effects are mainly limited to simultaneous administration of enteral medications but are also affected by perioperative nausea and vomiting and blood flow redistribution induced by anesthesia. Incompatibilities may also arise with administration of IV medications, but, usually, the only practical consequence is that the two incompatible agents cannot be administered through the same IV tubing at the same time. Distributional effects are usually secondary to competition for binding sites on proteins. Once the sites are saturated, the amount of free drug can increase if the metabolism and elimination pathways are intact and unsaturated. Clinically, drugs that compete with warfarin for protein binding sites may significantly increase the level of unbound warfarin and increase the risk of bleeding. Metabolic effects primarily involve induction or inhibition of CYP enzymes [see Table 2]. Elimination effects primarily involve impairment of renal function or competition for tubular secretion.

Pharmacodynamic interactions can either enhance or decrease the efficacy of a drug. For example, two antihypertensive medications from different classes may have additive or synergistic (greater than additive) effects when used together. In contrast, two β -lactam antibiotics may be antag-

onistic when used together if one induces production of a β -lactamase that subsequently metabolizes the other or prohibits binding of the second agent.

Adverse Drug Reactions

As noted (see above), critically ill and postoperative patients tend to present with multiple medical problems and receive multiple pharmacologic agents, making it difficult to determine the possible adverse effects of any single drug. Accordingly, a high index of suspicion is critical in these patients. Drugs can cause nephrotoxicity via acute tubular necrosis, interstitial nephritis, or glomerulonephritis. For example, aminoglycosides and amphotericin B can cause acute tubular necrosis, whereas penicillins tend to cause interstitial nephritis through immune responses. Hepatic dysfunction can be caused by direct hepatocellular effects or by cholestasis. True allergic reactions most commonly induced by perioperative antibiotics or neuromuscular blocking agents can occur. Relatively rare events such as malignant hyperthermia induced by volatile anesthetic agents or succinylcholine, severe and possibly fatal bradycardia and acidosis induced by prolonged/high dose propofol infusion, and local anesthetic toxicity are examples of adverse drug effects specifically associated with surgery, anesthesia, and critical care.

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24 DISORDERS OF WATER AND SODIUM BALANCE

Richard H. Sterns, M.D.

Overview of Body Fluid Homeostasis

Life takes place in an aqueous solution. Cells, the blood bringing nutrients and oxygen to them, and the interstitial fluid bathing them are all mostly water. Each day, water and salt are lost and replaced. To maintain stability of the internal milieu, body fluids are processed by the kidney, guided by intricate physiologic control systems that regulate fluid volume and composition.

DISTRIBUTION AND COMPOSITION OF BODY WATER

Water accounts for approximately half of an adult human's body weight. Because fat contains little water, individuals with more body fat have less body water. On average, total body water constitutes 60% of lean body weight in young men, 50% in young women and older men, and 45% in older women. Two thirds of body water is intracellular and the remainder is contained in the extracellular fluid compartment, which includes intravascular (plasma) and interstitial fluid. Small amounts of water are also contained in bone, dense connective tissue, digestive secretions, and cerebrospinal fluid.¹

Extracellular solutes are predominantly sodium salts (primarily a mixture of NaCl and NaHCO₃). Thus, extracellular fluid can be thought of as saltwater. Except for protein (present at a higher concentration in plasma [approximately 1 mmol/L] than in interstitial fluid), the compositions of the intravascular and interstitial subdivisions of the extracellular fluid compartment are similar.

The sodium-potassium adenosine triphosphatase (Na⁺,K⁺-ATPase) pump on cell membranes keeps intracellular sodium at low levels. Potassium, the dominant intracellular cation, is electrically balanced, in large part, by anionic charges on impermeant macromolecules. Stability in the number of intracellular anionic charges makes the total solute content of cells much less variable than that of the extracellular fluid.

Osmolality

Extracellular and intracellular fluids contain different types of solutes, but the concentrations of solutes inside and outside of cells are equal. Concentration differences exist only transiently because they create an extremely strong force for water movement across cell membranes. Osmotic pressure moves water rapidly to the fluid compartment with the higher solute concentration until concentrations once again become equal. The osmotic pressure responsible for water movement across cell membranes depends on the total number of solute particles (osmoles) dissolved in solution, a property known as osmolality.² Osmolality is usually expressed as milliosmoles of solute per kilogram of solvent (mOsm/kg), but it can be thought of more simply as the number of millimoles of solute particles per liter of solution. A solute particle's contribution to osmolality is independent of its charge and molecular size. Ionic substances such as sodium chloride that dissociate in solution contribute more than one osmotically active particle. Sodium salts, glucose, and urea, commonly measured as blood urea nitrogen (BUN), are responsible for most of the solute particles normally present in extracellular fluid. Plasma osmolality can be measured directly with an osmometer or can be esti-

imated with reasonable accuracy from the concentrations of the major extracellular solutes, as follows:

$$P_{\text{osm}} \approx 2 \times \text{plasma } [\text{Na}^+] + \frac{[\text{Glucose}]}{18} + \frac{\text{BUN}}{2.8}$$

The multiple of 2 reflects the anions accompanying sodium ions, and 18 and 2.8 are the corrections required to convert glucose and urea nitrogen concentration from mg/dl (the units used by most laboratories in the United States) to mmol/L. Exogenous solutes (e.g., ethanol, methanol, ethylene glycol, glycine, mannitol) are measured by osmometers but are not included in the formula shown above. A discrepancy between the measured and the calculated plasma osmolality values (an osmolar gap) is useful clinically as a way to recognize the presence of an exogenous solute.²

Fluid Movement between Body Fluid Compartments

The intravascular and interstitial subdivisions of the extracellular fluid compartment are separated by capillary walls that are freely permeable to small extracellular solutes but relatively impermeable to plasma proteins. Protein-free saltwater continuously moves across the capillary endothelial barrier by filtration, driven by a hydrostatic pressure gradient (generated by contractions of the heart), which forces fluid from the capillary into the interstitium, and an oncotic pressure gradient (the consequence of the osmotic force created by intravascular protein), which draws interstitial fluid into capillaries [see Figure 1]. These so-called Starling forces, which regulate the disposition of fluid within the extracellular compartment, determine how much extracellular saltwater is contained in intravascular plasma and how much is in interstitial fluid [see Disorder of Saltwater Excess: Edematous States, below]. Sodium salts, urea, glucose, and other small extracellular solutes freely cross the capillary wall, achieving similar concentrations in the interstitial fluid and plasma. Thus, changes in plasma osmolality do not influence water movement between the intravascular and interstitial fluid compartments.

Fluid movement between the extracellular and the intracellular fluid compartments is unaffected by Starling forces. Rather, transcellular water movement is driven by osmotic forces, a function of the concentration of solutes in the extracellular fluid. A decrease in extracellular solute concentration (hypotonicity) drives water into cells, causing cell swelling; an increase in the concentration of exclusively extracellular solutes (hypertonicity) draws fluid out of cells, dehydrating them.

Not all solutes contribute to the tonicity of extracellular fluid.² Permeant solutes such as urea and ethanol readily cross cell membranes, achieving equal concentrations in the extracellular and intracellular fluid compartments without driving transcellular water movement and without affecting cell volume. Such solutes, which increase plasma osmolality without altering plasma tonicity, are sometimes called ineffective osmoles. Impermeant solutes are excluded from cell water either by active transport (e.g., sodium ions) or because the cell membrane is impermeable to them (e.g., mannitol).

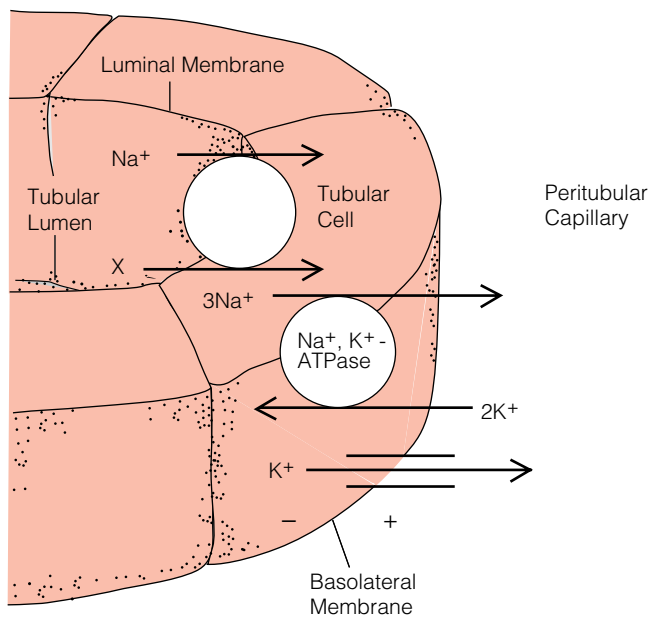


Figure 1 Sodium reabsorption by the renal tubules is driven by the $\text{Na}^+, \text{K}^+ \text{-ATPase}$ pump in the basolateral (blood side) membrane, which maintains a low sodium concentration within the tubular cell. Filtered sodium in the tubular lumen enters the cell down its concentration gradient via a transmembrane carrier (which may also transport another solute, X) or via a channel in the luminal membrane [see Figure 2].

Such solutes, which cause both hyperosmolality and hypertonicity, are sometimes called effective osmoles.

Body Fluid Tonicity and the Plasma Sodium Concentration

Normally, sodium salts are the major effective osmoles in extracellular fluid, and potassium salts are the major effective osmoles in cells. Given that effective osmolality is equal in all fluid compartments, body fluid tonicity can be described by the following equation:

$$\begin{aligned} \text{Tonicty} &\approx \\ 2 \times \text{Plasma } [\text{Na}^+] &\approx \frac{2 (\text{Exchangeable } \text{Na}^+ + \text{Exchangeable } \text{K}^+)}{\text{Total body water}} \\ \text{therefore,} \\ \text{Plasma } [\text{Na}^+] &\approx \frac{\text{Exchangeable } \text{Na}^+ + \text{Exchangeable } \text{K}^+}{\text{Total body water}} \end{aligned}$$

(Only the exchangeable fractions of sodium and potassium are included in the equation, because one third of overall body sodium is bound to bone and is therefore osmotically inactive.)

Thus, the plasma sodium concentration is, in effect, a measure of the concentration of tonicity of all body fluids.³ In the absence of an osmolar gap, the plasma sodium concentration is a more valid measure of body fluid tonicity than plasma osmolality (which includes the ineffective osmole, urea). With a few exceptions, most notably hyperglycemia, a low plasma sodium concentration indicates hypotonicity and cell swelling, whereas a high plasma sodium concentration indicates hypertonicity and cellular dehydration.

RENAL PROCESSING OF BODY FLUIDS

Glomerular Filtration

Approximately 170 L of extracellular saltwater containing over 25,000 mmol of sodium are filtered by the glomerulus each day. Although glomerular hydrostatic pressure is considerably higher than the pressure of other capillary beds, the Starling forces that control fluid movement between intravascular and interstitial fluid also drive glomerular filtration. The glomerular filtrate contains the same concentrations of sodium and other solutes as interstitial fluid and is nearly protein free.

Tubular Reabsorption

On a conventional diet, all but 2 L of filtered fluid and all but 175 mmol of filtered sodium is reabsorbed by the renal tubules. Regulation of tubular reabsorption of salt and water is the key to renal regulation of body fluid balance.⁴

At the end of the proximal tubule, the remaining filtrate has the same sodium concentration as plasma has; as the filtrate passes through downstream tubular segments, it undergoes major changes in composition. In these more distal segments, sodium and water reabsorption are uncoupled; salt can be reabsorbed without water, and water can be reabsorbed without salt. Thus, depending on conditions, the sodium concentration of the final urine can vary from less than 1 mEq/L to nearly 300 mEq/L, and urine osmolality can vary from one sixth (50 mOsm/kg) to four times (1,200 mOsm/kg) that of plasma.

The process of sodium reabsorption is mediated by carriers or channels embedded in the tubular cell's luminal and basolateral (blood side) membranes. In each nephron segment, sodium reabsorption is powered by the so-called sodium pump, $\text{Na}^+, \text{K}^+ \text{-ATPase}$, which is located on the blood side of the tubular cell [see Figure 1]. This sodium pump exports sodium from the cell, lowering the intracellular sodium concentration. The lowered concentration of cellular sodium creates an electrochemical gradient driving sodium from the tubular lumen into the cell. Tubular segments at various regions of the nephron utilize different luminal mechanisms for sodium reabsorption [see Table 1 and Figure 2]. Luminal ex-

Table 1 Sodium Transport in Different Nephron Segments

Nephron Segment	Glomerular Filtrate Reabsorbed	Mechanism of Luminal Sodium Entry	Physiologic Regulation	Diuretic Site of Action
Proximal tubule	60%–70%	$\text{Na}^+ \text{-H}^+$ exchange; cotransport with glucose and other organic solutes	Angiotensin II; renal nerves; peritubular Starling forces	Carbonic anhydrase inhibitors (e.g., acetazolamide)
Loop of Henle	20%–25%	$\text{Na}^+ \text{-K}^+ \text{-2Cl}^-$ cotransport	Flow dependent; peritubular Starling forces	Loop diuretics (e.g., furosemide, bumetanide, ethacrynic acid)
Distal tubule	5%	$\text{Na}^+ \text{-Cl}^-$ cotransport	Flow dependent	Thiazide diuretics
Collecting tubule	4%	Na^+ channels	Aldosterone; atrial natriuretic factor	Potassium-sparing diuretics (e.g., amiloride, triamterene, spironolactone)

changers, cotransporters, and ion channels along the nephron are subject to physiologic control, and they can be inhibited pharmacologically by specific diuretic agents.⁵ Mutations in these transport proteins are responsible for well-defined clinical disorders.⁶

The luminal membrane of the collecting duct is impermeable to water in the absence of arginine vasopressin, an antidiuretic hormone (ADH). Thus, when plasma ADH levels are low, this segment progressively reduces the osmolality and sodium concentration of the final urine and permits the excretion of large volumes (as much as 20 L daily) of dilute urine. In the presence of ADH, water chan-

nels—called aquaporins—are inserted in the luminal membrane of the distal tubule and collecting duct.^{7,8} When plasma levels of ADH are high, water is attracted osmotically from the tubular lumen to the hypertonic medullary interstitium, permitting excretion of a small volume (as little as 0.5 L daily) of concentrated urine.

REGULATION OF BODY FLUID VOLUMES

Saltwater (isotonic saline) is confined to the extracellular space. Accumulation of saltwater expands extracellular volume; loss of saltwater causes volume depletion. In either case, changes in saltwater balance do not alter the plasma sodium concentration or cell volume. By contrast, so-called electrolyte-free water, or pure water, is distributed throughout body fluids, affecting both extracellular and intracellular fluid compartments. Because only one third of body water is extracellular, electrolyte-free water has only one third the impact on extracellular volume that saltwater has; however, unlike saltwater balance, electrolyte-free water balance has a major impact on the plasma sodium concentration, body fluid tonicity, and cell volume.

Extracellular and intracellular fluid volumes are maintained by separate but interacting control systems [see Table 2]; the extracellular system primarily regulates urinary sodium excretion, whereas the intracellular system regulates the intake and excretion of water. Extracellular fluid volume maintains a proper degree of vascular fullness, a variable that is sensed by atrial stretch receptors and arterial baroreceptors. Intracellular volume is regulated by hypothalamic osmoreceptor cells that swell or shrink in response to changes in plasma tonicity.

Control of Extracellular Fluid Volume

In a healthy person, the amount of sodium in the extracellular space can vary considerably, depending on dietary salt intake. On the other hand, under normal conditions, the extracellular sodium concentration remains almost constant because of physiologic control systems that tightly regulate water intake and excretion. In healthy persons, more salt in the extracellular space means an expanded extracellular fluid volume; less salt means a smaller extracellular volume. In either case, the extracellular sodium concentration does not change.

Sodium balance and intravascular volume are affected by numerous hormonal and nonhormonal mediators; in addition to aldosterone and angiotensin—the best known mediators of sodium excretion—the sympathetic nervous system, natriuretic peptides, and changes in the renal circulation all play important regulatory roles [see Table 2].⁹ Because of redundancy and overlap in the control system, failure of a single factor does not cause major, sustained abnormalities in intravascular volume. The relative importance of the various mediators that affect urinary sodium excretion are incompletely understood, and it is likely that some sodium regulatory factors remain undiscovered.

Control of Intracellular Fluid Volume

Water balance and cell volume are controlled by a single hormonal mediator, arginine vasopressin [see Tubular Reabsorption, above], which is released into the systemic circulation by the neurohypophysis [see Table 2 and Figure 3]. The hormone activates V_2 receptors on the basolateral membrane of principal cells in the renal collecting duct, initiating a cyclic adenosine monophosphate-dependent (cAMP-dependent) process that culminates in the insertion of water channels (aquaporins) into the cells' luminal membranes.^{7,8} Modulation of the number of water channels controls urine osmolality and the rate of water excretion by the kidney. Vasopressin's short half-life in the circulation and continuous shuttling of

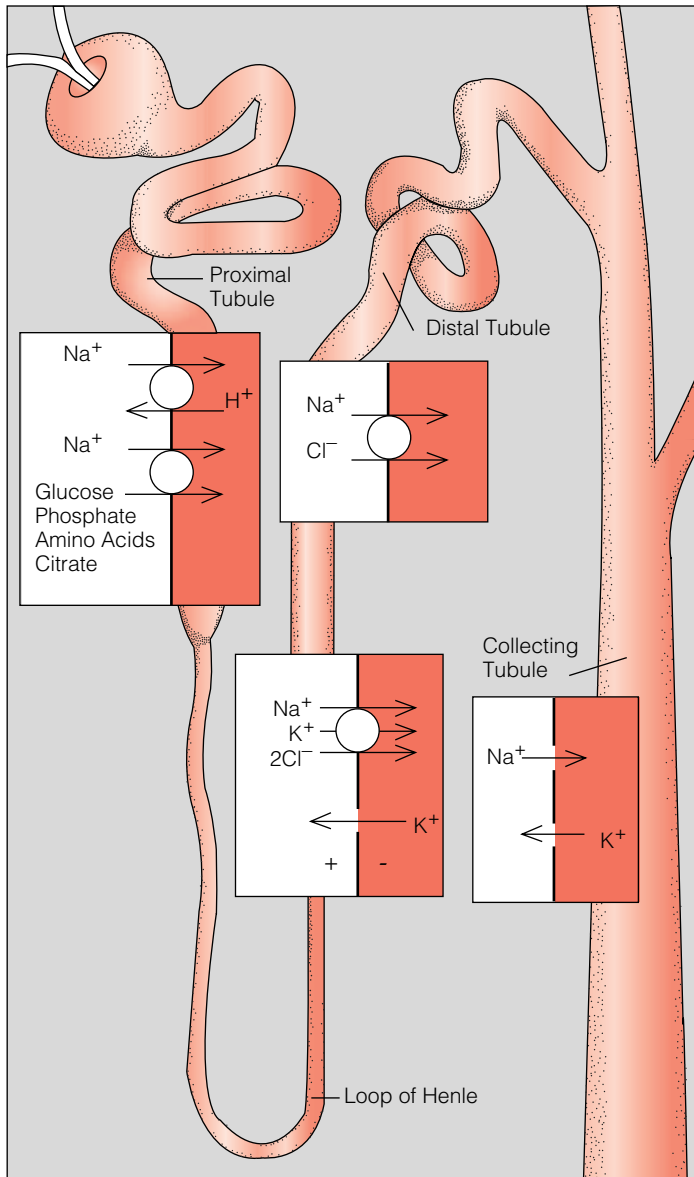


Figure 2 In each tubular segment, sodium enters the tubular cell passively, down the favorable electrochemical gradient created by the Na^+ , K^+ -ATPase pump. Luminal sodium enters by a different mechanism in each of the nephron segments. The proximal tubule reabsorbs filtered bicarbonate and other solutes, such as glucose, phosphate, amino acids, and citrate. An Na^+ , K^+ , 2Cl^- transporter mediates Na^+ entry into the ascending limb of the loop of Henle. The distal tubule has an Na^+ , Cl^- cotransporter. Na^+ enters the principal cells of the cortical collecting tubules through Na^+ channels in the luminal membrane.

Table 2 Control of Body Fluid Volumes

	Saltwater Balance	Electrolyte-Free Water Balance	
		Day to Day	Emergency Backup
Regulated variable	Extracellular volume Vascular fullness	Cell volume	Arterial filling
Clinical indicator	Blood pressure Edema	Plasma sodium concentration	Blood pressure Edema
Sensors	Baroreceptors, atrial volume receptors	Hypothalamic osmoreceptors	Baroreceptors, atrial volume receptors
Mediators	Renin-angiotensin-aldosterone system Sympathetic nervous system Atrial natriuretic peptide Starling forces in peritubular capillaries	Antidiuretic hormone (arginine vasopressin) Thirst	Antidiuretic hormone (arginine vasopressin) Thirst
Affected variable	Urinary sodium excretion	Urine osmolality Water intake	Urine osmolality Water intake

aquaporins between the collecting duct’s cell membrane and cytosol ensure that urinary water excretion responds rapidly to changes in body fluid tonicity.

Vasopressin levels are normally unmeasurable when the plasma sodium concentration falls to 135 mEq/L or lower [see Figure 3]. Low levels of the hormone result in the excretion of large volumes of a maximally dilute urine (50 mOsm/kg). Above a sodium level of 135 mEq/L, plasma vasopressin levels are linearly related to the plasma sodium concentration and increase measurably in response to changes in the plasma sodium concentration of as little as 1 mEq/L. Once the plasma sodium concentration reaches approximately 142 mEq/L, plasma vasopressin levels are high enough to promote the excretion of maximally concentrated urine (1,200 mOsm/kg). A rising plasma sodium concentration also causes hypothalamic cell volume receptors to relay signals to nearby thirst centers. Mediated by thirst and changes in vasopressin secretion, the plasma sodium concentration is normally prevented from rising above 142 mEq/L or falling below 135 mEq/L.

Under day-to-day conditions, water intake, vasopressin secretion, and urinary free water excretion primarily respond to changes in the plasma sodium concentration created by variations in electrolyte-free water balance. Unlike sodium excretion, which is affected only by changes in intravascular volume, free water excretion can be affected by two types of stimuli—intravascular volume and tonicity. Under pathologic conditions, osmotic control of vasopressin secretion and thirst can be overridden by hemodynamic stimuli. The hypothalamic neurons that secrete vasopressin receive neural input from baroreceptors in the great vessels and volume receptors in the atria. When these receptors are stimulated by hypotension or by a major reduction in plasma volume, impulses are carried via cranial nerves IX and X.⁸ Vasopressin and thirst responses to hypovolemia and hypotension can be regarded as back-up systems that serve to maintain arterial blood volume under emergency conditions, sacrificing tonicity to tissue perfusion.

CELL VOLUME REGULATION IN HYPOTONICITY AND HYPERTONICITY

Cell volume is determined by the amount and concentration of intracellular solute. Because intracellular and extracellular solute concentrations must be equal, the relation between cell water and extracellular osmolality can be described by the following equation:

Cell volume = $\frac{\text{Cell water}}{\text{Extracellular osmolality}}$

Normally, water intake and excretion are modulated to maintain body fluid tonicity within a narrow physiologic range. However, under pathologic conditions, body cells can be exposed to a hypotonic or hypertonic milieu.¹⁰ The first response to osmotic stress is a compensatory adjustment to intracellular electrolytes: loss of potassium in hypotonicity and accumulation of sodium and potassium in hypertonicity. With time, changes in organic solutes dominate the response.

Most cells maintain relatively high concentrations of small, osmotically active organic molecules known as organic osmolytes. Or-

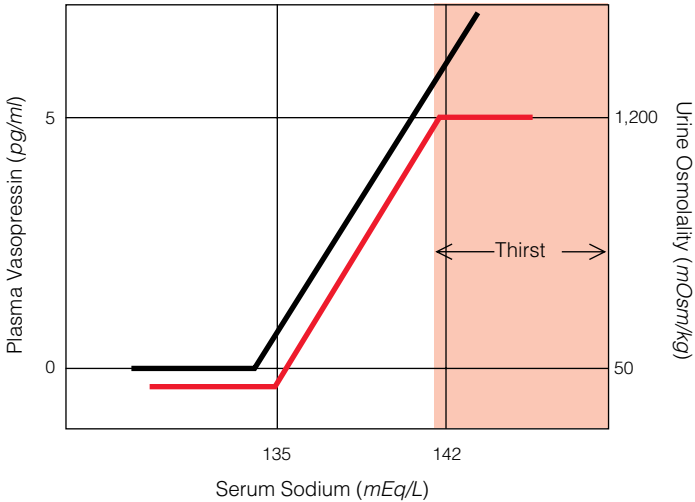


Figure 3 Graph depicts the normal relation between plasma vasopressin levels and urine osmolality (black line) and the plasma sodium concentration (red line). Plasma vasopressin levels change within minutes in response to changes in plasma sodium, and urine osmolality changes within minutes in response to changes in vasopressin levels. When hydration reduces the plasma sodium level below 135 mEq/L, plasma vasopressin becomes undetectable and the urine becomes maximally dilute (osmolality, 50 mOsm/kg). Between sodium concentrations of 135 and 142 mEq/L, vasopressin levels are linearly related to the plasma sodium, causing nearly a 100 mOsm/kg increase in urine osmolality for every 0.5 mEq/L increase in sodium concentration. Above a plasma sodium concentration of 142 mEq/L, the urine is maximally concentrated; increased water intake, mediated by thirst, then becomes the major defense against progressive hypernatremia.

ganic osmolytes are nonperturbing solutes; unlike sodium and potassium, their intracellular concentrations may vary widely without affecting tertiary protein structure. Cells accumulate organic osmolytes under hypertonic conditions and lose them when confronted with hypotonicity.

The need for cell volume regulation is most imperative in the brain, where the rigid calvaria places sharp limits on the degree of tissue expansion or contraction that can be tolerated.¹⁰⁻¹³ An increase in brain water content of more than about 5% to 10% is incompatible with life. Variations in the intracellular concentration of organic osmolytes provide the brain with an astonishing ability to adapt to chronic osmotic disturbances. However, because changes in the osmolyte content of brain cells require a few days to develop fully, the brain is imperiled by rapid osmotic changes. Thus, acute hyponatremia or hypernatremia may be fatal at plasma sodium concentrations that are well tolerated chronically.

With sustained osmotic disturbances, adaptations that protect against brain swelling and shrinkage also predispose to injury when the osmotic disturbance is suddenly corrected. In chronic hyponatremia, cellular solutes lost in the adaptive phase must be recovered when the plasma sodium concentration returns to normal—a process that may require several days. Unless solute recovery keeps pace with the rising extracellular osmolality, brain cells will become dehydrated.^{11,12} This phenomenon may cause clinical complications [see Disorder of Water Excess: Hyponatremia, Chronic Hyponatremia, Complications of Therapy: Myelinolysis and Osmotic Demyelination Syndrome, *below*]. Similarly, in chronic hypernatremia, accumulated solutes must be shed during correction of the electrolyte disturbance.^{10,13} Cells that have become acclimated to a hypertonic environment lose organic osmolytes slowly because of slow turnover of the efflux mechanism, slow downregulation of hypertonically stimulated uptake pathways, or both. Thus, when chronic hypernatremia is corrected rapidly, brain cells swell to a greater than normal volume.

Disorder of Water Excess: Hyponatremia

Hyponatremia simply means a low plasma sodium concentration. In most cases, hyponatremia is associated with a low plasma osmolality level and body fluids that are too dilute (hypotonic hyponatremia). However, there are exceptions to this rule [see Differential Diagnosis for Hyponatremia, *below*].

PATHOGENESIS OF HYPONATREMIA

Hypotonic hyponatremia results from two basic mechanisms individually or together: (1) massive water intake, exceeding the capacity to excrete electrolyte-free water, or (2) impaired water excretion. Normally, the capacity for water excretion is rather large. In the absence of vasopressin, urine osmolality falls to approximately 50 mOsm/kg. A typical American diet provides 600 to 900 mOsm of electrolytes and urea that must be excreted each day. At this rate of solute excretion, the volume of maximally dilute urine equals 12 to 18 L. Water intake can occasionally exceed the normal excretory capacity, primarily in psychotic patients who frantically ingest gallons of water over a few hours¹⁴ and in very heavy beer drinkers who ingest large volumes of fluid but take in small amounts of salt and protein.¹⁵ More commonly, hyponatremia occurs in patients with a diminished ability to excrete free water.^{8,12}

Impaired Water Excretion

Water excretion is obviously compromised in severe renal failure; oliguric patients become hyponatremic if they are given too much water. However, most cases of hyponatremia occur in patients

whose normal kidneys are unable to excrete maximally dilute urine. A pathologically low plasma sodium concentration occurs when water is taken in at a time when renal diluting mechanisms are not functioning maximally because either (1) diuretics or tubular transport defects are blocking sodium reabsorption in the renal diluting segments or (2) antidiuretic hormone levels are elevated.

Nonosmotic Release of Vasopressin

Vasopressin is a water-retaining hormone that is released when water is needed. Because hypotonic hyponatremia normally inhibits vasopressin secretion, detectable vasopressin in a patient who is hyponatremic indicates that a nonosmotic stimulus for vasopressin release must be present. Vasopressin action increases the urine osmolality, which can be thought of as a bioassay for the hormone.

Hemodynamic stimuli for vasopressin Hypovolemia, heart failure, and cirrhosis are the most common nonosmotic stimuli for antidiuretic hormone secretion.¹⁶⁻¹⁸ The hemodynamic abnormalities that stimulate vasopressin release also promote sodium reabsorption by the renal tubules; thus, these conditions result in both sodium and water retention.

Inappropriate antidiuretic hormone secretion Nonosmotic release of vasopressin without a hemodynamic stimulus to account for it is considered “inappropriate.” Patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) retain water because of nonosmotic release of vasopressin but have no abnormality in sodium balance, evidence of volume depletion, or tendency to form edema; in the steady state, sodium excretion matches intake.^{8,12,19} Because of water retention, SIADH causes mild, subclinical volume expansion. Any additional volume expansion is met by a brisk increase in urinary sodium excretion.

Reset osmostat Reset osmostat is a variant of SIADH, commonly seen in patients with chronic, debilitating illness; it is also a characteristic of normal pregnancy. Patients with this condition are able to dilute their urine normally but at a lower set-point than in normal individuals. Such patients are thus mildly hyponatremic, but unlike other patients with SIADH, they are not predisposed to progressive water retention and do not require dietary water restriction or other measures used to treat chronic hyponatremia.¹¹ Reset osmostat can, however, be seen in malignancies, and like other causes of SIADH, it requires a diagnostic evaluation to determine its cause.

Urinary Electrolyte Losses: Desalination and Hyponatremia

If the urine is concentrated, urinary sodium and potassium losses can contribute to the pathogenesis of hyponatremia. The plasma sodium concentration can be reduced either by loss of sodium or potassium or by water gain. However, to lower the plasma sodium concentration, electrolytes must be lost in urine that has a higher electrolyte concentration than plasma. The combination of high vasopressin levels (which concentrate the urine) and a high rate of sodium and potassium excretion can yield hypertonic urine capable of generating free water, which in essence desalinates the plasma.²⁰

DIFFERENTIAL DIAGNOSIS FOR HYPONATREMIA

Several conditions can lower the plasma sodium concentration without causing hypotonicity and are referred to as nonhypotonic hyponatremia [see Table 3]. The diagnostic and therapeutic approach to these conditions differs fundamentally from the approach to hypotonic hyponatremia. Thus, it is important that nonhypotonic hyponatremia be excluded whenever a low plasma sodium concentration is encountered.

Table 3 Causes of Nonhypotonic Hyponatremia

Condition	Plasma Osmolality	Pathogenesis	Therapeutic Implications
Hyperglycemia	High	Extracellular glucose osmotically draws water into the ECF, diluting extracellular sodium	During treatment of hyperglycemia, anticipate 3 mEq/L increase in serum sodium for every 200 mg/dl reduction in blood sugar
Intravenous hypertonic mannitol therapy	High	Water shift from ICF to ECF as with hyperglycemia	Mannitol is rapidly excreted when renal function is normal
Intravenous γ -globulin therapy	High	Maltose present in solution acts like mannitol	Measure plasma osmolality when hyponatremia is suspected
Irrigant absorption (prostatectomy or intrauterine surgery)	Normal or low (when hypoosmolar irrigants are used)	Absorbed solute—mannitol, sorbitol, or glycine (most common)—initially confined to ECF, causing severe hyponatremia but little change in plasma osmolality	Mannitol is rapidly excreted; sorbitol is metabolized, causing late-onset hypotonic hyponatremia; glycine is neurotoxic and causes transient blindness and is metabolized to ammonia, causing encephalopathy; consider hemodialysis
Pseudohyponatremia (severe hyperlipidemia, multiple myeloma, macroglobulinemia)	Normal	Laboratory artifact; plasma water constitutes a smaller fraction of the plasma sample, causing a more serious underestimate of the true sodium concentration	Suspect when serum is lactescent; compare measured plasma osmolality with calculated osmolality or measure plasma sodium with direct-reading sodium electrode

ECF—extracellular fluid ICF—intracellular fluid

Hyperglycemic Hyponatremia

Hyperglycemia lowers the plasma sodium concentration; in the absence of insulin, glucose is an effective osmole that attracts water from cells and thereby dilutes extracellular sodium. Therefore, the blood glucose level should always be examined when a low plasma sodium concentration is being evaluated. The plasma sodium concentration falls by approximately 3 mEq for every 200 mg/dl (10 mmol) increase in blood glucose and will increase by this amount when hyperglycemia is corrected with insulin. To evaluate hyponatremia in the presence of hyperglycemia, the serum sodium concentration must be “corrected” for the osmotic effect of glucose. In effect, the clinician must ask the question, What would the serum sodium concentration be if the excess glucose were no longer present? The correction factor most commonly used today is a 1.6 mEq/L decrease in serum sodium concentration for every 100 mg/dl increase in blood glucose. A small study has suggested that the true correction factor is approximately 2.4 mEq/L for every 100 mg/dl increase in blood glucose.²¹ A precise correction factor is probably unobtainable because in practice, hyperglycemia develops, in part, from the ingestion of glucose with water and resolves, in part, from the urinary excretion of glucose with water.²²

Exogenous solutes such as mannitol and maltose (a sugar contained in intravenous immunoglobulin preparations) are confined to the extracellular space and have an effect on the plasma sodium concentration similar to that of hyperglycemia. When the clinical setting suggests that these solutes might be responsible for hyponatremia, their presence can be confirmed by measuring the plasma osmolality and comparing it with the calculated value to identify an osmolar gap [see Overview of Body Fluid Homeostasis, Distribution and Composition of Body Water, Osmolality, *above*].^{2,11}

Postprostatectomy Syndrome and Hysteroscopic Hyponatremia

Irrigants containing mannitol, sorbitol, or glycine are used for endoscopic transurethral and intrauterine procedures [see Table 3].^{2,23} Occasionally, several liters of irrigant may be absorbed systemically, reducing the plasma sodium in a matter of minutes. Immediately after surgery, the serum sodium concentration is much lower than would be anticipated, because the electrolyte-free solution is initially confined to the extracellular space. Glycine, the most commonly used irrigant in the United States, is metabolized to ammonia and

eventually to urea and glucose. Hyperammonemia may be responsible for most of the symptomatology, and glycine itself has direct neuroinhibitory effects and may cause hypotension, bradycardia, and visual disturbances.

Pseudohyponatremia

High plasma concentrations of lipid or protein cause mild nonhypotonic hyponatremia because of an artifact of laboratory measurement [see Table 3].^{2,11} With extremely high concentrations of lipid (enough to cause lactescent serum) or protein (from multiple myeloma or Waldenstrom macroglobulinemia), plasma water may constitute a smaller fraction of the plasma sample than normal, which can result in an underestimate of the “true” sodium concentration. The plasma osmolality and the sodium concentration in plasma water (as measured by a sodium-sensitive electrode) are unaffected. There are no symptoms, and no therapy is required.

ACUTE HYPONATREMIA (WATER INTOXICATION)

The term water intoxication was coined in the early 1920s to describe a neurologic syndrome that develops when large volumes of water are retained within a relatively short period of time (< 48 hours). The syndrome is often called acute hyponatremia.^{12,24}

Etiology

Acute hyponatremia develops when water intake is large and electrolyte-free water excretion is impaired. Potentially, hyponatremia can develop rapidly in any patient predisposed to water retention who takes in a large volume of water in a short period of time. However, this is likely to occur in a limited number of settings [see Table 4], and such instances account for most cases of severe symptomatic hyponatremia and for most of the recorded fatalities.

Postoperative hyponatremia Vasopressin is released immediately after surgical procedures in what appears to be a stress response [see Table 4].^{20,25} Particularly during the first 24 hours, the concentration of urinary cations (sodium plus potassium) may greatly exceed the plasma sodium concentration. As a result, even isotonic fluids may be “desalinated” and can lower the plasma sodium concentration.²⁰ Thus, all hypotonic fluids and excessive amounts of isotonic fluids should be avoided after surgery. As discussed earlier, endoscopic prostatectomy and intrauterine proce-

Table 4 Causes and Treatment of Acute Hyponatremia

Causes	Pathogenesis	Effect of Treatment	Recommendations
Postoperative stress*	Vasopressin is secreted in response to surgical stress for 2 or more days; free water from hypotonic I.V. fluids is retained and sodium and potassium are excreted in urine at high concentrations	Normal saline ineffective for correction—administered sodium excreted in concentrated urine, “desalinating” isotonic fluid and causing water retention	Avoid hypotonic fluid (e.g., D5W, 0.45% saline) and excessive volumes of isotonic fluid (lactated Ringer solution or 0.9% saline) after surgery; treat symptomatic hyponatremia with 3% saline and furosemide
Oxytocin	Used in obstetrics to induce labor; direct antidiuretic effect of drug mimics SIADH; free water from I.V. fluids retained	Urine becomes dilute when oxytocin is discontinued	Avoid administration of oxytocin in or with hypotonic fluids; treat hyponatremia by discontinuing drug
Cyclophosphamide	Drug has antidiuretic effect that persists for as long as 12 hours; patients are encouraged to drink large volumes of water to prevent chemically induced cystitis	Normal saline ineffective for correction as in other causes of persistent SIADH	Treat symptomatic hyponatremia with 3% saline and furosemide
Psychotic self-induced water intoxication	Extreme polydipsia (> 1 L/hr) common among patients with severe psychosis; retained water causes hyponatremia by late afternoon or evening, and water diuresis restores normonatremia by morning	Normal ability to dilute urine in most patients so hyponatremia self-corrects when water intake stops; some patients have vasopressin release (often transient) from stress, smoking, or medications (e.g., carbamazepine)	Monitor diurnal weight in institutionalized patients for early detection; avoid antidiuretic medications; treat hyponatremia with water restriction; use hypertonic saline and furosemide for occasional patient with SIADH
Marathon running	Extracellular volume depletion caused by saltwater losses from sweating and possibly stress are nonosmotic stimuli for vasopressin secretion; large volumes of sugar water consumed during race are retained	Isotonic saline restores ability to dilute urine	3% saline without furosemide for seizures; isotonic saline and water restriction for more moderate symptoms
Ecstasy (MDMA) use	Excessive fluid intake and inappropriate antidiuretic hormone secretion, induced by MDMA, is implicated	Isotonic saline ineffective; self-correction typical but may be delayed	Hypertonic saline for severe symptoms

*Excluding irrigant absorption syndromes [see Table 3].
D5W—5% dextrose in water MDMA—methylenedioxymethamphetamine SIADH—syndrome of inappropriate antidiuretic hormone

dures can cause hyponatremia if irrigant used in the procedures is absorbed systemically. The management of irrigant absorption syndromes differs from that of other causes of postoperative hyponatremia [see Postprostatectomy Syndrome and Hysteroscopic Hyponatremia, *above*].²⁵

Oxytocin infusions Oxytocin, which is used in obstetrics to induce labor, has a direct antidiuretic effect. If the drug is administered in 5% dextrose in water (formerly a common practice), symptomatic hyponatremia may emerge after the infusion of less than 3 L of fluid [see Table 4].¹¹ Termination of the infusion permits a water diuresis and correction of hyponatremia; however, the syndrome is best avoided by using isotonic saline as a vehicle for the drug.

Cyclophosphamide infusion Intravenous cyclophosphamide impairs water excretion by an unknown mechanism.²⁶ The antidiuretic effect of the drug begins 4 to 12 hours after injection and persists for as long as 12 hours. Patients receiving cyclophosphamide are particularly susceptible to hyponatremia, because they are encouraged to drink large volumes of water to prevent chemically induced cystitis [see Table 4].

Psychotic self-induced water intoxication Extreme polydipsia is relatively common in patients with psychiatric illnesses, particularly schizophrenia, and it may lead to symptomatic hyponatremia [see Table 4].¹⁴ Daily intake of 10 to 15 L has been documented, and much of the intake may take place over a few hours. Many patients become hyponatremic in the late afternoon and

evening; however, water diuresis typically restores normonatremia by the following morning. Occasionally, individuals drink enough water to produce seizures. By monitoring diurnal changes in body weight, water intoxication can be recognized before the onset of severe neurologic symptoms. Transient release of vasopressin (most commonly provoked by nausea and vomiting) may contribute to water retention. There is little evidence that any of the major tranquilizers has a significant antidiuretic effect; however, carbamazepine, an anticonvulsant, enhances sensitivity to vasopressin.

Water intoxication during exercise During a race, runners sweat profusely, losing large volumes of saltwater. Extracellular volume contraction and possibly the stress of exertion cause the release of vasopressin. When saltwater losses are replaced by the intake of sugar water, water retention and symptomatic hyponatremia may occur.^{27,28} Most severe cases have been reported after marathons or ultramarathons. However, symptomatic hyponatremia may occur after recreational running and military fitness training.

Water intoxication from “ecstasy” During the 1990s, 3,4-methylenedioxymethamphetamine (MDMA, or ecstasy) gained widespread popularity as a recreational drug taken at dances.²⁹ When malignant hyperthermia was recognized as a complication associated with this drug, MDMA users were advised in underground magazines and the lay press to drink plenty of fluids. Subsequently, acute water intoxication emerged as a potentially lethal complication of the drug [see Table 4]. Excessive fluid intake and inappropriate ADH secretion, induced by MDMA, have been implicated.

Diagnosis

Symptoms of water intoxication include headaches, weakness, nervousness, and vomiting, progressing to disorientation, delirium, tremulousness, and ultimately convulsions and coma.^{12,24} The pupils are often dilated, and bilateral Babinski signs may be present. On occasion, patients may present with hemiparesis, mimicking a cerebrovascular accident. The syndrome reflects cerebral edema, which can lead to herniation of the brain and death. Clinical findings may emerge explosively. Complaints of headache and mild confusion may be followed within hours by respiratory arrest and, in some cases, neurogenic pulmonary edema. For reasons that remain obscure, almost all reported fatalities from acute postoperative hyponatremia have been in women (usually of childbearing age) and young children. Fatal cases of acute hyponatremia from other etiologies have been recorded in men and women.

Acute hyponatremia should be suspected in any patient who has unexplained neurologic symptoms, especially in psychiatric patients, marathon runners, users of ecstasy, and patients receiving hypotonic fluids intravenously (e.g., after surgery). Serum electrolytes should be obtained immediately. In the proper setting, a tentative diagnosis of water intoxication is advisable when symptoms develop in a patient whose serum sodium concentration is lower than 130 mEq/L (provided that causes of nonhypotonic hyponatremia have been excluded). Although severe neurologic symptoms do not usually appear until the sodium level has fallen below 120 mEq/L, some patients may be unusually susceptible to brain edema when they become acutely hyponatremic; rare fatalities have been reported at plasma sodium concentrations between 120 and 128 mEq/L.^{20,25}

Computed axial tomography demonstrates cerebral edema in severe cases of water intoxication, and it rules out other potential explanations for neurologic findings. However, when symptoms are severe, therapy should not be delayed while imaging studies are being obtained.

Treatment

Free-water intake should be stopped immediately whenever water intoxication is suspected. Hypertonic saline is the treatment of choice for water-intoxicated patients who cannot autocorrect their electrolyte disturbance.^{24,25} Each 1 ml of 3% saline contains 0.5 mEq of sodium. Because there are approximately 0.5 L of body water for every 1 kg of body weight, 1 ml of 3% saline per 1 kg of body weight can be expected to increase the plasma sodium concentration by 1 mEq/L. For patients with severe neurologic symptoms, an infusion of 3% saline at 1 to 2 ml/kg/hr will increase the plasma sodium concentration by approximately 1 to 2 mEq/L/hr, a rate that is considered appropriate for initial therapy. Hypertonic saline is best infused in 100 ml containers to avoid inadvertently giving an excessive dose. Except when volume depletion is suspected (as in marathon runners), concurrent administration of a loop diuretic (furosemide, bumetanide, or torsemide) is advisable. The diuretic prevents volume overload and, by blocking sodium reabsorption in the loop of Henle, impedes the formation of concentrated urine.

The goal of therapy in acute hyponatremia is to decrease the severity of cerebral edema and to stop seizures. A 4 to 6 mEq/L increase in plasma sodium concentration is usually sufficient to accomplish these goals. Thus, the plasma sodium concentration should be monitored frequently during therapy and emergency treatment with hypertonic saline should be stopped after 2 to 3 hours. Once initial therapy with high-dose hypertonic saline has been completed, more conservative measures should be substituted

Table 5 Causes of the Syndrome of Inappropriate Antidiuretic Hormone

Tumors	Bronchogenic (small cell)
	Pancreatic
	Duodenal
	Urethral
	Nasopharyngeal
	Leukemia
	Hodgkin disease
Neurologic disorders	Thymoma
	Psychosis
	Trauma
	Neoplasms (primary and metastatic)
	Vascular (hemorrhage, infarction, and vasculitis)
	Infection (meningitis, brain abscess, and encephalitis)
	Miscellaneous (Guillain-Barré syndrome, multiple sclerosis, hydrocephalus, Shy-Drager syndrome)
Pulmonary disorders	Infectious (bacterial, viral, and fungal pneumonia and tuberculosis)
	Functional (asthma, acute respiratory failure, and mechanical ventilation)
Endocrine diseases	Glucocorticoid deficiency (hypopituitarism)
	Hypothyroidism
Drugs	Antidiuretic hormones (vasopressin, DDAVP, and oxytocin)
	Psychotropic agents (tricyclic antidepressants, serotonin reuptake inhibitors, monoamine oxidase inhibitors, and carbamazepine)
	Ecstasy (MDMA)
	Antineoplastic agents (cyclophosphamide, vincristine, and vinblastine)
	Nonsteroidal anti-inflammatory drugs
	Diabetic agents (chlorpropamide and tolbutamide)
	Miscellaneous (bromocriptine and nicotine)
Other causes	Postoperative stress
	Alcohol withdrawal
	AIDS
	Nausea

DDAVP—1-desamino-8-D-arginine vasopressin MDMA—methylenedioxymethamphetamine

to gradually return the plasma sodium concentration to normal. To avoid complications from excessive correction of hyponatremia, the plasma sodium concentration should not be intentionally increased by more than 12 mEq/L during the first day of therapy or by more than 6 mEq/L/day thereafter.

CHRONIC HYPONATREMIA

The distinction between acute and chronic hyponatremia is somewhat arbitrary. We consider hyponatremia to be chronic when it has evolved over the course of 48 hours or more.^{11,12,24} Although the precise duration of an electrolyte disturbance cannot be known when it develops outside the hospital (except for psychotic water drinkers, marathon runners, and users of ecstasy) outpatients can be assumed to have chronic hyponatremia.³⁰ Prolonged hyponatremia cannot occur unless there is a sustained defect in water excretion. Except for patients with renal failure, virtually all chronically hyponatremic patients have some abnormality in vasopressin secretion.

Etiology

Advanced renal failure A low glomerular filtration rate limits the ability to excrete electrolyte-free water. Many patients with advanced renal failure excrete urine that has the same osmolality as plasma regardless of physiologic conditions (fixed isosthenuria). In

acute oliguric renal failure, the ability to excrete free water is virtually nil; administration of hypotonic fluids must be scrupulously avoided to avoid hyponatremia.

Diuretics Thiazide diuretics are commonly the sole cause or a major contributing factor of hyponatremia requiring hospital admission.^{30,31} For unknown reasons, severe hyponatremia caused by thiazides affects elderly women much more often than other groups. By blocking the reabsorption of sodium and chloride in the distal tubule, thiazides and metolazone prevent the generation of maximally dilute urine.³² Because sodium reabsorption in the ascending limb of the loop of Henle is left unaffected by these agents, they permit excretion of maximally concentrated, hypertonic urine and can lead to simultaneous retention of water and depletion of sodium and potassium. Extraordinarily severe hyponatremia can result from thiazides, with plasma sodium levels as low as 100 mEq/L. Vasopressin levels are usually elevated in patients who present with thiazide-induced hyponatremia, sometimes because of diuretic-induced volume depletion but more often because of the stress of minor intercurrent illnesses. Patients with thiazide-induced hyponatremia do not usually appear clinically volume depleted, presumably because retained water partially sustains extracellular fluid volume. Patients who have become hyponatremic on thiazides should not be given these agents again; recurrent episodes of severe hyponatremia are common.

Hypovolemia Hypovolemic hyponatremia is most often associated with gastrointestinal fluid losses caused by vomiting, diarrhea, or laxative abuse. Surprisingly, particularly in alcoholics, patients who continue to drink while vomiting repeatedly can still absorb enough ingested water to become hyponatremic. Electrolyte losses in the vomitus, combined with urinary sodium and potassium losses that result from metabolic alkalosis, lower the plasma sodium concentration.

Beer potomania Patients who subsist on beer (a practice known as beer potomania) are susceptible to hyponatremia because of their low rates of solute excretion (beer contains little protein or electrolyte). Nonosmotic stimuli to vasopressin secretion caused by nausea or gastrointestinal fluid losses or by treatment with thiazide diuretics are often contributing factors.¹⁵

Edematous conditions Any disease that can cause edema also predisposes to water retention and hyponatremia. The same hemodynamic factors that promote sodium retention are nonosmotic stimuli for vasopressin release.^{8,16-18} Elevated vasopressin levels have been reported in hyponatremic patients with congestive heart failure, cirrhosis, and nephrotic syndrome. In heart failure, hyponatremia is associated with a low cardiac output and a poor prognosis.

SIADH Nonosmotic release of vasopressin that has no hemodynamic explanation is termed inappropriate [see Table 5].^{12,19} A number of tumors (most commonly small cell carcinoma of the lung) ectopically synthesize and secrete vasopressin.³³ Unexplained, persistent hyponatremia should be considered a marker for an underlying malignancy.

SIADH may also complicate the course of a wide variety of conditions in which there is damage to or inflammation of the central nervous system.^{8,12} In patients with subarachnoid hemorrhage, natriuretic peptides released by the brain may directly promote urinary sodium loss, regardless of extracellular volume (cerebral salt wasting).^{34,35} Urinary salt losses combined with vasopressin-induced water retention are responsible for hyponatremia. SIADH is

a common complication of chest infection. Antidiuretic activity has been demonstrated by bioassay in patients with tuberculous lung tissue, and tuberculosis causes SIADH.¹¹ In pneumonia, vasopressin levels are increased during the acute phase of the disease and return to baseline within a few days. Isolated glucocorticoid deficiency caused by anterior pituitary dysfunction also causes hyponatremia; patients with hypopituitarism develop inappropriate ADH secretion, but unlike patients with Addison disease, they have normal levels of mineralocorticoid and do not become hypovolemic or hyperkalemic. Hyponatremia caused by glucocorticoid deficiency promptly resolves when cortisol is replaced. Hypothyroidism also causes inappropriate ADH secretion; hyponatremia gradually resolves when thyroid hormone is replaced.³⁶ A number of therapeutic agents can induce SIADH.^{12,37} Nonsteroidal anti-inflammatory drugs (NSAIDs) decrease water excretion because they inhibit formation of prostaglandin E₂, which modulates vasopressin action.⁸ Rare cases of hyponatremia solely attributable to NSAIDs have been reported, but these commonly used agents may exacerbate other causes of hyponatremia.

Hyponatremia in AIDS Hyponatremia is an extremely common finding in AIDS.³⁸ Many AIDS patients have features of SIADH associated with opportunistic infections that cause pneumonia and meningitis. Others have clinical signs of volume depletion without low urine sodium values, a finding that may indicate coexistent renal disease or adrenal insufficiency.³⁹ Hyponatremia often occurs when antibiotics are administered in hypotonic intravenous solutions.

Diagnosis

Hyponatremia should be approached in a systematic fashion. First, the various disorders that can lower the plasma sodium concentration without causing hypotonicity should be excluded [see Differential Diagnosis for Hyponatremia, *above*]. Once it has been established that hypotonic hyponatremia is present, the mechanism for impaired water excretion is identified (hypovolemia versus an edematous condition versus SIADH), and the differential diagnosis that applies to that mechanism is considered. The most challenging goals of the diagnostic process are to determine whether chronic SIADH is present and, if it is, to define the specific disease responsible for the syndrome.

Clinical manifestations Because cerebral edema is usually not severe, the symptoms of chronic hyponatremia are much more subtle, vague, and nonspecific than those of acute water intoxication.^{12,24} The electrolyte disturbance is often asymptomatic at sodium levels that may be lethal to a patient with acute water intoxication. As the plasma sodium concentration falls below 115 to 120 mEq/L, patients often experience anorexia, nausea, vomiting, muscle weakness, and muscle cramps. They may be irritable and show personality changes, becoming uncooperative, confused, hostile, or simply slow to respond. At plasma sodium concentrations below 110 mEq/L, gait disturbances, falling, stupor, tremulousness, and, more rarely, seizures may occur.

Chronic hyponatremia itself is rarely, if ever, fatal. However, because hyponatremia can be a marker for severe underlying illness, hospitalized patients with hyponatremia often have a high mortality rate, dying with but not of chronic hyponatremia. There is little evidence that chronic hyponatremia itself leads to permanent sequelae, even when the plasma sodium concentration falls below 105 mEq/L.^{30,40} However, patients with prolonged severe hyponatremia are susceptible to iatrogenic injury if their electrolyte disturbance is corrected too rapidly [see Treatment, *below*].

History and physical examination The history of patients with chronic hyponatremia should include information about diet, fluid intake, gastrointestinal fluid losses, and use of diuretics, antidiuretics, or other antidiuretic drugs. During the physical examination, physicians should look for clinical signs of volume depletion or an edematous condition. Evidence of volume depletion may not always be definitive, however. For example, vomiting may be a symptom rather than the cause of hyponatremia; extreme hyponatremia may occasionally impair baroreceptor reflexes causing postural hypotension and a false impression of volume depletion; and retained water may mask underlying volume depletion. When the distinction between hyponatremia caused by hypovolemia and hyponatremia caused by inappropriate antidiuretic hormone secretion is not obvious, laboratory clues may be helpful.

Laboratory tests Measurement of the urinary sodium, chloride concentration, or both is often the most helpful test.⁴¹ Water retention caused by hypovolemia or by an edematous condition is usually associated with a urinary sodium concentration lower than 20 mEq/L. Hypovolemia caused by upper gastrointestinal fluid losses is an important exception. Loss of gastric fluid causes a metabolic alkalosis that may increase urinary sodium excretion despite volume depletion; the diagnosis can be made by measuring the urine chloride concentration, which is reduced in this condition. In SIADH, urinary sodium matches intake; as the urine is usually concentrated, the urinary sodium concentration exceeds 40 mEq/L unless dietary sodium intake is very low. Measurements of the BUN and serum uric acid complement these measurements. When a hemodynamic abnormality is responsible for hyponatremia, the kidney is underperfused, urea and uric acid clearances are diminished, and the BUN and serum uric acid levels are usually elevated. Conversely, SIADH is a volume-expanded state, and BUN and uric acid levels are usually low. Uric acid is a more reliable indicator of volume status than the BUN, because the latter value is affected by dietary protein intake as well as renal clearance. Assessment of acid-base and potassium balance may provide helpful clues to the diagnosis. The serum potassium and bicarbonate levels are normal in SIADH. Hypokalemia and metabolic alkalosis suggest diuretic therapy or vomiting, which can be surreptitious. Hyperkalemia and metabolic acidosis suggest the possibility of adrenal insufficiency. Hypokalemia and acidosis are found in diarrhea and raise the possibility of surreptitious laxative abuse.

Withdrawal of hyponatremic drugs When a patient is taking a drug that can cause hyponatremia, it is important to exclude another underlying cause for hyponatremia before attributing the electrolyte disturbance to the medication. For example, thiazide diuretics can exacerbate hyponatremia caused by SIADH. The best way to make a diagnosis of drug-induced hyponatremia is to eliminate the offending agent and be sure that water excretion returns to normal when the patient is off the drug. Full resolution of hyponatremia and full recovery of diluting function may be delayed for a week or two in patients with thiazide-induced hyponatremia. During repair of sodium and potassium deficits, transient resetting of the osmostat is common and should not necessarily prompt an extensive search for an underlying cause.

Response to therapy On occasion, evidence regarding the cause of hyponatremia can be equivocal. In such cases, the patient's response to isotonic saline (or a generous oral salt intake and the passage of time) is the best clue to the diagnosis. Patients with subclinical edematous conditions will retain the administered sodium,

developing clinically obvious edema. Volume-depleted patients initially retain the administered sodium, but as soon as hypovolemia is corrected, the urine becomes dilute, the rate of urinary sodium excretion increases to match intake, and hyponatremia improves as water is excreted in the urine. Urinary sodium excretion promptly increases in patients with SIADH, but the urine remains concentrated and hyponatremia persists. Isotonic saline should be given with extreme caution to patients with very low plasma sodium concentrations; in SIADH, saline can exacerbate hyponatremia, whereas in volume depletion, hyponatremia may correct too rapidly.

Identifying a specific cause for SIADH SIADH is a mechanism for developing hyponatremia, not a diagnosis. In all patients with SIADH, a specific etiology for inappropriate vasopressin secretion should be sought. When hyponatremia develops in the hospital, the cause is sometimes obvious (e.g., pneumonia, meningitis, acute respiratory failure) and no further testing is indicated. In a patient with clinical features of SIADH but no obvious cause for it, a more extensive evaluation is indicated. The workup should include a careful search for malignancy and central nervous system pathology and an endocrine evaluation to exclude hypothyroidism and hypocortisolism. Sometimes, no cause for SIADH is found, especially in elderly patients and patients with psychiatric disorders, mental retardation, or alcoholism.⁴² Careful follow-up is important, because malignancies may become clinically apparent after several years in so-called idiopathic SIADH.

Treatment

Patients with very low plasma sodium concentrations usually have some neurologic symptoms, and they are at risk of injuries from falls. However, unlike acute water intoxication, there is little risk of an explosive onset of seizures or a fatal outcome in chronic hyponatremia. On the other hand, patients with chronic hyponatremia are at considerable risk of neurologic injury caused by over-aggressive correction. Thus, there are four major goals in managing chronic hyponatremia: (1) prevention of a progressive decrease in plasma sodium concentration; (2) amelioration of symptoms caused by hyponatremia; (3) avoidance of excessive correction; and (4) gradual restoration and maintenance of a normal plasma sodium concentration.

Free-water restriction should be instituted in all patients until the plasma sodium concentration has begun to increase. Intravenous fluids should be at least isotonic, and oral fluid intake should be limited to 500 to 1,000 ml/day, depending on the severity of the electrolyte disturbance. In patients with reversible defects in water excretion, limitations on free-water intake should be lifted once the plasma sodium concentration has begun to increase.

Attempts to calculate the dose of sodium chloride needed to correct hyponatremia are doomed to failure. The increase in plasma sodium concentration depends on the amounts of administered sodium and potassium that have been retained without being excreted, as well as on the amount of electrolyte-free water that is eliminated in the urine. Indeed, in some cases, the plasma sodium concentration will return to normal solely because of a water diuresis, with no sodium given. The measures required to increase the plasma sodium concentration, along with the likelihood of inadvertent rapid correction, vary depending on the cause of hyponatremia. For therapeutic purposes, the causes can be divided into reversible and persistent defects in water excretion.

Reversible defects in water excretion Hyponatremia corrects easily when the cause for defective water excretion can be

eliminated by volume expansion, by withdrawal of a therapeutic agent, or by treatment of an underlying illness [see Table 4]. In patients with reversible defects in water excretion, prevention of excessive correction may become a major challenge.

Hypovolemic hyponatremia responds readily to 0.9% sodium chloride because the sodium concentration of isotonic saline is higher than the cation concentration of the excreted urine. Once the volume deficit is repaired and the hemodynamic stimulus to vasopressin secretion is removed, the urine becomes dilute and a water diuresis may rapidly return the plasma sodium concentration to normal. Similarly, patients with diuretic-induced hyponatremia are extremely susceptible to rapid correction; restoration of the renal diluting mechanism when the diuretic is discontinued and replacement of sodium and potassium deficits contribute to the increase in plasma sodium concentration.

Intravenous saline should be discontinued once clinically apparent hypovolemia has been corrected and the plasma sodium concentration has begun to increase. Saline should be given cautiously, if at all, to hypokalemic patients who require potassium replacement. During repair of a potassium deficit, potassium enters cells, displacing sodium, which then returns to the extracellular fluid; administered potassium is therefore as effective as sodium in raising the plasma sodium concentration. Diuretic-induced hyponatremia does not usually necessitate use of intravenous saline; for most patients, an adequate diet, replacement of potassium deficits, and discontinuance of thiazide diuretics are sufficient. In severely hyponatremic patients, the plasma sodium concentration should be monitored every 6 to 8 hours for the first 2 to 3 days of therapy. If it appears that a water diuresis is going to increase the plasma sodium by more than the desired amount, replacement of fluid losses with oral water or 5% dextrose in water may become necessary.

Persistent defects in water excretion: SIADH Patients with SIADH tend to be resistant to rapid changes in plasma sodium concentration (unless the cause of SIADH is short-lived). Water restriction is the cornerstone of therapy, but if used alone, water restriction often leads to an extremely slow resolution of hyponatremia. Isotonic saline is ineffective and may even be counterproductive. Furosemide and loop diuretics are often useful therapeutic adjuncts because by blocking sodium reabsorption in the ascending limb of the loop of Henle, they interfere with the renal-concentrating mechanism, partially blocking the effect of vasopressin. Loop diuretics can be combined with oral salt or a slow infusion (approximately 15 mL/hr) of 3% saline. Oral and intravenous urea have been used extensively to treat SIADH in some parts of Europe, but experience with this agent in the United States is very limited. Demeclocycline, a tetracycline that blocks the effect of vasopressin on the collecting duct, is another therapeutic option in chronic SIADH; however, its expense and long duration of action limit its effectiveness. Several orally active vasopressin receptor blockers have been developed and are currently in clinical trials.^{43,44}

Persistent defects in water excretion: edematous conditions and renal failure Saline should rarely, if ever, be given to correct hyponatremia in edematous patients or patients with renal failure (except for those with prerenal azotemia). Because it has no effect on water excretion, 1 L of 0.9% saline will increase the plasma sodium concentration by only 1 mEq/L.¹² In addition, saline exacerbates edema and ascites in patients with cirrhosis and may cause pulmonary edema in patients with congestive heart failure or renal failure.

Although thiazide diuretics are contraindicated, loop diuretics

are the mainstay of treatment of hyponatremia for patients with edematous conditions because they increase free-water excretion and improve hyponatremia, particularly when dietary salt intake is increased. There is a natural inclination to discontinue loop diuretics when severely edematous patients develop hyponatremia. The usual problem, however, is oliguria and diuretic resistance rather than overdiuresis; the proper response is to increase the dose of loop diuretics and restrict water intake. The combination of a loop diuretic and an angiotensin converting enzyme (ACE) inhibitor is particularly effective in patients with congestive heart failure. The beneficial effect of an ACE inhibitor can be explained by reduced thirst and vasopressin secretion attributable to angiotensin II and by a direct effect on the hydro-osmotic effect of vasopressin, mediated by prostaglandins.¹¹

Hyponatremia in edematous conditions is mediated by vasopressin. Clinical trials have shown that vasopressin receptor antagonists can be effective in managing patients with hyponatremia and edema.^{43,44}

Treatment of hyponatremic seizures A small percentage of chronically hyponatremic patients with very low plasma sodium concentrations present with seizures. Regardless of the suspected duration or cause of the electrolyte disturbance, active seizures may be resistant to anticonvulsants alone and should be treated with hypertonic saline. The therapeutic approach is similar to that used for patients with acute water intoxication, except that even more vigilance is required to prevent an excessive increase in plasma sodium concentration once emergency measures have been discontinued.^{12,24}

Complications of Therapy: Myelinolysis and Osmotic Demyelination Syndrome

Excessive correction of chronic hyponatremia may be complicated by neurologic injury.^{40,45} Typically, the patient's hyponatremic symptoms improve as the plasma sodium concentration increases, but after a delay of one to several days, new findings emerge. The patient may become confused and may exhibit psychotic or catatonic behavior, pathologic crying, or a movement disorder. Swallowing dysfunction, progressive unresponsiveness, and a spastic quadriparesis may develop. In severe cases, locked-in syndrome occurs—that is, the patient is awake but unable to move or respond. The stereotypical pattern of delayed neurologic deterioration after rapid correction of hyponatremia has been named the osmotic demyelination syndrome,⁴⁵ because these clinical features are associated with brain lesions (myelinolysis) characterized by disruption of myelin and sparing of neurons and axons.^{46,47} Lesions, which are best identified by magnetic resonance imaging, are typically found in the center of the basal pons (central pontine myelinolysis [CPM]), but histologically similar lesions may also occur in a symmetrical distribution in extrapontine areas of the brain where there is a close admixture of gray and white matter. The osmotic demyelination syndrome has been reproduced in animal studies⁴⁶; these experiments have shown that the disorder is a complication of rapid correction of hyponatremia rather than the electrolyte disturbance itself. Observational studies in severely hyponatremic patients suggest that this therapeutic complication can be avoided if rates of correction are maintained below 10 to 12 mEq/L/day and 18 mEq/L/48 hr. Because large increases in the serum sodium concentration are seldom required to relieve hyponatremic symptoms and because unintentional excessive correction is common, the goal of therapy should be to increase serum sodium concentration by 8 mEq/L/day or less.¹²

Disorder of Water Deficiency: Hypernatremia

PATHOGENESIS

Persistent hypernatremia results from one of two basic mechanisms: water is lost and not adequately replaced or, less commonly, too much salt is taken in without enough water [see Table 6].^{13,48-50} In either case, electrolyte-free water is needed to return the plasma sodium concentration to normal. Because thirst is the primary defense against hypertonicity, persistent hypernatremia means there is a defect in water intake. A maximally concentrated urine minimizes but does not prevent water losses. Insensible water losses from the skin and lungs are unavoidable and urea excretion obligates some urinary losses. Maintenance of a normal serum sodium concentration (135 to 142 mEq/L) requires that daily water losses be replaced.

Most hypernatremic patients are too sick, too young, or too old to obtain water themselves or ask for it.^{13,48} Sometimes, the thirst sensation itself is impaired, so that the patient has no desire to drink when the plasma sodium concentration increases above the normal range. Inadequate water intake by itself will lead to hypernatremia. When impaired intake is coupled with excessive water losses, severe hypernatremia results.

ETIOLOGY

Electrolyte-free water can be lost as pure water, with no accompanying electrolyte, or it can be lost in hypotonic fluids, which have lower electrolyte concentrations than plasma. Hypotonic losses can be thought of as mixtures of isotonic fluid and free water. Pure-water and hypotonic fluid losses, the most common causes of hypernatremia, are typically associated with a contracted extracellular fluid volume.¹³ However, this is not always the case. When hypernatremia is caused by a rapid intake of salt (acute salt poisoning), the extracellular volume expands because of water drawn from the intracellular space.⁴⁸ In critically ill patients, extracellular volume expansion with edema often coexists with hypernatremia^{49,51}; the finding reflects free-water losses in patients who become edematous after fluid resuscitation for shock or underlying conditions such as congestive heart failure, renal disease, and hepatic cirrhosis.

Pure-Water Losses

If pure-water losses are responsible for hypernatremia, each body-fluid compartment loses an equal percentage of its volume.^{13,48} Plasma constitutes only one twelfth of total body water (one quarter of extracellular fluid volume), and plasma volume is defended by oncotic pressure, which increases with water loss. Thus, plasma volume contracts by less than 83 ml for each 1 L of water lost; clinical signs of hypovolemia are unusual unless the water deficit is extremely large.

Insensible water losses Water is constantly lost by evaporation from the skin and lungs and must be replaced to avoid dehydration. Daily insensible water losses, normally about 0.5 L, can be increased severalfold by high environmental temperature, fever, or hypermetabolic states such as thyrotoxicosis.

Increased urea excretion Although urea is an ineffective osmole that freely crosses most cell membranes, urinary urea excretion can play an important role in water balance. High rates of urea excretion caused by protein-rich diets, catabolism, or recovery from renal failure obligate increased rates of water loss. When the urine solute is composed almost exclusively of urea, the urine becomes an electrolyte-free water solution, regardless of its osmolality.

Table 6 Causes of Hypernatremia

Electrolyte-free water losses	Extrarenal Insensible loss (skin and lungs)
	Renal Neurogenic (central) diabetes insipidus Nephrogenic diabetes insipidus Congenital X-linked (V_2 vasopressin receptor defect) Recessive (aquaporin defects) Acquired Electrolyte abnormalities: hypokalemia, hypercalcemia Drugs: lithium, demeclocycline, methoxyflurane Pregnancy (vasopressinase) Excess urea excretion
Hypotonic losses	Extrarenal Sweat Upper GI tract Osmotic cathartics
	Renal Glycosuria, mannitol, glycerol, diuretics
Salt poisoning	Oral Parenteral NaHCO ₃ , 3% or 5% I.V. saline, therapeutic abortion (inadvertent 29% I.V. saline) Hemodialysis with hypertonic dialysate

Diabetes insipidus Because sodium excretion is unaffected in diabetes insipidus (see below), the excess fluid lost in the urine is pure water. As long as water is available and the patient is able to drink, hypernatremia does not occur. Without water replacement, however, hypernatremia develops within a few hours

Hypotonic Losses

Hypernatremia caused by hypotonic fluid loss is associated with extracellular volume depletion.

Sweat Sweat is a hypotonic solution containing water, sodium, potassium, and chloride. Sweat glands respond to aldosterone by lowering the sodium concentration and increasing the potassium concentration of their secretions.

Gastric fluid losses Fluid lost by vomiting or nasogastric suction is hypotonic to plasma. Without adequate water replacement, large gastric fluid losses can cause hypernatremia.

Osmotic cathartics Fecal losses of water contain electrolytes at a concentration comparable to that of plasma, except when osmotic cathartics such as sorbitol or lactulose are given. These cathartic agents osmotically attract electrolyte-free water to the intestinal lumen, leading to hypotonic fluid losses. Oral sorbitol is a nonabsorbable solute, given with sodium polystyrene sulfonate (Kayexalate) to treat hyperkalemia or with charcoal to treat poisoning; the sugar osmotically attracts electrolyte-free water into the intestinal lumen, where it is eliminated in the stool. Similarly, lactulose, which is used to treat hepatic encephalopathy, can promote large electrolyte-free water losses, causing a high incidence of hypernatremia unless the lost water is replaced.

Osmotic diuretics and glycosuria Glucose in the extracellular fluid acts as an effective osmole that attracts water to the extracellular fluid, dehydrating cells and lowering the plasma sodium

concentration.^{22,48} Excretion of glucose in the urine acts as an osmotic diuretic that can provoke the loss of several liters of hypotonic fluid. Electrolyte-free water losses induced by glycosuria raise the plasma sodium concentration, offsetting the hyponatremic effect of the high blood glucose levels. Intravenous hypertonic mannitol has a similar effect on body fluids.

Acute Salt Poisoning

Water losses increase the serum sodium concentration over hours or days. The oral ingestion of large amounts of salt without water—1 tsp of salt contains nearly 350 mEq of NaCl, enough to increase the plasma sodium concentration by 8 mEq/L—or the intravenous infusion of hypertonic salt solutions can increase the plasma sodium concentration much more rapidly (i.e., cause acute salt poisoning).^{13,48}

DIAGNOSIS

Clinical Manifestations

An acute onset of hypernatremia (seen virtually exclusively in acute salt poisoning) causes the brain to shrink, leading to vascular injury and intracranial bleeding. Patients present with seizures, coma, hyperventilation, hyperreflexia, hypertonia, and high fever. Acutely hypernatremic patients with plasma sodium levels above 170 mEq/L often die.^{13,48}

Given time to adapt, brain cells protect their volume by accumulating organic osmolytes, preventing the hemorrhages caused by acute hypernatremia. Thus, the clinical manifestations of chronic hypernatremia are less dramatic than those seen in acute salt poisoning, ranging from lethargy to coma, depending on the severity of the electrolyte disturbance.^{13,48,50}

The clinical signs of pure-water loss and acute salt poisoning are primarily neurologic. Hypotonic fluid losses may be associated with signs and symptoms of extracellular fluid volume depletion in addition to symptoms related to hypernatremia.

Recognition of Water Deficit

The plasma or serum sodium concentration can be used to determine how much water is needed to restore normotonicity; it seriously underestimates the magnitude of the water deficit in diabetic patients with hyperglycemic dehydration [see Treatment, Diabetic Dehydration, below]. In patients without severe hyperglycemia, the percentage increase in the serum sodium concentration approximates the percentage decrease in total body water, as stated more precisely in the following:

$$\text{Water deficit} = \text{Normal body water} (1 - \text{serum } [\text{Na}^+]/140)$$

The value for body water is based on the patient's usual body weight (often an estimate), age, and sex.

The calculated water deficit is the amount of water that will return the serum sodium concentration to normal. It reveals nothing about the volume status of the extracellular fluid. Extracellular fluid volume deficits (or surfeits) must be estimated from the history and physical examination, not from the serum sodium concentration.

TREATMENT

Correction of severe extracellular volume depletion takes precedence over correction of hypernatremia. When the patient is hypotensive, initial therapy should include a rapid infusion of isotonic saline to quickly achieve hemodynamic stability. In hemodynamically stable patients, pure-water losses should be replaced with pure water, and isotonic saline is not required. Edematous patients with hy-

pernatremia can be given diuretics along with electrolyte-free water to replace urinary electrolyte-free water losses; the net effect is reduction of the extracellular volume surfeit and restoration of normotonicity and cell volume.

Electrolyte-free water can be given intravenously in a 5% dextrose solution (D5W) to patients who are unable to drink. Dextrose solutions cannot be infused more rapidly than approximately 500 ml/hr. More-rapid infusions provide more glucose than can be metabolized and therefore cause hyperglycemia, glycosuria, and urinary water losses, which are counterproductive to the correction of hypertonicity. Water replacement should not be based on formulas alone; the serum sodium concentration and urine output should be monitored frequently so that the fluid prescription can be adjusted appropriately.

Rate of Correction

In the vast majority of cases, the onset of hypertonicity is slow enough for brain adaptations to minimize cerebral dehydration. Organic osmolytes that accumulate in the adaptation to hypernatremia are slow to leave the cell during rehydration. If hypernatremia is corrected too rapidly, cerebral edema results.^{13,48} To be safe, the serum sodium concentration should be reduced by no more than 10 to 12 mEq/L/day. To achieve the desired rate of correction, electrolyte-free water intake should exceed free-water losses by no more than 2 L daily.

Acute salt poisoning causes devastating brain injury that is largely irreversible. In rare cases when acute salt poisoning can be rapidly diagnosed (e.g., in a case of inadvertent intravenous infusion of hypertonic saline during therapeutic abortion), an effort to prevent a neurologic catastrophe can be made with rapid infusions of electrolyte-free water along with a loop diuretic before the results of the serum electrolyte measurements are known.

Diabetic Dehydration

Hypertonicity associated with diabetes mellitus is a complex disorder.²² The osmotic diuresis induced by glycosuria results in both saltwater and electrolyte-free water losses; the accumulation of glucose in the extracellular fluid adds impermeant solute, which contributes to hypertonicity and neurologic symptoms. Severely dehydrated hyperglycemic patients may not appear hypovolemic at first, because the high glucose concentration in the extracellular fluid osmotically attracts water from cells, masking the loss of saltwater. With correction of hyperglycemia, marked hypovolemia may emerge. Initial treatment should include 1 to 2 L of isotonic saline in anticipation of this complication, even in patients who are initially normotensive. With volume expansion, excess glucose will be excreted in the urine, creating an ongoing requirement for both saline and electrolyte-free water. An infusion of 0.45% saline at a rate that exceeds urine output by approximately 250 ml/hr will serve to replace the electrolyte-free water deficit and remaining saltwater deficits. The serum sodium concentration, blood glucose level, and urine output should be monitored carefully so that fluid replacement can be tailored to the patient's needs. Rapid correction of hypertonicity should be avoided because of the risk of cerebral edema.

Patients with oliguric renal failure do not become dehydrated when they become severely hyperglycemic. Such patients often experience hypertension or congestive heart failure because of fluid shifts from cells to the extracellular fluid. Even after adjusting for the effect of hyperglycemia, the serum sodium concentration is often low. Insulin is the only required treatment; neither isotonic saline nor 0.45% saline is indicated.

Disorder of Water Conservation: Diabetes Insipidus

PATHOGENESIS

Neurogenic diabetes insipidus (DI) is caused by deficient secretion of vasopressin^{8,52,53}; nephrogenic DI results from the kidney's unresponsiveness to normally secreted hormone.⁵⁴ Both disorders present with polyuria (loosely defined as the passage of excessive volumes of urine—generally more than 3 to 4 L daily) and polydipsia (excessive thirst). Most patients with polyuria do not become hypernatremic, because thirst maintains electrolyte-free water balance.

Defective responsiveness to vasopressin (nephrogenic DI) may be inherited as an X-linked trait, caused by a mutation in the gene encoding for the V₂ vasopressin receptor or as an autosomal recessive trait caused by a mutation in the gene encoding for the vasopressin-responsive water channel (aquaporin 2). Acquired nephrogenic DI may be caused by lithium or demeclocycline therapy, hypokalemia, or hypercalcemia; or it may complicate a number of renal diseases [see Table 6]. Vasopressin-resistant DI may emerge during the late stage of pregnancy as a result of vasopressinase released by the placenta; many affected patients have underlying, subclinical partial neurogenic or nephrogenic DI that has been exacerbated by increased catabolism of circulating vasopressin.

DIAGNOSIS

Clinical Manifestations

Patients with DI complain of polyuria, nocturia (the need to urinate during the night), and polydipsia. The only significant physical findings or laboratory abnormalities are those of the underlying cause.

Laboratory Tests

A diagnosis of DI can be made if the urine osmolality is less than 250 mOsm/kg despite hypernatremia.⁸ When the disease is suspected in a polyuric patient whose serum sodium concentration is normal or borderline, the urine osmolality level can be monitored while the patient is deprived of water, allowing the serum sodium level to increase to higher than 143 mEq/L. Exogenous vasopressin increases urine osmolality by more than 150 mOsm/kg in patients with neurogenic, but not nephrogenic, DI. It is possible to misdiagnose DI in patients who actually have a primary thirst disorder. Excessive water intake suppresses vasopressin secretion and causes polyuria with dilute urine. Because patients with primary polydipsia secrete vasopressin normally, they do not become hypernatremic during diagnostic water deprivation. Correlation with plasma vasopressin levels is often necessary in borderline cases. Polyuric patients whose urine osmolality equals or exceeds plasma osmolality should be distinguished from patients with DI; polyuria in such cases is usually caused by excessive excretion of salt, urea, or glucose or by an osmotic diuretic (solute diuresis).

Magnetic resonance imaging of the brain can be helpful in the evaluation of patients with suspected DI.^{8,53} In 85% to 90% of healthy adults and children, the posterior pituitary emits a hyperintense signal, or so-called bright spot, on T₁-weighted magnetic resonance images, apparently related to the vasopressin release of the gland. This bright spot is also normal in 85% to 90% of patients with primary polydipsia, but it is almost always absent or greatly diminished in patients with pituitary DI.

TREATMENT

When access to water is limited, patients with DI are more susceptible to dehydration than normal persons. Thus, water losses must be carefully replaced during superimposed illnesses. Neuro-

genic DI is best treated with a synthetic antidiuretic hormone, 1-desamino-8-D-arginine vasopressin (DDAVP), which can be given parenterally or intranasally.^{8,53} Chlorpropamide or carbamazepine, both of which enhance vasopressin action, or thiazide diuretics, which limit the ability to maximally dilute the urine, can be used in patients with mild disease. Limiting dietary salt and protein intake is also helpful. Nephrogenic diabetes can also be treated with dietary measures or with thiazides and indomethacin (which helps concentrate the urine by inhibiting prostaglandin synthesis). Lithium-induced nephrogenic DI may be improved by amiloride, which blocks lithium entry into the collecting duct cell.

Disorder of Saltwater Excess: Edematous States

Edema, a swelling of the soft tissues that can be indented or pitted by the examiner's fingers, is the clinical manifestation of an expanded interstitial fluid volume. To be detected clinically, interstitial volume must increase by at least 2.5 to 3 L, nearly equaling the total amount of fluid in the intravascular space. Thus, generalized edema requires an increase in the total amount of saltwater in the extracellular space, and it implies retention of dietary or infused sodium, with an impaired ability to excrete saltwater.

PATHOGENESIS

Excess fluid collects in the interstitial space in response to Starling forces, which govern the movement of extracellular fluid into and out of the vasculature. Edema occurs when there is increased capillary blood pressure, decreased plasma oncotic pressure, increased capillary permeability to protein, or obstruction to lymph flow.

When fluid overflows from an overfilled vascular space into the interstitium, impaired sodium excretion is clearly implicated. However, even when edema formation results from decreased oncotic pressure or increased capillary permeability, renal sodium retention is required to replace the saltwater that has been lost from the vasculature.

ETIOLOGY

Primary Renal Sodium Retention: Edema Caused by Renal Disease

Nephrotic syndrome The nephrotic syndrome is characterized by heavy urinary protein losses (in excess of 3 g/day), hypoalbuminemia, and edema.⁵⁵ The syndrome, which can be seen in a variety of glomerular diseases, is caused by increased permeability of the glomerular capillary to protein. Traditionally, edema in the nephrotic syndrome has been ascribed to decreased plasma oncotic pressure. This no longer appears to be the sole explanation. Correction of hypoalbuminemia by infusing albumin does not consistently improve the edema, and resolution of edema in steroid-responsive cases may precede improvement of hypoalbuminemia. Thus, in most patients, primary sodium retention by the kidney, independent of an underfilled vasculature, plays a major contributing role.

Nephritic edema Glomerular diseases characterized by proliferation of mesangial cells (e.g., diffuse proliferative glomerulonephritis and membranoproliferative glomerulonephritis) often cause primary sodium retention that is not associated with heavy proteinuria or hypoalbuminemia (the nephritic syndrome). Patients with nephritic edema are typically hypertensive and may present with congestive heart failure because of an overexpanded vascular volume.

Secondary Renal Sodium Retention: Edema Caused by Extrarenal Disease

In congestive heart failure and hepatic cirrhosis, the body responds as if it were volume depleted. Despite an expanded interstitial fluid volume, as well as increased total body sodium content, the kidney avidly retains salt and water. The normal renal response to a high salt intake is lost, and progressive salt retention occurs. In these conditions, volume regulatory mechanisms are responding to reduced fullness of the arterial portion of the vascular system, which normally contains about 15% of the total blood volume.

Congestive heart failure Advanced stages of the many disorders that affect the pericardium, myocardium, or heart valves can produce congestive heart failure, a disorder characterized by renal sodium retention and interstitial edema in systemic or pulmonary capillary beds.^{16,17} Arterial receptors are activated when cardiac output falls (low-output congestive failure) or when cardiac output is not high enough to compensate for decreased peripheral resistance (high-output failure).

Cirrhosis Patients with severe liver disease may exhibit profound salt retention, often excreting less than 10 mEq of sodium in the urine each day. Scarring of the hepatic parenchyma increases resistance to blood flow in the postsinusoidal venules, resulting in high sinusoidal pressures and venous hypertension throughout the portal system. Portal hypertension and hypoalbuminemia promote the formation of ascites. In addition, the cirrhotic patient is vasodilated because of endotoxins, vasodilatory prostaglandins, nitric oxide, various gut hormones, and other mediators. The combined effects of blood pooling in the splanchnic circulation (caused by portal hypertension) and systemic vasodilatation lead to underfilling of the arterial circulation and subsequent activation of sodium-retaining factors.⁵⁶

Idiopathic edema Idiopathic edema is a benign disorder of young, menstruating women who have no cardiac, hepatic, or renal disease.⁵⁷ Fluid retention often begins premenstrually and then becomes persistent. Depression and neurotic symptoms are commonly present, and affected patients are often weight conscious and markedly concerned about even minor degrees of edema. Some patients episodically fast for days at a time and then accumulate edema on refeeding. In many others, diuretics play an important role in the pathogenesis of idiopathic edema. Long-term diuretic or cathartic use leads to persistent hypovolemia and chronic activation of sodium-retaining mechanisms, which include hypertrophy of the nephron segments distal to the site of action of the diuretic. When the diuretic is stopped, marked sodium retention occurs because the sodium-retaining forces cannot be shut off rapidly. The patient thus becomes convinced of the need for diuretics, and the cycle continues.

DIAGNOSIS

The symptoms and laboratory findings associated with edematous conditions depend on the underlying cause. Dyspnea on exertion and orthopnea provoked by pulmonary interstitial edema are prominent features in patients with left ventricular failure or nephritic edema, but these symptoms are usually absent when edema is caused by right heart failure, nephrotic syndrome, or cirrhosis. Mild peripheral edema collects in the dependent portions of the anatomy and is usually asymptomatic. Although more severe edema, which can extend to the thighs and buttocks, may be uncomfortable, it is usually harmless. A large volume of ascites not only causes discomfort but also may elevate the diaphragm, causing shortness of breath; promote reflux of gastric fluid, causing bleeding from esophageal varices; or become infected spontaneously.

The diagnosis of edema should be approached systematically, looking for evidence of heart, renal, or liver disease. A diagnosis can usually be made from the history and physical examination, urinalysis, liver function tests, and chest x-ray. More puzzling cases may require echocardiography or, rarely, right heart catheterization. Plasma levels of B-type natriuretic peptide (BNP) are increased in patients with heart failure. Used in conjunction with other clinical information, rapid-measurement BNP is useful in establishing or excluding the diagnosis of congestive heart failure in patients who present with acute dyspnea.⁵⁸

TREATMENT

Dietary salt restriction is important for patients with edema, but this measure alone is impractical or insufficient when urinary sodium excretion is reduced to very low levels. Thus, most edematous patients whose underlying condition cannot be reversed require treatment with diuretics.^{5,59} Salt restriction and diuretics are adjunctive treatments for heart failure. Therapy is also directed at improving cardiac performance by using digoxin and vasodilators to reduce afterload. Recombinant human BNP (nesiritide) has become available for the treatment of acute decompensated heart failure. The agent reduces pulmonary capillary wedge pressure and systemic vascular resistance, improves cardiac performance, and has a diuretic effect, in part because of its effect on sodium reabsorption in the distal nephron.⁶⁰

Ascitic fluid is a separate compartment of the extracellular fluid compartment that is much more difficult to mobilize than peripheral edema. Thus, cirrhotic patients who have ascites but no peripheral edema are susceptible to intravascular volume depletion when they are treated with diuretics; weight loss should thus be limited to 0.5 kg daily. Repeated large-volume paracenteses combined with intravenous albumin is a safe and effective alternative to diuretics that avoids intravascular volume depletion.⁶¹ The subsequent administration of diuretics prevents reaccumulation of ascitic fluid.

Use of Diuretics

Diuretics increase saltwater excretion by impairing tubular reabsorption of the sodium filtered by the glomerulus. The diuretic effect is dose-dependent; the maximum response is determined by the diuretic's site of action within the nephron, the filtered load of sodium, and the amount of sodium reabsorbed by nephron segments unaffected by the diuretic.

Mechanism of action All diuretics except spironolactone are specific inhibitors of luminal transporters and must gain access to the tubular fluid to block sodium reabsorption.^{5,59} Because diuretic agents are highly protein bound, they are not readily filtered at the glomerulus; instead, they are actively transported into the urine by the organic acid (e.g., acetazolamide, thiazide, and loop diuretic) or organic base (e.g., amiloride and triamterene) secretory pumps in the proximal tubule. A dose-response curve links the amount of drug reaching the urine to the amount of sodium excretion that is elicited [see Figure 4]. Spironolactone binds to the cytosolic receptor for aldosterone, and its diuretic action, unlike that of other diuretics, does not depend on secretion into the tubular lumen.

The most potent agents are those that block sodium transport in the loop of Henle. At high doses, loop diuretics almost totally block sodium reabsorption in this nephron segment, causing about 20% of the filtered load of sodium to be excreted in the urine; at low glomerular filtration rates, the same percentage of filtered sodium is excreted, but the total amount is reduced. Conditions such as volume depletion, heart failure, and cirrhosis, which cause avid sodium reabsorption in the proximal and distal tubules, blunt the maximum response to the diuretic.

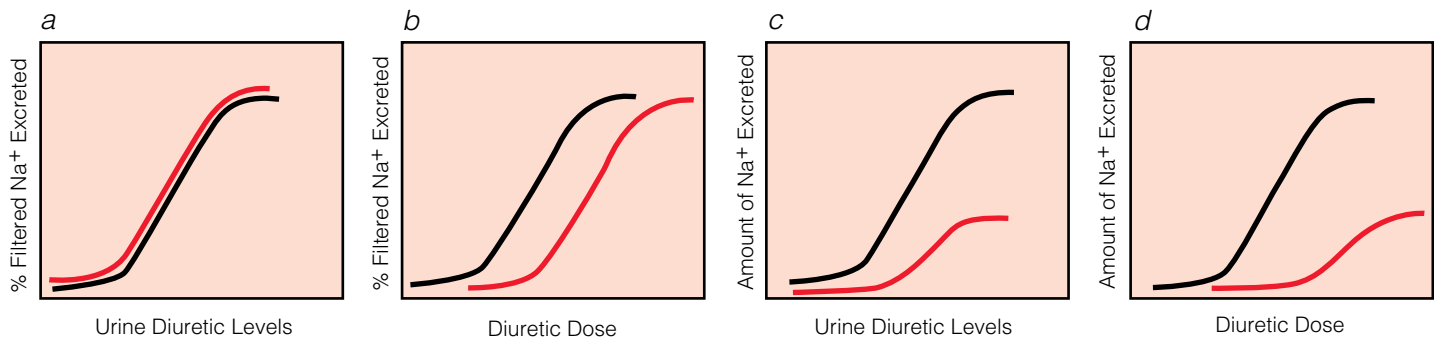


Figure 4 Dose-response curves for a loop diuretic in patients with normal (black line) and reduced (red line) renal function. Urinary sodium excretion responds to diuretic levels in the tubular lumen (as reflected by urinary drug levels). The diuretic effect reaches a maximum at approximately 20% of the filtered load of sodium regardless of renal function (a). Secretion of the diuretic into the tubular lumen is reduced in renal failure; thus, higher doses are required in azotemic patients to achieve the same urinary drug levels found in patients with normal renal function (b). Because the filtered load of sodium is reduced in patients with renal failure, absolute sodium excretion is also reduced, even at high doses (c and d).

Because gastrointestinal absorption of diuretics is often delayed in edematous conditions (presumably because of bowel edema), higher oral doses must be used to achieve adequate blood levels. In renal disease and cirrhosis, organic anions such as hippurate and bile acids compete with the diuretic for secretion into the proximal tubule; thus, higher plasma levels may be required to achieve adequate drug levels in the urine. Similarly, severe hypoalbuminemia can diminish drug secretion into the tubular lumen, because albumin binding of most diuretics maximizes the rate of diuretic delivery to the organic anion secretory pump in the proximal tubule. Reduced renal blood flow also limits delivery of drug to the tubular lumen. Some patients with advanced cirrhosis who are resistant to furosemide respond to spironolactone, a generally weak diuretic whose effectiveness does not depend on tubular secretion.

Agents that act in the proximal tubule, loop of Henle, or distal tubule cause potassium wasting and hypokalemia because they increase delivery of tubular fluid to the cortical collecting tubule, where potassium secretion is flow dependent. Potassium-sparing diuretics, which act in the cortical collecting tubule, cause hyperkalemia because sodium reabsorption at this site favors potassium secretion. The carbonic anhydrase inhibitor, acetazolamide, causes metabolic acidosis, as do the potassium-sparing diuretics. Thiazides and loop diuretics cause metabolic alkalosis because of increased distal delivery of sodium to sites where sodium reabsorption stimulates hydrogen ion secretion.

Clinical use Diuretic doses should be adjusted to achieve explicit therapeutic goals. Outpatient therapy is usually designed to produce a gradual loss of fluid, increasing the dose until a desired target weight is reached. The patient should be instructed to keep a daily log that records weight and diuretic dose. Patients are instructed to stop the diuretic if their weight falls too low, resuming at a lower dose when enough saltwater has been retained to restore the target weight.

Inpatient diuretic management should also employ the target-weight concept, but dose adjustments can be made more often and more aggressively, particularly at the start of therapy. It is important to rapidly define the dose that can deliver enough drug to the tubular lumen to reach the steep portion of the dose-response curve. Once an effective dose is defined, larger doses of diuretic provide little benefit. If a greater response is needed, the effective dose should be repeated several times during the day, or alternatively, a continuous infusion can be given to maintain effective urinary drug levels. Continuous infusion of loop diuretics induces a slightly larger natri-

uretic response than does bolus administration and is associated with a shorter hospital stay in patients with advanced heart failure.⁶²

Diuretic resistance Resistance to high doses of loop diuretics may be overcome by administering loop diuretics in combination with thiazide or metolazone. Acetazolamide may be used along with or in place of a thiazide or metolazone. This strategy blocks sodium reabsorption at several sites along the nephron, avoiding resistance caused by increased sodium reabsorption proximal or distal to the loop of Henle. Careful monitoring is extremely important, because these combinations can be extremely potent, causing large potassium and sodium losses.

Diuretic complications All diuretic agents may cause volume depletion and azotemia, but these complications are most likely to occur with loop diuretics.⁴ Hypokalemic alkalosis, hyperglycemia, and hyperuricemia (sometimes with clinical gout) are common dose-dependent complications of both thiazides and loop diuretics. Thiazides decrease calcium excretion and may cause hypercalcemia in patients with underlying conditions that increase gastrointestinal calcium absorption (e.g., sarcoidosis) or bone reabsorption (e.g., hyperparathyroidism). Thiazides are also much more likely to cause hyponatremia than other agents and should be avoided in patients who habitually drink large amounts of fluid. Potassium-sparing agents (e.g., triamterene, amiloride, and spironolactone) may cause hyperkalemia; these agents should generally not be given with potassium supplements, and they should be used with caution in patients with renal insufficiency (particularly diabetic nephropathy) and patients receiving ACE inhibitors or angiotensin II blocking agents. Loop diuretics can predispose to hearing loss, particularly when high doses are administered by bolus injection to patients receiving other ototoxic drugs.³² Hearing loss from ethacrynic acid is more likely to be permanent.

Disorder of Saltwater Deficiency: Volume Depletion

PATHOGENESIS OF VOLUME DEPLETION

Volume depletion occurs when saltwater is lost from the extracellular fluid at a rate that exceeds intake. Saltwater can be lost from the gastrointestinal tract, kidney, or skin, or it can result from extravascular sequestration (third-space losses) in the abdominal cavity or in traumatized tissues.

Underfilling of the arterial circulation triggers a cascade of physiologic responses that preserve blood flow to vital organs. Volume receptors and baroreceptors activate the sympathetic nervous system and the renin-angiotensin-aldosterone system. Except when renal salt wasting is the cause, these responses reduce urinary sodium excretion so that nearly all ingested salt is retained. Volume-depleted persons also become thirsty; ingested water is retained because vasopressin, released in response to volume depletion, concentrates the urine, decreasing water excretion. The plasma sodium concentration can be high, normal, or low in volume-depleted persons, depending on electrolyte-free water intake and excretion. Vasoconstriction maintains the systemic blood pressure and also reduces renal blood flow. Initially, efferent arteriolar resistance, mediated by angiotensin II, predominates, sustaining intraglomerular pressure and the glomerular filtration rate; in more severe hypovolemia, renal blood flow is further reduced and glomerular filtration falls.

ETIOLOGY

Because renal sodium conservation can reduce urinary sodium losses to less than 10 mmol/day, volume depletion is unlikely to occur from decreased intake alone. The small bowel and colon are the most common sources of isotonic fluid loss. Spectacular amounts of isotonic saltwater can be lost in diarrhea. For example, rice-water stool losses in cholera can reach 20 L/day, causing death within a few hours without fluid replacement. Small bowel obstruction causes pooling of several liters of saltwater within the bowel lumen. Fluid may also be sequestered in the abdominal cavity in patients with pancreatitis or peritonitis. Sequestration of fluid in the soft tissues may also complicate crush injuries with rhabdomyolysis or burns.

Renal salt wasting can cause volume depletion, but only a few disorders can cause enough renal salt loss to be clinically apparent. Diuretics and osmotic diuresis caused by glycosuria are the most frequent causes of renal salt wasting. Transient renal salt wasting may occur in the recovery phases of acute tubular necrosis or obstructive uropathy, and it can also occur in toxic nephropathies. Renal salt wasting also occurs in adrenal insufficiency.

DIAGNOSIS

Clinical Manifestations

Minor degrees of volume depletion (less than 10% of plasma volume, equivalent to the loss of one unit of blood) cause an increase in heart rate and may also be associated with complaints of fatigue, thirst, or muscle cramps. With modest hypovolemia, arteriolar vasoconstriction is sufficient to maintain the blood pressure when the patient is recumbent. However, dizziness and hypotension emerge on standing or during physical exertion. Severe fluid losses cause hypotension in recumbency and, ultimately, signs of tissue ischemia and shock (e.g., cool, clammy extremities, decreased urine output, lethargy, and confusion). Irreversible tissue injury may occur if this

condition is allowed to continue.

Loss of weight within a short period is the most reliable sign of volume depletion. Physical findings include a low jugular venous pulse rate and orthostatic changes in blood pressure and heart rate.^{63,64} However, because postural hypotension can occur in up to 30% of normovolemic persons older than 65 years, these changes must be interpreted with caution. Decreased skin turgor and dry mucous membranes are generally unreliable findings in volume-depleted adults; these signs can be absent in severe hypovolemia, and they can be present (particularly in mouth breathers and the elderly) when the patient is actually volume overloaded. The presence of edema makes true volume depletion unlikely.

Laboratory Tests

Laboratory findings are related to the decreased volume of intravascular saltwater and to decreased renal perfusion. Hematocrit increases in proportion to the contraction of plasma volume, and the serum albumin may be increased as well. Urinary sodium is usually less than 20 mEq/L except in metabolic alkalosis (in which the urine chloride is low) or when renal sodium wasting is the cause of the condition.^{41,65} Renal blood flow is reduced, but unless the patient is frankly hypotensive, the glomerular filtration rate is maintained by vasoconstriction of the efferent glomerular arteriole. Thus, except in severe volume depletion, the serum creatinine changes very little. Unlike creatinine, urea is reabsorbed from the glomerular filtrate. Thus, in volume depletion (prerenal azotemia), the BUN is increased disproportionately to the increase in creatinine.⁶⁵ Azotemia may be blunted in patients with a poor dietary-protein intake and may be exacerbated in patients who are catabolic, bleeding, or receiving steroid therapy.

TREATMENT

Patients with mild volume depletion can be treated by increasing their dietary intake of salt, relying on normal thirst mechanisms to provide the appropriate amount of water. For most patients, the familiar (but misguided) order to drink fluids should be replaced with an order to salt one's food. Even severe volume depletion can be treated with oral solutions containing electrolytes, sugar, and amino acids.⁶⁶ Glucose and amino acids promote intestinal absorption of sodium through cotransport mechanisms similar to those found in the proximal tubule of the kidney. Rice-based oral replacement solutions have been a major advance in the treatment of diarrhea in developing countries.

Intravenous fluids are necessary when fluids cannot be taken orally. If the patient is hypotensive, isotonic saline should be given as rapidly as possible until tissue perfusion is adequate. Colloid-containing solutions have no proven advantage over crystalloids.⁶⁷ There is no accurate way to estimate the total fluid deficit in hypovolemia other than continued clinical observation of the patient's response to therapy.

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Figures 3 and 4 Marcia Kammerer.

26 METABOLIC RESPONSE TO CRITICAL ILLNESS

Palmer Q. Bessey, M.D.

Metabolic Responses in Surgical Patients

Debility commonly accompanies surgical illness. It occurs in varying degrees after elective operations, major trauma, burns, infections, and other critical illnesses. Debility is caused by a variety of factors, including specific biochemical and physiologic alterations that usually occur in response to injury and disease, especially those that persist for a long time. Some aspects of surgical care that are common to almost all patients can also cause debility. This discussion will review these clinical factors and metabolic responses in critically ill surgical patients and will indicate how the clinician can manage them so as to minimize patient debility.

The metabolic responses to critical illness have been studied in a variety of critically ill patients, especially those with trauma, burns, or sepsis. The responses are often grouped into phases on the basis of their temporal relation to the injury or insult. The so-called ebb phase, which is the early phase of the injury response, is characterized by (1) an elevated blood glucose level, (2) normal glucose production, (3) elevated free fatty acid levels, (4) a low insulin concentration, (5) elevated levels of catecholamines and glucagon, (6) an elevated blood lactate level, (7) depressed oxygen consumption, (8) below-normal cardiac output, and (9) below-normal core temperature.¹ The subsequent phase, the so-called flow phase, is characterized by (1) a normal or slightly elevated blood glucose level, (2) increased glucose production, (3) normal or slightly elevated free fatty acid levels, with flux increased, (4) a normal or elevated insulin concentration, (5) high normal or elevated levels of catecholamine and an elevated glucagon level, (6) a normal blood lactate level, (7) elevated oxygen consumption, (8) increased cardiac output, and (9) elevated core temperature.¹

The ebb phase is dominated by cardiovascular instability, alterations in circulating blood volume, impairment of oxygen transport, and heightened autonomic activity. Emergency support of cardiopulmonary performance is the paramount therapeutic concern. Shock [see 8:3 Shock] is the prototypical clinical manifestation of the ebb phase. After effective resuscitation has been accomplished and restoration of satisfactory oxygen transport has been achieved, the flow phase comes into play. These responses are marked by hyperdynamic circulatory changes, signs of inflammation, glucose intolerance, and muscle wasting. Surgical patients in the ICU usually exhibit these clinical features; these patients and the clinical challenge they pose are the focus of this chapter.

When wounds are closed and infection has resolved, repletion of lean tissue and fat stores and restoration of strength and stamina can begin. This final, anabolic phase often begins near the time of hospital discharge and may persist for months before the patient fully recovers.

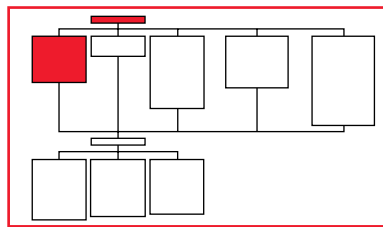
Features of Critical Illness That Can Cause Debility

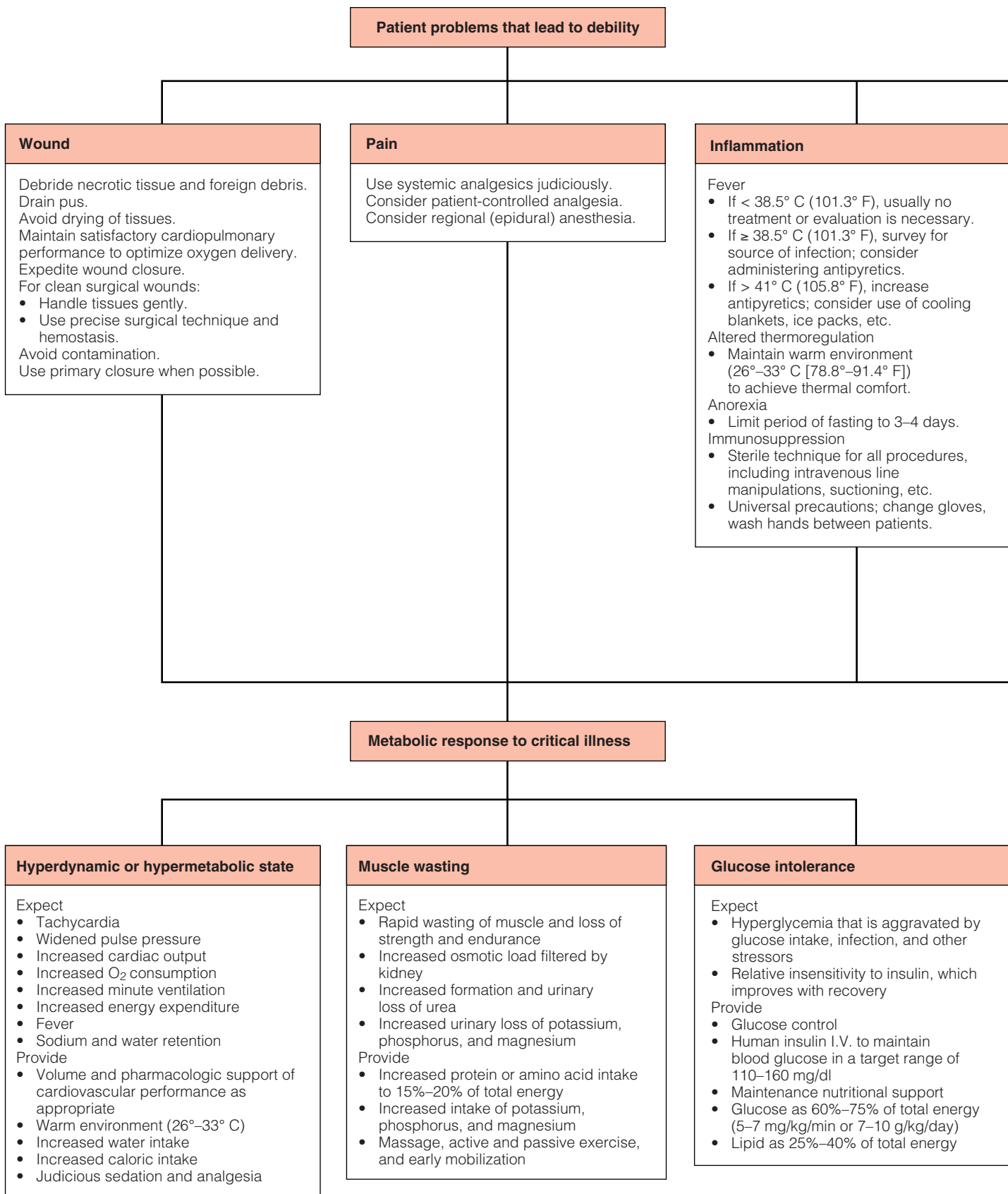
THE WOUND

The surgical wound is not only a site of tissue disruption but also a site of inflammation and repair [see 1:7 Acute Wound Care]. After resuscitation, the surgeon's principal task is to expedite and promote wound healing and restore tissue integrity. Because the wound is often the proximate cause of patient debility, providing optimal wound care amounts to providing the best patient care.

Wounds with necrotic or devitalized tissue (e.g., from ischemic necrosis, gangrene, or burns), foreign debris, or grossly contaminated material do not heal readily, if they heal at all. Necrotic tissue and eschar (slough) must be debrided, usually surgically, although application of enzymatic agents to wounds has also been effective in some cases. Foreign material must be removed by either hydrotherapy or debridement. Pus must be drained or removed by irrigation and dressing changes. Contaminated wounds are left open so that they can be repeatedly examined and further necrotic material can be removed. Open wounds should be covered with a dressing to prevent drying (i.e., tissue oxidation) and further tissue slough, to reduce bacterial contamination, and to prevent further mechanical injury. Unfortunately, none of the currently available dressing materials achieve all of these goals. Once it becomes apparent that the wound tissues are viable and uninfected, the wound should be closed primarily if possible or with a skin graft.

The cellular processes involved in wound healing are critically dependent on adequate perfusion and delivery of oxygen, glucose, and other essential nutrients. Inadequate perfusion may result in relative tissue ischemia and delay wound healing. A principal responsibility of the clinician is therefore to ensure adequate tissue perfusion during the entire period of wound healing. For instance, resuscitation from shock should be continued after blood pressure is stabilized and until there is clinical evidence of adequate flow—usually associated with warm extremities, pink nail beds, brisk capillary refilling, full peripheral pulses, urine output greater than 0.5 ml/kg/hr (50 to 70 ml/hr in adults), clear sensorium, and improving metabolic acidosis. Adequate oxygenation must also be ensured. Occasionally, invasive monitoring of cardiopulmonary performance [see 8:4 Cardiovascular Monitoring] and tissue oxygenation as well as pharmacologic support may be required to ensure adequate perfusion and oxygen delivery.





Infection	Hospital treatment
Initially diagnose by abrupt changes in fever, leukocytosis, hyperglycemia, pulmonary function, or pulse and blood pressure. Culture appropriately to establish microbiologic diagnosis. Administer broad-spectrum antibiotics empirically to cover likely pathogens if signs of organ system dysfunction and of sepsis develop. Debride necrotic tissue. Establish drainage; remove catheters. Prevent contamination of different sites on same patient. Prevent cross-contamination between patients.	Bed rest: • Encourage frequent turning, coughing, and deep breathing. • Encourage active, assisted exercise in bed when feasible. • Move to chair as soon as possible. • Use incentive spirometer or similar device. • Practice good hygiene and skin care, and provide massage. Food deprivation: • Limit period of fasting to 3–4 days. • Begin nutritional support as soon as needed. • Provide enteral feeding when possible. Invasive devices: • Remove as soon as no longer required. • Remove I.V. lines placed under suboptimal conditions as soon as feasible. • Consider changing I.V. lines or rotating site every 2 or 4 days. • Change I.V. site if redness or inflammation develops. Sleep deprivation: • Reduce lighting and noise in ICU periodically, especially at night. • Orient patient frequently to time of day and situation. • Use sedation judiciously.

Metabolic Responses in Surgical Patients

Contused tissue, fractures, tissues surrounding an abscess or site of infection, inflammatory sites such as the pancreas in pancreatitis or the lung in acute respiratory distress syndrome (ARDS)—in fact, any mass of inflammatory tissue—can be considered to constitute the patient's wound because resolution of those focal sites of inflammation depends on the same basic cellular processes as does healing of an external wound.

Patients with a large total mass of inflammatory tissue—large wounds—usually are critically ill and clearly manifest most of the metabolic responses associated with critical illness [see *Metabolic Responses That Can Cause Debility, below*]. In contrast, patients with small wounds do not appear critically ill and are not significantly debilitated. Although elective operations result in wounds, the incisions are made under sterile, controlled conditions; there is minimal direct tissue injury, little contamination, no shock, and limited net loss of blood and fluid. The incisions are closed primarily and most often heal expeditiously. With the current proliferation of minimally invasive surgical techniques, operative incisions are now even more limited, patients recover more rapidly, and the resultant debility is minimal—often little more than a transient indisposition.

PAIN

Virtually all surgical patients experience some pain. Pain usually occurs in association with an incision or with a wound resulting from fracture, burn, contusion, or another type of injury. In addition to creating an unpleasant subjective experience, pain often limits physical activities, such as turning in bed, deep breathing, coughing, and walking, and thereby directly interferes with recovery. A variety of techniques are available for pain management. However, each approach has side effects, the potential for abuse, or other features that limit its application.

Acute pain has traditionally been managed by intermittent parenteral administration of narcotic analgesics when requested by the patient or when the nurse perceives the patient to be in pain. The intravenous route is now preferred, because it does not require a painful injection and avoids potential uptake abnormalities. Intravenous analgesics have a short duration of action and must be given frequently to maintain good, sustained pain control; the dose also must be relatively small to minimize the side effects of sedation and impaired gastric motility. Thus, this approach to pain control is relatively labor intensive. Theoretically, this approach can prevent overuse of narcotics; in practice, it often results in inconsistent pain control and underdosing.

Continuous infusion of narcotic analgesics provides more consistent pain control and is common in the ICU. The dose should be adjusted upward before painful procedures but otherwise should be kept as low as possible to avoid ileus and prolonged sedation. Patient-controlled analgesia (PCA) is an extension of this approach. The patient controls a pump that administers a prescribed dose of the agent when activated; the clinician determines the amount of drug in each dose and the total dose permissible in a given period. This technique has been well accepted by patients who are awake and alert and are capable of controlling the system. One benefit is that the total amount of drug administered for pain relief is usually less than is given in a conventional as-needed dosing schedule.²

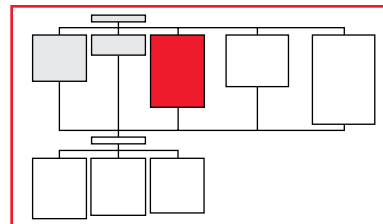
Administration of local anesthetics or narcotics into the epidural space may provide effective local pain relief without the sedating effects of parenteral narcotics. In addition, epidural anesthetics (but not opioids) reduce postoperative ileus.³ Effective epidural analgesia can be maintained for several days and may have a beneficial effect

on pulmonary function in patients with rib fractures or truncal wounds.⁴ This technique requires placement of a catheter in the epidural space.

Patients must be monitored closely, and the dosage schedule must be individualized. This technique is best suited to patients who will be relatively inactive for 24 to 36 hours postoperatively and who can be observed closely, such as patients in the ICU.

INFLAMMATION

Elevation of body temperature above normal, leukocytosis, and other signs of inflammation are common features of critical surgical illness and should be expected. The extent of temperature elevation is generally



proportional to the severity of illness. In a patient with a major burn—an extreme example of critical surgical illness—body temperature may be as high as 39° C (102.2° F). The leukocyte count is also typically elevated and may be as high as 20,000 cells/mm³ during satisfactory recovery. A normal or subnormal body temperature or white blood cell count is atypical and may indicate sepsis, drug-induced leukopenia, or limited physiologic reserve. For example, a critically ill elderly patient with a major injury or infection may be afebrile and have a white blood cell count in the normal range.

Fever, however, is also a cardinal sign of infection. It may be difficult to distinguish between a typical postoperative or posttraumatic fever and a fever caused by invasive infection. An acute elevation in rectal temperature of 1.0° to 1.5° C (1.8° to 2.7° F) that occurs within a short period or a rectal temperature higher than 38.5° C (101.3° F) should be considered indicative of infection and should be investigated thoroughly. Sputum, urine, and blood cultures should be obtained, and all wounds should be inspected carefully for signs of inflammation or infection. Devices commonly associated with nosocomial infection—intravenous cannulas, urinary catheters, and endotracheal tubes—should be removed as soon as feasible or else changed (see below).

Because inflammation is such a prominent feature of all critical illness, including that in patients with serious infectious complications of chronic diseases, several clinical syndromes have been defined in an effort to stratify patients according to the severity of their inflammatory responses [see *Table 1*].⁵ These syndromes are associated with increased mortality, even in the absence of documented infection.⁶ In the remainder of this chapter, I will refer repeatedly to the metabolic responses to critical illness; this term incorporates these inflammatory syndromes and more besides, and its use permits a more comprehensive discussion.

Mild elevation of body temperature is usually well tolerated and requires no specific treatment. However, a higher fever may impose significant stress on the patient, as indicated by pronounced tachycardia, tachypnea, malaise, and, occasionally, restlessness. Thus, a body temperature higher than 39° C (102.2° F) is usually treated with antipyretics (e.g., acetaminophen, aspirin, indomethacin, or ibuprofen).

The fever experienced by critically ill patients is an upward adjustment of the thermoregulatory center in the brain, the central thermostat. A consequence of this adjustment is that the patient usually prefers a warmer environmental temperature than do normal individuals. An ambient temperature in the hospital that is comfortable for the staff is often perceived as cool by the patient, who must generate extra heat to maintain the adjusted body temperature. Thus, patient areas of the hospital should be kept warm, usually in the range of 26° to 33° C (78.8° to 91.4° F). This temperature range will

Table 1 Components of Inflammatory Syndromes⁵

Systemic inflammatory response syndrome (SIRS)—two or more of the following are required:

- Temperature > 38° C (100.4° F) or < 36° C (96.8° F)
- Heart rate > 90 beats/min
- Respirations > 20/min
- WBC > 12,000/mm³, < 4,000 mm³, or > 10% bands

Sepsis

- SIRS
- Clinically likely source of infection (does not require bacteriologic confirmation)

Severe sepsis

- Sepsis
- Impaired cardiovascular performance necessitating fluid resuscitation

Septic shock

- Severe sepsis
- Impaired cardiovascular performance necessitating inotropic support

promote patient comfort and reduce the physiologic demands of cold stress. When moved into the OR, radiology suite, or other typically cool environments, patients should be insulated, or the room should be warmed.

Attempts to treat a patient with fever by surface cooling (ice packs, alcohol rubs, cooling blankets) are not uncommon. Rather than addressing the altered physiology underlying the fever, however, surface cooling imposes a marked cold stress on an already critically ill and stressed patient. Except in the presence of hyperpyrexia (temperature $\geq 41^{\circ}\text{C}$ [105.8°F]), surface cooling should be avoided; antipyretics should be administered first to reduce body temperature.

During acute surgical illness, patients typically have a poor appetite. Even when able to eat, they often do not consume sufficient nutrients even to approximate their needs. Accordingly, the clinician should initiate exogenous nutritional support early in the patient's course, especially if it is likely to be prolonged by the need for additional reparative procedures, such as fracture fixation or delayed wound closure.

Some degree of immunosuppression is also a common feature of inflammation. Thus, critically ill patients are more susceptible than normal to colonization and infection with a variety of microorganisms. Special attention to sterile technique during bedside procedures, the use of universal precautions, and hand washing after each patient encounter by all care providers should help reduce the risk of nosocomial infection.

INFECTION

Infections in hospitalized patients fall into two categories: they may be directly related to the patient's primary disease or injury (e.g., invasive burn wound sepsis, gangrene of an ischemic limb, or intra-abdominal abscess after perforated diverticulosis), or they may develop as a complication of physiologic support (e.g., pneumonia after prolonged mechanical ventilatory support).

Early diagnosis and treatment of infection in surgical patients can minimize debility. Most critically ill surgical patients experience fever, leukocytosis, tachycardia, widened pulse pressure (reduced vascular resistance), glucose intolerance, fluid retention, some impair-

ment of oxygenation, and other signs associated with the septic response. The challenge for the clinician is to distinguish patients in whom this response is caused by established infection from those in whom it is not the result of an infectious focus. A temperature higher than 38.5°C (101.3°F) or an acute increase in temperature accompanied by an abrupt change in the white blood cell count should prompt investigation for a developing infection [see Figure 1], which would include appropriate cultures and other diagnostic studies. Other signs that suggest underlying infection include relative hypothermia, leukopenia, thrombocytopenia, abrupt elevation or depression of the blood glucose level, restlessness, lassitude, hyperpnea, and failure to progress as expected.

If the presence of infection is suggested by the clinical setting, the magnitude of fever, or any other systemic signs (such as renal or respiratory dysfunction, marked hyperglycemia or hypoglycemia, hypothermia, or hypotension), broad-spectrum antibiotic coverage should be instituted empirically before culture results are available [see 8:14 *Clinical and Laboratory Diagnosis of Infection*]. Specific antimicrobial therapy should be begun once the presence of infection has been confirmed and the microbiologic diagnosis has been established. Other therapeutic measures may also be necessary to treat the infection. Draining an abscess, debriding or excising necrotic tissue, removing indwelling catheters and placing new ones at other sites, performing therapeutic bronchoscopy to ensure drainage of major airways, or creating a tracheostomy in the patient who requires an airway for improved bedside pulmonary toilet may also be advisable.

Because all critically ill patients are at risk for infection, efforts directed at prevention are worthwhile. Medical and nursing personnel can prevent the transmission of organisms from one patient to another by effective hand washing between patient contacts. Gloves used by health care workers for their own protection whenever they have contact with patients must be changed between patients. Of course, sterile techniques should be used during invasive procedures.

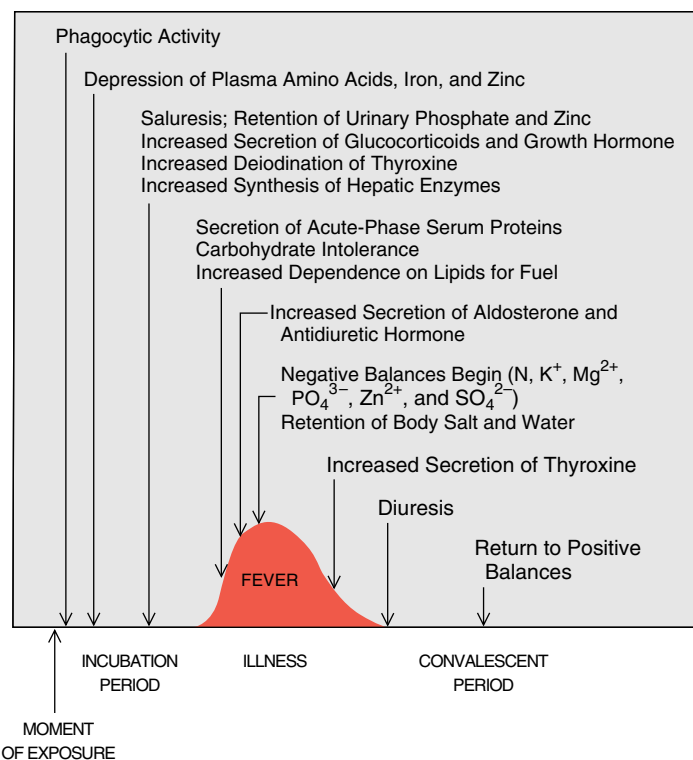
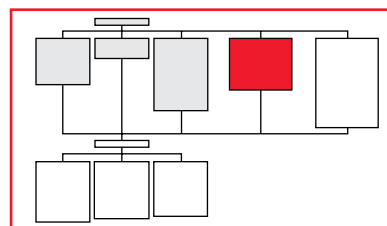


Figure 1 Illustrated is the time course of events that constitute the classic response to bacterial infection.²⁵³

Sites of insertion of intravascular cannulas should be inspected regularly, and the catheters should be moved to a new site if the skin becomes reddened or if pus is observed. Antibiotic-impregnated central venous catheters may reduce the incidence of catheter-related infection and thereby lower the frequency with which lines must be replaced.⁷ The prophylactic use of antibiotics in the ICU is controversial⁸⁻¹⁰ and cannot be encouraged at present.

IATROGENIC FACTORS

Bed Rest

Bed rest and inactivity both contribute to loss of muscle mass and strength. Immobility may result in progressive atelectasis, respiratory insufficiency, and pulmonary sepsis. If immobility is prolonged, open pressure sores may develop over bony prominences. Thus, patients should be turned frequently, and their position should be changed often. Patients who are able to participate actively in repositioning themselves should be encouraged to do so by helping to turn or lift themselves. They should be urged to take deep breaths and cough. An incentive spirometer is inexpensive and is often helpful in this regard. When patients are hemodynamically stable, they should be moved to a chair, provided that no musculoskeletal contraindications are present. This position improves ventilation and helps preserve postural reflexes. Patients should assist in sitting up as much as is feasible. Even simple actions such as standing in place or bearing weight during the transfer may be beneficial. Active and passive range-of-motion exercises can help maintain joint function. Proper positioning of the extremities may be necessary to prevent contractures and to preserve range of motion.

Skin integrity is preserved not only by frequent position changes but also by attention to hygiene. Patients should be bathed regularly, with special attention paid to intertriginous areas. Any soilage with blood, stool, urine, or other material should be removed and the skin thoroughly dried. Massage and application of moisturizing lotions are also helpful. The use of foam or air mattress pads that distribute body weight over a large area or low-air-loss beds may also benefit the patient confined to bed for a prolonged period. However, these devices are no substitute for good nursing care.

Food Deprivation

Food is commonly withheld from the patient before and during various diagnostic and therapeutic procedures as well as before operations or after injury. Starvation for several days appears to be well tolerated by patients who were relatively well nourished before their critical illness. However, if food deprivation is prolonged, the complications of starvation will compound the effects of critical surgical illness. Total starvation should usually be limited to a period no longer than 3 or 4 days. Nutritional support should be instituted via the most effective and safest route possible [see 8:22 *Nutritional Support*].

Invasive Devices

A variety of tubes, catheters, and drains are essential for the proper care and monitoring of critically ill patients. However, each of these devices transgresses a normal barrier to infection, and each is associated with infectious risks and other complications. An invasive device should be removed as soon as it is no longer required. Intravenous lines placed in the emergency room or under less than ideal conditions (e.g., at the scene of an accident or while the patient is en route to the hospital) should be removed as soon as possible and replaced, if necessary, with new devices by means of appropriate sterile

technique. Such lines should also be changed if the puncture site is red, inflamed, or purulent. With most of these devices, the risk of infectious complications increases after 3 or 4 days.¹¹ Regular replacement is commonly practiced, especially if the patient becomes febrile. Catheters impregnated with antibiotics appear not to require such frequent exchanges and may be safely used for longer periods.⁷

Sleep Deprivation

Normal sleep patterns are disturbed in ICU patients, in part because of the constant light and noise in the ICU and because of repetitive stimulation by the ICU staff. Such disturbances, in combination with other stresses associated with illness, often result in confusion, disorientation, anxiety, and, occasionally, frank psychosis. As many efforts as possible should be made to orient the patient, including the use of wall calendars, clocks, and other methods that serve as normal day-night indicators (e.g., turning the lights down at night). Even the personal activities of daily living, such as bathing and shaving, can serve as time cues. Patients should be reassured and reminded about the date, the time, their location, and the reason for their hospitalization. Sedatives and hypnotics may be useful in critically ill patients but occasionally have a paradoxically excitatory effect.

Metabolic Responses That Can Cause Debility

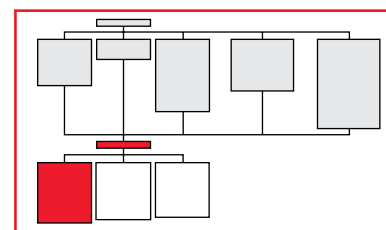
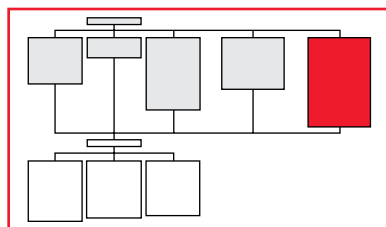
All of the clinical factors of surgical care contribute to or affect various physiologic and biochemical alterations that occur in response to critical illness; these physiologic and biochemical alterations collectively constitute the metabolic response to critical illness. The intensity and duration of this response determine debility. Current critical care management generally supports rather than modifies the response. Three major features of the metabolic response to critical illness affect clinical care: the hyperdynamic or hypermetabolic state, muscle wasting, and glucose intolerance.

HYPERDYNAMIC OR HYPERMETABOLIC STATE

In recovery from critical illness, several organ systems function at an accelerated pace. Principal among these is the cardiovascular system. Tachycardia and a widened pulse pressure are typically present and reflect cardiac output greater than that expected in a resting, healthy individual. The increased blood flow is distributed to most vascular beds, especially to inflammatory tissue or the wound, and supports increased cellular activity in the healing wound. In the kidneys, increased flow is associated with an elevated glomerular filtration rate. Thus, drug excretion may be accelerated, and increased dosages may be required to maintain therapeutic plasma concentrations.

Accompanying the increases in cardiac output and regional blood flow is an increase in oxygen delivery (transport) to the microcirculation. This increase in oxygen delivery supports the enhanced oxygen requirements of several organ systems. Total body oxygen consumption ($\dot{V}O_2$) is greater than normal because of the increased oxidation of body fuels—carbohydrates, fats, and amino acids—needed to provide the energy to drive the cellular machinery at this accelerated pace [see Figure 2]. These reactions produce heat. Heat production, also referred to as energy expenditure or metabolic rate, is increased in critically ill patients, who thus are said to be hypermetabolic.

The increase in $\dot{V}O_2$ is paralleled by increased carbon dioxide production ($\dot{V}CO_2$), which, under normal conditions, stimulates breathing and augments minute ventilation. For patients who require ven-



tilatory assistance, the ventilator should be set to deliver a minute ventilation that is greater than normal.

As discussed earlier, critically ill patients typically have a fever and prefer warmer ambient temperatures than normal individuals. In these patients, metabolic rates increase in part to maintain a higher than normal core temperature. A warm environment may help blunt the patient's increased heat production and energy needs.

Associated with the hyperdynamic state of critical illness is expansion of the extracellular fluid (ECF) compartment. Total body water and total body sodium are increased. This expansion occurs perioperatively or with resuscitation after injury. Short-term changes in body weight reflect alterations in body water and in lean tissue mass. Slow, persistent expansion of the ECF may mask loss of tissue mass. Conversely, spontaneous diuresis of sodium and water during recovery may lead to pronounced weight loss in a patient who otherwise appears to be progressing well.

During critical illness, the daily loss of body water is increased in several ways. Fever accelerates insensible loss of body water, and renal loss may be greater than normal because of the increased osmotic load caused by the breakdown of lean tissue (see below). If there are open wounds, evaporative water loss is markedly increased, in proportion to the size of the open wound. Thus, maintenance water requirements may be greater than normal. It is often necessary to monitor both the intravascular fluid volume, using values for central venous or pulmonary arterial wedge pressures, and the ECF composition or tonicity, as indicated by changes in serum sodium concentrations.

The clinician should provide not only volume and possible pharmacologic support to maintain a hyperdynamic circulation but also an increased amount of calories to meet the patient's elevated energy needs. These needs can often be reliably estimated on the basis of the patient's age, sex, body size, and critical illness. Occasionally, it may be helpful to measure the patient's $\dot{V}O_2$ and $\dot{V}CO_2$ and to use these values to calculate daily caloric requirements.

In addition to providing cardiopulmonary and nutritional support to critically ill, hyperdynamic patients, the clinician should try to neutralize factors that may augment the hyperdynamic response to critical illness. Judicious analgesia and sedation provide metabolic benefits and relieve pain and anxiety. Providing a warm environment mitigates the hyperdynamic response by reducing cold stress. Antipyretics reduce the heart rate during periods of extreme fever.

MUSCLE WASTING

The distinguishing feature of the debility of critical illness is marked muscle wasting and weakness. Wasting is in part a consequence of accelerated muscle protein breakdown, which is generally related to the severity of illness [see Figure 2]. The increased protein breakdown presumably serves to mobilize amino acids for synthesis of new protein in wounds; for proliferation of phagocytes, macrophages, and other cellular components involved in wound healing; and for synthesis of acute-phase proteins and glucose in the liver. The increased synthetic work and processing of amino acids in the liver result in increased production of urea, which is filtered and excreted by the kidneys. In the presence of renal dysfunction, blood urea nitrogen (BUN) may rise rapidly.

To reduce muscle wasting, additional exogenous protein or amino acids are provided through nutritional support. In general, protein needs increase in proportion to caloric requirements. However, for the critically ill surgical patient, it may be beneficial to provide at least

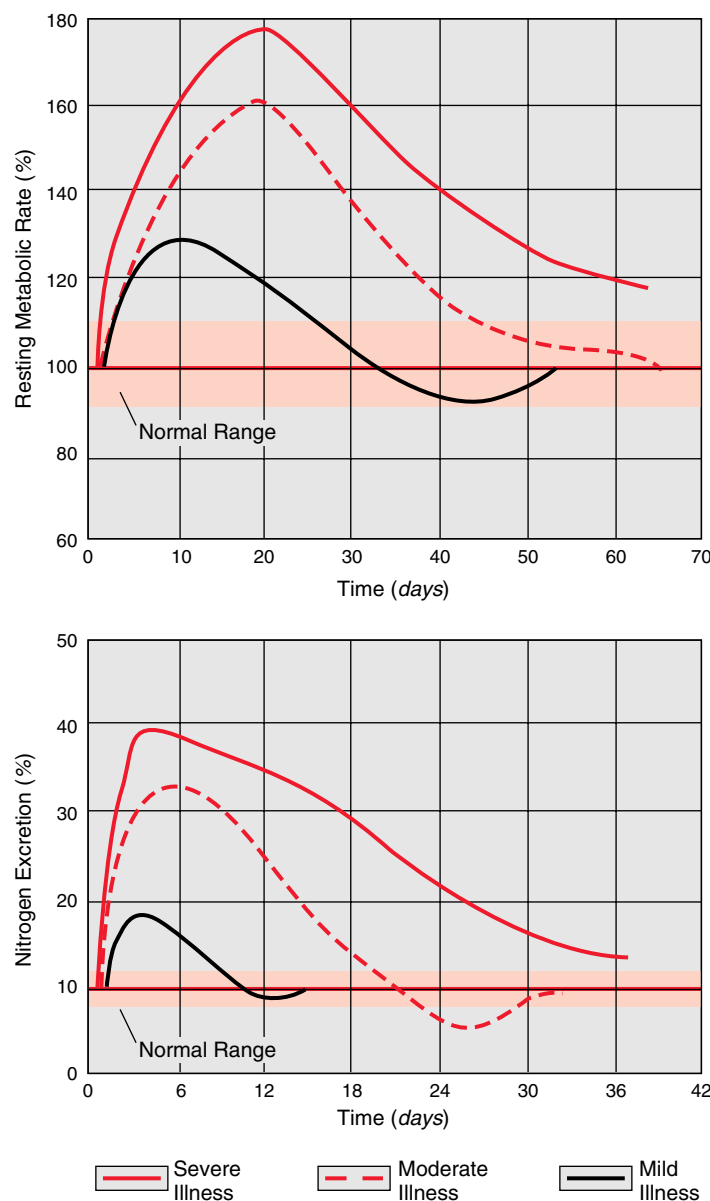
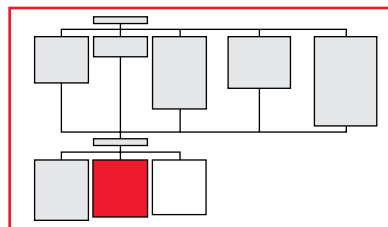


Figure 2 Increased resting metabolic activity (hypermetabolism) and increased nitrogen loss are closely related during critical surgical illness. Both correlate with the severity of illness and return to normal as the patient recovers. Patients with severe illness are represented by the solid red line, those with moderate illness by the broken red line, and those with mild illness by the solid black line; the normal range is shown by the light-red bar.

20% to 25% of total calories as protein or amino acids. BUN may be higher than normal (at least 20 to 30 mg/dl) with this level of amino acid intake, even if renal function is normal.

In addition to amino acids, other intracellular constituents are released by these catabolic processes and subsequently excreted. Thus, metabolic alkalosis often develops, associated with mild hypochloremia and with reduction in total body potassium and magnesium. Repletion with potassium chloride and magnesium sulfate is usually effective. During nutritional support, generous amounts of potassium (≥ 100 mEq/day), magnesium (≥ 30 mEq/day), phosphate (20 to 30 mmol/day), and trace minerals should be provided to promote synthesis and restoration of intracellular proteins and other constituents.

Muscle mass is also lost as a result of disuse. The critically ill patient is usually confined to bed and may be further immobilized because of

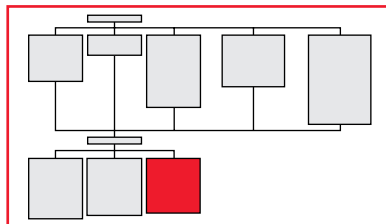
Table 2 Blood Glucose and Insulin Concentrations in Burn Patients¹

Group	N	Burn Size (% TBS)	Postburn Day Studied	Fasting Blood Glucose		Basal Insulin (μU/ml)
				(mmol/L)	(mg/dl)	
Control subjects	12	—	—	3.88 ± 0.11	69.8 ± 1.9	22 ± 3
Resuscitated burn patients	4	71	1	7.77 ± 0.61	139.9 ± 10.9	20 ± 6
Hypermetabolic burn patients	17	42	9	6.27 ± 0.28	112.9 ± 5.0	22 ± 2
Convalescing burn patients	5	56.5	69	4.05 ± 0.33	72.9 ± 5.9	14 ± 1
Septic burn patients	15	71	10	6.43 ± 0.55	115.8 ± 9.9	22 ± 4
Treated septic burn patients	4	72	11	6.11 ± 0.83	110.0 ± 15.9	12 ± 3

traction, monitoring devices, mechanical ventilation, and sedation. Massage, passive range-of-motion exercises, early mobilization, and limited bed exercises (e.g., moving from bed to chair, use of a trapeze bar to assist with positioning) may be helpful in reducing muscle wasting and debility.

GLUCOSE INTOLERANCE

Critically ill patients usually exhibit glucose intolerance similar to that seen in diabetic patients [see Table 2]. Hyperglycemia during critical illness is a result of both increased production of glucose by the liver and decreased uptake of glucose by insulin-dependent tissues. These processes occur despite normal or exaggerated insulin responses to hyperglycemia.



Hyperglycemia may be marked, especially if the patient is receiving a large glucose load, such as might be provided with nutritional support. Hyperglycemia may exacerbate ventilatory insufficiency, contribute to hepatic dysfunction, and provoke osmotic diuresis, thereby leading to dehydration and a hyperosmolar state. Hyperglycemia has also been associated with an increased risk of postoperative infection, renal failure, increased transfusion requirements, and death in critically ill patients. Vigorous attempts to control the blood glucose concentration are therefore warranted.

The provision of safe amounts of glucose and the administration of exogenous recombinant human insulin are the mainstays of therapy for glucose control. Because insulin resistance is present in patients with critical illness, relatively large quantities of insulin may be required to control the blood glucose level. Intravenous administration of insulin provides rapid control and prevents unpredictable

subcutaneous uptake caused by variations in blood flow. Because of its short half-life, intravenous insulin must be administered either in frequent intermittent doses or by continuous infusion. Both techniques can be used with a reasonable margin of safety. Blood glucose levels may be determined rapidly by using a portable glucose analyzer at the bedside on a small blood sample drawn every 1 or 2 hours. On the basis of the blood glucose value, a predetermined insulin dose may be administered (on a so-called sliding scale) or the infusion rate may be adjusted. Current data suggest that the optimal range for blood glucose values in critically ill surgical patients is 80 to 110 mg/dl (4.4 to 6.1 mmol/L).¹² One half to two thirds of the total insulin dose required to maintain blood glucose in this target range in a 24-hour period may be added to the intravenous feeding regimen on the next day. In this way, the blood glucose level is ultimately maintained in an acceptable range.

The degree of glucose intolerance will vary over the course of the critical illness. Therefore, regular monitoring of blood glucose concentrations is advisable, even after adequate control has been achieved. Further episodes of stress-inducing conditions, especially infection, may exacerbate glucose intolerance; an abrupt rise in blood glucose concentration may be the first indication of impending sepsis. As the patient recovers, glucose tolerance improves and the requirement for insulin decreases. When the patient is transferred from intravenous nutrition to enteral nutrition, insulin requirements often decrease despite similar nutrient intake.

Glucose remains an important fuel during critical illness, especially for healing wounds. However, the ability to utilize glucose effectively appears to be reduced. Most of the total energy administered in nutritional support should be provided by glucose (60% to 75% of total calories). The dose of glucose should, however, be limited if marked hyperglycemia cannot be readily controlled with insulin. The remaining calories can be provided by fat emulsion.

Discussion

The clinical features of all critical illnesses are similar, regardless of the type of insult sustained, be it injury, operation, or infection. Similar responses can be seen in a wide variety of animals that have been injured or challenged by invasive infection.^{13,14} These responses to critical illness presumably evolved because they confer an advantage with respect to survival. In fact, it seems indisputable that when an individual organism acquires an enhanced ability to recover from an injury or infection, the species is thereby benefited. Accordingly, the metabolic responses to critical illness are often considered to be adaptive reactions that serve to promote recovery.

There is a cost for this benefit, however, and that is debility. In addition, the metabolic responses to critical illness can lead to organ system dysfunction. Critically ill patients also typically have

immunologic abnormalities that may make them more susceptible to invasive infection by a variety of microorganisms, including those that are not usually pathogenic. The syndrome of multiorgan failure and sepsis that may develop in association with the metabolic responses to critical illness is often the final route to death [see 8:13 *Multiple Organ Dysfunction Syndrome*]. Thus, in some ways, certain metabolic responses seem maladaptive in that they retard recovery and lead to organ failure and death.

An improved understanding of the metabolic responses to critical illness may benefit patients in two ways. First, it may facilitate the development of improved supportive therapies. Much of current critical care practice is based on our understanding of these processes and has been designed to support them. Second, a better under-

standing of the mechanisms underlying the metabolic responses to critical illness may lead to strategies for altering the responses so as to stimulate those features that are beneficial and promote recovery and to suppress or limit those features that are debilitating or lead to organ system dysfunction.

Integrated Metabolic Response to Critical Illness

The metabolic responses to injury and critical illness occur simultaneously. They primarily involve the liver, skeletal muscle, the gut, the kidneys, and the wound or focus of inflammation [see Figure 3]. The heart also plays a major role by providing the motive force for the high rate of blood flow that is required to support increased exchange of nutrients and other substances between organs. The central and autonomic nervous systems and endocrine tissues are mainly involved in regulation of the responses.

The wound, which may include one or more foci of infection and other sites of inflammation in addition to external injuries, plays a principal role. It acts as a large arteriovenous shunt, robbing the host of blood supply and demanding increased cardiovascular work. The wound also induces and controls profound metabolic changes, which subside as the wound heals. Tissues are broken down, presumably to provide substrates for a variety of synthetic and energy-producing processes. The cost to the patient is increased metabolic work, elevated energy requirements, erosion of lean body tissue, and debility.

The healing wound is a site of intense metabolic activity. Dissolution and removal of necrotic tissue, containment and killing of bacteria, collagen synthesis and wound repair, cellular proliferation, and restoration of tissue integrity occur, often simultaneously. These processes require energy and a variety of substrates, particularly amino acids for protein synthesis. The microenvironment of a wound is often relatively hypoxic. However, inflammatory cells have a marked capacity for glycolytic metabolism,¹⁵ in which adenosine triphosphate (ATP) can be generated without the consumption of oxygen. This capacity persists even when oxygen delivery is sufficient. Glucose is thus the principal fuel for the healing wound. It is metabolized to lactate, which is then released into the circulation for transport to the liver.

The liver produces the additional glucose that is required by the wound. It is capable of manufacturing glucose from lactate. In this manner, glucose is recycled between the liver and the wound, and there is no net gain or loss of carbon atoms. The liver also synthesizes glucose from amino acids, principally alanine, which comes from both skeletal muscle and the gut. This mechanism is termed gluconeogenesis. The nitrogen contained in the amino acids is converted to urea and excreted. The liver also synthesizes a variety of circulating proteins in response to inflammation and infection (so-called acute-phase proteins). All of these synthetic processes require energy, produced in part by fat oxidation, and therefore contribute to a general increase in energy utilization, heat production, and metabolic rate.

Skeletal muscle protein breaks down at an accelerated rate after injury and critical illness, releasing a variety of substances into the circulation, including creatine and creatinine, 3-methylhistidine, potassium, magnesium, and amino acids. The amino acids serve as precursors for protein synthesis in the wound and in the liver. The released amino acids do not reflect a simple dissolution of protein. Rather, alanine and glutamine are disproportionately released. Alanine can be readily converted to glucose in the liver. Glutamine serves both as a fuel—especially for the gut and for rapidly proliferating cells, including inflammatory cells and fibroblasts—and as a precursor for renal ammonia production, which is an important mechanism for neutralizing excreted acid loads.

Although muscle tissue in healthy persons is usually quite sensitive to insulin and commonly serves as a site of glucose storage, mus-

cle is resistant to insulin after injury or critical illness, and its capacity for glucose storage is reduced significantly. This response contributes to glucose intolerance and helps direct glucose to the healing wound.

The gut was long considered to be essentially inactive during convalescence, but it now appears to play a central role in the metabolic response to critical illness [see 8:22 *Nutritional Support*]. During critical illness, the gut utilizes glutamine as its principal fuel, converting glutamine to alanine, which is transported to the liver by the portal circulation. More important, perhaps, the gut can be a portal of entry for bacteria and bacterial toxins, which can worsen or perpetuate critical illness [see 8:13 *Multiple Organ Dysfunction Syndrome*].

The kidneys also contribute to the generalized increase in physiologic work and energy requirements that accompanies critical illness. The kidneys must excrete an increased solute load consisting of urea, potassium, magnesium, weak acids, and other intracellular constituents. In addition, many drugs and their metabolites depend on renal excretion. Production of ammonia from glutamine may be increased to neutralize acid loads. Many of these processes require energy.

All of these regional metabolic processes occur simultaneously. The net integrated metabolic response is evident clinically as increased energy expenditure and heat production, fever, accelerated nitrogen excretion and muscle wasting, and glucose intolerance. The wound appears to exert a controlling influence on the intensity and duration of the responses to critical illness or injury: the intensity is proportional to the size of the wound or the mass of inflammatory tissue. The larger the wound, the more intense the metabolic responses. As the wound heals and as inflammation subsides, the heightened metabolic demands abate. Expedient wound closure and definitive treatment of infection are the most effective forms of anticatabolic therapy.

Hypermetabolism

Because humans maintain fairly constant body temperature, the heat generated by the body is equal to the heat lost in biochemical and physiologic processes and is an indicator of overall metabolic activity. This heat ultimately results from the oxidation of organic fuels. The rate of heat production, or metabolic rate (MR), is therefore related to $\dot{V}O_2$ and $\dot{V}CO_2$. It may be measured directly by means of direct calorimetry, or it may be calculated from measurements of $\dot{V}O_2$, $\dot{V}CO_2$, and body surface area (BSA) by means of indirect calorimetry:

$$\text{MR (kcal/m}^2\text{/hr)} = \frac{[(3.9 \times \dot{V}O_2 \text{ [L/min]}) + (1.1 \times \dot{V}CO_2 \text{ [L/min]})] \times 60 \text{ (min/hr)}}{\text{BSA (m}^2\text{)}}$$

A third term, $-3.3 \times \text{urea nitrogen loss (g/time)}$, is sometimes added to account for the heat produced by urea formation. However, it is usually a small factor, adjusting MR by only 2% to 3%.¹⁶

Values determined by direct and indirect calorimetry under steady-state conditions are comparable.¹⁷ When metabolic rates of normal individuals are determined under controlled basal conditions, the values are reproducible and predictable ($\pm 12\%$) on the basis of age, sex, and body size.¹⁸ When metabolic rates of critically ill patients with satisfactory hemodynamic function are determined under similar conditions, the rates are greater than predicted. Thus, patients are said to be hypermetabolic.

The degree of hypermetabolism is proportional to the severity of illness. This phenomenon was most dramatically demonstrated in careful studies of burn patients performed in the 1970s.¹⁹ The increase in resting metabolic rate was proportional to the extent of tissue injury—that is, to the amount of the BSA that was burned. Hypermetabolism has also been demonstrated in a variety of other critically ill patients, but it has usually been less severe than that seen in patients with major burns.²⁰

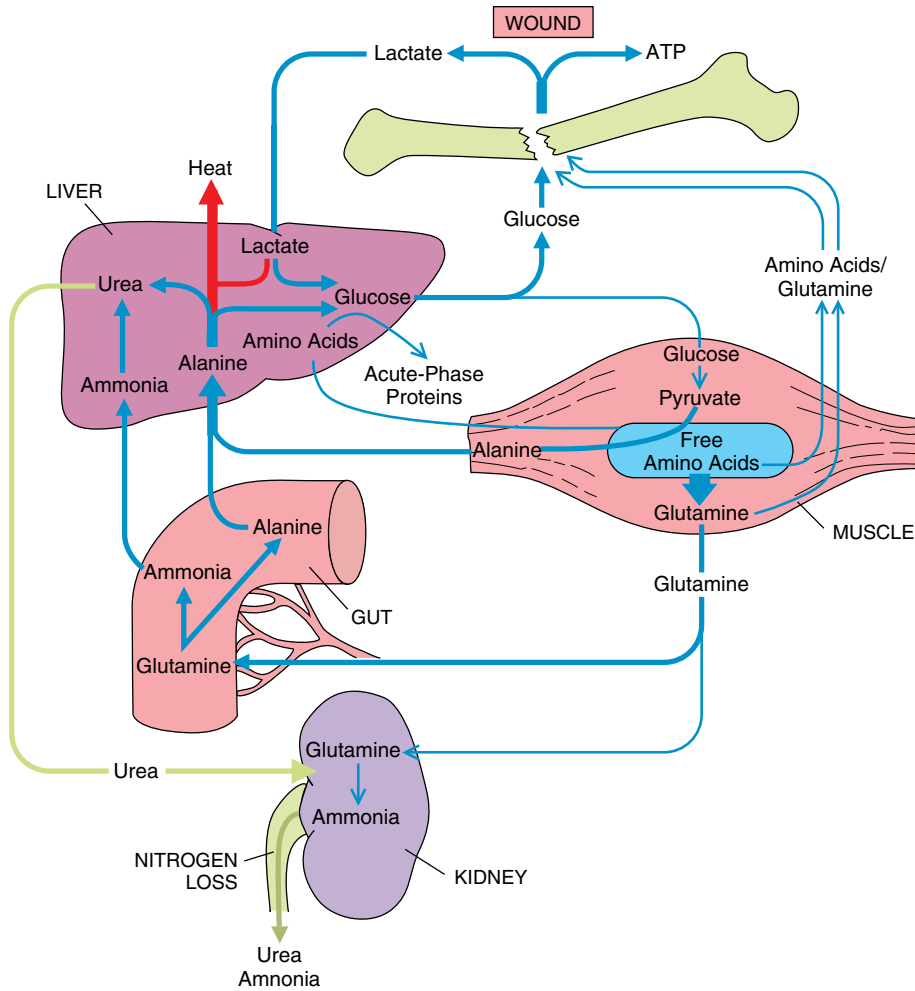


Figure 3 The metabolic response to critical illness includes characteristic alterations in the exchange of substrates between organs. Presumably, these responses occur in support of the healing wound and are facilitated by a hyperdynamic circulation. The wound requires glucose (and probably glutamine) as a primary respiratory fuel. Glucose is converted to lactate; this conversion can occur in an aerobic environment. Lactate is transported to the liver for conversion back into glucose. The recycling of lactate to glucose is a major pathway that requires the input of energy and thereby contributes to increased energy utilization. Most of the glucose required for the healing wound (i.e., inflammatory tissue) is produced by the liver, not only from lactate but also from alanine and other glucogenic amino acids. These reactions require energy and also result in the formation of urea. Muscle is the major source of amino acids, which are used for protein synthesis both in the wound and in the liver. The most abundant amino acids released from muscle are alanine and glutamine. Glutamine serves as a primary fuel for the gut, producing ammonia and other products (e.g., alanine) that are processed by the liver. In addition, glutamine may help buffer filtered acid loads in the kidneys by the formation of ammonia. These metabolic processes contribute to the hypermetabolism, hyperdynamic circulation, increased nitrogen loss, and glucose intolerance that are clinically evident in critically ill patients.

In the burn patients, moreover, there was a limit to the hypermetabolism: metabolic rates of patients with extensive burns were little different from those of patients with burns covering 50% to 60% of BSA.

These observations suggest that there is a limit to the metabolic activity that patients can support in response to critical illness. The difference between this limit and the magnitude of the patient's actual responses defines physiologic reserve [see Figure 4]. Physiologic reserve is presumably also affected by the patient's age and state of health before the critical illness. It reflects the patient's ability to meet additional complicating stresses, such as infection, volume loss, pain, anxiety, and cold ambient temperatures. For example, when patients are exposed to progressively colder ambient temperatures, the metabolic rate generally increases. However, when a group of patients

with very large burns were exposed to cold temperatures, their already high metabolic rates did not increase but actually fell.¹⁹ None of these patients survived the injury, presumably because of inability to respond to new stresses. In another group of burn patients, the inability to increase metabolic rate to facilitate rewarming after skin grafting procedures also identified nonsurvivors.²¹ When patients are cared for in a warm environment, hypermetabolism is reduced and physiologic reserve is increased.

Hypermetabolism refers to an increase in total body oxidative metabolism that is manifested by increases in total body $\dot{V}O_2$, cardiac output, and MR. Regional $\dot{V}O_2$ is generally increased throughout most tissue beds, but regional blood flow is not. The additional total body flow is directed largely to the wound or site of inflammation

and to the splanchnic circulation, and it appears to supply the wound with increased amounts of glucose and other nutrients. In studies of patients who had sustained a large burn on one leg and no burn on the other, Wilmore and colleagues found that $\dot{V}O_2$ of both limbs was increased in proportion to the total BSA burned and represented a fairly constant 6% of total body $\dot{V}O_2$.²² However, blood flow to the injured extremity was approximately twice that to the uninjured limb. Blood flow was proportional to the extent of the local injury and was directed to the surface wound.²³

Oxygen consumption by the splanchnic and renal circulations also increases in proportion to total body $\dot{V}O_2$ and hence in proportion to total body injury.²⁴ Splanchnic flow increases in proportion to total body flow (cardiac output), and together with the blood flow to the wound, it accounts for a large part of the increase in cardiac output in critically ill patients.²⁵ The increase in renal blood flow correlates with solute load rather than with $\dot{V}O_2$. From these and other studies, it is possible to calculate how oxygen consumption and cardiac output are partitioned among different vascular beds.²⁶

Altered Temperature Regulation

Body temperature is determined by the balance between heat production and heat loss. It is normally closely regulated and maintained within a narrow range. Critically ill patients typically have an elevated body temperature, even in the absence of clinical infection.²⁷ Heat production, as measured by metabolic rate, is increased in the critically ill patient. Heat loss may also be elevated in these patients.

It was once thought that increased evaporative heat loss was the driving force for hypermetabolism, at least in burn patients.^{28,29} Barr and associates tested this assumption.³⁰ Although patients treated in warm, dry air showed substantially increased evaporation of water from the burn wound and more rapid drying of the wound surfaces than did patients exposed to normal ward conditions, they had reduced hypermetabolism and a smaller degree of weight loss.

Several other studies have examined the relation between thermoregulatory factors (evaporative heat loss and ambient temperature) and hypermetabolism. For example, the metabolic rates of burn patients were determined at several ambient temperatures, ranging from 19° to 33° C (66.2° to 91.4° F) [see Table 3].³¹ Metabolic rate decreased as ambient temperature was increased, but core temperature remained elevated at all ambient temperatures, indicating that thermoregulation in these patients occurred in relation to an elevated central reference temperature. When febrile burn patients in another study were allowed to set the ambient temperature to achieve thermal comfort, they invariably preferred higher than normal temperatures, in the range of 30° to 33° C (86.0° to 91.4° F).³² The patients' unburned skin remained relatively vasoconstricted at the higher temperatures as an additional way of maintaining the febrile state. However, even under these conditions of thermal comfort, the patients continued to maintain elevated metabolic rates. Thus, although thermoregulatory factors may influence hypermetabolism, the increased rate of heat production appears to be determined primarily by metabolic factors. Hypermetabolism is temperature sensitive but not temperature dependent.

Altered Protein Metabolism

MUSCLE WASTING, NITROGEN LOSS, AND ACCELERATED PROTEIN BREAKDOWN

One of the most striking features of the metabolic response to critical illness is the marked degree of muscle wasting. This atrophy is associated with increased urinary excretion of nitrogen. Sir David Cuth-

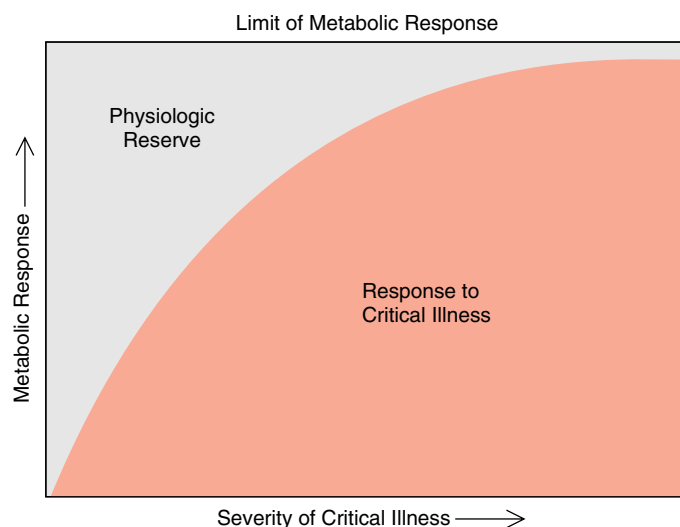


Figure 4 The intensity of the metabolic response to critical surgical illness increases as a function of the severity of illness. In patients with extremely severe critical illness (e.g., patients with burns covering 60% of the body surface area), responses are near maximal, and physiologic reserves, with which patients respond to additional stressors (e.g., infection, hemorrhage, or cold exposure), are limited. Patients may also have limited physiologic reserves because of preexisting disease, starvation, or advanced age. Therapies that attenuate the stressors of critical surgical illness improve physiologic reserve.

bertson first described this phenomenon in patients with long-bone fractures.²⁷ Similar observations were made by Howard and associates in the United States.³³ Cuthbertson concluded that injured and uninjured skeletal muscle was the source of the excreted nitrogen.^{34,35} As skeletal muscle protein is degraded, a variety of markers are released into the circulation and then excreted by the kidneys. Increased excretion of several of these markers^{36,37} has been observed in patients with trauma,^{36,38} burns,³⁹ and infections.⁴⁰

There are other sources of nitrogen loss in critically ill patients, including loss of tissue from slough or excision, loss of blood and exudate, and loss of mucosa from the GI tract. Cuthbertson estimated that in the first 10 days after a burn, the amounts of nitrogen lost as a result of direct tissue injury, wound exudation, generalized catabolism, and atrophy were roughly equivalent.⁴¹ Moore and coworkers measured nitrogen loss in the wound exudate of burn patients. This wound loss accounted for as much as 20% to 30% of total nitrogen loss during the early postburn period.⁴²

The time course of nitrogen excretion during critical illness is

Table 3 Effect of Ambient Temperature on Metabolic Rate and on Core and Skin Temperatures

Ambient Temperature (°C)	N	Core Temperature (°C)	Skin Temperature (°C)	Metabolic Rate (kcal/m ² /hr)
Normal subjects				
21	3	36.7	30.0	41.2
25	4	36.8	31.4	35.6
33	4	36.8	34.2	36.3
Burn patients (45% TBS)				
21	9	38.1	32.1	83.7
25	20	38.5	33.1	63.5
33	20	38.0	36.2	62.0

distinctive. Cuthbertson observed that nitrogen excretion peaked several days after injury and gradually returned to normal during a period of several weeks.³⁴ The pattern was similar to that of increased oxygen consumption. Thus, both hypermetabolism and muscle proteolysis peak shortly after the onset of critical illness and gradually return to normal as recovery proceeds. This too appears to be a characteristic feature of the metabolic responses to critical illness [see Figure 2].⁴³⁻⁴⁵

Protein turnover is an indicator of overall protein metabolic activity. It is determined through use of tracers. Both extracellular and intracellular amino acids are considered part of a free amino acid pool. Nitrogen is added to this pool by nitrogen intake (diet) and by protein breakdown. Nitrogen is removed by protein synthesis and by conversion to urea. When a small quantity of a labeled amino acid is infused, the rate of appearance of nitrogen in the free amino acid pool can be determined. Under steady-state conditions, this appearance rate represents protein turnover and matches protein disappearance.⁴⁶ During critical illness, protein turnover is increased.⁴⁷ When nitrogen turnover data are combined with measurements of nitrogen intake and loss, rates of total body protein synthesis and catabolism can be estimated. These estimates indicate that protein catabolism is increased in critically ill patients.⁴⁸ Synthesis rates remain normal during fasting but increase to approach or match catabolic rates when feeding is adequate. Thus, the increase in net nitrogen loss during critical illness appears to result from an increase in protein breakdown. Decreased protein synthesis is less of a factor as long as nutritional intake is satisfactory [see Table 4].

ALTERED AMINO ACID METABOLISM

Protein synthesis and breakdown are processes that occur in cells and involve intracellular amino acids. It has been estimated that skeletal muscle contains as much as 80% of the free amino acid pool.⁴⁹ Intracellular concentrations of free amino acids in skeletal muscle are approximately 30 times greater than plasma concentrations of free amino acids.⁵⁰ Thus, the total muscle mass of a 70 kg man contains approximately 87 g of free amino acids in the intracellular water, whereas the extracellular pool contains only 1.2 g.

The relative amounts of individual free amino acids in cells differ from the proportions found in protein. Glutamine, a nonessential amino acid, accounts for only about 5% to 6% of protein, but it is the most abundant intracellular free amino acid, accounting for about 60% of the total intracellular free amino acid pool. In contrast, the eight essential amino acids together account for only 8.4% of the intracellular pool. The intracellular concentration of glutamine decreases under many catabolic conditions, including starvation, inactivity,⁵¹ elective operation,⁵² trauma,⁵³ and sepsis.⁵⁴ This decrease occurs early in the course of the acute illness, persists until late in convalescence, and appears to be related to the severity of illness.^{55,56} The intracellular concentrations of phenylalanine, tyrosine, alanine, and the branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine—typically increase after trauma and infection.^{51,54} These levels return to normal during convalescence, usually before glutamine levels do.

Plasma concentrations of free amino acids generally decrease after operation, injury, or infection, largely because of a fall in the concentrations of the nonessential amino acids. Changes in extracellular concentrations of specific amino acids have been inconsistent between studies, presumably as a reflection of differences in patient selection, analytic methods, or treatment.⁵⁴

The ECF compartment is important for amino acid transport between organs and between regions of the body. Aulick and Wilmore calculated amino acid release rates from peripheral tissues of burn patients on the basis of measurements of leg blood flow and of femoral arterial and venous plasma concentrations of 10 amino

Table 4 Alterations in Rates of Protein Synthesis and Catabolism That May Affect Hospitalized Patients

	Synthesis	Catabolism
Normal—starvation	↓	0
Normal—fed, bed rest	↓	0
Elective surgical procedure	↓	0
Injury/sepsis—I.V. dextrose	↑↑	↑↑↑
Injury/sepsis—fed	↑↑↑	↑↑↑

↓—decrease ↑—increase 0—no change

acids.⁵⁷ The net release of amino acid nitrogen was five times greater in burn patients than in control subjects. Alanine was the only amino acid whose release rate was significantly elevated (glutamine concentration was not determined). Alanine release was related to total burn size (injury severity) and to total body $\dot{V}O_2$. In related studies, the accelerated peripheral amino acid release was matched by increased uptake across the splanchnic bed.²⁴ Alanine uptake was three to four times control values. This increased release of amino acids from the periphery and transport to splanchnic tissues appears to be another characteristic metabolic response to critical burn injury.

Garber and colleagues observed that glutamine and alanine together constituted as much as 70% of the amino acids released from skeletal muscle in vitro.⁵⁸ Furthermore, the release rates of alanine and glutamine reflected the net rates of formation from other amino acids.⁵⁹ Thus, during critical illness, skeletal muscle protein is broken down into amino acids that are largely converted to glutamine and alanine, which are then released into the ECF for transport. Although all amino acids are required for protein synthesis at remote locations, glutamine and alanine are the major nitrogen carriers from muscle. These two amino acids have other roles as well. Alanine is a precursor of glucose production in the liver. In that process, urea is also formed and subsequently excreted by the kidneys. Although there may be some minor recycling of urea nitrogen under certain conditions,⁶⁰ formation of urea is the final step in the loss of body protein, representing an irreversible loss of nitrogen.

Glutamine is a precursor for production of ammonia in the kidneys, an important buffering mechanism for excreted acid loads. Increased breakdown of intracellular constituents could result in such an acid load, and ammonia excretion is often increased after injury. Intracellular skeletal muscle glutamine may be an important determinant of net skeletal muscle protein breakdown.^{61,62} After a standard operation in an animal model, net amino acid efflux from the hindquarter was increased as the glutamine concentration fell. However, if the intracellular glutamine concentration was maintained by the provision of exogenous glutamine, net efflux was reduced.

Glutamine also appears to be an important respiratory fuel for rapidly dividing cells. Glutamine can be converted to glutamate and then to α -ketoglutarate for participation in the citric acid cycle. The nitrogen of glutamine is used to form ammonia, alanine, and citrulline.⁶³ This process occurs in colonocytes, enterocytes, fibroblasts, and, possibly, inflammatory cells such as macrophages. Phagocytic cells are found in fixed locations in the GI tract, such as Peyer's patches and other regions containing Kupffer's cells, as well as in the wound, at other sites of inflammation, and in the bone marrow. Windmueller measured the nutrient requirements of the rat intestine using an isolated, perfused segment of small bowel.⁶³ The intestinal segment extracted large amounts of glutamine from the recirculated perfusate. Souba and Wilmore measured amino acid uptake by the gut in conscious animals and demonstrated that the consumption of glutamine by the gut was significantly increased after celiotomy, even

though the circulating glutamine concentration was reduced (i.e., glutamine was actively taken up by the intestine).⁶⁴

Dissolution of skeletal muscle protein during critical illness seems to serve many purposes. First, it provides amino acids to support protein synthesis at remote sites such as the wound, other inflammatory foci, and the liver. Proteolysis also provides amino acid precursors for glucose production by the liver and for production of ammonia in the kidneys. Finally, it provides glutamine, which appears to be a specific fuel for the gut and possibly for other tissues with rapid cell turnover, such as the wound, bone marrow, and fixed macrophages of the GI tract. This mobilization of amino acids from muscle protein, however, leads to an irretrievable loss of nitrogen in the form of urea, ammonia, creatinine, uric acid, and other compounds. The cost to the patient is rapid erosion of muscle mass and debility.

Altered Carbohydrate Metabolism

ACCELERATED ENDOGENOUS GLUCOSE PRODUCTION

The liver normally produces sufficient glucose to permit maintenance of the blood glucose concentration within narrow limits, even during periods of fasting. During critical illness, the rate of endogenous glucose production is increased.^{24,65,66} Increased basal glucose production is matched by an increase in glucose uptake, so that glucose levels remain relatively stable. Thus, the mass flow, or turnover, of glucose is increased. In studies of patients with burns, glucose turnover was related to total body $\dot{V}O_2$ and thus to the size of the burn (i.e., to injury severity).⁶⁷ Regional uptake was closely related to regional blood flow and regional lactate release but not to regional $\dot{V}O_2$. Thus, glucose was directed by the circulation to the wound, where it was taken up and converted via glycolysis to lactate, even in the presence of adequate or increased oxygen delivery.

The liver produces glucose by a variety of mechanisms. Hydrolysis of hepatic glycogen mobilizes glucose rapidly to serve as an energy source in times of acute need. This mechanism is most important immediately after injury and during acute stress states, such as shock, fever, pain, and anxiety (ebb-phase responses). Glycogen reserves are limited, however, and glycogen is not the major source of hepatic glucose production during recovery from critical illness.

Glucose can also be formed from lactate and from alanine.⁶⁸ The conversion of lactate to glucose occurs via the Cori cycle in the liver. Lactate is formed from pyruvate, which is the end product of glycolysis. In critically ill patients with adequate oxygen delivery, the wound is a major source of lactate. Adenosine triphosphate (ATP) is formed during glycolysis and provides energy for the wound, but ATP is required to convert lactate back to glucose. The increased mass flow of glucose serves as a fuel for the healing wound. It may also reflect an inefficient biochemical cycle that requires energy but in which there is no net gain or loss of substrate. Accelerated glucose cycling has been documented both in burn patients and in blunt trauma patients.^{69,70} The purpose of these so-called futile cycles is not clear. Because they result in the net generation of heat, they presumably contribute to hypermetabolism. That overall conversion requires net input of ATP and is thus another energy drain for the patient.

GLUCOSE INTOLERANCE AND INSULIN RESISTANCE

When glucose is administered to critically ill patients, hyperglycemia often results. Glucose tolerance tests typically yield abnormal results after injury.⁷¹ During shock, immediately after injury or operation, and in the course of ebb-phase responses, the insulin response to hyperglycemia may be blunted. During the flow phase, however, after resuscitation and stabilization, the response to glucose is normal or even exaggerated.^{72,73} Both glucose and insulin levels are higher in

trauma patients than in control subjects [see Table 5], and the increase in insulin is proportionally greater than the rise in glucose.

Black and associates maintained a fixed level of hyperglycemia in patients recovering from trauma by adjusting a glucose infusion on the basis of bedside glucose readings and a negative-feedback algorithm.⁷⁴ Because the glucose concentration was at steady state, the glucose infusion rate reflected the rate of total body glucose uptake or disposal. Control subjects demonstrated continuously increasing glucose disposal over time; the glucose infusion rate was increased repeatedly to maintain fixed hyperglycemia. Glucose disposal was closely related to insulin concentration, which increased steadily during the 2-hour study. In contrast, glucose disposal in trauma patients was markedly lower than in control subjects, and it did not increase appreciably over time. The insulin concentrations did, however, increase throughout the study and were always greater than corresponding control values. The trauma patients were therefore less responsive (i.e., were resistant) to insulin.

These investigators also infused insulin into trauma patients and control subjects to maintain specific fixed levels of hyperinsulinemia. During these infusions, the glucose concentration was maintained at basal values (i.e., euglycemia). The glucose infusion rate again reflected total body glucose disposal, which was a function of tissue responsiveness to the insulin level. At all insulin levels, glucose disposal was lower in trauma patients than in control subjects. These studies quantitated posttraumatic insulin resistance and suggested that this response was caused by a postreceptor defect. In similar conditions, Brooks and associates demonstrated reduced forearm glucose uptake, indicating that peripheral tissue—principally skeletal muscle—was a major site of insulin resistance⁷⁵ [see Table 6].

ALTERED FUEL METABOLISM

The studies by Black and associates⁷⁴ demonstrated that in recovering trauma patients, there is an upper limit to glucose disposal of 5 to 6 mg/kg/min, despite hyperglycemia and hyperinsulinemia. Additional studies have confirmed that critically ill patients are limited in their ability to utilize glucose as a fuel. Long and coworkers studied the effect of increasing carbohydrate intake on net nitrogen loss in recovering burn patients.⁷⁶ They found that nitrogen loss was reduced as carbohydrate was increased to 60% to 70% of total caloric needs (also approximately 5 to 6 mg/kg/min). Very little additional reduction in nitrogen loss was observed with higher carbohydrate levels. Wolfe and associates used isotope-labeled glucose to measure glucose oxidation in postoperative⁷⁷ and burn patients^{66,78} and found that both groups exhibited an upper limit of glucose oxidation. These studies also suggested that maximum glucose oxidation is inversely related to injury severity.

Lipid metabolism is also affected by critical illness. In an elegant series of kinetic studies performed in blunt trauma patients, Shaw and Wolfe⁷⁰ documented a greater than twofold increase in glycerol turnover, reflecting an accelerated rate of triglyceride hydrolysis to form free fatty acid (FFA) and glycerol. They also demonstrated a doubling of FFA oxidation rate; however, the measured turnover of FFA was only 30% greater than the control value, which suggested that some of the FFA released from triglyceride was oxidized in the

Table 5 Basal Glucose and Insulin Concentrations*

	N	Plasma Glucose (mg/dl)	Serum Insulin (μU/ml)
Normal subjects	49	98 ± 1	12 ± 1
Trauma patients	19	104 ± 2	17 ± 2
P		< 0.02	< 0.01

*Mean ± SEM.

cell and did not enter the circulating pool. These studies further demonstrated a high rate of FFA recycling, a phenomenon also described in burn patients.⁶⁹

Askanazi and associates studied the metabolic effects of hypercaloric, glucose-based total parenteral nutrition (TPN) on starved patients.⁷⁹ Patients who were nutritionally depleted but were not critically ill showed an increase in $\dot{V}CO_2$ and an increase in the respiratory quotient (RQ, the ratio of $\dot{V}CO_2$ to $\dot{V}O_2$) to 1.0 or greater. These findings indicated that these patients were able to meet all of their energy needs with glucose and that fat oxidation was suppressed. Patients who were depleted and also manifested hypermetabolic responses showed an increase not only in $\dot{V}CO_2$ but also in $\dot{V}O_2$, and the RQ remained below 1.0; therefore, these critically ill patients could not meet all of their energy needs by oxidation of glucose. Not only was there a limit to the ability of these critically ill patients to use glucose as a metabolic fuel, but the high glucose load intensified hypermetabolism as well. Thus, overfeeding with glucose can aggravate critical illness. The mechanisms of this phenomenon are not clear, but they may involve the futile cycling of glucose via fructose 1,6-diphosphate and its associated heat generation.⁶⁹

In addition to protein, nutritional support of critically ill patients often consists of a mixture of carbohydrate and fat to meet energy requirements. In such a system, exogenous carbohydrate is oxidized directly, but exogenous lipid is added to body fat stores.⁸⁰ Lipid is mobilized from these endogenous stores for oxidation. Such a mixed-fuel preparation should provide sufficient glucose for those tissues that require it (i.e., central nervous system, renal medulla, hematopoietic cells, and inflammatory cells), prevent excessive hyperglycemia, stimulate insulin elaboration, and approach nitrogen equilibrium.

Systemic Mediators

It was once generally thought that the metabolic alterations associated with injury and critical illness were derived from some harmful substance (e.g., a toxin) or dysfunctional process (e.g., a deranged endocrine mechanism). We now appreciate that the regulatory mechanisms affecting these processes are intricate and highly complex and depend on the actions of a myriad of mediators that influence the proliferation, development, and behavior of cells. It is hard to judge which, if any, of these mediators is maladaptive or harmful: those that seem to have harmful effects that exacerbate debility and organ dysfunction in some settings often promote healing and recovery in others.

These mediators may be synthesized by one or many cell types. Some mediators may affect the cell that made them, thus exerting an autocrine effect. Others may affect cells in close proximity, thus exerting a paracrine effect. If they gain access to the ECF, they can be transported via the circulation and affect cells far removed from their site of origin, thus exerting an endocrine effect. Most interact with a specific receptor, usually on the surface of the target cell. This molecular interaction can influence the cell's biology in a number of ways.

First, it may alter the cell membrane, affecting its permeability to certain substances or changing the availability or affinity of other receptors for interaction with their specific mediators. Second, it may alter the structural organization of the cell, making certain intracellular constituents more or less available to exert their effects on cell behavior. Finally, it may initiate one of several intracellular molecular mechanisms that ultimately affect the nucleus, thereby altering gene expression for protein synthesis or DNA replication and cell proliferation.

These mediators have been categorized as endocrine hormones, inflammatory mediators, and growth factors. But as our knowledge about them has grown, it has become apparent that the distinctions are not always clear-cut, and some mediators can fit in more than one category. For example, the hormone insulin exerts definite endocrine metabolic effects that are well known, but it is also an important growth factor. Insulin receptors have been identified in embryos and in plants, and insulin is an important constituent of many cell culture media.⁸¹ Insulin may also affect certain inflammatory responses. In a 2002 study, otherwise normal subjects manifested enhanced and prolonged hemodynamic and cytokine responses to endotoxin under conditions of hyperinsulinemia and euglycemia.⁸²

The metabolic response to critical illness is a clinical phenomenon that dominates the clinical presentation and course of critically ill patients. It involves alterations that affect either the whole body or specific organ systems. In what follows, I discuss several ways in which these clinical events may be regulated.

HORMONES

During critical illness, the concentrations of several hormones are altered. The levels of the counterregulatory or so-called stress hormones—cortisol, glucagon, and the catecholamines epinephrine and norepinephrine—are typically increased. These hormones have several direct and indirect effects and appear to function as important regulating signals in the response to critical illness.

The sympathetic-adrenal axis is one of the major systems by which the body initiates responses to critical illness. It also modifies the elaboration and effects of other hormones and thus serves as a link between the central nervous system and the endocrinologic organs. Many of the changes in vital signs observed during critical illness, such as tachycardia, tachypnea, and widened pulse pressure, are ascribed to adrenergic and catecholamine effects; in addition, many of the signs of shock indicate autonomic overactivity. The catecholamine levels are increased in proportion to the severity of injury.⁸³ During the flow phase of critical illness, concentrations of the catecholamines may be persistently elevated; catecholamine turnover after burn injury is markedly increased.^{44,84} $\dot{V}O_2$ and metabolic rate have been directly related to the excretion of catecholamines. In one study, alpha- and beta-adrenergic blockade significantly reduced the metabolic rate in burn patients, although the rate did not return to control levels.¹⁹ This effect was not produced by alpha-adrenergic blockade alone, which indicates that beta-adrenergic stimulation

Table 6 Glucose Disposal and Forearm Glucose Uptake during Hyperinsulinemia and Euglycemia

Target Dose	N	Plasma Glucose Concentration (mg/dl)	Serum Insulin Concentration (μU/ml)	Glucose Disposal Rate (mg/kg/min)	Arterial–Deep Venous Glucose Difference (mg/dl)	Forearm Glucose Uptake (mg/dl/min)
Normal subjects						
100 μU/ml	7	92 ± 2	106 ± 6	9.32 ± 1.04	21 ± 3	0.76 ± 0.12
200 μU/ml	6	92 ± 2	183 ± 19	8.91 ± 0.78	26 ± 4	1.10 ± 0.11
Injured patients						
200 μU/ml	4	97 ± 1	145 ± 11	5.29 ± 0.80	8 ± 4	0.36 ± 18
500 μU/ml	1	117	506	5.79	2	0.20

predominates in the flow phase of the response to critical illness.

The sympathetic-adrenal axis also affects the endocrine pancreas. Porte and Robertson determined that the insulin response to glucose in normal individuals was reduced substantially with alpha-adrenergic stimulation but was enhanced with beta-adrenergic stimulation.⁸⁵ Catecholamines may also modulate the peripheral action of insulin. When epinephrine was infused into normal individuals at doses low enough to allow beta-adrenergic effects to predominate, insulin resistance was observed in uninjured forearm tissue.⁸⁶ Despite its apparent catabolic effects on metabolic rate and insulin resistance, epinephrine alone reduces the release of amino acid from skeletal muscle *in vitro*.⁸⁷

Cortisol⁸⁸ and glucagon⁸⁹ levels are elevated after major injury and during critical illness. The degree of elevation appears to be related to the extent or severity of the injury. An increased cortisol level is associated with glucose intolerance.⁹⁰ Patients with Cushing's syndrome manifest reduced muscle mass and loss of protein from the skin. Owen and Cahill administered hydrocortisone to starved obese patients.⁹¹ Although they observed an increase in ammonia excretion and a decrease in urea excretion, there was no net change in total nitrogen loss. Glucagon promotes gluconeogenesis.⁹² This effect may be overcome by increased concentrations of insulin.⁹³ Wolfe and colleagues administered glucagon to fasting normal individuals and observed a slight increase in nitrogen excretion, primarily as urea.⁹⁴ However, net nitrogen loss from peripheral tissues did not increase.

Although injury and critical illness clearly affect hormone levels, it has not been possible to ascribe all of the physiologic responses observed in patients to the known actions of individual hormones. A number of studies, however, have identified interacting effects by altering more than one hormone level simultaneously. For example, when Shamoon and coworkers infused a combination of hydrocortisone, glucagon, and epinephrine, they observed a synergistic effect on glucose production.⁹⁵

Bessey and associates extended these observations.⁹⁶ In an attempt to simulate the endocrine environment of injured patients, they infused the same combination of hormones for 3 days in normal individuals. The infusion maintained elevated catabolic hormone levels, similar to those observed in patients with mild to moderate injury. The investigators monitored a variety of metabolic parameters and compared these results with measurements obtained in a control study of the same individuals, in which the patients received an infusion of saline. The alteration in the hormonal environment increased the resting heart and respiratory rates, widened the pulse pressure, and slightly elevated the rectal temperature. In addition, hypermetabolism, a negative potassium balance, increased endogenous glucose production, insulin resistance, sodium retention, and leukocytosis were observed [see Table 7]. During the control study, the individuals maintained nitrogen equilibrium, but during the triple-hormone infusion, they were in persistently negative nitrogen balance, even though nutritional intake was identical in the two studies. Whole body protein turnover, as measured by ¹⁵N kinetics, was increased in the subjects who received the hormone infusion because of an increase in protein catabolism. These changes, which are typically seen in critically ill patients, occurred in the absence of a wound or inflammatory focus.

The negative nitrogen balance and increased turnover of whole body protein observed during the triple-hormone infusion were also associated with a significant decrease in total intracellular amino acid nitrogen in skeletal muscle.⁹⁷ This decrease was caused primarily by a fall in the intracellular glutamine level. Although these changes suggest that the posttraumatic hormonal environment plays a causative role in increasing net muscle proteolysis, the triple-hormone infusion did not appreciably alter either whole blood amino acid concentra-

tions or amino acid efflux from the forearm. A potential explanation for these findings is that the triple-hormone infusion, particularly the glucagon component, may have affected processing of amino acid by the liver, thereby reducing the net retention of dietary amino acids.⁹⁸

The endocrine environment in critically ill patients, however, is not static. Although catabolic hormone levels may be persistently elevated, insulin is often suppressed during the early phases of critical illness but elevated later, during the flow phase. Bessey and Lowe attempted to simulate this changing hormonal environment in normal subjects by administering a somatostatin analogue during the first 24 hours of a 3-day infusion of catabolic hormones so as to inhibit the elaboration of insulin in response to hyperglycemia.⁹⁹ They compared the findings to those obtained from studies of the same individuals during triple-hormone infusion, when insulin levels were allowed to rise unchecked. Early whole body nitrogen loss was increased in the studies with the somatostatin analogue, but there was no difference in forearm nitrogen release at 24 hours; however, 2 days later, when glucose and insulin concentrations were similar in the two studies, total body nitrogen loss was equivalent, but forearm nitrogen release was increased in the patients receiving the somatostatin analogue. Coadministration of exogenous insulin with somatostatin prevented this acceleration of net muscle protein breakdown (P. Q. Bessey, K. A. Lowe, D. C. Blake; unpublished data). Thus, the interacting effects of multiple hormones and the changing relationships among them over time appear to be capable of inducing, at least qualitatively, most of the metabolic responses to critical illness.

Several investigators have attempted to modulate the catabolic responses of critical illness by altering the endocrine environment. For example, Hulton and colleagues monitored hind-leg amino acid efflux after abdominal operation in an animal model.¹⁰⁰ The accelerated efflux of skeletal muscle amino acids observed postoperatively was attenuated by complete alpha- and beta-adrenergic blockade or by thoracic epidural anesthesia. Both pharmacologic techniques are known to attenuate the hormonal response to operative stress. Brandt and coworkers measured hormonal and protein catabolic responses after abdominal hysterectomy.¹⁰¹ In the patients who underwent epidural anesthesia, concentrations of cortisol and catecholamines were lower and nitrogen loss was less than in patients who received general anesthesia alone. Tsuji and associates reported similar findings.¹⁰² Subsequent studies have shown that perioperative management of patients with high thoracic epidural analgesia and intravenous somatostatin and etomidate to inhibit elaboration of glucagon and cortisol prevents the typical postoperative increases in amino acid clearance and urea synthesis.¹⁰³

In summary, the altered endocrine environment characteristically

Table 7 Effect of Infusion of Cortisol, Glucagon, and Epinephrine on Metabolism

	Saline	Hormones*
Metabolic rate (kcal/m ² /hr)	32.24 ± 1.05	38.42 ± 1.31
Nitrogen balance (g/day)	-0.2 ± 0.4	-3.2 ± 0.4
Protein catabolic rate (g nitrogen/day)	38.4 ± 1.9	46.5 ± 2.5
Plasma glucose (mg/dl)	94 ± 2	133 ± 4
Serum insulin (μU/ml)	8 ± 1	22 ± 3
Glucose production rate (mg/kg/min)	2.08 ± 0.06	2.55 ± 0.06
Insulin-mediated glucose disposal (mg/kg/min)	8.62 ± 0.51	3.22 ± 0.51
Insulin-mediated forearm glucose uptake (mg/dl/min)	1.03 ± 0.09	0.48 ± 0.12

*All significantly different from control values.

associated with critical illness and the influence of the sympathoadrenal axis appear to play a major role in mediating the metabolic responses observed in critically ill surgical patients. Simple alteration of the stress hormonal environment in healthy individuals is capable of inducing many of these metabolic changes; however, the magnitude of these changes is generally less than that observed in critically ill patients. Blunting of the stress hormonal changes after operation or injury can modulate acute catabolic responses.

Although changes in stress hormones seem to dominate the clinical picture, characteristic alterations of other endocrine hormones also occur. Levels of thyroxine (T_4) and triiodothyronine (T_3) are typically reduced after critical illness, and levels of an inactive form of T_3 , reverse T_3 (rT_3), are elevated; however, administration of thyroxine to critically ill patients seems to have little clinical effect.¹⁰⁴ Hormones of the gonadal axis are typically suppressed during critical illness. Levels of testosterone are decreased in men, as are levels of luteinizing hormone, follicle-stimulating hormone, and estradiol in women, apparently in proportion to injury severity.¹⁰⁵⁻¹⁰⁷ These changes interrupt the menstrual cycle and decrease libido. Although growth hormone (GH) levels are increased after injury, patients demonstrate muscle wasting and weight loss.¹⁰⁸ The anabolic effects of GH depend on the synthesis and elaboration of insulinlike growth factor-1 (IGF-1), whose activity is affected also by the presence of various IGF-binding proteins (IGFBPs).¹⁰⁹ Despite elevation of circulating GH levels, IGF-1 concentrations are reduced, as are IGFBP-3 levels.

Taken together, all of these endocrine changes (1) mobilize amino acids and fuel substrates to support wound healing, resolution of inflammation, and tissue repair and (2) turn down anabolism and growth in the rest of the body. This response to acute illness would seem to be an adaptive one: wounds heal and patients recover, despite a transient loss of lean tissue. However, patients with protracted critical illnesses, who have been maintained for weeks or months in the ICU, may present a different clinical picture. Despite closure of the wound, drainage of pus, provision of nutrients, and treatment of infection, they remain catabolic and are extremely slow or unable to recover. Current evidence suggests that this syndrome may reflect a different endocrine pattern. Many of the anterior pituitary hormones (e.g., adrenocorticotropic hormone, thyroid-stimulating hormone, and GH) are present in reduced concentrations, or the pattern of their secretion is altered.¹¹⁰ These alterations may reflect a change in hypothalamic function; infusion of various releasing factors can restore normal hormone responsiveness in the thyrotropic, somatotropic, and gonadotropic axes.¹¹¹

CYTOKINES

A number of cell types appear in a healing wound soon after injury.¹¹² These cells are actively involved in angiogenesis, production and remodeling of collagen, scavenging of necrotic debris, and engulfment and killing of bacteria. Many of them release substances that influence cellular proliferation, development, and function and so regulate local inflammation and wound healing. These substances, collectively known as cytokines, can be produced by and interact with a wide variety of cells in addition to inflammatory cells and appear to be major mediators of multiple cellular responses to injury and infection [see 8:26 *Molecular and Cellular Mediators of the Inflammatory Response*].

Some cytokines primarily stimulate inflammatory responses and thus are known as proinflammatory cytokines, whereas others retard these responses and thus are known as anti-inflammatory cytokines. In addition, specific receptor antagonists have been identified that interfere with the interaction between a cytokine and its cellular receptor. Finally, there are specific soluble receptors, unassociated with a cell, that can effectively neutralize the cytokine before it interacts with

a target cell. Both proinflammatory and anti-inflammatory mechanisms may be stimulated together in acute illness.¹¹³ The balance and interactions between them determine the course of the inflammatory process.

The major proinflammatory cytokines, tumor necrosis factor (TNF), interleukin-1 (IL-1), and IL-6, are closely related in that they are elaborated in a characteristic pattern (or cascade) in response to an inflammatory stimulus, such as trauma¹¹⁴ or endotoxin.¹¹⁵ TNF appears first, followed by IL-1 and then IL-6. The elaboration of TNF and IL-1 is relatively brief, but IL-6 persists longer.

Cytokines appear to regulate cell recruitment, proliferation, development, and other cellular events that occur in the wound, but how and to what extent they exert systemic effects and modulate the metabolic responses to critical illness is less clear. One conceptual model proposes that when local cytokine production is particularly abundant, owing to extensive wounds or uncontrolled infection, certain cytokines spill over into the circulation and then affect tissues at distant sites [see Figure 5]. Although elevated circulating cytokine levels have been detected in critically ill patients, only IL-6 has been consistently associated with severe illness and outcome.^{116,117}

TNF can initiate the cytokine cascade, ultimately producing fever, leukocytosis, and other signs and symptoms of critical illness.¹¹⁸ To characterize the role of TNF in proteolysis associated with endotoxin or sepsis, Michie and coworkers analyzed the responses of both animals and humans during prolonged infusions of TNF.¹¹⁹ Negative nitrogen balance was related to the onset of anorexia and reduced food intake and not to the development of hypermetabolism. Mealy and associates performed adrenalectomies and abrogated the increase in nitrogen loss associated with TNF infusion.¹²⁰ Hall-Angeras and colleagues found that a steroid antagonist prevented the increase in myofibrillar protein breakdown usually seen in an animal model of intra-abdominal sepsis.¹²¹ These observations suggest that even though TNF may be a major initiating signal for a variety of cellular events in critical illness, other mediators are required for the full development of the metabolic responses to injury and infection.

IL-1 was one of the first fever-producing cytokines, or pyrogens, to be identified.^{122,123} Early in vitro studies appeared to present conflicting findings,¹²⁴⁻¹²⁶ but the preponderance of the data currently available indicate that IL-1 can increase proteolysis, especially in intact animals. For example, Zamir and colleagues measured increased muscle protein breakdown in vitro after administration of IL-1 to intact animals.¹²⁷ In another study, they were able to reduce but not prevent the increased proteolysis that followed endotoxin administration by pretreating animals with IL-1 receptor antagonist (IL-1ra).¹²⁸

To characterize the metabolic effects of IL-1 in vivo, Watters and associates gave daily intramuscular injections of etiocholanolone to normal individuals.¹²⁹ (This steroid stimulates the development of an inflammatory focus and the production of IL-1.) The subjects manifested an acute-phase response: fever, leukocytosis, increased concentrations of acute-phase proteins, and hypoferrremia. They were not hypermetabolic, however, and they remained in nitrogen equilibrium when fed a standard diet. The concentrations of catabolic hormones were not affected by this treatment. When hydrocortisone, glucagon, and epinephrine were administered in conjunction with etiocholanolone, however, both inflammatory and metabolic responses were observed.¹³⁰ These healthy subjects exhibited the same clinical features as did patients with infection. These findings suggested that both endocrine and cytokine mechanisms influence the responses to critical illness.

IL-6 can induce many of the components of the acute-phase response¹³¹ and may be measured in the blood of patients experiencing trauma,¹³² sepsis,¹³³ pancreatitis,¹³⁴ or other critical illnesses (e.g., myocardial infarction).¹³⁵ Mateo and associates identified IL-6 in

wound fluid from both animals and humans, and they found that the capacity of wound macrophages to produce IL-6 increased with time.¹³⁶ Thus, IL-6 might be one mechanism by which the wound influences critical illness. Persistent measurable levels of IL-6 have been related to mortality in both trauma¹¹⁶ and burn¹¹⁷ patients.

Stouthard and associates infused recombinant IL-6 (rIL-6) into uninjured cancer patients for 4 hours, then measured glucose and lipid kinetics, metabolic rate, and hormonal profiles during the infusion and during a saline control infusion.¹³⁷ IL-6-induced hypermetabolism and energy expenditure increased by 25%. Glucose production, lipolysis, and fatty acid oxidation also increased. Glucose clearance was also increased; serum glucose concentrations were not significantly affected by IL-6 infusion. Tsigos and colleagues administered increasing doses of IL-6 subcutaneously to healthy subjects and demonstrated a dose-response relationship between IL-6 dose and circulating level and glucose concentration.¹³⁸ In both of these studies, IL-6 also induced elevations in circulating stress hormone levels.

IL-6 also affects protein metabolism. Transgenic mice that overexpress IL-6 exhibit retarded growth and muscle atrophy. These observations have been correlated with reduced circulating concentrations of insulinlike growth factor-1 (IGF-1).¹³⁹ In another report, a specific IL-6 receptor antibody administered to the young IL-6 transgenic mice restored muscle growth to normal.¹⁴⁰ The muscle atrophy in these studies was associated with an increase in the synthesis and activity of several enzymes that catalyze muscle protein breakdown, and these changes too were blocked by IL-6 receptor antibody. The effects of IL-6 on long-term protein accretion in humans have not yet been elucidated, but severely burned children who survive after a long period of critical illness often experience growth retardation.¹⁴¹

Both endocrine and inflammatory mediators affect metabolic responses in critically ill patients. In fact, the two systems are closely linked—perhaps inseparably—and probably influence each other.¹³⁰ For example, Bornstein and colleagues identified IL-6 messenger RNA (mRNA) expression in the steroid-producing cells of the adrenal gland, which were located not only in the cortex but also in the medulla, adjacent to catecholamine-producing cells.¹⁴² In a subsequent study, they detected IL-6 and IL-6 receptor expression in adrenal cell cultures, both with macrophages present and with macrophages absent.¹⁴³ They also found that IL-6 stimulated release of steroid hormones, aldosterone, cortisol, and androgens *in vitro* in a dose-dependent manner; however, these effects developed over a period of 24 hours. These findings indicate not only that IL-6 exerts autocrine and paracrine effects on adrenal cellular synthetic function but also that it is probably involved in the long-term regulation of adrenal steroidogenesis rather than being responsible for acute changes in adrenal function.

On the other hand, glucocorticoids have long been known to exert anti-inflammatory effects. They interfere with the proliferation and function of leukocytes and other immune cells, and they inhibit the synthesis and cellular action of cytokines and other molecules important for cellular responses.¹⁴⁴ In a clinical study, Barber and colleagues demonstrated that glucocorticoid administration led to a dose- and time-dependent reduction in TNF production and symptoms in response to endotoxin.¹⁴⁵

Cytokines and hormones may also affect metabolic responses at the end-organ level via different mechanisms. For example, skeletal muscle protein breakdown can occur via any of at least four intracellular proteolytic systems.¹⁴⁶ One of the major pathways affecting myofibrillar proteins is energy dependent (i.e., ATP-dependent) and involves the cytosolic peptide cofactor ubiquitin. In animals, glucocorticoids stimulate an ATP-dependent proteolytic system and increase the expression of ubiquitin.¹⁴⁷ Zamir and colleagues administered a gluco-

corticoid antagonist to rats with intraperitoneal sepsis and demonstrated that it reduced but did not eliminate the increased muscle proteolysis.¹²⁷ In a subsequent study, they induced accelerated skeletal muscle proteolysis by injecting IL-1 intraperitoneally.¹²⁸ Previous adrenalectomy, which eliminated glucocorticoid elaboration, had little effect on the proteolysis observed.¹⁴⁸ These observations suggest

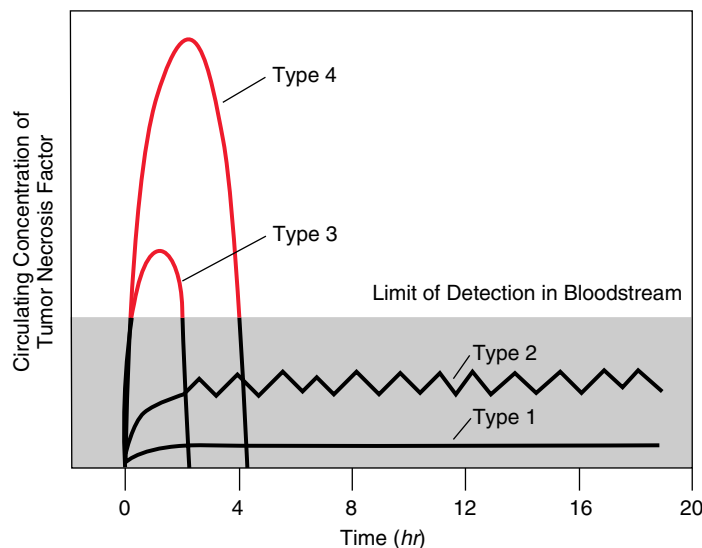


Figure 5 Different infectious states are likely to be associated with different patterns of cytokine release into the circulation.²⁵⁴ Type 1 in this figure could be considered to represent localized cellulitis, such as might be present at an infected intravenous catheter infusion site. Generation of tumor necrosis factor (TNF) and other cytokines occurs locally to produce local responses that aid host defense and tissue repair. Overspill into the circulation is minimal.

The second type might represent the responses ensuing from appendiceal abscess. There is local generation of cytokines, and as bacteria or their endotoxins leak into the circulation, circulating mononuclear cells also elaborate cytokines and give rise to moderate systemic responses. The low level of persistent endotoxemia is reflected in the cytokine response. Because only a small number of cytokine-producing cells are stimulated at any one time, the responses of these cells, although of long duration, are not strong enough to be detectable in the bloodstream. However, this signal is sufficient to generate systemic manifestations of the localized infection.

A third type of infection might be one that follows manipulation of a catheter in the biliary tree or urinary bladder to resolve an obstruction. A few cytokine-producing cells simultaneously elaborate TNF to produce a high-amplitude signal. Because the endotoxemia is transient, both the signal and the host responses are short-lived. Clinical features include a brief episode of hyperpyrexia with rigors and severe symptoms, but the cytokine response is too short and of insufficient amplitude to give rise to life-threatening, irreversible host alterations.

A fourth type of infection might be precipitated by sudden dehiscence of a colonic anastomosis or by meningococcal septicemia. An acute, massive entry of endotoxins into the circulation stimulates virtually every cytokine-producing cell in the body. A very high amplitude signal occurs, but its duration is short, despite the host's continuing exposure to endotoxin. The short duration of the strong signal is caused by the quick disappearance of cytokines from the circulation; their half-life is short, and the cytokine-producing cells become refractory after their simultaneous explosive response to the initial, lethal signal. This high-amplitude signal is misinterpreted by the host, causing the entire body to behave as if it were a massive wound. The entire vascular tree shows increased permeability and vasodilatation, resulting in the clinical state of irreversible shock. These situations have been reversed or prevented by the use of TNF antibodies in animals and occasionally by the use of plasmapheresis in humans.

that both glucocorticoid-dependent and glucocorticoid-independent proteolytic mechanisms can be activated during critical illness.

Role of the Central Nervous System

The CNS plays a major role in the regulation of the metabolic response to critical illness. Hume and Egdahl were among the first to demonstrate its role in mediating early responses to injury.¹⁴⁹ They measured the rise in 17-hydroxycorticosteroids in adrenal venous blood in response to a burn to the lower limb of an animal under anesthesia. The limb was almost completely separated from the body, so that the only connections between the limb and the rest of the animal were the femoral vessels and the sciatic nerve. The prompt rise in the venous adrenocorticoid concentration after the burn could be prevented by sectioning of the sciatic nerve or of any portion of the CNS up to the level of the midbrain.

To characterize the role of the CNS in the regulation of later hypermetabolic flow-phase responses, Wilmore and associates administered inert gas anesthesia to hypermetabolic burn patients and demonstrated reduced core temperature and metabolic rates.¹⁵⁰ Fried and coworkers studied patients with head injuries during barbiturate coma.^{151,152} Metabolic rate and nitrogen excretion were reduced to basal values during barbiturate administration. Given that its global suppression reduces the intensity of hypermetabolic responses, the CNS appears to be necessary for the full expression of both the ebb phase and the flow phase of the metabolic response to critical illness.

The CNS has long been considered part of a neuroendocrine reflex arc,¹⁵³ a view that has proved useful for explicating underlying regulatory mechanisms. According to this concept, there must be afferent input whereby (1) the body is alerted to an injury or any other threat to its integrity and (2) the wound or inflammatory focus signals its presence, its extent, and its resolution or closure. After reception and interpretation of this input, the CNS generates efferent signals that regulate the regional and systemic metabolic alterations observed clinically. This model is most obviously relevant to the early phase of the response to critical illness (the ebb phase). The hypothalamus, the peripheral and spinal neural pathways, and the adrenals all participate in the classic fright-flight-flight syndrome. Pain, hypovolemia, acidosis, and hypoxia stimulate neural afferent signals to the CNS. The importance of these neural pathways in transmitting afferent signals to the CNS during hypermetabolism is less clear. For example, when lidocaine was applied to burn wounds to anesthetize them, no decrease in hypermetabolism was observed.¹⁵⁴

The CNS may play a role in a variety of immunologic and inflammatory responses.¹⁵⁵ Early studies demonstrated that a small amount of IL-1 injected intrathecally elicited the same increase in body temperature as a much larger dose administered intravenously. This suggested that IL-1 could act centrally and that it might function as an afferent signal from the wound to the CNS.¹⁵⁶ Demonstration of IL-1 immunoreactivity in the hypothalamus of humans lent weight to this suggestion.¹⁵⁷ Later studies, however, showed that astrocytes and microglia could express cytokines and cytokine receptors themselves.^{158,159} In addition, these cells increased expression of IL-1 and IL-6 *in vitro* in response to hypoxia or endotoxin *in vitro*,^{160,161} and systemic administration of endotoxin to intact animals increased cytokine expression in the CNS.^{162,163}

Hill and colleagues used an animal model to assess the metabolic effects of IL-1 continuously infused either subcutaneously or into the lateral ventricle for 6 days.¹⁶⁴ Subcutaneous IL-1 was given in different doses, which induced fever, anorexia, increased protein catabolism, and weight loss in a dose-dependent manner. Intracerebroventricular (ICV) IL-1 evoked qualitatively similar responses.

Subcutaneous IL-1, however, resulted in a greater leukocytosis and a more pronounced acute-phase response than did ICV IL-1, even though the other systemic alterations were quantitatively similar. Thus, IL-1 produced in the CNS may not have the same physiologic consequences as IL-1 produced in other anatomic sites.

In another study, Hill and colleagues pair-fed control animals with animals receiving ICV IL-1.¹⁶⁵ They observed that the pair-fed animals also lost weight, but the weight loss was significantly less severe than in the animals receiving ICV IL-1. Long-term ICV IL-1 infusion also caused increased adrenal gland weight and corticosteroid levels in comparison with values in both pair-fed and chow-fed controls. The ICV IL-1-induced catabolic changes were not, however, attenuated by previous adrenalectomy. This finding indicates that the protein-catabolic effects induced by ICV IL-1 may involve not only glucocorticoid-dependent ATP-ubiquitin proteolysis but also systems that are independent of glucocorticoids. Such a conclusion is consistent with the finding by Zamir and associates that intraperitoneal IL-1 increased total and myofibrillar proteolysis in both adrenalectomized animals and sham controls.¹⁴⁸ Thus, the CNS may be able to influence metabolic responses via both endocrine pathways and other mechanisms that do not involve endocrine activation.

Elaboration of IL-6 typically follows elaboration of IL-1, and IL-6 is a potent activator of corticosteroid synthesis and release.^{115,166} Long-term IL-1 infusion leads to increased muscle protein breakdown and nitrogen loss over and above what is attributable to reduced food intake, and it results in elevated circulating levels of IL-6.¹⁶⁷ When Hill and associates infused IL-6 into the CSF of rats, it had no effect, unlike ICV IL-1.¹⁶⁵ Reyes and Coe followed the appearance of IL-6 in CSF in primates after intravenous injection of IL-1 α , IL-1 β , and IL-6.¹⁶⁸ All three cytokines raised the circulating levels of IL-6, IL-1 α , and cortisol, but only IL-1 β raised the CSF level of IL-6. Furthermore, IL-6 appeared in CSF from the lumbar region 2 hours after it peaked in CSF from the cervical region. These data suggest that the IL-6 in the CSF after the appearance of IL-1 in the periphery is elaborated by the brain.

Romero and colleagues gave an ICV injection of IL-1 β to rats and measured IL-6 concentrations in CSF and in blood from the superior sagittal sinus and the aorta.¹⁶⁹ IL-6 was elevated in all three compartments, and the concentration gradient between the sagittal sinus and the aorta was widened in comparison with the control value. Both adrenergic pathways and adrenal activation are known to be stimulated by IL-1 administration, but the changes observed in this study were not affected by sympathetic blockade. In addition, ICV corticotropin-releasing hormone did not result in alterations in IL-6 levels in CSF or in blood. The investigators concluded that the IL-6 that appeared in both the CSF and the blood was derived from the brain.

Injury and inflammation also appear to affect nerve function. Compounds elaborated by platelets, neutrophils, and other inflammatory cells can alter the phenotype of neurons, affecting their growth, function, and electrical properties.¹⁷⁰ The complex of IL-6 and its receptor can activate specific neuronal signal transduction systems on sensory neurons and so affect gene expression and protein synthesis.¹⁷¹ Sensory nerve injury induces the expression of IL-6 and IL-6 receptor in more central neurons, and this may influence nerve repair.¹⁷² Current studies further suggest that IL-1, IL-6, and other proinflammatory cytokines may play a key role in generating pain syndromes associated with inflammation.¹⁷³ Inflammatory activation of sensory neurons, as opposed to strictly neural mechanisms of activation, also requires the participation of spinal cord astrocytes and microglia. Persistent inflammation, rather than altered neural properties, thus may be the major mechanism responsible for complex re-

gional pain syndromes (e.g., reflex sympathetic dystrophy and causalgia) after injury.¹⁷⁴

Thus, pain, acidosis, hypoxia, and hypovolemia, as well as cytokines and other substances produced by inflammatory cells, generate afferent signals to the CNS through a variety of mechanisms. Some signals may elicit a rapid effector response, whereas others appear to induce mechanisms that result in delayed and more prolonged end-organ functional alterations. The CNS affects both metabolic and inflammatory processes, and it may do so in multiple complementary but largely independent ways. Activation of the hypothalamic-pituitary-adrenal axis is one of these mechanisms, but the CNS also appears to be able to induce catabolic responses without this intervention. The CNS may also be a source of mediators that are released into the circulation for systemic distribution, thus acting as an endocrine organ.

Role of the Gut

Although the idea that endotoxin absorbed from the gut lumen during shock states might result in irreversible critical illness was first proposed more than 40 years ago,^{175,176} most clinicians thought that the gut was inert after operation and injury until recently. It is now generally recognized that the gut plays an important role in augmenting or perpetuating the response to critical illness.¹⁷⁷

Gram-negative pathogens are the predominant infectious organisms in the ICU, and the gut appears to be a major source of contamination. The gut lumen forms a large reservoir for gram-negative enteric bacteria, but the normal GI mucosa protects the host from intraluminal bacteria and their toxins. The maintenance of tight intracellular junctions between epithelial cells prevents the transepithelial migration of bacteria.¹⁷⁸ The GI tract is also richly supplied with macrophages and fixed immune cells. The elaboration of surface immunoglobulins (e.g., IgA) aids in the recognition of foreign antigens.¹⁷⁹ Finally, the liver and the spleen serve as backup systems for trapping bacteria and neutralizing absorbed toxins. The combination of an intact gut mucosa and a normally functioning immune system provides maximal barrier function. Even in immunosuppressed states, the mucosa can still maintain an effective barrier to infection. This suggests that cell-mediated immunity is secondary in importance to an intact intestinal epithelial lining.

When the barrier function of the GI epithelium is impaired, intraluminal bacteria and toxins can invade the host. In one set of experiments in rabbits, fatal endotoxic shock was observed after temporary occlusion of the superior mesenteric artery or a 30% scald burn¹⁸⁰; however, if the enteric flora was reduced, the animals did not die. Endotoxemia has been observed in patients with a variety of critical illnesses.¹⁷⁶ Wellmann and associates reported that whole gut lavage with saline reduced the concentration of circulating endotoxin and improved the clinical outcome in a large group of patients with inflammatory bowel disease that was unresponsive to medical therapy.¹⁸¹ Moreover, bacteremia in portal blood has been observed at the time of operation in as many as 30% of patients with noninflammatory bowel disease.¹⁸² Ambrose and associates cultured both intestinal serosa and mesenteric lymph nodes during abdominal operation.¹⁸³ In patients without inflammatory bowel disease, the incidence of positive cultures was low, but in patients with Crohn disease, the incidence increased markedly, to approximately 30%.

Bacterial translocation is the migration of bacteria across the bowel wall to invade the host. In a review of the available animal and human data on this process, Berg identified three conditions that appear to promote translocation: altered permeability of the intestinal mucosa, decreased host defenses, and an increased number of bacteria within the intestinal lumen.¹⁸⁴ Deitch and colleagues observed this

phenomenon in animals after a variety of insults, including burns,¹⁸⁵ hemorrhagic shock,¹⁸⁶ and endotoxin administration.¹⁸⁰ Malnutrition alone did not lead to translocation, but it made the gut barrier more susceptible to endotoxin.¹⁸⁷

The extent of bacterial translocation in critically ill patients is not well defined. Moore and colleagues obtained both portal venous and systemic venous blood cultures in patients at risk for multiorgan failure after laparotomy for severe trauma.¹⁸⁸ Only 2% of cultures were positive in the first 5 days, which suggests that translocation of bacteria in sufficient quantities to cause portal vein bacteremia is not a major determinant of organ failure soon after injury.

Subsequent studies focused on the gut as a source of cytokines. Even the normal gut contains a large number of intestinal lymphocytes that elaborate proinflammatory cytokines, and these are counteracted by expression of anti-inflammatory cytokines in a state of so-called controlled inflammation.¹⁸⁹ Guy-Grand and colleagues detected measurable levels of TNF, IL-6, and interferon gamma in proximal small bowel secretions in humans.¹⁹⁰ The presence of bacterial overgrowth, especially colonic-type bacteria, however, was associated with increased IL-6 concentrations. Wyble and associates investigated the cytokine response to intestinal ischemia-reperfusion in ex vivo perfused segments of human intestine.¹⁹¹ Concentrations of TNF and IL-1 increased in the venous effluent after reperfusion. The investigators subsequently exposed cultured human endothelial cells to physiologic concentrations of TNF and IL-1 that were lower than those observed after ischemia-reperfusion. The cytokines upregulated expression of E-selectin and intercellular adhesion molecule-1 (ICAM-1), which are thought to mediate the adhesion of neutrophils in the microcirculation and their transmigration across the capillary membrane into tissue, thus initiating tissue inflammation.

Mainous and colleagues produced sterile peritonitis with both a nonlethal and a median lethal dose (LD₅₀) of zymosan.¹⁹² They detected increased IL-6 and TNF in both blood and lymph, but these changes did not correlate with zymosan dose or with bacterial translocation. Thus, the gut appears capable of producing cytokines in response to an inflammatory insult, and this may occur even in the absence of bacterial translocation.

Mochizuki and associates were among the first to demonstrate the importance of enteral feedings in maintaining gut mucosal integrity and modulating catabolic responses in critical illness.¹⁹³ They measured intestinal mucosal weight and several metabolic parameters in experimental animals after a standard burn injury. In one group of animals, feedings were delivered through a gastrostomy tube and were begun soon after the burn injury, whereas in a second group, feedings were oral and were begun after a 72-hour fast. Mucosal weight was preserved in the first group but reduced in the second group. In the animals that fasted, postburn hypermetabolism developed, but this response was attenuated in the ones that received early enteral feedings. Intravenous feeding did not preserve mucosal mass or modify postburn metabolic responses.¹⁹⁴ In an early clinical study, Alexander and colleagues documented improved survival in children with burns who were nourished enterally.¹⁹⁵ Furthermore, Border and associates found that the provision of enteral protein was one of only two factors statistically associated with improved survival in a large group of severely injured patients.¹⁹⁶

Ogle and colleagues extended these observations by comparing intestinal and splenic cytokine expression in animals nourished by parenteral nutrition but allowed no oral intake with cytokine expression in control animals allowed food ad libitum.¹⁹⁷ After 7 days of infusion, mRNA expression for IL-1, IL-6, and TNF was increased in the intestine and decreased in the spleen. Lyoumi and associates also reported that protein malnutrition alone enhances intestinal IL-6 expression and acute-phase responses.¹⁹⁸ These findings suggest that

augmented intestinal cytokine production is responsible, in part, for the earlier clinical observations that bowel rest or inadequate enteral protein amplifies the responses to critical illness and may adversely affect outcome.

The presence of food in the gut lumen is known to be a major stimulus for mucosal cell growth. Mucosal atrophy is observed in the absence of enteral nutrition (as occurs during starvation¹⁹⁹ or periods of parenteral nutrition²⁰⁰) and in defunctionalized intestinal segments.²⁰¹ Enteral feeding not only provides nutrients but also stimulates the elaboration of trophic hormones for the intestinal mucosa.^{202,203} In addition to luminal bulk, specific nutrients (e.g., glutamine and butyrate) are important for the growth of gut mucosa. Glutamine is a major respiratory fuel for the gut, especially during critical illness (see above). Colonocytes also utilize butyrate, a short-chain fatty acid that is produced by bacterial fermentation of polysaccharides in the colonic lumen. In solution, glutamine decomposes into toxic substances; it is therefore not included in any commercially available parenteral amino acid solutions or in most enteral nutrition products. When glutamine was added to parenteral nutrition in place of other nonessential amino acids, however, increased mucosal cellularity was observed in the jejunum, ileum, and colon in an animal model.^{204,205} In other studies, the toxic effects of methotrexate were alleviated and mucosal cellularity and nitrogen balance improved when parenteral solutions containing glutamine were used.²⁰⁶

Endotoxin, Bacteria, Inflammation, and Organ Failure

Endotoxin is a lipopolysaccharide component of bacterial cell walls that can reproduce the syndrome of sepsis and shock when given to animals or humans.²⁰⁷ The presence of endotoxin is considered a major determinant of the clinical sequelae of bacterial infection. A low continuous dose of endotoxin in animals produces a hypermetabolic state that exhibits all of the features of the response to critical illness.²⁰⁸

Revhaug and associates administered *Escherichia coli* endotoxin to normal individuals under controlled conditions of activity and diet and compared the metabolic responses with those of subjects given only saline.²⁰⁹ About 2 to 4 hours after administration of endotoxin, the subjects experienced headache, chills, malaise, nausea, fever, tachycardia, and an increased respiratory rate. In these and subsequent studies, endotoxin injection was also associated with leukocytosis, mild glucose intolerance, an increased metabolic rate, and elevated concentrations of adrenocorticotrophic hormone, cortisol, catecholamines, and growth hormone.

Michie and colleagues found that the symptoms that followed a single dose of endotoxin in normal subjects were preceded by an abrupt and transient rise in circulating TNF concentration.²¹⁰ The symptoms developing after endotoxin injection were similar to those developing during TNF infusion, but they appeared 60 to 90 minutes after injection, in contrast with the appearance of symptoms 30 minutes after the start of TNF infusion.¹¹⁸ In these studies, IL-1 was not detected, but Fong and associates detected both a peak rise in TNF and a later peak of IL-1 after administration of a lethal dose of bacteria in primates.²¹¹ In those studies, death was prevented by an anti-TNF antibody. Thus, TNF is the first in a characteristic cascade of cytokines that mediate the physiologic responses to endotoxin.

Circulating endotoxin can be detected in patients who have experienced trauma¹¹⁶ or burns¹¹⁷ and even in those who have undergone cardiopulmonary bypass.²¹² In healthy persons, repeated doses of endotoxin result in tolerance. In injured or critically ill patients, however, the responses to sustained or repeated doses of endotoxin have not been well characterized.

O'Dwyer and associates measured intestinal permeability in healthy human volunteers after a single dose of *E. coli* endotoxin or saline.²¹³

Lactulose and mannitol were administered orally as markers of intestinal permeability. (Lactulose is not absorbed to any significant extent under normal conditions.) After endotoxin administration, the urinary excretion of lactulose was increased almost twofold, which indicated that intestinal permeability was markedly altered. This change was closely associated with increases in norepinephrine and cortisol levels, which suggested that these hormonal changes or other systemic responses induced by endotoxin were responsible for the change in permeability. If alteration of the gut barrier led to increased absorption of endotoxin, that could be another mechanism by which the systemic responses to critical illness were amplified and perpetuated.

Patients with infectious disease (e.g., typhoid fever or malaria)^{214,215} manifest many of the clinical features observed in critically ill surgical patients; however, these phenomena are less intense in patients with infectious disease. Surgical patients with uninfected wounds also usually manifest relatively mild responses to injury; those with infected wounds exhibit the most intense metabolic alterations. The infection may be associated with the wound (e.g., surgical site infection, mature abscess, or ARDS and pulmonary sepsis), or it may be remote (e.g., pneumonia in a patient with multiple fractures). Peak catabolic responses in surgical patients often occur several days after operation or injury. This period corresponds to the development of the cellular phase of wound healing¹¹² and to colonization of the wound or another site.

Aulick and colleagues examined the possible contribution of bacteria or bacterial products to the metabolic response to injury in animals.²¹⁶ They measured $\dot{V}O_2$ and core temperature in animals for up to 3 weeks after a standard scald burn. Some of the wounds were seeded with bacteria (virulent and nonvirulent *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*), and some of the infected wounds were treated with topical antibacterial agents. The use of topical antibiotics was associated with a reduction in hypermetabolism. In addition, in animals that became bacteremic, the degree of hypermetabolism was at least twice that in nonbacteremic animals. The metabolic effects of infection thus appear to be proportional to the severity and invasiveness of the infection. In analogous studies, Wilmore and associates examined burn patients with and without bacteremia.²⁴ Although total body $\dot{V}O_2$ and cardiac index were already elevated, the onset of bacteremia resulted in further increases in these parameters. In addition, hepatic glucose production and splanchnic uptake of lactate and alanine were significantly increased in patients with systemic infection. Hypermetabolism decreased, however, once organ failure occurred.

Bacteria are ubiquitous in both health and critical illness. The mechanisms by which bacteria become infective and invade host tissues and produce physiologic responses have yet to be fully elucidated. In part, these involve intracellular regulatory systems that respond to complex reciprocal interactions with the host and that can modify bacterial virulence. Guo and associates investigated the dual peptide system PhoP-PhoQ in *Salmonella*.²¹⁷ PhoP-PhoQ regulates genes required for the synthesis of lipid A, the active component of endotoxin. It is capable of modifying the structure of lipid A, and this structurally modified lipid A can affect the expression both of adhesion molecules by host endothelial cells and of TNF by neighboring monocytes. This capability may be a mechanism by which bacteria can not only increase their chances of survival in host tissues but also affect the character or intensity of host inflammatory responses to the infection. PhoP-PhoQ and other intracellular systems respond to characteristics of the host environment, such as pH, PO_2 , and ionic composition.²¹⁸ Thus, the condition of the patient may influence the virulence characteristics of resident bacteria, and these characteristics, in turn, may modulate the patient's responses to critical illness.

The cellular response to localized injury or other inflammatory stimuli initially consists of the recruitment and proliferation of neutrophils. This process appears to be mediated in part by the expres-

sion of adhesion molecules by endothelial cells. These molecules capture passing circulating neutrophils and facilitate their passage through the capillary wall.²¹⁹ Neutrophils, macrophages, and other inflammatory cells have the capacity to engulf and dispose of necrotic debris and to kill bacteria. These same properties also make them potentially toxic to normal cells. Neutrophil infiltration of specific organs, such as the lung, appears to be a first step in the development of organ failure after shock, endotoxin, and other insults.²²⁰ This finding suggests that neutrophils activated by potent inflammatory stimuli can invade unaffected tissues and so contribute to organ dysfunction in critically ill patients.

Not surprisingly, anti-inflammatory mechanisms exist to limit the intensity and toxicity of inflammatory processes. One such mechanism is apoptosis, or programmed cell death, which is thought to participate in the clearing of inflammatory cells as the wound heals and the inflammatory process subsides. Biffl and colleagues demonstrated that IL-6 inhibited apoptosis in human neutrophils *in vitro*.²²¹ They proposed that circulating IL-6 in critically ill patients retarded neutrophil apoptosis and thus enhanced and prolonged the toxic effects of the neutrophils. This could be another mechanism by which the responses to critical illness could be prolonged and lead to worsening organ failure and death.

Several investigators have sought to understand how neural mechanisms might also influence physiologic responses to infection and inflammation. The vagus nerve has been of particular interest because its fibers are widely distributed, especially in organs that contain large amounts of inflammatory cells (e.g., the liver, the spleen, the lungs, the thymus, the GI tract, and the lymph nodes). Nijima gave varying doses of IL-1 β to rats by portal vein injection.²²² He observed a dose-dependent increase in the afferent activity of the hepatic branch of the vagus nerve. He also detected efferent signals in autonomic nerves to the spleen and the thymus after intraportal administration of IL-1. Because these signals were eliminated by vagotomy, they appeared to be the result of reflex activation. These findings suggested that there may be sensors in the hepatoportal system of vagal origin that can detect IL-1 and other inflammatory mediators and generate neural afferent activity, stimulating the brain to generate signals that affect host defense and other responses.

Maier and colleagues sought also to understand how the vagus nerve might influence the neural and behavioral changes associated with sickness.²²³ Subdiaphragmatic vagotomy blocked or ameliorated many of the responses to intraperitoneal endotoxin or IL-1 β that could be detected physiologically and behaviorally, as well as certain biochemical changes within the brain. Hansen studied the pyrogenic effects of different doses of intraperitoneal IL-1 β .²²⁴ Vagotomy abolished the fever after a low dose, reduced it after a medium dose, and had no effect after a high dose. Circulating IL-1 β levels were increased only after the medium and high doses. Romanovsky also found the vagus nerve to be sensitive to low doses of IL-1 β and suggested that prostaglandins mediated the communication in the periphery.²²⁵ These data support the concept that peripherally elaborated cytokines may signal the brain either via the bloodstream or via the nervous system.

Goehler and associates used a labeled form of IL-1ra to try to identify IL-1 receptors associated with the vagus.²²⁶ There was no specific binding to neural tissue, but there was intense binding to tissues closely surrounding the vagal fibers. These tissues consist primarily of chromaffin tissue and were formerly thought to serve primarily as chemosensors for oxygen and carbon dioxide tension in both the abdomen and the lung. These investigators further demonstrated that endotoxin administration induced IL-1 β expression in dendritic cells and macrophages within the connective tissues associated with the abdominal vagus nerve, which suggested that these cells

were the source of proinflammatory cytokines that could initiate afferent signals to the brain via the vagus.²²⁷

The vagus nerve also contains efferent fibers that are widely distributed. Tracey and colleagues performed bilateral cervical vagotomies in rats and stimulated the distal nerves electrically before and after administering a lethal dose of endotoxin.²²⁸ Stimulation of the distal vagus attenuated endotoxic shock and blunted the rise in circulating TNF. Electrical stimulation also resulted in decreased TNF in homogenates of liver, which suggested that vagal efferent activity diminished hepatic TNF elaboration in response to endotoxin.

These investigators also established primary cultures of human macrophages. These cells, in response to lipopolysaccharide, elaborated IL-1, TNF, and other proinflammatory cytokines, as well as the anti-inflammatory cytokine IL-10. Incubation with the parasympathetic neurotransmitter acetylcholine substantially reduced the endotoxin-stimulated synthesis of the proinflammatory cytokines but not that of IL-10. This group subsequently identified an acetylcholine receptor on human macrophages.²²⁹ Thus, efferent parasympathetic vagal activity appears to dampen inflammation by suppressing elaboration of proinflammatory cytokines by tissue macrophages.

Thus, there is an emerging appreciation of a role for the parasympathetic arm of the autonomic nervous system, especially the vagus. Proinflammatory cytokines produced at the site of the inflammatory process may induce afferent neural activity that directly signals the brain, independent of any change in circulating cytokine levels. If the localized inflammatory response is intense or extensive enough, however, perhaps as a result of invasive infection or systemic bacteremia, locally produced cytokines may spill over into the circulation and also reach the brain via the bloodstream. The afferent branches of the vagus terminate in the nucleus tractus solitarius in the medulla. From there, neural fibers traverse the brain stem, terminating on specific cells in the hypothalamus. Thus, parasympathetic nerves may provide neural circuitry by which a focus of inflammation can signal the brain and activates the hypothalamic-pituitary-adrenal (HPA) axis.

Activation of the HPA axis, whether by neural signaling or by elevation of circulating cytokine levels, may result in sympathetic efferent activity, the characteristic elaboration of classic stress hormones, and alteration of the thyrotropic, somatotropic, and gonadotropic endocrine axes. These neuroendocrine responses induce systemic and metabolic alterations that serve to promote wound healing, such as increased blood flow, mobilization of amino acids from muscle, glucose intolerance, and insulin resistance. In addition, efferent parasympathetic activity may modulate the intensity of the inflammatory processes at specific sites of inflammation. Thus, neural mechanisms enable the CNS and the brain to direct and regulate the physiologic responses to injury, infection, inflammation, and critical illness.

Manipulating the Response to Critical Illness

The metabolic response to critical illness has survival value. Young patients are able to mount more intense hypermetabolic responses than elderly persons and in general have higher survival rates. However, these responses are debilitating in all patients and may be associated with organ failure and death. Many have sought to develop therapeutic strategies that would reduce the debilitating aspects of these responses, accelerate recovery, or both.

The endocrine response to injury or operation has been attenuated by adrenergic blockade or regional anesthesia (see above). These maneuvers are associated with an improved postoperative nitrogen balance^{101,102} and decreased muscle protein breakdown.¹⁰⁰ Herndon and colleagues reported that continuous administration of propranolol to children with burns reduced cardiac work without adversely affecting

mortality, postburn course, or wound healing.²³⁰ This technique may benefit elderly, critically ill patients with limited cardiovascular reserve.

Several studies have evaluated the effectiveness of combined neural and humoral blockade in inhibiting the metabolic responses to operative injury. Schulze and associates compared the responses of patients receiving morphine and acetaminophen for pain control after colonic surgery with those of patients managed with methylprednisolone pretreatment, thoracic epidural analgesia, intrathecal anesthesia, and intravenous indomethacin.²³¹ In the patients receiving combined therapy, postoperative pain and fever were prevented, pulmonary function was improved, and fatigue was reduced. Synthesis of acute-phase proteins and IL-6 was reduced. Similarly, Heindorff and coworkers prevented the typical increases in amino acid clearance and urea synthesis with a combination of intravenous somatostatin and etomidate (to inhibit the elevation of glucagon and cortisol levels) and high thoracic epidural analgesia (to provide neural blockade).¹⁰³

Advances in cell and molecular biology have led to an extraordinary expansion of knowledge about the mechanisms involved in the many local and systemic responses to injury, sepsis, and other critical illness. Developments in technology have also led to the formulation of novel strategies for inhibiting various components of these responses that were thought to be particularly deleterious. Thus, antibodies to endotoxin, IL-1, and TNF were developed and studied in clinical trials, along with receptor antagonists and other compounds designed to interfere with systemic inflammatory responses. None of these demonstrated clinical benefit in controlled trials.²³² Given that the regulatory mechanisms are highly complex and that the same ones that may be harmful in some cases promote recovery in others, it is not surprising that blockade of one component of the response might offer no net benefit.

An alternative strategic approach is to enhance or accelerate those components of the response to critical illness that seem to be primarily restorative and lead to wound healing and recovery.

Nutritional support of critically ill patients is important both for promoting protein synthesis and other anabolic processes essential to recovery and for reducing the net drain on the patient's fuel and protein stores. Enteral nutrition is preferred, but the availability of effective intravenous techniques allows the clinician to provide appropriate nutrition to virtually all patients. Exercise and mobility have clear anticatabolic effects and should be initiated as early as is practicable.

Previously, provision of glutamine to critically ill patients had not been possible; glutamine had not been included in most commercial nutrient preparations because of its instability in aqueous solutions. When added to standard TPN, however, glutamine can promote nitrogen retention in postoperative patients.²³³ Ziegler and associates demonstrated that glutamine-supplemented TPN improved nitrogen balance, diminished clinical infection, and shortened hospital stay in a group of critically ill patients recovering from bone marrow transplantation.²³⁴ Enteral preparations enriched with glutamine are now commercially available.

Kudsk and associates randomly selected patients with moderately severe injuries to receive either an enteral formulation enriched with glutamine, arginine, omega-3 fatty acids, and nucleotides or a standard formula that provided an isonitrogenous, isocaloric diet.²³⁵ In both cases, protein content was moderately high (2 g/kg/day). Infectious complications in patients surviving to recovery were less frequent in those receiving the enhanced formula than in those receiving the standard diet.

Growth hormone, when administered to normal subjects, improves nitrogen balance, even if caloric intake is less than energy expenditure.²³⁶ Jiang and associates administered growth hormone and hypocaloric parenteral nutrition perioperatively to patients undergoing elective abdominal operations.²³⁷ They monitored a variety of metabolic parameters and compared the results with those from a

Table 8 Factors Affecting Metabolic Response to Critical Illness and Patient Outcome

Factors that <i>cannot</i> be directly controlled or influenced at present
Patient's genetic makeup and premorbid state of health
Gene transcription and translation
Expression of hormones, cytokines, and growth factors
Expression of hormone, cytokine, growth factor, and other specific cell receptors
Expression of secondary messengers
Generation of nitric oxide and other reactive oxygen intermediates
Signal transduction mechanisms
Intracellular transporters and other regulatory peptides and organelles
CNS neural pathway traffic and cytokine expression
Futile cycles
Enzymes controlling protein synthesis and breakdown
Bacterial virulence factors
Expression of adhesion molecules
Inflammatory and noninflammatory cell proliferation
Apoptosis
Wound-healing biology
Factors that <i>can</i> be directly controlled or influenced at present
Whole-body oxygenation
Whole-body perfusion
Pain, anxiety
Body temperature
Acid-base balance
ECF electrolyte composition and balance
Nutrient supply
Glucose concentration
Anabolic factors
Gut mucosal integrity
Focal infection and bacteremia
Wound repair and closure

control group of patients receiving parenteral nutrition alone. Growth hormone markedly reduced cumulative nitrogen loss. Although both groups of patients lost weight, those receiving growth hormone lost less. Bioelectric impedance data indicated that most of the weight lost by patients receiving growth hormone came from fat mass and not from the muscle compartment. Growth hormone also preserved muscle strength.

Herndon and colleagues administered growth hormone to severely burned children in a randomized trial.²³⁸ Growth hormone accelerated donor site healing, allowing earlier reharvesting of skin. As a result, the time between skin graft procedures and the total length of time required for the children's recovery were both reduced. Knox and associates gave growth hormone to a group of severely burned adults and compared their outcome with that of a similar group of patients cared for without growth hormone in the immediately preceding years²³⁹; mortality was lower in the growth hormone group.

The favorable results reported in burn patients and patients who have undergone elective abdominal operations have not been duplicated in more diverse groups of surgical patients.

Two large multi-institutional randomized trials were conducted in Europe. They included trauma patients, patients who had undergone cardiac procedures, and patients with other acute surgical illnesses. The combined mortality of the patients receiving growth hormone was 42%, more than twice the 18% mortality in the control subjects. Although the reasons for this adverse outcome have not yet been fully elucidated, the manufacturer of the recombinant product issued a safety statement recommending that recombinant growth hormone not be used in catabolic patients.²⁴⁰

An anabolic steroid, oxandrolone, was introduced over 50 years

ago as an adjunct to restoring weight loss. It has a good margin of safety and may play a beneficial role in critical illness by promoting nitrogen retention and accelerating recovery. Combined with a high-protein diet (2 mg/kg/day), oxandrolone promoted weight gain and functional improvement in a randomized study of burn patients who had recovered sufficiently to enter a rehabilitation program.²⁴¹ Hart and associates demonstrated improved efficiency of protein synthesis in nutritionally depleted burned children who received oxandrolone.²⁴² They observed the same benefit in patients who had received appropriate nutritional support from the time of injury.²⁴³ In this group, oxandrolone was also associated with an improvement in lean body mass and increased expression of genes for several functional muscle proteins.

Insulin attenuates cortisol-induced breakdown of skeletal muscle protein *in vitro*.²⁴⁴ Inculet and associates demonstrated improved nitrogen utilization in patients receiving TPN and insulin after operation.²⁴⁵ The apparent mild beneficial effects of TPN enriched with branched-chain amino acids may be caused by increased insulin elaboration.²⁴⁶ Bessey and Lowe induced accelerated skeletal muscle protein catabolism in normal subjects by blocking insulin elaboration during the first day of a 3-day infusion of stress hormones,⁹⁹ thereby simulating the typical hormonal profiles of injured patients. When insulin elaboration was allowed to rise unchecked or when exogenous insulin was administered to limit the rise of blood glucose, net muscle protein breakdown did not increase.

Although some degree of hyperglycemia may facilitate glucose uptake by the inflammatory cells in the wound, excessive elevations—in excess of 10 mmol/L (180 mg/dl)—have been associated with a variety of adverse effects, including impaired phagocytosis and immune function, increased CO₂ production and ventilatory requirements, increased vascular tone and reduction of regional blood flow, and altered collagen formation. Gore and associates demonstrated an association between hyperglycemia and increased net breakdown of muscle.²⁴⁷ Thus, close control of blood glucose concentration with insulin therapy may not only prevent these effects but also exert a beneficial effect on net protein loss. The insulin resistance in critically ill patients blunts the hypoglycemic effects of insulin, so that it may be administered continuously and regulated safely at the bedside by means of a standardized algorithm (sliding scale).²⁴⁸ Using two such algorithms, van den Bergh and colleagues administered insulin to a large group of critically ill patients (N = 1,548) to maintain blood glucose either in a normal range (80 to 110 mg/dl) or in a moderately hyperglycemic range (180 to 200 mg/dl).¹² Maintenance of normoglycemia was associated with a reduction in mortality from 8.0% to 4.6%. In a subsequent analysis, the investigators further showed that the benefit was related to the glucose concentration, not to the insulin dose.²⁴⁹ Patients with mild hyperglycemia (110 to 150 mg/dl) had worse outcomes than those maintained in the normal range.

One of the most effective means of manipulating the metabolic response to critical surgical illness, however, remains excellent surgical care. Such care is directed toward reducing, limiting, preventing, or neutralizing the signals that initiate these debilitating responses. Aggressive and prompt resuscitation, restoration of tissue oxygenation, debridement of necrotic tissue, drainage of pus, and wound repair all should have a high priority in the early management of a critically ill patient. Maintenance of effective cardiopulmonary function and tissue oxygenation, provision of a warm environment, preservation of GI tract integrity, and control of infection are clinical objectives of later management.

Over the course of the past few decades, close attention to these details has resulted in improved outcome for critically ill patients. For example, Pruitt and Mason analyzed a population of over 8,000 burn patients treated at the US Army Burn Unit from 1950 through 1991.²⁵⁰ Since the mid-1970s, the burn size associated with a 50% mortality steadily rose from 57% of BSA to 77%. Similarly, Milberg and colleagues demonstrated a reduction in ARDS-related mortality from nearly 70% to 30% between 1983 and 1993.²⁵¹

In a 1995 study, Kelleman and colleagues determined the effect of burn size on resting energy expenditure.²⁵² This study reproduced that of Wilmore done at the same institution almost 20 years before. In the earlier study, the resting metabolic rate increased steadily with burn size and plateaued at about twice the basal level with burns larger than 50% of BSA. Kelleman found that energy expenditure plateaued at only 1.5 times the basal level with burns of about 25% of BSA or more. This dramatic change in the relationship between burn size (injury severity) and metabolic activity (hypermetabolism) probably reflects the combined effects of improvements in all aspects of burn care, including resuscitation, cardiopulmonary and metabolic support, wound care, nursing practice, occupational and physical therapy, and reduced time to excision and grafting and wound closure. Improvements in care have thus reduced the metabolic cost of critical surgical illness.

Conclusion

The physiologic impact of major trauma, burns, intra-abdominal catastrophe, sepsis, or other critical illness reverberates throughout the body and affects all organ systems. Knowledge about the mechanisms that regulate this comprehensive and commanding response is growing at an exponential rate. These mechanisms are intricate, interrelated, and redundant. Where we once looked for a simple, direct answer, we now see dizzying complexity. The critically ill patient is a true example of controlled inflammation, suspended between anabolic and catabolic forces and between inflammatory and anti-inflammatory forces.

Unfortunately, our ability to apply our improved understanding to the care of critically ill patients still lags far behind. When the patient is not progressing well, we lack the ability to make a specific bedside diagnosis that will pinpoint the part of the system that is out of balance. Even if we could make such a diagnosis, however, we still lack the accurately targeted therapies that would allow us to intervene precisely.

Thus, a wide variety of factors and processes, with both beneficial and adverse effects, appear to be involved in the metabolic response to critical illness, but we are unable to affect many of them directly with the means currently available [see Table 8]. We can remove necrotic tissue, repair wounds, and drain pus. We can also usually ensure excellent cardiovascular performance and maintain extracellular electrolyte and nutrient composition and acid-base balance. We can often suppress bacteremia and can treat some infections effectively with antibiotics. We can prevent many additional insults to and stresses on our patients. These measures may seem unsophisticated and clumsy in the light of our contemporary understanding of the biology of convalescence, but they clearly are capable of nudging the metabolic response to critical illness toward a successful outcome. At present, such measures constitute the essentials of excellent comprehensive care of critically ill patients, and they give these patients their best hope for recovery.

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Acknowledgments

Figures 1 and 5 Al Miller.

Figure 3 Nancy Lou Makris.

27 MOLECULAR AND CELLULAR MEDIATORS OF THE INFLAMMATORY RESPONSE

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The Inflammatory Response

The inflammatory response to injury is complex, involving not only the area of injury but also systemic tissues. The four cardinal signs of acute inflammation—calor (heat), rubor (redness), dolor (pain), and tumor (swelling)—were first described by Celsus in the first century A.D. Subsequent descriptions added a fifth sign, *functio laesa* (loss of function). Although the descriptive features of acute inflammation have long been known, there is still no single satisfactory definition of this phenomenon. It is commonly considered to be the reaction of living tissues to all forms of injury and involves vascular, neurogenic, humoral, and cellular responses.

The vascular events associated with inflammation typically involve changes in blood flow and alterations in permeability. In 1924, Lewis first described the so-called triple response, in which drawing a blunt instrument across the skin induced a flush, a flare, and a wheal. Thus, directly after injury, local arteriolar dilatation, preceded by a fleeting interval of vasoconstriction, is the dominant vascular response. Precapillary sphincters dilate, leading to increased flow in already active capillaries as well as to the opening of inactive capillary beds. At the same time, postcapillary venules dilate to cope with the increased flow of blood. The rise in hydrostatic pressure is followed by fluid exudation through the vascular bed, leading to edema (wheal). As the edema increases, the wheal turns pale as a result of the increased interstitial pressure compressing the capillaries. The changes observed in the skin after mechanical trauma are typical of those seen in other organs after various injuries.

In what follows, we focus on humoral and cellular responses to injury, making use of several types of clinically important events (e.g., ischemia-reperfusion and sepsis) to illustrate important inflammatory pathways.

Neutrophil

That leukocytes are involved in inflammation was first demonstrated in 1887 by Metchnikoff, who found that rose thorns inserted into the body of starfish resulted in the local accumulation of leukocytes within hours.¹ Metchnikoff also documented the existence of different types of leukocytes and the ability of these cells to kill and digest bacteria, and he was the first to suggest that products released by white blood cells could damage vessel walls. In 1960, Marchesi and Florey, using electron microscopy to follow the movement of neutrophils across blood vessel walls in rat mesentery, found that neutrophils penetrated vascular endothelium at or near cell junctions and that after their diapedesis, no sign of a passageway could be seen.² Furthermore, they demonstrated that the site at which such diapedesis occurred was the postcapillary venule.

MECHANISM OF NEUTROPHIL-MEDIATED INJURY

Once it was established that neutrophils were invariably present during an acute inflammatory reaction, efforts were launched to explore their role in mediating this response. In the 1960s and 1970s it became clear that during inflammation, neutrophils actively secreted products that were injurious^{3,4}; these products included reactive oxygen metabolites (ROMs) as well as proteases such as elastase and collagenase. The importance of the neutrophil in mediating inflammation was further underscored by the finding that the increased permeability resulting from an injection of the eicosanoid leukotriene B₄ (LTB₄), the complement fragment C5a, or the formylated bacterial peptide formyl-methionyl-leucyl-phenylalanine (fMLP) into the skin was prevented by previous neutrophil depletion. That neutrophil depletion did not affect the release of serotonin, histamine, and bradykinin from mast cells in response to these stimuli suggested that these mast cell-derived agents did not play a major role in mediating permeability.⁵

In the early 1980s, it was shown that neutrophils stimulated with phorbol myristate acetate damaged endothelial cells via a mechanism that could be interrupted by catalase, a hydrogen peroxide scavenger.⁶ Subsequent investigations demonstrated that neutrophil-mediated endothelial damage was also caused by elastase.⁷ The mechanism of injury required further clarification, given that normal plasma was known to contain potent protease inhibitors and superoxide dismutase (SOD), which inactivate circulating proteases and ROMs, respectively. Furthermore, a better understanding of how neutrophils were selectively activated was needed, given that indiscriminate release of proteases and ROMs would clearly be both inefficient and dangerous.

The mechanism by which the neutrophil is currently thought to produce its injurious effects on target cells involves the formation of a protected environment in which there is close contact between cells. This concept, though not proved, has some evidence to support it. Neutrophils lyse substrate protein only when in close contact.⁸ Phorbol myristate acetate-induced lung injury occurs only when neutrophils are in direct contact with the endothelium.⁹ When neutrophils are stimulated with fMLP,⁷ C5a, or endotoxin,¹⁰ they must adhere to the endothelium to cause vascular injury, which is governed by molecules expressed on the surfaces of both cell types.

The normal immune action of the neutrophil is to phagocytose its target cell. This process results in the creation within the neutrophil of a protected microenvironment known as a phagosome, which contains the targets for destruction [see Figure 1]. When the phagosome has been established, the neutrophil releases large quantities of ROMs and proteases into it. Any plasma protease inhibitors gaining access to this restricted space are themselves inhibited by the neutrophil secretory products hydrogen peroxide

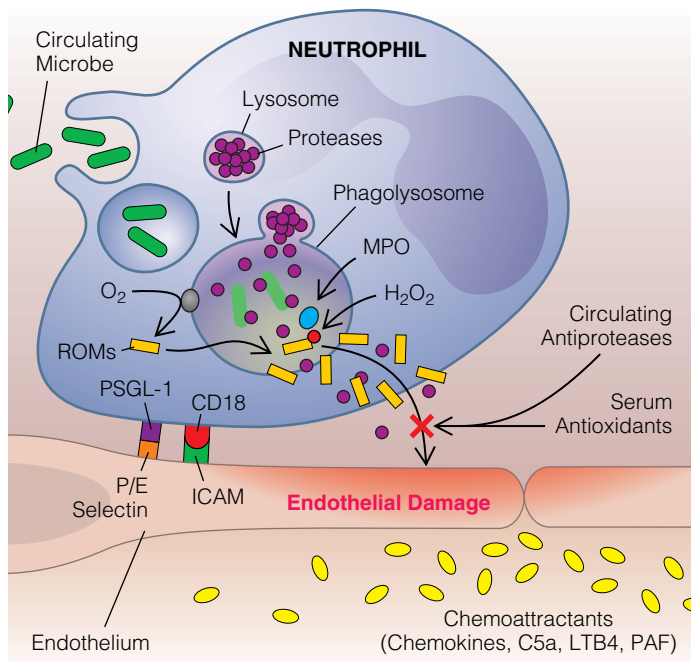


Figure 1 Proteases and ROMs are stored in intracellular lysosomes. These fuse with microbe-containing phagosomes, forming phagolysosomes that initiate destruction of the microbes. Anti-proteases that gain entry to this area, such as serum α_1 -antitrypsin, are inhibited by hydrogen peroxide and myeloperoxidase secreted by neutrophils. The same neutrophil products that cause microbial destruction may also damage surrounding endothelial tissue. Tissue damage is somewhat reduced by natural protective mechanisms, such as ROM scavenging by SOD, catalase, and α_1 -antitrypsin.

and myeloperoxidase, either of which is capable of neutralizing α_1 -antitrypsin, the major protease inhibitor.^{11,12} Furthermore, myeloperoxidase activates other neutrophil proteases, such as collagenase and gelatinase.⁴ Thus, ROMs and proteases act in synergy to digest phagocytosed matter.

In cases of strong neutrophil activation, the cells may release their toxic products in concentrations that overwhelm the body's regulatory defenses, causing substantial damage to surrounding tissues through excess vascular permeability and parenchymal injury.

ROLE IN REPERFUSION INJURY

The importance of neutrophils in the generation of reperfusion injury was first demonstrated in the context of myocardial ischemia.¹³ Histologically, the injury was characterized by an extensive early accumulation of extravasated neutrophils, thus resembling an acute inflammatory process. Depletion of neutrophils by means of an antiserum led to a significant reduction in the size of myocardial infarction after temporary occlusion of the left circumflex coronary artery.¹³ Restoration of blood flow to ischemic skeletal muscle was also associated with significant leukocyte infiltration,¹⁴ whereas leukocyte depletion attenuated the associated increase in microvascular permeability and vascular resistance.¹⁵

Besides enhancing permeability, neutrophils were shown to cause skeletal myocyte injury after ischemia, as evidenced by membrane dysfunction. Such dysfunction was indicated by depolarization of resting skeletal muscle that persisted after restoration of blood flow despite repletion of intracellular high-

energy phosphates; in contrast, such depolarization was limited during hindlimb reperfusion in neutropenic animals.¹⁶

Neutrophils have also been implicated as mediators of the remote lung injury observed to occur as a consequence of skeletal muscle ischemia. Investigators documented leukosequestration and increased lung permeability during reperfusion after hindlimb tourniquet ischemia.¹⁷ Neutropenia, however, was protective in this setting, maintaining normal microvascular permeability and lung histology.

Adhesion Molecules

To patrol the body effectively for infectious organisms and to repair injuries in disparate regions of the body, neutrophils must be able both to circulate as nonadherent particles in blood and lymph and to adhere to and migrate through specific tissues sites where they are needed. Evidence from the past 20 years indicates that inflammatory sites emit signals that activate the adjacent endothelium and circulating phagocytes. Inflammatory events also trigger release of circulating mediators such as cytokines, which produce more generalized activation of endothelial cells and leukocytes, thereby rendering one or both cell types more adhesive.¹⁸ Circulating phagocytes then adhere to endothelium; in response to a chemical chemoattractant gradient across the microvessel, they undergo diapedesis between the junctions of endothelial cells, migrate through the subendothelial matrix, and participate in the parenchymal inflammatory reaction. This phagocyte adherence, though essential to the immune response and the repair of injury, may induce pathologic consequences.

For the first few hours of the inflammatory response, the neutrophil is the predominant leukocyte at inflammatory sites.¹⁹ After 12 to 24 hours, mononuclear phagocytes predominate.²⁰ When injury is extensive and the inflammatory response robust, this second phase may be accompanied by immunomodulation and increased susceptibility to infection.

The importance of leukocyte adhesion to the endothelium in maintaining host defenses against infection is illustrated by the example of patients with a congenital deficiency of CD11/CD18, a family of adhesion-promoting leukocyte surface proteins.²¹ This condition, known as leukocyte adhesion deficiency I (LAD I), results in a profound defect in phagocyte accumulation because the leukocytes, though stimulated, cannot adhere and migrate to extravascular sites.⁷ Patients with LAD I have little or no pus at bacterial infection sites and suffer recurrent life-threatening bacterial infections.²¹ On the other hand, unmoderated leukocyte adhesion to the endothelium can also have pathologic consequences, such as lung failure (i.e., the acute respiratory distress syndrome [ARDS]) or organ transplant rejection.^{22,23} Thus, a better understanding of the mechanism of adhesion may lead to better therapy for a number of disease states. Such therapy will have to balance the benefit of reducing tissue damage caused by leukocyte adhesion against the possible increased risk of infection.

Adhesion molecules on endothelial cells and neutrophils may be classified into three groups: selectins, integrins, and immunoglobulins [see Table 1].

SELECTINS

The selectins are expressed only on cells within the vasculature or the lymphatic system. To date, three selectins have been identified: L-selectin, P-selectin, and E-selectin, or endothelial leukocyte adhesion molecule-1 (ELAM-1). These molecules are also collectively referred to as lectin cell adhesion molecules

Table 1 Adhesion Molecules Involved in Adherence of Leukocytes to Endothelium

Family	Members
Selectins	L-selectin (LAM-1, Mel-14, Leu-8, LECCAM-1) E-selectin (ELAM-1) P-selectin (CD62, GMP-140, PADGEM)
Integrins	LFA-1 (CD11a/CD18) Mac-1 (CD11b/CD18, Mo-1, CR3) gp 150,95 (CD11c/CD18)
Immunoglobulins	ICAM-1 ICAM-2 VCAM-1

(LEC-CAMs). In general, the selectins are responsible for the earliest interaction of circulating cells, setting the stage for integrin-mediated firm adherence. All three help regulate the initial leukocyte rolling on activated endothelium. Without selectins, leukocytes interact poorly with endothelium. Leukocyte adhesion deficiency II (LAD II), a genetic deficiency of glucosyl-transferase, prevents formation of sialyl Lewis^x (sLe^x), the key selectin counterreceptor, thereby increasing the risk of infection.

L-selectin, the smallest member of the selectin family, is present on the surface of neutrophils, monocytes, and lymphocytes and binds both constitutive and inducible carbohydrate ligands on the endothelial cell surface. The migration of neutrophils into certain inflammatory sites is significantly attenuated by L-selectin blockade²⁴; however, other molecules play a greater role in neutrophil adhesion than L-selectin does. Where L-selectin plays a dominant role in cell trafficking is in the lymphocyte: L-selectin-deficient knockout mice have small, poorly formed lymph nodes and defective T cell function.²⁵

P-selectin, the largest member of the family, plays a key part in leukocyte rolling.^{26,27} It is constitutively associated with the α -granules of platelets²⁸ and the cytoplasmic Weibel-Palade bodies of endothelial cells²⁹ and is rapidly translocated to the endothelial cell surface after stimulation by histamine or thrombin.²⁹ Expression of P-selectin may also be induced by exposure of the vascular endothelium to free radicals (particularly superoxide),³⁰ C5a, the complement membrane attack complex (C5b-C9),³¹ and tumor necrosis factor- α (TNF- α).³² The extracellular N-terminal domain of the molecule binds to its carbohydrate ligand, sLe^x. An additional P-selectin mechanism of neutrophil-endothelial interaction involves platelets. By adhering to endothelial surfaces, platelets provide a rich surface of exposed P-selectin to which neutrophils can bind. Platelet-endothelial binding may occur via fibrinogen attachment to endothelial intercellular adhesion molecule-1 (ICAM-1) and to platelet GPIIb/IIIa. Platelet endothelial cell adhesion molecule-1 (PECAM-1) can also mediate attachment.

E-selectin, the third member of the selectin family, is a glycoprotein found exclusively on the surface of endothelial cells. Although not expressed on resting endothelium, E-selectin is markedly upregulated in response to the cytokines interleukin-1 (IL-1) and TNF- α as well as to lipopolysaccharide (LPS). E-selectin plays an important role in slightly later leukocyte adhesion to the microvascular endothelium.³³

For all three selectins, P-selectin glycoprotein ligand-1 (PSGL-1), which is rich in sLe^x moieties, is the principal counterreceptor; it is located on the surface of circulating leukocytes and participates in the earliest inflammatory responses.

INTEGRINS

The integrin family comprises a vast number of adhesion molecules that mediate intercellular recognition and cellular binding to the extracellular matrix. These molecules are heterodimeric transmembrane receptors composed of α and β subunits. The β_2 subfamily, collectively known as the leukocyte integrins or leukocyte cell adhesion molecules (LeuCAMs), is expressed exclusively by leukocytes. This subfamily comprises three related heterodimers, each made up of a common β subunit (CD18) complexed with a unique α subunit (CD11a, CD11b, or CD11c).

CD11a/CD18, also known as lymphocyte function-associated antigen-1 (LFA-1), is expressed on all leukocytes and mediates the attachment of unstimulated neutrophils to the vascular endothelium through a specific interaction with ICAM-1 and ICAM-2. CD11b/CD18, previously referred to as complement receptor type 3 (CR3) because of its ability to bind the complement fragment iC3b but now more generally known as Mac-1, is constitutively expressed on the surface of neutrophils, monocytes, and macrophages. It binds to endothelial ICAM-1 at a site distinct from the LFA-1 binding domain.³⁴ In addition to the Mac-1 expressed on the cell surface, an intracellular pool of preformed Mac-1 is stored within specific granules in neutrophils. Translocation of Mac-1 from intracellular pools to the neutrophil surface via granule fusion with the plasma membrane is stimulated by chemotaxins, including C5a, LTB₄, IL-8, and platelet-activating factor (PAF).³⁵ Unlike the adhesive interactions between LFA-1 and ICAM-1, which can be demonstrated in both stimulated and unstimulated cells, Mac-1-mediated adherence to endothelial ICAM-1 requires chemotactic activation.³⁶ CD11c/CD18, also referred to as gp150,95, has been identified on the surfaces of neutrophils and monocytes and is believed to play its primary role in monocyte adhesion.

IMMUNOGLOBULINS

Leukocyte integrins bind to endothelial surface receptors belonging to the immunoglobulin supergene family. Members of this superfamily, which includes major histocompatibility complex (MHC) antigens I and II, T cell receptors, ICAM-1, and ICAM-2, share an immunoglobulin domain composed of 90 to 100 amino acids arranged in two sheets of antiparallel β strands stabilized at the center with a disulfide bond. Although constitutively expressed, copies of ICAM-1 are increased after stimulation by TNF- α , IL-1, LPS, lymphotoxin, or interferon gamma (IFN- γ). IL-1-induced upregulation can be observed 30 minutes after incubation, after which time it increases steadily, reaching a peak after 24 hours.³⁷ ICAM-1 is the counterreceptor for CD11a and CD11b.

STUDIES USING ANTIBODIES TO ADHESION MOLECULES

The development of monoclonal antibodies (mAbs) that bind to the functional epitopes of adhesion molecules has yielded useful data on adhesion mechanisms. In addition, a number of studies have aroused clinical interest.

In two trials, survival was significantly increased in rabbits and baboons treated with a CD18 mAb after hemorrhagic shock.^{38,39} In a canine model of myocardial ischemia-reperfusion, treatment with a CD11b mAb led to reduced infarct size and neutrophil sequestration.⁴⁰ In a murine model of liver cell injury induced by LPS and galactosamine, a CD11b mAb reduced liver cell injury by more than 90% (as determined by assessment of alanine aminotransferase levels) but reduced neutrophil sequestration by only 40%.⁴¹ In this setting, it is likely that neutrophils were bound to a large extent by CD11a, which may explain the dis-

crepancy between the degree of protection afforded by the antibody and the reduction in neutrophil sequestration. The beneficial effects of CD11b antibodies may well be related more to the inhibition of neutrophil signaling and function than to sequestration per se.

In another study, treatment with a mAb to ICAM-1 led to a reduction in phorbol myristate acetate–stimulated neutrophil accumulation in rabbit lungs.⁴² This mAb also reduced lymphocyte sequestration and acute graft rejection after renal transplantation in primates.²³ Attempts to modify acute allograft rejection in humans have met with little success. It must be kept in mind, however, that our understanding of the effects of antibodies to adhesion molecules on the immune system is still in its infancy. This rapidly developing field promises to offer powerful tools that may well prove applicable to the control of inflammatory and immunologic reactions.

Cytokines

The term cytokine refers to a diverse group of polypeptides and glycoproteins that are important mediators of inflammation. They are produced by numerous cell types but primarily by leukocytes. Cytokines are potent intercellular messengers that exert most of their actions on immune and inflammatory cells. Taken separately, they have a wide range of effects; considered as a group, their principal functions are to coordinate the immune response to foreign antigens by acting as growth factors and cellular activators and also to moderate this response via various feedback mechanisms.

Cytokines are not stored intracellularly: upon antigenic stimulus of the cell, they are synthesized rapidly by novel mRNA transcription, then quickly released. For example, LPS from bacterial cell walls causes macrophage activation and induces TNF release. The mRNA encoded during this process tends to be unstable, which ensures that cytokine synthesis after cell activation will be brief and self-limiting. Cytokines exert their effects through very high-affinity binding to various receptors on target cells. Thus, as a rule, very small amounts of cytokines suffice to produce their biologic effects. External signals increase the number of receptors on a cell, thereby enhancing the cellular response to a particular cytokine. For example, antigenic stimulation of lymphocytes leads to increased cytokine receptor expression. The cytokine itself can also stimulate cytokine receptor upregulation via a positive feedback mechanism.

Cytokines usually act on cells locally in an autocrine and paracrine fashion, thereby ensuring that the inflammatory response is evoked at the site of infection or injury. When they are produced in very large quantities, they can enter the circulation and exert significant systemic effects. On one hand, a single cytokine may act on more than one cell type, causing a number of different consequences (pleiotropism); on the other, several different cytokines may produce the same functional effects (redundancy). This relative nonspecificity of action limits the clinical usefulness of exogenously administered cytokines: the likelihood is high that such agents will either have unwanted side effects or be functionally useless as a result of compensation by other cytokines.⁴³ Another common feature of cytokines is that they often act in a cascade, with one cytokine leading to the production of another. They may also act synergistically or may antagonize the actions of other cytokines.

Discussion of cytokines is complicated by the often confusing nomenclature. Several of the earliest identified cytokines were

Table 2 General Classification of Cytokines by Primary Activity

Proinflammatory Cytokines	Anti-inflammatory Cytokines
TNF	IL-10
IL-1	IL-4
Chemokines	IL-13
Interferons	TGF- β
IL-2	
CSFs	
IL-6	

discovered in a variety of different settings and consequently bear several different names associated with specific functions. For example, TNF, initially named for its ability to cause tumor necrosis, is also known as cachectin because of its association with cachexia. Current cytokine nomenclature follows a more consistent naming system, in which the term interleukin (IL), referring to a substance that acts between leukocytes, is used in conjunction with a number (e.g., IL-10); however, many of the cytokines are still commonly referred to by their historical (and frequently misleading) names.

The cytokines we address in the following discussion do not constitute an exhaustive list. Such a list would be beyond the scope of this chapter; furthermore, given the rate at which new cytokines are being found and classified, it would be out of date before it was published. Accordingly, we focus on the better-known and more thoroughly studied cytokines.

To facilitate understanding of cytokine function, it may be helpful to classify them on the basis of their primary actions. Various classification systems have been proposed; however, none have proved entirely satisfactory, because these agents, being pleiotropic by nature, often have conflicting actions. In our view, the most useful approach is to categorize the cytokines according to whether they exert primarily proinflammatory or primarily anti-inflammatory effects [see Table 2]. Admittedly, the boundary between the two categories is frequently blurred.

PROINFLAMMATORY CYTOKINES

The general distinction between proinflammatory and anti-inflammatory cytokines is based on the observation that certain cytokines—principally TNF, IL-1, and IL-8—promote the inflammatory response by upregulating expression of genes encoding phospholipase A₂, cyclooxygenase-2 (COX-2), or inducible nitric oxide (NO) synthase, thereby increasing production of the corresponding proinflammatory mediators (PAF, eicosanoids, and NO, respectively). In addition, proinflammatory cytokines mediate neutrophil action, acting as chemoattractants, upregulating expression of leukocyte-endothelial adhesion molecules, causing cell migration into the tissues, and activating neutrophil degranulation—all of which lead to tissue damage.

Tumor Necrosis Factor and Interleukin-1

Although TNF and IL-1 are structurally dissimilar, their functions overlap considerably, and they are known to act synergistically. Originally discovered as a substance causing ischemic necrosis of tumors in rabbits treated with endotoxin, TNF is produced principally by monocytes and macrophages but also by various other immune and endothelial cells. The most potent stimulus for its production is LPS (endotoxin) from gram-nega-

Table 3 Systemic Actions of TNF

Fever
Acute-phase protein synthesis
Cachexia
Myocardial depression
Disseminated intravascular coagulation (DIC)
Hypoglycemia

tive bacteria, but other stressors (e.g., infection, trauma, ischemia, and toxins) can also induce its release.

In small concentrations, TNF acts in an autocrine and paracrine fashion, causing increased expression of endothelial E-selectin and leukocyte integrins and promoting leukocyte adhesion to the endothelium. TNF causes neutrophils to be attracted first, followed by monocytes and lymphocytes, thereby helping to regulate the inflammatory response. It also stimulates endothelial cells to produce a cytokine subset known as the chemokines (e.g., IL-8), which promote leukocyte migration into the tissues, and induces mononuclear phagocytes to produce IL-1. Finally, TNF can cause apoptosis in some cell types, an event that is of unknown physiologic significance.⁴³

In large concentrations, TNF mediates a number of physiologic effects that are well-recognized components of infection. It acts on the hypothalamus via prostaglandin synthesis to cause fever [see Table 3]. It also induces hepatocyte production of some of the acute-phase proteins, the best known of which are C-reactive protein, fibrinogen, serum amyloid A, and α_1 -antitrypsin. Prolonged TNF production also leads to cachexia, probably by reducing appetite. Massive doses of TNF produce the classic symptoms of septic shock. Hypotension results from reduced vascular smooth muscle tone and myocardial depression; disseminated intravascular coagulation (DIC) results from endothelial expression of tissue factor and inhibition of throm-

bomodulin; and profound hypoglycemia results from tissue overutilization of glucose and impaired liver function.⁴³

Like TNF, IL-1 is produced primarily by macrophages and to a lesser extent by other leukocytes and endothelial cells. IL-1 is a primary responder in the inflammatory cascade, and its actions are very similar to those of TNF. It mediates local inflammatory responses at low concentrations and exerts adverse systemic effects at higher concentrations. Unlike TNF, it cannot induce apoptosis. IL-1 also minimizes the perception of posttraumatic pain by causing the release of β -endorphins from the pituitary gland and increasing the number of central opioid receptors. TNF and IL-1 act synergistically to produce the acute innate immune response to invading microorganisms, manifested by neutrophil activation and release of other cytokines that promote further immune activity.

Chemokines

The chemokines are a group of cytokines that regulate migration of leukocytes from blood to other tissues. Chemokines bind to heparan sulfate proteoglycans on endothelium, thus presenting themselves to white blood cells that have become loosely attached to endothelial cells via the action of selectins and that roll along the endothelium. When a white cell interacts with a chemokine, its shape changes rapidly, becoming flatter and more motile. At the same time, surface integrins are exposed, allowing firmer attachment to the endothelium. Chemokines also induce rhythmic contraction of cellular actin filaments, causing cellular migration from the blood vessel at an interendothelial cell junction across a chemokine concentration gradient to the region of tissue injury [see Figure 2].

For the purposes of this discussion, chemokines may be classified into two main subsets, CC and CXC, depending on whether their two terminal cysteine residues are adjacent (CC) or separated (CXC). The CXC group, which includes IL-8 (probably the best known of the chemokines), acts mainly on neutrophils, whereas the CC chemokines act on monocytes, eosinophils, and lymphocytes. Both subsets are produced by leukocytes, endothelial cells, and fibroblasts in response to

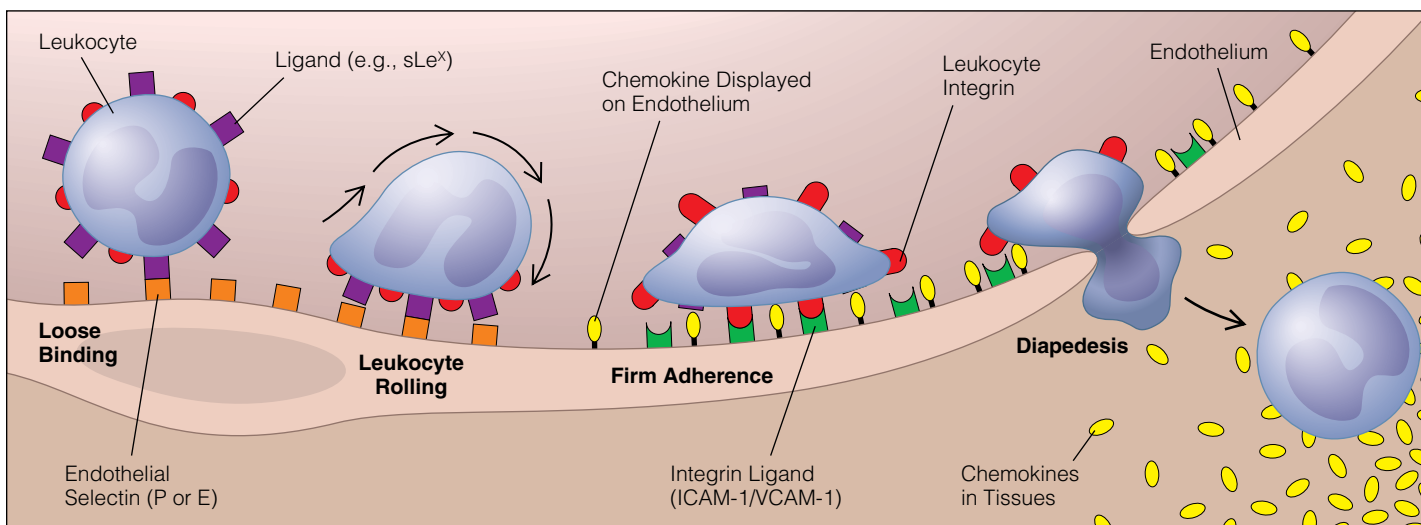


Figure 2 Leukocytes bind loosely to the endothelium via low-affinity interaction between selectins and their ligands. Once loosely bound, they begin rolling slowly along the endothelium. Chemokines cause a conformational change in the leukocyte, exposing the leukocyte integrins that bind to endothelial ICAM-1 and VCAM-1 and thus inducing firm adherence. The leukocyte then undergoes diapedesis into tissues along the chemokine gradient.

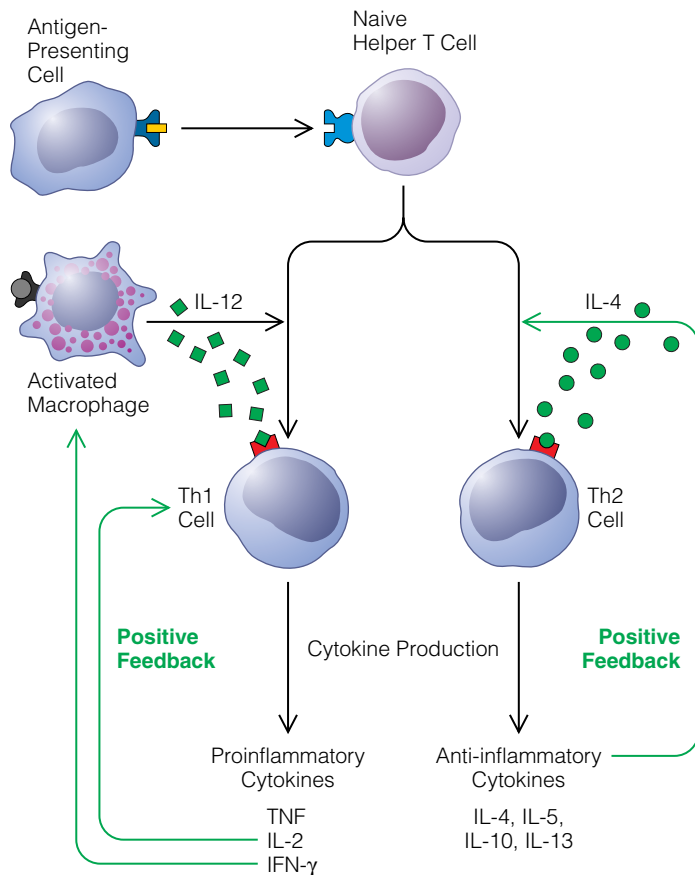


Figure 3 The function of T helper cells is to secrete cytokines in response to antigenic stimulation; these cytokines then act to regulate an appropriate immune response by triggering proliferation and stimulation of T cells, B cells, and other leukocytes. There are two distinct subsets of T helper cells—Th1 and Th2—which are descended from the same precursors, namely, naive CD4⁺ T cells. The development of Th1 and Th2 subsets occurs in response to naive T cell stimulation by different cytokines. In turn, each subset secretes a distinct set of cytokines. IL-12 is the major stimulant for Th1 subset development. This subset assists in phagocyte-mediated responses, with IL-12 being produced by phagocytes in response to a variety of antigens (most of which are intracellular). Th1 cells secrete the proinflammatory cytokines, mainly IFN- γ , IL-2, and TNF. IL-2 acts in an autocrine fashion, stimulating further growth of this subset. Th2 cell growth is stimulated by the anti-inflammatory cytokine IL-4. This subset produces the anti-inflammatory cytokines IL-4, IL-5, IL-13, and IL-10, with IL-4 acting as an autocrine growth factor through a positive feedback mechanism. These cytokines also mediate the immune response to helminths and allergens.

stimulation by either antigens or other cytokines (e.g., TNF and IL-1). Some are also produced constitutively by lymphocytes to regulate the flow of these cells through the lymphatic system.

Interleukin-12

When activated by intracellular microbes (e.g., viruses, *Listeria*, and mycobacteria), mononuclear phagocytes and dendritic cells (professional antigen-presenting cells [APCs] located in lymph nodes) produce IL-12, the essential action of which is to mediate the early immune response. The most important single action of IL-12 is to stimulate synthesis and release of IFN- γ by T cells and natural killer (NK) cells (see below).

Interferon Gamma

IFN- γ is produced by T cells and NK cells in response to antigen, an event greatly enhanced by IL-12. It activates macrophages, inducing them to kill microbes by activating enzymes that trigger synthesis of ROMs and NO. In addition, by increasing IL-12 release from the macrophages it activates, IFN- γ increases differentiation of T helper cells into the Th1 cell subset that produces it while inhibiting proliferation of the Th2 subset, which produces anti-inflammatory cytokines [see Figure 3].

Interleukin-6

It is probably most accurate to think of IL-6 as a mixed proinflammatory/anti-inflammatory cytokine. IL-6 is produced by mononuclear phagocytes as well as by endothelial cells and fibroblasts. It acts in a proinflammatory manner by providing a potent stimulus for hepatocyte synthesis of acute-phase proteins. It is also involved in promoting T cell differentiation and maturation and immunoglobulin production and in enhancing NK cell activity.⁴⁴ However, IL-6 also has important anti-inflammatory effects. It has been shown to inhibit production of TNF and IL-1 by mononuclear cells and to reduce release of TNF secondary to endotoxin challenge.⁴⁵ Furthermore, IL-6 leads to reduced plasma concentrations of soluble TNF receptors and IL-1 receptor antagonist (IL-1Ra), which are naturally occurring anticytokines.⁴⁶

Interferon Alfa and Interferon Beta (Type I Interferons)

IFN- α and IFN- β are two functionally similar cytokines that are often jointly referred to as the type I interferons; they are also known as the antiviral interferons because they are produced by antigen-stimulated T cells in response to viral infection. They act in a paracrine fashion to inhibit viral replication, preventing infection of neighboring cells and putting cells into an antiviral state. IFN- α and IFN- β also increase the efficiency of cytotoxic T cell-mediated cell lysis by upregulating expression of MHC class I molecules on infected cells. They are frequently used in the clinical setting: IFN- α seems to be effective therapy for viral hepatitis, and IFN- β has been used, with some success, to treat multiple sclerosis.

Interleukin-2

Unlike the cytokines already mentioned, which exert most of their effects via the innate immune system, IL-2 mediates acquired immunity—that is, the proliferation and differentiation of lymphocytes after antigen recognition. Originally known as T cell growth factor, IL-2 acts in an autocrine manner on the T cells that produce it (i.e., T helper cells), upregulating IL-2 receptors and thereby causing preferential proliferation of T cells specific for the stimulating antigen.⁴³ It also promotes growth and differentiation of NK cells.

IL-2 has an immunomodulatory function as well, in that it potentiates apoptosis of antigen-stimulated T cells. This action appears to limit immune responses. It is noteworthy that IL-2 knockout mice experience overproduction of lymphocytes with hyperplasia of lymphoid organs and the development of autoimmune diseases (most strikingly, autoimmune hemolytic anemia and inflammatory bowel disease). These events are probably attributable to loss of the regulatory apoptosis function.

Hematopoietic Cytokines

The hematopoietic cytokines—including the colony-stimulating factors (CSFs), IL-7, and IL-3—are, strictly speaking, proinflammatory, in that they induce the growth and differentiation of

bone marrow progenitor cells; however, this is a normal component of bone marrow hematopoiesis. CSFs are produced by bone marrow stromal cells and act to stimulate the formation of bone marrow cell colonies. There are several different varieties, named according to the type of cell line they promote (e.g., granulocytes [G-CSF], monocytes [M-CSF], or both [GM-CSF]). IL-7 is synthesized by fibroblasts and bone marrow cells and induces the differentiation of B and T cells. IL-3 is also known as multilineage colony-stimulating factor (multi-CSF) because its actions promote the differentiation of bone marrow precursors into all known mature cell types.

ANTI-INFLAMMATORY CYTOKINES

The anti-inflammatory cytokines exert their effects by inhibiting the production of proinflammatory cytokines, countering their actions, or both. In so doing, they reduce gene expression of agents such as TNF, IL-1, and the chemokines, thereby mitigating or preventing their subsequent inflammatory effects.

Interleukin-10

IL-10 is important in the homeostatic control of both innate and acquired immunity. It is produced by activated macrophages and is a potent inhibitor of these cells, regulating them via negative feedback; it is also produced by Th2 cells and B cells. IL-10 antagonizes a broad range of immune functions: it inhibits IL-12 production by activated macrophages, thereby reducing IFN- γ release and, consequently, decreasing macrophage activation. It also inhibits Th1 cells, thereby reducing production of proinflammatory cytokines (e.g., TNF, IFN- γ , and IL-2). However, IL-10 also has proinflammatory effects, stimulating B cell function and enhancing the development of cytotoxic T cells.⁴⁷

The importance of IL-10 in normal regulation of the immune response is demonstrated by studies of IL-10 knockout mice, which experience fatal inflammatory bowel disease and show markedly increased levels of TNF in response to endotoxin challenge.⁴⁸ Administration of recombinant IL-10 before lethal doses of endotoxin reduces TNF release and prevents death.⁴⁹ In humans, it prevents fever, proinflammatory cytokine release, and clotting cascade activation during endotoxin challenge.

Interleukin-4 and Interleukin-13

IL-4 and IL-13 are structurally similar, and both are produced by Th2 cells as well as by mast cells and basophils. They are considered anti-inflammatory cytokines by virtue of their ability to antagonize INF- γ and thereby reduce macrophage activation. Because INF- γ is the major promoter of Th1 cells, these two agents indirectly suppress cytokine production by Th1 cells in much the same way that IL-10 does.

IL-4 is the principal growth factor for Th2 cells, which, in addition to their immune suppressor functions, mediate the immune response to helminths and are responsible for allergic reactions. It is also the major stimulus for production of IgE by B cells.

Transforming Growth Factor- β

Transforming growth factor- β (TGF- β) is produced by a large variety of cells, including activated T cells, phagocytes, and endothelial cells. It has potent anti-inflammatory effects, inhibiting T cell differentiation and proliferation and macrophage activation. It also counteracts the effects of proinflammatory cytokines, causing downregulation of endothelial intercellular adhesion molecules,⁵⁰ downregulation of TNF endothelial receptor expression, and inhibition of chemokine action. TGF- β

knockout mice acquire multifocal inflammatory disease, particularly involving the heart and the lungs.⁵¹

THERAPEUTIC IMPLICATIONS

Interleukin-1 Receptor Antagonist

A naturally occurring cytokine inhibitor is the endogenously secreted protein IL-1Ra, which competitively binds the IL-1 receptor without signaling. IL-1Ra is secreted by mononuclear phagocytes and has nearly the same affinity for the IL-1 receptor as IL-1 itself does.⁵² IL-1Ra is present in high concentrations in the serum of patients with a variety of diseases, often in much higher concentrations than IL-1.⁵³ In patients with sepsis, juvenile rheumatoid arthritis, and inflammatory bowel disease, IL-1Ra levels have been found to correlate with disease severity; presumably, IL-1Ra acts as a natural negative feedback mechanism in inflammatory states. Unfortunately, the results of clinical trials evaluating recombinant IL-1Ra in the setting of septic shock have been largely disappointing.⁵⁴

TNF Antagonists

There are two cell surface receptors for TNF, p55 and p75. These are normally shed after activation and are found in the circulation. In the presence of disease and in response to endotoxin challenge, they circulate in much higher concentrations.⁵⁵ It is thought that p55 and p75 act as carriers for TNF, thereby reducing the amount of TNF available to act on cells. TNF itself induces the production of its soluble receptors. Elevated levels of TNF receptors have been recorded in cancer patients, and these levels correlate well with tumor burden and the extent of metastasis.⁵⁶ Elevated TNF receptor levels in blood or joint fluid have also been recorded in patients with a variety of autoimmune and inflammatory diseases.

In response to such observations, commercial anti-TNF drugs began to be developed. The first such drug to be approved was etanercept, in 1998. This agent, a recombinant TNF p75 receptor, has proved to be effective in treating rheumatoid arthritis and spondyloarthropathies. Infliximab, approved in 1999, is a genetically engineered anti-TNF mAb that is capable of binding to both cell-bound and soluble TNF. It causes lysis of TNF-producing cells via complement- and antibody-dependant cytotoxicity.⁵⁷ Infliximab is approved for use in patients with Crohn disease, in whom it can induce and maintain remissions, bring about endoscopically and histologically demonstrable mucosal healing, reduce the number of perianal fistulae, and decrease inflammation in ileoanal pouches.⁵⁸ Infliximab also shows great promise in the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis.

Modulation of Cytokine Activity in Sepsis, SIRS, and CARS

Key terms and concepts associated with the systemic activation of the body's inflammatory mechanisms—systemic inflammatory response syndrome (SIRS), sepsis, septic shock, and multiple organ dysfunction syndrome (MODS)—are defined and discussed more fully elsewhere [see VI:10 *Clinical and Laboratory Diagnosis of Infection*, VI:11 *Blood Cultures and Infection in the Patient with the Septic Response*, and VII:7 *Multiple Organ Dysfunction Syndrome*].⁵⁹ The general understanding is that systemic inflammatory activity (i.e., SIRS), which may occur in response to either infectious or noninfectious stimuli, is the fundamental phenomenon; in this view, sepsis may be understood as SIRS occurring specifically in response to microbial invasion. This whole-body inflammatory response can lead ultimately to MODS, which is associated with mortalities higher than 50%.

The role of cytokines in the pathophysiology of SIRS and sepsis was first appreciated when experimental studies demonstrated that antibodies to TNF reduced mortality in animals to which endotoxin had been administered.^{60,61} Further research revealed that the proinflammatory cytokines TNF and IL-1 were both able to evoke a clinical picture mimicking that of sepsis (i.e., hypotension and fever). In addition, TNF activated the coagulation cascade.⁵⁴ Accordingly, it was postulated that SIRS and sepsis were attributable to an overwhelming proinflammatory immune response mediated by TNF and other cytokines. A great deal of research on sepsis has now been carried out in animal and clinical trials, mostly using TNF mAbs and soluble TNF receptors. The initial results were positive, in that TNF amelioration led to increased survival in endotoxin-sensitized animals. Subsequently, however, these findings were countered by the observation that TNF had no significant effect in animal sepsis models of cecal ligation and puncture (which would be more relevant to clinical application in humans). Large-scale clinical trials employing TNF mAbs and receptors or IL-1 ablation with IL-1Ra have met with little success.⁶²

The disappointing clinical results from proinflammatory cytokine ablation have brought into question the thesis that sepsis is entirely understandable in terms of persistent and uncontrolled inflammation. Another view—which is not incompatible with the basic concept of sepsis as a systemic inflammatory response—is that the body also mounts a countering anti-inflammatory reaction to an insult, which then can lead to what is referred to as the compensatory anti-inflammatory response syndrome (CARS).⁶³ According to this hypothesis, when the proinflammatory response to an insult predominates, SIRS and shock result, and when the anti-inflammatory response predominates, CARS, immunosuppression, and increased susceptibility to infection ensue. Homeostasis and return to health reflect a state in which the two responses are in balance. It is likely that in cases of trauma or infection, the body's first response is proinflammatory, and the resulting SIRS is responsible for early mortality. This initial response is followed by an anti-inflammatory response, and the resulting CARS is responsible for late mortality secondary to immunodepression.⁶²

Numerous studies have measured cytokine concentrations in the peripheral vasculature in an effort to identify markers of sepsis, predictors of mortality, and possible clinical interventions. Perhaps surprisingly, levels of the proinflammatory cytokines (TNF, IL-1, IL-12, and IFN- γ) are not consistently correlated with either disease severity or mortality in patients with septic shock. This finding provides some evidence for the CARS hypothesis. It must be remembered, however, that systemic blood sampling is not indicative of tissue cytokine dynamics. In patients with pneumonia, for example, concentrations of TNF, IL-1, and IL-12 were found to be markedly higher in bronchial lavage samples than in serum.⁶⁴ The cytokine for which peripheral blood levels seem to correlate best with disease severity is IL-6; it is unclear why this is so, given that IL-6 certainly does not produce shock. A 1994 study found that circulating levels of the anti-inflammatory cytokine IL-10, which are normally unmeasurable, were detectable in more than 80% of patients with severe sepsis.⁶⁵ A so-called refractory immunologic state developing after infection or trauma has also been described,⁴⁷ characterized by reduced proinflammatory cytokine production by mononuclear cells but increased synthesis of IL-1Ra (which correlates with CARS).

Several studies have examined therapies aimed at promoting cytokines that enhance the proinflammatory response and there-

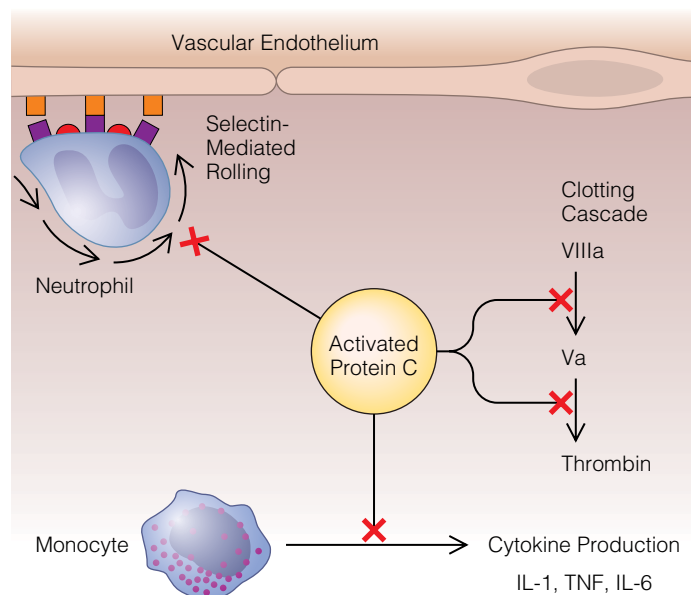


Figure 4 Activated protein C has both anti-inflammatory and antithrombotic actions that make it a valuable antisepsis drug. It reduces cytokine release by mononuclear phagocytes, reduces leukocyte adhesion to the vascular endothelium, and inhibits thrombin formation.

by presumably combat CARS. In one, administration of G-CSF to patients with community-acquired pneumonia resulted in reduced rates of systemic complications and sepsis.⁶² INF- γ was employed in a small clinical study of patients with sepsis and later in a multicenter study of burn patients,⁶⁶ the rationale being that monocyte function had been found to be depressed in severely ill patients. In these settings, the goal of restoring monocyte activity, as defined by HLA-DR expression, was achieved, though no clinical benefit was noted with regard to mortality or incidence of infectious complications.

It is clear that the role of cytokines in sepsis is a complex one: both hypoinflammation and hyperinflammation occur, and both are major determinants of clinical outcome. To date, no therapy has been found that reliably regulates cytokine activity and reduces sepsis-related mortality. It may be that future treatments will be chosen and given on a patient-to-patient basis, with markers of immune competence (e.g., HLA-DR, IL-6, and TNF) indicating whether a proinflammatory approach or an anti-inflammatory approach is preferable in a specific instance.

Activated Protein C

It has long been recognized that the clotting system plays a major role in inflammation and in the response to invading organisms; DIC is one of the cardinal signs of sepsis. The proinflammatory cytokines TNF, IL-1, and IL-6 are known to trigger activation of the clotting cascade by stimulating the release of tissue factor from monocytes and endothelium, leading to thrombin formation and a fibrin clot. These cytokines also inhibit endogenous fibrinolytic mechanisms by stimulating the release of plasminogen-activator inhibitor-1 (PAI-1) from platelets and endothelium. At the same time, thrombin stimulates many inflammatory pathways and suppresses natural anticoagulant response by activating thrombin-activatable fibrinolysis inhibitor (TAFI).⁶⁷ This procoagulant response leads to microvascular thrombosis and is implicated in the multiple organ failure associated with sepsis.

Protein C is an endogenous anticoagulant that, when activated by thrombin bound to thrombomodulin, reduces the generation of thrombin by inactivating clotting factors Va and VIIIa. It also exerts an anti-inflammatory effect by inhibiting monocyte production of TNF, IL-1, and IL-6 and limiting leukocyte adhesion to endothelium by binding selectins⁶⁸ [see Figure 4]. Activation of protein C is impaired during the inflammatory response because endothelial injury results in reduced levels of thrombomodulin. Decreased circulating levels of activated protein C are usually present in sepsis and are associated with increased mortality.⁶⁹

These observations have led to the investigation of activated protein C as a potential treatment for severe sepsis. A multicenter, placebo-controlled phase III clinical trial comprising 1,690 patients documented a 6.1% reduction in total mortality in patients treated with drotrecogin alpha (the generic name for recombinant human activated protein C).⁶⁷ The only major side effect noted with this agent was an increased risk of serious bleeding: 3.5%, compared with 2% in the placebo group. Drotrecogin is thus the first therapy to have shown a real clinical benefit in sepsis trials, and high hopes are held for its future therapeutic use. The United States Food and Drug Administration has recently approved this agent for treatment of sepsis, and further clinical trials are planned. It is marketed under the brand name Xigris.

Reactive Oxygen Metabolites

Oxygen and its metabolites [see Table 4] are often very toxic, and this toxicity seems to have influenced the early evolution of metabolic pathways to detoxify oxygen and make life possible in an aerobic environment.⁷⁰ Although aerobic organisms are capable of exploiting oxygen's high reactivity for cellular energy, this reactivity also poses a continual assault on living tissues. Whenever the rate of endogenous oxidant generation exceeds the body's endogenous antioxidant capacity, tissue injury ensues. This occurrence is known as oxidative stress.

Free radicals and other ROMs have been implicated in a diverse array of human disease processes, including reperfusion injury, ischemic hepatitis and pancreatitis, inflammatory bowel disease, and ARDS. The common pathway for the tissue injury in these illnesses is the action of free radicals.

CHEMICAL STRUCTURE

The high reactivity of free radicals is a consequence of their chemical structure. Free radicals are molecules that contain one or more unpaired electrons in their outer orbits. As a result, they possess higher energy levels than molecules with full outer orbits and, accordingly, are less stable and more reactive.

The most abundant radical in the biologic system is molecular oxygen itself (O_2), which has two unpaired electrons in its outer orbit. In this ground (i.e., low-energy) state, the two electrons have parallel spins, rendering the molecule relatively unreactive. When the electrons have antiparallel spins, the radical—termed singlet oxygen (1O_2)—is much more reactive. Various oxygen-centered free radicals and ROMs are believed to play important roles in tissue injury. The superoxide anion ($O_2^{\bullet-}$) and the hydroxyl radical ($OH^{\bullet}$) each have one unpaired electron in the outer orbit. The latter is particularly unstable: it reacts within 10^{-6} seconds of its formation and within a distance of 15 nm. Consequently, the hydroxyl radical is not only highly toxic but also very difficult to scavenge effectively.

Some ROMs, technically speaking, are not true radicals but are still quite toxic. For example, much of superoxide's tissue toxicity is actually mediated by its oxidant reduction products.

Table 4 Reactive Oxygen Metabolites and Other Free Radicals

Radicals and Metabolites	Chemical Symbol	Comments
Oxygen-centered free radicals		
Molecular oxygen		
Ground state (triplet) oxygen	3O_2	Constitutes 20% of the atmosphere
Singlet oxygen	1O_2	Much more reactive than 3O_2
Superoxide radical	$O_2^{\bullet-}$	Initial product of respiratory burst of neutrophils
Hydroxyl radical	$OH^{\bullet}$	Highly unstable; extremely toxic
Alkoxy radical	$RO^{\bullet}$	Important toxic intermediate of free radical chain reactions
Peroxy radical	$ROO^{\bullet}$	Important mediator of DNA damage
Lipoxy radical	$LOO^{\bullet}$	Important toxic metabolite of lipid peroxidation
Non-oxygen-centered free radicals		
Nitrogen centered		
Nitric oxide	$NO^{\bullet}$	Neurotransmitter
Peroxynitrite	$OONO^{\bullet}$	Important endogenous toxin
Carbon centered		
Lipid radical	$L^{\bullet}$	Important toxic metabolite of lipid peroxidation
Sulfur centered		
Thiyl	$R-S^{\bullet}$	Metabolites of cysteine and D-penicillamine
Hydrogen centered		
Hydrogen atom	$H^{\bullet}$	—
Iron centered		
Perferryl radical	$Fe^{3+}-O_2-Fe^{2+}$	Important final mediator of tissue injury (along with $OH^{\bullet}$)
Non-free radical reactive metabolites		
Ozone	O_3	Major air pollutant
Hydroperoxides		
Hydrogen peroxide	H_2O_2	Important endogenous tissue toxin
Lipid peroxide	$LOOH$	Intermediate lipid peroxidation
Hypochlorous acid	$HOCl$	Important mediator of neutrophil toxicity
Chloramines	$R^{\bullet}R'NCl$	Important final mediator of neutrophil toxicity

The hydroperoxides constitute an important class of toxic ROMs, with hydrogen peroxide (H_2O_2) playing a particularly important part. Much of the superoxide-initiated tissue damage caused by neutrophils and macrophages can be attributed to halogenated oxidants (e.g., hypochlorous acid [$HOCl$]) and chloramines, which are formed by the secondary reaction of halogenated radical species with nitrogen compounds. This production of toxic ROMs as redox products substantially amplifies the toxicity of free radicals.

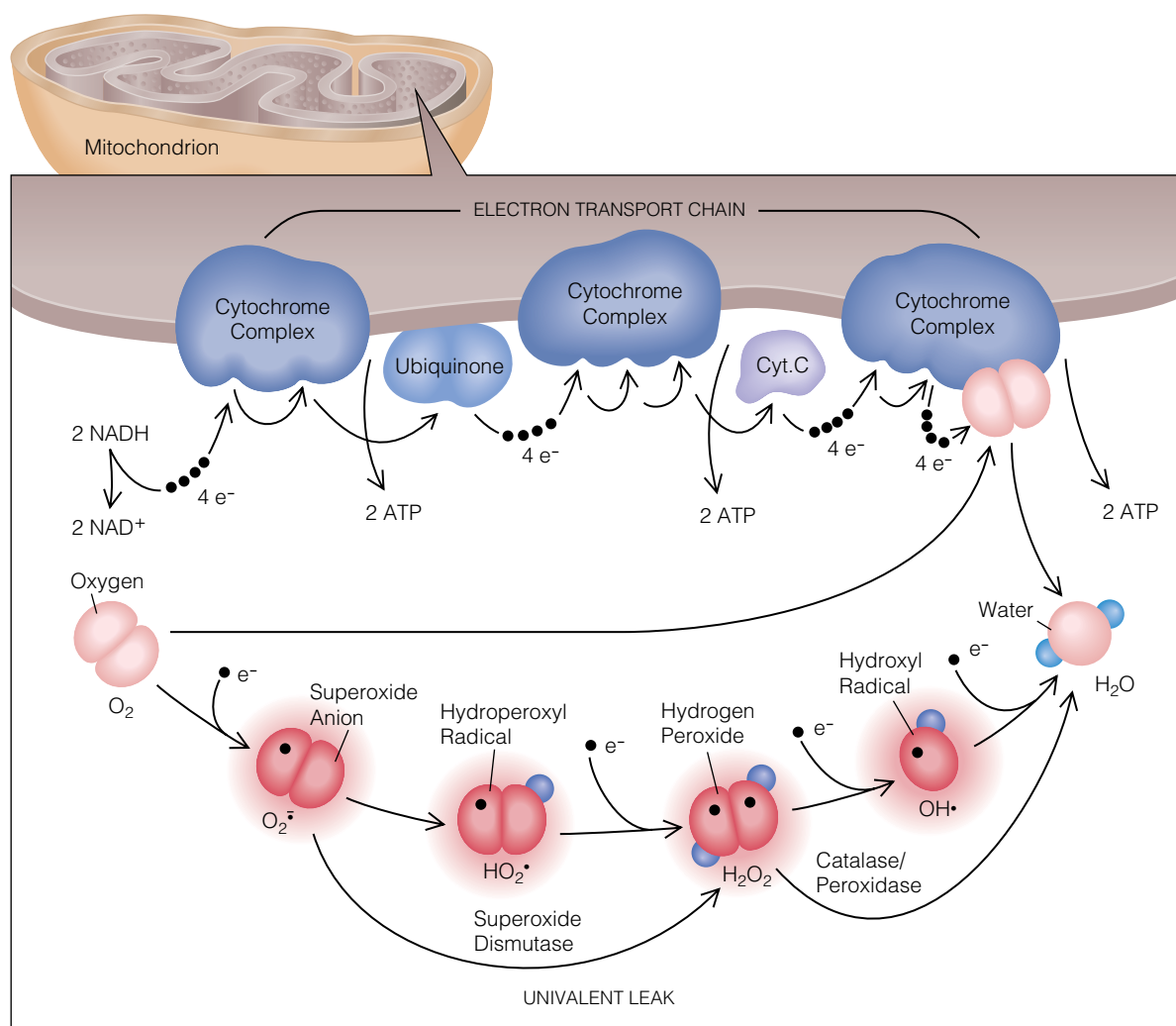


Figure 5 The mitochondrial cytochrome oxidase complex reduces molecular oxygen by the essentially simultaneous addition of four electrons, producing water and generating adenosine triphosphate (ATP) without the production of free reactive oxygen intermediates. However, 1% to 5% of oxygen leaks from this pathway and undergoes stepwise, univalent reduction. The one-electron reduction of molecular oxygen generates the superoxide free radical (superoxide anion). This can subsequently be reduced to hydrogen peroxide (H_2O_2), most commonly in a dismutation reaction catalyzed by SOD. Hydrogen peroxide can be directly reduced to water (by a catalase- or peroxidase-catalyzed reduction), or it can be reduced to the hydroxyl radical ($\text{OH}^{\cdot}$) (usually in an iron-catalyzed reaction). The highly reactive hydroxyl radical can subsequently abstract a hydrogen atom to reduce itself to water. Normally, protective biochemical mechanisms detoxify the toxic intermediates generated by this so-called univalent leak. When increased concentrations of oxygen generate excessive amounts of reactive oxygen metabolites, however, protective mechanisms may be overwhelmed and tissue injury may result.

FORMATION

All cells continuously generate ROMs as normal by-products of metabolism. During oxidative phosphorylation, mitochondrial cytochromes couple the production of adenosine triphosphate (ATP) to the tetravalent reduction of molecular oxygen to water [see Figure 5]. In the course of this process, all four electrons are effectively added to the oxygen molecule at once. No intermediaries are formed, and thus no free radicals are generated. However, about 1% to 5% of the oxygen reduced to water within the mitochondria leaks from this pathway and undergoes a stepwise, noncatalyzed reduction—the so-called univalent leak—that produces a series of toxic intermediaries. These ROMs must then be detoxified by endogenous antioxidants to prevent tissue injury.

ROMs are also formed in many other circumstances. Certain cellular oxidases (e.g., cytochrome P-450, mixed-function oxidase,

and peroxidases) can generate ROMs.⁷¹ The arachidonic acid cascade, which produces eicosanoids [see Eicosanoids, below], also generates peroxy compounds and hydroxyl radicals as by-products.

In inflammatory cells, ROMs are the primary product of a highly specialized NADPH-dependent oxidant system. When activated, they cause reduction of oxygen to the superoxide anion. This process, known as the respiratory burst, may account for more than 90% of the oxygen consumption of an activated neutrophil [see Figure 6].⁷² It is followed by formation of the major toxic product, HOCl , catalyzed by an enzyme (myeloperoxidase [MPO]) that is unique to phagocytes.

MECHANISM OF TISSUE DAMAGE

All biochemical cell components are potentially subject to attack by free radicals; however, lipids, proteins, and nucleic acids are particularly vulnerable. It should also be noted that the

toxic and mutagenic effects of ionizing radiation and those of many toxic chemicals (e.g., carbon tetrachloride [CCl_4]) are in fact mediated by the formation of ROMs. ROMs exert their inflammatory effects in five major ways.

1. **Lipid peroxidation.** Because ROMs are so reactive, they generally react with the first molecule encountered, which is often a cell membrane lipid. By removing a hydrogen atom from the carbon chain of a polyunsaturated fatty acid, a ROM can form a fatty acid radical ($\text{LOO}^\bullet$), which is then able to react with neighboring lipids, proteins, or nucleic acids, in a chain reaction. Thus, a single free radical can cause the breakdown of several polyunsaturated fatty acids, generating damaged and reactive products along its path. The reaction products include aldehydes, hydrocarbon gases (e.g., pentane, methane, and ethane) and various chemical residues; these agents cause cell edema, influence vascular permeability, give rise to inflammation and chemotaxis, and alter the activity of cell enzymes, including phospholipase. This destructive sequence is terminated only when two of these radicals react together or when the radicals are scavenged by an electron acceptor.

2. **Protein denaturation.** Both structural and enzymatic proteins are vulnerable to free radical-mediated denaturation. This process can lead to loss of membrane fluidity and structural disintegration, which can cause the destruction of organelles or even entire cells. Calcium adenosine triphosphatase (ATPase) is particularly susceptible to oxidative damage; denaturation of this enzyme results in increased intracellular calcium concentration with subsequent swelling and injury.
3. **Nucleic acid denaturation.** Free radicals can attack nucleic acids directly, causing base hydroxylation, cross-linking, or scission. Such attacks may be facilitated by the presence of DNA-bound iron acting as a catalyst. Depending on the extent of DNA damage, the effect may be mutagenic or lethal. Ionizing radiation exerts most of its damaging effect by this mechanism.
4. **Cell matrix injury.** Free radicals also attack extracellular proteins and glycoproteins (e.g., collagen and hyaluronic acid). When these molecules lose their structural integrity, damage to the connective tissue basement membrane and the extracellular matrix may ensue, which can affect vascular permeability and epithelial membrane integrity and can even result in petechiae.⁷³ This process may be the cause of certain con-

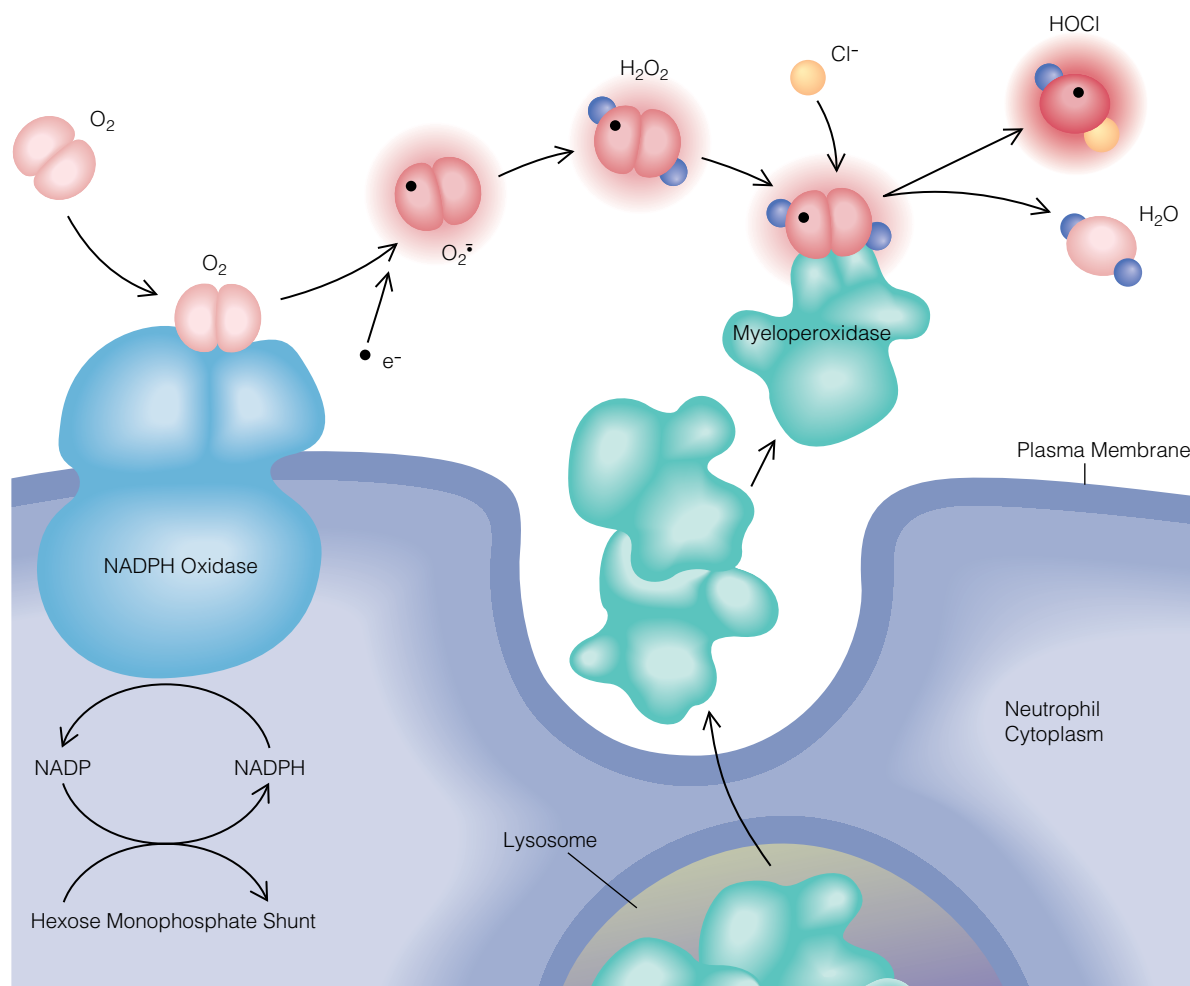


Figure 6 Neutrophils and other phagocytes generate the superoxide radical via the membrane-integrated enzyme NADPH oxidase. On stimulation, more than 90% of the oxygen used by the neutrophil is consumed in this respiratory burst. Although the superoxide radical itself is toxic to many invading microorganisms, the secondary generation of HOCl from hydrogen peroxide and chloride ions, catalyzed by the neutrophil-generated enzyme myeloperoxidase, substantially increases the bactericidal potential of the neutrophil.

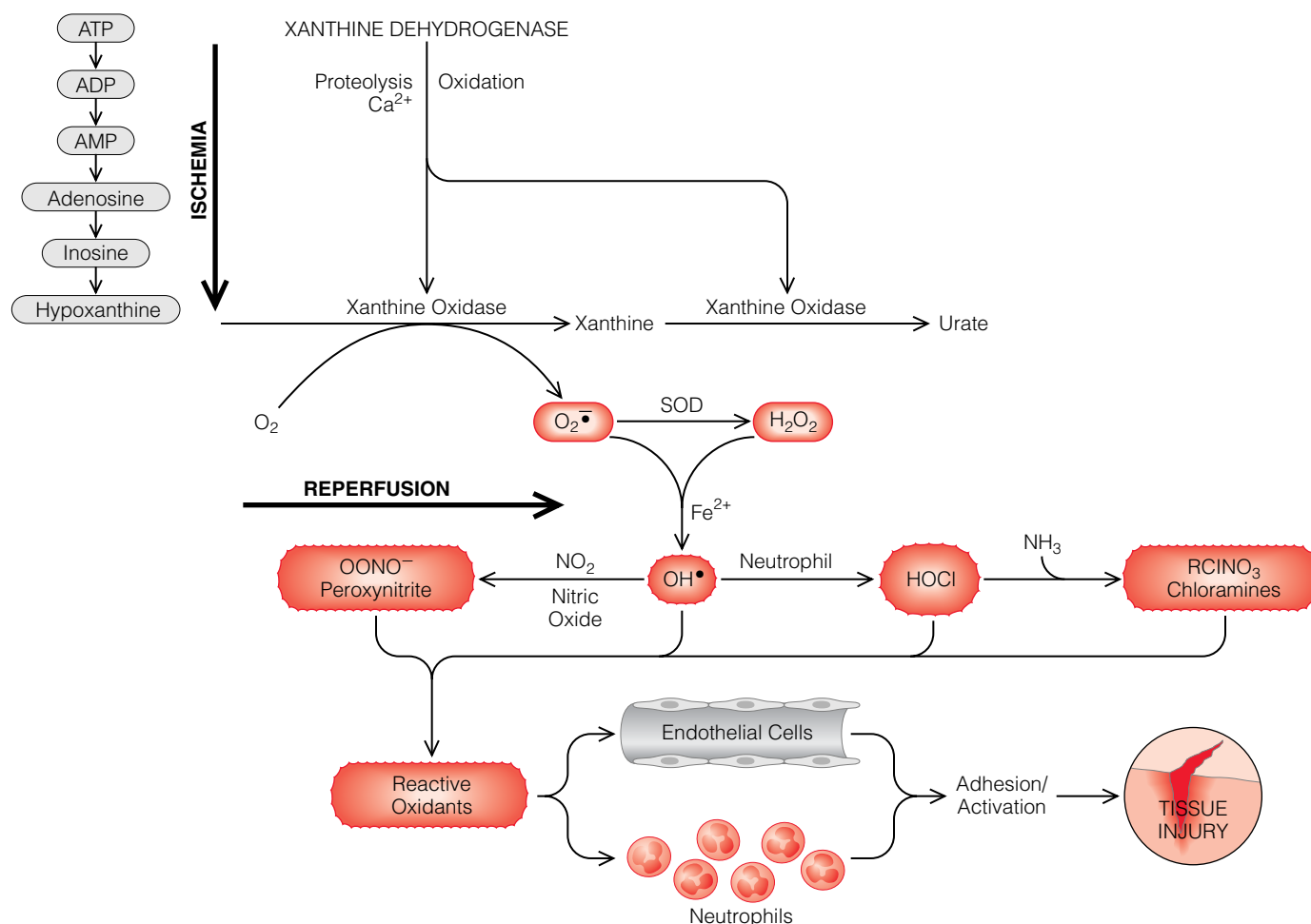


Figure 7 Xanthine oxidase may serve as the initial source of free radical generation in postischemic reperfusion injury. With the onset of ischemia, ATP is degraded to its purine bases (e.g., hypoxanthine), the concentration of which increases. Simultaneously, xanthine dehydrogenase is converted by ischemia to xanthine oxidase. Although the concentrations of substrate and enzyme are high during ischemia, the absence of oxygen prevents purine oxidation until reperfusion. At reperfusion, oxygen becomes available, suddenly and in excess, and the oxidation of hypoxanthine (and xanthine) proceeds rapidly, generating a burst of superoxide radicals as a by-product, probably at or near the endothelial cell surface.

nective tissue diseases (e.g., osteoarthritis and rheumatoid arthritis), with inflammatory cells serving as the source of ROMs.

5. Apoptosis. Apoptosis, a genetic mechanism that regulates cell numbers, is characterized by cell shrinkage (pyknosis), in contrast with the cell swelling and rupture typical of necrosis. Pyknotic cells are cleared by macrophages with minimal inflammation. Apoptosis is induced by ROMs, acting via diverse mechanisms.

ANTIOXIDANT DEFENSE MECHANISMS

Various endogenous mechanisms have evolved to limit or counteract the tissue damage caused by ROMs. An example is the production and release of enzymatic and nonenzymatic antioxidants such as vitamin E, vitamin C, provitamin A, glutathione, superoxide dismutase (SOD), and glutathione peroxidase, which act by scavenging ROMs. The enzymatic antioxidants require trace metals as cofactors for maximal effect: selenium for glutathione peroxidase; copper, zinc, or manganese for SOD; and iron for catalase.

These endogenous antioxidants are generally present at sites where free radicals are produced, which ensures that scavenging

can occur immediately after formation—a critical point, in view of the short radii of the antioxidants' activity. For example, SOD is located almost exclusively in the mitochondrial matrix, where it scavenges superoxide radicals formed via the univalent leak, and vitamins A and E are found in cell membranes, where they inhibit lipid peroxidation.

ROLE IN REPERFUSION INJURY

Postischemic reperfusion disease provides the classic example of free radical-mediated tissue injury. This phenomenon was first demonstrated in 1981 in the feline small intestine, where administration of SOD near the end of the ischemic period but before reperfusion largely prevented the microvascular and epithelial injury seen after periods of partial ischemia.⁷⁴ Since that initial study, SOD has been shown to attenuate reperfusion injury in many organs, including skeletal muscle⁷⁵ and the heart.⁷⁶ In similar models, injury was ameliorated by (1) scavenging of hydrogen peroxide by catalase,⁷⁷ (2) scavenging of hydroxyl radicals by dimethyl sulfoxide or mannitol,⁷⁸ or (3) prevention of radical formation by chelating iron with transferrin or deferoxamine.⁷⁹ Equivalent protection was provided by inhibiting generation of superoxide by xanthine oxidase through

administration of allopurinol, pterin aldehyde, or tungsten.⁸⁰ These studies suggest that xanthine oxidase, which is known to be present in high concentrations in the intestinal mucosa, is the initial trigger of free radical generation at reperfusion.

In nonischemic tissue, the dehydrogenase form of xanthine oxidoreductase predominates. Ischemia appears to mediate the conversion of xanthine dehydrogenase to xanthine oxidase via a mechanism that remains to be defined. At the same time, catabolism of ATP during ischemia leads to an increased concentration of the purine metabolites, xanthine and hypoxanthine. At reperfusion, oxygen is suddenly reintroduced in excess. The subsequent generation of superoxide by xanthine oxidase triggers a free radical chain reaction and subsequent tissue injury [see Figure 7]. That either scavenging the hydroxyl radical or blocking its generation by an iron-catalyzed reaction has the same protective effect as more proximal blockage of the cascade suggests that the hydroxyl radical, or one of its metabolites, is the final agent of injury.⁷⁷

Reperfusion injury is also known to be mediated by neutrophils, which would seem to suggest that the injury is entirely accounted for by neutrophil superoxide generation. This thesis is unlikely to be true, however: a more plausible thesis is that neutrophils act in concert with ROMs. Thus, in some models of injury, neutrophil depletion fails to ameliorate injuries that are blocked by SOD and catalase. It has been observed that free radical scavengers prevent neutrophil infiltration into postischemic tissue,⁸¹ which has led to the hypothesis that ROMs act primarily as neutrophil chemoattractants.

Clinical Trials

In view of the success achieved in moderating reperfusion injury with antioxidants in animal models, it is perhaps surprising that similar approaches have not met with comparable success in humans. A 1989 study using human recombinant SOD to treat myocardial ischemia-reperfusion injury after angioplasty and renal ischemia failed to demonstrate any benefit.⁸² However, a renal transplant study in which SOD was infused immediately before reperfusion reported reduced rates of acute renal failure in graft recipients who underwent cold ischemia for longer than 30 hours⁸³; graft survival was longer as well.

In general, ROM scavengers are partially effective at best. Despite the enormous amount of data that has been collected, the precise relationship between ROM generation and tissue injury remains unclear.

Nitric Oxide

NO• is produced in a variety of tissues (e.g., endothelial cells and platelets) by either a constitutive or an inducible form of NO• synthase. In the setting of inflammation, the inducible enzyme is activated by cytokines such as TNF. NO• is a potent inhibitor of leukocyte and platelet adhesion, exerting its effects via activation of soluble guanylcyclase and generation of cyclic guanosine monophosphate (cGMP).⁸⁴ With regard to platelets, NO• has been shown to inhibit the binding of fibrinogen to GPIIb/IIIa and to limit the expression of P-selectin.⁸⁵ Another important anti-inflammatory role of NO• is its ability to scavenge superoxide at least as fast as SOD does. Finally, inhaled NO• moderately reduces the pulmonary hypertension seen with ARDS; however, it does not increase cardiac output or reduce mortality in these patients.

Moreover, NO• acts as a source of potent free radicals when it interacts with superoxide to form peroxynitrite, a strong oxi-

dizing agent. Experimental studies using NO• donors and antagonists have not yielded sufficiently consistent results to permit a clear definition of the role of NO• in mediating or moderating inflammatory events.

Complement

Complement was discovered in 1889 by Bordet while he was studying the bactericidal action of serum.⁸⁶ Bordet demonstrated that if fresh serum containing an antibacterial antibody was added to the bacteria at physiologic temperature, the bacteria were lysed, but if the serum was heated to a temperature of 56° C or higher, the bacteria were not lysed. Reasoning that the serum's loss of lytic capacity could not have been caused by decay of antibody activity—because antibodies were known to be heat stable, and even heated serum remained capable of agglutinating the bacteria—Bordet concluded that serum must contain another heat-labile component that assisted or complemented the lytic function of antibodies.

COMPLEMENT CASCADE

The complement cascade consists of the classical and alternative pathways, each of which comprises a series of plasma proteins that are known to mediate several aspects of the inflammatory response. This cascade has four principal biologic functions:

1. Osmotic cell lysis, effective in the killing of foreign organisms.
2. Binding of complement proteins to the surfaces of foreign organisms or particles. These opsonins bind to specific counterreceptors on macrophages and leukocytes, facilitating phagocytosis.
3. Augmentation, potentiation, and promotion of the inflammatory response. Complement fragments bring about chemotaxis of inflammatory cells. In addition, C3a and C5a stimulate a neutrophil oxidative burst and mast cell degranulation, which potentiate the inflammatory response.
4. Clearance of immune complexes from the circulation.

The classical pathway and the alternative pathway have different activating mechanisms; however, both result in the formation of the membrane attack complex C5b-C9, which leads to the creation of pores in the cell membrane and consequently to abnormal ion transport, impaired signaling, and potential lysis, particularly of nonnucleated cells. Activation of either pathway leads to production of the biologically active anaphylatoxins C3a and C5a. These peptides are generated via cleavage of native C3 and C5 complement components by C3 convertase and C5 convertase, which are formed at intermediate steps in the process of complement activation. C3a and C5a exert a variety of physiologic effects, including vasodilatation and increased vascular permeability. The effects on neutrophils include chemotaxis, diapedesis, degranulation, and free radical production as well as translocation of intracellular complement receptors to the neutrophil-plasma membrane. In addition, the complement fragments C3b and C4b serve as opsonins, thus facilitating phagocytosis of particles to which they have attached. Inactive C3b (iC3b) is a counterreceptor for the neutrophil CD11b/CD18 (Mac-1) receptor and thus has the ability to enhance neutrophil binding and signaling in response to complement-coated molecules, thereby facilitating their phagocytosis.

The complement cascade has specific features that make it an important effector mechanism in the inflammatory response. Many of its components, once activated, possess enzymatic

activity. As the cascade proceeds, these activated components cause substantial amplifications at each step. In addition to this important positive feedback loop, there are multiple levels at which inhibitory proteins can intervene in the cascade to prevent its accidental or inappropriate generalized activation. Another important property of the complement cascade is that it has both specific and nonspecific activators. Once a specific antibody and antigen have reacted, the classical pathway can be activated by several closely spaced IgG molecules or by a single IgM pentamer. The alternative pathway is triggered by direct binding of components to the surface of foreign organisms. In this way, the alternative pathway participates in nonspecific immunity.

Classical Pathway

The classical pathway [see Figure 8] is usually initiated by interaction between C1 and an antigen-antibody complex. It may also be activated by infectious organisms (e.g., *Mycoplasma*) or certain molecules (e.g., DNA, heparin, and chondroitin sulfate).⁸⁷

C1 does not interact with IgG or IgM until the antibody has bound its specific antigen. The subunit of C1 that binds is C1q. C1q attaches either to the C_H3 domain of IgM or to the C_H2 domain of IgG, both of which reside in the Fc portion of the antibody. A single C1q molecule must bind to at least two Fc portions of an immunoglobulin. Because IgM is secreted as a pentamer containing five separate Fc portions, a single molecule is an efficient activator of complement. Because IgG is secreted as a monomer, C1q must bind to two or more adjacent IgG molecules to be activated. C1q is uniquely able to bind these different Fc regions of immunoglobulins because it consists of six identical subunits, each of which has a projecting head.

Once C1q is bound to an immune complex, the other components of C1—C1r and C1s—become operative. A tetramer consisting of two C1r and two C1s molecules is formed and bonded with C1q. This process results in a serum esterase-type enzyme that acts on the next two components in the cascade, C4 and C2. C4, like several other complement proteins, has an internal thioester bond. C4 is split into two parts, C4a and C4b, with the former diffusing away. Generation of C4b results in a reactive molecule called metastable C4b, which possesses an internal thioester. Many C4b molecules react with water at the site of the internal thioester, thereby inactivating the C4 complex; alternatively, some of the C4b thioesters may esterify to cell surface proteins or carbohydrates, thereby stabilizing the C4 complex.

In the presence of magnesium, C2 binds to C4b molecules that in turn are bound to cell surface proteins or carbohydrates. A C1s molecule splits C2, generating C2a and C2b. The latter may diffuse away, whereas the C2a fragment remains complexed with C4b, resulting in C4b2a, which is the C3 convertase of the classical pathway [see Figure 8]. In the presence of calcium and magnesium, this C3 convertase binds C3 and cleaves it into C3a and C3b. Like C4b, C3b has an internal thioester, and this thioester may form a covalent bond with C4b2a or be inactivated by reacting with water. The addition of C3b to the preexisting C4b2a complex yields C4b2a3b, which is the C5 convertase of the classical pathway. This C5 convertase cleaves C5 and initiates the common terminal sequence of the complement cascade, which results in the formation of C5b-C9, the membrane attack complex.

Alternative Pathway

The alternative pathway [see Figure 8] was so named because it was discovered after the classical pathway was described, but it

seems actually to have evolved before the classical pathway. Both pathways require the production of C3 and C5 convertases to generate the terminal sequence leading to generation of the membrane attack complex; however, each uses a different series of activators and proteins to produce these convertases.

The alternative pathway is in a constant state of low-level activation as a result of spontaneous hydrolysis of the internal thioester bond in the α chain of C3 (the so-called tickover of C3), a process that is believed to be ongoing at a low intensity in the circulation at all times. This hydrolysis leads to the unstable intermediate C3b. (The classical pathway may also initiate the alternative pathway by serving as the source of the first C3b molecules.) C3b is usually hydrolysed by water, but sometimes it reacts with amino or hydroxyl groups of cell surface proteins or polysaccharides to form stable amide or ester bonds. The cell-bound C3b then attaches to factor B, which in turn is proteolytically cleaved by factor D to form C3bBb, the solid-phase alternative pathway C3 convertase, which requires properdin for stabilization.

The C3 convertase then acts on additional C3b to form the C3bBbC3b complex, which is the C5 convertase of the alternative pathway. This C5 convertase initiates hydrolysis of C5, which, as in the classical pathway, eventually results in the formation of the membrane attack complex.

Membrane Attack Complex

Both of the C5 convertases cleave C5 into C5a and C5b. The C5b component binds to C6 and C7, and the resulting C5b67 complex is then inserted into the lipid bilayer of the plasma membrane. Once in place in the membrane, this molecule becomes a receptor for and binds to C8, at which point pore formation, ionic movement, and cell lysis may begin. The C5b678 complex undergoes hydrophilic association within the plasma membrane, weakening it and causing the formation of transmembrane channels. This process may lead to cell death by osmotic lysis because of the cell's inability to maintain critical intra- and extracellular concentration gradients. Because of the amplification mechanisms involved in both pathways, as many as 12 to 15 C9 molecules may be added to the C5b678 complex, resulting in the formation of C5b-C9, the membrane attack complex. Scanning electron microscopy suggests that the membrane attack complex acts as a pore within the cell membrane, allowing the collapse of ionic and osmotic gradients.

Regulation

To prevent inappropriate activation and damage to the host, the complement cascade must be tightly regulated. There are a number of circulating soluble factors that inactivate various aspects of the complement cascade, including C1 inhibitor, C4-binding protein, factor H, and factor I. Molecules that inhibit membrane attack complex formation include homologous restriction factor and the membrane inhibitor of reactive lysis, both of which are thought to play a key role in protecting normal surrounding cells in adjacent areas where complement activation and cell lysis are taking place.

In addition, there are several regulatory proteins that are found within the membranes of most cells of the myeloid line as well as those of platelets and mast cells; these include complement receptor type 1 (CR1), membrane cofactor protein, and decay-accelerating factor. CR1 is present on erythrocytes and in smaller quantities on neutrophils, monocytes, macrophages, eosinophils, and lymphocytes. It has at least three important functions: (1) it can inhibit C3 convertase activity, (2) it enhances the ability of leukocytes to ingest C3b- or C4b-coated

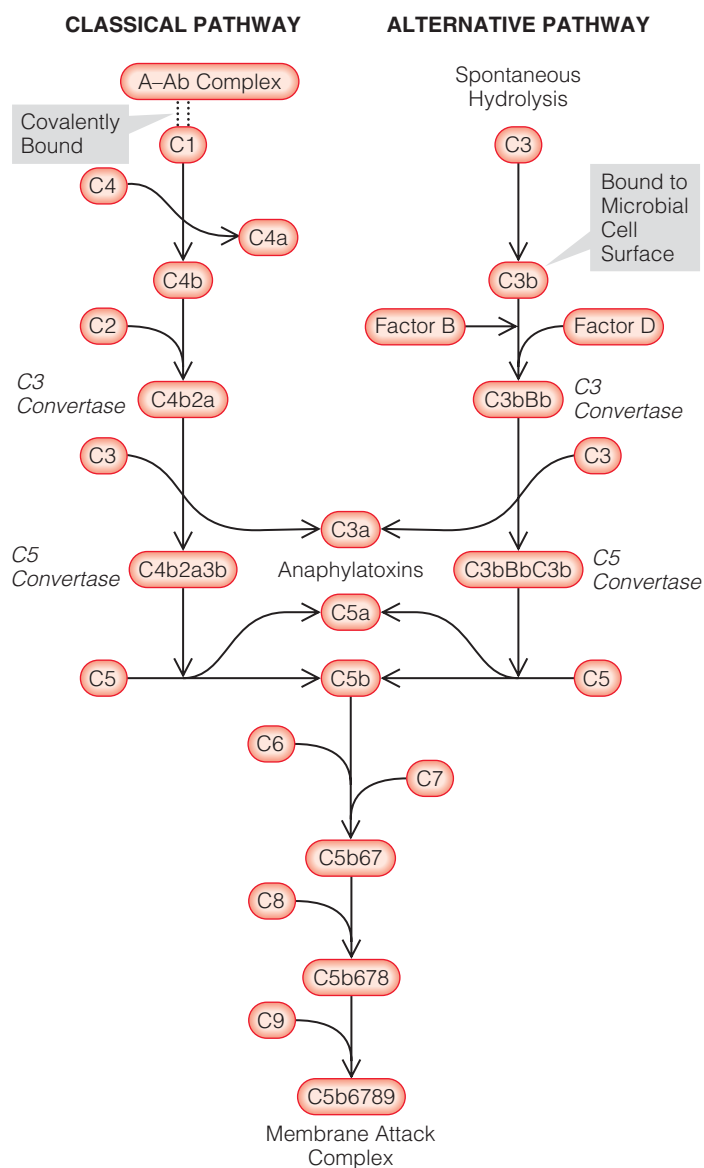


Figure 8 Shown are the classical and alternative pathways of the complement cascade.

particles, and (3) it facilitates clearance of immune complexes from the circulation. CR1 also inhibits the activity of C4b and thus is capable of preventing activation of the classical pathway. This powerful inhibitor of both complement pathways is currently the subject of much attention among researchers. A soluble form of CR1 that lacks the cytoplasmic and transmembrane domains has been engineered from human erythrocytes. This human soluble complement receptor type 1 (sCR1) retains the C3b- and C4b-binding activities of membrane-associated CR1.

ROLE IN REPERFUSION INJURY

The first evidence that complement might play a role in the pathogenesis of ischemia-reperfusion injury was the finding that myocardial ischemia induced complement activation.⁸⁸ It was also reported that mitochondrial fragments in cardiac lymph activated both classical and alternative complement pathways. Later studies using cobra venom factor to deplete complement by triggering its activation demonstrated reductions in myocardial necrosis after coronary artery occlusion.⁸⁹ Researchers

examining therapeutic use of sCR1 in animals documented significant reductions in myocardial infarct size and dramatic reductions in the number of neutrophils sequestered in the myocardium.⁹⁰ Moreover, treatment with sCR1 did not appear to impair healing of the infarcted area. Immunoperoxidase staining for the membrane attack complex demonstrated little or no myocardial deposition of C5b-C9 in the sCR1-treated group in comparison with untreated animals.

Several studies have examined the role of complement in skeletal muscle ischemia-reperfusion injury. In one, concentrations of C3a and C5a were elevated in patients with ischemic limbs.⁹¹ Levels of these anaphylatoxins returned to normal after amputation, which suggested that complement was activated by acute limb ischemia. In another study, there was a significant dose-dependent reduction in muscle permeability with sCR1 treatment after hindlimb ischemia-reperfusion.⁹² Subsequently, it was found that during reperfusion, skeletal muscle permeability was dependent on the presence of IgM natural antibody and on activation of the classical complement pathway. These investigations lend strong support to the thesis that complement is a significant mediator of skeletal muscle injury after ischemia-reperfusion.

In further studies, it was postulated that ischemic injury led to expression or unmasking of a neoantigen. Immunohistochemistry demonstrated colocalization of IgM and C3, indicating the formation of an immune complex in conjunction with complement activation (shown by other techniques to involve the classical pathway). Animals genetically depleted of immunoglobulins—specifically, IgM—were protected from reperfusion injury.

Mast Cell

Although mast cells were first identified more than a century ago, only comparatively recently have major advances been made in understanding their biology. All mast cells are derived from progenitors present in the bone marrow, which migrate to peripheral tissues as immature cells and undergo differentiation in situ. Thus, unlike neutrophils, mature mast cells are not found in the circulation but are located throughout the body near blood vessels and nerves, beneath epithelia, and in lymphoid organs.

STRUCTURE AND TYPOLOGY

Mast cells have (1) a mononuclear nucleus, (2) numerous cytoplasmic granules containing mediators (including peptides, proteins, proteoglycans, and amines, and (3) a plicated cell membrane. The cell membrane contains a number of receptors for important regulatory compounds, such as growth factors, activators of secretion (e.g., receptors for the Fc portion of the IgE molecule), and receptors for adhesive molecules that enable the mast cell to attach to certain sites.

Mast cells can be differentiated into two types, those found in mucosa and those found in connective tissue. These two phenotypes are relatively easy to distinguish in rodents because they stain differently, differ in size, and are found in different tissues. GI mucosal mast cells have chondroitin sulfate as their major granule proteoglycan and contain little histamine. In contrast, connective tissue mast cells (found in the lungs and in the serosa of body cavities) have heparin as their major granule proteoglycan and produce large quantities of histamine.

Two techniques have enabled researchers to distinguish between the two types of mast cells in humans. One uses electron microscopy to examine the completeness of the scroll or whorl structure of the granule (only connective tissue mast cells

have a complete scroll). The other uses mAbs to identify mast cell subtypes on the basis of their constituent protease enzymes. All human mast cells contain tryptase, but only connective tissue mast cells contain chymase. Furthermore, there are a number of chymase isotypes that are unique to particular organs, which suggests that the pattern of mediators produced by mast cells might vary with anatomic location.

ACTIVATION

In diseases associated with mast cell activation, increases in the total number of mast cells and variations in the relative abundance of mast cell phenotypes occur at different tissue sites. The best understood immunologic stimulus of mast cell activation is an immune IgE complex. Other important immunologic triggers are cytokines and various histamine-releasing factors generated by neutrophils, platelets, mononuclear leukocytes, and macrophages as a consequence of the immune response.

Numerous nonimmunologic stimuli are also important in mast cell activation associated with wheal-and-flare reactions. Such stimuli include the complement fragments C3a, C4a, and C5a; various neuropeptides, including calcitonin gene-related peptide; substance P; neurotransmitters; and drugs. These non-immunologic activators are generally more effective on connective tissue mast cells than on mucosal mast cells.

When mast cells are activated, their granules move to the surface, dissolve, and release their contents. Some of these products (e.g., histamine and other low-molecular-weight components) are freely soluble; others (e.g., proteoglycans, enzymes, and larger proteins) are poorly soluble. Differential release of these materials may have a bearing on the mast cell's role in disease.

ROLE IN ACUTE LUNG INJURY

The central role played by mast cells in the immediate hypersensitivity reaction has long been known. In the lung, this reaction is typically manifested either by an asthma attack or by a more generalized systemic hypersensitivity reaction (i.e., anaphylactic shock).

Asthma is characterized by paroxysms of bronchial constriction and increased production of thick mucus, which leads to bronchial obstruction and exacerbation of respiratory distress. The smooth muscle in the airway is often hypertrophied and hyperreactive to constricting stimuli. Anaphylactic shock is characterized by vasodilation and exudation of plasma in vascular beds throughout the body, usually resulting from the presence of a triggering antigen that gains systemic access via injection, an insect sting, or absorption across an epithelial surface (e.g., skin or GI mucosa). The decrease in vascular tone and leakage of plasma lead to a fall in blood pressure that may be fatal. The cardiovascular effects are complicated by constriction of the musculature surrounding the upper and lower airways, increased mucosal reactivity with outpouring of mucus in the gut and the respiratory tract, and urticarial lesions on the skin.

In both asthma and anaphylaxis, mast cell activation takes place in response to an immunologic trigger. Specifically, IgE antibody insertion on mast cell surface Fcε receptors leads to the production and release of inflammatory mediators. Mast cell-derived leukotrienes and PAF are thought to be major mediators of acute airway constriction. In addition, mast cell-derived cytokines (e.g., TNF-α, IL-4, and IL-5) are thought to be the major factors causing sustained airway inflammation via the recruitment of eosinophils and basophils.

Nonimmunologic mechanisms may also play a part in mast cell-mediated lung injury. In one study, when pulmonary alveo-

lar mast cells were exposed to hypoxia, they released their granules, thereby causing lung injury.⁹³ Perivascular mast cells from the hypoxic lungs showed none of the morphologic changes associated with IgE-mediated mast cell degranulation, such as granule swelling, fusion, and exocytosis.

In a murine model of hindlimb ischemia-reperfusion that made use of two congenic animal strains, one mast cell-sufficient and the other mast cell-deficient, it was demonstrated that pulmonary mast cells mediated neutrophil sequestration and pulmonary edema, probably through the production and release of leukotrienes.⁹⁴ Vagal efferent nerves appeared to play an important role in the induction of remote lung injury after hindlimb ischemia; in this setting, bilateral cervical vagotomy limited mast cell degranulation and associated lung injury.⁹⁵

Vagal mechanisms also appear to play a key role in mast cell activation in a murine model of acid aspiration.⁹⁶ Blocking substance P, a neuropeptide released at the end of C-fibers located near mast cells, modified the lung injury; the C-fibers travel with vagal nerves. A similar benefit was obtained by using the chymase antagonist chymostatin, which blocked the effect of a key mast cell secretory product. The reduction in injury achieved with these two approaches was the same as the injury reduction observed in mast cell knockout mice.⁹⁶ This similarity suggested that the final common pathway of lung damage in aspiration was activation of the alternative complement pathway. These data indicate that vagal stimulation with release of substance P leads to release of mast cell-derived chymase that triggers activation of the alternative complement pathway, thereby causing aspiration lung injury.

Eicosanoids

Eicosanoids are vasoactive and immunomodulatory derivatives of membrane fatty acids that can be produced by virtually all cells in the body. They may be divided into three major subgroups: prostaglandins, thromboxanes, and leukotrienes. These agents are not stored but are rapidly synthesized in response to signaling stimuli. After release, they act in an autocrine and paracrine fashion. They have very short half-lives (largely because of their susceptibility to spontaneous hydrolysis or active enzymatic conversion to inactive metabolites) and thus rarely act as circulating hormones.

Prostaglandins were discovered in the 1930s by von Euler when a substance in human semen was found to cause myometrial contraction. The active agent, an acidic lipid, was thought to be a product of the prostate gland and hence was named prostaglandin. The next major observation was the description of the slow-reacting substance of anaphylaxis (SRS-A) in the early 1940s. Thromboxanes were discovered in 1975 and leukotrienes in 1979. In 1980, SRS-A was identified as a combination of the three cysteinyl leukotrienes: LTC₄, LTD₄, and LTE₄.

FORMATION

Liberation of Arachidonic Acid

Arachidonic acid (eicosatetraenoic acid), the major substrate for eicosanoid synthesis, is a long-chain polyunsaturated fatty acid that is incorporated into the phospholipid mammalian cell membrane. It is also present in plasma, but it is tightly bound to plasma proteins and therefore biologically unavailable. The first step in eicosanoid synthesis is liberation of arachidonic acid from the cell membrane. An agonist binds to the membrane receptor, causing activation of the enzyme phospholipase C, which generates

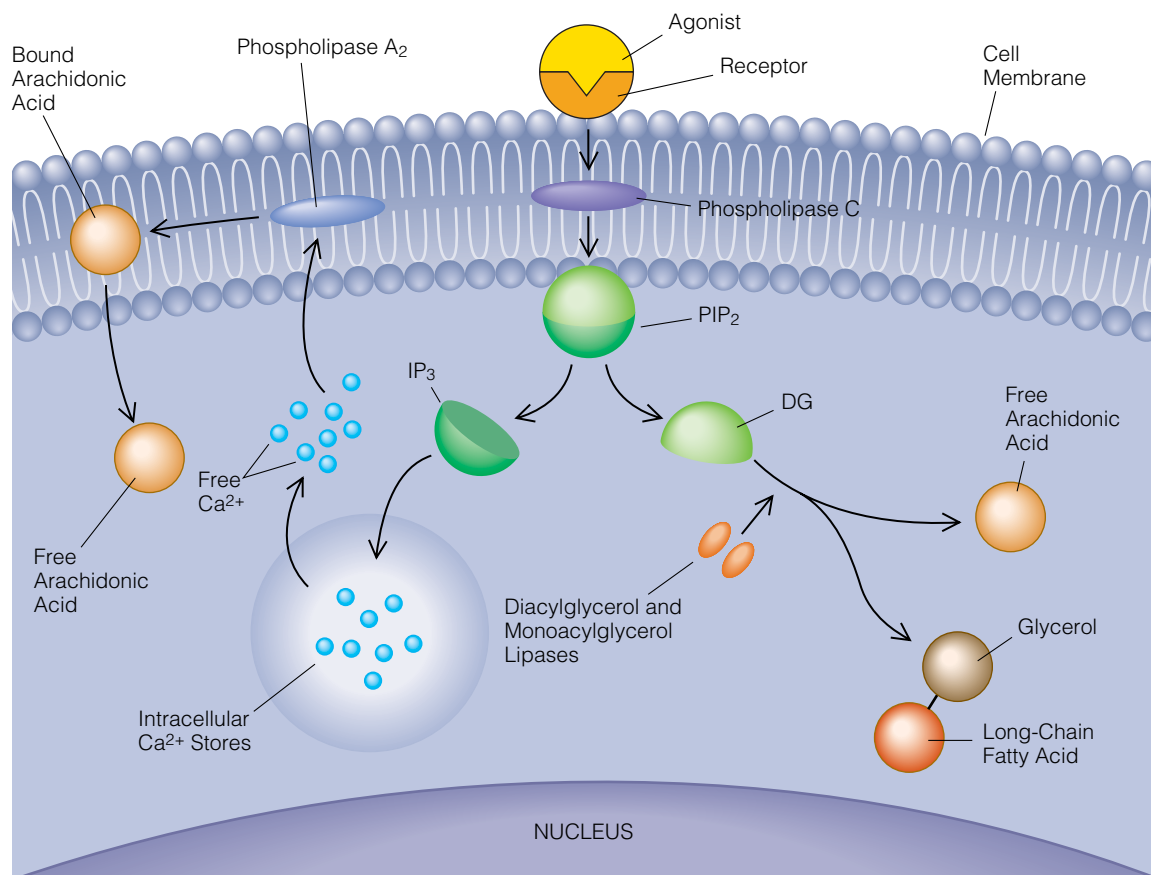


Figure 9 Shown is the production of free arachidonic acid in the cytosol. The binding of an agonist to a receptor activates phospholipase C, which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP₂) to inositol 1,4,5-trisphosphate (IP₃) and diacylglycerol (DG). From this point, free arachidonic acid can be generated in two ways. First, IP₃, by increasing the intracellular calcium ion concentration, activates phospholipase A₂, which then liberates arachidonic acid from the cell membrane. Second, DG is broken down enzymatically into several products, one of which is arachidonic acid.

free arachidonic acid via the production of the intracellular second messengers inositol triphosphate and diacylglycerol. These messengers, in turn, activate phospholipase A₂ [see Figure 9].

Phospholipase activation is a crucial step in arachidonic acid liberation; in fact, it serves as the rate-limiting step in all eicosanoid production. Once freed, arachidonic acid is metabolized via two pathways. The cyclooxygenase pathway produces prostaglandins and thromboxanes (collectively referred to as prostanoids), and the lipoxygenase pathway, present in cells of myeloid origin, produces leukotrienes.

Cyclooxygenase Pathway

All cells except nonnucleated red cells are capable of generating cyclooxygenase products. Two related but distinct cyclooxygenase isozymes have now been identified, COX-1 and COX-2. COX-1 is constitutively present in cells, and its products are considered to have housekeeping functions (e.g., gastric mucosal protection). COX-2 is an inducible enzyme that is rapidly upregulated in response to various immune and inflammatory mediators (e.g., cytokines, growth factors, and tumor promoters), and its products play a more inflammatory role [see Figure 10]. Admittedly, this polarized view of the functions of COX-1 and COX-2 products is somewhat oversimplified; nevertheless, we believe it is useful for the purposes of general discussion.

Both COX-1 and COX-2 convert arachidonic acid into an endoperoxide, prostaglandin G₂ (PGG₂), which in turn is con-

verted to PGH₂. PGH₂ is then metabolized by different pathways to prostaglandins, prostacyclin (PGI₂), and thromboxanes [see Figure 11].

Cells typically synthesize one or two COX products, depending on the enzymes they express. Platelets, for example, produce thromboxane A₂ (TXA₂) through the action of thromboxane synthetase, whereas endothelial cells primarily produce PGI₂ through the action of prostacyclin synthetase.

Six cyclooxygenase products are currently in widespread use in clinical settings. Alprostadil (PGE₁) is used for its smooth muscle-relaxing effects; misoprostol, a synthetic analogue of PGE₁, is used for gastric cytoprotection; PGE₂ and latanoprost (PGF_{2α}) are used in obstetrics and gynecology; latanoprost is used in ophthalmology, and PGI₂ is used for its properties as a potent vasodilator and a moderate inhibitor of platelet aggregation. At present, however, greater clinical importance is attached to inhibition of the synthesis of cyclooxygenase products by means of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors, which act as anti-inflammatory and analgesic compounds [see Therapeutic Implications, Cyclooxygenase Inhibition with NSAIDs and COX-2 Antagonists, below].

Lipoxygenase Pathway

There are several differences between the cyclooxygenase and lipoxygenase pathways. Unlike cyclooxygenase, which is ubiquitous, lipoxygenase is present only in inflammatory cells.

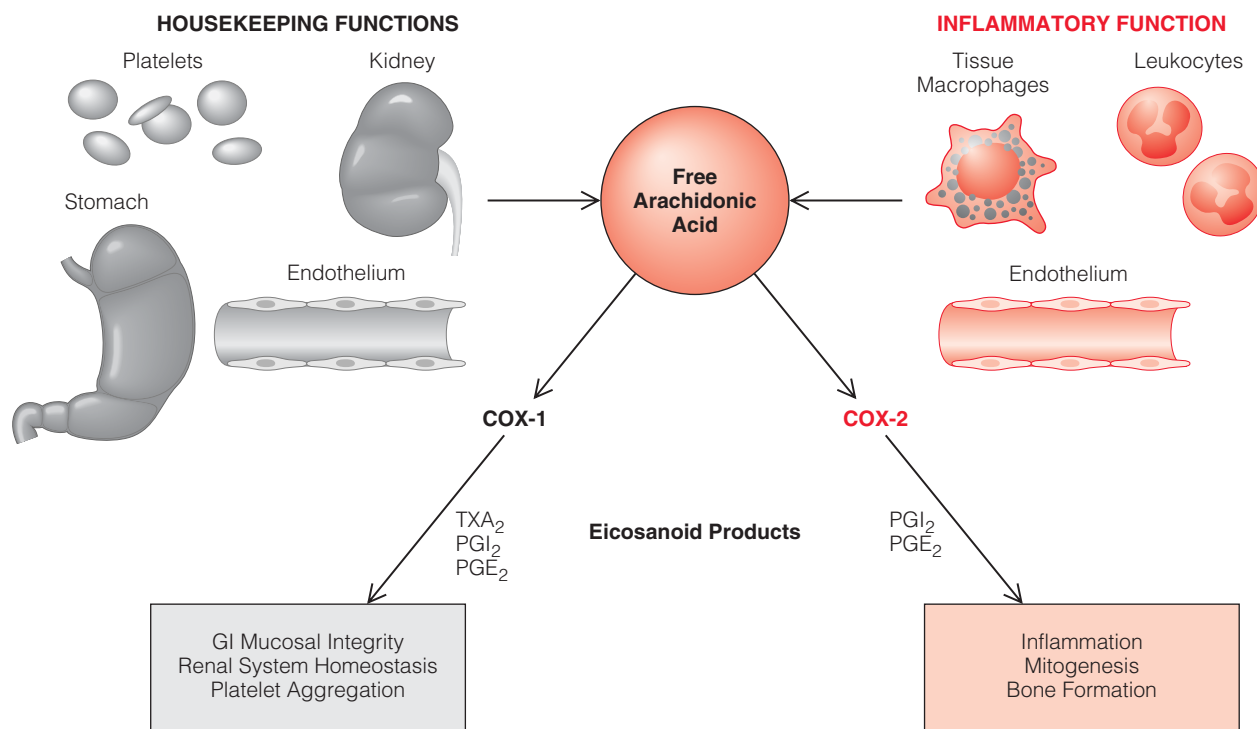


Figure 10 The products of COX-1 tend to have so-called housekeeping functions. This enzyme is constitutively present in cells. In contrast, the COX-2 enzyme is induced in cells in response to inflammatory stimuli. The products of both enzymes tend to cause inflammation.

Furthermore, whereas cyclooxygenase is always active, requiring only the presence of arachidonic acid for endoperoxidase production, lipoxygenase is quiescent and must be activated for leukotriene synthesis to occur. Activating stimuli for the lipoxygenase pathway include GM-CSF, C5a, and fMLP.

In the lipoxygenase pathway, liberated arachidonic acid is converted to 5-hydroperoxyeicosatetraenoic acid (5-HPETE) by 5-lipoxygenase (5-LO). This same enzyme then converts 5-HPETE into LTA₄, which then is either metabolized by LTA₄ hydrolase to LTB₄ or conjugated by LTC₄ synthetase with reduced glutathione to form LTC₄. LTC₄, in turn, is converted into LTD₄ and LTE₄ [see Figure 11].

LTA₄ may diffuse extracellularly and be taken up by cells that possess LTA₄ hydrolase and LTC₄ synthetase (e.g., erythrocytes and endothelium), with the result that leukotrienes may be produced by nonmyeloid cell lines that do not possess 5-LO and thus do not ordinarily generate leukotrienes. This process can amplify the inflammatory response.

PROSTAGLANDINS

There are nine prostaglandin groups: A, B, C, D, E, F, G, H, and I. With some prostaglandins (e.g., PGA₂), the letter refers to the chemical structure of its five-member ring. With others, however, the letter means something else: for example, E originally stood for "ether" and F for "phosphate buffer," which were the substances in which PGE and PGF were most readily soluble. Within a prostaglandin group, the subscript numerals 1, 2, and 3 are used to indicate the number of unsaturated double bonds present in the two side chains. Finally, the subscript Greek letters α and β are used to indicate the spatial orientation of the hydroxyl groups on the side chains in relation to the ring.

Prostaglandins primarily exert their effects on the smooth muscle of the GI tract, the airways, the vasculature, and the

reproductive tract; however, they also play important roles in platelet regulation and in the nervous system. Their main biological actions may be summarized as follows:

1. Effects on the vasculature. PGI₂ is a vasodilator that is synthesized by both smooth muscle and endothelial cells in response to agents such as bradykinin, thrombin, serotonin, platelet-derived growth factor, and IL-1. Its actions are essentially antagonistic to those of TXA₂: it causes vasodilatation, inhibits platelet aggregation, and is thought to control the release of tissue plasminogen activator. In contrast, PGF_{2 α} is a potent vasoconstrictor.
2. Effects on the nervous system. PGE₁ and PGE₂ are responsible for the increase in body temperature associated with inflammation. Their synthesis in the hypothalamus is promoted by TNF and IL-1 (also known as endogenous pyrogen), which are released by phagocytes in response to viruses, bacteria, fungi, endotoxin, and antigen-antibody complexes. PGE₂ also exerts a strong hyperalgesic effect: it increases sensitivity to a variety of mechanical and chemical pain stimuli, with additive effects occurring over time and with increasing concentration. At high concentrations, PGE₂ can even stimulate nociceptive nerve endings directly.
3. Effects on the renal system. PGE₁, PGE₂, and PGI₂ increase the glomerular filtration rate and moderate renal blood flow by means of local vasodilatation. They also increase sodium and water excretion, though the mechanisms by which they do so are unclear.
4. Effects on the GI tract. Prostaglandins play a central role in gastric epithelial defense and repair and are produced in large amounts by the gastric mucosa. Most of them induce contraction of GI smooth muscle. Specifically, PGE₂ and PGF_{2 α} contract longitudinal smooth muscle, whereas PGI₂ and

PGF_{2α} contract circular smooth muscle. Administration of these agents causes colicky abdominal pain.

5. Effects on the respiratory tract. PGE₁, PGE₂, and PGI₂ relax respiratory smooth muscle, and PGF_{2α} contracts it.
6. Effects on the reproductive system. Prostaglandins have potent effects on the uterus and the cervix, moderating uterine contraction during delivery. Although they were originally discovered in semen, their function there remains unknown.

THROMBOXANES

TXA₂, originally called rabbit aortic contracting substance, was identified in 1975 as an agent that contracted vascular smooth muscle and caused platelet aggregation.⁹⁷ In picogram amounts, it exerts five major biologic effects.

1. Vasoconstriction. TXA₂ is one of the most potent naturally occurring constrictors of smooth muscle. It acts on virtually all vascular beds, but its effects are particularly prominent in small arteries and arterioles.
2. Bronchoconstriction. TXA₂ exerts a marked spastic effect on tracheal rings and pulmonary parenchymal strips and causes bronchoconstriction in intact animals.
3. Enhanced platelet aggregation. TXA₂ activates platelets, inducing aggregation with subsequent stimulation to synthesize and release more TXA₂. This autocrine action leads to further platelet activation.
4. Increased membrane permeability. TXA₂ increases vascular endothelial permeability, possibly via restructuring of the endothelial cytoskeleton. It also causes the breakdown of actin microfilaments, leading to increases in intercellular junction size and loss of microvascular barrier function.
5. Neutrophil activation. TXA₂ is both a chemoattractant and chemoactivator of neutrophils; accordingly, it increases neutrophil oxidative activity and diapedesis.

TXA₂ is usually produced at low baseline concentrations; however, there are a number of triggers that can rapidly

increase its synthesis and release from platelets or white blood cells. The presence of thrombin or contact with collagen can stimulate release of TXA₂ from platelets, and cytokines, complement fragments, and PAF all can directly stimulate release of TXA₂ from white blood cells. Thus, clinical situations associated with increased thromboxane production include vascular injury; arteriosclerosis; conditions associated with complement activation, such as sepsis, dialysis, and ischemia; and cytokine production.

TXB₂ is the metabolite of TXA₂, produced via nonenzymatic hydrolysis. Although it is only one tenth as potent as TXA₂, it does have some degree of biologic activity (e.g., enhancement of endothelial permeability, activation of neutrophils, and promotion of neutrophil diapedesis).

LEUKOTRIENES

Leukotrienes derive their name from their origin and their chemical structure: they are products of leukocytes that have a conjugated triene as their common structural feature. They can be divided into two classes on the basis of differing biologic actions: (1) LTB₄ and (2) the cysteinyl leukotrienes (LTC₄, LTD₄, and LTE₄). The most important actions of the leukotrienes have to do with their central role in allergic and inflammatory diseases.

The primary effects of LTB₄ are neutrophil chemotaxis and activation. Neutrophils activated by LTB₄ exhibit increased oxidative activity, granule release, and enhanced integrin expression. LTB₄ is also weakly chemotactic for eosinophils. The primary effects of the cysteinyl leukotrienes are bronchoconstriction and stimulation of mucus secretion. LTC₄ and LTD₄ are 1,000 times more potent than histamine at causing smooth muscle contraction in human bronchi. LTE₄ also causes bronchoconstriction, but it is less potent. All of the cysteinyl leukotrienes are potent mucus secretagogues. They also contribute to plasma extravasation and tissue edema by increasing vascular permeability.

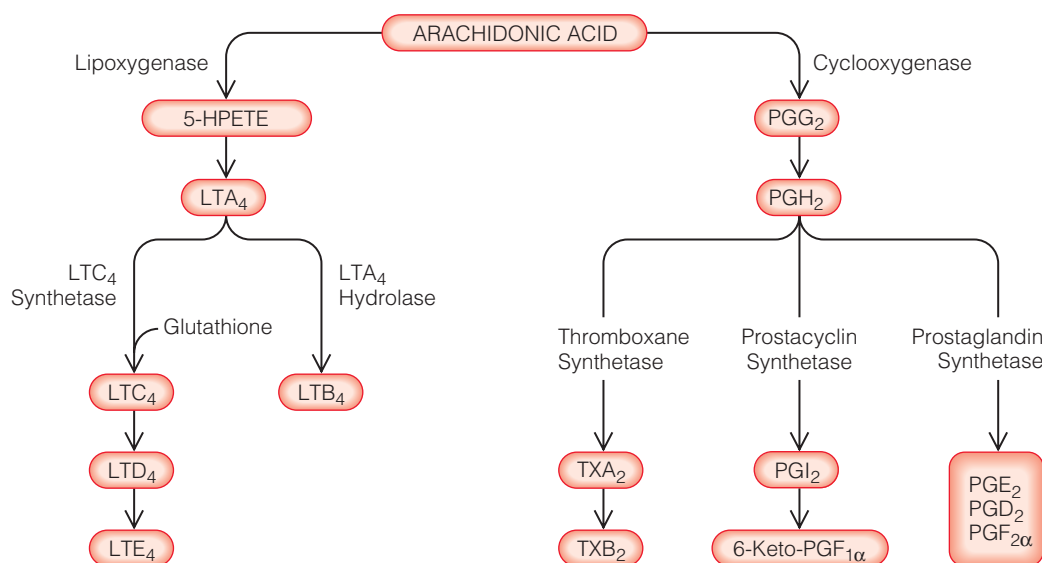


Figure 11 Arachidonic acid is metabolized by two different enzymes, cyclooxygenase (including both COX-1 and COX-2 variants) and lipoxygenase. The products of cyclooxygenase are the prostaglandins and the thromboxanes; the products of lipoxygenase are the leukotrienes.

THERAPEUTIC IMPLICATIONS

Antileukotrienes in Asthma

It is now recognized that the pathogenesis of asthma is more complicated than was previously realized: airway smooth muscle contraction in response to an irritant is only part of a larger overall picture. Asthma has been defined as “a chronic inflammatory disease of the airways,”⁹⁸ in which many cells and cellular elements are involved, particularly mast cells, eosinophils, T cells, neutrophils, and epithelial cells.

Leukotrienes have been shown to play a major role in asthma, producing the characteristic pathophysiologic signs (bronchoconstriction, mucus, airway edema, and cellular infiltration). The clinical manifestations of asthma can be reproduced by administering leukotrienes. Furthermore, increases in bronchoalveolar lavage and urinary leukotriene concentrations have been documented in patients with asthma.⁹⁹

These findings have led to the development of a new class of antiasthma drugs, the antileukotrienes. Two types of antileukotrienes are now in clinical use. The first type, currently exemplified by zafirlukast and montelukast, acts through competitive antagonism of the cysteinyl leukotriene receptor, thereby blocking the action of LTC₄, LTD₄, and LTE₄. The second type, of which zileuton is the only example currently available, competitively inhibits 5-LO, thereby blocking all leukotriene synthesis. Both types are highly effective at moderating asthma: their use leads to improved airway function, less frequent nighttime awakenings, fewer episodes of asthma exacerbation necessitating steroid therapy, and lower required dosages of inhaled steroids. An additional benefit of the antileukotrienes is their ease of use: they are orally administered, are well tolerated, and need be taken only once or twice daily.¹⁰⁰ Routine use of these agents is now recommended as part of the multitiered pharmacologic approach to asthma management.

Whether the antileukotrienes might also be useful in the management of other inflammatory disease states is currently under investigation. Preliminary reports suggest that they might someday play a part in the management of rheumatoid arthritis, systemic lupus erythematosus, urticaria, and atopic dermatitis.

Exogenous Prostaglandins in Obstetric and Gynecologic Settings

Prostaglandins are potent stimulators of myometrial smooth muscle contractility, as are other prostanoids (e.g., TXA₂ and eicosatetraenoic acid). These mediators are thought to play an important—though not yet fully explained—role in normal fetal delivery. Concentrations of certain prostanoids and their metabolites are known to increase before the onset of spontaneous labor and continue to increase during birth. NSAIDs, which inhibit prostanoid synthesis, are known to reduce myometrial contractions and delay or even prevent labor.¹⁰¹ PGE₂ and PGF₂ also induce the cervical ripening that must occur before normal delivery.

Prostaglandin receptors are present on myometrial tissue throughout gestation, unlike many other receptors, such as those for oxytocin, which are only induced in the latter phase of pregnancy. Consequently, therapy with prostaglandins is possible throughout pregnancy. Gemeprost (the methyl ester of PGE₁) and dinoprostone (PGE₂) are currently approved for cervical ripening and labor induction. When given vaginally, they are safe and effective, posing no risk to the fetus even though they cross the placental barrier. These agents are safe in promoting first- and second-trimester terminations, whether used alone or given in combination with mifepristone or methotrexate; moreover,

they are effective for inducing cervical softening before surgical termination of pregnancy.

Cyclooxygenase Inhibition with NSAIDs and COX-2 Antagonists

Management of inflammation Histologically, acute inflammation is characterized by vasodilatation, edema, and early neutrophil accumulation. Production of eicosanoids at the inflammatory site by damaged vessels, leukocytes, and platelets leads to vasodilatation (caused by PGI₂ and PGE₂), increased vascular permeability (caused by TXA₂ and leukotrienes), and neutrophil recruitment and activation (caused by LTB₄ and TXA₂). In addition, LTB₄ is a potent stimulus for production of the proinflammatory cytokines IL-1 and TNF, and PGE₂ gives rise to pain. Eicosanoids have been implicated in the pathophysiology of many inflammatory diseases, including rheumatoid arthritis, ulcerative colitis, Crohn disease, and asthma.

The use of NSAIDs to treat the symptoms of inflammation is a long-standing practice. NSAIDs counteract inflammation by inhibiting cyclooxygenase, thereby decreasing the synthesis of all prostanoids and exerting antipyretic and analgesic effects. NSAIDs are routinely used in the management of chronic inflammatory diseases such as rheumatoid arthritis and are among the most widely prescribed drugs for musculoskeletal conditions and pain. By inhibiting cyclooxygenase, NSAIDs may also effectively redirect arachidonic acid into the lipoxygenase pathway, thus indirectly increasing leukotriene synthesis. This redirection is hypothesized to be the mechanism by which aspirin can trigger asthma in susceptible individuals.

Regulation of blood flow Eicosanoids modulate blood flow to organs and tissues by adjusting local balances between production of vasodilators and production of vasoconstricting components. Loss of these controls, such as occurs when age, diabetes, or atherosclerosis decreases the capacity of the vascular endothelium for PGI₂ production, may impair normal regulatory mechanisms. For example, in occlusive vascular disease, ischemia may cause elevated TXA₂ levels by stimulating the synthesis of TXA₂ by neutrophils and platelets. This would explain why output of TXA₂ is significantly elevated in the clinical settings of unstable angina and acute myocardial infarction and variably elevated after cerebrovascular accidents. Without enhanced PGI₂ production, the resulting vasoconstriction and platelet aggregation may exacerbate ischemia in these settings.

Aspirin, alone among the NSAIDs, causes irreversible methylation of COX-1 and COX-2. It is 50 to 100 times more potent at the COX-1 site than at the COX-2 site. Accordingly, it is capable of permanently eliminating platelets' ability to produce TXA₂ even when given only once daily in low doses; however, to antagonize COX-2, which is largely responsible for inflammation, much higher and more frequent doses are necessary. Platelets, being nonnucleated, are unable to resynthesize COX-1 and COX-2. Because somewhat less than 10% of the platelet population is turned over each day, it takes several days for platelet production of prostanoids to return to normal levels. Nucleated cells, on the other hand, rapidly resynthesize COX-1 and COX-2 enzymes and thus can resume producing prostaglandins a few hours after aspirin administration.

Aspirin, therefore, is antithrombotic when given in small amounts and at wide intervals. When so used, it permits synthesis of vasodilating, antithrombotic prostaglandins while inhibiting platelet synthesis of thromboxane. Accordingly, aspirin has been widely applied to the management of atherosclerotic dis-

ease. One large international trial reported that in patients who took a single 162.5 mg tablet of aspirin daily, starting within 24 hours of a suspected myocardial infarction and continuing for 5 weeks, mortality was reduced by 23%, the incidence of nonfatal reinfarction by 49%, and the incidence of nonfatal stroke by 46%, with no increase in the incidence of either GI bleeding or hemorrhagic stroke.¹⁰² It is now believed that long-term low-dose (75 to 180 mg/day) aspirin therapy may benefit all persons who have unstable angina, have a history of myocardial infarction, or are at risk for ischemic stroke, as well as many other persons at high risk for atherosclerotic events.

Prostaglandins also play an essential role in regulating neonatal circulatory changes. Very soon after birth, the fetal ductus arteriosus starts to contract, thereby reducing the size of the large vascular shunt present in the fetus, which diverts 90% of right ventricular output away from the lungs and into the aorta. In approximately 20% of full-term infants, the ductus arteriosus is functionally closed at 24 hours post partum, and in all, the ductus is closed at 96 hours. The ductus is extremely sensitive to the vasodilatory action of PGE₂. Normally, the high circulating fetal concentration of this prostaglandin decreases after birth; however, in preterm, low-birth-weight infants, this decrease does not occur, and thus the ductus does not close. In these instances, administration of indomethacin is a safe and effective way of promoting duct closure.¹⁰³

There are, however, two groups of patients in whom maintenance of a patent ductus arteriosus is necessary: (1) newborns whose systemic blood flow depends on shunting from the pulmonary artery to the aorta (e.g., those who have an interrupted aortic arch) and (2) newborns whose pulmonary blood flow depends on shunting from the aorta to the pulmonary artery (e.g., those who have pulmonary valve atresia). For both groups, infusions of PGE₁ have proved highly beneficial, enabling resuscitation and stabilization even in the face of major respiratory and electrolyte disturbances.

Prevention of tumors An exciting new potential therapeutic use of NSAIDs derives from epidemiologic studies that document a reduced incidence of colorectal carcinoma in subjects taking aspirin. Of the more than 90 rodent studies of carcinogen-induced and genetically induced colorectal tumors carried out to date, the majority showed definite decreases at all stages of tumorigenesis with NSAID therapy.¹⁰⁴ The results from observational human studies suggest that NSAID therapy is associated with approximately a 40% relative risk reduction with respect to the incidence of colorectal carcinoma. This issue should be clarified further when the results of three ongoing phase III clinical trials of aspirin in colorectal carcinoma prevention become available. COX-2 antagonists have been less well studied, but there is some evidence suggesting that such agents may modify the growth of bladder tumors.

Precisely how NSAIDs exert their antitumor effects is not yet fully understood. Colorectal carcinomas are known to overexpress COX-2 and PGE₂,¹⁰⁵ and it is possible that these agents act to promote cellular proliferation and inhibit cell apoptosis, thereby giving rise to cancer. PGE₂, the eicosanoid most prevalent in GI tissue, has immunosuppressive effects that may reduce tumor surveillance.

Side effects of NSAIDs and development of COX-2 inhibitors The ability of aspirin to cause gastric ulceration and bleeding, originally documented in the first half of the 20th century, is now understood to be attributable to prostaglandin

inhibition. Endogenous prostaglandins play a central role in maintenance of the gastroduodenal mucosal defense barrier by regulating mucosal bicarbonate production, stimulating mucosal blood flow, and modulating epithelial cell proliferation. Oral therapy with misoprostol has proved effective in healing both gastric and duodenal ulcers.

The coxibs, of which rofecoxib and celecoxib are the best-known examples, were developed specifically with the aim of overcoming the ulcerogenic side effects of COX-1 antagonists. The coxibs selectively inhibit COX-2 and thus should be capable of exerting anti-inflammatory effects without interfering with the gastric protection afforded by COX-1 products. To date, they have been at least partially successful in achieving the desired aim. The coxibs are as effective as conventional NSAIDs at treating rheumatoid arthritis and osteoarthritis and reducing pain.¹⁰⁶ In addition, patients receiving coxibs show significantly lower rates of gastric ulceration than patients receiving conventional NSAIDs.¹⁰⁷ Use of coxibs is not, however, without drawbacks. These agents are associated with dyspepsia, though to a lesser degree than conventional NSAIDs are. Moreover, they exert the same delaying effect on ulcer healing that NSAIDs do; this is because both COX-1 products and COX-2 products are necessary for angiogenesis.

Another important side effect of NSAIDs is their nephrotoxicity, which results from interference with prostaglandin-mediated control of local renal vascular flow. PGE₂, PGI₂, and TXA₂ play important roles in regulating the glomerular filtration rate, especially in disease states such as shock, cirrhosis, and congestive heart failure. In these settings, there is a compensatory increase in renal PGE₂ production, leading to improved blood flow. Administration of NSAIDs may cause fluid retention. In addition, NSAIDs are responsible for 20% of cases of drug-induced acute renal failure. To date, the coxibs have not been shown to possess substantial advantages over NSAIDs in regard to nephrotoxicity: they appear to produce the same degree of fluid retention as conventional NSAIDs do, though it is possible that their effect on the glomerular filtration rate is less damaging.

Because TXA₂ is a COX-1 product, the coxibs do not inhibit thromboxane-mediated platelet aggregation. Therefore, it is unlikely that they will be able to reduce the thrombotic complications of vascular disease, as NSAIDs do. Indeed, a recent clinical report indicated that COX-2 inhibitors were associated with a slight but significant increase in myocardial infarction.

Dietary Fatty Acids

The long-chain polyunsaturated fatty acids that are the precursors of eicosanoids cannot be synthesized in the human body and must therefore be supplied through diet. In North America and western Europe, the primary dietary source for eicosanoid synthesis is linoleic acid, the precursor of arachidonic acid. Linoleic acid is found predominantly in vegetable oils. It and its derivatives are termed omega-6 fatty acids because the last of their four double bonds occurs at the sixth carbon atom from the methyl end of the chain. α -Linolenic acid, found in marine fish and to a lesser extent in green vegetables, is the precursor of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are also eicosanoid precursors. These substances are termed omega-3 fatty acids because their last double bond occurs at the third carbon atom from the methyl end of the chain.

The relative prevalence of the various fatty acid precursors has important clinical implications, in that higher proportions of one precursor or another will affect which eicosanoid products

are generated. For example, when EPA is the substrate for cyclooxygenase, TXA_3 , which is biologically inactive, is produced; EPA also competitively binds cyclooxygenase, thereby reducing TXA_2 synthesis. However, PGI_3 synthesized from omega-3 fatty acids is fully active. In this setting, therefore, with thromboxane activity reduced but prostacyclin activity maintained, the overall effects are to increase platelet survival, to reduce platelet aggregation, and to increase bleeding time.

Interest in the possible clinical use of dietary omega-3 fatty acids came from the observation that Greenland Eskimos had a low incidence of myocardial infarction despite eating a high-fat diet.¹⁰⁸ Their plasma and platelet lipids were found to contain a high proportion of omega-3 long-chain polyunsaturated fatty acids. Furthermore, they had hypoaggregable platelets and increased bleeding times. The same effects were noted in other populations who were fed dietary supplements containing omega-3 fatty acids. The potential long-term benefits of increased omega-3 fatty acid intake were suggested by epidemiologic studies in the Netherlands and Japan that showed a reduced incidence of coronary artery disease in men whose diet contained a large amount of fish supplements.^{109,110} Subsequent randomized, controlled clinical trials demonstrated that dietary supplementation with either fish or fish oil conferred significant benefits on men who had recently had myocardial infarctions, reducing the risk of death and especially of sudden cardiac death. In particular, increased dietary intake of omega-3 fatty acids had a potent antidysrhythmic effect, apparently because incorporation of these substances into the myocyte cell membrane increased the stability and lengthened the refractory period of these cells.

Although the precise mechanisms underlying the protective effect associated with dietary omega-3 fatty acids have not been determined, it is likely that reduced TXA_2 production is a major contributor. Altered leukotriene biochemistry may also play a role: the main leukotriene synthesized from omega-3 fatty acids

is LTB_5 , which is less active than LTB_4 . Reduced synthesis of LTB_4 by neutrophils may underlie the observation that fish supplements reduce symptom severity in patients with rheumatoid arthritis. It has also been noted that fewer low-birth-weight children are born in northern European populations, who typically consume substantial amounts of fish, than in non-fish-eating populations. In animal studies, experimental subjects that either are deficient in omega-6 fatty acids or have been fed diets high in omega-3 fatty acid exhibit decreased prostaglandin synthesis and longer gestation periods.

It is believed that early hominids evolved on a diet containing roughly equal proportions of omega-3 and omega-6 fatty acids. In contrast, the typical diet in North America and western Europe today, which is high in dairy, meat, and fried foods, contains 10 to 25 times more omega-6 than omega-3 fatty acids. This relative deficiency of omega-3 fatty acids may be a major cause of the high rates of cardiac and inflammatory diseases recorded in the more developed areas of the world.

Conclusion

Inflammation is a highly complex process that involves many interacting systems, which may complement each other, antagonize each other, or both. A degree of redundancy is built in, so that antagonism of one pathway may lead to augmentation of another alternative inflammatory mechanism. Furthermore, simultaneous or sequential production of both proinflammatory and anti-inflammatory signals often occurs. Accordingly, the success of a therapeutic intervention depends not only on the type of injury or insult present but also on the timing of the intervention. Unfortunately, the clinical trials done to date, evaluating a host of anti-inflammatory agents of different classes, have been largely disappointing. For more successful therapies to be developed, much more information regarding the fundamental mechanisms of the inflammatory response will be needed.

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28 SEVERITY OF ILLNESS SCORING SYSTEMS IN CRITICAL CARE

Mark T. Keegan, MD, and Bekele Afessa, MD

There are approximately 94,000 critical care beds in the United States, and provision of critical care services costs approximately \$80 billion per year. In 2005, critical care consumed 4.1% of national health expenditure and 0.65% of US gross domestic product.¹ Of the approximately 6,000 intensive care units (ICUs) in the United States, 65% are mixed medical-surgical ICUs located in nonteaching community hospitals and only 25% of them are staffed by intensivists.² The enormous costs and the heterogeneity of critical care have led to scrutiny of patient outcomes and cost-effectiveness by a variety of governmental and nongovernmental organizations. Individual critical care practitioners and their hospitals also need to evaluate the care delivered. It is essential to consider the severity of disease when assessing the effectiveness of care delivery. This chapter discusses the models that have been developed for assessment of illness severity and estimation of prognosis in patients admitted to the ICU and delineates systems used for evaluation of organ dysfunction.

Scoring Systems in Medicine

Over many years in medicine and surgery, a variety of tools have been used to quantify the nature of the disease and to estimate the probability of survival. The Killip classification has been used for several decades to stratify patients' severity of illness following acute myocardial infarction (MI).³ Patients are stratified based on the severity of heart failure, if any, after MI. The Pneumonia Severity Index (PSI) and the CURB-65 score were developed and validated to risk-stratify patients with community-acquired pneumonia.^{4,5} CURB-65 scores are based on the presence or absence of confusion, elevated blood urea nitrogen (BUN) or respiratory rate, decreased systolic or diastolic blood pressure, and age over 65 years.⁵ National and international professional societies have incorporated the pneumonia severity scores in their guidelines to aid physicians in the decision-making process.^{6,7} Although a recent study showed poor performance in predicting severity, Ranson's criteria have been used for many years to determine the severity of acute pancreatitis.⁸⁻¹⁰ The Child-Pugh classification has been used to determine the severity of liver disease but has now been replaced by the Model for End-stage Liver Disease (MELD) scoring system.^{11,12} MELD uses patients' laboratory values of serum bilirubin and creatinine and the international normalized ratio for prothrombin time (INR) to predict survival in chronic liver disease.¹² It is currently used by the United Network for Organ Sharing (UNOS) in prioritizing allocation of deceased donor organs for liver transplantation. Furthermore, two of the most widely used systems include the Apgar score for neonates and the

American Society of Anesthesiologists (ASA) classification system for surgical risk, both of which have been available for decades.^{13,14}

Critical Care Systems

Single and multiple organ severity assessment systems have been used in the critical care setting for several years. The Murray score was developed to assess the extent of acute lung injury in the critically ill.¹⁵ Similarly, the Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) and Acute Kidney Injury Network (AKIN) criteria are used to describe the severity of acute kidney injury.^{16,17} A variety of scoring systems have been developed to quantify dysfunction of multiple body systems. These "organ failure models" (discussed further below) include the Multiple System Organ Failure (MSOF) score, Multiple Organ Dysfunction Score (MODS), Sequential Organ Failure Assessment (SOFA) score, and Logistic Organ Dysfunction Score (LODS).¹⁸⁻²¹

The first ICU model used to assess patients' overall disease severity was the Therapeutic Intervention Scoring System (TISS).²² TISS was developed as a method to evaluate nursing workload. It reflects severity of illness on the basis that more severely ill patients require more frequent nursing interventions. TISS was not designed as a prognostic model and is now rarely used for severity assessment. Newer nursing workload models have been developed.

During the last three decades, several physiologically based ICU prognostic models have emerged, mainly focused on predicting hospital mortality [see Table 1]. The main prognostic models for assessing the overall severity of illness in critically ill adults are the Acute Physiology and Chronic Health Evaluation (APACHE), Simplified Acute Physiology Score (SAPS), and Mortality Probability Model (MPM).²³⁻³⁵ Each system is discussed in detail below.

Table 1 Three Main Intensive Care Unit Prognostic Models

Generation	APACHE	SAPS	MPM
First	APACHE I ²³		
Second	APACHE II ²⁴	SAPS I ²⁶	MPM I ²⁸
Third	APACHE III ²⁵	SAPS II ²⁷	MPM II ²⁹
Fourth	APACHE IV ³⁴	SAPS 3 ^{32,33}	MPM III ⁶⁷

Adapted from Afessa B et al.³⁵

APACHE = Acute Physiology and Chronic Health Evaluation; MPM = Mortality Probability Model; SAPS = Simplified Acute Physiology Score.

Development, Validation, Performance, and Customization of the Models

MODEL DEVELOPMENT AND VALIDATION

A prognostic model includes one or more outcome and several predictor variables. Each of the predictor and outcome variables should be clearly and precisely defined.³⁶ The process for the development of a good prognostic model requires the identification of reliable predictor variables, collection of data on the predictive and outcome variables, and analysis of the relationship between the predictor and outcome variables.³⁶ Predictor variables entered in a model should be routinely available, reliable, and independent of ICU intervention (to eliminate treatment effect). The predictor variables in the adult ICU prediction models are selected and scored subjectively by expert consensus or derived objectively using statistical methods. Commonly used predictor variables include age, comorbidities, physiologic abnormalities, acute diagnoses, and lead-time bias. The main outcome measure is usually short-term (in-hospital) mortality, although 28-day mortality and 6-month mortality have also been proposed as outcomes of interest. The APACHE III and IV models have also included the length of ICU and hospital stay, duration of mechanical ventilation, and need for active treatment as outcome measures.^{34–39} A prognostic model derived from relatively few medical centers and a small sample size is unlikely to produce generalizable, stable, and reliable performance. For acceptable external validity, the development of an ICU prognostic model requires a large database compiled from representative ICUs. The model should include the main prognostically important predictor variables, and these should be tested for their independent contributions and interactions.³⁵

Model development usually involves the statistical technique of logistic regression, which is suitable for the prediction of dichotomous outcomes such as death. The logistic function in a logistic regression analysis links predictor (independent) variables (e.g., age, disease, and blood pressure), denoted by x , to the outcome (dependent) variable (i.e., probability of death) by a series of coefficients (denoted by β). The natural logarithm ($\ln$) of the odds of death = $\beta_0 + \beta_1(x_1) + \beta_2(x_2) + \beta_3(x_3) + \dots$. The odds ratio of death for each unit increase in x_1 is e^{β_1} . The parameters (coefficients) of the logistic function are usually determined by maximum likelihood estimation using iterative algorithms.⁴⁰ The sign and the magnitude of the coefficients provide an indication of how strongly each predictor is associated with an increased risk of the outcome in question. Less commonly, neural networks and bayesian analyses may be used in model development.^{41,42}

The value of a prognostic model does not depend solely on its successful prediction in the initial development data.⁴³ The relation between the predictor and outcome variables of the development model should be validated in a new independent database.³⁶ A 1994 consensus conference in intensive care medicine recommended that discrimination and calibration should be assessed on both training (development) and test (validation) data.⁴⁴ Internal validation usually involves splitting one data set into two parts, developing the model in the first part, and validating it in the second.⁴³ Given that the validation set originates from the same population as the

development set, the results may not be reproducible in other populations. Temporal validation involves evaluating the performance of a model on subsequent patients from the same medical center.⁴³ Temporal validation is similar to internal validation by splitting a single data set by time. The generalizability of a model requires external validation, using new data from patients of different medical centers.

MODEL PERFORMANCE

A mortality prognostic model must differentiate between survivors and nonsurvivors and be well calibrated (accurate throughout all risk ranges) and reliable (provide identical and reproducible estimates for an individual patient independent of the observer).⁴⁵ It also has to be periodically updated to reflect the change in medical practice and case mix over time.^{35,46,47} The performance of the ICU prognostic models is assessed by the area under the receiver operating characteristic curve (AUC) for discrimination and the Hosmer-Lemeshow statistic for calibration.^{35,36,48–53} Some advocate the addition of R^2 as part of model evaluation.³⁶ The AUC is the measure of how well a model differentiates between groups—for example, between survivors and nonsurvivors. A model that performs perfectly will have an AUC of 1. An AUC of 0.5 indicates that the model predicts no better than chance. AUCs of 0.9 to 0.99, 0.8 to 0.89, 0.7 to 0.79, 0.6 to 0.69, and less than 0.6 represent excellent, very good, good, moderate, and poor discrimination, respectively [see Figure 1].⁵⁴ Calibration refers to the correlation between the predicted and actual outcome for the entire range of risk and is assessed by the Hosmer-Lemeshow H or C goodness-of-fit statistic.⁵⁵ The Hosmer-Lemeshow statistic is performed by grouping subjects into deciles of risk. The Hosmer-Lemeshow C statistic is based on 10 equal-sized groups, whereas the Hosmer-Lemeshow H statistic is based on fixed cutpoints.^{36,49,56} The calibration is considered good if the Hosmer-Lemeshow statistic p value is greater than .05 (i.e., not significant) and the C or H statistic is close to the degrees of freedom (usually 8) [see Figure 2]. The Hosmer-Lemeshow statistic is affected by sample size.^{57,58} The p value may be less than .05, suggesting falsely poor calibration, in very large samples and the opposite (falsely good calibration) in small samples, leading to inappropriate estimation of the calibration. Calibration can also be investigated by plotting the observed proportion of events against the predicted.⁵² If the observed proportion of events and the predicted probabilities agree over the whole range of risks, the plot will show a 45° line and slope of 1.⁵² R^2 represents the proportion of outcome variance explained by the model. The theoretical upper limit of R^2 is 1. For predicting hospital or 30-day mortality, the R^2 statistics reported by most models range from 0.045 to 0.388.³⁶

CUSTOMIZATION

Because of changes in case mix and clinical practice, the performances of prognostic models deteriorate over time.⁵⁶ To counterbalance the deterioration, models are often subjected to customization by creating a new equation (level 1 customization) or changing the weights of the constituent variables (level 2).^{59,60} At times, the addition of new predictor variables may be needed during customization.^{61,62} Models with performances that are good overall may not perform as well for regional or other subgroups.⁶³ The SAPS 3 model uses customized equations for the different regions to

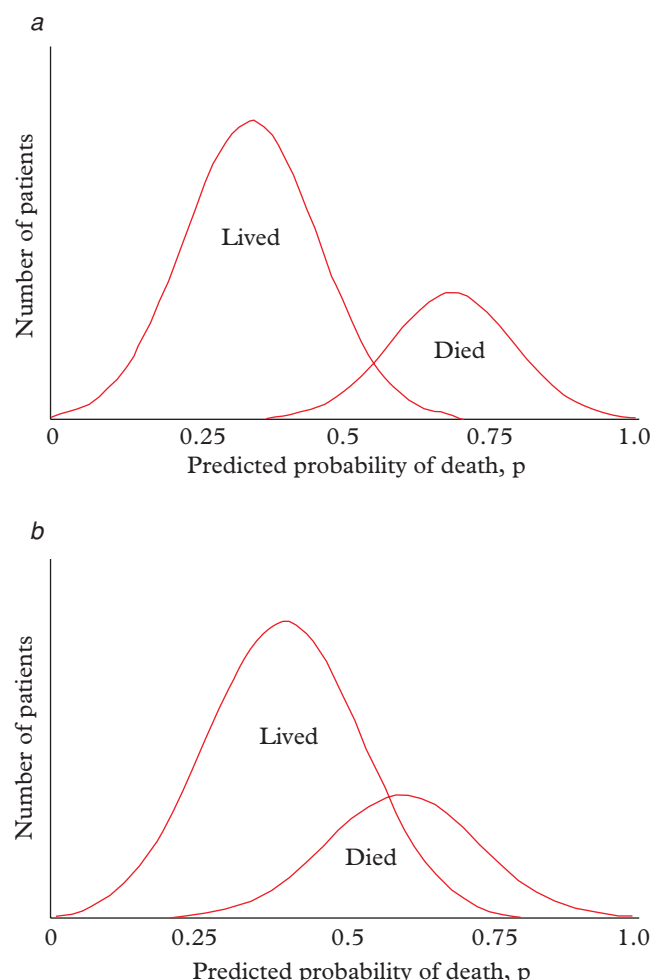


Figure 1 The distribution of predicted risk of death using two different prediction models among a population of patients who ultimately are observed to either live or die. In (a), the majority of the patients who died had a predicted probability of dying that was much higher than the majority of the patients who lived; it was able to “discriminate” between those who would live and die. In contrast, (b) represents a model that is poorly discriminant; the large central overlap reveals that the model does not easily discriminate who will live and who will die over a wide range of predicted probabilities of death. Adapted from Barnato AE and Angus DC.²⁰⁹

maintain its performance.^{32,33} Even the customized SAPS 3 equations are already undergoing further customization for region-specific benchmarking purposes.^{64,65} Recent data suggest that MPM₀ III may not be significantly affected by case mix.⁶⁶ However, highly specialized ICUs and studies of homogeneous cohorts of critically ill patients may benefit from use of customized models.⁶⁶

Adult ICU Prognostic Models

The main adult ICU prognostic models include APACHE, SAPS, and MPM.^{23–35} SAPS and MPM have been updated to their third versions and APACHE to its fourth version [see

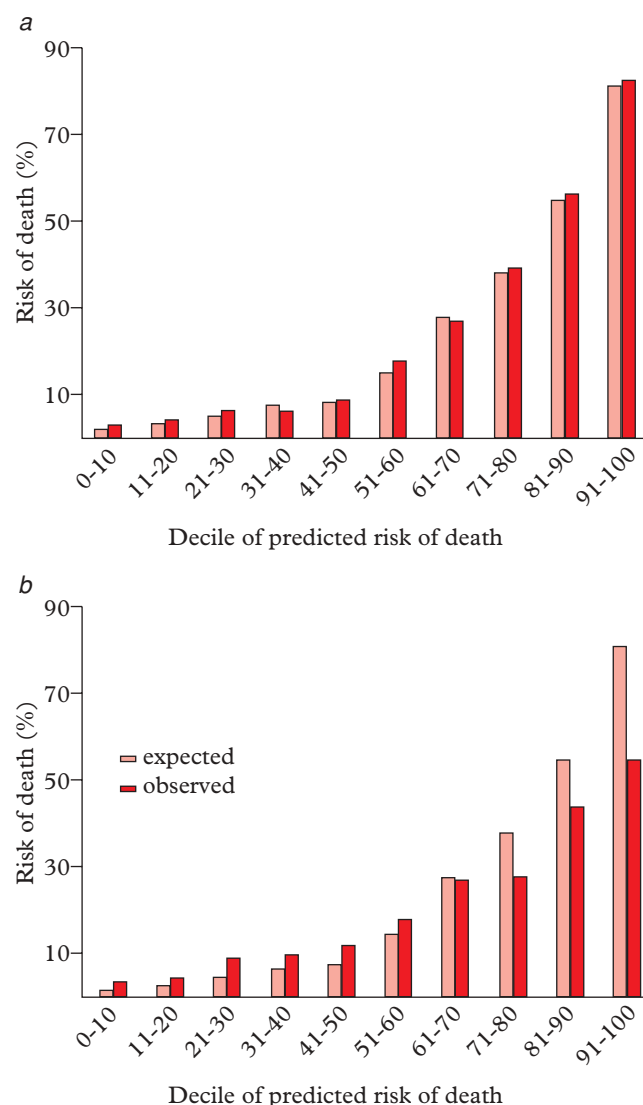


Figure 2 Both (a) and (b) compare “expected” deaths (based on the expectation that the predicted probability from the model is correct) to observed deaths within each of the 10 deciles of predicted risk. In (a), the expected and observed proportions of deaths in each decile are well matched, and the model is well calibrated. In contrast, (b) depicts a prediction model that does not perform well at the extremes; it overpredicts risk among patients in the lower risk deciles and underpredicts risk among patients in the higher risk deciles. For the model in (b), the sum of the squared differences between observed and expected deaths will be large, and the model will have a large Hosmer-Lemeshow C statistic and a small *p*, suggesting poor calibration. Adapted from Barnato AE and Angus DC.²⁰⁹

Table 1 and Table 2].³⁵ SAPS, MPM, and the earlier versions of APACHE focus on predicting mortality.³⁵ In addition to predicting mortality, the latest versions of APACHE (III and IV) provide predictions for ICU and hospital length of stay, duration of mechanical ventilation, risk of needing an active treatment during ICU stay, probability of pulmonary artery catheter use, and potential transfer from the ICU.^{34,35,37,38}

Table 2 Study Characteristics and Performance of the Fourth-Generation Prognostic Models

Characteristics	SAPS 3 ^{32,33}	APACHE IV ³⁴	MPM ₀ III ⁶⁷
Study population	16,784	110,558	124,855
Study period	Oct. 14–Dec. 15, 2002	Jan. 1, 2002–Dec. 31, 2003	Oct. 2001–Mar. 2004
Number of ICUs	303	104	135
Number of hospitals	281	45	98
Geographic regions	35 countries, 5 continents	USA	USA
Time of data collection	± 1 hr of ICU admission	24 hr of ICU admission	Within 1 hr of ICU admission
Variables in the model	20	142	16
Missing data	1 per patient		
Reliability	Excellent		
AUC	0.848	0.88	0.823
H-L C statistic	14.29	16.9	11.62
H-L P value	0.16	0.08	0.31
SMR	1.0	0.997	1.018

Adapted from Afessa B et al.³⁵

AUC = area under the receiver operating characteristic curve; H-L = Hosmer-Lemeshow; SMR = standardized mortality ratio.

ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION (APACHE)

APACHE was developed three decades ago.²³ The first APACHE model consisted of a large number of physiologic variables, and its performance was not subjected to robust statistical analyses. It is rarely mentioned in the medical literature, except for historical reasons. The APACHE II model used fewer physiologic measurements and became the ICU prognostic model most widely quoted in the medical literature.²⁴ APACHE III was developed from a database of 17,440 patients from 66 hospitals, 26 of them randomly selected to represent hospitals in the United States with more than 200 beds.²⁵ The model includes age, seven chronic health conditions, an acute physiology score (APS) derived from 17 physiologic variables, admission diagnosis category, and patients' location prior to ICU admission. For each of the physiologic variables, the worst value within the first 24 hours after ICU admission was included. The APACHE investigators also developed a real-time ICU database and scoring system that could be deployed in individual institutions and interfaced with existing ICU information systems. Patient age, chronic health conditions, and APS are combined to generate an APACHE III score, the basic severity indicator. The source of admission and admission diagnosis are then integrated with the APACHE III score to provide a prediction of mortality [see Figure 3]. Despite its excellent performance and potential for use, APACHE III was narrowly disseminated because the logistic regression coefficients and equations were proprietary and unavailable for the public unless with permission for research.

APACHE IV was developed from data collected on 110,558 patients in 104 ICUs of 45 non-randomly selected hospitals in the United States.³⁴ Of the most commonly used prognostic models, APACHE IV includes the largest number of variables. The APS variables and the seven chronic conditions of APACHE IV are the same as those of APACHE III, but new

diagnostic categories and new statistical techniques (use of “splines”) have been included. The explanatory powers of the APACHE IV model are attributable to acute physiology (65.6%), age (9.4%), chronic health conditions (5.0%), admission variables (2.9%), ICU admission diagnosis (16.5%), and use of mechanical ventilation (0.8%).³⁴

SIMPLIFIED ACUTE PHYSIOLOGY SCORE (SAPS)

SAPS was developed on data from eight ICUs in France.²⁶ The original model included age and 13 physiologic variables. SAPS II was developed on a data set of 13,152 patients from 137 ICUs in 12 countries.²⁷ Seventeen variables were entered to create the SAPS II model: 12 physiologic variables, age, type of admission (scheduled surgical, unscheduled surgical, or medical), and three underlying disease variables (AIDS, metastatic cancer, and hematologic malignancy). Specification of a primary diagnosis was not required.

SAPS 3 was developed in cooperation with the European Society of Intensive Care Medicine from data collected from 16,784 patients in 303 ICUs from five continents.^{32,33} The hospitals volunteered to participate in the model development. The SAPS 3 model includes fewer variables than APACHE IV, and in contrast to APACHE, SAPS 3 is based on data obtained within 1 hour of patients' admission to the ICU. Unlike APACHE IV, the explanatory powers of the SAPS 3 model were mostly attributable to the patients' characteristics before ICU admission (50% of the predictive ability) and the circumstances of ICU admission (22.5%) and less dependent on the physiologic abnormalities at ICU admission (27.5%). The original description of SAPS 3 provided logistic regression equations customized for the different geographic locations.

MORTALITY PROBABILITY MODEL (MPM)

The first MPM was created from a small number of easily available variables.²⁸ The development model was derived

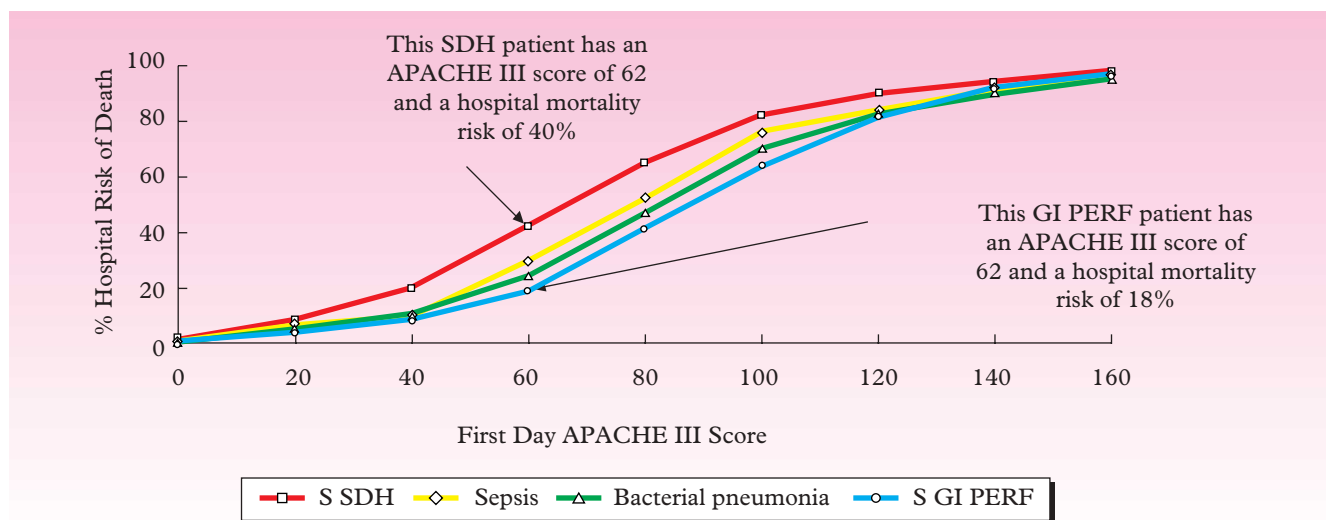


Figure 3 This figure illustrates the importance of disease in the risk of death equation. Four patients with different diagnoses are displayed. On the x-axis is the first-day APACHE III score. On the y-axis is the hospital risk of death. Despite having a similar first-day APACHE III score of 62, each patient (or, strictly speaking, cohort of patients) has a very different risk of hospital mortality. Adapted from Knaus WA et al.²⁵ GI PERF = gastrointestinal perforation; S = surgical procedure; SDH = subdural hematoma.

from data of 755 patients from the ICU of a single medical center. MPM I assigned weights to the predictor variables based on statistical techniques rather than expert opinions. MPM I had two models: MPM₀ I, based on data obtained at ICU admission, and MPM₂₄ I, based on data obtained within 24 hours of ICU admission.²⁸ The training and development sets of MPM₀ II included 12,610 and 6,514 patients, respectively, from 12 countries.²⁹ Fifteen variables were used in the admission model, MPM₀ II, and 12 variables in the 24-hour model, MPM₂₄ II. MPM₀ II produces a probability estimate of death available at ICU presentation, independent of ICU interventions, and does not require specifying a diagnosis. Models based on data collected at 48 hours, MPM₄₈ II, and 72 hours of ICU admission, MPM₇₂ II, were also developed for predicting mortality on the second and third ICU days.³⁰

MPM₀ III was developed from data of 124,855 patients from the United States.⁶⁷ Only five acute diagnoses (presence or absence of acute renal failure, cardiac dysrhythmia, cerebrovascular accident, gastrointestinal bleeding, and intracranial mass lesion) and three physiologic variables (coma, heart rate ≥ 150 beats/min, and systolic blood pressure ≤ 80 mm Hg) were included in the model.⁶⁷ To these were added age; the presence or absence of chronic renal insufficiency, cirrhosis, or metastatic neoplasm; the use of cardiopulmonary resuscitation before ICU admission; the use of mechanical ventilation; and surgical status. MPM₀ III is based on data obtained within 1 hour of ICU admission and, in addition to the parameters mentioned above, includes “do not resuscitate” status. It is the only “fourth-generation” model to include “code status” as a predictor variable.

FOURTH-GENERATION ADULT ICU PROGNOSTIC MODELS

Studies from several countries evaluating the performance of the older generations of the adult prognostic models had shown that, overall, discrimination was good but calibration

was poor.⁴⁰ Customization was attempted to maintain good performance of the models over time. However, the initial improvement in the performance of the older models with customization was not maintained because the older models no longer reflected current case mix, practice patterns, and treatment, necessitating the development of the fourth-generation models.^{32–34,67} All three fourth-generation prognostic models (APACHE IV, SAPS 3, MPM III) excluded readmissions in their development and assumed missing values to be normal. Although the performances of each of these models appear to be good, there are differences. Data for SAPS 3 were collected as part of a research project specifically designed to develop the model. The data for APACHE IV and MPM III were obtained from ICUs that had bought the APACHE or Project Impact Critical Care systems (both owned by Cerner Corporation, Kansas City, MO) as part of their efforts for performance improvement. Given that institutions that participated in the development of these models were not randomly selected and were likely to have more interest in research and performance improvement, the findings may not apply to other ICUs.⁶⁸ Given that several medical centers continue to participate in Cerner Corporation-owned APACHE and Project Impact activities, upgrades and newer versions are likely to be developed when APACHE IV and MPM III show performance degradation.⁶⁹ So far, the focus of SAPS 3 has been on highlighting the need for institutional or regional customization.^{64,65,70–75}

MPM₀ III and SAPS 3 are based on data obtained within 1 hour of ICU admission. Thus, they can be used to assess the severity of illness before ICU interventions take place. They avoid contamination of data by patients who are allowed to deteriorate after ICU admission. Limiting data to those obtained within 1 hour of ICU admission may not adversely affect the performance of MPM₀ III because the variables included in the model are easily available and do not require

special laboratory testing. However, the unavailability of some physiologic data may compromise the performance of SAPS 3.⁷⁶ Because of the multiplicity of data to be collected, missing data may have the highest impact on the performance of APACHE IV and the lowest impact on MPM₀ III.

The predictors of MPM₀ III include age and 15 easily available binary variables. Only five acute diagnoses are included in the MPM₀ III model. The SAPS 3 model includes 20 variables, six of which require laboratory testing [see Table 3]. APACHE IV consists of 142 predictor variables, 10 of them requiring laboratory testing. Vital signs, urine output, and Glasgow Coma Scale (GCS) score are almost always measured in critically ill patients. However, there is no standardized laboratory testing in most individual ICUs, let alone nationally or internationally. The lack of standardization may adversely affect the performance of ICUs that do not routinely perform certain laboratory tests and may also compromise the performance of the prognostic models. Although the characteristics of MPM₀ III may help minimize errors arising from the misclassification of the diagnosis and missing or incorrect data entry, the exclusion of prognostically important variables from the model may lower its performance.⁷⁶

Several ICUs use computer interfaces with their laboratory and bedside monitor systems to extract data. Others still enter data manually. SAPS 3 was calibrated for manual acquisition of data. The performance of ICUs as measured by the severity models and the performance of the prognostic models in predicting outcome is likely to be compromised by the lack of uniformity in data acquisition. Compared with data entered manually, data extracted automatically by computerized information systems are likely to lead to higher severity of illness and predicted mortality.⁷⁷ Based on the recent advances in information technology, automating ICU risk adjustment is not only possible but also preferable.^{78,79}

All patients included in the development of APACHE IV and MPM III were from the United States. In contrast, patients from five continents were included in the development of SAPS 3, although most were from Europe. With its customized models, SAPS 3 appears to be a good candidate for an international benchmark. However, the number of patients included from some of the countries is very small and the results may not be generalizable.

The calibration of the initial fourth-generation models was good. The AUC of SAPS 3, APACHE IV, and MPM₀ III were 0.85, 0.88, and 0.82, respectively.^{32–34,80} All three fourth-generation models need external validation in independent data sets with a large sample size and a good patient mix. There are external SAPS 3 validation data from different countries. However, most of these data are limited to small sample size and narrow patient case mix.^{70,72–75,81–83} A recent SAPS 3 external validation study of 28,357 patients from 147 Italian ICUs showed good discrimination but poor calibration.⁷¹ Similar findings were noted in an Austrian multicenter study.⁶⁴ APACHE IV and MPM₀ III were validated in a multicenter study of 11,300 ICU patients from California.⁸⁴ MPM₀ III was recently validated on 55,459 patients from 103 ICUs—25 of which did not participate in the original development—with good discrimination and calibration.⁶⁹ The fact that all three fourth-generation models are free of charge may increase their use for research, health care delivery, and performance measurement. APACHE IV is the most complex and may require software support. MPM₀ III is the least complex.

Model Use

Knowledge about the probability of clinical outcome has the potential to help hospital administrators, clinicians, patients, and families select treatment options, taking into

Table 3 Variables Included in the Fourth-Generation Prognostic Models

Predictive Variable	SAPS 3 ^{32,33}	APACHE IV ³⁴	MPM ₀ III ⁶⁷
Age	Yes	Yes	Yes
Length of hospital stay before ICU admission	Yes	Yes	No
ICU admission source	3	8	No
Type of ICU admission	Yes	Yes	Yes
Chronic comorbidities	6	7	3
CPR before ICU admission	No	No	Yes
Resuscitation status	No	No	Yes
Surgical status at ICU admission	Yes	Yes	No
Anatomic site of surgery	5	No	No
Reasons for ICU admission/acute diagnosis	10	116	5
Acute infection at ICU admission	Yes	No	No
Mechanical ventilation	Yes	Yes	Yes
Vasoactive drug therapy prior to ICU admission	Yes	No	No
Clinical physiologic variables	4	6	3
Laboratory physiologic variables	6	10	0

Adapted from Afessa B et al.³⁵
CPR = cardiopulmonary resuscitation; ICU = intensive care unit.

Table 4 Potential Uses of Adult Intensive Care Unit Prognostic Models

National level
Benchmarking
Institution level
Internal use of quality improvement efforts such as comparing performance of a hospital against the national average
Institutional self-monitoring for competitive or contractual reasons
Monitoring by regulatory agencies and payors
Adjustment of outcomes in clinical trials
Helping patients select among different hospitals
Physician level
Quality improvement for individual physician
Institution's use of outcome information on individual physicians
Help patients select physician
Use of persistent poor performance for sanctions or license withdrawal
Patient level
Help patients in the decision-making process
Resource allocation

account costs and potential benefits. Rising costs of health care and concerns about quality of care have led to efforts aimed at determining outcome associated with medical services. Quality of care is often measured by comparing observed and predicted outcomes. Discordance between the predicted and observed outcomes is considered to indicate better or worse than average quality of care. The ICU adult prognostic models are attractive to measure the predicted mortality rates in the critically ill. However, the prognostic models have to jump several hurdles before they are applied to assess quality of care.³⁵ The cost of their implementation should be reasonable. The predictor variables included in the model should be resistant to manipulation and subjectivity. The models should be reliable and valid. The use of the prognostic models for clinical purposes requires caution. There are several factors—such as patients' preferences for life support and response to disease, the surrounding environment, and effect of treatment—that influence outcome and may have not been included in the prognostic models.⁴⁰ Despite their limitations, the predictive models have potential uses at the national, hospital, physician, and patient levels [see Table 4].³⁶

BENCHMARKING

It is possible that some ICUs save more lives than others. Clinicians and investigators need to know why.⁸⁵ Informing the public, transparency, and severity-adjusted outcome measures linked to the process of care are likely to lead to this path. *US News and World Report* has been ranking thousands of hospitals in the United States for several years.⁸⁶ Thomson Reuters produces yearly reports of what it deems to be the top 100 US hospitals.⁸⁷ Several Web sites claim to provide physician ratings, and ICUs have been ranked based on their performances. Most of these rankings are based on administrative data. The Centers for Medicare and Medicaid Services (CMS) is planning to transition from a fee-for-service payment systems, which pays on the basis of quantity and consumption of resources, to value-based purchasing, which aligns payment directly to the quality and efficiency of care (pay for performance).

Severity-adjusted mortality rates are increasingly used to assess the quality of critical care provided by hospitals and physicians. Compared with the severity models derived from administrative data, the ICU adult prognostic models are better tools for risk-adjusted quality assessment. If continuous attempts are made to upgrade the models in a timely fashion to reflect changes in case mix and practice, the fourth-generation models are well positioned for use as ICU benchmarks. Although not yet implemented, the Joint Commission has a plan requiring hospitals to publicly report their risk-adjusted mortality and length of stay as part of the ICU quality core measures.⁸⁸ Some states have already started participating in ICU prognostic model severity-adjusted benchmarking.^{84,89}

Because mortality is the most objective outcome measure and not prone to error, the standardized mortality ratio (SMR) is widely used to evaluate performance. The SMR is the ratio of the observed to the predicted mortality. The SMR should be reported with its 95% confidence intervals (CI).⁵¹ If the 95% CI of the SMR includes 1, the performance is considered average. If the 95% CI does not include 1, SMRs less than 1 and greater than 1 are considered indicative of good and poor performances, respectively. Similar measures can be established for other outcomes, such as length of stay and duration of mechanical ventilation.⁹⁰ A number of studies have demonstrated that SMRs may be influenced by case mix in addition to differences in the quality of ICU care.⁴⁰

Benchmarking helps identify variations in clinical outcome and changes in practice patterns over time.⁹¹ The appropriate application of benchmarking at the national and community levels may provide reliable information to regulatory agencies, payors, health care providers, and patients. However, it requires buy-in by governments, payors, hospitals, health care providers, and the public. Moreover, because case mix and patient location before ICU admission ("lead-time bias") influence SMR, the performance of a prognostic model needs to be validated for differences in case mixes and patient locations prior to ICU admission before its use for benchmarking.⁹²⁻⁹⁵ Over two decades ago, hospitals, physicians, and employers from the Cleveland metropolitan area formed the Cleveland Health Quality Choice to implement a standardized measurement system to evaluate patient outcome in the ICU.⁹¹ They used the APACHE III prognostic system for severity adjustment. Although the overall study was compromised by the use of a nonrecalibrated model and changing hospital discharge practices, it highlighted the feasibility of community-based benchmarking. Hospital discharge practices influence hospital mortality. In a multicenter study from California, Vasilevki and colleagues described the association between acute care hospital transfers and early postdischarge mortality and recommended using SMR based on 30-day, instead of hospital, mortality.⁸⁹ Benchmarking provides opportunities to improve performance based on the findings from good and bad performers.^{90,96-99} The use of adult ICU models for benchmarking should be limited to regions in which they have been shown to perform well. The fourth-generation models are based on data obtained several years ago. From the last three decades of experience with the adult ICU prognostic models, we have learned that their performances deteriorate over time. For appropriate

benchmarking, the performances of the models need to be evaluated periodically and updated when needed. To the best of our knowledge, the APACHE group is the only one that routinely upgrades the model based on current data. Appropriate benchmarking also depends on accurate data entry, with external auditing and freedom from internal manipulation.

Although the ICU prognostic models have focused on mortality, other important outcome measures can be used for benchmarking. The APACHE prognostic system has models for predicting ICU length of stay and duration of mechanical ventilation.^{34,37,38,100} The MPM researchers introduced and subsequently revised a two-dimensional graphical tool (Rapoport-Teres graph) for benchmarking performance and resource use [see Figure 4].^{101,102} The Rapoport-Teres graph is constructed by plotting the normalized differences between actual and predicted survival rates (Standardized Clinical Performance Index) on the x-axis and normalized differences expected and actual weighted hospital days values (Standardized Resource Use Index) on the y-axis.^{101,102} The APACHE III database also provides accessories to track low-risk monitor admissions and readmissions.^{39,90,103}

PERFORMANCE IMPROVEMENT

Performance improvement requires data collection for measuring outcome, adjusted for confounding variables. A well-performing prognostic model helps make meaningful comparisons of a hospital's current performance with its past. This will allow hospitals to identify their weaknesses and initiate interventions aimed at quality improvement and allow patients and third-party payors to choose health care providers based on performance. The ICU prognostic models may facilitate the accreditation process by external organizations, such as the Joint Commission. The ICU severity models may also serve as tools for evaluation of the impact of new therapies as well as organizational and process of care changes.^{90,96,103}

The APACHE Critical Care series and Project Impact have taken the prognostic models to a higher level by adding accessories to track readmission, sentinel event, TISS, reimbursement, and resource consumption.¹⁰⁴ They regularly provide standardized and customized reports of outcome. Based on data from the APACHE III database, Zimmerman and colleagues highlighted the policies and practices of ICUs with low mortality rate and efficient resource use.⁹⁰ Defining

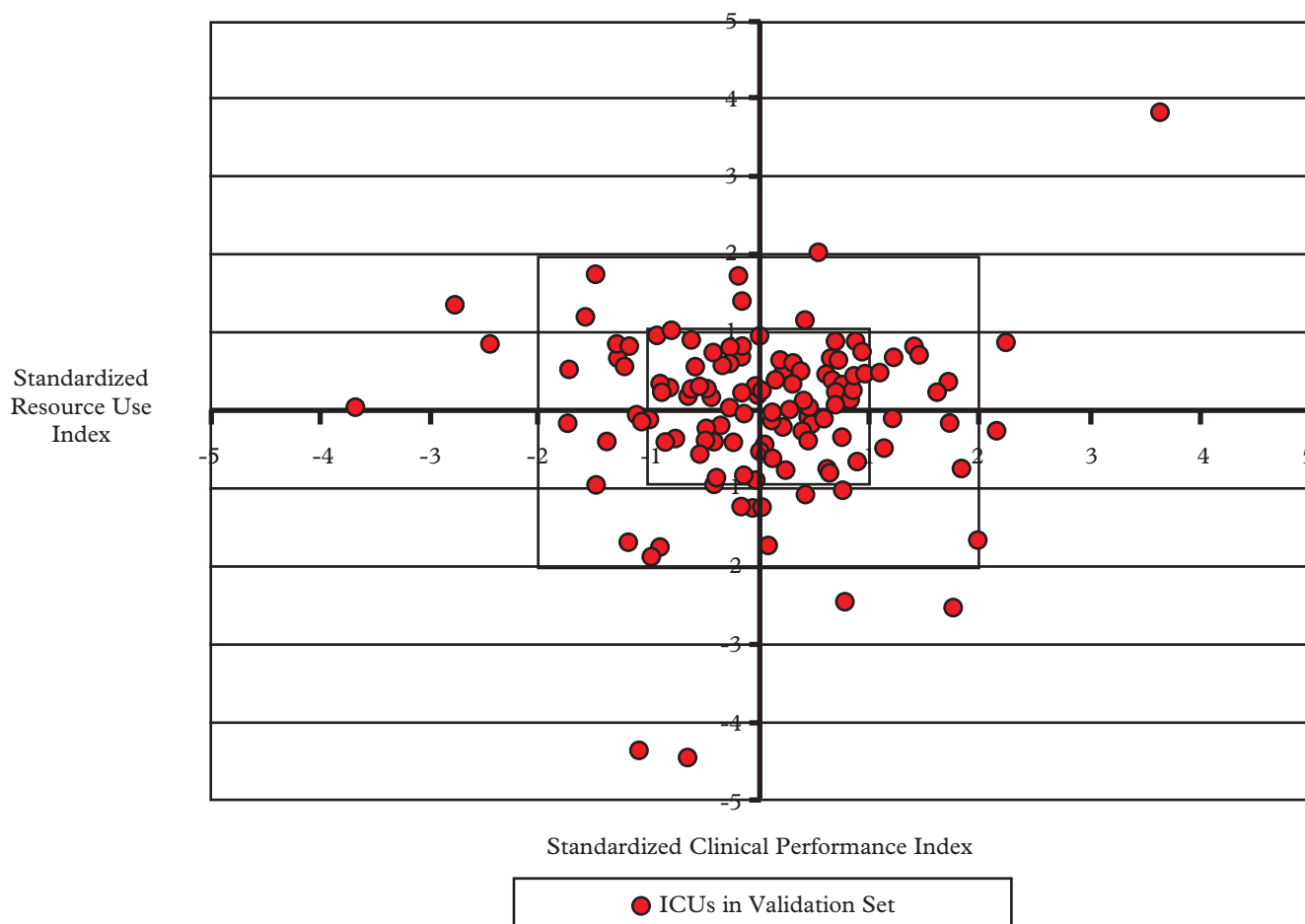


Figure 4 The revised Rapoport-Teres graph for intensive care units (ICUs) in the Project IMPACT validation set. Rectangles mark 1 and 2 standard deviations from the origin. Adapted from Nathanson BH et al.¹⁰¹

good performance by low SMR, short adjusted ICU length of stay, and low ICU admission rate for low-risk monitoring, they described the structural characteristics and process of care in ICUs with good performance.

RESOURCE USE

Accurate estimation of severity of illness has the potential to help in the appropriate allocation of scarce ICU resources. Unsalvageable patients and patients who require simple monitoring can be discharged from the ICU. However, current models are far from perfect to support such decisions and have not been validated for these purposes. Using APACHE III data, Seneff and colleagues reported an accurate prediction of the average duration of mechanical ventilation for groups of ICU patients.³⁸ The MPM researchers developed and updated models for predicting patients' weighted hospital days.^{101,102} If validation shows good performance, such predictions may be useful for resource allocation. Using demographic, physiologic, and treatment information obtained during the first 24 hours in the ICU and over the first 7 ICU days of the APACHE III database, Zimmerman and colleagues identified low-risk patients who were unlikely to require active ICU treatment.³⁹ Such capability can be used to assess ICU resource use and develop strategies for providing care in intermediate (or progressive) care units at a reduced cost. Even in the best performing ICUs, 10 to 38% of the admissions are for low-risk monitoring.⁹⁰ The APACHE prognostic system provides prediction for next-day need of life support. Such predictions can supplement physicians' judgment to improve ICU discharge decisions.¹⁰⁵

CLINICAL DECISION SUPPORT

Some of the organ- or disease-specific prognostic models are used as adjuncts for clinical decision making in non-ICU settings. For example, the adoption of the MELD score as the determinant of donor organ allocation for liver transplantation has led to a reduction in waiting list mortality.^{106,107} The American Thoracic Society/Infectious Diseases Society of America and the British Thoracic Society guidelines recommend using severity assessment to guide the management of patients with community-acquired pneumonia.^{6,7} However, the main adult ICU prognostic models have rarely been used in supporting individual clinical patient decision making, and such a use is fraught with difficulty.^{61,108} The adult ICU prognostic models need to be subjected to the same scrutiny as drugs and medical equipment before they are used in decisions that impact on health care delivery and individual patient care.

Although most prognostic models perform well at a population level, their poor calibration on an individual level has prevented their use at the bedside. Probabilities of hospital mortality provide meaningful information to physicians when discussing patient prognosis with patients and their families. However, use of probabilities should not be employed for making treatment decisions at the individual patient level.¹⁰⁸ Even severity of illness models demonstrating good agreement for describing patients in the aggregate do not perform as well for individual patients. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT) showed that survival estimates combining an objective prognosis with a physician's clinical

estimate had a better ability to identify patients with high probabilities of survival or death.¹⁰⁹ This can be attributed to the fact that physician estimates of low ICU survival may lead to subsequent life support limitation and thus a high mortality rate.¹¹⁰ Currently, most patients and their families rely on prognostic information given to them by the physicians to make decisions. However, because of the biases of subjective estimates, physicians' ability to correctly predict mortality is highly variable.¹¹¹ Overconfident physicians tend to underestimate mortality, whereas those who lack self-confidence tend to overestimate mortality.¹¹²

Assessment of futility is another important potential application for the use of severity of illness systems. Trends in the severity of illness provide important prognostic information.¹¹³ In patients with a high risk of death at ICU admission, lack of improvement in predicted mortality indicates a poor prognosis.^{113–115} In a small study including patients with an APACHE III predicted mortality rate of greater than 95%, 23% of them survived to hospital discharge.¹¹⁶ However, all except one survivor were severely disabled and the 1-year survival rate was 10%. Whether the addition of the probability of death derived from the prognostic models improves the clinicians' estimates awaits future studies. In the meantime, the probabilities derived from the prognostic models should be used as "the drunken man uses the lamppost, for support rather than illumination" in making clinical decisions.¹¹⁷

Despite these cautions, the administration of recombinant human activated protein C (rhAPC) in severe sepsis has been guided by severity score. Two international randomized clinical trials have evaluated the role of rhAPC in severe sepsis, with conflicting results.^{118,119} Its survival benefit was limited to patients with an APACHE II score of 25 or higher. As a result, many ICUs limit the administration of rhAPC to patients with severe sepsis and an APACHE II score of 25 or greater.

With the scarcity of ICU beds in many hospitals, avoiding unnecessary ICU admission and transferring patients who do not need ICU care are important. The ICU prognostic models have the potential to be used for decision support for these purposes. MPM₀ III and SAPS 3 could potentially be used as decision support for ICU admission triage because most of their predictor variables are available at admission.^{32,33,67} Patients who are unlikely to require active ICU intervention can be identified and early transfer out of ICU arranged. The Critical Care Series of the APACHE III clinical support system provides estimates for the risk of requiring specific critical care interventions, potential transfer from the ICU, and TISS score for individual patients.¹⁰⁴ However, the real impact of this clinical support system on clinical outcome has not been well described.

CLINICAL RESEARCH

The level of clinical detail, attention to ICU-specific diagnoses and variables, and size make the current adult prognostic models attractive for use in critical care outcomes research questions.¹²⁰ The ICU severity scoring systems can be used for risk stratification of patients before randomization for clinical trials, but this is a controversial use of such systems.¹²¹ Post hoc analysis of completed trials using risk stratification of subgroups may lead to the generation of further hypotheses, resulting in further clinical trials.^{118,119}

Limitations

There are several limitations inherent in the ICU prognostic models.¹²² Errors in collecting and entering data and flaws in model development and validation weaken the performance of prognostic models. A prognostic model accurately predicts outcome only if the case mix is similar to the one used in its development. Each of the fourth-generation adult ICU prognostic models was developed in non-randomly selected ICUs, compromising the generalizability of their findings.^{32–34,67} Application of prognostic models requires unambiguous definitions of predictor and outcome variables and reproducible measurements easily available in clinical practice.¹²³ Predictor variables such as GCS scores may not be easily measured, and certain laboratory values required for some models may not be routinely obtained. Because of its simplicity and availability, APACHE II is the most widely used adult ICU prognostic model. However, its wide use does not mean adequate prediction, necessitating the development of newer APACHE versions.¹²³ A few years usually pass between performing a study and publishing its result. By the time the prognostic model studies are published, their prognostic accuracy may have degraded as a result of changes in practice over time.¹²³ Several factors, including lead-time bias, pre-ICU location, acute diagnosis, physiologic reserve, and patients' preferences for life support, influence mortality. Most of these prognostically important variables are not included in some of the latest prognostic models. Although the models are unlikely to include all predictor variables, a balance needs to be struck between model simplicity and performance. Although the ICU models perform reasonably well in the general ICU population, they are far from perfect in identifying which individual patient will live or survive. In a well-calibrated model, one can reasonably expect that 75% of patients with a probability of mortality of 0.75 will die. However, one cannot know in advance which 25% will survive. These 25% will have confirmed the validity of the model, not falsified the odds. Most importantly, long-term survival and quality of life, issues that may be more important than simple mortality, are not forecast by the prediction models.

Prognostic Models in Trauma Care

Along with the development of specialized trauma centers, assessment of the severity of illness of trauma victims has been refined. These scoring systems, especially if used in the prehospital setting for field triage, must be straightforward.¹²⁴ In addition to their use in the prehospital setting, trauma scoring systems may be used for quality assurance, the evaluation of trauma care delivery, trauma research, and, potentially, reimbursement assessment.^{124,125}

One of the earliest trauma scoring systems was the GCS, developed by Teasdale and Jennett in Scotland and used since 1974 to quantify the severity of head injury by evaluating motor, sensory, and verbal responses.¹²⁶ Admission GCS is predictive of injury severity for both diffuse and focal head injuries. The GCS has been incorporated into other trauma scoring systems.

In 1981, Champion and colleagues published the Trauma Score (TS) as a system for field triage.¹²⁷ The TS included

five variables (GCS score, respiratory expansion, respiratory rate, systolic blood pressure, and capillary refill) and was predictive of survival for blunt and penetrating injuries. However, assessment of some of the variables was difficult, especially at night, and the Revised Trauma Score (RTS) was introduced by the same authors.¹²⁸ The RTS has become the most widely used prehospital field triage tool. RTS makes use of three variables: GCS score, respiratory rate, and systolic blood pressure. Each variable is given a score of between 1 and 4 (0 to 4 in the case of the GCS score), with a maximum score of 12. Lower scores represent increasing severity of illness. The RTS was validated against the Washington Hospital Center database (the database of the principal author) and the Major Trauma Outcome Study (MTOS) database of the American College of Surgeons. An RTS of 11 or less accurately identified 97% of the fatally injured and most of the severely injured. The RTS demonstrated better calibration than the original TS.¹²⁸ A potential weakness of the RTS is its underestimation of the severity of illness of patients with very severe single body area injuries, in which case, consideration of anatomic criteria is advisable.

The Injury Severity Scale (ISS) is one such anatomy-based system.¹²⁹ Developed in the 1970s, it was not designed to be a field triage system. Rather, the ISS was intended to define injury severity for comparative and research purposes. The ISS uses a combination of anatomic and severity indices to categorize patients. Five of the nine anatomic areas used in the Abbreviated Injury Scale (AIS), a system developed in 1974, are used in the ISS.^{124,130} The AIS scores each anatomic area between 0 (no injury) and 5 (critical injury, survival uncertain). The ISS is calculated by identifying the three most severely injured anatomic areas, squaring the AIS score of each and taking the sum. An ISS of 16 or greater is associated with a mortality of 10%, although it should be remembered that the ISS is a retrospective tool and not an instrument of field triage. Originally, the ISS was designed to evaluate only victims of blunt trauma, but a 1990 revision of the AIS (AIS90) has allowed improved quantification of both penetrating and blunt trauma victims. The ISS prediction of outcomes for patients with a severe single body area injury (e.g., gunshot wound to the abdomen that injures multiple organs) remained suboptimal. The New Injury Severity Score (NISS) is a modification of the ISS, which is calculated as the sum of the squares of the AIS scores of each of a patient's three most severe injuries, regardless of the body area in which they occur.¹³¹

TRISS combines the anatomic criteria of the ISS with the physiologic criteria of the RTS.¹³² The TRISS method correlates RTS with ISS to create an isobar on which a 50% survival is predicted. TRISS methodology, which is statistically complex, allows any trauma service to compare itself with the MTOS database in both preliminary outcomes-based evaluation and definitive outcomes-based evaluation.¹³³ It has been used by individual programs to identify preventable deaths and to assess the efficacy of new interventions.^{125,132} A further refinement of TRISS comes with A Severity Characteristic of Trauma (ASCOT) using the Anatomic Profile, which is based on AIS scores.¹³⁴ ASCOT uses three body area components, GCS score, systolic blood pressure, and respiratory rate, and a stratification for age to calculate a score from which survival probabilities are estimated.

Adoption of ASCOT has been relatively slow as it provides only slightly improved predictive power over TRISS at the cost of significantly increased complexity of calculation. For both blunt and penetrating trauma, the AUC of both the TRISS and ASCOT models were greater than 0.9.¹³⁴ Calibration of ASCOT was slightly better than that of TRISS (Hosmer-Lemeshow statistic 13.3 versus 30.7 for blunt trauma and 20.3 versus 138.4 for penetrating trauma).¹³⁴

A more recent innovation in trauma scoring systems is the incorporation of International Classification of Disease (ICD) codes into scoring systems. For example, the ICD-9 Injury Severity Score (ICISS) uses survival risk ratios for each ICD-9 discharge diagnosis and applies them to each of the patient's injuries. In the ICISS, all injuries contribute to the prediction and individual injuries are more accurately modeled. Furthermore, ICD-9 codes are more readily available, even in smaller centers. However, factors such as "patient reserve" are not accounted for in such systems.

Perioperative Scoring Systems

Multiple prognostic systems have been developed to specifically evaluate the risk of mortality for patients undergoing operative intervention. Some of these (e.g., the Physiological and Operative Severity Score for enUmeration of Mortality and morbidity [POSSUM]) are generic surgical scores.¹³⁵ Others, for example, the Society of Thoracic Surgeons (STS) cardiac surgery risk models, relate to specific surgical procedures (e.g., isolated valve surgery).^{136–138}

POSSUM was developed for surgical care quality review rather than for decision making regarding the need for operative intervention.¹³⁹ Twelve factors (age, cardiac history, respiratory history, arterial blood pressure, heart rate, GCS score, hemoglobin concentration, white cell blood count, BUN, sodium concentration, potassium concentration, and electrocardiogram) are used to generate a physiologic score that ranges from 12 through 88. This is combined with a six-factor operative severity score (OSS) that includes blood loss, peritoneal soiling, malignancy, urgency of surgery, need for multiple procedures, and an estimate of the "severity" of the procedure. A prediction of mortality is subsequently calculated using logistic regression coefficients. There are data from meta-analyses suggesting that POSSUM may be the most appropriate risk score for surgical practice.^{140,141} A modification to POSSUM (P-POSSUM) was developed to address some problems with negative risk values in the original model.¹⁴² POSSUM and modified versions of POSSUM have been studied in different countries and in both general and specialty surgical groups.^{143–167} There are limited and inconclusive data comparing POSSUM with the main adult ICU prognostic models.¹⁶⁸ POSSUM has proven quite useful in vascular disease and has also been applied with success to colorectal surgical populations. It does not address patients in whom surgery is not performed, trauma patients, or pediatric patients; it may overestimate mortality rates in minor and intermediate surgical procedures and does not account for the need for reoperation resulting from a complication of the original surgery.¹³⁹

The STS prognostic models are based on the National Cardiac Surgery Database, which has grown over two decades. In addition to a prediction of mortality, the models predict

the occurrence of cerebrovascular accident, renal failure, prolonged ventilation, deep sternal wound infection, reoperation, composite adverse outcome, and prolonged and short lengths of stay. The most recently developed models (for coronary artery bypass alone, valve surgery alone, and both) have very good discrimination for mortality, but the performance is not as good for the other end points. The STS Web site provides a risk calculator that may be used for estimation of perioperative morbidity and mortality.¹⁶⁹ A European equivalent, the European System for Cardiac Operative Risk Evaluation (EuroSCORE), has also been developed for adult patients undergoing cardiac surgery under cardiopulmonary bypass.^{170–173} The EuroSCORE needs modification for risk stratification when applied to patients undergoing off-pump coronary artery bypass.¹⁷⁴ A single-center study from North America suggested that the EuroSCORE and the STS score are good predictors of postoperative mortality in cardiac surgery patients.¹⁷⁵

Assessment of Organ Failure

Multiple organ failure is a major cause of morbidity and mortality in the ICU and is the subject of a separate chapter in *ACS Surgery Principles and Practice*. The desire for objective assessment of the extent and severity of organ dysfunction has led to the development of a number of models.⁶¹ Most organ failure assessment systems consider six organ systems: cardiovascular, respiratory, central nervous system, renal, hematologic, and hepatic. The values assigned to them depend on the degree of derangement from normal and can be dichotomous or continuous. Although derangement of the gastrointestinal system is known to be important in the critically ill, its incorporation into such organ dysfunction scores has been difficult because of its complexity and the associated difficulty in measuring its function. Despite the complexity and difficulties, some researchers have tried to define gastrointestinal failure, with some success.¹⁷⁶ The prognostic importance of endocrine or metabolic dysfunction has been appreciated only recently.^{177,178} Future organ failure assessment systems need to incorporate gastrointestinal and endocrine organ dysfunctions.

ORGAN DYSFUNCTION ASSESSMENT MODELS

One of the earliest organ failure assessment tools, Multiple Organ System Failure (MOSF), used dichotomous variables.^{18,179} More recent tools, however, have used continuous scales, which is more consistent with the consideration of organ failure as a process rather than an event. There are three main organ failure scoring systems in current use: the Multiple Organ Dysfunction Score (MODS), the Logistic Organ Dysfunction System (LODS) score, and the Sequential Organ Failure Assessment (SOFA) score, the latter being most commonly used [see Table 5].^{19–21} An Organ Failure and Infection Score (ODIN) has been popular in France but is not widely used elsewhere.¹⁸⁰ Most of the variables included in these systems are readily available and usually obtained regularly in the critically ill. Based on the severity of each organ dysfunction, SOFA and MODS assign scores between 0 and 4. The variables used in these two systems were developed in a subjective manner as a result of consensus and literature review. In contrast, LODS scores were derived

Table 5 Variables Included in the Calculation of the Organ Failure Scores

Organ	Variable	SOFA ²⁰	LODS ²¹	MODS ¹⁹
Respiratory	Pao ₂ /F _I O ₂	Yes	Yes	Yes
	Mechanical ventilation	Yes	Yes	
Hematology	Platelets	Yes	Yes	Yes
	WBC		Yes	
Liver	Bilirubin	Yes	Yes	Yes
	Prothrombin time		Yes	
Cardiovascular	Mean arterial pressure	Yes		
	Systolic blood pressure		Yes	
	Heart rate		Yes	
	Pressure-adjusted heart rate			Yes
	Dopamine	Yes		
	Dobutamine	Yes		
	Epinephrine	Yes		
	Norepinephrine	Yes		
Central nervous system	Glasgow Coma Scale score	Yes	Yes	Yes
Renal	Creatinine	Yes	Yes	Yes
	Blood urea nitrogen		Yes	
	Urine output	Yes	Yes	

Adapted from Afessa B et al.³⁵

F_IO₂ = fraction of inspired oxygen; LODS = Logistic Organ Dysfunction System; MODS = Multiple Organ Dysfunction Score; Pao₂ = arterial oxygen tension; SOFA = Sequential Organ Failure Assessment; WBC = white blood cell count.

from objective data subjected to robust statistical analysis.²¹ Instead of assigning scores based on arbitrarily selected cutpoints, LODS assigns scores to each organ system based on the impact on mortality. MODS uses pressure-adjusted heart rate (calculated as central venous pressure × heart rate/mean blood pressure) to measure cardiovascular dysfunction. This poses difficulties for the use of MODS in patients who do not have central venous catheters.¹⁸¹

Organ failure scoring systems are intended to provide objective measures of organ derangement and the sequence of development of complications. The primary intention is not to predict mortality. However, such organ failure scores can accurately discriminate survivors from nonsurvivors. Knaus and colleagues demonstrated that a single organ failure lasting more than a day resulted in a mortality rate approaching 40%.¹⁸ Mortality increased to 60 and 98%, respectively, for two and three organ failures lasting more than a day. In the surgical ICU patients on whom MODS was based, the score correlated well with mortality (AUC > 0.9).¹⁹

The most widely used and studied organ failure assessment system is SOFA [see Table 6]. The accuracy and reliability of SOFA scoring by physicians are good.¹⁸² The initial trends in SOFA scores correlate well with mortality.^{183,184} A SOFA score greater than 11 was associated with a mortality rate greater than 90% in a prospective study by Ferreira and colleagues.¹⁸³ During the first 96 hours, regardless of the initial score, the mortality rate was at least 50% when the score increased, 27 to 35% when it remained unchanged, and

less than 27% when it decreased. LODS scores have also been found to correlate with mortality.¹⁸⁵

Few investigators have compared the performance of organ failure assessment systems in a common patient population. Peres Bota and colleagues failed to find a significant difference between SOFA and MODS in survival prediction, and in a cohort of 1,685 patients in French ICUs, daily LODS and SOFA scores showed good accuracy and internal consistency.^{186,187}

Acquisition of daily organ dysfunction scores may be used to follow a patient's course throughout the ICU stay. This is in contrast to prognostic scoring systems, which are mostly designed to make predictions based on data acquired during the first 24 hours in the ICU.¹⁸⁸ By the observation of daily scores, the natural history of ICU syndromes or diseases may be evaluated and the effects of therapies in clinical practice and during clinical trials may be studied. Unlike the severity of illness prognostic models, however, the organ failure assessment systems have not been studied in large patient populations.

The organ failure assessment systems are based on easily obtainable variables, with the exception of pressure-adjusted heart rate in the MODS. They can be measured daily and have the potential to be used for prognostication, evaluation of the success or failure of treatments, and allocation of resources. They can also be used in clinical trials as entry criteria, risk adjustment, and outcome measures. However, these potential roles have not yet been supported by data. Future studies are needed to better define these roles as well

Table 6 Sequential Organ Failure Assessment (SOFA)²⁰

Organ Failure	Variable	Score				
		0	1	2	3	4
Respiratory	Pao ₂ /F _I O ₂ , mm Hg	≥400	< 400	< 300	< 200 on MV	< 100 on MV
Hematology	Platelets, 10 ⁹ /L	≥ 150	< 150	< 100	< 50	< 20
Liver	Bilirubin, mg/dL	< 1.2	1.2–1.9	2.0–5.9	6.0–11.9	> 12.0
Cardiovascular	Mean arterial blood pressure, mm Hg	≥ 70	< 70			
	Dopamine, µg/kg/min			≤ 5	> 5	> 15
	Dobutamine, µg/kg/min			Any dose		
	Epinephrine, µg/kg/min				≤ 0.1	> 0.1
	Norepinephrine, µg/kg/min				≤ 0.1	> 0.1
Central nervous system	Glasgow Coma Scale score	15	13–14	10–12	6–9	< 6
Renal	Creatinine, mg/dL	< 1.2	1.2–1.9	2.0–3.4	3.5–4.9	≥ 5.0
	Urine output, mL/day	≥ 500			< 500	< 200

Adapted from Afessa B et al.³⁵

F_IO₂ = fraction of inspired oxygen; MV = mechanical ventilation; Pao₂ = arterial oxygen tension.

as to compare the performance of the organ failure assessment systems in a large sample size.

Severity of Illness and Organ Dysfunction Scoring in Children

Although this chapter focuses on prognostic scoring systems used in adult critical care, it should be recognized that similar attempts at describing the severity of illness and predicting outcome have been made in neonatal and pediatric patients.^{189,190}

In neonatal ICUs, the Clinical Risk Index for Babies (CRIB) and the Score for Neonatal Acute Physiology (SNAP) are used. The former was developed in the United Kingdom and pertains primarily to infants with birth weights less than 1,500 g.¹⁹¹ It uses six variables: birth weight, gestational age, congenital anomalies, the highest and lowest fraction of inspired oxygen (F_IO₂) values, and the worst base deficit, collected during the first 12 hours after birth. The AUC of the CRIB for prediction of death in a validation cohort was 0.9, a figure significantly greater than for birth weight alone (0.78).¹⁹¹ Developed in the early 1990s, CRIB may require recalibration for current neonatal ICU practices. The SNAP is a physiology-based score for assessment of neonatal severity of illness.^{192–194} The second iteration, SNAP II, was developed from the study of more than 27,000 neonates in the United States and Canada. SNAP II involves measurement of mean blood pressure, temperature, pH values, ratio of arterial oxygen tension (Pao₂) to F_IO₂, urine output, and the occurrence of multiple seizures for an assessment of illness severity and includes birth weight, small for gestational age status, and Apgar scores for mortality prediction.¹⁹⁵ The AUC for the SNAP was greater than 0.85, and the Hosmer-Lemeshow statistic indicated good calibration.¹⁹²

The two most commonly used prognostic scoring systems for pediatric ICU patients are the Pediatric Risk of Mortality (PRISM) and the Pediatric Index of Mortality (PIM).^{190,196–201}

Three versions of PRISM have been published. The first version, published in 1987, was named the Physiologic Stability Index, and it contained 24 predictor variables. The Pediatric Risk of Mortality Score (named PRISM II by some) was published in 1991 and contained 14 variables. The current version, PRISM III, was published in 1996. It was developed on a cohort of 11,165 admissions to 32 pediatric ICUs. The PRISM III score has 17 physiologic variables, including systolic blood pressure, pH, and GCS score, similar to adult models. The variables most predictive of mortality were minimum systolic blood pressure, abnormal pupillary reflexes, and stupor or coma. Other risk factors, including two acute and two chronic diagnoses and four additional risk factors, were used in the final predictors. Data are collected within the first 12 hours of ICU admission (PRISM III-12) or during the first 24 hours of ICU stay (PRISM III-24). PRISM III-24 has been demonstrated to have an AUC of 0.944, with excellent calibration (Hosmer-Lemeshow chi-square statistic $p = .55$). PRISM III-12 also appeared to have excellent discrimination and calibration.¹⁹⁶ PRISM has been validated on a large sample of patients in multiple ICUs. It is a proprietary system, however, which has limited its application outside North America.

PIM was introduced in 1997 and updated in 2003 (PIM-2).^{199,201} This nonproprietary system includes 10 variables that are measured on admission to the ICU: Pao₂, base excess, systolic blood pressure, elective versus nonelective admission, pupillary reaction, mechanical ventilation, cardiac bypass, postoperative or postprocedure status, high-risk diagnosis, or low-risk diagnosis. PIM-2 has been validated in almost 21,000 children in Australia, New Zealand, and the United Kingdom. Both its discrimination and calibration are good (AUC 0.9, 95% CI 0.89 to 0.91, and chi-square goodness of fit statistic 17.5, respectively). PIM 2 compared favorably with PRISM III in a cohort of 26,000 pediatric ICU patients in Australia and New Zealand, although its suitability for use elsewhere in the world has been debated.²⁰⁰

In addition to generic prognostic scoring systems, prediction of mortality in specific pediatric disease states (e.g., *Neisseria meningitidis* infection, near-drowning, acute renal failure, bone marrow transplantation) has led to a variety of disease-specific prognostic systems.^{190,195} Furthermore, scores evaluating functional pediatric ICU outcome (e.g., Pediatric Cerebral Performance Category and Pediatric Overall Performance category) and pediatric adaptations of trauma scores (e.g., Pediatric Trauma Score) have also been developed.¹⁹⁵

In a fashion analogous to the evaluation of the severity of illness in adult patients, descriptive indices of organ dysfunction have been developed for critically ill pediatric patients. Pediatric multiple organ dysfunction syndrome may be quantified by the Pediatric Logistic Organ Dysfunction (PELOD) score and the Pediatric Multiple Organ Dysfunction Score (P-MODS).^{202–207} The PELOD was published in 1999. It was developed based on expert opinion and refined after an epidemiologic study in three multidisciplinary university-affiliated pediatric ICUs. The PELOD consists of 12 variables from six systems (respiratory, cardiovascular, neurologic, hepatic, renal, and hematologic).¹⁹⁰ The score has been validated in a study of 1,806 patients in seven pediatric ICUs in Canada, France, and Switzerland, with an AUC of 0.91 and good calibration ($p = .54$, 5 df).²⁰⁵ A more recent South American study, however, raised concerns regarding its calibration.²⁰⁸ A daily PELOD score has also been evaluated, as has the use of PELOD in the context of sepsis. The delta PELOD (the worst PELOD after randomization into a clinical trial minus the daily PELOD score at day of randomization) has been advocated to be of use in performing

studies in critically ill pediatric patients.¹⁹⁰ P-MODS, which includes descriptors for organ dysfunction in five organ systems (although not the neurologic system), is a more recently developed score that may also provide an objective assessment of organ dysfunction in the pediatric ICU.²⁰⁷

Future Directions

Compared with etiologic, diagnostic, and therapeutic research, prognostic research has received limited attention. This is in spite of the fact that prognosis is an important medical concept.¹²³ In advance of the application of a new prognostic model, researchers should perform a validation study in their patient populations. Recalibration or model revision may be required when a prognostic model does not perform well in a population different from the derivation cohort.¹²³ The use of prognostic models in individual patients is controversial but may aid health care providers and patients in decision-making processes.²⁰⁹ The adult ICU prognostic models have been refined and revised several times to improve their performance, but there is a paucity of data addressing their impact on health care providers' behavior and patient outcome. Future studies need to address the effect of using a prognostic model on health care providers' behavior, patient outcome, and cost-effectiveness.¹²³ Currently existing hospital and health care provider ranking systems are based on administrative databases and are greatly influenced by the public relation policies of the individual hospital or health care provider. The development and application of robust prognostic models are prerequisites for meaningful ranking.

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30 ANTIBIOTICS

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Antibiotic Therapy in Surgical Patients

Several important advances in antimicrobial therapy have been made since the early 1980s. Among these advances are (1) improved understanding of the microbiologic spectrum of so-called optimal therapy, (2) better application of pharmacokinetic principles to drug administration, (3) the development of several new classes of antibiotics, and (4) greater insight into the interplay among host resistance factors, microorganisms, and chemotherapy.

General Principles of Antimicrobial Therapy

EMPIRICAL THERAPY

Even with the most rapid bacteriologic tests currently available, it may not be possible to identify a pathogen in less than 24 hours, and antimicrobial sensitivities can rarely be obtained in less than 48 to 72 hours. In seriously ill patients, treatment cannot be delayed for 2 to 3 days until these data become available. If therapy is to be successful, it must be started as soon as a life-threatening infection is diagnosed or, in some patients, as soon as such an infection is suspected. Which antimicrobial agents are to be used depends on the suspected site of infection and on the organisms that are commonly pathogenic at this site. Therapy is initiated with an agent or combination of agents whose action is broad enough to cover all the suspected microbial pathogens. The application of such broad-spectrum antibiotic therapy in the absence of microbiologic confirmation is termed empirical therapy.

To make a rational decision regarding empirical therapy, the surgeon must be familiar with the organisms that are likely to be encountered when a particular infection (e.g., an intra-abdominal abscess) is suspected. Selection of the agent or agents is based on the history, the physical examination, where the infection was likely to have been acquired, the host defense status, the overall clinical severity of the infection, and the response of the host. Definitive therapy is initiated after the host response to the infection and to the empirical treatment has been monitored and the results from the microbiology laboratory—specifically, identification of the isolated organisms and the minimal inhibitory concentrations (MICs) of various antimicrobial agents—have been assessed.

LABORATORY TESTS

Many laboratory tests, if used in the proper context, can guide selection of optimal antimicrobial therapy.

In vitro susceptibility tests are indicated when the susceptibility of an organism is not completely predictable or when certain other specific problems arise, such as the necessity of determining whether resistance has developed during the course of therapy. An organism is generally considered susceptible if the concentration of antimicrobial agent necessary to inhibit its growth is lower than that usually attainable in body fluids, particularly blood, cerebrospinal fluid, or urine.

The disk diffusion method has been standardized by the

National Committee for Clinical Laboratory Standards (NCCLS)¹ for in vitro susceptibility testing. Commercially available paper disks containing specific amounts of antimicrobial agents are placed on Mueller-Hinton agar plates that contain a standard bacterial inoculum. A zone of inhibition of bacterial growth develops around each active antibiotic after overnight incubation. The size of the zone determines the organism's susceptibility or resistance; prior studies have correlated zone sizes with MICs obtained through dilution tests. Arbitrary zone-size break points for susceptibility have been established by clinical and laboratory investigators on the basis of such additional factors as achievable serum levels, degree of protein binding, and toxicity.

The broth dilution method exposes an inoculum of bacteria to various concentrations of an antimicrobial agent during incubation. The MIC of an agent that inhibits growth can be determined, and this value can be correlated with blood, urine, or other body fluid levels of the antimicrobial agent. Moreover, those tubes that show inhibition of growth can be subcultured to an antimicrobial-free medium, and the minimal bactericidal concentration (MBC) can be determined. Unfortunately, this test is not well standardized at present, and its reproducibility is poor when it is subjected to intralaboratory and interlaboratory comparisons.²

The agar dilution method works in much the same way as the broth dilution method, except that the former employs agar plates that contain various dilutions of antimicrobial agents, and as many as 36 organisms can be efficiently inoculated on each plate by means of a replicator device. The MIC is determined by reading inhibition of colony growth on the agar surface. Agar dilution has the advantage of producing MIC data efficiently in a laboratory that performs large numbers of tests daily.

In the serum bactericidal test (SBT), samples of the serum of the treated patient are obtained and incubated with the infecting organism in doubling dilutions with broth to determine the highest dilution that is bactericidal. (Not all antimicrobial agents exhibit bactericidal activity; some exhibit only bacteriostatic activity [see Table 1].) The drawing of serum specimens can be timed to coincide with anticipated peak and trough antimicrobial levels. In effect, this test indirectly assesses both the susceptibility of the organism and the serum concentration of the antimicrobial agent, as well as the interactions between serum and organism and serum and drug. The NCCLS has developed proposed guidelines for the SBT.³ A comprehensive review of the technical and clinical considerations associated with the SBT has been published.⁴

Factors Influencing Application of Antimicrobial Therapy

ROUTE OF ADMINISTRATION

Many antibiotics are absorbed sufficiently well via the oral route to provide effective blood levels in patients with normal GI function.⁵ The enteral absorption of some antimicrobials is

impeded by food and some medications (e.g., antacids). Many antibiotics cannot be given intramuscularly because of local pain or necrosis at the injection site. Intravenous administration must be used in the treatment of major and life-threatening infections such as suppurative diffuse peritonitis. In many cases, patients are clinically stable during intravenous treatment, and it is often possible to discharge them and to administer parenteral antibiotics on an outpatient basis. Supervision by special teams of physicians, nurses, and pharmacists is required⁶; antibiotics can be administered either in the hospital outpatient department or at home if competent family members are available. New antibiotics with long half-lives can be used with improved intravenous catheters and delivery devices in simplified regimens; this leads to substantial economic benefits, enhanced patient comfort, and good therapeutic results with few complications.⁷

HOST FACTORS

Hypersensitivity to Antibiotics

Because of widespread exposure to antimicrobial agents, many patients develop allergies to them.⁸ A careful history of hypersensitivity should thus be obtained [see Hypersensitivity Reactions, *below*].

Concurrent Illnesses

Patients with immunosuppressive illnesses are vulnerable to opportunistic pathogens. These patients may require broader antimicrobial coverage as well as intense therapy for ordinary pathogens. The same is true to a lesser extent for patients with a chronic debilitating illness. Patients with renal insufficiency or liver disease may be unusually susceptible to direct drug toxicity.

Pregnancy

The administration of antimicrobial agents during pregnancy and in the postpartum period poses several problems. Foremost is the question of safety, both for the mother and the fetus or neonate. Although most antibiotics cross the placenta and enter maternal milk, the concentrations to which the fetus or neonate is exposed vary widely. Because the immature liver may lack the enzymes required to metabolize certain drugs, pharmacokinetics and toxicities in the fetus are often very different from those in older children and adults. Teratogenicity is a major concern when any drug is administered during pregnancy. Finally, it may be necessary to alter the dosage schedules of drugs that appear to be safe to use during pregnancy; increases in maternal blood vol-

ume, glomerular filtration rule (GFR), and hepatic metabolic activity often reduce the maternal serum levels of antimicrobials by 10% to 50%, especially late in pregnancy and in the early postpartum period. In some women, delayed gastric emptying may reduce the absorption of antibiotics that have been administered orally during pregnancy.

Even though 25% to 40% of women receive antibiotics during pregnancy, data regarding safety and efficacy in this setting are often scarce. Some general recommendations have been proposed, but they are intended only as a guide [see Table 2]; in all cases, therapy must be individualized, and both the indications for antibiotics and the possible risks to mother and fetus must be considered. Individual decisions are also required for lactating mothers; although most antimicrobials appear safe for breast-fed infants, chloramphenicol and the tetracyclines should be avoided.⁹

Advanced Age

Physiologic changes that occur with age can alter the pharmacokinetics of antimicrobial agents. For example, decreased gastric acidity and intestinal motility can impair drug absorption; increased body fat and decreased serum albumin levels can alter drug distribution; and decreased hepatic blood flow and enzymatic action can delay drug metabolism. Although these factors have not consistently affected antibiotic levels in the elderly, the decrease in GFR that occurs with age can lead to the accumulation of drugs excreted by the kidney. The high therapeutic index of the penicillins and cephalosporins obviates major changes in dosage schedules in elderly patients who have normal serum creatinine levels. However, in the case of aminoglycosides and vancomycin, decreased dosage schedules are often required; ideally, drug levels should be measured and renal function should be monitored when these agents are given. The dosage of amantadine and rimantadine should also be reduced in elderly patients.

Antibiotic Selection for Infections in Surgical Patients

The term surgical infection is difficult to define, but for the purposes of this chapter, it means infections that are related to surgical procedures or that require, in addition to antibiotic therapy, surgical debridement or control of the source of the infection. Such infections include infections of the soft tissues of the integument; muscles; bones; and body cavities (e.g., empyema, intra-abdominal infections, pyelonephritis, and infections of the retroperitoneum).

A framework for antibiotic selection for intra-abdominal infections is presented [see Table 3]; this framework can be modified for the selection of antibiotic for other types of surgical infection. A therapeutic regimen for the treatment of intra-abdominal infection should include agents that are active against *Staphylococcus aureus*, enteric gram-negative bacilli, and anaerobes, including *Bacteroides fragilis*. The regimen that has been regarded as the gold standard consists of an aminoglycoside, to cover the enteric gram-negative organisms, and clindamycin or metronidazole, to cover the anaerobes; other approaches, however, look promising.

A well-designed, controlled, prospective, randomized trial that compared imipenem therapy with acceptable aminoglycoside-based regimens supports the use of imipenem as monotherapy for intra-abdominal infections in which an enteric mixed flora is anticipated.¹⁰ When the analysis was restricted to the residual effect of treatment assignment, a significant improvement in outcome was found in the patients receiving imipenem ($P = 0.043$).

Table 1 Bactericidal and Bacteriostatic Agents¹⁵⁵

Bactericidal Agents	Bacteriostatic Agents
Aminoglycosides*	Chloramphenicol
Aztreonam	Clindamycin
Bacitracin	Erythromycin
Cephalosporins	Sulfonamides
Imipenem	Tetracyclines
Penicillins	Trimethoprim
Polymyxins†	
Quinolones‡	
Vancomycin	

*Including streptomycin, neomycin, kanamycin, gentamicin, tobramycin, amikacin, and netilmicin.

†Including polymyxin B and colistimethate.

‡Including norfloxacin and ciprofloxacin.

Table 2 Antibiotics in Pregnancy¹⁵⁵

Drug	Major Toxic Potential		Pharmacology	
	Maternal	Fetal	Maternal Serum Levels	Excreted in Mother's Milk
Considered safe Cephalosporins Erythromycin base Penicillins Spectinomycin	Allergies Allergies, GI intolerance Allergies ?	None known None known None known None known	Decreased Decreased Decreased ?	Trace Yes Trace ?
Use with caution Aminoglycosides Clindamycin Ethambutol Isoniazid Rifampin Sulfonamides (contraindicated at term)	Ototoxicity, nephrotoxicity Allergies, colitis Optic neuritis Allergies, hepatotoxicity Hypersensitivity, hepatotoxicity Allergies, crystalluria	Ototoxicity None known Probably safe Neuropathy, seizures Probably safe Kernicterus (at term), hemolysis (G6PD deficiency)	Decreased Unchanged ? Unchanged Unchanged Unchanged	Yes Trace ? Yes Yes Yes
Avoid if possible Metronidazole	Hypersensitivity, alcohol intolerance, neuropathy	None known (teratogenic in animals)	Probably unchanged	Yes
Contraindicated Chloramphenicol Erythromycin estolate Nalidixic acid Nitrofurantoin Norfloxacin, ciprofloxacin, ofloxacin, lomefloxacin Tetracyclines Trimethoprim	Blood dyscrasias Hepatotoxicity GI intolerance Allergies, neuropathy, GI intolerance GI intolerance Hepatotoxicity, renal failure Hypersensitivity	Gray syndrome None known Increased intracranial pressure Hemolysis (G6PD deficiency) Arthropathies in immature animals Tooth discoloration and dysplasia, impaired bone growth Teratogenicity	Unchanged Decreased ? Decreased ? Probably unchanged Unchanged	Yes Yes ? Trace ? Yes Yes

Meropenem was found to be as effective as imipenem for the treatment of moderately severe intra-abdominal infections.¹¹

Ertapenem has a pharmacokinetic profile and an antimicrobial spectrum that support its use as a once-daily agent for the treatment of common mixed aerobic and anaerobic infections. A prospective, randomized, controlled, double-blind trial compared ertapenem with piperacillin-tazobactam as therapy following adequate surgical management of complicated intra-abdominal infections. The modified intent-to-treat population consisted of 633 patients, of whom 396 met all criteria for the evaluable population. Patients with a wide range of infections were enrolled. A prospective expert-panel review was conducted to assess the adequacy of surgical source control in patients in whom therapeutic failure was a component of evaluability. For the modified intent-to-treat groups, 245 of 311 patients treated with ertapenem (78.8%) were cured; 232 of 304 patients (76.3%) treated with piperacillin-tazobactam were cured. Of 203 microbiologically evaluable patients treated with ertapenem, 176 (86.7%) were cured; 157 of the 193 patients (81.3%) treated with piperacillin-tazobactam were cured. In this study, ertapenem, 1 g once a day, was equivalent to piperacillin-tazobactam, 3.375 g every 6 hours, in the treatment of a range of intra-abdominal infections. Ertapenem may be a useful option that could eliminate the need for combination therapy, multidose antibiotic regimens, or both for the empirical treatment of intra-abdominal infections.¹²

Appropriate surgical control of the source of the intra-abdominal infection is of utmost importance in determining outcome; antibiotics play a necessary but secondary role.^{13,14} The controversies regarding the pathogenicity of enterococci have been

addressed by guidelines published by members of the Surgical Infection Society.¹⁵ The third-generation cephalosporins have been proposed as candidates for single-agent therapy for infection in the abdominal cavity because their spectra of activity encompass both the aerobic gram-negative bacilli and some of the anaerobic isolates that cause infection in this region. No cephalosporin, of any generation, has been shown to have a clear advantage over an aminoglycoside-clindamycin combination in the treatment of intra-abdominal infections.

Interpretation of overall results in intra-abdominal infections is difficult because of the numerous variables involved, including the diversity of the possible infectious processes, the variable quality of the surgical technique employed, the variety of the patient characteristics observed, the possibility of one or more underlying diseases, and the differing doses of antibiotics used in individual studies.¹⁶ Most third-generation cephalosporins do not cover anaerobes well and should be used in conjunction with an antianaerobic agent, such as clindamycin or metronidazole, for empirical therapy for serious intra-abdominal infections. In a recent prospective, randomized, double-blind study, cefoxitin was found to be comparable to imipenem with regard to outcome (defined as survival); failure to cure infections was attributed to resistant organisms at the primary site in the cefoxitin arm of the trial.¹⁷

Adverse Reactions to Antimicrobial Agents

There are three general types of adverse reactions to antimicrobial agents: hypersensitivity reactions (which are not dose related), direct drug toxicity (which usually is dose related and

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Table 3 Antibiotic Selection for Infections in Surgical Patients

Type of Infection	Expected Pathogen	First Choice I.V. Rx	Second Choice I.V. Rx	Switch to P.O. Choice
Brain infection (abscess, subdural empyema, intracranial suppurative thrombophlebitis)				
Traumatic brain injury	<i>Staphylococcus aureus</i> , Enterobacteriaceae, <i>Pseudomonas aeruginosa</i>	Cefepime, 2 g I.V. q. 8 hr	Meropenem, 1 g I.V. q. 8 hr	Not recommended
Postneurosurgical procedure	<i>S. aureus</i> , <i>S. epidermidis</i>	Nafcillin, 2 g I.V. q. 4 hr or Cefepime, 2 g I.V. q. 8 hr or If methicillin resistant: Linezolid, 600 mg I.V. q. 12 hr	Meropenem, 1 g I.V. q. 8 hr	Linezolid, 600 mg p.o., q. 12 hr
Vascular graft infection				
Arteriovenous graft/shunt	<i>S. aureus</i> , Enterobacteriaceae, enterococci	Vancomycin, 1 g I.V. plus Gentamicin, 240 mg I.V. and remove graft	Meropenem, 1 g I.V. q. 8 hr and remove graft	Moxifloxacin, 400 mg p.o. and remove graft
Aortic graft (treat with antibiotics until graft is replaced)	<i>S. aureus</i> , <i>S. epidermidis</i> , Enterobacteriaceae	Cefepime, 2 g I.V. q. 12 hr or Imipenem, 1 g I.V. q. 8 hr or Meropenem, 1 g I.V. q. 8 hr	Ceftizoxime, 2 g I.V. q. 8 hr or Cefotaxime, 2 g I.V. q. 6 hr	Levofloxacin, 500 mg p.o., q. 24 hr or Moxifloxacin, 400 mg p.o., q. 24 hr
Intra-abdominal infection (peritonitis, abscess)				
Gastric perforation (peptic ulcer disease)	<i>Candida</i> , oral anaerobes, <i>S. aureus</i>	Cefazolin, 1 g I.V. q. 8 hr	Ceftizoxime, 2 g I.V. q. 8 hr or Cefotaxime, 2 g I.V. q. 6 hr	Levofloxacin, 500 mg p.o., q. 24 hr or Moxifloxacin, 400 mg p.o., q. 24 hr
Gastric perforation (malignancy)	<i>S. aureus</i> , <i>S. epidermidis</i> , Enterobacteriaceae, <i>Candida</i>	Cefepime, 2 g I.V. q. 12 hr or Imipenem, 1 g I.V. q. 8 hr or Meropenem, 1 g I.V. q. 8 hr	Ceftizoxime, 2 g I.V. q. 8 hr or Cefotaxime, 2 g I.V. q. 6 hr	Levofloxacin, 500 mg p.o., q. 24 hr or Moxifloxacin, 400 mg p.o., q. 24 hr
Cholecystitis with gangrene/perforation	<i>Escherichia coli</i> , <i>Klebsiella</i> , enterococci	Piperacillin-tazobactam, 4.5 g I.V. q. 8 hr	Cefotaxime, 2 g I.V. q. 6 hr	Levofloxacin, 500 mg p.o., q. 24 hr or Moxifloxacin, 400 mg p.o., q. 24 hr
Emphysematous cholecystitis	<i>Clostridium perfringens</i>	Piperacillin-tazobactam, 4.5 g I.V. q. 8 hr	Ertapenem, 1 g I.V. q. 24 hr	Clindamycin, 300 mg p.o., q. 8 hr
Ascending cholangitis	<i>E. coli</i> , <i>Klebsiella</i> , enterococci	Imipenem, 1 g I.V. q. 8 hr or Meropenem, 1 g I.V. q. 8 hr	Cefoperazone, 2 g I.V. q. 12 hr	Levofloxacin, 500 mg p.o., q. 24 hr or Moxifloxacin, 400 mg p.o., q. 24 hr
Infected hemorrhagic/ necrotizing pancreatitis	Enterobacteriaceae, <i>Bacteroides fragilis</i>	Imipenem, 1 g I.V. q. 8 hr or Meropenem, 1 g I.V. q. 8 hr or Ertapenem, 1 g I.V. q. 24 hr	Piperacillin-tazobactam, 4.5 g I.V. q. 8 hr or Ampicillin-sulbactam, 3 g I.V. q. 6 hr	Clindamycin, 300 mg p.o., q. 8 hr plus Levofloxacin, 500 mg p.o., q. 24 hr or Moxifloxacin, 400 mg p.o., q. 24 hr
Liver abscess (bacterial)	Enterobacteriaceae, <i>B. fragilis</i>	Imipenem, 1 g I.V. q. 8 hr or Meropenem, 1 g I.V. q. 8 hr or Ertapenem, 1 g I.V. q. 24 hr	Metronidazole, 1 g I.V. q. 24 hr plus Levofloxacin, 500 mg I.V. q. 24 hr or Moxifloxacin, 400 mg I.V. q. 24 hr	Metronidazole, 500 mg p.o., q. 12 hr plus Levofloxacin, 500 mg p.o., q. 24 hr or Moxifloxacin, 400 mg p.o., q. 24 hr
Liver abscess (amebiasis)	<i>Entamoeba histolytica</i>	Metronidazole, 750 mg p.o., q. 8 hr	Tinidazole, 2 g/day p.o. in three divided doses	Not applicable

(continued)

Table 3 (continued)

Type of Infection	Expected Pathogen	First Choice I.V. Rx	Second Choice I.V. Rx	Switch to P.O. Choice
Intra-abdominal Infection (peritonitis, abscess) (continued)				
Distal small bowel, appendix, colon, rectum perforation in nonhospitalized patient (mild to moderate infection)	Enterobacteriaceae, enterococci, <i>B. fragilis</i>	Piperacillin-tazobactam, 4.5 g I.V. q. 8 hr or Ertapenem, 1 g I.V. q. 24 hr	Cefoxitin, 2 g I.V. q. 6 hr or Ampicillin-sulbactam, 3 g I.V. q. 6 hr	Ciprofloxacin, 250–750 mg p.o., q. 12 hr plus Metronidazole, 500 mg p.o., q. 12 hr
Distal small bowel, appendix, colon, rectum perforation in hospitalized patient (severe infection requiring ICU support)	Enterobacteriaceae, enterococci, <i>B. fragilis</i> , <i>P. aeruginosa</i> , <i>Acinetobacter</i>	Imipenem, 1 g I.V. q. 8 hr or Meropenem, 1 g I.V. q. 8 hr	Tobramycin, 5 mg/kg load-ing dose, then 3 mg/kg I.V. q. 8 hr plus Clindamycin, 900 mg I.V. q. 8 hr	Moxifloxacin, 400 mg p.o., q. 24 hr
Spontaneous bacterial peritonitis	Enterobacteriaceae	Ciprofloxacin, 400 mg I.V. q. 12 hr	Cefepime, 2 g I.V. q. 12 hr	Ciprofloxacin, 250–750 mg p.o., q. 12 hr plus Metronidazole, 500 mg p.o., q. 12 hr
Pelvic inflammatory disease (tubo-ovarian abscess, salpingitis, endometritis, infected abortion)				
Mild to moderate infection (outpatients)	Enterobacteriaceae, <i>B. fragilis</i> , <i>Neisseria gonorrhoeae</i> , <i>Chlamydia trachomatis</i>	Moxifloxacin, 400 mg p.o., q. 24 hr	None	Ciprofloxacin, 250–750 mg p.o., q. 12 hr plus Doxycycline, 100 mg p.o., q. 12 hr
Severe infection (hospitalized patient)	Enterobacteriaceae, <i>B. fragilis</i> , <i>N. gonorrhoeae</i> , <i>C. trachomatis</i>	Doxycycline, 200 mg I.V. q. 12 hr plus Clindamycin, 600 mg I.V. q. 8 hr	Levofloxacin, 500 mg p.o., q. 24 hr plus Metronidazole, 1 g I.V. q. 24 hr	Moxifloxacin, 400 mg p.o., q. 24 hr

manifests in a single organ or, occasionally, in several organs), and microbial superinfection.

HYPERSENSITIVITY REACTIONS

A history of allergies should be taken before antimicrobial therapy is initiated in any patient. More information is available regarding allergies to the penicillins than allergies to other agents, but skin eruptions, drug fever, and even anaphylaxis may be produced by many antibiotics. Allergic reactions occur in 1% to 10% of patients who receive penicillin. Fatal anaphylactic reactions are much less frequent.

DIRECT DRUG TOXICITY

Although antimicrobials can produce damage to virtually all human organ systems, the potential for toxicity varies widely from drug to drug.¹⁸ The principal antibiotics that are directly toxic to the kidney are aminoglycosides, polymyxins, and amphotericin B; azotemia and renal tubular damage may be caused by any of these drugs. Patients with preexisting renal insufficiency are at increased risk for toxic reactions to various antibiotics, including nephrotoxicity, coagulopathies and other hematologic toxicities, seizures, and ototoxicity and other neurotoxicities.

Penicillins, cephalosporins, tetracyclines, and rifampin can cause hemolytic anemia, thrombocytopenia, and leukopenia that involve an immune mechanism, but these reactions are uncommon. Macrolides and trimethoprim-sulfamethoxazole have been associated with agranulocytosis. Trimethoprim can produce anemia, leukopenia, and thrombocytopenia from folate deficiency; the effect is reversible with folinic acid. Amphotericin B commonly produces a reversible normocytic normochromic anemia,

probably secondary to injury to the red cell membrane. Flucytosine causes bone marrow suppression (leukopenia or pancytopenia) when its excretion is reduced by renal failure. Linezolid can also produce myelosuppression; although experience is limited, bone marrow function usually recovers when the drug is discontinued. Neutropenia can occur during therapy with penicillins, cephalosporins, or vancomycin. It may be severe, but it is self-limited; recovery occurs 1 to 7 days after the antibiotic is withdrawn. Penicillins inhibit platelet aggregation by adenosine diphosphate, which may account for the bleeding that occurs in some patients receiving these antibiotics in high doses. Various cephalosporins may produce coagulopathies by prolonging the prothrombin time; the methylthiotetrazole side chain present in cephalosporins such as cefotetan appears to be responsible.

Antibiotics may produce a wide range of toxic effects on the central and peripheral nervous systems. Ototoxicity, either vestibular or auditory, can be produced by any of the aminoglycosides; neuromuscular blockade is much less common. Minocycline has occasionally been reported to produce significant vestibular reactions. Vancomycin can cause auditory neurotoxicity. Intravenous administration of large doses of penicillin and other β -lactams may produce seizures, especially when administered in very high doses or when given to azotemic patients or to patients with underlying epilepsy.

Metronidazole can sometimes cause ataxia, encephalopathy, seizures, or peripheral neuropathies. Ofloxacin has been reported to cause seizures; mania has been attributed to clarithromycin. Optic neuritis, usually manifested by decreased visual acuity and decreased perception of the color green, may occur as a side effect of ethambutol.

Table 4 Antimicrobial Drugs of Choice for Various Infections in Adults¹⁸

	Causative Organism	Drug of Choice	Alternative Drugs
Gram-Positive Cocci	<i>Staphylococcus aureus</i> Methicillin-sensitive Methicillin-resistant ¹	Vancomycin, ² with or without rifampin or gentamicin Penicillinase-resistant penicillin ⁵	Linezolid; quinupristin-dalfopristin Trimethoprim-sulfamethoxazole (TMP-SMX), ² with or without rifampin ² ; a fluoroquinolone ³ ; a tetracycline ⁴ A cephalosporin, ⁶ clindamycin, vancomycin, ⁷ meropenem or imipenem, ⁸ ticarcillin-clavulanic acid, ampicillin-sulbactam, amoxicillin-clavulanic acid, piperacillin-tazobactam, a fluoroquinolone ³
	Coagulase-negative staphylococci ⁹	Vancomycin, ⁷ with or without rifampin ² or gentamicin	Linezolid, quinupristin-dalfopristin, a cephalosporin, a penicillinase-resistant penicillin, meropenem or imipenem, ⁸ a fluoroquinolone ³
	Anaerobic streptococcus (<i>Peptostreptococcus</i>)	Penicillin G ¹⁰	Clindamycin, a cephalosporin, ⁶ vancomycin ⁷
	<i>Streptococcus bovis</i>	Penicillin G ^{10,11}	A cephalosporin, ⁶ vancomycin ⁷
	Groups A, G, and C streptococci	Penicillin G ^{10,12} or penicillin V	A cephalosporin, ⁶ vancomycin, ⁷ an erythromycin, ¹³ clindamycin, clarithromycin, azithromycin
	Group B streptococcus	Penicillin G ^{10,12} or ampicillin	A cephalosporin, ⁶ vancomycin, ⁷ an erythromycin
	<i>S. pneumoniae</i> (pneumococcus) Penicillin sensitive	Penicillin G ^{10,12} or penicillin V, amoxicillin	An erythromycin, ^{12,13} a cephalosporin, ⁶ meropenem or imipenem, ⁸ vancomycin, ^{7,12} azithromycin, clarithromycin, a fluoroquinolone; a tetracycline ⁴
	Non-penicillin sensitive	Vancomycin; ceftriaxone or cefotaxime ⁶ ; levofloxacin, moxifloxacin, or gatifloxacin ³ ; linezolid; quinupristin-dalfopristin; imipenem or meropenem	—
	Viridans streptococcus	Penicillin G, ^{10,11} with or without gentamicin	A cephalosporin, ⁶ vancomycin ⁷
Gram-Positive Bacilli	Enterococcus Endocarditis or other serious infection Uncomplicated urinary tract infection	Penicillin or ampicillin, plus gentamicin ¹⁴ or streptomycin Ampicillin or amoxicillin	Vancomycin, ⁷ with gentamicin or streptomycin; linezolid; quinupristin-dalfopristin A fluoroquinolone, ³ nitrofurantoin, ¹⁵ fosfomycin
	<i>Bacillus cereus</i> , <i>B. subtilis</i> <i>Bacillus anthracis</i> <i>Clostridium difficile</i> <i>C. perfringens</i>	Vancomycin Penicillin G Metronidazole ¹⁶ Penicillin G; clindamycin	Meropenem or imipenem, ⁸ clindamycin Ciprofloxacin, ³ a tetracycline, ⁴ an erythromycin ² Vancomycin ¹⁶ Metronidazole, meropenem or imipenem, ⁸ chloramphenicol ⁷
	<i>C. tetani</i> <i>Corynebacterium diphtheriae</i> <i>Corynebacterium</i> , JK group <i>Listeria monocytogenes</i> <i>Propionibacterium</i>	Metronidazole An erythromycin Vancomycin Ampicillin, with or without gentamicin Penicillin G	Penicillin G, a tetracycline ⁴ Penicillin G Penicillin G, with gentamicin; an erythromycin TMP-SMX Clindamycin, an erythromycin
	<i>Moraxella</i> (formerly <i>Branhamella</i>) <i>catarrhalis</i>	Cefuroxime, ⁶ a fluoroquinolone ³	TMP-SMX, amoxicillin-clavulanic acid, an erythromycin, a tetracycline, third-generation cephalosporins, clarithromycin, azithromycin
	<i>Neisseria gonorrhoeae</i> ¹⁷	Ceftriaxone or cefixime, ⁶ ciprofloxacin, ofloxacin, or gatifloxacin ³	Cefotaxime, ¹⁰ penicillin or ampicillin
	<i>N. meningitidis</i> Meningitis, bacteremia	Penicillin G	A third-generation cephalosporin, ⁶ TMP-SMX, a fluoroquinolone, ³ chloramphenicol ⁷
	Carrier state	Rifampin	Minocycline, ciprofloxacin
	<i>Bacteroides</i> GI tract strains (<i>B. fragilis</i>)	Metronidazole or clindamycin	Cefoxitin, cefotetan, ceftizoxime, or cefmetazole; chloramphenicol ¹⁸ ; imipenem or meropenem ⁸ ; ticarcillin-clavulanic acid; ampicillin-sulbactam, piperacillin-tazobactam
	Respiratory tract strains	Penicillin G or clindamycin	Metronidazole, cefoxitin, ⁶ cefotetan, ceftizoxime, cefmetazole, chloramphenicol ⁷
Enteric Gram-Negative Bacilli	<i>Campylobacter fetus</i> <i>C. jejuni</i> <i>Citrobacter</i>	Imipenem or meropenem ⁸ Azithromycin or an erythromycin Imipenem or meropenem ⁸	Gentamicin A fluoroquinolone, ³ a tetracycline, ⁴ gentamicin ⁷ A fluoroquinolone, ³ amikacin; TMP-SMX; a tetracycline ⁴ ; a third-generation cephalosporin ⁶
	<i>Enterobacter</i>	Imipenem or meropenem ⁸	A third-generation cephalosporin ⁶ ; for serious infections, use with a fluoroquinolone ³ or gentamicin; gentamicin, tobramycin, amikacin, a fluoroquinolone, ³ a carboxypenicillin or acylaminopenicillin, ¹⁹ aztreonam ²⁰
	<i>Escherichia coli</i>	Ampicillin, a cephalosporin, ⁶ a fluoroquinolone, ³ TMP-SMX ²²	Gentamicin, ²¹ tobramycin, amikacin, imipenem or meropenem, ⁸ aztreonam ²⁰

Note: all superscript numbers refer to footnotes that follow table.

Table 4 (continued)

	Causative Organism	Drug of Choice	Alternative Drugs
Enteric Gram-Negative Bacilli (continued)	<i>Helicobacter pylori</i>	Tetracycline with metronidazole and bismuth subsalicylate or omeprazole with amoxicillin and clarithromycin	Amoxicillin with metronidazole and bismuth subsalicylate; tetracycline with clarithromycin and bismuth subsalicylate; clarithromycin with omeprazole; amoxicillin with clarithromycin
	<i>Klebsiella</i>	A cephalosporin ⁶	Imipenem or meropenem, ⁹ gentamicin, ²³ tobramycin, amikacin, TMP-SMX, ²¹ a carboxypenicillin or acylaminopenicillin, ²¹ amoxicillin-clavulanic acid, ampicillin-sulbactam, ticarcillin-clavulanic acid, piperacillin-tazobactam, aztreonam, ²⁰ a fluoroquinolone ³
	<i>Proteus mirabilis</i>	Ampicillin	A cephalosporin, gentamicin or tobramycin, chloramphenicol, ⁷ a carboxypenicillin or acylaminopenicillin, ¹⁹ imipenem or meropenem, ⁸ TMP-SMX, aztreonam, ²⁰ a fluoroquinolone ³
	non-mirabilis, including <i>P. vulgaris</i> , <i>Morganella morganii</i> , and <i>Providencia rettgeri</i>	A third-generation cephalosporin ⁶	Gentamicin, tobramycin, amikacin, a carboxypenicillin or acylaminopenicillin, ¹⁹ imipenem or meropenem, ⁸ aztreonam, ²⁰ ampicillin-sulbactam, ticarcillin-clavulanic acid, piperacillin-tazobactam, amoxicillin-clavulanic acid, a fluoroquinolone ³
	<i>Providencia stuartii</i>	A third-generation cephalosporin ⁶	An aminoglycoside, TMP-SMX, ²¹ imipenem or meropenem, ⁸ aztreonam, ²⁰ a carboxypenicillin or acylaminopenicillin, ¹⁹ a fluoroquinolone ³
	<i>Salmonella typhi</i> Other <i>Salmonella</i> species	Ceftriaxone or a fluoroquinolone ³ Ceftriaxone or cefotaxime or a fluoroquinolone ³	Chloramphenicol or ampicillin, ²² TMP-SMX Ampicillin or amoxicillin, TMP-SMX, chloramphenicol ⁷
	<i>Serratia</i>	Imipenem or meropenem	A third-generation cephalosporin, ⁶ gentamicin or amikacin, a carboxypenicillin or acylaminopenicillin, ¹⁹ chloramphenicol, ⁷ aztreonam, a fluoroquinolone ³
	<i>Shigella</i>	A fluoroquinolone ³	TMP-SMX, ampicillin, ceftriaxone, azithromycin
Other Gram-Negative Bacilli	<i>Acinetobacter (Herellea)</i>	Imipenem or meropenem ⁸	Tobramycin, gentamicin, amikacin, doxycycline, minocycline, a carboxypenicillin or acylaminopenicillin, ¹⁹ TMP-SMX, a fluoroquinolone, ³ ceftazidime
	<i>Aeromonas hydrophilia</i>	TMP-SMX ²	A fluoroquinolone, ³ gentamicin, tobramycin, imipenem or meropenem ⁸
	<i>Bartonella henselae</i> (cat-scratch disease)	Azithromycin	Ciprofloxacin, ³ TMP-SMX, gentamicin; rifampin, erythromycin
	<i>Bartonella henselae</i> (bacillary angiomatosis)	Erythromycin	Doxycycline, azithromycin
	<i>Bordetella pertussis</i> (whooping cough)	Erythromycin	TMP-SMX; azithromycin or clarithromycin
	<i>Brucella</i>	A tetracycline, with rifampin	A tetracycline with gentamicin or streptomycin; chloramphenicol, ⁷ with or without streptomycin; TMP-SMX ² with or without gentamicin; ciprofloxacin ³ with rifampin
	<i>Eikenella corrodens</i>	Ampicillin	An erythromycin, a tetracycline, ⁴ amoxicillin-clavulanic acid, ampicillin-sulbactam, ceftriaxone
	<i>Francisella tularensis</i> (tularemia)	Streptomycin	Gentamicin, a tetracycline, ⁴ chloramphenicol, ⁷ ciprofloxacin ³
	<i>Fusobacterium</i>	Penicillin	Clindamycin, metronidazole, chloramphenicol ⁷ ; cefoxitin
	<i>Gardnerella</i> (formerly <i>Haemophilus</i>) <i>vaginalis</i>	Metronidazole ² (oral)	Intravaginal metronidazole, intravaginal or oral clindamycin
	<i>Haemophilus influenzae</i> Bronchitis, otitis media	TMP-SMX	Ampicillin or amoxicillin; a tetracycline ⁴ ; amoxicillin-clavulanic acid, cefuroxime axetil, ceftizoxime, clarithromycin, azithromycin, a fluoroquinolone ³
	Meningitis, epiglottitis, life-threatening infections	Cefotaxime or ceftriaxone	Chloramphenicol, ²⁴ meropenem ⁹
	<i>Legionella</i> species	Azithromycin or a fluoroquinolone ³	Erythromycin, rifampin, ²⁵ TMP-SMX, ² doxycycline ⁴
	<i>Pasteurella multocida</i>	Penicillin G	A tetracycline, ⁴ a cephalosporin, ⁶ amoxicillin-clavulanic acid, ampicillin-sulbactam
	<i>Calymmatobacterium granulomatis</i> (granuloma inguinale)	TMP-SMX	A tetracycline ⁴ ; ciprofloxacin with or without rifampin
	<i>H. ducreyi</i> (chancroid)	Ceftriaxone or azithromycin	A fluoroquinolone ³
	<i>Pseudomonas aeruginosa</i> Urinary tract infections	Ciprofloxacin ³	Levofloxacin; gentamicin or tobramycin; amikacin; ceftazidime, ⁶ with or without gentamicin or tobramycin; imipenem or meropenem ⁸ ; aztreonam, ²⁰ a carboxypenicillin or acylaminopenicillin ¹⁹
	Other infections	Gentamicin or tobramycin, with or without a carboxypenicillin or acylaminopenicillin ¹⁹ ; ceftazidime or cefipime; imipenem or meropenem ⁸ ; aztreonam, ²⁰ alone or with gentamicin or tobramycin	Amikacin, with or without a carboxypenicillin or acylaminopenicillin ¹⁹ ; ciprofloxacin ⁷
	<i>P. cepacia</i>	TMP-SMX	Chloramphenicol, ⁷ ceftazidime, ² imipenem ^{2,8} or meropenem ⁸
	<i>Streptobacillus moniliformis</i> (rat-bite fever)	Penicillin G	A tetracycline, ⁴ streptomycin

Note: all superscript numbers refer to footnotes that follow table.

Table 4 (continued)

	Causative Organism	Drug of Choice	Alternative Drugs
Other Gram-Negative Bacilli (continued)	<i>Vibrio cholerae</i>	A tetracycline ⁴	TMP-SMX, a fluoroquinolone ³
	<i>V. vulnificus</i>	A tetracycline ⁴	Cefotaxime
	Agents of Vincent stomatitis (trench mouth)	Penicillin G	A tetracycline, ⁴ an erythromycin
	<i>Stenotrophomonas</i> (formerly <i>Xanthomonas</i>) <i>maltophilia</i>	TMP-SMX	Minocycline, ceftazidime, ⁶ a fluoroquinolone ³
	<i>Yersinia enterocolitica</i>	TMP-SMX ²	A fluoroquinolone, gentamicin, ² tobramycin, ² amikacin, cefotaxime ^{2,6} or ceftizoxime ^{2,6}
	<i>Y. pestis</i> (plague)	Streptomycin with or without a tetracycline	A tetracycline, ⁴ chloramphenicol, ⁷ gentamicin, ² TMP-SMX
Acid-Fast Bacilli	<i>Mycobacterium avium</i> complex	Clarithromycin or azithromycin plus one or more of the following: ethambutol, rifabutin, ciprofloxacin	Rifampin, amikacin
	<i>M. fortuitum</i>	Amikacin ² with clarithromycin	Rifampin, ² cefoxitin, a sulfonamide, doxycycline, ethambutol, linezolid
	<i>M. kansasii</i>	Isoniazid with rifampin, with or without ethambutol or streptomycin	Cycloserine, ethionamide, clarithromycin
	<i>M. leprae</i>	Dapsone ⁷ with rifampin, with or without clofazimine	Minocycline, ⁴ ofloxacin or sparfloxacin, ³ clarithromycin
	<i>M. marinum</i> (bath ²⁶)	Minocycline	TMP-SMX, rifampin, clarithromycin, doxycycline
	<i>M. tuberculosis</i> ²⁷	Isoniazid with rifampin, and pyrazinamide with or without ethambutol or streptomycin	Ciprofloxacin or ofloxacin; third-line agent
Actinomycetes	<i>Actinomyces israelii</i>	Penicillin G	A tetracycline ⁴ ; an erythromycin; clindamycin
	<i>Nocardia</i>	TMP-SMX	Minocycline, sulfisoxazole, imipenem or meropenem, ⁸ amikacin, ² cycloserine, linezolid
Chlamydia	<i>Chlamydia psittaci</i> (psittacosis)	A tetracycline ⁴	Chloramphenicol ⁷
	<i>C. trachomatis</i>		
	Inclusion conjunctivitis	An erythromycin (oral or I.V.)	A sulfonamide (topical plus oral)
	Lymphogranuloma venereum	A tetracycline ⁴	An erythromycin
	Pneumonia	An erythromycin	A sulfonamide
	Trachoma	Azithromycin	A tetracycline ⁴ (topical plus oral), a sulfonamide (topical plus oral)
Mycoplasma	Urethritis or pelvic inflammatory disease	Doxycycline or azithromycin	Erythromycin, ofloxacin, amoxicillin
	<i>C. pneumoniae</i>	An erythromycin or clarithromycin or azithromycin; a fluoroquinolone	A tetracycline
Mycoplasma	<i>Mycoplasma pneumoniae</i>	An erythromycin, clarithromycin or azithromycin; a fluoroquinolone, ³ doxycycline ⁴	—
	<i>Ureaplasma urealyticum</i>	An erythromycin	A tetracycline, ⁴ clarithromycin, or azithromycin; ofloxacin ³
Rickettsia	Various rickettsial organisms Rocky Mountain spotted fever, epidemic and endemic (murine) typhus, rickettsial pox, Q fever, scrub typhus	Doxycycline ⁴	Chloramphenicol, ⁷ a fluoroquinolone, ³ rifampin
Spirochetes	<i>Borrelia burgdorferi</i> (Lyme disease)	Doxycycline or amoxicillin or ceftriaxone	Penicillin, an erythromycin, clarithromycin, azithromycin, cefuroxime
	<i>B. recurrentis</i> (relapsing fever)	A tetracycline ⁴	Penicillin G
	<i>Leptospira</i>	Penicillin G	A tetracycline, ⁴ an erythromycin
	<i>Treponema pallidum</i>	Penicillin G	A tetracycline, ⁴ an erythromycin, ceftriaxone

1. Some strains of *S. aureus* and most strains of coagulase-negative staphylococci are resistant to penicillinase-resistant penicillins; these strains are also resistant to cephalosporins.

2. Not approved for this indication by the FDA.

3. None of these drugs is recommended for children. In 1999, the FDA limited trovafloxacin to inpatient use for limb- or life-threatening infections.

4. Doxycycline is the safest tetracycline for treatment of extrarenal infections in renal insufficiency. Tetracyclines should be avoided in pregnant women and in children younger than 8 yr.

5. For severe infections, I.V. nafcillin or oxacillin should be used. For mild infections, oral cloxacillin, dicloxacillin, or oxacillin may be employed. Between 1% and 2% of *S. aureus* strains are resistant to penicillinase-resistant penicillins (and usually to cephalosporins) but are susceptible to vancomycin. High doses of penicillin G, ampicillin, amoxicillin, carbenicillin, or ticarcillin do not overcome the clinical resistance of penicillinase-producing staphylococci to these drugs.

6. Cephalosporins are sometimes used as alternatives to penicillin in patients with sus-

pected penicillin allergy but not in patients with serious hypersensitivity (especially immediate anaphylactic or accelerated urticarial reactions). Patients allergic to penicillin may be hypersensitive to cephalosporins. Only third-generation cephalosporins are effective in bacterial meningitis.

7. In view of the occurrence of adverse reactions, this drug should be used only for serious infections and when less toxic drugs are ineffective.

8. Imipenem and meropenem are β -lactam antibiotics that should be used with caution in patients who are allergic to penicillins and cephalosporins.

9. In vitro sensitivity testing with cephalosporins or penicillins may be misleading because of heteroresistance and because these antibiotics may be bacteriostatic only. For serious infections, vancomycin is preferred (see text).

10. Crystalline penicillin G is administered parenterally for serious infections. For less severe infections caused by pneumococci, group A streptococci, gonococci, or *T. pallidum*, procaine penicillin is administered I.M. once or twice daily. For mild infections caused by streptococci and pneumococci, oral penicillin V is preferable to oral penicillin G. Benzathine penicillin G is given I.M. (once monthly for the prophylaxis of rheumatic fever,

Table 4 (continued)

a single injection for the treatment of group A streptococcal pharyngitis) when patients' compliance for oral medication is questionable and for treatment of syphilis, in one to three doses at weekly intervals, depending on the stage of the disease.

11. The combination of penicillin G with streptomycin for the first 2 wk of treatment of endocarditis caused by viridans streptococci is preferred by some.

12. In patients with major allergy to penicillin, erythromycin is the alternative for respiratory tract infections; chloramphenicol is the preferred alternative for meningitis. Occasional strains of pneumococci have high-level resistance to penicillin and to most other antibiotics except vancomycin.

13. Some strains of pneumococci and group A streptococci are erythromycin resistant.

14. Various aminoglycosides have been used in synergistic combination with penicillin or vancomycin. Because of the appearance of enterococcal strains resistant to the synergistic action with streptomycin (but not gentamicin), gentamicin is preferred for use in the combination.

15. Contraindicated in pregnancy or in the presence of renal insufficiency.

16. Antibiotics may be administered orally for antibiotic-associated pseudomembranous enterocolitis. Vancomycin and metronidazole are equally effective but metronidazole is much less expensive.

17. Large doses of penicillin G or ampicillin (or amoxicillin) may be required because some strains are resistant to these drugs. Penicillinase-producing gonococci, which are more resistant to penicillin, have appeared in the United States; spectinomycin is the treatment of choice for infections with such strains.

18. In CNS infection, metronidazole or chloramphenicol should be used.

19. The carboxypenicillins are carbenicillin and ticarcillin; the acylaminopenicillins are mezlocillin, azlocillin, and piperacillin. When one of these drugs is used for a severe infection, an aminoglycoside is often recommended as well.

20. Aztreonam is a β -lactam antibiotic; cross-sensitivity has not occurred, but use with caution in patients allergic to penicillins, cephalosporins, or imipenem.

21. Principally in treatment of uncomplicated urinary tract infections.

22. Ampicillin or amoxicillin may be effective in milder cases.

23. In severely ill patients, an aminoglycoside is combined with a cephalosporin.

24. Some encapsulated *H. influenzae* (type b) strains and some unencapsulated strains are resistant to ampicillin, and rare strains are resistant to chloramphenicol. Chloramphenicol plus ampicillin (or chloramphenicol alone) should be used for initial treatment of meningitis or epiglottitis in children until the organism is identified and its susceptibility is determined. For adults with meningitis of unknown etiology and an indeterminate Gram stain and in whom *H. influenzae* is suspected, chloramphenicol is added to ampicillin (or penicillin G) for the first 24 hr until the results of culture are available. Ampicillin is preferred when the infecting strain of *H. influenzae* is susceptible.

25. Not an FDA-approved use. Evidence for possible efficacy comes only from in vitro susceptibility testing and from treatment of infections in experimental animals. In both cases, *L. pneumophila* is highly susceptible to rifampin.

26. Most infections are self-limited without therapy.

27. Various combination treatments are available.

Trovaflaxacin was restricted for use in seriously ill patients because of hepatotoxicity, but other fluoroquinolones have not been implicated. The tetracyclines can occasionally cause fatty liver; hepatotoxicity is most likely to occur in patients receiving 2 g or more daily by the intravenous route. Patients receiving high-dose β -lactam antibiotics may develop hepatitis or cholestasis, presumably as a result of hypersensitivity reactions. Nitrofurantoin may cause chronic active hepatitis in some patients. Erythromycins and sulfonamides have been associated with acute hepatitis, and a case of fatal hepatic necrosis has been attributed to fluconazole.

GI reactions to antibiotics result either from direct irritation by the drug, the occurrence of which is usually dose related, or from bacterial overgrowth.¹⁹ Irritative GI side effects are usually produced when antibiotics are administered orally rather than parenterally. The predominant site of irritation varies from drug to drug; for example, erythromycin more commonly produces gastric irritation with epigastric distress and nausea, whereas tetracyclines may produce diarrhea as well as upper GI symptoms. Some qualitative and quantitative changes in the intestinal flora occur after antibiotic administration; they may contribute to flatulence and other lower GI symptoms, which are quite common when broad-spectrum antibiotics are administered orally. Selective overgrowth of *Clostridium difficile* can result in antibiotic-induced pseudomembranous enterocolitis.²⁰

Antibiotics may cause various other toxicities. Erythromycin and other macrolides can cause prolongation of the QT interval and polymorphic ventricular tachycardia; in rare instances, this toxicity occurs in the absence of predisposing factors, but it is more likely to occur in patients with significant heart disease and in patients taking terfenadine, astemizole, or cisapride. Several fluoroquinolones, such as moxifloxacin, gatifloxacin, and sparflaxacin, can have similar effects on cardiac conduction.^{21,22} All fluoroquinolones can cause tendinitis. Trimethoprim-sulfamethoxazole can cause hyperkalemia, particularly in azotemic patients. Sulfonamides, fluoroquinolones, and tetracyclines can produce photosensitivity.²³

MICROBIAL SUPERINFECTION

Antimicrobial therapy reduces susceptible organisms from the normal flora of the skin, oral and genitourinary mucosae, and GI tract and exerts selective pressures that favor survival of drug-resistant organisms. Such resistant organisms can occasionally establish a superinfection, either at the site of the original infection or at remote sites.

Public Health Considerations

ANTIMICROBIAL RESISTANCE

The extensive use of antimicrobial agents, especially in ICUs²⁴ and other health care facilities, strongly favors the selection of resistant microbial species, particularly bacterial strains harboring plasmids that confer transmissible resistance.^{25,26} Although antibiotics have played a major role in the treatment of such infections, the pathogens have responded to the antibiotic challenge, developing resistance to all available antimicrobial agents to a greater or lesser degree. Specific mechanisms of resistance are evident in the reduced permeability of cell wall membranes, changes in the target sites of antimicrobial agents, enzymatic inactivation of antibiotics, and the development of pathways bypassing antimicrobial targets.²⁷

The widespread use of antibiotics for animals compounds the problem; about 50% of the 25,000 tons of antibiotics that are sold annually in the United States are used in agriculture and aquaculture.²⁸ Infections from highly resistant strains of *Enterococcus*, *Pneumococcus*, *Staphylococcus aureus*, *Gonococcus*, *Salmonella*, *Serratia*, *Klebsiella*, *Acinetobacter*, *Enterobacter*, and *Mycobacterium* have become important problems. Infections from resistant strains can spread rapidly, first within an institution, then throughout a community, and eventually even globally.²⁹ Although antibiotic resistance is a worldwide problem, control depends on local measures, beginning with the judicious prescription of antibiotics by individual practitioners³⁰ and with formulary restrictions that reinforce prudence.³¹ Patients harboring resistant strains should be identified rapidly, treated appropriately, and isolated as needed to prevent the spread of infection.

The incidence of suprainfection with cephalosporin therapy is actually quite low (< 5%); however, the organisms encountered are often more virulent and difficult to eradicate than the original infecting pathogen.³² Commonly seen suprainfecting pathogens include *Enterobacter* species, *Pseudomonas aeruginosa*, *S. aureus*, *Acinetobacter* species, enterococci, and *Candida* species. Because these organisms are generally multiresistant, therapy with antibiotic combinations, including aminoglycosides, is usually necessary. There appear to be no significant differences among the cephalosporins with respect to the incidence of suprainfection or the types of suprainfecting pathogens found.

The most worrisome resistance is that of vancomycin-resistant enterococci (VRE). Risk factors for bloodstream infection with VRE are an increasing APACHE II (Acute Physiology and

Table 5 Antimicrobial Drug Dosages for Treatment of Bacterial Infections in Adults with Normal Renal Function¹⁵⁵

Class of Agent	Specific Agent	Trade Names	Modest Infections*			
			Oral		Intramuscular	
			Daily Dose	Interval	Daily Dose	Interval
Penicillinase-susceptible penicillins	Penicillin G	Pentids, Crystifor, Pfizerpen, etc.	0.8–3.2 million units	6 hr	1.2 million units	8 hr
	Penicillin G benzathine	Bicillin	—	—	1.2–2.4 million units	See fn. 1
	Penicillin G procaine	Crysticillin, Duracillin, etc.	—	—	0.6–4.8 million units	6–24 hr
	Penicillin V	Pen-Vee K, V-Cillin K, etc.	0.8–3.2 million units (0.5–2.0 g)	6 hr	—	—
Penicillinase-susceptible penicillins with activity against gram-negative bacilli	Amoxicillin	Amoxil, Larotid, etc.	750–1,500 mg	8 hr	—	—
	Ampicillin	Omnipen, Polycillin, etc.	1–4 g	6 hr	1–2 g	6 hr
	Azlocillin	Azlin	—	—	—	—
	Carbenicillin indanyl sodium	Geocillin	—	—	—	—
	Mezlocillin	Mezlin	—	—	—	—
	Piperacillin	Pipracil	—	—	See fn. 3	See fn. 3
	Ticarcillin	Ticar	—	—	See fn. 4	See fn. 4
Penicillinase-resistant penicillins	Cloxacillin	Tegopen	1–3 g	6 hr	—	—
	Dicloxacillin	Dynapen, Pathocil	1–2 g	6 hr	—	—
	Nafcillin	Nafcil, Unipen	2–4 g ⁵	6 hr	2–3 g	4–6 hr
	Oxacillin	Bactocill, Prostaphlin	2–4 g	6 hr	1–2 g	6 hr
Penicillins with β -lactamase inhibitors	Amoxicillin-clavulanate	Augmentin	750 mg–1.5 g (amoxicillin)	8 hr	—	—
	Ampicillin-sulbactam	Unasyn	—	—	1 g (ampicillin)	6 hr
	Piperacillin-tazobactam	Zosyn	—	—	—	—
	Ticarcillin-clavulanate	Timentin	—	—	—	—
Cephalosporins	Cefaclor	Ceclor	750 mg–1.5 g	8 hr	—	—
	Cefadroxil	Duricef, Ultracef	500 mg–2g	12–24 hr	—	—
	Cefamandole	Mandol	—	—	2–4 g	6 hr
	Cefazolin	Ancef, Kefzol	—	—	750 mg–1.5 g	8 hr
	Cefdinir	Omnicef	600 mg	24 hr	—	—
	Cefditoren pivoxil	Spectracef	200–400 mg	12 hr	—	—
	Cefepime	Maxipime	—	—	—	—
	Cefixime	Suprax	400 mg	24 hr	—	—
	Cefmetazole	Zefazone	—	—	—	—
	Cefonicid	Monocid	—	—	See fn. 7,8	See fn. 7,8
	Cefoperazone	Cefobid	—	—	See fn. 7,8	See fn. 7,8
	Ceforanide	Precef	—	—	See fn. 7,8	See fn. 7,8
	Cefotaxime	Claforan	—	—	See fn. 7,8	See fn. 7,8
	Cefotetan	Cefotan	—	—	See fn. 7,8	See fn. 7,8
	Cefoxitin	Mefoxin	—	—	2–4 g	6 hr
	Cefpodoxime	Vantin	200–800 mg	12 hr	—	—
	Cefprozil	Cefzil	500 mg–1 g	12–24 hr	—	—
	Ceftazidime	Fortaz, Tazidime	—	—	See fn. 7,8	See fn. 7,8
	Ceftibutin	Cedax	400 mg	—	—	—
	Ceftizoxime	Cefizox	—	—	See fn. 7,8	See fn. 7,8
	Ceftriaxone	Rocephin	—	24 hr	See fn. 7,8	See fn. 7,8
	Cefuroxime	Zinacef, Ceftin (p.o.)	250–500 mg	12 hr	See fn. 7,8	See fn. 7,8
	Cephalexin	Keflex	1–4 g	6 hr	—	—
	Cephapirin	Cefadyl	—	—	2–3 g	6 hr
	Cephradine	Anspor, Velosef	1–4 g	6 hr	2 g	6 hr
	Loracarbef	Lorabid	400–800 mg	12 hr	—	—
Carbapenems	Imipenem-cilastatin	Primaxin	—	—	—	—
	Meropenem	Merrem	—	—	—	—
	Ertapenem	Ivanz	—	—	—	—

Note: all superscript numbers refer to footnotes following table.
*Infections of the upper respiratory tract, soft tissues, etc.

(continued)

Table 5 (continued)

Uncomplicated Urinary Tract Infections		Major and Systemic Infections [†]			
Oral		Intramuscular		Intravenous	
Daily Dose	Interval	Daily Dose	Interval	Daily Dose	Interval
—	—	—	—	4–24 million units	2–4 hr
—	—	—	—	—	—
—	—	—	—	—	—
—	—	—	—	—	—
750–1,500 mg	8 hr	—	—	—	—
2–4 g	6 hr	—	—	4–12 g	2–4 hr
—	—	—	—	12–18 g	4 hr
4–8 tablets ²	6 hr	—	—	—	—
—	—	—	—	12–18 g	4 hr
—	—	See fn. 3	See fn. 3	12–18 g	4 hr
—	—	—	—	16–24 g	3–6 hr
—	—	—	—	—	—
—	—	—	—	—	—
—	—	—	—	4–12 g	4–6 hr
—	—	—	—	4–12 g	4–6 hr
750 mg (amoxicillin)	8 hr	—	—	—	—
—	—	1–2 g (ampicillin)	6 hr	1–2 g (ampicillin)	6 hr
—	—	—	—	12 g (piperacillin)	6 hr
—	—	—	—	12–18 g (ticarcillin)	4–6 hr
750 mg–1.5 g	8 hr	—	—	—	—
500 mg–2 g	12–24 hr	—	—	—	—
—	—	—	—	4–12 g	2–4 hr
See fn. 6	See fn. 6	2–3 g	6–8 hr	2–6 g	6–8 hr
—	—	—	—	—	—
—	—	—	—	2–6 g	8–12 hr
400 mg	24 hr	—	—	—	—
—	—	—	—	2–4 g	12 hr
—	—	—	—	4–8 g	6–12 hr
—	—	—	—	0.5–2.0 g	12–24 hr
—	—	—	—	2–12 g	6–8 hr
—	—	—	—	1–2 g	12 hr
—	—	—	—	2–12 g	4–6 hr
—	—	—	—	2–6 g	12 hr
—	—	—	—	4–12 g	4 hr
200 mg	12 hr	—	—	—	—
—	—	—	—	—	—
—	—	—	—	2–6 g	8–12 hr
400 mg	24 hr	—	—	—	—
—	—	—	—	2–6 g	8–12 hr
—	—	—	—	1–4 g	12–24 hr
—	—	—	—	3–6 g	6 hr
1–4 g	6 hr	—	—	—	—
—	—	—	—	4–12 g	2–4 hr
2 g	6 hr	—	—	3–8 g	4–6 hr
400 mg	12 hr	—	—	—	—
—	—	—	—	1–4 g	6–8 hr
—	—	—	—	3 g	8 hr
—	12 hr	—	—	1 g	24 hr

[†]Osteomyelitis, peritonitis, bacteremia, meningitis, endocarditis, etc.

(continued)

Table 5 (continued)

Class of Agent	Specific Agent	Trade Names	Modest Infections*			
			Oral		Intramuscular	
			Daily Dose	Interval	Daily Dose	Interval
Monobactams	Aztreonam	Azactam	—	—	1–2 g	8–12 hr
Aminoglycosides	Amikacin	Amikin	—	—	—	—
	Gentamicin	Garamycin	—	—	3–5 mg/kg ¹¹	8 hr
	Kanamycin	Kantrex	—	—	—	—
	Neomycin	—	See fn. 15	See fn. 15	—	—
	Netilmicin	Netromycin	—	—	4–6 mg/kg ^{11,12}	8 hr
	Streptomycin	—	—	—	1–2 g	12 hr
	Tobramycin	Nebcin	—	—	3–5 mg/kg ¹¹	8 hr
Tetracyclines	Demeclocycline	Declomycin	600 mg	6 hr	—	—
	Doxycycline	Vibramycin, etc.	100–200 mg ¹⁷	12 hr	—	—
	Minocycline	Minocin	200 mg ¹⁹	12 hr	—	—
	Oxytetracycline	Terramycin	1–2 g	6 hr	See fn. 21	See fn. 21
	Tetracycline	Achromycin, Panmycin, Sumycin, Tetracyn, etc.	1–2 g	6 hr	See fn. 21	See fn. 21
Macrolides	Azithromycin	Zithromax	500 mg day 1 250 mg days 2–5	24 hr	—	—
	Clarithromycin	Biaxin	500 mg–1 g	12 hr	—	—
	Dirithromycin	Dynabac	500 mg	24 hr	—	—
	Erythromycin	E-Mycin, Erythrocin, Ilotycin	1–2 g	6 hr	See fn. 21	See fn. 21
	Erythromycin estolate ²³	Ilosone	1–2 g	6 hr	—	—
Sulfonamides	Sulfadiazine	—	2–4 g ²⁴	6 hr	—	—
	Sulfisoxazole	Gantrisin	2–6 g ²⁴	6 hr	—	—
	Trimethoprim-sulfamethoxazole	Bactrim, Septra	4 tablets ²⁵	12 hr	—	—
Miscellaneous antibacterial agents	Clindamycin	Cleocin	600 mg–1.8 g	6 hr	600 mg–1.2 g	6–8 hr
	Chloramphenicol	Chloromycetin	1.5–3.0 g	6 hr	See fn. 26	See fn. 26
	Metronidazole	Flagyl	250 mg	8 hr	—	—
	Spectinomycin	Trobicin	—	—	2 g ²⁸	Single injection
	Trimethoprim	Proloprim, Trimplex	200 mg	12 hr	—	—
	Vancomycin	Vancocin	2 g ²⁹	6 hr	—	—
Urinary tract disinfectants	Fosfomycin	Monurol	—	—	—	—
	Methenamine mandelate	Mandelamine	—	—	—	—
	Methenamine hippurate	Hiprex	—	—	—	—
	Nalidixic acid	NegGram	—	—	—	—
	Nitrofurantoin	Furadantin, Macrochantin	—	—	—	—
Antifungal drugs	Amphotericin B	Fungizone	—	—	—	—
	Fluconazole ³¹	Diflucan	100–200 mg ³²	24 hr	—	—
	Flucytosine	Ancobon	50–150 mg/kg ³³	6 hr	—	—
	Itraconazole	Sporanox	100–400 mg	12 or 24 hr	—	—
	Ketoconazole	Nizoral	200 mg ³³	24 hr	—	—
	Miconazole	Monistat	—	—	—	—
	Nystatin	Mycostatin	1.5–3.0 million units ³⁵	8 hr	—	—
Fluoroquinolones ³⁶	Alatrofloxacin ³⁶	Trovan I.V.	—	—	—	—
	Ciprofloxacin	Cipro	500 mg	12 hr	—	—
	Levofloxacin	Levaquin	500 mg	24 hr	—	—
	Lomefloxacin	Maxaquin	400 mg	24 hr	—	—
	Norfloxacin	Noroxin	—	—	—	—
	Ofloxacin	Floxin	400–800 mg	12 hr	—	—
	Sparfloxacin	Zagam	400 mg first day, then 200 mg	24 hr	—	—
	Trovafloxacin ³⁶	Trovan	See fn. 36	See fn. 36	—	—
	Gatifloxacin	Tequin	400 mg	24 hr	—	—
	Moxifloxacin	Avelox	400 mg	—	—	—

(continued)

Table 5 (continued)

Uncomplicated Urinary Tract Infections		Major and Systemic Infections [†]			
Oral		Intramuscular		Intravenous	
Daily Dose	Interval	Daily Dose	Interval	Daily Dose	Interval
—	—	—	—	3–8 g	6–8 hr
—	—	15 mg/kg ⁹	8–12 hr	15 mg/kg ¹⁰	8 hr
—	—	3–5 mg/kg	8 hr	3–5 mg/kg ¹²	8 hr
—	—	15 mg/kg ¹³	8–12 hr	15 mg/kg ¹⁴	8 hr
—	—	—	—	—	—
—	—	4–6 mg/kg	8 hr	4–6 mg/kg ¹⁶	8 hr
—	—	1–2 g	12 hr	—	—
—	—	3–5 mg/kg	8 hr	3–5 mg/kg ¹⁶	8 hr
600 mg	6 hr	—	—	—	—
100–200 mg ¹⁷	12 hr	—	—	100–200 mg ¹⁸	12 hr
200 mg ¹⁹	12 hr	—	—	200 mg ²⁰	12 hr
1–2 g	6 hr	—	—	—	—
1–2 g	6 hr	See fn. 21	See fn. 21	750 mg–1.0 g ²²	6–12 hr
—	—	—	—	—	—
—	—	—	—	—	—
—	—	—	—	—	—
—	—	See fn. 21	See fn. 21	2–4 g	6 hr
—	—	—	—	—	—
2–4 g ²⁴	6 hr	—	—	—	—
2–6 g ²⁴	6 hr	—	—	100 mg/kg ²⁴	4–6 hr
4 tablets ²⁵	12 hr	—	—	8–12 mg/kg ²⁵ (trimethoprim)	6 hr ²⁵
—	—	1.2–2.4 g	6–8 hr	1.8–3.0 g	6–8 hr
1.5–2.0 g ²⁷	6 hr	See fn. 26	See fn. 26	2–4 g	6 hr
—	—	—	—	30 mg/kg	6 hr
—	—	—	—	—	—
200 mg	12 hr	—	—	—	—
—	—	—	—	1–2 g	6–12 hr
3 g	1 dose	—	—	—	—
4 g	6 hr	—	—	—	—
2 g	12 hr	—	—	—	—
2–4g	6 hr	—	—	—	—
200–400 g	6 hr	—	—	Not recommended	—
—	—	—	—	0.25–1.0 mg/kg ³⁰	24 hr
—	—	—	—	200 mg ³¹	24 hr
—	—	—	—	—	—
—	—	—	—	—	—
—	—	See fn. 32	See fn. 32	See fn. 32	See fn. 32
—	—	—	—	600 mg–3.6 g ³⁴	8 hr
—	—	—	—	—	—
—	—	—	—	200 mg	24 hr
200–500 mg	12 hr	—	—	400 mg	12 hr
500 mg	24hr	—	—	500 mg	24 hr
400 mg	24 hr	—	—	—	—
800 mg	12 hr	—	—	—	—
400 mg	12 hr	—	—	800 mg	12 hr
—	—	—	—	—	—
—	—	—	—	—	—
400 mg	24 hr	—	—	400 mg	24 hr
400 mg	24 hr	—	—	—	—

(continued)

Table 5 (continued)

Class of Agent	Specific Agent	Trade Names	Modest Infections*			
			Oral		Intramuscular	
			Daily Dose	Interval	Daily Dose	Interval
Streptogramins	Quinupristin-dalfopristin	Synercid	—	—	—	—
Oxazolidinones	Linezolid	Zyvox	400 mg	12 hr	—	—

Note: all superscript numbers refer to footnotes following table.

*Infections of the upper respiratory tract, soft tissues, etc.

†Osteomyelitis, peritonitis, bacteremia, meningitis, endocarditis, etc.

1. Benzathine penicillin G is used primarily in three circumstances. (1) Treatment of streptococcal pharyngitis in cases in which patient compliance is questionable (a single dose of 1.2 million units I.M.). (2) Prophylaxis of rheumatic fever recurrences (1.2–2.4 million units I.M. once monthly). (3) Treatment of syphilis: for primary, secondary, or early (< 1 yr) latent syphilis, a single dose of 2.4 million units I.M.; for late syphilis (late latent, cardiovascular, neurosyphilis, etc.), 2.4 million units I.M. weekly for three doses has been recommended, but many authorities now treat neurosyphilis with high-dose I.V. penicillin.

2. Each tablet of carbenicillin indanyl sodium is equivalent to 382 mg of carbenicillin (usual dosage is one to two tablets p.o., q.i.d.).

3. Piperacillin is most often used in the treatment of serious infections caused by susceptible *Pseudomonas*, *Klebsiella*, *Enterobacter*, and non-*mirabilis* *Proteus* strains; the agent is given in maximal dosage (12–18 g I.V. daily). It is commonly used in synergistic combination with tobramycin or gentamicin for treatment of *Pseudomonas* infections. Occasionally, it is given in smaller dosages (1.0–1.5 g I.M. or I.V. q. 6 hr) to treat an uncomplicated urinary tract infection caused by the same organisms.

4. Ticarcillin, piperacillin, mezlocillin, and azlocillin are usually used in the treatment of serious infections caused by susceptible *Pseudomonas*, *Enterobacter*, and non-*mirabilis* *Proteus* strains and are given in maximal dosage (12–24 g I.V. daily). One of these agents is commonly used in synergistic combination with tobramycin or gentamicin for treatment of *Pseudomonas* infections. Occasionally, they are given in smaller dosages (1 g I.M. or I.V. q. 6 hr) to treat an uncomplicated urinary tract infection caused by the same organisms.

5. Nafcillin is not reliably absorbed by the oral route.

6. Cefazolin may be used in the treatment of acute uncomplicated urinary tract infections caused by susceptible gram-negative bacilli (*E. coli*, *P. mirabilis*, and *Klebsiella*). It is administered I.M. in a dosage of 2 g daily (given as aliquots q. 8 hr).

7. Although the second- and third-generation cephalosporins can be used for milder infections at the lower end of their recommended dosage range, these potent but expensive agents should generally be reserved for treatment of serious infections or for the treatment of resistant organisms when the alternative is a more toxic antimicrobial drug.

8. The I.M. route is acceptable for milder illnesses, but the I.V. route is recommended for serious infections, including bacteremias and meningitis. The range for the I.M. dosage is the same as that for the I.V. dosage.

9. Dosage must be reduced in the presence of renal insufficiency. The daily parenteral dose should not exceed 15 mg/kg, and the total daily amount administered should not exceed 1.5 g, regardless of the patient's weight.

10. The I.V. dose should be infused during a period of 30–60 min q. 8 hr.

11. For urinary tract infections caused by resistant organisms.

12. Dosage must be reduced in the presence of renal insufficiency. The I.V. dose should be administered for a period of 30–60 min q. 8 hr. In patients with meningitis caused by susceptible gram-negative bacilli, intrathecal gentamicin (5 mg for adults, 1–2 mg for infants) is often administered once daily along with parenteral gentamicin until CSF cultures are negative.

13. Dosage must be reduced in the presence of renal insufficiency. The daily parenteral dose should not exceed 15 mg/kg (daily dose should not exceed 1.5 g, regardless of the patient's weight); the total quantity administered in a therapeutic course should not exceed 15 g.

14. The I.V. route should be employed only when I.M. administration is not possible. The I.V.

dose should be administered during a period of at least 60 min q. 8 hr.

15. There are no clinical indications for the parenteral administration of neomycin in view of its marked toxicity and the availability of safer alternative drugs. The drug is given p.o. or by nasogastric tube (4–6 g daily in 4 divided doses) to reduce the number of ammonia-forming bacteria in the intestine in the short-term treatment of acute hepatic coma. It is also given in a total daily dose of 2–3 g in long-term therapy for chronic hepatic encephalopathy or episodic hepatic coma. Nephrotoxicity and ototoxicity have followed prolonged high-dose therapy in hepatic coma, particularly in patients with some renal impairment. Neomycin is also used along with vigorous mechanical cleansing of the large bowel as preoperative prophylaxis for bowel surgery. In this situation, it is administered for 1–3 days preoperatively (40 mg/kg p.o. daily in 6 divided doses).

16. Dosage must be reduced in the presence of renal insufficiency. The I.V. dose should be administered during a period of 30–60 min q. 8 hr.

17. Usually administered as 100 mg p.o. q. 12 hr on the first day of treatment, followed by 50 mg q. 12 hr. For more difficult infections, the dosage may be continued at 100 mg q. 12 hr.

18. Usually administered as 100 mg I.V. q. 12 hr on the first day of treatment. Thereafter, it may be given as 50–100 mg I.V. q. 12 hr. Each I.V. dose should be given during a period of 1–4 hr.

19. Usually administered initially as 200 mg p.o., followed by 100 mg q. 12 hr.

20. Usually given initially as 200 mg I.V., followed by 100 mg q. 12 hr. Maximum dose in any 24-hr period is 400 mg.

21. I.M. administration is generally unsatisfactory because of poor absorption and local irritation.

22. In special circumstances, it may be given in higher doses but not in excess of 500 mg q. 6 hr.

23. Cholestatic hepatitis may develop as a hypersensitivity response to erythromycin estolate but not to the other erythromycin preparations. For this reason, erythromycin base or erythromycin stearate is preferable.

24. A loading dose of one half the daily dose is given initially. In severe infections, the dosage of sulfonamide is adjusted to provide a blood level of 10–15 mg/dl. Sulfonamides must be used with caution in patients with renal insufficiency. Sulfisoxazole is the preferred sulfonamide.

25. Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole. Double-strength tablets are also available (usual dosage is 1 tablet q. 12 hr). Pediatric suspensions contain 40 mg trimethoprim and 200 mg sulfamethoxazole/5 ml. Trimethoprim-sulfamethoxazole has also been used in the treatment of typhoid fever in the same dosage as recommended for urinary tract infections. It has been used in a dosage of 4–8 standard tablets daily in the treatment of brucellosis. For pneumonia caused by *Pneumocystis carinii*, the oral dosage is 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole/24 hr (equally divided doses q. 6 hr). The I.V. dosage of trimethoprim-sulfamethoxazole ranges from 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole/24 hr to 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole/24 hr. The lower dosage range is used in the treatment of urinary tract infections that require parenteral antimicrobial therapy and in the treatment of shigellosis; the larger dosage is employed in the treatment of *P. carinii* pneumonia.

26. Chloramphenicol sodium succinate, the parenteral preparation, should only be used I.V. It is ineffective when administered I.M.

27. Chloramphenicol should not be used in the treatment of a urinary tract infection that could

(continued)

Chronic Health Evaluation II) score, treatment with vancomycin, and a diagnosis of hematologic malignancy. Thus, severe illness, underlying disease, and the use of vancomycin are major risk factors for infection of the bloodstream with VRE.³³ Fueling the excessive use of broad-spectrum antimicrobial drugs is the lack of reliable tests that would permit physicians to discern when antimicrobial drugs are not needed. When antimicrobial therapy is needed, improved diagnostic tests would permit better targeting and thereby reduce the widespread administration of broad-spectrum drugs. Selective pressure exerted by widespread antimicrobial use is the driving force in the development of antibiotic resistance. The association between increased rates of antimicro-

bial use and resistance has been documented for nosocomial infections³⁴ and community-acquired infections in studies associating resistance patterns with rates of drug use on a regional or national basis.³⁵

Resistance to antimicrobial drugs is a global problem. Multidrug-resistant pathogens travel not only locally but globally. Because of increased international travel and increased foreign trade in fresh-food products, the threat of global spread of antibiotic resistance is greater than ever. There is no national or global surveillance system for the monitoring of antibiotic resistance in animals or humans. New classes of antimicrobials are being developed to deal with drug resistance.

Table 5 (continued)

Uncomplicated Urinary Tract Infections		Major and Systemic Infections [†]			
Oral		Intramuscular		Intravenous	
Daily Dose	Interval	Daily Dose	Interval	Daily Dose	Interval
—	—	—	—	7.5 mg/kg	8 hr
—	—	—	—	600 mg (i.v. or p.o.)	12 hr

[†]Osteomyelitis, peritonitis, bacteremia, meningitis, endocarditis, etc.

be managed with another, safer, effective antimicrobial.

28. The only approved indication for the use of spectinomycin is in the treatment of anogenital and urethral gonorrhea in a penicillin-allergic patient or when the infecting organism is highly penicillin resistant. In geographic areas where antibiotic-resistant gonococci are prevalent, treatment with 4 g of spectinomycin (2 g in each gluteal region) may be indicated.

29. Vancomycin is not absorbed through the GI tract. Its use orally is for treatment of staphylococcal enterocolitis or antibiotic-associated enterocolitis.

30. The dry powder is reconstituted by addition of Sterile Water for Injection, USP, without a bacteriostatic agent. The solution is then added to a bottle of 5% Dextrose Injection, USP. The pH of the dextrose solution should first be checked to verify that it is above 4.2. If it is not, a buffer solution (as described in package insert) should be added. Amphotericin B solutions should be administered promptly after preparation and should be protected from light during administration. It is given once a day over 6 hr. (Later in the course of administration, double the daily dose is sometimes given on an alternate-day schedule.) Dosage is 1 mg on the first day and then increased in 5 mg increments each day until maintenance dosage is reached. The daily dose is determined by the susceptibility of the organism and the occurrence of toxic side effects. In some instances (e.g., cryptococcal meningitis), combination therapy with flucytosine p.o. may allow employment of smaller daily doses (0.3–0.4 mg/kg) of amphotericin B. In fungal meningitis, intrathecal administration may be necessary (0.1 mg initially, increased gradually to 0.5 mg q. 48–72 hr), depending on the evaluation of the patient's condition.

31. Fluconazole is very useful for the treatment of oropharyngeal, esophageal, and disseminated infections caused by *Candida* and for control of cryptococcus, especially chronic suppression of cryptococcal meningitis in patients with AIDS. To initiate therapy, a loading dose of twice the usual daily dose should be used. A daily dose of 400 mg can be used for cryptococcal meningitis, depending on the patient's response to therapy. The dose should be reduced in patients who have renal insufficiency.

32. Used in the treatment of urinary tract infections and visceral infections caused by *Candida*. Also used in cryptococcal infections in which amphotericin B is not tolerated. Resistance to flucytosine may develop during treatment of candidal and cryptococcal infections. Sometimes

used in combination with amphotericin B to treat systemic fungal infections.

33. Ketoconazole is indicated in the treatment of patients with susceptible fungal infections that have failed to respond to amphotericin B or in the treatment of patients unable to tolerate the toxic effects of amphotericin B. In either role, it is generally preferred to therapy with miconazole when the patients can take oral medications. It is also the drug of choice in the long-term treatment of chronic mucocutaneous candidiasis. It has been useful in the treatment of histoplasmosis, coccidioidomycosis, chromomycosis, and paracoccidioidomycosis. In view of its poor penetration of the CSF, it should not be used in the treatment of coccidioidal or cryptococcal meningitis. Ketoconazole requires gastric acidity for dissolution and absorption. Antacids and cimetidine, if needed, should be given at least 2 hr after a dose of ketoconazole. The most frequent side effects have been nausea and vomiting. Several cases of liver injury of varying severity, possibly the result of idiosyncratic reactions, have occurred during ketoconazole therapy. Liver function tests, therefore, should be evaluated before and periodically during treatment, especially in patients who are on prolonged therapy or who have preexisting hepatic disease. Ketoconazole, in daily dosages of 200–1,800 mg p.o., is used in major and systemic fungal infections for which the mycotic agent is susceptible and amphotericin B cannot be employed.

34. Miconazole is available for parenteral therapy for systemic mycoses. Experience is relatively limited, and it should probably be reserved for patients who cannot tolerate or who do not respond to amphotericin B and flucytosine. Miconazole is metabolized by extrarenal mechanisms, and patients with fungal bladder infections require supplementary bladder irrigation with the drug. Side effects of miconazole include phlebitis, fever, rash, nausea and vomiting, anemia, thrombocytopenia, and transient hyperlipidemia caused by the diluent used.

35. Not absorbed from the GI tract. Use only in treatment of intestinal tract colonization by *Candida* species and not for any systemic mycotic infection. Nystatin suspension (400,000–600,000 units q.i.d.) is used as a mouthwash in treatment of oral thrush. The suspension can also be swallowed for use in the treatment of candidal esophagitis.

36. None of these drugs is recommended for children. In 1999, the FDA limited trovafloxacin to inpatient use for limb- or life-threatening infections.

Discussion

The antimicrobial agents of choice for various infections (e.g., community-acquired pneumonia^{7–9}) in adults are well established [see Table 4], as are their dosages in patients with normal renal function [see Table 5]. Excellent reviews and practice guidelines have been published.^{18,19}

Penicillins

Although the original penicillins are still useful against specific bacteria, there are some infections in which both they and the penicillinase-resistant semisynthetic penicillins are ineffective because of the emergence of penicillinase-producing staphylococci and methicillin-resistant staphylococci. The penicillins can be classified by structure, β -lactamase susceptibility, and spectrum of action [see Figure 1].

The action of the penicillins depends on the presence of a bacterial cell wall containing peptidoglycans that are accessible to the agent. In actively growing bacteria, interference with biosynthesis of the peptidoglycan structure—specifically, of the cross-linkages between the peptide chains—prevents the bacterium from developing its normal structural firmness, and this lack of firmness leads to lysis.

NATURAL PENICILLINS

Aqueous Crystalline Penicillin G

Aqueous crystalline penicillin G is used when a high serum concentration of the agent is required.³⁶ Its half-life is normally 30 minutes but may be as long as 10 hours in patients with anuria. Approximately 50% of penicillin G is bound to plasma proteins.

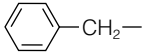
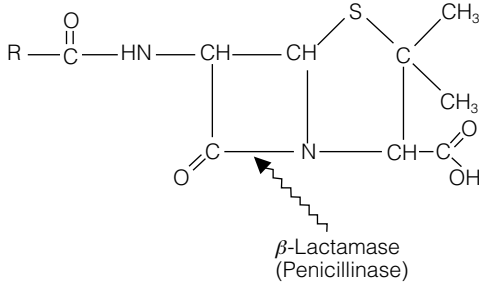
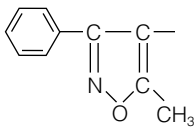
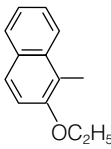
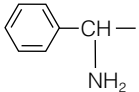
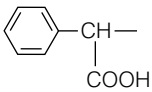
Generic Name	Side-Chain Substituent (R)	Penicillin Structure
Penicillin G		
Oxacillin		
Nafcillin		
Ampicillin		
Carbenicillin		

Figure 1 Various semisynthetic penicillins have been produced by modifying the structure of the side chain (R) attached to the penicillin nucleus (right). In this way, penicillins have been developed that lack some of the drawbacks of penicillin G, such as poor gastrointestinal absorption, limited spectrum of antibacterial activity, and inactivation by penicillinase-producing microorganisms; for example, oxacillin and nafcillin are resistant to inactivation by penicillinase. This bacterial enzyme (also termed β -lactamase) cleaves the β -lactam ring of penicillin to form an inactive product; the site of action of penicillinase is shown at right.

Penicillin G sodium contains approximately 2 mEq of sodium per one million units. Therefore, the potassium salt of penicillin G should be used except in patients with renal insufficiency, who may not be able to tolerate the 1.7 mEq of potassium contained in each one million units. This agent is destroyed by gastric acid when given orally.

Penicillin G Benzathine

Penicillin G benzathine, 1.2 to 2.4 million units I.M., is used in the definitive management of certain infections, such as streptococcal sore throat, and as prophylaxis for several conditions, such as rheumatic fever, in which reinfection by β -hemolytic streptococci is a constant threat.

Penicillin G Procaine

Penicillin G procaine is used intramuscularly when a long-acting preparation is preferred and high blood levels are not required. It is indicated for the treatment of pneumococcal pneumonia, uncomplicated cases of which are adequately treated by administration of one or two daily doses of 300,000 units, and for treatment of acute genitourinary gonorrhea, for which a dose of 4.8 million units is divided and injected at two sites and 1 g of probenecid is given orally before the injection.

Penicillin V

Phenoxymethyl penicillin, or penicillin V, is resistant to gastric acid and therefore reaches higher serum concentrations, when given orally, than penicillin G does at similar doses. Penicillin V should not be substituted for parenterally administered penicillin G when such therapy is needed, but it can be given orally to treat

mild infections of the throat, the respiratory tract, or soft tissue in doses of 125 to 500 mg given four to six times daily.

PENICILLINASE-RESISTANT PENICILLINS

Methicillin

Methicillin is the least protein-bound of this group (39%); nafcillin (90%), oxacillin (94%), cloxacillin (95%), and dicloxacillin (98%) all have higher rates of protein binding. Methicillin was the first of the semisynthetic penicillinase-resistant penicillins.³⁷ It must be administered parenterally and is usually given every 4 to 6 hours in a total daily dose of 100 to 300 mg/kg body weight.

Oxacillin and Nafcillin

Oxacillin seems to be as effective as methicillin against staphylococcal infections, and it causes interstitial nephritis less often. For parenteral use, oxacillin or nafcillin can be given in dosages of 100 to 300 mg/kg/day for children and up to 4 to 12 g/day for adults.

Cloxacillin and Dicloxacillin

If penicillinase-producing organisms are identified or suspected and oral therapy is desired, cloxacillin or dicloxacillin, 1 to 2 g/day, can be given.

AMINOPENICILLINS

Ampicillin

Ampicillin is active against a variety of bacteria, including many strains of *Escherichia coli*, *Proteus mirabilis*, *Salmonella*, *Shigella*,

Listeria, and *Haemophilus influenzae*. Most strains of *Klebsiella* and all strains of *P. aeruginosa* are resistant.

Because it is stable in gastric juices, ampicillin is suitable for oral as well as parenteral use. When it is given orally, peak serum levels are reached in about 2 hours, but they seldom exceed 0.3 µg/ml. When it is given intramuscularly, peak serum levels are achieved in 1 hour, and they are both higher and more prolonged than the peak levels achieved after oral administration. About 10% of ampicillin is bound to plasma proteins. The recommended daily dose is 1 to 4 g; parenteral administration of up to 12 g/day is recommended for major systemic infections.

Amoxicillin

Amoxicillin is closely related to ampicillin, both in chemical structure and in spectrum of antibacterial activity.³⁸ Amoxicillin, however, is more completely absorbed than ampicillin: approximately 70% of a dose of amoxicillin is absorbed, compared with approximately 50% of a dose of ampicillin. Consequently, the blood levels attainable with a given dose of amoxicillin are usually about twice those attainable with a comparable dose of ampicillin. Amoxicillin is at least as effective as ampicillin in the treatment of respiratory disorders that are caused by susceptible bacteria, including otitis media, sinusitis, and bronchitis.

CARBOXYPENICILLINS

Carbenicillin

Carbenicillin has an antibacterial range similar to that of ampicillin, with the added benefit of activity against certain strains of *P. aeruginosa*,³⁹ indole-positive *Proteus* species, and *Enterobacter* species.⁴⁰ Because carbenicillin is inactivated by penicillinase, penicillinase-producing *S. aureus* is resistant to it. *Klebsiella* species are resistant to carbenicillin, as are many *Serratia* organisms. Carbenicillin is bactericidal and is recoverable from blood, urine, lymph, CSF, and most body tissues. About 50% of the drug is bound to serum proteins.⁴¹

Ticarcillin

The antibacterial spectrum of ticarcillin is similar to that of carbenicillin; however, it is two to four times more active against *P. aeruginosa*. It is frequently preferred to carbenicillin in the treatment of serious gram-negative infections because of its greater potency and the lower incidence of adverse effects.⁴² The primary use of ticarcillin is in the treatment of proven or suspected *Pseudomonas* infections. The recommended dosage is 16 to 24 g/day.

UREIDOPENICILLINS

Mezlocillin, Azlocillin, and Piperacillin

Mezlocillin, azlocillin, and piperacillin are semisynthetic penicillins derived from the ampicillin molecule with side-chain adaptations. The ureidopenicillins are generally bactericidal and act primarily by inhibiting cell wall synthesis in dividing bacteria. In comparison with the carboxypenicillins carbenicillin and ticarcillin, the ureidopenicillins exhibit less pronounced plasma protein binding, a shorter serum half-life, and a greater volume of distribution.^{43–45} They are minimally metabolized (10%) and are primarily excreted in an active form by glomerular filtration and tubular secretion. Unlike carbenicillin and ticarcillin, the ureidopenicillins achieve high concentrations in bile because of increased biliary excretion.

In vitro, the ureidopenicillins are active against streptococci,

enterococci, most Enterobacteriaceae, *Pseudomonas*, β-lactamase-negative staphylococci, *Neisseria*, and *Haemophilus*.^{46–48} β-Lactamase-producing staphylococci and *H. influenzae* are resistant. The major advantage the ureidopenicillins have over other penicillins in clinical use is their increased activity against *P. aeruginosa* and *Klebsiella*.

The recommended dosages of the ureidopenicillins are 6 to 16 g/day for mild to moderate infections and 18 to 24 g/day for severe to life-threatening infections. Small doses may be given intramuscularly, but large doses must be given intravenously. The dosing interval is usually 4 to 6 hours.

Cephalosporins

Cephalosporium acremonium was discovered in 1948. This fungus was found to produce cephalosporin C, from which cephalothin, the first cephalosporin to be introduced, was in turn derived. The basic cephalosporin structure consists of a dihydrothiazine ring fused to a β-lactam ring.

Substitutions at the acyl side chain have led to differences in antibacterial spectrum and β-lactamase stability. The side chains substituted at this position interfere with proper stereotactic binding of the molecule to the β-lactamase active site, thus preventing degradation of the cephalosporin. Some of the side effects involving platelet aggregation that have been observed with the use of moxalactam can be traced to substitutions at this position.

For convenience, cephalosporins are divided into four generations or groups according to the nature and extent of their antibacterial spectra. More specifically, the division into generations is based on the number of gram-negative bacterial species against which each cephalosporin demonstrates clinical activity. It must be remembered, however, that although the members of each generation are sufficiently similar to be grouped together, they also are different from one another in a number of ways [see Table 6].

FIRST-GENERATION CEPHALOSPORINS

First-generation cephalosporins have good activity against aerobic gram-positive cocci such as *S. aureus*, group B streptococci, and *Streptococcus pneumoniae*. In addition, they are effective against three aerobic gram-negative bacilli—*E. coli*, *K. pneumoniae*, and *P. mirabilis*—although even among these three, resistance is common, occurring in as many as 30% of cases. First-generation cephalosporins are also active against most anaerobic cocci and bacilli (other than *B. fragilis*). They have little or no activity against *Enterobacter*, *Serratia*, *Acinetobacter*, *Pseudomonas*, methicillin-resistant *S. aureus*, *S. epidermidis*, and enterococci. They are also inactive against *B. fragilis*, *Citrobacter*, *Listeria monocytogenes*, *Proteus* (except for *P. mirabilis*), and *Providencia*.

First-generation cephalosporins are used for infections caused by gram-positive cocci, such as skin infections and osteomyelitis, although penicillins are the agents of choice for all streptococcal infections and for infections proven by culture to be caused by susceptible staphylococci. The best use for first-generation cephalosporins is in surgical prophylaxis. For this application, cefazolin sodium is the preferred agent.

SECOND-GENERATION CEPHALOSPORINS

Second-generation cephalosporins possess the same spectrum of activity as the first-generation cephalosporins, with the addition of broader coverage of gram-negative organisms, including *H. influenzae*, *E. aerogenes*, and some *Neisseria* species. Fewer than

Table 6 Properties of Cephalosporins¹⁵⁵

	Specific Agent	Trade Names	Comment*
First Generation	Oral		
	Cefadroxil	Duricef, Ultracef	Longer half-life
	Cephalexin	Keflex	Most experience with this agent
	Cephadrine	Anspor, Velosef	Properties are similar to those of cephalexin
	Parenteral		
	Cefazolin	Ancef, Kefzol	Longer half-life; well tolerated when given I.M.
Second Generation	Cephapirin	Cefadyl	Properties are similar to those of other first-generation cephalosporins
	Cephadrine	Anspor, Velosef	Properties are similar to those of other first-generation cephalosporins
	Oral		
	Cefaclor	Ceclor	Moderately active against <i>Haemophilus influenzae</i>
	Cefprozil	Cefzil	Active against <i>H. influenzae</i>
	Cefuroxime axetil	Ceftin	Active against <i>H. influenzae</i>
	Loracarbef	Lorabid	A carbacephem with properties and spectrum similar to those of cefuroxime
	Parenteral		
	Cefamandole	Mandol	Active against <i>H. influenzae</i> ; may cause bleeding
	Cefmetazole	Zefazone	Spectrum and half-life similar to cefoxitin; may cause bleeding
	Cefonicid	Monocid	Spectrum similar to that of cefamandole
Third Generation	Ceforanide	Precef	Spectrum similar to that of cefamandole
	Cefotetan	Cefotan	Spectrum similar to that of cefoxitin; longer half-life than cefoxitin; may cause bleeding
	Cefoxitin	Mefoxin	Active against <i>Bacteroides fragilis</i> , <i>Serratia</i> , <i>Neisseria gonorrhoeae</i>
	Cefuroxime	Zinacef, Kefurox	Active against <i>H. influenzae</i> ; only second-generation drug approved for meningitis (selected pathogens)
	Oral		
	Cefixime	Suprax	More active against gram-negative bacilli, gonococci, <i>Moraxella catarrhalis</i> , and <i>H. influenzae</i> than other oral cephalosporins but much less active against <i>Staphylococcus aureus</i> ; not active against <i>Pseudomonas</i>
	Cefpodoxime	Vantin	Similar to cefixime but more active against <i>S. aureus</i>
	Ceftibuten	Cedax	Similar to cefixime but has poor activity against pneumococci and staphylococci
	Parenteral		
	Cefepime	Maxipime	Active against most gram-positive cocci (except enterococci and methicillin-resistant staphylococci), <i>Neisseria</i> , <i>Haemophilus</i> , enteric gram-negative bacilli, and <i>Pseudomonas</i>
	Cefoperazone	Cefobid	Increased activity against <i>Pseudomonas aeruginosa</i> but less against Enterobacteriaceae; may cause bleeding
	Cefotaxime	Claforan	More active against gram-positive cocci
	Ceftazidime	Fortaz, Tazidime, Tazicef	Most active against <i>Pseudomonas</i>
	Ceftizoxime	Cefizox	Properties are similar to those of cefotaxime
	Ceftriaxone	Rocephin	Longer half-life; less active against <i>Pseudomonas</i> , <i>B. fragilis</i>

Note: detailed information about the various cephalosporins is covered in the text.

*Agents are being compared with other members of the same generation of cephalosporins.

5% of *E. coli* and *Proteus* strains are resistant to second-generation cephalosporins. The activity of second-generation agents against *S. pyogenes* and *S. pneumoniae* is equal to that of the first-generation agents, but their activity against staphylococci is variable: the MIC ranges from 0.20 to 25 µg/ml. Of the second-generation agents, the most active against staphylococci is cefamandole, which has an MIC of 0.6 µg/ml for *S. aureus*. Cefotetan and cefoxitin have significant activity against *B. fragilis*. Cefoxitin is less active against *H. influenzae* and *E. aerogenes* than other second-generation cephalosporins, but it is more active against *Serratia* species. Cefoxitin by itself is effective in patients with community-acquired peritonitis who are unlikely to be infected with *Enterobacter* or *P. aeruginosa*.⁴⁹ Cefuroxime and cefamandole have been used with some success in empirical therapy for community-acquired pneumonia.⁵⁰ Cefotetan, a cephamycin introduced in 1986, has a spectrum of activity very similar to that of cefoxitin.⁵¹ It is as active as cefoxitin against *B. fragilis* but is less active against other strains in the *B. fragilis* group. Unlike cefoxitin, cefotetan is active against *H. influenzae*. Cefotetan has proved effective and safe in a variety of clinical situations, including gynecologic infections and surgical prophylaxis.⁵²

Cefprozil is an oral agent whose spectrum of activity includes gram-positive and gram-negative pathogens. It has achieved good results in patients with pharyngitis or tonsillitis.⁵³

Loracarbef is an oral agent of the carbacephem class that is active in vitro against the common pathogens associated with skin infections, otitis media, sinusitis, bronchopulmonary infections, and urinary tract infections.⁵⁴

THIRD-GENERATION CEPHALOSPORINS

In the third-generation cephalosporins, activity against gram-positive cocci is replaced by broader gram-negative coverage. This development is illustrated by susceptibility testing done on *S. aureus*: the MIC of first-generation cephalosporins is 1 µg/ml, that of second-generation cephalosporins is 2 µg/ml, and that of third-generation cephalosporins is 3 µg/ml. Third-generation cephalosporins are more active against the enteric gram-negative bacilli covered by first- and second-generation cephalosporins. Their spectrum of activity includes *Serratia* and *Citrobacter*. They are also highly active against *H. influenzae* and *N. gonorrhoeae* and moderately active against *P. aeruginosa* and some anaerobes. At first, the third-generation cephalosporins seemed capable of providing the same spectrum of activity as the aminoglycosides but without their inherent toxicity; however, they have failed to gain wide popularity in the treatment of high-risk patients or patients with extensive infections. The reasons for this failure include their incomplete spectra of activity against the range of organisms likely to be encountered in polymicrobial infections, their unexpect-

ed agent-specific toxicity, their suboptimal pharmacokinetic properties, and their high propensity for inducing resistance.

Cefixime, an orally absorbed iminomethoxyaminothiazolyl cephalosporin, inhibits 90% of *S. pneumoniae*, *H. influenzae*, and *H. parainfluenzae* strains, whether they produce β -lactamase or not, at concentrations of less than 0.25 mg/L. It inhibits 90% of *Moraxella catarrhalis* strains at concentrations of less than 1 mg/L.

Ceftibuten is an orally active third-generation cephalosporin that possesses increased potency against members of the Enterobacteriaceae.⁵⁵ Generally, it is about 16 times more active than cefuroxime, cefaclor, cephalixin, or amoxicillin-clavulanate; its activity is comparable to that of cefixime. Ceftibuten is ineffective against staphylococci and only partially effective against *S. pneumoniae*. *H. influenzae* and *Neisseria* species, however, are highly susceptible to this agent.

Pharmacokinetics

After I.V. administration, third-generation cephalosporins conform to an open, two-compartment model, characterized by an initial rapid distribution phase followed by a slower terminal elimination phase. The relatively long elimination half-lives of many of the newer β -lactam antibiotics make less frequent dosing possible. Most third-generation cephalosporins are primarily eliminated renally, with two exceptions: cefoperazone and ceftriaxone. Cefoperazone is primarily eliminated unchanged in the bile, and only about 25% of an administered dose is recovered in the urine after 24 hours.⁵⁶ Peak biliary concentrations of cefoperazone approach or exceed 2,000 μ g/ml after a 2 g I.V. dose.⁵⁷ Fifty percent of an administered dose of ceftriaxone is eliminated in the bile; the rest is eliminated renally. Ceftriaxone elimination is decreased to a small extent in end-stage renal disease; however, because the drug is normally given every 12 to 24 hours, there is little accumulation and therefore no need to adjust the dose. In general, third-generation cephalosporins penetrate most tissue and fluid compartments in amounts that, though variable, usually exceed the MIC for most susceptible pathogens. Sputum concentrations in the range of 0.3 to 6.0 μ g/ml are attained with all the agents, and higher concentrations are found in purulent sputum. Ascitic fluid concentrations ranging from 2.4 μ g/ml with ceftizoxime to greater than 60 μ g/ml with cefoperazone are seen in patients with peritonitis.⁵⁸

Concentrations in excess of the MIC for susceptible aerobic and anaerobic organisms (except for *B. fragilis*) are achieved in female genital tissue with all these agents.⁵⁹ These compounds also appear to penetrate the prostate, the testes, the ureters, and renal tissue in significant amounts.⁶⁰

With each of these agents, therapeutic concentrations can be obtained in the gallbladder wall; these concentrations may be as high as 60 μ g/g with cefoperazone. Bone-penetration studies reveal penetration with each of these agents.⁶¹

Clinical Utility

Many studies have compared third-generation cephalosporins in an effort to establish a superior drug or drug combination for life-threatening infections; most have found no statistically significant differences. It is important to remember that even if there is a difference in efficacy between two or more antibiotics, that difference may not be apparent if the study group is not large enough. For example, if one agent fails in 10% of patients and another in only 5%, a study group of 250 to 500 patients would be required to show a statistical difference.^{62,63} Most comparative antibiotic trials, however, have reported on fewer than 60 patients and thus have not been able to pinpoint small differences in effi-

cacy between antibiotics.⁶⁴ Many studies that find no difference between two regimens are in fact subject to this type of error.

FOURTH-GENERATION CEPHALOSPORINS

Cefepime is an extended-spectrum parenteral cephalosporin that provides coverage against both gram-positive and gram-negative organisms, including *S. aureus* and *P. aeruginosa*. Cefepime, which is a zwitterion, has a net neutral charge that allows it to penetrate the outer membrane of gram-negative bacteria faster than third-generation cephalosporins. It is more stable against β -lactamases because of the lower affinity of the enzymes for cefepime when compared with third-generation cephalosporins. In comparison with third-generation cephalosporins, cefepime appears to be less likely to induce resistance, because of a lower rate of hydrolysis by β -lactamases, a low affinity for these enzymes, and more rapid permeation into the cell. It has been used to treat patients with pneumonia, with results comparable to those obtained with ceftazidime.⁶⁵ Because of its antibacterial coverage and proven tissue penetration in acute pancreatitis, cefepime should be studied in patients with severe acute pancreatitis.⁶⁶ However, it offers poor coverage against *Bacteroides* and must be combined with metronidazole or clindamycin. The combination of cefepime and metronidazole was found to be equivalent to imipenem in a prospective, randomized study of intra-abdominal infections.⁶⁷

ADVERSE EFFECTS

Cephalosporins are associated with a number of adverse side effects. The adverse reactions associated with their use are similar to those associated with use of other β -lactam compounds, such as local pain and irritation, hypersensitivity reactions, positive Coombs reaction, leukopenia, thrombocytopenia, transient abnormalities in liver function enzyme levels, and GI disturbances.^{68,69} These reactions are usually mild and reversible, except in those rare patients who manifest life-threatening hypersensitivity reactions. Cephalosporins may be administered to most patients who are allergic to penicillin, because only 5% to 15% of penicillin-allergic patients react adversely to cephalosporins.⁷⁰ An excellent review of cephalosporin allergy and its treatment has been published.⁷¹

Aminoglycosides

Aminoglycosides are composed of two or more amino sugars bound by glycosidic linkage to a central hexose (aminocyclitol) nucleus. Their highly polar, polycationic structure contributes to their poor GI absorption and their meager ability to penetrate the blood-brain barrier. They bind irreversibly to the 30S bacterial ribosome and interfere with protein synthesis. Aminoglycosides also disturb calcium homeostasis and induce cell death as a result of efflux of potassium, sodium, and other essential bacterial constituents. Unlike most other antimicrobial agents that inhibit protein synthesis, aminoglycosides are bactericidal.

All aminoglycosides share certain pharmacokinetic properties. Because they are poorly absorbed when given orally, adequate serum concentrations can be obtained only through parenteral administration. Protein binding is negligible,⁷² and the volume of distribution approximates the volume of the extracellular space.⁷³ In adults with normal renal function, the aminoglycosides have a half-life of about 2 hours, but there is considerable variation between individual patients.⁷⁴ In patients with deteriorating renal function, the half-life of an aminoglycosides increases, often exceeding 24 hours in patients with end-stage renal disease.⁷⁵

The prolonged half-lives of aminoglycosides are substantially shortened during hemodialysis⁷⁶; these agents are much less efficiently removed by peritoneal dialysis.⁷⁷ The aminoglycosides do not penetrate the blood-brain barrier well, even in patients with meningeal inflammation.^{78,79} Drug levels in pulmonary secretions are typically 20% to 40% of serum levels. Low concentrations of aminoglycosides in purulent fluids are probably related to local inactivation caused by DNA released from leukocytes⁸⁰ and by the low regional pH.

The aminoglycosides are rapidly excreted, primarily by glomerular filtration. Urine concentrations may be 100 times the serum level in patients with normal renal function. The aminoglycosides accumulate in the renal cortex; sensitive assay techniques can detect them in urine and serum for up to 10 days after cessation of therapy.

STREPTOMYCIN

Widespread resistance among Enterobacteriaceae has limited the usefulness of streptomycin. At present, streptomycin is almost always employed in combination with other antimicrobial agents. With penicillin or vancomycin, streptomycin is used to treat infective endocarditis caused by viridans streptococci or susceptible enterococcal streptococci. It may also be given in conjunction with other antituberculous drugs to treat mycobacterial diseases and in conjunction with tetracycline to treat brucellosis. Streptomycin is used alone in the treatment of tularemia and plague.

KANAMYCIN

Because of widespread resistance among Enterobacteriaceae and *P. aeruginosa*, kanamycin is rarely used today. It is occasionally used as a second-line agent in combination with other antibiotics in the treatment of tuberculosis.

GENTAMICIN

Gentamicin is used for serious hospital-acquired infections caused by Enterobacteriaceae and most strains of *P. aeruginosa* in institutions in which there is minimal background resistance to this agent (other *Pseudomonas* species are predictably resistant to aminoglycosides). Gentamicin is given with penicillin to treat enterococcal endocarditis and with vancomycin plus rifampin to treat prosthetic valve endocarditis caused by *S. epidermidis*.

TOBRAMYCIN

Tobramycin closely resembles gentamicin with respect to antimicrobial spectrum and pharmacokinetics. Tobramycin is more active against some strains of *A. calcoaceticus* but less active against *S. marcescens*. Although tobramycin has slightly greater intrinsic activity against *P. aeruginosa*, most gentamicin-resistant strains of this organism are also resistant to tobramycin. The difference in nephrotoxicity between gentamicin and tobramycin is clinically insignificant.⁸¹⁻⁸³

AMIKACIN

Amikacin is a semisynthetic derivative of kanamycin. Its major advantage is its resistance to aminoglycoside-modifying enzymes, the production of which is the principal mechanism of bacterial resistance to aminoglycosides. Amikacin may therefore be used against gentamicin-resistant organisms, and it is clearly the aminoglycoside of choice where gentamicin resistance is prevalent. Fortunately, no substantial increase in amikacin resistance has been noted, even in medical centers where it has been used extensively.⁸⁴

NETILMICIN AND SISOMICIN

Netilmicin, a semisynthetic derivative of sisomicin, is not metabolized by most of the aminoglycoside-modifying enzymes and therefore is active against some strains of Enterobacteriaceae that are resistant to gentamicin and tobramycin; however, it is less active against *P. aeruginosa*. Animal studies suggest that netilmicin may be less nephrotoxic than other aminoglycosides,^{82,85} and human studies suggest that it is somewhat less likely to exert toxic effects on cranial nerve VIII.⁸² Sisomicin is more active than gentamicin against Enterobacteriaceae and *P. aeruginosa*, but the nephrotoxicity it has exhibited in animal studies exceeds that of other aminoglycosides.⁸⁶

ADVERSE EFFECTS

Unlike β -lactam antibiotics, aminoglycosides, have a narrow range between therapeutic and toxic levels and are thus more likely to cause side effects. Their ototoxicity is potentially more significant than their nephrotoxicity because it is often irreversible. Cochlear toxicity has been reported in 8% to 10% of patients and has been clinically evident in as many as 4% of patients treated with aminoglycosides for various infections.⁸⁷ Vestibular toxicity, as manifested by electronystagmographic changes, has been found in 5% to 10% of patients and has been clinically significant in 1% to 5%.⁸² Vestibular toxicity is more frequently associated with streptomycin, gentamicin, and tobramycin, whereas auditory toxicity is more typical of kanamycin and amikacin. Ototoxicity and vestibular toxicity are difficult to monitor, particularly in hospitalized patients for whom formal audiometry and caloric testing may be cumbersome or uncomfortable. Because aminoglycoside-associated auditory toxicity generally affects the higher frequencies, early bedside detection is difficult. Toxic effects on cranial nerve VIII seem to be related to advanced age, previous aminoglycoside treatment, and excessive serum levels.

AMINOGLYCOSIDE PHARMACOKINETICS

Peak aminoglycoside concentrations higher than 5 $\mu\text{g/ml}$ are associated with improved survival in patients with gram-negative infections.^{88,89} With gram-negative pulmonary infections, peak concentrations of 8 to 10 $\mu\text{g/ml}$ are necessary because of poor penetration of aminoglycosides into the lungs.^{90,91} It has been shown that a loading dose of gentamicin or tobramycin of 2 mg/kg of lean body weight cannot guarantee adequate peak concentrations in acutely ill patients. The most likely explanation for the usually low peak serum concentrations of aminoglycosides in acutely ill patients is an expanded volume of distribution.⁹²⁻⁹⁶ Dosage adjustments based on blood levels should be made as soon as possible after the beginning of therapy and after the steady state has been reached.

Once-Daily Dosing of Aminoglycosides

Efforts to improve the toxic-to-therapeutic ratio of aminoglycosides include once-daily dosing schedules and reevaluations of the recommended therapeutic ranges. In conventional administration of aminoglycosides to patients with normal renal function, divided doses are administered at 8- to 12-hour intervals. In an effort to improve efficacy and decrease toxicity and cost, once-daily regimens have been compared with conventional regimens. In most protocols, the total doses were equivalent in the single and divided-dose regimens. Two meta-analyses of such trials have concluded that once-daily dosing is as effective as divided dosing and has a lower risk of toxicity in patients with normal renal function.^{97,98} Although most trials evaluated immunocompetent

adults, similar trends were noted for children and for patients with febrile neutropenia. In elderly patients, however, the high peak serum concentrations that occur with once-daily dosing may increase the risk of nephrotoxicity,⁹⁹ probably because of diminished renal clearance. There are several excellent reviews of the subject in the literature.^{100,101}

Tetracyclines

The tetracyclines act against microorganisms by inhibiting protein synthesis; their site of action is the bacterial ribosome. Resistance to the tetracyclines appears slowly and in a stepwise fashion and is mediated by plasmids. Plasmids impart resistance by coding for proteins that interfere with active transport of tetracycline through the cytoplasmic membrane. Microorganisms that acquire resistance to one tetracycline are usually resistant to the other tetracyclines as well.

At appropriate dosages, peak serum concentrations 1 hour after intravenous administration of tetracycline, doxycycline, or minocycline are typically 10 to 20 µg/ml. The newer semisynthetic tetracyclines—doxycycline, methacycline, and minocycline—have considerably longer serum half-lives than the older agents.

Tetracyclines are metabolized by the liver and concentrated in the bile. Biliary concentrations of these agents are, on average, five to 10 times higher than concurrent plasma concentrations. The tetracyclines penetrate body tissues well and are capable of entering the CSF even in the absence of inflammation of the meninges. They readily cross the placental barrier, and relatively high concentrations are found in human milk.

Tetracyclines are useful in the treatment of sexually transmitted diseases. Tetracyclines are also effective for the treatment of other chlamydial infections, such as lymphogranuloma venereum, psittacosis, inclusion conjunctivitis, and trachoma. A tetracycline may also be used in the treatment of gonococcal infections in patients who are unable to tolerate penicillin G. Other sexually transmitted diseases that may be treated with tetracyclines are chancroid and granuloma inguinale.

A tetracycline or erythromycin is the agent of choice for the treatment of *Mycoplasma pneumoniae* infection. Tetracyclines are also effective against rickettsial infections, tularemia, and cholera; in patients unable to tolerate penicillin, they may be used to treat actinomycosis. Doxycycline is useful as prophylaxis against traveler's diarrhea caused by toxicogenic strains of *E. coli*. Unfortunately, the widespread use of tetracyclines as additives to livestock feed has resulted in increasing bacterial resistance to these agents.

Macrolides

ERYTHROMYCIN

Erythromycin is a macrolide that contains a many-membered lactone ring to which one or more deoxy sugars are attached. Erythromycin and other macrolide antibiotics inhibit protein synthesis through reversible binding to the 50S ribosomal subunits of susceptible microorganisms.

Erythromycin is well absorbed from the GI tract. The presence of food in the stomach reduces absorption of the drug, except when it is in the estolate form.¹⁰² Erythromycin is excreted primarily in the bile; only 2% to 5% of a given dose is excreted in the urine. Concentrations in the bile may be more than 10 times those in plasma. Erythromycin diffuses readily into most tissues, except for the brain and the CSF.

Erythromycin is the agent of choice for the treatment of *M. pneumoniae* and *Legionella* infections. It is also effective against infections caused by group A β -hemolytic streptococci or *S. pneumoniae*. Accordingly, it is the agent of choice for the treatment of community-acquired pneumonia in nonimmunosuppressed patients who do not require hospitalization and who are allergic to penicillin.¹⁰³ In addition, erythromycin may be used to treat gonorrhea and syphilis in patients who are unable to tolerate penicillin G or tetracycline. The incidence of serious erythromycin-related adverse effects is low.

CLARITHROMYCIN AND AZITHROMYCIN

Clarithromycin and azithromycin are new semisynthetic macrolides that are structurally related to erythromycin. They inhibit protein synthesis in susceptible organisms by binding to the 50S ribosomal subunit. Clarithromycin and azithromycin are well absorbed and widely distributed, with excellent cellular and tissue penetration. Both agents have a broader spectrum of activity than erythromycin does; in addition, they have fewer GI side effects (a major obstacle to compliance with erythromycin therapy).

Clarithromycin is several times more active against gram-positive organisms in vitro than erythromycin, whereas azithromycin is two to four times less potent than erythromycin. Azithromycin has excellent in vitro activity against *H. influenzae*; clarithromycin, although less active against *H. influenzae* according to standard in vitro testing, is metabolized into an active compound with twice the in vitro activity of the parent drug. Azithromycin and clarithromycin also are active against some unexpected pathogens (e.g., *Borrelia burgdorferi*, *Toxoplasma gondii*, *M. avium* complex, and *M. leprae*). At present, clarithromycin appears to be the more active of the two against atypical mycobacteria, giving new hope to surgeons faced with what has become a difficult group of infections to treat.

Superior pharmacodynamic properties distinguish these new macrolides from the prototypical macrolide, erythromycin. Azithromycin has a large volume of distribution, and although serum concentrations remain low, it concentrates readily within tissues, demonstrating a tissue half-life of approximately 3 days; a 5-day course of therapy will provide therapeutic tissue concentrations for at least 10 days. These properties allow novel dosing schemes. For instance, azithromycin can be given once daily for 5 days to treat respiratory tract and soft tissue infections, and administration of a single 1 g dose of azithromycin can effectively treat *Chlamydia trachomatis* genital infections; these more convenient dosing schedules improve patient compliance.

DIRITHROMYCIN

Dirithromycin is an oral macrolide antibiotic with an antibacterial spectrum similar to that of erythromycin; it can be administered once daily but has no other advantages over erythromycin. The drugs produce similar GI side effects, and dirithromycin is substantially more expensive.

Clindamycin

Clindamycin is a 7-deoxy-7-chloro derivative of lincomycin that consists of an amino acid attached to a sulfur-containing octose. Clindamycin binds exclusively to the 50S subunit of bacterial ribosomes and suppresses the synthesis of protein. Clindamycin, erythromycin, and chloramphenicol all act at the same site, and the binding of one of these antibiotics to the ribosome may inhibit the binding of the others. Plasmid-mediated

resistance to clindamycin has been reported in *B. fragilis*; this may be caused by methylation of bacterial RNA found in the 50S ribosomal subunit.¹⁰⁴ Peak serum concentrations 1 hour after intravenous administration of a 600 mg dose are approximately 10 to 12 µg/ml. Clindamycin is metabolized by the liver and excreted in an inactive form in the urine. It readily penetrates most body tissues but not the CSF.¹⁰⁵

Clindamycin is active against *B. fragilis* and other anaerobic microorganisms and is useful in the treatment of patients with intra-abdominal, pelvic, and pulmonary infections. It is associated with a modest number of adverse effects.

Chloramphenicol

Chloramphenicol is unique among antibiotics in that it contains a nitrobenzene moiety and is a derivative of dichloroacetic acid. Like clindamycin, it inhibits bacterial protein synthesis by binding reversibly to the 50S ribosomal subunit, thus keeping the amino acid-containing end of aminoacyl-transfer RNA (tRNA) from binding to the ribosome. Chloramphenicol is rapidly and completely absorbed from the GI tract, and absorption is not impaired by concomitant ingestion of food or administration of antacids. It is inactivated in the liver by glucuronyl transferase. Chloramphenicol and its metabolites are excreted rapidly in the urine. About 80% to 90% of a dose is excreted in this way, about 5% to 10% of which is in the biologically active form. The drug penetrates well into all tissues, including the brain; it also penetrates well into the CSF and the aqueous humor.

Because of the risk of serious or fatal bone marrow toxicity, chloramphenicol should be used only against those infections for which the benefits of its use outweigh the risks of its potential toxicity. It still plays a major role in the treatment of typhoid fever, although plasmid-mediated resistance of *S. typhi* to chloramphenicol has been reported. Chloramphenicol is effective therapy for bacterial meningitis and brain abscesses caused by susceptible microorganisms; in conjunction with penicillin, it is effective empirical therapy for brain abscesses.

Vancomycin

Vancomycin is a narrow-spectrum antibiotic derived from *Nocardia orientalis*. Vancomycin exerts its bactericidal effect by inhibiting the biosynthesis of the major structural cell wall polymer, peptidoglycan.¹⁰⁶ Vancomycin is about 55% protein bound. Its activity is not significantly affected by pH values between 6.5 and 8.0. It is poorly absorbed from the GI tract. Because patients invariably experience pain after intramuscular injections, parenteral administration is limited to the intravenous route. Vancomycin is primarily excreted by the kidneys; about 80% to 90% of the dose is eliminated in a 24-hour period. Its half-life is approximately 6 hours in patients with normal renal function. In anuric patients, the half-life may be prolonged to approximately 7 days.¹⁰⁷ Vancomycin is not removed by hemodialysis or peritoneal dialysis.

Vancomycin is mainly effective against gram-positive organisms. No cross-resistance has been demonstrated between vancomycin and other antibiotics, and resistance is uncommon. Vancomycin, given alone, is the agent of choice in the treatment of methicillin-resistant *S. aureus* infections.^{108,109} Some strains of methicillin-resistant *S. aureus*, however, are resistant to vancomycin. If vancomycin therapy is ineffective against severe infections caused by such strains, the addition of either an aminoglycoside or rifampin, or both, should be considered. Several reports

have indicated that vancomycin is not bactericidal for enterococci.¹¹⁰ Vancomycin is indicated for other serious infections caused by organisms with multiple antibiotic resistance, such as CSF shunt infections and prosthetic valve infection caused by *S. epidermidis* or *Corynebacterium diphtheriae*.¹¹¹ It is the agent of choice for infections caused by penicillin-resistant group JK corynebacteria¹¹² and is uniformly active against rare, multiply resistant strains of *S. pneumoniae*.¹¹³ Given orally, vancomycin is also the agent of choice for *C. difficile*-associated enterocolitis,¹¹⁴ although less expensive agents, such as bacitracin¹¹⁵ and metronidazole,¹¹⁶ may be as effective.

Anaphylactoid reactions to vancomycin have been reported since the earliest clinical trials. Such reactions can occur with the first dose; signs and symptoms range from mild pruritus to dramatic hypotension and cardiovascular arrest. The rapid intravenous infusion of vancomycin can cause a peculiar reaction consisting of pruritus; an erythematous or maculopapular rash involving the face, neck, and upper torso; and possible hypotension.

Metronidazole

Metronidazole acts by disrupting bacterial DNA and inhibiting nucleic acid synthesis¹¹⁷; it is bactericidal against almost all anaerobic gram-negative bacilli, including *B. fragilis*, and against most *Clostridium* species. Although true anaerobic streptococci are generally susceptible to it, microaerophilic streptococci as well as *Actinomyces* and *Propionibacterium* species are often resistant.

Metronidazole is excellent for anaerobic infections of the abdomen and pelvis. For serious anaerobic infections, the drug is administered intravenously; a loading dose of 15 mg/kg is given, followed by 7.5 mg/kg every 6 hours until the patient is well enough to take an oral dosage of 7.5 mg/kg every 6 hours. The dosage need not be reduced in azotemic patients, but it should be reduced in patients with hepatic insufficiency. Because of its bactericidal action and excellent tissue penetration, intravenous metronidazole may be the treatment of choice for *B. fragilis* endocarditis and central nervous system infections, both of which are uncommon. When metronidazole is administered orally, it is well absorbed and is widely distributed in body tissues, including those of the CNS.

Side effects of metronidazole include dry mouth (associated with a metallic taste) and nausea. Concurrent use of alcohol may cause a reaction similar to that produced when alcohol is ingested after taking disulfiram. Neurologic symptoms, including peripheral neuropathy and encephalopathic reactions, and neutropenia are uncommon. Pancreatitis has been reported,¹¹⁸ but alternative drugs are available.

Carbapenems

Imipenem and meropenem were the first carbapenems available for clinical use in the United States; the third, ertapenem, was released in 2002. Like other β -lactam antibiotics, they are bactericidal and act by inhibiting bacterial cell wall synthesis.¹¹⁹ Three properties account for the extraordinarily broad antibacterial spectrum of the carbapenems: there is no permeability barrier excluding the drugs from bacteria; they have high affinity for penicillin-binding protein 2, which is a crucial component of cell wall structure; and they are extremely resistant to hydrolysis by β -lactamases.

Carbapenems are extraordinarily active against gram-negative bacteria. Whereas imipenem tends to be more active against gram-positive cocci, meropenem appears to be more active

against gram-negative bacilli. Virtually all Enterobacteriaceae are susceptible. *Haemophilus* and *Neisseria* species are also susceptible to carbapenems but at concentrations somewhat higher than those of third-generation cephalosporins. *Acinetobacter*, which is resistant to most other β -lactam antibiotics, is susceptible to imipenem and meropenem, as are *Serratia*, *Salmonella*, *Citrobacter*, *Yersinia*, and *Brucella* species. Gram-negative anaerobes, including *B. fragilis*, are susceptible. *P. aeruginosa* is also susceptible, but some resistant strains have emerged during therapy; as a result, imipenem or meropenem should probably be combined with a second antipseudomonal drug when they are used to treat serious pseudomonal infections. Certain nosocomial pathogens, such as *Stenotrophomonas maltophilia* and *P. cepacia*, are resistant, as are *Flavobacterium* species.

Imipenem is extensively degraded in the renal tubule, which results in low urinary levels of the drug. This drawback can be prevented by using cilastatin, an inhibitor of the brush-border enzyme dehydropeptidase-1. Cilastatin also appears to prevent the tubular damage that is occasionally observed in animals given imipenem alone in high doses. For clinical use, imipenem and cilastatin are administered simultaneously in equal doses.

Meropenem is pharmacologically similar to imipenem except that it is not susceptible to degradation by dehydropeptidase; as a result, it can be administered without cilastatin. About 70% of both meropenem and imipenem is excreted in the urine; the dosage should be reduced in azotemic patients. Like imipenem, meropenem is active against most clinically active gram-positive and gram-negative bacteria, including anaerobes; however, neither drug is active against methicillin-resistant staphylococci or *E. faecium*. Resistant strains of *P. aeruginosa* have emerged during therapy with each drug.

The clinical efficacy and toxicity of meropenem are similar to those of imipenem, except that meropenem appears more likely to be effective in meningitis and less likely to cause seizures.

Because the newest carbapenem, ertapenem, has a longer half-life than the other members of the group, it can be administered in a single daily intravenous dose.¹²⁰ Like the other carbapenems, ertapenem is excreted in the urine, and the dosage should be reduced in azotemic patients. The antibacterial spectrum of ertapenem is similar to that of meropenem, except that *Pseudomonas* and *Acinetobacter* strains are less susceptible, and *E. faecalis* is resistant.¹²¹ Ertapenem appears effective against community-acquired pneumonias, intra-abdominal infections, complicated skin and soft tissue infections, and complicated urinary tract infections, but experience is limited.

The carbapenems have broader antibacterial spectrums than any other β -lactam antibiotics. They are active against most gram-positive bacteria—both aerobes and anaerobes. Exceptions include some enterococci; many *E. faecalis* strains are sensitive to imipenem and meropenem but not ertapenem, and most *E. faecium* strains are resistant to all three drugs. Some diphtheroids are resistant. Although most *S. aureus* strains are very sensitive, the susceptibility of methicillin-resistant *S. aureus* and coagulase-negative staphylococci is highly variable. Methicillin-resistant *S. aureus* and *Listeria* exhibit carbapenem tolerance. Finally, some strains of *C. difficile* are resistant.

Ertapenem has a spectrum of activity similar to that of meropenem, except that *Pseudomonas* and *Acinetobacter* strains are much less susceptible, and *E. faecalis* is resistant.

The safety of carbapenems seems comparable to that of other β -lactam antibiotics. Nausea and vomiting, local pain at injection sites, and hypersensitivity are the most common reactions. Seizures, although unusual, are a potential concern with imipen-

em; they have been observed in 0.9% of patients who have received the drug; risk factors for seizure include excessive dosages of the drugs, preexisting CNS lesions, epilepsy, and renal insufficiency. Meropenem is less likely to provoke seizures.¹¹⁹ Transient elevations of liver enzymes and leukopenia can occur in patients who are given carbapenems. Antibiotic-associated pseudomembranous colitis has occurred.

Because the structure of the carbapenems resembles that of the penicillins and cephalosporins, there is potential for cross-reactivity in patients allergic to other β -lactam antibiotics. Clinical experience in this situation is limited, but it appears prudent to avoid carbapenems in patients with anaphylactic sensitivity to β -lactam drugs and to use them with caution in patients with milder allergies to penicillins or cephalosporins.¹²²

Carbapenems have been used successfully in patients with pneumonia, intra-abdominal infections, urinary tract infections, endocarditis, bacteremia, osteomyelitis, cellulitis, and febrile neutropenia. The broad spectrum and apparent low toxicity of carbapenems is impressive, but they should be used selectively and with restraint.

Monobactams

The monobactams are monocyclic β -lactam antibiotics that lack the thiazolidine ring found in penicillins and the dihydrothiazine ring found in cephalosporins. Although there are several monobactams under investigation, only aztreonam has been approved for clinical use in the United States. It has been evaluated in open and comparative studies against a number of agents currently used to treat infections.^{123,124} It inhibits only aerobic gram-negative species. It can be administered two or three times daily. It is a poor hapten and has been successfully administered to small numbers of patients with proven allergy to penicillins and cephalosporins.¹²⁵

Aztreonam has been shown to be effective against bacteremia caused by *E. coli*, *K. pneumoniae*, *P. mirabilis*, *S. marcescens*, *P. aeruginosa*, *Enterobacter* species, *Proteus* species, and *Providencia* species.^{126,127} It has also been used, alone or in combination with clindamycin, to treat gram-negative aspiration pneumonia, with results comparable or superior to those obtained with an aminoglycoside-clindamycin combination.^{128,129}

Aztreonam has been advocated as directed therapy to obviate more toxic drugs. It seems possible that aztreonam could replace aminoglycosides in many situations in which they are combined with other agents.

β -Lactamase Inhibitors

A novel approach to antibacterial chemotherapy is the use of β -lactamase inhibitors with β -lactam agents. Clavulanate has been combined with both amoxicillin and ticarcillin. Because neither clavulanate nor sulbactam inhibits the β -lactamases that function primarily as cephalosporinases in *Enterobacter*, *Serratia*, and *P. aeruginosa* infections, the addition of clavulanate or sulbactam does not enhance ticarcillin's activity against *Pseudomonas*. The principal use of amoxicillin-clavulanate has been in the treatment of upper respiratory tract infections caused by β -lactamase-producing *H. influenzae* or *M. catarrhalis*. Ticarcillin-clavulanate has been used to treat pneumonia caused by *P. aeruginosa* and mixed β -lactamase-producing flora as well as intra-abdominal infections and gynecologic infections in which the infecting organisms often possess β -lactamases. In febrile neutropenic patients, its efficacy is comparable to that of other agents, but superinfections may be

a problem.^{130,131} Because some strains of *K. pneumoniae* are not adequately inhibited by ticarcillin-clavulanate, addition of an aminoglycoside would be appropriate in neutropenic patients. Sulbactam has also been combined with ampicillin.

Clavulanate, sulbactam, and tazobactam have all been combined with piperacillin in an attempt to enhance the agent's activity against β -lactamase-producing bacteria.^{132,133} Tazobactam enhances the spectrum of action and potency of piperacillin to a greater extent than sulbactam does. Although piperacillin-clavulanate is more potent than piperacillin-tazobactam, the two combinations are effective against virtually the same spectrum of resistant β -lactamase-producing gram-negative organisms. Piperacillin-tazobactam is more potent than ticarcillin-clavulanate and is effective against a wider range of gram-negative enteric organisms. Combinations of piperacillin with tazobactam or clavulanate have a broader spectrum of activity than combinations of piperacillin with sulbactam against bacteria that produce characterized plasmid-mediated enzymes of clinical significance. In particular, piperacillin-tazobactam and piperacillin-clavulanate inhibit TEM-1, TEM-2, and SHV-1 β -lactamases, but piperacillin-sulbactam does not. In mice infected with β -lactamase-producing *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *S. aureus*, both tazobactam and clavulanate have provided greater enhancement of the therapeutic efficacy of piperacillin than sulbactam has. Reviews of the TEM-type β -lactamases¹³⁴ and the piperacillin-tazobactam combinations¹³⁵ have been published.

Quinolones

The addition of a fluorine group and a piperazine substituent to the first quinolones has greatly improved the antibacterial spectrum of this class of drugs; the addition of a methyl group on the piperazine ring appears to further enhance the bioavailability of these compounds.

The fluoroquinolones are bactericidal compounds that act by inhibiting DNA gyrase, the bacterial enzyme responsible for maintaining the supertwisted helical structure of DNA; DNA topoisomerase IV is a secondary target.¹³⁶ The fluoroquinolones rapidly kill bacteria, probably by impairing DNA synthesis and possibly by mechanisms involving the cleaving of bacterial chromosomal DNA. Bacterial resistance to the fluoroquinolones depends on a change in their DNA gyrase. Bacterial strains that are resistant to one fluoroquinolone tend to be cross-resistant to related compounds; such resistance is usually mediated by chromosomes, but plasmid-mediated resistance raises the possibility of transferable resistance.

The fluoroquinolones are broad-spectrum antimicrobials. Most enteric gram-negative bacilli, including *E. coli*, *Proteus*, *Klebsiella*, and *Enterobacter*, are highly susceptible; common GI pathogens, such as *Salmonella*, *Shigella*, and *Campylobacter* species, are also very sensitive. Other gram-negative organisms that are killed by low concentrations of the fluoroquinolones are *N. gonorrhoeae* and *N. meningitidis*, *H. influenzae*, *P. multocida*, *M. catarrhalis*, and *Y. enterocolitica*. *Acinetobacter* and *Serratia* are somewhat less susceptible. *P. aeruginosa* is susceptible to ciprofloxacin and trovafloxacin; ofloxacin and levofloxacin are moderately active, but the other quinolones are not effective. *P. cepacia* and *S. maltophilia* are quinolone-resistant. Ciprofloxacin is the drug of choice for *Bacillus anthracis*; ofloxacin and levofloxacin are also active in vitro.¹³⁷ Among gram-positive cocci, methicillin-sensitive strains of *S. aureus* and coagulase-negative staphylococci are usually susceptible to quinolones, but methicillin-resistant *S. aureus* and enterococci are not. Lomefloxacin is not active against pneumococci and

other streptococci; ciprofloxacin and ofloxacin are moderately active; and levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin, and trovafloxacin are highly effective, even against non-penicillin-sensitive pneumococci. Even fastidious intracellular pathogens can be inhibited by the quinolones; *Chlamydia*, *Mycoplasma*, *Listeria*, *Legionella*, and *M. tuberculosis* are in this category. Only trovafloxacin is highly active against anaerobes. Levofloxacin, gatifloxacin, moxifloxacin, and sparfloxacin demonstrate some activity against anaerobes, but the other quinolones do not. *C. difficile* is resistant to quinolones.

The fluoroquinolones are rapidly absorbed from the GI tract. Penetration into body fluids and tissues is generally excellent; therapeutic concentrations are readily achieved in blister fluid, bile, urine, saliva and sputum, bone, and muscle. Excellent concentrations of these drugs are achieved in the prostate, and stool levels are extraordinarily high. The fluoroquinolones appear to penetrate the CSF in the presence of meningeal inflammation,¹³⁸ but experience in treating meningitis is scant.

Although serum protein binding is modest, the fluoroquinolones have long serum half-lives, which range from 3 to 4 hours for ciprofloxacin to 12 hours for moxifloxacin. Most fluoroquinolones are eliminated by glomerular filtration and tubular secretion, and their dosages should be reduced in the presence of moderately severe renal failure. Trovafloxacin and moxifloxacin, however, are excreted chiefly by the liver.

The fluoroquinolones appear to be very well tolerated, with mild GI side effects (nausea, vomiting, or anorexia), CNS side effects (light-headedness, dizziness, somnolence, or insomnia), or rash occurring in fewer than 10% of treated patients. Lomefloxacin and sparfloxacin can cause phototoxicity. Less common side effects include allergic intestinal nephritis, pseudomembranous colitis, and neutropenia. Sparfloxacin and moxifloxacin may cause QT interval prolongation and should not be used by patients who have conditions or are using drugs known to prolong the QT interval or predispose to arrhythmias.¹³⁹ Tendinitis has been reported; in severe cases, it has resulted in rupture of the tendons of the shoulder and hand and the Achilles tendon. Crystalluria has been reported after the use of very large doses. Because fluoroquinolones have caused arthropathy in young animals, these drugs should be avoided in children and in women who are pregnant or nursing. Ciprofloxacin is safe in long-term use; there is less long-term experience with the other fluoroquinolones.

The fluoroquinolones have been useful clinically in a variety of infections, including urinary tract, genital, prostatic, GI, respiratory tract, soft tissue, and bone infections. Because of its excellent activity against anaerobes, trovafloxacin was considered useful in intra-abdominal and pelvic infections, but concerns about serious hepatotoxicity have restricted its use to infections deemed life- or limb-threatening and for patients in whom the benefit of trovafloxacin outweighs its potential risks. If it must be used, liver function must be monitored carefully.

The fluoroquinolones, administered in various regimens ranging from a single dose to 5 days of therapy, are effective in preventing and treating traveler's diarrhea and shigellosis. They have been highly effective in the treatment of typhoid fever. However, prolongation of the carrier state limits their role in nontyphoidal *Salmonella* enteritis, and the development of resistance limits their role in *Campylobacter* enteritis. The fluoroquinolones may be useful in the empirical treatment of severe community-acquired gastroenteritis, particularly if treatment is started early.

Because of their extraordinarily broad antimicrobial activity, their favorable pharmacokinetics, and their low toxicity,¹⁴⁰ the

fluoroquinolones are extremely valuable new drugs. Like all antimicrobials, however, fluoroquinolones should be used judiciously, especially in view of new concerns about resistance^{141,142} and toxicity and practical considerations about expense.

ADVERSE EFFECTS

Adverse reactions to the quinolones are estimated to occur in 4% to 8% of cases.¹⁴³ Most such reactions are not severe: cessation of therapy has been necessary in only about 1% to 2% of patients, and in all cases, the reactions have been reversible. The most common adverse effects are gastrointestinal—namely, nausea, vomiting, and diarrhea. The next most common are CNS effects, which include dizziness, headache, insomnia, hallucinations, agitation, and seizures. (The last three have been attributed to coadministration of enoxacin and theophylline.) Other effects include skin rash, pruritus, photosensitivity (with ofloxacin and pefloxacin), and mild alterations in hematologic and biochemical laboratory values.

Streptogramins

Quinupristin and dalfopristin are two structurally distinct streptogramins that bind to separate sites on the bacterial 50S ribosomal subunit; they thus act synergistically to inhibit protein synthesis. The drugs are marketed together in a 30:70 ratio as Synercid.¹⁴⁴

Although quinupristin-dalfopristin is active against a variety of bacteria, its major use is in the treatment of serious infections caused by vancomycin-resistant strains of *E. faecium*. The drugs may also be useful in occasional vancomycin-intolerant patients with severe infections caused by methicillin-resistant *S. aureus* or coagulase-negative staphylococci. Resistance to quinupristin-dalfopristin is emerging.¹⁴⁵

Quinupristin-dalfopristin is administered intravenously; because of a high incidence of phlebitis, a central line should be used. Other adverse effects include arthralgias and myalgias, which may be severe, and elevated bilirubin levels. The antibiotic may elevate levels of drugs that are metabolized by the hepatic enzyme CYP3A4; nifedipine and cyclosporine are examples.

The usual dose of quinupristin-dalfopristin is 7.5 mg/kg given intravenously over 1 hour every 8 hours. The drug is metabolized by the liver, so no dose reduction is required in azotemic patients. Quinupristin-dalfopristin is extremely expensive.

Oxazolidinones

In 2000, linezolid became the first member of the oxazolidinone class to be approved for clinical use in the United States.¹⁴⁶ Linezolid is a synthetic antibiotic that inhibits protein synthesis by binding to a site on the bacterial 23S ribosomal RNA of the 50S subunit, thus preventing function of the initiation complex that is required for ribosomal function.¹⁴⁷ Because no other antibiotic acts in this way, bacteria that have developed resistance to other ribosomally active antimicrobials do not display cross-resistance to linezolid.

Linezolid is active against nearly all aerobic gram-positive cocci at concentrations of 4 mg/ml or less,¹⁴⁸ including penicillin-resistant pneumococci, methicillin-resistant staphylococci, and vancomycin-resistant enterococci; however, resistant strains have been isolated.¹⁴⁹ The drug is bacteriostatic against staphylococci and enterococci, but it is bactericidal against most streptococcal strains. Linezolid is also active against *L. monocytogenes*, *M. catarrhalis*, *H. influenzae*, *N. gonorrhoeae*, *Bordetella pertussis*, *Pasteurella*

multocida, and *Nocardia* species. *C. difficile*, *C. perfringens*, and *Bacteroides* species are susceptible, but enteric gram-negative bacilli and *Pseudomonas* species are not.¹⁵⁰

Intravenous and oral preparations of linezolid are available; the oral form is absorbed rapidly and completely with 100% bioavailability that is not affected by meals. Linezolid is widely distributed in well-perfused tissues. Nonrenal mechanisms account for 65% of the drug's clearance. Patients with mild to moderate renal or hepatic insufficiency do not appear to require reduced doses; linezolid is removed by hemodialysis.

Linezolid is well tolerated. Adverse effects have been reported in about 2.8% of all patients¹⁵⁰; nausea, vomiting, and headaches are the most common side effects, but reversible marrow suppression, including thrombocytopenia, leukopenia, and anemia, can also occur. Because linezolid is a reversible inhibitor of monoamine oxidase, patients taking linezolid may experience an exaggerated hypertensive response to sympathomimetic agents. In addition to avoiding decongestants, patients taking linezolid should avoid foods or beverages with a high tyramine content; aged cheeses, air-dried meats, tap beer, red wine, soy sauce, and sauerkraut are examples. Monoamine oxidase inhibitors and other antidepressants should not be administered during linezolid therapy.

Linezolid has been used successfully in the therapy of multidrug-resistant gram-positive bacterial infections.^{146,147,151} The drug is approved for vancomycin-resistant enterococcal infections and for pneumonias and skin and soft tissue infections. The usual dosage is 600 mg every 12 hours (p.o. or I.V.); uncomplicated skin and soft tissue infections may be treated with 400 mg every 12 hours.

Linezolid is a very promising new antimicrobial agent, but clinical experience is still limited. Although resistance is uncommon, it can develop during therapy. As a result, it may be wise to reserve this unique antibiotic for serious infections in hospitalized patients; in particular, linezolid should be useful for infections caused by methicillin-resistant *S. aureus* or coagulase-negative staphylococci that do not respond to vancomycin, for penicillin-resistant pneumococcal infections that do not respond to other agents, and for vancomycin-resistant enterococcal infection. An excellent general review of the use of linezolid in serious gram-positive infections has been published.¹⁵²

Fosfomycin

Fosfomycin is a broad-spectrum antibiotic that inhibits cell wall synthesis in infections caused by *E. coli*, *S. saprophyticus*, and many other common urinary tract pathogens.¹⁵³ Although it has been used parenterally in Europe for many years, the drug is approved in the United States only for the single-dose treatment of uncomplicated urinary tract infections in women. A 3 g dose is generally effective and well tolerated; diarrhea is the most common side effect. Because of its activity against vancomycin-resistant enterococci (VRE), fosfomycin may be a useful alternative to linezolid and quinupristin-dalfopristin in the treatment of VRE infections in certain clinical situations (e.g., uncomplicated urinary tract infections). In addition, the use of fosfomycin could limit the use of newer agents, thus reducing the chance of development of further resistance in the enterococci.¹⁵⁴

Concerns for the Future

Despite a century of often-successful prevention and control efforts, infectious diseases remain an important global problem in

public health, causing over 13 million deaths each year. Changes in society, technology, and the microorganisms themselves are contributing to the emergence of new diseases, the reemergence of diseases once controlled, and the development of antimicrobial resistance. Two areas of special concern in the 21st century are food-borne disease and antimicrobial resistance. The effective control of infectious diseases in the new millennium will require effective public health infrastructures that will rapidly recognize and respond to outbreaks and will prevent emerging problems.

Over the past 40 years, the search for new antibiotics has been largely restricted to well-known classes of compounds that are

active against a standard set of drug targets. Although many effective compounds have been discovered, insufficient chemical variability has been generated to prevent a serious escalation in clinical resistance. Recent advances in genomics have provided an opportunity to expand the range of potential drug targets and have facilitated a fundamental shift from direct antimicrobial screening programs toward rational target-based strategies. The application of genome-based technologies such as expression profiling and proteomics will lead to further changes in the drug discovery paradigm by combining the strengths and advantages of both screening strategies in a single program.

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31 ACQUIRED IMMUNODEFICIENCY SYNDROME

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Approach to Human Immunodeficiency Virus Infection

In June 1981, the Centers for Disease Control and Prevention (CDC) published a report of *Pneumocystis carinii* pneumonia (PCP) in five previously healthy homosexual men living in Los Angeles.¹ At that time, the CDC was the sole distributor of pentamidine, the only treatment for this rare pulmonary infection. This outbreak represented a unique cohort for PCP, which until then had been seen only in severely immunosuppressed patients who were receiving chemotherapy for disseminated cancer. Even in this select group, PCP was rare, and *P. carinii* was not considered pathogenic in otherwise healthy adults. The sudden increase in demand for pentamidine in one geographic area raised the prospect of a new disease process. In July 1981, the CDC reported a group of young homosexual men with Kaposi sarcoma.² Like PCP, Kaposi sarcoma was a rare lesion not commonly seen in young adults. Many of these Kaposi sarcoma patients also had severe infections caused by organisms associated with immunodeficiency, including PCP, toxoplasmosis, candidiasis, cryptococcosis, and cytomegalovirus (CMV) infections.

These two accounts represented the first recognition of AIDS. The cause of the severe immunodepression in these patients, who were not otherwise at risk for opportunistic infection, was controversial until late 1983 and early 1984, when the human immunodeficiency virus (HIV) was isolated in AIDS patients.³ This retrovirus—formerly known as human T cell lymphotropic virus (HTLV) type III and lymphadenopathy-associated virus (LAV)—is now recognized as the agent that causes AIDS. Presumably, the patients in the 1981 reports had become infected with HIV at least 3 to 4 years earlier.

In September 1987, the definition of AIDS was expanded to include symptomatic HIV-infected patients suspected of having an opportunistic infection. This new definition precipitated a potentially misleading sudden increase in new cases.⁴ Since 1986, the percentage of homosexual or bisexual AIDS patients has steadily declined, and the percentage of AIDS patients who are I.V. drug abusers or are heterosexual has increased.

June 1, 2001, marked the 20th anniversary of the AIDS epidemic. Over those 2 decades, more than 20 million people died of AIDS, leaving an estimated 36 million people infected.⁵ No immediate end to the epidemic is in sight, but current therapies have significantly altered the course of the illness. Until the advent of highly active antiretroviral agents (HAART), it was believed that everyone with an opportunistic infection or tumor associated with AIDS (e.g., Kaposi sarcoma or non-Hodgkin lymphoma) would die as a direct result of severe immunosuppression; that is no longer the case.⁶ HIV-infected persons are living longer, are less likely to die of opportunistic infections, and are more likely to present with relatively well-preserved immune function.⁷ With this increase in the prevalence of HIV infection, it is all the more important that surgeons have a basic under-

standing of HIV disease and its treatment and be familiar with prophylaxis after occupational exposure.

Recognition of HIV Infection

PATHOGENESIS

HIV is an oncovirus belonging to the retrovirus family. The potential of retroviruses to cause neoplasia was first recognized in 1911 by the American pathologist Rous, who associated them with certain malignant disorders in animals.⁸ For example, HTLV-I, a retrovirus related to HIV, has been identified as a cause of leukemia in humans.⁹

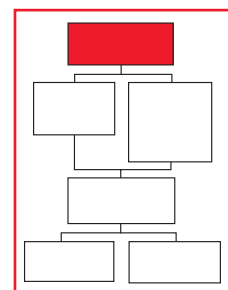
One of the characteristic features of retroviruses is the presence of an enzyme called reverse transcriptase. This enzyme allows the virus to transcribe viral RNA to DNA. The virus can synthesize double-stranded DNA from single-stranded DNA that has been liberated from the RNA-DNA hybrid. This double-stranded DNA inserts itself into the nucleus of the host cell and serves as a template for viral replication. Thus, whenever the infected host cell divides, new HIV particles are also reproduced. HIV has been isolated in many cell types, but it is thought that helper T cells (CD4⁺ cells) are most frequently infected. It is believed that when an HIV-infected CD4⁺ cell is activated by a secondary infection, the virus is replicated, resulting in the dissemination of mature virions and the death of the cell.

The latency period between acquisition of HIV infection and onset of AIDS has been estimated to be about 5 years. This estimate is probably misleading because it is based on experience with patients in high-risk groups, who are frequently exposed to other infectious challenges. Exposure to these other pathogens activates the T cells that harbor HIV, which promotes dissemination of the virus throughout the host and significant impairment in cellular immunity. Because the incidence of concomitant infections is lower in the general population than in high-risk groups, the latency period of HIV infection is probably longer in the general population.

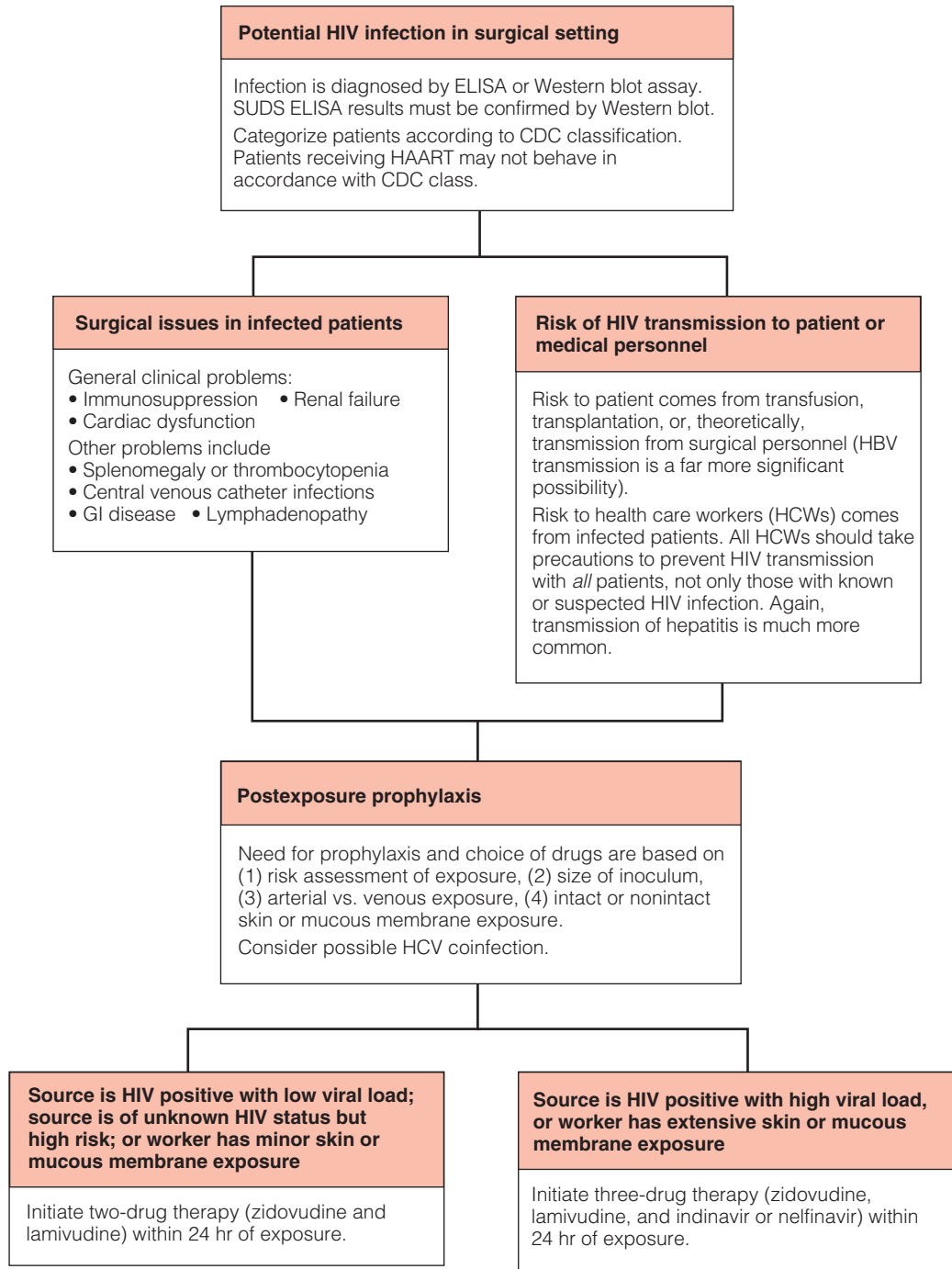
DIAGNOSTIC TESTS

The enzyme-linked immunosorbent assay (ELISA) and the Western blot assay are designed to detect the presence of HIV antibody in serum. ELISA is considered very sensitive (93% to 100%; i.e., its false negative rate is low). The specificity of a repeatedly reactive ELISA approaches 99%. The weakness of the ELISA is that some persons have antibodies that react with HIV antigens but are not specific for HIV.

The Western blot assay is more specific than ELISA but is cumbersome and less sensitive. It is therefore not a good screen-



Approach to Human Immunodeficiency Virus Infection



ing test; it is used most effectively for confirming ELISA results. However, most blood banks will not use blood that has demonstrated a positive ELISA reaction, even if HIV antibody was not detected by Western blot testing.¹⁰

The Single-Use Diagnostic System (SUDS; Murex Diagnostics, Norcross, Georgia) provides a rapid ELISA technology that can yield a reliable result in 15 minutes. A positive SUDS result must still be confirmed by Western blot assay. SUDS is especially useful in occupational-injury investigation.

There is a window period of 25 days between infection with HIV and seroconversion detectable by ELISA. It has been estimated that since 1985, when all banked blood began to be tested for HIV, 35 persons in the United States have contracted HIV infection from transfusions containing blood collected from an HIV-infected individual during this window period.^{11,12} For that reason, on August 8, 1995, the Food and Drug Administration recommended that all blood donated for transfusion be screened for the p24 antigen (the core structural protein of HIV).¹³ Additional laboratory tests that may help in the diagnosis of patients believed to have HIV infection in whom HIV antibody screening yields negative results include DNA polymerase chain reaction (PCR), antigen testing after immune complex disruption, and RNA reverse transcriptase PCR.¹⁴

In February 2002, the FDA approved a nucleic acid test system that detects ribonucleic acid from HIV and hepatitis C virus (HCV) in whole blood and blood component donors, thus permitting earlier results than tests based on detection of antibodies or antigens (<http://www.fda.gov/cber/approvltr/hivhcvgen022702L.htm>). Like ELISA, the nucleic acid test has a window period during which the virus can be present but escape detection; however, this window period is substantially shorter than that associated with antibody-based tests (12 versus 22 days, on average, for HIV; 25 versus 82 days, on average, for HCV).

CDC Classification of HIV Infection

In 1993, the CDC revised the classification of the HIV-infected adult and adolescent [see Table 1]. In this classification, a CD4⁺ count below 200 cells/μl is considered an indicator of AIDS, regardless of the patient's symptoms. Once classified into a given group, a patient is not reclassified to a more favorable category, even if symptoms resolve or the CD4⁺ cell count rises. However, if the disease progresses or the CD4⁺ count falls, the patient is reclassified into the next less-favorable group. This system allows uniformity in patient classification for research trials and scientific communication and, of particular importance, facilitates formulation of health care policy and strategy.

Unfortunately, the system does not take into account the immune reconstitution that occurs with HAART. After successful treatment with HAART, patients originally classified as having AIDS (on the basis of their CD4⁺ count or level of immunocompromise) often will no longer have signs and symptoms in accordance with their original CDC classification. A number of studies have now shown that secondary prophylaxis for PCP, CMV retinitis, *Toxoplasma* encephalitis, and cryptococcal meningitis may be safely discontinued in patients whose CD4⁺ counts have risen and remained above 200 cells/μl because of HAART.¹⁵ Similarly, recent studies of gynecologic procedures in HIV-infected patients have found that postoperative infection rates correlate only with the current CD4⁺ count. In these studies, a CD4⁺ level below 200 cells/μl at the time of the procedure was an independent risk factor for surgical complications, whereas the previous nadir had no influence on outcome.¹⁴

Surgical Issues

GENERAL

As a group, HIV-infected patients present the surgeon with three notable clinical problems: immunosuppression, renal failure, and cardiac dysfunction. Surgeons need to be aware of the immune status of their HIV-infected patients, because this has the greatest bearing on outcome. For example, in HIV-infected patients with normal CD4⁺ counts, the risk of infectious complications after surgery for a perforated appendix is comparable to the risk in patients without HIV infection. In patients with AIDS (< 200 CD4⁺ cells/μl), the risk of infection is higher, though it is from opportunistic organisms associated with severe immunosuppression rather than common pathogens.¹⁶⁻²⁰

Renal failure in HIV-infected patients can be the result of specific HIV-related nephropathy, which occurs in up to 10% of this population.²¹ Another possible cause is drug toxicity from antiviral and antimicrobial medications: pentamidine, foscarnet, and aminoglycosides cause acute tubular necrosis; acyclovir, indinavir, and sulfadiazine cause intratubular obstruction.

Until recently, the risk of cardiac disease in HIV-infected patients had not been as well documented as that of renal failure. With HIV-infected patients living longer, the problems of acquired heart disease have been increasingly appreciated.²²⁻²⁴

In addition, malignancy has been increasingly recognized over the past 2 decades as a consequence of HIV infection. Initially, the occurrence of AIDS-defining tumors, such as B cell lym-

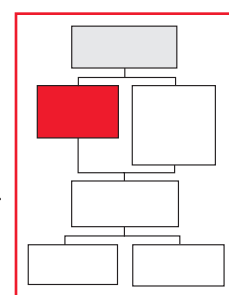


Table 1 1993 Revised Classification for HIV Infection and Expanded AIDS Surveillance Case Definition for Adolescents and Adults⁸¹

CD4 ⁺ T Cell Categories	Clinical Categories		
	A	B	C
	Asymptomatic, Acute (Primary) HIV, or PGL	Symptomatic, Not A or C Conditions	AIDS Indicator Conditions
≥ 500/μl	A1	B1	C1
200–499/μl	A2	B2	C2
< 200/μl AIDS-indicator T cell count	A3	B3	C3

PGL—persistent generalized lymphadenopathy

phoma and Kaposi sarcoma, was thought to relate to the immunosuppression of the host. Other tumors have now been associated with HIV infection, including squamous cell cancers of the cervix and anus and lung cancer. It is believed that at some point after infection with HIV, activation of oncogenes and loss of tumor suppressor genes give rise to microsatellite alterations. These are highly pleomorphic segments of DNA associated with the AIDS-defining malignancies.²⁵⁻²⁷

Treatment of patients with AIDS involves multimodal therapy and consultation with oncology and infectious disease specialists. It is beyond the scope of this discussion to describe the specific therapeutic approaches to the complications of HIV infections; however, three principal problems must be addressed. First, any opportunistic infection or secondary malignant disorder must be treated; second, the underlying immunodeficiency must be corrected; and finally, the cause—HIV infection—must be controlled. The role of the surgeon in the management of these chronically ill, and sometimes critically ill, patients includes performing diagnostic biopsies, giving supportive care, and managing complications of malignancy of infection.

SPLEEN

The role of splenectomy in patients with marked splenomegaly or with thrombocytopenia must be individualized. Some experts believe that coinfections such as HCV infection contribute to the development of HIV-related immune thrombocytopenic purpura (ITP). Thrombocytopenia occurs in AIDS patients as a result of the deposition of circulating immune complexes on platelets rather than as a result of a specific antiplatelet antibody.^{28,29} Splenectomy has been extremely effective in the management of AIDS-related ITP, with a success rate of over 90%. Occasionally, patients who have debilitating fevers associated with significantly enlarged spleens experience dramatic palliation after splenectomy. Some data indicate that splenectomy favors a slower progression of HIV dissemination and progression to AIDS.^{30,31} In patients with massive splenomegaly and fever, simple splenomegaly is sometimes difficult to distinguish from abscess or parenchymal necrosis, and splenectomy may be indicated to resolve the uncertainty. In addition, splenectomy may be indicated in instances in which there is merely a likelihood of injury and in those in which a large spleen compresses the stomach, thereby contributing to malnutrition.

IMPLANTABLE VENOUS ACCESS DEVICES

Placement of an indwelling central venous catheter is a request frequently directed to the general surgeon from the primary care physician, infectious disease consultant, or hematologist caring for an AIDS patient. Long-term venous access for treating fungal infections or, occasionally, for providing nutritional support in patients with debilitating diarrheal syndromes can enhance the care of these patients. However, lines are often placed when the patient is febrile, as a result of either the underlying infection or treatment with amphotericin B. Therefore, a close watch should be kept postoperatively to ensure that fevers are not related to a catheter infection. Although catheter-related infection develops in as many as 30% of AIDS patients with implanted lines, these infections do not increase mortality.³² The high rate of infection relates in part to the high incidence of *Staphylococcus* colonization in these patients.

GASTROINTESTINAL DISEASES

Cryptosporidiosis and CMV infection of the biliary tree have been reported to cause both acute cholecystitis and acute cholan-

gitis, necessitating emergency surgical interventions.¹² Choledochenteric bypass is thought to provide the best palliation in these patients. It is not known whether the biliary tree is ever cleared of the pathogens. *Candida* infection and Kaposi sarcoma have also caused cholangitis, necessitating bypass surgery.¹⁷ The gallbladder is infected with unusual pathogens in over 50% of HIV-infected patients with cholangitis; therefore, the gallbladder wall should be sent for culture, and the pathologist should be alerted so that the tissue may be processed with special stains.³³⁻³⁶

Acute perforations of the GI tract from CMV infection, cryptosporidiosis, and candidiasis, as well as from necrotic lymphoma, have been reported in HIV-infected patients.^{18,37,38} Obstruction of the GI tract by Kaposi sarcoma or lymphoma may also be an indication for resection, bypass, or colostomy. One study of AIDS patients requiring a laparotomy identified four distinct clinical syndromes that called for surgical intervention: (1) peritonitis secondary to CMV enterocolitis and perforation; (2) non-Hodgkin lymphoma of the GI tract (usually the terminal ileum), presenting as obstruction or bleeding; (3) Kaposi sarcoma of the GI tract; and (4) mycobacterial infection of the retroperitoneum or the spleen.³⁹

Another GI lesion that has been increasingly associated with homosexual men who are infected with HIV is squamous cell carcinoma of the anus (SCCA). It is estimated that the risk of developing SCCA is nearly 25 times greater in HIV-infected homosexual men than in the general population. The underlying relationship is not well understood, because the development of SCCA is not related to the duration of the HIV infection. Some experts believe that human papillomavirus 16 (HPV-16) and HPV-18 are important cofactors in the evolution of SCCA.^{40,41}

LYMPHADENOPATHY

Another group of HIV-infected patients defined by the CDC comprises those with persistent generalized lymphadenopathy—that is, palpable lymphadenopathy with nodes measuring greater than 1 cm in diameter in at least two extrainguinal sites and persisting for longer than 3 months. Before the introduction of HIV antibody testing, the relationship of such lymphadenopathy to systemic manifestations of immunosuppression (systemic symptoms, neurologic symptoms, secondary infections, or cancers) was not known. It is now clear that lymphadenopathy is part of the general clinical spectrum associated with HIV infection, and that opportunistic infection, Kaposi sarcoma, or large cell lymphoma will develop in some, if not all, patients with lymphadenopathy. The precise reason that lymphadenopathy occurs in some, but not all, patients with HIV infection is not known.

Lymph node biopsy in these patients is only of academic interest because of the development of serologic tests for HIV infection.³⁷ The histologic appearance of a clinically enlarged lymph node has prognostic value (see below); however, when the decision as to whether to perform a lymph node biopsy is being made, the value of the biopsy findings must be weighed against the value of the information that can be obtained by means of clinical staging with the ratio of helper T cells to suppressor T cells and the total lymphocyte count. The total number of helper T cells in the circulation has been correlated with the risk of AIDS in patients with generalized lymphadenopathy^{20,42-44}; the Walter Reed classification provides the most detailed clinical staging system.^{43,45} Should the clinical condition warrant, a lymph node biopsy may help in the diagnosis of an opportunistic infection. Performing a gallium scan to locate the most suspicious node can enhance the yield of the biopsy.

Four basic histologic patterns have been described in persistent generalized lymphadenopathy and have been correlated

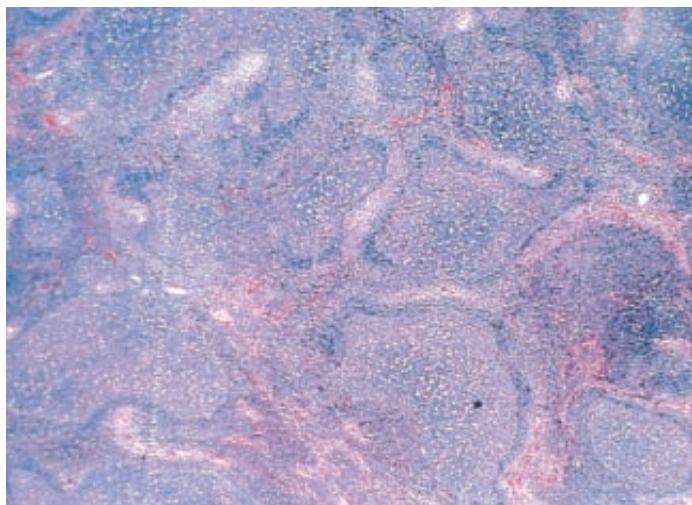


Figure 1 Lymph node viewed under low power exhibits explosive follicular hyperplasia.

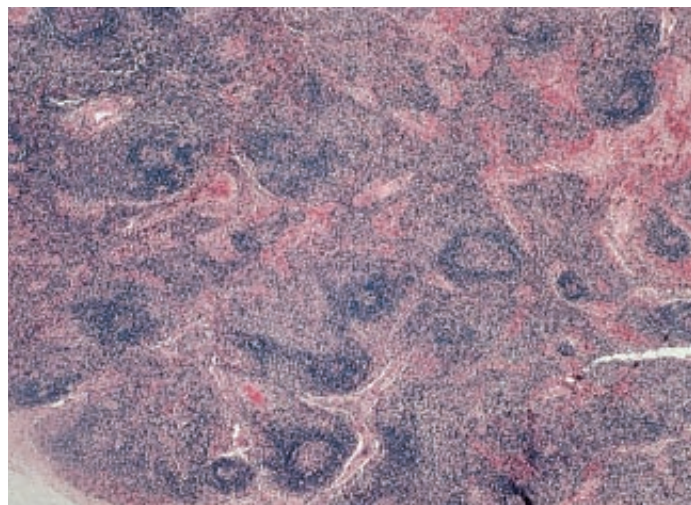


Figure 2 Lymph node viewed under low power exhibits follicular involution.

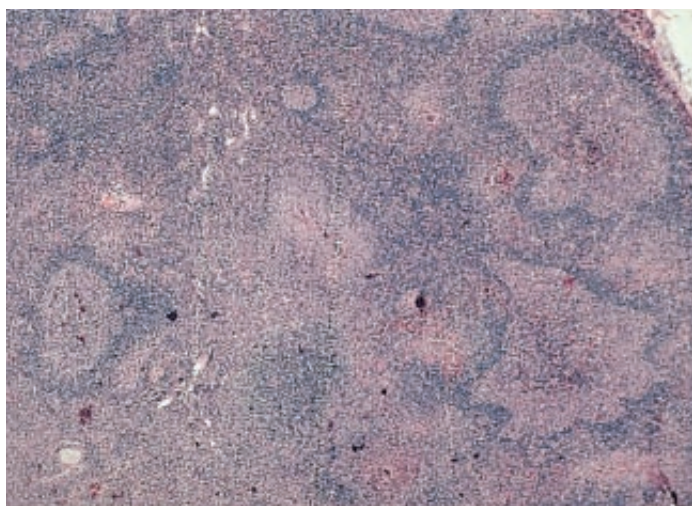


Figure 3 Lymph node viewed under low power exhibits a mixed pattern of both explosive follicular hyperplasia and follicular involution.

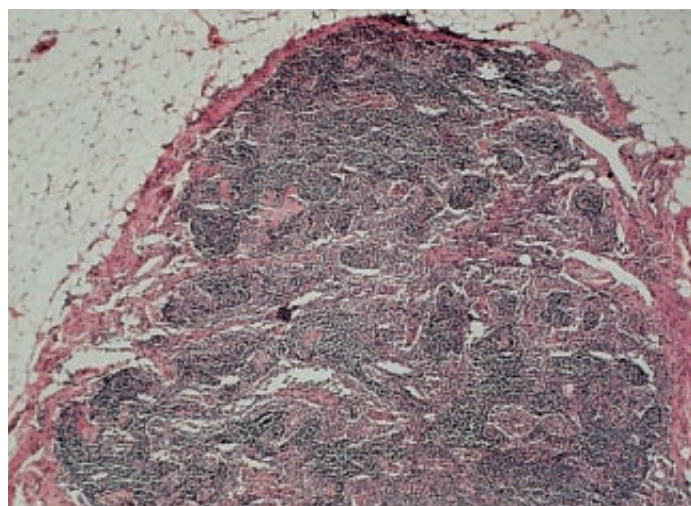


Figure 4 Lymph node viewed under low power exhibits a pattern of lymphocyte depletion.

with prognosis: explosive follicular hyperplasia, follicular involution, a mixed pattern, and a lymphocyte-depleted pattern. Explosive follicular hyperplasia describes a pattern of enlarged confluent follicles with disruption of the medullary zone of the lymph node [see Figure 1]. Follicular involution is associated with a hypocellular, frequently hyalinized follicle and with hyperplasia of the paracortical areas [see Figure 2]. The mixed pattern contains explosive follicular hyperplasia and follicular involution in the same lymph node [see Figure 3]. Finally, the lymphocyte-depleted pattern is characterized by the total absence of follicular and paracortical areas. The loss of lymphocytes in the lymph node is associated with the predominance of histiocytes and plasma cells [see Figure 4].

The presence of enlarged follicles is associated with a good immunologic response and slower progression of disease, whereas the presence of involuted, hyalinized follicles is more frequently associated with opportunistic infections, Kaposi sarcoma, and lymphoma. Evidence suggests that patients with either explosive follicular hyperplasia or the mixed pattern of explosive follicular hyperplasia and follicular involution have rather pro-

longed survival, even if they have Kaposi sarcoma. The presence of follicular involution in a lymph node is associated with a survival time of less than 1 year. Lymphocyte depletion was seen as a terminal finding in several autopsy cases, suggesting that the pattern represents the end stage of the hyperplastic process.²⁵ The pathologic findings reflect a progressive loss of the CD4⁺-bearing area of the lymph node.

After a lymph node is removed from an HIV-infected patient and before the tissue is removed from the operative field, representative specimens should be placed in sterile containers for routine bacterial culture, culture and smear for tuberculosis, fungal culture, and viral culture. Tissue from the same lymph node should then be delivered to the pathologist as quickly as possible. It is important that culture material from the same lymph node be examined microscopically, because granulomas or actual organisms may be detected before the culture results are available. Data from the pathologist may aid the microbiology laboratory staff in its handling of the cultures.

The pathologist needs to receive the fresh, gently handled specimen, in saline, as soon after the biopsy as possible, for two

important reasons. First, because the tissue is not in formalin, it will rapidly autolyze if not processed immediately. Second, if the diagnosis is lymphoma, the pathologist must have the tissue when it is fresh to perform lymphocyte marker studies. Because different lymphomas respond to different chemotherapeutic regimens, the cell type of the lymphoma is critical. Most surgical pathology laboratories are equipped to perform membrane marker studies on lymph node tissue.

Prevention of Disease Transmission

GENERAL

A key question for surgeons, operating room committees, infection control committees, and clinicians involved with endoscopy is how to effectively clean instruments, equipment, or other inanimate objects to be used with AIDS patients. Those agents that are effective against mycobacteria, the most resistant group of organisms encountered in this population, are also the agents considered most effective against other bacterial and viral pathogens.⁴⁶ A complete list of agents and their efficacies can be obtained from the Disinfectants Branch of the Office of Pesticides, United States Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460.

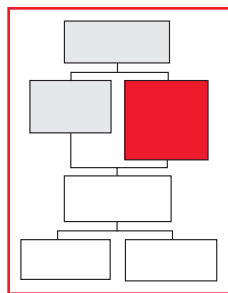
Agents are classified according to whether they are to be used for sterilization, disinfection, or antisepsis.⁴⁷ Agents that sterilize inanimate objects kill all microbial organisms as well as bacterial endospores. Disinfectants are not quite as effective, in that they are not capable of killing bacterial spores. In many cases, an agent may serve as a disinfectant when placed in contact for a short time with the object requiring cleansing and may be capable of sterilizing surgical instruments that are exposed to it for longer periods. Disinfectants are subclassified as having high-level, intermediate-level, or low-level germicidal activity. High-level agents are effective against bacterial spores. Intermediate-level disinfectants are less effective against spores but are mycobactericidal. Low-level disinfectants do not kill *Mycobacteria* and some fungi. Antiseptic agents are used on tissue and therefore must be less toxic than sterilants or disinfectants.

According to current CDC recommendations, agents classified by the United States Environmental Protection Agency as sterilants can be used for sterilization or high-level disinfection, depending on contact time. All instruments entering the bloodstream or other sterile tissues should be sterilized before use. Instruments that contact mucosal surfaces, such as endoscopes, should receive high-level disinfection, which can be achieved with solutions of glutaraldehyde (2%), hydrogen peroxide (3% to 6%), or formaldehyde (1% to 8%).

RISKS TO PATIENTS

Transfusions

Fresh whole blood, packed red blood cells, platelets, plasma, cryoprecipitate, and leukocytes can all carry HIV. In addition, clotting factor concentrates that are not generated by recombinant methods may also carry the virus. Some preparations of γ -globulin can temporarily cause a false positive ELISA result for HIV, but they do not contain the virus or transmit it to recipients. Albumin and plasma extracts (Plasmanate), although prepared from whole blood, do not carry HIV, hepatitis B virus (HBV), or



HCV, because the process by which they are purified inactivates the virus particles. Since adequate antibody testing became available in May 1985, the incidence of undetected HIV in transfused blood has been extremely low, and only anecdotal cases involving contaminated blood have been reported to the CDC. It is currently estimated that the risk of receiving a unit of blood that is contaminated with HIV is one in 150,000 ($< 0.0007\%$).⁴⁸

To minimize the risk of HIV being transmitted by transfusion, patients have increasingly requested the use of predeposited autologous blood donations (PAD) or blood donated by family members or friends (directed donations). This approach has been increasingly discouraged by blood bank and hospital administrators.⁴⁹ Both directed donations and PAD are very expensive methods of preserving homeostasis during surgery. Half of the PAD units of blood are discarded. In addition, the risk of an ABO mismatch error is as great as the risk of HIV transmission in standard bank blood. The use of intraoperative blood salvage and acute normovolemic hemodilution in combination with intravenous iron and erythropoietin provides a reasonable alternative to blood transfusion.⁵⁰

Transplantation

Because it has been shown that HIV can be present in semen, blood, urine, tears, breast milk, cerebrospinal fluid, and saliva and because it is suspected that HIV can be present in all secretions and excretions, as well as all body tissues,⁵¹ potential donors of tissue for transplantation must be tested for serum antibodies to HIV to prevent inadvertent transfer of the virus. Parenthetically, transmission of HIV by artificial insemination has also been documented, so this risk should be considered whenever artificial insemination is planned.⁵²

Transmission from Surgical Personnel

An HIV-infected surgeon could theoretically transmit the virus to his or her patients. Although this concern has been well publicized,⁵³ there have been no documented reports of transmission from surgeon to patient. Furthermore, the CDC has not recommended restricting HIV-positive surgeons from operating.⁵⁴

Unlike surgeon-to-patient transmission of HIV, HBV transmission from surgeon to patient is a significant concern. In a well-documented report involving a nonimmunized cardiac surgeon who acquired HBV infection in the workplace, transmission of the virus occurred in 19 of 122 patients (16%) on whom the surgeon operated over a 12-month period.⁵⁵ The surgeon's blood was positive for hepatitis B e antigen (HBeAg), and sweat from inside his glove was found to contain both HBV antigen and HBV DNA. No deficiencies were found in the surgeon's infection control practice by the CDC, which suggested that the virus might have spread through microperforations in his gloves. This case did not receive the same publicity that cases of HIV transmission have received in the lay press. However, its significance is clear: contact between health care workers who are HBV (HBeAg) positive and patients should be restricted.

RISKS TO HEALTH CARE WORKERS

The CDC now recommends that precautions to prevent HIV transmission be taken with all patients, not only those known to be infected with HIV or at high risk for such infection [see 8:21 *Viral Infection*].^{18,20,38,39} It is important that any hospital personnel who come in contact with patients, their patients' tissues, or their blood, body fluids, or excreta know of the potential risk in

Table 2 Preventable Exposures to HIV among Health Care Workers*⁴⁹

Circumstances of Preventable Exposure	Number of Health Care Workers (% of 938 Exposed Health Care Workers)
Recapping of needle	152 (16%)
Injury from improper disposal of needle or sharp object	119 (13%)
Contamination of open wound	93 (10%)
Use of needle-cutting device	9 (1%)
Total preventable exposures	373 (40%)

*The total sample under surveillance consisted of 938 health care workers exposed to blood or other body fluids of a patient with AIDS or an AIDS-related illness.

handling materials from these patients and take appropriate precautions. Patients in high-risk groups should be placed on enteric precautions to protect health care workers not only from HIV infection but also from HBV infection (up to 80% of such patients are HBV carriers). As part of any operative procedure on HIV-infected patients, all operating room, nursing, and anesthesia personnel, as well as employees of surgical pathology laboratories and any other laboratories, should employ universal precautions. Employees in ancillary areas, such as housekeeping and dietary services and the venipuncture team, need to be trained in the use of universal precautions.

Exposure to the virus in the workplace is considered to be preventable in many cases.⁵⁶ Most injuries result from carelessness in handling sharp objects, such as needles [see Table 2]. Self-inflicted puncture incurred in the course of recapping used needles is the most common cause of inadvertent exposure to HIV. Consequently, the most important rule to follow when handling used needles is to discard them uncapped in a container that is large enough to accommodate the attached syringe. Tissue specimens, wastes, soiled linen, blood samples, and sharp objects (e.g., surgical instruments, needles, and glassware) must be handled with extreme care. Dressings and other disposable materials should be discarded in specially marked containers and not with the regular hospital refuse.

The use of double gloves has been shown to minimize the possibility of contact with patient blood through small defects in the gloves, and it reduces the likelihood of blood contact with skin when a glove puncture occurs.^{57,58} The following are additional precautions health care workers should take when handling any potentially infectious materials:

1. Wear gloves when handling body fluids.
2. Wear a gown to prevent contamination of clothing.
3. Wash hands after contact with body fluids.
4. Place fluid from a potentially contaminated host in two impervious containers.
5. Clean spills with either a 1:10 dilution of 5.25% sodium hypochlorite in water or with some other type of sterilant.
6. Wear masks and protective eyeglasses when there is a possibility of aerosolization of material.

Even health care workers who do not have exfoliative dermatitis or an open wound should wear gloves during patient care. Evidence suggests that the affinity of HIV for Langerhans cells may permit the virus to invade a host through intact skin or mucous membranes.⁵⁹

RISKS TO SURGEONS

HIV Transmission

The risk that a surgeon will acquire an HIV infection while treating a patient who has undetected AIDS is quite low.^{54,56} The CDC has prospectively evaluated nearly 1,500 health care workers who cared for AIDS patients. Serum samples were taken from these workers when they first began to work with AIDS patients and were stored in anticipation of a test for HIV. Of these workers, 666 were exposed to HIV through needlesticks or through cuts from sharp instruments. When tests were performed on these exposed individuals, none were found to have undergone seroconversion after their exposure to HIV. However, two health care workers for whom no baseline blood sample had been drawn did test positive for antibody to HIV after an injury. Because they did not belong to a known risk group for AIDS, they were believed to have generated antibody to HIV as a result of exposure in the workplace. On the basis of this study, the risk to a health care worker of acquiring HIV infection after an accidental needle-stick exposure was concluded to be 2 divided by 666, or 0.3%. A follow-up study found the rate of infection to be 0.5%.⁶⁰ Subsequent surveillance of health care workers identified 151 individuals who acquired HIV infection in the workplace [see Table 3]; 49 had proven seroconversion, and 102 were HIV positive but had no HIV-negative baseline serum sample.

The CDC conducted a serosurvey of 770 surgeons practicing in two inner-city areas where more than 3,000 cases of AIDS have been reported.⁶¹ Accompanying the assay for HIV, HBV, and HCV was a questionnaire designed to elucidate the practice patterns of the surgeons tested. Of the 770 surgeons, 1 (0.13%) was HIV positive; he had practiced for more than 25 years and had performed more than 300 operations in the past year. The study did not specify how the surgeon acquired HIV, and it was noted that he did not participate in high-risk behavior. To date,

Table 3 Health Care Workers with Documented or Suspected HIV Infection⁹

Health Care Workers	No. of Workers	
	With Documented HIV (%) [*]	With Suspected HIV (%) [†]
Dental	0	7 (7%)
Mortician	0	3 (3%)
Emergency medical team/paramedic	0	9 (9%)
Health aide	1 (2%)	12 (12%)
Housekeeper	1 (2%)	7 (7%)
Laboratory technician	18 (37%)	15 (15%)
Nurse	19 (39%)	24 (24%)
Physician		
Surgeon	9	4 (4%)
Nonsurgeon	6 (12%)	10 (10%)
Respiratory therapist	1 (2%)	2 (2%)
Surgical technician	2 (4%)	1 (1%)
Other	1 (2%)	8 (8%)
Total	49	102

^{*}Evidence of seroconversion after occupational exposure to HIV.

[†]HIV seropositivity in health care workers with occupational exposure to HIV who do not have behavioral or transfusion risks for HIV infection.

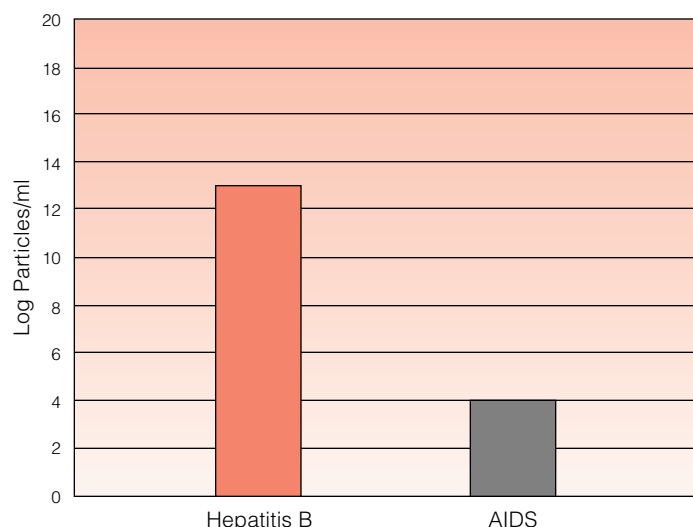


Figure 5 The numbers of infectious viral particles per milliliter of blood in patients with active hepatitis B infections and in AIDS patients are compared.⁶⁷

there has been no documented seroconversion in operating room personnel after a solid-bore needle injury in the OR.

Transmission via skin contact with body fluids was documented in the case of a woman whose infant had received a transfusion from an HIV-infected donor at 3 months of age. The mother was closely involved in the baby's care and took no precautions against contact with the child's blood and body fluids. Seventeen months after the child received the contaminated blood, the mother tested positive on ELISA for HIV. No other risk factors accounted for the change in the mother's HIV antibody titer.⁶²

Exposure to blood in the OR has been of great concern to all operating room personnel since the AIDS epidemic began. The average practicing surgeon has 30 parenteral exposures to blood a year.⁶³ The fact that hollow-bore needles carry more blood than solid-bore needles may be the reason that transmission in the operating room has not yet occurred. Four studies from the early 1990s established a blood-skin exposure rate of approximately 20% and a parenteral exposure rate of approximately 4% during surgical procedures.^{46,64-66} Long operative procedures requiring transfusions are most likely to be associated with blood exposure. Types of procedures that pose a high risk of exposure to blood are cardiac surgery; obstetrics, especially cesarean sections; trauma surgery; and emergency surgery. Special care must be taken to minimize exposure in these procedures; eye protection and use of double gloves are barrier precaution measures that can reduce the likelihood of contact with the patient's blood.

Transmission of HIV to hospital workers is uncommon when compared with transmission of HBV because of the relatively low concentration of HIV in the blood of AIDS patients [see Figure 5]. The concentration of virus particles is estimated to be 10^4 particles/ml in an AIDS patient, whereas it is 10^{13} particles/ml in a patient who has an active HBV infection.⁶⁷

Although HIV transmission is uncommon in the hospital environment, the risk to surgeons is very real. This is evidenced by the fact that even the lower reported rate of transmission by needle stick, 0.3%, is comparable to the 0.4% (1 in 250) rate of transmission by unprotected anal intercourse, which is considered high-risk behavior.^{68,69} Three independent factors are important in determining a surgeon's risk of acquiring HIV infection: (1) the num-

ber of needle sticks or punctures contaminated with the patient's body fluids, (2) the percentage of HIV-infected patients in the surgeon's patient population, and (3) the number of years a surgeon is at risk for acquiring an HIV infection. If the risk of HIV transmission by a contaminated needle is 0.3% to 0.5%, if the HIV-infected population is 10%, if the number of needle sticks averages 30 a year, and if the surgeon has 40 years of exposure, then the lifetime risk of acquiring HIV infection can be as high as 60%.⁷⁰

HEPATITIS TRANSMISSION

The primary health risk to surgeons caring for patients with HIV infection or AIDS is that of acquiring hepatitis B or hepatitis C. The hepatitis D virus (HDV) has been identified as posing an additional risk of death in patients with acute hepatitis; persons who are infected with both HBV and HDV have a higher mortality.⁷¹

The epidemiology of hepatitis B has been well studied because there are numerous antigen and antibody markers of the virus in the blood of chronic carriers. On the basis of data from assays of these markers, it is estimated that more than 200,000 persons in the United States acquire new HBV infections each year.⁷² Of these 200,000, 25% will have symptoms of hepatitis, 5% will require hospitalization for their acute illness, and 1% to 2% of these hospitalized patients will develop fatal fulminant hepatitis [see Figure 6].

Between 5% and 10% of patients infected with HBV become chronic carriers—that is, they do not effectively clear the antigen from their systems, and they have a subclinical hepatic infection for prolonged periods. This group of patients is at risk for cirrhosis, with subsequent hepatic failure or hepatoma. Many chronic hepatitis carriers are unable to clear the infection because of immunosuppression as a result of another disease process, such as advanced HIV infection. AIDS patients are very likely to have had an HBV infection and to be chronic carriers. HIV-infected patients are also less likely to manifest an inflammatory response to hepatic infections. The CDC has estimated that as many as 80% of homosexual men, intravenous drug users, mentally retarded persons, and hemodialysis patients have serologic markers indicating a previous HBV infection.⁷³ Household contact or sexual relations with these high-risk individuals also involves a significant risk of acquiring HBV infection. It is estimated that up to 60% of such contacts have positive serology for HBV.

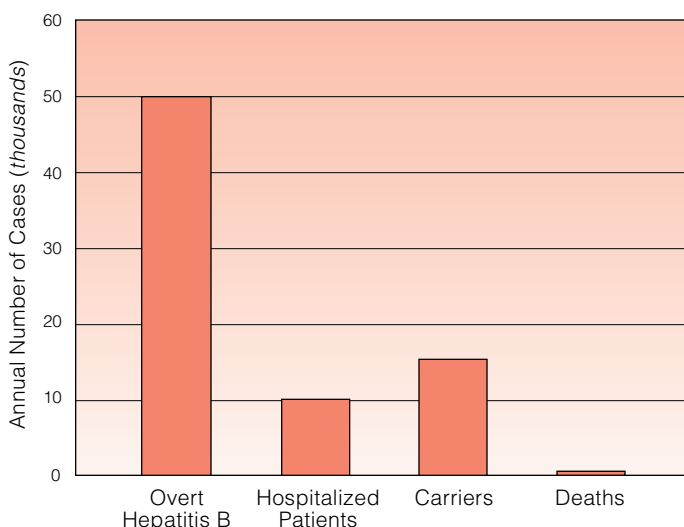


Figure 6 The annual incidence of hepatitis B infection in the United States is 200,000 cases. Various subgroups of hepatitis B patients are shown.⁷²

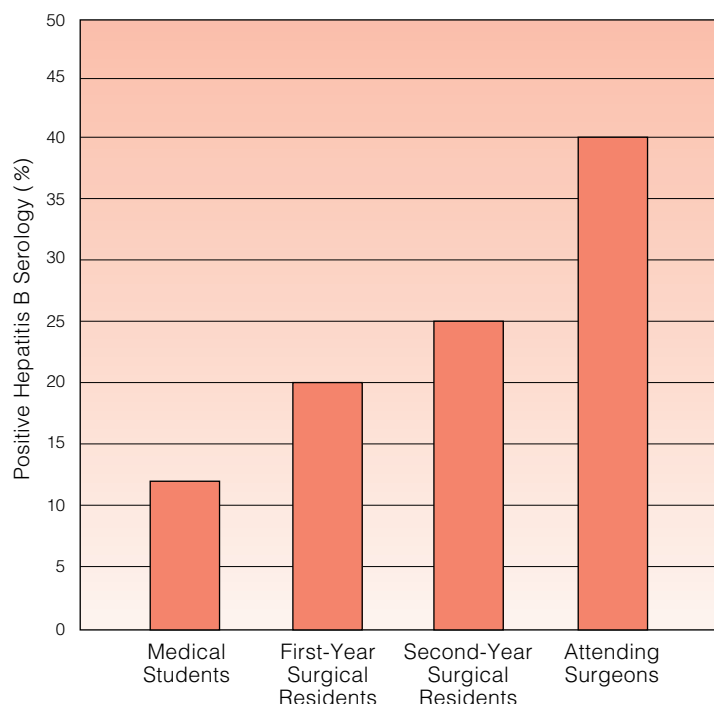


Figure 7 The prevalence of positive serology for hepatitis B increases among individuals in successive stages of a surgical career.⁷²

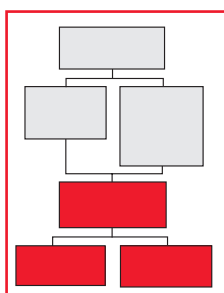
Exposure to hepatitis carriers is a risk for health care workers, particularly for those who work with blood products [see 8:20 *Viral Infection*]. Physicians involved with direct patient care are at especially high risk.⁷⁴ Those in administrative situations who do not have clinical contact with patients have a relatively low risk of acquiring hepatitis, whereas surgeons, particularly cardiac surgeons and transplant surgeons, are at especially high risk. The risk of hepatitis infection also increases with age.^{71,75} The incidence of positive hepatitis B serology is between 12% and 13% in students in their last year of medical school, nearly 20% in surgical residents at the end of their first year, and about 25% in surgical residents after the second year. During the course of an unimmunized senior surgeon's career, the risk of having hepatitis B approaches 50% [see Figure 7]. These risks are exceedingly high and emphasize the importance of widespread use of the hepatitis B vaccine [see 8:20 *Viral Infection*].

At least two studies have shown that there are numerous unimmunized practicing surgeons who finished medical school, training, or both before the hepatitis B vaccine first became available.^{61,76} These surgeons are at substantial risk for HBV infection and consequently need to be immunized. Surgeons who were immunized 5 or more years ago should have their titers checked; if titers are low, a booster is advisable.

Postexposure Prophylaxis

MANAGEMENT AFTER EXPOSURE TO HIV

If a health care worker is injured by a sharp object that was contaminated by exposure to fluid or tissue from an HIV-positive patient, a series of blood samples should be drawn at the time of injury and again at 6 weeks and 3, 6, and 12 months after the injury to determine whether HIV



infection has occurred. Although administration of antiretroviral therapy is recommended,⁷⁷ to date, no prospective trials have been performed to confirm its effectiveness in humans. A retrospective case-control study published in 1996 supported the post-exposure use of zidovudine.⁷⁸ The current recommendations for prophylaxis after a needle-stick injury are based on the likelihood of transmission from the incident.⁷⁹ In lower-risk situations, the risk of drug toxicity must be carefully weighed against the benefits of protection against HIV transmission.

The average risk of acquiring HIV after a percutaneous exposure is estimated to be 0.3%,⁸⁰ and the risk of acquiring HIV through mucocutaneous exposure approaches approximately 0.09%. It has been shown that the more blood transferred by a hollow-bore needle, the greater the likelihood of transmission. Clearly, patient factors such as viral burden and the presence of syncytia-inducing strains of virus will also influence the likelihood of seroconversion. Host factors such as cytotoxic T cell responses and perhaps T cell C3a/C5a receptors may also influence the outcome. With all this in mind, the CDC has formulated specific recommendations for postexposure prophylaxis (PEP).⁸¹

Because systemic infection after HIV exposure is thought not to occur immediately in primates, prompt initiation of antiretroviral therapy may sufficiently inhibit the initial replication to keep the inoculum of virus low and allow for effective immune clearance. Animal models are imperfect but have suggested that greatest efficacy of PEP was achieved when therapy was instituted within 24 hours of exposure. Overall efficacy of PEP is impossible to ascertain, because the incidence is fortunately low enough not to allow for a prospective study with sufficient statistical power to determine efficacy.

The current recommendations are based partly on the combination of simian studies, the experience with zidovudine in a retrospective case-control study of health care workers, and collective experience with the prevention of vertical transmission through the use of antiviral prophylaxis. It is also recognized that as HIV-infected patients are increasingly likely to have been treated with a variety of retroviral agents, their likelihood of having multidrug-resistant strains of HIV increases correspondingly. Arbitrary selection of PEP agents may not be optimal; it is possible that knowledge of the patient's antiretroviral history and the results of genotypic antiretroviral resistance studies may need to be taken into account for optimal PEP selection. Whenever possible, physicians familiar with the source patient and local resistance patterns should be consulted on the choice of PEP regimens. However, institution of PEP should never be delayed for consultation, because the regimen can always be altered later if further information is obtained.

The choice of agents is largely empirical, but the need for PEP and the number of drugs to be used should be predicated on (1) the risk assessment of the injury, taking into account the source's HIV status (and, if the patient is HIV positive, the patient's clinical status and viral load); (2) solid-bore versus hollow-bore needle injury (large or small inoculum); (3) whether the source needle was used for arterial or venous puncture; and (4) whether the injury involved intact or nonintact skin or mucous membrane exposure.

A two-drug PEP regimen is probably adequate for situations in which the source is known to be HIV positive but thought to have a relatively low viral load, in which the source's HIV status is unknown but he or she is known to participate in high-risk activity, or in which the worker sustains either a minor percutaneous or mucous membrane exposure. A three-drug regimen would be advised with more severe percutaneous exposure, with

Table 4 Nucleoside Reverse Transcriptase Inhibitors

Agent	Toxicity
Zidovudine	Marrow suppression, myopathy, nausea
Stavudine	Peripheral neuropathy, pancreatitis, increased liver function tests
Lamivudine	Nausea, possible lipoatrophy, especially with concurrent stavudine
Didanosine	Pancreatitis, peripheral neuropathy, diarrhea
Abacavir	Life-threatening hypersensitivity reaction in approximately 5%

extensive exposure of intact skin or mucous membranes, or when the source is thought to have a high viral load. Because all the drugs used for PEP can have significant side effects, even in the short term, the potential risks of two-drug or three-drug therapy should be weighed against the likelihood of acquiring an HIV infection. With cases in which the source patient can be identified but the HIV status is unknown, a rapid HIV test such as the SUDS should be employed. If the results of such testing is negative, PEP should not be given. If rapid testing is not available, PEP can be offered until the source patient is proved to be HIV negative by conventional tests.

For the choice of agents, the 1998 CDC guidelines suggest zidovudine and lamivudine (3TC) for two-agent therapy, with the addition of indinavir or nelfinavir for three-drug therapy. Zidovudine and 3TC are now available in a combination pill that is taken twice a day, which makes it a more convenient alternative; however, the increasing prevalence of the 184 mutation that confers 3TC resistance makes this less likely to be effective in situations involving patients who have been treated with 3TC. Newer drugs such as efavirenz may offer more tolerable alternatives to adding a protease inhibitor, as was recommended in the past. The 2001 guidelines leave the choice more open to local expertise.

No discussion of occupational exposure is complete without mention of HCV coinfection. Approximately 40% of all HIV-infected patients are coinfecting with HCV; in intravenous drug users, the incidence of HCV coinfection can be as high as 90%. Medical personnel exposed to HCV via occupational injury should undergo baseline testing for HCV antibodies and a baseline alanine transaminase (ALT) determination, with repeat testing in 4 to 6 months. There is no prophylactic regimen available, but some authorities recommend early intervention with HCV therapy (interferon alfa and ribavirin) if HCV remains detectable—a finding that would indicate persistence of infection.

TOXICITIES OF HIGHLY ACTIVE ANTIVIRAL THERAPY

Nucleoside Reverse Transcriptase Inhibitors

Long-term exposure to antiretroviral agents has not only improved survival but also introduced a variety of significant toxicities that physicians evaluating an HIV-infected patient must take into account. Nucleoside toxicities became apparent with the introduction of the first nucleoside reverse transcriptase inhibitor, zidovudine, 15 years ago, but a multitude of side effects are now known to be associated with all agents in this class. These agents appear to be toxic primarily through their ability to inhibit mitochondrial DNA synthesis. When critical

levels of mitochondrial depletion are reached, the patient becomes symptomatic [see Table 4]. All the nucleoside transcriptase inhibitors have been associated with hepatotoxicity to some degree. All these agents may also cause increased levels of lactic acid, which may be asymptomatic or present as fulminant lactic acidosis and shock. Patients on combination therapy that includes both didanosine and stavudine seem to be at particular risk for severe lactic acidosis and hepatic steatosis. Patients may present with nausea, vomiting, abdominal pain, and diarrhea and become progressively more acidotic and hypotensive. Lactate levels in excess of 10 mmol/L are associated with multi-organ failure and a mortality of greater than 80%. Symptoms may develop gradually or suddenly and may occur from weeks to years after the start of antiretroviral therapy. Routine monitoring of lactic acid levels is of no benefit, because the results of such monitoring are not predictive of progression to symptomatic lactic acidemia. Once patients become asymptomatic, the keys to survival are early recognition, discontinuance of the offending drugs, and adequate oxygenation of tissues.

Nonnucleoside Reverse Transcriptase Inhibitors

The nonnucleoside reverse transcriptase inhibitors [see Table 5] are increasingly used in triple-drug regimens. They are known to cause rashes and have also been associated with hepatitis. Nevirapine has been implicated in fulminant hepatic failure in the setting of postexposure prophylaxis and in South African women. There is some concern that it may be more hepatotoxic in patients with hepatitis C infection.

Protease Inhibitors

The protease inhibitors [see Table 6] have been more frequently associated with metabolic syndromes involving alterations in fat metabolism, blood glucose, and lipids than with hepatitis or lactic acidemia. Hypercholesterolemia and hypertriglyceridemia have been associated with HAART, especially in regimens that include protease inhibitors. It is well recognized that there is a

Table 5 Nonnucleoside Reverse Transcriptase Inhibitors

Agent	Toxicity
Nevirapine	Rash, fever, hepatitis
Delavirdine	Rash, fever, hepatitis
Efavirenz	Rash, somnolence, insomnia, nightmares

Table 6 Protease Inhibitors

Agent	Toxicity
Indinavir	Nephrolithiasis, elevated bilirubin, fat redistribution, hyperglycemia, dry mouth
Nelfinavir	Diarrhea, abdominal pain
Ritonavir	Femoral numbness, diarrhea, hyperlipidemia
Saquinavir	Diarrhea, liver function abnormalities
Amprenavir	Diarrhea, nausea
Lopinavir/ritonavir	Diarrhea, hyperlipidemia

higher incidence of cardiac disease in HIV-infected patients receiving HAART than in age-matched control patients and that the presence of other traditional risk factors such as smoking and hypertension magnifies the risk. This has led most HIV practitioners to aggressively attempt to correct lipid abnormalities through the use of lipid-lowering agents. The increased risk of premature cardiac disease has also led physicians to consider

tests to attempt to identify occult coronary disease. Patients on protease inhibitors have been found to have insulin resistance even in the absence of overt diabetes, which also contributes to increased risk of coronary artery disease. For that reason, when HIV-infected patients with blood lipid abnormalities are being evaluated for elective surgical procedures, it is prudent to include a cardiac assessment.

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1 THE ELDERLY SURGICAL PATIENT

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Older persons are the fastest-growing demographic group in the United States. It is estimated that by 2020, Americans older than 65 years will account for more than 20% of the total population. By 2030, their numbers will have doubled to 70 million [see Figure 1], one fourth of whom will be 85 years of age or older.¹ This segment of the U.S. population uses a substantial share of total health care resources. Centers for Disease Control and Prevention (CDC) National Hospital Discharge Survey data for 2004 indicate that the rate of interventional and surgical procedures in Americans aged 65 years or older is 4,382.3/10,000. More than 50% of coronary artery bypass graft procedures and large bowel resections—and approximately 35% of all procedures—are performed in persons belonging to this age group.² These numbers will continue to increase as the elderly segment of the population continues to grow. Accordingly, surgical care of elderly patients is likely to account for an increasing share of surgeons' workloads.

It must be kept in mind that the elderly are not a homogeneous population. The average additional life expectancy for a 65-year-old American is 18.4 years, and that for an 85-year-old is 6.8 years³; however, there is significant variability within each of these age groups. For example, there can be dramatic differences between "fit" and "frail" elderly persons of the same age. On the one hand, a fit 85-year-old woman may have an additional 10 years of life expectancy. On the other hand, the life expectancy of a frail 85-year-old man may be closer to 2 years [see Figure 2]⁴—and possibly much less (e.g., a few months) if an acute event should occur that necessitates hospitalization.⁵ Given that chronologic age, by itself, alone is a poor predictor of life expectancy, a more reliable approach to estimating life expectancy involves assessing overall functional reserve, taking into consideration the myriad factors that define the aging process.

Aging is a multifactorial process that encompasses more than just physiologic changes. Although physiologic factors are undoubtedly significant and must always be taken into account, there are several other factors (e.g., potential functional limitations, depression, or polypharmacy) that should also be considered in dealing with older patients. Surgeons are often well trained in addressing the former but not the latter; however, they will be able to achieve a more comprehensive assessment of an elderly person's wellness and reserve by considering all of these factors.

Various scoring systems are being applied in the elderly population in an effort to evaluate their overall functional status in a more accurate and quantifiable manner. One example is the Comprehensive Geriatric Assessment (CGA), a tool that is commonly used within the geriatric medicine community and is currently being used with increasing frequency in the nascent field of geriatric surgery. Because chronologic age alone is a poor predictor of performance

status and advanced age is not considered an acceptable contraindication to surgery, adequate assessment of functional age and physiologic reserve are of paramount importance in the elderly surgical patient.

Nature and Clinical Impact of Physiologic Changes Associated with Aging

CARDIAC CHANGES

Aging is characterized by progressive loss of physiologic reserve in nearly all organ systems [see Table 1]. The changes in cardiac function that occur in the elderly are particularly significant. Cardiac output is the product of the heart rate and the stroke volume (which correlates with the end-diastolic volume, or preload). In elderly myocardium, the resting heart rate, stroke volume, cardiac output, and ejection fraction are all maintained,⁶ but the way in which these variables respond to stress is altered.⁷ The increased myocardial stiffness typical of aging leads to decreased ventricular compliance and impaired end-diastolic filling.^{8,9} In addition, the blunted chronotropic and inotropic response of aged myocardium to adrenergic stimuli¹⁰ results in depression of both the maximal heart rate and the increase in ejection fraction in response to stress.¹¹ Older persons thus are more dependent on preload to maintain cardiac output in the face of increased demand¹² and, accordingly, are especially sensitive to the dangers of hypovolemia.

Cardiac complications remain a leading cause of perioperative morbidity and mortality, especially in older patients. Myocardial infarction (MI) and congestive heart failure (CHF) are responsible for one fourth of all cardiac complications and perioperative deaths in elderly patients.¹³

The first preoperative cardiac risk index for noncardiac surgical procedures was developed by Goldman and colleagues in 1977.¹⁴ This index used nine clinical variables that had been found to correlate with an increased risk of perioperative cardiac complications to determine a patient's overall level of cardiac risk. Several of these variables reflect correctable conditions, which suggests that in selected patients, delaying surgery to permit medical treatment may be a reasonable strategy. In 1999, Lee and colleagues developed a simplified index known as the Revised Cardiac Risk Index (RCRI), which included six variables that had been found to be independent predictors of cardiac complications [see ECP:4 Risk Stratification, Preoperative Testing, and Operative Planning].¹⁵ In the RCRI, one point is given for each of the following cardiac risk factors: (1) a history of CHF, (2) a history of ischemic heart disease, (3) a history of cerebrovascular disease, (4) preoperative treatment with insulin, (5) a preoperative serum creatinine level higher than 2.0 mg/dl, and (6) a high-risk surgical procedure. If none of

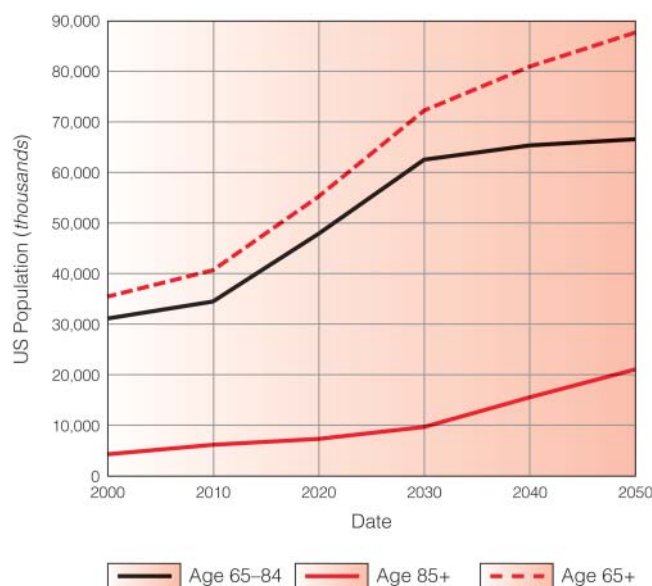


Figure 1 Shown is projected U.S. population by age, 2000–2050.¹

these risk factors is present, the probability of a major cardiac complication is 0.4% to 0.5%; if one factor is present, 0.9% to 1.3%; if two factors are present, 4% to 7%; and if three or more risk factors are present, 9% to 11%.¹⁵

A 2007 report from an American College of Cardiology (ACC)/American Heart Association (AHA) task force for perioperative cardiovascular evaluation recognized the utility and efficacy of the RCRI and delineated a stepwise approach to perioperative cardiac assessment.¹⁶ The first step is a basic clinical evaluation (history, physical examination, and 12-lead electrocardiography). The patient is assessed for any active cardiac conditions or clinical risk factors that might have to be treated before surgery. (Obviously, such assessment may not be feasible in emergency situations.)

Active cardiac conditions include unstable coronary syndromes (e.g., recent MI or unstable angina), decompensated heart failure, significant dysrhythmias (e.g., Mobitz II block, third-degree block, symptomatic ventricular arrhythmia, supraventricular arrhythmia with uncontrolled ventricular rate, symptomatic bradycardia, and new ventricular tachycardia), and severe valvular disease (e.g., severe aortic stenosis with a pressure gradient greater than 40 mm Hg or a valvular area smaller than 1 cm², symptomatic aortic stenosis, or symptomatic mitral stenosis). If any of these conditions is present, the surgical procedure should be postponed until further testing and treatment are complete. If no active cardiac conditions demanding immediate attention are present, the patient's functional status should be evaluated. For patients with good functional capacity (as evidenced by the ability to perform activities of daily living [ADL]), additional testing may not be necessary. For patients with limited or unknown functional capacity, formal cardiovascular stress testing may be required, especially if the planned procedure is an intermediate-risk (e.g., intra-abdominal or intrathoracic) or high-risk (e.g., aortic, major vascular, or peripheral vascular) operation.

A number of randomized studies have examined the use of perioperative beta blocker therapy to reduce the risk of MI and death in noncardiac surgical patients [see *ECP:4 Risk Stratification, Preoperative Testing, and Operative Planning*]. Although the benefits demonstrated in early trials^{17,18} were not seen in several later studies,^{19,20} most of the evidence still suggests that perioperative beta blockade is beneficial, especially in high-risk patients, such as those who have a history of cardiac disease or who have risk factors and are undergoing major surgery.¹⁶ A 2005 meta-analysis of all randomized controlled trials evaluating the use of preoperative beta blockade in noncardiac surgery demonstrated that this measure had a protective effect.²¹ Aggregate data showed decreases in long-term cardiac mortality (from 12% to 2%) and in the incidence of myocardial ischemic events (from 33% to 15%).

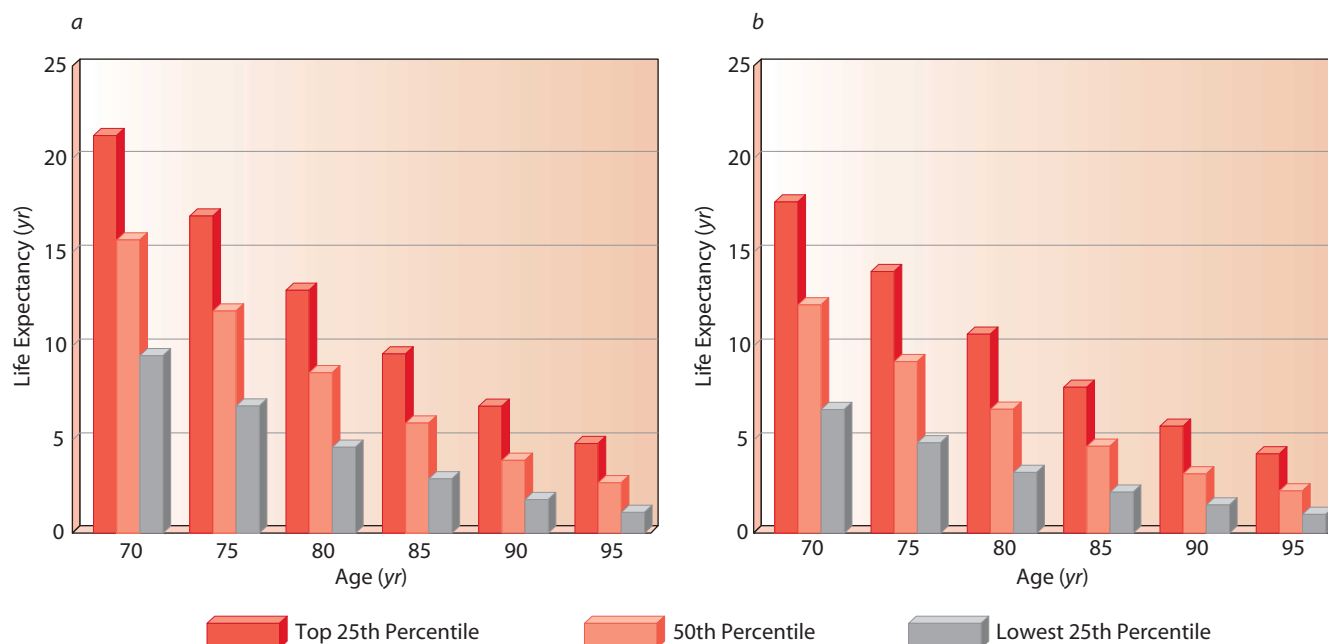


Figure 2 Shown are upper, middle, and lower percentiles for life expectancy in (a) women and (b) men at selected ages.⁴

Table 1 Physiologic Changes Associated with Aging¹⁷²⁻¹⁷⁴

	Age-Related Changes	Clinical Consequences	Interventions
Cardiovascular system	Decreased maximal heart rate, cardiac output, and ejection fraction Decreased ventricular compliance with slowed ventricular filling; increased reliance on atrial contribution Decreased inotropic and chronotropic responses to sympathetic stimuli Decreased baroreceptor sensitivity Thickening of valvular ring and leaflets Thickening of vessel walls; tendency toward vasoconstriction Increased prevalence of CAD (clinically apparent or occult) Lowered threshold for dysrhythmias	Greater reliance on preload or end-diastolic volume and ventricular filling to achieve increases in cardiac output Intolerance of hypovolemia Intolerance of tachycardia and dysrhythmias such as atrial fibrillation	Initiate vigorous fluid resuscitation to achieve and maintain optimal ventricular filling Avoid tachycardia; correct dysrhythmias Avoid dysrhythmogenic medications If pharmacologic support required, consider nonvasoconstricting inotropes and afterload reduction
Respiratory system	Decreased lung compliance Decreased strength and endurance of respiratory muscles Increased stiffness of chest wall and increased reliance on diaphragm function Decreased vital capacity and expiratory flow rate Increased residual volume and functional residual capacity Increased alveolar-arterial gradient Decreased arterial oxygen tension Decreased compensatory responses to hypoxia or hypercarbia Decreased airway sensitivity; reduced efficiency of mucociliary clearance mechanisms Increased sensitivity to narcotic respiratory depression	Decreased pulmonary capacity and reserve Increased work of breathing Predisposition to aspiration and increased risk of pulmonary infections Predisposition to hypoxemia Increased small airway closure, especially postoperatively and in supine position, leading to increased atelectasis and shunting Tachypnea and increased tidal volume may be less apparent as respiratory failure develops	Encourage early mobilization and upright, rather than supine, position Provide effective pain relief to facilitate early mobilization and deep breathing; monitor closely if narcotics used Use supplemental oxygen postoperatively as needed Use nasogastric tubes sparingly Encourage preoperative smoking cessation if applicable Assess influenza and pneumococcal immunization status Recognize decreased ventilatory responses to hypoxia and hypercarbia
Renal function, fluids, electrolytes	Decreased glomerular filtration rate Reduced renal mass, renal blood flow, glomerular filtration area, and permeability Decreased renal tubular function with impaired ability to concentrate urine and conserve water and solute Reduced efficiency of water and solute excretion Dysregulation of renin-angiotensin system Lowered sensitivity to fluid and electrolyte perturbations Impairment of vitamin D metabolism Decreased thirst mechanism Increased renal glucose threshold	Predisposition to hypovolemia with increased risk of dehydration and prerenal azotemia Predisposition to extracellular fluid volume expansion resulting in electrolyte disorders (e.g., hyponatremia) Predisposition to hyperglycemia and hyperosmolar states Increased risk of nephrotoxicity as consequence of decreased creatinine clearance	Pay meticulous attention to fluid and electrolyte status Estimate creatinine clearance using age-adjusted formulas, recognizing that “normal” serum creatinine value actually reflects decreased creatinine clearance because of concurrent decreased muscle mass (with decreased creatinine excretion) Avoid nephrotoxic drugs Adjust drug doses appropriately for renally eliminated drugs to compensate for diminished creatinine clearance and altered pharmacokinetics
Gastrointestinal tract	Decreased salivary flow and impaired swallowing Decreased stimulated gastric acid output Impaired GI mucosal protective mechanisms Decreased intestinal motility and absorption Impairment of hepatic drug clearance	Decreased mucosal absorption of medications Decreased intestinal motility Decreased pancreatic exocrine function Decreased elimination of hepatically metabolized drugs	Exercise caution in prescribing medications utilizing cytochrome P-450 pathway Take bowel history and prescribe laxatives, especially when concurrent narcotics used
Musculoskeletal system	Significantly decreased muscle mass Increased fat mass Decrease in bone mass	Erosion of muscle mass during acute illness may result in rapid loss of muscle strength with clinical consequences (e.g., impairing coughing, decreased mobility) Altered volumes of drug distribution Increased risk of falls and fractures with delayed healing of fractures	Support and maintain physical function by providing effective pain relief, avoiding unnecessary tubes and drains that impair mobility, and encouraging and assisting early mobilization Minimize fasting and provide early nutritional support Adjust drug doses for volume of distribution

Table 1 Continued

	Age-Related Changes	Clinical Consequences	Interventions
Thermoregulation	Diminished sensitivity to ambient temperature Reduced efficiency of heat conservation, production, and dissipation Blunted febrile response	Predisposition to hypothermia	Initiate active warming measures to maintain normothermia during surgery
Endocrine system	Decrease in thyroxine Decrease in free and total testosterone and estrogen Elevated fasting glucose level and impaired sensitivity to insulin	Decreased fever response Decreased libido with sexual dysfunction Increased risk of developing diabetes Increased bone demineralization as result of increased serum PTH	Monitor patient closely for glucose intolerance Maintain high index of suspicion for infection, even in absence of fever
Immunologic system	Changes in T cell- and B cell-mediated immunity Decreased neutrophil turnover and function with decreased phagocytosis	Increased susceptibility to infection Increased risk of cancer secondary to perturbed immune surveillance Impaired response to vaccines	Maintain heightened awareness of increased risk of infections Provide early, effective, and appropriate antibiotic treatment
Neurologic system	Neuronal loss Impaired memory and cognition Prolonged reaction time Impaired sensory function with visual, auditory, and olfactory loss Decreased peripheral nerve myelin	Increased risk of delirium Increased susceptibility to development of peripheral neuropathy Altered pain perception Difficulty in obtaining informed consent and assessment of decision-making capacity	Reduce risk of delirium through screening, monitoring and treatment of infections, and regular orientation of patients, with frequent contact Assess and treat pain appropriately Work with family and caregivers

CAD—coronary artery disease PTH—parathyroid hormone

Invasive hemodynamic monitoring has been employed in efforts to improve perioperative fluid management and reduce postoperative morbidity and mortality. Historically, it has been common practice to admit high-risk patients to the intensive care unit preoperatively for placement of a pulmonary arterial catheter and optimization of cardiac function. Data concerning the efficacy of this practice are conflicting. Some prospective studies and retrospective reviews suggested that monitoring with a pulmonary arterial catheter was beneficial, especially in high-risk patients (e.g., elderly patients with high cardiac risk indices who were scheduled to undergo major abdominal or vascular surgery).^{22,23} A number of prospective, randomized, controlled trials, however, failed to show any improvement in postoperative morbidity or mortality with such monitoring, even in high-risk patients undergoing major noncardiac surgery.^{24,25} Several large-scale studies actually found that invasive cardiac monitoring yielded increased morbidity, without providing any demonstrable benefit.^{26,27} Increased rates of pulmonary embolism, CHF, dysrhythmia, and noncardiac complications have been observed in elderly, high-risk surgical patients who underwent pulmonary arterial catheter monitoring, compared with those who did not.^{27,28} The current ACC/AHA task force guidelines for perioperative cardiovascular evaluation acknowledge the potential benefit of such monitoring in selected cases but do not endorse its routine use.¹⁶

PULMONARY CHANGES

With aging comes a significant decline in respiratory function.²⁹ Decreased elastic recoil of the lung and increased stiffness of the chest wall lead to reduced lung and chest wall compliance and, consequently, to decreases in maximal

inspiratory and expiratory forces.³⁰ Forced expiratory volume (FEV₁) is reduced as well. Increased collapse of the small airways leads to uneven alveolar ventilation and ventilation-perfusion mismatch. Control of ventilation is also impaired, with decreased responses to both hypoxia and hypercapnia. Finally, reduced ability to clear the airway leads to an increased risk of aspiration and pneumonia.

Pulmonary complications account for nearly 50% of postoperative complications in the total population of surgical patients.³¹ They are even more frequent in the elderly surgical population and are one of the most common complications seen in older patients.^{32,33} One large review of older patients undergoing surgery for colorectal cancer found that the incidence of respiratory complications increased with advancing age: such complications occurred in 5% of patients aged 64 years or younger, 10% of those aged 65 to 74, 12% of those aged 75 to 84, and 15% of those aged 85 years or older.³⁴ Elderly patients undergoing major abdominal surgery are at higher risk for postoperative pneumonia than younger patients are. These numbers are grounds for concern, in that the development of pneumonia is associated with increased 30-day postoperative mortality.³³

Risk factors for pulmonary complications include smoking, chronic obstructive pulmonary disease (COPD), poor exercise capacity, shortness of breath, and active pulmonary infection.³⁵ Elderly patients should be screened with a baseline chest x-ray and baseline arterial blood gas determinations. Preoperative routine pulmonary function testing has not been demonstrated to be useful for procedures other than lung resection.³⁶ Smoking cessation should be strongly encouraged.³⁷ Bronchodilators and incentive spirometry may also be beneficial. Active respiratory infections should be treated before elective surgical procedures are performed.

RENAL CHANGES

Aging is associated with a number of morphologic and histologic changes in the renal system, including reduced cortical mass and cortical area, interstitial fibrosis, tubular atrophy, and glomerulosclerosis.³⁸ As a result of these changes, glomerular function declines with advancing age³⁹: by the age of 80, the glomerular filtration rate (GFR) may be as much as 45% lower. Impaired renal tubular function is evident as well, resulting in disturbances of water, glucose, and electrolyte balance.⁴⁰ The renin-angiotensin axis is also altered with aging.⁴¹ Decreased plasma renin activity, renal vasoconstriction, reduced antidiuretic hormone responsiveness, and an impaired thirst mechanism all may develop in this setting.

These physiologic changes place elderly surgical patients at increased risk for dehydration and prerenal azotemia. Acute renal failure can increase postoperative mortality substantially in these patients.⁴² Fluids and electrolytes should be carefully monitored, exposure to nephrotoxic drugs should be minimized, and oliguria should be addressed promptly and aggressively. Renal drug elimination is also impaired, and creatinine clearance is decreased; drug dosing should be modified accordingly.

GASTROINTESTINAL CHANGES

GI changes associated with aging include decreased basal and stimulated salivary flow rates (which can lead to impaired swallowing),⁴³ reduced mucosal protection of the stomach,⁴⁴ and prolonged intestinal motility.⁴⁵ Hepatobiliary function is altered by age-related decreases in liver size and volume,⁴⁶ as well as by histopathologic changes leading to impaired elimination of drugs, especially drugs metabolized by the cytochrome P-450 system.⁴⁷ Clinicians should be aware of the risk of potentially important cytochrome P-450-mediated drug interactions, particularly in the setting of polypharmacy.

CHANGES IN THERMOREGULATION

Aging is associated with disruption of thermoregulation. In comparison with younger patients, elderly patients are less sensitive to alterations in environmental temperature and less able to maintain thermal homeostasis.⁴⁸ These changes account for the higher risk of both hypothermia and heat-stroke in this population. Heat conservation is impaired in the elderly, and the capacity for vasoconstriction in response to cold stimulus may be decreased. The ability to shiver to produce metabolic heat is also impaired, and when this ability is used, it can impose substantial metabolic stress on an older person.⁴⁹ Therefore, maintaining normothermia during surgical procedures is of particular importance in elderly patients.^{50,51} Intraoperative hypothermia has been associated with increased wound infection rates and longer hospital stays in elderly patients undergoing major abdominal surgery.⁵²

Abnormal thermoregulation accounts for the blunted febrile response seen in elderly persons fighting infections. The immune system is also affected by aging,⁵³ with both cellular⁵⁴ and humoral⁵⁵ immunity being impaired. The increased sensitivity to infection and the reduced ability to mount a febrile response underscore the importance of maintaining a high index of suspicion for postoperative infection in all elderly patients, even when fever is absent.

MUSCULOSKELETAL CHANGES

Aging is associated with various structural and functional changes in the musculoskeletal system. Muscle mass is lost, muscle strength declines, and body fat mass increases.⁵⁶ By the age of 80 years, lean muscle mass may have fallen by as much as 40% to 50%.^{57,58} In addition, bone mass decreases, and bone remodeling and cartilage healing are impaired, resulting in cartilage damage and arthritis.⁵⁹ These changes predispose the elderly to progressive loss of mobility, gait and balance disorders, and falls. To counter this predisposition, early ambulation in the postoperative period, with assistance as necessary, should be encouraged. The changes in body composition that occur with aging also leave the elderly vulnerable to protein malnutrition from depleted protein reserves.⁵⁸ Finally, the various structural changes predispose elderly patients to soft tissue and joint injury. One should therefore take extra care when positioning patients in the OR, ensuring that appropriate padding and joint protection are provided.

CLINICAL IMPLICATIONS

A solid understanding of the physiologic changes associated with aging can facilitate preoperative assessment of the elderly patient's functional reserve and thus, ultimately, help ensure a more accurate assessment of the operative risk. An appreciation of the characteristically diminished functional reserve in this population also highlights the increased vulnerability of elderly patients to the effects of surgical complications, thereby underscoring the need for meticulous perioperative care aimed at minimizing the likelihood of potential complications whenever possible. Studies have shown that the development of postoperative complications (e.g., pulmonary infection and renal insufficiency) is associated with a higher 30-day postoperative mortality,⁶⁰ as well as an increased risk of death within the first 3 months after surgery.⁶¹ The occurrence of a postoperative complication has also been identified as a predictor of impaired recovery of functional independence in elderly patients who have undergone major abdominal surgery.⁶²

Preoperative Assessment of the Elderly Patient

COMPREHENSIVE GERIATRIC ASSESSMENT

In 1987, the National Institutes of Health (NIH) Consensus Conference on Geriatric Assessment Methods for Clinical Decision-making defined the CGA as a "multidisciplinary evaluation in which the multiple problems of older persons are uncovered, described, and explained, if possible, and in which the resources and strengths of the person are catalogued, need for services assessed, and a coordinated care plan developed to focus interventions on the person's problems."⁶³ The CGA differs from a standard preoperative evaluation in that it is a truly multidimensional evaluation of the elderly patient. In addition to assessing comorbid conditions, cognitive ability, mental function, socioenvironmental factors, and nutrition status, it also scrutinizes medications and functional ability.

The CGA may be used both to identify at-risk individuals and to guide interventions. When evaluated as a screening tool in the geriatric community, it has been shown to detect

new and unsuspected problems in 76% of elderly persons living at home.⁶⁴ It has been found to be potentially beneficial in reducing the incidence of hospitalization, falls, delirium, and readmission in geriatric medical studies.⁶⁵ It is predictive of both morbidity and mortality in older patients.⁶⁶

Because the CGA is designed to take into account the multidimensional nature of aging, it may provide the best estimate of functional reserve in the elderly population, as well as a gross estimate of life expectancy.⁶⁷ Although the CGA has not yet been standardized, there are several elements that, in our view, should always be included in the evaluation [see Table 2].

Function

Functional status may be measured in several different ways. In geriatric medicine, evaluation of functional status typically includes assessment of the patient's ability to perform ADL and instrumental activities of daily living (IADL). ADL are personal care tasks, such as bathing, showering, eating, getting in and out of a bed or chair, using the toilet, maintaining continence, and walking⁶⁸; they are skills necessary for maintaining independent living at home. IADL are everyday tasks, such as housework, laundry, preparing meals, shopping, managing personal finances, negotiating transportation, and taking medications⁶⁹; they are skills necessary for maintaining independence within the community. Impaired ability to perform ADL and IADL has been associated with increased mortality in older patients both within the community and in the hospital.^{64,70} In particular, preoperative impairment of ADL or IADL capacity has been found to place elderly surgical patients at increased risk for

postoperative morbidity and mortality.⁷¹ The preoperative level of functional performance has also been shown to be an independent predictor of the extent to which elderly patients recover functional independence after major abdominal surgery.⁶²

The performance status scores commonly used in oncology include the Eastern Cooperative Oncology Group (ECOG) grade [see Table 3] and the Karnofsky score [see Table 4]. Both of these are essentially global indicators of overall functional status. Studies involving older cancer patients have shown that adding assessment of ADL and IADL substantially enhances the functional status evaluation provided by Karnofsky scores or ECOG grades alone. In one study of older patients with ECOG grades of at least 2, more than half had significant limitations in IADL.⁷²

Recognizing the limitations of questionnaire-based assessments for predicting true functional status, some groups have elected to integrate objective performance-based measures of functional status into the CGA. Among the most commonly

Table 2 Multidisciplinary Workup of Elderly Patients: Elements of Comprehensive Geriatric Assessment^{67,106,112,113}

Domain	Measure
Functional status	Activities of daily living Instrumental activities of daily living Karnofsky score ECOG grade Timed up and go test Number of falls within past 6 months
Comorbidity	Cumulative Illness Rating Scale—Geriatrics Charlson Comorbidity Index Older American Resources and Services Subscale
Nutrition	Mini Nutritional Assessment Body mass index Percentage of unintentional weight loss within past 6 months
Cognition	Mini-Mental State examination Blessed Orientation-Memory Concentration Test
Depression	Geriatric Depression Scale Hospital Anxiety and Depression Scale Beck Depression Scale
Social support	RAND Medical Social Support Scale Medical Outcome Study Social Support Survey Seeman and Berkman Social Ties Score
Polypharmacy	

ECOG—Eastern Cooperative Oncology Group

Table 3 Eastern Cooperative Oncology Group* Performance Assessment¹⁷⁵

Grade	Patient Description
0	Fully active and able to carry out all predisease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled and not capable of any self-care; confined to bed or chair
5	Dead

*Used by permission of Eastern Cooperative Oncology Group, Robert Comis, M.D., Group Chair

Table 4 Karnofsky Score¹⁷⁶

Score	Patient Description
100	Normal, with no complaints or signs of disease
90	Showing minor signs and symptoms but capable of normal activity
80	Showing some signs or symptoms but capable of normal activity with some effort
70	Capable of self-care but unable to do active work
60	Requiring occasional assistance but able to take care of most personal needs
50	Requiring frequent medical care
40	Disabled, requiring special care and assistance
30	Severely disabled, hospitalized
20	Hospitalized and very ill, requiring active supportive treatment
10	Moribund, with rapidly progressing fatal disease process
0	Dead

used measures of physical mobility is the timed “up and go” performance test,⁷³ which measures (in seconds) the time it takes a person to stand up from a standard armchair with a seat height of 46 cm, walk a distance of 3 m, return to the chair, and sit again. Other measures include walking a short course, assessing grip strength, and having the patient stand on one leg. Many patients who have good performance status according to their ECOG grades have been found to have poor performance when timed tests of basic mobility are employed.⁷⁴ Such measures also seem to be predictive of progressive declines in the ability to carry out ADL and IADL at 1 year and 4 years.⁷⁵ Whether these measures correlate with overall survival in elderly surgical patients remains to be studied. It is likely that they will prove to be just as important as the well-established comorbidities of the cardiac, pulmonary, and renal systems.

Comorbidity

Comorbid conditions are common in elderly surgical patients and frequently translate into adverse outcomes.^{76,77} The scoring system that is almost universally employed for assessing comorbidity in surgical patients is the American Society of Anesthesiologists (ASA) physical status classification [see Table 5].⁷⁸ For decades, the ASA score has been used to stratify the operative risk of all patients who undergo surgery. It accurately reflects how the severity of a patient’s comorbidities reliably predicts surgical outcome in terms of postoperative morbidity and mortality [see Figure 3]. In one multicenter prospective study, the ASA score was the single best predictive measure of postoperative morbidity and the second best predictive indicator of postoperative mortality.⁷⁹ Analyses aimed at identifying risk factors predictive of adverse outcome specifically in geriatric surgical patients have shown that a high ASA score is an independent predictor of postoperative morbidity and mortality in older surgical patients.^{80,81}

Additional measures of comorbidity include the Cumulative Illness Rating Scale–Geriatrics (CIRS-G)⁸² and the Charlson Comorbidity Index (CCI).⁸³ The CIRS-G is a global assessment of the severity of comorbid disease. Fourteen organ systems are evaluated for the presence of comorbid disease. Weights are assigned according to the severity of disease in terms of disability, chronicity, and end-organ failure. A total score is then calculated; higher

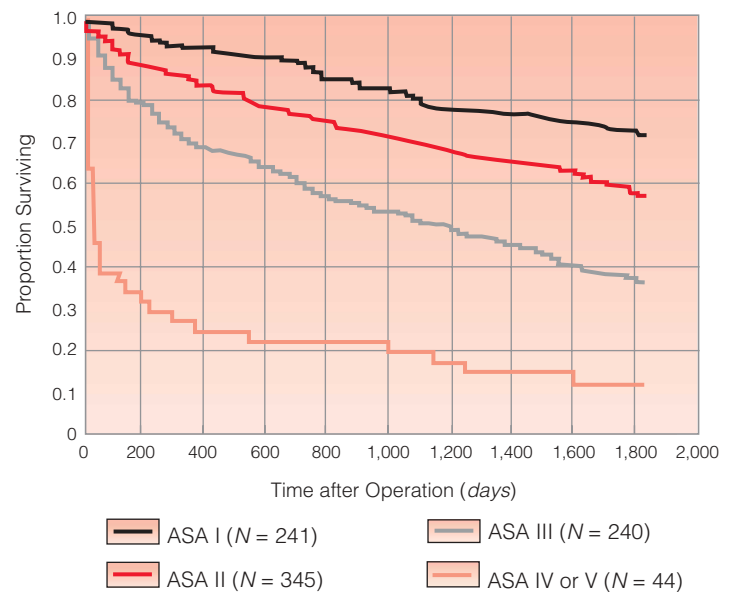


Figure 3 Depicted is correlation between American Society of Anesthesiologists (ASA) grade and postoperative survival.¹⁷¹

scores are independently predictive of mortality in older surgical patients.⁷⁰ The CCI, initially developed as a method of estimating the risk of death on the basis of comorbid disease and designed for prospective use in longitudinal studies, examines 19 categories of comorbidity, each weighted according to the adjusted risk of 1-year mortality [see Table 6]. According to the original study by Charlson and colleagues, with each increase in the level of the comorbidity index, there is a statistically significant, stepwise increase in the cumulative mortality attributable to comorbid disease.⁸³ The 1-year mortality rates for a score of 0, 1–2, 3–4, and 5 or greater were 12%, 26%, 52%, and 85%, respectively. The CCI can be used today to provide a summary score denoting the burden of illness, which correlates both with ability to tolerate treatment and with overall survival.^{84,85}

Nutrition

Impaired nutritional status is highly prevalent among the elderly. As many as 12% of men and 8% of women in the healthy geriatric population are undernourished.⁷¹ Nutritional impairment is even more common among hospitalized patients, with reported rates ranging from 37% to 85%.^{86–88} Malnutrition is known to be associated with adverse surgical outcomes. Higher rates of surgical complications⁸⁹ and increased postoperative mortality have been observed in patients with poor nutritional status, as determined by a low body mass index (BMI),⁷⁰ weight loss,⁹⁰ a low preoperative serum albumin level,^{89,91} or a low Mini Nutritional Assessment (MNA) score.⁹² In the National Veterans Affairs (VA) Surgical Risk Study, declining serum albumin levels were associated with an exponential increase in mortality (from less than 1% to 29%) and morbidity (from 10% to 65%) in patients undergoing major noncardiac operations.⁹¹ In a 2002 study, the MNA, which measures 18 factors by means of a self-reporting questionnaire and anthropometric measurements to assess nutritional status in elderly patients, was predictive of mortality in hospitalized geriatric patients.⁹²

Table 5 American Society of Anesthesiologists Physical Status Classification

Class*	Patient Status
I	Healthy patient
II	Patient with mild systemic disease
III	Patient with severe but not incapacitating systemic disease
IV	Patient with severe systemic disease that poses constant threat to life
V	Moribund patient who is not expected to survive without surgery
VI	Patient who has been declared brain-dead and whose organs are being removed for donor purposes

*Suffix E added for emergency operations.

Table 6 Charlson Comorbidity Index⁸³

Condition	Assigned Weight
Myocardial infarction Congestive heart failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Liver disease, mild Diabetes	1
Hemiplegia Renal disease, moderate or severe Diabetes with end-organ damage Any malignancy Leukemia Malignant lymphoma	2
Liver disease, moderate or severe	3
Metastatic solid malignancy AIDS	6

Preoperative identification of malnourished patients and nutritional supplementation before major surgical procedures may reduce the chances of an adverse outcome.^{93,94}

Cognition

Preoperative cognitive dysfunction has been associated with increased postoperative complications and worse survival in elderly surgical patients.^{95–97} Such dysfunction may take the form of either dementia or delirium. Dementia is a chronic baseline impairment of cognitive function. Demented patients are known to experience higher postoperative mortality than patients with intact cognitive function.⁹⁸ Delirium is an acute confusional state associated with multiple possible causes. The incidence of postoperative delirium in older patients ranges from 20% to 60%.^{99,100} This state is associated with a prolonged hospital stay, functional decline, and increased mortality.^{101–104} Risk factors for the development of postoperative delirium include preexisting dementia, visual impairment, alcohol consumption, infection, narcotic use, and polypharmacy.

Cognitive ability can be assessed with the Mini-Mental State examination (MMSE) [see Table 7].¹⁰⁵ Baseline cognitive function should be established preoperatively. Studies in elderly cancer patients that used a screening cognitive examination as part of the CGA found that in 25% to 50% of patients, abnormalities were discovered that prompted further evaluation.¹⁰⁶ Cognitive impairment assessed by the MMSE within an ambulatory primary care setting has been associated with an increased risk of mortality, even after confounding effects from chronic comorbid conditions have been controlled for.¹⁰⁷ In addition to identifying at-risk patients, the MMSE provides a standard measure that may be applied if postoperative cognitive deterioration becomes a concern.

Depression

Depression and the lack of social support are also linked to adverse outcomes in older surgical patients. As many as 14%

to 40% of geriatric patients routinely screened for depression as part of a CGA may exhibit depressive symptoms.¹⁰⁶ Depression has been linked to decreased survival in older patients undergoing orthopedic¹⁰⁴ or oncologic surgical procedures.¹⁰⁸ The lack of social support has also been correlated with higher mortality in the geriatric and geriatric oncology literature.^{109,110} A tool that is commonly employed in screening for depression in the elderly is the Geriatric Depression Scale (GDS) [see Table 8]. According to this simple 15-point scale, a score greater than 5 in an elderly patient diagnoses depression with 69% sensitivity and 77% specificity rates.

Social Support

Several tools are available for quantifying social support resources in elderly patients. One such tool is the Medical Outcome Study Social Support Survey (MOS-SSS), which yields a score on a scale of 0 to 100 and includes “emotional” and “tangible” subscales.¹¹¹ Another commonly used measure of social support is the Seeman and Berkman Social Ties Score, which measures social ties in four areas: marital status, close contact with at least two close friends or relatives, church attendance, and membership in other groups. The presence of social ties has been found to be inversely related to mortality in the elderly.¹⁰⁹

Polypharmacy

The physiologic changes associated with aging lead to alterations in pharmacokinetics, and these alterations, in conjunction with polypharmacy, leave the older patient susceptible to adverse drug interactions. Review of the patient’s medication list is an integral component of the CGA. Nonessential medications should be discontinued and potential drug interactions screened for.

Summary

The variables examined during the course of the CGA are often predictive of morbidity and mortality in elderly patients. Accordingly, there is growing support for use of the CGA in the assessment of older patients undergoing evaluation for surgery.^{112,113}

In the field of geriatric surgical oncology, this assessment is taken one step further by the tool known as the Preoperative Assessment of Cancer in the Elderly (PACE).⁷¹ The PACE incorporates several components of the CGA, as well as the ECOG performance grade, the ASA classification, and the Brief Fatigue Inventory (BFI) score. It is currently being assessed in a multinational study as a tool for evaluating functional capacity and overall health status in older cancer patients being considered for surgery. Preliminary results with this tool support the correlation between functional status (as measured by capacity for ADL and IADL) with subsequent postoperative outcomes.

Special Surgical Considerations

The elderly account for the majority of cancer patients: according to data from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program for the 5-year period from 2000 to 2004 (inclusive), 56% of all newly diagnosed cancers and 70% of cancer deaths are found within the group of patients aged 65 years and older [see Figure 4].¹¹⁴ The increased incidence and preva-

Table 7 Mini-Mental State Examination for Cognitive Function¹⁰⁵

Maximum Score	Score	Item
5	()	<i>Orientation</i> 'What is the date?' Give 1 point each for year, season, date, day, month.
5	()	'Where are we?' Give 1 point each for state, county, town, building, floor, or room.
3	()	<i>Registration</i> Name three objects. Take 1 second to say each, then ask patient to name all three. Give 1 point for each correct answer. Repeat until patient learns all three (for later testing).
5	()	<i>Attention and Calculation</i> Ask patient to subtract serial sevens, starting at 100. Give 1 point for each correct answer. Stop after five answers. (Alternatively, ask patient to spell 'world' backward.)
3	()	<i>Recall</i> Ask patient to name the three objects mentioned previously. Give 1 point for each correct answer.
9	()	<i>Language</i> Point to a pencil and a watch and ask patient to name them. Give 1 point for each correct answer. Ask patient to repeat the following: 'No ifs, ands, or buts.' Give 1 point if successful. Give patient a three-stage command: 'Take a paper in your right hand, fold it in half, and put it on the floor.' Give 1 point for each correct action. Ask patient to read and obey the following: 'Close your eyes.' Give 1 point if patient closes eyes. Ask patient to write a sentence. Give 1 point if sentence has a subject and a verb and makes sense. Ask patient to copy a simple design. Give 1 point if drawing is correct.
30	()	Total Score*

*A score of 24 or more is considered normal.

Table 8 Geriatric Depression Scale (Mood Scale) (Short Form)¹⁷⁷

Patient Name: Date: Choose the best answer for how you have felt over the past week:	Give 1 point if answer is:
1. Are you basically satisfied with your life?	No
2. Have you dropped many of your activities and interests?	Yes
3. Do you feel that your life is empty?	Yes
4. Do you often get bored?	Yes
5. Are you in good spirits most of the time?	No
6. Are you afraid that something bad is going to happen to you?	Yes
7. Do you feel happy most of the time?	No
8. Do you often feel helpless?	Yes
9. Do you prefer to stay at home, rather than going out and doing new things?	Yes
10. Do you feel you have more problems with memory than most?	Yes
11. Do you think it is wonderful to be alive now?	No
12. Do you feel pretty worthless the way you are now?	Yes
13. Do you feel full of energy?	No
14. Do you feel that your situation is hopeless?	Yes
15. Do you think that most people are better off than you are?	Yes
Total:	—

For clinical purposes, a score > 5 points is suggestive of depression and warrants a follow-up interview. Scores > 10 almost always indicate depression.

lence of cancer in older patients, coupled with the increased projected longevity within the geriatric population, make cancer treatment in the elderly a common concern.

The cancer treatment plans employed in elderly patients differ from those employed in younger patients. One difference is that elderly patients may not receive surgical treatment for many potentially curable cancers. In a comprehensive SEER database analysis published in 2004, the rates of curative surgery for adenocarcinoma of the breast, esophagus, stomach, pancreas, colon, or rectum; non-small cell lung carcinoma (NSCLC); and sarcoma were compared across age groups.¹¹⁵ For all categories of local-stage cancers, oncologic resection rates declined steadily with increasing age. Whether this decline is a reflection of appropriate patient selection based on objective risk assessment or of undertreatment of elderly cancer patients is difficult to determine. Those elderly patients who do undergo oncologic resection can fare well. The Surgical Task Force report from the International Society for Geriatric Oncology (Société Internationale d'Oncologie Gériatrique; SIOG) reported in 2004 that for many neoplasms, surgical outcomes were much the same for older patients as for younger patients.¹¹⁶

Another difference is that adjuvant treatment measures, such as chemotherapy¹¹⁷ and radiation therapy,¹¹⁸ may be underused in older cancer patients. Yet another difference is that the elderly are substantially underrepresented in cancer treatment trials, especially in view of the much greater cancer burden in the geriatric population.^{119–122}

In what follows, we focus on selected topics germane to the treatment of elderly patients with some of the more commonly seen cancers, where surgical intervention is generally accepted to be part of the standard of care.

BREAST

The incidence of breast cancer is six times higher in older patients than in younger ones.¹²³ Many elderly breast cancer patients may be undertreated¹¹⁹: studies have shown that

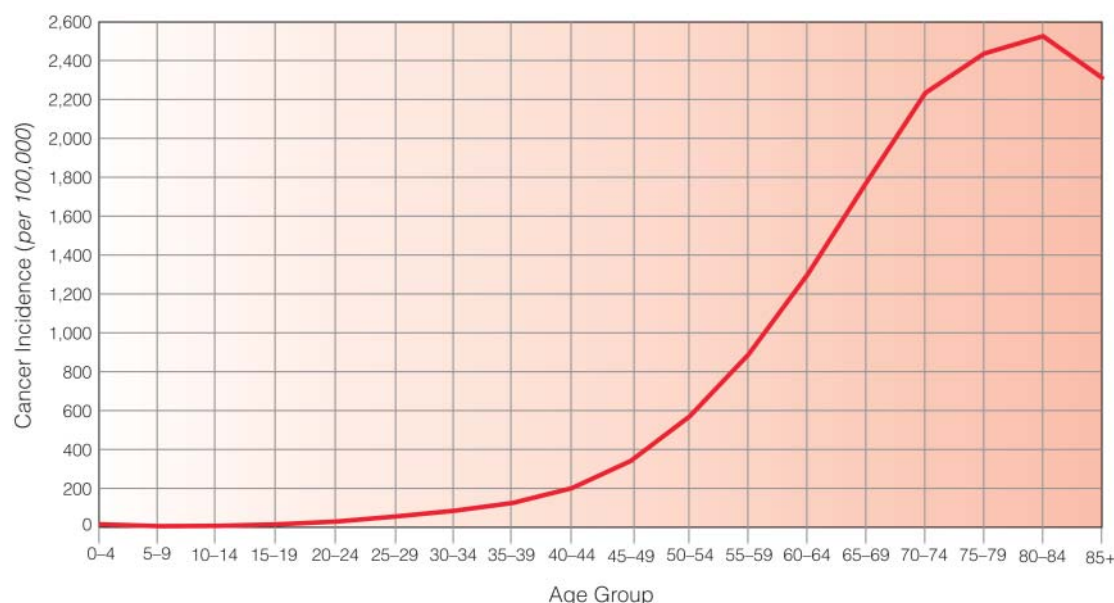


Figure 4 Depicted is cancer incidence for 1994–1998 by age group (all SEER sites combined, both sexes).¹¹⁴

such patients are less likely to undergo radiation treatment, chemotherapy, or axillary dissection.^{124–126} Even when comorbidity is adjusted for, patient age is predictive of prescribed treatment plans.¹²⁴ Choosing to proceed with adjuvant treatment in an elderly patient can be a difficult decision. Whereas older women are more likely than younger women to present with advanced-stage breast cancer,¹²⁷ their disease may be less aggressive than it would be in a nongeriatric population. There is evidence to suggest that the biologic behavior of breast tumors differs in the elderly. Older women with breast cancer are more likely to have estrogen receptor (ER)-positive tumors that are amenable to hormonal therapy.¹²⁸ In addition, they are more likely to have a lower rate of tumor cell proliferation, diploidy, normal *p53* expression, and reduced *HER-2/neu* expression.¹²⁹ The potential differences in tumor biology seen in older patients, the common comorbid conditions, and the typical functional impairments must be taken into consideration in planning treatment, along with the understanding that undertreatment is associated with higher recurrence rates and increased mortality.^{130,131}

Surgery remains a mainstay of breast cancer treatment [see 3:5 *Breast Procedures*]. Older patients tolerate breast-conserving therapy (BCT) and mastectomy as well as younger patients do. In elderly women with breast cancer, overall operative mortality is typically quite low: less than 1% for relatively fit patients.¹³² Generally, operative morbidity and mortality reflect the severity of any comorbid conditions present, rather than the patient's chronologic age.¹³³ Axillary lymph node dissection had been considered part of the standard of care in breast cancer surgery as a means of controlling nodal disease and providing accurate staging. Whereas it is clear that fewer elderly breast cancer patients are offered axillary dissection, it is not clear whether the morbidity associated with the procedure is indeed more prevalent among the elderly. Ultimately, this may be a moot point. With the increasingly widespread application of sentinel lymph node biopsy, the issue of whether axillary lymph node dissection

offers a real therapeutic benefit has come under scrutiny and remains controversial.¹³⁴

Postoperative radiation therapy is an important adjunctive measure for preventing local recurrence after BCT.^{135,136} The benefit of adding radiation therapy has been confirmed by studies that look selectively at older breast cancer patients.¹³⁷ In a 2004 trial involving older patients with early breast cancer, the recurrence rate was lower in those who were treated with BCT, tamoxifen, and radiation (0.6%) than in those who were patients treated with surgery and tamoxifen alone (7.7%).¹³⁸ Despite the benefits with regard to local control and survival, radiation therapy is often omitted in the elderly population.¹²⁴ A 2006 report addressing the omission of radiotherapy in older breast cancer patients found that the frequency of omission increased significantly with increasing age (7% in those aged 50 to 64, 9% in those aged 65 to 74, and 26% in those aged 75 and older).¹³⁹ Omission of radiotherapy was associated with reductions in local control, cancer-specific survival, and overall survival. The risks of omitting radiation treatment should be carefully considered in the light of the patient's overall life expectancy, the comorbid conditions present, and the toxicity of treatment. Although serious adverse effects are rare (incidence < 1%), they can be severe, including radiation pneumonitis, pericarditis, and possible rib fractures.

Hormonal treatment is commonly employed in the elderly breast cancer population. In particular, tamoxifen has proved beneficial in numerous studies.^{140,141} These findings are particularly germane to older patients, more than 80% of whom are likely to be ER positive and endocrine responsive. In approximately 1% of patients treated with tamoxifen, serious adverse effects may occur, including endometrial carcinoma and thromboembolism. The newer aromatase inhibitors (e.g., anastrozole, letrozole, and exemestane) may have better toxicity profiles than tamoxifen does and may confer a survival benefit. The American Society of Clinical Oncology (ASCO) recommends the aromatase inhibitors for postmenopausal

women with ER-positive breast cancers¹⁴²; however, the optimal timing and duration of treatment have not yet been established. The optimal approach to endocrine therapy in elderly patients remains to be determined.¹⁴³

The use of chemotherapy in elderly breast cancer patients is also an area under scrutiny.¹⁴⁴ According to the latest SEER registry data, a substantial proportion of elderly breast cancer patients have poor prognostic factors that warrant consideration of adjuvant chemotherapy. In a study involving more than 23,000 elderly (> 65 years old) women with breast cancer, 35% had positive lymph nodes, and as many as 24% had other poor prognostic markers, such as a large tumor or ER-negative status.¹²⁹ At present, little evidence is available concerning the performance of elderly patients on chemotherapy regimens, in part because of the underrepresentation of elderly participants in clinical trials. However, one analysis of SEER registries done by a group from the Memorial Sloan-Kettering Cancer Center did demonstrate a survival benefit in patients aged 66 years or older who had endocrine-unresponsive tumors that were treated with adjuvant chemotherapy.¹⁴⁵ Optimal chemotherapy regimens for elderly patients have yet to be established. Commonly used regimens include cyclophosphamide with methotrexate and fluorouracil (CMF) and an anthracycline (e.g., doxorubicin) with cyclophosphamide (AC). Anthracycline-containing regimens are known to have cardiotoxic side effects (including CHF) and must therefore be used cautiously in the elderly. At lower doses, however, AC therapy may prove to be less toxic and more effective in older breast cancer patients.^{146,147} Trials aimed at determining optimal treatment of breast cancer in older women are currently under way.

LUNG

Lung cancer is the leading cause of cancer-related death in Western nations.¹⁴⁸ More than 50% of persons diagnosed with lung cancer are older than 65 years. According to the latest SEER data, the median age of lung cancer patients is 73 years.¹⁴⁹

For patients with early NSCLC, surgery affords the best chance of a cure [see 4:14 *Pulmonary Resection*]. Lobectomy (i.e., removal of one of the five lobes of the lung, along with associated lymph nodes) is currently the surgical standard of care for these patients. Traditionally, advanced age has been considered a risk factor for postoperative death after thoracotomy. In multiple early single-institution studies, postoperative mortality for patients aged 70 years or older was as high as 14% after lobectomy and higher than 20% after pneumonectomy.¹⁵⁰ Subsequent improvements in perioperative care, anesthesia, and patient selection, however, have caused the reported postoperative mortality to drop below 5%.¹⁵¹ Because the morbidity and mortality of lung cancer surgery are directly correlated with the amount of tissue removed, considerable attention has been focused on examining the efficacy of lung-sparing procedures such as segmentectomy and wedge resection. These procedures are now being performed with increasing frequency in elderly lung cancer patients, with good long-term results.^{151,152} An extensive analysis of SEER data from 5,219 patients aged 65 to 74 years and 2,382 patients aged 75 years or older who underwent curative surgery for early NSCLC concluded that wedge resection and lobectomy had similar long-term survival benefits for patients older than 71 years.¹⁵³

The advent of minimally invasive techniques, such as video-assisted thoracoscopic surgery (VATS) [see 4:10 *Video-Assisted Thoracic Surgery*], has also made an impact on lung cancer treatment in the elderly. Several studies have shown VATS to be efficacious in the treatment of early NSCLC.^{152,154} One study found that whereas survival rates did not differ significantly between patients who underwent thoracotomy and those who underwent VATS, patients in the latter group experienced fewer postoperative complications, despite having more comorbid conditions.¹⁵⁵ VATS, being less invasive than thoracotomy, can allow patients with impaired cardiopulmonary reserve to tolerate surgery. However, patients with poor performance status who are unable to perform their ADL will have a high perioperative mortality even with minimally invasive surgery¹⁵⁶—a result that, once again, underscores the importance of appropriate patient selection.

COLORECTAL

Colorectal cancer is the second most common cancer in the United States, with over 150,000 new cases and 50,000 deaths estimated for 2007.¹⁵⁷ It is predominantly a disease of the elderly. Whether elderly colorectal cancer patients have a worse prognosis than younger patients is a subject of debate. A large cancer database study from the United Kingdom reported that outcomes grew progressively worse with increasing age in elderly patients who underwent colorectal cancer surgery.¹⁵⁸ However, these elderly patients also had higher ASA grades, more frequent emergency operations, and more frequent palliative procedures, all of which would portend worse outcomes for any age group. In contrast, other studies have been able to demonstrate good oncologic outcomes in selected elderly colorectal cancer patients after surgery,^{159,160} thereby emphasizing the importance of using other criteria besides chronologic age alone in the process of patient selection.

The mainstay of curative treatment for colorectal cancer is surgery: segmental resection for colon cancer and additional total mesorectal excision (TME) for rectal cancer [see 5:34 *Segmental Colon Resection* and 5:35 *Procedures for Rectal Cancer*]. In selected elderly patients, functional outcomes after low anterior resection may be as good as those in younger patients, with similar subjective findings of satisfaction with bowel function and similar objective findings from manometry data.¹⁶¹

Minimally invasive procedures may have an emerging role to play in surgical management of colorectal cancer in the elderly. A number of series have shown laparoscopic colectomy to be safe and efficacious for treatment of colon cancer.^{162,163} It yields complication rates and survival outcomes comparable to those of open colectomy, and it results in faster recovery and earlier return to daily activity.¹⁶² Such advantages may be especially important with elderly patients, for whom postoperative alterations in the ability to carry out ADL can precipitate the transition from independence to dependent living situations.

Since randomized trials established that fluorouracil-based adjuvant chemotherapy after resection of stage III colon cancers reduces mortality by as much as 30%, adjuvant chemotherapy has become the standard of care for stage III colon cancer.¹⁶⁴ The extent to which adjuvant therapy is

employed in the elderly population has been studied by some investigators. One large retrospective cohort study using a SEER/Medicare linked database found that the chemotherapy treatment rate declined markedly with chronologic age.¹¹⁷ The cause of this apparent reluctance to use chemotherapy in the elderly population is probably multifactorial. One factor is the underrepresentation of the elderly in clinical trials, which hinders the extrapolation of study results to treatment recommendations for these patients. Another is the higher prevalence of comorbid conditions in older persons; these conditions are competing causes of mortality. Impaired functional status may also impair the ability of elderly patients to tolerate the toxic effects associated with current

chemotherapy protocols. Some studies have suggested that toxicity rates are higher in elderly patients undergoing adjuvant chemotherapy than in younger patients,¹⁶⁵⁻¹⁶⁷ but the data are by no means unanimous on this point. There is, in fact, a growing body of evidence supporting the idea that elderly patients are capable of tolerating adjuvant chemotherapy and deriving a demonstrable survival benefit comparable to that observed in younger patients.¹⁶⁸⁻¹⁷⁰ Increasingly, the data suggest that elderly patients who are fit enough to tolerate chemotherapy will reap its benefits. Judicious use of chemotherapy in the elderly surgical population should therefore be considered and should not be rejected solely on the basis of the advanced age of the patients.

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2 THE PEDIATRIC SURGICAL PATIENT

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Surgical care of neonates, infants, and children differs in many respects from that of adults.¹ Accordingly, it is essential that surgeons caring for preadult patients be capable of recognizing and managing certain clinical problems that occur frequently in this population. To this end, we begin this chapter by discussing several basic considerations related to pediatric physiology, which is markedly different from adult physiology. With this general discussion as a background, we then provide an overview of specific surgical problems commonly encountered in pediatric patients.

Physiologic Considerations

HOMEOSTASIS

Fluids and Electrolytes

Management of fluids and electrolytes in neonates and infants requires a thorough understanding of the changes in body fluid compartments that occur during development [see Figure 1].²⁻⁷ At birth, total body water accounts for roughly 75% of total body weight (TBW), but this percentage

decreases rapidly in the first few days, falling slowly toward 60% over the first year. Similarly, extracellular fluid volume accounts for 45% of TBW at birth but only 20% by the end of the first year. Newborns have lower glomerular filtration rates and reduced renal concentrating ability^{8,9}; consequently, they tolerate dehydration poorly and cannot excrete a water load as effectively as older persons with mature kidneys can. For this reason, adequate fluid management is especially challenging in these patients.

Measurement of urine output is a useful guide to fluid management, provided that accurate urine collections can be obtained. In critically ill infants and children, a urinary catheter should be inserted to ensure accurate urine collections. Catheterization of male neonates and infants carries a significant risk of trauma to the small urethra; in these patients, the use of properly secured collection bags may allow accurate measurement of urine output without the need for catheter insertion. An appropriate urine output is 1 to 2 mL/kg/hr.

Insensible water loss results from continuous evaporative loss of water through the respiratory tract and the skin.¹⁰ In premature infants, a large proportion of insensible water loss occurs transcutaneously. Insensible water loss from the skin can be minimized by using incubators in the neonatal intensive care unit (NICU) and extremity coverings in the operating room (OR). Insensible water loss from the lungs can be decreased by humidifying the inspired gases.

In general, the maintenance fluid requirement of a neonate is considered to be 70 mL/kg/24 hr initially; this figure rises to 100 mL/kg/24 hr after a few days of life. Neonates with surgical problems may require dramatically increased amounts of fluid.

The sodium requirement of a full-term infant is, on average, 2 mEq/kg/24 hr. Conditions such as intestinal obstruction [see Common Surgical Problems in Newborns, Intestinal Obstruction, *below*] and peritonitis increase sodium loss and therefore increase sodium requirements. Although full-term infants can retain sodium as well as adults do in the face of a sodium deficit, they are unable to excrete excess sodium as effectively. As a result, excessive infusion of sodium can rapidly result in hyponatremia.

The generally accepted potassium requirement is 2 mEq/kg/24 hr after the first 2 to 3 days of life. However, the need for potassium replacement can be significant in the first few days of life as well, especially after a major surgical intervention. Thus, potassium should be administered in the

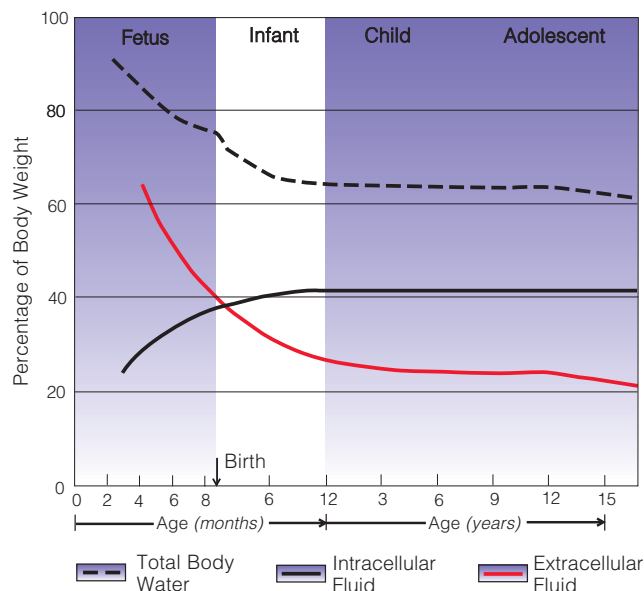


Figure 1 Total body water and extracellular fluid decrease between fetal life and adulthood, and intracellular fluid increases.

first 1 or 2 days of life after an operation once urine output has been established.

In view of the various fluid and electrolyte requirements of neonates and infants, the initial fluid used in surgical management of these patients, both preoperatively and postoperatively, should be 5 or 10% dextrose in 0.2% saline at a dosage of 100 to 150 mL/kg/24 hr [see Table 1].

Acid-Base Status

Metabolic alkalosis caused by loss of electrolytes (specifically, chloride) may occur with prolonged gastric suction or vomiting; usually, it is easily corrected by replacing the lost electrolytes (e.g., by administering potassium chloride). Metabolic acidosis, on the other hand, is usually the result of poor tissue perfusion and lactic acidosis; it is best corrected by treating the underlying cause of the poor perfusion and by temporarily administering buffers (e.g., sodium bicarbonate). It should be noted that standard sodium bicarbonate solutions are extremely hypertonic and should be diluted before administration, especially when they are being given to neonates.

Temperature

In neonates, strict regulation of the environmental temperature is critical for preventing hypothermia. Compared with older children and adults, infants have a higher ratio of body surface area to weight, less subcutaneous fat (and therefore poorer thermal insulation), and less lean body mass (which is required for generating and retaining heat).

Maintaining the body temperature of neonates and young infants is critical both in the NICU and in the OR. In the NICU, the infant may be placed in an incubator (which is designed to reduce airflow across the skin and provide a tightly regulated, thermally neutral environment) or on a bed with an overhead radiant heater. In the OR, the ambient room temperature may be raised, overhead radiant warmers may be used, circulatory warm air blankets may be applied, and the head and extremities may be wrapped in plastic. Ventilatory gases are warmed and humidified, and warm intravenous and irrigation fluids are used.

NUTRITION

Whereas the nutritional requirements of children and teenagers do not differ significantly from those of adults [see 8:22 *Nutritional Support*], the requirements of infants do. Not only must the metabolic demands that a major illness or operation imposes on all patients be taken into account, but special

consideration must also be given to the smaller body size of infants, their rapid growth, their highly variable fluid requirements, and the immaturity of most organ systems. These characteristics, coupled with the low caloric reserves present if the infant is premature or sick, make adequate nutritional intake particularly important. Consequently, infants whose nutritional needs are not met as the result of a functional or organic disorder of the gastrointestinal (GI) tract can rapidly acquire protein-calorie malnutrition. Even a relatively short period of inadequate nutrition can lead to impaired host resistance, an increased risk of infection, and poor wound healing, all of which contribute appreciably to morbidity and mortality in infants and children with surgical disease.

Nutritional Requirements

Infants have higher weight-adjusted caloric requirements than older children and adults do [see Table 2], and these requirements are further increased by periods of active growth and extreme physical activity.^{11,12} Major illness or surgical trauma may raise caloric requirements even further. However, measured energy expenditures do not appear to be elevated in neonatal surgical patients and critically ill premature infants.^{13–15} In general, calories should be provided in the proportions found in a well-balanced diet: 50% carbohydrate, 35% fat, and 15% protein.

The protein needs of infants are based on the combined requirements for maintenance and growth. Most of the increase in body protein occurs during the first year of life, which explains why protein requirements are highest in infancy and decrease with age. Of the 20 amino acids from which proteins are synthesized, eight are essential in adults, but it is believed that in addition, histidine is essential in infants and cysteine and tyrosine in premature infants.

In general, infants require more vitamins and minerals than adults do. Increased amounts of calcium and phosphorus are particularly important because of the rapid growth rate of the infant's skeleton.

Nutritional Assessment

In many cases, a sick infant's history and overall appearance provide sufficient grounds for initiating nutritional support. For example, a preterm infant with respiratory distress who is small for his or her gestational age clearly requires parenteral nutrition, as does a newborn with gastroschisis. Physical variables that should be considered in nutritional

Table 1 Daily Fluid Requirements for Neonates and Infants	
Weight	Fluid Requirements*
Premature < 1.5 kg	150 mL/kg
Neonates and infants 1.5–10 kg	100 mL/kg
Infants and children 10–20 kg	1,000 mL + 50 mL/kg over 10 kg
Children > 20 kg	1,500 mL + 20 mL/kg over 20 kg

*Maintenance Na⁺ and K⁺ requirements range from 2 to 4 mEq/kg; solution can generally be given as 0.2% saline, with 5% or 10% dextrose and K⁺ added.

Table 2 Daily Kilocalorie and Protein Requirements for Infants and Children		
Age (yr)	Kilocalorie Requirements* (kcal/kg)	Protein Requirements (g/kg)
0–1	90–120	2.0–3.5
1–7	75–90	2.0–2.5
7–12	60–75	2.0
12–18	30–60	1.5
18+	25–30	1.0

*These numbers represent volume administered when 1 kcal/mL solutions are used. Growth can be maintained with 10 to 20% fewer calories if parenteral nutrition is employed.

assessment include weight, length, head circumference, chest circumference, and triceps skinfold thickness. No blood test reflects changes in the patient's nutritional status with ideal accuracy, but serum albumin, prealbumin, and transferrin levels are frequently used as markers.

Enteral Nutrition

The type of nutritional support to be employed depends on the disease affecting the patient and on the patient's overall health status. From a physiologic standpoint, enteral nutrition is preferable and is the first choice for patients whose GI tract is functioning adequately.¹⁶ For infants younger than 1 year, breast milk or a standard infant formula is delivered orally or via a tube.¹⁷ For older children who are unable or unwilling to eat, a liquid diet consisting of either blenderized food or liquid formula may be employed. A number of nutritionally complete liquid formulas are commercially available. Specialized formulas are available for use in patients who have lactose intolerance or protein sensitivity or who are experiencing renal or hepatic failure.

The use of predigested or elemental diets may allow patients with injured intestine or inadequate intestinal length to absorb enteral feedings. In children who cannot manage oral feedings, nasogastric and nasojejunal tubes are used. If the child's condition necessitates long-term tube feeding, a gastrostomy may be necessary.

Postoperative Feeding

Infants have more difficulty in feeding during the early months of life. This is especially true of premature infants, in whom the complex physiology of sucking and swallowing is not yet fully developed. In addition, the work of feeding accounts for most of an infant's caloric expenditure in the early months, and a stressed infant tires easily. For this reason, gavage or gastrostomy tube feedings are often employed for the early stages of postoperative feeding in infants. Feeding is begun after the resolution of postoperative ileus has been demonstrated by the passage of meconium or stool. Further evidence that the bowel is beginning to function is the disappearance of the bilious green color of the gastric aspirate and the decrease in the volume of the aspirate from the nasogastric or gastrostomy tube. Initially, small volumes of rehydration fluid are given orally or via a gastrostomy tube. If these are tolerated, the feedings are increased incrementally until the nutritional goals for the patient have been reached.

Infants tolerate increases in volume more readily than increases in osmolality. Accordingly, it is often best to start with diluted formulas (three-quarter-strength, half-strength, or quarter-strength), then, as nutritional requirements grow, increase the volume first and subsequently increase the concentration as necessary to supply the required amount of calories.

Elemental or chemically defined diets require a minimum of digestive work and are free of residual bulk. They may be accepted by infants if given orally; however, they are unpalatable and thus are usually given by tube. Because of the high osmolality of these diets, constant infusion with a pump may be necessary to prevent the development of dumping syndrome. The ease of GI absorption and the minimal residue make elemental diets useful as an intermediate step between

parenteral nutrition and regular feedings. In infants, whenever possible, oral feedings or oral stimulation should accompany tube feedings.

Parenteral Nutrition

The concept of total parenteral nutrition (TPN) had been entertained for decades before its initial development, but it was not until the 1960s that the major breakthrough occurred, when Dudrick and colleagues successfully administered a hypertonic glucose solution into a central vein.^{18,19} In the early years after the group's initial success, this approach to TPN began to be widely used in newborns with GI anomalies.^{20,21} Since then, the technique has been applied to the care of patients of all age groups, with dramatic results [see 8:22 *Nutritional Support*]. Less concentrated solutions are available for administration into peripheral veins.

Generally, TPN is reserved for infants and children who are threatened by catabolic or nutritional deficits because feeding via the GI tract is hazardous, inadequate, or impossible. Conditions that may necessitate TPN include intestinal obstruction from congenital disorders, prolonged postoperative ileus, peritonitis, intestinal fistulas, chronic nonspecific diarrhea, necrotizing enterocolitis, short bowel syndrome, extensive burns, and abdominal neoplasms treated with surgery, chemotherapy, and radiation. Besides being used for nutritional repletion of malnourished children, TPN may also be employed prophylactically when prolonged starvation is expected, as in cases of gastroschisis. In infants, TPN is indicated if nutrition is inadequate for longer than 3 days; however, in older children and adults, a longer period of inadequate nutrition may be tolerated, depending on patients' nutritional status before operation or at the onset of illness. The benefits of improved nutrition in terms of reducing mortality and morbidity must be weighed against the risks of serious complications, especially sepsis. TPN should not be employed when enteral nutrition is feasible. Every effort should be made to use the enteral route for feeding, including the use of transpyloric feeding tubes.

Infants receiving TPN must be carefully monitored. Essential clinical measurements include weight, length, and intake and output volumes. Blood tests must be employed judiciously and sparingly in infants and children because of their small total blood volume. At the start of therapy and once a week thereafter, a complete blood count should be done, blood urea nitrogen should be measured, and serum levels of electrolytes, glucose, calcium, phosphorus, magnesium, and albumin should be assessed. Serum levels of liver enzymes, bilirubin, and creatinine should be measured at the start of therapy and every week thereafter.

On average, neonates gain 15 to 25 g/day with TPN, and older children gain 0.5% of TBW/day. Greater weight gains may signal excessive administration of fluids or intake of calories.

The main complications of parenteral nutrition include catheter-based problems (e.g., sepsis, malfunction, and venous thrombosis), electrolyte abnormalities, and (especially in infants receiving long-term TPN) hepatic cholestasis, which ultimately can result in cirrhosis and hepatic failure. Strategies to minimize liver damage include early and aggressive treatment of infection, avoidance of excessive caloric

intake, cycling the TPN, limitation of protein and fat intake, and supplemental trophic enteral nutrition.

HEMODYNAMIC IMBALANCE AND SHOCK

For proper assessment of shock in infants and children, it is necessary to be familiar with the normal vital signs in these age groups [see Table 3]. The two types of shock most frequently seen are hypovolemic shock and septic shock; in infants and children, septic shock is the most common form.²² The response of newborns and infants to hypovolemic or septic shock is significantly different from the response of older children and adults. For example, neonates affected by profound shock tend to become bradycardic, whereas adults are more likely to become tachycardic. Moreover, neonates, especially premature neonates, normally have a low blood pressure; consequently, shock often does not evoke any further significant reduction of blood pressure. The hypovolemia caused by the shock results in decreased venous return, which lowers cardiac output; the reduced cardiac output leads to poor tissue perfusion and the development of lactic acidosis.

Gram-negative bacteria are the organisms most often responsible for septic shock. Peritonitis resulting from intestinal perforation is a common cause of septic shock in neonates and infants; other causes are urinary tract infections, respiratory tract infections, and contaminated intravascular catheters. The pathophysiology of septic shock differs substantially from that of hypovolemic shock; however, in both states, stasis and pooling of blood in the capillary bed lead to reduction of the circulating blood volume.²³

Treatment

The mainstay of therapy for hypovolemic shock is administration of fluid and blood. In neonates with shock, the hematocrit should be maintained at 45% to ensure adequate oxygen delivery. In many infants, hypovolemic shock is caused not by hemorrhage but by dehydration (e.g., from severe gastroenteritis). This dehydration is usually hypertonic because of the significant loss of hypotonic fluid. As a rule, neonates and infants in hypovolemic shock lose much more water than electrolytes, and as a result, serum sodium levels may exceed 150 mEq/L. Emergency treatment involves infusion of isotonic solutions of sodium chloride with careful monitoring of serum electrolyte concentrations.

Because septic shock, like hypovolemic shock, is characterized by reduced circulating blood volume, initial therapy involves infusion of large volumes of colloid solutions. Most of the experimental and clinical data suggest that colloid solutions are preferable to crystalloid solutions in this setting,

both for children and for adults. In addition, broad-spectrum antibiotics should always be administered.

If fluid infusion has been maximally effective (as evidenced by a normal to elevated central venous pressure) but hypotension persists, pharmacologic agents must be given to improve myocardial contractility. The most commonly used agents are the alpha and beta agonists dopamine and dobutamine, which primarily have inotropic and mild vasodilatory effects at lower doses. Infants and children in shock require continuous monitoring and close clinical observation and should therefore be managed in the intensive care unit (ICU).

Common Surgical Problems of Newborns

Neonatal surgical problems often present as emergencies and necessitate rapid stabilization and transfer of the patient to a pediatric surgical center. Proper initial management is crucial and may have a pronounced effect on overall outcome. The organ systems most commonly affected are the respiratory tract and the GI tract.

EMERGENCY SURGICAL PROBLEMS

In many communities, the general surgeon is frequently called on to assist in the diagnosis and initial care of a neonate with an apparent surgical problem. After stabilization measures have been carried out and preliminary tests have been performed to establish a diagnosis, the baby may be transported to a pediatric center that is specially equipped and staffed to manage the specific surgical problem present.

The steps in the stabilization of a critically ill neonate before transport are similar to the ABCs of initial care in an adult (airway, breathing, circulation). By the time the surgeon is consulted, the neonatologist or pediatrician may have accomplished initial stabilization and begun to prepare the baby for transfer. The surgeon's immediate responsibility may be to establish vascular access. In some cases, a peripheral venous cannula may be appropriate; more often, a central catheter is inserted via an umbilical vein or artery. In babies with omphalocele or gastroschisis, the intravenous (IV) line ideally should be placed in the upper extremities or the neck. Appropriate fluids should be infused to prevent dehydration and to correct any fluid or electrolyte deficits. When required, a nasogastric or esophageal pouch suction tube should be placed and decompression initiated. This maneuver is extremely important if transport by air is considered: trapped gases change in volume with alterations in barometric pressure, and such changes may have particularly deleterious

Table 3 Normal Values for Vital Signs in Children¹³⁰

Age (yr)	Pulse Rate (beats/min)	Systolic BP (mm Hg)	Respirations (breaths/min)	Urinary Output (mL/kg/hr)
0–1	< 160	> 60	< 60	2.0
1–3	< 150	> 70	< 40	1.5
3–5	< 140	> 75	< 35	1.0
6–12	< 120	> 80	< 30	1.0
> 12	< 100	> 90	< 30	0.5

BP = blood pressure.

effects on infants who have intestinal gas, pneumothorax, or pneumomediastinum.

Vitamin K should be given in the form of phytonadione, 1 mg (0.5 mg for babies who weigh less than 1,500 g). Appropriate antibiotics should also be administered. Finally, the infant should be wrapped and placed in an incubator or a radiant warmer to stabilize body temperature and maintain it at normal levels.

The use of sophisticated transport teams with appropriate equipment and supplies is the safest method of moving these babies between hospitals. Early stabilization and close communication between the referring physician, the accepting physician, and the transport team are essential for minimizing the potential risks and morbidity associated with patient transfer.

The following seven emergency surgical problems are commonly encountered in neonates. Each involves special considerations in the preparation of the patient for interhospital transfer.

1. *Congenital diaphragmatic hernia (CDH)*. Insert a nasogastric or orogastric tube. Ventilation by face mask is contraindicated; if ventilation is required, intubate.
2. *Esophageal atresia*. Insert a tube to aspirate secretions from the pouch (use a Replogle tube, if available). If possible, avoid mechanical ventilation; if intubation is required, use high-frequency, low-pressure ventilation to prevent distention and possible perforation of the stomach.
3. *Congenital lobar emphysema*. Support normal oxygenation. Minimize mean airway pressure.
4. *Intestinal obstruction*. Use nasogastric or orogastric suction. Confirm placement and function of IV lines.
5. *Omphalocele or gastroschisis*. Use nasogastric or orogastric suction. Cover the sac with nonadherent gauze and take care not to rupture the membrane (if present); cover the intestine with saline-soaked gauze and a see-through bowel bag. Place the IV line in the upper extremity or the neck, if possible. Maintain hydration by increasing fluid administration to replace fluid lost from the exposed bowel. Support the bowel with dressings. Maintain body temperature.
6. *Exstrophy of the bladder*. Cover the exposed bladder with a nonadherent dressing.
7. *Meningomyelocele*. Cover the sac with a nonadherent dressing.

RESPIRATORY PROBLEMS

Cystic Disease of the Lung

Cystic lung disease, especially congenital cystic adenomatoid malformation (CCAM) of the left lower lobe, can mimic diaphragmatic hernia both clinically and radiographically [see Figure 2a].^{24,25} Unlike a newborn with diaphragmatic hernia, however, a newborn with CCAM will have an abdomen with the normal degree of protuberance. If an infant with CCAM experiences marked respiratory distress that necessitates intubation and mechanical ventilation, it is better to perform an emergency lobectomy than to subject the baby to a period of mechanical ventilation, with its attendant risks (i.e., barotrauma and oxygen toxicity). If the lesion is asymptomatic, it can be resected later in infancy to prevent infectious complications and possible (albeit rare) transformation into a malignancy.

Diaphragmatic Hernia

Infants with CDH may be quite ill at birth, often suffering from acute respiratory distress and hemodynamic instability. Because the intestines are located in the chest, an infant with CDH appears to have a scaphoid abdomen [see Figure 2b]. The entire stomach may be in the chest, and as a result, it may be difficult to pass a nasogastric tube into the stomach. A plain x-ray usually establishes the diagnosis.

CDH is an embryopathy that results from abnormal development of the diaphragm and the lungs. The defect in the diaphragm allows herniation of abdominal contents. On the affected side, as well as on the contralateral side, the lung shows hypoplasia, which varies in severity. The small vessels (arterioles) are excessively muscularized and can easily constrict.²⁶ The primary pathophysiologic consequence of CDH is not the presence of the hernia but, rather, severe pulmonary hypertension.²⁷ Accordingly, initial treatment is aimed at preventing or, if prevention is not possible, mitigating pulmonary hypertension and its sequelae.

Babies with CDH require immediate resuscitation, correction of acidosis, and, in most cases, endotracheal intubation. Placement of an orogastric tube can help decompress the GI tract. Once the baby is relatively stable, surgical intervention should be delayed to allow time for the pulmonary hypertension to decrease or disappear. There is evidence to suggest that gentle ventilation with permissive hypercapnia may decrease secondary barotrauma and long-term morbidity.²⁸ If the baby cannot be stabilized with conventional, jet, high-frequency, or oscillation ventilation and inhaled nitrous oxide,²⁹ extracorporeal membrane oxygenation (ECMO) may be indicated; the hernia should be addressed after the ECMO run is completed.^{30–32} During the procedure, the intestines are reduced into the abdominal cavity, and the diaphragmatic defect is repaired, either in the OR or in the NICU.³³ However, the operative procedure usually does not significantly alter the underlying pathophysiologic condition. In many cases, the newborn's condition improves at first after the operation but then begins to deteriorate. This response is seen less frequently with delayed surgical repair. If conventional treatment fails to control the pulmonary hypertension, ECMO may be instituted postoperatively. The precise impact of ECMO on overall outcome for CDH is still a matter of debate, although most pediatric surgeons agree that this technique has a role as a lifesaving measure if all other interventions fail.^{34–36}

Lobar Emphysema

The term *lobar emphysema* refers to overexpansion of a segment of lung, which can compromise ventilation in a newborn if significant compression of a healthy lung or a mediastinal shift occurs [see Figure 2c].³⁷ If the patient is exhibiting symptoms, urgent resection is usually required, although emergency bronchoscopic decompression has also been employed in this setting.³⁸ If the patient shows no significant symptoms, follow-up directed toward the affected areas of the lung is appropriate; occasionally, the condition resolves spontaneously.

Pulmonary Sequestration

The term *pulmonary sequestration* denotes a condition in which lung tissue is supplied with blood by the systemic circulation. Often this condition is diagnosed prenatally by

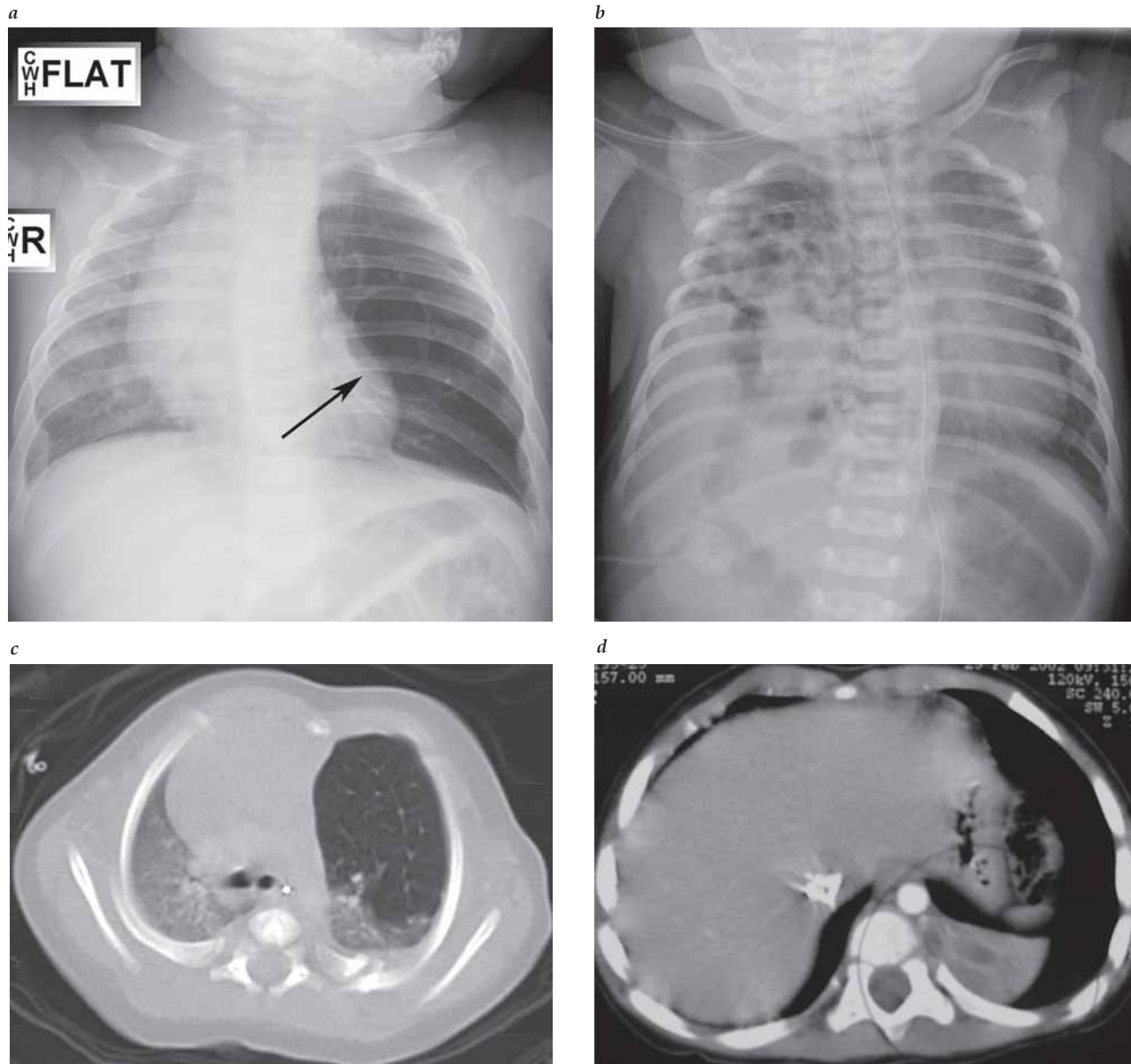


Figure 2 Shown are common neonatal chest abnormalities: (a) congenital cystic adenomatoid malformation with a large cyst in the left lung (arrow) and mediastinal shift; (b) congenital diaphragmatic hernia on the right side, with the liver and intestines within the chest cavity; (c) hyperinflated left lung with mediastinal shift caused by lobar emphysema; and (d) pulmonary sequestration with consolidation caused by pneumonia.

means of fetal ultrasonography.³⁹ Patients with pulmonary sequestration are often asymptomatic at birth, but if respiratory distress develops, urgent surgical intervention is required.⁴⁰ If the lesions remain asymptomatic, removal later in life is recommended so that they do not become a nidus for infection [see Figure 2d].

INTESTINAL OBSTRUCTION

Not uncommonly, surgeons are asked to evaluate newborns for possible obstruction of the GI tract. These patients usually present with choking or vomiting. The list of possible causative conditions is fairly extensive, and most of these conditions must ultimately be managed by a pediatric surgeon. Nevertheless, it may be helpful in the initial stages to employ

an algorithmic approach, which often serves to narrow the range of possible causes [see Figure 3].⁴¹

The color of the emesis helps establish the level of the obstruction. If the emesis is nonbilious, the obstruction is proximal to the ampulla of Vater. If an orogastric tube cannot be placed, the diagnosis is esophageal atresia, which can be confirmed by a chest x-ray that demonstrates a curled-up tube in the upper esophageal pouch. If the x-ray shows air below the diaphragm, the diagnosis is a distal tracheoesophageal fistula. If there is no mechanical obstruction of the esophagus, the diagnosis may simply be gastroesophageal reflux (GER). Other surgical causes of nonbilious emesis are preampullary duodenal atresia or web, neonatal pyloric stenosis (uncommon), and pyloric atresia (extremely rare).

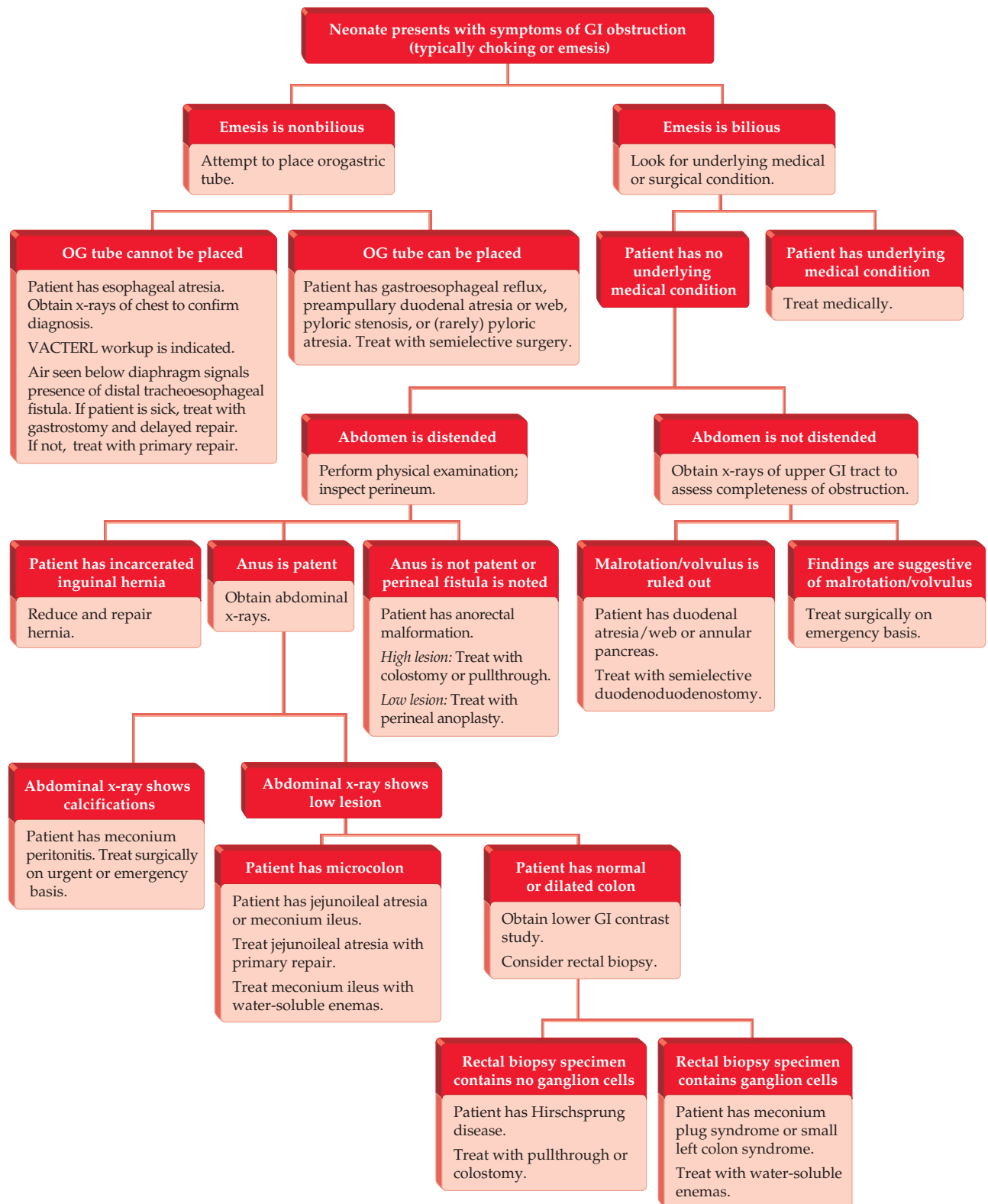


Figure 3 Algorithm illustrates approach to management of neonatal gastrointestinal (GI) obstruction.⁴¹ OG = orogastric; VACTERL refers to a nonrandom association of birth defects: vertebral anomalies, anal atresia, cardiac defect, tracheoesophageal fistula, renal abnormalities, and limb abnormalities.

Bilious emesis in a newborn is a potentially more serious problem. Except for medical ileus, the main causes are all related to underlying surgical problems. If the baby's abdomen is not distended, he or she may have a proximal obstruction. If an abdominal x-ray series shows a double-bubble sign without distal air, duodenal atresia is likely. If distal air is seen, the diagnosis is either a duodenal web or malrotation with possible volvulus. Malrotation of the bowel is a true surgical emergency, which must be diagnosed quickly by means of an upper GI study. In a newborn with midgut volvulus, prompt exploration is required to prevent extensive necrosis of the midgut.

If the abdomen is distended, the obstruction is more distal. Physical examination is warranted to rule out an incarcerated inguinal hernia. Inspection of the perineum is necessary to look for possible anorectal malformation. Stippled calcifications on an abdominal film are pathognomonic of meconium peritonitis (in utero bowel perforation), which usually necessitates surgical exploration. If the anus is patent, a contrast enema study helps establish a diagnosis. A microcolon represents an unused lower GI tract, which may be seen with jejunoileal atresia or meconium ileus. Meconium ileus, often associated with cystic fibrosis, is usually characterized by the presence of large amounts of meconium in the terminal ileum and can often be treated successfully by administering water-soluble contrast enemas. Other meconium-related functional obstructions occur without microcolon, such as meconium plug syndrome and small left colon syndrome, both of which usually respond to treatment with enemas. If the lower GI study shows a normal or slightly dilated colon with a narrowed or spastic-appearing rectosigmoid, the likely diagnosis is Hirschsprung disease, which can be confirmed by suction biopsy of the rectum.

ABDOMINAL WALL DEFECTS

The overall incidence of neonatal abdominal wall defects is approximately one in every 2,000 births; however, the incidence of gastroschisis appears to be rising slowly.⁴²⁻⁴⁴ Omphalocele represents an arrest in development, which may explain the increased frequency of chromosomal abnormalities and other structural birth defects in children with this condition.⁴⁵ The exact cause of gastroschisis is unclear, but it does not represent a normal stage of development; it appears to be more common with younger mothers, and environmental factors seem to play a role.^{43,46} The extra-abdominal intestine is prone to vascular compromise, which explains the higher incidence of bowel atresia in these patients.⁴⁷

Although omphalocele is associated with a higher overall mortality than gastroschisis is, the latter is more challenging to manage in the immediate postnatal period. The exposure of bowel results in greater insensible loss of fluid and heat. Kinking of the intestinal blood supply may lead to venous congestion and ischemia. It is crucial to place children with gastroschisis in a warm environment and to protect the bowel (which is easily accomplished with the help of a plastic bowel bag). Intravenous access should be established immediately, and resuscitation should be initiated, guided by the infant's heart rate. Transfer to a pediatric surgical center is mandatory. The surgical options are (1) primary repair of the defect, if the abdominal cavity accommodates the exposed organs

easily, and (2) gradual reduction of the intestines by means of a silo technique.⁴⁸

Emergency surgical intervention is rarely required for management of omphalocele. Such defects may be either closed primarily or repaired with any of several staged approaches, depending on their size. Giant omphaloceles are best treated observantly, with the overlying membrane used as a temporary silo and definitive repair delayed until a reasonable intra-abdominal domain has developed.

CIRCUMCISION

Circumcision remains one of the most commonly performed procedures in male newborns. Approximately 1.2 million circumcisions are performed in the United States each year, at a total cost of at least \$150 million.⁴⁹ There continues to be a great deal of controversy regarding the medical benefits and risks of this procedure. Some authors argue that urinary tract infections, sexually transmitted diseases, and genital cancer occur less frequently in circumcised males; however, others dispute these findings.⁵⁰⁻⁵² Circumcision can be performed either in an outpatient setting or in the nursery. The use of local anesthesia is recommended.⁴⁹ Complications are rare and usually minor, but mutilating injuries to the penis have been reported.^{53,54}

Common Surgical Problems in Infants and Children

PYLORIC STENOSIS

Hypertrophic pyloric stenosis affects between two and five of every 1,000 children; it is more common in white boys.⁵⁵ Patients typically present with progressive, projectile, nonbilious emesis 2 to 6 weeks after birth. They may show signs of severe dehydration with a hypochloremic, hypokalemic metabolic alkalosis (although the literature suggests that the incidence of this finding may be decreasing).⁵⁶ Medical approaches to managing this problem have been described,^{57,58} but surgical correction after resuscitation is the treatment of choice. The classic open pyloromyotomy developed by Fredet-Ramstedt is still performed, although advances in minimally invasive techniques have made it possible to perform laparoscopic pyloromyotomy with safety and efficacy.^{59,60}

GASTROESOPHAGEAL REFLUX

For appropriate treatment of GER in infants, it is important to distinguish between uncomplicated physiologic GER and symptomatic GER.⁶¹ Symptoms that necessitate treatment include poor weight gain, esophagitis, apnea, apparent life-threatening events, and pulmonary complications. Upper GI contrast studies and 24-hour continuous pH monitoring are the gold standards for assessment. Endoscopy and esophageal biopsy may be useful for diagnosis and the evaluation of treatment. If GER does not resolve with simple feeding and positioning adjustments, acid suppressants, prokinetic therapy, or surface agents may prove effective. If GER is associated with anatomic abnormalities (e.g., hiatal hernia), apparent life-threatening events, or symptoms that persist despite optimal medical therapy, surgical intervention is usually indicated. In infants and younger children who require a feeding gastrotomy, a protective fundoplication may be necessary if severe reflux is demonstrated on the upper GI study.

In the United States, the procedure most commonly performed to treat GER is a 360° Nissen fundoplication,⁶² although partial posterior (Toupet) fundoplication appears to yield comparable results.^{63,64} Both procedures are usually performed laparoscopically. Initial success rates with surgical treatment are high, but long-term complications (especially recurrent reflux) are frequent, resulting in redo rates ranging from 7 to 26%.⁶⁵

NECK AND SOFT TISSUE MASSES

A neck mass [see 2:3 Neck Mass] is a common reason for a child to be seen by a surgeon. Even though the vast majority of these masses are benign, they often cause significant worries for parents. A detailed history and a thorough physical examination are crucial for narrowing down the otherwise extensive differential diagnosis [see Table 4].

The masses that are most commonly encountered in infants and children are enlarged lymph nodes caused by reactive postinfectious hyperplasia. Such masses feel soft, are often slightly tender on palpation, are mobile, and tend to shrink over time. A higher degree of concern is appropriate with neck masses that are located supraclavicularly, grow rapidly, develop at multiple sites, are fixed to surrounding tissues, or feel hard. Swift diagnosis of the underlying process is crucial in this situation. Fine-needle aspiration biopsy may render an initial diagnosis,^{66,67} but most treatment protocols require more tissue, which can be obtained through open surgical biopsy. Before the procedure, a chest x-ray should be obtained to determine whether the mass involves the mediastinum.

A mass in the anterior midline may be a remnant of the thyroglossal duct. Such masses should be excised at diagnosis to prevent any subsequent infectious complications. To minimize the risk of recurrence, the procedure includes the removal of the midportion of the hyoid bone.⁶⁸ A lateral neck mass, with or without a sinus tract to the skin, may be

a remnant of the fetal branchial apparatus. Such masses should also be completely excised to reduce the risk of complications.

ABDOMINAL WALL HERNIA

Inguinal and umbilical hernia repairs are among the most commonly performed procedures in pediatric surgery. Umbilical hernias are commonly diagnosed at birth but tend to close spontaneously. The complication rate is very low; thus, most pediatric surgeons postpone surgical repair until the patient is 2 to 4 years old. Inguinal hernias, on the other hand, pose a substantial risk of incarceration, especially during infancy, and should therefore be repaired as soon as they are diagnosed. High ligation of the sac is the treatment of choice. This operation is usually straightforward, but it can be challenging at times, particularly in premature infants with large hernias. Complications are rare; they tend to occur more frequently if the infant is premature or if the procedure was done on an emergency basis.⁶⁹ To minimize the risk of injury to the spermatic cord, a “no touch” technique should be employed. Whether the contralateral side should be explored remains controversial; some surgeons now use laparoscopy to assess the processus vaginalis of the opposite side.⁷⁰

UNDESCENDED TESTICLES

Approximately 4% of male neonates have an undescended testis at birth, but only about 1% still have this condition at the age of 1 year.⁷¹ Accordingly, most pediatric surgeons recommend that neonates with an undescended testis be observed during the first year of life. If the testicle has not descended by the end of this period, inguinal orchiopexy may be performed; the success rate with this option is higher than 80%.⁷² It is not unusual to find a structurally abnormal testicle during exploration. Potential complications include testicular atrophy and recurrent ascent of the gonad. Hormonal treatment (with human chorionic gonadotropin or luteinizing hormone-releasing hormone) is widely employed in Europe but has a success rate of only about 50%. Laparoscopy is a useful and cost-effective option for the evaluation of nonpalpable testes.^{73,74}

ABDOMINAL PAIN

Abdominal pain is a common finding in children and may arise from any of a wide variety of causes. Among surgical diseases, acute appendicitis is the most common cause of abdominal pain. In addition, however, the differential diagnosis must include perforated duodenal ulcer, Meckel diverticulum, ulcerative colitis, Crohn disease, ruptured ovarian cyst, pelvic inflammatory disease, and, in younger children, intussusception. It is important to remember that medical problems (e.g., constipation, gastroenteritis, pancreatitis, and pneumonia) can also give rise to substantial abdominal discomfort.

Appendicitis

The diagnosis of appendicitis is based on the presence of localizing physical findings in the right lower quadrant of the abdomen. Even if the history and laboratory data are not typical, the presence of such findings should allow the surgeon to make the diagnosis and proceed with appropriate management.

Table 4 Differential Diagnosis of Pediatric Neck Mass

Location	Conditions to Be Considered
Anterior midline	Epidermoid inclusion (sebaceous) cyst Thyroglossal duct cyst Benign reactive hyperplasia of lymph node Thyroid nodule Ectopic thymus Thymic cyst Ectopic thyroid tissue Lipoma Dermoid
Lateral	Branchial cleft remnant Lymphangioma/hemangioma Benign reactive hyperplasia of lymph node Neoplasms (lymphoma, rhabdomyosarcoma, neuroblastoma) Lipoma Torticollis

Although there is some debate regarding the utility of imaging studies in patients with the classic findings of acute appendicitis, it appears that ultrasonography or computed tomography (CT) can be helpful in patients with delayed presentations or atypical symptoms.⁷⁵⁻⁷⁷ If perforated appendicitis with an abscess is identified, a safe and cost-effective treatment approach is to give antibiotics (first IV, then oral), drain the collection percutaneously, and perform an interval appendectomy 6 weeks later.⁷⁸⁻⁸²

Crohn Disease

Occasionally, a teenager who exhibits the classic signs and symptoms of appendicitis turns out to have Crohn disease of the terminal ileum. This condition will be obvious at operation, when the mesenteric fat is seen to be creeping up along the sides of the inflamed ileum. If the base of the appendix is free of disease, an appendectomy should be performed at the time of exploration.⁸³ When the child has fully recovered from the operation, a definitive workup, including a small bowel series and a colonoscopy with biopsy, should be performed to ascertain the extent of the Crohn disease. If an enterocutaneous fistula develops, TPN will be required for a prolonged period. If an intestinal stricture develops (typically, in the terminal ileum), resection may be required. Associated perianal Crohn disease can be very challenging to treat. Medical therapy and surgical therapy should be carried out conjointly. Conservative surgical options (e.g., local drainage, fistulotomy, and setons) are preferred; if sepsis does not resolve or if severe incontinence persists, a stoma may be required.⁸⁴

Intussusception

Idiopathic intussusception usually develops between the ages of 6 months and 2 years. The invagination of small bowel into the cecum results in severe, crampy, intermittent abdominal pain, often associated with obstructive symptoms and bloody stools. Marked lethargy is also a frequent symptom. Air enemas and ultrasound-guided hydrostatic reduction have both been employed to treat this condition, with great success.⁸⁵⁻⁸⁷ Surgical exploration should be reserved for patients in whom reduction is unsuccessful and patients in whom there is reason to suspect an anatomic lead point that is causing the intussusception.

Meckel Diverticulum and Lower GI Hemorrhage

Meckel diverticulum represents a remnant of the omphomesenteric duct. It occurs in approximately 2% of the pediatric population. If symptomatic, it can be associated with acute and substantial lower GI bleeding, obstruction, or diverticulitis.⁸⁸ The differential diagnosis of lower GI bleeding in children also includes GI infections, colonic polyps, duplication cysts, and inflammatory bowel disease. Meckel diverticulitis presents with symptoms very similar to those of acute appendicitis and should always be ruled out if the appendix appears normal on exploration. Management of an asymptomatic diverticulum discovered during an abdominal operation remains controversial, even though resection has been shown to carry a low risk of complications.^{89,90}

VENOUS ACCESS

To obtain venous access in an infant, a venous cutdown is performed, and a pediatric silicone (Broviac) catheter is

passed through the common facial, external jugular, or internal jugular vein to the superior vena cava. This procedure is carried out in an OR or, if necessary, in the NICU. Adequate exposure must be obtained, proper instruments and fluoroscopy devices should be available, and strict aseptic conditions must be maintained. The venous catheter is tunneled from the point of entry into the vein to a skin exit site 5 to 10 cm away, with the aim of minimizing the likelihood of bloodstream contamination from dressing changes at the skin exit site. The catheter is brought out on the chest wall, where it is easily accessible and unlikely to be disrupted by an active patient. When no vein sites are available in the neck, the catheter may be advanced into the central venous circulation via a cutdown on the great saphenous vein and tunneled to an exit site on the abdominal wall or the leg.⁹¹ In older children and adults, percutaneous puncture of the subclavian vein is often performed in place of venous cutdown; this technique can also be used in infants.^{92,93} Regardless of the technique employed, manipulation of the catheters must be done with close attention to asepsis and antisepsis to minimize the risk of bacterial and fungal infection.

Pediatric Trauma

Whereas accidents are the third most common cause of death in the US population as a whole, they are the single most common cause of death in children between the ages of 1 and 15 years.⁹⁴ Every year, about 20 million injuries occur in children, resulting in approximately 15,000 deaths and 100,000 cases of permanent disability. The first approach to be considered in managing pediatric trauma is clearly prevention. In fact, preventive efforts have been gaining momentum, thanks in part to support from federal funds and from dedicated individual advocates. These efforts have included greater emphasis on the use of pediatric restraint devices in automobiles, improvements in the design of motor vehicles, the wearing of helmets by bicycle and motorcycle riders, improvements in the design of space heaters, the use of fire-retardant material for children's clothes (as dictated by the Flammable Fabrics Act), proper packing and labeling of poisons and medications, and the installation of appropriate fencing around swimming pools.

GENERAL PRINCIPLES

Although the general principles of trauma care are essentially the same for children as for adults, several significant differences must be taken into account in the care of pediatric accident victims.⁹⁵ For example, children do not react to trauma in the same way as adults do. They often have difficulty in expressing pain and in articulating their complaints. They are often extremely frightened after an accident, and this fear may cause them to give misleading signals (e.g., by exhibiting signs of an acute abdomen even though no intra-abdominal injury has occurred). Children who experience stress often undergo developmental regression, typically accompanied by severe depression. All of these psychological factors must be considered in the treatment of a pediatric accident victim.

Another key difference between children and adults is that children are still growing. Postoperative metabolic management after any form of stress, whether from a surgical

procedure, from trauma, or from some other event, must take this difference into account. Children can compensate for hypovolemia effectively and keep their vital signs in the normal range, even in the presence of shock. However, a small blood loss that would be insignificant in an adult can result in marked hemodynamic changes in a small child. Moreover, water and heat loss can be far more extensive in small children than in older children and adults because smaller children have a greater surface area in relation to their weight and have a relative lack of insulating subcutaneous fat. Hypothermia aggravates acidosis and makes hemodynamic resuscitation much more difficult. Gastric dilatation, which can result in vomiting and pulmonary aspiration, is very common in young children after all forms of trauma. Finally, the nutritional requirements of injured children are greater than those of injured adults because children, as growing organisms, naturally have a high metabolic rate. Consequently, TPN often must be started earlier in the treatment of a child than it would be in the treatment of an adult in a comparable condition.

Not only are there significant physiologic and psychological differences between children and adults after trauma, but there also are differences in accident patterns. Most childhood injuries result from blunt trauma. Head trauma is far more common in children than in adults: in fact, it accounts for most of the morbidity and mortality in the pediatric population. After motor vehicle accidents, which are the major cause of trauma in both children and adults, the next most frequent causes of trauma in children are events that are less important causes in adults: falls, bicycle accidents, drowning, poisoning, and burns from fires. Nonaccidental trauma (NAT) [see Nonaccidental Trauma, *below*] is a unique and important cause of trauma in children.

Pediatric accident victims must be treated in centers that have experience in the care of traumatized children.^{96,97} Such centers must have an emergency department with a section that is specifically set aside for the care of children and is staffed by nurses and physicians who are familiar with the management of pediatric trauma. They must have a hospital with a pediatric ICU that is also staffed by experienced medical and paramedical personnel. Finally, they must have a transportation system that is capable of rapidly transporting critically ill pediatric trauma victims both by air and by land or water. The Pediatric Trauma Score [see Table 5] has been successfully used not only as a tool for grading severity of injury but also as a means of comparing trauma care across institutions.

AIRWAY MANAGEMENT, PAIN RELIEF, AND SEDATION

Establishing and maintaining a secure airway are of the utmost importance in treating any injured child. Most pediatric trauma programs have mechanisms in place that delegate this responsibility to the attending emergency physician or anesthesiologist so that the surgical team can continue assessing the patient. The airway team can also provide conscious sedation or elective intubation if a painful procedure (e.g., reduction of fractures or suturing of lacerations) proves necessary.

MANAGEMENT OF HEAD INJURY

Closed head injuries (CHIs) are the most common cause of death in children and account for close to 7,000 fatalities in the United States each year.⁹⁸ Any child who had a

witnessed loss of consciousness, is mentally altered, or has an abnormal Glasgow Coma Scale (GCS) score should undergo urgent CT scanning of the head. If the GCS score is lower than 8, intubation is necessary to protect the airway. The main focus of therapy for severe CHI is on minimizing secondary insult to the brain by optimizing oxygen delivery. Management involves close monitoring of cerebral perfusion pressure and judicious use of sedatives, anticonvulsants, pressors, intraventricular drainage, or even surgical decompression to optimize cerebral perfusion. Evidence-based practice guidelines for the management of pediatric CHI patients are now available.⁹⁹

Because children with even minor structural injuries to the brain are at risk for hyponatremia, close monitoring of sodium levels is required.^{100,101} Patients who have postconcussive

Table 5 Pediatric Trauma Score

Variable	Coded Value
Size	
> 20 kg	+2
10–20 kg	+1
< 10 kg	–1
Airway status	
Normal	+2
Maintainable	+1
Not maintainable	–1
Systolic BP	
> 90 mm Hg	+2
50–90 mm Hg	+1
< 50 mm Hg	–1
In the absence of proper size BP cuff, assess BP by assigning these values:	
Pulse palpable at wrist	+2
Pulse palpable at groin	+1
Pulse not palpable	–1
CNS status	
Awake	+2
Partially conscious or unconscious	+1
Comatose or decerebrate	–1
Open wounds	
None	+2
Minor	+1
Major	–1
Skeletal injury	
None	+2
Closed fracture	+1
Open/multiple fractures	–1
Range of possible scores	–6 to +12
Scoring triage criterion for direct transport of patient to trauma center	< 9

BP = blood pressure; CNS = central nervous system.

symptoms (e.g., vomiting, seizures, or headache) should be admitted, even if the head CT reveals no structural injury. It is our practice to follow these patients for 3 weeks after the injury to determine whether postconcussive symptoms are persisting. If these symptoms have not resolved, patients undergo a more detailed cognitive evaluation.

CERVICAL SPINE CLEARANCE

Cervical spine injuries in children are very rare but can have catastrophic consequences if missed. As with adult trauma patients, it is crucial to follow established protocols for systematically clearing the cervical spine. Early immobilization, clinical examination, plain x-rays, and advanced imaging studies can all be useful. Because of the anatomic differences between children and adults, certain modifications to adult protocols are necessary.^{102,103}

BLUNT SOLID-ORGAN INJURY

Abdominal trauma in children is usually blunt. Penetrating injuries occur in only about 20% of children who sustain trauma and are managed in essentially the same way as they are in adults [see Section 7: Trauma and Thermal Injury].

Children who sustain major trauma often have intra-abdominal injuries. Because gastric dilatation and reflex ileus are far more common in children than in adults after a major injury, the initial clinical evaluation of the child's abdomen may be highly misleading. Early insertion of a nasogastric tube decompresses the stomach and allows more accurate physical examination of the abdomen; in addition, it reduces the risk of aspiration pneumonitis. Once the child is stable with respect to hemodynamic and respiratory status, the abdomen should be carefully examined for external evidence of trauma (e.g., ecchymoses, abrasions, and tiretracks). The abdomen should then be carefully and gently palpated, with the awareness that a frightened child often tightens his or her rectus muscles in a way that gives a false impression of intra-abdominal injury. Serial abdominal examinations are essential.

CT has become the gold standard for evaluation of blunt abdominal injury in stable trauma patients.¹⁰⁴ This modality is extremely accurate in evaluating solid-organ injuries and determining the amount of blood in the peritoneal cavity [see Figure 4, Figure 5, and Figure 6]. It is also useful for detecting pneumoperitoneum resulting from intestinal perforation.¹⁰⁵ To minimize exposure to radiation, the scan should be performed at the lowest radiation level feasible, and repeat scans should be avoided if possible.¹⁰⁶ The usefulness of the focused assessment for the sonographic examination of the trauma patient (FAST) in children remains controversial at present.^{107–109}

Because hollow viscus injury is uncommon in children who sustain blunt abdominal trauma, nonoperative treatment is the accepted method of management for most hepatic and splenic injuries. Associated fractures of the lower ribs are rare in children with injuries to the liver or the spleen, although they are fairly common in adults with such injuries.¹¹⁰

A CT scan can accurately confirm the diagnosis of a splenic injury. A major reason why nonoperative treatment is recommended for pediatric splenic injuries is that the risk of overwhelming postsplenectomy infection (OPSI) is far higher in children than in adults; the younger the child, the higher the risk of OPSI. OPSI develops in 3.3% of pediatric

patients who have undergone splenectomy and carries a mortality of 50%.¹¹¹

Once a hepatic or splenic injury has been diagnosed, management should follow the established guidelines for treatment of blunt solid-organ injuries in children.^{112–114}

Ongoing hemodynamic instability despite aggressive resuscitation is the main indication for operative intervention; fortunately, it is a rare occurrence. The likelihood of successful nonoperative management of hepatic and splenic injuries continues to be higher in designated pediatric trauma centers.¹¹⁵

The finding of intraperitoneal fluid on a CT scan without evidence of solid-organ injury remains a challenging clinical



Figure 4 Shown is an abdominal computed tomographic scan from a patient who sustained multiple blunt injuries after being hit by an object through the windshield while driving. A deep central liver laceration is visible (black arrow), as is soft tissue emphysema (white arrow). The hepatic injury did not necessitate operative intervention.



Figure 5 Shown is an abdominal computed tomographic scan from a child who sustained blunt trauma. Several large cracks in the spleen are apparent (white arrow). A significant amount of intraperitoneal blood can be seen over the liver (black arrow).



Figure 6 Blunt abdominal trauma can result in injury to multiple solid organs. Abdominal computed tomographic scan shows partial devascularization of the left kidney (black arrow) and multiple splenic contusions (white arrows).

problem. Management of patients with this finding should be individualized; treatment options include observation with serial examinations, laparoscopy, and surgical exploration.^{105,116}

Among the less common injuries to intra-abdominal organs that occur in children are perforation of the stomach when an accident occurs shortly after eating (while the stomach is distended), perforation of the small intestine and large intestine at a point of fixation (e.g., the ligament of Treitz or the cecum), rupture of the left diaphragm, and damage to the duodenum or pancreas. The likelihood of visceral injury increases dramatically if bruising from a lap belt or a chance fracture is present.^{117–119} Retroperitoneal perforation is suggested by the presence of air around the right kidney on a plain abdominal x-ray. Traumatic pancreatic injury is suggested by an elevation in serum amylase and lipase levels and by the presence of pancreatic edema on ultrasonography or CT. Obviously, perforations of the stomach, the intestine, or the duodenum call for exploratory laparotomy; in most cases, simple suture repair of the laceration is sufficient. Injury to the pancreas, on the other hand, can usually be managed nonoperatively with nasogastric decompression and IV fluids. Fracture of the pancreatic duct is quite rare in children and is usually secondary to compression of the pancreas against the vertebral column. In the past, this injury was usually treated with exploratory laparotomy and distal pancreatectomy, but current experience indicates that it can often be successfully treated by nonoperative means, although there is a risk that pseudocysts will subsequently develop.^{120–122} Intramural duodenal hematoma is relatively uncommon in children and is usually well managed by providing nasogastric decompression for about 10 days and instituting TPN.¹²³

In any child who has sustained abdominal trauma, the diagnosis of a pelvic fracture should be seriously considered.

Pelvic fractures can result in significant bleeding into the retroperitoneum, as well as injuries to the bladder and the urethra. The diagnosis can be confirmed by x-ray studies of the pelvis. In most cases, the fracture can be treated with bed rest, immobilization, and the replacement of lost blood.¹²⁴

Children with blunt multisystem trauma seldom die if they are alive when brought to an emergency department, unless they have sustained head injuries. Care of these patients requires aggressive, coordinated efforts on the part of a multispecialty team that is under the direction of a pediatric surgeon. The establishment of specifically designated pediatric trauma centers around the country was one of the most important developments in the care of children to occur in the 1980s; since then, multiple studies have demonstrated that this measure has substantially improved outcomes for injured children.¹²⁵

NONACCIDENTAL TRAUMA

One of the unique varieties of pediatric trauma is NAT, or the battered child syndrome. It is a sad fact that intentional trauma is the most common cause of fatal injury in children younger than 1 year. The exact incidence of NAT is not known, but it is believed that in the United States, about 160,000 children are seriously injured by deliberate abuse each year.¹²⁶ Risk factors include a low socioeconomic background, a single-parent family, low birth weight, and multiple siblings.^{127,128} The victims tend to be younger than 2 years, except when sexual abuse is involved, in which case, the average age is about 10 years. The abuse can take many different forms, such as physical or mental injury, nutritional or hygienic neglect, delayed or inadequate treatment of disease, sexual abuse, and verbal abuse. Salient clues to the diagnosis include an unreasonable delay in seeking medical help for the child, inconsistencies between the trauma observed and the injury mechanism described, poor hygiene, and marked depression or lack of emotion in the child. The injuries most commonly seen are soft tissue injuries, burns, fractures, and head trauma. X-ray evidence of healing fractures of different ages (a finding described as long ago as 1946) and of rib fractures is highly correlated with abuse.^{110,129} Visceral injuries (e.g., hepatic fractures, splenic fractures, duodenal hematomas, and pancreatic fractures) are also associated with abuse, although less frequently.

Once a physician suspects NAT, he or she is both legally and ethically obligated to report the situation to the appropriate hospital team and to the social services agency of the local jurisdiction. The typical hospital team usually includes a physician, a social worker, and a nurse. Prompt and full reporting often improves the chances that the parents will receive positive counseling, which may well reduce their subsequent abuse of the child.

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3 THE PREGNANT SURGICAL PATIENT

David C. Brooks, MD, FACS, and Ali Tavakkolizadeh, MD, FRCS, FACS

Approach to Abdominal Pain in Pregnant Patients

Since the early 1990s, the number of live births in the United States has ranged from 3.88 to 4.12 million per year.¹ Complications related to nonobstetric surgery are relatively uncommon, occurring in only 1 to 2% of pregnancies; however, when they occur, they often raise significant challenges.² Management of the pregnant patient differs from that of other patients in several ways. First, pregnancy induces a variety of mechanical, hormonal, and chemical alterations that may confuse and mislead even the most experienced surgeon [see Physiologic Changes of Pregnancy, *below*]. Second, and most important, a surgeon treating a pregnant woman is actually caring for two patients and has the same responsibility to both. As a result, a surgeon's natural inclination, when faced with a pregnant patient experiencing abdominal pain, is to temporize. This tendency, which generally arises from the misconception that surgical intervention may injure the fetus, is responsible for delays in diagnosis and ultimately for the unfavorable outcomes often associated with acute abdominal pathology in pregnant patients. To avoid such pitfalls, the management of pregnant patients requires a multidisciplinary approach to care that involves the surgeon, the obstetrician, the radiologist, and the anesthesiologist.

In what follows, we first review the normal physiologic changes that occur during pregnancy, followed by a review of the surgical problems in the pregnant patient. Finally, we address certain nonurgent surgical problems associated with pregnancy.

Physiologic Changes of Pregnancy

A variety of physiologic alterations occur during pregnancy. These include mechanical, hormonal, chemical, and hematologic changes [see *Table 1* and *Table 2*] that are essential for maintenance of the pregnancy during the 40 weeks of gestation but that may also complicate the evaluation of abdominal problems in the pregnant patient.

RESPIRATORY CHANGES

The respiratory system undergoes several measurable changes as a result of the hormonal and physiologic influences of pregnancy [see *Table 2*]. Elevated progesterone and estrogen levels cause blood volume and cardiac output to increase; as a result, pulmonary blood flow increases. With the added component of decreased blood albumin concentration and thus decreased oncotic pressure, mild pulmonary edema may ensue.³

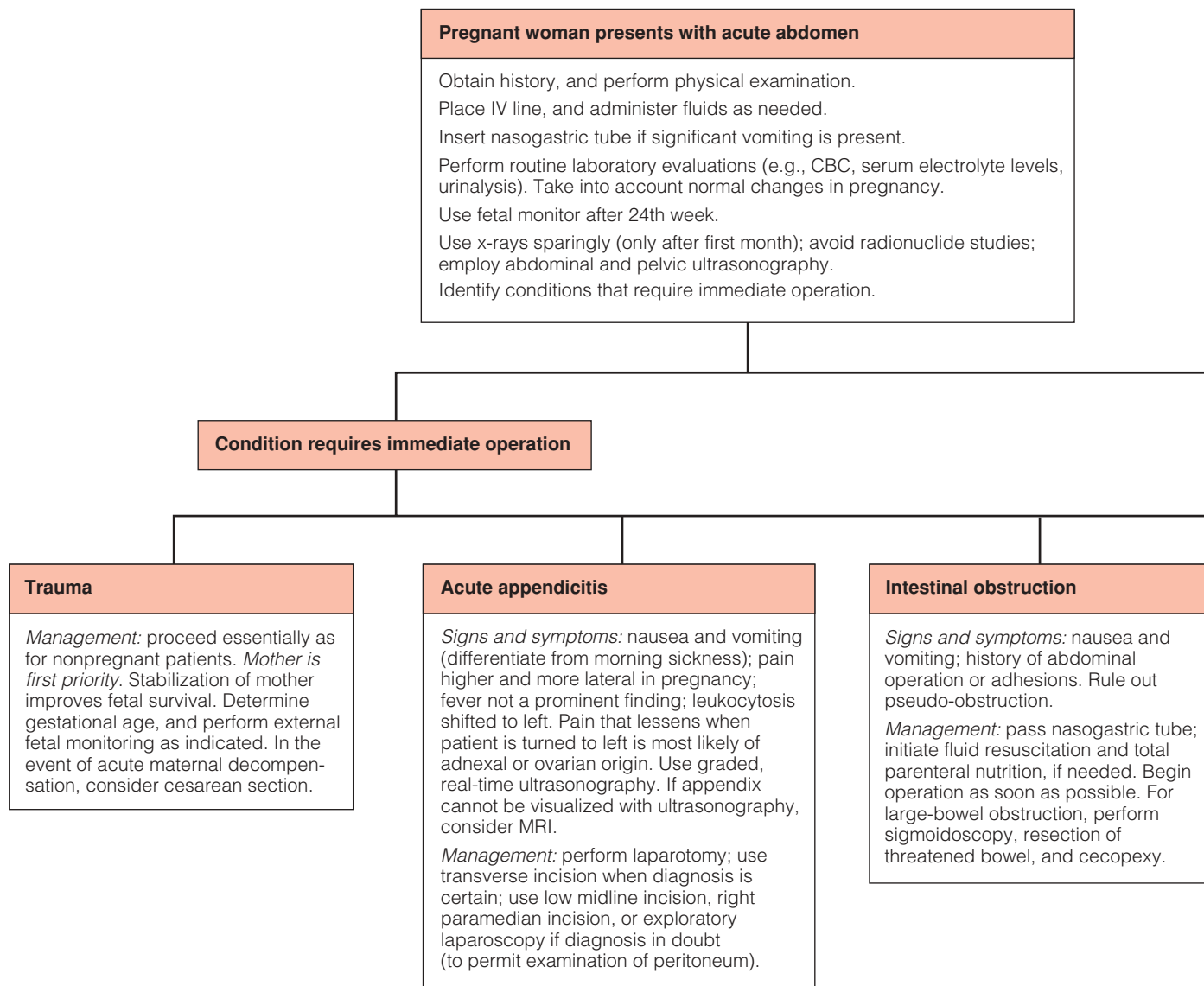
In pregnant patients, both O₂ consumption and CO₂ production increase as gestation progresses. Progesterone, which is a direct respiratory stimulant and increases the chemosensitivity of the respiratory center to CO₂, rises from 25 ng/mL at 6 weeks to 150 ng/mL at term. As the progesterone level rises, chemosensitivity to CO₂ increases and minute ventilation progressively rises by up to 30%.⁴ Progesterone and increased CO₂ production are the main forces behind the condition known as hyperpnea of pregnancy. This condition results in a reduction in arterial CO₂ tension (Paco₂) from 40 mm Hg to 34 mm Hg and an increase in arterial oxygen tension (Pao₂) from 60 to 100 mm Hg. This exaggerated

Table 1 Chemical and Hematologic Alterations in Pregnant Patients

Laboratory Test	Normal Values	
	Nonpregnant	Pregnant
Urinary acetone	Negative	Faint positive
Serum total protein (g/dL)	6.5–8.5	6.8
Serum albumin (g/dL)	3.5–5.0	2.5–4.5
Blood urea nitrogen (mg/dL)	10–25	5–15
Fasting blood glucose (mg/dL)	70–110	65–100
Two-hour postprandial blood glucose (mg/dL)	< 110	< 120 (plasma)
Serum calcium (mEq/L)	4.6–5.5	4.2–5.2
Serum phosphate (mg/dL)	2.5–4.8	2.3–4.6
Alkaline phosphatase (IU/L)	35–48	35–150
Cholesterol (mg/dL)	120–290	177–345
Triglycerides (mg/dL)	33–166	130–400
Serum folic acid (ng/mL)	5–21	4–14
Vitamin B ₁₂ (pg/mL)	430–1,025	Decreased
Hemoglobin (g/dL)	12	> 11
Hematocrit (%)	36	33
Serum iron (µg/dL)	> 50	> 60
TIBC (µg/dL)	250–400	300–600
% TIBC saturation	30	> 20
Serum zinc (µg/dL)	65–115	55–80
Urinary zinc (µg/dL)	200–450	200–450

TIBC = total iron-binding capacity.

Approach to Abdominal Pain in Pregnant Patients



Perforated duodenal ulcer

Management: plication of the perforation. Definitive ulcer operation should not be attempted. If patient is close to term, avoid cesarean section because of risk of uterine contamination.

Spontaneous visceral rupture

General signs and symptoms: intra-abdominal hemorrhage, shock, acute abdomen.

- Hepatic rupture: severe right upper quadrant pain; complication of preeclampsia
- Renal rupture: probably secondary to hydronephrosis
- Splenic rupture: occurs in conjunction with splenic artery aneurysm or capsular rupture, usually secondary to hypervolemia and splenomegaly
- Esophageal rupture: may be associated with excessive vomiting during pregnancy (hyperemesis gravidarum)
- Ruptured ectopic pregnancy

Note: in operation for hepatic rupture, cesarean section should be performed simultaneously.

Other conditions requiring urgent operation

Ectopic pregnancy.
Ovarian torsion.

Condition requires operation only if disease does not respond to medical management

Acute cholecystitis: presents with epigastric or upper right quadrant pain, nausea and vomiting, occasional radiation of pain to right scapula; use ultrasonography to visualize. Do not use HIDA scan. Manage nonoperatively during first and third trimesters (fluid resuscitation and antibiotics); during second trimester, perform cholecystectomy. Use intraoperative cholangiography. Evidence increasingly supports minimally invasive surgical management of symptomatic gallbladder disease.

Pancreatitis: presents with unremitting visceral pain that may radiate to the back and with raised amylase levels (2,000–3,000 IU). Operative intervention (preferably during second trimester) indicated by evidence of biliary obstruction but no evidence of stone passage or by failure of medical management.

Peptic ulcer disease: treatment is based on symptomatic relief. Prompt operative intervention is indicated in the event of perforated duodenal ulcer.

Inflammatory bowel disease: operative intervention is last resort if medical therapy ineffective. Indications for operation include abscess, fistula, or bowel obstruction (Crohn disease) or toxic megacolon (ulcerative colitis). Active Crohn disease with rectal involvement may preclude vaginal delivery.

Table 2 Hemodynamic Values in Healthy Nonpregnant, Pregnant, and Postpartum Subjects

Parameter	Nonpregnant	36–38 Weeks' Gestation*	Postpartum
Heart rate (beats/min)	60–100	83 ± 10	71 ± 10
Central venous pressure (mm Hg)	5–10	3.8 ± 2.5	3.7 ± 2.6
Mean pulmonary arterial pressure (mm Hg)	15–20	—	—
Pulmonary arterial wedge pressure (mm Hg)	6–12	7.5 ± 1.8	6.3 ± 2.1
Mean arterial pressure (mm Hg)	90–110	90.3 ± 5.8	86.4 ± 7.5
Cardiac output (L/min)	4.3–6.0	6.2 ± 1.0	4.3 ± 0.9
Stroke volume (mL/beat)	57–71	74.7	60.6
Systemic vascular resistance (dyne·cm·s ⁻⁵)	900–1,400	1,210 ± 266	1,530 ± 520
Pulmonary vascular resistance (dyne·cm·s ⁻⁵)	< 250	78 ± 22	119 ± 47

*Values in pregnant patients were determined with the patient in the left lateral decubitus position.

gradient between the mother and the fetus facilitates efficient exchange of gases. With the decreased PaCO_2 , the pregnant patient also experiences respiratory alkalosis in relation to the fetus. The oxyhemoglobin dissociation curve is thus shifted to the right, again facilitating delivery of oxygen to the fetus. To prevent harmful pH increases, the kidneys respond appropriately by excreting bicarbonate. Respiratory alkalosis with compensatory metabolic acidosis is normal in pregnancy.

As pregnancy progresses, tidal volume rises by as much as 40% as a result of a 5 cm increase in chest circumference. Although the growing uterus forces the diaphragm upward by as much as 4 cm, tidal volume is maintained, thanks to increased use of accessory muscles. By week 12 of gestation, however, the functional residual capacity (FRC) decreases by 10 to 25% as a result of decreased chest wall compliance.⁵

As many as 75% of pregnant women are affected by dyspnea. Dyspnea of pregnancy comprises mild pulmonary edema, increased breathing load, increased drive, and greater use of accessory muscles.³ It can complicate the assessment of any pregnant patient with an underlying surgical issue. In addition, pregnant women typically have decreased oxygen reserve and thus are subject to rapid development of hypoxia and hypercapnia with hypoventilation or apnea. This vulnerability becomes especially important when such patients undergo intubation and anesthesia.

CARDIOVASCULAR CHANGES

During pregnancy, cardiac output rises by 30 to 50% [see Table 2]. This rise is attributable to an increased heart rate (HR) and, to a lesser extent, an increased stroke volume.⁵ The HR increase may begin as early as 6 weeks after conception⁶; by the third trimester, the HR is 15 to 20 beats/min faster than the baseline rate. The increase in the plasma volume may be as great as 50%. Despite the increases in cardiac output and blood volume, blood pressure (BP) actually decreases because of the overwhelming effect of reduced systemic vascular resistance. BP reaches a nadir in the second trimester and returns to baseline levels by the time of delivery.⁷

The gravid uterus may press on the inferior vena cava, decreasing venous return and causing cardiac output to decrease by as much as 30%. Pregnant women may even experience dizziness or syncope. To optimize cardiac output,

the pregnant patient should be placed in the left lateral decubitus position.⁴

Cardiovascular evaluation of the pregnant patient must take into account the altered cardiac output, blood volume, HR, and BP. Hypovolemia may not manifest itself as tachycardia or hypotension, as would normally be predicted; alternatively, tachycardia of pregnancy may be mistaken for hemorrhage. Careful analysis of the data is necessary whenever hypovolemia is under consideration.

GASTROINTESTINAL CHANGES

Appetite can vary greatly from one pregnant woman to another. The recommended dietary allowance (RDA) is increased by 300 kcal/day during pregnancy—more if the pregnant patient is an adolescent or especially physically active.⁸ As many as 70% of pregnant patients experience nausea and vomiting. Nausea of pregnancy, or morning sickness, frequently occurs between weeks 4 and 16 of gestation. Most patients respond to conservative treatment, including selective eating and avoidance of dehydration. Persistent nausea and vomiting, termed hyperemesis gravidarum, can lead to dehydration, electrolyte imbalance, and organ failure. It is important to exclude other possible causes of nausea before attributing symptoms to nausea of pregnancy. This condition can complicate the diagnosis of appendicitis, gallbladder disease, pancreatitis, or bowel obstruction.

Between 40 and 80% of pregnant women experience gastroesophageal reflux disease (GERD).⁹ Esophagogastric junction tone decreases as intra-abdominal pressure increases, with reflux being the result. In addition, under the influence of estrogen and progesterone, the stomach exhibits decreased motility and an increased emptying time. Transit through the small bowel and the colon is also slowed. Few gastrointestinal changes have a critical impact on pregnancy. It should be kept in mind, however, that prolonged emptying time and other effects of progesterone increase the likelihood of aspiration with general anesthesia.¹⁰

Estrogens and progesterone are thought to influence cholestasis of pregnancy as well. The net effect of the two hormones is to increase the cholesterol concentration in bile. Estrogen also decreases bile flow. Progesterone promotes smooth muscle relaxation and stasis throughout the biliary system.¹¹ In the evaluation of cholestasis or any liver disease,

it is important to remember that placental alkaline phosphatase can increase measured alkaline phosphatase levels by a factor of 3 or 4 [see Table 1].

URINARY CHANGES

As cardiac output increases, the glomerular filtration rate increases by 30 to 50%. This increase reaches a peak at the end of the first trimester. Accordingly, creatinine clearance and blood urea nitrogen (BUN) levels fall by 25% over the first trimester. The kidneys themselves increase in size by 1.5 cm as a result of increased vascularity.¹² The ureters become dilated as a consequence of the relaxing effects of progesterone on smooth muscle. Dextrorotation of the uterus causes further dilatation of the right ureter.

HEMATOLOGIC CHANGES

Normal pregnancy causes numerous changes in coagulation and fibrinolysis. Platelets become more reactive, and destruction is enhanced; to compensate, the pregnant patient increases production of platelets. Normal pregnancy increases hepatic and endothelial cell synthesis of many procoagulant factors. Pregnant women have normal anticoagulant factor levels except for a sharp decrease in protein S antigen and activity. In general, fibrinolytic activity is impaired during pregnancy; however, bleeding time and clotting time are unchanged. Overall, pregnancy is a hypercoagulable state.¹³ The risk of thromboembolism doubles during pregnancy.¹⁴ Accordingly, compression stockings should be used whenever surgical management is embarked on.

Leukocytosis is normally seen in pregnancy. What the net effect of a decrease in CD4⁺ cells, an increase in CD8⁺ cells, and an unchanged number of B cells may be remains somewhat controversial.¹⁵ More important than the higher total number of cells is the altered activity exhibited by all leukocytes, a complicated picture that is still not fully understood.

Although pregnancy may appear to be an anemic state, it is not: blood volume actually increases, and red cell mass rises by 30% [see Table 1].

General Perioperative Considerations in Pregnant Patients

The use of anesthesia in the course of an operation does not pose a teratogenic risk to the fetus.¹⁶ Surgical treatment can be acceptably safe if appropriate attention is given to certain key perioperative considerations—namely, fetal monitoring, anesthesia, and the timing of the operation. Gestational age plays a pivotal role in all surgical decision making for a pregnant patient and should be accurately determined preoperatively, using ultrasonography when an accurate history cannot be obtained.

FETAL MONITORING

Monitoring consists of measuring uterine contractions with a tocometer, fetal HR with a Doppler transducer, and fetal movement and tone with ultrasonography. Together, these measurements yield a good indication of fetal health.

The fetal HR is routinely measured both preoperatively and postoperatively.¹⁷ Although the fetal HR can be heard 14 weeks after conception, it serves as an indicator of fetal

oxygenation only after week 26. Specific fetal HR abnormalities—absence of variability, late or variable decelerations, and bradycardia—are predictive of impending fetal hypoxia, physical damage, or death. In the absence of these extreme (and hence obvious) fetal HR patterns, interpretation of fetal tracings can be complex.¹⁸ There are no conclusive data to suggest that any single monitoring technique reflects fetal outcome.¹⁷ Optimization of maternal physiologic status is more important than any mode of fetal monitoring.

In general, fetal monitoring is done before and after surgery. Continuous intraoperative monitoring is not routinely employed unless the fetus is viable. This decision needs to be done in conjunction with obstetric and anesthetic colleagues.

RADIOLOGIC INVESTIGATION

X-rays and computed tomographic (CT) scans must be employed judiciously, given the risk that radiation poses to the pregnant patient. Depending on the exposure time and the total dose, radiation may cause failure to implant, malformation, growth retardation, central nervous system (CNS) abnormalities, or fetal loss.

The standard units of measure for radiation are the Gray (Gy) and the rad; 1 Gy is equivalent to 100 rad; thus, 1 rad is equivalent to 1 cGy or 10 mGy. The International Commission on Radiological Protection (ICRP) has stated that radiation doses lower than 100 mGy do not increase the risk of fetal death, malformation, or developmental delay.¹⁹ Doses between 200 and 500 mGy during weeks 8 to 15 of gestation, however, result in measurable IQ reductions, and doses higher than 600 mGy result in growth retardation and CNS damage. Most diagnostic procedures fall within the accepted safe range [see Table 3].

Table 3 Radiation Dose Absorbed by Unshielded Gravid Uterus from Radiographic Studies Often Performed in Trauma Patients

Radiographic Study	Unshielded Uterine Dose (mGy)
Cervical spine	No detectable contribution
Chest (AP)	0.003–0.043
Pelvis (AP)	1.42–4.86
Abdomen (AP)	1.33–4.51
IVP	2.02–8.15
Full spine (AP)	1.54–5.27
Femur (AP)	0.016–0.12
Humerus (AP)	< 0.00001
Cystography	1.35–4.41
CT scan	
Head	< 0.5
Thorax	< 10
Upper abdomen	< 30
Cumulative dose (without CT scan)	7.68–27.36
Cumulative dose (with CT scan)	> 7.68–67.86

AP = anteroposterior; CT = computed tomographic; IVP = intravenous pyelography.

In many instances, alternate diagnostic modalities that do not employ ionizing radiation, such as ultrasonography and MRI, are sufficient to determine the proper treatment. If, however, diagnostic radiation does prove necessary, the fetus should be shielded, radiation exposure should be minimized, and radiation doses should be carefully documented. Careful cooperation with the radiologist will help limit radiation exposure. It is of particular importance that the patient be informed of the risks associated with radiation in comparison with the expected benefits of diagnostic radiation in her case.

ANESTHESIA

The physiologic changes associated with pregnancy have implications for anesthetic management. As noted, oxygen reserve decreases with pregnancy. On intubation, hypoxia and hypercapnia with hypoventilation or apnea may develop rapidly. In one clinical study of obstetric anesthesia, airway difficulties occurred in 7.9% of intubated patients compared with 2.5% of nonintubated patients²⁰; it is noteworthy that the primary reasons for difficult intubation were airway anatomy and technique, just as would be the case in nonpregnant patients. During intubation, pregnant women are also at increased risk for gastric aspiration owing to the decreased esophagogastric sphincter tone. Because of this increased risk of aspiration, nasogastric suction should be freely employed. The stomach should be emptied before emergency procedures and continually decompressed throughout the operation and the early postoperative period.

Anesthesia can suppress the normal physiologic compensation for aortocaval compression, in which event hypotension can ensue. Positioning of the patient in a leftward tilt or the left lateral decubitus position can minimize hypotension.^{4,17} Liberal use of indwelling urinary catheters allows gross estimation of the adequacy of blood volume and splanchnic perfusion during general operative procedures.

According to retrospective studies, all anesthetic, opioid, sedative-hypnotic, and anxiolytic agents pose some degree of risk to the fetus; none of them appear to be significantly more teratogenic or safer than any other.¹⁷ If vasopressors are necessary, ephedrine is the drug of choice in that it causes less uterine vasoconstriction than epinephrine or norepinephrine does. Small doses of phenylephrine are also safe for use in pregnant women who are hypotensive [see Table 4].

TOCOLYTICS

Even though surgical procedures have been associated with a higher incidence of preterm labor, especially in the third trimester, routine prophylactic use of tocolytics is not recommended. Tocolytics have several side effects and have not been shown to improve outcome when used prophylactically. Tocolytics are best employed to treat active uterine irritability. Uterine irritability can also be reduced by controlling maternal pain and anxiety.²¹

General Surgical Principles in Pregnant Patients

TIMING OF SURGERY

If a surgical problem arises during pregnancy, the urgency of surgical treatment must be balanced against the risk such treatment poses to the mother and the fetus. Urgent

procedures, such as appendectomy, should be carried out in the usual timely fashion [see Urgent Surgical Problems, below]: in such cases, the risks to both mother and fetus outweigh the risks of miscarriage and preterm labor. Semielective procedures are best done during the second trimester.²² In the first trimester, when organogenesis is ongoing, concerns arise about the teratogenic risks of medications and surgical interventions. During the first trimester, surgical procedures are also associated with a miscarriage rate of 12%; during the second trimester, this rate falls to 0 to 5.6%. The incidence of preterm labor with surgical procedures is 5% in the second trimester but rises to 30 to 40% in the third trimester.²³ Elective procedures should be delayed until 6 weeks after delivery.

LAPAROSCOPY IN PREGNANT PATIENTS

The role of laparoscopic surgery in the management of pregnant patients is becoming increasingly established, although most current recommendations are based on retrospective and animal studies. Laparoscopy would appear to offer some significant benefits. For example, it leads to rapid postoperative recovery and mobilization and thus reduces the risk of thromboembolism associated with pregnancy. Because there is less incision-related discomfort as a result of the growing uterus and increasing intra-abdominal pressure, often less narcotic analgesia is required during recovery, and fetal depression from narcotic exposure is thereby minimized.²³ Moreover, laparoscopic surgery involves less manipulation of the uterus and so may be less likely to induce uterine irritability, preterm labor, premature delivery, or spontaneous abortion.²² Finally, when the diagnosis is uncertain, the surgeon can often use laparoscopy to identify appendicitis, ovarian masses, ovarian torsion, and ectopic pregnancy.

Pregnancy adds a level of risk to any laparoscopic procedure. Insufflation with CO₂ and increased intra-abdominal pressure lead to decreased uterine blood flow, decreased maternal vena cava return, and decreased maternal FRC.²¹ The combination of CO₂ pneumoperitoneum, the reverse Trendelenburg position, general anesthesia, and aortocaval compression by the gravid uterus can decrease maternal cardiac output by 50%.²⁴ Animal studies suggest that CO₂ pneumoperitoneum may also cause an increase in maternal PaCO₂, resulting in maternal and fetal acidosis; however, there is active controversy as to whether these intraoperative alterations caused by CO₂ pneumoperitoneum actually affect fetal health.²⁵ Finally, when laparoscopic surgery is performed in a pregnant patient, the uterus is susceptible to direct damage, irritation, or penetration by a Veress needle or trocar.

Certain measures need to be taken to limit the risks associated with laparoscopic surgery during pregnancy. Prophylaxis against thromboembolism is recommended, with an appropriate dose of heparin administered preoperatively and pneumatic compression devices employed intraoperatively. The patient should be maintained in the left lateral decubitus position to prevent compression of the inferior vena cava by the gravid uterus. The Trendelenburg position should be used no more than is necessary. Ideally, a Hasson technique should be employed to avoid injury to the gravid uterus during entry. The patient's end-tidal CO₂ should be monitored, ventilation adjusted in accordance, and maternal PaCO₂

Table 4 Safety of Various Drugs Used during Pregnancy

Drug (FDA Pregnancy Category)	Toxicity	Comments
Analgesics/tranquilizers Ibuprofen (B) Meperidine (B) Morphine (C) Codeine (C) Acetaminophen (B) Aspirin (C) Barbiturates (C) Diazepam (D)	Risk of postpartum hemorrhage; premature patent ductus arteriosus closure; no teratogenic effects Decreased neonatal respiration; CNS depression Small size for gestational age; respiratory depression; fetal death Possible congenital anomalies None known Anticoagulation effect; fetal bleeding; possible prolongation of pregnancy; no teratogenesis known Fetal addiction; neonatal bleeding; ? teratogenesis ? Cleft palate; ? heart defects; hypotonia; hypothermia; withdrawal symptoms	Use with calcium toward end of pregnancy Greatest risk near term Greatest risk near term Avoid in first trimester Analgesic of choice Use with caution, especially toward end of pregnancy; not recommended for routine analgesia Long-term administration not recommended Long-term administration not recommended
Anesthetics Bupivacaine (C) Lidocaine (B) Halothane (C) Nitrous oxide Muscle relaxants (C)	Bradycardia Bradycardia; CNS depression Uterine relaxation ? Teratogenesis in early pregnancy Fetal curarization	Use with caution in late pregnancy Use with caution in late pregnancy Can cause abortion in early pregnancy Can be used in late pregnancy Relatively safe; incidence of problems extremely low
Antibiotics Ampicillin (B) Aztreonam (B) Cephalosporins (B) Clindamycin (B) Erythromycin, azithromycin (B) Fluoroquinolones (C) Gentamicin (C) Imipenem (C) Metronidazole (B) Nitrofurantoin (C) Penicillin G (B) Streptomycin (D) Tetracycline (D) Trimethoprim-sulfamethoxazole (C) Vancomycin (C)	None known Not teratogenic in rodents No embryocidal reports None known Risk of cholestatic hepatitis; no reported congenital defects Irreversible arthropathy in immature animals Possible eighth nerve toxicity; no reported congenital defects, neonatal ototoxicity, or nephrotoxicity None known Carcinogenic in rodents; possibly teratogenic Hemolytic anemia in newborns; no known teratogenic effects None known Eighth cranial nerve abnormality Adverse effects on fetal teeth and bones; maternal hepatotoxicity; congenital defects Hemolysis in G6PD-deficient patients; risk of kernicterus Potential fetal ototoxicity, nephrotoxicity	Safe Safety in pregnancy unclear Safe Safety in pregnancy unclear Avoid in pregnancy Avoid in pregnancy Avoid in pregnancy Avoid in pregnancy Safety in pregnancy unclear Contraindicated in first trimester; use with caution thereafter Contraindicated at term Safe Contraindicated Contraindicated Contraindicated at term Avoid in pregnancy

CNS = central nervous system; FDA = Food and Drug Administration; G6PD = glucose-6-phosphate dehydrogenase deficiency.

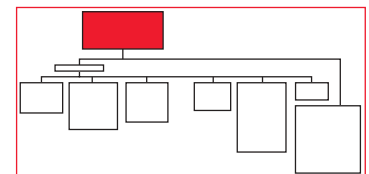
kept between 25 and 33 mm Hg. The pneumoperitoneum should be kept to 10 to 12 mm Hg; this level of pressure is associated with the best outcomes for the procedure. General anesthesia is preferred; ideally, an obstetric anesthesiologist should be present.^{22,26}

Currently, the general tendency is to limit laparoscopic surgery in pregnant women to the first 28 weeks of gestation. Later in pregnancy, when the uterus is no longer confined within the pelvis and the lower abdomen, laparoscopic surgery becomes substantially more difficult, although an increasing number of reports are documenting the feasibility of this approach even in the third trimester.²⁷

When appropriate precautions are employed, laparoscopy poses no more risk to either the mother or the fetus than laparotomy.²² Again, there are no significant differences between the two approaches with respect to preterm delivery rate, birth weight, Apgar score, growth restriction, infant mortality, or risk of fetal malformation.²¹

Urgent Surgical Problems

Initial management of any pregnant patient presenting with an acute abdomen or an acute surgical problem should include a thorough history and physical examination,



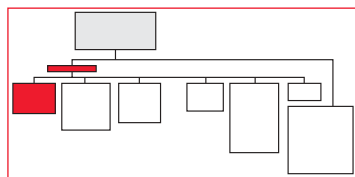
with particular consideration given to the historical aspects of the pregnancy, the expected date of delivery, and the presence of any pregnancy-related complications. Whenever possible, an obstetrician should be consulted and included in the decision-making process. Initial maneuvers should include administration of supplemental oxygen, placement of an intravenous (IV) line with the capacity to deliver ample amounts of fluid or blood, insertion of a nasogastric tube if significant vomiting is present, and performance of routine laboratory evaluations, such as a complete blood

count, assessment of serum electrolyte levels, and urinalysis. If the pregnancy has passed the 24th week, a fetal monitor should be employed. Radiographic investigations should be kept to a minimum, although abdominal and pelvic ultrasonography may be especially useful not only in assessing the maternal pathology but also in evaluating the fetus.

Acute abdominal surgical problems must be dealt with immediately. Management of less acute problems, however, must take into account the stage of the pregnancy.

TRAUMA

Trauma is believed to occur in approximately 6 to 7% of gestations, complicating as many as one in 12 pregnancies.²⁸



Trauma remains the leading cause of maternal death. Homicide is the most common cause of traumatic maternal death, followed by motor vehicle accidents, accidental injury, and suicide. The more severe the injury to the mother, the greater is the risk of injury to the fetus. When the mother survives, fetal death is most commonly related to abruptio placentae. Major trauma causes placental abruption in 40 to 66% of cases; minor trauma causes placental abruption in 5% of cases.²⁹ Signs and symptoms of abruption typically become manifest within 4 hours of observation; however, a delayed presentation may also occur. Penetrating trauma during the latter portions of the pregnancy invariably causes fetal damage.

Domestic or partner violence is common during pregnancy, affecting 7 to 23% of all pregnancies,³⁰ and thus is a common source of traumatic injuries. If the patient is in an abusive relationship, the severity and frequency of assault typically increase during pregnancy. In addition, 20% of abused pregnant women attempt suicide or abuse alcohol or drugs.³¹ Unfortunately, partner violence often goes undiagnosed and hence untreated. If a suspicion of partner violence arises, the physician should ask direct questions about threats and should provide appropriate contacts and support. In all 50 states, domestic violence is a crime, and in some, failure to report suspected violence is a crime as well.

Blunt Injury

In the mother, blunt trauma (as in motor vehicle accidents) may cause multiple life-threatening injuries. Pelvic fractures are a particular concern: because of the extensive vascular supply in this area, there is a significant risk of substantial hidden blood loss. Because the uterus consumes approximately 20% of the cardiac output (i.e., 500 to 600 mL/min), a uterine injury can place a pregnant woman at substantial risk for massive hemorrhage within a short period. Uterine expansion displaces the bladder into the abdomen, thereby increasing the risk of traumatic bladder injury. The upper urinary tract is generally spared from injury, however, because the gravid uterus shields the retroperitoneum from direct injury. Hepatic, splenic, and uterine injuries are common in high-speed motor vehicle accidents, but injuries to the gastrointestinal tract, surprisingly, appear to be uncommon, largely because of the protective effects of the gravid uterus.³² Direct injury to the fetus as a result of blunt trauma is unusual

because of the protection afforded by the maternal abdominal wall and the uterus. Blunt trauma may result in fetal skull fractures, fetal intracranial hemorrhage, or abruptio placentae; nevertheless, fetal demise is rare in this setting and usually is secondary to maternal demise.

Many women refrain from using seat belts during pregnancy because of discomfort or out of misplaced concern that the seat belt might injure the fetus. When unbelted women are ejected from an automobile, maternal mortality is 33% and fetal mortality is 47%.³³ Three-point restraint (both a lap strap and a shoulder strap) is the safest choice for pregnant women in motor vehicles. Airbags are also safe during pregnancy and should not be turned off. General recommendations for pregnant women who are passengers include sitting in the rear seat.

Penetrating Injury

Penetrating injury is usually more damaging to the fetus than to the mother. Mortality is actually lower for pregnant women with penetrating injuries than for nonpregnant women with similar injuries, presumably because of the shielding effect of the uterus and the fetus.³⁴

Penetrating trauma, however, often results in direct fetal injury. Fetal mortality in this setting ranges from 40 to 70%, whereas maternal mortality ranges from 5 to 10%.³⁵ In the first trimester, trauma generally poses little direct threat to fetal viability because the uterus is protected within the pelvis. In the second and third trimesters, however, when the uterus is located within the abdomen, penetrating trauma may result in direct fetal injury or rupture of the membranes. With penetrating abdominal trauma, the prognosis depends on which and how many organs are injured.

General principles of trauma management are applied when the need for laparotomy is under consideration. Visceral injury occurs 95% of the time if the peritoneum has been penetrated.⁴ For this reason, many authorities advocate exploratory laparotomy for all high-velocity penetrating injuries to the abdomen. How best to manage low-velocity penetrating injuries remains somewhat controversial. Low-velocity injuries above the fundus of the uterus are almost always associated with visceral injury and thus call for exploratory laparotomy. Injuries occurring below the fundus and anteriorly are seldom associated with visceral injury⁸ and thus can generally be managed nonoperatively. Subsequent laparotomy is indicated for worsening maternal symptoms. Subsequent cesarean section is indicated for a viable fetus in distress.

Management

Trauma is managed in essentially the same way in pregnant patients as in nonpregnant patients. The mother is the first priority: stabilization of the mother improves both maternal and fetal survival. Initial measures include efforts to support the airway, breathing, and circulation (the ABCs).

Several physiologic changes associated with pregnancy bear relevance to the assessment of the patient. Hypovolemia can be masked by the increased blood volume and enhanced cardiac output of the pregnant patient. Tachycardia and hypotension may not be accurate indicators of hypovolemia. Use of military antishock trousers (MAST) may decrease

maternal venous return by compressing the uterus on the inferior vena cava; accordingly, their use is not recommended. Vasoconstrictive agents should never be used for hemodynamic stabilization until hypovolemia has first been treated. Epinephrine and norepinephrine lead to uteroplacental vasoconstriction and fetal compromise; ephedrine and phenylephrine may be used during pregnancy.

An important concern with advancing gestation is the possibility that the expansion of the gravid uterus [see Figure 1] can produce aortocaval compression, leading to supine hypotension. Left lateral displacement of the uterus is necessary to improve blood flow to both the mother and the fetus after the 20th week.

There are very few diagnostic procedures for which pregnancy is a contraindication. Radiographic investigation should be performed whenever necessary if the results are expected to affect management [see Table 3]. Ultrasonography is now being used for acute trauma assessment in both pregnant and nonpregnant patients; the results to date have been good. Peritoneal lavage done in an open fashion through a supraumbilical incision may facilitate rapid assessment of intra-abdominal hemorrhage in cases of blunt trauma. A Kleihauer-Betke test for fetal red blood cells in the maternal circulation will reveal any fetomaternal hemorrhage present. (Fetomaternal hemorrhage is the passage of fetal blood into the maternal vascular system; it occurs more frequently in pregnant women who have suffered traumatic injury than in those who have not and can lead to fetal anemia, arrhythmias, and fetal exsanguination.³⁶) In Rh-negative mothers, a 300 µg dose of Rh₀(D) immune globulin will be protective against exposure to as much as 15 mL of fetal cells (30 mL of RhD-positive whole blood). Rarely does fetomaternal hemorrhage exceed this level. Tetanus toxoid should be administered when indicated.

Early determination of gestational age by means of ultrasonography is a critical guide to further management decisions. Ultrasonography can also be used to monitor fetal heart tones, fetal activity, and amniotic volume. As many as 40% of women experience preterm contractions, but only 3% progress to premature delivery.²⁹ Preterm contractions in a pregnant trauma patient should initiate an evaluation for abruptio placentae, uterine hemorrhage, and intra-abdominal hemorrhage. Given that placental abruption occurs in 66% of cases of major trauma and 5% of cases of minor trauma, the patient should be evaluated for ruptured membranes, which usually occur within 4 hours of injury. Ultrasonography is not sensitive enough to detect this condition; therefore, cardiotocographic monitoring should be continued for 4 to 6 hours after stabilization and longer if any irregularity in the mother or fetus is noted.³⁷ If the fetus has not yet reached the gestational age of 23 weeks or is not viable, the mother should receive supportive care. In these circumstances, cesarean section is reserved for cases of disseminated intravascular coagulation (DIC). If the fetus is viable and the mother is stable, cesarean section can be carried out safely; if the fetus is viable and the mother is unstable as a result of trauma, cesarean section should be carried out with exploratory laparotomy.²⁹ Typically, surgical intervention for a worrisome fetal heart tracing is not carried out until after the 24th week of pregnancy.

In the event of acute maternal decompensation or cardiac arrest, a cesarean section may be appropriate. Cesarean section may increase maternal circulating volume. Occasionally, cardiopulmonary resuscitation (CPR) is more effective after the gravid uterus is emptied. There is also less risk of supine hypotension after cesarean section, although the associated surgical blood loss may exacerbate maternal instability. Timing is critical: if anoxia is limited to 4 to 6 minutes, the

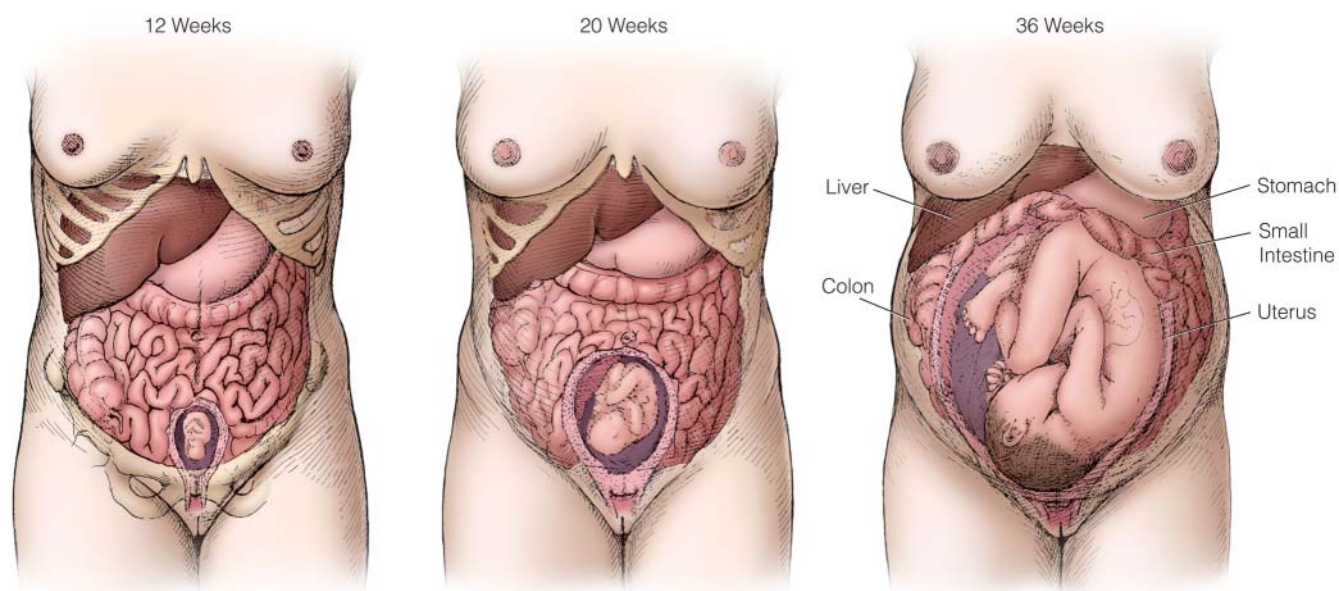


Figure 1 Enlargement of the uterus to accommodate the developing fetus shifts intra-abdominal contents superiorly and compresses retroperitoneal structures. These effects are particularly important during the second and third trimesters.

fetus generally will not be harmed. Therefore, any attempt to deliver the fetus should begin within 4 to 6 minutes after maternal cardiac arrest. The survival of the fetus after delivery is dependent on its having reached a gestational age greater than 28 weeks. CPR of the mother should be continued during and after the delivery because it may improve maternal status and survival.

Two caveats should be kept in mind: (1) cesarean section should not be performed in an unstable patient because of an anticipated cardiac arrest and (2) if CPR is successful before surgical delivery is attempted, cesarean section should not be performed, because in utero resuscitation is likely.³⁸ In utero resuscitation may have to be continued for 10 to 20 minutes before reassuring elements reappear on a fetal heart tracing.

APPENDICITIS

Appendicitis is the most common surgical problem in pregnancy, occurring in 0.05 to 0.1% of pregnancies, but it occurs no more often in pregnant women than in nonpregnant women.^{27,39} The incidence is approximately the same in all three trimesters. The low maternal mortality—0.5% in 1977 and 0% in recent studies⁴⁰—notwithstanding, of all surgical problems during pregnancy, appendicitis causes the most fetal loss.²⁸ The particular dangers of appendicitis in pregnancy lie in the varied presentation of symptoms, the higher chance of delayed diagnosis, and the significant risk that surgery presents to the fetus.

The symptoms of appendicitis mimic symptoms of normal pregnancy—namely, anorexia, nausea, vomiting, and abdominal discomfort. The most reliable symptom of appendicitis during pregnancy is periumbilical or diffuse abdominal pain that later localizes to the right lower quadrant. Although as the gravid uterus grows, it pushes the appendix cephalad and posteriorly, right lower quadrant pain remains the most consistent symptom of appendicitis in any trimester.⁴¹

On physical examination, appendicitis presents with tenderness in the right lower quadrant. It can be differentiated from adnexal or uterine pain with the help of the Adler sign: if the point of maximal tenderness shifts medially with repositioning on the left lateral side, the etiology is generally adnexal or uterine. Abdominal guarding, rebound tenderness, or referred tenderness is present in 60 to 70% of patients with appendicitis; however, these findings are less common during the third trimester because of the laxity of the abdominal wall muscles. Elevated body temperature is not a consistent finding in pregnant patients with appendicitis.^{40,41}

Laboratory values can be misleading in that pregnancy can cause a leukocytosis as high as 15,000 leukocytes/ μ L in the absence of any source of infection. The white cell differential is more useful than the absolute count; increased levels of band cells or immature forms suggest that the leukocytosis may be secondary to an infectious process. Urinalysis is necessary to rule out a urinary tract infection, which occurs in 10 to 20% of pregnant women.

Diagnostic radiology should be employed deliberately and judiciously. Ultrasonography of the lower abdomen or transvaginal ultrasonography can often visualize an inflamed

appendix without risk to the fetus. It can also distinguish other causes of abdominal pain, such as an ovarian cyst. The clinical presentation and an ultrasonogram are often sufficient to establish the diagnosis of appendicitis.

If the ultrasonography is nondiagnostic, magnetic resonance imaging (MRI), when available, is the imaging modality of choice. MRI does not expose the fetus to radiation and is known to be safe overall in the setting of pregnancy. In one small series, MRI had an overall sensitivity of 100%, a specificity of 93.6%, and an accuracy of 94.0% in the evaluation of potential acute appendicitis.⁴² Its negative predictive value was 100%. These results suggest that MRI is an excellent tool for excluding acute appendicitis in pregnant women with acute abdominal pain whose appendix cannot be visualized by means of ultrasonography. This approach has not yet been widely accepted, and there is obviously a need for larger studies to confirm its value; however, the findings to date indicate that the use of MRI in obstetric patients with appendicitis is a promising strategy.

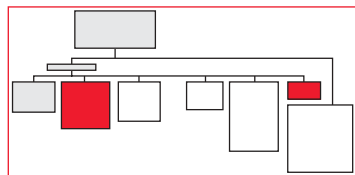
In circumstances where an MRI is not readily available, a CT study of the pelvis can be done to elucidate a complicated presentation. A pelvic CT study yields a total radiation dose of 25 mGy, and a directed helical, or spiral, CT study yields a total exposure of 30 mGy. Directed spiral CT has a sensitivity and a specificity of 98%.⁴³ For both pelvic CT and directed spiral CT, the total radiation doses are well below the threshold of safety established by the ICRP, which is 100 mGy, and helps reduce the incidence of negative appendectomy.⁴⁴ With plain films, the chance of obtaining valuable information is seldom worth the risk associated with the radiation. In certain cases, diagnostic laparoscopy may be appropriate to diagnose and treat appendicitis.

Differential Diagnosis

The condition most often confused with appendicitis is pyelonephritis, which occurs in 1 to 2% of pregnant women. The two diseases may present remarkably similar clinical pictures, especially when pyelonephritis occurs on the right side. Because of the mechanical effects of the gravid uterus on the ureter, pyelonephritis is more common in pregnant women than in nonpregnant ones. Furthermore, urinalysis yields abnormal results—either pyuria or hematuria—in as many as 20% of patients with appendicitis as a result of extraluminal irritation of the ureter by the inflamed appendix. Nephrolithiasis can also be mistaken for appendicitis.

Right lower quadrant pain during early pregnancy may also be a presentation of ectopic implantation. Typically, a patient misses a period and then experiences some degree of vaginal bleeding or spotting. Abdominal or pelvic pain as well as cervical motion tenderness is present, and a mass is often appreciated on pelvic examination. When ectopic pregnancy is suspected, a serum human chorionic gonadotropin (hCG) assay should be performed along with transvaginal ultrasonography. If the serum hCG level is higher than 2,000 IU/L and an intrauterine gestational sac is not visualized by transvaginal ultrasonography, laparotomy or laparoscopy is indicated.

Torsion of an ovary or an ovarian cyst is also difficult to distinguish from appendicitis. Although rare in pregnant patients, torsion of an ovarian cyst may occur in the early



stages of the pregnancy. The physical examination is notable for pain in the right or left adnexa and the occasional presence of a tender mass. Transvaginal ultrasonography will frequently detect the cyst. Treatment requires laparotomy. The differential diagnosis of acute abdominal pain in pregnancy should also include ovarian cysts, mesenteric adenitis, degenerating fibroid tumors, salpingitis, inflammatory bowel disease (IBD), cholecystitis, ovarian vein thrombosis, ruptured corpus luteum, rectus hematoma, round ligament pain, abruptio placentae, chorioamnionitis, and adhesions.

Management

When there is evidence of appendicitis and no alternative diagnosis seems likely, operative intervention is warranted no matter what stage the pregnancy has reached.⁴¹ The risk of the procedure to mother and child is minimal in comparison with the risks posed by delayed diagnosis, perforation, and abscess formation. Appendectomy in a pregnant patient does not increase the incidence of congenital malformation or stillbirth.²⁶ With routine surgical management, maternal mortality is negligible and fetal mortality is 2 to 8%.⁴⁰ For a ruptured appendix, the maternal and fetal mortality rates have been presumed to be higher, encouraging an aggressive surgical approach for women with a possible diagnosis of appendicitis. As a result, the negative appendectomy rate is usually high in pregnancy. In our own series of 968 women undergoing appendectomy, the negative appendectomy rate was 14% for nonpregnant versus 36% for pregnant patients. Recent studies are, however, suggesting that negative appendectomies are associated with adverse fetal outcomes and a 4% fetal demise, highlighting the importance of preoperative imaging in making the diagnosis of appendicitis in pregnancy.⁴⁵

For appendectomy in the pregnant patient, a right lower quadrant muscle-splitting approach should be employed over the point of maximal tenderness. With third trimester pregnancies, this point of maximal tenderness may be higher than the traditional McBurney point. The patient should also be turned 30° to the left to reduce pressure on the inferior vena cava and to facilitate exposure of the cecum.

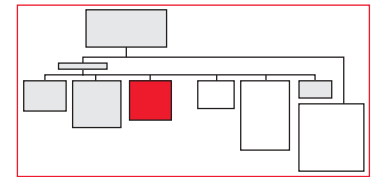
Laparoscopic appendectomy, like all laparoscopic procedures, was formerly considered controversial in the setting of pregnancy [see Laparoscopy in Pregnant Patients, *above*]. Recent studies, however, have demonstrated the safety and utility of laparoscopic appendectomy during pregnancy. Earlier reports suggested that fetal loss was slightly higher during laparoscopic appendectomy, but recent publications suggest that there are similar rates of fetal loss between open and laparoscopic appendectomy.⁴⁶ When the diagnosis of appendicitis is uncertain, a laparoscopic approach can help rule out salpingitis, adnexal mass, or ectopic pregnancy.⁴⁷

For a laparoscopic appendectomy in a pregnant patient, the first trocar (i.e., that for the camera) is placed in the sub-xiphoid area under direct vision via an open technique; this step allows visualization of all pelvic structures and the appendix. Once the appendix has been visualized, the right upper quadrant and right lower quadrant trocars should be placed under direct vision. If the size and position of the uterus make laparoscopic appendectomy difficult or impractical, the camera can be used to help locate the best available spot for an open incision.

Antibiotics should be given preoperatively. Postoperative wound infection can be minimized if adequate attention is paid to aseptic technique and preoperative administration of antibiotics.

INTESTINAL OBSTRUCTION

The incidence of bowel obstruction in pregnant patients ranges



from one in 1,500 to one in 66,000.⁴⁸ The most common cause of small bowel obstruction during pregnancy is adhesions, which account for 55% of cases; volvulus accounts for 25% of cases, with hernia, cancer, and intussusception accounting for the remainder.⁴⁹ As the incidence of operative procedures and the average age of the mother at gestation have risen, the likelihood of adhesive obstruction has risen as well. This problem may be further exacerbated by the hypomotility or dysmotility known to occur during pregnancy. The need for laparotomy and lysis of adhesive bands during pregnancy is extremely low; however, when surgical management is necessary, fetal mortality is 26% and maternal mortality is 5%. With intestinal obstruction, the main concern is to ensure that diagnosis is not delayed. Accordingly, any pregnant patient presenting with nausea, vomiting, and a history of abdominal surgery should be presumed to have a small bowel obstruction until it is proved otherwise.

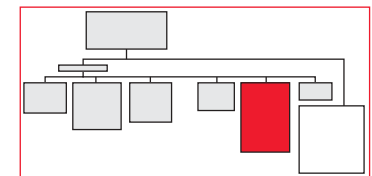
Large bowel obstruction is less common than small bowel obstruction but can be seen more often as the pregnancy progresses. The most common cause of large bowel obstruction is cecal or sigmoid volvulus.

Management

Any sign of bowel ischemia or perforation in a pregnant patient with intestinal obstruction should prompt immediate operation; otherwise, standard conservative management is appropriate. A flat-plate and an upright abdominal film can confirm the diagnosis of small bowel obstruction and rule out free air, with a lower radiation exposure. Use of a CT scan of the abdomen and pelvis early in the course of a possible small bowel obstruction offers little to assist in the management and can be deferred unless there is concern for a closed-loop obstruction or if there has been little progress over a reasonable period of time (24 hours).

SPONTANEOUS VISCERAL RUPTURE

Spontaneous rupture during pregnancy can involve the liver, the kidney, the spleen, or the



esophagus. Spontaneous hepatic rupture during pregnancy is extremely uncommon, occurring no more frequently than in one in 50,000 pregnancies and perhaps as infrequently as one in 250,000 pregnancies.⁴⁹ Typically, it develops in older, multiparous women in the third trimester. Patients present with several days of severe right upper quadrant or substernal pain radiating to the back. The pain may precede the actual rupture by as much as a few days. In some cases of rupture, the patient presents with hypovolemic shock. A right upper

quadrant ultrasonogram often visualizes the rupture or the preceding subcapsular hematoma.

A limited number of renal ruptures have been described in conjunction with hydronephrotic kidneys; they are thought to be secondary to the physiologic hydronephrosis seen in pregnancy. Ultrasonography is the best imaging technique for diagnosis of renal rupture.⁵⁰

Splenic rupture is the most common nonobstetric cause of intra-abdominal hemorrhage during gestation. It usually occurs in conjunction with splenic artery aneurysms or spontaneous capsular rupture. In most cases, it is probably secondary to the increased blood volume and splenic enlargement seen toward the latter part of pregnancy.

Esophageal rupture has also been described, generally in association with heavy vomiting. Patients report sudden epigastric pain on vomiting that may radiate to the back and the chest. X-rays may reveal air in the mediastinum. An upper gastrointestinal series with water-soluble contrast material will demonstrate the site of the rupture. Although esophageal rupture is not more common in pregnancy, it may be associated with the frequent nausea and vomiting seen with hyperemesis gravidarum.

Management

Standard management is recommended for each condition, which often requires prompt institution of volume support followed by emergency surgery and correction of any coagulopathy.

SPLenic AND OTHER VISCERAL ARTERY ANEURYSMS

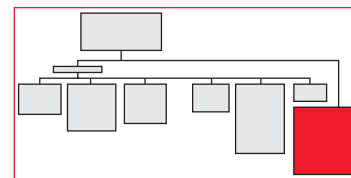
Splenic artery aneurysms are rare, with an incidence of less than 1%. They are, however, four times more common in women than in men, and 25% of all splenic artery ruptures in women occur during pregnancy. Several factors contribute to the relatively high incidence of such ruptures in pregnant women. Splenic arterial pressure is unusually high during pregnancy as a result of the increased cardiac output, the increased blood volume, and the pressure placed on the abdominal aorta and the iliac arteries by the gravid uterus. Pregnancy is also believed to break down the connective tissue component of the arterial wall. Multiparous women in the third trimester are at highest risk for a ruptured splenic artery aneurysm. In the nonpregnant population, splenic artery rupture is associated with a 25% mortality; however, in pregnant women, it is associated with maternal and fetal mortalities ranging from 75 to 95%, mainly as a consequence of erroneous diagnosis. On diagnosis of rupture, immediate operative repair is necessary. If a splenic artery aneurysm larger than 2 cm is found in a woman of childbearing age, elective resection is indicated.⁵¹

Renal artery aneurysms are uncommon, appearing in 0.09% of the population; most are diagnosed incidentally in the course of CT scanning done for other indications. Renal artery aneurysms not only are associated with brittle hypertension but also carry a high mortality when they rupture. Because of the connective tissue laxity that develops during pregnancy, the risk of rupture is higher in pregnant than in nonpregnant women. When renal artery rupture occurs, immediate operative repair of the aneurysm is necessary.

Conditions for Which Medical Management Should Be Attempted

BILIARY TRACT DISEASE

Acute cholecystitis is the second most common



nonobstetric emergency in pregnant women. Symptomatic gallstone disease is far more common in women than in men because of the differential effects of the sex steroids on bile lipid composition and cholesterol saturation. The difference in incidence begins at menarche, increases during the childbearing years, and decreases at menopause. By the age of 75 years, at least 35% of women and 20% of men have gallstones.

Gallstone disease is a result of cholesterol supersaturation and biliary stasis, both of which are promoted by pregnancy.⁵² The elevated estrogen levels during pregnancy increase cholesterol secretion by the liver. Estrogen enhances hepatic cholesterol uptake, increases cholesterol synthesis, and inhibits catabolism of cholesterol to bile acids. High concentrations of cholesterol in the bile overwhelm the solubilizing ability of bile salts, with the result that cholesterol stones form.⁵³ Elevated progesterone levels lead to bile stasis and decreased gallbladder contraction. Progesterone also causes incomplete emptying of the gallbladder after stimulation by cholecystikinin (CCK).⁵⁴ The mechanisms are not understood, but it is thought that progesterone may decrease gallbladder reactivity to CCK. The decrease in small bowel motility that occurs secondary to progesterone elevation may alter enterohepatic circulation and decrease bile acid return to the liver. The balance of bile salts and cholesterol is further altered in such a way as to favor cholesterol supersaturation and stone formation. Pregnancy also alters the pool of bile acids. The decreased percentage of chenodeoxycholic acid and the increased percentage of cholic acid during pregnancy also promote stone formation.

The incidence of biliary sludge and gallstone disease in pregnant women is up to 31% and 3%, respectively, with biliary sludge often resolving in the postpartum period.^{55–57} Of those with gallstones, only 30 to 40% of patients will have symptoms.⁵⁸ Most of these patients have biliary colic that can be managed medically. Fewer than 11% of symptomatic patients progress to a more serious complication (e.g., cholecystitis, choledocholithiasis, or pancreatitis). Cholecystectomy during pregnancy is reserved for recurrent biliary colic or the aforementioned complications. It follows that cholecystectomy is rarely necessary in pregnant patients: it is undertaken once in every 10,000 live births.⁵⁹

The clinical symptoms are similar to those of the nonpregnant patient. Elevated liver function test results indicate that complicated biliary tract disease or choledocholithiasis is likely; however, elevated alkaline phosphatase levels are seen in normal pregnancies and thus are diagnostically unhelpful.

Ultrasonography is the radiologic test of choice, with an accuracy of 97%.⁵² Radionuclide scans are seldom performed as they introduce the risk of fetal exposure to radiation, which often outweighs the potential value of any information to be gained from such a scan.

Management

Conservative management has been the traditional, initial approach to symptomatic gallstones and is successful in the majority of cases, with operative intervention reserved for those who fail medical therapy or have recurrent disease or intractable nausea. If cholecystectomy during pregnancy is necessary but not urgent, it is best to perform the operation in the second trimester: fetal mortality from a first-trimester cholecystectomy can be as high as 12%. The rate of fetal loss decreases through gestation; however, beginning in the third trimester, the risk of preterm labor increases.

Surgical treatment during pregnancy consists of either open or laparoscopic cholecystectomy. The advantages of laparoscopic over open cholecystectomy include earlier recovery, earlier mobility, reduced use of narcotics, smaller incisions, and fewer surgical site infections.²² When carried out with standard precautions, laparoscopic cholecystectomy does not increase the rate of fetal loss (5%) or of spontaneous abortion, nor does it have a greater adverse effect on birth weight, Apgar scores, or the rate of preterm delivery than open cholecystectomy does. Laparoscopic cholecystectomy can be performed safely and effectively throughout pregnancy.⁶⁰

With the introduction of laparoscopic cholecystectomy, there is now a degree of controversy regarding the relative merits of conservative management and aggressive surgical intervention for patients with symptomatic gallbladder disease. In one study using a Markov decision analysis model that took into account all available English data, conservative (nonoperative) management was compared with laparoscopic cholecystectomy.⁶¹ In the conservative management group, the estimated fetal mortality was 7%, and the recurrence rates were 55%, 55%, and 40% for the first, second, and third trimesters, respectively. The rate at which emergency surgery was necessary after nonoperative management was 19.5%. In the laparoscopic group, the estimated fetal mortality was 2.5%. Accordingly, the authors concluded that laparoscopic cholecystectomy was superior to nonoperative management of biliary tract disease in the setting of pregnancy.

In patients with choledocholithiasis, intervention should be performed without delay. The common bile duct (CBD) should be explored by means of endoscopic retrograde cholangiopancreatography (ERCP), with fluoroscopy used economically and lead aprons worn to shield the fetus. ERCP with sphincterotomy successfully addresses choledocholithiasis without increasing fetal mortality or the rate of preterm delivery. Surgical management of choledocholithiasis with open or laparoscopic cholecystectomy and CBD exploration should be reserved for patients in whom ERCP fails.

PANCREATITIS

Pancreatitis is rare during pregnancy, occurring in every 1,000 to 5,000 pregnancies.⁶² Its incidence, like that of gallstone disease, increases with gestational age. Associated gallstone disease is present in 70 to 90% of pregnant women presenting with pancreatitis,^{57,62} although other etiologies can also give rise to pancreatitis in pregnancy: alcohol, hypertriglyceridemia, thiazide administration, and hyperparathyroidism. At present, there is little evidence to suggest

that pregnancy itself is an etiologic mechanism in the development of pancreatitis. Pancreatitis in pregnancy was traditionally regarded as a morbid condition with high maternal and fetal mortality rates, although contemporary series are reporting significant improvements in care.⁶²

The signs and symptoms of pancreatitis in pregnant women are indistinguishable from those seen in the general population. The hallmark of the condition is diffuse abdominal pain combined with hyperamylasemia and lipase elevations.⁶³ Albumin, calcium, and bilirubin levels should be measured and liver function tests performed. The results should be interpreted with caution in light of the alkaline phosphatase elevation known to occur in normal pregnancies. Ultrasonography should be undertaken with the aim of searching for evidence of cholelithiasis and choledocholithiasis. Visualization of the inflamed pancreatic head may be informative; however, this structure is often difficult to locate.

Management

Treatment should be aimed at correction of the hypovolemia that invariably accompanies pancreatitis. Restriction of oral intake is necessary. In cases of intractable nausea, a nasogastric tube should be placed. Antibiotics should be reserved for treatment of a specific infectious complication. Calcium levels should be kept within the normal range. Arterial blood gases should be monitored as indicated. Prolonged pancreatitis may necessitate lengthy periods of bowel rest. During extended periods without oral feeding, pregnant women should be maintained on total IV hyperalimentation.⁶⁴

In patients with pancreatitis caused by extrahepatic biliary obstruction, endoscopic management has achieved excellent results. ERCP and sphincterotomy can both be performed safely during pregnancy.

Although the standard of care for nonpregnant patients with biliary pancreatitis is to undergo a cholecystectomy within 2 weeks of their attack, operative intervention in pregnant patients has been traditionally postponed to the postpartum period.

In a series from our own institution, 21 pregnant patients with acute biliary pancreatitis who were treated conservatively and for whom surgery was deferred had a recurrence rate of 50%, ultimately requiring a cholecystectomy during their pregnancy. Accordingly, we recommend a laparoscopic cholecystectomy after such attacks. Given that in the first trimester, loss of the fetus is common, the surgery can be deferred to the second trimester. Routine intraoperative cholangiography is not indicated unless there are indications for bile duct stones.

Although unusual, pseudocyst formation has been reported in pregnant women. It is managed conservatively, without operative intervention. Laparotomy, débridement, drainage, and cholecystectomy are indicated for severe cases with pancreatic necrosis.

PEPTIC ULCER DISEASE

During pregnancy, symptoms of upper abdominal pain, nausea, and vomiting are common, which may also be consistent with peptic ulcer disease. In general, however, women with peptic ulcer disease usually experience symptomatic improvement during pregnancy. Elevated estrogen levels are

The diagnosis is made in much the same way in pregnant patients as in nonpregnant ones, except that physicians treating pregnant women should rely more on clinical information and less on radiologic intervention. Intractable pain that is not relieved by the usual therapeutic interventions should prompt endoscopic evaluation with a tissue biopsy for *Helicobacter pylori* culture, which is treated accordingly.

Surgery is also indicated if significant hemorrhage—necessitating transfusion of more than 6 units over a 24-hour period—is observed. In this setting, maternal mortality is 14% after operation; however, it is 44% if surgical treatment is not provided.⁶⁵

IBD has a peak incidence in the age group that is of child-bearing age. Although pregnancy does not affect the severity of either ulcerative colitis or Crohn disease to any great degree, a third of patients tend to have a flare-up during their pregnancy.⁶⁶ Although in population-based studies, there is an increase in the risk of adverse pregnancy outcomes in patients with IBD, there appears to be no correlation with the severity of disease flare and pregnancy outcomes.⁶⁶⁻⁶⁸ If the pregnant patient, however, requires inpatient aggressive therapy and surgical intervention, the incidence of preterm labor is increased, with the newborn weighing significantly less than controls.⁶⁹

Management

ahead of any attempt at conception. The treatment objective is to maintain remission and avoid flare-ups that would require administration of toxic agents.⁶⁶ Both steroids and sulfadiazine have been reported to cause congenital malformations in animal studies; however, because of the increased risk of fetal and maternal mortality in untreated cases of IBD, it is recommended that steroids and sulfadiazine be administered together as necessary to minimize the active effects of the disease.⁷⁰

If the disease does not respond to medical management, operative intervention may be undertaken, but only as a last resort. In patients with ulcerative colitis, the most common indication for operation is toxic megacolon, which, if left untreated, can cause significant infant and maternal mortality. In patients with Crohn disease, the uncommon problems of abscess, fistula formation, and bowel obstruction may force operation; these conditions should be treated in the usual fashion. Greater reliance should be placed on fecal diversion in pregnant patients because of the increased risk of anastomotic dysfunction. Active Crohn disease may necessitate complete bowel rest and maintenance of nutrition by central IV feedings.

In any pregnant patient with IBD, particularly Crohn disease, the mode of delivery must be carefully considered. If the patient has active Crohn disease with rectal involvement, vaginal delivery may be contraindicated so as to avoid the potential consequence of rectovaginal fistula formation.

Patients with ulcerative or granular proctitis should not receive systemic treatment with steroids or sulfadiazine, because of the potential toxicity to the fetus. Steroid enemas or enemas concocted from an elixir preparation of sulfasalazine may be administered. Low-residue diets may help control particularly bothersome symptoms.

The incidence of heart disease during pregnancy is 1.5%, with rheumatic heart disease accounting for 60 to 75% of cases.⁷¹ The current trend in the United States, however, is that fewer pregnant women are presenting with rheumatic heart disease and more are presenting with congenital heart disease.⁷² Heart disease becomes an active issue during pregnancy because gestation places great stress on the cardiovascular system: cardiac output increases by 30 to 50%, HR by 15 to 20 beats/min, and plasma volume by 50%. Delivery places added stress on the heart as a result of physical exertion, pain, and drastic fluid shifts. There is some blood loss with delivery, but there is also an increase in venous return resulting from the release of the pressure imposed by the gravid uterus on the inferior vena cava. In addition, excess extracellular fluid is drawn into the vasculature after delivery. If the diseased heart has little reserve, pregnancy can push the patient into florid heart failure. Recognition of heart failure may be delayed because normal pregnant patients typically present with peripheral edema, dyspnea, and poor exercise tolerance.

Ideally, women of childbearing age who have heart disease should receive counseling before planned conception. Such counseling should address the risks of pregnancy, the issues related to anticoagulation, and the fetal mortality and morbidity associated with specific clinical situations. Any significant congenital heart condition should be corrected before pregnancy if possible.

MALIGNANCIES DURING PREGNANCY

Cancer during pregnancy occurs in 0.07 to 0.1% of births.⁷³ The types most commonly encountered in this setting are breast cancer (19%), thyroid cancer (17%), cervical cancer (11%), Hodgkin disease (7%), and ovarian cancer (6%).⁷⁴ All cancers except for melanoma and hematologic tumors metastasize to the placenta but not to the fetus.⁷⁵ The major risk factor for malignancy during pregnancy is age greater than 40 years. Pregnant women with malignancies are more likely to experience complicated hospitalizations, as are their babies. Malignancy during pregnancy also increases the chances of low birth weight and premature labor.⁷⁴

The measures commonly employed to treat cancer—surgery, irradiation, and chemotherapy—all pose significant risks to the fetus, especially in the first trimester. The degree of risk associated with operation depends not only on the gestational age but also on the disease, the stage of the cancer, and the nature of the procedure. Chemotherapy during the first trimester can cause fetal malformations, premature delivery, and restricted fetal growth in as many as 25% of cases; however, chemotherapy during the second and third trimester generally has a favorable long-term outcome.⁷⁶ Finally, any radiation therapy administered is likely to exceed the safety threshold for fetal radiation exposure.

Breast Cancer

Pregnancy-associated breast cancer is defined as cancer diagnosed during pregnancy or up to 1 year after delivery. It is associated with a worse outcome than other types of breast cancer are. The poorer prognosis may be attributable to aggressive tumor growth in response to hormones of pregnancy. In addition, diagnosis of pregnancy-associated breast cancer is often delayed because of the normal hypertrophic thickening of the breast during pregnancy, the inability of mammography and ultrasonography to differentiate between normal breasts and breasts with malignancies in pregnant women, or the reluctance of surgeons to perform biopsies during pregnancy.⁷⁷

Management of breast cancer in pregnant patients does not vary greatly from that in nonpregnant patients. Once the diagnosis of breast cancer is made, modified radical mastectomy should be done expeditiously; it should not be delayed because of the pregnancy.⁷⁷ Given the high doses required, radiation therapy is contraindicated during pregnancy. Accordingly, lumpectomy with radiation therapy is an option only if radiation therapy can commence after delivery. As noted, chemotherapy is relatively safe during the second and third trimesters. For patients with stage III or IV breast cancer, termination of pregnancy may be considered to allow unrestricted treatment with chemotherapy and radiation. For all patients, treatment plans should be formulated on an individual basis, taking into account the risks facing both the fetus and the mother.

BURNS DURING PREGNANCY

Burns occurring during pregnancy should be evaluated in the same manner as burns occurring in the nonpregnant population. The total body surface (TBS) burned should be measured and documented (ideally with photographs).

Adjustments must be made for the increased abdominal surface area seen in the later stages of gestation. Fetal outcome is dependent on the mother's condition: fetal mortality is 89% when the mother has burns over more than 50% of her TBS but falls to 21% when the mother has burns over less than 50% of her TBS.⁷⁸

Management

Generally, burns are treated in much the same way in pregnant patients as in nonpregnant patients; however, special attention should be paid to securing the airway and ensuring adequate breathing. Because pregnant patients have a lower FRC, they are less able to compensate for hypoxia. Moreover, exposure to burns often puts the mother at risk for carbon monoxide inhalation. The fetus is especially susceptible to carbon monoxide poisoning because fetal hemoglobin has a higher affinity for carbon monoxide than maternal hemoglobin does; thus, carbon monoxide can easily lead to fetal hypoxia. Silver sulfadiazine cream should not be used near term because of its association with kernicterus in the infant. Finally, if the fetus is older than 24 weeks and the mother sustains burns over 50% or more of her TBS, cesarean section is indicated.

Electrical accidents are associated with a fetal mortality of 50%. Any woman who has experienced electric shock should undergo serial ultrasonography until delivery. Maternal mortality with such injuries is minimal.

Minor Surgical Problems of Pregnancy

CONSTIPATION

Increased levels of sex steroid hormones during pregnancy are thought to produce decreases in smooth muscle motility and subsequent functional decreases in bowel motility. Moreover, the pressure exerted on the bowel by the expanded and displaced uterus is thought to interfere with normal peristaltic activity.

Management

Stressing good bowel care and bowel training is helpful. Nonpharmacologic methods of increasing bowel activity, such as increasing the fiber and roughage in the diet to maximize stool bulk, are also useful. Foods with laxative properties, such as prunes, figs, apples, and citrus fruits, may facilitate stool passage. The patient should take at least eight to 10 extra glasses of fluid a day; water is preferable, but non-caffeine-containing liquids are also acceptable. Increased exercise may help in the passage of stool. A bulk laxative (e.g., Metamucil) or a stool softener (e.g., Colace) should be prescribed, regardless of whether the natural roughage foods are effective. Mild laxatives may be given when all other measures are inadequate. Small doses of magnesium hydroxide (Milk of Magnesia) and similar osmotic reactive laxatives are useful. Small amounts of mineral oil may be cautiously administered; prolonged use of mineral oil can cause liver degeneration and interferes with the absorption of fat-soluble vitamins.

HEMORRHOIDS

Nearly 10% of obstetric patients have hemorrhoids at some point during their pregnancy.⁷⁹ The development of

hemorrhoids during pregnancy results from the decreased motility and the tendency toward constipation that occur in all pregnancies. These changes lead to straining at stool, during which the shearing force generated in the rectal canal can exacerbate and intensify preexisting hemorrhoid disease. Furthermore, the weight and pressure of the uterus itself tend to decrease venous return and increase the amount of pooling in vascular structures in the lower pelvis. Hemorrhoids can present with itching, bleeding, or severe pain if the hemorrhoids thrombose.

Management

The best method of preventing hemorrhoids is to maintain adequate bowel function; when that is not feasible, the following general measures should be taken:

1. Warm sitz baths
2. A local astringent, such as a Tucks pad or witch hazel
3. Supine positioning with the legs elevated whenever that is possible
4. Manual replacement of the hemorrhoids after each bowel movement, regardless of the pain incurred
5. Astringent suppositories or creams, such as Anusol or Anusol HC
6. Minimization of constipation (see above)

Acutely thrombosed hemorrhoids should be incised with the patient under local anesthesia; the clot should be evacuated, astringent ointments applied, and bowel care resumed.

Surgery is seldom indicated. In a study of 12,455 pregnant women, only 25 required surgical excision of the symptomatic tissue, which was done under local anesthesia. There were no maternal or fetal problems as a result of the procedure.⁸⁰

VARICOSE VEINS

Varicosities become a problem with successive pregnancies. Generally, they are only a minor nuisance in the primipara but become more bothersome the more children a woman has. Thrombophlebitis is not uncommon, but embolism is a rare complication. Varicose veins develop in women who are predisposed to this problem as a result of weakness in the valvular structures in the veins. The increased stasis and venous pressure created by the expansion of the uterus lead to progressive enlargement and engorgement of the veins. Besides cosmetic problems, varicosities can cause muscle aching, swelling, and, in severe cases, ulceration.

Management

Increased exercise that includes regular walking and activity is suggested. Elevation of the legs at rest is advised; prolonged sitting is not. Support stockings and, in poor weather, support panty hose should be used. The stockings should be placed on the legs in the early morning, before substantial pooling has occurred. Injection therapy is contraindicated during pregnancy. Ligation of veins causing ulceration or phlebitis is recommended only in extreme cases.

DEEP VEIN THROMBOSIS

Pregnant women are more prone to deep vein thrombosis (DVT) during the later stages of pregnancy and the early postpartum period, largely because of alterations in the

normal blood coagulation system, such as increased levels of clotting factors and decreased fibrinolytic activity. These intrinsic factors may be exacerbated by the venous stasis and increased blood viscosity that occur during pregnancy. Compression of the iliac veins by the growing uterus also predisposes pregnant women to thrombosis. Although venous thrombosis affects only 4.1% of women during pregnancy,⁸¹ recognition and management of the disorder are important to prevent the potentially life-threatening sequelae of pulmonary embolism. The risk of DVT is increased fivefold postpartum.

Real-time B-mode ultrasonography is an extremely sensitive examination that is useful in detecting DVT. This technique achieves good visualization of venous thrombi within vessels; however, although it can readily visualize clots in leg veins, it is less specific above the inguinal ligament. Noninvasive screening is not useful during pregnancy because of the high false positive and false negative rates; it is not uncommon for DVT to occur immediately after a screening examination. Radioactive fibrinogen should not be used near term, because of the potential hazard to the fetal thyroid.

Management

When the diagnosis is made, therapy with a low-molecular-weight heparin (LMWH) should be instituted for the duration of pregnancy, with postpartum anticoagulation, in the form of an LMWH or warfarin, continued for 6 weeks. LMWH doses should be adjusted according to weight and thus may increase throughout pregnancy and decrease after delivery. Therapeutic anti-factor Xa levels typically range from 0.5 to 1.2 mg/dL. Current experience with LMWHs suggests that they are as efficacious and safe as unfractionated heparin.⁸² In addition, LMWHs have certain advantages over unfractionated heparin: once-daily or twice-daily subcutaneous administration, a predictable dose response, reduced passage across the placenta, and lower incidences of heparin-induced thrombocytopenia and heparin-induced osteoporosis. Warfarin should not ordinarily be given for maintenance anticoagulation: it has teratogenic potential during the first trimester and may induce bleeding during the latter part of pregnancy.

ROUND LIGAMENT PAIN

The general surgeon is occasionally asked to evaluate the pregnant woman in the late stages of her pregnancy with a possible inguinal hernia. Groin hernia in the pregnant patient is extremely uncommon because the expanded uterus acts as a shield against the abdominal wall, preventing incarceration or strangulation of bowel contents. Groin pain is generally caused by excessive traction on the round ligament, usually on the left, during the latter part of pregnancy. As the uterus rotates and the patient's position changes, this pain can become quite severe.

Management

Local heat and abdominal support are the mainstays of treatment. Positional changes are necessary, and the patient should rest in the supine position.

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Acknowledgment

Figure 1 Carol Donner

4 UROLOGIC CONSIDERATIONS FOR THE GENERAL SURGEON

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An understanding of the urogenital system is a necessary component of general surgical education. Specifically, surgeons must be aware of the anatomic, physiologic, and pathologic features of urologic processes. Accordingly, in this chapter, we review the key features of genitourinary anatomy and discuss urologic problems that are commonly encountered by the general surgeon, including urologic trauma, iatrogenic injuries to the urogenital system, urologic malignancies, and benign prostatic hyperplasia (BPH).

Anatomic Considerations

KIDNEY AND URETER

The kidneys are obliquely placed on either side of the spine, deep within the retroperitoneum,¹ with the upper poles slightly more medial than the lower poles. On top of each kidney sits an adrenal gland, and these two structures are jointly surrounded by a perinephric fascial layer known as Gerota fascia (an important anatomic structure that can act as a barrier to contain renal pathologic processes). The anterior and posterior leaves of Gerota fascia, which extend anterior and posterior to the kidney, become fused around the kidney on three sides: laterally, medially, and superiorly. Inferiorly, however, Gerota fascia remains an open potential space, containing the ureter and the gonadal vessels on either side. Gerota fascia is surrounded by retroperitoneal fat.

A clear understanding of the position of the kidneys in the retroperitoneum is vital for surgical exploration. Generally, the right kidney is situated slightly lower than the left kidney, as a consequence of the mass effect of the liver; however, the positions of the kidneys vary somewhat with respiration. Posteriorly, the right and left kidneys have similar relations with adjacent structures. The diaphragm and the pleural reflections cover the upper posterior aspect of each kidney, and the 12th rib crosses the upper pole. On the left side, the 11th rib is directly posterior to the upper aspect of the kidney. The quadratus lumborum and the transversus abdominis aponeurosis cover the posterior surface, and the renal hilum lies against the psoas muscle. Anteriorly, the left kidney is in contact with the adrenal gland, the spleen, the stomach, the pancreas, the jejunum, and the splenic flexure of the colon [see Figure 1]. The anterior surface of the right kidney is covered to a large extent by the liver. The inferior portion of the right kidney is covered by the hepatic flexure, and the hilum is covered by the duodenum. It is important to recognize the

planes between Gerota fascia, the peritoneum, and the retroperitoneal organs.

Each kidney is supplied by a renal artery and drained by a renal vein. The renal arteries typically branch off the aorta just below the superior mesenteric artery at the level of the second lumbar vertebra, and the renal veins meet the vena cava at the same level. The left renal vein passes in front of the aorta and lies most anteriorly in the renal hilum. Behind the vein lies the renal artery, and the renal pelvis lies most posteriorly. Although, in general, there is one renal artery and one renal vein for each kidney, anatomic variations are common. The most common variation (occurring in 23 to 49% of persons) is the presence of supernumerary renal arteries arising from the lateral portion of the aorta.²⁻⁷ Whereas there is extensive collateral circulation for the renal veins, the renal arteries are end arteries. Consequently, injury to the main renal artery or an accessory artery typically results in the loss of renal parenchyma. On the right side, the adrenal and gonadal vein drain directly into the vena cava; on the left side, these vessels drain into the renal vein [see Figure 2].

The renal collecting system includes the minor calices, the major calices, the renal pelvis, and the ureter. The ureter connects the renal pelvis to the bladder, and its role is to propel urine toward the bladder by means of peristalsis. The normal adult ureter is 22 to 30 cm long, and it exhibits three distinct narrowings as it travels through the abdomen and the pelvis: one at the ureteropelvic junction, one at the pelvic brim as it crosses over the iliac vessels, and one at the ureterovesical junction. For the purposes of surgical or radiographic description, the ureter is commonly divided into discrete segments. In surgical terms, the portion of the ureter that runs from the renal pelvis to the iliac vessels is the abdominal ureter, and the portion that runs from the iliac vessels down to the bladder is the pelvic ureter. In radiographic terms, the portion of the ureter that runs from the renal pelvis down to the upper border of the sacrum is the proximal ureter, the portion that runs from the upper border of the sacrum to the lower border is the medial ureter, and the portion that runs from the lower border of the sacrum down to the bladder is the distal ureter.

The ureter receives its blood supply from multiple branching vessels along its course. The proximal ureter is supplied medially by branches from the renal artery, the medial ureter is supplied medially by branches from the gonadal artery and the aorta, and the distal ureter is supplied laterally by branches from the common and internal iliac arteries. The arterial vessels then course longitudinally within the periureteral

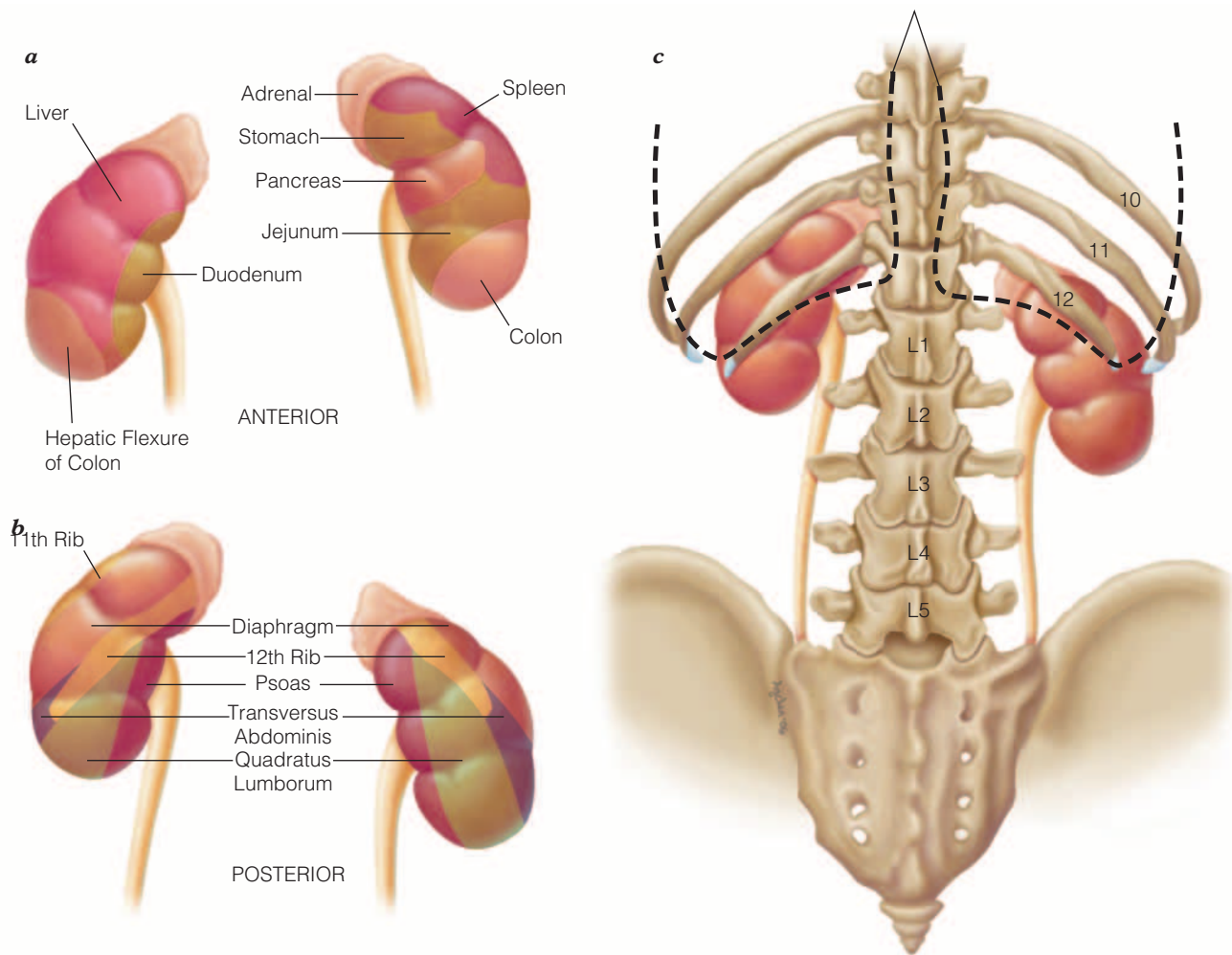


Figure 1 Shown are the anatomic relations of the kidneys to (a) the abdominal organs anteriorly, (b) the body wall muscles and the ribs posteriorly, and (c) the pleural reflections and the skeleton posteriorly.

adventitia in an anastomosing plexus that can be extensively mobilized as long as it remains intact.

Posteriorly, the ureter runs along the psoas muscle to the point where the muscle crosses over the iliac vessels near the bifurcation of the common iliac arteries. Anteriorly, the right ureter is in contact with the ascending colon, the cecum, the appendix, the terminal ileum, and the corresponding mesenteries. The left ureter is in contact with the descending colon, the sigmoid colon, and the corresponding mesenteries. It is important to recognize that when these anterior structures are reflected during operation, the ureter tends to adhere to them rather than remain adherent to the psoas muscle. In women, specific attention must be paid to the status of the ureter at the pelvic brim, where it may be in contact with the fallopian tube and the ovary. Attention should also be paid to the uterine arteries, which cross anterior to the ureters near the cervix.

BLADDER

The bladder is a hollow organ that stores and expels urine. The normal adult bladder has a capacity of 400 to 500 mL.

When empty, the bladder rests in the pelvis behind the pubic symphysis. As it fills, the bladder rises above the pubic bone, and if it is quite distended, it may be palpated in the lower abdomen.

The bladder is anatomically related to many other anatomic structures. Anteriorly, the bladder is tethered to the abdominal wall by the median umbilical ligament (i.e., the obliterated urachus). In rare cases, adenocarcinoma may develop in the urachal remnant; in other cases, the connection may remain patent and predispose to infection or drainage from the umbilicus. The superior aspect of the bladder is covered by a peritoneal layer that sweeps down from the anterior abdominal wall to meet the peritoneum covering either the anterior rectum (in males) or the uterus (in females). Laterally, the bladder is separated from the pelvic side walls by loose connective tissue and both retropubic and perivesical fat. In males, the base of the bladder is adjacent to the seminal vesicles, the ampullae of the vasa deferentia, the distal ureters, and the rectum. In females, the uterus and the vagina are interposed between the bladder and the rectum.

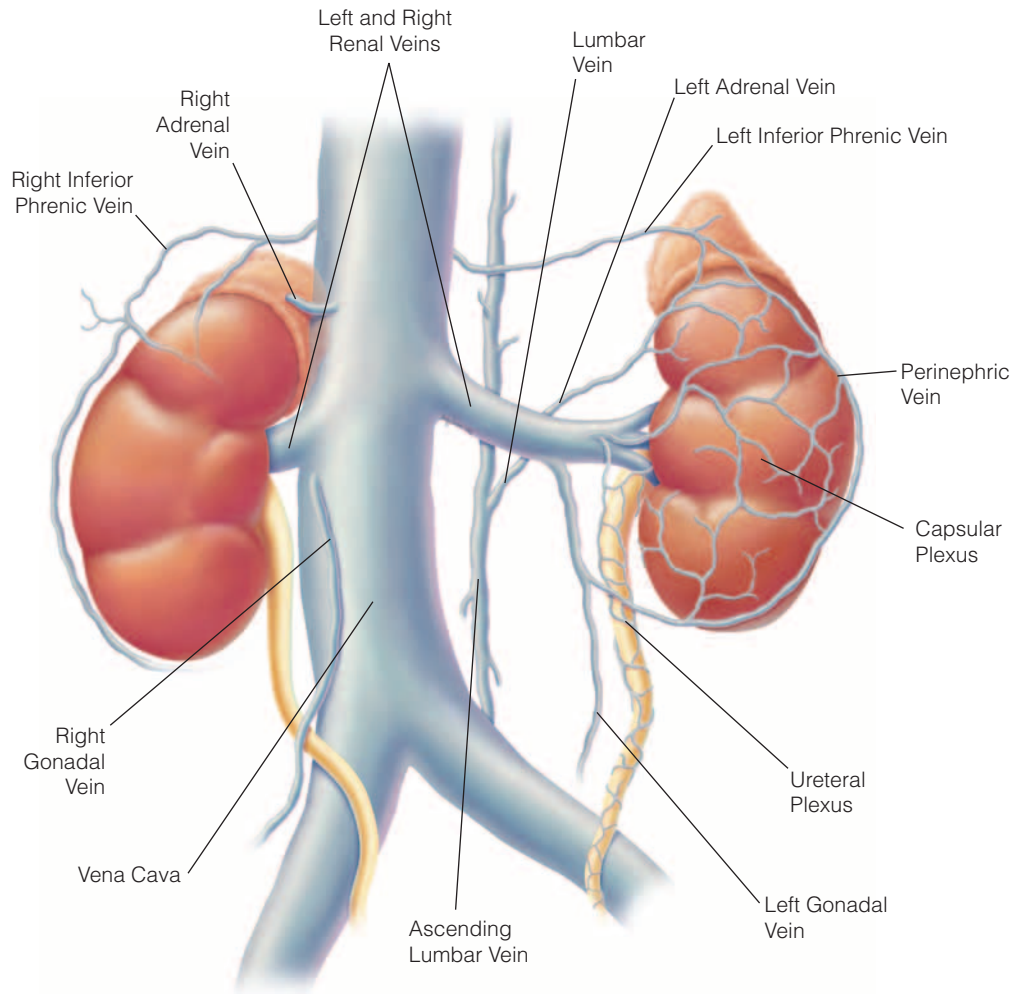


Figure 2 Illustrated is the venous drainage of the kidneys.

The bladder is very well vascularized and thus may be mobilized or partially resected without compromise of the blood supply. Most of the bladder's blood supply comes from the superior, middle, and inferior vesical arteries, which branch off from the anterior trunk of the internal iliac artery. In females, the bladder is further supplied by branches of the vaginal and uterine arteries. The veins of the bladder come together to form several plexuses that drain into the internal iliac veins.

PROSTATE AND SEMINAL VESICLES

The prostate and the seminal vesicles produce constituents of the ejaculate. The normal prostate weighs between 18 and 20 g and is composed of glandular elements and fibromuscular stroma. Toward the apex, the prostate is tethered to the pubic bone by the puboprostatic ligaments. Laterally, the prostate is in direct contact with the pubococcygeal portion of the levator ani and is related to its overlying endopelvic fascia. Posteriorly, the prostate is separated from the rectum by the two layers of Denonvilliers fascia. The prostate can be divided into transitional, central, and peripheral zones, and an anterior fibromuscular stroma extends from the bladder neck to the striated urethral

sphincter. The transitional zone is the area that gives rise to BPH, which can cause increased urinary resistance and voiding symptoms. The peripheral zone makes up the bulk of the prostate tissue and is the area where the majority of prostate cancers arise.

The seminal vesicles are about 6 cm long and lie in contact with the base of the bladder. Each seminal vesicle joins the ipsilateral vas deferens to form the ejaculatory ducts, which exit the prostate at the verumontanum (i.e., the colliculus seminalis).

The prostate and seminal vesicles are supplied by the inferior vesical, internal pudendal, and middle rectal arteries; the seminal vesicles are also supplied by the vesiculodeferential artery, a branch of the superior vesical artery.

PENIS AND URETHRA

The penis is composed of three bodies: the two corpora cavernosa, which are responsible for erectile function, and the corpus spongiosum, which contains the urethra and is contiguous with the glans. Individually, these bodies are covered by a dense fascial layer known as the tunica albuginea; together, they are covered by a thick layer of Buck fascia. If one or more of the penile bodies is torn, the bleeding will be

contained in Buck fascia, and ecchymosis will be limited to the penile shaft.

The penis is supplied by the common penile artery, which is the terminal branch of the internal pudendal artery. This vessel travels through the Alcock canal and terminates in three branches: the bulbourethral artery, which supplies the urethra, the corpus spongiosum, and the glans; the deep artery, which travels within the corpus cavernosum and supplies the cavernous sinuses; and the dorsal artery, which runs in the neurovascular bundle beneath Buck fascia and supplies the corpus spongiosum and the urethra.

The male urethra is approximately 20 cm long and can be divided into four anatomic sections: the prostatic urethra, the membranous urethra, the bulbous urethra, and the penile urethra. The sphincteric mechanism is located in the membranous urethra. The female urethra is approximately 4 cm long and travels from the bladder neck below the pubic symphysis to open anterior to the vagina.

TESTES

The testes have two important functions: spermatogenesis and production of testosterone. Each testis is approximately 20 mL in size and is surrounded by tunica albuginea, which projects inward to form the mediastinum testis.

The testis is supplied by the gonadal or testicular artery, the vasal artery, and the cremasteric artery. The gonadal artery arises from the aorta, just below the renal artery, and courses through the spermatic cord to the testis; the vasal artery is a branch of the superior vesical artery; and the cremasteric artery branches off from the inferior epigastric artery. At the level of the internal ring, these three arteries are in close proximity, and particular care must be taken to keep from injuring them. Venous outflow is provided by the gonadal vein. The right gonadal vein empties into the inferior vena cava below the renal vein, and the left gonadal vein empties directly into the left renal vein.

Urologic Injuries

UROGENITAL TRAUMA IN PATIENTS WITH MULTIPLE INJURIES

Urologic injuries are common when multiple organ systems are damaged, occurring in about 10% of cases of major trauma. Although the majority of injuries to the urogenital tract are not life-threatening, they can result in substantial morbidity if they are not promptly diagnosed and treated. Accordingly, a surgical team treating a patient with multiple injuries must always keep in mind the possibility of concomitant urogenital trauma so that any urologic injuries found can be addressed in a timely manner.

Initial evaluation and resuscitation are generally carried out by an emergency department physician and a trauma surgeon; however, it is important that a urologist be involved as well. Assessment should proceed as outlined by advanced trauma life support (ATLS) protocol. The presence of gross hematuria, flank ecchymosis, rib fractures, pelvic fractures, or blood at the urethral meatus should raise the level of concern for urologic injury and serve as an indication for an expeditious urologic consultation.

Management of urologic trauma is addressed in more detail elsewhere [see 7:11 *Injuries to the Urogenital Tract*].

IATROGENIC INJURY TO THE UROGENITAL TRACT

Ureter

The majority of injuries to the ureter are iatrogenic. Iatrogenic ureteral injuries may be sustained during any open or laparoscopic procedure in the abdomen or the pelvis and may result from transection, ligation, laceration, resection, crushing, or ischemia. Such injuries are most likely to occur during gynecologic procedures; they also occur during general surgical and urologic procedures and, rarely, during orthopedic⁸ and vascular procedures.⁹ The ureter is most vulnerable to iatrogenic injury at several anatomic locations: at the pelvic brim, where gonadal and ovarian vessels cross; lateral to the uterus, where the ureter crosses under the uterine artery; over the iliac vessels, near the apex of the obturator foramen; and at the insertion of the trigone.

Although most ureteral injuries occur during routine, uncomplicated surgical procedures in which the pelvic anatomy appears normal,¹⁰ the likelihood of such injuries is increased by the presence of conditions that disrupt the architecture of the ureter, such as a large mass, a malignancy, inflammatory disease, endometriosis, a previous operation, irradiation, and congenital abnormalities. Increased blood loss, longer operating times, increased transfusion requirements, and longer hospitalizations are all associated with ureteral injury.^{11,12}

The best way of preventing iatrogenic ureteral injury is to clearly identify the ureter in the surgical field and in those regions where it is most susceptible to injury. Every attempt should be made to limit bleeding and to avoid placing sutures or using the electrocautery in areas where exposure is poor.

Placement of ureteral stents at the beginning of the procedure may facilitate identification of the course of the ureter. A 5-year review of prophylactic ureteral catheterization in patients undergoing colon surgery concluded that whereas stents did not prevent ureteral injuries, they could help surgeons recognize such injuries more quickly.¹³ Accordingly, the authors recommended stenting in patients at high risk for ureteral injury. A subsequent study from another group also recommended the use of stents in doubtful cases, on the grounds that prevention is better than treatment.¹⁴ Other authors, however, have argued that prophylactic ureteral stents are not without risk and have not affected the rate of ureteral injury.¹⁵ Prophylactic ureteral stenting continues to be a controversial practice.

Bladder

The bladder is the genitourinary organ that is most frequently injured during an operation.¹⁶ Fortunately, the bladder is very forgiving of incidental injuries, and most such injuries are recognized intraoperatively, when they can easily be repaired with a two-layer closure using absorbable sutures. Bladder injury should be suspected when, during an operation, the Foley catheter is exposed, a laceration is noticed, urinary extravasation is present, urine in the Foley catheter becomes bloody, or (in the case of a laparoscopic procedure) gas begins to escape through the Foley catheter. Most patients have an identifiable predisposing factor that complicates the

operation. Typically, this factor is previous surgery or inflammation, although bladder injuries resulting from surgery performed vaginally or laparoscopically do not seem to have a predisposing cause. The incidence of laparoscopic bladder injuries reportedly ranges from 0.02 to 0.3%.¹⁷ Foley catheter drainage is maintained for 1 to 2 weeks after repair, and the resulting success rates are quite high.

Urologic Malignancies

RENAL CELL CARCINOMA

It is currently estimated that deaths attributable to cancer of the kidney and the renal pelvis in 2009 account for approximately 3% of all cancer deaths in the United States,¹⁸ and the annual incidence of renal cell carcinoma (RCC) continues to rise.¹⁸ Moreover, in 22% of patients, despite improvements in imaging and detection, the cancer will have already metastasized at the time of diagnosis.¹⁹ Approximately 85% of kidney cancers originate in the parenchyma; the remaining 15% are transitional cell carcinomas and develop in the collecting system.

In most instances, RCC is diagnosed incidentally during an imaging procedure that is performed to address some other problem. The classic triad of flank pain, hematuria, and a palpable abdominal mass is present in as many as 10% of cases.²⁰ Patients may present with symptoms related to paraneoplastic manifestations, such as cachexia and fever (caused by cytokines), renin-mediated hypertension, nephropathy from immunoglobulin formation, hypercalcemia, cytokine-induced myelosuppression, polycythemia related to erythropoietin production, amyloidosis, or Stauffer syndrome (nonmetastatic hepatic dysfunction). Paraneoplastic symptoms tend to disappear once localized disease is treated.

All patients with hematuria (gross or microscopic) or a renal mass should undergo further evaluation. Prompt initial evaluation of a renal mass consists of contrast evaluation of the kidneys and the ureters (with either triple-phase computed tomography [CT] or magnetic resonance imaging with or without gadolinium). Patients with hematuria should undergo cystoscopy as well. No further assessment is required for simple cysts. Renal masses evaluated by means of CT are classified according to the Bosniak system, which correlates the appearance of the mass with the risk of malignancy [see Table 1].²¹ Bosniak classes I, II, III, and IV roughly correspond to cancer risks of less than 2%, less than 12%, 52%, and greater than 90%, respectively.^{22–28} The evaluation of a patient with a renal mass also includes a complete history, a physical examination, liver function tests, a comprehensive metabolic panel, and a chest x-ray.

If imaging identifies invasion into the renal vein or a tumor thrombus, further assessment (by means of venography, magnetic resonance angiography or venography, or CT reconstruction) aimed at determining the extent of vena cava involvement is necessary for surgical planning. Traditionally, routine biopsies of kidney masses produce high false negative rates and tend to yield nondiagnostic results. Biopsies were usually reserved for cases with a possibility of metastasis from another primary cancer or in accordance with the protocol for minimally invasive treatment alternatives (e.g., cryoablation and radiofrequency ablation). Recent studies, however, show

Table 1 Bosniak System for Classification of Renal Cysts²¹

Category	Cyst Characteristics
I	Benign simple cyst with hairline-thin wall that has no septa, calcifications, or solid components; cyst has density of water and does not enhance
II	Benign cyst that may contain a few hairline-thin septa in which perceived (but not measurable) enhancement may be present; wall or septa may contain fine calcification or short segment of slightly thickened calcification; category includes uniformly high-attenuation lesions < 3 cm (“high-density cysts”) that are well margined and do not enhance; no further evaluation required
IIF	Cyst that may contain multiple hairline-thin septa or minimal smooth thickening of wall or septa; wall or septa may show perceived enhancement; calcification may be present in wall or septa that may be thick and nodular, but without measurable enhancement; lesions are generally well margined; category includes intrarenal nonenhancing high-attenuation lesions > 3 cm; follow-up studies required to confirm benign status
III	Indeterminate cystic mass with thickened irregular or smooth walls or septa that show measurable enhancement; surgical management required, although some lesions will prove benign (e.g., hemorrhagic cysts, chronically infected cysts, multiloculated cystic nephromas) and others malignant (e.g., cystic and multiloculated cystic RCCs)
IV	Clearly malignant cystic mass that can have all criteria of category III but also contain enhancing soft tissue components adjacent to (but independent of) wall or septa; category includes cystic carcinomas; surgical removal required

F = follow-up; RCC = renal cell carcinoma.

improvement in diagnostic accuracy in percutaneous renal biopsies (up to 97% sensitivity and 100% specificity).²⁹ With the incidence of renal cancer rising, especially in tumors smaller than 4 cm, some physicians are recommending CT-guided biopsy of all small renal masses to confirm malignancy and guide treatment.³⁰ Staging is a well-established predictor of prognosis. The TNM staging system developed by the American Joint Committee on Cancer (AJCC) has been widely used for prognostic purposes in RCC patients. In a European study, the 5-year and 10-year disease-specific survival probabilities were 95.3% and 91.4% for TNM stage pT1a RCC, 91.4% and 93.4% for stage pT1b disease, and 81.6% and 75.2% for stage pT2 disease.³¹ In another study, the 5-year disease-specific survival probabilities were found to be significantly worse for more advanced RCC: 67% for TNM stage III disease and 32% for stage IV disease.³² In the past few years, various other prognostic factors have been validated that are not included in the TNM staging system, including tumor grade, histologic subtype, sarcomatoid features, histologic tumor necrosis, collecting system invasion,

and performance status.³³ Accordingly, many institutions are now using a more comprehensive staging system for RCC.

Surgical extirpation (open or laparoscopic) remains the mainstay of treatment for localized RCC as standard chemotherapeutics and radiation have little efficacy. Immunotherapies typically yield poor response and durable cure rates.³⁴ Historically, treatment has been radical nephrectomy. This procedure involves removal of the entire kidney and the fat within Gerota fascia. To preserve adrenocortical function, ipsilateral adrenal sparing is performed. The benefit of routine adrenalectomy in this setting is extremely limited, especially in patients with small lesions and low-stage disease.³⁵ Nephron-sparing surgery (NSS or partial nephrectomy) has been shown to provide excellent oncologic and functional outcomes at 10 years or longer.³⁶ Several reports have shown that NSS provides equivalent oncologic, and, in some cases, superior renal functional outcomes, when compared with radical nephrectomy.³⁷ Indications for NSS include conditions that would render a patient dialysis dependent with tumor resection or significantly compromise renal function even with the presence of contralateral kidney. Traditionally, NSS has been reserved for tumors less than 4 cm, but larger tumors have been shown to be safely resected.

Metastatic RCC responds poorly to standard chemotherapy and radiation therapy. In patients with appropriate disease burden and adequate performance status, who are about to undergo immunotherapy with interferon or interleukin-2, cytoreductive nephrectomy should be considered. In selected patients with solitary or limited metastases, aggressive surgical resection of all disease may prolong survival, possibly in conjunction with immunotherapy.³⁸ Finally, targeted molecular therapy using tyrosine kinase inhibitors (e.g., sorafenib, sunitinib) has been approved by the Food and Drug Administration for metastatic RCC and has shown improved response rates and progression-free survival compared with immunotherapies.³⁹

BLADDER CANCER

Cancer of the urinary bladder currently accounts for approximately 3% of cancer deaths in the United States, with 52,810 estimated new cases per year.¹⁸ The median age at which bladder cancer is diagnosed is 73 years.¹⁹ In the United States, approximately 90% of bladder cancers are transitional cell carcinomas, 5% are squamous cell carcinomas, and 2% are adenocarcinomas. Cigarette smoking is the primary environmental risk factor, associated with 50 to 66% of bladder tumors in men and 25% in women.⁴⁰ Another risk factor is exposure to carcinogenic aromatic amines, especially benzidine and b-naphthylamine.⁴¹ Bladder cancer has been linked to occupational exposure in aromatic amine manufacturing, dyestuff manufacturing, rubber manufacturing, painting, the leather industry, the aluminum industry, and truck driving.⁴² In Africa and the Middle East, squamous cell carcinoma, associated with *Schistosoma haematobium* infection, is the most common form of bladder cancer.

In 80 to 90% of patients, bladder cancer presents as gross or microscopic hematuria, which commonly is painless and sporadic.⁴³ In some patients, the presenting complaint is a change in voiding habits, such as urgency, increased frequency, painful urination, or difficulty in voiding. Decreased

bladder capacity (as a result of a mass effect) and ureteral obstruction are less common presenting symptoms and are suggestive of more advanced disease. Systemic complaints are suggestive of metastatic disease.

The presence of hematuria should prompt a full evaluation consisting of upper urinary tract contrast imaging, cystoscopy, and urine cytology. Cystoscopy is the current standard for detecting bladder masses. Urine cytology has a specificity that approaches 100% and is useful in helping to identify small lesions, lesions that are atypical in appearance, and lesions that are located in the upper urinary tract.⁴⁴ All suspicious bladder lesions should be resected for pathologic diagnosis. Biopsy specimens should be obtained from the muscle layer to determine whether the tumor has invaded the muscle.

The stage and grade of the tumor are important for determining treatment and are independently correlated with prognosis. The AJCC's TNM system is commonly employed for staging. Bladder tumors that involve the mucosa (Ta) and the lamina propria (T1) are referred to as superficial disease, whereas tumors that extend beyond the lamina propria and invade muscle (T2a) are referred to as invasive disease. Three categories are used for grading, corresponding to well-differentiated (grade 1), moderately well-differentiated (grade 2), and poorly differentiated disease (grade 3). As the stage and grade of the tumor increase, the prognosis worsens. Carcinoma in situ is a separate disease entity whose presence is associated with a high risk of recurrence and a greater likelihood of disease progression.

Approximately 70% of bladder cancers initially present as superficial disease. Treatment consists of endoscopic resection. If pathologic examination confirms superficial disease, no further metastatic workup is necessary. Surveillance is mandatory, however, because of the risk of recurrence and progression. Low-grade Ta lesions recur in 50 to 70% of cases and progress in approximately 5% of patients, whereas high-grade T1 lesions recur in more than 80% of cases and progress in 50% of patients within 3 years.⁴⁵ Patients with high-risk superficial disease—defined as carcinoma in situ, stage T1 lesions, or large, high-grade, recurrent, or multifocal Ta lesions—should receive further treatment with intravesical bacillus Calmette-Guérin (BCG).⁴⁶

Approximately 25% of bladder cancers are invasive at the time of initial diagnosis. The standard treatment for organ-confined invasive bladder cancer is radical cystectomy with extended lymph node dissection and urinary diversion. Disease that extends through the muscle into the fat (T3), node-positive disease, or metastatic disease requires further treatment with neoadjuvant or adjuvant chemotherapy. In older series, if bladder cancer was left untreated, fewer than 15% of patients would survive 2 years.⁴⁷ In a 2001 study of 1,054 patients treated at the University of Southern California, the 5-year survival was 60 to 75% for pT2 tumors, 36 to 58% for pT3 tumors, and 4 to 35% for pT4 or node-positive tumors.⁴⁸

Urinary diversion after radical cystectomy is accomplished by interposing segments of intestine in the urinary tract. Generally, four types of diversions exist: noncontinent cutaneous diversions (e.g., ileal conduit), continent cutaneous catheterizable reservoirs (e.g., Indiana pouch), orthotopic bladder

replacement that allows voiding per urethra (e.g., Studer neobladder), and continent diversions that divert urine into the gastrointestinal tract (e.g., ureterosigmoidostomy). Complications of using intestinal diversions vary in type and severity depending on the type and length of intestinal segment used, as well as the time urine stays in contact with the absorptive surface of the bowel. Colon and ileum are often used for urinary tract reconstruction and can lead to a hypokalemic, hyperchloremic acidosis, bone demineralization, a higher rate of urinary tract infection, diarrhea, mucus production, stones, increased risk of malignancy at the enterourothelial anastomosis, and increased absorption of drugs normally excreted in the urine.⁴⁹

PROSTATE CANCER

Cancer of the prostate accounts for approximately 9% of cancer deaths in the United States.¹⁸ It is estimated that prostate cancer will be diagnosed in one of every six men,¹⁸ usually relatively late in life. Between 1998 and 2002, the median age at which prostate cancer was diagnosed was 69 years. Over the past two decades, the incidence of prostate cancer has risen, partly because of the widespread use of the prostate-specific antigen (PSA) screening test. This rise, however, has not been uniform. Between 1989 and 1992, the incidence of prostate cancer increased by an average of 18% per year, but between 1992 and 1995, it declined by 14% per year⁵⁰ and by 4.4% per year from 2001 to 2005. This change possibly reflects a reduction in detection rate and a decrease in undiagnosed cases.¹⁸

In the early stages, prostate cancer is generally asymptomatic. Currently, most cases of prostate cancer are detected by an abnormal digital rectal examination or an abnormal PSA test result that prompts prostate biopsy. Routine screening with a PSA test and a digital rectal examination should begin at the age of 40 in men whose life expectancy is greater than 10 years. African-American men and men who have a first-degree relative with prostate cancer are at higher risk for prostate cancer. The generally accepted threshold value for an abnormal PSA level has been 4.0 ng/mL; however, some investigators now question this value, on the grounds that a significant number of men have been found to have cancer with PSA values between 2.6 and 4.0 ng/mL.^{51–53} In addition, the rate at which the serum PSA level increases (i.e., PSA velocity) has become a very important factor in the diagnosis of prostate cancer.⁵⁴ For proper interpretation of PSA values, it is important to recognize that the serum PSA level can be influenced by multiple factors besides prostate cancer (including urinary retention, BPH, and prostatitis).

The stage and grade of the tumor play important roles in determining treatment and prognosis. The most widely accepted staging system is the AJCC's TNM system. The most widely accepted grading system for prostate cancer is based on the Gleason score. In this system, the biopsy specimen is examined under low-power magnification, and the most prominent glandular pattern seen is graded on a scale of 1 to 5, with 1 representing the highest degree of differentiation and 5 the lowest. The next most prominent glandular pattern seen is then graded in the same fashion. The two grades are added to yield the Gleason score, which can range from a minimum of 2 (1 + 1) to a maximum of 10 (5 + 5).

Cancers with scores of 6 or lower are considered well differentiated, scores of 7 are considered intermediate, and those with scores of 8 or higher are considered poorly differentiated. The more poorly differentiated the cancer is, the more aggressive it will be and the worse the prognosis will be. In addition to the Gleason score, the clinical stage and the PSA level have important implications for treatment.

There are many options for treating prostate cancer, and some controversy remains regarding what constitutes the most effective therapy. Treatment is based on the stage and grade of the tumor, the PSA level, and patient characteristics such as general health status, comorbid conditions, age, body habitus, and personal bias. Clinically localized prostate cancer may be treated with curative intent by means of surgery or irradiation (i.e., external-beam radiation therapy or brachytherapy). When the disease is more advanced or the patient is unwilling to undergo operative treatment or radiation therapy, antiandrogen therapies or watchful waiting may be considered.

The long-term use of 5 α -reductase inhibitors (e.g., finasteride) has been associated with a reduction in the risk of developing prostate cancer, but its use as a chemopreventive agent must be weighed against potential risks of developing high-grade prostate cancer and other side effects (e.g., erectile dysfunction, gynecomastia).⁵⁵ Dietary supplements, including vitamin C and E, selenium, and lycopene, have been studied but have not shown efficacy in reducing the risk of prostate cancer.^{56,57}

TESTICULAR CANCER

Testicular cancer accounts for only about 1 to 2% of all malignancies in men; however, it is the most common cancer in males between 15 and 34 years of age.⁵⁸ The American Cancer Society estimates that about 8,400 new cases of testicular cancer will be diagnosed in 2009.⁵⁹ Moreover, since the middle of the 20th century, the incidence of testicular cancer has been increasing in the United States.⁶⁰ The exact cause of testicular cancer remains unknown. It has been hypothesized that testicular atrophy is a common pathway by which several etiologic factors may be involved in tumor development in the testis.^{61,62} Familial tendency, white race, and a history of cryptorchidism are established risk factors.^{63–65}

The classic presentation of testicular cancer is painless swelling or enlargement of the testis. A 1987 study of 5,172 patients with testicular cancer, however, found that the initial presenting complaints for this condition included a swollen or enlarged testis (58%), a mass in the testis (27%), a painful testis (33%), tender breasts (3%), and a history of trauma (4%).⁶⁶ Acute trauma is not a proven cause of testicular cancer, but it may lead to the awareness of a mass. Examination generally reveals an enlarged testis or a nodule on the testis. Ultrasonography, which has been shown to be highly reliable in differentiating between intratesticular and extratesticular lesions, may be performed to supplement the evaluation.^{67,68} Testicular cancer may rarely present with manifestations of systemic disease (e.g., pulmonary complaints or an abdominal mass).

Measurement of serum levels of tumor markers (i.e., human chorionic gonadotropin [hCG], α -fetoprotein [AFP],

and lactate dehydrogenase [LDH]) is a well-established component of the management of testicular germ cell tumors and facilitates diagnosis, prognosis, monitoring of treatment, and prediction of relapse. Elevated serum concentrations of these markers are strongly suggestive of cancer, but the absence of such elevated concentrations in a patient with a testicular mass does not rule out cancer. hCG is secreted by the syncytiotrophoblasts present in certain germ cell tumors (i.e., embryonal tumors, teratomas, choriocarcinomas, and fewer than 20% of seminomas). AFP is synthesized by yolk sac components of germ cell tumors. Its presence is diagnostic of nonseminomatous disease; it is never produced by pure seminomas or choriocarcinomas. AFP concentrations peak between gestational weeks 12 and 14 and start to decline after week 16, falling to undetectable levels after the first year of life. LDH, although not a highly sensitive tumor marker, has proved to be an independent prognostic variable in several large multivariate analyses of testicular germ cell tumors. Serum tumor marker concentrations are followed after radical orchiectomy and should fall in proportion to their respective half-lives.

Treatment is determined by the pathology and stage of the tumor. Most testicular tumors are of germ cell origin and are classified as either seminomatous or nonseminomatous. Non-metastatic disease can often be treated surgically by means of radical orchiectomy, which is completed through an inguinal incision after vascular control of the spermatic cord has been achieved. Follow-up with diagnostic imaging and measurement of serum tumor marker levels is carried out to look for metastatic disease.

Seminomas account for nearly 48% of germ cell tumors and usually present during the fourth and fifth decades.⁶⁹ Initial metastasis is typically to either the periaortic lymph nodes near the renal hilum (for left-side lesions) or the precaval lymph nodes between the aortic bifurcation and the renal pedicle (for right-side lesions). Crossover to the periaortic nodes is common with right-side lesions. Seminomas may also spread hematogenously to the lungs, the liver, the brain, bone, the kidneys, the adrenal glands, the gastrointestinal tract, or the spleen. These lesions are highly radiosensitive; thus, irradiation is a key part of early-stage treatment. Low-stage disease is treated with radical orchiectomy and radiation therapy, whereas advanced or bulky disease is treated with chemotherapy.

Nonseminomatous germ cell tumors tend to be more locally aggressive than seminomas, and they have a high metastatic potential. Overall, the patterns of lymphatic and hematogenous spread are similar to those of seminomatous germ cell tumors; however, choriocarcinoma demonstrates a particularly aggressive natural history, with early hematogenous spread. Nonseminomatous germ cell tumors are treated with surgery and/or platinum-based chemotherapy, depending on the disease stage. Low-stage disease is treated with radical orchiectomy, followed by chemotherapy if tumor marker concentrations do not normalize. If the tumor marker concentrations normalize, subsequent options include surveillance and nerve-sparing retroperitoneal lymph node dissection (RPLND); without additional treatment, 30% of patients will experience relapses. The presence of lymphatic,

vascular, scrotal, or spermatic cord invasion increases the likelihood of retroperitoneal lymph node involvement, and RPLND may therefore be preferred in these circumstances.⁷⁰ Disease with minor nodal involvement is treated with radical orchiectomy and RPLND, followed by chemotherapy if RPLND demonstrates the presence of cancer. Disease with more extensive nodal involvement and metastatic disease are treated with chemotherapy. Close follow-up is the rule. Because testicular cancer affects men of reproductive age and RPLND, radiotherapy, and chemotherapy can all adversely affect the male reproductive function, sperm cryopreservation should be recommended to all men prior to initiating any treatment.

Benign Prostatic Hyperplasia

BPH becomes increasingly common in men as they age: histologic evidence from autopsy studies suggests that the incidence of BPH exceeds 50% in men older than 50 years and exceeds 75% in men older than 70 years.⁷¹ The prostate is composed of stromal and epithelial components, which can give rise to hyperplastic nodules. Typically, nodules occur in the transition zone of the prostate. The etiology of BPH is multifactorial and not completely understood. It is clear, however, that the endocrine system plays an important role and that testosterone is a significant factor. A family history and early onset of symptoms are associated with an increased risk of progression to more severe BPH. There may be an autosomal dominant or codominant pattern of inheritance.⁷²

Patients with BPH may present with obstructive or irritative lower urinary tract symptoms. Obstructive symptoms include incomplete emptying, intermittency, a weak stream, and straining; irritative symptoms include urgency, frequency, and nocturia. Although most patients present with one or more of these complaints, some patients may present with urinary tract infections, acute urinary retention, or renal failure. Because lower urinary tract symptoms are not disease specific, one must consider other urologic and medical conditions besides BPH, such as urinary tract infection, stones, prostatitis, strictures, cancer, and neurologic disease.

Patients should be evaluated with a thorough history and physical examination. Symptoms should be quantified by using the International Prostate Symptom Score (I-PSS) questionnaire. I-PSS scores can be used to help determine treatment and assess its effectiveness, and their utility in this setting has been reliably validated. A complete urologic and limited neurologic examination should be carried out. Routine PSA screening (for healthy persons of suitable age) and urinalysis should be performed. Additional evaluation may include measurement of serum creatinine concentration, urine culture, cystoscopy, biopsy, or urodynamic testing.

Treatment of BPH may involve observation, medical therapy, or surgical management. Symptoms tend to wax and wane, and many patients tolerate their symptoms reasonably well and prefer to avoid therapeutic interventions. Watchful waiting is a viable option for patients who have minimal symptoms and no evidence of renal or bladder dysfunction. Medical therapy focuses on relaxing the bladder neck and shrinking the prostate to facilitate more complete emptying of the bladder. Two classes of medications are used: alpha

blockers and 5 α -reductase inhibitors. Alpha blockers are considered first-line treatment for all BPH patients. These medications act on the alpha-adrenergic receptors of the bladder neck and the prostate to help relax and open the channel. Their main side effects are related to their blood pressure-lowering effect. In 2003, the Medical Therapy of Prostatic Symptoms (MTOPS) Research Group published a study advocating combination therapy with an alpha blocker and a 5 α -reductase inhibitor to reduce the risk of overall clinical progression of BPH and the long-term risk of acute urinary retention and need for invasive therapy.⁷³ Surgical intervention is generally reserved for patients with acute urinary retention, prostatic bleeding, or continued significant symptoms despite medical treatment. Surgical treatment is most often performed endoscopically. Prostatic tissue is removed via transurethral resection with electrocautery or ablated with a laser. If the prostate is extremely large (> 80 g), an open or laparoscopic^{74,75} simple prostatectomy may be performed.

Postoperative urinary retention, which occurs in 3.8 to 9% of cases,^{76,77} is a particularly troubling development. It has

been associated with preexisting voiding issues, immobility, analgesics, administration of high fluid volumes during operation, and impaired mental status. Treatment is based on eliminating as many of these predisposing factors as possible. After an unsuccessful first voiding attempt, a single catheterization is successful in resolving postoperative urinary retention in 39% of cases.⁷⁶ Generally, patients are given an alpha blocker first, and a voiding trial is administered once they have become ambulatory and are using less pain medication. Patients with a history of lower urinary tract symptoms should be started on an alpha blocker preoperatively, and administration of the medication should resume as soon as they are capable of tolerating liquids.

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Figures 1 and 2 Alice Y. Chen.

5 GYNECOLOGIC CONSIDERATIONS FOR THE GENERAL SURGEON

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For many general surgeons, gynecologic surgery is not a major component of practice. In a report published in 1995, surgical residents who graduated that year had handled, on average, only 1.6 gynecologic cases.¹ Nevertheless, it is clear that some surgeons devote a significant portion of their practice to treating gynecologic disorders. In a prospective registry of consecutive cases reported by seven rural general surgeons, 20% of the procedures were classified as gynecologic.² Furthermore, in a National Survey of Ovarian Carcinoma published in 1993, 21% of the primary surgical procedures for ovarian cancer were actually performed by general surgeons.³ At present, more than half of the general surgery residency programs in the United States offer no formal rotation in gynecology; accordingly, both residents and practicing surgeons may benefit from a discussion of basic gynecologic problems and their surgical management. In what follows, we consider the gynecologic conditions that are most commonly encountered by general surgeons. These conditions may be broadly classified as gynecologic emergencies, outpatient gynecologic problems (e.g., pelvic masses and abnormal uterine bleeding), or squamous dysplasias and gynecologic malignancies.

Gynecologic Emergencies

BLEEDING FROM OVARIAN CYSTS

Each month, the ovary of a premenopausal woman undergoes a cycle of hormonally driven changes characterized by follicular development, the emergence of a dominant follicle, ovulation, and the formation of a corpus luteum. Cystic enlargement of one of these physiologic structures is relatively common and is considered functional rather than neoplastic. Approximately 7% of asymptomatic women between the ages of 25 and 40 years have ovarian cysts larger than 2.5 cm.⁴ Functional ovarian cysts should not cause pain unless accompanied by bleeding, rupture, or torsion.

Follicular cysts are fluid-filled structures that arise from a normal follicle that fails to ovulate or does not undergo atresia. Rupture of follicular cysts may result in acute pain, which is usually of brief duration. Corpus luteum cysts arise from a mature, well-vascularized corpus luteum and may be associated with prolonged secretion of progesterone. They tend to be larger than follicular cysts and are more likely to cause clinical symptoms. Corpus luteum cysts range in severity from masses that cause no symptoms to ruptured cysts that cause catastrophic bleeding. Dull, unilateral lower abdominal and pelvic pain is the typical presenting complaint. Pelvic examination may show an enlarged, tender ovary. Unruptured corpus luteum cysts are followed conservatively. However, events such as coitus, exercise, or trauma may rupture the cyst, resulting in slight to significant intraperitoneal bleeding, in which case the patient usually experiences the sudden onset of severe lower abdominal or pelvic pain. The acute pain of a bleeding corpus luteum cyst is indistinguishable from that of a ruptured ectopic pregnancy.

A negative serum β -human chorionic gonadotropin (β -hCG) determination rules out an ectopic pregnancy. In hemodynamically stable patients, pelvic ultrasonography may establish a diagnosis and permit expectant management even if some intraperitoneal bleeding has occurred. The appearance of hemorrhagic cysts on computed tomography depends on the age of the clot: blood from an acute hemorrhage has a high attenuation value, whereas blood from a previous hemorrhage has an attenuation value approaching that of water. In an acute setting, CT typically demonstrates a cystic adnexal mass with areas of high attenuation at intramural and intracystic sites. A hemoperitoneum may also be present, with high-attenuation clot and blood accumulating in the dependent pelvis. Laparoscopy may be useful when the diagnosis is uncertain or when a stable patient has a moderate hemoperitoneum. In hemodynamically unstable patients, adequate volume and blood replacement are initiated and emergency laparotomy is performed. Once it is confirmed that the bleeding is from a ruptured cyst, conservative therapy, consisting of removing the cyst and achieving hemostasis, is initiated.

ADNEXAL TORSION

Abnormal enlargement of the adnexa, either by neoplasms or by cysts, may predispose to torsion of the tube and the ovary around the infundibulopelvic ligament, resulting in vascular compromise. Adnexal torsion is a gynecologic emergency: if untreated, it will result in infarction of the adnexa with eventual peritonitis. Although torsion can occur in postmenopausal women, it is most common in patients of reproductive age.

The presenting complaint is severe pelvic pain of abrupt onset, often accompanied by nausea and vomiting of sudden onset. The pain may be colicky or knifelike and is usually related to the degree of vascular compromise. There may be a history of waxing and waning pelvic pain corresponding to previous episodes of partial twisting and detorsion. Physical examination often demonstrates an acute abdomen with lower abdominal tenderness and guarding. Pelvic examination usually demonstrates a mass that may be difficult to assess because of tenderness. Low-grade temperature elevations may be noted, but significant fevers are unlikely. In most series, the accuracy with which adnexal torsion is diagnosed is approximately 70%.⁵ Ultrasonography demonstrates a mass in nearly all affected patients. However, the presence of arterial flow on Doppler ultrasonography does not exclude ovarian torsion: early in the development of ovarian torsion, lymphatic and venous flow may be obstructed while arterial perfusion is preserved.⁶ CT may demonstrate ovarian enlargement, smooth-wall thickening of the mass or tube, and uterine deviation towards the affected adnexa. On occasion, a twisted vascular pedicle (torsion knot or whirling sign) or lack of contrast enhancement within the twisted ovarian mass may be observed. Prompt surgical intervention is necessary to prevent adnexal infarction.

In the past, adnexal torsion was commonly treated aggressively, with salpingo-oophorectomy. This approach continues to be war-

ranted in perimenopausal and postmenopausal patients; however, a more conservative approach is now considered preferable for the treatment of women of reproductive age who desire future fertility. The traditional approach was based on two assumptions: first, that the twisted adnexum with vascular compromise was nonviable, and second, that detorsion was potentially dangerous because it might cause thrombus to be released from the clotted veins in the infundibulopelvic ligament. These assumptions proved to be unfounded. Accordingly, current management begins with untwisting the adnexum and assessing its viability. Once the torsion is unwound, the adnexum may demonstrate reperfusion or infarction without vascular recovery. Only a gangrenous adnexum must be completely removed.

Patients may be managed by means of either laparoscopy or laparotomy, depending on the clinical circumstances. In a series that included 40 young women with adnexal torsion, all of the patients were successfully managed conservatively, with unwinding of the torsion; laparotomy was performed in 26 of the 40 and operative laparoscopy in 14.⁷ Ideally, cystectomy, along with removal of the cause of the torsion, should be done at the time of detorsion. However, cystectomy on an edematous and fragile ovary may be technically difficult and may cause a further vascular insult to the remaining tissue. In such cases, it is advisable to evaluate the patient 6 to 8 weeks after the acute episode. If an ovarian mass is still found at that time, ovarian cystectomy may be performed via operative laparoscopy.

PELVIC INFLAMMATORY DISEASE

Pelvic inflammatory disease (PID) is an acute infection of the upper female genital tract that involves the uterus, the fallopian tubes, and the ovaries. It is a community-acquired disease and is initiated by a sexually transmitted agent that results in the ascent of vaginal flora into the upper genital tract. The resulting polymicrobial infection (caused by a mixture of anaerobes, facultative anaerobes, and aerobic organisms) can lead to a wide spectrum of disorders, including endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis.

Lower abdominal pain is the most frequent complaint. The pain usually is bilateral, rarely is of more than 2 weeks' duration, and often begins with or follows menses. Approximately half of the patients are febrile. Abdominal palpation demonstrates diffuse tenderness that is more pronounced in the two lower quadrants. Rebound tenderness and diminished bowel sounds are common. Pelvic examination reveals a purulent endocervical discharge with cervical motion and adnexal tenderness.

Empiric treatment of PID should be initiated in sexually active young women or women at risk in the clinical setting of lower abdominal tenderness, adnexal tenderness, and cervical motion tenderness. Additional criteria supporting the diagnosis include fever (oral temperature > 101° F), abnormal cervical or vaginal mucopurulent discharge, the presence of abundant white cells on saline microscopy of vaginal secretions, an elevated sedimentation rate, an elevated C-reactive protein level, and documentation of cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*.⁸ The differential diagnosis includes adnexal torsion, appendicitis, ectopic pregnancy, endometriosis, a hemorrhagic ovarian cyst, and urinary tract infection. Pertinent lab studies include determination of the serum β -hCG level (to rule out an ectopic pregnancy), microscopic examination of the vaginal discharge, a complete blood count, endocervical nucleic acid amplification tests for *N. gonorrhoeae* and *C. trachomatis*, sedimentation rate, and urinalysis. Clinical diagnosis of acute PID remains imprecise. Compared with laparoscopy (the gold standard for

Table 1 Recommended Outpatient and Inpatient Therapies for Pelvic Inflammatory Disease⁸

Type of Therapy	Regimen	Agents and Dosages
Outpatient	A	Ofloxacin, 400 mg p.o., once daily, for 14 days* or Levofloxacin, 500 mg p.o., once daily, for 14 days* with or without Metronidazole, 500 mg p.o., b.i.d., for 14 days
	B	Ceftriaxone, 250 mg I.M. in single dose or Cefoxitin, 2 g I.M. in single dose, and probenecid, 1 g p.o., administered concurrently or Another parenteral third-generation cephalosporin (e.g., cefotaxime or ceftizoxime) plus Doxycycline, 100 mg p.o., b.i.d., for 14 days with or without Metronidazole, 500 mg p.o., b.i.d., for 14 days
Inpatient	A	Cefotetan, 2 g I.V. q. 12 hr or Cefoxitin, 2 g I.V. q. 6 hr plus Doxycycline, 100 mg p.o. or I.V. q. 12 hr
	B	Clindamycin, 900 mg I.V. q. 8 hr plus Gentamicin, 2 mg/kg I.V. or I.M. loading dose, followed by maintenance dosage of 1.5 mg/kg q. 8 hr; once daily dosage may be substituted

*Should not be used in patients at increased risk for infection with quinolone-resistant *N. gonorrhoeae*.

diagnosis of PID), a presumptive diagnosis of PID has a positive predictive value of 65% to 90%.⁸ Unfortunately, many episodes of PID go unrecognized and subsequently give rise to infertility, ectopic pregnancy, chronic pelvic pain, or tubo-ovarian abscesses.

PID treatment regimens are designed to provide broad-spectrum empiric therapy of likely pathogens, including *N. gonorrhoeae*, *C. trachomatis*, anaerobes, and gram-negative facultative bacteria. Quinolone-resistant *N. gonorrhoeae*, prevalent in parts of Asia and the Pacific, is becoming increasingly common in California and Hawaii; this and other geographic variables associated with PID may affect the choice of antimicrobial agents. The Centers for Disease Control (CDC) has made specific recommendations for outpatient and inpatient (parenteral) antibiotic therapy [see Table 1].⁸ Criteria for inpatient therapy include inability to rule out a surgical emergency (e.g., appendicitis), severe symptoms, high fevers, failure to respond to oral antibiotics, and the presence of a tubo-ovarian abscess. Patients who are initially treated with parenteral antibiotics are usually switched to oral therapy within 24 hours after clinical improvement.

Tubo-ovarian abscess is the most serious manifestation of PID. There are no standardized diagnostic criteria for this condition, and a clinical diagnosis presents the same difficulties as a clinical diagnosis of PID itself. Most women with a tubo-ovarian abscess are young and desire future fertility. Fevers and pelvic pain are typical presenting complaints. Pelvic examination usually demonstrates a mass or extreme adnexal tenderness. Many

unruptured tubo-ovarian abscesses, unlike unruptured abscesses elsewhere in the body, can be successfully managed with antibiotics alone. Ultrasonography is useful for diagnosis and follow-up of cases that are managed conservatively. Medical management of an unruptured abscess consists of administration of appropriate antibiotics, close monitoring, and, possibly, drainage via colpotomy. Indications for surgical intervention include a questionable diagnosis, rupture of the tubo-ovarian abscess (a true surgical emergency), and failure of medical (i.e., antibiotic) therapy.

ECTOPIC PREGNANCY

Pelvic pain and vaginal bleeding in the first trimester are the complaints most commonly associated with ectopic pregnancy. Although hypotension, tachycardia, and guarding may be noted and alert the clinician to impending tubal rupture, most patients present with less alarming findings. Patients with a suspected ectopic pregnancy are initially assessed by means of transvaginal ultrasonography [see Figure 1]. Given the risk that an ectopic pregnancy may be coexisting with an intrauterine one (estimated to be between 1/4,000 and 1/15,000), the first task in the diagnostic evaluation is to exclude an intrauterine pregnancy.

Critical to the diagnosis of a suspected ectopic pregnancy is the concept of the so-called discriminatory cutoff,⁹ which is defined as the serum β -hCG level at which a normal intrauterine pregnancy can be ultrasonographically identified in nearly all patients. With a transvaginal approach, the discriminatory cutoff is usually between 1,500 and 2,500 mIU/ml; however, this value can be affected by the equipment used and by the experience (or inexperience) of the

sonographers. If the transvaginal ultrasonogram is nondiagnostic, a serum β -hCG test is performed to establish the serum level relative to the discriminatory cutoff. If an intrauterine pregnancy is not visualized above the discriminatory cutoff, the contents of the uterus are evacuated to distinguish an abnormal intrauterine gestation from an ectopic pregnancy. If the initial β -hCG is below the discriminatory cutoff, serial β -hCG measurements are required to document a viable or nonviable gestation. With a viable gestation, the β -hCG level should rise by at least 53% in 2 days.⁹ A precipitous decline in the β -hCG level suggests a spontaneous abortion; however, if the β -hCG level does not decline by at least 21% to 35% in 2 days (depending on the initial value), an ectopic pregnancy should be suspected [see Figure 1].⁹

The clinical scenario of hypovolemic shock, an acute abdomen, and a positive pregnancy test usually establishes the diagnosis of a ruptured ectopic pregnancy. The rupture of the ectopic gestation through the tube is followed by the abrupt onset of pelvic pain lateralized to the affected adnexa. The clinical manifestations of hemoperitoneum ensue, including abdominal pain, diaphragmatic irritation and syncope. If the site of tubal rupture is small or tamponades itself, the physical findings may be more subtle. The predominant symptom is pain, usually described as dull or cramping. A history of menstrual irregularity is usually present and may be accompanied by subjective symptoms of pregnancy. Current rapid urine β -hCG assays have a sensitivity of 20 to 25 mIU/ml and are readily available to confirm the diagnosis in a patient with an acute abdomen.

Once the diagnosis of a ruptured ectopic pregnancy is made,

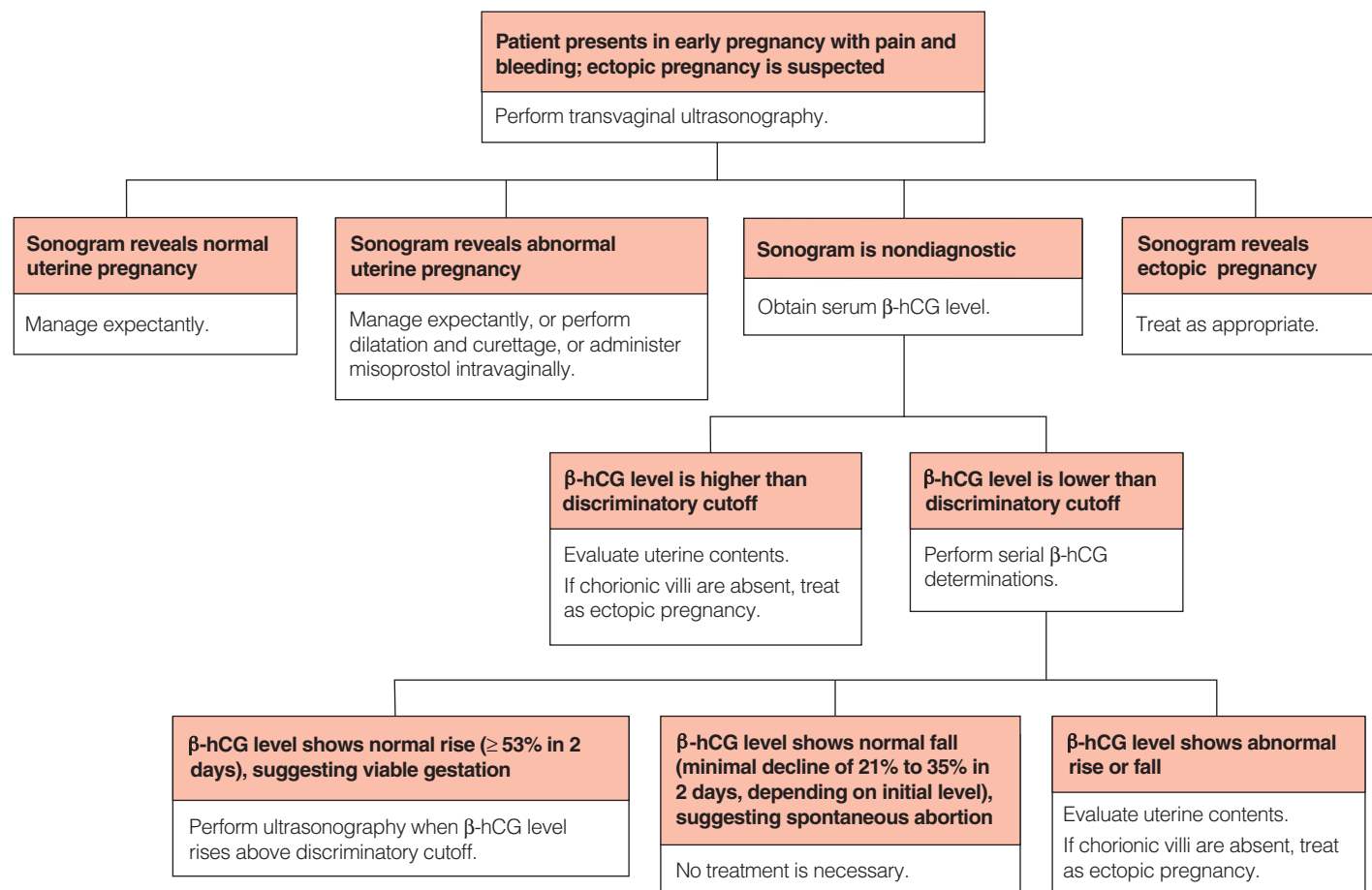


Figure 1 Algorithm illustrates evaluation of patients with suspected ectopic pregnancy.⁹

treatment consists of surgical removal of the ectopic gestation; there is no role for medical management (e.g., methotrexate) in the treatment of this condition. It should be kept in mind that not all ruptured ectopic gestations necessitate laparotomy. Hemodynamically stable patients can often be treated laparoscopically, depending on the clinical situation, the physical characteristics of the patient, and the equipment available. Diagnostic laparoscopy is an excellent tool for both diagnosis and treatment in such patients.

The patient's desire for future fertility must be considered before surgical intervention is initiated. For patients who wish to bear children in the future, conservative, tube-sparing surgery has been recommended. Linear salpingosotomy is performed by making an incision in the antimesenteric aspect of the tube overlying the bulge of the ectopic gestation. The products of conception are removed, hemostasis is achieved through electrocauterization, and the tubal defect is left open to heal by secondary intention. In cases of ectopic pregnancies at the distal or fimbrial portion of the fallopian tube, fimbrial expression with extrusion of the products of conception has also been performed. Patients undergoing conservative surgery should be followed with serial β -hCG determinations to ensure that there is no residual trophoblastic tissue. For patients who are hemodynamically unstable or who have no further desire of pregnancy, salpingectomy is the procedure of choice. Salpingectomy may also be necessary for adequate hemostasis after an unsuccessful attempt at salpingostomy.

VULVAR HEMATOMA

Vulvar hematomas are usually the result of blunt trauma (e.g., from straddle injuries, automobile accidents, or physical assault). The most important task in the management of a child with a vulvar hematoma is to determine the full extent of the problem. Management is usually conservative unless the hematoma is rapidly expanding. If the hematoma is not expanding after a minimum of 4 hours of observation, if the patient is able to void clear urine, and if the hematoma is not large enough to cause undue distress, nonsurgical treatment is indicated.¹⁰ Administration of analgesics and application of ice packs and pressure to the affected vulva for 8 to 12 hours after the event typically yield considerable symptomatic improvement. If the hematoma is expanding, is causing considerable pain, or is obstructing the urethra, it should be incised and evacuated with the patient under anesthesia. Any actively bleeding vessels should be ligated, and the cavity should be closed in layers. If the bed of the hematoma continues to ooze, a pack can be placed to tamponade any residual bleeding.

BARTHOLIN GLAND ABSCESS

Simple incision and drainage of a Bartholin gland abscess usually achieves prompt relief of symptoms, but it may increase the risk of later recurrence. The preferred approach has been to create a fistulous tract so as to marsupialize the gland cavity. To perform a marsupialization, a small elliptical incision is made in the vestibular mucosa overlying the wall of the abscess. The elliptical piece of mucosa is removed, exposing the wall of the Bartholin abscess. The wall of the abscess is then entered, and the contents of the abscess are evacuated. A portion of the wall underlying the elliptical mucosal defect is excised, and the wall of the cyst is approximated to the edge of the mucosa with a few 3-0 absorbable sutures. Alternatively, the Bartholin abscess may be stabilized manually and entered via a stab incision. The contents are evacuated, and a Word catheter is inserted into the cavity. The balloon is then inflated and left in place for drainage of the cyst. Marsupialization is accomplished by epithelializing the catheter tract.

Outpatient Gynecologic Problems

PELVIC MASS

The differential diagnosis of a pelvic mass is determined by the viscera occupying the pelvis and their potential pathologic alterations. The most common cause of an adnexal mass is an enlarged ovary. During the reproductive years, the majority of ovarian masses are functional cysts. Such cysts range in size from a few centimeters to 8 to 10 cm in diameter and usually disappear in 1 to 3 months. A premenopausal woman with a cystic adnexal mass less than 8 cm in diameter is usually followed for at least one menstrual cycle; the majority of such masses undergo spontaneous regression. Transvaginal ultrasonography may be particularly useful for establishing the size of the mass, as well as for distinguishing a simple cyst from a complex mass. A premenopausal patient with a large (> 8–10 cm), predominantly solid, fixed, or irregular mass should be surgically evaluated. A postmenopausal patient with a simple unilocular cyst measuring less than 5 to 6 cm in diameter can be followed expectantly, provided that the CA 125 level is normal. In an autopsy study of 234 postmenopausal women who died of nongynecologic causes, 15% had ovarian cysts, and 3.8% had an ovarian cyst between 2 and 5 cm in diameter.¹¹ A postmenopausal patient with a large, suspicious (i.e., bilateral, irregular, fixed, solid, or accompanied by ascites), or complex mass requires surgical intervention.

Endometriosis is a benign, progressive disease defined as the presence of ectopic endometrial glands and stroma in aberrant locations in the pelvis. Hemorrhage may occur within the glandular tissue, followed by fibroblastic proliferation. The ovaries are the most common site of involvement, and ovarian involvement often results in obvious endometriotic cysts. Approximately 10% of cases may involve the rectosigmoid as well, and, depending on the degree of scarification, such involvement may be difficult to distinguish from a primary bowel neoplasm. Symptoms include pelvic pain and infertility. Medical therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), combined oral contraceptives, progestins, or long-acting gonadotropin-releasing hormone (GnRH) agonists may be considered. The goals of conservative therapy are removal of gross endometriosis, lysis of adhesions, and restoration of normal anatomy. Definitive surgical treatment with hysterectomy and bilateral salpingo-oophorectomy is reserved for patients who experience intractable pain and who are no longer desirous of bearing children.

The majority of adnexal masses in women of childbearing age can be managed with cystectomy and ovarian preservation. Laparoscopic aspiration of an adnexal cyst as an isolated procedure is not recommended, because of the frequency of recurrence and the absence of any definitive pathology. Persistent cysts, cystadenomas, dermoids, and endometriomas may be managed with cystectomy, which removes the epithelial cyst lining and provides a tissue diagnosis. In a premenopausal patient with an adnexum that is not salvageable or is suspicious for malignancy, a salpingo-oophorectomy may be performed. In a postmenopausal patient with a mass, the entire ovary and tube should be removed for pathologic assessment. In carefully selected cases (e.g., patients with a negative CA 125 determination or a small, benign-appearing mass), removal of the ovary and tube can be done laparoscopically. Laparotomy is still considered the standard of care for the evaluation of potentially cancerous masses. A solid mass in a postmenopausal woman, the presence of ascites, and bilateral disease are all suggestive of malignancy. The two major concerns regarding the use of laparoscopy in the management of ovarian cancers remain the risk of tumor spillage and the delay in initiating definitive treatment.

In an open cystectomy, the ovary is immobilized, and the ovarian capsule is incised with a scalpel near the base of the cyst. Traction is placed on the incised ovarian capsule, and a Metzenbaum scissors is used to dissect the areolar tissue between the cyst wall and the capsule. After the cyst is removed, hemostasis is obtained in the bed of the cyst cavity. To reduce the risk of adhesions, the ovary usually is not sutured together. In a laparoscopic cystectomy, the utero-ovarian ligament is held so as to expose the antimesenteric aspect of the ovary. The ovarian capsule is incised with a monopolar scissors, and the cyst wall is exposed; the cyst wall is then bluntly separated from the ovarian capsule. The presence of an intact cyst wall facilitates the dissection. Eventually, the cyst is aspirated, and the remaining cyst wall is separated from the ovarian capsule by means of a 5 mm grasper. Repeated twisting of the cyst wall around the grasper (the so-called hair-curler technique) allows the cyst wall to be pulled away from the ovarian capsule. The collapsed cyst is then removed through one of the port sites and inspected for interior papillations or nodularities. The bed of the excision is inspected for hemostasis. To minimize adhesions, the edges of the ovary are not approximated with sutures.

In a postmenopausal patient with an ovarian mass, salpingo-oophorectomy is preferred, with the entire adnexum submitted for pathologic evaluation. In an open salpingo-oophorectomy, the broad ligament is entered by dividing the round ligament or by dividing the peritoneum lateral to the infundibulopelvic ligament. After the ureter is identified, the infundibulopelvic ligament is skeletonized, clamped, and ligated. The adnexum is mobilized toward the uterus, where the proximal fallopian tube and the utero-ovarian ligament are clamped, cut, and ligated. In selected postmenopausal patients with adnexal masses, salpingo-oophorectomy can be accomplished laparoscopically with bipolar electrodesiccation, suture ligation, or automatic staplers for control of the infundibulopelvic ligament.

LEIOMYOMAS

Leiomyomas, or myomas, arise as benign tumors from the myometrium and are the most common tumors of the uterus. Leiomyomas are often multiple and are grouped according to their location within the uterus; intramural, subserosal, and submucosal sites are the most common locations. Symptoms include pressure from an enlarging uterus, abnormal uterine bleeding, dysmenorrhea, and adverse pregnancy outcomes. The majority of women with myomas, however, are asymptomatic. In general, the severity of the symptoms is determined by the size and number of the fibroids, as well as by their location. The diagnosis of myomas is typically made through palpation of an irregular, enlarged uterus, though other causes of uterine enlargement or asymmetry must also be considered. Difficult cases may be resolved by employing ultrasonography or MRI to examine the uterus.

Small, asymptomatic leiomyomas may be managed with observation once a stable uterine size has been established. The need for intervention is determined on the basis of interval growth, lesion location, and patient symptoms. Rapid growth or enlargement of the uterus is another indication for surgical treatment because of the possibility of a uterine sarcoma, as well as an increased risk of operative complications. Women with symptomatic leiomyomas may be treated with myomectomy, hysterectomy, or, as is now becoming more common, uterine artery embolization. The choice between myomectomy and hysterectomy is usually determined by the patient's age, parity, and, most important, desire for future childbearing. The therapeutic effect of uterine artery embolization is thought to result from irreversible postembolic ischemia that

causes necrosis and shrinkage of the myomas.

Hysterectomy is the most commonly performed major nonobstetric operation in the United States, with approximately 600,000 done each year. Although hysterectomies can be performed via a vaginal or a laparoscopic approach, more than 60% are performed abdominally, especially for the treatment of leiomyomata.¹² An abdominal hysterectomy follows a clamp, cut, and tie approach and proceeds in a lateral-to-medial direction. The round ligaments are divided early in the procedure. Access to the broad ligament is gained by dividing the infundibulopelvic ligaments and performing salpingo-oophorectomy or by dividing the proximal tube at the utero-ovarian ligament and preserving the adnexa. The vesicouterine fold is transversely divided in an area where the bladder flap appears mobile. The bladder is reflected below the level of the uterine cervix, and the uterine arteries are skeletonized. Each uterine artery pedicle is clamped adjacent to the cervix, then cut and tied, and the cardinal ligaments are serially transected. Each pedicle is clamped, divided, and ligated medial to the previous purchase of tissue. Eventually, the vagina is entered, the specimen is amputated from the vaginal apex, and the open vaginal tube is closed. Potential urinary tract morbidity includes injury to the bladder (resulting in fistulas) and ureteral damage, most often occurring with clamping of the gonadal vessels (i.e., the infundibulopelvic ligament) or clamping of the uterine arteries.

ABNORMAL UTERINE BLEEDING

Abnormal uterine bleeding is one of the most frequent complaints expressed by patients seeking gynecologic care. Such bleeding is not in itself a diagnosis but, rather, a symptom that warrants evaluation. The term abnormal uterine bleeding includes excessive uterine bleeding (menorrhagia), bleeding between menses, and any combination of the two, as well as postmenopausal bleeding. Excessive uterine bleeding has been quantitatively defined as either menses persisting for longer than 7 days or a total menstrual blood loss that exceeds 80 ml. It is better, however, to define excessive bleeding in terms of the degree to which the abnormal bleeding deviates from a particular patient's established menstrual pattern—for example, an increase of two or more in the number of sanitary pads used daily or menses that persist for 3 or more days longer than normal. The differential diagnosis includes systemic disease (e.g., coagulopathies, hypothyroidism, and cirrhosis), reproductive tract disease (e.g., complications of pregnancy, benign disorders, and malignant lesions), iatrogenic causes (e.g., an intrauterine device [IUD]), and dysfunctional uterine bleeding. Dysfunctional uterine bleeding can only be established by excluding the other causes of abnormal uterine bleeding; it usually represents noncyclic bleeding resulting from disordered hormonal interaction.

The most important function of the history and the physical examination is to determine the source and the cause of the bleeding. A thorough examination is necessary to assess the lower genital tract, the cervix, the size of the uterus, and the status of the adnexal structures. If the patient is of reproductive age, determination of the urinary or serum β -hCG level should be considered at an early stage of evaluation. Serum β -hCG levels may remain elevated for as long as 38 days after a first-trimester abortion.¹³ Complications of pregnancy (e.g., threatened or incomplete abortions, ectopic pregnancies, retained placental tissue, or trophoblastic disease) are an important cause of abnormal uterine bleeding in women of childbearing age. An endometrial biopsy should be performed in women who have risk factors for endometrial cancer (e.g., obesity, chronic anovulation, or unopposed estrogen therapy), women with menorrhagia who are older than 35 to 40 years, and postmenopausal women who experience uterine bleeding. The

Table 2 Bethesda System for Reporting and Interpreting Results of Pap Smear

Section of Report	Explanation
Negative for intraepithelial lesion or malignancy	This section is where a "normal" result (the desired outcome) is reported. Abnormal findings not related to cancer risk are reported in two subcategories: (1) organisms (e.g., evidence of <i>Trichomonas</i> , fungal, herpesvirus, or some other infection) and (2) other nonneoplastic findings (e.g., evidence of injury and response to injury).
Endometrial cells present in woman 40 years of age or older	This section is to alert the physician that cells from the lining of the uterus are present when they normally should not be. It is a check on the status of the uterus and endometrium rather than the cervix.
Epithelial cell abnormalities*	This section is where abnormalities associated with the risk of developing cancer are reported. These abnormalities occur over a spectrum ranging from slight changes to definite cancer. They are initially classified into squamous cell changes and glandular cell changes. <i>Squamous cell abnormalities</i> Atypical squamous cells (ASC): cellular abnormalities that qualitatively or quantitatively fall short of definitive diagnosis of squamous epithelial lesion ASC of undetermined significance (ASC-US) ASC for which HSIL or high-grade changes cannot be excluded (ASC-H) Low-grade squamous intraepithelial lesion (LSIL): encompasses HPV infection, CIN I, and mild dysplasia High-grade squamous intraepithelial lesion (HSIL): encompasses CIN II and III, moderate dysplasia, severe dysplasia, and carcinoma in situ Squamous cell carcinoma (SCC): characterized by tumor diathesis (blood and necrotic debris), prominent macronuclei, and parachromatin clearing <i>Glandular cell abnormalities</i> Atypical glandular cells (AGC) (endocervical, endometrial, or not otherwise specified) AGC favoring neoplasia (endocervical or not otherwise specified) Endocervical adenocarcinoma in situ (AIS) Adenocarcinoma (endocervical, endometrial, extrauterine, or not otherwise specified)
Other malignancies	This section is where any malignant tumors other than primary SCC and glandular adenocarcinoma are reported.

* Patients with LSIL, HSIL, SCC, persistent ASC-US, ASC-US with high-risk HPV types, ASC-H, AGC, AIS, or adenocarcinoma undergo outpatient evaluation with colposcopy.

ectocervix is cleansed with antiseptic solution, and a flexible plastic catheter containing an obturator is advanced into the uterine cavity. The obturator is withdrawn, and tissue fragments are aspirated into the plastic catheter. Patients who are unable to tolerate this procedure may be evaluated by means of transvaginal ultrasonography. An endometrial stripe thinner than 5 mm is unlikely to represent an endometrial cancer.

Treatment of abnormal uterine bleeding depends on the underlying cause. Patients with demonstrated organic pathology are managed as appropriate for the specific condition present. Excessive uterine bleeding resulting from anovulation can be managed with cyclic progestins or an oral contraceptive. Acute severe menorrhagia (often accompanied by hemodynamic instability) can initially be managed with volume support and intravenous admin-

istration of estrogens to stabilize the endometrium and terminate bleeding; subsequently, after 24 hours of I.V. estrogen therapy, the patient is switched to an oral contraceptive. Excessive blood loss with ovulatory cycles can be managed with NSAIDs, an oral contraceptive, the levonorgestrel IUD, or surgical intervention (i.e., endometrial ablation). In one study, use of the levonorgestrel IUD resulted in an 87% reduction in menstrual blood loss after 3 months and a 95% reduction after 6 months, compared with blood loss recorded during pretreatment menses.¹⁴

Squamous Dysplasias and Gynecologic Malignancies

SQUAMOUS DYSPLASIAS OF LOWER GENITAL TRACT

Infection with low-risk human papillomavirus (HPV) types, such as HPV 6 and HPV 11, results in condylomas of the lower genital tract. Infection with high-risk types, such as HPV 16 and HPV 18, may result in dysplasias that have the potential to progress to invasive disease. The majority of sexually active women eventually become infected with high-risk HPV types. In most women, however, this infection proves transient: at 12 months' follow-up, 70% of HPV-infected women are HPV negative, and at 24 months' follow-up, 91% are HPV negative.¹⁵ Those women who experience persistent infections are at highest risk for the subsequent development of significant cervical dysplasias.

The Papanicolaou (Pap) smear is a screening test used to identify women who may have cervical dysplasia (also referred to as cervical intraepithelial neoplasia [CIN]) and early invasive disease. Patients with abnormal smears as determined by the Bethesda system [see Table 2] undergo outpatient triage with colposcopy. This technique uses a bright light source and magnification to examine the cervix after the application of dilute acetic acid, which acts as a mucolytic agent and accentuates epithelial and vascular changes suggestive of dysplasia. Small biopsies are obtained from abnormal-appearing areas to allow mapping of potential areas of dysplasia. Expectant management is recommended for patients with mild squamous cell dysplasia (i.e., CIN I); treatment aimed at eliminating the dysplasia is usually recommended for patients with more significant lesions (i.e., CIN II or CIN III). In the past, many patients with cervical dysplasia were treated with ablative therapies, such as cryotherapy or laser vaporization. Currently, a loop electrocautery excision procedure (LEEP) is often employed to treat

Table 3 International Federation of Gynecology and Obstetrics Surgical Staging System for Endometrial Carcinoma

Stage	Description
I	IA Tumor is limited to endometrium IB Tumor invades ≤ 50% of myometrium IC Tumor invades > 50% of myometrium
II	IIA Tumor involves endocervical glands IIB Tumor invades cervical stroma
III	IIIA Tumor invades uterine serosa or adnexa, peritoneal cytology is positive, or both IIIB Tumor metastasizes to vagina IIIC Tumor metastasizes to pelvic or para-aortic lymph nodes
IV	IVA Tumor invades bladder or bowel mucosa IVB Tumor metastasizes to distant sites, including intra-abdominal or inguinal lymph nodes

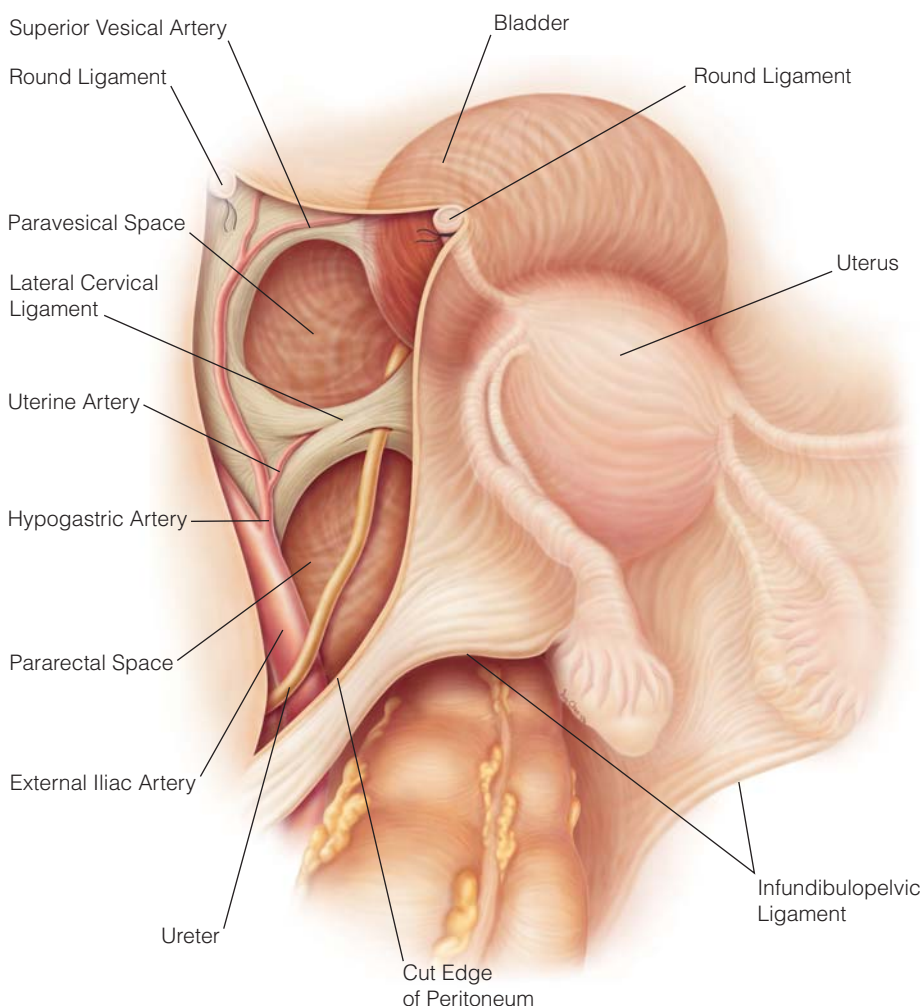


Figure 2 Depicted are the retroperitoneal spaces of the pelvis (i.e., the pararectal and paravesical spaces). Dissection of the pararectal and paravesical spaces demonstrates the base of the cardinal ligament separating the two spaces. In this representation, the superior vesical artery has been mobilized from the lateral wall of the bladder and relocated to a lateral position.²⁵

the dysplasia, as well as to submit tissue for pathologic analysis. Cold-knife cervical conization may be performed as an alternative to LEEP; it avoids creating thermal artifacts and may be more useful in patients who have glandular dysplasias or appear to be at risk for early invasive disease.

Women who have undergone a total hysterectomy for benign disease may discontinue Pap smear screening. Women who have undergone a hysterectomy and have a history of a significant cervical dysplasia (CIN II or CIN III) should continue annual Pap smear screening until three consecutive satisfactory negative cytology results have been obtained, at which point routine cytology screening can be discontinued. Women who have had high-grade squamous dysplasias of the cervix may also experience the development of vaginal dysplasia after hysterectomy.

Vaginal dysplasia is asymptomatic and typically is detected only after an abnormal Pap smear. Initial evaluation consists of colposcopy with directed biopsies of abnormal-appearing vaginal mucosa. Significant dysplasias may be either ablated with superficial laser vaporization or excised. Excision with partial vaginectomy is definitive treatment from a pathologic perspective, but it may be associated with a higher rate of complications.

Vulvar dysplasia may be visible in the form of discrete, slightly raised (papular), often pigmented lesions. Biopsy of the lesion establishes the diagnosis and rules out obvious invasive disease. Multifocal disease involving non-hair-bearing areas (often seen in young patients) can usually be treated with superficial laser vaporization or with topical application of imiquimod, an immune

response modifier in cream form that is currently used in the treatment of condyloma. Lesions in hair-bearing areas and confluent lesions (often seen in postmenopausal women) are best treated with wide local excision. Large unifocal confluent lesions may contain occult invasive foci that are identifiable only through excision and careful pathologic evaluation. The lesion, along with a 4 to 5 mm margin of normal tissue, is incised with a scalpel and dissected away from the underlying dermis with an electrocautery. The superficial defect is closed in one layer with interrupted sutures; a rhomboid flap may be required for more sizeable defects.

ENDOMETRIAL CANCER

Endometrial carcinoma is the most common gynecologic malignancy and accounts for more than 95% of uterine cancers. Although the majority of these carcinomas occur on a sporadic basis, an endometrial cancer can also be the initial manifestation of the Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) [see 5:14 *Hereditary Colorectal Cancer and Polyposis Syndromes*]. The lifetime risk of endometrial cancer for women with the Lynch syndrome is 40% to 60%, which equals or exceeds their risk of colorectal cancer.¹⁶ In the United States, approximately 40,000 new cases of endometrial cancer are diagnosed each year, of which 7,000 prove fatal. About 75% of these cases involve postmenopausal women, with the remaining 25% involving premenopausal women; only about 5% of cases involve women younger than 40 years. Endometrial cancers are adenocarcinomas and usually resemble the glands of the endometrial lining; howev-

er, approximately 10% have a nonendometrioid (i.e., papillary serous or clear cell) histology, a pattern associated with a biologically aggressive behavior. Abnormal vaginal bleeding or postmenopausal bleeding is the most common presenting complaint. Outpatient endometrial biopsy with aspiration of tissue from the uterine cavity often establishes the diagnosis. If the tissue obtained is insufficient or the patient cannot tolerate outpatient evaluation, dilatation and curettage (often with hysteroscopy) is performed with the patient under anesthesia.

Approximately 75% of patients with endometrial cancer have early disease. Therapy typically consists of hysterectomy, bilateral salpingo-oophorectomy, procurement of peritoneal specimens for cytologic examination, and staging. The regional lymph nodes are the most frequent site of occult metastatic disease. Accordingly, the surgical staging criteria [see Table 3] emphasize the pathologic status of the regional lymph nodes with selective pelvic and para-aortic lymphadenectomy. Although there are direct lymphatic channels from the uterus to the para-aortic area, it is uncommon to find positive para-aortic nodes in the absence of pelvic nodal involvement.

Selective pelvic lymphadenectomy removes the lymphatic tissue from the anterior and medial surfaces of the iliac vessels and from the obturator fossa superior to the obturator nerve. Sampling of the pelvic lymph nodes is facilitated by developing the pararectal and paravesical spaces in the retroperitoneum of the pelvis [see Figure 2]. The pararectal space is developed by means of blunt dissection between the ureter medially and the internal iliac (hypogastric) artery laterally. Dissection through the loose areolar tissue proceeds caudomedially toward the coccyx. The paravesical space is developed by sweeping the obliterated superior vesical artery and the bladder medially. The space is bordered by the pubic symphysis anteriorly and the obturator internus laterally. Development of the spaces provides the exposure necessary for skeletonizing the iliac vessels and the obturator nerve. Selective para-aortic lymphadenectomy consists of removing precaval and aortic lymphatic tissue from the level of the inferior mesenteric artery to the middle of the common iliac artery bilaterally. Sampling of the para-aortic lymph nodes is then accomplished via either a direct or a lateral approach. With a direct approach, an incision is made into the peritoneum overlying the right common iliac artery and extended over the aorta. With a lateral approach, an incision is made in the lateral paracolic gutters, with the right or left colon reflected medially. In one study, a median of 11 pelvic and three para-aortic lymph nodes were obtained at selective lymphadenectomy.¹⁷

OVARIAN CANCER

Of all the reproductive tract malignancies, ovarian cancer poses the greatest clinical challenge. Although ovarian cancers can arise from germ cells, sex-cord cells, or stromal cells, approximately 85% arise from the coelomic epithelium and thus are termed epithelial cancers. The peak incidence of invasive ovarian epithelial cancers is between 56 and 60 years of age. Approximately 5% to 10% of these cancers have a hereditary component; women with *BRCA1/BRCA2* or Lynch syndrome (HNPCC) germline mutations are at increased risk. Prophylactic salpingo-oophorectomy in patients with *BRCA1/BRCA2* mutations virtually eliminates the risk of ovarian and tubal cancer and reduces the risk of breast and primary peritoneal cancer.^{18,19}

Ovarian cancer is the second most common gynecologic malignancy, but it has the highest fatality-to-case ratio of any reproductive tract cancer. Ovarian epithelial carcinomas spread primarily through exfoliation of cells, which places the entire peritoneal cavity at risk for metastases. Moreover, early recognition is difficult because the majority of patients have only vague and nonspecific

complaints. Not surprisingly, 60% to 70% of patients have advanced (stage III or IV) disease at diagnosis. Detection of ovarian cancer is further hindered by the fact that there is no effective screening test. The tumor-associated antigen CA 125 is expressed by more than 80% of ovarian epithelial cancers; however, though CA 125 levels are employed in following up patients with documented disease, they are not useful for screening purposes. In a group of 1,110 women at increased risk for ovarian cancer, annual surveillance with serum CA 125 determinations and additional transvaginal ultrasonography was unable to detect tumors at an early enough stage to influence the prognosis.²⁰

Surgical intervention serves three purposes in the setting of ovarian epithelial cancer: diagnosis, staging, and tumor debulking (cytoreduction). The staging of ovarian cancer is based on the pathologic findings at surgery [see Table 4]. Only a minority of women have stage I disease at diagnosis, and the decision whether to employ paclitaxel and carboplatinum chemotherapy is predicated on the surgical extent of the disease. Unfortunately, thorough intraoperative staging is not always performed. In a series of 785 women found to have ovarian cancer in 1991, lymphadenectomy was not done in 66% of the patients with presumptive stage I or II disease.²¹

In patients who appear to have early rather than advanced dis-

Table 4 International Federation of
Gynecology and Obstetrics
Surgical Staging System for Ovarian Cancer

Stage	Characteristics
I	Tumor growth is limited to ovaries.
	IA Tumor is limited to one ovary; there is no ascitic fluid containing malignant cells; there is no tumor on external surface; capsule is intact
	IB Tumor is limited to the two ovaries; there is no ascitic fluid containing malignant cells; there is no tumor on external surface; capsules are intact
II	IC Tumor is either stage IA or IB, but (a) there is tumor on surface of one or both ovaries, (b) capsule is ruptured, or (c) ascitic fluid containing malignant cells is present or peritoneal washings are positive
	Tumor involves one or both ovaries, with pelvic extension.
	IIA Tumor extends or metastasizes to uterus or Fallopian tubes
III	IIB Tumor extends to other pelvic tissues
	IIC Tumor is either stage IIA or IIB, but (a) there is tumor on surface of one or both ovaries, (b) one or both capsules are ruptured, or (c) ascitic fluid containing malignant cells is present or peritoneal washings are positive
IV	Tumor involves one or both ovaries, with peritoneal implants outside pelvis, positive retroperitoneal or inguinal nodes, or both. Superficial liver metastasis equals stage III. Tumor is limited to true pelvis, but with histologically proven malignant extension to small bowel or omentum.
	IIIA Tumor is grossly limited to true pelvis, with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces
	IIIB Tumor involves one or both ovaries, with negative nodes but with histologically confirmed implants on abdominal peritoneal surfaces, none of which are > 2 cm in diameter
	IIIC Abdominal implants > 2 cm in diameter are present, retroperitoneal or inguinal nodes are positive, or both
IV	Tumor involves one or both ovaries, with distant metastasis. If pleural effusion is present, cytologic test results must be obtained to assign a case to stage IV.
	Parenchymal liver metastasis equals stage IV.

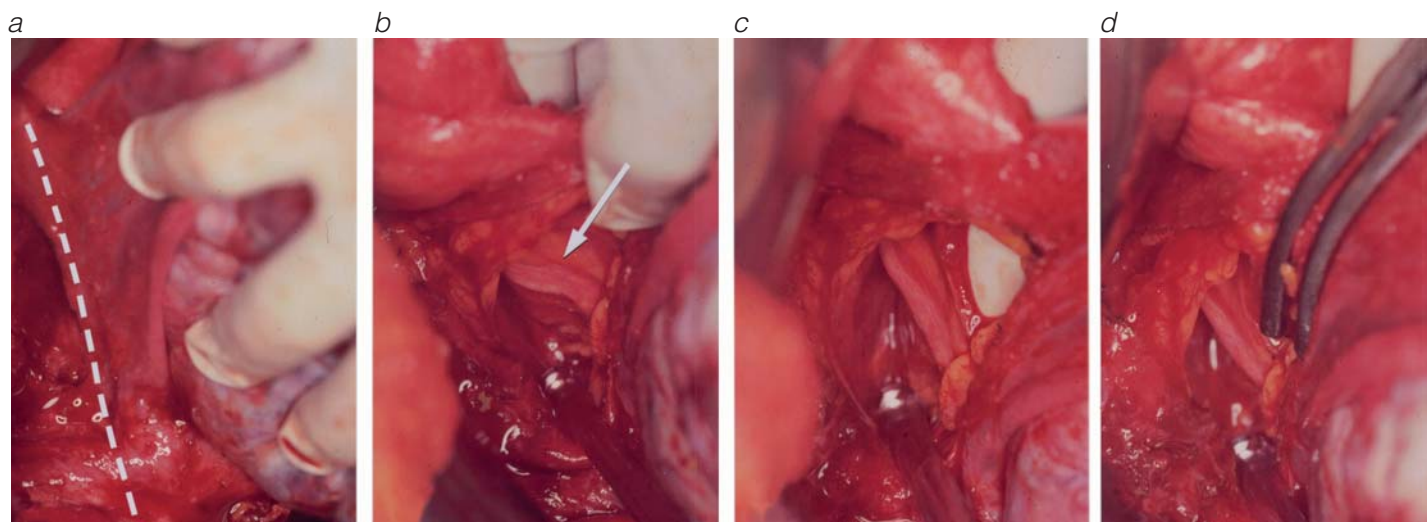


Figure 3 Shown is a retroperitoneal approach to a large, fixed ovarian mass that is adherent to adjacent structures. (a) The mass is drawn medially, and the peritoneum lateral to the infundibulopelvic ligament is divided (dotted line) to afford entry into the retroperitoneum of the pelvis. (b) The ureter (arrow) is identified on the medial leaf of the broad ligament in a location below the infundibulopelvic ligament. (c) An opening is made below the infundibulopelvic ligament and superior to the ureter, and the primary blood supply to the ovarian mass is thereby isolated. (d) The gonadal vessels are clamped, cut, and ligated. The mass is then dissected from the adjacent tissues in view of the ureter.

ease, the emphasis is on accurate staging. At least 30% of patients whose disease is seemingly confined to the pelvis show some evidence of upper abdominal or nodal spread. A midline incision is made, and upon entry into the peritoneal cavity, any free abdominal fluid is submitted for cytologic evaluation. If no abdominal fluid is present, pelvic washings are done with 50 to 100 ml of saline, and the saline is recovered and submitted for cytologic evaluation. The ovarian tumor should be removed intact (if possible) and submitted for frozen-section analysis. The intra-abdominal surfaces and the viscera are systematically inspected. Any suspicious areas or adhesions are subjected to biopsy. Random peritoneal biopsies are performed on the lateral upper and lower paracolic gutters, the bladder flap, the cul-de-sac, and the pelvic sidewalls. Sterile tongue depressors are used to obtain cytologic specimens from both infradiaphragmatic surfaces. An infracolic omentectomy is performed. The regional nodes are palpated, and any enlarged lymph nodes are removed. Finally, the pelvic and para-aortic nodes are sampled to allow detection of any occult spread.

Because the majority of patients with ovarian epithelial cancers present with advanced disease, the main goal of surgical intervention is often tumor debulking. The purpose of cytoreduction is to remove the primary cancer, as well as any metastases. If complete resection of metastases is not feasible, the aim is to reduce the bulk of the residual disease to, ideally, a diameter of 1 cm or less (so-called optimal debulking). Optimal cytoreduction enhances the response to I.V. paclitaxel and carboplatinum chemotherapy, and patients with minimal residual disease have a distinct survival advantage over those with more substantial residual disease. Furthermore, current data indicate that patients who have undergone optimal debulking may be candidates for intraperitoneal, as opposed to I.V., chemotherapy. There is evidence to suggest that the use of intraperitoneal chemotherapy may improve survival rates.²²

The removal of pelvic disease is accomplished via a retroperitoneal approach [see Figure 3]. Although ovarian cancers commonly involve and distort peritoneal surfaces, they usually do not have a significant effect on the retroperitoneal anatomy. The retroperi-

toneum is entered laterally along the surface of the psoas muscle. The procedure is initiated by either dividing the round ligament or entering the peritoneum lateral to the infundibulopelvic ligament. Upon entry into the retroperitoneal space, the infundibulopelvic ligament, the ureter, and the great vessels are identified. The pararectal and paravesical spaces may be developed to facilitate the removal of locally advanced pelvic disease [see Figure 2]. If the disease involves the bowel, its mesentery, or both, resection and reanastomosis may be necessary, either to remove an obstruction or to achieve optimal tumor debulking. Small bowel resection may be required to achieve optimal cytoreduction in as many as 10% of patients.^{23,24}

Primary peritoneal and tubal cancers are relatively rare malignancies whose presentation may include a mass, malignant ascites, or pain. These tumors are more frequent in patients with *BRCA1/BRCA2* mutations, and they bear a histologic resemblance to, as well as behave as, ovarian epithelial carcinomas. Treatment is identical to that of ovarian cancer, with initial surgical intervention establishing the diagnosis and the disease stage. After tumor debulking, paclitaxel and carboplatinum chemotherapy is administered. Patients with tubal cancers should undergo hysterectomy and bilateral salpingo-oophorectomy. If there is no evidence of gross tumor spread, a staging procedure is performed that includes sampling of the pelvic and para-aortic lymph nodes, infracolic omentectomy, and procurement of peritoneal specimens for cytologic examination through multiple peritoneal biopsies.

CERVICAL CANCER

Although cervical cancer is only the third most common gynecologic malignancy in the United States, it is the most common genital tract cancer in the world. Patients with early invasive carcinomas may present with nothing more than an abnormal Pap smear, but most complain of postcoital bleeding or a bloody vaginal discharge. With early disease, colposcopy or conization may be required to establish the diagnosis; however, the majority of patients have a gross cervical lesion, and punch biopsy is usually

Table 5 International Federation of Gynecology and Obstetrics Surgical Staging System for Cervical Cancer

Stage	Characteristics
I	IA Tumor is invasive carcinoma that can be diagnosed only by microscopy IA1: Tumor has measured stromal invasion of ≤ 3 mm and extension of ≤ 7 mm IA2: Tumor has measured stromal invasion of > 3 but < 5 mm and extension of ≤ 7 mm
	IB Tumor is clinically visible lesion limited to cervix or microscopic lesion more extensive than stage IA IB1: Tumor is clinically visible lesion with maximum diameter of ≤ 4 cm IB2: Tumor is clinically visible lesion with maximum diameter of > 4 cm
II	Tumor invades beyond uterus but does not reach pelvic wall or lower third of vagina.
	IIA Tumor does not obviously involve parametrium
	IIB Tumor obviously involves parametrium
III	Tumor extends to pelvic wall. On rectal examination, there is no cancer-free space between tumor and pelvic wall.
	Tumor involves lower third of vagina. All cases with hydronephrosis or a nonfunctioning kidney are included unless known to be attributable to another cause.
	IIIA Tumor involves lower third of vagina, with no extension to pelvic wall
	IIIB Tumor extends to pelvic wall, hydronephrosis is present, or kidney is nonfunctioning
IV	Tumor extends beyond true pelvis or involves mucosa of bladder or rectum (as proved by biopsy). Bullous edema per se does not permit case to be allotted to stage IV.
	IVA Tumor spreads to adjacent organs
	IVB Tumor spreads to distant organs

performed to establish the diagnosis. As a result of the necrotic debris and blood, cytology yields false negative results in as many as 50% of invasive cervical carcinomas. When a gross cervical lesion is present, biopsy and histologic evaluation are mandatory.

The staging of cervical cancer is based on the clinical findings and takes into account the results of pelvic examination, chest radiography, and intravenous pyelography (IVP) [see Table 5]. Stage I cervical cancer denotes disease that is limited to the cervix itself. It may be subdivided into stages IA (microscopic disease) and IB (more advanced or grossly visible disease). The assignment of a cervical cancer to stage IA requires that cervical conization be done to assess the depth and lateral extent of stromal invasion. Microinvasive carcinoma is a tumor that invades the cervical stroma to a depth of 3 mm or less, without lymphovascular space involvement. Stage II cancer denotes disease that involves the upper two thirds of the vagina or parametrial disease that has not reached the pelvic sidewall. Stage IIIB cancer denotes parametrial disease that has reached the pelvic sidewall or results in ureteral obstruction.

Treatment of cervical cancer is predicated on the patient's suitability for surgery and on the stage and bulk of the tumor. Young patients with early, genuine microinvasive carcinomas and a desire for future childbearing may be followed conservatively after conization with negative margins. For the majority of patients with microinvasive cancers, definitive treatment consists of simple abdominal or vaginal hysterectomy; the risk of pelvic nodal metastasis is lower than 1%. Patients with stage IA2, IB, and IIA disease may be treated with radical hysterectomy. This surgical procedure differs from simple abdominal hysterectomy in several respects. In

a simple hysterectomy for benign disease, the vascular pedicles are placed close to the uterus and the cervix. A radical hysterectomy dissects out the lower aspect of the ureters, allowing wider clearance of the central specimen and the adjacent adventitial tissues (e.g., cardinal ligaments and parametria). At an early point in the procedure, the pararectal and paravesical spaces are developed [see Figure 2]. If the disease appears to be limited to the central specimen, the uterine artery is divided at its point of origin from the superior vesical artery and mobilized over the ureter. The parametria, lying between the pararectal and paravesical spaces, are divided. The ureters are separated from the medial peritoneum of the posterior leaf of the broad ligament, then dissected out to the point where they insert into the bladder. Once the distal ureters have been mobilized, clamps are placed into the paravaginal tissues, and an extra margin of lateral tissue is removed. The rectovaginal septum is also developed to allow division of the uterosacral ligaments closer to their point of origin at the sacrum. The upper 2 cm of the vagina is removed in continuity with the rest of the specimen. A systematic pelvic lymph node dissection is then performed, with skeletonization of the common iliac artery, the external iliac artery, the external iliac vein, and the obturator nerve.

Patients who have more advanced disease (stage IIB or higher) or are unable to undergo surgery are treated with radiotherapy and chemotherapy as a radiation sensitizer. Initially, protracted, fractionated external beam radiotherapy is administered. By using a number of fields, external beam treatment distributes radiation to the central tumor and the pelvic lymph nodes in a relatively homogeneous fashion. External radiotherapy is followed by intracavitary radiotherapy, in which a radioisotope is placed into the uterus, the cervix, and the upper vagina. The radiation delivered by intracavitary radiotherapy is distributed according to the inverse square law: a substantial amount is delivered to the central tumor, but the dose falls off rapidly in adjacent tissues as the distance from the central lesion increases.

VULVAR CANCER

Vulvar cancers arise from the epidermis of the vulva and are usually of squamous histology. Approximately 30% to 40% of vulvar cancers are related to exposure to HPV, usually in younger patients and those with preexisting vulvar dysplasia. In the majority of patients, however, no clear cause can be identified. Vulvar carcinomas spread by embolization along lymphatic channels, which ter-

Table 6 Characteristics of Complete and Partial Moles

Parameter	Complete Mole	Partial Mole
Anatomy	No fetus or fetal parts present	Fetus or fetal parts present
Histology	Generalized villous swelling; diffuse trophoblastic proliferation	Focal trophoblastic proliferation and villous swelling; villous scalloping and prominent trophoblastic inclusions
Karyotype	Diploid, usually 46 XX (all genetic material is paternal)	Diandric triploidy
Presentation	Uterus large for dates; pre-eclampsia; hyperthyroidism; theca-lutein cysts	Missed or incomplete abortion
Natural history	20% chance of requiring chemotherapy	3% to 4% chance of requiring chemotherapy

minate at the inguinofemoral lymph nodes. Superficial and medial lymph nodes are the ones most commonly involved. The pelvic lymph nodes are rarely involved unless the ipsilateral inguinal nodes contain metastatic disease.

Treatment must take into account both the primary vulvar lesion and the possibility of inguinal node metastasis. Historically, radical vulvectomy with bilateral groin dissection was the standard of care for the treatment of vulvar cancers. Currently, the emphasis is on performing the most conservative surgical procedure that is consistent with cure of the disease. Radical local excision with surgical evaluation of the inguinal nodes has become the modern standard of care for most patients. The vulvar lesion is excised with margins of at least 1 cm. The incision is carried to the inferior fascia of the urogenital diaphragm, which is coplanar with the fascia lata of the thigh and the fascia over the pubic symphysis. If more than 1 mm of stromal invasion is noted, surgical evaluation of the inguinofemoral lymph nodes is required. Bilateral groin dissections are not necessary unless the lesion is on the clitoris, the anterior labia minora, or the perineum or lies within 1 cm of the midline. If the extent of stromal invasion is 1 mm or less, node dissection is not necessary, because the risk of groin metastasis is low.

Surgical evaluation of the inguinal nodes has also evolved over time. The current surgical options are (1) a superficial inguinal node dissection that removes the lymphatic tissue above the fascia lata and the cribriform fascia and (2) a complete inguinofemoral node dissection that removes both the superficial nodes and the deep nodes lying below the cribriform fascia and medial to the femoral vein. Advocates of the first option view the superficial inguinal nodes as the sentinel lymph nodes of the groin and consequently maintain that a more extensive dissection is generally not required.

Patients found to have positive inguinal nodes at groin dissection receive adjuvant radiotherapy. Patients with advanced, unresectable primary disease, who in the past were treated with exenteration, now are treated with radiation and chemotherapy as a radiation sensitizer. Local (perineal) recurrences are treated with wide local resection. Unfortunately, recurrences in the inguinal nodes after primary therapy usually are refractory to further therapy and often prove fatal.

GESTATIONAL TROPHOBLASTIC DISEASE

Gestational trophoblastic disease is a blanket term for a range of placenta-derived neoplasias that include hydatidiform mole, invasive mole, gestational choriocarcinoma, and placental site tumor. Of these conditions, the one most frequently encountered is hydatidiform mole, or molar gestation. In the United States, moles occur in approximately one of every 1,000 to 1,200 pregnancies. Patients present with vaginal bleeding, passage of mole tissue through the vagina, a uterus that is large for the gestational age (as determined on the basis of the last menstrual period), or medical complications deriving from the mole. The diagnosis is established through ultrasonographic examination of the uterus. Therapy consists of evacuation of the uterine contents (ideally by suction curettage) and subsequent serial serum β -hCG determinations, with adequate contraception during the follow-up period. Moles usually are complete but sometimes are partial (i.e., occur with fetal tissue or even a fetus). The distinction between complete and partial moles, though initially regarded as little more than a medical curiosity, actually reflects identifiable differences in anatomy, histology, presentation, and natural history [see Table 6].

If β -hCG levels rise or plateau or there is evidence of metastatic disease, further therapy for postmolar malignant gestational trophoblastic neoplasia is required. Before effective chemotherapy became available, it was common practice to perform hysterectomy, allowing pathologic assessment of the uterine contents (persistent mole, invasive mole, or choriocarcinoma).

Currently, most women with gestational trophoblastic disease can be successfully managed by means of chemotherapy, without risk to the reproductive organs. Patients are evaluated for metastases with various radiologic studies and are stratified according to prognostic risk factors (as assessed by criteria developed by the National Institutes of Health, the International Federation of Gynecology and Obstetrics, or the World Health Organization). Sites of metastatic disease are documented; however, to avoid the risk of a major hemorrhage, they are not subjected to biopsy. Therapy is governed by the level of risk present. Single-agent therapy (with methotrexate or actinomycin D) is given to patients with low-risk disease, and aggressive multiagent therapy is given to patients with high-risk disease.

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Acknowledgment

Figure 2 Alice Y. Chen.

6 ORGAN PROCUREMENT

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Improvements in immunosuppression, organ preservation, surgical technique, and recipient management have led to the widespread adoption of transplantation as a viable therapeutic option for end-stage organ disease. Consequently, more patients than ever are benefiting from organ transplantation. Unfortunately, the rate of organ donation has not kept pace with the increase in the number of recipients awaiting transplantation. For example, statistics from the United Network for Organ Sharing (UNOS) reveal that in 2006, more than 97,000 patients were awaiting transplantation, but only 28,000 transplants were performed.¹

The relative shortage of organs has necessitated an increasing reliance on creative strategies aimed at broadening or expanding the limits of the donor pool. For instance, organs now are frequently obtained from so-called extended-criteria donors (i.e., donors who are elderly or who have significant comorbid conditions)²⁻⁴ or from non-heart-beating donors.⁵ Kidneys from pediatric donors that previously would have gone unused are currently procured en bloc (i.e., together with a common patch of aorta and vena cava) for use in a single adult.^{6,7} Transplant surgeons now also routinely split livers so that two recipients can receive transplants from a single donor liver.⁸

A particularly important strategy for alleviating the organ shortage has been the broader application of living donor transplantation. In 2001, the number of organs transplanted from living donors actually exceeded the number of those transplanted from cadaveric donors.¹ Living kidney donation has been practiced for years, but technical advances in laparoscopic donor nephrectomy have made it even more appealing. Since the early 1990s, segmental livers from living donors have been successfully transplanted into pediatric recipients. Subsequently, transplantation of right or left hemilivers from live donors into adult recipients has gained widespread acceptance.⁸ Living donor transplantation has proved itself to be technically feasible; however, it has also raised certain new ethical and philosophical concerns that the transplant community has not yet fully resolved.

The procurement process includes not only the donor operation but also the evaluation of donors and potential recipients. Comorbid disease in a donor can render certain organs unsuitable for transplantation into particular recipients. Accordingly, careful consideration of any relevant factors affecting either the donor or the recipient is necessary to ensure optimal outcomes. Although clinical judgment is still paramount, it is based on a rising level of technical expertise and surgical experience. Procurement of multiple organs from a single cadaveric donor is now routine, and living donor options have been greatly expanded. It is possible to take the heart, one or both lungs, the kidneys, the liver (whole or split), the pancreas, and the intestines from one donor and

then to transplant them into as many as nine recipients at multiple transplant centers. In addition, it is possible to procure various nonvascularized tissues (e.g., bones, corneas, blood vessels, valves, and skin), which can be used to help many more patients.

One of the most important advances in the field of transplantation has been in the area of organ preservation. The widespread use of University of Wisconsin (UW) solution (Belzer solution) has improved the safety of organ preservation and relaxed the time constraints on the transplantation of all organs [see Table 1]. In the past few years, a newer preparation, crystalloid-based histidine-tryptophan-ketoglutarate (HTK) solution, has shown extremely promising results in liver, kidney, and pancreas transplantation.⁹⁻¹¹ A better understanding of the molecular basis of ischemia-reperfusion injury will pave the way for further advances in the future.

In what follows, we outline the current state of organ procurement from both cadaveric and living donors, including donor evaluation, perioperative management, and the various donor procedures. Cadaveric and living donors are discussed separately because these two groups differ vastly, both from a technical or surgical standpoint and from a medical standpoint.

Organ Procurement from Cadaveric Donors

POTENTIAL CADAVERIC DONORS

Because of advances in trauma and critical care medicine, many critically ill patients now survive who previously would have succumbed to their illnesses. A patient does not become a potential donor until all lifesaving efforts have failed. Once the patient has been declared brain dead and the decision has been made to proceed with organ donation, management of the donor is redirected toward optimizing potentially salvageable organs, a process that often necessitates aggressive fluid resuscitation.

It is imperative for health care providers to remember that whereas donors are not salvageable, dying patients waiting for transplants may be, and the lives of the recipients depend on the quality of the donated organs. Good donor management with careful attention to details (e.g., sterile technique, antibiotics, timely transfusion, and vasopressor management) is vital for achieving optimal transplantation outcomes. In addition, it is important to demonstrate to health care workers, lay people, and donor families that organ donors are treated with respect and dignity.

COORDINATION OF DONOR AND RECIPIENT ACTIVITIES

After a potential donor has been identified, the donor coordinator from the local organ procurement organization

Table 1 Composition of University of Wisconsin (UW) Solution*

Raffinose, 30 mmol/L	Potassium, 125 mmol/L
Lactobionate, 100 mmol/L	Sodium, 125 mmol/L
Hydroxyethyl starch, 50 g/L	Magnesium, 5 mmol/L
Sulfate, 5 mmol/L	Adenosine, 5 mmol/L
Phosphate, 25 mmol/L	Glutathione, 3 mmol/L
Allopurinol, 1 mmol/L	

*Penicillin and heparin are added within 2 hours of use.

(OPO) obtains a detailed medical and social history. The donor's acute physiologic status is assessed on the basis of blood pressure (measured via an arterial line), central venous pressure (CVP), urine output, arterial blood gas values, and serum chemistry. Serologic analysis must be done for syphilis (Venereal Disease Research Laboratory [VDRL]), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), hepatitis C virus (HCV), cytomegalovirus (CMV), human immunodeficiency virus (HIV), and human T cell lymphotropic virus type I (HTLV-1). In certain cases (e.g., kidney, pancreas, and intestinal transplants), inguinal lymph nodes must be removed through a small groin incision at the bedside to facilitate tissue typing, which takes an average of 4 hours. For kidneys in particular, genetic matching of donor and recipient has been shown to improve outcome.¹²

The OPO coordinator then contacts local and regional transplant programs about their needs for renal and extra-renal organs. UNOS maintains a national computer registry of potential recipients for all organs (<http://www.unos.org>). Potential organ recipients are categorized according to (1) ABO blood group, (2) degree of medical urgency, (3) length of time the patient has been on the transplant list (i.e., waiting time), (4) weight, (5) acceptable weight range of the donor, and (6) distance the recipient team is willing to travel for procurement.

Sharing of all organs is based on the principle that organs should be offered first to patients in the local area and then to patients within a larger geographic region. (UNOS has divided the United States into 11 geographic regions for the purposes of organ distribution [see Figure 1].) If no suitable recipient can be found locally or within the donor's UNOS region, the organ is offered to patients across the nation. An exception to this rule exists for kidneys. For kidneys, when there is a six-antigen match (i.e., a perfect histocompatibility match between a donor and a recipient on all six HLA-A, HLA-B, and HLA-DR antigens) or when there is at least phenotypic identity between a donor and a prospective recipient (i.e., no HLA mismatch), the kidney must be offered first to the matched recipient, regardless of geographic location.

Specific medical criteria for prioritizing patients on the waiting lists for various organs are constantly being reevaluated. Full discussion of these criteria is beyond the scope of this chapter. Briefly, allocation of kidneys currently depends most on waiting times, but new considerations related to net lifetime saved are being integrated into evolving algorithms. The system for distributing livers changed in spring 2002 from one that gave significant priority to waiting time to one that stratified patients according to medical urgency. The use

of the medical model for end-stage liver disease (MELD), a composite score based on total bilirubin, the international standardized ratio (INR), and the serum creatinine concentration, has dramatically changed the way in which cadaveric livers are allocated.¹³

Once organs are matched to specific recipients, the local OPO procurement coordinator arranges an operating room time for the donor procedure and organizes transportation of the participating surgical teams. Multiple-organ harvests require considerable coordination between the different institutions, surgeons, and coordinators. In the meantime, it is important that the donor be kept hemodynamically stable [see Cadaveric Donor Operation, *below*]. With the proliferation of experienced transplant centers, it has become common for most organs to be procured by local procurement teams and shipped to the recipient institutions. This collaboration has improved the coordination of the retrieval process, reduced the transportation costs associated with long-distance procurements, and helped ease the burden on the recipient teams. Certain organs (e.g., hearts, intestines, and multivisceral grafts) are still generally procured by the recipient institution.

EVALUATION OF DONOR ORGANS

The decision to use an organ is ultimately based on an experienced transplant surgeon's judgment at the time of the procurement. Careful evaluation of the donor, the prospective recipient's medical history, and any pertinent laboratory data is essential for ensuring the best outcome. As noted (see above), the persistent organ shortage and the resulting extension of donor criteria have led to the retrieval of more organs from older, more marginal, or even non-heart-beating donors. Donor selection criteria show considerable variation from one setting to another, depending on the organ being transplanted and the transplant center involved.

Liver

Several biochemical parameters are considered in the evaluation of liver grafts. With ideal donors, these parameters normally include the serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), and bilirubin levels. However, even with donors in whom the injurious event leading to death results in abnormal transaminase levels (which may be reversible), livers suitable for transplantation can often be salvaged after appropriate resuscitation. Livers from donors with viral hepatitis or alcoholism can also be successfully used for transplantation if an acceptable biopsy is performed. Sustained hyponatremia (serum sodium concentration > 170 mg/dl) is a recognized risk factor for primary nonfunction¹⁴ and should be aggressively treated with administration of free water. Hepatic steatosis, more commonly observed in livers from obese donors, has been associated with liver graft dysfunction and primary nonfunction. More specifically, the risk of dysfunction or nonfunction is associated with irreversible macrovesicular steatosis; microvesicular changes are often reversible, typically occurring as a result of an acute insult.¹⁵

When a liver is being considered for whole-organ transplantation, the size of the graft and the amount of space available within the recipient are important issues. In general, the mass of the liver graft to be transplanted must equal at least 2% of the recipient's ideal body mass.¹⁶ With this stipulation in mind, the liver may be split or reduced in accordance with the principles of hepatic segmental anatomy

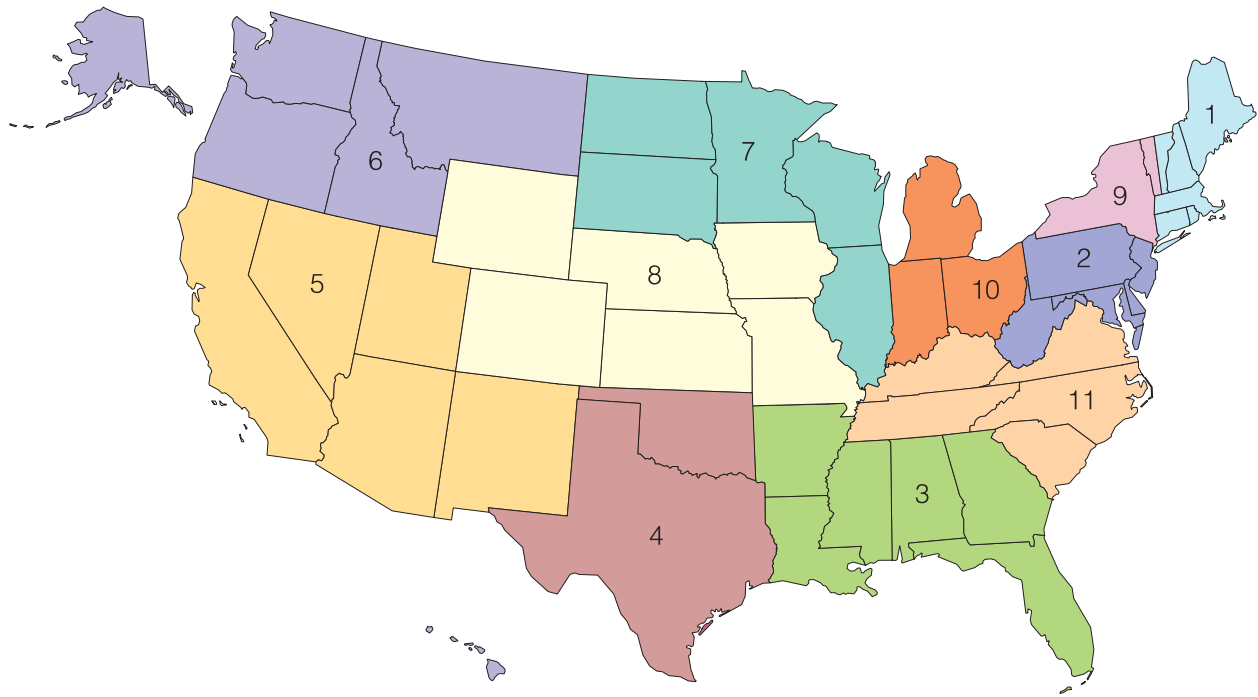


Figure 1 Shown are the 11 geographic regions employed by UNOS for distribution of organs.

[see 5:23 *Hepatic Resection*], thereby enabling liver transplants to be supplied to multiple recipients, including even the smallest of pediatric patients. Living donor transplantation of the right or left hemiliver into adults has also been popularized, thus making more options available to patients with end-stage liver disease.^{17,18}

Kidneys

When kidney transplantation is performed in a sensitized recipient, a negative crossmatch is essential for avoiding accelerated rejection. For the kidney graft itself, anoxia time and hypoperfusion time correlate with graft dysfunction. Donor-related factors (e.g., age, diabetes, hypertension, hypercholesterolemia, and obesity) contribute to native renal disease, which may prevent use of the kidneys for transplantation. Biochemical parameters (e.g., serum creatinine concentration and creatinine clearance) are important indicators of kidney function. If the donor is elderly and has multiple comorbid conditions, a renal biopsy is helpful in determining suitability for transplantation. Generally, if a biopsy shows less than 20% scarring, it is acceptable to proceed with transplantation. Currently, many OPOs maintain extracorporeal perfusion of kidney grafts; this practice purportedly offers some benefit to the graft beyond the prolongation of potential cold ischemia time. Pump parameters (resistive indices < 0.2 ml/min and flow > 100 ml/min) are also objective markers of graft function.¹⁹ Expansion of the kidney donor pool through cautious use of extended donor criteria is safe and effective.²⁰

Heart and Lung

The criteria for heart and lung donors are strict. Donors are usually young, with no cardiac disease and a normal chest

x-ray and electrocardiogram. Donors are also closely matched to recipients with respect to size (though the matching must also take into account the fact that recipients often have cardiomegaly as a consequence of heart failure). Echocardiography is valuable for documenting cardiac wall motion and the ejection fraction; however, coronary angiography is necessary in the assessment of older donors. The arterial oxygen tension (P_{aO_2}) of lung donors should be at least 350 mm Hg during ventilation, with a fraction of inspired oxygen (F_{iO_2}) of 1. In addition, bronchoscopy is useful in the evaluation of lungs for donation. The final determination of whether to use the heart or lungs for transplantation is based on inspection of the organs at the time of procurement by an experienced thoracic transplant surgeon.

Pancreas

Pancreas transplantation is not lifesaving; therefore, pancreas donors tend to be chosen more selectively than donors of other organs. Clearly, diabetes is an absolute contraindication to donation. Less commonly, fibrotic or fatty infiltration resulting from alcohol use and obesity may render pancreata unsuitable for transplantation. Serum amylase, lipase, and glucose measurements may be useful. A negative crossmatch is a necessity in sensitized patients. Ultimately, the gross appearance of the gland in the donor during procurement dictates whether the organ should be used for transplantation. Pancreata that are not used for whole-organ transplantation should be considered for clinical islet cell transplantation or research.²¹

Intestine

Patients with intestinal failure can be supported with total parenteral nutrition (TPN) until transplantation can

be undertaken. Frequent line infections, difficult access, and cirrhosis arising from TPN-related liver disease all pose substantial challenges to surgeons considering intestinal transplantation. Consequently, intestinal donors are chosen very carefully. The intestine is very sensitive to hypotension, as well as to the vasoactive agents commonly used to resuscitate hypotensive donors, which cause mesenteric vasoconstriction and thereby potentiate graft ischemia. Consideration should be given to matching recipients who are CMV naïve or Epstein-Barr virus (EBV) naïve with seronegative donors. In patients with short-gut syndrome, loss of abdominal domain is commonplace, making size matching between donor and recipient a paramount concern. Laparostomy is a predictor of poor outcome; therefore, the donor ideally should be 50% to 75% of the recipient's size. To reduce ischemia time, it is often necessary to begin the recipient operation before the donor operation is completed.

PERIOPERATIVE MANAGEMENT

Every effort is made to sustain the donor in a normal physiologic state up to the organ procurement procedure. Aggressive monitoring of BP, arterial oxygenation, central venous pressure, and urine output is key to donor management. Donor therapy is aimed at maintaining adequate circulation through aggressive restoration of intravascular volume and optimal ventilation, thereby providing maximal organ perfusion. Anemia can exaggerate tissue hypoxia and should be addressed with blood transfusion as indicated.

Often, brain death results in perturbation of the neurohormonal axis, leading to donor instability; relatively expeditious procurement is then necessary to preserve organ quality. Severe neurogenic shock and unopposed peripheral vasodilation ensue after brain death. Even with volume loading, vasopressor support must often be added to remedy the inadequate peripheral vascular resistance. These agents commonly produce severe visceral vasoconstriction, and careful balancing is necessary to guard against injury to the transplantable organs.

Severe head injury often leads to failure of pituitary function and thus to an absence of antidiuretic hormone (ADH). The ensuing diabetes insipidus produces a profound diuresis, giving rise to severe volume depletion and donor instability. Volume resuscitation should aim at replacing hypotonic losses with appropriately matched intravenous fluids so as to prevent hypernatremia, which can exert undue osmotic stress on the organs to be used for transplantation. Accordingly, electrolyte levels should be monitored frequently, and consideration should be given to I.V. administration of vasopressin to treat concomitant hypotension and diabetes insipidus. Triple hormonal resuscitation—comprising injection of a methylprednisolone bolus and infusion of both triiodothyronine and vasopressin—is also effective in improving the yield of transplantable organs from donors. In particular, hearts procured from donors treated with neurohormonal replacement not only are more likely to be used for transplantation but also exhibit enhanced early graft function.²²

Before the procurement procedure, the donor's chart is carefully reviewed by the transplant surgeon to confirm satisfactory completion of the declaration of brain death and the consent for organ donation.²³ In addition, the blood type, the serologic assays, and the laboratory test results should

be confirmed. Transport to the operative theater should be undertaken by skilled anesthesia personnel to ensure that hemodynamic insults are avoided. In the OR, the anesthetic team is charged with maintaining donor stability, as well as with facilitating the procedure through optimal muscle relaxation (often, spinal reflexes persist in the donor).

CADAVERIC DONOR OPERATION

The operation for multiple organ procurement must proceed in such a way that all of the transplantable organs can be removed without being jeopardized. There are as many ways to perform donor operations as there are surgeons performing them. In general, however, regardless of which organs are to be procured, the operation includes a preliminary dissection of the great vessels of the abdomen and the chest. The aorta is isolated at preplanned levels to allow cross-clamping, so that the organs to be removed can be core-cooled in situ with intra-aortic and intraportal infusions, thereby avoiding warm ischemia. This technique has been adopted as an international standard.

The most refined version of in situ core cooling, commonly known as the rapid-flush technique, can be completed from beginning to end in less than 1 hour.²⁴ The rapid-flush technique is the procedure of choice for unstable donors and in cases of donation after cardiac death (DCD). With this approach, no dissection is done until after circulatory arrest and in situ core cooling of the organs, at which point all that is required is rapid dissection and subsequent cannulation of the infrarenal aorta. Some surgeons perform all of their organ procurements with this method. Its major drawbacks are (1) that most of the dissection is done in bloodless organs that have been infused with preservative and are uniformly discolored white and (2) that cold ischemia times are generally longer because no preliminary dissection was performed.

The procurement procedure begins with a generous incision from the sternal notch to pubis with an electrocautery device [see Figure 2]. The sternum is opened with a sternal saw or a suitable substitute. (If a previous sternotomy was done, the opening of the sternum is delayed until the abdominal aorta has been encircled and cannulated. Although this approach provides more limited exposure at first, it helps ensure that the organs will not be lost should the heart be injured during the reopening of the sternum.) The pericardium is opened and the heart inspected. The abdominal and thoracic contents are grossly examined and palpated after a large Balfour-type retractor is in place for exposure [see Figure 3]. A cursory examination of the abdominal and thoracic contents is made, and the organs are evaluated for their quality. It is critical that all occult pathologic conditions be fully investigated and that biopsies be obtained when indicated. The heart should be evaluated with respect to strength of contractions (i.e., snap), donor volume status, and possible cardiac injuries (e.g. contusions). The liver should be examined for contour, color, and consistency, which may provide clues to the degree of fibrosis or steatosis present. The pancreas can be visualized through the lesser sac and should be evaluated for color and fat content. The intestines should be examined for peristalsis and good arterial pulsations in the mesentery, which are reliable indicators of a healthy graft.

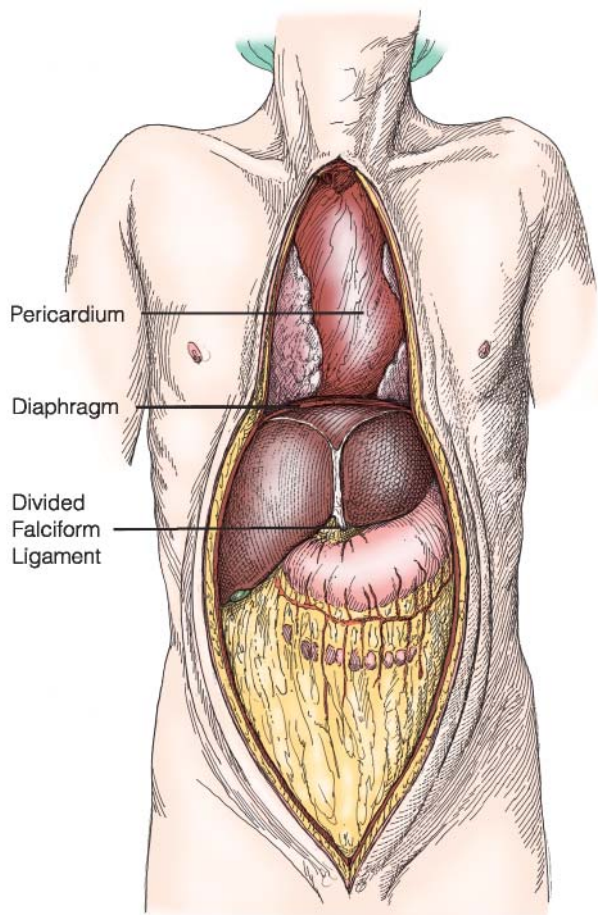


Figure 2 The incision used for multiple organ procurement is made from the suprasternal notch to the pubis. The falciform ligament is divided and the pericardium opened.

The order in which the steps of the procurement procedure are done varies from surgeon to surgeon, as does the ratio of “warm dissection” to “cold dissection.” The approach we describe here is only one of the many viable methods. The white line of Toldt is taken down on the patient’s right side, and the intestines are rotated medially until the aortic bifurcation is exposed. The aorta is encircled with a No. 2 silk suture. This step is then repeated, and both ties are clamped and set aside. The inferior mesenteric artery (IMA) may be either ligated and divided or simply left alone, but care must be taken not to injure any inferior-pole renal arteries that may be coming off the aorta or the common iliac artery aberrantly. If such an artery is present or if the distal aorta cannot be cannulated, the distal common iliac artery may be encircled and cannulated while the contralateral iliac artery is clamped.

Attention is then turned to the liver. The left triangular ligament is taken down, and the gastrohepatic ligament is examined for an accessory left hepatic artery. If such an artery is discovered, it should be preserved [see Figure 3]. Otherwise, the gastrohepatic ligament is divided; this measure may suffice for exposure of the common hepatic artery. A small, fine right-angle instrument (or an equivalent device) is used to divide the tissue overlying the artery until the proper plane

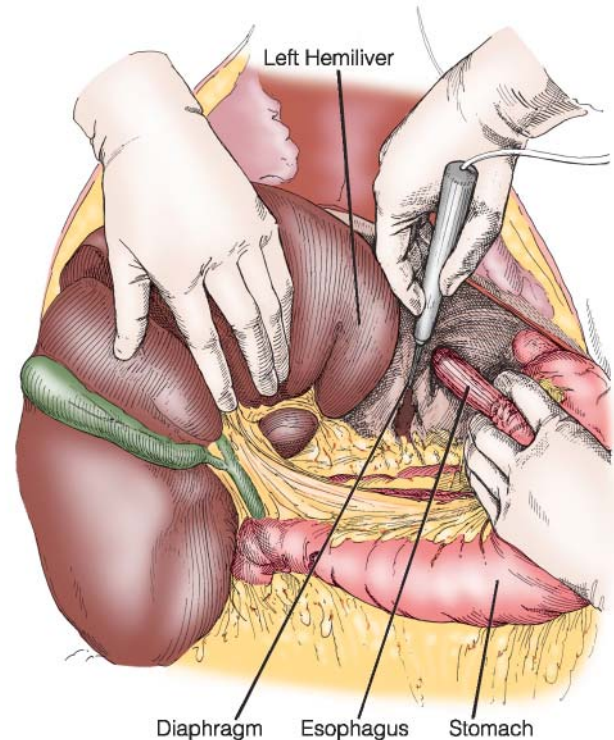


Figure 3 The left triangular and gastrohepatic ligaments are divided so that the left lobe of the liver can be retracted to the right. The diaphragmatic crura are divided between the esophagus and the vena cava to facilitate exposure and encirclement of the aorta at the level of the diaphragm.

is reached. At this point, exposure of the artery becomes easier, and the common hepatic artery can be exposed from the splenic artery to the gastroduodenal artery (GDA); however, dissection should not proceed beyond the GDA. The peritoneum overlying the porta hepatis is opened to yield a clearer view of the structures beneath, including the common bile duct (CBD). The CBD is divided just as it enters the pancreas, and the pancreas side is ligated (if the pancreas is being procured as well). Before division of the CBD, this area must be carefully examined and palpated to ensure that a right replaced or right aberrant artery is not inadvertently injured.

Once the CBD is divided, the gallbladder is opened just enough to allow insertion of a suction device and is then emptied of its contents, with care taken not to spill bile throughout the operative field. A bulb syringe is employed to flush any stones or debris through the CBD. At this point, it is reasonable to cross-clamp and then continue with either cold or warm dissection. (Often, different teams work at different paces, on different organs, and in different body cavities, and cross-clamping must be coordinated across all of the participating teams.) If a thoracic team is present, the supraceliac abdominal aorta should be clamped. This portion of the aorta is exposed by dividing the arcuate ligaments of the diaphragm. It need not be encircled: it need only be exposed sufficiently to permit proper clamping. (Small branches to the thoracic spine, the diaphragm, and other nearby structures are difficult to see and easy to avulse.) If no

thoracic team is present, the aorta may be cross-clamped in the chest. The thoracic aorta is exposed by sliding a finger or thumb between the posterior esophagus and the anterior thoracic aorta and working the overlying tissue back and forth until the vessel is encircled.

Before the actual cross-clamping, 300 U/kg of heparin is infused and allowed to circulate. The inferior silk suture around the abdominal aorta is tied down to keep the infusate from circulating through the lower extremities. The aorta is then opened, the cannula is placed into the lumen, and the second silk suture is tied down. (With proper exposure of and pressure on the aorta, placement of the cannula can be accomplished without blood loss [see Figure 4].) Once the cannula is in place (but before infusion of the preservation solution) and the heparin is circulating, the aorta is ready for cross-clamping. The surgeon should communicate with the other teams to coordinate the cross-clamping in the chest and the abdomen. In addition, the surgeon should ensure that adequate amounts of cold preservation solution and sterile ice are available to minimize potential injury to the organs during the ischemic time. Once the preservation solution begins to flow into the aorta, the supraceliac (or thoracic) aorta is clamped, and the right atrium (or the inferior vena cava [IVC]) is opened to vent the vasculature. Ice is then carefully

packed around the organs. (Pockets are usually created posterior to the kidneys and in the lesser sac to allow the maximum amount of surface area exposure to the ice [see Figure 5].)

The preservation solutions are designed to maintain the organs' cellular integrity. The impermeants and colloids they include prevent cell swelling, which is the major mechanism of organ injury. At present, UW solution is still the gold standard for preservation of the kidney, the liver, the pancreas, and the small bowel. However, HTK solution is increasingly being adopted by transplant centers for abdominal organ preservation. HTK solution has a low viscosity and contains less potassium than UW solution, which may be advantageous in liver preservation. Another option is Celsior (SangStat Medical Corporation, Fremont, California), an extracellular-type preservation solution that is primarily used for cardiac grafts, though it has been proved effective in preserving abdominal organs. Celsior possesses a strong buffer capacity and is an inert osmotic agent, thereby effectively combining the characteristics of UW solution and HTK solution. Other substances may be added to these preservation solutions, including heparin, antibiotics, and antioxidants (which mitigate the deleterious effects of reactive oxygen species) [see Table 1].

Static cold storage is the preferred organ preservation method in most centers. A 10°C fall in temperature results

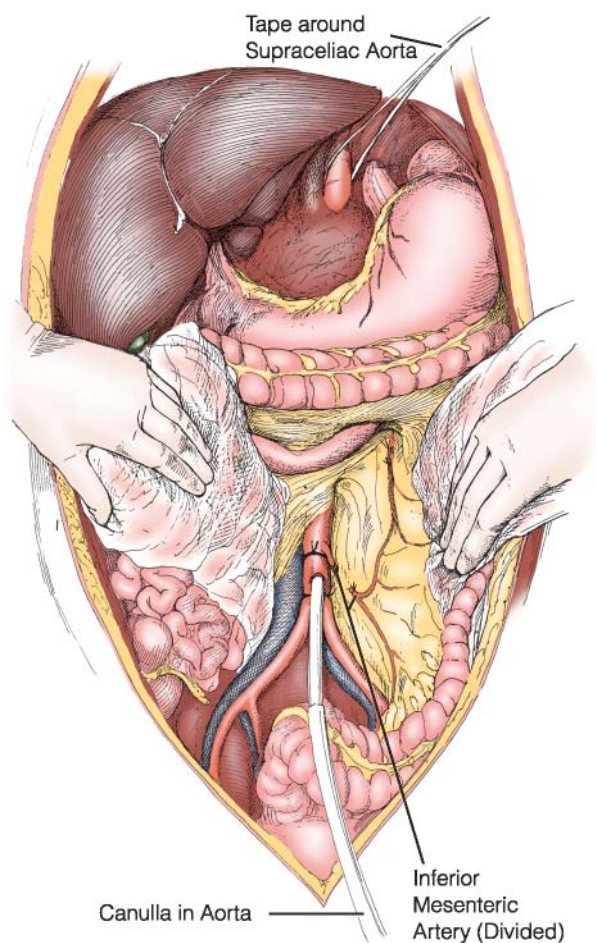


Figure 4 The small intestine is reflected, the distal aorta is exposed, and the inferior mesenteric artery is ligated and divided. A catheter is inserted into the distal aorta.

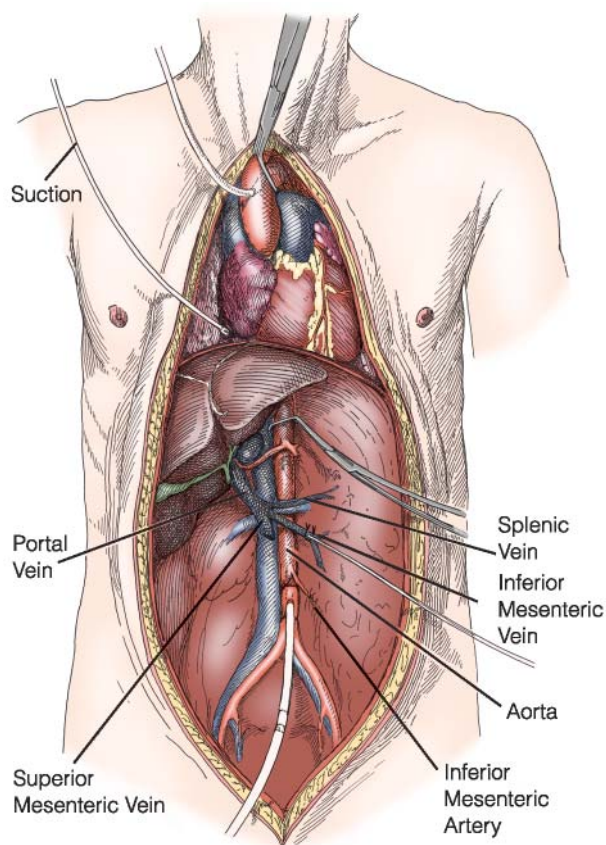


Figure 5 The aorta is cross-clamped at the diaphragmatic level and at the arch level in the chest at the time of rapid infusion.

in a halving of the metabolic rate, so that at 4°C, residual metabolic activity is only about 10% to 12%. Despite the beneficial effects of cooling, ongoing ischemia favors the depletion of cellular adenosine triphosphate (ATP), the switch to anaerobic metabolism with increasing acidosis, and the liberation of reactive oxygen species. Accordingly, every effort must be made to minimize cold ischemia time so as to maximize organ function in the recipient. Cold ischemia sets the stage for a complex cascade of inflammatory events occurring upon reperfusion, which result in early graft injury and dysfunction. Ischemia-induced activation of the endothelium leads to upregulation of permeability and adhesion molecules, which promote infiltration by immune effector cells. These leukocytes elaborate proinflammatory cytokines and reactive oxygen species, which cause cell death and organ injury.²⁵ Hypothermic machine storage (in which pulsatile perfusion of donor organs is maintained during transport) can help mitigate these deleterious effects. In particular, machine perfusion can reduce the incidence of delayed kidney graft function and is superior for preserving kidneys retrieved from extended-criteria and non-heart-beating donors.¹⁹

The various organs differ in their ability to tolerate cold ischemia. Kidneys can be preserved for as long as 72 hours—often longer when hypothermic machine storage is employed. Thus, there is sufficient time for tissue typing and matching, as well as for the subsequent export of kidneys to distant sites. Nonetheless, prolonging cold storage for more than 24 hours diminishes the likelihood that kidney grafts will function immediately in the recipient. Pancreas and liver grafts may be safely preserved for as long as 20 hours; however, the risk of primary liver graft nonfunction increases substantially when cold ischemic time exceeds 12 hours. The intestine may be preserved for as long as 12 hours, but it should be implanted as soon as possible. Time constraints are more rigid for the heart and the lungs; these organs should be transplanted within 6 hours.²⁵

Heart and Lung

After infusion of cold preservation solution, the cardiac team proceeds first, removing the heart, the lungs, or both as expeditiously as possible while the abdominal organs are covered with ice slush and perfused with the preservation solution. (As noted, the heart tolerates cold ischemia relatively poorly.) The heart is core-cooled with a potassium-rich cardioplegic solution infused via a cannula inserted into the ascending aorta. Blanching of the heart and cardiac arrest from the cardioplegic infusion occur within a few seconds. At the same time, systemic venous inflow is discontinued by bleeding the IVC into the chest. Care must be taken to leave enough suprahepatic IVC for both the liver and the heart [see Figure 6]. (In the event that the IVC within the pericardium is to be cross-clamped by the cardiothoracic team, the infrahepatic IVC must be vented into the lower abdomen to prevent venous hypertension.) The aorta is divided distal to the innominate artery, and the pulmonary artery is divided at its bifurcation. Most cardiac teams require approximately 10 minutes from the onset of cardioplegic infusion to complete the cardiectomy. The abdominal viscera are blanching and cooling while the cardiac team is completing its procurement.

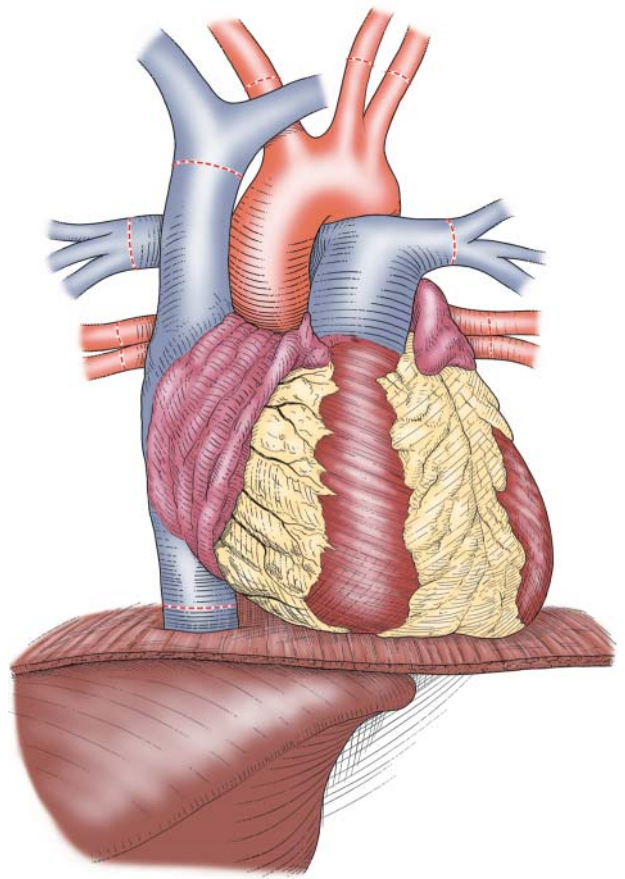


Figure 6 The heart is procured by dividing the aorta at the level of the arch and the suprahepatic vena cava, with care taken to leave adequate caval length with both the heart and the liver.

The operative technique for lung procurement is generally similar to that for heart procurement [see Figure 7]. After mobilization and isolation of the aorta and the superior vena cava (SVC), the trachea is dissected as far above the level of the carina as possible. Prostaglandin E₁ (PGE₁) is given via a catheter in the main pulmonary artery, causing pulmonary vasodilation and thereby optimizing lung perfusion. After infusion of PGE₁ and systemic heparinization, the SVC is ligated and divided. The distal ascending aorta is cross-clamped, the cardioplegic infusion is begun, and topical cold ice slurry is placed on the organs. The lungs are inflated, the endotracheal tube is withdrawn, and the trachea is stapled and divided. The posterior pleurae are incised, and the heart and the double-lung complex are removed from the thoracic cavity, taken to the back table, and separated.

Once the thoracic organs have been procured and the abdominal aortic flush completed, the ice is removed from the abdominal cavity—except for that around the kidneys, which are routinely the last organs to be removed.

Liver, Pancreas, and Intestines

Once the effluent coming from the IVC is clear, the process of removing the abdominal organs begins. The remainder of the celiac trunk is exposed down to the aorta. The left gastric artery and the splenic artery are divided. (If the pancreas is to be procured as well, a tag may be placed on the pancreatic

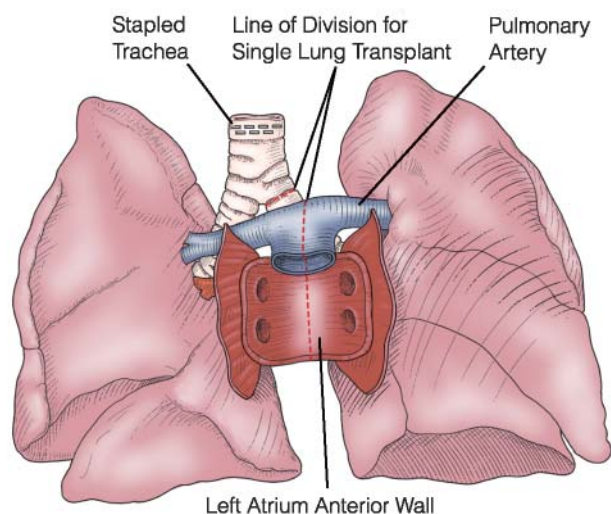


Figure 7 Shown is en bloc procurement of heart and lungs.

portion of the splenic artery to help identify it.) The celiac trunk is then removed with a Carrel patch. A fair amount of fibrous neural tissue must be transected to expose this area of the aorta. The hepatic artery is then dissected free from surrounding tissue as far as the GDA, with care taken not to stretch the artery unduly and thereby risk intimal damage. Near the GDA is the origin of the right gastric artery, a small branch that is easily avulsed if the surgeon is insufficiently careful. The GDA is then divided.

Once the hepatic artery is reflected toward the liver, the portal vein should come into view. If the pancreas is being procured as well, the portal vein is usually divided at the level of the coronary vein. If the pancreas is being sacrificed, the portal vein is divided back at the splenic confluence [see Figure 8]. Although the CBD was previously divided, some periportal neural tissue usually remains, and it is in this tissue that a careful search for a right replaced artery must be undertaken. If a right replaced artery is discovered, it should be traced back to the superior mesenteric artery (SMA), and the SMA should be kept with the liver for reconstruction on the bench [see Figure 9]. If no right replaced artery is identified, the tissue is divided, and the subhepatic IVC is exposed. The right and left renal veins are identified, and the IVC is divided cranial to them.

With the liver's vascular structures completely dissected, the liver is held solely by its diaphragmatic attachments. The left and right diaphragmatic surfaces are cut so as to leave the bare area attached, the coronary ligament intact, and a cuff of diaphragm still attached to the liver. (Caution must be exercised in pulling up on the right hemiliver because the capsule of the liver can easily be torn while the right triangular ligament—the “rookie ligament”—remains intact.) The right triangular ligament is taken down, and the peritoneum overlying the right adrenal gland is divided. The right adrenal gland is then transected, with a portion left attached to the liver. The final diaphragmatic attachments near the spine are divided, and the liver is removed from the body.

With this technique, removal of a cold and bloodless liver requires 15 to 30 minutes. The organ is taken to the back table and placed in a sterile, empty bag immersed in a basin of ice-slush solution. The portal vein is then flushed with

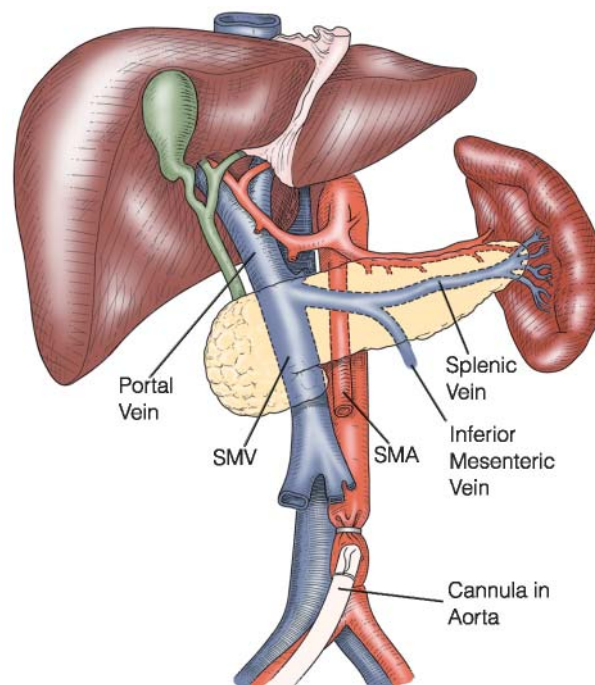


Figure 8 The junction of the superior mesenteric vein (SMV) and the splenic vein is behind the pancreas, as depicted here. A cannula is placed in the distal aorta. SMA—superior mesenteric artery.

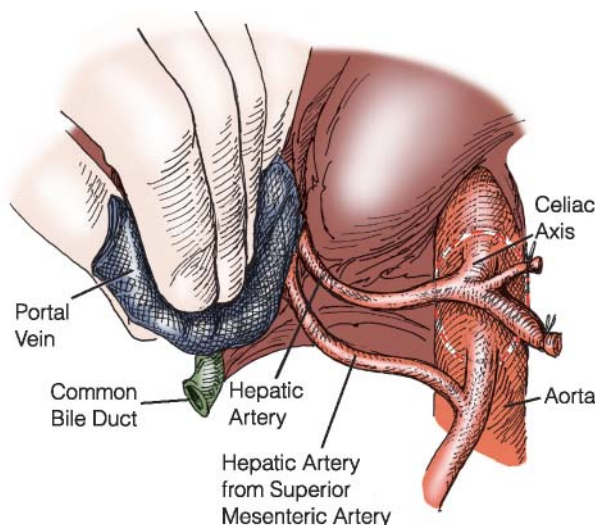


Figure 9 The typical replaced right hepatic artery originates from the first 2 cm of the superior mesenteric artery (SMA) near the aorta. It then runs posterior to the portal vein, with the portal vein depicted here schematically being reflected laterally. Also shown is the Carrel patch that will later be created to preserve the celiac axis and the SMA (dashed red line).

preservation solution. Finally, the organ is packed in the effluent remaining in the bag, placed in an ice-filled cooler, and transported to the recipient hospital, where it is cleaned and prepared for implantation in a formal back-table procedure that takes approximately 30 minutes.

The next step is procurement of the pancreas. Scissors are employed along the greater curvature of the stomach to divide the short gastric vessels all the way to the diaphragm. The

stomach is then divided with a stapler proximal to the pylorus and reflected cranially to expose the anterior surface of the pancreas. All splenic attachments are sharply divided to allow complete mobilization of the spleen. A complete Kocher maneuver (if not completed previously) is then undertaken. The jejunum is divided with a stapler just distal to the ligament of Treitz. The stapler is reloaded and used to divide any remaining colonic mesentery. The root of the small bowel mesentery is then divided and stapled, resulting in mobilization of the entire pancreas except for the area around the origin of the SMA. This area contains a fair amount of tough, fibrous neural tissue that must be divided before the root of the SMA can be exposed. The artery is divided in such a way as not to affect the cuff of aorta surrounding the orifice of each renal artery [see Figure 10]. At this point, the pancreas is

completely free. It, too, is taken to the back table, where the duodenum is opened, flushed with cold preservation solution, and then stapled closed again. The pancreas is packed in cold preservation solution and three sterile bags and placed on ice. The shorter portal vein segment remaining with the pancreas may be lengthened with an iliac vein graft from the donor. The donor celiac axis and hepatic artery stay with the liver. The splenic artery is divided near its origin from the celiac axis, and the SMA stays with the pancreas. In the case of a replaced right hepatic artery, the SMA must be divided distal to the replaced artery, and the SMA (including its aortic origin) must remain with the liver graft. The pancreatic arterial supply is then reconstructed with a donor iliac artery Y-graft anastomosed to the splenic artery and the SMA [see Figure 11].

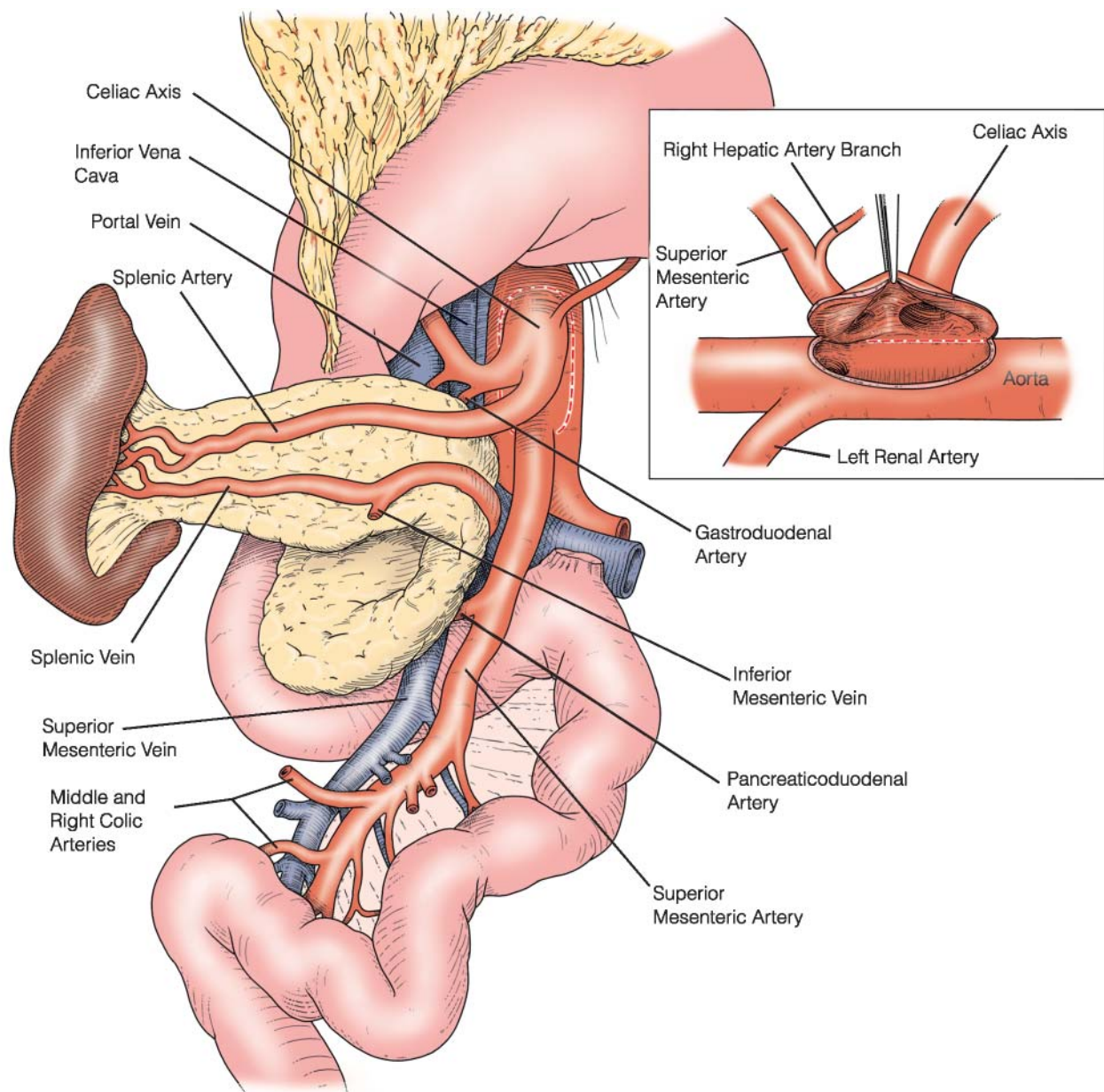


Figure 10 With the lateral attachments to the spleen and the pancreas divided, the entire pancreaticosplenic complex can be reflected medially. The aorta is thereby exposed and can be incised anteriorly at the level of the superior mesenteric artery so that the orifices of both renal arteries can be identified and preserved (inset).

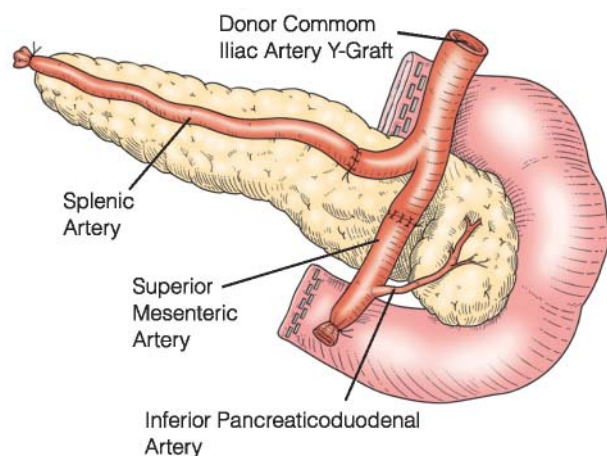


Figure 11 The pancreas is procured with a segment of duodenum. Shown is the posterior view of the pancreas and duodenum, with the spleen removed. The arterial reconstruction involves using a Y-shaped donor iliac artery graft and anastomosing it to the donor superior mesenteric and splenic arteries. Occasionally, a vein graft (not shown) is needed for use as an extension graft for the portal vein.

Kidneys

The last organs to be procured are the kidneys. The two organs may be removed either individually or en bloc; here, we describe the en bloc method.

The two ureters are located and divided as far distally as possible, with care taken not to strip the ureters of their blood supply. Each ureter is then freed back as far as the inferior pole of the kidney. Each kidney should have been freed to rotate medially when the pockets were created for the ice; if any attachments remain at this point, they are sharply divided. The two kidneys are brought to the midline, and the two ureters are tagged and reflected cranially to protect them. The IVC is then divided at the level at which the aorta was opened for placement of the infusion cannula. The cannula is removed, and both great vessels are completely transected. The aorta and the IVC are then clamped together, and scissors are used to remove the entire specimen by dividing the attachments of the vessels to the anterior spine [see Figure 12]. Everything is then reflected caudally and protected as the suprarenal aorta is divided (the IVC was previously divided at this level during the hepatic dissection), and any remaining attachments are severed.

The kidneys are then taken to the back table and placed on ice. The left renal vein is divided as it enters the IVC. The aorta is divided longitudinally, with equal cuffs left on the left and right renal arteries. All orifices are carefully examined to identify any separate renal arteries. The longitudinal division of the aorta is completed by sharply dividing the posterior surface between the paired lumbar arteries [see Figure 13]. The kidneys are then packed in cold preservation solution in three sterile bags and placed on ice.

The iliac arteries and veins are then removed with as much length as possible. These vessels may be used, if needed, either as conduits in liver transplantation or as grafts in pancreas transplantation. The skin is closed with a continuous baseball stitch, and the procurement procedure is complete.

NON-HEART-BEATING DONORS/DONATION AFTER CARDIAC DEATH

Since the mid-1970s, when the U.S. adopted the legal definition of brain death, the majority of cadaveric organs have been obtained from brain-dead donors.⁵ A brain-dead donor is fully supported with medication and mechanical ventilation throughout the donation process until the organs are flushed with cold preservation solution; thus, warm ischemia is eliminated entirely. As noted, however (see above), the ever-increasing disparity between the number of organs available and the number of patients awaiting transplantation has stimulated renewed interest in the procurement of organs from non-heart-beating donors (i.e., DCD). Donation from non-heart-beating donors begins after cardiopulmonary function has ceased and the prescribed additional amount of time (2 to 5 minutes) has passed before death can be declared and organ retrieval initiated. In other words, each DCD is associated with an unavoidable and variable period of warm ischemia. Accumulating data suggest, however, that despite the warm ischemia, kidneys, livers, lungs, whole pancreata, and pancreatic islet cells from non-heart-beating donors can be used for transplantation in selected situations.^{20,26-32}

The Institute of Medicine position paper regarding donation after cardiac death specified seven recommendations: (1) written, locally approved DCD protocols; (2) public openness in regard to DCD protocols; (3) antemortem administration of medications (e.g., heparin) done on an individual case basis; (4) antemortem cannulation only after consent from the next of kin; (5) policies to limit the potential for conflict of interest; (6) support of the donor family by allowing attendance at the time of withdrawal of care and protection from costs associated with the organ procurement; and (7) with controlled DCD, determination of death after 5 minutes of cardiac standstill as measured by arterial pressure and ECG monitoring.^{23,33} In keeping with the recommendation for local approval of protocols, policies (including the timing of heparin administration, where the patient is extubated, when and where the patient's death is declared, and whether or not antemortem cannulation is allowed) differ not only from one OPO to another but also from one hospital to another.

If the patient does not progress to cessation of cardiopulmonary function within a prescribed period (usually 60 to 90 minutes), he or she is returned to the intensive care unit. If the donor does progress to cessation of cardiopulmonary function and the procurement process begins, cannulation and flushing of the organs is started as soon as possible to shorten the duration of warm ischemia. The remainder of the procurement procedure is identical to that for a brain-dead donor.

In a 10-year analysis of DCD published in 2005, the average number of organs transplanted from each DCD donor was 2.02, compared with 3.18 from each brain-dead donor.³⁴ In other studies, the average number of kidneys obtained from each DCD donor (1.6) was identical to that from each brain-dead donor.²⁸ Such findings suggest that DCD is an important potential source of organs for patients on the kidney waiting list. In terms of long-term graft survival, outcomes with kidneys from DCD donors appear to be equivalent to those with kidneys from brain-dead donors. Nationally representative data from the U.S. Renal

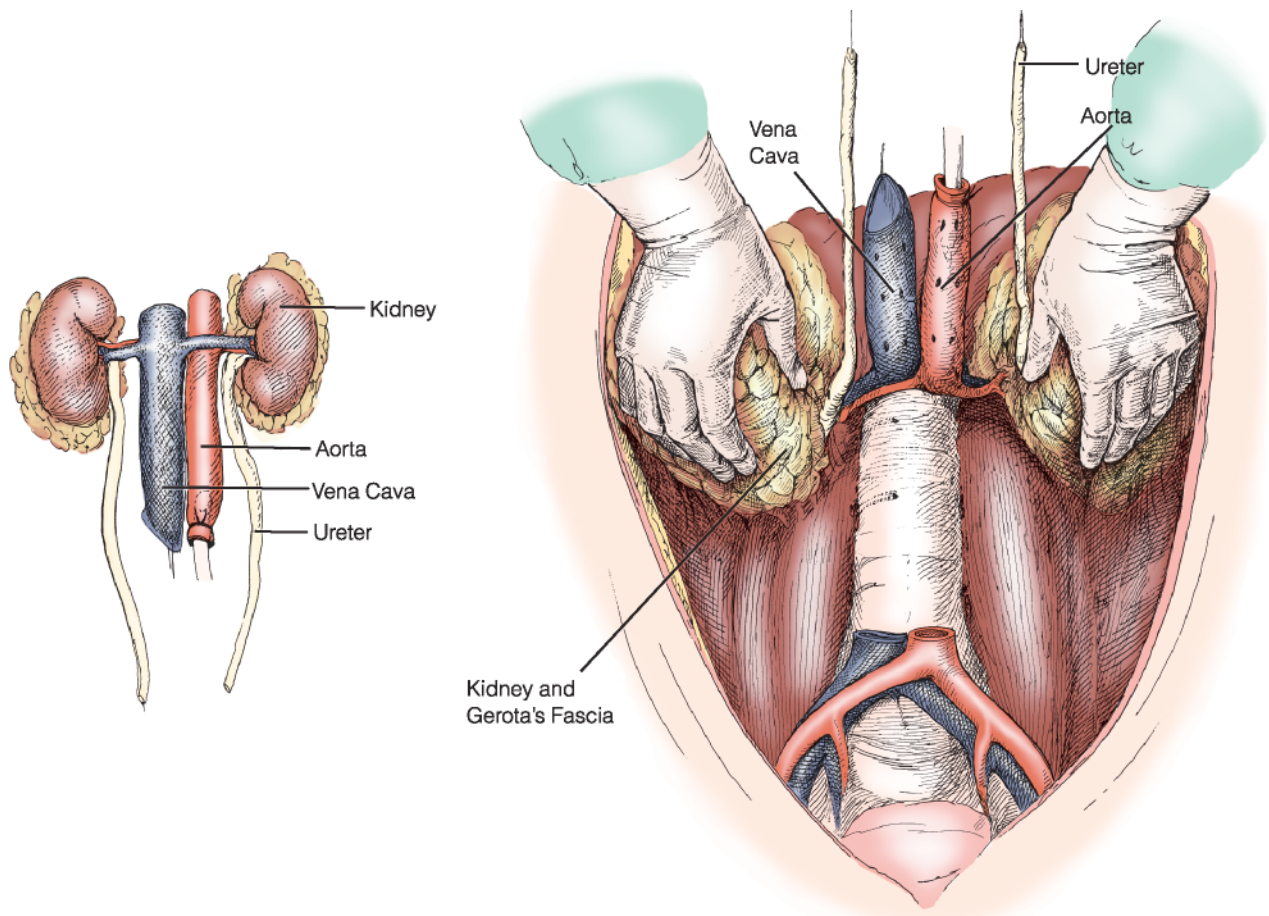


Figure 12 Shown are en bloc nephroureterectomies being performed from below upward (i.e., cranial to caudal).

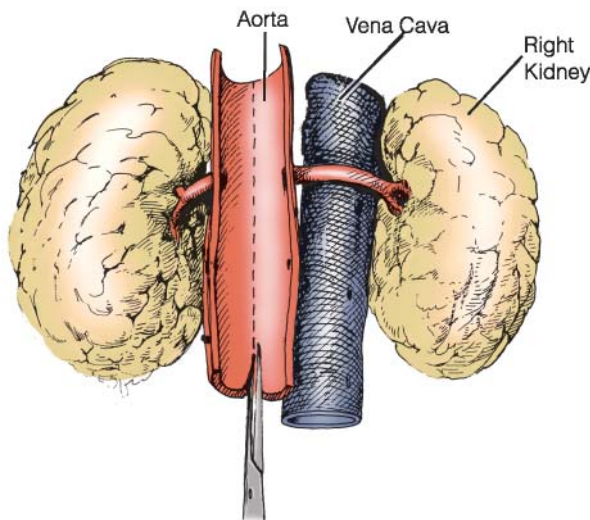


Figure 13 The aorta is opened posteriorly between the paired lumbar arteries.

Data System have documented 6-year graft survival rates of 73.2% for DCD donors and 72.5% for brain-dead donors.²⁹

A retrospective evaluation from 2004 used the national UNOS database to compare the survival of DCD donor liver

grafts with that of brain-dead donor grafts for the period between 1993 and 2001.³⁵ At 1 year, the survival rates were 70.2% for livers from DCD donors and 80.4% for livers from brain-dead donors; at 3 years, the respective rates were 63.3% and 72.1%. Although liver transplantation from controlled DCD donors results in similar patient survival and a similar incidence of posttransplant complications, it also results in a higher incidence of primary nonfunction and reduced allograft survival. Although the unavoidable period of warm ischemia may predispose hepatic allografts to an increased incidence of ischemic biliary strictures and cholangiopathy,³⁰ the results of liver transplantation from controlled DCD donors are encouraging. This approach should continue to be cautiously pursued as one way of helping to alleviate the current shortage of donor livers.³¹

To date, experience with transplantation of whole pancreata and islet preparations from DCD donors has been limited. Nevertheless, there is growing interest in islet cell transplantation from brain-dead donors, and some successes have been reported. A study performed in 2003 demonstrated that islet cells isolated from a single DCD pancreas can also result in stable insulin independence.³² These findings suggest that the use of DCD donors may help overcome the currently insufficient supply of cadaveric pancreata.

Organ Procurement from Living Donors

POTENTIAL LIVING DONORS

Living donor transplantation is not a new concept. In fact, the earliest successful kidney transplants were performed with living donors.³⁶ What began with kidneys has been extended to livers and, in some centers, to pancreata, intestines, and lungs. With living donors, even more than with cadaveric donors, good judgment and a high degree of technical skill are crucial for successful recipient and donor outcomes. Regardless of which organ is considered for donation, donor safety must be paramount. Informed, uncoerced consent is essential, and every effort should be made to ensure that nothing less is obtained.

Evaluation of a living donor must be careful and comprehensive³⁷: it is a substantially more complex process than evaluation of a cadaveric donor. A multidisciplinary group of physicians, both medical and surgical, should be involved in the evaluation, along with social workers and mental health professionals. It is imperative that there be no financial arrangements between recipients and donors. By the provisions of the National Organ Transplantation Act of 1984, the sale of organs is illegal in the United States, and this practice should be universally condemned.³⁸

Evaluation for living donation begins with the identification of a willing donor. In general, subjecting a healthy volunteer to physical or emotional distress is antithetical to the basic principles to which all physicians subscribe. *Primum non nocere* ("first, do no harm") is the basis of the Hippocratic oath. If the supply of cadaveric organs were sufficient to meet the demand and if patients were not dying on the waiting list because of organ shortages, it would be difficult to justify living donation on ethical grounds. Living donation should be considered warranted when the donor procedure has been shown to be safe and technically feasible and when the donor has at least an emotional attachment to the recipient. Even this definition is difficult to fully realize on a daily basis as more and more Good Samaritan donors are volunteering their organs to complete strangers. Practice guideline recommendations regarding living donors have been outlined by the Live Organ Donor Consensus Group.³⁹

For kidney and liver donation, donors and recipients must be compatible with respect to major blood types. Recipients of any blood type may receive an organ from a type O donor. Type O liver recipients may successfully receive livers from type A donors in subgroup 2.⁴⁰ In rare circumstances (i.e., acute fulminant liver failure) and in very young infants, blood group barriers may successfully be crossed in liver transplantation, but such cases are exceptional. In other settings, blood type incompatibility leads to hyperacute rejection. Currently, however, many living donor kidney transplant centers are introducing protocols allowing transplants across incompatible blood groups; the preliminary experience is encouraging.⁴¹

Any healthy adult (i.e., age >18 years) can be considered as a potential living liver donor. Many programs have upper age limits; virtually all would be reluctant to consider donors older than 60 years. The evaluation process should proceed in a logical and stepwise fashion, beginning with the confirmation of ABO compatibility. For most people, an evaluation for liver donation is the most intense physical and mental examination they have ever undergone. Not infrequently,

subclinical maladies are diagnosed in potential donors during the evaluation. Blood testing should be comprehensive and should include, at a minimum, a full set of blood chemistries; a complete blood count; a coagulation profile; thyroid function tests; serologic tests for hepatitis viruses (A, B, and C), HIV, cytomegalovirus, *Neisseria gonorrhoeae*, α_1 -antitrypsin, ferritin, ceruloplasmin, α -fetoprotein, antinuclear antibodies, antimitochondrial antibodies, and anti-smooth muscle antibodies; a lipid profile; serum protein electrophoresis; urinalysis; and pregnancy testing. An ECG and a chest x-ray should also be obtained. Additional tests should be ordered as clinically indicated on an individual basis.

Imaging studies must include computed tomography or magnetic resonance imaging for estimating hepatic volumes and for determining details of the hepatic arterial, hepatic venous, and portal venous anatomy. With MRI scanning, cholangiography is also possible. Some centers may require endoscopic retrograde cholangiopancreatography (ERCP) for complete biliary tract evaluation, angiography for complete vascular evaluation, or both. Many centers require that potential donors undergo liver biopsy in specific circumstances (e.g., a history of alcohol abuse, obesity, or hypercholesterolemia), and some require this of all potential donors. Matching an appropriate donor with an appropriate recipient is complex and requires an understanding of and an appreciation for multiple variables, including the severity of portal hypertension in the recipient, the volume of liver required by the recipient, the volume of liver remaining with the donor, and the anatomy of the donor (including the hepatic portal and venous anatomy, as well as the biliary anatomy). Successful transplantation and donor outcome depend on appropriate matching.¹⁶

LIVING DONOR OPERATION

Liver

Living donor liver transplantation Although inherently somewhat riskier than living donor kidney transplantation, living donor liver transplantation (LDLT) has been performed since the late 1980s. The first successful LDLT procedure was performed in 1989, when a mother donated segments 2 and 3 to her son.⁴² This achievement was quickly repeated by Nagasue and colleagues in Japan⁴³ and by Broelsch and colleagues in Chicago.⁴⁴ These initial successes gave impetus to the growth of LDLT, which not only has spread rapidly across Asia, where cadaveric donors are scarce, but also has become increasingly popular in Western nations.

Transplantation of the left lateral section evolved into transplantation of the left hemiliver into larger children, adolescents, and eventually small adults. Initial experience showed these small-for-size grafts to be frequently associated with morbidity. The first adult-to-adult transplantation of the right hemiliver was performed by Lo and coworkers in Hong Kong; this has since become the preferred graft for adult-to-adult LDLT.⁴⁵

Because initially there were no comprehensive registries for either the donors or the recipients of LDLT, the results of the procedure have been difficult to assess. The difficulty is compounded by the fact that LDLT is sometimes employed for patients who are outside the currently accepted listing criteria (e.g., non-Milan hepatocellular carcinoma [HCC]). Overall, however, outcomes seem to be improving: 1-year graft survival now approaches 85%,⁴⁶ and at least one center

has found there to be no difference in overall survival between LDLT and cadaveric donor liver transplantation.⁴⁷ Most centers have found morbidity and mortality to be low among donors; however, at least 11 donor deaths have been reported.⁴⁸

In the United States, nine transplant centers are participating in a National Institutes of Health (NIH)–sponsored prospective study of LDLT called the A2ALL (Adult-to-Adult Living donor Liver transplantation) Cohort Study. Preliminary results from this study document a 1-year graft survival rate of 81%,⁴⁹ which is consistent with other registry data worldwide. The continuing refinement of the operative technique and the ongoing dearth of deceased donors have gained LDLT an important place in the field of adult and pediatric liver transplantation.

Donor evaluation Central to the ethical debates surrounding LDLT is the recognition that an otherwise healthy person is undergoing an operation that is associated with considerable morbidity and potential mortality. Obviously, rigorous screening of the donor is essential. Donor evaluation should progress in several steps, and both the donor and the recipient should be provided with ample information about LDLT and sufficient time in which to assimilate that information. The least invasive tests should be done first, beginning with the determination of ABO compatibility. Psychological assessment is critical for ensuring that the donor's decision to provide a liver graft is truly voluntary and free of coercion.

As noted (see above), comprehensive blood testing should be carried out. An ECG and chest x-ray should also be obtained. Additional tests should be ordered as required on an individual basis. Comprehensive imaging of the liver—including high-quality MRI or CT to demonstrate the hepatic arterial, hepatic venous, and portal venous anatomy—is essential. Magnetic resonance cholangiopancreatography (MRCP) or CT cholangiography is indicated for preoperative assessment of the biliary anatomy. After cross-sectional imaging is performed, liver volumes should be estimated. A residual liver volume of 30% to 35% is generally considered safe for the donor, whereas a graft that provides at least 40% of the estimated standard liver volume or whose weight is at least 0.8% of the recipient's body weight is considered acceptable for the recipient.⁵⁰

Liver biopsies from the donor are not required by every program, but they may be indicated in certain cases (e.g., when the patient is obese or hypercholesteremic or has a history of alcohol abuse). Fatty liver disease is dangerous for both the recipient and the donor and should be factored into the process of donor selection.

Operative technique The overriding principle of the donor operation is to ensure the safety of the donor. Accordingly, only fully trained and experienced hepatobiliary and transplant surgeons with a good understanding of segmental liver anatomy [see Figure 14] should undertake liver procurement from living donors.

The main anatomic liver resections are discussed in greater detail elsewhere [see 5:23 *Hepatic Resection*]. In a living donor hepatectomy, the primary emphases are on limiting blood loss and preserving the anatomy of both the donated portion of the liver and the hepatic remnant. To this end, high-quality intraoperative cholangiography is essential.

Furthermore, ischemic injury to the liver section to be donated must be limited. The dissection must therefore proceed without vascular exclusion.

Open left lateral sectionectomy. In a left lateral sectionectomy, dissection is performed to isolate the left hepatic vein, the left portal vein, and the left hepatic artery. The portal vein branches to segments 1 and 4 are ligated to expose the main left portal vein. The arterial dissection begins distal to the branching of the right hepatic artery; the artery supplying segment 4 may have to be sacrificed. The parenchymal transection plane is just to the right of the falciform ligament and extends to the hilar plate. The hilar plate and the left bile duct are sharply transected. The liver parenchyma is then transected; this may be accomplished with any of a variety of instruments (see below). The left hepatic vein may be either clamped and transected or stapled with an endoscopic gastrointestinal anastomosis (GIA) stapler. The specimen is removed from the donor and immediately flushed with cold preservation solution (UW or HTK) on the back table.

Open donor right hepatectomy. In performing a right (or left) hepatectomy, it is necessary to isolate the inflow and outflow vessels in the hepatic hilum on the appropriate side; great care must be taken to neither injure nor devascularize the opposite side. After mobilization of the liver, the initial steps are cholecystectomy and intraoperative cholangiography to delineate biliary anatomy. Once the biliary anatomy is deemed suitable, hilar dissection can continue. Intraoperative ultrasonography to identify venous anatomy, once a common practice, has now been essentially replaced by preoperative imaging.

Hilar dissection is begun laterally, and the right artery is exposed to the right of the CBD. Segment 4 arteries are preserved whenever possible. The right portal vein is also identified and isolated. To diminish the risk of devascularization, extensive dissection of the CBD is avoided. The hilar plate is lowered and the right bile duct (or ducts) sharply transected. Again, preservation of the donor's CBD is of paramount importance. The right hepatic vein is isolated, and mobilization of the right hemiliver is completed. The liver parenchyma is then transected just to the left of Cantlie's line, along the border of the middle hepatic vein. Whether to include the middle hepatic vein with the graft remains somewhat controversial.^{48,51} Temporary inflow occlusion may be employed to help mark the transection line along the liver surface.

The aim of transection is to leave as little necrotic tissue as possible in both the donor and the recipient. To this end, various different instruments may be employed, such as crushing clamps, an ultrasonic dissector (e.g., Harmonic Scalpel; Ethicon Endo-Surgery, Inc., Cincinnati, Ohio), a hydro-jet dissector, a LigaSure device (Valleylab, Boulder, Colorado), or a monopolar or bipolar saline-linked electrocautery (e.g., Aquamantys; TissueLink, Dover, New Hampshire). Hydro-jet dissectors and ultrasonic dissectors allow the most precise dissection and may be used in combination with one of the other devices to achieve parenchymal transection with minimal blood loss.

Once parenchymal transection is complete, the inflow and outflow vessels are divided. Large short hepatic veins and significant segment 5 and 8 veins are preserved with the right hemiliver graft for subsequent reconstruction and

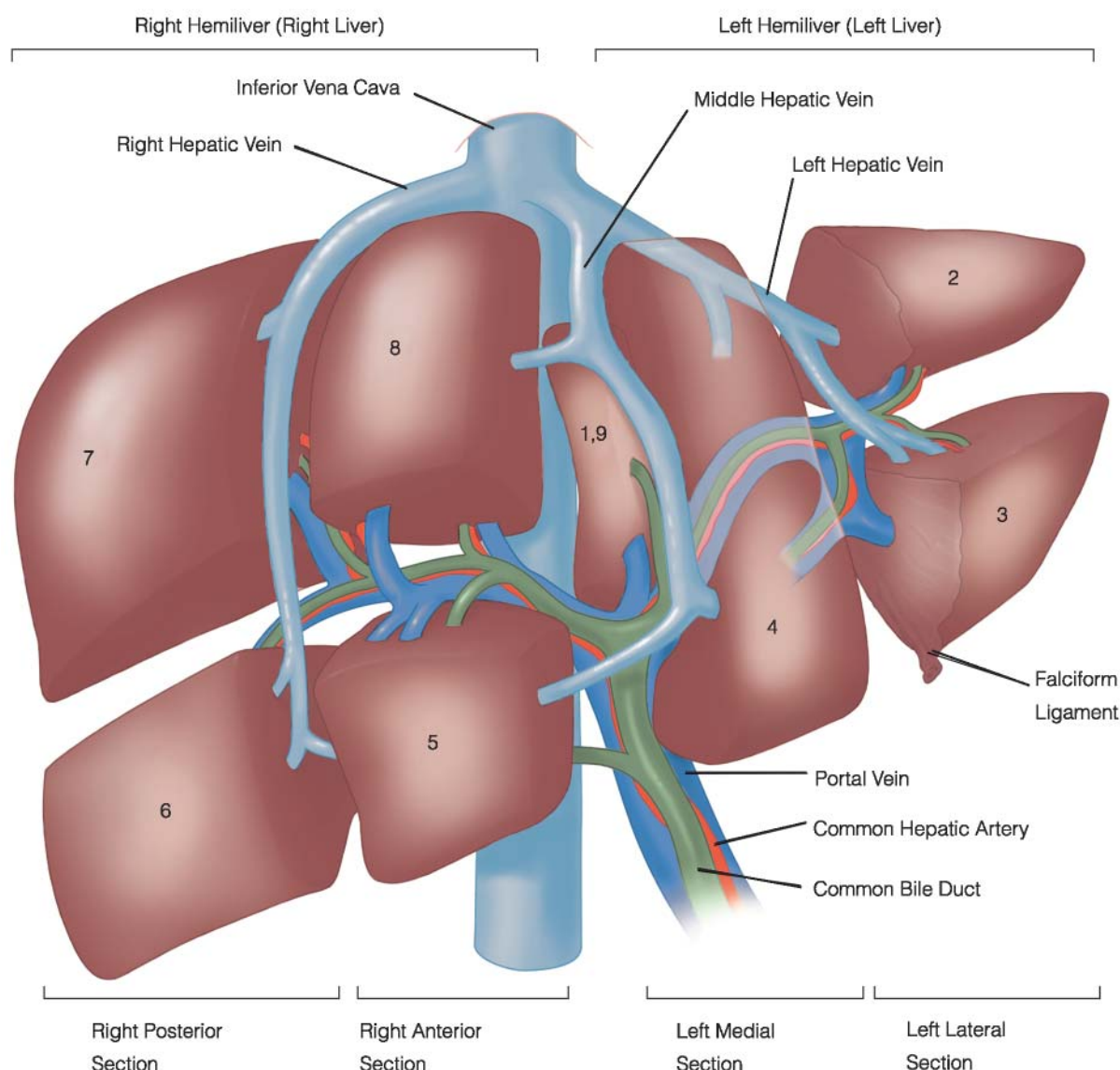


Figure 14 Illustrated are the anatomic divisions of the liver according to the Brisbane 2000 terminology, including first-order divisions (hemilivers), second-order divisions (sections), and third-order divisions (segments).

reimplantation in the recipient. Laparoscopic vascular staplers may be used to transect the right hepatic vein and right portal vein.

The graft is then removed and flushed on the back table with UW or HTK solution. If the middle hepatic vein has been preserved, venoplasty is performed on the back table. If the middle hepatic vein has not been included, vascular conduits are created to restore continuity to large segment 5 and 8 veins.

Before closure, the hepatic remnant is carefully examined for bile leakage. A repeat cholangiogram is obtained. Bile may leak from the hilar plate, from the transected bile duct stump, from the caudate lobe, or from the cut edge of the liver. Meticulous suturing is required to repair bile leaks without compromising the donor ducts. The hepatic remnant (i.e., the left hemiliver) should be reanchored to the anterior abdominal wall by recreating the falciform ligament.

Laparoscopic-assisted donor right hepatectomy. One of the major impediments to more widespread adoption of LDLT has been donor morbidity. The application of minimally invasive techniques to this operation has the potential to reduce this impediment and thereby broaden the pool of willing donors.

The technique of laparoscopic-assisted donor right hepatectomy was first described by Koffron and colleagues in 2006.⁵² With the patient in the supine position, an upper midline incision is made to allow placement of a hand port. Two laparoscopic trocars are placed, one through the umbilicus and one in the right lower quadrant. A bipolar coagulating/cutting device (e.g., LigaSure V) or an ultrasonic dissector (e.g., Harmonic Scalpel) is inserted through the lower quadrant port, the camera is inserted through the umbilical port, and the surgeon's right hand is inserted through the hand port. The right hemiliver is completely

mobilized by means of a hand-assisted technique. Once the liver has been fully mobilized and the vena cava exposed, the hand port and the laparoscopic instruments are removed, appropriate retractors are placed, and the remainder of the dissection is carried out in the same manner as for the equivalent open procedure (see above). Once the parenchyma has been transected and the vascular and biliary pedicles divided, the right hemiliver can safely be delivered through the upper midline incision.

Kidney

Kidney donation from a live donor may be accomplished either via an open approach or laparoscopically. Open donor nephrectomy is performed through a right or left flank incision, depending on which kidney is to be removed. The flank muscles are divided, and the perinephric space is developed. The renal artery and vein are dissected free, and the ureter is identified and divided at the pelvic brim. The vessels on the right side, particularly the renal vein, are significantly shorter than those on the left; in addition, exposure is often more challenging on the right side as a consequence of the subhepatic location of the right kidney. Before the vessels are clamped and the kidney removed, donors are routinely given

mannitol, both for its diuretic effects and for its antioxidant effects. Upon removal from the donor, the kidney is flushed with cold UW or HTK solution on the back table.

Although open donor nephrectomy has historically been the standard, the laparoscopic alternative is now the procedure of choice, particularly for left kidneys. Because of the relatively shorter vessels on the right side, some surgeons are reluctant to perform laparoscopic right nephrectomy, being concerned that the vessel shortening invariably caused by the stapler may make implantation more difficult. In addition, many donors have multiple renal arteries, an anomalous venous anatomy (e.g., a retroaortic left renal vein), or both, and these anatomic variations may preclude, or at least significantly complicate, laparoscopic donation.

Lung, Pancreas, and Intestines

Single-lung transplantation from a living donor has been performed with some success.⁵³ Procurement of the pancreas and the small intestine from living donors has been shown to be technically possible; however, serious concerns remain about the adequacy of partial grafts for correcting diabetes or short-gut syndrome. Such procedures are currently considered experimental.

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7 TRANSPLANTATION FOR THE GENERAL SURGEON

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Over the past 50 years, the field of transplantation has moved from an experimental endeavor to the standard therapy for end-stage organ disease in many patients. According to the United Network for Organ Sharing (UNOS), in 2008, 14,403 donors (including 6,313 living donors) provided organs for 30,531 recipients.¹ In contrast, over 100,000 patients are currently awaiting transplantation.¹ Advances in donor selection and management, organ preservation, recipient management, and immunosuppression have resulted in increased survival of organ recipients. As a welcome consequence, the number of recipients living with transplanted organs continues to grow. Although not all practitioners will have the opportunity to participate in the transplant process, the growing numbers of transplant survivors make it increasingly likely that the care of these complex patients will involve nontransplant personnel. For this reason, familiarity with the organ donation process, donor and recipient selection, organ procurement procedures, recipient procedures, and immunosuppression management is important for all practitioners. In addition, an understanding of the issues involved in managing common general surgical problems in patients with end-stage organ disease and in immunosuppressed organ transplant recipients will improve their care.

Overview of Organ Donation Process

HISTORY

To better coordinate transplantation activities, distribute donor organs, and collect data on transplantation issues, the US Congress passed the National Organ Transplant Act (NOTA) in 1984. The act called for the creation of a national, unified transplant network, the Organ Procurement and Transplantation Network (OPTN). The OPTN has been administered by UNOS since its creation 1986. The UNOS Organ Center assists in the placement of donated organs by maintaining national lists of patients awaiting transplantation, gathering donor information, running donor-recipient match lists, and acting as a resource for organ-sharing policies. NOTA also called for the creation of the Scientific Registry of Transplant Recipients (SRTR) to gather and analyze data on transplantation events in the United States. UNOS and the SRTR serve as valuable entities to coordinate and study nationwide transplantation activities.

FUNCTIONAL ORGANIZATION

UNOS has established 11 administrative regions within the United States. Within each region, there are multiple transplant centers and organ procurement organizations (OPOs). In 2009, 253 medical institutions were operating organ transplant programs, each known as a transplant center.¹ OPOs are nonprofit agencies responsible for evaluating the suitability of potential donors, approaching families about the option and process of donation, and coordinating the procurement of recovered organs. OPOs also serve to educate the public about organ donation and the need for organ donors. As part of this education mission, OPOs assist hospitals in developing policies and procedures relating to organ donation. Finally, OPOs are often involved in legislative efforts to promote organ donation initiatives.

Hospitals are required to notify their OPO of all deaths or imminent deaths. Organs donated within an OPO's service area are first offered to local recipients; if no matches are made locally, organs are then offered regionally and nationally. Exceptions to this policy may occur in special circumstances such as zero-antigen mismatched kidneys, which are shared nationally with highly sensitized recipients. Similarly, regional and national sharing of livers occurs for recipients with status 1 designation attributed to fulminant liver failure, primary nonfunction (PNF) of a transplanted liver, acute decompensated Wilson disease, or hepatic artery thrombosis (HAT) within 1 week of transplantation.

EVALUATION AND MANAGEMENT OF THE DECEASED DONOR

Organ donation can occur only after the pronouncement and documentation of the donor's death. In the United States, there are two legal definitions of death: brain death and cardiopulmonary death. Work by the ad hoc Committee on Brain Death at Harvard Medical School described "irreversible coma," "cerebral death," or brain death in 1968.² Death was legally defined by the Uniform Declaration of Death Act in 1980 as either "(1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brainstem."³ Most organ procurements in the United States are from brain-dead donors, although organ recovery from donors after cardiac death (DCD) is increasing.⁴ Clinical requirements for the determination for brain death include an

acute catastrophic cerebral event, exclusion of conditions that may confound determination of brain death (metabolic derangements, intoxications, or hypothermia), the presence of coma or unresponsiveness, absence of cerebral motor responses to pain, absence of brainstem reflexes, and apnea. A clinical examination documenting these findings is sufficient for a determination of brain death, but confirmatory testing using electroencephalography, transcranial Doppler sonography, somatosensory and brainstem auditory evoked potentials, or cerebral blood flow studies (angiography or nuclear medicine) may also be performed.⁵ Evaluation as a potential organ donor can only begin after declaration of brain death by a physician involved in the patient's care who is not associated with the transplant enterprise.

The number of organs procured after cardiac death is increasing.¹ The Maastricht classification defines five groups of non-heart-beating donors (NHBDs): (1) brought in dead; (2) unsuccessful resuscitation; (3) awaiting cardiac arrest; (4) cardiac arrest after brainstem death; (5) cardiac arrest in a hospital inpatient.⁶ In the United States, DCD typically occurs under controlled circumstances (group 3). Use of NHBDs or DCD refers to procurement of organs following withdrawal of care in a patient with either a devastating neurologic injury or other organ failure requiring ventilatory or circulatory support. Families of such patients are approached about the option of organ donation once a decision has been made to withdraw care. To be considered for donation, withdrawal of care is reasonably expected to result in the patient's death within 1 to 2 hours. Several assessment tools are available to help predict the likelihood of this outcome.

Once a potential donor has been identified, the OPO is responsible for determining the suitability of organs for transplantation. This process begins with a thorough medical and social history as well as a careful physical examination with an emphasis on identifying infectious and malignant conditions. An assessment of the potential donor's physiologic condition, including hemodynamic parameters, adequacy of oxygenation and ventilation, and urine output, is performed. ABO blood type is confirmed. Laboratory studies focusing on specific organ function as well as potential infectious risks are analyzed. Standard laboratory tests include complete blood count, chemistries, and blood and urine cultures. Transaminases, alkaline phosphatase, γ -glutamyltransferase (GGT), bilirubin, prothrombin time/international normalized ratio (INR), and partial thromboplastin time are also checked for potential liver donors, whereas amylase, lipase, and, increasingly, hemoglobin A_{1c} are checked for potential pancreas donors. Concern over transmission of infectious diseases has prompted testing of all donors for syphilis (rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL]), hepatitis B and C exposure (hepatitis B surface antigen, hepatitis B surface antibody, anti-hepatitis C virus [HCV]), cytomegalovirus (CMV), Epstein-Barr virus (EBV), HIV-1 and -2, and human T cell lymphotropic virus type I and II. Nucleic acid testing for hepatitis C and HIV may be used to increase sensitivity for detection of these viruses. Additional studies may be performed depending on clinical circumstances. For example, in donors with risk factors for significant hepatic steatosis, a percutaneous liver biopsy may be performed.

Management of the potential brain-dead donor focuses on preserving perfusion to the organs to be procured. The "rule of 100's" serves as a general guideline for managing donors: heart rate around 100 beats per minute, systolic blood pressure above 100 mm of mercury, oxygen saturation of 100%, and urine output of over 100 mL per hour. Donors with brain death often suffer from central diabetes insipidus with resultant diuresis, hypovolemia, and hypernatremia. Brain death also results in peripheral vasodilatation that may lead to circulatory collapse. Aggressive fluid resuscitation and judicious use of vasopressors or antidiuretic hormone are often required to maintain homeostasis. Knowledge of critical care principles is essential to balance the potentially conflicting requirement of the various organs to be procured. For example, severe hypernatremia (> 170 mEq/dL) is a risk factor for PNF of liver allografts. The hypotonic fluid often given to lower serum sodium may lead to pulmonary edema and inability to use the lungs for transplantation. Experienced donor management personnel are required to optimize the number and quality of organs that can be procured from each donor.

PROCUREMENT PROCEDURE

In general terms, for brain-dead donors, dissection of the major vascular structures of the chest and abdomen and mobilization of the organs to be recovered are performed "in the warm" prior to heparinization, aortic cross-clamping, and flushing with cold preservation solution. This dissection allows adequate time to assess the suitability of organs for transplantation. The procurement procedure for DCD emphasizes rapid cannulation of the aorta, cross-clamping, and flushing with the majority of the assessment and recovery of organs performed "in the cold."

LIVING DONATION

The original successful renal transplantations were performed with organs from identical twin living donors.⁷ With the advent of effective immunosuppression, deceased donor kidney transplantation became much more common. The number of living donor renal transplantations has increased since the late 1990s when the laparoscopic donor nephrectomy technique became widespread⁸ [see Figure 1]. Living donor liver transplantation commenced with adult-to-child donation of the left lateral segment followed by adult-to-adult donation of the right lobe.⁹ In 2007, living donors accounted for 35% of kidney transplantations and 4% of liver transplantations performed, although the proportion varies widely by center.¹ Recipient and graft survival following living kidney donation exceed those experienced by recipients of deceased donor renal transplants⁸ [see Table 1]. Additionally, the use of living kidney donors allows for preemptive transplantation, thus avoiding dialysis entirely in a subset of recipients and resulting in improved graft and patient outcomes.¹⁰ Short- and long-term outcomes for kidney donors have demonstrated a low rate of perioperative complications and survival that is better than for age- and sex-matched populations.¹¹ The elective nature of live kidney donation allows for specialized protocols. For example, ABO-incompatible pairs and highly sensitized recipients may undergo a preoperative

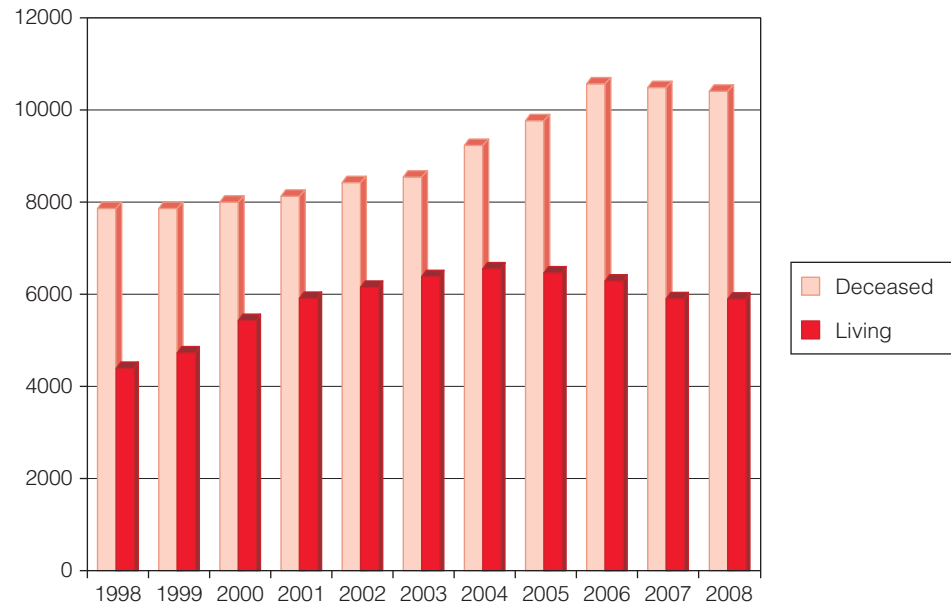


Figure 1 Deceased and living donor kidneys recovered from 1998 through 2008 (based on Organ Procurement and Transplantation Network data as of July 9, 2009).

regimen of desensitization. A growing practice of living donor paired exchange and “domino” procedures allows donor pairs who are ABO incompatible to be matched with other incompatible pairs, thus allowing ABO-compatible combinations to occur.¹²

Living donor liver transplantation has been controversial given the potential risks to the donor. The potential to expand the donor pool and improved survival of recipients of living donor liver grafts have renewed interest in this option.¹³ The benefits of living donor liver transplantation include decreased waiting time, elective rather than emergent procedure, decreased cold ischemia time, and potentially better quality donor when compared to deceased donor transplantation. The disadvantages of living donation include potential risk to the donor, smaller graft size, and increased rate of biliary complications. In a recent large multicenter review, 38% of living liver donors had complications.¹⁴ Donor complications included biliary leaks, infections, hernias, reexploration, neuropraxia, pleural effusions, and portal vein and inferior vena cava (IVC) thrombosis.¹⁴ Two percent of donors had life-threatening complications with a mortality of 0.8%.¹⁴ Living donation has also been reported for pancreas and intestinal transplantation, but these are not widely practiced procedures at this time and are beyond the scope of this text.^{15,16}

The living donor evaluation process must assess four factors. First, it must be determined whether the donor organ is suitable for use in the intended recipient. Next, the donor must be found to be medically suitable to undergo the donor procedure without significant adverse short- or long-term outcomes. Next, the donor’s motivation for donation must be appropriate and without coercion. Finally, both the donor and the recipient should have adequate information about the risks and benefits of the procedures to ensure the informed consent of both participants.

For potential kidney donors, evaluation starts with a complete history and physical examination as well as a psychosocial evaluation to assess the motivation to donate. Contraindications to donation include significant hypertension, coronary artery disease, renal disease, active or recent malignancy, or certain viral infections (i.e., hepatitis B virus [HBV], HCV, HIV), with some exceptions. Potential donors have ABO blood-type determination, and siblings of recipients are tested for human leukocyte antigen (HLA) type. Complete blood count, chemistry profile, coagulation studies, and urinalysis are routinely performed. Twenty-four-hour urine collection for determination of glomerular filtration rate ensures adequate donor renal reserve to tolerate donation. Chest radiography, electrocardiography, and cancer screening studies are performed as indicated by age- and disease-specific guidelines. Preliminary crossmatch between the donor and the recipient is performed to assess for recipient sensitization. Contrast-enhanced spiral computed tomography (CT) demonstrates the renal vasculature and collecting systems, confirms the presence of two functioning kidneys, and allows assessment for renal parenchymal abnormalities such as cysts or collecting system stones. The presence of multiple renal arteries may prompt use of the contralateral kidney, although reconstruction of kidneys with two or three arteries is relatively common. Once the donor has been approved based on history, examination, laboratory studies, and imaging, a final crossmatch is performed prior to scheduling the donor and recipient procedures.

Evaluation of living donors for liver transplantation includes the same basic elements as for kidney donors but also rests on the results of imaging studies. Cross-sectional imaging with CT or magnetic resonance imaging (MRI) evaluates liver volume, assesses for parenchymal lesions and degree of steatosis, and delineates arterial, portal venous, and biliary

Table 1 Recipient Survival Following Living and Deceased Donor Transplantation^s

Organ Transplanted	Patient 1 Yr Survival (%)	Patient 5 Yr Survival (%)	Graft 1 Yr Survival (%)	Graft 5 Yr Survival (%)
Kidney				
Deceased donor	94.8	80.6	90.0	67.5
Living donor	98.0	90.3	97.3	80.2
Liver				
Deceased donor	86.9	73.6	82.3	67.6
Living donor	90.6	76.1	84.1	68.6

anatomy. As a general guideline, the potential graft should be at least 0.8% of the recipient's body weight. Liver biopsy may be necessary to quantitate the hepatic fat content or evaluate for other histologic abnormalities. Techniques to accommodate abnormal arterial, portal venous, and biliary anatomy exist but are beyond the scope of this chapter. As a general rule, vascular and biliary connections of the donated segment, section, or lobe should be able to be reconstructed in the recipient, although the remnant liver in the donor should not be compromised by devascularization or poor biliary drainage.

Renal Transplantation

Renal transplantation is the most common form of solid-organ transplantation performed and should be considered for all patients with chronic or end-stage renal disease (ESRD). Patients do not need to be on dialysis therapy to be considered for transplantation, and preemptive transplantation has been associated with improved outcomes when compared to patients who received dialysis prior to transplantation.¹⁷ In 2008, over 16,000 kidney transplantations were performed with nearly 6,000 organs donated by living donors.¹

INDICATIONS AND EVALUATION

The main causes of renal failure that lead to transplantation include hypertension, diabetes mellitus, polycystic kidney disease, chronic glomerulonephritis, IgA nephropathy, focal segmental glomerulosclerosis (FSGS), systemic lupus erythematosus, membranoproliferative glomerulonephritis (MPGN), chronic pyelonephritis, and retransplantation for prior graft failure. Contraindications for transplantation include reversible renal disease, medical unsuitability for transplantation or general anesthesia attributed to extrarenal disease, recent malignancy, active infection, active substance abuse, uncontrolled psychiatric disorders, and prior noncompliance.

The pretransplantation recipient evaluation focuses on identifying and correcting potential medical and surgical contraindications to transplantation. A detailed history includes the etiology of renal disease, dialysis history, amount of urine currently produced, urologic problems, and exposures that may have lead to sensitization, including blood transfusions, prior transplantations, and pregnancy. Physical examination focuses on prior abdominal procedures and locations of incisions. The vascular examination, especially the symmetry, strength, and presence of bruits over the femoral pulses, may provide information on the degree of calcification of the external iliac arteries. Routine laboratory studies are performed as

well as ABO and HLA typing, panel reactive antibody (PRA), and evaluation for infectious diseases, including CMV, EBV, HBV, HCV, HIV, varicella-zoster virus (VZV), RPR, and screening for tuberculosis. Chest radiography and electrocardiography are performed, as are age- and sex-appropriate cancer screening (i.e., Papanicolaou smear, mammography, colonoscopy, prostate-specific antigen level). Cardiac evaluation with echocardiography and stress testing is indicated in most patients, whereas pulmonary function tests, urologic assessment, and imaging of the aortoiliac system are performed when indicated by the history or physical examination. A crossmatch between the potential donor and the recipient must be negative unless desensitization of the recipient is performed. Finally, a psychosocial evaluation must be satisfactorily completed prior to listing for transplantation to ensure adequate psychiatric stability, social support, and financial resources needed to maintain a functioning renal allograft.

PROCEDURE

Either the right or left iliac fossa is suitable for transplantation, and the choice of side is determined by prior incisions (i.e., appendectomy or peritoneal dialysis [PD] catheter), vascular integrity, and surgeon preference. Patients with type 1 diabetes mellitus who may undergo subsequent pancreas transplantation often have their kidneys placed on the left. The incision may be curvilinear or oblique running from just medial to the anterior superior iliac spine to the pubic tubercle. Dissection continues through the external oblique aponeurosis, internal oblique, and transversalis to expose the peritoneum. The peritoneum is swept medially to expose the external iliac artery and vein. The venous anastomosis is created using 5-0 monofilament, nonabsorbable suture followed by the arterial anastomosis using 6-0 suture [see Figure 2]. The kidney should demonstrate brisk color change to pink, and its consistency should become firm. A palpable pulse and thrill in the renal artery and its branches confirm the patency of these vessels. Preparation of the ureter for implantation into the bladder starts with confirming the appropriate length so as to allow a tension-free anastomosis without excessive redundancy. The end of the ureter is spatulated, and a stent may be placed. The bladder is filled with sterile irrigant to facilitate its identification and dissection. The cystotomy is performed by excising the pericyclic fat, dividing the musculature of the bladder wall, and exposing the bladder mucosa. An opening in the mucosa is created, and the ureter is anastomosed to the mucosal edge using an absorbable suture. The bladder musculature is closed over the ureteroneocystostomy using a 4-0 absorbable monofilament

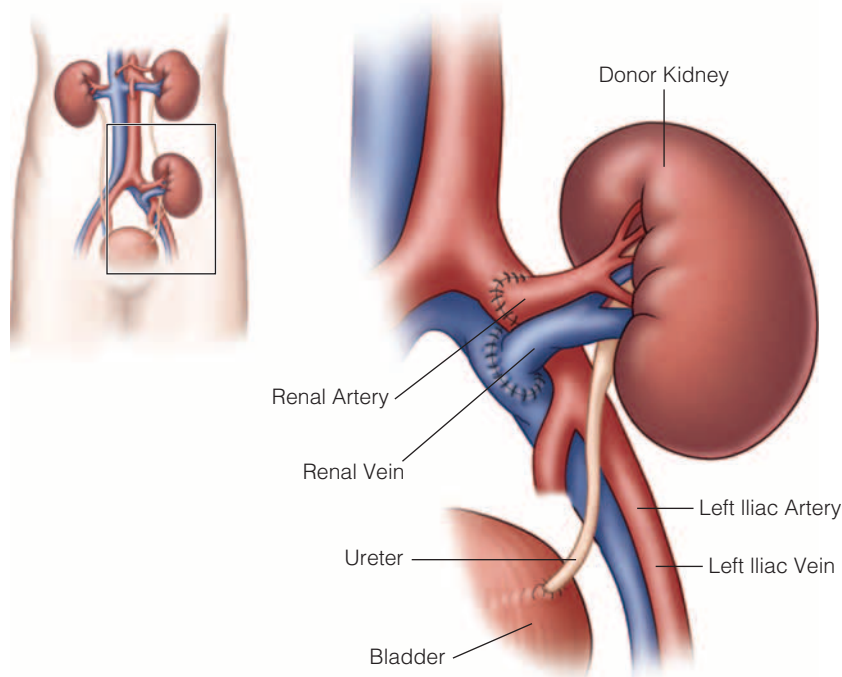


Figure 2 Kidney in iliac fossa with completed vascular and ureteral anastomoses.

suture. Intraperitoneal placement of the kidney allograft may be required in small recipients (i.e., children under 15 kg) or as part of a simultaneous pancreas-kidney (SPK) transplantation. A midline incision allows access to both sets of iliac vessels.

POSTOPERATIVE MANAGEMENT

Technical Complications

Immediate postoperative complications include thrombosis of the graft, bleeding, urine leak, and wound complications. Urine leaks are uncommon and may be diagnosed by determining the creatinine level of fluid draining from the wound or drain. Any level above that of the serum creatinine is suggestive of a leak. Axial imaging may reveal a fluid collection, whereas nuclear medicine studies or cystography may demonstrate a leak. Treatment with prolonged Foley catheter drainage and ureteral stent placement may allow some leaks to close, whereas reoperation may be required for persistent leaks.

Thrombosis of the graft should be suspected when a previously functioning graft has a sudden cessation of urine production. Ultrasonography may be used to confirm thrombosis but adds unnecessary delay in cases where thrombosis is strongly suspected. Operative reexploration, thrombectomy, and anastomotic revision may allow salvage in cases where thrombosis was immediately detected, but long-term outcomes are poor.

Ureteral stenosis or obstruction may occur due to ischemia of the ureter or scarring at the ureteroneocystostomy. Ultrasound examination performed for elevated creatinine will demonstrate hydronephrosis and hydroureter. Nuclear medicine evaluation with diuretic challenge will demonstrate

delayed excretion into the bladder. Percutaneous nephrostomy or retrograde cystoscopy can confirm and treat a stricture by placing a stent that spans the stenosis. In strictures that do not respond to stenting, operative revision may be required. Surgical options include reimplanting the transplanted ureter into the bladder, ureteroureterostomy to the native ureter, or ureteropyelostomy.

Lymphocele formation occurs because of leakage of lymphatic vessels surrounding the recipient iliac vessels or from the hilum of the transplanted kidney. Such collections may cause compression of the transplanted ureter or recipient iliac vein, thus leading to elevated creatinine or ipsilateral leg edema, respectively. Percutaneous aspiration of fluid demonstrates elevated white blood cell counts with a predominance of lymphocytes. Definitive treatment of a lymphocele may require fenestration of the peritoneum to allow drainage. Laparoscopic and open approaches may be used to create a window in the peritoneum, thus allowing reabsorption of lymph by the peritoneum. Care must be taken to avoid injuring the transplant ureter when creating the window. If available, omentum may be placed through the defect to avoid closure.

Delayed Graft Function

Approximately 25% of kidneys from deceased donors and 5% of kidneys from living donors do not have immediate function.¹⁸⁻²⁰ Delayed graft function (DGF) has been variably defined but commonly refers to the need for dialysis in the first week following renal transplantation. Many risk factors have been associated with DGF, including donor factors (age, hypertension, elevated creatinine, diabetes mellitus, vascular disease), duration of cold ischemia time, and recipient factors (hypotension, prior dialysis, retransplantation, elevated

PRA, elevated body mass index).¹⁸⁻²⁰ Treatment for DGF is supportive with optimization of blood pressure and recipient volume status. Delay of introduction of calcineurin-based immunosuppression has also been described to allow recovery of the graft. A low threshold for graft biopsy is required as acute rejection may accompany DGF and would require specific therapy if present.

Long-Term Complications

Long-term complications of transplantation are common and include organ-specific problems such as rejection and recurrence of the original disease, as well as systemic problems including infections, hypertension, hyperlipidemia, posttransplantation diabetes mellitus, and malignancy related to immunosuppression. Acute rejection may occur at any time following transplantation and is often manifested by elevated creatinine, pain at the site of the allograft, and fever. Allograft biopsy often reveals T cell infiltration of the tubules in cases of acute cellular rejection. Biopsy in antibody-mediated rejection demonstrates endothelial injury with evidence of complement deposition by staining with anti-C4d antibodies. Recipient sera may demonstrate the presence of donor-specific antibodies. Treatment of acute rejection is beyond the scope of this text but depends on the type and severity of rejection. Options for acute cellular rejection include steroid therapy or anti-T cell antibodies, whereas acute antibody-mediated rejection may be treated with plasmapheresis and administration of intravenous immune globulin or rituximab. The occurrence of rejection should prompt the treating team to investigate whether compliance with antirejection medications, inadequate goal levels, or other factors contributed to the episode, with appropriate education or medication adjustments as needed.

Chronic rejection, or chronic allograft nephropathy, refers to the gradual deterioration of renal function seen over time that cannot be explained by other factors. Histologic examination reveals interstitial fibrosis, glomerular sclerosis, and vascular changes. The etiology of chronic allograft nephropathy has not been fully elucidated but is thought to include immunologic factors, sequelae of ischemia and reperfusion injury, hyperfiltration effects, and toxicity attributed to immunosuppressive agents.

The incidence of recurrent disease following transplantation varies by original diagnosis, as does the rate of graft loss if recurrence occurs. The diseases most likely to recur in a transplant kidney (> 50% of transplants) include FSGS, diabetes mellitus, IgA nephropathy, MPGN, oxalosis, cystinosis, and Henoch-Schönlein purpura. The likelihood of graft loss in the setting of disease recurrence is highest with MPGN type I, FSGS, oxalosis, and hemolytic-uremic syndrome. Monitoring for disease recurrence and treatment (if possible) is important to prevent graft loss in these conditions.

The type of infectious complications seen following transplantation can be grouped by the timeframe of occurrence and degree of immunosuppression. Infections during the first month following transplantation tend to be bacterial or fungal and are often related to the surgical procedure, such as wound infections or nosocomially acquired infections such as urinary tract infections, pneumonias, and catheter-related bloodstream infections. Between 1 and 6 months after transplantation,

opportunistic infections are more prevalent, including CMV infection, *Pneumocystis jiroveci* pneumonitis, toxoplasmosis, invasive aspergillosis, cryptococcosis, nocardiosis, and VZV infection. Reactivation of *Mycobacterium tuberculosis* from prior exposure may also occur during this period. Beyond 6 months after transplantation, when immunosuppression has often decreased, the risk of opportunistic infections also decreases, whereas standard community-acquired infections are again prevalent. Various approaches to prophylactic use of antimicrobial, antifungal, and antiviral agents are used; suspicion for opportunistic infections should be high in the time following withdrawal of such agents. Additionally, resumption of prophylaxis should be considered any time immunosuppression is increased to treat episodes of acute rejection.

Infectious complications specific to renal transplant recipients include BK polyomavirus-associated nephropathy and adenovirus. BK virus is commonly acquired as a respiratory infection that remains latent in the kidney and urothelium. Reactivation occurs in the setting of immunosuppression. Viruria is common in transplant recipients and does not indicate clinical infection, whereas viremia does suggest clinical infection, which manifests as increased creatinine. Biopsy may reveal interstitial infiltrate and tubulitis, whereas immunohistochemical staining will reveal evidence of viral particles. Treatment consists of reduction in immunosuppression. Cidofovir and leflunomide are antiviral agents that may be used in persistent cases.²¹ Adenovirus infection may cause hemorrhagic cystitis, fever, and graft dysfunction in renal transplant recipients. This infection is often self-limited, but reduction of immunosuppression and cidofovir have been used in protracted cases.^{22,23}

Metabolic and neoplastic complications related to immunosuppression are common to all types of solid-organ transplantation. Hypertension may be related to use of steroids and calcineurin inhibitors (CNIs). Antihypertensive regimens using calcium channel blockers may reduce CNI-induced vasoconstriction, but diltiazem and verapamil significantly increase CNI levels. Hyperlipidemia is also common among transplant recipients, with steroids, CNIs, and rapamycin all altering lipid profiles, and may be managed with HMG-CoA reductase inhibitors. Development of posttransplantation diabetes mellitus has been related to both steroid and CNI use. Standard therapies are used as indicated.

The incidence of certain types of malignancies is increased after solid-organ transplantation, including lymphomas and skin cancers. The most common lymphomas following transplantation are the B cell lymphomas, often called posttransplantation lymphoproliferative disease (PTLD). PTLD is often related to infection with EBV. PTLD is often extranodal and may involve the central nervous system, head and neck, lungs, gastrointestinal tract, or kidney. Treatment for PTLD ranges from reduction of immunosuppression, antiviral agents, chemotherapy, and/or radiotherapy. The incidence of melanoma and nonmelanoma skin cancers is also increased in transplant recipients. Skin cancers in transplanted patients are often more aggressive than in nonimmunosuppressed patients. Transplant recipients should be counseled to avoid sun exposure, use sunscreen daily, and have routine skin evaluations. Recent investigations suggest that rapamycin may have antitumor effects in transplant recipients. A large review compared patients receiving CNI-based regimens to TOR-inhibitor

regimens and found a significant decrease in both skin and solid malignancies in the latter group.²⁴ Although many factors are weighed in choosing immunosuppression regimens, this antitumor effect may be considered in future protocols.

OUTCOMES

Patient and graft survival following renal transplantation are generally good, with both donor and recipient factors influencing outcomes. Recipients of living donor allografts have 1-, 5-, and 10-year survival rates of 98.7%, 93.0%, and 80.6% with graft survival rates of 95.5%, 80.9%, and 57.1%, respectively, over the same time.⁸ The graft and patient survival rates for recipients of deceased donor kidneys depend on classification as expanded-criteria donor (ECD) or non-ECD. ECDs are donors with age greater than 60 years or age between 50 and 59 years with two or more of the following: death from cerebrovascular accident, a history of hypertension, or creatinine greater than 1.5 mg/dL. Graft survival rates at 1, 5, and 10 years for non-ECD deceased donors are currently 92.0%, 70.9%, and 43.1%, respectively, whereas rates for ECDs are 85.1%, 54.9%, and 26.6%, respectively.⁸ Similarly, patient survival rates are better for non-ECD organs (96.7%, 85.4%, 65.6%, respectively) than for ECD organs (92.9%, 72.0%, 50.1%, respectively).⁸ Increased cold ischemia time, increased recipient PRA, increasing time on the waiting list, and retransplantation all resulted in reductions of patient and graft survival.⁸ When compared to patients maintained on dialysis, renal transplantation improved patient survival.^{25,26}

Liver Transplantation

Liver transplantation is the treatment of choice for acute and chronic end-stage liver disease (ESLD). The duration of symptoms or jaundice prior to encephalopathy determines whether acute liver failure is fulminant (less than 8 weeks) or subfulminant (more than 8 weeks). Causes of acute liver failure include acetaminophen toxicity, acute viral infections, drug toxicity, Wilson disease, mushroom intoxication, and autoimmune hepatitis. Chronic liver disease is considered ESLD or decompensated cirrhosis once complications occur, such as intractable ascites or encephalopathy, portal hypertensive bleeding, spontaneous bacterial peritonitis, portopulmonary syndrome, or synthetic dysfunction. Patients with Model for End-Stage Liver Disease (MELD) scores of 15 or greater generally derive a survival benefit from transplantation. The main diagnoses leading to ESLD include viral hepatitis, especially hepatitis C, alcoholic liver disease, non-alcoholic steatohepatitis, and cholestatic liver diseases such as primary sclerosing cholangitis (PSC) and primary biliary cirrhosis. Transplantation for hepatocellular carcinoma (HCC) and, more recently, cholangiocarcinoma is an option for carefully selected patients with advanced cirrhosis. The most widely used criteria, the Milan classification, support transplantation for patients with a single tumor between 2 and 5 cm in diameter or up to three tumors with no tumor larger than 3 cm.²⁷ The University of California-San Francisco group argued that outcomes are preserved in patients with more liberal criteria: specifically, one tumor no larger than 5 cm or up to three tumors with no tumor larger than 4.5 cm and a total tumor size of less than 8 cm.²⁸ Metabolic liver diseases such as Wilson disease, hereditary hemochromatosis,

and α_1 -antitrypsin disease may also lead to ESLD and require transplantation. Finally, a number of diagnoses specific to the pediatric population may also lead to transplantation, including biliary atresia, progressive familial intrahepatic cholestasis, Alagille syndrome, urea cycle defects, and tyrosinemia.

RECIPIENT EVALUATION

Evaluation of the potential recipient must accomplish the following goals: (1) assessment of the etiology and severity of liver disease to ensure that transplantation will improve outcome; (2) evaluation for comorbid conditions that may preclude transplantation; and (3) evaluation of the patient's psychosocial situation to ensure adequate resources to support the patient following transplantation. Complete history and physical examination supplemented by laboratory evaluation and selected imaging and functional studies will provide characterization of liver disease and comorbid conditions. Standard blood tests include serologies for hepatitis B and hepatitis C, autoimmune markers, α_1 -antitrypsin levels, ceruloplasmin, 24-hour urine copper, genetic testing for hemochromatosis, α -fetoprotein (AFP), carcinoembryonic antigen, CA 19-9, blood group, and hypercoagulable evaluation. Testing for common viral infectious diseases such as HIV, syphilis, CMV, EBV, and toxoplasmosis may also be performed. Electrocardiography, echocardiography with evaluation for shunting (bubble study), and pulmonary function testing with arterial blood gas are standard studies. Cardiac stress testing or right- and left-heart catheterization may be required in cases of suspected coronary artery disease or pulmonary hypertension. Imaging of the liver with ultrasonography, CT, or MRI is required to evaluate for HCC and to assess the patency of the portal vein. A patient with PSC may undergo endoscopic retrograde cholangiopancreatography (ERCP) to evaluate for cholangiocarcinoma. Colonoscopy is required in patients with PSC but also as part of age-appropriate cancer screening. Mammography and Papanicolaou smear evaluations for breast and cervical cancer should be performed in women, whereas older men should have a prostate-specific antigen level assessed. Patients with HCC need evaluation for metastatic disease, including bone scanning and chest CT. Pediatric patients with syndromic disorders such as Alagille syndrome should have appropriate evaluation for cardiopulmonary anomalies as well as abdominal imaging to evaluate for anomalous vascularity that may require complex reconstruction. Absolute contraindications to transplantation include active extrahepatic malignancy and uncontrolled extrahepatic infection. In patients with decompensated liver disease who are critically ill, decisions about "transplantability" are made on an offer-by-offer basis based on the patients' current condition and amount of support (i.e., requirement for multiple pressors or significant ventilatory support).

Social work and psychiatry services are essential in evaluating patients and their support system to ensure the necessary commitment to posttransplantation care. Financial resources for the transplantation event itself as well as immunosuppressive and other medications following transplantation should be identified. Patients with alcoholic cirrhosis are often required to demonstrate 6 months of abstinence from alcohol and complete formal alcohol rehabilitation programs.

Intentional or accidental acetaminophen toxicity is responsible for nearly half of the cases of fulminant hepatic failure in the United States.²⁹ Timely treatment with *N*-acetylcysteine can prevent hepatic injury and avoid the need for transplantation. As with all forms of acute liver failure, expedited evaluation of comorbid conditions, maximal supportive medical therapy, and assessment of neurologic status are required. Unlike patients with chronic liver disease, patients with acute liver failure may develop cerebral edema, resulting in elevated intracranial pressure (ICP), herniation, and brain death. Invasive ICP monitoring is indicated in comatose patients to avoid transplantation in the setting of irreversible brain injury. Patients presenting in fulminant hepatic failure as a result of intentional acetaminophen overdose present a special challenge to psychiatry consultants, who must rely on a history of depression and past suicide attempts as well as interviews with the patient's family to assess the risk of future suicidality. In cases where conservative measures do not lead to hepatic recovery, liver transplantation must be considered. Scoring systems may help predict which patients will recover, but the decision to proceed with transplantation depends on the clinical team's assessment of each patient³⁰ [see Table 2]. The presence or persistence of encephalopathy, worsening coagulopathy, and renal failure portend poor outcome without transplantation.

PROCEDURE

Liver transplantation requires the timely and coordinated performance of the donor procurement procedure, recipient hepatectomy, and implantation of the donor liver. On receipt of an appropriate liver offer, the recipient should be evaluated to ensure that no new contraindications to transplantation have developed. Once the procurement team has evaluated the donor organ, the recipient procedure commences with induction of anesthesia and placement of appropriate monitoring lines. Antibiotics and immunosuppression are given per protocol.

The recipient procedure consists of mobilizing the liver from its diaphragmatic and retroperitoneal attachments to expose the IVC and isolation of the portal structures to allow for removal of the recipient's native liver while preserving length on the vessels. The donor liver is then implanted by anastomosing the donor vena cava to the recipient vena cava or hepatic veins as well as completing the portal vein and hepatic artery anastomoses. Specific techniques vary and may need to be modified because of variable recipient or

donor vascular anatomy. After reperfusion of the liver and hemostasis, the donor bile duct is anastomosed to either the recipient bile duct or jejunum via Roux-en-Y hepaticojejunostomy [see Figure 3].

COMPLICATIONS

Although uncommon, PNF of a liver allograft is a catastrophic complication. PNF occurs in approximately 5% of liver transplants and is characterized by persistent hemodynamic instability, renal failure, acidosis, coagulopathy, hypothermia, hypoglycemia, lack of bile production, poor graft reperfusion, and persistent unconsciousness. Immediate retransplantation is required for patient survival. Donor-derived risk factors for PNF include advanced age, hepatic steatosis, and hypernatremia. Procurement-related risk factors include prolonged cold ischemia time and, potentially, NHBDs. More severely ill recipients appear to be at increased risk for PNF. Prevention of PNF involves avoiding grafts or graft-patient combinations at high risk for its occurrence. Treatment with prostaglandins and *N*-acetylcysteine may potentially improve hepatic function after transplantation, but data to support the widespread use of these agents are lacking. Graft hepatectomy with portocaval shunting may allow temporary stabilization of the patient while awaiting retransplantation. According to UNOS policy, PNF following liver transplantation qualifies the recipient for listing as status 1 for retransplantation.

Postoperative hemorrhage requiring return to the operating rooms occurs in approximately 5% of liver transplant recipients. Coagulopathy following liver transplantation is common, and administration of fresh frozen plasma, cryoprecipitate, and platelets should be considered as indicated by clinical and laboratory findings. Careful attention to the patient's hemodynamic status, serial hemoglobin levels, urine output, and nature and quantity of drain output may provide clues to the presence of ongoing bleeding. Hemodynamic

Table 2 King's College Criteria for Poor Outcome of Fulminant Liver Failure³⁰	
Acetaminophen Induced	Non-Acetaminophen Induced
Arterial pH < 7.30	Non-A, non-B hepatitis or drug reaction
Prothrombin time > 100 seconds	Age < 11 yr or > 40 yr
Creatinine > 300 µmol/L	Duration of jaundice > 7 days before onset of encephalopathy
	Bilirubin > 300 µmol/L
	Prothrombin time > 50 seconds

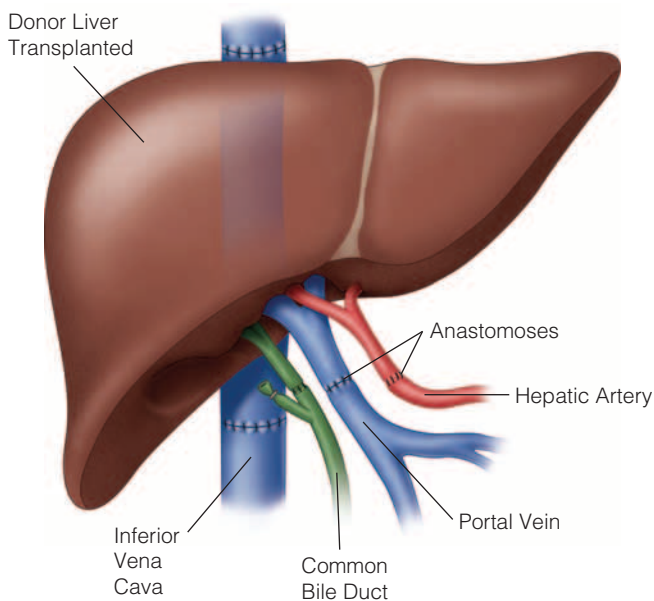


Figure 3 Liver transplantation with cava, portal venous, hepatic arterial, and biliary reconstructions.

instability or significant transfusion requirement often prompts a return to the operating room to identify ongoing sources of bleeding and evacuate intraperitoneal blood.

Early thrombosis of the hepatic artery occurs in 5 to 10% of cases and may be the result of technical problems at the anastomosis or may reflect a transient hypercoagulable state. Thrombosis may present as a sudden increase in transaminases, prolonged prothrombin time, and a change in mental status. Although both Doppler ultrasonography and angiography can confirm HAT, operative revision is usually required to avoid complications, including graft necrosis and sepsis. Biliary strictures, recurrent cholangitis, and secondary biliary cirrhosis are all late consequences of HAT as biliary blood supply to the graft is provided solely by the donor hepatic artery. Hepatic artery stenosis may be suspected because of elevated bilirubin and demonstrated on Doppler ultrasonography. Endovascular or operative revision is indicated to prevent thrombosis.

Portal vein thrombosis is less common than HAT and often results from technical errors such as kinking, twisting, or compression of the vein. Elevated liver enzymes, development of ascites, and variceal hemorrhage all suggest portal vein thrombosis. Doppler ultrasonography may confirm this finding. Operative thrombectomy and revision of the anastomosis are often required. Portal vein stenosis often presents later in the patient's course and can be seen on ultrasonography. Both endovascular and operative approaches to management may be used to correct this condition. Hepatic vein thrombosis is uncommon and often related to an underlying hypercoagulable state. Stricture at the caval anastomosis may be suspected in the setting of new ascites in combination with lower extremity edema and renal insufficiency. Doppler ultrasonography and venography can confirm this condition. Endovascular dilatation and stent placement will suffice in many cases; operative intervention is indicated if percutaneous efforts fail.

Bile leaks occur in fewer than 10% of liver transplants and may be heralded by bile-tinged drain output. In the absence of drains, bile leak may be suggested by increased bilirubin, alkaline phosphatase, or GGT. Ultrasonography or CT may demonstrate a fluid collection, which should be drained. Doppler interrogation should be performed to assess the patency of the hepatic artery. Early or large-volume leaks often require operative revision for anastomotic defects or necrosis of the bile duct. Low-volume leaks may be managed by endoscopically placed stents across the sphincter of Oddi to provide a low-pressure egress for bile. Cut-surface bile leaks may occur in living donor grafts or split cadaveric grafts. Leaks from the cut surface often resolve with endoscopic stenting; persistent leaks may require operative oversewing of the leaking duct on the cut surface. Biliary anastomotic strictures may occur early in the postoperative course because of edema at the anastomosis; these strictures often respond to endoscopic stenting. Later or severe strictures may respond to endoscopic or percutaneous procedures, whereas persistent strictures may require operative revision or conversion to Roux-en-Y choledochojejunostomy.

Elevation of liver function tests following liver transplantation has a broad differential diagnosis. Two general patterns of liver enzyme elevations may suggest etiologies, although overlap occurs. Hepatocellular damage is reflected in elevated transaminases (alanine aminotransferase [ALT], aspartate

aminotransferase [AST]), whereas cholestatic processes cause elevations in alkaline phosphatase, bilirubin, and GGT. In the immediate postoperative period, ALT and AST may rise in response to ischemia and reperfusion injury. By 12 to 24 hours, however, these values should peak and start to decrease. Persistent increase suggests hepatic arterial or portal vein thrombosis, hepatic infarction or necrosis, or PNF. Outside of the immediate postoperative period, elevated hepatocellular enzymes suggest rejection, ischemia, or recurrent viral hepatitis. Elevation of the cholestatic markers suggests biliary tract problems, including bile leak, biliary stricture, or infection, but may also be seen in rejection. Doppler ultrasonography is often the first diagnostic study performed to evaluate for perihepatic collections, vascular complications, or biliary dilatation. Magnetic resonance cholangiography, percutaneous transhepatic cholangiography (PTC), and endoscopic retrograde cholangiography (ERC) are used to diagnose and, in the case of PTC and ERC, treat biliary strictures or leaks. Percutaneous or transjugular biopsy is often required to provide tissue confirmation of recurrent hepatitis C, acute or chronic rejection, or infection with CMV.

Immunosuppression-related infectious and neoplastic risks following hepatic transplantation are similar to those described for renal transplantation. Specific infectious concerns following liver transplantation include biliary-derived infections and recurrence of hepatitis B and C. Recurrent hepatitis B can often be prevented with the use of hepatitis B immunoglobulin and antiviral agents, including lamivudine, entecavir, or tenofovir. Early recurrent hepatitis C may mimic rejection on biopsy, leading to injurious increases in immunosuppression. There are no preventive strategies for hepatitis C, but treatment with interferon and ribavirin may be attempted. Tolerance of this approach is poor, with many patients requiring dose reduction or cessation of therapy, and evidence of improvement in outcome is lacking.³¹

Patients transplanted for HCC require continued surveillance for recurrence. Features on explant pathology that suggest an increased risk for recurrence include micro- or macrovascular invasion, tumor involvement of lymph nodes, tumor size greater than 5 cm, and increased total number of tumors.³² Serial serum AFP measurements and imaging may demonstrate recurrent disease. Localized recurrence may be treated with liver-directed therapies or resection; however, many patients present with disseminated disease not amenable to resection or local therapy.

OUTCOMES

Overall patient survival rates for recipients of deceased donor liver grafts at 1, 5, and 10 years are 87.9%, 74.2%, and 58.5%, respectively.⁸ Graft survival rates are 82.3%, 67.2%, and 50.8%, respectively.⁸ For recipients of living donor grafts, patient survival rates are 93.4%, 83.8%, and 82.0%, respectively, whereas graft survival rates are 88.1%, 75.3%, and 74.3%, respectively⁸ [see Table 1]. Although it appears that outcomes are better for living donor grafts, it is difficult to directly compare survival rates for deceased and living donor recipients because of potential selection bias of patients who receive living donor grafts. Other factors that may impact patient survival include recurrent HCC, retransplantation, cold ischemia time, and whether the recipient was hospitalized or required intensive care prior to transplantation.^{8,32}

Pancreas Transplantation

The main indication for pancreas transplantation is treatment for type 1 diabetes mellitus. Approximately 850 SPK transplantations and 450 isolated pancreas transplantations are performed annually in the United States for diabetic uremic patients and those with brittle diabetes and frequent episodes of hypoglycemic unawareness, respectively.¹ Seventy-five percent of isolated pancreas transplantations occur following successful kidney transplantation (pancreas after kidney [PAK]), whereas 25% occur in nonuremic patients who do not require renal transplantation (pancreas transplantation alone [PTA]).⁸

RECIPIENT EVALUATION

Standard history, physical examination, laboratory studies including HLA typing and panel reactive antibody percent, infectious disease exposures, evaluation of cardiopulmonary status, and age- and sex-specific cancer screenings are performed as for other potential transplant recipients. In addition, confirmation of the diagnosis of type 1 diabetes mellitus is performed by measuring the serum C-peptide level; patients with type 1 diabetes mellitus should have undetectable levels of C-peptide, confirming a lack of insulin production. Complications seen with long-term diabetes may complicate the transplant procedure and postoperative management. Vascular disease in the coronary, lower extremity, and cerebral vessels is common and should be assessed. Severe gastroparesis may make oral administration of immunosuppressive medications difficult, requiring aggressive management with promotility agents. Blindness is not a contraindication to transplantation, but adequate social support to aid with medication compliance is required.

Patients with ESRD and type 1 diabetes are candidates for SPK transplantation. The added surgical risk of transplanting a pancreas is relatively low. Because of a shortage of suitable pancreas allografts, many type 1 diabetic patients are more likely to receive a renal allograft from either a living or deceased donor. These patients may be excellent candidates for PAK transplantation as they are already on immunosuppressive medications. Although this approach requires a second operation for pancreas transplantation and exposes the recipient to a second set of donor antigens, it is a growing option for many diabetic uremic patients. For nonuremic diabetic patients, the decision to proceed with PTA requires that the current complications (i.e., hypoglycemic unawareness, brittle diabetes, frequent hospitalizations) be of significant burden to offset the risks of surgery and lifelong immunosuppression.

PROCEDURE

Proper selection and preparation of donor organs require an experienced team. Ideal donors are between 10 and 50 years of age, are thin, have no surgical or traumatic damage to the pancreas, and do not have type 1 or type 2 diabetes mellitus. Intraoperative assessment of the potential pancreas allograft by the transplanting team is essential with attention paid to the size of the gland and vessels, fat content, and presence of fibrosis. Back-table preparation of the pancreas graft involves removal of the spleen and ligation of the splenic vessels, shortening of the bowel left with the graft, and

preparing the portal vein and superior mesenteric (SMA) and splenic arteries for implantation. A donor iliac artery Y graft may be attached to these SMA and splenic arteries to simplify arterial anastomosis to the donor.

Significant variation exists in the techniques of pancreatic transplantation. The goals of the operation are establishment of arterial inflow from the recipient iliac artery into the donor Y graft, portal venous outflow to either the systemic (iliac vein or IVC) or portal venous systems via the superior mesenteric vein, and drainage of the exocrine secretions of the pancreas into either the recipient bladder or bowel [see *Figure 4*]. Portal venous drainage of the pancreas allograft mimics the normal physiology of first-pass metabolism in the liver and may provide immunologic benefit.³³ Currently, the majority of pancreas grafts have exocrine drainage into the recipient jejunum. Bladder drainage requires that the duodenum and head of the pancreas be oriented in the recipient's pelvis. The advantages to bladder drainage of pancreas grafts include the ability to monitor urine amylase levels as a marker of rejection and decreased morbidity of anastomotic leaks. The disadvantages of bladder drainage include metabolic acidosis from pancreatic bicarbonate secretion, cystitis, and hematuria from constant mucosal exposure to pancreatic enzymes; reflux pancreatitis from urine entry into the pancreatic duct; and urethral injury. The advantages to enteric drainage include a more physiologic management of pancreatic secretions and more options for placement of the pancreas graft relative to vascular reconstructions. The main disadvantage to enteric drainage is the significant morbidity in rare cases of leakage from the enteric anastomosis.

COMPLICATIONS

Early postoperative thrombosis occurs in fewer than 5% of transplants but often requires removal of the graft. Portal vein thrombosis happens more frequently than arterial thrombosis and is the most common nonimmunologic cause of pancreatic graft failure. The etiology of thrombosis is not always clear, but many centers report use of antiplatelet agents and heparin-based anticoagulation. Venous thrombosis may be seen on Doppler ultrasonography. Early intervention may result in salvage of the graft, but graft loss is often the result.^{34,35}

Other early technical complications of pancreas transplantation include postoperative hemorrhage and, rarely, leakage from the duodenal anastomosis. Given the multiple vessels in the peripancreatic tissues and mesentery of the graft and the common use of anticoagulation following pancreas transplantation, bleeding complications are common. Hemodynamic instability or significant transfusion requirement may require exploratory laparotomy for hemostasis and to remove hematoma. Additionally, lower gastrointestinal bleeding may occur several days after pancreas transplantation, occasionally requiring blood transfusion support. Potential etiologies include mucosal sloughing from the transplanted duodenum or bleeding from the cut edges of the duodenal-jejunal anastomosis.

Elevated pancreatic enzymes are expected in the immediate posttransplantation period but should demonstrate a rapid decline. Persistent elevation or elevation of enzymes later in the patient's course should prompt further investigation for vascular thromboses or episodes of acute rejection. Imaging studies can confirm vascular patency, whereas tissue

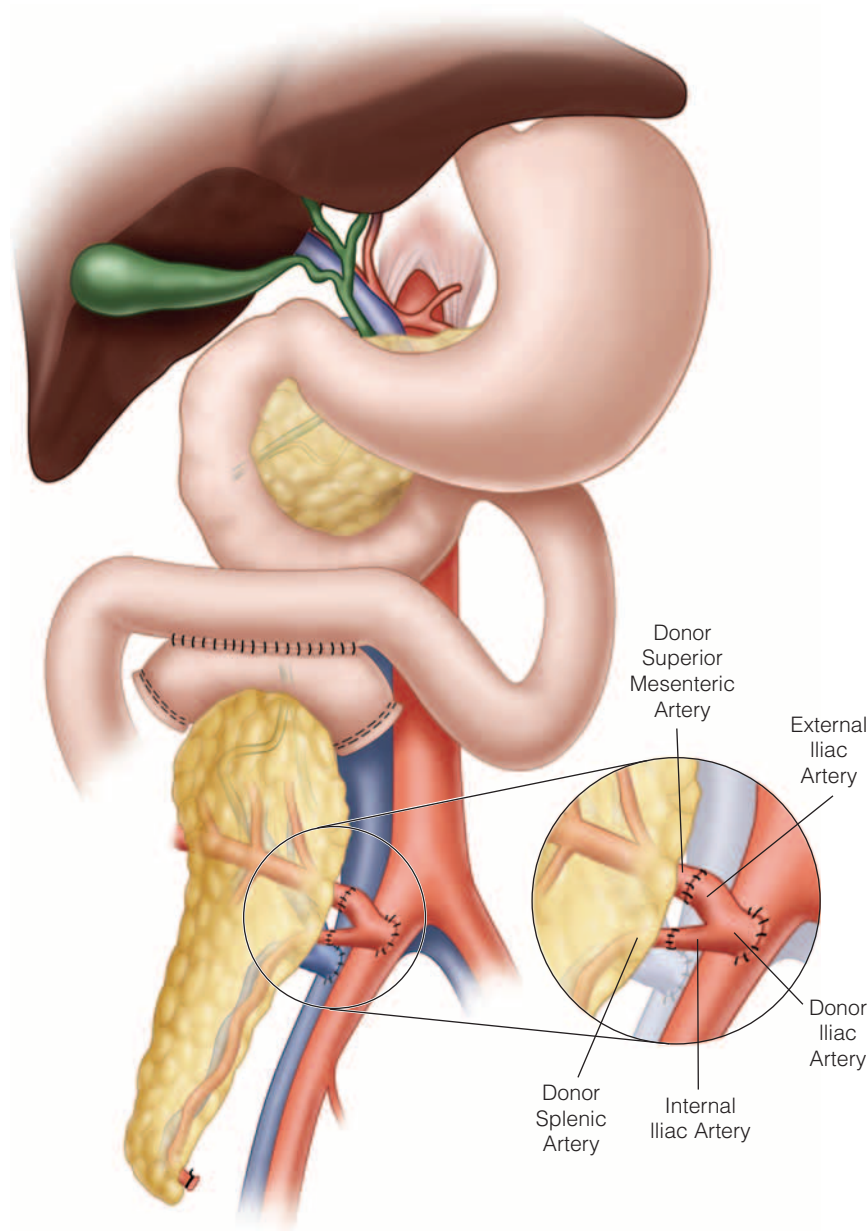


Figure 4 Pancreatic transplantation. Iliac Y graft reconstruction of superior mesenteric and splenic arteries, systemic drainage of graft portal vein, and duodenojejunostomy.

diagnosis is required for suspicion of rejection. In SPK transplants, it is uncommon (1 to 2% of cases) to have pancreas rejection without kidney rejection and an elevated creatinine. Percutaneous kidney biopsy is often more easily performed than pancreas biopsy and can provide histologic evidence of rejection. In PAK transplantation or PTA, image-guided biopsy of the pancreas is often necessary to diagnose rejection. Bladder-drained pancreas grafts offer two advantages in the diagnosis of rejection: (1) rejection results in a decrease in urinary amylase excretion and (2) cystoscopic transduodenal biopsy of the pancreas allograft may be performed. Of note, hyperglycemia occurs only after destruction of substantial beta-cell mass and thus is a late marker of pancreas rejection.

OUTCOMES

All forms of pancreas transplantation (SPK, PAK, PTA) have shown improved outcome over the past 20 years despite the increasing use of high-risk donors and recipients.³⁶ Patient survival for all forms of pancreas transplantation is similar, although the best pancreas graft survival rates are seen with SPK transplantation⁸ [see Table 3].

Intestinal Transplantation

Approximately 1,700 small intestinal transplantations have been performed in the United States over the past 20 years with 2% of grafts donated by living donors.¹ Small intestinal transplantation is indicated in patients with intestinal failure

Table 3 Patient and Graft Survival Following Pancreas Transplantation^a

Survival (yr)	SPK	PAK	PTA
Patient			
1	95.2	97.8	98.2
5	85.4	83.4	87.2
10	67.4	61.1	68.6
Pancreas			
1	87.1	77.4	85.1
5	71.6	59.4	52.3
10	54.1	25.8	18.6

PAK = pancreas after kidney; PTA = pancreas transplantation alone;
SPK = simultaneous pancreas-kidney.

attributed to extensive small bowel resection, severe malabsorption, or motility disorders. A detailed description of the selection processes, surgical procedures, and complications is beyond the scope of this text. An excellent review is available.³⁷

Immunology and Immunosuppression

PRINCIPLES OF IMMUNOLOGY

Immune-mediated destruction of an allograft, or rejection, requires a multistep process in the recipient. First, antigens from the donor are presented in the context of recipient major histocompatibility complex (MHC, also known as HLA) by recipient antigen-presenting cells. Recipient T cells bind to the MHC-antigen complex via the T cell receptor (TCR). Binding is not sufficient to activate the immune system, however, as costimulatory signals are also required to allow internalization of the TCR and activation of the cell to produce interleukin-2 (IL-2). IL-2 acts to stimulate proliferation of T cells, thus augmenting the immune response. Other cytokines and chemokines are also elaborated that serve to activate various other aspects of the immune system, including B cells, complement, neutrophils, and natural killer cells. Immunosuppressive agents block various steps in these pathways.

Rejection may be classified by the timeframe of occurrence and the types of reactions that occur. Hyperacute rejection results immediately on reperfusion of the allograft and is attributed to the presence of preformed antibodies against HLA class I or ABO blood antigens circulating in the recipient. These antibodies attach to the donor organ vascular epithelium, fix complement, attract neutrophils, and destroy the endothelium within minutes to hours, resulting in near-immediate graft loss. The crossmatch performed prior to transplantation mixes donor lymphocytes with recipient serum to detect these preformed antibodies. Accelerated rejection may occur if the recipient has had prior sensitization to donor antigens but does not have circulating antibody. Memory responses allow for a rapid proliferation of T cells or antibodies against the antigens of the graft.

In the absence of immunosuppression, acute rejection occurs toward the end of the first week following transplantation. Nonspecific inflammatory processes including infiltration

with mononuclear cells, edema, and decreased blood flow in combination with destruction of parenchymal and endothelial cells by lymphocytes leads to blood vessel destruction and loss of function. Acute rejection may also occur at any time that insufficient immunosuppression exists in the recipient. If detected early, acute rejection may be reversed by increased immunosuppression, but long-term outcomes of renal grafts having episodes of acute rejection are diminished compared to those grafts without this complication. Acute cell-mediated rejection in the kidney is characterized by interstitial mononuclear cells and disruption of tubular basement membranes, or tubulitis. In liver allografts, histologic evidence of acute rejection includes portal infiltrates consisting of mixed inflammatory cells, lymphocyte-mediated bile duct injury, and endothelialitis. In acute antibody-mediated (humoral) rejection, endothelial swelling and arteritis, glomerulitis with neutrophils, and plasma cell infiltration can occur. Immunohistochemical staining for complement components (C4d) also suggests humoral rejection. Measurement of serum donor-specific antigens levels may help confirm humoral rejection. Of note, cellular and humoral rejection may coexist.

Chronic rejection refers to the gradual loss of function of a transplanted organ. Its pathogenesis is not fully understood but may be related to immunologic and other factors. Across organs, intimal thickening, parenchymal atrophy, and interstitial fibrosis are common findings. Following renal transplantation, chronic rejection is also known as chronic allograft nephropathy and is characterized by interstitial fibrosis and tubular atrophy. Chronic rejection after liver transplantation is reflected in scarring of the bile ducts (vanishing bile duct syndrome). Current immunosuppressive medications do not prevent or reverse chronic rejection, although episodes of acute rejection may set the stage for chronic rejection despite apparent resolution.

IMMUNOSUPPRESSIVE AGENTS

Immunosuppressive agents may be divided into induction agents, usually given only around the time of transplantation or to treat rejection, and maintenance agents, given continuously after transplantation. Induction agents are typically used once or for a few doses in combination with initiation of maintenance agents at the time of transplantation. Antilymphocyte and antithymocyte globulins are polyclonal antibodies directed at multiple antigens of lymphocytes. OKT3 is a monoclonal antibody directed against the TCR (CD3). The side effects of these agents include acute cytokine release syndromes, allergic reactions, and development of neutralizing antibodies to OKT3. Because of their potent effects, prolonged use may also increase the risk of opportunistic infection or lymphoma. CD25 forms part of the interleukin-2 receptor (IL-2R) on activated T cells. Two monoclonal antibodies against CD25, basiliximab (Simulect) and daclizumab (Zenapex), bind the IL-2R and prevent activation of the cell. Alemtuzumab (Campath), another monoclonal antibody, targets CD52 and results in a profound depletion of lymphocytes for several months.

Maintenance agents are used in various combinations to provide ongoing immunosuppression. The number of agents and the doses or target blood levels may be decreased as the rejection-free time from transplantation accumulates. Corticosteroids have many effects on the immune response,

including general antiinflammatory properties and inhibition of cytokine production and secretion by altering gene transcription. Prolonged use of corticosteroids results in many side effects, including weight gain, diabetes, hypertension, peptic ulcers, muscle wasting, osteopenia, cataract formation, personality changes, and cushingoid changes. CNIs, cyclosporine (Sandimmune, Neoral) and tacrolimus (Prograf), block the TCR from signaling through immunophilin to stimulate IL-2 production. The side effects of the CNIs include nephrotoxicity, hypertension, hyperkalemia, and neurotoxicities. Cyclosporine is also known to cause hirsutism and gingival hyperplasia, whereas tacrolimus may cause alopecia and has been associated with an increased incidence of posttransplantation diabetes. For both agents, blood levels are monitored carefully to maintain adequate immunosuppression and minimize side effects. The metabolism of many medications affects or is affected by these agents; thus, addition or cessation of medications should be done in conjunction with the transplant center. Rapamycin or sirolimus (Rapamune) blocks the IL-2R signal to the T cell nucleus and stops cell-cycle progression. Rapamycin may contribute to hypertriglyceridemia, limits wound healing, and has been linked to HAT. Antiproliferative agents prevent clonal expansion of activated lymphocytes as well as other rapidly dividing cells, including the gastrointestinal tract and hematopoietic cell lines. Azathioprine (Imuran) was the first agent in clinical use, whereas mycophenolate mofetil (CellCept, Myfortic) is now commonly used. The side effects include gastrointestinal toxicity and leukopenia.

Pre- and posttransplantation protocols exist for transplantation between ABO-incompatible donor and recipient pairs, for patients with a positive cytotoxic crossmatch, and for patients with high PRA attributed to prior transplantation, transfusion, or pregnancy. A detailed discussion of these topics is beyond the scope of this review.

General Surgery in Patients with End-Stage Organ Disease

END-STAGE RENAL DISEASE

General Principles

As kidney transplant waiting list times may exceed 5 years in some regions, it is likely that most practitioners will encounter patients with ESRD who have general surgery problems. Coordination of the patient's care with a nephrology team and careful management of the patient's volume status and electrolytes are crucial to a successful outcome. The effect that comorbid conditions, including coronary artery disease, congestive heart failure, and peripheral vascular disease, may have on the safe conduct of the operation or perioperative management cannot be minimized. Use of desmopressin (ddAVP) aids in correcting uremic coagulopathy by increasing factor VIII and von Willebrand factor, whereas platelet transfusion may be needed in patients requiring emergent surgery who have been on aspirin or other antiplatelet agents. Additionally, patients with ESRD have poor wound healing attributed to a combination of nutritional factors, depressed immune function, and poor circulation. Chronic renal failure and dialysis lead to a hypercatabolic state attributed to loss of amino acids and cytokine

activation.³⁸ ESRD has an immunosuppressive effect because of decreased neutrophil function, impaired phagocytosis, reduced natural killer cell activity, and decreased lymphocyte function.³⁹ Strict glycemic control in the perioperative period has also been shown to decrease infectious complications, although differences in mortality were not seen in a recent meta-analysis of studies comparing tight glucose control to usual care.⁴⁰ Careful surgical technique combined with appropriate antibiotic management, nutritional support, and maximal medical management of comorbidities is required for good outcomes in this population.

General and Peripheral Vascular Surgical Procedures

Patients with ESRD exhibit many of the same general surgical diagnoses as patients with normal renal function. In a comparison to patients without ESRD, laparoscopic cholecystectomy was performed in patients with ESRD with no difference in blood loss, conversion rate, morbidity, mortality, or hospital length of stay.⁴¹ Similarly, patients with ESRD may undergo liver resection for HCC with no difference in overall and disease-free survival despite more associated disease, more postoperative complications, and longer hospital stays than patients without ESRD.^{42,43} *Clostridium difficile*-associated colitis, diverticulitis, and mesenteric ischemia are all common diagnoses in patients with ESRD and often result in increased morbidity and mortality in this population.⁴⁴⁻⁴⁶ Patients with polycystic kidney disease appear to be at increased risk of complicated diverticulitis than patients with other etiologies of renal failure.⁴⁶ Segmental necrosis of the ascending colon has been frequently reported in dialysis patients and is likely caused by low-flow states and changes in blood viscosity.⁴⁷⁻⁴⁹ In patients managed with PD, a high degree of suspicion should be maintained to differentiate acute surgical diagnoses from peritonitis caused by infected peritoneal dialysate fluid. Although peritonitis as a result of contamination of the dialysate or system is most common, other causes should be considered. An 8-year review of a single center found six cases of peritonitis in PD patients caused by a perforated appendix or diverticulitis with a mortality of 16%.⁵⁰ The average time to diagnosis in this group was 10 days, with CT of the abdomen being nondiagnostic in all cases.⁵⁰ Clinical and radiologic findings may be nonspecific, but the presence of polymicrobial infection should prompt further investigation.

Patients with ESRD are at increased risk for peripheral vascular disease. The stage of chronic kidney disease (CKD) has been found to predict survival curves and risk for major amputation in patients undergoing lower extremity bypass surgery.⁵¹ In comparison to patients with CKD and patients with normal renal function, patients with ESRD have similar perioperative mortality and graft patency rates but a higher rate of amputation despite a patent graft.⁵² Patients with ESRD appear to have an increased risk of more distal vascular lesions (popliteal-tibial) compared to more proximal (aortoiliac) lesions, which may influence the type of reconstruction required.⁵³

Obese patients suffer increased complications following surgery, including renal transplantation. To address perioperative morbidity as well as long-term health concerns, several centers have recently reported performing bariatric surgery in patients with ESRD prior to renal transplantation.⁵⁴⁻⁵⁶ One group reported that 93% of patients reached institutional

body mass index limits for transplantation, and obesity-associated comorbidities resolved or improved in all patients.⁵⁵ Similarly, several series reported improvement in renal function following bariatric surgery, in some cases obviating the need for renal transplantation.^{57,58}

Vascular Access Procedures

Vascular access options for long-term hemodialysis (HD) include arteriovenous fistula (AVF; direct connection of artery and vein), arteriovenous grafts (AVGs; artery and vein connected with prosthetic material), and catheter-based dialysis. Use of AVFs has been shown to have lower rates of complications (thrombosis or infection) and results in fewer hospitalizations, less morbidity, and less cost than use of AVGs or catheter-based dialysis.^{59,60} The National Vascular Access Improvement Initiative, sponsored by the Centers for Medicare and Medicaid, sought to reach the goal of AVF creation in at least 50% of all new patients starting HD and 40% of prevalent patients on HD.⁶¹ This “Fistula First” campaign promotes early identification and referral of patients with CKD for consideration of AVF creation in time for maturation of the fistula by the time it is needed to start HD. Recent reports suggest that AVF use increased in the United States from 24 to 47% from 1996 to 2007, whereas AVG use decreased from 58% to 50% over the same time period.⁶²

Assessment for placement of arteriovenous access starts with an emphasis on the likely time until the start of dialysis and prior attempts at access creation or central venous catheter placement. Ideally, access creation occurs several months prior to the need for dialysis to allow for maturation of the access. Severe heart failure may preclude fistula creation attributed to increased cardiac output required to support the fistula. On clinical examination, the status of distal pulses in the upper and lower extremities is assessed. Similarly, the superficial veins (cephalic, basilic) of the arm are assessed for patency or scarring from prior phlebotomy or previous attempts at access creation. If no veins are apparent or their patency is questionable, imaging studies such as ultrasonography or venography can be performed. Venography can also provide information about the patency of the central venous system in patients who have had prior central venous catheters. Once a site has been chosen, phlebotomy and peripheral intravenous line insertion should be performed in the contralateral arm. In choosing sites for access creation, the nondominant upper extremity is preferred, with the most distal site used first. A vein diameter of more than 2.5 mm is preferred, but use of smaller veins may be attempted if necessary.

Sites for upper extremity AVF creation in the distal arm include the radiocephalic (Brescia-Cimino), snuff-box, and ulnar-basilic fistulas [see Figure 5]. More proximally, a brachiocephalic fistula may be created just above or below the elbow crease. A brachio-basilic fistula may be created but will likely require transposition and elevation of the basilic vein either during the initial procedure or as a second, staged procedure once the vein has matured. Attempts to cannulate the basilic vein in its native position may be difficult because of its distance from the skin and may risk injury to the adjacent nerves and artery. Fistula creation can usually be performed under local or regional anesthetic. Most commonly, the vein is anastomosed in an end-to-side configuration to the artery, although side-to-side fistulas may also be used. At the end of

the case, a palpable thrill or audible bruit on the venous side of the fistula confirms patency. Postoperatively, patients are instructed to palpate the fistula daily to confirm the presence of a thrill. Exercises such as squeezing a rubber ball may help maturation of the fistula by increasing resistance to flow in the hand, thus increasing flow through the fistula. Maturation of the fistula implies that the venous limb has expanded to more than 6 mm and typically takes 4 to 6 weeks to occur. Lack of maturation may require ligation of branches of the vein or fistulogram to diagnose and potentially treat inflow (arterial) or outflow (venous) stenoses. AVGs can be placed when options for AVFs have been exhausted. The most commonly placed AVGs in the arm are straight grafts from the radial artery to basilic vein or loop grafts from the brachial artery to the basilic vein. The axillary artery can also be used with outflow via upper arm, neck, or chest veins. AVGs may be used once the graft material has been incorporated into adjacent tissues, thus preventing hematoma formation around the graft during cannulation. Two to 3 weeks is often required for incorporation and resolution of edema from placement.

Access creation in the lower extremity is usually reserved for patients who have no upper extremity options for access given a higher rate of wound infection and the need to preserve the saphenous vein as a conduit for future coronary artery bypass or lower extremity arterial reconstruction. Lower extremity fistulas may be constructed using transposed saphenous vein to connect the common femoral artery and vein. The saphenous vein may also be used as a loop (to the common femoral artery) or straight (to the distal superficial artery above the knee). Either leg vein may also be translocated to the upper extremity to create a loop or straight graft. AVGs may be created in the thigh but have higher risks of infection. An excellent review of AVF options is available.⁶³

Complications of AVFs and AVGs include failure of a fistula to mature, stenosis or thrombosis of the access, infection, ischemia or steal distal to the access creation, and pseudoaneurysm formation. Failure to mature may be due to use of small vessels, central stenosis, or competing flow through collateral vein branches. Stenosis may also occur at the anastomosis or at sites of turbulence or needle-stick injury. Poor flows through the access during dialysis sessions, persistent edema, prolonged bleeding, and a change in the nature of the thrill or bruit suggest stenoses that may be diagnosed and often treated by percutaneous interventions. Thrombosis may occur as a result of technical problems, hypercoagulable states, or persistent hypotension. A recent review suggested that use of antiplatelet agents including aspirin, clopidogrel, and dipyridamole decreased the risks of thrombosis in AVFs and AVGs, whereas use of warfarin resulted in unacceptably high rates of hemorrhagic events.⁶⁴ AVFs and AVGs may be at increased risk of thrombosis during unrelated surgical procedures. Care should be taken to protect fistulas and grafts from inadvertent pressure either on the access itself or central to it.

PD Catheter Placement

PD is an alternative to HD for many patients. Suitable candidates have had no or few prior abdominal operations with minimal adhesions and do not have ascites, malignancy, or fibrosis. Additionally, the patient or family should be motivated and able to perform PD in the home. Patients may opt

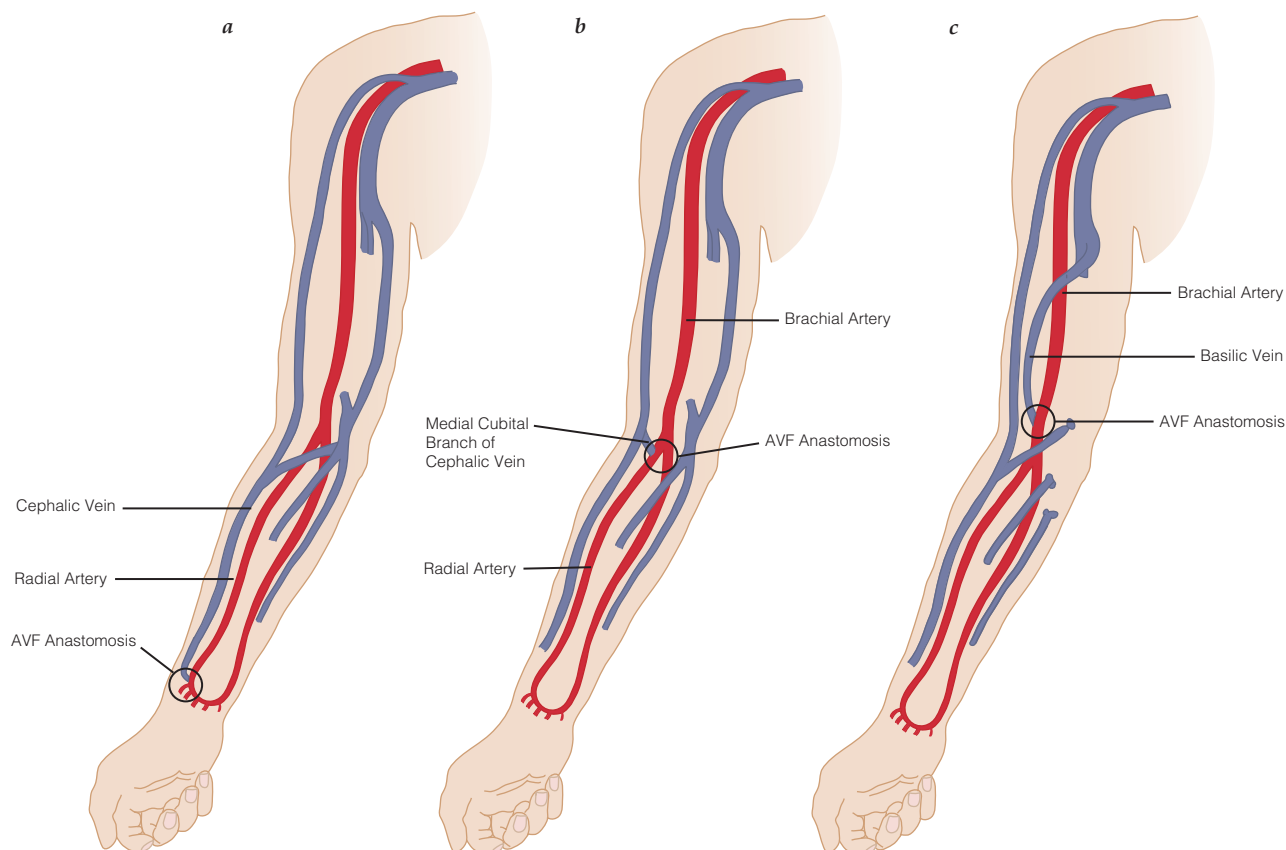


Figure 5 Upper extremity arteriovenous fistula (AVF) options include the (a) radiocephalic, (b) brachiocephalic, and (c) brachiocephalic fistulas.

for continuous ambulatory PD with four to five manual exchanges of fluid daily or continuous cycling PD, in which the patient is attached to a machine for automatic exchanges while sleeping. Catheter placement may be performed open or laparoscopically. The open technique uses an incision over the rectus sheath inferior to the level of the umbilicus. The rectus fibers are separated to expose the peritoneum to allow the creation of a small peritoneal incision. The catheter is inserted over a trocar through this incision and directed into the pelvis. One cuff is placed at the level of the fascia and may be secured in the fascial closure to avoid migration. The external end is tunneled in the subcutaneous tissues to an exit site remote from the fascial entry site. The skin exit site should be chosen to avoid interfering with clothing but in a position that is easy for the patient or caregivers to access. Use of laparoscopy for placement of PD catheters allows potential lysis of adhesions and direct placement of the catheter in the pelvis. Additionally, the catheter can be secured in the pelvis using a stitch to the anterior abdominal wall to avoid migration. Ideally, the catheter should not be used for 2 to 3 weeks to allow for healing and reduce the risk of leakage, but low-volume exchanges may be started sooner in urgent cases.

Complications of PD catheter placement include technical problems such as bowel injury, leakage from the fascial closure, malposition of the catheter, and obstruction of the catheter by omentum or adhesions. Some surgeons prefer to perform omentectomy during the initial placement of a PD catheter, whereas others prefer to wait and perform omentectomy only if there are problems with dialysate flow.

Laparoscopic revision may be attempted to reposition the catheter in the pelvis, lyse adhesions, or remove the omentum. Peritonitis and catheter tract and exit-site infections may also occur. Treatment of peritonitis using systemic and intraperitoneal antibiotics may be successful in some cases, whereas treatment of tract infections usually requires removal of the catheter. Over time, efficiency of solute exchange may decrease to the point that PD no longer provides adequate dialysis therapy, thus requiring conversion to HD.

END-STAGE LIVER DISEASE

General Principles

Whether emergent or elective, performing an operation on a patient with ESLD should be approached cautiously. The first step in appropriate management of the cirrhotic patient with a general surgery problem is determining the degree of underlying liver disease. Assessment of the severity of liver disease may be made using either the Child-Turcotte-Pugh (CTP) score or MELD score. The CTP score is calculated using the patient's serum albumin, serum bilirubin, prothrombin time, and presence or degree of ascites and encephalopathy.⁶⁵ Based on total score, patients are classified as Child's A, B, or C with increasing morbidity and mortality with increasing score. Another scoring system, the MELD score, was developed to predict 3-month mortality following transjugular intrahepatic portosystemic shunt (TIPS) creation in cirrhotic patients. The MELD score is based on the patient's serum bilirubin, serum creatinine, and INR for

prothrombin time. The MELD score is now used to determine the listing priority for liver transplantation and to provide a general gauge of the severity of liver disease. A recent comparison of the CTP and MELD systems demonstrated that a MELD score of 14 or greater was a better predictor of death, progression to liver transplantation, or prolonged hospital stay than a CTP class of C.⁶⁶ Following major digestive, orthopedic, or cardiovascular surgery, patients with MELD scores of less than 8 had a 30-day mortality of 6%, whereas patients with scores above 20 had a 50% mortality.⁶⁷ An online tool has been developed to determine the postoperative mortality following surgical procedures based on MELD score <<http://www.mayoclinic.org/meld/mayomodel9.html>>.

Once the underlying severity of liver disease has been established, the decision to operate and the timing of the operation depend on a number of factors, including the following:

1. Acuity of the problem (i.e., ruptured umbilical hernia versus asymptomatic hernia)
2. Options for nonoperative management (i.e., percutaneous cholecystostomy)
3. Availability of liver transplantation in case of hepatic decompensation
4. Likelihood of transplantation (i.e., defer repair of umbilical hernia if the MELD score is high)
5. Ability to use TIPS placement to manage ascites and portal hypertension⁶⁸
6. Ability to transfer the patient to the care of a transplant surgeon
7. Availability of consulting services (i.e., hepatology, radiology, anesthesia)
8. Ability to optimize the patient's medical status prior to operation
9. Skill and experience of the team to perform a specific intervention

If the decision is made to proceed with the operation, several general principles may aid in achieving a good outcome. Patients with advanced cirrhosis typically exhibit whole-body sodium overload despite serum hyponatremia. Administration of excessive sodium in the form of 0.9% normal saline will exacerbate formation of ascites, thus worsening volume overload and edema formation, putting stress on surgical incisions, and potentially compromising respiratory function. Minimization of sodium administration through the use of 5% dextrose in water solutions and albumin and judicious use of loop diuretics and aldosterone antagonists will aid in controlling ascites. Preservation of adequate intravascular volume and renal perfusion will help avoid precipitating pre-renal azotemia or hepatorenal syndrome.

Patients with cirrhosis and ESLD often suffer protein-calorie malnutrition and may have specific vitamin and micronutrient deficiencies.⁶⁹ Early enteral nutrition should be considered in all cirrhotic patients undergoing general surgical procedures. In patients with compensated cirrhosis, feeding goals should be 25 to 35 kcal/kg/day of nonprotein calories and 1 to 1.2 g/kg/day of protein; decreased amounts of protein are provided to patients with encephalopathy.⁶⁹ Use of branched-chain amino acid supplementation in patients with cirrhosis has variably affected outcome, but studies suggest an improvement in encephalopathy as well as mortality and quality of life.^{70,71} Preoperative use of immune-

enhancing diets containing components such as arginine, omega-3 fatty acids, and nucleotides has been shown to improve recovery after transplantation and decrease infectious complications.⁷² Use of such formulas may be beneficial in cirrhotic patients undergoing general surgical procedures. As patients with cirrhosis are often deficient in vitamins A and D and zinc, supplementation of these compounds should also be considered in the perioperative period. Finally, administration of vitamin K may aid in reversal of hemostatic deficiencies in those patients suspected of having poor preoperative nutrition, cholestasis, or infection. Use of parenteral nutrition should be avoided if possible given the risk of worsening liver function by promoting cholestasis.

Use of peritoneal drains after intra-abdominal procedures in patients with cirrhosis is controversial. Some surgeons advocate their short-term use in patients with tense ascites who have undergone surgery to provide a controlled means of draining ascites. This practice may allow peritonealization and initial sealing of surgical wounds, thus avoiding incisional ascites leaks, which can lead to postoperative bacterial peritonitis, wound dehiscence, or hernia formation. The presence of such drains, however, provides an entry site for bacteria, which may lead to peritonitis. Additionally, as the presence of drains will allow a low-pressure egress of ascites fluid, patients may lose a substantial amount of volume and protein if drain output is not carefully monitored and replaced. Postoperative ascites can often be managed with careful fluid and sodium balance, use of diuretic agents, and intermittent paracentesis in the case of tense ascites that is not controlled by medical therapy. TIPS placement may also be considered in carefully selected patients. Some authors advocate use of temporary PD catheters to allow at-home controlled drainage of ascites; however, because of concerns over infection and volume and protein loss, the use of this technique is not recommended.⁷³ A randomized, controlled trial of 104 patients with chronic liver disease who had elective hepatic resection showed that patients with drains had higher operative morbidity (mainly wound complications) and postoperative length of stay than the nondrained cohort.⁷⁴ In general, drains should not be left to manage ascites but may be considered for use in specific cases (i.e., concern for bile leakage after difficult cholecystectomy, after biliary reconstruction, or to drain an abscess cavity).

TIPS creation may be used in patients with intractable ascites or severe portal hypertension prior to elective surgery.⁶⁸ Contraindications to TIPS include encephalopathy, right-heart failure, and elevated bilirubin.

Abdominal Hernias

The incidence of symptomatic umbilical hernia is increased in patients with ESLD and ascites attributed to increased intra-abdominal pressure. The indications and timing of repair of umbilical hernias depend on whether the hernia presents as a surgical emergency and whether the patient is a candidate for liver transplantation. Hernias with thinned skin or eschars and ruptured or incarcerated umbilical hernias are repaired emergently. Repair of asymptomatic hernias in patients who are candidates for liver transplantation may be deferred until the time of transplantation. In patients who are not candidates for transplantation, multiple studies support elective repair of umbilical hernias.⁷⁵⁻⁷⁷ Failure of conservative management occurred in 77% of patients followed in one

series, resulting in hospital admission for incarceration, emergent repair in 46%, and death in 15% of patients.⁷⁵ Two other groups found that elective surgical morbidity in cirrhotic patients with umbilical hernia was the same as in noncirrhotic patients, whereas morbidity following emergent surgery was significantly increased.^{76,77} Based on the risks associated with observation of umbilical hernias in patients with cirrhosis and the increased risks of emergent surgery, elective repair in medically optimized patients appears to be the safest course.

In approaching umbilical herniorrhaphy in patients with cirrhosis, several technical points deserve consideration. If at all possible, maintenance of the integrity of the hernia sac should be attempted to decrease the risk of ascites leakage in the postoperative period. Small hernias may be closed without mesh, acknowledging that the risk of recurrence may be increased. Our preference is to close the subcutaneous tissues in multiple layers while the skin is closed using a running, locking nylon suture. We place a layer of skin adhesive (Dermabond or Indermil) over the suture line to provide another layer of protection from leakage. Sutures are removed 3 to 4 weeks postoperatively. Postoperative ascites is controlled as outlined above.

The management of inguinal hernias in patients with cirrhosis is not significantly different from that in noncirrhotic patients. One series reported the results of 13 inguinal or femoral hernia repairs in 11 patients.⁷⁸ There were no major complications and four minor complications, including two wound complications, and one case each of prerenal azotemia and encephalopathy.⁷⁸ Another group reported significant improvement in quality of life after repair of inguinal hernias, with the greatest benefit seen in patients with Child's class C cirrhosis and/or refractory ascites.⁷⁹ Despite these good results, any operation performed on patients with advanced liver disease carries increased risk of ascites leakage, bleeding, or decompensation.

Cholelithiasis

Multiple series have reported good outcomes with laparoscopic cholecystectomy for symptomatic cholelithiasis in patients with Child's class A and B cirrhosis.^{80–84} As seen in patients without cirrhosis, laparoscopic cholecystectomy results in less morbidity, shorter operative time, and reduced hospital length of stay when compared with open cholecystectomy.^{80–83} Series that included patients with Child's class C cirrhosis reported much higher morbidity and mortality with deaths as a result of liver failure and sepsis after laparoscopic cholecystectomy.⁸⁴ Even in open series, mortality for patients with Child's class C cirrhosis approached 25%.⁸⁵ Operative intervention appears reasonable for Child's class A and B patients, whereas those with Child's class C cirrhosis should be managed nonoperatively if possible (see below).

Intra- and postoperative hemorrhage or decompensation of previously stable liver disease are two major risks of laparoscopic cholecystectomy in patients with cirrhosis. In addition to careful surgical technique, several specific points deserve consideration in making the procedure safer. First, many patients with cirrhosis and portal hypertension have a recanalized umbilical vein. Therefore, initial periumbilical port placement should be done using an open technique to avoid lacerating this vein. Bleeding from the gallbladder fossa is a

common problem that can be managed with the laparoscopic argon beam coagulator. In cases where it is difficult to remove the back wall of the gallbladder from the gallbladder fossa, a patch of the back wall may be left attached and cauterized. Communication with anesthesia staff before and during the case will ensure appropriate fluid management and avoidance of hypotension, which may lead to renal or hepatic failure in the postoperative period.

For patients with more advanced liver disease (Child's class C or MELD score greater than 15 to 20), all efforts should be focused on avoiding operative intervention. Maximal medical management with bowel rest, intravenous fluids, and antibiotics may allow resolution of acute cholecystitis. In cases with persistent symptoms despite intensive management, placement of a transhepatic percutaneous cholecystostomy tube may be considered and has been used with some success.⁸⁶ The risks of this approach include hemorrhage from the liver during tube placement, ascites leakage around tube skin exit sites, and spread of infection into ascites. An alternative approach using ERCP-placed stents draining from the gallbladder into the duodenum has also been described.⁸⁷ In one series, 57% of patients had Child's class C cirrhosis and diagnoses of recurrent biliary colic, acute calculous and acalculous cholecystitis, and gallstone pancreatitis.⁸⁷ All patients were successfully treated with stents without major complications.⁸⁷

Disorders of the Intestine

Patients with cirrhosis may present with conditions requiring either emergent or elective surgery, including appendicitis, cancer, diverticulitis, and ischemic colitis. In the setting of imminent transplantation, indications for elective intervention may be deferred until after the transplantation has occurred. If the patient is not a candidate for transplantation or the indication requires urgent or emergent surgery, optimization of the patient and careful technique and perioperative management are the only options. A large series of patients with cirrhosis undergoing elective and emergent colorectal procedures demonstrated a high level of morbidity (77%) and mortality (26%).⁸⁸ Risk factors for poor outcome included Child's class B or C or preoperative presence of ascites, whereas a preoperative finding of peritonitis, occurrence of postoperative complications or infections, and the need for total colectomy all predicted mortality.⁸⁸ Appendicitis may occur in patients with cirrhosis. A comparison of open versus laparoscopic appendectomy in patients with cirrhosis demonstrated decreased pain, length of stay, wound infection, and bleeding complications in the laparoscopic group without a difference in overall hospital cost.⁸⁹

Patients with concomitant PSC and ulcerative colitis present a special dilemma to treating surgeons. Assessment of the relative degree of disease in each organ aids in determination of the order of colectomy and liver transplantation, if indicated. Either extreme of the spectrum presents a relatively straightforward course: acute, toxic megacolon unresponsive to medical management in the setting of mild liver disease necessitates urgent colectomy, whereas mild dysplasia in the setting of advanced cirrhosis warrants liver transplantation followed by colectomy. Use of a living donor for liver transplantation could also be considered in this setting. Successful combined liver

transplantation and total abdominal colectomy followed by delayed ileal pouch-anal anastomosis (IPAA) has also been reported.⁹⁰ Laparoscopic proctocolectomy with IPAA in patients with mild liver disease from PSC has been shown to be feasible, with decreased hospital stay and no difference in complications when compared to the open procedure.⁹¹ Numerous reports support an increased incidence of colorectal cancer in patients who have undergone liver transplantation for PSC.^{90,92} Vigilant colonoscopic surveillance of immunosuppressed patients following liver transplantation is required.

General Surgery in Transplant Recipients

Following transplantation of an abdominal organ, surgical intervention on that organ should typically be performed by the original transplant team or another transplant team with extensive knowledge of the details of the operation. An understanding of both standard transplant vascular and enteric reconstructions as well as common variants (i.e., infrarenal aortic conduits for reconstruction of the hepatic artery) is required to avoid injury. If patient transfer is not possible, consultation with the transplant center is advised.

Abdominal operation is common following transplantation. A large center reported that 24% of liver transplant patients had another surgical procedure in the 10 years following transplantation.⁹³ Of patients who underwent elective procedures, the rate of complications and length of stay were not increased; however, following emergent procedures, this population experienced increased morbidity.⁹³ Common general surgery diagnoses are somewhat less common following transplantation. A review of over 8,000 patients following liver, heart, kidney, and pancreas transplantation revealed an appendicitis rate of 0.2%.⁹⁴ A review of over 4,000 liver transplant patients demonstrated small bowel obstruction in 48 patients (1.2%).⁹⁵ Etiologies included adhesions, internal hernias, volvulus, abdominal wall her-

nias, and neoplastic causes.⁹⁵ Internal hernias were most commonly related to residual mesenteric defects following construction of Roux-en-Y hepaticojejunostomy, whereas hernias around nonanatomic vascular reconstructions have also been reported.^{95,96} Long-term follow-up of 2,091 kidney transplant recipients revealed 12 patients with peritonitis from acute colonic complications, including diverticulitis, bowel ischemia, and perforation.⁹⁷ All surviving patients required operative intervention, most commonly as emergent laparotomy, although one patient died of diffuse colonic ischemia prior to exploration.⁹⁷ Aggressive medical management and early operative intervention are suggested when faced with transplant patients with peritonitis.

In general, immunosuppression is often decreased during episodes of significant infection or sepsis by either stopping agents or decreasing goal therapeutic levels. Perioperative management of steroids deserves special consideration. A series of kidney transplant recipients underwent operative procedures without stress-dose steroids with no evidence of adrenocortical insufficiency.⁹⁸ A review of renal transplant recipients who had lymphocele surgery similarly demonstrated no signs of adrenal insufficiency.⁹⁹ Wound complications and lymphocele recurrence were similar in both groups, whereas hyperglycemia was more common in the group that received stress-dose steroids.⁹⁹ In the absence of clinical signs of adrenocortical insufficiency, increased steroid dosing is not recommended in the perioperative period.

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Figures 2, 3, and 4 Christine Kenney

3 CLINICAL TRIAL DESIGN AND STATISTICS

Julie Ann Sosa, MA, MD, FACS

Definition and Overview of Study Design

A clinical trial is a planned experiment designed to prospectively measure the efficacy or effectiveness of an intervention by comparing outcomes in a group of subjects treated with the test intervention with those observed in a comparable group of subjects receiving another intervention.¹ The best clinical trials are randomized and double-blinded, but it is sometimes impractical or unethical to conduct them in clinical medicine and surgery. Conventional outcomes traditionally have been clinical end points; with the rise of new technologies, however, they are increasingly being supplemented and/or replaced by surrogate end points, such as serum biomarkers.²

Subjects can be animals or humans, but the focus of this chapter is on patients in actual practice as opposed to an ideal setting; therefore, effectiveness, rather than efficacy, is the appropriate metric. Because patients are involved, safety considerations and ethical principles must be incorporated into all phases of clinical trial design, conduct, data analysis, and presentation. Investigators cannot dictate what participants do during trial; they can strongly encourage compliance with protocol. Imperfect compliance must be anticipated, and accommodation must be made. As a result, clinical trials require investigators to assume significant responsibility and often consume significant human and financial resources.³

Three important principles separate clinical trials from other study designs and potentially afford them superiority of data quality and robustness of findings. First, all participants in a clinical trial must be followed forward in time from a well-defined starting point or baseline; this separates clinical trials from case-control studies, which can be retrospective. Second, interventions must be applied in a standard fashion across groups. They can be preventive, diagnostic, or therapeutic and can include drugs, devices, or procedures. By definition, clinical trials are experimental and not observational. Finally, a clinical trial must include a control group against which the intervention group is compared. A novel intervention can be compared with a current standard intervention or to no intervention at all (placebo).⁴ Participants in both groups can be on additional therapies and regimens other than those under study, but cases and controls should be as comparable as possible to facilitate teasing out the independent effect on outcomes of the intervention under study.⁵

History of Clinical Trials

The history of clinical trials has been best described by Bull and Lilienfeld.^{6,7} The fundamental underpinnings are ancient;

in the first Book of Daniel (verses 12 to 15), a planned experiment with a baseline assessment and follow-up is described:

Prove thy servants, I beseech thee, 10 days; and let them give us pulse to eat, and water to drink. Then let our countenances be looked upon before thee, and the countenance of the children, that eat of the portion of the King's meat: and as thou seest, deal with thy servants. So he consented to them in this matter, and proved them 10 days. And at the end of 10 days their countenances appeared fairer and fatter in flesh than all the children which did eat the portion of the King's meat.⁸

The first clinical trial with a concurrently treated control group involved 12 scurvy patients and was done in 1746 by Lind while at sea on board the *Salisbury*. Six dietary regimens were employed, and those seamen who received a daily ration of oranges and lemons fared best. In spite of the compelling trial results, the high cost of fresh fruit inhibited adoption of lemon juice for prevention of scurvy by the British Navy until 1795.⁹

Amberson introduced the concepts of randomization and blinding for treatment assignment in a clinical trial by using a coin flip to determine whether two comparable groups of patients with pulmonary tuberculosis received sanocrysin or distilled water in 1931; only the ward nurse and two of the investigators were aware of the treatments administered.¹⁰

The Nuremberg Code for Human Experimentation was issued in 1946 to address ethical issues surrounding the protection of human subjects. The first multicenter trials involved treatment of pulmonary tuberculosis with streptomycin and were published in the United Kingdom in 1948 and the United States in 1952. The Veterans Administration, together with the US Armed Services, continued multicenter trials for tuberculosis over the next two decades. The US poliomyelitis vaccine trials involved tens of thousands of volunteers and represented a significant increase in clinical trial scale. Creation of the National Cancer Institute in 1937 designated the start of federally sponsored medical research in the United States, which ultimately was recognized as the National Institutes of Health (NIH) in 1981.

A major stimulus for clinical trials in the United States arose from the Kefauver-Harris amendments of 1962 to the US Food, Drug and Cosmetic Act; they set forth legal requirements for "adequate and well-controlled investigations" that have to be satisfied before a drug can be approved by the Food and Drug Administration (FDA). In 1966, the US Public Health Service regulations leading to creation of Institutional Review Boards for research involving humans were published. In 1976, the Medical Device Amendments extended some of the testing requirements established for

drugs to medical devices as well. In the 1980s, Chalmers and colleagues led a movement to eliminate potential bias when physicians are permitted access to study data during the course of a clinical trial by separating patient care from treatment evaluation functions.¹¹

Clinical Trial Phases

Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from the legal requirement. An Investigational New Drug (IND) application is the means through which the sponsor technically obtains the FDA exemption. There are three IND types: (1) an investigator IND is submitted by a physician who both initiates and conducts an investigation and under whose immediate direction the investigational drug is administered; (2) an emergency use IND allows the FDA to authorize use of an experimental drug in an emergency situation; and (3) a treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or life-threatening conditions while the final clinical work is conducted and the FDA review takes place. INDs can be in commercial or research categories. Applications must contain information about animal pharmacology and toxicology studies, manufacturing information, and clinical protocols and investigator information [see Other Resources, below, for an Internet primer].

There are three phases of clinical trials. Phase I trials technically do not meet the criteria used to define a clinical trial. Nevertheless, they are necessary for showing that a novel intervention with promising preclinical data from in vitro and animal studies can be tolerated from a safety perspective in a small number of human patients. Typically, subjects already have tried and failed to improve on existing therapies and are willing to accept greater risk with potentially little or no benefit. The design is simple: a very small number of patients are exposed to escalating dosages of a novel drug to identify the maximally tolerated dosage (MTD) whereby intolerable side effects or precalculated pharmacokinetic safety levels are reached. There are also more sophisticated designs, whereby a sampling scheme using a step-up or step-down approach is employed, and a statistical model permits estimation of the MTD with a standard error of the mean.

Phase II trials are performed on larger groups of patients after the initial safety of a study drug has been confirmed. They are designed to continue to assess drug safety and dosing requirements but also to measure how well the drug works. When the development process of a new drug fails, it usually occurs during phase II.

The “classic” clinical trials are phase III studies, or randomized, controlled, multicenter trials on large patient populations that are aimed at being the definitive assessment of how effective a drug or other intervention is compared with the current gold standard treatment or even placebo if there is no standard of care. Because of their size and long duration, phase III trials are the most expensive and difficult trials to design and run. They can continue while appropriate regulatory agencies such as the FDA and/or the European

Medicines Agency (EMA) review the regulatory submission that combines animal and human study results, manufacturing procedures, formulation details, and shelf life.

Phase IV trials are known as postmarketing surveillance trials and represent safety surveillance and technical support for drugs after they receive permission from appropriate regulatory agencies to be sold. There is no control group in a phase IV trial. Rofecoxib (Vioxx) was removed from the market when harmful effects were identified in phase IV.¹²

Despite the fact that the FDA has quickened its review and approval of new medicines, clinical development is taking longer because of the complex nature of the diseases for which the new therapeutics are being created. The average time for the FDA to approve new drugs declined to 1.1 years in the 2005 to 2007 period, but the longer average clinical phase time means that the combined clinical and approval time is approximately 8 years.

Ethical Issues

Three general ethical principles guide clinical research. *Respect for persons* requires investigators to treat subjects as autonomous individuals, and they must obtain their informed consent to participate in the research project prior to any preparatory screening or intervention. The principle of *beneficence* requires investigators to design protocols that will provide valid and generalizable knowledge and ensure that the benefits of the research are proportionate to the risks assumed by the subjects. Finally, *justice* requires that the benefits and burdens of research are distributed fairly. In particular, disadvantaged, vulnerable, and minority groups (including racial and ethnic minorities, children, immigrants, disabled, and high medical need patients) should not be asked to bear a disproportionate share of risk in a trial.

Adherence to the principles of Good Clinical Practices (GCPs), including adequate human subject protection, is universally recognized as a critical requirement to the conduct of clinical trials involving human subjects.¹³ The Department of Health and Human Services has guidelines for human research. Risks to subjects must be minimized and proportionate to the anticipated benefits and knowledge. Data must be monitored to ensure the safety of subjects, and selection of subjects must be equitable. If subjects are vulnerable, additional safeguards should be included; for example, investigators must obtain both the permission of parents and the assent of the child when conducting research involving children. Institutional Review Board approval is required prior to screening and enrolling subjects.

Informed consent is required prior to screening patients for enrolment, and written consent forms are generally required. Informed consent must address the nature of the research project, including the purposes of the research, and the names and affiliations of the investigators. The procedures of the study must be described, along with how they differ from conventional care. Alternative procedures or treatments that may be available outside the study also should be discussed. Concepts of blinding and randomization should be explained in a simple, transparent fashion in simple language that is understandable.¹⁴

The potential risks and benefits of the study should be described, including their probability and magnitude. These

include medical, psychological, social, and economic ramifications. Assurances that participation in the study is voluntary should be provided because subjects must be able to withdraw from a trial at any time. Withdrawal cannot result in any penalty or loss of benefits. Protection of patient confidentiality and privacy must be guaranteed. Finally, investigators should offer to answer questions and provide further information if requested by potential subjects.

Randomized, blinded, clinical trials and placebo-controlled trials have unique ethical concerns. Reasonable people, and even experts, can disagree over the judgment regarding whether the null hypothesis can be rejected on the basis of previous evidence, which is the ethical basis for randomization. In addition, clinicians who believe that evidence already exists supporting use of one treatment alternative over another cannot justify enrolling patients if that treatment is available outside the trial. Analysis of preliminary data and interim analyses are essential for determining whether a trial should be stopped early, but such repeated analyses can undermine the power or validity of the study. In some situations, withholding active treatment from the control group can lead to serious complications, although this possibility is usually balanced by the possible hazards of active treatment. Also, blinding can cause problems in clinical management; for example, if a patient requires emergency surgery, the trial protocol must include a plan that permits unblinding in a rapid fashion, around the clock.

Investigators must realize that the different roles they play may create conflicts of interest. The Statement of Investigator Form FDA 1572 is a formalized agreement signed by the investigator to provide certain information to the sponsor and ensure that he or she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic. An investigator who is also the personal physician for a study subject must appreciate that what is best for the patient's medical care may be in conflict with what is best for the clinical trial. Other problems can arise when the investigator has a financial interest in the therapy or procedure being studied; such interests always must be revealed in the consent and at the time of trial data presentation.¹⁵ Just the appearance of a conflict of interest can undermine research acceptance.

Implementing the Study

FORMULATING THE PROTOCOL FROM THE STUDY QUESTION

Clinical trials are ideally suited for trials of therapy for subjects with known diseases; this is what Alvin Feinstein called "remedial trials."¹⁶ Clinical trials are less well suited to studies of preventive measures because the outcome could be lengthy, and it might be impossible to keep subjects from being exposed to treatments that could impact the measured outcomes. They are also generally poorly suited for multiple therapeutic modalities, because too many subjects are needed to evaluate all of the treatment combinations, and for treatments with only rare outcomes or outcomes that are very far out in the future. As a result, clinical trials rarely produce good information about the adverse effects of therapies. Clinical trials should not be used to study therapies that may

be changed during the course of the study, such that the results of the study are obsolete prior to study completion. Finally, clinical trials are resource intensive, and, generally, their cost is not justified by the study of small changes in a therapeutic plan that will have a relatively small impact on clinical practice.

Defining the eligible population and selecting subjects from it before experimental or control status is assigned are essential.¹⁷ Development of the treatment protocol is predicated on asking a clinical relevant question; it must be easily replicable, capable of being "blinded," and resistant to drift or change during the course of the study. A major problem in many drug trials, for example, is that the dose of the drug must be adjusted to optimal serum levels or to obtain a visible clinical response, so a plan must be devised to allow for manipulation of the drug dose without giving away the fact that the patient is receiving the active agent or the placebo or alternative drug.

Selection of the alternative treatment(s) must be done with care, especially if it is a placebo. A crossover design is one in which subjects are exposed sequentially to both active treatment and a control or placebo intervention. This design is appealing in that subjects can serve as their own controls and might be more willing to enroll in a placebo-controlled study because they might be allowed to cross over to active treatment if they are initially assigned to the placebo and their condition progresses. Crossover studies have the potential to require smaller sample sizes than conventional parallel clinical trials, but not all interventions can be tested in this manner.

The two common plans for the design of clinical trials are either fixed- or variable-duration follow-up. In a fixed-duration follow-up trial, each patient is followed for the same prescribed period of time, regardless of when that patient entered the study. Fixed-duration trials are often employed to assess short-term objectives. Long-term studies employ variable follow-up duration, where patients are followed until a common closing date, regardless of when they were randomized. Regardless, the duration of follow-up should be based on the period of time needed to assess the trial's objectives and the frequency of follow-up visits on conventional clinical practice for the treatment and condition under study.¹⁸

Randomization is the best approach in the design of a clinical trial. It increases the likelihood that different treatment groups will be comparable in terms of variables that are recognized and measurable, as well as variables that are not affecting but still might affect outcomes. The randomization process can be modified in several ways. Blocked randomization ensures that the number of subjects is equally distributed among the study groups at periodic intervals during the process of randomization. Stratified blocked randomization ensures that an important baseline prognostic variable (associated with the outcome) is more evenly distributed between groups than chance alone would dictate; in so doing, it increases the power of a study by reducing variation in outcome that comes from chance. Finally, adaptive randomization uses a "biased coin" to alter the probability of assigning each subject to balance the distribution of baseline prognostic variables between study groups. Special analytical techniques other than the *t*-test and chi-square analysis should

be used for testing statistical significance with stratified block and adaptive randomization.

INCLUSION AND EXCLUSION CRITERIA

Specific clinical and demographic characteristics of the target population should be established and should be well suited to the research question. Inclusion criteria define the main characteristics of the target and accessible study populations. Exclusion criteria indicate subsets of individuals who meet the eligibility criteria but are likely to interfere with the quality of the data or interpretation of the findings. Exclusion criteria can improve the feasibility of the study at the cost of generalizability, so they should be used sparingly.¹⁹ Some exclusions are established by ethical considerations or by a patient's unwillingness to participate. Accessible populations can be clinic based or population based. Clinic-based samples are inexpensive and easy to recruit, but selection factors that determine who comes to the hospital or clinic may have an important and unwanted effect. Population-based samples are useful for guiding public health and clinical practice in the whole community, but this is more difficult to do and is much more expensive, particularly for relatively uncommon diseases.

PRETESTING AND QUALITY CONTROL

Pilot or feasibility studies should be conducted to pretest study methods as a study protocol should not be changed once the study has begun. These studies are useful for guiding decisions about how to design recruitment and measurement approaches. For example, pilot studies can provide estimates of the number of subjects who are likely to be available and willing to enroll and also can test the efficiency of different recruitment approaches. Finally, they can provide useful information about the age, gender, and demographic profile of the sample population.

MISSING DATA

Patients may agree to be randomized, but following randomization, they may not comply with the assigned treatment. Noncompliance may be overt or covert. When a subject overtly refuses to comply or outright stops participating in the study, the subject is called a dropout. However, a subject may just stop taking the agent under investigation without admitting this to the research team; this problem is more difficult to identify. Whenever possible, checks on potential noncompliance should be built into the study and could include regular pill counts for drug studies or urine tests for the agent under investigation or for one of its metabolites. Dropins are a more uncommon problem; they represent subjects who inadvertently take the agent assigned to the other group. This can occur when control patients take over-the-counter preparations of drugs under study without knowing it. It is important to anticipate noncompliance and dropouts or dropins in the study design as this will reduce any observed differences in the final analysis because the treatment group will include some subjects who did not receive the therapy. The size of the enrolled sample should be increased prior to the start of the clinical trial if noncompliance is an anticipated problem.

In the end, noncompliance and dropouts result in missing data, which should be anticipated prior to embarking on the

clinical trial to try to minimize the problem ($< 5\%$ of observations as a target), and an analytical method of dealing with the missing data should be anticipated. Options include (1) discarding data from all patients who did not complete the trial; (2) analyzing only the observed data; (3) using a single or multiple imputation to replace the missing observations with plausible values and then analyzing the "completed" data set; or (4) building a longitudinal model for the data, which includes a model for the dropout process. The technique "last observation carried forward" is a method whereby missing values are replaced by the last observed value of that variable; in so doing, it ignores trends in data and reduces variability in a somewhat arbitrary fashion. "Propensity scores" are classes of similar patients that represent more sophisticated imputation models; missing values are filled in by selecting randomly from observations in the same class of patients.²⁰

The fundamental efficacy data set includes all patients as randomized, regardless of protocol violations, withdrawals, and dropouts; this is called intent-to-treat (ITT). Modified ITT relaxes this to patients who have had at least one treatment.²¹ An alternative is the per-protocol data set, which includes only those subjects who had no protocol violations. In the end, it is important to examine the comparability of groups and outcomes and to provide various analysis data sets, especially given that the FDA and other regulatory agencies will expect to have access to all data and may audit a portion of it.

STANDARDIZATION, BLINDING, AND RANDOMIZATION

All clinical trials should employ a standard system of outcome evaluations in all patients randomized, such that judgments are unbiased and precise. To the extent possible, all trials should be double-blinded, meaning that neither the subject nor the investigator is aware of the treatment randomly assigned to the patient.²² Under no circumstances should the masking be violated, unless there is a serious adverse event. Complete double-blinding is impossible in some clinical trials, especially those in which a surgeon must know which procedure to perform. In this case, it is essential that outcome evaluations be masked at least to the evaluator. This is one reason that many trials employ a central laboratory or reading center for imaging studies (e.g., using Response Evaluation Criteria in Solid Tumors [RECIST]).²³ As much as possible, standardization of evaluation using manuals and definitions of normal versus abnormal or stabilization versus progression or partial response of disease to treatment should be ensured.

PLANNING FOR DATA MANAGEMENT, MONITORING, AND AUDITS

Prior to embarking on a clinical trial, data entry, editing ("cleaning"), and analysis should be anticipated. Planning for data management begins with developing rules for coding the variables for computer entry. The appropriate hardware and software programs should be selected and standardized across study sites. Software can include spreadsheet programs, database managers, and/or statistical or graphics programs. All data should be backed up, and storage should be secure and password protected, with access limited to recognized members of the investigational team.²⁴

To facilitate quality control of data management, prior to the start of the study, a decision should be made to be parsimonious with data collection. Forms for data collection should be precoded and self-explanatory. They should be coherent and clearly formatted, easy to read, pretested, and validated, and every page should be labeled with a date, name, and identification number for the protocol. In large studies, it is useful to have a quality control coordinator who is a member of the research team and/or an external monitor whose responsibility it is to check data entry against source documentation. For large collaborative trials, a governance system with a steering committee made up of the principal investigators with subcommittees should be formed, and a coordinating center with central review (i.e., for evaluation of radiologic studies) should be established to facilitate communication, data entry, and analysis.²⁵

INTERIM ANALYSES

Periodic tabulations and reports should be issued to ensure that missing, inaccurate, or imprecise measurement is not a significant problem. Experiments that administer drugs in a blinded fashion, in particular, require special attention to quality control. In addition, clinical trials that employ laboratory procedures require ongoing attention to labeling and blinding; in this setting, it can be useful to also use blinded duplicates or standard pools.²⁶ In drug trials, in particular, reports describing significant adverse events and unanticipated drug toxicities should be issued concurrent with their occurrence, such that if there is a need to modify the protocol or the informed consent based on a changing safety profile, it can be done in a timely fashion to maintain patient safety.

Interim analyses should be specified a priori in the protocol. They are essential for several reasons: (1) examining the safety of an intervention at an early time to ensure that subjects are not being harmed; (2) examining efficacy at an early time (i.e., the study should stop if the intervention is very good or very bad); and (3) reestimating sample size (if variability is too large or treatment effect is too small, sample size might need to be increased). However, care should be taken when performing interim analyses because they carry the risk of unblinding.

RESEARCH TEAM AND OTHER TRIAL PRAGMATICS

Members of the research team should be selected carefully. There should be a formal system for training staff who will carry out measurements of importance and for testing and certifying their competence to do so. Often there are basic competencies and certifications that are required by Institutional Review Boards, the NIH, sponsors, or other governing bodies, and these should be kept current and on file in a regulatory binder. Accountability is essential, and a system of supervision should be clearly outlined; this same system should be employed to provide performance review. From the earliest planning phase, the investigator should lead a series of regular meetings with all members of the research team.

Before embarking on a clinical trial, it is important to ensure that funding is adequate to support it to conclusion. Virtually all funding groups require a budget and justification as part of a research proposal if grant support is solicited. Administrative staff should be consulted to provide needed

information for calculating budget needs to ensure that the final product conforms to regulations and is also a realistic projection. Categories of expenses that should be considered include personnel, consultant costs, equipment, supplies, travel, patient care costs, alterations and renovations, consortium or contractual costs, and other expenses. These are all direct costs. Indirect costs are generally calculated as a percentage rate that is applied to the anticipated direct cost budget that will cover the departmental or organizational administration costs that each clinical trial program should bear.

For personnel, each staff member's name, position, function, hours/week, or percent effort with salary and fringe benefits should be described. Subcontracting can be a useful mechanism for minimizing the cost of research activities that require special skills that are not readily available from existing staff. Research costs for clinical trials also can be minimized by using existing data collected for other purposes and by incorporating research tasks in the ongoing responsibilities of existing staff. A contract should be negotiated with the assistance of legal counsel; no change in study objective, scope, or methods can be made prior to explicit funding agency approval.

Generally speaking, as few changes to the protocol as possible should be made after the clinical trial has begun as they will affect analysis and, ultimately, interpretation of study results.

Basic Biostatistics for Data Analysis

Biostatistics is a specialized field that is critically important to planning, conducting, and interpreting the results of a clinical trial.²⁷ A brief overview of broad principles and an introduction to the basic lexicon of fundamentals will be provided, but this is not a substitute to undergoing formal training in the discipline or to having a trained biostatistician serve as a member of the clinical trial research team.

HYPOTHESES AND UNDERLYING PRINCIPLES

A study should begin with a good hypothesis based on a good research question; the hypothesis can be simple or complex, but it should be specific and without ambiguity. It should be stated in writing at the outset of the study. Hypotheses are classified by the way they describe the anticipated difference between study groups. The null hypothesis states that there is no association between the predictor and outcome variables; it is the formal basis for testing statistical significance. The proposition that there is an association is called the alternative hypothesis; it cannot be tested directly and is accepted by exclusion.

A one-sided (or one-tailed) hypothesis specifies the direction of the association between the predictor and outcomes, whereas a two-sided (or two-tailed) hypothesis asserts only that an association exists and does not specify the direction. A one-sided hypothesis permits a smaller sample size than a two-sided hypothesis but is sometimes inappropriate for application.

TYPE I AND II ERROR

A type I error (false positive) occurs if an investigator rejects a null hypothesis that is actually true in the population. A type II error (false negative) occurs if the investigator

fails to reject a null hypothesis that is false in the population. Neither of these errors can be avoided entirely, but their likelihood can be reduced by increasing the sample size of the study population for the trial; that is, the larger the sample size, the less likely it is that it will differ significantly from the population.

The likelihood that a trial will detect an association between a predictor and an outcome depends, in part, on the actual magnitude of that association in the population. Unfortunately, the actual magnitude of the association is usually not known. Therefore, the investigator must choose the size of the association that he or she would like to be able to detect in the sample; this quantity is known as the effect size. Choosing an appropriate effect size is the most difficult aspect of sample size planning. Data can be used from the literature or from pilot studies when there are no data to support an estimate. Usually, it is wise to choose the smallest effect size that would be clinically meaningful.

The probability of committing a type I error is called α (alpha), or the level of statistical significance. The probability of making a type II error is called β (beta). The quantity $(1-\beta)$ is called power, or the probability of observing an effect in the sample if one of a specified effect size or greater exists in the population. Many studies set α at 0.05 and β at 0.20 (a power of 0.80). These are somewhat arbitrary values, and others are sometimes used: the conventional range for α is 0.01 to 0.10 and for β between 0.05 and 0.20. Sample size planning aims at choosing a sufficient number of subjects to keep α and β at an acceptably low level without making the study unnecessarily expensive or difficult to perform.

The p value is the probability of obtaining the study results by chance if the null hypothesis is true. The null hypothesis is rejected in favor of its alternative if the p value is less than α , or the predetermined level of statistical significance. Nonsignificant results (i.e., with p values greater than α) do not imply that there is no association in the population; rather, they mean that the association observed in the sample is small compared with what could have occurred by chance alone. Because an alternative hypothesis has two tails, either or both can be tested in the sample by using one- or two-tailed statistical tests, respectively. When a two-tailed statistical test is used, the p value includes the probabilities of committing a type I error in each of the tails, which is twice as great as the probability in either tail alone. Conversion from one- to two-tailed p values is easy; for example, a one-tailed p value of .05 is identical to a two-tailed p value of .10. Unnecessary use of two-tailed hypotheses increases the sample size needlessly, but some statisticians and journal editors insist on their use in all situations.

Variability of effect (in addition to size of effect) is an important statistical consideration. The greater the variability (or spread) in the outcome among clinical trial subjects, the more likely it is that the values in the groups will overlap, and the more difficult it will be to demonstrate a difference between them. When variables are dichotomous, variability is included in other parameters entered into the sample size formulation and does not need to be specified. When one of the variables is continuous, however, its variability needs to be estimated.

Variables that are not the subject of study in a trial can confound the apparent association between the predictor and

outcome under study. In general, analytical approaches that adjust for confounding variables will increase the required sample size. A rough approximation can be made by increasing the sample size by 10 to 20% for each major confounder.

Finally, in advance of a trial, it is important to establish as many hypotheses as make sense but to specify one as the primary hypothesis to provide a clear basis for the main sample size calculation. In addition, a single primary hypothesis can be tested statistically without argument about whether to adjust for multiple hypothesis testing. One controversial but stringent approach to multiple hypotheses testing (Bonferroni) is to divide the significance level (e.g., .05) by the number of hypotheses tested; this can substantially increase the anticipated sample size of the trial.²⁸

ESTIMATING SAMPLE SIZE AND POWER

A t -test is used to determine whether the mean value of a continuous outcome variable in one group differs significantly from that in another group. It assumes a normal (bell-shaped curve) distribution of the variable in the two groups. A z statistic can be used to compare the proportion of subjects in each of two groups in a clinical trial who are expected to have a dichotomous outcome. The z statistic resembles the chi-square test, except that it can be one- or two-tailed, whereas the chi-square test is always two-tailed.

To summarize, the steps in estimating sample size for a clinical trial are the following:

1. State the null hypothesis and a one- or two-tailed alternative hypothesis.
2. Select the appropriate statistical test based on the predictor and outcome variables employed in the hypotheses.
3. Choose a reasonable effect size and variability.
4. Set α and β .
5. Use a standardized table or calculator, some of which are available on the Internet or in biostatistics manuals, to estimate sample size.

Often there is insufficient information for estimating sample size; this is especially true when a clinical trial includes a study sample that has not previously been examined. In these situations, an extensive literature search from previous findings on the topic should be conducted.²⁹ Other investigators in the field should be contacted for their judgment regarding reasonable expectations, or a pilot study could be conducted. Dichotomization of a variable can be helpful. When all else fails, an educated guess can be made to yield a reasonable estimate.³⁰

STRATEGIES FOR MINIMIZING SAMPLE SIZE

When continuous variables are an option, they permit a smaller sample size than dichotomous variables. For example, measuring blood pressure in millimeters of mercury (mm Hg) (continuous) rather than as the presence or absence of hypertension (dichotomous) permits a smaller sample size for a given power. When the outcome is dichotomous, using a more frequent outcome is a good way to increase power because power depends more on the number of outcomes that occur than it does on the number of subjects in the study. The number of outcomes, in turn, can be increased by extending the follow-up period, liberalizing the definition of

what makes up an outcome, and enrolling subjects at higher risk for developing the outcome.

More precise variables permit a smaller sample size because they reduce variability. Techniques for increasing the precision of a variable, such as making measurements in duplicate, require that more resources be put into measurement and may require that resources be taken away from other aspects of the trial, such as recruitment. Generally speaking, fewer measurements on more subjects is a good rule for study planning. Use of paired measurements, with one at baseline and another at the end of the study, often permits a smaller sample size because it reduces variation of the outcome variable, which is the change between these two measurements. A *t*-test is used to compare the mean value of the change in the two groups. Finally, use of unequal group sizes in a clinical trial can be helpful for increasing power; in general, the gain in power when the size of one group is increased to twice the size of the other is considerable, whereas tripling or quadrupling one of the groups provides progressively smaller gains.

STATISTICAL TESTS OF SIGNIFICANCE

Descriptive statistics should be provided based on data gathered about the baseline demographic and clinical characteristics obtained for subjects in the study. The most basic analyses carried out are bivariate; these are tests of the relationship between an independent variable and a dependent variable, or outcome. Statistical tests in which normal distributions of data are assumed are parametric tests; if both independent and dependent variables are numerical, a Pearson *r* correlation coefficient can be reported, which is derived from the process of linear regression. It is an estimate of the relationship between the two variables. If the data are not normally distributed, they may need to be transformed or nonparametric tests (e.g., ranked correlation tests, such as Kendall or Spearman correlation) employed.

When the association between a numerical dependent variable and a categorical independent variable needs to be measured, a *t*-test can be performed. The *t*-test is also appropriate if the dependent variable is categorical and dichotomous and the independent variable is numerical. In some clinical trials, patients may serve as their own controls, in which case, a paired *t*-test is needed. When the independent or dependent variable is categorical but has more than two categories, an analysis of variance (ANOVA) is used.

When both the independent and dependent variables are categorical, a chi-square test is performed based on a two by two table. The chi-square test is very sensitive to sample size. For small samples where the expected value for any cell is less than 5, a Fisher exact test should be used instead of the chi-square.

After the investigator performs a series of bivariate analyses, it is often necessary to deal with potential confounding variables. This can be done either with stratification or multiple regression analyses. In stratification, the investigator tests for the association between independent and dependent variables in subsamples that have been stratified in terms of the potential confounding variable. Multiple regression tests for the association between two variables while simultaneously controlling for other variables; linear regression is used when the dependent variable is continuous; and

logistic regression is used when the dependent variable is categorical.

RELATIVE RISK

In medical research, relative risk (RR) has become one of the standard measures. It is expressed as the risk ratio in randomized, controlled trials and cohort studies, whereas odds ratios are favored for case-control studies and retrospective studies. RR, or risk ratio, is the risk of an event (or of developing a disease) relative to an exposure; it is a ratio of the probability of the event occurring in the exposed group versus the nonexposed group. It is amenable to logistic regression modeling, typically in a Poisson regression framework.³¹ A relative risk of 1 means that there is no difference in risk between the two groups, whereas an RR less than 1 means that the event is less likely to occur in the experimental group than in the control group, and an RR greater than 1 means that the outcome is more likely to occur in the experimental group than in the control group.

SUBGROUP ANALYSES

A subgroup analysis is sometimes undertaken to assess treatment effects for a specific patient characteristic; the assessment is often listed as a primary or secondary study objective. Alternatively, it is undertaken to investigate the consistency of the trial conclusions among different subpopulations defined by each of multiple baseline characteristics of patients. However, the reporting of subgroup analyses has been problematic and inconsistent. It should always be revealed whether the subgroup analyses were prespecified or were performed post hoc, and the potential effect on type I errors attributable to multiple subgroup analyses and how this effect was addressed in the data analysis should be described. When multiple subgroup analyses are performed, the probability of a false positive finding can be substantial.³²

Heterogeneity of treatment effects across the levels of the baseline variable refers to the circumstance in which the treatment effects vary across the levels of the baseline characteristic. The appropriate statistical method for assessing the heterogeneity of treatment effects among the levels of a baseline variable begins with a statistical test for interaction. Many trials lack the power to detect heterogeneity in treatment effect. Therefore, the inability to find significant interactions does not show that the treatment effect seen overall necessarily applies to all subjects. Common mistakes are to claim heterogeneity on the basis of separate tests of treatment effects within each of the levels of the baseline variable and to claim heterogeneity on the basis of the observed treatment effect sizes within each subgroup, ignoring the uncertainty of these estimates. When possible, analyses of the heterogeneity of treatment effects should be based on tests for interaction and should be presented along with effect estimates (including confidence intervals) within each level of each baseline covariate analyzed. A forest plot is an effective method for presenting this information. Overinterpretation of subgroup differences should be avoided as much as possible.

Other Resources

A useful resource for patients and for investigators is www.ClinicalTrials.gov, a Web-based registry of federally and

privately supported clinical trials conducted in the United States and around the world. The NIH-sponsored Web site gives information about each trial's purpose, who can participate, locations, and telephone numbers for more information. In addition, the FDA (www.fda.gov) includes the Center for Biologics Evaluation and Research (CBER), which is responsible for evaluation of biologics (i.e., cellular/gene therapy products, tissue/tissue products, allergenics, blood/blood products, and vaccines); the Center for Devices and Radiological Health (CDRH), which is responsible for evaluating surgical implants and prosthetics, personal protective equipment, LASIK and radiation-emitting products; and the

Center for Drug Evaluation and Research (CDER), which reviews the evaluation of new drugs prior to their going to market. The CDER offers a pre-IND application consultation program to foster early communication between sponsors and new drug review divisions to provide guidance on the data necessary to warrant IND submission. A useful resource on the Internet is <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/default.htm>.

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4 EVIDENCE-BASED MEDICINE

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Descriptions of “evidence-based” approaches to medical care are now ubiquitous in both the popular press and medical journals. The term *evidence-based medicine* (EBM) was first coined in 1992, and over the last two decades, the field has experienced rapid growth, and its principles now permeate both graduate medical education and clinical practice.¹ To be clear, the field has been in constant evolution since its introduction and continues to undergo refinements as its principles are tested and applied in a wide variety of clinical circumstances.

Brief History of Evidence-Based Medicine

Although the term *evidence-based medicine* is relatively new, the first recognized randomized controlled trial (RCT), which examined the treatment of pulmonary tuberculosis, was published in 1948. In addition, several other seminal documents paved the way for modern-day clinical trials: the publication of the Nuremberg Code in 1947 and the Declaration of Helsinki in 1964, which established ethical codes and principles of protection of human subjects in clinical research. The first well-known RCTs studying surgical interventions were published in 1964. One of these examined surgical treatments for duodenal ulcer, and the other examined the survival benefits of portocaval shunt surgery in cirrhotic patients.^{2,3}

One of the earliest and most important figures in the modern-day EBM movement was Archie Cochrane, who practiced in Wales and authored the influential book *Effectiveness and Efficiency: Random Reflections on Health Services* in 1972.⁴ He emphasized the importance of the RCT as a means to determine the most effective therapies so that health care resources could be more equitably distributed. In 1992, 4 years after his death, the opening of the first Cochrane Centre in Oxford, United Kingdom, marked his important contributions to the field. A second seminal figure in the field was Alvan Feinstein, who is now recognized as one of the founders of modern-day clinical epidemiology. As the founding director of the Robert Wood Johnson Foundation Clinical Scholars program at Yale University, he contributed importantly to the field of clinical research methods, coining the term “comorbidity” and describing the now well-known “Will Rogers phenomenon.”

Perhaps the most widely recognized name in the field of EBM is David Sackett, who established Canada’s first department of clinical epidemiology and biostatistics at McMaster University in Hamilton, Ontario. His many accomplishments include his important role in the education of clinicians in understanding modern-day clinical evidence and applying its principles to the care of patients, as best illustrated by the book *Evidence-Based Medicine: How to Practice and Teach*

EBM.⁵ Furthermore, he founded the University of Oxford’s Centre for Evidence-Based Medicine (CEBM) in 1994, the world’s first center for EBM.

Evidence-Based Medicine: Fundamental Tenets

DEFINITION

EBM has been commonly defined as the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.⁶ EBM also emphasizes the integration of the best available evidence with clinical expertise and patient preferences. Much emphasis has been placed on defining the best available sources of evidence, usually described in the form of evidence hierarchies. However, the founders of EBM specifically envisioned this evidence being integrated into the framework of clinical decision making.

CLINICAL DECISION MAKING

Clinical Expertise

The importance of clinical expertise cannot be overestimated because without this, the evidence, no matter how good its quality, cannot be properly applied. The skills of physical examination, development of a differential diagnosis, and evaluation of a symptom complex must be mastered before external evidence can be applied to an individual patient. Furthermore, comorbid conditions and other limitations that may affect the patient’s ability to undergo a particular therapy (e.g., financial constraints, difficulties with compliance, and geographic logistics) must be assessed before selecting the most appropriate therapy for an individual. Sackett and colleagues described the interdependence of clinical expertise and evidence well: “Good doctors use both individual clinical expertise and the best available clinical evidence, and neither alone is enough. Without clinical expertise, practice risks being tyrannized by evidence... Without current best evidence, practice risks becoming rapidly out of date.”⁶

Patient’s Values and Preferences

An evaluation of the patient’s values and preferences is the third and perhaps most essential component of EBM. This requires that the clinician understand and incorporate the value that an individual patient would place on a given outcome and on a given risk. The patient’s perspectives on the time required, cost incurred, and expected change in symptoms must be appreciated for a decision to be rendered. This is clearly the most difficult aspect of the practice of EBM, and no one method of assessing and integrating each patient’s values has been established.

EVIDENCE HIERARCHY

Examples of Evidence Hierarchies

To establish the relative strength of evidence for clinicians, hierarchies of clinical study designs have been formulated. These pyramidal structures have been popularized by many groups and have undergone evolution as EBM has matured. The hierarchies currently used most frequently include those from the Evidence-Based Medicine Working Group [see Table 1] and the CEBM [see Table 2 and Table 3]. The Evidence-Based Medicine Working Group revised its initial hierarchy and published the current version in 2000.⁷ The CEBM is currently seeking comment on its updated version. Importantly, these hierarchies have been simplified here to include only those levels of evidence specific for treatment trials. Studies looking at diagnostic accuracy, prognosis, harms, and screening require a separate analysis and are not discussed.

Rationale behind the Hierarchy

It is important to recognize that despite the widespread acceptance of this evidence hierarchy, the rationale behind the ordering of these systems has not been as clearly delineated. It is often assumed that because randomization controls for all confounding factors, it would eliminate bias attributable to confounders. Although randomization does

Table 1 Strength of Evidence for Treatment Decisions (Evidence-Based Medicine Working Group)⁷

1. *n*-of-1 randomized trial
2. Systematic reviews of randomized controlled trials
3. Single randomized controlled trial
4. Systematic review of observational studies with patient-centered outcomes
5. Single observational study with patient-centered outcome
6. Physiologic studies
7. Unsystematic clinical observations

Table 2 Oxford Centre for Evidence Based Medicine Levels of Evidence⁶¹

Level	Therapy/Prevention/Etiology/Harm
1a	Systematic review with homogeneity of randomized controlled trials
1b	Single randomized controlled trial with narrow confidence interval
1c	All or none studies
2a	Systematic review with homogeneity of cohort studies
2b	Individual cohort study and low-quality randomized controlled trials
2c	"Outcomes" research
3a	Systematic review with homogeneity of case-control studies
3b	Individual case-control studies
4	Case series (and poor quality cohort and case-control studies)
5	Expert opinion, physiology studies, bench research

Table 3 Oxford Centre for Evidence Based Medicine Revised Levels of Evidence⁶²

Level	Treatment Benefits
1	Systematic review of randomized trials or <i>n</i> -of-1 trials
2	Randomized trials or observational studies with dramatic effect
3	Nonrandomized controlled cohort/follow-up study
4	Systematic review of case-control studies, historically controlled studies
5	Opinion without critical appraisal, mechanistic studies

Caveat: The level may be graded down on the basis of study quality, imprecision, indirectness, inconsistency between studies, or small absolute effect size. The level may be graded up if the effect size is large.

eliminate statistical bias as it applies to the entire sample space, this requires a trial to be repeated indefinitely. With any particular allocation (i.e., one RCT within the entire sample space), the probability of any one confounder being unequally balanced between groups is high. Only in the very unpractical indefinite sequence of randomized trials will the effect of unbalanced confounders be negated, eliminating statistical bias.⁸

The most compelling argument to date is that the hierarchy is based instead on comparative internal validity: a measure of how likely the results of any given study are to be true for the subjects involved. One essential method of ensuring internal validity is to ensure that the control of the allocation of patients into treatment groups does not lie with the investigator. This is best accomplished by randomization but can also be achieved by other study designs that are prospective and experimental.⁸

It is important to emphasize that although internal validity is essential to properly interpret the results of a given clinical trial, it is not sufficient for the application of the trial's results to a variety of patient groups. This is the domain of external validity, which refers to how well the results can be applied to patients unlike those randomized in the study. In fact, those conditions that enhance internal validity usually serve to decrease external validity. The lack of generalizability is not addressed by the evidence hierarchy and remains a challenge for EBM.

Evolution of the Hierarchy

Although evidence hierarchies were an important tool in the field's development, they have now been largely supplanted by the use of systems to grade the strength of a body of evidence, which is discussed below. A further development along these lines is the addition of a new hierarchy that guides users with respect to most efficiently locating high-quality evidence, coined the "4S" approach⁹ [see Table 4]:

1. In this conception, the most efficient way to access evidence is from a well-designed system. These systems are not currently well developed but would ideally provide a concise summary of all the available high-quality evidence and apply it directly to a given clinical scenario. At present, these systems can offer much less, but there are nevertheless some options for an integrated approach, such as the *British Medical Journal's* Clinical Evidence system.

Table 4 “4S” Approach to Finding Resources for Evidence-Based Medicine⁹

Type of Resource (in descending order)	Example
1. Systems	Decision support tools in EMRs, <i>BMJ Clinical Evidence</i>
2. Synopses	<i>ACP Journal Club</i> , DARE
3. Syntheses	Cochrane Reviews, other systematic reviews
4. Studies	Medline Clinical Queries, Cochrane Central Register of Controlled Trials

EMR = Electronic Medical Record.

- When no system is well developed enough to provide adequate guidance, the reader is directed toward synopses. These take the form of structured abstracts summarizing high-quality evidence and providing further context and commentary that will help the reader understand the limitations of the data presented. The best known example of this at present is the *ACP Journal Club*.
- Syntheses represent a third level of access to evidence and are represented largely by systematic reviews that collate all available evidence on a given topic. The popular Cochrane reviews epitomize these syntheses, although multiple other groups have produced similar high-quality systematic reviews.
- Individual studies are the foundation of all the previously listed levels and by themselves can supply all the same information. However, this means of access to the medical literature is inefficient because the reader must not only be able to identify the relevant primary studies but must also be able to proficiently appraise them. Although it is important for each clinician to possess these skills, it is not always feasible in a limited amount of time to use primary studies as the first-line approach to the medical literature.

Critical Appraisal of a Single Study

At the core of the basic tenants of EBM is undoubtedly the ability to critically appraise a single study. The basic skills required for critical appraisal apply to all study types, but the specific considerations vary. Here we consider the central tenants of critical appraisal as they apply to the types of studies most commonly reviewed by surgeons: RCTs, observational studies, and systematic reviews of each [see Table 5 for a summary of the text below].

ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL

Although the principles behind the analysis of an RCT are not complicated, the literature surrounding the assessment of their quality certainly is. In 2002, the Agency for Healthcare Research and Quality (AHRQ) undertook an evaluation of all available systems that rated the quality of evidence.¹⁰ At that time, nearly 50 separate tools were available to evaluate RCTs. Because there is currently no universally accepted tool for analyzing the quality of a RCT, we provide a summary of the considerations that appear in most of the commonly employed systems.^{11–14}

Assessment of Internal Validity

The first priority in analyzing any RCT is to determine the degree to which the results of the study are accurate for the sample of patients included in the study. This is the most essential component of critical analysis. To ensure that the results are valid, the following components should be assessed.

Randomization and its concealment Concealed randomization ensures that the treating clinician’s subjective impression of the patient’s state of health and likelihood of benefiting from the experimental treatment do not influence the patient’s chance of receiving that therapy. Taking the allocation out of the hands of clinicians is essential to the avoidance of selection bias that can result in fundamentally different groups at baseline. Well-concealed and truly randomized designs serve to increase the likelihood that the treatment and control groups will be similar in terms of important prognostic factors at the trial’s outset.

Blinding and its effectiveness Three separate groups should be assessed for the adequacy of blinding: the subject, the clinician, and the outcome assessors. If the subject is aware of the treatment group, it is clear that this may influence both subjective and objective outcomes. The subjects in the treatment arm may benefit from the placebo effect if they are aware of their assignment, whereas those in the control group (ironically getting the placebo) will not. Furthermore, the treating clinician may alter the other treatments (called cointerventions) that a patient receives based on his or her assessment of the effectiveness of the intervention. This introduces a type of performance bias and may well affect the results of the trial. The assessors of the outcome of interest should also be blinded to the treatment group assignment to prevent the possibility that it will affect the more subjective outcome measures, so-called detection bias. This is perhaps both the easiest and the most important group to blind in an RCT.

Equivalence between treatment groups Although randomization is intended to minimize the differences between treatment groups in terms of baseline characteristics, this is not a guaranteed result, especially with smaller sample sizes. It is therefore essential to gauge the success of the randomization by comparing the groups at baseline with respect to known prognostic factors. Ensuring that the unknown prognostic factors are equally distributed is simply not possible and remains a source of concern, but the likelihood will increase with increasing sample size. It is also important to maintain equivalence between the treatment groups throughout the study period by treating them identically in all ways except for the treatment under study. This includes, among other things, additional visits to the clinic, diagnostic tests, or other therapeutic changes.

Completeness of follow-up Even if there is well-concealed randomization with effective blinding and equivalent treatment groups, incomplete follow-up can significantly jeopardize the validity of an otherwise well-conducted RCT. This is because there is generally not a random pattern to the occurrence of dropout, and it must be assumed that it could be related to the treatment itself, its side effects, or other

Table 5 Critical Appraisal of Individual Studies Examining Therapeutic Decisions

Type of Study	Important Aspects to Consider in Critical Analysis (see text for detailed explanation)	Examples of Representative Quality Assessment Tools
Randomized controlled trial	Randomization and its concealment Blinding and its effectiveness Equivalence of treatment groups Completeness of follow-up Accuracy of analysis Magnitude and precision of treatment effect Generalizability of findings	Oxford's CEBM critical appraisal sheet ¹¹ Cochrane handbook's tool for assessing bias ¹² Sackett and Guyatt's users' guide for articles about therapy ¹³
Systematic review of RCTs	Importance of question Appropriateness of search Explicitness of inclusion criteria Validity of included studies Homogeneity of included studies Reproducibility of results	Oxford's CEBM critical appraisal sheet ¹⁵ Sackett and Guyatt's users' guide for summarizing the evidence ¹⁶ BMJ's "How to read" a paper series ¹⁷
Observational study	Rational creation of treatment groups Baseline comparability between groups Reliability of data collection Adequacy of follow-up	MINORS assessment tool ¹⁸ University of Cambridge's quality domains ¹⁹ AHRQ's description ²⁰ NHS Health Technology Assessment's a priori criteria for quality ²¹
Systematic review of observational studies	Completeness of search Assessment of study quality Similarity of studies in combined analyses	

AHRQ = Agency for Healthcare Research and Quality; CEBM = University of Oxford's Centre for Evidence-Based Medicine; MINORS = Methodological Index for Non-randomized Studies; NHS = National Health Service; RCT = randomized controlled trial.

related variables. A systematic difference in withdrawals between groups is described as attrition bias and can significantly impact the trial's results. To determine the likelihood of a substantial change in outcome, the worst-case scenario with all subjects lost to follow-up having the undesired outcome should be computed.

Accuracy of analysis Provided that all the above features have been satisfied, the last step is to ensure that the results are properly analyzed. Perhaps the most essential component in this area is that the final analysis compares the originally randomized groups rather than the treatment groups that result during the conduct of the study. This is essential because the crossover from one group to another is usually reflective to some degree of the treatments being compared. This is especially true in surgical trials, where patients who are particularly ill and randomized to surgical arms may end up crossing over to the nonsurgical arm, likely enhancing the surgical group with respect to baseline prognosis. This is referred to as an analysis by intention-to-treat (ITT) and is essential to maintaining a lack of selection bias. Another important aspect of analyzing the trial's results is to ensure that outcomes have not been reported selectively. This can be done by looking at the primary and secondary aims specified in the clinical protocol, which is now readily available by requiring the registration of clinical trials prior to inception. In addition, the methods of analysis and planned subgroups can also be examined to ensure that there has not been significant reporting bias.

Assessment of External Validity

Because a study's results may be accurate for the patients enrolled, this in no way implies that a recommendation for a change in therapy should automatically result. Instead,

it must also be determined that the trial results are both important and generalizable.

Assessing the importance of results For the result of the trial to change practice, it must have an effect of sufficient magnitude. The measurement of a therapy's effect can be reported in many ways, but many EBM groups have advocated that the number needed to treat (NNT) be an important component. This allows the clinician to determine the significance of any given relative risk reduction by considering the number of patients who would need to be treated to prevent one bad outcome. This must necessarily be weighed against the adverse effects of the treatment. Further discussion assessing the magnitude and precision of treatment effects is beyond the scope of this chapter but can be found in many sources of EBM.¹⁴

Assessing the generalizability of results To determine if the trial results can be applied to a particular patient, the clinician must determine if the randomized patients are sufficiently similar in terms of disease severity, comorbid conditions, and willingness to comply with therapy. Furthermore, the treatment as administered in the trial must be feasible for both the patient and the health care system. Most importantly, the patient's values and preferences must be considered to determine if the benefits of the new therapy outweigh the inconvenience, cost, and perceived harms for each patient.

ANALYSIS OF A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS

Although the systematic review of RCTs is usually placed near the top of an evidence hierarchy, this does not imply that this methodology ensures high-quality evidence. In fact, because of the weight placed on this type on analysis, it is of

particular import that clinicians understand how to critically appraise their content. As with individual RCTs, there is no uniformly accepted quality assessment tool for assessment, but the following considerations are generally accepted in most evidence-based medicine schemas.^{15–17}

Quality of the Search Process

The most essential step in the production of a high-quality systematic review is the conduct of the literature search. To ensure that all eligible studies are available for analysis, this process must be thorough, careful, and unbiased.

Importance of the clinical question To have the systematic review be useful to clinicians, the precise clinical question to be answered during the process of the search must be clearly stated. This is often formulated in a prescribed way, often described by the acronym PICO (population, intervention, comparison, and outcome).¹⁵ It is important to explicitly define these variables to ensure that the search process includes all the relevant studies but does not include ones that will not address the specific clinical question being posed.

Appropriateness of search strategy Because the goal of a systematic review is to systematically include all the relevant primary data, the search strategy must be deliberately thorough and organized. It should be described explicitly enough that it could be reproduced. It is important that all available and relevant databases were used and that studies were not unnecessarily excluded as a result of narrowness of the search strategy. The citations of all identified studies should be systematically reviewed (ancestral searching). Furthermore, the inclusion or exclusion of “gray literature” should be described, as should the use of unpublished reports and registries.

Explicitness of criteria for study inclusion The criteria used to include or exclude a study from inclusion in the systematic review should be clearly defined, uniformly employed, and clinically reasonable. This will help decrease the possibility that the reviewer’s bias about the desired conclusion will affect the studies selected. These criteria should describe the specifics of the population to be studied, the intervention(s) that addresses the clinical question, the outcome measures of interest, and the range of acceptable study designs.

Quality of the Analytic Process

Once the comprehensive search has been completed and the relevant studies have been identified, the details of the analytic process will then determine the quality of the evidence that will be produced.

Validity of the included studies In addition to ensuring that the studies meet the criteria for inclusion, it is important for the internal validity of the individual RCTs to be separately assessed. It has been previously suggested that each trial be weighted according to quality, but because no validated method of accomplishing this has been produced, it has become preferred instead to provide an analysis of the quality of each study according to its ability to maintain internal validity.

Homogeneity of the included studies It is also important to have an assessment of the similarity of results between studies, a characteristic referred to as homogeneity. If there is significantly more heterogeneity than expected by chance, it is important to determine if methodological differences in the included studies that would account for the variability exist. However, if significant unexplained variability remains, the clinician should be skeptical about the appropriate application of the review’s conclusion.

Reproducibility of results Because there are many variables in the conduct of the search and the analysis that can significantly impact the review’s outcome, it is essential that the conclusion be reproducible. This is often addressed by having multiple reviewers involved in the systematic search and extraction of the data so that systematic bias is minimized. Furthermore, the concept of conducting a sensitivity analysis of the results has been proposed. This entails making minor systematic changes in the analysis of the data (such as exclusion of low-quality studies, inclusion of only the most recently published reports) to determine if the results of the analysis are robust enough to remain the same. If, instead, the analysis is sensitive to such minor variations, its results should be questioned and implemented only with caution.

ANALYSIS OF AN OBSERVATION STUDY

Although the critical assessment of RCTs follows fairly well-accepted principles, the analysis of the quality of an observational study is the subject of much debate. Some of the proponents of EBM have routinely discounted observational studies as being poor quality a priori given their non-randomized design. Although there is certainly some truth to that position, the fact remains that for the vast majority of clinical questions, the only evidence available comes from nonrandomized observational studies. This is particularly true for surgical disciplines. Therefore, it seems important that any reader of the medical literature be able to adequately assess the quality of observational studies. Some of the general principles discussed by multiple groups are described below.^{18–21}

Rational Creation of Treatment Groups

The central criticism of observational studies is that they are, by their very nature, biased in the assignment of patients to the treatments being compared. If the treating clinician willfully assigns some patients to one treatment and others to another, there is frequently a difference in demographic or prognostic variables between groups. It is therefore essential for the reader to clearly understand by what means the treatment groups were created. This includes a description of the larger group from which the subjects of the report were chosen and the specific factors related to the patient’s health status that led to the choice of the treatment selected. For example, it should be stated if the patients in the treatment group were selected by the acceptance of locally recognized inclusion criteria (i.e., practice patterns), by patient preference after being given multiple options, or by a wholesale change in practice with the introduction of a new therapy. A detailed description will help the reader assess if there was significant confounding by indication.²⁰ Similarly, defining how the comparison group was selected and if the groups were treated contemporaneously is also informative.

Baseline Comparability between Treatment Groups

As stated above, the comparison of nonrandomized groups should always be approached with caution. Whatever method has been used to select the treatment groups, it is important that the reader be able to objectively compare them with respect to essential baseline characteristics. The relevant prognostic features, demographic information, and diagnostic evaluation should be clearly compared. Factors that may not be well known to the reader but are clearly different between treatment groups should be explicitly considered by the authors. Examples of this type of consideration include a difference in geographic distribution (e.g., those living locally receive one treatment preferentially, whereas those who must travel usually receive another), choice of treating clinician (e.g., patients who see one clinician are offered one therapy as a default, whereas those seeing another clinician are routinely offered a different therapy), and economic considerations (e.g., patients with supplemental insurance received the more expensive therapy, whereas those with less economic assistance received the other alternative).

Reliability of Data Collection

Given that the groups being compared in observational studies may be different from one another, it is important to ensure that the data collection is as reliable and unbiased as possible. This includes explicitly stating the following:

- Were the data collected prospectively, retrospectively, or in a mixed fashion?
- Were the specific outcome measures explicitly defined and systematically collected and by whom?
- What sources of information were used to determine if the outcome occurred and to which was priority assigned if a discrepancy existed?
- Was the assessment of the outcome made with knowledge of the participant's treatment group?

Adequacy of Follow-up

As with RCTs, the length and completeness of follow-up are essential to assessing the quality of an observation study. It is important for the following to be detailed:

- The length of the follow-up period in each group and the distribution of the range of follow-up lengths
- The specific method by which the patient was followed: regular interval versus sporadic, telephone call versus clinic follow-up, symptomatic versus routine testing
- The number of patients in each group lost to follow-up, a description of their baseline characteristics, and an estimation of the likely reason for attrition

ANALYSIS OF A SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES

In general, the analysis of a systematic review is similar in nature, regardless of whether the included studies are RCTs, observational studies, or a combination of study types. However, those reviews that include observational studies encounter some unique challenges.²²

Completeness of Search

Because observational studies are not specifically catalogued by search engines, the details of the search strategy

must be explicit and must include significant redundancy. The criteria for study inclusion must be particularly complete and topic specific.

Assessment of Study Quality

Because of the difficulty in assessing the quality of an observational study in general, it is difficult to incorporate quality assessment into a systematic review. It is, however, essential that some description of each study's quality be given so that the reader can be assured that the level of evidence being used to compare treatment groups is roughly equivalent.

Similarity of Studies Combined in Analysis

Observational studies may have differences in design so profound that it is simply unreasonable from a clinical perspective to combine their results in any meaningful way. The reader of systematic reviews must therefore view some of these reviews as a descriptive and hypothesis-generating exercise. This is in contrast to the quantitative combination of RCTs in a meta-analysis.

Reporting Guidelines for Single Studies

It is important to recognize that the quality of a study's design and conduct is a wholly separate consideration from the quality of its reporting. It is plausible to assume that there is some association between these two measures of quality, but they are not directly related and should be assessed separately. Fortunately, there are now several well-publicized guidelines for the reporting of particular types of trials that will be enumerated below. Many journals are now using these in the process of manuscript review and are therefore gaining popularity.

The name and year of the last update of the most widely recognized tools are listed in Table 6. These tools each provide a checklist for reviewers in addition to a document that more thoroughly explains the rationale and the implementation of the checklist.²²⁻²⁶

The advantage of standardized reporting guidelines is that they require that the design and conduct of the study and its subsequent analysis be explicitly described. Elements of a study's conduct that are not ideal cannot simply be omitted if the expectation is that all items on a given checklist will be entertained by the authors. A second advantage is that studies can now be more reliably assessed for their inclusion in a systematic review. Finally, it is likely that as more attention is

Table 6 Reporting Guidelines by Study Design

Type of Study Design	Reporting Guidelines	Last Update
Randomized trials	CONSORT ²³	2010
Systematic reviews and meta-analysis	PRISMA ²⁴ (formally QUORUM)	2009 1999
Observational studies	STROBE ²⁵	2007
Meta-analysis of observational studies	MOOSE ²²	2000
Studies of diagnostic accuracy	STARD ²⁶	2003

being paid to the quality of reporting, an improvement in the quality of a trial's design and conduct will follow.

Critical Appraisal of a Body of Evidence

When compared with the evaluation of a single study, the critical appraisal of a larger body of evidence has many more challenges. The foundation of any particular body of evidence fundamentally rests on the critical appraisal of each study. However, making an adequate assessment of an entire body of evidence is difficult and requires consideration of additional elements that need not be considered for an individual study.

GRADING OF EVIDENCE AND MAKING OF RECOMMENDATIONS

In considering a body of evidence, two separate types of conclusions can emerge. The first and most obvious is a summary statement (a “grade”) of the overall assessment of the quality of the body of evidence. This, in general, takes into account the types of study designs, the consistency of results between studies, and the applicability of the available evidence to the clinical question. On the contrary, “recommendations” are not simply a reflection of the grade of the evidence being summarized but instead reflect an evaluation of the quality of the overall evidence in context. Because the varying weight placed on these broader considerations is quite subjective and will not be separable from the viewpoints of the recommenders, summary recommendations should be carefully evaluated by the reader. The primary data on which they are based should be considered in the context of values and preferences when making a clinical recommendation to a particular patient.

Evolution of Grading Systems

As EBM has gained popularity, there has been a proliferation of schemas by which a body of evidence can be evaluated. These have been useful in helping the reader to understand the type of evidence on which a recommendation is based. Unfortunately, because of the multiplicity of systems currently in use, it is no longer clear to the reader what is meant by “level 1” evidence as this can be variably described in the literature with different combinations of Roman numerals, letters, and words. Because of the resultant confusion in the literature, several groups have attempted to popularize a single system that could be employed universally.

Specific Systems Used to Grade a Body of Evidence

Although more than 25 systems to evaluate a body of evidence have been described,¹⁰ the discussion here is limited to three separate examples to illustrate the diversity being employed.

GRADE system In 2000, an informal international collaboration began that evolved into the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group. This was largely pioneered by Gordon Guyatt from McMaster University but includes many well-known international experts. This group's goal was to create a system to grade the strength of a body of evidence that could be easily employed and understood by a diverse group of

authors and readers and that would accurately reflect the quality of the underlying evidence.²⁷

Strength of evidence grade This group has created a system the grades the evidence quality using the following: high-, moderate-, low-, or very low-quality evidence. This is based primarily on the quality of the study design, consistency of effect between studies, generalizability of the outcomes from each study to the population of interest, and effect size as reflected in the measurement of the odds ratio, relative risk, or hazard ratio.

Recommendation grade The GRADE system further characterizes recommendations dichotomously, as strong or weak. In considering the strength of a recommendation, four factors are emphasized: the quality of the evidence, the balance between the benefits and harms, the consideration of variability of values and preferences of the population at hand, and, finally, a consideration of whether the intervention represents a wise use of health care resources.

Examples in practice The GRADE system has been widely employed and is accepted by several important stakeholders, making it arguably the leading classification. For example, the *British Medical Journal (BMJ)* and its EBM publication *Clinical Evidence* both request use of the GRADE system. Other groups using GRADE include the Cochrane Collaboration, the World Health Organization, the American College of Physicians, and UpToDate. In addition, the American Thoracic Society, one of the leading surgical groups focused on EBM, has endorsed the GRADE system.

The SORT system The Strength of Recommendation Taxonomy (SORT) system was developed by the editors of major US family medicine and primary care journals and was published in 2004.²⁸ This system was designed to be uniform and straightforward enough that primary care physicians could readily use it in daily practice.

Strength of evidence grade The grades assigned in the SORT system are levels 1 through 3. These are based on the following essential features: if the outcome is patient oriented, the quality of the reported evidence base, and the consistency of the findings.

Strength of recommendation grade Recommendations in the SORT system are categorized as A through C. Features considered in the recommendation grade are the consideration of patient-centered outcomes, the quality of the underlying evidence, and, interestingly, the grading of the recommendation by other groups.

The AHRQ system The Comparative Effectiveness Reviews published by the AHRQ reviewed the systems for grading evidence in 2002, and it immediately became clear that a number of systems of variable quality were being used to grade the quality of evidence and to make recommendations of varying strengths. The value of having a uniform system was recognized, and a system was designed for the evidence-based practice (EPCs) systems that they supported.²⁹

Strength of evidence grade The levels of strength in this system include high, moderate, low, and insufficient. The guiding principles used to determine the grade in this system are primarily risk of bias, consistency, directness, and precision. The GRADE system can be used by the EPCs as well

so that a more quantitative approach can be employed when needed.

Strength of recommendation grade Interestingly, this group explicitly avoids the making of recommendations because its members view their purpose as proving the information on which decision makers can make recommendations. Given that the EPC reports are used by a wide spectrum of agencies and societies with different priorities and goals, the aim was to create summaries of the evidence with an evaluation of their quality so that recommendations could then be drawn from those data in the context of the values of the group making the recommendation.

CENTRAL TENANTS TO APPRAISING A BODY OF EVIDENCE

Formulating a “Grade” for a Body of Evidence

Although many different systems exist that can help specific groups apply similar principles and arrive at consistent grades for bodies of evidence, these can best be understood by considering the central tenants employed by the majority of systems. These are similar to those employed in the appraisal of a single study but include additional considerations that help deal with the issues that arise by trying to combine a multiplicity of studies.

Evaluating the risk of bias Perhaps the most important characteristic of a body of evidence is its overall susceptibility to bias.

Study design This assessment includes consideration of both study design and conduct. Having several well-controlled, blinded, RCTs will clearly help assure the reader that there is a relatively low risk of bias. However, even in the absence of RCTs, the overall risk of bias can still be quite low. This can occur, for example, with observational studies where the effect of the treatment on the disease state is obvious (so-called “all or none” effects) or those that have a dramatic effect size.

Reporting bias In addition to the particular study design, the possibility of reporting bias should be considered. When only a few studies are available and all show some marginal benefit, it should be carefully considered whether those that showed some marginal harm have not been considered because of the failure to be included in the published literature. This can be ascertained by examining the registry of RCTs, comparing the study protocol with the reported study results, and talking to experts in the field involved with review of manuscripts for publication.

Quantity In estimating the risk of bias, it is helpful to have an understanding of the total number of patients who have been studied and the number of separate groups and/or institutions that have conducted the studies of interest. At the extreme, one RCT with a limited number of patients from a single institution is much more likely to be susceptible to bias than is the evidence culled from a large number of studies from multiple institutions. Although no absolute number should be used, an estimation of the quantity of data points should be explicitly stated.

Evaluating consistency between studies Even if the studies being considered have a low risk of bias, there is no guarantee that their results will necessarily be consistent.

Direction of effect An evaluation of the direction of the effect measured should be considered first. If some studies show harm, whereas others demonstrate benefit, this clearly raises concern for consistency. Evaluators of the evidence should look carefully to try to determine if such inconsistency can be explained by differences in populations selected, details of the treatment employed, or biologic differences in the disease under study. If such an explanation appears rational and accounts for the differences, the evidence can still be considered consistent. If not, then the overall assessment of the quality of evidence is lowered. Statistical tests of heterogeneity can be employed if meta-analysis is appropriate (e.g., Cochrane’s Q test of I^2 statistics) but are not necessary to determine the overall consistency of a body of literature.

Evidence of dose response When a clear difference in effect size can be seen with different doses of the treatment under study, the biologic principle of a dose-response curve bolsters the validity of the data.

Evaluation of a single study When only a single study is available, consistency cannot be assessed. Even with a large, well-designed trial, the fact that only a single study exists precludes any evaluation of consistency.

Evaluating generalizability of study results Even if high-quality and consistent evidence is available, it is critical that it be applicable to the study question. This is often referred to as “directness” and can be viewed as a measure of how obviously the available evidence applies to the patient being treated.

Patient-oriented outcomes One important consideration is the specific outcome measured by the evidence. Surrogate outcomes are those that do not represent the actual outcome of interest but rather more intermediate and mechanistic outcomes. For example, the ability of a particular orthopedic procedure to improve radiographic findings but not the symptom complex would be an example of indirect evidence. In addition, the outcome being evaluated need not only have a direct link to the evidence but must also be one that is of interest to the patient. These include measures such as morbidity, mortality, quality of life, and symptom relief but not improvement in laboratory values, degree of pathologic response, or tumor measurements.

Directness of comparisons When comparing multiple treatments, the directness of the comparisons between each treatment should be assessed. The idealized comparison would be between each treatment separately within the same study. Because this is rarely possible, the reader is often comparing treatment 1 with treatment 2 in one study and treatment 2 with treatment 3 in another, with no direct evidence comparing treatments 1 and 3. Although some comparisons can be made by way of effect size and consistency of outcomes, this evidence must still be judged as indirect.

Assessing external validity To determine if the results of a body of evidence can be applied to a given patient, it must be determined that the patient was adequately represented in the population under study. For example, if high-quality and consistent evidence exists that shows treatment A results in improved quality of life, but the majority of participants in the study were more than 65 years old, it cannot be assumed that this same treatment will have identical effects on a younger patient population.

Evaluating the effect size The strength of the association between treatment and effect should be considered. The effect size can be measured in many different ways but is commonly reported as an odds ratio, a relative risk, or a hazards ratio.

Assessing the magnitude of the effect The magnitude of the effect size refers to absolute change in the risk or likelihood of the outcome of interest before and after a particular treatment or exposure. Although there is no evidence for a particular magnitude of effect that is acceptable, the GRADE group has used effect sizes of more than 5 and less than 0.2 as most significant and those of more than 2 and less than 0.5 as of lesser significance.²⁷

Assessing the precision of the effect In addition to the absolute magnitude of the effect, the relative precision of the pooled effects is also important. This reflects the degree of certainty surrounding the estimate of effect and is measured by the pooled confidence interval. The narrower the pooled confidence interval, the easier it is to estimate the effect seen so that it may be more reliably compared with the effects of other treatments. Should the pooled confidence interval be so wide that it includes both the possibility of benefit and of harm, no conclusion about the effect can be rendered.

Formulating a Recommendation

The formulation of a recommendation from an assessment of the quality and strength of a body of evidence seems at first to be straightforward. However, this process ultimately requires that values be assigned to relative benefits and risks, costs, convenience, and system-wide issues. The process of making recommendations is therefore quite subjective, and the procedures, values, and interests of the group making the recommendations should therefore be carefully explored before simply accepting the level of recommendation made.

The strength of a given recommendation should include an assessment of the overall quality of the evidence. Clearly, a strong recommendation should not be made on the basis of weak evidence. Furthermore, recommendations should consider the balance of the desirable and undesirable effects of any particular treatment. For example, the negative effects of chemotherapy on quality of life, symptoms, and even fertility should be weighed against the benefit of extension of life or prolongation of disease-free interval. These types of judgments are difficult enough for a given patient and physician to make together but are nearly impossible to determine on the population level. This is because the values and preferences of the individual patient are undoubtedly variable, making a summary statement at times impossible.

The difficulties in making recommendations also include issues surrounding the value that the system should place on given outcomes relative to their costs. This dilemma is central to the debate over health care in general and cannot be simplified in any given recommendation. Some interventions will result in effects that are profound enough and of low enough cost that there is little room to debate their merits. Those decisions about interventions that have either modest effect but high costs or minimal effects irrespective of cost warrant the majority of the discussion.

Evidence-Based Surgery

Although EBM has been maturing over the last 20 years, the field of evidence-based surgery has been slower to develop.

In fact, the idea of evidence-based surgery has frequently been derided. For example, an editorial in 1996 written by the editor of the *Lancet* was entitled “Surgical Research or Comic Opera: Questions, But Few Answers.”³⁰ A more recent example of the fairly broad-based disdain for evidence-based surgery is the presentation given by the editor of *BMJ* in 2004.³¹ The title of the presentation given in 2004 was “Is Surgery an Anachronism in an Evidence Based Age?”³¹ These statements from prominent advocates of EBM illustrate significant questions about the state of evidence-based surgery today and the challenges that it faces moving forward.

HISTORY

Although the first RCTs in surgery were published in 1964, the popular application of the RCT to surgical therapies has been quite slow. For example, in a systematic review of the literature from 1966 to 2000, Wentz and colleagues found that only 15% of all published clinical trials dealt with surgical issues.³² Furthermore, of all the articles published in the five leading surgical journals, only 3% were RCTs. Of these, about half did not deal directly with surgical therapy but rather issues of medical therapies in surgical patients. Although there was a significant increase in the number of surgical RCTs from the 1960s to the early 1980s, the number appears more stagnant from the 1980s to 2000.

Several recent developments have been important steps in the development of evidence-based surgery. In 2000, under the leadership of Samuel Wells, the American College of Surgeons Oncology Group (ACSOG) was established and given responsibility for studying the surgical treatment of cancer. The group became one of nine cooperative clinical trial groups funded by the National Cancer Institute and has now initiated about 30 multiinstitutional trials of surgical therapies. Similar central organization of surgical resources has occurred internationally as well. The German Surgical Society established a center for the German study of surgery, known as the SDGC, in 2005. Furthermore, the Royal Australasian College of Surgeons has established the Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S), which began in 1998. This group does not sponsor clinical trials but does serve to produce systematic reviews of surgical topics and help identify areas of innovation in surgery when RCTs may be best applied.

CHALLENGES TO EVIDENCE-BASED SURGERY

As the slow uptake of the RCT into the field of surgical research empirically demonstrates, there are inherent challenges to the execution of RCTs in surgical disciplines.^{33,34} These are enumerated below.

Methodological Issues

Difficulty with standardization One of the fundamentals in the execution of a RCT is that all the participants are treated similarly. When compared with the administration of medicines, the delivery of surgical care is much more difficult to standardize.

Technical variability Between individual surgeons, there is a wide array of technical skill and experience. Although key components of an operative procedure can be specified, it is

difficult to specify and monitor the degree of skill with which these steps are executed. Furthermore, pre- and postoperative care introduce additional variables that are difficult to standardize and likely introduce confounders.

Effect of the learning curve When new procedures or methodologies are introduced, it has clearly been demonstrated that a learning curve exists. The shape of this curve differs by procedure, and there is currently no well-accepted method for predicting in advance the shape of the curve. This clearly introduces variability into any RCT that includes a new procedure or technology and biases the results in favor of the older therapy with which the operators are more familiar.

Evolution of a procedure Even after the learning curve has reached a plateau, surgical procedures continuously evolve by iterative change. Technical modifications to the procedure itself, the postoperative care pathways, and the preoperative selection criteria are constantly occurring but are not easily measured objectively.

Difficulties with placebo control One of the major differences between a surgical therapy and a medical therapy is the ease with which placebo controls can be instituted. Because a surgical procedure itself is known to have a clear placebo effect, it can be important for trials of surgical therapy to include a placebo arm. However, the issue of sham surgery for the benefit of research purity has ignited much debate. Given the Common Rule's insistence on fundamental principles of risk minimization and the balance between risks and potential benefits for the subjects, there are clear ethical challenges to the use of surgical placebo arms.

Difficulties with blinding Although it is possible to blind the clinician prescribing therapy in a trial involving medical treatment, it is not possible to blind the surgeon who performs a surgical procedure to the type of procedure he or she is to perform. Further, it can be difficult to blind patients to the type of surgical procedure performed because there can be differences in associated incisional discomfort or side effects known to occur only with one arm of the trial.

Feasibility Issues

Assuming that the methodological issues could all be dealt with in some way, additional barriers still exist to the conduct of a surgical RCT.

Difficulties with recruitment Although surgical RCTs have been successfully completed, many have suffered from difficulties with recruitment. There are several potential reasons for this. It is clear that patients have strong feelings with regard to their willingness to undergo a surgical procedure and that these are magnified when patients are asked to consider being randomized to either a medical or a surgical therapy (e.g., chemotherapy or surgical excision of a tumor) or to one of two fundamentally different surgical procedures (e.g., continence-preserving procedures or procedures that entail creation of an ostomy). Even if a group of amenable patients could be assembled for an RCT, doubt about the external validity of the trial would still remain given that the majority of patients might have refused enrolment. The patient's unwillingness to participate has been identified as the most common reason for nonentry into surgical RCTs.³⁵

For example, when asked about their willingness to participate in a hypothetical RCT comparing vaginal delivery with elective cesarean section, only 14% of pregnant women indicated that they would participate.³⁶ Such a low level of willingness to participate in an otherwise reasonable RCT is clearly a problem for investigators trying to study surgical therapies.

Lack of equipoise Once a new surgical therapy has been developed and standardized to the point at which it is appropriate to study in a large-scale clinical trial, collective clinical equipoise may no longer be present. It has also been suggested by some that because it is routinely necessary for effective surgeons to make important clinical decisions rapidly in the face of limited data, they are as a group by nature and/or training less capable of having the ambivalence necessary for clinical equipoise to exist.³⁷

Interest in rare outcomes Because surgical therapies are often compared on the basis of complication rates, it can be difficult to have a study that is adequately powered to look at rare events of harm. For example, one of the most relevant outcomes for liver surgery is the rate of postoperative mortality, which generally occurs at a rate of about 1%. One group has calculated that to have an adequately powered study in liver surgery to answer the question of whether a particular technique changes the rates of postoperative death would require enrolling more than 15,000 patients.³⁸ Given that only about 7,000 liver resections are performed annually in the United States, it is unlikely that this volume could be accrued in a reasonable period of time.

Lack of funding Because of the requirement of the Food and Drug Administration (FDA) for evidence from RCTs for new drug applications, the pharmaceutical companies trying to bring these drugs to market are obligated to conduct and, usually, to fund these trials. This experience with drug trials has helped establish the infrastructure of clinical trials at many centers and is the basis on which they fund their clinical research efforts. Interestingly, there is no agency similar to the FDA for surgeons.³⁹ Although it is clear that surgical therapies can inflict as much harm on patients as can medical ones, there is no governmental body that protects patients from surgical interventions. Because of the lack of a requirement for RCTs for surgical procedures and devices, there is little motivation and, consequently, industry funding for surgical trials. Although some progress has been made in this area, the extraordinary cost of a surgical RCT that may require the labor-intensive process of teaching and monitoring the procedures of all surgeons involved is at times viewed as prohibitive.

Lack of oversight Similarly, the lack of a body overseeing the approval of new surgical therapies has left them currently in the domain of experimental therapies. Should a given surgeon participate in a clinical trial and the patient experience harm as a result of an unproven therapy, some physicians are concerned about the possibility of malpractice litigation in this setting.⁴⁰ This added concern and the lack of universal procedures for dealing with legal matters in the conduct of clinical trials serve to further decrease the feasibility of RCTs in surgery.

ISSUE OF THE OBSERVATIONAL STUDY

Introduction to the Problem of Observational Studies

The place of the observational study in the field of EBM has been a contentious topic. As evidence hierarchies began to be popularized, there was clear recognition of some of the limitations of nonexperimental observational studies. There was concern about the fact that observational studies are more vulnerable to certain biases than randomized studies, and some have even gone so far as to advocate that observational studies should not even be considered by the reader.

Although the concerns about the validity of observational studies are rational, it cannot be disputed that they continue to represent the vast majority of the evidence available in many fields. If only data from RCTs were considered, it would be difficult to make any rational clinical decisions about the vast majority of clinical questions that arise on a daily basis, particularly in surgical fields. To simply discount the value of observational studies completely would be flippant. However, the use of data generated from the observational study must be cautiously incorporated into clinical decision making.

Evidence to Support the Difference between RCTs and Observational Studies

One of the arguments central to the controversy over the utility of observational studies is how their results have compared with the outcomes of RCTs. The discussion often centers on several notable examples of how observational studies led to the widespread acceptance of therapies that were later demonstrated in RCTs to be harmful. Two prominent examples frequently given to support the fallacies of observational studies are the effect of hormone replacement therapy on myocardial infarction in postmenopausal women and the use of certain antiarrhythmics to prevent sudden death after myocardial infarction. These are clear examples of how observational data can be misleading, but the question as to the frequency with which they do so remains.

Perhaps the most comprehensive analysis of this topic was sponsored by the United Kingdom's National Health Service and was published in 2003.²¹ This review looked carefully at eight separate studies published that compared the results of observational studies with those of randomized ones. The authors concluded that these studies as a whole were inconclusive given difficulties with metaepidemiologic methodology but suggested that they all supported the claim that observational studies are sometimes, but not always, biased. Importantly, in this analysis, 82 clinical topics were included, only four of which were primarily surgical topics.

However, since that time, at least three separate analyses have compared the results of surgical observational studies with those of randomized ones. The first of these compared RCTs with observational studies in the field of digestive surgery.⁴¹ The authors found that only 25% of the time did the observational studies give different results than RCTs. A second study compared the results of studies of open and laparoscopic cholecystectomy and concluded that the results differed in at least 20% of outcomes and that the observational studies had significantly more heterogeneity.⁴² A final study examined these two study types in the comparison of laparoscopic and open resection of colorectal cancer and found that the results were remarkably similar.⁴³ This study

included only studies coming from a recent era that were published at a similar time, suggesting that this may be a more accurate type of comparison.

It can certainly be concluded that the observational study has certain limitations when compared with the RCT. However, at least in surgical disciplines, the evidence to date suggests a reliable but not constant relationship between the outcomes of observational studies and RCTs. It would therefore behoove the surgical community to continue to increase the number of questions being answered by RCTs but also to simultaneously work on improving the design and reporting of observational studies. Some progress along these lines is already being made, but this field continues to be in its infancy.⁴⁴

Current Place of the Observational Study in Surgery

Importantly, when the scientific objective is to detect and measure a small but clinically important difference between two therapies, the standard should continue to be a well-designed and executed RCT. However, because of some of the issues that differentiate surgical from pharmacologic studies, the observational study will likely continue to be a significant part of the evidence base in surgical disciplines.⁴⁵ This is most reasonable in the following situations:

- When ethical considerations prevent the use of a surgical placebo arm
- When the unwillingness of patients to be randomized to two radically different therapies prevents adequate accrual in an RCT
- When the rare effects of different therapies, particularly harms, are to be compared
- When the need to examine the generalizability of a given therapy to a broader population is paramount

POTENTIAL SOLUTIONS FOR EVIDENCE-BASED SURGERY

Although significant challenges confront investigators when conducting surgical trials, many of these issues can be addressed by novel strategies that will allow the quality of surgical research to continue to improve. The study of the adaptations necessary for surgical trials is still in its beginning stages but will likely continue to be fruitful as surgeons continue to push forward in the field of evidence-based surgery.

Some Solutions to Methodological Issues

Standardization Although it is difficult to standardize a surgical procedure, several groups have demonstrated that with significant effort, a group of surgeons can be taught to perform a given step in a procedure with reasonable similarity (e.g., total mesorectal excision for rectal cancer). This can be accomplished by standardized training and, importantly, real-time mentoring during a designated number of procedures. Further, the requirement for routine assessment of intraoperative videos or photographs and standardized assessment of the pathologic specimens can further enhance our ability to standardize a surgical RCT. It should be noted that this type of effort requires a significant investment of resources and should be undertaken only when the technique of the procedure itself is central and performed with significant enough variability to reasonably impact outcomes. In addition, the use of preliminary studies, termed phase II surgical studies (or phase IIS), has been advocated as a means to test methods

of surgical quality, to practically define the relevant end points, and to more accurately estimate the sample size needed for phase III studies.³⁷

Placebo control Ethical concerns around surgical placebo controlled trials have been addressed by the Council on Ethical and Judicial Affairs of the American Medical Association.⁴⁶ This document provides some guidance in this arena and suggests a basis on which the appropriateness of a surgical placebo arm can be evaluated. These considerations include the feasibility of no other trial design, the susceptibility of the outcome in question to the placebo effect, and small risks associated with the surgical placebo arm.

Blinding Although the surgeon cannot be blind to the treatment group, it is possible at times with careful technique to blind the subject. Further, the assessors of the outcome measures of interest can be blinded to the treatment group, decreasing the likelihood of introducing bias by the absence of blinding.

Some Solutions to Feasibility Issues

Recruitment Because patients' preferences can clearly influence their willingness to enter randomized trials, patient preference arms conducted alongside an RCT (often called comprehensive cohort designs) have been investigated and represent a potentially useful adjunct to surgical trials.⁴⁷ The development of tools that aid in decision analysis strategies may help patients better understand their own preferences and choices.

Equipoise To address the issue of equipoise on the part of the surgeon, a novel trial design termed "expertise-based randomized controlled trials" has been suggested.⁴⁸ This strategy randomizes patients to clinicians with expertise in one or the other treatment arms. This has several advantages as it removes the learning curve from consideration, allows each group of surgeons to treat patients similarly, and resolves the issue of clinical equipoise in the sense that a given surgeon does not need to perform the procedure that he or she feels is inferior. It does, however, require some collective sense of equipoise on behalf of the larger community.

Rare outcomes Because of the concern for harmful but rare outcomes from the introduction of surgical innovation, a group of thought leaders in the field, termed the Balliol Collaboration, has begun to define the process by which surgical innovation should be evaluated.⁴⁹ This group emphasizes that different considerations need to be entertained at different stages of innovation (known as the IDEAL paradigm). Such a framework is useful for surgeons as they consider the introduction of new procedures and how to safely monitor rare outcomes outside of the confines of a typical RCT.

Solutions to Bias in the Observational Study

A much more complex topic is how the approach to the observational study can be modified in such a way as to allow more valid evidence to result. One suggestion has been to develop a variety of nonrandomized study designs that would allow for nonexperimental studies but decrease the elements

of bias. Others have suggested that we simply reject the idea that judgments made together by patients and their surgeons are too complex to be quantitatively understood and instead focus on ways in which these confounders could be more reliably measured. This sentiment was stated well by Lantos: "Rather than constraining human choices to meet the needs of statisticians, I think we should encourage statisticians to devise methods of evaluating the source of choices that free and intelligent citizens make all the time."⁵⁰ It is clear that new methodologies that account for the known confounders in observational studies would help encourage progress in surgical fields as they would allow for improved recruitment into studies, decreased costs, and more generalizable results. The ability to more accurately account for confounding variables in observational trials would serve to further our knowledge in the areas of surgical care where RCTs are not needed.

RESOURCES FOR EVIDENCE-BASED SURGERY

Given the relatively new interest in evidence-based surgery, there are still a limited number of EBM resources that focus on surgical issues. These are, however, growing in number, and new resources continue to appear. However, those EBM resources that have focused primarily on medical issues contain relevant information for many surgical topics. See Table 7 for a list of some of the helpful resources currently available.

Limitations in Evidence-Based Medicine

SITUATIONS IN WHICH RANDOMIZED CONTROLLED TRIALS ARE NOT USEFUL

All-or-None Situation

In response to what was felt to be a dogmatic insistence on evidence from RCTs, a group from the University of Cambridge in 2003 wrote the now classic article in the *British Medical Journal* entitled "Parachute Use to Prevent Death and Major Trauma Related to Gravitational Challenge: Systematic Review of Randomised Controlled Trials."⁵¹ In this brief but pointed piece, the authors demonstrate clearly one of the major limitations of EBM: its exuberant application of RCTs to any clinical problem. The authors demonstrated that there were no RCTs of parachute use and that the data to support their use were purely observational and suggested that those who feel that RCT data are needed should be participants in the trial. This satire provoked reasoned discussion about the limitations of EBM. This situation wherein the treatment effect is dramatic enough not to raise the specter of the effect of bias has been termed the "all-or-none" criterion. Even the proponents of EBM readily recognize that in similar situations, an RCT is not only unnecessary but unethical.

Large Treatment Effects

One way of thinking about treatment effects that are dramatic in nature is to consider the outcome of the treatment ("signal") relative to the expected outcome without treatment ("noise").⁵² It has been proposed that if the signal-to-noise ratio is greater than 10, the likelihood of bias being responsible for the purported effect of the treatment is unlikely

Table 7 Key Resources for Evidence-Based Surgery

Resource	Features	Relevance to Surgery
Cochrane Collaboration Database of Systematic Reviews Database of Abstracts of Reviews of Effects (DARE)	Contains comprehensive reviews by the Cochrane Review Groups and abstracts of reviews by others that have been quality assessed	Many surgical topics reviewed
PubMed's Clinical Queries	PubMed filter designed by Brian Haynes from McMaster University to assist in finding the highest-quality information when searching Medline	Can be used for any topic
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S)	Systematic reviews of many surgical procedures and their outcomes New and Emerging Techniques—Surgical (NET-S) provides reviews of new surgical technologies prior to introduction into practice	Only surgical topics
CAGS/ACS Evidence-Based Reviews in Surgery (EBRS)	An online journal club format that reviews 12 current surgical publications a year that illustrate important methodological issues An archive is available with 10 years of studies with abstracts discussing clinical and methodological issues	Only surgical topics
McMaster University's Surgical Outcomes Research Centre (SOURCES)	A series of 13 articles focused on the methodology required to critically appraise the surgical literature Modeled on the "Users' Guides to the Medical Literature" published in <i>JAMA</i>	Methodology with surgical relevance
<i>BMJ's Clinical Evidence</i>	Comprehensive EBM tool Publishes and updates systematic reviews, identifies and rates recent primary literature, and provides links to relevant guidelines.	Some surgical topics
<i>ACP Journal Club</i>	Selects both primary studies and reviews from 100 clinical journals and presents them as structured abstracts with commentaries and key references Aimed at advances in internal medicine.	Includes some surgical journals
BestBETS	Provides brief reviews of the best evidence on topics specific to primarily emergency medicine From the Manchester Royal Infirmary	Some surgical topics in emergency medicine
Turning Research Into Practice (TRIP) Database	A search engine that allows simultaneous searching of multiple EBM sites to help clinicians answer common clinical questions Located in South Wales, UK	Some surgical topics
AHRQ's Effective HealthCare Program	Focuses on comparative effectiveness reviews authored by their evidence-based practices	Limited surgical topics

AHRQ = Agency for Healthcare Research and Quality; CAGS = Canadian Association of General Surgeons; EBM = evidence-based medicine.

enough to consider an RCT unnecessary. An important caveat is that it is possible to accurately determine the effect of treatment without RCTs only in disease states that are stable or progressive. Those disease states known to be fluctuating or intermittent are prone to errors unless RCTs are used because there may be as much noise as signal.

Rare or Distant Outcomes

When either the disease or outcome of interest is sufficiently infrequent that an RCT would never be expected to accrue enough patients to decipher a difference, RCTs are logistically impossible.⁵³ Instead, the use of comprehensive registries with methodical prospective documentation of therapeutic interventions and outcomes is the only realistic way to study these rare events. A similar consideration is if the outcome of interest will occur far enough in the future that follow-up will be impractical. This would occur, for example, if one were trying to determine which of two methods of pediatric hernia repair would lead to the lowest incidence of adult hernias; a gap would be expected to be separated by more

than 40 years. Again, registries and cohort studies are much better suited to the study of these outcomes.

No Alternative Treatments

If the natural history of a given disease is known and stable or progressive and no other treatments exist, a new treatment would clearly not need to be studied in a randomized fashion. If the disease course is fluctuating by nature, it would be necessary to study the new treatment compared with placebo unless the effect were dramatic.⁵³

FAILURE TO RECOGNIZE THE IMPACT OF LIMITED GENERALIZABILITY

Because RCTs frequently include only a highly selected group of participants relative to the whole population affected with the condition under study, there have been significant concerns of the generalizability of their results. Many have argued that the results from a given trial do not directly translate to the treatment decisions of the majority of patients in "real-world" situations.⁵⁴ It has been noted in several fields

that there is a significant discrepancy between clinical trial results and clinical practice decisions.⁵⁵ Part of this is, no doubt, related to the fact that the results must be disseminated. In addition, it has been noted that most clinicians require an accumulation of supportive evidence before they will change practice patterns, not simply the result of a single RCT.

DISMISSING OF OTHER FORMS OF EVIDENCE AS INVALID

Use of the Bradford Hill Criteria of Causation

Given that the accumulation of evidence is necessary to convince most clinicians to change practice, EBM cannot afford to dismiss evidence that does not come from an RCT. A thoughtful analysis of how different types of evidence can support a given causal hypothesis is therefore necessary. This type of analysis has built on the principles that Sir Austin Bradford Hill eloquently described in his presidential address in 1965.⁵⁶ In that address, he described the nine aspects of an association that should be considered before concluding causation existed. These so-called “Bradford Hill criteria” have been revisited and serve as a useful means by which the need for the incorporation of non-RCT data can be best understood.

Incorporation of Mechanistic and Parallel Data

One author has proposed thinking of evidence as coming in the forms of direct evidence and indirect evidence that is either mechanistic or parallel.⁵⁷ Direct evidence evaluates the strength of the association, rules out the influence of plausible confounders, and evaluates the possibility of a so-called biologic gradient (called the dose-response curve). Although direct evidence is necessary to support causation, it is not sufficient because it does not explain how the intervention caused the outcome. Rather, mechanistic evidence provides support for the causal process that links that treatment to the observed effect. Key components of mechanistic evidence are the description of a plausible mechanism and coherence of that mechanism with previously accepted knowledge. Parallel evidence refers to the consideration of the replicability of the findings.

If the field of EBM is conceived too narrowly, some important types of evidence will be excluded unnecessarily. Rather, it would benefit EBM if these other types of more indirect data were incorporated with more direct lines of evidence as they certainly serve to complement and extend the type of evidence generated from RCTs.

LIMITED EMPHASIS ON THE INDIVIDUAL

Patient Preferences

Perhaps the biggest objection to the idea of EBM stemmed from the concern that medicine would become “cookbook”

in nature. The fear on the part of clinicians has been that the results of RCTs would be applied to their patients without consideration of the circumstances of the specific patient. The concern for the potential for deemphasis of the needs of specific patients is well articulated in an opinion piece by a breast cancer survivor entitled “‘Evidence of Me’ in Evidence Based Medicine?”⁵⁸ This piece highlights the limitations of the use of data from RCTs, perhaps most poignantly by pointing out that the evidence on which guidelines for chemotherapy in breast cancer have been developed does not include a consideration of the effect of the varying treatments on fertility. Because these types of issues are of critical importance to patients, there are clear limitations on the application of data from RCTs to premenopausal women whose personal preferences for fertility might alter the treatment option recommended.

Clinical Expertise

Not only are patients wary of losing their autonomy in their health care decisions, but physicians have been equally concerned about negating the value of clinical expertise.⁵⁹ In fact, clinical expertise allows the correct diagnosis to be made so that the results of EBM can be properly applied. Further, physician insight can frequently lead to an appreciation that a given patient is likely not to tolerate a particular therapy, is likely to be noncompliant, or may be more likely to suffer adverse affects.

IRONY OF EXPERT OPINION

Perhaps one of the most pointed criticisms of EBM is that its fundamental tenets are not, in fact, evidence based.⁸ Several astute authors have pointed out the obvious hypocrisy among some groups in EBM regarding the utility of expert opinion.⁶⁰ On the one hand, proponents of EBM have insisted that the individual clinician should not rely on expert opinion and have even placed this at the bottom of the evidence hierarchy. Instead, it is suggested that the individual clinician search the literature and learn how to properly evaluate, process, and summate information on a given clinical question. The proponents of EBM rightly acknowledge that this type of searching is too time consuming for the busy clinician and therefore encourage reliance on “preprocessed” sources of information, such as guidelines and reviews authored by experts. The reader can clearly see the irony in simply substituting one type of expert opinion for another. This type of hypocrisy could be more easily accepted if high-quality trials had demonstrated that employing recommendations that come from these sources results in better patient outcomes. Until this is accomplished, EBM may have to live with the criticism that it is not evidence based.

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9 PHARMACOLOGIC CONSIDERATIONS IN THE ELDERLY SURGICAL PATIENT

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In 2000, the population of Americans aged 65 or greater was estimated to be 35 million, roughly 10% of the total population.¹ The latest census figures project a doubling of the elderly population by 2030, after which the proportion of elderly Americans will stabilize at approximately 20%. The aging of the US population is expected to cause a 31% increase in the general surgery workload by 2020.²

Elderly patients are not a homogeneous group; functionally, they can range from quite healthy and active to frail. However, because age-related changes occur in each organ system in all elderly individuals, this population merits special consideration when undergoing surgical procedures. In this chapter, we examine common medication and dosing issues relevant to elderly patients during the perioperative period.

The most rapidly growing segment of the elderly population corresponds to persons aged 85 and over. Thus, perioperative management must take into account the high probability that older adults will have multiple chronic medical problems such as diabetes, coronary artery disease, and chronic kidney disease. The presence of multiple medical problems is a complex medication management challenge. Medication dose adjustment and an increased frequency of medication-related adverse events are inevitable in the elderly. That said, precautions can and should be taken to reduce medication-associated risks in this population.

The medication issues most relevant to older adults include prescription of inappropriate medications, inappropriate dosing of medications, adverse drug events, drug-to-drug interactions, and polypharmacy. Polypharmacy has been identified as a medication safety issue in Healthy People 2000, a report issued by the US Department of Health and Human Services.³ Age-related changes occur in the realm of pharmacokinetics (relation between drug dose and plasma concentration) as a result of alterations in absorption, distribution, metabolism, and excretion of medications. Changes also occur at the pharmacodynamic level (relationship between plasma concentration and clinical effect), arising from altered interactions between medications and their receptors. Age-related changes affect the number of receptors, binding affinity of medications, and the resultant biologic impact of medications on the organism.

Pharmacologic Impact of Physiologic Changes Associated with Aging

Compared with young patients, elderly patients tend to have less muscle mass, more adipose tissue, and decreased total body water.⁴ These changes cause hydrophilic drugs to

have a smaller volume of distribution and a higher plasma concentration in the elderly, leading to greater pharmacologic effect for a given dose. Conversely, hydrophobic drugs will have a smaller plasma concentration but a larger volume of distribution, leading to slower clearance for a given dose.⁵

In general, organ function is inversely proportional to age. Two organ systems intimately connected to pharmacokinetics are the renal and hepatic systems. Contributors to glomerulosclerosis include normal aging as well as age-associated comorbidities such as chronic hypertension and diabetes. These changes are particularly prominent in the renal cortex, where the glomeruli become replaced by fat and fibrotic tissue over time.⁶ In addition, renal blood flow decreases with age, in parallel with a decrease in cardiac output. As a result of a reduction in glomerular capillary plasma flow rate and a depressed capillary ultrafiltration coefficient, the aging kidney has a marked reduction in glomerular filtration rate.⁷ Therefore, the rate of elimination for drugs primarily cleared by the kidneys is decreased in elderly patients. Delayed drug elimination can lead to prolonged sedative effects of anesthetic and narcotic medications. In addition, reduced renal function renders elderly patients more vulnerable to acute renal dysfunction caused by nonsteroidal antiinflammatory drugs (NSAIDs), diuretics, and aminoglycoside antibiotics.⁶

Hepatic metabolism is also compromised by aging. This arises from both reduced parenchymal hepatic mass and a 40% decrease in hepatic blood flow between the ages of 25 and 65. The synthetic function of the liver also decreases with age. A reduction in the serum albumin concentration leads to an increase in the unbound or pharmacologically active fraction of a given dose of medication.⁸ When combined, these effects are synergistic and markedly increase the potency of a given medication dose in the elderly.

Initial Medication Assessment

Older adults are the biggest consumers of medications, being responsible for 30% of prescription drug purchases and 40% of nonprescription drug purchases nationally.⁹ As such, an essential component of preoperative assessment is a complete review of all medications that the patient is taking. This includes not only prescription drugs but also nonprescribed medications such as over-the-counter medications, supplements, vitamins, and herbal preparations. The most common drugs taken by elderly Americans are shown in Table 1.

Approximately 80% of community-dwelling older adults routinely take at least one prescription medication, and 30% take at least five prescription medications concurrently.¹⁰ As

Table 1 Top 20 Prescription and Nonprescription Drugs Used by Adults Aged 57 to 85 Years in the United States¹⁰

Medication	Available OTC	Weighted Prevalence (%)
Aspirin	Yes	28
Hydrochlorothiazide	No	16
Atorvastatin	No	13
Levothyroxine	No	12
Lisinopril	No	12
Metoprolol	No	11
Simvastatin	No	10
Atenolol	No	9
Amlodipine	No	8
Metformin	No	8
Acetaminophen	Yes	8
Furosemide	No	6
Ezetimibe	No	5
Valsartan	No	5
Alendronate	No	5
Warfarin	No	4
Omeprazole	Yes	4
Clopidogrel	No	4
Albuterol	No	4
Conjugated estrogens	No	4

OTC = over the counter.

many as one in 25 older adults is potentially at risk for a major drug-drug interaction. Thus, polypharmacy is a reality and concern for all medical professionals caring for the elderly. The definition of polypharmacy is varied. Some definitions are based solely on the number of medications; the Health Care Financing Administration (HCFA), for example, defines polypharmacy as taking nine or more medications. Other definitions take medication appropriateness into account. Not all polypharmacy can be avoided, especially given that multidrug regimens are the standard of care in the management of common chronic diseases such as diabetes, congestive heart failure, coronary artery disease, and chronic obstructive pulmonary disease. The risk of adverse events increases with age and polypharmacy, with the risk being as high as 82% in elderly persons taking seven or more medications.⁹

Certain specific classes of prescription medications merit particular attention during the perioperative period. The first class is composed of drugs exhibiting additive adverse effects [see Table 2]. Given that almost all surgical patients are administered sedatives, anesthetics, or other central nervous system (CNS) depressants perioperatively, one must account for the potential additive effect these agents may have when combined with other CNS depressants commonly taken by elderly patients on a routine basis. A theme we will revisit throughout this chapter is the fact that anticholinergic medications are strongly associated with cognitive impairment in normal elderly individuals,¹¹ as well as those with existing

Table 2 Drugs with Additive Adverse Effects

CNS depressants
Opiates
Benzodiazepines
Antiepileptics
Sleep aids (both prescribed and over the counter)
Anticholinergics
Baclofen
Haloperidol
Atropine
Scopolamine
QTc prolongation
Tricyclic antidepressants
Methadone
Macrolide antibiotics
Quinolone antibiotics

CNS = central nervous system.

chronic neurologic conditions such as Alzheimer disease and Parkinson disease.^{12,13} Therefore, the surgical team is responsible for both taking note of anticholinergic medications routinely taken by the patient and avoiding the addition of more such medications perioperatively. Prolongation of the QT or corrected QT (QTc) interval is associated with the development of torsades de pointes, a potentially lethal ventricular tachyarrhythmia. Normal aging is associated with progressive mild increases in the QTc interval. Medications that prolong the QTc interval in an additive fashion are listed in Table 2. Inhaled anesthetic agents prolong the QTc interval,¹⁴ and this effect may be more pronounced in the elderly.¹⁵

A second class of medications that merits special attention both preoperatively and perioperatively constitutes those that alter the activity of the cytochrome P-450 (CYP) enzyme superfamily [see Table 3]. CYP enzymes, which catalyze the oxidation of organic substrates, play a critical role in the elimination of many medications. Thus, agents that inhibit or induce CYP activity have great potential to cause drug-drug interactions. A classic example is the inhibition of benzodiazepine metabolism by azole antifungal agents, which can result in a prolonged sedative effect. Another interaction relevant to cardiovascular surgeons is the inhibition of CYP-dependent clopidogrel activation by omeprazole.¹⁶

A large proportion of the US population uses nonprescription medications. In fact, about half of adults aged 65 and older regularly use over-the-counter medications.¹⁰ Research regarding the clinical benefit of herbal medications and supplements is limited. However, the increasing popularity of these supplements has spurred recent studies examining some of the most widely used supplements, such as chondroitin sulfate and St. John's wort, which is often taken by women for menopausal symptoms. St. John's wort can decrease absorption while increasing clearance of prescription drugs such as immunosuppressants and antiretrovirals, leading to lower plasma concentrations and efficacy.¹⁷ In addition, St. John's wort may also contribute to serotonin syndrome, a potentially life-threatening adverse drug reaction, when used in combination with other serotonergic drugs.¹⁸ The lack of information regarding potential side effects, drug interactions, and adverse drug events associated with supplements and herbal medications complicates medication review in older surgical patients.

Table 3 Drug Interactions Involving the Cytochrome P-450 Enzyme System⁶⁷

Enzyme	Potent Inhibitors	Potent Inducers	Substrates
CYP1A2	Amiodarone, cimetidine, ciprofloxacin	Carbamazepine, phenobarbital, rifampin, tobacco	Caffeine, clozapine, theophylline
CYP2C9	Amiodarone, fluconazole, fluoxetine, metronidazole, trimethoprim-sulfamethoxazole	Carbamazepine, phenobarbital, phenytoin, rifampin	Carvedilol, celecoxib, glipizide, ibuprofen, irbesartan, losartan
CYP2C19	Fluvoxamine, isoniazid	Carbamazepine, phenytoin, rifampin	Omeprazole, phenobarbital, phenytoin
CYP2D6	Amiodarone, cimetidine, diphenhydramine, fluoxetine, paroxetine, quinidine, terbinafine	No significant inducers	Amitriptyline, carvedilol, codeine, donepezil, haloperidol, metoprolol, paroxetine, risperidone, tramadol
CYP3A4 and CYP3A5	Clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole	Carbamazepine, <i>Hypericum perforatum</i> (St. John's wort), phenobarbital, phenytoin, rifampin	Alprazolam, amlodipine, atorvastatin, diazepam, estradiol, simvastatin, sildenafil, verapamil, zolpidem

Medication Reconciliation

Medication reconciliation is a formal process of identifying the most complete and accurate list of medications a patient is taking and using that list to provide correct pharmacotherapy for the patient anywhere within a health care system. The goal of medication reconciliation, put simply, is to eliminate unexplained differences among documented medication regimens across the continuum of care. Such discrepancies are, unfortunately, very common, occurring in up to two thirds of inpatients.¹⁹ The elderly surgical patient is particularly vulnerable as both age (odds ratio 1.16 per 5-year increase in age) and admission to a surgical service (odds ratio 3.31) have been identified as independent risk factors for medication discrepancies.²⁰ Unexplained differences in admission medications most commonly involve cardiovascular drugs.

The perioperative period represents a transition from one level of care to another, usually from an outpatient to an inpatient setting or, in a significant fraction of elderly adults, from a long-term care facility to an inpatient setting. Often certain outpatient medications, most notably anticoagulants or antiplatelet agents, are deliberately discontinued in preparation for surgery and must be thoughtfully reinstated postoperatively. New medications, such as analgesics and antibiotics, may be initiated. Opportunities for medication reconciliation and, thus, the avoidance of preventable medication errors include admission to the acute care setting and transfer or discharge to a lower level of care. We have already discussed the importance of preoperative medication assessment. At discharge, verification of the indication or pertinent diagnosis for each medication and duration of treatment, when applicable, is also essential. For example, in the event that a surgical patient develops a perioperative infection, the indication and duration of treatment of the antibiotic should be clearly labeled on the medication at the time of discharge. In this way, the complexity of medication management may be reduced for the other health care providers as well as patients and their families during the period of recovery.

Guidelines for Medication Use in the Elderly

Although a large number of medications are prescribed for the elderly, few guidelines exist for appropriate medication use in this population. Most clinical guidelines regarding

medication use arise from studies of young, generally healthy adults. Elderly individuals, particularly those older than 80 and medically complex frail elderly patients, are underrepresented in clinical drug trials; thus, the primary literature on best medication practices in this group is limited.

The Beers criteria were first introduced in 1991 as a screening tool to be used in nursing home patients and consisted of specific drugs or drug classes that should be avoided in the elderly.²¹ In 2003, the Beers criteria were updated to reflect modern medication use patterns [see Table 4] and to describe specific drug-disease combinations that should be avoided in the elderly.²² Common medication-related pitfalls in elderly surgical patients include the following:

- *Administration of diphenhydramine (Benadryl) for insomnia.* The anticholinergic effect greatly increases the risk of delirium in hospitalized elderly patients.²³
- *Administration of long-acting benzodiazepines (chlordiazepoxide, diazepam) for agitation.* These agents may cause prolonged sedation lasting for days. It is preferable to substitute short-acting benzodiazepines (lorazepam, oxazepam) at low dosages in the elderly.
- *Administration of meperidine for postoperative pain.* Meperidine is associated with delirium, hallucinations, and inadequate pain relief. Accumulation of its metabolite, normeperidine, may lead to convulsions.²⁴
- *Administration of metoclopramide (Reglan) as an antiemetic in patients with Parkinson disease.* Antidopaminergic effects may exacerbate symptoms of Parkinson disease.
- *Administration of calcium channel blockers, anticholinergics, and tricyclic antidepressants in patients with constipation.* These agents may exacerbate constipation.

Specific patient characteristics associated with increased risk of medication-related adverse events include six or more medical diagnoses, receipt of more than 11 total doses of medications per day, receipt of more than nine different medications, a history of prior adverse drug events, patients with a low body mass index, age greater than 85 years, and creatinine clearance less than 50 mL/min. Many, if not all, of these characteristics could pertain to the older patient undergoing elective or emergent surgery.

The Assessing Care of Vulnerable Elders or (ACOVE) project was launched in 2001 to develop a comprehensive set of quality assessment tools for community-dwelling persons

Table 4 Updated (2002) Beers Criteria for Potentially Inappropriate Medication Use in Older Adults²²

Drug	Category	Concern
Pentazocine (Talwin)	Opioid	More adverse CNS effects than other narcotic drugs
Meperidine (Demerol)	Opioid	Ineffective orally; may cause confusion; better alternatives exist
Naproxen (Naprosyn, Aleve), oxaprozin (Daypro), piroxicam (Feldene)	NSAID	Longer half-life; non-COX selective; long-term use at full dosages may produce GI bleeding, renal failure, hypertension, and heart failure
Indomethacin (Indocin)	NSAID	Produces the most CNS adverse effects among NSAIDs
Ketorolac (Toradol)	NSAID	May cause GI bleeding as many elderly patients have asymptomatic GI pathologic conditions
All barbiturates (unless used to control seizures)	Sedative/hypnotic	Highly addictive; cause more adverse effects than other sedative/hypnotic drugs in elderly patients
Flurazepam (Dalmane), chlordiazepoxide (Librium), diazepam (Valium)	Benzodiazepine	Very long half-life in elderly patients (often several days), producing prolonged sedation and increased risk of falls
Trimethobenzamide (Tigan)	Antiemetic	Limited effectiveness, extrapyramidal adverse effects
Amitriptyline (Elavil)	Antidepressant	Strong anticholinergic effect, sedation
Doxepin (Sinequan)	Antidepressant	Strong anticholinergic effect, sedation
Methocarbamol (Robaxin), carisoprodol (Soma), cyclobenzaprine (Flexeril), oxybutinin (Ditropan), orphenadrine (Norflex)	Muscle relaxants and antispasmodics	Anticholinergic effects, sedation, weakness; limited effectiveness in elderly patients
Chlorpheniramine (Chlor-Trimeton), diphenhydramine (Benadryl), hydroxyzine (Vistaril and Atarax), promethazine (Phenergan)	Antihistamines	Strong anticholinergic effects; nonanticholinergic antihistamines (loratadine, cetirizine) are preferred in treated elderly patients with allergic reactions
Doxazosin (Cardura)	Antihypertensive	Potential for hypotension, dry mouth, and urinary problems
Short-acting nifedipine (Procardia and Adalat)	Antihypertensive	Potential for hypotension and constipation
Clonidine (Catapres)	Antihypertensive	Potential for orthostatic hypotension and CNS adverse effects
Disopyramide (Norpace)	Antiarrhythmic	Potent negative inotrope; may induce heart failure in elderly patients; strong anticholinergic effect
Ticlopidine (Ticlid)	Antiplatelet	More toxic and less effective than aspirin; safer alternatives exist
Dicyclomine (Bentyl), propantheline (Pro-Banthine), belladonna alkaloids (Donnatal)	GI antispasmodic drugs	Limited effectiveness; strong anticholinergic effects
Chlorpropamide (Diabinese)	Antidiabetic	Long half-life; risk of prolonged hypoglycemia in elderly patients; may cause SIADH
Bisacodyl (Dulcolax)	Laxative	Long-term use may exacerbate bowel dysfunction
Cimetidine (Tagamet)	Histamine-2 blocker	CNS adverse effects, including confusion
Desiccated thyroid	Hormone	Concerns about cardiac effects; safer alternatives available.
Nitrofurantoin (Macrochantin)	Antibiotic	Potential for renal impairment; safer alternatives available

CNS = central nervous system; COX = cyclooxygenase; GI = gastrointestinal; NSAID = nonsteroidal antiinflammatory drug; SIADH = syndrome of inappropriate antidiuretic hormone.

65 years and older who are at high risk for death or functional decline.²⁵ The quality indicator domains, developed through literature review and expert panel consideration, range broadly across topics such as fall prevention, management of diabetes mellitus, and end-of-life care. A specific domain concerns appropriate medication use in the elderly.²⁶ These indicators focus on clearly identifying indications for medications, avoiding inappropriate medications according to the Beers criteria, patient or care provider education, documentation of medications, and drug monitoring after prescribing. In view of the increased demand for surgical services in the older

population, McGory and colleagues from UCLA have specifically developed quality indicators for elderly patients undergoing abdominal operations.^{27,28} Quality indicators pertaining to medication use in elderly surgical patients are listed in Table 5.

Perioperative Medications and Cognitive Dysfunction in the Elderly

From the perspective of the patient and the patient's family, one of the most important perioperative concerns in the care

Table 5 Quality Indicators for Pharmacologic Care in Elderly Patients^{26,28}

Preoperative Medication Management
IF an elderly patient is undergoing a major abdominal operation and is taking one of the following classes of medications, THEN specific instructions regarding preoperative management of the following classes of medications should be given to the patient: a. Anticoagulation medications b. Diabetes medications c. Cardiovascular medications d. Hormonal medications e. Herbal medications f. Over-the-counter medications
Perioperative Beta Blockade
IF an elderly patient is undergoing a major abdominal operation and meets the criteria for perioperative beta blockade, THEN, unless contraindicated, beta-blocker therapy should be initiated prior to operation.
IF an elderly patient undergoes a major abdominal operation and meets the criteria for perioperative beta-blockade, THEN, unless contraindicated, beta-blocker therapy should be continued postoperatively at least until discharge from the hospital.
Bowel Preparation
IF an elderly patient is undergoing a major abdominal operation and requires a mechanical bowel preparation, THEN the patient should be offered admission for the mechanical bowel preparation if he has any of the following and has no support at home: a. Impaired functional status with dependence in one or more activities of daily living b. Impaired cognition c. Inability to ambulate d. History of previously failed bowel preparation
Prophylaxis for Endocarditis
IF an elderly patient is undergoing a major abdominal operation and has valvular or congenital heart disease, an intracardiac valvular prosthesis, hypertrophic cardiomyopathy, mitral valve prolapse with regurgitation, or a previous episode of endocarditis, THEN endocarditis prophylaxis should be given.
Prophylaxis for Venous Thromboembolism
IF an elderly patient undergoes a major abdominal operation and does not have cancer or previous venous thromboembolism, THEN preoperative and postoperative deep vein thrombosis prophylaxis should be provided with low-dose unfractionated heparin or low-molecular-weight heparin.
IF an elderly patient undergoes a major abdominal operation and has cancer or previous venous thromboembolism, THEN preoperative and postoperative deep vein thrombosis prophylaxis should be provided with low-dose unfractionated heparin or low-molecular-weight heparin, in addition to mechanical prophylaxis (intermittent pneumatic compression or graduated compression stockings, or both).
Drug Indication
IF an elderly patient is prescribed a new drug perioperatively, THEN the prescribed drug should have a clearly defined indication documented in the record BECAUSE the medication may have been prescribed for an indication that was unclear or transient.

Table 5 Continued

Medication Reconciliation and Patient Education
IF an elderly patient undergoes a major abdominal operation, THEN the inpatient medical record should contain the most recent outpatient medications with dosages.
IF an elderly patient undergoes a major abdominal operation, THEN the patient or caretaker should receive the following: a. A complete list of all medications and dosages to continue on discharge from the hospital. b. A discussion with the patient or caretaker about the purpose of the drug, how to take it, and the expected side effects or important adverse reactions for all medications prescribed for outpatient use.
Avoiding Inappropriate Medications
IF an elderly patient undergoes a major abdominal operation, THEN the patient should not be prescribed any potentially inappropriate medications according to the Beers criteria, unless documented why the medication is appropriate.

of the elderly is the goal of returning to independent living. Postoperative delirium and postoperative cognitive dysfunction have both been found to predict increased morbidity and poor functional recovery after surgery,^{29,30} highlighting the central role of thoughtful perioperative medication management in older patients.

Postoperative delirium (POD) is defined as a transient confusional state with alterations in attention and consciousness.³¹ In contrast, postoperative cognitive dysfunction (POCD) is a more persistent problem defined by changes in cognitive performance. The *Diagnostic and Statistical Manual of Mental Disorder*, fourth edition (DSM-IV), recognizes POCD as a neurocognitive disorder with symptoms including difficulty staying focused on tasks and declines in learning, memory verbal abilities, perception, attention executive functions, and abstract thinking. The diagnosis of POCD requires preoperative neuropsychological testing to establish a baseline and postoperative testing to delineate the decline in cognitive function. Elderly patients are more susceptible to developing both POD and POCD.^{32,33} After noncardiac surgery, the incidence of POD ranges from 10 to 60%, whereas that of POCD ranges from 7 to 26%.^{34,35} These figures are higher after cardiac surgery, where the incidence of POD ranges from 25 to 80%, whereas that of POCD ranges from 3 to 47%.³⁶ Because POD and POCD occur so commonly in the elderly, the cumulative societal costs attributable to these potentially avoidable conditions are significant. POD has been linked to higher mortality rates, increased length of hospitalization, and increased costs of care.³⁷

The etiology of POD and POCD is still not well understood. However, there is consensus that medications, patient comorbidities, and the type of surgery all play an important role in their incidence.³⁸ Among elderly surgical patients, perioperative use of opioid analgesics, sedative-hypnotics, antihistamines, and anticholinergics is associated with POD and POCD. The specific drugs that should be avoided have been discussed above. Other contributing factors include increasing age, preoperative cognitive impairment or prior history of delirium, anemia, pain, respiratory complications, admission to the intensive care unit, infection, metabolic

derangements, and intraoperative hemodynamic fluctuations.^{30,32} Interestingly, a systematic review of anesthetic techniques did not demonstrate a benefit from neuraxial anesthesia when compared with general anesthesia in decreasing the incidence of postoperative cognitive dysfunction.³⁹

Perioperative medications play an important role in both the causation and possible prevention of POD and POCD. Although consideration to avoiding medications associated with delirium and cognitive dysfunction should, no doubt, be taken, it is difficult, if not impossible, to entirely avoid certain classes of medications, such as opioids, benzodiazepines, and other sedative-hypnotics, in the care of the elderly surgical patient. Likewise, polypharmacy and its associated risks are to some degree unavoidable in the perioperative setting. Therefore, the surgical team is best served by understanding the pharmacology of common perioperative medications in the setting of age-related physiologic changes, with the goal of making appropriate medication choices and dose adjustments to minimize drug-associated morbidity.

PHARMACOTHERAPY OF POSTOPERATIVE DELIRIUM

When strategies for avoidance of postoperative delirium have failed, pharmacotherapy may be initiated alongside other measures, such as preserving the sleep-wake cycle and maximizing cues that orient the patient to time, place, and person (it is often helpful to engage the family in orienting the patient to self in the context of familiar relationships). Systematic reviews indicate that low-dose haloperidol (< 3.0 mg/day) is equally efficacious as the atypical antipsychotics olanzapine and risperidone in the treatment of delirium. High-dose haloperidol (> 4.5 mg/day) is associated with extrapyramidal adverse effects (parkinsonism) and should be avoided. Benzodiazepines can worsen confusion and sedation in patients with non-alcohol withdrawal delirium and should also be avoided. Our preference is to initiate low-dose risperidone (0.5 mg b.i.d.) and wait 24 hours for clinical effect. Short courses lasting fewer than 5 days are generally sufficient.

Specific Drug Classes and the Elderly Surgical Patient

OPIOIDS

Opioids, such as fentanyl, meperidine, morphine, and hydromorphone, are the main mediators of analgesia and are used for nearly all patients in the perioperative setting. Their high lipid solubility accounts for their ability to rapidly cross the blood-brain barrier and bind to opioid receptors within the CNS. High lipid solubility also allows these compounds to distribute into adipose tissue. Given that the body composition of older adults is characterized by a relatively high proportion of adipose tissue, the volume of distribution for opioids is markedly increased, resulting in slower clearance.⁴ Decreased hepatic metabolism in the elderly further contributes to delayed clearance of these agents. Opioids exhibit a high degree of protein binding and are therefore affected by reduced hepatic synthetic function, particularly in malnourished patients. The increased unbound drug fraction leads to increased potency for a given dose of opioids.

Morphine exhibits a unique pharmacokinetic property not shared by the other opioids in that both the native drug

and its metabolite, morphine-6-glucuronide, have analgesic properties. Morphine-6-glucuronide is primarily eliminated by the kidney. Patients with renal insufficiency may have impaired elimination of this morphine metabolite, which may partially account for the relatively augmented analgesic effect from a given dose of morphine in the elderly population.⁴⁰ On the pharmacodynamic side of the equation, the aging brain is more sensitive to opioids irrespective of changes in drug disposition as predicted by altered physiology and pharmacokinetics.⁴¹ Dosage requirements for morphine, fentanyl, alfentanil, and remifentanyl have been shown to be roughly decreased by half.⁴²

SEDATIVES AND HYPNOTICS

Benzodiazepines, such as midazolam, diazepam, and lorazepam, are commonly administered in the perioperative period to treat anxiety and agitation. They act by enhancing the inhibitory effect of γ -aminobutyric acid (GABA) within the CNS. Like opioids, benzodiazepines are characterized by high lipid solubility, high protein binding, and predominantly hepatic metabolism. All of these factors contribute to a reduced rate of clearance in the elderly that mandates dose reduction.

Pharmacodynamic evidence also shows an increased sensitivity of older patients to benzodiazepines. Age-dependent changes in the number of GABA type A receptors have been demonstrated and may be responsible for alterations in drug sensitivity.⁴³ A 50% reduction in midazolam dosing should be considered in patients older than 70, and a 75% reduction should be considered in those older than 90.⁴²

INHALATIONAL ANESTHETIC AGENTS

Anesthetic drugs can be generally categorized as inhalational or intravenous. Contemporary inhalational drugs such as sevoflurane, desflurane, and isoflurane are delivered with an anesthesia machine via an airway conduit. Dosage in terms of partial pressure can be easily adjusted and titrated by the anesthesiologist using an agent-specific vaporizer. Inhaled anesthetic requirements are usually described in terms of the minimum alveolar concentration (MAC) that prevents movement in response to noxious stimulation. MAC declines by roughly 0.6% for each year above age 40, as shown in Figure 1,⁴⁴ a phenomenon reflecting the increased sensitivity of the aging brain to inhalational anesthetic agents. The mechanisms underlying age-related changes in sensitivity to these drugs remain unknown. However, declining neuronal bioenergetics attributable to acquired mutations in mitochondrial DNA and age-related oxidative stress were both recently shown to play a potential role.⁴⁵

Inhalational anesthetics are characterized by high lipid solubility. Recovery from inhalational anesthetics may thus be prolonged in the elderly because of their increased body fat, resulting in a higher volume of distribution. Desflurane, which is the least lipid soluble of the contemporary inhalational anesthetics, may be the agent of choice for elderly patients.

INTRAVENOUS ANESTHETIC AGENTS

Intravenous anesthetics include sodium thiopental, etomidate, and propofol. In general, they facilitate GABA-mediated inhibitory neurotransmission within the reticular

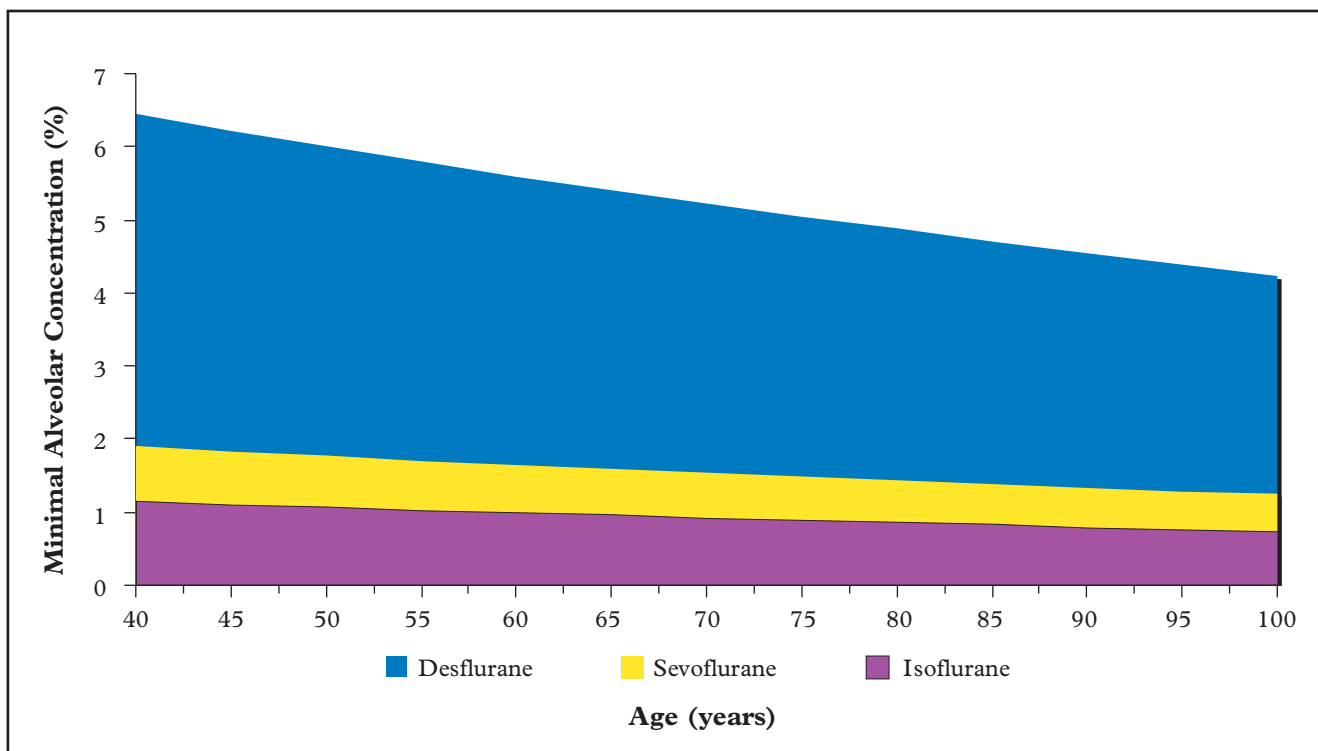


Figure 1 Minimal alveolar concentration (MAC) as a function of age. The MACs for desflurane, sevoflurane, and isoflurane decrease by about 6% per decade above the age of 40 years. The age-adjusted MAC values for this graph are based on the formula $\text{MAC fraction} = 1.32 \times 10^{-0.003 \times \text{age}}$, where MAC is the MAC fraction based on 1 MAC = MAC at age 40 years. We assume MAC at age 40 years for desflurane, sevoflurane, and isoflurane to be 6.45, 1.9, and 1.2%, respectively. Data and formula are from Eger.⁴⁴

activating system, the area of the brain principally involved in regulating arousal. Their high lipid solubility allows rapid penetration into the CNS and thereby facilitates rapid onset of action for anesthesia induction. High lipid solubility also results in a high volume of distribution over time. However, during the immediate period of anesthesia induction, only the plasma concentration of the anesthetic agent drives CNS penetration. Therefore, the initial volume of distribution is small, especially in the elderly with decreased total body water, resulting in a higher plasma concentration for a given dose. High protein binding is a characteristic of thiopental and, to a lesser extent, etomidate. In the setting of low serum albumin in the elderly, we observe the recurring theme of an increased fraction of unbound drug, resulting in increased potency for a given dose. Both thiopental and etomidate are hepatically cleared. The age-adjusted dose for both agents is therefore reduced by roughly 30 to 50%.⁴⁶

In contrast to what is observed with inhalational anesthetics, end-organ sensitivity to thiopental and etomidate does not appear to change with age, as confirmed by pharmacodynamic studies.⁴⁷ Thus, the dose required to achieve anesthesia using thiopental or etomidate is reduced solely as a function of pharmacokinetic principles.

Propofol is perhaps the most commonly used modern intravenous anesthetic for induction of general anesthesia. The high lipid solubility of propofol results in rapid onset of action. Awakening from a single bolus dose is more rapid and accompanied by less of a “hangover effect” than recovery

from thiopental or etomidate. Although these characteristics seem to make propofol more favorable in the elderly, compared with thiopental and etomidate, propofol causes more cardiovascular depression.⁵ Propofol causes a dose-related drop in blood pressure that results primarily from a decline in systemic vascular resistance. Pharmacokinetic evidence supports the need for reduced dosing of propofol in the elderly. As seen with the other intravenous anesthetic agents, propofol displays the triad of small initial volume of distribution, high protein binding, and hepatic metabolism. The half-life of propofol is prolonged in elderly individuals.⁴ For these reasons, a propofol dose reduction of 30 to 50% is prudent.⁴⁶ The clinical pharmacology of anesthetic agents in the elderly is summarized in Table 6.

NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents are ionized, highly water-soluble compounds that have a small volume of distribution, particularly in elderly patients, who possess a reduced extracellular fluid volume.⁴⁸ A delayed onset of action for most of these drugs has been attributed to decreased cardiac output and decreased regional blood flow to skeletal muscle. The duration of neuromuscular blockade in the elderly varies according to the specific agent. Aminosteroids, such as pancuronium, vecuronium, and rocuronium, undergo organ-dependent clearance by the kidney and, to a lesser extent, the liver. The duration of these agents, as measured by their recovery indices, can be increased by as much as 200% in the elderly when compared with young adults.⁴⁹

Table 6 Clinical Pharmacology of Anesthetics and Analgesics in the Elderly

Drug	CNS Sensitivity	Pharmacokinetics	Dose Adjustment
Inhalational anesthetics	↑		↓
Thiopental	↔	↓ initial distribution volume	↓
Etomidate	↔	↓ initial distribution volume	↓
Propofol	↑	↓ initial distribution volume	↓
Midazolam	↑	↓ clearance	↓
Morphine	↑	↓ clearance	↓
Hydromorphone	↑	↓ clearance	↓
Fentanyl	↑	↓ clearance	↓

CNS = central nervous system.

In contrast, newer (and more costly) benzylisoquinolinium compounds, such as atracurium and cisatracurium, are cleared in an organ-independent fashion via Hofmann degradation and ester hydrolysis. The recovery period for these agents is therefore not significantly prolonged in the elderly. Likewise, the recovery period for succinylcholine, a depolarizing relaxant, is not different in elderly patients. No changes in the sensitivity of the neuromuscular junction to blocking agents with age have been demonstrated. Thus, the clinical differences observed with neuromuscular blocking agents in the elderly are purely ascribed to pharmacokinetic alterations.

Regional versus General Anesthesia in the Elderly Patient

In the elderly population, postoperative complications most commonly involve neurologic, pulmonary, and cardiovascular compromise. When feasible, regional anesthesia has many purported benefits over general anesthesia for the elderly. Established benefits involving the CNS include reduced stress, decreased postoperative pain, decreased opioid requirements, and the potential to reduce or avoid anesthetic agents.⁵⁰ In regard to the pulmonary system, regional anesthesia may permit avoidance of endotracheal intubation and mechanical ventilation, thus reducing respiratory complications such as pneumonia and respiratory depression.⁵¹ From a cardiovascular standpoint, the superior analgesia provided by a regional technique over intravenous or oral opioids may reduce myocardial stress, thereby decreasing the incidence of postoperative cardiac events.⁵² Despite these benefits, no survival advantage has been demonstrated for regional or epidural anesthesia when compared with general anesthesia. As mentioned above, multiple studies comparing intravenous opioid analgesia with epidural analgesia in the elderly showed no significant difference in regard to postoperative mental capacity and cognitive function.³⁸

Antibiotic Use in the Elderly Surgical Patient

Optimal perioperative antibiotic management in elderly patients is, in some respects, similar to that applicable to the general adult population. Prophylactic antibiotics should be administered within 1 hour prior to skin incision and

discontinued within 24 hours after surgery in keeping with the Surgical Care Improvement Project performance measures.⁵³ The consequences for failing to follow these guidelines appear to be more severe in the elderly. Older patients who did not receive appropriately timed preoperative antibiotics were found to have a twofold increase in the 60-day mortality rate following general or orthopedic surgery in a matched control study.⁵⁴ Timely discontinuation of prophylactic antibiotics is essential to minimizing the risk of *Clostridium difficile* colitis, a condition that is both disproportionately common and disproportionately lethal in older adults.⁵⁵

Drug-drug interactions are a concern when administering antibiotics for both prophylaxis and the treatment of established infections. Antianaerobic second-generation cephalosporins that possess an *N*-methylthiotetrazole side chain, such as cefamandole and cefotetan, can potentiate the anticoagulant effect of warfarin. Aminoglycosides and vancomycin are both associated with nephrotoxicity and ototoxicity. Nephrotoxicity can be exacerbated by coadministration of NSAIDs as well as radiographic contrast agents, whereas ototoxicity can be exacerbated by concurrent loop diuretic use.⁵⁶ Although aminoglycosides have been, to some degree, replaced by fluoroquinolones in the treatment of resistant gram-negative infections, the fluoroquinolones are not without their own dangers. Gatifloxacin, levofloxacin, and moxifloxacin prolong the QT interval and have been associated with torsades de pointes, particularly when administered in conjunction with class III antiarrhythmic drugs such as ibutilide, sotalol, and amiodarone.^{57,58}

Perioperative Management of Anticoagulation and Antiplatelet Therapy in the Elderly

A significant fraction of elderly surgical patients receive chronic warfarin anticoagulation. The most common indication for anticoagulation is atrial fibrillation, which is associated with advancing age and male sex. The prevalence of atrial fibrillation in persons aged 80 and above is approximately 10%.⁵⁹ Because anticoagulation is recommended only for patients at intermediate or high risk for ischemic stroke according to the Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke (doubled) risk scoring system (CHADS₂), slightly more than half of all patients with atrial fibrillation are maintained on warfarin.⁶⁰

Warfarin should generally be stopped 5 days prior to major elective surgery. Bridging therapy with either intravenous unfractionated heparin or, more commonly, subcutaneous therapeutic dose low-molecular-weight heparin (e.g., enoxaparin 1 mg/kg b.i.d.) is recommended for patients with mechanical heart valves or atrial fibrillation with a moderate to high risk of thromboembolism.⁶¹ No bridging therapy is required in patients with a low risk of thromboembolism.

When considering the timing of resumption of anticoagulation postoperatively, it is important to remember that, in almost all cases, the risk of death or disability attributable to major hemorrhage far exceeds that attributable to thromboembolism.⁶² For this reason, it is recommended that initiation of therapeutic doses of unfractionated or low-molecular-weight heparin be delayed 24 to 72 hours after surgery or until that time at which hemostasis is secured. Warfarin, because of its delayed onset of action, can generally be resumed 12 to 24 hours after surgery.⁶¹

In contrast to warfarin, which is a vitamin K antagonist, the novel orally bioavailable anticoagulants dabigatran, rivaroxaban, and apixaban act by directly inhibiting thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban). They carry the advantages of rapid onset of action and predictable anticoagulant effect, such that monitoring of the international normalized ratio is not necessary. These agents may achieve Food and Drug Administration approval soon after the

publication of this chapter. The elderly have already been identified as an at-risk population for adverse drug events involving novel oral anticoagulants, which all undergo metabolism by CYP enzymes prior to renal elimination.⁶³ They also interact with aspirin as well as NSAIDs, which are frequently prescribed for arthritis relief in the elderly.

The majority of coronary stents being placed during modern percutaneous coronary interventions are drug-eluting stents.⁶⁴ As stent thrombosis is associated with high rates of myocardial infarction and death,⁶⁵ it is currently recommended that patients receiving drug-eluting stents receive an uninterrupted 12-month course of dual-antiplatelet therapy with aspirin and clopidogrel. For bare metal stents, a minimum of 6 weeks is recommended.⁶¹ Elective noncardiac surgery should be postponed beyond this time period whenever possible.

VENOUS THROMBOEMBOLISM PROPHYLAXIS

The risk of thromboembolism increases with age. In elderly patients at moderate or high risk for perioperative venous thromboembolism, pharmacologic prophylaxis with low-dose unfractionated heparin or low-molecular-weight heparin should be considered. Age-associated reductions in renal function can impair the clearance of low-molecular-weight heparins.⁶⁶

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10 ADVANCE DIRECTIVES, DO NOT RESUSCITATE ORDERS, AND POWER OF ATTORNEY FOR HEALTH CARE

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In 1975, Karen Ann Quinlan suffered an anoxic brain injury that left her neurologically devastated.¹ Her parents, devout Catholics, fought her physicians (who insisted on continuation of life-supporting therapy because she did not meet the criteria for brain death) all the way to the New Jersey Supreme Court. Julia and Joseph Quinlan requested discontinuation of life-supporting therapy, believing that Karen would not have wanted to continue life without cognitive function attached to a ventilator. In 1976, the court decided in favor of Karen's parents; however, when Karen's physicians discontinued the ventilator, she continued to live without its support. Although she died 9 years later in a nursing home from fulminant sepsis associated with her persistent vegetative state, her case started a national discussion about end-of-life care, withdrawal of life-supporting therapy, and protection of patient preferences in the setting of incapacity.

As they watched the Quinlan case unfold, many Americans became concerned about their own ability to protect personal preferences for end-of-life therapies in the setting of a future event that would render them unable to state their choices. In the 1970s, respect for patient autonomy had emerged as the dominant concept for the ethical care of patients. The Quinlan case raised concern that patients' autonomy may no longer be respected once they lost the capacity to state their choices, particularly choices about long-term, invasive therapies such as ventilatory support or dialysis. Although Karen Ann Quinlan's clinical course did not evolve in line with expectations, the legacy of her ordeal is the resulting national interest in documenting future wishes for life-supporting therapy in the event that a person can no longer speak for himself or herself.

Advance Directives and Living Wills

An advance directive is a legally binding document designed to express patients' treatment preferences when they are no longer able to do so themselves. Typically, the advance directive assumes the form of a living will whereby the "will" is carried out while the patient is still alive but is unable to make treatment decisions. Other forms of advance directives include but are not limited to a directive to forego cardiopulmonary resuscitation (CPR) in the event of cardiac arrest (do not resuscitate [DNR]) and designation of a health care decision maker (durable power of attorney [POA] for health care).

LIVING WILL

In its most simple form, the living will is a set of conditional instructions formally documented by a patient to enumerate his or her wishes in the setting of future incapacity. The primary aim of the directive is to protect patient autonomy: the patient's right to choose or refuse therapy at any given time. Although a majority of advance directives express wishes for limitation of life-supporting therapy, it should not be assumed that all advance directives state a preference for withdrawal of life-supporting therapies as some patients may prefer aggressive therapies in nearly all clinical situations.

The living will is structured in language designed to ensure that the patient's treatment preferences are honored [see *Figure 1*]. For example, many directives will provide a conditional statement such as "In the event that I develop a terminal illness . . ." or "In the case that I suffer permanent brain injury such that I no longer have cognitive functioning . . ." These hypothetical states are then followed by a list of the patient's preferences for continuation or withdrawal of life-supporting therapies. For example, "The following therapies should be continued: tube feedings and intravenous hydration" and "The following therapies should be discontinued: ventilator support, hemodialysis, and blood transfusions." Unfortunately, in practice, these hypothetical clinical states tend to be dominated by vague and nonspecific language that typically requires significant interpretation and abstraction of the patient's desires.²

Most advance directives are created with the assistance of the patient's primary care physician, nurse practitioner, social worker, lawyer, or clergy member. Nearly all hospitals receiving federal funding have access to resources to support their patients' creation of an advance directive [see Patient Self-Determination Act of 1990, *below*]. In addition, there are state-sponsored Web sites and government offices to assist patients in formulating their own advance directive (see <http://www.nationalhealthcaredecisionsday.org/resources.htm> and <http://www.caringinfo.org/stateaddownload>). Ideally, an advance directive is best created in consultation with a physician or other qualified health care provider who can both illustrate the clinical situations that patients might anticipate and discuss the advantages and disadvantages of treatment options. In this way, patients are more fully informed about their treatment choices and have greater potential to express their autonomous wishes for clinical states with which they may be unfamiliar.

9. STATEMENT OF DESIRES, SPECIAL PROVISIONS OR LIMITATIONS

This form is part of my Power of Attorney for Health Care. The following are some specific provisions for my health care agent(s) or others providing my care.

I, _____, have initialed or have had initialed for me each choice that represents my preferences for future medical care. I have drawn a line through any written instructions below that I do not want. These preferences should be considered by my physician and agent when I am incapable to make my own decisions. I have defined quality of life as meaningful interactions with my family, friends and environment.

CARDIOPULMONARY RESUSCITATION (CPR)

NOTE: My CPR preference may be reconsidered by my agent in light of my other instructions or new medical information, if I become incapable of making my own decisions. If I do not want CPR attempted, my physician should be made aware of the preference. A "No CPR" preference if indicated below will not, in itself, stop paramedics from attempting CPR in an emergency.

☐ I want Cardiopulmonary Resuscitation (CPR) attempted if my heart stops.

☒ I want CPR attempted if a successful attempt may result in the recovery of my ability to meaningfully interact with myself, my family, friends and environment. (The question of a meaningful recovery if my heart stops needs to be considered by me or my agent and physician before an emergency.) *If I have Alzheimer's, have had a severe stroke or have a terminal illness I do NOT want CPR.*

☐ I do not want CPR attempted if my heart stops.

☒ I want to be intubated and placed on a respirator if this may result in the recovery of my ability to meaningfully interact with myself, my family, friends and environment. (The question of a meaningful recovery needs to be considered by me or my agent and physician before an emergency.) *If I have Alzheimer's, have had a severe stroke or have a terminal illness I do NOT want to be intubated or on a respirator.*

☐ I do not want to be intubated or placed on a respirator.

LIFE PROLONGING TREATMENTS

☒ I reach a point when it is reasonably certain that I will not recover my ability to meaningfully interact with myself, my family, friends and environment, I want to have all treatments used to prolong my existence stopped or withheld. Treatments would include tube feedings, antibiotics, anti-arrhythmic drugs, kidney dialysis, IV's, and long term respirator.

PAIN CONTROL

☒ In the event that life-prolonging treatments are discontinued, I want medical and nursing care that will make me comfortable, even it hastens my death.

Figure 1 A living will designating conditions for resuscitation.

USE OF ADVANCE DIRECTIVES

There has been significant debate in the literature regarding the effectiveness of advance directives whereby many small investigations³⁻⁵ and one very large⁶ investigation of the use of advance directives showed minimal effectiveness of these documented preferences to limit life-supporting therapy. The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT) is a randomized, controlled trial that enlisted a trained nurse to facilitate and encourage communication about prognosis and preferences for end-of-life therapies (including creation of advance directives) between physicians and over 2,500 patients (in the intervention group) admitted to the intensive care unit (ICU).⁶ Despite this aggressive intervention, there was no

significant reduction in the provision of aggressive therapy at the end of life demonstrated by specific end points such as days in the ICU, number of days patients spent comatose before death, and even reported pain. This study called into question the effectiveness of advance directives and specifically raised concerns that active intervention to improve communication and elicit patient preferences could not reduce unnecessary and potentially unwanted care at the end of life. Although this study was criticized for using a potentially ineffective intervention (nurse advocate) rather than other mechanisms to change physician behavior (peer-to-peer education or key opinion leader demonstration),⁷ SUPPORT has been widely cited as evidence that advance directives are ineffective for protecting patient preferences regarding end-of-life therapy.

Recently, one robust study from the University of Michigan documented the value of advance directives.⁸ This study examined 3,746 retired citizens over a period of 6 years and found that just over 70% of patients died in the setting of physical incapacity to make personal health care decisions. For these patients, the advance directive was present 67% of the time and was in concordance with the care provided at the end of life based on retrospective interviews with family members. Although this study was unable to verify whether the care provided was truly in line with the preferences stated in the patient's directive, it is encouraging that the patients' surrogates found the advance directive informative and that, clinically, this was effective for limiting unwanted aggressive therapy at the end of life.

BARRIERS TO THE USE OF ADVANCE DIRECTIVES

Although a living will may provide important information about an incapacitated patient's preferences, there are many barriers to the effective use of written advance directives. Perhaps the most substantive barrier is that only a small proportion of the American population has a living will or advance directive. Reports vary on the percentage of Americans who actually have an advance directive, estimating that anywhere between 20 and 40% of citizens have either a living will or durable POA for health care.^{9,10} However, studies have documented that the percentage of patients who have an advance directive who are older or frail is substantially higher, on the order of 60 to 80%.^{8,11}

Other barriers to the use of advance directives exist. These barriers include a failure to understand the consequences of the decision to be made, a document that is vague or not applicable to the clinical condition at hand, inability to find the document when it is needed, and failure to update the advance directive as clinical conditions or patient preferences change over time. One additional barrier is the failure of the patient to discuss personal preferences with family members or failure to inform members of his or her decisions such that conflict arises when an unfamiliar or unprecedented choice has been documented. In this setting, family members who raise issues regarding the validity of the directive (rightly or wrongly) impede implementation of the directive as it was created.

PATIENT SELF-DETERMINATION ACT OF 1990

Increased recognition of the problem of underuse of advance directives arose in the late 1980s. Concerns grew that with improvements in technology, many elderly or terminally ill patients were receiving care they would have refused had they had an advance directive to delineate their choices. To reverse this trend, Congress enacted the Patient Self-Determination Act of 1990 (PSDA).¹² This law mandates that all health care facilities receiving federal funding (i.e., Medicare and Medicaid) inform patients that they have the right to accept or refuse care at any time. Although the law was designed to increase the use of advance directives, this mandate is distinctly limited in its scope. Hospitals are required only to inform the patient in writing that he or she has the right to have or create an advance directive, to offer information regarding the creation of such directives, and to ask patients whether they already have an advance directive.¹³ There is no requirement within the mandate to ask patients

directly whether they would like to create an advance directive at the time of the admission; the mandate requires only that the hospital provide information about the mechanics of creating an advance directive. Furthermore, there are no specifications about who should have this discussion with the patient, and as such, the PSDA is typically satisfied by answering one of many questions on the nursing intake form at the time of the patient's admission to the hospital.

Other initiatives to increase the use of advance directives have had success at the local and regional levels. One example of a successful program implemented at the state level is the Physician Orders for Life-Sustaining Treatment (POLST) project, which was started in Oregon in 1991 and implemented in 1995.¹⁴ This physician order sheet is linked physically (typically, the order set is located in the patient's place of residence) to the patient and is used to assert preferences for an array of life-supporting therapies, including CPR, tube feedings, and even antibiotics. Currently, seven states have adopted a POLST program (Washington, Oregon, California, West Virginia, California, Tennessee, and North Carolina) through either legislative mandate or regulatory oversight. Programs and program initiatives are different in each state, but the unifying dimension of each POLST program is the set of medical orders that clearly delineate issues such as "comfort measures," instructions for hospital transfer, and continuation or suspension of life-sustaining therapies frequently needed in patients with advanced progressive illness.¹⁵ A recent study demonstrated the effectiveness of this program for both documenting the care preferences of POLST participants and effecting limitations of unwanted life-supporting therapy while maintaining preferences for medical interventions for those who choose more aggressive care.¹⁶

On the local level, over 90% of the residents who die in La Crosse, Wisconsin, have an advance directive because of significant effort by local hospitals, concerned physicians, and health care providers.¹⁷ Gundersen Lutheran Hospital and its director of medical ethics, Dr. Bernard (Bud) Hammes, have spent over 15 years training social workers, nurses, physicians, and other providers to create advance directives with their patients using extensive conversations and involvement of family members to design a directive tailored more specifically to the patient's preferences than a typical living will. This initiative, called "Respecting Your Choices," overcomes the main barriers to advance directive use by creating consensus among family members, promoting the ready availability of these directives, and tailoring the proscribed treatments or limitations for therapy according to an informed patient's choice.¹⁸ The program is highly effective in establishing advance care planning for members of this community and preserving preferences for treatments at the end of life.

USE OF ADVANCE DIRECTIVES IN SURGICAL PATIENTS

To date, there is barely any information regarding how frequently surgeons use advance directives for their patients.¹⁹ Other than the literature regarding the use of DNR orders in the operating room (see below), little is known about how surgeons use advance directives or whether the presence of an advance directive influences surgical decision making. To date, the modest data available reveal a broad range of attitudes about advance directives whereby some surgeons report

routine inquiry and use of advance directives as an important part of their practice, whereas others see advance directives in direct conflict with the surgical plan.²⁰ Nonetheless, there is some information to suggest that surgeons value the utility of an advance directive as it can serve as a guide to patients' preferences in the postoperative setting when life-supporting therapy has become ineffective or patient survival is unlikely.²⁰

Two studies have attempted to implement increased use of advance directives for surgical patients by employing a nurse facilitator or consultant anesthesiologist to discuss advance directives during the patient's preoperative clearance visit.^{21,22} Although both studies were able to enhance the effectiveness of the relationship between the patient and the patient's health care POA, the surgeon was uniquely circumvented in both trials. As such, these interventions were unable to evaluate the effect of advance directives on surgical decision making or how patients' preferences for life-supporting therapy would be considered perioperatively.

Do Not Resuscitate Orders

A DNR order is another form of advance directive designed to protect and enhance patient autonomy. Although physicians frequently imply alternative meaning to a patient's DNR status,²³⁻²⁶ particularly inferences about the patient's goals of therapy, a DNR order indicates only that the patient does not want CPR in the event of a cardiac arrest. DNR orders are particularly desirable for patients for whom CPR is unlikely to provide an effective resuscitation. Patients who have terminal illness or are debilitated or frail may prefer to avoid the trauma and violence that accompanies the performance of chest compressions and intubation during the resuscitative efforts at the time of cardiac arrest.

There is significant confusion in practice regarding the meaning of DNR orders. This includes both making assumptions that the patient who has a DNR order does not want treatment for an acute or chronic condition²⁷ and failing to provide other components of the resuscitative effort (vasoactive agents, intubation, cardioversion) to patients who have DNR orders. In some institutions, the DNR form can read like a menu of interventions whereby patients, with their physician's help, are asked to check off therapies from a list of therapies that they do and do not want.²⁸ Remembering that DNR means simply "no CPR" can help prevent misapplication of the DNR directive during a critical moment when other lifesaving measures may be needed and would be in line with patient preferences. Patients who wish to avoid intubation, cardioversion, or injections of epinephrine should have this clearly stated in their chart and health care providers should be apprised of these choices.

Some patients with a poor long-term prognosis who would benefit from avoiding CPR during cardiac arrest do not have a DNR order.^{29,30} Sometimes this occurs because patients fear that their DNR status will translate a message about other therapies they would truly prefer, particularly aggressive therapy that may provide significant improvement in their quality of life. Also, this occurs because the patient or physician has an overly optimistic perception of the patient's prognosis or chance of survival based on assumptions about the patient's disease state. Additionally, some patients for whom

CPR is very unlikely to be successful refuse to change their resuscitation status because they are overly optimistic about the effectiveness of CPR. Although there are many possible reasons for this, the influence of the popular media cannot be overlooked. One study found that the success of CPR in television dramas was greater than 60%, whereas rates of actual in-hospital survival of cardiac arrest vary from 6 to 15%.³¹ Patients may be overly optimistic about their chances of surviving a cardiac arrest and as such are not willing to forego the opportunity to undergo what they believe to be a potentially lifesaving procedure.

DNR in the Operating Room

A decision to create a DNR order should result from a thoughtful and informative conversation between a patient, his family members or social support, and his physician. In this way, clarification of the directive to forego CPR in the event of a cardiac arrest and consideration of the patient's goals of therapy can be well delineated. A patient who chooses to forego CPR would not necessarily also choose to forego aggressive interventions to improve or prolong his or her life. As such, patients who have active DNR orders may desire and present for surgical therapy.³² This has led to a significant conundrum for surgeons and anesthesiologists who provide care for these patients.

In the operating room, patients frequently require intubation or vasoactive medications based on their anesthetic requirements. Furthermore, surgical therapy (apart from the anesthetic) has the potential to cause cardiac arrest depending on the patient's comorbidities or the type of surgery required (e.g., cardiac surgery). As such, surgeons and anesthesiologists alike have historically assumed that DNR orders should be suspended intraoperatively.³³ This stance may seem justified given that cardiac arrest in the operating room is frequently iatrogenic or potentially treatable and is certainly distinct from cardiac arrest that occurs outside the operating room. Nonetheless, assuming that all DNR orders should be suspended during an operation completely violates the patient's right to make an autonomous decision about his or her health care.

Although it may be perfectly appropriate to suspend a DNR order intraoperatively, this should be done only after the surgeon has a detailed discussion with the patient, his or her family, and the anesthesiologist.³⁴ The desire for a surgical procedure to improve quality of life while foregoing the additional trauma of CPR intraoperatively is not necessarily inconsistent with therapeutic goals and should be respected by both surgeons and anesthesiologists. The American Society of Anesthesiologists and the American College of Surgeons support patient autonomy in this setting and have codified this in their guidelines to physicians.^{35,36} The recommendation from both societies is to "review and reconsider" the order not to perform CPR prior to a surgical procedure. After involving the patient in the decision-making process in consultation with the anesthesiologist, a decision can be made to either suspend or continue the patient's DNR order intraoperatively.³⁷ The not uncommon practice of routinely suspending a patient's DNR order without first discussing this with the patient or by refusing to operate on a patient unless the DNR order is suspended should not be continued as this is a clear violation of patient autonomy.

Power of Attorney for Health Care

In conjunction with or instead of a living will, patients will frequently name a durable power of attorney for health care decision making (POA, DPOA, or, in some regions, DPHC). By appointing a dedicated surrogate decision maker, patients can avoid some of the problems of deciphering the vagaries of a specific clinical situation associated with the use of a living will. To be effective, patients should appoint a decision maker who understands their desires for medical therapy and their beliefs regarding the pursuit of life-supporting therapy. Ideally, the person appointed should be able to make decisions according to the preferences of the patient and in line with the patient's previously stated choices regarding life-supporting therapy.

DECISION-MAKING CAPACITY

When patients are unable to make decisions about their health care, surgeons should turn to the person designated as the patient's POA to obtain consent for therapy and to discuss the goals of care. It is not always obvious when patients are unable to make decisions about their health care; as such, it is important to consider the patient's capacity to make a decision, particularly when the decision the patient is making seems irrational or diametrically opposed to medical advice. It must be noted that decision-making capacity is distinct from competence. Competence is typically a legal determination made by a judge, and decision-making capacity is relegated to the physician³⁸ and is typically specific to the decision at hand, although it may apply to all medical decisions for a specific period of time.

Decision-making capacity is clearly defined as the patient's ability to decide according to his or her wishes as related to the specific medical decision at hand. To have decision-making capacity, the patient must understand the clinical choices presented, have insight into the consequences of the decision, be able to manipulate the information rationally, and be able to state his or her preferences.³⁹ (One helpful mnemonic for quickly assessing decision-making capacity in critical situations is CURVES: Choose and Communicate, Understand, Reason, Value, Emergency, and Surrogate.⁴⁰ Emergency refers to the emergency situation in which provision of care is required to prevent immediate loss of life or limb, a unique instance for which consent is implied or assumed when an appropriate surrogate decision maker cannot be found rapidly.)

By definition, patients heavily sedated in the ICU do not have decision-making capacity as they are unable to state their preferences even though they may understand the choices and consequences if they were not sedated to receive life-supporting therapy. Although determination of decision-making capacity for the unconscious patient is straightforward, there are many situations in which consultation from other health care providers is necessary to determine a patient's decision-making capacity. Although disagreement with recommended therapy is a sign that patients may not have decision-making capacity, it is important to note that simple refusal of medical therapy is not evidence of a lack of capacity. Furthermore, patients who acquiesce to medical therapy cannot be assumed to have capacity as well, although often it is more difficult to determine that they lack capacity in the setting of consent to medical care.

It is important to note that some patients who are legally competent to make decisions about other aspects of their life may have limited insight or understanding about the specific medical decision with which they are confronted. A noted example of this problem is the case of Mary Northern, a 72-year-old female who presented to a Tennessee hospital in 1978 with gangrenous feet. The patient was perfectly lucid and able to competently decide for herself regarding all other aspects of her life and care; nonetheless, she maintained a delusional belief that her feet were black from soot and dirt. The court decided in this case that the patient lacked the capacity to make a decision about amputation but did not lack the capacity to make other health care or personal decisions. Her delusion about the cause of her necrotic feet interfered with her ability to understand the critical nature of her illness. Without understanding and insight, the court declared that she did not have the decision-making capacity to refuse an amputation; however, the court affirmed her ability to decide about other aspects of her care, unrelated to treatment for her lower extremity gangrene.⁴¹

For help determining decision-making capacity, surgeons should turn to colleagues in psychiatry, neurology, social work, or psychology or obtain an ethics consultation. In turn, these consultants will assess the patient's mental functioning, cognition, and understanding and insight into the decision to be made. In some cases, it may be helpful to have more than one consultant evaluate and document the patient's capacity for decision making as the determination may be nuanced. Once it has been determined that the patient does not have the capacity to make a decision about treatment, a surrogate decision maker is required to make the decision for the patient.

ACTIVATION OF THE DURABLE POWER OF ATTORNEY

When it has been determined that a patient does not have decision-making capacity, the patient's durable POA (if the patient has named a POA) is "activated." Once the POA is activated, all medical decisions must be made by the POA unless the patient's POA is subsequently inactivated. Because of the potential to forget to inactivate the POA, in practice, it is unusual to activate a patient's POA when patients appear to be temporarily unconscious or heavily sedated in the ICU. In this setting, surrogate decision makers are still used for medical decision making; however, the formal activation of a POA does not occur. The process for activating a POA typically requires documentation in the patient's chart by more than one health care provider that the patient does not have decision-making capacity. Many states specify which health care providers have the expertise to formally determine capacity. In addition, hospitals may require completion of a specific form to activate the patient's POA. As this varies from state to state, it is helpful to refer to the policy of the hospital or institution where care is being provided to comply with specific policy. It is important to remember that the POA will need to be inactivated formally if the patient regains the capacity to make medical decisions. Failure to document resumption of capacity can interfere with the patient's right to make autonomous decisions.

SURROGATE DECISION MAKING

When patients do not have decision-making capacity, physicians are obliged to find someone who can make decisions

for the patient. If the patient has previously designated a durable POA for health care, the POA is the first person health care providers should turn to for decision making. Often the patient's POA is not the person who accompanied the patient to the hospital or may not be as emotionally close to the patient as other family members or friends. Although the POA has legal authority to make decisions for the patient, it is appropriate, if not essential, to involve other family members and close friends in the decision-making process, particularly for decisions about the withdrawal or continuation of life-supporting therapy.

A significant portion of patients will not have appointed a POA, and as such, a surrogate decision maker must be determined. In the state of Illinois, the list of potential surrogates is codified according to the following priority: the patient's guardian (if a guardian exists), spouse, adult son or daughter, parent, adult brother or sister, grandchild, close friend, or guardian of the estate.⁴² Although this is not codified quite so specifically in other states, many hospitals employ a similar priority status in their institutional policy regarding appropriate surrogates. Although this delineation is designed to give authority to those highest on the list, surgeons should recognize that those with lower status on the priority list may at times be better decision makers for the patient than an estranged spouse or family member who has had little to no recent contact with the patient. In addition, although decision making has the potential to create conflict, consensus among multiple interested parties is preferable to simply ceding authority to the surrogate decision maker highest on the list.

Once a surrogate has been designated, he or she will be asked to make medical decisions in accordance with choices the patient would have for himself or herself if he or she had the capacity to make a decision. Sometimes the patient will have previously documented or discussed his wishes for specific clinical situations with the surrogate. Often this is not the case, and the surrogate will have no direct information with which to make a decision. In this case, the surrogate will need to use his or her knowledge of the patient's values and goals to make a decision that is most likely to be in line with

the patient's preferences. This method for making a medical decision when specific choices are unknown is called "substituted judgment." If the surrogate is unfamiliar with the patient's values or is unable to use this information to make an informed decision, the surrogate should decide in accordance with what is in the patient's best interest (called the best interest standard).

Sometimes surrogates may be making decisions that seem inconsistent with the patient's best interest or contrary to the physician's impression of the patient's previously stated wishes. It is understandable that a patient's relative or friend may want to pursue aggressive therapy for his or her loved one. Often, with gentle guidance, the surrogate can be redirected to make a decision for the patient in line with the patient's preferences rather than in line with the desires of the decision maker. On rare occasions, a surrogate decision maker will decide in accordance with ulterior motives such as dependence on a social security check or other secondary gains. In this situation, the surrogate may need to be disqualified as a decision maker to establish an alternative surrogate who will honor the patient's preferences. Consultation with the ethics service or other institutional support for dispute reconciliation is recommended in such difficult cases.

Conclusion

Advance directives such as a living will, a DNR order, and a designation of a durable POA for health care are legally binding mechanisms to preserve patient autonomy when patients have lost decision-making capacity. Although these directives are frequently used to make decisions regarding life-supporting therapy, surgeons may also need to refer to these documents or to patients' surrogates for surgical decision making to treat patients in accordance with their autonomous wishes.

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12 TRANSPLANT IMMUNOLOGY: BASIC IMMUNOLOGY AND CLINICAL PRACTICE

Philip Wai, MD, and David P. Foley, MD

Engraftment of a transplanted organ into an allogeneic host triggers a cascade of immunologic responses in the host that are designed to facilitate graft rejection. Modern donor-to-host matching techniques and immunosuppression protocols have successfully tempered this natural immune response, so graft survival has dramatically improved. Currently, solid-organ transplantation has become the definitive therapy for decreasing mortality in patients with end-stage organ disease. However, transplant immunosuppression remains less than ideal because of its adverse effects, some of which include increased risks of opportunistic infections and malignancy. Optimizing graft survival by precisely downregulating the host response to graft rejection while preserving host immune defenses against pathologic and infectious agents remains poorly understood and elusive in current clinical practice.

In the following discussion, we have divided the chapter into two parts. The first part focuses on the basic immunology underlying alloantigen recognition and host response to a transplanted organ. The second part discusses the clinical management of donor organ and host compatibility in the context of kidney transplantation. Topics include graft rejection, recipient desensitization, and potential future approaches to manipulating allorecognition.

Transplant Immunology: Host versus Graft and the Basis of Allorecognition

Generation of a significant immune response against the transplanted graft involves sequentially coordinated events. First, recognition of the graft as nonself is mediated by the innate and adaptive immune responses. In the setting of deceased donor organ transplants, the initiation of this cascade begins in the deceased donor. Brain death results in significant hormonal and physiologic changes that elicit a profound inflammatory response in individual organs resulting in cellular injury prior to the preservation process. Organ preservation followed by a prolonged period of cold ischemia, surgical implantation, and reperfusion of the transplanted organ result in ischemia-reperfusion injury (IRI). IRI is a complex process in which cells of the innate immune system; neutrophils, macrophages, and natural killer (NK) cells become activated, migrate to the transplanted organ, and engender a marked inflammatory response. This response triggers the activation and maturation of antigen-presenting cells (APCs), leading to antigen processing, presentation, and recognition by the cells of the adaptive immune system. Second, recognition of alloantigen leads to activation of

antigen-specific T and B lymphocytes. At this step, modern immunosuppression strategies have been successful in altering the intracellular signaling mediated by the T cell receptor (TCR) complex (calcineurin) and the inhibition of costimulatory molecules (belatacept, alefacept). Third, graft rejection ultimately occurs when the activated lymphocytes bring about direct cellular damage through effector cells that include monocytes, cytolytic CD8⁺ cells, and NK cells and by mediating B cell antibody-dependent cellular cytotoxicity (ADCC). In the following section, these three coordinated events are discussed in further detail.

ALLOANTIGEN RECOGNITION: INNATE AND ADAPTIVE IMMUNE RESPONSES

The innate immune system has evolved to be the first line of defense against invading microorganisms. APCs such as dendritic cells (DCs) are equipped with pattern recognition receptors (PRRs) that recognize specific molecules derived from different microorganisms known as pathogen-associated molecular patterns (PAMPs).¹ There are many types of PRRs, but the class most recently studied are Toll-like receptors (TLRs) found on the cell surface. TLRs are expressed on many cell types but are predominantly found on APCs, including macrophages, DCs, and B cells. They are also found on other cells of the innate immune system, including mast cells, basophils, neutrophils, and eosinophils.² When TLRs recognize bacteria- or virus-specific PAMPs, they trigger a proinflammatory response mediated by neutrophils, macrophages, and complement.³ The activation and maturation of DCs through these nonspecific receptor-ligand interactions result in the regulation of the adaptive immune response. Mature DCs secrete cytokines and chemokines, present alloantigen to T cells, and provide costimulatory molecules to the T cell, resulting in T cell activation and a profound alloimmune response to exogenous pathogen.^{4,5}

The innate immune system is also triggered by the binding of endogenous ligands that are released from damaged cells. These ligands, called damage-associated molecular patterns (DAMPs), bind and act in the same fashion as PAMPs.⁶ During the process of transplantation, cellular injury of the allograft occurs at multiple time points, and this damage results in the release of DAMPs into the circulation. After their release from necrotic cells, these ligands engage TLRs and induce an inflammatory response that results in the activation and maturation of DCs. These cells are now primed to regulate an adaptive immune response. When alloantigen is processed by mature DCs and recognized by T cells, T cell

activation occurs and a profound adaptive immune response follows. This has been demonstrated clinically in the setting of kidney transplantation, where deceased donor kidneys that sustain significant injury during the transplantation process and develop delayed graft function (DGF) demonstrate higher rates of rejection than those without DGF.⁷ In a clinical trial of cyclosporine-treated kidney transplant patients, intraoperative treatment of IRI with the free radical scavenger superoxide dismutase significantly reduced the incidence of acute rejection and early immune graft loss and improved long-term graft outcome. These findings demonstrate that nonspecific tissue injury to renal allografts can have a significant impact on the development of cellular rejection.⁵

Receptors of Adaptive Immunity

Histocompatibility and the human leukocyte antigen system In human immunity, recognition of foreign antigens is governed by the human leukocyte antigen (HLA) system. HLA represents the human equivalent of the major histocompatibility complex (MHC). HLA is encoded on chromosome 6, spans approximately 4 Mb, and contains more than 250 expressed genes, many of which have immune functions. The subpopulation of HLAs that do not generate a self-reactive response to host antigens is the same repertoire of HLAs that can recognize foreign antigens as short peptides. These HLAs bind donor antigens and mediate T cell signaling by self-restricted T lymphocytes. HLA polymorphism has evolved to efficiently bind and present the vast array of foreign antigens from infectious sources, cancerous cells (altered self), or donor organs. The variance in evolutionary pressures changes with geography and time, and HLA phenotypes differ across populations. The HLA genes with clinical relevance to donor-host matching are segregated into class I and class II. Although class III genes exist and encode complement factors C2, C4A, and C4B; tumor necrosis factor (TNF); lymphotoxin α and β ; heat shock proteins; and properdin factor B, these genes are not typically taken into consideration during the pretransplantation match run that identifies a recipient on the list for a given donor organ.

HLA class I genes cover an approximately 2 Mb region of chromosome 6 and encode the classic transplantation antigens HLA-A, HLA-B, and HLA-C. These antigens are normally constitutively expressed on almost all nucleated cells. Class I gene encodes a 44 kDa transmembrane heavy chain consisting of three extracellular domains (α_1 , α_2 , and α_3) that associates noncovalently with β_2 -microglobulin [see Figure 1]. The highly polymorphic distal α_1 and α_2 domains contribute residues to the peptide-binding cleft that regulates antigen recognition. The proximal α_3 domain that lies closest to the cell membrane is highly conserved and ligates CD8 expressed on T lymphocytes. This interaction confers HLA class I restriction on CD8⁺ T lymphocytes, which in turn regulates direct antigen presentation. Other class I loci (H, J, K, L, N, P, S, T, U, V, W, X, Y, Z) exist, but their function in clinical transplantation remains to be determined.

Class II HLAs consist of three primary loci: *HLA-DP*, *HLA-DQ*, and *HLA-DR*. In contrast to class I antigens, class II antigens are expressed only on B lymphocytes, activated T lymphocytes, and APCs (monocytes, macrophages, and dendritic cells). Class II antigen expression may be induced

on a variety of cell types during inflammation by regulatory cytokines, including interferon gamma and TNF- α . Class II genes encode a structurally different extracellular glycoprotein to class I. In class II, two separate transmembrane proteins, α and β chain, cooperate to regulate antigen recognition [see Figure 1]. The α_1 and β_1 distal extracellular domains form the peptide-binding cleft. The β_1 domains are highly polymorphic and control the repertoire of peptides that are recognized. The β_2 domain associates with CD4 on T lymphocytes with predominantly helper/inducer function and confers HLA class II restriction. This association between class II and CD4 regulates indirect antigen processing.

Direct and indirect antigen presentation This elaborate system of cell surface antigens provides two essential functions for regulating the host immune system. First, the extensive repertoire of class I and II HLAs contained on the host and donor serve as labels that allow distinction of “self” (host) from “foreign” (derived from donor, viral, bacterial, or transformed self). Second, HLAs function as binding elements for screening and recognizing peptide antigens. The expansion and deletion of self versus nonself HLAs occur during maturation in the thymus, where T cells that respond to self-antigens are deleted. This process is called negative selection. Alternatively, antigens specific for foreign peptides displayed by self-HLA molecules are allowed to expand. This process is called positive selection. These positively selected T cells recognize foreign HLA in allografts and induce graft rejection. In the context of clinical transplantation, the host immune system is specifically directed against foreign HLA and efforts directed to improve immunosuppression, prevent rejection, and prolong graft survival depend on manipulating these donor-host interactions.

The nature of the HLA molecules recognized by alloreactive T cells varies according to the pathway of alloantigen presentation. In turn, the activated pathways generate a distinct immune response. Direct alloantigen recognition occurs when T cells recognize foreign or self-peptides loaded onto donor HLA. APCs derived from the allograft “directly present” donor HLA found on the donor-derived APC cell membrane to alloreactive host T cells [see Figure 2a]. The T cells responding to direct antigen presentation recognize determinants on the allogeneic HLA molecule itself as well as structures composed of both donor-derived HLA and bound peptide. The peptides presented by foreign HLA molecules may be derived from either polymorphic proteins (HLAs) or nonpolymorphic proteins (enzymes, scaffolding, or structural proteins).

In contrast, the response to foreign peptides processed and loaded onto self-HLA is termed indirect alloantigen recognition. Indirect recognition first requires antigen processing and then presentation by recipient-derived APCs [see Figure 2b]. The indirect alloresponse is analogous to the immune response to invading microbes, which are also presented to T cells as peptides displayed by self-HLA molecules on host APCs. Acute rejection of an allograft is primarily dependent on direct alloantigen recognition. The ratio of T cells that are activated by the direct pathway to indirect pathway is estimated at 100:1. Alternatively, experimental evidence suggests that in chronic rejection, the dominant mechanisms are mediated by the indirect pathway. Given

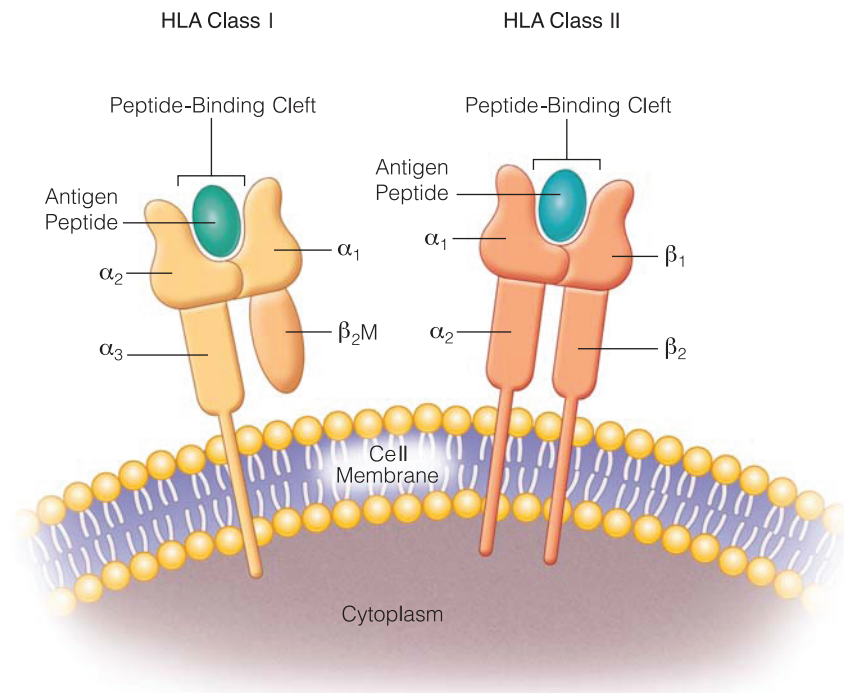


Figure 1 Human leukocyte antigen (HLA). HLA class I is composed of three extracellular domains (α_1 , α_2 , and α_3) that associate noncovalently with β_2 -microglobulin (β_2 M). The α chains are highly polymorphic and contribute residues to the peptide-binding cleft. HLA class II is composed of α and β chains. The α_1 and β_1 distal extracellular domains form the peptide-binding cleft.

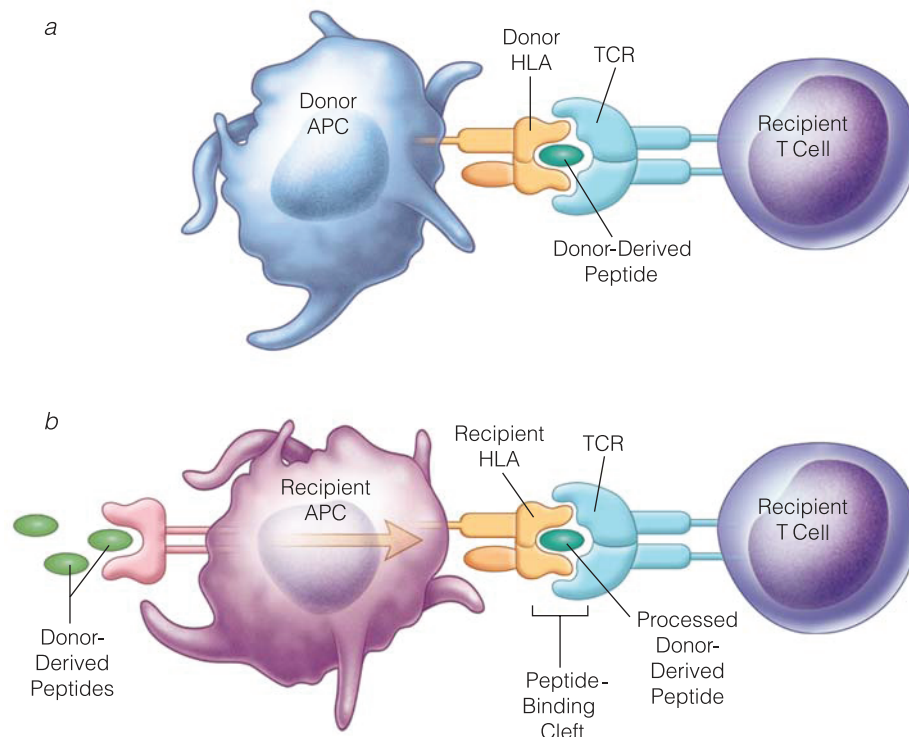


Figure 2 (a) Direct allorecognition. T cells responding to direct antigen presentation by donor-derived antigen-presenting cells (APCs) recognize determinants on the allogeneic HLA molecule as well as structures found on the bound peptide. (b) Indirect allorecognition. Indirect recognition requires antigen processing and presentation by recipient-derived APCs. HLA = human leukocyte antigen; TCR = T cell receptor.

that chronic rejection is a major cause of graft loss, further investigation and understanding of the indirect pathway may yield therapeutic approaches to prevent chronic rejection.

Minor histocompatibility antigens The major immunologic barrier to solid-organ transplantation (heart, lung, kidney, and pancreas) is primarily regulated by HLA. However, HLA does not define the full repertoire of antigens that can generate a response that culminates in rejection. Both human and murine studies have demonstrated that non-MHC molecules, referred to as minor histocompatibility antigens, can also mediate rejection. The clinical importance of minor antigens is demonstrated by the fact that HLA-matched siblings (unlike identical twins) require immunosuppression to prevent graft rejection. By definition, this alloresponse is targeting minor (or non-HLA) antigens. The mechanism of the alloresponse to minor antigens is similar to the response to microbial antigens in that host-HLA molecules present foreign peptides to host T cells (indirect presentation).

One example of a minor antigen is the major histocompatibility complex class I-related chain A (MICA) antigen. This antigen is structurally similar to MHC class I antigens and can be expressed on a variety of cells, including monocytes, epithelial cells, and endothelial cells. MICA is polymorphic and can elicit production of antibodies in transplant recipients, more so than the closely related major histocompatibility complex class I-related chain B (MICB antigen). The development of anti-MICA antibodies may be associated with worse graft survival, especially in recipients of well-MHC-matched kidneys.⁸

ACTIVATION OF ANTIGEN SPECIFIC T AND B LYMPHOCYTES

T Cell Response

Recipient T cells that react to donor antigen are critically important in the immunologic response that results in allograft rejection. T cell recognition of alloantigen is the primary event that leads to activation, proliferation, and differentiation of alloreactive T cells.

T cell receptor and intracellular signaling Host T cells do not directly bind and recognize isolated antigens. Rather, T cells recognize a complex composed of peptide fragment of foreign antigen bound to an HLA molecule, and this process confers HLA restriction on any antigen. Recognition of the peptide-HLA complex is then mediated by the TCR. Structural and genetic analysis of the TCR reveals significant homology with B cell immunoglobulin receptors. The TCR is composed of separate α and β chains encoded by loci on chromosomes 14 and 7, respectively. Each locus comprises a series of V, D, and J (variable) and C (constant) domains. Variability in the α -chain locus is conferred by V and J genes, whereas β -chain locus variability is mediated by V and D regions. These loci undergo rearrangements during T cell development, maturation, and differentiation, following the principles of gene arrangement and allelic exclusion to generate receptor diversity capable of recognizing an extensive repertoire of antigens.

T cells may also express alternative TCR γ and δ chains encoded on chromosomes 7 and 14, respectively. These chains are similar to α and β but demonstrate less diversity

and are structurally more similar to immunoglobulins. Interestingly, $\gamma\delta$ T cells can be found among the intraepithelial lymphocytes of the gastrointestinal tract, providing support to the theory that $\gamma\delta$ T cells contribute to immunologic surveillance of pathogens. Soluble forms of the TCR exist, resulting from alternative messenger RNA splicing or from proteolytic cleavage of surface receptors. The function of soluble TCR is not well understood.

Similar to surface immunoglobulin, the TCR is not expressed alone in the membrane. The TCR requires the coexpression of a complex of invariant chains termed cluster of differentiation 3 (CD3) [see Figure 3]. CD3 plays a significant role in proper TCR cell surface expression and TCR-mediated intracellular signaling. A monoclonal antibody to CD3, OKT3, was developed and approved to be used to treat severe T cell-mediated rejection in kidney and pancreas transplant recipients. Muromonab OKT3 binds to CD3 and inactivates T cells. This drug has been used less frequently over recent years as a result of systemic inflammatory responses seen with drug infusion. More recently, monoclonal antibodies that selectively bind to α and β chains of the TCR have been developed and are currently being studied in clinical trials in kidney transplantation. The hypothesis being studied is that by avoiding the inhibition of γ and δ chains of the TCR, the risk of infection will decrease while maintaining adequate prevention of rejection.

A variety of downstream intracellular signaling pathways have been identified in T cells that regulate the immune response to TCR activation. Key components of these pathways have also been targeted for use in immunosuppression. Ligation of the TCR results in phosphorylation of second messengers and activation of three principal biochemical pathways: calcineurin, protein kinase C, and Rac-mitogen-activated protein (MAP) kinase pathways [see Figure 4]. The primary function of calcineurin involves dephosphorylation of nuclear factor of activated T cells (NFAT), allowing NFAT to translocate from the cytoplasm to the nucleus. Once in the nucleus, NFAT binds to DNA regulatory sequences and increases the transcription of genes for several cytokines, including the T cell growth factor interleukin-2 (IL-2). Cyclosporine exerts its immunosuppressive effects by binding to cyclophilin, an intracellular protein, and the cyclosporine/cyclophilin complex subsequently inhibits the activity of calcineurin. Tacrolimus (FK506) binds to FK-binding protein (FKBP), and the tacrolimus/FKBP complex similarly inhibits the activity of calcineurin [see Figure 4].⁹ This class of drugs is termed calcineurin inhibitors (CNIs).

CD4 versus CD8 and T helper type 1 versus T helper type 2 Mature T cells can be distinguished by the presence of either CD4 or CD8 cell surface proteins (CSPs). CD8 molecules directly ligate HLA class I (through β_2 -microglobulin) and define the class I-restricted subset of CD8⁺ cytolytic T lymphocytes [see Figure 5a]. Alternatively, CD4 molecules directly bind HLA class II (through the β_2 subunit) and define the class II-restricted subset of CD4⁺ helper T lymphocytes [see Figure 5b]. In simplified terms, CD4⁺ T cells mediate the initial recognition of an alloantigen and help amplify and coordinate the subsequent immune response. Activated CD8⁺ T lymphocytes that have responded to these signals function as downstream effectors to eliminate threats to the host. This

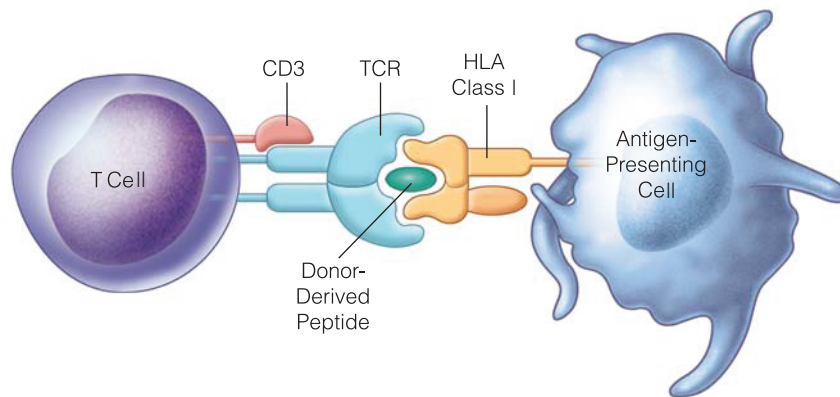


Figure 3 T cell receptor (TCR) and CD3. The TCR is composed of α and β chains and requires the coexpression of a complex of invariant chains termed cluster of differentiation 3 (CD3). CD3 regulates proper TCR cell surface expression and TCR-mediated intracellular signaling. HLA = human leukocyte antigen.

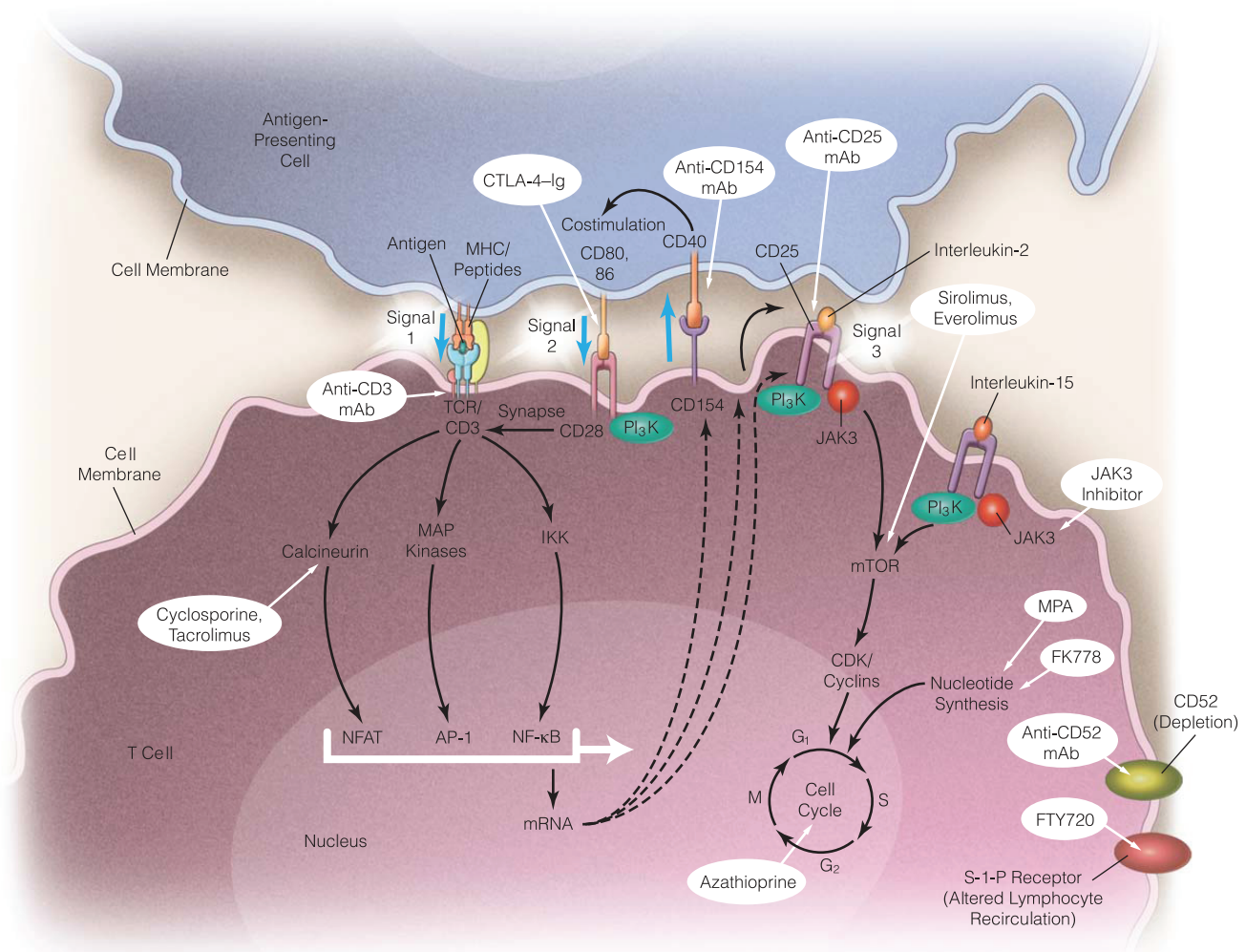


Figure 4 T cell-associated second messenger signaling pathway. Key components of the T cell signaling cascade have been targeted for therapeutic immunosuppression. Adapted with permission from Halloran PF.⁹ AP = activator protein; CD = cluster of differentiation; CTLA = cytolytic T lymphocyte antigen; IKK = inhibitor of nuclear factor κ B kinase; MHC = major histocompatibility complex; MAP = mitogen-activated protein; MPA = mycophenolic acid; mRNA = messenger RNA; mTOR = mammalian target of rapamycin; NF = nuclear factor; NFAT = nuclear factor of activated T cells; PI₃K = PI₃ kinase; TCR = T cell receptor.

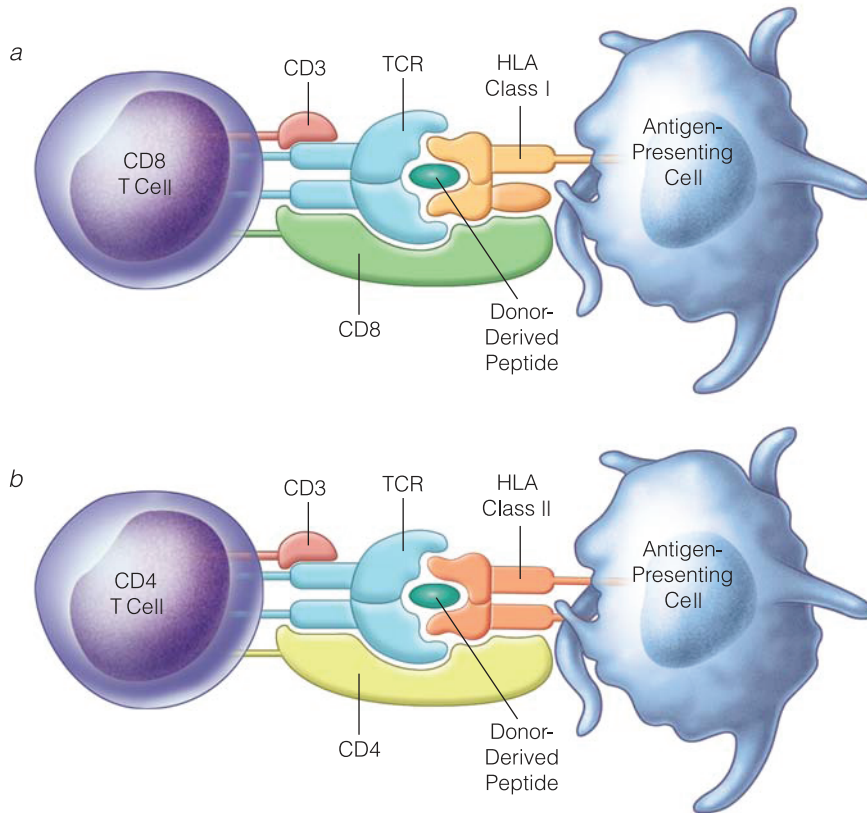


Figure 5 (a) CD8 molecules directly ligate class I human leukocyte antigens (HLAs), and this confers restriction to CD8⁺ cytolytic T lymphocytes. (b) CD4 molecules directly bind HLA class II and define the class II-restricted subset of CD4⁺ helper T lymphocytes. APC = antigen-presenting cell; CD = cluster of differentiation; TCR = T cell receptor.

functional division of labor between immune induction (CD4) and target cell lysis (CD8) is not definitive or mutually exclusive. For example, CD4⁺ cells restricted to class II can have cytolytic function in the appropriate cellular context. Similarly, CD8⁺ cells can produce many of the cytokines elaborated by CD4⁺ lymphocytes. Importantly, in a model of mouse heart transplantation, CD4-deficient mice are unable to reject grafts, whereas CD8-deficient mice have their rejection response intact.¹⁰ This is one of several models in which a CD4⁺ T cell-mediated delayed-type hypersensitivity (DTH) response is sufficient to cause rejection without requiring the cytolytic CD8 effectors. In contrast, data from other experimental models demonstrate that inhibition of CD8 by CD8 antibody alone prevents rejection, suggesting that functional CD8⁺ T lymphocytes are necessary but not sufficient.¹¹ Together, these data confirm the redundancy of the various components of the alloresponse and the highly conserved mechanisms that lead invariably to allograft rejection.

Activated CD4⁺ T cells produce different cytokine profiles according to the pathway by which cellular differentiation occurs. With specific antigenic stimulation, CD4⁺ T lymphocytes differentiate into either helper type 1 (Th1) cells or helper type 2 (Th2) cells. Th1 cells secrete cytokines, IL-2, interferon gamma, IL-12, and TNF. These cytokines stimulate DTH activity, cytolytic activity, and production of opsonizing and complement-fixing IgG antibodies. Th2 cells secrete cytokines that include IL-4, IL-5, IL-10, and IL-13. These cytokines are critical for the induction of humoral immunity, specifically stimulating the production of immunoglobulin E (IgE) and activating eosinophils.

The regulation of these two types of responses has been extensively studied in CD4⁺ helper T lymphocytes, but the dichotomous responses can also apply to CD8⁺ cytolytic cells. Activating stimuli for Th1 responses include interferon gamma and IL-12, whereas IL-4 promotes Th2 responses. Complementary inhibitory signals including interferon gamma-mediated downregulation of Th2 and IL-4-mediated inhibition of Th1 ensure that each pathway becomes increasingly polarized after the initial activation. Th1 responses have been hypothesized to mediate rejection, whereas Th2 responses have been implicated in tolerance, or decreased donor-derived T cell responsiveness. These generalizations have been derived from observations that Th1 cytokines promote damage to the graft via effector cell DTH and cytolytic activity, whereas Th2 cytokines antagonize these functions. Experimental studies have shown that acute rejection is associated with an expansion of Th1 cytokines, whereas prolonged survival is associated with reduced levels of these cytokines. However, other studies have shown that rejection is associated with the production of type 1 and type 2 cytokines, whereas tolerance is associated with a reduction in both types of cytokines.

For now, attempts to effect graft rejection by manipulating cytokines have been largely unsuccessful. However, ongoing studies continue to define new cytokines and their roles in immune responses. For example, a third type of cytokine profile has been reported in cells that produce IL-17. This Th17 response appears to have a strong inflammatory effect and may potentially become a target of antirejection therapies. Early involvement of IL-17 in the rejection of kidney

allografts has been shown in both murine and human models, and in the absence of the Th1 response, Th17 cells can clearly mediate transplant rejection.¹²

Costimulatory pathways The interaction between a given TCR and the unique epitopes on the HLA/peptide complex is antigen specific and determines the specificity of the immune response. However, efficient T cell activation requires other accessory cell surface molecules called costimulatory molecules to stabilize the TCR:HLA/peptide complex [see Table 1]. T cell activation requires one primary signal through the TCR and a second costimulatory signal through these accessory molecules. Costimulatory molecules stabilize the TCR by prolonging contact adhesion between the T lymphocyte and the APC, thereby providing time for the TCR to sample APC cell surface antigens. In addition, costimulation allows efficient transduction of the TCR-initiated signals that activate the calcineurin, MAP kinase, and nuclear factor κ B pathways. Multiple costimulatory molecules have been identified, but the most potent secondary signals regulating T cell clonal expansion and differentiation are provided by the CD28/B7 and TNF/tumor necrosis factor receptor (TNF-R) families of molecules.

CD28 is expressed on most T lymphocytes, and engagement of CD28 increases T cell proliferation by a variety of mechanisms, including the production of IL-2 and other cytokines. APCs express two ligands for CD28: B7-1 (CD80) and B7-2 (CD86). Upregulated expression of both B7 molecules occurs when APCs are activated by a variety of inflammatory stimuli, including microbial infection and cytokines. B7-1 and B7-2 can both provide T cell costimulation through

CD28 but have distinct patterns of expression and binding kinetics for CD28, suggesting significant differences in their roles. B7-1 and B7-2 also regulate T cells by binding cytolytic T lymphocyte antigen-4 (CTLA-4). In this fashion, CD28 provides a stimulatory signal, whereas CTLA-4 inhibits T cell proliferation. Targeting the CD28/B7 pathway can elicit antigen-specific unresponsiveness or T cell anergy that occurs only at the time of transplantation, allowing the recipient to be free of the effects of chronic long-term immunosuppression. In experimental models, blockade of B7 molecules on APCs has been shown to significantly prolong graft survival. However, in most in vivo models of B7 blockade, anergy assigned to specific antigens has been difficult to demonstrate, mostly because of the redundancy and complexity of costimulatory mechanisms. Induced costimulatory molecule (ICOS), programmed death-1 (PD-1), and B7-H3 represent other homologous members of the CD28/B7 family that exert a functional role in costimulation [see Table 1].

The TNF-R family is expressed on T cells and its ligand, TNF, is expressed on complementary APCs. The TNF-R also regulates dual functions with death domain (DD)-mediated apoptosis on the one hand and TNF-R associated factor (TRAF)-mediated T-cell activation representing the other extreme. APC-derived CD40 receptor and its corresponding T cell ligands, CD154 and CD40L, belong to the TNF and TNF-R superfamilies and play a critical role in T cell costimulation. CD40 engagement activates B cell antibody production, DCs, and monocytes and upregulates expression of the B7 family of molecules during antigen presentation.¹³ Blockade of the CD40/CD154 pathway in experimental models of transplantation has proven to be extremely effective in

Table 1 Costimulatory Molecules

T Cell	APC	Comments	Study
CD28	B7-1 (CD86) B7-2 (CD80)	B7-1 and B7-2 can both provide T cell costimulation through CD28	Acuto and Michel ⁴⁴
PD1	PDL-1, PDL-2	PD-1 can be induced on CD4 ⁺ , CD8 ⁺ T, NK, and B cells and monocytes, and ligation delivers an T cell inhibitory signal	Durrbach et al ¹³
CTLA4	B7-1(CD86) B7-2 (CD80)	CTLA-4 binding by B7-1 and B7-2 inhibits T cell proliferation	Larsen et al ⁴⁵
ICOS	ICOS-L, B7h	In experimental studies, anti-ICOS blocking mAb can significantly prolong allograft survival	Ozkaynak et al ⁴⁶
CD28	B7-H3	B7-H3 is induced in dendritic cells; monocytes; and T, B, and NK cells and increases T cell proliferation	Steinberger et al ⁴⁷
TNF-R	TNF	The TNF-R regulates dual T cell functions through apoptosis and also TRAF-mediated T cell activation.	Durrbach et al ¹³
CD40L, CD154	CD40	CD40 engagement activates B cell antibody production and upregulates expression of the B7 family	Durrbach et al ¹³
OX40	OX40L	OX40 is expressed on activated CD4 and the Th2 T cells and activates B cell proliferation	Acuto and Michel ⁴⁴
CD27	CD70	CD27 activation induces high levels of IL-2 and TNF- α Blockade of CD27 may prevent chronic allograft vasculopathy	Yamada et al ⁴⁸

CD = cluster of differentiation; CTLA = cytolytic T lymphocyte antigen; ICOS = induced costimulatory molecule; IL-2 = interleukin-2; mAb = monoclonal antibody; NK = natural killer; PD = programmed death; Th2 = T helper type 2; TNF- α = tumor necrosis factor- α ; TNF-R = tumor necrosis factor receptor; TRAF = tumor necrosis factor receptor associated factor.

preventing graft rejection. Other members of the TNF-R/TNF family include CD27, OX40, and OX40L [see Table 1]. Clinical applications of costimulatory blockade are discussed below.

B Cell Response

Hyperacute rejection and antibody-mediated rejection The importance of B cells and antibodies in the rejection of an allograft is most dramatically illustrated by hyperacute rejection. This process occurs within minutes and up to 24 hours after transplantation in patients who were previously sensitized and had developed antibodies to ABO blood group antigens or to allogeneic HLA molecules. This most commonly occurs in patients who have had previous transplants, blood transfusions, or pregnancies. During the previous era, hyperacute rejection became a rare phenomenon because ABO blood typing and crossmatching detected these critical antibodies. Delayed antibody-mediated rejections (AMRs) occurring later than 24 hours after transplantation were described as a result of either the presence of low antibody levels missed by low-sensitivity crossmatching techniques or the reactivation of memory B cells. However, AMR has become more prevalent in the current transplant era as a result of increased rates of transplantation in highly sensitized patients. In reality, mixed cellular and antibody-mediated rejection probably represents a spectrum of immunologic reactions as the genesis of one may be determined by the other. The cellular component (mediated by T cells) induces antibody elaboration (mediated by B cells) that can lead to allograft destruction. This antibody component of rejection is characteristically identified in biopsy specimens by the deposition of the C4d complement protein from the classic complement pathway. Although the histologic findings in these cases are variable, the presence of C4d in the peritubular capillaries of kidney allografts with evidence of circulating donor-specific antibodies (DSAs) correlates closely with AMR. Antibodies may also play an important role in chronic rejection (see below). Both acute and chronic AMR can potentially be treated with biologic agents that target the B cell-specific marker CD20.

EFFECTOR PATHWAYS FOR CELLULAR DAMAGE

Once CD4⁺ T cells recognize foreign class II HLA molecules, they play a critical role in regulating various areas of the effector response. The initial innate immune inflammatory response to the injury associated with transplantation is antigen independent. The antigen-specific activation of CD4⁺ T cells leads to expression of cell surface molecules and production of cytokines that in turn stimulates monocytes. This cooperation between CD4⁺ T cells and monocytes, or DTH response, plays an important role in the destruction of a graft.

The activation of CD4⁺ T cells and production of cytokines also stimulate activation and proliferation of both cytolytic CD8⁺ T cells and NK cells. On recognition of HLA class I molecules on allograft cells, CD8⁺ T cells cause cell death by two main mechanisms. First, the release of soluble cytotoxic factors such as granzymes and perforin causes direct damage on target cells. Second, the upregulation of Fas ligand on T cells, which finds Fas receptor (CD95) on target cells, initiates a death signal or cascade. Ligation of FAS on CD95

receptor found on cells of the allograft initiates apoptosis or programmed cell death.

Cytokines that are released by CD4⁺ T cells also stimulate B cells. On binding of specific antigen by the B cell receptor or cell surface immunoglobulin, B cells proliferate and differentiate into plasma cells. Plasma cells release soluble immunoglobulins, or antibodies, which subsequently bind allogeneic cells. Antibodies can cause cell damage by fixing complement and mediating ADCC.

Clinical Management of the Transplanted Allograft

DONOR GRAFT–RECIPIENT HOST MATCHING

A favorable clinical outcome after solid-organ transplantation relies on obeying defined immunologic principles. Graft rejection is regulated by recipient lymphocytes that recognize CSPs from donor tissue. Allograft CSPs are categorically different from recipient CSPs, and this discrimination of self from nonself triggers the series of reactions that lead to antigen-specific, immune-mediated rejection. Specifically, the two major categories of CSPs include ABO blood group and HLAs.

The importance of matching these CSPs between donors and recipients varies based on the organ that is transplanted. In kidney transplantation, increasing HLA mismatching between donor and recipient has been associated with increased rates of rejection and decreased allograft survival. As a result, donor-recipient HLA matching is incorporated into the deceased donor kidney allocation algorithm. However, HLA mismatching in liver transplantation has not been shown to significantly impact graft survival and therefore is not used as part of the liver allocation scheme. Clearly, the precise immunologic risk varies not only with the immunologic determinants in each donor-recipient pair but also according to the antigenicity of the type of organ transplanted. In the following section, we describe (1) optimal immune matching between donor and recipient using ABO and HLA type, (2) the techniques used to define HLA type and to assess immunologic risk in the recipient, and (3) current methods used for desensitization.

ABO Blood Group and ABO-Incompatible Transplantation

In most cases of organ transplantation, donor-recipient matching involves consideration of ABO blood group compatibility. The vast majority of solid-organ transplantations occur with ABO-identical blood type matching. ABO-nonidentical but ABO-compatible organ transplantations occur and are successful, as is the case with a blood type O donor organ transplanted to a non-O recipient [see Table 2]. When transplantations are performed across these ABO barriers without highly specialized desensitization protocols, hyperacute rejection is expected to occur. In selected cases, A₂ kidney donors can be safely used in non-A recipients such as B or O recipients. This, in part, is attributable to the diminished antigenicity of the A-antigen in A₂ donors, so recipients with an anti-A titer less than 1:32 can be considered for successful transplantation.¹⁴

Transplantation using ABO-incompatible allografts was developed as a potential solution for the problem of organ shortage, increasing waiting times, and high mortality on the

Table 2 ABO Blood Group Compatibility for Solid-Organ Transplantation	
Recipient Blood Group (IgM) with Associated Antibodies	Compatible Donors
A (anti-B)	A, O
B (anti-A)	B, O
AB (none)	A, B, AB, O
O (anti-A and anti-B)	O

renal transplant waiting list. Using living related donors, successful ABO-incompatible transplants have been performed in over 1,000 patients in Japan.¹⁵ In North America, an analysis of the United Network for Organ Sharing (UNOS) registry data for centers performing single-kidney ABO-incompatible transplantations with pretransplantation antibody removal has shown that long-term graft survival can be comparable to ABO-compatible kidney transplantations.¹⁴ However, many centers have reported an early and significant immunologic risk, with approximately 10 to 30% of patients developing acute AMR and approximately 10% of patients experiencing early graft loss.¹⁶ These types of specialized transplantations should be considered only at centers using protocols dedicated to pretransplantation removal of antibodies. Desensitization for ABO incompatibility is currently being performed according to protocols based on (1) high-dose intravenous immune globulin (IVIg) treatment and (2) combinations of plasmapheresis and low-dose IVIg.¹⁷ Improvements in these strategies will need to address the problem of early graft loss, early rejection rates, and the subsequent impact on long-term outcomes.

HLA Typing: Serologic Typing versus DNA-Based Techniques

HLA functions as the predominant cell surface protein that is targeted for immune detection. As previously stated, the utility of HLA matching between donor and recipient is organ specific and most critical in kidney and pancreas transplantation. Matching for class I HLA-A and HLA-B and class II HLA-DR MHC antigens has historically had the most profound effect on increasing allograft and patient survival. Seminal studies by Patel and Terasaki determined that crossmatch-positive recipients observed a graft failure rate of 80% within 2 days after kidney transplantation compared with only 4% in crossmatch-negative patients.¹⁸ Currently, the beneficial effects of HLA matching are based on compatibility at the *HLA-A*, *HLA-B*, and *HLA-DR* loci. Although multiple factors regulate transplant outcomes, optimal graft survival is achieved in transplants that have no donor-recipient HLA mismatches (zero mismatch). Transplants with a match at the *HLA-DR* locus (while allowing mismatches at the other loci) also have increased survival outcome. Decreased allograft and patient survival resulting from HLA mismatch has been tempered with significant improvements in immunosuppression.

A variety of clinical tests have evolved for characterizing HLA type. These are based on either serologic tests or molecular DNA sequencing methods. The specificity and precision of HLA typing are a function of the technique employed.

DNA techniques have largely supplanted serologic tests. Traditionally, HLA typing was determined using the serologically based complement-dependent cytotoxicity (CDC) test. In this assay, HLA molecules are detected on the surface of separated T cells (HLA class I) and B cells (HLA class II) by obtaining lymphocytes from the patient. Activating antigens, derived from panels of sera from either multiparous women or multiple local volunteers, are then combined with these separated lymphocyte lineages. Once complement is added to the mix, the resulting damage to the lymphocyte membrane is detected by the uptake of vital dye and forms the basis of this cytotoxic test.¹⁹ The disadvantages to this test include the need for obtaining functional lymphocytes in the form of tissue, maintaining serum that is representative of the given donor population, and, ultimately, a low typing resolution inherent in the test.

DNA-based molecular methods employing sequence-specific polymerase chain reaction (SSP), sequence-specific oligonucleotide probes (SSOP), reference strand conformation (RSCA), or sequence-based typing (SBT) provide a number of advantages to CDC and represent the current standard of care. Live lymphocytes are not required, and DNA is easily extracted and stored from any nucleated cell. In these assays, DNA probes replace the role of the antisera used in the CDC test and the need for renewing pooled serum becomes unnecessary as the DNA reagents are easily replenished. Typically, peripheral blood lymphocytes are used as the source of DNA. Each of these methods employs polymerase chain reaction (PCR) amplification with primers or oligonucleotides, and they differ primarily in their resolution of the DNA typing. For example, SSP is rapid, capable of detecting allele groups, and considered a “low-resolution” technique as it is inefficient at achieving allele-level typing. SSOP uses short oligonucleotide DNA probes and is useful for typing large numbers of samples in batches. A variant of this technique uses probes coupled to fluorescence-labeled microbeads in a flow cytometric assay using X-Map technology (Luminex, Austin, TX).¹⁹ SBT provides high fidelity and resolution as are typically used to achieve allele-level HLA typing as required for stem cell transplantation programs.

Pretransplantation Alloantibody Detection, Crossmatching, and Immunologic Risk

In addition to HLA typing, the detection of pretransplantation alloantibodies in the recipient directly affects outcomes after transplantation. Sensitization against donor HLAs arising from pretransplantation pregnancies, blood transfusions, or prior transplantation can elaborate antibodies from recipient memory cells at the time of transplantation. Circulating antibodies primed in this fashion prior to transplantation may result in hyperacute or accelerated acute rejection after reperfusion of the implanted graft. These deleterious effects of AMR can be avoided by screening for DSAs in the recipient. These assays are generally based on (1) membrane-based/peripheral cell line-based testing (CDC, flow cytometry) or (2) solid-phase testing involving HLA affixed to particles in the form of multiplex bead or single antigen bead. These are limited in that many of them are not quantitative, are not functional, or are overly sensitive, with batch-to-batch variation between tests. The technical variations can be broad, with false positive and negative results built into the assays.

Finally, many of these assays do not evaluate non-HLAs. In this section, we briefly describe the various assays that can screen for antibodies.

CDC assay In addition to being used as a serologic test for HLA typing, the CDC assay can be used to determine the presence of alloantibodies in the recipient. As described above, the CDC test relies on live separated T cells for class I antibody identification and live B cells for class I and class II antibody detection in tests performed against the intended recipient's serum. The CDC assay is relatively inefficient and involves testing several panel donors to cover all major specificities or relying on commercially available frozen cell trays or immortalized lymphoblastic cell lines. These panel cells are not donor specific, and this particular application of the CDC assay for antibody detection should not be confused with the CDC "crossmatch" (see below). A major limitation with the CDC assay is that it can only detect complement-fixing antibodies.

Enzyme-linked immunosorbent assay Enzyme-linked immunosorbent assay (ELISA)-based methods use antigens that have been stripped off cells for the detection of HLA class I and II. These assays have an advantage over cell-based tests as large numbers of cells do not have to be collected and separated and a variety of antibodies, including non-complement-binding antibodies, can be detected. In addition, testing is efficient and fast (< 2 hours), and HLA antibodies can be specifically targeted [see Figure 6]. ELISA screening is capable of screening large numbers of patient samples in a

short period of time with a higher sensitivity than the CDC assay. However, the physical stripping of antigens from cells may promote conformational changes that do not reflect the in situ clinical function of an individual antibody-antigen couple.

Flow cytometry/X-Map assay These assays currently represent the gold standard for detecting and identifying deleterious alloantibodies. Soluble or recombinant HLA molecules are bound to polystyrene particles, and patient serum is mixed together to allow antibody-antigen binding. Particles are stained with varying amounts of two fluorochromes to facilitate identification, and a second antihuman antibody linked to a reporter molecule is then added to the reaction mixture, with measurement of reporter fluorescence as a quantification of antibody [see Figure 6]. X-Map and flow cytometric assays have the advantage of detecting both complement-fixing and non-complement-fixing antibodies. They can independently identify HLA class II specificities in the context of class I, and specific single antigenic alleles can be discriminated to allow precise determination of acceptable HLA mismatches. One drawback to this technique is that the HLAs are in a conformation altered from what occurs in situ, and this technique may identify antibody-antigen binding matches that have no clinical significance.

Patient-donor crossmatch Prior to any kidney transplantation, it is necessary to perform a functional assay or crossmatch to determine that no clinically significant donor-specific antibodies are present in the recipient-donor pair

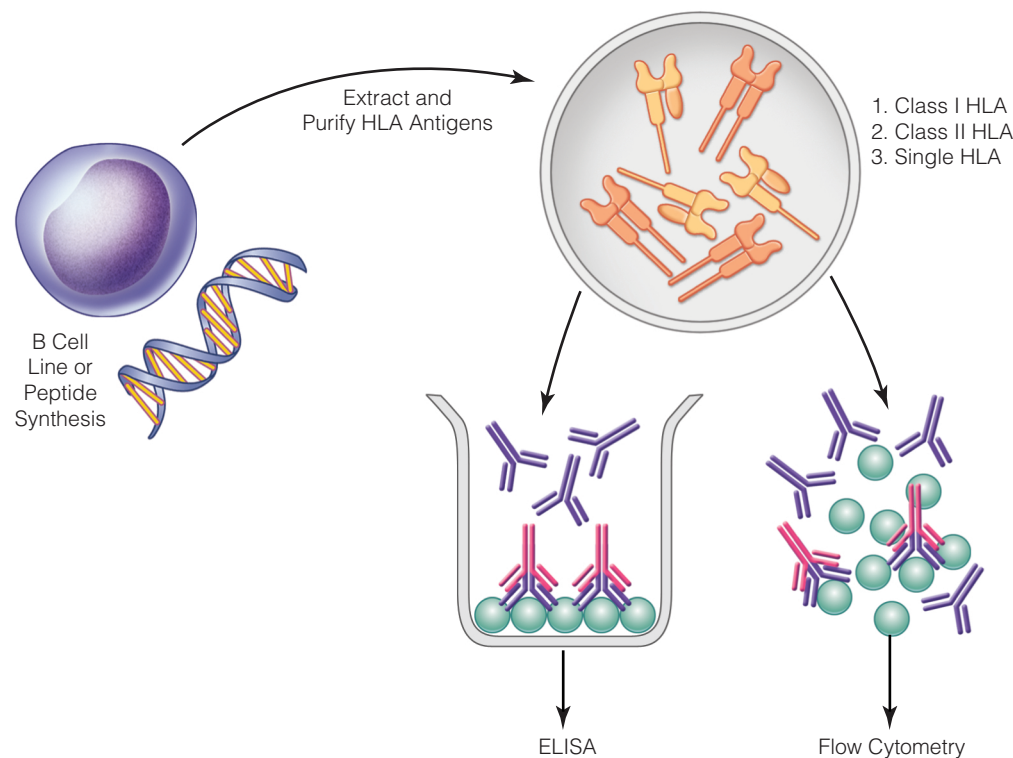


Figure 6 Detection of alloantibodies by enzyme-linked immunosorbent assay (ELISA) or flow cytometry. HLA = human leukocyte antigen.

being considered. Crossmatching is normally performed using one or both of the following methods: (1) CDC crossmatching and/or (2) crossmatching by flow cytometry. In CDC crossmatching, recipient serum samples containing potential DSA are incubated with separated T and B cells from the intended organ donor. In this mixture, if antibody is bound to T or B cells, the addition of complement will result in donor cell lysis, yielding a “positive” crossmatch.¹⁸ T cell–positive crossmatches are usually attributable to anti-HLA class I antibodies and should preclude transplantation. B cell–positive crossmatches (in the absence of T cell positivity) may refer to either HLA class II antibodies or weak class I antibodies. This assay almost completely eliminated the hyperacute AMR response that can occur within minutes to hours after graft reperfusion. However, this original technique was relatively insensitive and early graft loss continued to occur in a minority of patients with a negative crossmatch. This assay was also limited by its inability to distinguish between HLAs and non-HLAs.

Some antibodies bind strongly to target cells yet poorly fix complement and therefore may not be picked up with the standard CDC crossmatch. These antibodies are still relevant in transplantation as they can cause cell damage through other immune mechanisms. The ability of the CDC crossmatch to identify these antibodies has been augmented by adding antihuman globulin (AHG) prior to adding complement in the CDC crossmatch assay [see Figure 7a]. The AHG crosslinks IgM or IgG antibodies, enhances the binding of complement, and thus increases the sensitivity of the CDC crossmatch assay.^{20,21}

Crossmatching by flow cytometry (FC-XM) is more sensitive than the traditional CDC approach. In this technique, donor lymphocytes are incubated with the recipient sera, and after washing, antihuman IgG (with fluorochrome stain conjugated) is added to the mixture. Additional antibodies (conjugated with a different fluorochrome) are added to identify either T or B lymphocytes. Flow cytometry then interrogates the mixture [see Figure 7b]. This technique is not reliant on complement activation for detecting antibodies and can be more than 10 times as sensitive as the CDC assay.²² Optimal decisional making is achieved after combining data from both CDC and FC-XM assays as some donor-recipient pairs may be FC-XM positive but CDC negative as a result of the highly sensitive nature of the FC-XM assay. The FC-XM is widely regarded as the most sensitive test for assessing the presence of DSA and is the gold standard in most transplant centers in the United States.²³ One drawback to the FC-XM is the lack of specificity with determining clinically relevant antibodies, and this assay may rule out transplantation between compatible donor-recipient pairs.²⁴

Recently, virtual crossmatching, whereby the HLA type of the donor is compared with the recipient’s HLA-antibody specificities determined by solid-phase assays,²⁵ is being investigated as a predictive tool to use in place of CDC or FC-XM. This assay does not require mixing between donor lymphocytes and recipient serum. Correlation of the virtual crossmatch with FC-XM was approximately 85% in reported studies.²⁶ Although its utility and precision in replacing the FC-XM are debated, it does provide an expedited screening tool for assessing organ allocation so that centers can rapidly screen donors who would likely yield a positive crossmatch

and allow the organ to be quickly allocated to a more appropriate recipient at another center.

CLINICAL MANAGEMENT OF GRAFT REJECTION

Although a thorough discussion regarding the management of transplant graft rejection is beyond the limits of this chapter, we discuss some of the clinical applications of the concepts described in the first part of this chapter in the following section. The different types of allograft rejection and common immunosuppressive medications are discussed.

Hyperacute, Acute, Accelerated, and Chronic Rejection

Prior to the establishment of the Banff working schemas, rejection of the renal allograft was traditionally classified into the following four categories: (1) hyperacute, (2) accelerated acute, (3) acute, and (4) chronic. Hyperacute rejection was defined as immediate rejection (minutes to hours) after reperfusion as a result of the presence of preformed antibodies. These alloreactive antibodies bind HLAs on the vascular endothelium of the allograft, leading to complement deposition and rapid graft thrombosis. As mentioned above, the sensitivity of both ABO testing and pretransplantation HLA crossmatching has traditionally precluded hyperacute rejection, which usually only otherwise results from clerical or technical errors in the crossmatch process. Currently, the risk of hyperacute rejection has increased because of the higher frequency of transplantations performed in sensitized patients and across immunologic barriers. Treatment for hyperacute rejection invariably involves transplant nephrectomy.

Accelerated acute rejection was defined as rejection occurring within 5 days of transplantation as a result of the formation of antibodies from activated memory B cells or the generation of cytotoxic T cells. Acute rejection was defined as rejection occurring after 5 to 7 days to weeks after transplantation as a result of alloantigen-specific activated T cells. This injury pattern can also be seen out to 12 months after transplantation. Chronic rejection was defined as slow progressive graft dysfunction starting after 3 months as a result of a combination of antibody-mediated and T cell–dependent cellular damage. This injury ultimately led to a phase of tissue remodeling stimulated by cytokines resulting in allograft dysfunction.

The Banff working group of pathologists, nephrologists, and transplant surgeons who standardized the nomenclature and classification of renal allograft pathology has met at regular intervals from 1993 to the present to update our working definition of transplant allograft rejection. Within the current definitions, the notions of hyperacute, acute, and chronic have been largely replaced by pathophysiologic and histologic classifications based on either acute AMR, T cell–mediated rejection, or chronic allograft rejection and nephropathy.²⁷ For example, a diagnosis of acute AMR of a kidney transplant requires the presence of C4d, a split-product of C4 from the classic complement cascade, morphologic evidence of acute tissue injury, and the presence of circulating DSAs. Acute T cell–mediated rejection is categorized based on whether the infiltration of lymphocytes is localized to the interstitium (stage IA: moderate tubulitis; stage IB: severe tubulitis) or involving the arteries as well (stage IIA: mild to moderate intimal arteritis; stage IIB: severe intimal arteritis; stage III: transmural arteritis with fibrinoid changes and necrosis of

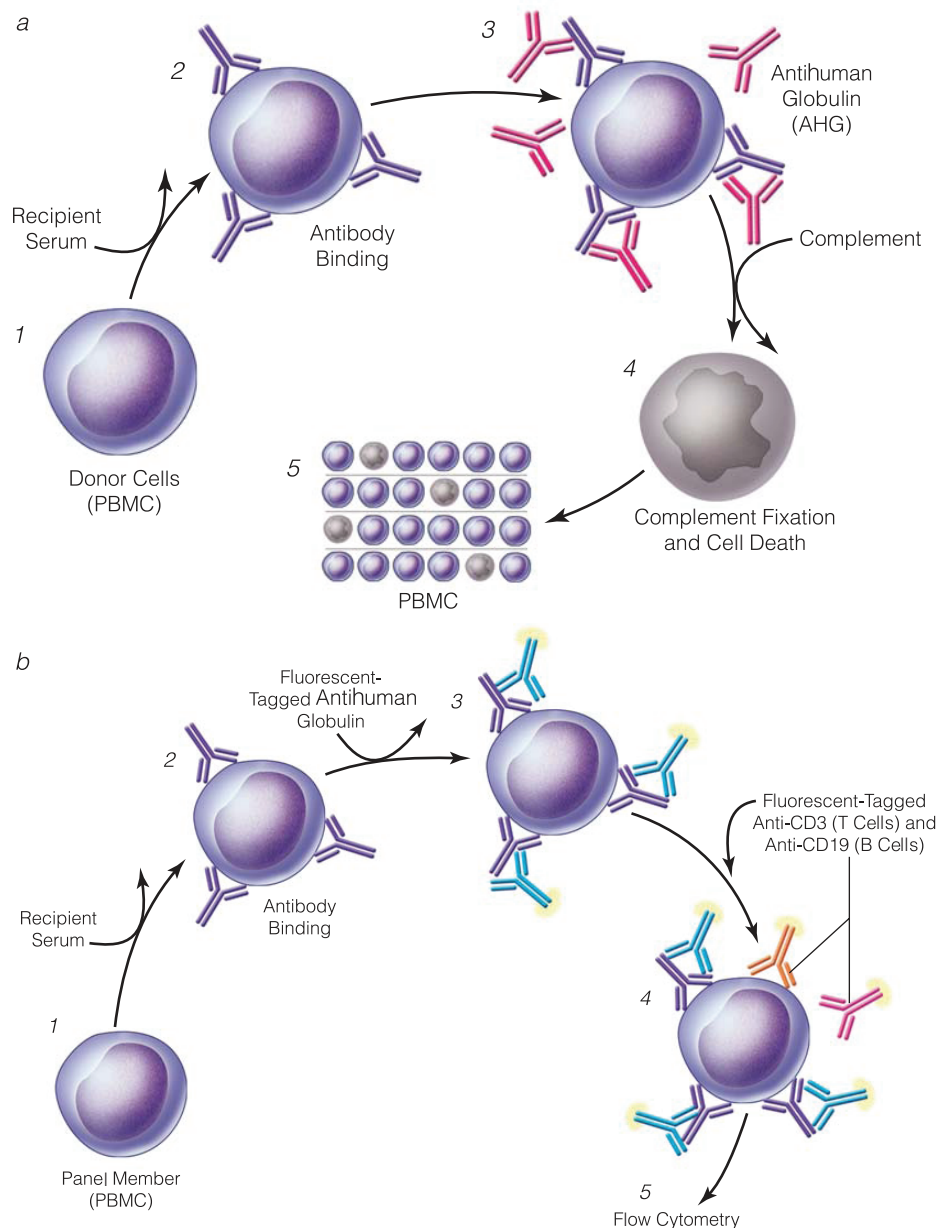


Figure 7 Recipient-donor crossmatch. (a) The sensitivity is enhanced by adding antihuman globulin (AHG) prior to adding complement in the complement-dependent cytotoxicity (CDC) crossmatch assay. (b) Crossmatching by flow cytometry is not reliant on complement activation for detecting antibodies and can be severalfold more sensitive than the CDC assay. PBMC = peripheral blood mononuclear cells.

smooth muscle cells with lymphocytic inflammation). Chronic active T cell-mediated rejection, usually termed “chronic allograft arteriopathy,” is characterized by arterial intimal fibrosis with mononuclear cell infiltration and the formation of neointima within the graft. Kidney allograft biopsies may also demonstrate interstitial fibrosis and tubular injury without a specific etiology, and these are graded as mild, moderate, or severe depending on the percentage of kidney cortex that is involved.²⁷ Use of these new classifications of immunologic injury to the renal allograft is the current standard of care, and they have essentially supplanted the previous categories, which were more focused on the timing

of the injury. Future therapies for rejection will be guided based on these updated criteria.

Cellular Rejection versus Antibody-Mediated Rejection

Transplant allograft rejection is defined by a combination of clinical features and characteristic histologic findings. As described above, hyperacute rejection, mediated by preformed antibodies, presents as a blue-black kidney with poor tissue turgor immediately after reperfusion. The kidney can subsequently swell with medullary congestion, cortical necrosis, and vessel thrombosis. Urine output is either never established or drops off precipitously. Histologic analysis will

reveal polymorphonuclear lymphocytes in the glomeruli, fibrin deposition, and platelet thrombi.

In the hours to days after transplantation, delayed hyperacute rejection or accelerated acute rejection can occur and is best characterized by positive C4d immunostaining on vascular endothelium from the allograft biopsy, with or without the features of lymphocytic infiltration, tubulointerstitial neutrophils, or acute tubular necrosis as seen in classic cell-mediated rejection [see Figure 8]. C4d deposition in peritubular capillary endothelium is a marker for complement activation associated with humoral rejection and currently represents the only specific indicator of AMR. The presence of C4d staining in the peritubular capillaries with evidence of DSA supports the diagnosis of AMR. DSA can be demonstrated pretransplantation or be shown to have developed subsequent to reperfusion often by using the solid-phase X-Map assays described above.

Acute T cell-mediated rejection of the kidney typically occurs in the weeks to months following transplantation. The most common presentation is an asymptomatic patient with a greater than 10% rise in serum creatinine above baseline. In addition, some patients will present with decreasing urine output, fluid retention, peripheral edema, and proteinuria. Patients may have low-grade fever or tenderness over the graft, but most commonly they are asymptomatic. The workup of these patients should include a detailed history determining exposure to infections, compliance with medications, and recent illnesses that may have contributed to prerenal azotemia [see Figure 9]. Trends of recent immunosuppressive drug levels can help determine the relative risk of rejection and the possibility of calcineurin toxicity and guide the surgeon's index of suspicion. Duplex ultrasonography of the transplanted allograft should be performed to document the patency of vessels and rule out a vascular cause of organ dysfunction. The sonogram also provides anatomic information, including the presence of hydronephrosis caused by either an ischemic ureteral stricture or external ureteral compression by an adjacent lymphocele. When rejection is suspected, allograft biopsy is performed and will provide an assessment of the presence and severity of cellular rejection.

In addition to the histologic features of cellular rejection, the biopsy should also be evaluated for C4d deposition to assess for AMR as this may uncommonly present later after transplantation. Appropriate correlation with DSA should be made in conjunction with the biopsy results.

Immunosuppressive Therapies

Induction agents A variety of agents are available for induction immunosuppression, and currently their selective use is based on an assessment of the recipient's risk of rejection for the intended allograft. In reality, the choice of induction agent is institution specific as definitive level 1 long-term data (with follow-up > 15 years) comparing different regimens and their outcomes do not exist.

Antithymocyte globulin Thymoglobulin is a rabbit-derived, antithymocyte globulin used for the treatment of acute rejection. Its mechanism of action involves blocking CD2, CD3, and CD45 and altering T cell function and ultimately leads to depletion of peripheral blood lymphocytes. When used as an induction agent for 3 to 10 days, thymoglobulin can establish profound T lymphocyte depletion that lasts beyond a year.^{9,28} Side effects can include cytokine release, serum sickness, anaphylaxis, leukopenia, and thrombocytopenia. Typically, it is infused over a period of 4 to 8 hours in a central vein with preadministration of acetaminophen and corticosteroids for prophylaxis against fever and allergic reactions. Because of thymoglobulin's profound T cell depletion, serious late sequelae can include cytomegalovirus infection and posttransplantation lymphoproliferative disease (PTLD). The overwhelming lymphocyte depletion and significant infective risk that results from thymoglobulin administration has raised questions over which population of recipients would benefit most from its administration.²⁹ A shorter duration of treatment has been shown to be efficacious in low-risk kidney transplant recipients.³⁰ In addition, in patients with DGF who have an increased risk of rejection, the 5-year incidence of acute rejection has been demonstrated to be lower in patients treated with rabbit antithymocyte globulin than among those treated with basiliximab.³¹

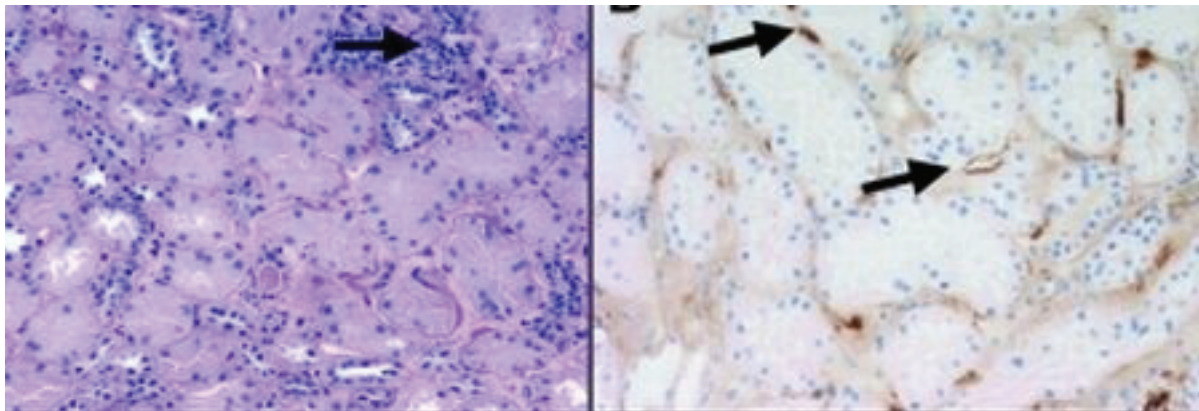


Figure 8 Histopathology of kidney allograft with antibody-mediated rejection. Immunohistochemical staining showing C4d complement deposition on renal peritubular capillaries is associated with humoral rejection after transplantation. In normal kidneys, C4d is detectable in the glomerular mesangium and at the vascular pole. Reproduced with permission from Pascual J et al.⁴⁹

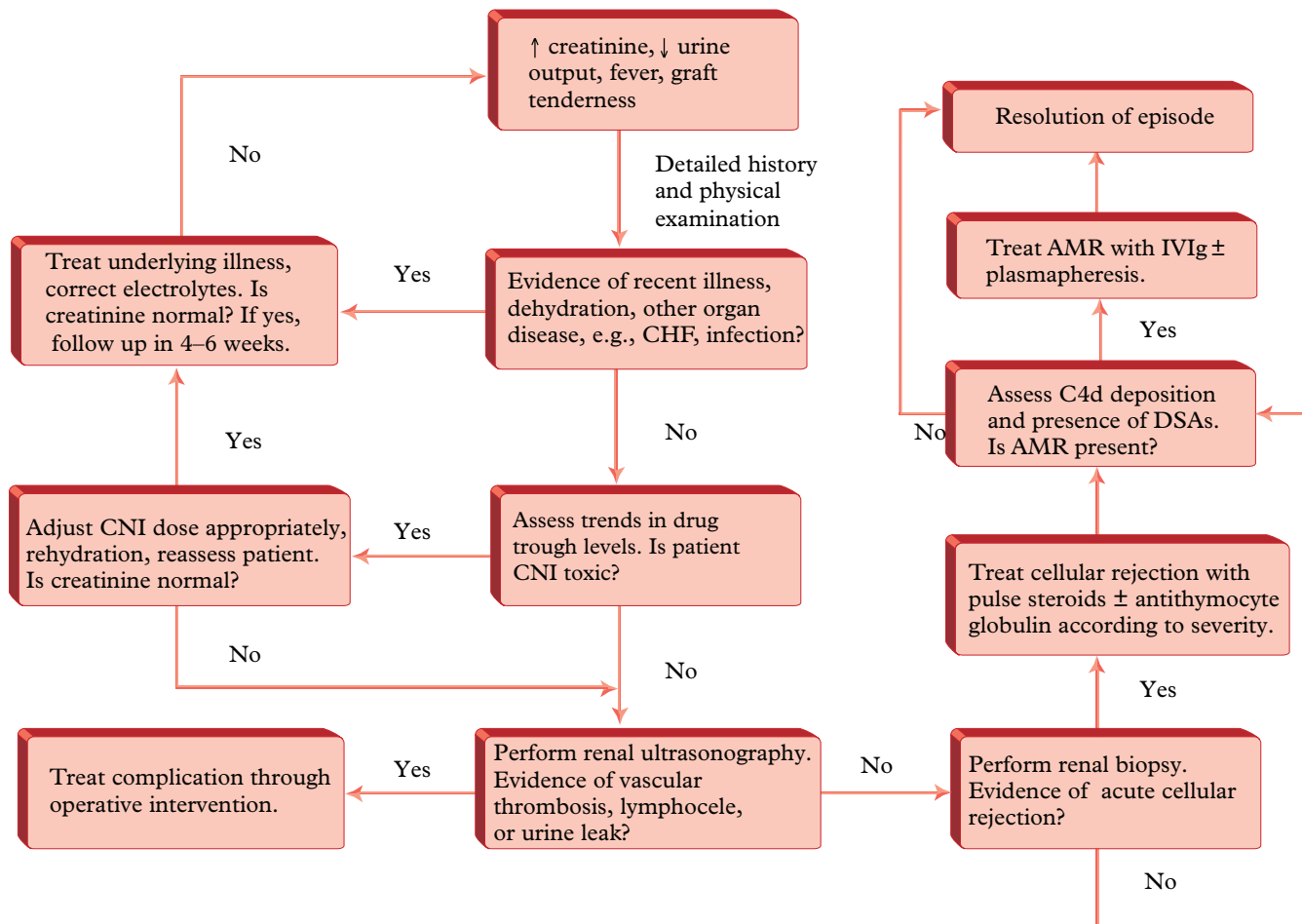


Figure 9 Algorithm for the assessment and management of renal allograft rejection. AMR = antibody-mediated rejection; CHF = congestive heart failure; CNI = calcineurin inhibitor; DSA = donor-specific antibody; IVIg = intravenous immune globulin.

Anti-CD25 monoclonal antibodies The prototypes for this class include basiliximab and daclizumab. Daclizumab was recently withdrawn from clinical use in transplantation. These anti-CD25 monoclonal antibodies that target the α chain of the IL-2 receptor on T cells and inhibit IL-2-mediated T cell proliferation on binding were designed to prevent rejection and not to treat active rejection. Typically, they are used in combination with other maintenance immunosuppression medications, such as CNIs and corticosteroids (see below). The advantages of basiliximab include its low immunogenicity, relatively long half-life in peripheral blood, low first dose-associated reactions, and the lack of need for drug-level monitoring. Administration of basiliximab at two 20 mg intravenous doses, preoperatively and then on postoperative day 4, produces saturation of the IL-2 α receptor sites for 30 to 45 days.³² This induction agent is best used in patients who have a low risk of graft rejection.³³

Alemtuzumab and rituximab Other agents used for lymphocyte depletion include alemtuzumab and rituximab. Their use in solid-organ transplantation remains controversial and should be reserved for selected patient populations. Alemtuzumab is a humanized monoclonal antibody used in the treatment of B cell chronic lymphocytic leukemia. It acts against CD52 and functions by causing cell lysis with prolonged and

significant depletion in a wide variety of immune cells. It use has been expanded as an induction immunosuppressive agent in kidney transplantation. The initial hope for its use was that it would allow for the development of immunosuppression protocols that would allow for sparing or avoidance of CNIs or corticosteroids.³⁴ Subsequent studies have shown a higher incidence of AMR in simultaneous kidney and pancreas transplant recipients receiving alemtuzumab.³⁵ Definitive, controlled trials are needed to establish the optimal dosing, long-term safety, and efficacy of alemtuzumab in transplant recipients.

Rituximab is a monoclonal antibody raised against CD20 that eliminates most B cell populations. It is approved for treating non-Hodgkin B cell lymphomas and was initially used in transplant recipients for treating PTLN.⁹ Currently, rituximab is used off-label in combination with plasmapheresis, IVIgG, and maintenance immunosuppression to treat deleterious alloantibodies.³⁶ It is unclear if the additional use of rituximab with plasmapheresis and IVIgG provides a significant benefit over plasmapheresis and IVIgG alone in the treatment of AMR in kidney transplant recipients.

Maintenance immunosuppression The choice of maintenance immunosuppression regimen varies from center

to center. The general strategy involves combining synergistic medications to maximize suppression while minimizing systemic toxicity.³⁷ Many regimens include the use of an antiproliferative agent (e.g., mycophenolate, sirolimus, everolimus), a CNI, and corticosteroids. Although azathioprine was the mainstay of antiproliferative agents in early regimens, it has now been largely replaced by mycophenolate.

Mycophenolate inhibits inosine monophosphate dehydrogenase (IMPDH), a critical enzyme in purine synthesis, and is available as mycophenolate mofetil (MMF; CellCept, Roche) or enteric-coated mycophenolate sodium (MPA; Myfortic, Novartis). MMF is a prodrug and requires conversion to the active compound MPA. Lymphocytes rely on de novo purine synthesis because salvage pathways for generating guanosine nucleotides are absent. Therefore, MPA selectively blocks T and B lymphocyte proliferation. The most common side effects include gastrointestinal distress, most notably diarrhea, and leukopenia.

Other antiproliferative agents include the mammalian target of rapamycin (mTOR) inhibitors sirolimus and everolimus. Sirolimus (Rapamune) is a macrolide antibiotic, structurally similar to tacrolimus, that binds FKBP-12 and inhibits mTOR, resulting in cell cycle arrest in the G₁ to S transition. Everolimus (Certican) has comparable function but has a shorter half-life. Although the efficacy of sirolimus has been demonstrated in randomized clinical trials in kidney transplantation, large, prospective, randomized trials have not directly compared MMF with sirolimus. The adverse effects of sirolimus include hyperlipidemia, impaired wound healing, and nephrotoxicity associated with potentiation of CNI toxicity. If CNIs are used in conjunction with sirolimus, the CNI dose should be reduced. Sirolimus has also been associated with higher rates of wound complications and hernias and is usually avoided until complete wound healing has occurred.

CNIs revolutionized the field of transplantation and allowed long-term graft survival that made solid-organ transplantations an acceptable form of therapy for end-organ failure. As described above, the two prototypical agents, tacrolimus and cyclosporine, bind intracellular FKBP and cyclophilin, respectively, to inhibit T cell production of IL-2 [see Figure 4]. Toxicities associated with CNI include neurotoxicity, nephrotoxicity, hypertension, hyperglycemia, and hyperlipidemia. Cyclosporine-associated hirsutism and gingival hyperplasia may prevent its use in certain patients, whereas tacrolimus-associated hyperglycemia and alopecia may also be limiting. Drug levels are monitored with both tacrolimus and cyclosporine to maximize immunosuppression and minimize potential toxicities from elevated levels.

Corticosteroids continue to be an important component in most immunosuppressive regimens used in solid-organ transplantation and are often used as first-line therapy to treat rejection.³⁷ Corticosteroids function through multiple mechanisms to provide immunosuppression. Steroids are lymphotoxic; limit lymphocyte distribution; inhibit IL-1, IL-2, IL-3, IL-6, TNF- α , and interferon gamma; and decrease antigen presentation by inhibiting DCs. Steroids mediate these functions by intracellular diffusion and binding to glucocorticoid response elements found on the promoter regions of critical cytokines. In liver transplantation, an intraoperative bolus of intravenous steroids is commonly used as the primary

induction agent. Adverse effects associated with steroids include obesity, hypertension, impaired wound healing, hyperglycemia, osteoporosis, and neuropsychosis.

As a result of these diffuse and nonspecific side effects, many centers have investigated the use of steroid-sparing or steroid avoidance protocols.^{38–40} In these studies, early withdrawal of steroids and steroid-free regimens were associated with an increase in biopsy-proven rejection but also demonstrated no significant differences in graft survival up to 5 years. Long-term (> 5 years) outcomes of steroid withdrawal protocols in kidney transplantation remain unknown. Many of these studies noted an improvement in other steroid-associated side effects, including cardiovascular risk factors, lipid profile, and weight gain, in the regimens using reduced steroids.

Costimulatory blockade Limitations to current immunosuppressive regimens include the lack of antigen specificity and the indiscriminate nature of global immunosuppression leading to opportunistic infection and the development of PTLTD. In addition, CNIs may contribute to diminished long-term allograft survival through direct nephrotoxicity and the development of chronic allograft nephropathy. Additional adverse effects associated with CNIs include hypertension, diabetes, and dyslipidemia. Costimulatory blockers have been investigated as novel therapeutic agents designed to avoid the chronic toxicities associated with CNIs and improve long-term allograft survival. Belatacept, a human fusion protein that combines a modified extracellular portion of cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) with the constant region fragment (Fc) of human IgG1, has been evaluated in phase II and phase III studies of kidney transplantation. In these trials, recipients who received belatacept versus cyclosporine had comparable patient and graft survivals at 12 months. However, the belatacept group had a higher incidence and grade of early acute rejection episodes and a higher rate of PTLTDs.^{41,42} Future questions to be answered include whether the higher rates of more severe rejection in the belatacept group will lead to a lower long-term graft survival with longer follow-up.

Treatment of rejection The approach to the management of allograft rejection depends on the type of rejection, the severity, and whether the episode represents a first occurrence or refractory rejection. In each case, the severity of rejection is best demonstrated by core-needle biopsy and histopathologic analysis. C4d staining and correlative DSAs are useful to evaluate for AMR. A stepwise approach to ruling out the other causes of rising creatinine in a kidney transplant recipient or other signs and symptoms suspicious for allograft rejection should be undertaken concurrently [see Figure 9]. Diagnostic tests to confirm or rule out these confounding causes should be undertaken, if indicated, before committing to additional immunosuppression.

In cases involving a first occurrence of rejection or mild acute cell-mediated rejection, pulse steroids in the form of intravenous methylprednisolone for 3 to 5 days are effective in reversing the majority of these episodes. When the rejection is severe or involves vasculopathy (Banff grade IIB or greater), or when the rejection episode is refractory to pulse steroids, treatment with rabbit antithymocyte globulin

(thymoglobulin) is indicated. Severe rejections may also benefit from increasing the drug levels of CNi temporarily to provide additional immunosuppression.

Therapeutic options in the patient with documented AMR include plasmapheresis alone, plasmapheresis with administration of IVIg, and plasmapheresis, IVIg, and rituximab. In cases where antibody levels are significantly high, the addition of rituximab may help lower the burden of antibody and ameliorate graft injury. However, the definitive benefits with the addition of rituximab in these patients remain unknown. In select cases, use of bortezomib (Velcade), a proteasomal inhibitor, may help reduce DSAs and help treat AMR in kidney transplant recipients.⁴³ It is important to remember that AMR may trigger a cascade of graft injury that can result in episodes of cellular rejection and that appropriate monitoring is required after treatment.

Summary

The clinical management of transplant recipients is based on the complex immunologic interactions between the donor organ and recipient outlined in the first part of this discussion. The innate immune system is the first line of defense,

with APC-derived TLRs engaging DAMPs and triggering the subsequent adaptive immune response. Optimal matching of a donor-recipient pair depends on precise HLA typing and accurate assessment of the immunologic risk in the recipient by evaluating preformed donor-specific antibodies. Cross-matching by flow cytometry and assessment of alloantibodies through solid-phase assays such as X-Map have become the standard of care. Carefully designed desensitization protocols have been used to limit the deleterious effects of alloantibodies and are used to supplement other creative approaches, such as kidney registries that match sensitized patients, to overcome the immunologic barrier. Treatment of allograft rejection requires a thorough understanding of the immunologic basis for allograft injury and currently involves histopathologic and immunohistochemical analysis of biopsied tissue. A variety of established agents form the mainstay of maintenance immunosuppression, but a host of novel agents are being developed that may play a role in selectively targeting alloimmunity without compromising host defense against pathogens.

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13 SURGICAL CONSIDERATIONS IN SOLID-ORGAN TRANSPLANT RECIPIENTS

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In 2008, over 27,000 patients received solid-organ transplants in the United States alone.¹ Advances in the management and the surgical techniques of solid-organ transplantation have led to a growing number of patients living long term with transplanted organs. In fact, the 5-year survival of living donor renal transplant and liver transplant has been reported at 91% and 79%, respectively.¹ As a result, general surgeons have a greater likelihood of encountering a posttransplant patient now than ever before.

Despite commonly held concerns, a large number of studies have demonstrated that immunosuppression is not a contradiction to surgery and good outcomes can be expected in the majority of patients.²⁻⁷ Additionally, abdominal surgery in transplanted patients is not infrequent, with reports of up to 10% of renal transplant patients experiencing a severe gastrointestinal (GI) complication within 10 years⁸ and 24% of liver transplant patients having another surgical procedure within 10 years.⁹

The extensive medication list of transplant recipients frequently seems complicated to caregivers with limited experience, often causing hesitation in evaluating these patients as surgical candidates. Additionally, it can be a challenging task to determine whether the benefits of the procedure outweigh the risks in this special population of patients. In general, as long as the surgeon adheres to basic surgical principles with frequent reevaluation and a low threshold for operative intervention, the disease processes should be manageable, with good outcomes.

It should be emphasized that these patients often present with surgical diseases in a manner unlike their immunocompetent counterparts and need aggressive intervention to achieve cures. Additionally, an appreciation for the balance between preventing graft rejection and infection or malignancy is essential.

This chapter focuses on special considerations in the solid-organ abdominal transplant patient. The goal of this chapter is to provide information for the practicing surgeon who is not at a transplant center to help decide when to perform an intervention or operation, how to modify standard procedures, and when to consider transfer to a transplant center if possible. It cannot be stressed enough that surgical intervention in these patients ideally should be carried out by the original transplant team. However, because the unstable or noncompliant patient is a reality, knowledge of perioperative management of transplant patients is critical for all nontransplant providers.

Preoperative Considerations

Discharge from the hospital is often met with anxiety in both the recent transplant recipient and his or her family

members and can be minimized by assurance and education. The transplant patient should have been counseled in medications, including the doses, functions, side effects and potential drug interactions, and recognition of signs and symptoms of rejection and infection. Therefore, patient participation should not be underestimated.

An extensive and expensive workup is unnecessary for minor ambulatory surgery in this population as there is a small complication rate and a low risk of compromising graft function.⁹ The surgeon should remember that the workup should focus more on the indicated procedure rather than the patient's immune status.^{9,10} Nevertheless, a thorough preoperative evaluation and understanding of the special considerations in this population are necessary to reduce risk.¹¹ There is typically no need to change medications around a minor procedure, except in select cases [see Management of Immunosuppression during the Perioperative Period, below].

When planning a major surgical procedure, it is essential for the surgeon to have knowledge of the patient's graft function. This will aid the surgeon in optimizing perioperative management of fluid and electrolyte status, medications, blood pressure, and ventilation as well as anticipating immediate postoperative care.¹² Consideration of transplant patients undergoing major surgery should follow the algorithm shown in Figure 1. Patients should provide a thorough history of symptoms related to their graft. For example, renal transplant patients vary in their ability to concentrate urine, and to avoid further graft dysfunction, it is critical to provide adequate hydration and careful monitoring of serum electrolytes. Liver transplant recipients should be asked about jaundice, pruritus, change in the color of urine or stool, and fluid retention.

Renal transplant patients often have associated multiorgan disease as a result of their primary condition (i.e., diabetes mellitus, hypertension) and should be evaluated for symptoms of underlying disease on a physical examination. Liver transplant recipients should be evaluated for underlying liver dysfunction: asterixis, ascites, and edema. As with renal and liver transplant recipients, pancreas transplant recipients should have a thorough physical examination with particular attention to the abdomen.

In most cases, standard laboratory values are adequate. For instance, in renal transplant recipients, an assessment of creatinine, urine protein/creatinine ratio, and glomerular filtration rate (GFR) may suffice. In liver transplant patients, assessment of coagulation and liver function tests (LFTs) may be adequate. In general, bilirubin and synthetic function becomes normal within 3 months following transplantation, and trends in LFTs should be monitored for abnormalities. Pancreas transplant recipients should have serum amylase and lipase, urine amylase (for bladder-drained transplants), and glucose levels monitored. Additionally, as the nutritional

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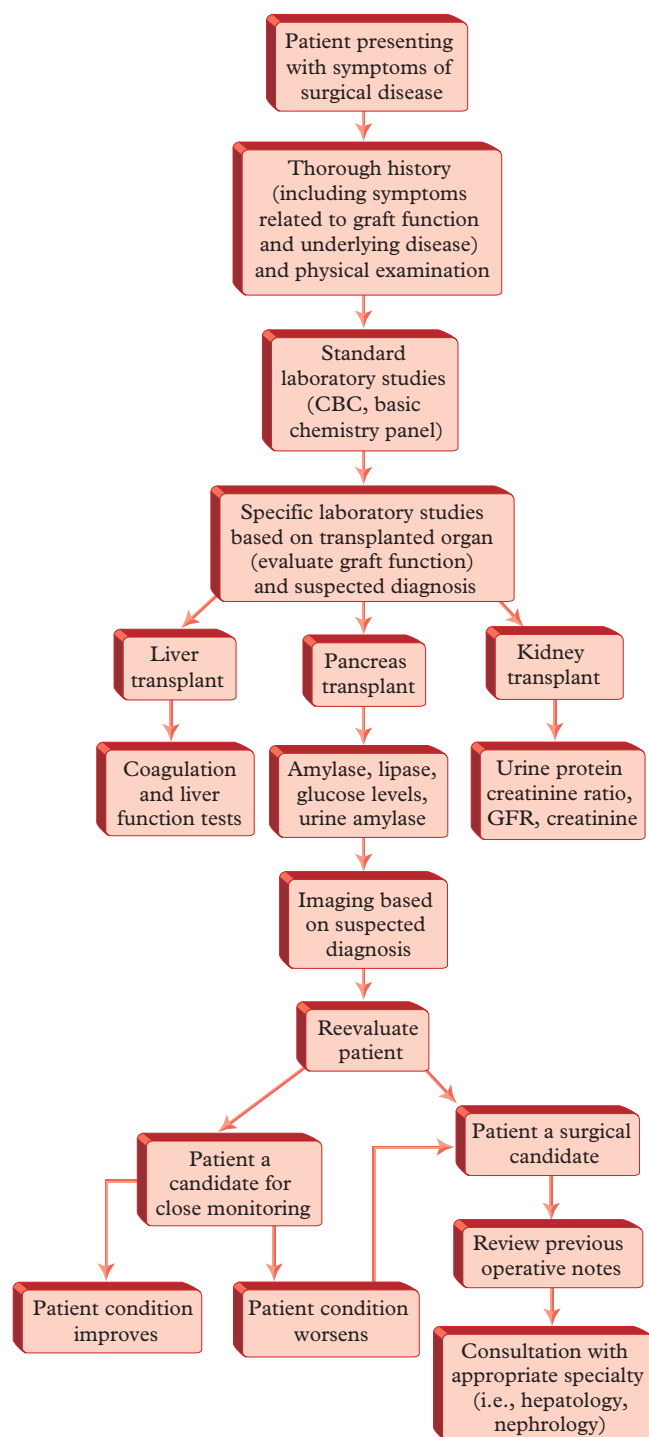


Figure 1 Algorithm for transplant patients who may need surgical management. CBC = complete blood count; GFR = glomerular filtration rate.

status of any patient is critical to decrease the risk of infection and improve wound healing, it is especially important in this particular patient population.^{9,11–15} Whenever possible, appropriate specialists (i.e., nephrologists, hepatologists) should follow the patient in the perioperative period.

As in any surgical procedure, it is essential to know the patient's anatomy and examine previous operative notes if at all possible [see Table 1 for a summary of common locations

and procedures for each transplant]. This will allow consideration of altered anatomy that can lead to unexpected complications. For instance, in patients who have had kidney transplants, the location of the organ, particularly the ureter, is crucial to avoid injury. A previously transplanted ureter looks remarkably like an adhesion even to the trained eye, and many have been divided during uncomplicated lysis of adhesions. This is particularly likely if the kidney was placed through a midline incision and the surgeon does not know on which side the graft was placed.

In patients who have undergone a pancreas transplant, one must consider if a Roux-en-Y reconstruction for drainage of the duodenum was used (or if the pancreas was bladder drained, although this is far less common in recently transplanted pancreata) or if the vein drains via the superior mesenteric vein or the iliac vein in the recipient. Likewise for the liver, knowledge of any vascular reconstructions is critical.

Diagnostic and Radiologic Considerations

Although the physical examination is critical in the evaluation of any surgical patient, caution must be exercised in the transplant patient, particularly those patients who have been on immunosuppression for many years. It is not unheard of to explore a patient with a near-normal examination and be surprised to find an abdomen full of succus. For this reason, we are aggressive in obtaining abdominal imaging in the majority of transplant patients who are being evaluated for an intra-abdominal process.

Consideration should be made for diagnostic sampling of any fluid collections or free intra-abdominal fluid that is not expected to rule out surgical causes. Fluid is typically sent for Gram stain and culture, bilirubin, amylase, creatinine, and any other biochemical marker that is relevant to the situation. In general, it is acceptable to follow patients conservatively if that is the judgment of the caregiver, but frequent reassessments are necessary. If the patient does not improve quickly, consideration should be made for aggressive intervention or at least reimaging.

When it comes to choosing radiologic imaging, similar algorithms should be used, as in the nontransplant patient. As in their immunocompetent counterparts, immunocompromised patients may undergo ultrasonography to evaluate the biliary tree, kidneys or ureters, and the female reproductive organs. Computed tomography (CT) is the best tool for assessment of intra-abdominal fluid.¹⁶

Transplanted patients being evaluated for trauma should be assessed as any other trauma patient.^{10,17} Kidney transplant patients often have creatinine levels that run higher than those in the nontransplant patient, with values in the range of 2 mg/dL or above even with stable function. Appropriate hydration decreases the risk of nephrotoxicity similar to that of nontransplant patients,¹⁷ and standard bicarbonate protocols are similarly helpful. If CT is warranted for safe management of the trauma, it should be conducted. It may be useful to hold the calcineurin inhibitor (cyclosporine or tacrolimus) for a few days following the contrast load as these drugs are nephrotoxic. Holding a calcineurin inhibitor for a few days in the setting of a trauma

Table 1 Anatomic and Diagnostic Details of Abdominal Organ Transplants

<i>Solid-Organ Transplantation</i>	<i>Anatomic Location and Variability</i>	<i>Anastomoses</i>	<i>Relevant Laboratory Studies</i>	<i>Common Medical Sequelae, Presentation, and Diagnostic Tests</i>
Liver	Bilateral subcostal incisions with midline extension. Liver is placed in an orthotopic position.	In a piggyback technique, the suprahepatic vena cava of the donor is anastomosed to the orifice of the hepatic veins of the recipient. In caval replacement, recipient cava is removed and the suprahepatic and the infrahepatic cava of the donor are anastomosed end to end. End-to-end arterial anastomosis using aortic Carrel patch of donor celiac artery and branch patch of recipient artery at right and left bifurcation. Variations are possible. Also consider aortic jump graft from supraceliac or infrarenal aorta to donor celiac. Biliary anastomosis via duct to duct or hepaticojejunostomy with a Roux-en-Y reconstruction depending on underlying biliary pathology.	PT/PTT, AST/ALT for liver function; bilirubin, GGT, alkaline phosphatase for biliary stricture or cholangitis	1. Acute rejection: elevated LFTs; biopsy advised 2. Chronic rejection: elevated LFTs, liver dysfunction, ascites; biopsy advised 3. Recurrent disease (HCV most common): elevated LFTs, liver dysfunction, ascites, portal hypertension; biopsy and HCV PCR advised 4. Biliary pathology (i.e., stricture, cholangitis, biloma); assess arterial patency with ultrasonography or CTA; ERCP for direct assessment; if Roux-en-Y hepaticojejunostomy, MRCP and/or PTC
Pancreas	Midline incision used most frequently. Rarely, two lateral incisions for simultaneous pancreas-kidney transplantation. Usually, pancreas is on right side, placed head (duodenum) up posterior to the right colon.	Donor iliac bifurcation graft (that is reconstructed to the SMA and splenic artery of the donor pancreas) anastomosed end to side to recipient common iliac artery. Donor portal vein to recipient vena cava or common iliac artery. Some centers use superior mesenteric vein tunneled retrocolic with a jump graft. Duodenum usually enterically drained to jejunum. Occasionally, bladder is drained, in which case will sit head (duodenum) down.	Amylase, lipase	1. Allograft pancreatitis: elevated amylase/lipase; CT 2. Fistula and abscess: fevers, sepsis, pain; CT 3. Urologic complications in bladder-drained pancreas: urethritis, hematuria, frequency, metabolic acidosis; cystoscopy
Kidney	Retroperitoneal entry through oblique incision (Gibson) above the inguinal ligament	Renal artery(s) end to side to common or external iliac artery. Renal vein to common or external iliac vein. Ureter plugged directly into bladder. Occasionally, ureter sewn to native ureter (ureteroureterostomy).	Creatinine, urine protein/creatinine ratio, GFR	1. Acute cellular rejection: elevated creatinine, leg swelling and fluid overload; biopsy advised 2. Chronic allograft nephropathy (i.e., interstitial fibrosis/tubular atrophy): elevated creatinine, fluid overload; biopsy advised 3. Hydronephrosis: elevated creatinine, pain; ultrasonography or CT, nephrostography 4. UTI: fevers, dysuria, dehydration, elevated creatinine; UA/culture 5. Recurrent disease: elevated creatinine; biopsy advised

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; CTA = computed tomographic angiography; ERCP = endoscopic retrograde cholangiopancreatography; GFR = glomerular filtration rate; GGT = γ -glutamyl transferase; HCV = hepatitis C virus; LFT = liver function test; MRCP = magnetic resonance cholangiopancreatography; PCR = polymerase chain reaction; PT = prothrombin time; PTC = percutaneous transhepatic cholangiography; PTT = partial thromboplastin time; SMA = superior mesenteric artery; UA = urinalysis; UTI = urinary tract infection.

typically is safe. Depending on the patient, extra steroids (such as the equivalent of 10 to 30 mg of prednisone per day) can be considered during this period, although, again, if use is limited to a few days, it is probably unnecessary. Ideally, this would be done in consultation with an appropriate specialist or transplant center.

Intraoperative Considerations

Since the introduction of minimally invasive techniques, transplant surgeons have been active participants in its use, from ultrasound-guided biopsy to laparoscopic donor nephrectomy. As in immunocompetent patients, the use of minimally invasive techniques in immunocompromised patients is safe and provides the same benefits, such as decreased hospital stay and narcotic use, as well as comparable or even improved complication rates.^{18–21} A skilled laparoscopic surgeon should always offer the immunocompromised patient the laparoscopic alternative when available and feasible.

During any reoperation following a kidney transplantation, one should always be thinking of the ureter. If one does come across and divide the ureter unexpectedly, the most likely repair will be a ureteroureterostomy, using the patient's native ureter and sewing it end to end over a stent after spatulation. Most commonly, this does not require a native nephrectomy even if the patient's native kidney makes urine, although, in occasional cases, hydronephrosis can follow, requiring a native nephrectomy at a later time point.

As a general rule, similar principles of surgical technique should hold with the transplant patient. Additionally, any procedure that is reasonable in the nontransplant patient can be used in the transplant patient. We do caution the practitioner who has not had a lot of experience with transplant patients that the long-term immunosuppressed patient in particular certainly has an increased risk of poor healing or wound or anastomotic dehiscence. Moreover, the patient will not always show the signs of sepsis that are commonly noted when this happens. Note that there is no real definition of "long term," and this is an anecdotal observation. In general, those patients who have been immunosuppressed for a decade or more seem to be at higher risk for complications related to healing. Therefore, any transplant patient who simply does not progress and heal in a fashion that seems reasonable should be considered for a complication, and aggressive radiologic assessment is recommended.

Antibiotics and Pain Medicine in the Perioperative Period

It is well established that immunocompromised patients encounter many more infections than their immunocompetent counterparts, in particular rare fungal, bacterial, and viral infections.^{10,15,22–28} Fifty to 70% of transplant patients have at least one episode of bacterial infection, and 30 to 60% have at least one serious viral infection.^{10,29} In general, posttransplant patients have a predictable infectious course: within the first posttransplant month, infections are comparable to those of their immunocompetent counterparts and are usually bacterial in nature; in months 1 through 6, patients are at risk for opportunistic infections, including

Pneumocystis carinii, *Listeria monocytogenes*, and *Aspergillus* species; more than 6 months posttransplantation, two thirds of patients suffering from an infection will develop a community-acquired respiratory virus, whereas the remainder will develop chronic viral infections (such as hepatitis B and C viruses). A group at particular risk are those who received excessive amounts of immunosuppression as a result of early rejection or delayed graft function, causing the greatest risk of infection from opportunistic pathogens such as *Cryptococcus neoformans*, *P. carinii*, and *L. monocytogenes*.^{30,31} Other viruses that are quite well known to transplant physicians are cytomegalovirus and BK virus, which can cause nonspecific symptoms such as fevers or diarrhea but can also cause graft dysfunction or loss of a graft. Certainly, any transplant patient who is suffering from more than an easily diagnosable and treatable urinary tract infection, pneumonia, or line infection should undergo workup for these pathogens, and consideration should be given to transferring to a transplant center.

There is no evidence of prolonged perioperative antibiotic (greater than 24 hours) use despite the widespread use of prophylactic antibiotics in a patient's medication regimen. This is attributable to an increased risk of viral and fungal infections in addition to superinfection with resistant bacteria and/or *Clostridium difficile*.^{11,32} Surgical prophylaxis should include therapies against skin flora such as staphylococci and streptococci and, in renal transplant patients, the inclusion of therapies against urine species such as *Escherichia coli*, *Klebsiella*, and *Proteus*. In suspected infection, empirical therapy should be guided by the suspected anatomic site and organism, previous antibiotic therapy, renal and hepatic function, and immunosuppression status. Continued therapy after identification of an organism should be as specific as possible with consideration of renal and hepatic function.

Postoperatively, consideration of hepatic and renal function is necessary when choosing medications such as narcotics and antihypertensives. For example, in patients with suboptimal liver function, morphine, meperidine, or propoxyphene for pain management and clonidine or nifedipine for hypertension are preferred.⁹

Management of Immunosuppression during the Perioperative Period

Immunosuppression in the solid-organ transplant patient often includes several agents with different mechanisms to use lower doses and decrease potential toxicity.³¹ Additionally, in the late postoperative period (2 to 6 months), immunosuppression is usually decreased as the allograft is typically functioning well and rates of rejection are highest in the first 6 months, with decreasing incidence thereafter. When considering elective procedures, it may make sense to delay them for up to 6 months after transplantation or at least the point where they are down to their baseline maintenance immunosuppression. This, of course, has to be balanced with the urgency or risk of delaying the surgical procedure.

Immunosuppression is associated with an increased susceptibility to infection and poor wound healing.^{10,33} However, a balance between preventing graft rejection

and anticipating the patient's response to surgical stress must be appreciated. If the procedure is unable to be performed by the original transplant team, the surgeon should not hesitate to consult a transplant service for immunosuppressive guidelines.⁹

Although historically there has been concern over a immunocompromised patient's ability to undergo surgical procedure, a number of studies demonstrate that these patients are able to undergo a variety of procedures with complication rates similar to those of their immunocompetent counterparts^{34–37} and without an increased risk of wound healing problems.^{9,38,39} In general, immunosuppression is not altered during the perioperative period unless the patient is demonstrating significant infection or sepsis. It should be given at the same schedule and dose as the patient's home regimen.⁹ If the patient is unable to take anything orally, azathioprine and mycophenolate mofetil (MMF) can be safely withheld for 2 to 3 days. Intravenous cyclosporine can be used at one third the total daily oral dose over 4 to 8 hours. Until the patient is able to tolerate immunosuppression by mouth, immunosuppression levels should be checked daily, with the goal of having no variation from baseline greater than 25%.⁹ There are some exceptions to this, however. Most transplant surgeons would suggest discontinuing sirolimus and changing to a calcineurin inhibitor as sirolimus has been known to impair wound healing.^{11,40}

In our own practice [see Table 2 for a summary of the medicines and recommended adjustments], for minor procedures, we do not recommend any change in immunosuppression. Patients can take their medicines on the morning of surgery and resume them that night or the next morning, depending on how they are feeling. It is important that patients stay well hydrated perioperatively as the calcineurin inhibitors are nephrotoxic, and this is compounded by a prerenal state. Therefore, we are more aggressive about admitting patients for a day or two after surgery or at least following their laboratory results (organ specific labs are drawn as outpatients at their local clinic/hospital, and results are faxed to the transplant unit) as outpatients and seeing them more frequently if admission is not necessary or feasible. For more extensive procedures, particularly those that will require patients to be nihil per os (NPO) for a period of time, we typically hold their calcineurin inhibitor and put them on the equivalent of 20 to 30 mg of intravenous prednisone per day (we typically use dexamethasone, 2 mg every 8 to 12 hours IV, until they can return to their home dose). This obviously depends on what organ they have received, how recent the transplantation was, and what their rejection history is.

If the patient is well clinically and at high risk for rejection (young, recent transplant, previous episodes of rejection, African American, kidney transplant recipient), then consideration can be made for using intravenous cyclosporine if the patient is on that medication or sublingual tacrolimus (typically half the dose of oral). If this is done, levels should be followed daily until they return to the patient's normal oral dose and baseline levels have been achieved. If at all possible, we do recommend at least discussing the plan with the transplant physician prior to the surgery and, ideally, having his or her input in the perioperative period. If the

patient is on MMF, we usually continue this drug intravenously. A well-known side effect of this drug is diarrhea or other GI symptoms, so if the procedure is a major GI operation, it may be necessary to hold this until bowel function normalizes.

We would offer caution considering any operation on a patient who is on sirolimus. This drug has a dramatic effect on wound healing, and, ideally, we stop this drug 2 months before an elective procedure, substituting a calcineurin inhibitor if possible. We would prefer that the patient remain off this drug at least 2 months after the procedure, assuming that the wound has healed well. For those patients who have more urgent procedures, we would at least recommend that sirolimus is held postoperatively for 2 months or more, again substituting alternative agents. All of these decisions should be made in concert with the transplant physicians.

A common concern for nontransplant practitioners is the use of stress-dose steroids in the transplant patient population. Although patients on immunosuppressive medications may have abnormalities of the pituitary-adrenal axis, there is no evidence to support the use of increased steroids in the perioperative period.^{9,33,41} In fact, the use of high-dose steroids promotes poor wound healing, causing both slower healing and decreased strength of the wound.^{9,10} This effect has been offset by the administration of vitamin A supplementation.^{10,42} Stress-dose steroids may be indicated when a patient demonstrates adrenocortical insufficiency, as evidenced by clinical symptoms of weakness, nausea, vomiting, and fever.² To reiterate, the use of stress-dose steroids is not supported or advocated prophylactically in any procedure. It may be reasonable to consider stress-dose steroids in the septic patient or those patients undergoing major surgery with unexplained hypotension or other signs of adrenocortical insufficiency but otherwise may not be necessary.

Complications

Fortunately, the complication rate for elective procedures in this patient population is similar to that of immunocompetent patients. However, emergent procedures are associated with increased morbidity and length of hospital stay.⁹ Most authors would advocate an aggressive approach to this group of patients, with surgical revision early if possible.¹¹ It is crucial to remember that transplant patients can have very subtle findings even with major postsurgical complications or infections. As a general rule, any patient who is not progressing as expected should undergo aggressive workup for complications, including liberal use of imaging and diagnostic tapping or reoperation in response to unexpected fluid collections. All fevers should be worked up aggressively either for preexisting infections or peri- or postsurgically acquired infections.

Follow-up

Follow-up for the immunocompromised patient after surgery should proceed in the same manner as performed in an immunocompetent patient. Generally, patients are seen 2 weeks after discharge depending on the hospital course and condition of the wound. Patients are continued on their

Table 2 Considerations for Common Immunosuppressive Agents

Common Immunosuppressive Agent	Mechanism of Action	Therapeutic Levels	Perioperative Management	Sepsis Management	Relevant Known Impact on Surgery	Common Side Effects	Main Advantages
Steroids	Inhibition of macrophage cytokine production; inhibition of IL-1, IL-6, TNF secretion; suppress T cell cytokine production	Not measured	Stress-dose steroids (10–30 mg prednisone/day) is appropriate in a trauma setting, sepsis, or demonstration of adrenocortical insufficiency. No data supporting use in elective cases.	Stress-dose steroids may be considered	Poor wound healing, increased risk of infection. In general, can proceed with surgery.	HTN, weight gain, peptic ulcer disease, GI bleeding, personality changes, cataract formation, hyperglycemia, increased susceptibility to pyogenic and opportunistic infection	Cheap, wide-spread use
Calcineurin inhibitors (cyclosporine, tacrolimus)	Cyclosporine: inhibition of helper T cell cytokine production, particularly IL-2; impairs maturation and propagation of thymic CD4 ⁺ and CD8 ⁺ T cells Tacrolimus: inhibits T cell activation, blocks induction of IL-2; blocks cytokine production; indirectly blocks T cell proliferation	Cyclosporine trough levels: kidney transplant < 6 months—aim for 250–350 µg/L; > 6 months—aim for 100–200 µg/L Tacrolimus trough: typically 8–10 ng/mL	Hold for 2–3 days following radiographic contrast load; if NPO, calcineurin inhibitors are held and patients placed on 20–30 mg of prednisone/day IV; high-risk patients may have oral calcineurin inhibitors held and be placed on IV cyclosporine or sublingual tacrolimus	Consider holding and maintain only on prednisone	Very narrow therapeutic window requires great care in prescribing medications also metabolized by the P-450 system	Cyclosporine and tacrolimus: nephrotoxic posttransplantation diabetes, HTN, headache, tremors	Cyclosporine: no myelosuppression Tacrolimus: more potent, no hirsutism or gum hypertrophy
Mycophenolate mofetil (MMF)	Prevent differentiation and division of immunocompetent lymphocytes	Typically levels not measured, although MPA levels are available	If NPO, may be changed to IV or safely held for 2–3 days if major GI procedure	Consider holding and using steroids alone		GI upset/diarrhea	Potent
Azathioprine	Prevent differentiation and division of immunocompetent lymphocytes		May be held for 2–3 days if patient is NPO	Consider holding and using steroids alone		Bone marrow suppression, liver toxicity, skin cancers	Not used as much as MMF
Sirolimus	Inhibition of IL-2 signaling to cell nucleus		If major procedure, hold for 2 months previously and substituted with calcineurin inhibitor; if emergent, hold for at least 2 months postoperatively and substituted with alternative agents	Consider holding and using steroids alone	Delayed wound healing, which can be severe; increased incidence of lymphocele formation	Increased triglycerides; decreased platelets; decreased hemoglobin; increased proteinuria	Decreased nephrotoxicity

GI = gastrointestinal; HTN = hypertension; IL = interleukin; IV = intravenous; MPA = mycophenolic acid; NPO = nihil per os; TNF = tumor necrosis factor.

home immunosuppression, and, as stated previously, unless there is a specific reason, antibiotics are not extended. In our practice, wounds are left covered for 48 hours after surgery, and staples are typically removed 3 weeks after surgery to account for slow healing. Obviously, clinical assessment of wounds may override these recommendations. Levels of calcineurin agents (cyclosporine or tacrolimus) should be followed closely for a few weeks after surgery until the preoperative therapeutic range is achieved. It is common for people to have either high or low levels after surgery, particularly until bowel function has returned to normal. There is a risk that rejection can occur in the postoperative period if levels are too low, and if a patient is having difficulty getting the level up quickly, extra steroids (or another agent) may be required for a few weeks while the level is returning to baseline.

When to Consider Transfer to a Transplant Center

The decision on when to transfer a patient to a transplant center will depend on many factors, including geography, comfort level of the caregivers, desires of the patient, size of the procedure, organ that was transplanted, and postoperative course. Many procedures can be conducted safely on transplant patients without specialized care from a transplant center. However, some patients are reluctant to have anyone other than their transplant physicians treat them once they have received a transplant, and some transplant physicians likewise will agree with that. Ideally, a discussion will take place with both the patient and the transplant physician prior to the procedure to make a plan. If a surgeon is comfortable performing a procedure or operation, the same attention to good technique will apply to these patients. All postoperative complaints or findings should be evaluated very carefully, and if at any point a patient is not progressing appropriately, contact should be made with the transplant center with consideration of transfer. A transplant physician or specialist with some comfort in transplant medications or infections should be consulted if at all possible. Discussions with transplant physicians or pharmacists regarding medications and any alterations in them should be conducted daily if possible.

Special Considerations

ACUTE APPENDICITIS

Although the occurrence of acute appendicitis in the general population is widespread, its frequency in transplant recipients is quite rare, with a reported rate of 0.2% in liver, heart, kidney, and pancreas recipients.⁴³⁻⁴⁶ Nevertheless, given the rising number of transplant recipients, knowledge of the management of this disease in this patient population is important.

In the past, appendectomies in conjunction with a pancreas transplant were routine to prevent misdiagnosis of transplant pancreatitis. However, the low incidence and reliability of modern imaging in visualizing acute appendicitis no longer make this current practice at most institutions.

Ultimately, transplant recipients found to have acute appendicitis should be managed similarly to nontransplant

patients with the use of laparoscopy based on surgeon preference. As with any intra-abdominal pathology in a transplant recipient, clinical signs can be subtle. Therefore, imaging is crucial in securing the diagnosis.

Our institution is aggressive about proceeding with operative management in patients with acute appendicitis. If management of nontransplant patients includes consideration of percutaneous drain placement and interval appendectomy in perforated and walled-off appendicitis, the same can be considered in the transplant patient. These patients do require close monitoring with serial examinations and reimaging. It cannot be stressed enough that the signs and symptoms of progression can be subtle. A low threshold to abandon conservative management in favor of operative intervention should be considered in patients who do not rapidly improve.

SMALL BOWEL OBSTRUCTION

As a result of medical immunosuppression, transplant recipients rarely develop extensive adhesions causing small bowel obstruction. However, it has been hypothesized that transplant and nontransplant patients develop small bowel obstruction similarly, mainly the formation of adhesions following intra-abdominal surgery. Additionally, there have been reports of small bowel obstruction secondary to internal hernias in pancreas transplant recipients.^{47,48} The increased risk of malignancy in this patient population should also make the surgeon suspicious of a malignant etiology.

As in nontransplant patients, obstruction can be fatal and should be managed similarly. Conservative management with nasogastric tube decompression, hydration, and close monitoring is appropriate. If the patient does not improve quickly, operative management is imperative.

PEPTIC ULCER DISEASE

Prior to the advent of histamine₂ blockers, mortality from peptic ulcer disease in this patient population was as high as 40%^{49,50} and was even reported to be approximately 4% only a few years ago.⁵¹ The cause of peptic ulcer disease in this patient population is multifactorial. There have been reports of up to 62% of living donor liver recipients^{52,53} and approximately 30% of renal transplant recipients with *Helicobacter pylori* colonization.^{8,51,53,54} Additionally, high-dose steroids used to treat rejection have been found to be ulcerogenic,⁵⁵ and MMF has been found to cause ulcer perforation or bleeding in 3 to 8% of patients within 6 months.⁵⁶

Transplant patients are typically placed on prophylactic medications in the perioperative period to prevent the development of peptic ulcer disease. Fortunately, in our practice, we have rarely had to operate on this as in our nontransplant patient population. Surgical management, when necessary, should be no different than in the nonimmunosuppressed patient.

BILIARY TRACT PATHOLOGY

Cyclosporine therapy has been associated with biliary calculous disease and primary choledocholithiasis.¹⁰ However, studies have demonstrated the safety of cholecystectomy

following transplantation despite previously held beliefs regarding immunosuppression and surgery.⁴⁹

Biliary tract pathology is common in liver transplant recipients, with an incidence of 10 to 30% and the majority seen within the first 6 months posttransplantation.⁵⁷ Most commonly, anastomatic stricture of the bile duct following duct to duct reconstruction occurs, resulting in patients who present with symptoms of cholangitis. Elevated bilirubin, fevers, and sepsis warrant urgent endoscopic cholangiopancreatography and broad-spectrum antibiotics. Because of the tenuous condition of these patients, transfer to a transplant center is highly recommended.

DIVERTICULITIS

Diverticulitis in the transplant patient population is higher (1% versus 0.02%)⁵⁸ and more aggressive⁵⁹ than in the general population. In a study comparing immunosuppressed and immunocompetent patients with acute diverticulitis, immunosuppressed patients were found to have an increased risk of free perforation (43% versus 14%) and postoperative mortality (39% versus 2%).⁶⁰ Therefore, patients are typically offered surgical intervention following a single episode of uncomplicated diverticulitis if it is safe and once the acute episode resolves.⁶¹ Although there is a paucity of data to support this in the literature, the risk of complications from recurrent episodes and difficulty in diagnosing these patients until they progress to a later stage of disease may be an incentive to intervene earlier than in nontransplant patients.

Acute episodes of diverticulitis are managed conservatively with broad-spectrum antibiotics and percutaneous drain placement. However, frequent reassessment and reimaging are critical. Interval surgical intervention should always be considered if the patient does not progress. In our practice, we have been cautious in performing a primary anastomosis in acute complicated diverticulitis in the sigmoid region, particularly in patients on long-term immunosuppression. We favor reestablishing continuity 3 to 6 months later. Of note, great caution should be taken with patients on sirolimus at the time of presentation. These patients are notoriously poor at healing, and strong consideration should be given for diverting these patients in the acute setting.

MALIGNANCY

Clinicians should have an appreciation for the increased risk of cancer associated with immunosuppression. Although the exact risk remains controversial, the incidence of malignancy in transplant recipients is increasing, and there are estimates that after 10 years of chronic immunosuppression, the incidence of malignancy is 20%.⁶² The risk of malignancy can vary based on the medication and type of cancer and is believed to be closely associated with overall exposure to immunosuppression.⁶²

In general, solid-organ tumors of the GI tract have an approximately 1.25 to 5 times and lymphomas a 10 times greater incidence in transplant patients.⁶³ In solid-organ transplant recipients, nonmelanotic skin cancers are extremely common,^{64,65} with transplant patients at a 65-fold increased risk of developing squamous cell carcinoma.⁶⁶ For this reason, all patients should be followed by a dermatologist.

As with nontransplant patients, transplant patients with solid tumors should be followed under the same oncologic principles. Multidisciplinary teams including transplant physicians, oncologists, and surgeons are necessary for the care of these patients.

A special note should be made regarding posttransplantation lymphoproliferative disorder (PTLD). PTLD is the second most common malignancy seen in renal transplant patients⁶⁷ and the most common malignancy in liver transplant patients.⁶⁸ It can have variable presentations, including abdominal pain, small bowel obstruction, weight loss, and GI bleed. The presence of masses on a CT scan is suggestive of PTLD, with 25% involving the small bowel and 6% involving the colon.⁶⁹ PTLD may cause bowel obstruction, necessitating emergent surgery. Interestingly, simply reducing immunosuppression can sometimes cause eradication of disease. Additionally, as the majority of cases are B cell in nature and associated with Epstein-Barr virus, B cell-directed therapies such as anti-cd20 antibody rituximab, may eliminate the disease. Consequently, patients with PTLD should be managed at a transplant center where graft loss or mortality can be minimized by the modification of immunosuppression and other therapies.

GASTROINTESTINAL PROBLEMS

Immunosuppressants often have GI effects that modify symptoms and therefore the presentation of GI diseases.⁴⁹ It is quite common for transplant patients to develop diarrhea, sometimes severe episodes. This can sometimes be related to transplant medications, and a careful drug history should be the initial step in evaluating a transplant patient with diarrhea. For example, up to 50% of patients on MMF develop GI complaints.⁷⁰ Ruling out other causes, particularly infections, is important and can be challenging. Infectious processes often seen in the transplant population include *C. difficile* superinfection, cytomegalovirus colitis, more common GI viruses, and opportunistic infections. The initial workup should be no different from that for the nontransplant patient but may ultimately require colonoscopy and biopsy to rule out the above.

Summary

General surgeons can certainly have some level of comfort with the knowledge that with careful attention to medications and symptoms, general principles will hold true with transplant patients. Minor procedures can usually be conducted without much modification, and more major procedures may require some adjustment of medication regimen. The most important point is to watch these patients closely as their physical examination, including vital signs and laboratory studies, can be misleading, and frequent reassessment with imaging may be necessary. If a patient does not proceed along the expected recovery, attention must be given to a possible complication. Most transplant centers have a program for following up with their patients and a contact to call for questions about their care and organ function. It is always recommended to communicate with a program. Consideration for transfer to a transplant center may be appropriate in complicated cases or in the setting of complications.

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21 MINIMALLY INVASIVE SURGERY: EQUIPMENT AND TROUBLESHOOTING

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The field of minimally invasive surgery has evolved rapidly since the first laparoscopic appendectomies and cholecystectomies were performed nearly 30 years ago.¹ Minimally invasive approaches are now widely used for gastrointestinal resection, hernia repair, antireflux surgery, bariatric surgery, and solid-organ surgery, such as hepatic, pancreatic, adrenal, and renal resections. Although the techniques and equipment needed to access, expose, and dissect vary according to the type of operation and surgeon's preference, a basic set of equipment is essential for any laparoscopic procedure: laparoscope, camera, light source, signal processing unit, video monitor, insufflator and gas supply, trocars, and surgical instruments. Understanding how to use and troubleshoot this equipment is critical for any surgeon who performs minimally invasive surgery.

In this chapter, we review the essentials of basic laparoscopic equipment, including the mechanics of normally functioning equipment and the various types of laparoscopic trocars and instruments. Additionally, we discuss potential technical difficulties that surgeons may encounter while using laparoscopic equipment and instruments and provide suggestions for troubleshooting these problems.

Laparoscopic Equipment

LAPAROSCOPE AND CAMERA

The purpose of the laparoscope and camera unit is to transmit high-quality images from the surgical field to the signal processing unit, which relays the images to the video monitor. Traditional laparoscopes have two separate channels. One channel contains a series of glass rods (known as the Hopkins rod-lens system²) that transmit images from the surgical field to the eyepiece of the laparoscope. The second channel contains light fibers, which transmit light from an external source to the surgical field.

Laparoscopes may be straight or angled at the tip. Straight (0°) laparoscopes offer a view of whatever lies directly ahead of the laparoscope, whereas angled (e.g., 30° or 45°) scopes allow the surgeon to look around structures by rotating the scope [see Figure 1]. Typically, laparoscopes are either 5 or 10 mm in diameter and are usually 25 to 30 cm in length. Smaller diameter laparoscopes, such as 3 mm scopes, are also available, although they tend to be less durable [see Figure 2]. Longer laparoscopes (e.g., 40 to 45 cm) are also available and are frequently used in bariatric cases.

To transmit images from the laparoscope to the signal processing unit, a camera is attached to the eyepiece via a coupler [see Figure 3]. First-generation cameras developed in

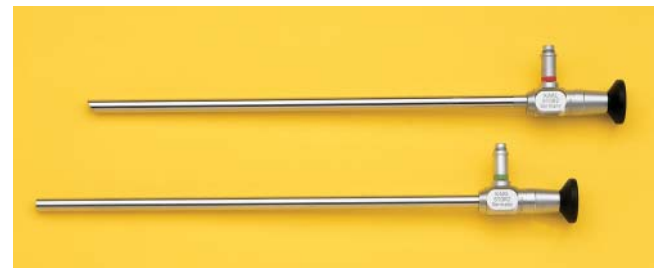


Figure 1 Angled (upper image) versus straight (lower image) laparoscope. Courtesy of KARL STORZ Endoscopy-America, Inc.



Figure 2 Laparoscopes, 10, 5, and 3 mm. Courtesy of KARL STORZ Endoscopy-America, Inc.



Figure 3 Laparoscope, coupler (black), and camera assembled as one unit. Courtesy of KARL STORZ Endoscopy-America, Inc.

the 1980s used a “one-chip” system to convert colors into electrical charges and relay those images. Most current-generation laparoscopic cameras use “three-chip” charge-coupled device systems, which sense primary colors (red, blue, green) and convert these colors to electrical charges. This enhancement allows for a higher image resolution. In one study, three-chip cameras provided up to 800 lines of horizontal resolution compared with 640 lines for a one-chip camera.³ Interestingly, the clinical impact of this superior resolution is unclear. In a 1995 study, surgeons and nurses who were blinded to either a one-chip or a three-chip system actually preferred the one-chip system.⁴ The authors concluded that the enhanced resolution offered by three-chip imaging may not have been appreciable to the human eye. However, subsequent improvements in color detection and light sensitivity over the last 15 years have made three-chip systems the standard in many operating rooms. Modern high-definition three-chip systems can offer more than 1,000 lines of resolution.

Digital laparoscopes are also available. These devices combine the laparoscope and camera into one unit. Rather than using the traditional rod-lens system, they contain an image sensor at the distal end of the laparoscope that transmits images. One advantage of digital laparoscopes is that flexible-tipped scopes can be used to provide additional visibility compared with traditional straight or angled scopes, which are rigid cylinders [see Figure 4]. However, these systems may not be compatible with video systems that use the traditional rod-lens laparoscopes.

LIGHT SOURCE AND CABLE

One of the early limitations of laparoscopic surgery was the need to place the light source in the surgical field, often at the distal end of the laparoscope. As a result, images were relatively low quality, and intra-abdominal thermal burns were not uncommon. This changed in the 1950s with the development of the “cold light source,” which included the quartz light rod and, subsequently, fiberoptic technology.^{5,6} Light could now be generated by an external source and



Figure 4 Flexible-tipped laparoscope, which offers wider visibility of the surgical field. Courtesy of KARL STORZ Endoscopy-America, Inc.

transmitted to the surgical field through fiberoptic bundles. This provided clearer, brighter images and reduced the likelihood of thermal injuries.

Several types of light sources are used during minimally invasive procedures today. Halogen (150 watt), metal halide (50 to 270 watt), xenon (300 watt), and, more recently, light-emitting diodes (LEDs) are all high-intensity light sources capable of producing quality images on a video monitor. One of their main differences is their life span. Halogen and metal halide light sources typically last several hundred hours, whereas xenon bulbs may last up to 500 hours.

Despite their classic label as “cold light sources,” each of these light sources generates a substantial amount of heat. One study of three different xenon light sources found that temperatures near the outlet of the light source exceeded 1,000°F, whereas those near the tip of the fiberoptic cable approached 500°F. Temperatures at the tip of the laparoscope ranged from 140 to 212°F. Evidence of small bowel injury occurred after only 5 seconds of direct contact between the laparoscope and the bowel.⁷ In another study, charring of the surgical drapes occurred after 3 to 6 seconds of contact between the tip of the light cable and the surgical drapes.⁸ The surgeon must be cognizant of the risk of thermal burns from either the lighting equipment or the laparoscope.

LED light sources are a fairly recent addition to the laparoscopic armamentarium and are purported to have numerous advantages. They are more efficient than other light bulbs (they release more light per watt) and emit less heat than standard light sources. Additionally, their life spans are anywhere from 10 to 100 times longer than standard light sources. However, they are more costly than traditional light sources (e.g., xenon).

SIGNAL PROCESSING UNIT (CAMERA CONTROL UNIT)

Once the camera has processed the images from the surgical field, the images are transmitted to a signal processing unit. The purpose of the signal processing unit is to transmit the signal from the camera to a variety of end devices, including printers, recording devices, and, most importantly, the video monitor. Several analog output signal formats are commonly used by signal processing units, including composite, Y/C (super video), and RGB (red/green/blue) signals [see Figure 5]. Composite signals, which use a single pin connection, are typically lower quality than Y/C or RGB signals. RGB signals, which use three wires for color and one wire for synchronization, often offer the best image.⁹

Digital video interface (DVI) and serial digital interface (SDI) signals are the two most commonly used digital signal outputs. DVI signals are essentially a digital version of an RGB signal. One limitation of DVI is that the cable length cannot be longer than 15 feet because of signal degradation.⁹ On the other hand, SDI cable lengths can be much longer without causing significant signal degradation.

VIDEO MONITOR

Most traditional video monitors used in the operating room will accept input from three types of analog signals: composite, Y/C, and RGB. Older laparoscopic camera systems typically output either composite or super video signals, whereas many current-generation systems also generate RGB output, which often provides higher-resolution images. However, even with the use of RGB signals, the resolution provided by traditional cathode ray tube monitors is somewhat limited (typically 600 lines or less).¹⁰ For enhanced resolution, including high-definition formats, digital monitors that accept DVI and SDI digital signals may be used with high-definition video cameras. These flat-panel digital monitors, which are also capable of accepting analog signals, are often ceiling-mounted displays that are capable of providing more than 1,000 lines of resolution (nearly twice the resolution of a typical television image).¹⁰

INSUFFLATOR AND GAS SUPPLY

The creation of pneumoperitoneum is one of the essential steps of laparoscopic surgery because it distends the abdominal wall and significantly enhances visualization of intra-abdominal structures. One of the first physicians to insufflate

the abdomen was Dr. George Kelling, a German surgeon who is also credited with performing the first laparoscopic procedure in 1901.¹ Interestingly, improved intra-abdominal visualization was not one of his primary goals. Rather, he wanted to arrest gastrointestinal bleeding by injecting large amounts of air into the peritoneal cavity to create extremely high intra-abdominal pressures (50 to 100 mm Hg).¹¹ Shortly thereafter, a Swedish internist named Hans Christian Jacobaeus used a trocar with a bulb and a one-way valve to manually insufflate air into the abdomen. He referred to this new procedure as “laparoscopy.” His first 17 human cases were diagnostic procedures in patients with ascites. Unlike Kelling, Jacobaeus realized that laparoscopy had tremendous potential and published several articles in the European literature.¹¹ Manual insufflation would remain the standard technique for the creation of pneumoperitoneum for another five decades.

In the 1960s, Dr. Kurt Semm, a German gynecologist who performed the first laparoscopic appendectomy in 1983, developed an automatic insufflator that monitored the pressure of pneumoperitoneum.¹² This device not only provided surgeons with a reliable estimate of intra-abdominal pressure; it also allowed surgeons to operate with both hands because intermittent manual injection of air was no longer needed for maintenance of pneumoperitoneum.

One of the main areas of uncertainty during this time period was the optimal gas for pneumoperitoneum. The laparoscopic pioneers used room air primarily because it was readily available and cheap. Studies published as recently as 1980 suggested that the creation of pneumoperitoneum with room air was safe and cost-effective.¹³ However, its combustibility, poor solubility in the blood, and concern for venous air embolism have nearly eliminated the use of room air insufflation in today’s operating rooms.¹⁴ Likewise, insufflation with nitrous oxide was popular throughout the 1970s. Yet reports of intra-abdominal explosions have subsequently limited its popularity.¹⁵ Carbon dioxide is currently the most commonly used gas during insufflation. It is odorless, nonflammable, and highly soluble in blood, which reduces the likelihood of air embolisms. Although clinically significant hypercarbia and acidemia can occur, particularly in patients with cardiopulmonary comorbidities, most patients tolerate carbon dioxide pneumoperitoneum without any adverse effects.

To establish standard pressure pneumoperitoneum (typically 12 to 16 mm Hg), the insufflator must first be connected to the carbon dioxide cylinder. Tubing is then used to connect the insufflator to either a Veress needle or a laparoscopic port within the peritoneal cavity. Next, gas flow from the insufflator is initiated. Although the amount of gas needed to create adequate pneumoperitoneum varies according to patient size, abdominal wall compliance, and degree of gas leakage, several liters of carbon dioxide are usually adequate. To maintain pneumoperitoneum throughout a case, substantially more gas is needed. One report estimated that an average laparoscopic colectomy requires approximately 110 to 180 L of carbon dioxide.¹⁶

Most conventional insufflators use an intermittent pressure monitoring system. This allows the insufflator to decrease the gas flow if the intra-abdominal pressure exceeds a preset value. Conversely, it can increase gas flow to account for a



Figure 5 This signal processing unit (camera control unit) can transmit a variety of analog signals (composite or “COMP VIDEO”; Y/C or “S-Video”; “RGB”) and digital signals (“DVI OUT” and “SDI OUT”). Courtesy of KARL STORZ Endoscopy-America, Inc.

loss of gas either externally or through peritoneal absorption. Rather than cycling gas continuously, insufflators alternate between injecting gas every 2 to 3 seconds and monitoring the intra-abdominal pressure. One study that examined different types of low- and high-flow insufflators (9, 10, 16, and 30 L) found that those with high flow rates (e.g., 30 L) compensated for gas leakage better but produced higher intra-abdominal pressure peaks. Flow resistance and the rate of gas leakage, rather than flow capacity, were seen as the critical determinants of intra-abdominal pressure maintenance.¹⁷

The possibility of peritoneal contamination or disease transmission through the flow of intraperitoneal fluid or particulate matter from the patient to the insufflator (and then to the next patient) has been a concern since the early days of laparoscopy. To address this concern, insufflation filters composed of mesh with 0.1- to 0.3-micron pores have been developed. The literature surrounding the effectiveness of these filters is limited. One study published in 1989 reported that rust, dust, and metal filings could be detected on insufflator filters.¹⁸ Another found that the use of a 0.3-micron filter reduced microbial colonization of gas cylinders and insufflators.¹⁹ However, a subsequent examination that used microscopy, mass spectrometry, and bacterial analysis showed no evidence of microbial or particulate matter trapping by the filters.²⁰ To our knowledge, there have been no published reports of disease transmission related to insufflation. However, given the theoretical possibilities of contamination and disease transmission, insufflation filters are commonly used today.

GASLESS LAPAROSCOPY

Despite the near-universal use of insufflators during laparoscopy, a relatively small number of “gasless” laparoscopic cases have been performed since the early 1990s.²¹ Rather than using an insufflator to create pneumoperitoneum, “gasless” laparoscopy involves the use of an abdominal wall retraction system to enhance intra-abdominal visualization. The purported benefits of this technique are the absence of the physiologic risks of pneumoperitoneum, decreased cost, and increased intraoperative flexibility for the surgeon. For example, surgeons can use unlimited suction and can operate with conventional surgical instruments, such as right-angled clamps.²² However, the use of gasless laparoscopy remains uncommon today. This is likely attributable to the favorable safety profile of carbon dioxide pneumoperitoneum and limited visualization if pneumoperitoneum is not established. Additionally, most surgeons are not familiar with the technical aspects of “gasless” laparoscopy, including the retraction setup. There may be a role for gasless laparoscopy in the future, particularly for patients at high cardiopulmonary risk who may have difficulty tolerating carbon dioxide pneumoperitoneum.²¹

Laparoscopic Trocars

There are a wide variety of commercially available laparoscopic trocars, with their own specific characteristics. In general, trocars consist of two different components. The head of the trocar includes a diaphragm to prevent leakage of gas around the inserted instruments and a port for insufflation.

The shaft is the portion that is inserted through the abdominal wall into the abdominal cavity and can vary in both length and diameter to accommodate patients with larger abdominal walls and instruments of various sizes. These components can be purchased either separately or as one unit and can be either disposable or reusable depending on the type of trocar used.

Additionally, all trocars come with an obturator, which inserts through both the head and the shaft to facilitate introduction of the trocar through the abdominal wall. The end of the obturator can be bladed (“cutting trocar”) or nonbladed (“noncutting trocar”). Cutting trocars sharply cut the abdominal wall on entry. They often come with a shield that retracts under force but reengages once that force has dissipated, such as on entry into the abdominal cavity. These trocars tend to create larger defects in the abdominal wall, which can lead to eventual hernia formation. Noncutting trocars also come in a variety of forms, all of which either pass through the abdominal wall bluntly or in a radially expanding fashion and thus leave a smaller fascial defect than cutting trocars of a similar diameter. In one prospective, multicenter, randomized study of noncutting versus cutting trocars in 244 elective laparoscopic procedures, the use of noncutting trocars was associated with significantly lower rates of intraoperative cannula site bleeding and postoperative wound complications. There were no significant differences in operative times or pain scores between the two groups. Although the authors routinely closed 10 mm or greater fascial defects when cutting trocars were used, similarly sized defects in the noncutting group were left open. There were no occurrences of late port-site hernias despite these defects remaining open. Thus, the authors felt that these ports did not require routine closure and likely have a lower rate of port-site hernia formation.²³

Initial trocar placement and establishment of pneumoperitoneum typically occur via either an open technique or a direct puncture of the abdominal cavity. Each technique is associated with its own set of potential complications, and no single technique is absolutely safe. In the open technique, which was first described by Hasson in 1974,²⁴ a small incision is made at the level of the umbilicus and the skin and soft tissue are sharply or bluntly dissected down to the linea alba. The linea alba is then opened sharply, and the peritoneum is opened under direct vision. Once inside the abdominal cavity, stay sutures are placed on the fascia and a blunt-tipped Hasson trocar is inserted into the defect and held in place by the fascial sutures. Pneumoperitoneum is then established through this trocar. Once the procedure is complete, the fascial defect can be closed using the previously placed sutures or with any additional sutures that are necessary to ensure proper closure.

The direct puncture technique employs the use of either a Veress needle to establish pneumoperitoneum or direct trocar placement into the abdominal cavity prior to the establishment of pneumoperitoneum. The Veress needle is a spring-loaded, hollow-bore, self-protecting needle created for accessing the abdominal cavity. When the needle meets resistance, the safety retracts, thus exposing the sharp point of the needle and allowing it to pass through the layers of the abdominal wall. As the needle enters the peritoneum, the resistance is lost and the safety reengages to protect the

intra-abdominal contents. The needle position can then be tested via a saline drop test or connected to the insufflation tubing to assess the opening pressure and initial flow. Once pneumoperitoneum is obtained and additional ports have been placed, the site of Veress entry should always be inspected to ensure that no bowel or vascular injuries have occurred.

Although trocars may be safely inserted into the peritoneal cavity prior to the establishment of pneumoperitoneum, this technique is not employed by many surgeons because of fear of injury to intra-abdominal contents. Within the past decade, several manufacturers have developed “optical trocars.” These optical trocars, which may be bladed or nonbladed, have been designed with a clear tip to allow visualization of the layers of the abdominal wall while the trocar is being inserted. Manufacturers of these trocars contend that this added level of visibility during trocar insertion enhances the safety of trocar insertion. However, randomized data supporting this assertion are currently lacking. As each access technique has its own set of complications, it is helpful for the surgeon to be familiar with a variety of techniques so that he or she may employ the technique most suitable for the specific situation.

Laparoscopic Instruments

In general, laparoscopic instruments are designed such that their end effectors will mimic the instrumentation of open surgery. These end effectors are typically mounted on a 30 cm shaft that measures 5 mm in diameter [see Figure 6]. Some instruments can come on 45 cm shafts designed for use in bariatric surgery, and some are available only in shafts with 10 mm diameters, thus necessitating a larger trocar. Nearly all instruments are designed such that the shaft will rotate through 360° of rotation while keeping the handles stationary. The handles come in a variety of sizes and grip styles and should be trialed to find a set that provides both comfort and proper ergonomics. Additionally, a variety of ratcheting and locking mechanisms are available, and surgeons should find the set that best suits their specific needs.

There are a variety of instruments designed for laparoscopic dissection. The Maryland dissector [see Figure 7] has an end effector that is curved similar to a curved snap and is one of the more popular dissecting instruments. It can be used to dissect ductal and vascular structures but should not be used to grasp delicate tissue as crush injuries may ensue. Additionally, the pointed tips can inadvertently injure intra-abdominal structures, so care must be taken to keep the instrument in view as much as possible. Laparoscopic



Figure 6 A typical laparoscopic instrument. Courtesy of KARL STORZ Endoscopy-America, Inc.



Figure 7 A laparoscopic Maryland dissector. Courtesy of KARL STORZ Endoscopy-America, Inc.

right-angled dissectors are also available for dissection of vascular and ductal structures. Blunt graspers come in a wide variety of shapes and sizes. Some, such as the laparoscopic Babcock grasper [see Figure 8], are designed to be atraumatic and are used for the manipulation of most intra-abdominal structures. Others are more traumatic, such as the laparoscopic Allis grasper, but allow for a stronger purchase on tougher or thicker tissue, such as the gallbladder. Laparoscopic biopsy forceps, needle drivers, scissors, staplers, clip applicators, probes, sponges, and retractors are also all commercially available in a wide variety of forms. It is worthwhile to become familiar with several different instruments as instrumentation will likely vary between institutions.

Laparoscopic Energy Sources

The energy sources used to obtain hemostasis in laparoscopic surgery are similar to those employed in open surgery. Monopolar, bipolar, and ultrasonic energy sources all come in forms suitable for use in laparoscopic cases. Bipolar and ultrasonic energy sources have significantly decreased operative times for more complex laparoscopic cases as larger vessels can now be controlled with these instruments rather than with staplers, Endo-Loops (Ethicon Endosurgery, Cincinnati, OH), or laparoscopic suturing. Although the physics principles that govern these energy sources are the same in open and laparoscopic surgery, there are several aspects of laparoscopic surgery that have unique implications and merit further discussion.

When using monopolar electrocautery, an alternating current of 50,000 Hz is created in a generator and is passed onto an active electrode, through the patient, and eventually back to the generator via a return electrode. Significant heat will be generated in the tissue adjacent to the active electrode. Thus, the active electrode should have a very small surface area (such as a hook or the tip of a Maryland dissector) to allow the electricity to be focused on a small area. Conversely, the return electrode, which is the grounding pad normally placed on the patient's lower extremity, should have a large



Figure 8 A laparoscopic Babcock grasper. Courtesy of KARL STORZ Endoscopy-America, Inc.

surface area so that minimal heat is generated at the site and no inadvertent thermal injuries occur.

In open surgery, it is standard practice to grasp a bleeding vessel with a pair of forceps and then touch the forceps with the tip of the electrocautery to obtain hemostasis. This phenomenon of electrical transference from the active electrode to another conducting instrument is referred to as direct coupling. In laparoscopic surgery, direct coupling can occur purposefully but can also occur inadvertently when an instrument is placed in close proximity to another instrument that is electrically active. The current may transfer to the nonactive instrument or any other metal substance, including the laparoscope itself. These instruments may then discharge their electrical current to surrounding structures, resulting in accidental thermal injuries. Thus, whenever monopolar electrocautery is being employed, it is important to ensure that there is a safe distance between the active instrument and all other metallic objects. Additionally, if there are disruptions in the insulation of the active instrument, electricity may be discharged to surrounding structures through these cracks, again leading to inadvertent thermal injury. The Insulscan (Medline Industries, Mundelein, IL) is a device designed to look for insulation disruptions in laparoscopic instruments. Although it does add time to the setup of the case as instruments must be passed through the unit individually, it may aid in preventing thermal injuries, which could require significantly more time to repair laparoscopically.

In addition to direct coupling, capacitive coupling can occur in laparoscopic cases where metal trocars are being used. Capacitive coupling occurs when two conductors are separated by a nonconductor. If the active electrode of a laparoscopic instrument is inserted through a metal trocar, the insulation surrounding the instrument acts as a nonconductor and can function as a capacitor. The capacitor generates an electrostatic field between the active electrode and the metal trocar. As electricity passes through the active electrode, the electrostatic field can transfer energy to the metal trocar, which will then discharge the energy in the form of heat, leading to burns of the skin and abdominal wall. The use of nonconductive plastic trocars will avoid this phenomenon.

Two bipolar energy sources are now commercially available for laparoscopic use. These devices, the LigaSure (ValleyLab, Boulder, CO) and the EnSeal (Ethicon Endosurgery), both pass low-voltage, high-frequency current between two active electrodes at the tips of the instruments. According to the manufacturers, the tissue between these two electrodes is effectively coagulated and sealed for vessels as large as 7 mm in diameter. Both instruments include a blade to divide the tissue once it has been coagulated. The instruments themselves generate very little heat, so there is minimal lateral spread of thermal injury.

Ultrasonic shears use mechanical energy rather than electrical current to seal vessels and divide tissue. The most commonly used device is the Harmonic Ace (Ethicon Endosurgery), which requires a generator that produces an electrical signal, which in turn is converted into a mechanical vibration at a frequency of 55,500 Hz. This mechanical vibration is amplified as it travels down the shaft of the instrument and into the active blade of the device, which generates heat to coagulate vessels and divides tissue without requiring a

separate knife for cutting. The active blade of the instrument will remain hot for some time after use, and direct contact with surrounding tissues should be avoided.

Diamantis and colleagues compared the various sources of energy by using monopolar electrocautery, bipolar electrocautery, the LigaSure, and the UltraCision (Ethicon Endosurgery, ultrasonic shears) to ligate the short gastric vessels in rabbits.²⁵ They found that monopolar and bipolar electrocautery frequently failed to achieve adequate hemostasis and resulted in significant thermal spread, leading to perforation of the adjacent gastric wall. The LigaSure and UltraCision devices successfully coagulated 100% of the vessels for which they were used. Both modalities had minimal side thermal injury, but the LigaSure had slightly less histologic evidence of inflammation and thermal injury than the UltraCision on postoperative days 7 and 14. These two modalities were clearly safer and more effective than either monopolar or bipolar electrocautery.²⁵

Troubleshooting Laparoscopic Equipment

Although few studies have measured the frequency, etiology, cost, or clinical impact of laparoscopic equipment misuse and malfunction, equipment problems during laparoscopic surgery are quite common. One study that used video recording during 30 laparoscopic cholecystectomies found that 90% of cases were affected by a problem with the basic technical equipment.²⁶ Fifty-five percent of these incidents were the result of equipment malfunction related to an equipment defect, improper device setting, or faulty connection. Another study that examined 62 laparoscopic cases concluded that at least one equipment failure occurred in 42% of cases.²⁷ Human error contributed to nearly half of these failures.

Given the multitude of potential sources for equipment failure, a systematic approach to equipment troubleshooting is key. In this section, we discuss some of the most common equipment problems that the surgeon may experience in the operating room and offer a methodical approach to address these issues [see Table 1].

IMAGES ON THE VIDEO MONITOR ARE TOO DARK

The light source, light cable, laparoscope, camera, and video monitor must all function optimally to provide video images with adequate lighting. If the lighting is poor, several steps can be taken to address the issue. Blood will absorb a significant portion of the light, making the overall image appear darker; thus, blood should be cleared from the field if possible. Next, connections between each of the components should be checked to ensure that each component is properly attached to the system. In the aforementioned observational study of laparoscopic cholecystectomies, “faulty” equipment connections were present in nearly one third of cases.²⁶ If the connections are intact, the current settings for both the video monitor and the light source should be checked. If the settings on the video monitor have been altered (e.g., brightness), they should be adjusted back to the default settings. The light intensity from the light source can also be increased. While making this adjustment, the surgeon should note the number of hours that the current light bulb has been in use. Many light sources display this number on the front of the machine. If the number of hours exceeds the accepted life

Table 1 Laparoscopic Equipment Troubleshooting

Main Problem	Equipment Issue	Relevant Equipment	Troubleshooting Maneuver
Images on the video monitor are too dark	A connection between two pieces of equipment is faulty	Light source, light cable, laparoscope, camera, video monitor	Confirm that each piece of equipment is properly connected to the system
	Improper setting (e.g., brightness, gain)	Video monitor, camera, light source	Adjust back to default settings
	Poor light intensity from the light source	Light source	Ensure that bulb is within accepted life span; increase intensity of light source or replace bulb
	Light intensity from the source is adequate, but light from the laparoscope tip is poor	Light cable, laparoscope	If there are numerous breaks in the fiberoptic bundles of the light cable, replace the cable; if not or if the fiberoptic bundles cannot be inspected, replace either the cable or the scope and assess for improvement in light intensity
Images on the video monitor are foggy or blurry	Laparoscope is not focused	Laparoscope, camera	Focus the laparoscope
	Condensation is present on the tip of the laparoscope	Gas warming/humidifying devices, laparoscope, warming devices, antifogging solutions	Use of any of these warming or antifogging techniques is reasonable (although data are lacking)
	Liquid or particulate matter is present on the tip of the laparoscope	Laparoscope	Wipe the tip of the laparoscope off (ideally using gauze rather than the viscera)
	Smoke is obscuring the surgical field	—	Open one of the ports to let smoke escape
	Condensation has accumulated within the laparoscope or coupler	Laparoscope, coupler	Detach laparoscope from camera (and coupler if possible) and wipe lens; if condensation is within the scope lens system, the scope should be replaced
Images on the video monitor are abnormally colored	Improper setting (e.g., color, brightness)	Video monitor	Adjust back to default settings
	White balancing has not been performed correctly	Laparoscope, camera, camera control unit	White balance the laparoscope
	Video monitor has become magnetized	Video monitor	“Degauss” the video monitor (applies to cathode ray tube systems only)
There is no image on the video monitor	Connection between two pieces of equipment is faulty, or a piece of equipment is not turned on	Light source, light cable, laparoscope, camera, video monitor	Confirm that each piece of equipment is properly connected to the system and is turned on
	Analog or digital cables are not correctly plugged in	Video signal processor, analog or digital cable, video monitor	Ensure that the cables are plugged into the appropriate “out” connector of the signal processing unit and the “in” connector of the video monitor
	Light bulb has burned out	Light source/bulb	Replace the light bulb
Abdominal insufflation is inadequate	No gas in the cylinder	Gas cylinder	Replace the cylinder
	Cylinder valve is closed	Gas cylinder	Open the cylinder valve
	Veress needle or trocar is not within the peritoneal cavity	Veress needle or trocar	Place Veress needle or trocar into the peritoneal cavity
	Something is compressing the insufflation tubing	Insufflation tubing	Remove source of external compression
	Stopcock on the trocar is set to block airflow	Trocar	Adjust stopcock so that gas flow may proceed
	Flow rate or maximum insufflation pressure settings are incorrect	Insufflator	Adjust flow rate or maximum insufflation pressure appropriately
	Incompatibility between insufflator and filter	Insufflator, filter	Ensure that the filter is compatible with insufflator (relevant for high-flow insufflators)
	There is an air leak somewhere in the system	Trocars	Ensure that gaps between trocars and fascia are minimized; close valves on ports so that intraperitoneal gas does not escape
	Inadequate abdominal wall relaxation	None	Additional sedation or paralytic

span for that bulb, the bulb should be replaced. Room light sources should also be dimmed if their brightness is impairing the quality of the video monitor images.

If troubleshooting maneuvers targeted toward the connections, settings, and light source do not resolve the issue, the light cord and laparoscope should be evaluated. Breaks in the fiberoptic bundles can cause degradation in the quality of the images. Some lighting cables have a transparent covering that allows these breakages to be seen. These will appear as points of light along the length of the cable. If there are numerous breaks in the bundles, the cable should be replaced. If there are no visible breakages, the laparoscope should be replaced and the effect on the video image should be noted. Some surgeons also recommend setting the light source and camera shutters to “manual” in poor lighting scenarios.¹⁰ An improvement in the image quality following either of these maneuvers reflects a problem with the shutter in either the light source or the camera, respectively.

The brightness of the light that is emitted from the laparoscope tip can be deceiving. The light may appear to be bright enough when simply looking at the tip, but this does not ensure that the intensity is adequate. Additionally, although the surgeon may be tempted to increase either the gain on the camera control unit or the brightness on the monitor, these maneuvers should be performed with caution. They may increase the image brightness on the monitor, but the need to perform these steps suggests that there is a defect somewhere in the system. Increasing either the gain or brightness can also reduce the image quality.

IMAGES ON THE VIDEO MONITOR ARE FOGGY OR BLURRY

Foggy or blurry images on the video monitor are a common cause of impaired visualization during laparoscopic surgery. One reason for a blurry image is that the laparoscope simply is not focused. To prevent this problem, surgeons can focus the laparoscope before it is inserted by pointing the laparoscope at an object on the surgical field, such as a piece of gauze or a suture packet. Alternatively, the scope can be focused after insertion into the abdomen (e.g., using the liver as a focal point).

Perhaps the most common cause of blurry imaging is the presence of liquid, particulate material (e.g., adipose tissue), or smoke on either the laparoscope lens or in the surgical field. Liquids such as irrigation fluid, ascites, and blood can all obscure the surgical field. Condensation on the laparoscope lens is probably the most common cause of lens fogging because of liquids. This condensation forms on the lens because the temperature of the lens (i.e., the laparoscope) is usually lower than body temperature during the establishment and maintenance of pneumoperitoneum. Given that the intra-abdominal humidity typically ranges from 85 to 95% during laparoscopy, the presence of lower temperatures near the front lens causes the dew point to be reached, which results in the production of condensation on the lens.²⁸ At an intra-abdominal humidity of 85%, the scope temperature must exceed 93°F to prevent lens condensation. Some recommend maintaining a scope temperature of at least 98.6°F.²⁹

Given these observations and recommendations, there has been a substantial amount of interest in the use of warmed (typically 98.6 to 113°F) and humidified (50 to 95%) gas. If

gas flows directly from the insufflator to the patient (without warming or humidification), it will enter the peritoneal cavity at approximately 70°F and 0% humidity. On the other hand, if warmed, humidified gas is sent from the insufflator (or gas is sent from the insufflator through a warming, humidification system and then to the patient), it can enter the peritoneal cavity at body temperature.¹⁶ In addition to the potential benefit of improved visualization attributable to condensation prevention, there is some evidence that warm, humidified gas can also reduce hypothermia and pain.^{30,31} However, several randomized controlled trials have failed to show either a clinical benefit or a decrease in lens fogging with the use of warmed, humidified air.^{16,32–34} Although the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) has not issued formal recommendations regarding this issue, the European Association for Endoscopic Surgery guidelines for pneumoperitoneum state that the clinical effects of warmed, humidified gas are “minor” and the data regarding its influence on pain are “contradictory.”³⁵

Additional maneuvers to reduce laparoscopic lens fogging include laparoscope warming and the use of antifogging solutions. Numerous warming techniques have been described, including placing the scope into a container of warm liquid, using warm sterile towels, or even modifying the scope to include a built-in warming mechanism. Antifogging solutions, such as the Fog Reduction and Elimination Device (FRED; Covidien Autosuture, Mansfield, MA) and Reso-clear (Resorba Wundversorgung; Nuremberg, Germany), have also been developed and used extensively. Although these maneuvers are anecdotally effective and have strong face validity, definitive data regarding these laparoscopic warming techniques and antifogging solutions are lacking.³⁶

Wiping the laparoscope tip on the viscera—often the liver or small bowel—is another maneuver that is commonly used and is often effective. However, this should be performed cautiously as laparoscope tip temperatures can exceed 200°F. One study found microscopic evidence of thermal injury to the bowel after only 5 seconds of direct contact between the laparoscope and viscera.⁷

Moisture can also accumulate at various points within the system, including between the laparoscope lenses, on the eyepiece of the laparoscope, and on the coupler. Condensation on the eyepiece and coupler can be addressed by detaching the camera (and coupler if possible) and wiping the lenses. Condensation between the laparoscope lenses suggests a malfunction in the seal and will most likely require laparoscope replacement and repair.

IMAGES ON THE VIDEO MONITOR ARE ABNORMALLY COLORED

When presented with this scenario, the surgeon should first ensure that the monitor settings are correct. The previous surgical team may have intentionally changed the monitor settings during a previous case, or maintenance staff could have inadvertently changed the settings between cases. The surgeon should also ensure that the camera has been “white balanced” appropriately. White balancing is typically performed by placing a white object, such as gauze, in front of the laparoscope-camera unit. After focusing on this white object, a white balance button can be pushed on either the camera head or the camera control unit. This maneuver

allows the camera to set the video output voltage levels so that a white image is created when the scope is targeted on a white object.³⁷ If white balancing is omitted or performed incorrectly, the images on the video monitor may appear abnormally colored.

Traditional video monitors that use a cathode ray tube can also become magnetized over time, creating distorted colors and images. This often appears as a purplish discoloration around the image.¹⁰ Although most monitors will automatically remove the magnetic forces when turned on (referred to as “degaussing”), manual degaussing may need to be performed as well. Many video monitors have manual degauss buttons for this reason.

THERE IS NO IMAGE ON THE VIDEO MONITOR

This scenario usually occurs when a component in the system is improperly connected or not powered on. The surgeon should first ensure that the light source, signal processing unit (camera control unit), and video monitor are all turned on and properly connected to each other. The bulb in the light source should also be checked to ensure functionality. Next, the connections between the signal processing unit and the video monitor should be inspected to ensure that the analog or digital cables are connected to the appropriate “out” or “in” connectors. These cables are typically plugged into the “out” connector of the signal processing unit and the “in” connector of the video monitor. Similarly, if a second video monitor is used, the monitor-to-monitor cable should be plugged into the “out” connector of the first monitor and the “in” connector of the second monitor. Finally, the analog or digital signal connector that the video cable is plugged into should match the type of video signal that is selected on the monitor interface. These recommendations are summarized succinctly in the *SAGES Laparoscopy Troubleshooting Guide*.³⁸

ABDOMINAL INSUFFLATION IS INADEQUATE

Before insufflation is initiated, the surgical team should ensure that the amount of gas in the cylinder is adequate and the cylinder valve is open. The surgeon should verify that the Veress needle or the laparoscopic trocar is within the peritoneal cavity rather than the preperitoneal space, retroperitoneum, omentum, or another intra-abdominal structure. Insufflation into a location other than the peritoneal cavity usually results in low or absent flows and high pressures. Once intraperitoneal placement of the access device has been achieved, insufflation can proceed at a flow rate selected by the surgeon. If the gas flow remains poor, the team should ensure that the insufflator, the insufflation tubing, and the Veress needle or trocar are connected appropriately. Sources of external compression on the tubing should be addressed, and if the tubing is connected to a trocar, the stopcock on the

trocar should be adjusted to allow for insufflation. The minimal flow rate and maximal intra-abdominal pressure should also be checked.

Incompatibility between the insufflator and the filter or blockage of the filter can also cause a disruption in gas flow. In this scenario, the insufflator senses a high intra-abdominal pressure and consequently reduces flow, which leads to inadequate pneumoperitoneum. This is mainly an issue for high-flow insufflators (30 to 40 L per minute) because specialized filters may be needed to accommodate the high flow rates. Although many companies have addressed this issue by manufacturing compatible tubing and filters, the surgical team must be mindful of this problem, particularly in settings where products from multiple manufacturers are used.

Once the desired intra-abdominal pressure has been reached, the surgeon may have difficulty maintaining an adequate pneumoperitoneum. In addition to performing each of the steps outlined above (i.e., checking the gas cylinder, sources of tubing compression, ensuring that stopcocks on additional trocars are closed), the surgeon should ensure that there are no leaks around the trocar sites or through the trocars themselves. If leaks are detected around the trocar sites, gaps between the trocars and the surrounding fascia and abdominal wall tissue should be minimized or occluded. Additional fascial sutures may be needed. If air is leaking through a trocar, the trocar cap should be checked to ensure that it is properly secured to the shaft. If leakage persists, an instrument should be inserted and removed to realign the diaphragm with the trocar. If these measures fail to resolve the problem, the trocar may need to be replaced. Adequate abdominal muscle relaxation should also be confirmed. If the surgeon suspects inadequate relaxation (the patient is moving or the abdominal wall appears to be “tight”), a discussion with the anesthesia team regarding additional sedation or paralysis is appropriate.

Conclusion

As laparoscopic procedures continue to increase in frequency and complexity, it will become progressively more important to be mindful of these simple troubleshooting maneuvers to keep these procedures flowing smoothly and safely. Although surgeons must have intricate knowledge of their laparoscopic instrumentation, it is equally important for the other members of the surgical team to be familiar with both the equipment and the myriad of potential problems that can arise during these procedures. When all members of the surgical team can work together to quickly overcome any equipment issues during laparoscopic cases, operating room efficiency will improve and better outcomes can be anticipated.

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22 PRINCIPLES AND TECHNIQUES OF ABDOMINAL ACCESS AND PHYSIOLOGY OF PNEUMOPERITONEUM

Jon C. Gould, MD, FACS, and Ancil Philip, MD

Abdominal Access in Laparoscopic Surgery

When compared with the open approach to many abdominal operations, the laparoscopic technique is often associated with decreased morbidity and a quicker recovery. Unfortunately, there are also specific complications related to the laparoscopic approach that would not necessarily be seen with a laparotomy. Many of the most significant complications occur very early in the operation during the act of attaining abdominal access.

There are three general types of laparoscopic access, with many variations and modifications. The Veress needle technique is the oldest and most traditional method of laparoscopic entry. The direct trocar insertion technique involves direct penetration of the fascia and peritoneum by the trocar. Finally, in the open or Hasson technique, a minilaparotomy is performed so that the initial trocar can be placed under direct visualization.

VERESS NEEDLE ACCESS

Molloy and colleagues assessed 155,987 gynecologic procedures and reported that the Veress needle was used in 81% of them.¹ In addition, of the 17,216 general surgery procedures assessed, the Veress needle was used in 48%, whereas in the remaining 52%, other methods were used. Kelling first described preliminary insufflation of the peritoneal cavity prior to trocar placement in 1901.² The Veress technique remains popular today. In the Veress technique, gas is insufflated until an adequate volume has been added to create space in the peritoneal cavity between the abdominal wall and the intra-abdominal as well as the retroperitoneal organs. Once insufflation is complete, a sharp trocar is placed into the peritoneal cavity. In the blind technique, a bladed trocar is inserted into the insufflated peritoneal cavity without direct visualization. A modification of this technique involves the use of a trocar into which a laparoscope can be inserted. Visualization of the abdominal wall layers and the insufflated peritoneal cavity is possible because of the clear tip of these optical-viewing trocars.

Janos Veress first introduced the spring-loaded needle currently used to introduce pneumoperitoneum, originally to induce pneumothorax.³ Modern needles are 12 to 15 cm long, with an external diameter of 2 mm. The outer cannula of a Veress needle consists of a beveled needle point for cutting through tissues. A spring-loaded inner stylet is located

within the outer cannula [see Figure 1]. The tip of the inner stylet is dull, protecting the viscera from injury by the sharp outer cannula. Direct pressure on the tip of the Veress needle pushes the dull stylet into the shaft of the outer cannula. When the tip of the needle enters a space such as the peritoneal cavity, the dull inner stylet springs forward.

Technique

The location on the abdominal wall selected for initial Veress placement depends on a variety of factors. The type of procedure, location of previous incisions, and patient's body habitus may all have an influence. The initial trocar does not always need to be placed through the same incision as the Veress needle, although this is the most common practice. The advantage to using the same site includes the fact that easy Veress placement and insufflation in a particular location provides some level of reassurance that this is a safe site. Prior to insertion of the Veress needle, it is a good practice to ensure that the stomach is decompressed with a gastric tube as gas is often insufflated into the stomach during induction of anesthesia. A large, gas-filled stomach can be injured by the Veress needle or primary trocar. The distended stomach may also displace other intra-abdominal organs, putting these at increased risk for injury.

The abdominal wall is relatively thin in the periumbilical location, and the umbilicus is tethered to the fascia, making this an ideal location for initial Veress access. An alternative location (e.g., subcostal) or a different technique (open Hassan) may be best in patients with a prior midline incision near the umbilicus. Insertion of the Veress needle and primary trocar through a site in the left upper quadrant is recommended by some surgeons to decrease the risk of complications related to intra-abdominal adhesions.^{4,5} The

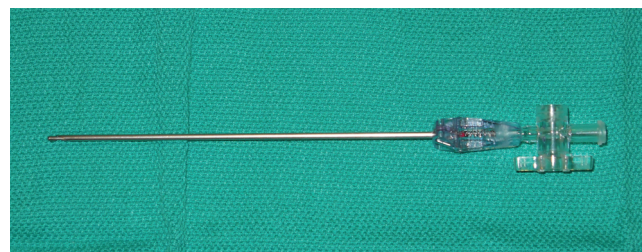


Figure 1 Veress needle.

left upper quadrant insertion site (Palmer point) is located 3 cm below the middle of the left costal margin.⁶ Anatomic studies indicate that the abdominal wall is uniformly thin in this location and the distance from the skin to the retroperitoneal structures is greater than 11 cm in most patients.⁷ For the periumbilical Veress needle insertion, a skin incision is made, typically of sufficient size to easily accommodate the intended trocar to be placed at this site. Penetrating towel clips can be placed in the skin near the incision and used to elevate the abdominal wall. This maneuver helps create some space between the anterior aspect of the peritoneal cavity and the intra-abdominal contents as well as the retroperitoneal major vascular structures. It also minimizes the chance for downward pressure with the Veress needle to push the fascia closer to these vital structures. In obese patients, there is a tendency for the skin and subcutaneous fat to be lifted instead of the fascia with this towel clip maneuver. Because of this, a slightly larger incision is sometimes necessary. The base of the umbilicus or the fascia itself should be grasped. Now that the fascia is elevated, the surgeon takes the Veress needle and advances it at a right angle to the fascia. The needle is advanced until there is a perceptible change in force as the needle penetrates the fascia and enters the peritoneal cavity. An audible click is usually heard or felt as the spring-loaded tip advances into the peritoneal cavity. A surgeon should feel or hear two clicks as a Veress needle is placed through the abdominal wall. The retracted blunt needle tip will suddenly extend after it passes through the anterior rectus abdominus fascia and again when it enters the peritoneal cavity.⁸ In the waggle test, the hub of the Veress needle should move freely about a fulcrum point located within the anterior abdominal wall. Lack of free movement suggests that the needle tip has entered an intraperitoneal or retroperitoneal structure and the needle should be partially withdrawn. Opponents of this maneuver point out that, if done forcefully, it is likely to enlarge an injury to a fixed vessel or viscus.⁹ It is also likely, however, to alert surgeons to the possibility of retroperitoneal placement before insufflation.

Drop test A syringe partially filled with saline is attached to the Veress needle. The first maneuver is to aspirate the syringe. The appearance of blood indicates that a blood vessel was entered. The needle can be removed and reinserted, with the procedure continuing in the absence of hemodynamic instability.¹⁰ The aspiration of enteric fluid indicates that the needle has been placed into bowel. It is best to leave this needle in place to identify the specific segment of bowel that has been injured. Options at this point include converting to an open procedure or inserting a second Veress needle in a different location and establishing access in this alternate location. The location of the Veress needle should be ascertained and any bowel injury immediately repaired. In the event that no obvious perforation is found, several options exist. The procedure could be aborted at this point followed by close clinical observation (may be considered in laparoscopic incisional hernia procedures where a permanent prosthetic will be placed into the peritoneal cavity). A laparotomy could be made to continue the search for the possible bowel injury. The final option is to continue with the procedure laparoscopically as planned. The risk with the latter approach is of delayed peritonitis from an unrecognized bowel injury,

and caution should be employed if this option is selected. Any signs of postoperative peritonitis or early sepsis should be taken seriously and investigated thoroughly in these cases.

In the absence of blood or enteric fluid, saline is then injected. The inability to inject saline suggests that the tip of the needle may be in a tissue plane. Next, the saline drop test is performed to further assess the location of the tip of the needle [see Figure 2]. A drop of saline is placed in the hub of the needle while maintaining abdominal wall elevation. The passage of saline through the needle is consistent with the tip of the needle being located in the peritoneal cavity. It is important to realize that a successful drop test does not rule out the possibility that the tip of the needle is in bowel.¹¹

Insufflation Once these placement tests are completed to the satisfaction of the surgeon, the gas tubing is connected to the Veress needle, and insufflation is commenced at a low rate of flow (5 mm Hg) while continuing to elevate the abdominal wall. Once insufflation is initiated, it is important to note both the flow rates and the intra-abdominal pressure. The measured pressure will vary according to the length and size of the needle, depth of anesthesia, patient's body habitus, and location of the tip of the needle. A flow rate of zero and a pressure of 20 mm Hg or more indicate that the tip of the needle is not situated freely within the peritoneal cavity. The most likely locations include the abdominal wall or an intra-abdominal organ such as the omentum. In the latter case, lifting the abdominal wall further and slightly angulating the needle may free the tip to allow insufflation to proceed. The needle should not be advanced further without withdrawing it completely and beginning the entire sequence described above from the beginning because of the risk of penetrating the retroperitoneum.

Once insufflation is begun, the strongest predictor of intra-peritoneal placement seems to be an initial filling pressure of less than 10 mm Hg.¹² If the initial intra-abdominal pressure is low and flow seems to be occurring through the needle, the flow rate on the insufflator can be set to a higher rate. Many high-flow insufflators can accommodate flow rates up to 40 L/min, but flow rates in excess of 1 to 2 L/min are rarely

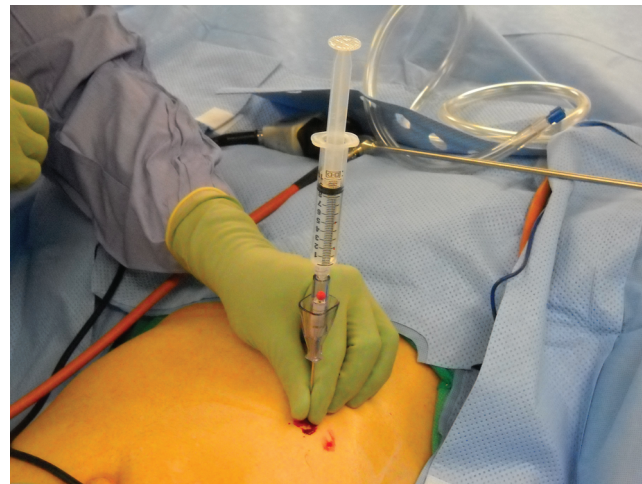


Figure 2 Saline drop test.

exceeded through the long, narrow Veress needle. During insufflation, it is important to continue to observe the abdominal wall morphology, flow rates, volume insufflated, intra-abdominal pressure, and patient's vital signs. Eccentric elevation of the abdominal wall may suggest extraperitoneal insufflation or insufflation into a visceral structure such as the stomach or another piece of small or large bowel. Percussion for tympany is a useful maneuver for ensuring uniform insufflation of the abdominal cavity.

Trocar insertion After an adequate volume of gas has been insufflated, the Veress needle is removed. In the blind technique for initial trocar insertion, a bladed trocar is inserted through an adequately sized incision. The operating table should be set to a height that allows the surgeon to adequately control the force and vector of initial trocar placement. When the table is placed too high, the surgeon must elevate his or her arm, resulting in reduced control and perhaps a greater risk of injury. Countertraction on the abdominal wall should be maintained to minimize the chance of intra-abdominal injury from the trocar blade. Bladed trocars are equipped with a spring-loaded safety shield that retracts when passed through the abdominal wall. Bladed configurations vary by manufacturer, and the recommended technique for trocar insertion differs as well. Trocars with a three- or four-sided blade shaped like a pyramid are placed by steadily rotating the trocar back and forth as the blade is advanced. Disadvantages to these trocars include the large size of the fascia defect created. Incisional trocar-site hernias may be more common with pyramidal than with conical or flat trocar blades. In one comparative study, the risk of incisional hernia was more than 10 times greater when a disposable pyramidal device was used than when access was gained with a reusable conical trocar cannula system (1.83 versus 0.17%).¹³ Potential advantages to the pyramidal-bladed trocars may include the possibility that less force is required to access the abdominal cavity than other blade configurations.¹⁴ Conical flat-bladed trocars [see Figure 3] are placed with direct axial pressure and little rotation. The advantage to bladed trocars with this configuration is that for smaller trocars, the fascia defect is so small that it does not need to be closed at the end of the case. During bladed trocar insertion, a perceptible change in the insertion force signals entry into the peritoneal cavity. This is often accompanied by an audible click as the blade retracts. Advancement of the trocar is halted at this

point. The bladed trocar is removed from its outer cannula. If the insufflation port on the cannula is opened, an audible hiss of escaping gas indicates that the tip of the cannula is located in the insufflated peritoneal cavity. The laparoscope is then inserted through this port, both to confirm the successful placement of the cannula in the peritoneal cavity and to rule out intra-abdominal injury from either Veress needle or trocar insertion. If the cannula is located in the peritoneal cavity, the gas tubing is connected to the gas port of the cannula, and insufflation commences through this port to the set pressure (typically 15 mm Hg). The remaining cannulas are then placed under direct visualization from within the peritoneal cavity.

The Veress technique can also be used to place a primary optical-viewing trocar. Optical trocars can be bladed or bladeless [see Figure 4]. As is the case for the bladed trocars, insertion techniques vary according to trocar tip configuration.¹⁵

DIRECT TROCAR INSERTION

In the direct insertion technique, the primary trocar is placed without preinsufflation. This can be performed with either a bladed trocar and a blind technique or an optical trocar under some measure of direct visualization. Theoretical advantages include decreased time to establish abdominal laparoscopic access.¹⁶ Potential disadvantages may include a higher rate of trocar-related intra-abdominal injuries. Several published series evaluating the direct trocar placement technique have demonstrated that very low rates of injury are possible.¹⁷ This technique is safe in the hands of experienced laparoscopists—those most likely to publish their results. For inexperienced surgeons, the direct access technique is likely associated with unnecessary increased risk when compared with alternative techniques.^{1,18,19}

Technique

If a bladed trocar is selected, it is important to ensure that the patient is completely relaxed, that the skin incision is sufficiently large, and that adequate countertraction on the fascia is maintained during placement. When a bladed trocar with a safety shield is used as described above, a change in resistance signifies that the tip of the trocar may be in the peritoneal cavity. Prior to the initiation of insufflation, the laparoscope should be inserted into the cannula. If the



Figure 3 Conical flat-bladed trocar.

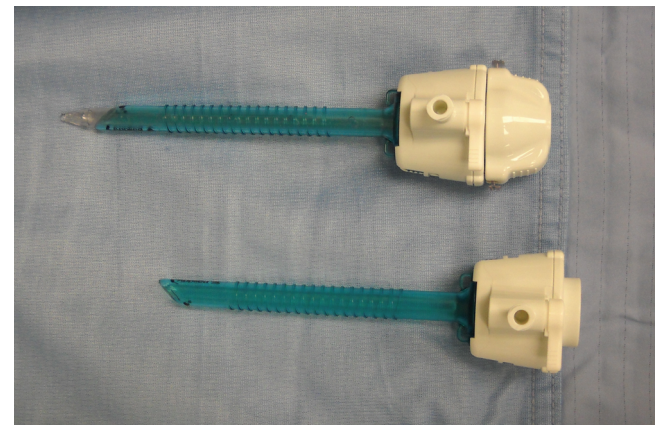


Figure 4 Nonbladed optical trocar.

peritoneal cavity has been safely entered, insufflation can commence at a high rate of flow. If the cannula has not entered the peritoneal cavity, it should be removed and the sequence above reinitiated from the beginning or an alternate technique such as a Veress or open access technique selected.

Optical trocars can also be placed with a direct technique. Once again, the patient needs to be completely relaxed, an adequate skin incision should be made, and adequate countertraction should be applied. A gradual twisting motion is employed, and distinct layers of the abdominal wall can be seen during entry.²⁰

OPEN (HASSON) ACCESS

In an effort to decrease the incidence of injuries associated with the blind penetration of the abdominal cavity during laparoscopy, Hasson proposed a blind minilaparotomy technique.²¹ He developed a reusable device similar to a standard laparoscopic port with a cork-shaped sleeve on the outside. The sleeve could be slid up or down on the cannula shaft depending on the thickness of the patient's abdominal wall. Sutures in the fascia were used to anchor the outer sleeve and to create an airtight seal. Disposable Hasson cannulas are currently available. Hasson-type cannulas that are fixed to the abdominal wall between a balloon and a dense foam cuff are also commercially available [see Figure 5]. Regardless of the configuration of the cannula, the basic method for peritoneal access in the open technique remains the same.

In the open technique, the peritoneal cavity is entered under direct visualization. Theoretical advantages to the open technique may include a decreased likelihood of injury to adherent bowel,^{5,22} although this has been a matter of debate. Major vascular injuries during initial trocar insertion are likely minimized with the open technique, although they can still occur. Potential disadvantages may include increased operative time (especially in obese patients) and an increased risk of late port-related complications such as hematoma, wound infection, or hernia.⁷ Leakage of gas around the cannula is occasionally a problem, but balloon-tipped cannulas and high-flow insufflators prevent these issues from being clinically significant.

Technique

The periumbilical location is most often chosen for initial Hasson cannula placement. An adequately sized incision is made, and the abdominal wall fascia is identified. Two Kocher clamps are secured to the fascia on either side of the midline linea alba. The Kocher clamps are elevated, and the abdominal fascia is incised vertically in the midline. An

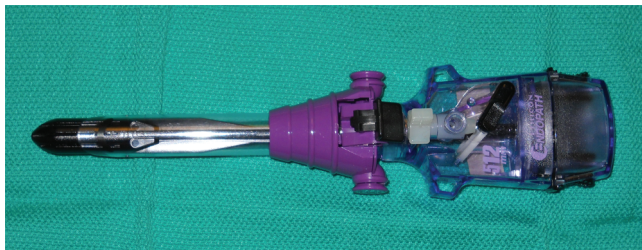


Figure 5 Hasson cannula.

approximately 1.5 to 2.0 cm defect is created in the fascia. If the defect is too large, air leakage may be a problem. Depending on the patient's body habitus, it may be easy to become lost in the preperitoneal space. Entry into the peritoneal cavity should be confirmed visually. Two heavy sutures should be placed in either side of the fascial defect prior to releasing the fascia from the Kocher clamps. The Hasson cannula with its blunt obturator is advanced into the peritoneal cavity, and the sutures are firmly attached to the fixation obturator. Gas is insufflated through the cannula at a high rate of flow, and the laparoscope is inserted.

If gas leaks excessively around the cannula, there are several techniques for addressing this. The first option is to remove the stay sutures and secure these to the cannula more firmly. A penetrating towel clip can be used to seal the skin around the cannula. The cannula can be removed, and another fascial suture can be placed and tied to decrease the size of the fascial opening. Finally, a balloon-tipped fixation trocar can be placed to seal the leak.

COMPLICATIONS

Insertion of the Veress needle and primary trocar for initial entry remains the most hazardous part of laparoscopy, accounting for 40% of all laparoscopic complications and the majority of the fatalities.²³ Despite decades of research and development to find safer methods for initial laparoscopic entry, major vessel injuries have been reported using virtually all types of trocar insertion methods. The overall morbidity and mortality rates related to laparoscopic access are low. The life-threatening complications include injury to the bowel, bladder, major abdominal vessels, and anterior abdominal wall vessel. Injuries to the bowel (1.8 per 1,000 cases) are most common, followed by injuries to the abdominal vessels (0.9 per 1,000 cases).²⁴ A recent Cochrane review included 17 randomized, controlled trials concerning 3,040 individuals undergoing laparoscopy. Overall, there was no evidence of advantage using any single abdominal access technique in terms of preventing major complications. However, there were two advantages with direct trocar entry when compared with Veress needle entry in terms of avoiding extraperitoneal insufflation (odds ratio [OR] 0.06, 95% confidence interval [CI] 0.02 to 0.23) and failed entry (OR 0.22, 95% CI 0.08 to 0.56). There was also an advantage with radially expanding access system (Step bladeless trocars, Covidien, Norwalk, CT) trocar entry when compared with standard trocar entry in terms of trocar site bleeding (OR 0.06, 95% CI 0.01 to 0.46). Finally, there was an advantage of not lifting the abdominal wall before Veress needle insertion when compared with lifting in terms of failed entry without an increase in the complication rate (OR 5.17, 95% CI 2.24 to 11.90). However, studies were limited to small numbers, excluding many patients with previous abdominal surgery and women with a raised body mass index, who often had unusually high complication rates. The authors concluded that there appears to be no evidence of benefit in terms of the safety of one technique over another. However, the included studies were small and cannot be used to confirm the safety of any particular technique.²⁵

Vascular Injury

Vascular injury can occur regardless of the method of access, largely because of the relatively close proximity of the

abdominal wall to the great vessels that are located retroperitoneally, which, in thin individuals, can be as little as 2 cm.²⁶ Most vascular injuries (up to 80%) occur at the initial access.⁵ Recent studies have suggested that the incidence of major vascular injury is slightly higher with the closed technique (Veress and direct trocar insertion) as opposed to the open (Hasson) technique. Molloy and colleagues' study suggests that the open technique decreased the rate of vascular injury to 0.01% compared with a rate of 0.04% associated with closed techniques using a Veress needle.¹ A recent systematic review specifically evaluating injuries related to Veress needle insertion included 38 selected articles, 696,502 laparoscopies, and 1,575 injuries (0.23%). Of these injuries, 98 (6.2%) involved blood vessels, 8 (8.1%) of which were injuries to major retroperitoneal vessels.²⁷ Although the incidence of major vascular injuries is low, the mortality rate arising from these lesions reportedly ranges between 8 and 17%.²⁸ It is difficult to determine the exact prevalence of iatrogenic injury during laparoscopy because certain complications are not usually reported,²⁹ for obvious reasons.

Vessel injuries attributable to trocars are usually more obvious and catastrophic than injuries related to Veress needle insertion. Transmural vessel injury related to trocars is the rule rather than the exception.³⁰ When recognized, the trocar and cannula should be left in place and a conventional vascular repair performed. An expanding retroperitoneal hematoma, hemodynamic instability in the face of active bleeding, and active intra-abdominal hemorrhage that cannot be managed laparoscopically are all indications for conversion to laparotomy and exploration or vascular repair. Trocar-related major vascular injuries reported to the Food and Drug Administration (FDA) by the medical device industry between 1993 and 1996 were reviewed.³¹ Of the 408 injuries reported, 26 resulted in death and 87% occurred despite the use of trocars with safety shields. The most common site of injury was the aorta (23%), followed by the vena cava (15%). A more recent review of FDA reports focused on two optical access devices that purported to provide a degree of safety by allowing the operator to insert a clear but sharp trocar with a laparoscope positioned within it.³² In that report, 37 major vascular injuries of the aorta, vena cava, and iliac vessels were described, and four deaths were described in relation to vascular injury. These reports seem to validate the notion that safety shields, designed to protect vessels and viscera, do not provide such protection and justify the FDA decision to forbid the term in product labeling. From these reports, it also seems as if in some cases, the diagnosis of major vascular injury may be delayed, usually because of retroperitoneal bleeding, with symptoms manifesting in the recovery room.

Abdominal wall vascular complications are typically managed with devices designed to facilitate fascial closure of laparoscopic port sites (suture passers) when possible. It is important to visualize all trocar sites after each trocar is removed at the end of the case to minimize the possibility that an abdominal wall vessel has been injured but has not yet bled because of tamponade by the trocar itself.³³

Visceral Injury

Although studies have suggested that the open technique of initial trocar placement may be associated with a lower incidence of major vascular injuries, the same cannot be said

for visceral injuries.³⁴ The incidence of this complication is about 0.05% of all open access procedures.³⁵ The main difference between bowel injuries occurring during the open technique compared with the closed technique is that with the open procedure, it is more likely that the injury will be immediately obvious and repaired without delay. Veress needle injuries to the large and small bowel may be associated with a higher incidence of peritonitis and other complications than injuries to the stomach, which can often be managed conservatively.¹⁰ If it is suspected that the Veress needle has penetrated the bowel, the needle should be left in place and a second needle placed in another location. Once abdominal access is established, the location of the needle should be ascertained, and repair of any injuries should proceed as appropriate related to the nature of the injury.

Physiology of Pneumoperitoneum

The introduction and widespread acceptance of laparoscopy have created new challenges for anesthesia providers. Laparoscopic surgery and carbon dioxide (CO₂) insufflation have introduced unique management concerns and physiologic consequences for patients. When one considers the fact that many patients undergoing laparoscopic surgery are likely to be sent home shortly following the procedure, it becomes important for surgeons to understand these physiologic consequences and potential ramifications as well.

CARDIOVASCULAR EFFECTS

Intraoperative Position

Patient position is important during laparoscopic surgery to help facilitate visualization of the operative field. For upper abdominal surgery, the reverse Trendelenburg position (head up) can enhance exposure of the operative field. The extreme reverse Trendelenburg position with the aid of a padded footboard has been advocated in bariatric surgery as a means of maximizing exposure. In lower abdominal and pelvic surgery, the Trendelenburg position (head down) enhances operative exposure. It has been demonstrated that intra-abdominal volume varies as a patient's position changes.³⁶ When compared with the supine position in laparoscopic surgery, the Trendelenburg position is associated with increased intra-abdominal volume, and the reverse Trendelenburg position is associated with decreased volume. Decreased intra-abdominal volume may correlate with impaired visualization for the surgeon, possibly extending the operative time and impacting the ultimate outcome in other ways (e.g., increasing doses of muscle relaxation in a quest to see better and poorly visualized anatomy).

An increase in intra-abdominal pressure up to 12 to 15 mm Hg decreases venous return, which results in reduced preload and cardiac index (CI), without adequate intravascular volume loading. The common belief is that changes in body position, especially the reverse Trendelenburg position, intensify these negative effects of pneumoperitoneum, whereas the Trendelenburg position has a positive effect on venous return and hence cardiac output (CO). These physiologic effects are likely minimized in euvoletic patients.³⁷ Invasive hemodynamic monitoring can be used to determine the hemodynamic consequences of laparoscopic surgery in healthy

volunteers. Joris and colleagues determined that CO decreased by as much as 50% of the preoperative value after the beginning of the laparoscopy and that systemic vascular resistance (SVR) increased accordingly.³⁸ Hirvonen and colleagues conducted a similar study but took measures to prevent the peripheral pooling of blood, which can happen with the reverse Trendelenburg position, and increased intra-abdominal pressure related to pneumoperitoneum.³⁹ Before laparoscopy, the patients received an intravenous infusion of colloid solution if cardiac filling pressures were low and their legs were wrapped from toes to groin with elastic bandages. A 20% decrease in CO and a 30% decrease in stroke volume (SV) were observed during laparoscopic cholecystectomy in healthy subjects when compared with preoperative values. With the change in position from the supine to the reverse Trendelenburg position in awake and anesthetized patients, the CI, stroke index (SI), central venous pressure (CVP), and pulmonary capillary wedge pressure (PCWP) decreased and SVR increased.

In robotic prostatectomy, where patients are placed in a steep (40°) Trendelenburg position for several hours, it has been demonstrated that mean arterial pressure (MAP) and CVP increased significantly.⁴⁰ First, the observed increase in pressure is the result of increased hydrostatic pressure at the external auditory meatus caused by the tilting of the table. In addition, because MAP increased by a greater absolute amount than CVP, at least part of the observed increase in MAP must also be caused by increased CO, SVR, or both. Several additional investigators have demonstrated that placing the patient in the Trendelenburg position is associated with an increase in the CVP, with the CO remaining the same or increasing.^{41,42} The induction of pneumoperitoneum has been reported to reduce, elevate, and have no effect on CO in different reports.^{37,43,44} Position as an independent factor on the hemodynamic profile is much less studied than the hemodynamic consequences of pneumoperitoneum.

Pneumoperitoneum

Insufflation of the peritoneal cavity with CO₂ during laparoscopic surgery leads to an increase in the intra-abdominal pressure. Drawing conclusions on the effect of pneumoperitoneum alone on hemodynamic function is difficult as a result of the confounding variables of study methodology, anesthesia, position of the patient, surgical stimulus, and condition of the patient. The effects of pneumoperitoneum on cardiac physiology have been found to depend on the magnitude of the pressure increase, intravascular volume, and underlying cardiovascular status of the patient. The creation of pneumoperitoneum to an intra-abdominal pressure of less than 20 mm Hg in the supine position is generally associated with an increase in the MAP and SVR, although the clinical impacts of these changes are determined by a variety of patient-specific factors.^{45,46} Older animal studies have looked at the impact of pneumoperitoneum in relation to intravascular volume status. It has been demonstrated that at very high intra-abdominal pressures in a dog model, CO decreased by 53% in hypovolemic dogs and by 15% in normovolemic dogs but increased by 50% in hypervolemic dogs.^{47,48} At low and normal right atrial pressures (low and normal volume status), the inferior vena cava (IVC) is compressed and collapses, causing a decrease in venous return. In hypovolemic dogs,

the poor cardiac performance is postulated to be further compounded by the increase in total peripheral resistance related to the compression of the splanchnic arterioles by the increased intra-abdominal pressure. On the other hand, at high right atrial pressures (hypervolemic status), the venous return to the heart is actually augmented as the IVC resists compression. CO in these animals is likely increased related to the Starling mechanism. In humans, the effects of varying pneumoperitoneum-induced changes in intra-abdominal pressure have been studied at much lower pressures.^{49,50} Invasive monitoring and echocardiography were used to evaluate the hemodynamic changes as the intra-abdominal pressure increased from low (7 mm Hg) to higher (15 mm Hg) in healthy patients undergoing elective laparoscopic cholecystectomy. At low insufflation and intra-abdominal pressures, an overall mild increase in MAP, SV, and CO was observed. At 15 mm Hg insufflation pressure, the SV and CO were observed to decrease to a similar degree. There are few published data on the effect of higher insufflation pressures in humans during laparoscopy. In 100 healthy women undergoing elective gynecologic procedures, initial insufflation to an intra-abdominal pressure of 30 mm Hg was attained prior to insertion of the primary trocar. Heart rate, blood pressure, and pulmonary compliance were measured at 15 versus 30 mm Hg. A significant increase in MAP and a decrease in pulmonary compliance were observed at 30 mm Hg compared with 15 mm Hg.⁵¹ Unfortunately, CO and other hemodynamic parameters were not evaluated.

Bradyarrhythmias have been reported to occur with the induction of pneumoperitoneum. These arrhythmias are most likely related to the vagal stimulation induced by peritoneal stretching on insufflation.⁵² In one recent study of patients undergoing laparoscopic urologic surgery, 28% of patients developed bradycardia perioperatively compared with 0% of patients randomly assigned to a treatment group to receive a dose of atropine prior to pneumoperitoneum induction.⁵³ Treatment of bradycardia on induction of pneumoperitoneum consists of immediate cessation of surgical stimulation, abdominal deflation, and the administration of anticholinergic drugs such as glycopyrrolate or atropine.

Carbon Dioxide

CO₂ is the preferred gas for abdominal insufflation in laparoscopy as a result of its lack of flammability, solubility, and ready availability. CO₂ insufflation results in diffusion of CO₂ into the blood and an increase in its elimination through the lungs. The CO₂ load is greatest during extraperitoneal insufflation (e.g., preperitoneal inguinal hernia repair) compared with intraperitoneal insufflation.⁵⁴ The cardiovascular effects of hypercarbia seen during laparoscopic procedures are not as significant when compared with the effects of patient position and pneumoperitoneum provided that the arterial carbon dioxide tension (Paco₂) is kept below 50 torr by controlled ventilation (increased ventilation to increase CO₂ exchange and decrease Paco₂). Hypercarbia has effects on the myocardium (myocardial irritability with transient arrhythmias, increased contractility), central nervous system (increased sympathetic tone), and periphery (vasodilation with a decrease in the SVR). The net effect is the negligible hemodynamic consequences of hypercarbia.⁵⁵ Studies comparing CO₂ pneumoperitoneum to pneumoperitoneum created with

alternative gases such as nitric oxide and helium have demonstrated that the hemodynamic effects are independent of the type of gas insufflated.⁵⁶

CO₂ embolism is a potentially fatal complication caused by the insufflation of CO₂ directly into the circulation. CO₂ embolism occurs most frequently on the induction of pneumoperitoneum but can occur at any point in the operation.⁵⁷ Certain procedures, such as laparoscopic hepatectomy, are very commonly associated with small CO₂ gas embolisms that are usually subclinical, although clinically significant CO₂ embolism is still a major concern in these cases.⁵⁸ Cardiovascular collapse can occur rapidly with a large CO₂ embolism. Gas obstructs the right ventricular outflow tract, resulting in cyanosis, increased venous pressure, ventricular arrhythmias, and a decrease in the end-tidal carbon dioxide tension (P_{CO₂}). Immediate recognition of the problem is essential. Treatment consists of the immediate cessation of insufflation, positioning the patient in the head-down left lateral position, hyperventilation, and even aspiration of gas from the right atrium through a central venous catheter.

RESPIRATORY EFFECTS

The respiratory effects of laparoscopic surgery include those of pneumoperitoneum and positioning and are superimposed on the effects caused by the anesthetic itself. Lung volumes and compliance are decreased during laparoscopic surgery.

Effect of Pneumoperitoneum

The increase in intra-abdominal pressure caused by pneumoperitoneum also affects the pulmonary system by impeding diaphragmatic movement, leading to a decrease in the functional residual capacity (FRC) of the lung. Compliance is also decreased, mostly as a result of a cephalad displacement of the diaphragm and the chest wall. This disturbance in compliance is immediately reversible on abdominal deflation.⁵⁹ Airway pressures increase during CO₂ pneumoperitoneum because of decreased compliance and the need to increase minute ventilation to excrete the increased CO₂ load absorbed from the peritoneal cavity.

Hasukic and colleagues measured pulmonary function tests in postoperative patients who underwent laparoscopic cholecystectomy.⁶⁰ Pulmonary function tests demonstrated a decrease in forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC). In spite of these documented effects of pneumoperitoneum on pulmonary function, studies have shown that the pulmonary status of patients after a laparoscopic procedure is actually less detrimentally affected than when compared with the open procedure.⁶¹

Oxygenation

Increasing pneumoperitoneum also causes an increase in alveolar dead space, leading to potential hypoxemia.⁶² This leads to ventilator-perfusion mismatching and intrapulmonary shunting. The risk of hypoxemia is counteracted by controlled mechanical ventilation during laparoscopic surgery with increased tidal volumes and the addition of positive end-expiratory pressure (PEEP).⁴⁰

Carbon Dioxide Absorption and Excretion

CO₂ is the most common gas used to obtain pneumoperitoneum during laparoscopic surgery. It is absorbed into the

bloodstream, where it is finally excreted by the lungs. Most of the CO₂ combines with water found in the red blood cells to form carbonic acid. Carbonic acid further breaks down into hydrogen, which is carried by hemoglobin, and bicarbonate, which diffuses into the plasma. A small amount of CO₂ does get dissolved directly in the bloodstream and is transported to the lungs for excretion.⁶³ Subcutaneous emphysema is a frequent occurrence and is commonly caused by leakage around an abdominal insufflating port. Extensive subcutaneous emphysema can be associated with significant respiratory acidosis, necessitating prolonged postoperative ventilation.⁶⁴

PAIN AFTER LAPAROSCOPIC SURGERY

Laparoscopic surgery has been shown to cause less postoperative pain when compared with the equivalent open technique for many operations. Some examples of common general surgery procedures where laparoscopic surgery has been shown to reduce postoperative pain include cholecystectomy, hemicolectomy, appendectomy, and inguinal hernia repair.^{65–67} In addition to incisional and visceral pain, laparoscopic surgery has been associated with shoulder tip pain. This referred pain is thought to be caused by the increased intra-abdominal pressure caused by the laparoscopic gas, resulting in diaphragmatic stretching and phrenic nerve irritation. As a result, shoulder tip pain is unique to laparoscopy and usually dissipates in 1 to 3 days as the CO₂ is absorbed into the systemic circulation. One method to reduce shoulder tip pain is by employing a lower pressure during the procedure; however, this can reduce the size of the surgical field.⁶⁸ Other techniques, such as intraperitoneal irrigation with local anesthesia, have shown promising results.⁶⁹

NAUSEA AND VOMITING AFTER LAPAROSCOPIC SURGERY

A common complaint by patients who have undergone a laparoscopic procedure is postoperative nausea and vomiting (PONV). This can be seen in as many as 40 to 75% of patients and can delay discharge of patients, especially during outpatient surgery.⁷⁰ Patients rank vomiting as the number one complication of surgery they want to avoid and rank nausea in the top five. When patients are given the option of allocating \$100 out of pocket to the prevention of postoperative complications, they choose to allocate approximately \$30 for the prevention of PONV.⁷¹ The etiology of PONV from a purely surgical standpoint (not taking into account the effects of anesthetic gas) is likely attributable to a combination of peritoneal gas insufflation and bowel manipulation.⁷² Postoperative opioids, female sex, history of motion sickness, history of migraine, duration of the operation, and a previous history of PONV have all been demonstrated in a predictive model as significant independent variables with marked association with PONV.⁷³ The newest guidelines delineated in the 2008 consensus guidelines for the management of PONV suggest that the clinical team should evaluate the patient's risk for PONV, reduce baseline risk factors for PONV, evaluate the patient's preferences, and determine the cost-effectiveness of antiemetic prophylaxis before deciding to administer PONV prophylaxis to the patient.⁷⁴ Other than identifying patients at the greatest risk for PONV, guidelines include reducing baseline risk factors (avoid general anesthesia when possible, use propofol for induction and maintenance of anesthesia, avoid nitrous oxide and volatile anesthetics, minimize opioids and

neostigmine, and maintain adequate hydration) and administering antiemetics prophylactically in moderate- and high-risk patients in the appropriate dose and at the appropriate time. A recently published economic analysis of routine prophylaxis of PONV in all surgical patients determined that the study site hospital's net profit increases linearly with increased

PONV prophylaxis administration. Economic analysis showed that PONV prophylaxis was economically beneficial for the hospital when weighed against the expense generated by treating patients returning to the hospital with PONV.⁷⁵

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23 TECHNICAL ASPECTS OF LAPAROSCOPIC SURGERY

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Laparoscopic surgery is one of the most important technical advancements in general surgery in the last century. From its initial pioneering application for appendectomy and cholecystectomy in the late 1980s and early 1990,¹ laparoscopic surgery has grown to be routinely used in almost all known surgical procedures. Its proper use is associated with many benefits to both patients and health care systems. Documented advantages over open techniques include faster patient recovery, shorter hospital stay, decreased pain and analgesic requirements, and faster return to work.²⁻⁵ For many procedures, reduced rates of surgical complications have been documented, such as postoperative ileus, surgical site infection, and pulmonary complications.⁶⁻¹² Other long-term benefits are lower incidence of postoperative ventral hernias and intra-abdominal adhesions, as well as better cosmetic results.¹³⁻¹⁷

During its first years, laparoscopic surgery employed a combination of simple diagnostic laparoscopic instruments with endoscopic graspers and laparoscopic biopsy forceps used for diagnostic laparoscopy. For many decades, diagnostic laparoscopy had been used to evaluate pelvic diseases, abdominal pain, liver diseases and to perform liver biopsies.¹⁸ In contrast, laparoscopic surgery requires skills, techniques, facilities, and equipment far beyond those required for diagnostic laparoscopies. Improvement in instruments and the understanding of the multiple technical details that are necessary to safely perform laparoscopic surgery were fundamental to the rapid growth that followed the introduction of the technique. The purpose of this chapter is to highlight the technical aspects of laparoscopic surgery, operating room and patient preparation, proper choice and use of selected instruments, and training to acquire basic and advanced technical skills.

Operating Room Setup and Patient and Surgery Team Positioning

Until recently, most laparoscopic procedures were performed in operating rooms that were originally designated for traditional open surgery. With the growth of advanced laparoscopic technology, larger suites specially designed for laparoscopic surgery are recommended to facilitate patient, anesthesia, and surgical team positioning and accommodate all ancillary equipment that may be needed.

OPERATING TABLE LOCATION AND REQUIREMENTS

The operating table should be located at the center of the room. It should be positioned far enough from the doors and allow adequate room for the anesthesia equipment and personnel to have access to fluoroscopic and other imaging and endoscopy equipment. The operating table should enable

intraoperative access for fluoroscopy and endoscopy equipment. It should also be versatile to allow safe controlled movement of the patient in all directions, as is commonly required during advanced laparoscopic procedures. Access to the upper abdomen or pelvis is greatly facilitated by placing the patient in a reverse Trendelenburg or Trendelenburg position. Mechanical support and appropriate padding are recommended to prevent patients from sliding, as well as enabling the variety of patient positions that are necessary during most laparoscopic procedures. Lastly, laparoscopic instruments are usually longer than handheld instruments used in open surgery; therefore, the best operating table position in laparoscopic cases is considerably lower. In larger or obese patients, inability to lower the operating table may result in inappropriate surgeon positioning with prolonged abduction of the shoulders during the procedure. Adding a standing platform allows proper surgeon positioning.

SURROUNDING THE OPERATING TABLE

The location of the laparoscopic tower and the monitors varies according to the planned procedure; however, video monitors should be placed for convenient viewing by both the surgeon and the assistant. A minimum of two video monitors is suggested, especially in cases where the surgeon and the assistant(s) stand on different sides of the operating table. It has been demonstrated that the optimal height of the monitor is no higher than the surgeon's eye level.^{19,20} The preferred position of the laparoscopic tower is on the side opposite the doors to the operating room so that heavy instruments can be wheeled in when needed.

Numerous hospitals around the world are undertaking the conversion of traditional operating rooms into state-of-the-art laparoscopic suites. Such renovations require careful planning.²¹ In modern laparoscopic operating rooms, the heavy-wheeled towers are replaced by overhead ceiling-mounted booms that can be positioned as needed. All laparoscopic control equipment should be mounted on the booms. This includes light source, CO₂ insufflators, camera controls, and processors [see *Figure 1*]. Moreover, cautery and ultrasonic dissector units, as well as suction and irrigation units, are mounted on the booms to maintain a cable-free floor and avoid potential obstacles that may compromise both the patient's and the surgical team's safety. It is advisable to establish a control desk for the circulating nurse, allowing full control over all lights, monitors, and equipment on the booms. Camera processors and monitors should contain multiple input and output sources all controlled through a video router. This will allow multimedia communication, which may be required in certain procedures. A short and not all-inclusive list of possible media communication includes



Figure 1 Schematic representation of a ceiling-mounted articulated boom for laparoscopic surgery with high-definition monitors. Reproduced with permission from Stryker Instruments, Kalamazoo, MI.

laparoscopic camera, fluoroscopy, endoscopy, ultrasonography, anesthesia monitor, digital video recording, outside hospital video receiver, and transmitter.

Wireless high-definition video has also been introduced to the operating room recently, which has helped improve the workflow in the operating room, eliminate clutter, and streamline the continuum of care. Wireless technology will also help enable the electronic transfer of data to centralized repositories such as electronic medical records systems or remote and even overseas training facilities.

PATIENT POSITIONING

The exact patient position varies from one procedure to another and among different surgeons [see Table 1]. For example, for a simple laparoscopic cholecystectomy, most surgeons will place the patient supine and stand on the left side. However, some surgeons will prefer the split leg position and will place themselves between the patient's legs. All common patient positions apply for different laparoscopic surgeries, although some aspects need to be highlighted. During laparoscopy, the position of the operating table is often rotated to extremes to enhance gravity forces that act mainly on the bowel. For such angles, restraints, supports, and proper patient padding are mandatory. Liberal use of anchoring devices, leg and arm support, straps, and a foot board is recommended. It should be routine to move the patient into the desired position(s) that will be used during the proposed procedure before patient draping. This ensures that the patient will not slide or have inappropriate pressure applied to extremities or other body parts during the procedure itself. The preferred position of the patients' hands is alongside the patient's body, allowing maximal range and freedom of movement for both the surgeon and the assistant.

It is still controversial as to whether laparoscopic surgery alters the risk of a thromboembolic event. Two factors may lead to an increase in the risk of a thromboembolic event: longer operating times in selected cases and reduced venous return from the inferior extremities as a result of pneumoperitoneum and reverse Trendelenburg position. Conversely,

Table 1 Different Patient Positions Used for Laparoscopic Surgical Procedures	
Procedure	Possible Patient Positions
Esophagectomy	Supine, split leg, left/right lateral decubitus
Paraesophageal hernia Nissen fundoplication	Supine, split leg
Splenectomy	Supine, split leg
Gastrectomy	Supine, split leg
Bariatric surgery Adjustable gastric banding Sleeve gastrectomy Roux-en-Y gastric bypass	Supine, split leg
Cholecystectomy, liver resection	Supine, split leg
Adrenalectomy	Lateral decubitus
Appendectomy	Supine
Adhesiolysis	Supine
Hernia Inguinal/umbilical/ventral	Supine
Abdominal colectomy	Supine
Rectal surgery Low anterior resection Abdominoperineal resection Total proctocolectomy	Lithotomy

laparoscopic surgery seems to be associated with less operative trauma and inflammatory response,²² earlier ability to ambulate, decreased pain, and shorter hospital stays, all of which are thought to decrease the risk of a thromboembolic event. Intraoperative intermittent pressure compressions are recommended for all prolonged laparoscopic procedures.²³ Three randomized clinical trials have evaluated the need for chemical thromboprophylaxis in laparoscopic surgery; the results suggest that use of chemical thromboprophylaxis should be based on assessment of patients' risk factors and prolonged cases.^{24–27} Current guidelines by the American College of Chest Physicians do not support the routine use of chemical thromboprophylaxis for patients who do not have additional thromboembolic risk factors and recommend early and frequent ambulation for patients undergoing entirely laparoscopic procedures.²⁸

SURGEON POSITIONING

The position of the surgeon varies according to the planned procedure and the surgeon's preference. The surgeon should plan where to place the assistant and the camera holder, and if rotation of positions is necessary, it is important to place the operating table surroundings in a reasonable fashion.

Alignment is key to both the surgeon's convenience and optimal eye-hand coordination. The surgeon's eye, hand, camera, operative field, and monitor ought to be aligned in one line.

In 2009, van Det and colleagues²⁰ summarized guidelines for optimal laparoscopic surgery suites:

Monitor position:

- Straight ahead of each person in line with the forearm-instrument motor axis

- No higher than the surgeon's eye level (preferred 15° downward)
- Distance according to monitor size

Patient position:

- Ensure that arms or legs do not interfere with the surgeon's movements
- Enable surgeon's alignment with the operating field

Equipment position:

- Does not disrupt the eye-hand-target axis
- No view blockage for the surgeon, assistants, and nurses
- Allows free axis to the patient and surgeon and assistant position rotation

Laparoscope and Instruments

The essential equipment needed to perform laparoscopic surgery is the laparoscope, light source, camera head, video system, and CO₂ insufflation device.

LAPAROSCOPE

The laparoscope is obviously required to perform laparoscopic surgery. It has evolved over the past two decades from a handheld to the eye instrument [see Figure 2] to the articulating flexible 5 mm scopes [see Figure 3a], three-dimensional video coding, higher resolution and higher definition cameras and monitors, and split-screen monitors that can combine sonograms, CT scans, and real-time endoscopy images.

Endoscopes are usually attached to a camera—either built-in or separate. Another important component is the light source that connects to the endoscope through a light cable. All three components deliver the image to a processor that projects the image on the monitor, and the combination of all elements determines final image quality. Most light sources have a brightness control feature, but the features of the camera differ by manufacturer. Zoom, focus, and white balance are principal actions present in virtually all cameras [see Figure 3b].

The most commonly used endoscope is a rigid apparatus with a set of lens and fiberoptic bundles that project the image to the camera. The diameters of endoscopes range from 2 to 10 mm. Endoscopes are traditionally divided into angled and nonangled scopes. A nonangled (0°) endoscope has a flat end and offers the surgeon only a straight-ahead look. This obviously limits the ability to properly view the entire surgical field. To overcome this limitation, angled endoscopes were produced available at 30 or 45°. The angled scope may rotate 360° and thus offer better viewing. The use of angled endoscopes has been demonstrated to decrease the incidence of complications in laparoscopic cholecystectomies.^{29,30} The new generation of endoscopes has mobile tips, which can flex, and employ “chip-in-the-tip” technology—video chips in the distal end of the endoscope, which, on top of magnification, offers the surgeon a view around obstructing structures.

The combination of the endoscope and the camera projects the image to the monitor. Major progress has been made in this technology. Analogue images transferred via S video cable are now in the process of being replaced by digital and high-definition cameras and monitors. High-definition cameras offer benefits for surgeons performing operations

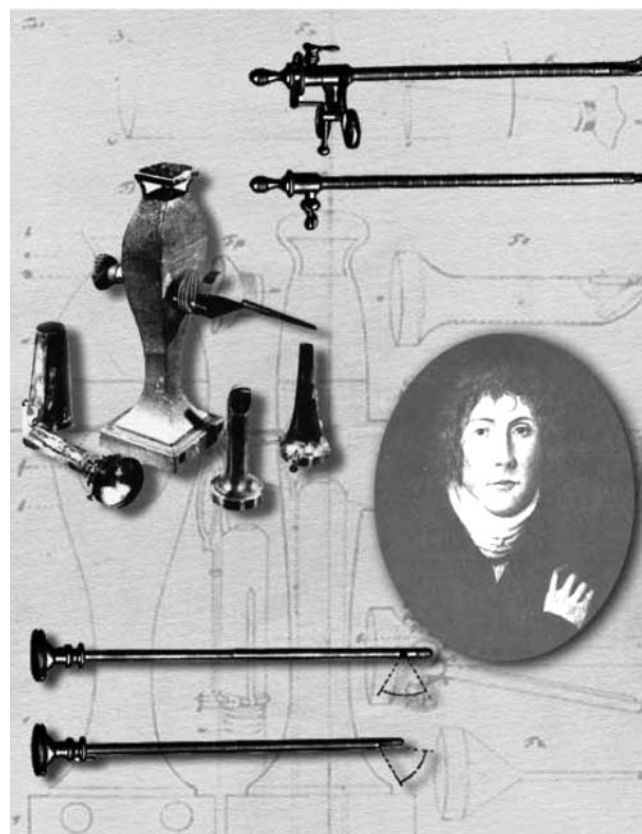


Figure 2 Blueprints and photographs of the first endoscope. Introduced by Phillip Bozzini of Frankfurt, Germany. Despite accurate blueprints and a fine design (background), his work was repudiated by the Vienna School of Medicine. His early demise at age 36 years hampered further progress in the development of endoscopy until the work of Pierre Segalas of Paris, France, and Adulph Kussmaul of Frieberg, Germany. Reproduced with permission from Arch Surg 2004;139(10): 1110–1126 Figure 1. Copyright © 2004 American Medical Association. All rights reserved.

and those viewing a procedure at another location. In high-definition systems, the surgeon may see better even when there is blood on the field as a result of reduced red color saturation. With the new cameras, surgeons can have an optimal view of the surgical field, even when using smaller diameter scopes. High definition also provides a wide-angle view,



Figure 3 Articulated 5 mm scope (a) and high-definition camera head (b). With permission from Stryker Instruments, Kalamazoo, MI.

which allows surgeons to more quickly see instruments moving in and out of the surgical field, and depth of field is improved. Lastly, high-definition systems allow the use of a two-dimensional image but augment identification of visual clues used to judge depth of field. It has been shown in surgical training laboratories that high-definition systems improve certain functions, such as tying knots and suturing, and reduce “sword fighting” or moving instruments around before getting to the target.^{31–33}

One frustrating component of laparoscopic surgery is the fogging of the scope, which in turn forces the surgeon to stop the procedure until a clear image is reobtained. The fog is created because of the temperature difference between the endoscope and the abdominal cavity. For this reason, endoscopes are warmed in hot water before being introduced into the abdomen. Several antifog solutions are commercially available. These are hydrophilic solutions, and water vapor accumulates on the glass as a thin layer of water, preventing fog. Some new technology cameras include an integrated antifog pump that achieves longer periods of clear visualization.

INSTRUMENTS

Incredible progress has been made over the past two decades in instrumental development for laparoscopic procedures. This development was possible because of the full and intense cooperation between surgeons and industry. Surgeons dictated the need and in many instances were involved in the actual development of specific instruments. Instruments are inserted through the trocars, and the range of movements is limited by trocar mobility. Most laparoscopic instruments include two basic movement-adjustment abilities. First, all instruments can be pushed in and out of the trocar and the abdominal cavity. Second, instruments can be rotated 360° either by rotating the hand that holds the instrument or by manually turning the rotating knob. Some devices are equipped with an articulating feature that enables angularity of the instrument’s end. These limited movements and the diminished tactile sensation were the basis for continuous and ongoing device development. The list of available instruments and devices and their description are beyond the scope of this chapter. A few examples of the most common are depicted in Figure 4: graspers, dissectors, scissors, and other basic surgical instruments are available in different sizes (3 to 10 mm) and lengths, but their mechanism of action and utility are similar to those for open surgery. Below we discuss in detail hemostatic devices and endoscopic staplers and the importance of ergonomics.

Hemostatic Devices

The importance of preventing and controlling intraoperative bleeding is common to all surgical procedures. Bleeding not only prevents visualization of the anatomy; also, the dark color of the blood absorbs the light and decreases image quality. In comparison with open surgery, knot tying a vessel laparoscopically is time consuming, and the ability to control massive bleeding is limited. Hence, bleeding has traditionally been the most common cause of conversion to open surgery,³⁴ and hemostatic devices therefore play an important role in laparoscopic surgery.



Figure 4 Assorted laparoscopic instruments: traumatic and atraumatic graspers, hook and spatula cautery, suction tip, scissor, and right angle dissector.

Monopolar devices These devices use a simple monopolar current and are similar to open monopolar cautery. Two unique instruments are available: the spatula electrode, with a flat end, is primarily used to dissect the gallbladder off its liver bed; the hook electrode can apply cautery and pose traction at the same time. Many dissecting and cutting instruments can also be connected to monopolar cautery and assist in achieving bloodless surgery. The exposed electrode tip must be visible whenever the unit is operating, and the tissue has to be placed in tension to achieve cutting. The minimal current and power settings needed to achieve desired results should be used, and it is generally recommended to avoid using over 30 watts of power. If the current is on for long periods, the chance of remote-site electrical injury or burn is increased.

Bipolar devices Bipolar devices induce hemostasis by transmission of current between the coupled plates of the tip. They achieve greater hemostasis than monopolar devices while minimizing thermal injury to surrounding tissues. A popular and effective electrothermal bipolar vessel sealing system is the Ligasure Vessel Sealing System (LigaSure, Covidien Energy-based Devices, Boulder, CO), which is available in both 5 and 10 mm sizes [see Figure 5, a and b]. It achieves hemostasis in small, medium, and large arteries and has been shown in a recent meta-analysis to reduce operative time by 25% without an increased risk of bleeding or other complications when compared with conventional mechanical hemostatic methods.³⁵

Both monopolar and bipolar devices generate smoke that may interfere with laparoscopic visualization. However, visualization is not the only issue. The National Institute for Occupational Safety and Health (NIOSH) has issued a warning regarding the possible health effects of exposure to surgical smoke plumes.³⁶ Although studied only in laboratory simulations, smoke evacuation systems are recommended.

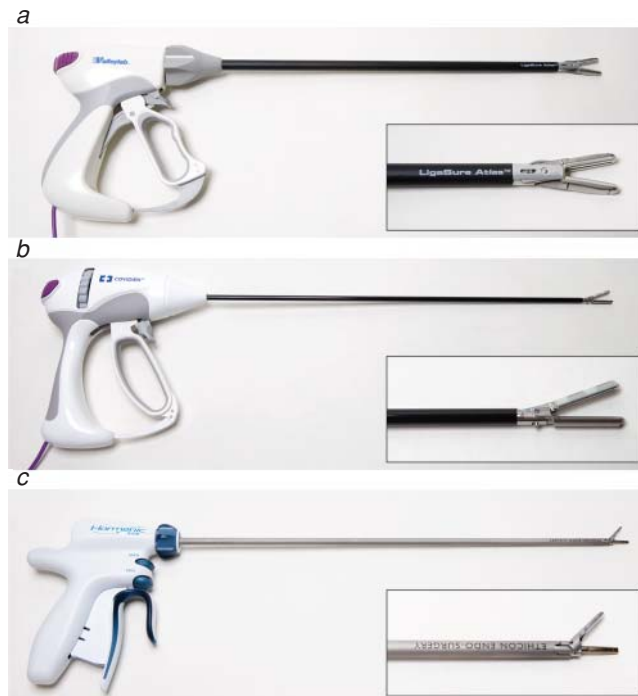


Figure 5 (a) Ten and (b) 5 mm LigaSure and (c) 5 mm harmonic scalpel.

Such systems are easily connected to one of the trocars to facilitate smoke evacuation.

Ultrasonic Shears

The introduction of ultrasonic shears (harmonic scalpel, Ethicon Endo-Surgery, Cincinnati, OH) into clinical practice in 1991 greatly advanced the practice of laparoscopic surgery [see Figure 5c]. Before that time, the requirement that all vessels be dissected, identified, and ligated or clipped resulted in longer operative time and increased bleeding. Similar to bipolar devices, harmonic shears enable the surgeon to grasp tissue and provide energy to that tissue alone. One blade of the shears oscillates at 55,000 cycles per second, generating localized heat of 50 to 100°C. This leads to denaturation of vascular proteins and focal coagulation. The lateral thermal spread is limited to 2 mm of surrounding tissue, making the device an efficient tool for both bowel and solid-organ laparoscopic surgery. Harmonic shears generate smoke to a lesser degree than electric current devices. Two important limitations must be kept in mind while using the harmonic shears. First, the oscillating blade remains hot for several seconds, during which avoidance of contact with delicate tissue (e.g., bowel) is advised. Second, the utility of harmonic shears to seal major vessels is limited. Named vessels are better transected after ligation using staples or clips.

Few studies have directly compared the use of ultrasonic energy methods (harmonic scalpel) with a electrothermal bipolar vascular system (LigaSure) in adrenal, hepatic, and colorectal surgery, but the design of these studies did not permit definitive conclusions.^{35,37}

Clips

Clips are used in a manner similar to that of open surgery. They are most efficient for sealing blood vessels or any other

luminal structure, such as ducts or ureter. The mechanical seal that they provide allows them to be used close to bowel wall or other delicate tissue. Clips are available in different sizes, materials, and lock mechanisms. Partial compression of the clip applicator handle closes the distal end of the tip first. This prevents tissue release and allows the clip applicator to slide along the structure to be clipped. Full compression of the handle will close the clip completely. Nearly all disposable laparoscopic clip applicators have multifire capabilities and 360° rotation, whereas only some clip applicators can articulate.

Loop Ligature (Endoloop)

The endoloop consists of a long preformed ligature inserted into a plastic tube [see Figure 6]. The plastic tube is narrow at one end and scored on the other. The suture protrudes from the narrow end and is formed in a ligature loop with a knot, which becomes secure after the device is activated.

Endoloops are simple to use and are used to place secure knots over thicker structures that could not be securely clipped (e.g., appendix's base, thick cystic duct). The surgeon should insert the endoloop and place the loop proximal to the structure to be ligated. At this point, a grasping instrument is placed through the loop and grasps the desired structure. The loop is then slid over the instrument and onto the structure and secured by pushing down the knot with the applicator using simple traction. Once tightened, the scored end is cut, the plastic tube is removed, and the ligature is divided close to the knot.

Other Hemostatic Devices

The field of hemostasis technology is constantly exposed to new innovations as well as laparoscopic application of open surgery techniques. Lasers are used to induce coagulation on the raw surface of solid organs such as the spleen and liver and in gynecologic surgery. Three types of lasers are most commonly used: CO₂, argon, and Nd:YAG. The CO₂ laser is the most precise laser but has limited coagulating ability. The argon laser has less precision but improved coagulating ability. The Nd:YAG laser has the best coagulation properties and the least amount of precision. The reaction of tissue to lasers varies according to wavelength and tissue characteristics. The most common complication is inadvertent laser burns, which account for 1.2% of all laparoscopic complications.³⁸

Fibrin sealing products (e.g., fibrin glue) provide insoluble fibrin matrix and are also used on raw surfaces, such as the liver, or on an oozing staple line.

STAPLERS

Suturing is the mainstay of tissue approximation during open surgery. However, as with open surgery, staplers are



Figure 6 Endoloop with a 2-0 polyglactin tie.

increasingly used for specific procedures. Laparoscopic staplers are similar to regular open surgery staplers and can have different lengths (30 to 60 mm) and staple heights, be linear or circular, and have two to three staplers rows. To overcome range of motion and angle limitations, the new-generation laparoscopic staplers articulate to allow proper placement of the stapler line. Before a staple line is applied, careful planning is mandatory. The surgeon should choose the stapler that is most suitable for the specific case: linear or circular, articulating or straight. Another consideration in linear staplers is the length of the staple line. Staple length varies from 30 to 60 mm, and the length selected should match tissue length. Multiple firings are needed in many situations. Another important consideration is the height of the staples. Height is usually represented by colors in the following order: gray, white, blue, gold, and green [see Table 2]. The number of staples per cartridge ranges from 44 to 88 and most cutting staplers leave a 2 to 4 mm undivided portion at the distal aspect of the staple line. Once the cartridge is selected, the stapler should be inserted through a large trocar (12 mm) that allows correct alignment with the designated tissue. At this point, it is important for the assistant to retract the tissue to achieve correct positioning. As in open surgery, it is crucial to confirm that no other tissues have been grasped by the stapler and to visualize the stapler end. Most staples allow a grasp-and-release mechanism to optimize tissue alignment. The upper jaw should be closed against the anvil and the staples deployed slowly to deliver steady and optimal compression on the tissues and create a uniform staple line. Once the firing trigger is deployed, the staple's wires in the cartilage are forced through the tissue and against the anvil to form staples. A correct staple line is one that is aligned, complete, and in form is similar to the letter B, with the points inverted throughout the tissue depth. Crossing staple lines are a weak point and should be avoided when possible. A newer technique has been introduced with the Tri-staple technology (Covidien Energy-based Devices). This technology seems to offer enhanced tissue compression; the taller outer row provides holding strength with reduced tissue stress, and the inner shorter row offers tighter closure and increased hemostasis.

Buttress additives to staplers are commonly used. Available buttressing includes bovine pericardium (Peri-Strips Dry, Bio-Vascular, Inc., St. Paul, MN), polytetrafluoroethylene

(Gore-Tex, W.I. Gore, Boulder, CO), bioabsorbable product (Seamguard, Gore & Associates, Inc., Flagstaff, AZ), and small intestinal submucosa (SIS, Cook, West Lafayette, IN). The literature is inconclusive regarding the actual added value of these products, but their use seems appropriate in selected patients.

Laparoscopic staple design continues to evolve. Both time and funds are invested by industry to constantly improve ergonomics and efficacy and reduce complication rates. Growing demand and industrial improvement ensure further innovations in the future.

RETRACTORS

Traction and countertraction of organs and tissues are mainstay features that allow proper visualization and safe performance of laparoscopic surgery. One simple and common example is the traction of the gallbladder during laparoscopic cholecystectomy. One instrument pushes the gallbladder dome above the liver, enabling a clear view and access to the hilum while simultaneously lifting the right liver lobe. The countertraction is achieved with another instrument that pulls on the Hartmann pouch and assists in identifying the correct dissection plane. Although most of the retraction is performed with different graspers, some specifically designated retractors are available especially for solid organs such as the liver.

Fan Retractors

Fan retractors are available from different manufacturers and may be inserted through 5 to 10 mm trocars. They are designed to retract the liver, the small bowel, or any other organ needed. Fan retractors may be straight or curved. They can articulate and be locked in position using a strong arm attached to the operating table.

Nathanson's Retractors

Nathanson's flex arm (Cook, Bloomington, IN) is a laparoscopic liver retractor that is designed for bariatric or general laparoscopic surgery [see Figure 7a]. It supports and retracts the liver in an evenly distributed fashion and connects to an external fixation device that is attached to the operating table. It is introduced through a small incision in the upper abdomen without the need for a trocar.

Snake Retractors

A flexible 5 mm laparoscopic flexible snake retractor (Genzyme Surgical Products, Tucker, GA) forms a loop that may support liver retraction [see Figure 7b]. The retractor is introduced into the peritoneal cavity in its straight, inactive form. Once inside the abdomen, the distal end is closed under laparoscopic visualization, and the retractor tip's final shape may be round or rectangular. The retractor also connects to an external fixation device that is attached to the operating table. Because of its atraumatic shape, the liver can be safely held clear of the operative site in this manner for extended periods of time.

External Retractors

External retractors such as the Buchwalter and Thompson retractors are used to apply external retraction of the abdominal wall for procedures involving the diaphragm or upper abdomen.

Table 2 Staple Heights and Colors

Color	Open Staple Height (mm)	Closed Staple Height (mm)
		
Gray	2.0	0.75
White	2.5	1.0
Blue	3.5	1.5
Gold	3.8	1.8
Green	4.1–4.8	2.0–2.2

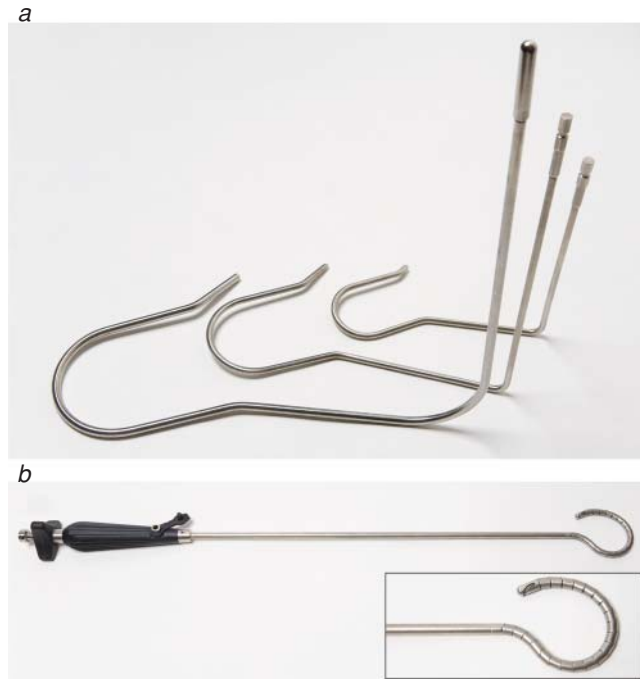


Figure 7 Various sizes of the (a) 5 mm Nathanson's retractor and (b) the round Snake retractor.

Hand-Assisted Laparoscopic Surgery

Perhaps the most versatile retractor is the surgeon's own hand. Silicone ports allow insertion of a single hand through the port without compromising the pneumoperitoneum. Some surgeons advocate this technique as it allows palpation, retraction, exposure, and manipulation of organs and tissue.

ERGONOMICS

Ergonomics play an important role in laparoscopic surgery and include the laparoscope, the instruments, and the patient and surgeon positioning. The manipulation of the instruments through the trocars; the position of the surgeon's body, arms, and fingers; and the different angulations are different than in open surgery. With proper insufflation of the pneumoperitoneum, patient positioning, angled scopes and instruments, laparoscopic surgery allows easier access to almost all areas of the abdominal cavity than open surgery. However, the trocars used in laparoscopic surgery provide reduced direct access to body cavities, reduced degrees of freedom in some interventions, and indirect visualization of the surgical field through the video system.

Laparoscopy-related discomfort has been reported by 40 to 60% of laparoscopic surgeons, and large survey studies report an incidence of strain symptoms (often persistent) in 12 to 89%.^{39,40} This strain is caused by several factors, including trocar, patient, and surgeon positioning and instrument ergonomics and design, among others. Some products today can be personalized to meet specific surgeons' needs. Nevertheless, although surgeons have different hand sizes, surgical instruments are produced in a single size. Most laparoscopic dissection and grasping instruments include a 360° rotating knob that reduces wrist movement and stress. However, most instruments are designed for finger-thumb grasp, resulting in hand symptoms accounting for up to 50% of strain symptoms

reported. Some grasping instruments are equipped with a ratchet locking mechanism that alleviates the need for the surgeon to apply constant grasping force. Stapling devices are also a continuous source of ergonomic stress. Most stapler systems still require two hands to close and deploy the device. Most needle drivers do not rotate and thus force the surgeon to manipulate his or her wrist, arms, and body to achieve the desired angle. The introduction of single port surgery has driven the industry to develop instruments that rotate in more than one axis. Possibly, further improvement will decrease the related discomfort.

Robotic surgery provides better ergonomic design for instrument handling, enabling the surgeon to manipulate instruments with increased freedom of movement and reduced physical strain. However, robotic surgery has not been proved to be of greater benefit in most minimally invasive procedures, requires operating room setup time, provides no tactile feedback, and costs more.

Laparoscopic Suturing

Laparoscopic suturing is an essential task and should be mastered by every general surgeon. Existing state-of-the-art clips and staplers do not replace sutures and cannot be relied on to do so in all cases. Laparoscopic suturing is, however, one of the more challenging aspects of laparoscopic surgery. Laparoscopic instruments are long, restrict ease of movement, and have diminished tactile feedback. Furthermore, the instrument's motion is inverted inside the abdomen with a varying scaling effect—a phenomenon known as the fulcrum effect. The fulcrum is defined as the point or support on which a lever pivots. The body wall acts as a fulcrum for surgical equipment so that when the surgeon moves the instrument to the right, the working end of the instrument moves to the left on the monitor, and vice versa. Surgeons are also limited by the imaging process. The magnification requires a proportional adjustment of the movement, and although the actual work is performed in three dimensions, it is guided by two-dimensional images. Fortunately, laparoscopic suturing and knot tying skills can be acquired via dedicated practice using box or virtual simulators.

POSITIONING AND INSTRUMENTS

Trocar and Surgeon Positioning

Trocars and surgeon positioning may either impede or simplify laparoscopic suturing. Ideally, the needle driver should reach the tissue parallel to the line of incision to be approximated to enable a 90° angle between the needle and the tissue. The angle between the needle driver and the grasping hand should not exceed 60 to 90° with the endoscope placed between the two instruments. Ports inserted too close to each other may create "sword fighting" and obscure visualization by the camera. In contrast, ports placed at a wider angle will force the surgeon to suture in a position with limited range of motion and excessive stress.

Standard laparoscopic suturing requires at least two instruments, with one or more inserted through a 10 mm trocar to allow needle insertion. A skilled assistant may ensure proper visualization by paying attention to the correct distance and angle of the camera at every stage of the procedure. The

surgeon should be positioned to create an eye-hand-camera-tissue alignment. The height of the operating table should be adjusted to avoid excessive arm and elbow abduction.

Instruments

Suture Selection of suture material is no different from that for open surgery. Multifilament sutures with memory features may ease handling and tying. The optimal suture length depends on the planned suturing technique. When intracorporeal suturing is attempted, an 8 to 15 cm suture is recommended for a single knot and up to 20 cm for a continuous segment. For extracorporeal tying, a suture length of 60 to 90 cm is required.

Needles The two most commonly used types of needles are the curved needle and the ski needle. The curved needle is more difficult to position and load but offers a clear pass through the tissue with a proper hand turn. The ski needle is easy to position and load because of its straight end but is inferior to the curved needle as it is associated with more tissue damage.

Needle drivers and graspers A needle driver [see Figure 8a] must hold the needle firmly but enable intended needle manipulation. The handles are either spring or ratchet loaded, and the jaw surface is coated with diamond to ensure proper gripping of the needle. In most needle drivers, one jaw is fixed to allow easier needle handling. Most needle drivers are handheld as opposed to the thumb and finger technique. The assisting instrument should be able to grasp both needle and suture with a preferred smooth end to avoid the loop catching on the instrument's shaft.

Endo Stitch suturing device The Endo Stitch (U.S. Surgical Corp., Norwalk, CT) [see Figure 8b] is a suturing device that has two jaws with a straight needle and suture material attached to each other and preloaded. A designated needle and suture material is held in one jaw and can be passed to the other jaw by closing the handles and flipping the toggle

levers. This apparatus is inserted through a 10 mm trocar and alleviates the need for needle loading; it also offers relatively simple knot tying. The Endo Stitch offers different suture materials (silk, nylon, and polyester) at different sizes (4-0 to 0). The length of the suture varies from 18 to 120 cm. As the Endo Stitch uses a straight and robust needle, it does not replace the standard techniques and materials. The Endo Stitch should not be used on all tissues, for example, the common bile duct and the pancreatic duct. It should also not be used for oversewing friable suture lines and tissues and other instances where finer needles and suture materials are indicated; thus, it is imperative that the modern laparoscopic surgeon be prepared to choose and use the appropriate instruments according to their specific indications.

Extracorporeal knot tying and the knot pusher

Extracorporeal tying is preformed with the suture pulled out of the 10 to 12 mm trocar. Once the knot is manually formed, the knot pusher is used to slide the knot through the trocar and tighten it around the tissue. This can be performed fairly easily with minimal training and repeated as many times as needed. As mentioned above, extracorporeal tying requires longer sutures that reach the operative field and return out of the same port.

Needle loading Placing the needle in the correct position is a challenging step in laparoscopic suturing. The suture is grabbed at 2 to 5 mm from the needle and inserted into the abdomen through the 10 to 12 mm trocar. At this point, the needle is grasped by the assisting hand and is introduced to the needle driver at the correct position if possible. There are different techniques for adjusting the needle position. Such techniques involve slightly releasing the needle grasp and adjusting it using the assisting grasper by either pulling on the suture or pushing gently on the needle. Training and experience are pivotal to mastering these techniques.

Suturing and Tying

The passage of the needle through the tissue is similar to open surgery. Carefully planned trocar placement allows the needle to be passed perpendicular to the tissue. In more difficult cases, the assistant may help with proper tissue alignment. Knot tying may be performed intra- or extracorporeally. The intracorporeal basic square knot is the most popular one. It is tied in a manner similar to that of open instrumental tying. After the needle is passed through the tissue, the suture tail is kept short and placed near the knot to allow easy grasping. After a C shape (C loop) with the suture is created, one of the instruments is brought into the loop, and the suture is wrapped twice around it. The tail is grasped by the instrument, and the knot is then tightened around the tissue [see Figure 9]. This is repeated with half-knots as needed. Numerous tying techniques exist and are less popular. Two other knots are worth mentioning. The Dundee jumping knot is used to initiate a running suture. A double loop is formed externally and introduced through the trocar. Once the needle is passed through the tissue, it is then passed through the loops, and the knot can be tightened. The Aberdeen knot is used to complete a running suture. An initial loop is brought beneath the last throw. A second loop is passed through the initial loop and tightened. The tail of the suture is inserted through the second loop to clinch the knot. The assistant should keep tension on the suture and prevent gaps in the

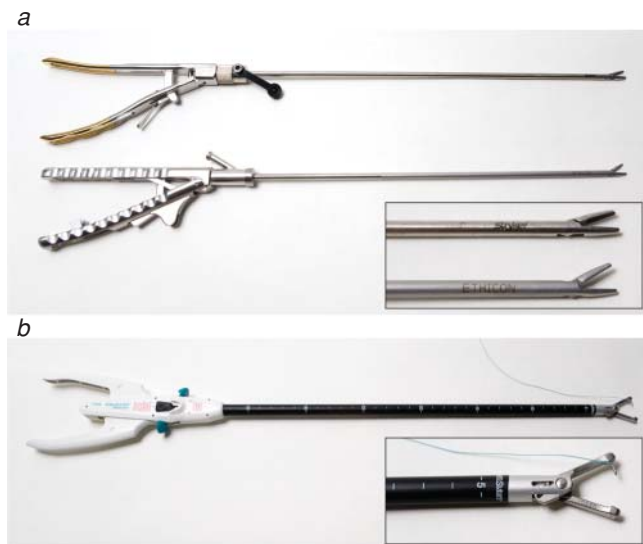


Figure 8 (a) Five millimeter needle drivers and (b) 10 mm Endo Stitch.

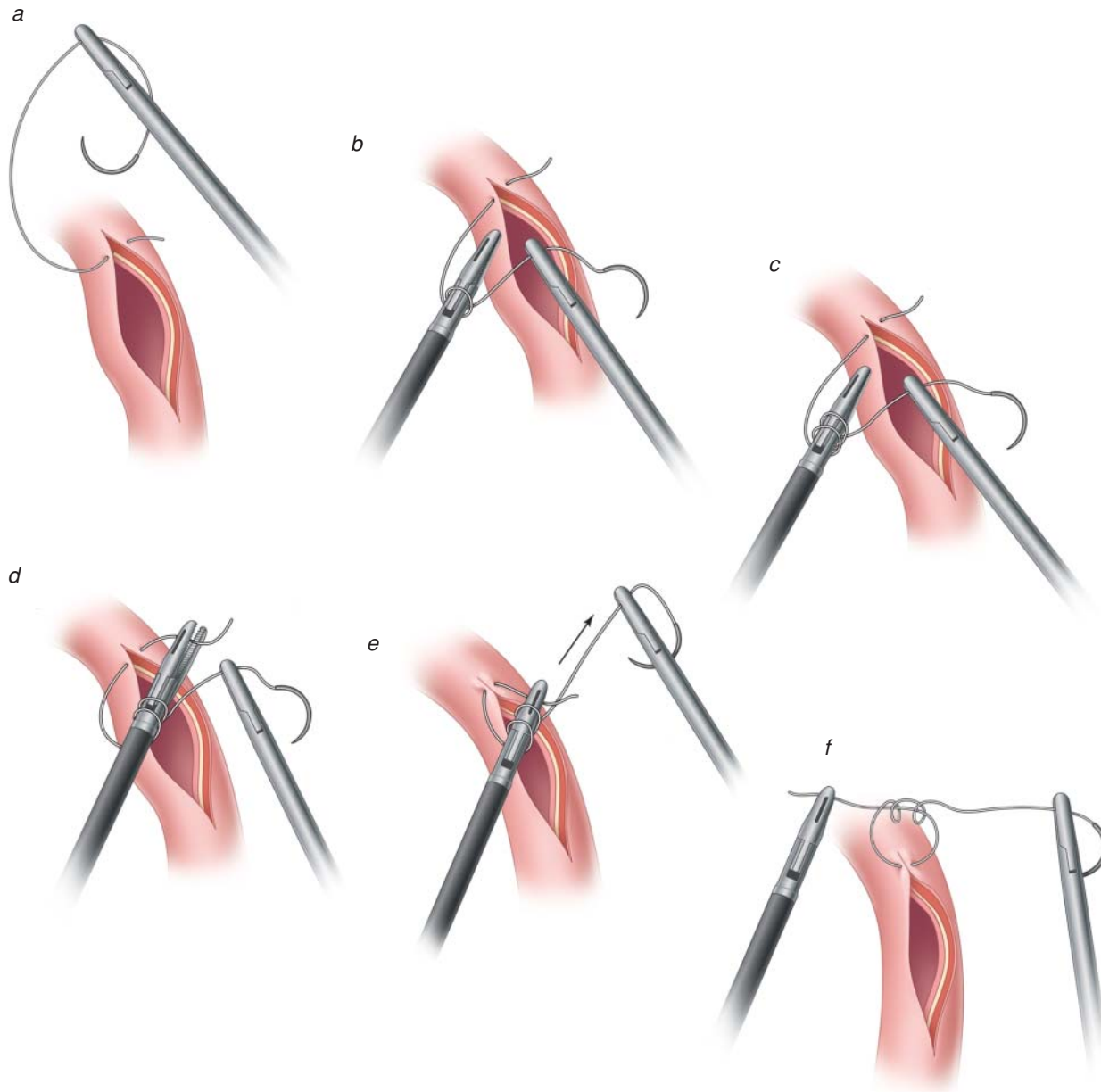


Figure 9 Illustration of laparoscopic suturing (square knot). Courtesy of Peter Polewski. (a) After the needle is passed through the tissue a C loop shape with the suture is created, then one of the instruments is brought into the loop and the suture is wrapped twice around the instrument (b, c). The tail is grasped (d) and the knot is tightened (e, f).

suture line. Laparoscopic suturing and tying is a fundamental skill that should be acquired before undertaking advanced laparoscopic surgery.

Laparoscopic Training and Simulators

Performing laparoscopic surgery requires specific skills that differ from the ones required for open surgery and may be improved by extensive training. These skills include accurate eye-hand coordination, the ability to perform procedures in a three-dimensional operating field reflected in a two-dimensional image, and the fulcrum effect (an inversion of the instrument's motion, which in turn increases surgeons' disorientation), among others. Learning laparoscopic skills

in simulators before entering the operating room results in improved performance during laparoscopic surgery with shorter procedure times, possible better patient outcomes, and decreased complication rates.^{31,32,41–43}

Laparoscopic training and simulators are now available in most teaching hospitals in the United States, and emerging technology has improved laparoscopy simulators dramatically. Today, three different laparoscopic simulators are used for training purposes: traditional video box trainers, virtual reality, and augmented (hybrid) reality simulators. All three have been demonstrated to enhance laparoscopic skills with proper training. Organic simulators (humans or animal) are not discussed in detail in this chapter. Organic simulators are still used; however, the validity and fidelity of the advanced

simulators seem comparable or better than those of organic simulators, and in the long term, there is a possible cost benefit for the simulators.⁴⁴

VIDEO BOX TRAINERS

Video box trainers were first introduced in the early 1990s as laparoscopic surgery gained acceptance. Although the technology has evolved, the basic principles of box trainers have remained constant. Today, video box trainers include a box, a positioned camera that reflects the image onto a monitor, and at least two trocars for instrument insertion. Different tasks may be performed using the box simulator, ranging from simple object grasping to complex suturing. Advantages of video box trainers include a relatively inexpensive and highly versatile device that enables the training on animal parts as well as synthetic inanimate models. The tactile perception is ideal for both the instruments and the tissues at hand. The obvious disadvantage is that box trainers do not offer the degree of fidelity possible in computer-based virtual reality trainers. Furthermore, performance metrics are somewhat limited to time to complete a task and penalties for committing predefined errors. Complex motion metrics such as path length and velocity of the instrument tips are not typically measured, as they can be in computer-based simulators. The added value to these computer-derived metrics in terms of training and assessment has yet to be proven. The American College of Surgeons and the Society of American Gastrointestinal and Endoscopic Surgeons sponsor a simulation-based laparoscopic skills training and assessment program known as the Fundamentals of Laparoscopic Surgery (FLS). The manual skills curriculum for FLS takes place in a video trainer, partly because of the cost-effectiveness, reliability, and reproducibility of the tasks in this environment. The FLS manual skills curriculum has been extensively validated. In fact, it is now a “high-stakes” examination that surgeons need to pass to be certified by the American Board of Surgery.⁴⁵

VIRTUAL REALITY SIMULATORS

Driven by extensive use of virtual reality (VR) simulators by the aviation industry, such simulators were introduced to teaching facilities toward the end of the 20th century. Basic VR simulators offer a limited variety of component skills, such as clipping, cutting, suturing, and use of diathermy. More advanced VR simulators rose to the challenge and enabled trainees to practice full laparoscopic procedures, such as cholecystectomy, ventral hernia repair, and even gastric bypass. Several studies, including a recent meta-analysis,⁴⁶ have shown the added value of VR simulators compared with standard laparoscopic training and its supplemental role to box training. An important drawback is that in contrast to flight simulators, where the variability is limited, anatomic variations are common; thus, skills acquired on a simulator may not be applicable in patients. Moreover, VR simulators lack the important tactile sensation of both instrument handling and tissue grasping and resistance. In addition to the relatively expensive pricing of VR simulators, proper maintenance is both time and resource consuming.

AUGMENTED REALITY

After VR simulators were introduced, the obvious next step was to develop a simulator that would feature tactile

sensation. This was accomplished by augmented reality simulators. These simulators provide both realistic haptic feedback and objective assessment after the performance.⁴⁷ With these two important characteristics, augmented reality simulators are considered ultimate training instruments. As with VR simulators, the main disadvantage is pricing and relatively high maintenance.⁴⁸ Both augmented reality and VR simulators have a limited number of programs available for full procedure practice, but constant development of new features promises an exciting future. Although tactile sensation is a major advance in laparoscopy simulators, it cannot replicate the actual haptic feedback for the trainee using the box trainer.

TRAINING PROGRAMS

It is now mandatory that all general surgical training programs in the United States have a skills laboratory. It is possible to create a functional skills laboratory with a relatively small investment. Old laparoscopic equipment can often be attained for a significant discount or donated by the hospital or the equipment manufacturer when new equipment is purchased or upgraded. Skills laboratories offer unique advantages that complement the traditional teaching in the operating room. Procedures and specific parts of procedures may be repeated as needed until a satisfactory level is reached. The laboratory can be accessed at all times and does not depend on the operating room schedule. Running a successful surgical skills laboratory does require a significant investment in terms of time (on behalf of the trainees and the trainers). A specific curriculum is vital, and it should be mandatory that trainees participate in the curriculum with protected time built into their schedule. Extensive practice is well known to improve surgical laparoscopy skills and technique, and it is therefore important to incorporate a skills laboratory schedule in to the curriculum.

Conversion to Open Surgery: When and Why

Laparoscopic surgery may be better than open surgery in several aspects, but conversion to open surgery is often necessary and should not be regarded as a complication. Every surgeon who attempts to complete a laparoscopic procedure must be prepared to convert to open traditional surgery under certain circumstances. An open surgery tray and instruments should always be available inside the operating theater during every laparoscopic procedure. The final decision to convert to open surgery is always made by the senior surgeon. There is no substitution for good judgment and clinical experience, but several guidelines may be considered and are outlined below.

INABILITY TO OBTAIN PNEUMOPERITONEUM

In some patients, it is very difficult to establish pneumoperitoneum. Patients with multiple previous abdominal procedures constitute the majority of this group.⁴⁹ Similarly, patients with distended abdomens attributable to severe ascites, distended bowel, or organomegaly may pose an obstacle in obtaining satisfactory pneumoperitoneum. Female patients with advanced pregnancy are another group that may benefit from open surgery.^{50,51}

LACK OF PROGRESS

Patients are exposed to additional risks as a result of prolonged anesthesia and surgery, such as rhabdomyolysis, hypothermia, disseminated intravascular coagulation, and deep vein thrombosis. Conversion attributable to a lack of progress is defined as being undertaken to avoid complication. The reasons for such conversion include lack of progression caused by unclear anatomy, obesity, and adhesions, among others. Such conversions were demonstrated to be associated with a better outcome than conversions reactive to intraoperative complications.⁵² It is often difficult for the surgeon to correctly evaluate lack of progress and decide on conversion to open surgery. Nevertheless, a carefully timed decision is important and may reduce complications.

PATIENT INSTABILITY

Hemodynamic instability is considered one of the only remaining formal contraindications for laparoscopic surgery. In cases where the patient becomes hemodynamically unstable during a laparoscopic procedure, the laparoscopic insufflation must be stopped and the need for conversion to open surgery must be evaluated.

UNCONTROLLED BLEEDING

Visualization is critical in every surgical procedure but to a greater extent during laparoscopic surgery because of the limited access. The ability to control bleeding (e.g., via packing) is limited in laparoscopic procedures; moreover, small amounts of blood absorb the light, thereby decreasing visibility. Bleeding in laparoscopic cholecystectomy has been shown to increase rates of common bile duct injuries.⁵³ Bleeding that is difficult to control should prompt the surgeon to evaluate the need to convert to open surgery.

POSSIBLE COMPROMISE OF ONCOLOGIC FUNDAMENTALS

Although laparoscopic surgery has been proven to be equal to open surgery for many malignancies, conversion to open surgery should be considered in certain oncologic circumstances. Large adrenal adenocarcinomas and high-stage gallbladder malignancies are better treated with open surgery. Similarly, large and locally invasive upper foregut and hepatobiliary malignancies, large retroperitoneal sarcomas, and others may also be better managed by open resection and, in some cases, managed only that way. Laparoscopic surgeons should never compromise basic oncologic fundamentals such as free margins or adequate lymphadenectomy.

With regard to the number of nodes retrieved, laparoscopy is not inferior to open surgery for esophageal, gastric, and colorectal cancer, while still offering the usual benefits of laparoscopic surgery. Long-term oncologic outcomes are reportedly similar for colorectal cancers but are still under scrutiny for the others.^{7–10,16}

SURGEON EXPERIENCE

Every laparoscopic procedure has its learning curve, and every surgeon must rationally understand his or her location on that learning curve. Although there is no consensus on the number of cases that constitute the learning curve for each procedure, it is agreed that this number increases with the procedure's complexity. For example, some studies document that a plateau in the complication rate is reached after 30 laparoscopic cholecystectomies, but the estimated number of laparoscopic gastric bypasses required to reach the same plateau is 75 to 100. Minimally invasive or laparoscopic clinical fellowships require completion of at least 150 advanced laparoscopic procedures and thus place their graduates at a higher level of performance.^{54,55}

INSTRUMENTAL OR EQUIPMENT FAILURE

Laparoscopic surgery involves numerous instruments and ancillary equipment, and its failure, although rare, may lead to the need for conversion to an open procedure. In non-experienced facilities, equipment failures are more prone to happen.⁵⁶ Preoperative confirmation that all equipment is working satisfactorily does not guarantee avoiding intraoperative failures.

Single Port or Single Incision Laparoscopic Surgery

A recent investigational technique under scrutiny is single port or single incision laparoscopic surgery. It uses a larger trocar, usually inserted through a periumbilical incision that can accommodate the camera, insufflator, and special angled laparoscopic instruments that enable traction as well as dissection through a single port. The skin incision is at least 20 mm long, and the fascial incision is 25 mm. It has been applied in limited circumstances, such as cholecystectomies and adjustable gastric banding, among others. It has not yet gained widespread acceptance because of the challenge of operating without the usual triangulation with standard trocars and because its benefit seems to only be cosmetic.

Conclusion

Laparoscopic surgery is an integral part of general surgery. An understanding of the different technical aspects of laparoscopic surgery is fundamental to performing basic and advanced procedures correctly, as well as to avoid some predictable difficulties and complications. Specific training to acquire laparoscopic skills is mandatory and essential. General surgery trainees and surgeons who wish to use laparoscopic techniques in their practices should participate in structured training programs using training models and operating room proctoring.

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24 ROBOTIC SURGERY

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The term “robot” was first used by the Czech playwright Karel Capek in 1920 in his play *Rossum’s Universal Robots*. The word is derived from the Czech noun “robota,” which means “drudgery” or “forced labor.” According to the *Oxford Dictionary*, the definition of “robot” is a machine capable of carrying out a complex series of actions automatically, especially one programmable by a computer.¹ Robots have revolutionized industrial production, from automobiles to pharmaceutical manufacturing, and offer an exciting, novel approach to surgical diseases. Robots employed in surgical use initially raised some concern related to malfunction and independent action. However, the surgeon’s decision-making capability is still crucial for each surgical procedure because of the anatomic or physiologic variables of each clinical situation. Currently, surgical robots consist of instruments that are remotely manipulated by a surgeon using an electromechanical interface and represent extensions of the surgeon’s mind and hands. In the future, surgical robots may be directed from remote locations and may even have computer-controlled or autonomous function.

The development of robotic surgery is the direct result of a number of contributing efforts, such as telepresence surgery, military medicine, and video-assisted endoscopic surgery.² The concept of telepresence surgery was that the surgeon did not need to be at the patient’s side to conduct the operation. Surgical robots manipulated by the surgeon from a remote site performed the actual procedure. This telepresence surgical system was created as a collaboration between researchers at NASA and engineers at the Stanford Research Institute in the late 1980s.³ This first model was a one-arm system that allowed the surgeon to manipulate a remote object and perform open surgical stabilization of battlefield trauma patients. Basic feasibility was demonstrated but has not been used in an actual battlefield scenario.⁴ However, the concepts of this initial system, such as three-dimensional (3-D) visualization, heightened dexterity, and fine-instrument manipulation, have been incorporated into the current surgical robotic systems.

The development of videosurgery or video-assisted endoscopic surgery is closely related to that of robotic surgery. Videosurgery came about as the direct result of the development of the cystoscope. In the earliest days of medicine, physicians have sought ways of looking into the living human body. In 1806, Philipp Bozzini invented an instrument that was the ancestor of the modern endoscope, the *Lichtleiter*, which was a sharkskin-covered instrument housing a candle within a metal chimney. In 1853, Antoine Desormeaux in Paris, considered by some to be the “father of endoscopy,” devised brighter illumination via the use of alcohol, turpentine, and a planoconvective focusing lens.⁵ In

1878, true endoscopy was born. Maximilian Carl-Friedrich Nitze, a German urologist, incorporated the revolutionary concept of distal illumination using a heated platinum filament and devised the forerunner of the modern cystoscope.⁶ In 1966, Kurt Semm performed the first laparoscopic gynecologic procedure.⁷ During the 1970s and 1980s, laparoscopy was used for the diagnosis and staging of pathologic processes in the abdomen, and the first laparoscopic cholecystectomy was performed in 1985.⁸ Following the advances of laparoscopic minimally invasive surgery in the abdomen, video-assisted thoracoscopic surgery (VATS) was born in the 1990s.

Video-assisted endoscopic surgical techniques play a significant role in the armamentarium of virtually all surgical subspecialties. However, these techniques are often not sufficient and have the following limitations: (1) current camera systems are two-dimensional images and usually driven by an assistant and not by the surgeon and (2) the instruments for video-assisted minimally invasive surgery are operated on a fixed fulcrum and there is limited range of motion, diminished tactile feel, and exaggeration of a surgeon’s natural tremor.

To address these limitations of conventional videoendoscopic techniques, computer-enhanced instrumentation was developed in the 1990s. The first computer-enhanced surgical instrument was RoboDoc (Integrated Surgical Systems, Sacramento, CA) in 1992, which enabled precise drilling of the shaft of the femur by orthopedic surgeons.⁹ The AESOP (Automated Endoscopic System for Optimal Positioning; Computer Motion Inc, Santa Barbara, CA) [see Figure 1] was introduced in 1993.¹⁰ AESOP’s primary purpose was to hold and maneuver an endoscope and provide a stable field of vision directed by the surgeon’s voice commands. The HERMES system (Computer Motion Inc, Santa Barbara, CA) [see Figure 2] was designed to allow the surgeon to control nearly every aspect of the minimally invasive operative theater, including the laparoscopic camera, lights, telephone, and table function.¹¹ AESOP is still available for purchase, with support for preexisting HERMES systems.

In the late 1990s, two robotic surgical systems were introduced to provide a surgeon with the ability to perform laparoscopic surgery with full control of not only the environment and the camera but the instruments as well. The da Vinci robotic surgical system (Intuitive Surgical, Sunnyvale, CA) [see Figure 3] was introduced in 1997. The first clinical robotic procedure performed with the da Vinci system was a cholecystectomy performed by Cadiere and colleagues in 1997.¹² The first robot-assisted cardiac procedure was performed in 1998,¹³ and the first totally endoscopic coronary artery bypass grafting was performed in 1998.¹⁴ In 2000, the Food and Drug Administration (FDA) approved the da Vinci system for general surgery. The other robotic surgical system, the ZEUS Surgical System (Computer Motion Inc)

Financial disclosure information is located at the end of this chapter before the references.



Figure 1 The AESOP 3000 robotic arm. Courtesy of Intuitive Surgical (Sunnyvale, CA), with permission.

[see Figure 4], was introduced in 1998. The ZEUS is credited with many clinical firsts in the field of cardiac surgery and was also used for the first clinical robotic nephrectomy. However, the ZEUS system is no longer sold worldwide.

The two robotic surgical systems share a similar concept. Both systems have a surgeon console connected by an



Figure 2 The HERMES system. Courtesy of Intuitive Surgical (Sunnyvale, CA), with permission.



Figure 3 The da Vinci robotic surgical system. Courtesy of Intuitive Surgical (Sunnyvale, CA), with permission.

electronic interface to robotic arms that are driven by cables and used to manipulate the videoendoscope and surgical instruments. The ZEUS Surgical System has an open workstation that gives the surgeon direct external view of the operating room [see Figure 4]. The ZEUS arms consist of three separate working arms that are independently mounted to the operating table [see Figure 5]. A potential advantage of the ZEUS system over the da Vinci system is that the arms can move with changes in table position. The instrument arms are controlled by the surgeon sitting at a console via form-fitted handles. The operation is visualized on a flat monitor but with a computer-simulated 3-D visualization system. The instruments used with this system have 6 degrees of freedom (MicroWrist). The fundamental difference



Figure 4 The ZEUS Surgical System. Courtesy of Intuitive Surgical (Sunnyvale, CA), with permission.



Figure 5 The ZEUS robotic arms. Courtesy of Intuitive Surgical (Sunnyvale, CA), with permission.

between the da Vinci and ZEUS systems is that the da Vinci system has all of its robotic arms on a self-contained robotic cart, and the console has all of its features integrated into one ergonomic unit. The da Vinci system has a console with two independent LCD monitors in front of the surgeon's eyes. With this system, the surgeon has true 3-D vision generated by a binocular camera and is immersed into the surgical field. Also, the da Vinci has 7 degrees of freedom with its instruments (EndoWrist) and hand positioning at the console. These features combine to give a more realistic impression that the robotic instruments inside the patient are actually extensions of the surgeon's hands. Recently, the da Vinci Si [see Figure 6] was introduced and has a fourth instrument arm that serves as a substitute for a second human assistant. The da Vinci Si has a dual console capability,



Figure 6 The da Vinci Si. Courtesy of Intuitive Surgical (Sunnyvale, CA), with permission.

which enables two surgeons to control the instruments and perform the procedure.

With the cumulative effect of the robotic system, surgeons may be able to perform complex procedures beyond the capabilities of conventional videoendoscopic techniques. As of this writing, over 800 hospitals in the United States are currently using the da Vinci surgical robotic system. The FDA has approved the da Vinci Surgical System for use in urologic surgical procedures (radical prostatectomy, pyeloplasty, cystectomy, nephrectomy, and urethral reimplantation), general laparoscopic surgical procedures (cholecystectomy, Nissen fundoplication, Heller myotomy, gastric bypass, adrenalectomy, splenectomy, and bowel resection), gynecologic laparoscopic surgical procedures (hysterectomy, myomectomy, and sacrocolpopexy), transoral otolaryngology surgical procedures (oropharyngeal, laryngeal, and hypopharyngeal resections), thoracic surgical procedures, and thoracoscopically assisted cardiectomy procedures (internal mammary artery [IMA] mobilization, cardiac tissue ablation, mitral valve repair, endoscopic atrial septal defect [ASD] closure, and coronary artery anastomosis for cardiac revascularization). In the following sections, particular surgical subspecialty uses of robotic surgery, specifically cardiac surgery, general surgery, and thoracic surgery, are described in detail.

Cardiac Surgery

During the last century, cardiac surgery has undergone several paradigm shifts.¹⁵ The first successful cardiac operation for heart stab wounds was performed in 1896 by Rehn,¹⁶ followed by the first successful cardiac valve operation in 1912 by Tuffier.¹⁷ The innovation of cardiopulmonary bypass (CPB) allowed for the repair of intracardiac lesions. In 1953, Gibbon closed a large secundum ASD using CPB.¹⁸ Since then, cardiac surgery has stepped out of its infancy and expanded to more complex diseases.

In the 1990s, the successes of laparoscopic operations in general surgery sparked an interest in minimally invasive approaches for cardiac surgery. In the mid-1990s, minimally invasive direct coronary artery bypass (MIDCAB) through a small thoracotomy and without CPB appeared in the literature.¹⁹ Navia and Cosgrove and Cohn and colleagues performed the first minimally invasive valve operations via a right parasternal and transsternal incision.^{20,21} In 1996, Carpentier and colleagues performed the first video-assisted mitral valve repair (MVR) through a mini-thoracotomy.²² Soon thereafter, they also performed the first completely robotic MVR using the da Vinci robotic surgical system²³ and the first case of a robot-assisted totally endoscopic coronary artery bypass grafting (TECABG).¹⁴

Over the past decade, a number of cardiac surgical procedures have been adapted to be performed endoscopically with robotic assistance. Currently, robotic cardiac surgical techniques are being applied to IMA harvest, coronary artery bypass grafting (CABG), valvular heart diseases, closure of ASDs, treatment of atrial fibrillation (AF), and therapies such as resynchronization for congestive heart failure.

ROBOTIC IMA HARVEST

The use of the left internal mammary artery (LIMA) for CABG has been shown to impart a clear survival advantage

for patients with single- or multivessel coronary artery disease.²⁴ Traditionally, the LIMA has been harvested via a full sternotomy; MIDCAB was proposed as an alternative to conventional CABG. In this procedure, the LIMA is partially harvested under direct vision via a partial sternotomy. However, inadequate mobilization of the LIMA caused avulsion and coronary steal syndrome,²⁵ which led to reluctance toward adoption of this technique. Thoracoscopic LIMA harvest was explored as an alternative.²⁶ However, most cardiac surgeons found this technique to be cumbersome, time consuming, and limited by the mobility of conventional thoracoscopic instruments. To solve these limitations, robotic surgical systems have been used with great success for LIMA harvest.

Single-lung ventilation using double-lumen endotracheal intubation is required.² The patient is positioned in the supine position on the operating table with a roll under the left shoulder to elevate the shoulder 30°. Three ports are then placed. The camera port is introduced in the left fifth intercostal space, the right robotic arm is placed in the left third space, and the left arm is placed in the sixth to seventh space, in the same line as the camera port. After accessing the left pleural space, a 30° endoscope is used and CO₂ insufflation is performed. The LIMA is identified and dissected from the chest wall from the first intercostal branch superiorly to the diaphragmatic border inferiorly.

There is an initial learning curve with the technique of robotic LIMA harvest. Kappert and colleagues reported 61 patients who underwent robotic LIMA harvest, and the median time for LIMA takedown was 50 ± 16.9 minutes.²⁷ Mohr and colleagues reported a median time of LIMA harvest of 48 ± 26.3 minutes and was under 40 minutes for the last 20 patients.²⁸ These studies show that the robotic surgical system provides excellent exposure for a safe LIMA harvest with acceptable harvesting times. The technique of robotic LIMA harvest is the initial step for robot-assisted single- or multivessel CABG.

MINIMALLY INVASIVE ROBOTIC CABG

CABG has been the mainstay for cardiac surgery for the last three decades. With the thrust toward minimally invasive surgery, cardiac surgeons have investigated operations designed to minimize the invasiveness of CABG. Coronary revascularization has evolved from on-pump CABG to off-pump procedures to MIDCAB/TECABG. Since the robotic surgical system has become available, single- or multivessel CABG with robotic IMA harvest can be performed via a small anterior thoracotomy. In 1998, Loulmet and colleagues performed the first case of a robot-assisted minimally invasive single-vessel TECABG.¹⁴ In 2000, Kappert and colleagues reported a robot-assisted two-vessel TECABG using bilateral IMAs.²⁷ Robot-assisted TECABG is currently limited to single-vessel (left anterior descending artery [LAD]) disease or occasionally two-vessel disease.

The operating room setup, anesthesia, patient positioning, and port placement are similar to those for robotic IMA harvest.² After completion of the IMA harvest, the camera port incision is lengthened and the arterial anastomosis is performed under direct visualization. The pericardium is opened along the suspected course of the LAD, the beating

heart is stabilized with devices (i.e., the Endostabilizer, Estech Corp, Danville, CA) or the endoscopic cardiac positioner (Starfish NS Medtronic Inc, Minneapolis, MN), and the IMA is anastomosed to the LAD.

In 2001, the FDA sanctioned a multicenter study of the safety and efficacy of the da Vinci system for robot assisted TECABG.²⁹ Ninety-eight patients requiring single-vessel LAD revascularization were enrolled at 12 centers between 2002 and 2004. Thirteen patients were excluded intraoperatively. In 85 patients who underwent TECABG, the CPB time was 117 ± 44 minutes and the cross-clamp time was 71 ± 26 minutes. There were no deaths or strokes, but there was one early reintervention and one myocardial infarction. Six patients were found to have a significant anastomotic stenosis at the 3-month follow-up angiography. This trial showed the safety of robot-assisted TECABG. Currently, this procedure is performed in a highly selected group with limited coronary disease. With continued technological advances, robotic coronary bypass surgery will become applicable to a wider patient population.

ROBOTIC MITRAL VALVE SURGERY

Traditionally, mitral valve surgery has been performed via a median sternotomy. Since the mid-1990s, minimally invasive mitral valve surgery via a small thoracotomy has become popular. Large series by Navia and Cosgrove and Cohn and colleagues showed that surgical mortality and morbidity were comparable to those of conventional mitral surgery.^{20,21} With experience, a shift from direct vision, to video-assisted, to robot-assisted techniques has occurred. In 1996, Carpentier and colleagues performed the first video-assisted MVR via a right mini-thoracotomy,²² and Mohr and colleagues reported the first case of “solo mitral surgery” using the AESOP system in 1997.²⁸ In 1998, Carpentier and colleagues performed the first truly robotic MVR using an early prototype of the da Vinci system.²³ In the United States, the first FDA safety and efficacy multicenter trial was performed in 2000³⁰ and the da Vinci system for mitral surgery was FDA approved in November 2002.

Currently, the following robot-assisted MVR procedures have been performed: robotic mitral valve triangular or quadrangular leaflet resection, posterior leaflet sliding repair, chordal transfer, expanded polytetrafluoroethylene (ePTFE) artificial chord replacement, resection annuloplasty, and annuloplasty band insertion.² Patients are prepared with the right side elevated by 30°. Cannulation for CPB is performed through the right femoral artery and vein and the right internal jugular vein. The camera port is placed in a 3 to 4 cm mini-thoracotomy incision on the right fourth ICS, and two robotic arms are inserted through the third and fifth ICSs. After accessing the pericardial space, the interatrial groove is dissected, the ascending aorta is clamped with the transthoracic aortic cross-clamp (Cardioventions Inc., Somerville, NJ), and the procedure is performed.

Chitwood and colleagues reported the largest single-center robotic MVR experience.³¹ In their series, 300 patients underwent robotic MVRs, including triangular leaflet resections, sliding repairs, chordal transfers or replacements, edge-to-edge approximations, and ring annuloplasties. The 30-day mortality was 0.7%, and late mortality was 2.0%. Five-year survival was 96.6% ± 1.5%, with 93.8% ± 1.6% freedom from reoperation. These initial results are encouraging,

and with continued advances in technique, this procedure should become more prevalent.

ROBOTIC MODIFIED MAZE OPERATION

The Maze operation was introduced by Dr. James Cox in 1987.³² The Cox-Maze procedure was designed to interrupt any and all macroreentrant circuits that might potentially develop in the atria, thereby precluding the ability of the atrium to flutter or fibrillate. A reiteration of this original procedure, the Cox-Maze III, has become the gold standard in the surgical treatment of AF. This procedure requires a full sternotomy; thus, patients with AF alone have been reluctant to undergo this procedure. Less invasive, catheter-based techniques have been effective for intermittent AF but have a significant failure rate for continuous AF.

The robotic Maze operation first began as a concomitant procedure to the robotic MVR but has since been performed on its own. Garrido and colleagues described 62 patients who underwent combined AF and mitral valve surgery, half with the da Vinci and half with the AESOP.³³ A variety of energy sources were used, including radiofrequency, microwave, and cryoablation. Operative mortality was 4.8%, with 65% of patients in normal sinus rhythm at the time of discharge. Twenty-seven percent of patients remained in AF, and 8% required pacemaker implantation at the time of discharge. The robotic Maze operation has not become a common procedure yet; however, with improved devices and continued success from pioneering centers, it may become a widely available clinical reality in the near future.

ROBOTIC CARDIAC RESYNCHRONIZATION THERAPY (EPICARDIAL PACEMAKER LEAD PLACEMENT)

Cardiac resynchronization therapy (CRT) is an adjuvant treatment for the patients with congestive heart failure and intraventricular conduction delay. Prospective, randomized trials have demonstrated improvements in ventricular function, exercise capacity, and quality of life among patients undergoing ventricular resynchronization therapy via biventricular pacing.^{34,35} Usually, the left ventricular (LV) lead implant is performed percutaneously through coronary sinus cannulation and advancing the lead into a major cardiac vein. However, technical limitations attributable to individual variations in coronary sinus and coronary venous anatomy result in a 10 to 15% failure,³⁶ and lead dislodgment contributes to an additional 5 to 10% late failure rate.³⁷ When percutaneous lead placement is unsuccessful, rescue therapy for these patients has typically involved LV epicardial lead placement via an anterior thoracotomy. This approach is limited by both its morbidity and access to the posterolateral surface of the left ventricle. Therefore, minimally invasive techniques including VATS or robotic-assist LV epicardial lead placement were developed. Recently, Joshi and colleagues reported a follow-up result for 42 patients with robotic LV epicardial lead placement.³⁸ Eighty-four epicardial lead placements were performed, and the operative time was 51 ± 32 minutes. LV injury and pleural adhesions necessitated conversion to mini-thoracotomy in two patients. This experience showed that robotic LV epicardial lead placement was safe and effective and should be considered when percutaneous approaches have been unsuccessful.

ROBOTIC CLOSURE OF ATRIAL SEPTAL DEFECT

ASD is one of the most common adult congenital heart defects. There are several different types of ASD: the secundum ASD in the region of the fossa ovalis (75% of cases), the primum ASD (15 to 20%) positioned inferiorly near the crux of the heart, the sinus venosus ASD (5 to 10%) located superiorly near the superior vena caval entry or inferiorly near the inferior vena caval entry, and the uncommon coronary sinus septal defect (less than 1%), which causes shunting through the ostium of the coronary sinus.³⁹ Traditionally, surgical treatment of secundum ASDs required a sternotomy. Since the development of percutaneous transcatheter closure techniques, the majority of secundum ASDs can be closed with a percutaneous catheter technique.⁴⁰⁻⁴² When this is not feasible, surgical closure is recommended.⁴³ Argenziano and colleagues reported the first US experience of totally endoscopic ASD repair with the da Vinci system in 2003.⁴⁴ Seventeen patients underwent repair of a secundum ASD ($n = 12$) or patent foramen ovale ($n = 5$) via a totally endoscopic approach. The aortic cross-clamping time was 32 minutes, and the CPB time was 122 minutes. In 16 patients, transesophageal echocardiography after 30 days confirmed successful repair. The median hospital length of stay was 4 days. A robotic approach is an option for patients with secundum ASD that is not appropriate for percutaneous repair who wish to avoid sternotomy or thoracotomy.

General Surgery

Since the innovation of the endoscope and the evolution of laparoscopic procedures in the 1970s and 1980s, general surgical procedures have dramatically switched from open to minimally invasive approaches. For example, the first laparoscopic cholecystectomy was performed in 1985⁸ and had become the standard procedure by the mid-1990s. The initial application of laparoscopic surgery was attractive because of the potential benefits, such as minimal incision, decreased postoperative morbidity, and a reduction in the total length of hospital stay.⁴⁵

In the development of robotics for general surgery, the first active robotic device for laparoscopic surgery was the voice-controlled endoscopic camera positioning system (AESOP). AESOP replaced the cameraperson, facilitated the performance of solo-surgeon laparoscopic operations, and provided a stable camera platform, avoiding motion sickness in the operative team.⁴⁶ Subsequently, the introduction of the da Vinci robotic system afforded the ability to perform laparoscopic surgery with full control of up to three surgical instruments and the camera. The first clinical robotic cholecystectomy was performed by Cadiere and colleagues in 1997.¹² In July 2000, the FDA approved the da Vinci system for general laparoscopic surgery such as cholecystectomy, Nissen fundoplication, Heller myotomy, gastric bypass, adrenalectomy, splenectomy, and bowel resection.

Potential advantages of the da Vinci system include tremor reduction, 3-D visualization, and wrist action at the surgical site compared with traditional laparoscopic instruments. However, over 10 years have passed since the first clinical application for robotic cholecystectomy, yet robotics has not been widely adopted into general minimally invasive surgery. One possible reason for this is that the da Vinci

system was primarily designed for cardiac surgery and, thus, is not configured for abdominal surgery.⁴⁷ Also, this system still has limited instrumentation and bulky arms and lacks tactile feedback. Lack of tactile feedback calls for expertise in interpreting visual cues to maneuver instruments in three dimensions and cannot accurately reflect how tightly tissues are grasped with instruments. The robot currently has no instrumentation for surgical stapling or a sealing and cutting instrument, which are both commonly used in bowel surgery, although both are “on the imminent horizon.” Many general laparoscopic procedures require moving throughout multiple quadrants in the abdomen, which is difficult with the robot. Compared with traditional laparoscopic systems, the da Vinci system is very bulky, and repositioning of the da Vinci arms requires a great deal of effort. In addition, the robot systems cost more than \$1 million, and the clinical results for general surgery procedures are, at best, comparable, not superior, to procedures with much cheaper laparoscopic instrumentation.

Currently, the da Vinci Surgical System has been used primarily in general surgery to perform: Heller myotomies, antireflux surgery, bariatric surgery, cholecystectomy, splenectomy, gastrectomy, and colorectal surgery.^{2,48} This section describes these particular robotic procedures briefly and the potential advantages and disadvantages of robotic approaches compared with conventional laparoscopic approaches.

ROBOTIC HELLER ESOPHAGEAL MYOTOMY

Achalasia is the most common primary motility disorder of the esophagus. The distinctive findings are the absence or primary peristalsis of the esophagus body and the increased or normal pressure of the lower esophageal sphincter (LES) that fails to relax in response to swallowing. The surgical treatment is to relieve the outflow obstruction at the level of the LES. Today, a Heller myotomy is considered the standard surgical procedure, relieving symptoms in approximately 85 to 90% of patients.⁴⁹ The laparoscopic Heller myotomy became the preferred approach in the mid-1990s.⁵⁰ In 2000, Melvin and colleagues reported the first robotic Heller myotomy using the da Vinci Surgical System.⁵¹ In terms of potential advantages of robotics in Heller myotomy, the working area, that is, the lower posterior mediastinum or upper abdomen, is small and often difficult, and the freedom of movement of the articulated robotic instruments enables the surgeon to operate with dexterity in this narrow field. Furthermore, the 3-D vision allows each individual muscular fiber to be visualized and divided, facilitating the accuracy of the myotomy. A superior view of the submucosal plane, as afforded by the da Vinci system, could potentially reduce the risk of mucosal perforation.²

When compared with standard laparoscopic Heller myotomy series, the current studies showed no esophageal perforations in a robotic procedure (0 of 102) and 11% (17 of 150) of esophageal perforations with 8 times fewer patients with robotic Heller myotomy suffering from this problem.⁴⁸ Hufmann and colleagues reported that the postoperative quality of life of the patients with robotic Heller myotomy was improved with respect to the role played and the general perception of health (two of nine categories).⁵² However, meta-analysis of these studies revealed no differences

in blood loss, surgery time, and the length of hospital stay.⁴⁸ In summary, the robotic Heller myotomy appears to be associated with a much lower risk of perforation and a better quality of life in experienced institutions.

ROBOTIC NISSEN FUNDOPLICATION

Considerable experience has now been acquired with robotic fundoplication for reflux disease. The patient is placed in the lithotomy position, and five trocars are placed. A 12 mm camera is placed supraumbilically, and two 7 mm trocars are placed in the midclavicular lines at the costal margin on either side for each robotic arm. Then a 10 mm trocar is placed laterally at the right subcostal margin, which functions as a liver retractor, and a 12 mm trocar is placed on the left side of the patient as an accessory port. The procedure itself follows much in the same way that it is performed laparoscopically.⁵³ Studies thus far have shown this approach to be safe, with similar results and outcomes when compared with laparoscopic fundoplication. However, longer operative times and higher total costs associated with the robotic device itself have limited the widespread adoptance of this procedure.⁵⁴

ROBOTIC BARIATRIC SURGERY (ADJUSTABLE GASTRIC BANDING AND GASTRIC BYPASS)

Laparoscopic Roux-en-Y gastric bypass operations are among the most difficult operations performed by even experienced laparoscopic surgeons. One must be able to suture, perform intracorporeal knots, and manipulate bowel throughout the entire abdomen within the limits of laparoscopic equipment.⁵⁵ Recently, a robotics approach has been developed that may reduce some of these technical difficulties. Six ports are used for the robotic procedure. A camera port is placed in the umbilicus, and five ports are strategically placed in the periphery of the upper abdomen. The results of a robotic gastric bypass when compared with a laparoscopic gastric bypass are similar in regard to operative time, outcomes, and hospital stay.⁴⁸ However, although there may be no differences in these aspects, a robotic approach may be easier to learn. It took less time to complete the procedure using a robot-assisted versus a standard laparoscopic approach for surgeons new to both procedures.⁵⁶ With further refinement of the robotic approach, these advantages may become more evident.

ROBOTIC CHOLECYSTECTOMY

Since the advent of laparoscopic cholecystectomy in the late 1980s, this procedure has become one of the most common procedures performed by general surgeons today. The benefits of laparoscopic cholecystectomy versus open cholecystectomy are well documented and include a shorter hospital stay and a quicker convalescence.⁵⁷ Robotic cholecystectomy was one of the first applications of the robotic device in general surgery. The setup and incisions used in both operations are similar. The patient is placed in the supine position, and four ports are placed in the upper abdomen. A study from 2008 comparing 50 robotic cholecystectomies with 50 laparoscopic cholecystectomies showed similar operating times, complication rates, and hospital stay between the two groups.⁵⁸ However, the total cost of a robotic cholecystectomy was significantly higher, which was

directly related to the cost of the robotic device. Thus far, robotic cholecystectomy has been shown to be safe but has not yet supplanted laparoscopic cholecystectomy.

ROBOTIC SPLENECTOMY

Robotic splenectomy has been performed with outcomes similar to those of the laparoscopic approach, although surgeons note the benefit of increased magnification and precision of the da Vinci instruments.⁵⁹ Only one study to date has compared the two. Bodner and colleagues reported their experience of 12 minimally invasive splenectomies (six robotic splenectomies via the da Vinci system and six laparoscopic splenectomies).⁶⁰ In this series, the robotic procedure was associated with an average increase of \$2,800 in total cost. The mean operative time with the robotic procedure was also 30 minutes longer, although this increase was not significant. The length of hospital stay was similar with both surgical methods (6 to 7 days), as was blood loss. No surgical conversions were necessary with either technique, nor was either associated with any major complications. It is hard to conduct any significant conclusions from a single study, although the information it provides suggests that the robotic approach is more expensive and tends to be a longer procedure than its laparoscopic counterpart.

ROBOTIC GASTRECTOMY

A laparoscopic approach for early-stage gastric cancer was introduced in the early 1990s. Subsequently, with the development of the da Vinci Surgical System, Hashizume and colleagues reported the first experience of robotic distal gastrectomy in 2002.⁶¹ Published results have been limited thus far. In 2010, Kim and colleagues reported their experience of 39 gastrectomies, including 16 robotic, 11 laparoscopic, and 12 open approaches, and compared these three groups to determine the clinical benefits of robotic gastrectomy.⁶² The estimated blood loss was significantly less in the robotic gastrectomy group than in the open group, and the postoperative hospital stay in the robotic group was significantly shorter than in the open and laparoscopic gastrectomy. This study demonstrates the feasibility of robotic gastrectomy and shows that there may be some benefit to this approach.

ROBOTIC COLORECTAL RESECTION

Since the first laparoscopic colorectal operation, a right hemicolectomy performed by Jacobs in 1990,⁶³ laparoscopic techniques have been adopted for a wide range of colorectal procedures.⁶⁴ Recently, a prospective, randomized, multi-institutional study demonstrated that the rates of tumor recurrence, overall survival, and disease-free survival after laparoscopy-assisted colectomy were comparable to those of open colectomy in patients with colon cancer.⁶⁵ Perioperative recovery was significantly faster after the laparoscopic procedure, although the operating time was significantly longer. Thus, the laparoscopic approach is becoming the new standard for colorectal disease.

The first robot-assisted colectomy was performed in 2001.⁶⁶ Since that time, several studies comparing robot-assisted and laparoscopic colon surgery have been published.^{67–69} According to these studies, the robotic approach was associated with a longer operating time, higher costs, and similar

outcomes. The robotic approach for total colectomy can be more difficult because of the limited range of motion of the current robotic setup and the need to access the colon in all four abdominal quadrants.⁷⁰ The only potential benefit of the robot for colorectal surgery may be in complex pelvic dissections, where visibility and space for dissection are usually limited.⁵⁹ An early comparative trial of robotic versus laparoscopic total mesorectal excision for rectal cancer showed low complication rates in both arms but a decreased hospital stay in the robotic arm of the study.⁷¹

Thoracic Surgery

Technological advances continue to shape how we approach the chest. The first report of thoracoscopic (VATS) lobectomy was published in 1992.⁷² Subsequently, VATS procedures have been widely adopted, and many studies have demonstrated the multiple advantages of a VATS lobectomy, including decreased postoperative pain, shortened hospital stay, and an increased likelihood that patients proceed to adjuvant therapies.⁷³ Currently, 30% of all lobectomies performed nationwide are via a VATS approach. In the past decade, the advent of robotic surgery has offered a new, perhaps improved, approach to the chest. Robotics has now been used for pulmonary resections and in the mediastinum.

ROBOT-ASSISTED THORACOSCOPIC PULMONARY RESECTION

Experience with robotic pulmonary resections has been limited to date. The advantages of using robotics versus thoracoscopic equipment include 3-D visualization and increased articulation, which are especially beneficial within the confined space of the chest cavity. The positioning of the patient and the incisions used in both operations are similar. The patient is placed in the flexed lateral decubitus position, and four incisions are made. A camera port is placed in the eighth interspace in the midaxillary line, a 3 cm utility incision is placed in either the fourth or fifth interspace, and the left and right arms of the robot are placed in the sixth interspace anteriorly and the seventh interspace posteriorly.⁷⁴ Park and colleagues reported their initial experience with 34 robotic lobectomies.⁷⁵ All types of lobes were removed, and a mediastinal lymph node dissection was performed in all cases. There were no significant intraoperative complications, although four cases were converted to an open thoracotomy. The mean operating time was 218 minutes, and the median length of hospital stay was 4.5 days. As experience accrues, pulmonary resections should become more amenable to robotic resection.

ROBOT-ASSISTED THORACOSCOPIC THYMECTOMY

Mediastinal lesions are perhaps particularly well suited to robotic dissection. The increased visibility and the increased range of motion of the robotic arms allow the surgeon to dissect in the restricted spaces of the mediastinum. There has been much experience already with robotic thymectomy for myasthenia gravis. The patient is placed in the flexed lateral position, and the approach is from the patient's right side given that the heart is encountered on the left. Four ports are used. The right half of the thymus is carefully

dissected away from the pericardium, taking care not to injure the phrenic nerve or innominate vein. Once the right half has been completely freed, attention is then directed toward the left. The robotic arms are maneuvered underneath the sternum, and the left half is carefully dissected paying particular attention to the phrenic nerve on the left. Rea and colleagues reported their experience with 33 robotic thymectomies.⁷⁶ The mean operative time was 120 minutes, there were no open conversions, and there were no significant intraoperative complications. The authors pointed out that dissection of the thymus in the lower neck and in the contralateral side is better facilitated via a robotics approach when compared with a VATS approach. As more experience with robotic thymectomy is gained, this may become the preferred approach to thymic resection.

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26 CANCER EPIDEMIOLOGY AND PREVENTION

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Cancer remains a significant public health problem in the United States and is now the leading cause of death for men and women younger than 85 years of age.¹ It is estimated that over 1.5 million new cancer cases and 500,000 cancer deaths will occur in the United States in 2010.¹ In addition, over 2 million basal and squamous cell skin carcinomas and 100,000 in situ cancers (primarily breast and melanoma) are expected. This represents a slight decrease in both incidence and mortality over the past decade, with progress being seen across gender and racial and ethnic groups. However, there is still significant room for progress with regard to cancer prevention, screening for early detection, and treatment.

The etiology of cancer development is often multifactorial, although direct links have been made between specific cancer types and environmental exposures, infections, pharmaceutical agents, and hereditary syndromes. The list of known human carcinogens is extensive and is represented in part in Table 1.^{2–7} Select carcinogens from this table are highlighted and expanded on in this chapter.

Although improvements in treatment play an important role in the decrease in cancer-related mortality observed over the past decade, primary prevention and early detection are paramount to progress in minimizing the morbidity and mortality associated with cancer. Primary prevention can occur through a variety of means, including avoidance of exposures (environmental, pharmaceutical, or infectious). Alternatively, direct prevention through chemoprevention or risk-reducing surgery is advocated in some circumstances. Finally, although not a true “prevention” strategy, screening plays an important role in detecting cancers early, especially as noninvasive lesions.

Cancer Epidemiology

PHARMACEUTICALS

Hormone Replacement Therapy

Numerous epidemiologic studies have been conducted evaluating the relationship between hormone replacement therapy and breast cancer risk. Studies evaluating the impact of hormone replacement have been summarized in a large pooled analysis that suggests that a small increase in breast cancer risk exists for ever-users of hormone replacement therapy (relative risk of 1.14), with the risk increasing with duration of use (greater than 5 years).⁸ Importantly, this increased risk appears to disappear within 5 years of cessation of use. However, only 12% of patients in this pooled analysis were taking a combined estrogen and progesterone pill, limiting the ability to draw conclusions on the relationship between

use of combination pills and breast cancer. This is significant as combination pills are the most commonly used form of hormone replacement therapy because of the elevated risk of endometrial cancer observed in women with an intact uterus who take estrogen-only pills.⁹

The best evidence regarding the association between combination pills and breast cancer risk comes from a randomized, controlled trial conducted by the Women’s Health Initiative. The objective of this trial was to evaluate the impact of hormone replacement therapy on chronic disease; postmenopausal women were randomized to combination or estrogen-only replacement based on the presence or absence of a uterus at the time of enrolment.¹⁰ The trial was stopped early in the combination arm because of an increased incidence of breast cancer observed at an interim analysis (hazard ratio 1.24 [95% CI 1.04–1.5]). The risk of breast cancer associated with combination therapy increased with duration of use.¹⁰ These data have been supported in multiple other observational and case-cohort studies and led to the conclusion by the International Agency for Research on Cancer to list both combined and estrogen-only hormone replacement therapy as a human carcinogen.⁹ As a result, the use of hormone therapy in the United States has decreased dramatically since the Women’s Health Initiative was reported.¹¹

INFECTIONS

Infectious agents have been known to be associated with cancer development for some time [see Table 1]. This relationship is significant as avoidance or treatment of these infections is a viable mechanism of cancer prevention and may have a role in cancer treatment. Cancer prevention through vaccination is discussed later in the chapter.

Human Papillomavirus

Human papillomavirus (HPV) is thought to be associated with almost all cervical cancers. Two specific subtypes of virus, HPV-16 and HPV-18, are thought to be responsible for approximately 70% of these cancers.¹² Additionally, the virus has been associated with cervical intraepithelial neoplasia, a preinvasive condition. Knowledge of the importance of this virus in the development of cervical cancer has led to improved screening techniques by combining the Papanicolaou smear with HPV DNA testing.¹³ Furthermore, vaccine development targeting these virus subtypes allows a mechanism of primary prevention.^{14,15}

Hepatitis Virus

Chronic infection with hepatitis viruses is a factor known to be associated with cancer development, specifically

Table 1 Known Human Carcinogens²⁻⁷

	Carcinogen	Cancer Type
Pharmaceuticals	Hormone replacement therapy Estrogen only Combined estrogen-progesterone	Endometrial, ovary Endometrial, breast
	Diethylstilbestrol	Breast (exposure during pregnancy), vagina/cervix (exposure in utero)
	Tamoxifen	Endometrial cancer
	Busulfan, treosulfan	Myelogenous leukemia
	Chlorambucil	Myelogenous leukemia
	Cyclophosphamide	Myelogenous leukemia, bladder
	Azathioprine	Non-Hodgkin lymphoma, skin
	Cyclosporine	Non-Hodgkin lymphoma, skin
	Melphalan	Leukemia
	Phenacetin	Renal pelvis, ureter
	Thiotepa	Leukemia
	Methoxsalen with ultraviolet light	Skin
Infections	Hepatitis B virus	Hepatocellular carcinoma
	Hepatitis C virus	Hepatocellular carcinoma, non-Hodgkin lymphoma
	Human papillomavirus	Cervical, vaginal, vulva, penis, anus, oropharyngeal
	Epstein-Barr virus	Nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin lymphoma
	Kaposi sarcoma virus	Kaposi sarcoma
	Human T cell lymphotropic virus type I	T cell lymphoma
	<i>Helicobacter pylori</i>	Gastric, mucosa-associated lymphoid tissue (MALT) lymphoma
	<i>Clonorchis sinensis</i>	Cholangiocarcinoma
	<i>Schistosoma haematobium</i>	Urinary bladder
Environmental and naturally occurring compounds	Aflatoxins	Liver
	Arsenic	Lung, skin, urinary bladder
	Beryllium	Lung
	Cadmium	Lung
	Chromium	Lung
	Nickel compounds	Lung, nasal cavity, paranasal sinus
	Asbestos	Lung, mesothelioma, larynx, ovary
	Erionite	Mesothelioma
	Silica dust	Lung
	Radon	Lung
	Wood dust	Nasal sinus
Other	Ionizing radiation	Thyroid, breast
	Tobacco	Lung, mouth, pharynx, larynx, esophagus, stomach, pancreas, bladder, kidney renal pelvis, cervix

hepatocellular carcinoma.¹⁶ Worldwide, hepatitis B is associated with the majority of liver cancers. Fortunately, the widespread availability in the United States of a vaccine against hepatitis B has decreased infection rates. Rates of hepatocellular carcinoma in the United States are actually rising, however, and may parallel the increasing incidence in hepatitis C infection.¹⁷ This is an increasing public health concern given the lack of vaccination or definitive treatment options for this virus.

Helicobacter pylori

Helicobacter pylori is a common infection observed in the United States and has great clinical significance because of the association between infection and ulcer development. However, infection has also been associated with the development of gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphomas.¹⁸ Treatment of the bacteria results in regression of MALT lymphomas and may be preventive for adenocarcinoma development.

OTHER

Ionizing Radiation

Ionizing radiation is well recognized as a human carcinogen.¹⁹ The effects of ionizing radiation have been most widely studied in association with the atomic bombings in Japan. However, significant information also comes from clinical settings where patients were exposed to radiation as a component of therapeutic procedures. Examples include an elevated risk of breast cancer in patients who underwent mantle radiation for Hodgkin lymphoma and increased rates of leukemia in patients who underwent high-dose radiation for cervical cancer. Ionizing radiation can lead to cancer development in almost any tissue, with certain sites, such as thyroid, breast, and bone marrow, being most susceptible. Age at exposure is a determinant of risk, and the greatest risk is in those individuals exposed as children or adolescents.

Significant attention has also been paid to the potential cancer risks associated with diagnostic imaging, especially computed tomographic (CT) scans. Overall, it is estimated that 0.4% of cancers in the United States can be associated with radiation from CT scan use.²⁰ This estimation is based on data from 1991 to 1996. Given the increased application of CT, it is estimated that this figure may now be 1.5 to 2.0%.²⁰ It is important to note, however, that no large-scale epidemiologic studies have been reported that systematically assess this risk. At the current time, the prudent use of CT scans as necessary to facilitate clinical care, with the use of alternative imaging when appropriate, is recommended.

Tobacco

Tobacco use is the leading cause of preventable cancer deaths worldwide and in the United States alone accounts for more than 400,000 premature deaths annually.²¹ Tobacco use is thought to be associated with more than 90% of all lung cancer cases, with multiple prospective epidemiologic studies consistently demonstrating this relationship.²² Smokers have an estimated 10- to 20-fold increase in the risk of lung cancer when compared with nonsmokers, and although some of this risk can be mitigated by smoking cessation, the risk never falls to the level of a lifelong nonsmoker. Risk is related to overall exposure, such as number of cigarettes smoked per day, number of years of active smoking, and depth of inhalation.²² Those individuals exposed to tobacco smoke (passive smoking) also have an elevated risk of lung cancer, estimated to be a 30% increase when compared with other nonsmokers.⁶ As a result, secondhand tobacco smoke has been classified as a known human carcinogen by the Environmental Protection Agency.⁶

Tobacco is also associated with a significantly increased risk of oropharyngeal cancer; this extends to cigarette, pipe, and cigar smoking as well as other smokeless forms of tobacco. This risk can be increased with excessive alcohol consumption. Although alcohol and tobacco both represent independent risk factors for oropharyngeal cancer development, their effects are synergistic and increase risk by 10 to 13 times that of nonusers.²³ Data also support a strong link between tobacco and bladder, esophageal, pancreatic, and gastric cancers.²² The effect size is smaller for these malignancies, ranging from 1.5- to 3-fold increases. Finally, a suggestive but yet unproven

relationship exists for many other malignancies, including breast and colorectal cancer.

Current tobacco use in the United States has remained relatively steady in recent years. Given the significant relationship and cancer burden associated with smoking, programs encouraging smoking cessation are paramount in the prevention of future cancers. Additionally, targeting of at risk-populations to prevent initiation of tobacco use holds great potential in decreasing cancer incidence.

DIET, OBESITY, AND PHYSICAL ACTIVITY

After tobacco use, management of diet and weight are the leading modifiable risk factors associated with cancer development.²⁴ The relationship between these factors and cancer is multifactorial, with other factors, such as genetics and environmental exposures, likely contributing to overall risk.²⁴

Strong support for a link between diet and cancer can be observed through geographic clustering of cancer and changes in cancer incidence observed in immigrant populations. Geographic clustering exists for a number of cancers, including high rates of gastric cancer in Japan and esophageal cancer in southern Africa. Japan's notably high rate of gastric carcinoma (upward of 78 cases per 100,000 people) is thought to be partially attributable to dietary factors, such as consumption of salty, smoked, or pickled foods.²⁵ Interestingly, these high rates drop in Japanese immigrants to the United States. Concomitantly, the rate of colon cancer (typically lower than that seen in the United States) increases to levels comparable to the US-born population within one generation.²⁵ It is hypothesized that at least some of these changes in incidence can be attributed to dietary modifications.

Specific, modifiable dietary factors are difficult to identify. The relationship between nutrition and cancer development is complex, with the epidemiologic studies performed often resulting in conflicting conclusions. The most complete recommendations have been developed by the World Cancer Research Fund in collaboration with the American Institute for Cancer Research. In their publication, they encourage the consumption of a healthy, balanced diet high in fruits and vegetables and limiting the consumption of processed and red meats.²⁶ Fiber has frequently been touted as preventive for the development of colorectal cancer, based on observations that populations with higher overall fiber intake trend toward lower rates of colorectal cancer. This relationship, however, has not been confirmed in the majority of prospective observational and randomized, controlled studies that have been performed to date.^{27,28} As a result, the World Cancer Research Fund and American Institute for Cancer Research consider there to be insufficient evidence to definitively determine whether fiber intake is associated with a decreased risk of colorectal cancer.²⁶ Additionally, data evaluating the importance of other dietary factors, such as carotenoids or vitamins, are considered to be insufficient.

Obesity has been associated with cancer development. Data suggest that esophageal, pancreatic, colorectal, breast, endometrial, and renal cancer may all be increased through obesity or overweight status. Additionally, there is evidence suggesting that increased body weight may also lead to increased mortality associated with a given cancer diagnosis.²⁹ Obesity is therefore one of the most modifiable risk factors for cancer prevention.

Finally, evidence suggests that physical activity is probably effective in protecting against colon, postmenopausal breast, and endometrial cancer.²⁶ There is some uncertainty, however, regarding how this risk factor interacts with other interrelated risk factors, such as obesity or overall healthy lifestyle.

HEREDITARY SYNDROMES

The recent progress in genomic health has led to an increased appreciation of hereditary factors in cancer development. Cancer develops through a variety of genetic mutations that transform a normal cell into a cancer cell. Such mutations may involve pathways that regulate cell replication, apoptosis, and DNA repair. Predisposition to cancer can, therefore, be inherited through mutations in these same pathways, including mutations in proto-oncogenes, tumor suppressor genes, or DNA repair genes. A suggestion of a mutation within a family can typically be identified through a clustering of cancers, with cancers often developing at an unusually early age. Such a history can prompt a referral to genetic counseling for consideration of genetic testing. In other syndromes, cancer is not the most common manifestation of disease, and other signs will be the first to suggest that a hereditary syndrome exists (i.e., neurofibromatosis). A list of common hereditary cancers and syndromes is included as Table 2.

Mutations in tumor suppressor genes are relatively common causes of hereditary cancer development. Cancer development in tumor suppressor genes follows the “two-hit hypothesis,” with a loss or inactivation of both alleles of the gene required to abolish its tumor suppressor function. Patients who inherit a mutation in a tumor suppressor gene require somatic inactivation of the second allele to lead to tumor development. This type of inheritance can be seen with the *RB1* (retinoblastoma) or *APC* (adenomatous polyposis coli) gene. Oncogenes, in contrast, are gain of function mutations; a mutation in a single allele of the associated proto-oncogene is enough to lead to cancer development. Multiple endocrine neoplasia type II develops as a result of an inherited mutation in the *RET* proto-oncogene resulting in the development of medullary thyroid cancer. Finally, cancer can be inherited through defects in DNA repair pathways. DNA repair is vital to the integrity of cells, and failure to faithfully repair DNA breaks may lead to genomic instability, resulting in cancer development. Two best known examples of hereditary syndromes associated with defective DNA repair include hereditary nonpolyposis colon cancer (associated with a defect in mismatch repair genes) and *BRCA1* and *BRCA2* mutations (associated with a number of DNA repair pathways).

Although germline mutations may exist that predispose to cancer development, the true likelihood of cancer is uncertain

Table 2 Common Hereditary Cancer Syndromes⁴⁷

Gene	Type	Locus	Inheritance Pattern	Familial Neoplasm/Syndrome
<i>BRCA1</i>	DNA repair	17q	Autosomal dominant	Hereditary breast and ovarian cancer
<i>BRCA2</i>	DNA repair	13q	Autosomal dominant	Hereditary breast and ovarian cancer
<i>hMSH2</i> <i>hMLH1</i> <i>hPMS1</i> <i>hPMS2</i>	Mismatch repair	2p 3p 2q 7p	Autosomal dominant	Hereditary nonpolyposis colorectal cancer (colorectal, endometrial, brain, urinary tract, other)
<i>NF1</i>	Tumor suppressor	17q	Autosomal dominant	Neurofibromatosis type 1 (neurofibroma, sarcoma)
<i>NF2</i>	Tumor suppressor	22q	Autosomal dominant	Neurofibromatosis type 2 (acoustic neuroma, brain)
<i>RB1</i>	Tumor suppressor	13q	Autosomal dominant	Hereditary retinoblastoma and other second cancers (sarcoma, melanoma, brain tumors)
<i>APC</i>	Tumor suppressor	5q	Autosomal dominant	Familial adenomatous polyposis (colorectal, duodenal, desmoids)
<i>P53</i>	Tumor suppressor	17p	Autosomal dominant	Li-Fraumeni syndrome (sarcoma, breast, brain, leukemia)
<i>MEN1</i>	Tumor suppressor	11q	Autosomal dominant	Multiple endocrine neoplasia type I (pituitary, parathyroid, pancreas)
<i>MEN2A (RET)</i>	Oncogene	10q	Autosomal dominant	Multiple endocrine neoplasia type IIA (medullary thyroid, pheochromocytoma parathyroid)
<i>MEN2B</i>	Oncogene	10q	Autosomal dominant	Multiple endocrine neoplasia type IIB (medullary thyroid, pheochromocytoma, neuromas)
<i>WT1 WT2 WT3</i>	Tumor suppressor	11p	Autosomal dominant	Hereditary Wilms tumor
<i>VHL</i>	Tumor suppressor	3p	Autosomal dominant	von Hippel-Lindau syndrome (hemangioblastoma, renal cell carcinoma)
<i>TSC1, TSC2</i>	Tumor suppressor	9q 16p	Autosomal dominant	Tuberous sclerosis (kidney, brain)
<i>ATM</i>	DNA repair	11q	Autosomal recessive	Ataxia-telangiectasia (breast in heterozygote, lymphoma in homozygote)
<i>PTEN</i>	Tumor suppressor	10q	Autosomal dominant	Cowden disease (breast, thyroid, skin)
<i>STK11</i>	Tumor suppressor	19p	Autosomal dominant	Peutz-Jehgers syndrome (breast, pancreas, hamartomas)

because of variable penetrance. Some syndromes, such as familial adenomatous polyposis, are associated with a 100% risk of developing colorectal cancer by the age of 40; others, such as multiple endocrine neoplasia type II, have a similarly high rate of cancer (medullary thyroid) but present at a much earlier age. Penetrance for all hereditary syndromes is not this complete, however, as cancer development in some syndromes, such as hereditary nonpolyposis colon cancer syndrome, is more variable, and the likelihood of cancer development is much lower.

Prevention

VACCINATIONS

Many infectious agents have been associated with cancer development. In addition to avoidance of these infections through behavioral modifications, vaccination may have an important role in cancer prevention. Two examples where vaccines have been beneficial are hepatitis B virus and HPV. Chronic hepatitis B infection has been associated with the development of hepatocellular carcinoma, increasing it nearly 200 times the population average.¹⁶ Vaccination against hepatitis B reduces an individual's risk of infection and minimizes additional spread of the virus. Hepatitis B vaccination is now offered as part of standard vaccination protocols in the United States for newborns and will likely result in hepatitis B virus being a less frequently associated causative agent for hepatocellular carcinoma in the United States.

HPV is associated with squamous cell carcinoma of the cervix and may have a causative role in squamous cell carcinomas of the head and neck. Two vaccines targeting HPV have been developed and approved by the Food and Drug Administration, the first receiving approval in 2006. Both vaccines target HPV types 16 and 18,^{14,30} with one vaccine additionally covering two HPV strains commonly associated with anogenital warts (types 6 and 11).³⁰ The HPV vaccines have been found to be highly effective at preventing infection, with sustained protection up to 4.5 years after dose administration.³⁰ Importantly, the vaccines have also been found in randomized, controlled trials to be highly efficacious in preventing high-grade cervical intraepithelial neoplasia; two randomized, controlled trials reported 98% efficacy in women who were HPV negative at the initiation of the trial and who completed the vaccination regimen.^{14,15} The bivalent vaccine is currently approved for girls ages 10 to 25 and the quadrivalent vaccine for boys and girls ages 9 to 26. The long-term effect of widespread immunization on cervical cancer incidence and mortality is unknown.

CHEMOPREVENTION

The most successful example of chemoprevention is seen with tamoxifen and raloxifene in women at increased risk for developing breast cancer. Tamoxifen has been most widely evaluated, with several well-designed randomized, controlled trials testing its efficacy in cancer prevention. Overall, the evidence demonstrates that tamoxifen is effective in reducing the risk of breast cancer with a reduction of 38%³¹; these findings are predominantly limited to the prevention of estrogen receptor-positive tumors. Toxicities associated with tamoxifen use include endometrial cancer and an increased

risk of thromboembolic events.³¹ Raloxifene has been tested in postmenopausal women and has been found to be as effective as tamoxifen in reducing the risk of invasive breast cancer (relative risk of 1.02 when compared with tamoxifen).³² However, raloxifene was less successful in preventing in situ cancers (relative risk of 1.4 favoring tamoxifen). Importantly, the toxicity profile of raloxifene differs from that of tamoxifen with fewer cases of endometrial cancer or thromboembolism. Currently, tamoxifen should be considered for chemoprevention in both pre- and postmenopausal women at increased risk for developing breast cancer; raloxifene is an acceptable alternative to tamoxifen for risk reduction in postmenopausal women.

Other examples of chemoprevention include the use of oral contraceptive pills for the prevention of ovarian cancer. This mechanism has been best studied through a collaborative reanalysis of 45 epidemiologic studies of ovarian cancer.³³ Overall, this combined analysis reported a relative risk of ovarian cancer for ever- versus never-users of oral contraceptive pills of 0.73 (95% CI 0.70 to 0.76). There is controversy surrounding the use of oral contraceptive pills as prevention for ovarian cancer, however, given the potential for increased breast cancer rates associated with hormone use. Another class of drugs that have received consideration as chemoprevention agents are the nonsteroidal antiinflammatory drugs (NSAIDs), specifically cyclooxygenase-2 inhibitors. These have been most extensively studied in the prevention of colorectal polyps. Although some data suggest that the use of NSAIDs may decrease the recurrence of colon polyps or decrease the polyp load (especially in high-risk populations),^{34,35} several other studies have not observed an effect.³⁶ Given the mixed results, in combination with the side-effect profile associated with long-term use of NSAIDs, the data cannot currently support the use of NSAIDs as a mechanism of chemoprevention in either the high-risk or general population.³⁶ Finally, a number of studies have evaluated the role of dietary supplements such as retinoids (vitamin A derivatives) or β -carotene but have not identified a clear benefit for cancer prevention associated with their use.²⁴

RISK-REDUCING SURGERY

Risk-reducing surgery is one option patients at increased risk for cancer (most commonly attributable to a genetic mutation) may consider to reduce their risk of developing cancer³⁵; examples where risk-reducing procedures would be considered are listed in Table 3. Patients making decisions for risk-reducing surgery must weigh the benefits associated with reducing their personal risk of cancer development against any potential morbidity or mortality associated with the procedure. Importantly, risk-reducing procedures rarely eliminate all of a patient's future risk of developing cancer. Morbidity associated with risk-reducing procedures may be limited to immediate risks associated with the surgical procedure itself (recurrent laryngeal nerve injury after a risk-reducing thyroidectomy for a patient with multiple endocrine neoplasia type II) or may have longer-lasting implications on overall quality of life (impact on sexuality of bilateral mastectomies for a patient with *BRCA* mutation or bowel function of total proctocolectomy for familial adenomatous polyposis). Each patient's personal decision of whether to undergo such a procedure is complex. It is important to remember that few

Table 3 Risk-Reducing Surgery and Associated Clinical Entities

Clinical Entity	At-Risk Cancer	Risk-Reducing Surgical Procedure	Timing
MEN IIA/B Familial medullary cancer	Medullary thyroid	Total thyroidectomy (with or without central neck dissection and parathyroidectomy)	Based on specific <i>RET</i> mutation (as early as 6 mo of age)
<i>BRCA1/2</i>	Breast	May consider bilateral mastectomies	Anytime
	Ovarian	Recommend bilateral oophorectomy	After childbearing is completed or after age 35
Familial adenomatous polyposis	Colorectal	Recommend total proctocolectomy or total colectomy with ileorectal anastomosis (combined with rectal surveillance)	In teenage years or earlier if polyps have been identified
	Desmoids Upper GI	No recommendation	
HNPCC	Colorectal	Consider total colectomy with ileorectal anastomosis with annual lower endoscopy	Attributable to variable penetrance; no timing recommendation
	Ovarian/Endometrial	No recommendation for risk-reducing oophorectomy or hysterectomy	
Diffuse hereditary gastric cancer	Gastric	No recommendation	
	Breast	No recommendation	
Ulcerative colitis	Colorectal	Consider total proctocolectomy if long-standing active disease	After 10 yr with active pancolitis or in patients with dysplasia
Barrett esophagus	Esophageal	Consider esophagectomy in setting of high-grade dysplasia	Consider after identification of high-grade dysplasia in otherwise healthy patient

HNPCC = hereditary nonpolyposis colorectal cancer; MEN = multiple endocrine neoplasia.

absolute mandates for risk-reducing surgery exist, and the optimal timing for such surgeries is not defined. Alternatives to risk-reducing surgery include chemoprevention in some cases or enhanced surveillance in the hope of detecting a cancer early.

Screening and Early Detection

The primary objective of screening is to identify cancers early (in situ or early stage of disease) when cancers are asymptomatic. This may improve overall outcomes associated with cancer treatment as treatment may be more effective when diagnosed at an earlier stage. However, there are risks associated with screening, and both false negative and false positive results are possible. Guidelines have been created for screening and early detection of common types of cancers; the recommendations from the American Cancer Society are outlined in Table 4.¹³ These recommendations apply to individuals at average risk for developing cancer and not those at increased risk because of family history or environmental exposures.

Mammography is widely recommended as part of breast cancer screening. Currently, the American Cancer Society recommends initiation of screening at the age of 40 for women at average risk for breast cancer.¹³ However, significant controversy has surrounded the age at initiation of screening after the publication of the U.S. Preventative Services Task Force recommendation statement for breast cancer screening in the fall of 2009.³⁷ In this statement, the recommendation was made against routine screening in women aged 40 to 49 who are at average risk for developing

breast cancer. The recommendation was made based on systematic literature reviews, pooled analyses, and models developed by the U.S. Preventative Services Task Force suggesting that the potential harms of screening in this age group (such as false positive findings, unnecessary biopsies, and overtreatment) may outweigh the benefits. However, other societies have interpreted the same data differently and continue to recommend the initiation of screening at the age of 40.¹³ At the current time, it is recommended that the optimal age at which to initiate screening mammography for a woman at average risk for breast cancer should be decided through an informed conversation with that individual's physician. No upper age limit to mammography screening currently exists.

Screening for prostate cancer is equally controversial, and discussions have been ongoing for decades. Two recent randomized, controlled studies evaluating the role of screening for prostate cancer through prostate-specific antigen (PSA) and digital rectal examination have been performed.^{38,39} In both studies, use of PSA blood testing resulted in an increase in the rate of prostate cancer diagnoses. However, it is unclear what the clinical significance of many of these prostate cancers is and whether survival benefit is associated with their early detection. Concerns regarding overdiagnosis and overtreatment of early-stage prostate cancer have made the true benefit of PSA population-based screening uncertain. Current recommendations are for clinicians to initiate discussions regarding prostate cancer screening with patients who can be expected to derive a benefit from treatment of a detected prostate cancer and in whom the benefits of such treatment will outweigh potential risks.⁴⁰

Table 4 American Cancer Society Screening Recommendations for Individuals of Average Risk

Cancer	Screening Modality	Age to Initiate	Frequency
Breast	Mammogram Clinical breast examination Self breast examination	40 20–30 20	Annual Every 3 yr during 20–30s, then annually To be considered
Colorectal	Flexible sigmoidoscopy, or colonoscopy, or DCBE, or CT colonography	50 50 50 50	Every 5 yr Every 10 yr Every 5 yr Every 5 yr
Cervix	Papanicolaou smear	21 or 3 yr after 1st intercourse	Annually until age 30; then may extend screening period based on prior history of normal tests
Prostate	PSA/digital rectal examination	50	Recommend discussion regarding pros and cons of testing
General	Health counseling and physical examination	20	Undefined

CT = computed tomographic; DCBE = double-contrast barium enema; PSA = prostate-specific antigen.

Options for screening of colon cancer have expanded in recent years and include annual fecal occult blood testing, sigmoidoscopy every 5 years, colonoscopy every 10 years, or a double-contrast barium enema every 5 years.¹³ This is recommended to occur beginning at age 50 and continuing until the age of 75. Most recently, virtual colonoscopy (every 5 years) has been included in the recommendations from the American Cancer Society; this recommendation has not been accepted by all organizations, however, in part because of radiation exposure associated with the procedure, cost, and continued requirement for a full bowel preparation.⁴¹

The primary means of screening for cervical cancer remains the Papanicolaou smear. Screening is recommended to start within 3 years after first vaginal intercourse or at the age of 21 and should continue annually until age 30.¹³ After age 30, screening can be tailored for each individual woman, with women who have had three consecutive normal Papanicolaou smears being recommended to either undergo every 2- to 3-year Papanicolaou smears or Papanicolaou smears every 3 years combined with HPV DNA testing. Screening is recommended as long as there is an intact cervix or until the age of 70.

Notably, some common cancers are not included in the screening recommendations. Currently, no recommendation

exists for screening of lung cancer. Early detection of lung cancer is uncommon, and significant attention has been paid toward the development of effective screening regimens. Initial efforts to screen for lung cancer have focused on chest radiographs with sputum cytology. The largest trial was the Mayo Lung Screening Project, a randomized, controlled trial in which chest x-ray and sputum cytology every 4 months over a 6-year period were compared with “usual-care.”⁴² This trial failed to demonstrate a difference in mortality between the trial arms, with a median follow-up time of 20.5 years. More recently, attention has been paid to the utility of helical CT scans. A number of observational trials evaluating helical CT scans have been conducted to date, with a number demonstrating increased detection of stage I lung cancers⁴³; however, limits to the study methodology in the available observational studies, including lead time and overdiagnosis bias, have made it impossible to determine whether early detection of lung cancer translates to any survival benefit.^{44–46} A number of randomized, controlled trials are currently ongoing that will attempt to definitively answer this question.⁴³

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27 MOLECULAR GENETICS OF CANCER

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Cancer is responsible for significant morbidity and mortality in the human population. In the United States, there will be an estimated 1.53 million new cases of malignancy in 2010, with approximately 570,000 cancer deaths; the lifetime risk of developing cancer approaches 40%.^{1,2} In the early 1970s, President Nixon declared a war on cancer, and since that time significant resources have been invested in the investigation of the etiology of cancer, including genetic and epigenetic alterations that lead to uncontrolled growth, expansion, invasion, and spread of transformed cells.

Malignancies, either solid tumors or hematopoietic in origin, are fairly rare in younger individuals; the incidence begins to rise exponentially after the age of 30, indicating the contribution of cumulative exposure to environmental carcinogens.³ Additionally, as cancer is fundamentally a genetic disorder, susceptibility also plays an important role. Classification can be generalized by hematologic, which includes leukemia and lymphoma versus solid tumors such as carcinomas and sarcomas.

Regardless of tissue type, the origin of cancer can be simplified by considering the tissue stem cell. In general, undifferentiated stem cells are responsible for generating cellular offspring via division and differentiation. Over a lifetime of environmental exposure, these stem cells and their offspring are vulnerable to transformation from carcinogens.³ In this time interval, alterations of selective genes occur, conferring a growth advantage; this may be either as sequential somatic events generating neoplastic change or as predisposition to familial cancer, in which somatic events are transposed on germline mutations. Somatic accumulation of genetic changes that occur spontaneously is responsible for sporadic forms of cancer, whereas a germline mutation that increases susceptibility to malignant disease is responsible for inherited forms of cancer. Both are discussed in this review.

One of the aims of cancer research is to better understand the etiology of malignancy, resulting in a reduction in incidence and more effective treatment of those with disease. The study of viral pathogens has facilitated elucidation of many aspects contributing toward malignant transformation. These DNA and RNA viruses require the host DNA replication machinery to duplicate its own genetic material. Thus, for their own survival benefit, viruses produce aberrations in growth via persistent induction of the cell cycle, overriding restriction points, abrogating apoptotic signals, and immortalizing the cell, providing limitless replicative potential.⁴

In addition to these qualities, human tumor formation also incorporates ingrowth of vessels to provide nutrients for the rapidly dividing malignant cells, which eventually become invasive and spread to distant organ systems. From this we can see that cancer is likely the result of an accumulation of

genetic alterations in which a stepwise progression of these events ultimately produces unregulated growth and invasion. These changes occur at the molecular level, in which genetic aberrations have been simplified into structural chromosomal alterations, including inversions, deletions, insertions, and amplifications, as well as numerical irregularities, such as losses or duplications of chromosomes.⁵ Unfortunately, these same cytogenetic heterogeneities result in difficulty treating cancer patients as tumors become insensitive to chemotherapeutics as well as radiotherapy treatments.⁶ Thus, knowledge of the precipitating genetic defects in the malignant growth of interest is vital to understanding the basis of cancer formation as well as producing possible treatments to combat the unregulated growth. Tumor formation is inextricably multifaceted, and this accumulation of characteristics underscores the transition from benign cell to malignant entity. This idea is the basis of this review, in which we hope to elucidate the accession of specific critical properties underlying neoplastic transformation.

Cell Cycle

CELL CYCLE BASICS

Cellular interactions constitute a complex network of signaling that mediates normal growth and development. Cells will commit to proliferation (or not) based on the extracellular environment, nutrient availability, growth factor presence or absence, interactions with other cells, and mitogenic signaling.⁷ Intrinsic to this process is cell cycle machinery, and this normally regulated routine occurs aberrantly in malignancy. Usually, a coordinated and supervised cascade of events, with malignant transformation, DNA replication, and cell division, proceeds unmitigated. Given that cancer is a disease of rampant cell proliferation, understanding the cell cycle, including control mechanisms and regulations, is appropriate and is discussed briefly here. A simplified schematic representing the cell cycle is demonstrated in Figure 1.

The basic cell cycle is composed of stages in which the cell coordinates events to promote successful cell division. Included are growth phases, G_1 and G_2 , which occur prior to and prepare the cell for DNA synthesis and mitosis. G_1 phase precedes S phase, allowing preparation of the cell for replication of genetic material. During the S phase, DNA synthesis briefly produces an aneuploid cell with chromosome content between $2N$ and $4N$ but eventually achieves tetraploidy. This is followed by another growth phase in which subsequent M phase or mitosis occurs. Cells that are not cycling are considered G_0 phase.

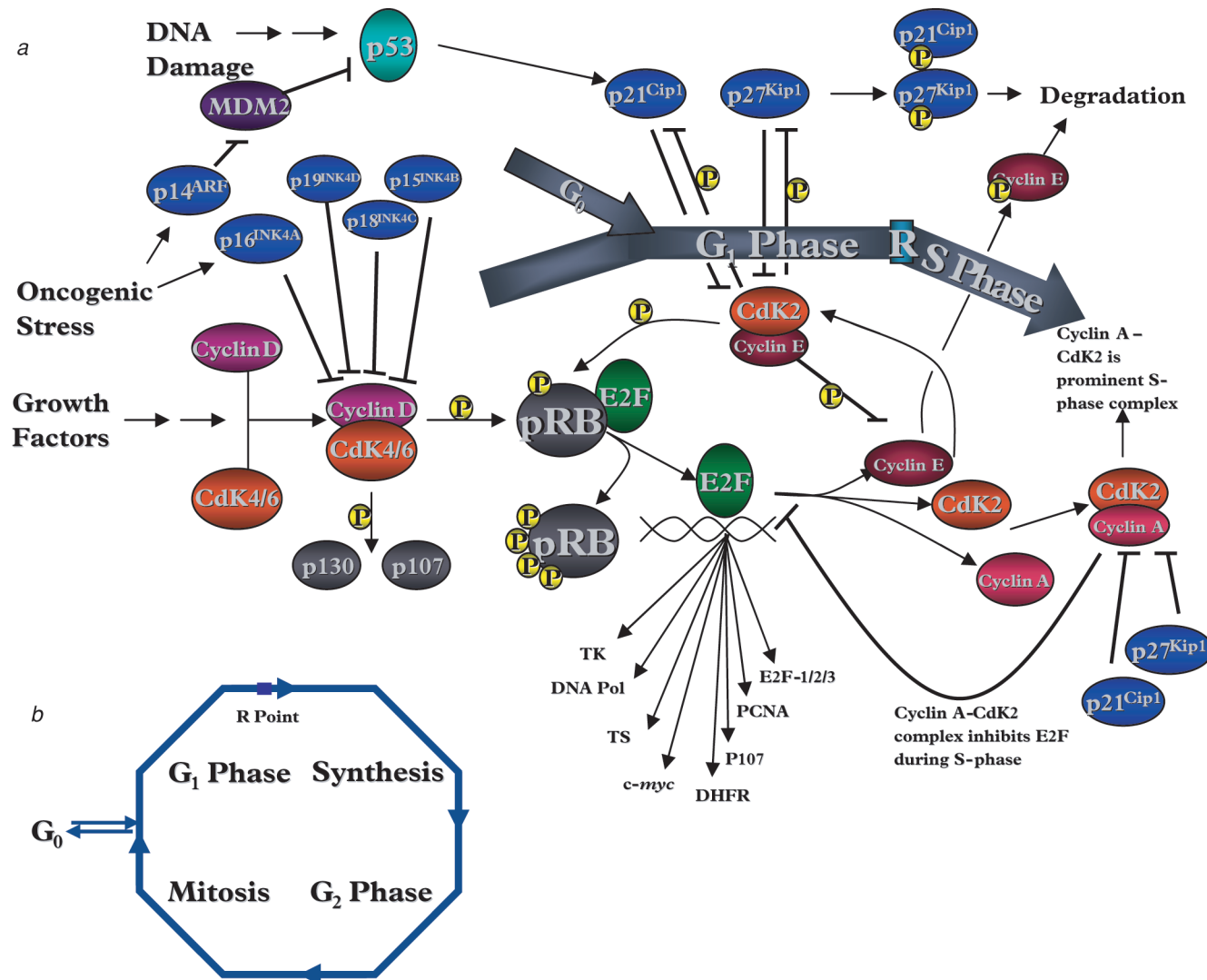


Figure 1 Simplified schematic of the cell cycle. (a) When prompted via growth factors, increased levels of cyclin D and Cdk4/6 form a complex functioning to promote E2F activity via phosphorylation and inhibition of retinoblastoma, p107 and p130. Activation of E2F results in transcription of numerous genes integral to progression of cell replication including thymidine kinase (TK), DNA polymerase, thymidylate synthase (TS), *c-myc*, dihydrofolate reductase (DHFR), p107, proliferating cell nuclear antigen (PCNA), cyclin E, cyclin A and Cdk2. The cyclin E-Cdk2 complex further stimulates E2F via phosphorylation of pRB; at this point the cycle becomes mitogen independent (cyclin E and cyclin D are main drivers of G₁ to S progression). Also inactivated via phosphorylation are p21 and p27, which are themselves negative regulators of Cdk2 activity. Additionally, the cyclin E-Cdk2 complex targets cyclin E for degradation which allows accumulation of Cdk2, favoring a switch to cyclin A-Cdk2 (a mediator in the DNA synthesis phase). With increased cyclin A-Cdk2 formation, E2F transcriptional activity is prohibited to allow transition into synthesis and subsequently G₂/M. On incurring oncogenic stress, the *INK4a* locus is activated, stimulating expression of p14^{ARF} and p16^{INK4A}. P14^{ARF} then enables p53 to halt cell cycle progression via inhibition of MDM2, a p53 inhibitor protein. In addition, p16^{INK4A} also promotes activity favoring cell cycle cessation via inhibition of pRB inhibitors (cyclin D-Cdk4/6). (b) Cell replication cycle in which the initial growth phase (G₁) proceeds to DNA synthesis (S), followed by a second growth phase (G₂) and subsequent mitosis. G₀ represents a cell that is currently not in cell division. The restriction point (R) represents the period in which withdrawal of growth factors will no longer halt progression from G₁ to S.

Depending on the cell type and growth factor with corresponding receptor, cells can be programmed to undergo differentiation and/or proliferation. For instance, cells residing in the quiescent phase (G₀) can be stimulated to proceed into the first growth phase (G₁) when exposed to various growth factors. These initial promoting proteins include viability factors such as epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and fibroblast growth factor

(FGF). Disruptions of this signal will cause regression to the resting state, whereas subsequent stimulation by complementary factors, such as insulinlike growth factor-1 (IGF-1), will allow continuation through this growth phase and into the synthesis phase (S).^{8,9} In contrast, cytokines such as tumor necrosis factor (TNF) and transforming growth factor-β (TGF-β) may oppose these proliferative effects, even late in the growth phase.¹⁰

REGULATORY OVERVIEW

There are two main types of cell cycle regulation, including a highly selective cascade of protein phosphorylation and cell cycle checkpoints; both ensure appropriate completion of necessary events prior to enabling progression to the subsequent stage.¹¹ The first regulatory mechanism implements kinases that relay information via phosphorylation. These kinases (cyclin-dependent kinases or CdKs) interact with their partner cyclin proteins and use adenosine triphosphate (ATP) to phosphorylate specific amino acid residues on target proteins. In addition, binding of cyclin to its respective CdK localizes the complex, where its functions are completed.⁴ Through highly coordinated expression and degradation profiles, the cyclins promote activity at specific time points, allowing for synchronized progression through the cell cycle.

The transition from G₁ to S phase appears to be a site of significant regulation and is contingent on many proteins, including cyclins, CdKs, retinoblastoma-susceptibility tumor suppressor protein (pRB), and p53 [see Figure 1].^{3,12} When growth factors stimulate the cell to proliferate, D-type cyclins detect these extracellular mitogenic cues and bind to CdK4 and/or CdK6. The cyclin-CdK complex is then phosphorylated by CdK-activating kinase (CAK), which enables the complex to promote progression of the cell from G₁ phase into S phase.¹² Notably, these D-type cyclins, such as cyclin D₁, turn over rapidly, with a half-life of approximately 15 minutes. The presence of mitogens stabilizes their expression. Conversely, loss of mitogenic stimuli prior to S phase results in rapid degradation of these regulatory proteins and return of the cell to a quiescent state.¹³

In addition to external stimuli, cyclin and CdK activity can also be regulated by the intrinsic CdK inhibitors. These inhibitors allow for cells to arrest in G₁, thereby enabling the repair of DNA damage, terminal differentiation, and cell senescence. The two major families of CdK inhibitors are Cip/Kip and inhibitors of CdK4 (INK4). Members of the Cip/Kip family include p21^{Cip1}, p27^{Kip1}, and p57^{Kip2}. These proteins bind and act as negative regulators of cyclin E- and cyclin A-CdK2 and cyclin B-CdK1 in a 1:1 stoichiometry.¹⁴ Additionally, the Cip/Kip family members also act as positive regulators of cyclin D-CdK4/6 complexes by mediating their assembly early in G₁.¹⁵ This early assembly results in the titration of p27^{Kip1} from and activation of the cyclin E-CdK2 complex. As a result, p27^{Kip1} is phosphorylated and degraded, thereby enabling the cell to progress through the cell cycle. In contrast, the INK4 family members directly compete for binding to CdK4/6 with the D-type cyclins.^{3,13,16-19} Forced expression of INK4 proteins can lead to G₁ arrest by promoting the redistribution of Cip/Kip proteins and the inhibition of cyclin E-CdK2 activity.

At the restriction point, progression through the cell cycle becomes mitogen independent and proliferation continues despite removal of growth stimuli.¹³ Phosphorylation by CdK4 of the target protein pRB allows desequestration of the E2F family of transcriptional regulators, which stimulates transcription of DNA sequences that form numerous proteins integral to the synthesis phase of cell replication.³ The significance of cyclin-CdK involvement in cell proliferation and tumorigenesis is emphasized by the finding that dysfunction of CdK activity is found in the majority of human tumors.⁷ Once deregulation occurs, the presence or withdrawal of

growth factors no longer dictates the cascade progression, and the cell is continuously coerced to replicate.

Ensuing progression through the cell cycle is regulated by several factors. However, this process can be considered to be the result of forward progress mediated by the expression of proteins responsible for increasing the expression of protein kinases responsible for driving the cell cycle. Alternatively, the lack of progress can be secondary to the identification of errors in the DNA that have accumulated in the S phase.

Retinoblastoma

Retinoblastoma protein exerts most of its influence in the first two thirds of G₁ phase, integrating various upstream signals and ordaining the fate of the cell with regard to progression into synthesis phase. The upstream determinants include growth factors and mitogens, which function to ultimately inhibit pRB via phosphorylation, as well as growth inhibitors, which act to maintain pRB in its hypophosphorylated state.¹³ When hypophosphorylated, pRB forms a stable, intracytoplasmic complex with the E2F proteins, suppressing their ability to form the necessary protein-protein interactions and DNA binding requisite for transcriptional activation.^{13,20} The E2Fs are a family of heterodimeric transcription activators, including E2F-like and DP-like subunits.²¹ Phosphorylation of pRB reverses the growth inhibitory effect as E2Fs are released, translocate to the nucleus, bind to DNA, and mediate transcription of several proteins integral to S-phase entry.^{18,22} In addition, E2F promotes expression of itself through a positive feedback loop, as well as cyclin E and CdK2, further perpetuating cell proliferation via phosphorylation of pRB [see Figure 1]. Progression of the cell beyond this point and into S phase does not rely on cyclin D-CdK4 but rather is driven by cyclin E-CdK2 in a mitogen-independent fashion.^{3,13} In conjunction, beyond the restriction point, the phosphorylation state of pRB becomes less relevant to progression into S phase.

Cyclins-CdKs

Multiple cyclin-CdK complexes are activated as the cell navigates the replicative cycle, often with overlapping substrate preferences [see Figure 2]. The expression levels of these complexes vary with the cycle stage, resulting in intricate interplay guiding the cell in its division. In human cells, cyclin D binding to CdK4/6 and cyclin E binding to CdK2 are essential and rate-limiting steps commencing E2F-dependent transcriptional activity (via phosphorylating pRB, p107, and p130) and transitioning into S phase.⁷ When signaled to proliferate, the cyclin D-CdK4/6 complex is phosphorylated and activated and consequently abrogates the inhibitory effect of pRB, p107, and p130. Subsequently, E2F responsive promoters are then disinhibited, with resultant transcription of numerous genes, among which are cyclin E and cyclin A₂. With accumulation of cyclin E bound to CdK2, the cell passes the restriction point, entering S phase, and is destined for cell division. Once synthesis of DNA (replication) has begun, progression through S phase is coordinated initially by cyclin E-CdK2, followed by cyclin A-CdK2 activity. This transition is coordinated by cyclin E-CdK2, which is responsible for the phosphorylation of cyclin E, leading to its degradation and subsequent accumulation of available CdK2, favoring a switch to the cyclin A-CdK2 complex. The cyclin

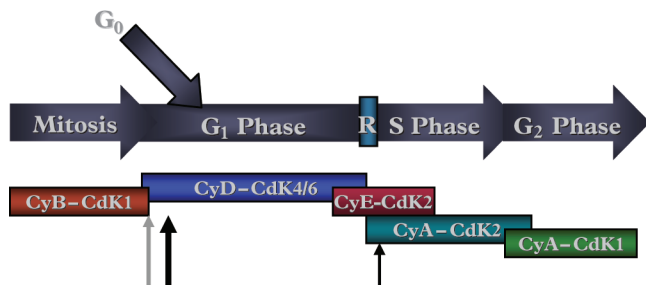


Figure 2 Cyclin-Cdk complex function during the cell cycle. On stimulation by various growth factors (large black arrow), upregulation of cyclin D (CyD) and Cdk4/6 results in the formation of cyclin D₁-Cdk4/6 complex. Subsequent phosphorylation of protein RB (pRB) allows desequestration of E2F and ensuing transcription of cyclin E (CyE), cyclin A (CyA), and Cdk2. Cyclin E binding to Cdk2 forms a complex that functions to further phosphorylate pRB. This releases the cell from growth factor dependence as the cell passes the restriction point (R) and becomes mitogen independent. The cell proceeds into DNA synthesis phase directed by cyclin A-Cdk2 as cyclin E is phosphorylated and targeted for degradation. Cyclin A-Cdk2 inhibits E2F promotion of transcription (small black arrow), allowing transition to the DNA synthesis phase. Cyclin A is prominent during G₂ phase as well but partners with Cdk1 during the second growth period. Finally, cyclin B (CyB)-Cdk1 promotes mitosis and cell division. Proteasome-mediated cyclin B degradation leads to exit of mitosis and reentry into G₁ (gray arrow).

A-Cdk2 complex in turn sequesters E2F, thereby blocking its DNA binding domain and effectively decreasing the E2F-responsive genes, a step integral toward the advancement of synthesis and subsequent entry into the second growth phase. Progression through G₂ remains similarly dependent on cyclin A. However, mitosis and cell division appear to be dependent on cyclin B-Cdk1 activity.⁷ Late in this final phase, proteasome degradation of cyclin B (with inactivation of respective Cdk1) allows completion of mitosis and ingress into G₁. Thus, through the coordinated effort of cyclins and their respective kinases, E2F activity is enhanced, perpetuated, and extinguished at appropriate time points.²¹ Interestingly, however, there is significant overlap and redundancy of these proteins such that knockout or inhibition of cyclins or respective kinases can still produce effective cell growth and proliferation.⁷ The implications of this overlap with respect to malignant transformation indicate that targeting this pathway with cancer therapeutics may prove difficult with such redundancy as tumor cells may “escape” via numerous mechanisms.

Cdk-cyclin activity is dependent on the heterodimerization and nuclear translocation of the complex; in contrast, phosphorylation of the individual subunits targets them for degradation.⁷ Alternatively, the activity of the Cdk-cyclin complexes can also be regulated by Cdk inhibitors, such as the INK4 family. Within the INK4 family are p15, p16, p18, and p19, all of which bind Cdks and form stable complexes at remote binding sites to effectively decrease cyclin heterodimerization, thereby facilitating its degradation.⁴ For example, p16, transcribed from the *INK4A* locus, is a critical regulator of pRB and has been shown to be involved in the inhibition

of the cyclin D-Cdk4/6 complex.²³ This unique locus also contains a second overlapping gene that is generated via an alternative reading frame (first exon 1 α versus 1 β with common downstream exons) from a separate promoter. The 1 α transcript is processed into p16^{INK4a}, whereas the 1 β reading frame is processed into a 14 kDa protein known as p14^{ARF} (ARF or alternative reading frame).²⁴ p14^{ARF} also participates in cell cycle regulation by inhibiting MDM2, the protein responsible for the degradation of p53.²⁵

p53

The second category of regulation involves checkpoints responsible for the propagation of “pure” genetic information. Activation of the checkpoint proteins blocks cell cycle progression, thereby preventing the replication or segregation of dysfunctional DNA.¹¹ These superimposed controls are not essential to the underlying workings of the cycle; however, they impede progression when stressors elicit DNA damage and allow repair to maintain genomic integrity. One such extensively investigated checkpoint regulator is p53, which stabilizes and accumulates in response to DNA damage.³ Remarkably, in addition to binding of specific sequences, p53 can recognize and bind multiple types of DNA damage such as breaks (free DNA ends), single-stranded DNA, and insertion or deletion mismatches.⁴ On survey and identification of damage to genetic material, p53 enlists various proteins via its transcriptional activator mechanism to delegate appropriate responsibilities. Among the most important genes promoted from transcriptional activation is *p21^{Cip1}*. This protein functions to arrest the cell by inhibiting cyclin-Cdk activity (specifically cyclin E-Cdk2 and cyclin A-Cdk2), resulting in the accumulation of hypophosphorylated pRB and inactivation of E2F.²⁶ In contrast to the INK4 family of inhibitors (which bind allosteric sites), however, inhibition by p21^{Cip1} can be overcome by elevated concentrations of cyclins.⁴

Like many cell cycle regulatory molecules, p53 regulates its own expression. One such regulatory mechanism involves increasing the expression of the MDM2 protein. MDM2 inhibits p53’s function by both blocking its ability to mediate transcription and serving as a ubiquitin ligase mediating p53 degradation.²⁷ Feedback inhibition is important to allow reentry into the cell cycle when damaged DNA is no longer present.

Although integral, p21-regulated inhibition is not the solitary function of p53. With the accumulation of an unsustainable number of deformations, p53 is also responsible for inducing cell suicide or apoptosis. This complex mechanism is achieved via increased expression of apoptosis inducers such as the *Bax* gene, which uses the intrinsic programmed cell death pathway to direct cell destruction [see Evading Apoptosis, below]. Given that the propagation of a significantly altered genome may have deleterious consequences to the organism, an option to eradicate such material would be advantageous. In fact, the apoptotic pathway is perhaps the most potent defense mechanism retarding cancer in that pre-malignant cells are destroyed prior to replication of toxic genetic material. Thus, whether instructing self-sacrifice as a result of dangerous levels of genotoxic damage or restoring DNA integrity to baseline, p53 has the extraordinary capability to assimilate input from multiple sources, integrate the

variegated signals, and coordinate the most appropriate response. Regrettably, because of its indispensable nature in ensuring genome stability, the gene is often mutated in malignant disease, with most modifications occurring in the DNA-binding domain, debilitating the protein's competency in transcriptional stimulation.²⁶

Primary Characteristics

Normal proliferation of a cell is a calculated balance between signals that promote and signals that inhibit growth. By definition, a cancer cell possesses all of the necessary components of cell growth, allowing it to proliferate indefinitely. Considering the number of distinct forms of malignancy, each with unique mechanisms to propagate survival, the concept of a shared progression of identical events seems unlikely. However, despite the unique genetic alterations that accompany any given cancer, the consequential change in fundamental processes appears to be distributed to all malignant growths. The end result encompasses adaptations characterized by continuous growth signaling, insensitivity to growth inhibition, evasion of apoptosis, angiogenic potential, immortalization, and invasion or metastasis. These changes leading to invasive cancer were elegantly described in 2000 by Hanahan and Weinberg.²⁸ The majority of this chapter is dedicated to reviewing these traits of cancer as defined by these authors.

Among the early transformations that occur as a cell traverses the expanse from benign to malignant disease are self-sufficiency in growth signals and insensitivity to growth inhibitory signals. Throughout the literature, the genes responsible for these phenotypes are classified as oncogenes and tumor suppressor genes. Regardless of the nomenclature, the significance of each is that one is considered a dominant mutation, whereas the other contributes to neoplastic transformation in recessive form. Self-sufficiency of growth signals may occur via a variety of mechanisms, including point mutations, chromosomal juxtapositions, insertions, and deletions; the result is a dominant form of disease such that a single allele need only be affected.²⁹ In contrast, insensitivity to growth inhibitory signals contributes to oncogenicity via inactivation of both alleles, indicating recessive behavior. Also deemed loss of heterozygosity (LOH), this may occur via loss of a gene, a region of a chromosome, or an entire chromosome. Illustrative of early events occurring in transformation are colon biopsy specimens in which adenomas carry a mutation activating the oncogene *K-ras*, whereas evolution into invasive carcinoma is associated with loss of the deleted in colon carcinoma (*DCC*) tumor suppressor gene and the *p53* tumor suppressor gene.³⁰

Although self-sufficiency in growth signaling and loss of growth inhibition are likely early events in malignant transformation, it is difficult to state with certainty when the complementary events occur within the spectrum of benign to malignant disease and in which sequence. For instance, a cell may suffer an activating mutation of an oncogene followed by LOH of the tumor suppressor gene *p53*, thereby overcoming growth inhibition and programmed cell death. The instability created may then predispose to recruitment of new blood vessel formation and limitless replication, with subsequent

invasion and metastasis. Regardless of succession, each characteristic is quite essential to the final product, which is the complex malignant disease known as cancer.

SELF-SUFFICIENCY IN GROWTH SIGNALS

Cells require a carefully orchestrated series of events to produce the signaling pathways that promote growth and proliferation. Growth factors bind receptors that convey the information to a multitude of intracellular proteins and, ultimately, alter DNA transcription and synthesis [see Figure 3]. Similar to other processes regulated within the cell, expression of these proto-oncogenes is carefully controlled to prevent aberrant growth signaling. Unfortunately, alterations of these genes result in a dominant phenotype recognized as gain-of-function mutations, and these lesions were the first genetic changes shown by investigators to promote cancer development.⁸ Thus, a cell may become independent from exogenous stimulation via alteration of ligands, the respective receptors, or intracellular targets. The resulting downstream effects of these transformed growth signaling proteins result in activation of signal transduction pathways that ultimately stimulate cell growth and proliferation. The genes involved are referred to as oncogenes. Interestingly, many different oncogenes may have the ability to promote growth signaling in any one specific tumor, suggesting redundancy in function; in contrast, a single oncogene may have this growth-promoting effect in another tumor type, indicating specificity.

Activation of an oncogene may occur via a number of mechanisms, including alterations to the gene itself, such as point mutations, deletions, or insertions, or from reformation in the promoter region, resulting in increased transcription. Additionally, gene amplification can produce increased chromosomal number, whereas translocations can enhance expression of key proliferative genes or generate unique constitutively active fusion proteins [see Figure 4]. Regardless of the mechanism, the result is deregulation of the oncogene. This deregulation, in combination with additional alterations of normal cell function, results in malignant transformation. Consistent with the multitude of growth stimulatory pathways, there are numerous recognized oncoproteins involved in mitogenic signal transduction. These include secreted growth factors, the respective growth factor receptors, proteins responsible for cytoplasmic signal transduction, and transcription factors.⁴ Table 1 displays a nonexhaustive list of oncogenes involved in malignant transformation.

Growth Factors and Growth Factor Receptors

The discovery of human receptor tyrosine kinases (RTKs) can be traced to early investigations into the functions of retroviral oncogenes.⁸ These receptor kinases resembled their viral counterparts in that the human homologues autophosphorylated tyrosine residues, which activated downstream signaling.⁸ For instance, the viral *src* gene encodes a kinase that phosphorylates tyrosine residues and has sequence similarity to the v-erb-B transforming protein (avian erythroblastosis virus), which is a truncated form of the human epidermal growth factor receptor (EGFR).³¹ Additionally, the viral-*sis* oncogene (simian sarcoma virus) is structurally similar to the β -chain of platelet-derived growth factor (PDGF- β).^{6,32} Therefore, this striking discovery of sequence

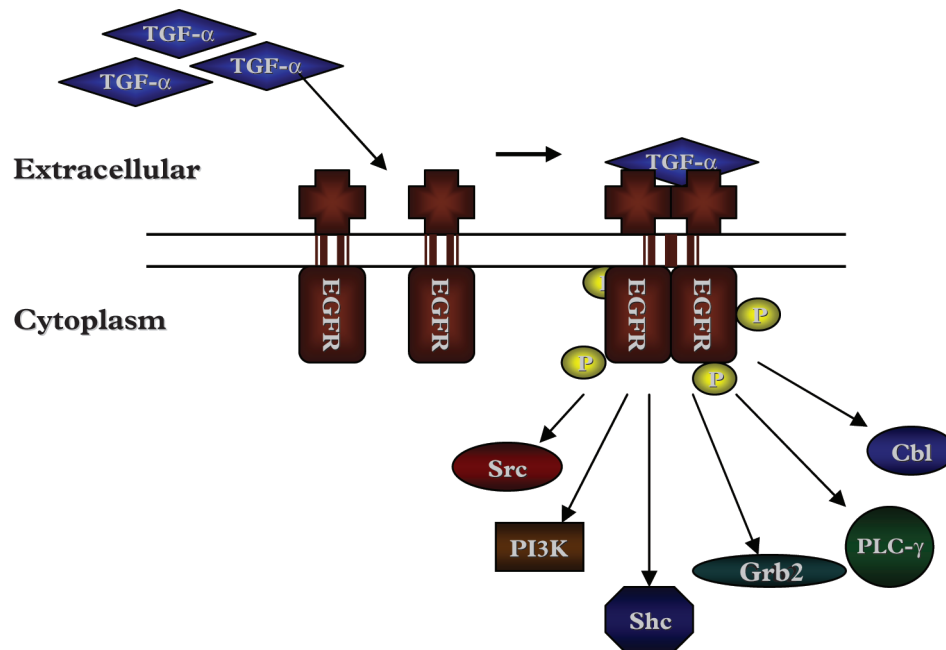


Figure 3 Growth factor binding receptor. Transforming growth factor- α (TGF- α) binds epidermal growth factor receptor (EGFR), which induces conformation change and subsequent receptor dimerization (or oligomerization) with transphosphorylation of tyrosine residues in the intracellular domain. Receptor phosphorylation recruits downstream signaling molecules such as Src, phosphoinositide-3-kinase (PI3K), phospholipase C (PLC- γ), Grb2, Shc, and Cbl. Propagation of signaling (i.e., from Grb2 to Ras) ultimately produces changes in gene expression favoring cell growth and proliferation.

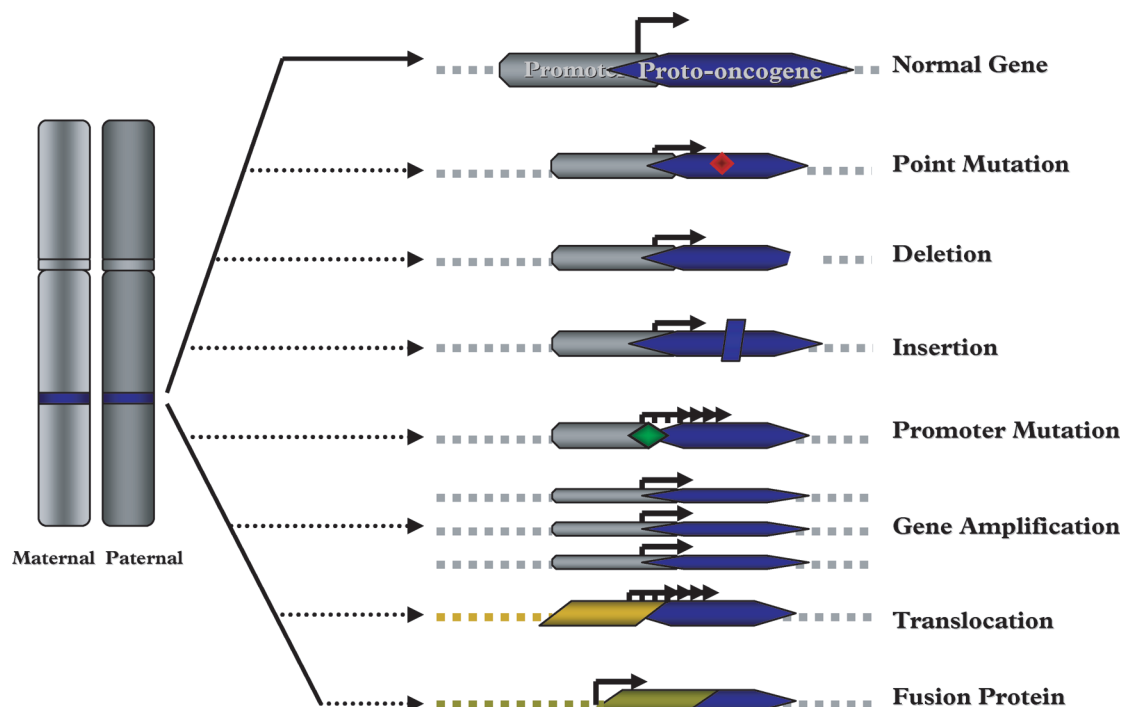


Figure 4 Mechanism of oncogene production. Activation of proto-oncogenes occurs in a dominant fashion. Point mutations, deletions, or insertions in the gene can lead to altered protein products that result in exaggerated activity in the presence of ligand or constitutive activation. Additionally, mutations in the promoter region may enhance transcription of the gene, whereas gene amplification can produce multiple gene copies, ultimately increasing the amount of proto-oncogene present in the cell. With translocations, promoters from a different chromosome region that are perpetually active may be aberrantly inserted upstream of the proto-oncogene. Again in conjunction with translocations, the resultant gene product may form a chimeric fusion protein that is no longer dependent on ligand binding or upstream signaling; instead, it is constantly activated.

Table 1 Nonexhaustive List of Oncogenes in Human Malignancy

Gene	Gene Product	Oncogene Mechanism	Cancer Association
<i>erb-B1</i> (EGFR/HER-1)	EGFR family RTK	Amplification, overexpression	Squamous cell carcinoma, glioblastoma
<i>erb-B2</i> (HER-2/ <i>neu</i>)	EGFR family RTK	Overexpression	Breast, stomach, ovary, lung adenocarcinoma
<i>Met</i> (HGFR)	HGFR RTK	Amplification, overexpression	Gastric, renal cell carcinoma
<i>Bek</i> (FGFR2)	FGFR RTK	Amplification, overexpression	Gastric, endometrial, lung, breast, ovarian cancer
<i>Ret</i>	GDNF family RTK	Point mutations, translocation	PTC; MEN IIA/IIB (familial), MTC (familial)
<i>K-ras</i>	Guanosine triphosphatase	Point mutations	Lung, colon, pancreatic, and other carcinoma
<i>N-ras</i>	Guanosine triphosphatase	Point mutations	AML, MDS
<i>B-Raf</i>	Serine/threonine kinase	Point mutations	Melanoma, CRC, HCC
<i>c-myc</i>	Transcription factor	Translocation, amplification, overexpression	NB, SCLC, B/T cell lymphoma, breast, esophageal, cervical, ovarian, head/neck cancer
<i>N-myc</i>	Transcription factor	Amplification	NB, SCLC
<i>L1-myc</i>	Transcription factor	Amplification	Ovarian cancer, SCLC
<i>CDK4</i>	Cyclin-dependent kinase	Amplification	Gliomas, sarcomas
<i>CycD1</i>	Cyclin D ₁	Translocation, amplification, overexpression	SCC head/neck, B cell lymphoma, SCLC, HCC, CRC, esophageal, bladder, breast cancer, sarcoma, melanoma
<i>MDM2</i>	p53 inhibitor	Amplification, overexpression	Sarcoma
<i>Cdc25b</i>	M-phase inducer phosphatase	Overexpression	Breast cancer
<i>Notch</i>	Surface receptor, transcription activator	Point mutations, translocation	T cell ALL
<i>Bcr-abl</i>	Chimeric constitutively active non-RTK	Translocation	CML, ALL, AML
<i>Alk-NPM1</i>	Chimeric TK	Translocation	Anaplastic large cell lymphoma
<i>NUP214-Abl1</i>	Chimeric TK	Translocation	ALL
<i>Runx1-Runx1tl</i>	Chimeric transcriptional repressor	Translocation	AML
<i>F111-EWSR1</i>	Chimeric transcriptional activator	Translocation	Ewing sarcoma
<i>Pml-RARA</i>	Chimeric transcriptional repressor	Translocation	Acute promyelocytic leukemia
<i>TMPRSS2-ERG</i>	Chimeric transcriptional promoter	Translocation	Prostate cancer

ALL = acute lymphoblastic leukemia; AML = acute myelogenous leukemia; CML = chronic myelogenous leukemia; CRC = colorectal cancer; EGFR = epidermal growth factor receptor; FGFR = fibroblast growth factor receptor; GDNF = glial cell line-derived neurotrophic factor; HCC = hepatocellular carcinoma; HGFR = hepatocyte growth factor receptor; MDS = myelodysplastic syndrome; MEN = multiple endocrine neoplasia; MTC = medullary thyroid cancer; NB = neuroblastoma; PTC = papillary thyroid cancer; RTK = receptor tyrosine kinase; SCC = squamous cell carcinoma; SCLC = small cell lung cancer; TK = tyrosine kinase.

homology between viral proteins with transforming capability and analogous human proteins facilitated the delineation of human proto-oncogene function. This distinction enabled a better characterization of mitogenic signaling and its implications.

The succession of events from binding of extracellular growth factor to DNA transcription is tightly regulated within the normal cell. Generally, the source of mitogenic growth factors arrives from another cell such that the proliferative fate is governed by exogenous signals.²⁸ Certain malignancies, however, have exploited this pathway via continuous generation of growth factors. For example, this level of regulation is

circumvented in sarcomas and breast cancer, in which autosecretion (autocrine stimulation) of transforming growth factor- α (TGF- α) allows persistent growth signaling on binding to EGFR.^{28,33} Receptors such as EGFR are transmembrane RTKs with intrinsic kinase capabilities (various transmembrane tyrosine kinases are depicted in Figure 5). When the growth factor ligand binds its corresponding receptor, a conformational change of the transmembrane receptor is induced, with resultant dimerization or oligomerization leading to activation of the kinase domain.

Subsequently, transphosphorylation of tyrosine residues in the cytoplasmic domain results in transduction of the

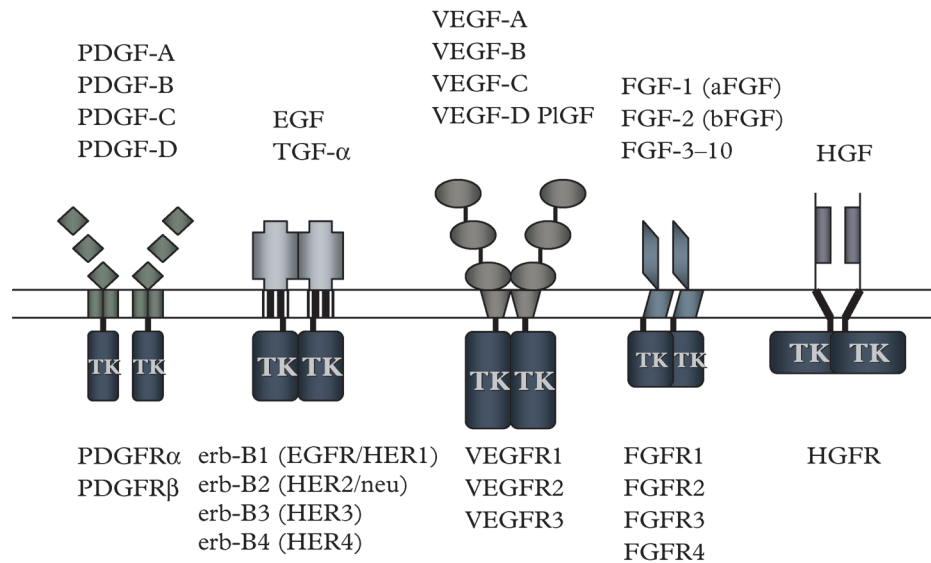


Figure 5 Various transmembrane tyrosine kinases. The receptor names are listed below with the designated ligands above. Each receptor has a conserved tyrosine kinase (TK) domain. On ligand binding, these receptors dimerize and subsequently transphosphorylate the intracellular domain. This allows recruitment of downstream signaling molecules. aFGF = acidic fibroblast growth factor; bFGF = basic fibroblast growth factor; EGF(R) = epidermal growth factor (receptor); FGFR = fibroblast growth factor (receptor); HGF(R) = hepatocyte growth factor (receptor); PDGFR = platelet-derived growth factor (receptor); PIGF = placental growth factor; TGF = transforming growth factor; VEGF(R) = vascular endothelial growth factor (receptor).

mitogenic signal via interaction with intracellular proteins.^{6,33,34} For instance, the EGFR family is composed of four receptors, including erb-B1 (EGFR/HER1), erb-B2 (HER2/neu), erb-B3 (HER3), and erb-B4 (HER4). With binding of complementary ligand (i.e., TGF- α), the sequence of events causing autophosphorylation of the cytoplasmic domain then enables propagation of the growth signal via multiple effector proteins, such as Src, phosphoinositide-3-kinase (PI₃ kinase), phospholipase C (PLC- γ), STATs, Grb2, Shc, and Cbl [see Figure 3].³³ Similarly, when PDGF binds its receptor (PDGFR), phosphorylation of the intracellular portion with consequent kinase activation recruits various intracellular proteins such as PLC- γ , PI₃ kinase, Ras guanosine triphosphatase (GTPase), Ras GTPase activating protein (GAP), and Src.⁸

Deregulation of these growth factor receptors can occur through many genetic events, including amplification, deletion, and truncation. Such deregulation can result in constitutive activation in the absence of ligand stimulation.³⁴ The favorable proliferative phenotype manifest by transformation of the RTKs justifies why this is a relatively common theme throughout cancer biology. Specific examples include erb-B2-4 seen in lung cancer, HER2/neu in breast cancer, and Kit mutation in gastrointestinal stromal tumors (GISTs), all of which are within the EGFR family.⁶ These modified proteins continuously transmit proliferative signals via their intrinsic signaling pathways. Vascular endothelial growth factor (VEGF) is another ligand, the effects of which are mediated by three RTKs: VEGFR1 (FLT 1), VEGFR2 (KDR/FLK1), and VEGFR3 (FLT4). This ligand-receptor pair is responsible for stimulation of angiogenesis in a number of malignancies and thus has become a target for chemotherapeutics [see Angiogenesis, below].

Notable for its role in familial syndromes of endocrine neoplasms, *Ret* encodes an RTK expressed in neural crest-derived and urogenital cells that is integral to normal development in cell lines of the peripheral nervous system (including the enteric nervous system), kidney morphogenesis, and spermatogenesis.³⁵ This receptor binds growth factors of the glial cell line-derived neurotrophic factor (GDNF) family in the presence of GDNF-family receptor- α (GFR- α) proteins. On ligand binding, the Ret receptor dimerizes and subsequently autophosphorylates its tyrosine residues, allowing for the propagation of the signal along its transduction pathway.³⁵ This growth signal is transmitted via the Ras/extracellular signal-related kinase (ERK) or PI₃ kinase-Akt pathway.³⁵ Somatic rearrangements of the *Ret* gene, which can be induced by ionizing radiation, lead to ligand-independent activation, as seen in papillary thyroid cancer.³⁶ In addition, germline point mutations in *Ret* result in autosomal dominant multiple endocrine neoplasia (MEN) types IIA and IIB and familial medullary thyroid carcinoma (FMTC).³⁷ These mutations in the *Ret* gene result in constitutive dimerization and activation of the receptor with persistent transmission of growth signals, giving the cells a genetic predisposition to malignancy.³⁵

From the establishment of growth signaling pathways and elucidation of aberrancies intrinsic to cancer, novel targeted therapeutics have been developed that specifically inhibit activity in select cancers. This is in contrast to various forms of chemotherapeutics, which generally target rapidly dividing cells. The strategy of implementing targeted molecules to combat the molecular alterations in cancer is frequently used when receptor activation is the underlying etiology of a sustained promotion of growth signals. Bevacizumab is a recombinant humanized monoclonal antibody that binds

soluble vascular endothelial growth factor A (VEGF-A), preventing receptor binding (VEGFR). This agent has been approved for use in colorectal cancer as well as non-small cell lung cancer and is currently being investigated in a variety of other cancers, including renal cell and ovarian cancer and glioblastoma.^{6,38}

Another drug within the antiangiogenic class is the tyrosine kinase inhibitor (TKI) SU5412 (sunitinib), which binds the intracellular RTK of VEGFR1 and R2, as well as PDGFR and Kit. When bound by SU5412, the transmission of growth signals by the VEGFR is blocked. SU5412 has been shown to be effective in GISTs and renal cell carcinomas.^{6,39}

Other targeted therapies that have been developed include cetuximab, erlotinib, and gefitinib. Cetuximab is a chimeric IgG1 monoclonal antibody directed against the extracellular, ligand-binding domain of the RTK EGFR.⁴⁰ Cetuximab is used in irinotecan-resistant metastatic colorectal cancer, advanced squamous cell cancer of the head and neck, and advanced non-small cell lung cancer.^{6,40,41} Erlotinib and gefitinib are small molecule inhibitors of the intracellular kinase domain that are used in non-small cell lung cancer.^{6,41} Trastuzumab is a monoclonal antibody directed against the HER2/neu RTK in breast cancer and was found to reduce the rate of death when implemented as adjuvant therapy for primary cancer and in metastatic disease.^{6,42}

Since the inception of cancer-directed treatment, there has been an expansion in the number of therapeutic agents available, each exploiting mechanisms used by cancer to sustain growth. These few examples are among the remarkable targeted therapies that represent the novel strategies recently implemented as a result of the intensive investigation delineating essential pathways in cancer genetics.

Intracellular Targets

The complexity of the intracellular compartment is astounding. Numerable interactions between immense numbers of proteins compound the difficulty in understanding sequential events that occur within the cell. As multiple signaling pathways comprise the internal circuitry of a cell, tumor cells incorporate several strategies to achieve self-sufficiency in growth signaling. As a result, substantial volumes of information could be included in the following section. However, the discussion here includes various intracellular proteins common to cancer and those involved in unique genetic interactions, such as translocations and fusion proteins.

Central to many of the growth factor receptor (GFR) pathways, as well as various cytokines and integrin signaling, Ras is altered in approximately one fourth of malignant tumors.²⁸ As demonstrated in Figure 3, with binding of growth factor to GFR, activation of multiple intracellular targets occurs. One such protein is Grb2 (or SOS), which can then activate Ras. Activation of Ras triggers phosphorylation of Raf kinase, which phosphorylates the mitogen-activated protein kinases (MAPKs) MEK1 and MEK2 (mitogen-activated protein ERK kinase); this signal is transduced to erk-1/2, which dimerizes and localizes to the nucleus to stimulate cellular proliferation.³⁸ Activating mutations in *Ras*, found in many cancers, including colon, pancreatic, and ovarian cancers, triggers this cascade independent of upstream regulation, rendering the cell in a constant proliferative state.³⁸ Additionally, mutated *Ras* has been found to be a poor prognostic indicator

in colon cancer.⁴⁰ In an attempt to interrupt the constitutively active cascade, a specific intracellular TKI, AZD6244, was developed that functions to bind the tyrosine kinases MEK-1/2. Trials with this agent have completed phase II in ovarian adenocarcinoma and are examples of strategies that can be used on discerning underlying disease mechanism and pathways.³⁸

Upregulation of various cyclins and their kinases is a common mechanism in malignancy as they are directly involved in cell cycle progression.³ For instance, cyclin D₁, which functions to inhibit pRB in response to growth signaling [see Cell Cycle, above], is amplified or overexpressed in many different malignancies [see Table 1]. In B cell lymphomas, an immunoglobulin heavy chain enhancer is translocated into the cyclin D₁ locus, resulting in increased synthesis.²³ In a transgenic mouse model, overexpression of cyclin D₁ in mammary epithelial cells induces mammary tumor formation, whereas nullizygous mice demonstrate deficits in breast development (despite normal hormone levels). Results such as these not only emphasize the importance of cyclin D₁ in normal cell growth and development but also demonstrate that dysregulation can result in a malignant phenotype.^{43,44}

The discovery of perhaps the best known oncogenic intracellular signaling molecule stemmed from the detection of a transforming sequence of the MC29 avian tumor virus that resulted in a form of leukemia called myelocytomatosis and thus was labeled *Myc*.⁴⁵ Interestingly, the discovery of this gene and ensuing studies regarding its involvement in cancer led to the realization that neoplastic transformation could occur in the absence of gene mutation. Instead, *Myc*, a nuclear phosphoprotein that functions as a transcriptional regulator of many genes involved in proliferation, differentiation, angiogenesis, and apoptosis, is activated via chromosomal translocation, gene amplification, or insertional mutation [see Figure 6].⁴⁵ In Burkitt lymphoma, Ig heavy and light chains (constitutively active in B cells) located on chromosome 14, 2, or 22 are translocated to chromosome 8 adjacent to the *Myc* locus, thus resulting in unregulated expression and cell proliferation.^{29,45}

Although translocation appears to be the aberration in hematogenous malignancy, amplification is the method of activation in solid tumors. Amplification of *N-Myc*, a gene usually expressed during development, was seen in neuroblastoma tumor samples and corresponded with older age at onset and later stage at presentation, portending a poorer prognosis.⁴⁶ Furthermore, amplification of either *Myc*, *N-Myc*, or *L1-Myc* was found to be a common genetic abnormality in small cell lung cancer.⁴⁷ In addition to revealing a new genetic anomaly in cancer cells, another important aspect of *Myc* investigation that advanced the understanding of neoplastic transformation involved cooperativity studies in which immortalization of cell lines did not occur unless *Myc* was paired with another oncogene, such as *Ras*.⁴⁸ These studies contributed to the basis for a multistep model in tumorigenesis.

An important regulatory protein that was also initially found to be involved in hematopoietic malignancy is Notch. Notch is a family of transmembrane proteins that, when bound by ligand, lead to an intracellular cascade of events. There are four transmembrane Notch receptors (Notch1 to Notch4), as well as five transmembrane ligands (jagged-1

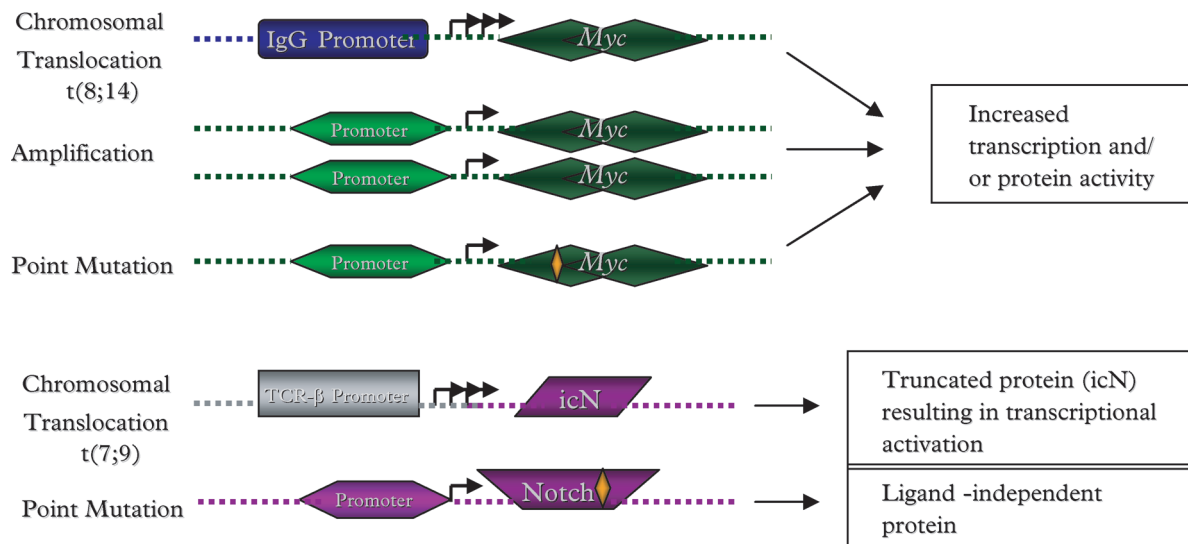


Figure 6 In Burkitt lymphoma, Ig heavy and light chains are translocated adjacent to the *Myc* locus on chromosome 8. These promoters are normally constitutively active and upon translocation, *c-myc* becomes deregulated. Additionally, *c-myc* may demonstrate enhanced activity thus promoting proliferation, angiogenesis and inhibition of apoptosis via amplification or point mutation. Chromosomal translocation t(7;9), in which the T cell receptor- β (*TCR-b*) promoter/enhancer is transposed next to a truncated form of *Notch1* (intracellular Notch [*icN*]), results in constitutive expression of *icN*. In addition, point mutations in the heterodimerization or proline, glutamine, serine, threonine-rich (PEST) domain both lead to increased Notch activity.

[JAG1], jagged-2 [JAG2], delta-like-1 [Dll1], Dll2, and Dll4), and the Notch cell-cell signaling pathway is expressed in most cells.⁴⁹ Subsequent to ligand binding, cleavage of Notch receptor via tumor necrosis factor- α converting enzyme (TACE) and presenilin (γ -secretase) releases the intracellular domain of Notch (*icN*).^{49–51} Nuclear translocation of *icN* allows formation of a coactivator complex with other binding proteins (CBF1/Su(H)/LAG1 or collective CSL complex), resulting in a potent transcriptional activator of various growth-promoting genes.⁵²

Crucial for cell signaling, normal development, and cell fate determination of adjacent cells via lateral communications, Notch also contributes to the malignant phenotype in many different cancers.⁵³ Its role in cancer was discovered from investigation of leukemia, in which overexpression of *icN* was driven via a t(7;9) translocation, juxtaposing *Notch* with the constitutively active T cell receptor- β enhancer.^{29,53} Despite its discovery of deregulation via translocation, activating point mutations in various domains are the much more common etiology resulting in dysfunction and are present in more than half of all T cell acute lymphoblastic leukemias [see Figure 6].⁵⁴ The findings of aberrant Notch activation and deregulated *Myc* activity (discussed above) are examples of the various methods in which growth advantage may be conferred (i.e., translocation, amplification, point mutation), and their investigation has allowed better understanding of the tumor model.

Notable for the first consistent chromosomal abnormality identified in patients with cancer, the Philadelphia chromosome is a t(9;22) translocation involving the *Bcr* gene (intracellular signaling molecule involved in phosphorylation and guanosine triphosphate [GTP] binding pathways) and the

Abl1 gene (intracellular tyrosine kinase).^{55–57} Although a translocation similar to *Myc* or *Notch*, the functional consequence is dissimilar in that in contrast to deregulated expression of a structurally normal gene, this chromosomal aberration results in a fusion gene with altered activity. The consequential chimeric protein underlies chronic myelogenous leukemia (CML) and encodes a constitutively active non-RTK functioning to overcome many of the requirements for cellular neoplastic change [see Figure 7]. Depending on the breakpoint in the *Bcr* gene, different variants in protein size occur, with the smaller p190^{Bcr-Abl} product associated with a more aggressive form of disease (versus p210^{Bcr-Abl}).^{29,57} Biologic actions include activation of cell cycle-promoting proteins, thus driving proliferation; impairment of the DNA repair process, with resultant enhancement of genomic instability; activation of other intracellular oncogenic proteins, such as Ras, further enhancing growth factor independence; and enhanced resistance to programmed cell death via interaction with Bcl-2.⁵⁷ This constellation of aberrant signaling is sufficient for tumorigenesis (in this case, leukemogenesis) and is in itself a cogent model for the multistep progression of malignant transformation. Also remarkable is that investigation to treat this disease prompted the advent of a novel therapeutic RTK inhibitor, imatinib mesylate, which occupies the nucleotide-binding pocket of the fusion protein, inhibiting substrate phosphorylation via blocking access to ATP.⁵⁷ This compound was initially recognized for blocking the kinase domain of PDGFR; however, it was subsequently demonstrated to inhibit both the *Abl1* kinase and *c-Kit* kinase, leading to its use in CML and GISTs.²⁹ Development of this compound provided the substratum for using specific molecular therapeutics and revealed that these targeted therapies can be efficacious. Of note, imatinib-resistant mutations

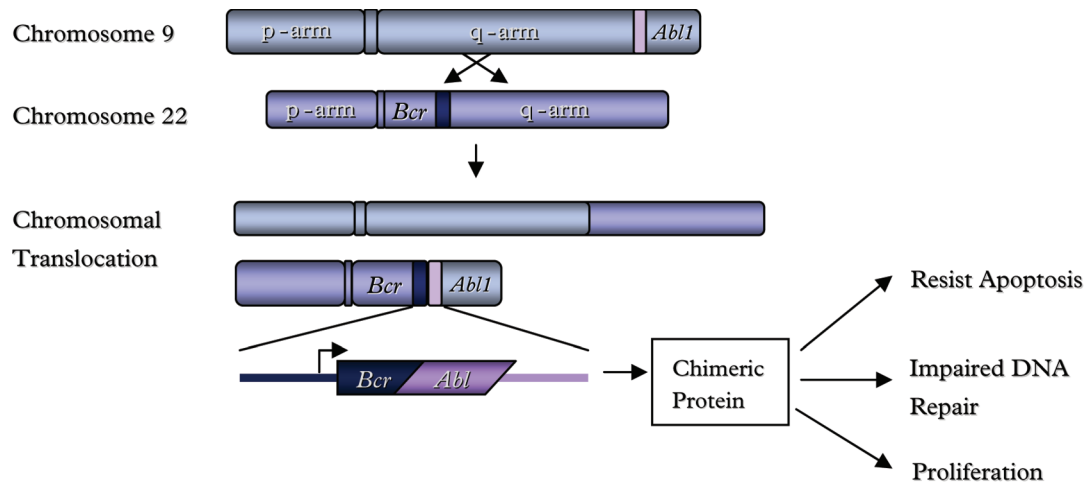


Figure 7 Translocation in chronic myelogenous leukemia. The t(9;22) chromosomal translocation produces a truncated chromosome 22 in which the *Bcr* breakpoint gene (22q11) is adjacent to the *Abl1* (9q34) gene. The resulting constitutively active chimeric protein is an intracellular tyrosine kinase functioning to promote proliferation, cell survival, and genomic instability.

have been identified in patients who relapse, which has led to the development of second- and third-generation small molecule inhibitors (dasatinib and nilotinib) of Bcr-Abl1.⁴²

Historically considered rare occurrences, given the number of cancers associated with chromosomal abnormalities, these events are no longer infrequently encountered in malignancy, and understanding the etiology and mechanism could allow directed treatment and focus on prevention. Moreover, improved diagnostic techniques, such as molecular cytogenetic analysis, have enabled elucidation of an increased number of fusion abnormalities, such as *Abl1* to *NUP214* in T cell acute lymphoblastic leukemia (transcriptional activation) and *PML* to *RARA*, *RUNX1-RUNX1T1*, or *CVFB-MYH11* (transcriptional repression inhibiting differentiation) in acute myeloid leukemia.^{29,42,58} Because the pathology underlying acute promyelocytic leukemia involves repression of transcription factors vital to normal myeloid differentiation, elucidation of the chimeric protein responsible led to successful treatment with all-*trans* retinoic acid and arsenic trioxide, which release the transcription inhibitors and/or degrade the aberrant protein, allowing differentiation to occur.⁴² Additionally, fusion aberrancies detected in virtually all cases of Ewing sarcoma include the *EWSR1* gene (potent transactivator domain) and *FLI1* (in 85%) or *ERG* (in 10%), which are genes encoding a member of the ETS family of transcription factors.^{59,60} This chimeric protein retains the DNA-binding domain of the transcription factors combined with the transactivation properties of *EWSR1* to promote tumor formation.⁴² Some fraction of prostate cancers were also recently found to harbor a chromosomal translocation that results in overexpression of a member of the ETS family of transcription factors such as the *ERG* gene or *ETV1* gene as a result of fusion with the prostate-specific, androgen-driven *TMPS2* promoter.^{29,42} Although information regarding chromosomal translocations contributing to malignant transformation continues to increase as more cancers are implicated, the causes of these rearrangement events remain unknown.

Other Mitogenic Signaling Systems

Binding of ligands to receptors other than transmembrane tyrosine kinases has been found to promote cell proliferation; among these are interleukins binding to membrane glycoproteins.⁸ For instance, interleukin-2 (IL-2) binding to its receptor activates an intracellular member of the Src family of tyrosine kinases (Lck) and results in cell growth. This is relevant in human T cell tumors that are associated with human T cell lymphotropic virus type I (HTLV-1) infection, which upregulate IL-2 as well as expression of its receptor. In normal lymphocytes, growth will occur for a restricted period in the presence of IL-2 and induction of the IL-2 receptor. Conversely, T cells infected with HTLV-I produce constitutive expression of IL-2 receptors; thus, the cells are able to grow indefinitely.⁶¹

Another recently discovered class of molecules found to be integral to both normal and tumor cell proliferation is the microRNAs (miRNAs). MicroRNAs are single RNA strands of approximately 21 to 23 nucleotides that can bind to messenger RNA (mRNA), thus blocking translation or promoting degradation of the mRNA. The RNA sequences found to be susceptible to miRNA-mediated degradation have been shown to be integral to normal development, differentiation, proliferation, and apoptosis.⁶² MicroRNAs have been implicated in various malignancies and are deregulated in a fashion similar to that of genetic lesions, including rearrangements, deletions, amplifications, or epigenetic alterations.^{6,63} The oncogenic action of miRNAs can occur when they are upregulated and bind to the mRNA, thereby inhibiting the activity of tumor suppressor genes. Alternatively, miRNAs that usually bind oncogenes can be downregulated with the same end result: an increase in growth signaling. For instance, in chronic lymphocytic leukemia (CLL), deletion at 13q14 results in decreased levels of miR-15a and miR-16-1. In this cell type, these two miRNAs function to suppress Bcl-2; thus, loss enables overexpression of Bcl-2, which protects the cell from apoptosis and provides a growth

advantage.^{62,64} In contrast, miR-21 has been found to be overexpressed in glioblastoma and cholangiocarcinoma. This miRNA appears to target and degrade the mRNA encoding *PTEN*, a tumor suppressor gene encoding a phosphatase that inhibits growth and survival pathways.^{62,65}

Interestingly, an miRNA may promote cell growth or, conversely, act to inhibit proliferation depending on the cell type and pattern of mRNA expression. Therefore, miRNAs can target multiple mRNAs contingent on the cell type and produce dichotomous effects on cell proliferation. Furthermore, a single mRNA can be targeted by many miRNAs, also conditional on cell specifications. For example, miR-15a and miR16-1 are downregulated in lymphocytes to allow for overexpression of Bcl-2, whereas they are overexpressed in pancreatic neuroendocrine tumors.^{62,66} Additionally, cellular miRNA profiles have been associated with prognosis together with response to treatment.⁶² Although understanding of miRNA involvement in cancer is relatively immature, further investigation in this area will provide better delineation of its utility in transformation to malignant disease, which may allow development of new strategies in cancer diagnosis and treatment.

INSENSITIVITY TO GROWTH INHIBITORY SIGNALS

Of the many proto-oncogenes and growth inhibitory genes that are dysfunctional in cancer, most alterations result in the activation of signaling pathways mimicking persistent exogenous stimulation. Whether ligand, receptor, intracellular protein, or downstream signaling molecule, the pathways appear to converge on the critical regulatory step of passage from G₁ into S. This is accomplished via promoting stimulators such as growth factor receptors, cyclins, and CdKs; additionally, this is achieved via overriding inhibitors and checkpoint controls, preventing cell cycle exit, and impeding programmed cell death.

Discovery of Tumor Suppressors

Oncogene gain of function and tumor suppressor loss of function are different physiologically, and both are necessary to achieve malignant status.³⁰ In normal replicating cells, proliferation mediated by proto-oncogenes is effectively counterbalanced by inhibition from tumor suppressor genes, thus carefully regulating the division of cells.³⁰ The foundation underlying tumor suppressor genes, including relevance toward cancer formation, was achieved via several distinct investigative studies. Early support from somatic cell hybridization fusing tumor cells with normal cells generated a non-tumorigenic hybrid, which led to the theory that normal cells contributed inhibitory genetic information that had been lost in the neoplastic counterparts.^{30,67} Also intriguing was the fact that with certain chromosomal loss in these hybrids, the cells would regain their tumorigenic status.^{29,67} Observations of specific chromosome losses were correlated with reversion to a malignant phenotype, which allowed for the identification of the presumptive growth suppressors. Although greatly enhancing the development of a tumorigenic model, specific genes were not elucidated at that time. However, this combination of findings led to the hypothesis that in addition to generation of growth stimulatory signals, growth inhibitory signals also exist and must be lost for cancer to occur.

Analysis of childhood malignancies associated with hereditary features also indicated the obligate loss of growth inhibitory signals for malignant transformation. The pediatric tumor retinoblastoma was used for a number of early studies in this field. Alfred Knudson studied this rare tumor and concluded that two discrete events are required to generate neoplastic change occurring in a hereditary or nonhereditary fashion (the so-called “two-hit hypothesis”).⁶⁸ His observations explained the familial form (referred to as the “dominant form”) in which an inherited germline lesion was followed by a single somatic mutation during life; the manifestations included earlier onset and bilateral disease. In addition, he determined that sporadic retinoblastoma was the result of both lesions sustained as somatic mutations (recessive form) characterized by unilateral disease later in life. Ensuing analyses of the tumor retinoblastoma revealed that the discrete events occurred on chromosome 13 and involved alteration of both copies of the retinoblastoma gene.⁶⁹ The initial insult compromising this genetic locus occurred via a germline or somatic mutation. Loss of one allele was then followed by chromosomal nondisjunction, mitotic recombination, gene conversion, or gross deletion. Given that the adjacent genetic material would also be affected by such events, DNA markers (such as restriction fragment length polymorphisms [RFLPs] or single nucleotide polymorphisms [SNPs]) of these contiguous sites would likewise reflect these changes. Therefore, specific chromosomal events generate a homozygous reduction in the chromosomal markers (and allele) where previously there had been heterozygous mapping (i.e., when only a single event was present). The LOH at these loci correlates with loss of tumor suppressor gene function.^{30,70}

Consequent studies of the pattern of DNA markers on chromosomes from numerous tumors led to the discovery of various loci containing tumor suppressor genes. As the years have progressed, these large loci have been focused, allowing characterization of specific genes. There are many known tumor suppressor genes with a vast array of cellular functions. It is now recognized that tumor suppressor genes regulate various cellular activities, such as checkpoint control, detection and repair of DNA damage, protein degradation, mitogenic signaling, cell migration, and cell differentiation [see Table 2].²³

Cell Cycle Genes and RB1 Pathway

Multiple cellular proteins interact during the early phase of the cell cycle, and the integration of these signals determines the fate of that cell. Sustained growth signals through any number of checkpoints within the cellular regulatory machinery can induce the cell to proceed inappropriately with replication. CdK4 inhibitor INK4a (CdkN2, Cdk4I, or Mts1, also known as p16^{INK4a}) is a critical regulatory protein that provides additional levels of regulation via inhibition of the cyclin D1–CdK complex. The actions of p16^{INK4a} lead to cell cycle arrest at the G₁ to S interface, just prior to the convergence point of pRB [see Cell Cycle, above]. Unfortunately, inactivation of p16^{INK4a} by any number of mechanisms leads to a constitutively phosphorylated state of pRB, providing the cell with a survival advantage. Mice nullizygous for the CdK inhibitor develop spontaneous tumors at an early age, and transformation occurs at an accelerated rate in response to carcinogens, indicating cooperation with other oncogenic

Table 2 Nonexhaustive List of Selected Tumor Suppressor Genes Associated with Inherited Susceptibility

Gene	Gene Product	Somatic Cancer Association	Germline Cancer Association
<i>PTEN</i>	Tyrosine phosphatase	Gliomas; breast, prostate, endometrial, and ovarian cancer	Prostate and endometrial cancer, melanoma, leukemia (Cowden syndrome)
<i>p16^{INK4a}</i> (CDKN2, MTS1, CDK41)	Cyclin-dependent kinase inhibitor	Biliary, esophageal, nasopharyngeal, bladder, NSCL, prostate, pancreatic, renal cell, colon, breast, ovarian cancer; gliomas; mesotheliomas; ALL; sarcoma	Familial melanoma and pancreatic cancer
<i>RB1</i>	E2F protein inhibitor	Retinoblastoma, SCLC, osteosarcoma, carcinoid, breast, prostate, and bladder cancer	Retinoblastoma
<i>p53</i>	Transcription factor	≈50% of all cancers (lung, breast, colon, esophageal, liver, bladder, ovarian, etc.)	Li-Fraumeni syndrome
<i>p14^{ARF}</i>	MDM2 antagonist	Breast and colon cancer	Familial melanoma
<i>APC</i>	Regulator of β -catenin	Colon and rectal cancer	Familial adenomatous polyposis
<i>PTCH</i>	TR involved in hedgehog signaling	Medulloblastoma, BCC, rhabdomyosarcoma	Basal cell nevus syndrome (Gorlin)
<i>Smad4</i> (DPC4)	TGF- β signaling	Pancreatic and colon cancer	Juvenile polyposis (hamartomas)
<i>TSC1/2</i>	GAP complex	Renal cell carcinoma, angiofibroma	Tuberous sclerosis (hamartomas)
<i>NF-1</i>	Ras GTPase	Sarcomas, gliomas	Neurofibromatosis
<i>WT1</i>	Transcription factor		Wilms tumor
<i>MLH1, MSH2</i>	DNA mismatch repair	Endometrial, gastric, ovarian, and bladder cancer	HNPCC (Lynch syndrome)
<i>ATM</i>	S/T PK involved in DNA break repair	Lymphoreticular malignancies	Ataxia-telangiectasia, T cell lymphoma
<i>NBS1</i>	Double-stranded break sensor complex protein	Lymphoreticular malignancies	Nijmegen breakage syndrome, T cell lymphoma
<i>CHK2</i>	S/T PK involved in DNA break repair		Li-Fraumeni syndrome
<i>BRCA1</i>	Double-stranded break repair protein	Ovarian cancer	Familial breast and ovarian cancer, pancreatic cancer
<i>BRCA2</i>	Double-stranded break repair protein		Familial breast and ovarian cancer, pancreatic cancer, melanoma
<i>TGFβRII</i>	TGF- β receptor	Colon and rectal cancer	
<i>VHL</i>	E3 ligase recognition factor for HIF α	Renal cell carcinoma, cerebellar hemangiosarcoma	von Hippel-Lindau syndrome

ALL = acute lymphoblastic leukemia; BCC = basal cell carcinoma; GAP = guanosine triphosphatase-activating protein; GTPase = guanosine triphosphatase; HIF = hypoxia-inducible factor; HNPCC = hereditary nonpolyposis colorectal cancer; NSCL = non-small cell lung; PK = protein kinase; SCLC = small cell lung cancer; S/T = serine/threonine; TGF = transforming growth factor; TR = transmembrane receptor.

mechanisms to produce tumors.⁷ In comparison, animals still possessing the *INK4a* locus were significantly more resistant, illustrating its function as a critical growth inhibitory (tumor suppressor) gene.⁷¹ Consistent with the hereditary nature in which tumor suppressor genes were discovered, germline mutations of *p16^{INK4a}* are responsible for cases of familial melanoma.⁷² Because of the significant role of *p16^{INK4a}* at a point where a delicate balance of progrowth and inhibitory signals converge, not surprising is the fact that mutations, deletions, or DNA methylation of *p16^{INK4a}* occur in a wide spectrum of malignant diseases, including pancreatic, esophageal, colon, breast, and ovarian cancer, among others [see Table 2].^{3,71}

Interestingly, both proteins from the *INK4a* locus are relevant toward inhibition of malignant transformation. A depiction of the *INK4a* locus is demonstrated in Figure 8. The *p16^{INK4a}* counterpart, *p14^{ARF}*, joins its alternatively spliced cohort as a tumor suppressor involved in many malignancies. Similar to *p16^{INK4a}*, an inherited germline mutation results in a familial form of melanoma.²³ However, whereas *p16^{INK4a}* provides regulatory activity of pRB, *p14^{ARF}* targets MDM2, a protein negatively regulating p53.^{25,27} Confirming the importance of this locus in tumor regulation, hyperproliferative signals, such as occur with constitutive activation of the *Ras* oncogene, result in transcription of both *p16^{INK4a}* and *p14^{ARF}*, promoting pRB and p53 function, respectively, thereby

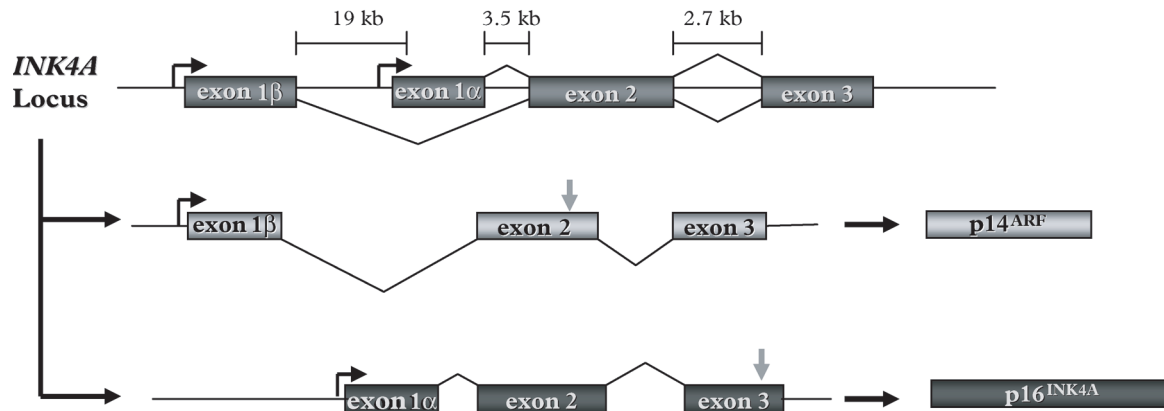


Figure 8 The *INK4A* locus.⁷¹ The *INK4A* locus possesses two alternatively spliced gene sequences (each has its own promoter region) encoding proteins critical for the tumor suppressor capabilities of a cell. The first protein, p14^{ARF}, is a 14 kDa protein in which the coding region is composed of exon 1 β and a portion of exon 2 (the termination region is depicted by a *small gray arrow*). The second protein, p16^{INK4A}, arises from alternative splicing using exon 1 α , exon 2, and exon 3 (the termination region is also depicted by a *small gray arrow*). Given that these proteins are responsible for deinhibition of p53 and pRB, respectively, the *INK4A* locus is targeted in many human cancers [see Table 2].

countering the growth-promoting signals of Ras.^{23,73} However, loss-of-function mutations in the p16^{INK4A} and p14^{ARF} genes would allow for growth selection of cells with a constitutively active form of Ras. Whereas inactivating mutations specifically targeting p14^{ARF} are uncommon, lesions disrupting the *INK4a* locus and transcription repression via epigenetic modification through promoter hypermethylation are more common strategies used by cancer.⁷⁴

In continuity with the CdK inhibitors and cyclin-CdK complexes, pRB is a convergence of the intricate interplay between these proteins. In its proliferative inhibitory state (hypophosphorylated), pRB sequesters the transcription activators E2Fs, rendering them unable to promote passage from G₁ into S. The retinoblastoma gene was the first tumor suppressor identified, and study of this gene led to Knudson's two-hit hypothesis. Following Knudson's seminal work, others studying tumor viruses provided insight into the function of pRB. For example, the E1A protein encoded by human adenovirus, the large T-antigen of simian virus 40 (SV40), and the E7 protein of human papillomavirus (HPV) all complex with and inhibit pRB function.^{29,30} Subsequently, it was determined that these proteins bind to the hypophosphorylated form of pRB and not the hyperphosphorylated counterpart, indicating E2F-suppressive activity of pRB only in the hypophosphorylated state.⁷⁵ Confirmatory evidence came from observations demonstrating that hypophosphorylated, but not hyperphosphorylated, pRB was able to bind to E2F.³⁰

Thus, transformation by these viruses is achieved in part by neutralizing the growth constraints imposed by pRB. Because of its significant involvement in growth inhibition, loss of this gene is implicated in numerous malignant tumor growths [see Table 2]. Further illustration of this critical point as a common target in cancer is that alteration of any upstream component in the pRB pathway generating the common end point of pRB inactivation is generally mutually exclusive with abnormalities of other components.⁷⁶ Thus, a malignant cell need

only achieve deregulation of pRB via targeting any constituent (i.e., CdK inhibitors, cyclins, CdKs, pRB) before continuing its selection for other requisite tumor characteristics. A remarkable finding emphasizing the importance of these pathways is that in almost 100% of lung and esophageal carcinoma, there are detectable lesions in *INK4a*, cyclin D₁, or the retinoblastoma gene.³ Another intriguing function of pRB is its ability to bind the catalytic domain of the nuclear tyrosine kinase c-Abl and inhibit its function. Similar to its interaction with E2F, loss of pRB's function leads to the activation of the catalytic domain of c-Abl, thereby enabling unregulated growth-promoting signals.¹³

A concept incongruous with many tumor suppressor genes is haploinsufficiency, in which selective advantage for growth occurs with loss of only one allele. An example is p27^{Kip1}, in which animals lacking the gene develop tumors spontaneously in addition to demonstrating increased sensitivity to carcinogens. Tumor formation is dose dependent in that a lack of both copies produces faster onset tumor formation than a lack of one copy alone.⁷⁷ Despite this, reduced levels of p27^{Kip1} are not a specific genetic target for cancer; however, reduced levels are associated with a poor prognosis in a multitude of malignant disease, such as breast, prostate, and gastric carcinoma.⁷

Inherited Susceptibility

Modeled after retinoblastoma for its resemblance of familial inheritance and sporadic cases, Wilms tumor (WT) of the kidney is a result of the loss of the tumor suppressor gene *WT1*.⁷⁸ *WT1* encodes a protein that functions as a transcription factor antagonizing growth stimulation.

Familial adenomatous polyposis (FAP) is a heritable disease leading to polyposis of the large intestine with impending colon cancer if left untreated. This disease is caused by germline mutation in the adenomatous polyposis coli (*APC*) gene. Although germline mutations predispose to cancer at a young age, *APC* gene mutations are found in more than 80% of

spontaneous colon and rectal cancers.²³ In fact, mutations in *APC* have been commonly identified within benign tumors such as small adenomas and later-stage colon cancers, indicating an early event in transformation.^{79,80} Functionally, the APC protein associates with β -catenin in a scaffold complex that allows phosphorylation by glycogen synthase kinase-3 β (GSK-3 β). Phosphorylated β -catenin is targeted for degradation via an E3 ubiquitin protein ligase. In the presence of Wnt signaling, the kinase activity of GSK-3 β is inhibited, resulting in stabilization of β -catenin and association with Tcf/Lef protein complexes promoting transcription of target genes, including *C-Myc* and *CCND1*.^{23,81} Although disruption of this pathway in the mouse model (Tcf7/2^{-/-} mice) depletes intestinal epithelial stem cells, *APC* mutations in humans generate deinhibition, resulting in sustained activation and persistent propagation of growth signals.⁸² Moreover, investigations implementing a mouse model heterozygous for mutations in the *APC* gene (multiple intestinal neoplasia or Min (*APC*^{Min/+}) mouse) revealed development of numerous adenomatous polyps throughout the small and large intestine on loss of the remaining wild-type gene.^{83,84} These findings indicate that this pathway is essential for normal development, but abuse of the pathway leads to a premalignant state.⁸⁵

Also identified as mutated in colon cancer, *Smad4* was first recognized as a tumor suppressor deleted in pancreatic cancer. *Smad4* is similar to *APC* in that it is likely an early event in transformation, and germline mutations in this gene result in familial juvenile polyposis, demonstrating the importance in growth inhibition of the normal protein.⁸⁶ Its mechanistic pathway begins when TGF- β binds the TGF- β R; Smad proteins are phosphorylated, resulting in hetero-oligomeric Smad complexes that function to activate transcription of TGF- β -responsive genes involved mostly with downregulation or inhibition of growth stimulators.²³ Thus, mutations in *Smad4* disrupt the growth inhibitory input provided by TGF- β in the colon or pancreatic epithelial cells.

Another signaling cascade that is important, as evidenced by the many associated predisposition syndromes, is the mammalian target of rapamycin (mTOR) pathway. One of the upstream regulators of mTOR is Akt, which, when activated, signals enhanced protein synthesis, cell growth and progression, angiogenesis, and survival via mTOR; in contrast, a key regulator of Akt is PTEN (for phosphatase and tensin homologue). This gene encodes a phosphatase protein that inhibits growth signaling via the PI₃ kinase-Akt-mTOR pathway.^{42,87} PTEN is frequently targeted in malignant disease and loss of PTEN inhibition creates a state of constitutive activation by PI₃ kinase. Loss of this gene via somatic mutations results in survival advantage and is prevalent in multiple forms of cancer, including gliomas and prostate, endometrial, and endometrioid ovarian cancer.⁸⁸ Germline mutation with LOH and subsequent silencing of the remaining allele are found in four rare human diseases, one of which is Cowden disease, characterized by hamartomas and predisposition to breast cancer.⁸⁹ As noted, the convergence point of the PTEN/Akt in conjunction with other pathways is mTOR, underlying the motivation for targeting this protein using pharmacotherapeutics. In an attempt to restore the growth inhibitory attribute of tumor suppression, use of mTOR inhibitors (sirolimus) has shown promise in PTEN-deficient tumors.^{42,87}

Genomic Integrity

In concordance with assimilation of growth signaling, another task of tumor suppressor genes is ensuring duplication of the appropriate genetic material. The substantial size of DNA and proclivity to accumulate lesions via numerous exogenous and endogenous mechanisms result in an immeasurable task of maintaining genomic integrity such that proper cell replication and survival occur. However, when lesions are undetected or undergo faulty repair, these gene mutations can be passed on to the daughter cells through mitosis. This genome instability is a hallmark of cancer.³⁰ Because of the critical nature regarding conservation of genetic information, an intricate network of surveillance, checkpoints, and effector systems is in place to ensure propagation of conserved material. Unfortunately, these systems are prone to dysregulation in malignant disease, which provides an avenue for transformation. The initial insult may establish growth advantage, but the vulnerability that follows permits additional genetic and epigenetic changes, facilitating complete malignant degeneration.⁹⁰ Genes susceptible to loss of suppressor activity that are charged with preventing instability and promoting integrity include *p53*, *BRCA*, and the mismatch repair genes *Msh2* and *Mlh1*.

An inhibitory protein that has been studied extensively is p53, a 53 kDa nuclear phosphoprotein integral to regulating cell proliferation, maintaining the integrity of the genome, and, in dire situations, promoting cell death through apoptosis. For instance, when DNA is damaged via irradiation, drug toxicity, hypoxia, or oncogene activation, p53 halts cell cycle progression to regain DNA integrity.^{23,27} Similar to pRB, p53 was found initially from its association with an oncoprotein of SV40 (large T antigen) in transformed cells; subsequent associations were also seen with adenovirus E1B and HPV E6 proteins.^{30,91} However, unlike pRB, p53 was expressed at low levels in normal cells and found to be significantly elevated in tumor cells, leading to postulation of *p53* as an oncogene; this theory was soon dismissed as wild-type p53 was shown to be an inhibitor of tumor formation.^{92,93} The rationale for elevated levels of mutant p53 in malignant cells stems from observations that the mutant form becomes bound to heat shock proteins (Hsc70), decreasing degradation. In addition, whereas normal p53 assembles into oligomeric structures prior to DNA binding, mutant forms from point mutations, deletions, or rearrangements also complex with normal p53 and block the DNA-binding function in a dominant negative fashion.⁹⁴ Thus, in its mutated state, p53 accumulates within the cell (half-life extends from 20 minutes to 24 hours), is unable to bind DNA due to misfolding, and therefore is unable to perform its normal effector functions. With loss of regulation, the resulting genetic instability leads to disturbance of the intact genome and ensuing disruption of chromosome integrity, which generates an environment conducive to malignant transformation.^{30,92} Successive aberrancies accumulate, which may provide favorable attributes such as avoidance of programmed cell death, promotion of angiogenesis, enhanced aggression, and invasiveness, ultimately producing a highly malignant, chemoresistant tumor.³

Further similarities to pRB constitute inherited disorders secondary to germline mutations, namely, Li-Fraumeni syndrome. Affirming p53 as a critical protein regarding tumor

suppression, patients with Li-Fraumeni syndrome develop tumors in a variety of organ systems, including the colon, breast, lung, larynx, and brain, as well as increased incidence of rhabdomyosarcoma, adrenocortical carcinoma, melanoma, and leukemia.³⁰ Similarly, sporadic loss of this crucial gene has also been detected in a multitude of cancers [see Table 2]. Additionally, although the normal protein has been shown to demonstrate antineoplastic properties in both in vitro and animal models, transgenic mice lacking p53 are prone to tumor development, substantiating the pivotal nature of p53 mutation in cancer formation.⁹⁵ With the understanding of its many regulatory functions, it is not surprising that p53 is the most frequently mutated gene in human cancer.^{96,97} In addition, given the many distinct codons in which potential debilitating alterations may occur, this gene then becomes quite susceptible and a propitious target to overcome antineoplastic defenses of the cell.⁹⁵

BRCA1 and BRCA2 are proteins involved in the repair of double-stranded DNA breaks by homologous recombination. Mutations in either of these genes confer a risk of developing breast cancer 10 to 30 times that of the general population, with manifestations of earlier onset and bilateral disease. Important for treatment options, breast cancers related to BRCA1 mutations are often high-grade, aneuploid malignancies that do not express estrogen receptor, progesterone receptor, or HER2 (triple negative).⁹⁸ Thus, alternative chemotherapeutic avenues have been investigated. Tumors deficient in one of these proteins were found to be potentially treatable by inhibitors of the single-stranded break repair protein poly ADP-ribose polymerase (PARP).⁹⁹ PARP proteins are enzymes that play an integral role in the repair of single-stranded DNA breaks. Thus, use of an inhibitor, olaparib, may lead to an accumulation of single-stranded breaks that consequently form double-stranded DNA breaks.¹⁰⁰ In normal cells, repair of the damaged genetic material would ensue, using the homologous recombination double-stranded DNA repair pathway (i.e., BRCA1 or BRCA2). However, cells that have lost BRCA functions are particularly susceptible to double-stranded breaks as no backup repair system exists.¹⁰⁰ The premise of cytotoxicity only to cancer cells was based on the idea that wild-type BRCA and PARP were sufficient to prevent cell death, whereas loss of BRCA itself promoted genomic instability and malignant transformation, but that loss of both BRCA and PARP generated an environment not conducive to survival. Phase I trials with olaparib have demonstrated antitumor activity in breast, ovarian, and prostate cancer.¹⁰⁰

Mutations in mismatch repair (*MMR*) genes have been discovered to play a role in hereditary nonpolyposis colorectal cancer (HNPCC). DNA replication errors, including single base mispairing and erroneous reproduction of microsatellite sequences (such as slipped strand mispairing), are frequently corrected by this class of DNA repair genes.² Microsatellites are tandem repeats of di-, tri-, or tetranucleotide sequences, and these microsatellite loci associate with alleles and serve as markers for loss of the mismatch repair gene functions.²⁹ The repair system encompasses the *MutS* genes (*Msh2*, *Msh3*, *Msh6*), which recognize DNA mismatch via assembly of *Msh2* with either *Msh6* or *Msh3*, and *MutL* genes (*Mlh1*, *Mlh3*, *Pms1*, *Pms2*), which function to correct the defect accomplished via excision by the *Mlh1*/*Pms1* complex.²³ HNPCC

comprises 1 to 3% of colon and rectal cancer, with approximately 95% of HNPCC derived from mutations in *Mlh1* and *Msh2*.² In addition to colon and rectal cancer, patients with this syndrome are also at risk for cancers of the ovary, endometrium, bladder, small intestine, and pancreas.¹⁰¹ Consistent with the characteristics of other inherited disorders, sporadic biallelic lesions also occur and are present in 15% of colon and rectal tumors, mostly arising from inactivation of *Mlh1*, which results in microsatellite instability. Whether sporadic or germline in nature, alteration of the repair system generates an unstable environment in which mutations in other genes occur. In this intriguing novel pathway of tumorigenesis, one can envision that targets of the so-called “mutator” phenotype could lead to activation of oncogenes as well as inactivation of tumor suppressor genes.²³ Indeed, microsatellites are present within the coding sequence of growth inhibitory genes such as transforming growth factor- β receptor II (*TGF- β R*), growth-promoting genes such as insulinlike growth factor II receptor (*IGF2R*) and *E2Fs*, apoptosis regulators including *Bax*, and mismatch repair genes themselves.² Given that mutations in the *MMR* genes confer significant risk of developing colon and rectal cancer, patients designated with inherited susceptibility must undergo lifelong surveillance to identify development of invasive disease.

Other response-and-repair mechanisms are also in place within the cell, each activated via specific mechanisms and functioning to maintain DNA integrity. One example is the ataxia-telangiectasia gene (*ATM*), which encodes a kinase that senses double-stranded DNA breaks occurring from ionizing radiation. Once activated, *ATM* phosphorylates a variety of proteins, such as p53, checkpoint kinase 2 (*CHK2*), nijmegen breakage syndrome 1 (*NBS1*), and BRCA1, which halts cell cycle progression and enlists DNA repair processes.²³ Patients with ataxia-telangiectasia have a germline mutation of the *ATM* gene and have a syndrome characterized by neuronal degeneration, immunodeficiency, genomic instability, and cancer predisposition. Somatic mutations of the *ATM* gene have been found in various T and B cell malignancies.¹⁰² It is clear that the DNA repair genes play a significant role in protecting cells from malignant change.

Although familial cancer susceptibility is a relatively infrequent cause of malignancy, there are implications in those families afflicted by this predisposition. Genetic testing for highly penetrant genes is available, and guidelines for which individuals should undergo testing have also been standardized.⁹⁸ Unfortunately, interpretation and clinical decisions have not been simplified. With certain tumor suppressor genetic lesions, there are defined therapeutic options, such as surveillance with eventual total proctocolectomy and ileal-pouch reconstruction in patients with FAP or prophylactic bilateral mastectomy in patients carrying BRCA1 or BRCA2 mutations. However, this is not the case for the majority of patients with an inherited predisposition to cancer. As we further our understanding of heritable cancer syndromes, treatment of the genetic defects giving rise to the susceptibility will evolve.

EVADING APOPTOSIS

Corresponding with the processes of growth signaling and inhibition, apoptosis (programmed cell death) is a normal physiologic process crucial for the development and proper function of each organ system. A hallmark of cancer is

the ability of the malignant cells to resist the induction of apoptosis. In fact, many biologic systems have evolved mechanisms by which to inhibit apoptosis. For example, many viruses have implemented methods in which to control programmed cell death. The adenovirus protein E1B55 disrupts p53 function to abate upstream apoptosis signaling; furthermore, proteins E1B19 and E3-14.7, which are a Bcl-2 homologue and a caspase-8 inhibitor, respectively, function to inhibit apoptosis at downstream junctures.¹⁰³ This ability to circumvent programmed cell death provided a distinct growth advantage for the infected cells, prolonging the duration of survival. Investigation of these strategies used by viruses has once again resulted in the identification of the mechanisms by which viruses usurp the apoptotic pathways of cells. These discoveries have been directly related to malignant cells, providing insight into the pathways that are commonly disrupted, resulting in escape from programmed cell death.

When a proapoptotic signal is received by the normal cell, cysteine proteases called caspases orchestrate events, resulting in subsequent morphologic changes such as cell shrinkage, membrane blebbing, and reduction into apoptotic bodies.¹⁰⁴ During this process, certain phospholipids (phosphatidylserine) become exposed externally, thereby triggering clearance via macrophages.¹⁰⁵ Two distinct signaling pathways are responsible for the induction of apoptosis in eukaryotic cells. The intrinsic pathway is p53 dependent and responsive to various intracellular stimuli such as DNA damage, growth factor withdrawal, corticosteroids, oncogene activation, hypoxia, or other stress-induced signals.¹⁰⁶ This pathway is ultimately regulated by the Bcl-2 family of proteins, which contains a member that inhibits apoptosis, Bcl-2, and members that stimulate apoptosis, Bax and Bak.^{107,108} When activated, Bax and Bak heterodimerize and promote pore formation in the outer mitochondrial membrane, with resultant release of cytochrome *c*. A complex then forms, including cytochrome *c*, Apaf-1 (adaptor protein), and procaspase-9 (the so-called apoptosome), which then activates caspase-9 and the subsequent executioner caspases [see Figure 9].¹⁰⁷ Inhibition of apoptosis induced by the activation of the apoptosome is a target of Ras and PI₃ kinase, which contribute to the phosphorylation and inactivation of caspase-9.¹⁰⁹

The extrinsic apoptotic pathway in eukaryotic cells is dependent on the activation of any number of cell death receptors binding to their respective ligands. Included among these are Fas and TNF, which bind the DR4 and DR5 receptors. Activation of these receptors by their respective ligands initiates the caspase pathway mediated by the Fas-associated protein with death domain (FADD) protein.¹¹⁰ For instance, when the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) binds to either DR4 or DR5, trimerization occurs, with conformational change in the intracellular death domain.¹⁰⁶ This conformational change in the intracellular death domain results in the binding of FADD as well as procaspase-8 or -10, inducing autoactivation. Activation of caspase-8 or -10 by this death-induced signaling complex (DISC) propagates its signal through the executioner caspases.¹¹⁰ The intrinsic and extrinsic pathways crosstalk at the induction of Bid into active tBid, stimulating Bax-mediated permeabilization of the mitochondrial membrane and release of cytochrome *c* [see Figure 9].¹¹¹

The executioner caspases include 3, 6, and 7, and they function to cleave and inactivate other cellular proteins vital for cell survival, such as DNA repair enzymes, protein kinases, MDM2, lamin, and gelsolin.¹¹² In addition, the caspase-activated DNase (CAD) is bound to its inhibitor, iCAD, rendering it inactive until apoptosis is triggered. DNA cleavage is induced when iCAD is cleaved by caspases releasing CAD.¹⁰³

Many normal processes use the apoptotic pathways to regulate cell number. For example, contact inhibition from adjacent cells can quickly trigger apoptosis, eliminating excess cells and preventing overgrowth of normal tissues.¹⁰³ Various oncogenes have also been shown to induce the programmed death cascade. Loss of the ability to induce apoptosis provides transformed cells with a growth advantage and results in uncontrolled proliferation.¹⁰³ Loss of p53 function provides transformed cells with this growth advantage.¹¹³ Gain-of-function mutations can also result in a growth advantage via inhibition of apoptosis. Specifically, overexpression of Bcl-2 protects cells from programmed cell death mediated by the intrinsic pathway. Transgenic mice overexpressing Bcl-2 have been shown to be more prone to developing lymphoid tumors than wild-type mice.¹¹⁴ Additionally, the importance of programmed cell death was demonstrated when lymphoid cells from mice with myc deregulation were found to be hyperproliferative, with a concomitant increase in apoptosis. When Bcl-2 was upregulated, inhibiting apoptosis in these cells, hematogenous malignancy developed at a relatively rapid rate.^{114,115} These findings were corroborated by investigations of human follicular B cell lymphomas in which the underlying pathogenesis involved Bcl-2 upregulation. Chromosomal translocation results in Bcl-2 overexpression mediated by the transcriptional enhancer of the immunoglobulin heavy chain (IgH).¹¹⁴

Bcl-2 is a master regulator of apoptosis. Its expression is controlled in a negative feedback loop involving the Bax protein. This member of the Bcl-2 family induces apoptosis by blocking Bcl-2's antiapoptotic effects. Bax^{-/-} mice have been found to have decreased levels of apoptosis and be susceptible to malignant brain tumors in response to inactivation of pRb by tissue-specific SV40 T-antigen activation when compared with wild-type mice.¹¹⁶ Other cellular proteins that interact with core members of the apoptotic pathways include the inhibitor of apoptosis proteins (IAPs). Increased expression of IAPs has been demonstrated to promote tumor resistance in a number of cancer cell lines.¹⁰⁶ Finally, cells can become resistant to the extrinsic apoptosis pathway by loss of death receptor expression. For example, some colon cancers have been shown to lack Fas receptor expression and have presumably gained a selective advantage through the evasion of immune-mediated destruction via cytotoxic lymphocytes.^{107,117} As another hallmark of cancer, resistance to apoptosis is clearly a complex process, and multiple mechanisms have been discovered that allow cells to circumvent this programmed cell death.

In addition to providing a selective growth advantage to transformed cells, resistance to apoptosis can contribute to resistance to treatment. For example, many chemotherapeutics rely on inducing apoptosis, and resistance to apoptosis, as occurs by upregulation of Bcl-2, has been found in a number of cancers and correlates with chemoresistance.^{103,118} Moreover, in various experimental models, loss of Bax or

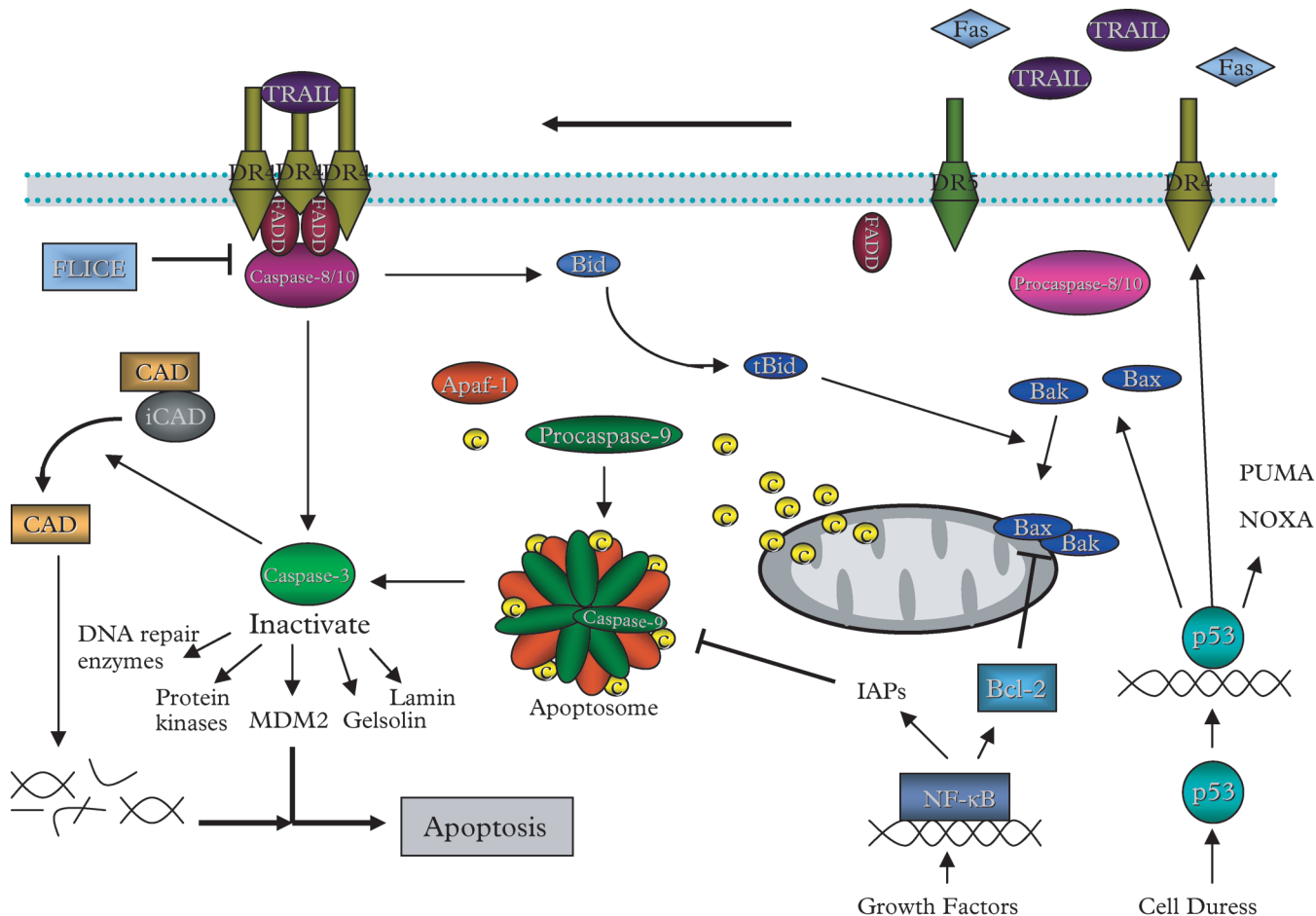


Figure 9 Apoptotic pathway. There are two generally recognized apoptotic pathways in humans. The intrinsic pathway is activated in response to DNA damage, growth factor withdrawal, oncogene activation, hypoxia, or stress; p53 promotes transcription of various proapoptotic genes, such as Bax, Bak, death receptors (DR4, DR5), Puma, and Noxa. These proapoptotic molecules, such as Bax and Bak, then oligomerize to promote outer mitochondrial membrane permeabilization and subsequent release of cytochrome *c*. Once in the cytosol, cytochrome *c* binds Apaf-1, which induces a conformational change and ensuing binding of seven Apaf-1 proteins with seven caspase-9 proteins. The complex formed is called the apoptosome and functions to activate effector caspases (caspase-3, -6, -7). These executioner caspases cleave and inactivate proteins essential for a normal functioning cell such as DNA repair enzymes, protein kinases, MDM2, gelsolin, and lamin. Additionally, the caspase-activated DNase (CAD) is released from its inhibitor (iCAD) and allowed to promote DNA cleavage. The extrinsic pathway occurs when ligands such as TRAIL or Fas bind the death receptors (DR4/5). On binding, receptor trimerization occurs, which then allows binding of FADD and caspase-8 and -10. The activated caspase-8 and -10 subsequently activate the executioner caspases (caspase-3, -6, -7) with similar downstream effects, ultimately resulting in apoptosis. Furthermore, caspase-8 and -10 can activate Bid to its functional form, tBid, which promotes Bax/Bak permeabilization of the outer mitochondrial membrane, demonstrating a crosspoint between the two pathways. Contrasting the proapoptotic molecules are proteins whose capacity include inhibition of these pathways, thus promoting cell survival. Bcl-2 is an important mediator and often exploited by malignant tumors to generate survival advantage. In addition, inhibitors of apoptosis (IAPs) are upregulated by nuclear factor- κ B (NF- κ B) in the presence of growth factors and function to inhibit caspase-3, -7, and -9. FLICE is limited to the ligand-induced pathway and blocks transmission of this signal via inhibiting the caspase-8 binding site on FADD. Apaf-1 = apoptotic protease-activating factor 1; Bak = Bcl-2 antagonist/killer; Bax = Bcl-2-associated x protein; Bid = BH3 interacting domain death agonist; FADD = Fas-associated protein with death domain; FLICE = FADD-like interleukin-1 β -converting enzyme; PUMA = p53 upregulated modulator of apoptosis; TRAIL = tumor necrosis factor-related apoptosis-inducing ligand.

overexpression of Bcl-2 has been shown to contribute to resistance to specific chemotherapeutics.^{118,119} However, not all changes in the apoptotic signaling pathway contribute to chemoresistance. For instance, caspase-8-deficient mice were found to be sensitive to apoptosis induction mediated by chemotherapeutics as well as gamma-irradiation; however,

caspase-9-deficient mice were quite resistant.^{103,120,121} In contrast to demonstrating resistance, investigations of human rectal carcinoma have revealed that tumors exhibiting higher rates of apoptosis have better local control, are associated with tumor regression when given preoperative chemoradiation, and portend a better prognosis.^{107,122} Whether conferring

tumor survival advantage or indicating response to chemotherapeutics and/or radiation, apoptosis is an essential element of tumor pathology, and most, if not all, tumors have acquired antiapoptotic modifications.

Advances in the understanding of apoptosis have resulted in new therapies targeting members of this pathway. For example, the taxane family of chemotherapeutics induces phosphorylation and inactivation of Bcl-2, and proteasome inhibitors target nuclear factor- κ B (NF- κ B), blocking the release of antiapoptotic proteins.¹⁰⁹ Rituximab, a monoclonal antibody directed against CD20, promotes cell death in B lymphocytes and provides a survival advantage to patients with B cell CLL when combined with the conventional chemotherapeutic regimen.¹²³ Rituximab has been shown to induce cell death via complement-mediated cell lysis, antibody-dependent cellular cytotoxicity (ADCC), and induction of apoptosis in cells specifically expressing CD20.¹²⁴ Other pharmaceuticals more specifically targeting apoptosis have also been developed. For instance, preclinical studies with the small molecule inhibitor of antiapoptotic proteins ABT-737 have found lymphoma and small cell lung carcinoma cells to be more sensitive to chemotherapeutics and ionizing radiation.¹²⁵ Although these preliminary in vitro studies are promising, proapoptotic drugs have also moved beyond the preclinical phase. In fact, recombinant TRAIL or antibodies designed to bind the TRAIL receptors DR4 and DR5 are under investigation in at least seven clinical trials.^{106,126} These agents, such as lexatumumab and mapatumumab (Human Genome Sciences), appear to preferentially induce apoptosis in cancer cells while producing minimal toxicity to normal cells.¹⁰⁶ Further evolution in understanding resistance to apoptosis will lead to advancement of novel therapies. Moreover, as we begin to elucidate the mechanisms of apoptosis resistance, accompanying this will be clear discernment of the role of programmed cell death in progression to the malignant phenotype.

ANGIOGENESIS

Blood vessels arise via two mechanisms, vasculogenesis and angiogenesis. Vasculogenesis is defined by a primitive vascular network created during embryonic development from multipotent mesenchymal progenitors, whereas angiogenesis encompasses the process of capillary sprouting from preexisting vessels to produce new vessels.^{127,128} When encouraged via increased proangiogenic factors and/or decreased antiangiogenic factors, proliferating endothelial cells disrupt the underlying basement membrane and migrate into surrounding stroma toward angiogenic stimuli, thus constructing new vessels.⁵¹ The process is completed with stabilization and maturation of the nascent vessels. An event essential for development and occurring in the adult during reproductive cycles or wound healing, this process is also exploited by solid tumors to sustain rapid growth.¹²⁸

Consistent with Folkman and colleagues' postulation years ago of diffusion-limited tumor growth, an expanding tumor is restrained by nutrient and oxygen supply; thus, overproliferation will be balanced with cell death, prohibiting the size attained by the tumor.^{129–131} That this restriction occurs was validated from studies in which tumor fragments were placed in the avascular cornea of rabbits, and subsequent prevention of capillary ingrowth effectively confined tumor size.^{128,129} Although tumors may acquire characteristics of hypoxic

growth, in general, cell function and survival require residence within 100 μ m of a capillary blood vessel.²⁸ Thus, tumors stimulate angiogenesis. The acquisition of neovascularization, or new vessel formation, occurs in a discrete step termed angiogenic switch, in which the previously quiescent vessels undergo angiogenesis, providing the necessary nutrient and oxygen supply and ensuing rapid expansion.¹²⁸

The ability of tumors to induce angiogenesis and the mechanism by which they accomplish this task remain active areas of investigation. Endothelial cells are among the most stable in the body, with only one in 10,000 involved in cell division at any given time (compared with one in seven for intestinal epithelial cells).¹²⁸ Therefore, the tumor-induced angiogenesis provides an interesting model for the study of vascular biology.

VEGF comprises a larger family of growth factors, designated A, B, C, D, and placental growth factor (PlGF). VEGF-A is recognized as the major member involved in tumor angiogenesis and is generally referred to as VEGF.¹³² VEGF binds to VEGF receptor 2 (VEGFR2/KDR/FLK1), which is upregulated in endothelial cells, participating in new blood vessel formation.⁴⁹ Additionally, basic fibroblast growth factor (bFGF or FGF-2) and its counterpart, acidic FGF (aFGF or FGF-1), are also involved in this process. During tumor progression, local hypoxia is induced as a tumor outgrows its blood supply. This relative hypoxic state is a potent inducer of hypoxia-inducible factors 1 α and 2 α (HIF-1 α , HIF-2 α), which are responsible for the upregulation of VEGF.¹³³ Whereas the normal von Hippel-Lindau (VHL) protein contributes to the degradation of the HIF proteins, mutations in the *VHL* gene result in constitutive activation of the HIFs, thereby promoting angiogenesis, red cell production, and glycolysis via the growth factors that are produced (VEGF, PDGF, TGF- α). Tumors that have been shown to have mutations in the *VHL* gene are highly vascular and include renal clear cell carcinomas, cerebellar hemangioblastomas, pheochromocytomas, and retinal angiomas.²³ In fact, the *VHL* gene is inactivated via deletion, mutation, or promoter methylation in up to 80% of sporadic clear cell carcinomas of the kidney.³⁹

Pathways other than VEGF have been shown to contribute to vascular cell proliferation. For example, the angiopoietin-1 tyrosine protein kinase receptor (Tie-2/TEK) is expressed predominantly in vascular endothelium and promotes endothelial proliferation when bound by angiopoietin 1 (Angpt1) or angiopoietin 2 (Angpt2). Interestingly, Angpt1 is a Tie-2 agonist and Angpt2 is a Tie-2 antagonist, but both cooperate with VEGF to promote vessel maturation and integrity.¹²⁷ In addition to their differences in function, the angiopoietin molecules also appear to be expressed at different times in development. Both appear to be integral for the in utero development of blood vessels, but only Angpt2 expression is substantially increased at sites undergoing vascular remodeling in postnatal time points.¹³⁴ Given the importance in vascular remodeling, the effect of Angpt2 antibodies on tumor vessel formation in experimental systems has been investigated. Experiments in xenograft models of epidermoid and colorectal cancer revealed a reduction in endothelial cell and tumor cell proliferation.¹³⁴ Additionally, a complete response was observed in a subset of treated mice, demonstrating the importance of this pathway in some fraction of tumors.¹³⁴ In

fact, other angiogenic factors, such as VEGF, PlGF, FGF-2, and Angpt2, have been shown to be upregulated in a number of cancers, demonstrating the importance of this hallmark of cancer on tumor potentiation.¹³⁴

A common theme in biology is the presence of a negative regulator for every positive regulator. To that end, inhibitors of angiogenesis have also been found. These include proteins induced by stimulators to regulate the angiogenic process, such as vasohibin, angiostatin, endostatin, thrombospondin-1, and tumstatin.^{49,128} Although use of two of these inhibitors, angiostatin and endostatin, demonstrated antitumor effects in mouse studies, these findings were not replicated in human trials.²⁹ Phase I clinical trials demonstrating the safety of the angiogenesis inhibitor thrombospondin-1 have been conducted.¹³⁵ This particular inhibitor is activated by p53 and contributes to angiogenesis inhibition by blocking the function of VEGF and FGF-2; it also induces apoptosis in endothelial cells.¹³⁵ Unfortunately, phase II trials in soft tissue sarcoma, renal cell carcinoma, and metastatic melanoma have not shown antitumor activity.^{136–138}

The Notch transmembrane protein also contributes to neovascularization. The Notch receptors are present on many different cell types and interact with various transmembrane ligands on neighboring cells, influencing the fate of the adjacent cell. Of the five known ligands, Notch-delta-like ligand 4 (Dll4), the expression of which is restricted to endothelial cells, was found to be essential for embryonic vascular development and arteriogenesis.^{49,139,140} Additionally, although intrinsic expression in mature vasculature is low, Dll4 is upregulated in the vasculature of various solid tumors and is increased on cells in response to VEGF-A stimulation.^{50,51,139} VEGF induction of Dll4 appears to provide a negative feedback loop in which VEGF-induced blood vessel sprouting is inhibited, whereas the growth of healthy vessels is encouraged.⁵⁰ Interestingly, although the Dll4-Notch pathway appears to suppress branching and promote vessel maturation, mice with reduced expression of Dll4 demonstrate increased density of haphazardly formed vessels, resulting in poor function.^{51,139} Similarly, in xenograft tumor models, antibodies to Dll4 increased angiogenic activity, but the neovasculature was erratic and dysfunctional, such that tumor growth was inhibited. This effect was also seen when treating tumors resistant to anti-VEGF therapy, whereas in susceptible tumors, the combination of both anti-Dll4 and anti-VEGF had a synergistic, enhanced inhibition of tumor growth.^{49,51,139,140} Furthermore, the effect was limited to the vascular compartment in areas of active vessel formation, sparing the mature vessels.¹⁴⁰ Because of these findings, selective inhibition of Dll4 may prove to be an advantageous target for cancer therapeutics.

It is apparent that tumor cells use a number of strategies to promote blood vessel formation. Initially, tumor growth may be stalled by angiogenic inhibitors. However, acquisition of the ability to promote blood vessel ingrowth may overcome this restriction. Thus, attainment of this hallmark quality allows the tumor to proliferate to a substantial size with disregard for surrounding environment.²⁸ Whether this attribute is acquired early in the course of transformation or later has not been resolved. However, studies appear to favor angiogenesis as an early- to midstage occurrence.²⁸ Investigation of separate transgenic murine models involved in multistep

tumorigenesis has revealed that angiogenesis occurred in midstage lesions prior to rapid clonal expansion or tumor formation.¹²⁸ Conclusions from these studies, in conjunction with other *in vitro* and *in vivo* findings, reveal that the ability to induce blood vessel formation appears to be required for cancer evolution and progression.

Current therapy is directed at inhibiting the interaction of VEGF-A with VEGFR2. Bevacizumab is a humanized monoclonal antibody directed against VEGF, which has been used in combination with conventional chemotherapy for the treatment of metastatic colon and rectal cancer.¹⁴¹ Antiangiogenic therapy has been shown to contribute to a survival advantage in patients with advanced colon and rectal cancer as well as an increase in overall survival in patients with non-small cell lung cancer.¹⁴² Additionally, two small molecule RTK inhibitors, sorafenib and sunitinib, that target the intracellular domain of VEGF R1 and R2 (among other RTKs) were found to improve survival in patients with metastatic renal cell carcinoma in addition to hepatocellular carcinoma.⁴⁹

Although antiangiogenic therapy conceptually has appeared quite promising, the redundancy in the proangiogenic process has proven to be a significant roadblock for the development of new drugs inhibiting tumor angiogenesis. For example, increased expression of a number of receptors, such as bFGF, PlGF, or VEGF, can promote angiogenesis by different mechanisms. Additionally, malignant cells may develop insensitivity to hypoxia via subsequent mutations in p53 or acquire the ability to rapidly form mature vessels in which drugs targeting immature vessels would become ineffective.⁴⁹ A deeper understanding of the elaborate process of angiogenesis is required to develop novel therapeutics capable of inhibiting tumor growth.

LIMITLESS REPLICATIVE POTENTIAL

In the normal state, proliferating cells undergo a defined number of cycles prior to arrest. Evidence favoring this arose from observations that human diploid fibroblasts were unable to immortalize spontaneously and underwent a characteristic number of population doublings.¹⁴³ On infection with the SV40, the cells were driven past their resting condition but only for another discrete number of cycles.¹⁴³ This stimulus eventually resulted in cell crisis, characterized by a balance between cell growth and death. The resultant genomic instability and ensuing rearrangements and chromosomal translocation events resulted in an immortalized state with some frequency (one in 10⁷ cells).^{28,144} The telomerase gene was found to be activated in these immortalized cells, and its activity was absent in cells that underwent arrest or death.¹⁴⁵

Telomerase is responsible for maintaining the integrity of the chromosomal telomere. Telomeres consist of long, repetitive hexameric nucleotide sequences located at the end of chromosomes and are accompanied by a protein complex, termed shelterin, which functions to protect the chromosome from end fusion, misrecognition as a single- or double-stranded breakpoint, and degradation.¹⁴⁴ With each cell division, these repeated sequences shorten secondary to inability to end-replicate. With continued shortening, a critical length is encountered, triggering the DNA damage repair system, and results in replication arrest as the cell is driven to senescence.¹⁴⁴ When premalignant cells replicate, telomeric repeats

at the ends of chromosomes are sequentially shortened until clonal outgrowth results in critically short telomeres signaling the DNA damage repair system to provoke cell cycle arrest and subsequent cell demise.⁹⁹ This drive toward senescence is an effective mechanism to curtail neoplastic growth, and it is therefore understandable why approximately 90% of cancers harbor reactivated telomerase.^{146,147}

Telomerase is a ribonucleoprotein complex composed of a reverse transcriptase protein subunit (hTERT) that uses its RNA template subunit (hTR) to synthesize and elongate telomeric DNA substrates, thus maintaining telomeres despite successive cell cycling.^{146,148} Its relevance in malignancy is suggested from studies evaluating immortalized cell lines that showed upregulation of telomerase activity in nearly all cell lines, whereas investigations of mortal cell lines revealed the absence of telomerase expression.¹⁴⁹ Additionally, biopsies of a variety of tumors revealed the presence of telomerase in the majority of specimens (90%) versus normal somatic tissues, which lacked evidence of the enzyme (except reproductive tissue).¹⁴⁹ Therefore, it appears that acquisition of telomerase activity is another key component in the multistep tumor process.^{143,150,151}

Drugs inhibiting the function of telomerase in cancers have been developed. Potential approaches include gene therapy, immunotherapy, or small molecule inhibitors.¹⁴⁴ One approach currently in phase I clinical trials delivers an enzyme prodrug, which forms a toxin on activation by an adenoviral vector.¹⁴⁴ The transcription of this complex is driven by the hTR promoter, which is frequently overexpressed in various cancers (e.g., ovarian, colon, pancreatic, gastric).¹⁴⁴ Oncolytic gene therapy involving adenoviruses engineered to selectively replicate within cancer cells expressing telomerase by targeting the hTERT promoter has also been investigated in phase I clinical trials.¹⁵² In preclinical studies, the telomerase-specific oncolytic adenovirus OBP-301, or telomelysin, proved efficacious both in vitro in multiple tumor cell types and in vivo using mice xenograft models with various tumors.¹⁵² A primary concern with any of these approaches centers around the presence of hTERT within normal tissues, including embryonic cells, bone marrow stem cells, and colonic crypt epithelial cells. However, these levels have been found to be significantly lower than in the malignant tissue, and no significant adverse effects have been observed thus far.¹⁴⁷

Although gene therapy manipulates tumor genetic material to achieve its response, immunotherapy directs the immune system to confront the neoplastic disease. The presence of telomerase in tumors has been exploited by immunobiologists revealing telomerase to antigen-presenting cells. Once sensitized to telomerase, cytotoxic T cells would become activated, killing any tumor cells expressing the enzyme.¹⁵³ Phase I/II clinical studies have been conducted in patients with metastatic prostate cancer and revealed a safe profile and encouraging initial results.^{144,153} Additionally, another phase I/II study using a slightly modified peptide from telomerase inducing T cell immunity toward the protein was performed on pancreatic cancer patients and is currently under evaluation in two large phase III trials.¹⁴⁷

Small molecule inhibitors are yet another category of anti-telomerase strategies developed. These small molecules cross the plasma membrane, binding to and inhibiting the function of telomerase. With proven inhibitory effects in vitro and, similarly, in vivo with xenograft models, GRN163L has

entered into early-phase trials in refractory or relapsed CLL to determine the safety profile and maximum tolerable dose.^{146,154,155} In addition, GRN163L is under investigation for combination therapy with paclitaxel and carboplatin in advanced-stage non-small cell lung cancer.¹⁴⁴

TISSUE INVASION AND METASTASIS

If discovered early enough, surgical excision of a malignant tumor is frequently curative. However, as tumors progress, the compounding nature of traits and heterogeneous populations of cells will eventually give rise to invasion. Although the nature of the invasive tendency is noteworthy, more remarkable is the fact that malignant cells can disseminate throughout the body, implant at various locations, sustain proliferation at these locations by recruiting assistance from neighboring cells, and potentiate the tumor. Although this is but one of the many attributes of cancer cells, it is irrefutably the most devastating as metastases are responsible for approximately 90% of cancer deaths.²⁸ Unfortunately, the complexities of metastases preclude an adequate understanding of the precise mechanism.

The foundation for obtaining a more encompassing depiction of metastatic pathophysiology has been generated, but this must be built on to fully comprehend the genetic alterations involved. A common consistency incorporates genomic instability of the primary tumor, providing an environment conducive for invasion. Reinforcing this mechanism includes observations that metastatic lesions at the genetic level tend to harbor an increased number of mutations and chromosomal abnormalities when compared with the primary lesion.^{156,157} Thus, the cells that metastasize are selected for their ability to invade and develop in a separate organ system. Similar to the multitude of steps required to generate the malignant primary cohort of cells, several discrete steps are necessary for invasion and metastasis. These include loss of cellular adhesion, promotion of motility, ability to penetrate barrier tissues, survival within the circulation, and extravasation with proliferation at a distant site.¹⁵⁷

Initially, metastatic cells must overcome the restraints of the tumor microenvironment. In particular, tumor cells lose contact with neighboring cells and extracellular matrix by overcoming the contact with cellular adhesion molecules (CAMs) and integrins.²⁸ This transition is accomplished via turning off expression of certain adhesion molecules while upregulating expression of others.¹⁵⁸ One such molecule that has received much attention is E-cadherin. E-cadherin maintains the tight interconnections between cells via interacting with α -, β -, and γ -catenin linking the adhesion molecule to the actin cytoskeleton.¹⁵⁸ In addition to maintaining tight junctions, E-cadherin is responsible for the transmission of antigrowth and other critical cell-cell signals.²⁸ Notably, E-cadherin's ability to mediate adhesion is lost in most human epithelial cancers via deletions, inactivation, protease-induced degradation of extracellular domain, epigenetic silencing (hypermethylation), transcriptional repression, and alterations in associated proteins.²⁸ The importance of cell adhesion has been demonstrated in vitro by the expression of E-cadherin reverting malignant cells to a more benign appearance. Furthermore, studies using transgenic mice have shown loss of E-cadherin as tumors transition from adenoma to invasive carcinoma.¹⁵⁸ From this, one can surmise that by altering cell-cell interactions, a tumor may become liberated

from adjacent inhibitions and seek to progress beyond local expansion into a more invasive phenotype.

Integrins are important mediators of a malignant cell's invasive and metastatic capability. These proteins facilitate an oncogenic phenotype and promote release from the local environment and subsequent incorporation into foreign matrix components that allow successful inhabitation of these distant sites. For instance, $\alpha_6\beta_4$ integrin interacts with oncogenic growth signaling receptors such as EGFR and HER2, whereas $\alpha_3\beta_1$ expression on tumor cells within the circulation were demonstrated to target laminin-5 in the vascular basement membrane of pulmonary metastases.¹⁵⁷ Another integrin, $\alpha_5\beta_3$, also appears to have a predilection toward adhesion of circulating tumor cells to vasculature.¹⁵⁷ The result of this dynamic interchange between a stable, locally restrictive group of adhesive molecules shifting toward an array of integrins promoting invasion and distant colonization is generation of a tumor adapted for metastasis.

In conjunction with alterations in cell-to-matrix binding is the use of matrix proteases by the malignant cell to disrupt the dense network of the basement membrane underlying epithelial and endothelial cell layers. Normally, a physical boundary with vast signaling capabilities and carefully regimented matrix protease activity, the basement membrane and extracellular matrix can be disturbed via release of various mediators such as matrix metalloproteinases (MMPs) from cancerous cells. For example, MMP-2 and MMP-9 have been implicated in cancer cell invasion, whereas MMP-1 appears to be critical for breast cancer spread to the lungs and bone.¹⁵⁹ This upregulation can either occur from the cancer cell itself or from induction of the supporting stroma and inflammatory cells. Regardless, once enlisted to degrade the surrounding matrix structure, the resulting milieu of cleaved peptides can then either facilitate or inhibit migration, proliferation, and invasion.²⁸

Although the molecular mechanisms regulating penetration of endothelial cells, including intravasation and subsequent extravasation, are unclear, these are certainly attributes that appear to be regulated by intercell signaling as well as cell-stroma interactions.¹⁵⁷ Similar to disruption of basement membrane and migration through extracellular matrix, ensuing invasion of endothelial layer to access the circulation is yet another limiting factor overcome by the unstable malignant neoplasm. Intravasation is the critical point at which the tumor cells can then circulate throughout the body, awaiting an opportunity to metastasize to distant organs. However, the overwhelming majority of cells released into the circulation are not able to effectively inhabit distant sites, as evidenced by animal models in which only one in 10,000 entering the circulation resulted in metastatic foci.¹⁵⁹ The question then arises regarding how malignant cells home in on the metastatic site of choice. For example, pulmonary involvement is relatively common with metastatic breast, gastrointestinal, and renal cancer as well as melanoma and sarcoma; liver spread is seen with metastatic foci from gastrointestinal, breast, and lung primary cancer; bone metastases arise from breast, lung, prostate, renal cell, and colorectal cancer.¹⁵⁹ An additional site that portends a dismal prognosis is distant spread to the brain, in which the circulating cancer cells must overcome the restrictions of the blood-brain barrier; this occurs with lung, breast, renal, and colon cancer as well as melanoma.¹⁵⁷

Recognizing that certain cancers have a predilection for certain locations unexplainable solely by circulatory patterns, preference for distant sites may be influenced by the tissue of origin, the developmental history, or even germline mutations. Therefore, permutations occur that are characteristic of the underlying malignancy. For instance, the proclivity of breast cancer spread to the lungs may be a result of increased Cxcr4 expression in the breast cancer cells matched to the lung tissue, which is replete with its respective ligand, Cxcl12.¹⁵⁷ Thus, a selective expansion of cells from an underlying tissue type with distinct genetic anomalies may allow transition from benign growth to invasive disease and consequent metastatic foci with a predilection toward locations conducive to colonization and further proliferation. However, elucidation of a specific mechanism will require continued investigation in both modeled systems and human studies. From this, we can gain a more in-depth understanding of the molecular mechanisms integral to metastasis.

Cancer Therapeutics

Although significant investigation regarding the underlying pathology involved in cancer formation has explicated many of the critical elements of transformation, pharmaceuticals based on these pathways are still being explored. Currently, surgical resection, chemotherapy, and radiation therapy are the modalities used for cancer treatment. Furthermore, the combined efforts of multiple individuals amassed in a multidisciplinary team are focused on the treatment of cancer. For instance, radiologists, medical oncologists, medical physicians, and surgeons (surgical oncologists) are responsible for intervention on behalf of the patient. By combining systemic treatment, either prior to, in conjunction with, or subsequent to local intervention (surgery, radiation), this team of physicians can attempt to render a cure. With improved treatment modalities, this task may be more easily accomplished.

The most widely used chemotherapeutics and radiation therapy trigger cell death by inducing DNA damage, blocking replication and division, and inducing significant cell stress in the hope that these effects will be more harmful to the malignant cells than the host. For instance, agents such as doxorubicin, 5-fluorouracil (5-FU), etoposide, actinomycin D, and irradiation promote DNA damage via various methods, ultimately activating the intrinsic apoptotic pathway and promoting cell death.¹⁰⁶ As discussed above, apoptosis is critical in both regulating overgrowth and determining response to therapy. However, recently, there has been increased attention devoted toward other mechanisms of cell death, such as mitotic catastrophe, autophagy, and necrosis, that occur during administration of therapeutics.¹⁰⁷ Unfortunately, regardless of the mechanism, these conventional options are limited as a result of toxicity and progressive resistance generated by the tumor cells. Therefore, new agents with higher potency and minimal systemic toxicity are necessary to overcome the current burden in cancer therapeutics.

Targeted therapies are now available demonstrating promising results and others in which efficacy is still being determined. For instance, molecules inhibiting RTKs in hematogenous and solid tumors, DNA breakpoint repair inhibitors in BRCA mutated tumors, and TRAIL agonists or antibodies for chemoradiation sensitization are all specific examples of directed therapy. Newer methods of combining

conventional therapy with directed therapy have been effective, such as rituximab with cyclophosphamide, hydroxydoxorubicin, vincristine (Oncovin), and prednisone (CHOP) in non-Hodgkin lymphoma; cetuximab in combination with 5-FU, oxaliplatin, leucovorin, and folic acid (FOLFOX-4) for metastatic colon or rectal cancer; or trastuzumab as an adjunct to doxorubicin/cyclophosphamide and paclitaxel in adjuvant chemotherapy for breast cancer. In addition to these currently implemented chemotherapeutics, we can begin to envision novel tumoristatic and tumoricidal agents that exploit many of the genetic changes attained by the tumor itself, for instance, combinations of specific therapies such as genetic fusion of recombinant TRAIL to tumor-specific CD19 antibodies to selectively navigate the drug to cancerous cells, as has been generated and subsequently used in patient-derived cell lines from acute B-lymphoblastic leukemia and B-CLL.^{106,160} An additional example is revealed by the use of recombinant TRAIL fused with EGFR transduction into mice with intraperitoneal renal cell carcinoma xenografts, resulting in significant tumor load reduction and increased long-term survival.¹⁶¹ These are a few examples illustrating the ingenuity in treatment that can be attained from furthering our understanding of malignant neoplastic disease. As evidenced by the progress encountered within the last decades, continued efforts toward the understanding of transformation from a benign to a malignant neoplasm with implementation of translational research and extensive clinical trials will provide further insight and superior methods to prevent and/or combat its negative sequelae.

Conclusion

In recent years, there has been an explosion in our understanding of the genetics involved in cancer. Through the depiction of requisite attributes necessary for malignant transformation, the model of multistep cancer formation arose.

Among these essential traits are sustained growth stimulation, disregard for inhibitory signals, indefinite replicative capabilities, avoidance of cell death, nascent vessel growth, and aggressive invasion with metastatic potential. As mentioned, the accrual of such traits to generate the multifaceted end product is by no means specifically sequential. Rather, these discrete attributes may be obtained in various points of evolution. Irrespective of the sequence, malignant cells have developed strategies in which to bypass the inborn protective mechanisms. Fortunately, through diligent investigation, clarification of certain aspects of the pathophysiology underlying tumor formation has been achieved. Notably, advancements continue and will allow further expansion of the current tumor model.

The introduction of new technologies such as improved imaging modalities and screening tools has enabled diagnosis of early-stage cancers, generating the possibility of treatment and cure. Additional advances, such as genome sequencing and other cell-specific techniques, such as microarrays with gene expression profiling, contribute toward characterization of candidate genes involved in tumorigenesis and give insight into prognosis through correlative studies. Advances such as these have furthered our understanding of the biology of cancer and resulted in new and improved therapies. We have entered a time period in which more specific and effective means of targeting tumor cells can be accomplished as opposed to generalized cell destruction. These therapies enhance tumor cell death while limiting normal cell toxicity. Targeting ligands, receptors, and downstream signaling molecules is currently implemented and has proven effective in various cancers. As we acquire a better understanding of the underlying mechanisms required for survival of malignant cells, therapies focused on preventive strategy may be feasible in the future.

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28 CANCER IMMUNOLOGY

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At first glance, the ability of the immune system to recognize and eliminate a seemingly near-infinite array of potential viral or bacterial antigens may appear to stand in stark contradistinction to its seeming inability to do the same for foreign cancer antigens. This paradox has motivated intense efforts to understand the interplay between the immune system and cancer. The picture that has emerged from this investigation is that of a complex interaction that begins with a continuous process of immunologic surveillance for new cancer cells that is probably capable of eradicating many potential malignancies before they become clinically evident. Unfortunately, the onset of tumor progression underscores the fact that this equilibrium is often upset by escape mechanisms, through which some nascent tumors may overcome this immunologic control. Moreover, it has become apparent that growing cancers take advantage of a number of potentially immunosuppressive mechanisms to facilitate their growth and metastatic dissemination. Despite the sobering presence of such subversive mechanisms, the likely ability of the immune system to control many potential cancers highlights the optimistic possibility that therapeutic manipulation of this balance between cancer and host may allow us to harness the immune system as an effective means of treating established tumors.

This chapter addresses the following objectives:

1. To understand fundamental aspects of the immunologic response that have specific relevance to the interaction between the immune system and cancer
2. To examine the theorized processes of immunoediting (immune surveillance, immune equilibrium, and immune escape) that appear to characterize the interactive balance between emerging cancers and the host immune system
3. To explore current experimental immunotherapeutic strategies that have demonstrated promise as potentially novel treatments for patients with cancer

The Immunologic Response

Immune function is broadly divisible into two responses. The *innate immune response* can be thought of as an early and slightly indiscriminate process in which foreign antigens activate a number of cell types, such as macrophages and natural killer (NK) cells. Importantly, these cells are capable of direct cell killing but do not recognize specific foreign antigen; rather, they can be triggered by antibodies that bind and coat the surfaces of foreign tumor cells. Alternatively, NK cells are capable of indiscriminately binding to major histocompatibility complex (MHC) class I molecules that are expressed almost ubiquitously on the cell surfaces of most cell types, including cancer cells.

Because of their inability to recognize specific antigens, macrophages and NK cells are incapable of durable memory

against future encounters with antigen. However, as a result of their ability to induce cytolysis, foreign cells are degraded into various peptide fragments, which are then presented on MHC class I and class II proteins on the cell surfaces of macrophages. Thus begins an inflammatory cascade of events that eventually triggers the second type of immune response, known as the *adaptive immune response*. Unlike the innate response, the adaptive response is based on recognition of specific antigenic targets. The combination of peptide and MHC molecule provides a unique three-dimensional configuration that is recognized by a T cell receptor (TCR) expressed on specific T cells. Proper presentation of these foreign peptide antigens on class I MHC proteins activates CD8⁺ cytotoxic T lymphocytes (CTLs), and presentation of these peptide antigens on class II MHC proteins activates CD4⁺ helper T cells. Importantly, for this MHC-TCR stimulatory interaction to be productive, a number of so-called “costimulatory” ligand-receptor interactions must take place. If a full complement of these interactions takes place, CTLs and helper T cells specific for the antigen being presented by the macrophage become activated to recognize and eliminate that target antigen [see Figure 1]. However, if the costimulatory interactions are not fully engaged, these same antigen-specific T cells are rendered anergic, effectively programmed to ignore their cognate antigen [see Figure 2a].

The adaptive immune response may be further subdivided into two responses. The *cellular response* is initiated by this activation of T cell populations. Like NK cells, activated CTLs are capable of directly killing foreign cells; unlike NK cells, their cytolytic mechanisms are directed specifically at cells expressing the antigen peptide against which they have TCR specificity. This circular process of cell killing, antigen presentation, and T cell activation is augmented when antigen is presented to T cells by so-called professional antigen-presenting cells (APCs) such as mature dendritic cells (DCs); mature DCs are particularly effective at mediating T cell activation because of their rich expression of costimulatory ligands. Proinflammatory cytokines such as interleukin-2 (IL-2) and interferon gamma released by DCs and activated T cells further magnify the cellular response, resulting in the profound proliferative expansion of activated T cells. As might be expected, a number of physiologic regulatory controls exist to prevent excessive T cell activation. Activated T cells upregulate expression of a cell surface protein known as CTLA-4, which, when properly engaged, initiates the process of downregulating T cell activity [see Figure 2b]. In addition, populations of regulatory lymphocytes such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) gradually increase after profound T cell activation and serve to downregulate T cell activity. The physiologic importance of these counterregulatory mechanisms is highlighted by genetic conditions where CTLA-4

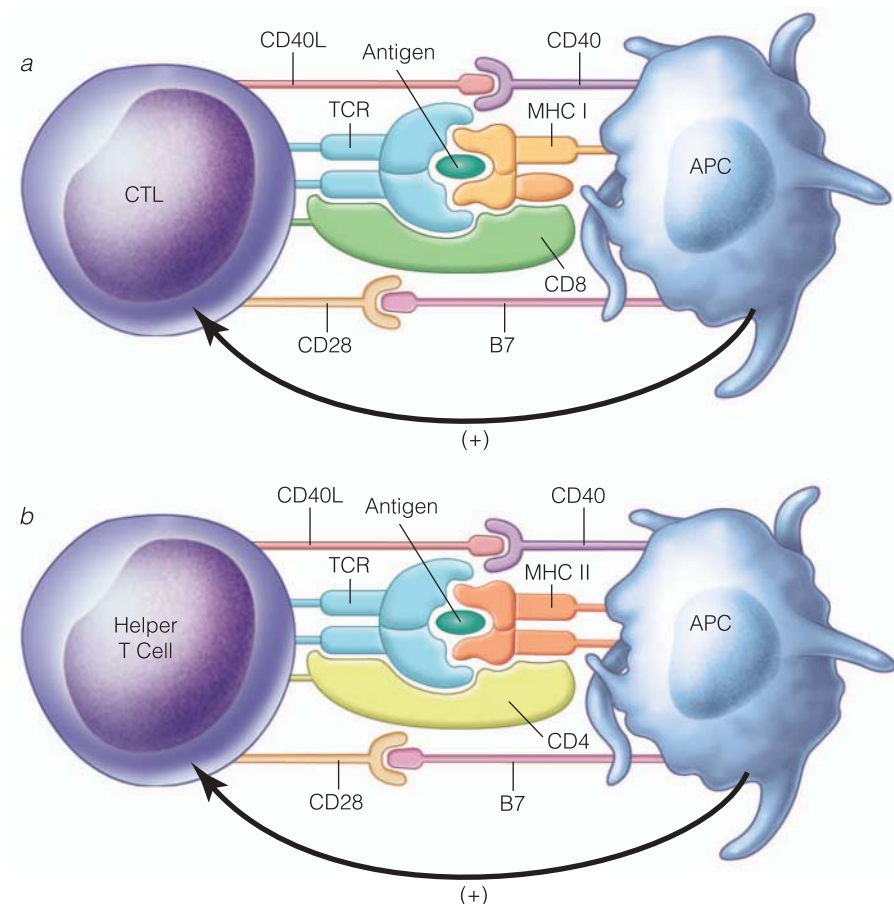


Figure 1 (a) Proper activation of a CD8⁺ cytotoxic T lymphocyte (CTL) by an antigen-presenting cell (APC) requires the interaction of T cell receptor (TCR) with cognate antigen presented on major histocompatibility complex (MHC) class I proteins, as well as a complement of costimulatory molecule interactions. (b) Proper activation of a CD4⁺ T helper cell by APC requires the interaction of TCR with cognate antigen presented on MHC class proteins, as well as a complement of costimulatory molecule interactions.

or Treg activity is congenitally absent or weak; such conditions are typically characterized by exuberant autoimmune processes that are often fatal.

In the case of bacterial or viral infections, the profound proliferative expansion of activated T cells typically results in the clearance of the offending antigen(s). This expansion phase is then followed by a contraction phase, during which counterregulatory mechanisms induce apoptotic involution of activated T cell populations. Importantly, a subset of activated T cells persist and eventually differentiate into memory T cells, which are uniquely capable of prolonged survival (even in the absence of antigen stimulation) and rapid response to later encounters with antigen [see Figure 3].¹

The second component of the adaptive immune response is the *humoral response*, which is characterized by the release of soluble antibodies. Here, CD4⁺ helper T cells promote a lineage of immune cells known as B cells, which are capable of secreting large quantities of immunoglobulin antibodies that possess specificity against tumor antigens in their native, nonprocessed state. As outlined above, recognition and binding of foreign antigens with antibodies promote innate immune responses that are capable of killing cells expressing those antigens.

Immunoediting

Accumulating clinical observations and experimental data suggest that the interaction between cancer and the immune system is far from unidirectional or static. Rather,

there is increasing scientific momentum in favor of the theory of immunoediting.^{2,3} In this theory, it is speculated that emerging cancers elicit immunologic responses that modify the antigenic nature of cancer cells. Through this interaction, it is likely that the immune system is capable of arresting the progression of many cancers; however, it is also apparent that immunologically induced modifications and active counterregulatory mechanisms eventually allow some cancers the ability to overcome immunologic control. The evolutionary nature of immunoediting has been described as consisting of three phases: immune surveillance, immune equilibrium, and immune escape.

IMMUNE SURVEILLANCE

Tumor cells often express MHC class I molecules on their cell surfaces and can therefore evoke cytolytic NK cell responses. This innate immunologic response can result in tumor cell destruction, after which tumor antigens can be presented on macrophages and other APCs to induce cellular and humoral adaptive immune responses. Interestingly, it appears that humoral immune responses comprise a relatively minor proportion of the overall immune response to cancer. However, it is evident that tumor cells can elicit a cellular immune response directed at tumor-specific antigenic targets.

It might be expected that the high frequency of somatic genetic mutations occurring among rapidly dividing cancer cells would generate many novel immunogenic targets capable of recognition by the adaptive immune system.

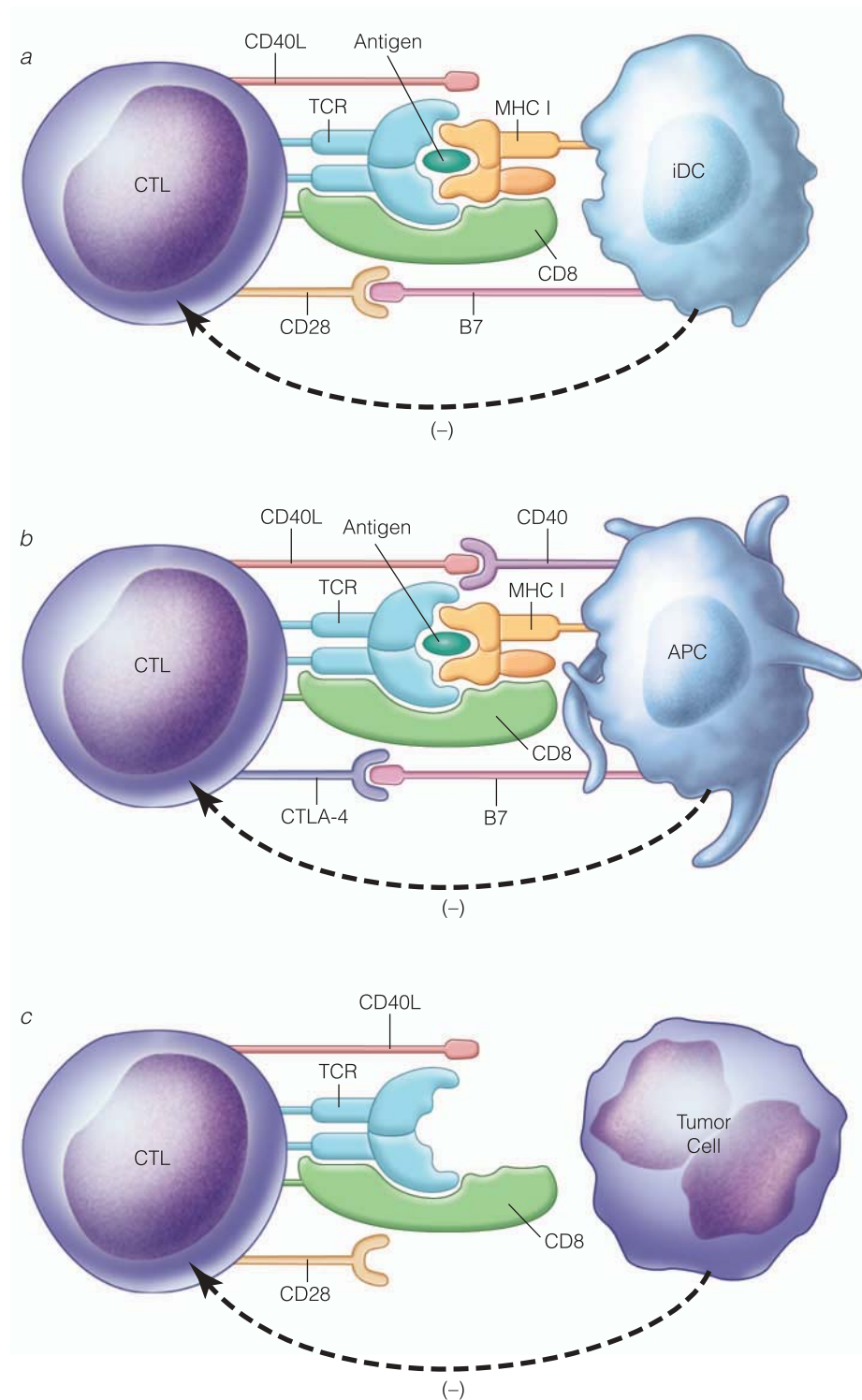


Figure 2 (a) The absence of a full complement of costimulatory interactions, as might be present on an immature dendritic cell (iDC), results in the inhibition of T cells specific for the antigen being presented. (b) Engagement of CTLA-4 (whose expression is upregulated on the cell surfaces of activated T cells) by B7 serves to downregulate T cell function. (c) Downregulated expression of major histocompatibility complex (MHC) proteins on the surfaces of tumor cells is a mechanism of avoiding tumor antigen presentation and activation of potentially tumor-reactive T cells. APC = antigen-presenting cell; CTL = cytotoxic T lymphocyte; TCR = T cell receptor.

Indeed, a number of antigens have been defined with relative specificity for various cancers. Some of these are classifiable as oncoviral proteins, or antigens expressed by virus-associated cancers that are actually encoded within the genomes of oncogenic viruses. Examples of these are Epstein-Barr viral proteins also expressed in nasopharyngeal carcinomas, Burkitt lymphoma, and various lymphoproliferative disorders and human papillomavirus proteins expressed in

cervical carcinomas. Cancer/testis antigens are cancer proteins typically expressed in male gonadal germline cells but not expressed in normal tissues. Because gonadal germline cells lack MHC protein expression, germline cancer/testis antigens are not immunogenic; in contrast, the presence of MHC proteins on cancer cells renders these antigens potential targets for T cell-mediated recognition. An example of this is the cancer/testis antigen NY-ESO-1, which is expressed

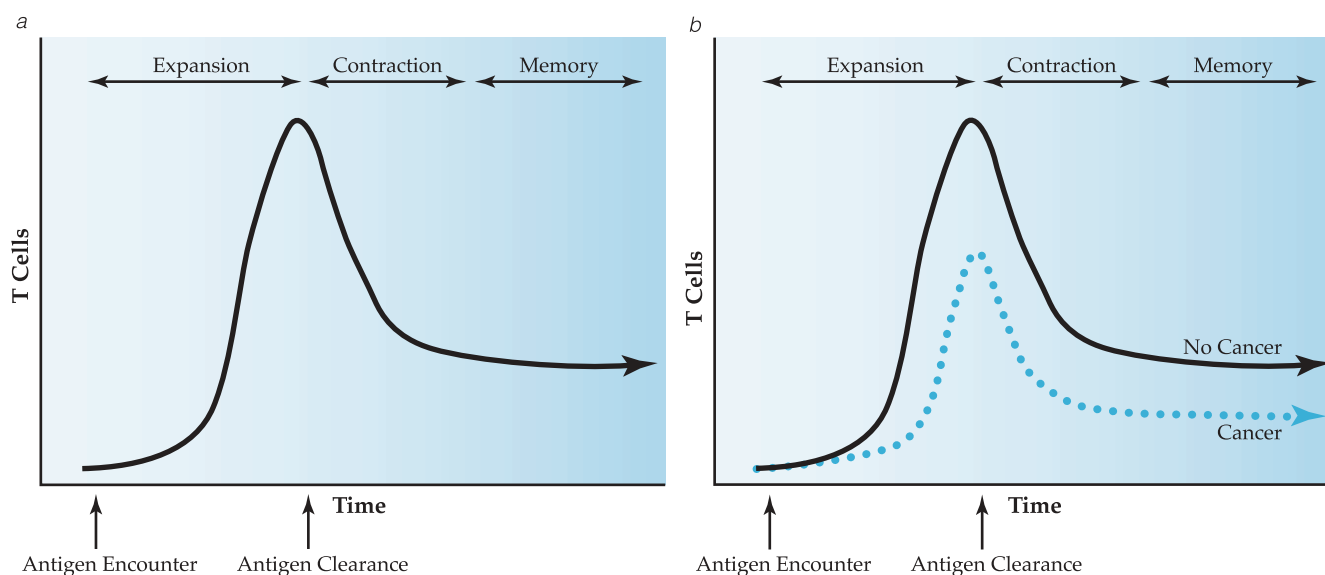


Figure 3 (a) The kinetics of activated T cell homeostasis initiated by antigen encounter follow a predictable pattern of expansion of antigen-specific T cells, followed by antigen clearance and apoptotic contraction of antigen-specific T cells and ultimately resulting in the persistence of antigen-specific memory T cells capable of long-term immunologic protection from future encounters with antigen. (b) The kinetics of activated T cell homeostasis are fundamentally altered in the presence of cancer, with suppressed expansion and potentiated contraction resulting in the induction of smaller populations of memory T cells.

on a number of different malignancies, including melanoma, lung, and breast cancer. In contrast to these, differentiation antigens are normally expressed in differentiated tissues but are also expressed in malignancies derived from those differentiated tissues. For example, MART-1, gp100, and tyrosinase are proteins normally expressed in melanocytes that are also expressed in melanoma cells. In addition to expressing unique tumor antigens, cells that have undergone malignant transformation also overexpress naturally occurring ligands that may permit immune recognition. One example is NKG2D. Typically expressed on NK cells and various subsets of T cells, NKG2D receptors appear capable of recognizing NKG2D ligands that are overexpressed on a broad range of cancers; moreover, initiation of this receptor-ligand interaction appears to be capable of inducing tumor rejection under experimental conditions. Indeed, these interactions may provide a means by which the immune system can differentiate cancer cells from normal cells.

Ultimately, it is likely that some transformed populations of cells will be completely eradicated by these mechanisms of immune surveillance before ever becoming clinically apparent. It is hypothesized that other populations may avoid immune-mediated destruction and enter a phase of variable duration, during which they coexist within the confines of the immune system; this phase has been termed *immune equilibrium*.

IMMUNE EQUILIBRIUM

A number of mechanisms have been highlighted by which nascent tumors may overcome immunologic surveillance and maintain self-preservation. One such mechanism takes advantage of the high frequency of somatic mutations occurring within these rapidly dividing populations of cells. Mutations within genomic sequences encoding antigenic peptides may

produce enough variability in their conformational structures as to render previous antigen-specific T cell responses incapable of mediating immunologic control of these so-called antigen escape variants. This process, referred to as antigenic drift, can initiate a darwinian process of progressively diminishing tumor antigenicity.⁴ Another mechanism involves downregulated MHC class I expression as a means of limiting tumor antigen presentation. In this way, routine detection by NK cells and normal presentation of tumor antigens to the adaptive immune system are restricted, allowing tumors to avoid immune detection [see Figure 2c]. Indeed, a number of malignancies, including breast, gynecologic, colorectal, and renal cancers and melanoma, exhibit little to no MHC expression on their cell surfaces, often as a result of mutations that prevent proper intracellular transport or assembly of MHC subunit proteins.^{5,6}

The interaction between the immune system and evolving cancers does not end when cancer cells acquire a phenotypic alteration that allows them to elude immune detection. Rather, a dynamic equilibrium develops between evolving cancers and the constantly reacting immunologic milieu. With the onset of new mutations, clonal populations of a cancer possessing a particular form of immunologic resistance emerge and proliferate; in time, the ability of the immune system to adaptively respond to these new antigenic features controls their proliferative capacity, and the cycle continues. Indeed, accumulating evidence points to the existence of a process termed *immunosculpting*, in which the various pressures of the immune system gradually modify and shape the evolutionary development of malignancies. The experimental observation that tumors arising in immunodeficient mice are more immunogenic than tumors arising in immunocompetent mice demonstrates that cancer phenotype is, in large part, influenced by the immune system.⁷ Some tumors may

eventually succumb to complete immunologic clearance during this period of immune equilibrium. For others, it is possible that this phase of immune equilibrium may simply represent a period of tumor dormancy between the moment of initial tumorigenesis and the onset of clinically detectable disease progression. In these latter cases, it is evident that a subset of developing cancers acquires some critical phenotypic advantage that confers the ability to overcome the détente of immune equilibrium; this phenomenon has been termed *immune escape*.

IMMUNE ESCAPE

A critical accumulation of mechanisms through which transformed cells can elude immunologic detection and clearance may permit the unimpeded and exponential cellular growth that characterizes cancer. This phenotypic shift may be particularly evident among clonal populations of cancer cells that acquire the ability to undergo systemic dissemination, setting the stage for metastasis. In addition to this ability to elude immune surveillance, mechanisms that actively suppress potential antitumor immunologic responses appear necessary for tumor progression and dissemination. A number of such mechanisms have been elucidated. Tumor cells have been shown to express membrane-bound and soluble forms of Fas ligand (FasL), which can downregulate local immune responsiveness by inducing apoptosis of lymphocytes.^{8,9} In addition, many tumor cells are capable of secreting soluble quantities of inhibitory cytokines, such as transforming growth factor- β (TGF- β) and IL-10, as well as soluble NKG2D ligands and inhibitors, such as indoleamine 2,3-dioxygenase (IDO), which downregulate local NK and T cell responses.^{10–13} This profile of chemoattractants within the tumor microenvironment appears to promote a unique pattern of inflammatory conditions that paradoxically promotes tumor progression by favoring the leukocytic infiltration of tumor-associated macrophages (TAMs)^{14,15} and immature dendritic cells (iDCs).¹⁶ Although technically capable of presenting antigen to T cells, the absence of a full complement of costimulatory molecules expressed on iDCs promotes the abortive differentiation of naive T cells toward anergy and tolerance (unlike mature DCs, which promote T cell activation) [see Figure 2a]. The ability of TAMs to secrete inhibitory cytokines and downregulate T cell function also promotes tumor progression. Productive T cell activation is also suppressed by CD4⁺CD25⁺FoxP3⁺ Tregs and MDSCs, which are also found in accumulated quantities within the tumor microenvironment.^{17–19} As a result of these actively suppressive influences, the ability to generate an effective adaptive immune response against tumor antigens is thwarted, and tumor progression is facilitated.

The influence of cancer on T cell function is also exemplified in the altered kinetics of activated T cell homeostasis. Antigen-driven T cell proliferative expansion is weakened in the presence of cancer; moreover, apoptotic contraction is potentiated, resulting in the induction of smaller populations of memory T cells [see Figure 3].²⁰

Clinical Strategies in Cancer Immunotherapy

The ability of the immune system to initiate responses against tumor antigens and the ability to experimentally

promote immune-mediated killing of tumor cells *in vitro* give hope to the possibility that therapeutic interventions to augment the immune response could result in effective tumor control. Conceptually, the precise antigenic specificity of the immune response (by which unwanted side effects and collateral toxicities could be avoided) and the ability to generate durable immunologic memory (through which future cancer recurrences could be prevented) make immunotherapy an ideal form of cancer-directed treatment. To date, a number of strategies have been employed in an effort to actualize these theoretical benefits; although these have generally been met with limited successes, some examples of promise have emerged.

One approach has been to administer systemic or intratumoral doses of a general immunostimulant. Most commonly, stimulatory cytokines such as IL-2 or interferon alfa have been administered, but immunologic adjuvants such as bacillus Calmette-Guérin (BCG) are used for treating and preventing early bladder cancers. Clinical trials using IL-2 and interferon alfa for patients with high-risk melanoma have identified modest efficacy for patients with advanced melanoma and renal cell carcinoma.^{21–24} However, the incremental benefit and the prevalence of significant treatment-related toxicities have tempered enthusiasm for this treatment. A preliminary single-institution experience using systemic interferon alfa administered in an adjuvant setting for patients with resected pancreas adenocarcinoma has shown promising efficacy; the results await multicenter confirmation.^{25,26}

The ability of vaccine-based therapies to prevent a broad array of infectious diseases has generated great enthusiasm for cancer immunotherapy. Melanoma trials have been undertaken to study the potential efficacy of tumor antigen vaccines in engendering productive immune responses against melanoma cells.^{27,28} Although evidence for modest clinical benefit exists, it is apparent that vaccine-based efforts will likely require additional adjuncts to improve the immunogenicity of injected vaccines (immunostimulatory cytokines, loading of tumor antigens onto efficient APCs such as DCs, or tumor cells expressing costimulatory molecules or strongly antigenic epitopes) to augment their clinical efficacy.^{29–31}

Antibody-based cancer therapies have shown little promise in clinical investigation. As stated earlier, humoral responses to tumor cells do not appear to contribute significantly to the host response to cancer. However, systemic administration of blocking or depleting antibodies designed to interfere with the function of suppressive lymphocyte populations have shown some promise. To date, anti-CD25 monoclonal antibodies complexed to toxins designed to eliminate CD4⁺CD25⁺ Tregs have exhibited little benefit in augmenting immune responses against cancer.³² However, recent clinical trials using blocking antibodies against CTLA-4 (intended to prevent the autoregulatory suppression of activated T cells mediated by CTLA-4 engagement) have resulted in cases of impressive and durable tumor regression or control.^{33–35}

Adoptive cell-based strategies have been a particularly promising avenue of clinical investigation. In this approach, lymphocyte populations with potential reactivity against tumor antigens are harvested from patients with cancer, expanded *ex vivo*, and transferred in large quantities back into patients in the hope of inducing immunologic tumor

regression.³⁶ Recent efforts to harvest tumor-reactive T cell populations from tumor-infiltrating lymphocytes (TILs) have shown promise. In these strategies, TILs are harvested from resected tumors and activated and expanded in vitro using TCR stimulation and exogenous IL-2. Adoptive transfer of these activated populations of cells has resulted in significant and prolonged responses in a subset of patients with advanced melanoma.^{37,38} Depletion of host lymphocytes prior to adoptive transfer (using myeloablative chemotherapeutic agents or

lymphoid irradiation) appears to further enhance the efficacy of adoptive immunotherapy; it has been speculated that this improvement may be from enhanced in vivo expansion of tumor-reactive lymphocytes or from the elimination of potentially suppressive lymphocytes populations (e.g., Tregs) that could weaken the ability of adoptively transferred T cells to recognize and clear tumor cells.^{39,40}

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Figures 1 through 3 Christine Kenney

29 PRINCIPLES OF CANCER TREATMENT

David F. Schneider, MD, MS, and Margo Shoup, MD, FACS

Multidisciplinary Care and the Surgical Oncologist

A multidisciplinary team approach to caring for cancer patients has become the benchmark in the modern era.^{1,2} This team involves oncologists, radiologists, pathologists, radiation oncologists, social workers, physical therapists, pharmacists, and surgeons. For most solid tumors, the best chance for a cure remains a complete surgical resection. The surgeon also plays a role in other phases of care, including obtaining tissue for a diagnosis, placing ports for chemotherapy, and palliation. In other words, the surgeon's role extends beyond cases of localized disease. For these reasons, the surgeon should play a prominent role on any multidisciplinary oncology team.² The following sections provide an overview of the various phases of caring for cancer patients along with the myriad modern treatment modalities.

Tumor Nomenclature

The broadest classification of neoplasms is the division between benign and malignant tumors. Benign tumors are designated by the *-oma* suffix and lack the normal cell cycle or growth regulation but do not invade through tissue layers or into surrounding organs. Malignant tumors, or cancers, do invade adjacent tissue layers. The tissue of origin determines the nomenclature of malignant tumors. Carcinomas are malignancies derived from epithelial tissues, whereas malignant neoplasms arising from mesenchymal tissues are termed sarcomas. Histology further subdivides cancers. Tumors cells that form glandlike structures are adenocarcinomas and include the most common cancers of the gastrointestinal tract and breast. When tumor cells organize as a squamous epithelium, they are called squamous cell carcinomas. Blastomas originate from embryonic tissues.³

TUMOR GRADE

The degree of cellular differentiation among cancer cells determines the tumor's grade. Many cancers have separate pathologic grading systems incorporating such factors as nuclear pleomorphism, necrosis, nucleus-to-cytoplasm ratio, necrosis, and number of mitoses. In general, a cancer's stage holds more prognostic value than its grade, but in certain cancers, such as sarcomas, the grade holds more significance. Finally, cancers are termed undifferentiated when the tissue of origin or histologic type cannot be determined, and this usually portends a poor prognosis.

TUMOR STAGE

In most cancers, the tumor stage usually determines a cancer's treatment and prognosis. Clinical staging relies on

noninvasive testing such as imaging studies or physical examination findings, whereas pathologic staging depends on histologic findings in resected tumor specimens. Pathologic staging is more reliable than clinical staging because it evaluates microscopic spread of disease that imaging cannot determine.

The American Joint Committee on Cancer (AJCC) has provided the most widely used staging system.⁴ It is based on the TNM classification, with *T* referring to tumor size, *N* referring to regional lymph nodes, and *M* referring to distant metastatic spread of cancer. *T* stage ranges from 0 to 4, with higher numbers referring to larger size or increasing level of invasion. Regional lymph nodes are classified from N0 to N3, with increasing number of involved lymph nodes. M0 indicates no metastatic disease, whereas M1 and M2 denote various levels of distant metastatic spread. Various combinations of *T*, *N*, and *M* categories comprise stages from 0 to IV, with higher stages representing increasingly widespread cancer and poorer prognosis.^{3,4}

Initial Evaluation of Cancer Patients

TISSUE DIAGNOSIS

As with all disease processes, the initial evaluation of cancer patients should begin with a complete history and physical examination. The surgeon's involvement often begins with obtaining tissue for diagnosis to complete the pathologic staging. There are several types of tissue biopsy, each uniquely suited for different types of cancer or location.

Regardless of the biopsy technique, the surgeon must follow certain principles to ensure a good oncologic result. First, achieving good hemostasis is imperative; hematomas make subsequent dissection more difficult and can allow tumor cells to spread along the plane of the hematoma. Second, any needle tract or incision should be oriented such that it can be included in subsequent resection of the entire specimen.⁵

Fine-Needle Aspiration Biopsy

Palpable tumors close to the skin surface can be easily sampled with a thin needle using local anesthesia in the office setting. Lymph nodes, thyroid nodules, and breast masses are well suited for this biopsy technique. Even masses that are too small or too deep to palpate can be evaluated with fine-needle aspiration biopsy (FNAB) by using computed tomography or ultrasound guidance. The main limitation of FNAB is that it only provides cells for evaluation by a cytopathologist; it does not provide histologic or architectural information about the tumor. Therefore, it will not differentiate between invasive or in situ cancers. Given that FNAB

uses a thin needle, sampling errors may occur in larger tumors.

Core-Needle Biopsy

Core-needle biopsy can also be done in the office setting under local anesthesia. It uses a larger needle that excises a thin cylinder of tissue, allowing the pathologist to interpret more histologic information from the tissue architecture. This technique is often used to evaluate breast, prostate, and liver lesions and sometimes sarcoma.⁵

Excisional Biopsy

Excisional biopsy removes the entire gross tumor. This technique is employed when a larger tissue sample is needed for accurate diagnosis or grading. The entire lesion is excised without removing adjacent structures. If this is not possible, then incisional biopsy is appropriate.⁵

Incisional Biopsy

Incisional biopsy removes a portion of a tumor, but it is not completely excised. This technique is appropriate when excisional biopsy is not possible because of involvement of adjacent organs or when the tumor is too large for complete excision. For example, extremity sarcomas that are greater than 5 cm should undergo incisional rather than excisional biopsy. In this case, the incision should be made longitudinally such that the entire scar can be removed during subsequent resection.⁵

Staging Operations

Less common in the modern era, surgeons are sometimes asked to perform operations to stage Hodgkin disease. In lung cancer and laryngeal cancer, the operation itself determines the stage. For example, in lung cancer, lymph nodes from each mediastinal station are sampled at the time of lobectomy or pneumonectomy to determine the tumor's stage.⁶ Laparoscopy is often performed as the initial maneuver in operations for gallbladder, gastric, or pancreatic cancer to determine the extent of disease within the abdomen.^{7,8} The presence of widespread tumor deposits or liver metastases can save patients from a more morbid laparotomy when there is little chance for cure.⁸

Principles of Surgical Therapy

For most solid tumors, the best chance of a cure remains a complete surgical resection. Operating for a cure, however, is not the only reason to operate on cancer patients. Staging, cytoreduction, or palliation may also be achieved with surgical therapy. The surgeon, in conjunction with the multidisciplinary team and the patient, should clarify the purpose of any operation before it is undertaken.²

CURATIVE SURGERY

Operating for a cure usually refers to removing the entire primary tumor with a margin of normal tissue to prevent local recurrence. Each tumor type requires a different distance of disease-free margins to minimize the chance for local recurrence. Margins are classified based on their degree of macroscopic or microscopic disease. An R0 resection is the most oncologically desirable margin, with no gross or

histologic evidence of disease. An R1 resection is defined as no residual gross disease but positive microscopic residual disease, whereas an R2 resection leaves residual gross disease after surgery and should prompt further resection if the goal of surgery is to cure.⁴

To achieve an R0 resection, often adjacent organs are resected with the tumor, in an en bloc resection. Any fixation or adherence to adjacent tissues or organs is considered malignant in nature; therefore, en bloc resection should be performed. In these situations, the surgeon should balance the extent of resection with the patient's functional status. In many cancers, modern data have demonstrated that a more limited approach is oncologically equivalent but functionally and/or cosmetically desirable. Examples include breast conservation, sphincter-sparing rectal surgery, or limb-sparing surgery for sarcoma.⁹

Multidisciplinary Care in Curative Surgical Therapy

A balance between extent of resection and functional or cosmetic outcome can also be modified by knowledge of other modalities that might be employed to achieve a cure. For example, postoperative radiation therapy has allowed breast conservation therapy and equivalent oncologic results. In this example, the use of postoperative radiation does not eliminate the need for adequate surgical margins but does allow for a more cosmetic result. When chemotherapy or radiation is used after the primary treatment (surgical therapy), it is referred to as an adjuvant therapy.²

When these other modalities are used in the preoperative setting, they are called neoadjuvant therapies, and this has revolutionized the care of certain tumors, such as esophageal and rectal cancers or liver metastases from colorectal cancer, because neoadjuvant therapy can potentially convert unresectable tumors into resectable ones, making a complete cure possible. Neoadjuvant therapy can also limit the extent of surgery that would otherwise have been necessary to achieve negative margins.^{2,10}

Regional Lymph Nodes

For most solid tumors, the regional lymph node basin is the first and most prevalent site of metastasis. The status of the regional lymph node basin provides staging information and can extend local control of tumor. For this reason, regional lymph node dissection or sampling is often performed at the time of curative resection.

Elective lymph node dissection refers to removal of clinically negative lymph nodes in the same setting as resection of the primary tumor. This is often part of curative surgery for most gastrointestinal, urologic, and head and neck malignancies. Performing a lymphadenectomy only when a patient has clinically positive lymph nodes is referred to as a therapeutic lymph node dissection.¹¹ Performing a lymph node dissection on clinically negative nodes obviously adds morbidity. For breast cancers and melanoma, the adoption of sentinel lymph node biopsy has allowed the ability to stage regional lymph nodes and select patients who would benefit from a complete lymph node dissection.¹² In this technique, radioactive tracers and/or dye are injected around the primary tumor and then mapped to regional lymph node basins. The first, or "sentinel," lymph node to take up the dye or tracer is then evaluated for the presence of cancer cells, guiding further lymph node dissection.^{5,13}

PALLIATIVE SURGERY

Patients whose cancer is unresectable often suffer from pain, bleeding, obstruction, malnutrition, or infection. The surgeon can relieve these problems, improving quality of remaining life.¹⁴ Palliative surgery includes bypass operations, stents, partial resection, and feeding tubes.¹⁵ Not all patients with advanced cancer are candidates for palliative surgery. It is very difficult to make asymptomatic patients feel any better. Furthermore, the surgeon must balance any potential benefit of a palliative procedure with the potential morbidity.¹⁶ Palliation is another area that should be considered a multidisciplinary approach as there are often medical or minimally invasive approaches that might benefit patients whose operative risk is unacceptably high. Radiation and chemotherapy can also be used in a palliative fashion.^{12,15}

PROPHYLACTIC SURGERY

Although genetic lesions play a role in the development of all cancers, the advent of genetic testing has focused much attention on heritable forms of cancer. Highly penetrant mutations in specific genes are associated with familial syndromes such as the Li-Fraumeni syndrome (breast cancer), multiple endocrine neoplasia (MEN) types IIA and IIB (medullary thyroid cancer), and hereditary nonpolyposis colorectal cancer (HNPCC).¹⁷ In addition, patients with chronic inflammatory conditions are known to be at high risk for malignant transformation. Surgical therapy is directed at removing the organ at risk once such genetic mutations or inflammatory conditions are identified. As with any surgery, the risk of any prophylactic surgery and its associated morbidities must be weighed against any potential benefit. Alternatives to surgery will involve a lifetime of close surveillance of the organ at risk. The surgical oncologist therefore must have a thorough understanding of genetics and the inherited risk for each particular inherited syndrome; a detailed discussion of the risks and benefits of prophylactic surgery should be undertaken with each patient.¹⁷ Table 1 contains inherited cancer syndromes for which prophylactic surgeries are performed.

CYTOREDUCTIVE SURGERY

Certain cancers tend to be widespread throughout the abdomen at the time of diagnosis. In these situations, there is benefit to removing as much of the tumor deposits as possible (i.e., “debulking”). This technique is often combined with radiation, chemotherapy, or intracavitary chemotherapy.¹⁸ In other cases, reducing the tumor burden improves the effectiveness of chemotherapy or reduces symptoms. Examples of cancers where a cytoreductive approach has been shown to be helpful include ovarian, peritoneal mesothelioma, neuroendocrine tumors, and pseudomyxoma peritonei.¹⁹

Principles of Cancer Pharmacology

GUIDING CONCEPTS

Tumors arise from our own native tissues. Therefore, pharmacologic targeting of cancer cells is difficult, and most chemotherapeutic agents have a very narrow therapeutic index. The major difference between neoplastic and nonneoplastic cells is the rate of cell division. Many drugs exploit this

fact and kill actively proliferating cells or are classified as cell cycle specific. In contrast, other drugs can kill cells that are not actively dividing at the time of exposure, and these agents are called cell cycle nonspecific. To achieve maximal cell killing, most chemotherapy protocols use combination therapy with multiple agents, each with a different mechanism of action. Only a fraction of cancer cells, the growth fraction, will be susceptible to chemotherapy at any given time. Therefore, most chemotherapy regimens rely on repeated dosing for maximal cell killing. Because of the narrow therapeutic index, the dosing interval usually depends on the regrowth and repair of normal tissues.³

Chemotherapy failures have multiple etiologies, including excessive tumor burden and inadequate drug delivery to the tumor. Drug resistance also plays a large role in chemotherapy failure. Although several mechanisms of tumor resistance are known, the multidrug resistance (*MDR*) gene encodes a protein that actively pumps many chemotherapy drugs out of tumor cells.²⁰ Given that genetic mutation is the underlying cause of all cancer, continued mutation may alter the protein targets of chemotherapy agents. Similarly, overproduction of a target protein can overwhelm the drug dose. Mutations that confer increased capability of DNA repair can cause failure of DNA alkylating or binding agents. Oncologists can overcome tumor resistance with combination chemotherapy. Prompt recognition of failure and altering the regimen can also prevent overt failure.

Certain toxicities are common to almost all chemotherapeutic agents because they target rapidly dividing cells, including nonneoplastic cells of the bone marrow or gastrointestinal tract. Therefore, common toxicities include diarrhea, nausea, vomiting, mucositis, alopecia, and myelosuppression.³

CLASSES OF CHEMOTHERAPY AGENTS

DNA Alkylating and Cross-linking Agents

These agents work by transferring alkyl groups to DNA, resulting in DNA strand breaks, cross-linking of DNA, or miscoding of DNA strands during cell division. Examples of agents in this class are nitrosoureas (carmustine, semustine, lomustine), cyclophosphamide, chlorambucil, dacarbazine, and procarbazine. They are effective for hematologic malignancies in addition to breast, lung, and endometrial cancers and melanoma. The most common adverse reactions are myelosuppression and hemorrhagic cystitis.¹²

Platinum Analogues

Similar to the DNA alkylating agents, platinum analogues bind DNA, forming intra- and interstrand cross-links that inhibit DNA synthesis and transcription. Examples include cisplatin, carboplatin, and oxaliplatin. Toxicities with these agents include myelosuppression, hemolytic-uremic syndrome, electrolyte abnormalities, and neuropathy. Platinum agents are used to treat colon, rectal, breast, gastric, esophagus, testicular, gynecologic, and head and neck cancers.^{3,21}

Antimetabolites

These drugs are analogues of nucleic acids or their precursors, and they work by becoming incorporated into the cell's nucleic acids. Antimetabolites can also bind the enzymes

Table 1 Prophylactic Surgery for Inherited Cancer Syndromes

Syndrome	Genetic Defect	Cancer(s)	Inheritance Pattern	Prophylactic Surgery(ies)	Associated Abnormalities
Hereditary breast cancer	<i>BRCA1</i> <i>BRCA2</i>	Breast, ovarian	Autosomal dominant	Bilateral mastectomy/ nipple-sparing mastectomy, bilateral salpingo-oophorectomy	Male breast cancer, prostate and pancreatic cancers
Li-Fraumeni syndrome	Germline <i>p53</i> mutation	Breast	Autosomal dominant	Bilateral mastectomy/ nipple-sparing mastectomy	Sarcomas, brain tumors, acute leukemias, adrenal cortical carcinomas
Cowden disease (multiple hamartoma syndrome)	Germline <i>PTEN</i> mutation	Breast, thyroid	Autosomal dominant	Bilateral mastectomy/ nipple-sparing mastectomy	Skin/mucous membrane hamartomas, endometrial cancer, renal cancers, Lhermitte-Duclos disease, glycogenic acanthosis of the esophagus
Familial adenomatous polyposis (FAP)	Germline mutation in <i>APC</i> gene	Colorectal	Autosomal dominant	Total proctocolectomy with permanent ileostomy, total colectomy with ileorectal anastomosis + surveillance, total proctocolectomy with ileal pouch anal anastomosis	Desmoids, duodenal, periampullary adenomas
Hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome)	Germline mutation in DNA mismatch repair (MMR) genes (<i>hMLH1</i> , <i>hMSH2</i> , <i>hMSH6</i> , and <i>PMS2</i>) or microsatellite instability (MSI)	Colorectal	Autosomal dominant	Segmental colectomy + surveillance, total colectomy with ileorectal anastomosis + surveillance, total proctocolectomy with ileal pouch anastomosis	Endometrial, ovarian, small bowel, ureter, or renal pelvis cancers
Multiple endocrine neoplasia (MEN) Type IIA	Germline mutation in <i>RET</i> proto-oncogene	Medullary thyroid	Autosomal dominant	Total thyroidectomy, central cervical lymph node dissection, subtotal parathyroidectomy with autotransplantation	Pheochromocytoma, hyperparathyroidism, cutaneous lichen amyloidosis, Hirschsprung disease
Type IIB	Germline mutation in <i>RET</i> proto-oncogene	Medullary thyroid	Autosomal dominant	Total thyroidectomy, central cervical lymph node dissection	Pheochromocytoma, neural gangliomas, megacolon, skeletal abnormalities, enlarged peripheral nerves
Familial medullary thyroid cancer (FMTC)	Germline mutation in <i>RET</i> proto-oncogene	Medullary thyroid	Autosomal dominant	Total thyroidectomy, central cervical lymph node dissection	

involved in nucleic acid production, thereby halting the cell's synthetic or dividing capability. Examples include methotrexate, mercaptopurine, thioguanine, and cytarabine. These drugs are used primarily for hematologic malignancies and colorectal cancers.²² Fluorouracil is an antimetabolite used for gastrointestinal malignancies. Skin rashes, myelosuppression, neuropathy, nausea, and vomiting are among the toxicities.³

Antimicrotubule Agents

This class of drugs includes plant-derived compounds that bind tubulins, obstructing the assembly of microtubules in the mitotic spindle and resulting in mitotic arrest in metaphase. Vinca alkaloids such as vinblastine and vincristine

inhibit tubulin polymerization and are used for hematologic malignancies and breast and lung cancers. Taxanes (paclitaxel and docetaxel) block tubulin depolymerization and are used to treat ovarian, breast, lung, and bladder cancers.²³ These drugs cause myelosuppression, weakness, peripheral neuropathy, and hypersensitivity reactions.

Topoisomerase Inhibitors

Two topoisomerase enzymes (I and II) function to maintain DNA strands, making transient single- or double-strand nicks in DNA to correct any alterations in topology that occur during replication or transcription. Inhibition of the topoisomerase enzyme(s) causes structural DNA damage. They are cell cycle specific, exerting their effects on rapidly

proliferating cells.²⁴ These drugs are used to treat hematologic malignancies and lung, prostate, bladder, colorectal, and testicular cancers. Etoposide, teniposide, and topotecan cause myelosuppression and diarrhea.

Antibiotics

Antibiotics are drugs derived from fungus that interfere with nucleic acid synthesis by intercalating DNA, blocking synthesis, and inducing strand breakage. Examples include doxorubicin, which causes cardiomyopathy. Bleomycin, used for testicular cancer, causes interstitial pulmonary fibrosis.¹²

Agents Targeting Epidermal Growth Factor Receptors

This class of agents exemplifies targeted therapy because they are used in patients whose cancer over-expresses a particular epidermal growth factor receptor (EGFR).^{3,25} Molecular diagnostics allow testing for overexpression or mutation of native receptors; antibodies or other small molecules can then be administered to block these receptors.

Trastuzumab is an IgG antibody that binds the extracellular domain of the Her-2/neu receptor, an EGFR with an intracellular tyrosine kinase. Breast cancers that express this Her-2/neu receptor exhibit increased proliferation, metastatic potential, and resistance to other therapeutic agents. Binding of trastuzumab to the Her-2/neu receptor diminishes downstream signaling, allowing cytotoxic chemotherapies to become effective.^{25,26}

Cetuximab is another antibody that binds EGFR, blocking the signaling events that lead to proliferation. It also enhances the effect of cytotoxic chemotherapies, blocks angiogenesis, and promotes apoptosis. If, however, a tumor has a K-ras mutation, it will not respond to cetuximab. This agent is used primarily in advanced colorectal cancer.

Bevacizumab

The vascular endothelial growth factor (VEGF) promotes angiogenesis and has become an anticancer target because tumors must develop their own blood supply for survival. Although it does not require a specific diagnostic test, many also consider bevacizumab a targeted therapy because it is a monoclonal antibody specific to the VEGF mechanism.³

Imatinib Mesylate

Imatinib is an adenosine-triphosphate inhibitor of *bcr-abl*, platelet-derived growth factor receptor, and *c-kit* tyrosine kinases. This drug is a small-molecule targeted therapy that is highly effective against gastrointestinal stromal tumors and Philadelphia chromosome-positive chronic myelogenous leukemia.²⁷

Hormonal Therapy

Hormones control the growth and differentiation of certain tissues. Modulation of the effect of sex hormones on prostate, uterus, and breast cancers has become a primary treatment modality or part of palliative care.

Selective estrogen receptor modulators This class of drugs mimic the structure of estrogen and binds to the estrogen-receptor complex. The effect varies depending on

the target tissue because these drugs can act as proestrogenic in some tissues while inhibiting the effect of estrogen in others. Tamoxifen is the most well-known example that is used to treat estrogen receptor-positive breast cancers or in women who are at high risk for developing breast cancer.²⁸ Because tamoxifen acts like estrogen in the uterus and blood vessels, patients taking tamoxifen are at higher risk for uterine cancer and deep vein thrombosis.¹²

Aromatase inhibitors The enzyme aromatase converts adrenal steroids to estrogen in fat cells. Therefore, postmenopausal women still produce some estrogen even though their ovaries are inactive. Anastrozole, a selective aromatase inhibitor, can treat metastatic breast cancer or be an adjuvant therapy in postmenopausal women whose breast tumors are positive for estrogen or progesterone receptors²⁹; anastrozole can also be given for prevention in high-risk patients.

Immunotherapy

Cancer cells evade immune response by a variety of mechanisms. Newer therapies either augment natural immune responses to tumor cells or train the immune system to attack tumor cells that would otherwise evade immunologic recognition.

PASSIVE IMMUNOTHERAPY

Passive immunotherapy involves the administration of monoclonal antibodies or cells. Monoclonal antibodies can be used as cancer therapy when they target tumor-specific antigens. These antibodies can be developed and purified in a laboratory and then administered to patients. Another form of passive immunotherapy isolates tumor-infiltrating lymphocytes from patient samples, cultures them in the presence of interleukin-2 (IL-2), and then administers these cells back to the patient. These lymphocytes are often manipulated prior to readministration to augment their tumor antigen recognition or cytolytic potential. Many such forms of adoptive immunotherapy are currently under investigation.³⁰

ACTIVE IMMUNOTHERAPY

Nonspecific forms of immunotherapy do not target particular tumor antigens. Rather, they include a variety of mediators, such as cytokines and interferons, that nonspecifically activate the immune system. Examples include IL-2, interferon alfa, and interferon gamma.¹²

Specific active immunotherapy refers to cancer vaccines where specific peptide antigens or autologous tumor cells are administered to patients in the hope of stimulating immune responses directed at their tumor. The single-peptide strategy has had only limited success for melanoma. Using the patient's own tumor cells as an autologous tumor cell vaccine avoids the technical complexities of choosing the ideal peptide that will be expressed by all patients suffering from a particular cancer and that will become displayed on HLA molecules. Currently, a variety of autologous tumor vaccines are under investigation.³⁰

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31 EVALUATION OF SURGICAL RISK, INCLUDING CARDIAC AND PULMONARY RISK ASSESSMENT

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All surgical procedures are associated with the risk of perioperative morbidity and mortality. Appropriate preoperative medical evaluation should assess whether a patient has a higher than average risk of having a surgical complication based on his or her current health status. The rationale behind preoperative risk assessment is to systematically address the patient's preexisting medical conditions and identify unrecognized comorbidities, thereby treating potential complications prior to surgical intervention. The risk assessment, although specific to the patient's condition, must also take into account the surgical procedure to be performed and the type of anesthesia to be administered. Preoperative evaluation also provides a medical plan that helps patients and their primary care physicians, anesthesiologists, and surgeons make the best treatment decisions regarding short-term and long-term clinical outcomes.

To properly evaluate surgical risk, a thorough history and physical examination are paramount not only to assess the state of a patient's preexisting medical condition but also to identify unrecognized disease processes. Laboratory tests should then be ordered to supplement the initial evaluation and most commonly include a complete blood count, electrolyte measurements, blood glucose, tests of renal and liver function, and coagulation studies. Diagnostic testing can also be directed at evaluating specific comorbidities, such as echocardiograms and stress tests in a heart failure patient and pulmonary function tests in a patient with chronic obstructive pulmonary disease (COPD). Once a patient has been fully evaluated, interventions can be initiated to ensure that all steps are taken to minimize the risk of surgery and provide for a satisfactory outcome for both the patient and the physicians involved in his or her care.

Cardiac Risk Assessment

Postoperative cardiac complications are a major cause of morbidity and mortality in surgical patients. The latest guidelines from the American College of Cardiology (ACC) Foundation and the American Heart Association (AHA) Task Force on Practice Guidelines, published in 2007, focus on the evaluation of patients undergoing noncardiac surgery who are at risk for perioperative cardiac morbidity and/or mortality.¹

PREOPERATIVE EVALUATION

According to the ACC/AHA guidelines, to determine the risk of cardiac events, patient-specific clinical variables,

exercise capability, and surgery-specific risk factors should initially be reviewed.¹ The evaluating physician should gather information from the patient's history, physical examination, and electrocardiogram (ECG) as an initial screen to assess the risk of perioperative cardiac complication.

History

A careful and meticulous history of the patient's past and present symptoms, clinical course, and exercise capability is of the utmost importance in evaluating surgical risk. The preoperative evaluation may often be the first cardiovascular assessment for a patient; therefore, symptoms of angina or dyspnea on exertion suggestive of cardiac disease may be diagnosed for the first time. The initial preoperative evaluation should specifically inquire about any previous history of heart disease, including stable or unstable angina, myocardial infarction (MI), heart failure, aortic stenosis, severe hypertension, and peripheral arterial disease.

Exercise Capability

A patient's exercise capability is an essential tool to assess general perioperative risk; patients with higher exercise tolerance usually have lower risk and vice versa. Various activity scales based on a set of questions are used to determine a patient's functional capacity [see Table 1].² Simple questions, such as if the patient is able to walk two blocks on level ground or carry two bags of groceries up one flight of stairs without symptoms, can provide a rough estimate of the patient's cardiac risk. These activities are approximately four metabolic equivalent of tasks (METs). Patients who are able to carry out these activities in their daily routine generally are at low risk for suffering major postoperative complications.³⁻⁵ In contrast, patients with poor exercise capability who are unable to perform these simple tasks have a higher incidence

Table 1 METs Assessment

- Can take care of self, such as ambulate, eat, dress, or use the toilet (1 MET)
- Can walk up a flight of steps or up a hill (4 METs)
- Can do heavy work around the house (scrubbing floors or lifting or moving heavy furniture; between 4 and 10 METs)
- Can participate in strenuous sports (swimming, football, basketball, tennis, and skiing; > 10 METs)

The metabolic equivalent of tasks (METs) expresses the rate of energy consumption for given activities, with 1 MET defined as 3.5 mL O₂ uptake/kg per min, the resting oxygen uptake in a sitting position. METs can be used to assess a patient's functional capacity.

of serious postoperative cardiac complications. However, it is important to consider the presence of physical disabilities or peripheral arterial disease that might limit a patient's capability to perform such simple tasks and thus make this part of the evaluation unreliable.

Physical Examination

The overall appearance of a patient provides important evidence regarding his or her clinical status. Cyanosis, pallor, dyspnea with minimal activity, poor nutritional status, obesity, and anxiety are potential clues of underlying cardiovascular disease that may need immediate attention and management. A cardiovascular physical examination of the patient must include measurements of blood pressure in both arms, inspection of jugular venous pulsations for any abnormalities, and palpation and auscultation of the carotid arteries for the presence of bruits. Precordial auscultation evaluates any abnormal heart sounds or murmurs. Abnormal heart sounds or murmurs may be indicative of heart failure or valvular stenosis, which increase perioperative risk. Although significant atrial or mitral stenosis increases the risk of heart failure, aortic and mitral regurgitation put a patient at increased risk for developing infective endocarditis in the setting of bacteremia following surgery; hence, prophylactic antibiotics should be considered in these circumstances.⁶ The presence of an implanted pacemaker indicates a need for detailed cardiac evaluation and testing. A thorough cardiovascular examination should also include auscultation of the lungs and examination of the extremities to check for edema and the presence of palpable peripheral pulses. The presence of peripheral vascular disease should raise the suspicion of possible coronary artery disease (CAD).

Resting Electrocardiogram

The 2007 ACC/AHA guidelines on perioperative cardiovascular evaluation recommend a resting 12-lead ECG in patients with known cardiovascular disease, peripheral arterial disease, or cerebrovascular disease.^{1,7} Although the presence of a significant ST segment change or a Q wave is known to be associated with an increased incidence of perioperative cardiac complications, a more recent retrospective study of preoperative ECGs compared with clinical characteristics suggests an association of right or left bundle branch block with perioperative MI and left bundle branch block with perioperative mortality.^{8–10}

Stress Testing

Recommendations for preoperative stress testing are based on the individual's clinical risk factors, functional capacity, and procedure-specific risk. The 2007 ACC/AHA guidelines advocate stress testing for patients who are at high risk (three or more revised cardiac index criteria) and have poor functional capacity (less than four METs) who are undergoing vascular surgery when the results of such testing can direct management [see Table 2].¹¹ Routine stress testing is not required in patients with at least one clinical risk factor and poor functional capacity (less than four METs) who are scheduled for intermediate-risk surgery or in patients with at least one clinical risk factor but good functional capacity (four or more METs) who are scheduled for vascular surgery.

Table 2 Revised Cardiac Risk Index to Predict Major Cardiac Risk Associated with Surgery

Independent predictors of major cardiac risk	
1. High-risk surgery (intraabdominal, intrathoracic, or suprainguinal vascular surgery) 2. Ischemic heart disease (MI, positive treadmill test, current chest pain, nitroglycerin therapy, pathologic Q waves on ECG) 3. Congestive heart failure (documented history, pulmonary edema, paroxysmal nocturnal dyspnea, pedal edema, S₃ heart sound, chest x-ray with pulmonary vascular redistribution) 4. Cerebrovascular disease (TIA/CVA) 5. Diabetes mellitus requiring insulin therapy 6. Renal failure (preoperative serum creatinine > 2.0 mg/dL (177 μmol/L))	
No. of Risk Factors	Risk, % (95% CI)
0	0.4 (0.1–0.8)
1	1.0 (0.5–1.4)
2	2.4 (1.3–3.5)
3+	5.4 (2.8–7.9)

CVA = cerebrovascular accident; ECG = electrocardiogram; MI = myocardial infarction; TIA = transient ischemic attack.

Patients who are not limited by claudication or orthopedic degenerative joint disease and are able to exercise adequately to reach the acceptable target heart rate can undergo exercise ECG testing. Patients with limited mobility should undergo pharmacologic stress testing with either dipyridamole-thallium radionuclide myocardial perfusion imaging or dobutamine stress echocardiography based on availability and expertise as well as the patient's needs.¹²

In a review of five large studies of thallium perfusion imaging, stress testing has a 90 to 100% negative predictive value for postoperative cardiovascular events but only a 6 to 67% positive predictive value.^{5,13} Thus, stress testing is very useful for decreasing estimated risk when found to be negative or normal. Notably, however, even a negative stress test does not ensure that perioperative cardiac events will not occur, and patients and physicians need to be aware of this.

Resting Echocardiography

Routine echocardiography is not recommended. However, a resting echocardiogram should be obtained to measure the extent of valvular dysfunction in patients with a murmur. It is also helpful in evaluating the degree of ventricular dysfunction, dyspnea of uncertain etiology, and cardiac causes of pulmonary hypertension.^{13,14}

Preoperative Revascularization

Very few noncardiac surgery patients require preoperative cardiac catheterization and revascularization.¹⁵ Using the approach described in the ACC/AHA guidelines, three independent studies found that coronary angiography is performed in only two to 11 patients and even fewer preoperative revascularizations are performed.^{16–18} Given that these studies included symptomatic patients who were more likely to undergo revascularization, an even lower rate of intervention in asymptomatic patients could be expected; hence,

routine preoperative revascularization is not indicated.¹⁵ However, to date, there is no clear evidence that revascularization improves perioperative outcome.^{19,20}

PATIENT-RELATED RISK FACTORS

Patient risk factors such as unstable or severe angina, recent MI, severe stenotic aortic or mitral valvular disease, decompensated or worsening heart failure, and significant arrhythmias are considered major predictors of perioperative cardiac complications, warrant intensive management, and potentially delay or cancel elective surgical procedures.¹ Overall, these predictors can be deduced from a careful history and physical examination combined with a resting ECG and can help direct the clinician regarding further evaluation and aggressive management as needed.

Coronary Artery Disease

The presence of CAD is evident in patients with a history of acute MI, coronary angioplasty, or coronary artery bypass grafting (CABG) or in patients with a coronary angiogram demonstrating luminal occlusion or irregularity. Yet many patients with severe double- or triple-vessel disease lack any clinical evidence of CAD as a result of atypical presentations or functional limitation resulting from advanced arthritis or peripheral vascular disease. A few of these patients may benefit from noninvasive revascularization independent of planned noncardiac surgery; however, recent data suggest a limited value to coronary revascularization before noncardiac surgery in the majority of patients.²¹ Advanced age also puts patients at increased risk because of a higher likelihood of CAD and the presence of an aging myocardium. The mortality of acute MI has been demonstrated to be significantly higher in the elderly population perioperatively.^{10,22–24} Gender also plays a key role in the risk and diagnosis of CAD.

Premenopausal women have a lower incidence of CAD, and women present with symptomatic CAD 10 years later than men.²⁵ Although premenopausal women have a lower incidence of CAD, in postmenopausal women, complication rates after an acute MI are greater than in men, possibly as a result of associated comorbidities. Phase II of the Thrombolysis in Myocardial Infarction trial compared the incidence of recurrent infarctions and deaths for women and men after acute MI.²⁶ The 6-week reinfarction and mortality rate was found to be significantly higher for women than for men. After a 1-year follow-up, the mortality rate among men and women was 6.5% and 11.1%, respectively. The risk factors associated with a higher incidence of reinfarction and death in women were age (with women presenting at a significantly older age than men), congestive heart failure (CHF), systemic hypertension, and the presence of diabetes mellitus.

Congestive Heart Failure

A history of CHF is positive if any of the following are present: a previous history of CHF, pulmonary edema, dyspnea on exertion or paroxysmal nocturnal dyspnea, bilateral rales or an S₃ gallop on physical examination, or a chest x-ray suggestive of pulmonary vascular redistribution. These are all considered to be independent predictors of cardiac risk.¹¹ CHF is known to be associated with a poorer outcome in patients undergoing noncardiac surgery.^{23,24} Therefore, every effort should be made to identify unsuspected CHF and its

probable cause and initiate treatment if possible. Preoperative assessment of left ventricular function by an echocardiogram can determine the severity of ventricular dysfunction and aid in perioperative management.

Valvular Heart Disease

Cardiac murmurs are frequently present in patients preparing to undergo noncardiac surgery. Severe, symptomatic aortic stenosis is a relative contraindication to elective noncardiac surgery and necessitates an aortic valve replacement prior to all other surgical interventions.^{23,27,28} In patients with severe aortic stenosis who are unwilling to undergo cardiac surgery or are otherwise not ideal candidates for an aortic valve replacement, noncardiac surgery poses a risk of developing an acute MI and a mortality risk of approximately 10%.^{29–31} In these patients, percutaneous balloon aortic valvuloplasty may be considered to minimize their perioperative risk of noncardiac surgery.^{27,32}

Although rare, mitral stenosis is important to recognize. In mild or moderate cases, ensuring control of heart rate is crucial perioperatively as tachycardia leading to a reduction in diastolic filling can lead to severe pulmonary congestion. Significant mitral stenosis increases the risk of CHF. However, unlike in the case of aortic stenosis, preoperative surgical correction of mitral valve disease is generally not indicated prior to noncardiac surgery except in the most severe cases, when cardiac complications and mortality are inevitable without correction.

When present, aortic regurgitation requires long-term follow-up and appropriate medical treatment to control volume and to reduce afterload. Mitral regurgitation often presents as a result of mitral valve prolapse or following an MI that leads to left ventricular remodeling. In cases of severe mitral regurgitation, afterload reduction with the use of diuretics provides maximal benefit in terms of hemodynamic stabilization before high-risk surgery. Perioperative antibiotic and anticoagulation prophylaxis is also recommended for patients with mitral valve regurgitation and those patients with a prosthetic valve to guard against bacteremia and the need for anticoagulation.⁶ For patients undergoing minimally invasive procedures, the American College of Chest Physicians Consensus Conference on Antithrombotic and Thrombolytic Therapy recommended briefly titrating the international normalized ratio (INR) to the low or subtherapeutic range and restarting the normal dose of oral anticoagulation immediately postprocedure.³³

Arrhythmias and Conduction Defects

Cardiac arrhythmias and conduction disturbances are also common findings on preoperative evaluation, specifically in the elderly population.²³ Both supraventricular and ventricular arrhythmias are known to serve as independent risk factors of cardiac events in the perioperative period; however, asymptomatic ventricular arrhythmias are considered harmless.^{23,34} Regardless, any arrhythmia must warrant a search for underlying causes, such as cardiopulmonary disease, silent myocardial ischemia or infarction, drug toxicity, or metabolic derangements.

Most often cardiac arrhythmias indicate an underlying cardiac problem. Atrial fibrillation is the most common type of supraventricular tachycardia encountered in elderly

patients. Atrial fibrillation or supraventricular arrhythmias can lead to ischemia by increasing myocardial oxygen demand in patients with CAD and may produce life-threatening ventricular fibrillation. Single, premature ventricular contractions, ventricular ectopy, and nonsustained ventricular tachycardia are not associated with an increased risk of nonfatal MI or cardiac death in the perioperative period and do not necessitate therapy unless the patient is hemodynamically compromised.^{34,35} Nevertheless, patients experiencing either sustained or nonsustained ventricular tachycardia perioperatively should be referred to a cardiologist for evaluation of their ventricular function and be screened for CAD. A patient found to have a complete atrioventricular block, which can increase operative risk, may require temporary or permanent transvenous pacing.

Implanted Pacemakers and Implantable Cardiac Defibrillators

Each year, more than 500,000 patients undergo placement of either a permanent pacemaker or an implantable cardiac defibrillator (ICD). The presence of a pacemaker or an ICD has a significant impact on preoperative, intraoperative, and postoperative patient management because of the potential for adverse interactions between electrical or magnetic activity and pacemaker or ICD function. These undue interactions occur as a result of the electrical current generated by use of electrocautery or cardioversion, use of antiarrhythmic agents, and anesthetic agents on pacing and sensing thresholds. Patients with ICDs and pacemakers must be recognized prior to surgery so that the correct records can be obtained that identify the type of device. Patients who are pacemaker dependent must have their device evaluated within 3 to 6 months before and after any major surgical procedures, particularly when the surgery involves large amounts of electrocautery. During surgery, the device should be inactivated and the patient should have both continuous ECG monitoring and continuous pulse oximetry monitoring to identify any life-threatening arrhythmias. In the event that an emergency cardioversion is required, the paddles must be placed away from the implanted device. Following surgery, the device should be reactivated and its function should be reassessed.

Cardiomyopathy

In patients with cardiomyopathy undergoing noncardiac surgery, preoperative recommendations should be made after a detailed understanding of the pathophysiology causing the cardiomyopathy. Understanding the primary cause is crucial to intraoperative and postoperative management of intravenous fluids. In the presence of signs and symptoms of heart failure, preoperative assessment of left ventricular function by an echocardiogram can determine the severity of systolic and diastolic dysfunction and help guide perioperative management.

In hypertrophic obstructive cardiomyopathy, a reduction in blood volume combined with a lower systemic vascular resistance and higher venous capacitance leads to outflow obstruction. The reduced filling pressures of the heart can cause a decrease in stroke volume with a risk of developing hypotension, arrhythmias, and heart failure. Major surgery and an increased duration of surgery were identified as independent risk factors for adverse cardiac outcomes in patients with cardiomyopathy.^{36,37}

Hypertension

Stage 1 (systolic blood pressure < 160 mm Hg and diastolic blood pressure < 100 mm Hg) and stage 2 (systolic blood pressure ≥ 160 mm Hg and diastolic blood pressure ≥ 100 mm Hg) hypertension are not independent risk factors for perioperative cardiovascular complications [see Table 3].³⁸ However, hypertension is a useful marker for potential CAD, with treatment of CAD reducing death as a result of stroke and CHF.³⁹ Intraoperative blood pressure fluctuations correlate with ECG changes suggestive of myocardial ischemia in patients; therefore, control of blood pressure preoperatively can lower the risk of perioperative ischemia.

A physical examination and a few basic laboratory tests can help detect important causes of hypertension. If there is a suspicion for pheochromocytoma, surgery should be delayed to permit its exclusion. A delay in the radial to femoral artery pulse suggests coarctation of the aorta, whereas a loud abdominal bruit may imply renal artery stenosis, and hypokalemia in the absence of diuretic therapy indicates the possibility of hyperaldosteronism.

If the preliminary evaluation determines hypertension to be mild or moderate, there is no evidence to suggest that it is beneficial to delay surgery. However, effective preoperative blood pressure control is beneficial, and antihypertensive medications should be continued. Care should be taken to avoid withdrawal of beta blockers and clonidine because of potential rebound changes in heart rate and blood pressure.

For stage 3 hypertension (systolic blood pressure ≥ 180 mm Hg and diastolic blood pressure ≥ 110 mm Hg), the possible risk of delaying surgery needs to be weighed against the benefit. Blood pressure can usually be lowered within a matter of several hours with rapidly acting intravenous agents if needed; however, there are no clear data favoring one type of medication.⁴⁰ Beta blockers are the predominant agents for the treatment of preoperative hypertension. Preoperative administration of beta blockers decreases the incidence of postoperative atrial fibrillation, and in patients who have or are at risk for CAD, treatment with beta blockers during hospitalization can reduce mortality and the incidence of cardiovascular complications.^{41,42} Finally, patients with preoperative hypertension are more likely to develop

Table 3 Classification of Hypertension

Stage	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Normal	< 120	< 80
Prehypertension	120–139	80–89
Stage 1	140–159	90–99
Stage 2	≥ 160	≥ 100
Stage 3	≥ 180	≥ 110
Isolated systolic	≥ 140	< 90
Isolated diastolic	< 140	≥ 90

Based on the 2007 guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC).³⁸
BP = blood pressure.

intraoperative hypotension than their normotensive counterparts, which is seen predominantly in patients who are on angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists, which may be attributable to a decrease in vascular volume.⁴³ Therefore, blood pressure should be closely monitored intraoperatively and patients should be resuscitated as needed.

PROCEDURE-RELATED RISK FACTORS

Preoperative cardiac evaluation can reliably predict postoperative cardiac outcomes to a reasonable extent and may alter the surgical decision-making process through interventions that reduce both perioperative risk and long-term mortality. Interventions must be made with the anticipation that the patient will live long enough to benefit from the elective surgery to prevent long-term mortality. Different cardiac risks are associated with each operation. The surgery-specific factors can be classified as low, intermediate, or high depending on the urgency, stress levels, duration of procedure, fluid shifts, episodes of hypotension, and blood loss [see Table 4].⁷ Short procedures in general are associated with minimal fluid shifts and minimal blood loss, whereas procedures requiring longer operative times are associated with large fluid shifts, higher risks of blood loss, and hypotension and pose greater risk of postoperative myocardial ischemia and respiratory depression.

Cardiac complications and mortality rates are more likely to occur with emergency surgical procedures than with elective operations as the need for immediate surgical interventions does not allow for optimal preoperative evaluation and management.⁴⁴ The mortality rate for elective repair of an asymptomatic abdominal aortic aneurysm is considerably lower (3.5%) than that for a ruptured aneurysm (42%).⁴⁵ For

elective surgery, cardiac risk depends on a number of factors, including the magnitude of the surgical procedure. The morbidity and mortality rates are low in superficial procedures performed in an outpatient setting.⁴⁶

Perioperative cardiac complications are common causes of morbidity and mortality in the surgical population. A complete preoperative assessment can identify risk factors, which can then be modified to minimize the risk of these complications occurring.

Pulmonary Risk Assessment

Assessment of perioperative risk has generally focused on minimizing cardiac complications, but pulmonary complications are found to be just as common in surgical patients. In a study of 3,970 patients undergoing noncardiac surgery, rates of pulmonary complications such as respiratory failure and pneumonia were found to be higher than pulmonary edema and MI, the most common cardiovascular complications.⁴⁷ Pulmonary complications range from minor complications such as atelectasis to more severe episodes of pneumonia and respiratory failure requiring mechanical ventilation. Depending on the severity of the postoperative pulmonary complication, the length of a hospital stay can be prolonged by up to 2 weeks.^{48,49} A study of the National Surgical Quality Improvement Program (NSQIP) found postoperative pulmonary complications to be the most costly complications, more so than cardiac, infectious, and thromboembolic events.⁵⁰

The risk of postoperative pulmonary complications depends on both patient factors such as smoking, a history of COPD, asthma, and obstructive sleep apnea and procedure-related risk factors.

PREOPERATIVE EVALUATION

History

A thorough history of the patient's past and present symptoms and clinical findings are extremely important in evaluating surgical patients for potential postoperative pulmonary complications. Care should be taken to obtain and evaluate for symptoms such as exercise intolerance, cough, and unexplained dyspnea that may indicate potential lung pathology. The Arozullah respiratory failure index is a promising tool for pulmonary risk assessment [see Table 5].⁵¹ In this classification scheme, the type of surgery, urgency of the surgery, serum albumin less than 3.0 g/dL, blood urea nitrogen (BUN) greater than 30 mg/dL, functional status of the patient, history of COPD, and age are awarded different points. Patients with 10 or fewer points have an associated 0.5% risk of respiratory failure, whereas those with more than 40 points have over 26% risk of respiratory failure.

Physical Examination

Signs of decreased breath sounds, wheezes, rhonchi, or prolonged expiratory phase will indicate underlying pulmonary disease.⁵² Patients with COPD can present with the symptoms of either emphysema or chronic bronchitis. Those with emphysema will have a barrel chest, increased respiratory rate, and use of accessory muscles of breathing, giving them the name "pink puffers." Patients with classic chronic bronchitis will present with signs of cyanosis, such as pursed blue lips, giving them the name "blue bloaters."

Table 4 Selected Surgical Procedures Stratified by Degree of Cardiac Risk

Degree of Cardiac Risk	Type of Procedure
Low (< 1%)	Endoscopic Ambulatory Ophthalmic Aesthetic Reconstructive Endocrine Gynecologic Breast Dental
Low intermediate (1–5%)	Minor vascular procedures (carotid endarterectomy) Abdominal Thoracic Neurosurgical Otolaryngologic
High intermediate (1–5%)	Orthopedic Urologic
High (> 5%)	Emergency Major vascular Extensive surgical procedures with profound estimated blood loss, large fluid shifts, or both Unstable hemodynamic situations

Table 5 Arozullah Respiratory Failure Index to Assess Preoperative Pulmonary Risk

Preoperative Predictor of Pulmonary Complication		Points Assigned
Abdominal aortic aneurysm		27
Thoracic procedure		21
Neurosurgery; upper abdominal, peripheral vascular procedure		14
Neck procedure		11
Emergency surgery		11
Albumin < 3.0 g/dL		9
BUN > 30 mg/dL		8
Suboptimal functional status		7
COPD		6
Age > 70 yr		6
Age 60–69 yr		4
Class	Cumulative Points	Predicted Respiratory Failure (%)
1	≤ 10	0.5
2	11–19	1.8
3	20–27	4.2
4	28–40	10.1
5	> 40	26.6

BUN = blood urea nitrogen; COPD = chronic obstructive pulmonary disease.

Based on the medical history and patient-specific variables, a preset point system is applied first. The cumulative point system is applied next to assess preoperative pulmonary risk.

Pulmonary Function Tests

Only patients who are scheduled for lung resection need to have preoperative pulmonary function tests performed. For the remaining procedures, the 2006 American College of Physicians guideline advocates against routine use of preoperative spirometry to estimate the risk of postoperative pulmonary complications.⁵³ However, for patients with unexplained dyspnea or exercise intolerance and those with COPD and poorly controlled asthma, pulmonary function tests should be ordered to determine disease severity as these patients will benefit from more aggressive preoperative management.⁵³

In addition to pulmonary function tests, a chest x-ray should be obtained in patients undergoing high-risk surgery who are over age 50 years or if cardiac or pulmonary disease is suggested by the clinical evaluation, unless one has been obtained in the past 6 months.⁵⁴

PATIENT-RELATED RISK FACTORS

Age and General Health Status

The role of age as an independent predictor of postoperative pulmonary complications is unclear. Although several

studies have suggested a higher risk of pulmonary complications with advanced age, the data were unadjusted for the patients' overall health status.⁵⁵ Using multivariate analysis and adjusting for age-related comorbidities, a more recent systematic review estimated that even otherwise healthy older patients carry a substantial risk of pulmonary complications after surgery.⁵⁶ As a result of the controversy regarding age as a risk factor, many physicians use the American Society of Anesthesiologists (ASA) score to assess the risk of complications as it is based on a patient's overall health status [see Table 6].

Smoking

Smoking is one of the most important independent predictors of postoperative pulmonary complications. Several studies since the 1980s have confirmed that cigarette smoking increases the risk of postoperative pulmonary complications.^{57–59} One study reported an odds ratio of 5.5 for increased risk of pulmonary complications following elective surgery in smokers compared with nonsmokers.⁵⁷ In another study, patients who had stopped smoking for less than 2 months had four times as many pulmonary complications as those who had quit smoking for more than 2 months.⁵⁸ To minimize pulmonary complications, patients should be instructed to quit smoking for at least 8 weeks prior to surgery.

Chronic Obstructive Pulmonary Disease

Patients with severe COPD can have up to a sixfold greater risk of developing a postoperative pulmonary complication than patients without the disease.^{60,61} Findings of COPD on a physical examination, such as decreased breath sounds, prolonged expiration, rales, wheezes, or rhonchi, correlate with a higher risk of postoperative complications.⁴⁹ In patients with pulmonary dysfunction, the risk-to-benefit ratio should be considered in making the ultimate decision regarding surgical intervention.

Asthma

It was initially believed that a history of asthma contributed to postoperative pulmonary complications, but studies have demonstrated that patients with well-controlled asthma do not have a higher than average surgical risk. One such study

Table 6 American Society of Anesthesiologists Score: Patient's Overall Health and Ability to Undergo Surgery

Class	Physical Status
1	Healthy patient with no systemic disease, not at any extreme of age
2	Patient with one-system, well-controlled disease not affecting daily activity
3	Patient with multisystem disease that limits daily activity
4	Patient with severe disease that is poorly controlled or end stage
5	Patient who is not expected to survive without an operation
6	Patient whose organs are being removed for donation

reported no major pulmonary complications and 14 minor complications, including bronchospasm and laryngospasm, in 706 asthma patients undergoing general surgery.⁶² In contrast, those with uncontrolled asthma, considered those patients with recent inhaler use or a visit to the emergency department, had a significantly higher incidence of pulmonary complications. Therefore, it is imperative to ask about recent medication use, particularly the need for rescue inhalers, and a course of systemic corticosteroids may be necessary to optimize the patient's pulmonary function.

Obstructive Sleep Apnea

Obstructive sleep apnea is an emerging risk factor for postoperative pulmonary complications. Pulmonary complications such as pneumonia and unplanned reintubation attributable to obstructive sleep apnea have only recently been appreciated.⁶³ The need to screen for obstructive sleep apnea prior to elective surgery is currently being investigated.

Obesity

Morbid obesity is associated with physiologic changes including reduction in lung volumes, ventilation/perfusion mismatch, and relative hypoxemia. Whereas earlier studies found neither obesity nor body mass index (BMI) to be an absolute risk factor for postoperative pulmonary complications, more recent prospective studies have found obesity (defined as BMI > 27 kg/m²) to be one of six independent risk factors for postoperative pulmonary complications.^{52,64,65} In another prospective study of 1,000 patients who underwent laparotomy, obesity (defined by BMI > 25 kg/m²) was found to be an independent risk factor for postoperative pulmonary complications. The inconsistencies found in these reports may be attributable to a difference in study design or failure of the authors to differentiate obesity from other comorbid conditions. A recent systematic review found that only one of eight studies using multivariate analysis identified obesity as an independent predictor of pulmonary complications postoperatively.⁵⁶ Hence, obesity is not considered a major risk factor for postoperative pulmonary complications and, therefore, should not affect surgical management of a given patient.

Pulmonary Hypertension

Even mild to moderate pulmonary hypertension predisposes surgical patients to higher postoperative complications such as cardiac dysrhythmias, congestive heart failure, renal insufficiency, and sepsis. Risk is greater in emergency procedures, major procedures, and those of extended duration and is irrespective of the etiology of pulmonary hypertension.⁶⁶ Pulmonary hypertension has been found to be an important predictor of adverse cardiopulmonary complications and is associated with higher rates of mortality and major morbidity.⁶⁷ Therefore, care should be taken while considering surgery and its potential risks in these patients, with efforts made to optimize medical management with supplemental oxygen, diuretics, vasodilators, and other appropriate medications.

Heart Failure

As per the systematic review that formed the foundation of the American College of Physicians guideline, the risk of

postoperative pulmonary complications appears higher in patients with heart failure than with COPD.⁵⁶ The collective adjusted odds ratio in this study for pulmonary complications was 2.93 (95% CI 1.02 to 8.43) for heart failure patients versus 2.36 (1.90 to 2.93) for patients with COPD. Therefore, a thorough perioperative assessment of clinical status and risk-to-benefit ratio should be performed while considering surgery in these patients.

PROCEDURE-RELATED RISK FACTORS

The surgical site is the single most important factor in predicting the overall risk of postoperative pulmonary complications. One of the factors responsible for postoperative pulmonary complications is a reduction in lung volume, which is a common occurrence after thoracic and upper abdominal surgery attributable to a reduced tidal volume, loss of sighing breaths, and an increased respiratory rate.⁶⁸ Diaphragmatic dysfunction, postoperative pain, and splinting also play a significant role in this aspect. Furthermore, the residual effects of anesthesia and use of postoperative opioids also lower a patient's respiratory drive, leading to inhibition of the cough response and impaired mucociliary clearance, which predisposes to the risk of postoperative infection.⁶⁹ A decrease in functional residual capacity increases the risk of atelectasis, pneumonia, and ventilation/perfusion mismatch, resulting in impaired gas exchange and postoperative hypoxemia.⁷⁰

In one systematic review, complication rates for upper abdominal surgery were found to be higher than those for lower abdominal surgery, most probably attributable to the effect of the incision on respiratory muscle and diaphragmatic function.⁵⁶ On the other hand, procedures such as laparoscopic cholecystectomy were associated with quicker recovery times, reduced pain, and lower reduction in lung volumes postoperatively.⁵⁶

Surgical procedures longer than 3 to 4 hours are also associated with a higher risk of pulmonary complications.^{52,71,72} Therefore, if possible, the length of the procedure should be considered when assessing the risk of surgery to its benefit in a high-risk patient.

It is yet to be determined if pulmonary risk of spinal or epidural anesthesia varies when compared with that of general anesthesia. The largest systematic review assessing this risk factor examined the results of 141 trials including 9,559 patients.⁷³ According to this study, there was a reduction in the incidence of pneumonia and respiratory depression among patients who received either epidural or spinal anesthesia with or without general anesthesia versus those who received general anesthesia alone.⁷³ It is likely that general anesthesia is associated with a higher risk of clinically important pulmonary complications than epidural or spinal anesthesia; hence, regional nerve block should be considered when possible for high-risk patients to minimize postoperative complications. Finally, the long-acting neuromuscular blocker pancuronium is also associated with a higher incidence of postoperative pulmonary complications than shorter-acting agents because of its residual neuromuscular blockade, leading to a higher incidence of postoperative pulmonary complications.⁷⁴

Perioperative pulmonary complications are recognized as a significant cause of morbidity and mortality, necessitating reintubation, prolonging hospital stay, and increasing health

care costs. By addressing the patient's pulmonary risk factors and the risks of the surgery to be undertaken, the physician performing the preoperative evaluation can decrease these complications.

Renal Risk Assessment

Mild to moderate renal impairment is often asymptomatic, with an incidental finding of elevated creatinine during preoperative evaluation. On the contrary, patients with severe renal failure often require dialysis treatment and eventual kidney transplantation. Renal failure can lead to many complications, including arrhythmias as a result of elevated potassium levels, shortness of breath as a result of pulmonary edema, and anemia. In patients undergoing surgery, these complications may worsen and become life-threatening. Renal insufficiency is also an independent risk factor for postoperative complications and requires dosage adjustments of anesthetics and other medications with potential nephrotoxic effects.¹¹

PREOPERATIVE EVALUATION

History

Although most patients with mild renal failure may not exhibit any symptoms, a detailed history may elucidate symptoms in patients who are unaware of having renal impairment. For instance, anemia, as a result of a decrease in erythropoietin production, may cause fatigue. Patients may also note an increase in lower extremity swelling, weight gain, or shortness of breath attributable to increased fluid.

Physical Examination

On physical examination, a physician may notice that a patient has an increased respiratory rate while attempting to eliminate carbon dioxide to compensate for metabolic acidosis. On lung examination, crackles can be heard in patients with pulmonary edema. Fluid overload will also cause generalized edema, which is most prominent in dependent areas, most commonly the lower extremities.

Laboratory Testing

All patients in whom there is a suspicion of renal impairment should undergo laboratory testing, to include the BUN level and serum creatinine. Likewise, these baseline tests should be ordered for patients who may be exposed to hypotension during the procedure or to nephrotoxic agents, such as contrast media used for computed tomographic (CT) scans, as this is a common cause of acute renal injury. In the setting of preexisting renal disease, a reduced glomerular filtration and/or a preoperative creatinine level greater than 2 mg/dL predisposes patients to postoperative renal dysfunction requiring dialysis and increases their long-term morbidity and mortality compared with patients without renal disease.⁷⁵⁻⁷⁷ Creatinine clearance is an additional marker to assess renal function and predict postoperative complications, determined from the serum creatinine concentration and the patient's age and weight. The creatinine clearance provides a more accurate assessment of renal function than serum creatinine alone.^{78,79} Once an elevated creatinine or creatinine clearance has been discovered, further workup can be done to assess the cause of the patient's renal impairment.

Analysis of the urine is a simple and cost-effective way to detect unsuspected renal disease and/or urinary tract infections. The detection of proteins on urinalysis indicates that the renal glomeruli are injured and are allowing large molecules to filter through into the urine. The presence of urinary casts can be associated with renal conditions such as acute interstitial nephritis, glomerulonephritis, and acute tubular necrosis. Urine sodium and creatinine, if included in the analysis of the urine, can be used to calculate the fractional excretion of sodium (FeNa) and aid the physician in distinguishing prerenal from postrenal causes of renal failure [see Table 7]. Urinary tract infections can also be detected with urinalysis by the presence of increased nitrites and white blood cells. Detection of a urinary tract infection preoperatively is important as it has the potential to cause bacteremia and postsurgical wound infections, particularly with prosthetic surgery.⁸⁰ Patients with positive urinalysis and urine culture can be treated with antibiotics and then taken into surgery without delay. Nonetheless, whether a positive urinary finding with consequent antibiotic treatment prevents postsurgical infections is uncertain as the findings in the literature have been contradictory.^{81,82} A cost-effective analysis established that for most types of clean-wound surgery, a routine preoperative urinalysis is not cost-effective.⁸³ Hence, routine urinalysis does not need to be ordered preoperatively for most surgical procedures, except in the setting of suspected urinary tract infections.

PATIENT-RELATED RISK FACTORS

Dialysis Patients

Patients on long-term dialysis have chronic renal dysfunction that places them at an increased risk for postoperative morbidity and mortality. Much of this increased risk is attributable to associated comorbidities such as CAD and hypertension, which necessitates appropriate cardiac preoperative evaluation. As a result of their dependence on dialysis, these patients may also experience electrolyte abnormalities, most commonly hyperkalemia, as well as fluid overload, which may lead to complications such as pulmonary edema and respiratory failure. All dialysis patients scheduled to undergo surgery must undergo a routine history and physical examination as well as baseline laboratory testing not only to evaluate their level of renal dysfunction but also to identify other potential risk factors for morbidity, such as anemia and poor nutritional status. In patients undergoing elective surgery, preoperative dialysis should optimize a patient's fluid and electrolyte levels. In the event of emergency surgery, dialysis is usually unable to be performed prior to operative

Table 7 Assessment of Renal Failure

FeNa (%)	Cause of Failure
< 1	Prerenal
> 1	Intrinsic
> 4	Postrenal

FeNa = $100 \times (\text{Urine sodium} \times \text{plasma creatinine}) / (\text{Plasma sodium} \times \text{urine creatinine})$
Fractional excretion of sodium (FeNa) is the percentage of sodium that is filtered by the kidney and excreted in the urine. It is most commonly used to assess the cause of acute renal failure.

intervention. In this instance, hyperkalemia is the most common and serious electrolyte abnormality that should be evaluated. This evaluation should include an ECG to rule out cardiac abnormalities attributable to the elevated potassium, as evidenced by peaked T waves. If the patient is stable, with no ECG changes and a potassium level less than 6.2 mEq/L, he or she should be able to undergo emergency surgery with careful intraoperative monitoring.⁸⁴ In the event that ECG changes are present and surgery must be undertaken, medical management in the form of calcium gluconate and insulin with D50W should be performed. In all dialysis-dependent patients undergoing surgery, arrangements should be made to provide for continued dialysis treatment during the patient's hospitalization.

Hepatic Risk Assessment

Patients with hepatic dysfunction are at increased risk for multiple complications after elective surgery. Depending on the severity of their liver disease, they may have a coagulopathy that puts them at increased risk for bleeding or an underlying hepatorenal syndrome that increases the risk of postoperative renal failure.

In certain settings, the risks of the above complications and the mortality rate are unacceptably high, so elective surgery is contraindicated. In patients with fulminant hepatitis, acute liver failure, and acute alcoholic hepatitis, early studies have reported mortality rates of 10 to 58%, making these conditions absolute contraindications to elective surgery.^{85,86}

In patients without the above conditions, the risk of perioperative complications increases with the increasing severity of liver disease. Two scoring systems have been widely used by physicians to assess the severity of liver disease, the Child-Pugh scoring system and the Model for End-Stage Liver Disease (MELD) score [see Table 8 and Table 9]. The

Table 8 Child-Pugh Score to Predict Mortality of Cirrhotic Patients and the Need for Liver Transplantation

Variables	Points		
	1	2	3
Total bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/L)	> 3.5	2.8–3.5	< 2.8
INR	< 1.7	1.7–2.3	> 2.3
Ascites	None	Mild (controlled with diuretics)	Severe
Encephalopathy	None	Stage I or II	Stage III or IV
Class	Points		
A	5–6		
B	7–9		
C	10–15		

INR = international normalized ratio.

Table 9 Model for End-Stage Liver Disease (MELD)

$$\text{MELD} = 3.78 [\ln \text{ total bilirubin (mg/dL)}] + 11.2 [\ln \text{ INR}] + 9.57 [\ln \text{ serum creatinine (mg/dL)}] + 6.43$$

INR = international normalized ratio; ln = natural log.

The MELD score is used to assess the severity of liver disease and prioritizes patients awaiting liver transplantation.

Child-Pugh scoring system was initially developed in the 1970s and was the standard for assessing morbidity and mortality in cirrhotic patients until the development of the MELD score. The MELD score was created to predict mortality after transjugular intrahepatic portocaval shunt (TIPS) placement but is now used to prioritize patients awaiting liver transplantation and as a predictive model of perioperative mortality. A 2010 study in patients undergoing abdominal surgery showed mortality rates of 2% in Child-Pugh class A patients and rates of 12% for both class B and C.⁸⁷ Because of this and various other studies, elective surgery is contraindicated in Child-Pugh class C cirrhotics.⁸⁸ The MELD score has also been shown to predict morbidity in patients undergoing cholecystectomy, hepatectomy, and cardiac surgery in numerous studies.^{89–91} It has been recommended that patients with a MELD score greater than 15 not undergo elective surgery as the risk of a complication outweighs any surgical benefit.⁹² Although both scoring systems are in use, numerous studies have demonstrated the MELD score to be superior to the Child-Pugh score in predicting perioperative morbidity and mortality.^{93,94}

PREOPERATIVE EVALUATION

History

The history of a patient with hepatic dysfunction is useful to identify not only patients in whom the risk of elective surgery would outweigh the benefits but also those with mild disease in whom medical management may be optimized to minimize those risks. A thorough history can identify worsening encephalopathy and spur treatment of increasing ammonia levels with lactulose. In an alcoholic cirrhotic patient, a complete history helps not only in assessing liver dysfunction but also in determining whether the patient continues to abuse alcohol. Surgical patients with alcohol abuse are not only at risk for withdrawal during their hospitalization but also have higher rates of postoperative hemorrhage, cardiac complications, and sepsis.⁹⁵

Physical Examination

The physical examination can identify patients with ascites, who may benefit from preoperative diuretic therapy or paracentesis to minimize the occurrence of wound complications. Physicians who perform complete examinations may also discover patients with previously undiagnosed hepatic dysfunction as a result of the presence of jaundice, which should then prompt further laboratory assessment.

Laboratory Evaluation

All patients with suspected or known hepatic dysfunction should have an assessment of their liver function. This should include a total bilirubin level, which can then be used to calculate a Child-Pugh or MELD score. This evaluation

should also include a measurement of the patient's INR. This is helpful not only in calculating a risk score but also in identifying patients at an increased risk for bleeding in whom treatment with vitamin K and/or fresh frozen plasma can be initiated to decrease their coagulopathy. Evaluation of renal function should also be performed in an initial assessment of a cirrhotic patient and should include a creatinine level to both calculate risk scores and identify patients at increased risk for developing acute renal failure. Small studies have demonstrated improvements in renal function in patients given a combination of midodrine, an α_1 -adrenergic agonist, and octreotide, a somatostatin analogue, as well as terlipressin, a vasopressin analogue, combined with albumin, but larger trials are yet to be done.^{96,97} In patients who do develop acute renal failure after surgery, dialysis may need to be initiated, and a surgeon should not hesitate to do so as the mortality of a patient in liver failure with hepatorenal syndrome is significantly worse than in a patient with adequate renal function.⁹⁸

All patients with liver disease risk hepatic decompensation with surgery; therefore, identifying these patients prior to surgical intervention can not only minimize the risk of complications but also can prepare the surgeon and the patient for such a possibility.

Hematologic Risk Assessment

The hematologic risk assessment should include an evaluation of conditions that can increase perioperative bleeding, as well as those that place the patient at an increased risk for the development of clots. The preoperative assessment of a patient's hematologic risk should take into consideration patient factors such as history, physical examination, and laboratory tests, as well as procedural risks.

PREOPERATIVE EVALUATION

History

A thorough history should include questions concerning easy bruising and prolonged bleeding, a previous need for blood transfusions, and the use of anticoagulants or antiplatelet drugs. This evaluation should also include questions regarding a history of blood clots and conditions that can increase hypercoagulability, such as malignancies, oral contraceptive use, and smoking.

Physical Examination

On physical examination, patients with bleeding disorders may display numerous petechiae and ecchymoses or bleeding mucosa suggestive of platelet dysfunction or deficiency. Deformed joints or bleeding into joints points to a diagnosis of hemophilia, which needs to be treated appropriately prior to surgery. Patients with a deep vein thrombosis may have a swollen and painful extremity on examination.

Laboratory Evaluation

In evaluating patients at risk for excess bleeding during surgery, prothrombin time (PT), partial thromboplastin time (PTT), and bleeding time should be performed. When done routinely, abnormalities in these tests are not clear indicators of the risk of perioperative hemorrhage.^{10,99–101} The finding of an abnormal PT in an otherwise normal patient does not

change patient management or modify the likelihood of a complication.³⁰ Therefore, the current ACC/AHA guidelines advise against routine preoperative measurement of hemostasis and recommend testing only patients with an existing bleeding disorder or an illness associated with an abnormal bleeding tendency.¹

PATIENT-RELATED RISK FACTORS

Hemophilia

Historically, hemophiliacs undergoing surgical procedures faced mortality rates up to 66%, but with the perioperative administration of coagulation factors, mortality has been significantly reduced.^{102,103} In hemophilia type A, with a deficiency in factor VIII, patients should have 100% of their factor levels replenished. Given that hemophilia type B (Christmas disease), attributable to a deficiency in factor IX, is not as severe as type A, it is recommended that 50% of factor levels be administered preoperatively.

Anemia

Anemia puts a strain on the cardiovascular system and a hematocrit less than 28% puts patients at a higher risk for perioperative ischemia and postoperative complications.^{104–106} In the Veterans Affairs NSQIP database, mild preoperative anemia or polycythemia led to an increase in cardiac events and mortality within the 30-day postoperative period in older, primarily male patients who underwent major noncardiac surgery.⁹⁹ Therefore, judicious use of preoperative transfusion in patients with advanced CAD or CHF may be beneficial in reducing perioperative cardiac morbidity.

Hypercoagulability

Factor V Leiden deficiency is the most common congenital cause of spontaneous venous thrombosis. Polycythemia vera, protein C or S deficiency, and antiphospholipid antibody syndrome also lead to an increased risk of thromboembolism in the postoperative period. Many of these patients will require heparin or warfarin therapy postoperatively.

PROCEDURE-RELATED RISK FACTORS

The type of surgery to be performed should also be considered when deciding whether a patient is at an increased risk for bleeding. Low-risk surgeries are those in which a limited amount of dissection takes place, no vital organs are involved, and the surgical site is exposed, allowing for direct hemostasis. An inguinal hernia repair would be considered low-risk surgery. On the contrary, exploratory laparotomies and thoracotomies are referred to as high-risk surgeries because they involve manipulation of vital organs and extensive dissection. In these cases, a thorough history and physical and laboratory testing should be performed to rule out disorders that could increase the risk of bleeding complications.

Preoperative Medication Management

One of the most important aspects of the preoperative evaluation is a review of the patient's medication history. A physician must know not only when to discontinue medications because of their potential surgical and anesthetic complications but also when to continue them to avoid the adverse effects of withdrawal and when to substitute medications

when their absorption may be decreased in the immediate postoperative period.

Close consideration should be given to any cardiovascular medications the patient is taking on a regular basis as abrupt discontinuation can compromise an otherwise hemodynamically stable patient [see Table 10]. Beta blockers are one of the most beneficial medications for patients to continue taking in the perioperative period. Beta blockers reduce ischemia by decreasing myocardial oxygen demand and may also prevent arrhythmias when taken perioperatively. ACE inhibitors and angiotensin II receptor blockers reduce blood pressure via the renin-angiotensin system. For patients with hypertension, these agents are continued unless the patient is hemodynamically unstable or there is a concern for renal insufficiency.¹⁰⁷ Alpha₂ agonists, such as clonidine, are centrally acting sympatholytic drugs that have also been shown to improve perioperative outcomes, and abrupt withdrawal can cause rebound hypertension; hence, these medications should be continued.^{108,109} In patients undergoing noncardiac surgery, the use of calcium channel blockers was found to reduce the incidence of ischemia and atrial arrhythmia, leading to the recommendation to continue these medications perioperatively.¹¹⁰ There is also evidence that perioperative fluvastatin, an HMG-CoA reductase inhibitor, improves postoperative cardiac outcomes and should be continued the day of surgery.¹¹¹

Diuretics can cause hypovolemia and significant hypotension in surgical patients and should not be taken the morning of surgery.¹¹² Other drugs to discontinue are the nonstatin hypolipidemic agents and fibric acid derivatives. These agents can cause myopathy and rhabdomyolysis, particularly when used in combination with a statin. Bile sequestrants such as

cholestyramine and colestipol should also be discontinued as they can interfere with the absorption of several medications given postoperatively.¹¹³

Many prescription and over-the-counter medications can increase the risk of bleeding postoperatively [see Table 11].¹¹⁴ Antiplatelet agents such as aspirin should be discontinued 7 to 10 days prior to surgery. For those patients whose risk of cardiovascular events is high, but the risk of postoperative hemorrhage is low, aspirin should be continued up to the day of surgery. Warfarin, the most common oral anticoagulant taken by patients, should be discontinued 5 to 7 days prior to surgery. For those patients whose INR remains elevated, fresh frozen plasma can lower the INR to a level acceptable to the operating surgeon.

Diabetic patients taking oral hypoglycemic agents and insulin are another group of patients needing special consideration. Perioperative diabetic management should be geared toward optimizing glycemic control and preventing ketoacidosis. Patients taking oral hypoglycemic agents are advised to withhold their oral medications on the day of surgery and, if necessary, should be treated with subcutaneous short-acting insulin.^{115,116} Likewise, in the postoperative period, if diabetic patients are unable to resume their oral hypoglycemic agents, subcutaneous or intravenous insulin may be required to prevent hyperglycemia. Diabetic patients on insulin therapy should continue their home regimen perioperatively for short procedures. For longer and higher-risk procedures, such as CABG or renal transplantation, intravenous insulin is usually recommended to prevent hyperglycemia and ketosis.^{115,116}

In addition to prescribed medications, many patients scheduled to undergo surgery may be taking herbal medications. These medications may be harmful to the liver, interfere with the coagulation cascade or platelet function,

Table 10 Recommendation for Cardiovascular Agents

Drug	Use	Recommendation for Continuation
ACE inhibitors and angiotensin receptor blockers	Antihypertensive: continuation can result in hypotension if low blood pressure at baseline Heart failure: can lead to hypotension	Continue medication up to and including the day of surgery if using to lower blood pressure. Discontinue on day of surgery if using to treat heart failure and blood pressure is low at baseline. Use IV enalapril postoperatively if needed.
Alpha ₂ agonists	Antihypertensive: abrupt withdrawal can result in hypertension and myocardial ischemia	Continue medication up to and including the day of surgery; switch to transdermal clonidine or IV methyl dopa
Beta blockers	Antihypertensive: abrupt withdrawal can result in hypertension, tachycardia, and myocardial ischemia	Continue medication up to and including the day of surgery; switch to IV propranolol, metoprolol, or labetalol if in a prolonged NPO state
Calcium channel blockers	Antihypertensive: increased risk of bleeding is controversial	Continue therapy up to and including the day of surgery. IV substitution necessary only if unstable hemodynamically (hypertension or arrhythmia).
Diuretics	Heart failure: continuation can lead to hypovolemia and hypotension	Continue medication up to and including the day of surgery but withhold morning dose, if needed give IV postoperatively.
Nonstatin, lipid-lowering agents	Niacin and fibric acid derivatives: rhabdomyolysis. Bile acid sequestrants interfere with absorption of other medications.	Discontinue the day prior to surgery. Can resume with oral intake.
Statins	Lipid-lowering agents: provide cardiovascular protection but may cause myopathy	Continue medication up to and including the day of surgery

ACE = angiotensin-converting enzyme; IV = intravenous; NPO = nihil per os.

Table 11 Recommendation for Antiplatelet Agents and Anticoagulants

Type of Drug	Agent	Effects	Recommendations for Discontinuation
Antiplatelet agents	Aspirin (ASA)	Irreversible platelet inhibitor	7–10 days prior to surgery; those on long-term ASA therapy for coronary/cerebrovascular pathology should continue ASA unless bleeding complications outweigh risk of thrombosis
	Thienopyridines: clopidogrel and ticlopidine	Inhibit platelet aggregation	Clopidogrel 7–10 days prior to surgery Ticlopidine 2 weeks prior to surgery In patients with coronary artery stents, delay elective surgery until patient has completed therapy
	Nonsteroidal antiinflammatory drugs (NSAIDs)	Reversible platelet inhibitor	At least 2 days prior to surgery
	Antiglycoprotein agents: abciximab, tirofiban, eptifibatide	Inhibit platelet aggregation	At least 12 hours prior to surgery
Oral anticoagulants	Warfarin	Inhibition of vitamin K–dependent clotting factors II, VII, IX, X	5–7 days prior to surgery; may need to bridge patient with heparin

Adapted from Backman S et al.¹¹⁴

ASA = acetylsalicylic acid.

Prescription and over-the-counter medications can have antiplatelet and anticoagulant effects, which increase the risk of bleeding perioperatively. Given the reasons for their use, these medications may need to be continued and elective surgery postponed.

Table 12 Recommendation for Herbal Medications

Herbal Medication	Use	Adverse Effect	Recommendation for Discontinuation
Chaparral	Alternative anticancer treatment	Hepatotoxicity	As soon as possible
Coltsfoot	Antitussive and demulcent	Carcinogenic	As soon as possible
Comfrey	General healing agent	Hepatotoxicity	As soon as possible
<i>Ephedra sinica</i>	Noncatecholamine sympathomimetic agent	Cardiac and CNS complications	24 hours prior to surgery
Echinacea	Immunostimulatory effect	Hepatotoxicity; possible allergy	As soon as possible in patients with hepatic dysfunction
Feverfew		Bleeding	At least 7 days prior to surgery
Garlic	Irreversible platelet inhibition	Bleeding	At least 7 days prior to surgery
Germander	Choleretic, antiseptic	Hepatotoxicity	As soon as possible
Ginkgo biloba	Inhibition of platelet-activating factor	Bleeding	At least 36 hours prior to surgery
Ginger	Inhibitor of thromboxane synthase	Bleeding	At least 36 hours prior to surgery
Ginseng	Inhibition of platelet aggregation; antihyperglycemic	Prolonged PT and PTT; hypoglycemia	At least 7 days prior to surgery
Goldenseal		May increase swelling and BP	At least 7 days prior to surgery
Lobelia	Antinausea; expectorant	Respiratory depression, tachycardia, hypotension, coma, death	As soon as possible
Sassafras	Stimulant; antispasmodic	Carcinogenic	As soon as possible
Saw palmetto		May interfere with hormone therapies	At least 7 days prior to surgery
St. John's wort	Inhibits reuptake of serotonin, norepinephrine, and dopamine	May interact with MAOIs	Day of surgery
Valerian	Modulation of GABA neurotransmitter	May potentiate effect of sedative anesthetics	24 hours prior to surgery

Table 12 Continued			
Herbal Medication	Use	Adverse Effect	Recommendation for Discontinuation
Vitamin E		Bleeding	
Yohimbe	Aphrodisiac, sexual stimulant	Hypertension, tachycardia, paralysis, death	As soon as possible

Adapted from Backman S et al.¹¹⁴
BP = blood pressure; CNS = central nervous system; GABA = γ -aminobutyric acid; MAOI = monoamine oxidase inhibitor; PT = prothrombin time; PTT = partial thromboplastin time.
Herbal medications have various adverse effects, and based on the severity of that risk, they should be discontinued accordingly.

or enhance the effects of various anesthetic agents. It is imperative for a physician to be aware of the side effects of certain herbal medications and to advise a patient on when to discontinue their use [see Table 12].¹¹⁴

Conclusion

A complete preoperative evaluation should optimize a patient’s medical status prior to surgical intervention. A thorough history and physical examination supplemented by indicated laboratory testing and studies may uncover

conditions that could lead to unnecessary perioperative complications such as acute MI and renal failure. Although the preoperative evaluation is essential to minimizing complications in surgical patients, it is important to remember that perioperative complications are unavoidable. Therefore, a physician should not only evaluate the patient’s ability to undergo surgery but also anticipate and treat postoperative complications in a timely manner to minimize morbidity and mortality.

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32 PERIOPERATIVE ANTITHROMBOTIC THERAPY MANAGEMENT AND VENOUS THROMBOEMBOLISM PROPHYLAXIS

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With expected increases in the elderly patient population requiring surgery, coupled with the overall trend toward increased comorbid conditions in surgical patients, surgeons can expect to encounter more patients receiving preoperative antithrombotic therapy that will need to be managed in the perioperative period. In addition, it can be expected that more patients will come to surgery with risk factors for perioperative venous thromboembolism (VTE) requiring perioperative prophylaxis. Furthermore, various organizations have developed process measure reporting requirements, such as the Centers for Medicare and Medicaid Services (CMS) Physician Quality Reporting Initiative (PQRI),¹ that require surgeons to document appropriate perioperative VTE prophylaxis. Thus, it is imperative that surgeons be able to identify patients at risk for perioperative VTE and provide appropriate and timely prophylaxis.

The management of perioperative anticoagulation and antiplatelet therapy and perioperative VTE prophylaxis is essentially a balancing act between patient risk factors for thrombosis and surgical risk factors for bleeding. The goals of this chapter are to assist the practicing surgeon with

- Identifying patient groups at increased risk for thromboembolism when antithrombotic therapy is interrupted
- Identifying patients for whom bridging anticoagulation should be considered
- Identifying patients who require perioperative VTE prophylaxis
- Identifying patients at increased risk for bleeding complications
- A brief review of the literature and major guidelines regarding perioperative antithrombotic therapy management and perioperative VTE prophylaxis

Perioperative Antithrombotic Therapy Management

The rationale for perioperative bridging anticoagulation for patients receiving long-term warfarin therapy is based on the following assumptions: patients with a therapeutic international normalized ratio (INR) are at increased risk for bleeding during invasive procedures; allowing the INR to fall outside the therapeutic range during the perioperative period exposes patients to an increased risk of thrombotic

complications; bridging anticoagulation (with unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) reduces the risk of thrombotic complications in the perioperative period while the INR is subtherapeutic; and the benefit of bridging anticoagulation outweighs the increased risk of post-procedural bleeding. For perioperative bridging anticoagulation to be beneficial, all of these assumptions need to be true for the individual patient.

For most invasive procedures, continuation of oral anticoagulants increases the risk of periprocedural bleeding.² However, there are some procedures for which warfarin may not need to be stopped if there are no additional bleeding risks (e.g., uremia, thrombocytopenia, coagulation factor deficiencies, or recent bleeding complications). These include cataract surgery,³ many dermatologic procedures,⁴ simple dental procedures, and joint and soft tissue aspirations and injections.⁵

For most other elective procedures, warfarin should be stopped for a period prior to the procedure that will allow the INR to fall to an acceptable level on the day of the procedure. For most patients with a steady-state INR between 2 and 3, withholding 4 doses of warfarin (i.e., stopping warfarin 4 days prior to the date of surgery) will allow the INR to fall to less than 1.2 on the day of surgery, with virtually all patients having an INR of 1.5 or less, a level that is safe for most operations except for those in which even minor bleeding can be catastrophic (e.g., intracranial or spine surgery). It may be necessary to stop warfarin sooner (i.e., > 4 doses) if patients have a higher INR (> 3.0) or if they are older as increasing age is a significant independent predictor of smaller decreases in the INR. After surgery, when resuming warfarin, most patients may resume their preoperative dose. After 3 to 5 days of resuming warfarin, the INR will typically be greater than 2.^{6,7} A loading dose may be given for the first dose if a more rapid resumption of therapeutic coagulation is desired. As a result of this delayed onset of anticoagulation with resuming warfarin therapy, warfarin should be restarted the night of surgery or the morning after.

The yearly rate of thromboembolism is as high as 4.5% for nonvalvular atrial fibrillation (AF),⁸ 8% for mechanical heart valves (MHVs),⁹ 15% for recurrent VTE,¹⁰ and 50% for acute VTE. It has been demonstrated that the risk of thromboembolism is reduced from 66 to 80% with anticoagulation

therapy for common indications, such as acute and recurrent VTE,¹¹ AF,¹² and MHV.⁹ If a patient discontinues warfarin 5 days prior to surgery and resumes warfarin the night after surgery, they can be expected to have approximately 4 days of a subtherapeutic INR, with 2 of these days falling in the postoperative period. Because it has been estimated that major surgery increases the short-term risk of thromboembolism approximately 100-fold,¹³ bridging anticoagulation during this subtherapeutic window has been proposed for certain high- to moderate-risk conditions.

Trials evaluating the rates of thromboembolic events and major bleeding with bridging anticoagulation have provided mixed results. The Prospective Peri-operative Enoxaparin Cohort Trial (PROSPECT) evaluated 260 patients at 24 North American centers on oral anticoagulation for AF or VTE who required invasive procedures or surgery during which the treating physician felt that bridging therapy was necessary.¹⁴ Thromboembolism occurred at a rate of 1.9% with a major bleeding rate of 3.5%. Although this study demonstrated that perioperative bridging with once-daily therapeutic enoxaparin is safe for invasive procedures and minor surgery (bleeding risk < 0.7%), the rate of bleeding for major surgery was 20%.

Kovacs and colleagues performed a prospective, multicenter, single-arm cohort study of 224 patients with MHV and high-risk AF on warfarin therapy who underwent bridging with LMWH.¹⁵ The majority of procedures were cardiac catheterizations, genitourinary surgery, dental procedures, and major orthopedic surgery. Eight patients (3.6%) had an episode of thromboembolism with 15 episodes of major bleeding (6.7%), five of which occurred during postoperative LMWH administration. The bleeding rate for major surgical operations was not specified.

Douketis and colleagues evaluated 650 consecutive patients with an MHV, AF, or embolic stroke who had warfarin held 5 to 6 days before an invasive procedure and received twice-daily dalteparin starting 3 days prior to the procedure.⁷ Warfarin was resumed on the evening of the procedure and twice-daily dalteparin was restarted on postoperative day 1 and continued until the INR reached 2 or greater. For patients undergoing a high-bleeding risk procedure or in whom hemostasis was incomplete, warfarin was resumed on the evening of the procedure, but dalteparin was held or not given after the procedure. In 542 patients who underwent a low-bleeding risk procedure, there was a 0.4% rate of thromboembolism and a 0.7% rate of major bleeding. In 108 patients who underwent a high-bleeding risk procedure, there was a 1.8% rate of thromboembolism and a 1.8% rate of major bleeding. This study included a higher percentage of major surgical operations than the PROSPECT¹⁴ or Kovacs and colleagues' trial¹⁵ and thus is more applicable to elective surgical practices.

The North American REGIMEN investigators conducted a multicenter, observational, prospective trial enrolling 901 patients on oral anticoagulation undergoing an elective surgical or invasive procedure who received either UFH ($n = 180$) or LMWH ($n = 721$) for perioperative bridging.¹⁶ Thromboembolic rates were 2.4% for UFH and 0.9% for LMWH, and rates of major bleeding were 3.3% for UFH and 5.5% for LMWH; neither of these differences was significant. Patients bridged with LMWH were more likely to be able to receive their preoperative heparin therapy as an outpatient. A

Charlson Comorbidity Index score greater than 1 and vascular, general, and major surgery were associated with an increased risk of major bleeding. It should be noted that these trials did not compare the rates of thromboembolic events and major bleeding with those of a control group that did not receive bridging anticoagulation, so it is impossible to determine the relative effect that bridging anticoagulation has on perioperative thromboembolic and bleeding risk.

Either UFH or LMWH can be used for bridging anticoagulation, with LMWH being more cost-effective if the patient is not hospitalized preoperatively for other reasons. UFH should be held at least 4 hours prior to surgery, whereas the last dose of LMWH should be given at most 24 hours prior to surgery. Because of the low risk of bleeding complications in minor surgical or invasive procedures, bridging anticoagulation can be resumed the day after the procedure. However, as noted above, major surgical operations have an increased risk of bleeding with postoperative bridging anticoagulation. Thus, after major surgery, bridging anticoagulation should be held for 2 to 3 days after surgery and hemostasis must be ensured. Alternatively, warfarin therapy can be restarted the day of surgery and postoperative bridging anticoagulation can be withheld altogether as the INR will approach therapeutic levels by 3 days in most people, as previously noted. If hemostasis is not adequate or bleeding occurs, warfarin and bridging anticoagulation should be held until deemed safe by the surgeon. In all cases, especially difficult or unusual cases, contacting the primary care provider or consulting an anticoagulation specialist is always an option.

Determining which patients on warfarin need bridging anticoagulation depends on the risk of thromboembolic events off anticoagulation. There are three major patient populations for whom perioperative bridging anticoagulation is indicated: patients with mechanical heart valves, patients with atrial fibrillation or flutter, and patients with prior VTE. Figures 1 and 2 provide an evidence-based approach for determining which patients with these conditions need bridging anticoagulation.

Perioperative Management of Antiplatelet Therapy

Antiplatelet agents have been increasingly used in patients with elevated cardiovascular or cerebrovascular risk and after cardiovascular and peripheral vascular interventions. The management of these agents in the perioperative setting is a unique challenge for the surgeon as the risk of increased bleeding with antiplatelet therapy and the risk of thrombotic complications related to withholding antiplatelet therapy have not been adequately established. By far, the two most common antiplatelet drugs used in the United States are aspirin and clopidogrel. Aspirin is a cyclooxygenase-1 inhibitor, whereas clopidogrel inhibits the adenosine diphosphate receptor of platelets. Both agents irreversibly inhibit platelet function; therefore, they must be discontinued for 7 to 10 days (the life span of platelets) for significant reversal of their antiplatelet activity to occur prior to surgery. They are usually restarted 24 hours after surgery if hemostasis is adequate.

There is mounting evidence that it is safe to perform minor excisional cutaneous surgery without discontinuing single-agent antiplatelet therapy, including clopidogrel.^{17,18} Surprisingly, there are insufficient data to quantify the risk of bleeding with aspirin or clopidogrel therapy during major

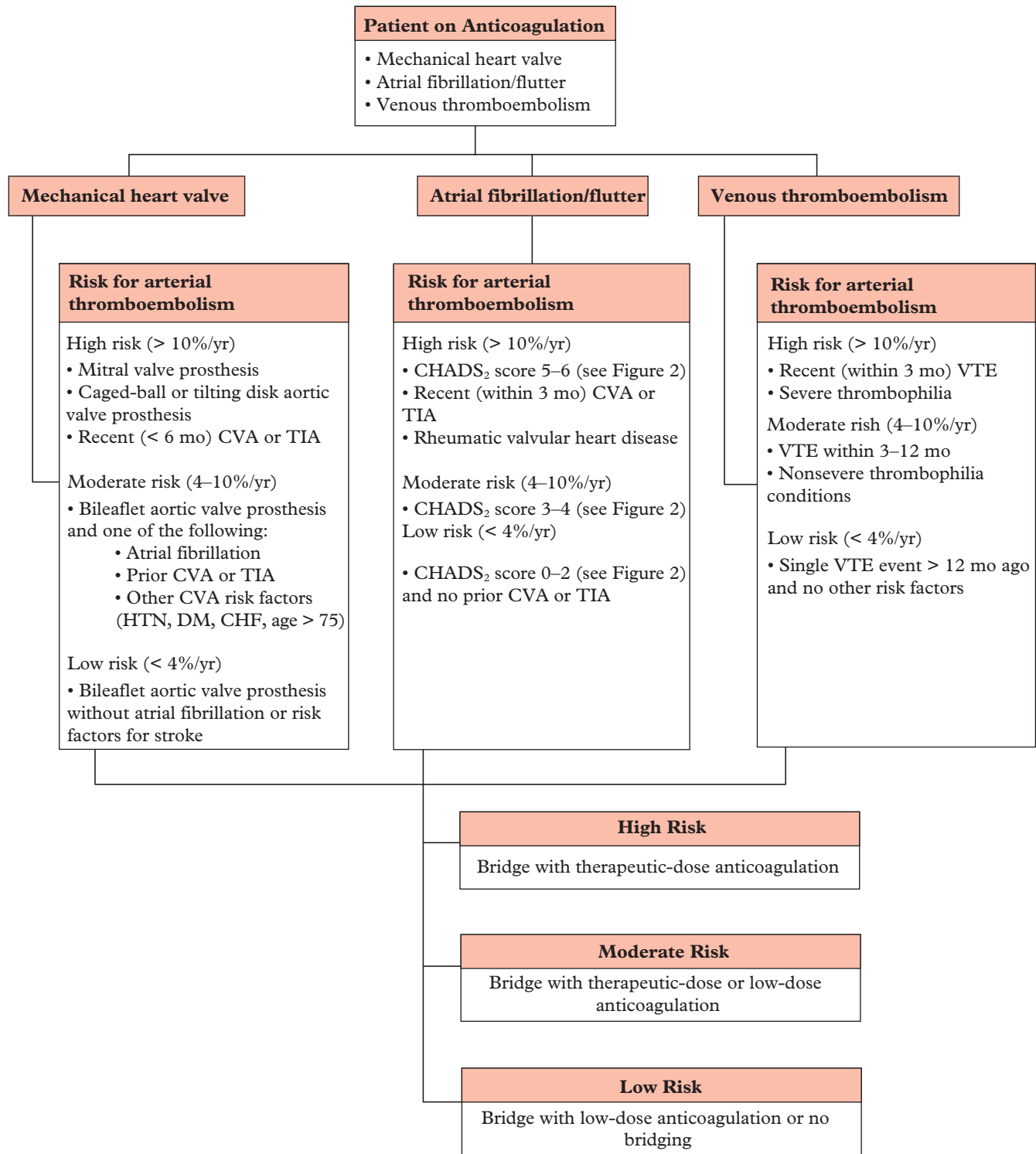


Figure 1 Approach to perioperative anticoagulation. Adapted from Douketis JD et al.⁵⁷ CHF = congestive heart failure; CVA = cerebrovascular accident; DM = diabetes mellitus; HTN = hypertension; TIA = transient ischemic attack; VTE = venous thromboembolism.

noncardiac surgery; however, there are some data to suggest increased bleeding complications with clopidogrel use.¹⁹ In contrast to noncardiac surgery, several studies have characterized the effect of antiplatelet therapy on postoperative bleeding after cardiac surgery. The Department of Veterans

Affairs Cooperative Study on Antiplatelet Therapy randomized 772 patients undergoing coronary artery bypass grafting (CABG) to receive preoperative aspirin versus placebo and found a significant increase in the risk of abnormal postoperative bleeding and the need for reoperation with aspirin.²⁰

		0 points	1.9%/yr	
C: recent CHF exacerbation	1 point	1 point	2.8%/yr	LOW
		2 points	4.0%/yr	
H: HTN, even if controlled	1 point			
A: age > 75	1 point	3 points	5.9%/yr	MODERATE
D: diabetes	1 point	4 points	8.5%/yr	
S: stroke history	2 points	5 points	12.5%/yr	HIGH
		6 points	18.2%/yr	

Figure 2 CHADS₂ score. Adapted from Gage BF et al.⁵⁸ CHF = congestive heart failure; HTN = hypertension.

Despite this potential for increased bleeding, preoperative aspirin is usually continued during CABG surgery as a result of an improvement in early graft patency.²¹ Clopidogrel use in CABG surgery is associated with an increase in major bleeding, bleeding-related complications, transfusion requirements, and potentially increased use of health care resources.²² However, unlike aspirin, there are no studies demonstrating a benefit of perioperative clopidogrel use prior to elective CABG.

Many large randomized trials have demonstrated a significant risk reduction with the long-term use of antiplatelet agents in patients who are at high risk for atherothrombotic and ischemic cardiac and cerebrovascular events^{8,23} and an increase in ischemic and bleeding events and mortality when these agents are discontinued.²⁴ Thus, in high-risk patients, there is a potential risk reduction in perioperative cardiac and stroke complications with the continuation of antiplatelet drugs during the perioperative period that justifies the potentially increased bleeding risk. Studies that have compared aspirin with clopidogrel²³ or dual aspirin and clopidogrel therapy with aspirin alone²⁵ have failed to show a clinically meaningful increased benefit for cardiovascular risk reduction with clopidogrel used in place of or in addition to aspirin. Because of this, as well as the empirical notion that clopidogrel has a higher bleeding risk than aspirin during surgery, aspirin should be continued in high-risk patients during the perioperative period and clopidogrel should be withheld. Patients who are receiving antiplatelet therapy because of bare metal or drug-eluting stents are a different matter. Premature discontinuation of antiplatelets, in particular clopidogrel, has been shown to increase the risk of in-stent thrombosis. This was demonstrated in a study of patients who underwent noncardiac surgery within 90 days of coronary stenting in which six of seven patients in whom thienopyridine antiplatelet therapy was discontinued prior to noncardiac surgery died postoperatively in a manner suggestive of stent thrombosis, compared with only one of 20 patients in whom the thienopyridine was continued.²⁶ For bare metal stents, dual antiplatelet therapy with aspirin and clopidogrel should be continued for up to 6 weeks to allow for neointimal coverage of the stent, after which time, clopidogrel may be discontinued if necessary prior to surgery.²⁷ For drug-eluting stents, the use of dual antiplatelet therapy

for a period longer than 12 months has not been shown to significantly reduce the rate of myocardial infarction or death from cardiac causes when compared with aspirin monotherapy.²⁸ Thus, for patients requiring surgery 12 months after drug-eluting stent placement, clopidogrel may be stopped as long as aspirin therapy is continued. Figure 3 provides an evidence-based approach for the management of perioperative antiplatelet therapy.

Perioperative VTE Prophylaxis

The Virchow triad describes the three primary contributing factors that lead to thrombosis: stasis, hypercoagulability, and endothelial injury. Surgical patients are frequently immobilized as a result of pain or prolonged bed rest and are generally hypercoagulable because of thromboplastin and tissue factor release after surgical trauma, and many surgical procedures involve the manipulation of blood vessels leading to endothelial injury. Thus, surgical patients are at a particularly increased risk for deep vein thrombosis (DVT) and its most feared complication, pulmonary embolism (PE). VTE rates in surgical patients vary depending on the type of surgery performed and patient-specific risk factors.

The highest rates of VTE in elective surgery occur in patients undergoing hip and knee surgery; asymptomatic DVTs are found in 30 to 60% of patients not receiving thromboprophylaxis who undergo routine screening with postoperative venography.²⁹ In general surgery patients undergoing elective abdominal surgery not receiving thromboprophylaxis, the rates of asymptomatic DVT range from 15 to 40%.³⁰ However, despite the high rate of asymptomatic DVTs reported in many studies that use routine screening, the rates of symptomatic DVT and PE are much lower. Unpublished data using the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) data set, which contains information on 363,884 patients who underwent surgery from 2005 to 2007 from 186 participating hospitals, provide an average rate of clinically significant DVT and PE in surgical patients of 0.96%. Using the Nationwide Inpatient Sample, Mukherjee and colleagues evaluated the VTE rates for various abdominal operations and found surprising results.³¹ Bariatric surgery, a procedure felt to be a high risk for VTE given the presence of significant

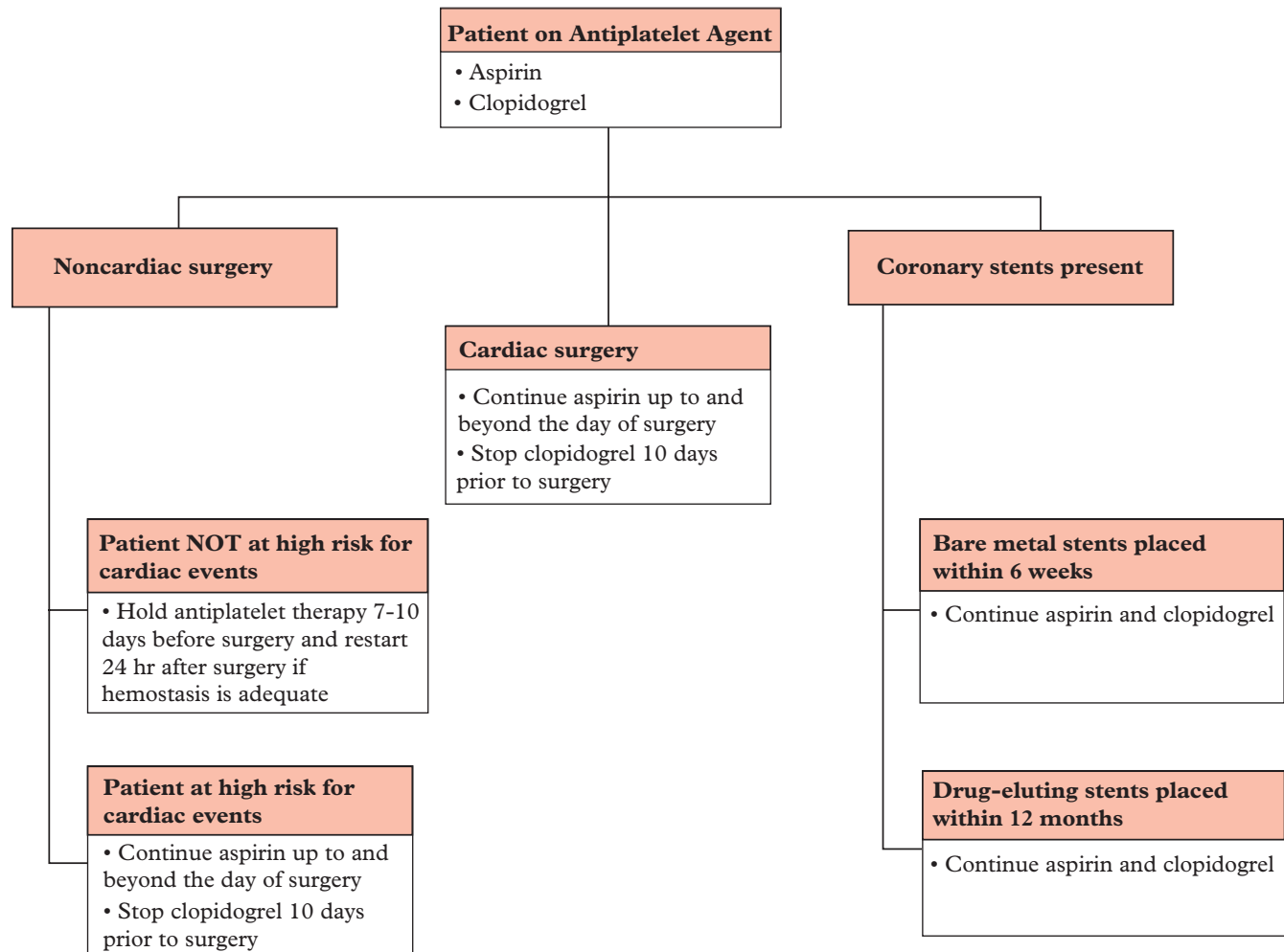


Figure 3 Approach to perioperative antiplatelet therapy.

patient risk factors, namely obesity, had, surprisingly, the lowest risk of VTE among the procedures studied, at 0.35%. VTE rates were 0.85% for nephrectomy, 1.76% for hepatectomy, 2.36% for splenectomy, 2.58% for gastrectomy, 2.91% for pancreatectomy, and 3.66% for esophagectomy. When multivariate analysis was performed to adjust for nonprocedural risk factors, bariatric surgery still had a lower likelihood of developing VTE [see Table 1]. Also in this study, mortality was 3.5 times higher in those who developed VTE than those who did not, and VTE was nearly 3 times as common following nonelective procedures compared with elective procedures. Certain low-risk procedures do not require VTE prophylaxis because of a low risk of thrombotic events. For example, the risk of DVT or PE complications in thyroidectomy and parathyroidectomy patients is very low at 0.16%, with a risk of bleeding requiring a return to the operating room that is 10-fold higher. VTE prophylaxis should be reserved for only the highest risk patients undergoing these procedures.³²

The rationale for VTE prophylaxis for high-surgical risk patients is based on the high prevalence of VTE complications for many surgical procedures; the excess morbidity, mortality, and cost attributed to these complications; and the safety, efficacy, and cost-effectiveness of VTE prophylaxis in

Table 1 Odds of Developing Venous Thromboembolism by Surgical Procedure Relative to Bariatric Surgery*

Procedure	All Procedures	Elective Procedures Only
Nephrectomy	1.19	1.0
Colorectal surgery	1.87	1.62
Pancreatectomy	2.07	1.46
Gastrectomy	2.44	1.68
Esophagectomy	2.47	2.06
Hepatectomy	2.55	2.13
Splenectomy	2.69	2.27

Adapted from Mukherjee D et al.³¹

* Adjusted for age, gender, year, Charlson Comorbidity Index score, length of stay, hospital teaching status, elective procedure status, trauma, and malignancy.

reducing these complications. The high prevalence of VTE complications has already been demonstrated in the previous paragraph. The incidence of fatal PE in general surgery patients is as high as 0.9%,³³ and the development of VTE can increase the median length of stay by as much as 11 days,

with an increase in median total hospital charges of up to \$50,000 for each event.³¹ Collins and colleagues reviewed 46 randomized trials of perioperative subcutaneous heparin that included nearly 13,000 patients who underwent general, orthopedic, and urologic surgery.³⁴ They found a 68% reduction in DVT, a 67% reduction in PE, and a 21% reduction in total mortality after surgery in patients who received perioperative heparin prophylaxis compared with controls, with a small increase in bleeding (5.9% compared with 3.8% for controls), most of which were not clinically significant. A systematic review of 33 randomized, controlled trials examined the rates of bleeding complications with pharmacologic VTE prophylaxis and found that bleeding complications requiring a change in care occur less than 3% of the time and major bleeding complications, such as gastrointestinal tract (0.2%) or retroperitoneal (< 0.1%) bleeding, were infrequent.³⁵ In cost-effectiveness studies, VTE prophylaxis has been found to be more cost-effective than no prophylaxis in orthopedic surgery, trauma, and general surgery.³⁶ Mamdani and colleagues demonstrated in abdominal surgery patients that overall costs (including costs of labor) associated with surgical prophylaxis with conventional low-dose heparin, dalteparin, and intermittent pneumatic compression (IPC) were \$84, \$122, and \$102, respectively, compared with \$112 for no prophylaxis.³⁷ Compared with no prophylaxis, the cost per mortality prevented was \$6,087 for conventional low-dose heparin, \$3,125 for IPC, and \$2,857 for dalteparin.

Despite the lower risk of VTE in bariatric surgery, bariatric surgeons have performed exceptionally well in adhering to thromboprophylaxis guidelines, with one study demonstrating a 95% adherence rate.³⁸ This is in contrast to the findings of the ENDORSE trial, a multinational cross-sectional survey that assessed the prevalence of VTE in the acute hospital care setting and the proportion of at-risk patients who receive appropriate prophylaxis based on American College of Chest Physicians (ACCP) criteria.³⁹ The authors found that 64.4% of all surgical patients were at risk for VTE, and of the surgical patients at risk, only 58.5% received ACCP-recommended VTE prophylaxis. Interestingly, of the surgical patients who were deemed to be at low risk for VTE, 34% received VTE prophylaxis that was not indicated. The proportion of patients receiving appropriate prophylaxis varied from 88% of patients undergoing hip or knee replacement to 69% of those undergoing colorectal surgery and 50% undergoing urologic procedures.

Clearly, passive strategies to promote adherence to VTE prophylaxis guidelines have not been successful. The ACCP evidence-based practice guidelines have provided four recommendations for hospital prophylaxis policy: for every general hospital, a formal, active strategy should be developed that addresses the prevention of VTE; the local thromboprophylaxis strategy should be in the form of a written, institution-wide thromboprophylaxis policy; strategies shown to increase thromboprophylaxis adherence should be adopted, including computer decision support systems, preprinted orders, and periodic audit and feedback; and passive methods, such as distribution of educational materials or educational meetings, are not recommended as sole strategies to increase adherence to thromboprophylaxis.³⁰ It is imperative that surgeons be active participants in their local institutional prophylaxis policy. An example of an institutional VTE policy is included in Table 2.

Table 2 Venous Thromboembolism Risk Assessment

1 Point Age 41–60 yr Procedure with local anesthesia Prior surgery (< 1 mo) History of inflammatory bowel disease Obesity (BMI 30–39) Acute myocardial infarction (< 1 mo) Heart failure exacerbation (< 1 mo) Swollen legs (current) Sepsis (< 1 mo) Serious lung disease, e.g., pneumonia (< 1 mo) Any patient currently on bed rest Leg plaster cast or brace 1 Point (for women only) Oral contraceptives or hormone replacement therapy Pregnancy or postpartum (< 1 mo) History of unexplained stillborn infant, spontaneous abortion (≥ 3), premature birth with toxemia, or growth-restricted infant 2 Points Age 61–74 yr Surgery lasting < 2 hr History of malignancy Central venous access Morbid obesity (BMI 40–49) 3 Points Age ≥ 75 yr History of SVT, DVT/PE Surgery lasting 2–3 hr BMI ≥ 50 Present cancer or chemotherapy Established thrombophilia 5 Points Elective lower extremity arthroplasty Hip, pelvis, or leg fracture (< 1 mo) Stroke (< 1 mo) Multiple trauma (< 1 mo) Acute spinal cord injury (< 1 mo) Surgery lasting > 3 hr		
Total Risk Factor Score	Risk Level	Prophylaxis Regimen
0–1	Low	Early and frequent ambulation
2	Moderate	Heparin 5,000 units SC every 8–12 hr
3–4	High	Heparin 5000 units SC every 8 hr OR LMWH SC (e.g., dalteparin 5000 units every 24 hr) ± Sequential compression devices OR Knee-high antiembolism stockings
≥ 5	Highest risk	Heparin 5,000 units SC every 8 hr OR LMWH SC (e.g., dalteparin 5,000 units every 24 hr) AND Sequential compression devices OR Knee-high antiembolism stockings

Adapted from Caprini JA.⁵⁹

BMI = body mass index; DVT = deep vein thrombosis; PE = pulmonary embolism; SC = subcutaneous; SVT = supraventricular tachycardia.

The type of anticoagulant used for prophylaxis depends on institutional or surgeon preference and patient factors. The two most commonly used anticoagulants are low-dose unfractionated heparin (LDUH) and LMWH. The efficacy of LDUH compared with no prophylaxis was convincingly demonstrated in the Collins and colleagues' meta-analysis, with the three times daily dosing being more efficacious than twice-daily dosing, without an increase in bleeding complications.³⁴ LMWH has also been shown to reduce VTE compared with no prophylaxis, with one meta-analysis showing a significant reduction in clinical VTE and a trend toward a reduction in the overall mortality rate. Higher doses of LMWH improved efficacy but increased the rates of bleeding, including major bleeding events.⁴⁰ Comparisons between LDUH and LMWH have not demonstrated one to be superior to the other in terms of efficacy for general surgical procedures. Figure 4 provides an evidence-based approach to the perioperative management of VTE prophylaxis in general surgery patients.

Koch and colleagues performed a publication-based meta-analysis of 36 double-blind studies comparing LDUH and LMWH for surgical prophylaxis.⁴¹ LDUH and LMWH had similar efficacy in general surgery patients, and LDUH had a decreased bleeding rate compared with higher-dose LMWH and an increased bleeding rate compared with lower-dose LMWH. The same group performed a meta-analysis based on original patient data and confirmed these findings, including a significantly lower risk of wound hematoma in low-dose LMWH compared with LDUH.⁴² In both studies, LMWH was more efficacious compared with LDUH in orthopedic patients. LMWH is also the standard of care for major trauma patients given its demonstrated superiority and equivalent bleeding risk compared with LDUH.⁴³

Fondaparinux, a synthetic pentasaccharide factor Xa inhibitor, also has been proven efficacious for VTE prophylaxis

both in placebo trials⁴⁴ and in comparison with LMWH.⁴⁵ The benefits of LDUH include reduced costs, its ability to be used in patients with renal failure, its shorter half-life, and its safety in patients with regional blocks and epidural catheters. LMWH and fondaparinux require less frequent dosing and may have a lower incidence of wound hematomas (for low-dose LMWH) and a lower risk of heparin-induced thrombocytopenia. However, the factor Xa inhibitors require renal and weight-based dosing and are contraindicated in patients with a creatinine clearance less than 30 mL/min. Newer agents, such as the orally active direct factor Xa inhibitor rivaroxiban, have been shown to be significantly more effective than once-daily LMWH (with equivalent safety) in patients undergoing elective total hip arthroplasty⁴⁶ and total knee arthroplasty.⁴⁷ These agents are promising for both their increased efficacy and the ease of continuing oral dosing after discharge from the hospital for extended prophylaxis.

Of the surgical patients found to be at risk for VTE in the ENDORSE trial, 9% were considered to have a bleeding risk high enough to be considered a contraindication to anticoagulant prophylaxis.³⁸ In patients who are at a high bleeding risk and also at risk for VTE who would otherwise be treated with anticoagulant prophylaxis, mechanical methods of thromboprophylaxis, such as graduated compression stockings, IPC, or venous foot pumps, should be used. Once the bleeding risk has resolved, anticoagulant prophylaxis can be substituted or added to mechanical prophylaxis.

The initiation of VTE prophylaxis is particularly challenging in multisystem trauma because of concomitant bleeding risks from intracranial, abdominal, thoracic, retroperitoneal, and spinal injuries. Furthermore, competing input from consulting services and the need for numerous surgical interventions can delay the initiation of VTE prophylaxis. Because of these challenges, a VTE prophylaxis protocol should be

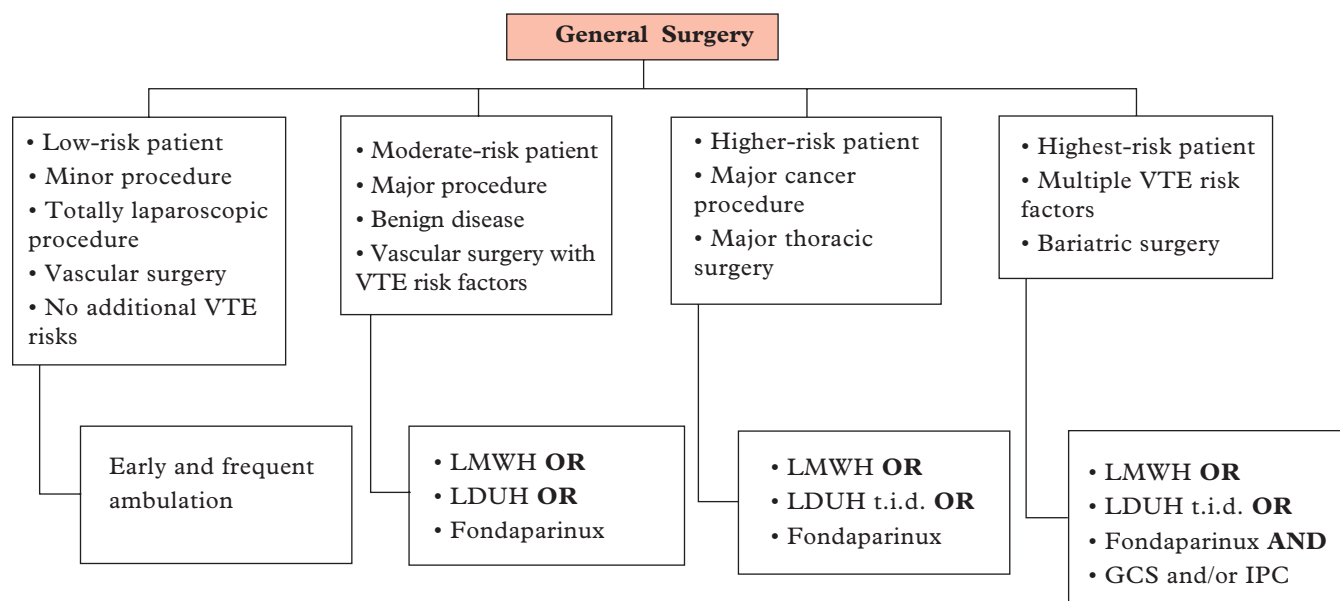


Figure 4 Approach to perioperative venous thromboembolism (VTE) prophylaxis: general surgery. Adapted from Geerts WH et al.³⁰ GCS = graduated compression stocking; IPC = intermittent pneumatic compression; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin.

instituted at any center that takes care of the multiply injured trauma patient. In trauma patients, there is evidence that VTE prophylaxis does not need to be withheld for most injuries, including traumatic brain injury, if ongoing hemorrhage has been ruled out. Cothren and colleagues placed patients at high risk for VTE, including patients with stable intracranial injuries, on a protocol that initiated once-daily dalteparin an average of 3 days postinjury and continued it through most surgical procedures.⁴⁸ This allowed a daily, uninterrupted prophylaxis regimen in 74% of patients and an overall DVT rate of 3.9%, a PE rate of 0.8%, a wound complication rate of 2.7%, blood transfusions in 3%, and no exacerbations of intracranial bleeding or deaths as a result of hemorrhage. Figure 5 provides an evidence-based approach to perioperative VTE prophylaxis in the trauma patient.

Prophylactic inferior vena cava (IVC) filters have been increasingly used over the last decade⁴⁹ as a result of the

advent of retrievable filters. Two groups that have seen the largest increase in prophylactic IVC filter placement are bariatric patients and multisystem trauma patients, particularly acute spinal cord injury (SCI) patients. As discussed previously, bariatric surgery patients do not have a higher risk of VTE events compared with other surgical patients, and the risk of a fatal PE after bariatric surgery is 0.2%.⁵⁰ Given that the vast majority of bariatric patients are able to receive perioperative thromboprophylaxis, prophylactic IVC filter placement in this population is not warranted. In fact, not only do prophylactic IVC filters for gastric bypass surgery not reduce the risk of pulmonary embolism, they may also lead to additional complications.⁵¹ In contrast to bariatric surgery, multisystem trauma does confer a greater risk of VTE complications. Furthermore, trauma patients are more likely to have a contraindication to anticoagulation, leading to a potential delay in the initiation of prophylaxis.

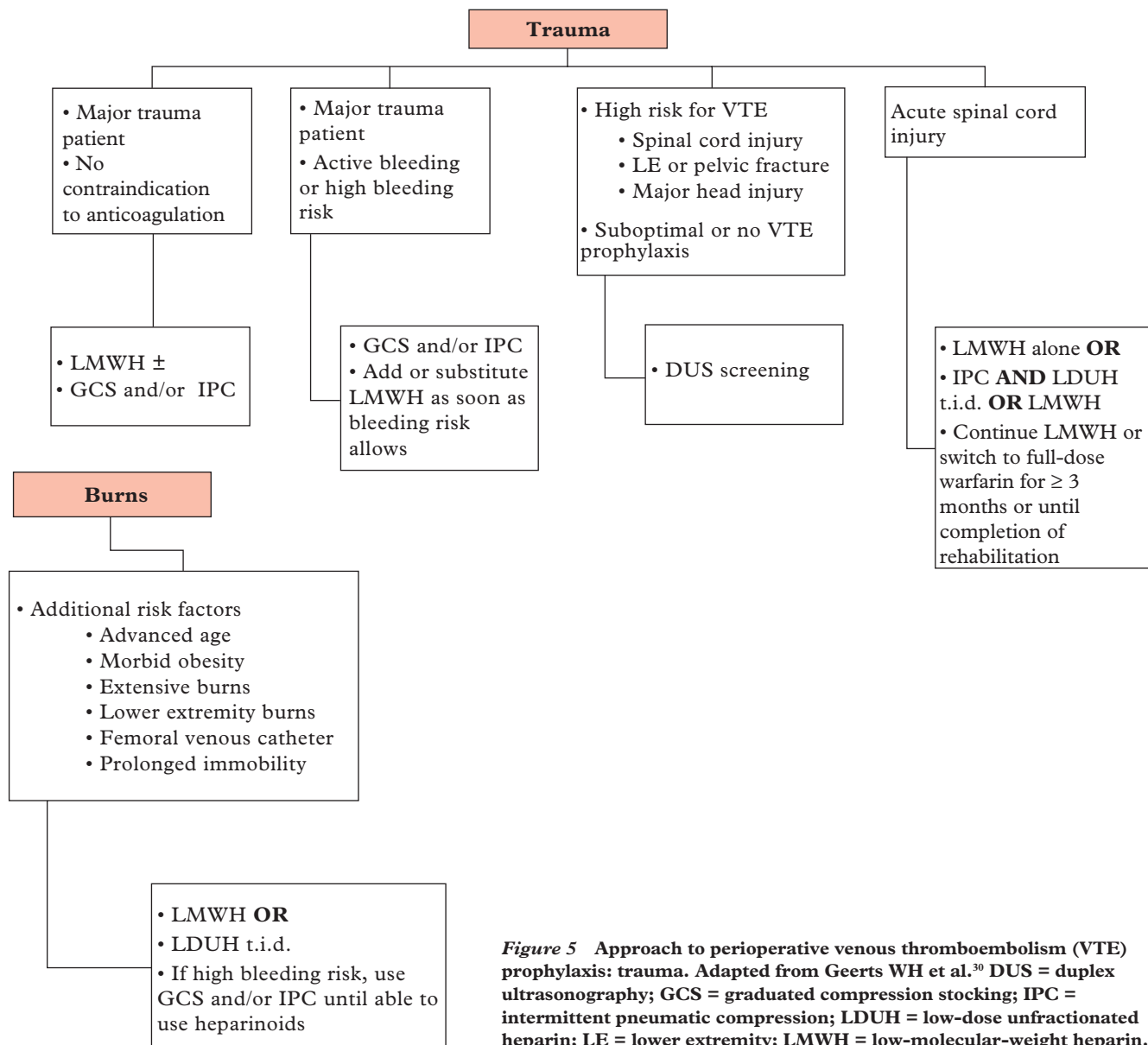


Figure 5 Approach to perioperative venous thromboembolism (VTE) prophylaxis: trauma. Adapted from Geerts WH et al.³⁰ DUS = duplex ultrasonography; GCS = graduated compression stocking; IPC = intermittent pneumatic compression; LDUH = low-dose unfractionated heparin; LE = lower extremity; LMWH = low-molecular-weight heparin.

The premise behind prophylactic IVC filters in trauma patients is to protect patients from a PE while they are not able to receive anticoagulation. However, there are no randomized, controlled trials demonstrating the efficacy of prophylactic IVC filters in trauma patients. Furthermore, complication rates for IVC filter placement are surprisingly high. In a review of the current literature up to 2005, the complication rate for prophylactic IVC filters was 13%, with a 1% rate of PEs (40% of these being fatal), a 2% rate of IVC thrombosis and occlusion, a 2% rate of insertion-site thrombosis, and a 1% risk each for filter migration, filter misplacement, and filter tilt.⁵² These rates are comparable to those in more recent studies conducted by experienced practitioners. Each of these complication rates exceeds the rates of PE in trauma patients (0.27 to 0.48%),^{53,54} Prophylactic IVC filters in high-risk patients who cannot receive pharmacologic prophylaxis were found to increase the risk of DVT in one study and were not cost-effective compared with serial duplex ultrasound screening, which was associated with better clinical outcomes and lower costs.⁵⁵ Patients with acute SCI represent perhaps the highest-risk group in terms of VTE risk. However, the incidence of VTE in SCI patients is similar to that of the overall trauma population when appropriate DVT prophylaxis is used, making routine placement of prophylactic caval filters unnecessary.⁵⁶ Patients

in whom prophylactic IVC filters may be appropriate include SCI patients with long bone and pelvic fractures, patients with DVT formation despite prophylactic anticoagulation, and patients with contraindications to anticoagulation and a DVT documented on serial duplex ultrasound screening.

Patients receiving LDUH for VTE prophylaxis should have the first dose administered 1 to 2 hours prior to general anesthesia as most of the LDUH thromboprophylaxis trials used this regimen and it is thought that the risk of VTE starts with the onset of general anesthesia. VTE prophylaxis for most patients should be continued until hospital discharge or for at least 7 days postoperatively as this is the time when most VTE events occur. However, certain high-risk groups are at risk for late VTE events and should receive extended VTE prophylaxis after hospital discharge. These patients include major cancer surgery patients and patients who have previously had a VTE (VTE prophylaxis up to 28 days after surgery); patients undergoing hip or knee replacement surgery (VTE prophylaxis from 10 to 35 days after surgery); major trauma patients (VTE prophylaxis continued during inpatient rehabilitation); and patients with acute SCI (VTE prophylaxis for at least 3 months or until the completion of inpatient rehabilitation).³⁰

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33 PERIOPERATIVE MANAGEMENT OF PATIENTS ON STEROIDS REQUIRING SURGERY

Alexandra Reiher, MD, and Rebecca S. Sippel, MD, FACS

Perioperative glucocorticoid replacement therapy can be challenging, but appropriate replacement is essential to optimize the patient's outcome. Intermittent and chronic steroid use results in decreased adrenocorticotrophic hormone (ACTH) secretion by the pituitary gland, which over several weeks results in adrenal gland atrophy, eventually leading to secondary adrenal insufficiency.¹ Patients with chronic lung disease, inflammatory bowel disease, rheumatoid arthritis, and solid-organ transplantations are often on steroid supplementation either intermittently or chronically. Determining which of these patients requires high-dose steroids perioperatively can be difficult. Insufficient dosing of glucocorticoids during the perioperative period can result in hypotension and even death. Excessive treatment with glucocorticoids decreases wound healing and increases susceptibility to infection, among a myriad of other complications. This chapter provides guidelines toward evaluation and treatment of secondary adrenal insufficiency during the perioperative period.

Historical Perspective

Iatrogenic adrenal insufficiency was first identified in 1952 by Fraser and colleagues.² A patient on chronic steroids underwent surgery and subsequently developed acute adrenal crisis attributable to preoperative withdrawal from glucocorticoid therapy. A similar case was reported by Lewis and colleagues in 1953.³ A patient who had surgical repair for a flexion contracture of the right knee died a few hours after surgery. The patient had been on cortisone daily for 5 months before surgery, but his cortisone had been held the day prior to and the day of his surgery. A postmortem examination revealed diffuse atrophy and hemorrhage of the adrenal glands, confirming the diagnosis of adrenal insufficiency. The authors then published the first set of guidelines regarding perioperative glucocorticoid management. They recommended increasing glucocorticoids fourfold to avoid intraoperative hypotension and death. These recommendations are probably what has led us to overtreat most patients today. We now know that this dose is in great excess to the normal physiologic response to surgery.

Hypothalamic-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenal (HPA) axis is activated during acute physical or emotional stress. Corticotropin-releasing hormone (CRH) is secreted by the hypothalamus as a result of stimulation by serotonin. CRH secretion is

inhibited by noradrenaline and cortisol. CRH secretion results in secretion of plasma ACTH from the pituitary gland, stimulating secretion of cortisol from the zona fasciculata in the adrenal glands [see Figure 1]. ACTH is also stimulated by adrenaline. Normal basal secretion of cortisol by the adrenal gland is 8 to 10 mg/day.⁴ A study using stable isotope dilution thermospray liquid chromatography–mass spectrometry confirmed that the average cortisol production rate per day was approximately 9.9 mg.⁵

During a minor procedure or surgery, the adrenal gland produces up to 50 mg/day of cortisol.^{6,7} A study by Plumpton and colleagues evaluated plasma cortisol levels in patients during and after major and minor surgeries.⁷ In patients undergoing major surgery, cortisol levels initially fell after premedication, followed by a rapid rise during surgery and a further rise in cortisol during the early postoperative period. A similar pattern of response was seen in patients undergoing minor surgeries, but with a smaller peak. Peak values occur within 4 to 6 hours after surgery or injury and return to baseline after 24 hours.⁸ After major surgery, such as cardiac surgery, cortisol secretion is 75 to 100 mg on the first day and can remain elevated for 48 to 72 hours.⁶ Secretion rates greater than 200 mg/day within the first 24 hours of surgery are rare.

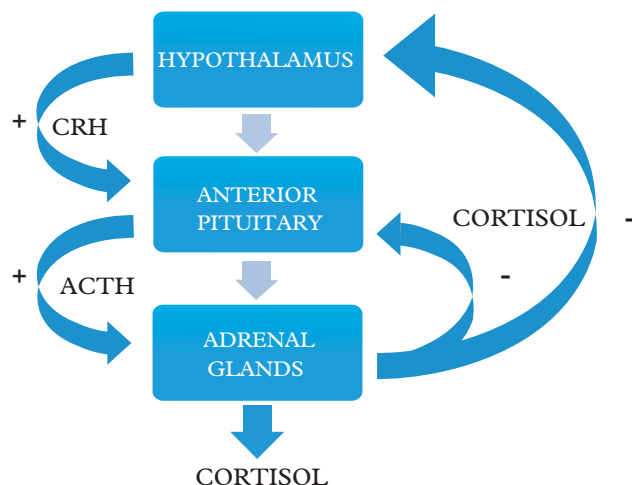


Figure 1 Hypothalamic-pituitary-adrenal axis. ACTH = adrenocorticotrophic hormone; CRH = corticotropin-releasing hormone.

Assessing a Patient's HPA Axis

BASELINE CORTISOL LEVELS

Determining whether a patient's HPA axis is functioning is the first step to deciding if glucocorticoid supplementation is indicated during the perioperative period. Random serum cortisol levels are of little utility because of diurnal variation, but early-morning serum cortisol levels drawn between 7 and 9 am will reflect maximal secretion. Morning cortisol levels of 18 to 20 µg/dL reflect an intact adrenocortical reserve. No further testing is needed in these patients.⁹ A morning cortisol level below 3 µg/dL strongly suggests adrenal insufficiency, and the level should be repeated. If it remains low, physiologic steroid replacement should be initiated, and no further testing is necessary. Patients with baseline cortisol levels between 3 and 11 µg/dL benefit from an additional workup for adrenal insufficiency to clarify their adrenal function. Dynamic testing is useful in this setting to determine a patient's ability to produce cortisol in response to stress or ACTH stimulation¹⁰ [see Figure 2].

Serum cortisol reflects primarily protein-bound cortisol levels. Estrogen, which increases cortisol-binding globulin, increases total cortisol concentrations. This can lead to falsely elevated cortisol levels. Low serum albumin concentrations can cause falsely low total serum cortisol levels, even though they have normal biologically active free cortisol concentrations. Measuring serum free (unbound) cortisol levels is thus more accurate in these patients.⁹

INSULIN-INDUCED HYPOGLYCEMIA

The insulin-induced hypoglycemia test is considered the gold standard but is rarely used today because of the associated risks, including coma and seizures. This test involves

administering intravenous (IV) insulin (0.10 to 0.15 units/kg) to a fasting patient until hypoglycemia (blood glucose < 40 mg/dL) is achieved. A normal stress response to hypoglycemia will elicit an increase in serum cortisol.⁹ A patient with an intact HPA axis will have a rise in cortisol to at least 18 to 20 µg/dL.¹¹ This must be performed in a controlled setting, preferably an experienced endocrine clinic with close supervision.

ACTH STIMULATION TEST

The ACTH stimulation test is more commonly used to determine adrenal function. Synthetic ACTH (cosyntropin [Cortrosyn]) is administered intravenously in a dose of 250 µg. Baseline, 30-minute, and 60-minute cortisol levels are obtained. Normal adrenal function will produce a peak cortisol of at least 18 to 20 µg/dL and typically a delta of more than 8 to 10 µg/dL. The delta level (change from baseline) is not recommended as the sole determinant of adequate response to ACTH stimulation. An expected delta of 8 to 10 µg/dL in the setting of a peak cortisol lower than 18 µg/dL should still be considered an abnormal response.¹²

Performing an ACTH stimulation test in the morning yields the best results. It is important to hold exogenous steroids for 24 hours prior to the test, and longer-acting glucocorticoids, such as prednisone, should be held for 5 to 7 days. This dose of cosyntropin is supraphysiologic and can stimulate cortisol levels to the normal range in a patient with partial adrenal insufficiency. A low-dose cosyntropin stimulation test with 1 µg can be performed to better evaluate patients with partial adrenal suppression or central adrenal insufficiency but is not currently recommended because of a need for further studies to determine the efficacy of this test. Also, this low dose of cosyntropin is not commercially

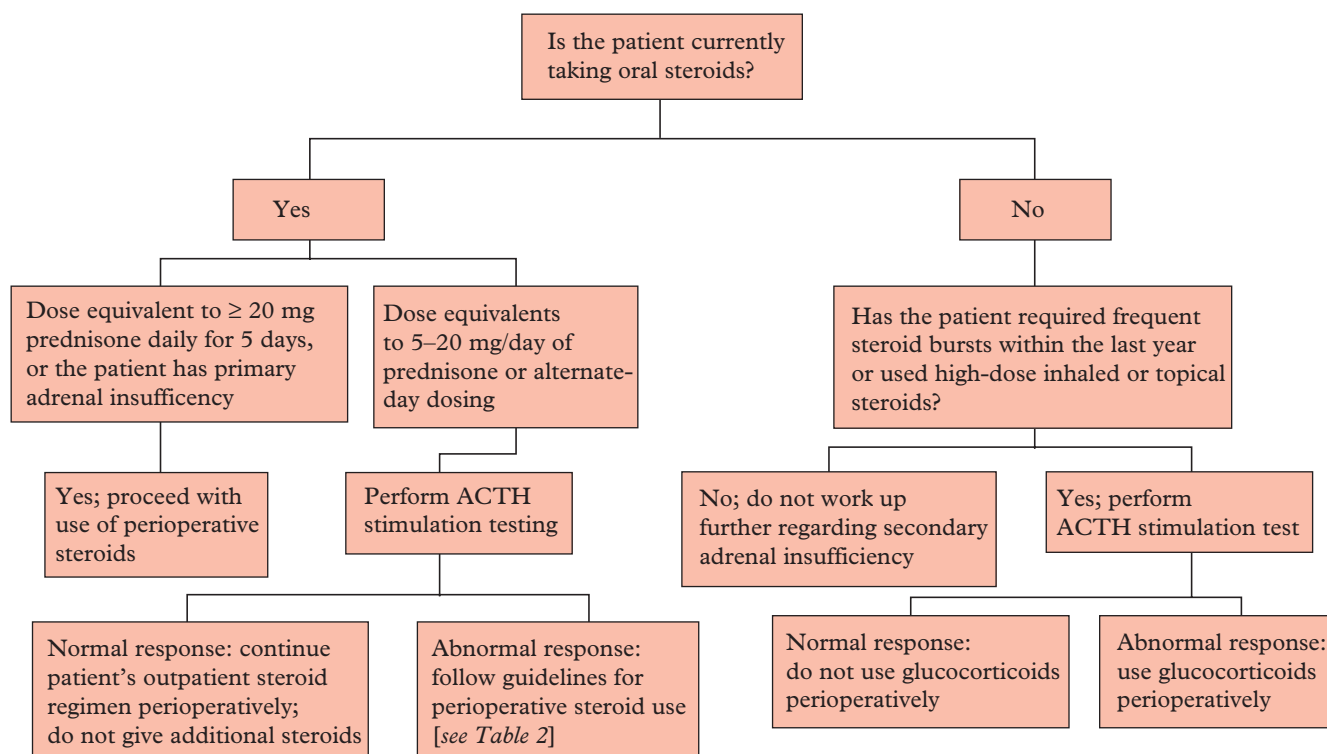


Figure 2 Algorithm for evaluation of the patient on steroids in the perioperative period. ACTH = adrenocorticotrophic hormone.

available, and serial dilutions are therefore required. This is both inconvenient and has the potential for inconsistent dosing.¹³

The ACTH stimulation test is easier to perform than the insulin tolerance test, requires less supervision, and does not carry the risks associated with inducing hypoglycemia. The ACTH stimulation test has been shown to have a close correlation with the insulin tolerance test ($r = .92$; $p < .0001$).¹⁴ The ACTH stimulation test is the recommended test for evaluating adrenal insufficiency.

When to Suspect an Impaired HPA Axis

PATIENTS CURRENTLY ON ORAL STEROIDS

The exact time period it takes for a patient to become adrenally suppressed while treated with glucocorticoids, and the time it takes to recover adrenal function after discontinuation of steroids, is not known. When evaluating for HPA suppression, one needs to consider both the dose and the duration of previous glucocorticoid therapy. In general, any patient who has received doses equivalent to 20 mg of prednisone for more than 5 days is at risk for suppression of the HPA axis. If the glucocorticoid doses are closer to but above the physiologic range, 1 month is likely the minimal interval. For patients on chronic steroids, if the dose is equivalent to 5 mg or less of prednisone daily [see Table 1 for steroid conversions], these patients have a normal response to HPA testing and do not require additional glucocorticoid treatment perioperatively. Patients receiving between 5 and 20 mg of prednisone daily (or an equivalent dose of another steroid) should undergo further testing.¹⁵ Patients receiving alternate-day glucocorticoid treatment (a short-acting glucocorticoid given every 48 hours, in the morning) tend to have less adrenal suppression than patients taking steroids on a daily basis. These patients should be evaluated for adrenal suppression as the response is not the same between patients.¹³

PATIENTS USING INHALED STEROIDS

A meta-analysis by Masoli and colleagues evaluated adrenal function in patients receiving inhaled corticosteroids.¹⁶ Many studies were eliminated because of insensitive measurements for testing the HPA axis, lack of placebo control, and inclusion of patients on oral steroids. Five randomized, controlled studies were analyzed. Patients receiving therapeutic doses of inhaled fluticasone (50 to 500 µg/day) were found to have minimal abnormal responses to a cosyntropin stimulation test. Four percent of patients had an abnormal response

to adrenal function testing. For each 500 µg/day increase in a patient's fluticasone dose, the odds ratio of an abnormal adrenal function test increased 1.4-fold. It is necessary to consider adrenal suppression in all patients on inhaled corticosteroids, particularly those receiving supratherapeutic doses.

PATIENTS USING TOPICAL STEROIDS

Although it is unknown what potency or dose of topical steroid can induce secondary adrenal suppression, the risk associated with topical steroids must be assessed. The following factors increase the risk of adrenal suppression: application to a large surface area of skin, long-term use, associated use of occlusive dressings, and use of high-potency (class I) glucocorticoid agents.¹⁷

PATIENTS PREVIOUSLY ON STEROIDS

Multiple studies have shown normal adrenal responses within 3 weeks of discontinuing short-term glucocorticoid therapy. It would therefore be safe to assume that recovery from suppression may be incomplete for approximately 2 months after glucocorticoid treatment. For patients who have had prolonged exposure to high doses of glucocorticoids, recovery can take up to 1 year. These patients should undergo formal testing, preferably an ACTH stimulation test, to determine adrenal responsiveness. A normal response eliminates the need for perioperative glucocorticoid supplementation.^{7,13} However, should such a patient develop hypotension perioperatively, there should be a low threshold to administer a dose of IV hydrocortisone. Obtaining a complete history regarding current and past use of glucocorticoids is necessary to avoid potential adrenal crisis in the perioperative period.

PATIENTS WITH KNOWN PRIMARY ADRENAL INSUFFICIENCY

Patients with primary adrenal insufficiency require both mineralocorticoid and glucocorticoid replacement therapy. The most common cause of primary adrenal insufficiency in the United States is autoimmune adrenal insufficiency, or Addison disease. A thorough review of a patient's medical history should elicit this information. These patients often have hyperpigmentation of their skin and mucosa because of elevated plasma β-lipotropin concentrations (derived from pro-opiomelanocortin) and increased synthesis of melanin by melanocytes.⁹ Patients with primary adrenal insufficiency typically take fludrocortisone 0.05 to 0.1 mg once daily, as well as hydrocortisone 15 mg daily divided into two to three doses (typically 10 to 15 mg in the morning and 5 to 10 mg in the evening).¹⁸ Glucocorticoid replacement must be continued in the perioperative period because of primary disease of the HPA axis. If a patient with primary adrenal insufficiency is receiving hydrocortisone in excess of 100 mg/day, mineralocorticoid supplementation can be held. Hydrocortisone has both mineralocorticoid and glucocorticoid properties at high doses. However, once the glucocorticoids are tapered to below 100 mg/day, fludrocortisone must be restarted.

Argument against Supraphysiologic Glucocorticoid Treatment in the Perioperative Period

Weighing the risks and benefits of glucocorticoid supplementation for surgery is quite difficult. The complications associated with high-dose glucocorticoids are well known,

Table 1 Steroid Conversions

Medication	Approximate Equivalent Dose (mg)	Relative Potency
Cortisol	20	1.0
Hydrocortisone	25	0.8
Prednisone	5	4.0
Prednisolone	5	4.0
Methylprednisolone	4	5.0
Dexamethasone	0.75	30–150
Triamcinolone	4	5.0

including hyperglycemia, impaired wound healing, and hypertension. In the postoperative setting, patients treated with steroids are at increased risk for decreased tissue repair rates and increased susceptibility to infections.¹⁹ Numerous studies have been performed over the past 30 years challenging the theory that patients on chronic steroids need additional steroids perioperatively. The reported incidence of perioperative adrenal insufficiency is rare, estimated at 0.01 to 0.7%.^{20,21}

Kehlet and Binder evaluated 104 glucocorticoid-treated patients undergoing surgery without supplemental stress doses of glucocorticoids.²² Glucocorticoid therapy was withheld 36 hours before surgery and restarted 24 hours after minor surgery and 72 hours after major surgery. Plasma corticosteroid doses were measured during the 24-hour postoperative period. The mean corticosteroid value 1 hour after skin incision increased significantly from baseline. This response was impaired in 39 patients undergoing major surgery (53%) compared with the control group. Seven episodes of hypotension were noted, all of which responded spontaneously or to fluid administration. All hypotensive episodes lasted less than 20 minutes. Nine patients undergoing minor surgery (30%) had an abnormal corticosteroid response. One patient undergoing minor surgery developed unexplained intraoperative hypotension. This patient had severe adrenocortical failure and responded to 50 mg of hydrocortisone along with fluid resuscitation.

A study by Udelsman and colleagues evaluated glucocorticoid replacement in the perioperative period on adrenalectomized primates.²³ Primates were given glucocorticoid replacement for 4 months after adrenalectomy. The monkeys were then stratified to receive different quantities of glucocorticoid replacement for 4 days prior to surgery: subphysiologic (one tenth the normal cortisol production rate), physiologic, or supraphysiologic (10 times the normal cortisol production rate). Sham adrenalectomized placebo-treated animals served as controls. The monkeys then underwent a cholecystectomy. The subphysiologically treated group was hemodynamically unstable before, during, and after surgery and had a significantly higher mortality rate than controls. However, the physiologically replaced group had intraoperative hemodynamics and postoperative outcomes similar to those of the supraphysiologically treated and sham-operated controls. This study suggests that replacing physiologic doses of glucocorticoids is sufficient for glucocorticoid replacement for moderate surgery in primates.

The need for high-dose steroids during orthopedic surgery was evaluated by Friedman and colleagues.¹⁵ The authors performed a prospective study of 28 patients on chronic, immunosuppressive doses of glucocorticoids who were undergoing major orthopedic operations. The patients were given their baseline doses of glucocorticoids (mean dose 10 mg prednisone), with no additional stress doses of steroids. Twenty-four-hour urinary free cortisol levels were obtained perioperatively and postoperatively. No evidence of adrenocortical insufficiency was documented. Seventy-one percent of patients demonstrated increased production of endogenous corticosteroids (urinary level of free cortisol) in response to the operative stress.

These studies by Kehlet and Binder, Udelsman and colleagues, and Friedman and colleagues all independently provide clinical evidence that supraphysiologic doses of

glucocorticoids in the perioperative period are likely of little benefit. The study by Kehlet and Binder provides evidence that it is necessary to continue glucocorticoids during the perioperative period as withholding glucocorticoids may result in hypotension.²² Udelsman and colleagues demonstrated that subphysiologic doses are not sufficient in the perioperative period either.²³ However, continuing a patient's outpatient glucocorticoid regimen during the perioperative period may be safe for minor or moderate surgeries based on recent clinical evidence.

Why Treat Patients with Impaired Adrenal Function?

Patients with normal adrenal function have increased secretion of plasma ACTH and cortisol concentrations, urinary free cortisol, and concentrations of urinary metabolites of cortisol when faced with surgery, trauma, or critical illness. The HPA response to surgical stress has a considerable inter-individual variation.¹⁹ Thus, it is necessary to cover a patient with impaired adrenal function sufficiently, but exactly how much coverage is needed is not entirely understood. The goal of treatment with glucocorticoids is to provide an amount equivalent to the normal physiologic response to surgical stress while avoiding overtreatment. To determine a proper dose replacement, one must consider the patient's adrenal status, as well as the severity and duration of surgery.

Guidelines for Dosing Glucocorticoids in the Perioperative Period

Once it is determined that a patient will require perioperative glucocorticoid replacement, the dose of glucocorticoids must be determined. Optimal dosing will mimic a normal physiologic response to surgical stress. Three factors will determine the dose of glucocorticoids required: the preoperative dose of glucocorticoid, the preoperative duration of glucocorticoid use, and the anticipated duration of surgery. Surgeries that require a longer duration or greater physiologic stress, such as cardiothoracic surgery, require a higher dose of glucocorticoid supplementation.¹⁹ IV steroids should be continued in all cases until a patient is able to tolerate enteral feeding. Should a patient develop postoperative complications and require close monitoring in the hospital, stress-dose steroids should be administered.

MINOR SURGERY

Minor surgeries, which include those lasting less than an hour, do not require additional glucocorticoid administration. Inguinal hernia repair, scheduled cardiac catheterization, and laparoscopic cholecystectomy are some examples of minor surgery. Patients should be instructed to continue their home regimen of steroids through the perioperative period, including the day of surgery. The HPA axis to minor surgery is minimal; additional steroid supplementation is not indicated.¹⁹

MODERATE SURGERY

For moderate surgeries, including nonlaparoscopic abdominal surgeries and total joint replacement, patients should receive their outpatient steroid dose preoperatively (either intravenously or by mouth). Hydrocortisone 50 mg IV should be administered intraoperatively, followed by hydrocortisone

25 mg IV twice daily for 24 to 48 hours postoperatively. Patients can return to their preoperative doses (either enterally or parenterally) on postoperative day 2 and, once tolerating oral feeding, can be continued on their outpatient glucocorticoid regimen.

MAJOR SURGERY

Major surgeries, including pancreatoduodenectomy, cardiac surgeries requiring cardiac bypass, and total proctocolectomies, require higher doses of glucocorticoids intraoperatively and postoperatively. The target glucocorticoid dosing is 100 to 150 mg of hydrocortisone per day (or another glucocorticoid in equivalent dosing) for 2 to 3 days. For example, hydrocortisone 50 mg every 8 hours for 72 hours. Stress-dose steroids can be initiated on the day of surgery, immediately prior to anesthesia induction. Once the patient is tolerating an enteral diet and is no longer in a critical condition, steroids can quickly be tapered to the outpatient regimen.

Table 2 provides an outline of recommended steroid replacement in the perioperative period based on the nature of surgery being performed. Recommendations are based on expert opinion.

Consulting a Specialist

Patients with suspected or known adrenal insufficiency attributable to pituitary disease should be followed by an endocrinologist as it is more difficult to assess the HPA axis in these patients. Endocrinologists can help with interpretation of ACTH stimulation tests that have produced confusing results. There are no clear guidelines on steroid tapering, but a slower taper should be initiated for complicated surgeries or patients with longer hospital stays postoperatively, and a specialist can help formulate the taper. A patient being treated for Cushing disease with pituitary or adrenal surgery must be followed by an endocrinologist. The endocrinologist can provide guidelines for a slow steroid taper after surgery and will likely follow the patient after hospital discharge in the clinic.

Conclusion

A patient with an intact HPA axis will mount a cortisol response to surgery or other stressors. The goal of glucocorticoid replacement in patients without an intact HPA is to mimic normal adrenal function. Most patients undergoing minor surgeries can continue their outpatient glucocorticoid

regimens alone. For patients undergoing moderate or major surgeries, their adrenal function needs to be determined, and an appropriate dose of glucocorticoids should then be administered. Although adrenal insufficiency in the perioperative setting is rare, it is easily avoided with a good history regarding prior steroid use within the previous year. It is important to ask patients regarding inhaled and topical steroids as well as these can impact adrenal function. Below are a few case examples for further review:

Case 1. A 51-year-old man with rheumatoid arthritis on prednisone 5 mg every other day chronically is undergoing a laparoscopic cholecystectomy.

Answer. The patient should take 5 mg prednisone the morning of surgery. If his postoperative course is uncomplicated, he can resume his outpatient glucocorticoid regimen.

Case 2. A 30-year-old woman with Crohn disease on prednisone 10 mg daily for the last 6 months is undergoing a total abdominal hysterectomy for fibroids.

Answer. The patient should receive prednisone 10 mg daily prior to surgery followed by hydrocortisone 50 mg IV intraoperatively. Postoperatively, continue hydrocortisone 25 mg IV every 12 hours. The patient can be transitioned to either prednisone 10 mg daily on postoperative day 2 if tolerating an oral diet or continue hydrocortisone 25 mg IV every 12 hours until the patient is tolerating enteral feeding.

Case 3. A 60-year-old man with chronic obstructive lung disease who has required frequent steroid burst over the past year is undergoing three-vessel cardiac bypass surgery.

Answer. Although the patient is not currently on glucocorticoids, he likely has an abnormal HPA axis. Prior to surgery, it would be appropriate to perform an ACTH stimulation test.

If his peak cortisol level is only 12 µg/dL, the patient should take an outpatient dose of glucocorticoid the morning of surgery. The patient should receive 50 mg IV intraoperatively and then stress-dose steroids: hydrocortisone 150 mg IV daily for 2 to 3 days (50 mg every 8 hours). After this time period, his dose can be quickly tapered to his outpatient regimen.

Table 2 Perioperative Glucocorticoid Treatment Recommendations^{13,19}

Surgery	Definition	Recommended Glucocorticoid Dose (in patient on chronic glucocorticoids or with abnormal ACTH-stimulation test)
Minor	Local anesthesia; surgery less than 1 hour duration	Continue outpatient regimen; no additional steroids needed
Moderate	Joint replacement; lower extremity revascularization	Take outpatient dose morning of surgery. Give hydrocortisone 50 mg intraoperatively (or equivalent); continue hydrocortisone 25 mg IV every 12 hours for 24–48 hours postoperatively.
Major	Cardiothoracic surgery; surgery lasting longer than 4 hours	Hydrocortisone 50 mg IV every 8 hours starting at induction of anesthesia. Continue for 48–72 hours and then quickly taper to outpatient regimen once patient is hemodynamically stable.

ACTH = adrenocorticotropic hormone.

If his peak cortisol level is 20 µg/dL or greater, he does not need supplemental steroids perioperatively. Should he develop hypotension, a random cortisol should be drawn, and he should receive hydrocortisone 50 mg IV followed by fluid resuscitation until his adrenal sufficiency is better

established. An endocrinology consultation would be appropriate at that point for recommendations on further management.

Financial Disclosures: None Reported

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35 THE SKIN AND THE PHYSIOLOGY OF NORMAL WOUND HEALING

Sahil K. Kapur, MD, and Timothy W. King, MD, PhD

The Skin

The skin is composed of epidermis and dermis, which interdigitate to form an irregular contour. The epidermis is primarily of ectodermal origin and is classified as stratified squamous keratinized epithelium. The major cell types found in this layer include keratinocytes, melanocytes, Langerhans cells, and Merkel cells. Regeneration of this layer occurs every 30 days via the mitotic activity of keratinocytes. The epidermis can be subdivided into five layers: stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale.

The stratum corneum is the most superficial layer of the epidermis, containing flattened dead cells (squames) along with keratin filaments. The next layer, the stratum lucidum, contains cells that lack nuclei or organelles and only contain cytoplasm packed with keratin filaments and eleidin. The stratum granulosum consists of nucleated keratinocytes that contain coarse keratohyalin granules associated with tonofilaments. Cells in this layer are arranged in three to five sublayers. The stratum spinosum contains nucleated keratinocytes that have a spiny appearance. Desmosomes associated with tonofilaments connect cells in this layer via intercellular bridges. Keratinocytes in this layer are mitotically active and contain membrane-coating granules. Langerhans cells also reside in this layer. The deepest layer of the epidermis is the stratum basale, which is composed of a single layer of tall, cuboidal, mitotically active keratinocytes along with Merkel cells and melanocytes.

The dermis is subdivided into a papillary layer and a reticular layer. The papillary layer is the superficial layer of the dermis; it is irregular and forms dermal ridges that interdigitate with down-growing epidermal ridges. This layer is composed of type I and type III collagen fibers, anchoring fibrils (collagen type VII), microfibrils (fibrillin), and elastic fibers. Meissner corpuscles and capillary loops are also found in this layer. The deeper reticular layer is far more extensive and contains thick bundles of type I collagen fibers and elastic fibers. This layer contains arteries, veins, lymphatics, pacinian corpuscles, nerves, and sweat glands and their ducts. The epidermis and dermis are separated by the basement membrane. The basement membrane is a thin sheet of fibers made up by the fusion of two layers (basal lamina and reticular lamina). The two layers attach to each other using type VII collagen and fibrillin. The basal lamina in turn consists of two layers: lamina lucida (made up of laminin) and lamina densa (composed largely of type IV collagen). The function of the basement membrane is to anchor down the epidermis to the dermis and to act as a mechanical barrier [see Figure 1].

Financial disclosure information is located at the end of this chapter before the references.

Adult Wound Healing

Adult wound healing can be broadly broken up into an inflammatory phase, a proliferative phase, and a remodeling phase. Each phase has multiple complex processes that are not clearly limited to that phase. So a more accurate description of wound healing would involve discussion of the complex processes as overlapping phases along a continuum.

INFLAMMATORY PHASE

On injury to the skin, the blood vessels constrict and the platelets form a fibrin plug. The degranulation of alpha granules in platelets leads to the release of adhesive proteins such as fibrinogen, fibronectin, thrombospondin, and von Willebrand factor. Fibrinogen, fibronectin, and thrombospondin act as ligands for platelet aggregation, whereas von Willebrand factor facilitates platelet aggregation to fibrillar collagens. The glycoprotein receptor on platelets, GPIIb/IIIa, allows adhesion of platelets to all four adhesive proteins.^{1,2}

The aggregated platelets release chemoattractants for inflammatory cells, factors for local fibroblasts and endothelial cells, and vasoconstrictors. Coagulation and complement cascades are also initiated. After the initial vasoconstriction, there is vasodilatation mediated by bradykinin, which is generated by the Hageman factor in the coagulation cascade.^{3,4} The complement cascade generates the C3a and C5a anaphylatoxins, which directly increased blood vessel permeability, allowing neutrophils and monocytes to enter the wound. C3a and C5a also stimulate the release of histamine and leukotrienes C₄ and D₄ from mast cells, resulting in endothelial cells losing their cell-cell contact, which then leads to increased permeability.

Initial inflammatory cells are neutrophils that predominate in the first 24 to 48 hours. They are primarily responsible for the oxidative burst and play a role in phagocytosing cellular debris, foreign bodies, and bacteria. Neutrophils are attracted to the wound site by a multitude of chemoattractants [see Table 1]. Free-flowing neutrophils in the bloodstream that reach the wound bed adhere to the blood vessel endothelium and transmigrate into the wound bed. Increased neutrophil surface expression of CD11/CD18 and the interaction of these complexes with Lewis factor X are responsible for this adherence.^{5,6} Neutrophils are also recruited to the wound by low-molecular-weight chemotactic factors belonging to the alpha-chemokine family that bear the motif C-X-C. Examples of molecules possessing this C-X-C motif include interleukin-8 (IL-8), growth-related protein (GRO), and melanoma growth-stimulating activity (MGSA).⁷ The neutrophils then degranulate and start phagocytosing foreign bodies and debris.

Once foreign bodies and debris have been removed, the granulocyte activation stimulus ends. If there are sustained

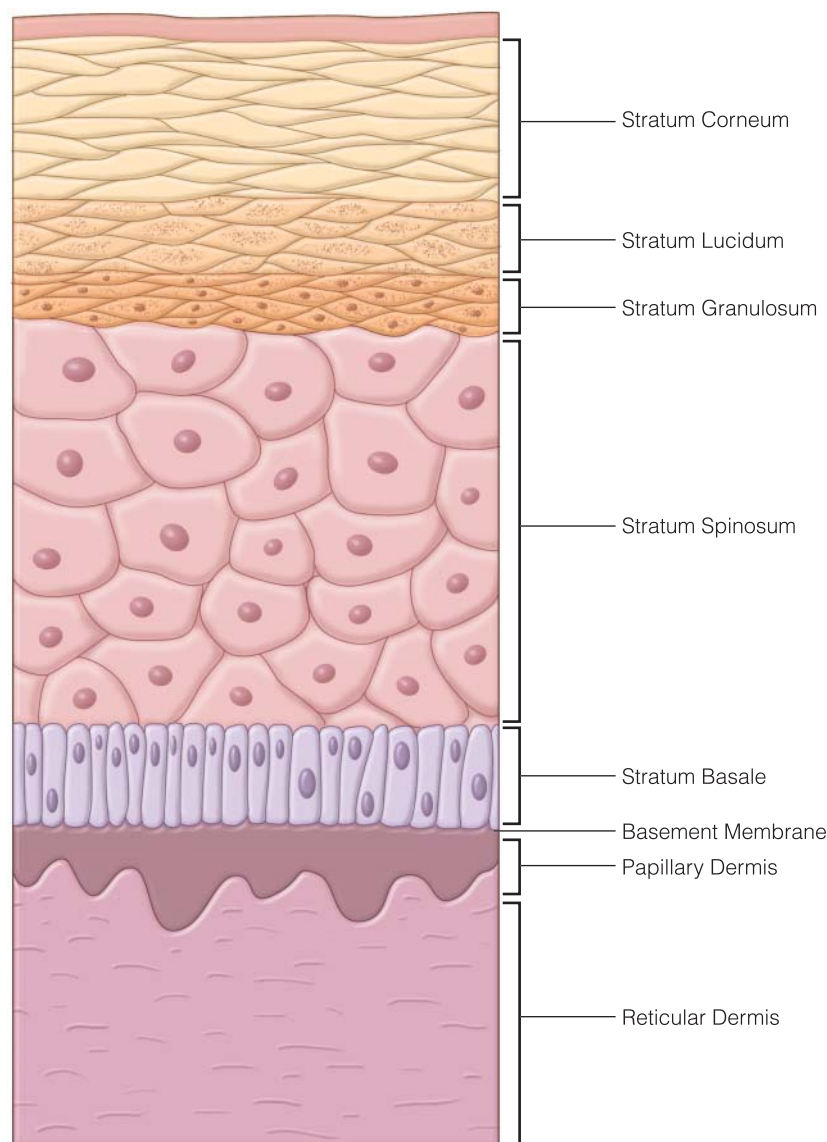


Figure 1 Layers of the skin.

Table 1 Chemoattractants that Recruit Neutrophils to a Wound

Chemoattractant	Source
Fibrinopeptides	Cleaved from fibrinogen by thrombin
Complement factors (e.g., C5a)	Activation of classical and alternate complement pathways
PDGF	Platelets
Platelet factor 4	Platelets
Formyl methionyl peptides	Cleaving of bacterial proteins
Leukotrienes (e.g., leukotriene B ₄)	Activated neutrophils
Platelet-activating factor (PAF)	Endothelial cells and activated neutrophils

PDGF = platelet-derived growth factor.

foreign substances, neutrophils continue to be attracted to the wound and continue to inflict significant toxic damage to surrounding tissues. Bacteria and retained foreign substances in wounds provide a surface on which alternate complement pathway proenzymes can be adsorbed. This leads to opsonization of these surfaces with C3b and continual generation of C3a and C5a anaphylatoxins. Consequently, neutrophils continue to be attracted to the area.⁸

In the normal wound healing process, chemoattraction of neutrophils to the wound bed ends once bacteria and foreign substances are removed, but the chemoattraction of monocytes continues. Unlike neutrophil-specific chemoattractants, chemoattractants generally specific to macrophages and lymphocytes belong to the beta-chemokine family and are characterized by the C-C motif [see Table 2]. Table 2 also lists macrophage and lymphocyte chemoattractants that are plasma protein derived, cell derived, extracellular matrix (ECM) derived, and bacteria derived. Chemical modification

Table 2 Monocyte and Macrophage Chemoattractants

Beta-chemokine chemoattractants Monocyte chemoattractant protein-1 (MCP-1) Macrophage inflammatory protein-1 α (MIP-1 α)
Plasma protein-derived chemoattractants C5a C5a des Arg Fibrinopeptides IgG-proteolytic fragments α -Thrombin
Cell-derived chemoattractants Leukotriene B ₄ Monocyte-chemoattractant proteins (MCP-1, -2, -3) RANTES Macrophage inflammatory proteins (MIP-1 β and MIP-1 α) Platelet factor 4 Platelet-derived growth factor (PDGF) Transforming growth factor- β (TGF- β)
ECM-derived chemoattractants Collagen fragments Elastin fragments Fibronectin fragments
Bacteria-derived chemoattractants Formyl methionyl peptides N-Acetylmuramyl-L-alanyl-D-isoglutamine

ECM = extracellular matrix.

of certain factors changes their chemoattractant properties. For example, C5a, a potent anaphylatoxin, attracts both neutrophils and macrophages. This factor, however, gets quickly modified in the wound bed to C5a des Arg, which results in a reduction of its anaphylatoxin properties and neutrophil-attractive properties but maintains its monocyte-attractive properties.

Once monocytes arrive at the wound bed, they are transformed into tissue macrophages. Monocytes bear β_1 integrin receptors to wound matrix fibronectin and not soluble fibronectin. Adherence to the matrix fibronectin induces phenotypical transformation of monocytes to macrophages.^{9,10} The adherence-specific phenotypical change involves selective messenger RNA (mRNA) expression of survival cytokines such as colony-stimulating factor-1 (CSF-1), inflammatory cytokines such as tumor necrosis factor- α (TNF- α), potent fibroblast chemoattractants and mitogens such as platelet-derived growth factor (PDGF), and c-fos and c-jun transactivating factors.^{11,12} mRNA expression of other cytokines is adherence independent and includes expression of transforming growth factor- β (TGF- β), IL-1, human leukocyte antigen-DR (HLA-DR), interferon gamma, transforming growth factor- α (TGF- α), PDGF, insulinlike growth factor-1 (IGF-1), and fibroblast growth factor (FGF).

The tissue débridement process is started by monocytes on arrival. By days 2 and 3, they are the predominant cell type within the wound.¹³ They secrete a multitude of tissue-degrading enzymes, which are similar to those secreted by neutrophils, macrophages, and fibroblasts. Specifically, they degrade collagen by secreting matrix metalloproteinase-1 (MMP-1) and MMP-9. They do not, however, secrete any MMP-3, and the levels of secreted MMP-1 and MMP-9 are

much lower than those secreted by macrophages. Monocytes constitutively secrete tissue inhibitor of matrix metalloproteinase-1 (TIMP-1), which inhibits the function of the above-mentioned metalloproteinases. Unlike macrophages, monocytes degrade elastin by secreting serine and cysteine proteases. As they transform into macrophages, they begin to secrete MMP-3; increase production of MMP-1, MMP-9, elastase, acid hydrolases such as cathepsins and glycosidases; and decrease production of serine/cysteine proteases. They therefore function not only to phagocytose bacteria but also to secrete a multitude of factors to activate endothelial cells, fibroblasts, and keratinocytes. Interestingly, macrophages and monocytes are the only inflammatory cells required for wound healing¹⁴ [see Figure 2].

The fibrin clot in the blood vessel that forms immediately after tissue injury serves to control hemostasis, whereas the fibrin clot within the wound provides the initial provisional matrix for migration of cells into the wound. Clot contains large amounts of fibrin and lesser amounts of fibronectin and vitronectin. Integrin receptors on migrating cells recognize fibrin, fibronectin, and vitronectin within the matrix.^{15,16} Clot lysis on the wound periphery is as tightly regulated as clot formation. Clot progression inhibition and lysis are carried out by local production of prostacyclin, which inhibits platelet aggregation; antithrombin III, which inhibits thrombin; and protein C, which degrades coagulation factors V and VIII. Tissue plasminogen activator (t-PA) and plasmin, which are usually inhibited by fluid phase proteases such as plasminogen activator inhibitor and α_2 -antiplasmin, escape lysis by binding to the fibrin clot.

PROLIFERATIVE PHASE

Fibroplasia

This phase begins with the degradation of the initial platelet-fibrin matrix. Growth factors released by the macrophages and local ECM components increase fibroblast proliferation. By days 3 to 5, fibroblasts are the predominant cell type in noninfected wounds. After proliferation, fibroblasts begin to synthesize and secrete ECM components. The initial platelet-fibrin matrix is replaced by a second provisional fibronectin-hyaluronic acid matrix. This process is complex and involves multiple growth factors that help regulate cellular function via transmembrane integrin receptors. The hyaluronic acid in the new wound matrix

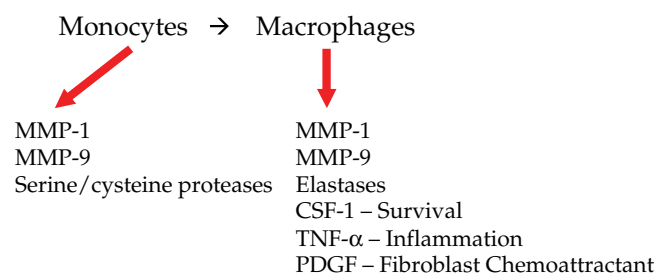


Figure 2 Phenotypic changes during the differentiation of monocytes to macrophages. CSF-1 = colony-stimulating factor-1; MMP-1 = matrix metalloproteinase-1; MMP-9 = matrix metalloproteinase-9; PDGF = platelet-derived growth factor; TNF- α = tumor necrosis factor- α .

facilitates cell migration because it is largely composed of water. Adhesion glycoproteins, which include fibronectin, laminin, and tenascin, facilitate cell migration and attachment. Extracellular components such as glycosaminoglycans (GAGs) and glycoproteins transmit signals intracellularly via integrin receptors on cell membranes. Fibroblasts that populate the wound release hyaluronidase to digest the provisional matrix and allow for larger sulfated GAGs to be deposited. New collagen is deposited by fibroblasts onto the fibronectin and GAG scaffold in a disorganized manner, resulting in scar formation [see Figure 3].

The main types of fibrillar collagens that compose the ECM in skin and scar tissue are types I and III and are present in a 4:1 ratio.¹⁷ About 19 different types of collagen are currently known.¹⁸ Most of these are synthesized by fibroblasts and some by keratinocytes.¹⁹ Coordinated transcription of various genes on fibroblasts, followed by multiple intracellular and extracellular modifications of the translated product, leads to the final collagen fiber.^{2,6,7,12,13,17,20} Tropocollagen is made in the ECM. These molecules laterally aggregate and are covalently cross-linked by the enzyme lysyl oxidase to form collagen fibrils.²¹ The high percentage of proline amino acid residues is the basis of their right-handed triple-helix structure.

Fibroblasts enter the wound by initially penetrating through blood clot, which has large amounts of fibrin and relatively lesser amounts of fibronectin and vitronectin. Fibroblasts bind to fibronectin, vitronectin, and fibrin through integrin receptors. The RGDS (Arg-Gly-Asp-Ser) tetrapeptide within the cell-binding domain of these matrix proteins is critical for binding of integrin receptors. Interaction with fibronectin through the $\alpha_4\beta_1$ integrin receptor induces migration, whereas interaction with the $\alpha_5\beta_1$ receptor retards movement of the fibroblast. PDGF and TGF- β stimulate fibroblasts to migrate. PDGF has a variable effect on fibroblasts based on the ECM environment. When fibroblasts migrate through a fibrin-fibronectin matrix, PDGF stimulates formation of receptors for fibronectin ligands,

whereas when these cells migrate through collagen gels, PDGF stimulates receptors for collagens.

Migration of fibroblasts is influenced by chemotactic, haptotactic, and contact guidance signals. Chemotactic signals cause fibroblasts to extend their lamellipodia in the direction of the signal and release other attachments, thereby allowing the cell to migrate. Haptotactic signals cause movement of fibroblasts relative to a surface adhesion gradient and can be described in the following manner. Fibroblasts randomly extend lamellipodia, each of which compete for cell membrane surface area. The lamellipodium that adheres the most wins, causing the entire fibroblast to migrate in that direction.²⁰ Fibroblasts, presented with a chemotactic signal, migrate faster along fibronectin fibrils rather than across these fibrils. This property is known as contact guidance. As they migrate through the tightly woven ECM, they secrete interstitial collagenases (MMP-1), gelatinases (MMP-2), and stromelysin (MMP-3) to aid in migration. PDGF and TGF- β stimulate the production and secretion of these collagenases.

Once fibroblasts have migrated into the wound, they undergo a phenotypical change and transform from primarily migratory cells to protein-secreting cells. Initially, they produce large quantities of fibronectin, which gives rise to a loose ECM. As the wound matures, their protein expression shifts to TGF- β , resulting in the production of collagen III and collagen I. Once abundant amounts of collagen are produced, the matrix suppresses fibroblast collagen production. In contrast, a fibronectin-rich ECM does not exert a similar suppressive effect.

Contraction

By the second week of wound healing, profibrotic fibroblasts begin to transform their phenotype into a myofibroblast phenotype. They accumulate large quantities of actin-containing microfilaments and present them along the cytoplasmic face of their plasma membranes. They then connect to fibronectin within the ECM using $\alpha_5\beta_1$ integrin receptors and to collagen fibrils using $\alpha_2\beta_1$ and $\alpha_1\beta_1$ receptors. Fibroblasts connect to each other through direct adherens junctions.^{22,23} The collagen bundles connected to fibroblasts within the matrix then form end-to-end contacts with collagen bundles at the wound edges and create covalent cross-linked bonds with collagen bundles within the adjacent dermis. This sets up an interconnected network that can transmit the force of contraction of the myofibroblasts to the periphery. Myofibroblasts are aligned along the contraction lines of wounds to better transmit this contractile force. PDGF isoforms AB and BB, released by platelets and macrophages, stimulate contraction. Interestingly, PDGF-AA released by fibroblasts has no such activity. It is therefore assumed that resident tissue macrophages release a wave of PDGF-BB or AB at the appropriate time to stimulate wound contraction. Open wounds undergo contraction, which leads to reduction in the size of the wound without new tissue formation. Eighty to 90% of wound closure can be carried out by contraction in the abdomen and the perineum²⁴ [see Figure 4].

Neovascularization

Activated macrophages that are attracted to the wound bed release FGF-2, which stimulates the endothelial cells to

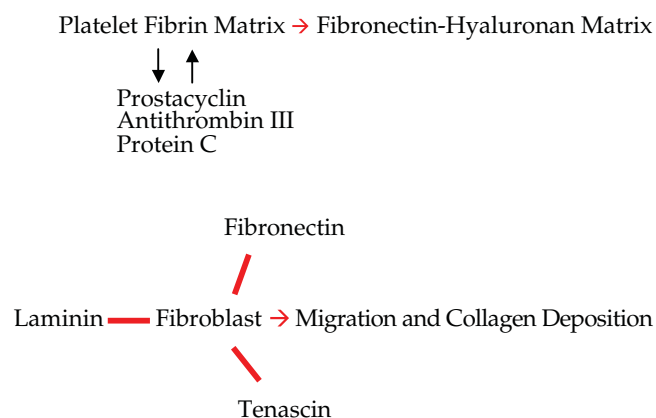


Figure 3 Proliferative phase. The platelet-fibrin matrix transforms into the fibronectin-hyaluronan matrix. Clot lysis at the wound periphery is tightly regulated by prostacyclin, antithrombin III, and protein C. Fibroblasts interact with fibronectin, laminin, and tenascin and deposit collagen as they migrate across the fibronectin-hyaluronan matrix. This leads to the transformation of the fibronectin-hyaluronan matrix into the collagen matrix.

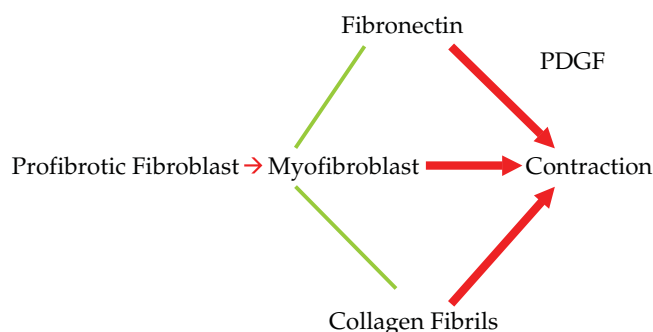


Figure 4 Wound contraction. Migratory fibroblasts transform into collagen-producing proliferative fibroblasts and then into myofibroblasts. These myofibroblasts connect to fibronectin and collagen fibrils with the matrix, align themselves along lines of tension, and contract under the influence of PDGF-BB and -AB. PDGF = platelet-derived growth factor.

release plasminogen activator and procollagenase. Plasminogen activator converts plasminogen to plasmin and procollagenase to active collagenase. These help digest the ECM, allowing the endothelial tubes to grow into the tissue. The endothelial cells that form tubes express $\alpha_v\beta_3$ integrin, which facilitates adhesion and migration. As the neovasculation grows into the wound bed, it first deposits its own provisional matrix, containing fibronectin and proteoglycans, and later forms a true basement membrane. FGF-1, FGF-2, and vascular endothelial growth factor (VEGF) stimulate endothelial proliferation and allow for a continual supply of cells as the tubes migrate into and revascularize the wound bed. TGF- β helps induce the correct endothelial cell type for capillary tube formation and helps stimulate fibronectin and proteoglycan synthesis. Whereas VEGF stimulates endothelial cell production and TGF helps induce the correct endothelial cell type, angiopoietin-1 (Ang-1) serves as a ligand that interacts with TIE-2 receptor tyrosine kinase (present on endothelial cells and endothelial progenitor cells) to mediate neovessel maturation. Ang-1-TIE2 interaction stimulates recruitment of periendothelial cells and helps reestablish the basement membrane, thereby enhancing neovessel integrity and allowing them to mature into more complex vascular structures²⁵ [see Figure 5].

Granulation

Granulation tissue is given the name because of its visual appearance. Its formation is stimulated by a high local concentration of growth factors, especially PDGF. Growth factors are present in the blood at a low concentration. Their local concentration is increased initially by the degranulation of platelets, and these high levels are sustained by macrophages. The major growth factor that induces the formation of granulation tissue is PDGF-BB.²⁶ Application of PDGF to a wound bed can increase granulation tissue by 200% compared with controls. Platelets, fibroblasts, and macrophages release endothelium-stimulating factors such as VEGF, which cause increased levels of endothelial cell division and migration.^{26,27} Macrophages that enter the wound produce high quantities of urokinase-related plasminogen activator (u-PA). Whereas tissue plasminogen activator plays an important role in the destruction of a

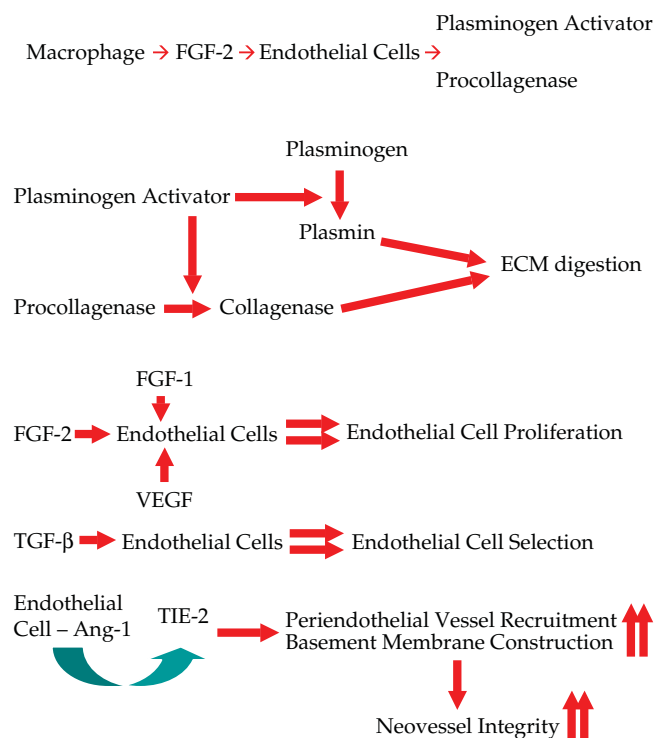


Figure 5 Neovascularization. Macrophages release FGF-2, which causes endothelial cells to release plasminogen activator and procollagenase, which help in ECM digestion. Endothelial cell proliferation is increased in the presence of FGF-1, FGF-2, and VEGF. TGF- β helps with endothelial cell selection. Ang-1-TIE-2 interaction leads to increased neovascular integrity. Ang-1 = angiopoietin-1; ECM = extracellular matrix; FGF-1 = fibroblast growth factor-1; FGF-2 = fibroblast growth factor-2; TGF- β = transforming growth factor- β ; TIE-2 = tyrosine kinase receptor; VEGF = vascular endothelial growth factor.

fibrin clot, u-PA is highly expressed in the endothelial cells, which are in the early stages of angiogenesis in developing granulation tissue. Regulation of u-PA is dependent on activities of basic fibroblast growth factor (bFGF)/FGF-2, TGF- β , hepatocyte growth factor (HGF also called scatter factor [SF]), and VEGF. bFGF increases u-PA activity and decreases plasminogen activator inhibitor activity, whereas TGF- β has the opposite effect. bFGF and VEGF synergistically increase endothelial plasminogen activator production and angiogenesis.²⁸ HGF/SF have structural homology similar to that of plasminogen and are activated by u-PA. Activated HGF in turn reactivates u-PA, thereby promoting angiogenesis in granulation tissue. These interactions result in the formation of a dense bed of capillary networks with embedded fibroblasts and macrophages, which we call granulation tissue. Wound beds that have sufficient granulation tissue readily accept skin grafts.

Proteoglycans are another class of macromolecule that plays an important role in the development of granulation tissue. After injury, there is a temporal expression of hyaluronan and sulfated GAGs in skin. Hyaluronan is deposited early and reaches its peak in the first few days following injury. It is subsequently replaced by sulfated GAGs, such as decorin, versican, and biglycan. Hyaluronan not only provides a low-impedance environment for the migration

of cells into the wound but also reduces inflammation by inhibiting neutrophil function. Unlike adult wounds, fetal wounds do not show a decrease in the level of hyaluronan. They consequently display decreased inflammation and superior dermal matrix reorganization.

Syndecans are heparin sulfate proteoglycans containing a type I transmembrane core protein that can be modified by heparin sulfate and sometimes chondroitin sulfate chains. They form the major proteoglycans in multiple organs and the vasculature. Intact human epidermis expresses syndecan-1 and -4, which are not seen in intact dermis. After injury, syndecan-1 and -4 expression is induced in the dermis. Syndecan-1 is mainly expressed in endothelial tissue, whereas syndecan-4 is expressed throughout granulation tissue, including fibroblasts and endothelia. This increased expression decreases to baseline levels 7 days following injury. In the epidermis, however, migrating keratinocytes significantly decrease syndecan expression from their baseline levels.

GAG such as chondroitin sulfate and dermatan sulfate also interact with matrix molecules, such as laminin and fibronectin. This interaction leads to decreased cell adhesion, thereby facilitating migration of cells within granulation tissue [see Figure 6].

EPITHELIALIZATION

Reepithelialization of the wound begins within 1 to 2 days of tissue injury. Keratinocytes at the wound edges undergo a significant morphologic change. They retract their intracellular tonotopic filaments, dissolve most intercellular desmosomal connections, form peripheral cytoplasmic actin filaments, and lose apical-basal polarity. New migrating epidermal cells are generated by a dividing layer of basal cells near the wound edge. This layer of basal cells is essential because migrating keratinocytes lose the ability to divide.²⁹ These cells do not terminally differentiate into keratinocytes, witnessed by the fact that they do not have the keratins found in terminally differentiated cells, nor do they contain fillagrin, a matrix protein in which these keratins are embedded. They have keratins that are similar to those found in the basal cells of the epidermis.^{30,31} They are, however, not identical to basal cells because they contain involucrin and transglutaminase, components of

cell walls that are found only in the stratum granulosum of normal epidermis.

If the basement membrane is destroyed, these keratinocytes migrate over a provisional matrix consisting of collagen, fibrin, fibronectin, tenascin, and vitronectin. If the basement membrane is intact, circulating fibronectin, deposited by macrophages, fibroblasts, and migrating keratinocytes, infiltrates the basement membrane. Migrating keratinocytes, in contrast to normal keratinocytes, express large numbers of active integrin receptors for fibronectin, which allows them to migrate over the basement membrane. As the keratinocytes migrate across the wound, they eventually reach areas where the basement membrane is no longer intact and the cells directly contact the underlying matrix. This cell-matrix contact induces production of large amounts of collagenases that help degrade type I and type III fibrillar collagens, which are not normally found in intact basement membranes. These collagenase-producing basal keratinocytes express $\alpha_5\beta_1$ integrin receptors, which allow them to migrate over fibronectin, and $\alpha_2\beta_1/\alpha_1\beta_1$ integrin receptors, which allow them to bind to type I collagen.³² Proinflammatory cytokines such as IL-1 and TNF- α modulate collagenase expression in these cells. Relatively few matrix molecules, mainly collagen I and collagen III, are degraded by collagenases. Other matrix molecules, such as fibronectin, laminin, type IV collagen, and GAGs, contact migrating keratinocytes and need to be degraded as well. Stromelysin-1 and -2 are the major MMPs produced by keratinocytes that perform this task. Stromelysin-2 production is strictly confined to keratinocytes in the epidermis. This is in contrast to stromelysin-1, which is mainly secreted by dermal cells and keratinocytes in chronic wounds.

As the process of reepithelialization continues, keratinocytes and fibroblasts secrete laminin and collagen IV and new basement membrane is laid down in zipperlike fashion.³³ The epidermal cells revert to a normal phenotype and connect to the basement membrane and to the underlying neodermis through hemidesmosome and type VII collagen fibrils, respectively [see Figure 7].

REMODELING PHASE

The ECM that is present in the wound bed begins remodeling from the start of the inflammatory phase. As stated earlier, the initial clot that forms at the site of injury provides an initial provisional matrix composed largely of fibrin and lesser amounts of a multitude of other proteins, including fibronectin, vitronectin, von Willebrand factor, thrombospondin, and other growth factors. Thrombin

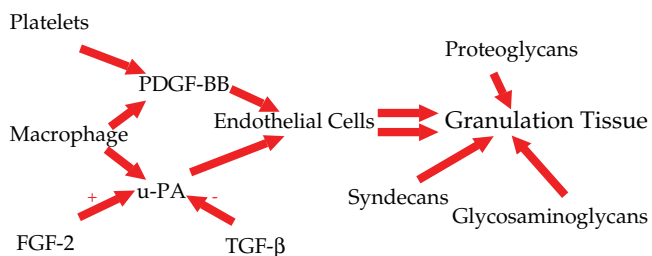


Figure 6 Granulation tissue formation. Macrophages release PDGF, which promotes granulation tissue formation, and uPA, which allows matrix digestion and passage of endothelial cells. FGF-2 = fibroblast growth factor-2; HGF = hepatocyte growth factor; PDGF-BB = platelet-derived growth factor isoform BB; TGF- β = transforming growth factor- β ; u-PA = urokinase plasminogen activator; VEGF = vascular endothelial growth factor.



Figure 7 Reepithelialization. Migrating keratinocytes make contact with the fibronectin matrix using integrin receptors. As they migrate along the matrix, they lay down basement membrane components, laminin and collagen IV, and use MMP-1 and MMP-3 to digest collagen to make room for migration. MMP-1 = matrix metalloproteinase-1; MMP3 = matrix metalloproteinase-3.

cleaves off fibrinopeptides A and B from fibrinogen to yield fibrin, which then noncovalently aligns laterally with other similar fibrin monomers to form protofibrils. These aggregate into fibrils and form a fibrin clot. The clot interacts with inactivated platelets via GPIIb/IIIa receptors, causing these platelets to begin binding von Willebrand factor, fibronectin, and vitronectin in addition to fibrin.

The initial degradation of this fibrin clot begins with the formation of t-PA. When tissue injury takes place, t-PA is released from blood vessel disruption and plasma extravasation. This is then activated by tissue kallikrein and factor Xa and begins clot lysis.

As platelets and inflammatory cells release chemoattractants, fibroblasts enter this initial fibrin-bound provisional matrix. They have a higher affinity for fibronectin, which is present in lesser amounts in the initial matrix. As they bind the RGD cell-binding domains on fibronectin fragments, they release MMP-1 (mammalian collagenase) and degrade the initial matrix. However, when they interact with $\alpha_4\beta_1$ integrin recognition sites found on intact fibronectin, they do not release collagenase and continue to migrate into the wound. As stated earlier, fibroblasts initially lay down loose fibronectin, followed by type III and type I collagen. By 3 to 5 weeks, fibroblasts have reached the center of the wound, and by 5 weeks, the matrix has diminished quantities of fibronectin and large quantities of type III and type I collagen. Deposition of type III and type I fibrillar collagens peaks at 7 to 14 days.

Collagen I is initially found only in the deep layers of the granulation tissue. By days 6 to 13, as the tissue goes under degradation and remodeling, collagen 1 is seen in upper layers. By days 13 to 23, the collagen production in the lower layers of granulation tissue is significantly reduced. Even though collagenases are produced largely by migrating keratinocytes, they are not restricted to the epidermis and are produced by dermal cells at important stages of wound repair and remodeling, such as formation and removal of granulation tissue and resolution of scar tissue. Collagen remodeling during transition of granulation tissue to mature scar is a balance between continued collagen synthesis and collagen catabolism. Lysyl oxidase is the major intermolecular collagen cross-linking enzyme and helps decrease collagen degradation and improve wound tensile strength. Degradation of collagen is carried out by a number of collagenase enzymes. The ones that are well studied include MMP-1 (interstitial collagenase), which cleaves collagen types I, II, III, XIII, and X; MMP-2 (gelatinase), which degrades denatured collagens of all types and native type V and XI collagens; and MMP-3 (stromelysin), which cleaves types III, IV, V, VII, and IX; proteoglycans; and glycoproteins.^{34,35} The functions of these molecules are further inhibited by TIMPs.

Various cytokines also play a regulatory role in this process. TGF- β has been shown to be coexpressed with collagen 1 in the early stages of wound healing and is therefore believed to promote its synthesis.³⁶ IL-1 has been shown to modulate expression of collagens I and III in a dose-dependent manner. Low levels of IL-1 stimulate expression of these molecules, whereas high levels of expression have an inhibitory effect.³⁷ IL-4 also promotes expression of

collagen I in wounds. Interferon gamma and TNF- α counter the effects of the above signals.³⁸

This process of deposition and degradation continues for a year after tissue injury and refers to creating and modifying the tissue scaffold as the wound matures. A balance of function between these groups leads to the formation of a stable scar at the site of the wound. The collagen that is present in the scar at the end of the wound healing process is densely packed as opposed to a reticular arrangement in normal skin. Furthermore, the scar lacks hair follicles, sweat glands, and other skin appendages that are found in normal skin.

The scar initially has a red hue because of the dense network of capillaries present in the wound bed. As the scar matures, the capillaries recede, and the final scar is either hypopigmented or hyperpigmented. The tensile strength of the wound rapidly increases from 1 to 8 weeks and correlates with collagen cross-linking. The strength has been shown to increase at a slower pace until about 1 year, with the maximal strength of the wounded tissue reaching 80% of that of normal skin.

REGULATION

Extracellular Matrix

The ECM consists of growth factors in latent forms. On disruption of the ECM in a wound scenario, the growth factors are released and activated at different time points during the wound healing process. These form the focal regulatory points of the repair process.

Transforming Growth Factor- β

This is a profibrotic growth factor that is released from platelets, macrophages, fibroblasts, and keratinocytes. It also acts in an autocrine manner and stimulates its own release. It influences almost every aspect of tissue repair. During the initial stages of wound repair, it acts as a potent chemoattractant for monocytes, lymphocytes, neutrophils, and fibroblasts. Low concentrations (femtomolar) stimulate chemotaxis. This stimulatory effect is lost at higher concentrations of the growth factor. TGF- β , however, plays its major role in stimulating the production of ECM molecules. The fibroblast is initially attracted to the wound bed by low concentrations of TGF- β and is then activated transcriptionally by high concentrations, as are keratinocytes, endothelial cells, and smooth muscle cells. TGF- β increases ECM synthesis by stimulating the production of collagen and elastin GAGs, increasing integrin expression and integrin-mediated cell-ECM interaction, downregulating MMPs, and upregulating TIMPs.^{39,40} This comes at the expense of increasing fibrosis, which, if high enough, could be detrimental to the normal skin healing process. Prolonged expression of TGF- β is found in wounds that have disrupted basement membranes. Some animal experiments have shown that a lack of TGF activity leads to accelerated healing and a low inflammatory response.⁴¹ TGF- β exists in three isoforms. In animals, TGF- β_1 is the main isoform, and there is reduced expression of the others. Human tissue analysis shows increased prevalence of TGF- β_3 in intact human dermis and predominant expression of TGF- β_1 in the region of reepithelialization of healing wounds.

Platelet-Derived Growth Factor

PDGF is released from the alpha granules of platelets as well as from activated macrophages, activated fibroblasts, smooth muscle cells of damaged arteries, thrombin-stimulated endothelial cells, and epidermal keratinocytes. When released initially from platelet alpha granules, it serves as a chemoattractant for neutrophils, macrophages, and fibroblasts to the wound. It stimulates fibroblasts within the wound to synthesize predominantly noncollagenous components of the ECM: fibronectin, hyaluronic acid, other GAGs, and adhesion proteins. It also induces contraction of collagen matrices and collagenase production during the wound remodeling phase.^{42–44} PDGF plays a role in angiogenesis, which is demonstrated by the appearance of PDGF on capillary endothelial cells and microvascular pericytes.⁴⁵ It promotes angiogenesis indirectly by increasing the secretion of endothelial cell growth factors from myofibroblasts. These angiogenic effects are, however, much weaker than those of other proangiogenic growth factors, such as FGF.

The major effect of PDGF is seen in the increased formation of granulation tissue, with PDGF-BB being much more effective than PDGF-AA. Experimental models show that local application of PDGF increases fibroblast and GAG-rich granulation tissue by 200% in 7 days compared with controls.⁴⁶ PDGF-BB application increases wound strength by 150 to 170% and decreases healing time compared with controls.⁴⁷ PDGF does not alter the sequence of wound healing but is known to greatly increase its rate. PDGF is being used in the treatment of diabetic wounds because of the powerful stimulus it provides to induce granulation tissue.

Fibroblast Growth Factor

FGF-1 and FGF-2 are synthesized by monocytes/macrophages, T lymphocytes, vascular endothelial cells, and dermal fibroblasts. They are secreted into the ECM and lie in a dormant form bound to heparin and GAG heparin sulfate, until injury takes place. They have multiple isoforms each with a broad range of biologic functions. FGF-1 (acidic FGF) and FGF-2 (bFGF) are released by endothelial cells, fibroblasts, and macrophages. Both FGF-1 and FGF-2 stimulate angiogenesis, causing endothelial cells to divide and form capillaries. FGF-2 is also found in the basement membrane, where it is present as a storage depot and is released from the heparin components of the basement membrane at sites of injury. It stimulates plasminogen activator and collagenase activity in endothelial cells, thereby causing the breakdown of basement membrane and migration of endothelial cells through the stroma. FGF-2 also stimulates the migration of fibroblasts and then stimulates fibroblasts within granulation tissue to produce collagenases, leading to remodeling of the matrix. Both FGF-1 and FGF-2 act as mitogens for keratinocytes during reepithelialization, although FGF-1 plays a more potent role.⁴⁸

FGF-7, also known as keratinocyte growth factor-1 (KGF-1), is synthesized by stromal cells and differs significantly from other members of the FGF family in that it is a highly specific mitogen for epithelial cells with no mitogenic activity for endothelial cells or fibroblasts. Its synthesis is induced by IL-1, and it acts as a paracrine mediator of epithelial cell proliferation. FGF-10 functions along with FGF-1 and epidermal growth factor to stimulate epithelialization.

Conclusion

Normal wound healing is a complex process that is generally carried out in three highly overlapping stages and under the influence of multiple cytokines, growth factors, and ECM signals. The process is based on the balance of tissue degradation and deposition, which is critically dependent on the successful interaction of multiple factors and processes.

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Acknowledgement

Figure 1 Christine Kenney

37 MANAGEMENT OF CHRONIC WOUNDS

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Chronic wounds are challenging for both the practitioner and the patient. These wounds often cause pain and can lead to unemployment, social activity disruption, and quality of life issues for the patient. With the world population advancing in age and increasing in body mass index, leading to an increase in the comorbidities of diabetes and venous insufficiency, there has been an increase in the number of patients with chronic wounds.¹

Chronic wounds affect 3 to 6 million patients in the United States, with treatment estimated to cost up to \$25 billion each year.² There was little consensus in the definition or treatment of chronic wounds until the members of the Wound Healing Society established a committee that took on this task.³ After several meetings and public hearings, they published the first set of guidelines and definitions in 1994.⁴ In 2003, the Wound Healing Foundation funded a grant to support the Wound Healing Society in their effort to advance their initial guidelines and develop the best treatment for chronic wounds.⁴ These guidelines, most recently published in 2006, represent the most complete synopsis of the understanding of chronic wound pathophysiology and current treatment recommendations.^{5–8} As a result of the continued research in the field of wound care, the board of directors of the Wound Healing Society and the Wound Healing Foundation established that these guidelines must remain dynamic and that revisions will be made as they become necessary.³

Disease Definition

Chronic wounds are those that have failed to proceed through an orderly and timely reparative process to produce anatomic and functional integrity of the injured site.⁴ Diagnosis and management of chronic wounds often depend on the inciting pathophysiology; therefore, they are traditionally divided into etiologic subtypes. Chronic wounds are rarely seen in individuals who are otherwise healthy and are usually associated with disease states such as diabetes or obesity. Peripheral vascular disease and venous insufficiency can also lead to lower extremity chronic wounds, as can other systemic diseases. The lower extremity ulcer caused by vascular insufficiency or diabetes is the most commonly encountered chronic wound and accounts for 98% of all lower extremity wounds.⁵ Other patient factors, such as malnutrition, immunosuppression, and infection, contribute to poor wound healing. Identification and treatment of these factors are the key to successful management of the chronic wound.⁹

Wound Healing Necessities

OXYGEN

Decreased blood flow in wound tissue limits oxygen delivery and leads to wound hypoxia. In addition to the low tissue

partial pressure of oxygen, decreased blood flow also causes a discrepancy between the delivery of nutrients to the wound and the metabolic demand of the tissue. Cells under hypoxic stress can either adapt to the challenge by increasing the rate of glycolysis and conserving energy or undergo cell death.¹⁰ Mild to moderate tissue hypoxia can be tolerated by tissues with an appropriate adaptive response. Chronic, extreme hypoxia will lead to tissue loss. Associated wound conditions such as infection intensify this cascade and lead to further and more rapid tissue loss and poor wound healing.^{11,12} Simply put, in situations of wound tissue hypoxia, the natural increase in oxygen demand of the injured tissue is further complicated by a decrease in the delivered oxygen. Mitochondrial respiration consumes 90% of oxygen in humans. Cells need oxygen as the final electron acceptor in aerobic metabolism of glucose to generate adenosine triphosphate (ATP), which acts as the fuel for cells needed for wound healing.¹³ A hypermetabolic state occurs in healing tissues, and additional energy is generated from oxidative metabolism, which in turn increases the oxygen demand of the healing tissue.^{14,15} The generated ATP powers tissue repair, and extracellular ATP at the injury site can be used as an additional energy source. ATP can also act as a signal in a wound to release other growth factors, such as epidermal growth factor with an independent downstream signaling mechanism.¹⁶ ATP levels correlate with levels of oxygen in the surrounding tissues and thus stimulate factors important to wound healing, such as those that cause local vasodilation and smooth muscle and endothelial cell proliferation.^{17,18} Therefore, local tissue hypoxia affects the wound at the cellular level directly via diminished production of ATP and downstream reduction in the ATP-induced signaling mechanisms necessary to improve the local wound healing environment.

It is important to realize that wound hypoxia is variable within a wound, ranging from anoxia to mild hypoxia, and that this range may vary in different portions of the wound.^{19,20} The anoxic areas of a wound lead to further injury in the surrounding areas because of inflammation and infection. Although hypoxia stimulates angiogenic factors, an appropriate increase in wound oxygen is often limited, for example, in disease states that affect the ability of oxygen to be delivered to the alveoli and attached to the red blood cell for transport or in the case of limited blood flow associated with peripheral vascular disease juxtaposed to the wound [see Table 1].

Simply increasing the partial pressure of oxygen is not a solution given that the cellular environment needs to maintain oxygen levels within a very narrow range. Damage occurs from excessive oxygen as a result of oxidative damage just as readily as metabolic demise results from insufficient oxygen. Tissues and cells have a set point where there is no signal of diminished or excessive oxygen levels. Lungs and vasculature

Table 1 Known Causes of Tissue Hypoxia

Pulmonary disease
Hepatic dysfunction
Hemodialysis
Anemia
Altitude hypoxemia
Nitroglycerin therapy
Critical illness
Vasoconstricting drugs
Pain
Hypothermia

have a relatively high set point, and organs such as the liver have a very low set point.²¹ Cells exposed to changes in the partial pressure of oxygen that differs from the normal set point will alter the set point to match the new state. This occurs as an adaptive function of the tissue to adjust its oxygen consumption required to perform its usual function.²² The cell's ability to perform this adaptive response is not completely understood and provides a potential avenue to investigate pharmacologic interventions aimed at stimulating the angiogenic response to augment wound healing.

Chronic intermittent systemic hypoxia is another common life-threatening condition that occurs in many disease states. This condition leads to an increase in production of reactive oxygen species—dependent responses that are linked to a variety of morbidities.²³ Nearly half of all patients with chronic wounds of the lower extremities have been found to suffer from chronic intermittent systemic hypoxia; however, it is not known whether development of the wound is a cause or a result of the hypoxia.²⁴

Despite a variety of causal relationships implicated in the development of chronic wounds, hypoxia is a common etiologic factor. Tumor biology has shown that moderate hypoxia is angiogenic when the condition is acute. The extreme hypoxia seen in many chronic wounds leaves a situation that is incompatible with cellular life or tissue repair. The limitations of a given wound must be analyzed and a strategy developed to address the limitations. Both too much and too little oxygen delivered to a chronic wound may adversely affect the healing process. Ideally, future research focused on investigating the oxygen-sensing pathways will aid the clinician prescribing appropriate oxygen therapy.

NUTRITION

Nutrition deficiencies affect the normal progression through the stages of wound healing by prolonging the inflammatory phase, decreasing fibroblast proliferation, and altering collagen synthesis.²⁵ Malnutrition is also known to decrease wound tensile strength and increase rates of infection. Nutritionally deficient patients experience delayed wound healing and are at significant risk for chronic wounds. Malnutrition is a common admission diagnosis for hospitalized patients. Up to 60% are either malnourished or at risk for malnourishment if subjected to the increased metabolic demands associated with injury, infection, or surgical wound healing. The number of at-risk patients is up to 85% for residents of nursing homes.²⁶ The etiology of malnutrition is most often multifactorial, including poor nutritional intake. Nutritional requirements increase in both acute injury and chronic wounds, resulting in nutritional deficit if not corrected.

Energy is required to maintain and rebuild the body after injury. Glucose is the major fuel source for collagen synthesis and the most efficient fuel source compared with protein and fat. Individual factors contribute to the energy needs, including gender, age, nutrition status, basal metabolic rate, severity of illness or injury, and stage of the healing process.^{25,26} The required calories for optimal wound healing are between 30 and 35 kcal/kg/day. An individual approach is required for every patient as patients with multiple comorbidities may need greater than 40 kcal/kg/day.^{27,28}

Simply increasing caloric intake is not enough as the correct composition of proteins, fats, and carbohydrates must be maintained. Protein is necessary for the synthesis of enzymes involved in wound healing, proliferation of cells and collagen, and the formulation of connective tissue.^{25–27} All stages of wound healing require protein to rebuild damaged tissue. Sufficient amounts of protein must be ingested to maintain an overall body positive nitrogen balance.²⁵ Protein loss occurs through open wounds and is directly related to the size of the wound. Wounds with excessive drainage have an even greater protein loss. The recommendation for protein intake in healthy adults is 0.8 g/kg/day, with this number increasing to 2 g/kg/day in those with large wounds and known nutritional deficits.^{25–27} Measurement of nitrogen balance by subtracting the grams of urine urea nitrogen excreted over a 24-hour period from the grams of protein ingested during the same period of time may be a useful estimate of net protein loss. Protein intake should be adjusted to maintain a positive balance.

Glutamine is the most abundant amino acid in plasma and provides 60% of the free intracellular amino acid supply and 20% of the total circulating amino acid pool.²⁵ Many of the amino acids have been studied for their effects on wound healing; however, glutamine is the only one with evidence to support its use.²⁵ Glutamine is a nitrogen donor for other amino acids, is critical in the synthesis of cell nucleotides, and is essential for gluconeogenesis.²⁵ Supplementing glutamine at a rate of 0.57 g/kg/day has been shown to improve nitrogen balance and enhance immune function after trauma and sepsis.²⁵

Appropriate vitamin intake is also important in patients with chronic wounds. Vitamin A increases the number of macrophages and monocytes in the wound during the inflammatory phase. It then stimulates epithelialization and increases collagen deposition by fibroblasts. Vitamin A is also lost with the stress of illness or injury; therefore, supplementation of 10,000 to 50,000 IU/day can maintain balance and enhance wound healing.^{25,27} Vitamin C is important in the synthesis of collagen connective tissue in wound healing and works to increase fibroblast proliferation, capillary formation, and neutrophil activity. Smoking and alcohol consumption increase the excretion of vitamin C. Those patients with large wounds or suspected deficiency of vitamin C will require up to 2,000 mg/day of oral supplementation of vitamin C to enhance wound healing.^{25,27}

All patients with chronic wounds and hospitalized patients who may be at risk for wound healing or the development of pressure ulcers should undergo a nutritional assessment on admission and after any major change in patient condition. The patient should then be provided with adequate calories with an appropriate balance of protein, carbohydrates, and

fat. Frequent monitoring of nutritional status will also allow for changes to be made as clinical condition dictates.

APPROPRIATE WOUND BED

It is unrealistic to expect a wound to heal if the systemic factors that affect wound healing are not addressed. In addition, wound-specific factors need to be addressed for wound healing to be possible. Examination of a chronic wound will reveal hyperproliferative margins, but this represents an ineffective proliferative area that will not advance to heal the wound.⁹ Microscopic examination of wound bed fibroblasts demonstrates various phenotypes that do not respond to normal stimulatory messages.^{9,29,30} Inflammation caused by various cellular products and cytokines, along with an increase in matrix metalloproteinases and a decrease in matrix metalloproteinase inhibitors, eventually leads to destruction of the extracellular matrix.³⁰ This profound inflammatory state is the main factor leading to delayed wound healing.

Recent scientific advances such as new techniques in tissue culture, the development of recombinant growth factors, and tissue engineering have led to an increase in understanding the science of wound bed preparation. The development of genetically engineered knockout murine models and the use of inducible genes have led to a better understanding of growth factors. Gene array technology has allowed us to understand functional pathways and the interactions of cellular components that play a part in wound healing.^{31,32}

There is also an art to the management of the wound bed in a chronic wound using clinical judgment. The presence of eschar or gangrenous infection mandates surgical débridement, giving the clinician the advantage of assessing the severity and extent of the underlying wound.³³ Sharp débridement is the appropriate initial therapy, but débridement alone may not be enough to maintain sustained healing as chronic wounds accumulate senescent cells, extracellular matrix products, and inflammatory enzymes that need to be continuously removed. The ultimate goal of débridement is to alter the wound bed so that the properties of an acute wound can be brought to a previously chronic wound.³⁴

The technique of nonselective, excisional débridement is the fastest way to débride a wound, but given that it also removes viable tissue, daily surgical débridement may also be detrimental to the healing wound. Other techniques, such as mechanical, autolytic, or chemical débridement, are often used in an attempt to maintain an appropriate wound bed. Mechanical methods of débridement include wet-to-dry dressing changes, hydrotherapy, and irrigation. These techniques are nonselective and may be painful and thus are usually reserved for large wounds or those with an excessive amount of necrotic tissue.³³ Autolytic débridement is facilitated by the use of moisture-retaining dressings that allow the body's own endogenous proteolytic enzymes and phagocytic cells to remove necrotic debris.³⁵ This process may be prolonged but, in theory, is less harmful to viable tissue. Chemical débridement products use enzymes to digest necrotic tissue. Two such enzymatic agents in use in the United States are papain-urea and collagenase. Papain comes from the *Carica papaya* plant and breaks down protein with cytosine residues.³⁴ The added urea alters the structure of the protein to expose the cytosine residues, making papain more effective.³⁶ Because the use of this product can cause pain,

there is another formulation with additional chlorophyllin that may be less painful. Collagenase, derived from *Clostridium histolyticum*, specifically breaks down native collagen but works only in the pH range of 6.0 to 8.0. Collagenase breaks down exposed collagen but not the collagen in intact viable tissue. Its use should be limited to wounds that are relatively free of chronic wound debris and eschar.

For those patients in whom surgical, mechanical, or chemical débridement of the wound bed is not an option because of confounding medical factors, biosurgery may be an option. Larvae of the green bottlefly, *Lucilia sericata*, will digest necrotic material and have bacteriostatic enzymes effective against common pathogens such as methicillin-resistant *Staphylococcus aureus* and β -hemolytic streptococcus.³⁷ If tolerated, wounds can be selectively débrided of necrotic tissue in up to 2 days.³⁸

Koch and colleagues, more than 150 years ago, isolated individual strains of bacteria and developed the pure culture method that is still in use today.³⁹ Clinical microbiologists worked with pure log-phase cultures in nutrient-rich media (planktonic growth) as this system is ideal for bacterial growth. Some believe that this model for the study of bacteria may have limited the development of a thorough understanding of microbial processes.⁴⁰

In chronic bacterial infections, the planktonic phenotype exists only transiently as a minor population.⁴⁰ It is now understood that bacterial populations are polymicrobial, sessile (attached), community-based collections within a self-secreted protective matrix or biofilm. The extracellular polymeric substances that hold bacterial communities together were first described more than 30 years ago and are found throughout nature.⁴¹ One of the fundamental differences that separate acute and chronic wounds is biofilm production. Biofilm adheres to the surfaces of organic and inorganic structures and provides a barrier against both environmental and pathogenic stressors. Additionally, biofilm provides protection from antibiotics up to 1,000 times the concentration that can inhibit growth in planktonic cells.⁴² Biofilm is effective against biocides, shear stress, and the body's own defenses, including phagocytes and macrophages.⁴² When bacteria make the natural transition from individual planktonic cells to a community of cells secreting protective polymers, creating a biofilm tissue, there is also a change in the transcriptional expression of the bacteria creating new cell-to-cell signaling mechanisms that can cross bacterial species, making biofilm a quite formidable opponent for the host.⁴³ Even wounds that are appropriately débrided of all necrotic tissue can still have active infection that limits wound healing as a result of the biofilm bacteria creating a continuous inflammatory state.

The exact method to characterize and detect biofilm in chronic wounds is an active area of research. A recent study detected biofilm-producing bacteria in 80% of all chronic wounds, and only those wounds without detectable biofilm showed signs of healing.⁴⁴ Treatment is difficult as biofilms are resistant to antibiotics⁴⁵ and biocides,⁴⁶ can evade the host immune system,^{47,48} and are impenetrable by many commonly used antibiotics.^{49–52}

The regulation of gene expression by bacteria to alter their phenotype according to the level of bioburden is known as quorum sensing. In chronic wounds, quorum sensing can

lead to the expression of virulence genes, for example, those encoding biofilm production.⁵³ Chronic wound treatment aims to tip the balance in favor of the host defense system with serial débridement to maintain the level of bacteria below quorum. Wound débridement facilitates healing by decreasing the microbial burden and removing nonviable tissue to allow reepithelialization.

Because topical and systemic agents alone are not effective in removal or suppression of biofilm, physical débridement is necessary to disrupt the biofilm. The bacteria must then increase proliferation and synthesis of the biofilm to regenerate and are subsequently most susceptible to antibiotics and biocides during the first 24 to 72 hours of the new growth phase.^{45,46} Débridement can remove the vast majority of bacteria, but it is unrealistic to expect sterilization of the wound as bacteria tend to integrate deep into the tissue and thus remain after débridement to reproduce the protective biofilm.⁵⁴ Frequent disruption of the biofilm forces it to continually reattach to the host, increasing its vulnerability to attack. Therefore, serial débridement must be integrated into the treatment strategy for all chronic wounds.⁵⁵

WOUND MOISTURE

Almost 50 years ago came the realization that maintaining appropriate wound moisture was important to improve the condition of chronic wounds.⁵⁶ This information led to the production of various wound dressings aimed at providing the wound with a moist healing environment, decreasing pain, minimizing odor, and removing excess fluid that retards cellular proliferation and angiogenesis.^{56–58} However, an appropriate amount of wound fluid containing matrix metalloproteinases, growth factors, and cytokines is necessary for wound healing.^{59–61}

An ideal dressing for chronic wounds is one that maintains appropriate wound moisture, absorbs exudate, prevents maceration of healthy tissue, prevents infection, minimally disturbs healing tissue, and is cost-effective. Unfortunately, this product does not exist. The choice of a suitable dressing must take into consideration the current wound conditions and the greatest threats to wound healing, realizing that dressings alone are inadequate to heal chronic wounds.⁶²

Moisture-retentive dressings are typified by their moisture vapor transmission rate less than 840 g/m²/24 hours.⁶³ Hydrocolloid dressings are the most effective moisture-retentive dressings, releasing moisture at a rate of 300 g/m²/24 hours. This is in comparison with cotton gauze, which loses moisture at a rate four times that of hydrocolloid dressings.⁶⁴ An understanding of the moisture properties of a dressing aids the clinician in choosing the appropriate dressing based on the wound characteristics. Wounds draining excessive exudate benefit from the use of dressings that facilitate removal of excessive moisture from the wound bed. A description of multiple dressings highlighting the moisture vapor transmission rate and appropriate uses appears in Table 2.

In addition to maintaining the moisture balance of a wound, a dressing can also function as a delivery vehicle for antimicrobial agents. Two such agents, cadexomer iodine and silver, offer broad-spectrum coverage and have shown efficacy against biofilms.^{65,66} Iodine was first discovered in 1811, but it was not until 1927 that Dr. Sunker Bisey, a Hindu scientist, found it to be useful on wounds, and it has been in use as an antiseptic agent ever since.⁶⁷ Cadexomer iodine is a

Table 2 Properties of Some Types of Wound Dressings

Dressing Type	Moisture Vapor Retention Rate (g/m ² /24 hr)	Properties
Polyurethane film	300–800	No absorptive capacity
Hydrocolloids	< 300	Not for infected or draining wounds Traumatic to wound with removal Risk of contact dermatitis May have offensive odor
Foams	800–5000	For wounds with excessive drainage, not dry Used with compression bandages
Absorptive wound fillers		Can get into tunneling wounds Atraumatic removal Very absorptive Hemostatic properties Nonallergenic Less patient pain
Hydrogels		Will hydrate wound Nonadhesive Minimizes pain Can be used to provide moisture to another dressing
Cotton gauze	1200	For heavily draining wounds Will adhere to viable tissue Useful as a second layer

Data from Seaman S.¹⁹⁰

polysaccharide starch lattice containing 0.9% elemental iodine that is released on exposure to wound exudate.⁶⁸ The antimicrobial activity of this extensively studied dressing can last for days and is safe and effective in reducing the bioburden of chronic wounds.⁶⁹

Silver is another commonly used antiseptic agent that has been in use for many years. Silver nitrate solution was one of the first formulations used extensively on burn wounds.⁷⁰ This led to the formulation of silver sulfadiazine cream, which was easier to use and effective in the treatment of burn wounds.⁷¹ The element silver is inert in its metallic form; however, it ionizes on contact with body fluid, transforming it into an effective antimicrobial agent.⁷² Additionally, silver absorbed by epidermal cells can induce the production of metallothionein, which, in turn, may increase the uptake of copper and zinc. These elements are postulated to promote cell proliferation and tissue repair through an increase in RNA and DNA synthesis.^{72,73}

Silver can be lethal to bacteria even at very low concentrations, thus prompting the development of several sustained-release dressings that deliver high concentrations of ionic silver at rates of 70 to 100 parts per million.^{74,75} Silver is toxic to human keratinocytes at higher concentrations both in vitro and in vivo in randomized, prospective clinical trials.⁷² Newer formulations of silver-containing products release silver into the wound at continuous low concentrations, negating the toxic effects that were previously unrecognized in clinical

practice. A recent meta-analysis found statistically improved wound healing, pain, odor, and exudate reduction with the use of silver-containing dressings.⁷⁶ However, there is a delicate balance between bacterial burden reduction and keratinocyte cytotoxicity. The toxic effects of systemic silver have been examined, and although it has been found in liver, brain, kidney, and bone marrow, no known risk has been identified. Argyria, when silver is absorbed and discolors the skin, is non-life-threatening.⁷⁴ Silver sulfadiazine was once thought to lead to leukopenia when used as a treatment for burns; however, postburn neutropenia is now attributed to the associated burn injury.⁷⁷ Further studies are required to fully understand the complete toxicity profile of silver.

Biologic Adjuncts to Wound Healing

VASCULAR ENDOTHELIAL GROWTH FACTOR

Wounds refractory to the normal healing process and timing may be candidates for growth factor therapy, which can stimulate missing or dysfunctional components of the chronic wound. Vascular endothelial growth factor (VEGF) is an angiogenic growth factor that may promote the healing of hypoxic, chronic wounds attributable to compromised blood delivery. VEGF is strictly investigational at this point in time but warrants discussion. VEGF functions as an endothelial cell mitogen⁷⁸ and a chemotactic agent⁷⁹ and induces vascular permeability.⁸⁰ VEGF is unique in that it affects multiple components of the wound-healing cascade, including angiogenesis, epithelialization, and collagen deposition.⁸¹ This homodimeric glycoprotein exists in five different isoforms varying by amino acid chain lengths. It is produced by a multitude of cells involved in wound healing, including endothelial cells, fibroblasts, smooth muscle cells, platelets, neutrophils, and macrophages. Stimulation of angiogenesis involves a stepwise process of vasodilation, basement membrane degradation, endothelial cell migration, and endothelial cell proliferation.⁸² This is followed by capillary tube formation, anastomosis of parallel capillary sprouts, and, finally, new basement membrane formation, with VEGF playing a part in all of these steps. The formation of granulation tissue, fibrovascular tissue with collagen and blood vessels, is essential to normal wound repair. Angiogenesis is at the heart of this process and begins as early as 3 days after wounding.⁸³ The capillary growth that follows allows a conduit to deliver nutrients and other mediators of the healing response. Inhibition of angiogenesis has been shown to inhibit wound healing.⁸⁴

Platelets are the first cellular component to arrive at the wound bed and, when activated, release VEGF. There is a continued cascade of events that respond to this initial stimulation by VEGF with recruitment of monocytes and macrophages to the wound by the chemotactic effects of VEGF, and these cells in turn release more VEGF to induce expression in keratinocytes and fibroblasts. Hypoxia within the wound bed is a strong stimulus to upregulate the secretion and receptor expression of VEGF in all cell types.⁸⁵ The effects of VEGF on wounds are found immediately after injury. It has a vital role in reducing wound hypoxia and metabolic deficiencies through angiogenesis, with maximal activity exhibited 3 to 7 days after injury. Once the wound is granulated, angiogenesis ceases and endothelial cells undergo

apoptosis, with a resultant decline in vasculature. Endogenous VEGF appears to have little effect in patients with chronic wounds. Initial studies using plasma-directed gene therapy to induce VEGF expression for patients with non-specific limb ischemia,^{86,87} Buerger disease,⁸⁸ and myocardial ischemia⁸⁹ have shown promise, with positive results and minimal complications.

Research investigating the positive effects of VEGF on diabetic ulcers, the prototypical model of impaired wound healing, is also under way. The diabetic wound is complicated by a multitude of factors that are explained later in this chapter, but one of the profound problems leading to a diabetic ulcer is low periwound transcutaneous oxygen pressure. Application of VEGF promotes angiogenesis, chemotaxis, and increased levels of nitric oxide. This results in restoration of endothelial cell function to improve nerve conduction, tissue oxygenation, epithelialization, and collagen deposition.⁸¹ VEGF may prove to be effective in the treatment of chronic wounds with deficiencies of blood delivery as gene therapy with VEGF has been shown to restore impaired angiogenesis found in ischemic limbs in murine animal models.⁹⁰

STEM CELL THERAPY

Stem cells serve as the source for replenishing lost cells necessary for repair and tissue regeneration. Tissue-specific stem cells provide daughter cells to repopulate the injured area through differentiation or by releasing signaling molecules to recruit other cells involved in tissue healing.^{91,92} During the inflammatory phase of wound healing, bone marrow-derived hematopoietic stem cells migrate to the wound site to supply leukocytes and differentiate into dendritic cells via the Notch signaling pathway.⁹³ These dermal mast cell precursors and other hematopoietic populations provide the inflammatory phase with macrophages and mature mast cells. Keratinocytes are derived from epithelial stem cells located within the hair follicle bulge and interfollicular populations that are thought to arrive at the wound via paracrine signaling.⁹⁴

Application of stem cells directly to a healing wound is strictly investigational at this time and has several hurdles to overcome, including cell sourcing and delivery, before the full potential is realized. The use of autologous versus allogeneic stem cells would exclude the potential problem of graft versus host disease. Various strategies for the delivery of autologous mesenchymal and epithelial stem cells, including spraying cells with thrombin on a wound,⁹⁵ intradermal injection,⁹⁴ and implanting hair follicle micrografts,⁹⁶ have been studied, with positive results in all phases of wound healing. An alternative stem cell-related wound healing strategy involves intradermal injection of chemokines to attract bone marrow-derived precursors to accelerate skin regeneration.^{97,98} This treatment showed promise; however, the effect was fleeting.

Ideally, a consistent, sustained, localized delivery method of these diffusible factors is necessary to augment the healing process of the chronic wound. The role for stem cell therapy in the treatment of a chronic wound is promising; however, the method of delivery to the wound, such as intradermal injection, topical delivery, or chemotactic stimulation, needs further investigation.

PLATELET-DERIVED GROWTH FACTOR

Platelet-derived growth factor (PDGF) is a dimeric glycoprotein with five different isoforms normally found in platelets, macrophages, and endothelial cells. It promotes cell mitogenesis, migration, and the synthesis of protein and extracellular matrix components. It also has a significant role in angiogenesis. In 1995, the effectiveness of PDGF in chronic wound healing was evaluated when 118 patients with non-healing, lower extremity ulcers of at least 8 weeks' duration were randomized to receive PDGF in a topical gel applied twice daily at a concentration of 30 µg per gram of gel or placebo.⁹⁹ The percentage of patients who healed in the PDGF group was twice that of the placebo group. Since then, several randomized, prospective, blinded, placebo-controlled studies have demonstrated that repeated, once-daily, topical application of PDGF with an increased concentration of 100 µg/g is safe and stimulates healing of chronic, full-thickness diabetic ulcers of the lower extremity.^{100–103}

SKIN GRAFTS

Autograft and allograft can accelerate the closure of ulcers if applied after revascularization and appropriate wound bed preparation. Even in refractory ulcers, they function as biologic dressings providing a matrix for growth. Extracellular matrix therapy is currently being investigated as it stimulates wound epithelialization, increases angiogenesis, and provides bioactive components to the wound bed.¹⁰⁴

Other Adjuncts to Wound Healing

ULTRASOUND THERAPY

Ultrasound therapy has been studied in pressure and venous ulcers and has its effect on wound healing through both thermal and nonthermal properties. It has been shown to augment the remodeling phase and change the cell permeability to improve the rate of healing.¹⁰⁵ However, there have been no randomized, controlled trials as of yet that prove efficacy.

NEGATIVE PRESSURE WOUND THERAPY

Topical negative pressure wound therapy has proven efficacy in ulcers with multiple etiologies by removal of exudate, reducing edema, increasing wound blood flow, and reducing bacterial counts. Thirteen randomized trials have analyzed negative pressure wound therapy against other conventional dressings on all types of chronic wounds. Although topical negative pressure therapy did not result in earlier complete wound healing, a nearly 10-day improvement in the time needed to prepare for secondary closure was observed.¹⁰⁶

HYPERBARIC OXYGEN

Hyperbaric oxygen improves tissue oxygen in ischemic tissue, enhances the rate of angiogenesis, and increases signal transduction of growth factors to the wound bed. These effects can last up to 4 hours after treatment conclusion, and increased oxygen by itself can diminish anaerobic bacterial counts deep within the wound.¹⁰⁷ For hyperbaric oxygen to be successful, the pretreatment wound should be hypoxic but not anoxic. The transcutaneous oxygen tension must be at least 10 mm Hg and less than 40 mm Hg. Levels measured

after therapy greater than 200 mm Hg suggest successful treatment.¹⁰⁸ The only absolute contraindications to hyperbaric oxygen therapy are untreated pneumothorax, restrictive airway disease, and concomitant chemotherapy. The time should not exceed 2 hours or pressure greater than three atmospheres.

Reimbursement for this therapy is currently approved by the Centers for Medicare and Medicaid Services only as an adjunct for wounds with a diabetic etiology and wounds unresponsive to standard therapy for a period of at least 30 days. There must also be measurable signs of healing within 30 days of treatment initiation for therapy to continue.¹⁰⁹

Arterial Insufficiency Ulcers

DIAGNOSIS

More than 10 million people suffer from peripheral arterial occlusive disease in the United States.¹¹⁰ These patients tend to have multiple organ systems, including the heart, kidney, and skin, that suffer from poor arterial perfusion. This combination of problems leads to significant morbidity and mortality, with a 35% 5-year mortality and a 2% rate of lower extremity amputation.¹¹¹ All patients with lower extremity ulcers should be assessed for peripheral arterial occlusive disease. The ulcer may be the first sign of an arterial disease process, and reduction of overall disease-related morbidity and mortality is best accomplished with early diagnosis and interventions.

It is important to distinguish ulcers caused by venous insufficiency from those caused by arterial disease with a history and clinical vascular examination. Relevant history includes timing of ulcer formation, previous treatments, and history of claudication. Symptoms of rest pain or nighttime waking attributable to lower extremity pain should alert you to a possibly more serious problem of limb-threatening ischemia.

A patient's history can easily lead to the diagnosis of arterial insufficiency as a contributing factor for a chronic wound. Those patients presenting with risk factors associated with atherosclerotic disease (such as smoking, diabetes, hypertension, hypercholesterolemia, advanced age, obesity, and hypothyroidism) are more likely to have arterial ulcers. However, other causes of vascular insufficiency, such as thromboangiitis, vasculitis, Raynaud phenomenon, pyoderma gangrenosum, thalassemia, or sickle cell disease, should be entertained as well.¹¹⁰ It is also important to inquire about symptoms of rest pain as this, along with signs of gangrene, has a much higher risk of limb loss than a nonhealing ulcer alone.¹¹²

The clinical examination should include skin quality and hair presence compared with the other extremity. Quantification of capillary refill and evaluation for dependent rubor, along with palpation of both the dorsalis pedis and the posterior tibialis artery, should follow. A bounding pulse can generally rule out arterial insufficiency as the cause of the ulcer, but performing an ankle/brachial index (ABI) can quantify the information. Any abnormal finding on a pulse examination should signal the necessity to perform an ABI [see Table 3]. The sensitivity of a nondetectable pulse for the diagnosis of peripheral arterial occlusive disease is between 17 and 32%, with a specificity approaching 99%.¹¹³ A dorsalis pedis pulse is absent in 8.1% of healthy individuals, and 2.9%

Table 3 Ankle/Brachial Index (ABI)

Steps to performing an ABI:

1. Record systolic blood pressure in each upper extremity; record the highest number
2. Use Doppler ultrasonography to identify dorsalis pedis or posterior tibial signal on the affected extremity
3. Place the sphygmomanometer just above the ankle and inflate it to a pressure higher than the recorded systolic blood pressure
4. Slowly release the pressure of the sphygmomanometer while listening for the return of signal from the dorsalis pedis or posterior tibial artery; record the value when the signal returns
5. The lower extremity value divided by systolic blood pressure is the ABI

lack a palpable posterior tibialis pulse. Both are absent in less than 2% of healthy individuals.¹¹⁴

Physical examination findings suggestive of arterial insufficiency include cold, pale feet in a warm environment; shiny, taut skin; and a punched-out appearance of the ulcer.¹¹⁵ Quantitative findings suggestive of peripheral arterial occlusive disease include a delay in the capillary refill response,¹¹⁶ ABI less than 0.90,^{110,112,114,116} and transcutaneous oxygen tension value of less than 40 mm Hg.^{9,112} Not all patients with an abnormal ABI will require revascularization, and the sensitivity and specificity of this test are reduced in patients with calcified, incompressible vessels. Transcutaneous oxygen tension is thought to be a more effective marker of clinically significant arterial disease than ABI but is not available in every clinic. A meta-analysis of 615 patients requiring lower extremity amputations found that oxygen tension less than 20 mm Hg provides the most accurate prediction of failure to heal or the need for more proximal amputation.¹¹⁷ Transcutaneous oxygen tension is also helpful in assessing the success of a vascular intervention.

MANAGEMENT

Once the diagnosis of arterial insufficiency has been made, a road map of the suspected large vessel vascular defect must be made. This is most often done through angiography, duplex angiography, magnetic resonance angiography, or contrast-enhanced computed tomographic angiography. Each of these diagnostic tools has its own sensitivity, specificity, and complication profile, which are not discussed here. Surgeon preference and individual technical abilities also play a role in the selection of diagnostic tests. In patients with arterial insufficiency, ulcers, and an identified surgically correctable arterial lesion compromising distal perfusion, revascularization is the intervention that represents the greatest opportunity to affect ulcer healing.¹¹⁶ Revascularization is accomplished through open or endovascular techniques. The effectiveness of the intervention is demonstrated by improvements in ABI and transcutaneous oxygen tension measurements. The natural history of patients with arterial insufficiency ulcers and nonreconstructable vessels is that of disease progression and eventual limb loss. The only available options are revascularization or amputation. Failure to correct the underlying vascular disease will lead to a consistently unsuccessful outcome.

TREATMENT

About 20% of patients with peripheral arterial occlusive disease will require revascularization surgery. Open lower extremity infrapopliteal bypass surgery has a 5-year patency rate of about 70% and a 1-year amputation rate of 2%.^{118,119} Infringuinal bypass does not fare as well, with a 57% 5-year primary patency rate and an overall 63% 5-year patency with secondary interventions to salvage the graft. Even with graft failure, 5-year limb salvage rates are 80% in both groups.^{118–120} Today, endovascular interventions are often the first line of treatment of this disease, but long-term patency and limb salvage rates are not yet available.

Although revascularization is the primary step in treating a patient with an arterial insufficiency ulcer, it does not guarantee sufficient delivery of oxygen and nutrients to the wound bed to facilitate healing. A patient's comorbidities require thoughtful consideration when offering any surgical intervention, and a careful risk/benefit analysis of all options must occur with every patient.

Wound Débridement

As stated earlier, initial care of the ulcer itself begins with débridement of the wound bed. If dry eschar covers the ulcer, all débridement should wait until revascularization has occurred because the eschar functions as a biologic dressing.¹²¹ Signs of local or systemic sepsis necessitate débridement prior to revascularization. After débridement, the appropriate wound environment must be maintained to optimize healing, including adequate intravascular volume to augment distal perfusion. Stressors such as pain or cold must be avoided as this increase in sympathetic tone will reduce distal perfusion. Smoking cessation is an absolute necessity in patients with vascular insufficiency ulcers secondary to peripheral arterial occlusive disease as continued smoking leads to vasoconstriction, causing further large vessel occlusive injury and diminished peripheral oxygenation.¹²²

Dressing and Adjuvant Therapies

In those patients who are not candidates for surgical or endovascular treatment of their peripheral arterial occlusive disease, identifying the correct dressing is vital to wound healing. A combination of a dressing and adjuvant therapy serves to débride the wound, maintain adequate moisture, and provide bacterial control. There is no evidence to suggest the superiority of any one dressing; however, the choice of dressings is aided by the aforementioned principles. Additionally, a cost-effective, once-daily dressing choice is suggested. Moist saline gauze dressings are often the most cost-effective dressing but can lead to increased patient discomfort, inappropriate débridement of viable tissue, and increased frequency of dressing changes.¹⁰⁴

Adjuvant therapies cannot replace revascularization but may be useful when revascularization is contraindicated, is unsuccessful, or does not result in the expected ulcer healing. There is a paucity of data on the use of adjuvant therapies to heal arterial insufficiency ulcers, but the initial results are promising. Direct local and spinal cord electrical stimulation have shown effectiveness in animal studies and case series, but randomized trials are lacking from the literature.^{105,123} Spinal cord stimulation has been shown to reduce pain associated with limb ischemia and in one randomized trial of

120 patients was shown to improve 2-year limb survival.¹²⁴ Topical negative pressure wound therapy is effective in ulcers with multiple etiologies as previously mentioned, but its role as an adjunctive therapy in vascular ulcers is not known. In patients in whom revascularization is not possible or the ulcer is nonhealing despite revascularization, hyperbaric oxygen therapy is also a consideration.

PREVENTION

Patients who present with arterial insufficiency ulcers as a result of peripheral arterial occlusive disease have a 10-year mortality risk approaching 60%, and this risk increases with age and the severity of the arterial disease. Management of the underlying disease not only helps prevent future ulcer occurrence but also reduces overall mortality. Smoking cessation, glucose control, and reduction of hypercholesterolemia and hypertension will decrease the risk of ulcer recurrence and cardiovascular complications such as myocardial infarction and stroke.¹²⁵ Most arterial insufficiency ulcers present when peripheral arterial occlusive disease is in its late stages; therefore, the best prevention occurs with early recognition of the signs and symptoms. Intermittent claudication is the hallmark sign of peripheral arterial occlusive disease, yet it presents in only one third of patients, with only a minority of those patients progressing to arterial ulceration.

Care providers must recognize the early warning signs and symptoms [see Table 4] of arterial disease to have a significant impact on ulcer incidence. It is also important to perform an appropriate peripheral vascular examination when patients present with a medical history that places them at significant risk [see Table 5]. When the history or one of these signs is identified, appropriate physical examination and diagnostic

studies can then confirm the presence of the disease. If immediate intervention is deemed unnecessary, the patient must be educated about the future morbidity and mortality this diagnosis carries and appropriate follow-up must be arranged. Reduction in ABI of 0.15 is significant, and referral to a peripheral vascular specialist should be strongly considered as this patient is at even greater risk for complications. Those patients who require revascularization for an arterial ulcer have a 20% risk of requiring contralateral revascularization for ulceration.¹²⁶ An increase in blood viscosity is a poor prognostic factor for those with peripheral arterial occlusive disease, and the use of antiplatelet therapy decreases the overall incidence of cardiovascular death.^{127,128} A randomized, controlled trial found that clopidogrel reduced the incidence of cardiovascular death by 3.7% and that aspirin reduced it by 4.9%.¹²⁷ In a more recent study with over 15,000 patients, double-antiplatelet therapy failed to show further reduction in mortality or ulcer incidence, and treatment was complicated by increased ulcer bleeding. Single-agent antiplatelet therapy is recommended for all patients with peripheral arterial occlusive disease.¹²⁸

Arterial insufficiency ulcers can begin as a result of trauma to an at-risk limb. Appropriate foot protection that is soft and conforming and fits properly will reduce trauma and is especially important for those patients with diminished sensation as they have delayed recognition of an injury. Extreme caution during toenail trimming is suggested for all patients, especially those with associated diabetes mellitus, as trauma to the surrounding tissue during nail clipping may evolve into ulceration. In those patients with an absent pulse and significant neuropathy, a podiatrist or other trained specialist should perform this procedure.¹²⁵

Despite all of this information, early revascularization of those patients without active ulceration is not recommended as the risk/benefit profile does not favor ulcer prevention. With the speed at which endovascular treatments are progressing, and the morbidity of the procedure diminishing, a formal analysis of the data will be necessary to examine when the risk/benefit profile suggests early intervention. Until then, lifestyle modifications remain the most important preventive measure.

Pressure Ulcer

Pressure ulcers affect up to 3 million people in the United States, with an increased prevalence in the elderly, the acutely ill, and those with spinal cord injuries.¹²⁹ A pressure ulcer is simply caused by a lack of blood flow to a section of dermal tissue. When pressure is applied over susceptible tissue, such as the skin over a bony prominence, dermal blood flow is impeded and necrosis develops as a result of tissue hypoxia. Conditions that lead to immobility, altered sensation, reduced tissue perfusion, or hypoxia greatly increase this risk. About 95% of all pressure ulcers occur on the lower portion of the body, with 36% on the sacrum and 30% at the heel.¹³⁰ Both hospital and nonhospital care facilities must report the incidence of pressure ulcer in patients under their care as a marker of quality care. There is a movement toward withholding payments if the pressure ulcer rate is above a set standard; however, this is a controversial area because not all pressure ulcers are avoidable.¹³¹

Table 4 Signs and Symptoms of Peripheral Arterial Occlusive Disease

Signs
Loss of hair
Shiny or dry skin
Dry, black toe
Devitalized soft tissue with dry crust
Thickened toe nails
Deep purple skin when dependent
Cool skin
Symptoms
Decreased walking distance
Exertional leg pain
Numbness or leg fatigue while walking
Nocturnal foot pain
Foot numbness at rest
Leg wounds heal more slowly

Table 5 Risk Factors for Peripheral Arterial Occlusive Disease

Age greater than 75
Known coronary artery disease
Known cerebrovascular disease
Smokers
Diabetes mellitus
Hyperlipidemia
Dialysis-dependent renal failure
Hyperhomocysteinemia
Elevated C-reactive protein

TREATMENT

Pressure ulcers are exceedingly resistant to any known medical therapy and fail to proceed through the normal healing process, as in acute wound healing. As few as 13% of pressure ulcers that develop in acute hospital settings heal within 14 days.¹³² The healing rate of any pressure ulcer is dependent on the stage of the ulcer at diagnosis. [see Table 6]. Stage III ulcers have healing rates of 60% at 6 months, but many require more than 1 year.¹³³

Assessing Severity

The most common staging is derived from the original Shea scale and is recommended by the National Pressure Ulcer Advisory Panel Task Force and Omnibus Reconciliation Act.¹³⁴ The staging consists of categories I to IV, defined by visual characteristics and the depth of the wound. Additionally, there is an unstageable category that denotes that further débridement is necessary to categorize the ulcer. This staging system has several limitations as there is an inability to distinguish progression between stages. Furthermore, not every pressure ulcer progresses through all the stages; for example, there can be significant damage to the deep tissues with only minimal skin changes.

Pressure Relief and Shear Reduction

Healing cannot occur unless pressure is removed from the ulcer. Six randomized, controlled trials with air-fluidized beds suggested improved healing rates when compared with low-air loss beds, and one trial showed improved healing in low-air loss beds compared with foam overlay.^{135–140} However, there is no definitive evidence that one pressure-relieving device is superior to another. Frequent turning and repositioning are the current and most popular method to avoid pressure and shear. Although ideal, it is not always possible to implement this because of patient comorbidities.

Wound Therapy

The principles of wound bed preparation and dressings discussed earlier in this chapter also apply to pressure ulcers. All pressure ulcers require débridement, and, currently, no data favor one form of débridement over another. Hydrocolloid dressings have been shown to significantly improve pressure ulcer healing when compared with dry dressings.¹⁴¹ Dressing choices for pressure ulcers are complicated by the location of the ulcer on the body. Dressings should not add

increased pressure to surrounding viable tissues or create further tissue injury. Difficulties in dressing adherence occur with the presence of ulcers over joints. Loss of the occlusive edge of the dressing will diminish the benefit of moisture retention. Given the inherent difficulty with dressing placement in those with pressure ulcers, topical negative pressure dressings are commonplace. When there is clinical evidence of infection, topical or systemic antibiotics are required. Commonly used topical antimicrobial agents include silver sulfadiazine cream, combination antimicrobial ointments, and solutions of 5% mafenide acetate. Systemic antibiotic therapy should be reserved for those patients in whom the infection has spread beyond the wound or into the bloodstream.

Surgical Treatment

Infection plays a major role in the decision to operate on patients with pressure ulcers, with the success of wound closure maximized when the ulcer is free of local and distant infection. After successful infection control, débridement, and appropriate pressure relief, the wound should show signs of contracture and secondary wound closure within 2 weeks. If these signs do not occur, a quantitative anaerobic and aerobic bacterial wound tissue culture should be obtained to diagnose the possible offending bacteria. Levels greater than 1×10^6 colony-forming units per gram of tissue will impede secondary healing and lead to failure of surgical closure.¹⁴² Topical antimicrobial treatment is recommended in this situation because systemic antibiotics are not effectively delivered to a granulating wound.¹⁴²

Primary closure is an option in patients with pressure ulcers; the efficacy is high in the short term but significantly reduced in the long term, even in younger patients.¹⁴³ About half of the patients will have ulcer recurrence in the same area and 70% will develop a separate ulcer within 6 months.¹⁴⁴ In those patients with stage III or greater ulcers, a myocutaneous flap is the recommended operative treatment. However, postoperative complications occur in 40% of patients undergoing flap procedure and 80% develop ulcer recurrence or new ulcer within 1 year.¹⁴⁵ Much lower rates of limb salvage and higher complication rates are observed in patients with heel ulceration plus end-stage renal disease; therefore, these patients may consider amputation as their primary surgical option even in the presence of a palpable foot pulse.¹¹²

Complications

The presence of pressure ulcers carries a significant mortality in both acute and long-term care settings. A 67% mortality risk is present for patients with pressure ulcers compared with 15% mortality in the same at-risk group of patients without a pressure ulcer. The risk of death is tripled if the pressure ulcer develops within 6 weeks of hospitalization. In long-term care settings, the risk is even more staggering, with a 92% mortality when a pressure ulcer develops within 6 months of admission compared with 4% mortality in those patients who do not develop a pressure ulcer. It is unknown how this correlates with mortality, although the ulcer severity does not correlate with the risk of death. The assumption remains that pressure ulcers develop in patients with associated comorbidities and contributes to the mortality risk. With this knowledge, pressure ulcers may stimulate end-of-life discussions given the inherent caregiving burden.

Table 6 Stages of Pressure Ulcer

Stage	Clinical Findings
I	Nonblanchable erythema Intact skin
II	Injury extends into dermis Presents clinically as an abrasion, blister, or shallow ulcer
III	Full-thickness skin loss Extends down to fascia Deep crater Surrounding tissue may be undermined
IV	Damage to muscle, bone, and supporting structures Frequent undermining and sinus tracts

Osteomyelitis is a frequent complication of pressure ulcers. Plain radiographs are not sufficient to confirm the diagnosis as it is difficult to differentiate between pressure changes to the bone and osteomyelitis.¹⁴⁶ Radionuclide studies are sensitive but have a 41% false positive rate.¹⁴⁷ Computed tomography is also a specific test, but the sensitivity is only 10%.¹⁴⁸ Bone biopsy is the best single test, with a sensitivity of 73% and a specificity of 96%.¹⁴⁹ Sepsis originating from the pressure ulcer is associated with significant mortality and most often requires surgical débridement to gain control of the bacteremia.

Overall, there is no gold standard for the treatment of pressure ulcers. As with all chronic wounds, control of all comorbidities, optimization of nutrition, and prevention of further skin injury are the best ways to begin treating this complex problem.

PREVENTION

The risk of pressure ulcer is complex and multifactorial. These risks are best identified immediately on admission to a health care facility by pressure ulcer risk screening performed by a qualified professional. The best practice process continues with a pressure ulcer risk assessment, formulation of a pressure ulcer prevention care plan, and implementation of the plan with frequent reassessment.

The Braden scale is the most extensively studied tool and consists of six scored parameters.¹⁵⁰ A higher score implies a lower risk of pressure ulcer development [see Table 7]. Reliable predictive ability of the Braden scale has yet to be shown, and it has inadequate performance outside the acute hospital setting. Further effort is needed in this area to identify those patients at risk as a scoring system with a poor positive predictive value will result in implementation of unnecessary and expensive preventive treatment.

Venous Ulcer

DIAGNOSIS

Venous ulcers are the most prevalent cause of chronic lower extremity ulcerations. The diagnosis begins with a detailed examination of the wound characteristics. Chronic venous ulcers of the lower extremity are shallow wounds, rarely involving muscle, fascia, or bone, located in the gaiter area with a surrounding hyperpigmentation. The pathophysiology of the venous ulcer is related to venous insufficiency leading to venous hypertension, which ultimately results

in ulceration. The lower extremity venous system includes the deep veins below the fascia that drain the muscles and the superficial veins above the fascia draining the cutaneous tissue. These systems are connected by the perforating venous system. Various factors are thought to contribute to formation of chronic venous ulceration through venous insufficiency from failure of the venous calf muscle pump, immobility, and valve dysfunction.

A correct diagnosis is paramount to establishing an appropriate treatment regimen for lower extremity venous ulcers. Treatment is ideally formulated with the underlying disease process in mind. According to the guidelines established by the Wound Healing Society, the presence of coexisting diseases such as arterial pathology or distinct entities such as malignancy, collagen vascular disease, or the dermal manifestation of systemic diseases such as sickle cell anemia, leukemia, immunosuppression, inflammatory bowel diseases, or systemic fungal or mycobacterial infections must be identified.^{8,151} Alternative etiologies of chronic lower extremity ulcerations should be entertained and excluded by biopsy if needed, especially if prolonged treatment has not resulted in ulcer improvement. Diagnosis of venous ulcers is accomplished with the aid of classification systems, identification of associated risk factors, and diagnostic imaging.

Various classifications tools have been developed for clinical and research use. The CEAP (clinical severity, etiology, anatomy, pathophysiology) classification is a well-known system that was initially developed in 1994 and revised in 2004.¹⁵² The CEAP is a descriptive classification of chronic venous disorders, aiding in diagnosis and communication of wound management between health care providers, as well as in documentation of clinical research involving chronic venous disorders [see Table 8]. Moving beyond classification, the venous clinical severity score (VCSS) is a dynamic measure that assesses outcomes of treatment. The Venous Severity Scoring system encompasses the CEAP classification and the VCSS to allow for dynamic descriptive characterization of venous ulcers to improve the evaluation of treatment.

A careful assessment of the risk factors associated with venous ulcers aids in developing a diagnosis. Immobility, obesity, lower extremity trauma, advanced age, the presence of varicose veins, especially in pregnancy, and a history of phlebitis are associated with an increased risk of venous ulcerations.¹⁵³ Hypercoagulable risk factors such as elevated factor VIII, von Willebrand factor, D-dimer, the presence of

Table 7 The Braden Scale

Examination of Ulcer	Value				Score
	1	2	3	4	
Sensory perception	Completely limited	Very limited	Slightly limited	No impairment	
Moisture	Constantly moist	Very moist	Occasionally moist	Rarely moist	
Activity	Bedridden	Up to chair	Walks occasionally	Walks frequently	
Mobility	Immobile	Very limited	Slightly limited	No limitation	
Nutrition	Very poor	Inadequate	Adequate	Excellent	
Friction and shear	Problem	Potential problem	No apparent problem		
Total score					

Table 8 Clinical Severity, Etiology, Anatomy, and Physiology (CEAP)¹⁵²

Clinical severity (C)
C ₀ : no visible or palpable veins
C ₁ : telangiectasias or reticular veins
C ₂ : varicose veins
C ₃ : edema
C _{4a} : pigmentation or eczema
C _{4b} : lipodermatosclerosis or atrophie blanche
C ₅ : healed venous ulcer
C ₆ : active venous ulcer
S: symptomatic
A: asymptomatic
Etiology (E)
Ec: congenital
Ep: primary
Es: secondary
En: no venous cause identified
Anatomy (A)
As: superficial veins
Ap: perforator veins
Ad: deep veins
An: no venous location identified
Pathophysiology (Basic) (P)
Pr: reflux
Po: obstruction
Pr, o: reflux and obstruction
Pn: no venous pathophysiology identifiable

lupus anticoagulant, and previous deep vein thromboses are associated with venous ulcers.^{154,155}

Methods to evaluate abnormalities in the veins include physical examination, handheld Doppler ultrasonography, color duplex ultrasonography, phlebography, and venography. Measurement of arterial insufficiency using ABI [see Table 3], transcutaneous oxygen tension, or magnetic resonance angiography can exclude the presence of arterial disease as an etiology. Phlebography was previously the gold standard for initial diagnostic evaluation; however, it is invasive and costly. Color duplex ultrasound scanning has replaced phlebography in most cases.¹⁵⁶ It provides anatomic and physiologic assessment of venous ulcers in a noninvasive method for confirmation of surgically correctable abnormal venous function. Use of color duplex imaging is essential to guide wound management when visual evidence of venous insufficiency such as varicosities is absent.¹⁵⁷ Once the diagnosis of venous ulcer is obtained, formulation of a directed management plan and prevention of ulcer recurrence are possible.

MANAGEMENT

Management goals include ulcer healing, symptom management to improve quality of life, prevention of ulcer recurrence, and edema improvement. Toward these goals, venous ulcers benefit from nonoperative and operative interventions such as compression dressings and venous surgery, as well as leg elevation, exercise, optimization of nutrition, and tissue perfusion. The extended health care team required for the comprehensive care of chronic wounds may include the patient's primary care provider, general surgeon, plastic surgeon, vascular surgeon, wound care nurse, and

nutritionist. Communication between all health care team members is essential for successful coordination of care.

TREATMENT

The treatment of chronic venous ulcers is multimodal and includes vigilant wound care, compression, and surgery. A chronic wound represents a delicate balance between host defense and infection. Débridement serves to tip the scale toward host defense by decreasing the microbial bioburden. In a retrospective review of two randomized, controlled trials, venous leg ulcers with serial surgical débridements at clinic visits were shown to have significantly higher median wound surface area reduction and higher rates of closure compared with less frequent débridement.¹⁵⁸ Nonsurgical methods of wound débridement, such as collagenase, autolysis, fibrinolysis, and wet-to-dry dressings, have also been used.¹⁵⁹

An ongoing assessment of wound healing is absolutely essential to evaluate if the current line of therapy is effective. This includes visual inspection of the wound with documentation of wound measurements, exudates, and condition of wound base and periwound tissue, as well as signs of infection. The bacterial relationship with a chronic wound is on a continuum from colonization to infection. Colonization is defined as replication of bacteria without tissue injury. All colonized wounds are at risk for infection, at which point the replicating bacteria cause destruction of the tissue. In addition to wound débridement to decrease bioburden, topical antimicrobials in the form of ointments, creams, or dressings may be used as an adjunct in the treatment of chronic venous ulcers.¹⁶⁰ Currently, the use of systemic antibiotics for chronic venous ulcer healing is not recommended except in the setting of acute cellulitis or osteomyelitis.^{161,162}

Infection can be a clinical diagnosis based on the appearance of the wound and should be considered if no progression in wound healing is observed after 2 weeks of débridement and initiation of wound therapy. Quantitative cultures can aid in the determination of subclinical wound infection. A wound biopsy has been the gold standard for quantification of wound infection; however, a prospective study comparing quantitative swab culture and biopsy in chronic wounds demonstrated that swab cultures were as effective as biopsy at predicting healing, noting that the presence of four or more bacterial genera in the wound was predictive of a nonhealing ulcer.¹⁶³ Previous reports showed that a level of bioburden greater than 10⁵ is indicative of an infected wound; however, Davies and colleagues demonstrated a 7-log difference in bacterial burden in a group of clinically noninfected wounds, suggesting that the number of bacteria in a chronic wound may be less important than in acute wounds.^{163,164}

Wound dressings provide multiple roles, including débridement, protection, and moisture control, as previously mentioned. Wound healing is supported in a moist wound environment; however, excessive moisture can cause further wound breakdown. Various dressings, including low-adherence dressings, hydrocolloids, foams, alginates, and hydrogel dressings, have been compared in randomized, controlled trials, although there is no strong evidence pointing toward one dressing that is superior.⁶² Factors such as availability, cost, ease of application, and comfort can help determine which dressing should be chosen. Most often, these dressings are used in combination with compression systems. Compression bandages act to combat the venous

hypertension that results in ulcerations. A multitude of compression systems are in use for chronic lower extremity ulcers. Studies have shown that elasticity in a compression system with multiple components is superior to that in a single-component system or no compression at all.¹⁶⁵ Venoactive agents such as pentoxifylline and micronized purified flavonoid fraction (Daflon) have shown promise in meta-analyses as systemic adjuncts to compression in venous leg ulcers.^{166,167}

Surgical management of venous ulcer disease attempts to decrease ambulatory venous hypertension by preventing abnormal transmission of pressure from deep to superficial veins and is reserved for patients with moderate to severe chronic venous insufficiency. Incompetence of the superficial venous system can be treated with ablation of saphenous vein reflux, saphenous vein ligation and stripping, stab avulsions or phlebectomy of varicosities, and endovenous laser therapy or radiofrequency ablation of the saphenous vein. Incompetent perforating veins are interrupted with techniques such as stab avulsions, open perforator interruption, ultrasound-guided sclerotherapy, laser or radiofrequency ablation, and subfascial endoscopic perforator surgery. Deep venous reflux attributable to incompetent valves can be corrected with internal or external valvuloplasty, although these procedures are less frequently performed. A randomized, controlled trial comparing venous surgery plus compression versus compression alone found that 12-month ulcer recurrence rates were reduced when venous surgery was performed in patients with superficial venous reflux and mixed superficial and deep venous reflux.¹⁶⁸

Autograft coverage of venous leg ulcers provides good initial healing; nevertheless, the persistence of the underlying venous insufficiency leads to high recurrence rates of the ulcers.¹⁶⁹ Multiple studies have assessed allogeneic cultured skin versus compression for healing chronic venous leg ulcers; unfortunately, the findings do not address long-term results more than 6 months postprocedure.^{170–172} If the underlying venous insufficiency is corrected, chronic venous ulcers may be grafted with autologous or allogeneic tissue to assist in more rapid wound closure. Topical negative pressure dressings may also prove advantageous prior to skin grafting to prepare the wound bed, remove excess fluid from tissue, and facilitate graft take.¹⁷³ Nonresponse to treatment as evidenced by a lack of progress in wound healing or an increase in the size of the wound should alert the provider to reassess the type of treatment to date, entertain an alternative diagnosis, determine if infection is present, and assess compliance with treatment.

PREVENTION

Prevention of chronic venous ulcers would save significant health care dollars and morbidity. Interventions focused on treating the risk factors of chronic venous ulcers may prevent the formation of the ulcers or their recurrence. Deep vein thrombosis is one risk factor associated with chronic venous ulcerations. Long-term compression has been shown to reduce postthrombotic sequelae.¹⁷⁴ In those patients with chronic venous insufficiency, a 6-month structured program of calf exercises was shown to improve calf function, which may translate into prevention of ulceration in those at risk.¹⁷⁵ Venous surgery, if performed in the at-risk populations who have signs of venous insufficiency, may also prevent the occurrence of chronic venous ulcers.

Diabetic Ulcers

Diabetes mellitus is the leading cause of nontraumatic lower extremity amputation in the United States and affects up to 15% of all diabetics in their lifetime.¹⁷⁶ Diabetic foot ulcers preceded 85% of these nontraumatic lower extremity amputations.¹⁷⁷ Diagnosis of diabetic ulcers requires an understanding of the factors that lead to the tissue damage. Diabetic neuropathy and peripheral vascular disease, alone or in combination, can lead to tissue destruction or prevent healing of acutely injured tissue and are considered major risk factors associated with diabetic ulcers.

DIAGNOSIS

To understand the nature of the wound, a careful history and physical examination, including history of previous ulcers, course of healing, trauma to the extremity, presence of peripheral vascular disease and/or neuropathy, and history of revascularization, are important pieces of information to gather in formulating a plan of care. Diabetic neuropathy results in decreased sensation and function loss as a result of foot deformities. There are multiple tools in use for the assessment of diabetic neuropathy; however, the most sensitive prediction test for ulceration is the neuropathy disability score to quantify the severity of diabetic neuropathy based on the examination of tendon reflexes and sensory modalities and the Semmes-Weinstein filaments (10-gauge SWF) examination¹⁷⁸ [see Table 9]. Deformities of the diabetic foot cause abnormal pressures, especially on the plantar surface, and can lead to ulceration when normal sensation of increased pressure is disturbed as a result of neuropathy.¹⁷⁹

The association of peripheral vascular disease warrants a detailed examination of the vascular status when confronted with a chronic ulcer in the diabetic patient. Noncompressible vessels in a diabetic patient may lead to a falsely elevated ABI, rendering this standard test for the presence of peripheral vascular disease inaccurate.^{180,181} ABI and pulse volume recordings identify problems with the macrovasculature. Alternative methods to diagnose peripheral microvascular disease must be pursued. Transcutaneous oxygen tension is one such test that looks at the microcirculation and skin perfusion, which is of great importance in the diabetic patient with nonhealing ulcers and apparently “normal” ABIs.¹⁸¹ Digital calcification is rarely encountered compared with

Table 9 Neuropathy Disability Score

Neuropathy Disability Score			
Exam	Score	Right	Left
Vibration perception threshold on great toe	Normal = 0 Abnormal = 1		
Temperature perception on dorsum of foot			
Pin-prick on dorsum of great toe (sharp vs not sharp)			
Achilles reflex	Normal = 0 Minimal = 1 Absent = 2		
	Total score		

lower extremity calcifications in ABI measurements; therefore, the toe/brachial index (normal > 0.65) can be used as a surrogate for the ABI.¹⁸¹ Another symptom common in peripheral vasculature disease, claudication, may be masked by the decreased sensation associated with diabetic neuropathy, further complicating the clinical evaluation of a diabetic patient with ulcer disease.

TREATMENT

Ulcers that develop as a result of high pressure on insensate areas of the foot need offloading as the first line of treatment. Acceptable methods of offloading include crutches, walkers, wheelchairs, custom shoes, standard shoes with modifications, and total-contact protective casts.

The wound bed requires preparation to optimize healing potential, as has been previously described. All necrotic and devitalized tissue requires removal by surgical, mechanical, enzymatic, or biologic means. The aim is to convert the wound from a chronic wound to an acute wound. The wound must be properly débrided, be in bacterial balance, and contain appropriate moisture. Wound cares should occur daily, including cleaning with a nontoxic solution followed by appropriate dressing placement that conforms to previously described principles. Simple soap and water provide the most cost-effective and most readily available agents for wound care. Frequent follow-up is recommended to document changes in the wound and evaluation of offloading and wound care effectiveness. Success of treatment is demonstrated by at least a 40% reduction in ulcer size after 4 weeks of appropriate therapy.¹⁸²

Any wound that has been appropriately débrided, offloaded, and subjected to appropriate wound care but has failed to progress in 2 weeks should undergo quantitative culture for suspected infection. Topical antimicrobial agents should be used in cases where there is no evidence of systemic infection as previously noted.¹⁴² In the acute diabetic wound with signs of local infection, systemic antibiotics are appropriate. The most frequent offending organism is aerobic gram-positive cocci, but infection can be attributable to any spectrum of bacteria. It is standard practice to initiate broad-spectrum antibiotic coverage after obtaining wound cultures. The spectrum of antibiotic therapy is narrowed once sensitivities from the wound cultures are available.¹⁸³

Bone underlying a diabetic ulcer is often infected as a result of direct extension from the ulcer. Although bone biopsy is the most effective way to make this diagnosis, x-rays, magnetic resonance imaging, and nuclear medicine scans can also be used. Infected bone should also be débrided followed by up to 4 weeks of culture-specific antibiotics. If the patient's

comorbidities preclude intraoperative débridement, osteomyelitis may be treated nonsurgically with long-term systemic therapy alone; however, this requires at least 6 weeks of antibiotic therapy.¹⁸⁴ Negative pressure wound therapy or hyperbaric oxygen therapy may be chosen when all other methods fail.

PREVENTION

Patients with sensory deficits from diabetic neuropathy are at risk for the development of ulcers. Those patients with associated arterial insufficiency are at even greater risk. Protective footwear, proven to be effective in reducing ulcer incidence,¹⁸⁵ is the first line of prevention and should be prescribed in any patient with significant neuropathy, previous amputation, previous ulcer, or anatomic foot deformity.¹⁸⁶ Those patients with healed ulcers have a nearly 60% risk of recurrence. For this reason, all at-risk patients need to be educated on daily foot care and inspection to identify at-risk areas to tailor interventions prior to ulcer formation. Appropriate long-term glucose control with reduction of hemoglobin A_{1C} is a necessity. Elevation of this serum marker has been correlated to cardiovascular disease, retinopathy, neuropathy, nephropathy, and a predictive factor for the formation of foot ulcers.¹⁸⁷

At-risk patients need annual foot examination that includes assessment for anatomic deformities, skin breaks, nail disorders, further loss of protective sensation, quantification of arterial supply, and proper footwear.¹⁸⁸ These evaluations should be done more frequently as the patient condition warrants. Thick callus or callus with adjacent subcutaneous hemorrhage suggests impending ulceration and requires removal to aid in reduction of the plantar surface pressure. Diagnosis of onychomycosis, fungal infection of the nails, carries additional morbidity to these patients and is present in about one third of patients with diabetes. These brittle nails provide a portal of entry for injection of harmful bacteria into the surrounding tissue, leading to a destructive infection. Treatment options include topical or systemic therapy and even nail ablation.¹⁸⁹

Chronic wounds are a distinct entity with multiple etiologies and contributing factors. They require a detailed evaluation of ulcer history, comorbidities, clinical examination, and diagnostic modalities to adequately formulate an effective treatment plan. Without this close attention, chronic wounds will consistently lead to significant morbidity and even mortality.

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38 POSTOPERATIVE AND ADJUNCTIVE WOUND CARE

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Physiology of Wound Healing

A discussion of postoperative and adjunctive wound care hinges on two major concepts. The first is that wounds are a major source of complications in surgery and the second is that many wound-related complications can be avoided by a sound, evidence-based approach to wound care. It is beyond the scope of this chapter to discuss all surgical wounds in detail; however, the guiding surgical principles of wound care can be equally applied to a variety of procedures, such as inguinal herniorrhaphy or median sternotomy. Both are examples of subspecialty surgical incisions that have a significant body of literature related to the prevention and treatment of postoperative wound complications. Likewise, many other surgical incisions (mastectomy, cesarean section, rotational flaps, etc.) have unique data that guide the surgeon's clinical management. The data associated with each operative procedure need to be understood in detail to optimize patient outcomes.

An understanding of the physiology of wound healing is important in understanding the clinical approach to wound care. There are well-described, classic stages of wound repair. Wounds in humans typically heal by scar formation; the injured soft tissue is replaced by an area of fibroblast-derived collagen matrix that bridges the defect in the normal tissue. The body's initial response to wounding is to achieve hemostasis. This is the start of the inflammatory phase of wound healing. Vasoconstriction, platelet plugging, and activation of the coagulation cascade stop ongoing hemorrhage from the wound. Chemoattractants are released to recruit functional cell types that promote the healing process. Inflammatory cells infiltrate the wound; neutrophils appear within hours to remove damaged tissue and bacteria, and monocytes and macrophages appear within 48 to 72 hours. The proliferative phase begins with this shift away from a neutrophil-dominated wound to one that is controlled by macrophages and lasts for 7 to 10 days. A variety of additional cell types infiltrate the wound, including endothelial cells for angiogenesis, fibroblasts and macrophages to restore extracellular matrix and scaffold, and keratinocytes to restore barrier function and resurface the wound. The remodeling phase begins after resurfacing of the wound surface by keratinocytes. It typically begins 1 to 2 weeks after wounding and is a longer-term process that organizes collagen and strengthens the wound as the role of the other cell types diminish.

There are many excellent reviews on wound healing physiology that should be referred to for greater detail.¹ Our goal as surgeons is to ensure that the phases of wound care proceed in an orderly fashion and are not disrupted by inadequate blood flow, bacterial contamination, necrotic

tissue, immunosuppression, or other factors associated with postoperative wound complications.

This chapter discusses the preoperative and intraoperative factors that impact postoperative wound care. Wound closure techniques are reviewed using the laparotomy incision as the model for discussion of postoperative and adjunctive wound care as these techniques can be applied to a variety of surgical incisions. A large part of this chapter focuses on the management of wound-related complications, particularly wound infection, or surgical site infection (SSI). In 1999, the Centers for Disease Control and Prevention (CDC) published the "Guideline for the Prevention of Surgical Site Infection" and categorized SSIs as superficial incisional, deep incisional, or organ/space² [see Table 1]. Many of the clinical data on postoperative wound complications focus on SSIs as the primary end point or study outcome; thus, prevention of SSIs becomes the benchmark for efforts to clinically improve postoperative wound care.

Preoperative Considerations

It is important to understand the etiology of wounds. Chronic wounds are secondary to a disease state or failure of one of the phases of wound healing and are discussed elsewhere. Acute wounds can be broadly described as incisional or traumatic, and incisional wounds can be created in either elective or urgent/emergent situations. Traumatic wounds have a higher risk of postoperative complications as the environment is not sterile, no antibiotics are administered prior to the wounding event, and there is often significant delay before the repair because of patient transport, stabilization, and prioritization of treatment goals. In this setting, wound complications are common and often unavoidable. Likewise, higher postoperative complication rates can be expected for surgically created wounds in emergent or urgent situations than for those created during elective surgical procedures.

The elective operation, therefore, is the model for best practices in the preoperative preparation of a surgical patient to optimize postoperative wound healing and reduce the incidence of postoperative wound complications to the lowest level attainable. Fortunately, the incidence of wound complications can be reduced by appropriate care, but the argument that SSIs are completely preventable is erroneous and distorts the patient's expectation of what impact the surgeon has on complications after surgery. It is important for patients to know, preoperatively, their individualized risk assessment for postoperative wound complications. It is also important for patients to know that the surgeon takes advantage of all measures designed to reduce these complications.

Table 1 Criteria for Defining a Surgical Site Infection (SSI)

Superficial Incisional SSI

Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision and at least one of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture negative
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician

Deep Incisional SSI

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if the implant is in place and the infection appears to be related to the operation and infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever ($> 38^{\circ}\text{C}$ [100.4°F]), localized pain, or tenderness, unless site is culture negative
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician

Organ/Space SSI

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if the implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:

1. Purulent drainage from a drain that is placed through a stab wound into the organ/space
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of an organ/space SSI by a surgeon or attending physician

Adapted from Mangram AJ et al.²

PREOPERATIVE RISK REDUCTION

Smoking Cessation

Tobacco abuse can have a profound negative impact on a variety of wound- and non-wound-related postoperative patient outcomes. Fortunately, smoking cessation can improve many of these outcomes. The most significant smoking cessation benefit is a reduction in postoperative wound complications. In a randomized trial of 120 patients, smoking cessation 6 weeks prior to elective surgery reduced cardiovascular and other complications and reduced the wound complication rate from 31% in smokers to 5% in those who stopped smoking.³ We can also conclude that in nonelective situations, or in elective surgeries in which the patient is unable to stop smoking for 6 weeks, wound-related complications would be expected to occur in almost one third of patients.

Patients respond positively to physician intervention for high-risk behaviors such as tobacco abuse, and the ability to quantify and personalize the risk associated with the behavior makes the intervention more powerful. There are a variety of methods for smoking cessation, including stopping cold turkey, counseling, help-lines, and prescription medications combined with counseling. Preoperative patient education and the risk-benefit consenting process should include information that smoking cessation would result in a major risk reduction prior to elective operation. Ideally, elective operations should be delayed until 6 weeks after successful smoking cessation.

Glycemic Control

Patients with diabetes mellitus are, in general, at increased risk for complications during and after surgical procedures,

and those with an elevated preoperative hemoglobin A_{1c} level greater than 7% have an increased risk of postoperative infectious complications.⁴⁻⁶ Hemoglobin A_{1c} levels are representative of long-term glucose control as elevated glucose levels result in increased glycosylation of hemoglobin. It seems reasonable to maximize the medical therapy for the patient with diabetes who requires elective surgery to reduce postoperative wound complications. Adjustments may need to be made to diet, activity, oral hypoglycemic agents, and/or insulin. Consultation with the primary care physician or endocrinologist may facilitate this process. Patients with diabetes and elevated hemoglobin A_{1c} should understand their elevated risk of wound-related complications. Patients should be educated on the postoperative infection risk reduction that accompanies improved blood glucose control prior to elective surgery. Postoperative glycemic control may also have additional, non-wound-related, patient benefits for those critically ill in an intensive care unit.

Weight Loss in the Obese Patient

Obesity, defined by the CDC as a body mass index (BMI) greater than 30, is also associated with a higher incidence of wound complications. BMI should be considered when deciding whether to perform elective operations; that is, the risk of the operation, the risk of operative delay, and the benefit of substantial weight loss should be weighed against the realistic chance that the patient may or may not be able to lose weight. Obesity is associated with an increased risk of SSIs, dehiscence, and hernia after colorectal surgery.⁷ In addition to wound complications, obese patients undergoing rectal resections have longer operative times and an increased risk of conversion to an open procedure.⁷

Preoperative Nutrition

Adequate nutrition is essential to provide metabolic support for wound healing. BMI and prealbumin and albumin levels are helpful in identifying patients who are malnourished and may need nutritional support. An assessment of all three parameters gives a more complete assessment of nutritional risk. For example, the patient with low BMI but normal albumin and prealbumin is likely not malnourished. Elderly patients, patients with chronic illnesses such as cancer, and patients institutionalized in long-term care facilities are at the greatest risk for malnutrition and postoperative complications. Malnutrition is associated with an increased risk of SSIs and fascial dehiscence. Importantly, in those who are able to tolerate delays in operative intervention, 4 weeks of preoperative nutrition improves wound healing.⁸ Even 7 to 10 days may result in patient benefit if elective surgery cannot be delayed for 4 weeks. In addition, reassessment of the at-risk patient is useful as nutritional supplementation after surgical procedures is also beneficial. Postoperative nutritional supplementation reduces length of stay and wound-related complications in malnourished and undernourished patients.⁹

Coagulopathy

Preexisting coagulopathy should be diagnosed through careful medical and family history taking. Coagulopathies attributable to medical treatment with drugs such as warfarin should be reversed prior to surgery and bridged with shorter-acting anticoagulants if necessary. Even in those patients without coagulopathy, prophylactic preoperative heparin is often administered. Heparin administration to prevent venous thromboembolism may be indicated depending on an individualized risk assessment using nationally published guidelines; however, the risk of venous thromboembolism should be weighed against the increased risk of wound hematoma.¹⁰

Antiplatelet agents such as aspirin or clopidogrel may need to be stopped 2 weeks prior to surgery to allow for full platelet recovery if intraoperative and postoperative hemorrhage would result in major complications, such as in ocular or neurologic surgery. Unfortunately, the number of patients who require anticoagulants or antiplatelet agents is increasing. The risks associated with the discontinuation of therapeutic anticoagulant or antiplatelet agents must be balanced with the patient's operative risks. In addition, the risks associated with initiating prophylactic anticoagulants must be balanced with the patient's risk of venous thromboembolism. In some patients, the anticoagulant or antiplatelet agents are self-limited. For example, the patient treated with clopidogrel after arterial stent placement or warfarin after venous thrombosis may have therapy discontinued after a set time period, that is, 3 or 6 months. Elective operations in this patient population should be delayed until therapy has been discontinued unless operative delay would be associated with additional patient risk or complications.

OPERATIVE DAY RISK REDUCTION

Skin Preparation Techniques

Preoperative bathing or showering has been extensively studied and has no proven reduction in SSIs. No differences

among chlorhexidine gluconate, bar soap, or placebo were detected in these trials.¹¹

Preoperative hair removal has also been extensively studied. The hair removal concern relates to the superficial damage to the skin that can occur while shaving with a razor blade. Microscopic injuries to the epidermis are thought to be portals of entry for bacteria. In a recent review of 11 randomized, controlled trials of hair removal prior to surgery, the overall conclusion is that hair removal by shaving with a blade is associated with an increase in SSIs and should be avoided when possible.¹² Depilatory creams or clippers should be used instead and have no proven increase in SSIs. Additionally, routine shaving is likely unnecessary and could be avoided completely in a variety of incisions. In those who require preoperative hair removal, the timing of hair removal is irrelevant. Hair removal by clipping or depilatory up to 24 hours prior to incision is well tolerated and not associated with an increase in SSIs.¹² In other words, hair removal the day prior to incision with an electric clipper is a better option than shaving with a blade in the operative suite.

Preoperative Antibiotic Administration

The rationale for preoperative antibiotic administration is specific to the particular procedure and disease state. For example, the rationale for the use of oral and intravenous antibiotics prior to colectomy, or the particular antibiotic regimen chosen prior to median sternotomy, hysterectomy, laryngectomy, etc., is supported by specific clinical data related to those subspecialty areas. The antibiotic chosen is guided by the bacterial spectrum that the patient is exposed to during the operation and the individual center's antimicrobial sensitivity biogram. Preoperative antibiotics are often routinely administered, but in short, elective, clean operations, such as inguinal herniorrhaphy, there are conflicting data, with prospective trials both advocating for and against preoperative antibiotics.^{13–15} If an antibiotic is to be administered, the tissue levels should be maximal at the time of incision and during the operation. Antibiotics administered too long prior to the operation lose effectiveness, as do antibiotics administered after incision. The timing of antibiotic administration clearly impacts wound infection rates; antibiotic administration within 2 hours prior to incision should result in a postoperative infection rate of less than 1% for clean and clean-contaminated, elective operations.¹⁶ Extended-length operations may require redosing of the antibiotic depending on the duration of the procedure and the half-life of the drug administered.

Preparation for Colonic Surgery

Randomized, controlled trials have shown that in elective colonic surgery, combined oral and systemic antibiotics are superior to systemic antibiotics alone in preventing SSIs.¹⁷ The oral antibiotic protocol is institutional dependent but often includes the nonabsorbable neomycin with or without erythromycin. The preoperative preparation prior to colectomy may or may not also include mechanical bowel preparation to remove fecal material from the colon prior to surgery. Mechanical bowel preparations use laxative solutions that cause diarrhea but may cause abdominal cramping, dehydration, and electrolyte imbalances. Mechanical bowel preparations are essential prior to colonoscopy to visualize the

mucosa, but as an adjunct to colectomy, there is no significant reduction in the rate of postoperative SSIs, anastomotic leaks, or intra-abdominal abscesses in patients who receive mechanical bowel preparation compared with no bowel preparation.¹⁸

Intraoperative Considerations

SURGICAL WOUND CLASSIFICATION

Specific intraoperative findings such as bacterial contamination will impact the risk of postoperative wound complications. The impact of the degree of intraoperative bacterial contamination on postoperative wound complications is well established. The Surgical Wound Classification has been widely adopted for assessment of patient risk [see Table 2].² In some, bacterial contamination occurs as part of the disease process, for example, in those with perforated sigmoid diverticulitis. In others, careful surgical technique is an essential, modifiable factor to prevent intraoperative contamination and subsequent postoperative wound complications. For example, laparotomy for lysis of adhesions in a patient with a small bowel obstruction is a class I/clean case unless an enterotomy is made, at which time, it becomes a class II/clean-contaminated case with an inherent higher risk of wound complications and SSI. Similarly, spillage from a colonic injury with fecal contamination would result in a class III/contaminated operation. Careful, meticulous surgical technique is essential to minimize patient risk of SSI.

Laparotomies are often class II/clean-contaminated procedures as a result of planned entry into the biliary, gastrointestinal, or urinary tract. Many of these procedures have a risk of wound complications only slightly higher than the risk in patients undergoing class I/clean operations. The colon, however, has very high concentrations of bacteria, and colonic resection is associated with bacterial contamination, SSIs, and wound complications. Colon resection is an example of an operative procedure in which best practices may be able to reduce postoperative wound complications. In a prospective study of 2,809 consecutive patients undergoing elective colorectal resection, the overall incidence of SSI was 4.7%.¹⁹ In this study, the factors that predicted SSI were American Society of Anesthesiologists (ASA) score, surgical wound class, blood transfusion, need for ostomy, type of operation, use of drains, male gender, and surgeon's experience.

The postoperative SSI rate after colectomy varies widely, ranging from 5 to 10% in randomized, prospective trials of elective colorectal resection.^{18,19} These rates of SSIs are clearly higher than the incidence of SSIs after class I/clean operations. A thorough preoperative risk assessment and risk reduction, if necessary, are important to maximize patient outcomes. SSIs and postoperative wound complications are complex and multifactorial and not completely preventable, and a thorough discussion of the 5 to 10% risk of SSI after colectomy should be held with the patient during the preoperative evaluation process.

HYPEROXIA AND WARMING

Perioperative Hyperoxia

Other clinical maneuvers, for example, perioperative hyperoxia and perioperative patient warming, have been studied in an effort to reduce the incidence of postoperative wound complications. Unfortunately, the initial promising results of perioperative hyperoxia have not been reproducible or have been outright refuted in follow-up trials, causing confusion. Perioperative hyperoxia, or 80% inspired supplemental oxygen, was shown to reduce SSIs by 10% in a randomized, controlled clinical trial of patients undergoing colorectal operation.²⁰ Another randomized, controlled trial of laparotomy patients had the opposite conclusion, with a 13% increase in SSIs in those who received supplemental perioperative oxygen.²¹

It should be noted that these trials showed a 24% incidence of SSI in patients prospectively evaluated following colorectal operations and an 11% incidence of SSI in patients prospectively evaluated following laparotomy. A more recent review of five randomized, controlled trials concluded that hyperoxia resulted in SSI absolute risk reduction of 3.0%, with the benefit being greater in colorectal operations.²² It seems reasonable to assess the overall institutional risk of SSI and wound complication after colectomy and use perioperative hyperoxia if the institutional risk is higher than the 5 to 10% acceptable risk described in the literature.

Perioperative Warming

Patient warming in the perioperative period reduces SSIs after colorectal and clean surgical procedures.^{23,24} A review of 19 randomized, controlled warming trials showed that perioperative warming of surgical patients is effective for reducing

Table 2 Surgical Wound Classification

Class I/Clean: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow nonpenetrating (blunt) trauma should be included in this category if they meet the criteria.
Class II/Clean-Contaminated: An operative wound in which the respiratory, alimentary, genital, or urinary tract is entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category provided that no evidence of infection or a major break in technique is encountered.
Class III/Contaminated: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract and incisions in which acute, nonpurulent inflammation is encountered are included in this category.
Class IV/Dirty-Infected: Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

Adapted from Mangram AJ et al.²

postoperative wound pain, wound infection, and shivering.²⁵ Patients often lose body heat during surgical procedures, and this effect is more pronounced with an open body cavity, such as with laparotomy. Laparotomies and thoracotomies often last for more than 1 or 2 hours, and the heat loss may be progressive if not carefully monitored and treated. Generalized warming options exist, including increasing the temperature of the room, the intravenous fluids, and the inspired gases. Forced air warming is readily available and easy to use during the operation and afterward during the recovery period. Early efforts at preventing heat loss are often easier than attempts to rewarm the patient. In particular, it is important to keep the patient covered and warm during anesthesia induction and patient preparation prior to sterile draping.

FASCIA CLOSURE TECHNIQUES

The laparotomy incision and closure are useful to examine further as the variety of patient disease states, procedures, incisions, and contamination classifications result in a wide variety of postoperative wounds that often require creative adjunctive techniques for definitive management. Given the wide variations among different patient populations and different surgical procedures, definitive prospective clinical data are difficult to generate.

One technique that has been studied prospectively is the suturing technique for closure of abdominal wall fascia. It is now fairly well accepted that a continuous suturing technique is as effective as an interrupted suturing technique, with the added advantage of being a faster fascial closure.²⁶ A prospective evaluation of the length of suture used highlighted the importance of the technical aspects of fascial closure. Multivariate analysis identified the ratio of suture length to wound length, age, and major wound infection as independent risk factors for the development of hernias.²⁷ A closure technique that uses a length of suture four times longer than the length of the fascial defect is important in reducing hernia formation. Placement of larger fascial bites closer together results in increased suture length use compared with smaller bites spaced further apart.

In summary, mass closure incorporating all layers of the abdominal wall (except skin) as one structure, in a simple running technique, using #1 or #2 absorbable monofilament suture material with a suture length to wound length ratio of 4 to 1, is recommended.²⁸ Absorbable monofilament sutures have longer wound duration and provide additional fascial security compared with more rapidly absorbed suture. Permanent suture material is associated with a risk, although small, of delayed stitch abscess formation that ultimately requires suture removal for cure. This is particularly true of braided permanent sutures, which have numerous interstices that can harbor bacteria.²⁹ Ultimately, the choice of a suture material should be individualized to the patient and clinical situation.

Postoperative Considerations

EARLY FASCIA COMPLICATIONS

Complications of fascia closure can be divided into those that occur in the immediate postoperative setting versus the

delayed complications of incisional hernia. Early fascia closure complications are often severe and life-threatening. These include SSI, dehiscence, evisceration, and necrotizing fasciitis. Dehiscence and evisceration are associated with significant morbidity and mortality [see *Figure 1*]. Fortunately, dehiscence with or without evisceration is unusual but common enough that every surgeon who performs abdominal surgery will have these complications. Clinically recognized acute laparotomy wound failure and dehiscence rates are 1 to 2%.^{26,30} Unrecognized dehiscence likely results in late hernia formation. Many nonpreventable comorbidities, such as ASA class, trauma, peritonitis, age, gender, chronic obstructive pulmonary disease, ascites, jaundice, anemia, emergency surgery, postoperative coughing, and class III–IV/contaminated or dirty-infected wounds, increase the risk of acute wound failure.^{31,32} The management of early fascia complications is summarized in Table 3.

Dehiscence and Evisceration

Dehiscence is often heralded by serosanguinous drainage from the wound between 5 and 10 days after surgery. In some cases, this may even occur after the patient is discharged. Dehiscence, and the rarer evisceration, is associated with significant morbidity and mortality; therefore, postoperative wound drainage cannot be ignored. It is a marker that the fascia has failed either from a primary failure of fascial closure or as a manifestation of an intra-abdominal complication such as anastomotic leak or intra-abdominal abscess.

One should perform fascial exploration by reopening the skin incision. Patients with dehiscence require urgent or emergent reexploration. It is important to realize that the abdominal wall can fail from pathology related directly to the abdominal wall fascia itself (deep incisional SSI) [see *Table 1*] or as a manifestation of an intra-abdominal catastrophe such as anastomotic leak or intra-abdominal abscess (organ/space SSI) [see *Table 1*]. Both should be treated therapeutically with antibiotics, that is, preoperative broad-spectrum antibiotics

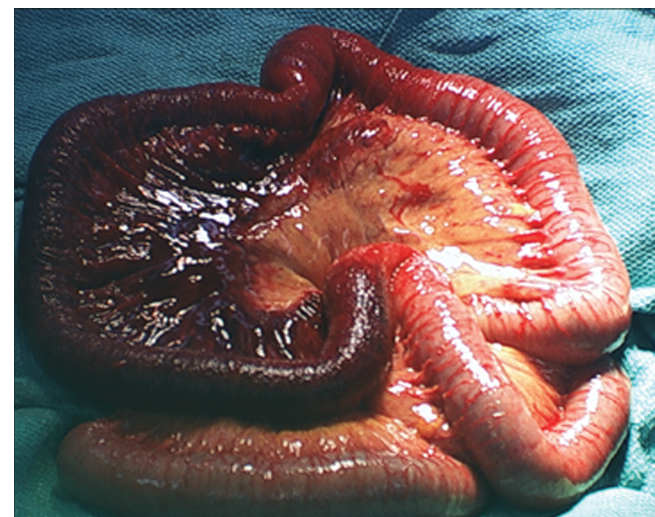


Figure 1 Postoperative dehiscence and evisceration through a laparoscopic port site after a vigorous coughing episode. Note the ischemic section of bowel that requires resection.

Table 3 Management of Early Fascia Complications

Diagnosis	Differential Diagnosis	Treatment	Fascia Closure Options	Skin Closure Options
Dehiscence or evisceration	Deep incisional SSI Organ/space SSI Necrotizing fasciitis	Bacterial culture Antibiotics Drainage of infection	Suture repair	Secondary intention
Necrotizing fasciitis	Superficial incisional SSI Deep incisional SSI Organ/space SSI	Bacterial culture Antibiotics Radical débridement	Suture repair if possible Absorbable mesh Biologic mesh Negative pressure wound therapy	Skin grafts Secondary intention
Abdominal compartment syndrome		Resuscitation Bogota bag Negative pressure wound therapy	Delayed suture repair after edema resolves Planned ventral hernia Biologic mesh	Secondary intention Primary closure only if planned ventral hernia or biologic mesh
Need for relook laparotomy		Temporary skin closure Bogota bag	Suture repair	Secondary intention
Fascia loss and skin cannot be closed			Absorbable mesh Biologic mesh Negative pressure wound therapy	Skin grafts Secondary intention
Fascia loss and skin can be closed			Planned ventral hernia Biologic mesh	Primary closure

and postoperative culture and sensitivity-directed antibiotics. Efforts should be made to fully evaluate the cause of the acute abdominal wall failure with preoperative imaging if possible and with a thorough abdominal exploration during the operation. Cultures should be taken at the fascial level and of any deeper fluid collections to guide antibiotic therapy.

Reclosure should incorporate all of the layers of the abdominal wall using running #1 or #2 absorbable monofilament suture material with a suture length to wound length ratio of 4 to 1.²⁸ However, an intraoperative decision is required as to whether the abdominal wall can be simply reclosed. There may be a need for reexploration at 24 or 48 hours that will delay definitive closure and require temporary closure techniques. In those patients who can be definitively reclosed at the time of laparotomy, all best practices should be followed (patient warming, timing of antibiotic administration, suture technique, etc.) and the skin should be left open to heal by secondary intention. The duration of antibiotic therapy should be guided by the patient's clinical course (fever, white blood cell count, evidence of granulation tissue ingrowth into the wound) but typically continues for 7 to 10 days.

Historically, large retention sutures were placed through the entire substance of the abdominal wall, including fascia and skin lateral to the linea alba at the midrectus-abdominus location. These sutures were placed as mechanical efforts to stabilize the abdominal wall in patients at high risk for postoperative acute laparotomy wound failure or at the time of reexploration in those patients with postoperative dehiscence. Retention sutures were thought to prevent bowel evisceration but have proven to be largely unsuccessful and associated with complications.^{33,34}

Necrotizing Fasciitis

Necrotizing fasciitis is a rare, often idiopathic, diagnosis that develops de novo, after trauma, or in patients with open

wounds. The risk factors of immunosuppression, obesity, or diabetes mellitus are found in 80% of patients.³⁵

Fortunately, necrotizing fasciitis is a rare complication after laparotomy, but the diagnosis can be difficult and the associated mortality is very high, especially with operative delay. Patients typically present with extreme pain, swelling, and fever.³⁶ The early examination may be fairly unremarkable, with pain, warmth, and erythema as the only changes noted to the skin. Often the initial diagnosis is superficial incisional SSI, and patients are treated with antibiotics; however, rapidly spreading erythema surrounding the wound requires emergent wound and fascial exploration. Other clues to the diagnosis of necrotizing fasciitis are bullae formation, skin necrosis, and crepitance. Roentgenograms may show subcutaneous emphysema.

In a review of 89 patients treated at a single institution, only four (4.5%) patients developed necrotizing fasciitis as a postoperative complication, so the vast majority of cases have no obvious source for the infection.³⁶ In these four cases, three occurred after class III/contaminated procedures and one occurred after a class II/clean-contaminated operation.

Once the diagnosis of necrotizing fasciitis is entertained, resuscitation, antibiotic administration, and emergent radical débridement of all involved tissues are essential to ensure patient survival.³⁷ Débridement must be performed without regard to later reconstruction as ensuring survival is the immediate goal. All tissue planes that are involved with the infectious process must be opened even if the overlying skin looks normal and uninvolved. Often the only clue to the spread of infection is "dishwater"-appearing fluid draining from between the tissues. Necrotizing fasciitis commonly dissects in the plane between the fascia and subcutaneous fat; this plane needs to be defined and opened, and all necrotic tissue débrided. Wide opening of the involved area facilitates postoperative dressing changes. Late reconstruction by secondary closure, flaps, or skin grafts is performed electively,

after granulation tissue forms, and in an otherwise stable patient. If the large open wound is beyond local capabilities, the patient can be transferred to specialized burn centers that have experience with patients with large open wounds. It is important to consider interhospital transfer only after radical débridement as any delay in controlling this rapidly spreading infection will worsen patient outcomes.

The Open Abdomen

Temporary closure for early reexploration There are patients in whom fascial closure is desired, but the fascia is unable to be closed primarily. This may be because the fascia has been extensively débrided as a result of necrotizing fasciitis or fascial necrosis. Massive edema of the bowel and intra-abdominal contents following trauma or abdominal catastrophe also prevents fascial closure to avoid abdominal compartment syndrome. Finally, there are patients with primary abdominal wall failure who require relook laparotomy at 24 or 48 hours. For example, in cases of damage control laparotomy after abdominal trauma or patients with small bowel thromboembolism, reexploration at 24 or 48 hours is common.

A variety of temporary abdominal closure techniques have been developed to aid in the management of this diverse group of patients. The fascia can be left open with skin-only closure using interrupted sutures or interrupted towel clips holding the skin edges together. Temporary skin closure offers the advantages of not further damaging the fascia with sutures, which require subsequent removal, as well as speed and ease of reopening at the time of reexploration. An alternative to the towel clip technique is to sew a large sterile sheet of plastic (Bogota bag) to the fascia or skin [see Figure 2a]. Typically, a 3 L irrigation bag is used as the size fits the midline laparotomy incision. The clear plastic allows for visualization of the abdominal contents postoperatively, which may be advantageous in the patient with bowel ischemia. This technique is also convenient in those patients who need rapid closure of the abdomen with planned reexploration but have significant bowel edema that precludes temporary skin closure with towel clips. Sewing the temporary plastic bag to the skin also offers the same advantage of avoiding injury from fascial suture placement until the time of definitive abdominal wall closure, that is, after resolution of bowel wall edema.

Planned ventral hernia In those in whom fascial closure is desired but not attainable because of fascial loss or intra-abdominal edema preventing primary suture repair, the morbidity and mortality are significant. Patients can be divided into two broad categories, one in which skin can be closed and one in which skin closure is not feasible. In patients in whom the skin can be primarily closed, one can simply close the skin over the fascial defect, essentially creating a large incisional hernia that will require delayed repair.

Another option is to use an absorbable mesh (e.g., polyglactin 910) to bridge the fascial closure and then close the skin over the top of the absorbable mesh. Obviously, in the setting of the open abdomen, permanent, prosthetic mesh (e.g., polypropylene) repair of the abdominal wall has an overwhelming rate of mesh infection and is contraindicated. Absorbable mesh gives some stability to the abdominal wall in the early postoperative period but will eventually form an

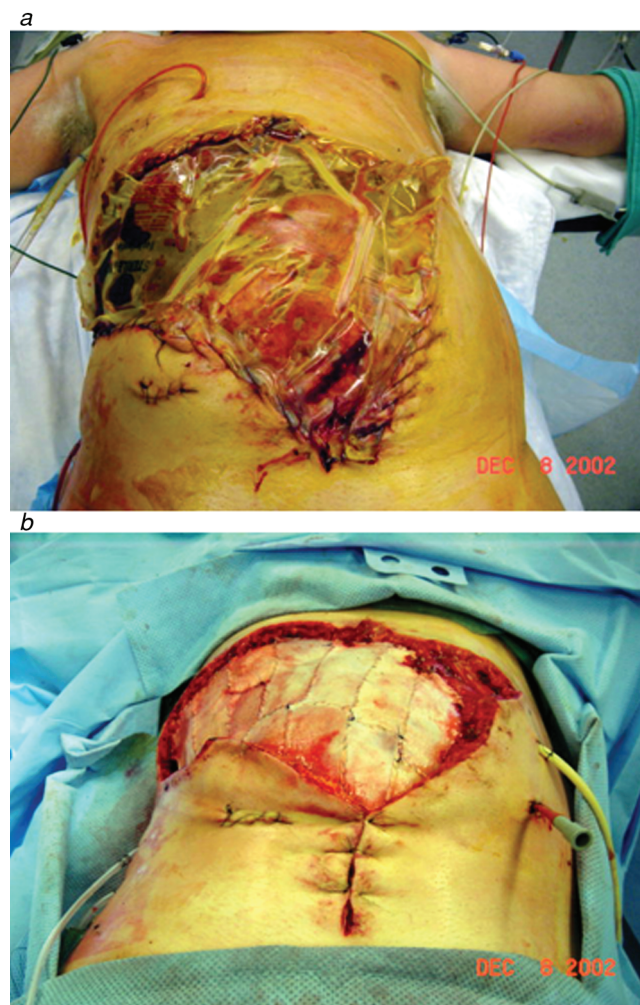


Figure 2 (a) Temporary closure of the abdominal wall after extensive blunt force trauma with a 3 L saline bag (Bogota bag). Note the extensive fascia loss and the fact that the skin cannot be closed. (b) Reconstruction of the abdominal wall with biologic mesh. After several weeks of granulation tissue ingrowth, skin grafts were placed for final wound closure.

incisional hernia that requires late repair. In addition, there are a wide variety of biologic meshes made from human dermis, pig dermis, or pig submucosa that are used in cases with bacterial contamination that preclude the use of permanent, prosthetic mesh. Advocates for the use of biologic mesh in this setting claim that the need for late ventral hernia repair can be reduced as the biologic material can result in long-term stability of the abdominal wall. Biologic mesh has been adopted by some for elective herniorrhaphy, but prospective clinical data comparing outcomes in complicated primary abdominal wall failure and the open abdomen are lacking.

Alternative closure techniques for the open abdomen In the patient in whom fascial closure is desired but not attainable, and in whom the skin cannot be closed, two approaches exist to eventually attain closure of the abdominal wall. These patients have significant morbidity and mortality and are at risk for the development of an enterocutaneous fistula.

Typically, either absorbable mesh or negative pressure wound therapy is used to stabilize the abdominal wall and oppose contractile forces from the rectus muscle components and lateral oblique muscles. Negative pressure wound therapy reduces bowel edema and encourages granulation tissue ingrowth so that split-thickness skin grafts can be placed over the granulating bed and close the wound. Alternatively, absorbable mesh (or biologic mesh) is used to bridge the fascial defect, followed by dressing changes until granulation tissue forms under the mesh. The mesh is removed, and split-thickness skin grafts are placed to close the wound [see Figure 2b].³⁸

In a single-institution, prospective, randomized trial comparing morbidity and mortality differences between the absorbable mesh and negative pressure wound therapy, the fistula rate was 21% in the negative pressure wound therapy group and 5% in the absorbable mesh group. There was no statistical significance between these groups, possibly because of a lack of power in the study, but this study demonstrates the morbidity associated with an open abdomen. The fistulas were felt to be related to feeding tubes, suture line areas, or bowel perforation remote to the anastomotic site.³⁹ All of these patients will require late abdominal wall reconstruction using complicated techniques for skin graft removal, fascial reconstruction, and restoration of skin continuity.

LATE FASCIA COMPLICATIONS (INCISIONAL HERNIA)

Risk factors for incisional hernia after laparotomy are similar to the risk factors for SSI. Redo laparotomy was the strongest factor associated with hernia, and other risk factors included smoking, postoperative wound complications, age, and male gender.⁴⁰ The incidence of incisional hernia after laparotomy is difficult to determine exactly but has been reported to be as high as 15 to 25% in different studies.⁴¹ Incisional herniorrhaphy techniques have evolved extensively in recent years, and a thorough understanding of the risks and benefits of primary repair, mesh closure by bridging or underlay technique, Rives-Stoppa repair, component separation, and laparoscopic versus open repair is essential to individualize the approach to the patient.

SKIN CLOSURE TECHNIQUES

Primary, Secondary, and Tertiary Closure

Intraoperative findings dictate how skin closure is managed after fascia closure. Class I/clean cases are typically closed by primary closure; that is, the skin is closed by suture or staple technique, and the technique of continuous versus running suture closure has not been shown to impact overall outcome. However, interrupted closure is advisable in those patients in whom primary closure is used in the setting of a class II/clean-contaminated operation so that a portion of the wound can be opened in patients who develop SSI. The interrupted closure allows an area of concern in a wound to be reopened without disrupting the entire wound. Staples are often used as a rapid, interrupted closure technique with good cosmetic outcome compared with interrupted sutures.

Class III–IV/contaminated or dirty-infected wounds are typically closed by secondary or tertiary closure. Secondary closure allows for the wound to heal completely by wound contracture, granulation tissue ingrowth, and keratinocyte

resurfacing from the margins of the wound. This process can be prolonged and associated with pain and quality of life issues [see Figure 3, a and b].

The last technique is tertiary, or delayed primary closure. The skin is not closed at the time of the original operation but at some delayed time after local wound management techniques are employed to reduce bacterial counts. Typically, sutures are placed at the time of the original operation but not tied or secured, and gauze dressing changes are performed in the open wound. When the wound bed changes from a draining, inert wound to a dry wound with healthy-appearing margins, the sutures are tied. This typically occurs 3 to 5 days later.

In a prospective evaluation of patients with class III–IV/contaminated or dirty-infected surgical wounds, tertiary closure was associated with a statistically significant reduction in SSI compared with primary closure.⁴² This reduction in SSIs using closure by secondary intention or delayed primary closure (tertiary closure) must not be minimized as SSIs are

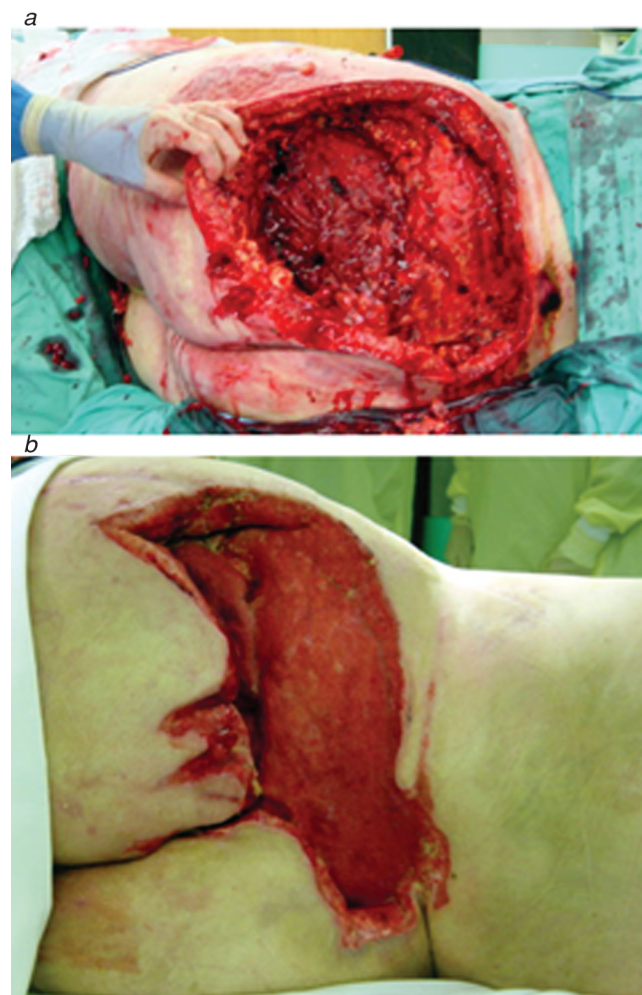


Figure 3 (a) Large traumatic gluteal wound after crush injury. Extensive intraoperative débridement of all necrotic and damaged tissue prevented postoperative infectious complications. (b) Dramatic healing by secondary intention. At this time, skin grafts were placed for final wound closure.

a major risk factor for dehiscence, evisceration, and necrotizing fasciitis. In a randomized, controlled trial of 48 patients with colon injuries in which the skin wound was primarily closed or left open, wound infection developed in 65% of those with closed skin incision and 36% of those whose wounds were left open to close by secondary intention. Importantly, dehiscence developed in 31% of patients with primarily closed skin incisions and in only 14% of those left to heal by secondary intention.⁴³ Prevention of SSIs in patients with class III–IV/contaminated or dirty-infected wounds avoids the morbidity and mortality associated with complicated fascial and abdominal wall reconstruction in patients with primary abdominal wall failure in the postoperative setting.

Open Wounds

A variety of techniques are available for the management of postoperative wound healing by secondary closure, reopened wounds after failed primary closure, or wounds planned for tertiary closure. Unfortunately, there are few clinical data to support the management of these complicated patients.

In a recent review of dressings for patients with wounds healing by secondary intention, 13 randomized, controlled trials provided little evidence for any specific technique or dressing that would improve outcomes.⁴⁴ The gauze dressing, whether placed dry in an actively draining wound or saline moistened in a dry wound, has great efficacy in preparing the wound for closure by secondary or tertiary intention or by skin grafting. Gauze dressings may be associated with more pain than other dressings, but the cost and convenience are hard to ignore.

Specialty dressings are commonly altered to control wound fluid and to promote wound healing; however, their effect is probably more significant in patients with a chronic wound compared with those with acute postoperative wound complications. One of the advantages of specialty dressings may be in a reduction in the evoked pain associated with the dressing change or a reduction in perceived and anticipated pain associated with a less frequent dressing interval. The cost of the dressing must be weighed with the potential patient benefit as specialty dressings have not been shown to improve wound healing over saline gauze dressings.

Hematoma or Seroma

Acute postoperative wound fluid collections include hematomas, seromas, or lymphatic fluid. Hematomas and seromas can impair wound healing by mechanically disrupting the wound, causing pressure-related ischemia of the overlying skin, or by becoming secondarily infected, resulting in an SSI. Wound hematomas are common in those patients with prophylactic or therapeutic anticoagulation or antiplatelet therapy.⁴⁵ Fortunately, most wound hematomas associated with prophylactic anticoagulation are minor and do not require further therapy.

The risk of hematoma must be balanced with the risk of deep veins thrombosis and pulmonary embolism. Wound seromas are common in operations that result in large undermined skin and subcutaneous flaps and are also common in procedures that implant foreign material. The open incisional hernia repair that results in large skin/subcutaneous flaps and uses prosthetic mesh for the fascial repair is particularly prone

to seroma formation. Prevention is important; coagulation should be normalized preoperatively and restarted after 24 hours if possible. Meticulous attention to intraoperative hemostasis by suture ligation of subcutaneous vessels and electrocautery of other bleeding sites should prevent hematoma formation in those with normal coagulation parameters.

Patients with abnormal coagulation or ongoing antiplatelet therapy need careful postoperative monitoring with return to the operating room for hematoma evacuation if a substantial collection develops. Seromas are predictable in patients with foreign material or large dissection fields and flaps; therefore, closed-suction drains should be placed through separate incisions into the potential space to encourage coaptation of the edges. Large postoperative seromas or hematomas that develop despite meticulous surgical technique and prophylactic drain placement (or after drain removal) should be therapeutically drained or evacuated to prevent infection or wound ischemia. Wound fluid collections may reach high enough pressure that capillary perfusion pressure is exceeded. The resulting wound ischemia can lead to necrosis or SSI. The wound hematoma is a potential nidus for bacterial growth. Evacuation of the fluid or hematoma should prevent these complications. The initial decision that must be made is whether or not the fluid is putting the patient at risk for a wound-related complication. The therapeutic options are observation and reevaluation or drainage. Drainage can either be performed percutaneously or by reopening the incision and placing closed-suction drains. Aspiration is often attempted as first-line therapy and may be repeated as necessary or converted to open drainage if it proves ineffective.

Traumatic Wounds

Traumatic wounds are a setup for complications and deserve separate discussion. The traumatic wound is created without the advantage of antimicrobial skin preparation or prewounding antibiotic administration, and there is no opportunity for prewounding reduction of risk factors such as tobacco abuse. There is significant delay to definitive treatment and often additional soft tissue or bony damage in close proximity to the wound itself. Wounds should be evaluated for the presence of adjacent soft tissue injury or hematoma that requires exploration, débridement, or drainage. Foreign bodies are also common in these wounds and are a nidus for infection if not removed.

Management of the traumatic wound follows many of the same principles described above. On arrival at medical care, it is important to rapidly assess for ongoing hemorrhage that could require early formal wound exploration with ligation or repair of major or minor vessels. Wounds that will require further delay for patient stabilization and prioritization of injuries should be cleansed with an appropriate skin preparatory solution and covered with sterile gauze until definitive repair. Antibiotic administration is typically governed by other injuries; however, depending on the wound size, location, and degree of contamination, it may be reasonable to administer an empirical 5- or 7-day course of antibiotics. Less concerning wounds should be treated with antibiotics prior to definitive operative repair and in the immediate postoperative period.

Operative management of the traumatic wound must focus first on skin cleansing and the removal of all foreign material from the wound. Small wounds with large undermined edges should be opened widely to accomplish this goal. All necrotic tissue must also be removed, regardless of the resulting size of the final defect [see Figure 3a]. Wound irrigation with saline is commonly performed to thoroughly wash the wound of all remaining foreign material, clotted blood, or devitalized cellular debris. Wound irrigation typically is performed with a low-pressure, passive drainage system; however, high-pressure pulsatile lavage systems are available. The high-pressure systems may cause additional soft tissue damage and should be used with caution.

Reconstruction options are as varied as the types and causes of wounds. Primary repair of simple wounds suffices when wounds are clean and do not require substantial débridement of tissue such that no undue tension exists on the wound closure. Other options also include closure by secondary or tertiary intention. The large, complex wound that involves skin and deeper soft tissue structures may require temporary allograft or negative pressure wound therapy as a temporizing measure until flaps or skin grafts can be placed.

ADJUNCTS TO POSTOPERATIVE WOUND MANAGEMENT

Treatment of Superficial Incisional SSI

All SSIs are expensive because of the costs associated with the antibiotics administered and the increased length of stay in the hospital. Prevention measures are effective in reducing the incidence of SSIs, but SSIs are not completely preventable and are commonly diagnosed and treated. Deep incisional and organ/space SSI after laparotomy may result in dehiscence, evisceration, or necrotizing fasciitis as described above and are typically managed by surgical exploration, percutaneous drainage, or intravenous antibiotics. Other subspecialty incisions have a body of literature that guides treatment for SSIs, for example, treatment of deep incisional SSI following median sternotomy or total knee arthroplasty.

Superficial incisional SSIs are commonly encountered in surgical practice and should be considered in postoperative patients noted to have increasing warmth, pain, erythema, or drainage at the surgical site. The management depends greatly on the type of wound and the circumstance in which it was created. It is essential to rule out deep incisional or organ/space SSIs masquerading as superficial incisional SSIs. It is also important to establish the cause of the SSI. For example, in the posttraumatic wound SSI, one should consider the possibility of a retained foreign body that led to the infectious process. Alternatively, the SSI may simply be a manifestation of the risks involved with colectomy in a patient with multiple risk factors and a high ASA score.

Antibiotics are commonly used in SSIs and are mandatory in the patient with systemic symptoms, such as fever, or locally advanced symptoms, such as surrounding cellulitis. Likewise, cultures should be obtained in all but the simplest SSI. If the wound has an area of drainage, then opening of the wound is required to allow for complete drainage of the infectious process and facilitate dressing changes [see Figure 4a]. Any necrotic tissue requires surgical débridement. Dry gauze is used in draining wounds and should be changed frequently until the drainage subsides [see Figure 4b].

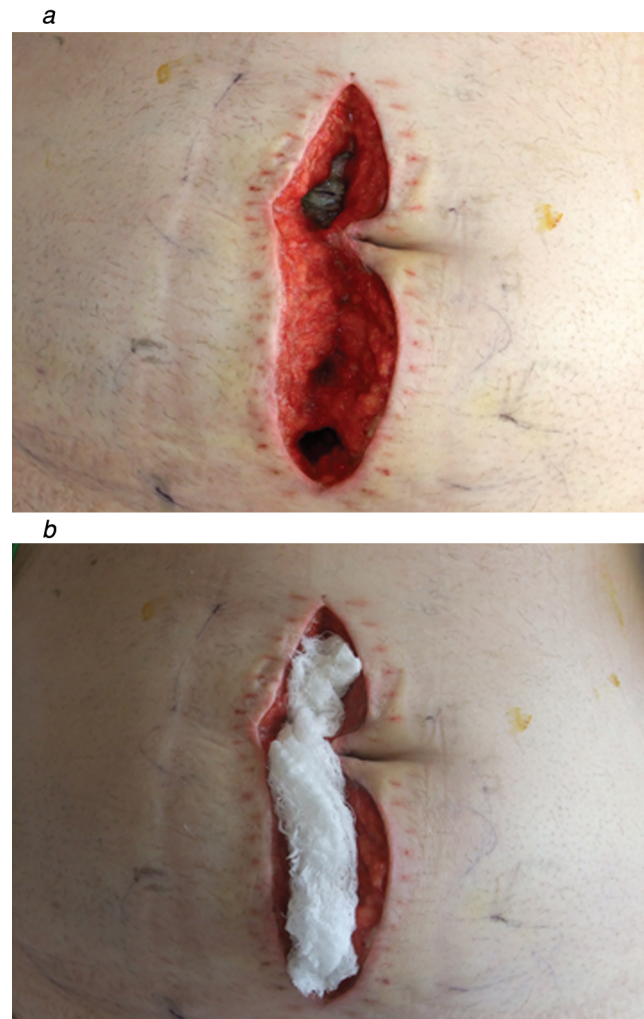


Figure 4 (a) Surgical site infection after laparotomy and bowel resection (class II/clean-contaminated). The skin was closed primarily with staples and reopened to heal by secondary intention. Note the small amount of necrotic material at the superior aspect of the wound and the resolution of the surrounding cellulitis after reopening the skin incision. (b) Gauze dressings are inexpensive, effective, and well tolerated for a wound this size.

Most superficial incisional SSIs will be left open to heal by secondary intention. A smaller subset of patients will have late presentation of SSI or failure of closure by secondary intention with the formation of a chronic wound sinus. The differential diagnosis should consider the presence of a foreign body, for example, a permanent suture knot with chronic infection, chronic infection of an implant, or the possibility of an enterocutaneous fistula.

Topical Silver

One of the significant ongoing debates in wound management focuses on the role of bacteria in impairment of wound healing. Class I–II/clean or clean-contaminated procedures can have primary closure of the skin with a very low and acceptable rate of SSI. Those with class III–IV/contaminated or dirty-infected operations are commonly managed with

closure by secondary intention or delayed primary closure. All would agree that postoperative wounds with surrounding cellulitis (edema, erythema, warmth, pain) require débridement of nonviable tissue, drainage of fluid collections, and systemic antibiotic therapy. Despite efficacy in those with thermal burns, it is unclear if additional topical antimicrobial agents (bacitracin, mupirocin, silver) improve healing of surgical wounds.

Many wound dressings are now impregnated with large quantities of silver, which can impair wound healing. It is recommended that silver-based products be avoided in situations where there are rapidly proliferating keratinocytes.⁴⁶ Preliminary in vitro and animal data on next-generation silver dressings containing lower silver concentrations show proliferation of cells involved in wound healing while reducing bacterial counts.⁴⁷ Unfortunately, there are no clinical trials demonstrating efficacy toward healing of the complicated, postoperative wound. Silver should probably be reserved for wounds with obvious bacterial contamination, and treatment should be stopped when the wound changes from one with purulent drainage to a dry wound with signs of ongoing healing.

Negative Pressure Wound Therapy

Negative pressure wound therapy deserves some additional discussion as it has gained tremendous popularity recently as a wound management technique. Negative pressure wound therapy has animal and preclinical data support, but prospective clinical human trials are lacking. The negative pressure applied to the wound through a suction apparatus connected to a sponge [see Figure 5] has been shown in animal studies to reduce bacterial counts and promote granulation ingrowth.⁴⁸ Negative pressure therapy has been applied to various wounds, including those with underlying exposed or infected bone, chronic wounds, temporary abdominal closure, and securing skin grafts with some success. For example, negative pressure wound therapy has been shown to be a safe and reliable option in poststernotomy mediastinitis compared with conventional treatment.⁴⁹ However, the role of negative pressure wound therapy in acute cutaneous wounds has fewer supporting data. Negative pressure wound

therapy offers some convenience to patients as dressings are typically changed every other day or every third day compared with the twice-daily schedule associated with gauze dressings. The reduction in the frequency of dressing changes must be weighed against the extra costs associated with negative pressure wound therapy and the limitations of patient mobility and freedom attributable to the required electrical or battery-powered apparatus.

Although preclinical and animal data suggest benefit, prospective clinical trials evaluating negative pressure wound therapy use in cutaneous wounds are required to define the cost/benefit of this technique. One contraindication to negative pressure wound therapy is infected wounds. Silver-based sponges are now available for this indication; however, clinical data to support the use of negative pressure wound therapy in the setting of infection are still pending.

Temporary Allograft Coverage

In the specialized burn patient population, temporary allografts are commonly used. Meshed cadaver skin promotes vascularization and reduces bacterial bioburden in cases where immediate autografting is not an option.⁵⁰ Cultured allogeneic keratinocyte grafts are another alternative and have been shown to speed healing of partial-thickness burns and improve cosmetic outcome.⁵¹ These techniques have also been applied to chronic wounds and complicated postoperative wounds, for example, the patient with large traumatic wounds or those patients requiring radical débridement of the abdominal wall, perineum, or extremity following necrotizing soft tissue infection.⁵² A temporary allograft can help control the pain associated with large open wounds, allows for physical therapy to resume, and can be a bridging, or temporizing, wound therapy until definitive closure is undertaken [see Figure 6].

Conclusions

Wounds are a major source of complications in surgery, and many wound-related complications can be avoided by a sound, evidence-based approach to wound care. A thorough evaluation for preoperative risk reduction with smoking



Figure 5 Negative pressure wound therapy after extensive débridement of necrotizing soft tissue infection. After granulation tissue ingrowth, skin grafts were placed.

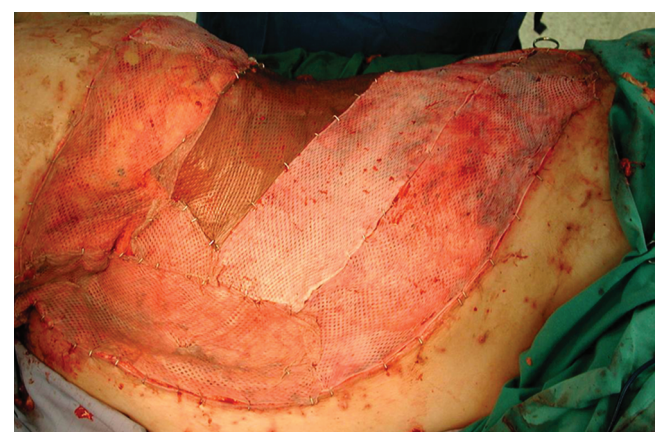


Figure 6 Temporary allograft (cadaver skin) to prepare wound bed for skin grafts after extensive débridement of necrotizing fasciitis after right flank incision.

cessation, glycemic control, weight loss in the obese patient, and nutritional supplementation in the malnourished patient all reduce postoperative wound complications. A sound strategy for the management of coagulopathy is essential to balance risk versus benefit. Proper skin preparation and dosing of antibiotics reduce SSIs, as do combined oral and systemic antibiotics prior to colectomy. Intraoperative hyperoxia and patient warming are effective for reducing postoperative wound complications.

Abdominal wall mass closure incorporates all of the layers of the abdominal wall (except skin) as one structure, in a simple running technique, using #1 or #2 absorbable monofilament suture material with a suture length to wound length ratio of 4 to 1. Unfortunately, dehiscence occurs in 1% of patients after colectomy and is heralded by serosanguinous drainage from the wound between 5 and 10 days after surgery. These patients may have primary failure of the abdominal wall attributable to a technical problem or

organ/space SSI and intra-abdominal pathology that requires further treatment.

Some patients, unfortunately, will develop an open abdomen and require advanced and prolonged treatment. Those in whom skin closure is not feasible are typically managed by the absorbable mesh technique or negative pressure wound therapy. Both options are associated with fistulas. Prevention is clearly a better option. In those with class III–IV/contaminated or dirty-infected surgical wounds, secondary closure is associated with a statistically significant reduction in SSI and dehiscence compared with primary closure. Gauze dressings are cheap and effective but associated with frequent and often painful dressing changes. A wide variety of adjuncts (specialized dressings, silver dressings, negative pressure wound therapy, temporary allograft coverage) may benefit patients, but clear clinical data are currently lacking.

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1 CARDIAC SYSTEM

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The circulatory system, which consists of the heart, arterial system, venous system, and lymphatics, has long remained a source of fascination for anatomists and physiologists alike. The unique anatomic and physiologic characteristics of the heart not only make it somewhat challenging for basic scientists to understand but also impose significant technical challenges for surgeons who operate on the heart. The heart not only pumps blood to the entire body: it is also responsible for supplying its own nutrition via the coronary arteries, damage to which could initiate a detrimental cycle. Several unique compensatory anatomic and physiologic mechanisms ensure the long-term durability and functional integrity of the heart. Over the average 70-year human life span, the heart contracts about 2.75 billion times without interruption—which still far exceeds the durability of some of the best mechanical devices made by humans.

History

Claudius Galenus, or Galen (129 to 217 AD) [see Figure 1], was the first to significantly describe the circulatory system in living and cadaveric animals. A Roman philosopher and physician of Greek ethnicity, Galen was unable to study human cadavers because human dissection was prohibited by Roman law. Yet his descriptions, not without flaw, held authority until further discoveries were reported in the 16th century.¹ Andreas Vesalius, the founder of modern anatomy, was the first physician to perform and document a systematic human cadaveric dissection, and his publication *De Humani Corporis Fabrica* was the first to challenge Galen's findings. Vesalius revealed that Galen had worked on animals, not humans, and that the venous system was connected to the heart rather than originating from the liver as Galen had theorized—a concept that had been widely embraced for 1,500 years.² Although Vesalius's book was significant in that it disproved the Galenic theory, it lacked any detailed description of the circulatory system except where necessary to explain defects in the Galenic proposition. Rather, William Harvey [see Figure 2] has been credited with the first detailed description of the human circulatory system in his 1628 publication *De Motu Cordis*.³ Dr. Harvey's description remained authoritative until the 20th century. Unlike Galen, who described a dual parallel circulation, Harvey proposed that both the arterial and the venous circulation were a serial circuit and one unified system.

Myocardial Anatomy

The cardiac muscle, an involuntary striated muscle, is the foundation of the myocardium. The cardiac muscle has a higher mitochondrial content than other types of muscle and

Financial disclosure information is located at the end of this chapter before the references.



Figure 1 Claudius Galenus, a Roman philosopher, was well known for his comprehensive description of the circulatory system. Although his work was based on animals, it held authority for more than 1,500 years. *Claude Galien*, Vigneron lithograph by G. Engelmann, France.

can better tolerate fatigue. The cardiac muscle maintains an orientation similar to that of striated muscles and is organized into myocardial fibers. The arrangement of the myocardial fibers follows a specific pattern that is essential for efficient contractile function of the cardiac chambers. The atrial and ventricular chambers have distinct features due to differences in the embryologic origins and the functional requirements of these chambers.

ATRIAL MYOCARDIUM

The atrial myocardium consists of a superficial transverse layer and a deep layer. Although the superficial transverse layer is shared by both atrial chambers, the deep layer is distinct for each atrium. The deep layer consists of loop fibers that anchor at the atrioventricular (AV) annulus and circular fibers that surround the fossa ovalis, caval orifices, and atrial appendages. The atrial myocardium is thin—about 1 to 2 mm thick—because it is required to generate only lower gradients. The atria are mostly containment chambers that receive blood and store it temporarily before it is pushed into the ventricles, which are the main pumping chambers.

VENTRICULAR MYOCARDIUM

The ventricular chambers consist of three layers: the subepicardial layer, the middle layer, and the subendocardial layer. The middle layer is known as the ventricular myocardial band and is unique to the left ventricle.

The ventricular muscle fibers have a distinct arrangement that was described only recently by Dr. Francisco

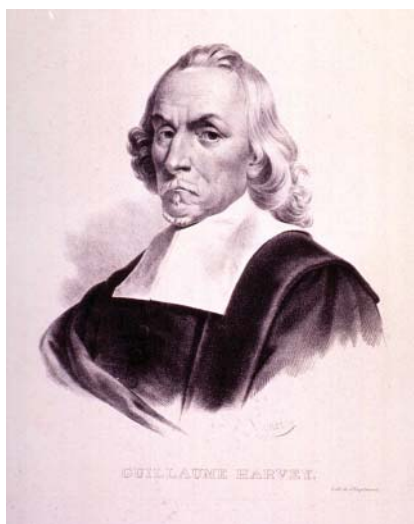


Figure 2 William Harvey is known for publishing the most accurate anatomic description of the human circulatory system and challenged the parallel circuit description of Galen. *Guillaume Harvey*, Vigneron lithograph by G. Engelmann, France.

Torrent-Guasp.⁴ The ventricular myocardium is, in fact, a single band of cardiac striated muscle that originates at the left ventricular outflow tract (LVOT) and ends at the right ventricular outflow tract [see *Figure 3* and *Figure 4*]. In its course, the band forms a dual spiral: the inner layer forms the apical loop, and the outer layer forms the basal loop. The basal and apical loops function in coordination like a cylinder and piston. This mechanism is believed to make the process of ventricular filling an active, rather than a passive, flow-related process.⁵ Because the ventricular myocardium is a single band, the wave of contraction progresses from one end of the band to the other. While this occurs, the basal loop stiffens to form a rigid cylinder. As the wave of contraction passes through, the apical loop is pushed away, causing a suction effect in the ventricular chamber.

The wave of contraction then progresses into the apical loop, causing it to stiffen and pulling the basal loop toward the apex, thereby ejecting blood from the ventricular chamber. This sequence is illustrated in *Figure 5* and *Figure 6*. This sequential dance of the ventricular myocardium has remained one of the unsolved mysteries of cardiac anatomy for more than two millennia.⁶ In fact, the spiral arrangement of the ventricular muscle was recognized first by Galen, but the exact course and direction of the muscle fibers were unknown until their discovery by Dr. Torrent-Guasp.⁷ Understanding the arrangement of these muscle fibers is the basis of surgical ventricular restoration. The spiral arrangement of the fibers in the ventricular apex maintains the Gothic “conical” configuration of the ventricular chamber, which is mechanically more efficient than the rounded structure seen in, for example, dilated cardiomyopathy. Surgical techniques designed to restore the conical shape of the ventricle in heart failure patients are more likely to succeed than procedures that do not restore ventricular geometry.

Cardiac Electrical System

SINOATRIAL NODE

Also known as the pacemaker, the sinoatrial (SA) node initiates the contractions of the heart. The SA node is typically a collection of specialized myocytes known as nodal myocytes, which, unlike the cardiac myocytes, are stellate cells.⁸ These cells occupy the center of the node, surrounding a central nodal artery. The central location of the artery of the SA node is a unique feature of this structure. The nodal myocytes, although a type of cardiac myocyte, are primitive in phylogenetic origin and thus retain a higher rate of depolarization than any other type of myocyte, which is responsible for the overdrive of these cells in suppressing activity from other, secondary pacemaker sites [see *Figure 7* and *Figure 8*]. The SA node is a subepicardial structure located at the junction of the embryonic sinus venosus and the right atrium proper [see *Figure 9*].⁹ A plaque of

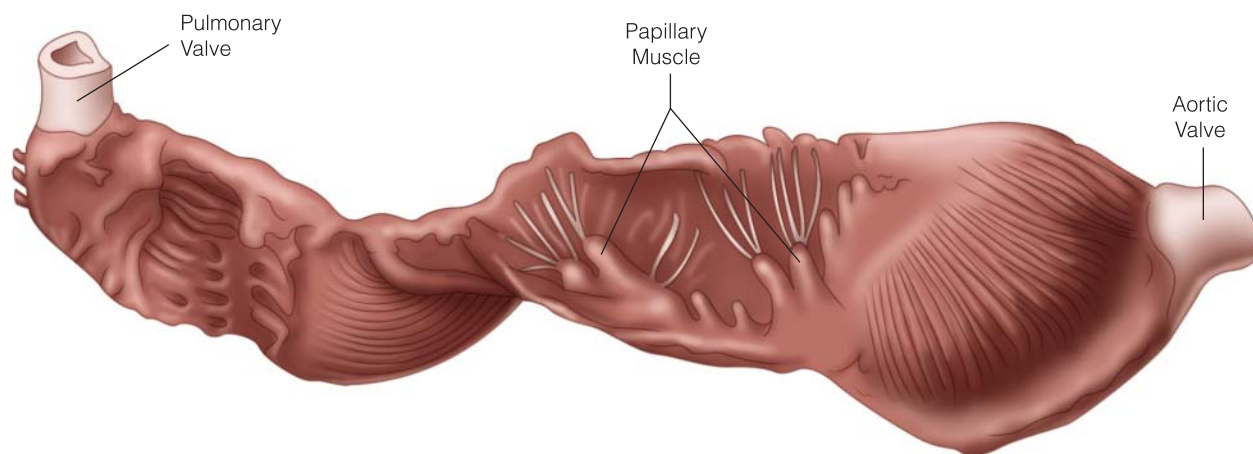


Figure 3 The ventricular myocardial band of Torrent-Guasp is a single band of ventricular myocardium that is wound in a complex spiral that maintains ventricular geometry and efficient contractility.

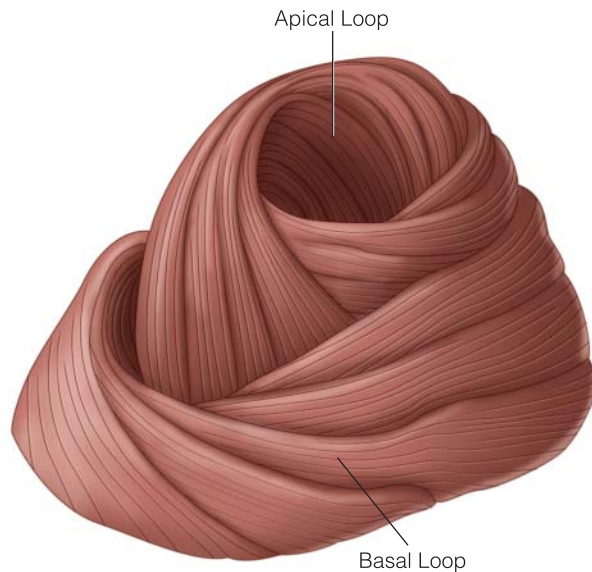


Figure 4 Spiral configuration of the ventricular myocardial band.

subepicardial fatty pad that occupies the groove between the terminal superior vena cava and the right atrial appendage clearly marks its location when seen intraoperatively.

ATRIOVENTRICULAR NODE

The AV node is located in the triangle of Koch on the right atrial side of the interatrial septum. The triangle of Koch is bounded by the origin of the coronary sinus, the tendon of Todaro, and the basal attachment of the septal leaflet of the tricuspid valve. The AV node is an oval structure about 8 mm long and is located just superior to the attachment of the tricuspid leaflet. The convex side of this structure faces the right atrium, whereas the concave side abuts the mitral annulus. Unlike the SA node, the AV node is composed of transitional myocytes that have a slower depolarization rate than the myocytes in the SA node.¹⁰ Importantly, the antero-inferior pole of the AV node is continuous with a specialized group of myocytes, known as the Purkinje myocytes, that in turn connects to the AV bundle.

BUNDLE OF HIS AND PURKINJE SYSTEM

The bundle of His, or AV bundle, is a continuation of the antero-inferior portion of the AV node and passes through the right fibrous trigone. Then the bundle traverses the antero-inferior portion of the perimembranous septum. This location is surgically important because it is likely to be injured during repair of ventricular septal defects.

The relation of the AV node and bundle to the aortic root is also important. Placement of valve sutures and incisions for root enlargement operations should be planned well, with close attention to the location of the membranous septum, the AV node, and the anterior mitral leaflet. Pre-operative angiograms should be reviewed to identify anomalous coronary arteries because these may preclude certain types of root enlargement options.

Immediately after traversing the perimembranous septum, the bundle of His separates into right and left fascicles. The right fascicle (otherwise known as the right bundle branch) is more discrete and rounded than the left fascicle

and courses along the right side of the interventricular septum. The structure gives off sparse branches until it reaches the papillary muscle, after which it divides into numerous fine subendocardial fascicles that permeate the ventricular musculature. The left bundle branch, on the other hand, is a flattened, sheetlike continuation of the bundle of His that has numerous fascicles that are individually sheathed. After following a short course in an apico-/subendocardial direction, this sheet splits into anterior and posterior sheets [see Figure 9]. Several fine branches, known as the Purkinje fibers, leave these sheets and form an intricate subendocardial network that encompasses the papillary muscles and ramifies through the entire ventricular chamber. The fibers are predominantly composed of Purkinje-type myocytes, which have a slower firing rate but a fast conduction pattern.

Cardiac Vasculature

ARTERIAL SYSTEM: CORONARY ARTERIES

The coronary arteries arise from the sinuses of Valsalva (SOVs) and are the first arterial branches of the aorta. The left coronary artery (LCA) arises from the left coronary sinus, which is located posteromedially, whereas the right coronary artery (RCA) typically arises from the right coronary sinus, which is located anteromedially in relation to the aortic root. The LCA, also called the left main coronary artery, averages about 2 to 3 cm in length and courses in a left posterolateral direction behind the main pulmonary artery trunk [see Figure 10, Figure 11, Figure 12, and Figure 13].

The LCA splits into the left anterior descending (LAD) and the left circumflex arteries. As the LAD runs anteriorly over the interventricular septum, it gives off the diagonal branches that supply the anterolateral wall of the left ventricle. The LAD is considered the most important surgical vessel because it supplies more than 50% of the left ventricular mass and most of the interventricular septum. The LAD has several septal perforating branches that supply the interventricular septum from the anterior aspect. The LAD extends over the interventricular septum up to the apex of the heart. Occasionally, it forms an anastomosis with the posterior descending artery (PDA), which is typically a branch of the right coronary system.

From its origin, the circumflex artery dives immediately into the AV groove and follows a clockwise course. Along its course, it gives off the obtuse marginal branches in a perpendicular fashion; these branches extend toward, but do not quite reach, the apex of the heart. The circumflex coronary artery typically terminates as the left posterolateral branch after taking a perpendicular turn toward the apex. The term *ramus intermedius* is used to designate a dominant epicardial coronary vessel that arises from the occasional trifurcation of the left main coronary artery. Some surgeons may use this term to refer either to a diagonal artery with a very high takeoff or to a very proximal obtuse marginal vessel. The ramus intermedius branch typically emerges from under the left atrial appendage, which is used as a landmark in identifying this vessel. This branch can be intramyocardial and difficult to locate at times during surgery.

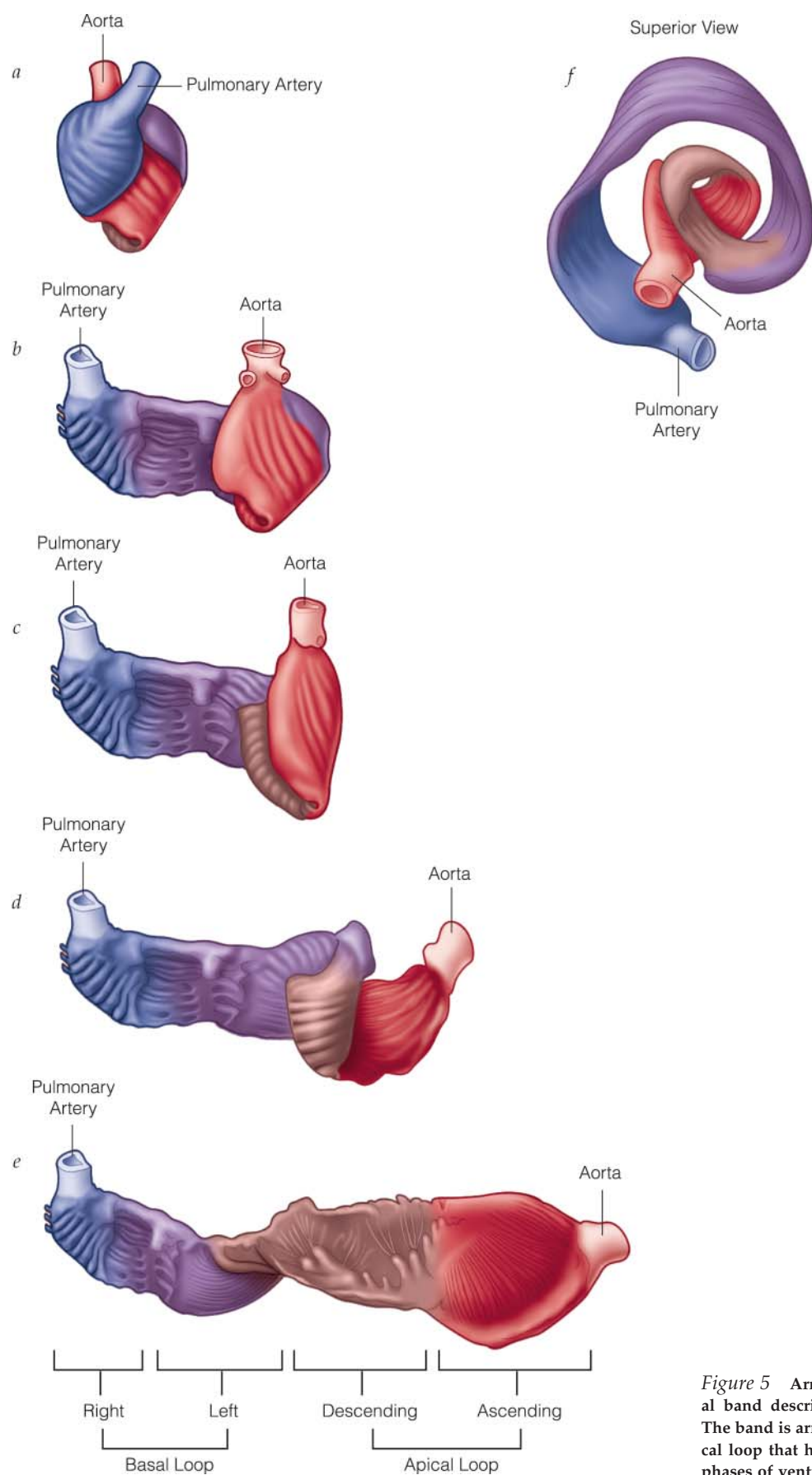


Figure 5 Arrangement of the ventricular myocardial band described by Dr. Francisco Torrent-Guasp. The band is arranged to form a basal loop and an apical loop that help in the active diastolic and systolic phases of ventricular ejection.

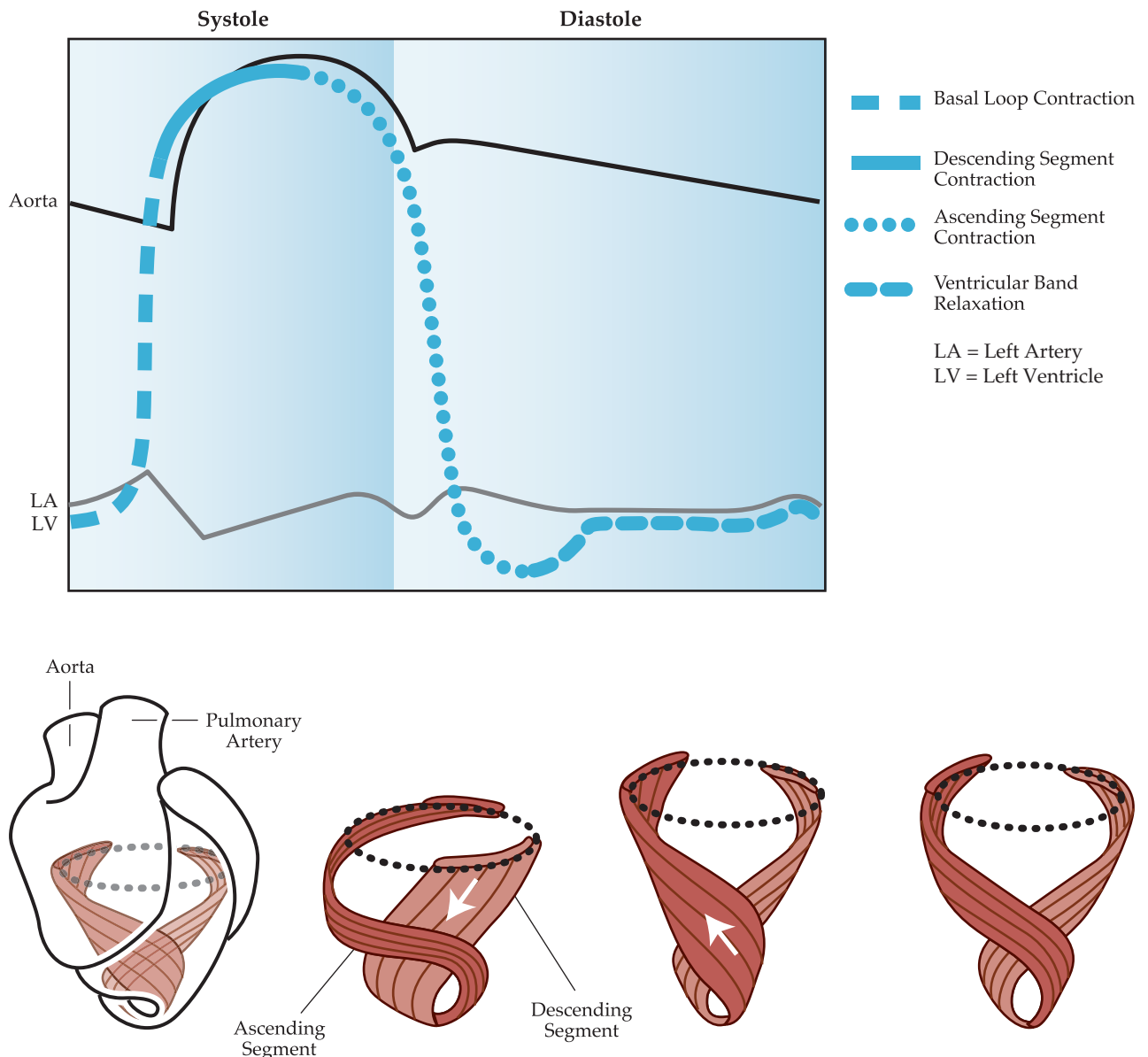


Figure 6 Dynamic interaction of the ventricular myocardial band.

The RCA supplies most of the right ventricle, as well as the posterior part of the left ventricle. The RCA emerges from its ostium in the right coronary sinus, passes deep in the right AV groove, and then turns posteriorly toward the crux and usually bifurcates into the PDA and the right posterolateral artery. The RCA also supplies multiple right ventricular branches known as the acute marginal arteries. Occasionally, the PDA arises from both the RCA and the LCA, and the circulation is considered to be codominant. Although the source of the PDA is often used clinically to define dominance of circulation in the heart, anatomists define it according to where the SA node artery arises. The AV node artery arises from the RCA in about 90% of patients. The SA node artery arises from the proximal RCA in 50% of patients.

All of the epicardial conductance vessels give rise to a multitude of branches that traverse perpendicularly into

the ventricular wall. The rich capillary plexus offers a low-resistance system that allows arterial blood flow to increase unimpeded when oxygen demand rises. Because the myocardial vascular bed extracts oxygen at its full capacity even in low-demand circumstances, additional oxygen demand can be met only through an increase in coronary blood flow.

CORONARY VEINS

An intricate network of veins drains the coronary circulation, and the venous circulation can be divided into three systems: the coronary sinus and its tributaries, the anterior right ventricular veins, and the thebesian veins [see Figure 14]. The coronary sinus predominantly drains the left ventricle and receives 85% of coronary venous blood. It lies within the posterior AV groove and empties into the right

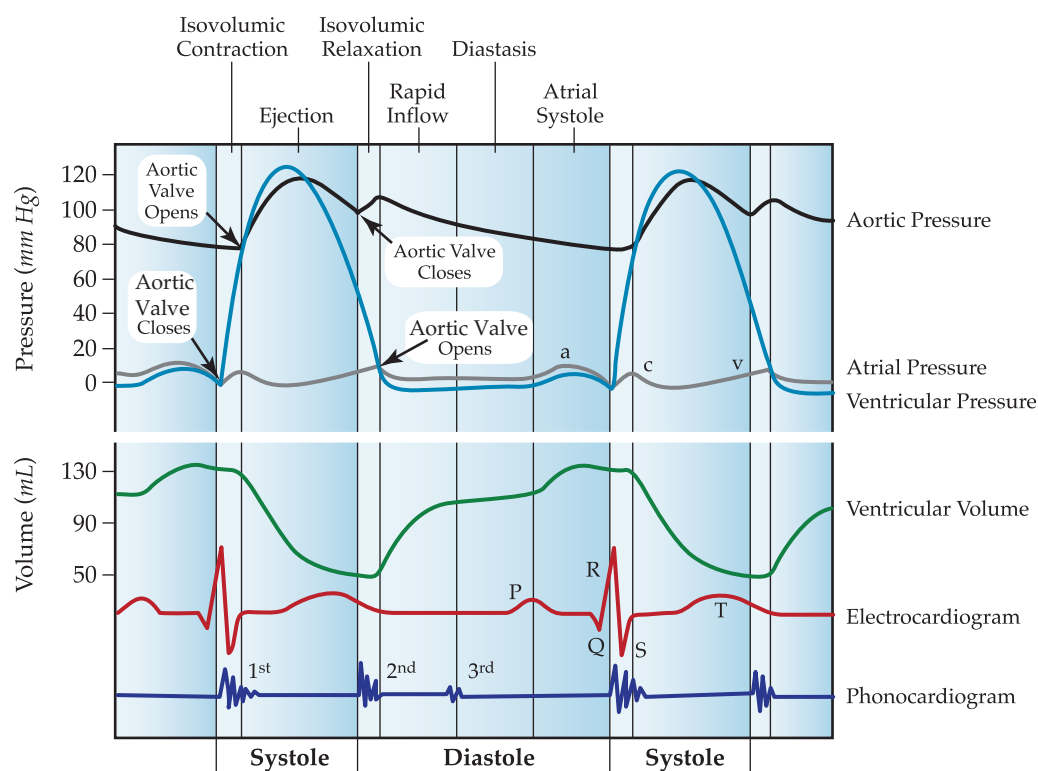


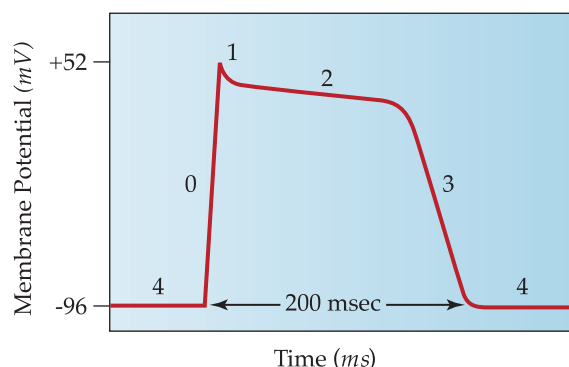
Figure 7 The cardiac depolarization cycle closely correlates with the mechanical contraction of the heart. The myocytes of the sinoatrial node have the highest depolarization rate of all cardiac myocytes.

atrium. The anterior right ventricular veins travel across the right ventricular surface to the right AV groove, where they form the small cardiac vein, which enters into the right atrium directly or joins the coronary sinus. The thebesian veins are small venous tributaries that drain directly into the cardiac chambers and exit primarily into the right atrium and right ventricle. Understanding the anatomy of the coronary sinus is essential for placing the retrograde cardioplegia cannula during cardiopulmonary bypass. The orifice of the coronary sinus is occasionally covered by a valve known as the thebesian valve [see Thesbian Valve, *below*].

PHYSIOLOGY OF CORONARY CIRCULATION

Under resting conditions, coronary blood flow is maintained at a fairly constant level through the process of

autoregulation. Normal coronary blood flow averages 0.7 to 0.9 mL/g of myocardium per minute, and more than 75% of the delivered oxygen is extracted in the coronary capillary bed. Any additional oxygen demand can be met only by increasing the flow rate. Unimpeded coronary blood flow for proper myocardial function is thus vital. In response to increased load, the healthy heart can increase myocardial blood flow fourfold to sevenfold. Autoregulatory mechanisms activated by a release of vasodilatory humoral factors contribute to a localized increase in blood flow. Several metabolic factors, including CO_2 , O_2 tension, hydrogen ions, lactate, potassium ions, and adenosine, contribute to this mechanism. Adenosine, a potent vasodilator and a degradation product of adenosine triphosphate (ATP), accumulates in the interstitial space and relaxes vascular smooth muscle during increased load. This results in vasomotor relaxation,



- Phase 0 = Rapid Depolarization (Increased Na^+ and Decreased K^+ Conductances)
- Phase 1 = Initial Repolarization (Decreased Na^+ and Increased K^+ Conductances)
- Phase 2 = Plateau Phase (Increased Ca^{2+} Conductance)
- Phase 3 = Repolarization (Increased K^+ and Decreased Ca^{2+} Conductances)
- Phase 4 = Resting Potential (Increased K^+ and Decreased Na^+ and Decreased Ca^{2+} Conductances)

Figure 8 Cardiac action potential schematic showing the flux of electrolytes across the cardiac myocytes during various phases of the depolarization cycle.

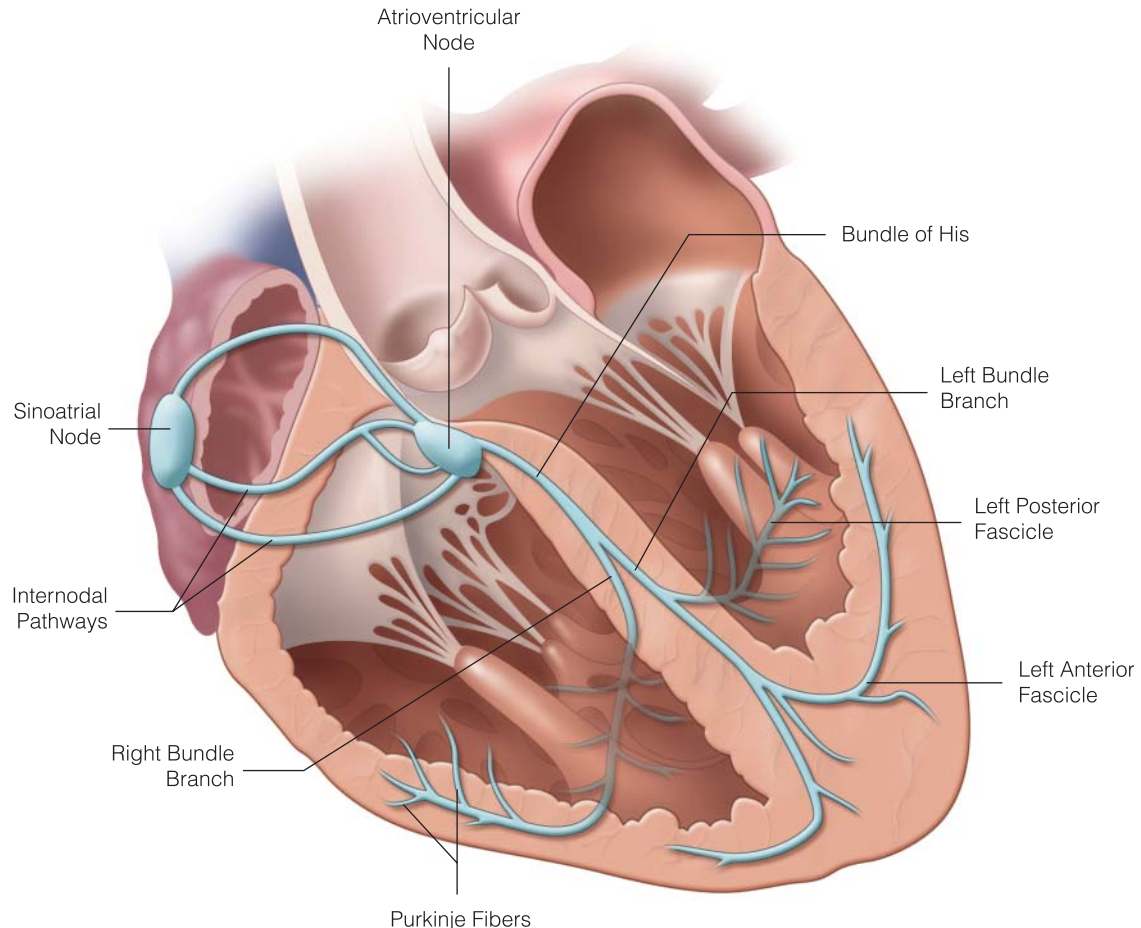


Figure 9 The cardiac conduction system, which consists of the sinoatrial node, the atrioventricular node, the bundle of His, and the Purkinje fibers. All these cells are various types of specialized myocytes.

coronary vasodilatation, and increased blood flow. Another important substance is nitric oxide (NO) produced from the endothelium. In the absence of endothelium, coronary arteries do not autoregulate, suggesting that the mechanism for vasodilatation and reactive hyperemia is endothelium dependent.

During systole, the intracavitary pressures generated within the left ventricular wall exceed intracoronary pressure, and blood flow is impeded. Hence, approximately 60% of the coronary blood flow occurs during diastole. During exercise, increased heart rate and reduced diastolic time can compromise flow time, but this effect can be offset by the vasodilatory mechanisms of the coronary vessels. Fixed coronary occlusion can significantly impair the compensatory mechanisms that maintain coronary blood flow while the heart rate is elevated. Our knowledge of this phenomenon makes it possible to uncover underlying occult coronary disease during exercise-induced stress tests.

Fibrous Skeleton of the Heart

A complex framework of connective tissue composed of collagen lies in a plane somewhat parallel to the AV groove and forms the anchoring foundation of the heart

[see Figure 15]. This framework has been referred to as the fibrous skeleton and consists of membranous and tendinous structures. Essentially, the annuli of all the cardiac valves abut each other, forming this complex structure. The fibrous skeleton of the heart was not recognized by early anatomists because the annulus and trigones of the mitral apparatus were presumed to be separate structures. The mitral, tricuspid, and aortic annuli are intimately associated.

The mitral and tricuspid annuli lie in a similar plane, whereas the aortic annulus is slightly anterosuperior to the mitral orifice and faces forward. The pulmonary annulus is distant from the main components of the fibrous skeleton and is attached to the aortic annulus by the conus ligament, which forms an integral component of the infundibulum. Although the primary function of the fibrous skeleton is to anchor the leaflets of the cardiac valves, it also acts as a physiologic barrier that prevents electrical continuity between the atrium and ventricles. As noted above, in normal circumstances, the bundle of His is the only structure that carries electrical activity from the atrium to the ventricle and penetrates through the fibrous skeleton of the heart. The fibrous skeleton is also the anchor point of the ventricular myocardial band.

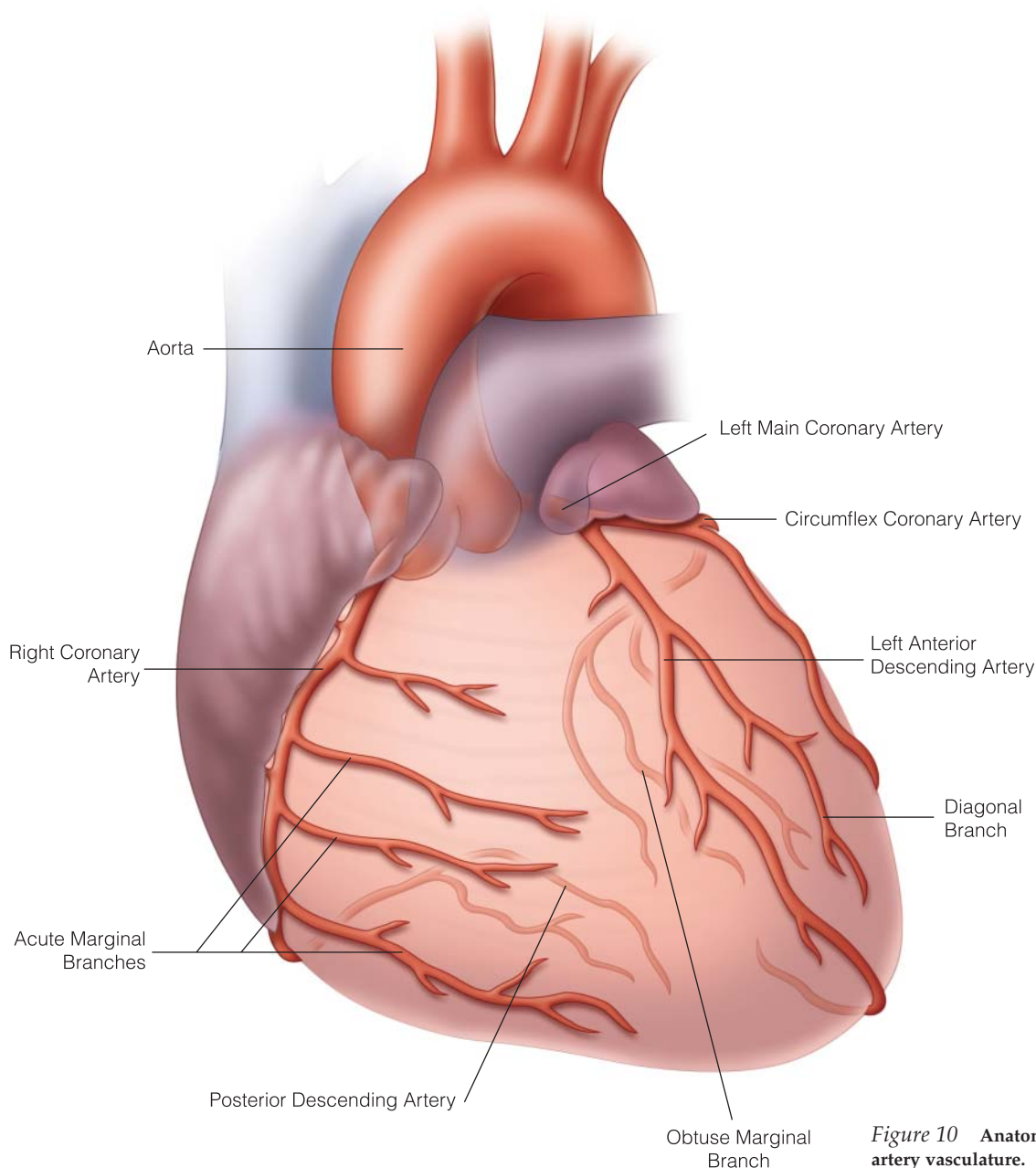


Figure 10 Anatomy of normal coronary artery vasculature.

Understanding the structural continuity of the fibrous skeleton is essential to understanding the three-dimensional relations of the cardiac valvular structures. The aortic valve occupies the central location and functions as a reference point during echocardiography. The aortic annulus, known as the annulus fibrosis, is the foundation of the aortic root, onto which the valve leaflets, interleaflet triangles (ILTs), LVOTs, and SOVs converge. The fibrous skeleton has remarkable tensile strength that anchors the aortic root to the LVOT, lest the aorta be torn from the point of its left ventricular attachment by the tremendous accelerative forces generated by ventricular systole. Derangements of fibroskeletal integrity, such as loss of aortomitral continuity, are noted in congenital heart defects such as tetralogy of Fallot and are pathognomonic of conotruncal anomalies.

Cardiac Valves

AORTIC VALVE

The aortic valve guards the outlet of the LVOT and prevents aortic blood from returning to the ventricle during diastole [see Figure 16]. The valve is similar in construction to the pulmonary valve and consists of three cusplike leaflets [see Figure 17 and Figure 18]. Although the aortic valve is located in a high-pressure zone, the leaflet structures are not as strong as the mitral leaflets. This is because the maximum pressure forced against the closed leaflets is typically the diastolic aortic pressure, which is considerably lower than the maximal systolic pressure forced against the closed mitral valve. Although anatomically the aortic valve is considered to consist of three semilunar cusps and the

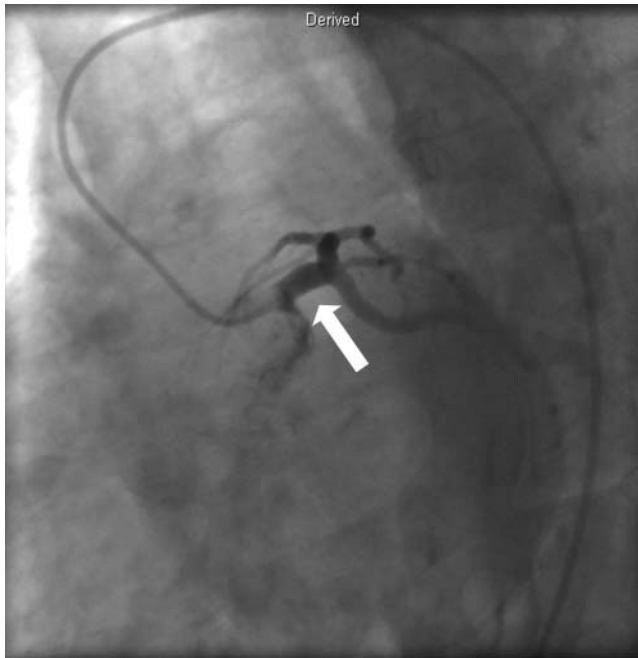


Figure 11 Left coronary angiogram (spider view) showing the left main coronary artery. Arrow marks the left main coronary artery.

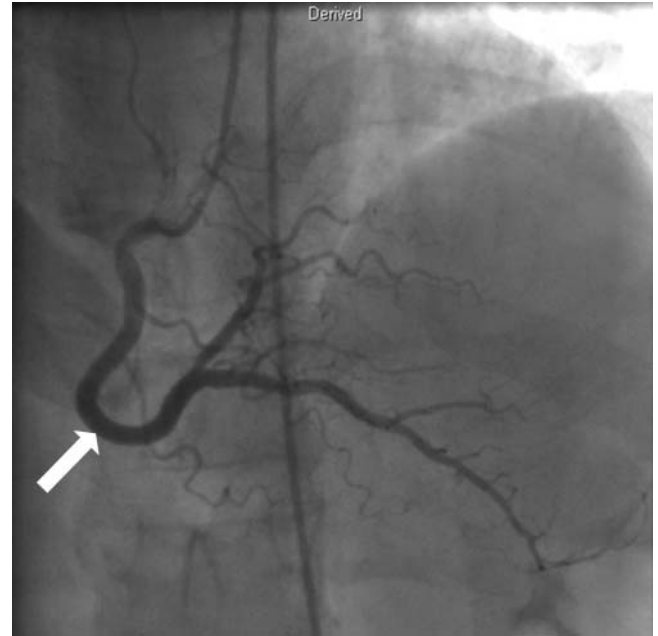


Figure 13 The right coronary artery as seen during cardiac catheterization. Arrow marks the right main coronary artery.

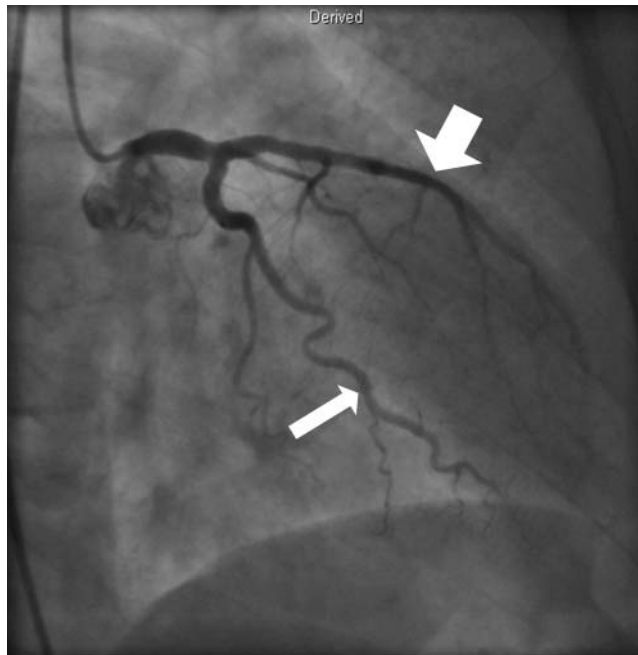


Figure 12 The left anterior and circumflex coronary arteries as seen during a routine cardiac catheterization. Large arrow marks the left anterior descending and small arrow marks circumflex coronary artery.

aortic annulus, this description discounts the fact that the aortic valve and the aortic root are a single, complex structure (which is described in detail in a subsequent section of this chapter).

The aortic semilunar cusps are essentially extensions of the endocardium and attach at the base to the annulus

fibrosus. The free margin of the aortic cusp is slightly thick and condenses into a nodular structure at the center, known as the nodulus Arantii. The aortic commissures are the highest point between two adjacent semilunar valves at the attachment of the annulus fibrosus. Because of the curvilinear attachments of the semilunar valves, the annulus fibrosus takes the shape of a coronet rather than a simple ring. Understanding the coronet shape of the annulus fibrosus is essential during valve replacement surgery because anchoring sutures for the aortic valve should be placed in the fibrous tissues of the annulus rather than the subannular tissues, which are relatively weaker. The aortic valve cusps are named according to the origin of the coronary arteries, such as the right coronary cusp, anterior in location; the left coronary cusp, left and posterior in location; and the noncoronary cusp, right and posterior in location.

MITRAL VALVE

The mitral valve guards the left AV orifice, which lies in a vertical plane that is tilted about 45° to the coronal plane. The mitral valve is intimately connected to the tricuspid and aortic valves through the fibrous skeleton [see Figure 19]. The mitral annulus has certain distinct features that make it physiologically functional. The mitral annulus is not a true circular structure but, rather, a flattened circle. When viewed from the left atrial aspect, this flattened aspect of the circumference extends from about the 10 o'clock to the 2 o'clock position [see Figure 20]. The remaining aspect of the annulus has a more circular shape. The junction between the flattened and circular aspects of the annulus is marked by dense concentrations of fibrous tissue on either side known as the trigones and forms an integral anchor point of the fibrous skeleton of the heart. The flattened aspect of the mitral annulus, in conjunction with the commissure between

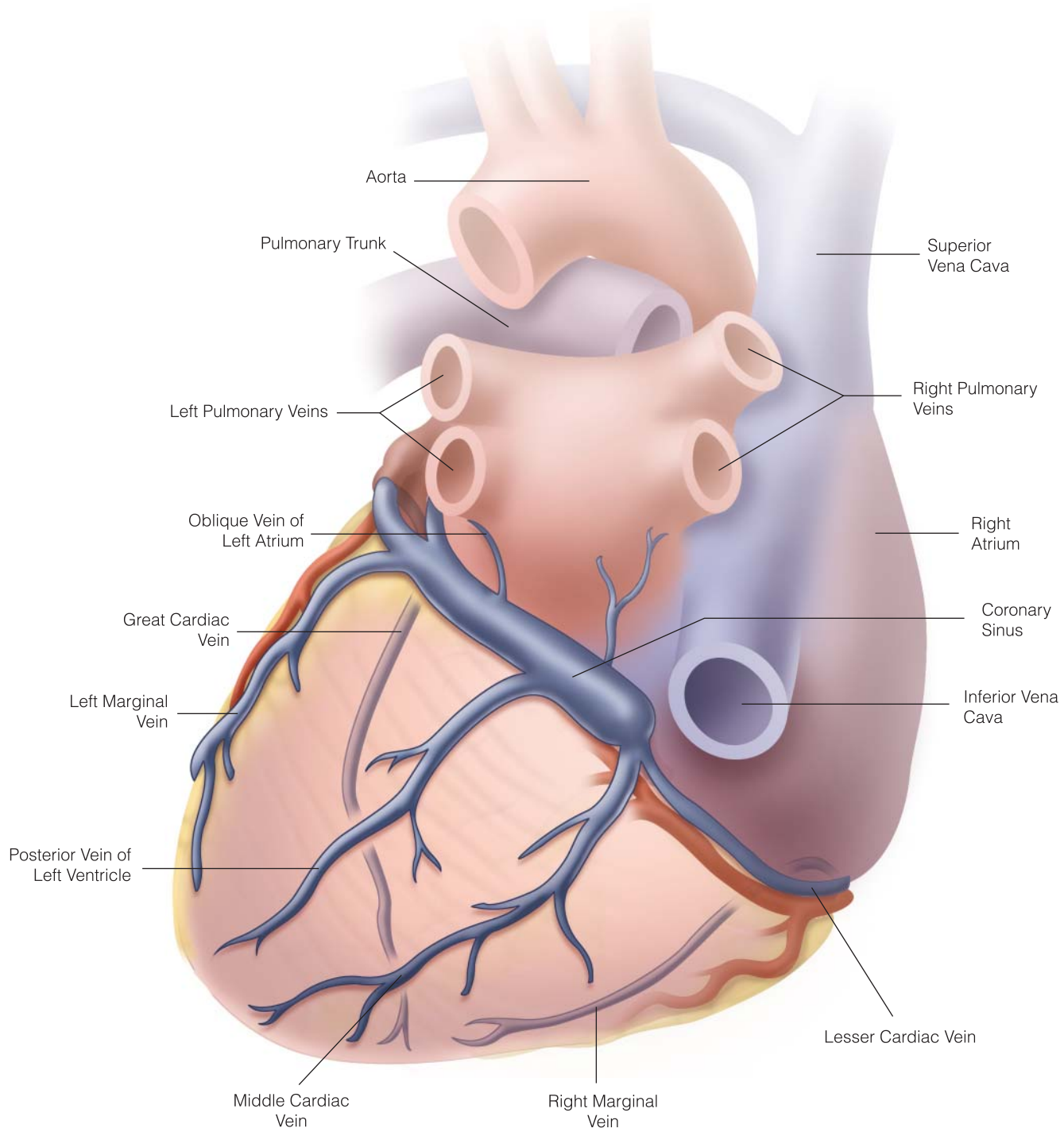


Figure 14 The coronary venous system, which drains either directly into the cardiac chambers or via the coronary sinus.

the left and noncoronary aortic cusps, forms a triangular area beneath the aortic valve that fades into the anterior leaflet of the mitral valve. This is defined as the aortomitral continuity, or the subaortic curtain, and it is intimately related to the LVOT, the intercommissural triangle of the aortic valve, and the anterior mitral leaflet [see Figure 20]. This

location of the anterior mitral leaflet places it between the left ventricular inflow and outflow tracts, making the anterior leaflet an interventricular aortic baffle. Changes in the position and flexibility of the annulus spanning the anterior mitral leaflet can push the mitral valve into the LVOT; this phenomenon, commonly known as systolic

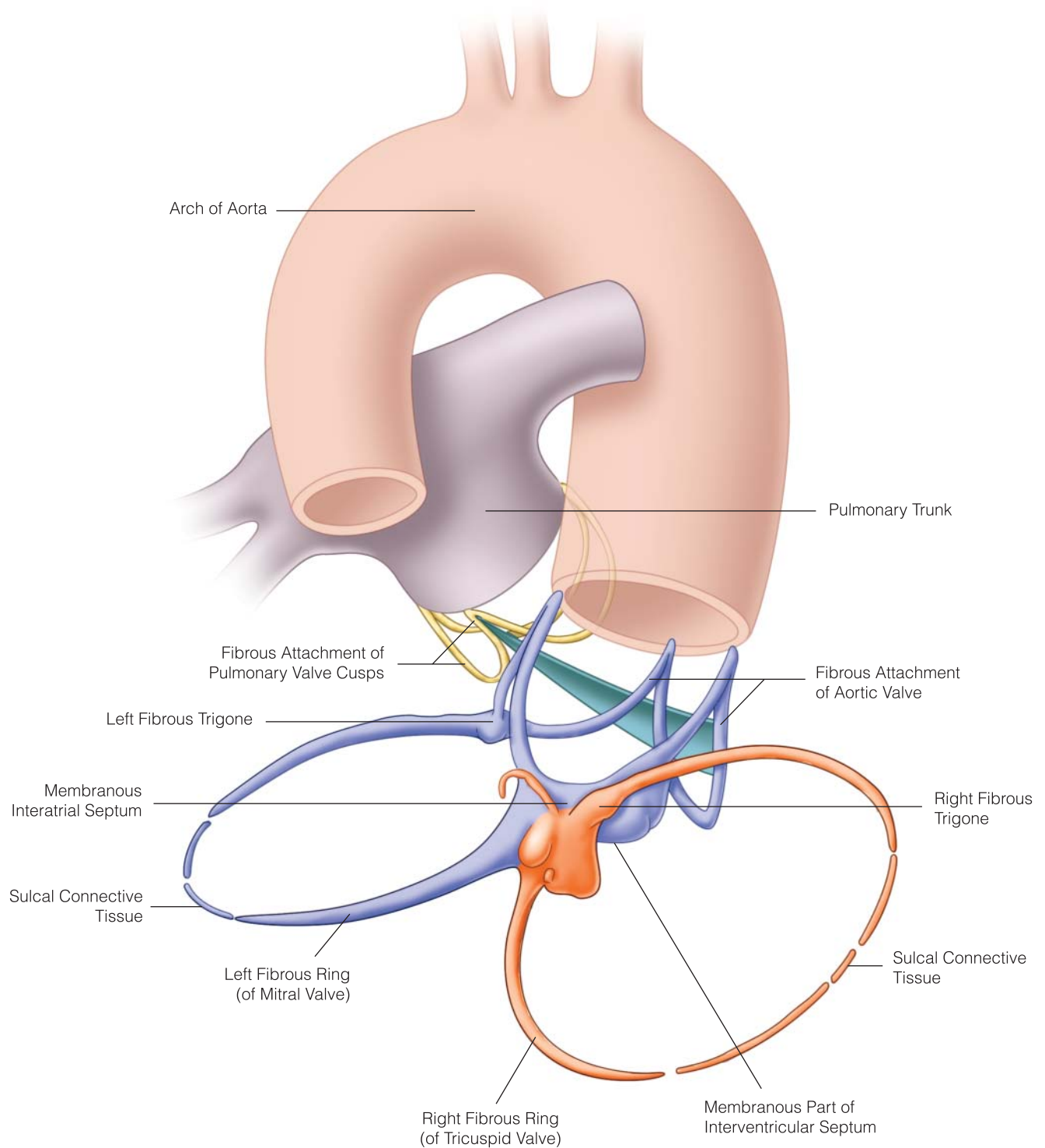


Figure 15 The fibrous skeleton of the heart.

anterior motion, can impede the ejection of blood from the ventricular cavity during systole.

The two mitral valve leaflets form a bicuspid valve with a deep central cleft resembling that of a miter (a bishop's headdress), from which the valve takes its name. Although, for clinical purposes, the two cusps are considered separate,

in reality, the mitral valve is a single circumferential curtain with multiple indentations along the edge, two of which are quite prominent and are designated as the left (postero-medial) and right (anterolateral) commissures. These commissures receive anchoring attachments from the papillary muscles via numerous chordae that fan out into the edges

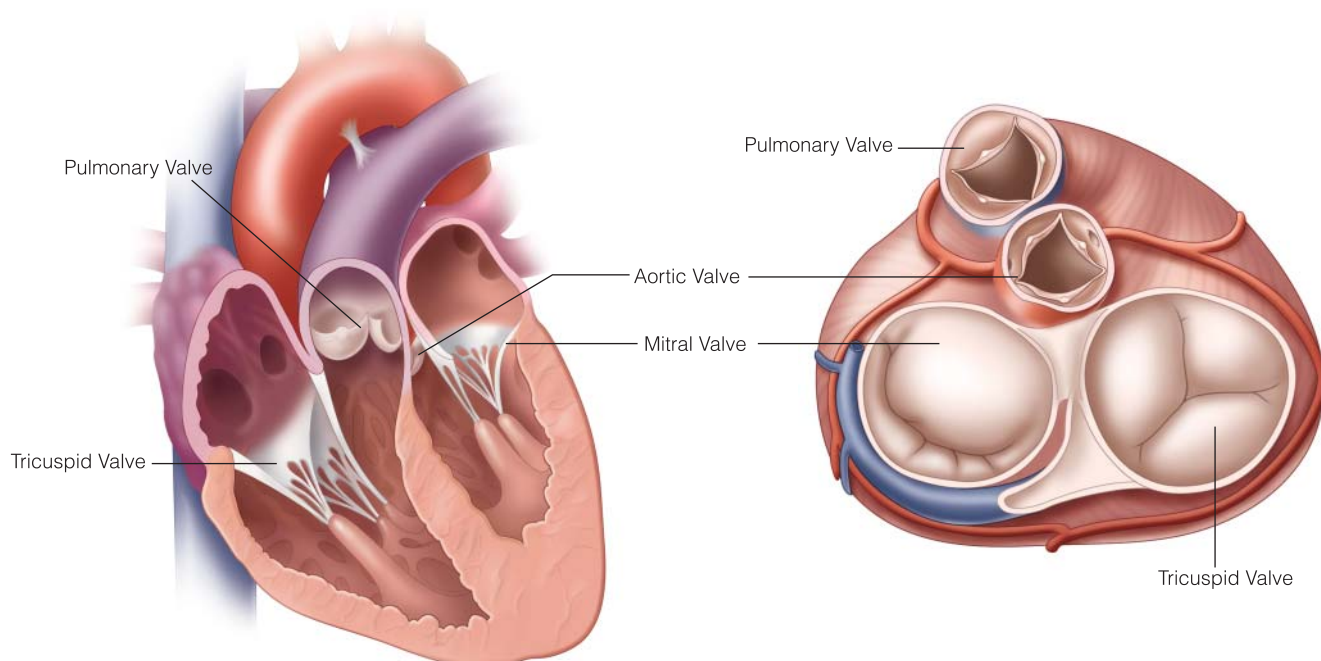


Figure 16 The cardiac valves in normal anatomic configuration.

of the anterior and posterior mitral leaflets [see Figure 21]. In addition, two medium-sized clefts are located along the posterior leaflet that divide it into three prominent scallops, labeled P1, P2, and P3 from left to right, on the basis of the surgeon's view of the mitral valve through the left atrium. The corresponding opposing aspects of the anterior leaflet are named A1 through A3, although no prominent clefts are identified.¹¹ This designation is essential for surgeons to describe and plan mitral reconstructive techniques. The location of the posterior mitral clefts varies significantly, and it is crucial to recognize them clinically for successful mitral repair surgery.

The posterior mitral leaflet includes all valvular tissue that spans the circular aspect of the mitral annulus, extending from one commissure to the other, and has a much broader attachment than the anterior leaflet. Each of the posterior leaflet's three scallops has a finely serrated edge that receives attachments from the chordae, which also extend to the ventricular aspect of the scallop. This area, which receives most of the chordal attachments, is known as the rough zone, which becomes more translucent as one progresses from the free margin to the annular base. The translucent clear zone is devoid of any chordal attachments.

The mitral annulus tends to calcify with age because of the shearing forces that occur over time. This calcification may be obvious on chest radiograms. Calcification of the mitral annulus is a relative contraindication for mitral valve surgery because it confers a high risk of mechanical AV disruption, which is potentially fatal. Also, calcification makes the annulus less deformable, lowering the odds of successful mitral valve annuloplasty. Because the posterior mitral leaflet has a wider area of attachment than the anterior leaflet, a more extensive chordal anchoring to the papillary muscle is associated with the posterior leaflet. The entire complex involving the posterior mitral leaflet, chordal

attachments, and both papillary muscles maintains the ventricle's conical, rather than globular, shape. Surgeons typically tend to spare the entire posterior mitral leaflet and minimize any resection during valve replacement so that the ventricular geometry is maintained; this practice has been credited with reducing the detrimental long-term ventricular remodeling that occurs when all chordal attachments are resected.

TRICUSPID VALVE

The tricuspid valve is integrally related to the mitral valve and the fibrous skeleton and is best described as an entire complex, similar to the mitral valve, composed of the valvular leaflets, the chordae tendineae, the papillary muscles, and the annulus [see Figure 22]. The right AV orifice is the largest valve orifice in the heart and is quite ill-defined. Unlike the mitral orifice, the tricuspid orifice is indistinct, and the attachments of the leaflets are the only landmarks of the separation between the right atrial and ventricular tissue. In the absence of leaflet attachments, the tricuspid annulus is hard to define, especially because of the interruption of and variations in the quantity of collagenous tissue in the annulus itself.

The tricuspid valve has three leaflets, known as the septal, anterior, and posterior leaflets. Like the mitral valve, the tricuspid valve is a continuous veil of tissue separated by indentations that demarcate the leaflets. Further intermediary indentations divide the posterior leaflet into three scallops, whereas the anterior and septal leaflets have a marginally distinct cleft. The anterior leaflet of the tricuspid valve is the largest leaflet, and the septal leaflet is the smallest. The attachment of the anterior and septal leaflets extends onto the membranous septum at the anteroseptal commissure. In contrast, the posterior leaflet is entirely flanked by atrial and ventricular myocardium. The attachment

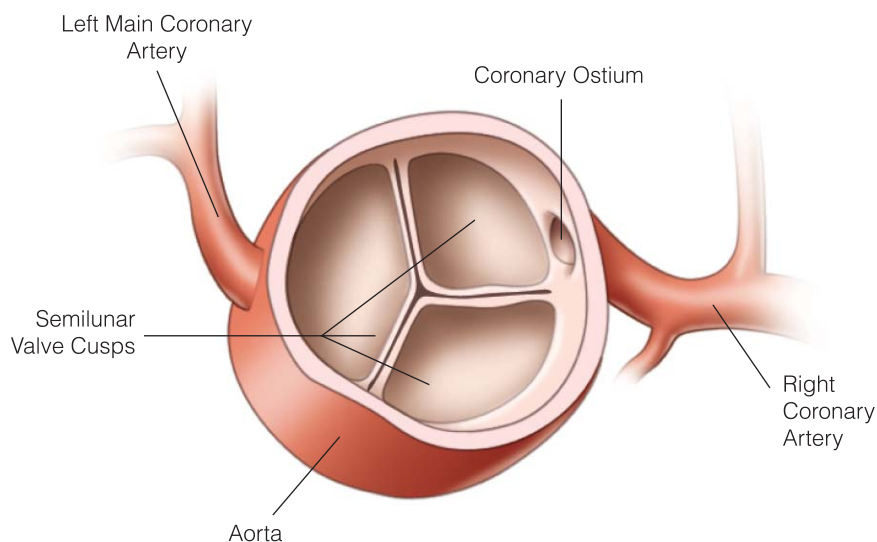


Figure 17 The aortic valve. This valve is composed of three semilunar valve cusps (also known as leaflets) and the aortic annulus.

of the septal leaflet spans the triangle of Koch, which contains the AV node. Any sutures placed in the annulus of the tricuspid valve are likely to injure the AV node; thus, in tricuspid valve replacement, the anchoring sutures are

placed in the leaflet tissue itself rather than the septal annulus. It is important that the septal leaflet not be completely resected in tricuspid valve replacements. For tricuspid repairs, only incomplete annuloplasty rings are used;

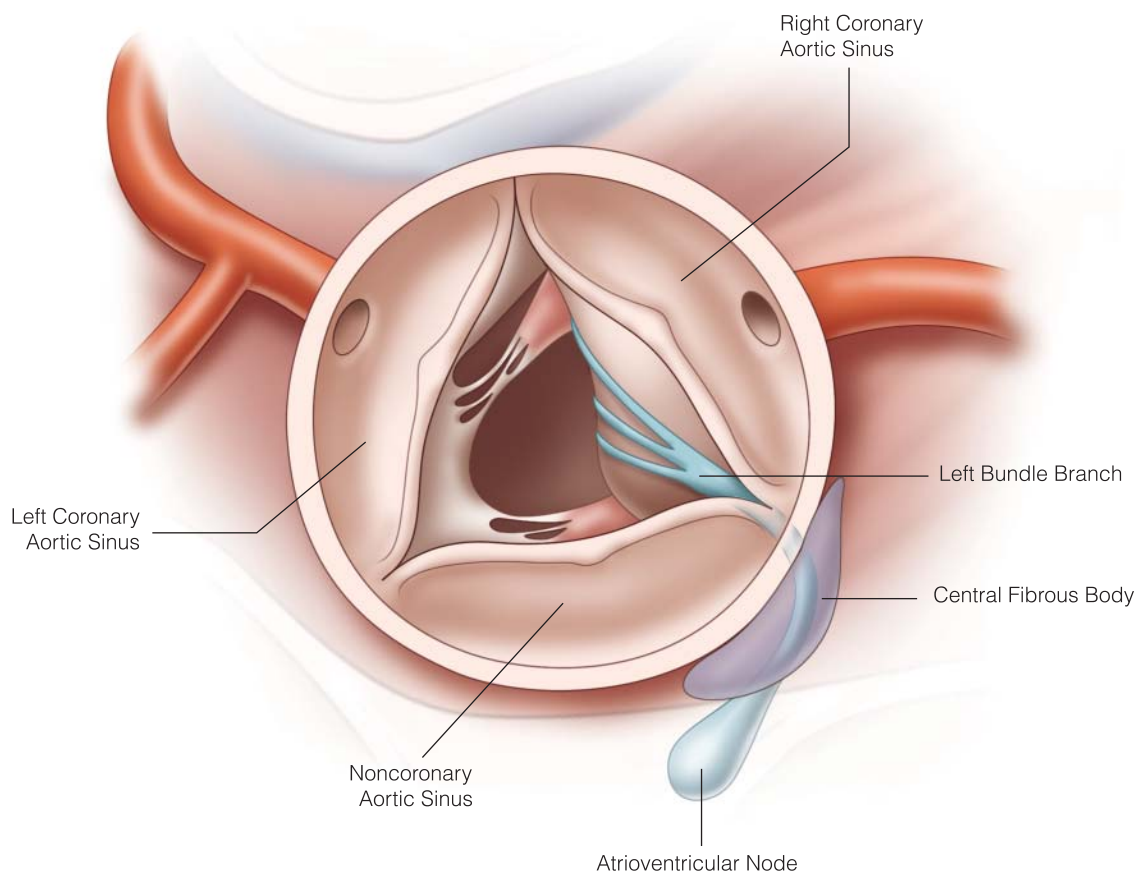


Figure 18 The aortic valve—surgeon's view and relation to surrounding cardiac structures.

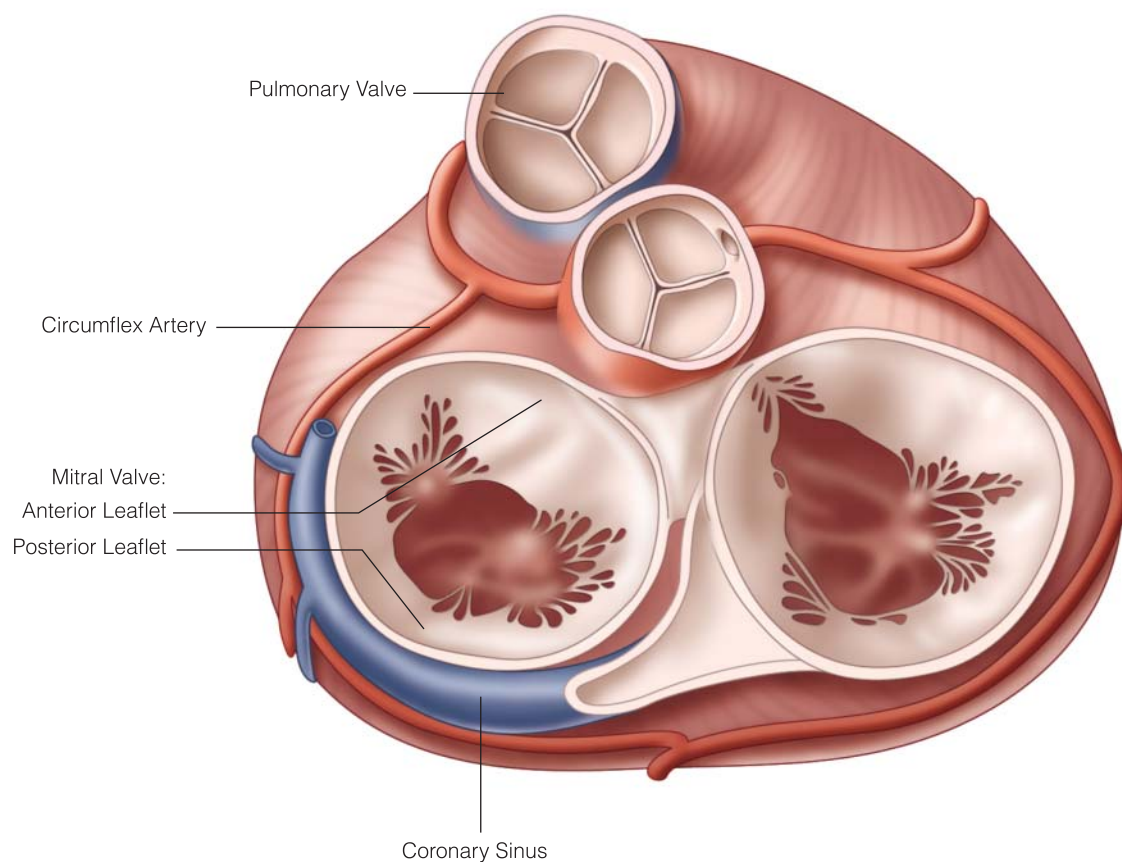


Figure 19 The mitral valve and its relation to surrounding cardiac structures.

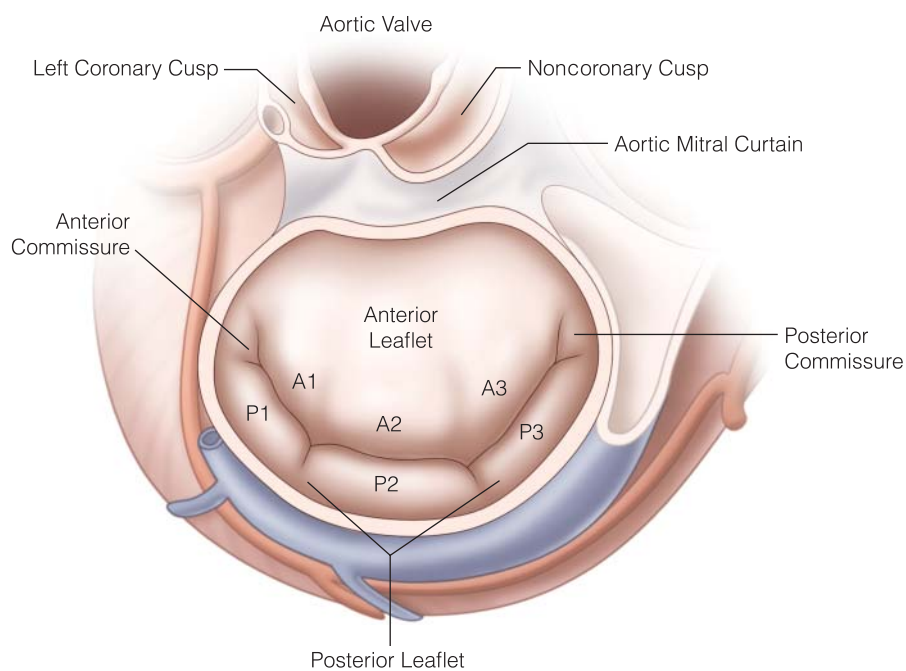


Figure 20 The mitral valve—surgeon's view, including segments of the valves and relation to the subaortic curtain.

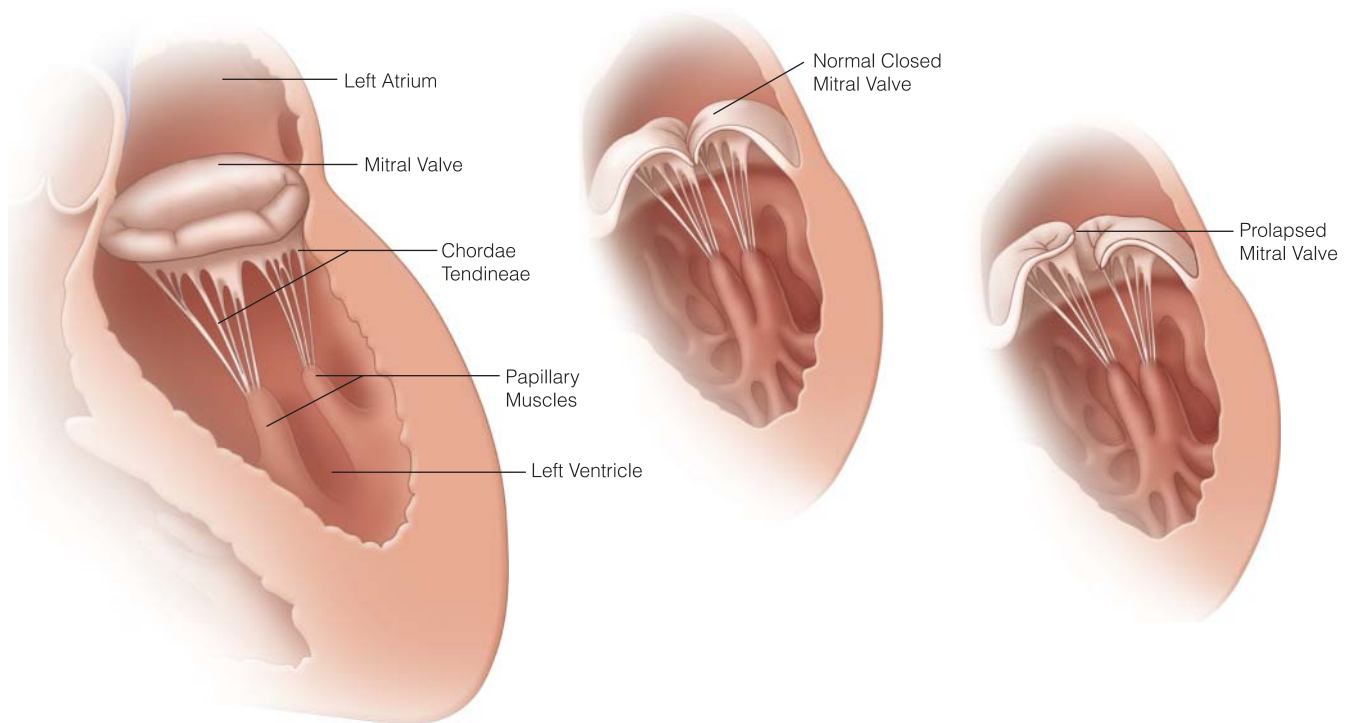


Figure 21 Attachment of the mitral valve leaflets with chordae and papillary muscles (front and side views). The entire mitral complex takes on the appearance of a parachute held by several chordae.

these rings are designed with a gap that spans the septal valve leaflet to avoid suture placement in the triangle of Koch.

The annular attachment of the tricuspid septal leaflet is more intimately associated with the mitral annulus and central fibrous tendon than the attachments of the anterior and posterior leaflets. Thus, the septal leaflet is less prone to stretching or deformation. This information is important in understanding the mechanism of tricuspid regurgitation due to annular dilation. Whereas the anterior leaflet partly extends over the membranous septum and is somewhat restricted to stretching, the posterior leaflet extends along the free wall of the right ventricle and is more prone to stretching in tricuspid annular dilation. Typically, for every unit increase in the basal circumference of the anterior leaflet, there is a two-unit increase in the attachment of the posterior leaflet, whereas the septal attachment remains constant. Thus, in sizing annuloplasty rings, the gap in the ring is chosen such that it corresponds to the width of the basal attachment of the septal leaflet because this component of the tricuspid valve is least altered by conditions that make annuloplasty necessary.

PULMONARY VALVE

The pulmonary valve guards the outlet of the right ventricle and is located away from the three other structural cardiac valves. The pulmonary valve, like the aortic valve, is a semilunar valve composed of three cusps. The cusps are located in left anterior, right anterior, and posterior orientations. As in the aortic valve, the cusps of the pulmonary valve are a derivation of the endocardial fold. The central

part of the leaflets is the lamina fibrosa, which is a condensation of collagenous tissues. The lamina fibrosa is of varying thickness but is typically more prominent at the edge and the base of the leaflet, where it merges with the pulmonary annulus. The nodulus Arantii and the sinus configuration of the pulmonary artery are very similar to those of the aortic valve. Except for differences in pressure-handling characteristics, the pulmonary valve is quite similar to the aortic valve. This remarkable similarity is of particular significance to surgeons because it makes the pulmonary valve usable as an autograft in the aortic position (Ross procedure). The relation of the base of the pulmonary valve and annulus to the ventricular septum is important because the first septal perforator from the LAD is closely related to this valve and can be injured during harvest of the valve for autograft purposes.

THEBESIAN VALVE

About 300 years ago, Adam Thebesius described the valve guarding the ostium of the coronary sinus, now known as the thebesian valve [see Figure 23]. Although it remained clinically insignificant for centuries, the development of innovations that require intervention via the coronary sinus has increased cardiologists' and surgeons' interest in this structure.¹² The thebesian valve is a remnant of the SA valves and can interfere with the cannulation of the coronary sinus for retrograde cardioplegia during cardiac surgery. Studies have shown that thebesian valves exist in anywhere between 70 to 80% of normal adult human hearts.^{13,14} These valves vary significantly in composition, ranging from membranous to muscular.¹⁵

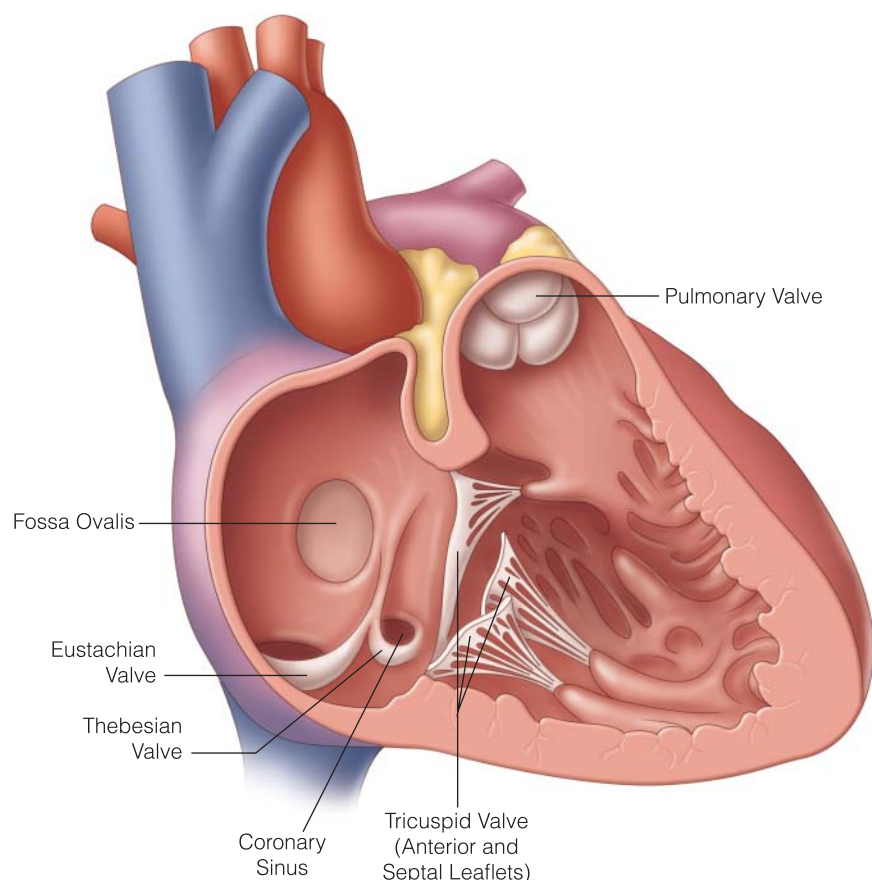


Figure 22 The relation of the tricuspid and pulmonary valves.

EUSTACHIAN VALVE

The eustachian valve is a fold of atrial remnant that guards the orifice of the inferior vena cava. It plays an important role in fetal circulation by acting as a baffle to direct returning oxygenated blood from the vena cava toward the atrial septum into the fetal systemic circulation. Typically, after birth, this valve reduces to a thin, nonfunctional ridge that is of no consequence. However, the eustachian valve occasionally remains prominent and is not reabsorbed, resulting in a persistent baffle.¹⁶ This may occasionally pose difficulties in deploying drainage cannulas in the inferior vena cava for cardiopulmonary bypass. Also, a prominent eustachian valve can be misidentified as the lower edge of an atrial septal defect and inadvertently included in the closure suture line. This may result in all venous return from the inferior vena cava being directed through the atrial septal defect into the systemic circulation, causing severe cyanosis.

Cardiac Valve Adjuncts

PAPILLARY MUSCLES

The left ventricle has two distinct papillary muscles that bear important clinical significance because of their involvement in acute myocardial infection and ischemia. The anterolateral papillary muscle arises in the free wall of the left ventricle that lies behind the costochondral

junctions, whereas the posteromedial papillary muscle arises from the inferior wall of the left ventricle, close to the ventricular septum. It should be noted that no papillary muscle arises from the septal area. The papillary muscles give out several chordae that fan out and attach to the mitral leaflets. Each papillary muscle contributes chordal attachments that span the corresponding commissure and anchor both the anterior and posterior leaflets. The papillary muscle–chordal complex connects the mitral leaflets and ventricular myocardium and functions in a symbiotic role for both structures. Although the complex tethers the mitral valve and prevents leaflets from prolapsing into the atrium, rendering the valve incompetent during high-pressure ventricular systolic forces, the complex also maintains the conical shape of the left ventricular chamber by anchoring it to the fibrous skeleton via the valves, which is essential for efficient ventricular contraction. The right ventricle has a prominent anterior papillary muscle that merges with the moderator band and anchors the anterior leaflet. Posterior to the moderator band are several small papillary muscles that tether the posterior and septal leaflets.

In acute myocardial infarction involving the inferior ventricular blood supply, the posterior papillary muscle can necrose and be avulsed off the attachment, resulting in an acutely incompetent mitral valve. This usually constitutes a surgical emergency that necessitates replacement of the mitral valve.

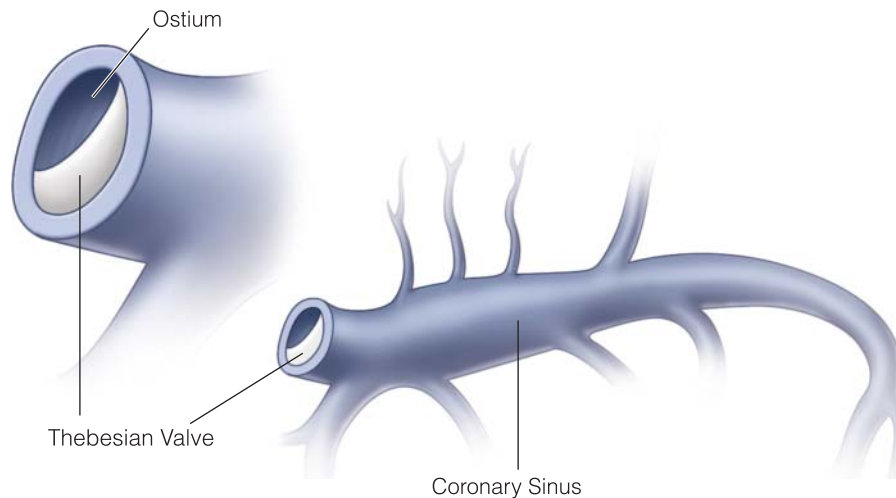


Figure 23 The thebesian valve, which guards the orifice of the coronary sinus.

CHORDAE TENDINAE

Chordae tendineae are collagenous cords that arise from the tip or apical third of the papillary muscle and are attached to some aspect of the leaflet.^{17,18} Chordae are classified as follows:

1. Fan-shaped chordae arise from the tips of papillary muscles, are flat, and fan out to the commissures and clefts.
2. Rough zone chordae are strong single chords attached to the free margin and the underside of the coapting surface of the leaflets. They are the chordae most commonly involved in chordal rupture and are a common cause of mitral regurgitation because they are subject to higher tensile forces.
3. Free-edge chordae are long, single chordae that attach only to the free edge of the leaflet at the midpoint of the scallops.
4. Deep chordae are attached to the undersurface of the leaflet in the clear zone.
5. Basal chordae are of variable shape and insert near the basal attachment of the leaflets. They play an important role in maintaining ventricular geometry and are spared in valve replacements.

AORTIC ROOT

Structure of the Aortic Root

Because of the close relation among the aortic valve, the aortic annulus, and foundation structures, the aortic root is considered a single entity with these various components: SOVs, sinotubular ridge, annulus fibrosus, aortic valve leaflets, ILTs, and coronary ostia [see Figure 24]. Each of these structures interacts significantly with the others, and together they are responsible for the performance of the aortic valve. Although one may consider the cusps alone to form the true aortic valve, the proper function of the semilunar cusps is heavily dependent on the integrity of the entire aortic root. By definition, the aortic root extends from the nadir of the hinge points of the valve cusps to the sinotubular junction. The aortic root has several key functions¹⁹:

- Supports the leaflets of the aortic valve
- Dynamically adapts to accommodate systolic efflux of blood from the left ventricle
- Directly influences the mechanism of leaflet function

The SOV, first described by Italian physician Antonio Maria Valsalva,²⁰ is bounded inferiorly by basal attachments of each cusp and is limited superiorly by the sinotubular ridge. The upper limit of the SOV extends more superiorly than the free cuspal border of the valve leaflets.^{21,22} The SOV has more collagen at its base than in the upper part and an increasing density of elastic lamellae superiorly. The coronary ostia originate at the superior aspect of the sinus. The SOV plays a functionally significant role in the valvular mechanism [see Aortic Valve: Closure Mechanism, below]. The midportion of the SOV can be twice the diameter of the ascending aorta, whereas the thickness is 50% that of the ascending aorta and 25% that of the sinotubular ridge. The sinotubular ridge is the circumferential thickening of the aortic wall at the junction between the sinusal and tubular portions of the aorta and is predominantly elastic. The elasticity of the sinotubular ridge allows a 16% increase in diameter when necessary and is manifested by splaying of the commissures during systole.²³ The annulus fibrosus is the collagenous condensation at the point of attachment of each leaflet; it forms the support structure of the aortic root and is the most important component of the fibrous skeleton. The annulus has the shape of a coronet rather than a circle. An imaginary circle connects the nadir points of the annulus fibrosus/semilunar attachments and is termed the “basal ring.” This ring serves as the proximal demarcation line between the LVOT and the aortic root.

The annulus fibrosus is a rigid structure and does not vary in dimension during different phases of the cardiac cycle. However, the annulus deforms significantly during ventricular contraction, with the basal aspect of the coronet remaining constant in shape, whereas the points of the coronet (commissure) move outward during systole. During systolic expansion, the sinotubular ridge, along with the commissural points, pulls the free edges of the cusp taut²⁴ to form a straight line. This ensures the laminar flow of blood and

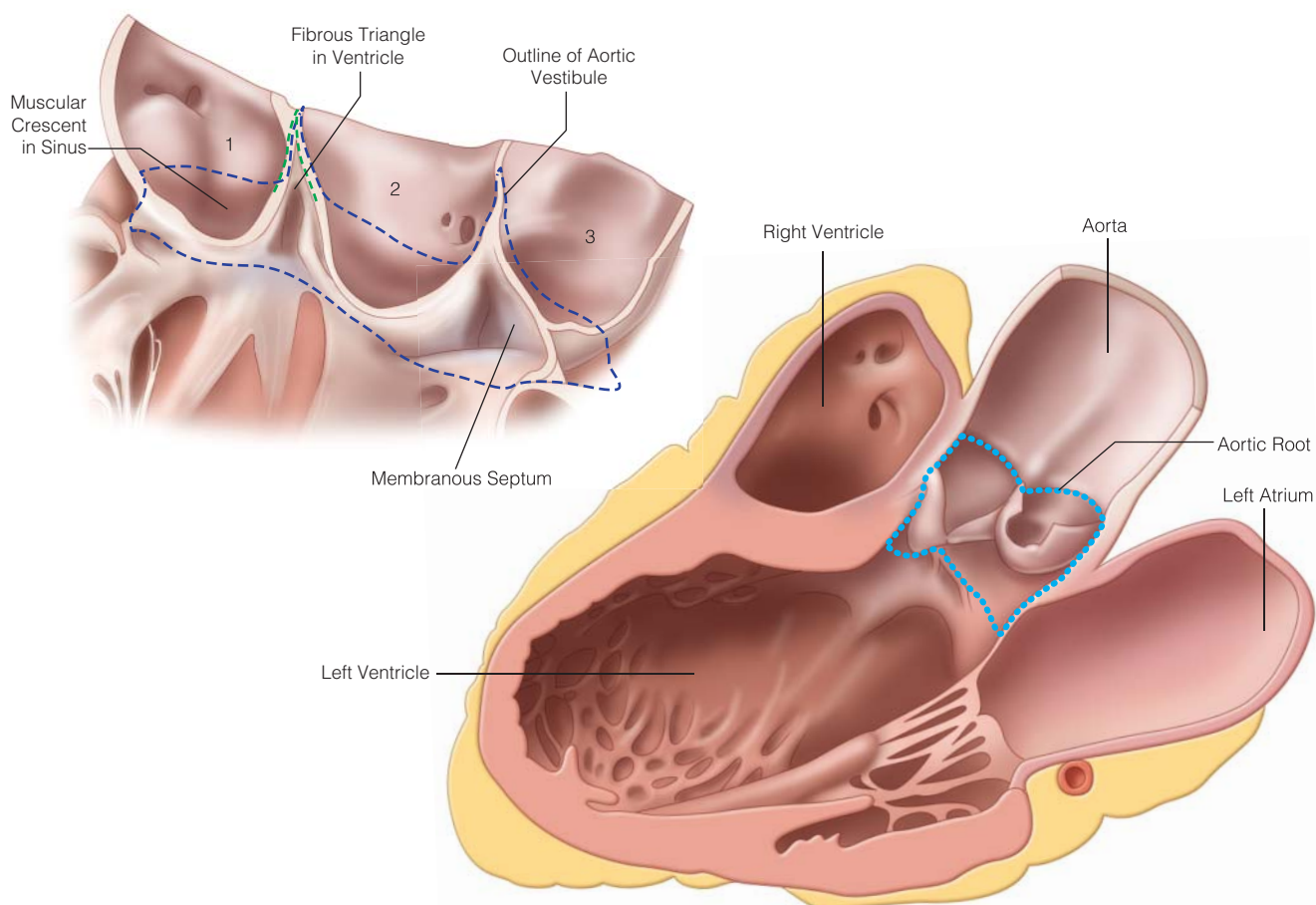


Figure 24 Structure of the aortic root. This longitudinal section shows the root's relation to surrounding structures.

helps create the sinusal vortex, which prevents apposition of the leaflets against the wall. Preventing leaflet apposition is important for valve closure and ensuring unimpeded coronary blood flow.

Dynamic Interaction of Aortic Root

Aortic valve: opening mechanism Contrary to the traditional belief that pressure from the ventricle forces the aortic valves to open passively, recent flow dynamic assays have shown that the opening of the aortic valve is an active process that begins even before the ejection of blood [see Figure 25].²⁵ Commissural displacement occurs just before ventricular ejection. This displacement, along with expansion of the sinotubular ridge, begins to pull the cusps of the aortic valve apart before enough ventricular pressure is generated to force them open. The ILTs play an important role in initiating commissural displacement before ventricular ejection commences.^{26,27} The ILTs are the layers of tissue between the commissures and are attached to the LVOT. An ILT is composed of circularly oriented layers of collagen and receives muscular attachments that may extend from the LVOT. The contraction of these muscle fibers initiates a tilting movement of the ILT outward when ventricular systole begins, well before enough intracavitary ventricular pressure is generated. Furthermore, the movement of blood against the inferior surface of the ILT further enhances the

outward displacement of the commissures that helps open the aortic valve leaflet. Root compliance contributes to aortic root dilation just before leaflet opening and thus helps pull closed leaflets apart, reducing friction at commissures [see Figure 26]. A minimal pressure gradient of approximately 2 mm is sufficient to spring leaflets open as systole is initiated. In a normal root, the effective valve orifice area progressively increases with an increase in gradient. This dynamic compliance is impaired in stiff or calcified roots. Aortic leaflet opening is thus a very controlled and complex process that is actively assisted by the commissure.

Aortic valve: closure mechanism The SOV plays an important role in initiating aortic valve closure. The sinus acts as a vortex generator. During systolic ejection, a small portion of the blood is diverted into the SOV and coronary ostia by the sinotubular ridge. This results in a laminar circular vortex of blood in the sinus that creates an equalizing and opposing pressure on the outer side of the valve cusps.²⁸ The valve cusp is thus floating in a zone of no pressure created by the opposing forces of the blood flowing in the luminal aspect of the aortic root and the vortex force on the sinusal aspect. This minimizes the valve stress on the leaflets during systole. As the systolic cycle progresses, the ejection velocity of the luminal blood diminishes, and the inward force of the vortex becomes unimpeded, forcing the valve

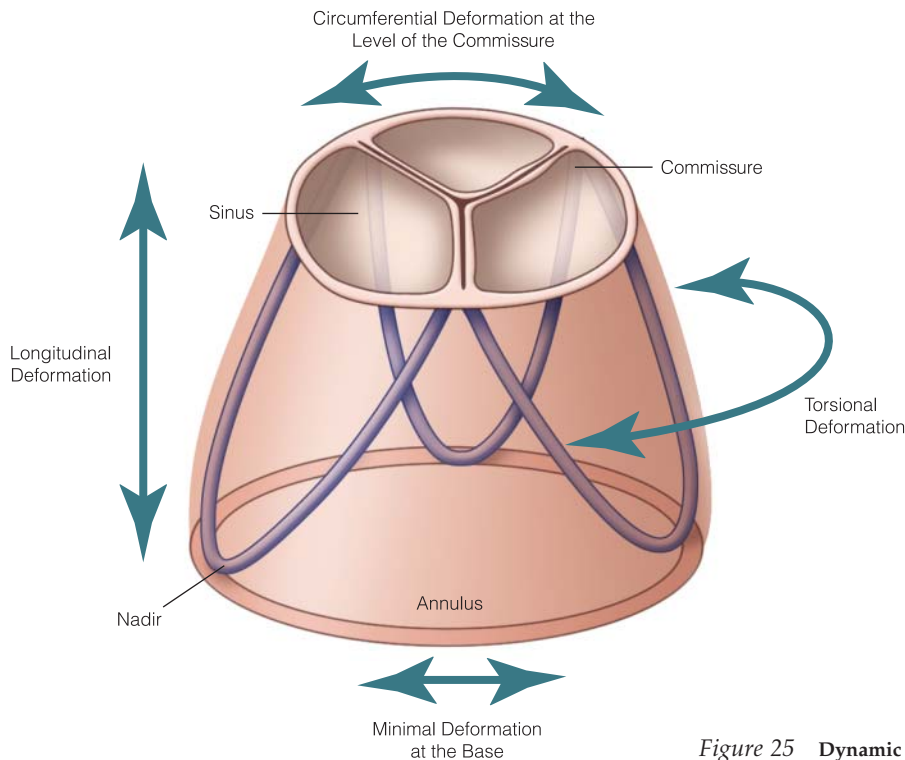


Figure 25 Dynamic interaction of the aortic root.

cuspid medially, thereby initiating closure. Typically, only 4% of blood volume regurgitates in normal aortas. When the SOV is calcified or absent (as in graft replacements of the aortic root), this mechanism is impaired, and as much as 25% of ejected volume must be captured by the leaflets to close the valve. Closing the valve is associated with significant leaflet cusp bending and shear, which could lead to accelerated degeneration.²⁹

As noted, there is a complex interaction of the various aspects of the aortic root that ensures a smooth laminar flow across the aortic valve. Any mechanism or disease process, such as calcification or replacement of the elastic tissue with a rigid structure (such as a prosthetic graft), could derange the active mechanism in aortic leaflet opening/closing, leading to higher shear stresses and accelerated valve degeneration.

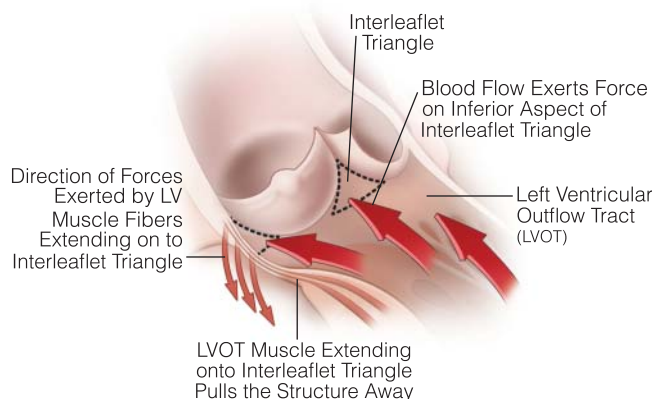


Figure 26 Mechanism of aortic valve leaflet opening. LV = left ventricular.

Cardiac Chambers

ATRIAL CHAMBERS AND APPENDAGE

The right atrium lies slightly anterior and to the right of the left atrium and forms the right heart border. The superior and inferior venae cavae open at the superior and inferior parts of the right atrium. The inner aspects of the right atrium contain a smooth posterior area derived from the sinus venosus remnant and a trabeculated anterior aspect derived from the true right atrium. The demarcation between the two embryologic components is marked internally by a vertical ridge known as the crista terminalis, which corresponds to a longitudinal groove on the outside, the sulcus terminalis. The right atrial appendage projects from the anterior aspect of the right atrium just below the entry of the superior vena cava and overlies the proximal RCA and the lateral aspect of the aorta.

VENTRICULAR CHAMBERS

Right Ventricle

The right ventricle is the most anterior chamber of the heart, and the convex anterior surface is separated from the chest wall only by the pericardium. This chamber is likely to be injured in penetrating wounds to the chest. The right ventricular wall is much thinner, varying between 3 and 5 mm in thickness. In cross section, the right ventricle is a crescent-shaped chamber into which the interventricular septum bulges [see Figure 27]. Internally, the right ventricle has an inflow tract guarded by the tricuspid valve. The chamber has numerous trabeculae, which are simply muscular ridges that meld with the papillary muscles. The moderator band, otherwise known as the septomarginal trabecula, is a prominent trabecula that extends from the anterior papillary

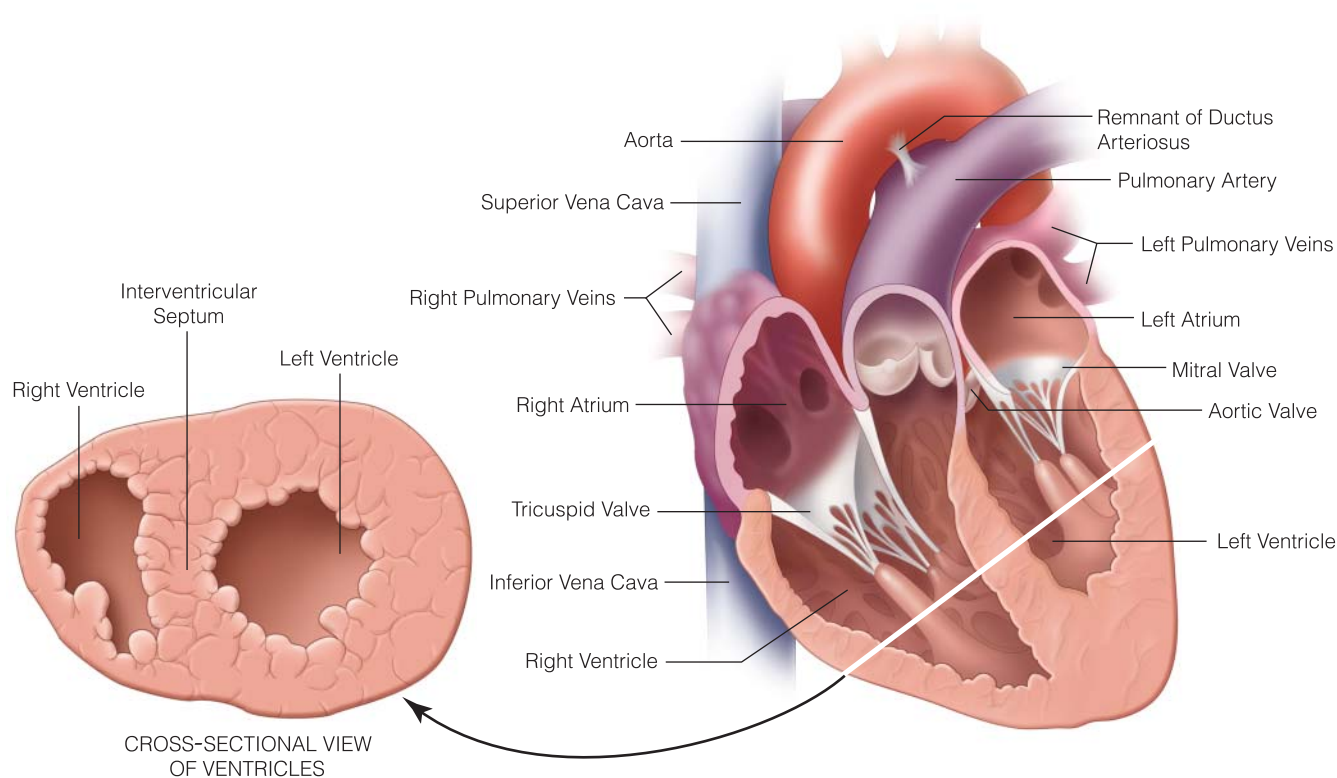


Figure 27 The ventricular chambers—cross-sectional and longitudinal cartoon showing the significant difference between the left and right ventricular chambers.

muscle to the septum and contains the right bundle branch. The outflow tract is known as the infundibulum and extends into the pulmonary orifice. The infundibulum is easily identified on the inside of the ventricular chamber at the level of the supraventricular crest. The infundibulum is a remnant of the bulbus cordis and maintains a foundation for the pulmonary annulus.

Left Ventricle

The left ventricle is a sturdy conical chamber that is three times thicker than the right ventricle. The left ventricle forms the left border of the heart. The base of the ventricle is formed by the left AV orifice and the LVOT. Both the left ventricular inflow and outflow tracts face the left ventricular apex, which efficiently directs blood flow toward the ventricular chamber. Transverse section of the left ventricle reveals a circular shape, unlike the crescent shape of the right ventricle. The inside of the left ventricular chamber has trabeculae similar to those in the right ventricle but much larger. The two papillary muscles form important landmarks within the left ventricle and have been described [see Papillary Muscles, *above*].

Intracardiac Structures

INTERATRIAL SEPTUM

The septal wall has more features and landmarks that are recognizable from the right side than from the left side [see Figure 28]. The fossa ovalis is the most prominent oval

depression in the lower part of the interatrial septum. The base of this depression is the remnant of the original septum primum. The limbus is the prominent superior and posterior margin of the fossa ovalis and marks the inferior border of the septum secundum. Occasionally, the limbus is not a complete fusion but has a slitlike opening that extends into the left atrium; this opening is known as a patent foramen ovale. The prevalence of patent foramen ovale is as high as 30% in adults. Although usually of no clinical consequence, it is believed to occasionally allow thrombus from the deep veins that extend into the right atrium to migrate into the left-sided circulation, causing a “paradoxical embolus.”

Anteroinferior to the fossa ovalis lies the right AV orifice. At this junction is a triangular zone known as the triangle of Koch. The septal attachment of the tricuspid leaflet, the coronary sinus orifice, and the tendon of Todaro—a subendocardial ridge that extends from the edge of the right fibrous trigone to the inferior vena cava orifice—bound this triangle. This triangle contains the AV node and the proximal aspect of the bundle of His.

INTERVENTRICULAR SEPTUM

The interventricular septum is a curved structure that bows into the right ventricular cavity. The structure of the interventricular septum is diverse, varying from membranous to muscular in different locations. Therefore, ventricular septal defects are broadly classified (according to their location) as perimembranous or muscular. The left ventricular side is quite smooth, with fine trabeculations, whereas

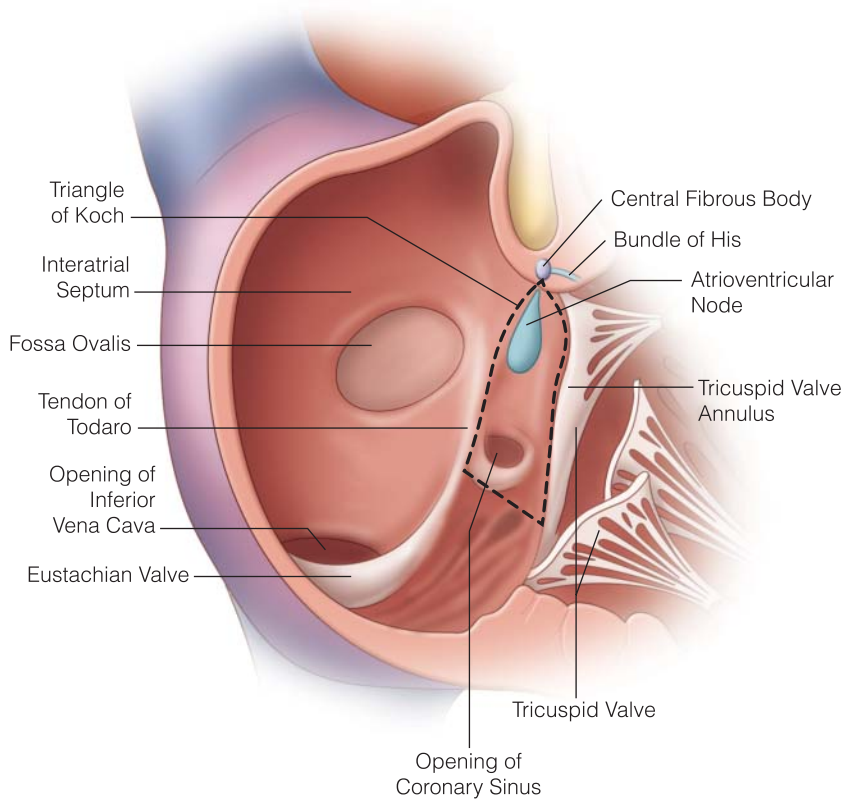


Figure 28 The interatrial septum. The figure depicts the fossa ovalis and its relation to surrounding structures. One of these, the triangle of Koch, is an important landmark to recognize because the atrioventricular node is located at the apex of this triangle.

the right size of the muscular septum is heavily trabeculated. The left side of the interventricular muscular septum has a smooth outlet portion that is devoid of trabeculations. The trabeculated sinus portion below the mitral valve is the inlet septum. The A3 component of the mitral valve, the right aortic cusp, and part of the noncoronary aortic cusp bear attachments to the left side of the interventricular septum. The septal aspects of the right ventricle are classified as the inlet, trabecular, and outlet portions. The inlet and trabecular portions are similar to the left ventricular surface. However, the outlet septum has three components, the conal or infundibular septum being the most prominent. The conal septum separates the pulmonary valve from the tricuspid and aortic valves. The infundibulum extends onto the free right ventricular wall, forming the parietal band, most commonly referred to as the crista supraventricularis because it extends above the ventricles. Defects in this portion of the ventricular septum are called supracristal ventricular septal defects [see Figure 29].

The membranous septum is the fibrous aspect of the septum that separates the LVOT from the right ventricle and right atrium. As described before, the attachment of the anterior and septal leaflets of the tricuspid valve extends onto the membranous septum, separating it into a ventricular and atrial component on the right side. The membranous septum has an interventricular and an AV component.

The AV septum is a distinct area of the cardiac septum that separates the left ventricle from the right atrium. This separation occurs because the septal attachment of the mitral valve is shifted more toward the atrial chamber than

the tricuspid valve. This septum has both a membranous and a muscular component, and the AV node lies in the junction between the two components. The AV septum is located within the triangle of Koch.

The Pericardium

The pericardium consists of two opposing serous lined surfaces separated by a fluid layer that allows unimpeded movement of the heart during contractions [see Figure 30]. The outer layer is the fibrous pericardium, and the inner layer is the serous pericardium. The outer, fibrous layer is attached to the tendinous portion of the diaphragm inferiorly, whereas the superior aspect is continuous with the great vessels of the heart. The fibrous pericardium is separated from the chest wall by the anteromedial aspects of both lungs, except for a small portion at the left of the left fourth and fifth costochondral junctions. All major vessels entering or leaving the heart, except the inferior vena cava, receive investing extensions from the fibrous pericardium.

The serous pericardium has parietal and visceral components. The parietal lining is closely apposed to the inner surface of the fibrous pericardium, whereas the visceral lining is otherwise known as the epicardium and closely blends with the epicardial musculature of the heart. The complex investment of the serous pericardium around the great vessels and the surface of the heart results in the formation of two important recesses in the pericardial cavity. One is the oblique sinus, which extends posteriorly and leftward

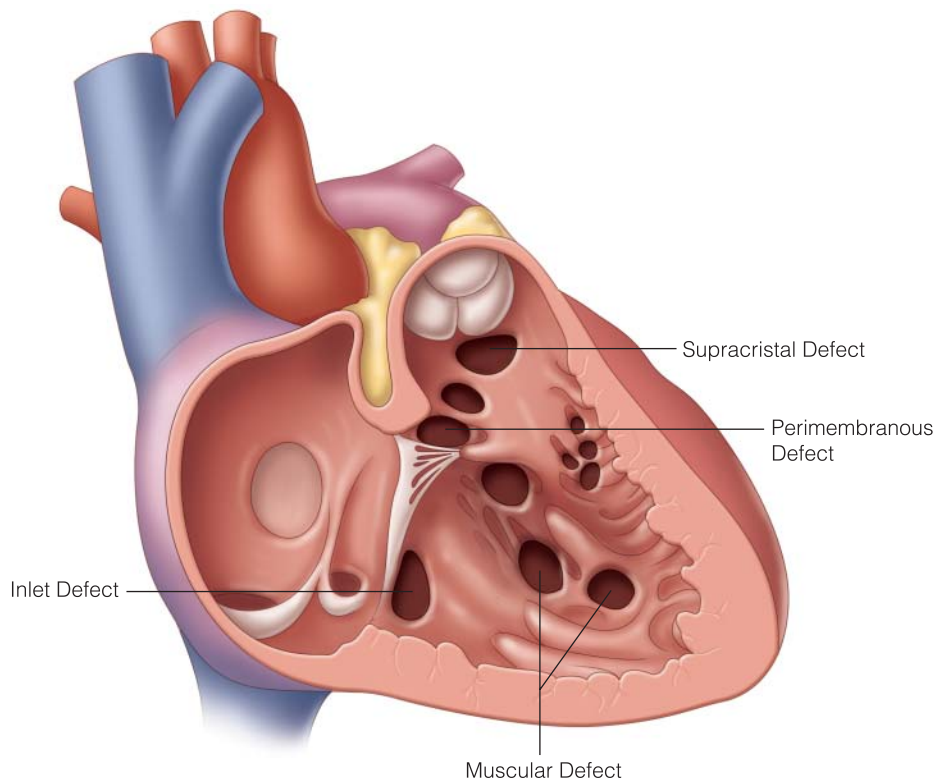


Figure 29 The interventricular septum. The figure depicts the inlet, muscular, perimembranous, and supracristal types of ventricular septal defect.

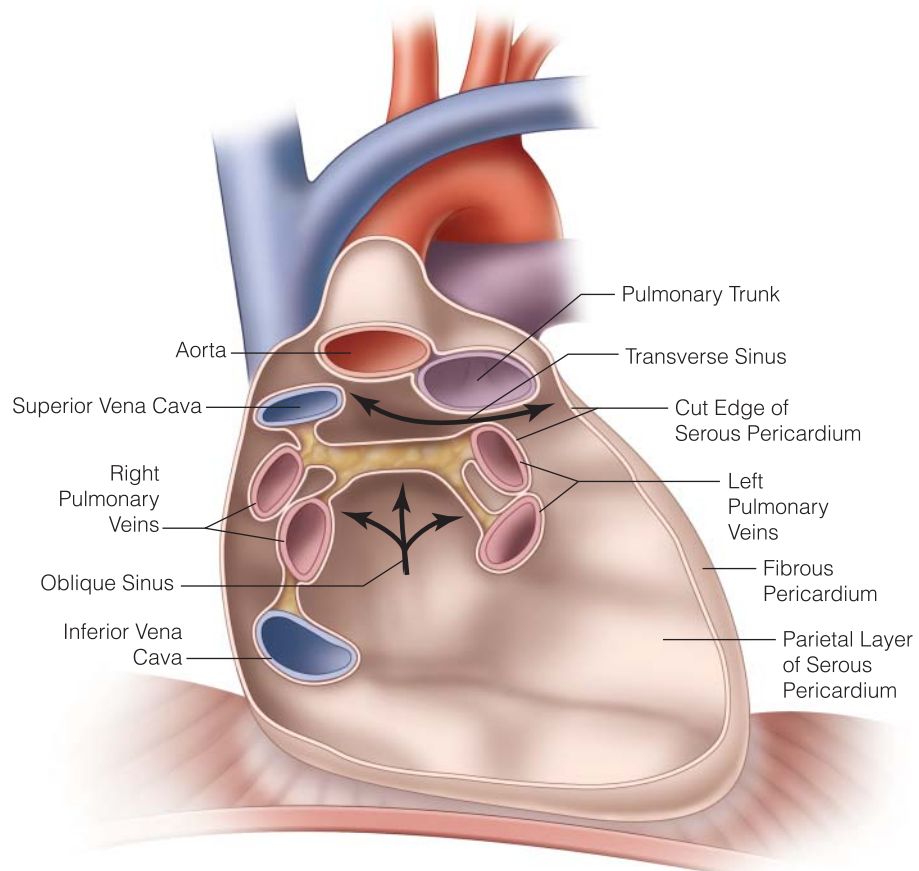


Figure 30 Drawing of the structure of the heart and its major vessels. The pericardium forms an investing layer around the heart and has two distinct recesses that function as important landmarks for surgeons: the transverse and oblique sinuses.

from the left ventricular apex behind the AV groove and posterior wall of the left atrium and terminates at the reflection between the left and right superior pulmonary veins. The other important recess is the transverse sinus, which extends behind the aortic and pulmonary trunks and lies in front of the left and right atria and the superior vena cava. These two sinuses provide landmarks and guidance during the placement of ablation devices for the surgical treatment of atrial fibrillation.

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5 THE ENDOCRINE SYSTEM: PITUITARY AND ADRENAL GLANDS

Haggi Mazeh, MD, Iddo Paldor, MD, and Herbert Chen, MD, FACS

Pituitary Gland

The pituitary gland, or hypophysis, is a unique endocrine-functioning part of the central nervous system (CNS). Located inside the sella turcica, it is separated from the rest of the CNS by its physiologic location outside the blood-brain barrier. The function of the gland is regulated by higher-order nervous systems, mainly the hypothalamus, which has synaptic and hormonal connections to the pituitary gland. This regulation may be a positive (i.e., stimulatory) effect, a negative (i.e., inhibitory) effect, or both. The pituitary gland governs hormonal secretion from all endocrine organs in the body and has elaborate feedback loops from all of these organs.

The hypophysis is, in fact, a combination of two separate hormone-secreting glands. These glands differ in embryologic development, in the origin of the hormones secreted, in function, and in the form of trigger for hormonal secretion.

EMBRYOLOGY AND DEVELOPMENT

The posterior hypophysis, or neurohypophysis, is derived embryologically from downward evagination of the neuroectoderm in the floor of the third ventricle. It remains functionally an extension of the hypothalamus, which lies superior to it, and the hormones secreted from it are synthesized in the neurons of the hypothalamus. These hormones—oxytocin and antidiuretic hormone (ADH)—are then transferred through axonal transport to the posterior hypophysis, where they are secreted into the systemic blood circulation. Therefore, the hormonal function of the neurohypophysis is not part of the portal system, described later in this chapter.

The anterior hypophysis, or the adenohypophysis, is derived embryologically from the epithelial ectoderm of the oropharynx, known as the stomodeum. This evagination occurs in the fourth week of development to form the Rathke pouch. During the sixth week of development, the anterior hypophysis develops to be anatomically separated from the oropharynx (the other major derivation of the same epithelial ectoderm) by the bones in the anterior skull base, mainly the sphenoid bone. The mature derivatives of the Rathke pouch are the anterior lobe of the hypophysis, the pars intermedia, and the pars tuberalis.^{1,2}

ANATOMY

The pituitary gland lies at the base of the skull, in the medial part of the middle fossa [see *Figure 1*]. It is encompassed by the bony sella turcica, which is made up of the tuberculum sellae in the anterior aspect and the dorsum sellae in the posterior aspect.

The tuberculum sellae is the posteromedial part of the lesser wing of the sphenoid bone. Hanging over the pituitary fossa in its anterolateral part are the paired anterior clinoid processes.

The dorsum sellae, the posterior bony part of the sella turcica, is the anterosuperior continuation of the clivus. The clivus is the posterior part of the sphenoid bone. Hanging over the pituitary fossa in its posterolateral aspect are the paired posterior clinoid processes.

The pituitary gland is separated superiorly by the sellar diaphragm, a dural fold that is pierced by the pituitary stalk. In close relation to the pituitary gland are the cavernous sinus on each lateral aspect, the sellar diaphragm, and the optic chiasm above it.

The pituitary gland is, in fact, an inferior protrusion of the hypothalamus, which is part of the diencephalon. It receives both neural and hormonal regulatory inputs from the hypothalamus. The pituitary gland is also subject to regulation by inputs from other areas of the brain, including autonomic, limbic, and even paracrine inputs from other cells within the gland itself.^{3,4}

The adenohypophysis is the rostral part of the gland. It is made of three lobes. The pars distalis, the largest part of the gland, is in the anterior part of the gland. The posterior pars tuberalis is the part of the adenohypophysis located around the entry zone and the inferior part of the infundibular stalk. The pars intermedia is a thin epithelial layer separating the pars tuberalis from the pars distalis.

The neurohypophysis is the posterior part of the gland. It does not function as a regular hormone-secreting gland in that the stimulus for release of its hormones is not an endocrine stimulus. The neurohypophysis is made of axonal projections arising from the paraventricular and supraoptic nuclei of the hypothalamus. The neurohypophysis is made of two parts: the pars nervosa and the infundibular stalk. The pars nervosa is the main functional part of the neurohypophysis. It is where the projections from the hypothalamus terminate and release their hormonal secretions into the general circulation via capillaries of the hypophyseal circulation, described later in this chapter. This secretion is not part of the pituitary portal system. Other than these axons, the pars nervosa is composed of pituicytes, which are glial cells that closely resemble the astrocytes of other parts of the CNS. The infundibular stalk is the site of entry for the hypothalamic projections and forms the neural (rather than portal) bridge between the hypothalamus and the hypophysis.⁵

The two parts of the hypophysis—the neurohypophysis and the adenohypophysis—are separated by a thin layer known as the CNS skin. Some refer to a middle lobe, which has significant roles in other species. The main function of the middle, or intermediate, lobe in humans is the secretion of melanocyte-stimulating hormone, as well as secretion of

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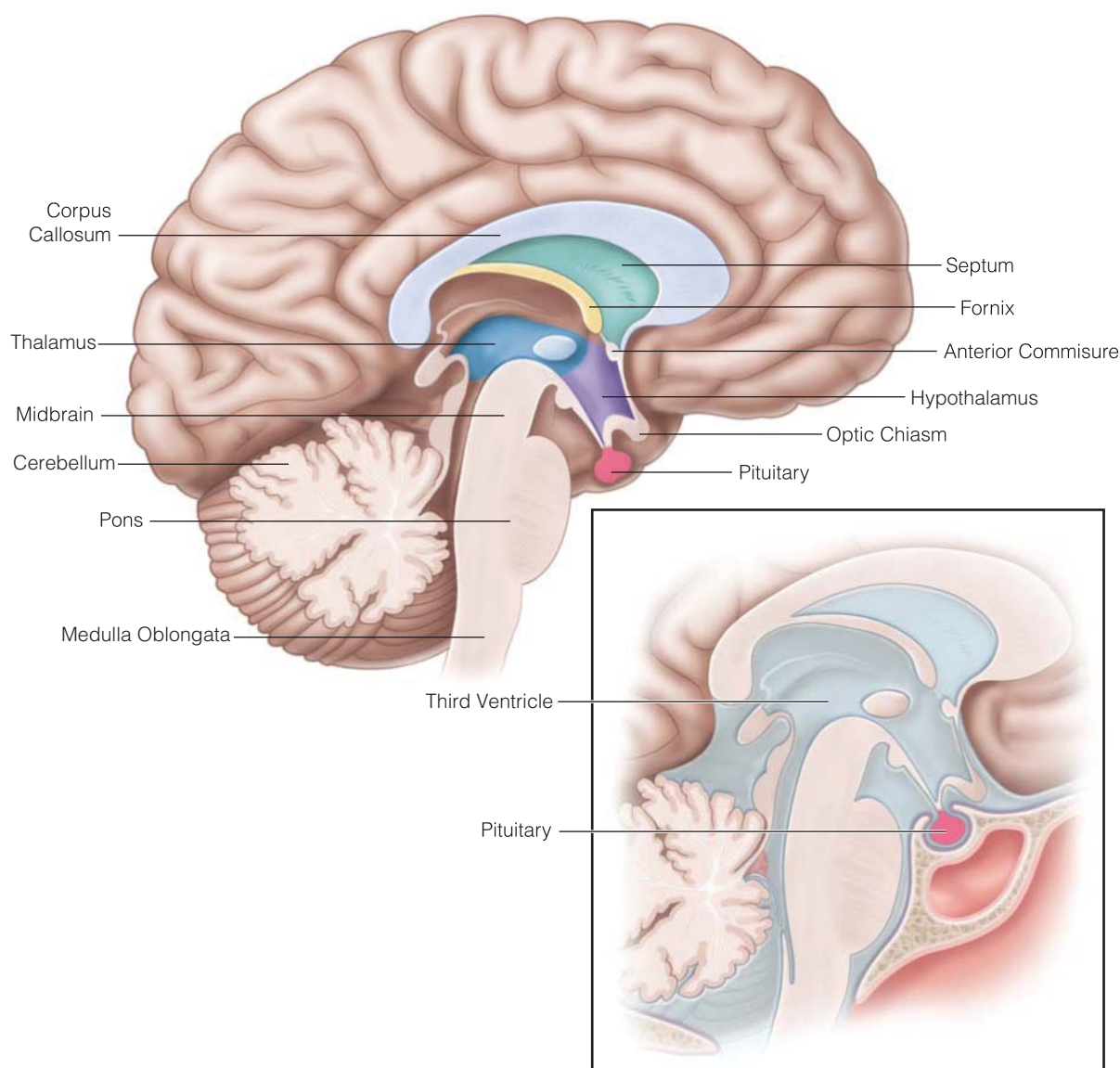


Figure 1 (a and b) Midsagittal view of the brain. Note the close anatomic relation of the pituitary gland to the overlying hypothalamus, third ventricle, and optic chiasm.

pro-opiomelanocortin (POMC). There is little known clinical significance of this lobe in humans. POMC serves as a precursor for some of the other hormones in other lobes of the hypophysis. Some refer to this lobe as part of the anterior lobe.⁶

Blood Supply and the Portal System

The blood supply to the pituitary gland is derived mainly from the internal carotid artery (ICA) and its main branches [see Figure 2].

The inferior hypophyseal artery arises from the ICA in its course through the cavernous sinus (i.e., it is a branch of the cavernous ICA). The inferior hypophyseal artery supplies the lower part of the infundibulum and the majority of the neurohypophysis.

The superior hypophyseal artery gives rise to the pituitary portal system, one of only two such systems in the human

body. This artery arises from the first part of the supraclinoid ICA. It supplies the lower part of the hypothalamus, where it receives projections from neurosecretory cells in the parvicellular portion of the hypothalamus. This first capillary bed occurs in the anterior part of the infundibulum, known as the median eminence. These capillaries are the site of presentation of hypothalamic neurosecretory factors, which serve as modulators of hormonal release. After receiving these factors, the capillaries reemerge as long portal veins, which descend along the anterior aspect of the pituitary stalk to reach the pars distalis in the anterior hypophysis. In this area, the long portal veins give rise to a second capillary bed, which supplies the anterior hypophysis. It is through this capillary bed that the regulatory hypothalamic hormonal inputs to the adenohypophysis are supplied.⁷

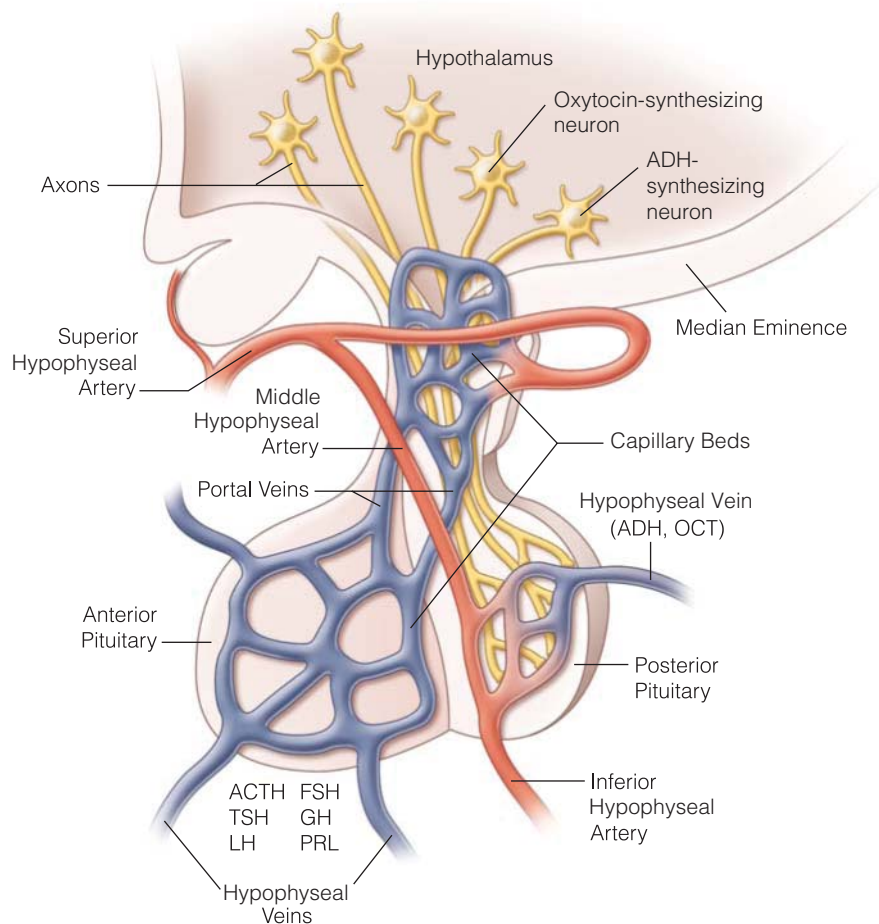


Figure 2 The pituitary blood supply, venous drainage, and portal system. ACTH = adrenocorticotrophic hormone; ADH = antidiuretic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; OCT = oxytocin; PRL = prolactin; TSH = thyroid-stimulating hormone.

There are other, smaller arteries supplying the gland. The infundibular artery arises from the posterior communicating artery.⁸ On the anterior aspect, the prechiasmal artery arises from the ophthalmic artery.

The capsular artery and the artery to the inferior cavernous sinus arise from the cavernous part of the ICA. These arteries anastomose with each other and create a vascular network supplying the pituitary gland. There are two arterial circles surrounding the gland: the circuminfundibular anastomosis incorporates the arteries from above the pituitary, that is, the superior hypophyseal, infundibular, and prechiasmal arteries, and the inferior hypophyseal arterial circle is created by the inferior hypophyseal artery, the capsular artery, and the artery to the inferior cavernous sinus.

The part of venous drainage through the long portal veins, part of the portal system, has been described earlier. Venous drainage of the anterior pituitary gland is through the short portal and adenohypophyseal veins. Drainage of the posterior pituitary is through the neurohypophyseal veins. Both of these venous systems drain to form the common lateral hypophyseal veins, which drain into the cavernous sinus.

NORMAL PHYSIOLOGY

Neurohypophysis

The endocrine function of the hypophysis is governed by many inputs from higher-order neuronal elements [see Figure 3]. The most significant modulator of this hormonal secretion is the hypothalamus. The neurohypophysis secretes two hormones. Oxytocin is involved in uterine contractions and other childbearing and breast-feeding functions. ADH is involved in modulation of water retention and blood pressure. These hormones are synthesized in hypothalamic nuclei and released in the neurohypophysis by axonal projections from these hypothalamic nuclei.⁹

The adenohypophysis secretes six hormones, which are discussed in detail in the following sections. In general terms, three of these hormones are released primarily in response to hypothalamic stimulation: adrenocorticotrophic hormone (ACTH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Two adenohypophysary hormones are subject to dual hypothalamic modulation. That is, they are under both hypothalamic stimulation and hypothalamic inhibition. These are the thyroid-stimulating hormone (TSH) and growth hormone (GH). The only pituitary

	Hypothalamic Hormone	Control	Pituitary Cell	Pituitary Hormone	Target Organ	Feedback Hormone	Action
Anterior Pituitary	Prolactin Release Inhibitory Factors (PIFs)*	⊖	Lactotrophs	Prolactin (PRL)	♂ ? ♀ Breast → ?		Lactation
	Thyrotropin-Releasing Hormone (TRH)	⊕	Thyrotrophs	Thyrotropin (Thyroid-Stimulating Hormone) (TSH)	Thyroid → T ₃ T ₄		Protein Synthesis, Thermogenesis
	Somato- statin (SRIH)	⊖	Somatotrophs	Growth Hormone (GH) (Somatotropin)	Epiphyses of Long Bones		Chondrocyte Proliferation
	Growth Hormone-Releasing Hormone (GH-RH)	⊕			Liver and Other Tissues → Insulinlike Growth Factor-1 (IGF-1)		Cell Proliferation, Insulin Antagonism
	Corticotropin-Releasing Hormone (CRH)	⊕	Corticotrophs	Corticotropin (Adrenocorticotrophic Hormone) (ACTH)	Adrenal → Cortisol		Stress Response, Homeostasis
	Gonadotropin-Releasing Hormone (GnRH)	⊕	Gonadotrophs	Luteinizing Hormone (LH) Follicle-Stimulating Hormone (FSH)	Gonads → ♂ Testosterone ♀ Estradiol		Secondary Sex Characteristics, Germ Cell Function

*Dopamine is the main PIF

Figure 3 Summary of pituitary hormones and their main actions.

hormone that is primarily under hypothalamic inhibition is prolactin (PRL).¹⁰

Oxytocin

Oxytocin is a nonapeptide hormone produced in the paraventricular and supraoptic nuclei of the hypothalamus. The hormone is transported to nerve endings in the neurohypophysis and is secreted in response to stimuli originating in the uterus and mammary glands. The main functions of this hormone are promotion of breast-feeding and initiation of uterine contractions during labor. In the female mammary glands, oxytocin acts to initiate the “let-down” reflex, causing milk to be secreted into the subareolar sinuses and from there via the mammary ducts to the nipple.¹¹

Oxytocin also binds to specific oxytocin receptors in the uterus, causing both uterine contractions and cervical dilatation during the second and third phases of labor. Due to this action, many women experience uterine contractions during the first few weeks of lactation.

Oxytocin has an unclear role in the sexual response. The hormone plasma levels have been shown to rise during the human orgasm in men and women. Other data suggest that

this increase in plasma levels occurs throughout sexual arousal, not specifically during the human orgasm. Some women also describe sexual arousal during lactation.

The production of oxytocin is upregulated in situations concerning pregnancy, lactation, and menstrual cycles. It is produced from its precursor along with the neurophysin-1 protein, which serves as a carrier for the hormone itself. The hormone is carried to the posterior hypophysis at a slow rate, with a lag time between production and secretion of about half a day.¹²

Uterine contractions are enhanced by oxytocin secretion. This secretion, in turn, augments further contractions. Thus, the main feedback loop involved in oxytocin release is a positive feedback.

When suction is applied on the female nipple, and at times during sexual intercourse, the magnocellular neurons in the hypothalamus are stimulated, and a pulsatile release of oxytocin is started. The stimuli for this release are elaborate, and other, higher-function neurologic stimuli may also play a role in it, such as sexual excitation and anticipation and recollection of breast-feeding. The main stimulatory neurotransmitter involved in oxytocin secretion is acetylcholine.

Antidiuretic Hormone

ADH, also known as arginine-vasopressin, is a nanopeptide hormone synthesized in the supraoptic nucleus of the hypothalamus. As described for oxytocin, the hormone is transferred through axonal transport to the neurohypophysis, where secretion into the systemic circulation takes place.

The stimuli for secretion of this hormone are mediated by baroreceptors, mainly in the left atrium, aortic arch, and carotid sinus. These receptors are sensitive to changes in blood pressure. Further inputs are received from sensors of plasma osmolality throughout the body, but mainly in the supraoptic and paraventricular nuclei in the hypothalamus. A third stimulus is deficiency in glucocorticoid levels, whether central (originating from lowered ACTH or corticotropin-releasing hormone [CRH] levels; see later in this chapter) or peripheral (originating from adrenal hyposecretion, e.g., Addison disease). This elaborate sensory input facilitates both the antidiuretic and vasoconstricting actions of arginine-vasopressin.

The effects of ADH are due to binding of the hormone to specific target cell membrane-bound receptors. Its effect on the muscularis mucosa cells of arteries throughout the body is a strong vasoconstricting effect. Its effect on the distal renal tubular cells is an increase in the permeability of these tubules to water, thus increasing water reabsorption and concentration of urine. This, in turn, results in a larger effective circulating plasma volume.

Adenohypophysis

The adenohypophysis secretes six hormones: thyrotropin, or TSH; corticotropin, or ACTH; GH; the two gonadotropins, FSH and LH; and PRL. These hormones maintain homeostasis through their action on the hormone-secreting organs of the thyroid, adrenal cortex, and gonads and their various actions on bone, kidney, and breast.

Thyroid-Stimulating Hormone

Thyrotropin-releasing hormone (TRH) is synthesized in the hypothalamus and released into the portal system. It acts on thyrotroph cells in the anterior hypophysis, causing the release of TSH. TSH acts on follicle cells in the thyroid gland and stimulates them to secrete both triiodothyronine (T_3) and thyroxine (T_4). The effect of TSH on the follicle cells is through all stages of hormonal release, that is, upregulation of hormone production, upregulation of hormone maturation, and a stimulant effect on hormone release.¹³

Negative feedback is exerted through thyroid hormone receptors in both the hypothalamus and the anterior hypophysis, which inhibit TRH and TSH secretion, respectively. A second inhibiting effect on TSH release is through the action of somatostatin, a hormone released from the hypothalamus that inhibits TSH release. Thus, TSH secretion is under dual hypothalamic control, both an inhibitory and a stimulatory effect.¹⁴

Growth Hormone

GH, or somatotrophin, is a 191-amino acid polypeptide that maintains normal growth through elaborate mechanisms of action. Its main action is on bone, causing bone

growth, elongation, and synthesis of cartilage material. Its secondary action is that of a hyperglycemic agent, stipulated to bring about availability of building blocks for growth and development. It has glucose-secreting effects on muscle and adipose tissue. It has a glucose-elevating effect on the liver, both by induction of glycogenolysis and by stimulating gluconeogenesis.

The secretion of GH is pulsatile, with two daily peaks in plasma levels.

Growth hormone-releasing hormone (GHRH), or somatotrophin, is synthesized in the arcuate nucleus of the hypothalamus and secreted into the portal circulation. It binds to receptors on the somatotroph cells in the anterior hypophysis and stimulates the release of GH from these cells.

Different cells in the arcuate nucleus synthesize a second hormone, called somatostatin. This hormone is the main hormone exerting negative feedback on the production and release of GH. Somatostatin release is mediated by many feedback loops from the body, specifically the sensing of hyperglycemia in the blood circulation. The main induction of somatostatin secretion is by insulinlike growth factor-1 (IGF-1), secreted and released by the liver.¹⁵

Gonadotropins: LH and FSH

LH and FSH are glycoproteins secreted by the gonadotroph cells of the anterior hypophysis. Their action is through the release of sex hormones from the gonads—the ovaries in females and the testes in males. FSH binds to specific receptors on the granulosa cells in the ovary. Its main action is the stimulation of germ cell maturation. Specifically, this refers to initiation of the ovulatory cycle, induction of follicular maturation, and selection of the most suitable follicle for development and ovulation. In males, FSH stimulates testicular Sertoli cells to secrete inhibin, which has a paracrine stimulatory effect on spermatogenesis and sperm maturation. It also has feedback effects (see below) on the hypophysis and hypothalamus.

LH binds to specific gonadotropin receptors and stimulates ovulation in females and the production of testosterone in males. In females, it binds to receptors on the follicle and stimulates the production and release of estrogen, eventually leading to the LH surge and to ovulation. Moreover, LH stimulates the maturation of the remaining follicle to a corpus luteum and the hormonal support for the possible zygote implantation in the uterus during the luteal phase. In males, LH exerts its main action on Leydig cells, which release testosterone in response to LH stimulation. This hormone has a stimulatory effect on spermatogenesis and sperm maturation.

The main stimulus for gonadotropin secretion is by the stimulatory effect of the hypothalamic gonadotropin-releasing hormone (GnRH). This hormone is secreted in a circulatory manner, with rhythms of secretion every 90 minutes.¹⁵

Feedback loops operating on the release of gonadotropins are simpler in males than in females. In males, the main feedback loop is the negative feedback effect of sex hormones on the hypothalamic release of GnRH and the pituitary release of gonadotropins. Apart from the direct effect of sex hormones, the inhibin-FSH negative feedback

loop is also significant in males. As already mentioned, FSH stimulates inhibin secretion from the Sertoli cells in the testes. Inhibin inhibits both FSH biosynthesis and its secretion from the gonadotroph cells of the anterior hypophysis. Inhibin also inhibits GnRH secretion from the hypothalamus.

In females, a complex cycle of feedback loops results in an ovulatory cycle, which occurs every 28 days in the average, healthy, ovulating female. Several effectors, including sex hormones and exogenous and limbic system inputs, influence this cycle of hormonal balance. During the first 2 weeks of the menstrual cycle, the follicular phase takes place. In this phase, estrogen-based (mainly estradiol) sex hormones are dominant in creating negative feedback on the release of GnRH from the hypothalamus. At the end of this phase, concentrations of estradiol peak in the bloodstream. This has a reverse effect on the hypothalamic-hypophysis axis and brings about a surge in LH secretion, which correlates to the time of ovulation. In the second phase of the menstrual cycle, the hypophysis plays a minor role, and the diminished effect of hormonal regulation brings about a change in the balance of progesterone-estradiol secretion from the ovary, ultimately leading to the secretory phase of menstruation.

Adrenocorticotrophic Hormone

ACTH is synthesized by the corticotroph cells in the anterior hypophysis. The stimulus for this secretion is dual. The first stimulant for ACTH secretion is CRH. This 41-amino acid peptide is released mainly from the parvocellular layer in the paraventricular nucleus of the hypothalamus. The stimulus for release of CRH is complex, involving several neurotransmitter molecules. It is released in response to acetylcholine and serotonin, and its secretion is inhibited by noradrenaline and γ -aminobutyric acid (GABA). A second stimulant for ACTH release is by vasopressin secreted by the hypothalamus into the portal system.

The effect of ACTH is mainly on the middle layer of the adrenal cortex. It promotes the release of cortisol from the cells in the zona fasciculata of the adrenal cortex. ACTH has other actions on the adrenal cortex. It binds to specific ACTH receptors and stimulates both biosynthesis and secretion of most hormones from the adrenal cortex: glucocorticoids, mineralocorticoids, and androgenic steroids. However, as described elsewhere, secretion of hormones other than glucocorticoids is regulated by other higher-order inputs, such as the renin-angiotensin system and the gonadotropin-gonad axis.

Negative feedback is exerted by plasma cortisol levels on both levels of the axis. Both CRH and ACTH production and secretion are inhibited by specific cortisol receptors, in both the hypothalamus and the anterior hypophysis.¹⁶

The secretion of ACTH, as well as that of cortisol, has a diurnal variation. It is influenced by sleep cycles and by light-dark external influence. It has been stipulated that one of the most significant contributions to this diurnal secretion is brought about by the effect of the suprachiasmatic nucleus.¹⁷

Of note, ACTH bears molecular and structural resemblance to the melanocyte-stimulating hormone, which stimulates melanin production. The two molecules share the same precursor protein, and their similar structure is significant in clinical practice.¹⁸

Prolactin

PRL is a peptide hormone secreted by the anterior hypophysis. The main hypothalamic effect on pituitary PRL release is inhibitory. This inhibition is exerted mainly by dopamine secretion into the portal system by the arcuate nucleus of the hypothalamus. The main hypothalamic secretory effect on prolactin is that of TRH.

PRL stimulates lactation in the mammary glands. It affects both the production of milk in the adenomatous parts of the female breasts and the myoepithelial expulsion of milk from the breast. During pregnancy, there is a delicate balance between the action of PRL and the action of progesterone. Increased levels of PRL stimulate the mammary glands to enlarge and prepare for the production of milk. Increased levels of progesterone, on the other hand, inhibit actual milk production. After birth, a fall in plasma progesterone levels causes unopposed prolactin action, which causes production of milk for the initiation of lactation.

PRL also has an inhibitory effect on the gonadal secretion of sex hormones—estrogen in females and testosterone in males. The pituitary hormone has also been shown to play a role in human sexual gratification and the sexual refractory period, both experienced after completion of the sexual act. Again, there is a delicate balance between the effect of PRL and the effect of another hormone—dopamine, in this instance. Dopamine is responsible for sexual arousal and is counteracted by the action of PRL. To simplify this balance, during sexual arousal and the sexual act, dopamine-related sensations predominate. After (and possibly during) an orgasm, the action of PRL predominates, and sexual gratification and the refractory period ensue. This delicate balance also plays a role in several pathologic scenarios, including elevated PRL levels and the resultant sexual dysfunction, the treatment of PRL-secreting macroadenomas with dopamine agonists, and the galactorrhea associated with dopamine antagonism in the treatment of psychosis.¹⁹

Secretion of PRL is a diurnal one. Other factors that influence the levels of PRL in the serum include the stage in the female ovulatory cycle, pregnancy status, and postpartum newborn breast-feeding activity. Sucking on the nipple affects the hypothalamic modulation of PRL secretion, thereby increasing PRL secretion by the adenohypophysis. Therefore, the newborn maintains a positive feedback loop with the mother's hypophysis and a negative feedback loop with the mother's hypothalamus. This positive feedback brings about an increase in milk production and maternal adaptation to the child's increasing metabolic needs.

CONCLUSION

The pituitary gland is the main point where the neural and endocrine systems function in continuity, maintaining homeostasis of many functional elements of the human body. Among these are thermoregulation; metabolism and metabolic rate; glucose and solute, as well as water balance; growth and development; blood pressure; and sexual drive, pregnancy, childbearing, birth, and breast-feeding. The devastating effects of pituitary dysfunction underscore the importance of the pituitary gland in maintenance of the various functions that underlie normal, everyday human activity. The complex interactions—between the nervous

system and the hormonal system, between the hypophysis and the hypothalamus, and between the hypophysis and the hormone-secreting organs it modulates—are a reflection of the narrow window of variability our body must maintain.

Adrenal Glands

Failure of adrenal function will result in disordered electrolytes and carbohydrate metabolism, which may lead to circulatory collapse, hypoglycemic coma, and death. The adrenal cortex produces a complex array of steroid hormones, whereas the medulla is part of the sympathetic nervous system and produces the catecholamines epinephrine and norepinephrine. The cortex and medulla of the adrenal glands differ embryologically and physiologically, but their hormones often act in a concerted manner.

EMBRYOLOGY AND DEVELOPMENT

The human adrenal glands are bilateral structures sitting above the kidneys and consist of an outer cortex and an inner medulla, both of which secrete hormones that are essential for life. The medulla accounts for about 10% of the mass of the adult adrenal gland and arises from the neuroectoderm; it is thus a modified sympathetic ganglion. By contrast, the cortex arises from mesodermal tissue.²⁰

The cells of the adrenal cortex originate from the intermediate mesoderm and are initially part of the adrenogonadal primordium within the urogenital ridge.^{21,22} They may be detected as early as human embryonic week 4¹⁶ and separate as a distinct adrenocortical primordium from the gonadal primordium by week 8.²³ This adrenocortical anlage consists of two layers: the outer definitive zone and the inner fetal zone. However, whether the cells of these two layers share a common precursor remains a conundrum.²⁴ By week 9 of gestation, neural crest cells migrate into the adrenal anlage to form the medulla, and the newly formed organ becomes encapsulated. At this time, the fetal adrenals are huge in proportion to other organs and continue to grow until the third trimester. The cortex's definitive zone appears steroidogenically quiescent until late gestation, and the inner fetal zone appears steroidogenically active throughout gestation. An additional transitional zone appears after 24 weeks' gestation and produces cortisol toward the end of the fetal development.^{23,25} At birth, the fetal adrenals weigh 8 to 9 g, twice the weight of the adult adrenals.

After birth, the large fetal zone of the fetal adrenal involutes and disappears by 6 months of age. Simultaneously, the definitive zone, possibly together with the transitional zone, develops into the fully differentiated zona glomerulosa and zona fasciculata by the age of 3 years. However, the zona reticularis starts to develop only after 4 years of age and may not be fully differentiated before the age of 15 years [see Figure 4]. The origin and regulation underlying the zonation of the human adrenal gland are still poorly understood.^{23,25,26}

ANATOMY

The adrenal (suprarenal) glands are located between the superomedial aspects of the kidney and the diaphragm. Each adrenal gland, together with the kidney, is enclosed in the renal fascia (of Gerota) and surrounded by fat. The

glands are separated from the kidney by a fibrous tissue but are enclosed by renal fascia, which firmly attaches them to the diaphragm.^{27,28}

Each adrenal gland has only anterior and posterior surfaces. The shape and anatomic relations of the adrenals differ on the two sides:

- The right adrenal is triangular in shape.
 - The anterior surface is bounded by the “bare area” of the liver superiorly and laterally, the inferior vena cava (IVC) medially, and the first part of the duodenum or peritoneum inferiorly.
 - The posterior surface is bounded by the diaphragm superiorly and the kidney inferiorly.
- The left adrenal gland is semilunar in shape. The anterior surface is bounded superiorly by the peritoneum (posterior wall of the omental bursa) and inferiorly by the body of the pancreas. The posterior surface is bounded medially by the left diaphragmatic crus and laterally by the medial aspect of the left kidney. The spleen is located anterolaterally and superiorly to the adrenal gland.

The adrenal glands are located 4 to 5 cm apart, and between the glands from right to left are the IVC, right crus of the diaphragm, celiac ganglion, celiac trunk, superior mesenteric artery (SMA), celiac ganglion, and left crus of the diaphragm.

Vessels of the Adrenal Glands

The endocrine function of the adrenal glands makes their abundant blood supply necessary [see Figure 5]. The adrenal arteries branch freely before entering each gland, so 50 to 60 arteries penetrate the capsule covering the entire surface of the glands.

Arterial Blood Supply

Six to eight superior adrenal (suprarenal) arteries branch from the inferior phrenic artery that is the first abdominal branch of the aorta. The middle adrenal (suprarenal) arteries (one or more) branches form the abdominal aorta just proximal to the origin of the renal arteries. They can be single, multiple, or absent and supply the perirenal fat only. Inferior adrenal (suprarenal) arteries (one or more) arise from the renal artery usually proximal to the bifurcation of the renal segmental arteries.

Venous Drainage

Venous drainage of the adrenal gland does not accompany the arterial supply. Venous drainage is into a large adrenal (suprarenal) vein.

On the right, the short right adrenal vein passes obliquely and drains directly to the IVC posteriorly. In contrast, the left adrenal vein passes downward over the anterior surface of the left adrenal gland. It is often joined by the left inferior phrenic vein and empties into the left renal vein.

Occasionally, an adrenal gland has two veins, one following a normal course and the other being an accessory vein that drains into the inferior phrenic vein.

Lymphatic Drainage

The adrenal lymphatic vessels arise from a plexus deep to the capsule of the gland and from one in the medulla. The

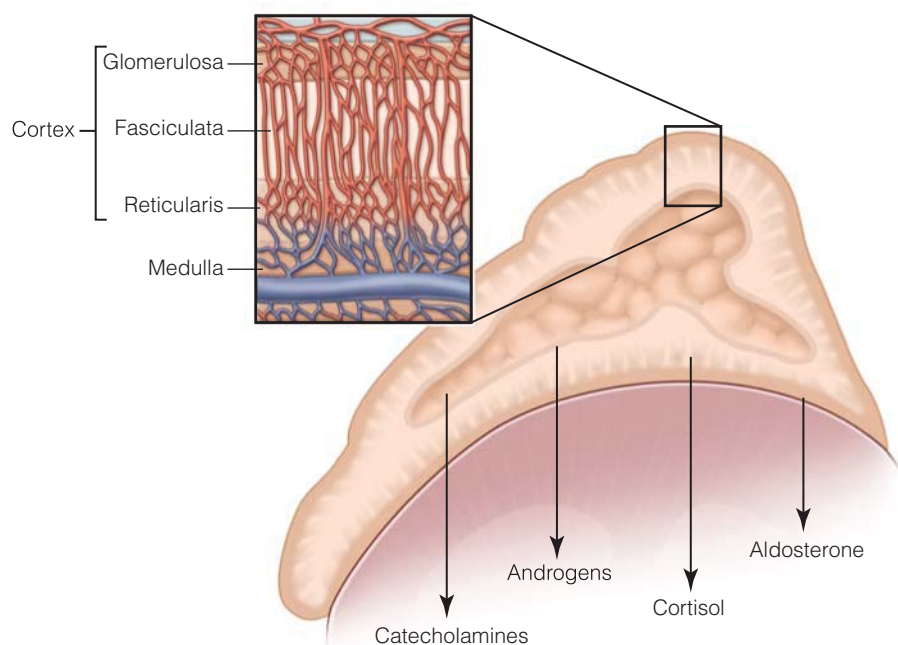


Figure 4 The adrenal layers and hormones.

subcapsular plexus follows the arteries, and the medullary plexus follows the adrenal veins. Drainage is to renal hilar nodes, lateral aortic nodes, and nodes of the posterior mediastinum above the diaphragm by way of the diaphragmatic orifices for the splanchnic nerves. The lymph passes to the lumbar lymph nodes. The lumbar nodes drain through the lumbar lymphatic trunks to the chyle cistern. However, the majority of capsular lymphatic vessels pass directly to the thoracic duct without the intervention of lymph nodes.

Lymphatic vessels of the upper pole of the right adrenal gland may directly enter the liver.

Nerves

The adrenal glands have a rich nerve supply from the celiac plexus and the thoracic (greater, lesser, and least) splanchnic nerves. Some of the abdominopelvic splanchnic nerves convey presynaptic sympathetic fibers that have passed through the paravertebral ganglia without synapsing

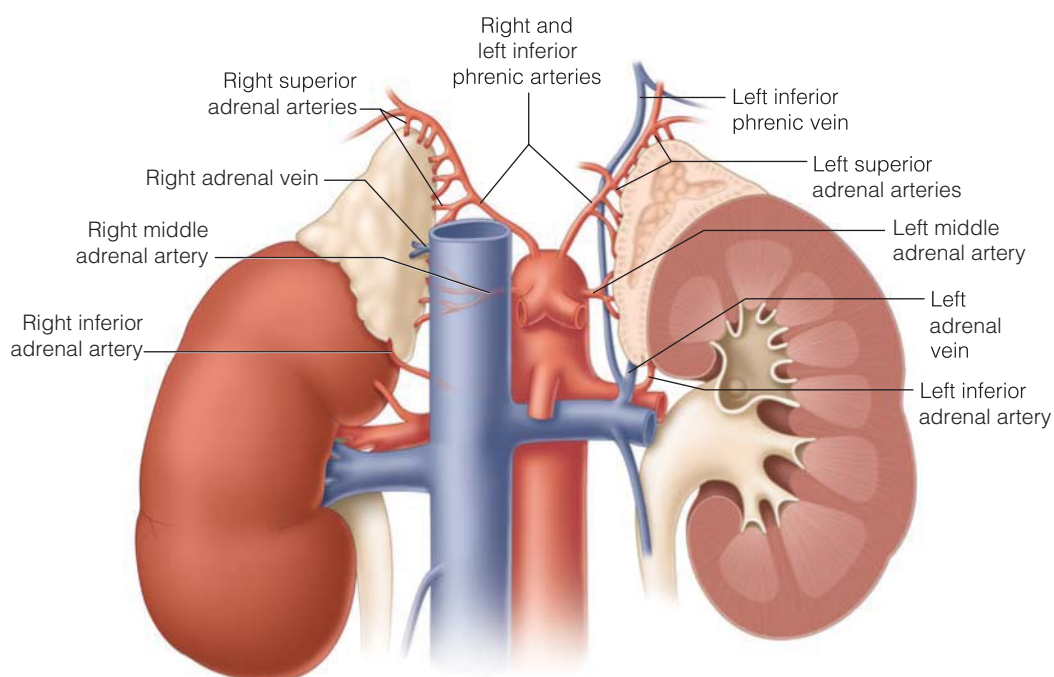


Figure 5 The adrenal blood supply and venous drainage.

to the prevertebral ganglia. The nerves are mainly myelinated presynaptic sympathetic fibers that derive from the lateral horn of the spinal cord and distributed to the chromaffin cells in the adrenal medulla. Exclusively in the case of the adrenal medulla, the presynaptic fibers also pass the vertebral ganglia without synapsing, to end directly on the secretory cells of the adrenal medulla.

NORMAL PHYSIOLOGY

Each adrenal gland is composed of two endocrine organs, one surrounding the other. The outer layers composing the adrenal cortex secrete glucocorticoids, aldosterone, and sex hormones. The inner layers compose the adrenal medulla and secrete catecholamines [see Figure 4]. This part of the chapter separately reviews the synthesis, action, and regulation of each hormone.

Glucocorticoids

Thomas Addison discovered in the mid-1800s that the adrenal cortex is essential for survival.²⁹ During the following century, many of the actions of glucocorticoids were characterized. Glucocorticoids were named for their hyperglycemic effect. In the mid-20th century, this effect was further clarified. In 1940, Long and colleagues demonstrated that glucocorticoids stimulate gluconeogenesis from amino acids and elicit steroid diabetes.³⁰ At the same time, steroids' role in stress and feedback regulation was established. The antiinflammatory effect of glucocorticoids was a matter of debate until two decades later.

Synthesis Synthesis of glucocorticoids is almost exclusively limited to the adrenal cortex, where it is closely tied to ACTH. ACTH is secreted by the hypophysis and exhibits circadian rhythm similar to glucocorticoid's plasma levels. ACTH stimulates steroidogenesis by binding to membrane receptors on adrenal cells, which activate adenylate cyclase and cause hypertrophy and hyperplasia of the adrenal cortex.³¹

Cholesterol is the substrate for the synthesis of all steroid hormones. Figure 6 demonstrates the synthesis sequence

of the different hormones. Both low-density lipoproteins (LDLs) and high-density-lipoproteins (HDLs) are used as substrates by cytochrome P-450 enzymes to synthesize cortisol. The rate-limiting process in steroidogenesis is the transport of free cholesterol through the cytosol to the inner mitochondrial membrane. Within the mitochondria, pregnenolone is derived from cholesterol and is then converted to progesterone. Progesterone is then converted to 17 α -hydroxypregesterone, which in turn is hydroxylated to 11-deoxycortisol, which is finally hydroxylated to cortisol.^{32,33}

Actions Glucocorticoids play an important role in carbohydrate, protein, and fat metabolism. Moreover, glucocorticoids have multiple effects on many different end-organs, and some of these effects are not yet fully understood:

1. Glucocorticoids raise blood glucose level. They protect the body from insulin-induced hypoglycemia. This is achieved by mobilizing gluconeogenic substrates from peripheral tissues, stimulating hepatic gluconeogenesis, enhancing the effect of glucagon and epinephrine on gluconeogenesis and glycogenolysis, inhibiting peripheral glucose use, stimulating lipolysis, and promoting liver glycogen synthesis. Glucocorticoids' actions interact with those of insulin during feeding and fasting, influencing appetite, feeding patterns, and body composition. Chronic high levels of glucocorticoids lead to massive catabolic effects on proteins, resulting in muscle wasting and lipolysis and redistribution of fat.³⁴
2. Glucocorticoids act on bone and cause osteoporosis by inhibiting the function of osteoblasts and collagen synthesis.³⁵
3. Glucocorticoids suppress the inflammatory and immune response. Blood counts of lymphocytes, monocytes, eosinophils, and basophils drop within 1 to 3 hours of glucocorticoid administration. Glucocorticoids protect against overactivity of immune reactions by suppressing proinflammatory cytokines and histamine and enhancing the production of antiinflammatory cytokines.³⁶
4. Glucocorticoids have complex effects on the cardiovascular system. Glucocorticoids enhance vascular reactivity to

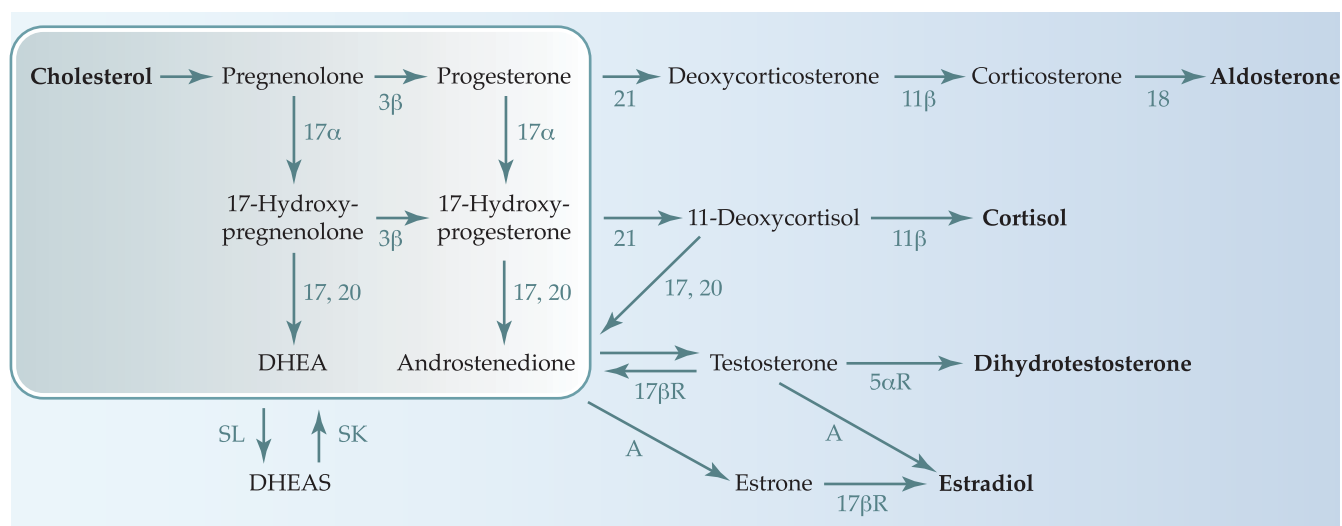


Figure 6 Synthetic pathways for adrenal steroid synthesis. DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate.

other vasoactive agents (angiotensin II, norepinephrine) and contribute to maintaining normal blood pressure. In contrast, chronic exposure to high levels of glucocorticoids frequently leads to hypertension.³⁷

5. Glucocorticoids directly increase Na^+ and K^+ secretion in the kidney and in the colon. Phosphaturia and diuresis are also induced.
6. Glucocorticoids influence behavior, mood, excitability, and electrical activity of neurons. Behavioral changes are frequently observed with both excess and deficit of glucocorticoids.³⁸

Regulation and feedback Cortisol secretion by the adrenal cortex is regulated by a negative feedback system involving the hypothalamus and anterior pituitary. As mentioned earlier, ACTH from the anterior pituitary stimulates the adrenal cortex to secrete cortisol. Cortisol inhibits the secretion of both CRH and ACTH by the hypothalamus and anterior pituitary, respectively.

It is now known that cytokines also play a role in the complex feedback. Cytokines communicate between the immune system and the hypothalamic-pituitary-adrenal axis. Interleukin-1 (IL-1), $\text{IL-1}\alpha$, $\text{IL-1}\beta$, IL-6 , and tumor necrosis factor- α increase levels of glucocorticoids, ACTH, and CRH.^{39,40}

Aldosterone

The steroid hormone aldosterone, synthesized in the zona glomerulosa of the adrenal cortex, plays a pivotal role in electrolyte and fluid balance. Aldosterone was first isolated in 1953 with the use of the toad urinary bladder as a model system.⁴¹

Synthesis The first synthesis steps of aldosterone resemble those of glucocorticoid. Progesterone is also the substrate for mineralocorticoid synthesis. In the zona glomerulosa, progesterone is hydroxylated to yield deoxycorticosterone. All three terminal steps in the conversion of this intermediate to aldosterone are catalyzed by a single mitochondrial P-450 enzyme, aldosterone synthase.³² The zona glomerulosa is well adapted for the production of aldosterone. It has a low concentration of 17-hydroxylase, the enzyme that directs substrate along the pathways to cortisol and androgen synthesis, and is the only adrenocortical zone that has the enzyme required for the sequential conversion of deoxycorticosterone to aldosterone.⁴² The restriction aldosterone synthase expression to the zona glomerulosa allows aldosterone production that is not effected by ACTH.

Action As the term mineralocorticoid implies, the classic effects of aldosterone reflect its role in the regulation of electrolyte flux across transporting epithelia. Aldosterone increases transepithelial sodium flux in the distal nephron and the distal colon.⁴² Aldosterone acts on the cells via the mineralocorticoid receptor to induce gene transcription of sodium channels. Water ultimately follows the movement of Na^+ via osmosis, establishing chronically increased blood volume and thus blood pressure.

Aldosterone acts on epithelial cells of the renal collecting duct and regulates sodium transport. The transcellular transport across these cells is electrogenic and dependent on

serosal Na^+/K^+ -ATPases and luminal amiloride-sensitive epithelial Na^+ channel (ENaC) and K^+ channels. Aldosterone increases the activity of both the serosal pump and luminal channels in the kidney and the colon.⁴³

Aldosterone has been shown to induce cardiac fibrosis in the hypertensive or failing heart and to alter cardiac remodeling after myocardial infarction.⁴⁴ Aldosterone also mediates substantial changes in blood pressure via CNS-regulated functions, including control of sodium intake.⁴⁵

The net effect of aldosterone is sodium resorption, volume expansion, hypertension, suppression of renin activity, hypokalemia, and metabolic alkalosis.

Regulation and feedback The most important feedback loop involves the renin-angiotensin system. Volume status is sensed by the renin-secreting juxtaglomerular cells of the kidney. When the volume (and sodium) is low, renin will be secreted. Renin release is stimulated by renal perfusion pressure, the sympathetic nervous system, and prostaglandins. The release is inhibited by dopamine, atrial natriuretic peptide (ANP), and angiotensin II. Renin acts on angiotensinogen to release angiotensin I, which in turn is subject to further proteolysis by angiotensin-converting enzyme to yield angiotensin II. Angiotensin II acts as a potent vasoconstrictor and stimulates aldosterone synthesis. The latter response promotes sodium retention and consequently increases plasma volume.⁴²

The secretion of aldosterone is also stimulated by potassium, so a negative feedback loop exists for potassium and aldosterone. Other stimulators include ACTH, vasopressin, and serotonin. Negative feedback on aldosterone secretion is carried out by somatostatin; ANP, which promotes natriuresis; and dopamine, which is a well-characterized inhibitor.⁴⁶

Adrenal Sex Hormones

The main site of sex hormone production is the gonads—the testes for androgens in males and the ovaries for estrogens in females. Accordingly, males have a preponderance of circulating androgens, whereas in females, estrogens predominate. However, no hormones are unique to either males or females because the adrenal cortex in both sexes produces small amounts of the sex hormone of the opposite sex. Adrenal sex hormones are synthesized in the zona reticularis and are identical to those produced by the gonads. The most abundant of the adrenocortical sex hormones is dehydroepiandrosterone (DHEA), a “male” sex hormone.⁴⁷

Synthesis Adrenocortical sex hormones are formed in the zona reticularis, which has no type 2,3 β -hydroxysteroid dehydrogenase.^{32,47} Therefore, 17-hydroxypregnenolone can be directed to DHEA. Androstenedione, another weak androgen, is produced by side-chain cleavage of 17 α -hydroxyprogesterone by P-450c17 and is subsequently converted to testosterone by 17-ketosteroid reductase, mainly in peripheral tissues. Because the enzymes required for the production of estrogens are found in very low concentrations in adrenocortical cells, the normal level of adrenal estrogen production is very low. There is also minimal synthesis of testosterone in the adrenal gland [see Figure 6].

Action Under normal circumstances, the adrenal androgens and estrogens are not produced in such levels to induce masculinizing or feminizing effect, respectively. Of all the adrenal sex hormones, only the androgen DHEA is of any physiologic importance. In males, DHEA has little effect as it is much weaker than the potent testosterone; nevertheless, in females who otherwise lack androgen, DHEA has a more significant effect. This androgen is responsible for androgen-dependent processes in the female such as the growth of pubic and axillary hair, enhancement of the pubertal growth spurt, and development and maintenance of the female sex drive.⁴⁸

Other than inducing the above processes in females, it is postulated that DHEA plays a role in aging. A surge of DHEA begins at puberty and peaks between ages 25 and 30. After age 30, DHEA levels slowly decrease, so by the age of 60, the levels are less than 15% of its peak. Supplementation with DHEA has been claimed to have antiaging effects, including increased libido, enhanced immune function, increased muscle mass, and improvements in energy, mood, and memory.^{49,50} The risks of DHEA supplements include reduction in HDL levels, increased facial hair in women, and possible increased risk of ovarian, breast, and prostate cancer.^{51–53}

Several extra-adrenal factors have been proposed as stimuli of adrenal androgen secretion. These factors include PRL, for which there are abundant receptors on adrenocortical cells. In women with prolactinomas, serum DHEA sulfate concentrations are weakly correlated with serum PRL concentrations.⁵⁴

Regulation and feedback Surprisingly, adrenal androgen production is controlled by ACTH and not by pituitary gonadotropic hormones. However, DHEA does inhibit the hypothalamic secretion of GnRH in the same manner as testicular androgens do.

PRL induces adrenal androgen secretion through the abundant PRL receptors present on adrenocortical cells.⁵⁴ Adrenal androgen secretion is also affected by lymphocytes. Lymphocytes increase DHEA secretion by adrenal cells fourfold in vitro, an effect greater than that of maximally stimulating ACTH concentrations. In contrast, androgen secretion is reduced in patients receiving T lymphocyte-suppressive drugs.⁵⁵

Catecholamines

The adrenal medulla is part of the sympathetic nervous system and consists of modified postganglionic neurons that secrete their transmitters directly into the circulation. The adrenal medulla synthesizes mainly epinephrine (80%) and, to a lesser degree, norepinephrine (20%); both belong to the chemical class of catecholamines and differ only by a methyl group that is present in the former. Although adrenomedullary hormones are not essential for life, virtually all organs in the body are affected by these catecholamines.⁵⁶

Synthesis Catecholamine synthesis begins with the amino acid tyrosine. Tyrosine hydroxylase converts L-tyrosine to dopa [see Figure 7]; therefore, tissue sources for catecholamines depend on the presence of the enzyme that is confined to dopaminergic and noradrenergic neurons of the

CNS and to sympathetic nerves and chromaffin cells of the adrenal medulla.⁵⁷ Dopa is decarboxylated to dopamine that is stored in granules. Dopamine is converted to norepinephrine by dopamine β -hydroxylase in the vesicles. In adrenal medullary chromaffin cells, norepinephrine is metabolized to form epinephrine, which is translocated into granules and awaits release.⁵⁸ The process of exocytosis is controlled primarily by acetylcholine release from innervating splanchnic cells.

Action As mentioned above, medullary catecholamines affect almost all body organs; to review all the effects is beyond the scope of this chapter. A simple way to understand the action of catecholamines is to consider them as hormones of the “fight or flight” response. The effects are mediated by two major subtypes of adrenergic receptors: alpha and beta receptors. The alpha-adrenergic receptors bind both catecholamines. The beta-adrenergic receptors, especially the β_2 receptor, are primarily receptors for epinephrine. This difference in affinity results in divergent effects⁵⁹:

- Heart: increased force and contractility (β_1)
- Blood vessels: peripheral vasoconstriction ($\alpha_1 > \alpha_2$), vasodilation (β_2)
- Kidney: increased renin release (β)
- Gastrointestinal: decreased motility and increased sphincter tone (α and β)
- Pancreas: decreased insulin (α) and increased glucagon (β)
- Liver: increased glucose and glucagon (α and β)
- Adipose: increased lipolysis (β_3)
- Skin: increased sweating (α)
- Bronchiole: dilation (β_2)
- Uterus: constriction (α) and relaxation (β_2)
- Most tissues: increased heat (β , along with thyroid hormone)

The combined effects of norepinephrine and epinephrine are to increase cardiac output, heart rate, blood pressure, and respiration (epinephrine is a powerful bronchodilator). They also increase blood flow to the muscles while decreasing splanchnic and renal blood flow. Finally, they increase alertness (chronic stimulation results in anxiety). The net effects are to reroute blood to the muscles and to prepare the brain to control the anticipated physical activity.

Epinephrine (and, to some extent, norepinephrine) has effects in all of the major tissues involved in energy metabolism. In the liver, these hormones stimulate glycogen and lipid breakdown. Epinephrine also stimulates gluconeogenesis and glucose release into circulation. The combination of the effects is a large increase in glucose availability, which can lead to hyperglycemia in cases of prolonged stimulation.

In skeletal muscle, epinephrine also stimulates glycogen breakdown. However, in muscle, epinephrine slightly stimulates glycolysis. The effect of epinephrine in muscle is a preparation for the demands of exercise. To further glucose availability, epinephrine stimulates lipolysis in adipose tissues, and both epinephrine and norepinephrine decrease pancreatic production of insulin and increase glucagon secretion.

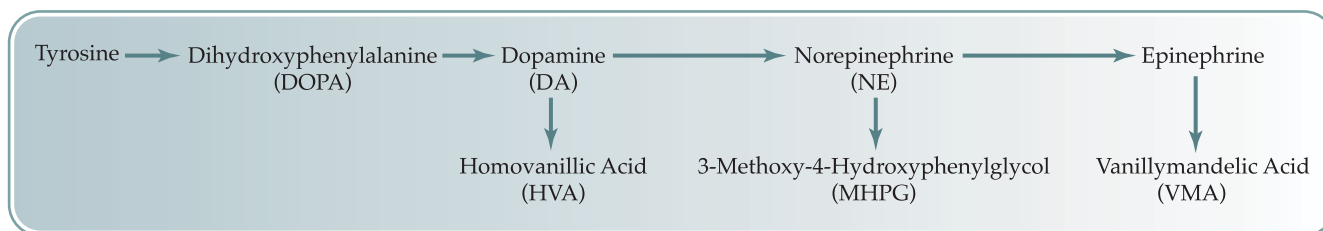


Figure 7 Major steps in catecholamine synthesis and degradation.

Regulation and feedback In the adrenal medulla, epinephrine and norepinephrine are stored in chromaffin granules with other compounds. Activation of the sympathetic nervous system is coordinated by the medulla oblongata and results in acetylcholine secretion. In turn, acetylcholine causes depolarization of the chromaffin cells, influx of calcium, and exocytosis of the granules. The release signal is triggered by stressors, such as anxiety, fear, pain, trauma, hemorrhage or other fluid loss, changes in pH of the blood, increased energy demand (especially for exercise), hypoglycemia, or exposure to excessive heat or cold. Most, if not all, of the granule contents play some role in preparing the body to respond to these types of stress.⁶⁰

The two enzymes that are involved in catecholamine inactivation are catechol-*O*-methyl transferase (COMT) and monoamine oxidase (MAO). Most of the metabolism of the catecholamines occurs in the liver, which contains COMT and MAO and a number of other enzymes. The two major metabolites produced by these enzymes are metanephrines (15%) and vanillylmandelic acid (VMA) (85%), which are secreted through urine⁶¹ [see Figure 7].

CONCLUSION

The adrenal glands constitute two different hormone-secreting organs: the cortex and the medulla. Whereas the cortex secretes steroids, the medulla produces catecholamines and as such is considered part of the sympathetic nervous system. Despite the differences in hormone secretion, both adrenal parts are vital for life. The adrenal anatomy differs between the left and right sides, and meticulous knowledge of the variations may prevent devastating complications when performing surgery. Every surgeon who attempts to manage patients with adrenal diseases must be familiar with the detailed physiology of hormone synthesis, feedback, and degradation. Such knowledge will enable proper understanding of both the preoperative evaluation and the correct intra- and postoperative management of these potentially complicated patients.

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Figures 1 to 7 Christine Kenney

9 ANATOMY AND PHYSIOLOGY OF THE PANCREAS

John A. Windsor, MBChB, MD, FRACS, FACS

The casual observer might be forgiven for assuming that the pancreas played an insignificant role given its size, morphology, and location. Indeed, Galen and anatomists for a millennium considered the pancreas a fatty cushion on which the stomach rested. Even the 1901 edition of *Gray's Anatomy* stated that the “pancreas presents but little of surgical importance.”¹ In truth, this largest digestive gland, situated in the center of the body, on either side of the transpyloric (L1) plane, is notable for its complex anatomy and the colocation of exocrine and endocrine organs. The pancreas is an organ of endless fascination, with the congenital anomalies giving rise to a range of anatomic variations; the anatomic relations challenging the most meticulous of surgeons; and the wide-ranging pathology of clinical significance.

Surgery of the pancreas requires a detailed understanding of the anatomy of the pancreas and its relation to adjacent vital structures, and the management of patients with diseases related to the pancreas requires a detailed understanding of the physiology of both the exocrine and the endocrine pancreas. The functional reserve of the gland is such that over 50% of its acinar tissue must be destroyed before there is marked evidence of an effect on digestion.

Morphology of the Pancreas

The pancreas, weighing about 80 g, is shaped like a tadpole, with a thicker head and a flatter neck, body, and tail [see Figure 1]. It is salmon pink with a smooth, lobulated surface. Fixed within the retroperitoneum, the pancreas is draped obliquely over the spinal column and major vessels,

with the head hugged by the duodenum and rising to where the tail touches the splenic hilum in the left upper quadrant. This obliquity accounts for why cross-sectional imaging does not display the entire pancreas on a single slice [see Figure 2]. Being within the retroperitoneum means that inflammatory extravasation of the pancreas can readily spread in many directions, including the anterior and posterior pararenal spaces, paracolic gutters, small bowel mesentery, transverse mesocolon, and even the mediastinum and scrotum [see Figure 3]. With severe acute pancreatitis, the extravasations can pass from the anterior to posterior pararenal spaces and are seen as subcutaneous discoloration in the flanks (Grey-Turner sign). If the extravasation tracks in the falciform ligament, the discoloration can present at the umbilicus (Cullen sign).

Lying as it does, the pancreas has intimate relations with more anatomic structures than any other organ in the body, including the duodenum, common bile duct (CBD), stomach, transverse colon, left kidney, left adrenal, and spleen [see Figure 4]. There are also vascular relations to the inferior vena cava and left renal vein, the aorta and its branches (celiac trunk and branches, superior mesenteric artery [SMA]), and portal, superior mesenteric, and splenic veins. The proximity of the pancreas to these structures makes them prone to invasion by malignant pancreatic disease. The pancreatic head bounded by the duodenum (above, below, and to the left) has an important relation with the CBD. As the duct descends behind the first part of the duodenum, it becomes enclosed by ($\approx 80\%$) or grooves ($\approx 20\%$) the pancreas as it passes to exit at the major duodenal papilla.*

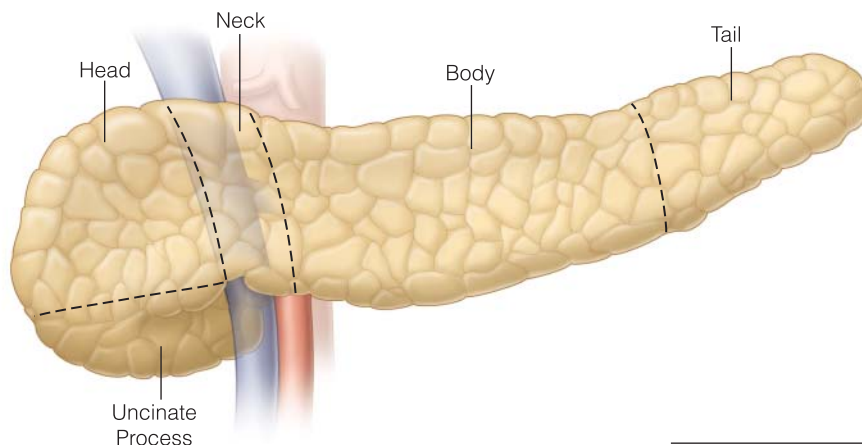


Figure 1 General morphology of the pancreas.

Financial disclosure information is located at the end of this chapter before the references.

* “Papilla” refers to the nipple appearance and projection of the duodenal mucosa through which the ampulla exits. The ampulla is increased caliber of the conjoined main pancreatic duct and the CBD, and is absent if these ducts exit separately.

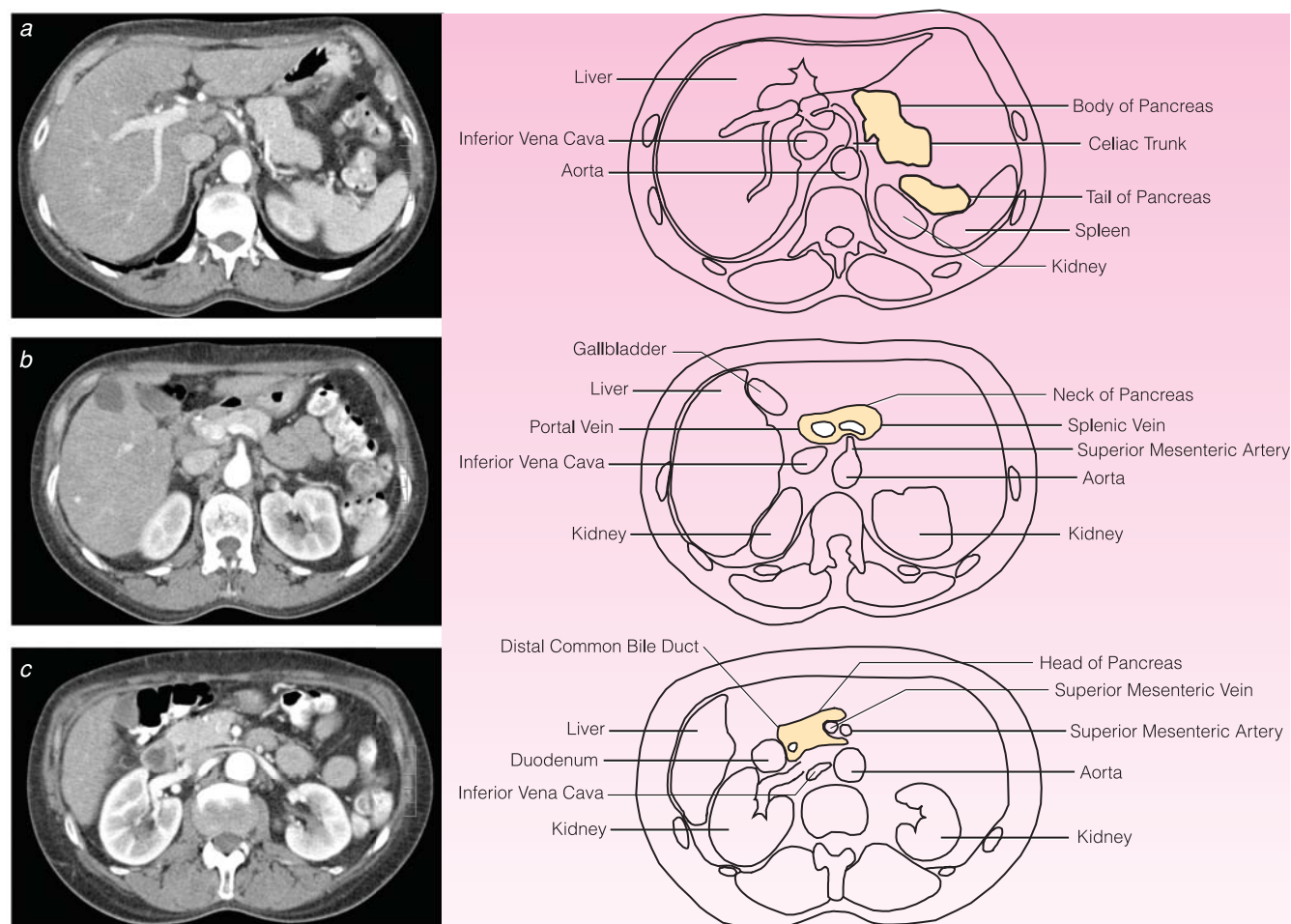


Figure 2 Computed tomography scans of normal pancreas. (a) Pancreatic body and tail. (b) Pancreatic neck. (c) Pancreatic head and uncinate process (demonstrating plane surrounding superior mesenteric artery and the inferior pancreaticoduodenal artery).

This close relation to the CBD is the reason why jaundice, by malignant encroachment of the duct, is often the first presenting sign of pancreatic head adenocarcinoma. For many years, the decision that a cancer of the pancreatic head was unresectable has been based on demonstration of invasion of the portal and superior mesenteric veins. However, in major centers today, the invasion of the SMA and, less commonly, the celiac and common hepatic arteries has become a more important determinant of unresectability. This is because en bloc venous resection can be performed safely and can be justified when all other resection margins are negative.

To display the anterior surface of the pancreas requires the gastrocolic omentum to be widely opened and division of the inevitable and variable congenital adhesions between the pancreatic peritoneum and the overlying lesser curve of the stomach. The transverse mesocolon arises away from the pancreas except where it crosses the second part of the duodenum and uncinate process of the pancreas. This means that the lower border of the uncinate process can be palpated and is often seen from the greater omental sac through the root of the transverse mesocolon. Full exposure of the anterior head of the pancreas (and the second and third

parts of the duodenum) requires this attachment of the transverse mesocolon to be divided. Complete exposure of the neck of the pancreas requires division of the gastrocolic trunk, and associated lymphatic nodes (see below), which crosses it. This trunk contains the gastroepiploic artery (from the SMA), the gastroepiploic vein (which drains into the superior mesenteric vein [SMV]), and lymph nodes. The trunk is also joined by the gastroduodenal artery (GDA; from the common hepatic artery) after it has descended on the pancreatic neck. Division of the lesser (gastrohepatic) omentum and caudal retraction of the gastric antrum and pylorus is another way to expose the anterior neck of the pancreas. Other aspects of the pancreas can also be accessed through different routes. The Kocher maneuver frees the horizontal and retroperitoneal second part of the duodenum to expose the posterior pancreatic head. The transverse mesocolon can be opened to the left from the greater omental sac to expose the inferior margin of the pancreatic body. The splenic flexure can be mobilized to expose the lower pole of the spleen, hilum, and pancreatic tail.

The head of the pancreas is the broadest part of the gland. The superior aspect of the head is derived from the dorsal anlage of the gut tube. The uncinate process of the pancreas

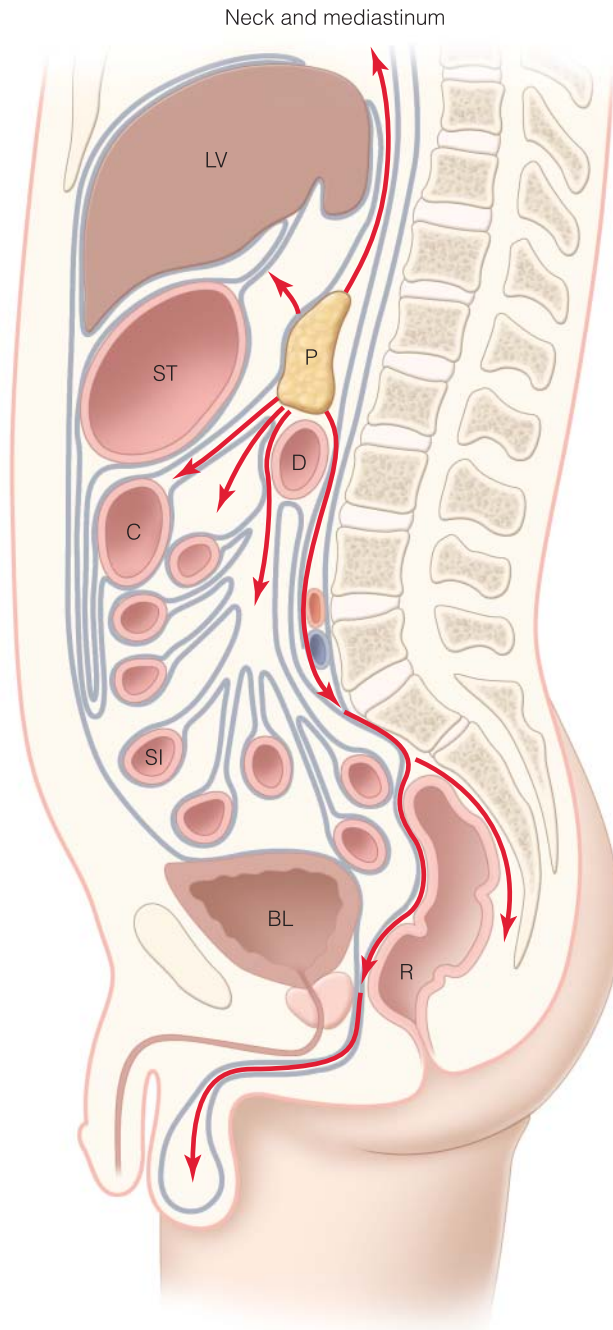


Figure 3 Pathways of pancreatic extravasations. BL = bladder; C = colon; D = duodenum; LV = liver; P = pancreas; R = rectum; SI = small intestine; ST = stomach.

is derived from the ventral anlage, which, through a process of rotation and fusion within the first month, forms the inferior portion of the pancreatic head.² It is highly variable in shape and occasionally absent, but it is called the uncinate process because it is considered hooklike, usually passing downward, to the left, and behind the superior mesenteric vessels but in front of the vena cava and aorta [see Figure 5]. The medial border of the uncinate process is the SMA, and this margin is the one most often positive with resection of the pancreatic head for adenocarcinoma. Special attention must be given to this margin by the radiologist when staging a cancer by cross-sectional imaging [see Figure 2c]

and by the surgeon by dissection on the SMA to minimize the chance of incomplete clearance. Branches of the SMA (the inferior pancreaticoduodenal artery [IPDA]) and tributaries of the SMV enter the medial aspect of the uncinate process.

The neck of the pancreas is defined as that portion of the gland that crosses the superior mesenteric vessels and is usually less than 2 cm wide [see Figure 4]. Anteriorly, it is partially covered by the pylorus, and posteriorly, the portal vein is formed by the confluence of the superior mesenteric and splenic veins. The inferior mesenteric vein terminates in the splenic vein in over a third of patients but can also

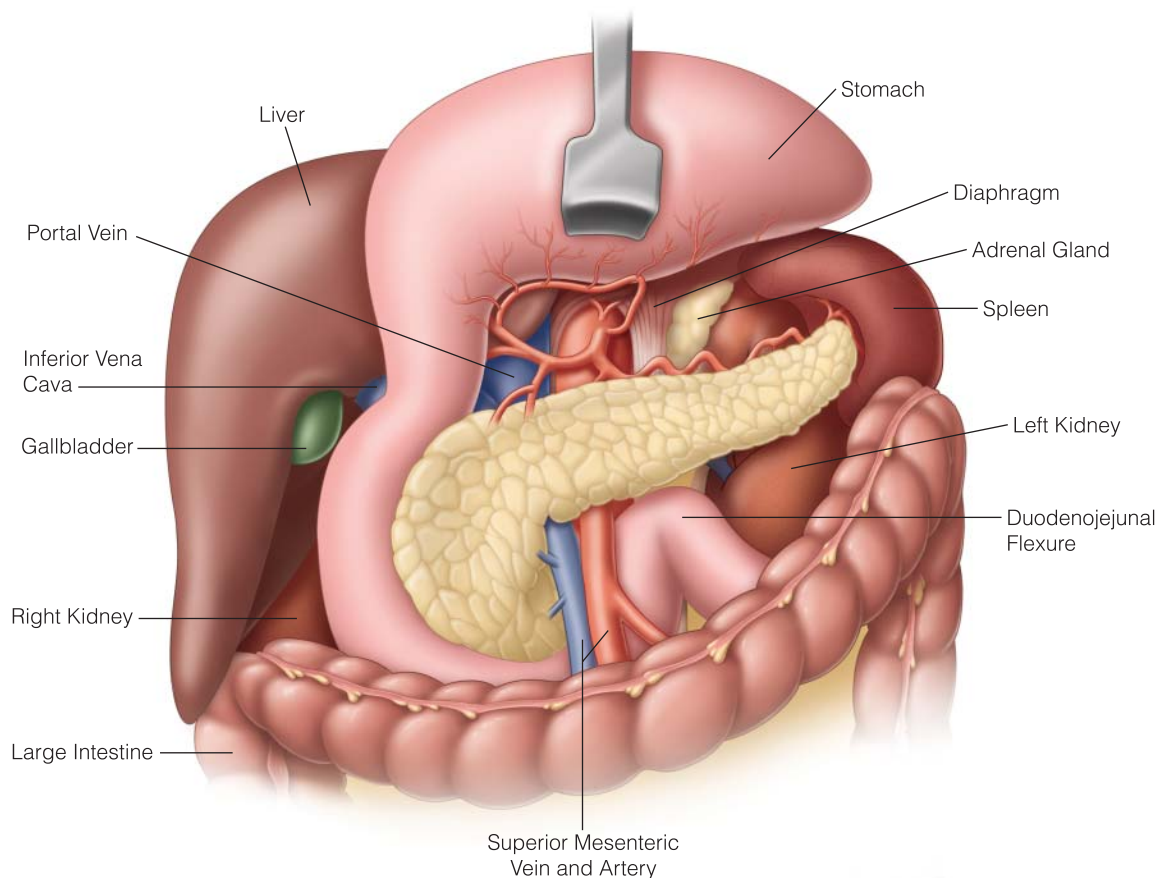
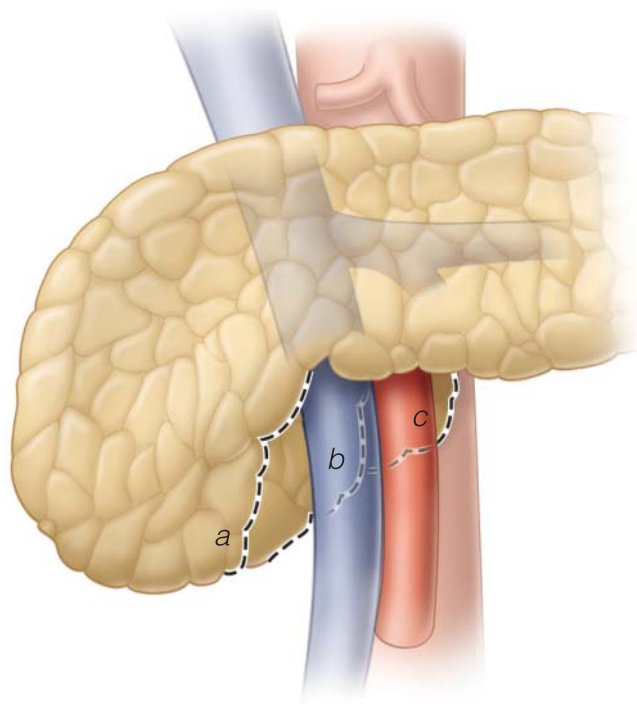


Figure 4 The relationship of the pancreas to other organs.



terminate in the SMV or at the confluence of the two. Establishing that there is no invasion of these subjacent veins is an important part of the staging and dissection of a pancreatic cancer of the head and neck. To that end, it is common practice to establish a plane between the neck and these veins, facilitated by the absence of an anterior tributary draining from the pancreas at this point. The celiac trunk and its trifurcation arise at the superior margin of the neck, and the superior mesenteric vessels leave the inferior margin to cross the third part of the duodenum and enter the mesentery of the small bowel.

The body of the pancreas lies along the floor of the lesser sac (or omental bursa) and is covered by peritoneum derived from the superior leaf of the transverse mesocolon. Posteriorly, the body of the pancreas is related to (from right to left) the aorta, the origin of the SMA that arises just above the left renal vein, the left crural pillar of the diaphragm, and the left kidney and its vessels. The splenic vein coursing posteriorly to the spleen has a variable relation with the pancreas. Receiving multiple small tributaries from the pancreas, the splenic vein may be separate from or covered

Figure 5 The uncinate process, which can vary in medial extent to the SMV (a), under the SMV (b), or behind the SMA (c).

by the gland. The splenic artery can be seen looping above the superior margin of the pancreas.

The tail of the pancreas is the most mobile part of the pancreas and has a variable relation with the spleen. The tail of the pancreas extends to the spleen (and occasionally onto the spleen) and can do so anterior to, posterior to, or within the splenic hilum. This relation should be defined at the time of splenectomy to avoid injury to the pancreatic tail. Also entering the splenic hilum are the short gastric vessels and the left gastroepiploic vein. Understanding the peritoneal reflections of the splenic hilum is important for accurate dissection of this area [see Figure 6].

Ductal System of the Pancreas

Secretions from the 20 to 200 acinar cells within each pancreatic lobule drain into small intercalated ducts. These merge to form intralobular ducts, which further merge to form secondary pancreatic ducts that drain at right angles into the main pancreatic duct (MPD or duct of Wirsung) [see Figure 7]. The MPD runs from the distal pancreatic tail to the head of the pancreas, gradually increasing in caliber from approximately 1 to 2 mm in the tail, 2 to 3 mm in the body, and 3 to 4 mm in the head. The entire volume of the pancreatic ductal system is usually less than 3 mL, and the injection of contrast into the duct should be low pressure and low volume at the time of endoscopic retrograde cholangiopancreatography (ERCP) to reduce the risk of procedure-related acute pancreatitis. Through the body and tail, the MPD usually lies slightly more superior and posterior

than the cross-sectional midpoint of the gland. It is common for the MPD to become more posterior and caudad as it passes from the neck into the head. The uncinete process has its own pancreatic duct, which usually drains into the MPD as it becomes more horizontal, just short of the major duodenal papilla. There is, however, significant variation in the arrangement of these ducts [see Figure 8].

The accessory pancreatic duct (of Santorini) is the proximal portion of the duct draining the dorsal pancreas. With fusion of the ducts from the dorsal and ventral pancreas, the accessory duct assumes a secondary role and tends only to drain the anterosuperior portion of the pancreatic head. However, when the ducts do not fuse ($\approx 10\%$), called pancreas divisum, the accessory duct drains the entire dorsal pancreas and none of the uncinete process. The minor duodenal papilla, located approximately 1 to 2 cm proximal and anterior to the major duodenal papilla, may be responsible for pancreatitis because the small-caliber duct causes a relative obstruction at the time of stimulated pancreatic secretion, although this contention is somewhat controversial. The minor duodenal papilla is absent in up to a third of the population. An anomalous junction between the MPD and the CBD has been described³ and is associated with fusiform dilatation of the CBD, the most common type of choledochal cyst. Whether this abnormal junction is a cause of recurrent pancreatitis is still disputed.

Major Duodenal Papilla

The major duodenal papilla is located on the posteromedial wall of the duodenum, in the second part, 7 to 10 cm distal to the pylorus. Although it has a variable appearance, one relatively constant feature, which can help with identification, is a longitudinal fold of mucosa (or frenulum) below the papilla that forms a T configuration with the transverse fold (or hood) above the papilla. If not readily seen at the time of surgery, palpation of the medial duodenal wall will usually declare it as a firm nodule.

A true ampulla, the dilation of the common channel formed by the MPD and the CBD, is not always present. The ducts can join before traversing the duodenal wall as a common channel, and in this situation, a true ampulla is present in three quarters of cases. In contrast, a true ampulla is not present when the ducts join in the duodenal wall just prior to exiting or when the ducts do not join at all with two orifices in the duodenum and a septum between them.

The anatomy of the sphincter complex at the major duodenal papilla, named after Boyden and Oddi, is also variable. There are several sphincters of smooth muscle within the complex, and they function independently of the duodenal wall, reflecting the separate embryonic origin. This variation is in part explained by the obliquity of the path through the duodenal wall and in part by the variations related to the junction of the biliary and pancreatic ducts. In some cases, the sphincter complex extends beyond the duodenal wall. The length of the sphincter complex may vary from 6 to 30 mm, which probably explains why it is sometimes difficult to achieve a complete endoscopic sphincterotomy. The sphincter complex comprises four elements: a superior biliary sphincter, an inferior biliary sphincter (submucosal), a common ampullary sphincter,

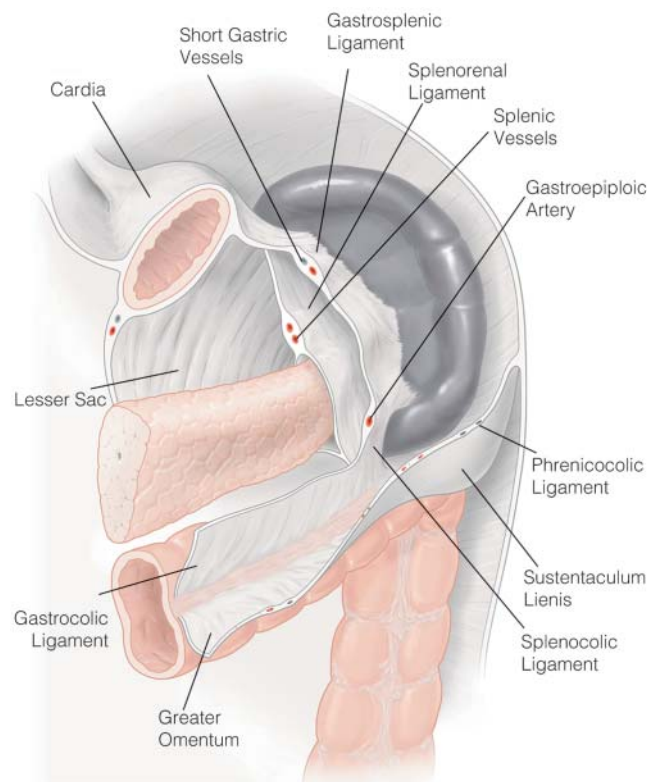


Figure 6 Pancreatic tail and spleen.

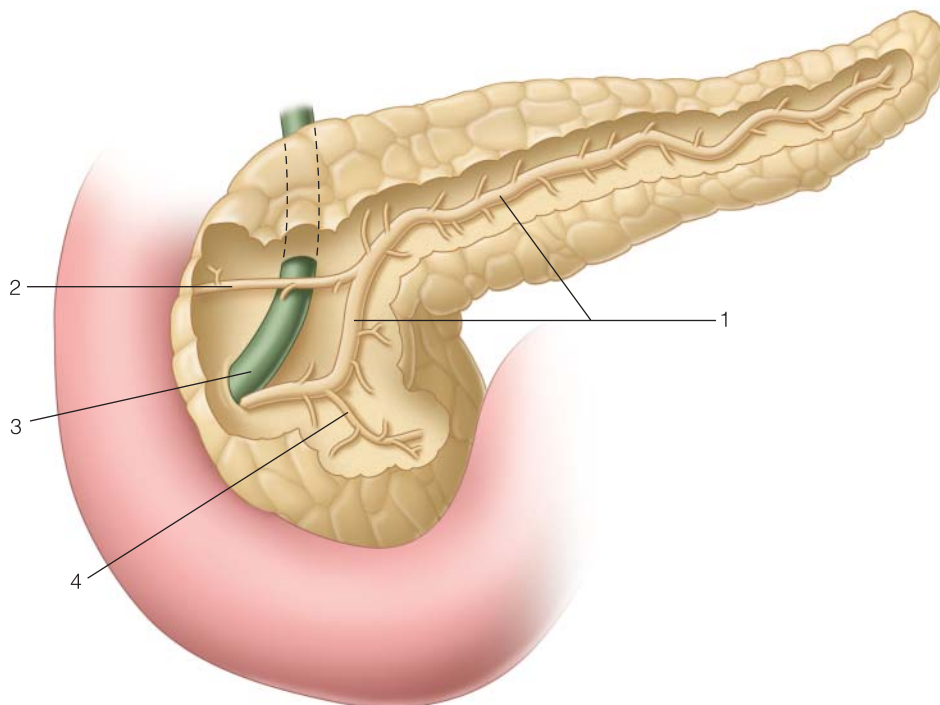


Figure 7 The pancreatic ductal system comprises the main pancreatic duct or duct of Wirsung (1), the accessory pancreatic duct or duct of Santorini (2), and the duct to the uncinus process (4). The intrapancreatic portion of the common bile duct (3) is also shown.

and a pancreatic sphincter [see Figure 9]. The main blood supply to the major duodenal papilla is from the posterior superior pancreatic artery (PSPA), through a plexus formed with the choledochal vessels.

Dysfunction of the sphincter of Oddi is invoked as a cause of idiopathic biliary pain and acute pancreatitis. And although this can be measured using endoscopic retrograde manometers, the role of endoscopic or surgical sphincterotomy and/or pancreatic duct septotomy remains controversial. Anatomic variation may account for some of the conflicting results.

Arterial Anatomy of the Pancreas

The pancreas is the best perfused organ by weight in the body, next to the lactating breast, underpinning the high rates of protein synthesis for exocrine and endocrine function. The blood supply to the pancreas is from branches of the celiac trunk and the SMA, but there is considerable variation in pattern and nomenclature. The head of the pancreas and related duodenum is supplied by anterior and posterior pancreaticoduodenal arcades within the pancreatic substance and running parallel to the concave duodenal wall and arising from the GDA/common hepatic artery/celiac trunk and the IPDA/SMA, respectively [see Figure 10]. Thus, the PSPA arises as a branch of the GDA as it arises from the common hepatic artery along with the supraduodenal and retroduodenal arteries. The anterior superior pancreatic artery (ASPA) arises from the GDA as it terminates at the right gastroepiploic artery. The ASPA and PSPA anastomose with complementary arteries from the anterior inferior pancreatic artery (AIPA) arising from the SMA and the posterior inferior pancreatic artery (PIPA) also often arising

from the SMA as a common trunk, the IPDA. The IPDA is an important landmark in resection of the pancreatic head and should be formally ligated, and in so doing opens up the plane for dissection of the SMA, the important postero-medial margin of resection. It is notable that the IPDA can be single, double, or absent. The neck of the pancreas is supplied predominantly by the splenic artery arising from the celiac trunk and giving off the dorsal or great pancreatic artery (sometimes called the pancreatica magna) in its middle third, which often contributes a branch to the posterior pancreaticoduodenal arcade. The body and the tail of the pancreas are supplied by branches from the splenic artery along the superior border of the pancreas, and these branches connect with a transverse or inferior pancreatic artery, a collateral vessel that is a continuation of the dorsal pancreatic artery and runs within the pancreas toward the inferior margin. This arrangement is present about half of the time, whereas in 22% of cases, the inferior artery is absent, and in 25%, the body and tail are supplied only by branches from the inferior pancreatic artery. This latter situation increases the risk of pancreatic infarction if thrombosis or embolus of this single vessel occurs.⁴ Near the tail of the pancreas, the splenic artery branches for segmental supply of the pancreas. In up to one third of cases, the tail of the pancreas does not receive blood supply from the arteries of the pancreatic body. In this setting, the supply can be from the left gastroepiploic artery.

Anomalies of the hepatic arteries are of importance to the pancreatic surgeon, and there are several variants [see Figure 11]. Although formal preoperative invasive angiography is no longer indicated, staging computed tomography (CT) should include an arterial phase and arterial anomalies specifically examined for. A replaced or, of less concern,

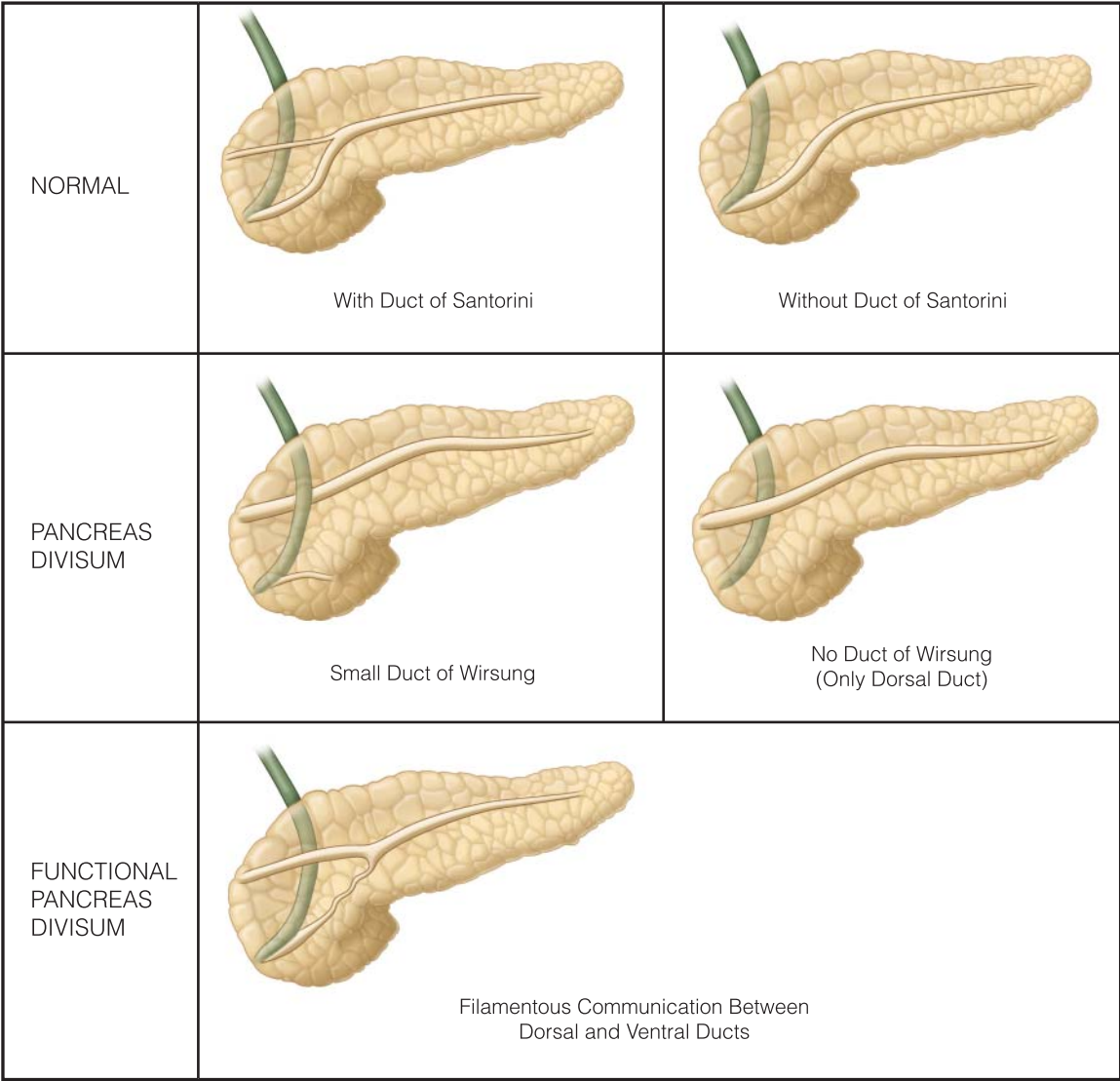


Figure 8 Main variations in main pancreatic duct junction with bile duct.

an accessory right hepatic artery arising from the SMA presents the most frequent challenge, and these variations occur in up to 15% of the population.⁵ At the time of surgery, these can usually be detected behind the CBD (and often the portal vein) adjacent to the posterosuperior aspect of the pancreatic head. When arising from the origin of the SMA, the anomalous right hepatic artery does not usually traverse the substance of the gland, but when arising more distally, it can take a variable course through the pancreatic head and even the uncinate process. It may also anastomose with the posterior pancreaticoduodenal arcade and the IPDA. An anomalous left hepatic artery does not usually present a problem to the surgeon unless it arises from the right side of the SMA or the GDA. An anomalous middle colic artery can arise from the dorsal pancreatic artery or the IPDA and may pass through the head of the pancreas or between the head and the duodenum.

Another important vascular consideration relevant to resection of the pancreatic head is the challenge of celiac axis stenosis. This is most commonly secondary to compression by the median arcuate ligament or is attributable to atheromatous disease.⁶ In this setting, the liver is more reliant on supply via the GDA or an anomalous hepatic artery, if present. Although preoperative detection is usual, it is important to temporarily occlude the GDA before division to test that hepatic artery pulsation in the porta hepatis is not lost, by so doing. If this were the case, then a jump graft from the aorta may be required to ensure hepatic artery inflow.

Serious arterial bleeding following pancreatic surgery, both primary and secondary, is most commonly from the ligated GDA or IPDA. Secondary bleeding commonly follows a leak from the pancreatic anastomosis and may be heralded by sentinel bleeding. This is important as there may be time to undertake CT angiography and lifesaving embolization.⁷

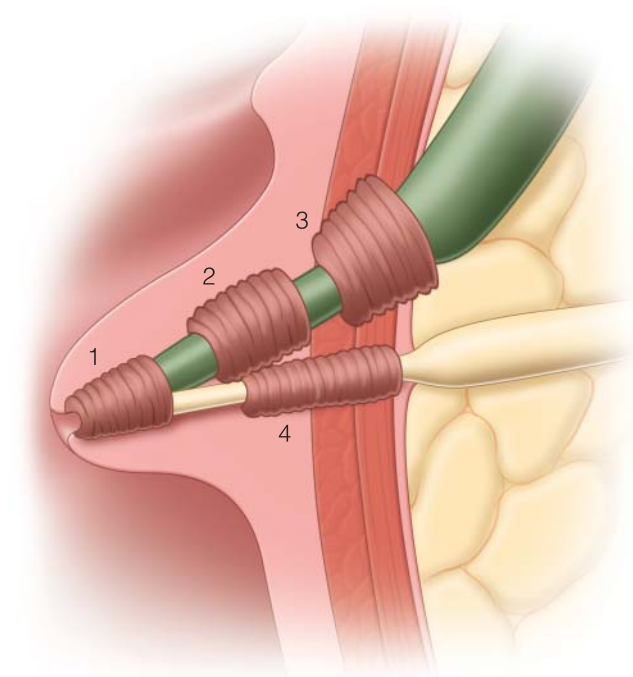


Figure 9 The Sphincter of Oddi complex comprises the common ampullary sphincter (1), the inferior biliary sphincter (2), the superior biliary sphincter (3) and the pancreatic sphincter (4).

Venous Anatomy of the Pancreas

The homonymous venous anatomy usually parallels the arterial anatomy, but with the former taking a more superficial course. Venous drainage of the pancreas is into the portal, superior mesenteric, inferior mesenteric, and splenic veins [see Figure 12]. Related to the head of the pancreas are

the four pancreaticoduodenal veins that form the anterior and posterior arcades. There is almost invariably a tributary entering the portal vein at the level of the superior margin of the pancreatic head. In addition, the pancreatic head, neck, and uncinate process drain by a variable number of unnamed tributaries directly into the portal and superior mesenteric veins. An inferior or transverse pancreatic vein can be present and drains into the splenic vein or the inferior mesenteric vein.

Venous bleeding during pancreatic surgery can occur from multiple sites, but it is worth mentioning the most common. The gastroduodenal vein arises from the right gastroepiploic vein, crosses the pancreatic neck, and receives the anterior superior pancreaticoduodenal vein and a variable number of venous tributaries from the transverse mesocolon. Troublesome bleeding can occur from this confluence unless these veins are specifically identified and divided. There is also a rare risk of bleeding if the posterior superior pancreaticoduodenal vein directly enters the anterior aspect of the portal-superior mesenteric vein, and is vulnerable when the plane between the pancreas and the subjacent veins is established. The left gastric (coronary) vein from the lesser curve of the stomach passes alongside the superior margin of the pancreas to enter the splenic ($\approx 70\%$) or the portal ($\approx 30\%$) veins.

The resection of a pancreatic head mass sometimes requires resection of a portion of the portal or superior mesenteric veins and reconstruction by primary closure, patch, or graft. Segmental resection of one of the two first-order branches of the SMV (jejunal or ileal) may be performed without venous reconstruction if mesenteric venous flow is preserved to the remaining first-order tributary [see Figure 13].⁸

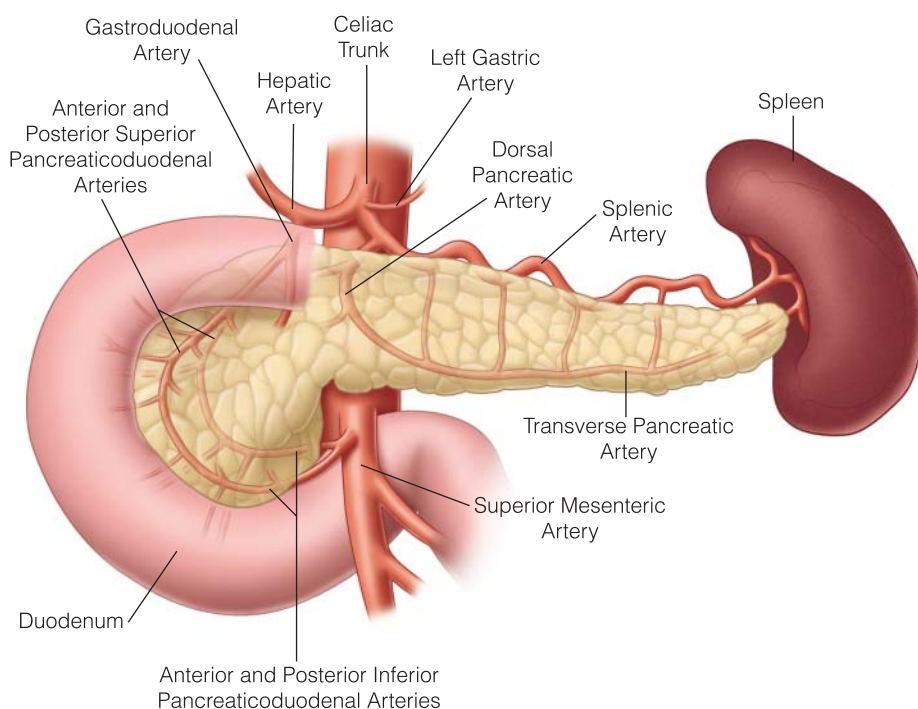


Figure 10 Arterial supply to the pancreas.

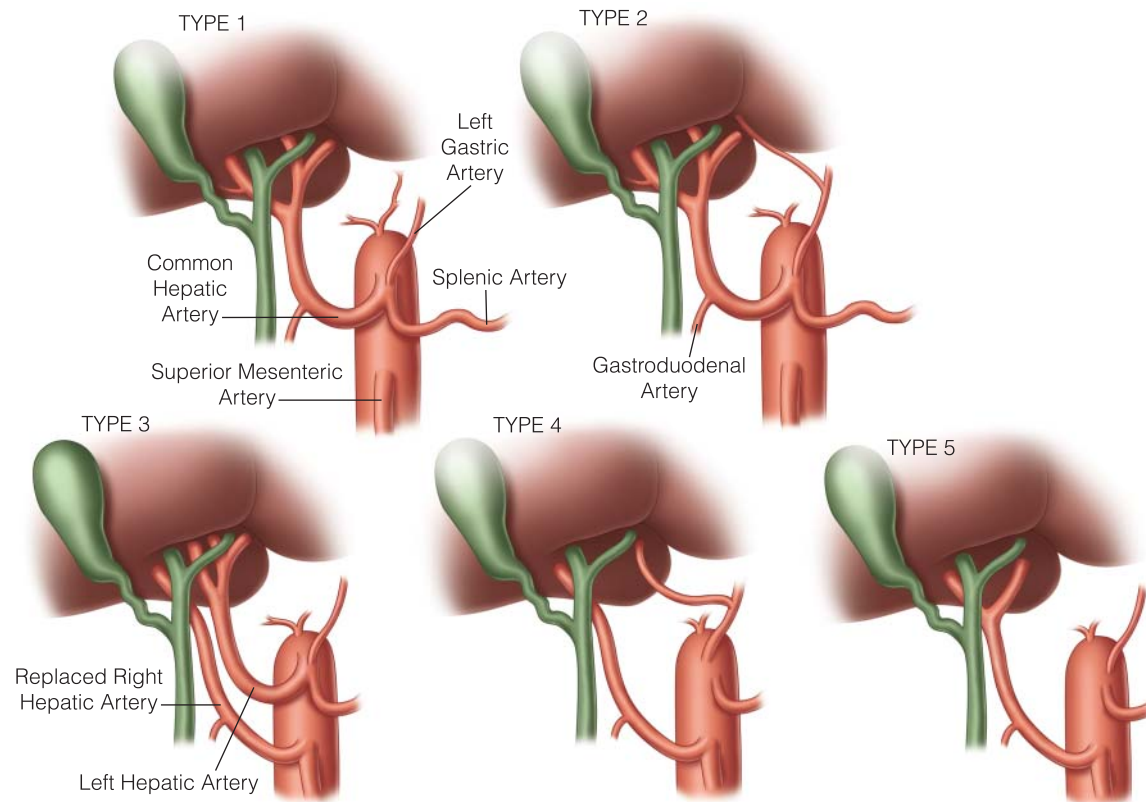


Figure 11 Variation of hepatic arteries.

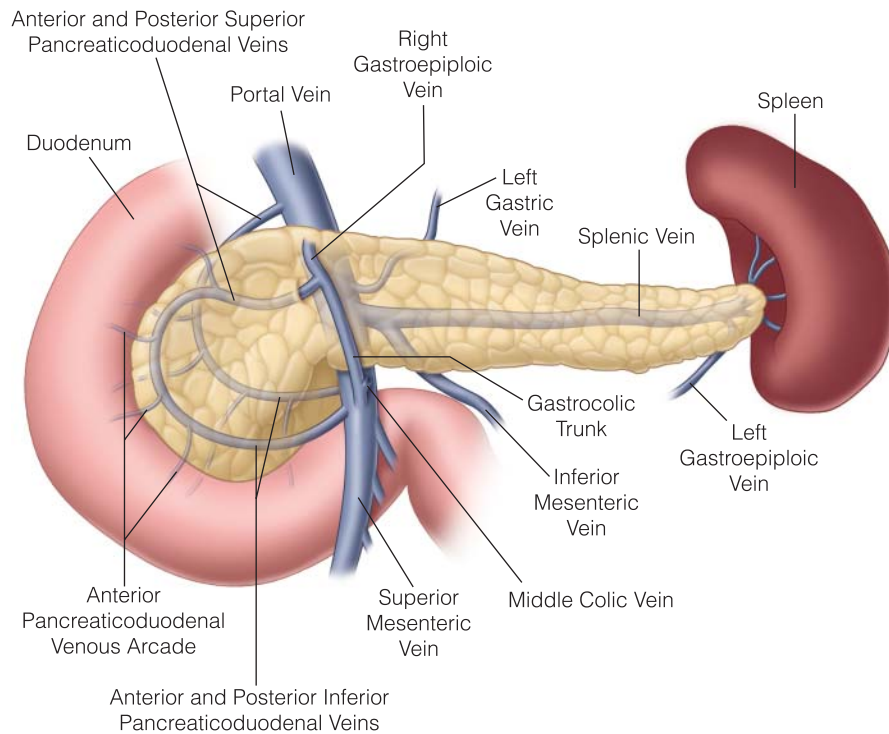


Figure 12 Venous drainage of the pancreas.

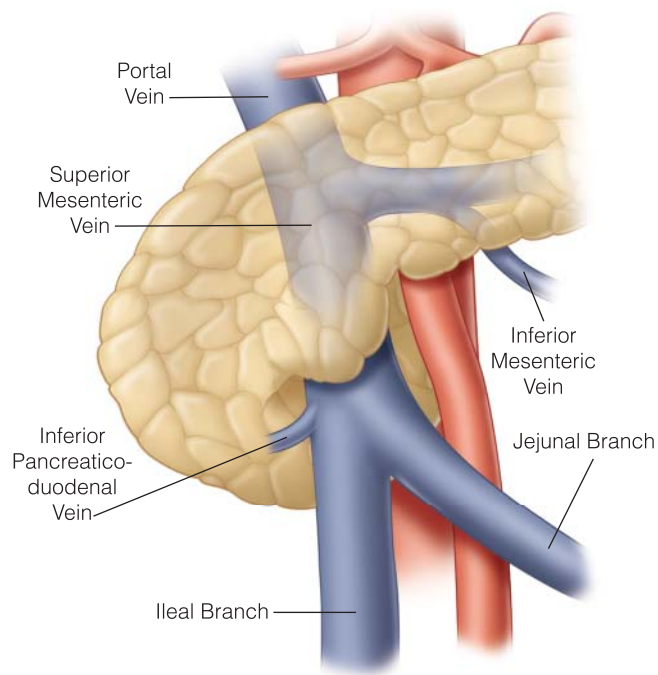


Figure 13 Tributaries of the superior mesenteric vein.

Lymphatic Drainage of the Pancreas

Lymph arises in the interstitium of the exocrine pancreas and collects within variable fine-walled intralobular lymphatic vessels that coalesce to become interlobular lymphatics. In contrast to the lobules, no lymphatic vessels have been identified within the islets of Langerhans. Lymph appears to be taken up by lymphatic ducts at the periphery of the islets. The intralobular lymphatics initially drain in the same direction as the ducts, but the flow then diverges toward the surface of the gland, in contrast to the ducts that drain toward the center of the gland. On the surface of the pancreas, the lymphatic vessels form a superficial network that converges toward lymph nodes, often at the periphery of the gland. Thus, the lymphatic drainage of the pancreas is centrifugal to peripheral lymph nodes. Efferent vessels from these nodes eventually empty into the thoracic duct.

Understanding the pattern of lymph node drainage is important in pancreatic cancer surgery, both for accurately staging the disease and for achieving clearance to reduce the risk of locoregional recurrence. It has not been possible to demonstrate survival benefit from extended lymph node excision, probably because of the rapid clearance of lymph into the thoracic duct.⁹ Formal reporting of lymph nodes according to the American Joint Committee on Cancer does not require anatomic division of regional lymph nodes.¹⁰ The superior lymphatic vessels are in close association with the splenic artery and vein, running along the upper border of the pancreas. The tail and left side of the pancreas drain toward lymph nodes in the hilum of the spleen, whereas the right side of the body and neck of the pancreas drain toward lymph nodes located near the upper border of the head of the pancreas. Both anterior and posterior aspects of the upper half of the pancreas drain to the superior lymphatic

vessels. There is a similar network of inferior lymphatic vessels that runs with the transverse pancreatic artery and vein. As with the superior lymphatic vessels, the tail and left side of the body drain toward lymph nodes in the hilum of the spleen, and the remainder of the pancreas drains toward nodes surrounding the head. There is a lack of clear demarcation within the regions of the pancreas that drain toward the spleen, those that drain toward the head of the pancreas, and those that drain to the superior or inferior vessels. This is because lymphatics richly anastomose and ramify together, and flow direction may be affected by local pressure changes. It is therefore difficult to accurately predict the direction of lymph drainage from carcinomas within the pancreas.

The external lymphatic network draining the head of the pancreas forms anterior and posterior vessels, which lie adjacent to the pancreaticoduodenal arteries and veins. These are situated in the groove between the duodenum and pancreas. In parallel with the blood vessels, there are four main lymph vessels that drain the head: anterior superior, posterior superior, anterior inferior, and posterior inferior. There is another route for lymph drainage of the head running with the GDA.

Although there is agreement on the general pattern of drainage, there is a lack of consensus on the nomenclature for regional nodes. The original descriptive classification was by Evans and Oschner in 1954,¹¹ and it was updated by Pansky in 1990.¹² The Japanese have provided more recent detailed studies and a numerical classification of peripancreatic lymph nodes [see Figure 14].¹³ There are two broad groups of lymph nodes: those forming a ring around the pancreas and those related to the aorta and its branches. Located in the hilum of the spleen are the splenic nodes, which lie in close proximity to the tail of the pancreas. These nodes drain lymph from the tail and left side of the body via the left superior and inferior external lymphatics. Within the gastrosplenic ligament is a group of related nodes, the gastrosplenic lymph nodes. Although these predominantly drain part of the stomach, they also receive some lymph from the tail and left side of the body of the pancreas. Along the splenic artery lie scattered nodes that drain the upper portions of the pancreas and some of the stomach. In the region of the upper part of the head of the pancreas are several small groups of nodes, which drain the anterior and posterior aspects of the upper head. The nomenclature of these subgroups is inconsistent between authors. They include gastroduodenal, pyloric, infrapyloric, and retropyloric groups. The hepatic group lies alongside the CBD and common hepatic artery. The pancreaticoduodenal nodes, divided into four subgroups, as with the vascular arcades, lie close to the blood vessels and lymphatics of the same name. The upper nodes drain the upper portions of the head, and the lower nodes drain the lower portions of the head. The infrapancreatic group of nodes completes the ring around the pancreas. These nodes lie along branches of the dorsal pancreatic artery. Evans and Oschner also included a mesocolic group of nodes, which lies within the transverse mesocolon.¹¹

The lymph nodes associated with the aorta have been divided into preaortic (in front of the aorta), lateral aortic (left of the aorta), and interaortocaval (between the aorta

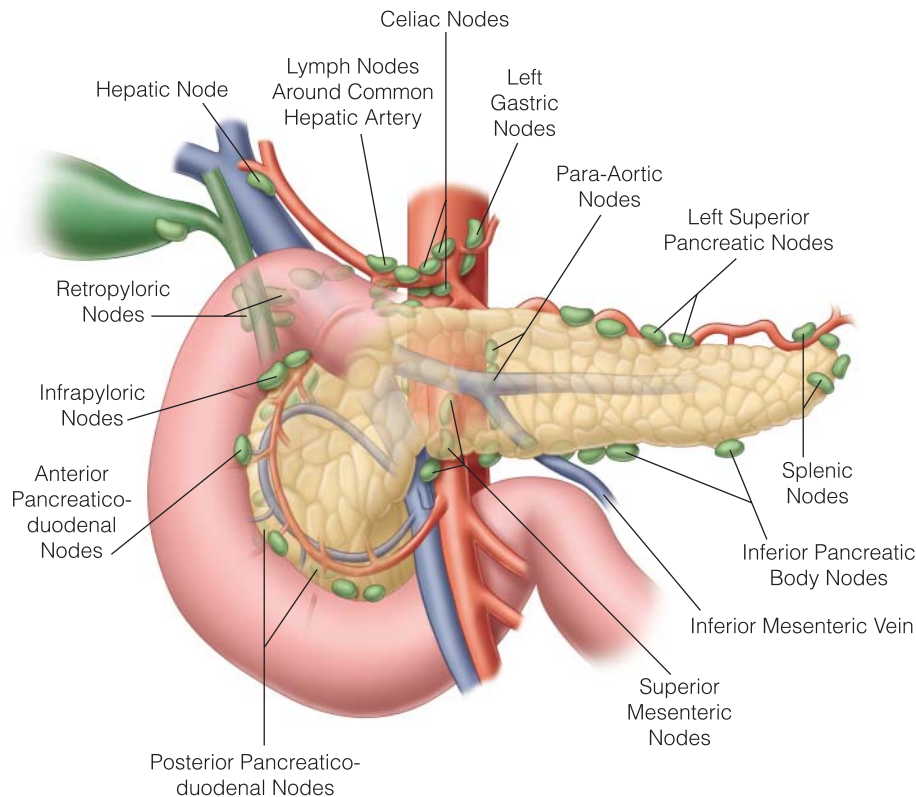


Figure 14 Peripancreatic lymph nodes.

and inferior vena cava) groups. These nodes lie between the celiac trunk and SMA. The preaortic nodes have two subgroups, the celiac group and the superior mesenteric group, which surround the vessels of the same name.

Nerve Supply of the Pancreas

Innervation of the pancreas occurs by the splanchnic nerves (sympathetic) and the vagus nerves (parasympathetic). Both contain efferent vasomotor fibers to the pancreatic acini, ducts, and blood vessels and afferent pain fibers. The former is critical to both exocrine and endocrine function, and the latter has significance because pain is an important feature of both benign and malignant pancreatic diseases. Pancreatic pain is multifactorial, and a full discussion is beyond the scope of this chapter, but factors include perineural infiltration by cancer, damage to perineurium, inflammatory mediators, ductal hypertension, and compartment syndrome. Pancreatic pain is poorly localized. Like other foregut structures, pain is most often referred to the epigastrium and to the midback. The interruption of pain is an important therapeutic goal, but the variety of methods used (including surgical, thoracoscopic, radiologic, and endoscopic chemical approaches) reflects the less than satisfactory response to neural ablation techniques. The mainstay of analgesia remains pharmacology.

The preganglionic sympathetic nerves are from the greater (T5-T10), the lesser (T9-T11), and sometimes the least splanchnic nerves. These pierce the diaphragm to reach ganglia within neural plexi associated with the origin of the celiac trunk and SMA. Postganglionic nerve fibers arising from

neurons in these ganglia reach the pancreas by accompanying branches of these arteries as periarterial plexi.

The preganglionic parasympathetic nerves, from the celiac division of the posterior vagal trunk, synapse with ganglia within the pancreas. The postganglionic fibers terminate at the pancreatic islet cells. Innervation of the islet cells is almost exclusively from the parasympathetic side, and fibers frequently synapse with acinar cells before reaching the islet cells, suggesting neural coordination between exocrine and endocrine components. Three types of neural termination with islets are recognized,¹⁴ but no selective termination is recognized with any particular islet cell type.

Arising in the pancreas, the afferent (visceral) pain fibers pass cranially through the celiac plexus to their cell bodies in the dorsal root ganglia within the splanchnic nerves, crossing to the spinal nerves by way of the white communicating rami and at a spinal level comparable to the preganglionic sympathetic fibers.

Physiology of the Exocrine Pancreas

The pancreas was not elected an organ until 1850, when Claude Bernard demonstrated that it had a function, namely, the production of digestive enzymes. The functional unit of the exocrine pancreas is the acini (meaning “cluster of grapes”), the collection of acinar cells responsible for the secretion of digestive enzymes, pancreatic fluid, and electrolytes via the ductal network.

Digestive enzymes are synthesized in the acinar cell endoplasmic reticulum, packaged by the Golgi apparatus in

zymogen granules, and released at the cell apex by exocytosis into the ductal system [see Figure 15]. The ductal epithelial cells are a continuous layer with tight junctions. Significant defenses exist to prevent premature intra-acinar enzyme activation (a key feature of acute pancreatitis), including compartmentalization in the granules, separation from lysozymes, trypsin inhibitors, and antiproteases. Activation of the enzymes normally occurs by cleavage of trypsinogen to trypsin by intestinal enteropeptidase, which in turn activates a cascade of the other digestive enzymes.

The exocrine pancreas secretes 800 mL/day or more of alkaline fluid, with a high HCO_3^- content (approximately 115 versus 25 mEq/L in plasma). Bicarbonate is generated within the ductal cells through the action of carbonic anhydrase and expelled into the lumen in exchange for chloride. Bile and intestinal juices along with pancreatic secretions help neutralize the gastric acid, raising the pH of the duodenal lumen toward 7.0.

Control of the exocrine function of the pancreas is via the hormones gastrin, cholecystokinin (CCK), and secretin, which are secreted by cells in the stomach and duodenum in response to distention and/or food and which cause secretion of pancreatic juices. Secretin acts via intracellular cyclic adenosine monophosphate (cAMP) in the centroacinar cells to produce copious secretion of very alkaline pancreatic juice that has low levels of digestive enzymes. CCK acts on the acinar cells to cause the release of zymogen granules and production of pancreatic juice rich in enzymes but low in volume. Its effect is mediated by phospholipase C. Like CCK, acetylcholine acts on acinar cells via phospholipase C to cause discharge of zymogen granules, and stimulation of the vagi causes secretion of a small amount of pancreatic juice rich in enzymes. There is evidence for vagally mediated conditioned reflex secretion of pancreatic juice in response to the sight and/or smell of food.

Approximately 80 to 90% of the pancreas can be surgically removed without producing pancreatic exocrine insufficiency. And if, by virtue of prior pancreatic disease, resection produces exocrine insufficiency, enzyme replacement is effective.

The Achilles heel and ever-present risk of pancreatic surgery is a leak from a pancreatic anastomosis or a pancreatic transection margin. The leak of pancreatic enzymes has dire potential consequences, including intra-abdominal collections, pancreatic fistulae, gastric and intestinal ileus, portal vein thrombosis and hypertension, pseudoaneurysm, and bleeding. The risk factors for leak have been well documented and include patient factors (malnutrition, age), pancreatic factors (soft gland, small duct, fatty replacement of pancreas), and surgeon factors (experience, precision, and technique).

Physiology of the Endocrine Pancreas

The pancreatic islets of Langerhans were discovered in 1869, and insulin was discovered in 1921. There are 1 to 2 million islets, which together weigh about a gram, and these are dispersed throughout the pancreas [see Figure 16]. These ovoid clusters of polyhedral cells are more plentiful in the tail than in the body and head and represent only 2% of the pancreatic mass.¹⁵ The perfusion of the islets is much greater than that of the acinar tissue, with each islet supplied by one or two arterioles and all the islet cells are in close proximity to fenestrated capillaries, which empty directly into the acinar capillary plexus.

The cells in the islets are divided into different types based on their immunostaining properties and morphology: A, B, D, E, and F cells. A cells secrete glucagon, B cells secrete insulin, D cells secrete somatostatin, E cells secrete ghrelin, and F cells secrete pancreatic polypeptide. B cells, which are

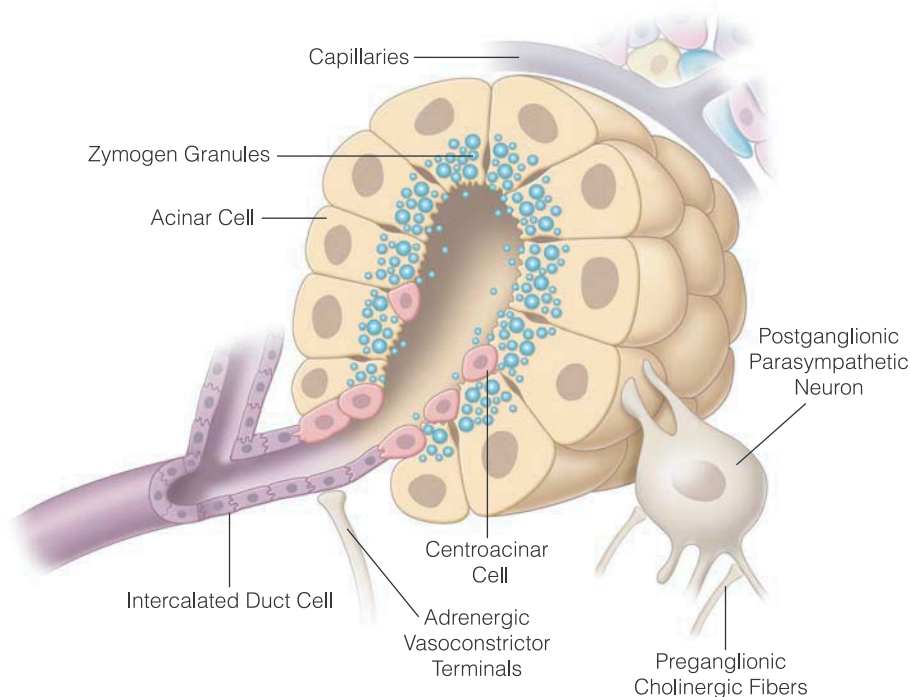


Figure 15 Microstructure and control of the exocrine pancreas.

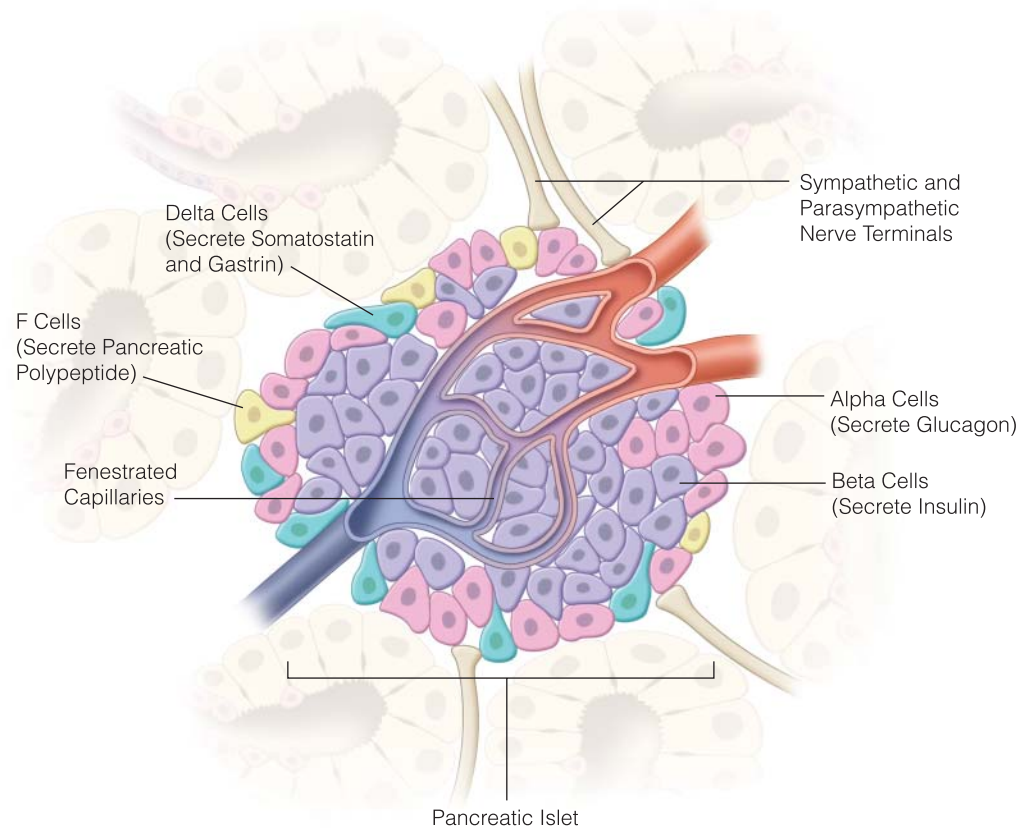


Figure 16 Microstructure and control of the endocrine pancreas.

the most abundant, account for 60 to 75% of the cells in the islets and are generally located in the center of each islet. They tend to be surrounded by A cells, which make up 20% of the total, and the less common D and F cells. The islets in the tail, the body, and the anterior and superior parts of the head of the human pancreas have many A cells and few, if any, F cells in the outer rim. The A cell-rich islets arise embryologically from the dorsal pancreatic bud, and the F cell-rich islets arise from the ventral pancreatic bud.

The importance of the endocrine pancreas lies in the fact that insulin plays a central role in the regulation of energy metabolism. Insulin is anabolic, increasing the storage of glucose, fatty acids, and amino acids. Glucagon is catabolic, mobilizing glucose, fatty acids, and the amino acids from stores into the bloodstream. These two hormones are reciprocally secreted in most circumstances. In the fed state, insulin stimulates the transport of glucose into tissues (to be consumed as fuel or stored as glycogen), the transport of amino acids into tissues (to build or replace protein), and the transport of fatty acids into tissues (to provide a depot of fat for future energy needs). In the fasting state, insulin secretion decreases and glucagon secretion increases. Liver glycogen stores, followed later by protein and fat stores, are mobilized to produce glucose. Ultimately, most nutrient needs are provided by fatty acids mobilized from fat stores.

The exocrine acinar tissue receives arterialized blood from two sources, directly and indirectly from the endocrine pancreas. The functional significance of the portal system

(insuloacinar axis), linking the exocrine and exocrine organs of the pancreas, is not well understood but suggests that the former may modulate the latter.

The islets contain many nerve endings. The autonomic neurotransmitter acetylcholine augments insulin and glucagon release, and noradrenaline inhibits glucose-induced insulin release. Both also modulate somatostatin and pancreatic polypeptide secretion. Islets can also influence each other through paracrine and autocrine communication. The paracrine effects of insulin are to activate beta cells and inhibit alpha cells; glucagon activates alpha cells, which activate beta and delta cells, and somatostatin inhibits alpha and beta cells.

Insulin excess causes hypoglycemia, which leads to convulsions and coma. Insulin deficiency, either absolute or relative, causes diabetes mellitus (chronic elevated blood glucose). Glucagon deficiency can cause hypoglycemia, and glucagon excess makes diabetes worse. Somatostatin plays a role in the regulation of islet cell secretion, and excess production causes hyperglycemia and other manifestations of diabetes. Pancreatic polypeptide is probably concerned primarily with the regulation of HCO_3^- secretion to the intestine. Glucagon, somatostatin, and possibly pancreatic polypeptide are also secreted by cells in the mucosa of the gastrointestinal tract.

Insulin causes hypokalemia as it increases the activity of Na^+ , K^+ -ATPase in cell membranes, with K^+ pumped into cells. Infusions of insulin and glucose significantly lower the plasma K^+ level in normal individuals and are an effective

way to treat hyperkalemia in patients with renal failure. Diabetic patients undergoing surgery require added potassium when insulin and glucose are given.

The panoply of neuroendocrine neoplasia arising from the islet cells partly reflects the different cell types, and these tumors can be nonfunctioning (no detectable secretion), of indeterminate malignant potential, undifferentiated, multifocal, and sometimes undetectable. These factors challenge diagnosis, and surgical treatment must be tailored, ensuring both clearance of the tumor and preservation of pancreatic function where possible. The surgical options include enucleation, median segment resection, spleen-preserving resection of the pancreas tail and/or body, distal pancreatectomy, subtotal pancreatectomy, and pancreaticoduodenectomy. It is unusual for a standard pancreatic resection to result in pancreatic endocrine deficiency. For instance, insulin deficiency does not occur unless more than 80% of the islet cell mass has been removed or the remaining pancreas is diseased, as in chronic pancreatitis, with a loss of islet cell mass or function.

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Figures 1 through 16 Christine Kenney

14 ANATOMY AND PHYSIOLOGY OF THE COLON, APPENDIX, RECTUM, AND ANUS

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The large intestine is composed of the cecum, appendix, ascending colon, transverse colon, descending colon, and sigmoid colon. It plays a role in immune function, nutrient absorption, and water and electrolyte absorption and secretion, whereas the rectum and anus function in the maintenance of continence and elimination of waste through defecation.

Colon

ANATOMY

The colon is composed of the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon and is approximately 0.9 to 1.5 meters long. The wall of the colon is made up of five distinct layers: mucosa, submucosa, circular muscle, longitudinal muscle, and serosa. The longitudinal muscle layer is divided into three distinct bands, named the taenia coli. The taenia coli converge and become circumferential proximally at the appendix and distally at the rectum; this convergence arbitrarily defines these structures. The haustra are the saccular protrusions of circular muscle between the taenia. The intraperitoneal colon is covered with serosa, whereas the retroperitoneal portions are not.¹ The muscular layers consist of smooth muscle cells connected by gap junctions that allow transmission of electrical signals and several types of interstitial cells of Cajal (ICC).²

The cecum is the first part of the large intestine and is located in the right lower quadrant of the abdomen in the iliac fossa in cases of normal embryologic intestinal rotation. The terminal ileum enters the cecum at the ileocecal valve; it enters obliquely and partially invaginates into it. The cecum is the widest portion of the colon at approximately 7.5 cm in both length and width and is therefore the most prone to perforation. When the cecum is distended, the folds of the ileocecal valve close, preventing reflux of cecal contents into the terminal ileum.¹

The ascending colon lies between the cecum and the transverse colon. The majority of the ascending colon is secondarily retroperitoneal. The transverse colon is the largest and most mobile portion of the large bowel and is defined proximally by the hepatic flexure and distally by the splenic flexure. The mesentery of the transverse colon, called the transverse mesocolon, often loops down and can adhere to the posterior border of the omentum. The descending colon again becomes retroperitoneal from the splenic flexure to the left iliac fossa, where it is continuous with the sigmoid colon. The sigmoid colon is characterized by an S-shaped loop and is of variable length. It extends from the iliac fossa

to the termination of the taenia coli, indicating the rectosigmoid junction. It has a long mesentery and significant freedom of movement, making it prone to volvulus.¹

Innervation

The colon receives innervation from four types of neurons: enteric, parasympathetic (excitatory), sympathetic (inhibitory), and intrinsic and extrinsic sensory² [see Figure 1].

The enteric nervous system (ENS) consists of two ganglionated plexuses and is estimated to contain more neurons than the spinal cord.³ The outer, myenteric (Auerbach) plexus lies between the longitudinal and circular muscle layers of the colon and contains motor neurons, which innervate the smooth muscle.^{2,3} The inner, submucosal (Meissner) plexus lies within the submucosal connective tissue and appears to be involved in mucosal functions such as secretion and blood flow.^{2,3}

The cecum, ascending colon, and proximal transverse colon receive modulatory nerve fibers traveling from the superior mesenteric plexus that carry both sympathetic and parasympathetic nerves. Parasympathetic innervation arises from the vagus nerve, which sends preganglionic cholinergic fibers, which synapse on ganglia within the enteric plexuses. Sympathetic innervation arises from the distal cervical to the third lumbar segments of the spinal cord. These nerve fibers enter the paravertebral sympathetic ganglia and emerge as splanchnic nerves, which travel through the preaortic ganglia, giving rise to the postganglionic adrenergic fibers supplying the colonic musculature. The descending and sigmoid colons receive parasympathetic fibers from the pelvic splanchnic nerves originating at S2, S3, and S4, whereas the sympathetic supply is from the lumbar portion of the sympathetic trunk and the superior hypogastric plexus.¹ The myenteric and submucosal plexuses also contain intrinsic sensory neurons, called intrinsic primary afferent neurons, which are sensitive to chemical and mechanical stimulation and synapse with ENS interneurons and myenteric motor neurons to regulate blood flow, secretion, and motility.^{2,4} There are two types of primary, extrinsic afferent neurons: vagal afferents sense thermal and chemical stimuli and regulate autonomic function, whereas spinal afferents sense mechanical stimuli and contribute to pain sensation.⁴

Blood Supply

The colon is supplied by branches of the superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA) [see Figure 2]. The cecum, ascending colon, and proximal transverse colon are part of the embryonic midgut and are therefore supplied by branches of the SMA. The distal transverse colon, descending colon, and sigmoid colon are part of the embryonic hindgut and are supplied by branches of the IMA.⁵ The cecum is supplied by the ileocolic artery, the

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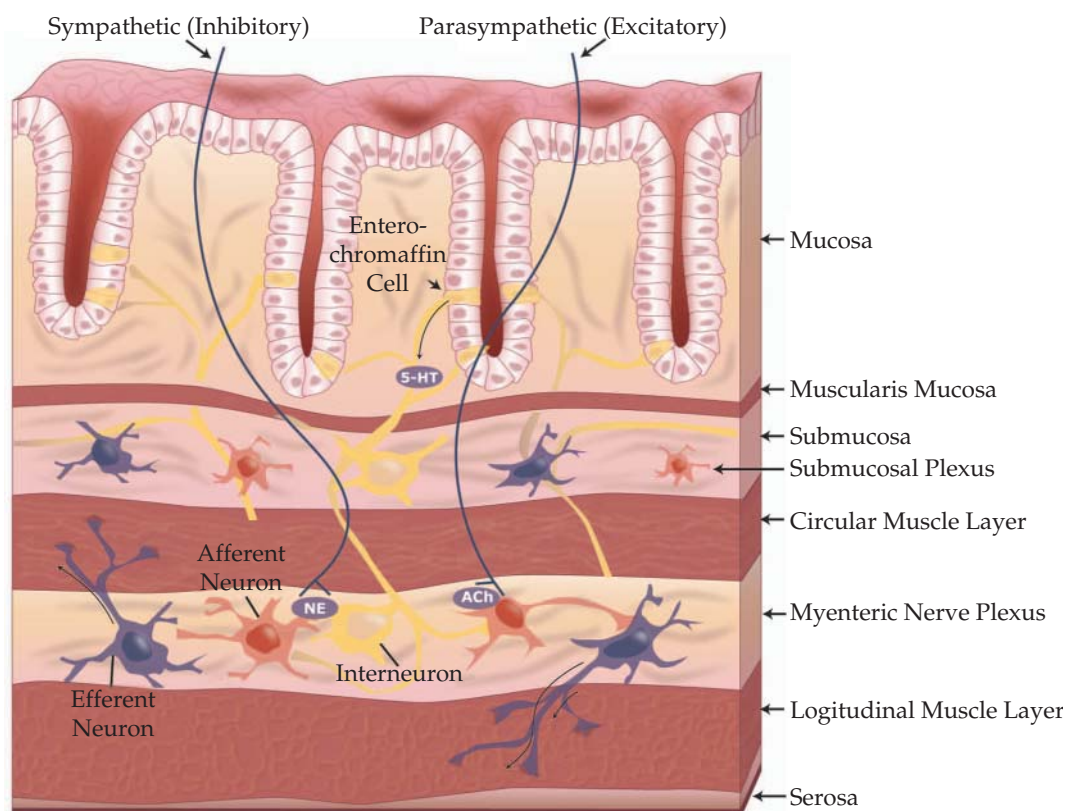


Figure 1 The layers of the colonic wall and the various components of the enteric nervous system and its interactions with the central nervous system. The two ganglionated plexuses, the submucosal (Meissner) plexus and the myenteric (Auerbach) plexus, are seen. Adrenergic, inhibitory input is via sympathetic afferent input, whereas cholinergic, excitatory stimulus is via parasympathetic afferent input. Sensory input begins with the enterochromaffin cells, which sample the luminal environment and transmit that information via intrinsic and extrinsic sensory neurons using serotonin as a messenger. 5-HT = Serotonin, NE = Norepinephrine, ACh = Acetyl Choline.

terminal branch of the SMA. Venous drainage is by the ileocolic vein into the superior mesenteric vein. The ascending colon is supplied by the ileocolic and right colic arteries, and the transverse colon is supplied by the middle colic artery. The ileocolic artery is the most constant anatomically, whereas the right and middle colic arteries are variable and may be missing in up to 25% of the population.⁵ The descending colon is supplied by the left colic artery, whereas the sigmoid colon is supplied by the left colic and superior sigmoid arteries, which are branches of the IMA. The veins of the colon mirror the arterial supply, except for the inferior mesenteric vein, which drains into the splenic vein.¹

The terminal branches of arteries supplying the colon form collateral branches with each other via the marginal artery of Drummond, which is complete in 15 to 20% of the population.¹ This major collateral arcade is located within the mesentery and lies about 2 to 3 cm from the mesenteric border of the bowel. The arc of Rioloan is an additional set of collateral branches that lie more centrally within the mesentery and form a connection between the middle colic and left colic arteries. The splenic flexure is considered a “watershed” area of variable arterial blood supply: in 89% of the population, the splenic flexure is supplied by the IMA, and in 11%, the supply is via the SMA. Limited collateral blood supply in this area makes it prone to ischemia.⁵

Lymphatic Drainage

The lymphatic drainage of the colon originates in the muscularis mucosa. Lymph nodes are found along the bowel wall, the inner mesenteric border of the bowel, and the named mesenteric vessels and adjacent to the origin of the superior and inferior mesenteric arteries, called the epicolic, paracolic, intermediate, and main lymph nodes, respectively. The lymphatic drainage of the cecum is via the ileocolic nodes that lie along the ileocolic artery and drain into the superior mesenteric lymph nodes. The ascending and transverse colons drain into the superior mesenteric lymph nodes that follow the supplying arteries. The descending and sigmoid colons drain along their vascular supply into the inferior mesenteric lymph nodes, although the splenic flexure can sometimes drain into the superior mesenteric basin.¹

PHYSIOLOGY

The colon has several important functions: mixing and propagation of luminal contents, water and electrolyte secretion and absorption, and salvage of nutrients not absorbed by the small intestine through bacterial metabolism of carbohydrates.

Motility

The circular and longitudinal muscle layers of the colon work together to accomplish mixing of fecal material and

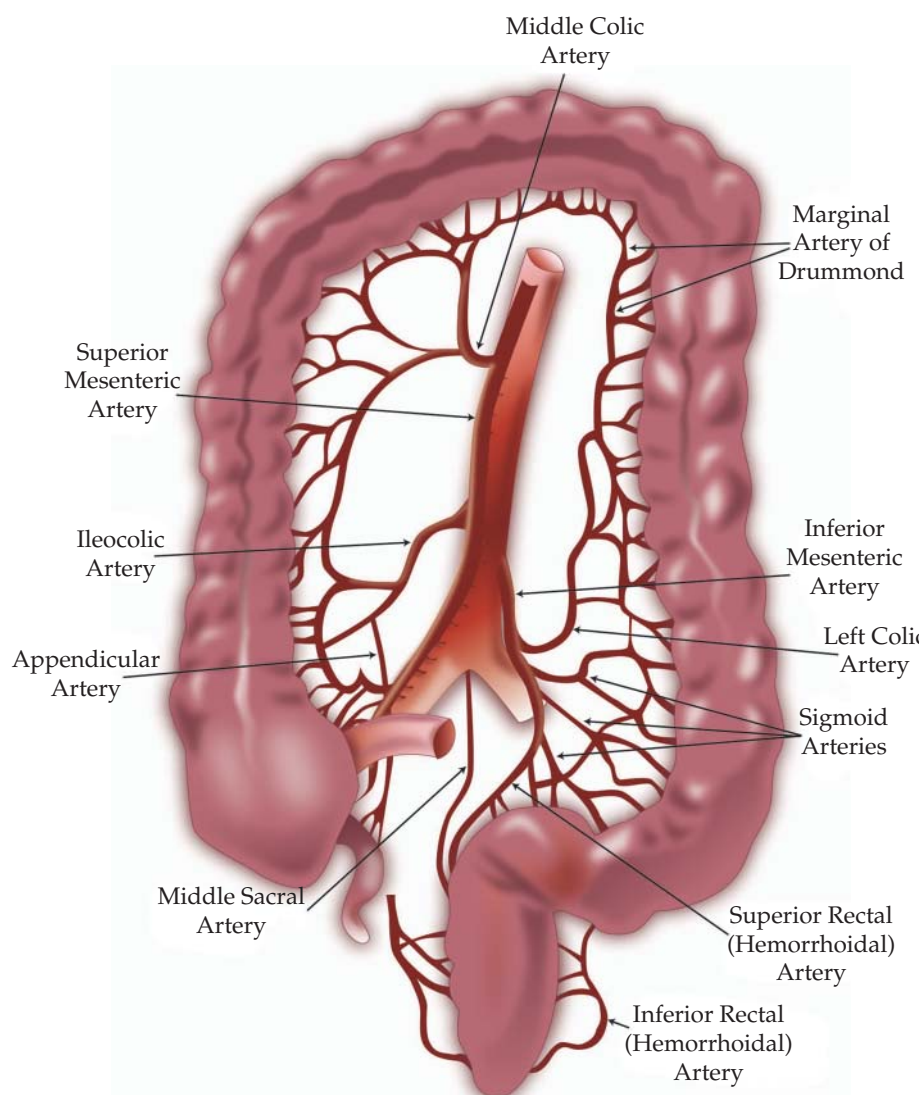


Figure 2 The blood supply to the colon. Major branches from the superior and inferior mesenteric vessels are depicted. In addition, the marginal artery of Drummond can be visualized as the collateral arcades in the distal mesentery.

propagation to the anorectum for evacuation. The three longitudinal muscle bands forming the taenia cause the circular muscle to bulge outward into pockets, which foster mixing. Conversely, when the circular muscle of the colon contracts, deep folds protrude into the colonic lumen, greatly reducing its diameter.⁶

Colonic motility is irregular and includes both tonic and phasic components.⁶ Basal motor activity is segmental, of low amplitude, with contractions occurring singly or in bursts and in random sequence⁷ [see *Figure 3*]. Motor patterns differ between the right colon and left colon: orad and anad peristalsis facilitate mixing in the ascending and proximal transverse colons, whereas the distal transverse and descending colons exhibit only caudal peristalsis with contracting circular rings that travel distally.⁶ Motor activity in the colon exhibits diurnal variation: activity is minimal during sleep but increases dramatically on awakening. Motor activity also starts promptly with food ingestion and lasts up to several hours after a meal⁷; postprandial contractile activity is associated with mass movement of fecal contents and is known as the gastrocolic reflex. High-amplitude propagated contractions (HAPCs), consisting of a pressure

wave greater than 50 mm Hg, propagate fecal contents over several segments, often producing an urge to defecate, and occur on average six times per day.^{6,7} The colocolonic reflex describes the phenomenon of colonic relaxation with rectal distention, which is mediated by the ENS independent of regulatory efferent input.⁶

Circumferential stretch has been shown to induce peristalsis, whereas longitudinal stretch inhibits peristalsis via nitric oxide (NO) release in animal models.⁸ Colonic tone, another important factor in motor regulation, is increased in the postprandial period and associated with a decrease in storage capacity and the production of a pressure gradient that moves intraluminal contents to areas of lower pressure. Additionally, colonic motility is significantly affected by its intraluminal contents. In the proximal colon, short-chain fatty acids (SCFAs) are produced through carbohydrate metabolism by bacteria and have an excitatory effect, although higher concentrations of SCFAs seem to have an inhibitory effect on colonic motility.⁶

Basal colonic contractions are controlled by pacemaking electrical signals generated by the ICC, a continuous network of electrically coupled cells.⁹ ICC networks extend

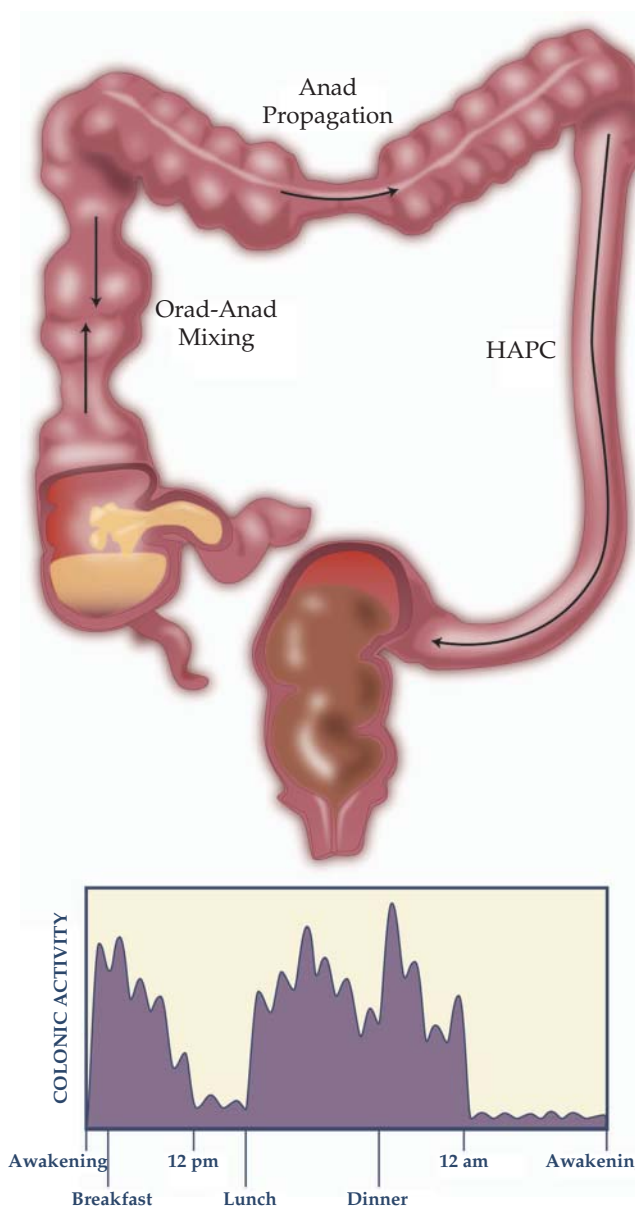


Figure 3 The various types of colonic motility: bidirectional mixing in the proximal colon, unidirectional propagation in the distal colon, and high-amplitude propagated contractions (HAPCs) over several segments. Colonic activity varies with time of day and is most evident on awakening and after meals.

along all portions of the gastrointestinal tract that are involved in phasic contractions, including the colon. These cells are coupled to smooth muscle and spontaneously generate and propagate slow waves through voltage-dependent Ca^{2+} channels.⁹ The ENS provides direct neuronal control of motility, whereas further modulation is effected by the sympathetic, parasympathetic, and extrinsic afferent sensory pathways.² The extrinsic spinal sensory neurons mediate sensation and activate sympathetic and parasympathetic pathways.² Normal colonic motility is maintained even if sympathetic and parasympathetic input is disrupted due to the intrinsic, integrated functionality of the ENS.¹⁰

Neurohormonal Influences

The regulation of colonic activity is quite complex, and numerous modulatory agents have been identified in recent years. Motor activity is regulated by muscarinic, α -2 adrenergic, serotonergic 5-hydroxytryptamine₃ (5-HT₃), and nitrergic mechanisms.¹¹ In addition to the sympathetic and parasympathetic pathways, nonadrenergic, noncholinergic (NANC) neurotransmitters also play an important role in modulating colon motility. Cholecystokinin (CCK), motilin, serotonin, and gastrin excite intestinal contractions. Excitatory neuropeptides include substance P, neurotensin, and γ -aminobutyric acid (GABA), whereas inhibitory neuropeptides include secretin, glucagon, vasoactive intestinal peptide, neuropeptide Y, and NO.^{12,13} There is evidence that NO is a major NANC neurotransmitter in the colon that causes inhibition of smooth muscle contractions.^{12,13}

Sensation, peristalsis, and secretion in the colon are mediated through the release of 5-HT, or serotonin, from enterochromaffin cells in the mucosal layer and both intrinsic and extrinsic sensory neurons in the ganglionated plexuses. 5-HT₃ receptors are found within both the central nervous system and the ENS, where they mediate transmission of sensation from the gut to the brain, but 5-HT_{1P} and 5-HT₄ receptors, which mediate peristalsis and secretion, are found only within the ENS. This differential distribution of receptors has led to the development of targeted therapies for colonic dysfunctional disorders.¹⁰

The most important dietary stimulant of colonic motility is fat through the mediator CCK. CCK₁ receptors are predominantly found within the myenteric plexus and the longitudinal muscle layer. The endogenous release of CCK is associated with the gastrocolic reflex, HAPCs, and pain sensation; CCK receptor antagonists significantly decrease these effects in vivo.¹⁴

Electrolyte and Water Secretion and Absorption

The colon is the final site at which electrolyte and water secretion and absorption can be performed in the gastrointestinal tract. Traditionally, surface epithelium has been associated with absorption, whereas colonic crypt cells were associated with secretion. However, both types of cells can perform either function.¹⁵ There are three main types of cells: columnar epithelial cells, mucus-secreting goblet cells, and enterochromaffin cells [see Figure 4]. The two major electrolytes absorbed by the colon include sodium (Na^+) and chloride (Cl^-) via electroneutral, luminal Na^+/H^+ and $\text{Cl}^-/\text{HCO}_3^-$ exchangers. Na^+/H^+ exchange occurs in both surface and crypt cells and is tightly coupled to $\text{Cl}^-/\text{HCO}_3^-$ exchange. There are several identified types of cell surface exchangers, each with a different regulatory profile based on location within the colon.¹⁵ The distal colon has an additional electrogenic exchanger, the epithelial Na^+ channel (EnaC). A large electrochemical gradient favors Na^+ transport into the apical cell, accompanied by Cl^- as the anion. Na^+ is then excreted at the basolateral membrane by Na^+/K^+ ATPase and Cl^- by Cl^- channels or $\text{Cl}^-/\text{HCO}_3^-$ exchange.¹⁵ This uptake of NaCl is highly regulated with multiple feedback mechanisms, including upregulation of absorption by aldosterone. Water absorption, an important function of the colon that osmotically follows the absorption of Na^+ and Cl^- , is approximately 1.5 L per day.¹⁵

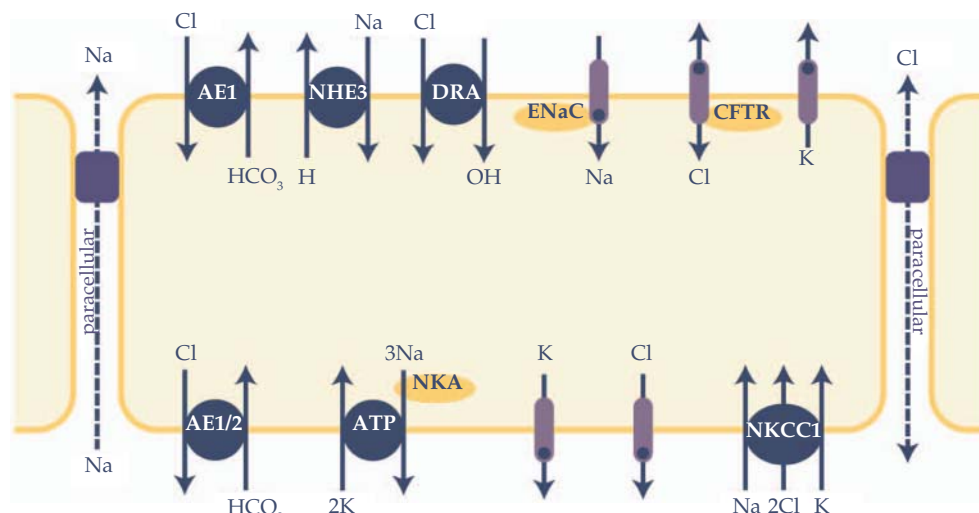


Figure 4 Electrolyte absorption and secretion are mediated by a complex system of electroneutral and electrogenic transporters. Sodium and chloride are primarily absorbed, whereas potassium and bicarbonate are primarily excreted by the colon. Water absorption, which is stimulated by short-chain fatty acids, also occurs in the colon and often follows NaCl absorption. AE = anion exchanger; ATP = adenosine triphosphate; CFTR = cystic fibrosis transmembrane regulator; DRA = Cl⁻/HCO₃⁻ exchanger SLC26A3 ("downregulated in adenoma"); ENaC = epithelial Na⁺ channel; NHE = Na⁺/H⁺ exchanger; NKA = Na⁺/K⁺ ATPase; NKCC1 = Na⁺-2Cl⁻-K⁺ cotransporter.

Secretion of electrolytes, mainly potassium (K⁺) and bicarbonate (HCO₃⁻), also occurs in the colon in a delicate balance to maintain homeostasis. The apical secretion of KCl is balanced by basolateral absorption of Na⁺, K⁺, and Cl⁻ via the Na⁺-2Cl⁻-K⁺ cotransporter type 1 (NKCC) protein. Cl⁻ is secreted via the cystic fibrosis transmembrane regulator (CFTR) protein and calcium-activated Cl⁻ channels. K⁺ is secreted by at least two different types of apical channels, which are upregulated by aldosterone and glucocorticoids in parallel with Na⁺ absorption.¹⁵ HCO₃⁻ secretion has specific roles, including pH control of the surface microenvironment and influence on surface mucus production.¹⁶ The expression of colonic HCO₃⁻ transporters is highly segmental: HCO₃⁻ and Cl⁻ secretion and absorption are higher in the proximal colon.¹⁶

Absorption and secretion are regulated by neurotransmitters released from the submucosal plexus as well as hormones and paracrine substances. Small gaseous molecules, such as NO, hydrogen sulfide (H₂S), and carbon monoxide (CO), also have a role in the regulation of colonic ion transport.¹⁷ NO acts through the cyclic guanosine monophosphate pathway and induces Cl⁻ secretion. H₂S relaxes smooth muscle and induces anion secretion across the apical epithelium. CO, a metabolite from the degradation of heme, also induces Cl⁻ and HCO₃⁻ secretion.¹⁷

SCFAs, primarily acetate, propionate, and butyrate, are the major anions in stool and are synthesized by the bacterial fermentation of carbohydrates not absorbed by the small intestine.¹⁸ SCFAs are absorbed by the colonic epithelium and stimulate the absorption of water in a Na⁺-dependent manner,¹⁸ facilitate the absorption of electrolytes, and reduce the osmotic load of carbohydrates.¹⁹ SCFAs are the primary fuel source for colonocytes and have been estimated to make up 5 to 15% of daily energy requirements.^{20,21} They additionally help regulate epithelial cell proliferation and differentiation.¹⁸ A recent study suggests that butyrate may exert a variety of effects, including inhibition of inflammation

and carcinogenesis, reinforcement of the mucosal defense barrier, and decreasing oxidative stress.²¹

Appendix

ANATOMY

The vermiform appendix is a blind intestinal diverticulum that arises from the posteromedial aspect of the cecum approximately 2 cm inferior to the ileocecal valve.^{1,22} The opening of the appendix is partially covered by a fold of mucosa called the valve of Gerlach.²³ It can range from approximately 6 to 10 cm in length, with an average of 9 cm,^{1,23} and has a short mesentery, the mesoappendix, which is derived from the mesentery of the terminal ileum.¹ Whereas the base of the appendix is in a relatively constant position, the tip of the appendix is highly variable, leading to differing presentations of pathology. The various positions of the appendiceal tip include preileal, postileal, pelvic, promontoric, subcecal, retrocecal, and paracolic locations,^{22,23} with the large majority (65%) in the retrocecal location.²⁴ The musculature of the appendix resembles the cecum and includes both circular and longitudinal layers.

Innervation

Appendiceal innervation mirrors that of the proximal colon. Parasympathetic innervation arises from the vagus nerve. Sympathetic innervation arises from thoracic and lumbar spinal cord via the paravertebral sympathetic ganglia.

Vasculature

The appendix is supplied by the appendicular artery, a branch of the ileocolic artery. It is drained by the ileocolic vein.

Lymphatic Drainage

The appendix contains a large number of lymph follicles within the submucosa, which peak in concentration in the

10 to 20 years age group and decline in number with age.²² The lymphoid system of the appendix drains via the mesoappendix to empty into the ileocecal nodes.²²

PHYSIOLOGY

Immunology

The definitive role of the appendix remains unclear; however, there is consensus that the appendix is not merely a vestigial organ but rather has an important immunologic function acting as a secondary lymphoid organ.

Studies in rabbits have indicated that the appendix is not only important for mucosal gut immunity but is also the primary site of antibody diversification.²⁵ The removal of the appendix from neonatal rabbits severely depletes the amount of intestinal IgA, IgM, and IgG, as well as IgA-producing plasma cells, supporting the concept that the appendix is involved in the early development of gastrointestinal mucosal immunity.²⁶ Other studies have shown that antibody diversification occurs in the lymphoid tissue of young rabbits²⁷ and that the appendix evolves into a secondary lymphoid organ as the rabbit matures.

Lymphoid tissue is abundant within the appendix and comprises a substantial portion of the MALT (mucosa-associated lymphoid tissue) system. Appendix-derived mesenchymal stem cells have been isolated from human appendices, indicating that the appendix plays a role in the development of mucosal immune cells in humans.²⁸ Additionally, stem cells isolated from the appendix have been shown to produce extrathymic T cells.²⁹ The removal of the appendix significantly lowers the level of secretory IgA in the serum, and this effect lasts from 3 months to 3 years.³⁰ The immune function of the appendix appears most prominent between the ages of 10 and 20, after which it wanes until lymph follicles disappear around age 60.²² Recent studies also indicate that the appendix may have an antiinflammatory, cardioprotective effect in childhood and early adulthood.^{31–33} Together these data suggest that the appendix may play a partial yet currently undefined role in overall immunologic function.

Rectum

The most distal portion of the gastrointestinal tract is the rectum and anal canal. Although comprising only a small portion of the overall anatomy, this region and its interactions are quite complex in their functioning to maintain fecal continence.

ANATOMY

The rectum begins with a coalescence of the taenia coli of the sigmoid colon to become the outer longitudinal muscle. The rectum is generally considered to be 12 to 18 cm in length and is contained within the pelvis. It is often divided into thirds due to the three visualized endoluminal folds (two on the left and one on the right) called the valves of Houston. The rectum ends with its exit through the pelvic floor musculature to begin the anal canal. The peritoneal reflection variably exists along the course of the rectum, making the anterior distal portion and the entire posterior rectum extraperitoneal. The rectum and mesorectum are

encompassed within the visceral layer of the endopelvic fascia. This fascia propria makes up the mesorectal envelope. The parietal layer of endopelvic fascia encompasses the sacrum.³⁴ Anteriorly, a potential plane exists between the fascia propria of the rectum and a thin fascial covering (Denonvillier fascia) of the prostate and seminal vesicles in males or rectovaginal septum in females.³⁵ Posteriorly, the rectum overlies the endopelvic fascia covering of the sacrum, which encompasses the sacral nerves, middle sacral artery, and presacral veins. Just cephalad to the coccyx, the two endopelvic fascial layers fuse to form the Waldeyer fascia (rectosacral fascia)³⁶ [see Figure 5]. Laterally, attachments exist, often referred to as the lateral rectal ligaments (stalks). Although it is often reported that these ligaments contain the middle rectal (hemorrhoidal) arteries, it has been shown that arteries exist here only 20% of the time.³⁷ More likely, these ligaments generally contain nerve branches stemming from the pelvic plexuses below the peritoneal reflection and onto the mesorectum.³⁸

Innervation

The organization of local rectal myenteric and submucosal plexuses mirrors that of the colon, as described above. The rectum receives parasympathetic innervation from the ventral roots of S2–S4 via the pelvic plexus, where sympathetic and parasympathetic nerve fibers mix.^{2,39} Sympathetic innervation arises from the thoracolumbar sympathetic ganglia, which enter the preaortic plexus as the inferior mesenteric nerves and then extend caudally to the mesenteric plexus. The fibers then branch into the hypogastric nerves at the upper rectum and join the parasympathetic nerve branches.^{34,39} As the mixed nerve fibers enter the rectum, a portion of them form thick bundles that transmit the electrical input up and down the distal colon.² Sensory innervation of the rectum is via spinal afferent neurons with cell bodies in the lumbar and sacral dorsal root ganglia.

Blood Supply

The blood supply to the rectum comes from the superior rectal (hemorrhoidal) artery and, when they exist, the middle rectal (hemorrhoidal) arteries, resulting in a rich intramural anastomotic network.⁵ The superior rectal artery is a continuation of the IMA, whereas the middle rectal artery begins from the hypogastric or inferior vesicle arteries and runs anterolaterally to the lower third of the rectum. The superior sacral artery arises from the back of the aorta just above the bifurcation of the common iliac arteries and supplies the posterior wall of the rectum.⁵ The venous drainage of the rectum is via the superior rectal (hemorrhoidal) vein into the inferior mesenteric vein to the portal system. The middle rectal (hemorrhoidal) veins drain through internal pudendal and hypogastric veins eventually to the inferior vena cava.^{34,40}

Lymphatic Drainage

The lymphatic drainage of the proximal rectum (two thirds) is via the inferior mesenteric nodes and eventually to the para-aortic region. The distal rectum can drain via this same system following the superior rectal artery or can drain laterally to the internal iliac nodes (following the middle rectal arteries).³⁴

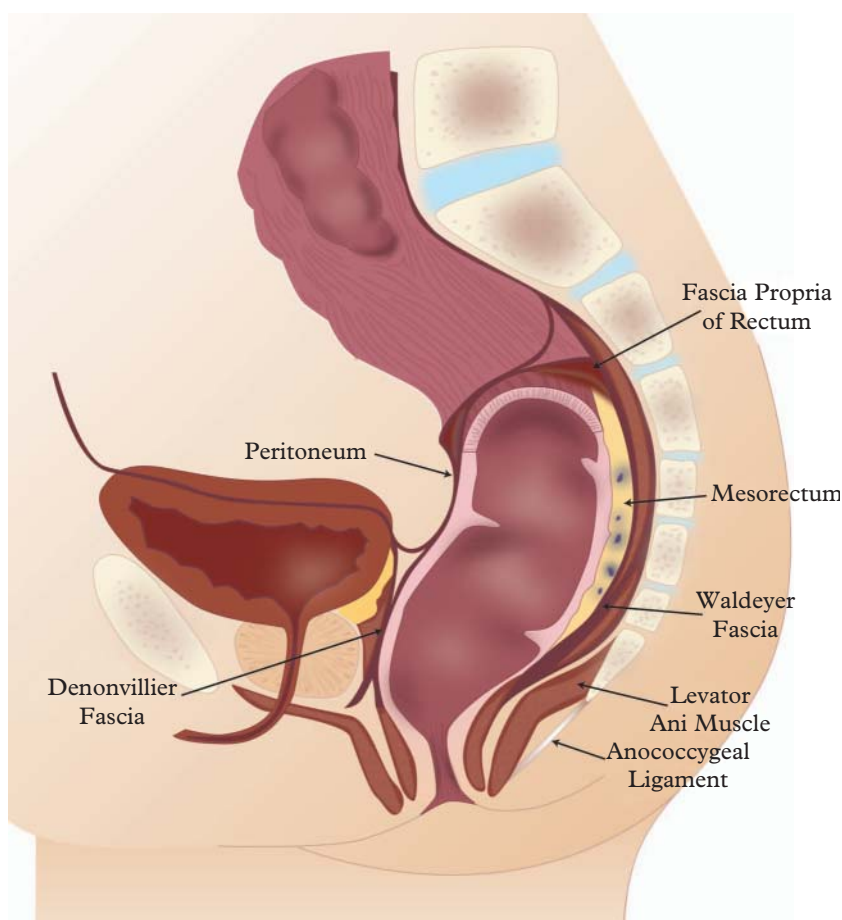


Figure 5 Lateral view of the rectum demonstrating the surrounding fascial components. The rectum and mesorectum are encompassed within the visceral layer of the endopelvic fascia. Denonvillier fascia can be seen anteriorly, whereas the rectosacral fascia is noted posteriorly.

PHYSIOLOGY

Storage

The rectum serves as a reservoir for fecal material until it is socially acceptable to defecate. The rectosigmoid junction and the sigmoid itself may also contribute to maintaining continence.⁴⁰ In a normally functioning rectum, increased stool volume is accompanied by passive distention of the rectum that maintains a low intraluminal pressure. This continues until a maximum volume is reached and defecation is initiated.⁴¹ The rectal wall contains mechanoreceptors that sense the filling state and level of contraction of the rectum.³⁹ Distention of the rectum sends a signal to begin the act of defecation, as described below. Rectal distention also delays both gastric emptying and intestinal transit.⁴⁰ The rectum has a low resting pressure of 5 mm Hg, with both low-amplitude and high-amplitude contractions observed on an infrequent basis. The pressure in the rectum is significantly less than that in the anal canal, and this pressure gradient helps keep the anal canal empty.⁴⁰

Anal Canal

ANATOMY

Musculature

Although there is some variation over the exact definition of the anal canal, most would agree that it exists distally

from the anal verge up to the anorectal ring proximally. The anorectal ring can be palpated at the top of the external anal sphincter/levator ani complex, whereas the anal verge can be described as the point of normal opposition of the anal opening in its usual resting state.^{34,42} The length of the anal canal may vary between 2.5 and 5 cm and is generally longer in males. The anal canal follows the length of the internal and external anal sphincters, with the external sphincter ending slightly more distal [see Figure 6]. The internal sphincter is a continuation of the circular smooth muscle layer of the rectum, whereas the external anal sphincter is composed of striated muscle circumferentially wrapping the entire anal canal.³⁹ Between the internal and external sphincter muscles exists the palpable intersphincteric groove. Historically, the external anal sphincter was described as containing three components, subcutaneous, superficial, and deep portions, whereas others consider this to be a continuous sheet of muscle closely associated with the puborectalis muscle of the levator ani.^{40,43} In addition, striated muscle fibers, called the conjoined longitudinal muscle, extend from the longitudinal muscle of the rectum to the levator ani and anorectal ring, eventually descending between the internal and external sphincter muscles to insert on the perianal skin as the corrugator cutis ani muscle.⁴⁰

The levator ani muscles essentially make up the pelvic floor. They extend bilaterally from the superior pubic rami to the ischium or coccyx and are composed of four striated muscles: the puborectalis, iliococcygeus, pubococcygeus,

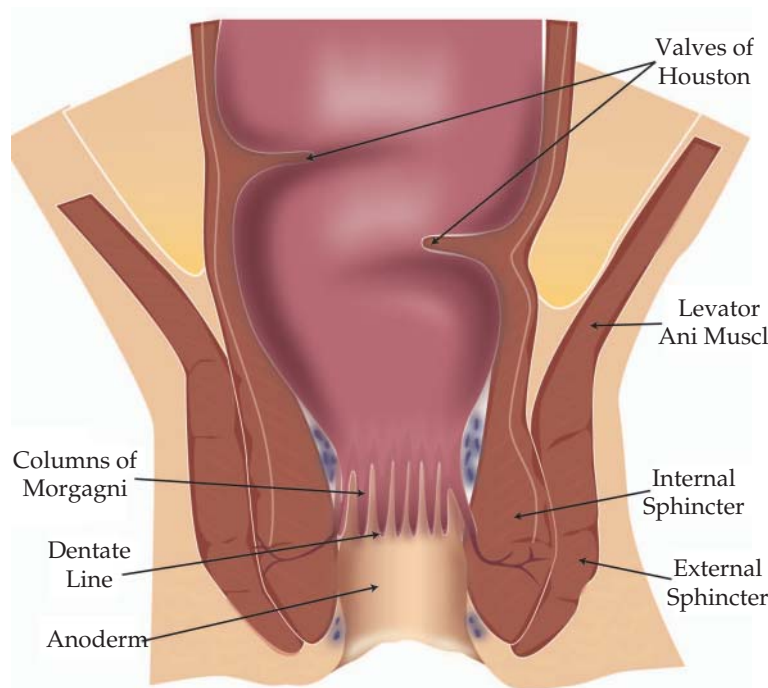


Figure 6 The anal canal is visualized, noting the relation of both the internal and external sphincters. The internal sphincter is a continuation of the circular smooth muscle layer of the rectum, whereas the external anal sphincter is composed of striated muscle wrapping the anal canal. Additionally, the dentate line is shown as the junction of the anal transition zone and the squamous epithelium. At this level, the columns of Morgagni are seen extending proximally. Finally, the valves of Houston can be seen within the rectum.

and, variably, ischiococcygeus. The puborectalis is the most medially located of these muscles and is felt to serve as both a portion of the pelvic floor and the sphincter mechanism.³⁴ This muscle is U shaped, acting as a sling to pull the anorectal junction anteriorly. This results in maintenance of an acute anorectal angle, approximately 90 to 110° in normal subjects, which aids in continence.^{44,45}

Canal Lining

The lining of the anal canal is variable. The most proximal portion is composed of columnar epithelium, whereas the distal portion is made up of squamous epithelium of the anoderm (lacking hair and glands). Within the midportion of the canal, there is a transition (cloacogenic) zone where the lining may be composed of columnar, transitional, or stratified squamous epithelium.³⁹ The dentate or pectinate line is formed by the junction of this transition zone and the squamous epithelium. Beginning at this level, several longitudinal folds extend proximally and are referred to as the columns of Morgagni [see Figure 6]. The anal valves form at their base and create small pockets or crypts. These crypts are connected by ducts to a variable number of anal glands (four to 12). Most of these glands are located posteriorly and extend into the intersphincteric space, usually entering through the internal sphincter.^{34,40} More distally beyond the anal verge, the skin becomes thicker, containing glands and hair follicles usually referred to as the anal margin.³⁴

Innervation

The anal canal is supplied by both sympathetic and parasympathetic nerves, including L5 and S2-S4 (pudendal nerve). The pudendal nerve passes through the Alcock canal to exit the pelvis. It then gives rise to both the inferior rectal (S2, S3) and perineal branches (S4). The motor innervation

to the pelvic floor musculature is via S2-S4 superiorly and S4 (perineal) inferiorly, with the puborectalis muscle innervated by the inferior rectal branches. The external anal sphincter is innervated by S2-S4 (both inferior rectal and perineal branches), whereas the internal anal sphincter maintains the same innervation as the rectal circular muscle (L5 and S2-S4). The sensory innervation comes from the inferior rectal nerve, variably extending just proximal to the dentate line. Above this level, the distal rectum senses only distention via parasympathetic afferent fibers.^{34,39}

Blood Supply

The arterial supply to the anal canal may arise from both the superior (originating as the inferior mesenteric artery) and inferior (from the internal pudendal artery) rectal vessels. In addition, middle rectal arteries from the internal iliac vessels can contribute, although this is more variable. Bilaterally, the inferior rectal vessels also supply the sphincter muscles while contributing to the rich intramural collateralization of the anorectum.³⁹

The venous drainage of the anal canal is bilateral via the middle and inferior rectal (hemorrhoidal) veins into the internal iliac veins and eventually to the inferior vena cava. In addition, the external and internal rectal plexuses below and above the dentate line, respectively, communicate in the perianal and submucosal spaces,³⁴ thus contributing to the makeup of the anal cushions.⁴⁶

Lymphatic Drainage

Lymphatic drainage of the anal canal varies in relation to the dentate line. Above this line, drainage feeds to the inferior mesenteric and internal iliac nodes, whereas below it drains into inferior rectal (hemorrhoidal) lymphatics to the superficial inguinal nodes.⁴⁰

PHYSIOLOGY

Although the exact function of the anal cryptoglandular components is unknown,³⁴ their presence sets the basis for potential perianal infection. With this in mind, several potential perianal/perirectal spaces exist containing areolar and adipose tissue that can become clinically relevant. These include the intersphincteric space, the ischioanal space (lateral to the external anal sphincter and extending to the levator ani), the posterior superficial and deep postanal spaces (communicating to the ischioanal space bilaterally and separated by the anococcygeal ligament, also extending to the levator ani), and the supralelevator space.³⁹

Anal Continence

Continence relies on the successful interaction of several factors. These include stool consistency, reservoir compliance and capacity, resting and squeeze sphincter pressures, and anorectal sensation.⁴¹ The anal orifice remains closed at rest due to the continuous circumferential contraction of the sphincter mechanism. The internal anal sphincter maintains 50 to 85% of the resting tone and thus acts to avoid involuntary stool loss. The normal mean resting pressure generally ranges from 50 to 70 mm Hg. The external anal sphincter accounts for 25 to 30% of the resting tone, whereas the anal cushions contribute 15%.⁴⁰ The external anal sphincter is unique in that it remains tonically contracted despite its striated nature. It can be voluntarily contracted for 40 to 60 second periods and can generally increase tone by two to three times above the resting pressure.³⁹ In addition, the puborectalis muscle also contributes to the preservation of gross fecal continence by maintaining an appropriate anorectal angle.⁴⁰

Normal Defecation

At rest, the above factors maintain fecal continence. However, once the rectal reservoir is distended, further events are set in motion for initiating defecation. The first begins after an initiation of the left colon to propel stool contents into the rectum by normal daily peristaltic waves. Once the rectum is distended, a reflex relaxation of the internal anal sphincter occurs (rectoanoinhibitory reflex [RAIR]). This allows contact of the contents with the sensitive anal canal, allowing distinction between flatus and stool (sampling mechanism). During this time, the external anal sphincter contracts to maintain continence. If appropriate emptying is then determined, a sitting or squatting position allows straightening of the anorectal angle. By further increasing intra-abdominal pressure (straining), the pelvic floor descends and the external anal sphincter further relaxes as its pressure resistance is overcome. This results in passage of the fecal contents through the relaxed pelvic floor. After passage, a closing reflex restores normal tone and closes the anal canal.^{39,40}

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Acknowledgement

Figures 1 to 6 Karen Williams.

NORMAL LABORATORY VALUES

Clinical Chemistry

<i>Analyte</i>	<i>Specimen</i>	<i>Units Used at MGH*</i>	<i>SI Units</i>
Acetoacetate	P	< 1 mg/dl	< 100 µmol/L
Albumin	S	3.5–5.5 g/dl	35–55 g/L
Aldolase	S	0–6 U/L	0–100 nkat/L
Alpha ₁ -antitrypsin	S	85–213 mg/dl	0.8–2.1 g/L
Alpha-fetoprotein	S	< 15 ng/ml	< 15 µg/L
Aminotransferases	S		
Aspartate (AST, SGOT)		0–35 U/L	0–0.58 µkat/L
Alanine (ALT, SGPT)		0–35 U/L	0–0.58 µkat/L
Ammonia, as NH ₃	P	10–80 µg/dl	6–47 µmol/L
Amylase	S	60–180 U/L	0.8–3.2 µkat/L
Angiotensin-converting enzyme (ACE)	S	< 40 U/L	< 670 nkat/L
Anion gap	S	7–16 mmol/L	7–16 mmol/L
Apolipoprotein	S		
Apolipoprotein A1		119–240 mg/dl	1.2–2.4 g/L
Apolipoprotein B		52–163 mg/dl	0.52–1.63 g/L
Apolipoprotein B-to-apolipoprotein A1 ratio		0.35–0.98	0.35–0.98
Arterial blood gases, sea level	WB, arterial		
Bicarbonate (HCO ₃ ⁻)		21–30 mEq/L	21–28 mmol/L
Partial pressure of carbon dioxide (PCO ₂)		35–45 mm Hg	4.7–5.9 kPa
pH		7.38–7.44	7.38–7.44
Partial pressure of oxygen (PO ₂)		80–100 mm Hg	11–13 kPa
β-Hydroxybutyrate	P	< 3 mg/dl	< 300 µmol/L
β ₂ -Microglobulin	S	1.2–2.8 mg/L	1.2–2.8 mg/L
	U	≤ 200 µg/L	≤ 200 µg/L
Bilirubin	S		
Total		0.3–1.0 mg/dl	5.1–17.0 µmol/L
Direct		0.1–0.3 mg/dl	1.7–5.1 µmol/L
Indirect		0.2–0.7 mg/dl	3.4–12.0 µmol/L
Brain natriuretic peptide (BNP)	P	< 167 pg/ml (age- and sex-dependent)	< 167 ng/L (age- and sex-dependent)
Calcium	S	9.0–10.5 mg/dl	2.2–2.6 mmol/L
Calcium, ionized	WB	4.5–5.6 mg/dl	1.1–1.4 mmol/L
CA15–3	S	0–30 U/ml	0–30 kU/L
CA19–9	S	0–37 U/ml	0–37 kU/L
CA27–29	S	0–32 U/ml	0–32 kU/L
CA125	S	0–35 U/ml	0–35 kU/L
Calcitonin	S		
Male		3–26 pg/ml	3–26 ng/L
Female		2–17 pg/ml	2–17 ng/L
Carbon dioxide			
Content, sea level	P	21–30 mEq/L	21–30 mmol/L
Partial pressure (PCO ₂), sea level	WB, arterial	35–45 mm Hg	4.7–5.9 kPa
Carbon monoxide content	WB		Symptoms with 20% saturation of hemoglobin
Carcinoembryonic antigen (CEA)	S	0–3.4 ng/ml	0–3.4 µg/L
Ceruloplasmin	S	27–37 mg/dl	270–370 mg/L
Cholinesterase	S	5–12 U/ml	5–12 kU/L
Chloride	S	98–106 mEq/L	98–106 mmol/L

Note: This table contains reference values for adults for laboratory tests commonly ordered at the Massachusetts General Hospital (MGH) and recorded in the Case Records. The table revises the most recently published data (Normal Reference Laboratory Values. N Engl J Med 339:1063-72, 1998). Laboratory values are expressed in the units used at the MGH and the units of the Système International d'Unités (SI units). The table is not intended to provide a comprehensive review of reference values, since this information is widely available in standard textbooks. To avoid suggesting an endorsement of commercial products by the hospital or the *Journal*, information on specific methods and instruments is not provided. Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at the MGH, as well as in chapters of *ACP Medicine*, may therefore not be appropriate for other institutions and may not be optimal in some situations.

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†The creatine kinase relative index is calculated as [MB isoenzyme (in nanograms per milliliter) ÷ total creatine kinase (in units per liter)] × 100.

JF—joint fluid P—plasma PRP—platelet-rich plasma RBC—red blood cell S—serum U—urine WB—whole blood

Clinical Chemistry (continued)

Analyte	Specimen	Units Used at MGH*	SI Units
Cholesterol	P		
Low-density lipoprotein (LDL) cholesterol			
Optimal		< 100 mg/dl	< 2.59 mmol/L
Near or above normal		100–129 mg/dl	2.59–3.34 mmol/L
Borderline high		130–159 mg/dl	3.36–4.11 mmol/L
High		160–189 mg/dl	4.13–4.88 mmol/L
Very high		≥ 190 mg/dl	≥ 4.91 mmol/L
High-density lipoprotein (HDL) cholesterol			
Low		< 40 mg/dl	< 1.03 mmol/L
High		≥ 60 mg/dl	≥ 1.55 mmol/L
Total cholesterol			
Desirable		< 200 mg/dl	< 5.17 mmol/L
Borderline high		200–239 mg/dl	5.17–6.18 mmol/L
High		≥ 240 mg/dl	≥ 6.18 mmol/L
Copper	S	70–140 µg/dl	11–22 µmol/L
	U	3–35 µg/24 hr	0.047–0.55 µmol/24 hr
Coproporphyrins, types I and III	U	100–300 µg/24 hr	150–460 µmol/24 hr
C-peptide	S	0.5–2.0 ng/ml	0.17–0.66 nmol/L
Creatine kinase	S		
Total			
Female		40–150 U/L	0.67–2.50 µkat/L
Male		60–400 U/L	1.00–6.67 µkat/L
MB isoenzyme	S	0–7 ng/ml	0–7 µg/L
Relative index [†]	S	Method-dependent	Method-dependent
Creatinine	S	< 1.5 mg/dl	< 133 µmol/L
Erythropoietin	S	5–36 IU/L	5–36 IU/L
Fatty acids, free (nonesterified)	P	< 8–25 mg/dl	0.28–0.89 mmol/L
Fibrinogen and fibrinogen-degradation products [see under Hematology and Coagulation]			
Folic acid	RBC	150–450 ng/ml/cells	340–1,020 nmol/L/cells
γ-Glutamyltransferase	S	1–94 U/L	1–94 U/L
Glucose	P		
Fasting			
Normal		75–115 mg/dl	4.2–6.4 mmol/L
Diabetes mellitus		> 125 mg/dl	> 7.0 mmol/L
2-hr postprandial	P	120 mg/dl	< 6.7 mmol/L
Hemoglobin A _{1c}	WB	3.8%–6.4%	0.038–0.064 hemoglobin fraction
Homocysteine	P	4–12 µmol/L	4–12 µmol/L
Hydroxyproline	U	0–1.3 mg/24 hr	0–10 µmol/24 hr
Iron	S	50–150 µg/dl	9–27 µmol/L
Iron-binding capacity	S	250–370 µg/dl	45–66 µmol/L
Iron-binding capacity, saturation	S	20%–45%	0.2–0.45
Ketone (acetone)	S, U	Negative	Negative
Lactate	P, venous	5–15 mg/dl	0.6–1.7 mmol/L
Lactate dehydrogenase	S	100–190 U/L	1.7–3.2 µkat/L
Lactate dehydrogenase isoenzymes	S		
Fraction 1 (of total)		14%–26%	0.14–0.25
Fraction 2		29%–39%	0.29–0.39
Fraction 3		20%–26%	0.20–0.25
Fraction 4		8%–16%	0.08–0.16
Fraction 5		6%–16%	0.06–0.16
Lead (adult)	S	< 10–20 µg/dl	< 0.5–1 µmol/L
Lipase	S	0–160 U/L	0–2.66 µkat/L
Lipids, triglyceride [see Triglycerides]			
Lipoprotein(a)	S	0–30 mg/dl	0–300 mg/L
Magnesium	S	1.8–3.0 mg/dl	0.8–1.2 mmol/L
Mercury	WB	0.6–59 µg/L	3.0–294 nmol/L
	U, 24 hr	< 20 µg/L	< 99.8 nmol/L

Clinical Chemistry (continued)

Analyte	Specimen	Units Used at MGH*	SI Units
Microalbumin	U		
24-hr		< 20 mg/L or < 31 mg/24 hr	< 0.02 g/L or < 0.031 g/24 hr
Spot, morning		< 0.03 mg albumin/mg creatinine	< 0.03 g albumin/g creatinine
Myoglobin	S		
Male			19–92 µg/L
Female			12–76 µg/L
5'-Nucleotidase	S	0–11 U/L	0.02–0.18 µkat/L
Osmolality	P	285–295 mOsm/kg serum water	285–295 mmol/kg serum water
	U	300–900 mOsm/kg	300–900 mmol/kg
Oxygen			
Content, sea level	WB, arterial	17–21 vol%	
	WB, venous (arm)	10–16 vol%	
Saturation, sea level	WB, arterial	97%	0.97 mol/mol
	WB, venous (arm)	60%–85%	0.60–0.85 mol/mol
Partial pressure (PO ₂)	WB	80–100 mm Hg	11–13 kPa
pH	WB	7.38–7.44	
Parathyroid hormone–related peptide	S	< 1.3 pmol/L	< 1.3 pmol/L
Phosphatase			
Acid	S	0–5.5 U/L	0.90 nkat/L
Alkaline	S	30–120 U/L	0.5–2.0 nkat/L
Phosphorus, inorganic	S	3–4.5 mg/dl	1.0–1.4 mmol/L
Porphobilinogen	U	None	None
Potassium	S	3.5–5.0 mEq/L	3.5–5.0 mmol/L
Prealbumin	S	19.5–35.8 mg/dl	195–358 mg/L
Prostate-specific antigen (PSA)	S		
Female		< 0.5 ng/ml	< 0.5 µg/L
Male			
≤ 40 yr		0–2.0 ng/ml	0–2.0 µg/L
> 40 yr		0–4.0 ng/ml	0–4.0 µg/L
PSA, free (men 45–75 yr with PSA values between 4 and 20 ng/ml)		> 25% associated with benign prostatic hyperplasia	> 0.25 associated with benign prostatic hyperplasia
Protein			
Total	S	5.5–8.0 g/dl	55–80 g/L
Fractions	S		
Albumin		3.5–5.5 g/dl (50%–60%)	35–55 g/L
Alpha ₁		0.2–0.4 g/dl (4.2%–7.2%)	2–4 g/L
Alpha ₂		0.5–0.9 g/dl (6.8%–12%)	5–9 g/L
Beta		0.6–1.1 g/dl (9.3%–15%)	6–11 g/L
Gamma		0.7–1.7 g/dl (13%–23%)	7–17 g/L
Globulin		2.0–3.5 g/dl (40%–50%)	20–35 g/L
Pyruvate	P, venous	0.5–1.5 mg/dl	60–170 µmol/L
Sodium	S	136–145 mEq/L	136–145 mmol/L
Transferrin	S	230–390 mg/dl	2.3–3.9 g/L
Triglycerides	S	< 160 mg/dl	< 1.8 mmol/L
Troponin			
I	S	0–0.4 ng/ml	0–0.4 µg/L
T	S	0–0.1 ng/ml	0–0.1 µg/L
Urea nitrogen	S	10–20 mg/dl	3.6–7.1 mmol/L
Uric acid	S		
Male		2.5–8.0 mg/dl	150–480 µmol/L
Female		1.5–6.0 mg/dl	90–360 µmol/L
Urobilinogen	U	1.0–3.5 mg/24 hr	1.7–5.9 µmol/24 hr
Vitamin A	S	20–100 µg/dl	0.7–3.5 µmol/L
Vitamin B ₁ (thiamine)	S	0–2 µg/dl	0–75 nmol/L

Clinical Chemistry (*continued*)

<i>Analyte</i>	<i>Specimen</i>	<i>Units Used at MGH*</i>	<i>SI Units</i>
Vitamin B ₂ (riboflavin)	S	4–24 µg/dl	106–638 nmol/L
Vitamin B ₆	P	5–30 ng/ml	20–121 nmol/L
Vitamin C (ascorbic acid)	S	0.4–1.0 mg/dl	23–57 µmol/L
Vitamin D ₃ (1,25-dihydroxyvitamin D)	S	25–45 pg/ml	60–108 pmol/L
Vitamin D ₃ (25-hydroxyvitamin D)	P	10–68 ng/ml	24.9–169.5 nmol/L
Vitamin E	S	5–18 µg/ml	12–42 µmol/L
Vitamin K	S	0.13–1.19 ng/ml	0.29–2.64 nmol/L

Therapeutic-Drug Monitoring and Toxicology

Drug	Therapeutic Level		Toxic Level	
	Units Used at MGH*	SI Units	Units Used at MGH*	SI Units
Acetaminophen	10–30 µg/ml	66–199 µmol/L	> 200 µg/ml	> 1,324 µmol/L
Amikacin				
Peak	25–35 µg/ml	43–60 µmol/L	> 35 µg/ml	> 60 µmol/L
Trough	4–8 µg/ml	6.8–13.7 µmol/L	> 10 µg/ml	> 17 µmol/L
Amitriptyline	120–250 ng/ml	433–903 nmol/L	> 500 ng/ml	> 1,805 nmol/L
Amphetamine	20–30 ng/ml	148–222 nmol/L	> 200 ng/ml	> 1,480 nmol/L
Barbiturates, most short-acting			> 20 mg/L	> 88 µmol/L
Bromide			> 1,250 µg/ml	> 15.6 mmol/L
Carbamazepine	6–12 µg/ml	26–51 µmol/L	> 15 µg/ml	> 63 µmol/L
Chlordiazepoxide	700–1,000 ng/ml	2.34–3.34 µmol/L	> 5,000 ng/ml	> 16.7 µmol/L
Clonazepam	15–60 ng/ml	48–190 nmol/L	> 80 ng/ml	> 254 nmol/L
Clozapine	200–350 ng/ml	0.6–1.0 µmol/L		
Cocaine			> 1,000 ng/ml	> 3,300 nmol/L
Cyclosporine	Varies with time after dose and type of transplantation, with ranges of 100–400 ng/ml	Varies with time after dose and type of transplantation, with ranges of 83–333 nmol/L	Varies with time after dose and type of transplantation	Varies with time after dose and type of transplantation
Desipramine	75–300 ng/ml	281–1,125 nmol/L	> 400 ng/ml	> 1,500 nmol/L
Diazepam	100–1,000 ng/ml	0.35–3.51 µmol/L	> 5,000 ng/ml	> 17.55 µmol/L
Digoxin	0.8–2.0 ng/ml	1.0–2.6 nmol/L	> 2.5 ng/ml	> 3.2 nmol/L
Doxepin	30–150 ng/ml	107–537 nmol/L	> 500 ng/ml	> 1,790 nmol/L
Ethanol			> 300 mg/dl	> 65 mmol/L
Behavioral changes			> 20 mg/dl	> 4.3 mmol/L
Clinical intoxication			> 100 mg/dl	> 1 g/L
Ethosuximide	40–100 µg/ml	283–708 µmol/L	> 150 µg/ml	> 1,062 µmol/L
Flecainide	0.2–1.0 µg/ml	0.5–2.4 µmol/L	> 1.0 µg/ml	> 2.4 µmol/L
Gentamicin				
Peak	8–10 µg/ml	16.7–20.9 µmol/L	> 10 µg/ml	> 21.0 µmol/L
Trough	< 2–4 µg/ml	< 4.2–8.4 µmol/L	> 4 µg/ml	> 8.4 µmol/L
Ibuprofen	10–50 µg/ml	49–243 µmol/L	100–700 µg/ml	485–3,395 µmol/L
Imipramine	125–250 ng/ml	446–893 nmol/L	> 500 ng/ml	> 1,784 nmol/L
Lidocaine	1.5–6.0 µg/ml	6.4–26 µmol/L		
Central nervous system or cardiovascular depression			6–8 µg/ml	26–34.2 µmol/L
Seizures, obtundation, decreased cardiac output				
Lithium	0.6–1.2 mEq/L	0.6–1.2 nmol/L	> 8 µg/ml	> 34.2 µmol/L
Methadone	100–400 ng/ml	0.32–1.29 µmol/L	> 2 mEq/L	> 2 mmol/L
Methotrexate	Variable	Variable	> 2,000 ng/ml	> 6.46 µmol/L
1–2 wk after low dose			> 9.1 ng/ml	> 20 nmol/L
48 hr after high dose			> 227 ng/ml	> 0.5 µmol/L
Morphine	10–80 ng/ml	35–280 nmol/L	> 200 ng/ml	> 700 nmol/L
Nortriptyline	50–170 ng/ml	190–646 nmol/L	> 500 ng/ml	> 1.9 µmol/L
Phenobarbital	10–40 µg/ml	43–170 µmol/L		
Slowness, ataxia, nystagmus			35–80 µg/ml	151–345 µmol/L
Coma with reflexes			65–117 µg/ml	280–504 µmol/L
Coma without reflexes			> 100 µg/ml	> 430 µmol/L
Phenytoin	10–20 µg/ml	40–79 µmol/L	> 20 µg/ml	> 79 µmol/L
Procainamide	4–10 µg/ml	17–42 µmol/L	> 10–12 µg/ml	> 42–51 µmol/L
Quinidine	2–5 µg/ml	6–15 µmol/L	> 6 µg/ml	> 18 µmol/L
Salicylates	150–300 µg/ml	1,086–2,172 µmol/L	> 300 µg/ml	> 2,172 µmol/L
Theophylline	8–20 µg/ml	44–111 µmol/L	> 20 µg/ml	> 110 µmol/L
Thiocyanate				
After nitroprusside infusion	6–29 µg/ml	103–499 µmol/L	> 120 µg/ml	> 2,064 µmol/L
Nonsmoker	1–4 µg/ml	17–69 µmol/L		
Smoker	3–12 µg/ml	52–206 µmol/L		
Tobramycin				
Peak	8–10 µg/ml	17–21 µmol/L	> 10 µg/ml	> 21 µmol/L
Trough	< 4 µg/ml	< 9 µmol/L	> 4 µg/ml	> 9 µmol/L
Valproic acid	50–150 µg/ml	347–1,040 µmol/L	> 150 µg/ml	> 1,040 µmol/L
Vancomycin				
Peak	18–26 µg/ml	12–18 µmol/L	> 80–100 µg/ml	> 55–69 µmol/L
Trough	5–10 µg/ml	3–7 µmol/L		

*Massachusetts General Hospital.

Immunology

<i>Analyte</i>	<i>Specimen</i>	<i>Units Used at MGH*</i>	<i>SI Units</i>
Autoantibodies			
Antiadrenal antibody	S	Negative at 1:10 dilution	Not applicable
Anti-double-stranded (native) DNA	S	Negative at 1:10 dilution	Not applicable
Anti-glomerular basement membrane antibody	S		
Qualitative		Negative	Negative
Quantitative		< 5 U/ml	< 5 kU/L
Antigranulocyte antibody	S	Negative	Not applicable
Anti-Jo-1 antibody	S	Negative	Not applicable
Anti-La antibody	S	Negative	Not applicable
Antimitochondrial antibody	S	Negative	Not applicable
Antineutrophil cytoplasmic autoantibody, cytoplasmic (c-ANCA)	S		
Qualitative		Negative	Negative
Quantitative (antibody to proteinase 3)		< 2.8 U/ml	< 2.8 kU/L
Antineutrophil cytoplasmic autoantibody, perinuclear (p-ANCA)	S		
Qualitative		Negative	Negative
Quantitative (antibody to myeloperoxidase)		< 1.4 U/ml	< 1.4 kU/L
Antinuclear antibody	S	Negative at 1:40 dilution	Not applicable
Anti-parietal cell antibody	S	Negative at 1:20 dilution	Not applicable
Anti-Ro antibody	S	Negative	Not applicable
Antiplatelet antibody	S	Negative	Not applicable
Anti-RNP antibody	S	Negative	Not applicable
Anti-Scl-70 antibody	S	Negative	Not applicable
Anti-Smith antibody	S	Negative	Not applicable
Anti-smooth muscle antibody	S	Negative at 1:20 dilution	Not applicable
Antithyroglobulin	S	Negative	Not applicable
Antithyroid antibody	S	< 0.3 IU/ml	< 0.3 kIU/L
Bence-Jones protein	S	None detected	Not applicable
Qualitative	U	None detected in 50-fold concentrated specimen	Not applicable
Quantitative	U		
Kappa		< 2.5 mg/dl	< 0.03 g/L
Lambda		< 5.0 mg/dl	< 0.05 g/L
β ₂ -Microglobulin	S	< 0.27 mg/dl	< 2.7 mg/L
	U	< 120 µg/day	< 120 µg/day
C1 esterase inhibitor protein	S		
Antigenic		12.4–24.5 mg/dl	0.12–0.25 g/L
Functional		Present	Present
C-reactive protein	S		
Routine		0.08–3.10 mg/L	0.08–3.10 mg/L
High sensitivity		0.02–8.00 mg/L	0.02–8.00 mg/L
Complement			
C3	S	86–184 mg/dl	0.86–1.84 g/L
C4	S	20–58 mg/dl	0.20–0.58 g/L
Total complement, enzyme immunoassay	S	63–145 U/ml	63–145 kU/L
Factor B	S	17–42 mg/dl	0.17–0.42 g/L
Cryoproteins	S	Negative	Not applicable
Immunofixation	S	Negative	Not applicable
Immunoglobulin			
IgA	S	60–309 mg/dl	0.60–3.09 g/L
IgD	S	0–14 mg/dl	0–140 mg/L
IgE	S	10–179 IU/ml	24–430 µg/L
IgG	S	614–1,295 mg/dl	6.14–12.95 g/L
IgG1	S	270–1,740 mg/dl	2.7–17.4 g/L
IgG2	S	30–630 mg/dl	0.3–6.3 g/L
IgG3	S	13–320 mg/dl	0.13–3.20 g/L

*Massachusetts General Hospital.

JF—joint fluid P—plasma S—serum U—urine WB—whole blood

Immunology (*continued*)

<i>Analyte</i>	<i>Specimen</i>	<i>Units Used at MGH*</i>	<i>SI Units</i>
IgG4	S	11–620 mg/dl	0.11–6.20 g/L
IgM	S	53–334 mg/dl	0.53–3.34 g/L
Joint-fluid crystal	JF	Negative	Not applicable
Joint-fluid mucin	JF	Only type I mucin present	Not applicable
Lupus erythematosus cell test	WB	Negative	Negative
Rheumatoid factor	S, JF	< 30.0 IU/ml	< 30 kIU/L
Serum protein electrophoresis	S	Normal pattern	Not applicable

Hematology and Coagulation

<i>Analyte</i>	<i>Specimen</i>	<i>Units Used at MGH*</i>	<i>SI Units</i>
Activated clotting time	WB	70–180 sec	70–180 sec
Activated protein C resistance (factor V Leiden)	P	Ratio > 2.1	Not applicable
Alpha ₂ -antiplasmin	P	80%–130%	0.80–1.30
Antiphospholipid-antibody panel			
Partial thromboplastin time–lupus anticoagulant screen	P	Negative	Negative
Platelet-neutralization procedure	P	Negative	Negative
Dilute viper-venom screen	P	Negative	Negative
Anticardiolipin antibody	S		
IgG		0–15 GPL units	0–15 arbitrary units
IgM		0–15 MPL units	0–15 arbitrary units
Antithrombin III	P		
Antigenic		22–39 mg/dl	220–390 mg/L
Functional		80%–130%	0.8–1.30 U/L
Anti-Xa assay (heparin assay)	P		
Unfractionated heparin		0.3–0.7 IU/ml	0.3–0.7 kIU/L
Low-molecular-weight heparin		0.5–1.0 IU/ml	0.5–1.0 kIU/L
Danaparoid		0.5–0.8 IU/ml	0.5–0.8 kIU/L
Bleeding time		2.0–9.5 min	2.0–9.5 min
Carboxyhemoglobin	WB		
Nonsmoker		0%–2.3%	0–0.023
Smoker		2.1%–4.2%	0.021–0.042
Clot retraction	WB	50%–100%/2 hr	0.50–1.00/2 hr
Cryofibrinogen	P	Negative	Negative
D-dimer	P	< 0.5 µg/ml	< 0.5 mg/L
Differential blood count	WB		
Neutrophils		40%–70%	0.40–0.70
Band forms		0%–10%	0–0.10
Lymphocytes		22%–44%	0.22–0.44
Monocytes		4%–11%	0.04–0.11
Eosinophils		0%–8%	0–0.08
Basophils		0%–3%	0–0.03
Erythrocyte count	WB		
Male		4.50–5.90 × 10 ⁶ /mm ³	4.50–5.90 × 10 ¹² /L
Female		4.00–5.20 × 10 ⁶ /mm ³	4.00–5.20 × 10 ¹² /L
Erythrocyte lifespan			
Normal survival	WB	120 days	120 days
Chromium labeled, half-life		25–35 days	25–35 days
Erythrocyte sedimentation rate	WB		
Female		1–25 mm/hr	1–25 mm/hr
Male		0–17 mm/hr	0–17 mm/hr
Factor II, prothrombin	P	60%–140%	0.60–1.40
Factor V	P	60%–140%	0.60–1.40
Factor VII	P	60%–140%	0.60–1.40
Factor VIII	P	50%–200%	0.50–2.00
Factor IX	P	60%–140%	0.60–1.40
Factor X	P	60%–140%	0.60–1.40
Factor XI	P	60%–140%	0.60–1.40
Factor XII	P	60%–140%	0.60–1.40
Factor XIII screen	P	No deficiency detected	Not applicable
Factor-inhibitor assay	P	< 0.5 Bethesda unit	< 0.5 Bethesda unit
Ferritin	S		
Male		30–300 ng/ml	30–300 µg/L
Female		10–200 ng/ml	10–200 µg/L
Fibrin and fibrinogen-degradation products	P	< 2.5 µg/ml	< 2.5 mg/L
Fibrinogen	P	150–400 mg/dl	1.50–4.00 g/L
Folate (folic acid)	S, P		
Normal		3.1–17.5 ng/ml	7.0–39.7 nmol/L
Borderline deficient		2.2–3.0 ng/ml	5.0–6.8 nmol/L
Deficient		< 2.2 ng/ml	< 5.0 nmol/L
Excess		> 17.5 ng/ml	> 39.7 nmol/L
Glucose-6-phosphate dehydrogenase, erythrocyte	WB	No gross deficiency	Not applicable
Ham test (acidified serum test)	WB	Negative	Negative

*Massachusetts General Hospital.

P—plasma PRP—platelet-rich plasma S—serum WB—whole blood

Hematology and Coagulation (continued)

Analyte	Specimen	Units Used at MGH*	SI Units
Haptoglobin	S	16–199 mg/dl	0.16–1.99 g/L
Hematocrit	WB		
Male		41.0%–53.0%	0.41–0.53
Female		36.0%–46.0%	0.36–0.46
Hemoglobin			
Plasma	P	1–5 mg/dl	0.01–0.05 g/L
Whole blood			
Male	WB	13.5–17.5 g/dl	8.4–10.9 mmol/L
Female	WB	12.0–16.0 g/dl	7.4–9.9 mmol/L
Hemoglobin electrophoresis	WB		
Hemoglobin A		95%–98%	0.95–0.98
Hemoglobin A ₂		1.5%–3.5%	0.015–0.035
Hemoglobin F		0%–2.0%	0–0.02
Hemoglobins other than A, A ₂ , or F		Absent	Absent
Heparin-induced thrombocytopenia antibody	P	Negative	Negative
Homocysteine	P	0–12 µmol/L	0–12 µmol/L
Iron	S	30–160 µg/dl	5.4–28.7 µmol/L
Iron-binding capacity	S	228–428 µg/dl	40.8–76.7 µmol/L
Leukocyte count	WB	4.5–11.0 × 10 ³ /mm ³	4.5–11 × 10 ⁹ /L
Mean corpuscular hemoglobin (MCH)	WB	26.0–34.0 pg/cell	26.0–34.0 pg/cell
Mean corpuscular hemoglobin concentration (MCHC)	WB	31.0–37.0 g/dl	310–370 g/L
Mean corpuscular volume (MCV)	WB	80–100 µm ³	80–100 fl
Methemoglobin	WB	≤ 1% of total hemoglobin	
Osmotic fragility of erythrocytes	WB	No increased hemolysis as compared with normal control	Not applicable
Partial thromboplastin time, activated	P	22.1–35.1 sec	22.1–35.1 sec
Plasminogen	P		
Antigenic		8.4–14.0 mg/dl	84–140 mg/L
Functional		80%–130%	0.80–1.30
Plasminogen activator inhibitor–1	P	4–43 ng/ml	4–43 µg/L
Platelet aggregation	PRP	> 65% aggregation in response to adenosine diphosphate, epinephrine, collagen, ristocetin, and arachidonic acid	Not applicable
Platelet count	WB	150–350 × 10 ³ /mm ³	150–350 × 10 ⁹ /L
Prekallikrein assay	P	60%–140%	0.60–1.40
Prekallikrein screen	P	Deficiency not detected	Not applicable
Protein C	P		
Total antigen		70%–140%	0.70–1.40
Functional		70%–140%	0.70–1.40
Protein S	P		
Total antigen		70%–140%	0.70–1.40
Functional		70%–140%	0.70–1.40
Free antigen		70%–140%	0.70–1.40
Prothrombin gene mutation G20210A	WB	Not present	Not applicable
Prothrombin time	P	11.1–13.1 sec	11.1–13.1 sec
Protoporphyrin, free erythrocyte	WB	16–36 µg/dl RBCs	0.28–0.64 µmol/L RBCs
RBC distribution width	WB	11.5%–14.5%	0.115–0.145
Reptilase time	P	16–24 sec	16–24 sec
Reticulocyte count	WB	0.5%–2.5% RBCs	0.005–0.025 RBCs
Reticulocyte hemoglobin content	WB	> 26 pg/cell	> 26 pg/cell
Ristocetin cofactor (functional von Willebrand factor [vWF])	P		
Blood group O		75% mean of normal	0.75 mean of normal
Blood group A		105% mean of normal	1.05 mean of normal
Blood group B		115% mean of normal	1.15 mean of normal
Blood group AB		125% mean of normal	1.25 mean of normal
Schilling test, orally administered vitamin B ₁₂ excreted in urine	U	7%–40%	Not applicable
Sickle cell test	WB	Negative	Negative
Sucrose hemolysis	WB	< 10%	< 0.1
Thrombin time	P	16–24 sec	16–24 sec

Hematology and Coagulation (continued)

Analyte	Specimen	Units Used at MGH*	SI Units
Transferrin receptor	S, P	9.6–29.6 nmol/L	9.6–29.6 nmol/L
Viscosity	P	1.7–2.1	1.7–2.1
	S	1.4–1.8	1.4–1.8
Vitamin B ₁₂	S, P		
Normal		> 250 pg/ml	> 185 pmol/L
Borderline		125–250 pg/ml	92–185 pmol/L
Deficient		< 125 pg/ml	< 92 pmol/L
vWF antigen (factor VIII:R antigen)	P		
Blood group O		75% mean of normal	0.75 mean of normal
Blood group A		105% mean of normal	1.05 mean of normal
Blood group B		115% mean of normal	1.15 mean of normal
Blood group AB		125% mean of normal	1.25 mean of normal
vWF multimers	P	Normal distribution	Normal distribution
White blood cells (WBCs) [<i>see</i> Leukocyte count]			

Microbiology

<i>Specimen</i>	<i>Organisms Routinely Cultured</i>	<i>Organisms Also Reported</i>	<i>Normal Flora</i>
Throat	Group A β -hemolytic streptococci, pyogenic groups C and G β -hemolytic streptococci, <i>Arcanobacterium haemolyticum</i>	If complete throat culture is requested: <i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i> , and yeast	α -Hemolytic streptococci, nonhemolytic streptococci, diphtheroids, coagulase-negative staphylococci, saprophytic <i>Neisseria</i>
Sputum	Pneumococci, <i>H. influenzae</i> , β -hemolytic streptococci, <i>S. aureus</i> , <i>Moraxella</i> (<i>Branhamella</i>) <i>catarrhalis</i> , gram-negative bacilli	Presence or absence of normal throat flora	Little or no normal throat flora, if specimen carefully collected
Urine	Aerobic bacteria and yeast: "abundant" if $> 10^5$ colony-forming units/ml, "moderate" if 10^4 – 10^5 colony-forming units/ml	"Few" if 10^3 – 10^4 colony-forming units/ml, "rare" if 10^2 – 10^3 colony-forming units/ml (either may indicate clinically significant bacteriuria if accompanied by pyuria, clinical symptoms, or both)	No mixed bacterial species (i.e., not more than one of the following: lactobacilli, non- β -hemolytic streptococci, diphtheroids, coagulase-negative staphylococci, or <i>Gardnerella vaginalis</i>) if specimen carefully collected
Blood	Aerobic and anaerobic bacteria, yeasts		None; common contaminants: aerobic diphtheroids, anaerobic diphtheroids, coagulase-negative staphylococci
Cerebrospinal and other fluids	Aerobic and anaerobic bacteria; yeasts (including <i>Cryptococcus</i>)	Any organism isolated	None
Stool	Enteric pathogens: <i>Salmonella</i> , <i>Shigella</i> , <i>Campylobacter</i> , <i>Plesiomonas</i> , and <i>Aeromonas</i> when predominant	Moderate or abundant yeast or <i>S. aureus</i> ; presence or absence of normal gram-negative enteric flora; if special cultures requested, <i>Yersinia</i> , <i>Vibrio cholerae</i> , <i>V. parahaemolyticus</i> , or hemorrhagic strains of <i>Escherichia coli</i> (O157)	Enterobacteriaceae, streptococci, <i>Pseudomonas</i> , small numbers of staphylococci and yeast (and anaerobes that are not routinely cultured)
Wounds	Aerobic and anaerobic bacteria, yeasts		
Cervical or vaginal	Gonococci, group A β -hemolytic streptococci, pyogenic groups C and G β -hemolytic streptococci, <i>S. aureus</i> (Gram stain for diagnosis of bacterial vaginosis according to Nugent score)	Yeasts and enteric gram-negative rods if present in large numbers	

Metabolic and Endocrine Tests

<i>Analyte</i>	<i>Specimen</i>	<i>Units Used at MGH*</i>	<i>SI Units</i>
Adrenocorticotropin (ACTH)	P	6.0–76.0 pg/ml	1.3–16.7 pmol/L
Aldosterone			
Supine, normal-sodium diet	S, P	2–9 ng/dl	55–250 pmol/L
Upright, normal-sodium diet	S, P	2–5 times supine value with normal-sodium diet	
Supine, low-sodium diet	S, P	2–5 times supine value with normal-sodium diet	
Random, low-sodium diet	U	2.3–21.0 µg/24 hr	6.38–58.25 nmol/24 hr
Androstenedione	S	50–250 ng/dl	1.75–8.73 nmol/L
Cortisol	S		
Fasting, 8 A.M.–noon		5–25 µg/dl	138–690 nmol/L
Noon–8 P.M.		5–15 µg/dl	138–414 nmol/L
8 P.M. –8 A.M.		0–10 µg/dl	0–276 nmol/L
Cortisol, free	U	20–70 µg/24 hr	55–193 nmol/24 hr
Dehydroepiandrosterone (DHEA)	S		
Male		180–1,250 ng/dl	6.24–41.6 nmol/L
Female		130–980 ng/dl	4.5–34.0 nmol/L
Dehydroepiandrosterone (DHEA) sulfate	S		
Male		10–619 µg/dl	100–6,190 µg/L
Female (premenopausal)		12–535 µg/dl	120–5,350 µg/L
Female (postmenopausal)		30–260 µg/dl	300–2,600 µg/L
Deoxycorticosterone (DOC)	S	2–19 ng/dl	61–576 nmol/L
11-Deoxycortisol (8 A.M.)	S	12–158 ng/dl	0.34–4.56 nmol/L
Dopamine	P	< 87 pg/ml	< 475 pmol/L
	U	65–400 µg/day	425–2,610 nmol/day
Epinephrine			
Supine (30 min)	P	< 50 pg/ml	< 273 pmol/L
Sitting	P	< 60 pg/ml	< 328 pmol/L
Standing (30 min)	P	< 900 pg/ml	< 4,914 pmol/L
	U	0–20 µg/day	0–109 nmol/day
Estradiol	S, P		
Female			
Menstruating			
Follicular phase		< 20–145 pg/ml	184–532 pmol/L
Midcycle peak		112–443 pg/ml	411–1,626 pmol/L
Luteal phase		< 20–241 pg/ml	184–885 pmol/L
Postmenopausal		< 59 pg/ml	217 pmol/L
Male		< 20 pg/ml	184 pmol/L
Estrone	S, P		
Female			
Menstruating			
Follicular phase		1.5–15.0 pg/ml	55–555 pmol/L
Luteal phase		1.5–20.0 pg/ml	55–740 pmol/L
Postmenopausal		1.5–5.5 pg/ml	55–204 pmol/L
Male		1.5–6.5 pg/ml	55–240 pmol/L
Follicle-stimulating hormone (FSH)	S, P		
Female			
Menstruating			
Follicular phase		3.0–20.0 mIU/ml	3.0–20.0 IU/L
Ovulatory phase		9.0–26.0 mIU/ml	9.0–26.0 IU/L
Luteal phase		1.0–12.0 mIU/ml	1.0–12.0 IU/L
Postmenopausal		18.0–153.0 mIU/ml	18.0–153.0 IU/L
Male		1.0–12.0 mIU/ml	1.0–12.0 IU/L
Fructosamine	S	1.61–2.68 mmol/L	1.61–2.68 mmol/L
Gastrin	S	< 100 pg/ml	< 100 ng/L
Glucagon	P	20–100 pg/ml	20–100 ng/L
Growth hormone (resting)	S	0.5–17.0 ng/ml	0.5–17.0 µg/L
Human chorionic gonadotropin (hCG)	S	< 5 mIU/ml	< 5 IU/L
(nonpregnant women)			
17-Hydroxyprogesterone	S		
Male		5–250 ng/dl	0.15 nmol/L
Female			

*Massachusetts General Hospital.

P—plasma S—serum U—urine WB—whole blood

Metabolic and Endocrine Tests (*continued*)

<i>Analyte</i>	<i>Specimen</i>	<i>Units Used at MGH</i>	<i>SI Units</i>
Menstruating			
Follicular phase		20–100 ng/dl	0.6–3.0 nmol/L
Midcycle peak		100–250 ng/dl	3.0–7.5 nmol/L
Luteal phase		100–500 ng/dl	3.0–15 nmol/L
Postmenopausal		≤ 70 ng/dl	≤ 2.1 nmol/L
5-Hydroxyindoleacetic acid (5-HIAA)	U	< 6 mg/24 hr	< 31 μmol/24 hr
Insulin	S, P	2–20 μU/ml	14.35–143.50 pmol/L
17-Ketosteroids	U	3–12 mg/24 hr	10–42 μmol/24 hr
Luteinizing hormone (LH)	S, P		
Female			
Menstruating			
Follicular phase		2.0–15.0 mIU/ml	2.0–15.0 IU/L
Ovulatory phase		22.0–105.0 mIU/ml	22.0–105.0 IU/L
Luteal phase		0.6–19.0 mIU/ml	0.6–19.0 IU/L
Postmenopausal		16.0–64.0 mIU/ml	16.0–64.0 IU/L
Male		2.0–12.0 mIU/ml	2.0–12.0 IU/L
Metanephrine	P	< 0.5 nmol/L	< 0.5 nmol/L
	U	0.05–1.20 μg/mg creatinine	0.03–0.69 mmol/mol creatinine
Norepinephrine	U	15–80 μg/24 hr	89–473 nmol/24 hr
Norepinephrine	P		
Supine (30 min)		< 110–410 pg/ml	650–2,423 pmol/L
Sitting		120–680 pg/ml	709–4,019 pmol/L
Standing (30 min)		125–700 pg/ml	739–4,137 pmol/L
Parathyroid hormone	S	10–60 pg/ml	10–60 ng/L
Pregnanetriol	U	Age- and sex-dependent	Age- and sex-dependent
Progesterone	S, P		
Menstruating female			
Follicular		< 0.2 ng/ml	< 0.6 nmol/L
Midluteal		3–20 ng/ml	9.54–63.6 nmol/L
Male		< 0.2–1.4 ng/ml	< 0.60–4.45 nmol/L
Prolactin	S		
Female		0–20 ng/ml	0–20 μg/L
Male		0–15 ng/ml	0–15 μg/L
Serotonin	WB	50–200 ng/ml	0.28–1.14 μmol/L
	Platelets	125–500 ng/10 ⁹ platelets	0.7–2.8 amol/platelet
Sex hormone-binding globulin	S		
Male		13–71 nmol/L	13–71 nmol/L
Female		18–114 nmol/L	18–114 nmol/L
Somatostatin	P	< 25 pg/ml	< 25 ng/L
Somatomedin C (insulinlike growth factor-I [IGF-I])	S		
16–24 yr		182–780 ng/ml	182–780 μg/L
25–39 yr		114–492 ng/ml	114–492 μg/L
40–54 yr		90–360 ng/ml	90–360 μg/L
> 54 yr		71–290 ng/ml	71–290 μg/L
Testosterone	S		
Total, morning			
Female		6–86 ng/dl	0.21–2.98 nmol/L
Male		270–1,070 ng/dl	9.36–37.10 nmol/L
Unbound, morning			
Female		0.2–3.1 pg/ml	6.9–107.5 pmol/L
Male		12.0–40.0 pg/ml	416–1,387 pmol/L
Thyroglobulin	S	0–60 ng/ml	0–60 μg/L
Thyroid-binding globulin	S	16–24 μg/ml	206–309 nmol/L
Thyroid-stimulating hormone	S	0.5–4.7 μU/ml	0.5–4.7 mU/L
Thyroxine	S		
Total (T ₄)		4.5–10.9 μg/dl	58–140 nmol/L
Free (fT ₄)		0.8–2.7 ng/dl	10.3–35.0 pmol/L
Triiodothyronine	S		
Total (T ₃)		60–181 ng/dl	0.92–2.78 nmol/L
Free (fT ₃)		1.4–4.4 pg/ml	0.22–6.78 pmol/L
Vanillylmandelic acid (VMA)	U	0.15–1.20 mg/24 hr	7.6–37.9 μmol/24 hr
Vasoactive intestinal polypeptide (VIP)	P	< 75 pg/ml	< 75 ng/L

Urine Analysis

<i>Analyte</i>	<i>Units Used at MGH*</i>	<i>SI Units</i>
Acidity, titratable	20–40 mEq/24 hr	20–40 mmol/24 hr
Ammonia	30–50 mEq/24 hr	30–50 mmol/24 hr
Amylase	4–400 U/L	0.07–7.67 nkat/L
Amylase-to-creatinine clearance ratio [†]	1–5	1–5
Calcium (with dietary calcium of 10 mEq/24 hr or 200 mg/24 hr)	< 300 mg/24 hr	< 7.5 mmol/24 hr
Creatine, as creatinine		
Female	< 100 mg/24 hr	< 760 µmol/24 hr
Male	< 50 mg/24 hr	< 380 µmol/24 hr
Creatinine	1.0–1.6 g/24 hr	8.8–14 mmol/24 hr
Eosinophils	< 100 eosinophils/ml	< 100 eosinophils/ml
Glucose, true (oxidase method)	50–300 mg/24 hr	0.3–1.7 mmol/24 hr
Microalbumin	0–2.0 mg/dl	0–0.02 g/L
Oxalate	2–60 mg/24 hr	228–684 µmol/24 hr
pH	5.0–9.0	5.0–9.0
Phosphate (phosphorus)	400–1,300 mg/24 hr (varies with intake)	12.9–42.0 mmol/24 hr (varies with intake)
Potassium	25–100 mEq/24 hr (varies with intake)	25–100 mmol/24 hr (varies with intake)
Protein	< 150 mg/24 hr	< 0.15 g/24 hr
Sediment		
Bacteria	Negative	Negative
Bladder cells	Negative	Negative
Broad casts	Negative	Negative
Crystals	Negative	Negative
Epithelial cell casts	Negative	Negative
Granular casts	Negative	Negative
Hyaline casts	0–5/low-power field	0–5/low-power field
RBC casts	Negative	Negative
RBCs	0–2/high-power field	0–2/high-power field
Squamous cells	Negative	Negative
Tubular cells	Negative	Negative
Waxy casts	Negative	Negative
WBCs	0–2/high-power field	0–2/high-power field
WBC casts	Negative	Negative
Sodium	100–260 mEq/24 hr (varies with intake)	100–260 mmol/24 hr (varies with intake)
Specific gravity	1.001–1.035	1.001–1.035
Urea nitrogen	6–17 g/24 hr	214–607 mmol/24 hr
Uric acid (with normal diet)	250–800 mg/24 hr	1.49–4.76 mmol/24 hr

*Massachusetts General Hospital.

[†]The amylase-to-creatinine clearance ratio is calculated as [amylase clearance ÷ creatinine clearance] × 100.